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5 Epidemiology of Communicable Diseases

"Infectious diseases will last as long as humanity itself"

I. RESPIRATORY INFECTIONS

SMALLPOX (VARIOLA)

An acute infectious disease caused by *variola virus*, and clinically characterized by a sudden onset of fever, headache, backache, vomiting and sometimes convulsions, especially in children. On the third day of fever, a typical rash appears which is centrifugal in distribution and passes through successive stages of macule, papule, vesicle, pustule, and scab with subsequent scarring.

Previously, it was one of the greatest killer disease. In 1967, WHO began an intensified worldwide campaign to eradicate smallpox, based on the technique of surveillance and containment. The last known case of smallpox in India occurred on 24th May 1975. India was declared smallpox free on 5th July 1975. The eradication of smallpox was confirmed in April 1977 by an international commission. The World Health Assembly confirmed the global eradication of smallpox in May 1980. All countries have discontinued routine vaccination against smallpox. However, WHO maintains a reserve stock of smallpox vaccine and vaccination needles – sufficient to protect more than 200 million people, should an emergency arise *(1)*.

Case definition for notification of smallpox under the International Health Regulations, 2005 *(2)*

Member states to the IHR (2005) are required to notify to WHO immediately of any confirmed case of smallpox. The case definition for a confirmed smallpox case includes the following :

Confirmed case of smallpox

An individual of any age presenting with acute onset of fever (≥38.3°C/101°F), malaise, and severe prostration with headache and backache occurring 2–4 days before onset of rash

AND

Subsequent development of a maculopapular rash starting on the face and forearms then spreading to the trunk and legs, and evolving within 48 hours to deep-seated, firm or hard and round well-circumscribed vesicles, and later pustules, which may become umbilicated or confluent

AND

Lesions that appear at the same stage of development (i.e. all are vesicles or all are pustules) on any given part of the body (e.g. the face or arm)

AND

No alternative diagnosis explaining the illness

AND

Laboratory confirmation.

Smallpox eradication surveillance

Despite the absence of smallpox, surveillance of "rumours" continues in order to sustain public confidence in the eradication of the disease. However, the final chapter of the smallpox story remains to be written, as the smallpox virus has not been completely destroyed. Stocks are still held at government research centres in the Russian Federation and at the United States.

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MPOX

Mpox, previously known as monkeypox, is a viral zoonosis (a virus transmitted to humans from animals) with symptoms similar to those seen in the past in smallpox patients, although it is clinically less severe. With the eradication of smallpox in 1980 and subsequent cessation of smallpox vaccination, monkeypox has emerged as the most important orthopoxvirus for public health.

Natural host

Various animal species have been identified as susceptible to mpox virus. This includes rope squirrels, tree squirrels, Gambian pouched rats, dormice, non-human primates and other species. Uncertainty remains on the natural history of mpox virus and further studies are needed to identify the exact reservoir(s) and how virus circulation is maintained in nature.

Transmission of disease *(1, 2)*

Animal-to-human (zoonotic) transmission can occur from direct contact with the blood, bodily fluids, or cutaneous or mucosal lesions of infected animals. Eating inadequately cooked meat and other animal products of infected animals is a possible risk factor. People living in or near forested areas may have indirect or low-level exposure to infected animals.

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Since 1970, cases of mpox have been reported across several countries in the African region where the disease is endemic. Mpox has been exported occasionally from these countries to other regions of the world. For instance, an outbreak of mpox occurred in the United States of America in 2003 linked to the co-housing of prairie dogs with infected imported small mammals. In May 2022, several countries without endemic mpox began reporting cases. These cases occurred in persons with no recent history of travel to endemic areas and without links to imported animals. As the outbreak grew, it was declared a public health emergency of international concern (PHEIC) by WHO on 23 July 2022. Over subsequent months and into 2023, the global outbreak subsided significantly and on 10 May 2023 the PHEIC was lifted. The global outbreak of mpox, driven by Clade IIb MPXV, primarily spread through sexual contact and mostly affected adult gay, bisexual and other men who have sex with men. However, due to the emergence of the new Clade Ib and a resurgence of cases in the African region, a PHEIC was once again declared on 14 August 2024.

Globally, from January 2022 through to the end of April 2024, WHO received reports of over 97,000 laboratory confirmed cases of mpox and 186 associated deaths. These confirmed cases were reported from 117 countries/territories/areas in all 6 WHO regions. Among globally reported cases with available data on gender, 96.4% were male, with a median age of 34 years. Of the mpox cases with known HIV status (around 40% of total cases), 52.1% were people living with HIV *(3)*.

India reported its first case of Mpox on 9th Sept. 2024, in a person returned from a country reporting the outbreak of the virus. Clade II strain was isolated, which is not part of the current public health emergency.

Agent factor

Mpox is an infectious disease caused by the monkeypox virus (MPXV) of the Orthopoxvirus genus. MPXV is a DNA virus comprising 2 clades - Clade I (formerly known as Congo Basin clade) and Clade II (formerly known as West African clade), which further divides into subclades Clade Ia and Ib; and IIa and IIb.

Mpox may spread from person to person mainly through close contact with someone who has mpox, including members of a household. Close contact includes skin-to-skin (such as touching or sex) and mouth-to-mouth or mouth-to-skin contact (such as kissing), and it can also include being face-to-face with someone who has mpox (such as talking or breathing close to one another, which can generate infectious respiratory particles). People with multiple sexual partners are at higher risk of acquiring mpox. People can also contract mpox from contaminated objects such as clothing or linen, through needle injuries in health care, or in community settings such as tattoo parlours.

During pregnancy or birth, the virus may be passed to the baby. Contracting mpox during pregnancy can be dangerous for the foetus or newborn infant and can lead to loss of the pregnancy, stillbirth, death of the newborn, or complications for the mother.

Groups that may be at high risk of mpox include *(4)* :

a. health and care workers at risk of exposure;

b. people in the same household or close community as someone who has mpox, including children;

c. people who have multiple sex partners, including men who have sex with men; and

d. sex workers of any gender and their clients.

In the absence of skin lesions, testing can be done using swabs of the throat or anus. Testing blood is not recommended. Antibody detection method may not be useful as they do not distinguish between different orthopoxiviruses.

HIV testing should be offered to adults with mpox, and children as appropriate. Diagnostic tests for other conditions should be considered where feasible, for example, varicella zoster virus (VZV), syphilis and herpes *(4)*.

Incubation period

The incubation period of mpox is usually from 6 to 13 days, but can range from 2 to 21 days.

Clinical picture

The infection can be divided into two periods :

- the invasion period (lasts between 1–5 days) characterized by fever, intense headache, lymphadenopathy, back pain, myalgia and intense asthenia. Lymphadenopathy is a distinctive feature of monkeypox compared to other diseases that may initially appear similar (chickenpox, measles, smallpox).
- the skin eruption usually begins within 1–3 days of appearance of fever. The rash tends to be more concentrated on the face and extremities rather than on the trunk. It affects the face (in 95 per cent of cases), and palms of the hands and soles of the feet (in 75 per cent of cases). Also affected are oral mucous membranes (in 70 per cent of cases), genitalia (30 per cent), and conjunctivae (20 per cent), as well as the cornea. The rash evolves sequentially from macules (lesions with a flat base) to papules (slightly raised firm lesions), vesicles (lesions filled with clear fluid), pustules (lesions filled with yellowish fluid), and crusts which dry up and fall off. The number of lesions varies from a few to several thousand. In severe cases, lesions can coalesce until large sections of skin slough off.

Mpox is usually a self-limited disease with the symptoms lasting from 2 to 4 weeks. Severe cases occur more commonly among children and are related to the extent of virus exposure, patient health status and nature of complications. Underlying immune deficiencies may lead to worse outcomes. Although vaccination against smallpox was protective in the past, today persons younger than 40 to 50 years of age (depending on the country) may be more susceptible to mpox due to cessation of smallpox vaccination campaigns globally after eradication of the disease. Complications of mpox can include secondary infections, bronchopneumonia, sepsis, encephalitis, and infection of the cornea with ensuing loss of vision. The extent to which asymptomatic infection may occur is unknown. The case fatality ratio has been around 3–6 per cent *(3)*.

Diagnosis

Polymerase chain reaction (PCR) is the preferred laboratory test given its accuracy and sensitivity. For this, optimal diagnostic samples for mpox are from skin lesions -

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the roof or fluid from vesicles and pustules, and dry crusts. Where feasible, biopsy is an option.

Treatment

Clinical care for mpox should be fully optimized to alleviate symptoms, manage complications and prevent long-term sequelae. Patients should be offered fluids and food to maintain adequate nutritional status. Secondary bacterial infections should be treated as indicated. An antiviral agent known as tecovirimat that was developed for smallpox was licensed by the European Medical Association (EMA) for mpox in 2022 based on data in animal and human studies. It is not yet widely available.

Vaccination

Vaccination against smallpox was demonstrated through several observational studies to be about 85 per cent effective in preventing mpox. Prior smallpox vaccination may result in milder illness. A still newer vaccine based on a modified attenuated vaccinia virus (Ankara strain) was approved for the prevention of mpox in 2019 *(1)*. This is a two-dose vaccine for which availability is limited.

Prevention *(1)*

Raising awareness of risk factors and educating people about the measures they can take to reduce exposure to the virus is the main prevention strategy for mpox. Scientific studies are now underway to assess the feasibility and appropriateness of vaccination for the prevention and control of mpox. Some countries have, or are developing, policies to offer vaccine to persons who may be at risk such as laboratory personnel, rapid response teams and health workers.

Reducing the risk of human-to-human transmission *(1)*

Surveillance and rapid identification and isolation of new cases is critical for outbreak containment. During human mpox outbreaks, close contact with infected persons is the most significant risk factor for mpox virus infection. Health workers and household members are at a greater risk of infection. Health workers caring for patients with suspected or confirmed mpox virus infection, or handling specimens from them, should implement standard infection control precautions. If possible, persons previously vaccinated against smallpox should be selected to care for the patient.

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CHICKENPOX (VARICELLA)

Chickenpox or varicella is an acute, highly infectious disease caused by *varicella-zoster* (V–Z) virus. It is characterized by vesicular rash that may be accompanied by fever and malaise. It is worldwide in distribution and occurs in both epidemic and endemic forms. Chickenpox and herpes zoster are now regarded as different host responses to the same aetiological agent. Inoculation of zoster vesicle fluid into children produces chickenpox, and children who have recovered from zoster virus related infection are resistant to varicella *(1)*.

Problem Statement

Based on conservative estimates, the global annual chickenpox disease burden includes 4.2 million severe complications leading to hospitalization and 4,200 deaths. In the pre-vaccine era in high-income developed countries, case fatality rate was about 3 per lac cases compared to 1–3 per 1000 cases for measles. Factors which influence the severity of disease and outcome in populations include the proportion of cases among infants, pregnant women and other adults, the prevalence of immunocompromising conditions including HIV infections and the extent of access to care and appropriate treatment. In otherwise healthy children, the disease is usually self-limiting *(2)*.

The incidence and severity of herpes-zoster disease increases with age, with marked increase after 50 years of age, which correlates with ageing related decline in cell-mediated immunity. Among adults who reach 85 years of age, it is estimated that approximately half will have suffered atleast one episode of herpes zoster *(2)*.

In India, during the year 2022, about 27,279 cases of chickenpox were reported with 15 deaths. The case fatality rate was about 0.0549 per cent. Kerala reported the highest number of cases (9,927) and maximum number of deaths (14) due to chickenpox *(3)*.

Epidemiological determinants

Agent factors

(a) AGENT : The causative agent of chickenpox, V–Z virus is also called "Human (alpha) herpes virus 3". Primary infection causes chickenpox. Recovery from primary infection is commonly followed by the establishment of latent infection in the cranial nerves, sensory, ganglia, and spinal dorsal root ganglia, often for decades, without clinical manifestations. When the cell-mediated immunity wanes with age or following immuno-suppressive therapy, the virus may reactivate, resulting in herpes zoster in about 10–30 per cent of persons *(4)*. It is, a painful, vesicular, pustular eruption in the distribution of one or more sensory nerve roots. The virus can be grown in tissue culture. (b) SOURCE OF INFECTION: Usually a case of chickenpox. The virus occurs in the oropharyngeal secretions and lesions of skin and mucosa. Rarely the source of infection may be a patient with herpes zoster. The virus can be readily isolated from the vesicular fluid during the first 3 days of illness. The scabs however are not infective *(5)*. (c) INFECTIVITY: The period of communicability of patients with varicella is estimated to range from 1 to 2 days before the appearance of rash, and 4 to 5 days thereafter *(5)*. The virus tends to die out before the pustular stage *(6)*. The patient ceases to be infectious once the lesions have crusted. (d) SECONDARY ATTACK RATE: Varicella is a highly contagious disease with secondary attack ratio of approximately 85 per cent (range between 61 per cent to 100 per cent) in susceptible household contacts. Herpes zoster is approximately 20 per cent as infectious as chickenpox; in susceptible people, contact with herpes zoster rash causes varicella, not herpes zoster *(9)*.

Host factors

(a) AGE : Chickenpox occurs primarily among children

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under 10 years of age. Few persons escape infection until adulthood. The disease can be severe in normal adults. (b) IMMUNITY : One attack gives durable immunity; second attacks are rare. The acquisition of maternal antibody protects the infant during the first few months of life. No age, however, is exempt in the absence of immunity. The IgG antibodies persist for life and their presence is correlated with protection against varicella. The cell-mediated immunity appears to be important in recovery from V–Z infections and in protection against the reactivation of latent V–Z virus *(8)*. (c) PREGNANCY : Infection during pregnancy presents a risk for the foetus leading to congenital varicella syndrome. It occurs in 0.4–2.0 per cent of children born to mothers who become infected with VZV during the first 20 weeks of gestation. Infants, whose mothers had chickenpox during pregnancy, have a higher risk of developing herpes zoster in the first years of life *(2)*.

Environmental factors

Chickenpox shows a seasonal trend in temperate settings and in most tropical settings, with peak incidence during winter and spring, or in coolest, driest months in the tropics. Periodic large outbreaks occur with an inter-epidemic cycle of 2–5 years *(2)*.

VZV is heat labile. Outside host cell, the virus survives in the external environment for only a few hours, occasionally for a day or two, and it is readily inactivated by lipid solvents, detergents, and proteases *(2)*.

Transmission

Chickenpox is transmitted from person to person by droplet infection and by droplet nuclei. Most patients are infected by "face-to-face" (personal) contact. The portal of entry of the virus is the upper respiratory tract or the conjunctiva. Since the virus is extremely labile, it is unlikely that fomites play a significant role in its transmission. Contact infection undoubtedly plays a role when an individual with herpes zoster is an index case. The virus can cross the placental barrier and infect the foetus, a condition known as congenital varicella.

Incubation period

Usually 14 to 16 days, although extremes as wide as 10 to 21 days have been reported.

Clinical features

The clinical spectrum of chickenpox may vary from a mild illness with only a few scattered lesions to a severe febrile illness with widespread rash. Inapparent infection is estimated to occur in no more than 5 per cent of susceptible children *(7)*. In the majority of cases, the disease tends to be mild and typical *(6)*. The clinical course of chickenpox may be divided into two stages :

(A) PRE-ERUPTIVE STAGE : Onset is sudden with mild or moderate fever, pain in the back, shivering and malaise. This stage is very brief, lasting about 24 hours. In adults, the prodromal illness is usually more severe and may last for 2–3 days before the rash comes out *(6)*.

(B) ERUPTIVE STAGE : In children the rash is often the first sign. It comes on the day the fever starts. The distinctive features of the rash are :

(a) *Distribution* : The rash is symmetrical. It first appears on the trunk where it is abundant, and then comes on the face, arms and legs where it is less abundant. Mucosal surfaces (e.g., buccal, pharyngeal) are generally involved. Axilla may be affected, but palms and soles are not usually affected. The density of the eruption diminishes centrifugally.

(b) *Rapid evolution* : The rash advances quickly through the stages of macule, papule, vesicle and scab. In fact, the first to attract attention are often the vesicles filled with clear fluid and looking like "dew-drops" on the skin. They are superficial in site, with easily ruptured walls and surrounded by an area of inflammation. Usually they are not umbilicated. The vesicles may form crusts without going through the pustular stage. Many of the lesions may abort. Scabbing begins 4 to 7 days after the rash appears.

(c) *Pleomorphism* : A characteristic feature of the rash in chickenpox is its pleomorphism, that is, all stages of the rash (papules, vesicles and crusts) may be seen simultaneously at one time, in the same area. This is due to the rash appearing in successive crops for 4 to 5 days in the same area.

(d) *Fever* : The fever does not run high but shows exacerbations with each fresh crop of eruption.

The main points of difference between chickenpox and smallpox are given in Table 1.

TABLE 1

Differences between smallpox and chickenpox

	Smallpox	Chickenpox
1.	*Incubation :* About 12 days (range: 7–17 days).	About 15 days (range 7–21 days).
2.	*Prodromal symptoms:* Severe.	Usually mild.
3.	*Distribution of rash :*	
	(a) centrifugal	(a) centripetal
	(b) palms and soles frequently involved	(b) seldom affected
	(c) axilla usually free	(c) axilla affected
	(d) rash predominant on extensor surfaces and bony prominences.	(d) rash mostly on flexor surfaces.
4.	*Characteristics of the rash:*	
	(a) deep-seated	(a) superficial
	(b) vesicles multilocular and umbilicated	(b) unilocular; dew-drop like appearance
	(c) only one stage of rash may be seen at one time	(c) rash pleomorphic, i.e., different stages of the rash evident at one given time, because rash appears in successive crops
	(d) No area of inflammation is seen around the vesicles.	(d) an area of inflammation is seen around the vesicles.
5.	*Evolution of rash :*	
	(a) evolution of rash is slow, deliberate and majestic, passing through definite stages of macule, papule, vesicle and pustule.	(a) evolution of rash very rapid
	(b) scabs begin to form 10–14 days after the rash appears	(b) scabs begin to form 4–7 days after the rash appears
6.	*Fever :* Fever subsides with the appearance of rash, but may rise again in the pustular stage (secondary rise of fever).	Temperature rises with each fresh crop of rash.

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Complications

In most cases, chickenpox is a mild, self-limiting disease. The mortality is less than 1 per cent in uncomplicated cases.

However, varicella may be accompanied by severe complications particularly in immunosuppressed patients and may also occur in normal children and adults. These include haemorrhages (varicella haemorrhagical), pneumonia, encephalitis, acute cerebellar ataxia and Reye's syndrome (acute encephalopathy associated with fatty degeneration of the viscera especially liver) *(10)*. Varicella pneumonia is rare in healthy children but is the most common complication in neonates, adults and immuno-compromised patients. It is related to many varicella-related deaths. Maternal varicella during pregnancy may cause foetal wastage and birth defects such as cutaneous scars, atrophied limbs, microcephaly and low birth weight, cataract, microphthalmia, chorioretinitis, deafness and cerebro-cortical atrophy. If varicella develops in a mother within 5 days after delivery, the newborn is at risk of disseminated disease and should receive varicella-zoster immunoglobulin *(4)*. The virus has a potential for oncogenicity.

Varicella-zoster virus is the major virus associated with acute retinal necrosis and progressive outer retinal necrosis, both of which occur with increased frequency among AIDS patients *(4)*.

Secondary bacterial infections, particularly with group A β-haemolytic streptococci and *staphylococcus aureus* are common. Cellulitis, erysipelas, epiglottitis, osteomyelitis, scarlet fever and rarely meningitis are observed. Pitted scars are frequent sequelae.

Immunocompromised patients are at increased risk of complications of varicella, including those with malignancies, organ transplants or HIV infection and those receiving high doses of corticosteroids. Disseminated intravascular coagulation may occur which is rapidly fatal. Children with leukaemia are especially prone to develop severe disseminated varicella-zoster virus disease *(1)*.

Laboratory diagnosis

During the smallpox post-eradication era the diagnosis of chickenpox is of great importance because of its resemblance to mild smallpox. Laboratory diagnosis is rarely required as clinical signs are usually clear-cut.

Laboratory confirmation of varicella or herpes zoster (HZ) is by detecting VZV DNA using polymerase chain reaction (PCR) or isolating VZV in cell culture from vesicular fluid, crusts, saliva, cerebrospinal fluid or other specimens. Direct immunofluorescence can also be used for rapid testing though this method has lower sensitivity than PCR. Detection of VZV-specific serum IgM antibody is considerably less sensitive than PCR and is not the method of choice for confirming varicella. Detection of serum IgM and PCR are of limited value for the confirmation of HZ. Serologic screening of serum for IgG antibodies is used to assess immunity or susceptibility to varicella in unvaccinated persons, e.g. in health-care workers *(2)*.

Control

The usual control measures are notifications, isolation of cases for about 6 days after onset of rash and disinfection of articles soiled by nose and throat discharges *(11)*.

Several antiviral compounds provide effective therapy for varicella including acyclovir, valaciclovir, famiciclovir and foscarnet. Acyclovir can prevent the development of systemic disease in varicella-infected immunosuppressed patients and can halt the progression of zoster in adults. Acyclovir does not appear to prevent post herpic neuralgia *(1)*.

Prevention

1. VARICELLA-ZOSTER IMMUNOGLOBULIN (VZIG)

Varicella-Zoster Immunoglobulin *(VZIG)* given within 72 hours of exposure has been recommended for prevention of chickenpox in exposed susceptible individuals particularly in immunosuppressed persons. These include (a) susceptible persons receiving immunosuppressive therapy; (b) persons with congenital cellular immunodeficiency; (c) persons with acquired immunodeficiency including HIV/AIDS; (d) susceptible and exposed persons, in particular pregnant women; (e) newborns; and (f) premature infants of low birth weight. It has no therapeutic value in established disease. *VZIG* is given by intramuscular injection in a dose of 12.5 units/kg body weight up to a maximum of 625 units, with a repeat dose in 3 weeks, if a high-risk patient remains exposed. Because *VZIG* appears to bind the varicella vaccine, the two should not be given concomitantly *(4)*.

2. VACCINE

A live attenuated varicella virus vaccine is safe and currently recommended for children between 12–18 months of age who have not had chickenpox.

Recommendations on dosage and interval between doses vary by manufacturer. Monovalent vaccine can be administered following one or two dose schedule (0.5 ml each by subcutaneous injection. A 2 dose schedule is recommended for all persons aged ≥13 years. When 2 doses are administered, the minimum interval between doses is from 4 weeks to 3 months for children (12 months to 12 years of age inclusive), and 4 or 6 weeks for adolescents and adults (13 years of age and older).

Combination vaccines (MMRV) can be administered to children from 9 months to 12 years. If 2 doses of MMRV are used, the minimum interval between doses should be 4 weeks. It is preferred that the 2nd dose be administered from 6 weeks to 3 months after the first dose or at 4–6 years of age *(2)*.

The duration of immunity is not known but is probably 10 years. Although the vaccine is very effective in preventing disease, breakthrough infections do occur – but are much milder than in unvaccinated individuals (usually less than 50 lesions, with milder systemic symptoms). Although the vaccine is very safe, adverse reactions can occur as late as 4–6 weeks after vaccination. Tenderness and erythema at the injection site are seen in 25%, fever in 10–15%, and a localized maculopapular or vesicular rash in 5%; a smaller percentage develops a diffuse rash, usually with five or fewer vesicular lesions.

Spread of virus from vaccinees to susceptible individuals is possible, but the risk of such transmission even to immuno-compromised patients is small, and disease, when it develops, is mild and treatable with acyclovir. Nonetheless, the vaccine, being a live attenuated virus, should not be given to immunocompromised individuals. The use of varicella vaccine may be considered in clinically stable HIV-infected children or adults with CD4+ T-cell levels ≥ 15 per cent including those receiving highly active antiretroviral therapy. HIV testing is not a prerequisite for varicella vaccination *(2)*. It is contraindicated in persons allergic to neomycin. For theoretic reasons, it is recommended that

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following vaccination, salicylates should be avoided for 6 weeks (to prevent Reye's syndrome).

Varicella vaccination is contraindicated during pregnancy and pregnancy should be delayed for 4 weeks after vaccination. Termination of pregnancy is not indicated if vaccination was carried out inadvertently during pregnancy *(9)*.

POST-EXPOSURE PROPHYLAXIS

Vaccine: Varicella vaccine is recommended for post exposure administration to un-vaccinated healthy people aged ≥12 months and without other evidence of immunity, to prevent or modify the disease. The vaccine should be administered as soon as possible within 5 days after exposure to rash, if there is no contraindication to use. Among children, protective efficacy was reported as ≥90 per cent when vaccination occurred within 3 days of exposure. However, administration of a second dose is recommended for exposed people to bring them up-to-date on vaccination and for best protection against future exposure *(9)*.

Several unresolved issues remain, including the need for booster doses, whether universal childhood vaccination will shift the incidence of disease to adolescence or adulthood with the possibility of more severe disease, and whether vaccination might prevent development of herpes zoster.

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MEASLES
(RUBEOLA)

An acute highly infectious disease of childhood caused by a specific virus of the group myxoviruses. It is clinically characterized by fever and catarrhal symptoms of the upper respiratory tract (coryza, cough), followed by a typical rash. Measles is associated with high morbidity and mortality in developing countries. Measles occurs only in humans. There is no animal reservoir of infection.

Problem statement

Measles is endemic virtually in all parts of the world. It tends to occur in epidemics when the proportion of susceptible children reaches about 40 per cent *(1)*. When the disease is introduced into a virgin community more than 90 per cent of that community will be infected *(2)*. While measles is now rare in industrialized countries, it remains a common illness in many developing countries. The primary reason for continuing high childhood measles mortality and morbidity is the failure to deliver at least one dose of measles vaccine to all infants *(3)*.

The challenges for measles elimination include : (1) weak immunization systems; (2) high infectious nature of measles; (3) populations that are inaccessible due to conflict; (4) the increasing refusal of immunization by some populations; (5) the changing epidemiology of measles which has led to increased transmission among adolescents and adults; (6) the gaps in human and financial resources at the country, regional and global levels *(6)*.

In 1980, before widespread use of measles vaccine, an estimated 2.6 million measles deaths occurred worldwide. Recognizing this burden, WHO and UNICEF developed an accelerated measles mortality reduction strategy of delivering 2 doses of measles containing vaccine (MCV) to all children through routine services and supplementary immunizing activities (SIAs), and improving disease surveillance. Implementation of this strategy began in 2001. At the 2010 World Health Assembly, member states endorsed the following targets to be met by 2015 as milestones towards eventual global measles eradication : (1) raise routine coverage with the first dose of MCV (MCV_1) to ≥90 per cent nationally, and ≥80 per cent in every district or equivalent administrative unit; (2) reduce and maintain annual measles incidence to <5 cases per million; and (3) reduce measles mortality by ≥95 per cent in comparison with the estimated level in the year 2000 *(5)*.

The Global Measles and Rubella Strategic Plan 2012–20 period saw a significant reduction in the measles and rubella disease burden, a steep increase in the introduction of a second dose of measles-containing (MCV_2) and rubella vaccines, and improvements in surveillance. An increase in measles cases in January and February 2022 is a worrying sign of a heightened risk for the spread of vaccine-preventable diseases and could trigger large outbreaks. Pandemic-related disruptions, increasing inequalities in access to vaccines and the diversion of resources from routine immunization are leaving too many children without protection against measles. In addition, with millions of people being displaced due to conflicts and crises, disruptions of routine immunization and COVID-19 vaccine services, lack of clean water, sanitation and overcrowding increase the risk of disease outbreak. Almost 17,338 measles cases were reported globally in January and February 2022, compared to 9,665 during the first two months of 2021. As measles is very contageous, cases tend to show up quickly when vaccination level declines (In 2020, 23 million children missed out on basic childhood vaccines through health services).

Based on updated annual data, the estimated number of measles cases decreased 79 per cent, from 3,67,63,000 in year 2000 to 75,49,000 in 2020; and estimated annual measles deaths decreased 94 per cent from 10,72,800 to 1,36,000 in year 2022. During 2000–2022, measles vaccination prevented an estimated 57 million deaths globally compared with no measles vaccination *(6)*.

In India, measles is a significant cause of childhood morbidity. Prior to the immunization programme, cyclical increase in the incidence of measles were recorded every third year. With the increase in immunization coverage levels, the intervals between cyclical peaks has increased and the intensity of the peak minimized. However, several outbreaks are reported in tribal and remote areas. The retrospective data indicate a declining trend of measles in the country. During 1987 about 2.47 lakh cases were reported, whereas, after implementation of UIP, the number of cases has come

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down to 7,434 with 4 death during the year 2022.

During the year 2022 the states majorly affected were Jharkhand (3,682 cases and no deaths), Assam (1,073 cases without any death), Karnataka (440 cases without any death), Sikkim (339 cases, no deaths), and Telangana (337 cases without any death), Lakshadweep recorded 3 deaths *(7)*. The country is making significant progress towards the goal of measles elimination and rubella/ congenital rubella syndrome control. The strategies for measles and rubella elimination include : (1) 95 per cent coverage with measles and rubella vaccination; (2) Case-based measles-rubella surveillance with adequate laboratory support; (3) Linkage with other child health interventions; and (4) Increased public confidence and demand for immunization *(8)*.

Epidemiological determinants

Agent factors

(a) AGENT : Measles is caused by an RNA paramyxovirus. So far as is known, there is only one serotype. The virus cannot survive outside the human body for any length of time, but retains infectivity when stored at sub-zero temperature. The virus has been grown in cell cultures. (b) SOURCE OF INFECTION : The only source of infection is a case of measles. Carriers are not known to occur. There is some evidence to suggest that subclinical measles occurs more often than previously thought. (c) INFECTIVE MATERIAL : Secretions of the nose, throat and respiratory tract of a case of measles during the prodromal period and the early stages of the rash. (d) COMMUNICABILITY : Measles is highly infectious during the prodromal period and at the time of eruption. Communicability declines rapidly after the appearance of the rash. The period of communicability is approximately 4 days before and 4 days after the appearance of the rash. Isolation of the patient for a week from the onset of rash more than covers the period of communicability *(9)*. (e) SECOND ATTACK RATE : There is only one antigenic type of measles virus. Infection confers life long immunity. Most so-called second attacks represent errors in diagnosis either in initial or second illness *(10)*.

Host factors

(a) AGE : Affects virtually everyone in infancy or childhood – between 6 months and 3 years of age in developing countries where environmental conditions are generally poor, and older children usually over 5 years in developed countries *(11)*. Following the use of measles vaccine, the disease is now seen in somewhat older age-groups *(12)*. This highlights the importance of periodic serological checking of the immunity status of the susceptible population. (b) SEX : Incidence equal. (c) IMMUNITY : No age is immune if there was no previous immunity. One attack of measles generally confers life-long immunity. Second attacks are rare. Infants are protected by maternal antibodies up to 6 months of age; in some, maternal immunity may persist beyond 9 months. Immunity after vaccination is quite solid and long-lasting. (d) NUTRITION : Measles tends to be very severe in the malnourished child, carrying a mortality upto 400 times higher than in well-nourished children having measles *(13)*. This may possibly be related to poor cell-mediated immunity response, secondary to malnutrition *(14)*. Additionally, severely malnourished children have been shown to excrete measles virus for longer periods than better nourished children indicating prolonged risk to themselves, and of intensity of spread to others *(15)*. Even in a healthy child, an attack of severe measles may be followed by weight loss, precipitating the child into malnutrition.

Environmental factors

Given a chance, the virus can spread in any season *(10)*. In tropical zones, most cases of measles occur during the dry season. In temperate climates, measles is a winter disease, probably because people crowd together indoors. Epidemics of measles are common in India during winter and early spring (January to April). Population density and movement do affect epidemicity *(16)*. In general, the less favourable the prevailing socio-economic conditions, the lower the average age at which children are attacked.

Transmission

Transmission occurs directly from person to person mainly by droplet infection and droplet nuclei, from 4 days before onset of rash until 4 days thereafter. The portal of entry is the respiratory tract. Infection through conjunctiva is also considered likely as the virus instilled into the conjunctiva can cause infection. Recipients of measles vaccine are not contagious to others *(17)*.

Incubation period

Incubation period is commonly 10 days from exposure to onset of fever, and 14 days to appearance of rash. When measles infection is artificially induced bypassing the respiratory tract (as with injection of live measles vaccine), the incubation period is somewhat shortened, averaging 7 days.

Clinical features

There are three stages in the natural history of measles, viz. the prodromal or pre-eruptive stage, eruptive stage and post-measles stage.

1. PRODROMAL STAGE

It begins 10 days after infection, and lasts until day 14. It is characterized by fever, coryza with sneezing and nasal discharge, cough, redness of the eyes, lacrimation and often photophobia. There may be vomiting or diarrhoea. A day or two before the appearance of the rash Koplik's spots like table salt crystals appear on the buccal mucosa opposite the first and second lower molars. They are small, bluish–white spots on a red base, smaller than the head of a pin *(10)*. Their presence is pathognomonic of measles.

2. ERUPTIVE PHASE

This phase is characterized by a typical, dusky–red, macular or maculo-papular rash which begins behind the ears and spreads rapidly in a few hours over the face and neck, and extends down the body taking 2 to 3 days to progress to the lower extremities. The rash may remain discrete, but often it becomes confluent and blotchy. In the absence of complications, the lesions and fever disappear in another 3 or 4 days signalling the end of the disease. The rash fades in the same order of appearance leaving a brownish discoloration which may persist for 2 months or more.

During the prodromal phase (2–4 days) and the first 2–5 days of rash, virus is present in tears, nasal and throat secretions, urine and blood. Just as the maculo-papular rash appears, the circulating antibodies become detectable, the viraemia disappears and the fever falls. The rash develops as a result of interaction of immune T cells with virus-infected cells in the small blood vessels. In patients with defective cell-mediated immunity, no rash develops *(10)*.

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Diagnosis of measles is based on the typical rash and Koplik's spots seen in oral mucosa. The diagnosis would normally be incorrect in any febrile exanthem in which red eyes and cough are absent. In developed countries, where measles is uncommon, specific IgM antibodies by ELISA, or the detection of measles virus RNA by RT-PCR (reverse transcriptase polymerase chain reaction) in throat swabs, oral fluid or nasopharyngeal mucus; or urine are being used for diagnosis *(18)*.

3. POST–MEASLES STAGE

The child will have lost weight and will remain weak for a number of days. There may be failure to recover and a gradual deterioration into chronic illness – due to increased susceptibility to other bacterial and viral infections, nutritional and metabolic effects and the tissue destructive effects of the virus. There may be growth retardation and diarrhoea, cancrum oris, pyogenic infections, candidosis, reactivation of pulmonary tuberculosis etc.

Complications *(18)*

The severity of measles varies widely, depending on several host and environmental factors. The risk of developing severe or fatal measles increases for children aged <5 years, and persons living in overcrowded conditions, those who are malnourished especially with vitamin A deficiency, and those with immunological disorders, such as AIDS. Complications occur in approximately 30% of reported cases depending on age and predisposing conditions. Relatively common complications of measles include otitis media, laryngotracheo-bronchitis (croup), diarrhoea and pneumonia. In children in developed countries, otitis media occurs in 7–9% of cases, diarrhoea in 8% of cases, and pneumonia in 1–6%. Post-infectious measles encephalitis occurs in about 1–4 per 1000–2000 cases, and sub-acute sclerosing panencephalitis (SSPE) develops several years after the infection in about 1 per 10,000–100,000 cases. Particularly severe complications of measles which occur in immunocompromised individuals are an acute progressive encephalitis (measles inclusion-body encephalitis), and a characteristic giant cell pneumonia. In developing countries, persistent diarrhoea with protein-losing enteropathy may ensue, particularly in infants. In these countries, where malnutrition, particularly vitamin A deficiency, and exposure to other infectious diseases are common, the case-fatality rate for measles is usually 3–6%, but can be as high as 30% particularly among displaced or isolated, immunologically naive populations. In developed countries death due to measles is rare and the case-fatality rate is usually 0.01–0.1%. The greatest risk of death is in children younger than 1 year and in adults older than 30 years. In HIV-infected children, the case-fatality rate has been reported to be as high as 50% *(18)*.

Measles during pregnancy is not known to cause congenital abnormalities of the foetus. However, it is associated with spontaneous abortion and premature delivery. Measles in the offspring of mothers with measles ranges from mild to severe; therefore, it is recommended that infants born to such mothers be passively immunized with immunoglobulin at birth *(19)*.

Treatment *(18)*

There is no specific treatment for measles. Case management of measles focuses on supportive care as well as the prevention and treatment of measles complications and secondary infections. Supportive care should be provided, including relieving common symptoms such as fever, cough, nasal congestion or rhinorrhea, conjunctivitis and sore mouth. Nutritional support is recommended to reduce the risk of malnutrition due to diarrhoea, vomiting and poor appetite associated with measles. Breast-feeding should be encouraged where appropriate. Oral rehydration salts should be used as needed to prevent dehydration.

Since measles is highly contagious, patient isolation is an important intervention to prevent further spread of the virus. However, increasing population immunity through vaccination is the most effective way to prevent outbreaks.

All cases of severe measles, and all cases of measles in areas with high case–fatality rates should be treated with vitamin A, as many children develop acute deficiency of vitamin A, which may lead to keratomalacia and blindness from corneal scarring. A high dose of vitamin A is given immediately on diagnosis and repeated the next day. The recommended age-specific daily doses are 50,000 IU for infants aged <6 months, 100,000 IU for infants aged 6–11 months, and 200,000 IU for children aged ≥ 12 months. If the child has clinical signs of vitamin A deficiency (such as Bitot's spots) a third dose should be given 4–6 weeks later *(20)*.

Measles and chickenpox

It has been noted that sometimes measles and chickenpox may occur together and one most remarkable finding in these cases of double infection is that the first infection may diminish the severity of the rash of the second infection *(21)*.

Prevention of measles

The following guidelines are important in combating measles:

a. achieving an immunization rate of over 95 per cent, and
b. on-going immunization against measles through successive generations of children.

1. Measles vaccination

Measles is best prevented by active immunization.

VACCINE : Only live attenuated vaccines are recommended for use; they are both safe and effective, and may be used interchangeably within immunization programmes. Person to person transmission of measles vaccine strains has never been documented. The vaccine is presented as a freeze-dried product. Before use, the lyophilized vaccine is reconstituted with sterile diluent. Each dose of 0.5 ml contains ≥1000 viral infective units of the vaccine strain; this is also true when it is presented as an MCV combination. Measles vaccine may also contain sorbitol and hydrolysed gelatin as stabilizers, as well as a small amount of neomycin, but it does not contain thiomersal. In general, it is recommended that freeze-dried vaccine be stored in a refrigerated condition *(20)*. The diluent must not be frozen but should be cooled before reconstitution. Reconstituted measles vaccine loses about 50 per cent of its potency after 1 hour at 20°C; it loses almost all potency after 1 hour at 37°C. The vaccine is also sensitive to sunlight, hence it is kept in coloured glass vials. After reconstitution, the vaccine must be stored in the dark at 2–8°C and used within 4 hours.

Measles vaccine is available in monovalent (measles only) form and in combination : measles-rubella (MR), measles-mumps-rubella (MMR) vaccine, and measles-mumps-rubella-varicella (MMRV) vaccine.

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Reaching all children with 2 doses of measles containing vaccine (MCV) should be the standard for all national immunization programmes. In countries with ongoing transmission in which the risk of measles mortality remains high, MCV_1 should be given at age 9 months. MCV_2 should be given between 15–18 months, as providing MCV_2 in the 2nd year of life reduces the rate of accumulation of susceptible children and the risk of an outbreak. The minimum interval between MCV_1 and MCV_2 is 4 weeks. Every opportunity (e.g. when children come into contact with health services) should be taken to vaccinate all children that missed one or both MCV routine doses, particularly those under 15 years of age. Policies which prohibit use of vaccine in children >1 year of age, older children and teenagers should be changed to allow these individuals to be vaccinated.

In countries with low levels of measles transmission (i.e. those that are near elimination or verified as having eliminated endemic measles virus transmission), and therefore the risk of measles virus infection among infants is low, MCV_1 may be administered at 12 months of age to take advantage of the higher sero-conversion rates achieved at this age. In these countries, the optimal age for delivering MCV_2 is based on programmatic considerations to achieve the highest coverage of MCV_2 and, hence, the highest population immunity. Administration of MCV_2 at 15–18 months of age ensures early protection of the individual, slows accumulation of susceptible young children, and may correspond to the schedule for other routine immunizations (for example, a DTP-containing booster, PCV, or meningococcal vaccines). This measure also supports the establishment of a policy on immunization and other health interventions in the second year of life. If MCV_1 coverage is high (>90%) and school enrolment is high (>95%), administration of routine MCV_2 at school entry may prove an effective strategy for achieving high coverage and preventing outbreaks in schools *(22)*.

MCV administered before 9 months of age should be considered a supplementary dose and recorded on the child's vaccination record as "MCV_0". Children who receive MCV_0 should also receive MCV_1 and MCV_2 at the recommended ages according to the national schedule. A supplementary dose of MCV should be given to infants from 6 months of age : (1) during a measles outbreak as part of intensified service delivery; (2) during campaigns in settings where the risk of measles among infants < 9 months of age remains high (e.g. in endemic countries experiencing regular outbreaks); (3) for internally displaced populations and refugees, and populations in conflict zones; (4) for individual infants at high risk of contracting measles (e.g. contacts of known measles cases or in settings with increased risk of exposure during outbreaks such as day-care facilities); (5) for infants travelling to countries experiencing measles outbreaks; (6) for infants known to be HIV-infected or exposed (i.e. born to an HIV-infected woman) *(22)*.

Given the severe course of measles in patients with AIDS, measles vaccination should be routinely administered to potentially susceptible, asymptomatic HIV infected children and adults. Vaccination may even be considered for those with symptomatic HIV infection if they are not severely immuno-suppressed according to conventional definitions. In areas where there is a high incidence of both HIV infection and measles, an initial dose of MCV may be offered as early as age 6 months (recorded as MCV_0). The 2 routine doses of MCV (MCV_1 and MCV_2) should then be administered to these children according to the national immunization schedule *(22)*.

CONTRAINDICATIONS TO VACCINATION *(23)* : MMR and other measles-containing vaccines are not recommended for HIV-infected persons with evidence of severe immunosuppression. MMRV is not approved for and should not be administered to a person known to be infected with HIV.

Persons with moderate or severe acute illness should not be vaccinated until the patient has improved. This precaution is intended to prevent complicating the management of an ill patient with a potential vaccine adverse reaction, such as fever. Minor illness (e.g., otitis media, mild upper respiratory infections), concurrent antibiotic therapy, and exposure to or recovery from other illness are not contraindications to measles vaccination.

Receipt of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, intravenous immune globulin) may interfere with sero-conversion after measles vaccine. The length of time that such passively acquired antibody persists depends on the concentration and quantity of blood product received. For instance, it is recommended that vaccination be delayed for 3 months following receipt of immune globulin for prophylaxis of hepatitis A; a 7 to 11 months delay is recommended following administration of intravenous immune globulin, depending on the dose.

Replication of vaccine viruses can be prolonged in persons who are immunosuppressed or immunodeficient. Severe immunosuppression can be due to a variety of conditions, including congenital immunodeficiency, HIV infection, leukaemia, lymphoma, generalized malignancy, or therapy with alkylating agents, antimetabolites, radiation, or large doses of corticosteroids. For this reason, persons who are severely immunocompromised for any reason should not be given measles containing vaccine.

Women known to be pregnant should not receive measles vaccine. Pregnancy should be avoided for 4 weeks following MMR vaccine. Close contact with a pregnant woman is not a contraindication to MMR vaccination of the contact. Breastfeeding is not a contraindication to vaccination of either the woman or a breastfeeding child.

Do tuberculin skin testing (TST) at the same visit as MMR vaccination, or delay TST at least 4 weeks if MMR is given first. The least favoured option is to do TST first and administer MMR when TST is read as it delays the vaccination. TST has no effect on the response to MMR vaccination. However, measles containing vaccines may transiently suppress the response to TST in a person infected with *M. tuberculosis (23)*.

ADMINISTRATION : The reconstituted vaccine is generally injected subcutaneously, but it is also effective when administered intramuscularly.

REACTIONS : When injected into the body, the attenuated virus multiplies and induces a mild "measles" illness (fever and rash) 5 to 10 days after immunization, but in reduced frequency and severity. This may occur in 15 to 20 per cent of vaccinees. The fever may last for 1–2 days and the rash for 1–3 days. There is no cause for alarm. The vaccines now given rarely cause severe reaction *(10)*. There is no spread of the virus from the vaccinees to contacts.

IMMUNITY : The vaccine has convincingly demonstrated to provide immunity to even severely malnourished children. Immunity develops 11 to 12 days after vaccination and appears to be of long duration, probably for life. One dose of the vaccine given at 11–12 months of age appears to give 95 per cent protection and with two doses 98 per cent

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protection. Infants vaccinated at the age of 9 months show sero-conversion of about 90 per cent *(20)*.

CONTACTS : Susceptible contacts over the age of 9–12 months may be protected against measles with measles vaccine, provided that this is given within 3 days of exposure. This is because, the incubation period of measles induced by the vaccine is about 7 days, compared with 10 days for the naturally acquired measles.

ADVERSE EFFECTS OF VACCINE : Toxic shock syndrome (TSS) occurs when measles vaccine is contaminated or the same vial is used for more than one session on the same day or next day. The vaccine should not be used after 4 hours of opening the vial. TSS is totally preventable and reflects poor quality of immunization services. The symptoms of TSS are typical. Severe watery diarrhoea, vomiting and high fever are reported within few hours of measles vaccination. There are usually a cluster of cases as all infants vaccinated from contaminated vial will be affected. This may cause death within 48 hours. Case fatality rates are high *(20)*.

2. Immunoglobulin

Measles may be prevented by administration of immunoglobulin (human) early in the incubation period. The dose recommended by WHO is 0.25 ml per kg of body weight (see Table 33 on page 116). It should be given within 3–4 days of exposure. The person passively immunized should be given live measles vaccine 8–12 weeks later. The need for immunoglobulin is now much reduced because of the availability of an effective live attenuated vaccine.

Global measles and rubella strategic framework 2021–2030 (MRSF) *(24)*

The measles and rubella strategic framework 2021–2030 aims to provide a high-level framework that will guide the regional and national strategies and operational plans, within the umbrella of the Immunization Agenda 2030 structure. It aims to establish convergence with other key agency strategy documents. It envisions "A world free from measles and rubella". The goal for the 2021–2030 period is to "achieve and sustain the regional measles and rubella elimination goals".

The core strategies identified in the 2012–20 MRSP will remain relevant in the post 2020 period. The strategic priorities are as follows :

1. Incorporate all measles and rubella activities, including surveillance and case management, as key components of effective PHC system in support of universal health coverage.
2. Improve ownership and accountability of measles and rubella goals and targets at all levels and improve community demand for uptake of measles and rubella containing vaccines.
3. Identify and close immunity gaps to measles and rubella by effectively utilizing all relevant contacts between individuals and the health system, establishing or strengthening new contact points where required, and using targeted approaches to reach under-served populations.
4. Leverage the life-course approach for delivery of the second routine dose of measles and rubella containing vaccines and for catch-up vaccination; and integrate measles and rubella activities with other health and non-health activities.
5. Ensure outbreak preparedness for timely detection and effective response to limit the spread of measles and rubella and reduce related morbidity and mortality.
6. Ensure continued, timely and quality supply of measles and rubella containing vaccines, vaccination supplies and laboratory reagents and that measles and rubella activities, including surveillance, are sustainably financed.
7. Foster research and innovation to overcome barriers to achieve high measles and rubella population immunity and to generate and use high quality disease and programme data.

Outbreak control measures

The following control measures have been recommended : (a) isolation for 7 days after onset of rash, (b) immunization of contacts within 2 days of exposure (if vaccine is contraindicated, immunoglobulin should be given within 3–4 days of exposure), and (c) prompt immunization at the beginning of an epidemic is essential to limit the spread.

Eradication of measles

It is believed that measles, like smallpox, is amenable to eradication. Measles immunization has in its favour the fact that only two doses are needed, and that a measles vaccine has now been developed which is more heat stable. It requires (a) achieving an immunization coverage of at least 96 per cent of children under one year of age, and that (b) the cumulation in the immunity gap be prevented.

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RUBELLA (GERMAN MEASLES)

Rubella or german measles is an acute childhood infection, usually mild, of short duration (approximately 3 days) and accompanied by low-grade fever, lymphadenopathy and a maculopapular rash. Infection in early pregnancy may result in serious congenital defects, including death of the foetus. The disease is worldwide in distribution and tends to occur in epidemics. In pre-vaccination era epidemics occurred every 5 to 9 years. However, extent and periodicity of rubella are highly variable in industrialized and developing countries. Worldwide over 100,000 babies are born with congenital rubella syndrome every year *(1, 2)*.

History

Rubella was considered a mild and benign disease until 1941 when Norman Gregg, an ophthalmologist reported an epidemic of congenital cataracts associated with other congenital defects in children born to mothers who had rubella during their pregnancies *(3)*. This discovery changed the concept that rubella is not merely a benign disease of childhood but also one with teratogenic potential. In 1962, the virus was isolated; in 1967, an attenuated vaccine was developed.

Epidemiological determinants

Agent factors

(a) AGENT : Rubella is caused by an RNA virus of the togavirus family. Only one antigenic type of the virus seems to exist. The virus has been recovered from the naso-pharynx, throat, blood, CSF and urine. It can be propagated in cell culture. (b) SOURCE OF INFECTION : Clinical or subclinical cases of rubella. A large number of rubella infections are, in fact, subclinical. This represents one of the major differences between measles and rubella. There is no known carrier state for postnatally acquired rubella. Infants born with congenital rubella may shed the virus for many months. The vaccine virus is not communicable. (c) PERIOD OF COMMUNICABILITY: Rubella is much less communicable than measles, probably because of the absence of coughing in rubella. It is difficult to state the exact period of infectivity. It probably extends from a week before symptoms to about a week after rash appears. Infectivity is greatest 1–5 days after the appearance of rash *(1)*.

Host factors

(a) AGE: Mainly a disease of childhood particularly in the age group 3 to 10 years. Persons older than 15 years now account for over 70 per cent cases in developed countries – this is similar to the changing epidemiological pattern with measles, following widespread immunization campaigns against the disease. (b) IMMUNITY : One attack results in life-long immunity; second attacks are rare. Infants of immune mothers are protected for 4 to 6 months. It is estimated that 10 to 40 per cent of the population could reach adulthood without experiencing rubella infection in the absence of immunization.

Environmental factors

Disease usually occurs in a seasonal pattern i.e. in temperate zones during the late winter and spring, with epidemics every 4–9 years.

Transmission

The virus is transmitted directly from person to person by droplets from nose and throat, and droplet nuclei (aerosols), from one week before onset of rash to one week after it has faded. The portal of entry is *via* the respiratory route. The virus is maintained in human population by chain transmission. The virus can cross the placenta (vertical transmission) and infect the foetus *in utero*, leading to congenital rubella in the newborn.

Incubation period

2 to 3 weeks; average 18 days.

Clinical features

A large percentage of infections (20–50 per cent) are asymptomatic *(2)*. In a typical case, the clinical features comprise the following: (a) PRODROMAL : The prodromal symptoms (coryza, sore throat, low-grade fever) herald the onset of viraemia. They are generally mild and insignificant, and less frequent in children. (b) LYMPHADENOPATHY : In susceptible individuals, the enlargement of the post-auricular, occipital and posterior cervical lymph nodes appears as early as 5–10 days before the appearance of the rash. This, however, is not pathognomonic since cases of clinical rubella without enlargement of lymph nodes have been documented *(2)*. The glands may be found enlarged for 10 to 14 days after the rash. (c) RASH: The rash is often the first indication of the disease in children. It appears first on the face, usually within 24 hours of the onset of prodromal symptoms. It is a minute, discrete, pinkish, macular rash and not confluent as the rash of measles and it may be pruritic. Conjunctivitis may occur. The rash spreads rapidly to the trunk and extremities, by which time it is often no longer apparent on the face. The rash spreads much faster and clears more rapidly than the rash of measles. It disappears altogether by the third day. The rash is an inconstant feature of the disease; it is absent in subclinical cases. The incidence of rubella infection without rash may be upto 25 per cent *(4)*. (d) COMPLICATIONS : In rare instances arthralgia may occur in several joints in adults, especially young women. Encephalitis is very rare. Thrombocytopenic purpura has also been observed as a complication. Mention has been made already about the congenital malformations.

Diagnosis

Because of its mildness and variability of symptoms, the disease can go unrecognized unless it is an epidemic. A definitive diagnosis of rubella is possible only through virus isolation and serology. Throat swabs should be cultured for virus isolation; it takes longer than serological diagnosis. The haemagglutination inhibition (HI) test is a standard serological test for rubella. However, serum must be pretreated to remove non-specific inhibitors before testing. ELISA tests are preferred because serum pretreatment is not required and they can be adapted to detect specific IgM. Detection of IgG is evidence of immunity because there is only one serotype of rubella virus. To accurately confirm a recent rubella infection, either a rise in antibody titer must be demonstrated between two serum samples taken at least 10 days apart or rubella-specific IgM must be detected in a single specimen. It is critically important in a pregnant woman *(6)*.

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CONGENITAL RUBELLA SYNDROME (CRS)

Congenital rubella syndrome (CRS) refers to infants born with defects secondary to intrauterine infection or who manifest symptoms or signs of intrauterine infection sometime after birth *(5)*. Congenital infection is considered to have occurred if the infant has IgM rubella antibodies shortly after birth (as IgM antibodies do not cross the placenta, their presence indicate that they must have been synthesized by the infant *in utero*) or if IgG antibodies persist for more than 6 months, by which time maternally derived antibodies would have disappeared. Intrauterine infection with rubella is associated with chronic persistence of the virus in the newborn. At birth, virus is easily detectable in pharyngeal secretions, multiple organs, cerebrospinal fluid, urine, and rectal swabs. Viral excretion may last for 12–18 months after birth, but the level of shedding gradually decreases with age *(6)*.

Rubella infection inhibits cell division, and this is probably the reason for congenital malformations and low birth weight *(7)*. The classic triad of congenital defects are deafness, cardiac malformations and cataracts.

Rubella infection in a woman who becomes infected (i.e. with asymptomatic or symptomatic disease) just before conception and upto the first 8–10 weeks of gestation causes multiple congenital abnormalities in upto 90% of infections, and may result in miscarriage or stillbirth. Congenital anomalies associated with maternal rubella infection are rare after the 16th week of pregnancy, although sensorineural hearing deficits may occur after exposure upto week 20 of gestation. The defects associated with CRS include ophthalmic (e.g. cataracts, microphthalmia, glaucoma, pigmentary retinopathy, chorioretinitis), auditory (e.g. sensorineural deafness), cardiac (e.g. peripheral pulmonary artery stenosis, patent ductus arteriosus or ventricular septal defects) and craniofacial (e.g. microcephaly) anomalies. CRS can also present with other manifestations, such as meningoencephalitis, hepatosplenomegaly, hepatitis, thrombocytopenia, interstitial pneumonitis and radiolucency in the long bones (a characteristic radiological pattern of CRS). Infants who survive the neonatal period may have serious developmental disabilities (such as autism, visual and hearing impairment), and developmental delay. Viral shedding can continue in CRS cases beyond 1 year of age, which may result in virus transmission *(2)*.

Prevention

The currently used rubella vaccines are based on the live attenuated RA 27/3 strain. Most rubella vaccines are available in combination with other vaccine antigens such as measles, mumps and varicella (MR, MMR, MMRV, respectively) and also in a monovalent formulation. Each dose of an RCV contains a minimum number of infectious units (≥1000 plaque-forming units or 50% cell culture infectious dose). When stored at 4°C, most RCVs have a shelf-life of 2–3 years. Monovalent rubella, MR and MMR vaccines should be stored at 2–8°C, protected from light. Diluent vials may be stored at ambient temperatures but must never be frozen. The standard volume of a single dose of RCV is 0.5 ml, and the vaccine is usually injected subcutaneously. The preferred site of injection is the anterolateral thigh or outer aspect of upper arm, depending on the age of the individual *(2)*.

Because rubella is not as highly infectious as measles and because the effectiveness of 1 dose of an RCV is >95%, even at 9 months of age, only 1 dose of rubella vaccine is required to achieve rubella elimination if high coverage is achieved. However, when combined with measles vaccination, it may be easier to implement a second dose of RCV's using the same combined MR vaccine or MMR vaccine for both doses. RCV's can be administered concurrently with inactivated vaccines. As a general rule, live vaccines should be given either simultaneously with RCV's, or at least 4 weeks apart. An exception to this is oral polio vaccine, which can be given at any time before or after RCV's without interfering in the response to either vaccine. Interference may occur between MMR and yellow fever vaccines if they are simultaneously administered to children <2 years of age *(8)*.

The vaccine induced immunity persists for life time. In order to provide direct protection against rubella, all non-pregnant women of reproductive age who are not already vaccinated or who are sero-negative for rubella receive one dose of RCV *(2)*.

Precautions and contraindications

RCVs should not be given to anyone who has experienced a severe allergic reaction after a previous vaccine dose or vaccine component. It is recommended not to provide the vaccine to those with active TB or severe immunodeficiency (including individuals with symptomatic HIV infection, AIDS, congenital immune disorders, malignancies or aggressive immunosuppressive therapy). Rubella vaccination should be avoided in pregnancy because of a theoretical (but never demonstrated) risk of teratogenic outcomes. Women planning a pregnancy are advised to avoid pregnancy for 1 month after rubella vaccination. Inadvertent vaccination with RCV during pregnancy is not an indication for terminating the pregnancy. People who receive blood products wait at least 3 months before vaccination with RCV, and, if possible, avoid administration of blood products for 2 weeks after vaccination *(2)*.

Global measles and rubella strategic framework (2021–2030)

Refer to page 168 for the details.

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MUMPS

An acute infectious disease caused by an RNA virus classified as genus *Rubulavirus* of the family paramyxoviridae which has a predilection for glandular and nervous tissues. Clinically, the disease is recognized by non-suppurative enlargement and tenderness of one or both the parotid glands. Other organs may also be involved. Constitutional symptoms vary, or may be inapparent. The disease occurs throughout the world. Although morbidity rate tends to be high, mortality rate is negligible.

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In countries which have introduced mumps-containing vaccines and have high 2-dose mumps coverage, incidence of mumps cases has dropped dramatically from about 100–1000 cases per 100,000 population to less than 1 case per 100,000 population. However, a few large, localized outbreaks of mumps have been reported in highly-vaccinated populations *(1)*.

Low childhood vaccination coverage (of less than 80 per cent) against mumps can result in an epidemiological shift of disease incidence to older age groups. This shift has been reported in many countries with associated higher risk of complications. Besides vaccine coverage, factors such as number of doses of vaccine, age at vaccination, vaccine failure and vaccine effectiveness may contribute to this epidemiological shift. As the coverage rate of mumps vaccination increases, the average age at infection increases until the level of seropositive population needed to stop spread of mumps has been achieved *(1)*.

Agent factors

(a) AGENT : The causative agent, *Myxovirus parotiditis* is a RNA virus of the myxovirus family. The virus can be grown readily in chick embryo or tissue culture. There is only one serotype. (b) SOURCE OF INFECTION : Both clinical and subclinical cases. Subclinical cases which account for 30–40 per cent of all cases *(2)* appear to be responsible for maintaining the cycle of infection. The virus can be isolated from the saliva or from swabs taken from the surface of Stenson's duct. Virus has also been found in the blood, urine, human milk and on occasion in the CSF. (c) PERIOD OF COMMUNICABILITY : Usually 4–6 days before the onset of symptoms and a week or more thereafter. The period of maximum infectivity is just before and at the onset of parotitis. Once the swelling of the glands has subsided, the case may be regarded as no longer infectious. (d) SECONDARY ATTACK RATE : Estimated to be about 86 per cent.

Host factors

(a) AGE AND SEX : Mumps is the most frequent cause of parotitis in children in the age group 5–9 years. The average age of incidence of mumps is higher than with measles, chickenpox or whooping cough. However, no age is exempt if there is no previous immunity. The disease tends to be more severe in adults than in children. (b) IMMUNITY : One attack, clinical or subclinical, is assumed to induce lifelong immunity. There is only one antigenic type of mumps virus, and it does not exhibit significant antigenic variation *(3)*. Most infants below the age of 6 months are immune because of maternal antibodies.

Environmental factors

Mumps is largely an endemic disease. Cases occur throughout the year, but the peak incidence is in winter and spring. Epidemics are often associated with overcrowding.

Mode of transmission

The disease is spread mainly by droplet infection and after direct contact with an infected person.

Incubation period

Varies from 2 to 4 weeks, usually 14–18 days.

Clinical features

Mumps is a generalized virus infection. In 30–40 per cent of cases mumps infection is clinically non-apparent. In clinically apparent cases, it is characterized by pain and swelling in either one or both the parotid glands but may also involve the sublingual and submandibular glands. Often the child complains of "ear ache" on the affected side prior to the onset of swelling. There may be pain and stiffness on opening the mouth before the swelling of the gland is evident. Mumps may also affect the testes, pancreas, CNS, ovaries, prostate, etc. In severe cases, there may be fever, headache and other constitutional symptoms which may last from 3–5 days. The swelling subsides slowly over 1–2 weeks.

COMPLICATIONS : Though frequent, are not serious. These include orchitis, ovaritis, pancreatitis, meningo-encephalitis, thyroiditis, neuritis, hepatitis and myocarditis. Testicular swelling and tenderness denote orchitis, which is the most common extrasalivary gland manifestation of mumps in adults. It is unilateral in about 75 per cent of cases. High fever usually accompanies orchitis, which develops typically 7–10 days after the onset of parotitis in about 25–40 per cent of post-pubertal men *(4)*. Bilateral orchitis is rare and the assumption that mumps orchitis may lead to sterility is ill-founded *(5)*. Upper abdominal pain, nausea and vomiting suggest pancreatitis. Mumps is a leading cause of pancreatitis in children. It occurs in about 4 per cent of patients *(6)*. Lower abdominal pain and ovarian enlargement suggest oophoritis which occurs in 5 per cent of post pubertal women, usually unilateral *(4)*. While some instances of diabetes have occurred in children following mumps infection, a causal relationship has yet to be demonstrated *(5)*. Rarer complications include nerve deafness, polyarthritis, hydrocephalus, encephalitis, cerebellar ataxia, facial palsy and transverse myelitis. Encephalitis is associated with cerebral oedema, serious neurologic manifestations and sometimes death *(4)*. Upto 15% of mumps patients may develop meningitis, and a much smaller proportion (0.02–0.03%) may develop encephalitis. Mumps is one of the main infectious causes of sensorineural deafness, which affects approximately 5 per 100,000 mumps cases *(6)*.

Mumps infection in the first trimester of pregnancy is associated with a 25% incidence of spontaneous abortion, although congenital malformations following mumps infection in pregnancy have not been reported *(6)*.

Prevention

VACCINATION : Highly effective live attenuated vaccine is now available for the prevention of mumps. Widely-used live attenuated mumps vaccine strains include the Jeryl-Lynn, RIT 4385, Leningrad-3, L-Zagreb and Urabe strains. Live attenuated mumps vaccine strains used only on a limited scale include the Hoshino, Torii and NKM-46 strains. The WHO recommends that the Rubini mumps vaccine strain should not be used in national immunization programmes because of its demonstrated low effectiveness *(6)*.

A single dose (0.5 ml) intramuscularly produces detectable antibodies in 95 per cent of vaccinees. The duration of long-term immunity is not known. It is recommended for routine immunization for children over 1 year of age, either alone or in combination with other virus vaccines, eg. in MMR vaccine or as a quadrivalent vaccine with varicella. A second dose is recommended for children at 4–6 years of age i.e., before starting the school. The current mumps strain (Jeryl Lynm) has the lowest associated incidence of post vaccine aseptic meningitis (from 1 in 150,000 to 1 in 1.8 million). There are no known cases of long-term sequelae associated with mumps vaccination *(4)*.

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Countries including mumps vaccines in their national immunization programme are advised by WHO to set disease control targets (control or elimination) and to design their mumps immunization strategy accordingly. Strategies to achieve mumps elimination include very high coverage with the first dose of mumps vaccine, ensuring a second opportunity for vaccination and conducting catch-up immunization of susceptible cohorts *(6)*.

As with most other live virus vaccines, mumps vaccine should not be administered to pregnant women, patients receiving immunosuppressive therapy or those who are severely ill. For further details, please refer to page 164.

Mumps surveillance *(6)*

Case definitions : WHO recommends the following case definitions for mumps surveillance :

a. *Clinical mumps :* acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland, lasting 2 or more days and without other apparent cause.

b. *Laboratory confirmed mumps :* a patient with clinical mumps and laboratory confirmation by positive-mumps IgM antibody (without mumps immunization in the previous 6 weeks) or; sero-conversion with 4–fold or greater rise in mumps IgG titre; or isolation of mumps virus from saliva, urine or cerebrospinal fluid.

c. *Epidemiologically–confirmed mumps :* a patient with clinical mumps who is epidemiologically linked to a laboratory–confirmed mumps case.

Control

The control of mumps is difficult because the disease is infectious before a diagnosis can be made. The long and variable incubation period, and the occurrence of subclinical cases make the control of spread difficult. However, cases should be isolated till the clinical manifestations subside. Steps should be taken to disinfect the articles used by the patient. Contacts should be kept under surveillance.

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INFLUENZA

Influenza is an acute respiratory tract infection caused by influenza virus, of which there are 4 types – A, B, C and D. All known epidemics are caused by influenza A and B strains. The disease is characterized by sudden onset of chills, malaise, fever, muscular pains and cough.

Problem statement

Influenza is truly an international disease. It occurs in all countries and affects millions of people every year. Its behaviour is unpredictable. It may occur in several forms. It may smoulder in a community without clinical recognition, being manifest only by serological surveys. It may occur in pandemics every 10–40 years due to major antigenic changes, as occurred in 1918 (Spanish influenza), 1957 (Asian influenza) and 1968 (Hong Kong influenza) *(1)*. More recently, influenza A (H_1N_1) virus of swine origin emerged in Mexico during the spring of 2009 and was given name – pandemic influenza A (H_1N_1) 2009 virus. It spreads with travellers worldwide, resulting in the first influenza pandemic of this century. In between pandemics, epidemics tend to occur at intervals of 2–3 years in case of influenza A and 3–6 years in the case of influenza B – but the periodicity is not regular as in the case of measles or whooping cough because several strains of the virus may be in simultaneous circulation, which means that there may be outbreaks of influenza practically every year, and sometimes even twice a year *(2)*.

Once an epidemic begins, the picture is quite characteristic. Preceded by a few early cases, there is a sudden outburst of the disease. This may be indicated by reports of increased febrile respiratory illness in children, followed by the same in adults. The next event is increased hospitalization of cases and sickness–absenteeism in schools and places of work. Attack rates tend to be high, varying from 5 to 10 per cent in adults and 20–30 per cent in children. The peak of the epidemic is reached in 3–4 weeks, before tending to decline. The time scale is compressed for smaller geographic areas *(1)*. The unique features of influenza epidemics are the suddenness with which they arise, and the speed and ease with which they spread. The short incubation period, large number of subclinical cases, high proportion of susceptible population, short duration of immunity, and absence of cross-immunity, all contribute to its rapid spread. Worldwide, the annual epidemics are estimated to result in about 3–5 million cases of severe illness and about 290,000 to 650,000 deaths *(3)*. The fate of the virus during inter-epidemic periods is not known. Possible explanations include transmission of virus to extra-human reservoirs (pigs, horses, birds), latent infection in humans or continuous transfer from one human to another. This explains the occurrence of sporadic cases.

At present three types of influenza virus are circulating in the world: A(H_1N_1), A(H_3N_2) and B viruses. Influenza A predominated in most countries accounting for 59 per cent of all influenza viruses detected.

SEASONAL INFLUENZA

Epidemiological determinants

Agent factors

(a) AGENT : Influenza viruses are classified within the family Orthomyxoviridae. There are four viral subtypes, namely influenza type A, type B, type C and type D. These four viruses are antigenically distinct. There is no cross immunity between them. Of importance are the influenza A and B viruses which are responsible for epidemics of disease throughout the world *(4)*. Influenza A virus has 2 distinct surface antigens – the haemagglutinin (H) and the neuraminidase (N) antigens. The H antigen initiates infection following attachment of the virus to susceptible cells. The N antigen is responsible for the release of the virus from the infected cell. The currently identified subtypes are 18 HA and 11 NA. Humans are generally infected by viruses of the subtype H1, H2 or H3, and N1 or N2. Type B virus does not exhibit antigenic shifts and is not divided into subtypes.

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The influenza A virus is unique among the viruses because it is frequently subject to antigenic variation, both major and minor. When there is a sudden complete or major change, it is called a **shift**, and when the antigenic change is gradual over a period of time, it is called a **drift**. Antigenic shift appears to result from genetic recombination of human with animal or avian virus, providing a major antigenic change. This can cause a major epidemic or pandemic involving most or all age groups. Antigenic drift involves "point mutation" in the gene owing to selection pressure by immunity in the host population. Antigenic changes occur to a lesser degree in the B group influenza viruses. Influenza C appears to be antigenically stable.

Since the isolation of the virus A in 1933, major antigenic changes have occurred twice – once in 1957 (H_2N_2) and again in 1968 (H_3N_2). Strains occurring between 1946 and 1957 have been called (H_1N_1) strains. The shift in 1968 involved only the H antigen.

(b) RESERVOIR OF INFECTION : It has become increasingly evident that a major reservoir of influenza virus exists in animals and birds. Many influenza viruses have been isolated from a wide variety of animals and birds (e.g., swine, horses, dogs, cats, domestic poultry, wild birds, etc). Some of these include the major H and N antigens related to human strains. It is hypothesized. There is an increasing evidence that the animal reservoirs provide new strains of influenza virus by recombination between the influenza viruses of man, animals and birds.

(c) SOURCE OF INFECTION : Usually a case or subclinical case. During epidemics, a large number of mild and asymptomatic infections occur, which play an important role in the spread of infection. The secretions of the respiratory tract are infective.

(d) PERIOD OF INFECTIVITY : Virus is present in the nasopharynx from 1 to 2 days before and 1 to 2 days after onset of symptoms.

Host factors

(a) AGE AND SEX : Influenza affects all ages and both sexes. In general, the attack rate is lower among adults. Children constitute an important link in the transmission chain. The highest mortality rate during an epidemic occurs among certain high-risk groups in the population such as old people (generally over 65 years of age), children under 18 months, and persons with diabetes or chronic heart disease, kidney and respiratory ailments *(5)*. (b) HUMAN MOBILITY : This is an important factor in the spread of infection. (c) IMMUNITY : Immunity to influenza is subtype-specific. Antibodies against HA and NA are important in immunity to influenza. Resistance to initiation of infection is related to antibody against HA, which neutralizes the virus, whereas decreased severity of disease and decreased ability to transmit virus to contacts are related to antibody directed against the NA. Antibodies against ribonucleoprotein are type-specific and are useful in typing viral isolates as in influenza A and B. Protection correlates with both serum antibodies and secretory IgA antibodies in nasal secretions. The local secretory antibody is probably important in preventing infection. Serum antibodies persist for many months, whereas secretory antibodies are shorter-lived (usually only few months). Antibody also modifies the course of illness. A person with low titres of antibody may be infected but will experience a mild form of illness. Immunity can be incomplete as reinfection with the same virus can occur. The three types of influenza viruses are antigenically unrelated and therefore induce no cross-protection. When a viral type undergoes antigenic drift, a person with pre-existing antibody to the original strain may suffer only mild infection with the new strain *(6)*. Antibodies appear in about 7 days after the attack and reach a maximum level in about 2 weeks. After 8 to 12 months, the antibody level drops to pre-infection level.

Environmental factors

(a) Season : The seasonal incidence is striking, epidemics usually occurring in winter months in the Northern Hemisphere and in the winter or rainy season in the Southern Hemisphere *(4)*. In tropical countries, influenza virus circulates throughout the year with one or two peaks during rainy season. *(b) Overcrowding* : Enhances transmission. The attack rates are high in close population groups, e.g., schools, institutions, ships, etc.

Mode of transmission

Influenza is spread mainly from person to person by droplet infection or droplet nuclei created by sneezing, coughing or talking. The portal of entry of the virus is the respiratory tract.

Incubation period

1–4 days.

Pathogenesis and clinical features

The virus enters the respiratory tract and causes inflammation and necrosis of superficial epithelium of the tracheal and bronchial mucosa, followed by secondary bacterial invasion. There is no viraemia. Both the viruses cause much the same symptoms – fever, chills, aches and pains, coughing and generalized weakness. Fever lasts from 1–5 days, averaging 3 days in adults. Frequent complications are acute sinusitis, otitis media, purulent bronchitis and pneumonia. The most dreaded complication is pneumonia, which should be suspected if fever persists beyond 4 or 5 days or recurs abruptly after convalescence *(1)*.

Reye syndrome (fatty liver with encephalopathy) is a rare and severe complication of influenza, usually A and B type, particularly in young children between 2 and 16 years of age. It consists of rapidly progressive hepatic failure and encephalopathy, and there is about 10–40 per cent mortality rate. The pathogenesis is unknown, but the syndrome is associated with aspirin use in a variety of viral infections *(7)*.

AVIAN INFLUENZA *(8)*
(BIRD FLU)

Avian influenza refers to a large group of different influenza viruses that primarily affect birds. On rare occasions, these bird viruses can infect other species, including pigs and humans. The vast majority of avian influenza viruses do not infect humans. However, avian H_5N_1 is a strain with pandemic potential, since it might ultimately adapt into a strain that is contagious among humans. Once this adaptation occurs, it will no longer be a bird virus – it will be a human influenza virus. Influenza pandemics are caused by new influenza viruses that have adapted to humans. Health experts have been monitoring a new and extremely severe influenza virus – the H_5N_1 strain – for almost 15 years. Fortunately, the virus does not jump easily from birds to humans or spread readily and sustainably among humans. Once a fully contagious virus emerges, its global spread is considered inevitable.

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Transmission

Human infections with avian influenza viruses, though rare, have been reported sporadically. Human infections are primarily acquired through direct contact with infected live or dead poultry birds or contaminated environments, such as live bird markets.

Incubation period

2–5 days.

Diagnosis

Diagnosis is confirmed by RT-PCR. Rapid influenza diagnostic tests (RDTs) are available, but they have lower sensitivity compared to RT-PCR.

Treatment

Some antiviral drugs, notably oseltamivir and zanamivir can reduce the duration of viral replication and improve prospects of survival.

Prevention

Public health management includes personal protective measures like regular hand washing and proper drying; good respiratory hygiene (covering mouth and nose when coughing or sneezing); early self-isolation; avoid close contact with sick people; and avoid touching eyes, mouth and nose.

Vaccine

In the year 2007, a vaccine for bird flu was licensed, this vaccine is for people 18 years through 64 years of age. It is an inactivated influenza vaccine given in two doses, 28 days apart. The recipient can have pain and tenderness at the injection site, headache, muscle pain and general ill feeling.

Some other vaccines were approved, but at the time of pandemic, (as the H_5N_1 continually mutates), the current sample of H_5N_1 cannot be depended upon to work.

PANDEMIC INFLUENZA A (H_1N_1) 2009 (SWINE FLU)

The pandemic influenza A (H_1N_1) 2009 virus differs in its pathogenicity from seasonal influenza in two key aspects. First, as the majority of human population has little or no pre-existing immunity to the virus, the impact of the infection has been in a wider age range, in particular among children and young adults. Secondly, the virus can infect the lower respiratory tract and can cause rapidly progressive pneumonia, especially in children and young to middle-aged adults.

Following its emergence in March 2009, pandemic A (H_1N_1) 2009 virus spread rapidly throughout the world, leading to the declaration of an influenza pandemic by WHO on 11th June 2009 *(9)*. The world is now in post-pandemic period. In India it causes local outbreaks. During 2022, India reported 13,202 cases and 410 deaths, a case fatality rate of 3.105 per cent *(10)*.

Based on knowledge about past pandemics, the (H_1N_1) 2009 virus is expected to continue to circulate as a seasonal virus for some years to come. While level of concern is now greatly diminished, vigilance on the part of national health authorities remains important, when the behaviour of H_1N_1 virus as a seasonal virus cannot be reliably predicted *(11)*. On 26th September 2011 WHO has adapted a new nomenclature as Influenza A (H_1N_1) pdm09 *(12)*.

Incubation period

The incubation period appears to be approximately 1–4 days, but could range upto 7 days.

Case definitions *(13)*

Suspected case : A suspected case of influenza A (H_1N_1) 2009 is defined as a person with acute febrile respiratory illness (fever ≥ 38°C) with onset (a) within 7 days of close contact with a person who is a confirmed case of influenza A (H_1N_1) 2009 virus infection, or; (b) within 7 days of travel to areas where there are one or more confirmed cases, or (c) resides in a community where there are one or more confirmed influenza A (H_1N_1) 2009 cases.

Probable case : A probable case of influenza A (H_1N_1) 2009 virus infection is defined as a person with an acute febrile respiratory illness who : (1) is positive for influenza A, but unsubtypable for H_1 and H_3 by influenza RT–PCR or reagents used to detect seasonal influenza virus infection, or; (2) is positive for influenza A by an influenza rapid test or an influenza immunofluoresence assay (IFA) and meets criteria for a suspected case, or; (3) individual with a clinically compatible illness who died of an unexplained acute respiratory illness who is considered to be epidemiollogically linked to a probable or confirmed case.

Confirmed case : A confirmed case of pandemic influenza A (H_1N_1) 2009 virus infection is defined as a person with an acute febrile respiratory illness with laboratory confirmed influenza A (H_1N_1) 2009 virus infection at WHO approved laboratory by one or more of the following tests :

a. Real Time PCR
b. Viral culture
c. Four–fold rise in influenza A (H_1N_1) virus specific neutralizing antibodies.

Clinical features *(14)*

A wide clinical spectrum of disease ranging from non-febrile mild upper respiratory illness, febrile influenza like illness (ILI), to severe or even fatal complications including rapidly progressive pneumonia has been described. The case fatality rate is smilar to seasonal influenza i.e. about 0.5 per cent; however this could change *(15)*. The clinical features are as described below :

(a) *Uncomplicated influenza*

(1) ILI symptoms include : fever, cough, sore throat, rhinorrhoea, headache, muscle pain, and malaise, but no shortness of breath and no dyspnoea. Patients may present with some or all of these symptoms.

(2) Gastrointestinal illness may also be present, such as diarrhoea and/or vomiting, especially in children, but without evidence of dehydration.

(b) *Complicated or severe influenza*

(1) Presenting clinical (e.g. shortness of breath/ dyspnoea, tachypnea, hypoxia) and/or radiological signs of lower respiratory tract disease (e.g. pneumonia), central nervous system (CNS) involvement (e.g. encephalopathy, encephalitis), severe dehydration, or presenting secondary complications, such as renal failure, multiorgan failure, and septic shock. Other complications can include rhabdomyolysis and myocarditis.

(2) Exacerbation of underlying chronic disease, including asthma, COPD, chronic hepatic or renal failure, diabetes, or other cardiovascular conditions.

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(3) Any other condition or clinical presentation requiring hospital admission for clinical management.
(4) Any of the signs of progressive disease.

As COVID-19 and influenza, both are respiratory illnesses, they share many similarities. It is very important to differentiate these both diseases so as to take timely appropriate action to manage the disease. The differentiating points are as follows *(16)* :

	COVID-19	INFLUENZA
Incubation period	2–14 days	1–4 days
Common symptoms	– Fever – Cough – Fatigue – Shortness of breath – Loss of smell – Loss of taste	– Fever – Chills – Cough – Fatigue – Body aches and pains – Headache – Runny or stuffy nose – Sore throat
Less common symptoms	– Body aches and pains – Headache – Runny or stuffy nose – Sore throat – Nausea or diarrhoea	– Nausea or diarrhoea
Symptom onset	– Gradual	– Rapid
Vaccine and medications	– Vaccines are available	– Seasonal and swine flu vaccine and antiviral medication available.

Signs and symptoms of progressive disease

Patients who present initially with uncomplicated influenza may progress to more severe disease. Progression can be rapid (i.e. within 24 hours). The following are some of the indicators of progression, which would necessitate an urgent review of patient management.

(a) Symptoms and signs suggesting oxygen impairment or cardiopulmonary insufficiency :
- Shortness of breath (with activity or at rest), difficulty in breathing, turning blue, bloody or coloured sputum, chest pain, and low blood pressure;
- In children, fast or laboured breathing; and
- Hypoxia, as indicated by pulse oximetry.

(b) Symptoms and signs suggesting CNS complications:
- Altered mental status, unconsciousness, drowsiness, or difficult to awaken and recurring or persistent convulsions (seizures), confusion, severe weakness, or paralysis.

(c) Evidence of sustained virus replication or invasive secondary bacterial infection based on laboratory testing or clinical signs (e.g. persistent high fever and other symptoms beyond 3 days).

(d) Severe dehydration, manifested as decreased activity, dizziness, decreased urine output, and lethargy.

Risk factors for severe disease *(14)*

Risk factors for severe disease from pandemic influenza A (H_1N_1) 2009 virus infection reported to date are considered similar to those risk factors identified for complications from seasonal influenza. These include the following groups :

(1) Infants and young children, in particular <2 years
(2) Pregnant women
(3) Persons of any age with chronic pulmonary disease (e.g. asthma, COPD)
(4) Persons of any age with chronic cardiac disease (e.g. congestive cardiac failure)
(5) Persons with metabolic disorders (e.g. diabetes)
(6) Persons with chronic renal disease, chronic hepatic disease, certain neurological conditions (including neuromuscular, neurocognitive, and seizure disorders), haemoglobinopathies, or immunosuppression, whether due to primary immunosuppressive conditions, such as HIV infection, or secondary conditions, such as immunosuppressive medication or malignancy
(7) Children receiving chronic aspirin therapy
(8) Persons aged 65 years and older.

A higher risk of severe complications from pandemic influenza A (H_1N_1) 2009 virus infection has also been reported in individuals who are obese particularly in those who are morbidly obese.

Laboratory diagnosis *(14)*

Laboratory diagnosis of pandemic influenza A (H_1N_1) 2009 virus, especially at the beginning of a new community outbreak or for unusual cases, has important implications for case managment, such as infection control procedures, consideration of antiviral treatment options and avoiding the inappropriate use of antibiotics. Currently, the diagnostic tests can be done by specialized laboratories in many countries. Reverse transcriptase polymerase chain reaction (RT–PCR) will provide the most timely and sensitive detection of the infection.

Clinical specimens to be collected for laboratory diagnosis are respiratory samples. Samples from the upper respiratory tract, including a combination of nasal or nasopharyngeal samples, and a throat swab are advised. Recent evidence supports viral replication and recovery of pandemic A (H_1N_1) 2009 virus from lower respiratory tract samples (tracheal and bronchial aspirates) in patients presenting lower respiratory tract symptoms and in these patients, such samples have higher diagnostic yields than samples from the upper respiratory tract.

When influenza viruses are known to be circulating in a community, patients presenting with features of uncomplicated influenza can be diagnosed on clinical and epidemiological grounds. All patients should be instructed to return for follow-up, should they develop any signs or symptoms of progressive disease or fail to improve within 72 hours of the onset of symptoms.

Diagnostic testing, when available, should be prioritized for patients in whom confirmation of influenza virus infection may affect clinical management, including patients considered at-risk and/or those with complicated, severe, or progressive respiratory illness. In addition, results of diagnostic testing may also be valuable in guiding infection control practices and management of a patient's close contacts. Under no circumstances should influenza diagnostic testing delay initiation of infection control practices or antiviral treatment, if pandemic influenza A (H_1N_1) 2009 disease is suspected clinically and epidemiologically *(14)*.

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Several rapid influenza diagnostic tests including (so-called *point-of-care* diagnostic tests) are commercially available. However, studies indicate that rapid diagnostic tests miss many infections with pandemic (H_1N_1) 2009 virus and, therefore, negative results cannot rule out disease, and should not be used as grounds to withhold therapy or lift infection control measures.

Infection control

Evidence to date suggests that pandemic (H_1N_1) 2009 virus is transmitted similarly as seasonal influenza A and B viruses. Appropriate infection control measures (standard plus droplet precautions) should be adhered to at all times, which includes strict adherence to hand hygiene with soap and water or an alcohol based hand sanitizer, and to cover mouth and nose with tissue or handkerchief when coughing or sneezing. If ill persons must go into the community e.g. to seek medical care, they should wear a face mask to reduce the risk of spreading the virus in the community.

Whenever performing high-risk aerosol-generating procedures (for example, bronchoscopy or any procedure involving aspiration of the respiratory tract) use a particulate respirator (N95, FFP2 or equivalent), eye protection, gown, and gloves, and carry out the procedure in an adequately ventilated room, either naturally or mechanically.

The duration of isolation precautions for hospitalized patients with influenza symptoms should be continued for 7 days after onset of illness or 24 hours after the resolution of fever and respiratory symptoms, whichever is longer, while a patient is in a health-care facility. For prolonged illness with complications (i.e. pneumonia), control measures should be used during the duration of acute illness (i.e. until the patient has improved clinically). Special attention is needed in caring for immunosuppressed patients who may shed virus for a longer time period and are also at increased risk for development of antiviral resistant virus.

Influenza vaccine

Currently, there are three different influenza technologies in use, to produce influenza vaccines. These include egg-based, cell-cultured, and recombinant technologies. Egg-based inactivated influenza vaccines (IIVs) are prepared from inactivated and detergent-solubilized virion particles containing HA and NA proteins prepared in embryonated chicken eggs. The live attenuated vaccine (LAIV) is prepared from attenuated, less virulent virus strains. Cell-cultured vaccines are produced by growing the influenza virus in animal cells, allowing for a faster manufacturing process. Although hen's eggs are not used, trace amounts of egg protein may be found in these vaccines. The recombinant flu vaccine is an alternative method that isolates the HA gene and proteins in order to obtain an immunogenic response without the use of chicken eggs. This vaccine is produced in insect cell cultures and contains three times the amount of HA compared with the standard-dose preparation. It is currently the only available influenza vaccine that is completely egg-free *(17)*.

Two types of influenza viruses are included in the Influenza vaccine: human influenza A virus and influenza B virus. Vaccine composition is reviewed annually and updated as needed based on the circulating viruses, extent to which those viruses are spreading, and how good the response was to the previous year's vaccine. The World Health Organization makes recommendations about the specific viruses to be included.

Inactivated influenza vaccine (IIVs)

IIVs are available since 1940. Trivalent IIVs contain three inactivated viruses: type A (H_1N_1), type A (H_3N_2), and type B. Quadrivalent influenza vaccines were introduced in the year 2013–2014 season. They contain the same antigens as trivalent vaccines, with addition of another B strain virus, increasing the likelihood for adequate protection. IIV is administered by intramuscular or intradermal route. The vaccine is available in both paediatric (0.25 ml) and adult (0.5 ml) dose formulation. One dose of IIV may be administered annually for persons 9 years of age and older. Children 6 months through 8 years of age receiving influenza vaccine for the first time should receive two doses administered at least 28 days apart. Annual immunization is recommended *(18)*.

The vaccine is about 60 per cent effective among healthy persons younger than 65 years of age. On vaccination, the vaccine becomes effective after 14 days. Those infected shortly before (1–3 days) or shortly after immunization can still get the disease *(18)*. Vaccinated individuals can also get infected with other strain of influenza virus for which the vaccine dose not provide protection *(18)*. The immunity lasts from 6–12 months. The vaccine is 50–60 per cent effective in preventing hospitalization and 80 per cent effective in preventing death among elderly persons *(18)*.

The vaccine should be stored at temperature of 2–8°C. It should not be frozen.

For those persons aged 65 years and older, there are currently two influenza vaccines designed to overcome the waning immune response found in this patient population high-dose IIV (HD-IIV) and adjuvanted IIV (aIIV). Both formulations are available only as a trivalent vaccine. The HD-IIV contains four times the HA-antigen compared with standard influenza vaccines, providing a better immune response and reducing clinical outcomes associated with influenza infection in this patient population. When compared with patients who received standard-dose trivalent influenza vaccines, HD-IIV was shown to be 24% more effective in preventing laboratory confirmed influenza *(17)*.

SIDE EFFECTS

Inactivated vaccines, administered by injection, commonly cause local reactions such as soreness, swelling and redness at the injection site, and less often can cause fever, muscle or joint-aches or headache. These symptoms are generally mild and do not need medical attention, and last for 1–2 days. Fever, aches and headaches can occur more frequently in children compared to elderly people. Rarely, these inlfuenza vaccines can cause allergic reactions such as hives, rapid swelling of deeper skin layers and tissues, asthma or a severe multisystem allergic reaction due to hypersensitivity to certain components.

CONTRAINDICATIONS

As a general rule, inactivated vaccines should not be administered to *(19)* :

(1) People who have a severe allergy to chicken eggs;
(2) People with a history of anaphylactic reactions or other life-threatening allergic reactions to any of the constituents or trace residue of the vaccine;
(3) People with history of a severe reaction to influenza vaccination;
(4) People who developed Guillain-Barre syndrome (GBS) within 6 weeks of getting an influenza vaccine;
(5) Children less than 6 months of age (inactivated influenza vaccine is not approved for this age group); and

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(6) People who have a moderate-to-severe illness with a fever (they should wait till they recover to get vaccinated).

Live attenuated influenza vaccine

Live attenuated influenza vaccine (LAIV) was approved for use in 2003. It contains the same influenza viruses as IIV. The viruses are cold-adapted, and replicate effectively in the mucosa of the nasopharynx. The vaccine viruses are grown in chicken eggs, and the final product contains residual egg protein. The vaccine is provided in a single-dose sprayer unit: half of the dose is sprayed into each nostril. LAIV dose not contain thimerosal or any other preservative. LAIV is approved for use only in healthy, non-pregnant persons 2 to 49 years of age. Vaccinated children can shed vaccine virus in nasopharyngeal secretions for up to 3 weeks.

LAIV is 87 per cent effective against culture confirmed influenza in children 60–84 months old; results in 27 per cent reduction in febrile otitis media; 28 per cent reduction in otitis media with accompanying antibiotic use.

SIDE EFFECTS

Live attenuated vaccines are given *via* a nasal spray, and can commonly cause runny nose, nasal congestion, cough and can less frequently cause sore throat, low grade fever, irritability and muscle-aches and headache. Wheezing and vomiting episodes have been described in children receiving live influenza vaccines *(19)*.

CONTRAINDICATIONS

Persons who should not receive LAIV include children younger than 2 years of age; persons 50 years of age and older; persons with chronic medical conditions, including asthma, a recent wheezing episode, reactive airways disease or other chronic pulmonary or cardiovascular conditions, metabolic disease such as diabetes, renal disease, or hemoglobinopathy, such as sickle cell disease; and children or adolescents receiving long-term therapy with aspirin or aspirin-containing therapy, because of the association of Reye syndrome with wild-type influenza infection. Persons in these groups should receive inactivated influenza vaccine.

As with other live-virus vaccines, LAIV should not be given to persons who are immuno-suppressed because of disease, including HIV, or who are receiving immuno-suppressive therapy. Pregnant women should not receive LAIV. Immuno-suppressed persons and pregnant women should receive inactivated influenza vaccine. Since LAIV contains residual egg protein, it should not be administered to persons with a history of severe allergy to egg or any other vaccine component. A history of Guillain-Barre syndrome (GBS) within 6 weeks following a previous dose of influenza vaccine is a precaution for LAIV.

Since the spread of the epidemics of influenza virus is unstoppable and there is limitation of vaccine availability, WHO recommends that all the countries should immunize their health care workers as the first priority to protect the essential health infrastructure, and to prevent initiation of nosocomial spread of disease to vulnerable patients. WHO recommends the following groups of persons be vaccinated according to their order of priority : (a) pregnant women; (b) individuals aged more than 6 months with one of the several chronic medical conditions; (c) healthy young adults between age 15–49 years, (d) healthy children; (e) healthy adults between age 49–65 years; and (f) healthy adults aged more than 65 years.

The time difference between a dose of COVID-19 vaccine and influenza vaccine should be atleast 7 days.

Treatment

Key principles for clinical management include basic symptomatic care, early use of antiviral drugs if available, for high risk populations, antimicrobials for co-infections, and proactive observation for progression of illness.

Hospital care requires early supplemental oxygen therapy to correct hypoxaemia, with saturation monitoring at triage and during hospitalization, if possible, careful fluid replacement, antimicrobials, and other supportive care. It is important to provide appropriate antimicrobials for other infections which also present with severe respiratory distress. A number of severely ill patients with pandemic (H_1N_1) 2009 disease develop respiratory distress requiring mechanical ventilation and intensive care support.

Antiviral therapy *(14)*

Pandemic influenza A (H_1N_1) 2009 virus is currently susceptible to the neuraminidase inhibitors (NAIs) oseltamivir and zanamivir, but resistant to the M2 inhibitors amantadine or rimantadine.

The following is a summary of treatment recommendations.

(1) Patients who have severe or progressive clinical illness should be treated with oseltamivir. Treatment should be initiated as soon as possible.
   (a) This recommendation applies to all patient groups, including pregnant women, and young children <2 years, including neonates.
   (b) In patients with severe or progressive illness not responding to normal treatment regimens, higher doses of oseltamivir and longer duration of treatment may be appropriate. In adults, a dose of 150 mg twice daily is being used in some situations.
   (c) Where oseltamivir is not available or not possible to use, or if the virus is resistant to oseltamivir, patients who have severe or progressive clinical illness should be treated with zanamivir.

(2) Patients at higher risk of developing severe or complicated illness, but presenting with uncomplicated illness due to influenza virus infection, should be treated with oseltamivir or zanamvir. Treatment should be initiated as soon as possible following onset of illness.

(3) Patients not considered to be at higher risk of developing severe or complicated illness and who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection need not be treated with antivirals.

If used, antiviral treatment should ideally be started early following the onset of symptoms, but it may also be used at any stage of active disease when ongoing viral replication is anticipated or documented. Recent experience strongly indicates that earlier treatment is associated with better outcomes. Therefore, antiviral treatment should be initiated immediately and without waiting for laboratory confirmation of diagnosis.

In patients who have persistent severe illness despite oseltamivir treatment, there are few licensed alternative antiviral treatments. In these situations, clinicians have considered intravenous administration of alternative antiviral drugs such as zanamivir, peramivir, and ribavirin. The use of such treatments should be done only in the

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context of prospective clinical and virological data collection and with regard to the following cautions:

- ribavirin should not be administered as monotherapy;
- ribavirin should not be administered to pregnant women; and
- zanamivir formulated as a powder for inhalation should not be delivered *via* nebulization due to the presence of lactose, which may compromise ventilator function.

Standard antiviral treatment regimens *(14)*

Oseltamivir

Oseltamivir is indicated for treatment of influenza. For adults the recommended oral dose is 75 mg oseltamivir twice daily for 5 days.

For infants less than 1 year of age recommended oral doses are as follows:

>3 months to 12 months	3 mg/kg, twice daily for 5 days
>1 month to 3 months	2.5 mg/kg, twice daily for 5 days
0 to 1 month *	2 mg/kg, twice daily for 5 days
* There are no data available regarding the adminstration of oseltamivir to infants less than one month of age.	

For children older than 1 year up to 12 years of age, the recommended oral doses according to body weight are as follows :

15 kg or less	30 mg twice a day for 5 days
15-23 kg	45 mg twice a day for 5 days
24-40 kg	60 mg twice a day for 5 days
>40 kg	75 mg twice a day for 5 days

Zanamivir

Zanamivir is indicated for treatment of influenza in adults and children (>5 years). The recommended dose for treatment of adults and children from the age of 5 years is two inhalations (2 x 5 mg) twice daily for 5 days.

Chemoprophylaxis *(13)*

Oseltamivir is the drug of choice for chemoprophylaxis to health care personnels and close contacts of suspected, probable or confirmed case of pandemic influenza A (H_1N_1) 2009. It should be given till 10 days after last exposure. The dose by body weight is a follows :

Weight less than 15 kg – 30 mg OD
15–23 kg – 45 mg OD
24–40 kg – 60 mg OD
> 40 kg – 75 mg OD

For infants

< 3 months – not recommended unless situation is critical
3–5 months – 20 mg OD
6–11 months – 25 mg OD

Influenza surveillance

Influenza surveillance is intended to monitor the prevalence of the circulating strains and to detect new strains necessary for vaccine information; to estimate influenza related impact on morbidity, mortality and economic loss; rapidly detect outbreaks; and disease control through rapid action.

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DIPHTHERIA

Diphtheria is an acute bacterial infectious disease caused by toxigenic strains of *Corynebacterium diphtheriae*. Three major clinical types have been described : anterior nasal, faucial and laryngeal; however, the skin, conjunctiva, vulva and other parts of the body may be affected. The bacilli multiply locally, usually in the throat, and elaborate a powerful exotoxin which is responsible for :

(a) the formation of a greyish or yellowish membrane ("false membrane") commonly over the tonsils, pharynx or larynx (or at the site of implantation), with well–defined edges and the membrane cannot be wiped away;
(b) marked congestion, oedema or local tissue destruction;
(c) enlargement of the regional lymph nodes; and
(d) signs and symptoms of toxaemia.

Fatality rate on the average is about 5–10 per cent which has changed little in the past decades in untreated cases, and in children under 5 years of age, and adults over 40 years of age, one out of 5 persons who get diphtheria dies *(1)*.

Problem statement

WORLD : Diphtheria is a rare disease in most developed countries owing to routine children vaccination. In countries where satisfactory vaccination schemes have been instituted the disease has so declined that it is no longer regarded as a public health problem. However the disease is seen occasionally among non-immunized children in developed countries.

Improved socio-economic conditions are changing the epidemiology of diphtheria. Changes in lifestyle allow far less opportunity to maintain natural immunity, such as through frequent skin infection with *C.diphtheriae (2)*. These epidemics are largely due to decreasing immunization coverage among infants and children, waning immunity to

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diphtheria in adults, movement of large groups of population in the last few years, and an irregular supply of vaccine *(3)*. These outbreaks highlight the need for booster vaccinations. Recent diphtheria outbreaks in a number of countries have demonstrated a shift in the age distribution of cases to older children and adults *(4)*. In developing countries, the disease continues to be endemic due to lack of adequate widespread immunization. The true numbers of diphtheria cases and deaths are unknown because of incomplete reporting from most countries where the disease occurs. During the year 2021, about 8,639 diphtheria cases were reported globally *(5)*.

INDIA : Diphtheria is an endemic disease. The available retrospective data indicate a declining trend of diphtheria in the country. It is due to increasing coverage of child population by immunization. During the year 2022, about 1,989 cases of diptheria were reported in India with about 2 deaths. Most of the cases reported were from Telangana (1,441 cases, 0 death), Rajasthan (182 cases and 0 death) and Gujarat (56 cases and 0 death) *(6)*.

Epidemiological determinants

Agent factors

(a) AGENT : The causative agent, *C. diphtheriae* is a gram–positive, non–motile organism. It has no invasive power, but produces a powerful exotoxin. Four types of diphtheria bacilli are differentiated – *gravis, mitis, belfanti* and *intermedius*, all pathogenic to man. In general, *gravis* infections tend to be more severe than *mitis* infections. Not all the strains of the organism are toxigenic. There is evidence that a non–toxigenic strain may become toxigenic when exposed to a particular bacteriophage – the beta phage – carrying the gene for toxin production *(7)*. The toxin can affect the heart leading to myocarditis or the nerves leading to paralysis. Diphtheria bacilli are sensitive to penicillin and are readily killed by heat and chemical agents. They may survive for short periods in dust and fomites. (b) SOURCE OF INFECTION : The source of infection may be a case or carrier: *(i) CASE* : Cases range from subclinical to frank clinical cases. Mild or silent infections may exhibit no more than a mere running nose or sore throat; these cases play a more important role than frank cases in spreading the infection. *(ii) CARRIER* : Carriers are common sources of infection *(8)*. Carriers may be temporary or chronic; nasal or throat carriers. The nasal carriers are particularly dangerous as source of infection because of frequent shedding of the organism into the environment, than do throat carriers. The temporary carrier state may last for about a month, but the chronic carrier state may persist for a year or so, unless the patient is treated. Immunization does not prevent the carrier state. (c) INFECTIVE MATERIAL : Nasopharyngeal secretions, discharges from skin lesions, contaminated fomites and possibly infected dust. (d) PERIOD OF INFECTIVITY : Unless treated, the period of infectivity may vary from 14 to 28 days from the onset of the disease, but carriers may remain infective for much longer periods. A case or carrier may be considered non-communicable, when at least two cultures properly obtained from nose and throat, 24 hours apart, are negative for diphtheria bacilli.

Host factors

(a) AGE : Diphtheria particularly affects children aged 1 to 5. In countries where widespread immunization is practised, a shift in age incidence has been observed from preschool to school age. (b) SEX : Both sexes are affected. (c) IMMUNITY : Infants born of immune mothers are relatively immune during the first few weeks or months of life. Before artificial immunization, large proportion of population in developing countries were acquiring active immunity through inapparent infection which resulted in widespread production of antitoxin in the population. Thus most members of the population except children were immune. By age 6–8 years, approximately 75 per cent of children in developing countries where skin infection with *C. diphtheriae* are common have protective serum antitoxin levels *(9)*.

Since diphtheria is principally the result of action of the toxin formed by the organism rather than invasion by the organism, resistance to the disease depends largely on the availability of specific neutralizing antitoxin in the bloodstream and tissues. It is generally true that diphtheria occurs only in persons who possess no antitoxin (or less than 0.01 Lf unit/ml.). Assessment of immunity to diphtheria toxin for individual patients can best be made by review of documented diphtheria toxoid immunizations and primary or booster immunization if needed *(9)*.

Environmental factors

Cases of diphtheria occur in all seasons, although winter months favour its spread.

Mode of transmission

The disease is spread mainly by droplet infection. It can also be transmitted directly to susceptible persons from infected cutaneous lesions. Transmission by objects (e.g., cups, thermometers, toys, pencils), contaminated by the nasopharyngeal secretions of the patient is possible, but for only short periods.

Portal of entry

(a) RESPIRATORY ROUTE : Commonly the portal of entry is the respiratory tract. *(b) NON–RESPIRATORY ROUTES* : The portal of entry sometimes may be the skin where cuts, wounds and ulcers not properly attended to, may get infected with diphtheria bacilli, and so is the umbilicus in the newborn. Occasionally, the site of implantation may be the eye, genitalia or middle ear. The non–respiratory routes of infection are less common in developed countries where spread by droplet infection is more common.

Incubation period

2 to 6 days, occasionally longer.

Clinical features

Respiratory tract forms of diphtheria consist of pharyngotonsillar, laryngotracheal, nasal, and combinations thereof. Patients with pharyngotonsillar diphtheria usually have a sore throat, difficulty in swallowing, and low grade fever at presentation. Examination of the throat may show only mild erythema, localized exudate, or a pseudo-membrane. The membrane may be localized or a patch of the posterior pharynx or tonsil, may cover the entire tonsil, or, less frequently, may spread to cover the soft and hard palates and the posterior portion of the pharynx. In the early stage the pseudo-membrane may be whitish and may wipe off easily. The membrane may extend to become thick, blue–white to grey–black, and adherent. Attempts to remove the membrane result in bleeding. A minimal area of mucosal erythema surrounds the membrane. Patients with severe disease may have marked oedema of the submandibular area and the anterior portion of the neck, along with lymphadenopathy, giving a characteristic "bull-necked" appearance *(1)*.

Laryngotracheal diphtheria most often is preceded by

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pharyngotonsillar disease, usually is associated with fever, hoarseness and croupy cough at presentation, and, if the infection extends into bronchial tree, it is the most severe form of disease. Initially it may be clinically indistinguishable from viral croup or epiglottitis. Prostration and dyspnoea soon follow because of the obstruction caused by the membrane. This obstruction may even cause suffocation if not promptly relieved by intubation or tracheostomy.

The diphtheria bacilli within the membrane continue to produce toxin actively. This is absorbed and results in distant toxic damage, particularly parenchymatous degeneration, fatty infiltration and necrosis in heart muscle, liver, kidneys, and adrenals, sometimes accompanied by gross haemorrhage. Irregularities of cardiac rhythm indicate damage to the heart. Later, there may be difficulties with vision, speech, swallowing, or movement of the arms or legs. The toxin also produces nerve damage, resulting often in paralysis of the soft palate, eye muscles, or extremities *(9)*. Patients who survive complications recover completely.

Nasal diphtheria, the mildest form of respiratory diphtheria, usually is localized to the septum or turbinates of one side of the nose. Occasionally a membrane may extend into the pharynx.

Non-respiratory mucosal surface i.e., the conjunctiva and genitals may also be sites of infection.

Cutaneous diphtheria is common in tropical areas. It often appears as a secondary infection of a previous skin abrasion or infection. The presenting lesion, often an ulcer, may be surrounded by erythema and covered with a membrane. Patients generally seek treatment because of the chronicity of the skin lesion.

CONTROL OF DIPHTHERIA

1. CASES AND CARRIERS

(a) ***Early detection :*** An active search for cases and carriers should start immediately amongst family and school contacts. Carriers can be detected only by culture method. Swabs should be taken from both the nose and throat and examined by culture methods for diphtheria bacilli. Tests should be made for the virulence of the organism. (b) ***Isolation :*** All cases, suspected cases and carriers should be promptly isolated, preferably in a hospital, for at least 14 days or until proved free of infection. At least 2 consecutive nose and throat swabs, taken 24 hours apart, should be negative before terminating isolation. (c) ***Treatment :*** (i) CASES : When diphtheria is suspected, diphtheria antitoxin should be given without delay, IM or IV, in doses ranging from 20,000 to 100,000 units or more, depending upon the severity of the case, after a preliminary test dose of 0.2 ml subcutaneously to detect sensitization to horse serum. For mild early pharyngeal or laryngeal disease the dose is 20,000–40,000 units; for moderate nasopharyngeal disease, 40,000–60,000 units; for severe, extensive or late (3 days or more) disease, 80,000–100,000 units *(10)*. In addition to antitoxin, every case should be treated with penicillin or erythromycin for 5 to 6 days to clear the throat of *C.diptheriae* and thereby decrease toxin production, (ii) CARRIERS : The carriers should be treated with 10 days course of oral erythromycin, which is the most effective drug for the treatment of carriers. The immunity status should be upgraded as discussed below.

2. CONTACTS

Contacts merit special attention. They should be throat swabbed and their immunity status determined. Different situations pose different options : (a) where primary immunization or booster dose was received within the previous 5 years, no further action would be needed (b) where primary course or booster dose of diphtheria toxoid was received more than 5 years before, only a booster dose of diphtheria toxoid need be given (c) non-immunized close contact should receive prophylactic penicillin or erythromycin. They should be given 1000–2000 units of diphtheria antitoxin and actively immunized against diphtheria. Contacts should be placed under medical surveillance and examined daily for evidence of diphtheria for at least a week after exposure. The bacteriological surveillance of close contacts should be continued for several weeks by repeated swabbing.

3. COMMUNITY

The only effective control is by active immunization with diphtheria toxoid of all infants as early in life as possible, as scheduled, with subsequent booster doses every 10 years thereafter. The aim should be to immunize before the infant loses his maternally derived immunity so that there will be continuous protection from birth without any gap in immunity to natural disease. The vaccine being a toxoid is not directed against organisms. Therefore immunization does not prevent the carrier state; consequently, the non-immune individuals are not protected by a high level of population immunity *(11)*. This implies that immunization rate must be maintained at a high level.

DIPHTHERIA IMMUNIZATION

Current prophylactics

These may be grouped as below :

a. Combined or mixed vaccines
- DPT (diphtheria–pertussis–tetanus vaccine)
- DTPw (diphtheria, tetanus, whole–cell pertussis)
- DTPa (diphtheria, tetanus, acellular pertussis)
- DT (diphtheria–tetanus toxoid)
- dT (diphtheria–tetanus, adult type)
- Pentavalent (diphtheria, tetanus, pertussis, hepatitis B and Hib).

b. Single vaccines
- FT (formal–toxoid)
- APT (alum–precipitated toxoid)
- PTAP (purified toxoid aluminium phosphate)
- PTAH (purified toxoid aluminium hydroxide)
- TAF (toxoid–antitoxin flocculus)

c. Antisera
- Diphtheria antitoxin.

a. COMBINED VACCINES

1. DPT vaccine

For immunizing infants, the preparation of choice is DPT. Firstly because, the infant can be immunized simultaneously against three diseases, viz., diphtheria, pertussis and tetanus which is a great gain administratively. Secondly the pertussis component in DPT vaccine enhances the potency of the diphtheria toxoid.

There are two types of DPT vaccines – plain and adsorbed. Adsorption is usually carried out on a mineral carrier like aluminium phosphate or hydroxide. Studies have shown that

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adsorption increases the immunological effectiveness of the vaccine. The WHO recommends that only adjuvant DPT preparations be utilized in immunization programmes *(12)*.

STORAGE : DPT/DT vaccines should not be frozen. They should be stored in a refrigerator between 2 to 8 deg. C.

(a) *Optimum age* : It has been found that young infants respond well to immunization with potent vaccines and toxoids even in the presence of low to moderate levels of maternal antibodies. Accordingly, the Global Advisory Group of the Expanded Programme on Immunization (EPI), has recommended that DPT vaccine can be safely and effectively administered as early as 6 weeks after birth.

(b) *Number of doses* : Three doses of DPT each of which is usually 0.5 ml, should be considered optimal for primary immunization. It is associated with higher and more sustained levels of diphtheria and tetanus antitoxin and acceptable level of pertussis protection i.e., vaccine efficiency 95 per cent *(13)*.

(c) *Interval between doses* : The current recommendation is to allow an interval of 4 weeks between the 3 doses, with a booster injection at 16–24 months, followed by another booster at the age of 5 to 6 years.

(d) *Mode of administration* : DPT should be administered intramuscularly in antero (lateral aspect) of the thigh.

(e) *Reactions* : Fever and mild local reactions following DPT immunization are common. It is estimated that 2 to 6 per cent of vaccinees develop fever of 39 deg. C or higher, and that 5 to 10 per cent experience swelling and induration or pain lasting more than 48 hours.

The most severe complications following DPT immunization are neurological (encephalitis/ encephalopathy, prolonged convulsions, infantile spasms and Reye's syndrome) and are thought to be due primarily to the pertussis component of the vaccine – the estimated risk is 1:170,000 doses administered.

(f) *Contraindications* : Minor illnesses such as cough, cold, mild fever are not considered contraindications to vaccination, only such children who are seriously ill or need hospitalization are not vaccinated. DPT should not be repeated if a severe reaction occurred after a previous dose. Such reactions include collapse or shock–like state, persistent screaming episodes, temperature above 40 deg.C, convulsions, other neurological symptoms and anaphylactic reactions. In the case of DPT, subsequent immunization with DT only is recommended, without the pertussis component. Local reactions at the site of injection or mild fever do not by themselves preclude the further use of DPT.

Since the severity of pertussis infection decreases with age, the pertussis component in DPT vaccine is not usually recommended after the age of 6 years *(1)*. Therefore, children over the age of 5 years who have not received DPT, need only 2 doses of DT vaccine, 4 weeks apart, with a booster dose 6 months to 1 year later. Those children who received the primary course of DPT earlier, should receive only DT as booster at 5–6 years or at school entry.

For immunizing children over 12 years of age and adults, the preparation of choice is dT, which is an adult–type of diphtheria tetanus vaccine *(13)*. This preparation contains no more than 2 Lf of diphtheria toxoid per dose, compared with 25 Lf in the ordinary (paediatric) DPT/DT vaccines. Administration of dT vaccine to adults is carried out in 2 doses at an interval of 4 to 6 weeks, followed by a booster 6 to 12 months after the second dose *(13)*. This vaccine (DT) is not followed by the high incidence of reactions associated with the use of DPT or DT. Alternatively, for primary immunization of adults, FT or TAF may be used and they cause fewer reactions than APT or PTAP.

2. Pentavalent vaccine

Pentavalent vaccine provides protection to a child from 5 life threatening diseases – diphtheria, pertussis, tetanus, hepatitis B and haemophilus influenzae type b (Hib). Giving pentavalent vaccine reduces the number of pricks to a child. When used, it replaces Hepatitis B and DPT primary vaccination schedule at 6, 10 and 14 weeks in the immunization programme, except that the birth dose of hepatitis B and booster doses of DPT are continued.

The UIP pentavalent vaccine comes in liquid form in a vial. Each dose (0.5 ml) is given by intramuscular injection in anterolateral aspect of the mid-thigh, using auto-disabled syringe. Pentavalent vaccine is a freeze sensitive vaccine and should be stored and transported at 2–8°C temperature.

Pentavalent vaccine is very safe. As with all medicines, a few side effects are possible. Pain, redness and swelling at the site of injection, fever, vomiting, loss of appetite, abnormal crying, irritability are the common side effects. The rare side effects are high fever (more than 39.5°C) and fits or seizures, and very rarely severe allergic reaction can occur.

b. SINGLE VACCINES

Single vaccines (e.g., FT, PTAP, APT, PTAH) are less frequently used. They are all good immunizing agents. APT is hardly used because it is prone to give rise to serious reactions. Each dose of these antigens generally contains 25 Loeffler *(Lf)* units of diphtheria toxoid.

c. ANTISERA

Diphtheria antitoxin prepared in horse serum is still the mainstay of passive prophylaxis and also for treatment of diphtheria.

It has been shown, protection against diphtheria toxin is a quantitative phenomenon, so that a serum antitoxin titre that protects against a small dose of toxin may not protect against a large dose: for this reason, failures of diphtheria immunization may take place *(14)*.

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WHOOPING COUGH (PERTUSSIS)

An acute infectious disease, usually of young children, caused by *B. pertussis*. It is clinically characterized by an insidious onset with mild fever and an irritating cough, gradually becoming paroxysmal with the characteristic "whoop" (loud crowing inspiration) often with cyanosis and vomiting. The spectrum of disease varies from severe illness to atypical and mild illness without whoop. The Chinese call it a "Hundred Day Cough" *(1)*.

Problem statement

Pertussis is an important cause of death in infants worldwide, and continues to be a public health concern even in countries with high vaccination coverage. During 2020, about 69,414 cases were reported to WHO globally *(2)* and the DPT_3 immunization rate was 83 per cent.

It is one of the most lethal diseases of the infants and young children who have not been immunized, particularly those with underlying malnutrition and other respiratory infections *(3)*. Pertussis is increasingly reported in older children, adolescents and adults. A serological study from the United States showed that 21 per cent of adults with prolonged cough (lasting more than 2 weeks) had pertussis *(4)*.

In India, there is marked decline of the disease after launch of universal immunization programme. During the year 1987; the reported incidence was about 1.63 lakh cases, whereas during 2022 only 12,642 cases with 11 deaths were reported showing a decline of about 99.13 per cent *(5)*.

Epidemiological determinants

Agent factors

(a) AGENT : The causative agent in a large proportion of cases is *B. pertussis*. In a small percentage of cases (less than 5 per cent), *B. parapertussis* is probably responsible. Certain viruses (e.g., adenoviruses, parainfluenza viruses) are also implicated in the whooping cough syndrome, but their presence in cases of whooping cough is probably coincidental and not causal *(6)*. *B. pertussis* occurs in smooth and rough phases, capsulated and non-capsulated forms, and elaborates an exotoxin and endotoxin. Clinical disease is associated with encapsulated, phase 1 strains. *B. pertussis* is antigenically highly complex. It carries 3 major agglutinogens – 1, 2 and 3 and several minor ones. The nature of the protective antigen is not known *(6)*. The bacterium survives only for very short periods outside the human body. (b) SOURCE OF INFECTION : *B.pertussis* infects only man. The source of infection is a case of pertussis. More often, the source may be mild, missed and unrecognized cases. There is no evidence that infection is ever subclinical *(6)*. A chronic carrier state does not exist. (c) INFECTIVE MATERIAL : The bacilli occurs abundantly in the nasopharyngeal and bronchial secretions, which are infective. Objects freshly contaminated by such discharges are also infective. (d) INFECTIVE PERIOD : Whooping cough is most infectious during catarrhal stage. The infective period may be considered to extend from a week after exposure to about 3 weeks after the onset of the paroxysmal stage although communicability diminishes rapidly after the catarrhal stage. Asymptomatic chronic carriers of *B. pertussis* are uncommon *(7)*. (e) SECOND ATTACK RATE : Averages 90 per cent in unimmunized household contacts *(7)*.

Host factors

(a) AGE : Whooping cough is primarily a disease of infants and pre-school children. The highest incidence is found below the age of 5 years. The median age of infection, i.e., the age when half the children are likely to develop whooping cough is between 20–30 months in developing countries as compared to 50 months in developed countries *(1)*. Infants below 6 months have the highest mortality. In older children, adolescents and adults, pertussis is often unrecognized because of its atypical course. However, older age groups represent an important source of infection for susceptible infants *(7)*. (b) SEX : Incidence and fatality are observed to be more among female than male children *(6)*. (c) IMMUNITY : Recovery from whooping cough or adequate immunization is followed by immunity. Second attacks may occur in persons with declining immunity, but these are usually mild. It is possible that the first defence against pertussis infection is the antibody that prevents attachment of the bacteria to the cilia of the respiratory epithelium *(8)*. Infants are susceptible to infection from birth because maternal antibody does not appear to give them protection. There is no cross immunity with *B. parapertussis*.

Environmental factors

Pertussis occurs throughout the year, but the disease shows a seasonal trend with more cases occurring during winter and spring months, due to overcrowding. Socio-economic conditions and ways of life also play a role in the epidemiology of the disease. Thus, the risk of exposure is greater in the lower social classes living in overcrowded conditions than in well-to-do groups.

Mode of transmission

Whooping cough is spread mainly by droplet infection and direct contact. Each time the patient coughs, sneezes or talks, the bacilli are sprayed into the air. Most children contract infection from their playmates who are in the early stages of the disease. The role of fomites in the spread of infection appears to be very small, unless they are freshly contaminated.

Incubation period

Usually 7 to 14 days, but not more than 3 weeks.

Clinical course

B. pertussis produces a local infection; the organism is not invasive. It multiplies on the surface epithelium of the respiratory tract and causes inflammation and necrosis of the mucosa leading to secondary bacterial invasion. Three stages are described in the clinical course of the disease: (a) catarrhal stage, lasting for about 10 days. It is characterized by its insidious onset, lacrimation, sneezing and coryza, anorexia and malaise, and a hacking night cough that becomes diurnal. (b) paroxysmal stage, lasting for 2–4 weeks. It is characterized by bursts of rapid, consecutive coughs followed by a deep, high-pitched inspiration (whoop). It is usually followed by vomiting. In young infants it may cause cyanosis and apnoea. In adults and adolescents, uncharacteristic, persistent cough may be the only manifestation of the disease, and (c) convalescent stage, lasting for 1–2 weeks. The illness generally lasts 6 to 8 weeks.

Complications occur in 5–6 per cent of cases, most frequently in infants aged less than 6 months. The chief

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complications of pertussis are bronchitis; bronchopneumonia and bronchiectasis. The violence of the paroxysms may precipitate subconjunctival haemorrhages, epistaxis, haemoptysis and punctate cerebral haemorrhages which may cause convulsions and coma.

Bronchopneumonia occurs in about 5.2 per cent of cases. It is the most prominent problem, with relatively high mortality. The incidence of pertussis-associated encephalopathy is 0.9 per cent 100,000. In industrialized countries, lethality of pertussis is very low (<1/1000), whereas in developing countries the average mortality is estimated at 3.9 per cent in infants and 1 per cent in children aged 1–4 years *(7)*.

Control of Whooping Cough

1. CASES AND CONTACTS

(i) Cases : Early diagnosis, isolation and treatment of cases, and disinfection of discharges from nose and throat are the general principles of control of whooping cough. Early diagnosis is possible only by bacteriological examination of nose and throat secretions which may be obtained by naso-pharyngeal swabs. The chances of isolating the organism are < 60 per cent if the material is obtained within 10–14 days from the onset of illness. The value of fluorescent antibody technique has been emphasized in facilitating the rapid diagnosis of pertussis. The patient should be isolated until considered to be non-infectious. Although several antibiotics are effective against *B. pertussis*, erythromycin is probably the drug of choice. A dose of 30–50 mg/kg of body weight in 4 divided doses for 10 days has been recommended. Possible alternatives are Azithromycin, Clarithromycin. Antibiotics may prevent or moderate clinical pertussis when given during incubation period or in early catarrhal stage. During paroxysmal phase of disease, antimicrobial drugs will not change the clinical course but may eliminate the bacterium from the nasopharynx and thus reduce transmission of disease *(7)*. They are useful in controlling secondary bacterial infections.

(ii) Contacts : Infants and young children should be kept away from cases. Those known to have been in contact with whooping cough may be given prophylactic antibiotic (erythromycin or azithromycin) treatment for 10 days to prevent the infecting bacteria to become established. The best protection that can be given to an infant is to administer a booster dose of DPT/DT to his siblings before he is born *(6)*.

2. ACTIVE IMMUNIZATION

The vaccine is usually administered in the national childhood immunization programme as combined DPT, DTWP or DTaP vaccine. In India, the national policy is to immunize against diphtheria, whooping cough and tetanus simultaneously, by administering 3 doses (each dose about 0.5 ml) of DPT vaccine intramuscularly, at one month interval, starting at the age of 6 weeks. A booster dose is given at 18–24 months. Children whose vaccination series has been interrupted should have their series resumed, without repeating previous doses. In some countries, an additional vaccine dose is now offered to health-care workers and young parents. Only acellular pertussis vaccines are used for vaccination of older children and adults *(7)*.

Despite major differences in the content, mode of preparation and efficacy among both whole-cell pertussis vaccines and acellular pertussis vaccines; comprehensive clinical trials have demonstrated that the most efficacious vaccines of either category will protect 85 per cent of the recipients from clinical disease. The duration of protection following the primary 3-dose course in infants and 1 booster dose atleast 1 year later is believed to be on an average 6–12 years for both whole-cell and acellular pertussis vaccines. This is similar to, or somewhat shorter than, immunity following natural infection *(7)*. Some studies suggest that pertussis vaccination affects pharyngeal colonization of *B. pertussis*, resulting in some reduction of bacterial transmission in the community *(7)*. All infants, including HIV-positive individuals should be immunized against pertussis.

In principle, the same type of acellular vaccine should be given throughout the primary course of vaccination. However, if the previous type of vaccine is unknown, any type of acellular vaccine may be used *(7)*.

Commercially available vaccines containing acelluar pertussis include combination with some or all of the following components : diphtheria toxoid, tetanus toxoid, Hib, HepB and IPV.

UNTOWARD REACTIONS : With some vaccines available in the early 1960s, persistent screaming and collapse were reported, but these reactions are rarely observed with the vaccines now available. Pertussis vaccines may give rise to local reactions at the site of injection, mild fever and irritability. The rare vaccine reactions are persistent (more than 3 hours) inconsolable screaming, seizures, hypotonic hypo-responsive episodes, anaphylactic reaction and very rarely encephalopathy. For details kindly refer to Table 36 of chapter 3 page 125.

CONTRAINDICATIONS : The contraindications to pertussis vaccination are anaphylactic reaction, encephalopathy, a personal or strong family history of epilepsy, convulsions or similar CNS disorders: any febrile upset until fully recovered: or a reaction to one of the previously given triple vaccine injections *(10)*.

3. PASSIVE IMMUNIZATION

The merit of hyperimmune globulin in pertussis prophylaxis has yet to be established. So far, there is no evidence of its efficacy in well-controlled trials *(9)*.

The control of pertussis by immunization is still an unsolved problem. Even if the level of immunization reaches 100 per cent, it is possible that the disease would not be entirely eliminated because whooping cough vaccines have never been claimed to be more than 90 per cent effective.

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MENINGOCOCCAL MENINGITIS

Meningococcal meningitis or cerebrospinal fever is an acute communicable disease caused by *N.meningitidis*. It usually begins with intense headache, vomiting and stiff neck and progresses to coma within a few hours. The meningitis is part of a septicaemic process. The fatality of typical untreated cases is about 50 per cent. With early diagnosis and treatment, case fatality rates have declined to less than 8–15 per cent.

Problem statement

Distribution worldwide, occurring sporadically and in small outbreaks in most parts of the world. In some regions this endemic situation may alternate with devastating, unpredictable epidemics. This is the case in the African meningitis belt, which is the region in sub-Saharan Africa stretching from Senegal in the west to Ethiopia in the east. This region is inhabited by around 400 million people. In the African meningitis belt, the WHO definition of a meningococcal epidemic is >100 cases per 100,000 population per year. In the endemic countries, the incidence of >10 cases, 2–10 cases and <2 cases per 100,000 population per year characterize high, moderate and low endemicity respectivety. An outbreak outside the meningitis belt may be defined as a substantial increase in invasive meningococcal disease in a defined population above that which is expected by place and time *(1)*.

During recent years, several serious outbreaks affecting numerous countries have occurred in tropical and temperate zones of other continents, viz, Americas, Asia and Europe. In Europe, the incidence of disease ranges from 0.2 to 14 cases per 100,000 population and majority cases are caused by serogroup B strains. In Americas, the incidence of disease is in the range of 0.3 to 4 cases per 100,000 population. In United States, the majority cases are caused by serogroups B, C and Y. In Asia, most meningococcal disease is caused by meningococci belonging to serogroup A or C *(1)*.

Meingococcal disesase is endemic in India. Cases of meningococcal meningitis are reported sporadically or in small clusters. During 2022, about 1,234 cases of meningococcal meningitis were reported in India with about 8 deaths. Majority of the cases were reported from only few states as shown in Table 1.

TABLE 1

Reported cases and deaths due to meningococcal meningitis in some states in India – 2022

State	Cases	Deaths
Odisha	348	0
Rajasthan	347	0
Telangana	236	0
Meghalaya	108	0
Karnataka	69	0
Tamil Nadu	31	8
Gujarat	28	0
Haryana	24	0
Nagaland	8	0
Jharkhand	8	0
Chandigarh	6	0
Bihar	6	0
India	1,234	8

Source : *(2)*

Epidemiological features

(a) AGENT : The causative agent, *N. meningitidis* is a gram-negative diplococci. 12 serotypes have been identified, viz. Groups A, B, C, 29E, H, I, K, L, W135, X, Y, Z based on the structure of the polysaccharide capsule. The majority of invasive meningococcal infections are caused by organisms of serogroups A, B, C, X, W135 and Y. Meningococci of these serogroups have the potential to cause both endemic disease and outbreaks. In African meningitis belt, subgroup A has been the most important cause of disease *(1)*. *N. meningitidis* is a delicate organism; it dies rapidly on exposure to heat and cold. (b) SOURCE OF INFECTION : The organism is found in the nasopharynx of cases and carriers. Clinical cases present only a negligible source of infection. More often the infection causes mild or even unnoticeable symptoms of naso-pharyngitis. 4 to 35 per cent of the normal population may harbour the organism in the nasopharynx during inter-epidemic periods. Carriers are the most important source of infection. The mean duration of temporary carriers is about 10 months *(3)*. During epidemics, the carrier rate may go up to 70–80 per cent. (c) PERIOD OF COMMUNICABILITY : Until meningococci are no longer present in discharges from nose and throat. Cases rapidly lose their infectiousness within 24 hours of specific treatment. (d) AGE AND SEX : This is predominantly a disease of children and young adults of both sexes with highest attack rate in infants aged 3–12 months. (e) IMMUNITY : All ages are susceptible. Younger age groups are more susceptible than older groups as their antibodies are lower. Immunity is acquired by subclinical infection (mostly), clinical disease or vaccination. Infants derive passive immunity from the mother. (f) ENVIRONMENTAL FACTORS : The seasonal variation of the disease is well established; outbreaks occur more frequently in the dry and cold months of the year from December to June. Overcrowding, as occurs in schools, barracks, refugee and other camps, is an important predisposing factor. The incidence is also greater in the low socio-economic groups living under poor housing conditions, with exposure to tobacco smoke, asplenia, HIV infection and travel to endemic areas.

Mode of transmission

The disease spreads mainly by droplet infection. The portal of entry is the nasopharynx.

Incubation period

Usually 3 to 4 days, but may vary from 2 to 10 days.

Clinical course

Most infections do not cause clinical disease. Many infected people become asymptomatic carriers of the bacteria and serve as a reservoir and source of infection for others. In general, susceptibility to meningococcal disease decreases with age. Meningococcal meningitis has a sudden onset of intense headache, fever, nausea, vomiting, photophobia, stiff neck and various neurological signs. The disease is fatal within 24–48 hours in 5–10 per cent of cases even with prompt antimicrobial treatment in good health care facility. Among individuals who survive, upto 15–20 per cent have permanent neurological sequelae. Meningococcal septicaemia, in which there is rapid dissemination of bacteria in the bloodstream, is a less common form of meningococcal disease, characterized by circulatory collapse, haemorrhagic skin rash and high fatality rate *(4)*.

Prevention and control

(a) CASES : Treatment with antibiotics can save the lives of 95 per cent of patients provided that it is started during

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the first 2 days of illness. Penicillin is the drug of choice. In penicillin-allergic patients, ceftriaxone and other third-generation cephalosporin should be substituted. A single dose of long-acting chloramphenicol or cetriaxone is used for treatment of epidemic meningococcal meningitis in sub-Saharan Africa. Septicaemic shock and raised intracranial pressure in meningitis are particular problems in the management of meningococcal disease. Treatment of cases has practically no effect on the epidemiological pattern of the disease because it only reduces the fatality rate of the disease according to the treatment efficiency *(3)*. Isolation of cases is of limited usefulness in controlling epidemics because the carriers outnumber cases.

(b) CARRIERS : Treatment with penicillin does not eradicate the carrier state; more powerful antibiotics such as rifampicin are needed to eradicate the carrier state *(5)*.

(c) CONTACTS : Close contacts of persons with confirmed meningococcal disease are at an increased risk of developing meningococcal illness. Antibiotics are effective in preventing additional cases through eradicating carriage of the invasive strain. Most secondary case occur within the first 72 hours after presentation of the index case; risk of secondary disease decreases to near baseline by 10–14 days. Close contacts include household, child care, and preschool contacts. In outbreaks involving limited populations, those with direct, prolonged contact with a case of meningococcal disease may also be offered clearance treatment. Ideally, where indicated, treatment should be started within 24 hours of identification of the index case. Antibiotics effective for this purpose include rifampicin, ciprofloxacin, ceftriaxone or azithromycin.

(d) MASS CHEMOPROPHYLAXIS : This is in fact mass medication of the total population some of which are not infected. It is recommended that mass chemoprophylaxis be restricted to closed and medically supervised communities. Mass treatment causes an immediate drop in the incidence rate of meningitis and in the proportion of carriers. The efficacy of this preventive measure depends to a large extent on the population coverage *(3)*. The drugs of choice are ciprofloxacin, minocycline, spiramycin and ceftriaxone.

(e) VACCINE *(1, 4)* : Currently available meningococcal vaccines include polysaccharide vaccines and polysaccharide–protein conjugate vaccines. The conjugate vaccines are more immunogenic and also induce immunogenic memory. Both vaccines are available against meningococci of serogroup A, C, W135 and Y.

Polysaccharide vaccines : Internationally marketed meningococcal polysaccharide vaccines are available in bivalent (A, C), trivalent (A,C, W 135), and quadrivalent (A, C, W135, Y) formulations. The vaccines contain 50 µg of each of the individual polysaccharides. Meningococcal polysaccharide vaccines are administered as a single dose to persons ≥2 years old; most of these vaccines are given subcutaneously.

Adverse reactions to polysaccharide meningococcal vaccines are usually mild; the most frequent reaction is 1–2 days of pain and redness at the site of injection, which occur in 4%–56% of vaccine recipients. Transient fever is reported in <5% of recipients.

Conjugate vaccines : Licensed meningococcal conjugate vaccines are monovalent (A or C) or quadrivalent (A, C, W135, Y), and also include a combination vaccine based on *Haemophilus influenzae type b* and *Neisseria meningitidis* serogroup C vaccines (Hib/MenC).

Conjugate vaccine should be given as intramuscular injection, preferably in the deltoid muscle (or in the anterolateral aspect of the upper thigh in children <12 months of age).

Monovalent Men A conjugate vaccine should be given as a single dose to individuals 1–29 years of age. For monovalent Men C conjugate vaccine, one single intramuscular dose is recommended for children aged ≥12 months, teenagers and adults. Children 2–11 months of age require 2 dose administration at an interval of at least 2 months and a booster about 1 year thereafter. Quadrivalent vaccines are administered as a single dose to individuals aged ≥ 2 years.

Meningococcal vaccines should be stored at 2–8°C. Conjugate vaccines are preferred over polysaccharide vaccines due to their potential for herd protection and their increased immunogenicity, particularly in children < 2 years of age. Both vaccines are safe when used during pregnancy *(1)*. WHO recommends that countries with high or medium endemic rates of invasive meningococcal disease and countries with frequent epidemics should introduce appropriate large-scale meningococcal vaccination programmes *(1)*.

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ACUTE RESPIRATORY INFECTIONS

Infections of the respiratory tract are perhaps the most common human ailment. While they are a source of discomfort, disability and loss of time for most adults, they are a substantial cause of morbidity and mortality in young children and the elderly. Many of these infections run their natural course in older children and in adults without specific treatment and without complications. However, in young infants, small children and in the elderly, or in persons with impaired respiratory tract reserves, it increases the morbidity and mortality rates.

Acute respiratory infections (ARI) may cause inflammation of the respiratory tract anywhere from nose to alveoli, with a wide range of combination of symptoms and signs. ARI is often classified by clinical syndromes depending on the site of infection and is referred to as ARI of upper (AURI) or lower (ALRI) respiratory tract. The upper respiratory tract infections include common cold, pharyngitis and otitis media. The lower respiratory tract infections include epiglottitis, laryngitis, laryngotracheitis, bronchitis, bronchiolitis and pneumonia.

The clinical features include running nose, cough, sore throat, difficult breathing and ear problem. Fever is also common in acute respiratory infections. Most children with these infections have only mild infection, such as cold or cough. However, some children may have pneumonia which is a major cause of death. In less developed countries, measles and whooping cough are important causes of severe respiratory tract infection.

Problem statement

Pneumonia continues to kill more children under five worldwide than any other single infectious disease, claiming an estimated 0.80 million children's life in 2018. Young children are at particularly high risk of developing severe pneumonia disease and death. More than 80 per cent of deaths associated with pneumonia occur in children during

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the first 2 years of life. It is more prevalent in the developing countries in South Asia and sub-Saharan Africa *(1)*. Before widespread introduction of PCV into national immunization programmes since 2006, the reported mean annual incidence of invasive pneumococcal disease (IPD) in children less than 2 years of age was 44.4 per lakh population per year in Europe and United States of America, 60 per 100,000 population in South Africa and somewhere in between in Asia and Latin America *(2)*.

It is difficult to determine the proportion of *Streptococcus pneumoniae* to pneumonia cases. In a compilation data, it was found to be responsible for 78 per cent of the lobar pneumonia cases and 13 per cent of bronchopneumonia cases.

The other common causes of pneumonia are *Haemophilus influenzae* type b (the second most common cause of pneumonia), respiratory syncytial virus is the most common viral cause of pneumonia, and in HIV infected infants *pneumocystis jirovecii* is the most common cause of pneumonia responsible for at least one quarter of all pneumonia deaths in HIV-infected infants *(3)*.

Continuous spread of infection from nasopharynx can cause otitis media or sinusitis. Pneumonia is often caused by aspiration of pneumococci from nanopharynx and may also be caused by blood-borne spread. When associated with bacteraemia, pneumonia is classified as IPD. Case fatality rates from IPD in children can be high, ranging up-to 20 per cent for septicaemia and 50 per cent for meningitis in low middle income countries. Long-term neurological sequelae such as hearing loss, mental retardation, motor abnormalities and seizures have been observed in 24.7 per cent of survivors of pneumococcal meningitis.

The risk of pneumococcal disease decreases after early childhood and increases again in old age, suggesting acquisition of natural immunity and loss of immunity in older adults due to immunosenescence and increased susceptibility due to other diseases. The mechanism of natural immunity are not fully understood *(2)*.

H. influenzae colonizes the upper respiratory tract of humans and is transmitted person–to–person by inhalation of respiratory droplets or by direct contact with respiratory tract secretions. Neonates can acquire infection by aspiration of amniotic fluid or contact with genital tract secretions during delivery. The contagious potential of invasive hib disease is considered to be limited. However, certain circumstances particularly close contact with a case (patient e.g. household, child care, institutional settings) can lead to outbreaks of direct secondary transmission of the disease *(4)*.

The exposure factors include household crowding, small household size, child care attendance, low socio-economic status, low parental educational levels and school-age siblings, chronic diseases, HIV infection, immunoglobulin deficiency, chemotherapy or stem cell transplant *(4)*.

In India, in the states and districts with high infant and child mortality rates, ARI is one of the major causes of death. ARI is also one of the major reasons for which children are brought to the hospitals and health facilities. Hospital records from states with high infant mortality rates show that upto 13% of inpatient deaths in paediatric wards are due to ARI. The proportion of death due to ARI in the community is much higher as many children die at home. The reason for high case fatality may be that children are either not brought to the hospitals or brought too late.

In India during 2022, about 1,93,92,926 cases of ARI were reported with 5,132 deaths. Same year 4,25,555 cases of pneumonia were reported with 2,692 deaths *(5)*.

Epidemiological determinants

Agent factors

The microbial agents that cause acute respiratory infections are numerous and include bacteria and viruses. Even within species they can show a wide diversity of antigenic type. The agents are those most frequently encountered in a normal population. The bacteria involved can all be isolated with varying frequency from carriers, and cause illness in only minority of infected persons. The viruses that have been found in association with acute respiratory disease are numerous. They are the primary cause of the great majority of respiratory illnesses. However, the severity of the illness is often determined by whether or not secondary bacterial infection occurs, particularly in the case of lower respiratory tract infections. The agents considered to be capable of acute respiratory diseases, the age group most frequently affected, and the characteristic clinical features are as shown in Table 1.

Host factors

Small children can succumb to the disease within a matter of days. Case fatality rates are higher in young infants and malnourished children. Age-specific mortality rates show wide differences between countries. In general, rates tend to be high in infants and young children, and in the elderly in all countries, although the age group with the highest rates can differ. In developing countries where malnutrition and low birth weight is often a major problem, the rates in children tend to be the highest. By contrast, in developed countries respiratory infections are only exceptionally fatal in infants but are commonly terminal in the elderly.

Upper respiratory tract infections, e.g., common cold and pharyngitis are several times higher in children than in adults. Rates for pharyngitis and otitis media increase from infancy to a peak at the age of 5 years. Illness rates are highest in young children and decrease with the increasing age, except in the third decade of life when young adults are exposed to infection by their own young children. Adult women experience more illness than men. The greater exposure of women to small children may be responsible for this. Under 3 years of age boys are affected more often and more severely.

Risk factors

Many risk factors for respiratory tract infections have been identified. They include not only the climatic conditions but also the housing, level of industrialization and socio-economic development. In developing countries, overcrowded dwellings, poor nutrition, low birth weight and intense indoor smoke pollution underline the high rates. Local mortality rates are particularly affected by the extent of influenza epidemics. Studies in developed countries have shown that higher rate of infection is common in younger sibling of school going children who introduce infection into the household. Maternal cigarette smoking has also been linked to increased occurrence of respiratory tract infections during the first year of life. Children from low socio-economic status tend to have more respiratory infections. The infection is more common in preschool children attending day-care centres. The infections tend to be more common in urban communities than in rural communities.

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TABLE 1

The agents causing ARI, age group affected and clinical features

Agent	Age group (s) most frequently affected	Characteristic clinical features
Bacteria		
Bordetella pertussis	Infants and young children	Paroxysmal cough
Corynebacterium diphtheriae	Children	Nasal/tonsillar/pharyngeal membranous exudate ± severe toxaemia
Haemophilus influenzae	Adults	Acute exacerbations of chronic bronchitis pneumonia
	Children	Acute epiglottitis (*H.influenzae* type B)
Klebsiella pneumoniae	Adults	Lobar pneumonia ± lung abscess
Legionella pneumophila	Adults	Pneumonia
Staphylococcus pyogenes	All ages	Lobar and broncho-pneumonia (esp. secondary to influenza) ± lung abscess
Streptococcus pneumoniae	All ages	Pneumonia (lobar or multilobular) Acute exacerbations of chronic bronchitis
Streptococcus pyogenes	All ages	Acute pharyngitis and tonsillitis
Virus		
Adenoviruses – endemic types (1,2,5)	Young children	Lower respiratory
– epidemic types (3,4,7)	Older children and young adults	Febrile pharyngitis and influenza-like illness
Enteroviruses (ECHO and Coxsackie)	All ages	Variable respiratory
Influenza A	All ages	Fever, aching, malaise, variable respiratory
B	School children	Occasional primary pneumonia Secondary bacterial pneumonia in elderly
C	Rare	Mild upper respiratory
Measles	Young children	Variable respiratory with characteristic rash
Parainfluenza 1	Young children	Croup re-infection in later life : mild upper respiratory
2		
3	Infants	Bronchiolitis and pneumonia
Respiratory syncytial virus	Infants and young children	Severe bronchiolitis and pneumonia
Rhinoviruses (multiple serotypes)	All ages	Common cold
Coronavirus		
Other agents		
Chlamydia type B (Psittacosis)	Adults exposed to infected birds	Influenza-like illness and atypical pneumonia
Coxiella burnetti (Q fever)	Adults exposed to sheep and cattle	Atypical pneumonia
Mycoplasma pneumoniae	School children and young adults	Febrile bronchitis and atypical pneumonia

Source : *(6)*

Mode of transmission

All the causative organisms are normally transmitted by the airborne route. As most viruses do not survive for long outside the respiratory tract, the chain of transmission is maintained by direct person-to-person contact.

CONTROL OF ACUTE RESPIRATORY INFECTIONS

Improving the primary medical care services and developing better methods for early detection, treatment and where possible, prevention of acute respiratory infections is the best strategy to control ARI. Effective reduction of mortality due to pneumonia is possible if children suffering from pneumonia are treated correctly. Education of mother is also crucial since compliance with treatment and seeking care promptly when signs of pneumonia are observed, are among the key factors which determine the outcome of the disease. The recommendations by WHO for the management of acute respiratory infections in children and the practical guidelines for out-patient care are discussed below *(7)*. The same guidelines are followed in India.

Clinical assessment

History taking and clinical assessment is very important in the management of the acute respiratory infections. Note the age of the child, for how long the child is coughing, whether the child is able to drink (if the child is aged 2 months upto 5 years), has the young infant stopped feeding well (child less than 2 months), has there been any antecedent illness such as measles, does the child have fever, is the child excessively drowsy or difficult to wake (if yes, for how long), did the child have convulsions, is there irregular breathing, short periods of not breathing or the child turning blue, any history of treatment during the illness.

Physical examination

Look and listen for the following :

(1) COUNT THE BREATHS IN ONE MINUTE : As the children get older, their breathing rate slows down. Therefore, the cut-off point used to determine if a child has fast breathing will depend on the age of the child. Count the respiratory rate for full one minute using the second's hand of the watch looking at the abdominal movement or lower chest when the child is calm. The chest and abdomen must be exposed for counting. Increased respiratory rate is of significance only if it persists.

Fast breathing is present when the respiratory rate is :

- 60 breaths per minute or more in a child less than 2 months of age
- 50 breaths per minute or more in a child aged 2 months upto 12 months
- 40 breaths per minute or more in a child aged 12 months upto 5 years.

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However, repeat the count for a young infant (age less than 2 months) if the count is 60 breaths per minute or more. This is important because the breathing rate of young infant is often erratic. Occasionally young infants stop breathing for a few seconds, and then breath very rapidly for a short period.

(2) LOOK FOR CHEST INDRAWING : Look for chest indrawing when the child breaths IN. The child has indrawing *if the lower chest wall goes in when the child breaths in*. Chest indrawing occurs when the effort required to breath in, is much greater than normal.

(3) LOOK AND LISTEN FOR STRIDOR : A child with stridor makes a harsh noise when breathing IN. Stridor occurs when there is narrowing of the larynx, trachea or epiglottis which interferes with air entering the lungs. These conditions are often called *croup*.

(4) LOOK FOR WHEEZE : A child with wheezing makes a soft whistling noise or shows signs that breathing *OUT* is difficult, wheezing is caused by narrowing of the air passage in the lungs. The breathing–out phase takes longer than normal and requires effort.

If the child is wheezing, ask the mother if her child has had a previous episode of wheezing within the past year. If so, the child should be classified as having recurrent wheeze.

(5) See if the child is abnormally sleepy or difficult to wake. An abnormally sleepy child is drowsy most of the time when he or she should be awake and alert.

(6) Feel for fever or low body temperature.

(7) CHECK FOR SEVERE MALNUTRITION : Malnutrition when present is a high risk factor and case fatality rates are higher in such children. In severely malnourished children with pneumonia, fast breathing and chest indrawing may not be as evident as in other children. A severely malnourished child may have an impaired or absent response to hypoxia and a weak or absent cough reflex. These children need careful evaluation for pneumonia as well as careful management.

(8) Cyanosis is a sign of hypoxia. Cyanosis must be checked in good light.

CLASSIFICATION OF ILLNESS AND TREATMENT

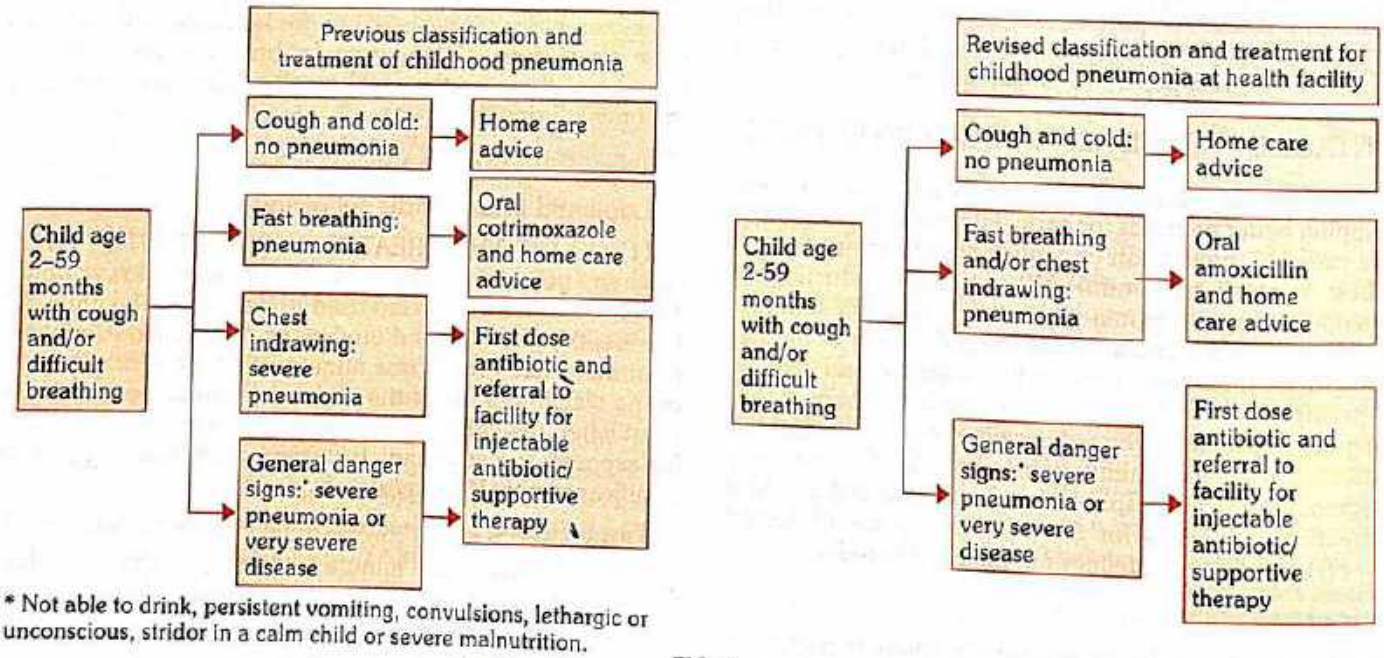
In the early 1980s, the global burden of childhood mortality due to pneumonia led the World Health Organization to develop a pneumonia control strategy suitable for countries with limited resources and constrained health systems. Management of pneumonia cases formed the cornerstone of this strategy. Simple signs were identified to classify varying severities of pneumonia in settings with little or no access to diagnostic technology; the classifications determined the appropriate case management actions. These pneumonia classification and management guidelines were based on evidence generated in the 1970s and early 1980s, and were incorporated into the original version of Integrated Management of Childhood Illness (IMCI). In the intervening time, new evidence has emerged which prompted the development of revised guidelines *(7)*.

The revisions include changing the recommendation for the first-line antibiotic and re-defining the classification of pneumonia severity. The data shows that oral amoxicillin is preferable to oral cotrimoxazole for the treatment of "fast breathing pneumonia" and is equivalent to injectable penicillin/ampicillin in cases of "chest indrawing pneumonia". Hence, in a programmatic context, the distinction between previously defined "pneumonia" (fast breathing) and "severe pneumonia" (chest indrawing) loses its significance. The new classification is therefore simplified to include only two categories of pneumonia; "pneumonia" with fast breathing and/or chest indrawing, which requires home therapy with oral amoxicillin, and "severe pneumonia", pneumonia with any general danger sign, which requires referral and injectable therapy. Fig. 1 shows the difference between previous and revised classification and the treatment recommended.

A. Child aged 2 months upto 5 years

The revised recommendations for children aged 2 months to 59 months are as follows *(7)* :

1. Children with fast breathing pneumonia with no chest indrawing or general danger sign should be treated with



* Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition.

FIG. 1

Comparison of previous and revised classification and treatment of childhood pneumonia at health facility

Source : *(7)*

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oral amoxicillin : at least 40 mg/kg/dose twice daily (80 mg/kg/day) for five days. In areas with low HIV prevalence, give amoxicillin for three days.
Children with fast-breathing pneumonia who fail on first-line treatment with amoxicillin should have the option of referral to a facility where there is appropriate second-line treatment.

2. Children age 2–59 months with chest indrawing pneumonia should be treated with oral amoxicillin : at least 40 mg/kg/dose twice daily for five days.
3. Children aged 2–59 months with severe pneumonia should be treated with parenteral ampicillin (or penicillin) and gentamicin as a first-line treatment.
   - Ampicillin : 50 mg/kg, or benzyl penicillin: 50,000 units per kg IM/IV every 6 hours for at least five days
   - Gentamicin : 7.5 mg/kg IM/IV once a day for at least five days

   Ceftriaxone should be used as a second-line treatment in children with severe pneumonia having failed on the first-line treatment.
4. Ampicillin (or penicillin when ampicillin is not available) plus gentamicin or ceftriaxone are recommended as a first-line antibiotic regimen for HIV-infected and HIV-exposed infants and for children under 5 years of age with chest indrawing pneumonia or severe pneumonia.
   For HIV-infected and HIV-exposed infants and for children with chest indrawing pneumonia or severe pneumonia, who do not respond to treatment with ampicillin or penicillin plus gentamicin, ceftriaxone alone is recommended for use as second-line treatment.
5. Empiric cotrimoxazole treatment for suspected *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia (PCP) is recommended as an additional treatment for HIV-infected and HIV-exposed infants aged from 2 months up to 1 year with chest indrawing or severe pneumonia.
   Empirical cotrimoxazole treatment for *Pneumocystis jirovecii* pneumonia (PCP) is not recommended for HIV-infected and HIV-exposed children over 1 year of age with chest indrawing or severe pneumonia.

Dosages of amoxicillin for pneumonia treatment at health facilities have been revised to reflect three age bands as shown in Table 2 : 2 months up to 12 months (4–<10 kg); 12 months up to 3 years (10–<14 kg); 3 years up to 5 years (14–19 kg). Dosages and age bands for treatment of fast breathing pneumonia by community health workers (CHWs) have not changed.

The revised recommendations present a number of advantages such as :

- Oral amoxicillin can be used to treat both fast breathing pneumonia and chest indrawing pneumonia;
- Pneumonia classification and management are simplified to two categories instead of three;
- Access to antibiotic treatment closer to home is increased;
- The need for referrals to higher level facilities is decreased;
- The probability of hospitalization and thus the risk of nosocomial and injection borne diseases is reduced;
- The probability of antimicrobial resistance is diminished, due to better adherence to the simplified treatment; and
- Training of health workers is simplified.

B. Pneumonia in Young Infants under 2 Months of Age

The treatment in these conditions is, basically the same. The child must be hospitalized. Treatment may be started by the health worker before referring the child. If pneumonia is suspected the child should be treated with intramuscular injections of benzyl penicillin or injection ampicillin, along with injection gentamycin. Chloramphenicol is not recommended as the first line of treatment in young infants. The treatment plan is as shown in Table 3.

TABLE 3

Treatment of pneumonia in children aged less than 2 months

ANTIBIOTIC	DOSE	FREQUENCY	
		Age < 7 days	Age 7 days to 2 months
Inj. Benzyl Penicillin	50,000 IU/kg/dose	12 hourly	6 hourly
OR			
Inj Ampicillin	50 mg/kg/dose	12 hourly	8 hourly
AND			
Inj. Gentamycin	2.5 mg/kg/dose	12 hourly	8 hourly

Besides antibiotics, therapy for the associated conditions, if any, must be instituted immediately. The child should be kept warm and dry. Breast-feeding must be promoted strongly as the child who is not breast-fed is at a much higher risk of diarrhoea.

MANAGEMENT OF AURI (NO PNEUMONIA)

Many children with presenting symptoms of cough, cold and fever do not have pneumonia (no fast breathing or chest indrawing) and DO NOT require treatment with antibiotics.

Antibiotics are not recommended for coughs and colds because majority of cases are caused by viruses and antibiotics are not effective, they increase resistant strains and cause side-effects while providing no clinical benefit, and are wasteful expenditure. Symptomatic treatment and care at home is generally enough for such cases. The mothers must be advised on how to take care of the child at home.

Prevention of Acute Respiratory Infections

Present understanding of risk factors of respiratory tract infection in childhood indicates several approaches for primary prevention. In developing countries, improved living conditions, better nutrition and reduction of smoke pollution indoors will reduce the burden of mortality and morbidity associated with ARI. Other preventive measures include better MCH care. Immunization is an important measure to

TABLE 2

Doses of amoxicillin for children 2–59 months of age with pneumonia

Tools	Category of pneumonia	Age/weight of child	Dosage of Amoxicillin dispersible tablets (250 mg)
ICCM tool for community health workers : no change	Fast breathing pneumonia	2 months up to 12 months (4–<10 kg)	1 tab twice a day × 5 days (10 tabs)
		12 months up to 5 years (10–19 kg)	2 tabs twice a day × 5 days (20 tabs)
IMCI tool for professional health workers at health facilities : revised	Fast breathing and chest indrawing pneumonia	2 months up to 12 months (4–<10 kg)	1 tab twice a day × 5 days (10 tabs)
		12 months up to 3 years (10–<14 kg)	2 tabs twice a day × 5 days (20 tabs)
		3 years up to 5 years (14–19 kg)	3 tabs twice a day × 5 days (30 tabs)

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reduce cases of pneumonia which occur as a complication of vaccine preventable disease, especially measles. It is obvious that community support is essential to reduce the disease burden. Families with young children must be helped to recognize pneumonia. Health promotional activities are specially important in vulnerable areas *(8)*.

Immunization

Vaccines hold promise of saving millions of children from dying of pneumonia. Three vaccines have potential of reducing deaths from pneumonia. These vaccines work to reduce the incidence of bacterial pneumonia.

1. MEASLES VACCINE

Pneumonia is a serious complication of measles and the most common cause of death associated with measles worldwide. Thus, reducing the incidence of measles in young children through vaccination would also help to reduce deaths from pneumonia. A safe and effective vaccine against measles is available for past 40 years. Please refer to page 166 for details.

2. HIB VACCINE

Haemophilus influenzae type B (Hib), is an important cause of pneumonia and meningitis among children in developing countries. Hib vaccine has been available for more than a decade. It reduces dramatically the incidence of Hib meningitis and pneumonia in infants and nasopharyngeal colonization by Hib bacteria. It's high cost has posed obstacle to its introduction in developing countries.

The vaccine is often given as a combined preparation with DPT and poliomyelitis vaccine. Three or four doses are given depending on the manufacturers and type of vaccine used, and is given intramuscularly. The vaccine schedule is at 6, 10, and 14 weeks of age or according to national immunization schedule. In many industrialized countries a booster dose is given between 12–18 months which provides additional benefit to limit burden of Hib disease among children *(9)*. For children more than 12 months of age, who have not received their primary immunization series a single dose is sufficient for protection. The vaccine is not generally offered to children aged more than 24 months *(9)*.

No serious side-effects have been recorded, and no contraindications are known, except for hyper-sensitivity to previous dose of vaccine. All conjugate vaccine have an excellent safety record, and where tested, do not interfere substantially with immunogenecity of other vaccines given simultaneously *(10)*.

3. PNEUMOCOCCAL PNEUMONIA VACCINE

a. *PPV23* : For years, the polysaccharide non-conjugate vaccine containing capsular antigens of 23 serotypes against this infection have been available for adults and children over 2 years of age. Children under 2 years of age and immunocompromised individuals do not respond well to the vaccine. It is recommended for selected groups, e.g., those who have undergone splenectomy or have sickle-cell disease, chronic diseases of heart, lung, liver or kidney; diabetes mellitus, alcoholism, generalized malignancies, organ transplants etc. In some industrialized countries like USA it is routinely advised for everyone aged above 65 years *(10)*.

A dose of 0.5 ml of PPV23 contains 25 micrograms of purified capsular polysaccharide from each 23 serotypes. For primary immunization, PPV23 is administered as a single intra-muscular dose preferably in the deltoid muscle or as subcutaneous dose. The vaccine should not be mixed in the same syringe with other vaccines, for e.g. with influenza vaccine, but may be administered at the same time by separate injection in the other arm. Simultaneous administration does not increase adverse events or decrease the antibody response to either vaccine. Protective capsular type-specific antibody levels generally develop by the third week following vaccination *(11)*.

Minor adverse reactions, such as transient redness and pain at the site of injection occur in 30–50 per cent of those who have been vaccinated, more commonly following subcutaneous administration. Local reactions are more frequent in recipients of the 2nd dose of the vaccine *(11)*.

b. *PCV* : Two conjugate vaccines are available since 2009, PCV_{10} and PCV_{13}. The PCV_7 conjugate vaccine is gradually being removed from the market *(1)*. Both PCV_{10} and PCV_{13} are preservative free and their recommended storage temperature is 2–8°C. The vaccine must not be frozen. The shake test is applicable to PCV vaccine.

For PCV administration to infants, WHO recommends 3 primary doses (the 3p+0 schedule) or, as an alternative, 2 primary doses plus one booster (the 2p+1 schedule). In 3p+0 schedule, vaccination can be initiated as early as 6 weeks of age with an interval betweeen doses of 4–8 weeks, with doses given at 6, 10 and 14 weeks or 2, 4, and 6 months, depending on programme convenience *(2)*.

If 2p+1 schedule is selected, the 2 primary doses are given during infancy as early as 6 weeks of age at an interval preferably of 8 weeks or more for young infant, and 4–8 weeks or more between primary doses for infants ≥7 months of age. One booster dose should be given between 9–15 months of age *(2)*.

The National Immunization Schedule of India recommends PCV for infants up to 1 year of age in three doses (2 primary doses and 1 booster dose) at 6 weeks, 14 weeks and 9 months. 0.5 ml is given using auto-disable syringe as intramuscular injection in the anterolateral aspect of the right mid thigh *(1)*.

PCV efficacy is more than 80 per cent for serotypes present in the vaccine. It can be co-administered with other UIP vaccines. If two injections are being given in the same limb, then they should be administered at least one inch apart *(1)*.

PCV is a safe vaccine. Severe reactions are extremely rare. The most common side effects are irritability, crying, swelling and tenderness at injection site, and transient fever >39°C (102°F). PCV should not be administered to children with severe allergic reaction to a prior dose, or to vaccines containing diphtheria toxoid, such as pentavalent vaccine *(1)*. It should not be given to a child with severe illness. It is not intended to be used for treatment of active infection.

HIV positive and preterm babies who have received their 3 primary doses of vaccine before reaching 12 months of age may benefit from a booster dose in the second year of life. Interrupted schedules should be resumed without repeating the previous doses *(2)*.

When primary immunization is initiated with one of these vaccines, it is recommended that remaining doses are administered with the same product. Interchangeability between PCV_{10} and PCV_{13} has yet not been documented. WHO recommends inclusion of PCVs in childhood immunization programme worldwide, particularly in countries with high under-five mortalities *(2)*.

The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea *(12)*

The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) proposes a

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cohesive approach to ending preventable pneumonia and diarrhoea deaths. It brings together critical services and interventions to create healthy environments, promotes practices known to protect children from disease, and ensures that every child has access to proven and appropriate preventive and treatment measures.

The specific goals for 2025 are to:

- reduce mortality from pneumonia in children less than 5 years of age to fewer than 3 per 1000 live births;
- reduce mortality from diarrhoea in children less than 5 years of age to fewer than 1 per 1000 live births;
- reduce the incidence of severe pneumonia by 75% in children less than 5 years of age as compared to 2010 levels;
- reduce the incidence of severe diarrhoea by 75% in children less than 5 years of age as compared to 2010 levels;
- reduce by 40% the global number of children less than 5 years of age who are stunted as compared to 2010 levels.

These goals are ambitious and will require significant political will and mobilization of additional resources if they are to be reached.

Coverage targets to be maintained or reached have also been set to define efforts needed to attain the above goals. These are:

- By the end of 2025:
  - 90% full-dose coverage of each relevant vaccine (with 80% coverage in every district);
  - 90% access to appropriate pneumonia and diarrhoea case management (with 80% coverage in every district);
  - at least 50% coverage of exclusive breast-feeding during the first 6 months of life;
  - virtual elimination of paediatric HIV.
- By the end of 2030:
  - universal access to basic drinking-water in health care facilities and homes;
  - universal access to adequate sanitation in health care facilities by 2030 and in homes by 2040;
  - universal access to handwashing facilities (water and soap) in health care facilities and homes;
  - universal access to clean and safe energy technologies in health care facilities and homes.

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SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

Severe acute respiratory syndrome (SARS) is a communicable viral disease, caused by a new strain of coronavirus, which differs considerably in genetic structure from previously recognized coronavirus.

The most common symptoms in patient progressing to SARS include fever, malaise, chills, headache myalgia, dizziness, cough, sore throat and running nose. In some cases there is rapid deterioration with low oxygen saturation and acute respiratory distress requiring ventilatory support. It is capable of causing death in as many as 10 per cent cases *(1)*.

Chest X-ray findings typically begin with a small, unilateral patchy shadowing, and progress over 1–2 days to become bilateral and generalized, with interstitial/confluent infiltration. Adult respiratory distress syndrome has been observed in a number of patients in the end stages.

Problem statement

The earliest case was traced to a health care worker in China, in late 2002, with rapid spread to Hong Kong, Singapore, Vietnam, Taiwan and Toranto. As of early August 2003, about 8,422 cases were reported to the WHO from 30 countries with 916 fatalities *(2)*.

Incubation period

The incubation period has been estimated to be 2 to 7 days, commonly 3 to 5 days *(1)*.

Mode of transmission

The primary mode of transmission appears to be through direct or indirect contact of mucous membranes of eyes, nose, or mouth with respiratory droplets or fomites. The use of aerosol–generating procedures (endotracheal intubation, bronchoscopy, nebulization treatments) in hospitals may amplify the transmission of the SARS coronavirus. The virus is shed in stools but the role of faecal–oral transmission is unknown. The natural reservoir appears to be the horseshoe bat (which eats and drops fruits ingested by civets, the earlier presumed reservoir and a likely amplifying host).

The SARS virus can survive for hours on common surfaces outside the human body, and up to four days in human waste. The virus can survive at least for 24 hours on a plastic surface at room temperature, and can live for extended periods in the cold.

Case definition *(4)*

The case definition is based on current understanding of the clinical features of SARS, and available epidemiological data. It may be revised as new information accumulates.

Case definition for notification of SARS under the International Health Regulation (2005)

In the period following an outbreak of SARS, a notifiable case of SARS is defined as an individual with laboratory confirmation of infection with SARS coronavirus (SARS-CoV) who either fulfils the clinical case definition of SARS or has worked in a laboratory handling live SARS-CoV or storing clinical specimens infected with SARS-CoV.

Clinical case definition of SARS

1. A history of fever, or documented fever
   AND
2. One or more symptoms of lower respiratory tract illness (cough, difficulty in breathing, shortness of breath)

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AND

3. Radiographic evidence of lung infiltrates consistent with pneumonia or acute respiratory distress syndrome (ARDS) or autopsy findings consistent with the pathology of pneumonia or ARDS without an identifiable cause

AND

4. No alternative diagnosis fully explaining the illness.

Diagnostic tests required for laboratory confirmation of SARS

(a) Conventional reverse transcriptase PCR (RT-PCR) and real-time reverse transcriptase PCR (real-time RT-PCR) assay detecting viral RNA present in:

1. At least 2 different clinical specimens (e.g. nasopharyngeal and stool specimens)
   OR
2. The same clinical specimen collected on 2 or more occasions during the course of the illness (e.g. sequential nasopharyngeal aspirates)
   OR
3. A new extract from the original clinical sample tested positive by 2 different assays or repeat RT-PCR or real-time RT-PCR on each occasion of testing
   OR
4. Virus culture from any clinical specimen.

(b) Enzyme-linked immunosorbent assay (ELISA) and immunofluorescent assay (IFA)

1. Negative antibody test on serum collected during the acute phase of illness, followed by positive antibody test on convalescent-phase serum, tested simultaneously
   OR
2. A 4-fold or greater rise in antibody titre against SARS-CoV between an acute-phase serum specimen and a convalescent-phase serum specimen (paired sera), tested simultaneously.

In the absence of known SARS-CoV transmission to humans, the positive predictive value of a SARS-CoV diagnostic test is extremely low; therefore, the diagnosis should be independently verified in one or more WHO international SARS reference and verification network laboratories. Every single case of SARS must be reported to WHO.

Epidemiological aspect

Health care workers, especially those involved in procedures generating aerosols, accounted for 21 per cent of all cases. Maximum virus excretion from the respiratory tract occurs on about day 10 of illness and then declines. The efficiency of transmission appears to be greatest following exposure to severely ill patients or those experiencing rapid clinical deterioration, usually during the second week of illness. When symptomatic cases were isolated within 5 days of the onset of illness, few cases of secondary transmission occurred. There was no evidence that patient transmits infection 10 days after fever has resolved.

Children are rarely affected by SARS. To date, there have been two reported cases of transmission from children to adults and no report of transmission from child to child. Three separate epidemiological investigations have not found any evidence of SARS transmission in schools. Furthermore, no evidence of SARS has been found in infants of mothers who were infected during pregnancy.

International flights have been associated with the transmission of SARS from symptomatic probable cases to passengers or crew. WHO recommends exit screening and other measures to reduce opportunities for further international spread associated with air travel during the epidemic period.

Complications

As with any viral pneumonia, pulmonary decompensation is the most feared problem. ARDS occurs in about 16% patients, and about 20–30% of patients require intubation and mechanical ventilation. Sequelae of intensive care include infection with nosocomial pathogens, tension pneumothorax from ventilation at high peak pressures, and non-cardiogenic pulmonary edema.

Treatment

Severe cases require intensive support. Although a number of different agents including ribavirin (400–600 mg/d and 4 g/d), lopinavir/ritonavir (400 mg/100 mg), interferon type 1, intravenous immunoglobulin, and systemic cortiocosteroids were used to treat SARS patients during the 2003 epidemic, the treatment efficacy of these therapeutic agents remains inconclusive and further research is needed. Subsequent studies with ribavirin show no activity against the virus in vitro, and a retrospective analysis of the epidemic in Toronto suggests worse outcomes in patients who receive the drug *(5)*.

Prognosis

The overall mortality rate of identified cases is about 14%. Mortality is age-related, ranging from less than 1% in persons under 24 years of age to greater than 50% in persons over 65 years of age. Poor prognostic factors include advanced age, chronic hepatitis B infection treated with lamivudine, high initial or high peak lactate dehydrogenase concentration, high neutrophil count on presentation, diabetes mellitus, acute kidney disease, and low counts of CD4 and CD8 on presentation. Many subclinical cases probably go undiagnosed. Seasonality, as with influenza, is not established *(5)*.

Prevention

As there is no vaccine against SARS, the preventive measures for SARS control are appropriate detection and protective measures which include :

1. Prompt identification of persons with SARS, their movements and contacts;
2. Effective isolation of SARS patients in hospitals;
3. Appropriate protection of medical staff treating these patients;
4. Comprehensive identification and isolation of suspected SARS cases;
5. Simple hygienic measures such as hand-washing after touching patients, use of appropriate and well-fitted masks, and introduction of infection control measures;
6. Exit screening of international travellers;
7. Timely and accurate reporting and sharing of information with other authorities and/or governments.

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CORONAVIRUS DISEASE-19

Coronavirus disease-2019 (COVID-19) is caused by SARS-CoV-2, a newly emergent coronavirus, that was first recognized in Wuhan, China, in December 2019. Genetic sequencing of the virus suggests that it is a betacoronavirus closely linked to SARS virus. It is from the family of single-stranded RNA virus (+ss RNA) with a crown like appearance

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under an electronic microscope, of approximately 60–140 nm diameter, contains large widely spread club or petal shaped spikes. Although high temperature decreases the replication of the virus, it can resist the cold temperature. It is sensitive to ultraviolet rays, and is effectively inactivated by lipid solvents including ether (75 per cent), ethnol, chlorine-containing disinfectants, peroxyacetic acid and chloroform except for chlorhexidine *(1)*.

The dynamics of SARS-CoV-2 are currently unknown, but it is speculated that it has an animal origin.

Global scenario

In late December 2019, investigation of a cluster of pneumonia cases of unknown origin in Wuhan, China, resulted in identification of a novel coronavirus. The virus is distinct from both Severe Acute Respiratory Syndrome (SARS) coronavirus and Middle East Respiratory Syndrome (MERS) coronavirus, although closely related. Early epidemiological findings suggest that the virus is more contagious than its predecessors. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a newly identified pathogen and it is assumed that there is no existing human immunity to the virus. Every one is susceptible, although there may be risk factors that increase an individuals illness severity.

The disease since its first detection in China, spread to over 220 countries/territories. COVID-19 was declared a Pandemic by WHO on 11th March 2020, resulting in shift of focus from China to Europe and North America and later on to the world. As such WHO advised countries to take a whole-of-government, whole-of-society approach, built around a comprehensive strategy to prevent disease, save lives and minimize the effect. Countries closed their borders against travel related activities (by air, road, railway or sea), and lockdown was imposed to minimize the public movements.

The pandemic has taught the world that "global problem requires global solution". International co-operation is the requirement of the day. Whether in detection of virus or development of vaccines or action on economic and social fronts. COVID-19 has imposed many restrictions on our daily behaviour whether it is social distancing or wearing masks. We have also discovered that work-from-home-study-from-home, and shop-from-home, no visit to malls and markets are workable concepts. E commerce portals witnessed record traffic, which may become a permanent feature *(2)*.

As of April 13, 2024, the coronavirus tracker is no longer being updated due to the unfeasibility of providing statistically valid global data, as the majority of countries have now stopped reporting the disease. Globally, the COVID-19 pandemic led to 14.9 million excess deaths and cost 336.8 million years of life lost in 2020–2021. This means that, on an average, each death directly or indirectly attributed to the COVID-19, 22 years of life lost. COVID-19 is a stark reminder that infectious diseases can emerge or re-emerge to cause harm potentially to everyone. The COVID-19 has highlighted the inequality of access to health care system, especially among the vulnerable population and developing nations. In addition, pandemic exposed inequality in health emergency preparedness around the world *(3)*.

When compared globally, India's cases per million population were amongst the lowest in the world. Like-wise the number of deaths per million was also one of the lowest. USA reported the highest number of cases and deaths.

SARS-CoV-2 variants

Viruses constantly change through mutation and sometimes these mutations result in a new variant of the virus. Some variants emerge and disappear while others persist. Most changes have little or no impact on the virus properties. However, some changes may affect the virus's properties, such as how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools or public health and social measures *(4)*.

Scientists monitor all variants but may classify certain ones as variants being monitored, variants of interest, variants of concern and variants of high consequence. Some variants spread more easily and quickly than other variants, which may lead to more cases of COVID-19. Even if a variant causes less severe disease in general, an increase in the overall number of cases could cause an increase in hospitalizations, put more strain on healthcare resources and potentially lead to more deaths.

Variants of concern

Following is the variant of concern :

Omicron - B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5.

First identified in South Africa. Spreads more easily than other variants. Data suggest that Omicron is less severe in general. However, a surge in cases may lead to significant increase in hospitalization and death. Breakthrough infection in people who are vaccinated are expected but being up to date on recommended vaccine, is effective at preventing severe illness, hospitalization and death.

Variants being monitored (VBM)

Variants designated as VBM include those where data indicates there is a potential or clear impact on approved or authorized medical countermeasures, or that have been associated with more severe disease or increased transmission but are no longer detected, or are circulating at very low levels. These variants do not pose a significant and imminent risk to public health.

The variants being monitored are as follows *(5)* :

WHO Label	Pango Lineage
Alpha	B.1.1.7 and Q lineages
Beta	B.1.351 and descendent lineages
Gamma	P.1and descendent lineages
Delta	B.1.617.2 and AY lineages
Epsilon	B.1.427 B.1.429
Eta	B.1.525
Iota	B.1.526
Kappa	B.1.617.1
N/A	B.1.617.3
Zeta	P.2

INDIA

In India, the first case of COVID-19 was reported on 30th January 2020 in Kerala. India currently has the largest number of confirmed cases in Asia. The outbreak of the disease was declared an epidemic and Epidemic Disease Act, 1897 was invoked leading to temporary closure of educational, religious, entertainment and commercial establishments. It was followed by gradual un-lockdown spread in 6 phases (one month each) upto 30th November 2020.

A three-tier arrangement of health facilities was created for appropriate management of COVID-19 cases : [(i) COVID Care Centre with isolation beds for mild or pre-symptomatic cases; (ii) Dedicated COVID Health Centre (DCHC) with oxygen supported isolation beds for moderate cases; and (iii) Dedicated COVID Hospital (DCH) with ICU

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beds for severe cases). Tertiary care hospitals under ESIC, Defence, Railways, paramilitary forces, Steel Ministry etc. leveraged for case management.

The top five states contributing to over 80 per cent active cases were Kerala, Maharashtra, Tamil Nadu, West Bengal and Karnataka. In India, about 92 per cent of the reported cases were having mild disease, 5.8 per cent cases required oxygen therapy and about 1.7 per cent cases required intensive care *(6)*.

As on April 13, 2024, India reported a cumulative total of 4,50,35,393 cases with 5,33,570 deaths with 4,50,34,776 closed case (cases which had an outcome), 4,45,01,206 (99 per cent) recovered/discharged cases, during the COVID-19 pandemic *(6A)*.

Aarogya Setu App : Aarogya Setu App was launched by the Government of India on the 2nd April 2020, and is available in 11 languages including Hindi and English. It is one of the many location-based surveillance app. to let the users check whether they have been in contact with infected people by using location and bluetooth data from smartphones. The app. is available on both Android and iOS devices. It asks a set of questions to the user to identify whether they are at the risk of the coronavirus infection.

Mode of transmission *(7)*

Transmission of SARS-CoV-2 can occur through direct, indirect or close contact with infected people through secretions such as saliva and respiratory secretions or their respiratory droplets, which are expelled when infected person coughs, sneezes or talks. Respiratory droplets are >5–10 µm in diameter whereas droplets ≤5 µm in diameter are droplet nuclei or aerosols. Respiratory droplet transmission can occur when person is in close contact (within 1 metre) with an infected person who has respiratory symptoms or who is talking. In these circumstances, respiratory droplets that include virus can reach the mouth, nose or eyes of a susceptible person and can result in infection.

Airborne transmission is defined as spread of an infectious agent caused by transmission of droplet nuclei (aerosols) that remain infectious when suspended in air over long distances and time. Airborne transmission of SARS-CoV-2 can occur during medical procedures that generate aerosols or it may also spread in indoor settings with poor ventilation. High variability is suggested between individuals in terms of particle emission rate speech, with increased rates correlate with increased amplitude of vocalization *(7)*.

Fomite transmission is possible. Respiratory secretions or droplets expelled by infected persons can contaminate surfaces and objects, creating fomites. Viable SARS-CoV-2 virus and or RNA detected by RT-PCR can be found on those surfaces for periods ranging from hours to days, depending on the ambient environment (including temperature and humidity) and the type of surface. Therefore, transmission may also occur indirectly through touching surfaces in the immediate environment or objects contaminated with virus from an infected person, followed by touching mouth, eyes or nose.

SARS-CoV-2 has also been detected in other biological samples, including urine and faeces of some patients. However, there have been no published reports of transmission of SARS-CoV-2 through faeces or urine.

Period of communicability

Knowing when an infected person can spread COVID-19 is important. Evidence suggests that COVID-19 can be detected in people 1–3 days before their symptoms appear, with the highest viral loads as measured by RT-PCR, observed around the day of symptom onset, followed by a gradual decline over time. The duration of RT-PCR positivity generally appears to be 1–2 weeks for asymptomatic persons, and up to 3 weeks or more for patients with mild to moderate disease. In patients with severe COVID-19 disease, it can be longer *(8)*.

A study of the first patients in the Republic of Korea showed that 9–13 secondary cases occurred among household contacts.

Incubation period

2–14 days.

Clinical spectrum of SARS-CoV-2 infection

Most patients with COVID-19 predominantly have a respiratory tract infection. However, in a small proportion of cases, they can progress to a more severe and systemic disease characterized by the Acute Respiratory Distress Syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury *(8, 9)*. The definition of a case, a contact, and clinical presentation and risk factors are as shown in Table 1. Table 2 shows the progress of mild disease to a severe disease.

TABLE 1
Symptoms and risk factors associated with COVID-19

Clinical presentation	Presenting signs and symptoms of COVID-19 vary Most persons experience fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), myalgias (11–35%). Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, have also been reported. Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported. Older people and immunosuppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, delirium, and absence of fever. Symptoms such as dyspnoea, fever, gastrointestinal (GI) symptoms or fatigue due to physiologic adaptations in pregnant women, adverse pregnancy events, or other diseases such as malaria, may overlap with symptoms of COVID-19. Children might not have reported fever or cough as frequently as adults.
Risk factors for severe disease	Age more than 60 years (increasing with age). Underlying non-communicable diseases (NCDs): diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, chronic kidney disease, immunosuppression and cancer have been associated with higher mortality. Smoking.

Source : *(8, 9)*

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TABLE 2

COVID-19 disease severity

Mild disease		Symptomatic patients (Table 1) meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.
Moderate disease	Pneumonia	Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including $SpO_2 \geq 90\%$ on room air. Child with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing (in breaths/min) : < 2 months : ≥ 60; 2–11 months : ≥ 50; 1–5 years : ≥ 40. While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Severe disease	Severe pneumonia	Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or $SpO_2 < 90\%$ on room air. Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: – Central cyanosis or $SpO_2 < 90\%$; severe respiratory distress (e.g. fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. – Fast breathing (in breaths/min) : < 2 months : ≥ 60; 2–11 months : ≥ 50; 1–5 years : ≥ 40. While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Critical disease	Acute respiratory distress syndrome (ARDS)	Onset : within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms. Chest imaging : (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. Origin of pulmonary infiltrates : respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present. Oxygenation impairment in adults : – Mild ARDS : 200 mmHg < PaO_2/FiO_2[a] ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH_2O).[b] – Moderate ARDS : 100 mmHg < $PaO_2/FiO_2 \leq 200$ mmHg (with PEEP ≥ 5 cmH_2O).[b] – Severe ARDS : $PaO_2/FiO_2 \leq 100$ mmHg (with PEEP ≥ 5 cmH_2O).[b] Oxygenation impairment in children : note OI and OSI.[c] Use OI when available. If PaO_2 not available, wean FiO_2 to maintain $SpO_2 \leq 97\%$ to calculate OSI or SpO_2/FiO_2 ratio : – Bilevel (NIV or CPAP) ≥ 5 cmH_2O via full face mask : $PaO_2/FiO_2 \leq 300$ mmHg or $SpO_2/FiO_2 \leq 264$. – Mild ARDS (invasively ventilated) : $4 \leq OI < 8$ or $5 \leq OSI < 7.5$. – Moderate ARDS (invasively ventilated) : $8 \leq OI < 16$ or $7.5 \leq OSI < 12.3$. – Severe ARDS (invasively ventilated) : OI ≥ 16 or OSI ≥ 12.3.
Critical disease	Sepsis	Adults : acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinaemia. Children : suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome (SIRS) criteria,[e] of which one must be abnormal temperature or white blood cell count.
	Septic shock	Adults : persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65mmHg and serum lactate level > 2 mmol/L. Children : any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or weak pulse; fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia.

Other complications that have been described in COVID-19 patients include acute, life-threatening conditions such as : acute pulmonary embolism, acute coronary syndrome, acute stroke and delirium. Clinical suspicion for these complications should be heightened when caring for COVID-19 patients, and appropriate diagnostic and treatment protocols available.

a If altitude is higher than 1000 m, then the correction factor should be calculated as follows: $PaO_2/FiO_2 \times$ barometric pressure/760.

b When PaO_2 is not available, $SpO_2/FiO_2 \leq 315$ suggests ARDS (including in non-ventilated patients).

c Oxygenation Index (OI) is an invasive measurement of the severity of hypoxaemic respiratory failure and may be used to predict outcomes in paediatric patients. It is calculated as follows: percentage of fraction of inhaled oxygen multiplied by the mean airway pressure (in mmHg), divided by the partial pressure of arterial oxygen (in mmHg). Oxygen saturation index (OSI) is a non-invasive measurement and has been shown to be a reliable surrogate marker of OI in children and adults with respiratory failure. OSI replaces PaO_2 with oxygen saturation as measured by pulse oximetry (SpO_2) in the OI equation.

d The SOFA score ranges from 0 to 24 and includes points related to six organ systems: respiratory (hypoxaemia defined by low PaO_2/FiO_2); coagulation (low platelets); liver (high bilirubin); cardiovascular (hypotension); central nervous system (low level of consciousness defined by Glasgow Coma Scale); and renal (low urine output or high creatinine). Sepsis is defined by an increase in the sepsis-related SOFA score of ≥ 2 points. Assume the baseline score is 0 if data are not available.

e SIRS criteria : abnormal temperature (> 38.5°C or < 36°C); tachycardia for age or bradycardia for age if < 1 year; tachypnoea for age or need for mechanical ventilation; abnormal white blood cell count for age or > 10% bands.

ABBREVIATIONS : BP blood pressure; bpm beats per minute; CPAP continuous positive airway pressure; CT computed tomography; FiO_2 fraction of inspired oxygen; MAP mean arterial pressure; NIV non-invasive ventilation; OI Oxygenation Index; OSI Oxygenation Index using SpO_2; PaO_2 partial pressure arterial oxygen; PEEP positive end-expiratory pressure; SBP systolic blood pressure; SD standard deviation; SIRS systemic inflammatory response syndrome; SOFA sequential organ failure assessment; SpO_2 oxygen saturation.

Source : *(8, 9)*

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Case definitions

1. Suspect case *(10)*

A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness of breath), AND a history of travel to or residence in a country/area or territory reporting local transmission of COVID-19 disease during the 14 days prior to symptom onset;

OR

A patient/health care worker with any acute respiratory illness AND having been in contact with a confirmed COVID-19 case in the last 14 days prior to onset of symptoms;

OR

A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness of breath) and requiring hospitalization and with no other etiology that fully explains the clinical presentation;

OR

A case for whom testing for COVID-19 is inconclusive.

2. Laboratory confirmed case *(10)*

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Definition of contact

A contact is a person that is involved in any of the following:

- Providing direct care without proper personal protective equipment (PPE) for COVID-19 patients
- Staying in the same close environment of a COVID-19 patient (including workplace, classroom, household, gatherings).
- Travelling together in close proximity (1 m) with a symptomatic person who later tested positive for COVID-19.

High risk contact

- Touched body fluids of the patient (Respiratory tract secretions, blood, vomit, saliva, urine, faeces)
- Had direct physical contact with the body of the patient including physical examination without PPE.
- Touched or cleaned the linens, clothes, or dishes of the patient.
- Lives in the same household as the patient.
- Anyone in close proximity (within 3 ft) of the confirmed case without precautions.
- Passenger in close proximity (within 3 ft) of a conveyance with a symptomatic person who later tested positive for COVID-19 for more than 6 hours.

Low risk contact

- Shared the same space (Same class for school/worked in same room/similar and not having a high risk exposure to confirmed or suspect case of COVID-19).
- Travelled in same environment (bus/train/flight/any mode of transit) but not having a high-risk exposure.

Long COVID or Post-COVID conditions *(11)*

Post-COVID conditions are a wide range of new, returning, or ongoing health problems that people experience after first being infected with the virus that causes COVID-19. Most people with COVID-19 get better within a few days to a few weeks after infection, so at least four weeks after infection is the start of time when post-COVID conditions could first be identified.

Post-COVID conditions can include a wide range of ongoing health problems; these conditions can last weeks, months, or years. The conditions are found more often in people who had severe COVID-19 illness, but anyone can experience post-COVID conditions, even people who had mild illness or no symptoms from COVID-19. People who are not vaccinated against COVID-19 and become infected are at higher risk of developing post-COVID conditions compared to people who were vaccinated and had breakthrough infections. There is no single test for post-COVID conditions. While most people with post-COVID conditions have evidence of infection or COVID-19 illness, in some cases, a person with post-COVID conditions may not have tested positive for the virus or known they were infected.

Symptoms of post-COVID conditions *(11)*

People with post-COVID conditions may experience many symptoms. The most common symptoms are as follows :

1. *General symptoms* : (a) Tiredness or fatigue that interferes with daily life; (b) Symptoms that get worse after physical or mental effort (also known as "post-exertional malaise"); and (c) Fever.
2. *Respiratory and heart symptoms* : (a) Difficulty in breathing or shortness of breath; (b) Cough; (c) Chest pain; and (d) Fast-beating or pounding heart (also known as heart palpitations).
3. *Neurological symptoms* : (a) Difficulty in thinking or concentrating (sometimes referred to as "brain fog"); (b) Headache; (c) Sleep problems; (d) Dizziness when you stand up (lightheadedness); (e) Pins-and-needles feelings; (f) Change in smell or taste; and (g) Depression or anxiety.
4. *Digestive symptoms* : Diarrhoea and stomach pain.
5. *Other symptoms* : Joint or muscle pain, rash, and changes in menstrual cycles.

Some people, especially those who had severe COVID-19, experience multiorgan effects or autoimmune conditions with symptoms lasting weeks or months after COVID-19 illness. Multiorgan effects can involve many body systems, including the heart, lung, kidney, skin, and brain. As a result of these effects, people who have had COVID-19 may be more likely to develop new health conditions such as diabetes, heart conditions, or neurological conditions compared with people who have not had COVID-19 *(11)*.

Living with post-COVID conditions can be hard, especially when there are no immediate answers or solutions. The best way to prevent post-COVID conditions is to protect yourself from becoming infected. Getting vaccinated is the best way to avoid the disease or getting serious illness. However, people experiencing post-COVID conditions can seek personal medical management plan that can help improve their symptoms and quality of life.

Black Fungus Infection

Mucormycosis or Black Fungus is a rare fungal infection caused by a group of fungi called 'mucormycetes'. They commonly exist in the environment, especially in animal

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dung, compost, soil, leaves, and rotting produce. These fungi can enter the body through exposed wounds in the skin, inhaling, and breathing. Once they enter the body, these fungi have the potential to affect the brain, skin, lungs, and sinuses.

The risk factors are uncontrolled pre-existing diabetes; rampant overuse of steroids in management of COVID-19; new onset of diabetes due to steroid overuse or severe cases of COVID-19; prolonged ICU stay and irrational use of broad spectrum antibiotics; pre-existing co-morbidities such as haematological malignancies, use of immunosuppressants, solid organ transplant etc.; and contamination through the pipes and prongs used for the mechanical supply of oxygen to patients.

Signs and symptoms : 1. Facial pain, pain over sinuses, pain in teeth and gums; 2. Decreased sensation over half of face; 3. Blackish discoloration of skin over nasolabial groove/alae nasi; 4. Nasal crusting and nasal discharge which could be blackish or blood tinged; 5. Conjunctival redness; 6. Periorbital swelling; 7. Blurring of vision or diplopia; 8. Loosening of teeth/discoloration of palate/ gangrenous inferior turbinates; and 9. Worsening of respiratory symptoms, haemoptysis, chest pain, alteration of consciousness, headache *(12)*.

Diagnosis

1. KOH staining and microscopy, histopathology of debrided tissue and culture.
2. Imaging techniques : CT scan of paranasal sinuses brain and lungs.
3. Molecular assays.

Treatment

Liposomal Amphotericin B in initial dose of 5mg/kg body weight (10 mg/kg body wt in case of CNS involvement) is the treatment of choice. Each vial contains 50 mg. It should be diluted in 5% or 10% dextrose, it is incompatible with normal saline/Ringer Lactate. It has to be continued till a favourable response is achieved and disease is stabilized which may take several weeks following which step down to oral Posaconazole (300 mg delayed release tablets twice a day for 1 day followed by 300 mg daily) or Isavuconazole (200 mg 1 tablet 3 times daily for 2 days followed by 200 mg daily). Conventional Amphotericin B (deoxy cholate) in the dose 1–1.5 mg/kg may be used if liposomal form is not available and renal functions and serum electrolytes are within normal limits.

In severe cases, surgery is required to remove dead or infected tissues. Surgery can lead to permanent damage, both mentally and physically, as it involves removing parts of the nose or eyes. India reported more than 11,000 cases of black fungus in COVID cases *(6)*.

Diagnosis of COVID-19

Testing strategies for Covid-19 diagnosis : There are two types of testings for SARS-CoV-2. (1) *Diagnostic testing* : It is intended to identify current infection at the individual level and is performed when a person has signs and symptoms consistent with COVID-19, or when a person is asymptomatic but has recent known or suspected exposure, and (2) *Screening testing* : It is intended to identify infected persons who are asymptomatic and without known or suspected exposure to SARS-CoV-2. Screening testing is performed to identify persons who may be contagious so that measures can be taken to prevent further transmission of the disease.

MOLECULAR TEST

Respiratory sample collection method (8)

A. Lower respiratory tract
   - Bronchoalveolar lavage, tracheal aspirate, sputum
   - Collect 2–3 mL into a sterile, leak-proof, screw-cap sputum collection cup or sterile dry container.

B. Upper respiratory tract
   - Nasopharyngeal swab and oropharyngeal swab

Oropharyngeal swab (e.g. throat swab) : Tilt patient's head back 70 degrees. Rub swab over both tonsillar pillars and posterior oropharynx and avoid touching the tongue, teeth, and gums. Use only synthetic fiber swabs with plastic shafts. Do not use calcium alginate swabs or swabs with wooden shafts. Place swabs immediately into sterile tubes containing 2–3 ml of viral transport media.

Combined nasal & throat swab : Tilt patient's head back 70 degrees. While gently rotating the swab, insert swab less than one inch into nostril (until resistance is met at turbinates). Rotate the swab several times against nasal wall and repeat in other nostril using the same swab. Place tip of the swab into sterile viral transport media tube and cut off the applicator stick. For throat swab, take a second dry polyester swab, insert into mouth, and swab the posterior pharynx and tonsillar areas (avoid the tongue). Place tip of swab into the same tube and cut off the applicator tip.

Nasopharyngeal swab : Tilt patient's head back 70 degrees. Insert flexible swab through the nares parallel to the palate (not upwards) until resistance is encountered or the distance is equivalent to that from the ear to the nostril of the patient. Gently, rub and roll the swab. Leave the swab in place for several seconds to absorb secretions before removing.

Clinicians may also collect lower respiratory tract samples when these are readily available (for example, in mechanically ventilated patients). In hospitalized patients in Dedicated Covid Hospitals (severe cases with confirmed COVID-19 infection), repeat upper respiratory tract samples should be collected to demonstrate viral clearance.

Nucleic acid amplification testing (NAAT) for SARS-CoV-2

Reverse transcriptase polymerase chain reaction (RT-PCR)-based diagnostic tests (which detect viral nucleic acids) are considered the gold standard for detecting current SARS-CoV-2 infection.

The CT score or value in the RT-PCR report is an important part of the result and stands for 'Cycle Threshold'. The RT-PCR test involves converting the RNA collected from the patient's sample into DNA and then amplifying it. The CT value or score in the RT-PCR test refers to the number of cycles it took for the fluorescence to be detected over the background signal. In simpler words, the CT score in RT-PCR is the number of cycles it took to detect the viral load. If the virus is not detected in a few cycles, the CT score of the RT-PCR test will keep increasing. A higher number of cycles means that the virus was undetectable in lower cycles. So, the CT value in RT-PCR report helps determine the viral load and transmission potential of the virus. If the CT value is low, it means it took a lesser number of cycles to detect the virus, implying a higher viral load and higher transmissibility. A higher CT value on the other hand means a lower viral load as well as transmissibility.

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The CT Range in RT-PCR

The ICMR has defined a basic CT range for RT-PCR tests to help diagnose the COVID-19 infection:

- *More than 35* : If the CT value in the report is 35 or more, it is considered to be a negative report. Additionally, it could also mean that the virus is in its initial stages and replication in the body has just started. It can also indicate later phases of the infection when the person is recovering. Clinical interpretation is necessary here.
- *25–35* : Moderate viral load and transmissibility. Whether the person is having symptoms or is asymptomatic, there is need for isolation and to begin treatment as soon as possible.
- *Less than 25* : High viral load and transmissibility. Immediate isolation and medical consultation.

More recently, NAATs have included a variety of additional platforms (e.g., real-time loop mediated isothermal amplification). Clinically, there may be a window period of up to 5 days after exposure before viral nucleic acids can be detected. However, false negative NAAT results can also occur outside of this 5-day window. Therefore, a single negative test result does not completely exclude SARS-CoV-2 infection in people with a high likelihood of infection based on their exposure history and/or their clinical presentation, and repeat testing using a NAAT should be considered.

SARS-CoV-2 poses several diagnostic challenges, including potentially discordant shedding of virus from the upper versus the lower respiratory tract. Due to the high specificity of NAAT, there is no need to obtain a lower respiratory tract sample to diagnose COVID-19 when a patient with recent onset of COVID-19-compatible symptoms has a positive NAAT on an upper respiratory sample.

Antigen testing for SARS-CoV-2

When compared with RT-PCR-based tests, antigen-based diagnostic tests (which detect viral antigens in nasal or nasopharyngeal swabs, also called RDT) are less sensitive but have a similarly high specificity. Antigen tests perform best early in the course of symptomatic SARS-CoV-2 infection, when the viral load is thought to be highest. When a person who is strongly suspected of having SARS-CoV-2 infection receives a negative result on an initial antigen test, repeat testing using a NAAT should be considered. Advantages of antigen-based tests are their low cost and rapid turnaround. The availability of immediate results makes antigen-based tests an attractive option for point-of-care testing in high-risk congregate settings where preventing transmission is critical. Antigen-based tests also allow for repeat testing to quickly identify persons with SARS-CoV-2 infection. Currently, there are limited data to guide the use of rapid antigen tests to detect or exclude SARS-CoV-2 infection in asymptomatic persons or to determine whether a person who was previously confirmed to have SARS-CoV-2 infection is still infectious.

Serologic or antibody testing for diagnosis of SARS-CoV-2

Unlike NAATs and antigen tests for SARS-CoV-2 that detect the presence of the virus, serologic or antibody tests are intended to identify persons with recent or prior SARS-CoV-2 infection. Because it may take 21 days or longer after symptom onset for seroconversion or detection of immunoglobulin IgM and/or IgG antibodies to SARS-CoV-2. The use of serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection is not recommended. Given that NAATs and antigen tests for SARS-CoV-2 occasionally yield false negative results, serologic tests have been used in some settings as an additional diagnostic test for patients who are strongly suspected to have SARS-CoV-2 infection. Using serology in combination with a NAAT to detect IgG or total antibodies 3 to 4 weeks after onset of symptoms maximizes the sensitivity and specificity to detect past infection *(10)*.

CHEST IMAGING

Chest X-ray examination

Since the disease manifests itself as pneumonia, radiological imaging has a fundamental role in the diagnostic process, management, and follow-up. Standard radiographic examination (X-ray) of the chest has a low sensitivity in identifying early lung changes in the initial stages of the disease. At this stage, it can be completely negative. In the more advanced stages of infection, the chest X-ray examination generally shows bilateral multifocal alveolar opacities, which tend to confluence up to the complete opacity of the lung. Pleural effusion can be associated.

Chest computed tomography

Given the high sensitivity of the method, chest computed tomography (CT), in particular high-resolution CT (HRCT), is the method of choice in the study of COVID-19 pneumonia, even in the initial stages. Several non-specific HRCT findings and patterns can be found. The most common findings are multifocal bilateral "ground glass" (GG) areas associated with consolidation areas with patchy distribution, mainly peripheral/subpleural and with greater involvement of the posterior regions and lower lobes. Other findings are the "reversed halo sign" which is a focal area of GG delimited by a peripheral ring with consolidation, and the findings of cavitations, calcifications, lymphadenopathies and pleural effusion *(10)*.

Lung ultrasound

Ultrasound can allow evaluating the evolution of the disease, from a focal interstitial pattern up to "white lung" with evidence often of subpleural consolidations. It should be performed within the first 24 hours in the suspect and every 24/48 hours and can be useful for patient follow-up, choice of the setting of mechanical ventilation, and for the indication of prone positioning.

Laboratory examinations (10)

- In the early stage of the disease, a normal or decreased total white blood cell count (WBC) and a decreased lymphocyte count can be demonstrated. Interestingly, lymphopenia appears to be a negative prognostic factor.
- Increased values of liver enzymes, lactate dehydrogenase (LDH), muscle enzymes, and C-reactive protein can be detected.
- Unless a bacterial overlap, a normal procalcitonin value is found.

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- The elevated neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (d-NLR) (neutrophil count divided by the result of WBC count minus neutrophil count), and platelet-to-lymphocyte ratio, can be the expression of the inflammatory storm. The correction of these indices is an expression of a favourable trend.
- Increased D-dimer.
- In critical patients, D-dimer value is increased, blood lymphocytes decrease persistently, and laboratory alterations of multiorgan imbalance (high amylase, coagulation disorders etc.) are found.

For COVID-19 patients with severe disease, collect blood for blood culture, ideally prior to initiation of antimicrobial therapy. Dual infection with other respiratory infections (viral, bacterial and fungal) have been found in COVID-19 patients. Depending on local epidemiology and clinical symptoms, test for other potential aetiologies, e.g., influenza, other respiratory viruses, malaria, dengue fever, typhoid fever as appropriate *(8)*.

Management of COVID-19

In the containment phase, to break the chain of transmission of COVID-19, patients with suspected or confirmed disease are isolated. Cases can be managed at Covid Care Centre, First Referral Units, Community Health Centres (CHC), Sub-district Hospitals, District Hospitals, and Medical Colleges.

Detailed clinical history is taken including that of co-morbidities. The patient is followed up daily for temperature, vitals and oxygen saturation (SpO_2). Patients should be monitored for signs and symptoms of complications that should prompt urgent referral. Patients with risk factors for severe illness should be monitored closely, given the possible risk of deterioration. If they develop any worsening symptoms (such as mental confusion, difficulty breathing, persistent pain or pressure in the chest, bluish coloration of face/lips, dehydration, decreased urine output etc.), they should be immediately admitted to a Dedicated Covid Health Centre or Dedicated Covid Hospital. Children with mild COVID-19 should be monitored for signs and symptoms of clinical deterioration requiring urgent re-evaluation. These include difficulty in breathing/fast or shallow breathing (for infants: grunting, inability to breast-feed), blue lips or face, chest pain or pressure, new confusion, inability to awaken/not interacting when awake, inability to drink or keep down any liquids.

An algorithm for clinical guidance for management of COVID-19 suspect/confirmed case is as shown in Fig. 1 and 2.

The mainstay of treatment is supplemental oxygen and other supporting therapy. No specific antivirals have been proven effective. However, drugs like Ivermectin, Hydroxychloroquine, inhalational Budesonide, Dexamethasone, Methylprednisolne and Low Molecular Weight Heparin have been recommended. In addition, provisions for Investigational Therapies have also been made using Remdesivir, and Tocilizumab for defined sub-group of patients under medical supervision *(6)*.

Prevention of complications

Implementation of the following interventions can prevent complications associated with critical illness.

Prevention of complications

Anticipated outcome	Interventions
Reduce days of invasive mechanical ventilation	• Use weaning protocols that include daily assessment for readiness to breathe spontaneously • Minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions • Early mobilization • Implementation of the above as a bundle of care (may also reduce delirium); such as the Awakening and Breathing Coordination, Delirium assessment/management, and Early mobility (ABCDE)
Reduce incidence of ventilator-associated pneumonia	• Oral intubation is preferable to nasal intubation in adolescents and adults • Keep patient in semi-recumbent position (head of bed elevation 30–45°) • Use a closed suctioning system; periodically drain and discard condensate in tubing • Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged, but not routinely • Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days
Reduce incidence of catheter-related bloodstream infection	• Use a checklist with completion verified by a real-time observer as a reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed
Reduce incidence of pressure ulcers	• Turn patient every 2 hours
Reduce incidence of stress ulcers and GI bleeding	• Give early enteral nutrition (within 24–48 hours of admission) • Administer histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding. Risk factors for GI bleeding include mechanical ventilation for ≥ 48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score
Reduce the development of antimicrobial resistance	• Utilize de-escalation protocols as soon as patient is clinically stable and there is no evidence of bacterial infection
Reduce the development of adverse drug effects	• Expose patient to empiric antimicrobial therapy for the shortest time possible, to prevent nephrotoxicity, cardiac and other side-effects from unnecessary antimicrobial use
Promote appropriate antimicrobial prescribing and use during the COVID-19 pandemic	• Do not prescribe antibiotics to suspected or confirmed COVID-19 patients with low suspicion of a bacterial infection, to avoid more short-term side-effects of antibiotics in patients and negative long-term consequences of increased antimicrobial resistance

Source : *(8)*

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Adult patient diagnosed with COVID-19

Mild disease	Moderate disease	Severe disease
Upper respiratory tract symptoms and/or fever WITHOUT shortness of breath or hypoxia	Any one of : 1. Respiratory rate ≥ 24/min, breathlessness 2. SpO_2 : 90% to ≤ 93% on room air	Any one of : 1. Respiratory rate > 30/min, breathlessness 2. SpO_2 < 90% on room air
Home Isolation & Care (Refer to relevant guideline)	ADMIT IN WARD	ADMIT IN HDU/ICU

MUST DOs
- Physical distancing, indoor mask use, strict hand hygiene
- Symptomatic management (hydration, anti-pyretics, anti-tussive)
- Monitor temperature and oxygen saturation (by applying a SpO_2 probe to fingers)
- Stay in contact with treating physician

Seek immediate medical attention if :
- Difficulty in breathing or SpO_2 <93%
- High grade fever/severe cough, particularly if lasting for >5 days
- A low threshold to be kept for those with any of the high-risk features*

***High-risk for severe disease or mortality**
- Age > 60 years
- Cardiovascular disease and CAD
- Diabetes mellitus and other immunocompromised states (such as HIV)
- Active tuberculosis
- Chronic lung/kidney/liver disease
- Cerebrovascular disease
- Obesity
- Unvaccinated

- Antibiotics should not be used unless there is clinical suspicion of bacterial infection
- Possibility of coinfection of COVID-19 with other endemic infections must be considered
- Systemic corticosteroids are not indicated in mild disease

DO NOT USE IN COVID-19
- Lopinavir-ritonavir
- Hydroxychloroquine
- Ivermectin
- Neutralizing monoclonal antibody
- Convalescent plasma
- Molnupiravir
- Favipiravir
- Azithromycin
- Doxycycline

Oxygen Support :
- Target SpO_2 : 94-96% (88-92% in patients with COPD)
- Preferred devices for oxygenation : non-rebreathing face mask
- Awake proning encouraged in all patients requiring supplemental oxygen therapy (sequential position changes every 2 hours)

Anti-inflammatory or immunomodulatory therapy :
- Dexamethasone 6 mg/day or equivalent dose of methylprednisolone (32 mg in 4 divided doses) usually for 5 to 10 days or until discharge, whichever is earlier.
- Patients may be initiated or switched to oral route if stable and/or improving
- There is no evidence for benefit for systemic steroids in those NOT requiring oxygen supplementation, or on continuation after discharge
- Anti-inflammatory or immunomodulatory therapy (such as steroids) can have risk of secondary infection such as invasive mucormycosis when used at higher dose or for longer than required

Anticoagulation :
- Prophylactic dose of unfractionated heparin or Low Molecular Weight Heparin (weight based e.g., enoxaparin 0.5mg/kg per day SC). There should be no contraindication or high risk of bleeding

Monitoring :
- Clinical Monitoring : Respiratory rate, Hemodynamic instability, Change in oxygen requirement
- Serial CXR; HRCT chest to be done ONLY if there is worsening
- Lab monitoring : CRP, D-dimer, blood sugar 48 to 72 hrly

Respiratory support :
- Consider use of NIV (Helmet or face mask interface depending on availability) in patients with increasing oxygen requirement, if work of breathing is LOW
- Consider use of HFNC in patients with increasing oxygen requirement
- Intubation should be prioritized in patients with high work of breathing /if NIV is not tolerated
- Use institutional protocol for ventilatory management when required
- Need for vasopressors to be considered based on clinical situation

Anti-inflammatory or immunomodulatory therapy :
- Dexamethasone 6 mg/day or equivalent dose of methylprednisolone (32 mg in 4 divided doses) usually for 5 to 10 days or until discharge, whichever is earlier. No evidence for benefit in higher doses.
- Anti-inflammatory or immunomodulatory therapy (such as steroids) can have risk of secondary infection such as invasive mucormycosis when used at higher dose or for longer than required

Anticoagulation :
- Prophylactic dose of unfractionated heparin or Low Molecular Weight Heparin (weight based e.g., enoxaparin 0.5mg/kg per day SC). There should be no contraindication or high risk of bleeding

Supportive measures :
- Maintain euvolemia (if available, use dynamic measures for assessing fluid responsiveness)
- If sepsis/septic shock : manage as per existing protocol and local antibiogram

Monitoring :
- Clinical Monitoring : work of breathing, Hemodynamic instability, Change in oxygen requirement
- Serial CXR; HRCT chest to be done ONLY if there is worsening
- Lab monitoring : CRP, D-dimer, blood sugar 48 to 72 hrly; CBC, KFT, LFT 24 to 48 hrly

After clinical improvement, discharge as per revised discharge criteria

Additionally in moderate or severe disease at high risk of progression

Consider Remdesivir for up to 5 days (200 mg IV on day 1 followed by 100 mg IV OD for next 4 days)
- To be started within 10 days of onset of symptoms, in those having moderate to severe disease with high risk of progression (requiring supplemental oxygen), but who are NOT on IMV or ECMO
- No evidence of benefit for treatment more than 5 days
- NOT to be used in patients who are NOT on oxygen support or in home setting
- Monitor for RFT and LFT (remdesivir not recommended if eGFR <30 ml/min/m2; AST/ALT >5 times UNL) (not an absolute contraindication)

Additionally in rapidly progressing moderate or severe disease

Consider Tocilizumab preferably within 24-48 hours of onset of severe disease/ ICU admission [4 to 6 mg/kg (400 mg in 60 kg adult) in 100 ml NS over 1 hour] if the following conditions are met :
- Rapidly progressing COVID-19 not responding adequately to steroids and needing oxygen supplementation or IMV
- Preferably to be given with steroids
- Significantly raised inflammatory markers (CRP and/or IL-6)
- Rule out active TB, fungal, systemic bacterial infection
- Long term follow up for secondary infections (such as reactivation of TB, flaring of Herpes)

FIG. 1
Clinical guidance for management of adult COVID-19 patients (Revised on 05.01.2023)

Source : *(13)*

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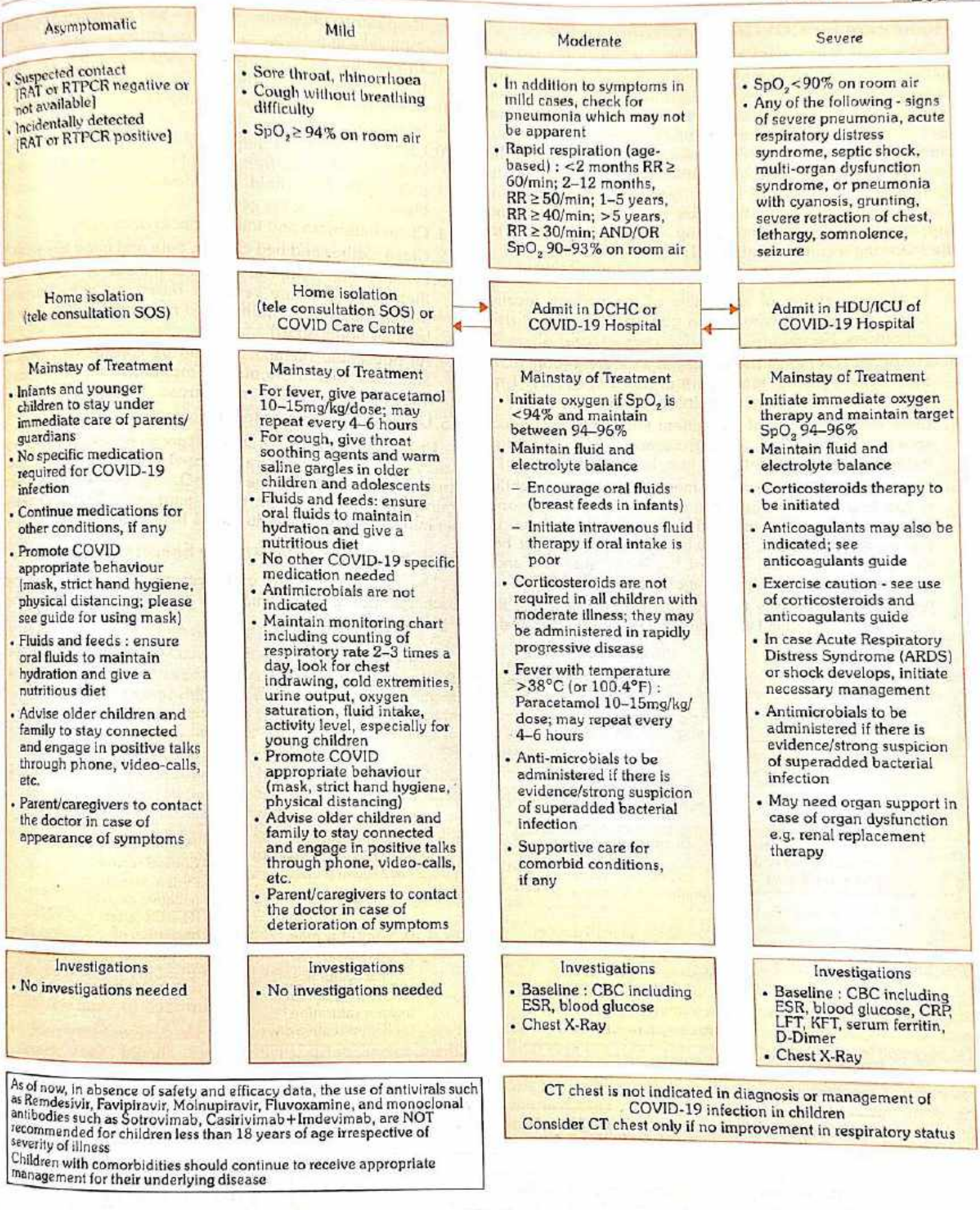

FIG. 2

Comprehensive guidelines for management of COVID-19 in children and adolescents (below 18 years) (Revised on 17.01.2022)

Source : *(14)*

Home care for COVID-19 patients

To ensure both safety and quality of health care of the patient, isolation and monitoring is preferable in a hospital setting. However, for several reasons, in situations when inpatient care is not available or in case of informed refusal for hospitalization, patients with mild symptoms and without chronic lung, heart or renal diseases may be cared for in the home environment. The same principle of care applies to symptomatic patients no longer requiring hospitalization. The patient and family should be provided with ongoing support, education and monitoring. They should adhere to the following recommendations *(15)* :

1. Place the patient in a well-ventilated single room.
2. Limit the number of caretakers of the patient, ideally assign one person who is in a good health without risk conditions. No visitors.
3. Household members should stay in a different room or, if that is not possible, maintain a distance of at least 1 m from the ill person (e.g. sleep in a separate bed).
4. Limit the movement of the patient and minimize shared space. Ensure that shared spaces (e.g. kitchen, bathroom) are well ventilated (e.g. keep windows open).
5. The caregiver should wear a medical mask fitted tightly to the face when in the same room with the ill person. Masks should not be touched or handled during use. If the mask gets wet or dirty with secretions, it must be changed immediately. Discard the mask after use and perform hand hygiene after removal of the mask.
6. Perform hand hygiene following all contacts with the ill persons. Refer to page 145 for details. Dry hands with towel.
7. Respiratory hygiene should be practiced by all, especially ill person.
8. Discard the material used to cover the mouth and nose or clean them appropriately.
9. Avoid direct contact with body fluid, particularly oral and nasal secretions.
10. Clean and disinfect frequently touched surfaces such as bedside tables, bedframes, and other bedroom furniture daily with household disinfectant containing diluted bleach.
11. Clean bathroom and toilet surfaces once daily.
12. Clean clothes and bed clothes, bath and hand towels etc.
13. Persons with symptoms should remain at home until their symptoms are resolved based on either clinical and/or laboratory findings (two negative RT-PCR tests at least 24 hours apart).
14. All household members should be considered contacts and their health should be monitored for respiratory infection, fever, cough, sore throat, difficult breathing.
15. Use of pulse oximeter to monitor oxygen saturation.

Pulse oximeter : It is a compact portable device, measures arterial blood oxygen saturation (SpO_2), heart rate and signal strength. Measuring range : SpO_2 30 to 100 per cent (minimum graduation 1 per cent), heart rate – 20 to 250 beats per minute (minimum graduation 1 beat per minute).

Revised discharge policy for hospitalized patients

The recommendation of Government of India on the discharge policy is summarized and is as shown in the algorithm in Fig. 3.

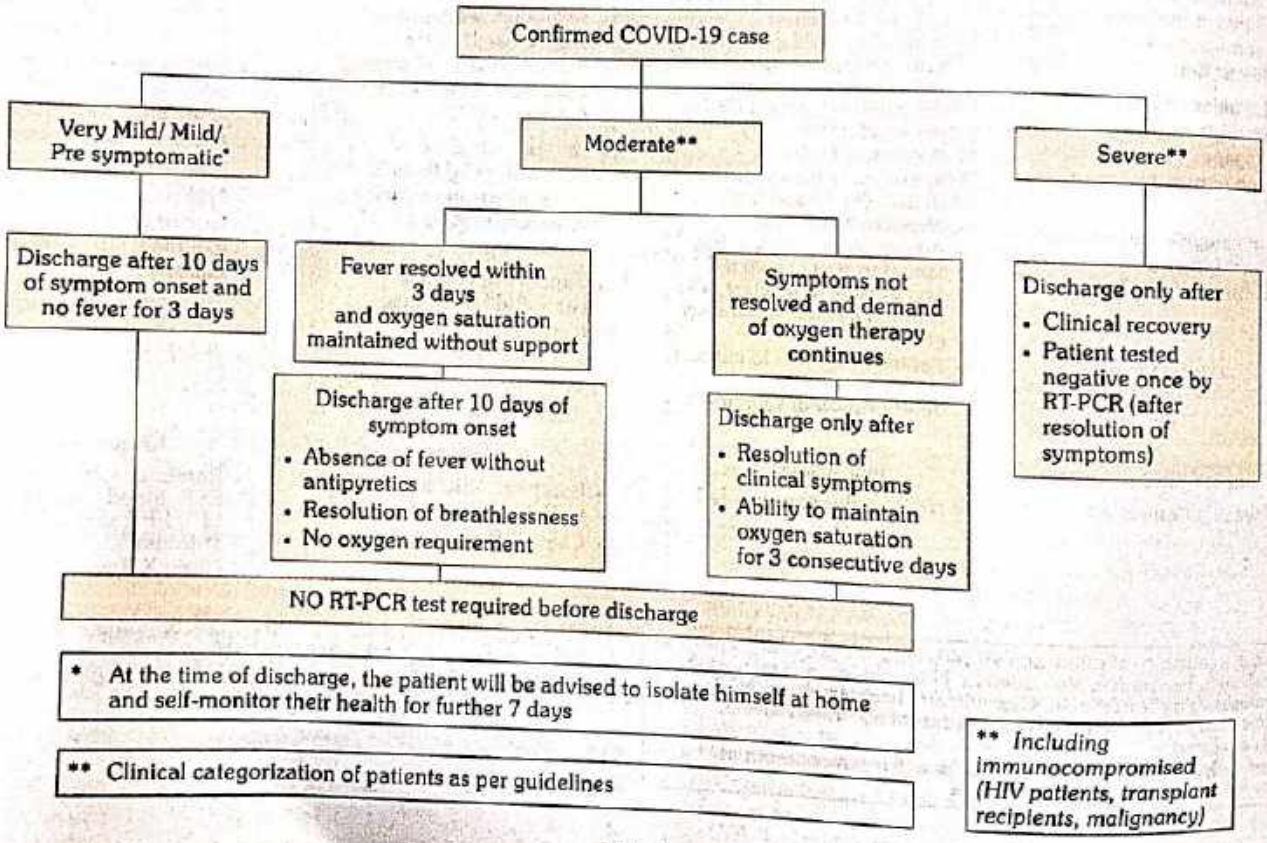

FIG. 3
Revised discharge policy for COVID-19

Source : *(16)*

Post COVID-19 management protocol (17)

After acute COVID-19 illness, recovered patients may continue to report wide variety of signs and symptoms including fatigue, body ache, cough, sore throat, difficulty in breathing etc. For details please refer to page 196. A holistic approach is required for follow-up care and well-being of all post-COVID-19 recovering patients. The recovery period is likely to be longer for patients who suffered more severe form of the disease and those with pre-existing illness.

POST-COVID FOLLOW-UP PROTOCOL

1. At individual level

- Continue COVID appropriate behaviour (use of mask, hand and respiratory hygiene, physical distancing).
- Drink adequate amount of warm water (if not contra-indicated).
- Take immunity promoting AYUSH medicine, to be practiced and prescribed by a qualified practitioner of AYUSH.
- If health permits, regular household work to be done. Professional work to be resumed in graded manner.
- Mild/ moderate exercise
  - Daily practice of yogasana, pranayama and meditation, as much as health permits or as prescribed.
  - Breathing exercises as prescribed by treating physician.
  - Daily morning or evening walk at a comfortable pace as tolerated.
- Balanced nutritious diet, preferably easy to digest freshly cooked soft diet.
- Have adequate sleep and rest.
- Avoid smoking and consumption of alcohol.
- Take regular medications as advised for COVID and also for managing comorbidities, if any. Doctor to be always informed about all medicines that the individual is taking (allopathic/AYUSH) so as to avoid prescription interaction.
- Self-health monitoring at home-temperature, blood pressure, blood sugar (especially, if diabetic), pulse oximetry etc. (if medically advised)
- If there is persistent dry cough / sore throat, do saline gargles and take steam inhalation. The addition of herbs/ spices for gargling/steam inhalation can help. Cough medications, should be taken on advice of medical doctor or qualified practitioner of Ayush.
- Look for early warning signs like high grade fever, breathlessness, SpO_2<95%, unexplained chest pain, new onset of confusion, focal weakness.

2. At the level of community

- Recovered individuals to share their positive experiences with their friends and relatives using social media, community leaders, opinion leaders, religious leaders for creating awareness, dispelling myths and stigma.
- Take support of community based self-help groups, civil society organizations, and qualified professionals for recovery and rehabilitation process (medical, social, occupational, livelihood).
- Seek psycho-social support from peers, community health workers, counsellor. If required seek mental health support service.
- Participate in group sessions of Yoga, Meditation etc. while taking all due precautions like physical distancing.

3. In health-care facility setting

- The first follow-up visit (physical/telephonic) should be within 7 days after discharge, preferably at the hospital where he/she underwent treatment.
- Subsequent treatment/follow-up visits may be with the nearest qualified allopathic/AYUSH practitioner/medical facility of other systems of medicine. Poly-therapy is to be avoided due to potential for unknown drug-drug interaction, which may lead to Serious Adverse Events (SAE) or Adverse Effects (AE).
- The patients who had undergone home isolation, if they complain of persisting symptoms, will visit the nearest health facility.
- Severe cases requiring critical care support will require more stringent follow-up.

Public health surveillance for COVID-19 (18)

The aim of national surveillance for COVID-19 is to enable public health authorities to reduce transmission of SARS-CoV-2, thereby limiting associated morbidity and mortality.

The objectives of COVID-19 surveillance are to :

- Enable rapid detection, isolation, testing, and management of cases
- Detect and contain clusters and outbreaks, especially among vulnerable populations
- Identify, follow-up and quarantine contacts
- Guide the implementation and adjustment of targetted control measures, while enabling safe resumption of economic and social activities
- Evaluate the impact of the pandemic on health care systems and society
- Monitor longer term epidemiologic trends and evolution of SARS-CoV-2 virus and monitor trends in COVID-19 deaths
- Contribute to the understanding of the co-circulation of SARS-CoV-2 virus, influenza and other respiratory viruses, and other pathogens.

Surveillance approaches

Most countries need significantly strengthened surveillance capacities to rapidly identify and care for cases of COVID-19, trace and quarantine their contacts and monitor disease trends over time. Comprehensive national surveillance for COVID-19 will require the adaptation and reinforcement of existing national systems, where appropriate, and the scale-up of additional surveillance capacities, as needed. Digital technologies for rapid reporting, contact tracing and data management and analysis may support these capacities.

Robust comprehensive surveillance, once in place, should be maintained even in areas where transmission has been suppressed or controlled, even if there are few or no cases. It is critical that new cases and clusters of SARS-CoV-2 infection be detected rapidly before outbreaks or widespread transmission occurs. Ongoing surveillance for COVID-19 is also important to understand longer-term epidemiological trends, such as incidence and mortality among different age groups, which population groups are at higher risk for severe disease and death, and potential epidemiological changes over time.

Key actions for comprehensive COVID-19 surveillance include:

- Use, adaptation and strengthening of existing surveillance systems

- Strengthen laboratory and testing capacities
- Use, adaptation and enhancement of public health workforce to carry out case finding, contact tracing and testing
- Include COVID-19 as a mandatory notifiable disease
- Implement immediate reporting
- Establish systems to monitor contact tracing activity.

It is important to maintain routine syndromic surveillance for other infectious diseases, especially those caused by respiratory pathogens, such as influenza and respiratory syncytial virus, through surveillance for influenza-like-illness (ILI), severe acute respiratory infection (SARI), atypical pneumonia and unexplained fever, with sampling and laboratory testing of all or a subset of cases. This is critical for understanding trends in other diseases with similar presentations to guide appropriate public health preparedness and clinical management.

Essential surveillance for COVID-19

Surveillance systems should be geographically comprehensive, and surveillance for vulnerable or high-risk populations should be enhanced. This will require a combination of surveillance systems including contact tracing for all levels of the health care system, at the community level, in closed residential settings and in other vulnerable groups. Table 3 shows how surveillance systems can be combined across different sites.

Global surveillance

The objectives of the global surveillance are as follows:

- Monitor trends in COVID-19 at national and global levels
- Monitor mortality caused by, and indirectly associated with, COVID-19
- Estimate morbidity and mortality for health care workers
- Assess the impact of control measures.

Weekly aggregated reporting

The aim of ongoing weekly aggregate reporting is to obtain further information on global COVID-19 trends for enhanced analysis. The variables are as follows *(19)* :

- Number of confirmed cases
- Number of probable cases
- Number of confirmed deaths
- Number of probable deaths
- Number of individuals hospitalized (confirmed and probable)
- Number discharged (confirmed and probable)
- Number of health care workers infected (confirmed + probable) as a subset of total cases count
- Number of health care workers who died due to COVID-19 (confirmed + probable) as a subset of total death count
- Number of persons tested
- Number of persons tested by PCR
- Confirmed + probable cases by age group and sex
- Confirmed + probable deaths by age group and sex

Categories for transmission pattern *(19)*

WHO recommends using the following categories to describe transmission patterns at national and sub-national levels to guide decisions for preparedness, readiness and response activities. The definitions of categories are as shown in Table 4.

Prevention of the disease

"Do gaj ki doori, mask hai jaroori" is the slogan of the day. Although the vaccine is now available in India, it is critical that people should continue to follow all the "COVID Appropriate Behaviour". They should use mask, maintain a physical distance of at least 6 feet when in public place, not touch nose, eyes and mouth, cover mouth and nose while coughing and sneezing and avoid spitting in open, prompt testing on observing symptoms, and isolation if having the disease or for contacts quarantine for 14 days.

While UK and USA have emerged as the first two countries in the world to launch the COVID vaccine, India has also launched one of the world's largest COVID vaccination drive. This is the first time that a vaccine for COVID-19 has been developed and launched in the country.

Dry run for the vaccine : The dry run is a mock drill to test the laid out mechanisms for COVID-19 vaccination roll out in the health system and to assess the operational feasibility of using Co-Win application in field environment for planning, implementation and reporting at the block, district and state levels *(20, 21)*.

TABLE 3

Surveillance systems across different sites/contexts

System / Site/ Context	Immediate case notification	Contact tracing	Virologic surveillance	Cluster investigations	Mortality surveillance	Serologic surveillance
Community	×	×		×	×	×
Primary Care Sites (non-sentinel ILI/ARI)	×		×	×		
Hospitals (non-sentinel ILI/SARI)	×		×	×	×	×
Sentinel ILI/ARI/ SARI sites	×		×			
Closed settings*	×	×		×	×	×
Health care-associated SARS-CoV-2 infection	×	×		×	×	×
Travellers at points of entry	×	×		×		

*Including but not limited to long-term living facilities, prisons and dormitories.

Source : *(19)*

TABLE 4

Definition of the categories for transmission pattern

Category name	Definition
No (active) cases	No new cases detected for at least 28 days (two times the maximum incubation period), in the presence of a robust surveillance system. This implies a near-zero risk of infection for the general population.
Imported / Sporadic cases	Cases detected in the past 14 days are all imported, sporadic (e.g. laboratory acquired or zoonotic) or are all linked to imported/sporadic cases, and there are no clear signals of further locally acquired transmission. This implies minimal risk of infection for the general population.
Clusters of cases	Cases detected in the past 14 days are predominantly limited to well-defined clusters that are not directly linked to imported cases, but which are all linked by time, geographic location and common exposures. It is assumed that there are a number of unidentified cases in the area. This implies a low risk of infection to others in the wider community if exposure to these clusters is avoided.
Community transmission – level 1 (CT1)	Low incidence of locally acquired widely dispersed cases detected in the past 14 days not linked to specific clusters; transmission may be focussed in certain population sub-groups. Low risk of infection for the general population.
Community transmission – level 2 (CT2)	Moderate incidence of locally acquired widely dispersed cases detected in the past 14 days; transmission less focussed in certain population sub-groups. Moderate risk of infection for the general population.
Community transmission – level 3 (CT3)	High incidence of locally acquired widely dispersed cases in the past 14 days; transmission not focussed in certain population sub-groups. High risk of infection for the general population.
Community transmission – level 4 (CT4)	Very high incidence of locally acquired widely dispersed cases in the past 14 days. Very high risk of infection for the general population.

Source : *(19)*

Vaccination for COVID-19 is voluntary. However, it is advisable to receive the complete schedule of COVID-19 vaccine for protecting one-self against this disease and also to limit the spread of this disease to the close contacts. It is advisable to receive complete schedule of COVID vaccine irrespective of past history of infection with COVID-19. This will help in developing a strong immune response against the disease. Person with confirmed or suspected COVID-19 infection may increase the risk of spreading the same to others at vaccination site. For this reason, infected individuals should defer vaccination for 14 days after symptoms resolution.

Based on the potential availability of vaccines the Government of India selected the priority groups which are at higher risk. The first group includes healthcare workers because they are at high risk of contracting the infection and protecting them helps to sustain essential health services. The vaccination of frontline workers (police, home-guard, municipal worker, armed forces etc.) will help in reducing the societal and economic impact by reducing COVID-19 mortalities. The next group to receive COVID-19 vaccine was persons over 50 years of age and persons under 50 years with comorbid conditions because there is high mortality in this category. The reason for including more than 50 years of age group for vaccination was that it will be able to cover 78% of persons having co-morbidities and thereby reduce mortality on account of COVID-19. More than 50 years of age group was divided into two sub-groups. One sub-group was 60 years and above, they were vaccinated first. Second sub-group was between 50 to 60 years age group, they were vaccinated after the first sub group is covered. In subsequent phases the vaccine was given to the remaining persons above 18 years of age. COVID-19 vaccination for children in the age group 15–18 years started from 3rd January 2022. Covaxin is the only option for them *(22)*. Only 100 persons were vaccinated at each designated vaccination site per day.

The vaccination may not be sequential. It can go in parallel for all beneficiaries depending on the availability of the vaccine. Photo ID is a must for both registration and verification of beneficiary at session site to ensure that the intended person is vaccinated.

Any of the following mentioned ID with Photo may be produced at the time of registration : Aadhar Card, Driving License, Health Insurance Smart Card issued under the scheme of Ministry of Labour, MGNREGA Job Card, official identity cards issued to MPs/MLAs/MLCs, PAN Card, passbooks issued by bank/post Office, passport, pension document, service identity card with photograph issued to employees by Central/State Govt./PSUs/Public Limited Companies, Voter ID and Smart card issued by RGI under NPR.

Following online registration, beneficiary will receive SMS on their registered mobile number for the due date, place, and time of vaccination. On getting due dose of COVID-19 vaccine, the beneficiary will receive SMS on their registered mobile number. After all doses of vaccine are administered, a QR code based certificate will also be sent to the registered mobile number of the beneficiary.

It must be ensured that the entire schedule of vaccination is completed by only one type of vaccine, as different COVID-19 vaccines are not interchangeable.

COVID-19 Vaccines

In the light of urgent need due to COVID pandemic in the country, Central Drugs Standard Control Organization (CDSCO) has granted permissions to following six COVID-19 vaccines for restricted use in emergency situation :

1. ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) (Covishield) manufactured by M/s Serum Institute of India Pvt., Ltd., Pune.
2. Whole Virion Inactivated Corona Virus Vaccine (Covaxin) manufactured by M/s Bharat Biotech International Limited, Hyderabad.

3. Gam-COVID-Vac Combined vector vaccine (SPUTNIK-V) imported by M/s Dr. Reddy's Laboratories Ltd, Hyderabad OR manufactured by M/s Ra (biologicals) Panacea Biotec Ltd., New Delhi.
4. mRNA-1273 COVID-19 vaccine (Moderna) imported by M/s Cipla Limited, Mumbai
5. Janssen/Ad 26. CoV2-S – Adenovirus vector platform based Vaccine manufactured by M/s Johnson & Johnson.
6. ZyCoV-D, a DNA based COVID-19 vaccine manufactured by M/s Zydus Cadilla Ltd.

Currently, three COVID-19 vaccines are being used under the vaccination program namely Covishield manufactured by M/s Serum Institute of India, Covaxin manufactured by M/s Bharat Biotech International Limited and Sputnik V vaccine developed by Gamaleya Research Institute, Russia (imported by Dr Reddy's Lab and is being administered in few private hospitals, presently).

Persons who are temporarily not eligible to get the vaccine are *(23)* :

(a) Persons showing active symptoms of SARS-CoV-2 infection;

(b) COVID-19 patients who have been given anti-SARS-CoV-2 monoclonal antibodies or convalescent plasma;

(c) The vaccine should be given with caution to persons with a history of any bleeding or coagulation disorder platelet disorder, clotting factor deficiency or coagulopathy; and

(d) Actually unwell and hospitalized patients (with or without intensive care) due to any illness.

Persons with a past history of COVID-19 infection can be administered the vaccine. Persons with a history of chronic disease and comorbidities (cardiac, neurological, pulmonary, and metabolic) are eligible for the vaccine although efficiency of the vaccine may be less in these patients. Administration of vaccine to pregnant women should only be considered when the potential benefits out weigh any potential risks for the mother and foetus. According to recent guidelines a pregnant women who opts for vaccination could be vaccinated at any time of pregnancy. It is unknown whether the vaccine is secreted in human milk. However the current guidelines of the Indian Government recommends COVID-19 vaccination for all lactating mothers. The vaccines are not interchangeable.

Covishield vaccine *(23)*

Covishield vaccine is a recombinant chimpanzee adenovirus vector vaccine, administered intramuscularly in deltoid muscle. Given in two doses, 12–16 weeks apart. The protective level of antibodies are generally developed two weeks after the 2nd dose of the vaccine. The vaccine has been approved for individuals 18 years of age and above. To be stored at 2–8°C.

Side effects

The common side effects with Covishield vaccine are : injection site pain and tenderness, headache, fatigue, myalgia, discomfort, pyrexia, chills and nausea. Very rare events of demyelination disorder have been reported following vaccine "without the causal relationship establishment".

Contraindications

1. Vaccine should not be given if there is severe allergic reaction after the previous dose of this vaccine;
2. Had a severe allergic reaction to any ingredient of this vaccine.

Covaxin vaccine *(23)*

The Bharat Biotech's vaccine, developed in collaboration with ICMR and NIV Pune, is a whole virion inactivated coronavirus vaccine. It is given intramuscularly in deltoid muscle in two doses 28 days apart, to persons above 18 years of age and recently approved for 15–18 year age group *(22)*. The vaccine should be stored at 2–8°C.

Side effects

The common side effects following Covaxin are : injection site pain, fatigue, fever, headache, bodyache, nausea, abdominal pain, dizziness, sweating, and cold and cough.

Contraindications

1. Those below 18 years of age;
2. Those with allergic reaction to any componant of Covaxin vaccine, plasma centrical products and notable food allergies;
3. Anyone who has had adverse reaction to COVID-19 vaccine earlier; and
4. Currently having an acute infection or fever.

Individuals with HIV infection or other immunocompromising conditions, or who take immunosuppressive medications might be at increased risk of severe COVID-19. However, data is not currently available to establish vaccine safety and efficacy in these groups. Individuals may not generate a full immune response to COVID-19. As Covaxin is not a live virus vaccine, it is not likely to pose a safety risk.

Sputnik V Vaccine

Sputnik V Vaccine (Gam-COVID-Vac) is manufactured by Gamaleya Research Institute, Russia. It is a non-replicating viral vector vaccine administered by intramuscular injection in two doses to people 18 years and above. The second dose is taken 21 days after the 1st dose. For both the Jabs, two different vectors are used (Adenovirus 26 and Adenovirus 5). The use of two varying serotypes is unique that provides long-lasting immunity. Vaccine can be stored at 2 to 8°C.

Some people reported mild side effects such as pain, redness or swelling at the site of injection, Asthenia, fatigue, body and muscle pain, cough and sore throat, runny nose, fever and chills, nausea and vomiting, diarrhoea and headache *(24)*.

In India vaccination is not mandatory. But if you choose to get vaccinated, you cannot choose which vaccine you will get. You will be vaccinated by the vaccine that is available at the site. 16th January, 2021 is the historical day when India launched the vaccination drive.

Pfizer-BioNtech COVID-19 Vaccine *(25)*

It is a messenger RNA vaccine with 95 per cent efficacy. People 16 years and older are eligible for the vaccine, administered in two doses intramuscularly, 3 weeks apart. It

is authorized for emergency use. It is not interchangeable. Storage is at –70°C.

Contraindications : (a) history of severe allergic reaction after the previous dose of this vaccine; (b) had a severe reaction to any ingredient of this vaccine.

Before taking the vaccine the provider must know the medical history of the person : any allergy, fever, bleeding disorder if any, or taking blood thinner, if the person is immunocompromised or on a medicine that affects immune system, pregnancy and breast-feeding, and have received another COVID-19 vaccine.

Side effects : Injection site pain, tiredness, headache, muscle pain, chills, joint pain, fever, injection site swelling and redness, nausea, feeling unwell, swollen lymph nodes. There are remote chances of severe allergic reaction (within a few minutes to one hour after getting the dose).

Moderna COVID-19 Vaccine *(26)*

It is a messenger RNA vaccine, with efficacy of about 94.1 per cent, meant for people 18 years of age and above, two doses given intramuscularly 1 month apart. It should be stored between –25°C and –15°C temperature.

The vaccine provider must know about the history of allergies, fever, bleeding disorders or history of taking blood thinner, pregnancy and breast-feeding in mothers, history of taking another COVID-19 vaccine and if the recipient is immunocompromised.

Side effects : Side effects reported are : (a) injection site reactions are pain, redness, swelling, tenderness; (b) general side effects are fatigue, headache, muscle pain, joint pain, vomiting, and fever. Severe side effects are difficulty in breathing, swelling of face and throat, fast heart beat, bad rash all over the body, dizziness and weakness.

COVID-19 dead body management

All staff identified to handle dead bodies in the isolation area, mortuary, ambulance and those workers in the crematorium/burial ground should be trained in the infection prevention control practices. The health worker attending to the dead body should perform hand hygiene, ensure proper use of PPE. Plug oral, nasal orifices of the dead body to prevent leakage of body fluids. Place the body in leak-proof plastic body bag. The exterior of the body bag be decontaminated with 1 per cent hypochlorite.The body bag can be wrapped with a mortuary sheet or sheet provided by the family members. Embalming of the dead body should not be allowed. Autopsies should be avoided. The crematorium/ burial ground staff should be sensitized that COVID-19 does not pose additional risk to them. Viewing of the dead body by unzipping the face, for the relatives to see the body for one last time is allowed. Bathing, kissing, hugging, etc. of the dead body should not be allowed. Religious rituals such as reading from religious scripts, sprinkling holy water and any other last rites that does not require touching of the body can be allowed. Large gathering at the crematorium/burial ground should be avoided. The funeral staff and family members should perform hand hygiene after cremation/burial *(27)*.

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TUBERCULOSIS

Tuberculosis is a specific infectious disease caused by *M. tuberculosis*. The disease primarily affects lungs and causes pulmonary tuberculosis. It can also affect intestine, meninges, bones and joints, lymph glands, skin and other tissues of the body. The disease is usually chronic with varying clinical manifestations. The disease also affects animals like cattle; this is known as "bovine tuberculosis", which may sometimes be communicated to man. Pulmonary tuberculosis, the most important form of tuberculosis which affects man, will be considered here.

Problem statement

WORLD

Tuberculosis remains a worldwide public health problem despite the fact that the causative organism was discovered more than 100 years ago and highly effective drugs and vaccine are available making tuberculosis a preventable and curable disease. Technologically advanced countries have achieved spectacular results in the control of tuberculosis. This decline started long before the advent of BCG or

chemotherapy and has been attributed to changes in the "non-specific" determinants of the disease such as improvements in the standard of living and the quality of life of the people coupled with the application of available technical knowledge and health resources.

It is estimated that about one-third of the current global population is infected asymptomatically with tuberculosis, of whom 5–10 per cent will develop clinical disease during their lifetime *(1)*. Most new cases and deaths occur in developing countries where infection is often acquired in childhood. The annual risk of tuberculosis infection in high burden countries is estimated to be 0.5–2 per cent *(2)*. Patients with infectious pulmonary tuberculosis disease can infect 10–15 persons in a year.

Ending the global TB epidemic remains a distant goal but there are several positive trends. The number of people falling ill with TB (TB incidence) has slowed down and started to stabilize. A total of 10.8 million people had TB during the year 2023. The TB incidence rate (new cases per 100,000 population) in 2023 was 134, a small increase compared to 2022. Most of the people who develop TB disease each year are in 30 high TB burden countries, which accounted for 87 per cent of the global total in 2023, of these 5 countries accounted for 56 per cent of the worldwide total : India (26%), Indonesia (10%), China (6.8%), the Philippines (6.8%) and Pakistan (6.3%) *(3)*.

In 2023, 55 per cent of people who developed TB were men, 33 per cent were women and 12 per cent were children and young adolescents.

The global number of deaths caused by TB fell in 2023, causing an estimated 1.25 million deaths. It includes 1.09 million among HIV-negative people and 161,000 among people with HIV. The total was down from best estimates of 1.32 million in 2022.

The global gap between the estimated number of people who developed TB and the reported number of people newly diagnosed with TB (notified cases) narrowed to a estimate of 2.7 million in 2023, down from 4 million in the year 2020 and 2021. Globally in 2023, 175,923 people were diagnosed and treated for multidrug-resistant or rifampicin resistant TB (MDR/RR-TB); this was 44% of the 400,000 people estimated to have developed MDR/RR-TB in 2023.

The treatment success rate for drug-susceptible TB remains high (at 88%) and has improved to 68% for MDR/RR-TB *(3)*.

In many developing countries, acquired drug resistance remains high, because national tuberculosis control programmes in these countries have not been able to achieve a high cure rate over a very long period of time, even after the introduction of short–course chemotherapy. Poverty, economic recession, malnutrition, overcrowding, indoor air pollution, tobacco, alcohol abuse and diabetes make populations more vulnerable to tuberculosis. Increase in human migration has rapidly mixed infected with uninfected communities. To make global situation worse, tuberculosis has formed a lethal combination with HIV.

The WHO has set *International Standards for Tuberculosis Care*. These standards are intended to facilitate the effective engagement of all care-providers in delivering high-quality care for patients of all ages, including those with smear-positive, smear-negative, extrapulmonary tuberculosis, drug-resistant tuberculosis, and tuberculosis combined with HIV infection. The basic principles of care for people with, or suspected of having tuberculosis are the same worldwide. The standards are intended to be complementary to local and national tuberculosis control policies that are consistent with WHO recommendations. They are not intended to replace local guidelines. There are 6 standards for diagnosis, 9 standards for treatment and 2 standards for public health responsibilities. Please refer to WHO publication : Weekly Epidemiological Record, No. 5, dated 3rd Feb. 2006 for further details.

For the past two decades, national and international efforts in TB prevention, diagnosis and treatment have been guided by the DOTS strategy (mid–1990 until 2005) and subsequently the Stop TB Strategy (2006–2015). The Stop TB strategy was designed to achieve global TB targets set for 2015 within the context of the Millennium Development Goals *(4)*. It focused on five indicators to measure the implementation and impact of TB control. They are case detection, treatment success, incidence, prevalence and death. The core of the strategy was DOTS. The WHO End TB strategy, adopted by the World Health Assembly in May 2014, is a blueprint for countries to end the TB epidemic by driving down TB deaths, incidence and eliminating catastrophic costs. It outlines global impact targets to reduce TB deaths by 90 per cent and to cut new cases by 80 per cent between 2015 and 2030, and to ensure that no family is burdened with the costs due to TB. Ending the TB epidemic by 2030 is among the health targets of the newly adopted Sustainable Development Goals. WHO has gone one step further and set a 2035 target of 95 per cent reduction in deaths and a 90 per cent decline in TB incidence – similar to current levels in low TB incidence countries today *(5)*. For further details, please refer to page 241.

Progress towards new global targets for 2027 set at the 2023 UN high-level meeting on TB can be summarized as follows *(3)* :

- *Coverage of rapid testing for TB* : target 100% of those newly diagnosed; status in 2023, 48%.
- *TB treatment coverage* : target 90%; status in 2023, 75%.
- *Coverage of TB preventive treatment* : target 90% among high-risk populations; status in 2023, 21% among household contacts of people diagnosed with TB, 56% among people living with HIV.
- *Availability of a new TB vaccine that is safe and effective* : target, preferably within 5 years; status in 2023, six vaccines in Phase III trials.
- *Funding for TB prevention, diagnostic and treatment services* : target US$ 22 billion; status in 2023, US$ 5.7 billion.
- Funding for TB research : target US$ 5 billion; status in 2022, US$ 1.0 billion.

INDIA

India is the highest TB burden country in the world in terms of absolute number of incident cases that occur each year. It accounts for 26 per cent of the estimated global incident TB cases in 2023. Table 1 shows the burden of tuberculosis in India, the estimated and reported cases for the year 2023.

TABLE 1

Burden of tuberculosis in India (2023)
(Population : 1,438 million)

	Number (thousands)	Rate (per 100,000 population)
Estimates of TB burden, 2023		
Total TB incidence	2800 (2360–3280)	195 (164–228)
HIV positive TB incidence	42 (36–50)	2.9 (2.5–3.5)
MDR/RR-TB incidence	110 (82–130)	7.4 (5.7–9.1)
HIV negative TB mortality	315 (233–428)	22 (16–30)
HIV positive TB mortality	8.2 (5.9–11)	0.57 (0.41–0.76)
Changes on TB incidence rate and total TB deaths		
Changes in the TB incidence rate 2015–2023		Reduction of 18%
Changes in the total number of TB deaths 2015–2023		Reduction of 24%
Universal health coverage and social protection		
TB treatment coverage (notified new and relapse cases/estimated incidence), 2023		85% (73–100)
TB case fatality ratio (estimated mortality/estimated incidence), 2023		12% (8–16)
TB case notifications		
People diagnosed with a new or relapse case of TB, 2023		2,382,714
– % tested with rapid diagnostics at time of diagnosis		32%
– % with known HIV status		96%
– % pulmonary		75%
– % of pulmonary cases that are bacteriologically confirmed		62%
– % women aged ≥ 15 years		37%
– % men aged ≥ 15 years		58%
– % children aged 0–14 years		5%
Total cases notified		2,517,810
TB/HIV care	Number	(%)
People with a new or relapse case of TB who are living with HIV, 2023	34,476	1.5%
People with a new or relapse case of TB who are living with HIV and who are on antiretroviral therapy, 2023	34,297	99%
Drug-resistant TB care		
% of people with a new case of bacteriologically-confirmed pulmonary TB tested for susceptibility to rifampicin, 2023		82%
% of people previously treated for TB with a case of bacteriologically-confirmed pulmonary TB tested for susceptibility to rifampicin, 2023		86%
% of people with bacteriologically-confirmed pulmonary TB that is resistant to rifampicin tested for susceptibility to fluoroquinolone, 2023		42%
People with bacteriologically-confirmed TB that is resistant to rifampicin and with no known fluoroquinolone resistance, 2023		52,015
People with bacteriologically-confirmed TB that is resistant to rifampicin and with no known fluoroquinolone resistance started on treatment, 2023		48,107
Total number of people with TB that is resistant to rifampicin and with no known fluoroquinolone resistance started on treatment, 2023		49,622
People with bacteriologically-confirmed TB that is resistant to both rifampicin and fluoroquinolone (pre-XDR-TB or XDR-TB), 2023		12,580
People with bacteriologically-confirmed TB that is resistant to both rifampicin and fluoroquinolone started on treatment, 2023		9,158
Treatment success rate and cohort size	Success	Cohort
People with a new or relapse case of TB started on treatment for TB 2022	89%	2,194,723
People with a previously treated case of TB (but not a relapse case) started on treatment for TB 2022	85%	146,377
People with a new or relapse case of TB with HIV started on treatment for TB 2022	79%	35,179
People started on treatment for TB that is resistant to rifampicin (MDR/RR-TB) 2021	73%	21,506
People started on treatment for TB that is resistant to rifampicin and fluoroquinolone (pre-XDR-TB or XDR-TB) 2021	69%	7,029
TB preventive treatment		
% of estimated numbers of household contacts of bacteriologically-confirmed TB cases on preventive treatment, 2023		31% (30–32)

Source : *(6)*

Age and sex distribution

TB affects people of all genders and ages. The TB India report 2024 reports that in 2023, about 58 per cent were men ≥15 years, 37 per cent were women ≥15 years and 5 per cent were children 0–14 years. About 0.04 per cent were transgenders *(7)*. Despite higher TB incidence in men, women and lesbian, gay, bisexual, transgender, queer, intersex, asexual and other identities (LGBTQIA++) individuals experience TB differently, facing discrimination and stigma in various aspects of life. These factors interact to determine TB exposure, risks, vulnerability and health-seeking behaviour.

Gendered vulnerabilities significantly impact how cis women, LGBTQIA++ individuals, and cis men access healthcare in both the public and private sectors. Notably, evidence indicates that smoking, alcohol use and substance use contribute to TB among men. On the other hand, women face a higher burden of undernutrition, rendering them susceptible to TB, as highlighted in National Family Health Survey 5 (NFHS-5). Women's vulnerabilities include hiding symptoms due to stigma, prioritizing household responsibilities, limited decision-making power, restricted mobility and autonomy over financial resources *(7)*.

Tuberculosis kills more women in reproductive age group than all causes of maternal mortality combined, and it may create more orphans than any other infectious disease. Nearly one-third of female infertility in India, is caused by tuberculosis. The indirect impact of tuberculosis on children is considerable, as nearly 3 lacs children of tuberculosis patients, either leave the school or take up employment to help support their families *(8)*. A patient of tuberculosis takes an average of three to four months to recuperate, losing that much income. The loss is disastrous for those struggling against poverty. They are most likely to be defaulters of treatment. The vast majority (more than 90 per cent) of the economic burden of TB in India is caused by the loss of life rather than morbidity.

The age and sex distribution of TB cases in India for the year 2023 is as shown in Fig. 1 *(7)*.

THE ECONOMIC AND SOCIAL BURDEN OF DISEASE : Besides the disease burden, TB also causes an enormous socio-economic burden to India. TB primarily affects people in their most productive years of life. While two-thirds of the cases are male, TB takes disproportionately larger toll among young females, with more than 50 per cent of female cases occurring before the age of 34 years *(8)*.

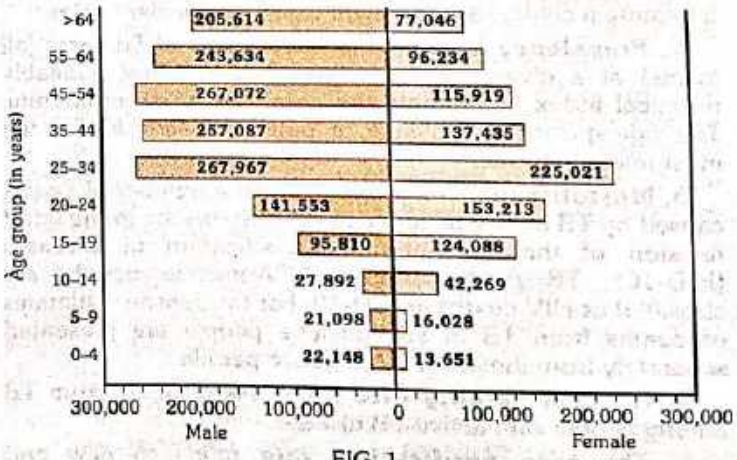


FIG. 1
TB notifications : Age-sex distribution, India (2023)
Source : *(7)*

In India, tuberculosis is mainly a disease of the poor. The majority of its victims are migrant labourers, slum dwellers, residents of backward areas and tribal pockets. Poor living conditions, malnutrition, shanty housing and overcrowding are the main reasons for the spread of the disease *(9)*.

HIV increases a person's susceptibility to tuberculosis infection, and tuberculosis is one of the earliest opportunistic disease to develop amongst persons infected with HIV. It increases morbidity and mortality in HIV infected persons. HIV is the most potent risk factor for progression of TB infection to disease.

Since death rate is declining and the disease is showing a decline in younger age groups, epidemiologists are beginning to think that perhaps we may have crossed the peak of the secular epidemic curve and are somewhere at the beginning of the declining limb.

Despite a comprehensive national TB control programme guiding states for implementation of TB diagnosis and treatment, there is still a long way to go. The vision of RNTCP is that the people suffering from TB receive the highest standards of care and support from healthcare providers of their choice. It is spelt out in the National strategic plan 2012–17 to extend the umbrella of quality TB care and control to include those provided by the private sector. Thus Standards of TB care relevant in Indian context and acceptable to medical fraternity were developed. These standards represent what is expected from Indian health care system *(10)*.

Epidemiological indices *(11)*

Indices or parameters are needed to measure the tuberculosis problem in a community as well as for planning and evaluation of control measures. Indices are also required for international comparison. The following epidemiological indices are generally used in tuberculosis problem measurement and programme strategy :

1. **Incidence** is defined as the number of new and recurrent (relapse) episodes of TB (all forms) occurring in a given year. Recurrent episodes are defined as a new episode of TB in people who have had TB in the past and for whom there was bacteriological confirmation of cure and/or documentation that treatment was completed. Relapse cases are referred to as recurrent cases because the term is more useful when explaining the estimation of TB incidence. Recurrent cases may be true relapses or a new episode of TB caused by reinfection. In current case definitions, both relapse cases and patients who require a change in treatment are called 'retreatment cases'. However, people with a continuing episode of TB that requires a treatment change are prevalent cases, not incident cases.

2. **Prevalence** is defined as the number of TB cases (all forms) at a given point in time. It is the best available practical index to estimate the case load in a community. The age-specific prevalence of patients is considered the most relevant index.

3. **Mortality** from TB is defined as the number of deaths caused by TB in HIV-negative people, according to the latest revision of the International Classification of Diseases (ICD-10). TB deaths among HIV-positive people are classified as HIV deaths in ICD-10. For this reason, estimates of deaths from TB in HIV-positive people are presented separately from those in HIV-negative people.

4. **The case fatality rate** is the risk of death from TB among people with active TB disease.

5. The **case notification rate** refers to new and recurrent episodes of TB notified to WHO for a given year, expressed per 100,000 population. The case notification rate for new and recurrent TB is important in the estimation of TB incidence. In some countries, however, information on treatment history may be missing for some cases. When data on treatment history are not available, recurrent cases cannot be distinguished from cases whose treatment was changed, since both are registered and reported in the category "retreatment". Patients reported in the "unknown history" category are considered incident TB episodes (new or relapse). This is a change from previous years in view of past difficulties to estimate with NTPs the proportion of true new, or relapse TB episodes in this category of patients.

6. **Case detection rate** : The case detection rate is calculated as the number of notification of new and relapse cases in a year divided by the estimated incidence of such cases in the same year.

7. **Prevalence of drug-resistant cases** : It is the prevalence of patient excreting tubercle bacilli resistant to anti-tuberculosis drugs. This index is directly related to chemotherapy.

(a) *Prevalence of infection* : It is the percentage of individuals who show a positive reaction to the standard tuberculin test. When the test is done in defined age-groups, it yields age-specific prevalence which is a far superior indicator than the mere percentage of positive reactors in the total population *(12)*. Prevalence represents a cumulative experience of a population to recent and remote infection with *M. tuberculosis*. It may be mentioned that the interpretation of tuberculin test has become complicated in countries with a high coverage of BCG vaccination at birth, since most of the vaccinees become positive reactors to tuberculin test. This presents a problem in identifying true prevalence of infection. Further, cross-sensitivity to atypical mycobacteriae, where it occurred, has also caused the prevalence to be over-estimated. Despite these limitations, tuberculin-testing is widely used for estimating the prevalence of tuberculous infection in a population.

(b) *Incidence of infection* : (Annual Infection Rate) : It is the percentage of population under study who will be newly infected by Mycobacterium tuberculosis among the non-infected of the preceding survey during the course of one year. It reflects the annual risk of being infected (or reinfected) in a given community. In other words, it expresses the attacking force of tuberculosis in a community *(13)*. In developing countries, every 1% of annual risk of infection is said to correspond to 50 new cases of smear-positive pulmonary tuberculosis, per year for 100,000 general population *(14)*. Also known as "tuberculin conversion" index, this parameter is considered one of the best indicators for evaluating the tuberculosis problem and its trend. The higher the rate, the greater the problem *(13, 15)*. It may be mentioned that a good treatment programme, lowers the risk of tuberculosis infection in the community.

Definitions of tuberculosis cases and treatment *(16)*

WHO has issued updated guidance on definitions of cases and treatment outcomes and associated reporting framework. These updates were necessary to accomodate diagnosis using Xpert MTB/RIF and other WHO-endorsed molecular tests, as well as offering an opportunity to improve aspects of the existing (2006) framework, such as inclusion of more comprehensive reporting of TB cases among children. The updated definitions are used from 2014 in global data collection *(11)*.

Presumptive case: Presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect).

A. CASE DEFINITIONS

a. *A bacteriologically confirmed TB case* is one from whom a biological specimen is positive by smear microscopy, culture or WRD (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.

b. *A clinically diagnosed TB case* is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to:

1. anatomical site of disease;
2. history of previous treatment;
3. drug resistance;
4. HIV status.

1. Classification based on anatomical site of disease

a. *Pulmonary tuberculosis (PTB)* refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB.

b. *Extrapulmonary tuberculosis (EPTB)* refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

2. Classification based on history of previous TB treatment (patient registration group)

Classifications based on history of previous TB treatment are slightly different from those previously defined. They focus only on history of previous treatment and are independent of bacteriological confirmation or site of disease.

New patients: Patients who have never been treated for TB or have taken anti-TB drugs for less than 1 month.

Previously treated patients: Patients who received 1 month or more of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment as follows:

a. *Relapse patients* have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

b. *Treatment after failure patients* are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.

c. *Treatment after loss to follow-up patients* have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as treatment after default patients.)

d. *Other previously treated patients* are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

e. *Patients with unknown previous TB treatment history* do not fit into any of the categories listed above. New and relapse cases of TB are incident TB cases.

3. Classification based on drug resistance

Cases are classified in categories based on drug susceptibility testing (DST) of clinical isolates confirmed to be *M. tuberculosis*:

a. *Monoresistance:* resistance to one first-line anti-TB drug only.

b. *Polydrug resistance:* resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).

c. *Multidrug resistance:* resistance to at least both isoniazid and rifampicin.

d. *Extensive drug resistance:* resistance to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.

e. *Rifampicin resistance:* resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

These categories are not all mutually exclusive. When enumerating rifampicin-resistant TB (RR-TB), for instance, multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are also included. While it has been the practice until now to limit the definitions of monoresistance and polydrug resistance to first-line drugs only, future drug regimens may make it important to classify patients by their strain resistance patterns to fluoroquinolones, second-line injectable agents and any other anti-TB drug for which reliable DST becomes available.

4. Classification based on HIV status

a. *HIV-positive TB patient* refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-ART register or in the ART register once ART has been started.

b. *HIV-negative TB patient* refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly.

c. *HIV status unknown TB patient* refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

B. TREATMENT OUTCOME DEFINITIONS

The new treatment outcome definitions make a clear distinction between two types of patients:

- patients treated for drug-susceptible TB;
- patients treated for drug-resistant TB using second-line treatment (defined as combination chemotherapy for drug-resistant tuberculosis which includes drugs other than the first-line drugs (see page 218).

The two groups are mutually exclusive. Any patient found to have drug-resistant TB and placed on second-line treatment is removed from the drug-susceptible TB outcome cohort. This means that management of the standard TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment.

1. *Treatment outcomes for TB patients (excluding patients treated for RR-TB or MDR-TB)*

All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome from this list except those with RR-TB or MDR-TB, who are placed on a second-line drug regimen.

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of cured and treatment completed.
Cohort	A group of patients in whom TB has been diagnosed, and who were registered for treatment during a specified time period (e.g. the cohort of new smear-positive cases registered in the calendar year 2011). This group forms the denominator for calculating treatment outcomes. The sum of the treatment outcomes, plus any case for which no outcome is recorded (eg. still on treatment) should equal the number of cases registered *(17)*.

Patients found to have an RR-TB or MDR-TB strain at any point in time should be started on an adequate second-line drug regimen. These cases are excluded from the main TB cohort when calculating treatment outcomes and included only in the second-line TB treatment cohort analysis. If treatment with a second-line drug regimen is not possible, the patient is kept in the main TB cohort and assigned an outcome from above table.

2. *Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment*

Outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: – lack of conversion[b] by the end of the intensive phase,[a] or – bacteriological reversion[b] in the continuation phase after conversion[b] to negative, or – evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or – adverse drug reactions (ADRs).
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown)
Treatment success	The sum of cured and treatment completed
Cohort	A group of patients where RR-TB has been diagnosed (including MDR-TB and XDR-TB), and who were started on a full course of a second-line MDR-TB drug regimen during a specified time period (e.g. the cohort of MDR-TB cases registered in the calendar year 2010). This group forms the denominator for calculating treatment outcomes. With the revised definitions, any patient found to have drug-resistant TB and placed on second-line treatment is removed from the drug-susceptible TB outcome cohort. This means that management of the basic management unit TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment *(11)*.

[a] For *Treatment failed*, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed and Treatment failed start to apply.

[b] The terms "conversion" and "reversion" of culture as used here are defined as follows:

Conversion (to negative) : culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

Reversion (to positive) : culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining treatment failed, reversion is considered only when it occurs in the continuation phase.

NATURAL HISTORY OF TUBERCULOSIS

Agent factors

(a) AGENT : *M. tuberculosis* is a facultative intracellular parasite, i.e., it is readily ingested by phagocytes and is resistant to intracellular killing *(18)*. Of importance to man are the human and bovine strains. The human strain is responsible for the vast majority of cases. The bovine strain affects mainly cattle and other animals. Regarding virulence, the Indian tubercle bacillus is said to be less virulent than the European bacillus. In recent years, a number of "atypical" mycobacteria have been isolated from man *(19)*. These have been classified into four groups – (i) photochromogens (e.g., *M. Kansasii*); (ii) scotochromogens (e.g., *M.*

scrofulaceum); (iii) non-photochromogens (e.g., *M. intercellulare*) and, (iv) rapid growers (e.g., *M. fortuitum*). All these are mainly saprophytic. Diseases attributed to them have resembled pulmonary tuberculosis and chronic cervical lymphadenitis.

(b) SOURCE OF INFECTION : There are two sources of infection – human and bovine. (i) *Human source* : The most common source of infection is the human case whose sputum is positive for tubercle bacilli and who has either received no treatment or has not been treated fully. An estimated annual average of 10–15 persons contract the infection from one case of infectious pulmonary TB. Such sources can discharge the bacilli in their sputum for years. The tubercle bacilli in a human case are usually a mixed group – some multiply very rapidly and some slowly. The more rapidly a bacillary strain multiplies the more susceptible it is to the bactericidal action of chemotherapeutic drugs. The slow multipliers are the source of persister or dormant bacilli; they can remain alive for years without causing harm to the host, but when conditions are favourable they may start multiplying again and cause active disease. That is, they are the seeds of a future relapse *(20)*. (ii) *Bovine source:* The bovine source of infection is usually infected milk. There is no definite evidence that bovine tuberculosis is a problem in this country because of the practice of boiling milk before consumption.

(c) COMMUNICABILITY : Patients are infective as long as they remain untreated. Effective anti-microbial treatment reduces infectivity by 90 per cent within 48 hours *(21)*.

Host factors

(a) AGE : Tuberculosis affects all ages. Developing countries show a sharp rise in infection rates from childhood to adolescence. In India, from an average of 2 per cent in the "0–14 years age group", the infection rate climbs to about 20 per cent at age 15–24 years age group. In the developed countries, the disease is now more common in the elderly. (b) SEX : More prevalent in males than in females. (c) HEREDITY : Tuberculosis is not a hereditary disease. However, twin studies *(22)* indicate that inherited susceptibility is an important risk factor. (d) NUTRITION : Malnutrition is widely believed to predispose to tuberculosis. As malnutrition is widely prevalent in developing world, it will continue to affect the development of active disease, out-come of treatment and spread of the disease. (e) IMMUNITY : Man has no inherited immunity against tuberculosis. It is acquired as a result of natural infection or BCG vaccination. Past infection with atypical mycobacteria is also credited with certain amount of naturally acquired immunity. It is now known that both delayed hypersensitivity and acquired resistance to tuberculosis are cell-mediated responses. In most cases, the cellular immunity proves adequate to limit further multiplication and spread of bacilli.

Social factors

Tuberculosis is a social disease with medical aspects. It has also been described as a barometer of social welfare. The social factors include many non-medical factors such as poor quality of life, poor housing, and overcrowding, population explosion, undernutrition, smoking, alcohol abuse, lack of education, large families, early marriages, lack of awareness of causes of illness, etc. All these factors are interrelated and contribute to the occurrence and spread of tuberculosis. In fact, tuberculosis began to decline in the western world long before the advent of chemotherapeutic drugs. This has been attributed to improvements in the quality of life.

Mode of transmission

Tuberculosis is transmitted mainly by droplet infection and droplet nuclei generated by sputum-positive patients with pulmonary tuberculosis. To transmit infection, the particles must be fresh enough to carry a viable organism. Coughing generates the largest number of droplets of all sizes. The frequency and vigour of cough and the ventilation of the environment influence transmission of infection. Tuberculosis is not transmitted by fomites, such as dishes and other articles used by the patients. Sterilization of these articles is therefore of little or no value. Patients with extrapulmonary tuberculosis or smear-negative tuberculosis constitute a minimal hazard for transmission of infection.

Incubation period

The time from receipt of infection to the development of a positive tuberculin test ranges from 3 to 6 weeks, and thereafter, the development of disease depends upon the closeness of contact, extent of the disease and sputum positivity of the source case (dose of infection) and host–parasite relationship. Thus the incubation period may be weeks, months or years.

THE CONTROL OF TUBERCULOSIS

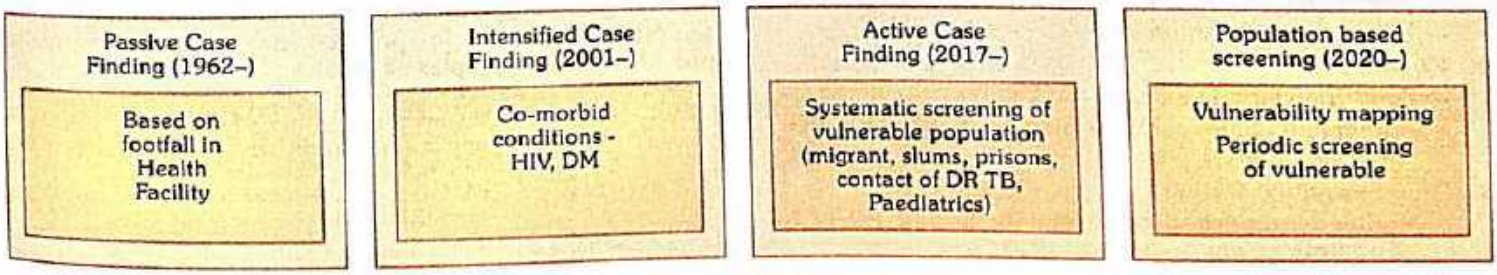
Tuberculosis control means reduction in the prevalence and incidence of disease in the community.

Since tuberculosis is an infectious disease, the basic principles of prevention and control are the same as for any other infectious disease. The control measures consist of a **curative** component – namely case finding and treatment; and a **preventive** component – namely BCG vaccination. These are the two fundamental components of a national tuberculosis programme. The most powerful weapon, however, is the combination of case-finding and treatment.

Case-finding in public sector *(23)*

The first step in a tuberculosis control programme is early detection of sputum-positive cases. This should be an intensive, on-going programme. The evolution of strategies for improving case findings are as shown below :

Evolution of strategies for improving case findings



STRATEGIES ADOPTED FOR CASE FINDING

a. *Passive case finding* : An overwhelming majority of patients of pulmonary tuberculosis have one or more of the symptoms referable to chest, such as persistent cough and fever, and many of them (over 60 per cent) seek medical advice on their own initiative. The chest symptoms often develop early, that is before the disease has gone on to an advanced stage. This is the most fertile group for case-finding.

b. *Intensified case finding* : Screening patients attending health facilities with comorbidities, for TB (HIV care settings, diabetes clinic, tobacco cessation clinic, nutritional rehabilitation centre) and OPDs (Gynaecology, orthopaedics etc.). This is a provider-initiated screening of outpatient clinic/hospital attendees for symptoms of TB.

c. *Active case finding* : Actively searching for TB patients among vulnerable population in the community (Slum, tribal, prison etc.). This activity adopted by the programme enables early detection of TB patients.

d. Vulnerability mapping is done followed by periodic screening of vulnerable population. Leveraging outreach of other Health Programmes in Health and wellness centres.

Screening strategies

1. Community screening can be done by :

Inviting people to attend screening at a mobile facility or a fixed facility. Invitations may target specifically people within a given vulnerable group, those

- who have had recent close contact with someone who has TB and people with symptoms of TB.
- Going door-to-door to screen households.

2. Institutional screening
   - In health care facilities : Systematically perform active screening of vulnerable individuals attending hospitals and other health care institution.
   - In congregate settings : Systematically perform active screening of vulnerable individuals in shelters, old age homes, refugee camps, correctional facilities and other specific locations such as workplaces.

Recommendations on at risk or vulnerable groups to be screened

A vulnerable group is any group of people in which the prevalence or incidence of TB is significantly higher than in the general population. The recommended vulnerable groups to be considered for intensified case finding are discussed in detail on page 243.

d. CASE-FINDING TOOLS

Tools for microbiological confirmation of TB are *(24)* :

1. Sputum Smear Microscopy (for AFB) :
   - Zeihl-Neelsen staining
   - Fluorescence staining
2. Culture :
   - Solid (Lowenstein Jensen) media
   - Automated Liquid culture systems e.g. BACTEC MGIT 960, BacT Alert or Versatrek etc.
3. Drug Sensitivity Testing:
   - Modified proportionate sensitivity testing (PST) for MGIT 960 system
   - Economic variant of proportion sensitivity testing (1%) using LJ medium
4. Rapid molecular diagnostic tests:
   - Line probe assay (LPA) for MTB complex and detection of RIF & INH resistance (FL LPA), and FQ and SLI resistance (SL LPA)
   - Nucleic acid amplification test (NAAT) (CBNAAT/ truenat)

Supportive tools for the clinical diagnosis of TB

- Chest X-ray and other radiological tests.
- Tuberculin skin test (TST), Interferon gamma release assay (IGRA) and other blood tests, histopathology and other tissue-based tests.

Smear microscopy being the most commonly used method for microbiological diagnosis of TB for the last several decades, has had enormous value in TB diagnosis but with limited sensitivity, more so in children and PLHIV. Under the programme, two methods of microscopy are currently being used – ZN stain-based microscopy using conventional microscope and light emitting.

Diode based fluorescent microscopy (LED FM) : Culture though highly sensitive and specific method for TB diagnosis, requires 2–8 weeks to yield results and hence does not help in early diagnosis. However, culture is used for follow-up of patients on drug resistant TB treatment to detect early recurrence. In addition, it is also used for long term follow-up for DS TB patients, to ensure relapse free cure.

Liquid culture system : Mycobacteria growth indicator tube system (MGIT-B) is an automated culture system that detects the growth of mycobacteria. The culture results are usually available upto 42 days. DST results are available 14–26 days after the cultures turn positive.

Molecular assays : Polymerase-chain-reaction (PCR) based technologies using various modifications are used for detecting the presence of putative resistance genes (rpoB for rifampicin, katG and inhA for Isoniazid etc.).

Sputum examination : Sputum smear examination by direct microscopy is now considered the method of choice. The reliability, cheapness and ease of direct microscopic examination has made it number one case-finding method all over the world. It enables us to discover the epidemiologically most important cases of pulmonary tuberculosis, i.e., those excreting tubercle bacilli in their sputum. This is the group which contributes most of the new cases to the "pool of infection" every year.

Collection of sputum samples

A pulmonary tuberculosis suspect should submit two sputum samples for microscopy. The chances of finding TB bacilli are greater with two samples than with one sample. Secretions build up in the airways overnight. So an early morning sputum sample is more likely to contain TB bacilli than one taken later in the day. It may be difficult for an out-patient to provide two early morning sputum samples. Therefore in practice an out-patient usually provides sputum samples as follows :

day 1	sample 1	Patient provides an "on-the-spot" sample under supervision when presenting to the health facility. Give the patient a sputum container to take home for an early morning sample the following morning.
day 2	sample 2	Patient brings an early morning sample.

If the patient is coming from a long distance or there is likelihood that the patient may default to give a second sample, 2 spot specimens are collected with a gap of one hour *(25)*.

Ziehl-Neelsen acid-fast stain

This simple stain detects acid fast bacilli. The procedure is as follows:

1. Fix the smear on the slide by passing the slide with the smear up about three times slowly through a flame. It can also be done by covering the smear with alcohol and letting this evaporate.
2. Cover with carbol fuchsin, steam gently for 5 minutes over direct flame (or for 20 minutes over a water bath). Do not permit slide to boil or dry out.
3. Wash with deionized water.
4. Decolourize in 3.0 per cent acid–alcohol (95 per cent ethanol and 3.0 per cent hydrochloric acid) until only a faint pink colour remains.
5. Wash with water.
6. Counter stain for 1 minute with Loeffler's methylene blue.
7. Wash with deionized water and let it dry.

Slide reporting *(26)*

The number of bacilli seen in a smear reflects disease severity and patient infectivity. Therefore, it is important to record the number of bacilli seen on each smear. The table below shows the standard method of reporting using 1000 X magnification.

Number of bacilli			Result reported
No	AFB	per 100 oil immersion fields	0
1-9	AFB	per 100 oil immersion fields	scanty (or number AFB seen)
10-99	AFB	per 100 oil immersion fields	+ (1+)
1-10	AFB	per oil immersion field	++ (2+)
> 10	AFB	per oil immersion field	+++ (3+)

Laboratory technicians should examine both the sputum samples from each TB suspect. They must record the result of each sputum sample with the laboratory reference number in the laboratory register and on the sputum request form. Results as indicated above are made available to the clinician who can then categorize the patient. It is advised that the smear examined by one microscopist should not exceed 20 per day as visual fatigue leads to a deterioration of reading quality *(27)*. One positive specimen out of the two is enough to declare a patient as smear positive TB.

Sputum smear microscopy for tubercle bacilli is positive when there are at least 10,000 organisms present per ml of sputum. The sputum smear positivity rate in TB/HIV patient depends on the degree of immunocompromise. If the degree of immunocompromise is mild, the likelihood of positive sputum smear is similar to HIV negative patient. If immunocompromise is severe, the likelihood of positive sputum smear is decreased because of decreased inflammation in lungs *(26)*.

False-positive results of sputum smear microscopy

A false-positive result means that the sputum smear result is positive even though the patient does not really have sputum smear-positive PTB. This may arise because of the following: red stain retained by scratches on the slide; accidental transfer of AFBs from a positive slide to a negative one; contamination of the slide or smear by environmental mycobacteria; presence of various particles that are acid-fast (e.g. food particles, precipitates, other microorganisms).

False-negative results of sputum smear microscopy

A false-negative result means that the sputum smear result is negative even though the patient really does have sputum smear-positive PTB. This may arise because of problems in collecting (patient provides inadequate sample, inappropriate sputum container used or sputum stored too long before smear microscopy), processing (faulty sampling of sputum for smear or faulty smear preparation and staining), or interpreting sputum smears (inadequate time spent examining smear or inadequate attention to smear examination), or because of administrative errors (misidentification of patient, incorrect labelling of sample or mistakes in documentation).

Fluorescence microscopy

Fluorescence microscopy is mainly used in industralized countries. It is performed with auramine stain. The advantage of FA microscopy is from the speed of examination. The field of view is 5–10 times bigger. Scanning of one length of smear will require only 1–2 minutes.

Light-emitting diode fluorescence microscopy (LEDs)

LEDs provide a much less expensive light source for fluorescence microscopy. In a recent WHO evaluation, the diagnostic accuracy of LED microscopy was found to be comparable to that of conventional fluorescence microscopy and superior to that of conventional Ziehl-Neelsen microscopy. It is therefore recommended that LED microscopy be phased in as an alternative to conventional Z–N light microscopy in both high and low-volume laboratories *(27)*.

Rapid diagnostic tools include

The CB-NAAT system detects DNA sequences, specific for Mycobacterium tuberculosis complex and rifampicin resistance by polymerase chain reaction. It concentrates mycobacterium tuberculosis bacilli from sputum samples, isolates genomic material from the captured bacteria by sonication and subsequently amplifies the genomic DNA by PCR. The process identifies clinically relevant, rifampicin resistance inducing mutations in the RNA polymerase beta (rpoB) gene in the Mycobacterium tuberculosis genome in a real time format using fluorescent probes called molecular beacons. Results are obtained from unprocessed sputum samples in 90 minutes.

Line Probe Assay (LPA) :

Line Probe Assays detect DNA sequences specific for Mycobacterium tuberculosis complex as well as mutations conferring resistance. Sputum samples are decontaminated and the concentrated deposit subjected to smear microscopy. DNA is extracted from all smear positive samples and subjected to PCR; while all smear negative samples are inoculated in liquid culture and LPA performed using the culture isolate obtained upon growth of Mycobacteria. The PCR amplified products are reverse

hybridized on nitrocellulose strips containing probes specific for detection of *M. tuberculosis* and mutations associated with drug resistance. First line LPA detects resistance to Rifampicin (rpoB) and Isoniazid (katG, inhA), while second line LPA detects fluoroquinolone class resistance (gyrA, gyrB) and second line injectable class resistance (rrs, eis).

Nucleic Acid Amplification Test (NAAT) provides accurate and rapid diagnosis of TB by detecting Mycobacterium tuberculosis (*M. tuberculosis*) and Rifampicin (Rif) resistance conferring mutations, in sputum specimen as well as specimen from extra-pulmonary sites. Under the programme, its use is recommended for diagnosis of DR-TB, in presumptive DR-TB patients and TB preferentially in key population such as children, PLHIV, Extra-pulmonary TB and in smear negative TB as per the diagnostic algorithm.

Radiography

Chest X-rays are useful for the diagnosis of smear negative pulmonary TB and TB in children. It is not routinely indicated in smear-postive cases. X-rays are valuable tools for the diagnosis of pleural and pericardial effusion, especially in early stages of the disease when clinical signs are minimal. It is essential in the diagnosis of miliary TB. The other indications are frequent or severe haemoptysis to exclude bronchiectasis or aspergilloma and in patients needing specific treatment for pneumothorax.

TUBERCULIN TEST

The tuberculin test was discovered by Von Pirquet in 1907. A positive reaction to the test is generally accepted as evidence of past or present infection by *M. tuberculosis*. The tuberculin test is the only means of estimating the prevalence of infection in a population.

Tuberculin : Only two tuberculins have been accepted as standard tuberculin by WHO, i.e., purified protein derivative–S (PPD–S) and PPD–RT 23. PPD is standardized in terms of its biological reactivity as tuberculin units (TU). A standard 5 tuberculin unit (5 TU) dose of PPD-S is defined as delayed skin activity contained in a 0.1 µg/0.1 ml dose of PPD–S. 1 TU of PPD–RT 23 is equivalent to 5 TU of PPD–S. In India PPD–RT 23 with Tween 80 is used. Tween 80 is a detergent added to tuberculin to prevent their adsorption on glass or plastic surface. Use of tuberculin strength of 1 TU is recommended for standard Mantoux test in India.

MANTOUX TEST : The Mantoux test is carried out by injecting 1 TU of PPD in 0.1 ml intradermally on the flexor surface of the left forearm, mid-way between elbow and wrist. The injection should be made with a tuberculin syringe, with the needle bevel facing upward. When placed correctly, injection should produce a pale wheal of the skin, 6 to 10 mm in diameter. The result of the test is read after 48–96 hours but 72 hours (3rd day) is the ideal.

Tuberculin reaction consists of erythema and induration. Since erythema is sometimes difficult to measure, induration alone is measured (horizontal transverse diameter of induration in millimetres, using a transparent plastic ruler or callipers). Reactions exceeding 10 mm are considered "positive". Those less than 6 mm are considered "negative". Those between 6 and 9 mm are considered "doubtful", i.e., the reaction may be due to *M. tuberculosis* or atypical mycobacteria. If there is no induration, the result should be recorded as '0'.

It has been further observed that strong reactors (i.e., those showing 20 mm or more induration) have greater chances of developing tuberculosis than those showing 10 mm induration. Those with less than 5 mm induration have more risk of developing tuberculosis than those with 6-9 mm induration. Studies indicate that 92 per cent of new cases occur in persons who are already tuberculin reactors *(28)*. These findings illustrate the prognostic significance of the test.

Classification of positive tuberculin skin test reaction *(29)*

A tuberculin skin test reaction is considered positive if the transverse diameter of the indurated area reaches the size required for the specific group. All other reactions are considered negative. The classification is as follows :

Induration size	Group
≥ 5 mm	1. HIV-positive persons. 2. Recent contacts of individuals with active tuberculosis. 3. Persons with fibrotic changes on chest films suggestive of prior tuberculosis. 4. Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of >15 mg/d of prednisone for 1 month or more).
≥ 10 mm	1. Recent immigrants (<5 years) from countries with a high prevalence of tuberculosis (eg, Asia, Africa, Latin America). 2. HIV-negative injection drug users. 3. Mycobacteriology laboratory personnel. 4. Residents of and employees in the following high-risk congregate settings: correctional institutions; nursing homes and other long-term facilities for the elderly; hospitals and other health care facilities; residential facilities for AIDS patients; and homeless shelters. 5. Persons with the following medical conditions that increase the risk of tuberculosis: gastrectomy, ≥ 10% below ideal body weight, jejunoileal bypass, diabetes mellitus, silicosis, advanced chronic kidney disease, some hematologic disorders, (eg. leukemias, lymphomas) and other specific malignancies (eg. carcinoma of the head or neck and lung). 6. Children <4 years of age or infants, children and adolescents exposed to adults at high risk.
≥ 15 mm	1. Persons with no risk factors for tuberculosis.

A negative tuberculin test must also be interpreted with caution. For many years, it has been assumed that a negative test constituted strong evidence against the presence of active tuberculous disease in the majority of cases. It has been shown that in the majority of patients with tuberculosis, the cellular immune response may be depressed. It means a negative tuberculin test cannot be relied upon to exclude tuberculosis. The dermal hypersensitivity to tuberculin can also be lost in various states of immune suppression, e.g., malignancy, Hodgkin's disease, HIV infection, malnutrition, severe bacterial infection (including TB itself), viral infections (e.g. measles, chickenpox, glandular fever), recent live-virus vaccination (e.g. measles), immunosuppresive drugs (e.g. steroids) and incorrect injection of PPD. Therefore, too great a diagnostic significance should not be placed on a negative tuberculin test *(18)*.

Two-step testing

Some people who were previously infected with TB may have a negative reaction when tested years after infection, as the immune system response may gradually wane. This initial skin test, though negative, may stimulate (boost) the body's ability to react to tuberculin in future tests. Thus, a positive reaction to a subsequent test may be misinterpreted as a new infection, when in fact it is the result of the boosted reaction to an old infection. Giving a second TST after an initial negative TST reaction is called a two-step testing. Use of two-step testing is recommended for initial skin testing of adults who will be retested periodically (e.g, health care workers).

- The first test is read 48–72 hours after injection.
  - If the first test is positive, consider the person infected.
  - If the first test is negative, give a second test one to three weeks after the first injection.
- The second test is read 48–72 hours after injection.
  - If the second test is positive, consider the person previously infected.
  - If the second test is negative, consider the person uninfected.

The validity of tuberculin test, like all medical tests, is subject to variability. It is limited by lack of specificity. Apart from errors associated with the mode of administration, reading of results and the test material used, there are other factors such as cross-reactions due to sensitization by other mycobacteria, which should be taken into account. In countries with a high coverage of BCG, which also produces tuberculin hypersensitivity, tuberculin test has lost its sensitivity as an indicator of the "true" prevalence of infection. The true prevalence rates of infection may be exaggerated by infection with atypical mycobacteria as well as the "boosting effect" of a second dose of tuberculin producing a larger reaction than the first *(30)*.

It is often assumed that delayed hypersensitivity as measured by tuberculin testing is a correlate of the protective immune response. But evidence indicates that this hypersensitivity is irrelevant to the ability of the host to combat the disease. Despite these limitations, the tuberculin test continues to be the only tool for measuring the prevalence of tuberculous infection in a community. It has been aptly said that tuberculin test "must be approached with respect, administered with care, read with deliberation and interpreted with sentient discrimination".

TB Interferon gamma release assays (IGRAs)

The Interferon Gamma Release Assays (IGRAs) are a new type of more accurate test for TB. IGRAs are blood tests that measure a person's immune response to the bacteria that cause TB. The immune system produces some special molecules called cytokines. These TB tests work by detecting a cytokine called the interferon gamma cytokine. In practice you carry out one of these TB tests by taking a blood sample and mixing it with special substances to identify if the cytokine is present. Two IGRAs that have been approved and are commercially available, are the QuantiFERON® TB Gold test, and the T-SPOT® TB test. The advantages of an IGRA TB test includes the fact that it only requires a single patient visit to carry out the TB test. Results can be available within 24 hours, and prior BCG vaccination does not cause a false positive result. Disadvantages include the fact that the blood sample must be processed fairly quickly, laboratory facilities are required, and the test is only for latent TB. It is also thought that the IGRAs may not be as accurate in people who have HIV. In low prevalence resource rich settings, IGRAs are beginning to be used in place of the TB skin test *(31)*.

Case-finding should not be an end in itself. It is of little value as a control measure unless followed by chemotherapy. Resources and efforts should be directed towards primary health care, rather than irrational case finding.

Please refer to page 220 for the flow chart for diagnosis of tuberculosis in adults, as followed by NTEP.

Chemotherapy

The development of effective treatment for tuberculosis has been one of the most significant advances during this century. With the evolution of controlled trials (see page 92), the chemotherapy of tuberculosis is now more rationally based, than in the treatment of other infectious diseases.

Chemotherapy is indicated in every case of active tuberculosis. The objective of treatment is cure – that is, the elimination of both the fast and slowly multiplying bacilli (including the persisters) from the patient's body. The effects of chemotherapy are judged not by the anatomic healing of lesions, but mainly by the elimination of bacilli from the patient's sputum. Chemotherapy should be easily available, free of charge to every patient detected. It should be adequate, appropriate and applied to the entire pool of infectors in the community. Patient compliance is critically important; the patient must take the correct drugs at the correct dosage for the correct length of time. Incomplete treatment puts the patient at risk of relapse and the development of bacterial resistance and, importantly, the community at risk of infection with resistant organisms.

Anti-tuberculosis drugs

There are now twelve or thirteen drugs active against ***M. tuberculosis***, of which, six are considered to be essential. An antitubercular drug should satisfy the following criteria : (a) highly effective (b) free from side-effects (c) easy to administer, and (d) reasonably cheap. The currently used drugs may be classified into two groups : bactericidal and bacteriostatic. The bactericidal drugs kill the bacilli *in vivo*. The bacteriostatic drugs inhibit the multiplication of the bacilli and lead to their destruction by the immune mechanism of the host. A brief review of these drugs is given below.

THE FIRST–LINE DRUGS

BACTERICIDAL DRUGS

Rifampicin (RMP)

RMP is a powerful bactericidal drug. It is a better sterilizing agent than INH. It permeates all tissue membranes including the blood-brain and placental barriers. It is equally effective against intracellular as well as extracellular bacilli. It is the only bactericidal drug active against the "persisters" or dormant bacilli which are found in the solid caseous lesions, all other drugs being inactive *(32)*. In this regard, it has a distinct advantage over INH. Rifampicin is of special value when the bacilli resists other drugs. In combination with INH, it can cure even extensive tuberculosis, in about 9 months.

RMP is used only as oral drug. It is so well absorbed that there is little need for parenteral administration. The dose should be taken at least one hour before or 2 hours after food because absorption is reduced by food. It is never used alone for the treatment of tuberculosis, but always used in combination with INH or another drug.

Many patients develop nausea at the start of treatment, but this passes off. The toxic effects include hepatotoxicity, gastritis, influenza–like illness, purpura, thrombocytopenia and nephrotoxicity. The patient should be told that the drug will turn the urine red; this can be used as test of compliance.

PAS delays its absorption; hence concurrent administration with PAS should be avoided. If RMP is stopped for some reason, it should not be restarted within 3 weeks to avoid hypersensitivity.

INH

INH ranks among the most powerful drugs in the treatment of tuberculosis. It can easily penetrate the cell membrane, and is thus active against intracellular and extracellular bacilli. Its action is most marked on rapidly multiplying bacilli. It is less active against slow multipliers. INH gets widely distributed in the body including CSF. Its ease of administration, freedom from toxicity and low cost makes it an ideal component for any drug regimen.

INH should be given as a single dose. INH reaches its peak level in blood 1 to 2 hours after the dose. It has been found that its peak level in serum is more important than sustained inhibitory level. It is for this reason, INH should not be given in divided doses *(33)*.

Patient may experience gastrointestinal irritation, peripheral neuropathy, blood dyscrasias, hyperglycaemia and liver damage. Those patients who are slow inactivators experience a higher incidence of toxicity. The addition of pyridoxine (10–20 mg daily) helps prevent the occurrence of peripheral neuropathy.

Streptomycin

Streptomycin is bactericidal. It acts entirely on rapidly multiplying bacilli. It has been shown that when bacilli are multiplying rapidly, they come out of the phagocytes and are mostly extracellular and are, therefore, susceptible to streptomycin. Streptomycin is less active against slow multipliers. It has no action on persisters. It does not permeate cell walls or normal biological membranes such as meninges or pleura.

The daily dose of streptomycin is 0.75 g in a single injection. This is a disadvantage because of the organizational problem involved in the long term treatment. It can cause side-effects which include vestibular damage and nystagmus rather than deafness. Renal damage may also occur.

Pyrazinamide

This drug is bactericidal and is particularly active against the slow-multiplying intracellular bacilli which are unaffected by other drugs. It has been found to increase the sterilizing ability of rifampicin. Therefore, pyrazinamide has been incorporated in short-course chemotherapy regimens.

Complications include hepatotoxicity and hyperuricaemia. Pyrazinamide achieves high levels in CSF and is, therefore, recommended in tuberculous meningitis.

Ethambutol

Ethambutol is bacteriostatic and is used in combination to prevent the emergence of resistance to other drugs. It is given orally. Its major side-effect is retrobulbar neuritis; this however does not occur at the usual dosage. Ethambutol has replaced para–aminosalicylic acid (PAS) almost entirely among adults.

THE SECOND–LINE DRUGS

Fluoroquinolones

Ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin and gatifloxacin are active against *M. tuberculosis*, even those resistant to other drugs. They are given orally or IV. They are useful in treating infections resistant to standard drugs and in cases with relapse.

Ethionamide

Ethionamide is structurally related to INH and acts by inhibiting the mycolic acid synthesis. It is effective against bacilli resistant to other drugs and has proved effective in infections due to atypical mycobacteria. It is effective against intracellular as well as extracellular organisms.

Capreomycin

It is bactericidal. Its mechanism of action, pharmacokinetics and adverse reactions are similar to those of streptomycin. It should be administered with caution in presence of renal impairment.

Kanamycin and amikacin

They are bactericidal and are active against bacilli resistant to streptomycin, INH and cycloserine.

Cycloserine

The drug is mainly bacteriostatic. It is effective against bacilli resistant to INH or streptomycin and against atypical mycobacteria, although antitubercular activity is less than that of these two drugs. It acts by inhibiting the synthesis of the bacterial cell wall.

Thioacetazone

It is a bacteriostatic drug. It rapidly diffuses into various body tissues and also crosses the placenta barrier. It is also secreted in milk. It should never be used in HIV patients as it can cause severe and fatal skin reactions. Side-effects include gastrointestinal disturbances, blurring of vision, haemolytic anaemia and urticaria. The incidence of these side-effects seem to differ in different ethnic groups.

Macrolides

Newer macrolides azithromycin and clarithromycin also have action against tubercular bacilli. They are used to treat atypical mycobacterial infection and cases with relapse.

Bedaquiline (BDQ)

Bedaquiline (BDQ) is a new class of drug diarylquinoline, that specifically targets mycobacterial ATP synthase, an enzyme essential to supply of energy to *mycobacterium*. It is a bactericidal drug with high volume of tissue distribution, highly bound to plasma proteins and hepatically metabolized. The drug has extended half-life, which means that it is still present in the plasma up to 5.5 months post stopping BDQ. The drug has shown significant benefits in

improving the time to culture convertion in MDR–TB patients. The basic criteria for patient selection is : (1) age of the patient should be ≥ 18 years having MDR–TB; (2) Pregnancy is a contraindication for BDQ therapy and the patient should be using non-hormonal based birth control measure throughout the treatment period or have been post-menopausal for past 2 years; and (3) Cardiac arrythmia is a contraindication for BDQ treatment *(34)*.

The following group of patients are eligible for BDQ therapy :

1. MDR/RR TB with resistance to any/all fluoroquinolones (FQ) or to any/all second-line injectable agents (SLI)
2. XDR–TB
3. Mixed pattern resistant TB (XDR–TB + additional first line / second line resistant TB)
4. Treatment failure of MDR–TB + FQ/SLI resistance or XDR–TB

Delamanid (DLM)

Delamanid is a recently approved drug for the treatment of TB conditional use under programmatic setting only. The phase III clinical trial results for safety and effectiveness of the drug is yet to be published. The Drug Controller General of India has issued permission to use Delamanid (50 mg) as part of an appropriate combination regimen for pulmonary MDR-TB in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability *(35)*.

For dosage of different second-line drugs, kindly refer to page 224.

Most TB patients complete their treatment without any significant drug side-effects. However, a few patients do develop major reactions and it is important to monitor clinically all the patients. A patient who develops one of the following reactions must never receive that drug again *(32)* :

Reaction	Drug responsible
a. Severe rash, agranulocytosis	Thioacetazone
b. Hearing loss or disturbed balance	Streptomycin
c. Visual disturbance (poor vision and colour perception)	Ethambutol
d. Renal failure, shock or thrombocytopenia	Rifampicin
e. Hepatitis	Pyrazinamide

Two-phase chemotherapy

It is well recognized that there are two phases in the effective treatment of tuberculosis : (i) the first is a short, aggressive or intense phase, early in the course of treatment, lasting 1–3 months. During this intensive phase, three or more drugs are combined to kill off as many bacilli as possible. The more rapidly the bacilli are killed initially, the less likely are "persisters" to emerge. The risk of relapse is also lessened. (ii) the second or "continuation" phase is aimed at sterilizing the smaller number of dormant or persisting bacilli. In the standard anti-tuberculous therapy, the duration of treatment was not less than 18 months to achieve complete sterilization of the bacilli. With the introduction of rifampicin and pyrazinamide, this period is now successfully reduced to 6–9 months.

DOMICILIARY TREATMENT

The self-administration of drugs (generally oral drugs) by the patients themselves without recourse to hospitalization is called domiciliary or ambulatory treatment. The classical controlled clinical trials *(36)* carried out at the Tuberculosis Chemotherapy Centre, Chennai showed that the incidence of tuberculosis was no greater in the contacts of patients treated at home than in the contacts of patients treated in sanatoria. It is now universally accepted that with good chemotherapy, hospital treatment has no advantage over domiciliary treatment, and domiciliary treatment is to be preferred because in the long run, it is so much cheaper than hospital treatment, and that it can be managed by the primary health care system and the general health services of the country. It may be mentioned that it was this study, the classical Chennai Study, that prompted a radical departure from the traditional sanatorium to ambulatory or domiciliary treatment.

SHORT-COURSE CHEMOTHERAPY

For a long time, the standard duration of tuberculosis chemotherapy was 18 months. In 1972, Wallace Fox and his colleagues from the British Medical Research Council showed that the addition of rifampicin or of pyrazinamide to regimens containing INH made it possible to reduce the duration of treatment.

There are a number of advantages of short–course chemotherapy, viz. rapid bacteriological conversion, lower failure rates and a reduction in the frequency of emergence of drug–resistant bacilli. Patient compliance is improved, they become non-infectious earlier. The disadvantage is that the high cost of short-term chemotherapy militates against its wider use in developing countries.

There are now a number of short–course regimens of 6 months duration that are highly effective, of low toxicity, and well–tolerated. These potent regimens are based on an initial intensive phase with 4 drugs (INH, rifampicin and pyrazinamide, supplemented by either streptomycin or ethambutol) for a period of 2 months, followed by 2 drugs in the continuation phase, (INH plus rifampicin or thioacetazone) given daily or intermittently. The treatment must be fully supervised and monitored mainly by bacteriological examination.

DIRECTLY OBSERVED TREATMENT, SHORT COURSE (DOTS) CHEMOTHERAPY

DOTS is a strategy to ensure cure by providing the most effective medicine and confirming that it is taken. It is the only strategy which has been documented to be effective worldwide on a programme basis. In DOTS, during the intensive phase of treatment a health worker or other trained person watches as the patient swallows the drug in his presence. During continuation phase, the patient is issued medicine for one week in a multiblister combipack, of which the first dose is swallowed by the patient in the presence of health worker or trained person. The consumption of medicine in the continuation phase is also checked by return of empty multiblister combipack, when the patien' comes to collect medicine for the next week. The drugs are provided in patient–wise boxes with sufficient shelf-life.

INTRODUCTION OF DAILY DOSE REGIMEN IN NTEP

The technical and operational guidelines–2016 for TB control in India, define major groups of TB patients who are

offered standard treatment regimen. Patient's classification is based on drug susceptibility result as drug-sensitive TB; and mono, poly, RR, multi and extensively drug resistant TB. For drug-sensitive TB patients, the thrice weekly intermittent TB regimen used since inception of the programme has been switched to a daily fixed dose combination regimen *(35)*.

1. MANAGEMENT OF DRUG SENSITIVE TUBERCULOSIS (2019)

Early identification of people with a high probability of having active TB (presumptive TB) is the most important activity of the case finding strategy. Screening and diagnosing patients with appropriate tests and strategies will largely determine the response to appropriate treatment. Passive case finding alone can lead to missed cases or delayed diagnosis.

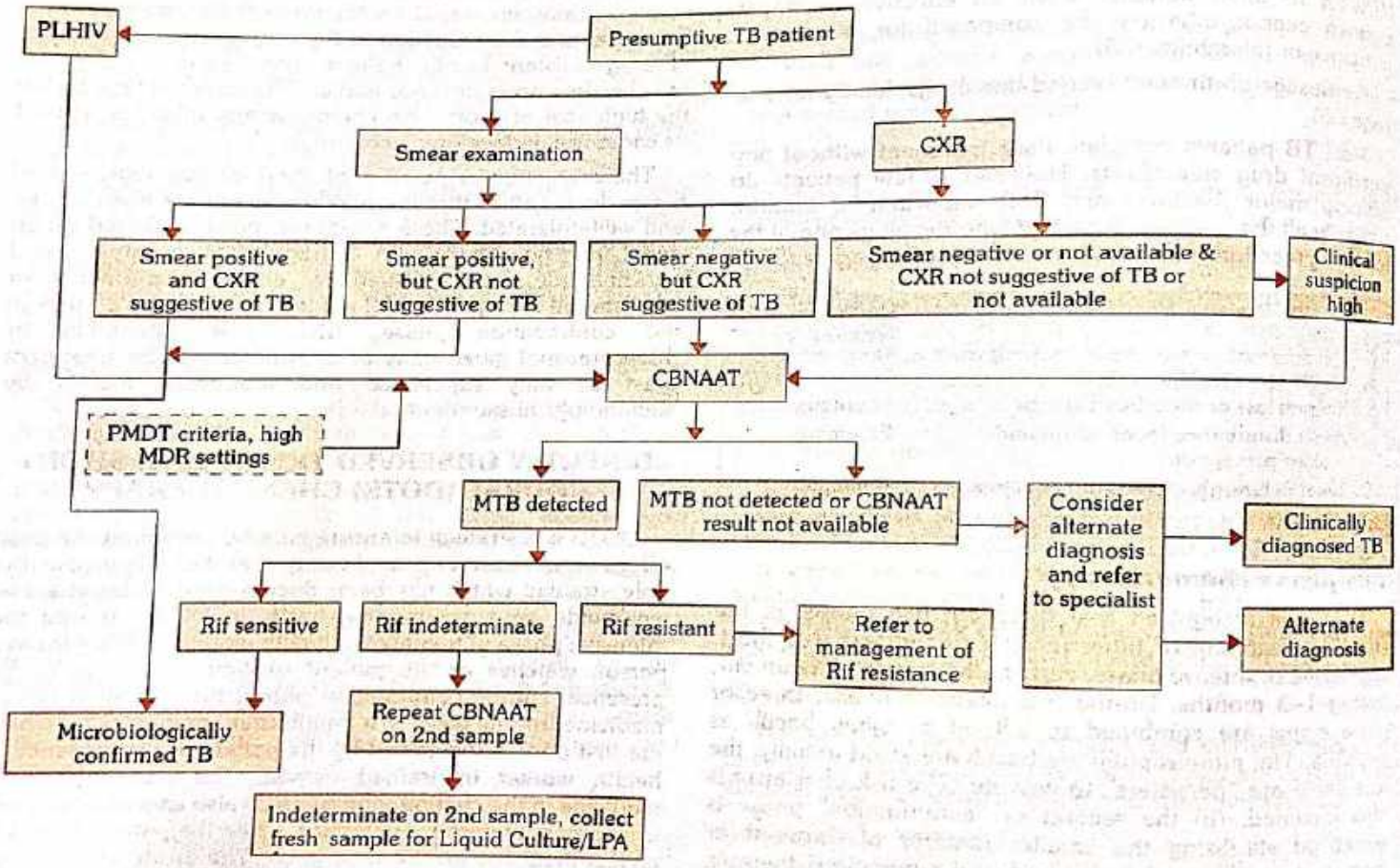
All presumptive TB will undergo sputum smear examination (ZN/LEDFM). Two specimens are collected (spot–early morning or spot–spot). If the first smear is positive and the patient is not at the risk of drug resistant TB, he will be categorized as microscopically confirmed TB (sensitivity status not known). If the first smear is negative, CXR may be considered and if reported as suggestive of TB, the 2nd sample will be subjected to smear and CBNAAT simultaneously. Based on CBNAAT results, patient will be categorized as microbiologically confirmed drug sensitive TB.

For NTEP endorsed TB diagnostics, Fig. 2 shows the diagnostic algorithm for pulmonary tuberculosis.

Pre-treatment counselling and evaluation

The patient and his/her family members should be counselled about the type of disease, mode of spread, the treatment duration and dosage schedule, common drug side-effects and methods to prevent them, importance of regular treatment and consequences of irregular treatment, screening of co-morbidities like diabetes, liver or renal diseases and neurological disorder etc. It is also important to look for substance abuse especially tobacco (in any form) and alcohol. Socio-economic status of the patient may be assessed to link him/her with appropriate treatment support schemes. HIV testing should be done in all the cases of TB. This is important to ensure that all HIV positive cases of TB receive anti-retroviral therapy and co-trimoxazole preventive therapy *(34)*.

Since the drugs used in the treatment of tuberculosis are known to produce adverse effects, a proper pre-treatment



*All presumptive TB cases should be offered HIV counselling and testing, however diagnostic work up for TB must not be delayed.

FIG. 2
Diagnostic algorithm for pulmonary TB

Source : *(37)*

evaluation is essential to identify patients who are at increased risk of developing such adverse effects. The pre-treatment evaluation includes the following :

1. Detailed history (including mental illness, seizure, drug and alcohol abuse etc).
2. Weight and height.
3. Complete blood count.
4. Blood sugar to screen for diabetes mellitus.
5. Liver function test.
6. Blood urea and creatinine to assess kidney function.
7. Urine examine – routine and microscopic.
8. Chest X-ray
9. Pregnancy test (for all women in child bearing age group).

Most TB patients on first line drugs complete their treatment without any serious drug side effects. Trivial side effects may lead to reduced compliance with the treatment, hence asymptom-based approach to the management of the common adverse effect should be adopted.

Pharmacovigilance in TB control programme : Pharmacovigilance is defined by the WHO as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem". It is fundamental activity to inform the management of patient safety measurement in health care. It is a public health surveillance activity. Priority is given to establish pharmacovigilance at drug resistance TB centres.

Recommended daily dose regimen for drug sensitive TB (2019)

The principle of treatment for tuberculosis (other than confirmed drug resistant forms of TB) with daily regimen is to administer daily fixed dose combinations of first-line anti-tuberculosis drugs in appropriate weight bands.

Fixed dose combinations (FDCs)

Fixed dose combinations (FDCs) refer to products containing two or more active ingredients in fixed doses, used for a particular indication(s).

In NTEP, for Adults – 4-FDC (given in IP) consists of HRZE and 3-FDC (given in CP) consists of HRE. For paediatric patients – dispersible 3 FDC consists of HRZ and dispersible 2 FDC consists of HR.

Advantages of FDCs

- Simplicity of treatment
- Increased patient acceptance
  - Fewer tablets to swallow
  - Prevents 'concealed' irregularity
- Increased health worker compliance
  - Fewer tablets to handle, hence quicker supervision of DOT
- Easier drug management
- Reduced use of monotherapy
  - Lower risk of misuse of single drugs
- Lower risk of emergence of drug resistance
- Easier to adjust dosages by body weight

Treatment is given in two phases (24):

- Intensive phase (IP) consists of 8 weeks (56 doses) of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) given under direct observation in daily dosages as per weight band categories.
- Continuation phase (CP), consists of 16 weeks (112 doses) of isoniazid, rifampicin and ethambutol in daily dosages. Only pyrazinamide will be stopped in the continuation phase. The CP may be extended by 12–24 weeks in certain forms of TB like CNS TB, skeletal TB, disseminated TB etc. based on clinical decision of the treating physician on case to case basis. Extension beyond 12 weeks should only be on recommendation of specialists.

Type of TB case	Treatment regimen in IP	Treatment regimen in CP
New and previously treated cases (H and R sensitive / unknown)	2 HRZE	4 HRE

– Prefix to the drugs stands for number of months.

Loose drugs could be used as substitutions in case of adverse drug reaction or with comorbid conditions.

Steroids as an adjunctive therapy is useful in patients with TB pericarditis and meningeal TB, with an initial high dose tapered downwards gradually over 6–8 weeks.

Drug dosages for first line anti-TB drugs

Drugs	Adults	Children	Maximum in children
Isoniazid	10 mg/kg daily (7–15 mg/kg)	5 mg/kg daily (4 to 6 mg/kg)	300 mg
Rifampicin	15 mg/kg daily (10–20 mg/kg)	10 mg/kg daily (8–12 mg/kg)	600 mg
Pyrazinamide	35 mg/kg daily (30–40 mg/kg)	25 mg/kg daily (20–30 mg/kg)	2000 mg
Ethambutol**	20 mg/kg daily (15–25 mg/kg)	15 mg/kg daily (12–15 mg/kg)	1500 mg
Streptomycin*	20 mg/kg daily (15–20 mg/kg)	15 mg/kg daily (15–20 mg/kg)	1000 mg

* Streptomycin is administered only in certain situations, like TB meningitis or if any first line drug need to be replaced due to ADR as per weight of the patient

** Ethambutol is given separately for children to monitor ophthalmic ADR.

Daily dose schedule for adults (as per weight bands) *(24)*

Weight category	Number of tablets (FDCs)	
	Intensive phase HRZE	Continuation phase HRE
	75/ 150/ 400/275	75/150/275
25–34 kg	2	2
35–49 kg	3	3
50–64 kg	4	4
65–75 kg	5	5
≥ 75 kg	6	6

During treatment if the weight of the patient increases by more than 5 kg and crosses to the next weight band category then patient should be given the next higher weight band FDC drugs.

Treatment of paediatric TB

Paediatric cases are to be treated under NTEP in daily dosages as per 6 weight band categories. All adolescents upto 18 years of age and weighing less than 39 kg, are to be treated using paediatric weight bands and children weighing more than 39 kg with adult weight bands.

Key product information (for paediatric)

1. Dispersible FDC, flavoured
   Rifampicin 75 mg + Isoniazid 50 mg + Pyrazinamide 150 mg
   Rifampicin 75 mg + Isoniazid 50 mg
2. Dispersible Loose drugs
   Ethambutol 100 mg
   Isoniazid 100 mg

Drug dosage for paediatric TB *(24)*

Weight category	Number of tablets (dispersible FDCs)			
	Intensive phase		Continuation phase	
	HRZ	E	HR	E
	50/75/ 150	100	50/75	100
4–7 kg	1	1	1	1
8–11 kg	2	2	2	2
12–15 kg	3	3	3	3
16–24 kg	4	4	4	4
25–29 kg	3 + 1A*	3	3 + 1A*	3
30–39 kg	2 + 2A*	2	2 + 2A*	2

* A=Adult FDC (HRZE = 75/150/400/275; HRE = 75/150/275). It is added in higher weight band categories i.e. > 25 kg as these children may be able to swallow tablets.

Change in weight bands to be effective upon crossing of weight bands irrespective of the quantum of weight gain/loss.

Pyridoxine may be given at a dosage of 10 mg per day to all children receiving INH containing therapy irrespective of age group.

Nikshay entry : Once the treatment regimen is finalized, all patients should be initiated on treatment after opening the treatment card and entries are done in Nikshay. MO-PHI should ensure that the treatment details are entered in Nikshay by the PHI staff. Nikshay entry should not be a separate activity. All events starting from notification to treatment outcome are from Nikshay as it is integrated part of documentation *(24)*.

Follow-up of the treatment

There are two components of the follow-up :

a. *Clinical follow up :* It should be done at monthly interval. Improvement in chest symptoms, increase in weight etc, may indicate good prognosis.

b. *Laboratory investigations :* Sputum smear microscopy should be done at the end of intensive phase and end of treatment. A negative sputum smear at the end of IP indicate good prognosis. However, in the presence of clinical deterioration, the medical officer may consider repeating sputum smear microscopy even during continuation phase. This will provide the patient an early opportunity to undergo drug susceptibility testing. At completion of the treatment, a sputum smear and/or culture should be done for every patient, as culture is more specific and sensitive compared to smear microscopy to detect the presence of *M. tuberculosis* in biological specimens.

Long term follow-up at the end of 6, 12, 18, and 24 months should be done. In presence of any clinical symptoms and /or cough, sputum microscopy and/or culture should be considered *(34)*.

2. MANAGEMENT OF DRUG-RESISTANT TB

Providing treatment to diagnosed DR-TB patients is extremely important. To begin with, only MDR-TB patients were offered treatment with a standard second-line regimen. Later, treatment with standard regimen was offered to extensively drug resistant (XDR) TB patients and MDR-TB with additional resistance to fluoroquinolones or second-line injectable. Procurement and supply chain management of second-line drugs is complex, since no standardized patient-wise boxes are manufactured and drugs do need temperature regulated storage and repacking.

Since 2016, new drugs like Bedaquiline (Bdq) are made accessible to DR-TB patients through expanded access under NTEP. In 2016, with the release of the Revised Technical and Operational Guidelines, regimens to treat other forms of drug resistance, such as mono and poly resistance to first and second-line drugs were also included.

The new guidelines of 2019 and later on 2020, has substaintially changed the approach to the treatment of MDR/XDR-TB. It recommends as follows *(24)* :

- policy recommendations on treatment regimens for isoniazid resistant TB and multidrug and rifampicin resistant TB (MDR/RR-TB), including longer and shorter regimens;
- culture monitoring of patients on treatment;
- the timing of antiretroviral therapy in MDR/RR-TB patients infected with HIV;
- the use of surgery for patients receiving MDR-TB treatment;
- optimal models of patient support and care; and
- fully oral regimens should have priority and should become option for most patients.

It needs to be emphasized that treatment for drug resistant TB should only be provided under the supervision of an experienced doctor. This includes the choice of a shorter or longer regimen, and also whether injectable drugs are used.

Accordingly, India has made some changes in its PMDT guidelines. The revised integrated DR-TB diagnostic algorithm recommends testing of all TB patients for rifampicin and isoniazid resistance and all RR-TB patients for fluoroquinolone and second line injectable. Fig. 3 on page 223 shows the integrated drug resistant TB algorithm.

The medicines recommended for longer MDR-TB regimens are classified into three groups (A, B and C) based on efficacy, experience of use and drug class and aligned with revised classification as per WHO consolidated guidelines for treatment of drug resistant TB. The groups are as listed below :

Grouping of medicines recommended for use in longer MDR-TB regimens

Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin OR moxifloxacin	Lfx Mfx
	bedaquiline	Bdq
	linezolid	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine OR terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid	Dlm
	pyrazinamide	Z
	imipenem–cilastatin OR meropenem	Ipm–Cln Mpm
	amikacin (OR streptomycin)	Am (S)
	ethionamide OR prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

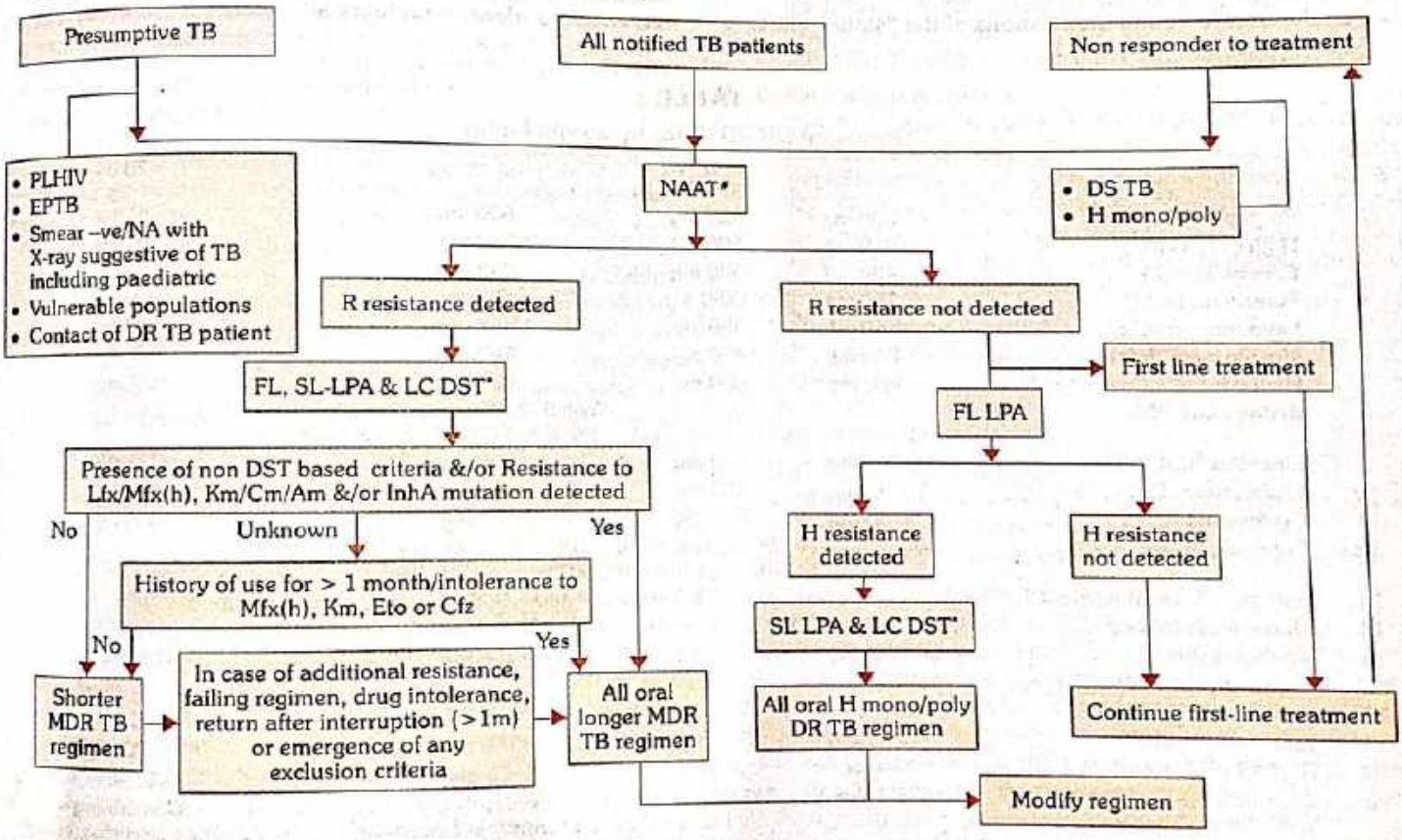
Source : *(24, 38)*

Inclusion criteria for newer drugs (Bdq/Dlm)

- Patient aged >6 years having MDR/RR TB. (Bdq/Dlm can be provided to the patient ≥18 yrs) for children & adolescents between 6 to 17 years, Dlm can be provided. Use of Bdq for 6 to 17 yrs and Dlm for 3 to 6 yrs may be considered only after approval of DCGI; and
- patients with controlled stable arrhythmia can be considered after obtaining cardiac consultation.

Exclusion criteria for newer drugs (Bdq/Dlm)

- Pregnancy & lactating mother
- currently having uncontrolled cardiac arrhythmia that requires medication;
- having any of the following QTcF interval characteristics at screening:
- QTcF ≥500 at baseline & normal electrolytes, ECG to be repeated after 6 hours and if both ECGs show QTcF>500 then the patient should not be challenged with cardiotoxic drugs.
- history of additional risk factors for Torsade de Pointes, e.g. heart failure, hypokalaemia, family history of long QT syndrome.



* NAAT include CBNAAT & TruNAAT
* LC DST will be done as per the diagnostic algorithm

FIG. 3
Integrated drug resistant TB algorithm (2019)

Source : *(24)*

Bedaquiline (24)

Week 0–2 : Bdq 400 mg (4 tablets of 100 mg) daily (7 days per week) + other drugs; Week 3–24 : Bdq 200 mg (2 tablets of 100 mg) 3 times per week (with at least 48 hours between doses) for a total dose of 600 mg per week + other drugs; and Week 25 (start of month 7) to end of treatment : Continue other second-line anti-TB drugs only as per NTEP recommendations.

If taking a light meal with Bdq and other anti-TB drugs, patients should not consume milk-containing products at the same time, as the calcium in these can decrease the absorption of FQs. Also, large fatty meals should be avoided, as these can impair absorption of some of the other anti-TB drugs (Cs, H, etc.).

The following medications are disallowed during the 24-week administration of Bdq and upto one month after the last dose of Bdq because of potential drug–drug interactions :

- systemic use of moderate and strong CYP3A4 inhibitors, e.g. azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolides such as telithromycin and macrolide antibiotics other than azithromycin for more than 2 consecutive weeks;
- systemic use of strong CYP3A4 inducers, e.g. phenytoin, carbamazepine, phenobarbital, St. John's wort and rifamycins (rifampin, rifabutin, rifapentine); and
- cholesterol lowering medications of the "statin" class.

Delamanid (24)

All patients >12 yrs of age will receive Tab. Delamanid 100 mg (two tablets of 50 mg) orally twice a day for 24 weeks in combination with other drugs in the regimen while patients belonging to 6 to 11 yrs of age group will receive Tab. Delamanid 50 mg (one tablet of 50 mg) twice a day for 24 weeks. Remaining drugs in regimen will be continued beyond the 24 weeks of Dlm administration for the NTEP recommended duration of treatment. It is important that Dlm be taken daily preferably after a standard meal to improve bioavailability.

Patients should not consume milk-containing products at the same time, as calcium can decrease the absorption of FQs. Also, large fatty meals should be avoided as these can impair absorption of some of the other anti-TB drugs (Cs, H, etc).

Dosage of DR TB drugs

The dosage for drugs used in various DR TB regimens by weight bands for adults are enumerated in Table 2. These are in accordance to the WHO recommended doses of anti-TB drugs for adults and paediatric patients.

Pretreatment evaluation for drug-resistant patients

Since the drugs used for the treatment of DR-TB have significant adverse effects, a pretreatment evaluation is essential to identify patients at increased risk of developing

TABLE 2

Dosage of DR TB drugs by weight bands

S.No.	Drugs	16–29 kg	30–45 kg	46–70 kg	>70 kg
1	Rifampicin (R)[1]	300 mg	450 mg	600 mg	750 mg
2	High dose H (H^h)	300 mg	600 mg	900 mg	900 mg
3	Ethambutol (E)	400 mg	800 mg	1200 mg	1600 mg
4	Pyrazinamide (Z)	750 mg	1250 mg	1750 mg	2000 mg
5	Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
6	Moxifloxacin (Mfx)	200 mg	400 mg	400 mg	400 mg
7	High dose Mfx (Mfx^h)	400 mg	600 mg	800 mg	800 mg
8	Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily Week 3–24: Bdq 200 mg 3 times per week			
9	Linezolid (Lzd)	300 mg	600 mg	600 mg	600 mg
10	Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
11	Cycloserine (Cs)[4]	250 mg	500 mg	750 mg	1000 mg
12	Delamanid (Dlm)	50 mg twice daily (100 mg) for 24 weeks in 6–11 years of age 100 mg twice daily (200 mg) for 24 weeks for >11 years of age			
13	Imipenem/cilastatin (Ipm/Cls)[4]	1000 mg imipenem/1000 mg cilastatin twice daily			
14	Meropenem (Mpm)[4]	1000 mg three times daily (alternative dosing is 2000 mg twice daily)			
15	Amikacin (Am)[2]	500 mg	750 mg	750 mg	1000 mg
16	Capreomycin (Am)[2]	-	-	-	-
17	Kanamycin (Km)[2]	500 mg	750 mg	750 mg	1000 mg
18	Ethionamide (Eto)[4]	375 mg	500 mg	750 mg	1000 mg
19	Na-PAS (60% weight/vol)[3,4]	10 gm	14 gm	16 gm	22 gm
20	Amoxyclav (Amx/Clv) (In child: WHO 80 mg/kg in 2 divided doses)	875/125 mg BD	875/125 mg BD	875/125 mg (2 morning + 1 evening)	875/125 mg (2 morning + 1 evening)
21	Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

[1] For H mono/poly resistant TB;

[2] For adult more than 60 years of age, dose of SLI should be reduced to 10mg/kg (max upto 750 mg)

[3] In patient of PAS with 80% weight/volume the dose will be changed to 7.5gm (16–29kg); 10gm (30–45 kg); 12 gm (46–70 kg) and 16 gm (>70 kg)

[4] Drugs can be given in divided doses in a day in the event of intolerance

Source : *(24)*

such adverse effects. This pretreatment evaluation is as follows :

Pretreatment evaluations

1. Detailed history (including screening for mental illness, seizure disorder, drug/alcohol abuse, etc.)
2. Previous history of ATT taken especially SLI/FQ
3. Weight & height
4. Thorough clinical examination
5. Complete blood count with haemoglobin & platelets count
6. Blood sugar to screen for Diabetes Mellitus
7. Blood urea and S. Creatinine to assess renal function
8. Urine examination – routine and microscopic
9. UPT (for all women in the child-bearing age)
10. Chest X-ray
11. HIV counselling and testing*
12. Audiogram
13. Liver function tests#
14. TSH levels to assess the thyroid function
15. Mental health evaluation
16. Surgical evaluation
17. ECG (if Mfx[h], Dlm, Bdq, Cfz used)
18. Serum electrolytes – potassium, magnesium, calcium
19. Serum proteins, lipase, amylase
20. Ophthalmologist opinion to rule out chorioretinitis/uveitis

* All DR-TB patients will be offered referral for HIV counselling and testing at the nearest centre if the HIV status is not known or HIV test result is negative with results more than 6 months old. If patient is HIV positive, refer to ART centre (if not on ART)

including HBsAg at baseline

Source : *(24)*

Pretreatment evaluation and treatment initiation must be done at the DR-TBC (Drug-Resistant TB centre) i.e., DDR-TBC (District DR-TBC) and NDR-TBC (Nodal DR-TBC). The concerned DR-TBC committee provides counselling, initiates activities related to active drug safety monitoring (aDSM) like, assessing the baseline history of known adverse/serious adverse events, biochemical investigations, ECG etc., and initiates him/her on an appropriate treatment regimen. Care must be taken to correct any electrolyte imbalance before treatment initiation.

Newer treatment regimen

NTEP provides simplified regimen for various types of DR-TB including shorter oral Bedaquiline-containing MDR/RR-TB regimen and longer oral M/XDR-TB regimen based on DST/DRT results with scope in difficult patients to extend Bdq beyond 6 months, combined use of Bdq and Dlm and Bdq use in pregnancy. As the fully oral regimens get scaled up nationwide, the current shorter MDR-TB regimen with injectable SLDs will be phased out. Injectable SLDs will be available for use under PMDT to substitute oral SLDs based on DST and ADR. Guidance is also provided for using Bdq for children above 5 years and Dlm for children above 6 years. Use of BPaL regimen consisting of Bdq, pretomanid (Pa) & linezolid (Lzd) are ongoing in select group of patients on a research mode. H mono/poly DR-TB treatment to be initiated at HF level. To further improve the quality of care offered by the DR-TB centres, difficult-to-treat TB clinics (DT3C) are established at state and national levels.

1. Shorter oral Bedaquiline-containing MDR/RR-TB regimen *(39, 40)*

Following the recommendations of WHO to implement short oral Bedaquiline-containing MDR/RR-TB regimen, Govt. of India decided on transitioning from the current shorter injectable containing MDR/RR-TB regimen to the shorter oral Bedaquiline-containing MDR/RR-TB regimen in patients >5 years of age weighing 15 kg or more in a phased manner starting with selected states to gain programmatic experience to guide future expansion within 2021.

Eligibility criteria *(39)*

Shorter oral Bedaquiline-containing MDR/RR-TB regimen is recommended for those MDR/RR-TB patients in whom resistance to the component drugs has been excluded or those who have not been previously treated for more than one month with second-line drugs used in shorter oral Bedaquiline-containing MDR/RR-TB regimen and have no other exclusion criteria. The criteria to include or exclude the patients from offering shorter oral Bedaquiline-containing MDR/RR-TB regimen are given below.

Inclusion criteria

1. DST based inclusion criteria
   - Rifampicin resistance detected/inferred;
   - MDR/RR-TB with H resistance detected/inferred based on InhA mutation only or based on KatG mutation only (not both); and
   - MDR/RR-TB with FQ resistance not detected.
2. Other inclusion criteria
   - Children, aged 5 years to less than 18 years of age and weighing at least 15 kg, given their special needs, in consultation with the pediatrician;
   - No history of exposure to previous treatment with second-line medicines in the regimen (Bdq, Lfx, Eto or Cfz) for more than 1 month (unless susceptibility to these medicines is confirmed);
   - No extensive TB disease;
   - No severe extra-pulmonary TB; and
   - Women who are not pregnant or lactating.

Exclusion criteria

1. DST based exclusion criteria
   - MDR/RR-TB patients with H resistance detected with both KatG and InhA mutation; and
   - MDR/RR-TB patients with FQ resistance detected.
2. Other exclusion criteria
   - If result for FL-LPA, SL-LPA and DST to Z, BDQ & Cfz is not available after pre-treatment evaluation is completed and it is a time to initiate the first dose of the regimen, then, exclude those with history of exposure for > 1 month to Bdq, Lfx, Eto or Cfz;
   - Intolerance to any drug or risk of toxicity from a drug in shorter oral Bedaquiline-containing MDR/RR-TB regimen (e.g. drug-drug interactions);
   - Extensive TB disease found in presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, presence of cavities or bilateral disease on chest radiography;
   - Severe EP-TB disease where there is a presence of miliary TB or TB meningitis or central nervous system (CNS) TB. In children aged under 15 years,

extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression);
- Pregnant and lactating women; and
- Children below 5 years.

The regimen consists of an initial phase of 4 months that may be extended up to 6 months and a continuation phase of 5 months, giving a total duration of 9–11 months. Bdq is used for a duration of 6 months.

(4–6) Bdq $_{(6\ m)}$, Lfx, Cfz, Z, E, H^h, Eto (5) Lfx, Cfz, Z, E

The composition or the duration of the initial or continuation phase cannot be changed :

1. From start to end of 4th month – Bdq, Lfx, Cfz, Z, E, H^h, Eto;
2. From start of 5th month to end of 6 th month – (If IP not extended) – Bdq, Lfx, Cfz, Z, E;
3. From start of 7th month to end of 9th month – Lfx, Cfz, Z, E; and
4. If the IP is extended up to 6 months then all 3 drugs Bdq, H^h and Eto are stopped together.

Treatment extension

- Total duration of shorter oral Bedaquiline-containing MDR/RR-TB regimen is for 9–11 months, depending on IP duration.
- IP should be given for at least 4 months. After 4th month of treatment, if the result of sputum microscopy is negative then CP should be initiated with Bdq continued for another 2 months.
- If sputum smear microscopy does not become negative by the 4th month of treatment, subject the patient to FL-LPA and SL-LPA and culture & DST and the IP should be extended. IP can be extended to 5th or 6th month based on smear results at the end of 4th and 5th month of treatment. This will be done for a maximum of 2 months (i.e., total duration of IP is not more than 6 months). If any additional resistant to Z/Cfz on C&DST of the baseline sample is detected or to FQ/InhA & KatG mutation of the 4th month sample is detected, the patient needs to be reassessed at N/DDR-TBC for stopping shorter oral Bedaquiline-containing MDR/RR-TB regimen and initiation of longer oral M/XDR-TB regimen, immediately on receiving the report.
- Duration of CP is fixed for 5 months.

Additional considerations for the use of Bdq

- Bdq can be provided to adults and children aged 5 years to less than 18 years of age and weighing at least 15 kg, given their special needs, in consultation with pediatrician;
- Patients with controlled stable arrhythmia can be considered after obtaining cardiac consultation; and
- Pregnancy & lactating women.

The drug dose administration is as shown in Table 2.

Shorter injectable containing regimen *(39)*

Till the complete geographical coverage by shorter oral Bedaquiline-containing MDR/RR-TB regimen, the states will continue to use shorter injectable containing regimen for MDR/RR-TB. The regimen composition and duration is as follows :

(4–6) Mfx^h, Km/Am, Eto, Cfz, Z, H^h, E/ (5) Mfx^h, Cfz, Z, E

- If the intensive phase is prolonged, the injectable agent is only given three times a week in the extended intensive phase;
- Neither replacement of drug (except the use of Am instead of Km) nor extension of treatment duration (beyond 11 months) is permitted; and
- Pyridoxine is to be given as per weight band.

The drug dose administration is as shown in Table 2.

Follow-up evaluation of Shorter oral Bedaquiline-containing MDR/RR-TB regimen

Duration	9–11 months (4–6m IP, 5m CP)
Clinical + Wt.	Monthly in IP or extended IP if previous month S+ve, quarterly in CP
Smear Microscopy	Monthly from 3rd month onwards till end of IP Monthly in extended IP only if previous month S+ve Conduct SM within 7 days, if the smear at 6 months is positive to rapidly ascertain bacteriological conversion/reversion
Culture	At the end of month 3, end of month 6 and/or end of treatment If the culture results of month 6 is positive, collect one repeat sample immediately to rapidly ascertain the bacteriological conversion/reversion If the repeat sample is culture negative, then do end of treatment specimen collection
DST	FL-SL LPA (Lfx, Mfx, Eto) and LC&DST (Z, Bdq*, Cfz*, Mfx, Lzd, Dlm*) if any – culture +ve (end of month 3 or later and end of treatment) or – smear +ve at end of IP, end of extended IP and end of treatment
UPT	As and when clinically indicated
CBC	As and when clinically indicated
TSH & LFT#	At end of IP, then as and when clinically indicated
CXR	At end of IP, then as and when clinically indicated, end of treatment
ECG$	At 2 weeks, then monthly in first 6 months, then as and when clinically indicated
S. Electrolytes (Na, K, Mg, Ca)	As and when indicated and in case of any QTcF prolongation
Specialist consultation	As and when clinically indicated
Color vision test	Once in two months (in children)

\# HBsAG and other viral markers (Hepatitis A, C & E) to be done in case of Jaundice.

$ In case of baseline ECG abnormality or QTcF ≥ 450ms with shorter oral Bedaquiline-containing MDR/RR-TB regimen that contains Bdq & Cfz, ECG must be done on daily basis for initial 3 days or as suggested by cardiologist. Repeat ECG with long II lead after an hour to reconfirm abnormal ECG

* DST whenever available

Source : *(39)*

2. H mono/poly DR-TB regimen *(39)*

H mono/poly DR-TB regimen (R resistance not detected and H resistance detected) under NTEP is as follows :

(6 or 9) Lfx R E Z

Total duration of H mono/poly DR-TB regimen is 6 months. It can be extended directly to 9 months in certain conditions. In patients with extensive disease; uncontrolled comorbidity; extra-pulmonary TB; if smear at the end of month 4 is found positive and when regimen is modified, the treatment may be directly extended to 9 months. There

would be no monthly extensions in this regimen. In patients who remain sputum smear positive at the end of month 5 or later, the treatment outcome will be declared as 'treatment failed' and the patient will be re-evaluated as per the diagnostic algorithm as a non-responder.

Follow-up evaluation schedule of H mono/poly DR-TB patients

Duration	6 or 9 months (no separate IP/CP)
Clinical + Wt.	Monthly till the end of treatment
Smear microscopy	Monthly from month 3 onwards till the end of treatment Conduct SM within 7 days, if the smear at month 4 or later is positive to rapidly ascertain bacteriological conversion/reversion
Culture	At end of month 3, end of treatment (month 6 and/or 9 if applicable) If the culture results of month 3 are positive, collect one repeat specimen for culture to rapidly ascertain bacteriological conversion/ reversion. If the repeat specimen is culture negative, then ensure specimen collection at the end of treatment
DST	NAAT, FL LPA, SL LPA (R, Eto, Lfx, Mfx) and LC DST (Mfx, Z, Lzd & Cfz) if smear/ culture +ve at month 3, end of treatment (month 6 and/or 9 if applicable)

3. Longer oral M/XDR-TB treatment regimen *(39)*

The longer oral M/XDR-TB regimen is as follows :

(18–20) Lfx Bdq $_{\text{(6 month or longer)}}$ Lzd#Cfz Cs

dose of Lzd will be tapered to 300 mg after the initial 6–8 months of treatment

Bdq will be given for 6 months & extended beyond 6 months as an exception

Pyridoxine to be given to all DR-TB patients as per weight band

For Pre-XDR-TB and XDR-TB patients the duration of longer oral XDR-TB regimen would be for 20 months with appropriate modifications.

Once a patient is placed on a longer oral M/XDR-TB regimen for at least 4 weeks, normally that patient can no longer be switched to the shorter oral Bedaquiline-containing MDR/RR-TB regimen because this 4-weeks treatment would represent an exposure to second-line medicines.

Treatment extension (39)

Total duration of longer oral M/XDR-TB regimen is 18–20 months.

a. After month 6 of treatment, the patient must be reviewed based on month 5 culture results. If month 5 culture result is not available at the end of month 6, decision to taper the dose of Lzd to 300 mg will be based on month 4 culture result. If the month 5 or 4 culture result (whichever applicable) remains positive, the dose of Lzd (600 mg) and the regimen is extended by 1 month to month 7 and for a maximum till month 8 based on monthly culture results of month 6 and 7 respectively and clinical/radiographic response. If the month 8 culture is also positive, subject the culture isolate to FL-LPA, SL-LPA and C&DST. If any additional resistant to Group A, B or C drugs in use is detected, the patient needs to be reassessed at N/DDR-TBC for modification of longer oral M/XDR-TB regimen immediately on receiving the report.

b. The duration of Bedaquiline is limited to 6 months. Extension beyond 6 months is to be considered in patients in whom an effective regimen cannot otherwise be designed if only 2 of 5 drugs are available from Groups A & B and adequate number of Group C drugs are not available due to high background resistance, non-availability or unreliability of DST.

c. Maximum duration of treatment is not more than 20 months. A treatment duration of 15–17 months after culture conversion is suggested for most patients. The duration may be modified according to the patient's response to treatment.

The drug dose administration is as shown in Table 2.

Follow up evaluation schedule of longer oral M/XDR-TB regimen during treatment is as follows

Duration	18–20 months (no separate IP/CP)
Clinical + Wt.	Monthly up to month 6 or 7 or 8 if previous month S+ve Quarterly in from month 7 or 9 onwards
Smear microscopy	With culture at C&DST lab Conduct SM within 7 days, if any smear at 6 month or later is positive to rapidly ascertain bacteriological conversion/reversion C&DST lab to update the result on Nikshay and inform the concerned field staff of collection center on same day
Culture	Monthly from month 3 onwards to end of 6 months or 7 or 8 if the previous month's culture is +ve Quarterly month 6 or 7 or 8 onwards based on previous month's culture results If the culture results of month 6 or any of the quarterly culture is positive, collect one repeat specimen immediately and send it for culture to rapidly ascertain bacteriological conversion/ reversion and if the repeat specimen is culture negative, then the subsequent quarterly or end of treatment specimen collection.
DST	FL & SL-LPA (Lfx, Mfx, Am, Eto) and LC&DST (Mfx, Lzd, Cfz*, Bdq*, Dlm*, Z) if culture +ve at the end of 6 months or any time beyond
UPT	As and when clinically indicated
CBC/platelets^	Day 15, monthly in first 6 months, 6 or 7 or 8 if previous month S+ve, then as and when clinically indicated
TSH & LFT#	LFT quarterly, then as and when clinically indicated. TSH every 6 months
CXR	At the end of month 6, end of treatment and as and when clinically indicated
ECG$	At 2 weeks, monthly in first 6 months and till Bdq/Mfx/Cfz/Dlm is extended, then as and when clinically indicated.
S. electrolytes (K, Mg, Ca)	As and when indicated and in case of any QTcF prolongation

^ If Lzd is part of the regimen to rule out bone marrow suppression

\# HBsAG and other viral markers (Hepatitis A, C & E) to be done in case of jaundice

$ In case of baseline ECG abnormality or QTcF ≥ 450ms with longer oral M/XDR-TB regimen that contains Bdq, Mfx, Cfz or Dlm, ECG must be done on daily basis for initial 3 days or as suggested by cardiologist. Repeat ECG with long II lead after an hour to reconfirm abnormal ECG.

* DST whenever available.

The most important evidence of response to DR-TB treatment is conversion of sputum smear and culture to negative. Good quality sputum specimen is therefore essential to get reliable results that form the basis of monitoring bacteriological response to treatment.

Treatment Interruptions & DRTB

Management of DR TB patients with treatment interruptions and lost to follow-up

All efforts must be made to ensure that DR TB patients do not interrupt treatment or are lost to follow-up. Action should be taken to promptly retrieve patients who fail to come for their daily dose by the treatment supporter. The following strategies are applicable for patients who interrupt treatment :

Patients who miss doses : In shorter MDR TB regimen, all missed doses during IP must be completed prior to switching the patient to CP. Similarly, all missed doses during CP must be administered prior to ending treatment. In longer MDR TB regimen, all missed doses during treatment must be administered prior to ending treatment.

Patients who interrupt treatment for less than one month : When the patient returns to resume treatment, the treatment will be continued. However, the duration of treatment will be extended to complete the regimen. The follow-up cultures will be done as per the schedule.

Patients who are "lost to follow-up" (interrupt treatment continuously for one month or more) and return back for treatment: Such patients will be given an outcome of "lost to follow-up". The patient would be subjected to repeat NAAT & FL/SL LPA and LC DST as per the diagnostic algorithm to restart with appropriate treatment. If there are signs of impending treatment failure for any MDR/RR TB patient with or without additional resistance to second line drugs, the patient should be switched to an all oral longer DR TB regimen and evaluated further to modify appropriately based on DST results if required. If a patient has received the shorter MDR TB regimen for more than one month and returns for treatment after an interruption of one month or more, the patient is not restarted on a shorter MDR TB regimen.

MDR/RR TB patients on Bdq/Dlm containing regimen who interrupt treatment or are "lost to follow-up" or recurrent DR TB :

Patients who interrupt Bedaquiline treatment during the first two weeks of Bdq course and return to resume the treatment :

- if interruption is upto 7 days, Bdq containing regimen will be continued to complete the doses and the duration of treatment will be extended to complete IP. Follow-up cultures will be done as per the revised schedule; and
- if interruption is more than 7 consecutive days, Bdq course will be reloaded (started afresh) and a fresh specimen collected for culture. The culture isolate must be stored for Bdq DST in future.

Patients who interrupt Bedaquiline treatment during 3–24 weeks of Bdq course and return to resume treatment *(24)* :

- if interruption is upto one month, Bdq containing regimen will be continued to complete the doses and duration of treatment will be extended to complete full course of Bdq. Follow-up cultures will be done as per revised schedule; and
- if interruption is more than one month, Bdq will be permanently discontinued. Such patients will be given an outcome of "Lost to follow-up" (LTFU), registered afresh and initiate all oral longer MDR TB regimen with appropriate modification. A sputum specimen will be collected for culture. The culture isolate must be stored for Bdq DST in future.

Delamanid : If the patient misses one or more doses of Dlm during treatment upto a maximum of one month, one should continue the treatment and complete the Dlm for rest of the period which may prolong the Dlm containing phase beyond 24 weeks from initiation of treatment to make the adjustment of missed dosage.

Patients who initiated on Bdq/Dlm containing regimen and return after treatment Interruption of one month or more will be declared as "lost to follow-up". Such patients would not be considered eligible for administration of same drug (Bdq/Dlm) anymore.

Where further treatment is concerned, if the patient has any indication of a treatment failure or recurrence, the NDR TBC Committee will be contacted to discuss whether s/he should be retreated. The decision will be made on a case-to-case basis, using all available bacteriological and clinical data.

The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen *(41, 42)*

WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. The Union Ministry of Health and Family Welfare of India has also approved introduction of the BPaLM regimen *(42)*. This regimen has been proven to be safe, more effective and a quicker treatment option than the previous MDR-TB treatment procedure. While traditional MDR-TB treatments can last up to 20 months with severe side effects, BPaLM regimen can cure the drug-resistant TB in just six months with high treatment success rate. India's 75,000 drug-resistant TB patients will now be able to avail benefit of this shorter regimen. With the other advantages, there will be an overall saving in cost.

Eligibility *(41)*

DST for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen - in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued. The BPaLM/BPaL regimen may be offered to patients with MDR/RR-TB in the following situations :

- pulmonary TB or all forms of extrapulmonary TB, except TB involving the CNS, osteoarticular TB and disseminated (miliary) TB;
- patient is aged 14 years or older;
- no known allergy to any of the BPaLM component drugs;
- no evidence of resistance to bedaquiline, linezolid, delamanid or pretomanid, or patient has not been previously exposed to any of the component drugs for 4 weeks or longer; when exposure to the component drugs is greater than 4 weeks in duration, the patient may receive the BPaLM regimens if resistance to the specific medicines with such exposure has definitively been ruled out;
- all people regardless of HIV status;
- no XDR-TB according to the 2021 WHO definitions; and
- patient is not pregnant or breastfeeding or, if the patient is a premenopausal woman, is willing to use effective contraception.

In cases of possible fluoroquinolone resistance (e.g. a history of >4 weeks of fluoroquinolone use or close contact with a person infected with a fluoroquinolone-resistant strain), it is best to initiate a BPaLM regimen until DST for fluoroquinolones is available, to decide whether moxifloxacin should be continued. If the result of fluoroquinolone DST is never determined or not done, the BPaLM regimen should be used throughout. This is often done even if fluoroquinolone resistance is suspected, because the toxicity of adding moxifloxacin is low and some patients with past use of a fluoroquinolone or contact cases may still be infected with susceptible strains. If resistance is highly likely (i.e. a treatment with a fluoroquinolone failed or the patient is a close contact of a fluoroquinolone-resistant case and was unlikely to get TB from another source, or in a setting with a high prevalence of fluoroquinolone resistance and in the absence of DST) it is reasonable to omit the moxifloxacin and use the BPaL regimen for treatment.

Dosing of component drugs for adults and adolescents (aged ≥14 years) for BPaLM

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards OR 200 mg daily for 8 weeks, then 100 mg daily
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily
Moxifloxacin (400 mg tablet)	400 mg once daily

Source : *(41)*

Duration of the regimen

The slight differences in the treatment duration of the BPaLM and BPaL regimens, as studied in the TB-PRACTECAL and ZeNix trials, were acknowledged and discussed during the GDG meeting, and the panel suggested standardizing treatment duration of BPaLM to 6 months (26 weeks) during programmatic implementation; for BPaL, the possibility of an extension to a total of 9 months (39 weeks) if sputum cultures are positive between months 4 and 6 was suggested. All medicines in the regimen are to be used throughout treatment duration, including a potential extension from 26 to 39 weeks (when BPaL is used). Ideally, missing doses of all three or four drugs in the regimen should be avoided; however, if doses are missed, any interruption of longer than 7 days should be made up for by extending the treatment duration (for the number of missed doses); therefore, 26 or 39 weeks of prescribed doses should be completed within an overall period of 7 or 10 months, respectively.

Providing health education and counselling to patient and family members (34) :

All MDR-TB cases are offered referral for counselling and HIV testing at the nearest centre. Patients should receive counselling on the nature and duration of treatment, need for regular treatment and possible side effects of these drugs and the consequences of irregular treatment or pre-mature cessation of treatment and cough etiquette. It is advisable to involve close family members during the counselling, since family support is an essential component in the management. Patients should be advised to report any side-effects experienced by them. Female patients should receive special counselling on family planning.

While the MDR-TB case is undergoing pre-treatment evaluation, the DTO should ensure an initial home visit to verify the address and meet the family members. The medical officer needs to open a treatment card for the patient at the time of initiating the treatment. Each patient must be given TB Identity Card. A DOT provider (who can either be a health care worker or a community volunteer), should be identified in consultation with the patient. The DOT centre can be either at the sub-centre of the health system or in the community. The DOT provider should be given training for drug administration, identification of adverse effects during treatment and the frequency of follow-up.

Monthly patient-wise box for DR-TB patients *(39)*

The district drug store will supply the monthly patient-wise boxes as per standard regimens. The shorter oral MDR/RR TB regimen will have two types of boxes – type A for intensive phase and type B for continuation phase. The longer oral M/XDR-TB regimen and H mono/poly DR-TB regimen will standard patient-wise box as there is no separate intensive and continuation phase. The DR-TB patients on longer/shorter injectable containing regimen will be supplied drugs continuously till the state/districts fully transitions to all oral regimen.

CHILDHOOD TUBERCULOSIS

Cases of tuberculosis in children usually represent between 6–8 per cent of all reported tuberculosis in the age group of under 15 years, although the estimates are about 11 per cent cases are in children *(43)*. The source of infection to a child is usually an adult, often a family member with sputum smear-positive tuberculosis. The frequency of childhood TB in a given population depends on : (a) the number of infectious cases; (b) closeness of contact with an infectious case; (c) the age of child when exposed to TB; and the age structure of the population.

Children rarely have sputum smear-positive TB and it is unlikely that they are a powerful source of transmission of TB. Tuberculosis in children is mainly due to failure of TB control in adults. The risk of infection to a child depends on extent of exposure to infectious droplet nuclei. An infant whose mother has sputum smear-positive PTB has a high chance of becoming infected. The chance of developing disease is greatest shortly after infection, and steadily decreases as the time goes by. Because of less-developed immune system, children under 5 years of age are more prone to develop (upto 20 per cent) the disease mostly within 2 years following infection *(26)*. The commonest age of childhood TB disease is 1 to 4 years. Young age is a risk factor for spread of disease to other parts of the body, i.e. dissemination.

In order to simplify the management of paediatric TB, RNTCP in association with Indian Academy of Paediatrics (IAP) has described criteria for suspecting TB among children, has separate algorithms for diagnosing pulmonary TB and peripheral TB lymphadenitis and a strategy for treatment and monitoring patients who are on treatment. In brief, TB diagnosis is based on clinical features, smear examination of sputum where this is available, positive

family history, tuberculin skin testing, chest radiography and histo-pathological examination as appropriate. The treatment strategy comprises of components. First, as in adults, children with TB are classified, categorized, registered and treated with daily dose short-course chemotherapy from treatment initiation to completion, given under direct observation of a treatment provider (DOT provider) and the disease status is monitored during the course of treatment. Based on their pre-treatment weight, children are assigned to one of the pre-treatment weight bands and are treated with good quality anti-TB drugs through "ready-to-use" fixed dose combination tablets in patient-wise boxes containing the patients' complete course of anti-TB drugs, made available to every registered TB patient according to programme guidelines. India is the first country to introduce paediatric patient-wise boxes.

Diagnosis of Paediatric TB

In children with presumptive paediatric TB, every attempt must be made to microbiologically prove diagnosis through examination of appropriate respiratory/non-respiratory specimens with quality assured diagnostic tests. Diagnosis of tuberculosis should not be made only on clinical features, and further investigations are always necessary to establish the diagnosis.

In case of suspicion of pulmonary TB, sputum examination should be carried out among children who are able to give good quality specimens. CBNAAT is the preferred investigation of choice. If CBNAAT is not readily available or testing is not possible even by referral, smear microscopy should be performed. If *M. tuberculosis* is detected, by either of methods patient is diagnosed as microbiologically confirmed pulmonary TB. In situations where *M. tubeculosis* is not detected or specimen is not available, chest X-ray and Tuberculin skin test (TST) by Mantoux technique using 2 TU of PPD RT 23 should be done. For interpretation and further course of action, refer to the diagnostic algorithm for childhood pulmonary TB (Fig. 4).

While following the flow chart, it is important to note the following points :

1. This algorithm is for children who are likely to have drug sensitive disease i.e. have not received ATT previously ever and are not presumptive drug resistant TB cases (lost to follow-up, recurrent, treatment failure, HIV).
2. Proper characterization of symptoms is very important starting point. Weight loss or not gaining weight should always be documented with appropriate and proper weighing.
3. Where CBNAAT is doable, smear examination may not be done. Whenever smear is used for diagnosis at least 2 samples should be sent while a single sample is subjected to CBNAAT. If a specimen is positive by any of these methods, the disease is labelled as microbiologically confirmed TB.
4. Highly suggestive chest X-ray refers to skiagrams showing either miliary or lymphadenopathy (hilar or mediastinal) or chronic fibro-cavitatory shadows. If the radiological picture is highly suggestive of TB, then proceed to do further investigations irrespective of the TST result as the sensitivity of the test is not 100%.

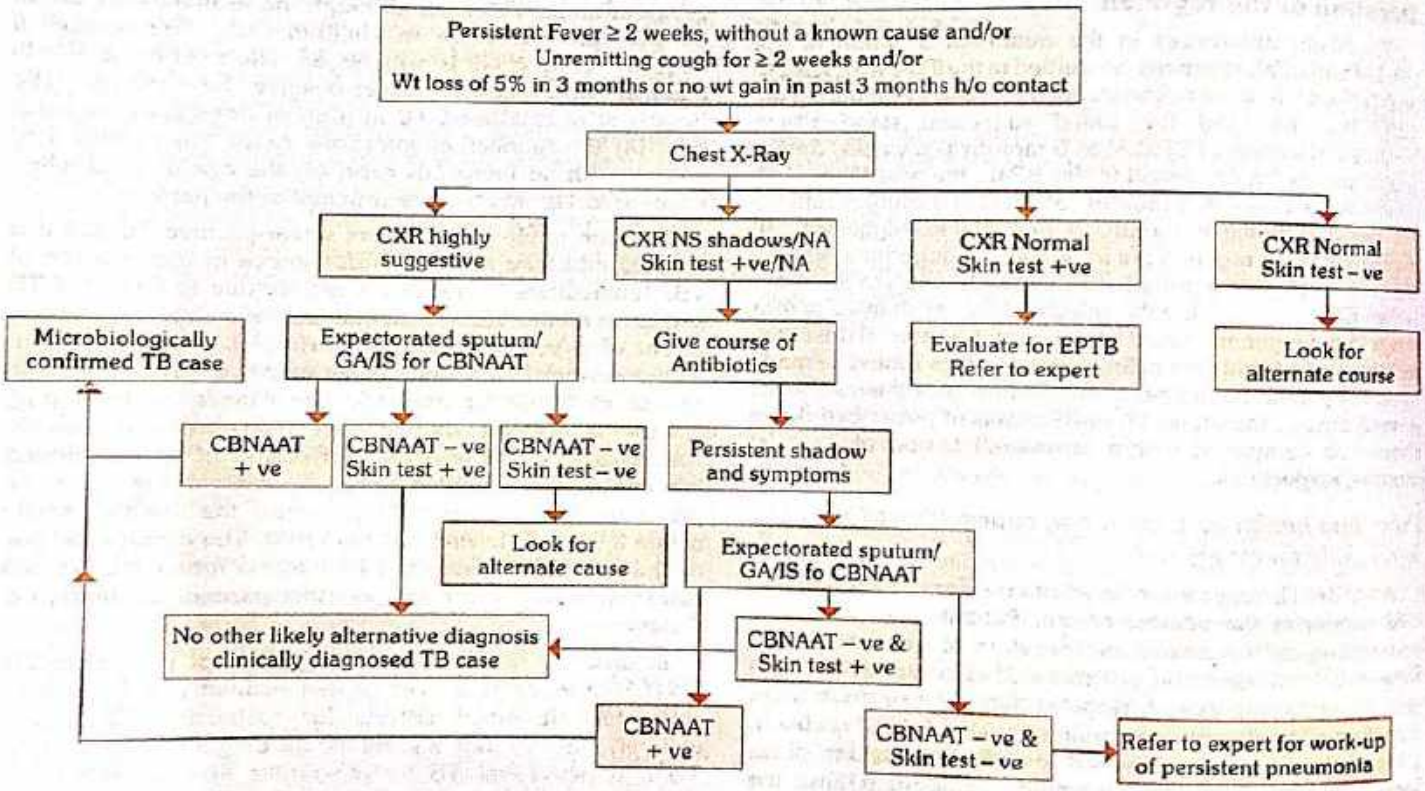


FIG. 4
Diagnostic algorithm for paediatric pulmonary tuberculosis

Source : *(37)*

Non specific chest X-ray : Refer to patterns other than highly suggestive like consolidations in homogenous shadows or bronchopneumonia, etc.

Whenever indicated, alternative specimens (gastric aspirate/induced sputum/bronchoalveolar lavage) should be collected by a skilled health care provider, depending upon available infrastructure and sample should be subjected to CBNAAT.

Antibiotics like linezolid or any quinolone or Amoxicillin-clavulanic acid should not be used as they have anti-TB action.

Children with persistent symptoms, non specific shadows and negative smears and negative other samples (GA/IS) by CBNAAT should be referred to experts for further work-up of persistent pneumonia.

All TB cases diagnosed must be offered testing for HIV.

0. Whenever Rif resistant result is reported on CBNAAT further management should be carried out as per the guidelines on drug resistant TB.

B preventive therapy :

The dose of INH for chemoprophylaxis is 10 mg/kg instead of earlier recommended dosage of 5 mg/kg) dministered daily for 6 months. TB preventive therapy hould be provided to:

a. All asymptomatic contacts (under 6 years of age) of a smear positive case, after ruling out active disease and irrespective of their BCG or nutritional status.

b. Chemoprophylaxis is also recommended for all HIV infected children who either had a known exposure to an infectious TB case or are tuberculin skin test (TST) positive (≥5 mm induration) but have no active TB disease.

c. All TST positive children who are receiving immunosuppressive therapy (e.g. children with nephrotic syndrome, acute leukemia, etc).

d. A child born to mother, who was diagnosed to have TB in pregnancy, should receive prophylaxis for 6 months, provided congenital TB has been ruled out followed by BCG vaccination.

Drug-resistant TB in children:

The principles of treatment of drug-resistant TB in children are : (1) Always treat the child in consultation with an expert; (2) Include at least 4–6 bactericidal medication to which the strain is known to or likely to be susceptible; (3) Do not add a single drug to a failing regimen; (4) Ensure treatment is given for at least 12 months after *M. tuberculosis* culture has converted to negative; and extend treatment to 24 months in case of HIV infection or cavitatory lesions.

The children are managed with regimen designs without newer drugs, depending on the DST pattern. The dosage for drugs used in various DR-TB regimens by weight bands for paediatric DR-TB patients are enumerated in Table 3 *(44)*.

TABLE 3
WHO recommended doses of anti TB drugs for paediatric patients

Drugs	Daily Dose (Paediatric)
Isoniazid [1]	7–15 mg/kg for patients less than 30 kg; max dose 300 mg daily
Rifampicin	10–20 mg/kg for patients less than 30 kg; max dose 600 mg daily
Pyrazinamide	30–40 mg/kg for patients less than 30 kg; max dose 2000 mg daily
Ethambutol	15–25 mg/kg once daily
Levofloxacin	5 years and under : 15–20 mg/kg split into two doses (morning and evening) Over 5 years: 10–15 mg/kg once daily
Moxifloxacin	7.5–10 mg/kg
Ethionamide/ Prothionamide	15–20 mg/kg
Cycloserine	10–20 mg/kg
p-aminosalicylic acid	200–300 mg/kg for patients less than 30 kg
Linezolid	10 mg/kg given three times daily (pyridoxine should also be given)
Clofazimine	Limited data, but 1 mg/kg once daily has been given
Amoxicillin clavulanic acid 7/1	80 mg/kg (based on the amoxicillin component) in two divided doses
Kanamycin	15–30 mg/kg once daily (Max 1000 mg)
Amikacin	15–30 mg/kg once daily (Max 1000 mg)
Capreomycin	15–30 mg/kg once daily (Max 1000 mg)
Imipenem cilastatin	Meropenem is preferred in children
Meropenem	20–40 mg/kg intravenous every eight hours
Bedaquiline	Refer to page 224
Delamanid	Refer to page 224

[1] Children at risk for peripheral neuropathy (e.g. malnutrition or HIV co-infection) should also receive pyridoxine 5–10 mg/day as therapeutic dose.

Source : *(44)*

TB IN PREGNANCY AND LACTATING WOMEN *(34)*

While the burden of TB is higher in men in India, the impact of TB in women is far-reaching, especially for women in the reproductive age group (15–49 years). Due to common non-specific symptoms in both TB and pregnancy, diagnosing TB disease in pregnant women is complex. TB in pregnancy has a wide spectrum of short and long-term implications and could have sequential effects : repeated reproductive failure, foetal ill-health, preterm delivery, and TB of the new-borns and infants, leading to high maternal and perinatal morbidity and mortality. For example, there is a six-fold increase in perinatal deaths and a two-fold risk of premature birth and low birth weight in mothers with active TB disease.

The NTEP and the Maternal Health (MH) division have developed a collaborative framework for management of TB in pregnant women to reduce morbidity and mortality due to TB in pregnant women and new-borns through prevention, screening for early detection, and prompt management of TB in pregnant women and achieve optimum maternal and perinatal outcomes. This screening for TB will be made an essential component of ANC services. The National-level sensitization workshop for all the state nodal officers of both the programmes has been conducted, and the training will be cascaded *(43)*.

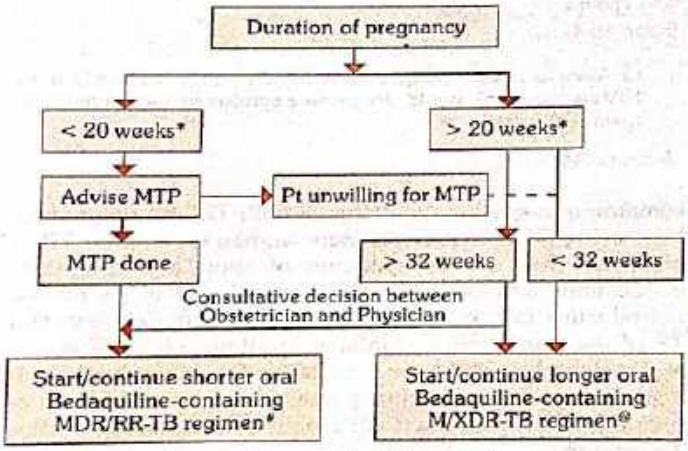
In 2021, the number of female patients screened for pregnancy was 47,185, out of which 4,048 were pregnant.

Before initiating treatment for tuberculosis, women of childbearing age should be asked about current or planned pregnancy and counselled appropriately. A successful treatment of TB is important for successful outcome of pregnancy. With the exception of streptomycin, the first line anti-TB drugs are safe for use in pregnancy. Streptomycin is oto-toxic to the foetus and should not be used during pregnancy.

A breast feeding woman should receive a full course of TB treatment. Correct chemotherapy is the best way to prevent transmission of TB to baby. Breast feeding has to be continued. After ruling out active TB, the baby should be given 6 months of isoniazid preventive therapy, followed by BCG vaccination. Breast-feeding should not be discouraged. The mother should be advised about cough hygiene measures such as covering the nose and mouth while coughing, sneezing or any act which can produce sputum droplets. Mothers receiving INH and their breastfed infants should be supplemented with vitamin B6 (pyridoxine). Recommended dose of Pyridoxine in infants is 5 mg/day.

Pregnancy with MDR-TB

All MDR-TB suspects and patients of child-bearing age should be tested for pregnancy as part of pre-treatment evaluation and while on treatment, if there is a history of amenorrhoea of any duration. They should be advised to use birth control measures because of the potential risk to both mother and foetus. Oral contraceptives should be avoided. Use of barrier methods (condoms/diaphragms), IUDs are recommended, based on individual preference and eligibility. The management of MDR-TB patients with pregnancy is summarized in Fig. 5.



* 24 weeks will apply wherever the bill is passed.

\# Regimen : 4–6 Bdq (6m) Lfx, Cfz, Eto, Hh, Z, E / 5 Lfx, Cfz, Z, E. No modifications allowed.

@ Regimen :18–20 Lfx, Bdq (6m or longer) Lzd#, Cfz, Cs. Lzd dose to be tapered to half after 6–8 months based on bacteriological response. Modify regimen if one or more drug cannot be used due to reasons of resistance, tolerability, contraindication, availability etc.
- in the order of Z E PAS.
- Eto may be considered after 32 weeks' gestation.
- Am may be considered in post-partum period only. Am will not be started in the final 12 months of treatment.

FIG. 5
Management of MDR-TB patients during pregnancy

Source : *(39)*

Pregnant DR-TB patients need to be monitored carefully, both in relation to the treatment and progress of the pregnancy. This approach should lead to good results, since the patient should be smear-negative at the time of parturition and mother and infant do not need to be separated. Breast-feeding should be encouraged as long as the patient is sputum negative.

In the end it may be stated that the main problem of chemotherapy today is not the need to introduce new regimens or more potent drugs, but to apply the existing ones successfully. The cornerstone of successful chemotherapy is adequate and regular drug intake. Patient compliance is critically important throughout the prescribed period of treatment. All other considerations are secondary.

BCG VACCINATION

Ever since Koch discovered *M. tuberculosis*, attempts have been made to prepare a prophylactic vaccine against tuberculosis using either attenuated or killed tubercle bacilli. Initially BCG was given orally during 1921 to 1925. The first human was vaccinated by the intradermal technique in 1927. Recognition of the value of BCG came in 1948 when it was accepted by tuberculosis workers from all over the world as a safe preventive measure.

(1) AIM : The aim of BCG vaccination is to induce a benign, artificial primary infection which will stimulate an acquired resistance to possible subsequent infection with virulent tubercle bacilli, and thus reduce the morbidity and mortality from primary tuberculosis among those most at risk.

(2) VACCINE : BCG is the only widely used live bacterial vaccine. It consists of living bacteria derived from an attenuated *bovine* strain of tubercle bacilli. The bacilli used for vaccine production are descendants of the original Calmette strain of BCG. Due to different methods of maintenance in various vaccine–production laboratories, many substrains have evolved during the past few decades. The WHO has recommended the "Danish 1331" strain for the production of BCG vaccine. Since January 1967, the BCG Laboratory at Guindy, Chennai, has been using the "Danish 1331" strain for the production of BCG vaccine *(45)*. Emphasis has been laid on regular checking of the quality of vaccines at the International Reference Centre for BCG quality control at Copenhagen.

(3) TYPES OF VACCINE : There are two types of BCG vaccine – the liquid (fresh) vaccine and the freeze-dried vaccine. Freeze-dried vaccine is a more stable preparation than liquid vaccine with vastly superior keeping qualities. Present–day vaccines are distributed in the freeze-dried form.

BCG vaccine is stable for several weeks at ambient temperature in a tropical climate, and for up to 1 year if kept away from direct light and stored in a cool environment preferably refrigerated at a temperature below 10 deg C *(46)*.

The vaccine must be protected from exposure to light during storage (wrapped up in a double layer of red or black cloth) and in the field. Normal saline is recommended as a diluent for reconstituting the vaccine, as distilled water may

cause irritation. The reconstituted vaccine may be used up within 3 hours, and the left-over vaccine should be discarded.

(4) DOSAGE : For vaccination, the usual strength is 0.1 mg in 0.1 ml volume *(47)*. The dose to newborn aged below 4 weeks is 0.05 ml. This is because the skin of newborn is rather thin and an intradermal injection with full dose (0.1 ml) in some of them might penetrate into deeper tissue and give rise to local abscess formation and enlarged regional (axillary) lymph nodes.

(5) ADMINISTRATION : The standard procedure recommended by WHO is to inject the vaccine intradermally using a "Tuberculin" syringe (Omega microstat syringe fitted with a 1 cm steel 26 gauge intradermal needle). The syringe and needle technique remains the most precise way of administering the desired dose. All other techniques (e.g., bifurcated needle, dermo-jet) are reported to be less accurate, and do not permit the desired dose to be injected *(48)*. If the vaccine is injected subcutaneously an abscess is more likely to develop *(49)*. The site of injection should be just above the insertion of the left deltoid muscle. If it is injected too high, too forward or too backward, the adjacent lymph nodes may become involved and tender. A satisfactory injection should produce a wheal of 5 mm in diameter.

The vaccine must not be contaminated with an antiseptic or detergent. If alcohol is used to swab the skin, it must be allowed to evaporate before the vaccine is given.

(6) AGE : The national vaccination policies differ from country to country *(47)*. In countries where tuberculosis is prevalent and the risk of childhood infection is high (as in India), the national policy is to administer BCG very early in infancy either at birth (for institutional deliveries) or at 6 weeks of age simultaneously with other immunizing agents such as DPT and polio. BCG administered early in life provides a high level of protection, particularly against the severe forms of childhood tuberculosis and tuberculous meningitis.

In countries with a low prevalence of tuberculosis, perhaps there is a diminishing need for widespread BCG vaccination. In this situation, it would seem reasonable to restrict BCG vaccination to high risk groups, for example, hospital personnel and tuberculin-negative contacts of known cases of tuberculosis particularly multi-drug resistant TB (MDR-TB) *(46, 50)*.

(7) PHENOMENA AFTER VACCINATION : Two to three weeks after a correct intradermal injection of a potent vaccine, a papule develops at the site of vaccination. It increases slowly in size and reaches a diameter of about 4 to 8 mm in about 5 weeks. It then subsides or breaks into a shallow ulcer, rarely open, but usually seen covered with a crust. Healing occurs spontaneously within 6 to 12 weeks leaving a permanent, tiny, round scar, typically 4–8 mm in diameter. This is a normal reaction *(51)*. However, with overdosage, the local lesion and the later scar may be considerably larger and of irregular size. Normally the individual becomes Mantoux-positive after a period of 8 weeks has elapsed, but sometimes about 14 weeks are needed.

(8) COMPLICATIONS : BCG has been associated with adverse reactions which include : prolonged severe ulceration at the site of vaccination, suppurative lymphadenitis, osteomyelitis, disseminated BCG infection and death. Ulceration and lymphadenitis occurs in 1–10 per cent of vaccinations, and disseminated infection occurs in less than one per million vaccinations. The disseminated infection is usually associated with severe abnormalities of cellular immunity. The risk of adverse reactions is related to the BCG strain used by different manufacturers, the dose, the age of the child, the method of immunization and the skill of the vaccinator *(52)*.

If there is a local abscess formation, it should be treated by aspiration, in case it does not clear spontaneously. If this is not successful, it should be incised and treated with local applications daily with PAS or INH powder. There is no need for systemic treatment with INH. The patient should be assured of the harmless nature of the lesion *(53)*. In order to avoid these complications, the vaccination should be strictly intradermal and no other injection should be given for at least 6 months into the arm which received BCG vaccine *(54)*.

(9) PROTECTIVE VALUE : The duration of protection is from 15 to 20 years. The local BCG infection generates an immunity response, which is associated with the development of tuberculin hypersensitivity and with it, possibly, some immunity. The first prospective control trial of BCG showed it to be 80 per cent effective over an observation period of 20 years *(55)*. Since then several well-planned, controlled trials have been conducted in various parts of the world, including the "Tuberculosis Prevention Trial" in South India *(56, 57)*.

Studies have shown that the range of protection offered by BCG varied from 0 to 80 per cent in different parts of the world. The full explanation for the varying degrees of protection has yet to be found *(58, 59)*. One suggestion for which there is an increasing epidemiological support, is that prior exposure to some non-tuberculous environmental mycobacteria (e.g., *M. vaccae, M. non-chromogenicum*) may have conferred partial immunity on the population and thus masked the potential benefit of BCG vaccination *(60)*. There is also evidence that exposure to other species (e.g., *M. kansasii, M. scrofulaceus*) have an antagonistic action against BCG *(55)*. This may be one reason why BCG was not found to be protective in the South Indian trial *(51)*. However, infants and young children, BCG-vaccinated before they had contact with environmental mycobacteria, derived protection.

There is a large body of evidence which supports the conclusion that BCG gives an appreciable degree of protection against childhood tuberculosis *(61)*. The WHO, on the basis of an extended review of BCG including the South Indian trial *(62)* holds that it would seem unreasonable to stop current BCG vaccination programmes *(59)* and recommends that the use of BCG should be continued as an antituberculosis measure *(62)*.

(10) REVACCINATION : The duration of protection conferred by BCG is a matter of dispute. Even 90 years after the development of the vaccine, it is not known whether booster doses are indicated or advisable. In fact, BCG revaccination has not been included in the official immunization schedule in India under the expanded programme on immunization.

(11) CONTRAINDICATIONS : Unless specifically indicated, BCG should not be given to patients suffering

from generalized eczema, infective dermatosis, hypogammaglobulinaemia, to those with a history of deficient immunity (symptomatic HIV infection, known or suspected congenital immunodeficiency, leukaemia, lymphoma or generalized malignant diseases), patients under immunosuppressive treatment (corticosteroids, alkylating agents, antimetabolites, radiation), and in pregnancy. The effect of BCG may be exaggerated in these patients.

(12) DIRECT BCG VACCINATION : Direct BCG vaccination, i.e., vaccination without a prior tuberculin test, has been adopted as a national policy in many developing countries, including India. It permits a more rapid and complete coverage of the eligible population, while reducing the cost. No adverse effects have been reported even if BCG is given to tuberculin–positive reactors *(51)*. However, it is sound practice to administer BCG during infancy before the child has had contact with environmental mycobacteria, than to resort to direct BCG at a later date, when the benefits of BCG are doubtful as shown by the South Indian trial *(63)*.

(13) IMPACT : BCG vaccination is less effective in controlling tuberculosis as compared to active case-finding and chemotherapy, as BCG offers only partial protection. In 1982, a WHO Expert Committee *(64)* concluded that although BCG vaccination of uninfected individuals (usually children) can prevent tuberculosis in them, it can have only a relatively small epidemiological effect in that it will not contribute significantly to the reduction in the overall risk of infection in the community as a whole.

(14) BCG VACCINATION AND HIV INFECTION : Following a review of relevant data, the Global Advisory Committee on Vaccine Safety (GACVS) has revised its previous recommendations concerning BCG vaccination of children infected with HIV.

WHO had previously recommended that in countries with a high burden of TB, a single dose of BCG vaccine should be given to all healthy infants as soon as possible after birth unless the child presented with symptomatic HIV infection. However, evidence shows that children who were HIV-infected, when vaccinated with BCG at birth, and who later developed AIDS, were at an increased risk of developing disseminated BCG disease. Among these children, the benefits of potentially preventing severe TB are out weighted by the risks associated with the use of BCG vaccine. GACVS, therefore, advised WHO to change its recommendation such that *children who are known to be HIV-infected, even if asymptomatic, should no longer be immunized with BCG vaccine (65)*. However, population with high prevalence of HIV also have the greatest burden of TB, and in such populations, uninfected children will benefit from the use of BCG vaccine. Furthermore, with the increasing range and coverage of interventions to prevent vertical transmission from mother to child – including early diagonsis of maternal HIV infections; management of sexually transmitted infections; safe delivery practices; maternal and infant preventive antiretroviral medicines or maternal antiretroviral therapy; and safe infant feeding – the majority of infants born to HIV-infected mothers are not infected and would also be expected to benefit from BCG vaccination *(65)*.

Unfortunately, accurate diagnosis of HIV infection in the first year of life relies upon direct demonstration of the HIV virus, as maternal HIV antibody is passively transferred to the infant *in utero*. Currently available assays that can be used to diagnose HIV in the first year of life are expensive and technically demanding in many countries with generalized HIV epidemics. WHO recommends that these tests are first performed at or around 6 weeks age, yet this is often after BCG vaccination has already been given *(66)*.

(15) COMBINED VACCINATION : BCG may be given at the same time as oral polio vaccine. DPT vaccine may also be given at the same time as BCG, but in different arm without reducing the immune responses or increasing the rate of complications *(56)*. Mixed vaccines containing BCG have not yet been introduced.

Adult TB Vaccination initiative *(67)*

The Government of India is piloting an adult BCG vaccination programme to help prevent tuberculosis in adults. The programme is part of the country's effort to eliminate TB by 2025. The programme goal includes evaluating the effectiveness of the BCG vaccine in preventing TB in adults.

The BCG vaccine is same one used for children. The vaccine is given to adults above the age of 18 years, identified as vulnerable groups. The eligibility for vaccination is as follows :

1. Individuals with at least one episode of TB in the past 5 years.
2. Individuals aged 60 years or above
3. Individuals with a Body Mass Index of less than 18 kg per m.sq.
4. Close contacts of TB patients
5. Individuals with a history of smoking tobacco (self-reported).
6. Individuals with a history of diabetes (self-reported).

The vaccine should not be given to persons who are immunosuppressed or who are likely to become immunocompromised. This includes people with HIV or those who are candidates for organ transplants.

An increasing number of industrialized countries are likely to reconsider their BCG vaccination policy during the coming years. To change from general to selective BCG vaccination, an efficient notification system must be in place in addition to the following "low endemicity" criteria : (a) an average annual notification rate of smear-positive pulmonary TB cases below 5 per 100,000; or (b) an average annual notification rate of tubercular meningitis in children aged under five years, below 1 per 10 million population during the previous five years; or (c) an average annual risk of tuberculosis infection below 0.1 per cent *(66)*.

To sum up, BCG vaccination is a fundamental component of a national tuberculosis programme. Despite the contradictory evidence of controlled trials, there is evidence that BCG plays a valuable role in preventing severe forms of childhood tuberculosis, viz. meningitis and miliary tuberculosis. Today, BCG vaccination is part of WHO Expanded Programme on Immunization. The greatest need for BCG vaccination today is undoubtedly in the developing countries of the world where tuberculosis is still a major health problem.

Tuberculosis Preventive Treatment (TPT) *(68)*

India has the highest estimated burden of tuberculosis infection (TBI) globally, with nearly 35–40 crore Indian population having TBI, of which 26 lakh people (18-36 lakh) are estimated to develop tuberculosis (TB) disease annually. From this large pool of infected but asymptomatic persons, most patients of TB disease will arise. Several studies have shown that, on average, 5–10% of those infected will develop TB disease over the course of their lives, usually within the first 2 years after initial infection. The risk for TB disease after infection depends on several factors, the most important being immunological status. This risk is increased >25 times among contacts of bacteriologically confirmed TB patients compared to general populations, 16–21 times in case of HIV co-infection and 3–4 times in other immune-compromised status like diabetes, etc.

Prevention of TB disease by treatment of TBI is a critical component of the National Strategic Plan (NSP) 2017–25 Treat-Prevent-Build approach and scaling up TPT would be key to hasten the rate of decline in TB incidence from 2.5% at present to 10% required annually. Rigorous, expansive and accountable "TB contact tracing and investigation" for secondary TB patient detection and treatment coupled with active screening for TB among HRGs and TPT is one of the key activities under the "Prevent" component of the NSP.

In the cascade of care approach, all target population who are at-risk of developing TB disease are systematically reached out, screened for TB disease and after ruling out TB disease, provided TPT as a part of continuum of care. The aim is to have significant impact on an individual's health as well as to reduce TB burden and transmission.

Identifying at-risk population *(68)*

It is important to identify those at highest risk of progression to active TB, to manage TBI in them, as not all individuals infected with *M. tuberculosis* develop active TB and currently there are no predictive tests to identify individuals who will progress to disease. Hence a targeted approach is considered as an appropriate public health response. Prevention of TB through TPT begins with exclusion of active TB among high risk groups (HRG) and the diagnosis of TBI.

In the typical screening process, asymptomatic and early active TB cases are also found, and case detection rates vary by the TB prevalence of the population targeted. Active TB case finding (ACF) process also offers an opportunity to simultaneously rule out active TB among HRG and identify the target population for TPT, wherein programatic management of tuberculosis preventive treatment (PMTPT) services can be integrated within existing ACF interventions. Hence, TPT is a continuum of care for routine programme activities including ACF. The programme has prioritized the following target population for TPT based on elevated risk of progression from infection to TB disease or increased likelihood of exposure to TB disease.

1. Expanded eligible groups

a. People Living with HIV (adults, adolescents and children)

TPT reduces the overall risk for TB by 60–90% among PLHIV. Following are the recommended actions :

- Adults and children (>12 months) living with HIV should be screened for TB using a four-symptom complex and TPT can be provided to those without symptoms or after ruling out active TB in those with TB symptoms. TPT should be given to all these individuals irrespective of the degree of immunosuppression, whether they are on antiretroviral treatment (ART), previous TB treatment, and/or pregnancy in women.
- Infants aged < 12 months living with HIV who are in contact with a patient of pulmonary TB and are investigated for TB should receive TPT with 6 months of isoniazid (6H) after active TB is ruled out.

b. All household contacts of pulmonary TB patients

All HHC of pulmonary TB patients notified in Nikshay from public and private sector, regardless of their age or TBI status, are at substantially higher risk for progression to active TB than the general population. Hence contact tracing is of paramount importance.

- All efforts need to be made to ensure that CXR & TBI testing is made available. However, TPT must not be deferred in their absence. (This includes close contacts of pulmonary TB patients at workplace and other settings, regardless of their age).

2. Expansion to other risk groups

Individuals with clinical risk factors who are on immunosuppressive therapy, having silicosis, on anti-TNF treatment, on dialysis, preparing for organ or hematologic transplantation should be tested and treated for TBI because of their increased risk for progression to active TB disease.

Systematic TBI testing and treatment is not recommended for people with diabetes mellitus, malnutrition, smoking, harmful alcohol abuse unless they have other risk factors for TB, such as HIV infection or history of contact with TB patient within their household.

High TB transmission settings (health-care workers, prisons, mines, slums, tribal, migrant laborers etc.) could be mapped out as part of a vulnerability mapping exercise done for ACF. This can be prioritized for specific TPT interventions guided by differential TB epidemiology by the state TPT committee if the risk of active TB among them is higher than that of the general population in the respective states.

Tests for TB infection

The currently recommended and available tests for TBI are Tuberculin Skin Test (TST) and Interferon-Gamma Release Assay (IGRA). Both tests measure immune sensitization (type IV or delayed-type II hypersensitivity) to mycobacterial protein antigens that occurs following infection by *M. tuberculosis*.

Assessing eligibility and providing TPT

The following algorithmic approach as shown in Fig. 6 would be used for programatic management of TB preventive treatment under the existing programmatic framework *(68)*.

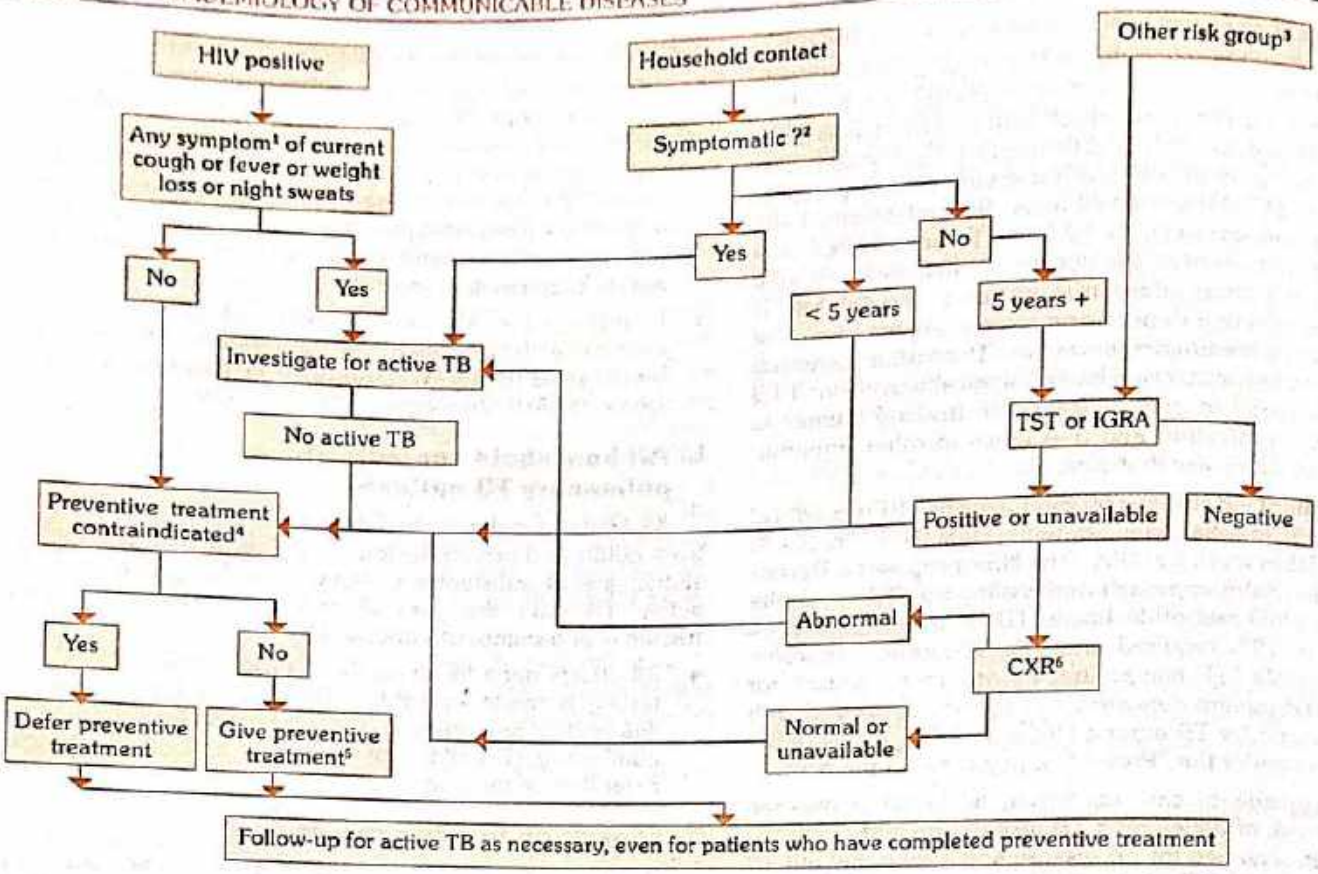


FIG. 6
Algorithm for TB screening and TPT in India *(68)*

Source : *(68)*

1. If <10 years, any one of current cough or fever or history of contact with TB or reported weight loss or confirmed weight loss >5% since last visit or growth curve flattening or weight for age <-2 Z-scores.
   Asymptomatic infants <1 year with HIV are only treated for TBI if they are household contacts of TB. TST or IGRA may identify PLHIV who will benefit most from preventive treatment. Chest radiography (CXR) may be used in PLHIV on ART, before starting TPT.
2. Any one of cough or fever or night sweats or haemoptysis or weight loss or chest pain or shortness of breath or fatigue. In children <5 years, they should also be free of anorexia, failure to thrive, not eating well, decreased activity or playfulness to be considered asymptomatic.
3. Including silicosis, dialysis, anti-TNF agent treatment, preparation for transplantation or other vulnerable risk groups where testing must precede before TPT.
4. Including acute or chronic hepatitis; peripheral neuropathy (if isoniazid is used); regular and heavy alcohol consumption. Pregnancy or a previous history of TB are not contraindications.
5. Regimen chosen based on considerations of age, strain (drug susceptible or otherwise), risk of toxicity, availability and preferences.
6. CXR may have been carried out earlier as part of intensified case finding.

TB preventive treatment

The following TPT treatment options are recommended under NTEP once active TB has been ruled-out :

a. Expanded eligible group :

Target population	Treatment option
• People living with HIV (adults and children >12 months)	• 6-months daily isoniazid (6H)
• Infants <12 months in contact with active TB • HHC below 5 years of pulmonary TB patients	• 3-month weekly Isoniazid and Rifapentine (3HP) in persons older than 2 years
• HHC 5 years and above of pulmonary TB patients (testing would be offered whenever available)	• 3-month weekly Isoniazid and Rifapentine (3HP) • 6-months daily isoniazid (6H)

b. Other risk groups expansion

• Children/adult on immunosuppressive therapy, silicosis, anti-TNF treatment, dialysis, transplantation	• 3-month weekly Isoniazid and Rifapentine (3HP) • 6-months daily isoniazid (6H)

Contraindications for TPT

TPT is contraindicated in the following situations :

- Active TB disease
- Acute or chronic hepatitis
- Concurrent use of other hepatotoxic medications (such as nevirapine)
- Regular and heavy alcohol consumption
- Signs and symptoms of peripheral neuropathy like persistent tingling, numbness and burning sensation in the limbs
- Allergy or known hypersensitivity to any drugs being considered for TPT

Rehabilitation

In recent years, there has been a good deal of fresh thinking on the subject of rehabilitation, because of the success achieved in treating patients on domiciliary lines without interfering with their normal work and life. The

proportion of patients who need rehabilitation and work under sheltered conditions is becoming less and less. The groups that need rehabilitation are those who are chronically ill and are still excreting tubercle bacilli. Some of those who had lung resection may require rehabilitation to suit their physical and mental abilities.

Surveillance

Surveillance is an integral part of any effective tuberculosis programme. It should be concerned with two distinct aspects : (a) surveillance of the tuberculosis situation, for example, by measuring the "annual infection rates" which will guide the epidemiologist and health administrator by indicating whether the TB problem is static, increasing or decreasing; (b) surveillance of control measures applied such as BCG vaccination and chemotherapy.

Role of hospitals

Inspite of effective domiciliary treatment services, there will always be some patients who will be needing hospitalization. The main indications for hospitalization are : (a) emergencies such as massive haemoptysis and spontaneous pneumothorax (b) surgical treatment (c) management of serious types of tuberculosis such as meningeal tuberculosis, and (d) certain social indications, such as when there is no one to look after the patient at home.

DRUG RESISTANCE

All drugs used in the treatment of tuberculosis tend to produce resistant strains. The resistance may be of two types : (a) *PRIMARY OR PRE–TREATMENT RESISTANCE :* It is the resistance shown by the bacteria in a patient, who has not received the drug in question before. That this is not always due to infection of the individual with drug–resistant bacilli, is well known. It is an accepted fact that when the bacilli are rapidly multiplying, resistant mutants appear irrespective of the administration of any particular drug. According to one hypothesis, drug resistance is induced by transference through what are called "episomes". Episomes are non–chromosomal heritable genes which can pass from one bacterial cell to another. If there is a direct contact between the cell containing episomes, the episomes leave the resistant cell and invade susceptible cells *(69).* (b) *SECONDARY OR ACQUIRED RESISTANCE :* Here the bacteria were sensitive to the drug at the start of the treatment but became resistant to the particular drug during the course of treatment with it.

Drug resistance means that certain strains of tuberculosis bacilli are not killed by the anti–tuberculosis drugs given during the treatment. Some strains can be resistant to one or more drugs.

Definitions

Please refer to page 211 for classification of cases based on drug resistance.

Causes of drug-resistant tuberculosis *(25)*

Drug-resistant TB has microbial, clinical and programmatic causes. From a microbiological perspective, the resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows drug-resistant mutants to become the dominant strain in a patient infected with TB. Table 4 summarizes the common causes of inadequate treatment. However it should be stressed that MDR-TB is man-made phenomenon – poor treatment, poor drugs and poor adherence lead to the development of MDR-TB.

In all countries and especially those where the number of cases of tuberculosis is rising rapidly because of the association with HIV, the development of resistant strains of tuberculosis is a serious concern. In 2016, about 0.60 million people worldwide, are estimated to be infected with strains of drug resistant tuberculosis. An accurate picture of drug resistance is not available because few countries have a reliable drug resistance surveillance system *(17).*

It is estimated that primary MDR-TB in India is around 2.8 per cent. The drug resistance in re-treatment cases is 12 (10–13) per cent. Although the level of MDR-TB in the country is low in relation to percentage and proportion, it translates into large absolute numbers *(70).*

XDR-TB has been reported in India by isolated studies with non-representative and highly selected clinical samples. The magnitude of the problem remains to be determined due to the absence of laboratories capable of conducting quality assured second line drug susceptibility test *(9).*

It has been observed that resistance to isoniazid alone does not affect the results of treatment so much, if proper regimens for treatment or retreatment are prescribed, but simultaneous resistance to isoniazid and rifampicin limits severely the results of the treatment.

The most serious danger of MDR Tuberculosis is that it is much more difficult to treat, even where second line drugs are available. Treatment of MDR tuberculosis can take at least two years and the results are poor. Second line drugs

TABLE 4

Causes of inadequate treatment

Providers/programmes : inadequate regimens	Drugs: inadequate supply/quality	Patients: inadequate drug intake
– Absence of guidelines or inappropriate guidelines	– Non-availability of certain drugs (stock-outs or delivery disruptions)	– Poor adherence (or poor DOT)
– Non-compliance with guidelines	– Poor quality	– Lack of information
– Inadequate training of health staff	– Poor storage conditions	– Non-availability of free drugs
– No monitoring of treatment	– Wrong dosages or combination	– Social and economic barriers
– Poorly organized or funded TB control programmes		– Malabsorption
		– Substance abuse disorders

cost 30 times as much as drugs used in SCC treatment of non-resistant tuberculosis patients. Patients with MDR tuberculosis may need to be hospitalised and isolated which adds to the cost of treatment, to prevent transmission of primary resistant strains to others. Careful precautions are necessary to prevent transmission, especially to health workers caring for MDR tuberculosis patients *(71)*.

The emergence of XDR-TB and high case fatality rate in patients with HIV infection was the subject of an emergency consultations held in Johannesburg on 7–8 September, 2006. The issues included strengthening treatment adherence to achieve high levels of completion (≥ 85 per cent) for all TB patients ensuring that second line drugs used to treat MDR-TB and XDR-TB are strictly controlled and properly used according to WHO guidelines. The steps required to limit the impact of MDR-TB and XDR-TB were identified and incorporated into a 7-point plan of action *(72)*.

In the short term, countries should :

1. develop national emergency response plans for MDR-TB and XDR-TB and ensure that basic TB control measures meet international standards for TB care and are fully implemented;
2. conduct rapid surveys of MDR-TB and XDR-TB using a standardized protocol to assess the geographical and temporal distribution of XDR-TB in vulnerable populations;
3. strengthen and expand national TB laboratory capacity by addressing all aspects of laboratory procedures and managment;
4. implement infection control precautions in health-care facilities according to WHO guidelines, with special emphasis on those facilities providing care for people living with HIV/AIDS.

In the long term, countries should:

5. establish capacity for clinical and public health managers to respond effectively to MDR-TB and XDR-TB;
6. promote universal access to antiretroviral therapy for all TB patients through close collaboration with treatment and care programmes for people living with HIV/AIDS;
7. support and increase funding for research into the development of new anti-tuberculosis drugs and rapid diagnostic tests for MDR-TB and XDR-TB.

Prevention of Drug Resistance : Since incomplete, inadequate and irregular treatment is the main cause of drug resistance, this can be prevented by (a) treatment with two or more drugs in combination (b) using drugs to which the bacteria are sensitive, and (c) ensuring that the treatment is complete, adequate and regular.

Please refer to page 222 for details of guidelines about management of MDR and XDR-TB.

TB comorbidities and special situations

The TB epidemic is strongly influenced by social and economic development and health-related risk factors. Key health-related risk factors for TB include, diabetes, HIV infection, alcohol use disorders, tobacco smoking and undernutrition. In addition, access to clean fuels, level of income inequality, poverty, social protection and living in informal settlements are broader socioeconomic determinants for TB. Thus, achieving targets for reductions in TB disease burden requires progress in addressing health-related risk factors and socioeconomic determinants.

The estimated number of cases of TB in India attributable to these comorbidities are as follows :

India estimates of TB cases attributable to selected comorbidities, 2021

Risk Factors	Estimates of number of cases attributable to risk factors (95% Confidence Interval) (Lakh)
Undernourishment	7.38 L (6.24 L - 8.61 L)
Alcohol Use Disorders	2.57 L (0.74 L - 5.53 L)
Smoking	1.09 L (0.21 L - 2.71 L)
Diabetes	1.05 L (0.31 L - 2.23 L)
HIV Infection	0.93 L (0.29 L - 1.93 L)

The National Tuberculosis Prevalence Survey, India, also reported that the prevalence of TB was higher among those survey participants having Body Mass Index (BMI) < 18.5 kg/m^2, diabetes, alcohol consumption and tobacco smoking.

The NTEP collaborates with different public health programs to design and implement interventions to address important comorbidities for TB. These interventions include joint training of staff, co-location of diagnostic/treatment services, bi-directional screening, cross-referral of presumptive and confirmed cases and prevention of TB through treatment for TB infection and Airborne Infection Control measures at Health Facilities.

TB-Nutrition *(73)*

TB and undernutrition have a bidirectional relationship. The vicious cycle between undernutrition and TB persists, being significant drivers of the burden of both diseases in India. While under nutrition is an established risk factor for the progression of TB infection to active TB (six to ten times), active TB by itself could lead to weight loss, wasting and worsening of nutritional status, and increases the risk of severe disease, death, drug toxicity, drug mal-absorption and relapse. Evidence has shown that for each unit reduction in BMI, the risk of TB increases by about 14%. Similarly, compared to individuals with normal body weight, the risk of relapse is four times higher for each unit reduction in BMI.

In addition, for children, pregnant and lactating women, the physiological requirement for nutrition is high, further aggravating the risk of TB disease if the demand for increased nutrition is not met. Adequate nutrition also helps in treatment adherence and an overall reduction in mortality. Hence, assessment and management of nutritional status are critical for TB treatment and care. Ni-kshay Poshan Yojna and Pradhan Mantri TB Mukt Bharat Abhiyaan, are committed to supporting the nutritional requirements of the patients for the period of treatment.

TB and alcohol use disorder

Alcohol use disorder is an important risk factor for TB. In 2022, 74% of notified TB patients were screened for alcohol consumption and alcohol use was reported in 7.2% of the

patients. Services provided to TB patients who use alcohol include (a) counselling, (b) linkages to de-addiction centres, and (c) social support systems.

TUBERCULOSIS AND HIV

Worldwide the number of people infected with both HIV and tuberculosis is rising. The HIV virus damages the body's natural defences – the immune system – and accelerates the speed at which tuberculosis progresses from a harmless infection to life–threatening condition. The estimated 10 per cent activation of dormant tuberculosis infection over the life span of an infected person, is increased to 10 per cent activation in one year, if HIV infection is superimposed. Tuberculosis is already the opportunistic infection that most frequently kills HIV–positive people.

Even in HIV positive cases, tuberculosis can be cured if diagnosed in time and treated properly. Good TB control programme is the best thing that can be done to cure and extend the lives of HIV positive individuals. With correct TB treatment, the HIV positive person having tuberculosis can gain, on an average two additional years of life *(74)*.

Epidemiological impact

HIV and tuberculosis interact in several ways *(71)* :

1. *Reactivation of latent infection* : People who are infected with both tuberculosis and HIV, are 25–30 times more likely to develop tuberculosis disease, than people infected only with tuberculosis. This is because HIV stops the immune system working effectively and tuberculosis bacilli are able to multiply rapidly. In developing countries HIV associated tubercular disease is very common.

2. *Primary infection* : People with HIV are at risk of being newly infected, if they are exposed to tuberculosis because their weakened immune system makes them more vulnerable. New tubercular infection in people with HIV can progress to active disease very quickly.

3. *Recurring infection* : People with HIV who have been cured of tuberculosis infection may be more at risk of developing tuberculosis again. However, it is not clear whether this is because of reinfection or relapse.

4. *In the community* : There are more new cases of active tuberculosis because more people infected with tuberculosis develop active disease, and those newly infected become ill faster. This means that there are more people in the community who are infectious to others. Larger number of people with active disease mean more people will die from tuberculosis unless they are treated. The association of tuberculosis with HIV means that people suffer additional discrimination. Community education is needed to increase awareness that tuberculosis is curable and, most important, that people are no longer infectious after the first few weeks of treatment.

Diagnosis of tuberculosis in people with HIV

The salient features are as follows *(34)* :

1. Emphasis on integrated TB and HIV services, eg., HIV screening at NTEP designated microscopy centre.
2. Focus on early detection and early care.
   a. Early detection of TB in PLHIV (persons living with HIV/AIDS) : Early suspicion of TB-symptoms of any duration among PLHIV; use of an expanded clinical algorithm for TB screening that relies on presence of four clinical symptoms (current cough, weight loss, fever or night sweats) instead of only cough, to identify patients with presumptive TB; strengthen intensified case finding at ART, Link ART centre and targeted intervention projects for high risk group specially injection drug users; female sex workers and men having sex with men etc. and offering upfront CBNAAT among presumptive TB cases among PLHIV.
   b. Early detection and care of HIV infected drug-resistant TB patients by strengthening HIV testing in presumptive DR-TB cases; ensure access to culture and drug susceptibility test for HIV infected TB patients, prompt linkage of HIV infected DR-TB cases to ART centres, and prompt initiation of ART in HIV infected DR-TB cases.
   c. Strengthen HIV/TB activities among children and pregnant women.

In most people in the early stages of HIV infection, symptoms of tuberculosis are similar as in people without HIV infection. In areas where many people have HIV infection, tuberculosis programmes should continue to focus on identifying infectious sputum–smear–positive cases through microscopy. However, diagnosis of tuberculosis in individual patients using the standard diagnostic tools can be more difficult if they have advanced HIV infection because :

(a) HIV positive people with pulmonary tuberculosis may have a higher frequency of negative sputum smears. Confirming the diagnosis may require sputum culture.

(b) The tuberculin skin test often fails to work in people who are HIV positive because it relies on measuring the response of a person's immune system. If the immune system has been damaged by HIV, it may not respond even though the person is infected with tuberculosis. HIV positive people with tuberculosis, therefore, have a higher frequency of false negative tuberculin skin test results.

(c) Chest radiography may be less useful in people with HIV because they have less cavitation. Cavities usually develop because the immune response to the tubercular bacilli leads to some destruction of lung tissue. In people with HIV, who do not have a fully functioning immune system, there is less tissue destruction and hence less lung cavitation.

(d) Cases of extra-pulmonary tuberculosis seem to be more common in people who are co–infected.

In short-screen for tuberculosis using sputum smear microscopy, if the result is positive, start treatment; if the result is negative, but it is suspected that the patient has tuberculosis, sputum culture should be carried out where feasible to confirm the diagnosis and give treatment to those with positive culture results.

Treatment for HIV infected TB patients

Based on the clinical history and investigation reports ART medical officer will categorize patients as rifampicin sensitive/rifampicin sensitivity status not known/clinically diagnosed TB case, prior history of taking anti-TB drugs (Cat I/Cat II), and initiate daily anti TB treatment in Fixed Dosage

Combination as per NTEP guidelines at ART centre itself. The treatment of HIV positive individual with MDR-TB is same as for HIV negative patients. However, treament is more difficult and adverse events more common, hence rigorous monitoring in this particular group of patients is required in order to ensure adherence to treatment, early detection and treatment of adverse events reduce "lost to follow-up" *(34)*.

ART must be offered to all patients with HIV and TB and HIV and MDR-TB, irrespective of CD_4 cell count. Start anti-tuberculosis treatment first and then start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months). In the absence of ART, TB treatment alone does not significantly increase the CD_4 cell count, nor does it significantly decrease the HIV viral load. The use of Highly Active Anti-Retroviral Therapy (HAART) in patients with TB can lead to a sustained reduction in the HIV viral load. It can also facilitate immunological reconstitution, and decrease AIDS – defining illness and mortality. This benefit is seen across different range of CD_4 counts.

In addition to TB treatment, all HIV-infected TB patients must be provided access to care and support for HIV disease, including co-trimoxazole preventive therapy to reduce mortality among PLHIV by preventing opportunistic infections.

Immune reconstitution inflammatory syndrome (IRIS) :

Occasionally, patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs of radiographic manifestations of TB after beginning TB treatment. This paradoxical reaction occurs in HIV-infected patients with active TB and is thought to be a result of immune restitution due to the simultaneous administration of antiretroviral and tuberculosis medication. Symptoms and signs may include high fever, lymphadenopathy, expanding intra-thoracic lesions and worsening of chest radiographic findings. The diagnosis of paradoxical reaction should be made only after a thorough evaluation has excluded other aetiologies, particularly TB treatment failure. For severe paradoxical reactions prednisone (1–2 mg/kg for 1–2 weeks, then gradually decreasing doses) may be used *(34)*.

Isoniazid preventive therapy for PLHIVs

Isoniazid preventive therapy (IPT) is one of the 3–I's globally recommended for prevention of incident TB among HIV infected individuals. It is the most effective bactericidal, anti TB drug available currently. While it protects against progression of latent TB infection to active disease i.e reactivation, it also prevents TB reinfection in persons who are exposed to open TB cases.

All children living with HIV who have completed treatment for TB successfully should receive INH for an additional six months. These children who do not have poor weight gain, fever or cough currently, are unlikely to have active TB. Those who have above symptoms may have TB and should be evaluated for TB and other conditions. If evaluation shows no TB, such children should be offered IPT regardless of their age. Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care services.

Providing IPT to people living with HIV does not increase risk of developing INH resistant TB later. Therefore, concern regarding development on INH resistance should not be a barrier to providing IPT *(34)*.

For details regarding HIV and TB co-activities please refer to chapter 7 also.

TUBERCULOSIS AND DIABETES

Diabetes has been shown to be an independent risk factor for tuberculosis in community based study from south India and multiple studies globally. It is suggested that diabetes accounts for 20 per cent of all tuberculosis and 10 per cent of smear positive TB *(34)*. People with weak immune system as in diabetes are at higher risk of progressing from latent to active tuberculosis. The risk is 2–3 times higher than people without diabetes. A large proportion of people with diabetes and TB are diagnosed very late.

It is suggested that all people with TB should be screened for diabetes and screening for TB in diabetes should be considered, particularly in setting with high TB prevalence. People with diabetes and TB have a high risk of death during TB treatment and of TB relapse after treatment. As diabetes is complicated by presence of other infectious diseases also, it is important to take proper care of diabetes in patients suffering from diabetes/TB *(75)*.

National framework for joint TB-diabetes collaborative activities are as follows *(34)* :

a. Activities to improve diagnosis and management of diabetes among TB patients :
   - screening of all registered TB patients for diabetes mellitus.
   - ensuring diabetes mellitus management among TB patients.

b. Activities to improve diagnosis and management of TB among diabetic patients :
   - Intensified detection of active TB disease among diabetic patients.
   - Ensuring TB infection control measures in health care settings where diabetes mellitus is managed.
   - Ensuring TB treatment and management in comorbid patients.

c. Joint monitoring and evaluation.

d. TB patients diagnosed with diabetes should receive the same duration of TB treatment with daily regimen as non-diabetic patients.

TB AND TOBACCO *(34)*

Tobacco smoke contains toxic chemicals which cause disturbances in the bronchial surface of the lung. It also weakens the immunity of the patient to fight with TB bacteria. The following evidence emerges from several studies conducted to look at the association of TB and tobacco in India :

- Almost 38% of TB deaths are associated with the use of tobacco.

- Prevalence of TB is 3 times as high among ever-smokers as compared to that of among never-smokers.
- Mortality from TB is 3 to 4 times as high among ever-smokers as compared to that among never-smokers.
- Smoking contributes to half the male deaths in 25–69 age groups from TB in India.

Exposure to tobacco smoke has also been found to affect TB in the following ways :

- Increase the risk of tuberculous infection and the risk of developing TB.
- Affect clinical manifestations and increase risk of relapse among TB patients.
- Affect microbiological conversion (sputum smear or culture) and outcome of treatment in TB patients.
- Increase tuberculosis mortality and drug resistance to anti-tubercular drugs.

When a patient gets registered as a TB case, the status of tobacco use is recorded in the TB treatment card. He/she is advised to quit tobacco use with 5 R's : Relevance of quitting; Risk of continuing; Reward of quitting; Roadblock to quitting; and Repeat at each visit.

THE END TB STRATEGY

Measured by the number of people who die each year due to tuberculosis, it is the deadliest infectious disease. It claims 3 lives every minute. Of the 9 million people who become ill with TB each year, more than 3 million are not diagnosed, treated or officially registered by national TB programmes. Collectively, these "missed" millions are a global public health failure. This is especially the case considering that TB is airborne and that each undiagnosed and untreated person can infect as many as 15 individuals per year. Moreover, TB continues to be leading cause of death among people living with HIV. Likewise drug resistant TB poses a grave challenge.

Many of history's greatest successes in the fight against preventable diseases have been characterized by momentous shift in peoples belief of what is possible. A paradigm shift is needed now – a change in the way we fight TB at every level, in every community, in every health facility, in every country *(76)*. The global resolve for intensifying the fight against TB and achieving an end to the global epidemic is illustrated by adoption of WHO's End TB Strategy by World Health Assembly and the inclusion of "ending the TB epidemic" as a target within the health related Sustainable Development Goal 3 by the United Nations General Assembly in September 2015.

Evolution of End TB Strategy *(77)*

The End TB Strategy, developed in the context of the UN Sustainable Development Goals, is a logical evolution and a paradigm shift from past global TB strategies. The DOTS strategy of 1994 helped revitalize national tuberculosis programmes and equivalent entities by putting in place the essential basics to address the TB epidemic. The stop TB strategy of 2006 broadened the response by addressing the emerging challenges of HIV associated TB and MDR-TB. It aimed to improve access to quality TB care by engaging all public and private care providers, civil society organizations and communities. The stop TB strategy also encouraged investment in research for better tools and approaches. The End TB Strategy encompasses a package of interventions that can be fully adopted at country level. It has ten components organized under 3 pillars and four underlying principles. Fig. 7 summarizes the evolution of WHO global TB strategies.

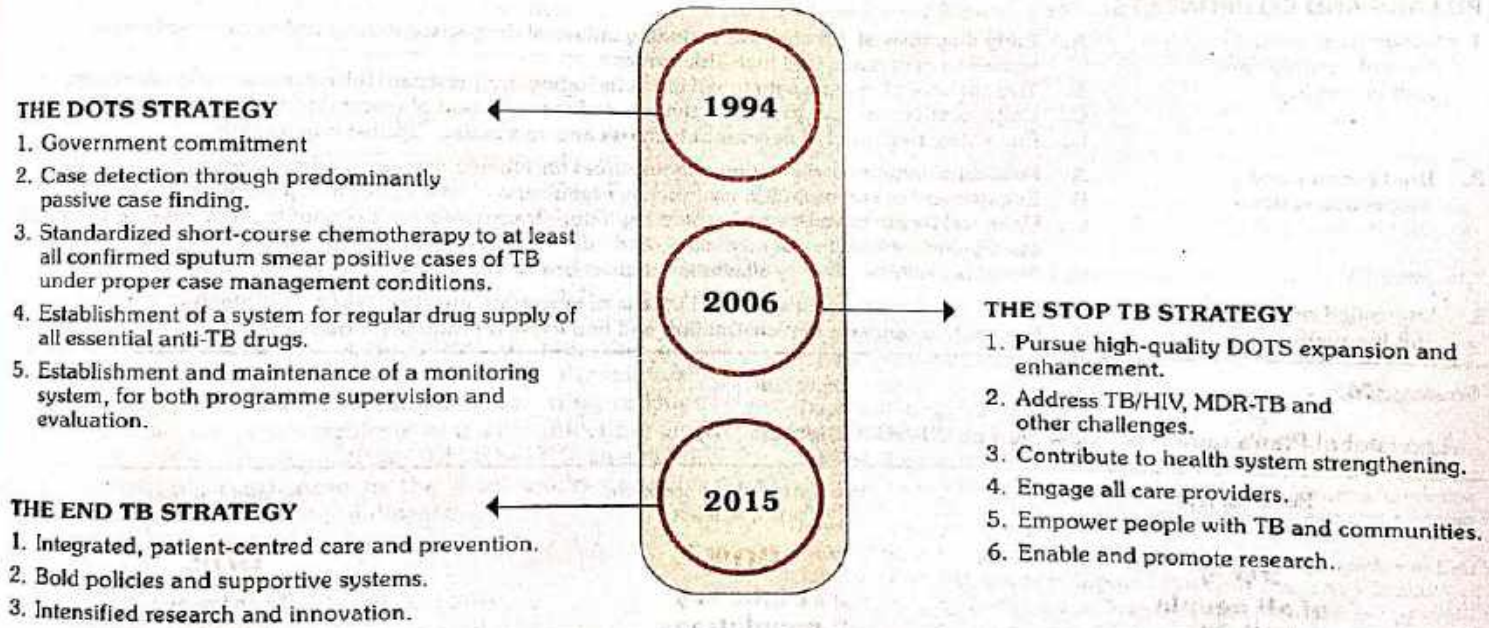


FIG. 7
Evolution of WHO Global TB Strategies.

Source : *(77)*

Through the implementation of the DOTS strategy (1994–2005) and the Stop TB Strategy (2006–2015), countries – especially those with a high burden of TB – established the basics required for providing high-quality TB diagnosis and treatment. These efforts contributed greatly to meeting the TB-related target of the Millennium Development Goals (MDGs) of halting and beginning to reverse the TB epidemic. Between year 2000 and 2014, improvements in quality-assured diagnosis and treatment of TB contributed to saving 43 million lives worldwide. It was apparent, however, that while enhancing access to diagnosis and treatment remarkably improved outcomes in terms of reducing suffering and death, it had very little effect on achieving the desired impact in terms of declining the incidence rates and driving down the TB epidemic. This is not entirely surprising: TB is not only a biomedical and a public health problem but also a disease associated with poverty; TB will continue thriving as long as poverty persists. The End TB strategy, whose aim is to end the TB epidemic, therefore combines a holistic mix of health and social interventions.

The strategy envisions universal access to high-quality TB care and goes beyond it to promote TB prevention. Ending the TB epidemic will also require new tools – a point-of-care test for diagnosing infection and disease; shorter and better regimens to treat disease and infection; and ideally, a pre and post-exposure vaccine.

The End TB Strategy identifies four barriers to achieving progress in the fight against TB. They are : (1) weak health system; (2) underlying determinants of TB such as poverty, undernutrition, migration and ageing population and risk factors such as diabetes, silicosis and smoking; (3) lack of effective tools; and (4) continuous unmet-funding needs.

The strategy is summarized as below :

END TB STRATEGY

VISION A world free of tuberculosis–zero deaths; disease and suffering due to tuberculosis.

GOAL End the global tuberculosis epidemic.

INDICATORS	**MILESTONES**		**TARGETS**	
	2020	2025	SDG 2030	End TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	zero	zero	zero	zero

PRINCIPLES

1. Government stewardship and accountability, with monitoring and evaluation.
2. Strong coalition with civil society organizations and communities.
3. Protection and promotion of human rights, ethics and equity.
4. Adaptation of the strategy and targets at country level, with global collaboration.

PILLARS AND COMPONENTS

1. Integrated, patient-centred care and prevention
   - A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups.
   - B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support.
   - C. Collaborative tuberculosis/HIV activities, and management of co-morbidities.
   - D. Preventive treatment of persons at high risk and vaccination against tuberculosis.
2. Bold policies and supportive systems
   - A. Political commitment with adequate resources for tuberculosis care and prevention.
   - B. Engagement of communities, civil society organizations, and public and private care providers.
   - C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control.
   - D. Social protection, poverty alleviation and actions on other determinants of tuberculosis.
3. Intensified research and innovation
   - A. Discovery, development and rapid uptake of new tools, interventions and strategies.
   - B. Research to optimize implementation and impact, and promote innovations.

Source : *(76)*

The Global Plan's targets are designed as 90–90–90 targets *(76)*.

Reach at least	As a part of this approach, reach at least	Achieve at least
90% **of all people with TB**	**90%** **of the key populations**	**90%** **Treatment success**
and place all of them on appropriate therapy– first-line, second-line and preventive therapy as required	the most vulnerable, underserved, at-risk populations	for all people diagnosed with TB through affordable treatment services, adherence to complete and correct treatment, and social support.

Key Population Groups (76)

The Global Plan defines "Key populations" as people who are vulnerable, underserved or at-risk of TB infection and illness. For purpose of the global plan, three key population groups are further expanded as shown below, along with examples of population within these groups. It is important to note that people who are likely to fall into one of these categories are also likely to be part of one or both of the other groups.

Key Populations for TB (76)

People who **have increased exposure** to TB due to where they live or work	Prisoners, sex workers, miners, hospital visitors, health care workers and community health workers. PEOPLE WHO : • live in urban slums • live in poorly ventilated or dusty conditions • are contacts of TB patients, including children • work in environments that are overcrowded • work in hospitals or are health care professionals.
People who **have limited access to quality TB Services**	Migrant workers, women in settings with gender disparity, children, refugees or internally displaced people, illegal miners, and undocumented migrants PEOPLE WHO : • are from tribal populations or indigenous groups • are homeless • live in hard-to-reach areas • live in homes for the elderly • have mental or physical disabilities • face legal barriers to access care • are lesbian, gay, bisexual or transgender.
People at **increased risk** of TB because of biological or behavioural factors that compromise immune function	PEOPLE WHO : • live with HIV • have diabetes or silicosis • undergo immunosuppressive therapy • are undernourished • use tobacco • suffer from alcohol-use disorders • inject drugs.

UN General Assembly Political Declaration

Please refer to page 208 for details.

Despite effective case-finding and therapeutic tools and declines in mortality and morbidity rates in some countries, tuberculosis appears to continue as an important communicable disease problem, worldwide, for several decades to come. The chronic nature of the disease, the ability of the tubercle bacilli to remain alive in the human body for years, the concentration of the disease in the older age-groups, the increased expectation of life, the high prevalence of infection rates in some countries, the relatively high reactivation rate, the emergence of drug-resistant strains, association of tuberculosis and HIV infection, and above all, the perpetuation of the "non-specific determinants" of the disease in the third world countries impede a rapid conquest of the disease.

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II. INTESTINAL INFECTIONS

POLIOMYELITIS

Poliomyelitis is an acute viral infection caused by an RNA virus. It is primarily an infection of the human alimentary tract but the virus may infect the central nervous system in a very small percentage (about 1 per cent) of cases resulting in varying degrees of paralysis, and possibly death.

Problem statement

In the pre-vaccination era, poliomyelitis was found in all countries of the world. The extensive use of polio vaccines since 1954 eliminated the disease in developed countries. In 1988, the World Health Assembly resolved to eradicate poliomyelitis globally. Since then, implementation of the eradication strategies has reduced the number of polio endemic countries from more than 125 in 1988 to 2 in 2021. A total of 12 cases of wild poliovirus were reported globally in 2023. Afghanistan and Pakistan reported six cases each *(1)*. All the reported cases are of type1 wild poliovirus *(1, 2)*. India was certified as polio free since 27th March 2014.

Since the 1988 World Health Assembly resolution to eradicate poliomyelitis, transmission of all the 3 types of wild poliovirus (WPV) has been greatly reduced. WPV type 2 has not been detected since 1999 and was declared eradicated in September 2015. Given that WPV type 3 has not been detected since November 2012, WPV type 1 is likely to be the sole WPV remaining in circulation. This marked progress has been achieved through widespread use of trivalent oral polio vaccine (tOPV). The attenuated polioviruses in OPV can undergo genetic changes during replication, and in communities with low vaccination coverage, rarely, results in vaccine derived polioviruses (VDPV) that can cause paralytic polio indistinguishable from the disease caused by WPV (3). Eliminating the risk of polio caused by VDPVs requires stopping of all OPV use. Recognizing the epidemiological opportunity, a new Polio Eradication and Endgame Strategic Plan 2013–2018 was developed. The plan was to eradicate all types of polio disease simultaneously – both due to WPV and VDPV.

Polio Eradication and Endgame Strategic Plan

The Polio Eradication and Endgame Strategic Plan 2013–2018 represents a major milestone in polio eradication and describes specific steps to take to successfully achieve eradication. The plan has four objectives as summarized in Fig. 1.

Under this endgame plan to achieve and sustain a polio-free world, the use of oral polio vaccine (OPV) must eventually be stopped worldwide, starting with OPV that contains type 2 poliovirus (OPV type 2). At least one dose of inactivated polio vaccine (IPV) must be introduced as a risk mitigation measure. The steps involved are *(5)* :

1. By end 2015, introduce at least 1 dose of IPV into all routine immunization systems, at least 6 months before the switch from trivalent oral polio vaccine (tOPV) to bivalent oral polio vaccine (bOPV, containing types 1 and 3 poliovirus).

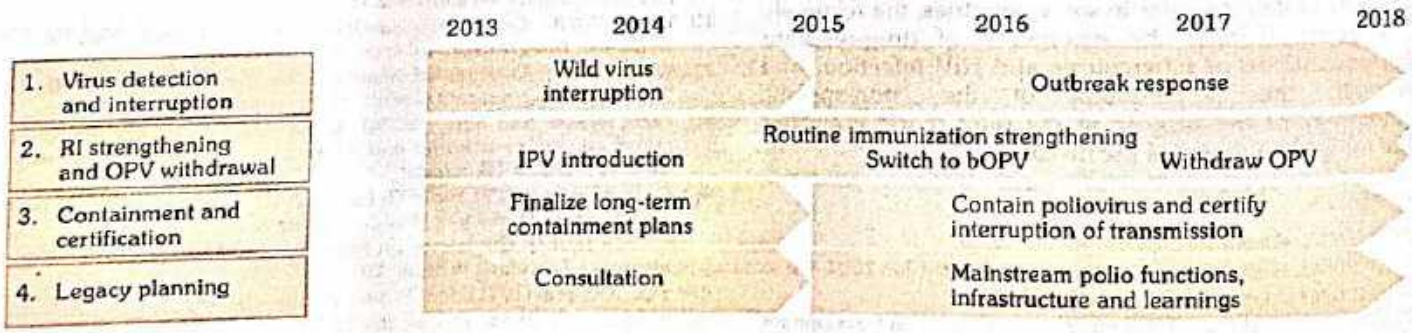

FIG. 1
The time–bound endgame objectives

Source : *(4)*

2. During 2016, switch from tOPV to bOPV, which does not contain type 2 virus, in routine immunization and polio campaigns, as before that bOPV was only licensed for use in SIAs.
3. Plan for the eventual withdrawal of all OPV.

The first stage of OPV withdrawal involved a global synchronized cessation of tOPV use between 18th April and 1st May 2016, replacing tOPV with bOPV containing only type 1 and 3 poliovirus and withdrawing OPV type 2 from all immunization activities called **"the Switch"**. Once switch is made, tOPV will no longer be used anywhere in the world and manufacturers will no longer supply tOPV *(3, 6)*.

The tOPV to bOPV switch is necessary because no WPV type 2 has been recorded since 1999. The risk of vaccine associated paralytic poliomyelitis and cVDPV to type 2 component of OPV now out weighs its benefits. Replacing the tOPV with bOPV is key to ensuring the eradication of type 2 poliovirus. The switch will serve as a dry run for withdrawal of other type of OPV. It needed IPV to be introduced on an accelerated timeline i.e. by end of 2015, so that OPV2 can be withdrawn. Introducing atleast one dose of IPV will ensure that a substantial proportion of the population is protected against type 2 serotype. It will also boost immunity to the remaining type 1 and 3 serotypes. It will mitigate paralysis risks in case of outbreak by priming the population against type 2 poliovirus and ensure better immune response to OPV if needed. IPV introduction sets the stage for ending OPV use entirely in 2019–2020 *(5)*.

In the endgame, polio eradication activities and strengthening routine immunization can be mutually beneficial as : (1) IPV will be introduced through routine immunization delivery systems; (2) Strengthening routine immunization is necessary to achieve and maintain high population immunity against polioviruses, especially type 2, after OPV type 2 is withdrawn. The magnitude, number and length of both wild poliovirus (WPV) and cVDPV outbreaks are closely correlated with weaknesses in routine immunization systems; (3) This is an opportunity for the global polio eradication initiative to use its infrastructure to contribute more systematically to strengthening routine immunization systems; and (4) One of the goals is to improve infant routine immunization coverage in a group of focus countries which have some of the lowest routine immunization coverage levels in the world and the greatest proportion of the world's unvaccinated children. The third dose of DPT-containing vaccine will be used to measure routine immunization coverage improvements.

It is recommended that the dose of IPV be added at 14 weeks when the 3rd dose of DPT or pentavalent vaccine is given or at the contact soon thereafter *(5)*.

Containment : The eradication of WPV2 means it does not circulate in human population any longer and it is not detectable in environment sample either. However, the virus is still present in a number of facilities including research laboratories and vaccine producing sites. The identification and destruction of any unneeded type 2 poliovirus or appropriate containment of needed type 2 poliovirus is now critical to sustain polio eradication efforts and to prevent accidental or malicious release of these viruses from facility and their subsequent transmission to people. Within two weeks of national switch date, the Ministry of Health of all countries were to submit a report confirming the withdrawal of tOPV *(7)*.

The Polio Eradication Strategy 2022–2026

Over the last decade, the Global Polio Eradication Initiative made steady progress for the eradication of polio, to achieve a polio-free world. The Polio Eradication Strategy 2022–2026 offers a comprehensive set of actions to permanently interrupt all poliovirus transmission in the final wild polio virus endemic countries of Afghanistan and Pakistan, and to stop circulating vaccine-derived poliovirus transmission and prevent outbreaks in non-endemic countries *(2)*.

Fractional dose IPV

As an alternative to the full dose intramuscular injection of IPV, countries may consider using fractional dose of IPV (FIPV) via intradermal route. Studies have demonstrated that 2 FIPV doses intradermally at 6th and 14th weeks provide higher seroconversion rates than a single full dose of IPV given intramuscularly at 14 weeks. Table 1 shows comparison between IPV full dose and FIPV.

TABLE 1
Comparing IPV and FIPV

	IPV	Fractional IPV (fIPV)
Volume per dose	0.5 mL	0.1 mL
Schedule	1 dose : 14 weeks	2 doses : 6 and 14 weeks
Administration	Intramuscular (IM) injection	Intradermal (ID) injection
Site of administration	Thigh	Upper arm
Syringe	0.5 mL AD syringe	0.1 mL AD syringe
Are two fractional doses as effective as a single standard dose ?	Two fractional doses of IPV (ID) given at 6 and 14 weeks produces better immunogenicity than a single standard dose (IM) given at 14 weeks	

Source : *(8)*

In response to an isolation of VDPV2 from a sewage sample taken in Telangana state, India conducted a massive compaign in June 2016, using an intradermal fractional dose (0.1 ml) of IPV over a period of 6 days. The campaign vaccinated 311,064 children aged from 6 weeks to 3 years, reaching an estimated coverage of 94 per cent. The campaign was implemented using fixed site approach. The success of the campaign indicates that with appropriate preparation, an emergency response using FIPV can be implemented promptly and effectively *(9)*. In April 2016, India introduced FIPV into routine immunization programme in 8 states. In August 2016, the use of FIVP was expanded to another 8 states *(8)*. Presently it covers the whole country.

Polio Surveillance *(10)*

Surveillance is the most important part of the whole polio eradication initiative. Without surveillance, it would be impossible to pinpoint where and how wild poliovirus is still circulating, or to verify that the virus has been eradicated. Surveillance identifies new cases and detects importation of wild poliovirus.

Acute flaccid paralysis surveillance

There are four steps of acute flaccid paralysis (AFP) surveillance:

1. *Finding and reporting children with acute flaccid paralysis (AFP) :* The first links in the surveillance chain are staff in all health facilities – from district health centres to large hospitals. They must promptly report every case of acute flaccid paralysis (AFP) in any child under 15 years of

age. In addition, public health staff make regular visits to hospitals and rehabilitation centres to search for AFP cases which may have been overlooked or misdiagnosed. The number of AFP cases reported each year is used as an indicator of a country's ability to detect polio – even in countries where the disease no longer occurs. A country's surveillance system needs to be sensitive enough to detect at least one case of AFP for every 100,000 children under 15 years, even in the absence of polio.

2. *Transporting stool samples for analysis :* In the early stages, polio may be difficult to differentiate from other forms of acute flaccid paralysis, such as Guillain-Barre Syndrome, transverse myelitis, or traumatic neuritis. All children with acute flaccid paralysis (AFP) should be reported and tested for wild poliovirus within 48 hours of onset, even if doctors are confident on clinical grounds that the child does not have polio. To test for polio, faecal specimens are analyzed for the presence of poliovirus. Because shedding of the virus is variable, two specimens – taken 24–48 hours apart are required. Speed is essential, since the highest concentrations of poliovirus in the stools of infected individuals are found during the first two weeks after onset of paralysis.

Stool specimens have to be sealed in containers and stored immediately inside a refrigerator or packed between frozen ice packs at 4–8°C in a cold box, ready for shipment to a laboratory. Undue delays or prolonged exposure to heat on the way to the laboratory may destroy the virus. Specimens should arrive at the laboratory within 72 hours of collection.

3. *Isolating poliovirus :* In a laboratory, virologists begin the task of isolating poliovirus from the stool samples. If poliovirus is isolated, the next step is to distinguish between wild (naturally occurring) and vaccine-related poliovirus. This is necessary because the oral vaccine consists of attenuated live polioviruses and resembles wild virus in the laboratory. If wild poliovirus is isolated, the virologists identify which of the two surviving types of wild virus is involved. Wild poliovirus type 2 has not been recorded since 1999.

4. *Mapping the virus :* Once wild poliovirus has been identified, further tests are carried out to determine where the strain may have originated. By determining the exact genetic make-up of the virus, wild viruses can be compared to others and classified into genetic families which cluster in defined geographical areas. The newly-found poliovirus sequence is checked against a reference bank of known polioviruses, allowing inferences about the geographical origin of the newly found virus. When polio has been pinpointed to a precise geographical area, it is possible to identify the source of importation of poliovirus – both long-range and cross-border. Appropriate immunization strategies can then be determined to prevent further spread of the poliovirus.

Environmental surveillance

Environmental surveillance involves testing sewage or other environmental samples for the presence of poliovirus. Environmental surveillance often confirms wild poliovirus infections in the absence of cases of paralysis. Systematic environmental sampling (e.g. in Egypt and Mumbai, India) provides important supplementary surveillance data. Ad-hoc environmental surveillance elsewhere (especially in polio-free regions) provides insights into the international spread of poliovirus.

Surveillance Indicators (10)

Indicator	Minimum levels for certification standard surveillance
Completeness of reporting	At least 80% of expected routine (weekly or monthly) AFP surveillance reports should be received on time, including zero reports where no AFP cases are seen. The distribution of reporting sites should be representative of the geography and demography of the country.
Sensitivity of surveillance	At least one case of non-polio AFP should be detected annually per 100,000 population aged less than 15 years. In endemic regions, to ensure even higher sensitivity, this rate should be two per 100,000.
Completeness of case investigation	All AFP cases should have a full clinical and virological investigation with at least 80% of AFP cases having 'adequate' stool specimens collected. 'Adequate' stool specimens are two stool specimens of sufficient quantity for laboratory analysis, collected at least 24 hours apart, within 14 days after the onset of paralysis, and arriving in the laboratory by reverse cold chain and with proper documentation.
Completeness of follow-up	At least 80% of AFP cases should have a follow-up examination for residual paralysis at 60 days after the onset of paralysis.
Laboratory performance	All AFP case specimens must be processed in a WHO accredited laboratory within the Global Polio Laboratory Network (GPLN).

VACCINE DERIVED POLIOVIRUS (VDPV) (11)

Although OPV is a safe vaccine, on rare occasions adverse events may occur. Vaccine-associated paralytic poliomyelitis (VAPP) is the most important of these rare adverse events. Cases of VAPP are clinically indistinguishable from poliomyelitis caused by WPV, but can be distinguished by laboratory analysis. The incidence of VAPP has been estimated at 4 cases/1000,000 birth cohort per year in countries using OPV. VAPP occurs in both OPV recipients and their unimmunized contacts; it is most frequently associated with Sabin 3 (60% of cases), followed by Sabin 2 and Sabin 1.

VDPVs resemble WPVs biologically and differ from the majority of vaccine-related poliovirus (VRPV) isolates in that they have genetic properties consistent with prolonged replication or transmission, which is substantially longer than the normal period of vaccine virus replication of 4–6 weeks in the OPV recipient *(12)*. All poliovirus isolates are characterized by Global Polio Laboratory Network. The diagnosis is made by real-time reverse transcription-polymerase chain reaction (rRT-PCR) nucleic acid amplification targetted to nucleotide substitution that occur early in VDPV emergence.

VDPVs are divided into three categories as (1) cVDPVs, when evidence of person-to-person transmission in the

community exists; (2) immunodeficiency-associated VDPVs (iVDPVs), which are isolates from persons with primary immunodeficiencies, who have prolonged VDPV infections; and (3) ambiguous VDPVs (aVDPVs), which are either clinical isolates from person with no known immunodeficiency or sewage isolates whose source is unknown *(12)*.

The prolonged large outbreak of $cVDPV_2$ in Nigeria and D.R. of Congo, the increased detection of iVDPV infection in developing countries and continued detection of aVDPVs that resemble cVDPV and iVDPV reaffirm the following points *(12)*:

1. The clinical signs and severity of paralysis associated with VDPV and WPV infections are indistinguishable.
2. cVDPVs pose the same public health threat as WPVs and require the same control measures.
3. Surveillance for WPVs and VDPVs should continue to be strengthened.
4. Environmental surveillance to detect VDPVs and WPV infection can serve as an important, sensitive supplement to AFP surveillance in many settings.
5. Persons with prolonged iVDPV infection may transmit poliovirus to others, raising the risk of VDPV circulation in settings of low population immunity to the corresponding poliovirus serotype.
6. Prolonged iVDPV excretion is uncommon among persons with primary immunodeficiencies exposed to OPV.
7. The prevalence of long-term iVDPV excretors may be higher than suggested.

Because of these risks of emergence of vaccine-derived polioviruses, OPV use will be discontinued worldwide once all WPV transmission has been interrupted (i.e. inactivated polio vaccine (IPV) will replace OPV) and strategies to strengthen global polio immunization and surveillance are needed to limit the emergence of VDPVs.

Epidemiological determinants

Agent factors

(a) AGENT : The causative agent is the poliovirus which has three serotypes 1,2 and 3. Most outbreaks of paralytic polio are due to type–1 virus. Poliovirus can survive for long periods in the external environment. In a cold environment, it can live in water for 4 months and in faeces for 6 months *(13)*. It is, therefore, well-adapted for the faecal–oral route of transmission *(14)*. However, the virus may be rapidly inactivated by pasteurization, and a variety of physical and chemical agents. (b) RESERVOIR OF INFECTION : Man is the only known reservoir of infection. Most infections are subclinical. It is the mild and subclinical infections that play a dominant role in the spread of infection; they constitute the submerged portion of the iceberg. It is estimated that for every clinical case, there may be 1000 subclinical cases in children and 75 in adults *(15)*. There are no chronic carriers. No animal source has yet been demonstrated. (c) INFECTIOUS MATERIAL : The virus is found in the faeces and oropharyngeal secretions of an infected person. (d) PERIOD OF COMMUNICABILITY : The cases are most infectious 7 to 10 days before and after onset of symptoms. In the faeces, the virus is excreted commonly for 2 to 3 weeks, sometimes as long as 3 to 4 months.

Host factors

(a) AGE : The disease occurs in all age groups, but children are usually more susceptible than adults because of the acquired immunity of the adult population. In developed countries, before the advent of vaccination, the age distribution shifted so that most patients were over the age of 5 years, and 25 per cent were over age 15 years *(16)*. In India, polio is essentially a disease of infancy and childhood. About 50 per cent of cases are reported in infancy. The most vulnerable age is between 6 months and 3 years. (b) SEX : Sex differences have been noted in the ratio of 3 males to one female. (c) RISK FACTORS : Several provocative or risk factors have been found to precipitate an attack of paralytic polio in individuals already infected with polio viruses. They include fatigue, trauma, intramuscular injections, operative procedures such as tonsillectomy undertaken especially during epidemics of polio and administration of immunizing agents particularly alum-containing DPT. (d) IMMUNITY : The maternal antibodies gradually disappear during the first 6 months of life. Immunity following infection is fairly solid although reinfection can occur since infection with one type does not protect completely against the other two types of viruses. Type–2 virus appears to be the most effective antigen. Neutralizing antibody is widely recognized as an important index of immunity to polio after infection *(17)*.

Environmental factors

Polio is more likely to occur during the rainy season. Approximately 60 per cent of cases recorded in India were during June to September *(18)*. The environmental sources of infection are contaminated water, food and flies. Polio virus survives for a long time in a cold environment. Overcrowding and poor sanitation provide opportunities for exposure to infection.

Mode of transmission

(a) FAECAL–ORAL ROUTE : This is the main route of spread in developing countries. The infection may spread *directly* through contaminated fingers where hygiene is poor, or *indirectly* through contaminated water, milk, foods, flies and articles of daily use. (b) DROPLET INFECTION : This may occur in the acute phase of disease when the virus occurs in the throat. Close personal contact with an infected person facilitates droplet spread. This mode of transmission may be relatively more important in developed countries where faecal transmission is remote.

Incubation period

Usually 7 to 14 days (range 3 to 35 days).

Clinical spectrum

When an individual susceptible to polio is exposed to infection, one of the following responses may occur (Fig. 2) (a) INAPPARENT (SUBCLINICAL) INFECTION : This occurs approximately in 91–96 per cent of poliovirus infections *(19)*. There are no presenting symptoms. Recognition only by virus isolation or rising antibody titres. (b) ABORTIVE POLIO OR MINOR ILLNESS : Occurs in approximately 4 to 8 per cent of the infections *(20)*. It causes only a mild or self–limiting illness due to viraemia. The patient recovers quickly. The diagnosis cannot be made clinically. Recognition only by virus isolation or rising antibody titre. (c) NON-PARALYTIC POLIO : Occurs in approximately 1 per cent of all infections *(21)*. The presenting features are stiffness and pain in the neck and

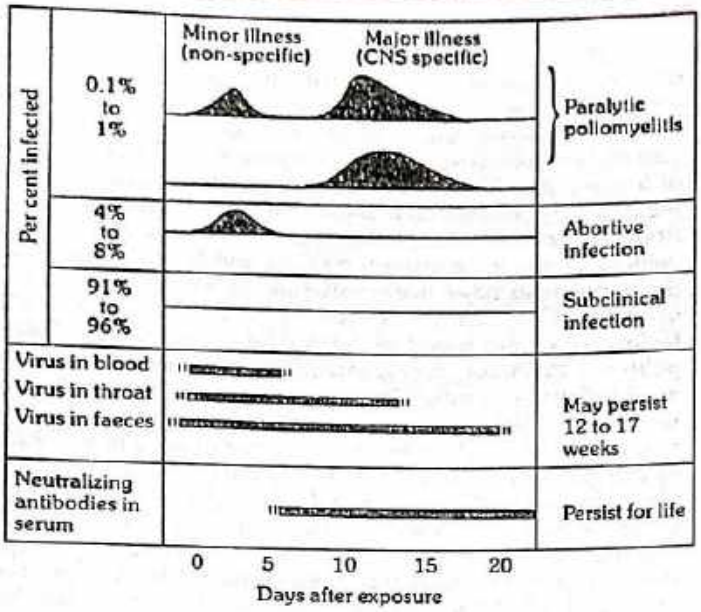

FIG. 2
Time course of events in infection with poliovirus.
Source : *(23)*

back. The disease lasts 2 to 10 days. Recovery is rapid. The disease is synonymous with aseptic meningitis. (d) PARALYTIC POLIO : Occurs in less than one per cent of infections. The virus invades CNS and causes varying degrees of paralysis. The predominant sign is asymmetrical flaccid paralysis. A history of fever at the time of onset of paralysis is suggestive of polio. The other associated symptoms are malaise, anorexia, nausea, vomiting, headache, sore throat, constipation and abdominal pain. There might be signs of meningeal irritation, i.e., stiffness of neck and back muscles. Tripod sign may be present, i.e. the child finds difficulty in sitting and sits by supporting hands at the back and by partially flexing the hips and knees. Progression of the paralysis to reach its maximum in the majority of cases occurs in less than 4 days (may take 4–7 days). The paralysis is characterized as descending, i.e. starting at the hip and then moving down to the distal parts of the extremity. As it is asymmetrical patchy paralysis, muscle strength varies in different muscle groups of different limbs. However, proximal muscle groups are more involved as compared to distal ones. Deep tendon reflexes (DTRs) are diminished before the onset of paralysis. There is no sensory loss. Cranial nerve involvement is seen in bulbar and bulbospinal forms of paralytic poliomyelitis. There might be facial asymmetry, difficulty in swallowing, weakness or loss of voice. Respiratory insufficiency can be life–threatening and is usually the cause of death. After the acute phase, atrophy of the affected muscles lead to a life with residual paralysis which is typical and relatively easy to identify as poliomyelitis *(22)*.

Progressive paralysis, coma or convulsions usually indicate a cause other than polio, as does a very high case fatality rate *(21)*.

There is no specific treatment for polio. Good nursing care from the beginning of illness can minimize or even prevent crippling. Physiotherapy is of vital importance. It can be initiated in the affected limb immediately. It helps the weakened muscles to regain strength. Very probably, the child may have to put on metal callipers.

PREVENTION

Immunization is the sole effective means of preventing poliomyelitis. Both killed and live attenuated vaccines are available and both are safe and effective when used correctly. It is essential to immunize all infants by 6 months of age to protect them against polio. Two types of vaccines are used throughout the world; they are :

1. Inactivated (Salk) polio vaccine (IPV).
2. Oral (Sabin) polio vaccine (OPV).

1. Inactivated (Salk) polio vaccine

The vaccine mixture is formulated to contain at least 40 units of type-1, 8 units of type-2 and 32 units of type-3 D-antigen (D-antigen, which is expressed only on intact poliovirus particles, is used to adjust the concentration of the individual viruses included in the trivalent IPV). All versions of IPV have higher antigenicity than the first-generation vaccines, and they are sometimes referred to as IPVs of enhanced potency. IPV may contain trace amounts of formaldehyde, streptomycin, neomycin or polymyxin B; some versions of IPV contain the preservative phenoxyethanol (0.5%), but neither thiomersal (incompatible with IPV antigenicity) nor adjuvants are used *(11)*.

IPV is administered by intramuscular injection or fractional dose by intradermal injection. The vaccine is stable at ambient temperature, but should be refrigerated to ensure no loss of potency. Freezing should be avoided as it could diminish potency. IPV is available either as a stand-alone product or in combination with ≥1 other vaccine antigens including diphtheria, tetanus, whole-cell or acellular pertussis, hepatitis B, or *Haemophilus influenzae* type b. In the combination vaccines, the alum or the pertussis vaccine, or both, have an adjuvant effect.

The primary or initial course of immunization consists of 4 inoculations. The first 3 doses are given at intervals of 1–2 months and 4th dose 6–12 months after the third dose. First dose is usually given when the infant is 6 weeks old. Additional doses are recommended prior to school entry and then every 5 years until the age of 18. Alternatively, one or two doses of live vaccine (OPV) can be given safely as boosters after an initial course of immunization with inactivated vaccine.

IPV induces, humoral antibodies (IgM, IgG and IgA serum antibodies) but does not induce intestinal or local immunity. The circulating antibodies protect the individual against paralytic polio, but do not prevent reinfection of the gut by wild viruses. For the individual, it gives protection from paralysis and nothing more; for the community, it offers nothing because the wild viruses can still multiply in the gut and be a source of infection to others. This is a major drawback of IPV. Further, in the case of an epidemic, IPV is unsuitable because : (i) immunity is not rapidly achieved, as more than one dose is required to induce immunity, and (ii) injections are to be avoided during epidemic times as they are likely to precipitate paralysis *(24)*. Therefore, IPV is not efficacious in combating epidemics of polio.

Advantages : Inactivated polio vaccine, because it does not contain living virus, is safe to administer (i) to persons with immune deficiency diseases (ii) to persons undergoing corticosteroid and radiation therapy (iii) to those over 50 years who are receiving vaccine for the first time, and (iv) during pregnancy.

Associated risks : No serious adverse reactions to IPV

vaccines currently in use have been reported except minor local erythema (0.5–1 per cent), induration (3–11 per cent) and tenderness (14–29 per cent).

2. Oral (Sabin) polio vaccine (OPV)

Oral polio vaccine (OPV) was described by Sabin in 1957. It contains live attenuated virus (types 1, 2 and 3) grown in primary monkey kidney or human diploid cell cultures. Ideally each virus type should be given separately as monovalent vaccine, but for administrative convenience, rather than efficacy, it is given as *bivalent* (bOPV) vaccine. The vaccine contains not less than $10^{6.0}$ $CCID_{50}$ of type 1 poliomyelitis virus Sabin strain and not less than $10^{5.8}$ $CCID_{50}$ of type 3 poliomyelitis virus Sabin strain.

National Immunization Schedule

The WHO Programme on Immunization (EPI) and the National Immunization Programme in India recommends a primary course of 3 doses of OPV at one–month intervals, commencing the first dose when infant is 6 weeks old (see page 135). It is recommended that a dose of OPV (zero-dose) is required to be given to all children delivered in health institutions before their discharge from the hospital. The vaccine should be given in maternity wards, the newborn should not be taken to regular immunization sessions to avoid infection. OPV is given concurrently with DPT or pentavalent vaccine. BCG can be given simultaneously with the first dose of OPV. It is very important to complete vaccination of all infants before 6 months of age. This is because most polio cases occur between the ages of 6 months and 3 years. One booster dose of OPV is recommended 12 to 18 months later.

Dose and mode of administration

The dose is 2 drops or as stated on the label. WHO recommends that vaccinators use dropper supplied with the vial of oral polio vaccine. This is the most direct and effective way to deliver the correct drop size. Tilt the child's back, and gently squeeze the cheeks or pinch the nose to make the mouth open. Let the drops fall from the dropper onto the child's tongue. Repeat the process if the child spits out the vaccine. If the vaccine is spoon–fed there is a chance that it will not all be licked up by the child *(25)*.

Development of immunity

On administration, the live vaccine strains infect intestinal epithelial cells. After replication, the virus is transported to the Peyer's patches where a secondary multiplication with subsequent viraemia occurs. The virus spreads to other areas of the body, resulting in the production of circulating antibodies which prevent dissemination of the virus to the nervous system and prevent paralytic polio. Intestinal infection stimulates the production of IgA secretory antibodies which prevent subsequent infection of the alimentary tract with wild strains of poliovirus, and thus is effective in limiting virus transmission in the community. Thus OPV induces both local and systemic immunity.

The vaccine progeny is excreted in the faeces and secondary spread occurs to household contacts and susceptible contacts in the community. Non-immunized persons may therefore, be immunized. Thus widespread "herd immunity" results, even if only approximately 66 per cent of the community is immunized *(14)*. This property of OPV has been exploited in controlling epidemics of polio by administering the vaccine simultaneously in a short period to all susceptibles in a community. This procedure virtually eliminates the wild polio strains in the community and replaces them by attenuated strains *(26)*. The duration of immunity produced by the OPV is not known, it may possibly even be lifelong *(27)*.

Advantages

The advantages of OPV are : (i) since given orally, it is easy to administer and does not require the use of highly trained personnel (ii) induces both humoral and intestinal immunity. (iii) antibody is quickly produced in a large proportion of vaccinees, even a single dose elicits (except in tropical countries) substantial immunity (iv) the vaccinee excretes the virus and so infects others who are also immunized thereby (v) useful in controlling epidemics, and (vi) relatively inexpensive.

Complications

OPV is remarkably free from complications. However, being living viruses, the vaccine viruses, particularly type 3 do mutate in the course of their multiplication in vaccinated children, and rare cases of vaccine–associated paralytic polio have occurred in (a) recipients of the vaccine, and (b) their contacts. For details please refer to page 242.

Contraindications

Diarrhoea should not be considered a contraindication to OPV. However, to ensure full protection, a dose of OPV given to a child with diarrhoea should not be counted as part of the series and the child should receive another dose at the first available opportunity. Live vaccines are not usually given to immunocompromised individuals *(23)*. Patients suffering from leukaemias and malignancy and those receiving corticosteroids may not be given OPV. IPV is an alternative to OPV for immunization of children with HIV infection *(23)*. There is as yet no indication that polio immunization may pose any danger to a pregnant mother or developing foetus. However, OPV should be delayed until after pregnancy unless immediate protection is required, when IPV is indicated *(14)*.

Storage

(a) Stabilized vaccine : Recent oral polio vaccines are heat stabilized by adding magnesium chloride. They can be kept without losing potency for a year at 4 deg. C, and for a month at 25 deg. C temperature *(16)*. *(b) Non-stabilized vaccine :* The vaccine should be stored at –20 deg C in a deep freeze until used. In case a deep freeze is not available, it might be stored temporarily in the freezing chamber of the refrigerator. During transport, the vaccine must be kept either on dry ice (solid carbon dioxide) or a freezing mixture (equal quantities of wet ice and ammonium chloride) *(28)*.

At the vaccination clinic, the bottle containing the OPV should not be frozen and thawed repeatedly, since repeated freezing and thawing has a deleterious effect on the potency of live polio vaccine. It would be preferable to keep the vials of the vaccine in ice during its administration to children *(28)*.

Studies indicate that breast-feeding does not impede the effectiveness of oral poliovirus vaccine *(29)*. Breast milk can be given whenever the child is hungry. However, hot water, hot milk or hot fluids should be withheld for about half an hour after the administration of the vaccine. The vaccine should be administered preferably in a cool room, rather than in a hot, humid and crowded room.

The problems with OPV may be summarized as follows (a) A primary problem is the instability of the vaccine at high ambient temperatures. The vaccine has to be kept frozen during storage, and kept cold during transportation, right up to the point of administration. (b) A second problem is the frequent vaccine failures even with fully potent vaccines. (c) A third problem is the very small residual neurovirulence in OPV.

Sequential administration of IPV and OPV

Over the past decade, a number of countries in central and eastern Europe, the Middle East, the Far East, and southern Africa have adopted sequential schedules of 1–2 doses of IPV followed by ≥ 2 doses of OPV. Combined schedules of IPV and OPV appear to reduce or prevent VAPP while maintaining the high levels of intestinal mucosal immunity conferred by OPV. In addition, such schedules economize on limited resources by reducing the number of doses of IPV, and may optimize both the humoral and mucosal immunogenicity of polio vaccination. The effectiveness of this approach in preventing polio caused by WPV as well as VAPP has been documented by 2 large studies *(11)*.

The difference between IPV and OPV are given in Table 2.

TABLE 2
Differences between IPV and OPV

	IPV (Salk type)	OPV (Sabin type)
1	Killed formolized virus	Live attenuated virus
2	Given subcutaneously or IM	Given orally
3	Induces circulating antibody, but no local (intestinal) immunity	Immunity is both humoral and intestinal. Induces antibody quickly
4	Prevents paralysis, but does not prevent reinfection by wild polio viruses	Prevents not only paralysis, but also intestinal reinfection
5	Not useful in controlling epidemics	Can be effectively used in controlling epidemics. Even a single dose elicits substantial immunity (except in tropical countries)
6	More difficult to manufacture	Easy to manufacture
7	The virus content is 10,000 times more than OPV. Hence costlier	Cheaper
8	Does not require stringent conditions during storage and transportation. Has a longer shelf-life	Requires to be stored and transported at sub-zero temperatures, unless stabilized

Human Normal Ig

The current widespread practice of immunization has virtually eliminated the need for passive immunization. Normal human Ig in a dose of 0.25–0.3 ml per kg of body weight has been found to be protective for a few weeks against paralytic disease but does not prevent sub-clinical infections. Immunoglobulin is effective only if given shortly before infection, it is of no value after clinical symptoms develop *(17)*. The subject shall be actively immunized against polio after a few weeks.

Epidemiological Investigations

The occurrence of a single case of polio is now considered as an epidemic, and should prompt an immediate epidemiological investigation, including an active search for other cases. Samples of faeces from all cases or suspected cases of polio should be collected and forwarded to the laboratory for virus isolation. In addition, where possible, paired sera should be collected, the first specimen at the clinical suspicion of paralytic polio and the second at the period of convalescence. A rising titre of poliovirus neutralizing antibody provides useful confirmatory evidence. The Indian Council of Medical Research has set up National Enterovirus Units at Mumbai, Coonoor, Chennai, Delhi and Kasauli where samples may be sent for examination.

The following check-list indicates the essential data to be collected when investigating an outbreak *(30, 31)*.

1. Name of the administrative area and locality
2. Date first case reported from locality
3. Period of field investigation
   From.....to.....(dates)
4. No.of paralytic polio cases detected
   - 4.1 Clinical diagnosis only
   - 4.2 Laboratory confirmed
   - 4.3 Type(s) of virus isolated
5. No. of deaths from paralytic polio
6. No.of paralytic cases of polio by age

–1 year	10–14 years
1–4 years	15–19 years
5–9 years	20+ years

7. No.of contacts of paralytic polio examined :
   Household contacts
   Other. (specify)
8. Brief description of field investigation
9. History of previous vaccination practice in the locality including the dates of the last community vaccination programme, and the type of vaccine used.
10. Name of the principal investigator and laboratory.

Within an epidemic area, OPV should be provided for all persons over 6 weeks of age who have not been completely immunized or whose immune status is unknown.

Under the International Health Regulations, polio is subject to international surveillance. The WHO should be notified as soon as possible of the occurrence of paralytic polio and to supplement reports on such outbreaks with additional epidemiological information such as the type of virus, and the number of cases and deaths reported. In addition a quarterly report (on prescribed form) should be sent to WHO, Geneva. The WHO has prepared guidelines to poliovirus isolation and serological techniques for polio surveillance.

Strategies for polio eradication in India

(a) Conduct Pulse Polio Immunization days every year until poliomyelitis is eradicated.

(b) Sustain high levels of routine immunization coverage.

(c) Monitor OPV coverage at district level and below.

(d) Improve surveillance capable of detecting all cases of AFP due to polio and non-polio aetiology.

(e) Ensure rapid case investigation, including the collection of stool samples for virus isolation.

(f) Arrange follow-up of all cases of AFP at 60 days to check for residual paralysis.

(g) Conduct outbreak control for cases confirmed or suspected to be poliomyelitis to stop transmission.

Even a single case is treated as an outbreak and preventive measures are initiated, usually within 48 hours of notification of the case. The complete and timely reporting of cases of poliomyelitis is an important element for the eradication of poliomyelitis. Reporting of all cases of acute flaccid paralysis in children under 15 years of age is mandatory, and line lists of all reported cases of poliomyelitis are maintained. Since 1992, the active surveillance has been extended to all cases of acute flaccid paralysis, including causes other than poliomyelitis.

Line listing of cases

Line listing of reported cases was started in the year 1989 to check for duplication (same case reported more than once if the child visited more than one health facility), year of onset of illness (to screen children with residual paralysis who developed poliomyelitis prior to the year of reporting), identification of high risk pockets (by analysis of residential status) and documentation of high-risk age groups.

Line listing of cases made it possible to take appropriate follow-up action in areas from where the cases had been reported. The line lists have also provided useful epidemiological data for programme purposes. For example, it provided information on the age at onset of illness and to understand the urgency for the early completion of the OPV immunization schedule.

All cases of acute flaccid paralysis must be reported immediately to the chief medical officer/district immunization officer with the following details :

- Name, age and sex of the patient
- Father's name and complete address
- Vaccination status
- Date of onset of paralysis and date of reporting
- Clinical diagnosis
- Doctor's name, address and phone number

Mopping Up

Mopping up activities are usually the last stage in polio eradication. The strategy of "mopping up" involves door-to-door immunization in high-risk districts, where wild polio virus is known or suspected to be still circulating. This strategy is being implemented in India.

Pulse Polio Immunization

In India NIDs have become the largest public health campaigns ever conducted in a single country. Government of India conducted the first round of PPI consisting of two immunization days 6 weeks apart on 9th December 1995 and 20th January 1996. The first PPI conducted targeted all children under 3 years of age irrespective of their immunization status. Later on, as recommended by WHO, it was decided to increase the age group from under 3 to under 5 years.

The term "pulse" has been used to describe this sudden, simultaneous, mass administration of OPV on a single day to all children 0–5 years of age, regardless to previous immunization. PPIs occur as two rounds about 4 to 6 weeks apart during low transmission season of polio, i.e. between November to February. In India, the peak transmission is from June to September. The dose of OPV during PPIs are **extra** doses which supplement, and **do not** replace the doses received during routine immunization services. The children including 0–1 year old infants should receive all their scheduled doses and PPI doses. There is no minimum interval between PPI and scheduled OPV doses *(32)*.

An important improvement in PPI during 1998 has been the use of vaccine vial monitor. Colour monitors or labels are put on vaccine bottles. Each label has a circle of deep blue colour. Inside it is a white square which changes colour and gradually becomes blue, if vaccine bottle is exposed to higher temperature. When the colour of the white square becomes blue like that of surrounding circle, the vaccine should be considered ineffective. Thereby, the health worker can easily ascertain that the vaccine being given is effective or not. This mechanism has been made mandatory in all vaccine procurements since 1998. This quality assurance will ensure that the children will have better protection against polio in 1999 and thereafter.

Following recommendations from the India Expert Advisory Group on Polio Eradication (IEAG), several strategies were utilized during 2005 and early 2006 to improve the impact of SIAs : (i) development and licensure of monovalent OPV1 (mOPV1) and mOPV3 for targeted use during SIAs based on surveillance data; (ii) deployment of additional peronnel to assist with intensified SIAs in the States of Bihar and UP and in Mumbai City; (iii) social mobilization targeted at reaching population groups missed during previous SIAs; (iv) use of mobile teams to vaccinate children at transit points (e.g. railway and bus stations) and on moving trains; and (v) increased engagement and accountability of political leaders and of health staff at all levels. To further improve population immunity in the most critical age group, the IEAG added a specific recommendation at its May 2006 meeting to identify and target all neonates in high-risk areas of UP with a "birth dose" of mOPV1 *(33)*.

The last case of polio in the country was reported from Howrah of West Bengal with date of onset of disease on 13th January 2011. Thereafter no polio case has been reported in the country. On 27th March 2014, India was declared as non-endemic country for polio.

The steps taken by the Government to achieve the target of polio eradication and maintain the polio-free state are as follows *(34)* :

1. All states and union territories in the country have developed a Rapid Response Team (RRT) to respond to any polio outbreak in the country. An Emergency Preparedness and Response Plan (EPRP) has also been developed by all states indicating steps to be undertaken in case of detection of a polio case.
2. In the states of UP and Bihar every new born child is being identified and vaccinated during the polio immunization campaigns and is being tracked for 8 subsequent rounds.
3. In order to reach every eligible child during the pulse polio round, apart from the strategy of vaccinating children at fixed booths and house to house visit, efforts in vaccinating children in transit at railway stations, inside long distance trains, major bus stops, marker places, religious congregations, major road crossings etc. throughout the country have been intensified. Special booths are established in areas bordering neighbouring countries like Wagah border and Attari train station in Punjab and Munabao train station in Barmer district of Rajasthan, to ensure that all children under 5 years of age coming from across the border are given polio drops.
4. An extremely high level of vigilance through surveillance across the country for any importation or circulation of poliovirus and Vaccine Derived Polio Virus (VDPV) is being maintained. Environmental surveillance is continuing at four sites with establishment of two new sites in 2012.

5. Government of India has identified 107 high risk blocks for polio where a multi-pronged strategy is being implemented to ensure sanitation, hygiene and clean drinking water in addition to vaccinating each and every child oral polio vaccine (OPV).
6. Migratory population from UP and Bihar are being identified in the states of Punjab, Haryana, Gujarat and West Bengal and these migratory children are being covered during the Sub National Immunization Day (SNID) in UP and Bihar.
7. Social mobilization activities are being intensified by involving the local influencers, community and religious leaders to improve community participation and acceptance of polio vaccine.
8. A rolling emergency stock of oral polio vaccine (OPV) is being maintained to respond to any wild polio vaccine (WPV) or circulating vaccine derived polio virus (cVDPV) detection.

As part of the polio endgame strategic plan, India has introduced IVP in the national immunization programme from 30th November 2015 and tOPV – bOPV switch was carried out in April 2016 *(35)*.

AFP SURVEILLANCE : PPI is supported by AFP surveillance system since 1997. It is being conducted through a network of surveillance medical officers (SMOs), who are specially trained and are responsible for a defined area. A national surveillance team is positioned in Delhi. The SMOs are located at the state headquarters and at regional places in case of larger states. A regular weekly reporting system has been established. As a result of more meticulous search/ reporting, the number of reported cases of AFP increased from 1,005 in 1996 to 11,675 and the completeness of stool specimen collection improved markedly from 59 per cent in 1998 to 82 per cent at the end of September 2020 *(36)*.

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VIRAL HEPATITIS

Viral hepatitis is a term commonly used for several clinically similar yet aetiologically and epidemiologically distinct diseases. It is caused by five different viruses with transmission either through contaminated food or water (hepatitis A and E) or through exposure to blood or body fluids (hepatitis B, C and D). Hepatitis A and hepatitis B have been recognized as separate entities since early 1940s and can be diagnosed with specific serological tests. Delta hepatitis is an infection dependent on the hepatitis B virus. It may occur as a coinfection with acute HBV infection or as superinfection of an HBV carrier.

HEPATITIS A

Hepatitis A (formerly known as "infectious" hepatitis or epidemic jaundice) is an acute infectious disease caused by hepatitis A virus (HAV). The disease is heralded by non-specific symptoms such as fever, chills, headache, fatigue, generalized weakness and aches and pains, followed by anorexia, nausea, vomiting, dark urine and jaundice. The disease spectrum is characterized by the occurrence of numerous subclinical or asymptomatic cases. The disease is benign with complete recovery in several weeks. The case fatality rate of icteric cases is less than 0.1 per cent, usually from acute liver failure and mainly affects older adults. Although the disease has, in general, a low mortality, patients may be incapacitated for many weeks.

Problem statement

Being an enterovirus infection like poliomyelitis, hepatitis A is endemic in most developing countries, with frequent outbursts of minor or major outbreaks. The exact incidence of the disease is difficult to estimate because of the high proportion of asymptomatic cases. However, based on an ongoing reassessment of the global burden of hepatitis A, WHO estimates suggest that about 1.4 million cases occur every year world-wide *(1)*.

Geographical areas can be characterized as having high, intermediate or low levels of hepatitis A infection *(2)*.

Areas with high levels of infection

In developing countries with very poor sanitary conditions and hygienic practices, most children (90%) have been

infected with the hepatitis A virus before the age of 10 years. Those infected in childhood do not experience any noticeable symptoms. Epidemics are uncommon because older children and adults are generally immune. Symptomatic disease rates in these areas are low and outbreaks are rare.

Areas with intermediate levels of infection

In developing countries, countries with transitional economies, and regions where sanitary conditions are variable, children often escape infection in early childhood. Ironically, these improved economic and sanitary conditions may lead to a higher susceptibility in older age groups and higher disease rates, as infections occur in adolescents and adults, and large outbreaks can occur. Thus, paradoxically, with the transition from high to intermediate endemicity, the incidence of clinically significant hepatitis A increases *(2)*.

Areas with low levels of infection

In developed countries with good sanitary and hygienic conditions, infection rates are low. Disease may occur among adolescents and adults in high-risk groups, such as injecting-drug users, homosexual men, people travelling to areas of high endemicity, and in isolated populations such as closed religious communities *(2)*.

The exact incidence of HAV in India is not known. The Indian literature is replete with numerous reports of sporadic and epidemic occurrence of this disease in various cities, residential colonies and campuses. Epidemics of hepatitis A often evolve slowly, involve wide geographic areas and last many months, but, common source epidemics (e.g., faecal contamination of drinking water) may evolve explosively.

Epidemiological determinants

Agent factors

(a) AGENT : The causative agent, the hepatitis A virus, is an enterovirus (type 72) of the Picornaviridae family *(3)*. It multiplies only in hepatocytes. Faecal shedding of the virus is at its highest during the later part of the incubation period and early acute phase of illness. Only one serotype is known. (b) RESISTANCE : The virus is fairly resistant to low pH, heat and chemicals. It has been shown to survive more than 10 weeks in well water *(4)*. It withstands heating to 60 deg C for one hour, and is not affected by chlorine in doses usually employed for chlorination. Formalin is stated to be an effective disinfectant. The virus is inactivated by ultraviolet rays and by boiling for 5 minutes or autoclaving. In short the virus survives for long periods under variable conditions and resists many procedures that eliminate or inactivate most bacterial agents. (c) RESERVOIR OF INFECTION : The human cases are the only reservoir of infection. The cases range from asymptomatic infections to severe ones. Asymptomatic (anicteric) infections are especially common in children. These cases play an important role in maintaining the chain of transmission in the community. There is no evidence of a chronic carrier state. (d) PERIOD OF INFECTIVITY : The risk of transmitting HAV is greatest from 2 weeks before to 1 week after the onset of jaundice. Infectivity falls rapidly with the onset of jaundice *(2)*. (e) INFECTIVE MATERIAL : Mainly man's faeces. Blood, serum and other fluids are infective during the brief stage of viraemia. (f) VIRUS EXCRETION : HAV is excreted in the faeces for about 2 weeks before the onset of jaundice and for up to 2 weeks thereafter. There is little evidence for HAV transmission by exposure to urine or naso-pharyngeal secretions of infected patients. Haemodialysis plays no role in the spread of hepatitis A infections to either patients or the staff *(5)*.

Host factors

(a) AGE : Infection with HAV is more frequent among children than in adults. However, people from all ages may be infected if susceptible. In young children, infections tend to be mild or subclinical; the clinical severity increases with age. The ratio of anicteric to icteric cases in adults is about 1:3; in children, it may be as high as 12:1. However, faecal excretion of HAV antigen and RNA persists longer in the young than in adults *(5)*. (b) SEX : Both sexes are equally susceptible. (c) IMMUNITY : Immunity after attack probably lasts for life; second attacks have been reported in about 5 per cent of patients. Most people in endemic areas acquire immunity through subclinical infection. The IgM antibody appears early in the illness and persists for over 90 days. IgG appears more slowly, and persists for many years.

Environmental factors

Cases may occur throughout the year. In India the disease tends to be associated with periods of heavy rainfall *(9)*. Poor sanitation and overcrowding favour the spread of infection, giving rise to water-borne and food-borne epidemics. Paradoxically, when standards of hygiene and sanitation are improved, morbidity from infection with enteric viruses may increase. This is what happened with hepatitis A *(6)*.

Modes of transmission

(a) *FAECAL–ORAL ROUTE :* This is the major route of transmission. It may occur by direct (person-to-person) contact or indirectly by way of contaminated water, food or milk. Water-borne transmission, is not a major factor in developed countries, where food-borne outbreaks are becoming more frequent. For example, consumption of salads and vegetables, and of raw or inadequately cooked shellfish and oysters cultivated in sewage polluted water is associated with epidemic outbreaks of hepatitis A *(5)*. Direct transmission comprises an array of routes such as contaminated hands or objects such as eating utensils. Direct infection occurs readily under conditions of poor sanitation and overcrowding.

(b) *PARENTERAL ROUTE :* Hepatitis A is rarely, if ever, transmitted by the parenteral route (i.e., by blood and blood products or by skin penetration through contaminated needles). This may occur during the stage of viraemia. This mode of transmission is of minor importance as viraemic stage of infection occurs during prodromal phase and there is no carrier state *(5)*.

(c) *SEXUAL TRANSMISSION :* As a sexually transmitted infection hepatitis A may occur mainly among homosexual men because of oral–anal contact *(7)*.

Food handlers are not at increased risk for hepatitis A, because of their occupation, but are noteworthy because of their critical role in common-source food-borne HAV transmission. Health care personnel do not have an increased prevalence of HAV infection and nosocomial HAV transmission is rare. Children play an important role in HAV transmission as they generally have asymptomatic or unrecognized illness *(8)*.

Incubation period

10 to 50 days (usually 14–28 days). The length of the incubation period is proportional to the dose of the virus ingested *(4)*.

Clinical spectrum

The onset of jaundice is often preceded by gastrointestinal symptoms such as nausea, vomiting, anorexia, and mild fever. Jaundice may appear within a few days of the

prodromal period, but anicteric hepatitis is more common. Hepatitis A resolves completely in 98 per cent of cases but relapse of symptoms are noted in 3–20 per cent cases *(10)*. The outcome of infection with HAV is as shown in Table 1.

TABLE 1
Outcomes of infection with hepatitis A virus

Outcome	Children	Adults
Inapparent (sub-clinical) infection	80-95%	10-25%
Icteric disease	5-20%	75-90%
Complete recovery	>98%	>98%
Chronic disease	None	None
Mortality rate	0.1%	0.3-2.1%

Source : *(5)*

Diagnosis

Tests for abnormal liver function, such as serum alanine aminotransferase (ALT) and bilirubin, supplement the clinical, pathologic, and epidemiologic findings.

A specific laboratory diagnosis of hepatitis A can be obtained by :

a. Demonstration of HAV particles or specific viral antigens in the faeces, bile and blood. HAV is detected in the stool from about 2 weeks prior to the onset of jaundice, up to 2 weeks after.
b. Anti-HAV appears in the IgM fraction during the acute phase, peaking about 2 weeks after elevation of liver enzymes. Anti-HAV IgM usually declines to non-detectable levels within 3–6 months. Anti-HAV IgG appears soon after the onset of disease and persists for decades. Thus, detection of IgM-specific anti-HAV in the blood of an acutely infected patient confirms the diagnosis of hepatitis A. ELISA is the method of choice for measuring HAV antibodies *(5)*.

The clinical, virologic and serological events following exposure to HAV are as shown in Fig. 1.

Prevention and containment

a. Control of reservoir

Control of reservoir is difficult because of the following factors: (a) faecal shedding of the virus is at its height during the incubation period and early phase of illness (b) the occurrence of large number of subclinical cases (c) absence of specific treatment, and (d) low socio-economic profile of the population usually involved. Strict isolation of cases is not a useful control measure because of (a) and (b). However, attention should be paid to the usual control measures such as complete bed rest and disinfection of faeces and fomites. The use of 0.5 per cent sodium hypochlorite has been strongly recommended as an effective disinfectant *(11)*.

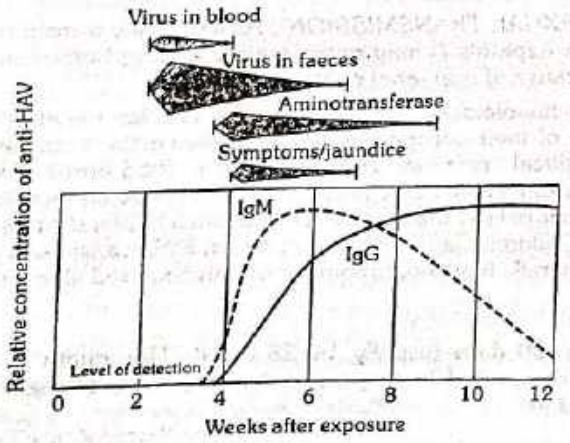

FIG. 1
Immunologic and biologic events associated with human infection with hepatitis A virus.

Source : *(5)*

b. Control of transmission

The best means of reducing the spread of infection is by promoting simple measures of personal and community hygiene, e.g., hand washing before eating and after toilet; the sanitary disposal of excreta which will prevent contamination of water, food and milk; and purification of community water supplies by flocculation, filtration and adequate chlorination. A question is often asked how much chlorine is needed to inactivate the virus. Studies indicated that 1 mg/L of free residual chlorine can cause destruction of the virus in 30 minutes at pH values of 8.5 or less *(12)*. The water treatment and distribution system should be improved. During epidemics, boiled water should be advocated for drinking purposes. Several countries of the world have achieved control of water-borne HAV infection. Other control measures include proper disposal of sewage within communities. If all these measures are properly implemented, a substantial reduction of HAV infection can be expected.

c. Control of susceptible population

Targeted protection of high-risk groups should be considered in low and very low endemicity, settings. Groups at increased risk of hepatitis A include travellers to areas of intermediate or high endemicity, those requiring life-long treatment with blood products, men having sex with men, workers in contact with non-human primates, and injection drug users. In addition, patients with chronic liver disease are at increased risk for fulminant hepatitis A and should be vaccinated *(10)*. Use of hepatitis A vaccine rather than passive prophylaxis with immune globuline should be considered for pre-exposure prophylaxis (e.g. for travellers) and post-exposure prophylaxis (e.g. for close contacts of acute cases of hepatitis A.

1. *Vaccines* : Two types of hepatitis A vaccines are currently used worldwide:

(a) Formaldehyde inactivated vaccines – produced in several countries and which are most commonly used worldwide.
(b) Live attenuated vaccinces – which are manufactured in China and are available in several countries.

Inactivated hepatitis A vaccine are licensed for use in persons ≥12 months of age. The complete vaccination schedule consists of 2 dose administration into the deltoid muscle. The interval between the first (primary) dose and second (booster) dose is commonly 6–12 months; however, the interval between the doses is flexible and can be extended to 18–36 months. It can be administered simultaneously with other vaccines. Following 2 doses of vaccine the protective efficacy is about 94 per cent.

The live attenuated vaccine is administered as a single subcutaneous dose.

Both inactivated and live attenuated hepatitis A vaccines are highly immunogenic and immunization will generate long-lasting, possibly life-long, protection against the disease in children and adults.

Recommendations for hepatitis A vaccination in outbreak situation depend on the epidemiologic features of disease in

the community and the feasibility of rapidly implementing a widespread vaccination programme. National immunization programmes may consider inclusion of single-dose inactivated hepatitis A vaccine in immunization schedule *(10)*.

Combination of hepatitis A and B, or hepatitis A and typhoid vaccines have been developed, mainly intended for use in adult travellers.

2. *Human immunoglobulin* : The protective efficacy of immune globulin (Ig) against HAV infection is well documented. The duration of protection is, however, limited to approximately 1–2 months and 3–5 months following administration of IgG at dose of 0.02 and 0.06 ml/kg body weight, respectively. Prophylaxis is achieved within hours of injection and is 80 to 90 per cent effective when administered before or no later than 14 days after exposure. The use of Ig worldwide is now declining because of insufficient concentration of anti–HAV IgG in non-specific Ig preparations, the high cost of specific HAV IgG preparations, the limited duration of protection following passive IgG prophylaxis against HAV infection, and because hepatitis A vaccines have been shown to induce rapid protection against HAV after first dose *(10)*.

HEPATITIS B

Hepatitis B (formerly known as "serum" hepatitis) is an acute systemic infection with major pathology in the liver, caused by hepatitis B virus (HBV). HBV infection can be either acute or chronic, and may range from asymptomatic infection or mild disease, to severe, or rarely fulminant hepatitis. Acute hepatitis B is usually a self-limiting disease marked by acute inflammation and hepatocellular necrosis with case fatality rate of 0.5 to 1 per cent. Chronic hepatitis B infection encompasses a spectrum of disease and is defined as persistent HBV infection with or without associated active viral replication and evidence of hepatocellular injury and inflammation. Age is a key factor in determining the risk of chronic infection. Worldwide, the majority of persons with CHB were infected at birth or in early childhood *(13)*. Hepatitis B virus can form a dangerous alliance with delta virus and produce a new form of virulent hepatitis which is considered to be widespread threat for much of the world.

Problem statement

WORLD

Hepatitis B is endemic throughout the world, especially in tropical and developing countries and also in some regions of Europe *(8)*. Its prevalence varies from country to country and depends upon a complex mix of behavioural, environmental and host factors. In general, it is lowest in countries or areas with high standards of living.

The HBV infection is a global problem, with 60 per cent of all the world's population living in areas where there are high levels of infection. The endemicity of active HBV infection is reflected in the serologic prevalence of the hepatitis B surface antigen (HBsAg) in the general population of a defined geographical area. HBsAg prevalence of ≥8% defines highly endemic areas, prevalence of 5%–7% defines high intermediate, 2%–4% low intermediate, and <2% defines low endemic areas.

WHO estimated that, in 2022, 254 million people were living with chronic hepatitis B infection (defined as hepatitis B surface antigen positive), including about 1.2 million people newly infected with the virus during that year. Hepatitis B prevalence is highest in the WHO African and Western Pacific regions where an estimated 97million and 65 million respectively, of the adult population have acquired the virus. Prevalence is lower in the South-East Asia 61 million, Eastern Mediterranean 15 million and European regions 11 million, and in the Region of the Americas 5 million.

Only 30.4 million people with chronic hepatitis B infection knew their hepatitis B status and 6.6 million were receiving treatment. The infection caused an estimated 1.1 million deaths in 2022, mostly from cirrhosis and hepatocellular carcinoma. Globally in 2022, people died from acute hepatitis B *(14)*, with the South-East Asia Region accounting about one third of those deaths (12,600).

Safe and effective vaccines exist for preventing hepatitis B infection. Their widening use has reduced the global proportion of children under five years of age who are chronically infected with hepatitis B virus to just under 1 per cent in 2019, down from around 5 per cent from the 1980s to the early 2000s before vaccines were available.

Most of the burden of HBV-related disease results from infections acquired in infancy through perinatal or early childhood exposure to HBV because infection acquired at an early age is more likely to become chronic than infection acquired later in life. The risk of chronic infection remains high until after 5 years of age when the rate stabilizes at around 5%.

Co-infections with other viral infections occur most frequently in high HBV endemic areas. About 2.7 million of the 36.7 million people infected with HIV worldwide are co-infected with HBV. Approximately 10%–15% of patients with chronic HBV infection are co-infected with HCV. HDV infection occurs exclusively in HBV-infected individuals, as the virus is deficient, requiring HBV surface proteins to form its envelope in HDV/HBV co-infected hepatocytes. Approximately 5% of HBV-infected persons are infected with HDV *(15)*.

Major progress in the global response to viral hepatitis has been achieved through the expansion of routine hepatitis B vaccination, which was facilitated by the introduction of new combination vaccines. By the year 2015, 185 countries had incorporated hepatitis B vaccination in the national infant immunization schedule, and 97 countries had introduced the recommended birth dose. In the absence of the universal birth dose or other effective interventions, the transmission HBV infection from mother-to-child remains a major source of chronic liver disease when infected children become adults *(15)*.

HBV infection also causes a significant economic burden in terms of years of life lost from liver disease in high-income settings as well as in developing countries and accounts for 5–10 per cent of liver transplants *(13)*.

Epidemiological determinants

Agent factors

(a) AGENT : Hepatitis B virus was discovered by Blumberg in 1963. Efforts to grow this virus have been so far unsuccessful *(16)*. HBV is a complex, 42–nm, double–shelled DNA virus, originally known as the **"Dane particle"**. It replicates in the liver cells. HBV occurs in three morphological forms in the serum of a patient: (a) small spherical particles with an average diameter of 22–nm. These particles are antigenic and stimulate production of surface antibodies; (b) tubules of varying length and diameter, and (c) the Dane particle which corresponds morphologically to hepatitis B virus. A person who is serologically positive for the surface antigen is circulating all morphological forms, of which 22–nm particles constitute the bulk. Of the three morphological forms, only the Dane particle is considered infectious, the other circulating morphological forms are not infectious.

(b) RESERVOIR OF INFECTION : Man is the only reservoir of infection which can be spread either from **carriers** or from **cases**. The continued survival of infection is due to the large number of individuals who are carriers of the virus. The persistent carrier state has been defined as the presence of HBsAg (with or without concurrent HBeAg) for more than 6 months. Cases may range from inapparent to symptomatic cases.

(c) INFECTIVE MATERIAL : Contaminated blood is the main source of infection, although the virus has been found in body secretions such as saliva, vaginal secretions and semen of infected persons.

(d) RESISTANCE : The virus is quite stable and capable of surviving for at least 7 days on environmental surfaces. It can be readily destroyed by sodium hypochlorite, as is by heat sterilization in an autoclave for 30 to 60 minutes.

(e) PERIOD OF COMMUNICABILITY : The virus is present in the blood during the incubation period (for a month before jaundice) and acute phase of the disease. Period of communicability is usually several months (occasionally years in chronic carriers) or until disappearance of HBsAg and appearance of surface antibody.

Host factors

(a) AGE : The outcomes of HBV infection are age-dependent. Acute hepatits B occurs in approximately 1 per cent of perinatal, 10 per cent of early childhood (1–5 years of age), and 30 per cent of late (>5 years age) HBV infections. Mortality from fulminant hepatitis B is approximately 70 per cent. The development of chronic HBV infection is inversely related to age and occurs in approximately 80–90 per cent of persons infected perinatally, in 30–50 per cent infected in early childhood (less than 6 years of age) and in <5 per cent occurring in otherwise healthy adults *(15)*.

(b) HIGH-RISK GROUPS : Certain groups carry higher risks. The annual incidence of HBV infection in surgeons is estimated to be 50 times greater than that in the general population, and is more than twice that of other physicians. Other high risk groups comprise reciplents of blood transfusions, health care and laboratory personnel, homosexuals, prostitutes, percutaneous drug abusers, infants of HBV carrier mothers, recipients of solid organ transplants and patients who are immunocompromised. Serological screening and vaccination of high-risk groups is highly recommended.

(c) HEPATITIS B AND HIV INFECTION : It is estimated that 10 per cent of the 40 million people infected with HIV worldwide are coinfected with HBV. Although HBV infection appears to have a minimal effect on the progression of HIV, the presence of HIV markedly increases the risk of developing HBV-associated liver cirrhosis and hepatocellular carcinoma. The mortality rate increases among HIV-positive people due to HBV coinfection both before and after commencement of highly active anti-retroviral therapy *(16)*.

(d) HUMORAL AND CELLULAR RESPONSES *(17)*: Hepatitis B virus has three distinct antigens – a surface antigen, also known as "Australia antigen" (HBsAg), a core antigen (HBcAg), and an "e" antigen (HBeAg). They stimulate the production of corresponding antibodies e.g., surface antibody (anti-HBs), core antibody (anti-HBc) and "e" antibody (anti-HBe). These antibodies and their antigens constitute very useful markers of HBV infection. Patients with HBV infection are expected to have one or more HBV markers. The course of a typical acute hepatitis is outlined in Fig. 2.

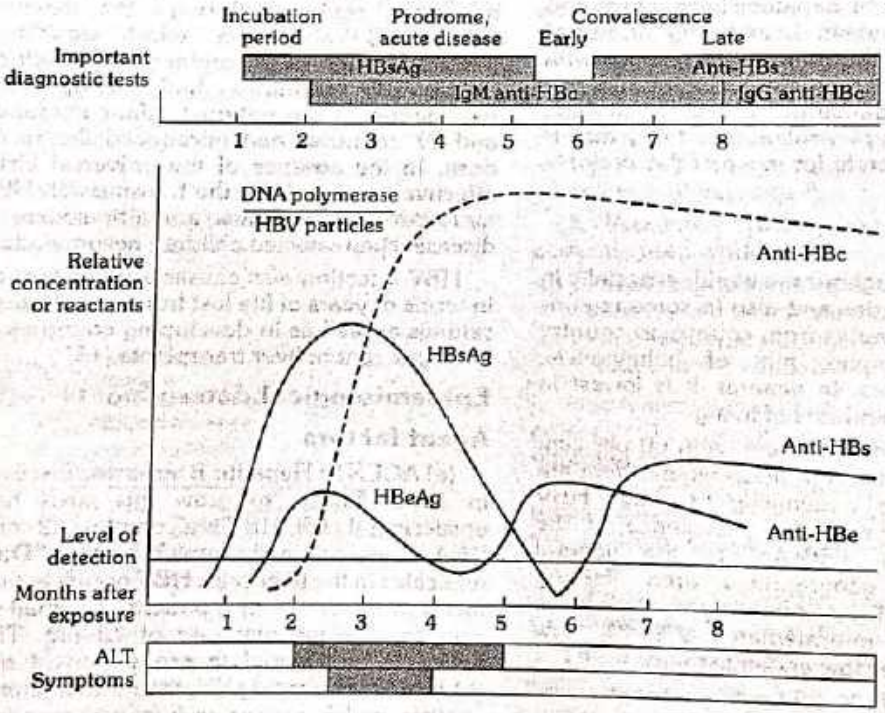

FIG. 2
Course of a typical acute hepatitis

ALT – alanine aminotransferase; anti-HBc – antibody to hepatitis B core antigen; anti-HBe – antibody to hepatitis Be antigen; anti-HBs – antibody to hepatitis B surface antigen; HBeAg – hepatitis B e antigen; HBsAg – hepatitis B surface antigen; HBV – hepatitis B virus; IgG – immunoglobulin G; IgM – immunoglobulin M.

Source : *(5)*

Modes of transmission

a. *Parenteral route*

Hepatitis B is essentially a blood-borne infection. It is transmitted by infected blood and blood products through transfusions, dialysis, contaminated syringes and needles, pricks of skin, handling of infected blood, accidental inoculation of minute quantities of blood such as may occur during surgical and dental procedures, immunization, traditional tattooing, ear piercing, nose piercing, ritual circumcision, accupuncture, etc. Accidental percutaneous inoculations by shared razors and tooth brushes have been implicated as occasional causes of hepatitis B *(13)*.

b. *Perinatal transmission*

Spread of infection from HBV carrier mothers to their babies appears to be an important factor for the high prevalence of HBV infection in some regions, particularly China and SE Asia. The risk of infection varies from country to country and unless vaccinated at birth, the majority of children born to mothers who are HBeAg–positive become chronically infected. The mechanism of perinatal infection is uncertain. Although HBV can infect the foetus *in utero*, this rarely happens and most infections appear to occur at birth, as a result of a leak of maternal blood into the baby's circulation, or ingestion or accidental inoculation of blood *(18)*. Infection of the baby is usually anicteric and is recognized by the appearance of surface antigen between 60–120 days after birth *(9)*.

c. *Sexual transmission*

There is ample evidence for the spread of infection by intimate contact or by sexual route. Various body fluids including saliva, vaginal, menstrual and seminal fluids have been implicated as vehicles of human transmission. The sexually promiscuous, particularly male homosexuals, are at very high risk of infection with hepatitis B.

d. *Other routes*

Transmission from child–to–child, often called horizontal transmission, is responsible for a majority of HBV infections and carriers in parts of the world other than Asia. The researchers believe that the spread occurs through physical contact between children with skin conditions such as cuts or grazes. Often transmission occurs when children play together or share the same bed *(19)*.

In short, transmission occurs in a wide variety of epidemiological settings. It can spread either from carriers or from people with no apparent infection, or during the incubation period, illness or early convalescence.

Incubation period

30 to 180 days. Lower doses of the virus result often in longer incubation period. The average incubation period is about 75 days *(16)*.

Clinical picture

The symptoms and manifestations of hepatitis B are similar to those of other types of viral hepatitis. The picture is complicated by the carrier state and by chronic liver disease, which may follow the infection. The spectrum of disease and natural history of chronic HBV infection are diverse. In some people, CHB is inactive and does not lead to significant liver disease. In others, it may cause progressive liver fibrosis, leading to cirrhosis with end-stage liver disease, and markedly increased risk of hepatocellular carcinoma, independent of the presence of cirrhosis – usually many years after initial infection. Longitudinal studies of untreated persons with CHB show 8–20 per cent cumulation risk of developing cirrhosis over 5 years. In those with cirrhosis, there is an approximately 20 per cent annual risk of hepatic decompensation and the annual incidence of hepatic B related HCC is high, ranging from 1 to 5 per cent. Untreated patients with decompensated cirrhosis have poor prognosis, with 15–40 per cent survival at 5 years. Several host and viral factors, especially coinfections with HIV, HCV and hepatitis D virus together with other cofactors such as alcohol use, may increase the rate of disease progression and risk of developing HCC *(13)*.

Diagnosis

There are three distinct antigen antibody systems that relate to HBV infection and a variety of circulating markers that are useful in diagnosis. The assays that detect the presence of either antigens or antibodies, typically in serum or plasma but also in capillary blood and oral fluid. These include rapid diagnostic tests (RDTs), and laboratory-based immunoassays. e.g. enzyme immunoassays (EIAs), chemiluminescence immunoassays (CLIAs), and electro-chemiluminescence immunoassays (ECLs). Interpretation of common serological patterns is as shown in Table 2.

TABLE 2

Common serologic patterns in hepatitis B virus infection and their interpretation

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	Interpretation
+	–	IgM	+	–	Acute hepatitis B
+	–	IgG[1]	+	–	Chronic hepatitis B with active viral replication
+	–	IgG	–	+	Chronic hepatitis B with low viral replication
+	+	IgG	+ or –	+ or –	Chronic hepatitis B with heterotypic anti-HBs (about 10% of cases)
–	–	IgM	+ or –	–	Acute hepatitis B
–	+	IgG	–	+ or –	Recovery from hepatitis B (immunity)
–	+	–	–	–	Vaccination (immunity)
–	–	IgG	–	–	False-positive, less commonly, infection in remote past

[1] Low levels of IgM anti-HBc may also be detected.

Source : *(17)*

PREVENTION AND CONTAINMENT

Since there is no specific treatment, prevention has been the major aim in managing viral hepatitis B. The following measures are available :

a. Hepatitis B vaccine

The recombinant hepatitis B vaccine was introduced in 1986 and has gradually replaced the plasma-derived hepatitis B vaccine. The active substance in recombinant hepatitis B vaccine is HBsAg.

Hepatitis B vaccine is available as monovalent formulation, or in fixed combination with other vaccines, including DPT, Hib, hepatitis A and inactivated polio. The immune response and safety of these combinations of vaccines are comparable to those observed when the vaccines are administered separately. When immunizing against HBV at birth, only monovalent hepatitis B vaccine should be used. Internationally marketed hepatitis B vaccines are considered immunologically comparable and can be used interchangeably *(20)*.

The dose for adults is 10–20 micrograms initially (depending on the formulation) and again at 1 and 6 months. Children under 10 years of age should be given half of the adult dose at the same time intervals. For greatest reliability of absorption, the deltoid muscle is preferred for injection as gluteal injection often results in deposition of vaccine in fat rather than muscle, with fewer serologic conversion. For infants and children under 2 years, anterolateral aspect of thigh is used as vaccination site. Intradermal administration is not recommended because the immune response is less reliable particularly in children. The hepatitis B vaccine does not interfere with immune response to any other vaccine and vice-versa. The birth dose of hepatitis B can be given safely together with BCG vaccine. However, the vaccines should be given at different sites.

There are multiple options for incorporating the hepatitis B vaccine into national immunization programmes. The choice of schedule depends on the local epidemiological situation and programme considerations. The recommended schedule for vaccination can be divided into those that include a birth-dose and those that do not. Schedules with a birth-dose call for the first dose at birth, followed by a second dose and third dose at the time of the first and third dose of DPT vaccination respectively. Alternatively, a four-dose schedule may be used (as in India) where the dose at birth is followed by three additional doses at 6, 10 and 14 weeks with DPT vaccination. These doses may be given either as monovalent vaccine or as a combination (eg. with DPT and/or Hib) following the schedules commonly used for these vaccines. The minimum recommended interval between the doses is four weeks. Longer dose intervals may increase the final anti-HBs titres but not the sero-conversion rates. These schedules will prevent most perinatally acquired infection. In countries where a high proportion of HBV infection is acquired perinatally, specifically in countries where the prevalence in the general population of chronic HBV infection is more than 8 per cent, the first dose of hepatitis B vaccine should be given within 24 hours after birth to prevent perinatal transmission *(21)*.

The complete vaccine series induces protective antibody levels in more than 95 per cent of infants, children and young adults. After the age of 40 years, protection following the primary vaccination series drops below 90 per cent; by 60 years, protective antibody levels are achieved in only 65–75 per cent of the vaccinees. The duration of protection is at least 15 years and based on current scientific evidence, life long *(21)*. Some infants born prematurely with low birth weight (< 2000 g) may not respond well to vaccination at birth. However, by one month of chronological age, all premature infants, regardless of initial birth weight or gestational age, are likely to respond adequately. In such cases the vaccine dose given at birth should not be counted towards the primary series and 3 additional doses should be given according to the national immunization schedule *(16)*. Immunosuppressive illness such as advanced HIV infection, chronic liver disease, chronic renal failure, and diabetes are associated with reduced immunogenicity of the vaccine.

Data on immunogenecity suggest that in any age group, interruption of the vaccination schedule does not require restarting of the vaccine series. If the primary series is interrupted after the first dose, the second dose should be administered as soon as possible and the second and the third doses separated by a minimum interval of 4 weeks; if only the third dose is delayed, it should be administered as soon as possible *(16)*.

Immunization in adults : Routine pre-exposure vaccination should be considered for groups of adults who are at increased risk of HBV infection. Adults 20 years of age and older should receive 1 ml of adult formulation. The usual schedule for adults is two doses separated by no less than 4 weeks, and a third dose 4 to 6 months after the second dose. If an accelerated schedule is needed, the minimum interval between first and second dose is 4 weeks and the minimum interval between the second and third dose is 8 weeks. However, the first and the third doses should be separated by no less than 16 weeks. Doses given at less than these minimum intervals should not be counted as part of the vaccination series. It is not necessary to restart the series or add doses because of an extended interval between doses *(8)*.

The high-risk persons for whom the vaccination is recommended are persons with high-risk sexual behaviour, partners and household contacts of HBsAg-positive persons, injecting drug users, persons who frequently require blood or blood products, recipients of solid organ transplantation, those at occupational risk of HBV infection, including health care workers, as well as for international travellers to HBV endemic countries.

Hepatitis B vaccine is contraindicated for individuals with a history of allergic reactions to any of the vaccine's components. Neither pregnancy nor lactation is a contraindication for use of this vaccine *(21)*.

The vaccine should be stored at 2–8°C. Freezing must be avoided as it dissociates antigen from the alum adjuvant.

Pentavalent Vaccine

It is a combined vaccine giving protection against diphtheria, pertussis, tetanus, hepatitis B and Hib. Kindly refer to page 181 for details.

b. Hepatitis B immunoglobulin (HBIG)

For immediate protection, HBIG is used for those acutely exposed to HBsAg-positive blood, for example (a) surgeons, nurses or laboratory workers (b) newborn infants of carrier mothers (c) sexual contacts of acute hepatitis B patients, and (d) patients who need protection against HBV infection after liver transplantation. The HBIG should be given as soon as possible after an accidental inoculation (ideally within 6 hours and preferably not later than 48 hours). At the same time the victim's blood is drawn for HBsAg testing. If the test

is negative, vaccination should be started immediately and a full course given. If the test is positive for surface antibody, no further action is needed *(23)*.

The recommended dose is 0.05 to 0.07 ml/kg of body weight *(24)*; two doses should be given 30 days apart *(24, 25)*. HBIG provides short-term passive protection which lasts approximately 3 months. Since the median incubation period is said to be lower than 100 days *(26)*, two doses of HBIG given one month apart should suffice. The general use of HBIG for long-term prophylaxis has not been recommended because of its limited availability, its high cost and risk (although remote) of complications through repeated use over a long period of time *(27)*.

c. Passive–active immunization

The simultaneous administration of HBIG and hepatitis B vaccine is more efficacious than HBIG alone. HBIG does not interfere with the antibody response to the hepatitis B vaccine. This combined procedure is ideal both for prophylaxis of persons accidentally exposed to blood known to contain hepatitis B virus, and for prevention of the carrier state in the newborn babies of carrier mothers. HBIG (0.05–0.07 ml/kg) should be given as soon as possible and within 24 hours, if possible. Hepatitis B virus vaccine 1.0 ml (20 mcg/1.0 ml) should be given intramuscularly within 7 days of exposure, and second and third doses should be given one and six months, respectively, after the first dose.

d. Other measures

All blood donors should be screened for HBV infection, and those positive for HBsAg also known as Australia antigen should be rejected. Voluntary blood donation should be encouraged because purchased blood has shown a higher risk of post–transfusion hepatitis *(8)*. Health personnel should be alerted to the importance of adequate sterilization of all instruments and to the practice of simple hygienic measures. Carriers should be told not to share razors or tooth brushes and use barrier methods of contraception; they should not donate blood.

Most international guidelines recommend that several high-risk groups be screened for HBsAg, and that those at risk and not immune should be offered hepatitis B vaccination. These include: household and sexual contacts of persons with CHB, HIV-infected persons, persons who inject drugs (PWID), men who have sex with men, sex workers, as well as other groups such as indigenous people, persons who are imprisoned, and persons of transgender. Blood and organ donors should also be screened for HBsAg and other bloodborne pathogens in accordance with WHO recommendations to prevent HBV transmission *(13)*.

Treatment

There is no specific treatment for acute hepatitis B. Care is aimed at maintaining comfort and adequate nutritional balance, including replacement of fluids lost from vomiting and diarrhoea.

CHRONIC HEPATITIS B AND HEPATITIS C INFECTION

Viral hepatitis is one of the communicable diseases for which deaths are increasing. About 1.3 million people died of viral hepatitis in 2022, similar to the number of deaths caused by tuberculosis. Viral hepatitis and tuberculosis were the second leading causes of death among communicable diseases in 2022, after COVID-19.

Hepatitis B caused 83% of these deaths and hepatitis C 17%. The increase in estimated mortality since 2019 suggests that the number of hepatitis-related cancer cases and deaths are increasing. Access to effective interventions must be urgently expanded to save lives and prevent a future generation of new infections, cancer cases and deaths.

The estimated number of people newly infected by viral hepatitis declined from 2.5 million in 2019 to 2.2 million in 2022. Of the 2.2 million new infections, 1.2 million were hepatitis B and nearly 1.0 million hepatitis C. The revised estimates are based on improved data from prevalence surveys. They also suggest that hepatitis B and C prevention, including immunization and safe injections, and the initial impact of expanding hepatitis C cure, have had an impact on reducing incidence *(22)*.

Overall, about 304 million people were living with viral hepatitis B and C in 2022. An estimated 254 million were living with hepatitis B and 50 million were living with hepatitis C. Half the burden of chronic hepatitis B and C infection is among people 30–54 years old; and men account for 58% of all cases. An estimated 12% of the burden is among children, in particular for hepatitis B. Hepatitis B and C affect the general population in many regions but also specific populations such as those at higher risk of or with a history of exposure through unsafe blood supplies, medical injections and other health procedures; newborns and children at risk through vertical (mother-to-child) transmission of hepatitis B, notably in settings with high hepatitis B prevalence; indigenous populations and mobile and migrant populations from countries with higher prevalence; and key populations, including people who inject drugs, people in prisons and other closed settings, sex workers and gay men and other men who have sex with men, who may be disproportionately affected in different contexts.

Despite the high global burden of disease due to chronic hepatitis B and C infection, and the advances and opportunities for treatment, most people infected with HBV and/or HCV remain unaware of their infection and therefore frequently present with advance disease. Early identification of the infection would enable infected persons to receive the necessary care and treatment to prevent or delay the onset of liver disease and in addition, prevent transmission by HBV vaccination of the non-immune household contacts and sex partners *(28)*.

The WHO "5Cs"

The WHO "5Cs" are principles that apply to all models of hepatitis testing and in all settings : Consent, Confidentiality, Correct test results, Counselling and Connection (linkage to prevention, treatment and care services). This means hepatitis testing for diagnosis must always be voluntary, and consent for testing informed by pre-test information *(28)*.

Fig. 3 and 4 show summary algorithm for diagnosis, initial assessment, treatment and monitoring of chronic HBV and HCV infection respectively.

Chronic hepatitis B infection can be treated with drugs. Treatment can slow the progression of cirrhosis, reduce incidence of liver cancer and improve long term survival. WHO recommends the use of oral treatments - tenofovir or entecavir, as these are the most potent drugs to suppress hepatitis B virus. They rarely lead to drug resistance as compared with other drugs, are simple to take (1 pill a day), and have few side effects so require only limited monitoring. In most people, however, the treatment only supresses the replication of the virus. Therefore, people who start hepatitis

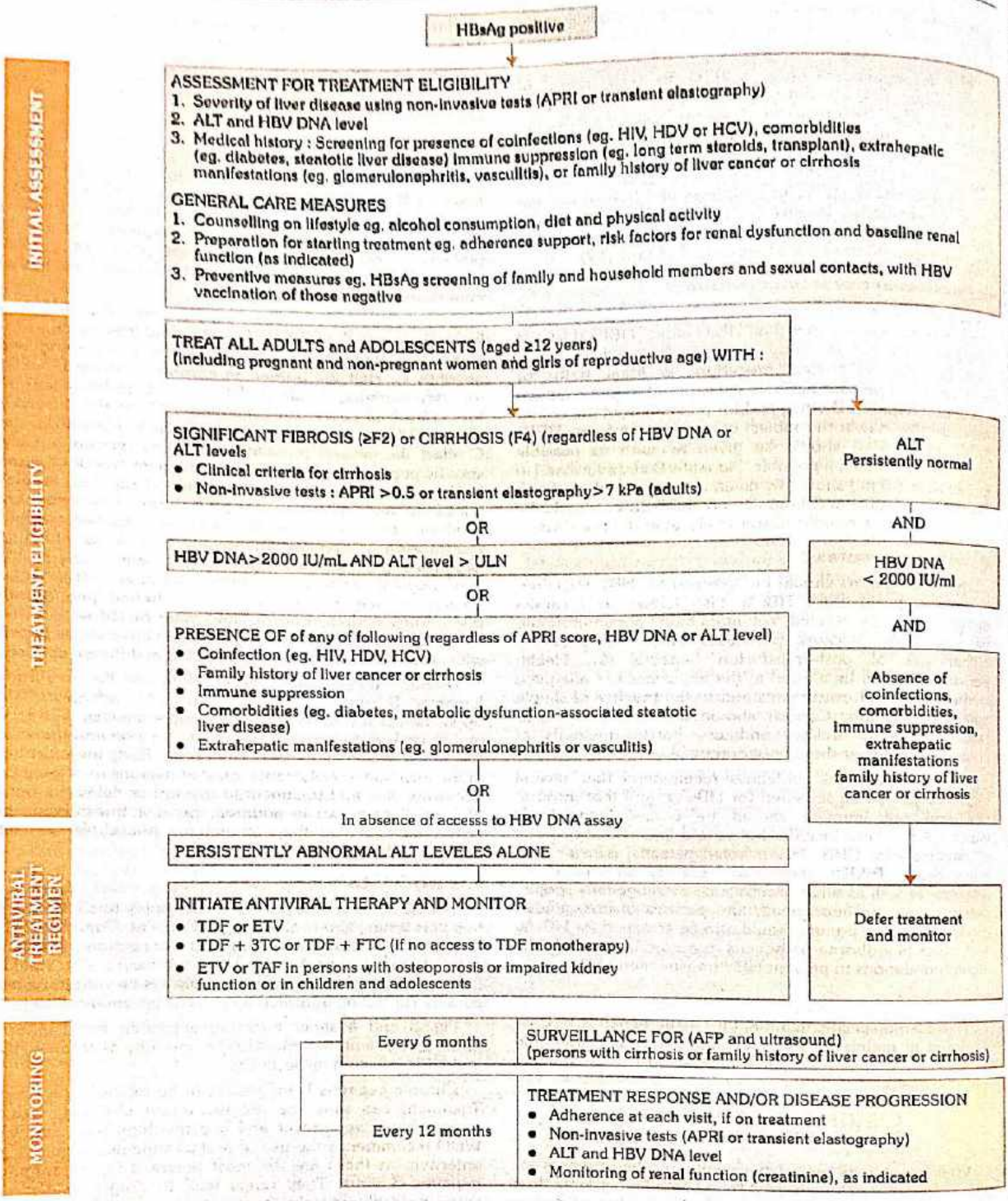

FIG. 3
Algorithm on managing people with chronic hepatitis B infection

Source : *(22)*

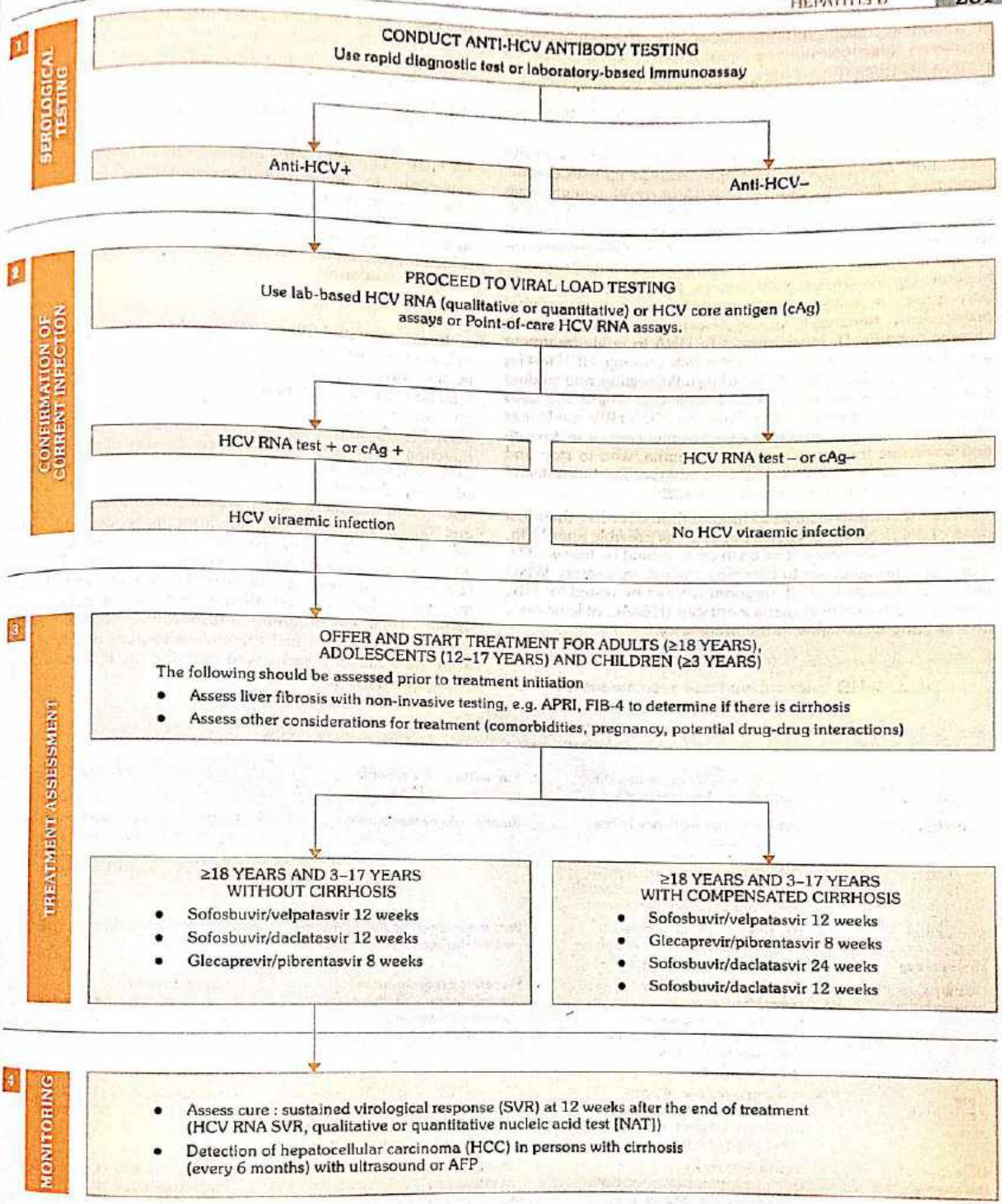

FIG. 4

Algorithm for testing and treatment of HCV

Source : *(22)*

B treatment must continue it for life. Treatment using interferon injections may be considered in some people in certain high-income settings, as this may shorten treatment duration. But its use is less feasible in low-resource settings due to high cost and significant adverse effects requiring careful monitoring *(29)*.

In March 2015, WHO launched its first "Guidelines for the prevention, care and treatment of persons living with chronic hepatitis B infection". Several significant developments have occurred since the 2015 guidelines were published. In 2024, WHO updated previous guidelines with new or updated recommendations in 11 key areas : using non-invasive tests for staging liver disease; who to treat among people with chronic hepatitis B; first-line antiviral therapy for chronic hepatitis B; preventing mother-to-child transmission using antiviral prophylaxis; treatment for adolescents and children with chronic hepatitis B; measuring HBV DNA to guide treatment and monitoring response; HBV DNA reflex testing; HDV testing - who to test and how to test, including reflex testing; and guiding principles for simplifying service delivery. There are also unchanged recommendations from the 2015 HBV guidelines on various aspects of monitoring for treatment response, toxicity and screening for hepatocellular carcinoma; who to stop and when to restart antiviral therapy; and using second-line antiviral therapy for managing treatment failure *(22)*.

WHO recommends that all infants should receive their first dose of the hepatitis B vaccine as soon as possible after birth, ideally within 24 hours. The birth dose should be followed by 2 or 3 additional doses to complete the primary series. WHO also recommends that all pregnant women be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg) at least once and as early as possible in the pregnancy.

Normative guidance for HCV *(22)*

In 2022, WHO released updated recommendations on treatment for adolescents and children with chronic hepatitis C infection. The updated guidelines expanded the treatment recommendations to include all adolescents and children with chronic hepatitis C infection aged three years or older, using the same pangenotypic direct-acting antiviral (DAA) regimens already recommended for adults.

Since 2021, WHO has recommended offering self-testing for HCV as an additional approach to HCV testing services, especially to reach priority populations that may not otherwise test using existing services and may prefer self-care options. The HCV test must be followed by linkage to appropriate post-test services, including confirming viraemic infection, treatment, care and referral services, according to national standards.

Surveillance *(30)*

Infections with HBV or HCV evolve in three phases. New infections (mostly asymptomatic but sometimes symptomatic in the form of acute hepatitis) may evolve into chronic infections (usually asymptomatic), which may further evolve into sequelae (cirrhosis and HCC) that lead to morbidity and mortality. As there can be more than 20–30 years between infection and mortality, viral hepatitis surveillance needs to capture these three phases to fully describe the epidemiological situation. Estimations of current, prevalent infections guide testing and treatment, which would prevent future morbidity and mortality. Current mortality from the sequelae of chronic infections acquired in the past quantifies the baseline burden and evaluates the impact of past interventions. The three components of viral hepatitis surveillance as shown in Table 3, may be implemented by different acts of the public health system. Thus, the programme responsible for viral hepatitis needs to consolidate and triangulate sources of information from these different systems to describe the epidemiological situation of HBV and HCV infection.

TABLE 3

Activities that contribute to surveillance for viral hepatitis

	1. Surveillance for acute hepatitis that reflects new infections	2. Surveillance for chronic, prevalent hepatitis	3. Surveillance for sequelae
Activities	– Syndromic surveillance in the general population – Event-based surveillance – Enhanced case reporting (with in-vitro diagnosis and collection of information on risk factors)	– Regular biomarker surveys	– Combination of data from death certificates, and testing of patients with cirrhosis and HCC for HBV and HCV infection
Population under surveillance	– Persons presenting with acute hepatitis to health-care facilities (discrete onset of symptoms)	– Persons without acute symptoms tested during population surveys	– Persons diagnosed with cirrhosis and HCC
Usual implementer	– Communicable disease surveillance – Communicable disease surveillance (if countrywide) – Hepatitis programme (if sentinel sites)	– Hepatitis programme in coordination with the other actors implementing biomarker surveys	– Vital registration – Sentinel sites caring for patients with cirrhosis and HCC – Cancer registries
Case definitions to use	– Presumptive case of acute hepatitis – Confirmed case of acute hepatitis (by type)	– Chronic HBV and HCV infection – Serological evidence of past or present HCV infection	– Cases of cirrhosis or HCC – Chronic HBV or HCV infection
Objective of the surveillance activity	– Detect outbreaks – Describe trends in type-specific acute hepatitis and identify risk factors	– Estimate the prevalence of infections – Model incidence trends	– Estimate mortality from HBV- or HCV-associated HCC and cirrhosis

HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus

Source : *(30)*

Global Health Sector Strategy on Viral Hepatitis 2022–2030 *(31)*

The key strategic and operational shifts required to eliminate hepatitis B virus and hepatitis C virus as public health threats by 2030 are as follows :

a. Promote greater public and political awareness of the importance of viral hepatitis B and C prevention, testing and treatment

b. Allocate increased financial resources to viral hepatitis B and C, which may include external catalytic funding and domestic funding for viral hepatitis prevention, testing and treatment as part of essential national health benefit packages

c. Scale up universal access to hepatitis B birth-dose vaccines and improved services for testing of pregnant women for preventing the vertical (mother-to-child) transmission of hepatitis B

d. Ensure continued investment in primary prevention, including improved safety of medical injections and procedures, comprehensive prevention including harm reduction and other evidence-based measures for people who inject drugs, and hepatitis B vaccination for infants and at-risk populations

e. Substantially increase access to hepatitis B and hepatitis C testing to reach people living with chronic hepatitis B virus and hepatitis C virus infection, of whom more than 80% and 90%, respectively are currently undiagnosed

f. Substantially increase treatment access by building on existing community and health facility based services

g. Promote simplified service delivery models that include decentralizing hepatitis B and C testing and treatment to lower-level health facilities including primary care; integrating with other services, such as at harm reduction and HIV services; and task-sharing with delivery of care and treatment by non specialists and nurses

h. Address the barriers faced by populations most affected and at-risk

i. Strengthen community and civil society engagement and innovative partnerships

j. Advance the research agenda focusing on developing curative treatment strategies for hepatitis B virus and a preventative vaccine for hepatitis C

Viral hepatitis targets

Table 4 presents impact and programmatic coverage indicators and targets for viral hepatitis *(31)*.

HEPATITIS C

Hepatitis C is a contagious liver disease that results from infection with the hepatitis C virus. It can range in severity from a mild illness lasting a few weeks to a serious, lifelong illness. It is among the most common virus that infect the liver and it has been shown to be a major cause of parenterally transmitted hepatitis.

TABLE 4

Impact and coverage indicators, targets and milestones for viral hepatitis by 2030

	Indicator	Baseline – 2020	Targets – 2025	Targets – 2030
Impact	Hepatitis B surface antigen (HBsAg) prevalence among children younger than 5 years old	0.94%	0.5%	0.1%
	Number of new hepatitis B infections per year	1.5 million new cases 20 per 100 000	850 000 new cases 11 per 100 000	170 000 new cases 2 per 100 000
	Number of new hepatitis C infections per year	1.575 million new cases 20 per 100 000	1 million new cases 13 per 100 000	350 000 new cases 5 per 100 000
	Number of new hepatitis C infections among people who inject drugs, per year	8 per 100	3 per 100	2 per 100
	Number of people dying from hepatitis B per year	820 000 deaths 10 per 100 000	530 000 deaths 7 per 100 000	310 000 deaths 4 per 100 000
	Number of people dying from hepatitis C per year	290 000 deaths 5 per 100 000	240 000 deaths 3 per 100 000	140 000 deaths 2 per 100 000
Coverage	Hepatitis B - percentage of people living with hepatitis B diagnosed / and treated	30%/30%	60%/50%	90%/80%
	Hepatitis C - percentage of people living with hepatitis C diagnosed / and cured	30%/30%	60%/50%	90%/80%
	Percentage of newborns who have benefitted from a timely birth dose of hepatitis vaccine and from other interventions to prevent the vertical (mother-to-child) transmission of hepatitis B virus	50%	70%	90%
	Hepatitis B vaccine coverage among children (third dose)	90%	90%	90%
	Number of needles and syringes distributed per person who inject drugs	200	200	300
	Blood safety - proportion of blood units screened for bloodborne diseases	95%	100%	100%
	Safe injections - proportion of safe health-care injections	95%	100%	100%

Source : *(31)*

Every year, 1.0 million people are infected with the hepatitis C virus. About 110 million people are HCV antibody positive and 50 million are chronically infected and are at risk of developing liver cirrhosis and/or liver cancer. More than 2,42,000 people died from hepatitis C – related liver diseases in 2022 *(22)*. It is estimated that about 2.3 million people were co-infected with HCV and HIV *(32)*.

Transmission

The hepatitis C virus is most commonly transmitted through exposure to infectious blood. This can occur through: (a) receipt of contaminated blood transfusions, blood products and organ transplants; (b) injections given with contaminated syringes and needle-stick injuries in health-care settings; (c) injection drug use; and (d) being born to a hepatitis C-infected mother.

Hepatitis C may be transmitted through sex with an infected person or sharing of personal items contaminated with infectious blood, but these are less common. Hepatitis C is not spread through breast milk, food or water, or by casual contact such as hugging, kissing and sharing food or drinks with an infected person.

Incubation period

The incubation period for hepatitis C is 2 weeks to 6 months.

Symptoms

Following initial infection, approximately 80 per cent of people do not exhibit any symptoms. Those people who are acutely symptomatic may exhibit fever, fatigue, decreased appetite, nausea, vomiting, abdominal pain, dark urine, grey-coloured faeces, joint pain and jaundice. About 15–45 per cent of infected persons spontaneously clear the virus within 6 months of infection without any treatment. The remaining 55–85 per cent of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis of liver is 15–30 per cent within 20 years *(32)*.

Diagnosis *(33)*

Diagnosis of acute infection is often missed because a majority of infected people have no symptoms. Common methods of antibody detection cannot differentiate between acute and chronic infection. The presence of antibodies against the hepatitis C virus indicates that a person is or has been infected. The hepatitis C virus recombinant immunoblot assay (RIBA) and hepatitis C virus RNA testing are used to confirm the diagnosis. Diagnosis of chronic infection is made when antibodies to the hepatitis C virus are present in the blood for more than six months. Similar to acute infections, diagnosis is confirmed with an additional test. Specialized tests are often used to evaluate patients for liver disease, including cirrhosis and liver cancer.

Early diagnosis can prevent health problems that may result from infection and prevent transmission to family members and other close contacts. Some countries recommend screening for people who may be at risk for infection. These include: (a) people who recevied blood, blood products or organs before screening for hepatitis C virus was implemented, or where screening was not yet widespread. (b) current or former injecting drug users (even those who injected drugs once many years ago); (c) people on long-term haemodialysis; (d) health–care workers; (e) people living with HIV; (f) people with abnormal liver tests or liver disease, and (g) infants born to infected mothers; people having invasive procedures in health care facilities with inadequate infection control; people who have had tattoos and piercings; and people with sexual partners who are HCV infected *(32)*.

Treatment *(32)*

Hepatitis C does not always require treatment as the immune response in some people will clear the infection, and some people with chronic infection do not develop liver damage. When treatment is necessary, the goal of hepatitis C treatment is cure. The cure rate depends on several factors including the strain of the virus and the type of treatment given. The standard of care for hepatitis C is changing rapidly. Until recently, hepatitis C treatment was based on therapy with interferon and ribavirin, which required weekly injections for 48 weeks, cured approximately half of treated patients, but caused frequent and sometimes life-threatening adverse reactions. Recently, new antiviral drugs have been developed. These medicines, called direct antiviral agents (DAA) are much more effective, safer and better-tolerated than the older therapies. Therapy with DAAs can cure most persons with HCV infection and treatment is shorter (usually 12 weeks) and safer. Although the production cost of DAAs is low, these medicines remain very expensive in many high- and middle-income countries. The cost of generic version of these medicines are low.

Prevention

Primary prevention

1. Hand hygiene: including surgical hand preparation, hand washing and use of gloves;
2. Safe and appropriate use of health care injections;
3. Safe handling and disposal of sharps and waste;
4. Provision of comprehensive harm-reduction services to people who inject drugs including sterile injecting equipment;
5. Testing of donated blood for hepatitis B and C;
6. Training of health personnel; and
7. Promotion of correct and consistent use of condoms.

Secondary and tertiary prevention

For people infected with the hepatitis C virus, WHO recommends:

- education and counselling on options for care and treatment;
- immunization with the hepatitis A and B vaccines to prevent coinfection from these hepatitis viruses to protect their liver,
- early and appropriate medical management including antiviral therapy if appropriate; and
- regular monitoring for early diagnosis of chronic liver disease.

For a number of technical reasons, the development of a vaccine to prevent HCV infection is unlikely for many years.

The epidemiologic and clinical features of hepatitis A, hepatitis B and hepatitis C are summarized in Table 5.

HEPATITIS E

The infection caused by the hepatitis E virus (HEV) which was discovered in 1980, is essentially a water-borne disease. Formerly termed enterically transmitted hepatitis non–A, non–B (HNANB), HEV is a 29–nm to 32–nm RNA virus with 4 genotypes (type 1, 2, 3 and 4).

TABLE 5

Epidemiologic and clinical features of viral hepatitis types A, B and C

	Viral Hepatitis Type A	Viral Hepatitis Type B	Viral Hepatitis Type C
Incubation period	10–50 days (avg. 25–30)	50–180 days (avg. 60–90)	2 weeks–6 months (avg. 40–120 days)
Principal age distribution	Children[1], young adults	15–29 years[2]	Adults[2]
Seasonal incidence	Throughout the year but tends to peak in autumn	Throughout the year	Throughout the year
Route of infection	Predominantly faecal-oral	Predominantly parenteral	Predominantly parenteral
Occurrence of virus :			
Blood	2 weeks before to ≤ 1 week after jaundice	Months to years	Months to years
Stool	2 weeks before to 2 weeks after jaundice	Absent	Probably absent
Urine	Rare	Absent	Probably absent
Saliva, semen	Rare (saliva)	Frequently present	Unknown
Clinical and laboratory features :			
Onset	Abrupt	Insidious	Insidious
Fever > 38°C (100.4°F)	Common	Less common	Less common
Duration of aminotransferase elevation	1–3 weeks	1–6+ months	1–6+ months
Immunoglobulins (IgM levels)	Elevated	Normal to slightly elevated	Normal to slightly elevated
Complications	Uncommon, no chronicity	Chronicity in 5–10%	Chronicity in 50% or more
Mortality rate (icteric cases)	< 0.5%	< 1–2%	0.5–1%
HBsAg	Absent	Present	Absent
Immunity :			
Homologous	Yes	Yes	?
Heterologous	No	No	No
Duration	Probably lifetime	Probably lifetime	?
Immune globulin intramuscular (IG, gammaglobulin, ISG)	Regularly prevents jaundice	Prevents jaundice only if immunoglobulin is of sufficient potency against HBV	?

[1] Non-icteric hepatitis is common in children.
[2] Among the age group 15-29 years, hepatitis B and C are often associated with drug abuse or promiscuous sexual behaviour. Patients with transfusion-associated HBV or HCV are generally over age 29.

Source : *(5)*

Hepatitis E is found worldwide and different genotypes of the hepatitis E virus determine differences in epidemiology. For example, genotype 1 is usually seen in developing countries and causes community-level outbreaks while genotype 3 is usually seen in the developed countries, and does not cause outbreaks. Hepatitis E prevalence is highest in East and South Asia with genotype 1 most commonly found in India. Countries with limited resources, i.e., limited access to essential water, sanitation, hygiene and health services are frequently affected. In recent years, some of these outbreaks have occurred in areas of conflict and humanitarian emergencies, such as war zones, and in camps for refugees or internally displaced populations. An estimated 20 million infections and 3.3 million acute cases occur annually worldwide. An estimated 44,000 deaths occurred in 2015 *(34)*. Over 60 per cent of all hepatitis E infections and 65 per cent of hepatitis deaths occur in East and South Asia, where seroprevalence rate of 25 per cent are common in some age groups *(35)*.

Transmission

The hepatitis E virus is transmitted mainly through the faecal-oral route, due to faecal contamination of drinking water. Other transmission routes have been identified, which include : (a) food-borne transmission from ingestion of products derived from infected animals; (b) transfusion of infected blood products; and (c) vertical transmission from a pregnant woman to her foetus.

Incubation period

The incubation period following exposure to the hepatitis E virus ranges from three to eight weeks, with a mean of 40 days. The period of communicability is unknown.

Symptoms

Symptomatic infection is more common in young adults aged 15–40 years. Although infection is frequent in children, the disease is mostly asymptomatic or causes a very mild illness without jaundice that goes undiagnosed. The typical symptoms are jaundice, loss of appetite, abdominal pain and tenderness, nausea and vomiting, fever and enlarged and tender liver. The symptoms are largely indistinguishable from those experienced during any acute phase of hepatic illness and last for one or two weeks.

In rare cases, acute hepatitis E can result in fulminant hepatitis (acute liver failure) and death. Fulminant hepatitis occurs more frequently during pregnancy. Pregnant women are at greater risk of obstetrical complications and mortality

from hepatitis E, which can induce a mortality rate of 20 per cent among pregnant women in their third trimester.

Cases of chronic hepatitis E infection have been reported in immunosuppressed people. Reactivation of hepatitis E infection has also been reported in immunocompromised people.

Diagnosis

Cases of hepatitis E are not clinically distinguishable from other types of acute viral hepatitis. Diagnosis of hepatitis E infection is, therefore, usually based on the detection of specific IgM and IgG antibodies to the virus in the blood. Additional tests include reverse transcriptase polymerase chain reaction (RT-PCR) to detect the hepatitis E virus RNA in blood and/or stool, but this assay may require specialized laboratory facilities.

Treatment

Hepatitis E is usually self-limiting. Prevention is the most effective approach against the disease as there is no specific treatment for altering the course of acute hepatitis. Hospitalization is required for fulminant cases and in symptomatic pregnant women. Recovery from disease is always complete. No specific immunoglobulin prophylaxis is available.

Prevention

The risk of infection and transmission can be reduced by maintaining quality standards for public water supplies and establishing proper disposal systems to eliminate sanitary waste. On an individual level, infection risk can be reduced by : (a) maintaining hygienic practices such as hand washing with safe water, particularly before handling food; (b) avoiding drinking water and/or ice of unknown purity; and (c) adhering to WHO safe food practices.

In 2011, the first vaccine to prevent hepatitis E infection was registered in China, although it is not available globally.

HEPATITIS D *(36)*

Hepatitis D is caused by hepatitis D virus that requires HBV for its replication. Hepatitis D cannot occur in the absence of HBV. The coinfection or super infection of HDV with HBV causes a more severe disease than HBV monoinfection.

Geographic distribution

It is estimated that globally, 5% of HBsAg positive people are coinfected with HDV and the distribution is resulting in a total of 15–20 million persons infected with HDV worldwide. High-prevalence areas include the Mediterranean, Middle East, Pakistan, Central and Northern Asia, Japan, Taiwan, Greenland and parts of Africa (mainly the horn of Africa and West Africa), the Amazon Basin and certain areas of the Pacific. Prevalence is low in North America and Northern Europe, South Africa, and Eastern Asia.

Route of transmission

The route of HDV transmission are the same as for HBV: percutaneously or sexually through contact with infected blood or blood products. Vertical transmission is possible but rare. Vaccination against HBV prevents HDV coinfection, and hence expansion of childhood HBV immunization programmes has resulted in a decline in hepatitis D incidence worldwide. However, in some settings, the increase of hepatitis D prevalence has been observed in people who inject drugs, or as a result of migration from areas where HDV is endemic.

Diagnosis

HDV infection is diagnosed by high titres of Immunoglobulin G (IgG) and Immunoglobulin M (IgM) anti-HDV, and confirmed by detection of HDV RNA in serum.

However, HDV diagnostics are not widely available and there is no standardization for HDV RNA assays, which are used for monitoring response to antiviral therapy.

Treatment

There is no specific treatment for acute or chronic HDV infection. Persistent HDV replication is the most important predictor of mortality and the need for antiviral therapy. *Pegylated* interferon alpha is the only drug effective against HDV; antiviral nucleotide analogues for HBV have no or limited effect on HDV replication. The optimal duration of therapy is not well defined, nor how long patients need to be HDV RNA negative after the end of therapy to achieve a sustained virological response. More than 1 year of therapy may be necessary.

The overall rate of sustained virological response remains low, including in children, and most patients relapse after discontinuation of therapy. Liver transplantation may be considered for cases of fulminant hepatitis and end-stage liver disease. New therapeutic agents and strategies are needed, and novel drugs, such as prenylation inhibitor or HBV entry inhibitors, have shown early promise.

Prevention

Prevention and control of HDV infection requires prevention of HBV transmission through hepatitis B immunization, blood safety, injection safety, and harm reduction services. Hepatitis B immunization does not provide protection against HDV for those already HBV infected.

HEPATITIS G

Hepatitis G virus HGV was discovered in 1996. The prevalence of this infection is still not known. A few publications provide information on the association of this infection with blood transfusion in India *(17)*.

The nomenclature and definitions used in the disease are shown in Table 6 (page 267).

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TABLE 6

Nomenclature and definitions of hepatitis viruses, antigens and antibodies

Disease	Component of system	Definition
Hepatitis A	HAV	Hepatitis A virus. Etiologic agent of infectious hepatitis. A *picornavirus*, the prototype of a new genus, *Hepatovirus*.
	Anti-HAV	Antibody to HAV. Detectable at onset of symptoms; lifetime persistence.
	IgM Anti-HAV	IgM class antibody to HAV. Indicates recent infection with hepatitis A; positive up to 4-6 months after infection.
Hepatitis B	HBV	Hepatitis B virus. Etiologic agent of serum hepatitis. A *hepadnavirus*.
	HBsAg	Hepatitis B surface antigen. Surface antigen(s) of HBV detectable in large quantity in serum; several sub-types identified.
	HBeAg	Hepatitis Be antigen. Soluble antigen ; associated with HBV replication, with high titers of HBV in serum, and with infectivity of serum.
	HBcAg	Hepatitis B core antigen.
	Anti-HBs	Antibody to HBsAg. Indicates past infection with and immunity to HBV, presence of passive antibody from HBIG, or immune response from HBV vaccine.
	Anti-HBe	Antibody to HBeAg. Presence in serum of HBsAg carrier suggests lower titer of HBV.
	Anti-HBc	Antibody to HBcAg. Indicates infection with HBV at some undefined time in the past.
	IgM Anti-HBc	IgM class antibody to HBcAg. Indicates recent infection with HBV ; positive for 4-6 months after infection.
Hepatitis C	HCV	Hepatitis C virus, a common etiologic agent of post-transfusion hepatitis. A flavivirus, genus *Hepacivirus*.
	Anti-HCV	Antibody to HCV.
Hepatitis D	HDV	Hepatitis D virus. Etiologic agent of delta hepatitis ; causes infection only in presence of HBV.
	HDAg	Delta antigen (delta-Ag). Detectable in early acute HDV infection.
	Anti-HDV	Antibody to delta-Ag (anti-delta). Indicates past or present infection with HDV.
Hepatitis E	HEV	Hepatitis E virus. Enterically transmitted hepatitis virus. Causes large epidemics in Asia and North Africa ; faecal–oral or waterborne transmission. Perhaps a *calicivirus*.
Hepatitis G	HGV	Hepatitis G virus, a *flavivirus*.
Immune globulins	IG	Immune globulin USP. Contains antibodies to HAV ; no antibodies to HBsAg, HCV, or HIV.
	HBIG	Hepatitis B immune globulin. Contains high titers of antibodies to HBV.

Source : *(5)*

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ACUTE DIARRHOEAL DISEASES

Diarrhoea is defined as the passage of loose, liquid or watery stools. These liquid stools are usually passed more than three times a day. However, it is the recent change in consistency and character of stools rather than the number of stools that is more important.

The term "diarrhoeal diseases" should be considered only as a convenient expression – not as a nosological or epidemiological entity – for a group of diseases in which the predominant symptom is diarrhoea.

CLINICAL TYPES OF DIARRHOEAL DISEASE *(1)*

It is most practical to base treatment of diarrhoea on the clinical type of illness, which can easily be determined. Four clinical types of diarrhoea can be recognized, each reflecting the basic underlying pathology and altered physiology :

(1) *Acute watery diarrhoea* – which lasts several hours to days; the main danger is dehydration, weight loss also occurs if feeding is not continued. The pathogens that usually cause acute diarrhoea include *V. cholerae* or *E. coli* bacteria, as well as rotavirus.

(2) *Acute bloody diarrhoea* – which is also called dysentery – the main dangers are damage of the intestinal mucosa, sepsis and malnutrition; other complications including dehydration, may also occur. It is marked by visible

blood in the stools. (The most common cause of bloody diarrhoea is *shigella*, a bacteria that is also a most common cause of severe cases).

(3) *Persistent diarrhoea* – which lasts 14 days or longer. The main danger is malnutrition and serious non-intestinal infection, dehydration may also occur. Persons with other illness, such as AIDS, are more likely to develop persistent diarrhoea.

(4) *Diarrhoea with severe malnutrition (marasmus and Kwashiorkor)* – The main dangers are severe systemic infection, dehydration, heart failure, and vitamin and mineral deficiency.

Problem statement

Acute diarrhoea is rivalled in importance only by respiratory infection, as a cause of morbidity on a worldwide scale. When the WHO initiated the Diarrhoeal Diseases Control Programme in 1980, approximately 4.6 million children used to die each year of the dehydration caused by diarrhoea. Diarrhoea is still a major killer of children under 5 years of age, although its toll has dropped by a third over the past decade. It kills around 4,43,832 children under 5 years of age and 50,851 children aged 5–9 years *(2)*. It accounts for 8 per cent of all under-five deaths. Most of these deaths occur among children less than 2 years of age *(2)*.

Comparing estimates of the current global burden of diarrhoeal disease with previously published estimates, highlights that the incidence of diarrhoea have not changed much, although overall diarrhoeal mortality has declined. For children aged under 5 years, a median of 3 episodes of diarrhoea occurred per child-year, which is similar to that reported previously. The current estimates in under-five children suggest that there are about 1.7 billion episodes of diarrhoea per year with 123 million clinic visits annually and 9 million hospitalizations worldwide, with a loss of 62 million disability-adjusted life years (DALYs) *(3)*.

In India, acute diarrhoeal disease accounts for about 10 per cent of deaths in under-5 years age group. During the year 2022, about 5.5 million cases with 246 deaths were reported in India *(4)*.

Diarrhoea is a leading cause of death during complex emergencies and natural disasters. Displacement of population into temporary, overcrowded shelters is often associated with polluted water sources, inadequate sanitation, poor hygiene practices, contaminated food and malnutrition – all of which affect the spread and severity of diarrhoea. At the same time, the lack of adequate health services and transport reduces the likelihood of prompt and appropriate treatment of diarrhoea cases.

Diarrhoeal disease causes a heavy economic burden on the health services. Much attention has been given to acute diarrhoeal disease and its management over the last decade, which is dominated by advances in oral rehydration technique and through integrated management of childhood illness. The treatment recommendations reflect a better understanding of what works to reduce child death from diarrhoea, as well as new insights into treatment feasibility. These changes in treatment recommendations and preventive measures have subsequently led to monitorable treatment and diarrhoea prevention indicators. They are as follows *(5)* :

(A) Diarrhoea prevention indicators

(1) Percentage of population using :
   (a) improved drinking water sources (urban, rural, total);
   (b) improved sanitation facilities (urban, rural, total);

(2) Percentage of one year old immunized against measles;

(3) Percentage of children who are :
   - under-weight (moderate and severe) – 0 to 59 months age
   - stunted (moderate and severe) – 0 to 59 months age
   - exclusively breast-fed – 0 to 5 months age
   - breast-fed with complementary food – 6 to 9 months age
   - still breast-feeding – 20 to 23 months age

(4) Vitamin A supplementation coverage rate (per cent full coverage) – 6 to 59 months (India–53%)

(B) Diarrhoea treatment Indicators

Percentage of children under-five years with diarrhoea receiving :

(1) ORT with continuous feeding
(2) ORS packet
(3) Recommended home made fluids
(4) Increased fluids
(5) Continued feeding

(C) Use of oral rehydration therapy

Percentage of children under-five years with diarrhoea receiving oral rehydration therapy (ORS packet or recommended home-made fluids or increased fluids with continued feeding)

(1) Gender – male, female
(2) Residence – Urban, rural
(3) Wealth index quintiles – poorest, second, middle, fourth, richest

Epidemiological determinants

Agent factors

In developing countries, diarrhoea is almost universally infectious in origin. A wide assortment of organisms cause acute diarrhoea, and many of them have been discovered only in recent years such as rotaviruses and campylobacters (Table 1).

TABLE 1
Infections causing diarrhoea

1. Viruses :	3. Others :
Rotaviruses	*Entamoeba histolytica*
Astroviruses	Giardia intestinalis
Adenoviruses	Trichuriasis
Caliciviruses	Cryptosporidium SPP
Coronaviruses	Intestinal worms
Norwalk group viruses	*Cyclospora*
Enteroviruses	
Cytomegalovirus	
2. Bacteria :	
Campylobacter jejuni	
Enterotoxigenic Escherichia coli	
Shigella	
Salmonella	
Vibrio cholerae	
Vibrio parahaemolyticus	
Bacillus cereus	
Staphylococcus aureus	
Clostridium perfringens	
Enterohaemorrhagic E. coli	
Clostridium difficile	
Enteroinvasive E. coli	
Aeromonas	
Yersinia enterocolitica	
Chlamydia	
Neisseria gonorrhoeae	

Source : *(6)*

Until recent years, the identification of pathogens in the stool was only feasible in about 25 per cent of patients with acute diarrhoea. At present, new techniques enable competent laboratories to identify these pathogens in about 75 per cent of cases. The infectious agents most often connected with diarrhoea in young children, in developing countries, are as shown in Table 2.

TABLE 2

Pathogens frequently identified in children with acute diarrhoea in treatment centres in developing countries

Pathogen		% of cases
Viruses	Rotavirus	15–25
Bacteria	Enterotoxigenic *Escherichia coli*	10–20
	Shigella	5–15
	Campylobacter jejuni	10–15
	Vibrio cholerae 01	5–10
	Salmonella (non-typhoid)	1–5
	Enteropathogenic *Escherichia coli*	1–5
Protozoans	*Cryptosporidium*	5–15
No pathogen found	–	20–30

Source : *(7)*

(a) *VIRUSES*

A great many diarrhoeal diseases are caused by viruses (Table 1).

ROTAVIRUSES : The rotavirus, first discovered in 1973, has emerged as the leading cause of severe, dehydrating diarrhoea in children aged <5 years globally, with an estimated more than 25 million out-patient visits and more than 2 million hospitalizations attributable to rotavirus infections each year. In developing countries, three-quarters of children acquire their first episode of rotavirus diarrhoea before the age of 12 months, whereas in developed countries the first episode is frequently delayed until the age of 2–5 years. Severe rotavirus gastroenteritis is largely limited to children aged 6–24 months. Fatal outcomes in children, estimated to be approximately 420,000–494,000 in 2008 *(8)*, occur predominantly in low-income countries. Rotavirus reinfection is common, although the primary infection is usually the most significant clinically. In temperate climates, the incidence of rotavirus gastroenteritis typically peaks during the winter season, whereas in tropical settings rotavirus occurs year round and a marked seasonality may be masked by high background levels *(9)*.

Rotaviruses are shed in very high concentrations ($>10^{12}$ particles/gram) and for many days in the stools and vomit of infected individuals. Transmission occurs primarily by the faecal-oral route, directly from person to person or indirectly *via* contaminated fomites. The universal occurrence of rotavirus infections shows that clean water supplies and good hygiene are unlikely to have a substantial effect on virus transmission *(9)*.

(b) *BACTERIAL CAUSES*

Besides the well-known bacterial causes of enteric infections and diarrhoeal diseases such as *V. cholerae* 01, Salmonella, *Shigella*, enterotoxigenic *E.coli* and *Campylobacter jejuni* are the most frequent cause of diarrhoea. They produce a potent enterotoxin similar to that produced by *V. cholerae*. The less-known pathogens which cause diarrhoea are *Yersinia enterocolitica*, and *V. parahaemolyticus*.

Enterotoxigenic *Escherichia coli* (ETEC) is an important cause of acute watery diarrhoea in adults and children in developing countries causing annually 280–400 million diarrhoeal episodes in children under 5 years of age, and an additional 100 million episodes in children aged 5–14 years. In adults it causes substantial disease (about 400 million cases per year). It is also the most common cause of traveller's diarrhoea. Being responsible for one-third to one-half of all diarrhoeal episodes in travellers to Africa, Asia and Latin America, the illness results in 0.3 to 0.5 million deaths per year mostly in young children *(10)*. ETEC does not invade the bowel mucosa and the diarrhoea it causes is mediated by toxins. There are two ETEC toxins, heat labile (LT) and heat stable (ST). Some strains produce only one type of toxin, some both. The LT toxin is closely related to cholera toxin. ETEC is spread mostly by means of contaminated food and water.

Salmonella cause inflammation of the bowel epithelium; *Vibrio cholerae* O1 do not. Both are endemic diseases in India. In cholera-endemic areas, cholera probably accounts for not more than 5 to 10 per cent of all acute diarrhoeas yearly, and in more than 90 per cent of instances is clinically indistinguishable from other acute diarrhoeas. *Campylobacters* are slim, highly motile, S-shaped, gram-negative rods, formerly classed as vibrios. They are one of the commonest causes of enteritis. They do not seem to produce any toxin. It is not clear how they cause diarrhoea *(11)*.

Shigella accounts for a high percentage of mortality due to diarrhoeal disease. The estimates suggest that it causes about 1 million deaths every year in children aged under-5 years, mostly in the developing countries. In addition about 164.7 million *Shigella* episodes are estimated worldwide, with 69 per cent of all episodes in young children *(12)*. It is a major cause of diarrhoea in India.

(c) *OTHERS*

Amoebiasis, giardiasis and other intestinal parasitic infections are associated with diarrhoea *(13)*. Giardiasis is a recognized cause of diarrhoea. It flourishes in the duodenum and jejunum. The organisms can be present in very large numbers, the lumen of the intestine teeming with them and the epithelial surfaces almost smothered with them *(14)*.

Cryptosporidium is a coccidian parasite that causes diarrhoea in infants, immunodeficient patients, and a variety of domestic animals. In developing countries most episodes of illness occur in the first year of life. Thereafter, infections are usually asymptomatic. Diarrhoea is usually neither severe nor prolonged, except in immunodeficient patients, such as those with severe malnutrition or AIDS. In such individuals cryptosporidium is an important cause of persistent diarrhoea with wasting *(14)*.

The enumeration of the germs causing the enteric infections which lead to acute diarrhoea should not overshadow the fact that diarrhoea may be caused by a parenteral infection (non-digestive origin) and particularly so in younger children. These include ENT infections, respiratory or urinary infections, malaria, bacterial meningitis, or even simple teething *(7)*.

Besides the above causes, malnutrition may lead to certain nutritional diseases such as kwashiorkor, sprue, coeliac disease and pellagra which are all associated with diarrhoea. In the developed countries, the causes of diarrhoea may be slightly different. Diarrhoea in the newborn is unusual and may be due to inborn errors of metabolism such as congenital enzyme deficiencies. It may

also be associated with severe infections like septicaemia or necrotizing enterocolitis *(15)*.

Persistent diarrhoea is one of the main clinical signs of AIDS in the tropics (an episode of diarrhoea lasting more than 30 days, according to the WHO definition of AIDS in children). This is associated with one or several other signs of the disease. Children with measles or who have had measles recently, run a high risk of developing severe or fatal diarrhoea *(7)*.

Reservoir of infection

For some enteric pathogens, man is the principal reservoir and thus most transmission originates from human factors ; examples are enterotoxigenic *E. coli, shigella spp., V. cholerae, Giardia lamblia* and *E. histolytica*. For other enteric pathogens, animals are important reservoirs and transmission originates from both human and animal faeces; examples are *Campylobacter jejuni, Salmonella spp* and *Y. enterocolitica*. For viral agents of diarrhoea, the role of animal reservoirs in human disease remains uncertain.

Host factors

Diarrhoea is most common in children especially those between 6 months and 2 years. Incidence is highest in the age group 6–11 months, when weaning occurs. It reflects the combined effects of declining levels of maternally acquired antibodies, the lack of active immunity in the infant, the introduction of contaminated food, and direct contact with human or animal faeces when the infant starts to crawl. It is also common in babies under 6 months of age fed on cow's milk or infant feeding formulas *(16)*. Diarrhoea is more common in persons with malnutrition. Malnutrition leads to infection and infection to diarrhoea which is a well known vicious circle. Poverty, prematurity, reduced gastric acidity, immunodeficiency, lack of personal and domestic hygiene and incorrect feeding practices are all contributory factors.

Environmental factors

Distinct seasonal patterns of diarrhoea occur in many geographical areas. In temperature climates, bacterial diarrhoea occur more frequently during the warm season, whereas viral diarrhoea, particularly diarrhoea caused by rotavirus peak during the winter. In tropical areas, rotavirus diarrhoea occurs throughout the year, increasing in frequency during the drier, cool months, whereas bacterial diarrhoeas peak during the warmer, rainy season. The incidence of persistent diarrhoea follows the same seasonal patterns as that of acute watery diarrhoea *(14)*.

Mode of transmission

Most of the pathogenic organisms that cause diarrhoea and all the pathogens that are known to be major causes of diarrhoea in many countries, are transmitted primarily or exclusively by the **faecal–oral route**. Faecal–oral transmission may be water-borne; food-borne, or direct transmission which implies an array of other faecal–oral routes such as *via* fingers, or fomites, or dirt which may be ingested by young children *(17)*.

CONTROL OF DIARRHOEAL DISEASES

It is now obvious that many different organisms – some known, probably many unknown – cause diarrhoea. It is also clear that they do not act in the same way to cause diarrhoea. But from an epidemiological point of view, they are considered together because of the common symptom, diarrhoea. It is now firmly established that regardless of the causative agent or the age of the patient, the sheet anchor of treatment is oral rehydration therapy such as the one advocated by WHO/UNICEF.

The Diarrhoeal Diseases Control (DDC) Programme of WHO has since its inception in 1980, advocated several interventional measures to be implemented simultaneously with mutually reinforcing and complementary impacts. These measures centre round the widespread practice of "oral rehydration therapy".

Components of a Diarrhoeal Diseases Control Programme

The intervention measures recommended by WHO *(15)* may be classified as below :

1. *Short-term*
   a. Appropriate clinical management.
2. *Long-term*
   b. Better MCH care practices.
   c. Preventive strategies.
   d. Preventing diarrhoeal epidemics.

a. Appropriate clinical management

(I) ORAL REHYDRATION THERAPY : With introduction of oral rehydration by WHO it is now firmly established that oral rehydration treatment can be safely and successfully used in treating acute diarrhoeas due to all aetiologies, in all age groups, and in all countries. The aim of oral fluid therapy is to prevent dehydration and reduce mortality. It has been the experience of workers at Kolkata that as many as 90–95 per cent of all cases of cholera and acute diarrhoea can be treated by oral fluids alone *(18)*. Oral fluid therapy is based on the observation that glucose given orally enhances the intestinal absorption of salt and water, and is capable of correcting the electrolyte and water deficit.

At first the composition of oral rehydration salt (ORS) recommended by WHO was sodium bicarbonate based. Inclusion of trisodium citrate in place of sodium bicarbonate made the product more stable and it resulted in less stool output especially in high-output diarrhoea as in cholera, probably because of direct effect of trisodium citrate in increasing intestinal absorption of sodium and water.

More recently an improved ORS formulation has been developed which is as safe and effective as the original in preventing and treating diarrhoeal dehydration but also reduced stool output or offers additional clinical benefit or both. It is focussed on reducing the osmolarity of ORS solution to avoid possible adverse effects of hypertonicity on net fluid absorption by reducing the concentration of glucose and sodium chloride in the solution. Decreasing the sodium concentration of ORS solution to 75 mOsm/l improved the efficacy of the ORS regimen for children with acute non-cholera diarrhoea. The need for unscheduled supplemental intravenous therapy in children given the new ORS fell by 33 per cent, the stool output decreased by 20 per cent and vomiting was reduced by 30 per cent. The reduced osmolarity (245 mOsm/l) solution also appears to be as safe and effective as standard ORS for use in children with cholera *(19)*.

Recommended formulation : Because of the improved effectiveness of reduced osmolarity ORS solution, WHO and UNICEF are recommending that countries manufacture and use the following formulation in place of the previously recommended ORS solution. Since January 2004, the new ORS formulation is the only one procured by UNICEF. India was the first country in the world to launch this ORS formulation since June 2004.

Composition of reduced osmolarity ORS

Reduced osmolarity ORS	**grams / litre**
Sodium chloride	2.6
Glucose, anhydrous	13.5
Potassium chloride	1.5
Trisodium citrate, dihydrate	2.9
Total weight	20.5
Reduced osmolarity ORS	**mmol / litre**
Sodium	75
Chloride	65
Glucose, anhydrous	75
Potassium	20
Citrate	10
Total osmolarity	245

Source : *(19)*

Guidelines for assessing dehydration and oral rehydration : The guidelines for assessing dehydration and oral rehydration are given in Tables 3 and 4 *(20, 21)*.

TABLE 3

Assessment of dehydration

	DEHYDRATION	
	Mild	Severe
(1) Patient's appearance	Thirsty; alert, restless	Drowsy; limp, cold, sweaty; may be comatose
(2) Radial pulse	Normal rate and volume	Rapid, feeble, sometimes impalpable
(3) Blood pressure	Normal	Less than 80 mm Hg; may be unrecordable
(4) Skin elasticity	Pinch retracts immediately	Pinch retracts very slowly (more than 2 seconds)
(5) Tongue	Moist	Very dry
(6) Ant. fontanelle	Normal	Very sunken
(7) Urine flow	Normal	Little or none
% body weight loss	4–5%	10% or more
Estimated fluid deficit	40–50 ml/kg	100–110 ml/kg

When obvious signs of dehydration exist, the water deficit is somewhere between 50 and 100 ml per kg of body weight. If the child's weight is known, the amount of ORS solution required for rehydration during the first four hours may be calculated by setting the deficit at approximately 75 ml/kg. If the child's weight is not known, the approximate deficit may be determined on the basis of age, although this procedure is less accurate. The guidelines for oral rehydration are given in Table 4.

TABLE 4

Guidelines for oral rehydration therapy (for all ages) during the first four hours

Age (*)	under 4 months	4–11 months	1–2 yrs.	2–4 yrs.	5–14 yrs.	15 yrs or over
Weight (kg)	under 5	5–7.9	8–10.9	11–15.9	16–29.9	30 or over
ORS solution (ml)	200–400	400–600	600–800	800–1200	1200–2200	2200–4000

(*) The patient's age should only be used if weight is not known. The approximate amount of ORS required in ml. may also be calculated by multiplying the patient's weight (expressed in kg) by 75.

Source : *(1)*

The actual amount given will depend on the patients desire to drink and by surveillance of signs of dehydration, keeping in mind the fact that greater amounts should be given to heavier patients, those with greater signs of dehydration and those who still have watery diarrhoea during rehydration. The general rule is that patients should be given as much ORS solution as they want, and that signs of dehydration should be checked until they subside.

Older children and adults should be given as much water as they want, in addition to the ORS solution.

Mothers should be taught how to administer ORS solution to their children. It is best for a demonstration to be given by a nurse or by a health worker following which the mother feeds the solution to her child under their supervision respecting the following rules :

- for children under age 2 years, give a teaspoon every 1 to 2 minutes, and offer frequent sips out of a cup for older children. Adults may drink as much as they like. Try to give the estimated required amount within a 4–hour period. As a general guide, after each loose stool, give – children under 2 years of age : 50–100 ml (a quarter to half a large cup) of fluid; children aged 2 up to 10 years : 100–200 ml (a half to one large cup); and older children and adults : as much fluid as they want.
- if the child vomits, wait for 10 minutes, then try again, giving the solution slowly – a spoonful every 2 to 3 minutes.
- if the child wants to drink more ORS solution than the estimated amount, and does not vomit, there can be no harm in feeding him/her more. If the child refuses to drink the required amount and signs of dehydration have disappeared, rehydration is completed. The treatment plan for non-dehydrated diarrhoeic children is then resumed.
- if the child is breast-fed, nursing should be pursued during treatment with ORS solution.

The introduction of oral rehydration fluid has not only reduced the cost of treatment, but also made possible treatment of patients in their own homes by primary health workers or relatives of patient. The ingredients required for the preparation of oral fluid are inexpensive and readily available, and the solution can be prepared with ordinary drinking water. The development of oral rehydration therapy is a major breakthrough in the fight against cholera and other diarrhoeal diseases.

Packets of "oral rehydration mixture" are now freely available at all primary health centres, sub-centres, hospitals and chemist shops. The contents of the packet are to be dissolved in one litre of drinking water. The solution should be made fresh daily and used within 24 hours. It should not be boiled or otherwise sterilized.

If the WHO mixture of salts is not available, a simple mixture consisting of table salt (one level teaspoon) and sugar (6 level teaspoon) dissolved in one litre of drinking water may be safely used until the proper mixture is obtained. The earlier the treatment is instituted the better it is for the patient.

Many countries have designated recommended house fluids. Wherever possible these should include at least one fluid that contains salt. Fluids that do not contain salt are water in which a cereal has been cooked e.g. rice water;

unsalted soup, yogurt drinks, green coconut water, weak tea etc. The mothers should be taught to add salt about 3 g/litre to an unsalted drink or soup during diarrhoea. A few fluids are potentially dangerous and should be avoided during diarrhoea. Especially important are drinks sweetened with sugar, which can cause osmotic diarrhoea and hypernatremia. Examples are commercial carbonated beverages, commercial fruit juices and sweetened tea. Other fluids to be avoided are those with stimulant diuretic or purgative effect, e.g. coffee and some medicinal tea or infusions *(1)*.

The infant's usual diet of cereals, vegetables and other foods should be continued during diarrhoea, and increased afterwards. Food should never be withheld and the child's usual food should never be diluted. The aim is to give as much nutrient rich food as the child will accept. Most children with watery diarrhoea regain their appetite after dehydration is corrected, whereas those with bloody diarrhoea often eat poorly until the illness resolves. These children should be encouraged to resume normal feeding as soon as possible.

Please refer to end of Chapter 9, Annexure A for plan A, Plan B and Plan C for the management of dehydration due to diarrhoea.

(II) INTRAVENOUS REHYDRATION

Intravenous infusion is usually required only for the *initial* rehydration of severely dehydrated patients who are in shock or unable to drink. Such patients are best transferred to the nearest hospital or treatment centre.

The solutions recommended by WHO for intravenous infusion are: (a) *Ringer's lactate solution* (also called Hartmann's solution for injection) : It is the best commercially available solution. It supplies adequate concentrations of sodium and potassium and the lactate yields bicarbonate for correction of the acidosis. It can be used to correct dehydration due to acute diarrhoeas of all causes. (b) *Diarrhoea Treatment Solution (DTS):* Also recommended by WHO as an ideal polyelectrolyte solution for intravenous infusion. It contains in one litre, sodium chloride 4 g sodium acetate 6.5 g potassium chloride 1g and glucose 10g *(21)*. It must meet purity and sterility requirements of fluid for injection.

If nothing else is available, *normal saline* can be given because it is often readily available. Normal saline is the poorest fluid because it will not correct the acidosis and will not replace potassium losses. It should be replaced by the above solutions as early as possible. Plain glucose and dextrose solutions should not be used as they provide only water and glucose.

The recommended dose of the IV fluid to be given is 100 ml/kg, divided as follows (Table 5) :

TABLE 5

Treatment plan for rehydration therapy

Age	First give 30 ml/kg in	Then give 70 ml/kg in
Infants (under 12 months)	1 hour	5 hours
Older	30 minutes	2½ hours

The initial rehydration should be fast until an easily palpable pulse is present. Reassess the patient every 1–2 hours. If dehydration is not improving give the IV drip more rapidly. The use of large-bore needle (No.18) will permit rapid infusion. After infusing 1–2 litres of fluid, rehydration should be carried out at a somewhat slower rate until pulse and blood pressure return to normal. When the patient can drink the oral fluids give ORS about 5 ml/kg/hour.

The patient must be examined at intervals during rehydration. After 4–6 hours of satisfactory treatment, all signs of dehydration should have disappeared except that the urine flow may not have yet started. Sometimes if too much rehydration fluid is given, the eyelids become puffy; if this occurs, IV fluid should be stopped. It is most helpful to examine skin elasticity and pulse strength, both of which should be normal. Rehydration must continue until all signs of dehydration have disappeared.

(III) MAINTENANCE THERAPY

After the initial fluid and electrolyte deficit has been corrected (i.e., the signs of dehydration (Table 3) have gone) oral fluid should be used for maintenance therapy. In adults and older children, thirst is an adequate guide for fluid needs; they can be told to drink as much as they want to satisfy their thirst. The guidelines for maintenance therapy are given in Table 6. The general principle is that the oral fluid intake should equal the rate of continuing stool loss, which should be measured. Diarrhoea usually lasts for 1 or 2 days.

TABLE 6

Maintenance therapy

Amount of diarrhoea	Amount of oral fluid
Mild diarrhoea (not more than one stool every 2 hours or longer, or less than 5 ml stool per kg per hour)	100 ml/kg body weight per day until diarrhoea stops
Severe diarrhoea (more than one stool every 2 hours, or more than 5 ml of stool per kg per hour)	Replace stool losses volume for volume; if not measurable give 10–15 ml/kg body weight per hour

(IV) APPROPRIATE FEEDING : Medical profession has reeled for centuries under the mistaken assumption that it is important to "rest the gut" during diarrhoea. The current view is that during episodes of diarrhoea, normal food intake should be promoted as soon as the child whatever its age, is able to eat. This is especially relevant for the exclusively breast-fed infants. Newborn infants with diarrhoea who show little or no signs of dehydration can be treated by breast-feeding alone. Those with moderate or severe dehydration should receive oral rehydration solution. Breast-feeding is continued along with oral rehydration solution given after each liquid stool. Not only breast milk helps the infant to recover from an attack of diarrhoea both in terms of the nutrients it supplies, and its rehydrating effect, but it helps to prevent further infection because it has protective properties.

(V) CHEMOTHERAPY : Unnecessary prescription of antibiotics and other drugs will do more harm than good in the treatment of diarrhoea. Antibiotics should be considered where the cause of diarrhoea has been clearly identified as shigella, typhoid or cholera. The symptomatic differential diagnosis of *shigella* and cholera are as shown in Table 7.

TABLE 7

Symptomatic differential diagnosis of *shigella* and cholera

Symptoms	Cholera	*Shigella*
Diarrhoea	Acute watery diarrhoea	Acute bloody diarrhoea
Fever	No	Yes
Abdominal cramps	Yes	Yes
Vomiting	Yes	No
Rectal pain	No	Yes
Stool	> 3 loose stools per day, watery like rice water	> 3 stools per day, with blood or pus

For diarrhoea due to cholera the drug of choice is doxycycline, tetracycline, TMP-SMX and erythromycin. For diarrhoea due to *shigella*, the drug of choice is ciprofloxacin as *shigella* is usually resistant to ampicillin and TMP-SMX.

The medicines that should not be used in the treatment of diarrhoea are as follows *(16)* :

- neomycin (damages the intestinal mucosa and can cause malabsorption);
- purgatives (worsen diarrhoea and dehydration);
- tincture of opium or atropine (dangerous for children and dysentery patients because of decreased intestinal transit time);
- cardiotonics such as Coramine; shock in diarrhoea must be corrected by intravenous fluids and not by drugs;
- steroids (expensive, useless, and may cause adverse effects);
- oxygen (expensive, unnecessary);
- charcoal, kaolin, pectin, bismuth (no value);
- mexaform (no value and can be dangerous).

(VI) ZINC SUPPLEMENTATION : When a zinc supplement is given during an episode of acute diarrhoea, it reduces the episode's duration and severity. In addition, zinc supplements given for 10 to 14 days lower the incidence of diarrhoea in the following 2 to 3 months. WHO and UNICEF therefore recommend daily 10 mg of zinc for infants under 6 months of age, and 20 mg for children older than 6 months for 10–14 days *(19)*.

b. Better MCH care practices

(a) MATERNAL NUTRITION : Improving prenatal nutrition will reduce the low birth weight problem. Prenatal and postnatal nutrition will improve the quality of breast milk.

(b) CHILD NUTRITION : *(i) Promotion of breast-feeding :* Any measures to promote breast-feeding are likely to reduce the diarrhoeal diseases in infants. The breast-fed child is at very much less risk of severe diarrhoea and death than the bottlefed child. Promotion of breast-feeding should include strong efforts to limit the use of commercial and artificial formulas. Breast-feeding should be continued as long as possible. *(ii) Appropriate weaning practices :* Poor weaning practices are a major risk factor for diarrhoea. The child should be weaned neither too soon, nor too late, in any case not earlier than the sixth month of life using nutritious and locally available foods, and the foods should be hygienically prepared and given. *(iii) Supplementary feeding :* This is necessary to improve the nutritional status of children aged 6–59 months. As soon as the supplementary food is introduced, the child enters the high-risk category. *(iv) Vitamin A supplementation :* Vitamin A supplementation is a critical preventive measure, and studies have shown mortality reductions ranging from 19 per cent to 54 per cent in children receiving supplements. This reduction is associated in large part with decline in deaths due to diarrhoeal diseases and measles. It also reduces the duration, severity and complications associated with diarrhoea *(2)*.

c. Preventive strategies

(i) SANITATION : Measures to reduce transmission emphasize the traditional improved water supply, improved excreta disposal and improved domestic and food hygiene. Without an adequate supply of clean water close to their homes, it is extremely difficult to promote personal and domestic hygiene. Simple hygienic measures like hand washing with soap before preparing food, before eating, before feeding a child, after defecation, after cleaning a child who has defecated, and after disposing off a child's stool should be promoted. All families should have a clean and functioning latrine. The latrine should be kept clean by regular washing of dirty surface. If there is no latrine, family members should defecate at a distance from the house, paths or areas where children play and at least 10 metres away from the water supply source. It should be recognized that in many communities, young children are often permitted to defecate indiscriminately. Because diarrhoea attack rates are higher among children, it is the defecation in this age group that deserves the most attention. Contaminated foods of all sorts have been identified as major vehicles for the transmission of faecal pathogens during early infancy, e.g., diluted milk, cereal gruels, etc. Delays in consumption add to the problem.

(ii) HEALTH EDUCATION : Environmental sanitation measures require educational support, to ensure their proper use and maintenance of such facilities. An important part of health worker's job is to help prevent diarrhoea by convincing and helping community members to adopt and maintain certain preventive practices such as breast-feeding, improved weaning, clean drinking water, use of plenty of water for hygiene, use of latrine, proper disposal of stools of young children etc.

(iii) IMMUNIZATION : Immunization against measles is a potential intervention for diarrhoea control. When administered at the recommended age, the measles vaccine can prevent upto 25 per cent of diarrhoeal deaths in children under 5 years of age.

The protect, prevent and treat framework of integrated global action plan for prevention and control of pneumonia and diarrhoea is summarized in Fig. 1.

Rotavirus vaccine *(9)*

Two live, oral, attenuated rotavirus vaccines were licensed in 2006 : the monovalent human rotavirus vaccine (Rotarix™) and the pentavalent bovine-human, reassortant vaccine (Rota Teq™). Both vaccines have demonstrated very good safety and efficacy profiles in large clinical trials. The rotavirus vaccines are now introduced for routine use in a number of industrialized and developing countries.

The Rotarix™ vaccine is administered orally in a 2-dose schedule to infants of approximately 2 and 4 months of age. The first dose can already be administered at the age of

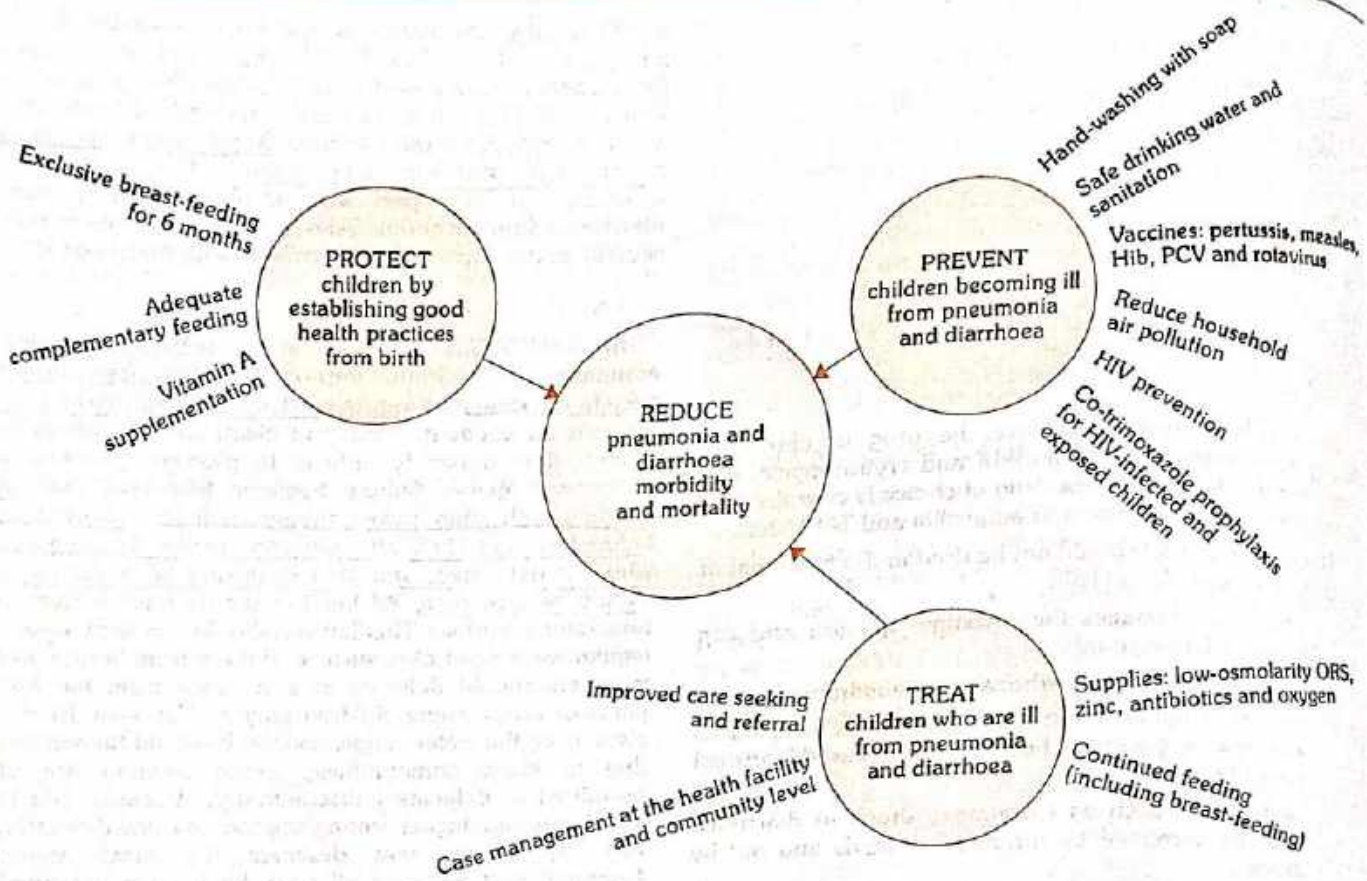

FIG. 1

Integrated global action plan for the prevention and control of pneumonia and diarrhoea

Source: *(2)*

6 weeks and should be given no later than at the age of 12 weeks. The interval between the 2 doses should be at least 4 weeks. The 2-dose schedule should be completed by age 16 weeks, and no later than by 24 weeks of age.

For RotaTeq™, the recommended schedule is 3 oral doses at ages 2, 4 and 6 months. The first dose should be administered between ages 6–12 weeks and subsequent doses at intervals of 4–10 weeks. Vaccination should not be initiated for infants aged >12 weeks. All 3 doses should be administered before the age of 32 weeks.

There is a potentially higher risk of intussusception when the first dose of these vaccines is given to infants aged >12 weeks; consequently, current rotavirus vaccines should not be used in catch-up vaccination campaigns, where the exact age of the vaccinees may be difficult to ascertain.

(iv) FLY CONTROL : Flies breeding in association with human or animal faeces should be controlled.

d. Control and/or prevention of diarrhoeal epidemics

This requires strengthening of epidemiological surveillance systems.

e. The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD)

Please refer to page 190 for details.

PRIMARY HEALTH CARE

The concept of primary health care involves the delivery of a package of curative and preventive services at the community level. An intersectoral approach centred upon primary health care involving activities in the fields of water supply and excreta disposal, communicable disease control, mother and child health, nutrition and health education is regarded as essential for the ultimate control of diarrhoeal diseases.

Diarrhoeal Diseases Control Programme in India

The Diarrhoeal Disease Control Programme was started in 1978 with the objective of reducing the mortality and morbidity due to diarrhoeal diseases. Since 1985–86, with the inception of the National Oral Rehydration Therapy Programme, the focus of activities has been on strengthening case management of diarrhoea for children under the age of 5 years and improving maternal knowledge related to use of home available fluids, use of ORS and continued feeding. For details, refer to chapter 7 and 11.

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CHOLERA

Cholera is an acute diarrhoeal disease caused by *V. Cholerae* O1 (classical or El Tor) and O139. It is now commonly due to the El Tor biotype and O139. Cases range from symptomless to severe infections. The majority of infections are mild or asymptomatic. Typical cases are characterized by the sudden onset of profuse, effortless, watery diarrhoea followed by vomiting, rapid dehydration, muscular cramps and suppression of urine. Unless there is rapid replacement of fluid and electrolytes, the case fatality may be as high as 30 to 40 per cent.

Problem statement

The number of cholera cases reported to WHO continues to rise. For 2022 alone, a total of 4,72,697 cases were notified from 44 countries, including 2,349 deaths. The case fatality rate was 0.5 per cent *(1)*. Many more cases were unaccounted for due to limitations in surveillance systems and fear of trade and travel sanctions. The true burden of the disease is estimated to be 1.3–4.0 million cases and 21,000–143,000 deaths annually *(2)*.

Two serogroups of *V. cholerae* – O1 and O139 – cause outbreaks. *V. cholerae* O1 causes the majority of outbreaks, while O139 – first identified in Bangladesh in 1992 – is confined to South–East Asia. Non–O1 and non–O139 *V. cholerae* can cause mild diarrhoea but do not generate epidemics. Recently, new El Tor variant strains have been detected in several parts of Asia and Africa. Observations suggest that these strains cause more severe cholera with higher case fatality rates. Careful epidemiological monitoring of circulating strains is recommended *(3)*.

Recent studies indicate that global warming creates a favourable environment for the bacteria.

Cholera transmission is closely linked to inadequate environmental management. Typical at-risk areas include peri-urban slums, where basic infrastructure is not available and in areas, where as a consequence of a disaster, disruption of water and sanitation system takes place, or the displacement of population to inadequate and overcrowded camps. Risk of cholera transmission increases, should the bacteria be present or introduced. Epidemics have never arisen from dead bodies *(3)*.

Cholera remains a global threat to public health and a key indicator of lack of social development.

The dynamics of cholera occurrences since 2005, combined with the emergence of new strains that lead to a more severe clinical presentation; increased antimicrobial resistance and climate change, suggest that cholera may well return to the forefront of the global public health agenda *(4)*.

INDIA

Since the introduction of Cholera El Tor biotype in 1964, the geographic distribution of cholera in India has considerably changed. West Bengal has lost its reputation as the "home" of cholera. Many of the States which never had cholera or were free from it for a long time, got infected and became endemic foci of El Tor infection. In several of the recently invaded areas, the disease is seen persisting as a smouldering infection. The classical severe epidemics with high mortality are now uncommon. Explosive outbreaks, particularly following large fairs and festivals are also now rare.

The bacteriology of cholera also presents a changed picture. For reasons that are not known, there has been no large scale epidemic of classical cholera since 1964. In short, the El Tor biotype of *V. Cholerae* O1 has rapidly replaced the classical biotype in all parts of the country. Most of the El Tor biotype isolated today belong to the serotype Ogawa.

During 2022, about 1,707 cholera cases were reported in India with 4 deaths. Majority of the cases were reported from Delhi (852) followed by Jharkhand (364), Punjab (144), Odisha (110) and Gujarat (96 with 4 deaths) *(5)*.

Epidemiological features

Cholera is both an epidemic and endemic disease. The epidemicity and endemicity of a disease will depend on the *characteristics* of the agent, and those of the *system* (environment). Characteristics of the agent which influence its distribution include its ability to survive in a given environment, its virulence, the average number of organisms required to cause infection, etc. Characteristics of the system which affect the distribution of the agent include the number of susceptibles, and the opportunities it provides for transmission of the infection. Global experience has shown that the introduction of cholera into any country cannot be prevented, but cholera can create a problem only in areas where sanitation is defective.

Epidemics of cholera are characteristically abrupt and often create an acute public health problem. They have a high potential to spread fast and cause deaths. The epidemic reaches a peak and subsides gradually as the "force of infection" declines. Often–times, by the time control measures are instituted the epidemic has already reached its peak and is waning. Thus, cholera epidemic in a community is self–limiting. This is attributed to the acquisition of temporary immunity, as well as due to the occurrence of a large number of subclinical cases.

The "force of infection" is composed of 2 components, namely the force of infection through water and the force of infection through contacts *(6)*. It is well-known that the elimination of contaminated water does not immediately bring an outbreak to an end, but a so-called "tail" of the epidemic is produced. This is due to the continuation of transmission through contacts *(6)*.

In areas where cholera is endemic, it does not show a stable endemicity like typhoid fever *(6)*. It undergoes seasonal fluctuations as well as epidemic outbreaks. The seasonal variation differs between countries and even between regions of the same country. The seasonal incidence is also subject to change. For example, the disease used to be most common in the summer in Kolkata and in the early winter in Bangladesh; now in both places, it is most frequent in the autumn *(7)*. In some parts of India, the peak incidence is in August.

The El Tor biotype, wherever it has spread, has become endemic with periodic outbreaks. It appears to have greater "endemic tendency" than its classical counterpart in that it causes a higher infection–to–case ratio (i.e., inapparent infections and mild cases).

Cholera occurs at intervals even in endemic areas. A question that is frequently asked is about the fate of *V. cholerae* in the inter–epidemic periods. Three explanations are offered : (a) the existence of long-term carriers *(8)*; (b) the existence of diminished but continuous transmission involving asymptomatic cases *(9)*, and (c) the persistence of the organism in a free–living, perhaps altered form in the environment *(10, 11)*. The existence of a free–living cycle may explain why cholera became endemic for varying periods in certain areas after introduction of the current pandemic strains *(10, 11)*. Atypical non-toxigenic *V. cholerae* O1 of the El Tor biotype have sometimes been found in surface waters in endemic and non-endemic areas without any related human infection or disease *(12)*. A question of considerable epidemiological significance is whether "transmission" of somatic antigen can occur in the natural environment, i.e., can non–O1 *V. cholerae* become *V. cholerae* O1 *(13)*. Such "transformation" has been claimed by many workers *(14)*.

Epidemiological determinants

Agent factors

(a) AGENT : The organism that causes cholera is labelled as *V. cholerae* O Group 1 or *Vibrio cholerae* O1 and O139. The term "epidemic strain" has also been used for these vibrios. Vibrios that are biochemically similar to the epidemic strains (*V. cholerae* O1 and O139) but do not agglutinate in *V. cholerae* O1 and O139 antiserum have been referred to in the past as non–agglutinating (NAG) vibrios or as non–cholera vibrios (NCV). These are now included in the species *V. cholerae* and are referred to as non–O Group 1V/ O139 *cholerae* (non-epidemic strains). It is now recognized that the NCV/NAG vibrios include some species that are pathogenic for humans (e.g., *Vibrio parahaemolyticus*) which have caused outbreaks of cholera-like diarrhoea. It is, therefore, necessary to identify *V. cholerae* O1 and O139 for specific diagnosis of cholera. Within the O–Group 1, two biotypes – classical and El Tor, have been differentiated. It may be mentioned that the El Tor biotype was first isolated at the El Tor quarantine station in Egypt in 1905. Cholera is now caused mostly by the El Tor biotype and O139. Classical and El Tor vibrios are further divided each into 3 serological types namely Inaba, Ogawa and Hikojima. Most of the El Tor vibrios isolated in India belong to the Ogawa serotype. The El Tor biotype which are known for their haemolytic property, lost this property as the pandemic progressed. They may be distinguished from classical vibrios by the following tests :

(1) El Tor vibrio agglutinate chicken and sheep erythrocytes
(2) they are resistant to classical phage IV
(3) they are resistant to polymyxin B–50–unit disc, and
(4) the VP reaction and haemolytic test do not give consistent results.

(b) RESISTANCE : *V. cholerae* are killed within 30 minutes by heating at 56 deg.C or within a few seconds by boiling. They remain in ice for 4–6 weeks or longer. Drying and sunshine will kill them in a few hours. They are easily destroyed by coal tar disinfectants such as cresol. Bleaching powder is another good disinfectant which kills vibrios instantly at 6 mg/litre. The El Tor biotype tends to be more resistant than do classical vibrios. (c) TOXIN PRODUCTION : The vibrios multiply in the lumen of the small intestine and produce an exotoxin (enterotoxin). This toxin produces diarrhoea through its effect on the adenylate cyclase–cyclic AMP system of mucosal cells of the small intestine. The exotoxin has no effect on any other tissue except the intestinal epithelial cells. (d) RESERVOIR OF INFECTION : The human being is the only known reservoir of cholera infection. He may be a case or carrier. *(i) Cases :* Cases range from inapparent infections to severe ones. About 75 per cent of people infected with *V. cholerae* do not develop any symptoms, although the bacteria are present in their faeces for 7–14 days after infection and are shed back into the environment, potentially infecting other people. Among people who develop symptoms, about 20 per cent develop acute watery diarrhoea with severe dehydration. People with low immunity, e.g., malnourished children and people living with HIV are at a greater risk of death if infected *(2)*. It is the mild and asymptomatic cases that play a significant role in maintaining endemic reservoir. *(ii) Carriers :* The carriers are usually temporary, rarely chronic. They also make an important contribution to the reservoir of infection. Since carriers excrete fewer vibrios than clinical cases, carriers are best detected by bacteriological examination of the purged stool induced by the administration of 30–60 gram of magnesium sulphate in 100 ml of water by mouth. (e) INFECTIVE MATERIAL : The immediate sources of infection are the stools and vomit of cases and carriers. Large numbers of vibrios (about 10^7–10^9 vibrios per ml of fluid) are present in the watery stools of cholera patients; and an average patient excretes 10–20 litres of fluid. Carriers excrete fewer vibrios than cases, 10^2–10^5 vibrios per gram of stools. (f) INFECTIVE DOSE : Cholera is dose–related. Infection occurs when the number of vibrios ingested exceeds the dose that is infective for the individual. Experimental work suggests that in the normal person a very high dose–something like 10^{11} organisms – is required to produce the clinical disease *(15)*. (g) PERIOD OF COMMUNICABILITY : A case of cholera is infectious for a period of 7–10 days. Convalescent carriers are infectious for 2–3 weeks. The chronic carrier state may last from a month up to 10 years or more.

Carriers in cholera *(16)*

A cholera carrier may be defined as an apparently healthy person who is excreting *V. cholerae* O1 (classical or El Tor) in stools. Four types of cholera carriers have been described *(17)* : (a) PRECLINICAL OR INCUBATORY CARRIERS : Since the incubation period of cholera is short (1–5 days), incubatory carriage is of short duration. The incubatory carriers are potential patients. (b) CONVALESCENT CARRIER : The patient who has

recovered from an attack of cholera may continue to excrete vibrios, during his convalescence for 2–3 weeks. Convalescent state has been found to occur in patients who have not received effective antibiotic treatment. The convalescent carriers can often become chronic or long-term carriers. (c) CONTACT OR HEALTHY CARRIER : This is the result of subclinical infection contracted through association with a source of infection, be it a case or infected environment. The duration of contact carrier state is usually less than 10 days; the gall bladder is not infected, and the stool culture is frequently positive for *V. cholerae* O1. Contact carriers probably play an important role in the spread of cholera. (d) CHRONIC CARRIER : A chronic carrier state occurs infrequently. The longest carrier state was found to be over 10 years *(17)*. Studies indicate that gall bladder is infected in chronic carriers. Since carriers excrete fewer vibrios than cases, selective media and proper enrichment are important for their diagnosis. In carriers, the antibody titre against *V. cholerae* O1 rises and remains positive as long as the person harbours the organism. This method may be used to detect long-term carriers along with bacteriological examination of stools.

Host factors

(a) AGE AND SEX : Cholera affects all ages and both sexes. In endemic areas, attack rate is highest in children. (b) GASTRIC ACIDITY : An effective barrier. The vibrio is destroyed in an acidity of pH 5 or lower. Conditions that reduce gastric acidity may influence individual susceptibility *(20)*. (c) POPULATION MOBILITY : Movement of population (e.g., pilgrimages, marriages, fairs and festivals) results in increased risk of exposure to infection. In this jet age, cases and carriers can easily transfer infection to other countries. (d) ECONOMIC STATUS : The incidence of cholera tends to be the highest in the lower socio-economic groups, and this is attributable mainly to poor hygiene. (e) IMMUNITY : An attack of cholera is followed by immunity to reinfection, but the duration and degree of immunity are not known. In experimental animals specific IgA antibodies occur in the lumen of the intestine. Similar antibodies in serum develop after the infection but only last a few months. Vibriocidal antibodies in serum (titer ≥ 1:20) have been associated with protection against colonization and disease. The presence of antitoxin antibodies has not been associated with protection *(18)*. Vaccination gives only temporary, partial immunity for 3–6 months.

Environmental factors

Vibrio transmission is readily possible in a community with poor environmental sanitation. The environmental factors of importance include contaminated water and food. Flies may carry *V. cholerae* but not vectors of proven importance. Numerous social factors have also been responsible for the endemicity of cholera in India. These comprise certain human habits favouring water and soil pollution, low standards of personal hygiene, lack of education and poor quality of life.

Mode of transmission

Transmission occurs from man to man *via* (a) FAECALLY CONTAMINATED WATER : Uncontrolled water sources such as wells, lakes, ponds, streams and rivers pose a great threat. (b) CONTAMINATED FOOD AND DRINKS : Ingestion of contaminated food and drinks have been associated with outbreaks of cholera. Bottle feeding could be a significant risk factor for infants. Fruits and vegetables washed with contaminated water can be a source of infection. After preparation, cooked food may be contaminated through contaminated hands and flies. There is growing opinion that El Tor cholera may in some instances be transmitted through a complex interaction of contaminated food, water and environment rather than through public drinking water supplies *(19)*. (c) DIRECT CONTACT : In developing countries, a considerable proportion of cases may result from secondary transmission, i.e., person to person transmission through contaminated fingers while carelessly handling excreta and vomit of patients and contaminated linen and fomites.

Incubation period

From a few hours upto 5 days, but commonly 1–2 days.

Pathogenesis

The main symptom of cholera is diarrhoea. Diarrhoea in cholera was attributed in the past to such factors as increased permeability of the intestinal epithelial cells, increased peristalsis, mucosal damage, an increase in mesenteric blood flow and failure of the "sodium pump", i.e., interference with the passage of sodium from the lumen to the plasma. None of these theories stood the test of time *(20)*.

According to current concepts, the cholera vibrio get through the mucus which overlies the intestinal epithelium. It probably secretes mucinase, which helps it move rapidly through the mucus. Then it gets attached or *adhered* to the intestinal epithelial cells, and this it probably does by an adherence factor on its surface. When the vibrio becomes *adherent* to the mucosa, it produces its enterotoxin which consists of 2 parts – the light or L toxin and the heavy or H toxin. The L toxin combines with substances in the epithelial cell membrane called *gangliosides* and this binds the vibrio to the cell wall. Binding is irreversible. The mode of action of H toxin is not fully clear. What we know is that there is a substance called "adenyl cyclase" in the intestinal epithelial cells, and H toxin activates this substance. The activated adenyl cyclase causes a rise in another substance, called 3, 5–adenosine monophosphate, better known as cyclic or cAMP (A physiologist got Noble Prize for describing this substance). cAMP provides energy which drives fluid and ions into the lumen of the intestine. This fluid is isotonic and is secreted by all segments of small intestine. The increase in fluid is the cause of diarrhoea, and not increased peristalsis. There is no evidence that *V. cholerae* invades any tissue, nor the enterotoxin to have any direct effect on any organ other than the small intestine *(20)*.

Clinical features

The severity of cholera is dependent on the rapidity and duration of fluid loss. Epidemiological studies have shown that more than 90 per cent of El Tor cholera cases are mild and clinically indistinguishable from other acute diarrhoeas *(21)*. However, a typical case of cholera shows 3 stages : (a) STAGE OF EVACUATION : The onset is abrupt with profuse, painless, watery diarrhoea followed by vomiting. The patient may pass as many as 40 stools in a day. The stools may have a "rice water" appearance. (b) STAGE OF COLLAPSE : The patient soon passes into a stage of collapse because of dehydration. The classical signs are : sunken eyes, hollow cheeks, scaphoid abdomen, sub–normal temperature, washerman's hands and feet, absent pulse, unrecordable blood pressure, loss of skin elasticity, shallow and quick respirations. The output of urine

decreases and may ultimately cease. The patient becomes restless, and complains of intense thirst and cramps in legs and abdomen. Death may occur at this stage, due to dehydration and acidosis resulting from diarrhoea. (c) STAGE OF RECOVERY : If death does not occur, the patient begins to show signs of clinical improvement. The blood pressure begins to rise, the temperature returns to normal, and urine secretion is re-established. If anuria persists, the patient may die of renal failure. The classical form of severe cholera occurs in only 5–10 per cent of cases. In the rest, the disease tends to be mild characterized by diarrhoea with or without vomiting or marked dehydration. As a rule, mild cases recover in 1–3 days.

Epidemiologically, cholera due to El Tor biotype differs from classical cholera in the following respects : (a) a higher incidence of mild and asymptomatic infection. This implies that the characteristic picture of rice–water stools and other signs of classical cholera described above may not be seen often; (b) fewer secondary cases in the affected families; (c) occurrence of chronic carriers, and (d) since El Tor vibrios are more resistant than classical cholera vibrios, they survive longer in the extra–intestinal environment.

Laboratory diagnosis of cholera *(22)*

The diagnosis of cholera can never be made with certainty on clinical grounds. Laboratory methods of diagnosis are required to confirm the diagnosis : (a) COLLECTION OF STOOLS : A fresh specimen of stool should be collected for laboratory examination. Sample should be collected before the person is treated with antibiotics. Collection may be made generally in one of the following ways : *(i) Rubber catheter :* Collection by the catheter is the best method but is complicated under field conditions. Soft rubber catheter (No.26–28) sterilized by boiling should be used. The catheter is introduced (after lubrication with liquid paraffin) for at least 4–5 cm into the rectum. The specimen voided may be collected directly into a transport (holding) media, e.g., Venkatraman–Ramakrishnan (VR) medium, alkaline peptone water. *(ii) Rectal swab :* Swabs consisting of 15–20 cm long wooden sticks, with one end wrapped with absorbent cotton, sterilized by autoclaving have been found to be satisfactory. Rectal swabs should be dipped into the holding medium before being introduced into the rectum. (iii) If no transport medium is available, a cotton–tipped rectal swab should be soaked in the liquid stool, placed in a sterile plastic bag, tightly sealed and sent to the testing laboratory *(23)*. (b) VOMITUS : This is practically never used as the chances of isolating vibrios are much less and there is no advantage. (c) WATER : Samples containing 1–3 litres of suspect water should be collected in sterile bottles (for the filter method), or 9 volumes of the sample water added to 1 volume of 10 per cent peptone water, and despatched to the laboratory by the quickest method of transport. (d) FOOD SAMPLES : Samples of food suspected to be contaminated with *V. cholerae* (or other enteric bacteria) amounting to 1 to 3 g are collected in transport media and sent to the laboratory. (e) TRANSPORTATION : (i) The stools should be transported in sterilized McCartney bottles, 30 ml capacity containing alkaline peptone water or VR medium. VR medium can be used if larger stool specimens can be collected. The specimen should be transported in alkaline peptone water or Cary–Blair medium if it is collected by a rectal swab. One gram or one ml of faeces in 10 ml of the holding medium will suffice. Rectal swabs should have their tops broken off so that caps of the containers can be replaced (ii) If suitable plating media are available (e.g., bile salt agar) at the bed-side, the stools should be streaked on to the media and forwarded to the laboratory with the transport media. (f) DIRECT EXAMINATION : If a microscope with dark field illumination is available, it may be possible to diagnose about 80 per cent of the cases within a few minutes, and more cases after 5–6 hours of incubation in alkaline peptone water. In the dark field, the vibrios evoke the image of many shooting stars in a dark sky. If motility ceases on mixing with polyvalent anti–cholera diagnostic serum, the organisms are presumed to be cholera vibrios. A presumptive diagnosis of cholera can thus be established. (g) CULTURE METHODS : On arrival at the laboratory, the specimen in holding fluid is well shaken, and about 0.5 to 1.0 ml of material is inoculated into Peptone Water Tellurite (PWT) medium for enrichment. After 4 to 6 hours incubation at 37 deg. C, a loopful of the culture from the surface is subcultured on Bile Salt Agar medium (BSA, pH 8.6). After overnight incubation, the plates are screened under oblique light illumination for vibrio colonies. (h) CHARACTERIZATION : *V. cholerae* usually appears on bile salt agar (BSA) as translucent, moist, raised, smooth and easily emulsifiable colonies about 1 mm in diameter. The typical colonies are picked up and tested as follows : *(i) Gram's stain and motility :* Gram negative and curved rods with characteristic scintillating type of movement in hanging drop preparations are very characteristic of *V. cholerae* *(ii) Serological test:* Slide agglutination test is done by picking up suspected colonies and making a homogeneous suspension in 0.85 per cent sterile saline and adding one drop of polyvalent anti–cholera diagnostic serum. If agglutination is positive, the test is repeated with *Inaba* and *Ogawa* antisera, to determine the subtype. (i) BIOCHEMICAL TESTS : Serologically positive colonies should be subcultured in one tube each of the sugar broths (mannose, sucrose, arabinose) and a tube of peptone water pH 7.2 for the cholera red reaction. Production of acid in sucrose and mannose, but not arabinose is characteristic of *V. cholerae*. (j) FURTHER CHARACTERIZATION : For further characterization of biotypes of *V. cholerae* organisms are identified by slide agglutination tests using anti–O1 or group 139 antisera and by biochemical reaction patterns.

Suspicious colonies that do not agglutinate with anticholera sera are tested further by the oxidase and string tests *(20)*.

CONTROL OF CHOLERA

It is now considered that the best way to control cholera is to develop and implement a national programme for the control of ALL diarrhoeal diseases because of similarities in the epidemiology, pathophysiology, treatment and control of cholera and other acute diarrhoeal diseases *(24)*. The following account is based on the "Guidelines for Cholera Control" proposed by the WHO *(12)*.

1. Verification of the diagnosis

It is important to have confirmation of the outbreak as quickly as possible. All cases of diarrhoea should be investigated even on the slightest suspicion. For the specific diagnosis of cholera, it is important to identify *V. cholerae* O1 in the stools of the patient. Once the presence of cholera has been proved, it is not necessary to culture stools of all cases or contacts. Bacteriological diagnosis of cholera envisages a well–organized system of laboratory services in the community. The diagnosis of cholera under field conditions has been reported to be facilitated by a sensitive and specific immunochromatographic dipstick test *(19A)*.

2. Notification

Cholera is a notifiable disease locally and nationally. Since 2005 cholera notification is no longer mandatory internationally. Health workers at all levels (particularly those who are closest to the community such as the community health workers and the multi-purpose workers) should be trained to identify and notify cases immediately to the local health authority. Under the International Health Regulations, cholera is notifiable to the WHO within 24 hours of its occurrence by the National Government; the number of cases and deaths are also to be reported daily and weekly till the area is declared free of cholera. An area is declared free of cholera when twice the incubation period (i.e., 10 days) has elapsed since the death, recovery or isolation of the last case *(25)*.

3. Early case-finding

An aggressive search for cases (mild, moderate, severe) should be made in the community to be able to initiate prompt treatment. Early detection of cases also permits the detection of infected household contacts and helps the epidemiologist in investigating the means of spread for deciding on specific intervention.

4. Establishment of treatment centres

In the control of cholera, no time should be lost in providing treatment for the patients. To achieve this objective, it is necessary to establish easily accessible treatment facilities in the community.

The *mildly dehydrated* patients (which account for over 90 per cent of cases) should be treated at home with oral rehydration fluid. *Severely dehydrated* patients, requiring intravenous fluids, should be transferred to the nearest treatment centre or hospital; if possible, they should receive oral rehydration on the way to the hospital or treatment centre. If there is no hospital or treatment centre within a convenient distance, a local school or public building should be taken over and converted into a temporary treatment centre, as close to the site of epidemic as possible. Transportation of cases over long distances is not desirable; it has been linked with the spread of the disease.

In areas where peripheral health services are poor and cholera is endemic or threatening, mobile teams should be established at the district level. When needed, these teams should be brought promptly into the epidemic area to assist the local workers.

5. Rehydration therapy

Cholera is now the most effectively treated disease. Mortality rates have been brought down to less than 1 per cent by effective rehydration therapy. The rehydration may be oral or intravenous. The guidelines for ORT and intravenous rehydration are discussed in detail on page 270–272.

6. Adjuncts to therapy

Antibiotics should be given as soon as vomiting has stopped, which is usually after 3 to 4 hours of oral rehydration. Injectable antibiotics have no special advantages. The commonly used antibiotics for the treatment of cholera are flouroquinolones, tetracycline, Azithromycin, ampicilline and Trimethoprim TMP-Sulfamethoxazole (SMX). No other medication should be given to treat cholera, like antidiarrhoeals, antiemetics, antispasmodics, cardiotonics and corticosteroids. In regions where cholera is present, it is important to identify those antibiotics to which the vibrio cholerae O1 is resistant. If diarrhoea persists after 48 hours of treatment, resistance to antibiotic should be suspected.

7. Epidemiological investigations

General sanitation measures must be applied at the onset of an outbreak (see under sanitation measures). At the same time, epidemiological studies must be undertaken to define the extent of the outbreak and identify the modes of transmission so that more effective and specific control measures can be applied. The epidemiologist must maintain contact with all health and civic units in his area to ensure detection of new foci of disease.

There are certain institutions which are able to assist in investigating outbreaks. These include the National Institute of Communicable Diseases, Delhi and the All India Institute of Hygiene and Public Health, Kolkata, where epidemiological teams are available for investigating epidemics. In addition, stools for phage typing may be sent to the National Institute of Cholera and Enteric Diseases, 3, Dr Isaque Road, Kolkata–700016, where the WHO International Centre for Vibrios is located.

8. Sanitation measures

(a) *WATER CONTROL* : As water is the most important vehicle of transmission of cholera, all steps must be taken to provide properly treated or otherwise safe water to the community for all purposes (drinking, washing and cooking).

Various approaches have been described for supplying safe water quickly and with limited resources *(26)*. Facilities selected and installed should be appropriate and acceptable to the community. The ultimate aim should be provision of piped water supply on a permanent basis and elimination of alternative unsafe water sources. Because of financial limitations and other competitive priorities, this measure cannot be applied immediately on a large scale in developing countries, such as India. As an emergency measure, in urban areas, properly treated drinking water containing free residual chlorine should be made available to all families; this water should be stored in the household in narrow-mouthed, covered containers. In rural areas, water can be made safe by boiling or by chlorination. The emergency measures should be followed by the development of more permanent facilities.

(b) *EXCRETA DISPOSAL* : Provision of simple, cheap and effective excreta disposal system (sanitary latrines) is a basic need of all human settlements. When cholera appears in a community, the need for these facilities becomes vital. With the cooperation of the community, sanitary system should be selected and constructed *(26)*, taking into consideration the customs and practices of the population, the existing terrain and geology, and the available resources. Simultaneously, health education messages should stress the proper use of such facilities, the dangers involved in depositing faeces on the ground, and in or near water, and the importance of handwashing with soap after defecation.

(c) *FOOD SANITATION* : Since food may be an important vehicle of infection, steps should be taken to improve food sanitation, particularly sale of foods under hygienic conditions. Health education must stress the importance of eating cooked hot food and of proper individual food handling techniques. Cooking utensils should be cleaned and dried after use.

The housefly plays a relatively small role in transmitting cholera, but its prevalence is a general indicator of the level of sanitation.

(d) *DISINFECTION* : Disinfection should be both concurrent and terminal. The most effective disinfectant for general use is a coal tar disinfectant with a Rideal–Walker (RW) coefficient of 10 or more such as cresol. A disinfectant with a RW coefficient of less than 5 should not be used *(27)*. Bleaching powder, if used, should be of good quality. For disinfection, attention should be paid to the following : patient's stools and vomit; clothes and other personal items that may have been contaminated; the latrine, if any; the patient's house and neighbourhood.

9. Chemoprophylaxis

Studies have shown that approximately 10–12 per cent of close household contacts of a cholera case may be bacteriologically positive, and some of these develop clinical illness. In contrast, a very small proportion (0.6–1 per cent) in the community may be excreting vibrios. Mass chemoprophylaxis is not advised for the total community because in order to prevent one serious case of cholera, some 10,000 persons must be given the drug. Further, the drug's effect is only short–lived for a few days. Whenever mass chemoprophylaxis was attempted, it failed to stop the spread of cholera. Because of these reasons, chemoprophylaxis is advised only for household contacts or of a closed community in which cholera has occurred.

Tetracycline is the drug of choice for chemoprophylaxis. It has to be given over a 3–day period in a twice–daily dose of 500 mg for adults, 125 mg for children aged 4–13 years, and 50 mg for children aged 0–3 years. Alternatively, the long–acting tetracycline (doxycycline) may be used for chemoprophylaxis, if the prevailing strains are not resistant. A single oral dose of doxycycline (300 mg for adults and 6 mg/kg for children under 15 years) has proved to be effective.

10. Vaccination

ORAL VACCINE (28)

Three types of oral cholera vaccines are available : (a) Dukoral (WC-rBS), (b) Sanchol and mORCVAX and (c) Euvichol. The live attenuated single-dose vaccine (CVD103-HgR) is no longer produced.

(a) Dukoral (WC-rBS)

Dukoral is a monovalent vaccine based on formalin and heat-killed whole cells (WC) of *V. cholerae* O1 (classical and El Tor, Inaba and Ogawa) plus recombinant cholera toxin B subunit. The vaccine is provided in 3 ml single-dose vials together with the bicarbonate buffer (effervescent granules in sachets to protect the toxin B subunit from being destroyed by gastric acid). Vaccine and buffer are mixed in 150 ml of water (chlorinated or not) for persons aged >5 years and in 75 ml of water for children aged 2–5 years. The vaccine has a shelf life of 3 years at 2–8°C and remains stable for 1 month at 37°C.

Vaccine schedule and administration

According to the manufacturer, primary immunization consists of 2 oral doses given ≥7 days apart (but <6 weeks apart) for adults and children aged ≥6 years. Children aged 2–5 years should receive 3 doses ≥7 days apart (but <6 weeks apart). Intake of food and drink should be avoided for 1 hour before and after vaccination. If the interval between the primary immunization doses is delayed for >6 weeks, primary immunization should be restarted. Protection may be expected about 1 week after the last scheduled dose.

Provided there is continued risk of *V. cholerae* infection, 1 booster dose is recommended by manufacturer, after 2 years for adults and children aged ≥6 years. If the interval between the primary series and booster immunization is >2 years, primary immunization must be repeated. For children aged 2–5 years 1 booster dose is recommended every 6 months, and if the interval between primary immunization and the booster is >6 months, primary immunization must be repeated.

Dukoral is not licensed for children aged <2 years.

(b) Sanchol and mORCVAX

The closely related bivalent oral cholera vaccines are based on serogroups O1 and O139. Unlike Dukoral, these vaccines do not contain the bacterial toxin B subunit therefore it does not require buffer. According to the manufacturer, vaccine should be administered orally in 2 liquid doses 14 days apart for individuals aged ≥1 year. A booster dose is recommended after 2 years *(28)*.

(c) Euvichol

It was prequalified in December 2015 and has same characteristics as Sanchol *(3)*.

11. Health education

The most effective prophylactic measure is perhaps health education. It should be directed mainly to (a) the effectiveness and simplicity of oral rehydration therapy (b) the benefits of early reporting for prompt treatment (c) food hygiene practices (d) hand washing after defecation and before eating, and (e) the benefit of cooked, hot foods and safe water. Since cholera is mainly a disease of the poor and ignorant, these groups should be tackled first.

Surveillance *(1)*

Cholera surveillance should be part of an integrated disease surveillance system that includes feedback at the local level and information-sharing at the global level. The detection of a suspected cholera case is based on clinical suspicion in patients aged two years and older with acute watery diarrhoea and severe dehydration or dying from acute watery diarrhoea. Rapid diagnostic tests (RDTs) can be useful tool to detect cholera outbreaks; however, to confirm the diagnosis, stool samples are sent to a laboratory for confirmation of *V. cholerae* O1 or O139 by culture or by polymerase chain reaction (PCR).

The monitoring of a cholera outbreak is by the reporting of patients with acute watery diarrhoea and regular testing of a subset of these patients. Local capacity to detect (diagnose) and monitor (collect, compile, and analyse data) cholera occurrence, is central to an effective surveillance system and to planning control measures. Countries affected by cholera are encouraged to strengthen disease surveillance and national preparedness to rapidly detect and respond to outbreaks. Under the International Health Regulations (IHR), notification of all cases of cholera is no longer mandatory. However, public health events involving cholera must always be assessed against the criteria provided in the regulations (IHR Annex 2, decision instrument) to determine whether there is a need for official notification.

Community engagement *(1)*

Community engagement means that people and communities are part of the process of developing and implementing programmes. Local culture, practices and beliefs are central to promoting actions such as good hygiene practices including handwashing with soap, safe preparation and storage of food and safe disposal of the faeces of children. Funeral practices for individuals who die from cholera may need to be adapted to prevent infection among attendees.

Ending cholera : a roadmap to 2030 *(1)*

In October 2017, GTFCC partners launched a strategy for cholera control Ending cholera: a global roadmap to 2030. The country-led strategy aims to reduce cholera deaths by 90% and to eliminate cholera in as many as 20 countries by 2030. The Global Roadmap focuses on three strategic axes :

1. early detection and quick response to contain outbreaks: the strategy focuses on containing outbreaks – wherever they may occur – through early detection and rapid multisectoral response including community engagement, strengthening surveillance and laboratory capacity, health systems and supply readiness, and supporting rapid response teams;
2. a targeted multi-sectoral approach to prevent cholera recurrence: the strategy calls on countries and partners to focus on cholera hotspots, the relatively small areas most heavily affected by cholera. Cholera transmission can be stopped in these areas, through measures including improved WASH (Water, Sanitation and Hygiene) and through use of OCV; and
3. an effective mechanism of coordination for technical support, advocacy, resource mobilization, and partnership at local and global levels. The GTFCC provides a strong framework to support countries to intensify efforts to control cholera, building upon country-led cross-sectoral cholera control programs and supporting them with human, technical and financial resources.

Cholera Kits *(1)*

To ensure efficient and effective deployment of necessary materials for the investigation and confirmation of cholera outbreaks, as well as the treatment of cholera patients, WHO has developed a set of cholera kits.

In 2016, after consultation with implementing partners, WHO revised the cholera kits to better meet field needs. There are 6 kits :

- 1 for investigation;
- 1 with supplies for culture confirmation in a laboratory;
- 3 for treatment at each of the community, peripheral and central levels; and
- 1 support kit with logistical materials including solar lamps, fencing, water bladders and taps.

Each treatment kit provides enough material to treat 100 patients. The revised cholera kits are designed to help prepare for a potential cholera outbreak and to support the first month of the initial response.

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TYPHOID FEVER

Typhoid fever is the result of systemic infection mainly by *S. typhi* found only in man. The disease is clinically characterized by a typical continuous fever for 3 to 4 weeks, relative bradycardia with involvement of lymphoid tissues and considerable constitutional symptoms. The term ***"enteric fever"*** includes both typhoid and paratyphoid fevers. The disease may occur sporadically, epidemically or endemically.

Problem statement

WORLD

Typhoid fever occurs in all parts of the world where water supplies and sanitation are sub-standard. The disease is now uncommon in the developed countries where most of the cases that occur are either acquired abroad or imported by immigrants *(1)*. Improved living conditions and the introduction of antibiotics in the late 1940s resulted in drastic reduction of typhoid fever morbidity and mortality in industrialized countries. In developing areas of Asia, Africa, Latin America, however, the disease continues to be a public health problem, albeit with incidence rate that vary considerably between and within countries. In the year 2019, WHO estimated the global typhoid fever disease burden at 9 million cases annually, resulting in an estimated 110,000 deaths per year, predominantly in children of school age or younger. Majority of this burden occurs in Asia *(2)*.

Since 1950, the organism's resistance to antibiotics has also been a growing problem; by 1989 resistance was reported in a number of countries, particularly in Asia and Middle East. Resistant strains have caused outbreaks of the disease in India and Pakistan in recent years. In South-East Asia, 50 per cent or more of the strains of the bacteria may already be resistant to several antibiotics *(3)*. Typhoid fever caused by multidrug-resistant (MDR) strains of *S. typhi* – that is resistant to all 3 of the first line of antibiotics (chloramphenicol, ampicillin and cotrimoxazole) – is associated with more severe illness and higher rates of complications and death, especially in children aged less than 2 years. Also, compared with typhoid fever caused by sensitive strains, a ten-fold higher rate of post-treatment symptomatic bacterial carriers has been reported with MDR *S. typhi* infection *(2)*. Without effective treatment, typhoid fever kills almost 10 per cent of those infected *(3)*.

The socio-economic impact of the disease is huge, because typhoid survivors may take several months to recover and resume work.

INDIA

Typhoid fever is endemic in India. Reported data for the year 2022 shows 1.235 million cases and 329 deaths. Maximum cases were reported from Uttar Pradesh (440,695 cases with 53 deaths) Andhra Pradesh (145,554 cases with 238 deaths), Telangana (98,714 cases no deaths), Madhya Pradesh (72,794 cases no deaths), Karnataka (58,541 cases no deaths) *(5)*.

Epidemiological determinants

Agent factors

(a) AGENT : *S. typhi* is the major cause of enteric fever. *S. para A and S. para B* are relatively infrequent *(6)*. *S. typhi* has three main antigens – O, H and Vi and a number of phage types (at least 80). Phage typing has proved a useful epidemiological tool in tracing the source of epidemics. *S. typhi* survives intracellularly in the tissues of various organs. It is readily killed by drying, pasteurization, and common disinfectants. The factors which influence the onset of typhoid fever in man are the infecting dose and virulence of the organism.

(b) RESERVOIR OF INFECTION : Man is the only known reservoir of infection, viz. cases and carriers. (i) CASES : The case may be mild, missed or severe. A case (or carrier) is infectious as long as bacilli appear in stools or urine. (ii) CARRIERS : The carriers may be temporary (incubatory, convalescent) or chronic. *Convalescent carriers* excrete the bacilli for 6 to 8 weeks, after which their numbers diminish rapidly. By the end of three months, not more than 4 per cent of cases are still excreting the organisms; and by the end of one year, the average carrier rate is around 3 per cent *(7)*. Persons who excrete the bacilli for more than a year after a clinical attack are called chronic carriers. In most chronic carriers, the organisms persist in the gall bladder and in the biliary tract. A chronic carrier state may be expected to develop in 2 to 5 per cent of cases. A chronic carrier may excrete the bacilli for several years (may be as long as 50 years) either continuously or intermittently. The famous case of "Typhoid Mary" who gave rise to more than 1300 cases in her life time is a good example of a chronic carrier. Faecal carriers are more frequent than urinary carriers. Chronic urinary carrier state is often associated with some abnormality of the urinary tract.

(c) SOURCE OF INFECTION : The primary sources of infection are faeces and urine of cases or carriers; the secondary sources contaminated water, food, fingers and flies. There is no evidence that typhoid bacilli are excreted in sputum or milk.

Host factors

(a) Age : Typhoid fever may occur at any age. Highest incidence of this disease occurs in the 5–19 years of age group. Prospective population-based surveillance in some Asian urban slum areas has shown that in the age group 5–15 years, the annual incidence of blood culture-confirmed typhoid fever may reach 180–494 per 100,000. In some of these areas, pre-school-age children less than 5 years, show incidence rates similar to those of school-age children *(2)*. After the age of 20 years, the incidence falls probably due to acquisition of immunity from clinical or subclinical infection. *(b) Sex :* More cases are reported among males than females, probably as a result of increased exposure to infection. But carrier rate is more in females. *(c) Immunity:* All ages are susceptible to infection. Antibody may be stimulated by the infection or by immunization; however, the antibody to the somatic antigen (O) is usually higher in the patient with the disease, and the antibody to the flagellar antigen(H) is usually higher in immunized individuals. Serum antibodies are not the primary defences against infection; *S. typhi* being an intracellular organism, cell-mediated immunity plays a major role in combating the infection. Natural typhoid fever does not always confer solid immunity; second attacks may occur when challenged with a large oral dose. Among the host factors that contribute to resistance to *S. typhi* are gastric acidity and local intestinal immunity.

Environmental and social factors

Enteric fevers are observed all through the year. The peak incidence is reported during July–September *(8)*. This period coincides with the rainy season and an increase in fly population.

Outside the human body, the bacilli are found in water, ice, food, milk and soil for varying periods of time. Typhoid bacilli do not multiply in water; many of them perish within 48 hours, but some may survive for about 7 days. They may survive for over a month in ice and icecream. They may survive for up to 70 days in soil irrigated with sewage under moist winter conditions, and for half that period under drier summer conditions *(9)*. Food being a bad conductor of heat, provides shelter to the bacilli which may multiply and survive for sometime in food. Typhoid bacilli grow rapidly in milk without altering its taste or appearance in anyway. Vegetables grown in sewage farms or washed in contaminated water are a positive health hazard. These factors are compounded by such social factors as pollution of drinking water supplies, open air defecation and urination, low standards of food and personal hygiene and health ignorance. Typhoid fever may therefore be regarded as an index of general sanitation in any country.

Incubation period

Usually 10–14 days. But it may be as short as 3 days or as long as three weeks depending upon the dose of the bacilli ingested.

Modes of transmission

Typhoid fever is transmitted *via* the faecal–oral route or urine–oral routes. This may take place *directly* through soiled hands contaminated with faeces or urine of cases or carriers, or *indirectly* by the ingestion of contaminated water, milk and/or food, or through flies.

Fig. 1 shows the dynamics of transmission. There are numerous sources of infection and many vehicles of transmission, each making its own contribution to the total magnitude of the problem. The situation is rendered more complex by the web of social, cultural and economic factors which determine the quality of life of the people.

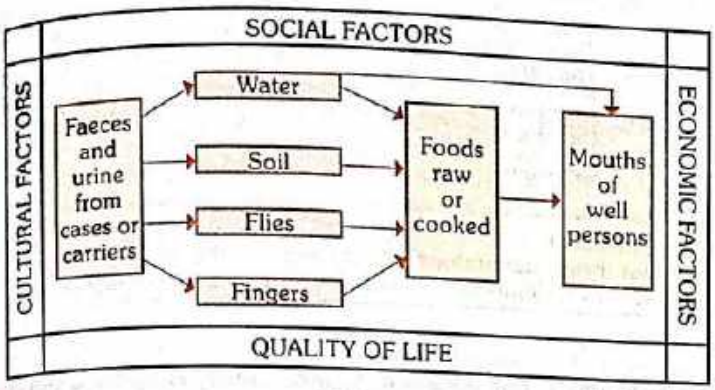

FIG.1

Dynamics of typhoid fever transmission

Clinical features

The onset is usually insidious but in children may be abrupt, with chills and high fever. During the prodromal stage, there is malaise, headache, cough and sore throat, often with abdominal pain and constipation. The fever ascends in a step–ladder fashion. After about 7–10 days, the fever reaches a plateau and the patient looks toxic, appearing exhausted and often prostrated. There may be marked constipation, especially in early stage or "pea soup" diarrhoea. There is marked abdominal distention. There is leukopenia and blood, urine and stool culture is positive for salmonella. If there are no complications the patient's condition improves over 7–10 days. However, relapse may occur for upto 2 weeks after termination of therapy.

During the early phase, physical findings are few. Later, splenomegaly, abdominal distension and tenderness, relative bradycardia, dicrotic pulse, and occasionally meningismus appear. The rash (rose spots) commonly appears during the second week of disease. The individual spot, found principally on the trunk, is a pink papule 2–3 mm in diameter that fades on pressure. It disappears in 3–4 days.

Serious complications occur in up to 10 per cent of typhoid fever patients, especially in those who have been ill longer than 2 weeks, and who have not received proper treatment. Intestinal haemorrhage is manifested by a sudden drop in temperature and signs of shock, followed by dark or fresh blood in the stool. Intestinal perforation is most likely to occur during the third week. Less frequent complications are urinary retention, pneumonia, thrombophlebitis, myocarditis, psychosis, cholecystitis, nephritis and osteomyelitis.

Estimates of case-fatality rates of typhoid fever range from 1 per cent to 4 per cent; fatality rates in children aged less than 4 years being 10 times higher (4.0%) than in older children (0.4%). In untreated cases, the fatality rates may rise to 10–20 per cent *(2)*.

Laboratory diagnosis of typhoid *(3)*

(a) MICROBIOLOGICAL PROCEDURES : The definitive diagnosis of typhoid fever depends on the isolation of *S. typhi* from blood, bone marrow and stools. Blood culture is the mainstay of diagnosis of this disease.

(b) SEROLOGICAL PROCEDURE : Felix-Widal test measures agglutinating antibody levels against O and H antigens. Usually, O antibodies appear on day 6–8 and H antibodies on day 10–12 after the onset of disease. The test is usually performed on an acute serum (at first contact with the patient). The test has only moderate sensitivity and specificity. It can be negative in upto 30 per cent of culture – proven cases of typhoid fever. This may be because of prior antibiotic therapy that has blunted the antibody response. On the other hand, *S. typhi* shares O and H antigens with other *salmonella* serotypes and has cross-reacting epitopes with other Enterobacteriacae, and this can lead to false-positive results. Such results may also occur in other clinical conditions, e.g. malaria, typhus, bacteraemia caused by other organisms, and cirrhosis.

(c) NEW DIAGNOSTIC TESTS : The recent advances for quick and reliable diagnostic tests for typhoid fever as an alternative to the Widal test include the IDL Tubex® test marketed by a Swedish company, which reportedly can detect IgM09 antibodies from patient within a few minutes. Another rapid serological test, Typhidot®, takes three hours to perform. It was developed in Malaysia for the detection of specific IgM and IgG antibodies against a 50 kD antigen of *S. typhi*. A newer version of the test, Typhidot-M®, was recently developed to detect specific IgM antibodies only. The dipstick test, developed in the Netherlands, is based on the binding of *S. typhi* – specific IgM antibodies in samples to *S. typhi lipopolysaccharide* (LPS) antigen and the staining of bound antibodies by an anti-human IgM antibody conjugated to colloidal dye particles.

CONTROL OF TYPHOID FEVER

The control or elimination of typhoid fever is well within the scope of modern public health. This is an accomplished fact in many developed countries. There are generally three lines of defence against typhoid fever :

1. control of reservoir
2. control of sanitation, and
3. immunization.

The weakest link in the chain of transmission is sanitation which is amenable to control.

1. Control of reservoir

The usual methods of control of reservoir are their identification, isolation, treatment and disinfection.

a. CASES

(i) Early diagnosis : This is of vital importance as the early symptoms are non-specific. Culture of blood and stools are important investigations in the diagnosis of cases. *(ii) Notification:* This should be done where such notification is mandatory. *(iii) Isolation :* Since typhoid fever is infectious and has a prolonged course, the cases are better transferred to a hospital for proper treatment, as well as to prevent the spread of infection. As a rule, cases should be isolated till three bacteriologically negative stools and urine reports, are obtained on three separate days. *(iv) Treatment :* The fluoroquinolones are widely regarded as the drug of choice for the treatment of typhoid fever. They are relatively inexpensive, well tolerated and more rapidly and reliably effective than the former first-line drugs, viz. chloramphenicol, ampicillin, amoxicillin and trimethoprim – sulfamethoxazole (TMP-SMX). The antibiotics used in uncomplicated typhoid fever are as shown in Table 1. Patients

TABLE 1

Treatment of uncomplicated typhoid fever

Susceptibility	Optimal therapy			Alternative effective drugs		
	Antibiotic	Daily dose mg/kg	Days	Antibiotic	Daily dose mg/kg	Days
Fully sensitive	Fluoroquinolone e.g. ofloxacin or ciprofloxacin	15	5–7 [a]	Chloramphenicol	50–75	14–21
				Amoxicillin	75–100	14
				TMP-SMX	8–40	14
Multidrug resistance	Fluoroquinolone or cefixime	15	5–7	Azithromycin	8–10	7
		15–20	7–14	Cefixime	15–20	7–14
Quinolone resistance [b]	Azithromycin or ceftriaxone	8–10	7	Cefixime	20	7–14
		75	10–14			

[a] Three-day courses are also effective and are particularly so in epidemic containment.
[b] The optimum treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, the third-generation cephalosporins, or a 10–14 days course of high-dose fluoroquinolones, is effective. Combinations of these are now being evaluated.

Source : *(10)*

seriously ill and profoundly toxic may be given an injection of hydrocortisone 100 mg daily for 3 to 4 days. *(v) Disinfection :* Stools and urine are the sole sources of infection. They should be received in closed containers and disinfected with 5 per cent cresol for at least 2 hours. All soiled clothes and linen should be soaked in a solution of 2 per cent chlorine and steam–sterilized. Nurses and doctors should not forget to disinfect their hands. *(vi) Follow-up :* Follow-up examination of stools and urine should be done for *S. typhi* 3 to 4 months after discharge of the patient, and again after 12 months to prevent the development of the carrier state. With early diagnosis and appropriate treatment, mortality has been reduced to about 1 per cent as compared to about 30 per cent in untreated cases.

(b) CARRIERS

Since carriers are the ultimate source of typhoid fever, their identification and treatment is one of the most radical ways of controlling typhoid fever. The measures recommended are : *(i) Identification :* Carriers are identified by cultural and serological examinations. Duodenal drainage establishes the presence of salmonella in the biliary tract in carriers. The Vi antibodies are present in about 80 per cent of chronic carriers. *(ii) Treatment :* The carrier should be given an intensive course of ampicillin or amoxycillin (4–6 g a day) together with Probenecid (2 g/day) for 6 weeks. These drugs are concentrated in the bile and may achieve eradication of the carrier state in about 70 per cent of carriers. Chloromycetin is considered worthless for clearing the carrier state. *(iii) Surgery :* Cholecystectomy with concomitant ampicillin therapy has been regarded as the most successful approach to the treatment of carriers. Cure rate may be as high as 80 per cent. Urinary carriers are easy to treat, but refractory cases may need nephrectomy when one kidney is damaged and the other healthy. *(iv) Surveillance :* The carriers should be kept under surveillance. They should be prevented from handling food, milk or water for others. *(v) Health education :* Health education regarding washing of hands with soap, after defecation or urination, and before preparing food is an essential element. In short, the management of carriers continues to be an unsolved problem. This is the crux of the problem, in the elimination of typhoid fever.

2. Control of sanitation

Protection and purification of drinking water supplies, improvement of basic sanitation, and promotion of food hygiene are essential measures to interrupt transmission of typhoid fever. For instance, typhoid fever is never a major problem where there is a clean domestic water supply. Sanitary measures, not followed by health education may produce only temporary results. However, when sanitation is combined with health education, the effects tend to be cumulative, resulting in a steady reduction of typhoid morbidity *(11)*.

3. Immunization

While ultimately, control of typhoid fever must take the form of improved sanitation and domestic and personal hygiene, these are long-term objectives in many developing countries. A complementary approach to prevention is immunization, which is the only specific preventive measure, likely to yield the highest benefit for the money spent. Immunization against typhoid does not give 100 per cent protection, but it definitely lowers both the incidence and seriousness of the infection. It can be given at any age upwards of two years. It is recommended to : (i) those living in endemic areas (ii) household contacts (iii) groups at risk of infection such as school children and hospital staff (iv) travellers proceeding to endemic areas, and (v) those attending *melas* and *yatras*.

ANTI-TYPHOID VACCINES *(2)*

The old parenteral killed whole-cell vaccine was effective but produced strong side-effects. Two safe and effective vaccines are now licensed and available. One is based on defined subunit antigens, the other on whole-cell live attenuated bacteria.

The Vi polysaccharide vaccine

This subunit vaccine was first licensed in the United States in 1994. It is composed of purified Vi capsular polysaccharide from the Ty2 S. Typhi strain and elicits a T-cell independent IgG response that is not boosted by additional doses. The vaccine is administered subcutaneously or intramuscularly. The target value for each single human dose is about 25µg of the antigen. The vaccine is stable for 6 months at 37°C, and for 2 years at 22°C. The recommended storage temperature is 2–8°C. The Vi vaccine does not elicit adequate immune responses in children aged less than 2 years.

Schedule

The vaccine is licensed for individuals aged ≥2 years. Only 1 dose is required, and the vaccine confers protection

7 days after injection. To maintain protection, re-vaccination is recommended every 3 years. The Vi polysaccharide vaccine can be co-administered with other vaccines relevant for international travellers, such as yellow fever and hepatitis A, and with vaccines of the routine childhood immunization programmes.

Safety

No serious adverse events and a minimum of local side-effects are associated with Vi vaccination. There are no contraindications to the use of this vaccine other than previous severe hypersensitivity reaction to vaccine components. Although the Vi polysaccharide vaccine is safe for HIV-infected individuals, the induction of protective antibodies is directly correlated to the levels of CD4 positive T-cells.

The Ty21a vaccine

This vaccine, which was first licensed in Europe in 1983 and in the USA in 1989, is an orally administered, live-attenuated Ty2 strain of *S. Typhi* in which multiple genes, including the genes responsible for the production of Vi, have been mutated chemically. The lyophilized vaccine is available as enteric coated capsules. Protection is markedly influenced by the number of doses and their spacing. There are currently no field trials to document the efficacy of Ty21a vaccine in children aged <3 years. Ty21a requires storage at 2–8°C; it retains potency for approximately 14 days at 25°C.

Schedule

The capsules are licensed for use in individuals aged ≥5 years. The vaccine is administered every other day; on 1, 3, and 5th day; a 3–dose regimen is recommended. With the 3–dose regimen, protective immunity is achieved 7 days after the last dose. The recommendation is to repeat this series every 3 years for people living in endemic areas, and every year for individuals travelling; from non-endemic to endemic countries. The Ty21a vaccine may be given simultaneously with other vaccines, including live vaccines against polio, cholera, and yellow fever, or the measles, mumps and rubella (MMR) combination.

Safety and precautions

Proguanil and antibacterial drugs should be stopped from 3 days before until 3 days after giving Ty21a, as such drugs may harm live bacterial vaccines. The vaccine is unlikely to be efficacious if administrated at the time of ongoing diarrhoea. It is not known whether this live attenuated vaccine may cause foetal harm when administered to pregnant women. Ty21a can be administered to HIV-positive, asymptomatic individuals as long as the T-cell count (CD_4) is >200/mm^3.

Ty21a is remarkably well tolerated and has low rates of adverse events.

The vaccine is not recommended in congenital or acquired immunodeficiency including treatment with immuno-suppressive and antimitotic drugs, acute febrile illness and acute intestinal infection.

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FOOD POISONING

Food poisoning is an acute gastroenteritis caused by ingestion of food or drink contaminated with either living bacteria or their toxins or inorganic chemical substances and poisons derived from plants and animals. The condition is characterized by: (a) history of ingestion of a common food (b) attack of many persons at the same time, and (c) similarity of signs and symptoms in the majority of cases.

High risk people

Some group of people are more likely to get sick and have a more serious illness. These groups include :

a. Adults age 65 and older;
b. Children younger than age 5 years;
c. Pregnant women; and
d. People whose immune systems are weekened by health conditions or medicines used to treat them including people with diabetes, liver or kidney disease, HIV/AIDS or cancer.

People who are more likely to get food poisoning should not eat undercooked food from animals, raw or lightly cooked sprouts, unpasteurized (raw) milk and juices and soft cheese (such as queso freso), unless it is labled as made with pasteurized milk *(2)*.

Types of food poisoning

Food poisoning may be of two types : non-bacterial and bacterial. *(a) Non-bacterial :* Caused by chemicals such as arsenic, certain plant and sea foods. In recent years, there has been a growing concern about contamination of food by chemicals, e.g., fertilizers, pesticides, cadmium, mercury etc. *(b) Bacterial :* Caused by the ingestion of foods contaminated by living bacteria or their toxins. The conventional classification of bacterial food poisoning into toxic and infective types is becoming increasingly blurred with the knowledge that in some types, both multiplication and toxin production are involved *(1)*. Bacterial food poisoning may be of the following types : Salmonellosis, Staphylococcal intoxication, *C. perfringens* illness, Botulism, B. cereus food poisoning, *E. coli* diarrhoea, Non-cholera vibrio illness, V. parahaemolyticus infection, streptococcal infection, Shigellosis Brucellosis. *(c) Viral diseases :* hepatitis A and E, Norovirus Gastroenteritis, Rotavirus. Some viruses can be transmitted by food consumption. It is characterized by nausea, explosive vomiting, watery diarrhoea and abdominal pain *(1)*. *(d) Parasites :* Taeniasis Hydatidosis, Trichinosis, Ascariasis, Amoebiasis, Oxyuriasis. Some parasites, such as fish-borne trematodes, are only transmitted through food. Others, for example tapeworms like *Echinococcus* spp, or *Taenia* spp, may infect people through food or direct contact with animals. Other parasites, such as *Ascaris*, *Cryptosporidium*, *Entamoeba histolytica* or *Giardia*, enter the food chain via water or soil and can contaminate fresh produce *(1)*.

1. Salmonella food poisoning

An extremely common form of food poisoning. Five reasons have been given for its increase in recent years : (a) an increase in community feeding (b) increase in international trade in human food (c) a higher incidence of salmonellosis in farm animals (d) widespread use of household detergents interfering with sewage treatment, and (e) wide distribution of "prepared foods" *(4)*.

(a) AGENT(S) : The species most often incriminated in human outbreaks are *S. typhimurium, S. cholera–suis* and *S. enteritidis*, besides many others. (b) SOURCE : Salmonellosis is primarily a disease of animals. Man gets the infection from *farm animals* and *poultry* – through contaminated meat, milk and milk products, sausages, custards, egg and egg products. Rats and mice are another source; they are often heavily infected and contaminate foodstuffs by their urine and faeces. Temporary human carriers can also contribute to the problem. (c) INCUBATION PERIOD : 12 to 24 hours commonly. (d) MECHANISM OF FOOD POISONING : The causative organisms, on ingestion, multiply in the intestine and give rise to acute enteritis and colitis. The onset is generally sudden with chills, fever, nausea, vomiting, and a profuse watery diarrhoea which usually lasts 2–3 days. Mortality is about 1 per cent. A convalescent carrier state lasting for several weeks may occur *(3)*.

Salmonellosis is described in detail separately, (Page 280).

2. Staphylococcal food poisoning

It is about as common as salmonella food poisoning. (a) AGENT : Enterotoxins of certain strains of coagulase–positive *Staphylococcus aureus*. At least 5 different enterotoxins have been identified, and a sixth may exist *(5)*. Toxins can be formed at optimum temperatures of 35 deg. to 37 deg. C. These toxins are relatively heat stable and resist boiling for 30 minutes or more. (b) SOURCE : Staphylococci are ubiquitous in nature, and are found on the skin and in the nose and throat of men and animals. They are a common agent of boils and pyogenic infections of man and animals. Cows suffering from mastitis have been responsible for outbreaks of food poisoning involving milk and milk products. The foods involved are salads, custards, milk and milk products which get contaminated by staphylococci. (c) INCUBATION PERIOD : 1–8 hours. The incubation period is short because of "preformed" toxin. (d) MECHANISM OF FOOD POISONING : Food poisoning results from ingestion of toxins preformed in the food in which bacteria have grown ("intradietetic" toxins). Since the toxin is heat–resistant, it can remain in food after the organisms have died. The toxins act directly on the intestine and CNS. The illness becomes manifest by the sudden onset of vomiting, abdominal cramps and diarrhoea. In severe cases, blood and mucus may appear. Unlike salmonella food poisoning, staphylococcal food poisoning rarely causes fever. Death is uncommon.

Botulism

Most serious but rare. It kills two-thirds of its victims. (a) AGENT : Exotoxin of *Clostridium botulinum* generally Type A, B or E. (b) SOURCE : The organism is widely distributed in soil, dust and the intestinal tract of animals and enters food as spores. The foods most frequently responsible for botulism are home preserved foods such as home–canned vegetables, smoked or pickled fish, home–made cheese and similar low acid foods. In fact, botulism derives its name from the Latin word for sausage (botulus). (c) INCUBATION PERIOD : 18 to 36 hours. (d) MECHANISM OF FOOD POISONING : The toxin is preformed in food ("intradietetic") under suitable anaerobic conditions. It acts on the parasympathetic nervous system. Botulism differs from other forms of food poisoning in that the gastrointestinal symptoms are very slight. The prominent symptoms are dysphagia, diplopia, ptosis, dysarthria, blurring of vision, muscle weakness and even quadriplegia. Fever is generally absent, and consciousness is retained. The condition is frequently fatal, death occurring 4–8 days later due to respiratory or cardiac failure. Patients who recover do not develop antitoxin in the blood. Since the toxin is thermolabile, the heating of food which may be subjected to 100 deg. C for a few minutes before use will make it quite safe for consumption *(6)*.

Botulism occurring in infants is called "infant botulism". It is due to infection of the gut by *C. botulinum* with subsequent in vivo production of toxin *(7)*.

Antitoxin is of considerable value in the prophylaxis of botulism. When a case of botulism has occurred, antitoxin should be given to all individuals partaking of the food. The dose varies from 50,000 to 100,000 units IV *(8)*. The antitoxin will be of no avail if the toxin is already fixed to the nervous tissue. Guanidine hydrochloride given orally in doses of 15 to 40 mg/kg of body weight has been shown to reverse the neuromuscular block of botulism. When combined with good medical and nursing care, the drug can be a useful adjunct in the treatment of botulism *(9)*. Active immunization with botulinum toxoid to prevent botulism is also available *(10)*.

C. perfringens food poisoning

(a) AGENT : *Clostridium (C.) perfringens (welchii)*. (b) SOURCE : The organism has been found in faeces of humans and animals, and in soil, water and air. The majority of outbreaks have been associated with the ingestion of meat, meat dishes and poultry. The usual story is that the food has been prepared and cooked 24 hours or more before consumption, and allowed to cool slowly at room temperature and then heated immediately prior to serving. (c) INCUBATION PERIOD : 6 to 24 hours, with a peak from 10 to 14 hours (d) MECHANISM OF FOOD POISONING : The spores are able to survive cooking, and if the cooked meat and poultry are not cooled enough, they will germinate. The organisms multiply between 30 deg. and 50 deg. C and produce a variety of toxins, e.g., alpha toxin, theta toxin, etc. Prevention consists either by cooking food just prior to its consumption or, if it has to be stored, by rapid and adequate cooling *(11)*. (e) CLINICAL SYMPTOMS : The most common symptoms are diarrhoea, abdominal cramps and little or no fever, occurring 8 to 24 hours after consumption of the food. Nausea and vomiting are rare. Illness is usually of short duration, usually 1 day or less. Recovery is rapid and no deaths have been reported.

B. cereus food poisoning

Bacillus cereus is an aerobic, spore–bearing, motile, gram positive rod. It is ubiquitous in soil, and in raw, dried and processed foods. The spores can survive cooking and germinate and multiply rapidly when the food is held at favourable temperatures. *B. cereus* has been recognized as a cause of food poisoning, with increasing frequency in recent years.

Recent work has shown that *B. cereus* produces at least 2 distinct enterotoxins, causing 2 distinct forms of food poisoning. One, the *emetic form* with a short incubation period (1–6 hours) characterized by predominantly upper gastro-intestinal tract symptoms, rather like staphylococcal food poisoning. The other, the *diarrhoeal* form, with a longer incubation period (12–24 hours) characterized by predominantly lower intestinal tract symptoms like *C. perfringens* food poisoning (diarrhoea, abdominal pain, nausea with little or no vomiting and no fever. Recovery within 24 hours is usual). The toxins are preformed and stable.

Diagnosis can be confirmed by isolation of 10^5 or more *B. cereus* organisms per gram of epidemiologically incriminated food. Treatment is symptomatic.

Differential diagnosis

Food poisoning may be mistaken for cholera, acute bacillary dysentery and chemical (arsenic) poisoning. The differentiating points between cholera and food poisoning are given in Table 1.

INVESTIGATION OF FOOD POISONING

(a) Secure complete list of people involved and their history : All the people who have shared part of the food should be interviewed. They may be supplied questionnaires concerning the foods eaten during the previous 2 days, and place of consumption; time of onset of symptoms; symptoms of illness (e.g., nausea, vomiting, diarrhoea, abdominal pain, headache, fever, prostration, etc.) in order of occurrence; personal data such as age, sex, residence, occupation, and any other helpful information. Questionnaires may be administered to kitchen employees and those working in the dining halls. *(b) Laboratory investigations :* An important part of the investigation. The object is not only to incriminate the causative agent from stool, vomit or remnants of food by inoculating into appropriate media, but also to determine the total number of bacteria and the relative numbers of each kind involved. This will give a better indication of the organism involved. Stool samples of the kitchen employees and food handlers should also be investigated. The samples should be examined aerobically and anaerobically. Phage typing of the organisms should be done to complete the laboratory investigation. *(c) Animal experiments :* It may be necessary to feed rhesus monkeys with the remnants of food. Protection tests are useful in the case of botulism; in this, a saline filtrate of food-stuff is injected subcutaneously into mice protected with antitoxic sera, keeping suitable controls. *(d) Blood for antibodies :* This is useful for retrospective diagnosis. *(e) Environmental study :* This includes inspection of the eating place(s), kitchen(s), and questioning of food handlers regarding food preparation. *(f) Data analysis :* The data should be analyzed according to the descriptive methods of time, place and person distribution. Food-specific attack rates should be calculated. A case control study may be undertaken to establish the epidemiologic association between, illness and the intake of a particular food.

PREVENTION AND CONTROL

(a) FOOD SANITATION : *(i) Meat inspection :* The food animals must be free from infection. This can be ensured by their examination by veterinary staff, both before and after slaughter. *(ii) Personal hygiene :* A high standard of personal hygiene among individuals engaged in the handling, preparation and cooking of food is needed. *(iii) Food handlers :* Those suffering from infected wounds, boils, diarrhoea, dysentery, throat infection, etc should be excluded from food handling. The medical inspection of food handlers is required in many countries; this is of limited value in the detection of carriers, although it will remove some sources of infection *(12). (iv) Food handling techniques :* The handling of ready-to-eat foods with bare hands should be reduced to a minimum. Time between preparation and consumption of food should be kept short. The importance of rapid cooling and cold storage must be stressed. Milk, milk products and egg products should be pasteurized. Food must be thoroughly cooked. The heat must penetrate the centre of the food leaving thereby no cool spots. Most food poisoning organisms are killed at temperatures over 60 deg. C. Separate raw meat, poultry, seafood and eggs from ready to

TABLE 1

Differential diagnosis of cholera and food poisoning

		Cholera	Food poisoning
1.	Epidemiology	Occurs often in epidemic form associated with other cases in the neighbourhood	Often a single group of persons who shared a common meal
		Secondary cases occur	No secondary cases
2.	Incubation	From a few hours upto 5 days	1 to 24 hours
3.	Onset	With purging	With vomiting
4.	Nausea and retching	None	Present
5.	Vomiting	Projectile, effortless, watery and continuous	Often single, severe vomit, mucus and blood streaked
6.	Stools	Copious rice watery, inoffensive	Frequent, may contain mucus and blood, offensive
7.	Tenesmus	None	Yes
8.	Abdominal tenderness	None	Yes
9.	Dehydration	Very marked	Distinct
10.	Muscular cramps	Constant and severe	Less constant
11.	Surface temperature	Subnormal	Often upto 100–102 deg.F.
12.	Headache	None	Often
13.	Urine	Suppressed	Seldom suppressed
14.	Blood	Leucocytosis	Normal

eat foods. Use separate cutting boards and keep raw meat away from other foods in shopping cart and refrigerator *(2)*. *(v) Sanitary improvements* : Sanitization of all work surfaces, utensils and equipments must be ensured. Food premises should be kept free from rats, mice, flies and dust. *(vi) Health education* : Food handlers should be educated in matters of clean habits and personal hygiene, such as frequent and thorough hand washing.

(b) REFRIGERATION : In the prevention of bacterial food poisoning, emphasis must be placed on proper temperature control. Food should not be left in warm pantries; a few germs can multiply to millions by the next morning. Foods not eaten immediately should be kept in cold storage to prevent bacterial multiplication and toxin production. "Cook and eat the same day" is a golden rule. When foods are held between 10 deg. C (50 deg. F) and 49 deg. C (120 deg.F) they are in the danger zone for bacterial growth. Cold is bacteriostatic at temperature below 4 deg. C (40 deg.F), and refrigeration temperature should not exceed this level.

SURVEILLANCE : Food samples must be obtained from the food establishments periodically and subjected to laboratory analysis if they were unsatisfactory. Continuing surveillance is necessary to avoid outbreaks of food-borne diseases.

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AMOEBIASIS

The term "amoebiasis" has been defined by WHO as the condition of harbouring the protozoan parasite *Entamoeba histolytica* with or without clinical manifestations. The symptomatic disease occurs in less than 10 per cent of infected individuals *(2)*. The symptomatic group has been further subdivided into intestinal and extraintestinal amoebiasis. Only a small percentage of those having intestinal infection will develop invasive amoebiasis. The intestinal disease varies from mild abdominal discomfort and diarrhoea to acute fulminating dysentery. Extraintestinal amoebiasis includes involvement of liver (liver abscess), lungs, brain, spleen, skin, etc. Amoebiasis is a potentially lethal disease. It carries substantial morbidity and mortality.

Problem statement

WORLD : Amoebiasis is a common infection of the human gastro-intestinal tract. It has a worldwide distribution. It is a major health problem in the whole of China, South East and West Asia and Latin America, especially Mexico. Globally it is estimated that 50 million people carry *E. histolytica* in their intestinal tract and approximately one-tenth of infected people suffer from invasive amoebiasis. It is probable that invasive amoebiasis accounted for about 50,000 deaths in the world *(3)*. Prevalence rates vary from as low as 2 per cent to 60 per cent or more in areas devoid of sanitation *(4)*. In areas of high prevalence, amoebiasis occurs in endemic forms as a result of high levels of transmission and constant reinfection. Epidemic water-borne infections can occur if there is heavy contamination of drinking water supply.

INDIA : It is generally agreed that amoebiasis affects about 15 per cent of the Indian population *(5)*. Amoebiasis has been reported throughout India : the prevalence rate is about 15% ranging from 3.6 to 47.4 per cent in different areas *(4)*. The reported variations in prevalence are attributed to variations in clinical diagnostic criteria *(6)* and to technical difficulties in establishing a correct diagnosis and lack of sampling criteria *(7)*.

Epidemiological determinants

Agent factors

(a) AGENT : Amoebiasis is caused by potentially pathogenic strains of *E. histolytica*. Studies have shown that *E. histolytica* can be differentiated into at least 18 zymodemes (a zymodeme is a population of organisms differing from similar population in the electrophoretic mobilities of one or more enzymes). It has furthermore been shown that pathogenic strains are all from particular zymodemes; that non-invasive strains are from quite distinct zymodemes; that invasive strains can give rise to faecal cysts, and the organisms breed true *(8)*. The iso-enzyme characteristics do not, however, determine why a particular zymodeme is able to invade. Isoenzyme electrophoretic mobility analysis have so far identified 7 potentially pathogenic and 11 non-pathogenic zymodems *(9)*.

E. histolytica exists in two forms – vegetative (trophozoite) and cystic forms. Trophozoites dwell in the colon where they multiply and encyst. The cysts are excreted in stool. Ingested cysts release trophozoites which colonize the large intestine. Some trophozoites invade the bowel and cause ulceration, mainly in the caecum and ascending colon; then in the rectum and sigmoid. Some may enter a vein and reach the liver and other organs.

The trophozoites are short-lived outside the human body; they are not important in the transmission of the disease. In contrast the cysts are infective to man and remain viable and infective for several days in faeces, water, sewage and soil in the presence of moisture and low temperature. The cysts are not affected by chlorine in the amounts normally used in water purification, but they are readily killed if dried, heated (to about 55 deg C) or frozen.

(b) RESERVOIR OF INFECTION : Man is the only reservoir of infection. The immediate source of infection is the faeces containing the cysts. Most individuals infected with *E. Histolytica* remain symptom free and are healthy carriers of the parasite *(12)*. The carriers can discharge upto 1.5×10^7 cysts daily *(6)*. The greatest risk is associated with carriers engaged in the preparation and handling of food *(6)*.

(c) PERIOD OF COMMUNICABILITY : As long as cysts are excreted; the period may be several years, if cases are unrecognized and untreated.

Host factors

Amoebiasis may occur at any age. There is no sex or racial difference in the occurrence of the disease. Amoebiasis is frequently a household infection. When an individual in a family is infected, others in the family may also be affected. Specific antiamoebic antibodies are produced when tissue invasion takes place. There is strong evidence that cell-mediated immunity plays an important part in controlling the recurrence of invasive amoebiasis *(10)*.

Environmental factors

Amoebiasis is more closely related to poor sanitation and socio-economic status than to climate. The use of nightsoil for agricultural purposes favours the spread of the disease. In countries with marked wet–dry seasons, infection rates are higher during rains, presumably since cysts may survive longer and the potential for transmission is thereby increased. Epidemic outbreaks are usually associated with sewage seepage into the water supply.

Mode of transmission

(i) Faecal–oral route : This may readily take place through intake of contaminated water or food. Epidemic water-borne infections can occur if there is heavy contamination of drinking water supply. Vegetables, especially those eaten raw, from fields irrigated with sewage polluted water can readily convey infection. Viable cysts have been found on the hands and under finger nails. This may lead to direct hand to mouth transmission. **(ii) Sexual transmission:** by oral–rectal contact is also recognized, especially among male homosexuals. **(iii) Vectors :** such as flies, cockroaches and rodents are capable of carrying cysts and contaminating food and drink.

Incubation period

About 2 to 4 weeks or longer.

PREVENTION AND CONTROL

1. Primary prevention

The measures aimed at primary prevention centre round preventing contamination of water, food, vegetables and fruits with human faeces. (a) **Sanitation :** Safe disposal of human excreta coupled with the elementary sanitary practice of washing hands after defecation and before eating is a crucial factor in the prevention and control of amoebiasis. But there are too many hurdles (both social and economic) in enforcing it in many developing countries. With the cooperation of the local community, the sanitary systems should be selected and constructed *(14)* taking into consideration the customs and practices of the population and the available resources. (b) **Water supply :** The protection of water supplies against faecal contamination is equally important because amoebic cysts may survive for several days and weeks in water. The cysts are not killed by chlorine in amounts used for water disinfection. Sand filters are quite effective in removing amoebic cysts. Therefore water filtration and boiling are more effective than chemical treatment of water against amoebiasis. (c) **Food hygiene :** Environmental measures should also include the protection of food and drink against faecal contamination. Uncooked vegetables and fruits can be disinfected with aqueous solution of acetic acid (5–10 per cent) or full strength vinegar *(1)*. In most instances, thorough washing with detergents in running water will remove amoebic cysts from fruits and vegetables. Since food handlers are major transmitters of amoebiasis, they should be periodically examined, treated and educated in food hygiene practices such as hand washing. (d) **Health education :** In the long-term, a great deal can be accomplished through health education of the public.

2. Secondary prevention

(a) **Early diagnosis :** Demonstration of trophozoites containing red cells is diagnostic. They are most readily seen in fresh mucus passed per rectum. Microscopy should be performed immediately before its cooling results. The absence of pus cells in the stool may be helpful in the differential diagnosis with shigellosis. Serological tests are often negative in intestinal amoebiasis, but if positive, they provide a clue to extraintestinal amoebiasis. Indirect haemagglutination test (IHA) is regarded as the most sensitive serological test. Newer techniques include counter immuno-electrophoresis (CIE) and ELISA technique *(11)*.

(b) **Treatment :** *(i) Symptomatic cases :* At the health centre level, symptomatic cases can be treated effectively with metronidazole orally and the clinical response in 48 hours may confirm the suspected diagnosis. The dose is 30 mg/kg of body weight/day, divided into 3 doses after meals, for 8–10 days. Tinidazole can be used instead of metronidazole. Suspected cases of liver abscess should be referred to the nearest hospital. *(ii) Asymptomatic infections :* In an endemic area, the consensus is not to treat such persons because the probability of reinfection is very high *(10)*. They may, however, be treated, if the carrier is a food handler. In non-endemic areas they are always likely to be treated. They should be treated with oral diiodohyroxyquin, 650 mg TDS (adults) or 30–40 mg/kg of body weight/day (children) for 20 days, or oral diloxanide furoate, 500 mg TDS for 10 days (adults) *(3)*.

At present there is no acceptable chemoprophylaxis for amoebiasis. Mass examination and treatment cannot be considered as a solution for the control of amoebiasis *(10)*.

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SOIL-TRANSMITTED HELMINTHIASIS

Soil-transmitted helminth (STHs) infections refer to a group of parasitic diseases in humans caused by intestinal roundworms (ascariasis), hookworms (*Necator americanus* and *Ancylostoma duodenale*) and whipworm (*Trichuris trichiura*). They are the most common infections worldwide.

More than 1.5 billion people, or about 24 per cent of the world's population are infected. Infections are widely distributed in tropical and subtropical areas, with the greatest numbers occurring in sub-Saharan Africa, the Americas, China and east Asia *(1)*. Over 267 million pre-school children and over 568 million school-age children and 250 million girls and adult women live in areas where these parasites are intensively transmitted and are in need of treatment and preventive interventions *(1)*.

Mode of transmission

Soil-transmitted helminths are transmitted by eggs that are passed in the faeces of infected people, as adult worms live in the intestine where they produce thousands of eggs each day. In areas that lack adequate sanitation, these eggs contaminate the soil. This can happen in several ways : (a) eggs that are attached to vegetables and salads are ingested when the vegetables are not carefully cooked, washed or peeled; (b) eggs are ingested from contaminated water sources; and (c) eggs are ingested by children who play in contaminated soil and then put their hands in their mouth without washing them.

In addition, hookworm eggs hatch in the soil, releasing larvae that mature into a form that can actively penetrate the skin. People become infected with hookworm primarily by walking barefoot on contaminated soil.

There is no direct person-to-person transmission, or infection from fresh faeces, because eggs passed in faeces need about three weeks to mature in the soil before they become infective. Since these worms do not multiply in the human host, reinfection occurs only as a result of contact with infective stages in the environment.

ASCARIASIS

An infection of the intestinal tract caused by the adult, *Ascaris lumbricoides* and clinically manifested by vague symptoms of nausea, abdominal pain and cough. Live worms are passed in the stool or vomited. Occasionally, they may produce intestinal obstruction or may migrate into the peritoneal cavity.

Geographic distribution and prevalence

Ascaris is cosmopolitan in distribution. It is the most common helminthic infestation. It is estimated that about 820 million people are infected world-wide annually with about 12 million acute cases and 20,000 or more deaths. Heavy infection is common in children aged 3–8 years *(2)*.

Epidemiological features

(a) AGENT : *Ascaris lumbricoides* lives in the lumen of small intestine, where it moves freely. Sexes are separate. The female measures 20–35 cm in length, and the male 12–30 cm. Egg production is very heavy – an estimated 2,40,000 eggs per day by each female, which counterbalances the heavy losses in the environment. The eggs are excreted in the faeces. They become embryonated in the external environment and become infective in 2–3 weeks. On ingestion by man, the embryonated eggs hatch in the small intestine. The resulting larvae penetrate the gut wall and are carried to the liver and then to the lungs *via* the blood stream. In the lungs, they moult twice. They break through the alveolar walls and migrate into the bronchioles. They are coughed up through the trachea and then swallowed by the human host. On reaching the intestine, they become mature into adults in 60–80 days. The life span of an adult is between 6–12 months, maximum reported being 1.5 years. (b) RESERVOIR OF INFECTION : Man is the only reservoir. (c) INFECTIVE MATERIAL : Faeces containing the fertilized eggs. (d) HOST : Infection rates are high in children; they are the most important disseminators of infection. Adults seem to acquire some resistance. There is a high degree of host–parasite tolerance. Roundworms rob man of his food and may possibly compete for vitamin A in the intestine *(3)*. They contribute to malnutrition especially in children who may show growth retardation. (e) ENVIRONMENT : Ascaris is a "soil–transmitted" helminth. The eggs remain viable in the soil for months or years under favourable conditions. Of the various ecological factors regulating the population of *Ascaris* eggs, the most important ones are the temperature, moisture, oxygen pressure and ultra-violet radiation from the sunlight *(4)*. A low temperature inhibits the development of eggs. Clay soils are most favourable for the development of ascariasis eggs, in contrast to moist porous soils for those of hookworms. (f) HUMAN HABITS : Seeding of the soil by ascariasis eggs takes place by the human habit of indiscriminate open air defecation. It is the most important factor responsible for the widespread distribution of ascariasis in the world *(4)*. Soil pollution is usually concentrated around houses where small children who have no regular habits pollute the house and surrounding areas. Infective eggs can then easily reach other children who play on the ground and contaminate their hands and food *(4)*. (g) PERIOD OF COMMUNICABILITY: Until all fertile females are destroyed and stools are negative.

Incubation period

18 days to several weeks.

Symptoms

The symptoms are related to the number of the worms harboured. People with light infection usually have no symptoms. Heavier infections can cause a range of symptoms including intestinal manifestations like diarrhoea, abdominal pain; general malaise, weakness, impaired cognitive and physical development. The WHO definition of heavy infection of roundworm is ≥ 50,000 eggs per gram of faeces *(5)*.

The larvae migration may cause fever, cough, sputum formation, asthma, skin rash, eosinophilia. The adult roundworm aggregate masses can cause volvulus, intestinal obstruction or intessusception; and wandering worm can cause bowel perforation in the ileococcal region, blocking of common bile duct or may come out with vomit *(5)*.

HOOKWORM INFECTION

Hookworm infection is defined as "any infection caused by *Ancylostoma duodenale* or *Necator americanus*" *(6)*. They may occur as single or mixed infections in the same person.

Problem statement

Ancylostoma duodenale and *Necator americanus* are the main nematodes causing hookworm infection in man. Almost eradicated from Europe and the USA *(4)*, hookworm infection is still seen in warm, moist climates in tropical and subtropical regions between 45°N and 30°S of the equator (e.g., Asia, Africa, Central and South America and the South Pacific). The geographic distribution of these two hookworms used to be regarded as relatively distinct, the

former being more prevalent in Europe and South-western Asia, and the latter in tropical Africa and in the Americas. However, over the past decades both parasites have become widely distributed throughout the tropics and subtropics, and rigid demarcations are no longer tenable *(7)*.

It is estimated that, the global prevalence of hookworm is about 460 million cases, and the number of years lost due to ill health or death is estimated to be about 3.2 million *(8)*.

Epidemiological determinants

Agent factors

(a) AGENT : Adult worms live in the small intestine, mainly jejunum where they attach themselves to the villi. Males measure 8 to 11 mm, and females 10 to 13 mm in length with dorsally curved anterior end. Eggs are passed in the faeces in thousands; one female *A. duodenale* produces about 10,000–30,000 eggs and one female *N. americanus* about 5,000–10,000 eggs per day *(7)*. High egg production ensures constant exposure to infection.

When deposited on warm, moist soil, a larva rapidly develops in the egg and hatches after 1 to 2 days. The newly hatched larva (rhabditiform larva) moults twice in the soil and becomes a skin-penetrating third stage infective larva within 5 to 10 days. These lie in wait in the soil to pierce the skin of the human host. They move very little horizontally, but migrate upwards on blades of grass *(4)*. They can survive in shaded, moist soil for up to one month. Infection occurs when the larva enters the body through the skin, most commonly through the feet. Larvae of *A. duodenale* are also infective by mouth. Once inside the body, they migrate via lymphatics and blood stream to the lungs. They break into the alveoli, ascend the bronchi and trachea and are coughed up and swallowed to reach the small intestine, where they become sexually mature. Adult *A. duodenale* and *N. americanus* are believed to be capable of surviving for an average about 1 and 4 years, respectively *(6)*. (b) RESERVOIR : Man is the only important reservoir of human hookworm infection. (c) INFECTIVE MATERIAL : Faeces containing the ova of hookworms. However, the immediate source of infection is the soil contaminated with infective larvae. (d) PERIOD OF INFECTIVITY : As long as the person harbours the parasite.

Host factors

(a) AGE AND SEX : All ages and both sexes are susceptible to infection. In endemic areas, the highest incidence is found in the age group, 15 to 25 years. (b) NUTRITION : Studies indicate that malnutrition is a predisposing factor; the chronic disabling disease does not occur in the otherwise healthy individual who is well-nourished and whose iron intake is adequate. (c) HOST-PARASITE BALANCE : In endemic areas, the inhabitants develop a host-parasite balance in which the worm load is limited. They harbour the parasite without manifesting clinical signs and symptoms. In some areas, the infection rate may be 100 per cent, but most infections are light and only a small proportion of the people are heavily infected *(6)*. This delicate balance may be upset by malnutrition and intercurrent infections. Little is known about host immunity. (d) OCCUPATION : It is to be expected that hookworm infection will have a higher prevalence in agricultural than in town workers, and in many tropical countries, it is an occupational disease of the farming community.

Environmental factors

Hookworm larvae live in the upper half-inch (1.2 cm.) of the soil. Favourable environmental conditions are, therefore, crucial for the survival of the hookworm larvae in the soil. These are : (a) SOIL : The soil must be suitable for the eggs and larvae. The type of soil that favours the survival of hookworm larvae is a damp, sandy or friable soil with decaying vegetation. In general, sandy soil is more favourable than clay soil. (b) TEMPERATURE : A temperature of 24 to 32 deg. C is considered favourable for the survival of the larvae. The eggs fail to develop at temperatures below 13 deg. C. Larvae are killed at 45 to 50 deg. C. (c) OXYGEN : This is required for the growth and development of the larvae. (d) MOISTURE : Moisture is necessary for survival; dryness is rapidly fatal. (e) RAINFALL : A rainfall of 40 inches (100 cm) and above is considered a favourable environmental factor. More important than the total annual rainfall is the number of rainy days spread out evenly throughout the year to keep up the moisture content of the soil. Flooding is an unfavourable factor. (f) SHADE : Direct sunlight kills the larvae whereas shade protects them. (g) HUMAN HABITS : The habits of the human host not only determine the mode and extent of soil pollution, but also the mode and extent of contact between infected soil and skin or mouth *(4)*. These include indiscriminate defecation, using the same places for defecation, going barefoot, farming practices using untreated sewage, children wading in the infected mud with bare-feet and hands. These habits are compounded by social factors such as illiteracy, ignorance and low standard of living.

Incubation period (prepatent period)

Following infection, the prepatent period for *N. americanus* is 7 weeks while that for *A. duodenale* is unpredictable, ranging from 5 weeks to 9 months *(6)*. This is because the invading larva of *A. duodenale* is capable of remaining arrested or dormant in the tissues of the host for as long as 9 months and then again resume development and migration.

Effects of the disease

(a) INDIVIDUAL : Hookworm infection causes chronic blood loss and depletion of body's iron stores leading to iron-deficiency anaemia. This has implications for child health in terms of retarded physical growth and development; for the health of mothers in terms of increased morbidity, low birth weight babies, abortion, stillbirths and impaired lactation; and for the health of adults in terms of diminished capacity for sustained hard work. Hookworm infection also causes a loss of blood plasma into the small intestine which can lead to hypoalbuminaemia in some subjects. (b) COMMUNITY : Hookworm infection exerts a significant and harmful effect on various aspects of the economy and quality of life of a community, especially in three major areas. These are nutrition, growth and development; work and productivity, and medical care costs.

WHIPWORM

Whipworm is the third most common soil-transmitted helminthiasis in the humans. According to current estimate, nearly 440 million people are infected, and majority of cases are children 4–10 years age. Heavy infection could lead to acute symptoms such as diarrhoea and anaemia, and

chronic symptoms such as growth retardation and impaired cognitive development. It is quite common in United States, South-East Asia, to a lesser extent equatorial Africa, Central and South America *(5)*.

Agent factor

Whipworms live in the large intestine, Male worm measures about 30–45 mm long while female is about 30–35 mm long. Female worm produces about 200–10,000 eggs per day for more than 5 years. Embryonization takes 21 days. It can withstand cold temperatures but not desiccation. The infection is directly from the faeces. Eggs hatch after being swallowed in the intestine, where shell is digested by intestinal juices and the larva emerges in the small intestine. It penetrates the villi and develops for a week until it re-emerges and passes to the cecum and colorectum where it attaches itself to the mucosa and becomes adult *(5, 7)*.

Incubation period

Period from ingestion of egg to appearance of egg in stool is 60–90 days *(5, 7)*.

Effect of the disease

Majority of infections are mild or asymptomatic. It causes epigestric pain, nausea, vomiting, distension flatulence, weight loss. Moderate infection causes growth deficit and anaemia. Severe infection causes severe chronic diarrhoea or dysentery with blood and mucous in stool, dehydration, rectal prolapse, colonic obstruction, hypoproteinaemia, chronic iron deficiency, anaemia etc. *(5)*.

PREVENTION AND CONTROL OF SOIL-TRANSMITTED HELMINTHS

Primary prevention

Methods based on primary prevention are the most effective in interrupting transmission. These are : sanitary disposal of human excreta to prevent or reduce faecal contamination of the soil, provision of safe drinking water, food hygiene habits, and health education of the community in the use of sanitary latrines, personal hygiene and changing behavioural patterns, measures of personal protection such as wearing protective footwear and making use of health facilities for diagnosis and treatment. Prevention, to be effective, must take into consideration the life cycle of the parasite and the peculiar ecological, social and cultural circumstances that prevail in a community.

Secondary prevention

Effective drugs are available for the treatment of the human reservoir. These are piperazine, mebendazole, levamisole and pyrantel; the last two drugs are effective in a single dose. (a) *Albendazole :* The usual dose for adults and children over 2 years is 400 mg as a single dose. Contraindicated in children below 2 years and in pregnancy. (b) *Mebendazole :* The usual dose is 100 mg twice daily for 3 days for all ages above 2 years. (c) *Levamisole :* It is the levorotatory form of tetramisole and is more active than the parent compound. For many it is now the drug of choice. A single oral dose of 2.5 mg/kg of body weight (maximum 150 mg) has been recommended. There are usually no side effects. It has been used successfully in the mass treatment of ascariasis.(d) *Pyrantel :* Effective in a single dose of 10 mg/kg of body weight *(9)* with a maximum of 1g.

Treatment of anaemia and other complications

Anaemia should be treated with iron and folic acid. Patient should be treated for hypoproteinaemia and hypereosinophilia.

Preventive chemotherapy *(3)*

The WHO strategy for control of soil-transmitted helminth infection is to control morbidity through periodic treatment of at-risk people living in endemic areas. The people at risk are : (a) preschool-aged children; (b) school aged children; (c) women of childbearing age including pregnant women in second and third trimesters and breast-feeding mothers; and (d) adults in certain high-risk occupations, such as tea-pickers or miners.

WHO recommends periodic deworming without previous individual diagnosis to all at-risk people living in endemic areas. Treatment should be given once a year when prevalence of soil-transmitted helminth infection in the community is over 20 per cent and twice a year if the prevalence is over 50 per cent. This reduces the morbidity by reducing the worm burden. Periodic deworming can easily be integrated with child health days or supplementation programmes for pre-school children, or can be integrated with school health programmes. Schools provide a particularly good entry point for deworming activities, as they allow easy provision of the health and hygiene education component – such as promotion of hand washing and improved sanitation.

The recommended medicines are albendazole (400 mg) and mebendazole (500 mg). They are effective and can be easily administered by non-medical persons. The drugs are donated by WHO.

Approximately 267 million pre-school-aged children, 568 million school-aged children and 560 million women of reproductive age group in 103 countries or territories were estimated to be in need of preventive chemotherapy against soil transmitted helminthiasis. Of these 436 million children were treated by preventive chemotherapy; 127 million women of reproductive age group were treated in 2016 principally through the lymphatic filariasis programme *(1)*.

The global target is to eliminate morbidity due to soil-transmitted helminthiasis in children by year 2020. This will be achieved by regularly treating at least 75 per cent of the children in endemic areas – an estimated 873 million children *(3)*.

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DRACUNCULIASIS

Dracunculiasis or guineaworm disease is a vectorborne parasitic disease, mainly of the subcutaneous tissues (usually leg and foot) caused by the nematode parasite, *Dracunculus medinensis*. Although not lethal, this parasitic disease can disable its victim temporarily.

Problem statement

Progress towards the elimination of dracunculiasis in the past decade has been spectacular, with the number of cases falling worldwide from an estimated 892,005 in 1989 (when most endemic countries began to report monthly cases from each endemic village) to a total of 14 cases in 2021. Compared with 2012 (542 cases), the largest decline in the number of cases occurred in South Sudan (4). At present only Ethiopia (1), Chad (7) and Mali (2), are reporting cases *(1)*.

In India, the last reported case was in July 1996. On completion of three years of zero incidence, India was declared free of guineaworm disease *(2)*.

Natural history

(a) AGENT : The adult parasite inhabits the subcutaneous tissue mainly of the legs but also of other parts of the body, including the head and neck. The female grows to a length of 55 to 120 cm, and the male is very short (2–3 cm). The gravid female makes it's way down to the infected person's lower limbs near the skin surface. There it penetrates into the dermis and induces an inflammatory reaction and subsequent blister formation. Upon contact with water, the blister soon ruptures and the parasite releases up to one million, microscopic, free–swimming larvae into water. The larvae may remain active in water for 3–6 days. They are picked up by small fresh–water crustaceans called cyclops. The larvae require a period of about 15 days for development in cyclops, which is the intermediate host.

Man acquires infection by drinking water containing infected cyclops. In the human body, digested by gastric juice, the parasites are released. They penetrate the duodenal wall. Subsequently they migrate through the viscera to the subcutaneous tissues of various parts of the body. They grow into adults in 10–14 months.

(b) RESERVOIR OF INFECTION : An infected person harbouring the gravid female. The possibility of an animal reservoir exists but not proved *(3)*.

(c) HOST FACTORS : Host susceptibility is universal. Multiple and repeated infections may occur in the same individual. The habit of washing and bathing in surface water and using step–wells is important.

(d) ENVIRONMENTAL FACTORS : The main link in the transmission of guineaworm disease is water infested with cyclops. The risk of transmission exists where such cyclops–infested water–sources are frequented by infected persons. *Season* : The seasonal variations in the incidence of the disease are marked. Where the step-wells are the source of water supply, peak transmission occurs during the dry season (March–May) when the contact between open cases of gunieaworm disease and the drinking water is the greatest; and there is little transmission when the wells are full during and after rains. Where the ponds are used, transmission appears to be confined to June–September, when the ponds contain water *(4, 5)*. *Temperature* : The larvae develop best between 25 and 30 deg C, and will not develop below 19 deg C. Therefore, the disease is limited to tropical and subtropical regions *(6)*.

Mode of transmission

The disease is transmitted entirely through the consumption of water containing cyclops harbouring the infective stages of the parasite. Guineaworm disease is a totally water–based disease and does not have an alternate pathway of transmission.

Treatment

No drug cures the infection but metronidazole and mebendazole are sometimes used to limit inflammation and facilitate worm removal. Wet compresses may relieve discomfort. Occlusive dressings improves hygiene and limit shedding of infectious larvae. Worms are removed by sequentially rolling them out over a small stick. When available simple surgical procedure can be used to remove worm. Topical antibiotics may limit bacterial superinfection.

Eradication

Guineaworm disease is amenable to eradication. The eradication strategy comprises the following elements :

i) Provision of safe drinking water (e.g., piped water, installation of hand pumps).

ii) Control of cyclops (See Chapter 15).

iii) Health education of the public in matters relating to boiling or sieving drinking water through a double–thickness cotton cloth for personal protection, and prevention of water contamination by infected persons.

iv) Surveillance : Active search for new cases, and

Guineaworm Eradication Programme

Refer to chapter 7 for details.

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III. ARTHROPOD–BORNE INFECTIONS

THE DENGUE SYNDROME

Dengue viruses are arboviruses capable of infecting humans, and causing disease. These infections may be asymptomatic or may lead to (a) "classical" dengue fever, or (b) dengue haemorrhagic fever without shock, or (c) dengue haemorrhagic fever with shock. The manifestations of the dengue syndrome are as shown in Fig. 1.

Dengue fever is a self–limiting disease and represents the majority of cases of dengue infection. A prevalence of *Aedes*

aegypti and *Aedes albopictus* together with the circulation of dengue virus of more than one type in any particular area tends to be associated with outbreaks of DHF/DSS *(1)*.

Problem statement

Dengue fever (DF) and its severe forms – dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) – have become major international public health concerns. Over the past three decades, there has been dramatic global increase in the frequency of dengue fever, DHF and DSS and their epidemics. It is found in tropical and subtropical regions around the world, predominantly in urban and semi-urban areas, and are now spreading to rural areas.

About 3.9 billion people in 129 countries are at risk of infection with dengue viruses. A recent estimate indicates 390 million dengue infections per year, of which 96 million manifest clinically with any severity of disease. The number of reported cases have increased from over 2.4 million in 2010 to the highest number of cases, i.e. 6.5 million cases and more than 7,300 deaths recorded in the year 2023 *(2)*. Not only the number of cases are increasing as disease is spreading to new areas, but explosive outbreaks are occurring. The year 2016 was characterized by large dengue outbreaks worldwide. In 2015, Delhi, recorded its worst outbreak since 2006 with over 15,000 cases.

Worldwide, annually about 500,000 people with DHF require hospitalization. Approximately 90 per cent of them are children aged less than five years, and about 2.5 per cent of those affected die. During epidemics, infection rate among those who have not been previously exposed to the virus are often 40 to 50 per cent, but can also reach 80 to 90 per cent *(3)*. Co-circulation of multiple serotypes/genotypes is evident.

Dengue and DHF is endemic in more than 100 countries in the WHO regions of Africa, the Americas, Eastern Mediterranean, South-East Asia and Western Pacific. The South-East Asia and Western Pacific regions are most seriously affected. The regions of Americas reported 4.5 million cases with 2,300 deaths. A high number of cases were also reported in Asia – Bangladesh (321,000), Malaysia (111,400), Thailand (150,000) and Viet Nam (369,000) *(2)*. Detection of all four serotypes has now rendered the countries hyperendemic. The countries of South-East Asia region are divided into 3 categories *(3)*.

Category A (Bangladesh, India, Indonesia, Maldives, Myanmar, Sri Lanka, Thailand and Timor-Leste)

a. Major public health problem;
b. Leading cause of hospitalization and death among children;
c. Hyperendemicity with all 4 serotypes circulating in urban areas; and
d. Spreading to rural areas.

Category B (Bhutan, Nepal)

a. Endemicity uncertain;
b. Bhutan reported first outbreak in 2004; and
c. Nepal reported first indigenous case in 2004.

Category C (DPR Korea)

No evidence of endemicity.

INDIA

In India, the risk of dengue has shown an increase in recent years due to rapid urbanization, lifestyle changes and deficient water management including improper water storage practices in urban, peri-urban and rural areas, leading to proliferation of mosquito breeding sites. The disease has a seasonal pattern i.e. the cases peak after monsoon, and it is not uniformly distributed throughout the year. However, in the southern states and Gujarat the transmission is perennial *(4)*.

Dengue is endemic in 35 states/UTs. During 2022, about 166,718 cases were reported with 243 deaths.

All the four serotypes i.e. dengue 1, 2, 3 and 4 have been isolated in India but at present DENV-1 and DENV-2 serotypes are widespread *(6)*.

TABLE 1

Dengue / DHF situation in India, 2021–2022 (P)

State/UT	2021		2022 (P)	
	Cases	Deaths	Cases	Deaths
Andhra Pradesh	4,760	0	6,391	0
Arunachal Pradesh	7	0	102	0
Assam	103	0	1,826	0
Bihar	633	2	13,281	32
Chhattisgarh	1,086	0	2,633	0
Goa	649	0	443	1
Gujarat	10,983	14	6,744	6
Haryana	11,835	13	8,996	18
Himachal Pradesh	349	0	3,326	1
Jharkhand	220	1	290	0
Karnataka	7,393	7	9,620	9
Kerala	3,251	27	4,432	29
Madhya Pradesh	15,592	11	3,205	2
Maharashtra	203	0	8,560	18
Manipur	129	0	503	4
Meghalaya	12,720	42	26	0
Mizoram	83	0	1,868	5
Nagaland	24	0	154	0
Odisha	7,548	0	7,063	0
Punjab	23,389	55	11,038	31
Rajasthan	20,749	96	13,491	10
Sikkim	243	1	260	0
Tamil Nadu	6,039	8	6,430	8
Telangana	349	0	8,972	0
Tripura	7,135	0	55	0
Uttar Pradesh	29,750	29	19,821	33
Uttarakhand	738	2	2,337	0
West Bengal	8,264	7	1,753	3
A&N Islands	175	0	1080	0
Chandigarh	1,596	3	910	1
D & N Haveli Daman & Diu	826	0	913	0
Delhi	13,089	23	10,183	9
Jammu & Kashmir	1,709	4	8,269	18
Ladakh	0	0	0	0
Lakshadweep	1	0	70	0
Puducherry	1,625	1	1,673	3
India	1,93,245	345	1,66,718	243

P – Provisional
Source : *(5)*

Epidemiological determinants

Agent factors

(a) AGENT : The dengue virus forms a distinct complex within the genus *flavivirus* based on antigenic and biological characteristics. There are four virus serotypes which are designated as DENV-1, DENV-2, DENV-3 and DENV-4. Infection with any one serotype confers lifelong immunity to that virus serotype *(7)*. Although all four serotypes are antigenically similar, they are different enough to elicit cross-protection for only a few months after infection by any one of them. Secondary infection with dengue serotype 2 or multiple infection with different serotypes lead to severe form dengue DHF/DSS *(3)*. The first infection probably sensitizes the patient, while the second infection with different serotype appears to produce immunological catastrophy.

The pathogenesis of severe syndrome involves pre-existing dengue antibody. It is postulated that virus antibodies are formed within a few days of the second dengue infection and that the non-neutralizing enhancing antibodies promote infection of higher numbers of mononuclear cells, followed by the release of cytokines, vasoactive mediators, and procoagulants, leading to the disseminated intravascular coagulation seen in the haemorrhagic fever syndrome *(8)*.

All four serotypes have been associated with epidemics of dengue fever (with or without DHF) with varying degree of severity.

(b) VECTOR : *Aedes aegypti* and *Aedes albopictus* are the two most important vectors of dengue. They both carry high vectorial competency for dengue virus, i.e., high susceptibility to infecting virus, ability to replicate the virus and ability to transmit the virus to another host. *Aedes aegypti* is a highly domesticated, strongly anthropophilic, nervous feeder (i.e., it bites more than one host to complete one blood meal) and is a discordant species (i.e., it needs more than one feed for the completion of the gonotropic cycle). This habit results in the generation of multiple cases and the clustering of dengue cases in the cities. On the contrary, *Ae. albopictus* partly invades peripheral areas of urban cities. It is an aggressive feeder and concordant species, i.e., the species can complete its blood meal in one go on one person and also does not require a second blood meal for the completion of the gonotropic cycle.

Transmission of disease

The *Aedes* mosquito becomes infective by feeding on a patient from the day before onset to the 5th day (viraemia stage) of illness. After an extrinsic incubation period of 8 to 10 days, the mosquito becomes infective, and is able to transmit the infection. Once the mosquito becomes infective, it remains so for life. The genital tract of the mosquito gets infected and transovarian transmission of dengue virus occurs when virus enters fully developed eggs at the time of oviposition.

Environmental factors

The population of *Aedes aegypti* fluctuates with rainfall and water storage. Its life span is influenced by temperature and humidity, survives best between 16°C–30°C and a relative humidity of 60–80 per cent. It breeds in the containers in and around the houses. Being a domestic breeder, it is a endophagic and endophilic. However, even with a 2°C increase in temperature the extrinsic incubation period of DENV will be shortened and more infected mosquitoes are available for a longer duration. Besides that the mosquitoes will bite more frequently because of dehydration and thus increase man–mosquito contact *(3, 6)*.

The failure of urban authorities to provide civil amenities and poor public health infrastructure raises the potential for the vector to breed at high level and makes the environment transmission conducive. The rural spread of the vector is relatively recent occurrence associated with the development of rural water supply schemes, improved transport systems, scarcity of water and lifestyle changes *(6)*.

Dengue in the community *(3)*

A number of factors that contribute to initiation and maintenance of an epidemic include: (i) the strain of the virus, which may influence the magnitude and duration of the viraemia in humans; (ii) the density, behaviour and vectorial capacity of the vector population; (iii) the susceptibility of the human population (both genetic factors and pre-existing immune profile); and (iv) the introduction of the virus into a receptive community.

DF/DHF syndrome

DF/DHF is characterized by the "iceberg" or pyramid phenomenon. At the base of the pyramid, most of the cases are symptomless, followed by DF, DHF and DSS. Clusters of cases have been reported in particular households or neighbourhoods due to the feeding behaviour of the vector.

Affected population

The population affected varies from one outbreak to another. Actual estimates can be made by obtaining clinical/subclinical ratios during epidemics. In a well-defined epidemic study in North Queensland, Australia, with primary infection, 20% to 50% of the population was found affected.

Severity of the disease

The serotype that produces the secondary infection and, in particular, the serotype sequence are important to ascertain the severity of the disease. All the four serotypes are able to produce DHF cases. However, during sequential infections, only 2% to 4% of individuals develop severe disease.

Studies in Thailand have revealed that the DENV-1/DENV-2 sequence of infection was associated with a 500 fold risk of DHF compared with primary infection. For the DENV-3/DENV-2 sequence the risk was 150-fold, and a DENV-4/DENV-2 sequence had a 50-fold risk of DHF. There is no time-limit to sensitization after a primary infection. The 1997 Santiago de Cuba epidemic clearly demonstrated that with the introduction of DENV-2, DHF had occurred 16–20 years after the primary infection with DENV-1.

High-risk patients *(3)*

The following host factors contribute to more severe disease and its complications :

1. infants and elderly ;
2. obesity;
3. pregnancy;
4. peptic ulcer disease;
5. women who are in menstruation or have abnormal bleeding;

6. haemolytic disease such as G–6PD, thalassaemia and other haemoglobinopathies;
7. congenital heart disease;
8. chronic diseases such as diabetes mellitus, hypertension, asthma, ischaemic heart disease, chronic renal failure, liver cirrhosis; and
9. patients on steroid or NSAID treatment.

Clinical mainfestations

Dengue virus infection may be asymptomatic or may cause undifferientiated febrile illness (viral syndrome), dengue fever(DF), or dengue haemorrhagic fever (DHF) including dengue shock syndrome (DSS) as shown in Fig.1

1. Undifferentiated fever

Infants, children and adults who have been infected with denuge virus, especially for the first time (i.e. primary dengue infection), may develop a simple fever indistinguishable from other viral infection. Maculopapular rashes may accompany the fever or may appear during defervescence. Upper respiratory and gastrointestinal symptoms are common.

2. Classical dengue fever

All ages and both sexes are susceptible to dengue fever. Children usually have a milder disease than adults. The illness is characterized by an incubation period of 3 to 10 days (commonly 5–6 days). The onset is sudden, with chills and high fever, intense headache, muscle and joint pains, which prevent all movement. Within 24 hours retroorbital pain, particularly on eye movements or eye pressure and photophobia develops. Other common symptoms include extreme weakness, anorexia, constipation, altered taste sensation, colicky pain and abdominal tenderness, dragging pain in inguinal region, sore throat and general depression. Fever is usually between 39°C and 40°C. Fever is typically but not inevitably followed by a remission of a few hours to 2 days (biphasic curve). The skin eruptions appear in 80 per cent of cases during the remission or during second febrile phase, which lasts for 1–2 days. The rash is accompanied by similar but milder symptoms. The rash may be diffuse flushing, mottling or fleeting pin–point eruptions on the face, neck and chest during the first half of the febrile period and a conspicuous rash, that may be maculopapular or scarlatiniform on 3rd or 4th day. It starts on the chest and trunk and may spread to the extremities and rarely to the face. It may be accompanied by itching and hyperaesthesia. The rash lasts for 2 hours to several days and may be followed by desquamation *(1)*. Fever lasts for about 5 days, rarely more than 7 days after which recovery is usually complete although convalescence may be protracted *(8)*. The case fatality is exceedingly low.

3. Dengue haemorrhagic fever

Dengue haemorrhagic fever (DHF) is a severe form of dengue fever. The course of dengue illness can be divided into three phases–febrile phase, critical phase and recovery phase, as shown in Fig. 2 *(9)*.

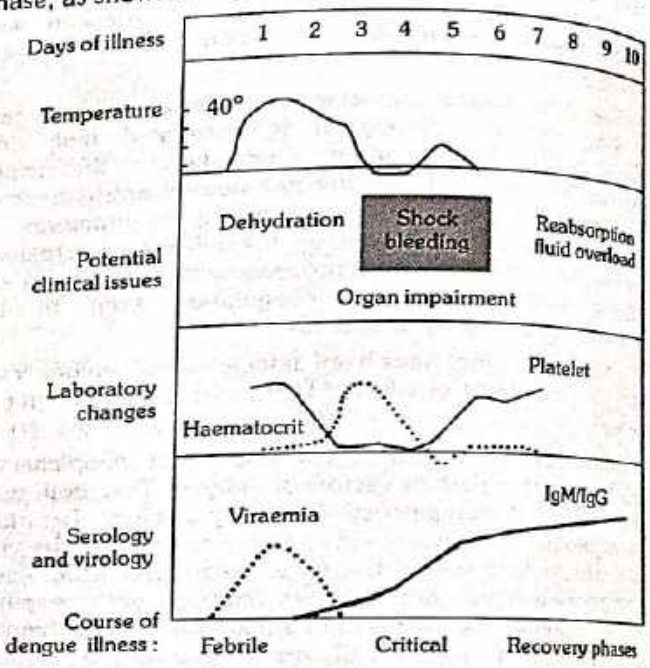

FIG. 2
The course of dengue illness

Source : *(10)*

1. Febrile phase

Following an incubation period of four to six days, the illness commonly begins abruptly with high fever

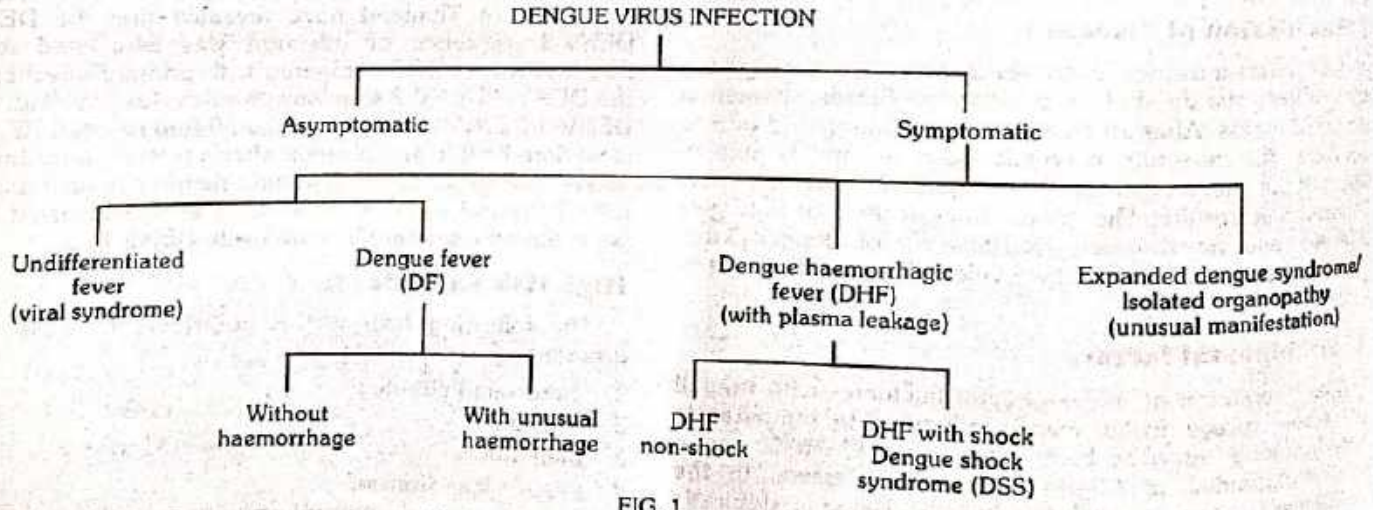

FIG. 1
Manifestations of the dengue virus infection

Source : *(3)*

accompanied by facial flushing and headache. Anorexia, vomiting, epigastric discomfort, tenderness at the right costal margin and generalized abdominal pain are common. During the first few days the illness usually resembles classical DF, but maculopapular rash usually rubelliform type, is less common. It may appear early or late in the course of the illness. Occasionally, the temperature may be 40°C to 41°C and febrile convulsions may occur particularly in infants *(1)*.

The major pathophysiologic changes that determine the severity of disease in DHF and differentiate it from DF are plasma leakage and abnormal haemostasis, as manifested by a rising haematocrit value and moderate to marked thrombocytopenia. These two clinical laboratory changes are distinctive and constant findings.

A positive tournicate test is the most common haemorrhagic phenomenon. The test is performed by inflating a blood pressure cuff to a mid point between systolic and diastolic pressure for 5 minutes. The test is considered positive when 10 or more petechiae per 2.5x2.5 cm (1 inch square) are observed. In DHF, the test usually gives a definite positive with 20 petechiae or more *(6)*.

2. Critical phase (10)

Around the time of defervescence, when the temperature drops to 37.5–38°C or less, and remains below this level, usually on days 3–7 of illness, an increase in capillary permeability in parallel with increasing haematocrit levels may occur. This marks the beginning of the critical phase. The period of clinically significant plasma leakage usually lasts 24–48 hours.

Progressive leukopenia followed by a rapid decrease in platelet count usually precedes plasma leakage. At this point patients without an increase in capillary permeability will improve, while those with increased capillary permeability may become worse as a result of lost plasma volume. The degree of plasma leakage varies. Pleural effusion mostly on right side and ascites may be clinically detectable depending on the degree of plasma leakage and the volume of fluid therapy. Gall bladder oedema has been found to precede plasma leakage. Hence chest X-ray and abdominal ultrasound can be useful tools for diagnosis. The degree of increase above the baseline haematocrit often reflects the severity of plasma leakage.

Shock occurs when a critical volume of plasma is lost through leakage. It is often preceded by warning signs of abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, liver enlargement more than 2 cm. and oliguria. The body temperature may be subnormal when shock occurs. With prolonged shock, the consequent organ hypoperfusion results in progressive organ impairment, metabolic acidosis and disseminated intravascular coagulation. This in turn leads to severe haemorrhage causing the haematocrit to decrease in severe shock. Instead of the leukopenia usually seen during this phase of dengue, the total white cell count may increase in patients with severe bleeding. In addition, severe organ impairment such as severe hepatits, encephalitis or myocarditis and/or severe bleeding may also develop without obvious plasma leakage or shock.

Those who improve after defervescence are said to have non-severe dengue. Some patients progress to the critical phase of plasma leakage without defervescence and, in these patients, changes in the full blood count should be used to guide the onset of the critical phase and plasma leakage. Those who deteriorate will manifest with warning signs. This is called dengue with warning signs. Cases of dengue with warning signs will probably recover with early intravenous rehydration. Some cases will deteriorate to severe dengue.

3. Recovery phase

If the patient survives the 24–48 hours critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48–72 hours. General well-being improves, appetite returns, gastrointestinal symptoms abate, haemodynamic status stabilizes and diuresis ensues. Some patients may have a rash of "isles of white in the sea of red". Some may experience generalized pruritus. Bradycardia and electrocardiographic changes are common during this stage.

The haematocrit stabilizes or may be lower due to the dilutional effect of reabsorbed fluid. White blood cell count usually starts to rise soon after defervescence but the recovery of platelet count is typically later than that of white blood cell count.

Respiratory distress from massive pleural effusion and ascites will occur at any time if excessive intravenous fluids have been administered. During the critical and/or recovery phases, excessive fluid therapy is associated with pulmonary oedema or congestive heart failure.

4. Severe dengue

Severe dengue is defined by one or more of the following : (i) plasma leakage that may lead to shock (dengue shock) and/or fluid accumulation, with or without respiratory distress, and/or (ii) severe bleeding, and/or (iii) severe organ impairment.

As dengue vascular permeability progresses, hypovolaemia worsens and results in shock. It usually takes place around defervescence, usually on day 4 or 5 (range days 3–7) of illness, preceded by the warning signs. During the initial stage of shock, the compensatory mechanism which maintains a normal systolic blood pressure also produces tachycardia and peripheral vasoconstriction with reduced skin perfusion, resulting in cold extremities and delayed capillary refill time. Uniquely, the diastolic pressure rises towards the systolic pressure and the pulse pressure narrows as the peripheral vascular resistance increases. Patients in dengue shock often remain conscious and lucid. The inexperienced physician may measure a normal systolic pressure and misjudge the critical state of the patient. Finally, there is decompensation and both pressures disappear abruptly. Prolonged hypotensive shock and hypoxia may lead to multi-organ failure and an extremely difficult clinical course.

The patient is considered to have shock if the pulse pressure is ≤20 mm Hg in children or he/she has signs of poor capillary perfusion (cold extremities, delayed capillary refill, or rapid pulse rate). In adults, the pulse pressure of ≤20 mm Hg may indicate a more severe shock. Hypotension is usually associated with prolonged shock which is often complicated by major bleeding.

Patients with severe dengue may have coagulation abnormalities, but these are usually not sufficient to cause major bleeding. When major bleeding does occur, it is almost always associated with profound shock since this, in combination with thrombocytopenia, hypoxia and acidosis, can lead to multiple organ failure and advanced disseminated intravascular coagulation. Massive bleeding may occur without prolonged shock in instances when acetylsalicylic acid (aspirin), ibuprofen or corticosteriods have been taken.

Unusual manifestations, including acute liver failure and encephalopathy, may be present, even in the absence of severe plasma leakage or shock. Cardiomyopathy and encephalitis are also reported in a few dengue cases. However, most deaths from dengue occur in patients with profound shock, particularly if the situation is complicated by fluid overload.

CRITERIA FOR CLINICAL DIAGNOSIS *(3, 6, 11, 12)*

A summary of clinical diagnosis of DF and DHF is as follows :

Dengue fever

Probable diagnosis

Acute febrile illness with two or more of the following:

- headache,
- retro-orbital pain,
- myalgia,
- arthralgia/bone pain,
- rash,
- haemorrhagic manifestations,
- leucopenia (wbc ≤ 5000 cells/mm^3),
- thrombocytopenia (platelet count <150,000 cells/mm^3),
- rising haematocrit (5–10%);

OR

- Non-ELISA based NS 1 antigen/IgM Positive (A positive test by RDT will be considered as probable due to poor sensitivity and specificity of currently available RDTs)

Confirmed dengue fever (12) :

A case compatible with the clinical description (see above) of Dengue Fever with at least one of the following :

- Isolation of dengue virus (Virus culture +VE) from serum, plasma, leucocytes
- Demonstration of IgM antibody titre by ELISA positive in single serum sample
- Demonstration of dengue virus antigen in serum sample by NS1-ELISA
- IgG seroconversion in paired sera after 2 weeks of four-fold increase of IgG titre
- Detection of viral nucleic acid by polymerase chain reaction (PCR)

Dengue haemorrhagic fever

All of following :

- acute onset of fever of two to seven days duration.
- haemorrhagic manifestations, shown by any of the following; positive tourniquet test, petechiae, ecchymoses or purpura, or bleeding from mucosa, gastrointestinal tract, injection sites, or other locations.
- platelet count ≤ 100,000 cells/mm^3
- objective evidence of plasma leakage due to increased vascular permeability shown by any of the following :
  - Rising haematocrit/haemoconcentration ≥20% from baseline or evidence of plasma leakage such as pleural effusion, ascites or hypoproteinaemia/ albuminaemia.

Dengue shock syndrome

Criteria for dengue haemorrhagic fever as above with signs of shock including :

- tachycardia, cool extremities, delayed capillary refill, weak pulse, lethargy or restlessness, which may be a sign of reduced brain perfusion.
- pulse pressure ≤ 20 mmHg with increased diastolic pressure, e.g. 100/80 mmHg.
- hypotension by age, defined as systolic pressure <80 mmHg for those aged <5 years, or 80 to 90 mmHg for older children and adults.

Laboratory diagnosis *(3, 6, 12)*

Rapid and accurate dengue diagnosis is of a paramount importance for : (1) clinical management; (2) epidemiological surveillance; (3) research; and (4) vaccine trials. Epidemiological surveillance requires early determination of dengue virus infection during the outbreak for urgent public health action towards control, as well as at sentinel sites for detection of circulating serotypes/genotypes during the inter-epidemic period for use in forecasting possible outbreak. The following laboratory tests are available to diagnose dengue fever and DHF :

ELISA BASED NS1 ANTIGEN TESTS : Dengue NS1 antigen, a highly conserved glycoprotein, produced in both membrane-associated and secretory forms, is abundant in the serum of patients during the early stages of dengue infection and has been found to be useful as a tool for the diagnosis of acute dengue infections. It is a simple test that is highly specific and shows high sensitivity. NS1 antigen enables early detection of cases i.e., in the viremic stage, which has epidemiological significance for containing the transmission. The dengue virus NS1 ELISA antigen assay is commercially available. This assay has been evaluated for sensitivity and specificity. The NS1 assay may also be useful for differential diagnosis between flaviviruses because of the specificity of the assay.

IGM-CAPTURE ENZYME-LINKED IMMUNOSORBENT ASSAY (MAC-ELISA) : MAC-ELISA has been widely used in the past few years.It is a simple test which does not require any sophisticated equipment. It is based on detecting the dengue-specific IgM antibodies in the test serum by capturing them using anti-human IgM that was previously bound to the solid phase. This is followed by addition of dengue antigen, if the IgM antibody from the patient's serum is anti-Dengue, it will bind to the Dengue antigen. An enzyme-substrate is added to give a color reaction for easy detection.

The anti-dengue IgM antibody develop faster than IgG and is usually detectable by day 5 of the illness. However, the rapidity with which IgM develops varies considerably among patients. Some patients have detectable IgM on days two to four after the onset of illness, while others may not develop IgM for seven to eight days after the onset. In some primary infections, detectable IgM may persist for more than 90 days, but in most patients, it wanes off to undetectable levels by 60 days. It is reasonably certain, however that the person had a dengue infection sometime in the previous two to three months. MAC-ELISA has become an invaluable tool for surveillance of dengue fever. In areas where dengue is not endemic, it can be used in clinical surveillance for viral illness or for random, population-based sero-surveys, with the certainty that any positives detected are recent infections. It is especially useful for hospitalized patients, who are generally admitted late in the illness after detectable IgM is already present in the blood.

ISOLATION OF DENGUE VIRUS : Isolation of most strains of dengue virus from clinical specimens can be accomplished in majority of cases provided the sample is taken in the first five

days of illness and processed without delay. Specimens that may be suitable for virus isolation include acute phase serum, plasma or washed buffy coat from the patient, autopsy tissues from fatal cases, especially liver, spleen, lymph nodes and thymus and mosquitoes collected in nature. Isolation of virus takes 7–10 days, hence may not be very useful for starting the management of patient with dengue fever.

PCR (POLYMERASE CHAIN REACTION) : Molecular diagnosis based on reverse transcription (RT-PCR), such as one-step or nested RT-PCR, nucleic acid sequence-based amplification (NASBA), or real-time RT-PCR, has gradually replaced the virus isolation method as the new standard for the detection of dengue virus in acute-phase serum samples.

IgG-ELISA : An IgG-ELISA has been developed that compares well to the Hemagglutination-Inhibition (HI) test. This test can also be used to differentiate primary and secondary dengue infections. The test is simple and easy to perform but not considered as a diagnostic test as it indicates past infections only.

SEROLOGICAL TESTS : Besides, MAC ELISA and IgG-ELISA, there are few serological tests available for the diagnosis of dengue infection like hemagglutination-Inhibition (HI), complement fixation (CF) and neutralization test (NT) which are not commonly used due to various technical problems.

RAPID DIAGNOSTIC TESTS : A number of commercial Rapid Diagnostic Test (RDT) kits for anti-dengue IgM/IgG antibodies and NS1 antigen are commercially available at present which give the results within 15 to 25 minutes. However, the accuracy of most of these tests is not known since they have not yet been properly validated. Some of the RDTs have been independently evaluated. The results showed a high rate of false positive compared to standard tests, while others have agreed closely with standard tests. The sensitivity and specificity of some RDTs were also found to vary from batch to batch. Hence, currently, the programme does not recommend the use of RDTs for diagnosis and guiding the management of Dengue fever cases.

CLINICAL MANAGEMENT

Grading of the severity of dengue infection

To decide where to treat the patient, it is important to classify the severity of dengue infection. The presence of thrombocytopenia with concurrent haemoconcentration and depending on the clinical manifestations, presence of warning signs and other high-risk factors, patients may be classified as following :

- Mild dengue (A) : May be managed on OPD basis
- Moderate dengue (B) : Observation or admission for in-hospital management
- Severe dengue (C) : Require emergency treatment and urgent referral

Fig. 3 summarizes the clinical case classification of dengue *(12)*.

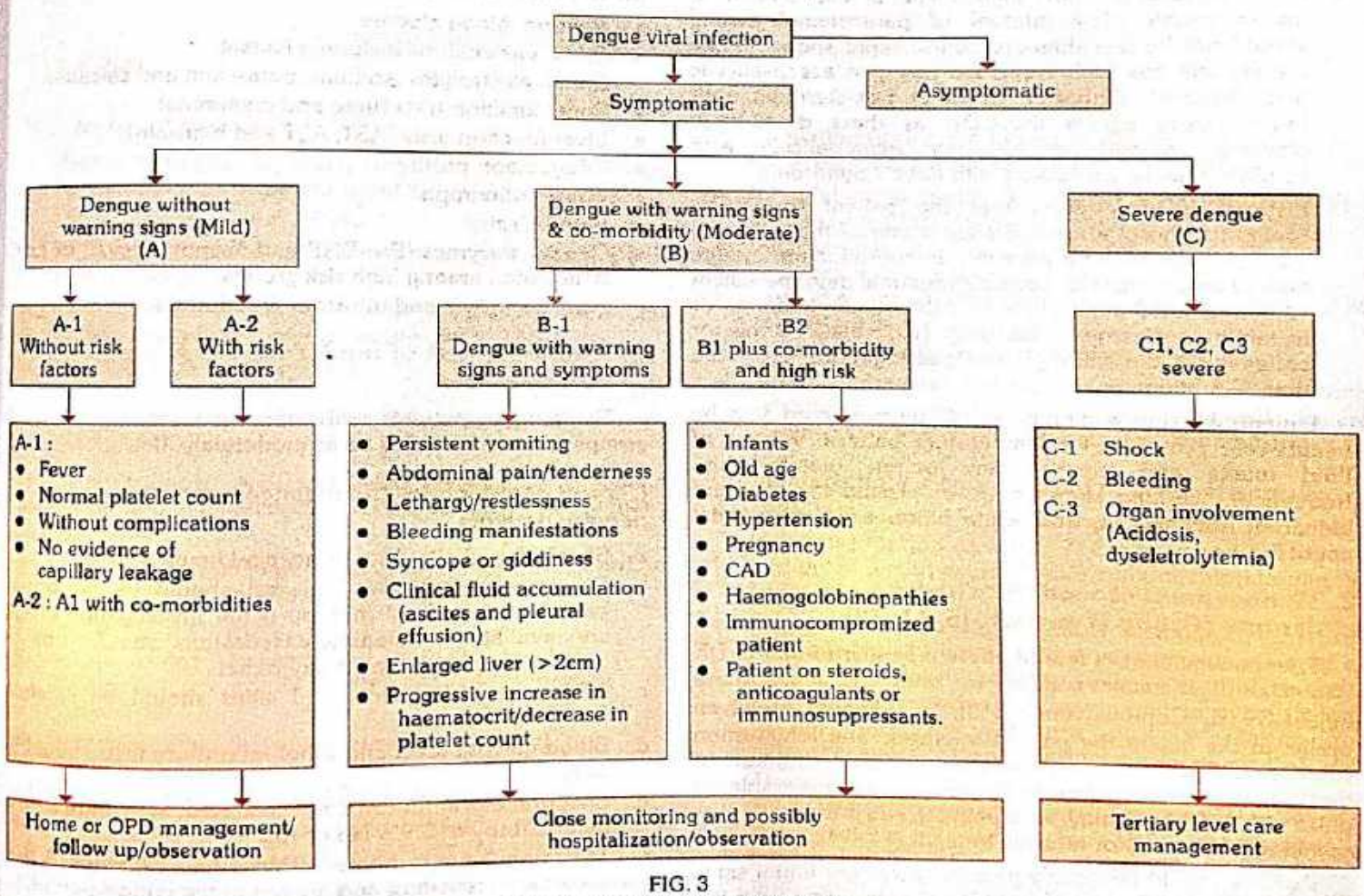

FIG. 3
Clinical case classification of dengue

Source : *(12)*

GUIDELINES FOR TREATMENT

A full blood count of the patient should be done at the first visit. A haematocrit test in the early febrile phase establishes the patient's own baseline haematocrit. A rapidly decreasing platelet count in parallel with a rising haematocrit compared to the baseline is suggestive of progress to the plasma leakage/critical phase of the disease. In the absence of the patients baseline, age specific population haematocrit levels could be used as a surrogate during the critical phase.

1. Management of mild dengue fever (Group A)

These are patients who are able to tolerate adequate volumes of oral fluids and pass urine at least once every six hours, and do not have any of the warning signs, particularly when fever subsides. Those with stable haematocrit can be sent home after being advised to return to the hospital immediately if they develop any of the warning signs, and to adhere to the following action plan :

(1) Encourage intake of oral rehydration solution (ORS), fruit juice and other fluids containing electrolytes and sugar to replace losses from fever and vomiting. Adequate oral fluid intake may be able to reduce the number of hospitalizations. (Caution : fluids containing sugar/glucose may exacerbate hyperglycaemia of physiological stress from dengue and diabetes mellitus.)

(2) Give paracetamol for high fever if the patient is uncomfortable. The interval of paracetamol dosing should not be less than six hours. Tepid sponge if the patient still has high fever. Do not give acetylsalicylic acid (aspirin), ibuprofen or other non-steroidal anti-inflammatory agents (NSAIDs) as these drugs may aggravate gastritis or bleeding. Acetylsalicylic acid (aspirin) may be associated with Reye's Syndrome.

(3) Instruct the care-givers that the patient should be brought to hospital immediately if any of the following occur; no clinical improvement, deterioration around the time of defervescence, severe abdominal pain, persistent vomiting, cold and clammy extremities, lethargy or irritability/restlessness, bleeding (e.g. black stools or coffee–ground vomiting), not passing urine for more than 4–6 hours.

Patients who are sent home should be monitored daily by health care providers for temperature pattern, volume of fluid intake and losses, urine output (volume and frequency), warning signs, signs of plasma leakage and bleeding, haematocrit, and white blood cell and platelet counts.

2. Management of moderate and severe dengue (Group B and C) *(6, 11, 12)*

The management of febrile phase is similar to that of DF. Paracetamol is recommended to keep the temperature below 39°C. Copious amount of fluid should be given orally, to the extent the patient tolerates, oral rehydration solution (ORS), such as those used for the treatment of diarrhoeal disesases and/or fruit juices are preferable to plain water. IV fluid may be administered, if the patient is vomiting persistently or refusing to feed.

Patients should be closely monitored for the initial signs of shock. The critical period is during the transition from the febrile to the afebrile stage and usually occurs after the third day of illness.

The following parameters should be monitored :

- General condition, appetite, vomiting, bleeding and other warning signs and symptoms.
- Peripheral perfusion assessment should be done as frequently as indicated because it is an early indicator of shock and is easy and fast to perform.
- Vital signs such as temperature, pulse rate, respiratory rate and blood pressure should be checked at least every 2-4 hours in non-shock patients and every 1-2 hourly in patients with shock.
- Serial haematocrit should be performed at least every four to six hours in stable cases and should be more frequent in unstable patients or those with suspected bleeding. It should be noted that haematocrit should be done before fluid resuscitation. If this is not possible, then it should be checked after the fluid bolus, but not during the infusion of the bolus.
- Urine output should be recorded at least every 8 to 12 hours in uncomplicated cases and on an hourly basis in patients with profound/prolonged shock or those with fluid overload. During this period the amount of urine output should be about 0.5 ml/kg/h (this should be based on the ideal body weight).

Additional laboratory investigations :

Adult patients and those with co-morbidities or patients in shock and/or those with complications should undergo the following laboratory investigations.

- Random blood glucose
- Blood gas analysis including lactate
- Serum electrolytes (sodium, potassium and calcium)
- Renal function tests (urea and creatinine)
- Liver function tests (AST, ALT and bilirubin)
- Coagulation profile
- Chest radiograph
- Blood Group
- Cardiac enzymes (Pro-BNP and Troponin level) or ECG if indicated among high risk groups
- Serum amylase and ultrasound abdomen.

2A. Management of moderate dengue patients (Group B)

The dengue patients with warning signs and high-risk groups are considered to be as moderately ill.

Clinical approach for the management of moderate dengue patients

a. Should be admitted for in-hospital management.
b. Baseline haematocrit (hct) test should be performed before starting fluid therapy if the investigation results are available immediately.Hydration should not be delayed due to unavailability of hct.
c. All warning symptoms and signs should be carefully observed.
d. Blood glucose level and other laboratory tests should be done.
e. Encourage oral fluids. If not tolerated, start intravenous fluid therapy of 0.9% NS or RL.
f. They can be sent home within 12 to 24 hours if they show rapid recovery and are not in the critical period.

Fig. 4 shows the algorithms for hospital management of moderate dengue patients with warning signs.

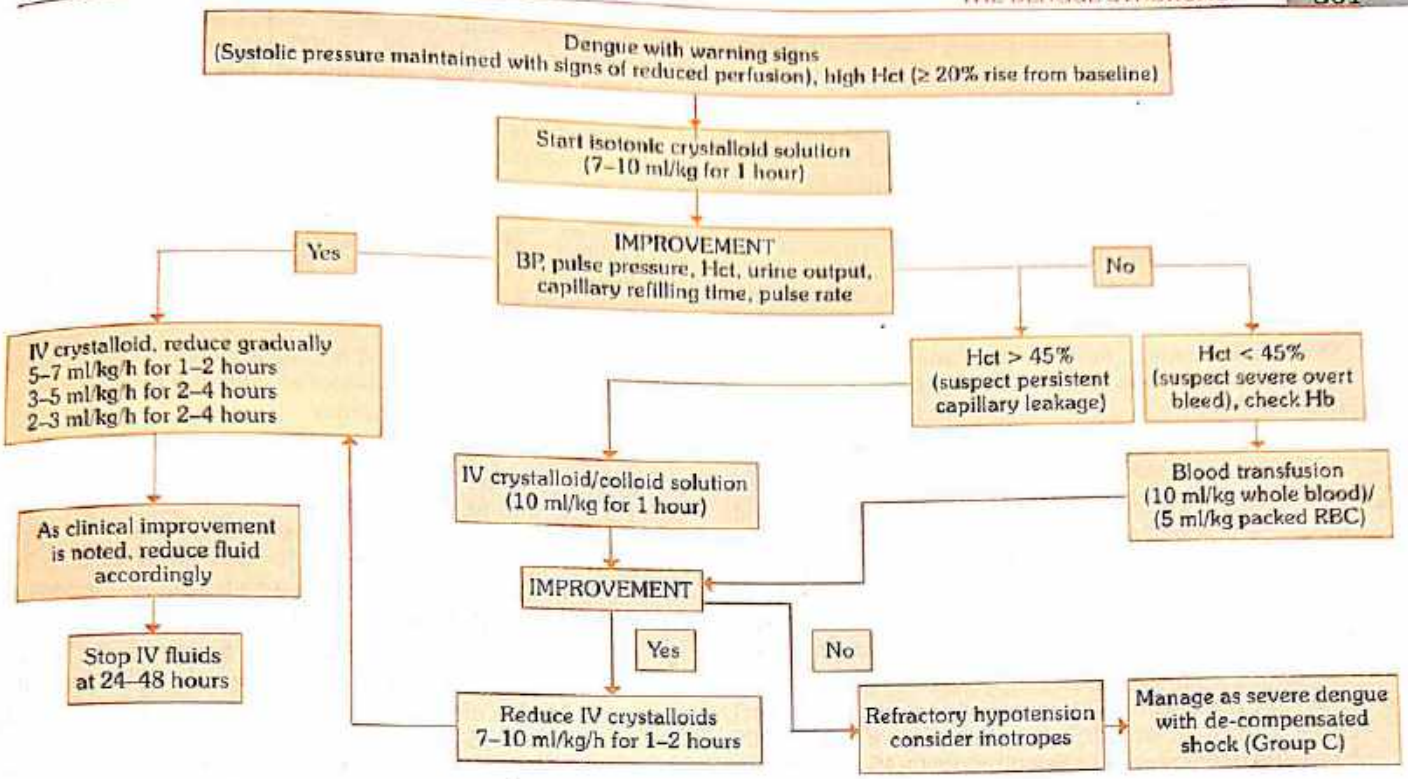

FIG. 4

Algorithms for hospital management of moderate dengue patients with warning signs

Source : *(12)*

Monitoring of the patient

a. Record temperature, pulse, respiratory rate, BP should be monitored until patient is out of critical phase;
b. Urine output record 6 hourly;
c. HCT determination before and after fluid replacement, then 8 hourly;
d. Investigation for blood glucose, renal profile, liver profile, coagulation profile, as indicated; and
e. Maintain fluid balance sheet.

2B. Management of Severe Dengue patients (Group C)

These patients are vulnerable and require urgent admission and management. Severe dengue has following characteristics :

a. Severe plasma leakage leading to dengue shock and/or fluid accumulation with respiratory distress.
b. Severe haemorrhages.
c. Severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis).
d. Severe metabolic abnormalities.

Principles of management of severe dengue (12) :

- All patients to be stabilised and referred for admission to a hospital which has blood transfusion facilities.
- Judicious IV fluid resuscitation is essential and lifesaving.
- Prefer a crystalloid solution (0.9% Normal saline or Ringer lactate) sufficient to maintain an effective circulation during the period of plasma leakage (usually for 24–48 hours) and adjust fluid as per the patient status
- It's advised to obtain hematocrit level before starting fluid therapy; lack of haematocrit should not delay fluid management.
- Monitor vital signs every 5–30 min.
- Use IBW for overweight and obese patients while calculating fluid rates.
- Blood group of the patient to be investigated
- Blood transfusion should be given to patients with established severe bleeding, or suspected severe bleeding (fall in Hct) with unexplained hypotension.

Intravenous fluid therapy during the critical period

- Isotonic crystalloid solutions should be used throughout the critical period except in the very young infants <6 months of age in whom 0.45% sodium chloride may be used.
- Hyper-oncotic colloid solutions (osmolarity of >300 mOsm/l) such as dextran 40 or starch solutions may be used in patients with massive plasma leakage, and those not responding to the maximum volume of crystalloid. Iso-oncotic colloid solutions such as plasma and hemaccel may not be as effective.
- The duration of intravenous fluid therapy should not exceed 24 to 48 hours for those with shock. However, for those patients who do not have shock, the duration of intravenous fluid therapy may have to be longer but not more than 60 to 72 hours. This is because the latter group of patients has just entered the plasma leakage period while shock patients have experienced a longer

duration of plasma leakage before intravenous therapy has begun.

- Always check for the signs of fluid overload.
- It should be noted that restoring the blood pressure is critical for survival and if this cannot be achieved quickly then the prognosis is extremely grave. Inotropes may be used to support the blood pressure at this stage.

Management of compensated shock *(12)*

The action plan for treating patients with compensated shock is as shown in algorithm of Fig. 5.

- Start intravenous fluid resuscitation with isotonic crystalloid solutions at 10–20ml/kg body weight/hour over one hour.
- Reassess the patient's condition (vital signs, capillary refill time, haematocrit, urine output)
- If the patient's condition improves, intravenous fluids should be gradually reduced to 7–10 ml/kg body weight/hr for 1–2 hours, then to 5–7 ml/kg body weight/hr for 1–2 hours, then to 3–5 ml/kg body weight/hr for 2–4 hours, then 2–3 ml/kg body weight/hr for 2–3 hours and then further depending on haemodynamic status, which can be maintained for up to 24–48 hours.
- If patient is not clinically improved (i.e. shock persists), check the haematocrit after the first bolus. If the haematocrit increases or is still high (>45%), repeat a second bolus of crystalloid solution at 10ml/kg body weight/hr for one hour. After this second bolus, if there is improvement, reduce the rate to 7–10 ml/ kg body weight/hr for 1–2 hours, and then continue to reduce as above.
- If haematocrit decreases compared to the initial reference haematocrit (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible. Give whole blood transfusion at 10ml/kg body weight or packed RBC at 5ml/kg body weight.

Management of Decompensated shock *(12)*

Patients with decompensated/hypotensive shock should be managed more vigorously. The action plan for treating patients with hypotensive shock is as shown in the algorithm of Fig. 6.

- Initiate intravenous fluid resuscitation with crystalloid or colloid solution (if available) at 20 ml/kg body weight as a bolus given over 15 minutes
- If the patient's condition improves, give a crystalloid/colloid infusion of 10 ml/ kg body weight/hr for one hour. Then continue with crystalloid infusion and gradually reduce to 5–7 ml/kg body weight/hr for 1–2 hours, then to 3–5 ml/kg body weight/hr for 2–4 hours, and to 2–3 ml/kg body weight/hr or less, which can be maintained for up to 24–48 hours
- If shock persists, review the haematocrit. If the haematocrit increases or is still high (>45%), repeat a second bolus of crystalloid solution at 10-20 ml/kg body weight over 15–30 minutes. After this second bolus, if there is improvement, reduce the rate to 7–10 ml/ kg body weight/hr for 1–2 hours, and then continue gradual reduction of fluid as mentioned above. Upto three rapid boluses may be given.
- If haematocrit decreases compared to the initial reference

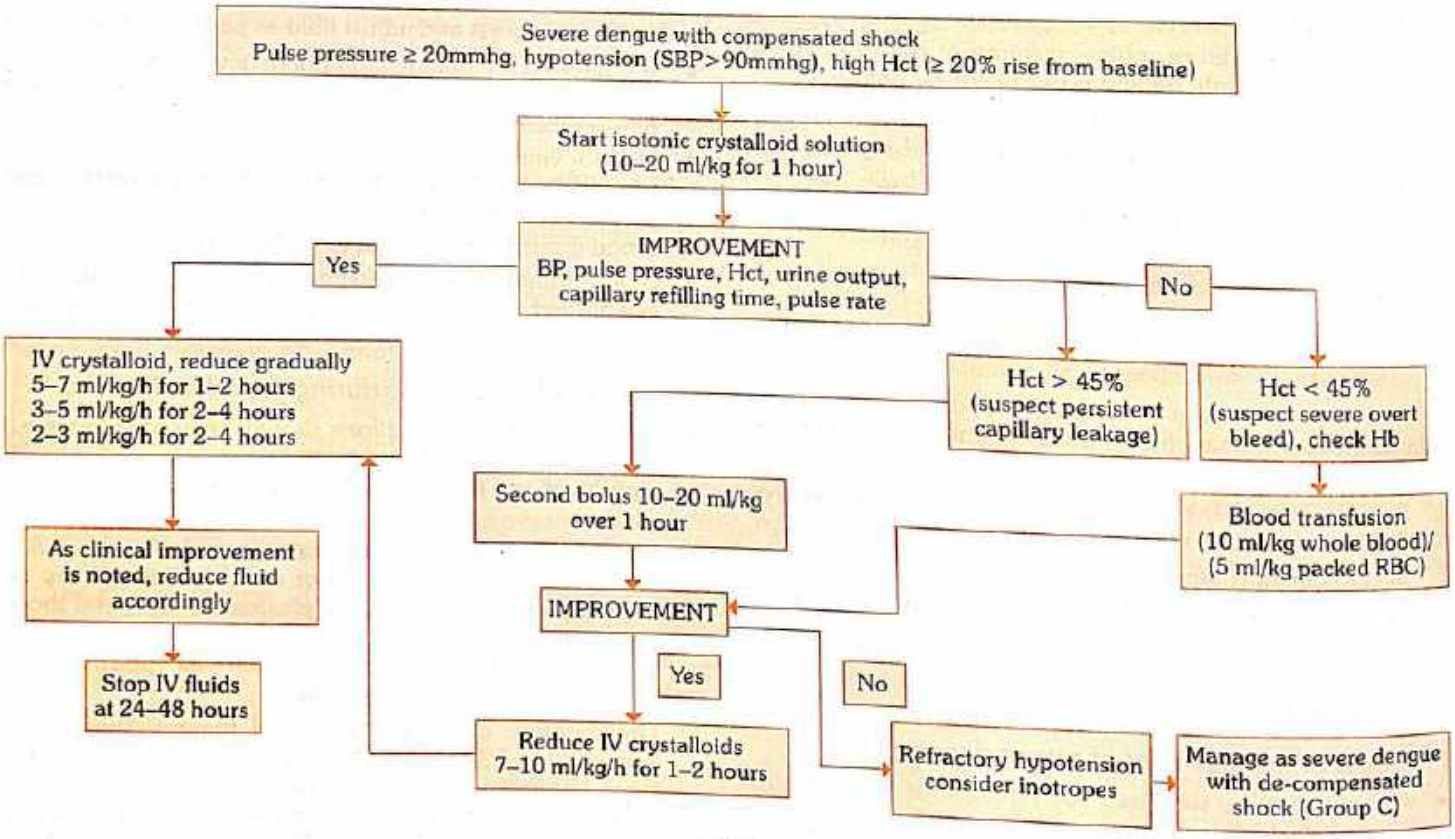

FIG. 5
Algorithm for management of severe dengue with compensated shock

Source : *(12)*

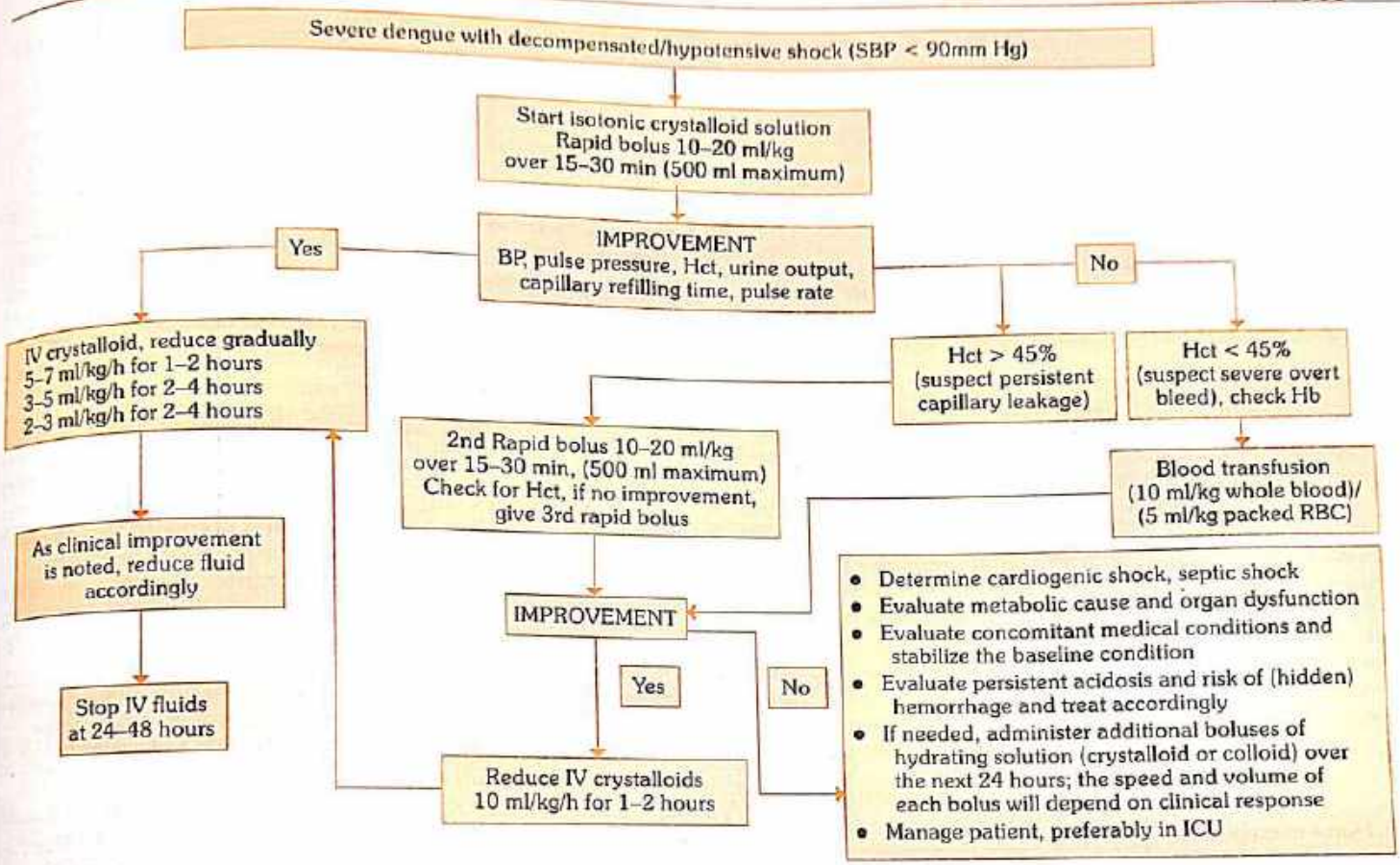

FIG. 6

Algorithm for management of severe dengue with decompensated shock

Source : *(12)*

haematocrit (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible. Give whole blood transfusion at 10ml/kg body weight or packed RBC at 5ml/kg body weight.

- If the shock is refractory
  - Use of inotropes should be considered.
  - Determine cardiogenic shock, septic shock
  - Evaluate metabolic cause and organ dysfunction
  - Evaluate concomitant medical conditions and stabilize the baseline condition
  - Evaluate persistent acidosis and risk of (hidden) hemorrhage and treat accordingly
  - If needed, administer additional boluses of hydrating solution (crystalloid or colloid) over the next 24 hours; the speed and volume of each bolus will depend on clinical response;
  - Manage patient, preferably in ICU.

Indications of red cell transfusion

1. Loss of blood (overt blood) – 10 per cent or more of total blood volume – preferably give whole blood or components to be used.
2. Refractory shock despite adequate fluid administration and declining haematocrit.
3. Replacement volume should be 10 ml/kg body weight at a time and coagulogram should be done.
4. If fluid overload is present packed cells are to be given.

Indications of platelet transfusion

In general there is no need to give prophylactic platelet even at < 20,000/cu.mm.

1. Prophylactic platelet transfusion may be given at level of < 10,000/cu.mm.
2. Prolonged shock; with coagulopathy and abnormal coagulogram.
3. In case of systemic massive bleeding, platelet transfusion may be needed in addition to red cell transfusion.

Criteria for discharge of patients

1. Absence of fever for atleast 24 hours without the use of anti-pyretic drugs.
2. Return of appetite.
3. Visible clinical improvement.
4. Good urine output.
5. Minimum of 2–3 days after recovery from shock.
6. No respiratory distress from pleural effusion or ascites.
7. Platelet count > 50,000/cu.mm.

Management and referral of dengue cases at Primary Health Centre (PHC) level

In the PHC, the following guidelines (as shown in Fig. 7) have to be followed for management of dengue cases and for referral of severe/complicated cases to higher centre :

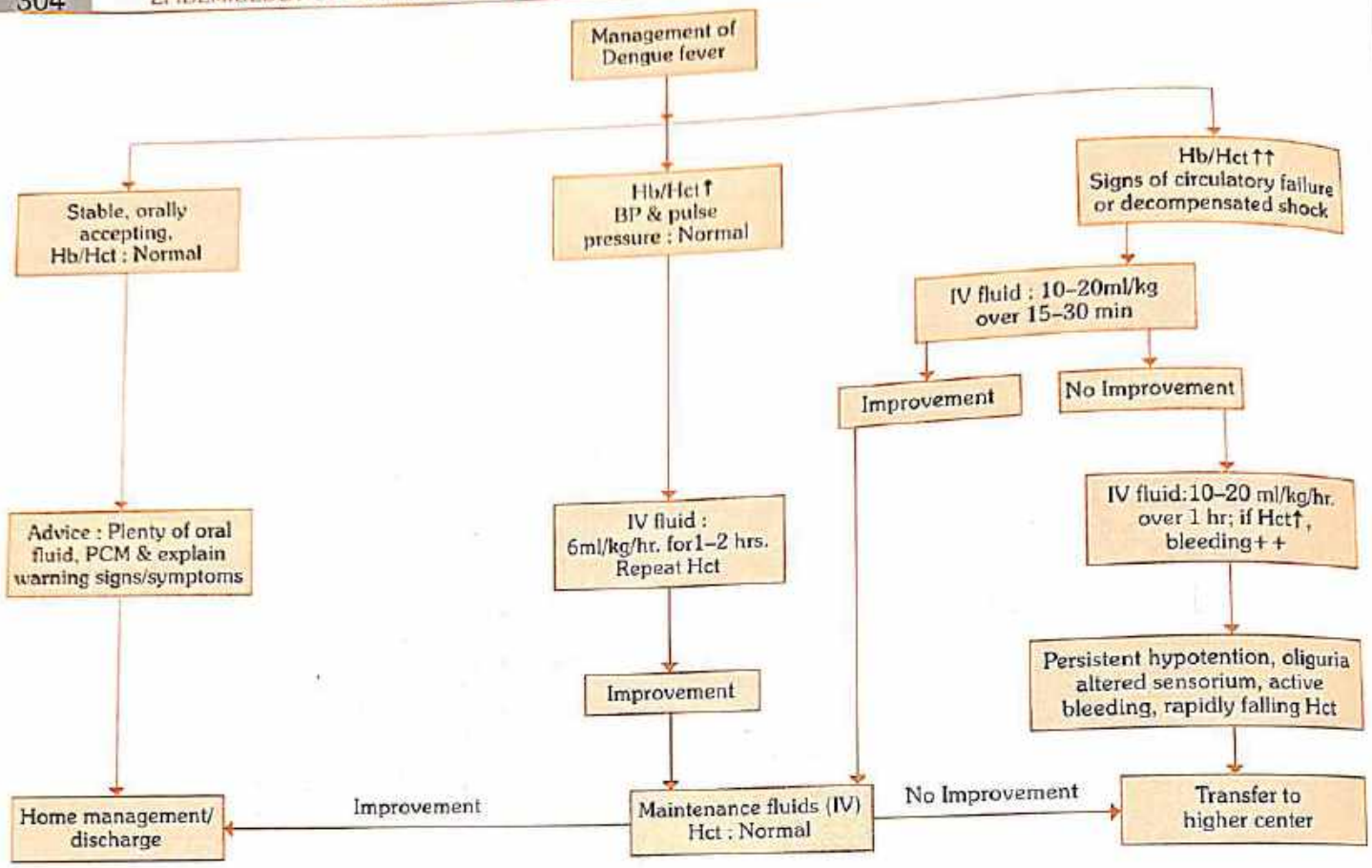

FIG. 7
Management and referral of dengue cases at PHC level

Source : *(12)*

Patient should be advised to come for follow-up after 24h for evaluation. He should report to the nearest hospital immediately in case of the following complaints :

- Bleeding from any site (fresh red spots on skin, black stools, red urine, nose bleed, menorrhagia)
- Severe abdominal pain
- Refusal to take orally / poor intake
- Persistent vomiting, not passing urine for 12 hr.
- Decreased urinary output
- Restlessness
- Seizure
- Excessive crying (young infants),
- Altered sensorium and behavioral changes
- Severe persistent headache
- Cold clammy skin
- Sudden drop in temperature.

Disease notification

In dengue-endemic countries, cases of suspected, probable and confirmed dengue should be notified as soon as possible so that appropriate health measures can be initiated.

CONTROL MEASURES

1. Mosquito control

The vectors of DF and DHF (e.g., *A. aegypti*) breed in and around houses and, in principle can be controlled by individual and community action, using antiadult and antilarval measures. These measures are outlined in chapter 15.

2. Vaccines *(13)*

There are currently 2 licensed dengue vaccines : CYD-TDV (Dengvaxia, Sanofi); and TAK-003 (Qdenga, Takeda). Both are tetravalent live-attenuated vaccines but differ in the extent of chimerization and the genome back-bone, as well as in efficacy and safety.

CYD-TDV vaccine

CYD-TDV consists of 4 live attenuated recombinant viruses (representing each of the 4 DENV serotypes) with an attenuated yellow fever 17D virus genome back-bone.

The vaccine schedule consists of 3 doses administered 6 months apart, with an indication for individuals aged 9–45 years or 9–60 years (depending on the country-specific regulatory approvals) living in dengue-endemic countries or areas. In clinical trials, CYD-TDV has been shown to be efficacious and safe in persons who have had dengue virus infection in the past (seropositive individuals), but increases the risk of severe dengue in those who experience their first natural dengue infection after vaccination (seronegative individuals). For countries considering vaccination as part of their dengue control programme, pre-vaccination screening for past dengue infection is the recommended strategy. Using this strategy, only persons with evidence of past dengue infection (based on an antibody test, or documented laboratory confirmation) would be vaccinated.

TAK-003 vaccine

The vaccine is tetravalent, live-attenuated vaccine and needs to be reconstituted using 0.22% saline solution. It is commercially available in single-dose vial or pre-filled syringes. The vaccine must be stored at a temperature of 2–8°C and has a shelf life of 18 months. The vaccination schedule for the primary series is 2 doses administered subcutaneously with an interval of 3 months between doses. The vaccine is licensed for use in individuals aged ≥4 years by the European Medicines Agency and the United Kingdom's Medicines and Healthcare products Regulatory Agency; in Indonesia, it is licensed for use in those aged 6–65 years. The age indication for use varies between countries.

The manufacturer stipulates that vaccination is contra-indicated in: (1) individuals with a history of severe allergic reaction to any component of the dengue vaccine or after prior administration of the dengue vaccine or a vaccine containing the same components; (2) individuals with congenital or acquired immune deficiency that impairs cell-mediated immunity; (3) individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function; (4) pregnant or breastfeeding women; and that vaccination should be postponed in individuals with moderate to severe febrile or acute disease.

3. Other measures

Isolation of the patient under bed-nets during the first few days; individual protection against mosquitoes.

The personal prophylactic measures are wearing of full sleeves shirts and full pants; use of mosquito repellent creams, liquids, coils, mats etc.; use of bed-nets for sleeping infants and young children during day time to prevent mosquito bite.

The environmental measurements are detection and elimination of mosquito breeding places, management of roof tops, porticos and sunshades, proper covering of stored water, observation of weekly dry day.

Global strategy for dengue prevention and control 2012–2020 *(14)*

Dengue is a global threat that requires a global response involving all possible partners. The global strategy promotes co-ordination and collaboration among multisectoral partners on integrated vector management approach and sustained control measures at all levels. The goals are :

a. to reduce dengue mortality by at least 50 per cent by 2020;
b. to reduce dengue morbidity by at least 25 per cent by 2020; and
c. to estimate the true burden of the disease by 2015.

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MALARIA

Malaria is a protozoal disease caused by infection with parasites of the genus **Plasmodium** and transmitted to man by certain species of infected female Anopheline mosquito. A typical attack comprises three distinct stages : cold stage, hot stage and sweating stage. The clinical features of malaria vary from mild to severe, and complicated, according to the species of parasite present, the patient's state of immunity, the intensity of the infection and also the presence of concomitant conditions such as malnutrition or other diseases. The febrile paroxysms occur with definite intermittent periodicity repeating every third or fourth day depending upon the species of the parasite involved.

Problem statement

WORLD

There were an estimated 249 million malaria cases in 2022 in 85 malaria endemic countries, increasing from 247 million in 2021. Malaria case incidence reduced from 81 in 2000 to 58 in 2022. The malaria mortality rate halved from about 29 in 2000 to 14.3 in 2022. Globally, malaria deaths declined from 8,64,000 in 2000 to 6,08,000 in 2022 *(1)*.

Approximately 95 per cent of malaria cases and deaths occur in sub-Saharan Africa, with the remainder occurring largely in South-East Asia (about 2 per cent of the estimated burden of malaria cases globally) and South America. Almost all malaria deaths are caused by *Plasmodium falciparum* and most occur in African children under 5 years of age. Adults who have lived in areas with high malaria transmission since childhood and remain resident in such areas are generally not at risk of death from malaria, as they usually have naturally acquired immunity as a result of repeated infections in childhood. *Plasmodium vivax* is an important cause of malaria morbidity outside sub-Saharan Africa. Vaccine development efforts have focused on preventing illness from *P. falciparum* and, to a lesser extent, *P. vivax (2)*.

WHO guidance defines malaria transmission levels as follows : high malaria transmission settings are those with an approximate annual parasite incidence (API) greater than 450 cases per 1000 population or a *P. falciparum* prevalence in children aged 2–10 years (PfPR) greater than 35%; moderate transmission settings are those with an API between 250 and 450 cases per 1000 population or between 10% and 35% PfPR; and low transmission settings are those with an API between 100 and 250 cases per 1000 population or between 1% and 10% PfPR. These thresholds are indicative and should not be regarded as absolutes for determining the applicability of WHO recommendations for malaria interventions *(2)*.

The specific risk groups for malaria includes the following population *(4)* :

1. young children in stable transmission areas who have not yet developed protective immunity against the most severe forms of the disease;
2. non-immune pregnant women as malaria causes high rates of miscarriage and can lead to maternal death;
3. semi-immune pregnant women in areas of high transmission. Malaria can result in miscarriage and low birth weight, especially during first and second pregnancies;
4. semi-immune HIV-infected pregnant women in stable transmission areas, during all pregnancies. Women with malaria infection of the placenta also have a higher risk of passing HIV infection to their newborns;
5. people with HIV/AIDS;
6. international travellers from non-endemic areas because they lack immunity.
7. immigrants and their children living in non-endemic areas and returning to their home countries to visit friends and relatives are similarly at risk because of waning or absent immunity.

Acquired immunity

Natural immunity to malaria is acquired gradually with repeated exposure to *Plasmodium* infection. Immunity is acquired more rapidly against the more severe forms of the disease. Hence, with increasing age, there is progressive protection first against severe malaria and ensuing mortality, then against uncomplicated malaria and, much more slowly, asymptomatic parasitaemia. In areas of moderate to high transmission, malaria mortality rates begin to fall by around 2 years of age, with the incidence of acute febrile malaria falling later in childhood *(3)*.

Naturally acquired immunity is believed to wane substantially in people who migrate out of a malaria-endemic region and are no longer regularly exposed to malaria infection for a number of years. The use of available preventive interventions can delay the development of naturally acquired immunity. Significant roles for both humoral and cell-mediated effectors have been demonstrated in animal models, and both humoral and cell-mediated immune responses are induced in humans after natural malaria infection *(3)*.

Malaria affects mainly poor, underserved and marginalized populations in remote rural areas which are characterized by inadequate control measures and limited access to health care. Higher malaria prevalence has been reported among ethnic and tribal groups living in remote forested and border areas, as well as among mobile and migrant populations.

The childhood deaths result mainly from cerebral malaria and anaemia. Fatality rates of 10–30 per cent have been reported among children referred to hospital with severe malaria. However, these rates are even higher in rural and remote areas where patients have restricted access to adequate treatment. Malaria also contributes indirectly to illness and deaths from respiratory infections, diarrhoeal disease and malnutrition. Deaths from malaria in countries outside Sub-Saharan Africa occur principally in non-immune people who become infected with *P. falciparum*.

Underreporting of malaria cases and deaths remain a major challenge. Drug-resistant parasites, poor treatment-seeking behaviour and the presence of counterfeit antimalarial drugs further hinder control efforts. Resistance of *P. falciparum* to the 4–aminoquinolines and sulfadoxine-pyrimethamine is widespread in almost all countries of SEAR, with varying levels of severity. Resistance to mafloquine was reported from Myanmar and Thailand. Quinine has reduced susceptibility in Thailand. With progress from mono-to-multidrug resistance, all malaria-endemic countries that have *falciparum* malaria adopted the highly effective artemisinin–based combination therapy (ACT).

The coverage of indoor residual spraying with insecticides (IRS) remains low (42 per cent). Insecticide-treated nets have been introduced in almost all countries to supplement IRS efforts, but the coverage remains extremely low.

INDIA

India has made substantial progress in reducing malaria burden. The country has achieved a reduction of 80.53% in malaria morbidity and 78.38% in malaria mortality between 2015 and 2023 *(5)*. In 2023, National Annual Parasite Incidence was 0.16 per 1000 population and total 34 States/UTs have achieved Annual Parasite Incidence less than one except 2 States i.e. Tripura (5.69) and Mizoram (14.23). In 2023, 122 districts in the country have reported 'zero malaria cases'. Malaria has been made notifiable in 34 States/UTs (except Andaman & Nicobar Islands and Bihar) *(5)*. Malaria surveillance data of the country is as shown in Table 1.

TABLE 1
Countrywide malaria surveillance data 2001–2022

Year	BSE (in millions)	Total malaria cases (in millions)	*P. falciparum* cases (in millions)	Pf %	API	ABER	SPR	SFR	Deaths due to malaria
2001	90.389	2.085	1.005	–	2.12	9.18	2.31	1.11	1005
2015	121.14	1.17	0.78	66.61	0.92	9.58	0.97	0.64	384
2016	124.93	1.09	0.71	65.53	0.85	9.74	0.87	0.57	331
2017	125.97	0.84	0.53	62.70	0.64	9.58	0.67	0.42	194
2018	124.44	0.34	0.16	47.93	0.32	9.31	0.35	0.17	96
2019	134.23	0.34	0.16	46.36	0.25	9.95	0.25	0.12	77
2020	97.17	0.19	0.12	63.84	0.014	7.08	0.19	0.12	93
2021	114.293	0.16	0.10	63.10	0.12	8.25	0.14	0.09	90
2022	512.082	0.176	0.98	57.26	0.13	10.89	0.12	0.07	83

Pf – Plasmodium falciparum
API – Annual parasite incidence
SPR – Slide positivity rate
BSE – Blood smear examined
ABER – Annual blood examination rate
SFR – Slide falciparum rate
Source : *(5)*

India is predominantly characterized by unstable malaria transmission. Transmission is seasonal with increased intensity related to rains. Due to the low and unstable transmission dynamics, most of the population has no or little immunity toward malaria. As a result, the majority of Indians living in malarious areas are at risk of infection with all age groups affected. However, surveys have shown that in some foci, mainly in forested areas, transmission is intense and the disease burden is to a large extent concentrated in children.

There are six primary vectors of malaria in India : (1) *An. culicifacies* is the main vector of rural and peri-urban areas and is widespread in peninsular India. It is found in a variety of natural and man-made breeding sites. It is highly zoophilic. Species A is an established vector for *P. Vivax* and *P. falciparum*, whereas species B is completely refractory to *P. Vivax* and partially refractory to *P. falciparum*. It has been demonstrated that species B, however, may play a role as a vector of *P. falciparum* in areas where the cattle population is very low or absent; (2) *An. stephensi* is responsible for malaria in urban and industrial areas. The type form is found in urban areas; intermediate form in urban and semi-urban localities and *mysorensis* form is present in rural areas (it is not a vector); (3) *An. fluviatilis* is the main vector in hilly areas, forests and forest fringes in many states, especially in the east; (4) *An. minimus* is the vector in the foot hills of North-Eastern states; (5) *An. dirus* is an important forest vector in the North-East; and (6) *An. epiroticus* is now restricted to the Andaman and Nicobar Islands *(6)*.

Prevalent major epidemiological types of malaria in India *(7)*

In the course of the stratification exercise, various problems and constraints responsible for the slow progress of malaria control have been identified. An analysis of these factors has resulted in the identification of malaria priority areas.

TRIBAL MALARIA : The population of tribal areas are contributing about 50 per cent of *P. falciparum* cases of the country *(6)*. Infants, young children and pregnant women have been identified as malaria high risk groups followed by mobile tribal population engaged in forest–related activities. Limited health infrastructure and lack of drugs at village level are the factors responsible for high morbidity and mortality due to malaria.

RURAL MALARIA : These include irrigated areas of arid and semiarid plains. Malaria is of moderate to low endemicity. *An. culicifacies* is the main vector and *P.vivax* is predominant during lean period and *P. falciparum* during periodic exacerbation. In these the health infrastructure is moderately developed.

URBAN MALARIA : 15 major cities including four metropolitans account for nearly 80 per cent of malaria cases covered under urban malaria control scheme. The health infrastructure is well developed. In peri-urban areas malaria situation is influenced by poor sanitary conditions and low socio-economic groups living in unplanned settlements prone to periodical epidemics.

MALARIA IN PROJECT AREAS : Project areas are those areas where construction and developmental activities are taken up and temporary tropical aggregation of labourers takes place bringing in different strains of malaria parasite and non-immune population. This results in disturbance in eco-system, prolific increase in vector breeding places and increased man–mosquito contact favouring high malaria transmission. These pockets contribute a large number of malaria cases which are highly disproportionate to the relatively small population groups inhabitating the area. One or more major vectors are involved in malaria transmission. Limited health facilities for prompt treatment is invariably associated with chloroquine resistant malaria parasite. Hence specific control strategy is required for such areas.

BORDER MALARIA : These are the high malaria transmission belts along the international borders and state borders. These areas have their own problems in regard to malaria control because of mixing of population and poor administrative control.

FOREST MALARIA : Forests and settlements in recently deforested areas are known to harbour very efficient malaria vectors. These vectors bite humans in their shelters, but return to rest in the forest, avoiding residual insecticides sprayed indoors in the shelters. Malaria transmission is therefore, more intense and more difficult to control in temporary or newly established forest settlements *(8)*.

FLOODS AND MALARIA : Floods may lead to a rise in incidence of malaria. Flooding may initially flush out mosquito breeding, but later result in pools of water creating mosquitogenic conditions. The lag time between the floods and possible malaria epidemic is estimated to be around 6–8 weeks *(8)*.

Some definitions *(8)*

Malaria control : reducing the malaria disease burden to a level at which it is no longer a public health problem.

Malaria elimination : the interruption of local mosquito-borne malaria transmission; reduction to 'zero' of the incidence of infection caused by human malaria parasites in a defined geographical area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required.

Certification of malaria elimination : can be granted by WHO after it has been proven beyond reasonable doubt that the chain of local human malaria transmission by *Anopheles* mosquitoes has been fully interrupted in an entire country for at least 3 consecutive years.

Malaria eradication : permanent reduction to 'zero' of the worldwide incidence of infection caused by a specific agent; applies to a particular malaria parasite species. Intervention measures are no longer needed once eradication has been achieved.

Epidemiological determinants

Agent factors

(a) AGENT

Malaria in man is caused by four distinct species of the malaria parasite – *P. vivax*, *P. falciparum*, *P. malariae* and *P. ovale*. *Plasmodium vivax* has the widest geographic distribution throughout the world. In India, about 50 per cent of the infections are reported to be due to *P. falciparum* and 4–8 per cent due to mixed infection and rest due to *P. vivax*. *P. malariae* has a restricted distribution and is said to be responsible for less than 1 per cent of the infections in India. The largest focus of *P. malariae* in India is reported to be in Tumkur and Hassan districts in Karnataka. *P. ovale* is a very rare parasite of man, mostly confined to tropical Africa. It has also been reported in Vietnam. The severity of malaria is related to the species of the parasite.

Life history

The malaria parasite undergoes 2 cycles of development – the human cycle (asexual cycle) and the mosquito cycle (sexual cycle). Man is the intermediate host and mosquito the definitive host (Fig. 1).

(i) *Asexual cycle:* The asexual cycle begins when an infected mosquito bites a person and injects sporozoites. A considerable amount of new knowledge about the parasite's life cycle has become available in recent years, concerning almost all phases of the cycle *(9)*. A brief description is as follows – four phases are described in the human cycle: (a) HEPATIC PHASE: The sporozoites disappear within 60 minutes from the peripheral circulation *(10)*. Many of them are destroyed by phagocytes, but some reach the liver cells. After 1–2 weeks of development (depending upon the species), they become hepatic schizonts, which eventually burst releasing a shower of merozoites. The number of merozoites produced from a single sporozoite varies considerably with the infecting species. A single *P. falciparum* sporozoite may form as many as 40,000 merozoites, whereas sporozoites from other species of plasmodia produce only 2,000 to 15,000 merozoites *(10)*. In the case of *P. falciparum*, the intrahepatic schizonts rupture almost simultaneously and there is no persistent tissue phase (the so-called exo-erythrocytic phase). On the contrary, the intrahepatic schizonts of the other plasmodia do not burst all at the same time. Some hepatic forms persist and remain dormant in the hepatocytes for considerable periods before they begin to grow and undergo pre-erythrocytic schizogony, thus liberating merozoites into the blood stream causing relapses of these infections. *P. vivax* and *P. ovale* may continue to relapse for 2 to 3 years and *P. malariae* may persist for 10 to 20 years or more. Once the parasites enter the RBC, they do not reinvade the liver. (b) ERYTHROCYTIC PHASE: Many of the merozoites are quickly destroyed, but a significant number attach to specific receptor sites on the RBC. The merozoites then penetrate the RBC and pass through the stages of trophozoite and schizont. The erythrocytic phase ends with the liberation of merozoites, which infect fresh red blood cells. The cycle is repeated over and over again until it is slowed down by the immune response of the host *(11)*. The duration of the erythrocytic cycle is constant for each species of malaria parasite – 48 hours for *P. falciparum*, *P. vivax* and *P. ovale*; and 72 hours for *P. malariae*. (c) GAMETOGENY: In all species of malaria some erythrocytic forms do not divide but become male and female gametocytes. These are the sexual forms of the parasite which are infective to mosquito.

(ii) *Sexual cycle:* The mosquito cycle (sporogony) begins when gametocytes are ingested by the vector mosquito when feeding on an infected person. The gametocytes continue further development in the mosquito. The first event to take place in the stomach of the mosquito is exflagellation of the male gametocyte; 4–8 thread–like

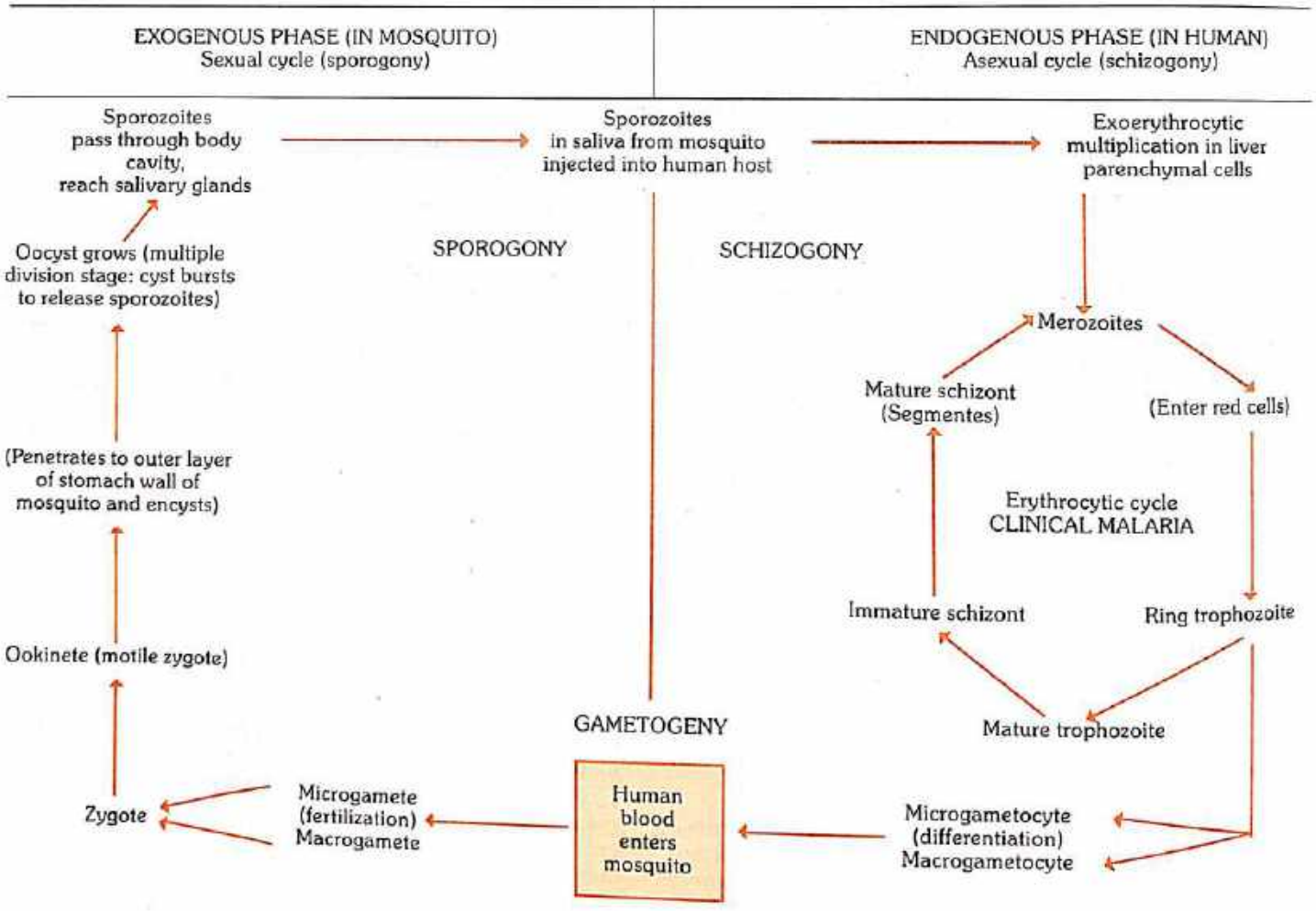


FIG. 1
Lifecycle of the malaria parasite.

Source : *(12)*

filaments called "micro-gametes" are developed. The female gametocyte undergoes a process of maturation and becomes a female gamete or "macrogamete". By a process of chemotaxis, microgametes are attracted towards the female gamete, and one of which (microgamete) causes fertilization of the female gamete. The resulting zygote is at first a motionless body, but within 18–24 hours, it becomes motile. This is known as *Ookinete*, which penetrates the stomach wall of the mosquito and develops into an oocyst on the outer surface of the stomach. The oocyst grows rapidly and develops within it numerous sporozoites. When mature, the oocyst bursts and liberates sporozoites into the body cavity of mosquito. Many of the sporozoites migrate to the salivary glands of the mosquito, and the mosquito now becomes infective to man. The period of time required for the development of the parasite from the gametocyte to sporozoite stage in the body of the mosquito is about 10–20 days depending upon favourable conditions of atmospheric temperature and humidity. This period is also referred to as the "extrinsic incubation period".

(b) RESERVOIR OF INFECTION

With the possible exception of chimpanzees in tropical Africa, which may carry the infection with *P. malariae*, no other animal reservoir of human plasmodia is known to exist *(11)*. A human reservoir is one who harbours the sexual forms (gametocytes) of the parasite. A patient can be a carrier of several plasmodial species at the same time. Children are more likely to be gametocyte carriers than adults. The child is thus epidemiologically a better reservoir than the adult. Certain conditions must be met before a person can serve as a reservoir: (i) the person must harbour both the sexes of the gametocyte in his blood. If the person harbours only male or female gametocytes, further development cannot take place in the mosquito vector, (ii) the gametocytes must be mature; immature forms do not undergo further development. It may take 2–4 days for the gametocytes to attain maturity after their appearance in the blood, (iii) the gametocytes must be viable, i.e., if the patient receives an antimalarial drug, the gametocytes lose their viability or infectivity to mosquitoes (iv) the gametocytes must be present in sufficient density to infect mosquitoes. The number of gametocytes necessary to infect mosquitoes is not definitely known, but it is thought by some that there must be at least 12 per cubic mm of blood.

(c) PERIOD OF COMMUNICABILITY

Malaria is communicable as long as mature, viable gametocytes exist in the circulating blood in sufficient density to infect vector mosquitoes. In vivax infections, gametocytes appear in blood 4–5 days after the appearance of the asexual parasites; in falciparum infections, they do not appear until 10–12 days after the first appearance of asexual parasites. Gametocytes are the most numerous during the early stages of the infection when their density may exceed 1,000 per cubic mm of blood. They also tend to occur in waves in peripheral blood.

RELAPSES: It is usual for vivax and ovale malaria to relapse more than 3 years after the patient's first attack. Recurrences of falciparum malaria usually disappear within 1–2 years. *P. malariae* has a tendency to cause prolonged low-level, asymptomatic parasitaemia *(13)*. The infection is known to persist for 40 years or more. It is probable that persons harbouring such infections are at least occasionally infective to mosquitoes.

It is now considered more likely that vivax and ovale relapses are derived from original, sporozoite-induced, liver schizonts which have lain latent long before bursting. In *P. falciparum* and *P. malariae* infections latent liver schizonts do not appear to occur. Relapses in these species, most authorities maintain, are due to a chronic blood infection, i.e., erythrocytic schizogony persisting at a low level.

Host factors

The main variables of the human element that have an influence on malaria epidemiology include the following :

(a) AGE : Malaria affects all ages. Newborn infants have considerable resistance to infection with *P. falciparum*. This has been attributed to the high concentration of foetal haemoglobin during the first few months of life, which suppresses the development of *P. falciparum (14)*. (b) SEX : Males are more frequently exposed to the risk of acquiring malaria than females because of the outdoor life they lead. Further, females in India are usually better clothed than males. (c) RACE : Individuals with AS haemoglobin (sickle-cell trait) have a milder illness with falciparum infection than do those with normal (AA) haemoglobin *(10)*. Persons whose red blood cells are "Duffy negative" (a genetic trait) are resistant to *P. vivax* infection. (d) PREGNANCY : Pregnancy increases the risk of malaria in women. Malaria during pregnancy may cause intrauterine death of the foetus; it may also cause premature labour or abortion. Primigravid women are at greatest risk *(15)*. (e) SOCIO-ECONOMIC DEVELOPMENT : Malaria has demonstrated the relationship between health and socio-economic development. It is generally accepted that malaria has disappeared from most developed countries as a result of socio-economic development *(15)*. (f) HOUSING: Housing plays an important role in the epidemiology of malaria. The ill-ventilated and ill-lighted houses provide ideal indoor resting places for mosquitoes. Malaria is acquired in most instances by mosquito-bites within the houses. The site, type of construction, nature of the walls, etc. influence the selection of control measures *(16)*. (g) POPULATION MOBILITY : People migrate for one reason or other from one country to another or from one part of a country to another. Labourers connected with various engineering, irrigation, agricultural and other projects and periodic migration of nomads and wandering tribes are outstanding examples of internal migration. Some of them may import malaria parasites in their blood and reintroduce malaria into areas where malaria has been controlled or eliminated. Imported malaria has become quite a public health problem in Europe, North America, and other temperate parts of the world, owing to the rising tide of air travel, tourism and migration *(12)*. (h) OCCUPATION : Malaria is predominantly a rural disease and is closely related to agriculture practices. (i) HUMAN HABITS : Habits such as sleeping out of doors, nomadism, refusal to accept spraying of houses, replastering of walls after spraying and not using measures of personal protection (e.g. bed nets) influence man-vector contact, and obviously the choice of control measures. (j) IMMUNITY: The epidemic of malaria is influenced by the immune status of the population. Immunity to malaria in humans is acquired only after repeated exposure over several years. Thus in endemic malarious areas a state of collective immunity becomes established slowly, so that infants, young children, migrants and travellers from non-endemic areas suffer most from the disease. Those, however, who survive to the adult age show

less evidence of adverse effects to the attenuated infection. Infants born of immune mothers are generally protected during the first 3–5 months by maternal IgG antibody; infants born of semi-immune mothers are only partially protected. Active immunity is species-specific, that is, immunity against one strain does not protect against another. People living in endemic areas exposed continually to malaria develop considerable degree of resistance to clinical disease, but their partial immunity to malaria declines with time after they leave their endemic countries. Semi-immune individuals may harbour malaria parasites without presenting any symptoms of disease. Both humoral and cellular factors play a role in this protection *(4)*.

Environmental factors

India's geographic position and climatic conditions had been, for long, favourable to the transmission of malaria. (a) SEASON : Malaria is a seasonal disease. In most parts of India, the maximum prevalence is from July to November. (b) TEMPERATURE: Temperature affects the life cycle of the malaria parasite. The optimum temperature for the development of the malaria parasite in the insect vector is between 20 deg. to 30 deg.C (68 deg. to 86 deg.F). The parasite ceases to undergo development in the mosquito if the mean temperature is below 16 deg.C (60.8 deg.F). Temperatures higher than 30 deg.C are lethal to the parasite. (c) HUMIDITY: The atmospheric humidity has a direct effect on the length of life of the mosquito, although it has no effect on the parasite. A relative humidity of 60 per cent is considered necessary for mosquitoes to live their normal span of life. When the relative humidity is high, mosquitoes are more active and they feed more voraciously. If the humidity is low, mosquitoes do not live long. (d) RAINFALL : Rain in general provides opportunities for the breeding of mosquitoes and may give rise to epidemics of malaria. Rain increases the atmospheric humidity which is necessary for the survival of mosquitoes. However, heavy rain may have an adverse affect in flushing out the breeding places. Paradoxically in some areas, (e.g., Sri Lanka) severe epidemics of malaria followed years of drought. It was because, the lesser monsoon rains led to the formation of small pools of water in river beds, which served as active breeding places for malaria vectors. The relationship between rainfall (total and its distribution) and mosquito breeding is of fundamental importance *(17)*. (e) ALTITUDE: As a rule, *Anophelines* are not found at altitudes above 2000–2500 metres, due to unfavourable climatic conditions. (f) MAN-MADE MALARIA: Burrow pits, garden pools, irrigation channels and engineering projects like construction of hydroelectric dams, roads, bridges have led to the breeding of mosquitoes and an increase in malaria. Malaria consequent on such human undertakings is called "man-made malaria".

Vector of malaria

Out of about 45 species of anopheline mosquitoes in India, only a few are regarded as the vectors of primary importance. These are: *An. culicifacies, An. fluviatilis, An. stephensi, An. minimus, An. philippinensis, An. sundaicus,* and *An. maculatus*. The vectors of major importance are *An. culicifacies* in rural areas and *An. stephensi* in urban areas.

In the absence of a vaccine, vector control is the only practical approach to malaria control. A knowledge of anopheline biology is essential for understanding the epidemiology of malaria and its prevention. The main factors which determine the vectorial importance of mosquitoes are: (a) DENSITY : To be an effective vector, a species must be present in adequate density in or near human habitations. A sudden increase in density of vectors, may be a cause of epidemic outbreaks. For each vector, there is what is known as "critical density" below which effective transmission cannot be maintained in a community. This level varies with different species. In the case of *An. culicifacies* a high density is required for the propagation of malaria; in the case of *An. fluviatilis* which is very efficient vector, a much lower density would suffice. (b) LIFE SPAN: The key factor in the transmission of malaria is the life span of the vector. The vector mosquito must live for at least 10–12 days after an infective blood meal to become infective. The strategy in malaria eradication is to shorten the life span of mosquitoes to less than 10 days by insecticides. (c) CHOICE OF HOST : Some mosquitoes prefer human blood, some animal blood, and some show great variation in their feeding habits. The percentage of human blood feeds in the case of *An. culicifacies*, an important vector in India, has been found to vary from 2–80 per cent *(10)*. In contrast, *An. fluviatilis* is a highly anthrophilic species. The anthrophilic species, i.e., those that have a high preference for human blood are better vectors of malaria than zoophilic species. (d) RESTING HABITS : After a blood meal, some mosquitoes rest indoors on the walls for quite sometime. This behaviour pattern is known as "endophily". But there are some species which rest outdoors (exophily). A knowledge of the resting habits (which must be under constant surveillance) is the basis for organizing rational anti-adult measures. In fact, the concept of malaria eradication is based on endophilism (indoor resting habits) of most malarial vectors. (e) BREEDING HABITS: The breeding habits of mosquitoes vary considerably. Some breed in moving water *(An. fluviatilis)*, some in brackish water *(An. sundaicus)* and some in wells, cisterns, fountains and overhead tanks *(An. stephensi)*. A knowledge of the breeding habits is required for conducting anti-larval operations. (f) TIME OF BITING : The majority of Indian mosquitoes bite at night excepting the Aedes mosquitoes. Anophiline mosquitoes have nocturnal feeding habits, between dusk and dawn. (g) VECTORIAL CAPACITY : The term vectorial capacity refers to the combined effect of the density of the vector population, its susceptibility to infection, life span and probability of feeding on man. It is distinct from physiological capacity to transmit infection. (h) RESISTANCE TO INSECTICIDES : A knowledge of the status of vector resistance to insecticides is also necessary. On this depends the choice of insecticides to be used. When an insect vector is resistant to a given insecticide, alternative insecticides have to be used.

Mode of transmission

(a) VECTOR TRANSMISSION: Malaria is transmitted by the bite of certain species of infected, female, anopheline mosquitoes. A single infected vector, during her life time, may infect several persons. The mosquito is not infective unless the sporozoites are present in its salivary glands. (b) DIRECT TRANSMISSION: Malaria may be induced accidentally by hypodermic intramuscular and intravenous injections of blood or plasma, e.g., blood transfusion malaria in drug addicts *(18, 19)*. Blood transfusion poses a problem because the parasites keep their infective activity for at least 14 days in blood bottles stored at –4 deg. C *(18)*. Persons who have lived in an endemic area (including those who have been taking antimalarials prophylactically) and

anyone who has had malaria should not be accepted as blood donor until 3 years afterwards *(20)*. (c) CONGENITAL MALARIA: Congenital infection of the newborn from an infected mother may also occur, but it is comparatively rare.

Incubation period

This is the length of time between the infective mosquito bite and the first appearance of clinical signs of which fever is most common. This period is usually not less than 10 days.

The duration of the incubation period varies with the species of the parasite, and in natural infections (in mosquito-transmitted malaria) this is 12 (9–14) days for falciparum malaria, 14 (8–17) days for vivax malaria, 28 (18–40) days for quartan malaria and 17 (16–18) days for ovale malaria. With some strains of *P. vivax*, the incubation period may be delayed for as long as 9 months; this may also occur with other species in persons who have been taking suppressive antimalarial drugs *(10)*.

Clinical features

The primary fever is marked by paroxysms which correspond to the development of the parasites in the red blood cells. The peaks of the fever coincide with the release into the blood stream of successive broods of merozites.

The typical attack comprises three distinct stages, i.e., the cold stage, the hot stage and the sweating stage. These are followed by an afebrile period in which the patient feels greately relieved.

COLD STAGE : The onset is with lassitude, headache, nausea and chilly sensation followed in an hour or so by rigors. The temperature rises rapidly to 39–41°C. Headache is often severe and commonly there is vomiting. In early part of this stage, skin feels cold; later it becomes hot. Parasites are usually demonstrable in the blood. The pulse is rapid and may be weak. This stage lasts for 1/4–1 hour.

HOT STAGE : The patient feels burning hot and casts off his clothes. The skin is hot and dry to touch. Headache is intense but nausea commonly diminishes. The pulse is full and respiration rapid. This stage lasts for 2 to 6 hours.

SWEATING STAGE : Fever comes down with profuse sweating. The temperature drops rapidly to normal and skin is cool and moist. The pulse rate becomes slower, patient feels relieved and often falls asleep. This stage lasts for 2–4 hours.

The febrile paroxysms occur with definite intermittent periodicity repeating every third or fourth day depending upon the species of the parasite involved. The classical 3 stages (cold, hot and sweating) may not always be observed due to maturation of generations of parasite at different times. Periods of latency may last several weeks or months *(10, 21)*. The disease has a tendency to relapse and is characterized by enlargement of the spleen and secondary anaemia. Febrile herpes is common in all malarial patients.

In patients with *P. falciparum* infection the primary fever in its first few days is usually irregular or even continuous and then the classical 48 hours periodicity becomes established or the fever may continue to be irregular and the hot and cold stages, so typical of other malarial infections are less clearly separated from one another. In persons with poor immunity the paroxysms are associated with marked prostration. Headache, nausea and vomiting are usually more severe, and there is greater tendency towards the development of delirium, haemolytic jaundice and anaemia. The mortality is much greater than in other forms of malaria.

With *P. vivax* infection, symptoms are same but are usually milder and more regularly divided into "hot" and "cold" stages than in *P. falciparum* infections.

P. ovale infections differ little from that of *P. vivax*. However, they tend to be milder than *P. vivax* and cease after a few paroxysms even if no treatment is given.

Clinically, *P. malariae* attacks resemble those of *P. vivax* but the cycle is of 72 hours instead of 48 hours. The tendency for long-term relapses to occur is marked.

The complications of *P. falciparum* malaria are cerebral malaria, acute renal failure, liver damage, gastro-intestinal symptoms, dehydration, collapse, anaemia, blackwater fever etc. The complications of *P. vivax*, *P. ovale* and *P. malariae* infections are anaemia, splenomegaly, enlargement of liver, herpes, renal complications etc.

Diagnosis

The diagnosis of malaria depends on demonstration of the parasite in the blood. Suspicion of the diagnosis is aroused by epidemiological and clinical evidence.

1. Microscopy

Two types of blood films are useful in searching for and identification of malaria parasite. The "thin film" and the "thick film". It is recommended that both types of film be prepared on a single microscope glass slide. The thick film is more reliable in searching for parasite, as large volume of blood is examined under each microscope field. When scanty, parasite may be found about 20 times more rapidly in thick slide than in thin slide. The thin slide is more valuable for identifying the species of the parasite present. In it they are seen more clearly.

The advantage of microscopy are : The sensitivity is high. It is possible to detect malarial parasite at low densities. It also helps to quantify the parasite load; It is possible to distinguish the various species of malaria parasite and their different stages.

2. Serological test

The malarial fluorescent antibody test usually becomes positive two weeks or more after primary infection, by which time the infection may have been cured. A positive test is therefore, not necessarily an indication of current infection. The test is of the greatest value in epidemiological studies and in determining whether a person has had malaria in the past *(22)*.

3. Rapid diagnostic test (RDT)

Rapid Diagnostic Tests are based on the detection of circulating parasite antigens with a simple dipstick format. Several types of RDTs are available. Some of them can only detect *P. falciparum* while others can detect other parasites also. The latter kits are expensive and temperature sensitive. RDTs are produced by different companies, so there may be differences in the contents and in the manner in which the test is done. The users manual should always be read properly to avoid false negative results *(23)*.

Measurement of malaria

PRE-ERADICATION ERA

In the pre-eradication era, the magnitude of the malaria problem in a country used to be determined mostly from the reports of the *clinically diagnosed malaria cases*. The

classical malariometric measures are spleen rate, average enlarged spleen, parasite rate etc. In a control programme, the case detection machinery is weak. Therefore, the classical malariometric measures may provide the needed information, i.e. the *trend of the disease.*

(a) SPLEEN RATE : It is defined as the percentage of children between 2 and 10 years of age showing enlargement of spleen. Adults are excluded from spleen surveys, because causes other than malaria frequently operate in causing splenic enlargement in them. The spleen rate is widely used for measuring the endemicity of malaria in a community. (b) AVERAGE ENLARGED SPLEEN : This is a further refinement of spleen rate, denoting the average size of the enlarged spleen *(24)*. It is a useful malariometric index. (c) PARASITE RATE : It is defined as the percentage of children between the ages 2 and 10 years showing malaria parasites in their blood films. (d) PARASITE DENSITY INDEX : It indicates the average degree of parasitaemia in a sample of well-defined group of the population. Only the positive slides are included in the denominator *(10)*. (e) INFANT PARASITE RATE : It is defined as the percentage of infants below the age of one year showing malaria parasites in their blood films. It is regarded as the most sensitive index of recent transmission of malaria in a locality. If the infant parasite rate is zero for 3 consecutive years in a locality, it is regarded as absence of malaria transmission even though, the Anopheline vectors responsible for previous transmission may remain. (f) PROPORTIONAL CASE RATE : Since the morbidity rate is difficult to determine, except in conditions when the diagnosis and reporting of each case is carried to perfection, proportional case rate is used *(10)*. It is defined as the number of cases diagnosed as clinical malaria for every 100 patients attending the hospitals and dispensaries. This is a crude index because the cases are not related to their time/space distribution.

ERADICATION ERA (current incidence levels)

During the eradication era, the *microscopic diagnosis* of malaria cases became the main method of diagnosis. The parameters used for the measurement of malaria were mostly parasitological in nature; the commonly used parameters were API, ABER, SPR and SFR. The same parameters are being used at the present time. These parameters are unlikely to reveal the true epidemiological picture, unless the case detection machinery is fully supervised and very efficient. The following parameters are in use at present :

a. Annual parasite incidence (API)
b. Annual blood examination rate (ABER)
c. Annual falciparum incidence (AFI)
d. Slide positivity rate (SPR)
e. Slide falciparum rate (SFR).

a. Annual parasite incidence (API)

API is given by the formula :

$$\text{API} = \frac{\text{Confirmed cases during one year}}{\text{Population under surveillance}} \times 1000$$

API is a sophisticated measure of malaria incidence in a community. It is based on intensive active and passive surveillance, and cases are confirmed by blood examination. Areas with API ≥ 2 per 1000 population per year have been classified as high risk areas in India, and thereby eligible for vector control.

b. Annual blood examination rate (ABER)

ABER is given by the formula :

$$\text{ABER} = \frac{\text{Number of slides examined}}{\text{Population}} \times 100$$

ABER is an index of operational efficiency. The annual parasite incidence (API) depends upon the annual blood collection and examination rates. A sufficient number of blood slides must be systematically obtained and examined for malaria parasite to work out accurately annual parasite incidence (API).

At present, about 100 million fever cases are screened every year in India. The aim is to screen 10 per cent of the population even though the disease transmission is expected to reduce. The surveillance system has not undergone any change *(6)*.

c. Annual falciparum incidence

Since the emergence of *P. falciparum* problem in India, data are collected separately for total malaria cases and *P. falciparum* cases.

d. Others

The slide positivity rate and slide falciparum rate are useful parameters. They provide information on the trend of malaria transmission.

Slide positivity rate : slide positivity rate is the percentage of slides found positive for malarial parasite, irrespective of the type of species.

Slide falciparum rate : It is the percentage of slides positive for *P. falciparum* parasite.

VECTOR INDICES

A malaria survey is not complete unless it includes investigations relating to the insect vector. Some of the important vector indices are: (a) HUMAN BLOOD INDEX : It is the proportion of freshly-fed female Anopheline mosquitoes whose stomach contains human blood. It indicates the degree of anthrophilism. (b) SPOROZOITE RATE : It is the percentage of female anophelines with sporozoites in their salivary glands. (c) MOSQUITO DENSITY : It is usually expressed as the number of mosquitoes per man-hour-catch. (d) MAN-BITING RATE (Biting density) : It is defined as the average incidence of anopheline bites per day per person. It is determined by standardized vector catches on human bait (e) INOCULATION RATE : The man-biting rate multiplied by the infective sporozoite rate is called the inoculation rate. All these rates are employed in the quantitative assessment of malaria and in building up a composite epidemiological picture of malaria.

APPROACHES AND STRATEGIES OF MALARIA CONTROL

As the concept of control replaces that of eradication in many national programmes, a reordering of priorities in the selection of control methods must occur. These priorities and approaches must be based on epidemiological considerations, adverse effects on health, economy, technical feasibility, functional resources, human resources and community participation. Recently WHO stressed a number of points relevant to future strategy of malaria control. The main emphasis is on the need to base it on an epidemiological approach. These aspects are discussed below.

National Strategic Plan : Malaria Elimination 2023–2027 (5)

Malaria Elimination in India by 2027 is aligned with the Global Technical Strategy 2016–2030 and National Framework for Malaria Elimination 2016–2023. The goals are to interrupt local transmission and achieve zero indeginous case throughout the country by 2027; and to provide an enabling environment to prevent re-establishment of malaria. The strategies are as follows :

(1) Transforming malaria surveillance as a core intervention for malaria elimination

(2) Ensuring universal access to malaria diagnosis and treatment by enhancing and optimizing case management - "testing, treating and tracking"

(3) Ensuring universal access to malaria prevention by enhancing and optimizing vector control

(4) Accelerating efforts towards elimination and attainment of malaria- free status

(5) Promoting research and supporting the generation of strategic information for malaria elimination and prevention of re-establishment of malaria transmission.

Targets

Building on the significant quantitative achievements after the NSP 2017–2022, the current NSP 2023–2027 has set specific targets to be achieved by 2030.

State wise targets for malaria elimination

2024	Category 1 States/UTs (28) should reach Category 0 Category 2 States/UTs (6) should reach Category 1 Category 3 States/UTs (2) should reach Category 2
2025	Category 0 States/UTs (28) maintain the status Category 1 States/UTs (6) will make the efforts to move to Category 0 Category 2 States/UTs (2) will make intensified efforts to move towards Category 1
2026	Category 0 States/UTs (34) maintain the status Category 1 States/UTs (2) will make intensified efforts to move towards Category 0
2027	All the States/UTs should reach Category 0, i.e., zero indigenous cases
2030	The re-establishment of local transmission prevented in areas where malaria has been eliminated. The malaria-free status maintained throughout the nation

Definitions

Category 0 – Transmission of malaria interrupted and Zero indigenous cases

Category 1 – States/UTs with API < 1 case/1000 population in all districts

Category 2 – States/UTs with API < 1 case/ 1000 population but some districts having API >1

Category 3 – States/UTs with API >1 case/ 1000 population

Strategic Approaches (5)

Transforming malaria surveillance as a core intervention for malaria elimination

The malaria surveillance is the process of ongoing systematic collection, analysis, and interpretation of malaria-specific data for the purpose of planning, decision-making and dissemination of relevant information. Malaria epidemiological surveillance is done at different levels of the health care system (e.g., health facilities, the community), with different detection systems (e.g., case-based : active or passive) and sampling strategies (e.g., sentinel sites, contact /mass surveys). The surveillance system in the elimination phase is to detect all malaria infections, whether symptomatic or suspected, and ensure that they are radically cured very early so that they do not generate secondary cases. An effective surveillance system enables program managers to :

(i) Identify and target the areas and population groups affected by malaria for delivering the necessary interventions.

(ii) Regularly assess the impact of interventions and measure the progress.

(iii) Detect and respond to an outbreak in a timely manner.

(iv) Monitor re-establishment of transmission to guide the response.

(iv) Provide relevant information for certification of elimination.

The GTS introduced the concept of a continuum, whereby progress towards malaria elimination is considered to be a continuous process. As transmission decreases, malaria becomes focal and the intensity and frequency of reporting increases.

Surveillance in different settings (5)

Areas with different magnitudes of transmissions will require a different approach of surveillance as given below :

1. Surveillance in high transmission settings : In high transmission setting, the surveillance through Passive case detection (PCD) and Active case detection (ACD) - proactive ACD will be intensified along with efficient recording and reporting systems. This will provide data for overall analysis of trends and permit stratification and planning of resource allocation. State/Districts have to identify annually the high-risk population by analyzing the information on (i) size, type, and location of high-risk groups. (ii) type and degree of mobility and support of any social organization. (iii) security concerns, connectivity and other operational factors. In addition, the assessment of risks of malaria amongst exposed population, e.g., area of known high risk, military paramilitary troops, non-immune populations etc., will also be considered. In these settings aggregate reporting on monthly basis will be required.

2. Surveillance in low transmission settings : Surveillance in the low transmission setting focusing on the identification, investigation, classification and elimination of continuing transmission will be intensified through ACD, PCD and reactive case detection. In the low transmission/elimination setting, each and every suspected case should be diagnosed, confirmed, notified, investigated, classified and followed up with foci response. This requires weekly aggregate reporting.

3. Surveillance in the area with zero indigenous case: prevention of reintroduction (POR) : Early identification of imported cases to prevent local cases and outbreaks to prevent reestablishment. Immediate notification has to be done.

Key activities/methods of malaria surveillance (5)

1. The surveillance activities to detect malaria cases will be carried out as routine (active, & passive), sentinel-based

surveillance, mass surveillance, case and foci-based surveillance. ACD will be carried out by trained community level health care worker (ASHAs/ CHOs/ MPHW/ ANM/ CHV) through door-to-door visit. PCD will be done at the facility level including sub centre and above. Active surveillance is further divided into proactive and reactive surveillance. Proactive case detection will be undertaken in high-risk groups, not prompted by detection of cases whereas, reactive case detection will be undertaken in a population potentially linked to a confirmed case or cluster of cases.

2. In low transmission settings, the investigating team for "case and foci based" investigation will comprise of DVBD officer/DMO (team leader), a skilled laboratory technician, entomological staff member/consultant and the local health facility personnel.
3. The aim of case investigation is to determine whether an infection was acquired locally with likely location of such infection and to classify cases as indigenous, imported, relapse, recrudescence, induced and introduced cases, as given below *(5)* :

Case classifications

Correct epidemiological classification of malaria cases is crucial in malaria elimination, as it is the basis for further surveillance and implementing appropriate elimination measures. The classification of cases as per WHO is as follows :

- *Relapse* : Malaria case attributed to activation of hypnozoites of *P. vivax* or *P. ovale* acquired previously. The latency of relapsing case can be >6–12 months. The occurrence of relapsing cases is not an indication of operational failure, but their existence should lead to evaluation of the possibility of ongoing transmission.
- *Recrudescence* : Malaria case attributed to the recurrence of asexual parasitemia after anti-malarial treatment, due to incomplete clearance of asexual parasitemia of the same genotype that cause the original illness.
- *Indigenous case* : A case contracted locally with no evidence of being imported or being directly linked to transmission from an imported case.
- *Induced case* : A case the origin of which can be traced to a blood transfusion or other form of parenteral inoculation of the parasite but not to transmission by a natural mosquito-borne inoculation.
- *Imported case* : Malaria case or infection in which the infection was acquired outside the area in which it is diagnosed.
- *Introduced case* : A case contracted locally, with strong epidemiological evidence linking it directly to a known imported case (first-generation local transmission).

  Locally acquired case (also called 'autochthonous') : A case acquired locally by mosquito-borne transmission (Note : Locally acquired cases can be indigenous, introduced, relapsing or recrudescent; the term 'autochthonous' is not commonly used).

GUIDELINES FOR DIAGNOSIS AND TREATMENT OF MALARIA IN INDIA *(25, 26)*

According to the revised drug policy, there is no scope of presumptive treatment in malaria control. The recommended guidelines are as follows :

Treatment of Uncomplicated Malaria

All fever cases diagnosed as malaria by microscopy or RDT should promptly be given effective treatment.

TREATMENT OF P. VIVAX CASES

Positive *P. vivax* cases should be treated with chloroquine in full therapeutic dose of 25 mg/kg divided over three days. Vivax malaria relapses due to the presence of hypnozoites in the liver. The relapse rate in vivax malaria in India is around 30%. For its prevention, primaquine may be given at a dose of 0.25 mg/kg daily for 14 days under supervision. Primaquine is contraindicated in G6PD deficient patients, infants and pregnant women. Caution should be exercised before administering primaquine in areas known to have high prevalence of G6PD deficiency. Primaquine can lead to haemolysis in G6PD deficiency. Patient should be advised to stop primaquine immediately if he develops symptoms like dark coloured urine, yellow conjunctiva, bluish discolouration of lips, abdominal pain, nausea, vomiting etc. and should report to the doctor immediately.

TREATMENT OF P. FALCIPARUM CASES

Artemisinin Combination Therapy (ACT) (Artesunate 3 days + sulphadoxine-pyrimethamine 1 day) should be given to all confirmed *P. falciparum* cases found positive by microscopy or RDT. This is to be accompanied by single dose of primaquine (0.75 mg/kg body weight) on Day 2.

However, considering the reports of resistance to SP drug in North Eastern states, the Technical Advisory Committee has recommended to use the coformulated tablet of Artemether (20 mg) + Lumefantrine (120 mg) as per age-specific dose schedule for the treatment of *Pf* cases in North Eastern states. This drug is not recommended during the first trimester of pregnancy and for children weighing < 5 kg. Production and sale of Artemisinin monotherapy has been banned in India, as it can lead to development of parasite resistance to the drug.

TREATMENT OF MALARIA IN PREGNANCY

ACT should be given for treatment of *P. falciparum* malaria in second and third trimesters of pregnancy, while quinine is recommended in the first trimester. *P. vivax* malaria can be treated with chloroquine. Primaquine is contraindicated in pregnant woman.

TREATMENT OF MIXED INFECTIONS

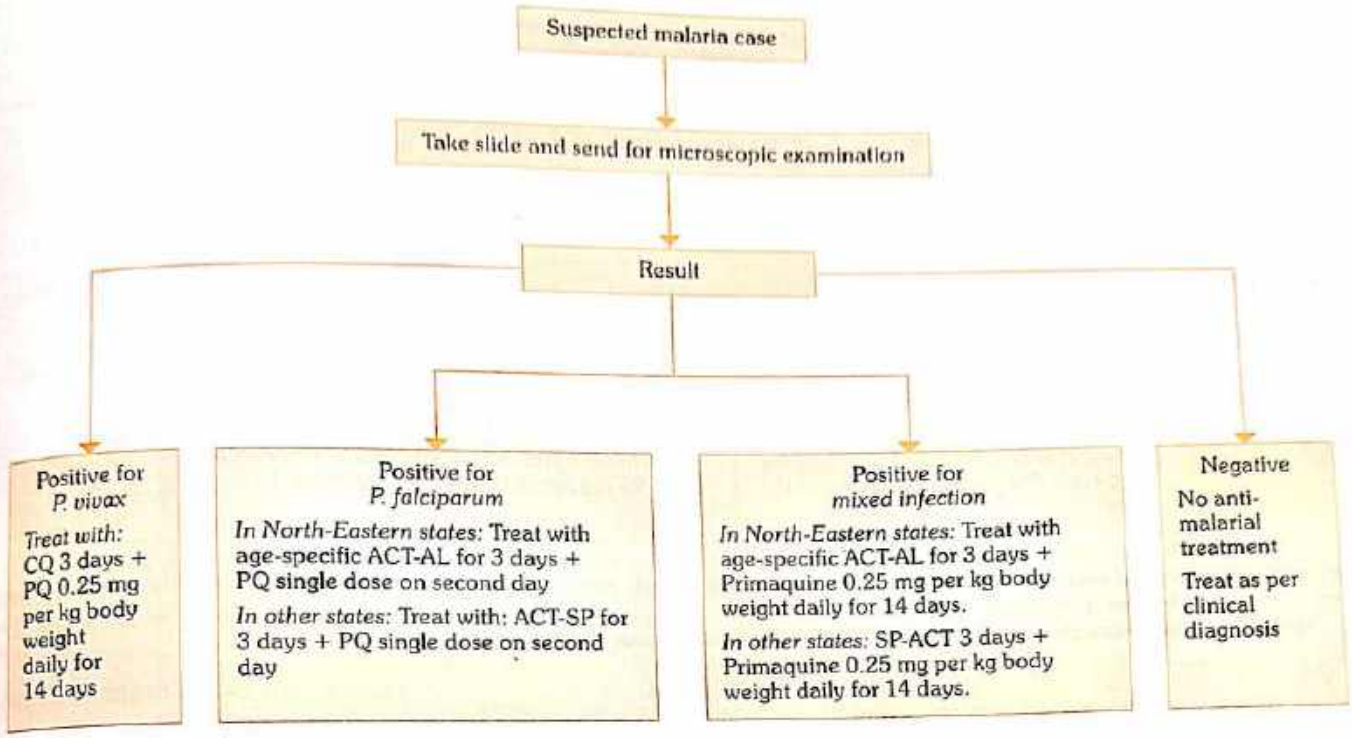
Mixed infections with *P. falciparum* should be treated as falciparum malaria.

Resistance should be suspected if inspite of full treatment with no history of vomiting, diarrhoea, patient does not respond within 72 hours, clinically and parasitologically. Such cases not responding to ACT, should be treated with oral quinine with tetracycline/doxycycline. These instances should be reported to concerned District Malaria/State Malaria Officer/ROHFW for initiation of therapeutic efficacy studies.

Diagnosis and treatment of malaria *(25, 26)*

All fever cases diagnosed as malaria by either RDT or microscopy should be promptly given effective treatment. The medicines chosen will depend upon whether the patient has *vivax* malaria or *falciparum* malaria. The flow charts in different settings for diagnosis and drug selection for the treatment of malaria are shown in Fig. 2, 3 and 4.

A. *Where microscopy result is available within 24 hours*

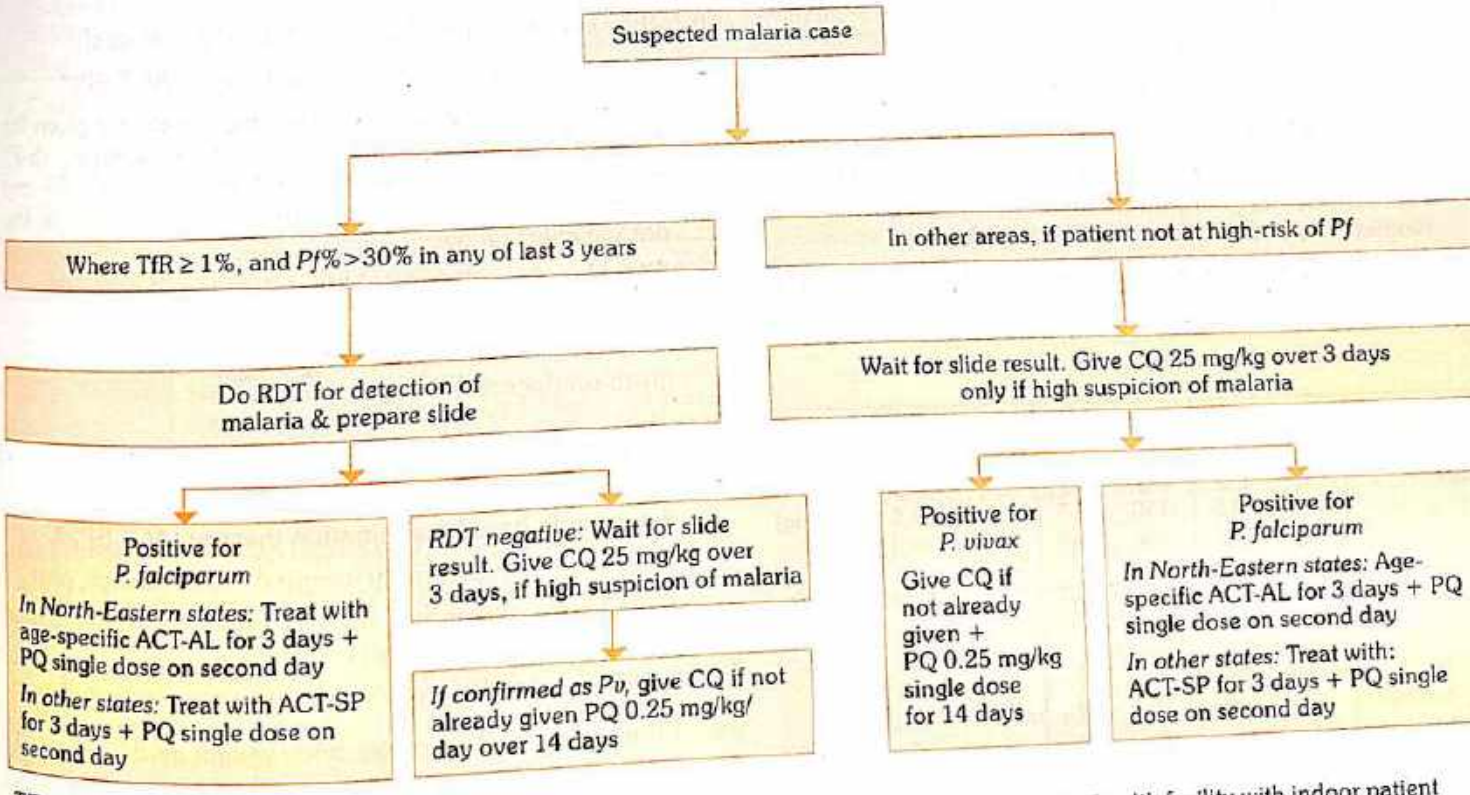


ACT-AL – Artemisinin-based combination therapy – Artemether – Lumefantrine
ACT-SP – Artemisinin-based combination therapy (Artesunate + Sulfadoxine-Pyrimethamine)

CQ – Chloroquine
PQ – Primaquine

FIG. 2

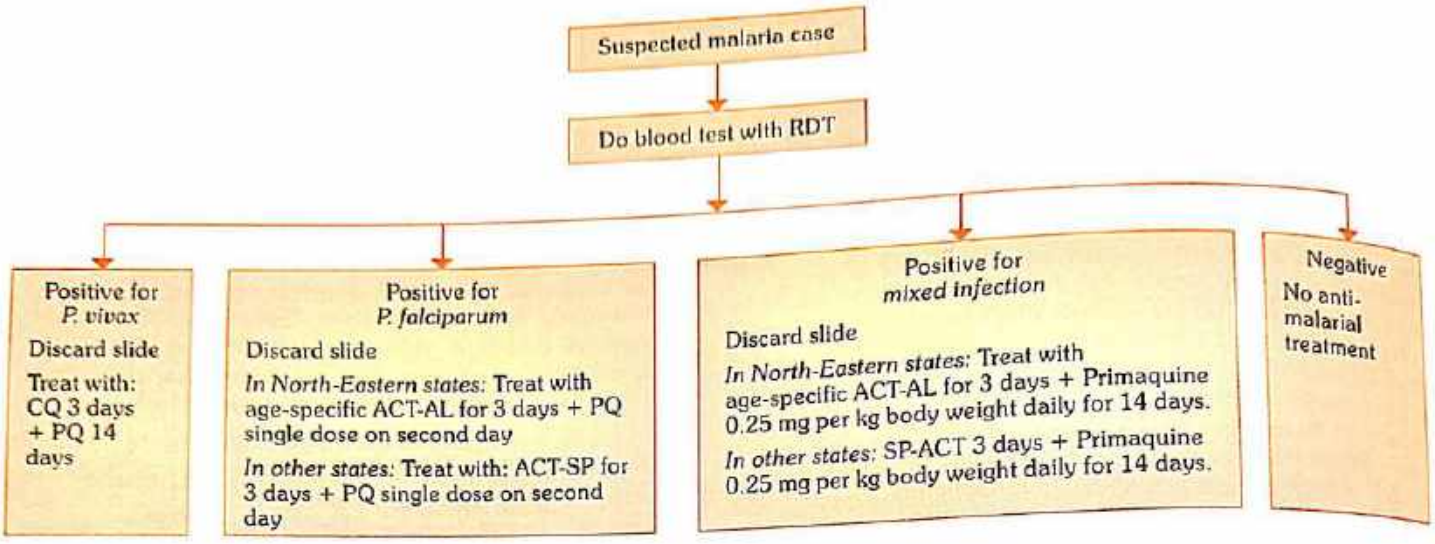
B. *Where microscopy result is not available within 24 hours and monovalent RDT is used*



TfR = Test falciparum rate
Note : If a patient has severe symptoms at any stage, then immediately refer to a nearest PHC or other health facility with indoor patient management or a registered medical doctor.

FIG. 3

C. *Where microscopy result is not available within 24 hours and bivalent RDT is used*



Note : (a) If a patient has severe symptoms at any stage, then immediately refer to a nearest PHC or other health facility with indoor patient management or a registered medical doctor.
(b) PQ is contra-indicated in pregnancy and in children under 1 year (Infant).

FIG. 4

Treatment of *vivax* malaria *(25, 26)*

Diagnosis of vivax malaria may be made by the used of RDT (Bivalent) or microscopic examination of the blood smear. On confirmation, following treatment is to be given :

Drug schedule for treatment of P. vivax malaria:

1. *Chloroquine:* 25 mg/kg body weight divided over three days i.e.

   10 mg/kg on day 1,

   10 mg/kg on day 2 and

   5 mg/kg on day 3.

2. *Primaquine:* 0.25 mg/kg body weight daily for 14 days.

   Primaquine is contraindicated in infants, pregnant women and individuals with G6PD deficiency.

   14 day regimen of Primaquine should be given under supervision.

Dosage chart for treatment of *vivax* malaria

Age	Day 1		Day 2		Day 3		Day 4 to 14
	CQ (150 mg base)	PQ (2.5 mg)	CQ (150 mg base)	PQ (2.5 mg)	CQ (150 mg base)	PQ (2.5 mg)	PQ (2.5 mg)
Less than 1 year	½	0	½	0	¼	0	0
1–4 years	1	1	1	1	½	1	1
5–8 years	2	2	2	2	1	2	2
9–14 years	3	4	3	4	1½	4	4
15 years or more*	4	6	4	6	2	6	6
Pregnancy	4	0	4	0	2	0	0

Note : CQ 250 mg tablet is having 150 mg base

Treatment of *falciparum* malaria *(25, 26)*

Diagnosis of falciparum malaria may be made by the use of RDT (monovalent or bivalent) or microscopic examination of the blood smear. It is imperative to start the treatment for falciparum malaria immediately on diagnosis. The treatment for falciparum malaria is as follows:

In other states (other than North-Eastern states):

1. Artemisinin based combination therapy (ACT-SP)*

   Artesunate (AS), available as 50 mg tablets are given for three days, and Sulfadoxine-Pyrimethamine (S-P) tablets, containing 500 mg Sulfadoxine and 25 mg pyrimethamine are given for one day, as shown in the dosage chart below.

   All tablets for a day should be taken together, swallowed with water.

   In addition, Primaquine (PQ large) tablets should be given on the second day.

Dose schedule for treatment of uncomplicated P. falciparum cases:

1. Artemisinin based combination therapy (ACT-SP) *

   Artesunate 4 mg/kg body weight daily for 3 days, plus

   Sulfadoxine (25 mg/kg body weight) – Pyrimethamine (1.25 mg/kg body weight) on first day.

   * ACT is not to be given in 1st trimester of pregnancy.

2. Primaquine * : 0.75 mg/kg body weight on day 2.

   With the introduction of different coloured blister packs for different age groups, treatment by the field level staff has been made easy. The colour code for different age groups for packing of tablet ACT+SP has been given as follows :

Dosage chart for treatment of *falciparum* malaria with ACT-SP

Age group (Years)	1st day		2nd day		3rd day
	AS	SP	AS	PQ	AS
0–1* Pink blister	1 (25 mg)	1 (250+12.5 mg)	1 (25 mg)	Nil	1 25 (mg)
1–4 Yellow blister	1 (50 mg)	1 (500+25 mg each)	1 (50 mg)	1 (7.5 mg base)	1 (50 mg)
5–8 Green blister	1 (100 mg)	1 (750+37.5 mg each)	1 (100 mg)	2 (7.5 mg base each)	1 (100 mg)
9–14 Red blister	1 (150 mg)	2 (500+25 mg each)	1 (150 mg)	4 (7.5 mg base each)	1 (150 mg)
15 & above White blister	1 (200 mg)	2 (750+37.5 mg each)	1 (200 mg)	6 (7.5 mg base each)	1 (200 mg)

* SP is not to be prescribed for children <5 months of age and should be treated with alternate ACT
* ACT-AL is not to be prescribed for children weighing less than 5 kg.

In North-Eastern states (NE states):

1. ACT-AL co-formulated tablet of Artemether (20 mg) – Lumefantrine (120 mg)

   (Not recommended during the first trimester of pregnancy and for children weighing <5 kg)

Recommended regimen by weight and age group
The packing size for different age groups based on Kg body weight.

Co-formulated tablet ACT-AL	5–14 kg (>5 months to <3 years)	15–24 kg (>3 to 8 years)	25–34 kg (>9 to 14 years)	>34 kg (>14 years)
Total dose of ACT-AL	20 mg/ 120 mg twice daily for 3 days	40 mg/ 240 mg twice daily for 3 days	60 mg/ 360 mg twice daily for 3 days	80 mg/ 480 mg twice daily for 3 days
	Pack size			
No. of tablets in the packing	6	12	18	24
Give	1 tablet twice daily for 3 days	2 tablets twice daily for 3 days	3 tablets twice daily for 3 days	4 tablets twice daily for 3 days
Colour of the pack	Yellow	Green	Red	White

2. Primaquine * : 0.75 mg/kg body weight on day 2

Treatment of uncomplicated P. falciparum cases in pregnancy:

1st trimester : Quinine salt 10 mg/kg 3 times daily for 7 days.

Quinine may induce hypoglycaemia; pregnant women should not start taking quinine on an empty stomach and should eat regularly, while on quinine treatment.

2nd and 3rd trimester : Area-specific ACT as per dosage schedule given above i.e. ACT-AL in North-Eastern states, ACT-SP in other states.

Primaquine (PQ) prevents transmission of falciparum malaria to others by its ability to kill gametocytes. PQ tablets should be taken after a meal; not on an empty stomach. Children less than the age of one year and pregnant women should not be given primaquine. As pregnant women having falciparum malaria require different medicines, they should be directed to go to the nearest PHC or hospital immediately, without delay.

Treatment of mixed infections (*P. vivax* + *P. falciparum*) cases (25, 26)

All mixed infections should be treated with full course of ACT and Primaquine 0.25 mg per kg body weight daily for 14 days.

In North-Eastern states: Treat with: Age-specific ACT-AL for 3 days + Primaquine 0.25 mg per kg body weight daily for 14 days.

In other states: ACT-SP 3 days + Primaquine 0.25 mg per kg body weight daily for 14 days.

Dosage chart for treatment of mixed (*vivax* and *falciparum*) malaria with ACT-SP

Age	Day 1			Day 2		Day 3		Day 4-14
	AS tablet (50 mg)	SP tablet	PQ (2.5 mg)	AS tablet (50 mg)	PQ (2.5 mg)	AS tablet (50 mg)	PQ (2.5 mg)	PQ (2.5 mg)
Less than 1 year	½	½	0	½	0	½	0	0
1–4 years	1	1	1	1	1	1	1	1
5–8 years	2	1½	2	2	2	2	2	2
9–14 years	3	2	4	3	4	3	4	4
15 years or more	4	3	6	4	6	4	6	6

Treatment of *P. ovale* and *P. malariae*

In India these species are very rarely found in few places. *P. ovale* should be treated as *P. vivax* and *P. malariae* should be treated as *P. falciparum*.

General recommendations for the management of uncomplicated malaria

1. Avoid starting treatment on an empty stomach. The first dose should be given under observation. Dose should be repeated if vomiting occurs within 15 minutes by opening a new blister pack (discard what remains of old pack). If the patient vomits the first dose again, it is considered a severe case of malaria and refer the patient immediately to the nearest Block PHC/CHC/Hospital. Special precaution should be taken in case of a child under-5 years of age, and in pregnant woman.
2. Explain to the patient or caretaker that : (a) if the treatment is not completed as prescribed, the disease may manifest again with more serious features and more difficult to treat; (b) to come back immediately, if there is no improvement after 24 hours, if the situation gets worse or the fever comes back; and (c) that regular use of a mosquito net (preferably insecticide treated net) is the best way to prevent malaria.
3. Patient should also be examined for concomitant illness.

Resistance to anti-malarial drugs

Resistance can be defined as either the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, but within the limits of tolerance of the patient.

Drug resistance is a complex phenomenon, where, by genetic mutation, a parasite acquires the ability to resist, partly or fully, the effects of one or more anti-malarial drugs. When the resistant parasites are exposed to the drug, they multiply selectively. If parasites are resistant to the drug being used, the patient may not respond to treatment. One of the commonest reasons for the development of drug resistance is that the parasites are exposed to insufficient amount of the drug due to low prescription dosage, lesser amount of drug dispensed, incomplete treatment taken by the patient, drug vomited out or low absorption of drug due to any other reason e.g., diarrhoea, poorly stored drug, poor quality drug when supplied or expiry date medicine. In such cases, most of the sensitive parasites are killed by even these small doses, but resistant parasites survive, multiply and spread to other people by mosquitoes. The new patient then gets infection from the resistant malaria parasites and does not respond to the drug at all, or responds only partly. Meanwhile, the earlier patient may appear cured because most of the parasites were killed by the drug, and the symptoms abated.

It should be kept in mind that the patient might have had a fresh reinfection, or in the case of *vivax* malaria, there might have been a relapse of malaria *(25)*.

Treatment failure *(27)*

After treatment patient is considered cured if he/she does not have fever or parasitaemia till day 28th. Some patients may not respond to treatment which may be due to drug resistance or treatment failure, specially in falciparum malaria. If patient does not respond and presents with following, he/she should be given alternative treatment.

Early treatment failure (ETF) : Development of danger signs or severe malaria on Day 1, 2 or 3, in the presence of parasitaemia; parasitaemia on Day 2 higher than on Day 0, irrespective of axillary temperature; parasitaemia on Day 3 with axillary temperature >37.5°C; and parasitaemia on Day 3, >25% of count on Day 0.

Late clinical failure (LCF) : Development of danger signs or severe malaria in the presence of parasitaemia on any day between Day 4 and Day 28 in patients who did not previously meet any of the criteria of early treatment failure; and presence of parasitaemia on any day between Day 4 and Day 28 with axillary temperature >37.5°C in patients who did not previously meet any of the criteria of early treatment failure.

Late parasitological failure (LPF) : Presence of parasitaemia on any day between Day 7 and Day 28 with axillary temperature <37.5°C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure.

Such cases of falciparum malaria should be given alternative ACT or quinine with Doxycycline. Doxycycline is contraindicated in pregnancy, lactation and in children upto 8 years. Treatment failure with chloroquine in *P. vivax* malaria is rare in India.

Treatment of severe malaria

CLINICAL FEATURES *(25)*

Severe manifestations can develop in *P. falciparum* infection over a span of time as short as 12–24 hours and may lead to death, if not treated promptly and adequately. Severe malaria is characterized by one or more of the following features:

(1) Impaired consciousness/coma
(2) Repeated generalized convulsions
(3) Renal failure (Serum Creatinine >3 mg/dl)
(4) Jaundice (Serum Bilirubin >3 mg/dl)
(5) Severe anaemia (Hb <5 g/dl)
(6) Pulmonary oedema/acute respiratory distress syndrome
(7) Hypoglycaemia (Plasma glucose <40 mg/dl)
(8) Metabolic acidosis
(9) Circulatory collapse/shock (Systolic BP<80 mm Hg, < 50 mm Hg in children)
(10) Abnormal bleeding and disseminated intravascular coagulation.
(11) Haemoglobinuria
(12) Hyperthermia (Temperature >106°F or 42°C)
(13) Hyperparasitaemia (<5% parasitized RBCs in low endemic and >10% in hyperendemic areas)

Foetal and maternal complications are more common in pregnancy with severe malaria; therefore, they need prompt attention.

Microscopic evidence may be negative for asexual parasites in patients with severe infections due to sequestration and partial treatment. Efforts should be made to confirm these cases by RDT or repeat microscopy. However, if the symptoms clearly point to severe malaria and there is no alternative explanation, such a case should be treated accordingly.

Criteria for immediate referral are as follows: (a) Persistence of fever after 24 hours of initial treatment; (b) Continuous vomiting and inability to retain oral drug; (c) Headache continues to increase; (d) Severe dehydration (dry, parched skin, sunken eyes etc.); (e) Too weak to walk in the absence of any other obvious reason; (f) Change in sensorium e.g. confusion, drowsiness, blurring of vision, photophobia, disorientation; (g) Convulsion or muscle twitchings; (h) Bleeding and clotting disorder; (i) Suspicion of severe anaemia; (j) Jaundice; and (k) Hypothermia *(25)*.

Treatment of severe malaria cases *(25)*

Severe malaria is an emergency and treatment should be given as per severity and associated complications which can be best decided by the treating physicians. Before admitting or referring patients, the attending doctor or health worker, whoever is able to do it, should do RDT and take blood smear, give a parenteral dose of artemisinin derivative or quinine in suspected cerebral malaria cases and send case sheet, details of treatment history and blood slide with patient. Parenteral artemisinin derivatives or quinine should be used irrespective of chloroquine resistance status of the area with one of the following options:

Chemotherapy of severe and complicated malaria

Initial parenteral treatment for at least 48 hours: *Choose one of the following four options*	Follow-up treatment, when patient can take oral medication following parenteral treatment
Quinine : 20 mg quinine salt/kg body weight on admission (IV infusion or divided IM injection) followed by maintenance dose of 10 mg/kg 8 hourly; infusion rate should not exceed 5 mg/kg per hour. Loading dose of 20 mg/kg should not be given, if the patient has already received quinine.	*Quinine* 10 mg/kg three times a day with: doxycycline 100 mg once a day OR clindamycin in pregnant women and children under 8 years of age. – to complete 7 days of treatment.
Artesunate: 2.4 mg/kg IV or IM given on admission (time=0), then at 12 h and 24 h, then once a day. OR *Artemether*: 3.2 mg/kg bw IM given on admission then 1.6 mg/kg per day. OR *Arteether*: 150 mg daily IM for 3 days in adults only (not recommended for children).	Full oral course of area-specific ACT: *In North-Eastern states:* Age-specific ACT-AL for 3 days + PQ single dose on second day *In other states:* Treat with: ACT-SP for 3 days + PQ single dose on second day

Note : The parenteral treatment in severe malaria cases should be given for minimum of 24 hours once started (irrespective of the patient's ability to tolerate oral medication earlier than 24 hours).

After parenteral artemisinin therapy, patients will receive a full course of area-specific oral ACT for 3 days. Those patients who received parenteral Quinine therapy should receive oral Quinine 10 mg/kg body weight three times a day for 7 days (including the days when parenteral Quinine was administered) plus Doxycycline 3 mg/kg body weight once a day, or Clindamycin 10 mg/kg body weight 12-hourly for 7 days (Doxycycline is contraindicated in pregnant women and children under 8 years of age) or area-specific ACT as described.

Note :

- Pregnant women with severe malaria in any trimester can be treated with artemisinin derivatives, which, in contrast to quinine, do not risk aggravating hypoglycaemia.
- The parenteral treatment should be given for minimum of 24 hours.
- Once the patient can take oral therapy; give:
- Quinine 10 mg/kg three times a day with doxycycline 100 mg once a day or clindamycin in pregnant women and children under 8 years of age, to complete 7 days of treatment, in patients started on parenteral quinine.
- Full course of ACT to patients started on artemisinin derivatives.
- Use of mefloquine should be avoided in cerebral malaria due to neuropsychiatric complications associated with it.

Some don'ts in severe malaria case management

Do not use corticosteroids, do not give intravenous mannitol, do not use heparin as anticoagulant, do not administer adrenaline or do not overhydrate.

Toxic hazards of drugs

Chloroquine has few side-effects. Nausea, vomiting, blurring of vision and headaches may occur, but they are mild and transient. Cases of retinal damage have been reported but only in persons exposed to large cumulative doses over many years. It is important to remember that chloroquine should not be given on empty stomach. Despite reports of teratogenicity in experimental animals, most authorities accept that pyrimethamine can safely be taken alone during pregnancy (28). The teratogenic effect of pyrimethamine in man is not proved. In regard to primaquine, although in recommended doses, no serious toxic manifestations have been encountered so far in India. It is useful to bear in mind the likely toxic symptoms, which may be of three types : *(a) Plasmocid types :* this is a rare toxic manifestation involving the CNS, *(b) Gastrointestinal :* cramps, nausea and vomiting, *(c) Cardiovascular :* This is probably the most serious toxic manifestation which is to be carefully observed during the administration of the drug. Even the first dose may bring about the warning sign of cyanosis. The surveillance worker/MPW must carefully check for all possible toxic symptoms before he administers the daily dose of primaquine. In the case of appearance of any of the toxic symptoms discussed above, primaquine treatment should be stopped immediately (29).

Chemoprophylaxis

Chemoprophylaxis against malaria has, with the development of drug resistance, become unreliable. Experts disagree on whether well-conducted prophylaxis gives an additional benefit if effective treatment is readily available. However, experts feel that it can play a useful role in reducing the risk of fatal disease (30).

Chemoprophylaxis is recommended for travellers from non-endemic areas and, as a short term measure for soldiers, police and labour forces serving in highly endemic areas. Chemoprophylaxis should be complemented by personal protection where feasible and by other methods of vector control (30).

The recommendations for short-term chemoprophylaxis (less than 6 weeks) are as follows (30) :

(1) Dosing schedules for the children should be based on body weight.

(2) Antimalarials that have to be taken daily (e.g. Doxycycline) should be started the day before arrival in the risk area.

(3) Weekly chloroquine should be started 1 week before arrival.

(4) Weekly mefloquine should preferably be started 2–3 weeks before departure, to achieve higher pre–travel blood level and to allow side-effects to be detected before travel so that possible alternative can be considered.

(5) All prophylactic drugs should be taken with unfailing regularity for the duration of the stay in the malaria risk area, and should be continued for 4 weeks after the last possible exposure to infection, since parasites may still emerge from the liver during this period.

The recommendations for the long-term chemoprophylaxis (more than 6 weeks) are as follows :

(1) The risk of serious side-effects associated with long-term prohylactic use of chloroquine and proguanil is low. However, anyone who has taken 300 mg of chloroquine weekly for over five years and requires further prophylaxis should be screened twice-yearly for early retinal changes. If daily dose of 100 mg chloroquine have been taken, screening should start after three years *(30)*.

(2) Data indicate no increased risk of serious side-effects with long-term use of mefloquine if the drug is tolerated in the short-term, as mefloquine does not accumulate during long-term intake.

(3) Available data on long-term chemoprophylaxis with doxycycline is limited.

Mefloquine is contraindicated in cases with history of convulsions, neuropsychiatric problems and cardiac conditions.

Chemoprophylaxis is still desirable for pregnant women living in areas where transmission is very intense and leads to parasitaemias, causing low birth weight and anaemia, or to a high risk of life–threatening malaria attacks. However, the choice of safe drugs is becoming increasingly narrow, and it may be necessary to replace chemoprophylaxis by prompt treatment of clinical episodes or periodic treatments during pregnancy. While the choice of strategy should be guided by the national malaria control policy, its implementation should normally be part of antenatal care *(31)*.

The recommended regimens for chemoprophylaxis are as given in Table 2.

TABLE 2

Drug regimens for prophylaxis of malaria

Drugs		Usual amount per tablet or capsule	Adult dose
Generic name	Common trade names		For prophylaxis
Chloroquine[a]	Aralen Avlochlor Nivaquine Resochin	100 or 150 mg (base)	300 mg (base) = 3 tablets of 100 mg or 2 tablets of 150 mg once a week, on the same day each week OR 100 mg (base) = 1 tablet of 100 mg daily for six days per week
Proguanil[b]	Paludrine	100 mg	200 mg = 2 tablets once a day
Mefloquine[c]	Lariam Eloquin Mephaquin	250 mg	250 mg = 1 tablet once a week, on the same day each week
Doxycycline[d]	Vibramycin	100 mg	100 mg=1 capsule once a day

a. Also available as suspension.
b. Recommended only in association with chloroquine.
c. The use of the higher treatment dose regimen is recommended for infections acquired in areas on the Thailand/Cambodia and Thailand / Myanmar borders only.
d. There is relatively little experience with this drug, and knowledge of its efficacy and toxicity is limited.

Source : *(30)*

ACTIVE INTERVENTION MEASURES

Neither chemotherapy nor chemoprophylaxis will be able to reduce significantly the malaria prevalence or transmission. It can be obtained only when proper anti–mosquito measures are introduced.

1. STRATIFICATION OF THE PROBLEM

Malaria is a complex disease, and its distribution and intensity vary from place to place. Stratification of the problem has become an essential feature for the planning and development of a sound control strategy to maximize the utilization of available resources. It can also provide guidelines as to which strategy could be most suited and economical under the existing conditions. For details please refer to chapter 7.

2. VECTOR CONTROL STRATEGIES

Vector control is still one of the primary weapons to control malaria in endemic areas. The methods used are as shown in Table 3.

(a) Anti–adult measures

(i) Residual spraying : The discovery of DDT in 1940s and followed by other insecticides revolutionized malaria control. The spraying of the indoor surfaces of houses with residual insecticides (e.g., DDT, malathion, fenitrothion) is still the most effective measure to kill the adult mosquito. It has been observed that discontinuation of spraying has very often led to the resurgence of malaria. This implies that spraying once applied may need to be continued for an indefinite period. If indoor spraying is to have any effect, then exhaustive coverage is needed. Indoor house spraying reduces the longevity of the vector.

Malathion and fenitrothion are organophosphate insecticides which are being used with increasing frequency for malaria control following the development of vector resistance to DDT *(33)*.

TABLE 3

Malaria vector control measures

Action	For individual and family protection	For community protection
Reduction of human-mosquito contact	Insecticide-treated nets, repellents, protective clothing, screening of houses	Insecticide-treated nets zoo-prophylaxis
Destruction of adult mosquitoes		Insecticide-treated nets, indoor residual spraying, space spraying, ultra low-volume sprays
Destruction of mosquito larvae	Peri-domestic sanitation	Larviciding of water surfaces, intermittent irrigation, sluicing, biological control
Source reduction	Small-scale drainage	Environmental sanitation, water management, drainage
Social participation	Motivation for personal and family protection	Health education, community participation

Source : *(32)*

(ii) Space application : This is a major anti-epidemic measure in mosquito-borne diseases. It involves the application of pesticides in the form of fog or mist using special equipment. The ultra-low-volume method of pesticide dispersion by air or by ground equipment has proved to be effective and economical. Outdoor space sprays reduce vector population quickly.

(iii) Individual protection : Man-vector contact can be reduced by other preventive measures such as the use of repellents, protective clothing, bed-nets (preferably impregnated with safe, long-acting repellent insecticides), mosquito coils, screening of houses etc. The methods of personal protection are of great value when properly employed. However, they have rarely been used on a large scale because of cost.

(b) Anti-larval measures

(i) Larvicides : During the first half of the 20th century, anti-larval measures such as oiling the collections of standing water or dusting them with paris green effectively controlled malaria (but the measures were eclipsed at the end of World War II). With the increase in insecticide resistance, the older methods of mosquito control have now become promising. Some modern larvicides such as temephos which confer long effect with low toxicity are more widely used. However larviciding must be repeated at frequent intervals and for this reason it is a comparatively costly operation.

(ii) Source reduction : Techniques to reduce mosquito breeding sites (often called source reduction) which include drainage or filling, deepening or flushing, management of water level, changing the salt content of water and intermittent irrigation are among the classical methods of malaria control to which attention is being paid again *(34)*. Whenever practicable, measures for the improvement of the environment by the permanent reduction of sources should be instituted.

(iii) Integrated control : In order to reduce too much dependance on residual insecticides, increasing emphasis is being put on "integrated" vector control methodology which includes bioenvironmental and personal protection measure *(35)*. This approach is important because there is no single and simple method that would ensure control of transmission.

By mid 1995 all malaria endemic countries in the region had adopted the revised malaria control strategy to reduce morbidity and mortality and to reduce its area of distribution, particularly of multidrug resistant malaria. The use of stratification approach by the majority of anti-malaria programmes in the Region has led to more cost-effective interventions. Vector resistance to insecticides has necessitated the use of more expensive pyrethroid, thereby limiting the coverage. Malaria control added impetus as **Roll Back Malaria** initiative was launched by WHO, UNICEF, UNDP and the World Bank in 1998.

The launch of Roll Back Back Malaria (RBM) in 1998, the United Nations Millenium Declaration in 2000, the Abuja Declaration by African Heads of State in 2000 (part of the African Summit on Roll Back Malaria), the World Health Assembly in 2005, and the RBM global strategic plan 2005–2015 have all contributed to the establishment of goals, indicators and targets for malaria control.

THE GLOBAL TECHNICAL STRATEGY FOR MALARIA (2016–2030)

Adopted by the World Health Assembly in May 2015, the strategy provides comprehensive technical guidance to countries and development partners for the next 15 years, emphasizing the importance of scaling up malaria responses and moving towards elimination. It also highlights the urgent need to increase investments across all interventions – including preventive measures, diagnostic testing, treatment and disease surveillance – as well as in harnessing innovation and expanding research. By adopting this strategy, WHO Member States have endorsed the bold vision of a world free of malaria and set the ambitious new target of reducing the global malaria burden by 90% by 2030. They also agreed to strengthen health systems, address emerging multi-drug and insecticide resistance, and intensify national, cross-border and regional efforts to scale up malaria responses to protect everyone at risk. By taking forward this strategy, countries will make a major contribution to implementing the post-2015 sustainable development framework. A major scale-up of malaria responses will not only help countries reach the health-related targets for 2030, but will contribute to poverty reduction and other development goals *(36)*.

The three pillars of Global Technical Strategy for malaria 2016–2030, and the goals, milestones and targets are as follows *(37)*:

Pillars	
Pillar 1	Ensure universal access to malaria prevention, diagnosis and treatment
Pillar 2	Accelerate efforts towards elimination and attainment of malaria free status
Pillar 3	Transform malaria surveillance into a core intervention

Goals	Milestones		Targets
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

Malaria vaccines *(2)*

Two malaria vaccines, RTS,S/AS01 and R21/Matrix-M, are WHO-prequalified and recommended for use. Both are pre-erythrocytic vaccines that prevent *P. falciparum* infection in children and subsequent illness and death; they are not designed to interrupt malaria transmission. The recommended malaria vaccines prevent *P. falciparum* malaria, and there is no known cross protection with other *Plasmodium* species.

The manufacturer of RTS,S/AS01 recommends that the first dose of the vaccine is given to children aged from 5 months to 17 months. The first 3 doses should be administered at one-month intervals, with a fourth dose given 18 months after the third dose. The manufacturer of

R21/Matrix-M recommends that the first dose of the vaccine is given to children aged from 5 months to 36 months of age. The first 3 doses should be administered at one-month intervals, with a fourth dose given 12 months after the third dose.

Neither of the vaccines includes preservative, and vials should therefore be discarded at the end of the vaccination session or within 6 hours after opening, whichever comes first. The vaccines should be stored at 2-8 °C. The shelf-life is 3 years for RTS,S/AS01 and 2 years for R21/Matrix-M. A vaccine vial monitor (VVM Type 14) is on the RTS,S/AS01 reconstitution vial and the R21/Matrix-M vial cap.

Vaccine safety : On the basis of clinical trial data and pilot evaluation, the most serious adverse reaction associated with RTS,S/AS01 and R21/Matrix-M is febrile seizures within 7 days (but mainly within 2–3 days) post-vaccination, with an attributable risk of 2.5 per 1000 doses of RTS,S/ AS01 administered and 1 per 2800 doses of R21/ Matrix-M administered. The seizures resolved without long-term consequences. The most commonly reported adverse reactions were fever (27% for RTS,S/ AS01 and 38% for R21/Matrix-M), followed less frequently by irritability, and injection site reactions such as pain and swelling.

National Malaria Control Progrmme

Please see chapter 7.

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LYMPHATIC FILARIASIS

The term "lymphatic filariasis" covers infection with three closely related nematode worms – *W. bancrofti, B. malayi and B. timori*. All three infections are transmitted to man by the bites of infective mosquitoes. All three parasites have basically similar life cycles in man–adult worms living in lymphatic vessels whilst their offspring, the microfilariae circulate in peripheral blood and are available to infect mosquito vectors when they come to feed *(1)*. The disease manifestations range from none to both acute and chronic manifestations such as lymphangitis, lymphadenitis, elephantiasis of genitals, legs and arms or as a hypersensitivity state such as tropical pulmonary eosinophilia or as an atypical form such as filarial arthritis. Though not fatal, the disease is responsible for considerable suffering, deformity and disability.

Problem statement

Filariasis is a global problem. It is a major social and economic scourage in the tropics and subtropics of Africa, Asia, Western Pacific and parts of the Americas, affecting over 39 countries. More than 657 million people live in areas where there is a risk of infection, of whom 120 million are infected and in need of treatment, including 40 million people with overt disease. This includes 15 million people with lymphoedema and 25 million men with urogenital swelling principally scrotal hydrocele. At least 36 million people remain with these chronic disease manifestations *(2, 3)*.

About 90 per cent of cases of lymphatic filariasis are caused by infection with *W. bancrofti*; other related parasites that infect humans are *Brugia malayi* in South-East Asia and *B. timori* in Indonesia.

The formal goal of the global lymphatic filariasis programme is to eliminate the disease "as a public health problem" and 2020 was the informal target date for interrupting transmission. The strategy to interrupt transmission of the disease calls for mass administration of a 2-drug regimen (ivermectin or DEC plus albendazole) administration as a single dose annually for 4–6 years.

Since 2000, the global programme provided a cumulative total of nearly 9.3 billion treatments to at least 935.3 million people. It represents about 73 per cent of the 1.4 billion people at risk *(2)*.

The current hypothesis is that reducing the prevalence of microfilaraemia in humans to <1 per cent will stop transmission. One provisional set of guidelines for stopping treatment would require ≥ 5 annual rounds of MDA with coverage of ≥ 65 per cent of the total population *(4)*.

INDIA

The overall estimated population at risk from filaria infection are in 345 endemic districts of 20 States/UTs, 75 per cent of mass drug administration (MDA) districts are from 5 states of Bihar, Jharkhand, Uttar Pradesh, Odisha and Telangana, 6 states have stopped MDA (Goa, Puducherry, Dadra & Nagar Haveli and Daman & Diu, Tamil Nadu, Lakshadweep, Andman & Nicobar Island). Also, 138 districts (40%) have stopped MDA and have cleared the Transmission Assessment Survey *(5)*.

An estimated 746 million people are at risk of lymphatic filariasis infection in 345 endemic districts in 20 states and UTs in India. Mapping was carried out using epidemiological data supplemented by data from filaria control units, filaria clinics, and survey units under the national filaria control programme. Morbidity surveys of filaria cases in the states/UTs revealed 6.21 lakh cases of lymphoedema and 1.27 lakh cases of hydrocele till Dec. 2023 *(5)*. The microfilaria survey reports received from 205 districts revealed microfilaria rate of about 0.45 per cent *(6)*.

Mass drug administration (MDA) is being implemented in India since year 2004. In 2007 India changed its strategy from delivery of DEC alone to delivery of DEC plus albendazole; since that time, the number of people treated with combination therapy has increased steadily. In 2014, about 86 per cent people at risk were treated with combination drug *(4)*. India has reduced the prevalence of microfilaria to less than 1 per cent in 192 out of 250 implementation units.

Epidemiological determinants

Agent factors

There are at least 8 species of filarial parasites that are specific to man *(7)*. These are shown in Table 1. The first three worms are responsible for lymphatic filariasis; and the rest for "non–lymphatic filariasis". The parasites causing non–lymphatic filariasis will not be described as they are not found in India. Table 2 shows the differences between the microfilariae *(Mf)* of *W. bancrofti* and *B. malayi*.

TABLE 1
Human filarial infections

	Organism	Vectors	Disease produced
1.	*Wuchereria bancrofti*	Culex Mosquitoes	Lymphatic filariasis
2.	*Brugia malayi*	Mansonia —"—	—"— —"—
3.	*Brugia timori*	Anopheles —"— Mansonia —"—	—"— —"—
4.	*Onchocerca volvulus*	Simulum flies	Subcutaneous; nodules; River blindness
5.	*Loa loa*	Chrysops flies	Recurrent, transient subcutaneous swellings
6.	*T. perstans*	Culicoides	Probably rarely any clinical illness
7.	*T. streptocerca*	Culicoides	—"—
8.	*Mansonella ozzardi*	Culicoides	—"—

TABLE 2
Differences between *Mf* of *W. bancrofti* and *B. malayi*

	Mf. W. bancrofti	*Mf. B. malayi*
1. General appearance	Graceful, sweeping curves	Crinkled, secondary curves
2. Length	244 to 296 μ	177 to 230 μ
3. Fee cephalic space	As long as broad	Nearly twice as long as broad
4. Excretory pore	Not prominent	Prominent
5. Caudal end	Uniformly tapering to a delicate point, No terminal nuclei present	Kinkled and two terminal nuclei present
6. Nuclear column	Nuclei discrete	Smudged

PERIODICITY

The *Mf* of *W. bancrofti* and *B.malayi* occurring in India display a nocturnal periodicity, i.e., they appear in large numbers at night and retreat from the blood stream during the day. This is a biological adaptation to the nocturnal biting habits of the vector mosquitoes. The maximum density of *Mf* in blood is reported between 10 pm and 2 am. When the sleeping habits of the host are altered, a reversal in periodicity has been observed.

In most parts of the world, *Mf* are nocturnally periodic but in the South Pacific islands and in limited foci in the Nicobar islands, Thailand and Vietnam, *W. bancrofti Mf* are non–periodic (sub-periodic), being detectable throughout the 24 hours with a slight peak during day or night. Sub-periodic *B.malayi* is found in parts of Malaysia and Indonesia.

LIFE CYCLE

Man is the definitive host and mosquito the intermediate host of Bancroftian and Brugian filariasis. The adult worms are usually found in the lymphatic system of man. The males are about 40 mm long and the females 50 to 100 mm long. The females are viviparous. They give birth to as many as 50,000 *Mf* per day *(8)* which find their way into blood circulation *via* the lymphatics. The life span of the *Mf* is not exactly known, probably up to a year or more. The adult worms may survive for 15 years or more *(8)*. There is a case on record of a woman, in whom live *Mf* were present 40 years after she left an endemic area *(9)*.

The mosquito cycle begins when the *Mf* are picked up by the vector mosquito during feeding. The following stages of development take place in the vector : *(a) Exsheathing :* The larva comes out of the sheath in which it is enclosed, within 1 to 2 hours of ingestion. This is known as exsheathing which takes place in the stomach of the mosquito. *(b) First stage larva :* After exsheathing, the larva is able to penetrate the stomach wall of the mosquito which it does in 6 to 12 hours and migrate to the thoracic muscles where it grows and develops into a sausage–shaped (short, thick) form. *(c) Second stage larva :* The larva moults and increases in length (long, thick form) with the development of an alimentary canal, but is relatively inactive. *(d) Third stage larva :* There is a final moult to the third stage or infective larva (long, thin form) which may be found in any part of the insect. It is highly active or motile. When it migrates to the proboscis of the mosquito, it is ready to be transmitted to a new host, and the mosquito is said to be infective. Under optimum conditions of temperature and humidity, the duration of mosquito cycle (extrinsic incubation period) is between 10 and 14 days. In the human host, the infective larvae develop into adult male and female worms.

RESERVOIR OF INFECTION

Although filarial infections occur in animals, human filariasis is not usually a zoonosis (sub-periodic *B. malayi* and *T. perstans* are exceptions). Animal reservoirs of Brugia are present in monkeys, cats and dogs *(8)*; these animals are believed to acquire their infections from man, and they are not regarded as important sources of infection to man *(1)*. There is no evidence that *W. bancrofti* has animal reservoirs in India.

In humans the source of infection is a person with circulating *Mf* in peripheral blood. In filarial disease (late obstructive stages) *Mf* are not found in the blood.

The minimum level of *Mf* which will permit infection of mosquitoes is not known. It was reported that a man with one *Mf* per 40 cu. mm of blood was infective to 2.6 per cent of the mosquitoes which fed on him *(10)*. On the other hand, when mosquitoes were fed on carriers having as many as 80 or more *Mf* per 20 cu. mm of blood, the heavily infected mosquitoes did not survive when a number of *Mf* began to reach maturity *(11)*.

Host factors

Man is a natural host. (a) AGE: All ages are susceptible to infection. In endemic areas, filarial infection has been found even in infants aged less than 6 months. Infection rates rise with age up to the age of 20–30 years and then level off. After a few years at this plateau level, *Mf* rates may decline in middle and old age. Filarial disease appears only in a small percentage of infected individuals, commonly in the age group over 10 years *(12)*, although there may be exceptions. (b) SEX : In most endemic areas the *Mf* rate is higher in men. (c) MIGRATION : The movement of people from one place to another has led to the extension of filariasis into areas previously non–endemic. (d) IMMUNITY : Man may develop resistance to infection only after many years of exposure *(8)*. The immunological basis of this resistance is not known *(13)*. (e) SOCIAL FACTORS : Lymphatic filariasis is often associated with urbanization, industrialization, migration of people, illiteracy, poverty and poor sanitation.

Environmental factors

(a) CLIMATE : Climate is an important factor in the epidemiology of filariasis. It influences the breeding of mosquitoes, their longevity and also determines the development of the parasite in the insect vector. The maximum prevalence of *Culex quinquefasciatus* (previously known as *C. fatigans*) was observed when the temperature was between 22 to 38 deg. C and optimum longevity when the relative humidity was 70 per cent. (b) DRAINAGE: Lymphatic filariasis is associated with bad drainage. The vectors breed profusely in polluted water. (c) TOWN PLANNING : Inadequate sewage disposal and lack of town planning have aggravated the problem of filariasis in India by increasing the facilities for the breeding of *C. quinquefasciatus (C. fatigans)*. The common breeding places are cesspools, soakage pits, ill–maintained drains, septic tanks, open ditches, burrow pits, etc.

Vectors of lymphatic filariasis

All three infections *(W. bancrofti, B. malayi and B. timori)* are transmitted to man by the bites of infective mosquitoes. No less than 5 genera are involved in different areas of the world – *Culex, Anopheles* and Aedes serve as vectors for *W. bancrofti;* and *Mansonia, Anopheles* and *Coquillettidia* serve as the vectors of the Brugia species.

The main vectors in India are : *C. quinquefasciatus (C. fatigans)* for Bancroftian filariasis, and *Mansonia (Mansonoides)* mosquitoes *(e.g., M. annulifers and M. uniformis)* for Brugian filariasis. The breeding of *Mansonia* mosquitoes is associated with certain aquatic plants such as *Pistia stratiotes*. In the absence of these plants, these mosquitoes cannot breed.

Mode of transmission

Filariasis is transmitted by the bite of infected vector mosquitoes. The parasite is deposited near the site of puncture. It passes through the punctured skin or may penetrate the skin on its own and finally reach the lymphatic system. The dynamics of transmission depends upon the man–mosquito contact (e.g., infective biting rate).

Incubation period

The time interval between inoculation of infective larvae and the first appearance of detectable *Mf* is known as "pre–patent period". Direct information on the duration of the prepatent period is lacking *(14)*.

The time interval from invasion of infective larvae to the development of clinical manifestations is known as the "clinical incubation period". This period, most commonly, is 8 to 16 months. This period may, however, be longer *(14)*.

Clinical manifestations

Only a small proportion of infected individuals exhibit clinical signs. The disease manifestations can be divided into two distinct clinical types : (a) *lymphatic filariasis* caused by the parasite in the lymphatic system, and (b) *occult filariasis* caused by an immune hyper-responsiveness of the human host (e.g., tropical pulmonary eosinophilia).

1. LYMPHATIC FILARIASIS

The following stages have been described *(14)*:

(i) Asymptomatic amicrofilaraemia : In all endemic areas a proportion of population does not show *Mf* or clinical manifestations of the disease although they have the same degree of exposure to infective larvae as those who become infected. With presently available diagnostic procedures it is not possible to determine whether persons in this group have detectable infections or whether they are free from infection.

(ii) Asymptomatic microfilaraemia : A considerable proportion of people are asymptomatic, although their blood is positive for *Mf*. They may remain without any symptoms for months – in some instances for years. They are an important source of infection in the community. These carriers are usually detected by night blood examination.

(iii) Stage of acute manifestations : In the first months and years there are recurrent episodes of acute inflammation in lymph glands and vessels. The clinical manifestations comprise filarial fever, lymphangitis, lymphadenitis, lymphoedema of the various parts of the body and of epididymo-orchitis in the male.

(iv) Stage of chronic obstructive lesions : The chronic stage usually develops 10–15 years from the onset of the first acute attack. This phase is due to fibrosis and obstruction of lymphatic vessels causing permanent structural changes.

In chronic Bancroftian filariasis, the main clinical features are hydrocele, elephantiasis and chyluria. Elephantiasis may affect the legs, scrotum, arms, penis, vulva and breasts,

usually in that order of decreasing frequency. The prevalence of chyluria is usually very low.

The Brugian filariasis is generally similar to Bancroftian filariasis, but strangely the genitalia are rarely involved, except in areas where Brugian filariasis occurs together with Bancroftian filariasis.

Not all elephantiasis is caused by lymphatic filarial infection. Even in endemic areas, a small proportion of cases may be due to other causes – i.e., due to obstructions following infections (such as tuberculosis), tumours, surgery or irradiation *(14)*. In Ethiopia, endemic leg elephantiasis is caused by silica in the iliac lymph glands *(15)*.

2. OCCULT FILARIASIS

The term occult or cryptic filariasis refers to filarial infections in which the classical clinical manifestations are not present and *Mf* are not found in the blood. Occult filariasis is believed to result from a hypersensitivity reaction to filarial antigens derived from *Mf*. The best known example is tropical pulmonary eosinophilia.

Lymphoedema management *(16)*

The recommended management of lymphoedema in areas where lymphatic filariasis is endemic involves simple activities that have demonstrated their effectiveness in significantly improving the quality of life of patients. These activities include providing early detection of lymphoedema, caring for the skin by washing and drying the affected limb or area, preventing and treating entry lesions and providing lymph drainage by elevating the limb and exercising. These are the minimum activities that need to be undertaken, and there is a standard care beyond this that can be accessed where available.

Since the prevention and management of disability caused by lymphatic filariasis is now viewed as public health issue, the guidelines for the first level care worker developed by WHO to manage acute dermato-lymphangio adenitis (ADLA) are as follows:

1. TREATMENT FOR UNCOMPLICATED ADLA

a. Give analgesic such as paracetamol (1g given 3–4 times a day);
b. Give oral antibiotic such as amoxicillin (1.5g in 3 divided doses or oral penicillin) for at least 8 days. In case of allergy to penicillin, oral erythromycin (1g given 3 times a day) can be used;
c. Clean the limb with antiseptic;
d. Check for any wounds, cuts, abscesses and interdigital infection (especially between the toes). Clean with antiseptic, if any present. If local superficial skin infection is found give antibiotic cream, apply antifungal cream if interdigital infection is present;
e. Give advice about prevention of chronic lymphoedema caused by lymphatic filariasis;
f. Do not give antifilarial medicine.
g. Home management includes drinking plenty of water, rest, elevation of the limb, wriggling the toes, cooling the limb with cold water and washing the limb if the patient can do it; and
h. Follow-up after 2 days at home. If situation does not improve, then refer the patient to physician.

2. MANAGEMENT OF SEVERE ADLA

a. Refer the patient to physician immediately to receive recommended antibiotic treatment
   - Intravenous benzylpenicillin (Penicillin G) 5 million units given 3 times a day or intramuscular procain benzylpenicillin 5 million units given 2 times/day until fever subsides, then give oral phenoxymethylpenicillin (penicillin V) 750 mg (1.2 million units) to 1g (1.6 million units) given 3 times/day. The minimum total treatment is atleast for 8 days.
   - In case of allergy to penicillin give IV erythromycin 1g 3 times/day until fever subsides, then give oral erythromycin 1g given 3 times/day or give other antibiotic according to local situation.
b. Give analgesic / antipyretic such as paracetamol;
c. Do not give any antifilarial medicine.

Hydrocele management

In the management of hydrocele, the objective of any lymphatic filariasis disability prevention programme should be to increase access to hydrocelectomy. One of the first activities of the programme should be to detect scrotal swelling using an existing community survey (such as enumeration of mass drug administration or other health initiatives). Individuals with scrotal swelling should be referred to a facility for diagnosis, and if necessary for surgery.

FILARIA SURVEY

The size of the sample to be examined in a filaria survey varies with the type of survey, whether it is a routine survey or survey for evaluation. The NICD (National Institute of Communicable Diseases, Delhi) standard is to examine 5–7 per cent of the population for routine surveys, and at least 20 per cent for evaluation studies. The sample must be random, representative and cover all ages and both sexes. Statistical advice should be obtained when surveys are being planned. A standardized schedule for conducting filaria surveys is given in a WHO Expert Committee Report on Filariasis *(17)*. A filaria survey comprises the following elements :

1. MASS BLOOD SURVEY

The definitive diagnosis of lymphatic filariasis depends upon the demonstration of living parasites in the human body. This calls for a night blood survey.

(i) The thick film : The thick film made from capillary blood is still the most commonly used method for epidemiological assessment. 20 cu. mm of blood is collected by a deep finger prick between 8.30 pm and 12 mid-night. A thick smear is prepared on a glass slide, and the slide is dried and serially numbered. The age, sex and other host factors are recorded on the survey card or register. On the next day or so, the blood films are dehaemoglobanized, stained, dried and examined for *Mf* under low power. The usual technique for enumeration of *Mf* on slides is to start at one end of the smear and work across to the other end, moving the slide field by field till the smear is covered.

(ii) Membrane filter concentration (MFC) methods : The most sensitive method currently available for detecting low-density microfilaraemia in the blood is by concentration techniques. It requires collection of blood by venepuncture and filtering large volumes of blood. Although MFC is the most sensitive method available, some very-low-density carriers will still not be detected *(14)*.

(iii) DEC provocation test : *Mf* can be induced to appear in blood in the daytime by administering diethylcarbamazine (DEC) 100 mg orally. *Mf* begin to reach their peak within

15 minutes and begin to decrease 2 hours later. The blood may be examined one hour after administration of DEC.

2. CLINICAL SURVEY

At the same time when blood is collected, the people are examined for clinical manifestations of filariasis which should be recorded in the suggested schedule.

3. SEROLOGICAL TESTS

Serological tests to detect antibodies to *Mf* and adults using immunofluorescent and complement–fixing techniques cannot distinguish between past and present infection, and heavy and light parasite loads in the human hosts *(18)*. Recent interest has focussed on the direct detection of parasite antigens in patient's blood or urine *(14)*.

4. XENODIAGNOSIS

The mosquitoes are allowed to feed on the patient, and then dissected 2 weeks later *(9)*. Where other techniques may fail, this may succeed in detecting low–density microfilaraemia.

5. ENTOMOLOGICAL SURVEY

This comprises of general mosquito collection from houses, dissection of female vector species for detection of developmental forms of the parasite, a study of the extent and type of breeding places and other bionomics of mosquitoes.

The data are assembled, analyzed and the results are expressed in terms of certain parameters (clinical, parasitological and entomological) as described below.

ASSESSMENT OF FILARIA CONTROL PROGRAMMES

The effect of filariasis control can be assessed using clinical, parasitological and entomological methods. These are :

1. CLINICAL PARAMETERS

The clinical parameters measured are the incidence of acute manifestations (adeno-lymphangitis, epididymo-orchitis, etc), and the prevalence of chronic manifestations (lymphoedema, elephantiasis, hydrocele, chyluria, etc).

2. PARASITOLOGICAL PARAMETERS

These are : (a) MICROFILARIA RATE : It is the percentage of persons showing *Mf* in their peripheral blood (20 cu. mm) in the sample population, one slide being taken from each person. Specify the species of the parasite. (b) FILARIAL ENDEMICITY RATE : It is the percentage of persons examined showing microfilariae in their blood, or disease manifestation or both. (c) MICROFILARIAL DENSITY : It is the number of *Mf* per unit volume (20 cu. mm) of blood in samples from individual persons. It indicates the intensity of infection. (d) AVERAGE INFESTATION RATE : It is the average number of *Mf* per positive slide, each slide being made from 20 cu.mm of blood. It indicates the prevalence of microfilaraemia in the population.

3. ENTOMOLOGICAL PARAMETERS

These comprise : (a) vector density per 10 man–hour catch (b) percentage of mosquitoes positive for all stages of development (c) percentage of mosquitoes positive for infective (stage III) larvae (d) the annual biting rate – for assessment of transmission (e) types of larval breeding places, etc.

The above parameters help to measure the conditions existing before and after control procedures began, and also to measure the progress of the control campaign against vectors from time to time.

CONTROL MEASURES

The current strategy of filariasis control is based on :

1. Chemotherapy
2. Vector control

Many years of experience with DEC chemotherapy has shown that, even after the full regimen of treatment, some microfilariae still persist in the body. Due to this and other reasons (e.g., toxic effects), it has not been possible to prevent the spread of filariasis by the administration of DEC alone. Chemotherapy must, therefore, be supplemented by an effective vector control programme, if the disease transmission has to be effectively prevented.

1. Chemotherapy

a. Diethylcarbamazine

Diethylcarbamazine (DEC) is both safe and effective. The dose of DEC that is most generally accepted for the treatment of Bancroftian filariasis is 6 mg/kg body weight per day orally for 12 days, given preferably in divided doses after meals. This amounts to a total of 72 mg of DEC per kg of body weight as a full treatment. For Brugian filariasis, recommended doses range from 3 to 6 mg of DEC/kg body weight per day, up to a total dose of 36–72 mg DEC/kg body weight as a full treatment *(14)*.

DEC is rapidly absorbed after oral administration, reaching peak blood levels in 1–2 hours. It is also rapidly excreted – the blood half-life is only 2–3 hours in alkaline urine and about 10–20 hours in acid urine.

DEC causes rapid disappearance of *Mf* from the circulation. It is effective in killing *Mf* The effect of the drug on the adult worm is uncertain. It has probably no effect on the infective stage larvae.

Toxic reactions :

DEC may produce severe side reactions. The reactions may be of two kinds : (a) those due to the drug itself, e.g., headache, nausea, vomiting, dizziness, etc, These reactions are observed a few hours after the first dose of DEC and generally do not last for more than 3 days, and (b) those which are allergic reactions due to destruction of microfilariae and adult worms, e.g., fever, local inflammations around dead worms, orchitis, lymphadenitis, transient lymphoedema and hydrocele. The local reactions tend to occur later in the course of treatment and to last longer. If the drug is given in spaced doses, systemic reactions are much less frequent and less intense after the second dose and are rare after subsequent doses. These reactions disappear spontaneously and interruption of treatment is not necessary.

b. Filaria control in the community

There are three reasons why filariasis never causes explosive epidemics : (a) the parasite does not multiply in the insect vector, (b) the infective larvae do not multiply in the human host, and (c) the life cycle of the parasite is relatively long, 15 years or more. These factors favour the success of control programme *(14)*.

The administration of DEC can be carried out in various ways :

(i) Preventive chemotherapy (2)

Elimination of lymphatic filariasis is possible by stopping the spread of the infection. Large-scale treatment involves a single dose of 2 medicines given annually to an entire at-risk population in the following way: albendazole (400 mg) together with either ivermectin (150–200 mcg/kg) or with diethylcarbamazine citrate (DEC) (6 mg/kg). These medicines have a limited effect on adult parasites but effectively reduce the density of microfilariae in the bloodstream and prevent the spread of parasites to mosquitoes. This recommended large-scale treatment strategy is called preventive chemotherapy when conducted annually for 4–6 years, and it can interrupt the transmission cycle.

(ii) Selective treatment

DEC is given only to those who are *Mf* positive. It is generally accepted that selective treatment may be more suitable in areas of low endemicity than in highly endemic areas.

The strategy is based on detection and treatment of human carriers and filaria cases. The recommended dose is 6 mg DEC per kg of body weight daily for 12 doses, to be completed in 2 weeks (i.e., 6 days in a week). In endemic areas, treatment must be repeated at specified intervals, usually every 2 years. This is partly because, despite remarkable antimicrofilarial properties, expected microfilaria clearance with DEC is incomplete at times even after adequate treatment. The other reason is that people living in endemic areas are exposed to reinfection.

(iii) DEC–medicated salt

The use of DEC–medicated salt is a special form of mass treatment using very low doses of the drug over a long period of time. Common salt medicated with 1–4 g of DEC per kg has been used for filariasis control in some endemic areas of *W. bancrofti* and *B. malayi*, particularly after an initial reduction in prevalence has been achieved by mass or selective treatment of *Mf* carriers. Treatment should be continued for at least 6 to 9 months. In the Lakshadweep islands, this regimen has been shown to be safe, cheap and effective *(14)*.

The combination of the long life of the adult parasite for several years and infectiousness of a patient with low parasitaemia represents a serious obstacle to control programmes based on chemotherapy alone *(19)*.

c. Ivermectin

Ivermectin is a semisynthetic macrolide antibiotic with a broad spectrum of activity against a variety of nematodes and ectoparasites. The dose is 150–200 µg/kg of body weight

There is no drug toxicity in normal persons. However, in microfilaraemic patients there may be a variety of reactions as a result of inflammatory response triggered by the cleared and dying microfilariae.

2. Vector control

Where mass treatment with DEC is impracticable, the control of filariasis must depend upon vector control. Vector control may also be beneficial when used in conjunction with mass treatment. The most important element in vector control is the reduction of the target mosquito population in order to stop or reduce transmission quickly. The techniques for controlling mosquitoes are given in chapter 14. Briefly they are :

I. Antilarval measures

The ideal method of vector control would be elimination of breeding places by providing adequate sanitation and underground waste-water disposal system. This involves considerable expenditure amounting to several crores of rupees. Because of financial constraints, this may not be feasible in developing countries such as India in the near future. For the time being, therefore, vector control must be based on temporary or recurrent methods.

The current approach in India is to restrict the antilarval measures to urban areas, because it is operationally difficult and very costly to cover the vast rural areas of the country. The urban areas include an extra 3–km peripheral belt because the flight range of *Culex quinquefasciatus (C. fatigans)* is about 3 km.

The anti-larval activities comprise the following *(20)*.

(1) CHEMICAL CONTROL : *(a) Mosquito larvicidal oil :* Mosquito larvicidal oil (MLO) is active against all preadult stages. It has been the main chemical used to control *C. quinquefasciatus* for some time. Since it has proved to be less efficient under field conditions and more expensive than other chemical preparations, it is being replaced by pyrethrum oil, temephos and fenthion. *(b) Pyrosene oil– E* : This is a pyrethrum–based emulsifiable larvicide. The emulsion concentrate contains 0.1 to 0.2 per cent pyrethrins by weight and is required to be diluted with water before use. The emulsion is diluted in the ratio of 1:4, *(c) Organophosphorus larvicides* : During the past 10 years, organophosphorus larvicides (e.g., temephos, fenthion) have been widely used with successful results. However, the vector mosquito has developed resistance to many of these chemicals. The frequency of application is once weekly on all breeding places.

(2) REMOVAL OF PISTIA PLANT : In the case of Mansonia mosquitoes, breeding is best controlled by removing the supporting aquatic vegetation such as the pistia plant from all water collections and converting the ponds to fish or lotus culture. Alternatively, certain herbicides such as phenoxylene 30 or Shell Weed Killer D may be used for destroying the aquatic vegetation.

(3) MINOR ENVIRONMENTAL MEASURES : Larvicidal operations are complemented by minor engineering operations such as filling up of ditches and cesspools, drainage of stagnant water, adequate maintenance of septic tanks and soakage pits, etc. Environmental management is the most efficient approach to the problem of controlling mosquito breeding.

II. Anti-adult measures

The vector mosquitoes of filariasis have become resistant to DDT, HCH and dieldrin. The use of these compounds for indoor residual spraying, tried earlier, has been discontinued. Pyrethrum, as a space spray, still holds promise. It is useful as a temporary means of personal protection, but has no practical value in present–day vector control programmes.

III. Personal prophylaxis

The most effective preventive measure is avoidance of mosquito bites (reduction of man–mosquito contact) by using mosquito nets. Screening of houses can substantially reduce transmission, but it is expensive.

Integrated vector control

None of the above vector control measures applied alone is likely to bring about sustained control of filariasis vectors.

An integrated or combined approach is needed to control filariasis using all the above strategies and approaches in optimum combination.

In filariasis four major breakthroughs have occurred. The first of these is the development of safe, single dose, annual drug treatment. Trials have proved that a single dose of DEC is very effective even two years after treatment. A single dose of ivermectin has proved to be equally effective. A combination of single dose of both drugs reduced microfilaraemia more than 95 per cent, 2 years after treatment. Secondly, intensive local hygiene on the affected limb, with or without the use of antibiotic and antifungal creams, has shown to have dramatic effects by halting the progression of, or even reversing elephantiasis and lymphoedema. Thirdly, DEC–medicated tablet or cooking salt has been introduced in India. The carefully controlled addition of very low concentration of DEC has long been recognized as an effective means of eliminating lymphatic filariasis infections in communities. However, the addition increases the price of the salt. During 1994, the first commercially prepared DEC salt went on sale in India, at about twice the price of ordinary salt. Finally, there has been the development of insecticide sprays and polystyrene beads to seal latrines and roof-top water-storage tanks, to eliminate or reduce populations of urban culex mosquitoes.

National Filaria Control Programme

Please see chapter 7 for details.

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ZIKA VIRUS DISEASE

Zika virus is a mosquito-borne flavivirus that was first identified in Uganda in 1947 through a network that monitored yellow fever. The first large outbreak of disease caused by Zika infection was reported from Island of Yap in 2007. In July 2015, Brazil reported an association between Zika virus infection and Guillain–Barre Syndrome. In October 2015, Brazil reported an association between Zika virus infection and microcephaly *(1)*.

Problem statement

Currently, WHO has reported 22 countries and territories in Americas from where local transmission of Zika virus has been reported. Zika virus disease has the potential for further international spread given the wide geographical distribution of the mosquito vector, a lack of immunity among population in newly affected areas and the high volume of international travel.

The disease has been present in India since 2016. There was outbreak in Maharashtra, cases were also reported from Karnataka, Kerala, Tamil Nadu, Madhya Pradesh, Rajasthan, Uttar Pradesh and Delhi *(2)*.

Agent factor

Zika virus disease is caused by Zika virus which belongs to the genre Flavivirus. This virus is transmitted by the bite from an infected mosquito hence also called arbovirus. The reservoir of infection is not known *(3)*.

Mode of transmission

Zika virus is transmitted through the bite of an infected mosquito from the Aedes genus, mainly Aedes aegypti, which usually bite during the morning and late afternoon hours. Transmission from an infected pregnant mother to her baby during pregnancy or around the time of birth is also now being seen as a distinct possibility. It is also transmitted through sexual contact, transfusion of blood and blood products and possibly through organ transplant *(2)*.

Clinical picture

The incubation period of Zika virus disease is not clear, but is likely to be a few days. The symptoms are similar to other arbovirus infections such as dengue, and include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache. These symptoms are usually mild and last for 2–7 days. Only one out of four infected people develops symptoms of the disease. Zika virus disease should be suspected in patients reporting with acute onset of fever, maculo-papular rash and arthralgia, among those individuals who travelled to areas with ongoing transmission during the two weeks preceding the onset of illness. Based on the available information of previous outbreaks, severe forms of disease requiring hospitalization is uncommon and fatalities are rare *(1, 3)*.

Diagnosis

Zika virus is diagnosed through PCR(polymerase chain reaction) and virus isolation from blood samples. Diagnosis by serology is not recommended.

Prevention

Aedes mosquitoes and their breeding sites pose a significant risk factor for Zika virus infection. Prevention and control relies on reducing mosquitoes through source reduction (removal and modification of breeding sites) and reducing contact between mosquitoes and people.

Treatment

Zika virus disease is usually relatively mild and requires no specific treatment. People sick with Zika virus should get plenty of rest, drink enough fluids, and treat pain and fever with paracetamol. If symptoms worsen, they should seek medical care and advice. There is currently no vaccine available.

NCDC, Delhi and National Institute of Virology (NIV), Pune, have the capacity to provide laboratory diagnosis of Zika virus disease in acute febrile stage. These two institutions would be the apex laboratories to support the outbreak investigation and for confirmation of laboratory diagnosis. Ten additional laboratories would be strengthened by ICMR to expand the scope of laboratory diagnosis. RT-PCR test would remain the standard test. As of now there is no commercially available test for Zika virus disease *(2)*.

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IV. ZOONOSES

Zoonotic diseases have been known since antiquity. Bubonic plague and rabies were known since biblical times. The discovery of causative agents during the "golden era" of microbiology called attention principally to diseases exclusively pathogenic to man. Zoonotic diseases were overshadowed by diseases peculiar to man alone. Only as human infections came under better control was attention drawn to zoonotic diseases.

More than 150 zoonoses have been recognized. In recent years, several new zoonotic diseases have emerged e.g. KFD, Monkey Pox etc., Quite apart from the morbidity and mortality they cause, zoonoses are responsible for great economic losses, particularly in animals, meat, milk and other foods and products of animal origin. The developing countries suffer much more severe losses than do the industrialized countries, partly because they have less well–developed public health and veterinary services and partly because of their unfavourable climatic and environmental conditions.

Zoonoses and human health are matters of particular concern in India – because nearly 68.86% of India's population is rural and live in close contact with domestic animals, and often not far from wild ones.

Zoonoses have been defined as "Those diseases and infections [the agents of] which are naturally transmitted between [other] vertebrate animals and man." G.S. Nelson has pointed out that it is essential to discuss the direction of transmission, as it is of little value to know that a particular organism is found in both man and animals. What one is really concerned about is its relative significance of man and animals, as maintenance hosts of the particular infection.

The zoonoses have been classified in terms of their reservoir hosts, whether these are men or lower vertebrate animals. Thus, the term anthropo-zoonoses has been applied to infections transmitted to man from lower vertebrate animals. The term zooanthroponoses is applied to infections transmitted from man to lower vertebrate animals; however, these terms have also been used interchangeably for all diseases found in both animals and man. A third term, amphixenoses, has been used for infections maintained in both man and lower vertebrate animals that may be transmitted in either direction.

A classification that is based upon the type of life cycle of the infecting organism and that divides the zoonoses into four categories, each with important shared epidemiologic features, has considerable teaching value.

The four categories are :

(1) Direct zoonoses are transmitted from an infected vertebrate host to a susceptible vertebrate host by direct contact, by contact with a fomite, or by a mechanical vector. The agent itself undergoes little or no propagative changes and no essential developmental change during transmission. Examples are rabies, trichinosis, and brucellosis.

(2) Cyclo–zoonoses require more than one vertebrate host species, but no invertebrate host, in order to complete the developmental cycle of the agent. Examples are the human taeniases, echinococcosis, and pentastomida infections.

(3) Meta-zoonoses are transmitted biologically by invertebrate vectors. In the invertebrate, the agent multiplies or develops, or both, and there is always an extrinsic incubation (prepatent) period before transmission to another vertebrate host is possible. Examples are numerous and include arbovirus infections, plague, and schistosomiasis.

(4) Sapro–zoonoses have both a vertebrate host and a non–animal developmental site or reservoir. Organic matter (including food), soil, and plants are considered to be non–animal. Examples include the various forms of larva migrants and some of the mycoses.

RABIES

Definition

Rabies, also known as *hydrophobia* is an acute, highly fatal viral disease of the central nervous system, caused by *Lyssavirus* type 1. It is primarily a zoonotic disease of warm–blooded animals, particularly carnivorous such as dogs, cats, jackals and wolves. It is transmitted to man usually by bites or licks of rabid animals. Classical hydrophobia is clinically characterized by a long and variable incubation period, a short period of illness due to encephalomyelitis ending in death, despite intensive care. It is the only communicable disease of man that is always fatal.

Problem statement

(i) GEOGRAPHIC DISTRIBUTION

Rabies is an enzootic and epizootic disease of worldwide importance. Some countries have achieved "rabies free" status by vigorous campaigns of elimination, while in others the disease has never been introduced. Geographic boundaries seem to play an important role here. Water appears to be the most effective natural barrier to rabies. Australia, China (Taiwan), Cyprus, Iceland, Ireland, Japan, Malta, New Zealand, the U.K. and the islands of Western Pacific are all free of the disease. The Liberian peninsula and Finland, Norway and Sweden are also rabies free *(1)*. In India, Union Territory of Lakshadweep and Andman and Nicobar islands are free of the disease *(2)*. A "Rabies-free" area has been defined as one in which no case of indigenously acquired rabies has occurred in man or any animal species for 2 years *(3)*. According to WHO reports, in many countries rabies is spreading inspite of great advances in research and field control methods.

Rabies occurs in more than 150 countries and territories. Although a number of carnivorous and bat species serve as natural reservoir, rabies in dogs is the source of 99 per cent of human infection, and posses a potential threat to more than 3.3 billion people.

In a number of countries, human deaths from rabies are likely to be grossly underreported, particularly in the youngest age groups. Vast majority of the estimated 55,000 deaths caused by rabies each year occur in rural areas of Africa and Asia. In India alone, 20,000 deaths (that is, about 2 per lac population at risk) are estimated to occur annually; in Africa, the corresponding figure is 24,000 (about 4 per lac population at risk) *(4)*.

Although all age groups are susceptible, rabies is most common in children aged less than 15 years; on an average, 40 per cent of post–exposure immunization are given to children aged 5–14 years, and the majority of those immunized are male. In the north–western part of the United Republic of Tanzania, the incidence of rabies was upto 5 times higher in children aged less than 15 years than in adults *(4)*. At the global level, more than 15 million people receive rabies prophylaxis annually, the majority of whom live in China and India. It is estimated that in the absence of post–exposure prophylaxis, about 327,000 persons would die from rabies in Africa and Asia each year *(4)*.

Epidemiological determinants

Agent factors

AGENT : The causative agent (*Lyssavirus* type 1) is a bullet shaped neurotropic RNA containing virus. It belongs to the family rhabdoviridae – serotype 1 (*Lyssavirus*, type 1) and is the causative agent of rabies. Serotype 2, 3 and 4 are *rabies–related* but antigenically distinct viruses; they cause rabies like disease in man and animals *(5)*. Available anti-rabies vaccines may not be effective against the rabies–related viruses *(6)*.

Rabies virus particles contain two distinct, major antigens : a glycoprotein (G protein) antigen from the virus membrane and an internal nucleoprotein antigen. The glycoprotein seems to be the only antigen capable of inducing the formation of virus–neutralizing antibodies *(7)*. The presence of neutralizing antibodies in the blood of man and animals is considered an index of protection against infection with rabies virus *(8)*. Recently, surface glycoprotein of rabies virus has been cloned and expressed in *E. coli* in a bid to develop genetically engineered rabies vaccine.

The virus is excreted in the saliva of the affected animals. The virus recovered from naturally occurring cases of rabies is called *"street virus"*. It is pathogenic for all mammals and shows a long variable incubation period (20–60 days in dogs). Serial brain–to–brain passage of the street virus in rabbits modifies the virus such that its incubation period is progressively reduced until it becomes constant between 4–6 days. Virus isolated at this stage is called a *fixed virus*. A "fixed" strain of virus may be defined as one that has a short, fixed and reproducible incubation period (4–6 days) when injected intracerebrally into suitable animals. It does not form Negri bodies. It no longer multiplies in extra–neural tissues. The *fixed virus* is used in the preparation of antirabies vaccine. There is evidence that *fixed virus* can be pathogenic for humans and mammals under certain conditions, as for example parenteral injection of antirabies vaccine inadequately inactivated *(7)*.

SOURCE OF INFECTION : The source of infection to man is the saliva of rabid animals. In dogs and cats, the virus may be present in the saliva for 3–4 days (occasionally 5–6 days) before the onset of clinical symptoms and during the course of illness till death *(9, 10)*.

Host factors

All warm blooded animals including man are susceptible to rabies. Rabies in man is a dead-end infection, and has no survival value for the virus. The overwhelming number of victims in India belong to the age group 1–24 years (2). Laboratory staff working with rabies virus, veterinarians, dog handlers, hunters and field naturalists face bigger risks of rabies than do general public.

Mode of transmission *(11)*

People are infected following a deep bite or scratch by an infected animal. Dogs are the main host and transmitter of rabies. They are the source of infection in almost all the rabies deaths annually in Asia and Africa.

Bats are the source of most human rabies deaths in the United States of America and Canada. Bat rabies has also recently emerged as a public health threat in Australia, Latin America and western Europe. However in these regions the number of human deaths due to bat rabies remains small compared to deaths following dog bites. Human deaths following exposure to foxes, raccoons, skunks, jackals, mongooses and other wild carnivore host species are very rare.

Transmission can also occur when infectious material – usually saliva – comes into direct contact with human mucosa or fresh skin wounds. Human-to-human transmission by bite is theoretically possible but has never been confirmed.

Rarely, rabies may be contracted by inhalation of virus-containing aerosol or *via* transplantation of an infected organ. Ingestion of raw meat or other tissues from animals infected with rabies is not a source of human infection.

Incubation period

The incubation period in man is highly variable, commonly 1–3 months following exposure but may vary from 7 days to many years *(4)*. The incubation period depends on the site of the bite, severity of the bite, number of wounds, amount of virus injected, species of the biting animal, protection provided by the clothing and treatment undertaken, if any. In general, incubation period tends to be shorter in severe exposures and bites on face, head, neck and upper extremities and bites by wild animals. In no other specific communicable disease is the incubation period so variable and dependant on so many factors as in rabies.

Pathogenesis

Rabies virus replicates in muscle or connective tissue cells at or near the site of introduction before it attaches to nerve endings and enters peripheral nerves. It spreads from the site of infection centripetally *via* the peripheral nerves towards the central nervous system; most likely it "ascends" passively through the nerve associated tissue space *(7)*. Following infection of the central nervous system, the virus spreads centrifugally in peripheral nerves to many tissues, including skeletal and myocardial muscle, adrenal glands and skin. The salivary glands invasion is crucial for the transmission of the virus to another animal or human *(5)*.

RABIES IN MAN

Clinical picture

Rabies in man is called hydrophobia. The disease begins with *prodromal symptoms* such as headache, malaise, sore throat and slight fever lasting for 3–4 days. About 80% of patients complain of pain or tingling at the site of the bite.

This is the only prodromal symptom which is considered reasonably specific *(12)*.

The prodromal stage is followed by widespread excitation and stimulation of all parts of nervous system usually involving, in order, the sensory system, the motor system, the sympathetic and mental system. The patient is intolerant to noise, bright light or a cold draught of air (sensory). Aerophobia (fear of air) may be present and is considered by some to be pathognomonic of rabies *(13)*. It can be elicited by fanning a current of air across the face which causes violent spasms of the pharyngeal and neck muscles. Examination may show increased reflexes and muscle spasms (motor) along with dilatation of the pupils and increased perspiration, salivation and lachrimation (sympathetic). Mental changes include fear of death, anger, irritability and depression.

The symptoms are progressively aggravated and all attempts at swallowing liquid become unsuccessful. At later stage the mere sight or sound of water may provoke spasm of the muscles of deglutition. This characteristic symptom of hydrophobia (fear of water) is pathognomonic of rabies and is absent in animals. The duration of illness is 2 to 3 days, but may be prolonged to 5–6 days in exceptional cases. The patient may die abruptly during one of the convulsions or may pass on to the stage of paralysis and coma. Intensive care may allow an occasional patient to survive *(10)*. To-date, only three people are on record who have been stricken with rabies and have survived *(1)*.

Diagnosis

A clinical diagnosis of hydrophobia can be made on the basis of history of bite by a rabid animal and characteristic signs and symptoms.

Rabies can be confirmed in patients early in the illness by antigen detection using immunofluorescence of skin biopsy, and by virus isolation from saliva and other secretions. Immunofluorescence of corneal impression smears has proved unreliable. Neutralizing antibodies are not usually detectable in serum or CSF before the eighth day *(5)*.

Treatment

There is no specific treatment for rabies. Case management includes the following procedure :

(a) The patient should be isolated in a quiet room protected as far as possible from external stimuli such as bright light, noise or cold draughts which may precipitate spasms or convulsions. (b) Relieve anxiety and pain by liberal use of sedatives. Morphia in doses of 30–45 mg may be given repeatedly. The drug is well tolerated and once the diagnosis is established there appears to be no reason to restrict the administration of a drug which does so much to allay acute suffering. (c) If spastic muscular contractions are present use drugs with curare–like action. (d) Ensure hydration and diuresis. (e) Intensive therapy in the form of respiratory and cardiac support may be given.

Patients with rabies are potentially infectious because the virus may be present in the saliva, vomits, tears, urine or other body fluids. Nursing personnel attending rabid patients should be warned against possible risk of contamination and should wear face masks, gloves, goggles and aprons to protect themselves. Persons having bruises, cuts or open wounds should not be entrusted to look after the patient. Where human cases of rabies are encountered frequently pre-exposure prophylaxis is recommended.

PREVENTION OF HUMAN RABIES

This may be considered under 3 heads.

a. Post-exposure prophylaxis.
b. Pre-exposure prophylaxis.
c. Post-exposure treatment of persons who have been vaccinated previously.

POST-EXPOSURE PROPHYLAXIS

1. General consideration

The vast majority of persons requiring anti-rabies treatment are those who were bitten by a suspected rabid animal. The aim of post-exposure prophylaxis is to neutralize the inoculated virus before it can enter the nervous system. Every instance of human exposure should be treated as a medical emergency. It is now well established that irrespective of the class of wound, the combined administration of a single dose of rabies immunoglobulin if indicated with a course of vaccine, together with local treatment of the wound is the best specific prophylactic treatment after exposure of man to rabies.

2. Local treatment of wound

Prompt and adequate local treatment of all bite wounds and scratches is the first requisite and is of utmost importance. The purpose of local treatment is to remove as much virus as possible from the site of inoculation before it can be absorbed on nerve endings. Local treatment of wounds is of maximal value when applied immediately after exposure (within minutes if possible) but it should not be neglected if several hours or days have elapsed *(3)*. Animal experiments have shown that local wound treatment can reduce the chances of developing rabies by upto 80% *(6)*. The local treatment comprises the following measures :

(a) Cleansing : Immediate flushing and washing the wound(s), scratches and the adjoining areas with plenty of soap and water, preferably under a running tap, for at least 15 minutes is of paramount importance in the prevention of human rabies. If soap is not available, simple flushing of the wounds with plenty of water should be done as first-aid. In case of punctured wounds, catheters, should be used to irrigate the wounds. This procedure is now standard worldwide. It does minimize the risk of contracting rabies. Unfortunately, very few patients get it in right time.

(b) Chemical treatment : Whatever residual virus remains in the wound(s), after cleansing, should be inactivated by irrigation with *virucidal* agents – either alcohol (400–700 ml/litre), tincture or 0.01% aqueous solution of iodine or povidone iodine.

(c) Suturing : Bite wounds should not be immediately sutured to prevent additional trauma which may help spread the virus into deeper tissues. If suturing is necessary, it should be done 24–48 hours later, applying minimum possible stitches, under the cover of rabies immunoglobulin locally.

(d) Antibiotics and anti-tetanus measure : The application of antibiotics and antitetanus procedures when indicated should follow the local treatment recommended above.

3. Immunization

Since their development more than four decades ago, concentrated and purified cell-culture vaccine (CCV) and embryonated egg-based vaccine (EEV) have proved to be safe and effective in preventing rabies. These vaccines are

intended for pre-exposure as well as post-exposure prophylaxis.

The internationally available cell-culture and embryonated egg-based vaccines (CCEEVs) consist of rabies virus that has been propagated in cell substrates such as human diploid cells (embryonic fibroblast cells), fetal rhesus diploid cells, Vero cells (kidney cells from the African green monkey), primary Syrian hamster kidney cells, primary chick embryo cells or in embryonated duck eggs. The more recently developed vaccines based on chick embryo cells and Vero cells have safety and efficacy records comparable to those of the human diploid cell vaccines and are less expensive *(4)*.

Rabies vaccines prequalified by WHO do not contain preservatives such as thimerosal. The shelf-life of these vaccines is ≥ 3 years, provided they are stored at +2°C to +8°C and protected from sunlight. Following reconstitution with the accompanying sterile diluent, the vaccines should be used immediately, or within 6–8 hours if kept at the correct temperature.

All CCEEVs should comply with the WHO recommended potency of ≥ 2.5 IU per single intramuscular dose (0.5 ml or 1.0 ml volume after reconstitution, depending on the type of vaccine).

The guidelines for the post–exposure treatment by the WHO are given in Table 1.

TABLE 1
Categories of contact and recommended post-exposure prophylaxis (PEP)

Categories of contact with suspect rabid animal	Post–exposure prophylaxis measures
Category I – touching or feeding animals, licks on intact skin	None
Category II – nibbling of uncovered skin, minor scratches or abrasions without bleeding	Immediate vaccination and local treatment of the wound
Category III – single or multiple transdermal bites or scratches, licks on broken skin; contamination of mucous membrane with saliva from licks, contacts with bats.	Immediate vaccination and administration of rabies immunoglobulin; local treatment of the wound

Source: *(11)*

All category II and III exposures assessed as carrying a risk of developing rabies require PEP. This risk is increased if *(11)*:

- the biting mammal is a known rabies reservoir or vector species;
- the animal looks sick or has an abnormal behaviour;
- a wound or mucous membrane was contaminated by the animal's saliva;
- the bite was unprovoked;
- the animal has not been vaccinated; and
- if biting animal cannot be traced or identified.

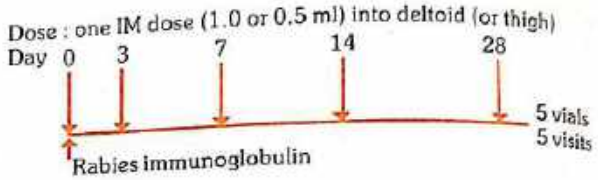
In developing countries, the vaccination status of the suspected animal alone should not be considered when deciding whether to initiate prophylaxis or not.

Post-exposure prophylaxis may be discontinued if the suspected animal is proved by appropriate laboratory examination to be free of rabies or, in the case of domestic dogs, cats or ferrets, the animal remains healthy throughout a 10 day observation period starting from the date of the bite *(4)*.

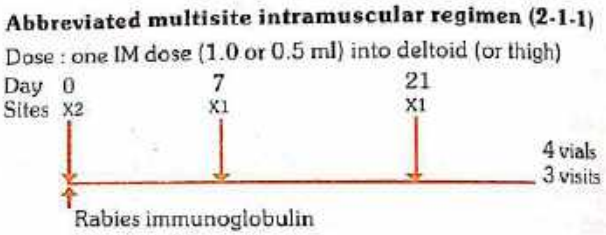
Intramuscular administration of vaccine for post-exposure prophylaxis

The post-exposure vaccination schedule is based on injecting 1 ml or 0.5 ml (the volume depends on the type of vaccine) into the deltoid muscle (or anterolateral thigh in children aged <2 years) of patients with category II and III exposures. The recommended regimen consists of either a 5-dose or a 4-dose schedule:

(i) *Essen regimen:* the 5-dose regimen prescribes 1 dose on each of days 0, 3, 7, 14, and 28; as shown below



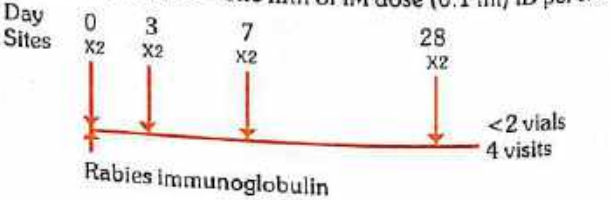
(ii) *Zareb regimen:* the 4-dose abbreviated multisite regimen prescribes 2 doses on day 0 (1 in each of the 2 deltoid or thigh sites) followed by 1 dose on each of days 7 and 21, as shown below.



An alternative for healthy, fully immunocompetent, exposed people who receive wound care plus high quality rabies immunoglobulin plus WHO prequalified rabies vaccines, is a post-exposure regimen consisting of 4 doses administered intramuscularly on days 0, 3, 7 and 14.

Intradermal administration for post-exposure prophylaxis

The 2-site regimen prescribes injection of 0.1 ml at 2 sites (deltoid or thigh) on days 0, 3, 7 and 28. The day 14 dose is missed. This regimen may be used for people with category II and III exposures in countries where the intradermal route has been endorsed by national health authorities. The regimen is as shown below :



Post-exposure prophylaxis for previously vaccinated individuals

For rabies-exposed patients who can document previous complete pre-exposure vaccination or complete post-exposure prophylaxis with a CCEEV, 1 dose delivered intramuscularly or a CVV delivered intradermally on days 0 and 3 is sufficient. Rabies immunoglobulin is not indicated

in such cases. This 1-site 2-day intradermal or intramuscular regimen also applies to people vaccinated against rabies who have demonstrated rabies-virus neutralizing antibody titres of ≥0.5 IU/ml . As an alternative to this regimen, the patient may be offered a single-visit 4-site intradermal regimen consisting of 4 injections of 0.1 ml equally distributed over left and right deltoids or thighs. Vaccination cards recording previous immunizations are invaluable for making correct decisions.

Immunization of immunocompromised individuals

In immunocompromised individuals including patients with HIV/AIDS, a complete series of 5 doses of intramuscular CCEEV in combination with comprehensive wound management and local infiltration with human rabies immunoglobulin is required for patients with category II and III exposures. When feasible, the rabies-virus neutralizing antibody response should be determined 2–4 weeks following vaccination to assess the possible need for an additional dose of the vaccine.

Rabies immunoglobulin for passive immunization

Rabies immunoglobulin for passive immunization is administered only once, preferably at, or as soon as possible after, the initiation of post-exposure vaccination. Beyond the seventh day after the first dose, rabies immunoglobulin is not indicated because an active antibody response to the CCEEV is presumed to have occurred. The dose of human rabies immunoglobulin is 20 IU/kg body weight; for equine immunoglobulin and F (ab')2 products, it is 40 IU/kg body weight. All of the rabies immunoglobulin, or as much as anatomically possible (but avoiding possible compartment syndrome), should be administered into or around the wound site or sites. The remaining immunoglobulin, if any, should be injected intramuscularly at a site distant from the site of vaccine administration. Rabies immunoglobulin may be diluted to a volume sufficient for all wounds to be effectively and safely infiltrated.

Most of the new equine immunoglobulin preparations are potent, highly purified, safe and considerably less expensive than human rabies immunoglobulin. However they are of heterologous origin and carry a small risk of anaphylactic reaction (1/45,000 cases). There are no scientific grounds for performing a skin test prior to administering equine immunoglobulin because testing does not predict reactions, and it should be given whatever the result of the test. The treating physician should be prepared to manage anaphylaxis which, although rare, could occur during any stage of administration *(14)*.

Guide for pre-exposure prophylaxis (PrEP) *(14)*

PrEP may be performed with any of the modern cell-derived vaccines and is recommended for anyone at increased risk of exposure to rabies virus. Traditionally, PrEP is recommended for anyone who is at continual, frequent or increased risk of exposure to the rabies virus either as a result of their residence or occupation (for example laboratory workers dealing with rabies virus and other lyssaviruses, veterinarians and animal handlers). Travellers with extensive outdoor exposure and children living in rural high-risk areas are at particular risk.

PrEP schedule requires intramuscular doses of 1ml or 0.5 ml, depending on the vaccine type, or intradermal administration of 0.1 ml volume per site (one site each day) given on days 0, 7 and 21 or 28. To lead to significant savings, intradermal PrEP sessions should involve enough individuals to utilize all opened vials within 6–8 hours.

Booster doses of rabies vaccines are not required for individuals living in or travelling to high-risk areas who have received a complete primary series of pre-exposure or post–exposure prophylaxis with a CCV. Periodic booster injections are recommended as an extra precaution only for people whose occupation puts them at continual or frequent risk of exposure. If available, antibody monitoring of personnel at risk is preferred to the administration of routine boosters. For people who are potentially at risk of laboratory exposure to high concentrations of live rabies virus, antibody testing should be done every 6 months. Those professionals who are not at continual risk of exposure through their activities, such as certain categories of veterinarians and animal health officers, should have serological monitoring every 2 years. Because vaccine-induced immunity persists in most cases for years, a booster would be recommended only if rabies virus neutralizing antibody titres fall to <0.5 IU/ml.

Adverse events following immunization *(4)*

In general, CCEEVs have been shown to be safe and well tolerated. However, in 35–45% of vaccinees, minor and transient erythema, pain and/or swelling may occur at the site of injection, particularly following intradermal administration of a booster. Mild systemic adverse events following immunization (AEFI), such as transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 5–15% of vaccinees.

Contraindications and precautions *(4)*

For pre-exposure prophylaxis, previous severe reaction to any components of the vaccine is a contraindication to further use of the same vaccine. Because rabies is a lethal disease, no contraindications exist to post-exposure prophylaxis following high-risk exposure. This is also the case for post-exposure prophylaxis during infancy or pregnancy, and for immunocompromised individuals, including children with HIV/AIDS. People taking chloroquine for malaria treatment or prophylaxis may have a reduced response to intradermal rabies vaccination. These patients should receive the vaccine intramuscularly.

NERVOUS TISSUE VACCINES

Nervous tissue vaccines are crude products capable of causing severe and even fatal reactions. Although apparently effective, they are generally of low or variable potency and are usually administered to exposed subjects in a large number of doses. The current trend is to limit or abandon completely the production of nervous tissue vaccines and replace them by safer and more effective inactivated cell-culture vaccines in both developed and developing countries. Government of India has stopped producing nervous tissue vaccine since 2004.

RABIES IN DOGS

In developing countries over 90% of human deaths from rabies are caused by dog bites and dog rabies control is the key that can lock the door against human rabies.

INCUBATION PERIOD

The incubation period in dogs ranges from 3–8 weeks, but it may be as short as 10 days or as long as a year or more *(15)*.

CLINICAL PICTURE

Rabies in dogs may manifest itself in two forms – Furious rabies and Dumb rabies.

(a) Furious rabies : This is the typical "mad-dog syndrome", characterized by *(i) a change in behaviour* : In animals, the cardinal sign is a change in behaviour. The animal loses its fear of people, becomes very aggressive, bites without provocation and bites unusual objects like sticks, straw and mud *(ii) running amuck*: i.e., tendency to run away from home and wander aimlessly and biting humans and animals who may come in its way *(iii) change in voice* : i.e., the dog barks or growls in a hoarse voice or often unable to bark because of paralysis of laryngeal muscles *(iv) excessive salivation* and foaming at the angle of the mouth, and *(v) Paralytic stage* : The animal enters into a paralytic stage, towards the later stages of illness. There is paralysis of the whole body leading to coma and death.

(b) Dumb rabies : In this type, the excitative or irritative stage is lacking. The disease is predominantly paralytic. The dog withdraws itself from being seen or disturbed. It lapses in to a stage of sleepiness and dies in about 3 days.

Once the symptoms of rabies develop in an animal, it rarely survives more than a week *(16)*.

LABORATORY DIAGNOSIS

The head of the animal is cut off and sent to the nearest testing laboratory, duly packed in ice in an airtight container. Alternatively, the brain may be removed with anti-septic precautions and sent in 50% glycerol–saline for examination *(17)*. This should be done by a qualified or trained person soon after the death of the animal.

Laboratory examination is made by : (a) FLUORESCENT ANTIBODY TEST : This is a highly reliable and the best single test currently available for the rapid diagnosis of rabies viral antigen in infected specimens. This test can establish a highly specific diagnosis within a few hours *(3)*. The accuracy of the test is considered equal to that of isolation of the virus by animal inoculation. If the brain is negative by FRA test, one can assume that the saliva contains no virus, and the bitten person need not be treated. Further, fluorescent antibody titres in clinical rabies have been well in excess of 1:10,000 a feature which helps to distinguish between rabies and vaccine reaction *(18)*. (b) MICROSCOPIC EXAMINATION : Although FRA test has largely supplanted other methods of diagnosis, the microscopic examination of brain tissue for Negri bodies is still a useful method for rapid diagnosis of rabies. The microscopic examination for Negri bodies identifies 75–90% of cases of rabies in dogs. (c) MOUSE INOCULATION TEST : Intracerebral mouse inoculation is still one of the most useful tests in the laboratory diagnosis of rabies. Suckling mice are generally more sensitive for virus isolation. A 10% emulsion of suspected brain tissue is prepared in normal saline and centrifuged at 2000 rpm for 5–10 minutes. 0.03 ml of the supernatant fluid is injected intracerebrally using a tuberculin syringe into at least 4 mice. If infected they show signs of rabies between 6–8 days. The virus can be identified by the FRA test or by the presence of Negri bodies. (d) CORNEAL TEST : Rabies virus antigen can be detected in live animals in corneal impressions or in frozen sections of skin biopsies by the FRA test. A positive result is indicative of rabies, but a negative result does not rule out the possibility of infection *(3)*.

Immunization of dogs

Prophylactic vaccination of dogs against rabies is one of the most important weapons in rabies control *(7)*. Studies have shown that, in general, 80–90% of the dog population is accessible for vaccination, thus confirming that the concept of controlling rabies through mass vaccination is a sound one *(19)*. All dogs should receive primary immunization at the age of 3–4 months and booster doses should be given at regular intervals, according to the type of vaccine used.

(1) *BPL inactivated nervous tissue vaccine (Single dose)* : This is based on 20% suspension of infected sheep brain. The dose is 5 ml for dogs and 3 ml for cats. Revaccination is advised after 6 months, and subsequently every year.

(2) *Modified live virus vaccine* : This is based on 33% chick embryo suspension infected with modified virus. The dose is 3 ml by single injection, and boosters every 3 years. As with the vaccines for human use, the adult-brain vaccines for use in animals should be replaced as soon as possible by cell-culture vaccines *(20)*.

Control of urban rabies

Since dog is the major source of infection, the most logical and cost-effective approach is elimination of stray and ownerless dogs combined with a programme of swift mass immunization, in the shortest possible time, of at least 80% of the entire dog population of the area.

Other methods include (i) registration and licensing of all domestic dogs (ii) restraint of dogs in public places (iii) immediate destruction of dogs and cats bitten by rabid animals (iv) quarantine for about 6 months of imported dogs and (v) health education of people regarding the care of dogs and prevention of rabies.

The discovery that foxes could be immunized against rabies by placing modified live virus vaccine directly into the mouths has generated a new control technique. So far no suitable oral bait is developed for use in dogs *(1)*.

Oral vaccines

The successful introduction of oral vaccines for the immunization of foxes is a great advancement in the rabies prophylaxis of wild life. An attempted live rabies vaccine harmless but immunizing to foxes, is placed in baits and distributed over the foxes habitat. Successful control of wild animal's rabies particularly foxes has been achieved in Canada, Germany and Switzerland by the use of "oral vaccine baits." The technique holds much promise for the future control of rabies not only in foxes but also in other wild life species.

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YELLOW FEVER

Yellow fever is a zoonotic disease caused by an arbovirus. It affects principally monkeys and other vertebrates in tropical America and Africa and is transmitted to man by certain culicine mosquitoes. It shares clinical features with other viral haemorrhagic fevers (e.g., dengue HF, Lassa fever) but is characterized by more severe hepatic and renal involvement. The spectrum of disease varies from clinically indeterminate to severe cases. Severe cases develop jaundice with haemorrhagic manifestations (black vomit, epistaxis, melena) and albuminuria or anuria, shock, agitation, stupor and coma *(1)*. In general death occurs between the fifth and tenth day of illness. The case fatality rate may reach 80 per cent in severe cases. Survivors exhibit long-lasting immunity.

Problem statement

47 countries in Africa and Latin America, with a combined population of more than 900 million, are at risk of yellow fever. In Africa, an estimated 508 million people live in 32 countries at risk. The remaining are in 13 countries of Latin America, with Bolivia, Brazil, Colombia, Ecuador and Peru at greatest risk *(2)*.

There were an estimated 84,000–170,000 cases and 29,000–60,000 deaths worldwide. Small number of imported cases occur in countries free of yellow fever. Although disease has never been reported in Asia, the region is at risk because the conditions required for transmission are present there *(2)*.

Epidemiological determinants

Agent factors

(a) AGENT : The causative agent, *Flavivirus fibricus* formerly classified as a group B arbovirus, is a member of the togavirus family. It shares group-specific antigens with other members of the genus (e.g., West Nile, dengue). Under natural conditions, the virus is pantropic but after continued culture in tissues, as in chick embryo, it loses all its pathogenic properties but retains its antigenicity. (b) RESERVOIR OF INFECTION : In forest areas, the reservoir of infection is mainly monkeys and forest mosquitoes. In urban areas, the reservoir is man (subclinical and clinical cases) besides *Aedes aegypti* mosquitoes. (c) PERIOD OF COMMUNICABILITY : (i) MAN : Blood of patients is infective during the first 3 to 4 days of illness. (ii) MOSQUITOES : After an "extrinsic incubation period" of 8 to 12 days, the mosquito becomes infective. The virus multiplies in the insect vector. After becoming infective, the mosquito remains so for life. Transovarian transmission of the virus in mosquitoes has been shown to occur in adverse conditions (e.g., during extended dry seasons), in the absence of susceptible hosts *(1)*.

Host factors

(a) AGE AND SEX : All ages and both sexes are susceptible to yellow fever in the absence of immunity (b) OCCUPATION : Persons whose occupation brings them in contact with forests (wood cutters, hunters) where yellow fever is endemic are exposed to the risk of infection (c) IMMUNITY : One attack of yellow fever gives lifelong immunity; second attacks are unknown. Infants born of immune mothers have antibodies up to 6 months of life.

Environmental factors

(a) CLIMATE : A temperature of 24 deg.C or over is required for the multiplication of the virus in the mosquito. It should be accompanied by a relative humidity of over 60 per cent for the mosquitoes to live long enough to convey the disease. (b) SOCIAL FACTORS : In Africa, urbanization is leading to the extension of yellow fever. In addition, the expanding population is encroaching on areas that were previously sparsely populated, thereby bringing man closer to the jungle cycles of yellow fever. The increasing number of people who travel and the greater speed with which they are transported from endemic areas to receptive areas, also gives a cause for concern *(3)*.

Modes of transmission

There are three known cycles of transmission, the jungle, intermediate and the urban cycles *(2)*.

- *Sylvatic (or jungle) yellow fever.* In tropical rainforests, yellow fever occurs in monkeys that are infected by wild mosquitoes. The infected monkeys then pass the virus to other mosquitoes that feed on them. The infected mosquitoes bite humans entering the forest, resulting in occasional cases of yellow fever. The majority of infections occur in young men working in the forest (e.g. for logging).
- *Intermediate yellow fever.* In humid or semi-humid parts of Africa, small-scale epidemics occur, Semi-domestic mosquitoes (that breed in the wild and around households) infect both monkeys and humans. Increased contact between people and infected mosquitoes leads to transmission. Many separate villages in an area can suffer cases simultaneously. This is the most common type of outbreak in Africa. An outbreak can become a more severe epidemic if the infection is carried into an area populated with both domestic mosquitoes and unvaccinated people.
- *Urban yellow fever.* Large epidemics occur when infected people introduce the virus into densely populated areas with a high number of non-immune people and Aedes mosquitoes. Infected mosquitoes transmit the virus from person to person.

Treatment

There is no specific treatment for yellow fever, only supportive care to treat dehydration and fever. Associated bacterial infections can be treated with antibiotics. Supportive care may improve outcomes for seriously ill patients, but it is rarely available in poorer areas.

Incubation period

3 to 6 days (6 days recognized under International Health Regulations).

CONTROL OF YELLOW FEVER

Jungle yellow fever

Jungle yellow fever continues to be an uncontrollable disease. The virus maintains itself in the animal kingdom. Mosquito control is difficult and can be considered only in restricted areas. Vaccination of humans with 17D vaccine is the only control measure.

Urban yellow fever

(1) VACCINATION : Rapid immunization of the population at risk is the most effective control strategy for yellow fever. For international use, the approved vaccine is the ***17D vaccine.*** It is a live attenuated vaccine prepared from a non–virulent strain (17D strain), which is grown in chick embryo and subsequently freeze–dried.

The sensitivity of the lyophilized 17D vaccine to heat is a major drawback to the use of this vaccine, in mass campaigns in tropical countries. It has to be stored between +5 and –30 deg.C, preferably below zero deg. C until reconstituted with the sterile, cold physiological saline diluent provided. Reconstituted vaccine should be kept on ice, away from sunlight, and discarded if not used within half an hour.

The vaccine is administered subcutaneously at the insertion of deltoid in a single dose of 0.5 ml irrespective of age. Immunity begins to appear on the 7th day and lasts possibly for life *(2)*.

The risk of death from yellow fever is much higher than the risks related to the vaccine. People who should not be vaccinated include *(2)* :

(a) children aged under 9 months for routine immunization (or under 6 months during an epidemic);

(b) pregnant women – except during a yellow fever outbreak when the risk of infection is high;

(c) people with severe allergies to egg protein; and

(d) people with severe immunodeficiency caused by symptomatic HIV/AIDS or other causes, or in the presence of thymus disorder.

Mild post-vaccinial reactions (e.g., myalgia, headache, low–grade fever) may occur in 2–5 per cent of vaccinees, 5 to 10 days after vaccination. Anaphylaxis is very rare, occurring mainly in those allergic to eggs *(4)*.

Cholera and yellow fever vaccines together or within 3 weeks interfere with each other, so whenever possible, they should be given 3 weeks or more apart *(5)*.

(2) VECTOR CONTROL : The other principal method of preventing yellow fever is through intensive vector control. The objective of vector control is to reduce rapidly the vector population to the lowest possible level and thereby stop or reduce transmission quickly. This approach has proved successful in the Americas to prevent urban epidemics.

The vector, *Aedes* mosquito is peri-domestic in habits. It can be controlled by vigorous anti-adult and anti-larval measures. The long-term policy should be based on organized "source reduction" methods (e.g., elimination of breeding places) supported by health education aimed at securing community participation.

Personal protection against contact with insects is of major importance in integrated vector control. Such protection may include the use of repellents, mosquito nets, mosquito coils and fumigation mats *(7)*.

(3) SURVEILLANCE : A programme of surveillance (clinical, serological, histopathological and entomological) should be instituted in countries where the disease is endemic, for the early detection of the presence of the virus in human populations or in animals that may contribute to its dissemination.

For the surveillance of Aedes mosquitoes, the WHO uses an index known as ***Aedes aegypti index.*** This is a house index and is defined as "the percentage of houses and their premises, in a limited well-defined area, showing actual breeding of *Aedes aegypti larvae" (8)*. This index should not be more than 1 per cent in towns and seaports in endemic areas to ensure freedom from yellow fever *(9)*.

International measures

India is a yellow fever "receptive" area, that is, "an area in which yellow fever does not exist, but where conditions would permit its development if introduced". The population of India is unvaccinated and susceptible to yellow fever. The vector, *Aedes aegypti* is found in abundance. The climatic conditions are favourable in most parts of India for its transmission. The common monkey of India *(Macacus spp)* is susceptible to yellow fever. The missing link in the chain of transmission is the virus of yellow fever which does not seem to occur in India.

The virus of yellow fever could get imported into India in two ways: (i) through infected travellers (clinical and subclinical cases), and (ii) through infected mosquitoes. Measures designed to restrict the spread of yellow fever are specified in the "International Health Regulations" of WHO *(8)*. These are implemented by the Government of India through stringent aerial and maritime traffic regulations. Broadly these comprise :

(i) TRAVELLERS : All travellers (including infants) exposed to the risk of yellow fever or passing through endemic zones of yellow fever must possess a valid international certificate of vaccination against yellow fever before they are allowed to enter yellow fever "receptive" areas. If no such certificate is available, the traveller is placed on quarantine, in a mosquito–proof ward, for 6 days from the date of leaving an infected area. If the traveller arrives before the certificate becomes "valid", he is isolated till the certificate becomes valid.

(ii) MOSQUITOES : The aircraft and ships arriving from endemic areas are subjected to aerosol spraying with prescribed insecticides on arrival for destruction of insect vectors. Further, airports and seaports are kept free from the breeding of insect vectors over an area extending at least 400 metres around their perimeters. The *"aedes aegypti index"* is kept below 1.

International certificate of vaccination *(10)*

India and most other countries require a valid certificate of vaccination against yellow fever from travellers coming from infected areas. A few countries (including India) require this even if the traveller has been in transit. It rests with each country to decide whether a certificate of vaccination against yellow fever shall be required for infants under one year of age, after weighing the risk of importation of yellow fever by unvaccinated infants against the risk to the infant arising from vaccination. In this regard, India requires vaccination of infants (≥ 9 months of age) too. The validity of the certificate begins 10 days after the date of vaccination. For the purpose of international travel, the vaccination must be given at an

officially designated centre, and the certificate must be validated with the official stamp of the Ministry of Health, Government of India. The certificate is valid only if it conforms with the model prescribed under the International Health Regulations. On the other hand, for their own protection, travellers who enter endemic areas should receive vaccination against yellow fever *(10)*.

New yellow fever vaccination requirement for travellers

In May 2014, the World Health Assembly adopted an amendment of International Health Regulations (2005), which stipulates that the period of protection afforded by yellow fever vaccination, and the term of validity of the certificate will change from 10 years to the duration of the life of the person vaccinated. On 11th July 2016, the amendment entered into force and is legally binding upon all IHR states. This lifetime validity applies automatically to all existing and new certificates, beginning 10 days after the date of vaccination. Accordingly, as of 11th July 2016, revaccination or a booster dose of yellow fever vaccine will not be required for international travellers as a condition of entry into a State Party, regardless of the date that their international certificate of vaccination was initially issued *(11)*.

In India, the lifetime validity of yellow fever vaccination applies automatically. The list of yellow fever endemic countries are as follows:

In Africa : Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Cote d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Mali, Mauritania, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, Sudan, South Sudan, Togo and Uganda; and in the Americas: Argentina, Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Panama, Paraguay, Peru, Suriname, Trinidad and Tobago (Trinidad only), and Venezuela (Bolivarian Republic of). *Note :* When a case of yellow fever is reported from any country, that country is regarded by the Government of India as a country with risk of yellow fever transmission and is added to the above list *(10)*.

Epidemic preparedness and response

WHO recommends that every at-risk country have at least one national laboratory where basic yellow fever blood tests can be performed. A confirmed case of yellow fever in an unvaccinated population is considered as an outbreak. A confirmed case in any context must be fully investigated. Investigation teams must assess and respond to the outbreak with both emergency vaccination campaigns and longer-term immunization plans *(2)*.

The Elimination of Yellow Fever Epidemic (EYE) Strategy *(2)*

The EYE Strategy was developed by WHO, UNICEF and GAVI, in response to increased threat of yellow fever urban outbreaks with international spread. It is guided by three strategic objectives :

1. Protect at-risk populations ;
2. Prevent international spread of yellow fever; and
3. Contain outbreaks rapidly.

These objectives are underpinned by five competencies of success :

1. Affordable vaccines and sustained vaccine market;
2. Strong political commitment at global, regional and country levels;
3. High-level governance with long-term partnerships;
4. Synergies with other health programmes and sectors; and
5. Research and development for better tools and practices.

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NIPAH VIRUS INFECTION

Nipah Virus is a zoonotic virus, an emerging infectious disease caused by virus of the family Paramyxoviridae, genus Henipavirus. It gets its name from the village in Malaysia where the person from whom the virus was first isolated succumbed to the disease in the year 1999 *(1)*.

Problem statement

Nipah virus infection was initially isolated and identified in 1999 during an outbreak of encephalitis and respiratory illness among pig farmers in Malaysia and Singapore. In 2001, it was again identified as the causative agent in the outbreak of human disease in Bangladesh and India. Since then it has been reported almost annually in Bangladesh and many times in India. A recent outbreak in India was in Kerala in the month of Sept. 2023.

Mode of transmission

Transmission of nipah virus to humans may occur after direct contact with infected bats, infected pigs or from other nipah virus infected people (as reported in Bangladesh and India), where it is seen in the family and caregivers of the infected patients. Transmission also occurs from direct exposure to infected bats. Example is consumption of raw date palm sap contaminated with infectious bat secretions, and excretions *(3)*.

Fruit bats of the family *Pteropodidae*, particularly species belonging to *Pteropus genus* are the natural host for nipah virus. There is no apparent disease in fruit bats *(1)*.

Incubation period

Usually 4 to 14 days.

Clinical manifestations

Human infection ranges from asymptomatic infection to acute respiratory infection and fatal encephalitis. Infected people initially develop fever, headache, myalgia, vomiting and sore throat. This can be followed by dizziness,

drowsiness, altered consciousness and neurological signs that indicate acute encephalitis. Some people can also experience atypical pneumonia and severe respiratory problems, including acute respiratory distress. Encephalitis and seizures occur in severe cases, progressing to coma within 24 to 48 hours. Most people who survive acute encephalitis make a full recovery. Long term neurologic conditions have been reported in survivors. Approximately 20% of patients are left with residual neurological consequences such as seizure disorder and personality changes. A small number of people who recover subsequently relapse or develop delayed onset encephalitis. The case fatality rate is estimated at 40% to 75%. This rate can vary by outbreak depending on local capabilities for epidemiological surveillance and clinical management *(2)*.

Diagnosis

The main tests are real time polymerase chain reaction (RT-PCR) from bodily fluids and antibody detection via ELISA. Other tests used include polymerase chain reaction assay, and virus isolation by cell culture *(1)*.

Treatment

No drug or vaccine specific to nipah virus is available. Intensive supportive care is recommended to treat severe respiratory and neurological complications.

Prevention

In the absence of a vaccine, the only way to reduce or prevent infection in people is by raising awareness of the risk factors and educating people about the measures they can take to reduce exposure to nipah virus.

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OTHER ARBOVIRAL DISEASES

During the past few years, a large number of arthropod–borne viruses (arboviruses) have been isolated from sick persons, animals and arthropods throughout the world. Arthropod-borne viruses are defined as viruses "which are maintained in nature principally, or to an important extent through biological transmission between susceptible vertebrate hosts by haematophagous arthropods; they multiply in the tissues of arthropods, and are passed on to new vertebrates by the bites of arthropod after a period of extrinsic incubation" *(1)*.

Yellow fever is historically the most prominent among the diseases in this group. In recent years, a number of other arboviruses have emerged as important public health problems in both tropical and temperate zones. The number of arboviruses known in India had risen from two (dengue and sandfly fever) in 1951 to over 40 *(2)*.

CLASSIFICATION

The huge family of heterogeneous arboviruses is divided into no less than 7 major groups, and 18 smaller groups *(3)*. Many remain unclassified. The current trend is to name the viruses after the places where they were discovered. Some of the arboviruses known to be prevalent in India are as shown in Table 1.

TABLE 1
Some Arboviruses known to be prevalent in India

Group A	**OTHERS**
(Alphavitruses)	*Umbre*
Sindbis	Sathuperi
Chikungunya	Chandipura
	Chittor
	Ganjam
Group B	Minnal
(Flavivirus)	Venkatapuram
Dengue	Dhori
KFD	Kaisodi
JE	Sandfly fever
West Nile	African Horse sickness
	Vellore

CLINICAL SYNDROMES

Although arboviruses are many, only a small number of them are known to be capable of infecting man, and a much smaller number capable of producing disease. A high proportion of the infections is inapparent. For convenience, three clinical syndromes have been described : (a) FEBRILE GROUP : This is the most common group which comprises a large number of relatively undifferentiated fevers, generally benign with or without rashes and joint pains. Viruses responsible for this group of illness in India are the sindbis, chikungunya and dengue viruses. (b) HAEMORRHAGIC FEVERS : The second group is that of haemorrhagic fevers, generally associated with moderate or high mortality. Viruses responsible for haemorrhagic fevers in India are the dengue, chikungunya and KFD viruses. (c) ENCEPHALITIDIS : The third group is that of encephalitidis or meningoencephalitis which is associated with a considerable and sometimes high mortality. The disease reported now frequently in some parts of India is the Japanese encephalitis.

1. The dengue syndrome

This is detailed separately at page 293.

2. Japanese encephalitis

Japanese encephalitis (JE) is a mosquito–borne encephalitis caused by a group B arbovirus (Flavivirus) and transmitted by culicine mosquitoes. It is a zoonotic disease, i.e., infecting mainly animals and incidentally man. The envelope glycoprotein of the JE virus contains specific as well as cross-reactive, neutralizing epitopes. The major genotypes of this virus have different geographical distribution, but all belong to the same serotype and are similar in terms of virulence and host preference. Following an infectious mosquito bite, the initial viral replication occurs in local and regional lymph nodes. Viral invasion of the central nervous system occurs probably *via* blood.

JE is the leading cause of viral encephalitis in Asia and occurs in almost 24 Asian and Western Pacific countries. Largely as a result of immunization, its incidence has been declining in Japan, the Korean peninsula and in some regions of China, but the disease is increasingly reported from Bangladesh, India, Nepal, Pakistan, northern Thailand and Vietnam. Transmission occurs principally in rural agricultural location where flooding irrigation is practised. Transmission is seasonal and mainly related to the rainy season in South-East Asia Region *(2)*.

The annual incidence of clinical disease varies both across and within countries, ranging from <10 to >100 per 100,000 population. A recent estimate puts nearly 68,000

clinical cases of JE globally each year, with upto 20,400 deaths due to JE *(3)*. The vast majority of cases occur among children less than 15 years of age. Nearly 10 per cent of cases are among those above 60 years, perhaps reflecting waning protective immunity.

The disease is rare in other parts of the world, and when seen, is generally associated with travellers returning from endemic areas *(3)*.

Major outbreaks of JE occur every 2–15 years. JE transmission intensifies during the rainy season, when vector population increases. However, there has not yet been any evidence of increased JE transmission following major floods. The spread of JE in new areas has been correlated with agricultural development supported by irrigation programmes *(3)*.

PROBLEM IN INDIA

Recognition of JE, based on serological surveys, was first made in 1955 in Tamil Nadu. JE has been reported from different parts of the country. The disease is endemic in 21 states. Assam, Bihar, Uttar Pradesh, Karnataka, West Bengal, Tripura and Tamil Nadu report out-breaks every year and contribute about 55 per cent of cases and deaths. In India about 375 million population is at risk. JE is reported under the umbrella of Acute Encephalitis Syndrome (AES), therefore, the data reported from states are for total AES including JE cases *(4)*. The state-wise reported cases of Acute encephalitis syndrome are as shown in Table 2.

TABLE 2

State-wise reported cases and deaths due to Acute encephalitis syndrome in India 2018–2020 (P)

State	2018		2019		2020 (P)	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
Assam	1492	183	2652	353	595	96
Bihar	124	33	292	82	172	23
Jharkhand	544	0	912	3	485	0
Karnataka	380	5	397	4	310	0
Manipur	283	3	1177	6	29	4
Meghalya	243	6	711	9	230	1
Odisha	1720	10	1962	8	373	3
Tamil Nadu	1287	5	1007	2	333	4
Tripura	311	0	325	2	244	0
Uttar Pradesh	3080	230	2185	126	1646	83
West Bengal	1762	146	1618	89	867	26
India Total	11,388	636	14,995	710	5,487	248

P – Provisional

Source : *(5)*

Epidemiological features

Unlike the dengue viruses, JE virus infects several extrahuman hosts, e.g., animals and birds. Available evidence indicates that the basic cycles of transmission are :

(a) Pig → Mosquito → Pig

(b) The Ardeid bird → Mosquito → Ardeid bird

The disease is transmitted to man by the bite of infected mosquitoes. Man is an incidental "dead–end" host. Man to man transmission has not so far been recorded.

(a) Animal hosts : Among the animal hosts, pigs have been incriminated as the major vertebrate hosts for JE virus. In some places, upto 100 per cent of pigs may be infected with JE virus. Infected pigs do not manifest any overt symptoms of illness but circulate the virus so that mosquitoes get infected and can transmit the virus to man. The pigs are thus considered as "amplifiers" of the virus *(6)*. Cattle and buffaloes may also be infected with the JE virus; although they may not be natural hosts of JE virus, they act as "mosquito attractants." Horses are the only domestic animals so far known which show signs of encephalitis due to JE virus infection. *(b) Birds :* Some species of birds such as pond herons; cattle egrets and perhaps poultry and ducks appear to be involved in the natural history of JE virus *(6)*.

MOSQUITO VECTORS

Culicine mosquitoes, notably *C.tritaeniorhynchus*, *C. vishnui* and *C. gelidus* along with some anophelines have been incriminated as the vectors of JE. Among these, *C.tritaeniorhynchus* and *vishnui* has been implicated as the most important vector in South India *(7)*. These mosquitoes generally breed in irrigated rice fields, shallow ditches and pools. The rice fields are probably the most important breeding places. These mosquitoes are zoophilic, feeding primarily on vertebrate hosts. Female mosquitoes get infected after feeding on a viraemic host, and after 9–12 days incubation period, they can transmit the virus to other hosts.

JE IN MAN

The incubation period in man, following mosquito bite is not exactly known. Probably, it varies from 5–15 days. Not all individuals bitten by infected mosquitoes develop disease. The ratio of overt disease to inapparent infection is about 1:250. Thus cases of encephalitis represent only the tip of the iceberg compared to the large number of inapparent infections. Encephalitis cases due to JE may show a scattered distribution.

The course of the disease in man may be divided into three stages : *(a) PRODROMAL STAGE* : The onset of illness is usually acute and is heralded by fever, headache, gastrointestinal disturbances, lethargy and malaise. The duration of this stage is usually 1–6 days. *(b) ACUTE ENCEPHALITIC STAGE* : Fever is usually high, 38 to 40.7 deg. C. The prominent features are fever, nuchal rigidity, focal CNS signs, convulsions signs of raised intracranial pressure, difficulty of speech, dystonia, ocular palsies, hemiplegia, quadriplegia, extra-pyramidal signs like coarse tremors and altered sensorium progressing in many cases to coma. *(c) LATE STAGE AND SEQUELAE* : This stage begins when active inflammation is at an end, i.e., the temperature and ESR touch normal. Neurological signs become stationary or tend to improve. Convalescence may be prolonged and residual neurological deficits may not be uncommon *(3)*. The case fatality rate varies between 20–40 per cent. The average period between the onset of illness and death is about 9 days *(3)*.

Confirmation of a suspected case of JE requires laboratory diagnosis. The aetiological diagnosis of JE is mainly based on serology using IgM-capture ELISA which detects specific IgM in the cerebrospinal fluid or in the blood of almost all patients within 7 days of onset of disease. Other methods include conventional antibody assays on paired sera for the demonstration of a significant rise in total JE–specific antibody, as well as a dot-blot IgM assay, suitable for use in the field. The virus is rarely recovered in tissue culture from blood or CSF, but may be found in encephalitic brain at autopsy. JE-viral RNA is rarely demonstrated in the CSF *(8)*.

Control of JE

(a) VACCINATION : Vaccination of population at risk has been recommended. Currently, the three types of JE vaccines in large-scale use are : (i) the mouse brain-derived, purified and inactivated vaccine, which is based on either the Nakayama or Beijing strains of the JE virus and produced in several Asian countries; (ii) the cell culture-derived, inactivated JE vaccine based on the Beijing P-3 strain, and (iii) the cell culture-derived, live attenuated vaccine based on the SA 14-14-2 strain of the JE virus. The mouse-brain derived, inactivated vaccine has been used successfully to reduce the incidence of JE in a number of countries, and is likely to be used nationally and internationally for some more years. Drawbacks of the mouse-brain vaccine are the limited duration of the induced protection, the need for multiple doses, and, in most countries, the relatively high price per dose. The cell culture-derived vaccines are manufactured and widely used in China, where the inactivated vaccine is gradually being replaced by the live attenuated vaccine. Several other promising JE vaccine candidates are in advanced stages of development.

The immunization schedules of the 3 licensed JE vaccines that are currently in large-scale use vary with the profile of the respective vaccines and depend on local epidemiological circumstances and recommended schedules of other childhood vaccines. When immunizing children 1–3 years of age the mouse brain-derived vaccine provides adequate protection throughout childhood following 2 primary doses 4 weeks apart, and boosters after 1 year and subsequently at 3-yearly intervals until the age of 10–15 years. The vaccine is given subcutaneously in doses of 0.5 ml for children under 3 years and one ml for children more than 3 years of age. Protective immunity develops in about one month time after the second dose. The vaccine is best used in the inter-epidemic period. It should be offered to the most vulnerable and high-risk groups *(6, 7)*. Equally good childhood protection is obtained by a single dose of the cell-culture based, live attenuated vaccine (SA-14-14-2) followed by a single booster given at an interval of about 1 year. This vaccine is available in India and is an integral part of Universal Immunization Programme in 83 endemic districts in Uttar Pradesh, Assam, West Bengal and Karnataka targeting children in age group 1–15 years *(9)*. The importance of achieving long-term protection is underlined by the observation that in some areas an increasing proportion of the JE cases occur in individuals older than 10 years of age *(8)*.

Given the most infrequent occurrence of JE in infancy and the likely interference with passively acquired maternal antibodies during the first months of life, vaccination is not recommended for children before the age of 6 months *(8)*.

For travellers aged more than one year, visiting rural areas of endemic countries for at least 2 weeks, the established current practice is to administer 3 primary doses at days 0, 7 and 28; alternatively 2 primary doses preferably 4 weeks apart. When continued protection is required, boosters should be given after one year and then every 3 years *(8, 10)*.

The vaccination of swine is extremely important for both public health and economic reasons. It prevents viraemia in these animals, and hence eliminates their role as amplifiers of the virus. An inactivated vaccine and more recent modified live virus vaccines are all in current use. However, it is difficult to maintain vaccination coverage in the swine of a given region because the population is renewed so rapidly *(11)*.

(b) VECTOR CONTROL : The vector mosquito(es) of JE are widely scattered and not easily amenable to control. An effective way to deal with them is to resort to aerial or ground fogging with ultra–low–volume (ULV) insecticides (e.g., malathion, fenitrothion). All the villages reporting cases should be brought under indoor residual spray. The spraying should cover the vegetation around the houses, breeding sites and animal shelters in the affected villages. Uninfected villages falling within 2 to 3 km radius of the infected villages should also receive spraying as a preventive measure. Villages within the proximity of infected villages should be kept under surveillance. The use of mosquito nets should be advocated.

GUIDELINES FOR MANAGEMENT OF AES INCLUDING JAPANESE ENCEPHALITIS IN INDIA (2014) *(12)*

Following an outbreak of JE in Gorakhpur and Basti divisions in eastern Uttar Pradesh during 2005, Directorate of NVBDCP developed surveillance guidelines for endemic states and advised that all the JE cases be reported under Acute Encephalitis Syndrome (AES) as they have common similar clinical manifestations. Their case management usually follows a common protocol along with situation specific treatment. Diagnosis of JE will depend on laboratory investigations. The case definitions and case classification in the programme are as follows *(12)* :

Case definition of suspected case

- Acute onset of fever, not more than 5–7 days duration.
- Change in mental status with/without
  - New onset of seizures (excluding febrile seizures)
  - Other early clinical findings – may include irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness.

Case classification

Laboratory-confirmed case

A suspected case with any one of the following markers:

- Presence of IgM antibody in serum and/or CSF to a specific virus including JE/Enterovirus or others
- Four fold difference in IgG antibody titre in paired sera
- Virus isolation from brain tissue
- Antigen detection by immunofluroscence
- Nucleic acid detection by PCR

In the sentinel surveillance network, AES/JE is to be diagnosed by IgM Capture ELISA, and virus isolation to be done in National Reference Laboratory.

Probable cases

Suspected case in close geographic and temporal relationship to a laboratory-confirmed case of AES/JE in an outbreak.

Acute Encephalitis Syndrome (AES) due to other agent

A suspected case in which diagnostic testing is performed and an aetiological agent other than AES/JE is identified.

Acute Encephalitis Syndrome (AES) due to unknown agent

A suspected case in which no diagnostic testing is performed/no aetiological agent is identified/test results are indeterminate.

While the above classifications are useful for clearer definitions of AES cases, for practical purposes, the two key definitions to be used are "suspected JE cases" for those that meet the criteria for AES, and "confirmed JE cases" for those AES cases which have laboratory confirmation for JE. In an epidemic situation fever with altered sensorium persisting for more than two hours with a focal seizure or paralysis of any part of body, is encephalitis. Presence of rash on body excludes Japanese Encephalitis. AES with symmetrical signs and fever is likely to be cerebral Malaria.

The causes of AES are as shown in Fig. 1.

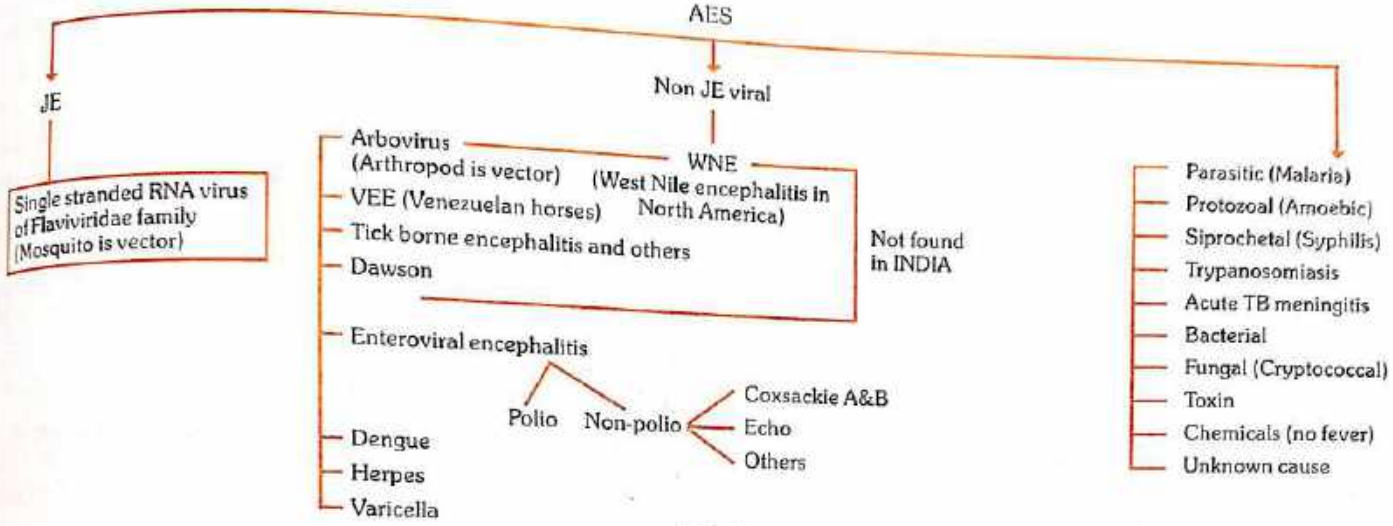

FIG. 1
Causes of Acute Encephalitis Syndrome

Source : *(13)*

Management of Acute Encephalitis Syndrome, including Japanese Encephalitis, is essentially symptomatic. To reduce severe morbidity and mortality, it is important to identify early warning signs and refer patients to health facility and to educate the health workers about the first line of treatment for management of the case at the grassroot level.

Fig. 2 summarizes the guidelines for management of a case of AES at PHC and FRU level and management of circulation as blood pressure should be maintained at about 95th centile for the age of the patient with the help of dopamine drip. Failure of autoregulation of the brain makes the cerebral circulation depend solely on systemic blood

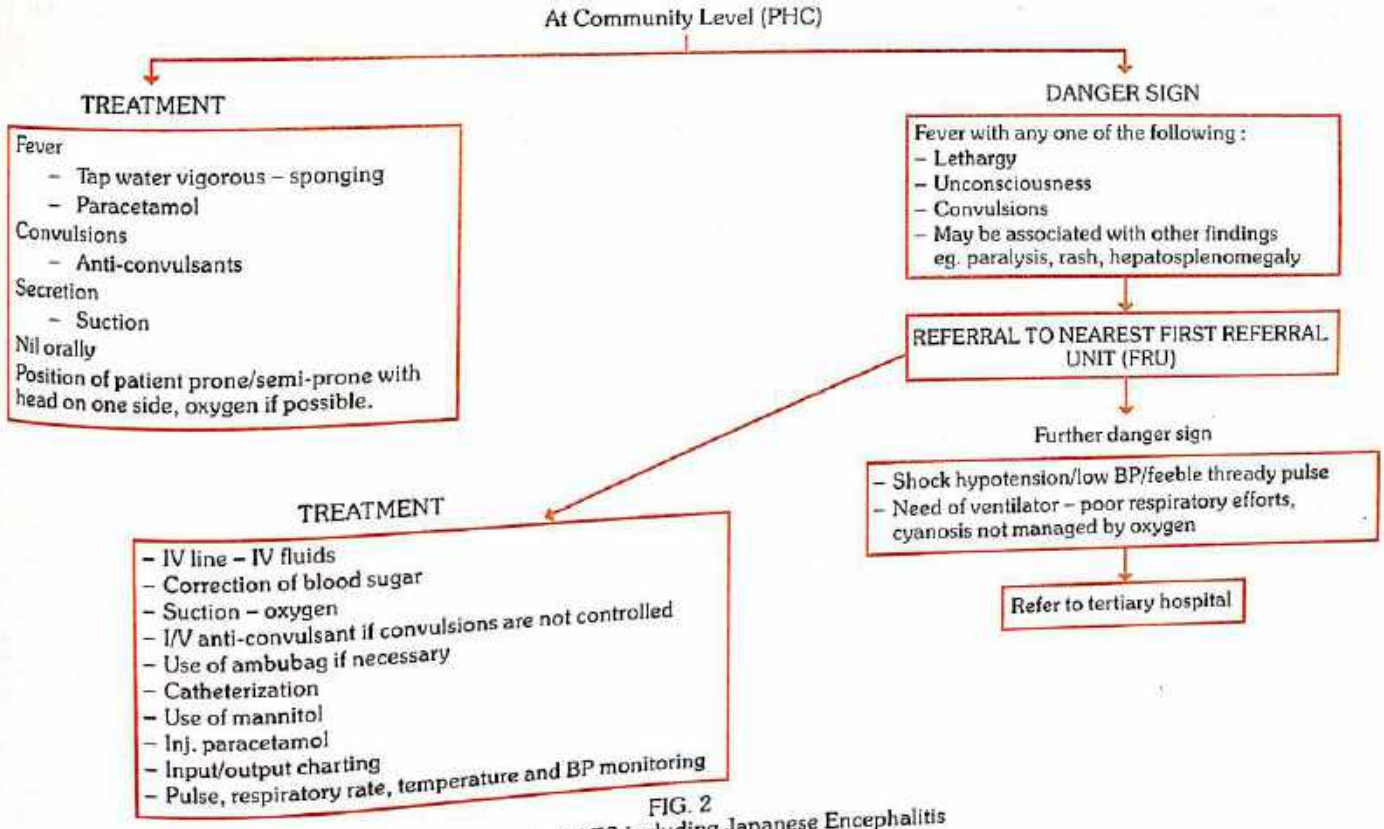

FIG. 2
Management of AES including Japanese Encephalitis

Source : *(12)*

pressure. Avoid fluid overload. The ultimate decision regarding the management depends upon the attending physician.

Treatment of specific cause

If laboratory investigation shows a non-JE cause, like herpes-zoster, varicella, malaria, pyogenic meningitis, tubercular meningitis, toxoplasmosis, amoebiasis, fungal infection or neurocysticercosis; the patient should be given specific treatment for that particular disease.

3. Kyasanur forest disease

Kyasanur forest disease (KFD) is a febrile disease associated with haemorrhages caused by an arbovirus flavivirus and transmitted to man by bite of infective ticks.

HISTORY

KFD was first recognized in 1957 in Shimoga district of Karnataka State in South India. Local inhabitants called the disease "monkey disease" because of its association with dead monkeys. The disease was later named after the locality – Kyasanur Forest – from where the virus was first isolated.

PROBLEM STATEMENT

Earlier the disease was found to be limited mainly to an area around the original focus (Shimoga district) covering about 800 sq.km. Newer foci have since been recognized. The disease is now restricted to four districts (Shimoga, North Kannada, South Kannada and Chikamagaluru) in Karnataka State in India covering over 6,000 sq.km. *(14)*. Serological surveys in different parts of India revealed antibodies to KFD or a closely related virus in human and animals, particularly in cattle in Kutch and Saurashtra *(15)*.

According to the reports, the disease continues to be active in its endemic foci. About 400–500 cases occur every year with case fatality rate of about 3–5 per cent. The Karnataka Government has established a surveillance system which monitors the occurrence of KFD in humans and mortality in monkeys in known epidemic areas, as well as neighbouring areas. Deaths of monkeys are considered as heralders of this disease in endemic areas *(16)*.

Epidemiological determinants

(a) AGENT

The agent KFD virus is a member of group B togaviruses (flaviviruses). It is antigenically related to other tick-borne flaviviruses, particularly the Far Eastern tick-borne encephalitis and Omsk haemorrhagic fever. Unlike in many other arbovirus infections, KFD has a prolonged viraemia in man for about 10 days or more.

(b) NATURAL HOSTS AND RESERVOIRS

Small mammals particularly rats and squirrels are the main reservoirs of the virus *(14)*. Birds and bats are less important hosts. The monkeys are recognized as amplifying hosts for the virus. However, they are not effective maintenance hosts because most of them die from KFD infection. Cattle provide *Haemaphysalis* ticks with a plentiful source of blood meals, which in turn leads to a population explosion among the ticks. Thus cattle are very important in maintaining tick populations but play no part in virus maintenance *(14)*. Man is an incidental or dead-end host, and plays no part in virus transmission.

(c) VECTORS

The virus has a complex life cycle involving a wide variety of tick-species. At least 15 species of hard ticks of the genus *Haemaphysalis*, particularly *H. spinigera* and *H. turtura* are known to transmit the disease. KFD has also been isolated from soft ticks *(17)*. The highest number of human and monkey infections occur during drier months, particularly from January to June. This period coincides with the peak nymphal activity of ticks.

(d) HOST FACTORS

(i) Age : Majority of cases affected were between 20 and 40 years. *(ii) Sex* : Attack rate was greater in males than in females. *(iii) Occupation* : The attacked people were mostly cultivators who visited forests accompanying their cattle or cutting woods and *(iv) Human activity* : The epidemic period correlates well with the period of greatest human activity in the forest, i.e., from January until the onset of rains in June.

(e) MODE OF TRANSMISSION

The transmission cycle involves mainly monkeys and ticks. The disease is transmitted by the bite of infective ticks, especially nymphal stages. There is no evidence of man to man transmission.

(f) INCUBATION PERIOD

Estimated to be between 3 and 8 days.

CLINICAL FEATURES

The disease appears with a sudden onset of fever, headache and severe myalgia, with prostration in some patients. The acute phase lasts for about 2 weeks. Gastrointestinal disturbances and haemorrhages from nose, gums, stomach and intestine may occur in severe cases.

In a number of cases, there is a second phase characterized by mild meningoencephalitis after an afebrile period of 7 to 21 days. It is manifested by a return of fever, severe headache followed by neck stiffness, coarse tremors, abnormal reflexes and mental disturbances. The case fatality rate has been estimated to be 5 to 10 per cent *(14)*.

Diagnosis is established only after detecting the presence of the virus in the blood and/or serological evidence.

CONTROL

(a) CONTROL OF TICKS : Since KFD is a tick-borne disease, control of ticks should be undertaken. For control of ticks in forests, application can be made by power equipment or by aircraft-mounted equipment to dispense carbaryl, fenthion, naled or propoxur at 2.24 kg of active ingredient per hectare *(18)*. The spraying must be carried out in "hot spots", i.e., in areas where monkey deaths have been reported, within 50 metres around the spot of the monkey deaths, besides the endemic foci. Since the heavy tick population in the forest areas is attributed partly to the free roaming cattle, restriction of cattle movement is thought to bring about a reduction in vector population. (b) VACCINATION : The population at risk should be immunized with killed KFD vaccine. (c) PERSONAL PROTECTION : Protection of individuals exposed to the risk of infection by adequate clothing and insect repellents such as dimethylphthalate (DMP, DEET) should be encouraged. They should examine their bodies at the end of each day for ticks and remove them promptly. The habit of sitting or lying down on the ground should be discouraged through health education.

4. Chikungunya fever

A dengue-like disease caused by a group A virus, the chikungunya virus and transmitted by *Aedes* mosquitoes. It is manifested by high fever and severe articular pains in the limbs and spinal column. The virus was first isolated from patients and mosquitoes during an epidemic in Tanzania in 1952–53. Chikungunya is a local word meaning "doubling up" owing to excruciating joint pains. The virus occurs widely in sub-Saharan Africa, India and in many areas in Asia.

After re-emergence of chikungunya in the year 2006, clinically suspected cases declined till the year 2014. However, the disease shows an upward trend since 2015. Chikungunya is endemic in 24 states and 6 UTs. During 2020, a total of 43,424 suspected cases were reported from 28 states. The maximum number of cases were from states as shown in Table 3.

TABLE 3

Top 10 states reporting suspected cases of Chikungunya, India (2018–2020)

States	2018 Cases	2019 Cases	2020 (P) Cases
Karnataka	20,411	43,698	16,111
Gujarat	10,601	8,084	8,120
Maharashtra	9,884	5,150	4,258
Puducherry	2,876	7,084	3,980
Kerala	77	109	2,302
Rajasthan	254	365	1,015
Tamil Nadu	284	623	1,461
Telangana	1,954	5,352	364
Madhya Pradesh	3,211	2,749	1,871
Tripura	683	1,105	454
India	57,813	81,914	43,424

P – Provisional

Source : *(5)*

The incubation period of chikungunya fever is 4–7 days, following which the disease has a sudden onset with fever, chills, cephalalgia, anorexia, lumbago and conjunctivitis. Adenopathy is also common. 60 to 80 per cent patients have a morbilliform rash, occasionally with purpura, on the trunk and limbs. The cutaneous eruption may recur every 3 to 7 days. Other symptoms are coffee-coloured vomiting, epistaxis and petechiae. A prominent symptom, seen especially in adult patients is arthropathy, from which the disease gets its name. The arthropathy is manifested by pain, swelling and stiffness, especially of the metacarpophalangeal, wrist, elbow, shoulder, knee, ankle and metatarsal joints. It appears between 3rd and 5th day after the onset of clinical symptoms, and it can persist for many months and even years. No deaths have been attributed to chikungunya fever *(11)*.

There is no specific treatment of chikungunya infection and it is usually self limiting. Analgesics, antipyretics like paracetamol, diclofenac sodium, chloroquine along with fluid supplementation are recommended to manage infection and relieve fever, joint pains and swelling. Drugs like aspirin and steroids should be avoided.

The disease occurs in the rainy season, when the mosquito vector population is at its peak. Research suggests that the virus has a wild cycle, similar to that of yellow fever, operating between jungle primates and mosquitoes, including *Aedes africanus* and members of the *A. furcifer-taylori* group.

DIAGONSIS

The virus can be isolated from the blood of febrile patients by the intracerebral inoculation in suckling mice or on VERO cells.

In serologic diagnosis, which is the approach most commonly used, sero-conversion is demonstrated by comparing acute – and convalescent – phase sera in the haemagglutination inhibition, serum neutralization, or complement fixation test. The enzyme-linked immunosorbent assay (ELISA) is used to detect IgM. A reverse-transcription polymerase chain reaction (RT-PCR) / nested PCR technique has also been shown to be useful in rapidly diagnosing the disease *(11)*.

CONTROL

(a) VECTOR CONTROL : The *Aedes aegypti* mosquito should be the main target of control activities. It requires active community involvement to keep water storage containers free of mosquitoes and to eliminate the other breeding places of mosquitoes in and around houses and dwellings *(4)*. Vector control strategies should address all life stages of the *Aedes* mosquito from the egg to larva and adult. Targeted residual spraying and space spraying/fogging when there is an outbreak is recommended to rapidly reduce the adult mosquito population. *(b) PERSONAL PROTECTION* : Personal preventive measures to avoid mosquito bites include clothing minimizing skin exposure, use of repellents, as well as window screens. The use of insecticide - treated bed nets is limited by the fact that *Aedes* mosquito bites during daytime. Eventually economic development will reduce mosquito-borne diseases by improving standard of living (e.g. people living in houses with solid floors and roofs, window screen and air conditioning) *(20)*. *(c) VACCINE* : No vaccine has yet been developed that is considered suitable for use.

5. West nile fever

An acute febrile illness caused by a group B arbovirus. The disease is endemic in Africa, the Middle East, South–West Asia and India, and transmitted by certain species of Culex mosquitoes. Clinically, it is manifested by a sudden onset of fever, severe headache and malaise lasting several days. In children, a maculopapular rash of short duration may appear. In the aged, a fatal meningo-encephalitis may be produced.

6. Sandfly fever

Sandfly fever is known to occur in the arid regions of West Pakistan and Middle East. Its occurrence in India was thought to be doubtful. However, in 1967, the sandfly fever virus was isolated in Aurangabad (Maharashtra) from febrile cases. The virus was also isolated from sandflies *(21)*. The control of sandfly fever is based on the control of insect vector.

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BRUCELLOSIS

Brucellosis is one of the major bacterial zoonoses, and in humans is also known as Undulent fever, Malta fever or Mediterranean fever. It is occasionally transmitted to man by direct or indirect contact with infected animals. It is caused by different species of the brucella group of organisms and characterized by intermittent or irregular febrile attacks, with profuse sweating, arthritis and an enlarged spleen. The disease may last for several days, months or occasionally years. Brucellosis is both a severe human disease and a disease of animals with serious economic consequences.

Problem statement

Brucellosis is a recognized public health problem with worldwide distribution. It is endemic wherever cattle, pigs, goats and sheep are raised in large numbers. Important endemic areas for brucellosis exist in Mediterranean zones, Europe, Central Asia, Mexico and South America. Eastern Mediterranean countries have experienced an increase in the number of cases. The disease is now rare in most European countries, North America and Australia *(1)*.

Animal brucellosis is reported from practically every State in India. However, no statistical information is available about extent of infection in man in various parts of the country *(2)*.

The prevalence of human brucellosis is difficult to estimate. Many cases remain undiagnosed either because they are inapparent or because physicians in many countries are unfamiliar with the disease.

Epidemiological determinants

Agent factors

(a) AGENT : The agents are small, gram-negative rod-shaped, non-motile, non-sporing and intracellular coccobacilli of the genus *Brucella*. Four species infect man : *B.melitensis, B.abortus, B.suis*, and *B.canis*. *B.melitensis* is the most virulent and invasive species; it usually infects goats and occasionally sheep. *B.abortus* is less virulent and is primarily a disease of cattle. *B.suis* is of intermediate virulence and chiefly infects pigs. *B.canis* is a parasite of dogs. (b) RESERVOIR OF INFECTION : Main reservoirs of human infection are cattle, sheep, goats, swine, buffaloes, horses and dogs. In animals the disease can cause abortion, premature expulsion of the foetus or death. Cross infections can often occur between animal species. The infected animals excrete Brucella in the urine, milk, placenta, uterine and vaginal discharges particularly during a birth or abortion. The animals may remain infected for life.

Host factors

Human brucellosis is predominantly a disease of adult males. Farmers, shepherds, butchers, and abattoir workers, veterinarians and laboratory workers are particularly at special risk because of occupational exposure. Immunity follows infection.

Environmental factors

Brucellosis is most prevalent under conditions of advanced domestication of animals in the absence of correspondingly advanced standards of hygiene. Overcrowding of herds, high rainfall, lack of exposure to sunlight, unhygienic practices in milk and meat production, all favour the spread of brucellosis. The infection can travel long distances in milk and dust. The environment of a cowshed may be heavily infected. The organism can survive for weeks, or months in favourable conditions of water, urine, faeces, damp soil and manure.

Mode of transmission

Transmission is usually from infected animals to man. There is no evidence of transmission from man to man (3). The routes of spread are :

(a) Contact infection : Most commonly, infection occurs by direct contact with infected tissues, blood, urine, vaginal discharge, aborted foetuses and especially placenta. Infection takes place through abraded skin, mucosa or conjunctiva (mucocutaneous route). This type of spread is largely occupational and occurs in persons involved in handling livestock and slaughter house workers.

(b) Food-borne infection : Infection may take place indirectly by the ingestion of raw milk or dairy products (cheese) from infected animals. Fresh raw vegetables can also carry infection if grown on soil containing manure from infected farms. Water contaminated with the excreta of infected animals may also serve as a source of infection.

(c) Air-borne infection : The environment of a cowshed may be heavily infected. Few people living in such an environment can escape inhalation of infected dust or aerosols. Brucellae may be inhaled in aerosol form in slaughter houses and laboratories, so these infections are notified as occupational. Human-to-human transmission is very rare *(6)*.

Incubation period

Highly variable. Usually 1–3 weeks, but may be as long as 6 months or more.

Pattern of disease

Brucella infection in man can vary from an acute febrile disease to a chronic low-grade ill-defined disease, lasting for several days, months or occasionally years.

The acute phase is characterized by a sudden or insidious onset of illness with (i) swinging pyrexia (upto 40–41 deg C), rigors and sweating. (ii) arthralgia/arthritis (usually

monoarticular) involving larger joints such as hip, knee, shoulder and ankle. (iii) low back pain. (iv) headache, insomnia. (v) small firm splenomegaly and hepatomegaly. (vi) leucopenia with relative lymphocytosis *(4)*. The most striking aspect of the clinical picture is the severity of the illness and the absence of clinical signs. The acute phase subsides within 2–3 weeks. If the patient is treated with tetracycline, the symptoms may disappear quickly, but the infection, being intracellular, may persist giving rise to subacute or relapsing disease.

In a few patients (upto 20 per cent), symptoms recur for prolonged periods. Diagnosis is established by isolation of the organism from cultures of blood, bone marrow, exudates and biopsy specimens during the acute phase of the disease; and by serological tests.

Control of brucellosis

(a) IN THE ANIMALS

The most rational approach for preventing human brucellosis is the control and eradication of the infection from animal reservoirs which is based on the combination of the following measures : *(a) Test and slaughter* : Case finding is done by mass surveys. Skin tests are available. The complement fixation test is also recommended. Those animals infected with brucellosis are slaughtered, with full compensation paid to farmers. This is the only satisfactory solution aimed at eradication of the disease. *(b) Vaccination* : Vaccine of *B. abortus* strain 19 is commonly used for young animals. A compulsory vaccination programme for all heifers in a given community on a yearly basis can considerably reduce the rate of infection. Systematic vaccination for a period of 7 to 10 years may result in the elimination of the disease. Control of the infection caused by *B. melitensis* in goats and sheep has to be based mainly on vaccination *(5)*. *(c) Hygienic measures* : These comprise provision of a clean sanitary environment for animals, sanitary disposal of urine and faeces, veterinary care of animals and health education of all those who are occupationally involved.

(b) IN THE HUMANS

(a) Early diagnosis and treatment : Treatment options include doxycycline 100 mg twice a day for 45 days, with streptomycin 1 g daily for 15 days. The main alternative therapy is doxycycline at 100 mg, twice a day for 45 days, plus rifampicin at 15mg/kg body wt./day (600–900mg) for 45 days. Streptomycin may be substituted with gentamicin 5mg/kg body wt./daily for 7–10 days. The optimal treatment for pregnant women, neonates and children under 8 year is not yet determined; for children, options include trimethoprim/sulfamethoxazole (co-trimoxazole) combined with an aminoglycoside (streptomycin, gentamycin) or rifampicin *(6)*. *(b) Pasteurization of milk* : This is a useful preventive measure which will render milk and milk products safe for consumption. Boiling of milk is effective when pasteurization is not possible. *(c) Protective measures* : The aim is to prevent direct contact with infected animals. Persons at risk such as farmers, shepherds, milkmen, abattoir workers should observe high standards of personal hygiene. They should exercise care in handling and disposal of placenta, discharges and foetuses from an aborted animal. They should wear protective clothing when handling carcasses. Exposed areas of the skin should be washed and soiled clothing renewed. *(d) Vaccination* : Human live vaccine of *B. abortus strain* 19–BA is available *(5)*.

Brucellosis would disappear if it were eradicated from animals. The national and international centre for brucellosis is located at FAO/WHO Brucella Reference Centre, Indian Veterinary Research Institute, Izatnagar, (Uttar Pradesh).

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LEPTOSPIROSIS

Leptospirosis is essentially animal infection by several serotypes of *Leptospira* (Spirocheates) and transmitted to man under certain environmental conditions. The disease manifestations are many and varied, ranging in severity from a mild febrile illness to severe, and sometimes fatal disease with liver and kidney involvement. Weils disease is one of the many manifestations of human leptospirosis.

Problem statement

Leptospirosis is considered to be the most widespread of the disease transmissible from animal to man *(1)*. It has high prevalence in warm humid tropical countries. Out breaks mostly occur as a result of heavy rainfall and consequent floodings *(2)*. Although the global burden of disease is unknown, more than 1 million cases of leptospirosis are estimated to occur worldwide each year including almost 60,000 deaths *(3)*. The incidence in some areas may be as high as 975 cases per lac population. During the past decade, the occurrence of outbreak has highlighted the strong links between leptospirosis and extreme weather events in Guyana, India, Philippines and Thailand etc *(4)*.

Epidemiological determinants

Agent factors

(a) AGENT : Leptospira are thin and light motile spirocheates 0.1–0.2 µm wide and 5–15 µm long with hooked ends. Only the strains of *L. interrogans* are pathogenic. The organisms are visible by dark–field illumination and silver staining. At present, 23 sero-groups and 200 serovars have been recognized from various parts of the world. They are serologically related with cross reactivity. (b) SOURCE OF INFECTION : Leptospira are excreted in the urine of infected animals for a long time, often for an entire life time in cases of rodents. (c) ANIMAL RESERVOIRS : Leptospirosis affects wild and domestic animals worldwide especially rodents such as rats, mice and voles. Most domestic animals including cattle, sheep, goats, water buffalo, pigs and horses may be infected through grazing in areas contaminated by the urine of the carrier host. Pet animals, particularly dogs may also be infected. Infection may spread from wild animals to domestic livestock, and then to humans. Rats and small rodents – particularly *R. norvegicus* and *Mus musculus* are the most important reservoirs *(5)*.

Host factors

(a) AGE AND SEX : Males suffer more frequently from leptospirosis than females because of greater occupational exposure to infected animals and contaminated

environment. Leptospirosis infections occur more frequently in persons 20–45 years of age group. Leptospirosis rarely occurs in young children and infants, possibly, because of minimal exposure *(6)*. (b) OCCUPATION : Human infections are usually due to occupational exposure to the urine of infected animals, e.g. agricultural and livestock farmers, workers in rice fields, sugarcane fields, and underground sewers, abattoir workers, meat and animal handlers, veterinarians etc. *(5)*. Leisure time activities such as swimming and fishing may also carry risks. (c) IMMUNITY : A solid serovar specific immunity follows infection.

Environmental factors

Leptospirosis infection is unique in that it is acquired through contact with an environment contaminated by urine and faeces from carrier (reservoir) animal or other infected animals. Leptospira shed in the urine can survive for weeks in soil and water, so environmental contamination may reach high levels in areas where carrier animals frequently urinate *(7)*. The association of poor housing, limited water supply, inadequate method of waste disposal, all combine to make the disease a significant risk for the poor population in both urban and rural areas. Soil salinity and water logging are inter-linked problems. The salinity of the soil and alkaline pH provides favourable environment for survival of leptospires for months. The soil of endemic areas in general has lower base saturation and mean annual soil temperature at the depth of 50 cm is 22°C or more and the difference between mean summer (June–August) and mean winter (December–February) temperature is less than 5°C. This favours the survival of leptospires for long duration *(6)*.

Mode of transmission

(a) DIRECT CONTACT : Leptospira can enter the body through skin abrasions or through intact mucous membrane by direct contact with urine or tissue of infected animal. (b) INDIRECT CONTACT : Through the contact of the broken skin with soil, water or vegetation contaminated by urine of infected animals or through ingestion of food or water contaminated with leptospirae. (c) DROPLET INFECTION : Infection may also occur through inhalation as when milking infected cows or goats by breathing air polluted with droplets of urine *(8)*.

Direct man to man infection is rare *(5)*.

Incubation period

Usually 10 days with a range of 4 to 20 days.

Clinical picture *(6)*

The clinical spectrum of leptospirosis is very wide, with mild anicteric presentation at one end to severe leptospirosis with severe jaundice and multiple organ involvement on the other. Many infections may go unnoticed because of lack of significant clinical illness.

Clinical types of leptospirosis are as follows:

1. *Anicteric leptospirosis :* It is the milder form of the disease. Patient presents with fever with chills, myalgia, conjunctival suffusion, headache, renal manifestation (some form of renal involvement is invariable), pulmonary manifestations (cough and chest pain are primary manifestations and haemoptysis may occur), and haemorrhagic tendencies. All the clinical features either decrease or disappear within two or three days, and then they may reappear and may progress to severe disease *(6)*.
2. *Icteric leptospirosis :* It is the more severe form of leptospirosis. The patient has jaundice and presents with fever, myalgia (calf muscle tenderness becomes more evident), headache, conjunctival suffussion, acute renal failure, nausea, vomiting, diarrhoea, abdominal pain, hypotension and circulatory collapse, pulmonary insufficiency. Combined renal and liver failure associated with leptospirosis is referred to as Weil's disease *(6)*.

Leptospirosis during pregnancy can cause foetal complications including foetal death or abortion. The case fatality rate for leptospirosis is approximately 5 per cent to 15 per cent among patients with severe illness. Among patients with severe pulmonary haemorrhagic syndrome, the case fatality can exceed 50 per cent *(3)*.

Diagnosis

It is not possible to diagnose leptospirosis with certainty on clinical grounds alone. Because of the wide spectrum of signs and symptoms, the diagnosis is made by isolation of leptospires from blood during the acute illness and from urine after the first week *(8)*. Early in the disease, the organism may be identified by dark–field examination of the patient's blood or by culture on a semisolid medium. Culture takes 1–6 weeks to become positive. The organism may also be grown from the urine from 10th day to 6 weeks. Diagnosis is usually made by means of serological tests, of which several are available. Agglutination tests (microscopic using live organism, and macroscopic using killed antigen) become positive after 7–10 days of illness and peak at 3–4 weeks and may persist at high level for many years. Indirect haemagglutination, immunoflourescent antibody and ELISA tests are also available. The IgM ELISA is particularly useful in making an early diagnosis, as it is positive as early as 2 days into illness *(9)*. Now Leptodipstick test is also available.

Control

(a) ANTIBIOTICS : Penicillin is the drug of choice but other antibiotics (tetracycline, amoxycillin, ampicillin and doxycycline) are also effective. The dosage of penicillin is 6 million units daily intravenously.

(b) ENVIRONMENTAL MEASURES : This includes preventing exposure to potentially contaminated water, reducing contamination by rodent control and protection of workers in hazardous occupation. Measures should be taken to control rodents, proper disposal of wastes and health education etc.

Vaccination

Immunization of farmers and pets prevent disease. In some countries for instance Italy, USSR and China, where certain occupations carry a high risk of infection, vaccines are available. It is important that they should incorporate strains of the serotypes that predominate in the particular area since immunity to one type of *Leptospira* may not protect against infection by another *(8)*.

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PLAGUE

Plague is primarily and basically a zoonoses, caused by *Y. pestis*, involving rodents and fleas. It exists in natural foci, and is transmitted by infected flea bites to humans living or intruding into the same ecological environment. Plague occurs in many forms – enzootically, epizootically, sporadically and in epidemics of all types including anthroponotic and primary pneumonic forms. Despite the enormous body of knowledge regarding plague, this communicable disease continues to pose a threat in many areas.

Problem statement

WORLD

Plague is often seen as a problem of the past or an ancient disease that is unlikely to reappear. But continued outbreaks throughout the world attest to its tenacious presence. Plague continues to be a threat because vast areas exist where wild rodents are infected, particularly in endemic countries in Africa, Asia and the Americas. Although plague is predominantly a rural disease, there have been outbreaks among urban populations in Madagascar, Democratic Republic of Congo and Peru. Plague is a major concern in countries where it remains endemic given its inherent communicability, its rapid clinical course and high mortality if left untreated.

The development of rapid diagnostic tests have contributed to better case-management and surveillane in Africa and other continents.

The data shows that from 2010 to 2015, a total of 3,248 cases of human plague, including 584 deaths, were reported globally *(1)*.

In 2004, India reported a localized outbreak of bubonic plague (8 cases and 3 deaths) in the Dangud village, District of Uttarkashi.

Absence of human plague may simply mean that there has been reduced human contact with plague bacteria circulating in nature. Therefore, there is a need to continue to make concerted effort to strengthen surveillance and improve control measures in order to manage human plague in endemic countries.

Epidemiological determinants

Agent factors

(a) AGENT : The causative agent, *Y. pestis* is a gram-negative, non-motile, cocco-bacillus that exhibits bipolar staining with special stains (e.g., Wayson's stain). The bacilli occur in great abundance in the buboes, blood, spleen, liver and other viscera of infected persons, and in the sputum of cases of pneumonic plague. The virulence of the organism is related to its ability to produce exotoxin, endotoxin, fraction 1 and many other antigens and toxins. It has been shown that plague bacilli can survive, and indeed multiply in the soil of rodent burrows where micro-climate and other conditions are favourable *(2)*.

(b) RESERVOIR OF INFECTION : Wild rodents (e.g., field mice, gerbils, skunks and other small animals) are the natural reservoirs of plague. These are found in mountains, deserts, cultivated areas and forests in temperate and tropical regions. Over 200 species of these small animals may carry plague *(3)*. In any given focus, rodent reservoirs may vary.

In India, the wild rodent, *Tatera indica* has been incriminated as the main reservoir, not the domestic rat, *Rattus rattus*, as once thought. Generally the disease is maintained and spread by the resistant species of wild rodents, i.e., rodents which have become immune to plague. The susceptible rodents die of the disease.

(c) SOURCE OF INFECTION : Infected rodents and fleas and case of pneumonic plague.

Host factors

(a) AGE AND SEX : All ages and both sexes are susceptible. (b)HUMAN ACTIVITIES : Man may come into contact with natural foci in the course of hunting, grazing, cultivation, harvesting and construction activities or while engaging in outdoor recreation. These activities offer numerous opportunities to flea–man contact. Social upheavals like war may also account for outbreaks, as had happened in Vietnam. (c) MOVEMENT OF PEOPLE : Plague is associated with movement of people and cargo by sea or land. Rats and rat fleas are transported in this way. Further, in these days of jet travel, it is possible for a person to acquire the disease and become ill thousands of miles away where plague would be least suspected. (d) IMMUNITY : Man has no natural immunity. Immunity after recovery is relative.

Environmental factors

(a) SEASON : Outbreaks of plague are usually seasonal in nature. In northern India, the "plague season" starts from September until May. The disease tends to die out with the onset of hot weather. Researches indicated that the curious phenomenon of "plague season" depended primarily on the field rodent factors; from May onwards all species of rodents in the fields commenced aestivation, closing themselves in their burrows and living on stored food reserves. Then the epizootic ceased to advance and at the same time infection of village rats came to an end. When the field rodents again became active, that is mid-October, when the monsoon floods had dried up, the epizootic revived in the fields followed by human plague *(4)*. On the contrary, in south India, there was no definite plague season. The disease was found to be active all the year round. This is attributed partly to the topographic and climatic conditions in the south, favourable for the breeding of the field rodents. (b) TEMPERATURE AND HUMIDITY : A mean temperature of 20 to 25 deg. C, and a relative humidity of 60 per cent and above are considered favourable for the spread of plague. (c) RAINFALL : Heavy rainfall, especially in the flat fields tend to flood the rat burrows. This factor may be responsible for keeping certain states (e.g., Bengal) free from plague *(5)*. (d) URBAN AND RURAL AREAS: Plague had failed to gain a foothold in many towns of India perhaps due to untoward ecological conditions and lack of efficient flea vectors (as in Chennai and Assam) *(5)*. (e) HUMAN DWELLINGS: Rats, frequent dwelling houses and where housing conditions are poor, there may be an abundance of rats and rat fleas all the year round, and contact with man occurs readily.

Vectors of plague

The commonest and the most efficient vector of plague is the rat flea, *X. cheopis*, but other fleas may also transmit the infection, e.g., *X. astia, X. brasiliensis* and *Pulex irritans* (human flea). Both sexes of the flea bite and transmit the disease.

Blocked flea

A flea may ingest upto 0.5 cu.mm of blood which may contain as many as 5,000 plague bacilli. The bacilli multiply enormously in the gut of the rat flea and may block the proventriculus so that no food can pass through. Such a flea is called a "blocked flea". A blocked flea eventually faces starvation and death because it is unable to obtain a blood meal. It makes frantic efforts to bite and suck blood over and over again; and in so doing, it inoculates (regurgitates) plague bacilli into the bite wound each time it bites. A blocked flea, therefore, becomes an efficient transmitter of plague. A partially blocked flea is more dangerous than a completely blocked flea because it can live longer. Infected fleas may live upto an year, and certain species survive in the burrow micro-climate for as long as 4 years *(2)*.

Flea indices

Flea indices are useful measurements of the density of fleas. They are also useful in evaluating the effectiveness of a spraying programme. The following flea indices are widely used in rat flea surveys : (a) TOTAL FLEA INDEX : It is the average number of fleas of all species per rat. (b) CHEOPIS INDEX : It is the average number of *X. cheopis* per rat. It is a specific flea index. It is a more significant index than the total flea index. If this index is more than 'one', it is regarded as indicative of potential explosiveness of the situation, should a plague outbreak occur *(6)*. (c) SPECIFIC PERCENTAGE OF FLEAS : It is the percentage of different species of fleas that are found on rats. (d) BURROW INDEX : It is the average number of free–living fleas per species per rodent burrow *(7)*.

Flea indices do not in themselves indicate an imminent plague epidemic. They serve as a warning that more stringent control measures are needed to protect the human population.

PLAGUE IN RODENTS

1. Rodents

Plague is primarily a disease of rodents in which man becomes accidentally involved. Approximately, 1,700 species of rodents are known, of which over 200 species are associated with plague. These are found in mountains, deserts, cultivated areas and forests throughout the world *(8)*.

Rodents may be classified into two distinct groups :

(a) WILD RODENTS : They are the reservoir of plague in nature. The common wild rodents in India are : *Tatera indica, Bandicota bengalensis varius, B. bengalensis kok (Gunomys kok), B. indica, Millardia meltada, M. gleadowi and Mus booduga*. In India, *tatera indica* has been incriminated as the main reservoir of plague, not the domestic rat (*R. rattus*) as once thought.

(b) COMMENSAL RODENTS : These are the rodents which live close to man. They may be further divided into domestic and peridomestic species. The domestic species include *Rattus rattus, Rattus norvegicus and Mus musculus*. The domestic species seldom live in fields. The peridomestic species live in both fields and houses; *R. norvegicus* which frequents sewers, drains as well as houses is a typical example of a peri-domestic species in India. Characteristics which are easily ascertainable of *Rattus rattus and R. norvegicus* are given elsewhere (see chapter 15).

2. Epizootiology

Plague is epizootic and enzootic in wild rodents. ***Two ecological cycles*** have been described :

a. WILD PLAGUE : Wild plague is defined as "plague existing in nature, independent of human populations and their activities" *(2)*. The disease spreads among wild rodents by wild rodent fleas. The epizootic wipes out the susceptible population. Those that survive (i.e., resistant species) maintain the enzootic in natural foci.

b. DOMESTIC PLAGUE : Is defined as "plague that is intimately associated with man and rodents living with him, and has a definite potential for producing epidemics *(2)*.

3. Natural foci

Worldwide, rodent plague is still firmly entrenched in its natural foci. A "natural focus" of plague has been defined as "a strictly delimited area where ecological conditions ensure the persistence of the aetiological agent for considerable periods of time, and where epizootics and periods of quiescence alternate, without introduction of infection from outside" *(2)*.

The long persistence of plague in some natural foci is not achieved through the usual simple chain of "Rat–flea–rat" transmission. Probably several other mechanisms are involved. They include : (a) latent infection in rodents, especially hibernating rodents, has been demonstrated; such animals may relapse and become bacteraemic, so initiating an epizootic. (b) development of resistance to plague infection by some rodents with subsequent localization of plague bacillus in some organ; such an animal may become a source of infection if eaten by another susceptible rodent. (c) survival of rat fleas for as long as 4 years in rat burrows under optimum micro-climatic conditions. This is considered the most likely mechanism of maintaining the natural focus. (d) variations in the pathogenecity of *Y. pestis*, and (e) survival and even multiplication of plague bacilli in the soil of rodent burrows. All these factors may combine to keep the infection alive in natural foci.

4. Epizootic process

The epizootic and enzootic process in each natural plague focus has its specific cyclic and periodical pattern. Researches into the epidemicity of plague indicated that the field rodents spread the infection very slowly from burrow to burrow, and from field to field taking months to cover several miles. In this process they infect the village rats (commensal rodents). The commensal rodents especially the peridomestic species (e.g., *R. norvegicus*) act as "Liaison rodents" between man and field rodents. An outbreak of human plague is always preceded by rodent plague. After the death of house rats, the fleas leave the dead rats and are forced to seek man for food. An unusual mortality among rodents should arouse suspicion of plague and should be investigated immediately.

5. Silent periods

Silences of long duration (10 years or more) followed by sudden explosive outbreaks of rodent or human plague have been repeatedly confirmed in some natural foci *(9)*. A number of explanations for this phenomenon have been put

forward. It has been suggested that plague disappears completely for long periods and that it is reintroduced from other areas by infected rodents, fleas or migrating birds. On the other hand, the plague bacillus can survive and indeed multiply in the soil of rodent burrows, where micro-climatic conditions are suitable. It has been demonstrated that healthy rodents re-occupying and excavating such burrows may become infected through contact with contaminated soil *(2, 10)*.

6. Plague in rodents

Animal disease is similar to that in man. The disease is inapparent or mild in resistant species *(11)*.

7. Investigations

(1) COLLECTION AND FORWARDING OF DEAD RATS : Rodents (house or field) found dead regardless of its stage of decomposition should be carefully packed in several layers of packing paper or preferably in plastic bags. Such rodents should not be handled with naked hands. The neck of the bag should be tied to avoid escape of ectoparasites. The bag should then be placed in a wooden box or tin. The empty space left in the box or tin should be filled with absorbent cotton or sawdust to eliminate chances of leakage of effluents outside the box. The box is labelled giving details of collection and sent to the nearest laboratory. (2) AUTOPSY AND COLLECTION OF SMEARS : The rat is held with a pair of tongs, and dipped in a solution of 5 per cent cresol. The animal is laid on its dorsum, stretched and the limbs nailed on a wooden board. The abdomen is swabbed with lysol or spirit. The skin is lifted and cut up to the chest. The instruments used are then put back into boiling water. Using another set of instruments, small portions of the viscera (spleen, liver, lungs, bubo) are cut and the freshly cut surface is first blotted on a blotting paper so as to remove excess of blood or plasma. Then the same surface of the tissue is gently pressed on the glass slides so as to make thin impressions (never rub the tissue on the slides). If the rat is completely decomposed and no tissue is left, smears should be obtained from the bone marrow. The smears are dried, treated with alcohol for three minutes and fixed by exposure to open flame. The fixed smears may be sent for examination. Persons handling infected rats are exposed to the risk of pneumonic plague and this danger should be borne in mind. (3) ANIMAL INOCULATION : It may be difficult to isolate the plague bacilli by cultural methods owing to gross contamination of the carcass. In such cases, small portions of liver or spleen are taken, ground in a mortar with a little saline and inoculated into a guinea pig or a white mouse. If there is plague infection, the guinea pig will die in 7 days and the white mouse in 48 hours. (4) PATHOLOGICAL CHANGES : The pathological changes in an animal infected with plague are as follows: (a) there is oedema and necrosis at the site of injection, (b) the lymph nodes are enlarged, (c) the spleen is enlarged and congested, and shows necrotic patches, (d) liver shows mottling, (e) lungs also show necrotic lesions, and (f) there is subcutaneous congestion and haemorrhages.

HUMAN PLAGUE

Mode of transmission

Human plague is most frequently contracted from : (a) the bite of an infected flea, (b) occasionally by direct contact with the tissues of the infected animal or (c) by droplet infection from cases of pneumonic plague. The dissemination of plague by plague patients (by the bite of the human flea, *Pulex irritans*) is a rare and exceptional occurrence.

There are at least 5 basic types of transmission cycles in plague. These cycles are as follows *(8)* :

1. *Commensal rats → rat fleas → man*
   This is the basic cycle in epidemic bubonic plague.
2. *Wild rodents → wild rodent fleas or direct contact → man*
   The disease is transmitted from rodent to rodent *via* wild rodent fleas or contaminated soil. Man contracts the infection from infectious wild rodent fleas or by direct contact with infected rodents.
3. *Wild rodents, peridomestic rodents, commensal rodents → wild rodent fleas, peridomestic rodent fleas, commensal rodent fleas → man*
   Plague foci impinge upon the habitats of peri-domestic or commensal rodents. Interaction of the rodents and their fleas convey the infection to man.
4. *Man → human flea (Pulex irritans) → man*
   This variety may be encountered in certain areas.
5. *Man → man*
   This results when a primary case of bubonic plague develops secondary pneumonic plague and infects contacts *via* the respiratory route.

Incubation period

(a)	bubonic plague	.....	2 to 7 days
(b)	septicaemic plague	.....	2 to 7 days
(c)	pneumonic plague	.....	1 to 3 days

Disease in man

There are three main clinical forms : ***(a) Bubonic plague :*** This is the most common type of the disease. The infected rat fleas usually bite on the lower extremities and inoculate the bacilli. The bacilli are intercepted by the regional lymphatic glands where they proliferate. Typically the patient develops sudden fever, chills, headache, prostration and painful lymphadenitis. Usually within a few days greatly enlarged tender lymph nodes (buboes) develop in the groin and less often in the axilla or neck, depending upon the site of the bite by the flea. When suppuration takes place it is considered a favourable sign. Bubonic plague cannot spread from person to person as the bacilli are locked up in the buboes and do not find a way or easy exit. ***(b) Pneumonic plague :*** Primary pneumonic plague is rare; it generally follows as a complication of bubonic–septicaemic plague. The incidence of pneumonic plague is usually below 1 per cent *(5)*. Pneumonic plague is highly infectious and spreads from man to man by droplet infection. The plague bacilli are present in the sputum. ***(c) Septicaemic plague :*** Primary septicaemic plague is rare except for accidental laboratory infections. However, bubonic plague may develop into septicaemic plague in the face of an overwhelming infection.

Laboratory investigations

The absolute confirmation of plague infection in human beings, rodents or fleas requires the isolation and identification of the plague bacillus. The important laboratory methods of diagnosis include the following :

(a) Staining : It is important to prepare smears of the clinical material (e.g., bubo fluid, sputum) which should be fixed with alcohol and then stained with Giemsa's or Wayson's stain to demonstrate bipolar bacilli in the specimen. ***(b) Culture :*** Blood for culture should be collected from all patients. Under ideal circumstances, appropriate culture media should be inoculated on the spot with blood, bubo fluid or sputum to ensure speedy isolation of the plague bacilli. When this is not possible, the specimen must be transported to the laboratory in Cary–Blair transport medium. ***(c) Serology :*** Acute and convalescent specimens of blood sera should be collected for antibody studies. ***(d) Other methods :*** These include inoculation of guinea pigs or mice or immunofluorescent microscopic test.

PREVENTION AND CONTROL

1. Control of cases

(a) EARLY DIAGNOSIS : During epidemic situations, diagnosis of plague can be made readily on clinical grounds, e.g., acute fever and painful lymph node enlargement developing into buboes in the inguinal and other regions of the body. In other situations, "rat falls" (dead rats) provide a useful warning of a possible outbreak. It is essential that plague-suspected humans and rodents be examined bacteriologically to confirm the presence of plague. It is often possible to arrive at a *prima facie* diagnosis by the examination of smears that show the characteristic bipolar stained plague bacilli *(8)*. *(b) NOTIFICATION :* If a human or rodent case is diagnosed, health authorities must be notified promptly. Case notification is required by International Health Regulations *(13)*. *(c) ISOLATION* : Although most bubonic plague patients are non-infectious, isolation is recommended whenever possible. All patients with pneumonic plague including suspected cases should be isolated. *(d) TREATMENT* : Treatment must be started without waiting for confirmation of the diagnosis *(2)*. Unless promptly treated, plague may have a mortality of nearly 50 per cent, and pneumonic plague 100 per cent. The drug of choice is streptomycin (30 mg per kg of body weight daily) administered intramuscularly in two divided doses for 7 to 10 days. Tetracycline orally (30–40 mg per kg of body weight daily) is an alternative drug, and is sometimes given in combination with streptomycin *(12)*. Gentamycin administered as a 2 mg/kg body wt. loading dose, then 1.7 mg/kg body wt. every 8 hours intravenously is effective. Penicillin is rather ineffective. Sulphonamides may be used if other drugs are not available. *(e) DISINFECTION* : Disinfection of sputum, discharges and articles soiled by the patient should be carried out. Dead bodies should be handled with aseptic precautions.

2. Control of fleas

The most effective method to break the chain of transmission (rodent → flea → man) is the destruction of rat fleas by the proper application of an effective insecticide. Flea control must precede or coincide anti-rodent measures. The choice of insecticide is dictated by the results of prior susceptibility tests. In general DDT and BHC should be used as dusts containing 10 per cent and 3 per cent of the active ingredient respectively. In areas where resistance to one or both of these insecticides occurs, dusts of carbaryl (2%) or malathion (5%) should prove effective. About 2 to 3 g of insecticide formulation will be needed for each sq. metre of surface requiring treatment *(8)*. Generally the organochlorine insecticides remain effective for 2 to 4 months.

Before spraying is to be done, the inhabitants of premises should be asked to remove all foodstuffs and eating and cooking vessels from their houses. Spraying is done inside the houses covering the entire floor area, bottoms of all walls up to 3 feet above floor level, back of the doors, roofing of thatched houses, crevices of walls, rat runs, clothing, bedding, cats, dogs and other pets. Rat burrows should be insufflated with the insecticidal dust with the help of a dust blower. Insecticidal spraying up to a radius of 5 miles around each infected locality is considered adequate *(8)*. Within 48 hours of application, the "flea index" should drop down to zero *(8)*.

3. Control of rodents

Continuous mass destruction of rodents is an important plague-preventive measure. The long-term policy for the control of rodents should be based on improvement of general sanitation, improvement of housing and quality of life. The various antirodent measures are given elsewhere.

4. Vaccination

Immunization with plague vaccine is a valuable preventive measure. The WHO recommends that under all circumstances, vaccination should be only for the prevention, not the control of human plague *(2)*. To be effective, vaccination should be carried out at least a week before an anticipated outbreak, and the vaccine should be given in 2 doses.

In 1897, Haffkine developed a killed plague vaccine while working in India and inoculated himself with his experimental vaccine *(14)*. The vaccine used currently is that of Haffkine, modified by Sokhey. It is a formalin-killed vaccine. Virulent strains of *Y. pestis* are grown in casein hydrolysate broth for 2 weeks at 27 deg. C and killed by treatment with 0.1 per cent formalin for 3 days at 37 deg. C. The final vaccine is a suspension of 2000 million killed organisms per ml *(15)*.

The vaccine is given subcutaneously in two doses of 0.5 and 1.0 ml at an interval of 7 to 14 days. A single dose will not result in dependable protection. However, in an emergency, when it is desired to carry out primary immunization by means of a single injection, the dose should be double the second dose, that is, 3 ml for adult males *(15)*. Immunity starts 5 to 7 days after inoculation, and lasts for about 6 months. Booster doses are recommended six-monthly for persons at continuing risk of infection (e.g., geologists, biologists and anthropologists). The recommended doses of the vaccine are given in Table 3. The reactions after inoculation (pain, tenderness, headache, etc) appear in a few hours and subside in 1 to 2 days. The vaccine is indicated for travellers to hyperendemic areas besides persons at special risk.

TABLE 3
Dosage of plague vaccine

Age and Sex	Primary inoculation		Booster dose six-monthly
	1st dose	2nd dose	
Adult males	1.0 ml	1.5 ml	1.0 ml
Adult females	0.75 ml	1.0 ml	0.75ml
Children			
1–4 years	0.2 ml		
5–10 years	0.3 ml	Double the first dose	Same as the first dose
11–16 years	0.4 ml		
Infants under 6 months are not immunized.			

Source : *(15)*

5. Chemoprophylaxis

Chemoprophylaxis is a valuable preventive measure, highly recommended. It should be offered to all plague contacts, medical, nursing and public health personnel exposed to the risk of infection. The drug of choice is tetracycline. For adults, the dose is 500 mg 6-hourly for 5 days *(16)*. A cheaper alternative is sulfonamide, 2 to 3 gram daily for 5 to 7 days.

6. Surveillance

Plague has a potential for spread into susceptible areas. Therefore, in areas where natural plague foci exist or where there is a history of past infection, surveillance is essential. Surveillance should cover all aspects of rodent and human plague, e.g., microbiology, serology, entomology, mammalogy, epidemiology and ecology. On the basis of information provided by surveillance, effective control measures must be established *(14)*. Surveillance of plague in its natural foci should, therefore, replace quarantine measures which have been shown to be ineffective *(2)*.

7. Health education

Health education is an essential part of any plague control programme. Education should aim at providing the public with the facts about plague and at enlisting their cooperation. Emphasis must be placed on the need for the prompt reporting of dead rats and suspected human cases so that preventive measures can be taken. Medical practitioners should keep plague in mind in differential diagnosis of any cases of fever with lymphadenopathy, or when multiple cases of pneumonia occur *(2)*.

Epidemiological investigations *(17)*

The determination of the source of infection and the distribution, prevalence, and potential spread of plague in human population is the main objective of epidemiological surveillance. This means that those engaged in surveillance must evaluate human plague in its relationship with epizootic factors and that the investigations must be based on direct contact with villages and other communities affected by plague. While the collection of demographic data and information on such subjects as population movements and local occupations, customs, and habits is important, special attention must be given to the factors bringing man into contact with the vertebrate reservoirs and vectors of *y. pestis*.

Some of the responsibilities of the surveillance team are as follows :

(1) to make a detailed study of all cases of human plague, giving special attention to dwellings where cases have occurred, in order to establish the rodent/vector source of the infection or the occurrence of man-to-man transmission;

(2) to keep complete and uniform records of each case of plague, using standardized forms, and to issue questionnaires to the population at risk;

(3) to isolate strains of *Y. pestis* and subject them to detailed biochemical analysis, samples being lyophilized for later study;

(4) to make a serological survey of the target population; such surveys are of value in investigation of possible cases of subclinical plague, of recovered untreated infections, and of asymptomatic pharyngeal infection in "carriers";

(5) to investigate changes in the human population, social or economic activities, and other features of natural foci where there is close contact between human populations and commensal rodents;

(6) to keep a watch on containerized cargoes of grain and other food crops originating in areas with natural plague foci and destined for national or international trade;

(7) to undertake surveillance in cooperation with adjacent countries when natural foci are common to two or more countries;

(8) to give special attention, in the case of seaports or airports, to the proximity of natural foci where there is contact between wild and commensal rodents, the proximity of epidemics, and the transport of cargo from enzootic areas.

The surveillance team should also be prepared to assist the national or community health service in organizing and carrying out the treatment of human cases and measures for the control and prevention of plague. An organizational basis should be established for rapid emergency services in the event of an epidemic.

Reporting of cases and outbreaks of plague *(17)*

The WHO should be informed promptly of the occurrence of any epidemic or isolated case of plague. The report should include details about the administrative area and exact locality involved. This preliminary notification should be followed up as soon as possible by a more detailed report containing the following information :

(a) The locality and administrative area, shown on a map if possible

(b) The date, the first case was noticed

(c) The period during which field investigations were made

(d) The number and types of cases of plague detected :
- clinical diagnosis only (presumptive)
- laboratory diagnosis (confirmed)
- recovered and confirmed serologically
- types of cases – bubonic, pneumonic, etc.
- age of patient with a confirmed diagnosis of plague
- number of deaths

(e) The contacts of known cases
- serological test results
- throat swab results

(f) Chemotherapy applied.
- number of frank cases
- number of contacts

(g) Vertebrate host population
- identification of domestic rodents
- identification of wild rodents
- results of laboratory test for plague

(h) Vector population
- identification of *X. cheopis*
- identification of other species of flea
- results of laboratory tests for infection
- results of insecticide resistance tests
- control measures applied.

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HUMAN SALMONELLOSIS

The term "salmonellosis" covers a complex group of foodborne infections affecting both man and animals *(1)*. The disease causes illness and even death in humans, as well as economic losses in the animal and food industries. The term "food poisoning" is also commonly applied to salmonellosis.

Problem statement

Salmonellosis is a global problem *(2)*. Human salmonellosis represents 60 to 80 per cent of all reported cases of foodborne diseases *(3)*.

While the incidence of typhoid fever has declined, the incidence of other *Salmonella* infections has increased in the developed countries. The problem is aggravated by the widespread use of animal feeds containing antimicrobial drugs that favour drug–resistant salmonellae and their potential transmission to humans. The disease can occur sporadically or in small outbreaks in the general population and usually from food contaminated at its source. The extent of the problem is not clear in developing countries where diarrhoeal diseases are widespread *(2)*.

Epidemiological determinants

Agent factors

AGENT : Salmonellae comprise a large and important group of bacteria. This group is now known to comprise more than 2,500 serotypes capable of infecting humans *(4)*, but in most countries only a small number of them (usually about 10) are endemic at any one time *(5)*.

Compared with other gram-negative rods, salmonellae are relatively resistant to various environmental factors. They have been shown to be resistant to drying, salting, smoking and freezing even for years. This explains why these organisms survive in many kinds of food. As a result, salmonellae have been isolated from divergent foods such as chocolates, biscuits, coconuts and spices. The bacterium is sensitive to heat and will not survive temperatures above 70 deg C.

From an epidemiological point of view, salmonellae can be classified into three main groups *(2)*.

(i) those which infect only man – e.g., *S. typhi, S. paratyphi A* and *C.*

(ii) those that are host–adapted for particular species of animals, e.g., *S. cholera–suis* in swine, *S. dublin* in cattle, *S. abortus equi* in horses, *S. gallinarum* in poultry, etc. Some of these are also pathogenic for man, e.g., *S. cholera–suis, S. dublin.*

(iii) those with no particular host preference and can infect both man and animals – e.g., *S. typhimurium, S.enteritidis.* In this group (approximately 2,200 serovars) are the principal agents of salmonellosis that occurs today (2). They can be transmitted from animals to man and vice versa. *S. typhimurium* is responsible for upto 50 per cent or more of all human salmonella infections all over the world. *S. enteritidis* has also emerged as an important pathogen.

RESERVOIR AND SOURCES OF INFECTION : The main reservoir of Salmonella is the intestinal tract of man and animals. The source of the infecting agent could be contaminated food, animals, man or the environment.

(a) Foods

Foods of animal origin, particularly commercially prepared foods such as meat, poultry and egg products are considered to be the primary sources of salmonellosis. Most of these foods, e.g., meat and poultry become contaminated during slaughter. Every food that is produced or processed (including chocolates, spices, coconut) in a contaminated environment may become contaminated. Cross-contamination of cooked foods from raw ingredients, kitchen utensils or surfaces has been described frequently as a cause of salmonellosis *(5)*. Eggs may be infected directly through shell–cracks. Recent investigations suggest that salmonellae may penetrate the ovaries of egg–laying chickens. What food will ultimately become the vehicle varies from country to country *(6)*. For example, in the USA, beef is the main source of salmonella infection, while in England and Wales poultry accounts for more than 50 per cent of Salmonellosis outbreaks *(2)*.

(b) Animals

Animals are the hosts and the principal vectors of zoonotic salmonellosis. Many animals including cattle, swine, rodents and fowl are naturally infected with a variety of salmonellae and have the bacilli in their tissues (meat), eggs or excreta. Carriers occur among both man and animals.

(c) Environment

Salmonellae are widely distributed in the environment – in dust, water, manure, sewage, sludge, vegetables, insects, birds, fish, rodents and other mammals. They can survive in soil for months *(6)*. They may even multiply in the warm environment provided by the high ambient temperatures of many countries. Man may be infected from these sources.

Multidrug resistant strains of *salmonella* are now encountered frequently. Resistance to fluoroquinolones and third generation cephalosporins is a serious development, which results in severe limitation of the possibilities for effective treatment of human infections *(4)*.

Mode of transmission

By ingestion of contaminated food or drink. In addition, man can contract infection following direct contact with domestic animals especially such as dogs, pigeons, rats, mice and insects. Once man is infected, he becomes a source (case or carrier) and the infection may spread to others by the faecal–oral route.

Transmission is facilitated by food handling methods, local customs, cooking and food habits, food processing, storage and distribution methods, and prevailing sanitary conditions.

Incubation period

6 to 72 hours (usually).

Clinical features

The disease arises from the ingestion of the living organisms. Recent studies indicate that *Salmonella spp.* possess both invasive and cholera–like enterotoxic properties *(6)*. Clinically, the disease may manifest by one of the three syndromes :

(i) Enteric fever : *S. typhi, S. paratyphi A* and *C* are human pathogens, and are not considered zoonotic agents *(2)*. *S. paratyphi B*, while predominantly found in man has also been isolated from turkeys, chickens, cattle, sheep, swine, mice and monkeys. This syndrome (enteric fever) is dealt with separately (see page 281 under typhoid fever).

(ii) Salmonella enterocolitis (gastroenteritis) : This is the most common manifestation of *Salmonella* infection. 6 to 48 hours after ingestion of *Salmonellae* there is nausea, headache, vomiting and diarrhoea. Low grade fever is common. Most infections are mild with diarrhoea as the only symptom. In severe cases there may be dehydration requiring replacement of fluids and electrolytes. The episode usually resolves in 2 to 3 days, but the stools often remain loose for several weeks. The excretion of salmonella may be prolonged by antimicrobial therapy. Blood cultures are usually negative but stool cultures are positive for salmonella and may remain positive for several weeks after clinical recovery. Death is rare and occurs primarily in neonates, infants and elderly.

(iii) Septicaemia with focal lesions : Non–typhoid salmonellae (e.g., *S. cholera–suis*) may occasionally invade the blood stream leading to generalized or localized infection presenting itself as pyrexia of unknown origin. Focal infection may result in osteomyelitis, pyelonephritis, arthritis, meningitis, cholecystitis and endocarditis. Stool cultures are negative but blood cultures are positive.

Prevention and control

Since salmonellosis is zoonotic in origin, preventive measures should begin at the farm and embrace all the elements of the food chain through live animals, animal products, processing, final food preparation to consumption. Approaches indicated at the farm level are : (i) disease control, e.g., immunization of farm animals against salmonellosis. (ii) the use of hygienic animal feed, and (iii) ensuring a sanitary environment for the animals. The aim is to raise "salmonella–free" animals.

The other approaches include : hygienic slaughtering and milking, pasteurization of milk and eggs; proper disposal of liquid and solid wastes, cold storage facilities, and health education and training.

Since the health sector alone cannot solve the problem of salmonellosis, responsibility for prevention and control measures may fall to agriculture, veterinary and other ministries, outside the health sector *(1, 7)*.

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RICKETTSIAL ZOONOSES
(Rickettsial diseases)

Rickettsial zoonoses are a group of specific communicable diseases caused by rickettsial organisms and transmitted to man by arthropod vectors, (Q fever excepted). Increasingly, it is realized that rickettsial diseases are under-diagnosed and that they contribute substantially to the acute febrile burden and preventive illness in many populations *(1)*.

Classification

Rickettsial diseases may be grouped on the basis of clinical features and epidemiological aspects as follows (Table 1).

TABLE 1
Rickettsial, Ehrlichial Diseases and Q Fever

Group	Organism	Disease	Geographic Distribution	Vector	Mammalian Reservoir
Typhus group	*Rickettsia prowazekii*	Epidemic typhus (louse-borne typhus), Brill-Zinsser disease	Worldwide : South America, Africa, Asia, North America	Louse	Humans
	Rickettsia typhi	Murine typhus, endemic typhus, flea-borne typhus	Worldwide (small foci)	Flea	Rodents
Scrub typhus group	*Orientia tsutsugamushi*	Scrub typhus	Asia, South Pacific, northern Australia	Mite	Rodents
Spotted fever group	*Rickettsia rickettsii*	Rocky Mountain spotted fever	Western Hemisphere (United States, South America)	Tick	Rodents, dogs
	Rickettsia conorii	Fievre boutonneuse, Mediterranean spotted fever, Israeli spotted fever, South African tick fever, African (Kenya) tick typhus, Indian tick typhus	Mediterranean countries, Africa, Middle East, India	Tick	Rodents, dogs
	Rickettsia sibirica	Siberian tick typhus (North Asian tick typhus)	Siberia, Mongolia	Tick	Rodents
Transitional group	*Rickettsia akari*	Rickettsial pox	United States; Russia; Korea; South Africa	Mite	Mice
	Rickettsia australis	Queensland tick typhus	Australia	Tick	Rodents, marsupials
Q fever	*Coxiella burnetii*	Q fever	Worldwide	Airborne fomites tick	Sheep, cattle, goats, others

Source : *(2)*

Causal agents

Rickettsiae are small bacteria that are obligate intracellular parasites. They are pleomorphic, appearing either as short rods, or as cocci and they occur singly, in pairs, in short chains, or in filaments. With Giemsa's stain they stain blue and are readily visible under microscope. They grow readily in the yolk sac of the embryonated egg. Rickettsial growth is enhanced by the presence of sulfonamides.

Clinical features

Excepting for Q fever, in which there is no skin lesion, rickettsial infections are characterized by fever, headache, malaise, prostration, skin rash and enlargement of the spleen and liver. Tetracycline is the drug of choice for specific treatment of all rickettsial diseases. Long–acting antibiotics (doxycycline, minocycline) now make single dose treatment possible *(3)*.

Diagnostic procedures

These include : (a) isolation of rickettsiae. (b) established serological tests such as indirect fluorescent antibody (IFA) test, the complement fixation test, and the Weil Felix reaction. The newer techniques include ELISA and the fluorescent antibody staining of frozen tissue sections from rickettsial lesions.

Among the major groups of rickettioses, the commonly reported diseases in India are scrub typhus, murine flea–born typhus, Indian tick typhus and Q fever. These are considered in more detail.

SCRUB TYPHUS

Distribution

Of the diseases caused by rickettsiae in man, the most widespread is scrub typhus. It exists as a zoonoses in nature between certain species of trombiculid mites and their small mammals (e.g., field mice, rats, shrews). Scrub typhus is endemic in Northern Japan, South East Asia, the Western Pacific Islands, Eastern Australia, China, Maritime areas and several parts of South-Central Russia, India and Sri Lanka. More than 1 million cases occur annually. Most travel-acquired cases of scrub typhus occur during visits to rural areas in endemic countries for activities such as camping, hiking or rafting, but urban cases have also been described *(4)*.

Epidemiological determinants

Agent factors

(a) AGENT : The causative agent of scrub typhus is *Orientia tsutsugamushi*. There are several serologically distinct strains. (b) RESERVOIR : The true reservoir of infection is the trombiculid mite *(Leptotrombidium delinese* and *L.akamushi)*. The infection is maintained in nature transovarially from one generation of mite to the next. The nymphal and adult stages of the mite are free–living in the soil; they do not feed on vertebrate hosts. It is the larva (chigger) that feed on vertebrate hosts and picks up the rickettsiae. The larval stage serves both as a reservoir, through ovarian transmission, and as a vector for infecting humans and rodents.

Mode of transmission

By the bite of infected larval mites. The transmission cycle may be depicted as below :

Mite → Rats and mice → Mite → Rats and mice
↓
Man

The disease is not directly transmitted from person to person.

Incubation period

Usually 10 to 12 days; varies from 6 to 21 days.

Clinical features

Scrub typhus resembles epidemic typhus clinically. The onset is acute with chills and fever (104°–105°F), headache, malaise, prostration and a macular rash appearing around the 5th day of illness. Generalized lymphadenopathy and lymphocytosis are common. One typical feature is the punched–out ulcer covered with a blackened scab (eschar) which indicates the location of the mite bite. The pyrexia falls by lysis in the 3rd week in untreated cases. The Weil Felix reaction is strongly positive with the *Proteus* strain OXK.

Control measures

(a) TREATMENT : Tetracycline is the drug of choice. With proper therapy the mortality is nil. (b) VECTOR CONTROL : Clearing the vegetation where rats and mice live; application of insecticides such as lindane or chlordane to ground and vegetation. (c) PERSONAL PROPHYLAXIS : Impregnating clothes and blankets with miticial chemicals (benzyl benzoate) and application of mite repellents (diethyltoluamide) to exposed skin surfaces *(5)*. No vaccine exists at present.

MURINE TYPHUS
(Endemic or flea–borne typhus)

Distribution

Murine typhus (MT) is a zoonoses. It is worldwide in distribution especially in areas of high rat infestation. It appears to be more prevalent in South-East Asian and Western Pacific countries than previously recognized. In USA, cases tend to be scattered. Successful isolation of the causative agent from rats, fleas and bandicoots was made at many places in India. Focal infections are often associated with docks and shipping places where rats abound.

Agent factors

(a) AGENT : *Rickettsia typhi* (*R. mooseri*). (b) RESERVOIR OF INFECTION : Rats are the reservoir *(Rattus rattus and R.norvegicus)*. Infection in rats is inapparent, long–lasting and non–fatal.

Mode of transmission

The infection spreads from rat to rat *(X. cheopis)* and possibly by the rat louse *(6)*. The actual mode of transmission is not by the bite of the rat flea, but by (i) inoculation into skin of faeces of infected fleas, and (ii) possibly by inhalation of dried infective faeces. There is no direct man to man transmission. Once infected the flea

remains so for life. The flea cannot transmit the rickettsiae transovarially. The transmission cycle may be shown as below :

Rat → Rat flea → Rat → Rat flea → Rat
↓
Man

Incubation period

1 to 2 weeks, commonly 12 days.

Clinical features

The clinical features resemble that of louse-borne typhus, but milder and rarely fatal. The Weil Felix reaction with *Proteus* OX-19 becomes positive in the 2nd week.

Control measures

(a) TREATMENT : Tetracycline is the only drug of choice. Since rickettsial growth is enhanced in the presence of sulfonamides, these drugs should not be given. *(b) CONTROL OF FLEAS* : Residual insecticides (e.g., BHC, malathion) are effective against rat fleas. Rodent control measures should be implemented in the affected areas. No murine typhus vaccine is currently available.

INDIAN TICK TYPHUS

Epidemiological determinants

Agent factors

(a) AGENT : The causative agent is *Rickettsia conorii*, a member of the spotted fever group of rickettsiae, the best known member of which is *R. rickettsii* the causative agent of Rocky Mountain spotted fever. (b) RESERVOIR OF INFECTION : The tick is the reservoir of infection. It is infective at all stages of its life cycle and remains infective for life (commonly 18 months). Various tick genera *(e.g., Rhipicephalus, Ixodes, Boophilus, Haemaphysalis)* have been incriminated as vectors. Infection in nature is maintained by transovarian and trans-stadial passage. The rickettsiae can be transmitted to dogs, various rodents and other animals, which assist in maintaining the disease cycle.

Mode of transmission

Man is only an accidental host. He acquires infection by the bite of an infected tick. Contamination of skin with crushed tissues or faeces of an infected tick may also cause infection. The cycle of transmission is as follows :

Tick → Tick → Tick → Tick
↓ ↓
Dog Man
↓
Tick → Man

Incubation period

Usually 3 to 7 days.

Clinical features

The patient usually gives history of a recent tick-bite and a careful examination will reveal a lesion or eschar at the site of the bite. After an interval of 3 to 7 days, there is an acute onset of fever, which may persist for 2 to 3 weeks, malaise and headache. A maculopapular rash appears on the third day. Unlike the rash in other rickettsial diseases, the rash appears first on the extremities (ankles and wrist), moves centripetally and involves the rest of the body. The clinical syndrome may be confused with atypical measles.

Control measures

(a) TREATMENT : Broad spectrum antibiotics have proved to be effective. (b) PERSONAL PROPHYLAXIS : Known tick-infested areas should be avoided. Daily inspection of the body for ticks is particularly important for those who are exposed to the risk of infection. Disinfection of dogs will minimize the tick population. Health education of the people in the mode of transmission by ticks, and the means of personal protection is equally important.

Q FEVER

Distribution

Q fever is a highly infectious zoonotic disease with world-wide distribution. It occurs mainly in persons associated with sheep, goats, cattle or other domestic animals.

Agent factors

(a) AGENT : The causative agent is *Coxiella burnetii*. It is found in ticks which act as vectors as well as reservoir. (b) ANIMAL HOSTS : Cattle, sheep, goats, ticks and some wild animals are natural reservoirs. Infected animals shed the disease agent in the faeces and urine and heavily contaminate the soil. The placenta of infected cows and sheep contains the infectious agent which may create infectious aerosols during parturition. Camels, horses, dogs and many other domestic animals have been shown to be capable of acting as maintenance hosts *(7)*.

Mode of transmission

Q fever differs from other rickettsial infections in that there is no arthropod involved in its transmission to man. Transmission results from : (i) inhalation of infected dust from soil previously contaminated by urine or faeces of diseased animals. The organism can also be transmitted through aerosols. (ii) the organism can also gain entry into the body through abrasions, conjunctivae or ingestion of contaminated foods such as meat, milk and milk products. In most countries, the respiratory route is regarded as most important.

Incubation period

Usually 2 to 3 weeks.

Clinical features

The disease has an acute onset with fever, chills, general malaise and headache. The clinical picture is one of influenza or non-bacterial pneumonia rather than a typhus fever. There is no rash or local lesion. The infection can cause pneumonia, hepatitis, encephalitis and rarely endocarditis. Inapparent infections also occur.

Control measures

(a) TREATMENT : Chronic Q fever requires prolonged treatment for 18 months or longer. Doxycycline is the drug of choice. *(b) PREVENTIVE MEASURES* : Pasteurization or boiling of milk to inactivate the causative agent; providing sanitary cattle sheds; adequate disinfection and disposal of

products. An inactivated *Coxiella* vaccine has also been prepared to protect occupationally exposed workers. Several purified vaccines are under development *(8)*.

OTHER RICKETTSIAL INFECTIONS

1. Epidemic typhus

Epidemic or louse borne typhus was in the past the most formidable disease caused by rickettsiae. It was the cause of devastating epidemics among military and refugee populations and in areas affected by famine. The advent of modern insecticides has considerably reduced the prevalence of epidemic typhus today.

No cases of this disease have been reported from South East Asia since 1978 or from the Western Pacific since 1969 *(1)*. It is still endemic in Africa (notably Burundi, Rwanda and Ethiopia) and South America (notably Peru, Bolivia, and Ecuador). All of them are known endemic areas of the disease.

The infection is transmitted from man to man by the infected louse *(P. corporis and P. capitis)*. The louse gets infected by feeding on an infectious patient during the febrile stage. The organisms multiply in the cells lining the intestinal tract of the louse and begin to appear in 3 to 5 days in the louse faeces. Man acquires the disease not by the bite of the louse, but : (i) by scratching and inoculating himself with the infected louse faeces (ii) by crushing an infected louse on his person, and (iii) possibly by inhalation of infected louse faeces or dust. The infected louse after 10–14 days of existence dies of the infection. In humans, the organisms can persist for many years as latent infection without any symptoms, and the disease may appear later as ***Brill–Zinsser disease,*** and can be transmitted to other humans by the louse.

The control measures comprise anti–louse measures and improvements in personal hygiene and living conditions. Under the International Health Regulations, louse–borne typhus is subject to international surveillance.

2. Rickettsial pox

Man gets the infection through the bite of certain infected mites, which are found on mice *(Mus musculus)*. Transovarial transmission occurs in the mite. The mouse acts as true reservoir as well as vector. Rickettsial pox may be confused with atypical cases of chickenpox.

3. Trench fever

This disease is limited to central Europe. The vector is louse and the disease is transmitted by louse faeces. Man is the only known reservoir.

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TAENIASIS

A group of cestode infections which are important zoonotic diseases. Three parasites of importance in taeniasis are *Taenia saginata, T. solium* and *T. asiatica*. These are classified as "cyclo–zoonoses" because they require more than one vertebrate host species (but no invertebrate host) to complete their developmental cycles.

Humans can become infected with *T. saginata* or *T. asiatica* when they consume beef meat or pig liver tissue, respectively, which has not been adequately cooked. Infection with the *T. solium* tapeworm occurs when humans eat raw or undercooked, infected pork. Tapeworm eggs pass with the faeces and are infective for pigs. Infection in humans with the *T. Solium* causes few clinical symptoms. However, infection with the larval parasite in the tissue (human cysticercosis) can result in devastating effect on human health. The larvae may develop in the muscle, skin, eyes and the central nervous system (neurocysticercosis). Neurocysticercosis is the most frequent preventable cause of epilepsy worldwide, and is estimated to cause 30 per cent of all epilepsy cases in countries where the parasite is endemic *(1)*.

Cysticercosis mainly affects the health and livelihood of communities in developing countries of Africa, Asia and Latin America. In 2010, the WHO added *T. solium* cysticercosis to the list of major Neglected Tropical Diseases. In 2015, the WHO Foodborne Disease Burden Epidemiology Reference Group identified *T. solium* as a leading cause of deaths from food-borne diseases resulting in a considerable total of 2.8 million DALYs lost and an estimated 2.56–8.30 million symptomatic and asymptomatic neurocysticercosis *(1)*.

Hosts of infection

T. saginata and *T. solium* pass their life cycles in two hosts. In man, the adult parasites live in the small intestine. The adult *T. saginata* measures 5 to 12 metres in length, and may be up to 24 metres; *T. solium* measures 2 to 6 metres.

TABLE 1
Hosts of infection

	Parasite	Definitive	Intermediate host
1.	*T. saginata*	Man	Cattle *(C. bovis)*
2.	*T. solium*	Man	Pig *(C. cellulosae)*

The larval stage of *T. saginata (C. bovis)* mainly occurs in cattle. The pig is the main host for the larval stage of *T. solium (C. cellulosae)* but man may also be infected. This may lead to muscular, ocular and cerebral cysticercosis.

The adult stages of *T. saginata* and *T. solium* may persist for several years in infected humans. Mixed infections of both the parasites can occur. Although the life span of *C. cellulosae* in man is not known, it is suspected to be some years.

Mode of transmission

These infections are acquired : (a) through the ingestion of infective cysticerci in undercooked beef *(T. saginata)* or pork *(T. solium)*; (b) through ingestion of food, water or vegetables contaminated with eggs; and (c) reinfection by the transport of eggs from the bowel to the stomach by retroperistalsis is considered to be rare.

Incubation period

For the adult tapeworm, from 8 to 14 weeks.

Clinical illness

The impact of tapeworm infection in man is difficult to quantify because in the vast majority of cases, they do not lead to clinical illhealth, except occasional abdominal discomfort, anorexia and chronic indigestion.

Straying of proglottids may sporadically cause appendicitis or cholangitis. The most serious risk of *T. solium* infection is cysticercosis.

Human cysticercosis

Human infection is caused by the ingestion of eggs of *T. solium* in contaminated water or food (hetero–infection) or regurgitated eggs from the small intestine (auto–infection). The eggs disintegrate and the infective stages leave the intestine via the hepatic portal system, and are dispersed throughout the body where they develop to form cysticerci. Cysticerci that develop in the central nervous system (neuro-cysticercosis), represent a serious threat to the individual and even to the community, if this condition is prevalent. As a result of mechanical pressure, obstruction or inflammation, a variety of pathological changes are produced, leading to epilepsy, intracranial hypertensive syndromes, hydrocephalus, psychiatric diseases or death *(2)*.

Control measures

The methods usually employed for control are : (a) treatment of infected persons, (b) meat inspection, (c) health education, and (d) adequate sewage treatment and disposal *(1, 2)*. Early detection and early treatment of *T. solium* cases is essential to prevent human cysticercosis. Effective drugs (e.g., praziquantel and niclosamide) are available for the treatment of these infections. Surgical removal of symptom-producing cysts is indicated although cure can seldom, if ever, be complete. In many countries, *T. solium* has been controlled by meat inspection and by the proper housing and feeding of pigs. Thorough cooking of beef and pork is the most effective method to prevent food–borne infections. Education of the public to prevent pollution of soil, water and food with human faeces, and washing of hands before eating and after defecation, are important health educational messages. Improvement of living conditions, especially safe treatment of sewage used for farming, should be aimed at.

Treatment

Praziquantel and niclosamide have replaced former taenicides (i.e., mepacrine). They are safe and effective in more than 90 per cent of patients. Praziquantel is given in a single dose of 10 mg/kg. body wt. It achieves cure rates of about 99 per cent. At this dose, side effects are minimal. With a single dose of 4 tablets (2 grams) of niclosamide, cure rates are over 90 per cent. This drug is given in the morning–empty stomach. The tablets must be chewed thoroughly and swallowed with water. Eating may be resumed after 2 hours. It usually produces no side effects. Pre and post-treatment purges are not used for either drug to treat *T. saginata*. For the treatment of *T. solium*, give moderate purgative 2–3 hours after the drug to rapidly eliminate segments and eggs from the bowels to avoid–theoretical possibility of cysticercosis *(3)*.

TREATMENT FOR CYSTICERCOSIS *(3)* : The treatment should be individualized, based on the number and location of cysts and their viability. Medical treatment is more effective for parenchymal cysts and less effective for intraventricular, subarachnoid, or racemose cysts. Albendazole and praziquantel are both effective in the treatment. 10–15 mg/kg body wt/day of albendazole is given twice daily with a fatty meal. The duration of treatment is unsettled. Seven to 14 days may be sufficient for some patients, but a longer course (up to 28 days) is advisable at present. It can be repeated as necessary. Up to 3 months of treatment may be needed for ventricular and subarachnoid cysts. Praziquantel is given in 50 mg/kg/day in three divided doses for 15 days.

Albendazole is the drug of choice because co-administration of albendazole and a steroid (to treat inflammation) results in increased albendazole absorption, whereas combined use of praziquantel and steroid greatly decreases plasma level of praziquantel. Both the drugs are given with fatty meals as this increases absorption four-fold to five-fold.

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HYDATID DISEASE

Hydatid disease is a zoonoses – a group of cestode infections which are important zoonotic diseases of man. The disease in man is caused by the metacystode stage (infective larva) of the canine intestinal tapeworm *Echinococcus;* the adult worms are found in dogs and other carnivores.

Geographic distribution

Hydatidosis has been recognized as a public health problem of nearly global dimensions. It is found in all sheep–raising countries, e.g., Australia, New Zealand, Tasmania, Middle East countries, Turkey, Greece, USSR, Cyprus, Latin America and the Far East etc. It is believed that there are relatively few countries in which cestodes of the genus *Echinococcus* are entirely absent *(1)*. Foci are also known to exist in India where the highest prevalence is reported in Andhra Pradesh and Tamil Nadu, than in other parts of the country. The prevalence of the disease is reported to be high in food animals in India.

More than 1 million people are living with cystic echinococcosis and alveolar echinococcosis worldwide at any one time. For cystic echinococcosis, there is an average of 2.2 per cent post-operative death rate for surgical patients and about 6.5 per cent of cases relapse after the interventions, thereby requiring prolonged recovery time. In 2015, WHO Foodborne Disease Burden Epidemiology Reference Group estimated echinococcosis to be the cause of 19,300 deaths and around 871,000 DALYs lost globally each year. Annual cost associated with cystic echinococcosis are estimated to be US $ 3 billion for treating the cases and losses to the livestock industry *(1)*.

Epidemiological determinants

Agent factors

Echinococcus species are small tapeworms, rarely more than 7 mm in length. The scolex bears four suckers, and

there are two rows of hooks, one small and one large on the rostellum. The number of proglottids varies from 2 to 6. At present four species are regarded as valid.

(a) E. granulosus : of worldwide distribution, is for the most part, maintained in the domestic transmission cycle involving the dog as final host. In man the infective larva causes hydatidosis, the "unilocular" type of echinococcosis. *(b) E. multilocularis :* is restricted to the northern hemisphere. It has been detected increasingly in various countries (e.g. Iran, Turkey). In man, the metacystode causes the "alveolar" type of the disease. *(c) E. oligarthus :* a species occurring in Central and South America is suspected to cause disease in man, and *(d) E. Vogeli :* a species occurring in Central and South America, has been shown to cause polycystic hydatidosis.

Life cycle

Basically it is a "dog–sheep" cycle with man as an accidental, intermediate host. The adult tapeworm lives in the small intestine of dogs (definitive host) for 2 to 4 years. The eggs are voided in the faeces and contaminate the soil, vegetation and drinking water. They are highly resistant and can survive for several months in pastures, gardens and around households. Sheep, cattle and other intermediate hosts become infected when they ingest vegetation which has become contaminated with faeces from infected dogs. Ingested eggs hatch in the intestine and the larvae penetrate the intestinal lining and migrate to various organs of the body. Most frequently, they lodge in such organs as liver, lungs and brain and develop into hydatid cysts. The life cycle is completed when sheep (cattle) viscera containing hydatid cysts are eaten by dogs. Infected dogs begin to pass eggs of the parasite approximately 7 weeks after infection. Man does not harbour the adult worm *(1)*.

Host factors

It is becoming increasingly evident that human behaviour, especially in relation to dogs and cats, uncontrolled slaughter of food animals, indiscriminate disposal of offal and carcasses, and eating habits of the people play an important part in the epidemiology of the disease. Human infection is acquired usually in childhood through contact with infected dogs. The impact of hydatidosis can be described only in terms of human suffering, cost of medical diagnosis, hospitalization and surgery, man–hours lost, as well as in terms of temporary or permanent incapacity. The retarded growth of animals, and reduction in the quality and yield of meat, milk and wool and condemnation of offal are also very great *(2)*. Hydatid disease is an occupational disease of certain groups, e.g., shepherds and their families in endemic areas and shoe–makers.

Mode of transmission

Human infection occurs by ingestion of the eggs of *Echinococcus* inadvertently with food, unwashed vegetables or water contaminated with faeces from infected dogs. Infection can also take place while handling or playing with infected dogs, e.g., hand to mouth transfer of eggs, or by inhalation of dust contaminated with infected eggs. The disease is not directly transmissible from person to person.

The disease is maintained in the "dog–sheep" cycle. Other animal combinations may also be involved, e.g., dog–goat, dog–cattle, and dog–camel. Carnivores get infected by eating viscera containing hydatid cysts. The disease is not directly transmissible from one intermediate host to another.

Incubation period

Variable, from months to years depending upon the number and location of cysts and how rapidly they grow.

Clinical features

In man, symptoms of hydatid disease are usually manifested several years after exposure. The cysts grow slowly from 5 to 20 years before they are diagnosed. The size of the cyst may vary from a pinhead to that of a small football. It has been estimated that more than 70 per cent of the cysts become located in the right lobe of the liver, and the rest in lungs, brain, peritoneum, long bones and kidney. The cysts are filled with watery fluid and contain a large number of tapeworm heads. If the cyst ruptures, the brood capsules can spill out of the cyst, metastasize to other sites and develops into a hydatid, thus ingestion of a single egg can give rise to several hydatid cysts, each containing several brood capsules *(3)*.

Cysts of small size are generally asymptomatic. Large cysts, however, cause pressure symptoms (e.g., jaundice in liver cysts). In vital organs they may cause severe symptoms and death.

Diagnosis

(a) Clinical : Based on the history of residence in an endemic area, close association with dogs and the presence of a slowly growing cystic tumour. *(b) X-ray :* A plain X-ray permits the location of the cyst. Modern techniques of diagnosis include ultrasonography, MRI and CAT scan. *(c) Serological :* Serological tests with a high degree of sensitivity and specificity have been introduced such as the indirect immunofluorescent test. ELISA is regarded as a relatively simple method with a high sensitivity superior to that of some other serological procedures *(1)*. The intradermal (Casoni) test is still in wide use, since it is simple to perform. This test often lacks specificity.

Treatment

There is no specific treatment excepting surgical removal of cysts which is not without considerable risk in as much as the accidental penetration of one of the cysts can lead to anaphylactic shock which may prove fatal.

Mebendazole (Vermox) has been tried and found very effective in mice. It may well become the drug of choice.

Prevention and control *(4)*

1. Wash fruits and raw vegetables before eating.
2. Wash hands before eating or smoking, after handling dogs and after contact with items that are likely to be soiled with dog faeces.
3. Discourage dogs from licking people's faces, and do not kiss dogs.
4. Do not allow dogs to defecate near vegetable gardens or children's play areas.
5. Reduce the amount of disease in dogs
   - Ensure dogs are kept away from the areas where animals are slaughtered and are not allowed to scavenge on carcasses.
   - Prevent dogs from eating uncooked offal.
   - Dispose of infected offal by deep burial or burning to prevent it from being consumed by dogs or other canines.

- Reduce dog populations on farms to the occupational need for them.
- Seek advice from your veterinarian about effective treatment to prevent infection in working, pet or visiting dogs. This is particularly important for dogs in rural areas or those that may have contact with wildlife or feral animals.

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LEISHMANIASIS

Leishmaniasis are a group of protozoal diseases caused by parasites of the genus *Leishmania*, and transmitted to man by the bite of female phlebotomine sandfly. They are responsible for various syndromes in humans – kala-azar or visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), muco–cutaneous leishmaniasis (MCL), anthroponotic cutaneous leishmaniasis (ACL), zoonotic cutaneous leishmaniasis (ZCL), post–kala-azar dermal leishmaniasis (PKDL), etc *(1)*. The visceral type of disease, kala-azar, is still an important disease in India. The majority of the leishmaniasis are zoonoses involving wild or domestic mammals (rodents, canines). Some forms (e.g., Indian kala-azar) are considered to be non-zoonotic infections *(2)*.

Problem statement

WORLD

Leishmaniasis is endemic in many countries in tropical and subtropical regions. The 3 main forms of the disease are distributed as follows (3):

1. *Visceral leishmaniasis (VL)*, also known as Kala-azar is fatal if left untreated in over 95% of cases. It is characterized by irregular bouts of fever, weight loss, enlargement of the spleen and liver, and anaemia. In 2023, 42 per cent of the new VL cases were reported by EMR and 37 per cent cases by African region. American region and South East Asian Region reported 14 per cent and 6 per cent cases respectively. Four countries, Brazil, Ethiopia, Kenya and Sudan each reported >1000 cases, representing 60 per cent (7059) of all cases globally. There were 399 relapse cases. About 374 deaths were reported globally in 2023 *(2A)*.
2. *Cutaneous leishmaniasis (CL)*, is the most common form of leishmaniasis and causes skin lesions, mainly ulcers, on exposed parts of the body, leaving life-long scars and serious disability. In 2023, there were 272,098 new CL cases, 94 per cent of the new CL cases were reported from East Mediterranean region (81%) and Region of Americas (13%). EMR and Algeria constitute an eco-epidemiological hotspot as together they reported 227,874 (84%) of all new cases. Afghanistan, Algeria, Brazil, Colombia, Iran, Iraq, Pakistan, Peru, Sri Lanka, Syrian Arab Republic and Yemen each reported >4000 CL cases for a total of 247,216 cases representing 91% of all cases globally. In 2023, 4830 CL relapse cases were reported to WHO *(2A)*.
3. *Muco-cutaneous lesihmaniasis* leads to partial or total destruction of mucous membranes of the nose, mouth and throat. Over 90% of muco-cutaneous leishmaniasis cases occur in Bolivia (the Plurinational State of) Brazil, Ethiopia and Peru.

Kala-azar situation is worsening due to the occurrence of asymptomatic cases, post-kala-azar dermal leishmaniasis (PKDL), undernutrition, and kala-azar/HIV coinfection. Case fatality rate has decreased perhaps due to improved case management in endemic countries.

INDIA

Kala-azar is endemic in 54 districts in Bihar (33), Jharkhand (4), West Bengal (11) and Uttar Pradesh (6). About 130 million population is at risk of the disease. The present situation is shown in Table 1. While both cutaneous (ZCL and ACL) and visceral (VL) disease occur in India, kala-azar is by far the most important leishmaniasis in India *(5)*. Kala-azar has been declared as notifiable disease in Bihar and West Bengal *(5)*.

TABLE 1

State-wise Kala-azar cases and deaths in India (2020–2022)

State	2020		2021		2022	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
Bihar	1,502	0	967	2	608	26
West Bengal	60	3	59	2	53	4
Uttar Pradesh	55	3	51	2	22	1
Jharkhand	431	0	279	2	193	8
India	2,052	6	1,357	8	881	39

Source : *(4)*

Epidemiological determinants

Agent factors

(a) AGENTS : The leishmania are intracellular parasites. They infect and divide within macrophages. At least nineteen different leishmania parasites have been associated with human infection. Further, the majority of these offer no cross immunity of one against the other *(6)*. *Leishmania donovani* is the causative agent of kala-azar (VL); *L. tropica* is the causative agent of cutaneous leishmaniasis (oriental sore); and, *L. braziliensis* is the causative agent of muco-cutaneous leishmaniasis. But this distinction is not absolute; visceral forms may produce cutaneous lesions, and cutaneous forms may visceralize *(7)*. The life cycle is completed in two different hosts – a vertebrate and an insect; in the former, it occurs in an amastigote form (called "leishmania bodies") and in the latter as a flagellated promastigote. *(b) RESERVOIRS OF INFECTION* : There is a variety of animal reservoirs, e.g., dogs, jackals, foxes, rodents and other mammals. Indian kala-azar is considered to be a non–zoonotic infection with man as the sole reservoir. This assumption is based largely on the absence of evidence *(8)*.

Host factors

(a) AGE : Kala-azar can occur in all age groups including infants below the age of one year. In India, the peak age is 5 to 9 years *(1)*. *(b) SEX* : Males are affected twice as often as females. *(c) POPULATION MOVEMENT* : Movement of population (migrants, labourers, tourists) between endemic and non–endemic areas can result in the spread of infection. *(d) SOCIO-ECONOMIC STATUS* : Kala-azar usually strikes the poorest of the poor. Poverty increases the risk for kala-

azar. Poor housing and domestic sanitary conditions (e.g. lack of waste management, open sewerage) may increase sandfly breeding and resting sites, as well as their access to humans. Sandflies are attracted to crowded housing as these provide a good source of blood-meal. Human behaviour, such as sleeping outside or on the ground, may increase risk. As a disease it more often debilitate than kills, and makes people become dependants on others; *(e) MALNUTRITION :* Diets lacking protein-energy; iron, vitamin A and zinc increases the risk that an infection will progress to kala-azar *(3)*. *(f) OCCUPATION :* The disease strongly associates with occupation. People who work in various farming practices, forestry, mining and fishing have a great risk of being bitten by sandflies. *(g) IMMUNITY :* Recovery from kala-azar and oriental sore gives a lasting immunity. During the active phase of kala-azar, there is impairment of cell mediated immunity, this is reflected in the negative skin reaction to leishmanin test.

Environmental factors

(a) ALTITUDE : Kala-azar is mostly confined to the plains; it does not occur in altitudes over 2000 feet (600 metres). (b) SEASON : In the past epidemics, two peaks, one in November and another in March–April were reported. Generally there is high prevalence during and after rains. (c) CLIMATE CHANGES : Kala-azar is climate sensitive, and is strongly affected by changes in rainfall, temperature and humidity. Global warming and land degradation together affect the epidemiology of kala-azar in many ways. It can have strong effects on vector and reservoir hosts by altering their distribution and influence their survival. Drought famine and flood resulting from climate changes can lead to massive displacement and migration of people to areas with transmission of kala-azar, and poor nutrition could compromise their immunity *(3)*. (d) RURAL AREAS : The disease is generally confined to rural areas, where conditions for the breeding of sandflies readily exist compared to urban areas. (e) VECTORS : In India, *P. argentipes* is a proven vector of kala-azar. Cutaneous leishmaniasis is transmitted by *P. papatasi* and *P. sergenti*. Sandflies breed in cracks and crevices in the soil and buildings, tree holes, caves etc. Overcrowding, ill-ventilation and accumulation of organic matter in the environment facilitate transmission. Their habits are primarily nocturnal. Only the females bite. (f) DEVELOPMENT PROJECTS : Ironically many development projects are exposing more people to leishmaniasis. Forest clearing, and cultivation projects, large water resource schemes, and colonization and resettlement programmes are bringing human beings into areas of high vector and reservoir concentration *(3)*.

Mode of transmission

In India, Kala-azar is transmitted from person to person by the bite of the female phlebotomine sandfly, *P. argentipes* which is a highly anthrophilic species. Transmission may also take place by contamination of the bite wound or by contact when the insect is crushed during the act of feeding. Cutaneous leishmaniasis is transmitted by *P. papatasi* and *P. sergenti*.

After an infective blood meal, the sandfly becomes infective in 4 to 25 days (extrinsic incubation period). This is the time required for the development of the parasite in the insect vector. Transmission of kala-azar has also been recorded by blood transfusion *(7)*, and is also possible by contaminated syringes and needles *(9)*.

Incubation period

The incubation period in man is quite variable, generally 1 to 4 months; range is 10 days to 2 years.

Clinical features

1. Kala-azar (VL)

The classical features of kala-azar are fever, splenomegaly and hepatomegaly accompanied by anaemia and weight–loss. A family history of the disease is also common. Darkening of the skin of the face, hands, feet and abdomen is common in India (kala-azar = black sickness). Atypical features of the disease (e.g., lymphadenopathy) may also occur. Kala-azar, if left untreated, has a high mortality.

PKDL : Post-kala-azar dermal leishmaniasis, caused by *L. donovani*, is common in India. It appears one to several years after apparent cure of kala-azar. The lesions consist of multiple nodular infiltrations of the skin, usually without ulceration. Parasites are numerous in the lesion.

2. Cutaneous leishmaniasis

Several forms of cutaneous leishmaniasis have been described – Anthroponotic or urban cutaneous leishmaniasis (ACL), Zoonotic or rural cutaneous leishmaniasis (ZCL), Diffuse cutaneous leishmaniasis (DCL), etc *(1)*. The disease may be mistaken for leprosy. The agent is restricted to skin. The disease is characterized by painful ulcers in the parts of the body exposed to sandfly bites (e.g., legs, arms or face) reducing the victim's ability to work.

3. Muco-cutaneous leishmaniasis

Ulcers similar to the oriental sore (CL) appear around the margins of mouth and nose. It can mutilate the face so badly that victims may become social outcasts.

Laboratory diagnosis

1. Rapid diagnostic test

The rapid dipstick test has become the mainstay in the serological diagnosis of Kala-azar, and is the method of choice for diagnosis of the disease.

The rk39 – rapid diagnostic test is based on the recombinant k39 protein. It is an epitope apparently conserved on amastigotes of *Leishmania* species that cause visceral infection. The test is simple to perform and yields result within five minutes. However, the test should not be used in Kala-azar relapse cases, Kala-azar reinfection cases and Kala-azar and HIV co-infection cases.

Kala-azar dipstick test strip is a membrane, pre-coated with a recombinant VL antigen on the test line region and chicken anti-protein A on the control line region. It is a immunochromatographic assay for qualitative detection of antibodies to *L. donovani* in human serum. During testing the serum sample reacts with the dye conjugate. The mixture then migrates upwards on the membrane chromatographically by capillary action to react with rk39 antigen on the membrane and generates a red line. Presence of this red line indicates a positive result while its absence indicates a negative result.

Regardless of the presence of antibody to VL antigen, as the mixture continues to migrate across the membrane to the immobilized chicken anti-protein A region, a red line at the

control line will always appear. The presence of this red line serves as a verification for sufficient sample volume and proper flow, and is a control for the reagent. If no lines appear at control and test line areas, the test is invalid. The test is also invalid if no control line appears, even though a test line is seen *(10)*.

2. Parasitological diagnosis

The demonstration of the parasite LD bodies in the aspirates of the spleen, liver, bone marrow, lymph nodes or in the skin (in the case of CL) is the only way to confirm VL or CL conclusively. The parasite must be isolated in culture to confirm the identity of the parasite.

3. Aldehyde test

The aldehyde test of Napier is a simple test widely used in India for the diagnosis of kala-azar. 1 to 2 ml of serum from a case of kala-azar is taken and a drop or two of 40 per cent formalin is added. A positive test is indicated by jellification to milk–white opacity like the white of a hard–boiled egg so that in ordinary light newsprint is invisible through it. If it occurs within 2 to 20 minutes, it is said to be strongly positive. Reaction after 30 minutes is not significant. The test usually becomes positive 2 to 3 months after onset of the disease, and reverts to negative 6 months after cure. Therefore, this test is good for surveillance but not for diagnosis. The test is non–specific and demands the use of venous blood. Further, the test is positive in many other chronic infections in which albumin to globulin ratio is reversed.

4. Serological tests

Of the numerous serological tests available, Direct Aggutination test (DAT), rk39 dipstick test, ELISA and the indirect fluorescent antibody test (IFAT) are considered most suitable *(10)*. Being a simple test where blood samples can be collected on a filter paper strip and examined at leisure in laboratory, the ELISA test has a wide potential both for diagnosis as well as for epidemiological field surveys.

5. Leishmanin (Montenegro) test

This test is based on skin reaction. Leishmanin is a preparation of 10^6 per ml washed promastigotes of leishmania, suspended in 0.5 per cent phenol saline or merthiolate. Sterile and standardized preparations are available commercially. An intradermal injection of 0.1 ml on the flexor surface of the forearm is given and examined after 48 to 72 hours. Induration is measured and recorded. An induration of 5 mm or more is considered positive. The test is usually positive 4 to 6 weeks after onset in the case of CL and MCL. It is usually negative in the active phase of kala-azar and becomes positive in 75 per cent patients within one year of recovery. The test is not species–specific. The test remains a valuable tool for distinguishing immune from non–immune subjects. From this information, it may be possible to infer the endemicity or epidemicity of the infection and to identify groups at risk of infection *(10)*.

6. Haematological findings

These include progressive leucopenia, anaemia and reversed albumin–globulin ratio, with greatly increased IgG. The WBC:RBC ratio is 1:1500 or even 1:2000 (normal 1:750). ESR is increased.

ICMR has developed a new kit to diagnose Kala-azar, which was launched on 3rd Sept. 2014. The test needs the sample of urine or oral fluid of the subject in question. It is mixed with the given solution in the 'tube' - part of the kit. Dip the stipulated strip in the solution thus created. Those infected would get two or one red bond on the strip once it comes out. Absence of the red bond means negative result.

Some definitions *(11)*

1. *Case definition of kala-azar* : A case of kala-azar is defined as a person from an endemic area with fever of more than 2 weeks duration and with splenomegaly, who is confirmed by an RDT or a biopsy.
2. *Treatment outcome definitions of kala-azar*
   a. *Cure* : a patient is considered clinically cured if he/she has completed full treatment and there are no signs and symptoms of kala-azar.
   b. *Non-response* : Signs and symptoms persist or recur despite satisfactory treatment for more than two weeks.
   c. *Relapse* : any reappearance of kala-azar signs and symptoms within a period of six months after the end of treatment.
   d. *Treatment failure* : non-response or relapse.
   e. *Final cure* : an initially cured patient who is symptom-free at six months after the end of treatment.
3. *Case definition of PKDL*
   a. *Probable PKDL* : a patient from kala-azar endemic area with multiple hypopigmented macules, papules or nodules, who is RDT positive.
   b. *Confirmed PKDL* : a patient from kala-azar endemic area with multiple hypopigmented macules, papules, plaques or nodules, who is parasite positive in slit-skin smear (SSS) or biopsy.

Treatment outcome in PKDL

a. *Initial cure* : Clinical improvement at the end of treatment – defined as a considerable reduction in the number and size of skin lesions.
b. *Final cure* : Clinical cure 12 months after the end of treatment – defined as a complete resolution of macules, papules, plaques and nodules.

Key indicators in the kala-azar elimination initiative *(11)*

1. *Detection rate (%)*

$$= \frac{\text{Number of new cases of KA detected per year in the district, UHC or subdistrict}}{\text{Total population in the same area}} \times 100$$

2. *Treatment completion rate (%)*

$$= \frac{\text{Number of patients that took a full course of first-line drugs}}{\text{All new KA cases that started treatment in a given period}} \times 100$$

3. *Coverage rate of vector control (%)*

$$= \frac{\text{Number of households protected}}{\text{All households at risk}} \times 100$$

Monitoring clinical outcomes (11)

1. *Final cure rate (%)*

$$= \frac{\text{Number of patients with final cure}}{\text{Total number who started treatment}} \times 100$$

2. *Treatment failure rate (%)*

$$= \frac{\text{Total number of non-response + relapse + KA - related deaths}}{\text{Total number who started treatment}} \times 100$$

3. *Loss to follow-up rate (%)*

$$= \frac{\text{Number of defaulters + Number of loss to follow-up}}{\text{Total number who started treatment}} \times 100$$

4. *Mortality (%)*

$$= \frac{\text{Number of deaths}}{\text{Total number who started treatment}} \times 100$$

CONTROL MEASURES

In the absence of an effective vaccine, the control measures comprise the following :

1. Control of reservoir

Since man is the only reservoir of kala-azar in India, active and passive case detection and treatment of those found to be infected (including PKDL) may be sufficient to abolish the human reservoir and control the disease. House-to-house visits and mass surveys may be undertaken in endemic areas for early detection of cases.

TREATMENT GUIDELINES (2017)

Following drugs are used for the treatment of kala-azar in Indian programme *(2, 7)* :

- Single dose Liposomal Amphotericin B (LAMB) injection intravenously across all age groups in dose of 10 mg/kg bw including paediatric, pregnant & elderly patients.
- Miltefosine capsules of 10 mg (paediatric) and 50 mg (adults) in the age group between 2–65 years. Not to be given to pregnant and lactating women and women who refuse contraception during treatment with Miltefosine. Dosages are: patients > 12 years, weight > 25 kgs– 100 mg daily in two doses of 50 mg each after meals for 28 days, and patients > 12 years, weight < 25 kgs, only one capsule of 50 mg daily × 28 days. Children 2–11 years miltefosine to be given at 2.5 mg/kg once daily after meals × 28 days.
- Amphotericin B deoxycholate injection intravenously at a dose of 1 mg/kg b.w. on alternate days × 15 doses.
- Combination of Paromomycin injection intramuscular & Miltefosine in a dose of 11mg/kg b.w. × 10 days together with Miltefosine for 10 days. Not to be given to chronic kidney patients, pregnant and lactating women, and those not inclined to contraception during treatment.
- HIV–coinfected patients – LAMB 40 mg /kg b.w as total dose of 3–5 mg/kg bw daily or intermittently for 10 doses, on days 1–5, 10, 17, 24, 31 and 38.
- PKDL – In order of preference: First drug of choice, miltefosine 100 mg orally per day × 12 weeks.
- Amphotericin 'B' deoxycholate injection 1 mg/kg bw over 4 months in 60–80 doses.

Given the high efficacy, safety, ease of use and assured compliance, Liposomal Amphotericin B (LAMB) is used as the first line of treatment. The drugs used in order of preference at all levels are:

- Liposomal Amphotericin B intra venous (LAMB) single dose 10 mg/kg bw
- Combination regimens (e.g. Miltefosine capsules plus Paromomycin inj IM)
- Amphotericin B emulsion
- Miltefosine capsule
- Amphotericin B deoxycholate inj in multiple doses
- Amphotericin B emulsion inj in selected districts on pilot project.

Miltefosine is relatively safe oral drug for the treatment of Kala-azar. The treatment is provided as Directly Observed Treatment (DOT) with patient coding system being followed for each patient registered at the treatment centre. The dose guide is as follows :

Dosage guide for children (2–11 years)

Body weight	Daily dosage (after meal)	Number of capsules
9–11 kg	20 mg	2 capsules of Miltefosine 10 mg
12–16 kg	30 mg	3 capsules of Miltefosine 10 mg
17–20 kg	40 mg	4 capsules of Miltefosine 10 mg
21–25 kg	50 mg	1 capsule of Miltefosine 50 mg
26–31 kg	60 mg	1 capsule of Miltefosine 50 mg & 1 capsule of Miltefosine 10 mg
32–39 kg	80 mg	1 capsule of Miltefosine 50 mg & 3 capsules of Miltefosine 10 mg
40 kg and above	100 mg	2 capsules of Miltefosine 50 mg

Miltefosine dosage guide for persons (>12 years)

Weight	Morning dose (after meal)	Evening dose (after meal)
More than 25 kg	1 capsule of Miltefosine 50 mg	1 capsule of Miltefosine 50 mg
Less than 25 kg	1 capsule of Miltefosine 50 mg	Drug not to be given at evening

National Road Map on Kala-azar elimination was developed in August 2014 with specific time line, roles and responsibility for states and district level vector borne diseases consultants and technical supervisors.

Animal reservoirs

If animal reservoirs (e.g., dogs) are involved, appropriate control measures against them should be undertaken. In many endemic countries, extensive dog and rodent control programmes have contributed greatly to the reduction in the number of human cases.

2. Sandfly control

The application of residual insecticides has proved effective in the control of sandflies. DDT is the first choice since the vector of kala-azar, *P. argentipes* is susceptible to DDT. (*P. papatasi* in north Bihar has been shown to be

resistant to DDT, but fortunately, it is not the vector of kala-azar in India). Insecticide spraying should be undertaken in human dwellings, animal shelters and all other resting places upto a height of 6 feet (2 metres) from floor level. DDT (two rounds per year) at the rate of 1–2 g per sq. metre is considered sufficient to control transmission. Spraying should be preceded and followed by an assessment of susceptibility. Any sign of resistance in vector should lead to an immediate change in insecticide. BHC should be kept as a second line of defence.

Spraying should be repeated at regular intervals to keep down the density of sandflies. For long-lasting results, insecticidal spraying should be combined with **sanitation measures**, viz elimination of breeding places (e.g., cracks in mud or stone walls, rodent burrows, removal of firewood, bricks or rubbish around houses), location of cattle sheds and poultry at a fair distance from human dwellings, and improvement of housing and general sanitation.

3. Personal prophylaxis

The risk of infection can be reduced through health education and by the use of individual protective measures such as avoiding sleeping on floor, using fine-mesh nets around the bed. Insect repellents (in the form of lotions, creams, or sticks) for temporary protection and keeping the environment clean. There are no drugs for personal prophylaxis.

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V. SURFACE INFECTIONS

TRACHOMA

Trachoma is a chronic infectious disease of the conjunctiva and cornea, caused by *Chlamydia trachomatis*, but other pathogenic microorganisms often contribute to the disease. Trachoma inflammation may undergo spontaneous resolution or may progress to conjunctival scarring which can cause inward deviation of eyelashes (trichiasis) or of the lid margin (entropion). The abrasion of the cornea by eyelashes frequently result in corneal ulceration, followed by scarring and visual loss.

From the public health point of view, trachoma is classified as blinding and non-blinding *(1)*. A community with blinding trachoma can be recognized by the presence of persons with lesions such as entropion, trichiasis and corneal ulcers. It is the blinding trachoma that requires urgent control measures. Non-blinding trachoma often becomes blinding trachoma when other ocular pathogens interact synergistically and enhance the risk of damage to eye sight *(2)*.

Diagnosis

In epidemiological studies, more stress is now put on the upper tarsal conjunctiva as a convenient index of trachomatous inflammation in the eye as a whole *(2)*. For the purpose of diagnosis in the field, cases must have at least 2 of the following diagnostic criteria *(3)*.

a. follicles on the upper tarsal conjunctiva
b. limbal follicles or their sequelae, Herbert's pits
c. typical conjunctival scarring (trichiasis, entropion)
d. vascular pannus, most marked at the superior limbus

Problem statement

Trachoma is a major preventable cause of blindness in developing countries. According to recent estimates, in 41 endemic countries about 1.9 million people suffer from visual impairment due to trachoma, of these 1.2 million are irreversibly blind, and about 190.2 million are at risk of infection *(4)*. In 2016, more than 260,000 people with trachoma were provided with curative surgery and 85 million in endemic communities were treated with antibiotics to eliminate trachoma *(4)*.

The incidence and prevalence of trachoma has shown a significant decrease in many endemic countries of SEAR during the past few decades. This decrease has been mainly due to improved sanitation, water and housing, and implementation of control measures.

India became the third country in SEAR to eliminate trachoma, joining Nepal and Myanmar. WHO declared India free from trachoma on 8th Oct. 2024 *(5)*.

Epidemiological determinants

Agent factors

(a) AGENT : The classical endemic trachoma of developing countries is caused by *C. trachomatis* of immune types A, B, or C. The sexually-transmitted *C. trachomatis* (serotypes D,E,F,G,H,I,J or K) may also infect, causing an eye disease difficult to differentiate from endemic trachoma. Milder cases of this are usually called "inclusion conjunctivitis". These strains rarely produce permanent visual loss – but they cause respiratory infections (pneumonia) in infants and genital tract infections in adults *(2)*. Other pathogenic organisms (e.g., Morax–Axenfeld diplobacillus, the Koch–Weeks bacillus, the gonococcus) often contribute to the disease process. The Morax–Axenfeld diplobacillus is the most innocuos; the Koch–Weeks bacillus is the most widespread, and the gonococcus the most dangerous *(6)*. *C. trachomatis*, originally believed to be a virus, is an obligatory intracellular bacteria, now classified as Chlamydia. (b) RESERVOIR : Children with active disease, chronically infected older children and adults. (c) SOURCE OF INFECTION : Ocular discharges of infected persons and fomites, and (d) COMMUNICABILITY: Trachoma is a disease of low infectivity. It is infective as long as active lesions are present in the conjunctiva, but not after complete cicatrization.

Host factors

(a) AGE : In endemic areas, children may show signs of the disease at the age of only a few months. But typically, children from the age of two to five years are the most infected, and this contributes not only to the high rate of blindness but also to the rate of occurrence among children. (b) SEX : Prevalence equal in younger age groups. In older age groups, females have been found to be affected more than males. The explanation for this may be that women remain more in contact with children who infect them. Further, females are more exposed to irritating factors such as smoke than males. (c) PRE-DISPOSING FACTORS : Direct sunlight, dust, smoke and irritants such as *kajal* or *surma* may predispose to infection.

Environmental factors

(a) SEASON : Seasonal epidemics are associated with vastly increased number of eye–seeking flies. The incidence of active trachoma is found generally high in India during April–May and again during July–September. The higher temperature and rainfall favours the increase in fly population. (b) QUALITY OF LIFE : Trachoma is associated with poor quality of life. The disease thrives in conditions of poverty, crowding, ignorance, poor personal hygiene, squalor, illiteracy and poor housing. As living conditions improve the disease tends to regress. (c) CUSTOMS : The custom of applying *kajal* or *surma* to the eyes is a positive risk factor.

Mode of transmission

In communities where trachoma is endemic, eye-to-eye transmission can be considered as a rule *(8)*. This may occur by direct or indirect contact with ocular discharges of infected persons or fomites, e.g., infected fingers, towels, *kajal* or *surma*. Eye-seeking flies (e.g., *Musca* spp., *Hippelatus* spp.) play some role in spreading the infection by mechanical transmission. In countries where only sporadic cases of trachoma occur, genital localization of *C. trachomatis* (urethral, cervical) may lead to venereal transmission *(6)*.

It has been shown that trachoma is a familial disease. When one case is detected, others will almost certainly be found in the family group. There is a continuous feedback of infection, partly as a result of grandfathers or sisters and brothers tending small children *(7)*.

Incubation period

5 to 12 days.

CONTROL OF TRACHOMA

Trachoma control still requires long-term efforts. It requires proper planning and organization, which should include the following elements :

1. Assessment of the problem

The primary objective of a programme for the control of trachoma is the prevention of blindness. Control programmes should be focussed on communities with a substantial prevalence of "blinding trachoma" – as indicated by the presence of : (a) corneal blindness (b) trachomatous trichiasis and entropion, and (c) moderate and severe trachomatous inflammation. Such communities are likely to be found in countries with blindness rates that are above 0.5 per cent. The first task, therefore, is to undertake an epidemiological survey to identify and delimit communities with blinding trachoma; assess the magnitude of the problem, local conditions and other causes of blindness and to obtain information on existing facilities. The basic principles of these surveys are set out in the WHO publication : "Methods of Assessment of Avoidable Blindness" *(8)*.

2. Chemotherapy

In trachoma control, the main activity is chemotherapeutic intervention. The objective of chemotherapy is to reduce severity, lower the incidence and in the long run decrease the prevalence of trachoma. The antibiotic of choice is 1 per cent ophthalmic ointment or oily suspension of tetracyclines. Erythromycin and rifampicin have also been used in the treatment of trachoma. Treatment may be given to the entire community – this is known as **mass treatment** (or blanket treatment). In some programmes, **selective treatment** is chosen, in which case, the whole population at risk is screened, and treatment is applied only to persons with active trachoma *(9)*.

(a) Mass treatment

A prevalence of more than 5 per cent severe and moderate trachoma in children under 10 years is an indication for mass or blanket treatment. The treatment consists of the application twice daily of tetracycline 1 per cent ointment to all children, for 5 consecutive days each month or once daily for 10 days each month for 6 consecutive months, or for 60 consecutive days *(2)*. An alternative antibiotic is erythromycin.

From the practical point of view, one of the main difficulties is the need for repeated applications of the antibiotic over long periods of time. Emphasis is now being placed on the active participation of the community itself in trachoma control activities and on the utilization of primary health care workers. This makes possible a wider coverage and a greater efficacy of the programme.

(b) Selective treatment

In communities with a low to medium prevalence, treatment should be applied to individuals by *case finding* rather than by community–wide coverage, the principals of treatment remaining the same. For the selective treatment to be effective, the whole population at risk must be screened for case finding.

3. Surgical correction

Antibiotic ointment is just one component of a trachoma control programme. Individuals with lid deformities (trichiasis, entropion) should be actively sought out, so that necessary surgical procedures can be performed and followed-up. It has an immediate impact on preventing blindness.

4. Surveillance

Once control of blinding trachoma has been achieved, provision must be made to maintain surveillance, which may be necessary for several years after active inflammatory trachoma has been controlled. Since trachoma is a familial disease, the whole family group should be under surveillance.

5. Health education

In the long run, most of the antibiotic treatment must be carried out by the affected population itself. To do this, the population needs to be educated. The mothers of young

children should be the target for health education. Measures of personal and community hygiene should also be incorporated in programmes of health education. Thus real primary prevention could only come through health education for the total elimination of transmission. This would require a permanent change in the behaviour patterns and in environmental factors. The final solution would be the improvement of living conditions and quality of life of the people *(9)*.

6. Evaluation

Lastly evaluation. Trachoma control programme must be evaluated at frequent intervals. The effect of intervention can be judged by the changes in the age-specific rates of active trachoma and in the prevention of trichiasis and entropion.

The 28th World Health Assembly in 1975, in a resolution requested the Director General of WHO "to encourage Member countries to develop national programmes for the prevention of blindness especially aimed at the control of trachoma, xerophthalmia, onchocerciasis and other causes". With this came the re-orientation of strategies away from single cause prevention, to the adoption of the concept of integrated delivery of eye care as part of primary health care. In this context, many countries have now integrated their trachoma control programmes into National Programmes for the Prevention of Blindness, to give simultaneous introduction of other specific measures for dealing with all causes of avoidable blindness.

The trachoma control programme in India which was launched in 1963. Later on, it was integrated with the National Programme for Control of Blindness (see chapter 7).

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TETANUS

An acute disease induced by the exotoxin of *Clostridium tetani* and clinically characterized by muscular rigidity which persists throughout illness punctuated by painful paroxysmal spasms of the voluntary muscles, especially the masseters (trismus or "lock-jaw"), the facial muscles (risus sardonicus), the muscles of the back and neck (opisthotonos), and those of the lower limbs and abdomen *(1)*. The mortality tends to be very high, varying from 40 to 80 per cent.

Problem statement

WORLD

Tetanus is now comparatively rare disease in the developed countries. Neonatal tetanus (NT) is a killer disease, second only to measles among the nine target diseases of the EPI. In the absence of high quality treatment, the case–fatality rate can be as high as 80–90 per cent. It tends to occur in areas with poor access to health care, hence it often remains hidden within the community.

Maternal and neonatal tetanus (MNT) is an important preventable cause of neonatal and maternal mortality, particularly in developing countries. Although easily prevented by maternal immunization with tetanus toxoid containing vaccines (TTCV) and aseptic obstetric and postnatal umbilical cord care practices, both maternal and neonatal tetanus persist as public health problems. Most cases occur in poor, remote and isolated communities where unhygienic obstetric and postnatal practices prevail along with poor access to health services.

The spores of tetanus are very resistant and remain in the environment in extremes of temperature for long periods. Hence, technically it is not possible to eradicate tetanus, including NT. However, MNT can be eliminated by reducing the disease incidence to such low levels that it ceases to be a public health problem. The disease is easily preventable through *(2)* :- (1) clean delivery and umbilical cord care practices to ensure infection is not contracted by mother or newborn during the delivery process; (2) delivery of appropriate doses of TTCV to pregnant women through antenatal care services and other routine contacts; (3) vaccination campaigns with TTCV targeting all women of reproductive age in high-risk areas; and (4) strengthening surveillance to identify women at risk, reasons for the risk, and potential clustering.

In the 1980s, over 1 million deaths every year were attributable to tetanus, with an estimated 787,000 deaths in 1988 from NT alone. Recognizing, the substantial burden of NT in developing countries, the 42nd World Health Assembly adopted a resolution to eliminate NT by 1995, through the increased availability of TTCV, clean deliveries and improved surveillance. The elimination of NT was defined as <1 case per 1000 live births in every district. In the early 1990s, it was estimated that maternal tetanus accounted for about 5% of maternal mortality, or 15,000– 30,000 deaths every year. As a result, in 1999, the elimination of maternal tetanus (MT) was added to the goals of the elimination programme for neonatal tetanus, and the programme title was changed to Maternal and Neonatal Tetanus Elimination (MNTE). Since NT is linked to the immunization status of mothers, elimination of NT has been adopted as a proxy for the elimination of MT *(2)*.

The implementation of various initiatives under the MNTE programme led to a significant reduction in cases of MNT. These initiatives included promotion of maternal tetanus immunization along with safe delivery and avoidance of unsafe abortion and umbilical cord care practices. According to WHO estimates, substantial progress has been made in the past decade in reducing neonatal incidence and deaths from an estimated 787,000 deaths in 1988 to 34,000 in 2015, a reduction of about 96 per cent *(3)*.

Maternal and Neonatal tetanus elimination in India *(2)*

A mix of strategies has been implemented in India to facilitate clean deliveries by training auxiliary nurse, midwives and other cadres of trained birth attendants who work at the village level, in addition to increasing routine TT protection. The Indian Ministry of Health & Family Welfare

in collaboration with WHO India, UNICEF and other partners, designed and implemented the following strategies to control neonatal tetanus :

- acceleration of TT immunization coverage through the WHO-recommended high risk approach, and strengthening routine TT immunization of pregnant women, and supplemental TT immunization activities targeting women of child-bearing age in high-risk districts;
- systematic vaccination of pregnant women attending antenatal care (ANC) with TT vaccine;
- promotion of institutional deliveries focusing on poor pregnant women with an institutional stay for 48 hours, through training of traditional birth attendants;
- intensive communication programme targeting communities to reduce harmful cord care practices (promotion of the 5 cleans – hand, delivery surfaces, instruments for cutting the umbilical cord, cord tie and caring of the umbilical cord); and
- distribution of disposable delivery kits to skilled birth attendants for each pregnancy.

The launch of the national rural health mission (NRHM) in 2005 also helped to strengthen these initiatives. Strategies to improve clean delivery included the innovative Janani Suraksha Yojana (JSY), a conditional cash transfer scheme, to encourage women to give birth in a health facility. Other interventions to improve TT protection and reduce maternal and neonatal mortality under the NRHM included:

- Integrating and extending outreach services through village health and nutrition days, including vaccination of children, adolescents and pregnant women with TT containing vaccines;
- Intense 3–week refresher training for all skilled birth attendants;
- Operationalization of selected sub-centres and community health centres to provide 24–hour services 7 days per week for obstetric and neonatal care;
- Strengthening of facility-based neonatal care by setting up newborn care corners in health facilities where deliveries take place, special neonatal care units in district hospitals and new born stabilization units in first referral units for the care of sick neonates;
- Engagement of more than 896,411 accredited social health activists (ASHA) to generate demand and facilitate use of health-care services by communities and poor women.

As a result, safe deliveries rose from 52 per cent in 2007 to 76 per cent in 2009. Janani Shishu Suraksha Karyakram, launched in 2011 also helped. India's successful implementation of a mix of strategies, and experience and knowledge gained from polio eradication efforts has led to a substantial decline in the number of MNT cases in the country. As of December 2014, 30 of the 36 states/UTs were validated as having achieved MNT elimination and in May 2015, India was officially certified as achieving maternal and neonatal elimination *(4)*.

Epidemiological determinants

Agent factors

(a) AGENT : *C. tetani* is a gram–positive, anaerobic, spore–bearing organism. The spores are terminal and give the organism a drum-stick appearance. The spores are highly resistant to a number of injurious agents, including boiling, phenol, cresol and autoclaving for 15 minutes at 120 deg. Centigrade *(5)*. They germinate under anaerobic conditions and produce a potent exotoxin ("tetanospasmin"). The spores are best destroyed by steam under pressure at 120 deg. C for 20 minutes or by gamma irradiation. (b) RESERVOIR OF INFECTION : The natural habitat of the organism is soil and dust. The bacilli are found in the intestine of many herbivorous animals, e.g., cattle, horses, goats and sheep and are excreted in their faeces. The spores survive for years in nature. The bacilli may be found frequently in the intestine of man without causing ill-effects. The spores are blown about in dust and may occur in a wide variety of situations, including operation theatres. (c) EXOTOXIN : Tetanus bacilli produce a soluble exotoxin. It has an astounding lethal toxicity, exceeded only by botulinum toxin. The lethal dose for a 70 kg man is about 0.1 mg *(6)*. The toxin acts on 4 areas of the nervous system : (a) the motor end plates in skeletal system (b) the spinal cord (c) the brain, and (d) the sympathetic system *(5)*. Its principal action is to block inhibition of spinal reflexes *(7)*. (d) PERIOD OF COMMUNICABILITY : None. Not transmitted from person to person.

Host factors

(a) AGE : Commonly, tetanus is a disease of the active age (5 to 40 years). This period predisposes to all kinds of trauma and therefore, the risk of acquiring the disease is pretty high. Tetanus occurring in the new-born is known as "neonatal tetanus". Infants typically contact the disease at birth, when delivered in non–aseptic conditions – especially when the umbilical cord is cut with unclean instruments or when the umbilical stump is dressed with ashes, soil or cowdung. (b) SEX : Although a higher incidence is found in males, females are more exposed to the risk of tetanus, especially during delivery or abortion leading to "puerperal tetanus". Males appear to be more sensitive to tetanus toxin than females *(8)*. (c) OCCUPATION : Agricultural workers are at special risk because of their contact with soil. (d) RURAL–URBAN DIFFERENCES : The incidence of tetanus is much lower in urban than in rural areas. Within the urban areas, there may be vast differences in the incidence of tetanus. For example, it was observed in one town that tetanus was more frequent on the outskirts where floors were earthen and animals lived close to human beings, than in the centre of the town where there were paved and mosaic floors. (e) IMMUNITY : No age is immune unless protected by previous immunization. The immunity resulting from 2 injections of tetanus toxoid is highly effective and lasts for several years. As a general rule, patients who have recovered from tetanus must be actively immunized, because the amounts of toxin responsible for the disease in man do not stimulate protective immunity *(7)*. Immunity lasting for a few weeks (less than 6 months) can be transferred to the baby, if the mother is immunized during pregnancy or if she already has a high level of immunity at the time she becomes pregnant. Tetanus is one disease in which herd immunity does not protect the individual.

Environmental and social factors

Tetanus is a positive environmental hazard *(9)*. Its occurrence depends upon man's physical and ecological surroundings – the soil, agriculture, animal husbandry – and

not on the presence or absence of infection in the population. The environmental factors are compounded by social factors such as unhygienic customs and habits (e.g., application of dust or animal dung to wounds); unhygienic delivery practices (e.g., using unsterilized instruments for cutting the umbilical cord); ignorance of infection and lack of primary health care services. In the developed countries, urbanization, industrialization and mechanization of agriculture have interfered with the normal process of distribution of *C. tetani* and have reduced the morbidity rate, as has occurred, for example in UK, USA and Germany during the last 40 years *(8)*.

Mode of transmission

Infection is acquired by contamination of wounds with tetanus spores. The range of injuries and accidents which may lead to tetanus – comprise a trivial pin prick, skin abrasion, puncture wounds, burns, human bites, animal bites and stings, unsterile surgery, intra-uterine death, bowel surgery, dental extractions, injections, unsterile division of umbilical cord, compound fractures, otitis media, chronic skin ulcers, eye infections, and gangrenous limbs *(7)*.

The sequence of events are : introduction of spores, germination and elaboration of the exotoxin and binding to the receptor.

Incubation period

The incubation period is usually 6 to 10 days. However, it may be as short as one day or as long as several months *(5)*. Long incubation is probably explained by the spores lying dormant in the wounds. Incubation is also prolonged by prophylaxis *(7)*.

Types of tetanus

(a) TRAUMATIC : Trauma is a major and important cause of tetanus. Sometimes tetanus may result from most trivial or even unnoticed wounds. (b) PUERPERAL : Tetanus follows abortion more frequently than a normal labour. A post–abortal uterus is a favourable site for the germination of tetanus spores. (c) OTOGENIC : Ear may be a rare portal of entry. Foreign bodies such as infected pencils, matches, and beads may introduce the infection. Otogenic tetanus is a paediatric problem, but cases, may occur in adults also. (d) IDIOPATHIC : In these cases there is no definite history of sustaining an injury. Some consider it to be the result of microscopic trauma. Others hold the view that it is due to the absorption of tetanus toxin from the intestinal tract. A third view is that the tetanus spores may be inhaled and may start the infection. (e) TETANUS NEONATORUM : In many countries, neonatal tetanus kills about 85 per cent of those afflicted. The common cause is infection of the umbilical stump after birth, the first symptom being seen about the 7th day. Therefore, tetanus is known as "8th day disease" in Punjab *(6)*. In any country where hygiene is poor, neonatal tetanus may be common.

PREVENTION

1. Active immunization *(10, 11, 12)*

Tetanus is best prevented by active immunization with tetanus toxoid. It stimulates the production of the protective antitoxin. The aim should be to vaccinate the entire community and ensure a protective level of antitoxin approximately 0.01 IU/ml serum throughout life. All persons should be immunized regardless of age.

Two preparations are available for active immunization

a. *Combined vaccine – DPT*
b. *Monovalent vaccines*
   i) Plain or fluid (formal) toxoid
   ii) Tetanus vaccine, adsorbed (PTAP, APT)

a. COMBINED VACCINE

Tetanus vaccine is offered routinely to infants (Expanded Immunization Programme) in combination with diphtheria vaccine and killed *B. pertussis* organisms as DPT vaccine. According to the National Immunization Schedule (see page 135), the primary course of immunization consists of 3 doses of DPT, at intervals of 4–8 weeks, starting at 6 weeks of age, followed by a booster at 18 months of age, and a second booster at 5–6 years of age and a third booster (Only TT) after 10 years of age.

Pentavalent vaccine: At present pentavalent vaccine is being given at 6th, 10th and 14th weeks of age instead of DPT vaccine. The DPT vaccine is used for booster dose.

b. MONOVALENT VACCINES

Purified tetanus toxoid (adsorbed) has largely supplanted plain toxoid because it stimulates a higher and longer–lasting immunity response than plain toxoid *(13)*. However, the latter may be employed for purposes of booster injection when rapid protection is indicated.

A primary course of immunization consists of two doses of tetanus toxoid adsorbed (each dose 0.5 ml, injected into the arm) given at intervals of 1–2 months. The longer the intervals between the two doses, the better is the immune response. The first booster dose (the third in order) should be given a year after the initial two doses. The opinion was expressed that no more than one additional booster dose (a total of 4 doses altogether) given 5 years after the third dose is required in adults (including pregnant women) in developing countries *(14)*. Frequent boosters must be avoided.

Reactions following the injections of tetanus toxoid are uncommon. They are less likely to occur with a refined and adsorbed toxoid such as Purified Tetanus Toxoid (Aluminium Phosphate Adsorbed). However, in persons giving history of allergy usual precautions should be observed. Purified tetanus toxoid should be stored between 2 and 8 deg. C. It must not be allowed to freeze at any time.

2. Passive immunization *(10, 11)*

Temporary protection against tetanus can be provided by an injection of human tetanus hyperimmunoglobulin (TIG) or ATS. (i) HUMAN TETANUS HYPERIMMUNOGLOBULIN : It is the best prophylactic to use. The dose for all ages is 250 IU. It does not cause serum reactions. It gives a longer passive protection upto 30 days or more compared with 7–10 days for horse ATS. Human tetanus Ig is now available in India – it is produced by the Serum Institute of India, Pune. (ii) ATS (EQUINE) : If human antitoxin is not available, equine antitoxin (anti-tetanus serum or ATS) should be used. The standard dose is 1500 IU, injected subcutaneously after sensitivity testing. ATS gives passive protection for about 7–10 days. Being a foreign protein, ATS is rapidly excreted from the body and there may be very little antibody

at the end of 2 weeks. Because of this drawback, ATS may not cover the tetanus incubation period in all cases. Horse ATS has other disadvantages too – (i) It causes sensitivity reaction in many people because it contains foreign proteins. A person receiving ATS for the first time may tolerate it well, but there is a possibility that subsequent injections of horse serum may lead to allergic reactions varying in severity from rash to anaphylactic shock. It is estimated that the incidence of serious systemic reactions to ATS is 5 to 10 per cent of the persons who receive it. It is well to remember that local tests for sensitivity are unreliable as to general sensitivity to horse serum. (ii) Another drawback of ATS is that it stimulates the formation of antibodies to it and hence a person who has once received ATS tends to rapidly eliminate subsequent doses. As such the value of second and subsequent doses of ATS becomes questionable. In practice, therefore, ATS becomes less and less reliable as a prophylactic. These drawbacks have been responsible for the growing unpopularity of ATS as an agent for immediate protection against tetanus.

3. Active and passive immunization

Simultaneous active and passive immunization is widely carried out in non-immune persons. The patient is given 1500 units of ATS or 250 units of Human Ig in one arm, and 0.5 ml of adsorbed tetanus toxoid (PTAP or APT) into the other arm or gluteal region. This should be followed 6 weeks later by another dose of 0.5 ml of tetanus toxoid, and a third dose one year later. The purpose of antitoxin is for immediate temporary protection, and the purpose of toxoid is for long–lasting protection.

4. Antibiotics

Active immunization with tetanus toxoid is the ideal method of tetanus prophylaxis, but it is of no immediate avail to a person who is non-immune and has sustained injury. ATS as an agent for immediate protection against tetanus has its drawbacks. For these reasons, antibiotics are indicated in the prophylaxis against tetanus. A single intramuscular injection of 1.2 mega units of a long–acting penicillin (e.g., benzathine penicillin) will provide a sustained concentration of the drug for 3 to 4 weeks, which is sufficient to kill any vegetative forms of tetanus bacilli that may emerge from the sporulating stage. Penicillin has no effect on tetanus spores. For patients who are sensitive to penicillin, a 7–day course of erythromycin estolate 500 mg 6–hourly by mouth will kill vegetative forms of *C. tetani* but not spores. Antibiotics should be given as soon as possible after an injury, before a lethal dose of toxin is produced in the wound, which may be as soon as 6 hours after injury. Antibiotic prophylaxis should not be relied upon for patients seen later than 6 hours after injury. Moreover, it is not certain whether the antibiotic can reach the bacilli, if there is dead tissue present in the wound. Therefore, antibiotic alone is ineffective in the prevention of tetanus; it is not a substitute to immunization.

Prevention of neonatal tetanus

Neonatal tetanus is well controlled in some industrialized countries through clean delivery practices alone. Over the last decade, most programmes in developing countries have concentrated on training the traditional birth attendants, providing home delivery kits and educating pregnant women about the "five cleans" – clean hands, clean delivery surface and clean cord care i.e., clean blade for cutting the cord, clean tie for the cord and no application on the cord stump. Operational research has shown that training of birth attendants alone can reduce death due to neonatal tetanus by 90 per cent *(15)*.

Tetanus toxoid will protect both the mother and her child. In **unimmunized** pregnant women, two doses of tetanus toxoid should be given, the first as early as possible during pregnancy and the second at least a month later and at least 3 weeks before delivery. According to the National Immunization Schedule (see page 135), these doses may be given between 16–36 weeks of pregnancy, allowing an interval of 1–2 months between the 2 doses. In previously **immunized** pregnant women, a booster dose is considered sufficient. There is no need for a booster at every consecutive pregnancy, because of the risk of hyper-immunization and side-effects.

In areas where the incidence of neonatal tetanus is high, the primary 2–dose course can be extended to all women of child-bearing age, particularly if the present coverage of antenatal care is low.

In developing countries, the majority of pregnant women are not seen antenatally. Since a pregnant woman coming for an antenatal visit may in fact never return again, immunization should be given regardless of the month of pregnancy as there is no evidence to suggest that tetanus toxoids are dangerous or harmful to the foetus. The golden rule is that no pregnant mother should be denied even one dose of tetanus toxoid if she is seen late in pregnancy.

The infants born to the mothers who have not previously received 2–doses of tetanus toxoid are exposed to the risk of neonatal tetanus. They can be protected by injection of antitoxin (heterologous serum, 750 IU), if it is administered within 6 hours of birth.

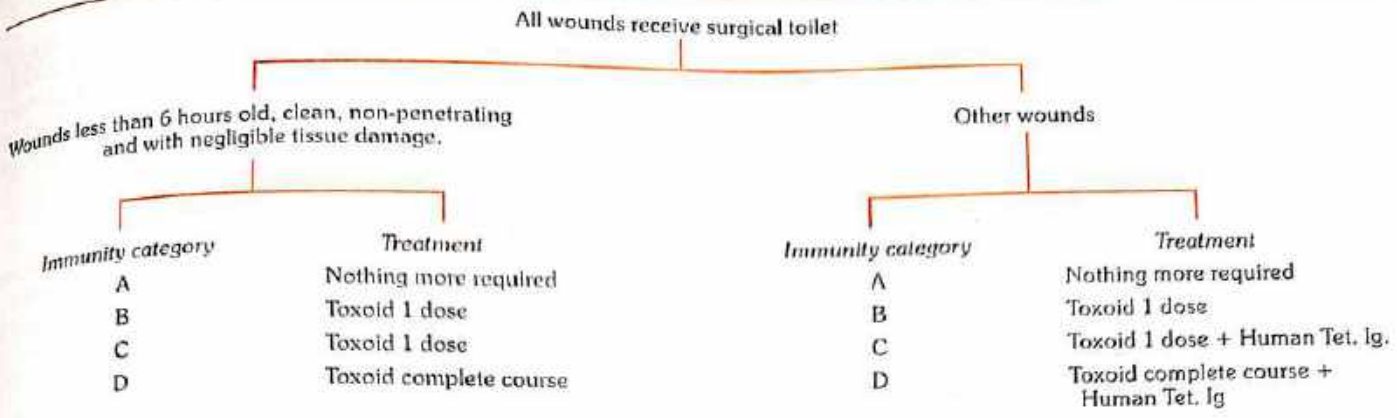
Prevention of tetanus after injury *(12)*

All wounds must be thoroughly cleaned soon after injury – removal of foreign bodies, soil, dust, necrotic tissue. This procedure will abolish anaerobic conditions which favour germination of tetanus spores.

A useful scheme for the prevention of tetanus in the wounded is given in Fig. 1.

When ATS is given, adrenaline solution 1 in 1000 for intramuscular injection in the dosage of 0.5 to 1 ml and hydrocortisone 100 mg for intravenous injection must be kept available in case of a generalized anaphylactoid reaction *(11)*. A test dose of ATS (0.1 ml in a tuberculin syringe) should be given subcutaneously (not intradermally) and the patient observed carefully (not casually) at least for half an hour for any evidence of general reaction (not only local reaction), e.g., alteration in pulse, fall in blood pressure, dyspnoea and distress. If there is reaction, the rest of the antitoxin should be given in gradually increasing fractions after treatment with adrenaline. In patients with history of allergy, e.g., asthma, eczema, food or drug idiosyncracy, the above test should be preceded by a dose of 0.05 ml of 1 in 10 dilution of the ATS. If there is reaction, ATS should be withheld.

Lastly, it should be pointed out that tetanus may occasionally occur inspite of active or passive immunization or both. Nevertheless, the aim is to provide as much protection as possible in the light of our present scientific knowledge.



A = Has had a complete course of toxoid or a booster dose within the past 5 years.
B = Has had a complete course of toxoid or a booster dose more than 5 years ago and less than 10 years ago.
C = Has had a complete course of toxoid or a booster dose more than 10 years ago.
D = Has not had a complete course of toxoid or immunity status is unknown.

FIG. 1
Recommendations for prevention of tetanus in the wounded

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LEPROSY

Leprosy (Hansen's disease) is a chronic infectious disease caused by *M. leprae*. It affects mainly the peripheral nerves. It also affects the skin, muscles, eyes, bones, testes and internal organs. The disease manifests itself in two polar forms, namely the lepromatous leprosy and tuberculoid leprosy, lying at the two ends of a long spectrum of the disease. Between these two polar types occur the borderline and indeterminate forms depending upon the host response to infection.

Leprosy is clinically characterized by one or more of the following cardinal features :

a. hypopigmented patches
b. partial or total loss of cutaneous sensation in the affected areas (the earliest sensation to be affected is usually light touch)
c. presence of thickened nerves, and
d. presence of acid–fast bacilli in the skin or nasal smears.

The signs of advanced disease are striking : presence of nodules or lumps especially in the skin of the face and ears; plantar ulcers; loss of fingers or toes, nasal depression, foot-drop, claw toes and other deformities.

Problem statement

WORLD

In 1991, WHO member states resolved to decrease the level of leprosy in the world by over 90 per cent. This has now been accomplished, and the overall target for the global elimination of leprosy as a public health problem has been attained *(1)*. The fall in prevalence rate is largely explained by an improvement in the management of cases, very low rates of relapse, high cure rates, absence of drug resistance and shorter duration of treatment with MDT *(2)*.

The achievement can be summarized as follows *(3)* :

(1) Over the past 20 years, more than 16 million leprosy patients have been cured.

(2) The prevalence rate of the disease has dropped from 21.1 cases per 10,000 population in 1985 to 16.9 per million population by end of 2020.

(3) The global burden of leprosy has declined dramatically from 5.2 million cases in 1985 to 165,459 cases at the end of 2020.

(4) The new case detection rate was 21.8 per million population at the end of 2022. The ten year trend shows a slow decrease in detection rate of new cases globally.

(5) Currently the emphasis is on 23 countries of global priority.

WHO has been regularly collecting data on several indicators from various WHO regions and member states. The indicators and reported data is as follows *(3)* :

1. 174,087 new cases of leprosy were detected during 2022. As in previous years, SEAR accounted for 71.4 per

cent of the global leprosy burden, where India, Brazil and Indonesia contributed 78.1 per cent of the new leprosy cases globally.

2. Among the new cases detected in 2022, the proportion of multibacillary cases of leprosy was about 68.9 per cent.
3. The proportion of female cases among newly detected cases in 2022 was 38.9 per cent (67,657 cases).
4. The proportion of children below 15 years of age was 5.1 per cent (10,302 cases).
5. The number of new cases with grade-2 disabilities were 9,554 (5.5 per cent) i.e. 1.2 case per million population.
6. The number of new child cases with grade-2 disabilities were 272.
7. The number of relapse cases in 2022 were 3,346.
8. The number of retreatment cases were 13,567.
9. The new case detection rate was 21.8 per million population.
10. Countries have been working to repeal laws that allow discrimination on the basis of leprosy.
11. Globally, 54 countries reported 0 new cases. Furthermore, 17 countries have reported 0 new cases in children for the past 5 years. Given the progress in the epidemiological situation of leprosy, WHO has developed the Leprosy Elimination Framework, reflecting a paradigm shift from control to elimination, guiding countries towards the goal of zero leprosy.

The 2023 WHO technical guidance on interrupting transmission and eliminating leprosy disease defines interruption of transmission as an epidemiological state in a country or area in which there is no more local transmission of *M. leprae*, evidenced by zero new autochthonous cases among children for at least 5 consecutive years. Elimination of disease is defined as no new autochthonous case in the past 3 years (and no child cases in the past 5 consecutive years). This achievement is followed by a period of post-elimination surveillance, in which sporadic cases may still be reported owing to the long incubation period of leprosy. Elimination of leprosy disease is verified in a bottom-up approach, from subnational level upwards. Given the new paradigm, reports of 0 cases are essential, including at subnational level *(3)*.

Significant acceleration of the current gradual decrease in leprosy cases will require optimal use of existing tools, such as mapping of endemic pockets, active case finding, including contact tracing, scaling up of preventive chemotherapy and also new tools such as diagnostic tests, newer drugs and a vaccine. Integrated control and management approaches, such as with other skin NTDs, present opportunities to overcome programmatic challenges by sharing resources and strengthening surveillance of leprosy. WHO encourages research on new drugs, shorter regimens, preventive tools and newer approaches to accelerate reduction of the incidence of leprosy *(3)*. The WHO has evolved the Global Strategy for further reducing the leprosy burden. The recent most is Global Leprosy Strategy 2021–2030 "Towards Zero Leprosy".

The Global Leprosy Strategy 2021–2030 "Towards Zero Leprosy" *(4)*

The new WHO global leprosy strategy, entitled "Towards Zero Leprosy" was released on 15th April 2021. This is one of the disease-specific strategy of the WHO road map for neglected tropical diseases 2021–2030 (NTDs 2021–2030). The strategy presents the basic direction, goals, challenges and strategic pillars at a global level. National NTD and leprosy programmes are urged to adopt it and to adopt its strategic pillars to their country context.

Vision, goal and targets

'Towards Zero Leprosy' is defined in the strategy's long term vision as zero infection and disease, zero disability, zero stigma and discrimination. The medium-term goal is the elimination of leprosy, defined as interruption of transmission. The four high level 2030 milestones and targets are as follows :

Indicator	2019 (reported)	2020 (projected)	2023 (milestone)	2025 (milestone)	2030 (target)
Number of countries with zero new autochthonous cases	34 (18%)	50 (26%)	75 (39%)	95 (49%)	120 (62%)
Number of new cases detected (disaggregated by sex and age)	202,256	184,000	148,000	123,500	62,500
Rate (per million population) of new cases with grade-2 disability	1.40	1.30	0.92	0.68	0.12
Rate (per million children) of new child cases with leprosy	7.83	7.81	5.66	4.24	0.77

Interruption of transmission in a country or a sub-national area is defined as no local transmission of *M. leprae* evidenced by zero occurrence of new indegenous (autochthonous) case among children ≤15 years for at least 5 consecutive years. Elimination of leprosy is achieved when country or a sub-national area reports zero new indigenous leprosy cases for at least 3 consecutive years after interruption of transmission *(4)*.

Strategic pillars *(5)*

To achieve these targets, the strategy incorporates four strategic pillars, each with a number of key components and a set of relevant indicators. The strategic pillars are :

1. Implement integrated, country-owned zero leprosy road-maps in all endemic countries.
2. Scale up leprosy prevention alongside integrated active case detection.
3. Manage leprosy and its complications, and prevent new disability.
4. Combat stigma and ensure human rights are respected.

INDIA

Leprosy is widely prevalent in India. Although the disease is present throughout the country, the distribution is uneven. After introduction of MDT in the country, the recorded leprosy case load has come down from 57.6 cases per 10,000 population in 1981 to less than one case per 10,000 population at national level in December 2005, and the country achieved the goal of leprosy elimination at national level.

Based on the reports received from the states/UTs, the leprosy situation in the country is as follows *(5)* :

Year	PR	% age of Child Cases	% age of MB	G2D Cases	Child G2D Cases (Among Total G2D Cases)	G2D%	G2D per million	ANC DR/ 100000	G1D Cases	Child G1D Cases (Among Total G1D Cases)	Reaction Cases from RFT	Relapse Cases
2017-18	0.67	8.15	50.88	4552	85	3.61	3.34	9.27	5188	NA	NA	457
2018-19	0.62	7.67	52.28	3666	84	3.05	2.65	8.69	4894	NA	8078	436
2019-20	0.57	6.87	54.28	2761	63	2.41	1.96	8.13	5076	NA	8014	505
2020-21	0.40	5.76	58.11	1572	35	2.41	1.10	4.56	3256	33	4340	498
2021-22	0.45	5.45	60.70	1863	41	2.47	1.36	5.52	3970	45	4223	510

PR – Prevalence rate, MB – Multibacillary leprosy cases, G2D cases – Grade 2 disability cases,
ANCDR – Annual new case detection rate, G1D cases – Grade one disability cases

Source : *(5)*

A total of 23 States/UTs have sustained the elimination status (PR <1 per 10,000 population) at state level since 2009–10 until 2021–22. Only Chhattisgarh and D & N Haveli are yet to achieve leprosy elimination, 22 States/UTs have ANCDR less than 10 per lakh population since 2009–10 to 2021–22. Data indicates major contributing states for average new leprosy cases per year are Uttar Pradesh (20,492), followed by Bihar (17,471) and Maharashtra (15,812), whereas, lowest being Lakshadweep which reported an average of 6 new leprosy cases per year *(5)*. Number of districts with G2D%, more than 2 were 221 and number of block were 794, in the year 2020–2021.

Epidemiological determinants

Agent factors

(a) AGENT : Leprosy is caused by *M. leprae*. They are acid–fast and occur in the human host both intracellularly and extracellularly. They occur characteristically in clumps or bundles (called globi). They have an affinity for Schwann cells and cells of the reticulo–endothelial system. They remain dormant in various sites and cause relapse. The bacterial load is the highest in the lepromatous cases. As many as 2 to 7 billion were estimated in one gram of leproma *(6)*. Numerous antigens (more than 20) have been detected in *M. leprae* by electrophoretic techniques. Some of these are shared by those of pathogenic and non–pathogenic mycobacteria, e.g., BCG, *M. smegmatis, M. vaccae, M. tuberculosis*, etc. Most interesting of these antigens is the phenolic glycolipid (PGL) which may be the specific *M. leprae* antigen. Recent years have witnessed the successful transmission of *M. leprae* to some experimental animals. Currently large quantities of *M. leprae* are being produced by multiplication in the 9–banded armadillo and nude mouse. Despite repeated claims, *M. leprae* has not yet been conclusively shown to grow in artificial medium *(7)*. It is perhaps mainly for this reason that progress in research has lagged behind than that of many other diseases.

(b) SOURCE OF INFECTION : It is generally agreed that multibacillary cases (lepromatous and borderline lepromatous cases) are the most important source of infection in the community. The inapparent infections are also source of infection. The role of individuals with tuberculoid forms of the disease as sources of infection is not clear. The current view is that all patients with "active leprosy" must be considered infectious *(8)*. Until recently man was considered to be the only host and source of infection. There is now evidence that natural infections with *M. leprae* are present in wild animals, e.g., armadillos, mangabey monkeys and chimpanzees. It is not yet known if leprosy in wild animals is a threat to public health.

(c) PORTAL OF EXIT : It is widely accepted that the nose is a major portal of exit. Lepromatous cases harbour millions of *M. leprae* in their nasal mucosa which are discharged when they sneeze or blow the nose. The bacilli can also exit through ulcerated or broken skin of bacteriologically positive cases of leprosy *(9)*.

(d) INFECTIVITY : Leprosy is a highly infectious disease but of low pathogenicity *(10)*. It is claimed that an infectious patient can be rendered non-infectious by treatment with dapsone for about 90 days *(11)* or with rifampicin for 3 weeks *(13)*. Local application of rifampicin (drops or spray) might destroy all the bacilli within 8 days *(12)*.

(e) ATTACK RATES : Among household contacts of lepromatous cases, a varying proportion – 4.4 per cent to 12 per cent – is expected to show signs of leprosy within 5 years *(12)*. This occurs despite treatment of the index case, most, if not all, cases having been infectious for long periods, before treatment is sought.

Host factors

(a) AGE : Infection can take place at any time depending upon the opportunities for exposure. Incidence rates generally rise to a peak between 20 and 30 years of age and then fall *(13)*. In areas where leprosy is rare, the first contact may not take place early in life and consequently, the disease may appear late. However, the presence of leprosy in child population is of considerable epidemiological importance. A high prevalence of infection among children means that the disease is active and spreading.

(b) SEX : Both the incidence and prevalence of leprosy appear to be higher in males than in females in most regions of the world. Sex difference is found least in children below 15 years, and more marked among adults; more marked among lepromatous cases than among non-lepromatous cases. The excess of cases in males has sometimes been attributed to their greater mobility and increased opportunities for contact in many populations.

(c) MIGRATION : In India leprosy was considered to be mostly a rural problem. However, because of the movement of population from rural to urban areas, leprosy is creating a problem in the urban areas also *(14)*.

(d) THE PREVALENCE POOL *(15)*: The prevalence pool of leprosy in a population in general is in a constant flux resulting from inflow and outflow. The inflow is contributed by the occurrence of new cases, relapse of cured cases, and immigration of cases. The outflow is mainly through cure or inactivation of cases, death of cases, and emigration of cases. Of the various factors that influence the prevalence pool, the importance of inactivation of disease and mortality are less well recognized.

(e) INACTIVATION OF DISEASE *(15)* : Where leprosy treatment facilities exist, inactivation or cure due to specific treatment is an important mode of elimination of cases from the prevalence pool. Even in the absence of specific treatment, a majority of patients, particularly of the tuberculoid and indeterminate types, tend to get cured spontaneously. An earlier study in India had shown that over a period of 20 years, the extent of spontaneous regression among children with tuberculoid leprosy was about 90%. A study in Culion Island in the Philippines showed that among children self-healing occurred in 77.7% of cases (Lara & Nolasco, 1956). A later study in South India involving long-term follow-up of a high endemic population showed that among newly detected tuberculoid cases of all ages and both sexes, the rate of inactivation was 10.9% per year, the bulk of inactivation in the study being spontaneous (Noordeen, 1975).

(f) IMMUNITY : It is a well-established fact that only a few persons exposed to infection develop the disease. A large proportion of early lesions that occur in leprosy heal spontaneously. Such abortive and self-healing lesions suggest immunity acquired through such lesions. Subclinical infections are far more common than was thought earlier; they are also believed to contribute to active immunity. A certain degree of immunity is also probable through infections with other related mycobacteria *(16)*.

It is now recognized that cell-mediated immunity (CMI) is responsible for resistance to infection with *M. leprae*. In lepromatous leprosy, there is a complete breakdown of CMI; in these cases the lepromin test is negative. CMI does not however, exclude the participation of humoral response. Antibodies have been demonstrated throughout the spectrum of leprosy; they are more pronounced at the lepromatous end. Similarly an increase of immunoglobulins of IgG and IgM classes is noted towards the lepromatous end *(17)*. Leprosy workers have found that the anergy of lepromatous leprosy is due to suppression of T cell production of interleukin–2 (T–cell growth factor). This is normally secreted by activated T cells to make other T cells proliferate. If exogenous interleukin–2 is added, the process may be reversed. However, further studies are needed to find out whether administration of IL–2 would benefit the lepromatous patient *(17)*.

(g) GENETIC FACTORS : There is now evidence that human lymphocyte antigen (HLA) linked genes influence the type of immune response that develops *(7)*.

Environmental factors

The risk of transmission is predominantly controlled by environmental factors *(11)* : (a) the presence of infectious cases in that environment. There is evidence that humidity favours the survival of *M. leprae* in the environment. *M. leprae* can remain viable in dried nasal secretions for at least 9 days and in moist soil at room temperature for 46 days *(7)*, (b) overcrowding and lack of ventilation within households.

Mode of transmission

The mode of transmission of leprosy has not been established with certainty. The following theories are frequently debated :

(A) DROPLET INFECTION : There is more and more evidence that leprosy may be transmitted *via* aerosols containing *M. leprae* (droplet infection). With the realization of the importance of the nose as a portal of exit, there has been increased emphasis on the respiratory tract as the portal of entry. The possibility of this route of transmission is based on (a) the inability of the organisms to be found on the surface of the skin; (b) the demonstration of a large number of organisms in the nasal discharge; (c) the high proportion of morphologically intact bacilli in the nasal secretions; and (d) the evidence that *M. leprae* could survive outside the human host for several hours or days *(15)*.

(B) CONTACT TRANSMISSION : Numerous studies indicate that leprosy is transmitted from person-to-person by close contact between an infectious patient and a healthy but susceptible person. This contact may be direct or indirect (e.g., contact with soil, and fomites such as contaminated clothes and linen).

Now that it is known that leprosy bacilli can survive for long periods of time in the soil under favourable environmental conditions, the hypothesis that leprosy can be transmitted by indirect contact has been strengthened *(18)*. In epidemiological studies, the first lesions were found in feet and legs of patients from hilly areas in India, where injury to the skin is common. In the Philippines 91 per cent of the first lesions were seen in extremities open to injury *(14)*. These observations lend support to indirect transmission. Although contact transmission has been a long-favoured hypothesis, leprologists opine that skin–to–skin contact is really not necessary to acquire infection, and that the disease is transmissible with far less than intimate contact *(8, 10)*.

(C) OTHER ROUTES : Bacilli may also be transmitted by insect vectors, or by tattooing needles. These transmission channels cannot be ruled out *(18)*. However, there is no evidence that any of these transmission routes is important in nature *(7)*.

Incubation period

Leprosy has a long incubation period, an average of 3 to 5 years or more. Symptoms can take as long as 20 years to appear. Failure to recognize early symptoms or signs may contribute to an assumed prolonged incubation period in some patients. Some leprologists prefer the term "latent period" to incubation period because of the long duration of the incubation period.

Knowledge of incubation period of relapses is also essential, as this will define the duration of surveillance after treatment has been stopped.

Pathogenesis of leprosy *(13)*

Onset of leprosy is insidious. It affects nerves, skin and the eyes, it may also affect mucosa (mouth, nose, pharynx), testis, kidney, voluntary/smooth muscles, reticulo-endothelial system and vascular endothelium.

Bacilli enter the body usually through respiratory system. It has low pathogenicity, only a small proportion of infected people develop signs of the disease. Though infected, majority of the population do not develop the disease. After entering the body, bacilli migrate towards the neural tissue and enter Schwann cells. Bacteria can also be found in macrophages, muscles cells and endothelial cells of blood vessels.

After entering Schwann cells or macrophages, fate of the bacterium depends on the resistance of the infected individual towards the organism. Bacilli start multiplying slowly (about 12–14 days for one bacterium to divide into two) within the cells, get released from the destroyed cells and enter other unaffected cells. During this state, person remains free from signs and symptoms of leprosy.

As the bacilli multiply, bacterial load increases in the body and infection is recognized by the immunological system. Lymphocytes and histiocytes (macrophages) invade the infected tissue. At this stage, clinical manifestation may appear as involvement of nerves with impairment of sensation and/or skin patch. If it is not diagnosed and treated in the early stages, further progress of the disease is determined by the strength of the patient's immune response.

Specific and effective cell mediated immunity (CMI) provides protection to a person against leprosy. When specific CMI is effective in elimination/controlling the infection in the body, lesions heal spontaneously or it produces pauci-bacillary (PB) type of leprosy. If CMI is deficient; the disease spreads uncontrolled and produces multi bacillary (MB) leprosy with multiple system involvement. Sometimes, the immune response is abruptly altered, either following treatment (MDT) or due to improvement of immunological status, which results in the inflammation of skin or nerves and even other tissues, called as Lepra reaction leading to temporary and permanent disabilities/deformities. Pathogenesis of leprosy is summarized in Fig. 1.

Classification

Leprosy is a disease bedevilled by classifications, e.g., the Madrid classification *(19)*, Ridley–Jopling classification *(20)*, the Indian classification *(21)*, etc. These classifications are based on clinical, bacteriological, immunological and histological status of patients.

The Indian and Madrid classification systems are the most widely used in field leprosy programmes; they are not essentially different, as the following comparison shows :

Indian classification	*Madrid classification*
indeterminate type	indeterminate
tuberculoid type	tuberculoid; flat; raised
borderline type	borderline
lepromatous type	lepromatous
pure neuritic type	

The Indian classification has an additional form, the pure neuritic in which no skin lesions exist.

The classification system of Ridley and Jopling *(22)* divides leprosy cases into five groups according to their position on an immuno-histological scale : tuberculoid (TT), borderline tuberculoid (BL), borderline (BB), borderline lepromatous (BL) and lepromatous (LL). The neuritic type of leprosy does not find a place in the Ridley and Jopling classification. This classification can be used only when full research facilities are available.

Clinical classification for control programme

After making a diagnosis of leprosy, one should group the patient based on certain characteristics. This is important because, it helps in selecting the correct combination of drugs for a given patient.

Criteria for classification (13)

Characteristics	PB (Pauci-bacillary)	MB (Multi-bacillary)
Skin lesions	1–5 lesions	6 and above
Peripheral nerve	No nerve / only one nerve involvement	More than one nerve involvement
Skin smear	Negative at all sites	Positive at any site

Diagnosis of leprosy *(13)*

A case of leprosy is diagnosed by eliciting cardinal signs of leprosy through systematic clinical (and wherever required bacteriological) examination. At least one of the following cardinal (unique and very important) signs must be present to diagnose leprosy.

a. Hypo-pigmented or reddish skin lesion(s) with definite sensory deficit;
b. Involvement of the peripheral nerves, as demonstrated by definite thickening with loss of sensation and weakness /paralysis of the corresponding muscles of the hands, feet or eyes;
c. Demonstration of *M. leprae* in the lesions.

The first two cardinal signs can be identified by clinical examination alone, while the third can be identified by examination of the slit skin smear.

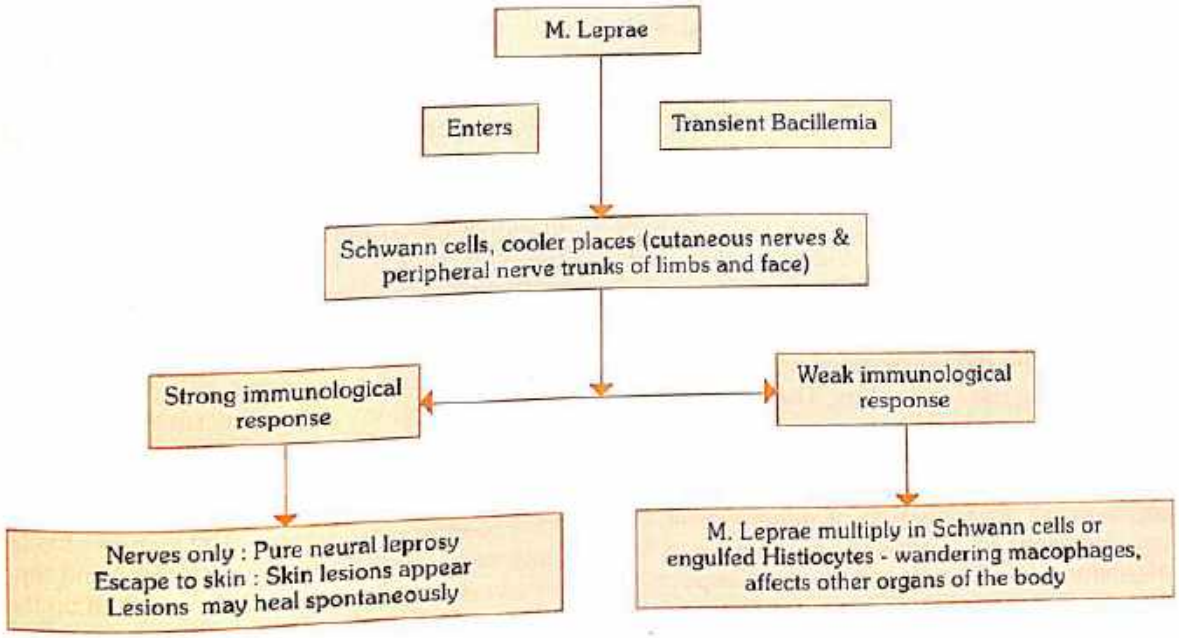

FIG. 1
Pathogenesis of leprosy

1. CLINICAL EXAMINATION

Clinical examination includes careful interview of the patient to get detailed history and examination of skin and nerves.

a. Case history

The leprosy history should elicit the following :

- Name, sex, age (year of birth), address, occupation etc.;
- Presenting complaints and their duration (A patch of a few days or that which is present since birth or an itchy patch is unlikely to be leprosy);
- History of recurrence (a recurrent lesion which "comes and goes" will not be due to leprosy);
- Any deformity, the time of its onset, and nature of its progress;
- Treatment history - treatment taken, what drugs for leprosy and how long;
- Any other associated illness (jaundice, cough, swelling of the feet at present or in the recent past);
- Any other person in the family or close contacts having similar disease or had the disease and was treated.

b. Physical examination

(i) A thorough inspection of the body surface (skin) to the extent permissible, in good natural light for the presence of suggestive, or tell tale evidence of leprosy

Testing the sensation over skin *(13)* :

It is very important to pick up the skill of eliciting sensory loss in skin patch. A light ballpoint pen (with plastic body) without cap will be needed. Explain to the person what you are going to do and demonstrate it. Touch the skin with the tip of the pen lightly and ask the individual to point to the spot touched with his index finger. Repeat this procedure a few times until the patient is familiar and comfortable with the procedure. Now ask the patient to close his eyes and repeat the procedure (first on the normal skin then over the affected area). While testing lesions over inaccessible areas (back, buttocks) the patient may be asked to count on each touch. Do not use other "instruments" like pin, cotton wool, feather, etc. When testing for sensation, touch the skin lightly with the pen. Do not stroke. The pen should be perpendicular to the surface of the skin. Do not keep asking the patient whether he feels the touch. You may get misleading results. Proceed from the normal skin to the patch. Give only one stimulus at a time. Vary the pace of testing.

c. Nerve examination (13)

Resource person should demonstrate nerve examination from head to toe and also use video clips. The cardinal sign is : "Involvement of the peripheral nerves, as demonstrated by definite thickening with a loss of sensation with or without weakness/paralysis of the corresponding muscles of the hands, feet or eyes". Examination of nerves in all the patients is very important for diagnosis, grouping and for prevention of deformity. This involves two aspects : (a) palpation of the nerves for thickening, tenderness and consistency; and (b) assessment of nerve function – sensory and motor. The commonly affected nerves are as shown in Fig. 2.

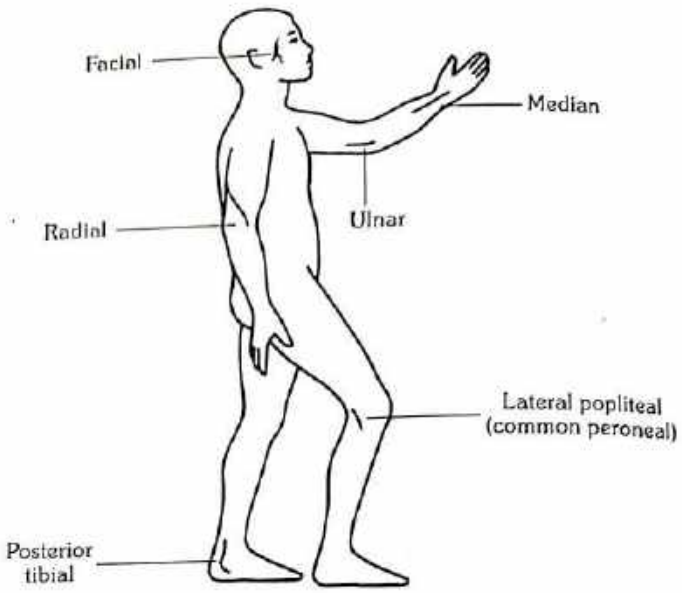

FIG. 2

Sites of nerve involvement

Source : *(22)*

Before the introduction of MDT, most leprosy cases were diagnosed by medical officer or specialized leprosy workers, and it often led to delay in diagnosis and initiation of treatment. Since the introduction of MDT, many procedures have been simplified, so that leprosy patients can be detected by health workers in the field.

2. BACTERIOLOGICAL EXAMINATION

Skin smears are useful for diagnosing multibacillary leprosy and were originally used for distinguishing between paucibacillary and multibacillary leprosy. However, the quality of skin smears and of microscopy is probably the weakest link in most leprosy elimination programmes. In view of this situation, and since it is possible to classify leprosy without skin smear results, it should not be a pre-requisite for implementing the MDT *(23)*.

A brief account of method of skin smear and nasal smear examination is as follows :

(i) Skin smears : Material from the skin is obtained from an active lesion, and also from one of the ear lobe by the "slit and scrape" method. Conventionally, two sites are examined. The skin is cleaned with ether or spirit and allowed to dry. A fold of the skin is nipped between the thumb and forefinger (of left hand in an operator). Enough pressure should be applied to stop or minimize bleeding. Holding the point of knife vertical to the apex of the skin fold, it is pushed into the skin to a depth of about 2 mm or so, to reach the dermis. A tiny incision is made 5 mm or so in length. If blood exudes, it should be wiped off with a small dry cotton-wool swab. The knife blade is rotated transversely to the line of the cut 90° and the knife point is used to scrape first on one side and then on the other side of the incision 2 or 3 times to obtain a tissue pulp from below the epidermis. This material is transferred on to a glass slide and spread over an area of about 8 mm diameter. Six smears can conveniently be made on one microscopic slide.

The sites of the smear should be accurately recorded so that the same sites can be used for successive sets of smears made for assesing the effect of treatment. The wound is dressed and closed with a piece of sticking tape applied over the site.

(ii) Nasal smears or blows : Nasal smears can be best prepared from early morning mucus material. The patient blows his nose into a clean dry sheet of cellophane or plastic. The smear should be made straightaway and fixed. This should be done in the early morning from the first blowing of the nose. Nose-blowing smears are used for assessing the patient's infectivity. In patients with untreated lepromatous leprosy, nose-blow smears may show a higher percentage of solid-staining bacilli than skin smears.

(iii) Nasal scrapings : An alternative is to use a nasal mucosal scrapper. After going in 4.5 cm, the blade is rotated towards the septum and scraped a few times and withdrawn. A small ball of cotton is introduced into the nostril to absorb any blood that may ooze out. Nasal scrapings are not recommended as a routine, because they are painful, and non-pathogenic atypical mycobacteria may be present in the nose of healthy persons. Leprosy bacilli are not found in nasal mucosa if they are absent in skin lesions. During treatment, *M. leprae* may disappear from the nasal mucosa before they disappear from the skin lesions *(24)*.

The skin or nasal smear is immediately fixed by lightly passing the underside of the slide over the spirit lamp flame and transported to the laboratory for staining with Ziehl–Neelsen method.

The glass slides used should be absolutely clean. They should not be reused for making smears a second time as organisms from a previous examination may give a false positive result *(21)*. Before a smear is declared negative, at least 200 fields should be examined *(8)*.

Bacterial index *(13)*

Bacterial index (BI) is the only objective way of monitoring the benefit of treatment. The Bacteriological (or Bacterial) Index indicates the density of leprosy bacilli in smears and includes both living (solid-staining) and dead (fragmented or granular) bacilli. According to **Ridley's logarithmic scale,** it ranges from zero to 6+ and is based on the number of bacilli seen in an average microscopic field of the smear using an oil-immersion objective.

- 0 No bacilli in any of the 100 oil-immersion fields
- 1+ 1–10 bacilli, on average, in 100 oil-immersion fields
- 2+ 1–10 bacilli on average, in 10 oil-immersion fields
- 3+ 1–10 bacilli, on average, in each oil-immersion field
- 4+ 10–100 bacilli, on average, in each oil-immersion field
- 5+ 100–1000 bacilli, on average, in each oil-immersion field
- 6+ More than 1000 bacilli, on average, in each oil-immersion field

The BI of the patient is calculated by adding up the index from each site examined and dividing the total by the number of sites examined.

(e.g. Right ear	5+	Left ear	5+
Back	4+	Chin	4+

$$\text{Bacteriological Index} = \frac{5+5+4+4}{4} = \frac{18}{4} = 4.5+$$

When the bacteriological index is BI 1+ and BI 2+, at least 100 oil immersion fields should be examined. When the index is BI 3+, BI 4+, BI 5+ and BI 6+, at least 25 oil-immersion fields should be examined *(24)*.

Morphological index

During the course of microscopic examination of smears, it is possible to distinguish and count the number of solid staining organisms (organisms that stain completely) and irregularly staining bacilli. The MI is calculated after examining 200 pink–stained free standing (i.e. not in clumps) bacilli. The percentage of solid staining bacilli in a stained smear is referred to as morphological index (MI). The total of the MIs for all sites divided by the number of sites gives the average MI for the body. The criteria for calling the bacilli solid rods are *(21)* :

a. uniform staining of the entire organism
b. parallel sides
c. rounded ends, and
d. length 5 times that of the width.

It has been widely believed that only solid–staining organisms are viable. Accurate evaluation of the MI requires much skill and experience. It is a valuable indicator of the patient's response to treatment with drugs, during the first few months and helps to signal drug resistance.

Solid-fragmented-granular (SFG) percentage (24)

The procedure for recording the percentages of solid, fragmented and granular bacilli is basically the same as that used for determining the MI. Since percentages of solid, fragmented and granular bacilli are mentioned separately. SFG percentages give a better picture of the bacterial morphology than the MI, and are a more sensitive indicator of the patient's response to treatment.

3. FOOT-PAD CULTURE

The only certain way to identify *M. leprae* is to inoculate the material into the foot-pads of mice and demonstrate its multiplication. Mouse foot-pad inoculation is 10 times more sensitive at detecting *M. leprae* than are slit–skin smears *(25)*.

The drawback of this technique is that it is time consuming and requires 6 to 9 months before the results are obtained. Newer *In vitro* methods such as macrophage culture have been evolved, which take only 3 to 4 weeks to obtain results.

Mouse foot–pad technique has been successfully used for (i) detecting drug resistance (ii) evaluating the potency of anti-leprosy drugs, and (iii) detecting the viability of the bacilli during treatment.

4. HISTAMINE TEST

The histamine test is a very reliable method for detecting at an early stage peripheral nerve damage due to leprosy. The test is carried out by injecting intradermally 0.1 ml of a 1:1000 solution of histamine phosphate or chlorohydrate into hypopigmented patches or in areas of anaesthesia. In normal persons, it gives rise to a wheal surrounded by an erythematous flare within a few minutes (Lewis triple response). In cases of leprosy where the nerve supply is destroyed, flare response is lost. Histamine test is recommended when difficulty is experienced in the diagnosis, as for example, indeterminate leprosy *(26)*.

5. BIOPSY

When the examinations detailed above do not yield diagnosis, histopathological examination may be necessary. It allows a more accurate classification of the disease. It also gives information about the bacterial content of the skin.

6. IMMUNOLOGICAL TESTS

There are now available different kinds of immunological tests. These may be classified as *(27)* :

a. tests for detecting cell mediated immunity (CMI)

b. tests for humoral antibodies (serological tests).

a. TESTS FOR DETECTING CMI

(i) LEPROMIN TEST

The test is performed by injecting intradermally 0.1 ml of lepromin into the inner aspect of the forearm of the individual. As a routine, the reaction is read at 48 hours and 21 days *(8)*. Two types of positive reactions have been described :

(a) EARLY REACTION : The early reaction is also known as Fernandez reaction. An inflammatory response develops within 24 to 48 hours and this tends to disappear after 3 to 4 days. It is evidenced by redness and induration at the site of inoculation. If the diameter of the *red area* is more than 10 mm at the end of 48 hours, the test is considered positive.

The early positive reaction indicates whether or not a person has been previously sensitized by exposure to and infection by the leprosy bacilli. In this sense, the early reaction is much superior to the late reaction. The early reaction has been described as delayed hypersensitivity reaction to "soluble" constituents of the leprosy bacilli. The reaction corresponds to the Mantoux reaction in tuberculosis, caused by the soluble antigens (PPD) of the tubercle bacilli.

(b) LATE REACTION : This is the classical Mitsuda reaction. The reaction develops late, becomes apparent in 7–10 days following the injection and reaching its maximum in 3 or 4 weeks. The test is read at 21 days. At the end of 21 days, if there is a *nodule* more than 5 mm in diameter at the site of inoculation, the reaction is said to be positive. The nodule may even ulcerate and heal with scarring if the antigen is crude.

It may be noted that the diameter of the *red area* in the early reaction, and the diameter of the *nodule* in the late reaction are measured. The early reaction is induced by the soluble constituents of the leprosy bacilli; and the late reaction by the bacillary component of the antigen. It indicates cell–mediated immunity.

In the first 6 months of life, most children are lepromin negative; some may become positive by the end of first year. Data obtained from different parts of the world indicate that in endemic areas, lepromin reaction is already positive in 20 per cent of children under 5 years of age, and this proportion increases to around 60 per cent or more in the 10–14 years age group, and to 80 per cent or more in persons over 19 years of age *(28)*. BCG vaccination is capable of converting the lepra reaction from negative to positive in a large proportion of individuals.

Value of the lepromin test

Lepromin test is not a diagnostic test. The two drawbacks that stand in the way of this test being used for diagnosis are : (i) positive results in non-cases, and (ii) negative results in lepromatous and near–lepromatous cases *(14)*.

The test has been generally accepted as a useful tool in evaluating the immune status (CMI) of leprosy patients. It is of considerable value in confirming the results of classification of cases of leprosy on clinical and bacteriological grounds. In other words, the test is widely used as an aid to classify the type of disease.

The test is also of great value in estimating the prognosis in cases of leprosy of all types. The test is usually strongly positive in the typical tuberculoid cases, and the positivity getting weaker as one passes through the spectrum to the lepromatous end, the typical lepromatous cases being lepromin negative indicating a failure of CMI. It is known that lepromin negative individuals are at a higher risk of developing progressive multibacillary leprosy, but those who are lepromin positive either escape the clinical disease (the majority) or develop paucibacillary disease (the minority).

(ii) LTT and LMIT

In recent years, newer *In vitro* tests such as lymphocyte transformation test (LTT) and leucocyte migration inhibition test (LMIT) have been developed. They give a measure of the cell mediated immunity. These tests have been used to detect subclinical infection. A disadvantage of these highly sophisticated tests is that they cannot be applied on a mass scale under field conditions *(29)*.

b. TESTS FOR HUMORAL RESPONSES TO *M. LEPRAE*

Probably the most important recent advance in the study of the epidemiology of leprosy is the development of serological tests. These tests are expected to have value in detecting subclinical infections, preclinical manifestations and follow-up efficacy of drug treatment. These tests include :

(i) FLA–ABS test

The Fluorescent Leprosy Antibody Absorption Test is now widely used for identification of subclinical infection. Studies revealed that FLA–ABS test is 92.3 per cent sensitive and 100 per cent specific in detecting *M. leprae* specific antibodies in all types of leprosy irrespective of the type and duration of the disease *(30)*.

(ii) Monoclonal antibodies

Monoclonal antibodies against *M. leprae* antigens have been produced. It has been shown that these antibodies recognize specific and non-specific epitopes of *M. leprae* antigens. If antibodies against specific antigens are found, they will become reagents of choice for identifying *M. leprae*. An antibody competition test (SACT) based on this approach has been found to be quite sensitive for detection of *M.leprae* antibody *(31)*.

(iii) Others

There are numerous other sensitive tests which include the radio-immune assay and ELISA tests. The ELISA test is based on a phenolic glycolipid (PGL) antigen.

For the present, the only practical approach is to use FLA–ABS test till some other more sensitive and specific tests are available for use on a large scale *(32)*.

LEPROSY CONTROL

The introduction of multidrug therapy has infused a new hope that the disease could be brought under effective

control in the not too distant future. A revised strategy of leprosy control has emerged based on multidrug therapy. The following elements are considered as a minimum requirement for all leprosy control programmes :

1. *Medical measures*
   - I. estimation of the problem
   - II. early case detection
   - III. multidrug therapy
   - IV. surveillance
   - V. immunoprophylaxis
   - VI. chemoprophylaxis
   - VII. deformities
   - VIII. rehabilitation
   - IX. health education
2. *Social support*
3. *Programme management*
4. *Evaluation*

The three main goals of leprosy control are *(8)* : (a) to interrupt transmission of the infection, thereby reduce the incidence of the disease so that it no longer constitutes a public health problem; (b) to treat patients in order to achieve their cure and where possible, complete rehabilitation; and (c) to prevent the development of associated deformities. Ultimate prevention is achieved by breaking the chain of transmission.

1. MEDICAL MEASURES

I. Estimation of the problem

The first step in a leprosy control programme is to define the size of the problem or disease load in the community by means of epidemiological surveys. Random sample surveys are good enough to collect baseline data. The survey should bring out not merely the prevalence of leprosy, but also the age and sex distribution of cases, the various forms of leprosy and the facilities available for providing the needed health care. A rough estimate of the prevalence can be determined by examining all school-age children; the total prevalence will be about 4 times the number of cases found *(27)*. Estimates of the prevalence of leprosy are essential for planning and implementing an anti-leprosy programme and also for evaluating the results of the programme.

II. Early case detection

The aim of case detection is to identify and to register all cases of leprosy as soon as possible after they become evident *(7)*. Ideally, patients should seek medical care voluntarily. However, because leprosy is frequently symptomless in the early stages, patients do not know they have the disease. By the time patient becomes aware of the disease and reports voluntarily, there is usually a lag period of 2 to 3 years *(33)*. Because of the social stigma, some patients are afraid to disclose themselves. It is, therefore, necessary to devise active methods of case detection *(8)*. Even in countries, with a satisfactory case-finding programme, new cases could still be found *(10)*. The current trend is to involve the primary health care workers (village health guides, multipurpose workers) in case detection with the active participation of the community *(10)*. These workers need to be adequately trained to make a tentative diagnosis of leprosy. The desirability of confirming the diagnosis by laboratory methods is not mandatory. It is important that criteria for identifying cases are valid, unambiguous and reproducible as far as possible. If data are to be compared between different areas and different times, it is important that diagnostic criteria used for leprosy around the world is standardized.

Case-finding methods : The choice of case-finding methods should be related to the prevalence rate of leprosy in the region : (a) CONTACT SURVEY : In areas where the prevalence of leprosy is generally low, (less than 1 case per 1000 population), the technique of choice is examination of all contacts (e.g., household contacts, especially children and persons reported to be suspected cases). These examinations will have to be arranged with discretion so as not to cause alarm. (b) GROUP SURVEYS : When the prevalence is about 1 per 1000 or higher, additional case finding methods should be employed such as screening of preschool and school children, people living in slums, military recruits, industrial labour and other selected groups for all types of skin diseases; this technique ("skin camps") may bring out additional cases of leprosy. It should be noted that the value of school surveys as a case finding method will be considerably diminished if the school enrolment is less than 70 per cent of all children in the 6–14 years age group *(12)*. (c) MASS SURVEYS : Total population surveys for examination of each and every individual, family by family by house-to-house visits are recommended only in hyperendemic areas, i.e., areas where the prevalence of leprosy is about 10 or more per 1000 population. In mass surveys, a coverage of not less than 95 per cent of the population should be obtained *(10)*. Mass surveys require high quality team work. They should be multipurpose covering not only leprosy but also possibly other diseases. They should have the full backing of the administration and whole-hearted participation of the local community.

Records : The case information should be collected for all patients in a standardized manner. The WHO has already a standard computer-based proforma for data collection from individual patients (see Annex 3 of WHO Expert Committee Report No. 716, page 58) which should be followed or suitably adapted. The Government of India had also approved a set of forms for keeping records and submitting reports.

Leprosy is an "iceberg" disease. The problem is one of discovering the subclinical cases, as considerable proportion of these cases lie outside the scope of existing case detection technology.

III. Multidrug therapy

In the absence of primary prevention by a leprosy vaccine, the strategy of leprosy control is based on effective chemotherapy (secondary prevention). Till recently, chemotherapy of leprosy has relied almost entirely on dapsone (DDS). Due to dependence on dapsone monotherapy for many years, drug-resistant leprosy bacilli (both primary and secondary resistance) have emerged in all parts of the world. This has led to relapse of the disease even in those in whom the disease had been arrested and the spread of dapsone-resistant strains to susceptibles jeopardizing the whole strategy of leprosy control *(34)*. In order to cope with this problem, a WHO Study Group on Chemotherapy of Leprosy, has recommended multiple drug therapy for both multibacillary and paucibacillary leprosy *(34)*.

OBJECTIVES

The main objectives of multidrug chemotherapy of leprosy are *(34)*

a. to interrupt transmission of the infection in the community by sterilizing infectious patients as rapidly as possible with bactericidal drugs;

b. to ensure early detection and treatment of cases to prevent deformities, and

c. to prevent drug resistance.

The multidrug treatment has the additional advantage of curtailing the duration of treatment of leprosy considerably. Shorter therapy has the added advantages of patient compliance, cost-effectiveness and decreased work load.

DEFINITIONS

Following the introduction of multidrug therapy, some changes in terminology have taken place. The following working definitions have been proposed by WHO *(7)*.

(i) Case of leprosy : A "case" of leprosy is a person showing clinical signs of leprosy with or without bacteriological confirmation of the diagnosis, and who has not yet completed a full course of treatment with MDT. This definition is for estimating the prevalence of leprosy.

(ii) Paucibacillary leprosy : A person having 1–5 skin lesions and/or only one nerve involvement *(35)*.

(iii) Multibacillary leprosy : A person having 6 or more skin lesions and/or more than one nerve involvement *(35)*.

(iv) Adequate treatment : Adequate treatment implies the completion of a regimen of multidrug therapy within a reasonably short period of time : (a) for paucibacillary cases, adequate treatment implies that the patient has received 6 monthly doses of combined therapy within 9 months. (b) for multibacillary cases, adequate treatment implies that the patient has received 12 monthly doses of combined therapy within 18 months.

(v) Regular treatment : A patient may be considered to have had regular treatment if he or she has received MDT for at least two-thirds of the months in any interval of time. For example, regular treatment for 12 months, implies that the patient has had at least 8 full months of combined therapy during that 12–month period.

(vi) Newly diagnosed case : A person who has been diagnosed as a leprosy case, and who has not taken MDT in the past.

(vii) Defaulter case : A defaulter is a leprosy patient on MDT, who has not collected treatment for 12 consecutive months.

Any patient who has been categorized as a defaulter should be removed from the register *(37)*.

(viii) Relapsed case : A patient whose therapy was terminated, having successfully completed an adequate course of multidrug therapy, but who subsequently develops new signs and symptoms of the disease, either during the surveillance period or thereafter, is considered to have "relapsed" *(7)*.

Drugs

In multidrug regimens, only bactericidal drugs are used. At present, only a small number of such drugs are available : these are rifampicin, dapsone, clofazimine, ethionamide and protionamide. A brief account of these drugs is given below :

(a) Rifampicin

Rifampicin (RMP) is the only drug that is highly bactericidal against *M. leprae*. A single dose of 1500 mg or 3–4 consecutive daily doses of 600 mg appear to kill 99 per cent of viable organisms *(36)*. Further the drug is effective when given at monthly intervals, which is a big advantage. The drug is expensive but safe.

The toxic effects of RMP are anorexia, nausea, abdominal pain and occasionally vomiting. It is hepatotoxic. The patient should be kept under supervision for 1 hour, after the administration of the drug since shock and collapse are known to occur.

RMP is now an essential drug in the chemotherapy of leprosy. Given alone, resistance to the drug develops. Hence it is given in combination with other anti-leprosy drugs.

(b) Dapsone

Dapsone (DDS) has been in use all over the world for the control of leprosy for more than 30 years. It continues to be an important drug in the multidrug chemotherapy of leprosy. It is cheap and effective in the dosage employed (1–2 mg/kg of body weight). When given orally, it is completely absorbed from the gut and fairly well tolerated. It has shown to be weak bactericidal against *M. leprae (38)*.

The common adverse effects following DDS administration are haemolytic anaemia, methaemoglobinaemia, agranulocytosis, hepatitis, peripheral neuropathy, psychosis and lepra reaction. A rare syndrome, known as *DDS-syndrome* consisting of fever, enlarged lymph glands, exfoliative dermatitis, hepatitis and maculopapular rash has also been reported. Since dapsone is a haemolytic drug, care should be taken that the haemoglobin level is not less than 60 per cent, and the dosage of DDS is strictly weight-based. Iron tablets are prescribed routinely to correct anaemia.

(c) Clofazimine

Clofazimine (CLF) was originally synthesized for the treatment of tuberculosis, but was subsequently found to have far greater value in leprosy. It has both anti–leprosy and anti–inflammatory properties. CLF though less effective than dapsone has the added advantage in suppressing and preventing reactions. CLF is relatively expensive and is reasonably free from toxic effects in the usual dosage. It is used as the third drug, whenever possible in leprosy chemotherapy.

Clofazimine may be unacceptable to some patients because it may give rise to darkish red coloration to skin, mucous membranes, urine and sweat. These symptoms are not serious. They would disappear after the drug is stopped. If totally unacceptable, it may be replaced by ethionamide or protionamide.

(d) Ethionamide and protionamide

These are bactericidal drugs killing 98 per cent of viable bacilli in 4 to 5 days. They are virtually interchangeable and gives rise to cross-resistance with each other. They are both more expensive and more toxic than dapsone. The WHO *(31)* has recommended that ethionamide or protionamide should be used as the third drug in the treatment of multibacillary leprosy in those patients, who find clofazimine unacceptable.

(e) Quinolones

These drugs work by inhibiting DNA synthesis during bacterial replication. Ofloxacin, a fluorinated quinolone is the most preferred drug in this group. Oral ofloxacin is 98 per cent bioavailable with elimination half-life of about 5 to 8 hours. 22 doses of ofloxacin kill about 99.9 per cent of viable *M. leprae (39)*. This is the basis of very short term clinical trials of a combination of 400 mg ofloxacin and 600 mg rifampicin daily for 28 days.

Side-effects include nausea, diarrhoea and other gastrointestinal complaints and a variety of central nervous system complaints.

(f) Minocycline

This is the most lipid–soluble of the tetracyclines and inhibits bacterial protein synthesis. In clinical trials, the clearance of viable *M. leprae* from the skin by minocycline was faster than that reported from dapsone or clofazimine and similar to that for ofloxacin. Minocycline may strengthen MDT, for multibacillary patients and thereby shorten the duration of treatment needed to treat leprosy effectively *(33)*. The standard dose is 100 mg daily. The side-effects include discoloration of teeth in infants and children, occasional pigmentation of the skin and mucous membrane, various gastrointestinal symptoms and central nervous system complaints. It should not be given to infants, children and during pregnancy *(23)*.

(g) Clarithromycin

Clarithromycin is a member of the macrolid group of antibiotics and displays a significant bactericidal activity against *M. leprae*. In patients with lepromatous leprosy, daily administration of 500 mg of clarithromycin killed 99 per cent of viable *M. leprae* within 28 days, and 99.9 per cent by 56 days. Side-effects include nausea, vomiting and diarrhoea.

RECOMMENDED REVISED REGIMENS OF CHEMOTHERAPY

The proper application of multidrug therapy is crucial to the success of leprosy control. The regimens recommended by WHO have been widely accepted in many countries, and India is implementing the regimen from 1st of April 2025 *(40)*.

a. Multibacillary leprosy

The WHO has recommended the following combination of drugs for treatment of adult multibacillary cases of leprosy :

- Rifampicin ..... 600 mg, once monthly, given under supervision
- Dapsone ..... 100 mg daily, self–administered
- Clofazimine ..... 300 mg once monthly supervised; and 50 mg daily, self–administered.

Where clofazimine is totally unacceptable owing to the colouration of skin, its replacement by 250 to 375 mg self–administered daily doses of ethionamide or protionamide has been suggested.

b. Paucibacillary leprosy

Paucibacillary cases should also receive combined therapy in view of primary dapsone resistance which is becoming widespread. The recommended standard regimen for adults is as for MB leprosy :

- Rifampicin ..... 600 mg once a month, supervised
- Dapsone ..... 100 mg (1–2 mg/kg of body weight) daily, self–administered
- Clofazimine ..... 300 mg once monthly supervised; and 50 mg daily, self administered. Previously only Rifampicin and Dapsone were used.

The standard treatment regimen for children aged 10–14 years is as follows :

a. Multibacillary leprosy

- Rifampicin ..... 450 mg once a month, given under supervision
- Dapsone ..... 50 mg daily, self administered
- Clofazimine ..... 150 mg once a month supervised; and 50 mg every other day.

b. Paucibacillary leprosy

- Rifampicin ..... 450 mg once a month, supervised
- Dapsone ..... 50 mg daily, self administered
- Clofazimine ..... 150 mg once a month supervised; and 50 mg every other day. Previously only Rifampicin and Dapsone were used.

Children under the age of 10 years should receive appropriately reduced doses of the above drugs.

Duration of treatment

The treatment duration varies according to the type of disease. The recommendations are as follows :

Multibacillary leprosy – MB blisterpacks for 12 months, within 18 months

Paucibacillary leprosy – PB blisterpacks for 6 months, within 9 months

A defaulter who returns to the health centre for treatment should be given a new course of MDT when he or she shows one or more of the following signs *(37)* :

- reddish and/or raised skin lesions;
- appearance of new skin lesions (since the previous examination);
- new nerve involvement (e.g. changes in skin sensation) since the previous examination;
- lepromatous nodules;
- signs of reversal reaction or ENL.

For registration purposes, returning defaulters are not considered as newly detected cases.

MDT is not contraindicated in patients with HIV infection. Management of leprosy and of lepra reactions is same as that of any other leprosy patient. The response of such patients to MDT is also similar *(37)*.

Since leprosy is exacerbated during pregnancy, it is important that MDT be continued. The evidence so far indicates that MDT is safe during pregnancy. Small quantities of anti-leprosy drugs are excreted through breast milk, but there is no report of adverse reaction as a result of this, except for mild discolouration of the infant's skin caused by clofazimine *(41)*.

Lepra reaction *(42)*

During the course of leprosy, immunologically mediated episodes of acute or subacute inflammation known as reactions may occur. Because peripheral nerve trunks are often involved, unless reactions are promptly and adequately treated, such episodes can result in permanent deformities.

Lepra reactions are usually diagnosed by clinical examination only. Inflammatory changes in skin lesions or appearance of new lesions, patches or nodules with acute onset, draw the attention of patient to report. Some cases develop signs of nerve damage without changes in skin lesions.

There are two types of reaction : Reversal reaction (or Type 1) and Erythema Nodosum Leprosum (ENL or Type 2). Both types can occur before the start of multi-drug treatment, during treatment, or after treatment has been completed. Both types can be mild or severe. Only severe reactions are treated with corticosteroids.

Distinguishing between the two types of reactions is usually not difficult. In a reversal reaction, the leprosy skin lesions themselves become inflamed, red and swollen. In an ENL reaction, new inflamed, red nodules (about 1–2 cm across) appear under the skin of the limbs or trunk, while the original leprosy skin patches remain as they were. In addition, ENL reactions cause a general feeling of fever and malaise, while reversal reactions cause less systemic upset. Common differentiating features are as shown in Table 1.

Because of the high risk of permanent damage to the peripheral nerve trunks, reversal reaction needs to be diagnosed as soon as possible, and treated adequately. The drug of choice is prednisolone, the cheapest and most widely available corticosteroid.

Most reversal reactions and neuritis can be treated successfully under field conditions, with a standard 12–week course of prednisolone. The potential risk of serious adverse effects caused by long-term corticosteroid therapy must not be ignored, particularly under field conditions. The more common problems of prolonged steroid therapy include weight gain, peptic ulcer, diabetes, hypertension, reactivation of tuberculosis, osteoporosis and psychiatric disorders.

ENL varies in severity, duration and organ involvement. Acute or subacute neuritis, with or without loss of nerve function, is one of the major criteria in distinguishing mild and severe ENL. Mild ENL can be treated with analgesic or antipyretic drugs such as aspirin, while severe ENL can be treated with prednisolone, as for reversal reaction.

Clofazimine is also effective for ENL, but is less potent than cortico-steroids and often takes 4–6 weeks to develop its full effects, so it should never be started as the sole agent for the treatment of severe ENL.

Signs of a severe reversal reaction

If any of the following signs are found, the reaction should be treated as severe :

- Loss of nerve function – that is, loss of sensation or muscle weakness in the area supplied by nerve.
- Pain or tenderness in one or more nerves.
- Silent neuritis/quiet nerve paralysis i.e. signs of nerve damage without symptoms.
- A red, swollen skin patch on the face, or overlying another major nerve trunk.
- A skin lesion anywhere that becomes ulcerated.
- Marked oedema of the hands, feet or face.

Signs of a severe ENL reaction

If any of the following signs is found, the reaction should be treated as severe :

- Pain or tenderness in one or more nerves, with or without loss of nerve function.
- Ulceration of ENL nodules.
- Pain of eyes with or without redness and loss of visual acuity.
- Painful swelling of the testes (orchitis) or of the fingers (dactylitis).
- Marked arthritis or lymphadenitis.

TABLE 1

Difference between reversal reaction and ENL

Type I (Reversal Reaction)	Type II (ENL)
1. Delayed hypersensitivity.	1. Antigen antibody reaction.
2. Occurs in both PB and MB cases in unstable types like BT.BB.BL.	2. Seen in MB cases only (BL and LL type).
3. Skin lesions suddenly become reddish, swollen, warm, painful, and tender. New lesions may appear.	3. Red, painful, tender, sub-cutaneous nodules – ENL may appear, commonly on face, arms, legs, bilaterally symmetrical. They appear in crops and subside within few days even without treatment (Evanescent skin nodules). Nodules are better felt than seen and these are recurrent (episodic).
4. Nerves close to skin may be enlarged, tender and painful (neuritis) with loss of its functions (loss of sensory, motor or autonomic) which may appear suddenly.	4. Nerves may be affected but not as common or severe and acute as in Type I.
5. Other organs – not affected.	5. Other organs like eyes, testis, and kidney may be affected.
6. General symptoms – not common.	6. Fever, joints pain, red eyes with watering may be associated.
7. Eye-Lagophthalmos and corneal anaesthesia due to neuritis.	7. Iritis/iridocyclitis

Source : *(13, 42)*

Treatment of Lepra reactions (moderate to severe cases)

It includes bed rest, rest to affected nerves by splint, analgesics, prednisolone. Each case of reaction should be assessed for his/her fitness to put on prednisolone as per check list given above *(13, 42)*.

Prednisolone regimen	Add Clofazimine in ENL
40 mg daily for first 2 weeks 30 mg daily for weeks 3 and 4	One capsule (100 mg) 3 times a day × 4 weeks
20 mg daily for weeks 5 and 6 15 mg daily for weeks 7 and 8	One capsule (100 mg) 2 times a day × next 4 weeks
10 mg daily for weeks 9 and 10 5 mg daily for weeks 11 and 12	One capsule (100 mg) once a day × third month
For neuritis, treatment with Prednisolone should be prolonged to four weeks from 20 mg onwards	

Prednisolone tablets issued must be entered in 'Prednisolone card'. Tapering of prednisolone may be done according to its response. Patient must be instructed on salt restriction, no prednisolone intake on empty stomach and reporting adverse effects/symptoms immediately.

Adding Clofazimine for Type II reaction may be extremely useful for reducing or withdrawing corticosteroids in patients who have become dependent on them. Total duration of Clofazimine therapy should not exceed 12 months.

If a patient develops lepra reaction during the treatment, do not stop MDT (rather complete the course of MDT). Lepra reactions, which occur after completion of treatment, should also be managed as mentioned earlier. MDT should not be restarted for such cases. Response to treatment should be monitored and assessed, including check on adverse effects of prednisolone.

Before starting the steroid treatment, the patient should be asked questions about epigastric pain and diarrhoea, with or without blood and or mucous; and examined for fungal infection, scabies, and worm infestations, as all these conditions may be made worse by steroids. Treatment of all these conditions can be started at the same time as steroids are started *(42)*.

Before starting the steroid treatment the patient should be explained the reason for treatment; the duration of the treatment; importance of taking daily dose and that the treatment should not be stopped suddenly (the dosage is decreased gradually) and importance of completing the full course of treatment; and possible side-effects.

Follow-up after treatment with steroids

People who have been given a course of steroids for reaction or nerve damage should be followed up closely because of the risk of recurrence. Each person must understand that a reaction or new nerve damage may recur. They must know how to recognize the early signs of nerve damage and be aware of how important it is to return promptly to the clinic for treatment. These signs include pain or tingling sensations, further loss of feeling or loss of muscle strength and inability to close the eye.

Patients still on MDT should have their nerve function checked monthly by the health worker when they come to collect their treatment. Any deterioration should be noted and the person referred. Patients who have already completed MDT, by the time they come to the end of a course of steroids, should be asked to come back three months and six months after the end of the course for review and nerve function assessment. Patients who still have lagophthalmos (weakness of eyelids) after completion of treatment with steroids should be referred to ophthalmic surgeon.

Groups requiring special precautions when prescribing steroids

The following groups of people require special precautions when steroids are prescribed. One must not give steroids to people with tuberculosis, diabetes, deep ulcers, osteomyelitis, corneal ulcers or other serious conditions without starting treatment for the underlying condition.

Pregnant women

All pregnant women should be treated at referral level, so as to minimize the steroid dose they are given and thus avoid harmful effects, such as growth retardation on the foetus. If steroids are given in the third trimester, this may cause adrenal suppression in the newborn infant. Ideally, such infants should be monitored in a referral centre for a few days after birth. The dose of prednisolone to be given during pregnancy are as follows :

- PB cases : start at 30 mg daily instead of 40 mg and limit the course to ten weeks rather than the usual twelve weeks regime.
- MB cases : starting at 30 mg daily but lasting for twenty weeks.

Children

All children under the age of twelve should be treated at referral level, so as to minimize the effects of steroids on their growth. Children can be given a course similar to that for pregnant women, but the starting dose of prednisolone should not exceed 1 mg per kilogram of body weight per day. Giving children steroids on alternate days may reduce the effect on their growth. A suitable regimen for PB cases would be 30 mg of prednisolone daily for two weeks, then 30 mg on alternate days for two weeks with a gradually reducing dose over the total course of ten weeks. For MB cases, one should double the duration of each stage of the course.

Diabetes

Patients who show symptoms that suggest diabetes or whose urine tests positive for glucose should be referred to confirm whether the diagnosis is correct and, if it is confirmed, for management of the diabetes condition. Steroids may increase the diabetic's requirement for insulin.

A person taking steroids may also develop diabetes for the first time. This possibility must be considered when patient develops typical symptoms of diabetes during the treatment with steroids. The condition usually resolves itself when steroids are stopped.

Ulcers or osteomyelitis

Patients with deep or dirty ulcers or osteomyelitis should be referred for surgical treatment and antibiotics. Starting steroids before such treatment may lead to a worsening of the sepsis and more permanent damage, including the need for amputation. One should suspect osteomyelitis if the

person's hand or foot is warmer than normal, with or without swelling. Any person with a wound discharging pus should be referred for surgical advice and debridement (removal of dead and infected tissue) before taking steroids, or osteomyelitis may develop.

Eye involvement

Patients who have corneal damage or iritis should be referred for specialist diagnosis and management at a centre properly equipped for eye care. Corneal ulcers and keratitis are inflammatory conditions of the cornea. They are often caused by exposure, as a result of the person being unable to close the eye properly. Steroids, whether taken by mouth or locally applied, may make these conditions worse. Iritis, uveitis, iridocyclitis and scleritis are all types of inflammation inside the eye and they can all occur as part of a Type-2 reaction. These conditions cause pain, redness, photophobia and loss of vision, although the symptoms are not always severe. The treatment includes atropine eye ointment to prevent adhesion.

Tuberculosis

If tuberculosis is suspected, the diagnosis must be confirmed and treatment started before giving steroids.

The crucial elements in the management of leprosy reactions and thereby, the prevention of disabilities are early diagnosis of reactions together with prompt and adequate treatment. Usually the diagnosis of leprosy reactions is relatively straightforward, but occasionally, in paucibacillary patients who have completed treatment, differentiation of a reversal reaction from relapse may be difficult. Nevertheless, it is essential that this distinction must be made correctly. The differences are as summarized in Table 2.

As a consequence of all these factors, the diagnosis and treatment of leprosy reactions may often be delayed and, by the time the patients arrive at the referral centres, they may have already developed permanent deformities. In order to avoid these problems, national leprosy programmes should try to ensure that patients are taught to recognize the early signs of reactions, and to report promptly for treatment; health workers are able to diagnose and treat reactions and to refer patients when necessary; and adequate stocks of prednisolone are maintained at the peripheral level *(23)*.

IV. Surveillance

Clinical surveillance of cases after completion of treatment is an important part of the current recommendations for multidrug therapy; it is essential for the assurance of long-term success of treatment and for the early detection of any relapses.

(a) Paucibacillary leprosy : It is recommended that paucibacillary cases be examined clinically at least once a year for a minimum of 2 years after completion of treatment *(7)*.

(b) Multibacillary leprosy : It is recommended that multibacillary cases be examined clinically at least once a year for a minimum period of 5 years after completion of therapy *(9)*.

A patient who has completed the required period of surveillance following the course of multidrug therapy and shows no evidence of relapse is considered to have completed surveillance. The phrase "release from control" should not be applied in the context of multidrug therapy *(6)*.

V. Immunoprophylaxis

The fact that a scientifically valid tool for the detection of infection is not yet available which could deepen the understanding of how leprosy is transmitted, and could lead to the development of an effective vaccine and other interventions. Trials in different population groups with BCG vaccine either alone or in combination with other vaccine (from killed *Mycobacterium leprae* or atypical *Mycobacteria*), have shown protective efficacy ranging between 28 per cent and 60 per cent. High BCG coverage remains an important contribution to reducing the disease burden due to leprosy *(43)*.

VI. Chemoprophylaxis

Chemoprophylaxis in chronic infectious diseases has an established benefit, particularly when given to persons who are known to be at higher risk of developing the disease. The immediate contacts of a case of leprosy, especially multibacillary, are known to have a higher risk of developing the disease than compared to the general population. It is important, therefore, to consider possible interventions to prevent the occurrence of leprosy among household contacts. However, there must be robust trial evidence to demonstrate that the drug/s used for chemoprophylaxis are

TABLE 2
Differences between reversal reaction and relapse

	Reversal reaction	Relapse
Time interval	Generally occurs during chemotherapy or within 3 years of stopping treatment	Usually occurs only when chemotherapy has been discontinued, after an interval of usually more than 3 years
Onset	Abrupt and sudden	Slow and insidious
Old lesions	Existing lesions become oedematous, erythematous or tender	Lesion may show erythema and infiltration, but no tenderness
New lesions	Several new lesions appear	New lesions are minimal
Ulceration	Lesions may ulcerate	Ulceration does not occur
Nerve involvement	Multiple nerve involvement common, painful and tender	Nerve involvement may occur only in a single nerve; usually no pain or tenderness
General condition	May have fever, joint pains, malaise	Not usually affected
Response to steroid treatment	Rapid	Nil

Source : *(25, 43)*

safe, effective and cost-efficient in terms of the number of new cases prevented.

On account of lack of consistent results from various studies using various drugs (dapsone, acedapsone, rifampicin) it is too premature to advise chemoprophylaxis as a public health measure. Further research is needed to use this as a routine tool to prevent the occurrence of disease among contacts *(43)*.

VII. Disability

It is estimated that approximately 25 per cent of the patients who are not treated at an early stage of disease develop anaesthesia and/or deformities of the hands and feet. As a single disease entity, leprosy is one of the foremost causes of deformities and crippling.

The deformities may result due to the disease process (e.g. loss of eye brows, other facial deformities), or those resulting from paralysis of some muscles due to damage to peripheral nerve trunk (e.g. claw-hand, foot-drop, lagophthalmos), or those resulting from injuries or infections to hands and feet (e.g. scar contractures of fingers, mutilation of hands and feet, corneal ulceration). Fig. 3 shows the process of disability in hands, feet and eyes.

Patients at high risk of developing disability :

People with the following features are more likely to develop lepra reaction and neuritis compared to others and thus subjected to developing disability -

- Multi-bacillary leprosy
- Past or present thickened/painful/tender nerve trunk
- Skin lesion on face
- Adolescents, pregnancy, old age
- Any inter-current infection

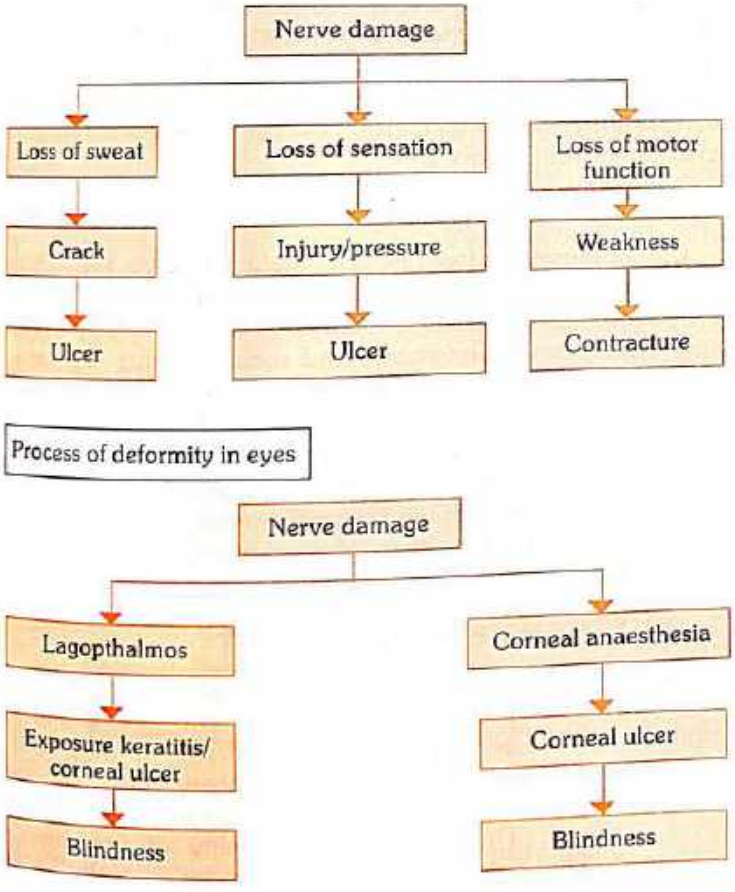

FIG. 3
Process of deformity in hands, feet and eyes
Source : *(13)*

Stages of involvement of nerve

Stage I : *Stage of nerve involvement* – Nerves become swollen (thickened) due to inflammatory response and tender, but no loss of function. This condition is reversible if action is taken early.

Stage II : *Stage of nerve damage* – Along with thickened and painful peripheral nerves, associated with loss of function (loss of autonomic, sensory and motor functions). This condition is reversible if suitable action is taken early preferably within 6 months.

Stage III : *Stage of nerve destruction* – In long standing case of nerve involvement (usually more than one year) nerve may become fibrosed, thin and atrophic. Involved nerve is completely destroyed and its function cannot be recovered to any useful degree.

There are two types of disabilities in leprosy :

1. *Primary* : These disabilities occur as a result of nerve damage – e.g. loss of sensation, paralysis, dryness
2. *Secondary* : These occur as a result of neglected primary disability – e.g. ulcer, contracture.

A **disability** is defined as lack of ability to perform an activity.

A **deformity** is a visible consequence of an impairment inside the body.

The findings of the examination are first noted in the Disability Assessment Form separately for right and left eyes, hands and feet. Thereafter each eye, each hand and each foot is given its own grade. Deformities are classified into three grades. The criterias are as follows *(13, 44)* :

Examination of parts	WHO Disability Grades	Sensory testing	Voluntary muscle testing	
Hands	0	Sensation present	Muscle power normal	
	1	Sensation absent	Muscle power normal	
	2	Sensation absent	Muscle power weak or paralyzed	
Feet	0	Sensation present	Muscle power normal	
	1	Sensation absent	Muscle power normal	
	2	Sensation absent	Muscle power weak or paralyzed	
Eye		Vision	Lid Gap	Blinking
	0	Normal	No lid gap	Present
	2	Cannot count fingers at 6 metres	Gap present/ red eye/ corneal ulcer or opacity	Absent

The highest grade given in any of the part is used as the Disability Grade for that patient. Eye, hand and feet score i.e. sum of all the individual disability grades for two eyes, two hands and two feet 0–12, should be recorded at each examination.

Table 3 shows deformities occurring in patients with leprosy.

TABLE 3

Deformities occurring in leprosy

Face	Mask face, facies leonina, sagging face, lagophthalmos, loss of eyebrows (superciliary madarosis) and eyelashes (ciliary madarosis), corneal ulcers and opacities, perforated nose, depressed nose, ear deformities, e.g. nodules on the ear and elongated lobules.
Hands	Claw hand, wrist-drop, ulcers, absorption of digits, thumb-web contracture, hollowing of the interosseous spaces and swollen hand.
Feet	Plantar ulcers, foot-drop, inversion of the foot, clawing of the toes, absorption of the toes, collapsed foot, swollen foot and callosities.
Other deformities	Gynaecomastia and perforation of the palate.

Source : *(22, 24)*

The measures to prevent disabilities include actions to take care of the dry, denervated skin of palms and soles, heal the wounds, ulcers and skin cracks in palms and soles, prevent injuries to hands and feet by using protective gloves and footwear, prevent joint stiffness in cases of paralytic deformities, protect the eyes, and assess periodically the commonly damaged nerves for loss of nerve function and its progression, using simple tests that can be carried out in the field.

Improvement of disabilities is achieved through the use of prostheses and orthopaedic devices, including corrective splints, as well as by corrective surgery. All these measures, however, require special expertise and facilities.

VIII. Rehabilitation

The WHO Expert Committee on Leprosy in its Second Report *(45)* defined rehabilitation as :

> *"the physical and mental restoration, as far as possible, of all treated patients to normal activity, so that they may be able to resume their place in the home, society and industry".*

Rehabilitation is, therefore, an integral part of leprosy control. It must begin as soon as the disease is diagnosed. The cheapest and surest rehabilitation is to prevent physical deformities and social and vocational disruption by early diagnosis and adequate treatment. The measures that are taken in this direction are known as "preventive rehabilitation". The approach to rehabilitation should, therefore, begin with preventing dehabilitation. We should never allow dehabilitation to take place and afterwards take up the uphill task of rehabilitation *(46)*.

Community-based rehabilitation defined by WHO and major NGOs is as follows (43) :

"Community-based rehabilitation is a strategy within general community development for the rehabilitation, equalization of opportunities and social inclusion of all people with disabilities. Community-based rehabilitation is implemented through the combined efforts of the people with disabilities themselves, their families, organizations and communities, and the relevant governmental and non-governmental health, education, vocational, social and other services".

Rehabilitation measures may appear to be simple; they require planned and systematic actions – medical, surgical, social, educational and vocational – consistently over years with sustained counselling and health education for training or retraining of the individual to the highest possible level of functional ability. For this purpose, coordinated efforts by the Departments of Health, Education and Social Welfare, as well as voluntary organizations are necessary.

IX. Health education

No anti-leprosy campaign is complete without health education. Health education aims at helping people develop attitudes and behaviour by their own actions and efforts and seeking professional help when needed. Health education should be directed towards the patient and his family and the general public. *(a) Patient and his family* : The main problem in leprosy control is poor patient compliance with the drug regimen and high drop-out rates. The patient and his family should be educated about the need for regular treatment, repeated examination of contacts, self care regarding prevention of disabilities and protection of children. Health education thus minimizes hurdles in implementing the leprosy control programme. *(b) General public* : There is a growing realization that technological advances alone cannot solve the leprosy problem, unless we succeed in involving the people in the control programme. Health education aims at ensuring community participation. The public should be made aware that leprosy is not a hereditary disease; it is a bacterial disease like tuberculosis; it is curable; not all leprosy patients are infectious; regular and adequate treatment is essential to obtain cure and prevent disabilities, and that the patient needs sympathy and social support. A nationwide mass education is needed to educate people on the true facts about leprosy and remove superstitions and wrong beliefs and the social stigma associated with leprosy *(33)*.

2. SOCIAL SUPPORT

Chemotherapy alone is not likely to solve the whole problem of leprosy. The economic and social problems of the patient and his family should be identified and met. This may include social assistance and social support. This may take various forms depending upon the local situation, e.g., assistance to the patient to travel to and from the clinic; help to the needy families in terms of foodgrains, clothes, care of children and their education, and job placement; programmes such as slum improvement, etc. Such care should be provided through voluntary agencies and Departments of Social Welfare.

3. PROGRAMME MANAGEMENT

Leprosy control is a long-term activity. Therefore planning and programme management are essential ingredients. It is generally assumed that with existing tools, we can achieve rapid control of leprosy, provided the "operational performance" is stepped up to the maximum level required. This is the responsibility of programme managers. These issues are discussed under evaluation (see operational indicators and epidemiological indicators below). Among the resources that are needed are adequate infrastructure, trained health personnel, adequate supply of drugs and vehicles, and financial allocation. The National

Leprosy Eradication Programme incorporates all these elements (see chapter 7).

4. EVALUATION

An important aspect of leprosy control is to assess the impact of the control operations on the endemicity of the disease, and to compare results between different times and places. Indicators are required for such an evaluation. It is important that these indicators can be easily used and satisfy the criteria of repeatability and validity. Ideally they should be conceived and treated as signals for action by programme managers *(7)*. There are two main types of indicators in leprosy control.

1. Epidemiological indicators

These are required to evaluate the effectiveness of the programme, that is to assess the impact of the action taken with regard to the problem reduction. These indices are : (a) INCIDENCE : Incidence rates are often calculated separately for different subgroups of population, e.g., age, sex, frequency of household contact. It is the most sensitive index of transmission of the disease. It is the only index for measuring the effectiveness of the measures taken, i.e., reduction of transmission. Thus they are useful in monitoring the success of a control programme. (b) PREVALENCE : This provides a measure of the "case load" and is useful in the planning of the treatment services. The continued reduction in the prevalence could also give information about the downward trend of the disease. It is often useful to calculate prevalence rates for different subgroups, e.g., age sex, geographic area. The fact that leprosy is not uniformly distributed should be borne in mind when these statistics are interpreted *(8)*.

2. Indicators to be monitored for disease surveillance and programme performance *(5)*

The list of indicators to be monitored for disease surveillance and programme performance including routine as well as new indicators for new interventions are enumerated below. Essential and additional epidemiological indicators include epidemiological indicators monitored over many years and express the results obtained due to activities. Performance indicators express how well the activities that are planned are implemented. Impact indicators express the extent of realization of goals under Roadmap 2023–27.

I. Essential indicators (with routine programme targets) :

1. Annual New Case Detection Rate (ANCDR) per 1,00,000 population (<10)
2. Rate of new cases with Grade II disabilities per million population per year (<1)
3. Treatment Completion Rate (TCR) as a proxy to cure rate (>90%)
4. Prevalence Rate (PR) per 10,000 population (<1)

II. Additional epidemiological indicators (with routine programme targets) :

1. Proportion of Grade II disabilities among new cases (%) (<2)
2. Proportion of females among new cases
3. Proportion of MB among new cases
4. Proportion of PB among new cases
5. Proportion of children (0–14 years) among new cases
6. Child rate per million child population
7. Scheduled Caste New Case Detection Rate
8. Scheduled Tribe New Case Detection Rate.

III. Quality of service indicators :

1. Patient month blister calendar pack stock
2. Absolute number of patients made RFT (Released from Treatment)
3. Number of Relapses reported.
4. Proportion of cases who developed new or additional disability after starting MDT
5. Proportion of treatment defaulters
6. Proportion of new cases correctly diagnosed

IV. New performance indicators for implementation of Roadmap 2023–27

1. No. of States/UTs specific roadmap developed
2. Percent increase in annual budget for leprosy at national level against baseline budget of 2021–22.
3. Percent increase in annual budget for leprosy at state level against baseline budget of 2021–22
4. Proportion of population covered under active case detection under LCDC in leprosy prevalent states/ UTs
5. Number (percentage) of new cases detected by active case detection
6. Proportion of annual new cases reported voluntarily
7. Proportion of annual new cases detected through ASHA
8. Proportion of new cases detected through other health programmes and community
9. Proportion of new cases with Grade 2 disabilities among child cases
10. Proportion of medical officers trained in the year against total number of medical officers in Govt. health facilities and institutions
11. Proportion of paramedical staff trained in the year against total number of paramedical staff in Govt. health facilities and institutions
12. Proportion of ASHAs trained in the year against total number of ASHAs
13. Proportion of new cases treated for lepra reactions against total number of new cases detected in the year
14. Proportion of new cases treated for adverse reactions against total number of new cases detected in the year
15. No. of patient samples sent for AMR testing
16. Proportion of persons affected by leprosy eligible for RCS undergone reconstructive surgery in the year
17. Proportion of new cases (in percentage) for whom contact tracing and screening done

18. Proportion of screened contacts (in percentage) who received SDR/ newer PEP regimen
19. Proportion of new cases of last 5 years (in percentage) for whom contact tracing for screening done
20. No. of new cases detected among contacts in the year
21. No. of states and UTs generating monthly progress report through digital surveillance system
22. Proportion of newly detected cases entered on Nikusth 2.0 in the year
23. No. of joint monitoring investigation and advisory group visits to states in the year
24. Independent evaluation conducted in the year
25. No. of states to be covered for validation of indicators in the year

V. Impact indicators :

1. Drop in percentage of annual new cases detected against baseline of 2019–20
2. Grade 2 Disability Rate in newly detected child cases with leprosy per million child population
3. Grade 2 Disability Rate in new cases of leprosy detected per million population
4. No. of districts with zero new indigenous child cases for last 5 consecutive years
5. No. of districts with zero new indigenous child cases for last 5 consecutive years followed by zero new indigenous cases for 3 years.

Anti-leprosy activities in India

The history of anti-leprosy work in India goes back to 1874 when the Mission to Lepers (now Leprosy Mission) was founded by Baily at Chamba, in the Himachal Pradesh. The headquarters of this organization later moved to Purulia in West Bengal. Since then, many voluntary organizations (now about 150) have sprung up in the cause of leprosy. Important among these are the Hind Kusht Nivaran Sangh (formerly the British Empire Leprosy Relief Association); Gandhi Memorial Leprosy Foundation, Sevagram, Wardha; the German Leprosy Relief Association; the Damien Foundation; the Danish Save the Child Fund; and the more recent JALMA which was taken over by the ICMR in 1975. A federation body, "National Leprosy Organization" came into being in 1965 to provide a common platform to discuss their problems and share their experiences. The campaign against leprosy in India is accomplished through an official programme, the National Leprosy Control Programme which was initiated in the middle of 1954. In 1983, it was converted into an eradication programme.

An account of the National Leprosy Eradication Programme is given in chapter 7.

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SEXUALLY TRANSMITTED DISEASES

The sexually transmitted diseases (STD) are a group of communicable diseases that are transmitted predominantly by sexual contact and caused by a wide range of bacterial, viral, protozoal and fungal agents and ectoparasites.

During the past few decades, STDs have undergone a dramatic transformation *(1)*. First, the change in name from venereal diseases (V.D.) to sexually transmitted diseases (STD) indicates this transformation. The list of pathogens which are sexually transmissible has expanded from the 5 "classical" venereal diseases (syphilis, gonorrhoea, chancroid, lymphogranuloma venereum and donovanosis) to include more than 20 agents, as shown in Table 1 *(2)*. Secondly, attention is now given not only to specific diseases, but also to clinical syndromes associated with STDs as shown in Table 3 *(1)*. Most of the recently recognized STDs are now referred to as **second generation STDs**. AIDS, is a totally new disease.

TABLE 1

Classification of sexually transmitted disease agents

A. Bacterial agents
- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- *Treponema pallidum*
- *Haemophilus ducreyi*
- *Mycoplasma hominis*
- *Ureaplasma urealyticum*
- *Calymmatobacterium granulomatis*
- *Shigella spp.*
- *Campylobacter spp.*
- Group B streptococcus
- *Bacterial vaginosis–associated organisms*

B. Viral agents
- Human (alpha) herpesvirus 1 or 2 (herpes simplex virus)
- Human (beta) herpesvirus 5 (formerly cytomegalovirus)
- Hepatitis virus B
- Human papilloma viruses
- Molluscum contagiosum virus
- Human immunodeficiency virus

C. Protozoal agents
- *Entamoeba histolytica*
- *Giardia lamblia*
- *Trichomonas vaginalis*

D. Fungal agents
- *Candida albicans*

E. Ectoparasites
- *Phthirus pubis*
- *Sarcoptes scabiei*

Extent of the problem

WORLD

The true incidence of STDs will never be known not only because of inadequate reporting but because of the secrecy that surrounds them. Most of them are not even notifiable. All available data, however, indicate a very high prevalence of STD.

STDs have a profound impact on sexual and reproductive health worldwide, and rank among the top 5 disease categories for which adults seek health care.

More than 1 million STIs are acquired every day in the age group 15–49 years worldwide, majority of which are asymptomatic. Each year, there are an estimated 374 million new infections with 1 of 4 STIs. During 2022, there were about chlamydia (129 million), gonorrhoea (82 million), syphilis (8 million) and trichomoniasis (156 million). More than 500 million people are living with genital HSV (herpes) infections. At any point in time, more than 300 million women have an HPV (Human Papilloma Virus) infection, one of the most common STIs. An estimated 254 million people are living with chronic hapatitis B globally *(3)*.

STIs can have serious consequences beyond the immediate impact of the infection itself. STIs like herpes and syphilis can increase the risk of HIV acquisition three-fold or more. Mother-to-child transmission of STIs can result in stillbirth, neonatal death, low-birth-weight and prematurity, sepsis, pneumonia, neonatal conjunctivitis, and congenital deformities. Over 1.1 million pregnant women were infected with syphilis resulting in approximately 390,000 adverse birth outcomes including stillbirth in 2022. HPV infection causes about 528,000 cases of cervical cancer and 311,000 cervical cancer deaths each year. STIs such as gonorrhoea and Chlamydia are major causes of pelvic inflammatory disease (PID) and infertility in women *(3)*.

INDIA

Sexually transmitted diseases are becoming a major public health problem in India.

(a) Syphilis : Serological surveys continue to be the best source of information on the prevalence of syphilis. During 2022, about 38,587 cases of syphilis (14,747 males and 23,840 females) were reported in the country with 49 death *(4)*.

(b) Gonorrhoea : Information on the morbidity of gonorrhoea is notoriously lacking as most cases are not reported. The general impression is that gonorrhoea is more widely prevalent than syphilis. During 2022, about 30,250 gonorrhoea cases (9,989 males and 20,261 females) were reported in the country with 10 deaths *(4)*.

(c) Chancroid : Chancroid or soft sore is reported to be fairly widely prevalent in India.

(d) LGV : It is reported to be more prevalent in the southern states of Tamil Nadu, Andhra Pradesh, Maharashtra and Karnataka than in the northern states.

(e) Donovanosis : Donovanosis or granuloma inguinale is endemic in Tamil Nadu, Andhra Pradesh, Orissa, Karnataka and Maharashtra. A greater prevalence along the coastal areas has been reported.

(f) Other STDs : Information on the other STDs is not readily available, as there is no reporting system for these diseases.

Epidemiological determinants

Agent factors

Over 20 pathogens have been found to be spread by sexual contact. A classification of these agents and the diseases caused by them are as shown in Table 2.

TABLE 2

Important sexually transmitted pathogens and the diseases caused by them

Pathogen	Disease or syndrome
Neisseria gonorrhoeae	Gonorrhoea, urethritis, cervicitis, epididymitis, salpingitis, PID, neonatal conjunctivitis
Treponema pallidum	Syphilis
Haemophilus ducreyi	Chancroid
Chlamydia trachomatis	LGV, urethritis, cervicitis, proctitis, epididymitis, infant pneumonia, Reiter's syndrome, PID, neonatal conjunctivitis
Calymmatobacterium granulomatis	Donovanosis (granuloma inguinale)
Herpes simplex virus	Genital herpes
Hepatitis B virus	Acute and chronic hepatitis
Human papillomaviruses	Genital and anal warts
Human immuno-deficiency virus (HIV)	AIDS
Molluscum contagiosum	Genital molluscum contagiosum
Candida albicans	Vaginitis
Trichomonas vaginalis	Vaginitis

Source : *(2, 5)*

Host factors

(a) Age : For most notifiable STDs, the highest rates of incidence are observed in 20–24 year-olds, followed by the 25–29 and 15–19 years age groups. The most serious morbidity is observed during foetal development and in the neonate *(2)*. *(b) Sex* : For most STDs, the overall morbidity rate is higher for men than for women, but the morbidity caused by infection is generally much more severe in women, as for example, pelvic inflammatory disease. *(c) Marital status* : The frequency of STD infection is higher among single, divorced and separated persons than among married couples. *(d) Socio-economic status* : Individuals from the lowest socio-economic groups have the highest morbidity rate.

Demographic factors

Certain demographic factors will undoubtedly contribute to increase in STDs in the developing countries. These include population explosion and marked increase in the number of young people, the group at high risk for STD in the population; rural to urban migration.

Social factors

Numerous social and behavioural factors are involved in the spread of STDs. These include : *(a) Prostitution* : This is a major factor in the spread of STDs. The prostitute acts as a reservoir of infection. In Asia, most STDs are contracted from prostitutes, whereas in many developed countries, the professional prostitute has largely been replaced by the "good-time girl". The male component of prostitution – the prostituant is equally important. Prostitution supplies a demand; if there were no prostituants, there would be no prostitutes. *(b) Broken homes* : Social studies indicate the promiscuous women are usually drawn from broken homes, e.g., homes which are broken either due to death of one or both parents or their separation. The atmosphere in such homes is unhappy, and children reared in such an atmosphere are likely to go astray in search of other avenues of happiness. *(c) Sexual disharmony* : Married people with strained relations, divorced and separated persons are often victims of STDs. *(d) Easy money* : In most of the developing world, prostitution is simply a reflection of poverty. It provides an occupation for earning easy money. It is fostered by lack of female employment and the prospect of a financial return impossible to achieve by other means *(6)*. *(e) Emotional immaturity* : This has been often stressed as a social factor in acquiring STDs. *(f) Urbanization and industrialization* : These are conductive to the type of lifestyle that contributes to high levels of infection, since long working hours, relative isolation from the family and geographical and social mobility foster casual sexual relationships. *(g) Social disruption* : Caused by disasters, wars and civil unrest have always caused an increase in the spread of STDs. *(h) International travel* : Travellers can import as well as export infection and their important role in the transmission of STD is exemplified by the rapid spread throughout the world of resistant strains of *N. gonorrhoea* and AIDS *(2)*. *(i) Changing behavioural patterns* : In modern society, the value traditionally set on chastity is in conflict with the more recent ideas of independence, freedom from supervision, and equal rights for both sexes. There has been a relaxation of moral and cultural values in present-day society. The tendency to break away from traditional ways of life is particularly marked among young people. *(j) Social stigma* : The social stigma attached to STDs accounts for the non-detection of cases, not disclosing the sources of contact, dropping out before treatment is complete, going to quacks for treatment, and self-treatment. *(k) Alcoholism* : The effect of alcohol seems to be more indirect than direct. Alcohol may encourage prostitution and conversely, prostitution may boost the sale of alcohol.

Clinical spectrum *(7)*

GONOCOCCAL INFECTION : Gonococcal infection causes inflammation of the genital tract involving the urethra in men and women, the cervix and rectum in women, and the rectum in men who have sex with men. Other sites are the throat (pharyngitis) and the eyes. The possible complications in women include pelvic inflammatory disease (PID). Long-term sequelae of PID are increased risk of ectopic pregnancy, infertility and chronic pelvic pain. In men, complications include inflammation of the epididymis. Long term consequences are sub-fertility and possibly urethral strictures. Serious consequences in infants include eye infection which can lead to blindness if not treated promptly. The antibiotics of choice are ciprofloxacin, ceftriaxone, cefixime or spectinomycin.

SYPHILIS : Syphilis causes ulceration of the uro-genital tract, mouth or rectum. Other signs of this infection, occurring in later stages, range from skin eruptions to complications of the cardiovascular and nervous system. Congenital syphilis is an important cause of stillbirth. The antibiotics used to treat syphilis are penicillin, doxycycline and erythromycin.

CHLAMYDIAL INFECTION : A high percentage of

individuals have no obvious clinical manifestations of this infection. If symptoms occur they are similar to those caused by gonorrhoea. Complications, which are similar to those of gonorrhoea, can result in steriltiy in women or vertical transmission during childbirth, leading to conjunctivitis or eye inflammation in the newborn. In men it can cause urethritis with possible epididymitis. The antibiotics used are doxycycline or azithromycin. The alternatives are amoxycillin, ofloxacin, erythromycin or tetracycline.

TRICHOMONIASIS : This parasitic infection leads to vaginitis and vaginal discharge in women. Usually, there are no symptoms. In most men there are no symptoms but it may cause urethritis. There is increasing evidence that *T. Vaginalis* may cause adverse outcomes in pregnancy, e.g. low birth weight and premature rupture of the membranes. The treatment option is metronidazole or tinidazole.

CHANCROID : After infection a small papule develops at the site of inoculation, normally within 2–3 days. The lesion then erodes into a deep ulcer that is extremely painful. In about 25 per cent of patients there is a painful swelling of one or the other inguinal lymph nodes (bubo). The antibiotics used are ciprofloxacin, erythromycin, ciftriaxone and azithromycin.

LYMPHOGRANULOMA VENEREUM : It commonly presents with swelling of lymph nodes in the groin. Although initially there is a small, painless ulcer of the genitalia 3–30 days after exposure it may pass unrecognized and resolve spontaneously. Untreated, the disease may cause extensive lymphatic damage resulting in elephantiasis of the genitalia. The antibiotics used are doxycycline, erythromycin and tetracycline. Benefit in late cases, e.g. with rectal stricture is slight. Surgical operation may be of benefit in cases with extensive elephantiasis or deformity.

DONOVANOSIS : Synonyms are granuloma inguinale, granuloma venereum. The first manifestation, appearing after a 3–40 days incubation period, is usually a small papule which ruptures to form a granulomatous lesion that is characteristically pain free and bleeds readily on contact, often elevated above the level of the surrounding skin. Antibiotics used are azithromycin and doxycycline, or alterantively erythromycin, tetracycline, trimethoprim–sulfamethoxazole.

GENITAL HERPES : Herpes simplex virus type 2 (HSV-2) is the primary cause of genital herpes. Classical genital herpes can be recognized by the presence of typical papular lesions that progress to multiple blisters and ulcers. However, the features can be variable in many people and the appearance can easily be confused with other genital infections. First episode of disease manifestation are frequently associated with a prolonged course of ulceration, lasting up to three to four weeks. Antiviral treatment of these episodes can be very effective in shortening the duration and alleviating pain. HSV-2 infection is life-long and recurrent ulcerative episodes occur. The median recurrence rate after a symptomatic first episode of genital herpes is four to five episodes per year. Asymptomatic or subclinical infection does occur, as do subclinical recurrences, accompanied by viral shedding without a visible ulcer. These subclinical episodes can be infectious to sexual partners. There is no cure for HSV-2 infection. However, oral antiviral medications such as acyclovir, valacyclovir and famciclovir are all effective in reducing the severity and duration of first-episode genital herpes. Topical creams are less effective. Episodic treatment has a limited role in reducing the duration of lesions as they tend to last less than a week.

HUMAN PAPILLOMA VIRUS : Human papilloma virus (HPV) causes ano-genital warts, which vary from the common soft, flesh-coloured protuberances which may become exuberant (cauliflower like) to papular flat warts on drier areas (eg. shaft of penis), which resemble those seen on other parts of the body. They can be seen anywhere in the genitalia including in the perianal region, even in those denying anal sexual intercourse. The other commonly recognized manifestation of genital HPV infection is cervical cancer, caused by some sub-types of HPV. Treatment is generally reserved for large lesions because sub-clinical infection tend to resolve on their own. For any viral infection the mainstay of control is prevention, especially in young sexually active individuals. Regular examination of the cervix and cervical cytology using Papanicolaou staining method is recommended for female patients and female contacts in order to detect progression of lesions to cervical cancer. Detection programmes based on cervical cytology screening and colposcopy services have been successful in curbing the incidence of, and mortality from cervical cancers in industrialized countries, but are expensive to run in developing countries.

Syndromic approach to STD

Many different agents cause sexually transmitted diseases. However, some of these agents give rise to similar or overlapping clinical manifestations. Common syndromes and sequelae are as shown in Table 3.

TABLE 3

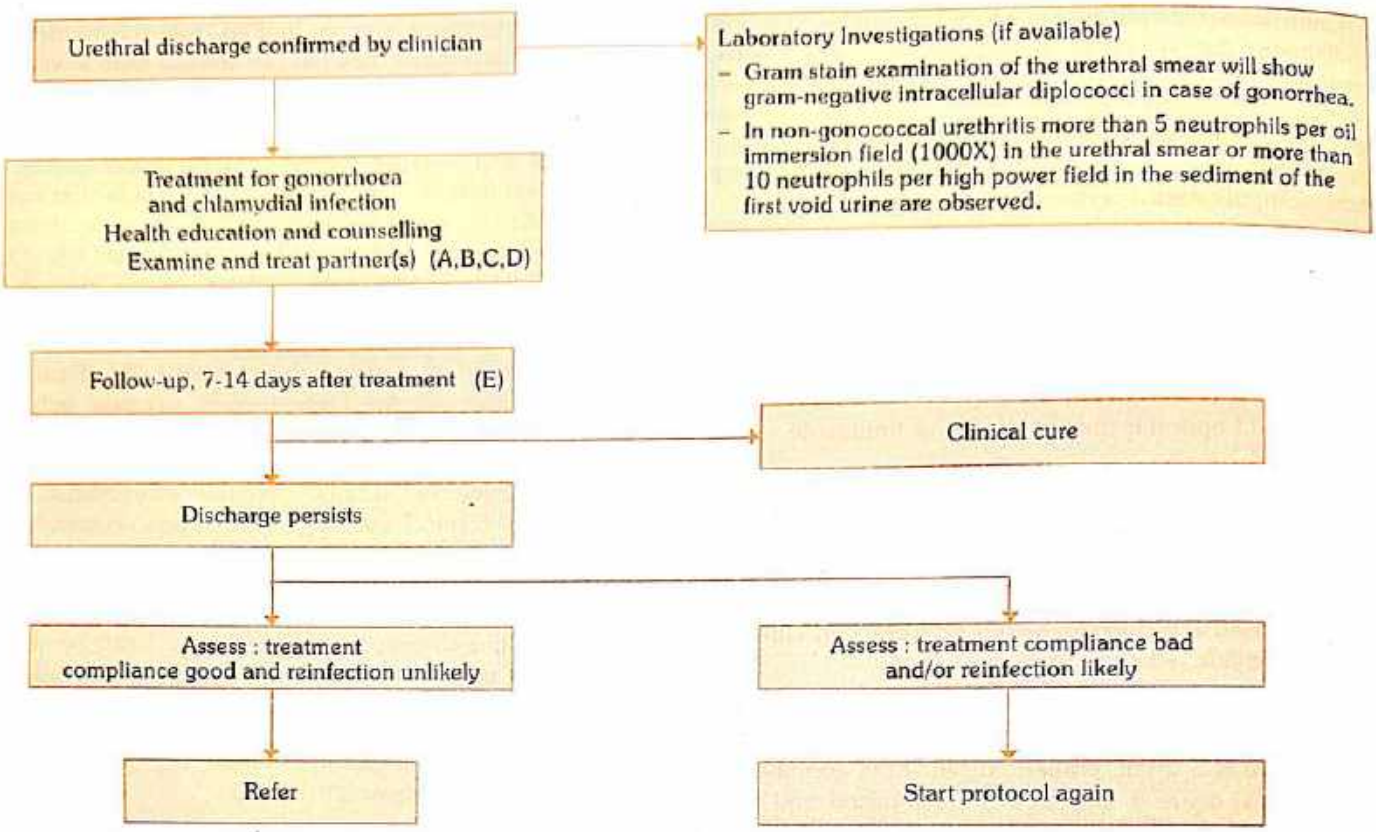
Common syndromes and sequelae for which sexual transmission is of epidemiological importance

Male urethritis
Lower genital syndromes in women : vaginitis/cervicitis/urethritis
Genital ulceration
Proctitis/colitis
Salpingitis
Epididymitis/orchitis
Infertility/ectopic pregnancy
Postnatal and perinatal morbidity
Hepatitis/hepatic carcinoma
Genital carcinoma
Acquired Immuno Deficiency Syndrome (AIDS)

Source : *(1)*

The traditional method of diagnosing STD is by laboratory tests. However, these are often not available or are expensive. Since 1990 WHO has recommended syndromic management of STDs in patients presenting with consistently recognized signs and symptoms of STD. The syndromic approach is a scientifically derived approach and offers accessible and immediate treatment, that is effective and efficient, management of STD using flowcharts (as shown in Fig. 1, 2, 3, 4, 5 and 6) is more cost-effective than diagnosis based on laboratory tests *(8)*.

1. Syndromic management of urethral discharge in males



(A) Notification and treatment of female partners of men with urethritis are of the highest priority as one of the best ways of identifying women at high risk of having asymptomatic gonococcal and chlamydial infections.

(B) Treatment :
As dual infection is common, the treatment for urethral discharge should adequately cover therapy for both, gonorrhea and chlamydial infections.
Recommended regimen for uncomplicated gonorrhea + chlamydia.

Uncomplicated infections indicate that the disease is limited to the anogenital region (anterior urethritis and proctitis).

- Tab. Cefixime 400 mg orally, single dose Plus Tab Azithromycin 1 gram orally single dose, under supervision.
- Advise the patient to return after 7 days of start of therapy.

When symptoms persist or recur after adequate treatment for gonorrhea and chlamydia in the index patient and partner(s), they should be treated for *Trichomonas vaginalis*.

If discharge or only dysuria persists after 7 days – Tab. Secnidazole 2 gm orally, single dose (to treat for T. vaginalis).

If the symptoms still persists – Refer to higher centre as early as possible.

If individuals are allergic to Azithromycin, give Erythromycin 500 mg four times a day for 7 days.

(C) Syndrome specific guidelines for partner management :

Treat all recent partners; Treat female partners (for gonorrhea and chlamydia) on same lines after ruling out pregnancy and history of allergies; advise sexual abstinence during the course of treatment; provide condoms, educate about correct and consistent use; refer for voluntary counselling and testing for HIV, syphilis and Hepatitis B, and schedule return visit after 7 days.

(D) Management of pregnant partner :

Pregnant partners of male clients with urethral discharge should be examined by doing as per speculum as well as per vaginal examination and should be treated for gonococcal as well as chlamydial infections.

- Cephalosporins to cover gonococcal infection are safe and effective in pregnancy.
  - Tab. Cefixime 400 mg orally, single dose OR Ceftriaxone 125 mg by intramuscular injection.
    +
  - Tab. Erythromycin 500 mg orally four times a day for seven days OR Cap Amoxicillin 500 mg orally, three times a day for seven days to cover chlamydial infection.
- Quinolones (like ofloxacin, ciprofloxacin), doxycycline are contraindicated in pregnant women.

(E) Follow up after seven days to see reports of tests done for HIV, syphilis and Hepatitis B; if symptoms persist, to assess whether it is due to treatment failure or re-infection; and for prompt referral if required.

FIG. 1
Syndromic management of urethral discharge (in the absence of laboratory support)

Source : *(8)*

2. Syndromic management of vaginal discharge

Causative Organisms

Vaginitis : Trichomonas vaginalis (Tv); Candida albicans; and Gardnerella vaginalis, Mycoplasma causing bacterial vaginosis (Bv).

Cervicitis : Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, and Herpes simplex virus.

History:
- Menstrual history to rule out pregnancy.
- Nature and type of discharge (amount, smell, color, consistency).
- Genital itching
- Burning while passing urine, increased frequency.
- Presence of any ulcer, swelling on the vulval or inguinal region.
- Genital complaints in sexual partners.
- Low backache.

Examination:
- Per speculum examination to differentiate between vaginitis and cervicitis.

(a) Vaginitis:

Trichomoniasis – greenish frothy discharge
Candidiasis – curdy white discharge
Bacterial vaginosis – adherent discharge
Mixed infections may present with atypical discharge.

(b) Cervicitis :
- Cervical erosion / cervical ulcer / mucopurulent cervical discharge.
- Bimanual pelvic examination to rule out pelvic inflammatory disease.
- If speculum examination is not possible or client is hesitant, treat both for vaginitis and cervicitis.

Laboratory investigations (if available):
- Wet mount microscopy of the discharge for Trichomonas vaginalis and clue cells.
- 10% KOH preparation for candida albicans.
- Gram's stain of vaginal smear for clue cells seen in bacterial vaginosis.
- Gram's stain of endocervical smear to detect gonococci.

Treatment:

Vaginitis (TV+BV+Candida)
- Tab. Secnidazole 2 gm orally, single dose OR Tab. Tinidazole 500 mg orally, twice daily for 5 days.
- Tab. Metoclopropramide taken 30 minutes before Tab. Secnidazole, to prevent gastric intolerance.
- Treat for candidiasis with Tab Fluconazole 150 mg orally single dose OR local Clotrimazole 500 mg vaginal pessaries once.

Treatment for cervical infection (chlamydia and gonorrhea):
- Tab cefixime 400 mg orally, single dose.
- Plus – Azithromycin 1 gram, 1 hour before lunch. If vomiting within 1 hour, give anti-emetic and repeat
  - If vaginitis and cervicitis are present treat for both.
  - Instruct client to avoid douching.
  - Pregnancy, diabetes, HIV may also be influencing factors and should be considered in recurrent infections.
  - Follow-up after one week.

Management in pregnant women:

Per speculum examination should be done to rule out pregnancy complications like abortion, premature rupture of membranes.

Treatment for vaginitis (TV+BV+Candida):

In first trimester of pregnancy
- Local treatment with Clotrimazole vaginal pessary/cream only for candidiasis. Oral Flucanozole is contraindicated in pregnancy.
- Metronidazole pessaries or cream intravaginally if trichomoniasis or BV is suspected.

In second and third trimester oral metronidazole can be given
- Tab. Secnidazole 2 gm orally, single dose or Tab. Tinidazole 500 mg orally, twice daily for 5 days.
- Tab. Metoclopropramide taken 30 minutes before Tab. Metronidazole, to prevent gastric intolerance.

Specific guidelines for partner management:
- Treat current partner only if no improvement after initial treatment.
- If partner is symptomatic, treat client and partner using above protocols.
- Advise sexual abstinence during the course of treatment.
- Provide condoms, educate about correct and consistent use.
- Schedule return visit after 7 days.

FIG. 2

Syndromic management of vaginal discharge

Source : *(8)*

3. Management of lower abdominal pain in females

Causative organisms:
Neisseria gonorrhoeae; Chlamydia trachomatis; and Mycoplasma, Gardnerella, Anaerobic bacteria (Bacteroides specially gram positive cocci).
Differential diagnosis : ectopic pregnancy, twisted ovarian cyst, ovarian tumor, appendicitis, and abdominal tuberculosis.

History:
- Lower abdominal pain
- Fever
- Vaginal discharge
- Menstrual irregularities like heavy, irregular vaginal bleeding.
- Dysmenorrhea
- Dyspareunia
- Dysuria, tenesmus
- Low backache
- Contraceptive use like IUD.

Examination:
- General examination : temperature, pulse, blood pressure.
- Per speculum examination : vaginal/cervical discharge, congestion or ulcers.
- Per abdominal examination : lower abdominal tenderness or guarding.
- Pelvic examination : Uterine/adnexal tenderness, cervical movement tenderness.

Note : A urine pregnancy test should be done in all women suspected of having PID to rule out ectopic pregnancy.

Laboratory investigations (if available):
- Wet smear examination
- Gram stain for gonorrhea
- Complete blood count and ESR
- Urine microscopy for pus cells

Treatment (out patient treatment):
In mild or moderate PID (in the absence of tubo ovarian abscess), out patient treatment can be given. Therapy is required to cover *Neisseria gonorrhoeae, Chlamydia trachomatis and anaerobes.*
- Tab. Cefixime 400 mg orally twice daily for 7 days + Tab. Metronidazole 400 mg orally, twice daily for 14 days.
  +
- Doxycycline, 100 mg orally, twice a day for 2 weeks (to treat chlamydial infection).
- Tab. Ibuprofen 400 mg orally, three times a day for 3-5 days.
- Tab. Ranitidine 150 mg orally, twice daily to prevent gastritis.
- Remove intra uterine device, if present, under antibiotic cover of 24-48 hours.
- Advise abstinence during the course of treatment and educate on correct and consistent use of condoms.
- Observe for 3 days. If no improvement (i.e. absence of fever, reduction in abdominal tenderness, reduction in cervical movement, adnexal and uterine tenderness) or if symptoms worsen, refer for In patient treatment.

Caution : PID can be a serious condition. Refer the patient to the hospital if she does not respond to treatment within 3 days and even earlier if her condition worsens.

Syndrome specific guidelines for partner management:
- Treat all partners in past 2 months.
- Treat male partners for urethral discharge (gonorrhea and chlamydia).
- Advise sexual abstinence during the course of treatment.
- Provide condoms, educate on correct and consistent use.
- Refer for voluntary counselling and testing for HIV, syphilis and Hepatitis B.
- Inform about the complications if left untreated and sequelae.
- Schedule return visit after 3 days, 7 days and 14 days to ensure compliance.

Management of pregnant women:
Though PID is rare in pregnancy,
- Any pregnant woman suspected to have PID should be referred to district hospital for hospitalization and treated with a parenteral regimen which would be safe in pregnancy.
- Doxycycline is contraindicated in pregnancy.
- Note : Metronidazole is generally not recommended during the first three months of pregnancy. However, it should not be withheld for a severly acute PID, which represents an emergency.

Hospitalization of clients with acute PID should be seriously considered when:
- The diagnosis is uncertain.
- Surgical emergencies e.g. appendicitis or ectopic pregnancy can not be excluded.
- A pelvic abscess is suspected.
- Severe illness precludes management on an out patient basis.
- The woman is pregnant.
- The patient is unable to follow or tolerate an out patient regimen.
- The patient has failed to respond to out patient therapy.

Note : All patients requiring hospitalization should be referred to the district hospital.

FIG. 3
Management of lower abdominal pain in females

Source : *(8)*

4. Management of genital ulcers

Causative organisms :
Treponema pallidum (syphilis),
Haemophilus ducreyi (chancroid),
Klebsiella granulomatis (granuloma inguinale),
Chlamydia trachomatis (lymphogranuloma venerum),
Herpes simplex (genital herpes)

History:
- Genital ulcer/vesicles
- Burning sensation in the genital region.
- Sexual exposure of either partner to high risk practices including orogenital sex.

Examination:
- Presence of vesicles.
- Presence of genital ulcer-single or multiple.
- Associated inguinal lymph node swelling and if present refer to respective flowchart.

Ulcer characteristics:
- Painful vesicles/ulcers, single or multiple – herpes simplex.
- Painless ulcer with shotty lymph node – syphilis.
- Painless ulcer with inguinal lymph nodes – granuloma inguinale and LGV.
- Painful ulcer usually single, sometimes – chancroid associated with painful bubo.

Laboratory investigations:
- RPR test for syphilis.
- For further investigations refer to higher centre.

Treatment:
- If vesicles or multiple painful ulcers are present treat for herpes with Tab. Acyclovir 400 mg orally, three times a day for 7 days.
- If vesicles are not seen and only ulcer is seen, treat for syphilis and chancroid and counsel on herpes genitalis.

To cover syphilis give
Inj Benzathine penicillin 2.4 million IU IM after test dose in two divided doses (with emergency tray ready).
(In individuals allergic or intolerant to penicillin, Doxycycline 100 mg orally, twice daily for 14 days).
+
Tab. Azithromycin 1g orally single dose OR
Tab. Ciprofloxacin 500 mg orally, twice a day for three days to cover chancroid.
Treatment should be extended beyond 7 days if ulcers have not epithelialized i.e. formed a new layer of skin over the sore.
Refer to higher centre
- If not responding to treatment.
- Genital ulcers co-existent with HIV.
- Recurrent lesion.

Syndrome specific guidelines for partner management:
- Treat all partners who are in contact with patient in last 3 months.
- Partners should be treated for syphilis and chancroid.
- Advise sexual abstinence during the course of treatment.
- Provide condoms, educate about correct and consistent use.
- Refer for voluntary counselling and testing for HIV, Syphilis and Hepatitis B.
- Schedule return visit after 7 days.

Management of pregnant women:
- Quinolones (like ofloxacin, ciprofloxacin), doxycycline, sulfonamides are contraindicated in pregnant women.
- Pregnant women who test positive for RPR should be considered infected unless adequate treatment is documented in the medical records and sequential serologic antibody titers have declined.
- Inj Benzathine penicillin 2.4 million IU IM after test dose (with emergency tray ready).
- A second dose of benzathine penicillin 2.4 million units IM should be administered 1 week after the initial dose for women who have primary, secondary, or early latent syphilis.
- Pregnant women who are allergic to penicillin should be treated with erythromycin and the neonate should be treated for syphilis after delivery.
- Tab. Erythromycin 500 mg orally four times a day for 15 days.
- (Note : Erthromycin estolate is contraindicated in pregnancy because of drug related hepatotoxicity. Only Erythromycin base or Erythromycin ethyl succinate should be used in pregnancy).
- All pregnant women should be asked history of genital herpes and examined carefully for herpetic lesions.
- Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally.
- Women with genital herpetic lesions at the onset of labour should be delivered by caesarean section to prevent neonatal herpes.
- Acyclovir may be administered orally to pregnant women with first episode genital herpes or severe recurrent herpes.

FIG. 4

Management of genital ulcers

Source : *(8)*

5. Management of scrotal swelling

Causative Organisms
Neisseria gonorrhoeae
Chlamydia trachomatis.

Differential diagnosis (non RTIs/STIs)
Infections causing scrotal swelling :
tuberculosis, filariasis, coliforms, pseudomonas, mumps virus infection.
Non infectious causes :
trauma, hernia, hydrocele, testicular torsion, and testicular tumors.

History of
- Swelling and pain in scrotal region.
- Pain or burning while passing urine.
- Systemic symptoms like malaise, fever.
- Sexual exposure of either partner to high risk practices including oro-genital sex.

Examination
Look for
- Scrotal swelling.
- Redness and edema of the overlying skin.
- Tenderness of the epididymis and vas deferens.
- Associated urethral discharge/genital ulcer/inguinal lymph nodes and if present refer to the respective flowchart.
- A transillumination test to rule out hydrocele should be done.

Laboratory Investigations *(If available)*
- Gram's stain examination of the urethral smear will show gram-negative intracellular diplococci in case of complicated gonococcal infection.
- In non-gonococcal urethritis more than 5 neutrophils per oil immersion field in the urethral smear or more than 10 neutrophils per high power field in the sediment of the first void urine are observed.

Treatment
- Treat for both gonococcal and chlamydial infections
  Tab Cefixime 400 mg orally twice daily for 7 days, Plus
  Cap. Doxycycline 100 mg orally, twice daily for 14 days and refer to higher centre as early as possible since complicated gonococcal infection needs parenteral and longer duration of treatment.
- Supportive therapy to reduce pain
  (bed rest, scrotal elevation with T-bandage and analgesics)

Note :
If quick and effective therapy is not given, damage and scarring of testicular tissues may result, causing sub-fertility.

Syndrome specific guidelines for partner management.
Partner needs to be treated depending on the clinical findings.

Management protocol in case the partner is pregnant
- Depending on the clinical findings in the pregnant partner (whether vaginal discharge or endocervical discharge or PID is present) the drug regimens should be used.
- Doxycycline is contraindicated in pregnancy.
- Erythromycin base/Amoxicillin can be used in pregnancy.

(Erythromycin estolate is contraindicated in pregnancy due to hepatotoxicity.
Erythromycin base or erythromycin ethyl succinate should be given).

FIG. 5
Syndromic management of scrotal swelling

Source : *(8)*

6. Management of inguinal bubo

Causative organisms
- Chlamydia trachomatis serovars L1, L2, L3, causative agent of lympho granuloma venerum (LGV).
- Haemophilus ducreyi causative agent of chancroid.

Differential diagnosis
- Mycobacterium tuberculosis, filarisis.
- Any acute infection of skin of pubic area, genitals, buttocks, anus and lower limbs can also cause inguinal swelling.

If malignancy or tuberculosis is suspected refer to higher centre for biopsy.

History
- Swelling in inguinal region which may be painful.
- Preceding history of genital ulcer or discharge.
- Sexual exposure of either partner to high risk practices including oro-genital sex.
- Systemic symptoms like malaise, fever.

Examination

Look for
- Localized enlargement of lymph nodes in groin which may be tender and fluctuant.
- Inflammation of skin over the swelling.
- Presence of multiple sinuses.
- Edema of genitals and lower limbs
- Presence of genital ulcer or urethral discharge, and if present refer to respective flowchart.

Laboratory Investigations.
Diagnosis is on clinical grounds.

Treatment
- Start Cap. Doxycycline 100 mg orally twice daily for 21 days (to cover LGV)
  Plus
- Tab Azithromycin 1g orally single dose OR
- Tab. Ciprofloxacin 500 mg orally, twice a day for three days to cover chancroid.
- Refer to higher centre as early as possible.

Note :
- A bubo should never be incised and drained at the primary health centre, even if it is fluctuant, as there is a high risk of a fistula formation and chronicity. If bubo becomes fluctuant always refer for aspiration to higher centre.
- In severe cases with vulval edema in females, surgical intervention may be required for which they should be referred to higher centre.

Syndrome specific guidelines for partner management
- Treat all partners who are in contact with patient in last 3 months.
- Partners should be treated for chancroid and LGV.
- Tab Azithromycin 1 g orally single dose to cover chancroid
  +
  Cap Doxycycline 100 mg orally, twice daily for 21 days to cover LGV
- Advise sexual abstinence during the course of treatment.
- Provide condoms, educate on correct and consistent use.
- Refer for voluntary counselling and testing for HIV, syphilis and Hepatitis B.
- Schedule return visit after 7 days and 21 days.

Management of Pregnant partner
- Quinolones (like ofloxacin, ciprofloxacin), doxycycline, sulfonamides are contraindicated in pregnant women.
- Pregnant and lactating women should be treated with the erythromycin regimen, and consideration should be given to the addition of a parenteral amino glycoside (e.g., gentamicin)

Tab. Erythromycin base, 500 mg orally, 4 times daily for 21 days and refer to higher centre.
(Erythromycin estolate is contraindicated in pregnancy due to hepatotoxicity. Erythromycin base or erythromycin ethyl succinate should be given)

FIG. 6

Syndrome management of inguinal bubo

Source : *(8)*

MANAGEMENT OF SEXUALLY TRANSMITTED DISEASES *(9)*

Health systems need to focus on reaching specific populations in order to achieve equitable progress against sexually transmitted infections, taking into account variations in incidence and prevalence, sexual behaviours and local contexts. Priority populations in many settings include adolescent girls and boys, young people, sex workers and their clients, men who have sex with men, transgender people, people living with HIV, people who have other sexually transmitted infections, and pregnant women. Other groups that are especially vulnerable to sexually transmitted infections in many settings include people who have experienced gender-based violence, indigenous peoples, children and young people living on the street, people affected by conflict and civil unrest, and people with disabilities *(9)*.

The service delivery of interventions are as follows :

1. Continuum of sexually transmitted infection services

For sexually transmitted infections, the continuum of services has two pathways reflecting the differences between infections that can be treated and cured, and those that are lifelong infections. Health services should be organized so that individuals with curable sexually transmitted infections are diagnosed and treated on the same day and individuals with lifelong sexually transmitted infections are retained in long-term care. The retention cascade should be monitored to determine where loss to follow-up is occurring and needs to be remedied. Diagnose-and-treat strategies and access to conveniently located referral services can help to optimize outcomes at the individual and population levels.

2. The intervention packages

The intervention package should be aligned with universal health coverage benefits packages and linked to primary health care where feasible and relevant.

3. Prevention of sexually transmitted infections

Scale up primary prevention interventions for different populations and locations. People may require different STI prevention options based on their age, sex and circumstances, and individual risks and need may change across the life-course. Key interventions include comprehensive education focused on sexual and reproductive health, access to condoms, providing partner services, post-exposure prophylaxis when needed, promoting voluntary medical male circumcision where appropriate, and suppressive therapy for people with herpes simplex virus.

4. Vaccines for sexually transmitted infections

Effective vaccines exist for preventing human papillomavirus infections and hepatitis B infection, and wider provision of these vaccines will drastically reduce new cases of cervical, penile and anal cancers, and cancer of liver.

5. Vertical transmission of STI

Prevent vertical (mother-to-child) transmission of sexually transmitted infections. Several sexually transmitted infections, including HIV, syphilis, gonorrhoea, chlamydia, herpes simplex virus, and HTLV-1, can be transmitted vertically. Reducing vertical transmission will require improving access to antenatal care services and ensuring that antenatal clinics have the means to effectively prevent and manage these infections. To prevent reinfection with curable sexually transmitted infections, pregnant women should be assisted to notify their sexual partners for treatment. For syphilis, the earlier in pregnancy a woman is screened and treated, the lower the risk of an adverse birth outcome, ideally in the first antenatal care visit. Infants born to untreated or mothers with syphilis not treated with benzathine penicillin G will require adequate follow up. Suppressive herpes simplex virus therapy should be considered for women with suspected primary genital herpes during the last trimester of pregnancy to prevent neonatal herpes, and their infants followed up. In addition, all newborns should be provided with their hepatitis B birth dose, and in settings in which mothers are not routinely screened for gonorrhoea and chlamydial infection, routine prophylaxis for ophthalmia neonatorum should be administered during delivery *(9)*.

6. Sexually transmitted infection awareness and treatment seeking behaviour

Despite considerable efforts to identify simple interventions that can reduce risky sexual behaviour, behaviour change remains a complex challenge. Information, education and counselling can improve people's ability to recognize the symptoms of STIs and increase the likelihood that they will seek care and encourage a sexual partner to do so. Unfortunately, lack of public awareness, lack of training among health workers, and long-standing, widespread stigma around STIs remain barriers to greater and more effective use of these interventions *(3)*.

7. Case management for symptomatic STIs

Provide effective and comprehensive case management for people with symptomatic sexually transmitted infections and prevent onward transmission. Individuals need to be able to access quality sexually transmitted infection services in an environment in which they feel comfortable and in which care is provided in a non-discriminatory and non-stigmatizing manner, including in primary health care settings and community settings. If possible, diagnosis should be supported by aetiologic testing and timely reporting. National case management guidelines need to be updated regularly to reflect advances in treatments and diagnostics and the development of resistance to medicines. As reliable and affordable new quality-assured diagnostic tests become available, national case management from syndromic management to causative management for gonorrhoea, chlamydia and syphilis, as well as trichomoniasis where possible, should be scaled up with high coverage in primary health care.

8. Sexual partner services for STIs

Partner services can make an important contribution to averting further transmission of sexually transmitted infections and reinfection. Partner services interventions should only be offered if engagement in services is voluntary. Confidentiality must be ensured for the index case and that person's partners.

9. Screening priority populations for STIs

National sexually transmitted infection policies and guidelines should define screening strategies based on available epidemiological data. All pregnant women should be screened for HIV and syphilis at least once and as early as possible during pregnancy, and priority

populations, including individuals taking pre-exposure prophylaxis for HIV, should be screened regularly for HIV and syphilis. In addition, priority populations should be screened with quality-assured diagnostic tests for gonococcal and chlamydial infections where possible.

10. Treatment for the complications and sequelae of STIs

Early diagnosis and treatment of sexually transmitted infections will prevent complications and sequalae such as pelvic inflammatory disease, ectopic pregnancy, neurosyphilis, disseminated gonococcal and chlamydial infection, among others. Early diagnosis and treatment also contribute to the prevention of cancers caused by some sexually transmitted infections such as human papilloma virus and HTLV-1.

11. Drug resistance in STIs

The development of antimicrobial resistance is a global challenge. There is widespread resistance to most medicines used to treat gonorrhoea in many parts of the world. Other sexually transmitted infection pathogens with potential antimicrobial resistance include *Mycoplasma genitalium* and *Trichomonas vaginalis*. Countries need to strengthen and expand surveillance and monitoring of treatment failures.

12. New diagnostics and testing strategies for STIs

There is a pressing need for affordable rapid diagnostics that can simultaneously diagnose multiple pathogens. The development of these tests will facilitate the shift from syndromic to causative treatment. Low-cost rapid point-of care diagnostic tests are needed for gonorrhoea, chlamydia, human papillomavirus screening for cervical cancer, and a rapid low-cost test that can differentiate active syphilis from ever infected. Human papillomavirus as well as sexually transmitted infection-related complications such as congenital syphilis and pelvic inflammatory disease would also benefit from the development of reliable low-cost diagnostic tools.

13. Linking STI services with other health services

Delivering sexually transmitted infection services alongside other health services has the potential to reduce costs, improve efficiency, and increase access to and uptake of services. Given the high morbidity of sexually transmitted infection across a range of populations, integrating sexually transmitted infection services into primary health care is essential. Prevention and case management for sexually transmitted infections should be linked closely with HIV prevention services, including community-based and outreach services for HIV key populations.

Global health sector strategy on HIV, hepatitis and sexually transmitted infections, 2022–2030 *(3, 9)*

With this framework, WHO :

1. develops global targets, norms and standards for STI prevention, testing and treatment;
2. supports the estimation and economic burden of STIs and the strengthening of STI surveillance;
3. globally monitors anti microbial resistance (AMR) to gonorrhoea; and
4. leads the setting of the global research agenda on STIs, including the development of diagnostic tests, vaccines and additional drugs for gonorrhoea and syphilis *(3)*.

As part of its mission, WHO supports countries to (3)

- develop national strategic plans and guidelines;
- create an encouraging environment allowing individuals to discuss STIs, adopt safer sexual practices, and seek treatment;
- scale-up primary prevention (condom availability and use, etc.);
- increase integration of STI services within primary healthcare services;
- increase accessibility of people-centred quality STI care;
- facilitate adoption of point-of-care tests;
- enhance and scale-up health intervention for impact, such as hepatitis B and HPV vaccination, syphilis screening in priority populations.

National STD Control Programme

See chapter 7 for details.

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ENDEMIC TREPONEMATOSIS

Endemic treponematoses (pinta, endemic syphilis (Bejel, yaws) continue to be public health problems in some tropical countries. Of these, yaws and endemic syphilis still constitute a considerable health hazard to the child population in medically under–served areas, particularly in West and Central Africa and, the Americas *(1)*. These diseases are caused by agents which are microscopically indistinguishable. Typically these diseases have a patchy distribution in population groups away from the network of health centres *(1)*. They are usually contracted in childhood, non–venereally. Intrauterine transmission is absent. The late cardiac and cerebral manifestations of venereal syphilis which are particularly severe in that disease, do not occur in these infections (excepting scanty or mild lesions in endemic syphilis). In most countries, the prevalence of these diseases was reduced to low levels, and in some areas their transmission was interrupted due to mass–treatment campaigns. However, complacency after successful mass campaigns and the premature discontinuation of surveillance activities have led to resurgence of these infections in a number of countries *(1)*.

PINTA

A chronic infectious disease caused by *T. carateum*.

Reports suggest that pinta has virtually disappeared from countries of Latin America *(1, 2)*. The disease is now restricted to the Philippines and some areas of the Pacific. The disease is essentially one of childhood, often beginning after the age of 10 to 15 years. Transmission is non-venereal, by direct contact with infectious lesions. After an incubation period of 7 to 21 days, an initial papular lesion appears on the hands and legs, followed by a maculo-papular, erythematous rash (pintides) lasting for years. A late stage is characterized by depigmented, leukodermic patches which may be permanent. Individuals with late pinta are resistant to infection with *T. pallidum*. In the treatment of pinta, the antibiotic of choice is benzathine penicillin G (BPG) which has replaced PAM. The dose for patients under 10 years is 0.6 mega units, and for those 10 years and over 1.2 mega units *(3)*.

ENDEMIC SYPHILIS

Endemic syphilis (Bejel is a local name for this disease in Syria) occurs in the arid areas of Syria, Saudi Arabia, Iraq, Iran, Yugoslavia, northern and southern Africa and Australia. It does not occur in the Americas. The causative agent is difficult to differentiate from *T. pallidum*. The claim that it is the same microorganism has yet to be substantiated *(4)*. It is transmitted non–venereally by direct or indirect contact – among children and adolescents through their play or by drinking vessels and common eating and other household utensils under primitive, crowded and substandard conditions of living. It is thought that poor hygiene rather than climatic conditions is a major factor in the continued transmission of Bejel. It is thought that 25 per cent of children acquire the infection before the age of 10 years. The figure is increased to 60 per cent before the age of 16 years *(4)*. Endemic syphilis produces highly infectious skin lesions. Late manifestations include gumatous lesions of the skin, nasopharynx and bones *(5)*. A single injection of benzathine penicillin G is the treatment of choice. For patients under 10 years the dose is 0.6 mega units, and for patients age 10 years and over, the dose is 1.2 mega units *(3)*.

YAWS

Yaws is a chronic contagious non-venereal disease caused by *T. pertenue*, usually beginning in early childhood. It resembles syphilis in its clinical course and is characterized by a primary skin lesion (mother yaw) followed by a generalized eruption and a late stage of destructive lesions of the skin and bone. Yaws is also known as pian, bubas or framboesia.

Geographic distribution

The disease is found primarily in poor communities in warm, humid and tropical forest areas of Africa, Asia, Latin America and the Pacific. The majority of affected populations live at the "end of the road" and therefore have limited access to basic social amenities and health care.

A review of historic documents from the 1950s shows that at least 88 countries and territories within the tropical belt 20 degrees north and south of the equator were endemic for yaws. Only 13 countries are known to be currently endemic for yaws. However, these countries need support to implement the WHO "Yaws Eradication Strategy" (the Morges Strategy). Recent estimates indicate that about 89 million people live in the 13 countries endemic for yaws.

Ecuador and India have reported no cases of yaws since 2003. A WHO International Verification Team (IVT) visited India in October 2015 to assess the status of interruption of transmission. Based on the report of the IVT and endorsed by the WHO NTD Strategic and Technical Advisory Group (STAG); WHO declared India free of yaws in May 2016 *(6)*.

Epidemiological determinants

Agent factors

(a) AGENT : Yaws is caused by *T. pertenue* which closely resembles *T. pallidum* culturally and morphologically. It measures 20μ in length with 8 to 12 rigid spirals. The agent occurs in the epidermis of the lesions, lymph glands, spleen and bone marrow. The organism rapidly dies outside the tissues. (b) RESERVOIR OF INFECTION : Man is the only known reservoir of yaws. He is an infected person. Clinical lesions may relapse 2 to 3 times or more during the first 5 years of infection, and serve as source for new infections *(1)*. Most latent cases are found in clusters centred around an infectious case. There are frequent relapses in latent cases within the first 3 to 5 years of infection. The source of infection is usually the skin lesions and the exudates from early lesions. (c) COMMUNICABILITY : Variable, and may extend over several years intermittently as moist lesions break out. Treponema are usually not found in late lesions.

Host factors

(a) AGE : Yaws is primarily a disease of childhood and adolescence. Over 75 per cent of cases occur before the age of 15 years, but the disease can occur at any age *(9)*. (b) SEX : Generally, the prevalence among males is greater than among females. (c) IMMUNITY : Man has no natural immunity. Acquired resistance develops slowly and may take months or years to develop fully unless suppressed by treatment. There is considerable experimental and epidemiological evidence *(3)* that yaws provides partial immunity to venereal syphilis. The near eradication of yaws in Haiti has been followed by a high prevalence of venereal syphilis.

Environmental factors

(a) CLIMATE : Yaws is endemic in warm and humid regions. High humidity for at least 6 months of the year and an average rainfall of at least 40 inches are considered favourable for the transmission of yaws. (b) SOCIAL FACTORS : Social factors are even more important than biological factors in the perpetuation of yaws in the endemic areas. Yaws is mostly endemic among the tribal people, whose ways of living favour its transmission. Scanty clothing, poor personal cleanliness, overcrowding, bad housing, low standard of living and the absence of soap are important socio-economic factors in the epidemiology of yaws. Yaws is a crippling disease; lesions on palms and soles may disable a person for long periods making him dependant on others.

Mode of transmission

Yaws is transmitted non–venereally by : (a) DIRECT CONTACT : That is, by contact with secretions from infectious lesions. (b) FOMITES : Yaws may also be transmitted by indirect contact. The organism may remain alive on fomites or on the earthen floor in hot and humid conditions long enough to cause infection, and (c) VECTOR : There is some evidence that small flies and other insects feeding on the lesion may possibly convey the infection mechanically for brief periods.

Transplacental, congenital transmission does not occur.

Incubation period

9–90 days (average 21 days).

Clinical features

(a) EARLY YAWS : The primary lesion or "mother yaw" appears at the site of inoculation after an incubation period of 3 to 5 weeks. The lesion is extra-genital and is seen on exposed parts of the body such as legs, arms, buttocks or face. The local lymph glands are enlarged and the blood becomes positive for STS. Within the next 3 to 6 weeks, a generalized eruption appears consisting of large, yellow, crusted, granulomatous eruptions often resembling condylomata lata in secondary syphilis. During the next 5 years skin, mucous membrane, periosteal and bone lesions may develop, subside and relapse at irregular intervals. The early lesions are highly infectious.

(b) LATE YAWS : By the end of 5 years, destructive and often deforming lesions of the skin, bone and periosteum appear. The lesions of sole and palms are called "crab yaws". The destructive lesions of soft palate, hard palate, and nose are called "Gangosa". Swelling by the side of the nose due to osteo–periostitis of the superior maxillary bone is called "Goundu".

CONTROL OF YAWS

The control of yaws is based on the following principles :

1. Survey

A clinical survey of all the families in endemic areas is made. The survey should cover not less than 95 per cent of the total population. During the survey, persons suffering from yaws and their contacts are listed.

2. Treatment

Treatment is based on the following observations : (a) treatment with a single dose of Azithromycin oral or a single injection of long-acting penicillin will cure infection. (b) the simultaneous treatment of all clinical cases and their likely contacts in the community will interrupt transmission in the community *(9)*.

Benzathine penicillin G is the penicillin of choice. It has now replaced PAM *(3)*. The dose of BPG is 1.2 million units for all cases and contacts, and half that dose (0.6 million units) for children under 10 years of age. Azithromycin is given as a single oral dose at 30 mg/kg body weight (maximum 2 gm).

The WHO *(3)* has recommended three treatment policies : (a) TOTAL MASS TREATMENT : In areas where yaws is hyperendemic (i.e., more than 10 per cent prevalence of clinically active yaws), a great part of the population is at risk. The entire population including the cases should be given penicillin in the doses mentioned above. (b) JUVENILE MASS TREATMENT : In meso-endemic communities (5 to 10 per cent prevalence), treatment is given to all cases and to all children under 15 years of age and other obvious contacts of infectious cases. (c) SELECTIVE MASS TREATMENT : In hypo-endemic or areas of low prevalence (less than 5 per cent) treatment is confined to cases, their household, and other obvious contacts of infectious cases.

3. Resurvey and treatment

It is unlikely that a single round of survey and treatment will cover the entire population. In order to interrupt transmission, it is necessary to find out and treat the missed cases and new cases. Resurveys should be undertaken every 6 to 12 months. Several such follow-ups may be needed before eradication is achieved.

4. Surveillance

With the decline of yaws to very low levels, emphasis has shifted to "Surveillance and containment" – a technique which has proved highly successful in the eradication of smallpox. The surveillance and containment measures would be concentrated on affected villages, households and other contacts of known yaws cases. The measures comprise epidemiological investigation of cases to identify probable source(s) of infection and contacts of each known case so as to discover previously unknown cases and prevent new cases; treatment of cases; prophylactic treatment of contacts with BPG; and, monthly follow-up of households with confirmed cases for at least 3 to 4 months after treatment of the last active case to assure interruption of transmission.

5. Environmental Improvement

In a disease like yaws, an attack on social and economic conditions of life is as important as an attack on the biological cause. Recrudescence of the disease is apt to occur unless environmental improvement is promoted, e.g., improvement of personal and domestic hygiene, adequate water supply, liberal use of soap, better housing conditions and improvement of the quality of life.

6. Renewed eradication efforts *(9)*

The WHO roadmap for neglected tropical diseases (NTDs) have set 2020 target for the eradication of yaws from the remaining countries.

Since January 2012, when the WHO roadmap for NTDs were set and an article in the Lancet on the efficacy of a single-dose azithromycin in the treatment of yaws was published, WHO has taken steps to move the renewed eradication efforts by developing a new eradication strategy based on single dose treatment with azithromycin. These are:

a. *Total community treatment (TCT)* – treatment of the endemic community, irrespective of the number of active clinical cases;
b. *Total targeted treatment (TTT)* – treatment of all active clinical cases and their contacts (household, school, playmates).

As a first step in implemeting the new eradication strategy, 7 countries were selected for the initial pilot treatment campaigns. In 2012 it was implemented in Betou and Enyelle districts of Congo. In 2013, implementation was carried out in Ghana, Papua New Guinea and Vanuatu, achieving a coverage of more than 90 per cent. In 2014, Cameroon, Indonesia, and Solomon Islands are to implement mass treatment activities *(9)*.

7. Evaluation

To determine whether or not yaws has really been brought under control, serological studies are needed. Ideally if no yaws antibodies were found among children born since the yaws mass campaign was completed, it would mean that the campaign had been totally successful. The actual sample of the population to be tested may be as low as 1 or 2 per cent.

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AIDS

AIDS, the acquired immuno-deficiency syndrome (sometimes called "slim disease") is a fatal illness caused by a retrovirus known as the human immuno-deficiency virus (HIV) which breaks down the body's immune system, leaving the victim vulnerable to a host of life–threatening opportunistic infections, neurological disorders, or unusual malignancies *(1)*. Among the special features of HIV infection are that once infected, it is probable that a person will be infected for life. Strictly speaking, the term AIDS refers only to the last stage of the HIV infection. AIDS can be called our modern pandemic, affecting both industrialized and developing countries.

Problem statement

WORLD

Recognized as an emerging disease only in the early 1980s, AIDS has rapidly established itself throughout the world, and is likely to endure and persist well into the 21st century. AIDS has evolved from a mysterious illness to a global pandemic which has infected tens of millions people.

Promising development have been seen in recent years in global efforts to address the AIDS epidemic, including increased access to effective treatment and prevention programmes. However, the number of people living with HIV continues to grow, as does the number of deaths due to AIDS. Of particular concern are trends affecting Eastern Europe and Central Asia, where the numbers of people acquiring HIV infection and dying from HIV-related causes continue to increase. The global HIV epidemic during 2023 is summarized in Table 1.

WHO and UNAIDS has defined different types of HIV epidemics. They are as follows *(3)* :

Low-level HIV epidemics

Although HIV may have existed for many years, it has never spread to substantial levels in any sub-population. Recorded infection is largely confined to individuals with higher risk behaviour e.g. sex workers, drug injectors, men having sex with other men. Numerical proxy : HIV prevalence has not consistently exceeded 5% in any defined sub-population.

Concentrated HIV epidemics

HIV has spread rapidly in a defined sub-population, but is not well-established in the general population. This epidemic state suggests active networks of risk within the sub-population. The future course of the epidemic is determined by the frequency and nature of links between highly infected sub-populations and the general population. Numerical proxy : HIV prevalence is consistently over 5% in at least one defined sub-population but is below 1% in pregnant women in urban areas.

Generalized HIV epidemics

In generalized epidemics, HIV is firmly established in the general population. Although sub-populations at high risk may contribute disproportionately to the spread of HIV, sexual networking in the general population is sufficient to sustain an epidemic independent of sub–populations at higher risk of infection. Numerical proxy : HIV prevalence consistently over 1% in pregnant women.

On the verge of fifth decade of the AIDS epidemic, the world has turned the corner – it has halted and begun to reverse the spread of HIV. The question remains how quickly the response can chart a new course towards vision zero discrimination, zero new HIV infection and zero AIDS–related deaths through universal access to effective HIV – prevention, treatment, care and support.

HIV incidence (the number of new HIV infections in a population per year) is the key parameter that prevention efforts aim to reduce, since newly infected persons contribute to the total number of persons living with HIV; they will progress to disease and death over time; and are a potential source of further transmission. Since 1995, the year in which annual new infections peaked to 3.3 million cases globally, the number of new infections has fallen to 1.3 million in 2023. This reduction in HIV incidence reflects natural trend of epidemic, as well as the result of prevention programmes resulting in behavioural changes in different contexts, like changes in sexual behavior; programmes targeting key populations such as harm-reducing programmes for people who inject drugs; maximizing the prevention benefits of ARVs, including for the prevention of mother-to-child transmission of HIV; and voluntary medical male circumcision in high HIV-prevalence settings *(4)*.

Women represent about half of all people living with HIV worldwide, and more than half (about 62 per cent) in sub–Saharan Africa. HIV is the leading cause of death among women in reproductive age. Gender inequalities, differential access to services and sexual violence increase women's vulnerability to HIV, and women, especially younger women, are biologically more susceptible to HIV *(5)*.

The UNAIDS 2016–2021 strategy is a bold call to action to get on the "Fast-Track" and reach people being left behind. The strategy focuses on the unfinished agenda. It is a call to reach the 90–90–90 treatment targets, to close the testing gap and to protect the health of the people living with HIV. It calls for 90 per cent of the people with HIV being aware of their infection, 90 per cent of people aware that they have HIV initiating ART and 90 per cent of those receiving ART having undetectable levels of HIV in their blood by 2020. Milestone targets also include a 75 per cent reduction in new infection between 2010 and 2020, achieving zero discrimination and reducing annual HIV-related deaths to less than 500,000 by 2020 globally *(6)*.

Only when above targets are met, the next set of goals will be 95–95–95 for treatment, i.e., 95 per cent of people living with HIV knowing their HIV status; 95 per cent of people who know their status on treatment; and 95 per cent of people on treatment with suppressed viral loads. Reduce the annual number of new HIV infection among adults to 200,000 and achieving zero discrimination *(7)*.

TABLE 1
Global HIV statistics (2023)

Global HIV statistics *(2)*	– 88.4 million (71.3 million–112.8 million) people have become infected with HIV since start of the epidemic. – 42.3 million (35.7 million–51.1 million) people have died from AIDS-related illnesses since start of the epidemic.
People living with HIV	– In 2023, there were 39.9 million (36.1 million–44.6 million) people living with HIV. • 38.6 million (34.9 million–43.1 million) adults (15 years or older). • 1.4 million (1.1 million–1.7 million) children (0–14 years). • 53% of all people living with HIV were women and girls. – 86% (69–>98%) of all people living with HIV knew their HIV status in 2023. – About 5.4 million people did not know that they were living with HIV in 2023.
People living with HIV accessing antiretroviral therapy	– At the end of December 2023, 30.7 million (27–31.9 million) people were accessing antiretroviral therapy, up from 7.7 million (6.7–8 million) in 2010, but still short of the 34 million target for 2025. – In 2023, 77% (61–89%) of all people living with HIV were accessing treatment. • 77% (62–90%) of adults aged 15 years and older living with HIV had access to treatment, as did 57% (41–75%) of children aged 0–14 years. • 83% (66–96%) of women aged 15 years and older had access to treatment; however, just 72% (56–84%) of men aged 15 years and older had access. – 84% (72–98%) of pregnant women living with HIV had access to antiretroviral medicines to prevent transmission of HIV to their child in 2023.
New HIV infections	– New HIV infections have been reduced by 60% since the peak in 1995. • In 2023, 1.3 million (1 million–1.7 million) people were newly infected with HIV, compared to 3.3 million (2.6 million–4.2 million) people in 1995. • Women and girls accounted for 44% of all new infections in 2023. – Since 2010, new HIV infections have declined by 39%, from 2.1 million (1.7 million–2.7 million) to 1.3 million (1 million–1.7 million) in 2023. However, this falls far short of the target of getting below 3,70,000 by 2025. – Since 2010, new HIV infections among children have declined by 62%, from 3,00,000 (2,20,000–4,40,000) in 2010 to 1,20,000 (83,000–1,70,000) in 2023. Although progress in reducing new HIV infections is greatest among children, progress has stalled in recent years.
AIDS-related deaths	– AIDS-related deaths have been reduced by 69% since the peak in 2004 and by 51% since 2010. • In 2023, around 6,30,000 (5,00,000–8,20,000) people died from AIDS-related illnesses worldwide, compared to 2.1 million (1.6 million–2.7 million) people in 2004 and 1.3 million (1 million–1.7 million) people in 2010. – The target for 2025 is fewer than 2,50,000. – AIDS-related mortality has declined by 56% among women and girls and by 47% among men and boys since 2010. – In 2023, someone died of HIV every minute.
People most affected by HIV	– Median HIV prevalence among the adult population (ages 15–49) was 0.8% globally. However, because of marginalization, discrimination and in some cases criminalization, median prevalence was higher among certain groups of people. • 2.3% higher among young women and girls aged between 15 and 24 in eastern and southern Africa • 7.7% higher among gay men and other men who have sex with men • 3% higher among sex workers • 5% higher among people who inject drugs • 9.2% higher among transgender people • 1.3% higher among people in prisons.
Women and girls	– Globally 44% of all new HIV infections were among women and girls (all ages) in 2023. – In sub-Saharan Africa, women and girls (all ages) accounted for 62% of all new HIV infections. In all other geographical regions, over 73% of new HIV infections in 2023 occurred among men and boys. – Every week, 4000 adolescent girls and young women aged 15–24 years became infected with HIV globally in 2023. 3100 of these infections occurred in sub-Saharan Africa.
Testing and treatment targets (95–95–95)	– In 2023, 86% (69–>98%) of all people living with HIV knew their HIV status. Among people who knew their status, 89% (71–>98%) were accessing treatment. And among people accessing treatment, 93% (74–>98%) were virally suppressed. – Among children ages 0–14 years the 95–95–95 targets were 66% (47%–>87%), 86% (62%–>98%), 84% (60%–>98%). Among women, the 95-95-95 targets were: 91% (72–>98%), 91% (73–>98%), and 94% (75–>98%). – Among men, the 95–95–95 targets were: 83% (65–97%) of adult men living with HIV knew their HIV status, 86% (68–>98%) were accessing treatment and 94% (74–>98%) were virally suppressed. – Among all people living with HIV, 86% (69–>98%) knew their status, 77% (61–89%) were accessing treatment and 72% (65–80%) were virally suppressed in 2023.

Source : *(2)*

The Sustainable Development Goal target is to end the AIDS epidemic by 2030. UNAIDS has led the development of a global strategy, "Fast Track : Ending the AIDS Epidemic by 2030". The main areas of focus post-2015 include *(4)* :

1. A focus on population left behind by the HIV response, such as adolescent girls, key population (sex workers, men who have sex with men, people who inject drugs and transgender people), migrants and children;
2. A focus on locations where the greatest HIV transmission is occurring and with the greatest HIV burden, and the use of data to support the impact of programmes;
3. An integrated HIV response that expands the contribution towards universal health care, including health workforce, procurement systems, injection and blood safety, and treatment of coinfections; and
4. Sustainable programmes with transitioning to domestic funding of essential HIV services.

The interaction of HIV/AIDS with other infectious diseases is an increasing public health concern. Tuberculosis, bacterial infection and malaria have been identified as the leading cause of HIV-related morbidity in Sub-Saharan Africa. HIV infection increases the incidence and severity of clinical malaria in adults *(8)*.

The national HIV strategic plans in most SEAR countries accord priority to prevention, care and treatment interventions to high-risk populations; however coverage of a comprehensive package of HIV interventions for sex workers, men having sex with men, transgender persons and injecting drug users remains low in all countries.

INDIA

Now into its fifth decade, India's epidemic is marked by heterogeneity – not a single epidemic but made up of a number of distinct epidemics, in some places within the same state.

Latest 2023 HIV estimates for India are as shown in Table 2. The HIV prevalence trend has been declining since the epidemic's peak in the year 2000.

The overall adult prevalence in India continues to be low, wherein stabilization is noted in total epidemic size in the recent years. As a successful National AIDS and STD Response, with the incorporation of gamechanger initiatives in last 10 years, the impact on the magnitude and direction of the epidemic is evident. After attaining a peak in year 2000, the HIV epidemic size started to decline. The decline in the size of the epidemic continued till 2015–18 and has been almost stable since then.

TABLE 2
Summary of HIV/AIDS epidemic in India, 2023

Indicators	Disaggregation	Value
Adult (15–49 years) Prevalence (in %)	Total	0.20 (0.17–0.25)
	Male	0.22 (0.18–0.28)
	Female	0.19 (0.16–0.23)
Number of people living with HIV (in lakh)	Total	25.44 (21.68–30.38)
	Adult (15+ years)	24.81 (21.15–29.61)
	Women (15+ years)	11.22 (9.56–13.32)
	Children (<15 years)	0.63 (0.51–0.79)
	Young people (15–24)	1.63 (1.27–2.17)
HIV incidence per 1000 uninfected population	Total	0.05 (0.03–0.08)
	Male	0.06 (0.04–0.09)
	Female	0.04 (0.03–0.07)
New HIV Infections (in thousand)	Total	68.45 (45.85–107.08)
	Adults (15+ years)	66.11 (44.41–102.86)
	Women (15+ years)	27.04 (18.10–42.16)
	Children (<15 years)	2.35 (1.37–4.34)
	Young people (15–24)	16.19 (10.76–25.28)
Decline in new HIV infections since 2010 (%)	Total	44.23
	Adults (15+ years)	39.94
	Female (15+ years)	41.01
	Children (<15 years)	81.45
	Young people (15–24)	46.99
AIDS-related deaths per 100,000 population	Total	2.61 (1.77–3.95)
	Male	3.39 (2.37–4.94)
	Female	1.78 (1.01–3.00)
AIDS-related deaths (in thousand)	Total	35.87 (24.32–54.40)
	Adults (15+ years)	34.68 (23.56–52.26)
	Women (15+ years)	11.32 (6.44–19.09)
	Children (<15 years)	1.19 (0.60–2.45)
	Young people (15–24)	0.90 (0.56–1.47)
Decline in AIDS related deaths since 2010 (%)	Total	79.26
	Adults (15+ years)	78.57
	Female (15+ years)	81.64
	Children (<15 years)	89.29
	Young people (15–24)	76.30
Need of services for EVTH (in thousand)	Total	19.96 (16.40–24.74)
Final MTCT rate of HIV (%)	Total	11.75 (7.93–17.66)

Source : *(9)*

The rapid scale-up of treatment services uptake contributed to both prevention of new infections in general and reductions in AIDS-related mortality among PLHIV. As per 2023 round of India HIV estimates, it was estimated that around 68.45 thousand (45.85–107.08 thousand) persons were newly infected with HIV in 2023 while 35.87 thousand (24.32–54.40 thousand) HIV-infected persons died due to AIDS-related illness.

With policy decisions augmenting the uptake of anti-retroviral treatment (ART) under NACP which in-turn fast-tracked attainment of viral suppression reducing mortality and increasing AIDS-free survival, aging of HIV epidemic is being noted. In 2022, around 36% of the total PLHIV were estimated to be in the age group of 50 years or older. This is significantly different from the period when the ART component of NACP was yet to be launched. In 2000, as per the India HIV Estimates 2022, only around 17% of the total PLHIV were aged 50 years or older.

Growing older with HIV has additional concerns from the perspective of public health planning and management. Even when the viral levels are suppressed among HIV-infected persons, there is evidence that higher rates of inflammation among HIV-positive individuals are linked to higher rates of cardiovascular, renal, neurocognitive, oncological and osteoporotic illness.

The change in the age-sex pattern, along with the declining fertility rates and improved uptake of ART services, resulted in reduced vertical transmission of HIV. Around estimated 20.74 thousand (16.91–25.75 thousand) HIV-positive women gave birth in the year 2022 and thus were in need of treatment and prophylaxis to prevent vertical transmission to the new-born. In FY 2022–23, a total of 15,975 HIV positive pregnant women, either newly initiated or already on-ART before the current pregnancy, were on-lifelong ART. This amounts to a treatment coverage of around 77%. With this coverage, around 4,100 (2500–6500) children are estimated to have acquired HIV through vertical transmission, with a final transmission rate of 19.91% (14.84–25.55%) *(10)*.

At the national level, estimated adult HIV prevalence (15–49 years) is the highest in the north-east region states followed by southern states. The declining trend is noted in all states/UTs excluding Puducherry, Arunachal Pradesh, Meghalaya, and Tripura. The highest decline is estimated in Chandigarh, Telangana, and West Bengal.

Key population affected in India *(10)*

The HIV epidemic in India is driven by sexual transmission, which accounts for 86 per cent of new infections. It is followed by parent-to-child, injecting drug users, homosexuals and blood and blood products use etc.

According to HIV sentinel surveillance during 2021, the overall HIV prevalence among ANC clinic attendees (considered as proxy for prevalence among general population) continues to be low at 0.22 per cent, with an overall declining trend at national level. India continues to portray a concentrated epidemic. HIV prevalence and targetted interventions among different risk groups and bridge population is summarized as below.

Each high risk group in a targetted intervention is provided free medical check-up/clinic visit once in a quarter.

In the context of 95–95–95, efforts are being make to achieve 100 per cent ART linkage and their retension to achieve viral load suppression *(10)*.

1. Female sex workers

Indicator	2022-23
1. Estimated size	9,95,499
2. Coverage (%)	≥95
3. Condoms distributed	19,22,99,332
4. Tested for HIV (April 2022-September 2022)	6,46,210
4.1 HIV sero-positive (%)	0.11
4.1.1 Linked to ART	594
5. Tested for HIV (October 2022 -March 2023)	7,07,658
5.1 HIV sero-positive (%)	0.11
5.1.1 Linked to ART	650
6. Clinic Visits	25,90,450
7. STI/RTI treated	32,799
8. Presumptive treatment	1,14,429

2. Men who have sex with men

Indicator	2022-23
1. Estimated size	3,51,020
2. Coverage (%)	≥95
3. Condoms distributed	6,42,92,815
4. Tested for HIV (April 2022-September 2022)	2,30,163
4.1 HIV sero-positive (%)	0.32
4.1.1. Linked to ART	615
5. Tested for HIV (October 2022 -March 2023)	2,52,874
5.1 HIV sero-positive (%)	0.28
5.1.1 Linked to ART	623
6. Clinic Visits	9,04,554
7. STI/RTI treated	6,788
8. Presumptive treatment	37,485

3. Injecting drug users

Indicator	2022-23
1. Estimated size	2,88,717
2. Coverage (%)	72
3. Needles distributed	4,16,33,379
4. Syringes distributed	3,02,04,290
5. On OST	44,553
6. Tested for HIV (April 2022–September 2022)	1,33,255
6.1 HIV sero-positive (%)	1.49
6.1.1 Linked to ART	1,594
7. Tested for HIV (October 2022–March 2023)	1,44,374
7.1 HIV sero-positive (%)	1.20
7.1.1 Linked to ART	1,231

4. Hijra/Transgender person

Indicator	2022-23
1. Estimated size	96,193
2. Coverage (%)	68
3. Condoms distributed	1,80,31,836
4. Tested for HIV (April 2022–September 2022)	46,806
4.1 HIV sero-positive (%)	0.47
4.1.1 Linked to ART	201
5. Tested for HIV (October 2022–March 2023)	51,872
5.1 HIV sero-positive (%)	0.33
5.1.1 Linked to ART	154
6. Clinic Visits	1,84,808
7. STI/RTI treated	1,790
8. Presumptive treatment	7,262

5. Migrants

Indicator	2022-23
1. Estimated size	72,00,000
2. Coverage (%)	≥95
3. Tested for HIV	9,52,755
3.1 HIV sero-positive (%)	0.12
3.2 Linked to ART	3,490

6. Truckers

Indicator	2022-23
1. Estimated size	20,00,000
2. Coverage (%)	53
3. Tested for HIV	2,91,130
3.1 HIV sero-positive (%)	0.12
3.2 On ART	289

7. Prison inmates

Indicator	2022-23
1. Total prisons	1,319
2. Prisons covered under programme	1,262
3. Total inmates admitted	21,25,147
4. Inmates Covered (%)	67
5. Tested for HIV	12,45,209
5.1 HIV sero-positive (%)	0.47
5.2 On ART (%)	84.83

8. Link worker scheme

Indicator	2022-23
1. Districts covered under scheme	168
2. Vulnerable population covered	22,83,094
3. Tested for HIV	13,62,169
3.1 HIV sero-positive (%)	0.27
3.2 Linked to ART (%)	95.7

Prevalence of HIV among injecting drug users (IDU) is high and major route of HIV transmission in India's north-eastern states. A 2018 study analyzed unsafe injecting and sexual risk behaviours among about 20,000 Indian men who injected drugs. Results suggest that beginning drug use at age 25 years or below, engagement in drug use for longer time, injecting three times or more per day, sharing needles and syringes, and sufferers of sexually transmitted diseases were all linked to an increased likelihood of HIV infection *(11)*.

HIV prevention efforts in the north-east of the country have been effective in reducing the number of new infections. However, there is evidence that the number of people who inject drugs is growing. In addition, evidence of higher HIV prevalence among sub-populations of people who inject drugs is also emerging. For instance, a 2015 study found prevalence to be more than three times higher among women who inject drugs than men *(11)*.

NACO categorizes groups of migrants as 'bridge populations', as they form links between urban and rural areas, and between groups that are at high-and low-risk of HIV transmission. HIV testing among these groups remains low, standing at 13.23 per cent in 2022 *(10)*. Despite being an important driver of the HIV epidemic in India, data on migrant sexual behaviour is limited. A high percentage of women testing positive in India have a husband who is a migrant labourer. A 2017 study found that HIV prevalence among the wives of migrant workers in rural northern India

was higher than among women in the general population at 0.59%. Only 15.5% of those questioned had heard of HIV.

A number of studies have reported high vulnerability of truckers to HIV transmission in India. NACO estimated that 0.12% of truck drivers were living with HIV in 2022 *(10)*. NACO also categorizes truck drivers as a bridge population because they often have unprotected sex with high-risk groups such as female sex workers as well as their regular sex partners, which increases the risk of transmitting HIV into the general population. A 2015 study found 49% of truckers in central India reported paying for sex, of whom 21.5% had a sexually transmitted infection. HIV testing among truck drivers remains low, standing at 21.74% in 2016 *(11)*.

Impoverished, unemployed, under employed, mobile and migrant youth, and street children are particularly vulnerable to HIV, as they are less likely to have information about HIV or access to preventive measures, and they may face repeated risks of HIV infection.

EPIDEMIOLOGICAL FEATURES

1. Agent factors

(a) AGENT : When the virus was first identified it was called "lymphadenopathy–associated virus (LAV)" by the French scientists. Researchers in USA called it "human T–cell lymphotropic virus III (HTLV–III)". In May 1986, the International Committee on the Taxonomy gave it a new name : human immunodeficiency virus (HIV).

The virus is 1/10,000th of a millimetre in diameter. It is a protein capsule containing two short strands of genetic material (RNA) and enzymes. The virus replicates in actively dividing T4 lymphocytes and like other retroviruses can remain in lymphoid cells in a latent state that can be activated. The virus has the unique ability to destroy human T4 helper cells, a subset of the human T–lymphocytes. The virus is able to spread throughout the body. It can pass through the blood–brain barrier and can then destroy some brain cells. This may account for certain of the neurological and psychomotor abnormalities, observed in AIDS patients. HIV mutates rapidly, new strains are continually developing. There are two types of HIV – HIV 1 and HIV 2, which exceeds 50 per cent.

The virus is easily killed by heat. It is readily inactivated by ether, acetone, ethanol (20 per cent) and beta–propiolactone (1:400 dilution), but is relatively resistant to ionizing radiation and ultraviolet light *(12)*.

(b) RESERVOIR OF INFECTION : These are cases and carriers. Once a person is infected, the virus remains in the body life-long. The risk of developing AIDS increases with time. Since HIV infection can take years to manifest itself, the symptomless carrier can infect other people for years.

(c) SOURCE OF INFECTION : The virus has been found in greatest concentration in blood, semen and CSF. Lower concentrations have been detected in tears, saliva, breast milk, urine, and cervical and vaginal secretions. HIV has also been isolated in brain tissue, lymph nodes, bone marrow cells and skin *(13)*.

2. Host factors

(a) AGE : Most cases have occurred among sexually active persons aged 20–49 years. This group represents the most productive members of the society, and those responsible for child-bearing and child-rearing.

(b) SEX : In North America, Europe and Australia, about 51 per cent of cases are homosexual or bisexual men. In Africa, the picture is very different; the sex ratio is equal. Certain sexual practices increase the risk of infection more than others, e.g., multiple sexual partners, anal intercourse, and male homosexuality. Higher rate of HIV infection is found in prostitutes.

(c) HIGH-RISK GROUPS : Male homosexuals and bisexuals, heterosexual partners (including prostitutes), intravenous drug abusers, transfusion recipients of blood and blood products, haemophiliacs and clients of STD.

Immunology

The immune system disorders associated with HIV infection/AIDS are considered to occur primarily from the gradual depletion in a specialised group of white blood cells (lymphocytes) called T–helper or T–4 cells. The full name of T–helper cell is CD4 + T lymphocyte and is also commonly known as CD4 + cell. These cells play a key role in regulating the immune response.

HIV selectively infects T–helper cells apart from several other cells in the immune system such as B–cells, microphages and nerve cells. When the virus reproduces, the infected T–helper cells are destroyed. Consequently people with AIDS tend to have low overall white blood cell count *(14)*. Whereas healthy individuals have twice as many "helper" cells as "suppressor" cells, in the AIDS patients the ratio is reversed. A decreased ratio of T–helper to T–suppressor cells may be an indirect indicator of reduced cellular immunity. One of the most striking features of the immune system of patients with AIDS is profound lymphopenia, with a total lymphocyte count often below 500/ cu. mm. It is the alteration in T–cell function that is responsible for the development of neoplasms, the development of opportunistic infections, or the inability to mount a delayed–type hypersensitivity response. The lack of an obvious immunological response by the host to the virus is one of the problems confronting scientists *(15)*. That is, those with antibodies to HIV, usually will have too few of HIV antibodies, and these antibodies are also ineffective against the virus.

Mode of transmission

The causative virus is transmitted from person-to-person, most frequently through sexual activity. The basic modes of transmission are :

(a) Sexual transmission

AIDS is first and foremost a sexually transmitted disease. Any vaginal, anal or oral sex can spread AIDS. Every single act of unprotected intercourse with an HIV–infected person exposes the uninfected partner to the risk of infection. The size of the risk is affected by a number of factors, including the presence of STD, the sex and age of the uninfected partner, the type of sexual act, the stage of illness of the infected partner, and the virulence of the HIV strain involved. A European study of heterosexual couples in which only one partner was infected at the start, suggests that chances of transmission of HIV infection from male to female is twice as likely as from female to male *(16)*. Generally, women are more vulnerable to HIV infection because a larger surface is exposed, and semen contains higher concentration of HIV than vaginal or cervical fluids.

Anal intercourse carries a higher risk of transmission than vaginal intercourse because it is more likely to injure tissues of the receptive partner. For all forms of sex, the risk of transmission is greater where there are abrasions of the skin or mucous membrane. For vaginal sex the risk is greater when woman is menstruating.

Exposed adolescent girls and women above 45 years of

age are more prone to get HIV infection. In teenagers the cervix is thought to be less efficient barrier to HIV than in mature genital tract of adult women. The thinning of mucosa at menopause is believed to lessen the protective effect. The production of mucus in the genital tract of adolescent girls and in postmenopausal women is not as prolific as in women between these life stages and this may also enhance their susceptibility to HIV infection.

An STD in either the HIV–negative or the HIV–positive partner facilitates the transmission of HIV. The risk of transmission is 8–10 times higher. If an STD, such as syphilis, chancroid or herpes, causes ulceration in the genital or perineal region of the uninfected partner, it becomes far easier for HIV to pass into his or her tissues. An STD causes inflammation. T–cells and monocytes/macrophages, get concentrated in the genital area. In a person already infected with HIV, some of these key cells of the immune system will be carrying the virus – which magnifies the risk of transmission to the uninfected partner.

As for HIV–infected people, they are more infectious to others in the very early stages, before antibody production i.e. during the "window period", and when the infection is well advanced, because levels of virus in the blood at that time is higher than at other times.

(b) Blood contact

AIDS is also transmitted by contaminated blood – transfusion of whole blood cells, platelets and factors VIII and IX derived from human plasma. There is no evidence that transmission ever occurred through blood products such as albumin, immunoglobulins or hepatitis vaccines that meet WHO requirements *(12)*. Contaminated blood is highly infective when introduced in large quantities directly into the blood stream. The risk of contracting HIV infection from transfusion of a unit of infected blood is estimated to be over 95 per cent. Since the likelihood of HIV transmission through blood depends on the "dose" of virus injected, the risk of getting infected through a contaminated needle, syringe or any other skin–piercing instrument is very much lower than with transfusion. Nevertheless, among drug users who inject heroin, cocaine or other drugs, this route of transmission is significant because exposure is repeated so often, in some cases, several times a day. As a result, needle–sharing by drug users is a major cause of AIDS in many countries, both developed and developing, and in some it is the predominant cause. Any skin piercing (including injections, ear-piercing, tattooing, accupuncture or scarification) can transmit the virus, if the instruments used have not been sterilized and have previously been used on an infected person. It may be mentioned that transfusion of blood and blood products has played a minor role in the spread of AIDS in the developed countries.

(c) Maternal–foetal transmission : mother-to child transmission

HIV may pass from an infected mother to her foetus, through the placenta or to her infant during delivery or by breast-feeding. In the absence of any intervention, rates of this form of transmission can vary from 20–25 per cent. Transmission during the peripartum period accounts for one-third to two-thirds of overall numbers infected, depending on whether breast-feeding transmission occurs or not, and this period has, therefore, become a focus of prevention efforts. The risk of infection is higher if the mother is newly infected, or if she has already developed AIDS. HIV infected infants and children progress rapidly to AIDS.

Transmission of HIV from mother to child can be prevented almost entirely by anti-retroviral drug prophylaxis, elective caesarean section before onset of labour and rupture of membranes, and by refraining from breast-feeding. However, in economically poor countries, elective caesarean section is not a safe option. A substantial efficacy of triple combination of drugs has been shown in industrialized countries, where the rate of transmission is now below 2 per cent in the absence of breast-feeding *(8)*.

There is no evidence that HIV is transmitted through mosquitoes or any other insect, casual social contact with infected persons including within households, or by food or water. There is no evidence of spread to health care workers in their professional contact with people with AIDS *(17)*.

Incubation period

While the natural history of HIV infection is not yet fully known, current data suggest that the incubation period is uncertain, (from a few months to 10 years or even more) from HIV infection to the development of AIDS. The virus can lie silent in the body for many years. The percentage of people infected with HIV, who will develop clinical disease remains uncertain – possibly 10–30 per cent will develop AIDS, and another 25–30 per cent will develop AIDS–related complex. However, it is estimated that 75 per cent of those infected with HIV will develop AIDS by the end of ten years *(18)*.

Clinical manifestations

The clinical features of HIV infection have been classified into four broad categories *(15)* :

I. Initial infection with the virus and development of antibodies
II. Asymptomatic carrier state
III. AIDS–related complex (ARC)
IV. AIDS.

(I) INITIAL INFECTION

Except for a generally mild illness (fever, sore throat and rash) which about 70 per cent of people experience a few weeks after initial infection with the virus, most HIV – infected people have no symptoms for the first five years or so. They look healthy and feel well although right from the start they can transmit the virus to others. Once infected, people are infected for life. Scientists have not found as yet, a way of curing them, or making them uninfectious to others.

HIV antibodies usually take between 2 to 12 weeks to appear in the blood-stream, though they have been known to take longer. The period before antibodies are produced is the "window period" during which, although the person is particularly infectious because of the high concentration of virus in the blood, he will test negative on the standard antibody blood test. Though the body's immune system reacts to the invasion of HIV by producing antibodies, these do not inactivate the virus in the usual way.

(II) ASYMPTOMATIC CARRIER STATE

Infected people have antibodies, but no overt signs of disease, except persistent generalized lymphadenopathy. It is not clear how long the asymptomatic carrier state lasts.

(III) AIDS-RELATED COMPLEX

A person with ARC has illnesses caused by damage to the immune system, but without the opportunistic infections (Fig. 2) and cancers associated with AIDS, they may exhibit one or more of the following clinical signs; unexplained diarrhoea lasting longer than a month, fatigue, malaise, loss of

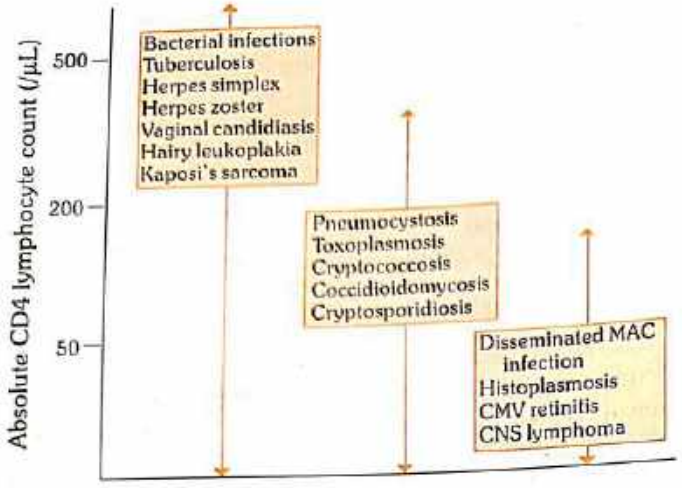

FIG. 2

Relationship of CD4 count to development of opportunistic infection

Source : *(19)*

more than 10 per cent body weight, fever, night sweats, or other milder opportunistic infections such as oral thrush, generalized lymphadenopathy or enlarged spleen. Patients from high-risk groups who have two or more of these manifestations (typically including generalised lymphadenopathy), and who have a decreased number of T–helper lymphocytes are considered to have AIDS-related complex *(1)*. Some patients with AIDS-related complex, subsequently develop AIDS.

(IV) AIDS

AIDS is the end–stage of HIV infection. A number of opportunist infections commonly occur at this stage (Fig. 2), and/or cancers that occur in people with otherwise unexplained defects in immunity. Death is due to uncontrolled or untreatable infection. Tuberculosis and Kaposi sarcoma are usually seen relatively early. Serious fungal infections such as *Candida oesophagitis*, *Cryptococcus meningitis* and *penicillosis*, and parasitic infections such as *Pneumocystis carinni* pneumonia or *Toxoplasma gondii* encephalitis tend to occur, when T–helper cell count has dropped to around 100. People whose counts are below 50 have the late opportunistic infections such as *cytomegaloviral retinitis*.

Many people with AIDS are affected by a wasting syndrome that is known, especially in Africa, as "slim disease". It involves chronic diarrhoea and severe weight loss. Another condition, seen worldwide, is AIDS encephalopathy or AIDS dementia, which is caused by HIV crossing "blood–brain barrier". In its late stages, AIDS encephalopathy resembles senile dementia or Alzheimer's disease. AIDS dementia appears to result not from opportunistic infection, but from the action of the virus itself.

TUBERCULOSIS. An alarming factor in the AIDS epidemic is the increasing link between HIV infection and tuberculosis. In countries where tuberculosis is endemic, many people are infected in childhood. When the immune system breaks down, as in HIV infection, tuberculosis becomes active and the person becomes contagious to others. Studies in Rwanda, the USA, Zaire and Zambia found that HIV–positive individuals were 30–50 times more likely to develop active tuberculosis than HIV–negative people. As a consequence, AIDS is reviving an old problem in developed countries e.g. in the USA, where there was sudden increase in tuberculosis cases. The situation in developing countries is still worst.

The emergence of drug resistance makes it essential that antibiotic sensitivity be performed on all positive cultures. Drug therapy should be individualized. Patients with multi drug resistance should receive atleast three drugs to which their organism is sensitive *(19)*.

PERSISTENT GENERALIZED LYMPHADENOPATHY. Lymph nodes are larger than one centimetre in diameter, in two or more sites other than the groin area for a period of at least three months.

KAPOSI SARCOMA. A tumour featuring reddish brown or purplish plaques or nodules on the skin and mucous membranes. Endemic in Africa prior to HIV, it used to affect mainly older men. With HIV infection it affects a wider age range and both sexes, and is characterized by lesions in the mouth or gut; or lesions are generalized (in two or more places) or rapidly progressive or invasive.

OROPHARYNGEAL CANDIDIASIS. Caused by a common yeast fungus, oral thrush presents with soreness and redness, with white plaques on the tongue, and in the mouth and throat; and sometimes a white fibrous layer covering the tonsils and back of the mouth. Infection of the oesophagus presents with pain behind the breastbone.

CYTOMEGALOVIRUS RETINITIS. Inflammation of the eye retina which may lead to blindness.

PNEUMOCYSTOSIS CARINII PNEUMONIA. Symptoms can include a dry, non-productive cough; inability to take a full breath and occasional pain on breathing; and weight loss and fever.

TOXOPLASMA ENCEPHALITIS. Protozoal infection in the central nervous system, presenting with focal neurological signs such as mild hemiplegia or stroke, resulting from damage to part of the brain, seizures or altered mental status.

HAIRY LEUKOPLAKIA. White patches on the sides of the tongue, in vertical folds resembling corrugations.

CRYPTOCOCCAL MENINGITIS. A fungal infection in the central nervous system which usually presents with fever, headache, vomiting and neck stiffness.

HERPES-ZOSTER OR SHINGLES. Viral inflammation of the central nervous system, presenting with localised pain and burning sensations, followed by vesicle eruption (skin blistering) and ulceration.

SEVERE PRURIGO OR PRURITIC DERMATITIS. Chronic skin inflammation in the form of a very itchy rash of small flat spots developing into blisters.

SEVERE OR RECURRENT SKIN INFECTIONS. Warts; dermatophytosis or ringworm; and folliculitis (inflammation of hair follicles).

DIAGNOSIS OF AIDS

CLINICAL

I. WHO case definition for AIDS surveillance

For the purposes of AIDS surveillance an adult or adolescent (>12 years of age) is considered to have AIDS if at least 2 of the following major signs are present in combination with at least 1 of the minor signs listed below, and if these signs are not known to be due to a condition unrelated to HIV infection *(20)*.

Major signs
- weight loss ≥ 10% of body weight
- chronic diarrhoea for more than 1 month
- prolonged fever for more than 1 month (intermittent or constant).

Minor signs
- persistent cough for more than 1 month[a, b]
- generalized pruritic dermatitis
- history of herpes zoster[b]
- oropharyngeal candidiasis
- chronic progressive or disseminated herpes simplex infection
- generalized lymphadenopathy.

The presence of either generalized Kaposi sarcoma or cryptococcal meningitis is sufficient for the diagnosis of AIDS for surveillance purposes.

a. For patients with tuberculosis, persistent cough for more than 1 month should not be considered as a minor sign
b. Indicates changes from the 1985 provisional WHO clinical case definition for AIDS ("Bangui definition")

The clinical definition is relatively *specific* (if used correctly), meaning that the vast majority of people diagnosed as having AIDS will have been correctly assessed. However, studies show that the definition is relatively *insensitive*, meaning that only half the patients who have severe illness related to HIV infection are included. This is because not all HIV–related opportunistic diseases are in the AIDS definition. Tuberculosis is widely recognized as the commonest opportunistic disease associated with HIV in Africa. But because TB causes wasting, cough and fever in most patients, the AIDS clinical case definition cannot reliably distinguish between HIV–positive and HIV–negative TB patients.

The clinical case definition was developed to enable reporting of the number of people with AIDS for the purposes of public health surveillance, rather than for patient care. However, for the purpose of individual case management, it is useful to be able to diagnose whether illnesses may be related to HIV infection (symptomatic HIV infection) because :

- clinical manifestations can be a reliable indicator of underlying HIV infection;
- over-use of HIV testing is avoided, testing is used to confirm suspected HIV infection, rather than as a diagnostic tool in the first instance;
- a patient with suspected HIV infection can be counselled about having an HIV test, the implications for them and their sexual partners, self-care and nutrition;
- many HIV–related illnesses can be treated, improving the patient's quality of life;
- certain drugs (such as thiacetazone) cause severe side effects in people with HIV infection, and should not be prescribed for them.

Children *(21)*

The case definition for AIDS is fulfilled if at least 2 major signs and 2 minor signs are present (if there is no other known cause of immunosuppression).

Major signs
- weight loss or abnormally slow growth
- chronic diarrhoea for more than 1 month
- prolonged fever for more than 1 month.

Minor signs
- generalized lymph node enlargement
- oropharyngeal candidiasis
- recurrent common infections, e.g. ear infection, pharyngitis
- persistent cough
- generalized rash

Confirmed HIV infection in the mother counts as a minor criterion.

The definition for children is not very specific, particularly in poor regions where childhood malnutrition and TB are common. Further, many children present with acute HIV-related illness such as *pneumocystis carinii pneumonia* without any clinical evidence of AIDS.

II. Expanded WHO case definition for AIDS surveillance

For the purposes of AIDS surveillance an adult or adolescent (>12 years of age) is considered to have AIDS if a test for HIV antibody gives a positive result, and one or more of the following conditions are present :

- ≥ 10% body weight loss or cachexia, with diarrhoea or fever, or both, intermittent or constant, for at least 1 month, not known to be due to a condition unrelated to HIV infection
- cryptococcal meningitis
- pulmonary or extra–pulmonary tuberculosis
- Kaposi sarcoma
- neurological impairment that is sufficient to prevent independent daily activities, not known to be due to a condition unrelated to HIV infection (for example, trauma or cerebrovascular accident)
- candidiasis of the oesophagus (which may be presumptively diagnosed based on the presence of oral candidiasis accompanied by dysphagia)
- clinically diagnosed life–threatening or recurrent episodes of pneumonia, with or without aetiological confirmation
- invasive cervical cancer.

Major features of this expanded surveillance case definition are that it requires an *HIV serological test*, and includes a broader spectrum of clinical manifestations of HIV such as tuberculosis, neurological impairment, pneumonia, and invasive cervical cancer. The expanded definition is simple to use and has a higher specificity *(20)*.

CLINICAL STAGING

WHO clinical staging system for HIV infection and HIV-related disease *(21)*

WHO has developed a clinical staging system (originally for prognosis), based on clinical criteria. The definition of symptoms, signs and diseases is according to clinical judgement. Clinical condition or performance score, whichever is the higher, determines whether a patient is at clinical stage 1, 2, 3, or 4 as shown in Table 3. Clinical stage is important as a criterion for starting antiretroviral (ARV) therapy.

TABLE 3
WHO clinical staging of HIV disease in adults and adolescents

Clinical stage 1
- Asymptomatic
- Persistent generalized lymphadenopathy

Clinical stage 2
- Moderate unexplained weight loss (under 10% of presumed or measured body weight)
- Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
- Herpes zoster
- *Angular cheilitis*
- Recurrent oral ulcerations
- Papular pruritic eruptions
- *Seborrheic dermatitis*
- Fungal nail infections

Clinical stage 3
- Unexplained severe weight loss (over 10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for longer than 1 month
- Unexplained persistent fever (intermittent or constant for longer than 1 month)
- Persistent oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Severe bacterial infections (e.g. pneumonia, empyema, meningitis, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anaemia (below 8 g/dl), neutropenia (below 0.5 x 10^9/l) and/or chronic thrombocytopenia (below 50 x 10^9/l)

Clinical stage 4
- HIV wasting syndrome[a]
- *Pneumocystis jiroveci* pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Cytomegalovirus disease (retinitis or infection of other organs, excluding liver, spleen and lymph nodes)
- Central nervous system toxoplasmosis
- HIV encephalopathy[b]
- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated mycosis (histoplasmosis, coccidiomycosis)
- Recurrent septicaemia (including nontyphoidal Salmonella)
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

[a] HIV wasting syndrome : weight loss > 10% of body weight, plus either unexplained diarrhoea for more than one month or chronic weakness, and unexplained fever for more than one month.

[b] HIV encephalopathy : clinical findings of disabling mental or motor dysfunction, interfering with activities of daily living, progressing over weeks and months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings.

Source : *(22, 23)*

Children
WHO clinical staging system for HIV infection and related disease in children

Stage 1 :
- Asymptomatic
- Persistent generalized lymphadenopathy

Stage 2 :
- Unexplained chronic diarrhoea
- Severe persistent or recurrent candidiasis outside the neonatal period
- Weight loss or failure to thrive
- Persistent fever
- Recurrent severe bacterial infections

Stage 3 :
- AIDS-defining opportunistic infections
- Severe failure to thrive
- Progressive encephalopathy
- Malignancy
- Recurrent septicaemia or meningitis.

Source : *(21)*

LABORATORY DIAGNOSIS

SCREENING TESTS : As antibodies to HIV are far easier to detect than the virus itself, their presence or absence in blood-stream is the basis for the most widely used test of HIV infection. A person whose blood contains HIV antibodies is said to be HIV–positive, or seropositive, meaning that he or she is infected with HIV. There is now a wide range of screening tests based on detection of HIV–antibodies. To be reliable, a screening test must be ***sensitive*** enough to identify all "true positives", while being ***specific*** enough to record few "false positives". The ideal test needs both the attributes.

At present, to ensure accuracy, two different tests are commonly applied. At first a sensitive test is used to detect the HIV–antibodies, while a second **confirmatory test** is used to weed out any false positive results. The first kind of test is normally the **ELISA**. The confirmatory test, usually a **Western Blot** is a highly specific test; it is based on detecting specific antibody to viral core protein (p24) and envelop glycoprotein (gp 41). This is a more difficult test to perform and requires trained and experienced laboratory workers to interpret the test.

VIRUS ISOLATION : A test for the virus itself would eliminate the painful uncertainty of AIDS infection. HIV can be recovered from cultured lymphocytes *(22)*. This type of testing is very expensive and requires extensive laboratory support.

The current trend in HIV–antibody tests is towards simple, cheap, reliable kits whose results can be read on the spot without much waiting and without the need for laboratory backup. HIV self testing kits are available in the market.

Non-specific laboratory findings with HIV infection may include anaemia, leukopenia (particularly lymphocytopenia) and thrombocytopenia in any combination, polyclonal hypergammaglobulinaemia. Cutaneous energy is frequent early in the course, and becomes universal as the disease progresses *(19)*.

Several laboratory markers are available to provide prognostic information and guide therapy decisions. The most widely used marker is the absolute CD4 lymphocyte count. As the count decreases, the risk of opportunistic infection increases. People with healthy immune system usually have more than 950 CD4 cells/μL of blood. The number falls over the course of HIV infection. People with AIDS usually have CD4 cell count below 200 (USA makes CD cell count below 200 in an HIV–infected person a definition of AIDS). The trend of the count is much more important than any single reading. The frequency of performance of counts depends on the patient's health system. Some studies suggest that the percentage of CD4 lymphocytes is more reliable indicator of prognosis than the

absolute count because the percentage does not depend on calculating a manual differential. Risk of progression to AIDS is high with percentage of CD4 lymphocyte less than 20 *(19)*.

The laboratory tests and their significance are as summarized in Table 4.

TABLE 4

Laboratory findings with HIV infection

Test	Significance
HIV enzyme-linked immunosorbent assay (ELISA)	Screening test for HIV infection. Sensitivity > 99.9%; to avoid false-positive results, repeatedly reactive results must be confirmed with Western blot.
Western blot	Confirmatory test for HIV. Specificity when combined with ELISA>99.99%. Indeterminate results with early HIV infection, HIV-2 infection, autoimmune disease, pregnancy and recent tetanus toxoid administration.
CBC	Anaemia, neutropenia, and thrombocytopenia common with advanced HIV infection.
Absolute CD4 lymphocyte count	Most widely used predictor of HIV progression. Risk of progression to an AIDS opportunistic infection or malignancy is high with CD4 < 200 cells/μL.
CD4 lymphocyte percentage	Percentage may be more reliable than the CD4 count. Risk of progression to an AIDS opportunistic infection or malignancy is high with percentage < 14%.
HIV viral load tests	These tests measure the amount of actively replicating HIV virus. Correlates with disease progression and response to antiretroviral drugs.
β_2 - Microglobulin	Cell surface protein indicative of macrophage – monocyte stimulation. Levels >3.5 mg/dL associated with rapid progression of disease. Not useful with intravenous drug users.
p24 antigen	Indicates active HIV replication. Tends to be positive prior to seroconversion and with advanced disease.

Source : *(19)*

The WHO has pointed out the danger of compulsory testing programmes in their tendency to social rejection of HIV–carrier and the resulting social and psychological consequences. Diagnostic testing may be useful in gauging the magnitude and course of the epidemic. It is a gateway to HIV prevention, treatment, care and other support services, including pre-test information and post-test counselling. The WHO five C's – consent, confidentiality, counselling, correct test results and connection to care and treatment – are principles that apply to all models of HIV testing services and in all circumstances.

Control of AIDS

There are four basic approaches to the control of AIDS :

1. Prevention

(a) EDUCATION

Until a vaccine or cure for AIDS is found, the only means at present available is health education to enable people to make life-saving choices (e.g., avoiding indiscriminate sex, using condoms). There is, however, no guarantee that the use of condoms will give full protection. One should also avoid the use of shared razors and toothbrushes. Intravenous drug users should be informed that the sharing of needles and syringes involves special risk. Women suffering from AIDS or who are at high risk of infection should avoid becoming pregnant, since infection can be transmitted to the unborn or newborn. Educational material and guidelines for prevention should be made widely available. All mass media channels should be involved in educating the people on AIDS, its nature, transmission and prevention; this includes international travellers.

(b) COMBINATION HIV PREVENTION *(24)*

Combination prevention programmes use a mix of biomedical, behavioural and structural interventions to meet the current HIV prevention needs of particular individuals and communities so as to have the greatest possible impact on reducing new infections.

ARV drugs play a key role in HIV prevention. People taking ART who achieve optimal viral suppression are extremely unlikely to pass HIV to sexual partners. ARV drugs taken by people without HIV as PrEP or PEP are highly effective in preventing HIV acquisition.

Other biomedical interventions that reduce HIV risk practices and/or the probability of HIV transmission per contact event include the following:

- *Male and female condoms and condom compatible lubricant* : male condoms are estimated to reduce heterosexual transmission by at least 80% and to offer 64% protection in anal sex among men who have sex with men, if used consistently and correctly. Fewer data are available for the efficacy of female condoms, but evidence suggests they can have a similar prevention effect.
- *Needle and syringe programmes* are highly associated with a reduction in HIV transmission through injecting drug use.
- *Opioid substitution therapy* with methadone or buprenorphine is the most effective form of treatment for opioid dependence and has the additional benefit of effectively reducing HIV risk behaviour and transmission through injecting drug use. Opioid substitution therapy also provides adherence support to people on ART.
- *Voluntary medical male circumcision (VMMC)* : three randomized clinical trials in Africa demonstrated an approximately 60% reduction in the risk of female-to-male sexual transmission. For high-burden settings, joint programme of WHO and United Nations on HIV/AIDS (UNAIDS) recommended the inclusion of VMMC as an additional important strategy for prevention of heterosexually acquired HIV infection in men.

(c) PREVENTION OF BLOOD-BORNE HIV TRANSMISSION

People in high-risk groups should be urged to refrain from donating blood, body organs, sperm or other tissues. All blood should be screened for HIV 1 & HIV 2 before transfusion. Transmission of infection to haemophiliacs can be reduced by introducing heat treatment of factors VIII and IX. Strict sterilization practices should be ensured in hospitals and clinics. Pre-sterilized disposable syringes and needles should be used as far as possible. One should avoid injections unless they are absolutely necessary.

2. Antiretroviral treatment

At present there is no vaccine or cure for treatment of HIV infection/AIDS. However, the development of drugs that suppress the HIV infection itself rather than its complications has been important development. These

antiviral chemotherapy have proved to be useful in prolonging the life of severely ill patients.

The availability of agents in combination suppress HIV replication. It has a profound impact on the natural history of HIV infection. Patients who achieve excellent suppression of HIV generally have stabilization or improvement of their clinical course which results from partial immunologic reconstitution and a subsequent decrease in complications of immunosuppression. Concept about the timing of such therapy have changed considerably.

Classification of drugs used for ART *(19)*

The drugs used for ART are classified as :

Nucleoside reverse transcriptase inhibitors (NRTIs)

Abacavir (ABC)
Didanosine (ddI)
Emtricitabine (FTC)
Lamivudine (3TC)
Stavudine (d4T)
Zidovudine (AZT)

Nucleotide reverse transcriptase inhibitors (NtRTIs)

Tenofovir (TDF)

Non-nucleoside reverese transcriptase inhibitors (NNRTIs)

Efavirenz (EFV)
Etravirine (ETV)
Nevirapine (NVP)

Protease inhibitors (PIs)

Atazanavir + ritonavir (ATV/r)
Darunavir + ritonavir (DRV)r)
Fos-amprenavir + ritonavir (FPV/r)
Indinavir + ritonavir (IDV/r)
Lopinavir/ritonavir (LPV/r)
Saquinavir + ritonavir (SQV/r)

Integrase strand transfer inhibitors (INSTIs)

Raltegravir (RAL)
Dolutegravir (DTG)

Fusion inhibitors

Enfuvirtide (T-20, Fuzeon)

HIV care and management recommendations (NACO 2021) *(23)*

Antiretroviral therapy (ART) in adults and adolescents

There has been a rapid decline in HIV-related mortality and morbidity due to the wider availability of affordable, more efficacious and less toxic ARVs over the last two decades. ART consists of the use of a combination of at least three ARV drugs from different classes to inhibit the replication of HIV and reduce viraemia to undetectable levels. Continued suppression of viral replication leads to the restoration of immune response, reflected by an increase in the CD4 count. Increase in CD4 count leads to slowing of the disease progression, reduced frequency of OIs, improvement in the quality of life and increased longevity. Successes achieved by ART have now transformed the perception about HIV infection from being a 'virtual death sentence' to a 'chronic manageable illness'. ART was earlier known as Highly Active ART (HAART) and as combination ART (cART).

Since 2016, WHO recommended that all people living with HIV be provided with lifelong ART, including children, adolescents and adults, pregnant and breast-feeding women, regardless of clinical status or CD4 cell count. The current HIV treatment guidelines include new ARV options with better tolerability, higher efficacy, and lower rates of treatment discontinuation when compared with previous recommended medicines.

The goals of ART are as follows *(23)* :

Clinical goals	Increased survival and improvement in quality of life
Virological goals	Greatest possible sustained reduction in viral load
Immunological goals	Immune reconstitution, that is, both quantitative and qualitative
Therapeutic goals	Rational sequencing of drugs in a manner that achieves clinical, virological and immunological goals while maintaining future treatment options, limiting drug toxicity and facilitating adherence
Preventive goals	Reduction of HIV transmission by suppression of viral load

Rapid ART initiation for newly diagnosed PLHIV at ART centre

The introduction of the 'Treat All' recommendation supports the rapid initiation of ART, including the offer of same-day initiation where there is no clinical contraindication. Rapid ART initiation is defined as "ART initiation within seven days from the day of HIV diagnosis". Following a confirmed HIV diagnosis and clinical assessment, same-day /rapid ART initiation should be offered to all PLHIV adequately prepared and ready for initiation. However, if an active OI is present, ART initiation may be deferred as required.

PLHIV should be assessed for readiness for ART initiation using the algorithm provided in Fig. 3 (with concurrent sample collection for CD4 testing and baseline investigation). This algorithm focusses on clinical screening of PLHIV for potential presence of common OIs/advanced HIV disease/comorbid conditions.

Antiretroviral Therapy Regimens *(23)*

Fixed-dose combinations (FDCs) of ARVs are preferred because they are easy to prescribe and easy for patients to take, thereby facilitating improved and desirable treatment adherence. This is essential for PLHIV as the treatment is life-long and we need to minimize the chance of developing drug-resistant mutants in their body and the resultant treatment failure. Further, FDCs have distinct advantages in drug procurement and distribution, essentially the drug stock management itself. National experience has shown that regimens with FDCs are more acceptable, well tolerated and adequately complied with.

The basic principle for first-line ART for treatment-naive adult and adolescent patients is to use a triple drug combination from two different classes of ARVs.

The first-line ART essentially comprises of a NRTI backbone, preferably Non-Thymidine (Tenofovir plus Lamivudine) and one INSTI, preferably DTG. Based on the evidence supporting better efficacy and fewer side effects, the preferred first-line ART regimen for all PLHIV with age >10 years and weight >30kg is as follows :

Tenofovir (TDF 300 mg) + Lamivudine (3TC 300 mg) + Dolutegravir (DTG 50 mg) regimen (TLD) as FDC in a single pill once a day (at a fixed time every day as per patient's convenience).

This regimen has the advantage of harmonization in the treatment of all adults, adolescents, pregnant women

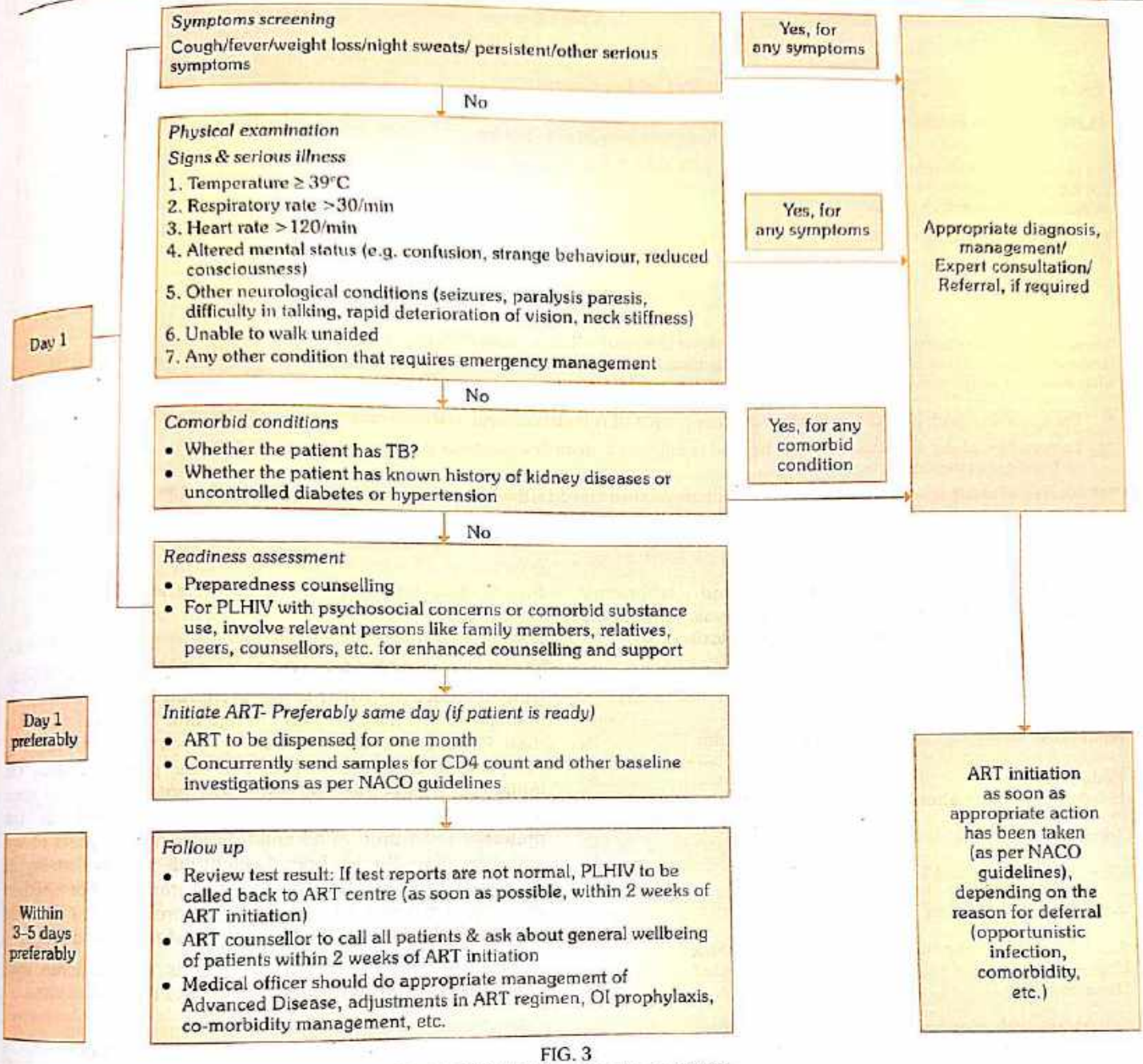

FIG. 3
Rapid ART initiation algorithm in PLHIV

Source : *(23)*

including those with HIV-1, HIV-2, HIV-1 & 2, women exposed to single dose nevirapine in the past and those co-infected with TB or Hepatitis.

It is a simple, potent and well-tolerated regimen that offers the advantage of a decentralized service delivery and monitoring. It also simplifies the supply chain and minimizes monitoring requirements.

In cases where the preferred first-line ARV regimen of TDF+3TC+DTG cannot be used, the alternative regimens are mentioned in Table 5.

General Guidance

- A single pill of TLD should be taken preferably at bedtime, and instances where additional dose of DTG is indicated should be taken preferably in the morning.
- Patients with severe Diabetes and Hypertension should be monitored more closely for TDF toxicity.
- Patients starting on DTG should be monitored for blood glucose (six monthly) and weight gain (on monthly visits). Appropriate physical activity should be advised to prevent weight gain.

Monitoring of Patients on ART

Follow-up and monitoring are essential in patients initiated on ART to track clinical progress, monitor well-being and to identify adverse drug reactions and toxicities. ART monitoring includes clinical monitoring and laboratory monitoring. Clinical monitoring includes monitoring of adherence to ART as well. The client should be monitored every month for clinical progress, side effects of the ARVs

TABLE 5

Alternate first-line ART in adults and adolescents

Condition	Alternate First-line Regimen
PLHIV with body weight <30 kg	ABC 600 mg + Lamivudine 300 mg, one tablet + DTG (50 mg) once daily in the morning or any fixed time every day as per patient's convenience
All patients with high (above ULN for laboratory) serum creatinine values (Calculate Creatinine clearance)	ABC 600 mg OD, Lamivudine (as per creatinine clearance**) and DTG 50 mg once daily in the morning or any fixed time every day as per patient's convenience
PLHIV on Rifampicin-containing ATT regimen	Tenofovir (300 mg) + Lamivudine (300 mg) + Dolutegravir (50 mg) - FDC one tablet once daily (in the morning or any fixed time every day as per patient's convenience) + Additional dose of DTG 50 mg to be provided (12 hours after taking their regular dose) until 2 weeks after completion of ATT
Women of childbearing potential who do not wish to take DTG-based ART after adequate and optimal counselling***	Tenofovir (300 mg) + Lamivudine (300 mg) + Efavirenz (600 mg) If Efavirenz is contraindicated (HIV-2/HIV-1&2/prior NNRTI exposure) then Tenofovir (300 mg) + Lamivudine (300 mg) + [Lopinavir (200 mg) + ritonavir (50 mg) twice daily]

* For all patients with high serum creatinine values (above ULN for laboratory), calculate creatinine clearance.

** Lamivudine, along with Abacavir, may be used in full dose if creatinine clearance is more than 30 ml per minute, with patient being closely monitored.

*** Women of childbearing potential receive full information and medical guidance that is appropriate to their situation and are supported in making an informed decision.

Source : *(23)*

and treatment adherence. Clinical and laboratory evaluations are carried out at specified intervals for patients on ART. Table 6 summarizes the monitoring tools *(23)*.

TABLE 6

Monitoring and follow-up schedule for patients on ART

Monitoring Tool	When to Monitor
Body weight Height / length in children	Every visit
Treatment adherence	Every visit
Clinical monitoring and T-staging	Every visit
4-symptom TB screening	Every visit
Screening for common NCD; Hypertension, Diabetes mellitus	Every 6 months or symptom directed
Laboratory evaluation based on ART regimen	Every 6 months or symptom directed
CD4 Count	CD4 must be done every 6 months*
Viral load	At 6 months, 12 months and then every 12 months**

**CD4 Count :*

1. As routine virological monitoring is available, CD4 testing should be done every 6 months and can be discontinued in PLHIV (except those with HIV-2 infection) when CD4 count reaches greater than 350 cells/mm^3 and viral load is less than 1000 copies/ml (when both tests are conducted at the same time).
2. CD4 monitoring should be restarted for any patient if
   a. the patient has been switched due to treatment failure, that is, virologic failure (Plasma Viral Load ≥ 1000 copies/ml); or
   b. when deemed necessary for clinical management by the clinician at any point in time.

** For patients on second/third-line ART, Plasma Viral Load testing to be done every 6 months.

Paediatric first-line ART regimens *(23)*

ART initiation

The choice of drugs depends on the child's age and body weight. Abacavir (ABC) is the preferred NRTI for initiation in children less than 10 years of age and body weight of less than 30 kg. For all children above 10 years and above 30 kg body weight, Tenofovir (TDF) is the preferred drug for initiation. This is the simplest, most potent and least toxic regimen. Lopinavir/ritonavir is recommended as the preferred third drug in all children less than 6 years of age and less than 20 kg body weight till the availability of Dolutegravir under the national programme. For children older than 6 years of age and of more than 20 kg body weight DTG is recommended as the preferred third drug.

First-line ART regimens for infants and children with HIV-1 and HIV-2 infection are as follows :

Particulars	Recommended Regimen
1. Age less than 6 years and body weight less than 20 kg	Abacavir + Lamivudine + Lopinavir/ritonavir (AL+LPV/r)
2. Age between 6 and 10 years and body weight between 20 kg and 30 kg	Abacavir + Lamivudine + Dolutegravir (ALD)
3. Age more than 10 years and body weight more than 30 kg	Tenofovir + Lamivudine + Dolutegravir (TLD)

Important considerations for ART regimens for infants and children include the availability of suitable paediatric drug formulations that can be taken in appropriate doses; simplicity of dose schedule; and the taste and palatability. All these are potential factors for better treatment adherence in young children. Fixed-dose combinations are increasingly available for younger children *(23)*.

Occupational HIV post exposure prophylaxis *(25)*

Postexposure prophylaxis (PEP) is recommended for healthcare personnel who have an occupational exposure to

blood, tissue, or other body fluids that may contain human immunodeficiency virus (HIV). Types of exposure that might place healthcare personnel at risk for HIV infection include any of the following : (1) Percutaneous injury (e.g., a needlestick or cut with a sharp object); and (2) Contact of mucous membranes or non-intact skin (e.g., exposed skin that is chapped, abraded, or irritated due to dermatitis) with blood, tissue, or body fluids that are potentially infectious.

The following fluids are considered potentially infectious : (a) Semen and vaginal secretions; (b) Cerebrospinal fluid; (c) Synovial fluid; (d) Pleural fluid; (e) Peritoneal fluid; (f) Pericardial fluid; and (g) Amniotic fluid.

The following are not considered potentially infectious unless they are visibly bloody : (a) Faeces; (b) Nasal secretions; (c) Saliva; (d) Sputum; (e) Sweat; (f) Tears; (g) Urine; and (h) Vomitus.

Treatment recommendations

HIV PEP should be initiated as soon as possible after the exposure, preferably within hours. Do not delay administration of PEP while awaiting HIV test results of the source patient. The rationale behind this practice includes the following : (a) Animal studies demonstrate that PEP is likely to be less effective when started more than 72 hours after exposure; (b) In the abscence of PEP, HIV replication occurs within 48 to 72 hours in regional lymph nodes close to the site of exposure, followed by viremia within 72 to 120 hours of virus inoculation; (c) If PEP initiation is delayed, the benefits might not outweigh the risks inherent in taking antiretroviral medications; and (d) Initiating therapy after a longer interval (eg, 1 week) might still be considered for exposures that represent an extremely high risk for transmission.

Preferred regimens

- Raltegravir 400 mg twice daily plus tenofovir disoproxil fumarate/emtricitabine (300 mg–200 mg) once daily for 4 weeks.
- Dolutegravir 50 mg once daily plus tenofovir disoproxial fumarate/emtricitabine (300 mg–200 mg) once daily for 4 weeks.

Lamivudine may be substituted for tenofovir disoproxial fumarate/emtricitabine in either regimen.

Since August 2019, dolutegravir has been considered an acceptable alternative to raltegravir in patients who intend to become pregnant and those who initiate therapy during the first trimester. However, patients should be advised of the small risk for teratogenicity when administered in the first trimester. There is no known elevated risk beyond the first trimester of pregnancy. Non-pregnant individuals of childbearing potential should be counseled about the need for birth control while completing a PEP regimen.

Use of co-trimoxazole prophylaxis for HIV-related infections *(24)*

Co-trimoxazole is a fixed dose combination of two antimicrobial drugs (sulfamethoxazole and trimethoprim) that covers a variety of bacterial, fungal and protozoan infections. The therapy is feasible, well tolerated and inexpensive intervention for people living with HIV to reduce HIV-related morbidity and mortality. The WHO recommendations (2016) for the use of co-trimoxazole is summarized in Table 7.

TABLE 7
Use of co-trimoxazole for HIV related infections, WHO (2016)

Adults (including pregnant women)

Co-trimoxazole prophylaxis is recommended for severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or for a CD4 count ≤ 350 cells/mm³.

- In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage.

Co-trimoxazole prophylaxis may be discontinued in adults (including pregnant women) with HIV infection who are clinically stable on antiretroviral therapy, with evidence of immune recovery and viral suppression.

- In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage.

Infants, children and adolescents

Co-trimoxazole prophylaxis is recommended for infants, children, and adolescents with HIV, irrespective of clinical and immune conditions. Priority should be given to all children younger than 5 years old regardless of CD4 cell count or clinical stage and to children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 ≤ 350 cells/mm³.

- In settings with a high prevalence of malaria and/or severe bacterial infections, co-trimoxazole prophylaxis should be continued until adulthood irrespective of antiretroviral therapy provision.
- In settings with low prevalence for both malaria and bacterial infections, co-trimoxazole prophylaxis may be discontinued for children 5 years of age and older who are clinically stable and/or virally suppressed on antiretroviral therapy for at least 6 months and CD4 > 350 cells/mm³.

HIV-exposed infants

Co-trimoxazole prophylaxis is recommended for HIV-exposed infants from 4–6 weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breast-feeding.

LPV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis among children younger than 10 years.

An age-appropriate alternative regimen can be identified among ATV/r, RAL, DRV, EFV and NVP.

HIV and TB coinfection

Routine co-trimoxazole prophylaxis should be administered to all HIV-infected people with active TB disease regardless of CD4 cell counts.

Source : *(24)*

HIV and Tuberculosis

Despite being preventable and curable, TB is the leading cause of HIV-associated mortality. Xpert MTB/RIF should be used rather than conventional microscopy, culture and drug susceptibility testing (DST) as the initial diagnostic test in adults and children suspected of having HIV-associated TB or multidrug resistant TB. Isoniazid preventive therapy and ART, given together, can reduce the risk of TB among people living with HIV by upto 97 per cent. For details, refer to page 239.

Monitoring the efficacy of ART

Efficacy is monitored by (20)

(a) clinical improvement
  - gain in body weight,
  - decrease in occurrence and severity of HIV-related diseases (infections and malignancies),

(b) increase in total lymphocyte count,

(c) improvement in biological markers of HIV (when available)
- CD4 + T-lymphocyte counts,
- plasma HIV RNA levels.

3. Specific prophylaxis

Until more effective antiviral therapy becomes available, the main aim of existing therapies will be to treat the manifestations of AIDS. Primary prophylaxis against *P. carinii* pneumonia should be offered to patients with CD4 count below 200 cells/μL. The regimens available are trimethoprim – sulfamethoxazole, aerosolized pentamidine and dapsone. Patients who develop *P. carinii* infection on a particular prophylactic regimen should be switched to the other drug or should receive a combination regimen.

M. avium complex occurs in at least one-third of AIDS patients. Rifabutin has been shown in a randomized trial to decrease the incidence of disseminated *Mavium–intracellulare* in persons with less than 200 CD4 cell/μL. Clinicians should make certain that patients do not have active *M. tuberculosis* infection before starting Rifabutin. Prophylaxis against *M. tuberculosis* is 300 mg isoniazid daily for 9 months to one year. It should be given to all HIV–infected patients with positive PPD reactions (defined for HIV–infected patients as more than 5 mm in induration). Kaposi's sarcoma might be treated in some stage with interferon, chemotherapy or radiation. Cytomegalovirus retinitis can be controlled by ganciclovir, cryptococcal meningitis with fluconazole. Esophageal candidiasis or recurrent vaginal candidiasis can be treated by fluconazole or ketoconazole. Herpes simplex infection and herpes zoster can be treated with acyclovir or foscamet.

4. Primary health care

Because of its wide–ranging health implications, AIDS touches all aspects of primary health care, including mother and child health, family planning and education. It is important, therefore, that AIDS control programmes are not developed in isolation. Integration into country's primary health care system is essential.

National AIDS Control Programme

Refer to chapter 7 for details.

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EMERGING AND RE-EMERGING INFECTIOUS DISEASES

Today the world stands on the threshold of a new era in which hundreds of millions of people will be safe from some of the most terrible diseases. Soon poliomyelitis, neonatal tetanus, guineaworm disease, river blindness, Chagas' disease will join smallpox as diseases of the past. On the other hand, the world also stands on the brink of a global crisis in infectious diseases. No country is safe from them and no country can afford to ignore their threat any longer. The optimism of a relatively few years ago that many of these diseases could easily be brought under control has led to a tragic complacency among the international community. This complacency is now costing millions of lives. Today the infectious diseases are not only a health issue; they have become a social problem with tremendous consequences for the well-being of the individual and the world we live in.

Some infectious diseases once thought to be all but conquered, have returned with a vengeance. Others have developed stubborn resistance to antibiotic drugs. New and previously unknown diseases continue to emerge (Table 1). Together, these trends amount to a crisis for today and a challenge for the future.

The factors responsible for emergence and re-emergence of infectious diseases are : (1) unplanned and under–planned urbanization; (2) overcrowding and rapid population growth; (3) poor sanitation; (4) inadequate public health infrastructure; (5) resistance to antibiotics; (6) increased exposure of humans to disease vectors and reservoirs of infection in nature; (7) rapid and intense international travel; and (8) microbial genetic mutation.

Emerging diseases

During the past 30 years, at least 30 new diseases have emerged to threaten the health of hundreds of millions of people. For many of these diseases there is no treatment, cure or vaccine and the possibility of preventing or controlling them is limited.

Emerging infectious diseases are those whose incidence in humans has increased during the last two decades or which threaten to increase in the near future. The term also refers to newly–appearing infectious diseases, or diseases that are spreading to new geographical areas – such as cholera in South America and yellow fever in Kenya.

The diseases in question involve all the major modes of

transmission – they are spread either from person to person, by insects or animals, or through contaminated water or food. The most dramatic example of a new disease is **COVID-19** in the year 2019. The ongoing COVID-19 pandemic has changed the whole world with virtual global lockdown, social distancing and use of mask as the only weapon against the uncontrolled spread of the disease. First case of COVID-19 was reported in the month of November, 2019 and on 11th March, 2020, it was declared a pandemic by the WHO. As of 20th Sept., 2022 about 618,141,427 cases with 6,533,467 deaths were reported worldwide. Although, now vaccines are available against COVID-19, the disease is yet to come under control. New strains of the virus are also now in circulation *(1)*.

Human Monkey pox, in May 2022 multiple cases of monkey pox were reported from several non-endemic countries. Studies are currently underway to further understand the epidemiology, source of infection and transmission patterns of the disease.

Tomato fever (tomatoflu), a virus infection has emerged in India in the state of Kerala in children younger than 5 years of age. It was first identified in Kollam district on May 6, 2022. Till date, this infection has been seen in the state of Odisha and Tamil Nadu along with Kerala. Tomato fever is so called because of the eruptions of red and painful blisters throughout the body. In the year 2007 also cases of tomato fever were reported in the state of Kerala.

AIDS, caused by the human immunodeficiency virus (HIV). The existence of the virus was unknown until 1983. About 38.4 million people are living with HIV globally in 2021. 1.5 million cases with 650,000 deaths were reported worldwide in 2021 *(2)*.

A new breed of deadly haemorrhagic fevers, of which **Ebola virus disease** (previously known as Ebola haemorrhagic fever) is the most notorious, has struck in Africa. Ebola appeared for the first time in Zaire and Sudan in 1976. Since then it has appeared periodically. Ebola virus is a member of Filoviridae family and comprises of 5 distinct species – Zaire ebolavirus; Reston ebolavirus; Sudan ebolavirus; Tai ebolavirus; and Bundibugyo ebolavirus. The recent epidemic started in December 2013 in Guinea and spread to South Africa. By 8th April 2015, a total of 25,515 cases have been reported with over 10,000 deaths. Case fatality rate may be as high as 70 per cent. Ebola has incubation period of 2–21 days, and is not infective during this period. Asymptomatic cases are also not infective. The virus is transmitted through direct contact with the blood, organs, body secretions or other body fluids of infected animals like chimpanzees, gorillas, monkeys, fruit bats etc. Human to human transmission is through blood or body fluids of an infected symptomatic person or through exposure to objects (such as needles) that have been contaminated with infected secretions. It is not transmitted through air, water or food. The illness is characterized by sudden onset of fever, intense weakness, muscle pain, headache, sore throat, vomiting, diarrhoea, rash, impaired kidney and liver functions and in some cases both internal and external bleeding. Currently there is no specific treatment for this disease. However, by intensive supportive care, the mortality can be reduced and spread of the disease can be prevented by instituting specific infection control measures. There is no vaccine against ebola *(3)*.

The United States has seen the emergence of **hantavirus** pulmonary syndrome, characterized by respiratory failure and a case fatality rate of over 50%. Since it was first recognized in 1993, this type of hantavirus infection has been detected in more than 20 states in that country, and has also surfaced in Argentina and Brazil. This hantavirus is carried by rodents, particularly deer mice. Other hantaviruses have been recognized for many years in Asia, where they cause haemorrhagic fever with renal involvement in humans.

Epidemics of foodborne and waterborne diseases due to new organisms such as cryptosporidium or new strains of bacteria such as ***Escherichia coli*** have hit industrialized and developing countries alike. The O157:H7 strain of *E.coli* was first reported in 1982 and has since then been implicated in many serious outbreaks of diarrhoeal illness, sometimes leading to kidney failure. The strain has been linked to undercooked hamburger beef and unpasteurized milk. A completely new strain of cholera, 0139, appeared in south–eastern India in 1992 and has since spread north and west to other areas of India, into western China, Thailand and other parts of South-East Asia.

The threat of a new global **influenza pandemic** is increasing. Major shifts in the make-up of influenza viruses occur every 20 years or so, triggering large epidemics in many parts of the world, and causing many thousands of deaths. The next such shift is expected to take place very soon. Epidemic strains of influenza viruses originate from China. The influenza virus is carried by ducks, chickens and pigs raised in close proximity to one another on farms. The exchange of genetic material between these viruses produces new strains, leading to epidemics of human influenza, each epidemic being due to a different strain. Currently avian H5N1 is the strain with pandemic potential, since it might adapt into a strain that is contagious among humans. Since 1997, 478 cases with 286 deaths have been reported to WHO. The first case was from Hong Kong. Other countries involved are Cambodia, Indonesia, Thailand and Vietnam *(6)*. In late 2002, a new disease called **SARS** was reported from China with rapid spread to Hong Kong, Singapore, Vietnam, Taiwan, and Toronto. During 2003, 8,422 SARS cases were reported from 30 countries with 916 fatalities *(7)*. More recently, pandemic due to influenza A (H1N1) 2009 strain is continuing worldwide involving 214 countries, already taking 18,156 lives. New strains such as those of cholera and influenza do not follow the usual pattern of being more common in younger people. They affect all age groups, since older people have not acquired immunity to them from previous infection.

Table 1 summarizes the aetiological agents and infectious diseases in humans and/or animals recognized since 1973. The year may differ from first appearance and first identification of cases.

Re-emerging diseases

The term re-emerging diseases refers to the diseases which were previously easily controlled by chemotherapy and antibiotics, but now they have developed antimicrobial resistance and are often appearing in epidemic form.

The emergence of drug–resistant strains of microorganisms or parasites is promoted by treatments that do not result in cure. The increasing use of antimicrobials worldwide, often in subtherapeutic doses and sometimes in counterfeit form, indicates that this problem will increase in the foreseeable future. Changes in lifestyle, behaviour (including injecting and non–injecting drug use) and cultural or social values are behind the emergence of some infectious diseases such as syphilis. Increases in the number of sexual partners have been the main factor in the spread of HIV infection and other sexually transmitted diseases. Travel,

TABLE 1

New infectious diseases recognized since 1973

Year	Agent	Type	Disease/Comments
1973	Rotavirus	Virus	Major cause of infantile diarrhoea worldwide
1975	Parvovirus B19	Virus	Aplastic crisis in chronic haemolytic anaemia
1976	*Cryptosporidium parvum*	Parasite	Acute and chronic diarrhoea
1977	*Ebola virus*	Virus	Ebola haemorrhagic fever
1977	*Legionella pneumophila*	Bacterium	Legionnaires' disease
1977	Hantaan virus	Virus	Haemorrhagic fever with renal syndrome (HRFS)
1977	*Campylobacter jejuni*	Bacterium	Enteric pathogen distributed globally
1980	Human T-lymphotropic virus 1 (HTLV-1)	Virus	T-cell lymphoma-leukaemia
1981	Toxin-producing strains of *Staphylococcus aureus*	Bacterium	Toxic shock syndrome
1982	*Escherichia coli 0157:H7*	Bacterium	Haemorrhagic colitis; haemolytic uraemic syndrome
1982	*Borrelia burgdorferi*	Bacterium	Lyme disease
1982	HTLV-2	Virus	Hairy cell leukaemia
1983	Human immunodeficiency virus (HIV)	Virus	Acquired immunodeficiency syndrome (AIDS)
1983	*Helicobacter pylori*	Bacterium	Peptic ulcer disease
1985	*Enterocytozoon bieneusi*	Parasite	Persistent diarrhoea
1986	*Cyclospara cayetanensis*	Parasite	Persistent diarrhoea
1986	BSE agent	Non-conventional agent	Bovine spongiform encephalopathy in cattle (Mad cow disease)
1988	Human herpes virus 6 (HHV-6)	Virus	Exanthem subitum
1988	*Hepatitis E virus*	Virus	Enterically transmitted non-A, non-B hepatitis
1989	Ehrlichia chaffeensis	Bacterium	Human ehrlichiosis
1989	*Hepatitis C virus*	Virus	Parenterally transmitted non-A, non-B liver hepatitis
1991	Guanarito virus	Virus	Venezuelan haemorrhagic fever
1991	*Encephalitozoon hellem*	Parasite	Conjunctivitis, disseminated disease
1991	*New species of Babesia*	Parasite	Atypical babesiosis
1992	*Vibrio cholerae 0139*	Bacterium	New strain associated with epidemic cholera
1992	*Bartonella henselae*	Bacterium	Cat-scratch disease; bacillary angiomatosis
1993	Sin Nambre virus	Virus	Hantavirus pulmonary syndrome
1993	*Encephalitozoon cuniculi*	Parasite	Disseminated disease
1994	Sabia virus	Virus	Brazilian haemorrhagic fever
1995	Human herpes virus 8	Virus	Associated with Kaposi's sarcoma in AIDS patients
1996	nvCJD Australian bat lyssavirus	Virus	–
1997	H5N1	Virus	Avian flu (Bird flu)
1999	Nipah virus	Virus	–
2003	Corona virus	Virus	SARS
2009	H1N1	Virus	Pandemic A (H1N1) 2009 influenza
2019	Corona virus	Virus	COVID-19 (SARS-CoV-2)

Source : *(4, 5)*

including tourism, also plays a role. The spread of syphilis in the 18th and 19th centuries was related to the movement of armies. Today, the introduction of HIV in many parts of the world is due to greatly increased human mobility. Studies show that whereas only a few generations ago most people in their lifetime travelled no further than 40 kilometres from their birthplace, many today go up to 1,000 times further, travelling the whole world.

The practices of modern medicine also contribute. The spread of viral hepatitis is related in part to techniques such as kidney dialysis and multiple blood transfusions, as well as to other forms of transmission. Relaxation in immunization practices can quickly result in the resurgence of diseases, as, for example, the recent spread of diphtheria in the Russian Federation and other former republics of the USSR.

New animal diseases pose potential foodborne risks to human health that are sometimes difficult to evaluate or predict. An example that has caused much public concern in Europe is bovine spongiform encephalopathy ("mad cow disease"). Fears have grown that the infectious agent responsible may be passed through the food chain to cause a variant of the incurable Creutzfeldt–Jakob disease in humans, in which the brain is attacked. The British beef market has been seriously affected and stringent public health safeguards have been introduced.

The reasons for outbreaks of new diseases, or sharp increases in those once believed to be under control, are complex and still not fully understood. The fact is however, that national health has become an international challenge. An outbreak anywhere must now be seen as a threat to virtually all countries, especially those that serve as major hubs of international travel. Despite the emergence of new diseases in the last 30 years, there is still a lack of national and international political will and resources to develop and support the systems that are necessary to detect them and stop their spread. Without doubt diseases as yet unknown, but with the potential to be the AIDS of tomorrow, lurk in the shadows.

Antimicrobial resistance

Resistance by disease–causing organisms to antimicrobial drugs and other agents is a major public health problem worldwide. It is making a growing number of infections virtually untreatable, both in hospitals and in the general community. It is having a deadly impact on the control of diseases such as tuberculosis, malaria, cholera, dysentery and pneumonia.

Antimicrobial resistance is not a new problem, but it has worsened dramatically in the last decade. During that time, the pace of development of new antimicrobials has slowed down while the prevalence of resistance has grown at an alarming rate. The increase in the number of drug-resistant bacteria is no longer matched by a parallel expansion in the arsenal of agents used to treat infections. There is strong evidence that a major cause of the current crisis in antimicrobial resistance is the uncontrolled and inappropriate use of antibiotic drugs, in both industrialized and developing countries. They are used by too many people to treat the wrong kind of infection, in the wrong dosage and for the wrong period of time. The implications are awesome : drugs that cost tens of millions of dollars to produce, and take perhaps 10 years to reach the market, have only a limited life span in which they are effective. As resistance spreads, the life span shrinks; as fewer new drugs appear, the gulf widens between infection and control. So far, the pattern of excessive or inappropriate use and the development of resistance has been repeated after the introduction of each new antimicrobial. The over-use of expensive drugs designed to cover a range of infections is a particularly serious problem in industrialized countries. In developing countries, the problem is compounded by the ready availability of over-the-counter drugs. This allows patients to treat themselves, either with the wrong medicine, or in quantities that are too small to be effective. Sub-standard and counterfeit drugs which lack adequate amounts of active ingredients further exacerbate the resistance problem.

The examples of bacterial resistance are as follows :

Strains of *M.tuberculosis* resistant to anti-tuberculosis drugs are widespread, although attention has recently focused on the alarming outbreaks of tuberculosis caused by multidrug-resistant strains in the United States. Drug resistance is the result of poor prescribing practices, or poor patient compliance with treatment. It is low in the few countries with effective tuberculosis programmes. The most dangerous form of the multidrug-resistant disease occurs when cases become virtually incurable and doctors face situations similar to those of the pre-antibiotic era.

Malaria presents a double resistance problem : resistance of the *Plasmodium* parasites, which cause the disease, to antimalarial drugs; and resistance of the *Anopheles* mosquitoes, the vectors of the disease, to insecticides. The arsenal of antimalarial drugs is limited. Most of them act by killing parasites when they are multiplying in the blood stream of the human host. Unfortunately, due to inadequate regimens, poor drug supply, and poor quality and misuse of drugs, rapid development of drug resistance has occurred in most areas of the world. Drug resistance is particularly important in falciparum malaria, the most severe form of the disease. Resistance to chloroquine, the most commonly used drug, has been found in all endemic countries except those of Central America and the Caribbean. Resistance to multiple drugs is common in South-East Asia. This serious obstacle to malaria control efforts is further complicated by mosquito resistance to insecticides. Many mosquitoes are reported to be resistant to the three classes of insecticides available for public health use, and some are becoming resistant to pyrethroids, widely promoted for bed-net and curtain impregnation.

Enterococci contribute to some of the most common infections acquired in hospitals, causing intra-abdominal abscesses, endocarditis, and infections of the urinary tract and soft tissues. In some countries, infections resulting from strains resistant to the main groups of antibiotics, such as the beta-lactams and the aminoglycosides, can only be treated with vancomycin, an expensive intravenous drug. Even resistance to vancomycin has developed in the last 10 years or so. Staphylococci, which can contribute to skin infections, endocarditis, osteomyelitis, food poisoning and other serious disorders, have developed resistance to all antibiotics except vancomycin. If vancomycin-resistant strains were to emerge, some of the most prevalent hospital-acquired infections would become virtually untreatable.

Streptococci have become increasingly resistant to some antibiotics. They are among the most common disease-causing bacteria, responsible for infections of the throat, middle ear, skin and wounds, and also necrotizing fasciitis and gangrene. Pneumococci and *Haemophilus influenzae* are the most common bacteria causing acute respiratory infections in children, particularly pneumonia. Both of these organisms are becoming more and more resistant to drugs. Strains of pneumococci, once uniformly susceptible to penicillin, are currently resistant to it in up to 18% of cases in the United States and, 40% in South Africa. In addition, they are becoming resistant to many other commonly used antibiotics, including cotrimoxazole, the drug recommended by WHO for treatment of pneumonia. The most virulent type of *Haemophilus influenzae* is today frequently resistant to ampicillin, and strains have been identified that are resistant to other drugs, including cotrimoxazole. In brief, doctors worldwide are losing some of the most useful and affordable antibiotics against the two bacteria which are the major cause of death in children.

Neisseria gonorrhoeae, cause of one of the most common sexually transmitted diseases, has acquired such resistance to penicillin and tetracyclines in most countries that the use of these antibiotics to treat it has become unacceptable and this infection now requires the use of much more expensive drugs which are often unavailable.

Shigella dysenteriae has been causing outbreaks of severe diarrhoeal disease in central and southern Africa in recent years, including those in refugee camps, with the epidemic strain acquiring increasing resistance to standard antibiotics. Epidemic dysentery caused by this strain results in the death of up to 15% of those infected. *Salmonella typhi*, the bacterium responsible for typhoid fever, has developed resistance to antibiotics commonly used in the past for treatment. Resistant strains have caused outbreaks of the disease in India and Pakistan. Without effective antibiotic treatment, typhoid fever kills almost 10% of those infected. In South-East Asia, 50% or more of the strains of the bacteria may already be resistant to several antibiotics.

More than half of the antibiotics produced worldwide are used in animals, largely in subtherapeutic concentrations which favour the onset of drug resistance. As a result, two important human pathogens of animal origin, *E.coli* and salmonellae, are today highly resistant to antibiotics in both industrialized and developing countries. For instance, in the United Kingdom, the increase of multidrug-resistant strains of *Salmonella typhimurium* isolated from cattle is paralleled by increasing resistance among strains of human origin. In Thailand, salmonellae isolated from food animals are also highly resistant to the common antibiotics. These bacteria

cause diarrhoeal disease and can lead to life-threatening complications. Due to the globalization of food supply and international travel, antimicrobial resistance among animal bacteria can affect consumers anywhere in the world.

Together, these factors have created perhaps the richest opportunities ever for the spread of infections, many of which become global problems that make the first line of defence – early recognition and adequate and timely response – essential.

Responding to epidemics

The process of response encompasses a multitude of activities including : diagnosis of the disease; investigation to understand the source of transmission; implementation of control strategies and programmes; research to develop adequate means to treat the disease and prevent its spread; and the production and distribution of the necessary drugs and vaccines.

The strategy for controlling re-emerging diseases is through available cost-effective interventions such as early diagnosis and prompt treatment, vector control measures and the prevention of epidemics, for malaria; and DOTS–directly observed treatment, short–course – for tuberculosis; by launching research initiatives for treatment regimens and improved diagnostics, drugs and vaccines; and above all by strengthening epidemiological surveillance and drug–resistance surveillance mechanisms and procedures with appropriate laboratory support for early detection, confirmation and communication.

The category of diseases – **"new diseases – new problems"**– such as Ebola and other viral haemorrhagic fevers, is probably the most frightening. The need, therefore, is for expanding research on infectious disease agents, their evolution, the vectors of disease spread and methods of controlling them, and vaccines and drug development. Much of this already applies to HIV/AIDS, one of the most serious diseases to emerge in recent decades.

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HOSPITAL-ACQUIRED INFECTION

Hospital-acquired infection is cross infection of one patient by another or by doctors, nurses and other hospital staff, while in hospital. A high frequency of nosocomial infection is evidence of a poor quality of health service delivery. Many factors contribute to the frequency of nosocomial infections: hospitalized patients are often immunocompromised, they undergo invasive examinations and treatments, and patient care practices and the hospital environment may facilitate the transmission of microorganisms among patients. The selective pressure of intense antibiotic use promotes antibiotic resistance. While progress in the prevention of nosocomial infections has been made, changes in medical practice continually present new opportunities for development of infection.

Definition of nosocomial infections

Nosocomial infections, also called "hospital-acquired infections", are infections acquired during hospital care which are not present or incubating at admission. Infections occurring more than 48 hours after admission are usually considered nosocomial. Definitions to identify nosocomial infections have been developed for specific infection sites (e.g. urinary, pulmonary).

Nosocomial infections may also be considered either endemic or epidemic. Endemic infections are most common. Epidemic infections occur during outbreaks, defined as an unusual increase above the baseline of a specific infection or infecting organism.

Changes in health care delivery have resulted in shorter hospital stays and increased outpatient care. It has been suggested that the term nosocomial infections should encompass infections occurring in patients receiving treatment in any health care setting. Infections acquired by staff or visitors to the hospital or other health care setting may also be considered nosocomial infections.

Simplified definitions may be helpful for some facilities without access to full diagnostic techniques. Table 1 provides definitions for common infections that could be used for surveys in facilities with limited access to sophisticated diagnostic techniques.

TABLE 1

Simplified criteria for surveillance of nosocomial infections

Type of nosocomial infection	Simplified criteria
Surgical site infection	Any purulent discharge, abscess, or spreading cellulitis at the surgical site during the month after the operation.
Urinary infection	Positive urine culture (1 or 2 species) with at least 10^5 bacteria/ml, with or without clinical symptoms.
Respiratory infection	Respiratory symptoms with at least two of the following signs appearing during hospitalization : – cough – purulent sputum – new infiltrate on chest radiograph consistent with infection.
Vascular catheter infection	Inflammation, lymphangitis or purulent discharge at the insertion site of the catheter.
Septicaemia	Fever or rigors and at least one positive blood culture.

Source : *(1)*

According to a French National Prevalence Survey the distribtution of sites of nosocomial infection are as shown in Fig. 1.

Hospital–acquired infection may be considered from three angles :

1. Source
2. Routes of spread; and
3. Recipients.

1. Sources

The sources are patients, hospital staff and the environment. (a) PATIENTS : Patients suffering from infectious diseases are potential sources of infection. These

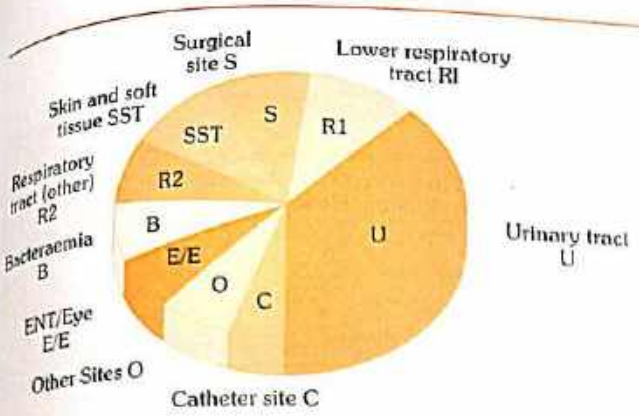

FIG. 1

Sites of the most common nosocomial infections

Source : *(1)*

cases may be certain **viral infections** (measles, german measles, influenza, viral hepatitis); **Skin infections** (discharging wounds, infected skin lesions, eczema, psoriasis, boils, bed sores); **respiratory infections** (sore throat, pulmonary tuberculosis, chest infection); and **urinary tract infection** (*B. coli* infection). All these are very common sources of hospital acquired infection. (b) STAFF: The hospital staff (viz doctors, nurses, ward boys) who come in close contact with patients may often be an important source of cross infection. For example, staphylococcus aureus is commonly carried in the nose or on the skin. *Haemolytic streptococci* may be carried in the throat and *salmonella* in the gut. (c) ENVIRONMENT : The hospital environment (viz. hospital dust, linen, bed clothes, furniture, sinks, basins, door handles and even the air) is laden with microorganisms, and is thus an important source of infection.

2. Routes of spread

The common routes of spread of cross infection are : (a) Direct contact, i.e. the organism may be transferred directly from the hands of a nurse or doctor to a susceptible patient; (b) Droplet infection, e.g. droplets released from nose and throat through coughing or sneezing; (c) Air-borne particles ; (d) Release of hospital dust into the air; (e) Through various hospital procedures, viz, catheterization, intravenous procedures, infected cat gut, dressings, sputum cups, bed pans, urinals etc.

3. Recipients

All patients in hospitals are potential recipients of cross infection. Some patients are more susceptible than others, especially those who are severely ill and those under corticosteroid therapy. Cross infection is greater in intensive care units, urological and geriatric wards and in special baby care units.

Preventive measures

The main preventive measures are : (a) Isolation : Infectious patients must be isolated. Patients who are susceptible to infection should not be placed in beds next to patients who are a source of infection. (b) Hospital staff : Those who are suffering from skin diseases, sore throat, common cold, ear infection, diarrhoea or dysentery and other infectious ailments should be kept away from work until completely cured. They should be careful about personal hygiene and in regular changes of aprons and outer clothing. (c) Hand-washing : The most common route of infection is *via* the hands. When dealing with patients, hand-washing must be thorough. When hand-washing with soap and water is not sufficient, a suitable alcohol-based disinfectant must be employed for hand-washing. In the year 2009, WHO developed guidelines for hand hygiene known as *"Clean Care is Safer Care"*. It should be followed to improve the standards of hand hygiene practices *(2)*. (d) Dust control : Hospital dust contains numerous bacteria and viruses. The dust is released during sweeping, dusting and bed making. Suppression of dust by wet dusting and vacuum cleaning are important control measures. (e) Disinfection : The articles used by the patient as well as patient's urine, faeces, sputum should be properly disinfected. Proper sterilization of instruments should be enforced. (f) Control of droplet infection : Use of face masks, proper bed spacing, prevention of overcrowding and ensuring adequate lighting and ventilation are important control measures. (g) Nursing techniques : Barrier nursing and task nursing have also been recommended to minimize cross infection. (h) Administrative measures : There should be a hospital "Control of Infection Committee" to formulate policies regarding admission of infectious cases, isolation facilities, disinfection procedures, and in fact all matters relating to control of hospital acquired infection.

The four most common nosocomial infections are urinary tract infections, surgical wound infections, pneumonia, and primary bloodstream infection. Each of these is associated with an invasive medical device or invasive procedure. Specific policies and practices to minimize these infections must be established, reviewed and updated regularly, and compliance monitored, as shown in Table 2.

Standard (routine) precautions

Standard precautions should be applied to the care of all patients. This includes limiting health care worker contact with all secretions or biological fluids; skin lesions, mucous membranes, and blood or body fluids. Health care workers must wear gloves for each contact which may lead to contamination, and also gown, mask and eye protection where contamination of clothes or the face is anticipated.

Considerations for protective clothing include :

- gown: should be of washable material, buttoned or tied at the back and protected, if necessary, by a plastic apron
- gloves: inexpensive plastic gloves are available and usually sufficient
- mask : surgical masks made of cloth or paper may be used to protect from splashes.

Standard precautions for all patients are as follows :

- Wash hands promptly after contact with infective material.
- Use no touch technique wherever possible.
- Wear gloves when in contact with blood, body fluids, secretions, excretions, mucous membranes and contaminated items.
- Wash hands immediately after removing gloves.
- All sharps should be handled with extreme care.
- Clean up spills of infective material promptly.

TABLE 2

Measures for prevention of infection

Infection	Proven effective	Proven not effective
Urinary tract infections	Limit duration of catheter Aseptic technique at insertion Maintain closed drainage Antiseptic added to drainage bag Antimicrobial-coated catheter Daily antiseptic perineal cleaning.	Systemic antibiotic prophylaxis Bladder irrigation or instillation of normal saline antiseptic or antibiotic
Surgical site infections	Surgical technique Clean operating environment Staff attire Limiting preoperative hospital stay Preoperative shower and local skin preparation of patient Optimal antibiotic prophylaxis Aseptic practice in operating room Surgical wound surveillance.	Fumigation Preoperative shaving
Pneumonia	Ventilator-associated Aseptic intubation and suctioning Limit duration Non-invasive ventilation Others Influenza vaccination for staff Isolation policy Sterile water for oxygen and aerosol therapy Prevention of *Legionella* and *Aspergillus* during renovations.	Digestive decontamination for all patients Changes of ventilator circuit every 48 or 72 hours
Vascular device infections	All catheters Closed system Limit duration Local skin preparation Aseptic technique at insertion Removal if infection suspected Central lines Surgical asepsis for insertion Limitation of frequency of dressing change Antibiotic-coated catheter for short term.	Antimicrobial creams for skin preparation

- Ensure that patient-care equipment, supplies and linen contaminated with infective material is either discarded, or disinfected or sterilized between each patient use.
- Ensure appropriate waste handling.
- If no washing machine is available for linen soiled with infective material, the linen can be boiled.

Health care workers are at risk of acquiring infection through occupational exposure. Hospital employees can also transmit infections to patients and other employees. Thus, a programme must be in place to prevent and manage infections in hospital staff.

Employee's health should be reviewed at recruitment, including immunization history and previous exposure to communicable diseases (e.g. tuberculosis) and immune status. Some previous infections (e.g. varicella-zoster virus (VZV) may be assessed by serological tests.

Immunizations recommended for staff include: hepatitis A and B, yearly influenza, measles, mumps, rubella, tetanus, and diphtheria. Immunization against varicella may be considered in specific cases. The Mantoux skin test will document a previous tuberculosis infection and must be obtained as a base-line.

Specific postexposure policies must be developed, and compliance ensured for: human immunodeficiency virus (HIV), hepatitis A virus, hepatitis B virus, hepatitis C virus, Neisseria meningitidis, Mycobacterium tuberculosis, varicella-zoster virus, hepatitis E virus, corynebacterium *diphtheriae*, bordetella *pertussis*, and rabies.

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