Epidemiology and prevention of TB, leprosy, malaria, filariasis and kala-azar

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Natural history of TB

- **Agent factors:**
  - **Agent:** ***Mycobacterium tuberculosis*** is the main agent. Besides few atypical mycobacteria are also responsible- ***M. kansasii, M. scrofulaceum, M. intercellulare*** etc.
  - **Source of infection:**
    - ✓ **Human source:** The most common source is human case.
    - ✓ **Bovine source:** The bovine source is usually infected milk.
  - **Communicability:** Patients are infective as long as they remain untreated.

Natural history of TB

- **Host factors:**
  - **Age:** TB affects all ages.
  - **Sex:** More prevalent in males than females.
  - **Heredity:** TB is not a hereditary disease.
  - **Nutrition:** Malnutrition predisposes to TB.
  - **Immunity:** Man has no inherited immunity against TB. It is acquired as a result of **natural infection or BCG vaccination**.

Natural history of TB

- **Social factors:** Poor quality of life, poor housing, overcrowding, population explosion, undernutrition, smoking, alcohol abuse, lack of education, large families, early marriage etc.
- **Mode of transmission:** Mainly transmitted by droplet infection and droplet nuclei.
- **Incubation period:** Incubation period may be weeks, months or years.

TB case definition

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

Classification of TB

- Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to:
  a. **anatomical site of disease**
  b. **history of previous treatment**
  c. **drug resistance**
  d. **HIV status**

Classification of TB based on anatomical site of disease

1. **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.
2. **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**.

Classification of TB based on history of previous TB treatment

1. **New patients** have never been treated for TB or have **taken anti-TB** drugs for **less than 1 month**.
2. **Previously treated patients** have 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).

Classification of TB based on history of previous TB treatment

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.

Classification of TB based on HIV status

1. **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.
2. **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.
3. **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.

Classification of TB based on drug resistance

- **Monoresistance:** resistance to one first-line anti-TB drug only.
- **Polydrug resistance:** resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
- **Multidrug resistance TB (MDR-TB):** resistance to at least **both isoniazid and rifampicin**.
- **Extensive drug resistance TB (XDR-TB):** resistance to **any fluoroquinolone** and to **at least one of three second-line injectable drugs** (capreomycin, kanamycin and amikacin), in addition to **multidrug resistance**.
- **Rifampicin resistance TB (RR-TB):** resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs.

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

- **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.

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

- **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.*

Classification of anti-TB drug

First-line anti-TB drug		
Description	**Drug**	**Abbreviation**
Oral drug	Isoniazid	H
	Rifampicin	R
	Ethambutol	E
	Pyrazinamide	Z
	Rifabutin	Rft
	Rifapentine	Rpt

Classification of anti-TB drug

Second-line anti-TB drug		
Description	**Drug**	**Abbreviation**
Group A: include all three medicines	Levofloxacin or Moxifloxacin	Lfx or Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add one or both medicine	Clofazimine	Cfz
	Cycloserine or Terizidone	Cs or Trd

Classification of anti-TB drug

Second-line anti-TB drug		
Description	**Drug**	**Abbreviation**
Group C: Add to complete the regimen and when medicines from Group A & B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrizinamide	Z
	Imipenem-cilastin or Meropenem	Ipm-Cln or Mpm
	Amikacin or Streptomycin	Am or S
	Ethionamide or Prothionamide	Eto or Pto
	P-aminosalicylic acid	PAS

TB treatment regimen

TB Category	Type of patient	Treatment regimen	
		Intensive phase (Daily)	Continuation phase (Daily)
New cases	Bacteriologically positive PTB patient	2 (HRZE)	4 (HR)
	Bacteriologically negative PTB patient		
	Extra-pulmonary TB		
	TB/HIV co-infected		
Previously treated cases	No resistance to TB drugs	6 HRZE	
	Clinically diagnosed PTB	6 HRZE	
	Complicated EP TB	12 HRZE-Lfx	
	Rif susceptible and INH resistant or unknown	6 HRZE-Lfx	

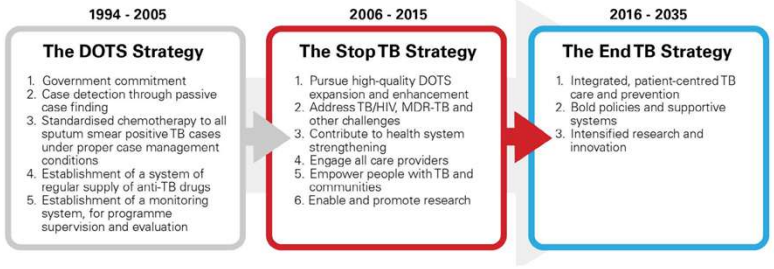
Diagnosis of TB

- **Tools for microbiological confirmation of TB:**
  - **Sputum for Microscopy (AFB):** Zeihl-Neelsen staining; Fluorescence staining
  - **Culture:** Lowenstein Jensen media; Automated liquid culture system
  - **Drug sensitivity test:** Modified proportionate sensitivity testing; Economic variant of proportion sensitivity testing
  - **Rapid molecular diagnostic test:** Nucleic acid amplification test (NAAT); GeneXpert test

Diagnosis of TB

- **Supportive tools for the clinical diagnosis of TB:**
  - Chest X-ray and other radiological tests
  - Tuberculin skin test (Mantoux test)
  - Interferon gamma release assay
  - Other blood test
  - Histopathology
  - Other tissue-based test

Evolution of WHO global TB strategy



The current WHO END TB Strategy envisions a world free to tuberculosis and has established ambitious targets to be achieved by 2035 [5].

WHO 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

Leprosy (Hansen's disease)

- Leprosy is a chronic infectious disease caused by ***Mycobacterium leprae***.
- It affects mainly the **peripheral nerves** but can also affect the **skin, muscles, eyes, bones, testes and internal organs**.
- 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
  c. Presence of **thickened nerves**
  d. Presence of **acid-fast bacilli** in the skin or nasal smears

Leprosy (Hansen's disease)

- The signs of advanced disease are striking:
  a. **Presence of nodules or lumps** especially in the skin of the face and ears
  b. **Plantar ulcers**
  c. **Loss of fingers or toes**
  d. **Nasal depression**
  e. **Foot-drop**
  f. **Claw toes and other deformities**

Epidemiological determinants of leprosy

- **Agent factors:**
  - **Agent:** Acid-fast bacilli ***Mycobacterium leprae***.
  - **Source of infection:** Multibacillary cases and inapparent infections
  - **Portal of exit:** Nasal discharge, ulcerated or broken skin
  - **Infectivity:** Highly infectious but of low pathogenicity.
- **Host factors:**
  - **Age:** Can affect any age
  - **Sex:** Higher in males than females

Epidemiological determinants of leprosy

- **Environmental factors:** The presence of infectious agent in the environment; overcrowding; lack of ventilation within the household
- **Mode of transmission:** Droplet infection and person-to-person transmission by close contact.
- **Incubation period:** Leprosy has a long incubation period, an average 3 to 5 years or more.

Classification of leprosy

❑ **Indian classification**

a. Indeterminate type
b. Tuberculoid type
c. Borderline type
d. Lepromatous type
e. Pure neuritic type

❑ **Madrid classification**

a. Indeterminate type
b. Tuberculoid; flat; raised
c. Borderline
d. lepromatous

Classification of leprosy

❑ **Ridley and Jopling classification**

a. Tuberculoid (TT)
b. Borderline tuberculoid (BT)
c. Borderline (BB)
d. Borderline lepromatous (BL)
e. Lepromatous (LL)

❑ **Clinical classification for control programme**

a. Pauci-bacillary leprosy (PB)
b. Multi-bacillary leprosy (MB)

Pauci-bacillary vs multi-bacillary leprosy

Characteristics	Pauci-bacillary (PB)	Multi-bacillary (MB)
Skin lesions	1-5 lesions	6 and more lesions
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

- **Clinical examination**
- **Bacteriological examination:** Skin smear, nasal smear, nasal scrapings
- **Foot-pad culture**
- **Histamine test**
- **Biopsy**
- **Immunological tests**
- Test for detecting cell mediated immunity: **Lepromin test**
- Test for humoral antibodies: **Serological test**

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**.
- Two types of positive reactions are seen.
  a. **Early reaction:** It is known as Fernandez reaction. If the diameter of the **red area is more than 10mm** at the end of 48 hours, the test is **considered positive**.
  b. **Late reaction:** It is known as Mitsuda reaction. At the end of 21 days, if there is a **nodule more than 5mm** in diameter at the site of inoculation, the reaction is **considered positive**.

Leprosy control program

- The **three main goals** of leprosy control are:
  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
  c. To **prevent the development of associated deformities**
- Ultimate prevention is achieved by breaking the chain of transmission

Leprosy control program

- 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

Recommended regimen of chemotherapy

- WHO has recommended the following combination of drugs for treatment of **multibacillary cases of leprosy**:

Drug	Adult	Child (10-14 years)	Duration
Rifampicin	600 mg, once monthly, given under supervision	450 mg, once monthly, given under supervision	12 months
Dapsone	100 mg daily, self-administered	50 mg daily, self-administered	12 months
Clofazimine	300 mg once monthly supervised and 50 mg daily, self-administered	150 mg once monthly supervised and 50 mg every other day, self-administered	12 months

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Recommended regimen of chemotherapy

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Dapsone	100 mg daily, self-administered	50 mg daily, self-administered	6 months

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Lepra reaction

- During the course of leprosy, immunologically mediated episodes of acute or subacute inflammation known as **lepra reactions** may occur.
- Lepra reactions are usually diagnosed by clinical examination only.
- There are two types of reaction:
  a. **Type 1 or reversal reaction**
  b. **Type 2 or Erythema Nodosum Leprosum (ENL)**
- Both types can occur before the start of multi-drug treatment, during treatment, or after treatment has completed.
- Only severe cases are treated with **corticosteroid**.

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Reversal reaction vs ENL

Reversal reaction (Type 1)	ENL (Type 2)
Delayed hypersensitivity	Antigen-antibody reaction
Occurs in both PB and MB cases	Seen in MB cases only
Skin lesions suddenly become reddish, swollen, warm, painful and tender	Bilaterally symmetrical red, painful, tender sub-cutaneous nodules may appear, commonly on face, arms, legs
Nerve may be enlarged, tender and painful with loss of function	Nerve may be affected but not so common as Type 1
Other organs are not affected	Eyes, testes and kidney may be affected
General symptoms are uncommon	Fever, joint pain, red eyes with watering
Lagophthalmos and corneal anaesthesia	Iritis/iridocyclitis

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Malaria

- Malaria is a **protozoal disease** caused by infection with the **parasite 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 **specific risk groups** for malaria includes the following:
  - Young **children**
  - Non-immune and semi-immune **pregnant women**
  - People with **HIV/AIDS**
  - **International travelers** from non-endemic areas

Epidemiological determinants of malaria

- **Agent factors:**
  - **Agent:** Malaria in man is caused by four distinct species of malarial parasite- ***P. vivax, P. falciparum, P. malariae*** and ***P. ovale***.
- **Host factors:**
  - **Man** is the **intermediate host** and **mosquito** is the **definitive host**.
- **Vector of malaria:**
  - Certain species of Anopheline mosquitoes are of primary importance: ***An. Culicifacies, An. Fluviatilis, An. Stephensi, An. Minimus, An. Philippinensis, An. Sundaicus***, and ***An. Maculatus***.

Epidemiological determinants of malaria

- **Mode of transmission:**
  - **Vector transmission:** Malaria is transmitted by the bite of certain species of infected, female anopheline mosquitoes.
  - **Direct transmission:** Blood transfusion, I/V drug abuse, Transplacental
- **Incubation period:**
  - Falciparum malaria- **12 (9-14) days**
  - Vivax malaria- **14 (8-17) days**
  - Quartan malaria- **28 (18-40) days**
  - Ovale malaria- **17 (16-18) days**

Diagnosis of malaria

- **Microscopy:**
  - The thin film
  - The thick film
- **Serological test:**
  - Malarial fluorescent antibody test
- **Rapid diagnostic test (RDT)**

Prevention and control of malaria

- Strategies for prevention and control of malaria are:

1. **Surveillance and case management**
   a. Case detection (active and passive)
   b. Early diagnosis and complete treatment
   c. Sentinel surveillance
2. **Integrated vector management**
   a. Indoor residual spray
   b. Insecticidal nets
   c. Antilarval measures including source reduction

Prevention and control of malaria

3. **Epidemic preparedness and early response**
4. **Supportive interventions**
   a. Capacity building
   b. Behavioural change communication
   c. Intersectoral collaboration
   d. Monitoring and evaluation
   e. Operational research and applied field research

Lymphatic filariasis

- The term **lymphatic filariasis** covers infection with three closely related nematode worms- ***W. bancrofti, B. malayi, B. timori***
- 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.
- The disease manifestations are- **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**.

Lymphatic filariasis: Clinical manifestation

- The disease manifestations can be divided into two distinct clinical types:
  1. **Lymphatic filariasis** caused by parasite in the lymphatic system
     a. Asymptomatic amicrofilaraemia
     b. Asymptomatic microfilaraemia
     c. Stage of acute manifestation
     d. Stage of chronic obstructive lesion
  2. **Occult or cryptic filariasis** caused by an immune hyper-responsiveness of the human host (e.g. **tropical pulmonary eosinophilia**). Microfilariae are not found in the blood.

Epidemiological determinants of filaria

- **Agent factors:**
  - Agent: ***W. bancrofti, B. malayi, B. timori***
- **Host factors:**
  - **Man** is the **definitive host** and **mosquito** is the **intermediate host**.
- **Vector of malaria:**
  - Culex, Anopheles and Aedes serve as vectors for *W. bancrofti* and Mansonia, Anopheles and Coquillettidia serve as the vectors of the *Brugia* species.

Epidemiological determinants of filaria

- **Mode of transmission:**
  - Filaria is transmitted from person-to-person by the bite of infected vector mosquitoes.
- **Incubation period:**
  - Generally, 8 to 16 months.

Filaria survey

a. **Mass blood survey**
   i. **The thick film**
   ii. **Membrane filter concentration (MFC) method**
   iii. **DEC provocation test**
b. **Clinical survey**
c. **Serological test**
d. **Xenodiagnosis**
e. **Entomological survey**

Lymphatic filariasis control measures

- Strategy of filariasis control is based on:

1. **Chemotherapy**
   a. **Diethylcarbamazine (DEC)**
   b. **Filaria control in the community**
      i. Preventive chemotherapy
      ii. Selective treatment
      iii. DEC-medicated salt
   c. **Ivermectin**
2. **Vector control**

Kala-azar (Visceral 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:
  a. **Visceral leishmaniasis or Kala-azar**
  b. **Cutaneous leishmaniasis**
  c. **Muco-cutaneous leishmaniasis**
  d. **Post-kala-azar dermal leishmaniasis**

Epidemiological determinants of kala-azar

- **Agent factors:**
  - **Agent:** Leishmania donovani
  - **Vector:** Sandfly
  - **Reservoirs of infection:** Man is the only reservoir of kala-azar
- **Host factors:**
  - **Age:** Can occur in all age group
  - **Sex:** Male are affected twice as often as female
  - **Socio-economic status:** Usually occurs in the poorest of the poor

Epidemiological determinants of kala-azar

- **Mode of transmission:**
  - Kala-azar is transmitted from person-to-person by the bite of female phlebotomine sandfly.
  - Transmission is also done by blood transfusion and contaminated syringes and needles.
- **Incubation period:**
  - Generally, 1 to 4 months; range is 10 days to 2 years.

Clinical features of kala-azar

- The classical features of kala-azar are **fever, splenomegaly and hepatomegaly** accompanied by **anaemia and weight loss**.
- **Darkening of the skin** of the face, hands, feet and abdomen is also common.
- Atypical features i.e. **lymphadenopathy** may also occur.
- **Post kala-azar dermal leishmaniasis (PKDL)** appears one to several years after apparent cure of kala-azar. The lesions consist of multiple nodular infiltrations of the skin, usually without ulceration.

Laboratory diagnosis of kala-azar

- **Rapid diagnostic test: rk39** dipstick test
- **Parasitological diagnosis:** Demonstration of parasite **LD bodies** in the aspirates of the spleen, liver, bone marrow, lymph nodes or skin.
- **Aldehyde test**
- **Serological test:** Direct agglutination test (DAT), rk39 dipstick test, ELISA, IFAT etc.
- **Leishmanin (Montenegro) test**
- **Hematological findings:** Progressive leucopenia, anaemia and reversed albumin-globulin ratio.

Case definition of kala-azar

- **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.
- **Case definition of PKDL**
  - **Probable PKDL:** A patient from kala-azar endemic area with multiple hypopigmented macules, papules or nodules, who is RDT positive.
  - **Confirmed PKDL:** A patient from kala-azar endemic area with multiple hypopigmented macules, papules or nodules, who is parasite positive in slit-skin smear (SSS) or biopsy.

Kala-azar control measures

- The control measures of kala-azar comprise the following:

❑ **Control of reservoir**
- Since man is the only reservoir of kala-azar in Indian subcontinent, active and passive case detection and treatment of those found to be infected may be sufficient to control the disease.

❑ **Control of sandfly**
- **Insecticides:** Spraying with DDT is done in the human dwellings, cattle sheds and other places.
- **Sanitation:** Sanitation measures such as removal of shrubs and vegetation within 50 yards of human dwellings.

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