TUBERCULOSIS

Tuberculosis (TB) is a contagious airborne disease, caused by inhalation of a bacterium called *Mycobacterium tuberculosis*, that mainly affects the lungs.

TUBERCULOSIS[1, 2]

- Tuberculosis is recognized as a **major global health problem** and one of the leading causes of death linked to a single infectious agent.
- Main countries concerned are low- and middle-income countries due to poverty and lack of access to proper sanitation.
- Seven countries account for 64% of TB-related deaths: India, Indonesia, China, Philippines, Pakistan, Nigeria and South Africa.
- Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. A global total of 206,030 people with multidrug-resistant TB were detected and notified in 2019, a 10% increase from 2018.
- Ending the TB epidemic by 2030 is one of the health targets of the United Nations Sustainable Development Goals (SDGs).

TRANSMISSION[1, 3]

- TB spreads through inhaling tiny droplets from the coughs or sneezes of a person with active TB disease (1 person can infect 15 others).
- Poverty and poor living conditions (overcrowding, lack of ventilation) lead to increased transmission of *Mycobacterium tuberculosis*.
- Mainly inter-human transmission (rare cases of bovine transmission).

THE BURDEN OF TUBERCULOSIS[1]

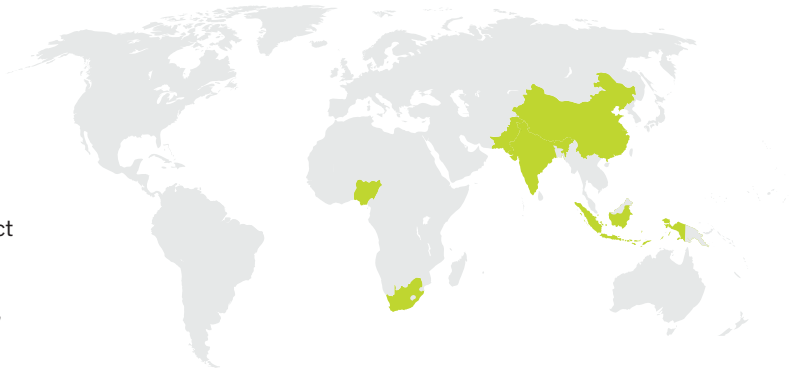
1/4 of the global population is infected with *Mycobacterium tuberculosis*, presenting a latent TB form, of which 10 to 15% will progress to active disease.

10 million people develop active TB disease each year

1.4 million people die annually from TB

>95% of TB deaths occur in LMIC* countries

64% of TB-related deaths occur in 7 countries



*LMIC: low- and middle-income countries

TUBERCULOSIS INFECTION[1]

Tuberculosis has 2 major forms: **latent TB infection (LTBI)** and **active TB disease**.

- 90 to 95% of people infected with TB develop immunity and do not transmit infection. This form is known as **latent TB infection**.
- 5 to 10% of people infected will develop **active TB disease**.

TB INFECTION

LATENT TB INFECTION (LTBI)[4]

- Inactive stage of TB infection in which the bacteria are alive, but do not replicate in the body
- People with latent TB infection do not feel sick, are asymptomatic, and cannot transmit TB infection to others
- People with LTBI represent a large human reservoir for TB infection

10 to 15% of the latent population will progress to active TB disease, mainly within 2-3 years after infection.

ACTIVE TB DISEASE

- Active stage of TB infection, in which the bacteria are replicating in the body
- Clinical signs and symptoms of active disease
- People with active TB can transmit the disease

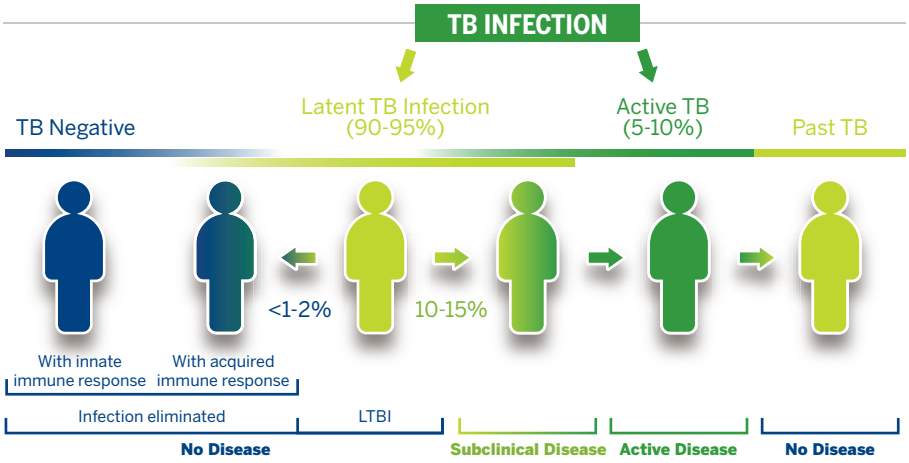
Diagnosing people with LTBI is important to prevent progression to active TB disease and stop the spread of TB.

TUBERCULOSIS

STAGES OF TUBERCULOSIS INFECTION[5, 6]

Tuberculosis infection is represented by a spectrum of stages.

Between the two main forms (latent and active), subclinical stages have been described.



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RISK GROUPS FOR LTBI[1, 3]

People at risk of being infected but with LOW RISK OF PROGRESSION to active TB disease:

- Health-care workers
- Contact of patients with active TB, **IF** the person is >5 years old
- People living in communities, such as prisoners or homeless
- Drug users

LTBI people at HIGH RISK OF PROGRESSION to active TB disease (preventive treatment can be considered):

- Contact of patients with active TB, **IF** the person is <5 years old
- People living with HIV
- People receiving dialysis or organ and hematological transplantation
- People receiving anti-TNF treatment
- People with silicosis

Other risk factors can be associated with progression from LTBI to active TB disease: aging, poor living conditions and diabetes.[7]

CLINICAL PRESENTATION OF ACTIVE TB DISEASE*[2]

- Prolonged cough
- Fever/chills
- Chest pain
- Blood in sputum
- Weakness/fatigue
- Weight loss/loss of appetite
- Night sweats

*Only active TB disease is symptomatic, persons with LTBI remain asymptomatic.

DIAGNOSTIC APPROACH[8]

Diagnosis is based on:

- Relevant epidemiological context (endemic region, potential exposure, proven contact with index case...)
- Anamnesis
- Clinical signs and symptoms
- Imaging: chest X-ray...
- Laboratory testing on blood and sputum samples

LABORATORY CONFIRMATION[7, 8]

2 DIAGNOSTIC PATHWAYS

Suspected infected people, mainly LTBI
(see Risk Groups for LTBI above)

BLOOD SAMPLE

TST: *in vivo*

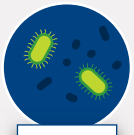
IGRA: *in vitro*

TST: tuberculin skin test IGRA: interferon gamma release assay

Suspicion of active TB disease
(clinical symptoms, abnormal chest X-ray)

SPUTUM SAMPLE

Microscopy



Culture

PCR

PCR: polymerase chain reaction

Indirect diagnosis based on host response

- **There is NO gold standard for diagnosis of LTBI.**
- **Tuberculin skin test (TST)** was the first tool used for detection of TB infection:
  - requires two doctor's visits (injection and reading 48-72 hours later)
  - reaction measurement is subjective
  - inexpensive, but lacks sensitivity and specificity (cross-reaction with BCG vaccination and non-tuberculous mycobacteria (NTM))
- Recently, **interferon gamma release assays (IGRA)** have been developed, which measure the release of interferon gamma produced by T-cells after stimulation by specific TB antigens. IGRA are now used more often than TST, especially in high income countries:
  - require only one visit
  - objective laboratory result
  - much more sensitive and specific (no cross-reactivity with BCG and very few with NTM)
- Neither TST nor IGRA are able to distinguish between active TB and LTBI, nor predict risk of LTBI progression to active TB.
- Both assays are negatively impacted by immune depression (e.g. HIV co-infection).

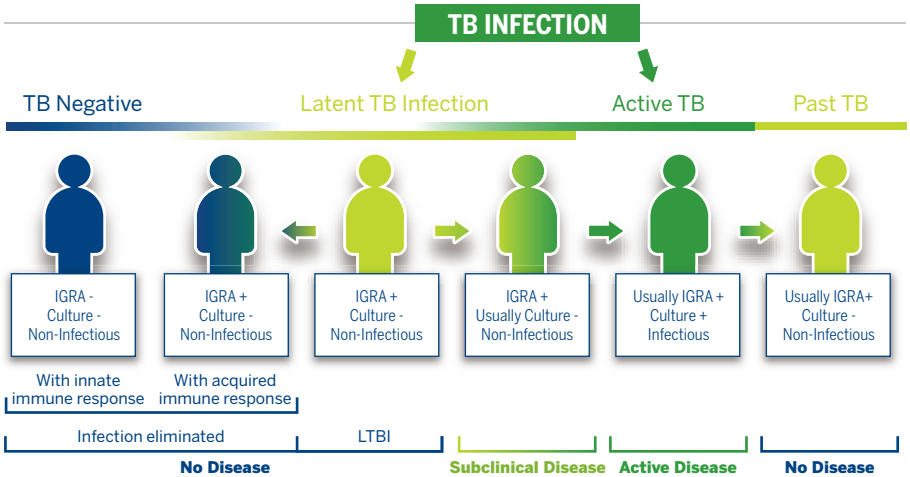
Direct diagnosis with pathogen detection/identification

- **Culture from sputum specimen is the gold standard for active TB diagnosis.**
- **Microscopy on sputum sample** remains the only diagnostic tool in many low income countries despite low sensitivity and specificity, being time-consuming and requiring skilled technicians.
- **Molecular biology** is increasingly used and WHO recommends its implementation in microscopy centers.

Antimicrobial susceptibility testing (AST)

- **The gold standard for AST remains phenotypic analysis** based on positive culture.
- **New approaches based on genotypic assays are now emerging:**
  - **PCR and Line Probe Assays (LPA):** mixing identification of strains and prediction of resistance to major antibiotics
  - **Whole genome sequencing (WGS):** a promising approach providing a complete picture of the bacterial identification and resistance profile

LABORATORY RESULTS ACCORDING TO TB INFECTION STAGES[5, 6]



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TREATMENT[10]

LATENT TB INFECTION

Preventive antibiotic treatment for people at risk of progressing to active TB disease.

- **Current treatment:** isoniazid (9 months)
- **Proposed new regimen:** rifampin (4 months)

ACTIVE TB DISEASE

Active TB is never treated with a single antibiotic in order to limit the emergence of TB drug resistance.[9]
Lack of treatment compliance is also a major cause of the emergence of resistance.[10]

- **Sensitive strain**
  - Four drug regimen for 8 weeks: rifampin, isoniazid, ethambutol, pyrazinamide
  - Followed by two drug regimen for additional 18 weeks: rifampin, isoniazid
- **Resistant strain**
  - Up to 2 years with second-line antibiotics: para-aminosalicyclic acid, cycloserine, ofloxacin, amikacin, etc.
- Two new drugs validated
  - bedaquiline (2012), delamanid (2013)
- Two drugs under evaluation
  - linezolid and pretomanid (2019)

TB DRUG RESISTANCE[9,10]

Resistance to TB antibiotics is a major obstacle to effective TB care and prevention globally.[2]

- Multidrug-resistant TB (MDR-TB) is defined as resistance to one of the first-line antibiotics used for treatment.
- Extensively drug-resistant TB (XDR-TB) is defined as resistance to first- and second-line antibiotics.

VACCINATION[11]

Bacille Calmette-Guérin (BCG) vaccine:

- Initially designed against tuberculous meningitis (newborns & children)
- Limited protection after 10-15 years post vaccination
- Since 2006, attenuated strain of *M. bovis*: BCG SSI®

The Tuberculosis Vaccine Initiative (TBVI) is continuously working on the development of new TB vaccine candidates.

References:

1. WHO. https://www.who.int/teams/global-tuberculosis-programme/tb-reports
2. WHO. https://www.who.int/news-room/fact-sheets/detail/tuberculosis
3. WHO. https://www.who.int/news-room/q-a-detail/tuberculosis
4. ECDC. https://www.ecdc.europa.eu/en/tuberculosis
5. Sousa J. and Saraiva M. Infection, Genetics and Evolution 2018;72:78-85
6. Pai M, et al. Nature Reviews Disease Primers 2016;2:16076
7. WHO. https://www.who.int/tb/areas-of-work/preventive-care/ltbi/faqs/en/
8. CDC. https://www.cdc.gov/tb/publications/factsheets/testing/diagnosis.htm
9. CDC. https://www.cdc.gov/tb/topic/drtb/default.htm
10. CDC. https://www.cdc.gov/tb/topic/treatment/default.htm
11. Tuberculosis Vaccine Initiative. https://www.tbvi.eu/what-we-do/pipeline-of-vaccines/

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