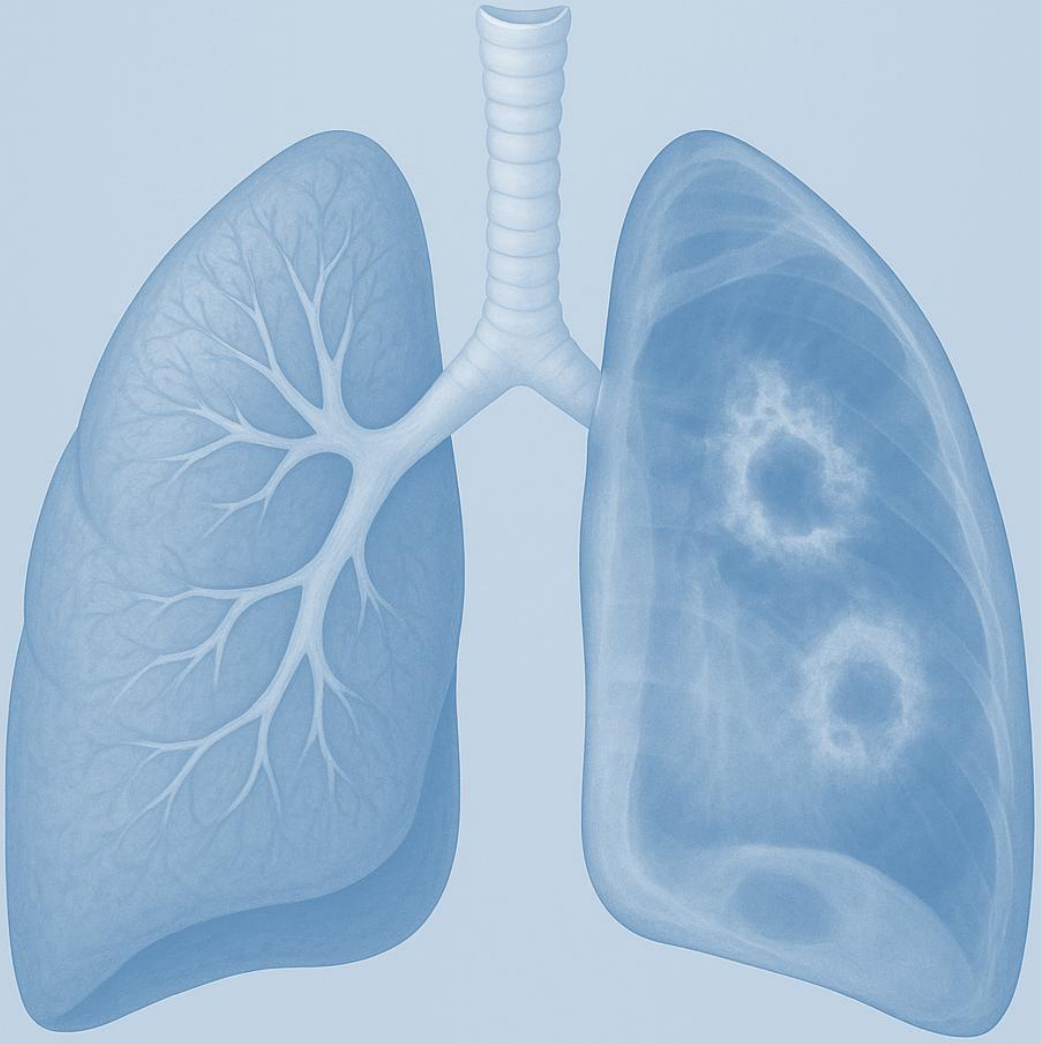
UPDATE ON TUBERCULOSIS



Update on Tuberculosis

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Book covert design: illustration of human lungs, with a healthy red lung on the left and a grayscale X-ray lung on the right showing characteristic tuberculosis lesions

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1. Epidemiology of tuberculosis

Key Points:

- Tuberculosis remains the world's deadliest infectious disease, with minimal progress toward global elimination goals.
- High-burden countries carry the majority of cases, and inadequate funding continues to hinder tuberculosis control and prevention strategies.
- While Spain maintains relatively low tuberculosis incidence rates, recent increases and shifting demographic trends highlight the need for sustained public health vigilance and targeted intervention strategies.

Global Epidemiology of Tuberculosis

Tuberculosis (TB) remains one of the most pressing public health concerns worldwide. As reported by the World Health Organization (WHO), an estimated 10.8 million individuals developed TB in 2023, including 8.2 million newly diagnosed cases, representing the highest annual figure since global surveillance commenced in 1995. That same year, TB overtook COVID-19 as the leading cause of death from a single infectious pathogen, accounting for approximately 1.25 million fatalities.

The burden of TB is disproportionately concentrated in 30 high-incidence countries, with India, Indonesia, China, the Philippines, and Pakistan alone contributing 56% of the global caseload.

Epidemiologically, the disease predominantly affects adult males (55%), followed by females (33%), with children and adolescents comprising 12% of cases.

Progress toward global control targets has been modest. Since 2015, the global TB incidence rate has declined by only 8.3%, significantly below the 2025 milestone of a 50% reduction. Similarly, TB mortality has decreased by just 23%, falling short of the 75% reduction goal. Multidrug-resistant TB (MDR-TB) continues to pose a major threat to TB control efforts; in 2023, only 44% of the estimated 400,000 MDR-TB cases were diagnosed and received appropriate treatment.

A significant impediment to TB elimination remains the insufficient funding. In 2023, only $5.7 billion was allocated globally for TB control efforts, merely 26% of the $22 billion annual target outlined by international health agencies.

Tuberculosis in Spain

Although the incidence of TB in Spain is relatively low compared to global figures, the disease continues to pose a public health concern. In 2023, a total of 3,944 TB cases were reported, corresponding to an incidence rate of 8.2 per 100,000 population, representing a 7% increase from the previous year's rate of 7.7 per 100,000.

The majority of reported cases were among males (65.3%), with pulmonary tuberculosis (PTB) accounting for 69% of infections.

A notable epidemiological shift has been observed in the distribution of cases among foreign-born individuals. The ratio of native-born to foreign-born TB cases has steadily declined, from 2.2 in 2015 to near parity (1.1) in 2023.

Treatment outcomes in Spain are generally favorable, with 78.6% of cases with documented outcomes achieving successful treatment. However, despite these advances, the reduction in TB incidence remains insufficient to meet the objectives set by the WHO’s End TB Strategy

2. Ethiopathogeny of tuberculosis

Key Points:

- Tuberculosis is caused by members of the Mycobacterium tuberculosis complex, with Mycobacterium tuberculosis being the predominant species affecting humans.
- It is primarily transmitted through airborne particles, though less common routes such as digestive, cutaneous, urogenital, and transplacental transmission exist.
- While pulmonary tuberculosis is contagious, most extrapulmonary forms are not, except for laryngeal tuberculosis and certain open lesions.

Etiological agents

Tuberculosis (TB) is caused by a group of closely related mycobacteria collectively known as the Mycobacterium tuberculosis complex (MTC). This complex encompasses several species with varying geographic and host specificities:

- Mycobacterium tuberculosis: the principal causative agent of TB in humans worldwide.
- Mycobacterium bovis, including subspecies bovis, caprae, and BCG, is primarily associated with zoonotic TB.
- Mycobacterium africanum: predominantly found in West Africa and responsible for a significant proportion of TB cases in that region.
- Mycobacterium microti, Mycobacterium canetti, and Mycobacterium pinnipedii: less common members with limited human pathogenicity but relevant in specific ecological or host contexts.

Mycobacterium tuberculosis

Mycobacterium tuberculosis is an obligate aerobic bacillus whose growth is strictly dependent on the availability of oxygen. Its preferred site of infection is the well-oxygenated regions of the lungs, particularly the apical and posterior segments of the upper lobes and the superior segments of the lower lobes.

The bacterium's cell wall is rich in lipids, contributing to its unique properties:

- Reduced permeability, which enhances resistance to many antimicrobial agents.
- The hallmark acid-fast characteristic, making it resistant to decolorization by acid-alcohol in staining procedures.

Person-to-person transmission

Humans serve as the primary reservoir for Mycobacterium tuberculosis. The predominant mode of transmission is airborne, via inhalation of droplet nuclei measuring 1–5 micrometers in diameter. Once inhaled, these particles may reach the alveoli and initiate infection. The incubation period generally ranges from 2 to 12 weeks, though it may vary depending on host immunity and exposure intensity.

Although respiratory spread is the principal route, TB can occasionally be transmitted through other means:

- Digestive route: Ingestion of infected materials, although rare.
- Urogenital route: Transmission through urine or, less frequently, via sexual contact.
- Cutaneous and mucosal inoculation: Typically seen in healthcare or laboratory personnel following exposure to infected specimens or during procedures such as autopsies.
- Transplacental (congenital) transmission: Occurs when maternal disseminated (miliary) TB results in hematogenous spread of mycobacteria to the fetus, leading to congenital infection.

Zoonotic transmission

Zoonotic transmission is primarily due to Mycobacterium bovis and can occur through ingestion of unpasteurized milk or dairy products or through inhalation of aerosols generated by infected livestock, especially among agricultural workers and veterinarians.

Extrapulmonary Tuberculosis

TB can affect organs outside the lungs, a condition known as extrapulmonary tuberculosis (EPTB).

While most forms of EPTB are not infectious, exceptions exist. Laryngeal TB poses a significant transmission risk due to the generation of infectious aerosols. Similarly, discharging tuberculous fistulas may serve as a source of infection if open lesions are exposed to others.

3. Terminology and Classification of tuberculosis

Key Points:

- Tuberculosis may manifest in drug-susceptible or drug-resistant forms, with resistance classified based on specific patterns and the number of drugs affected.
- Drug resistance arises through either primary transmission or treatment failure, and confirmation requires molecular and phenotypic diagnostic tools.
- Accurate classification of treatment outcomes is critical for evaluating patient progress and guiding public health strategies.

Classification and Drug Resistance in Tuberculosis

Tuberculosis (TB) may present as either drug-susceptible (DS-TB) or drug-resistant (DR-TB), depending on the susceptibility of the infecting Mycobacterium tuberculosis strain to first- and second-line antituberculosis medications.

DS-TB refers to TB caused by strains that are fully susceptible to all first-line antituberculosis drugs, including isoniazid and rifampicin.

DR-TB arises when Mycobacterium tuberculosis develops the ability to survive despite the presence of one or more antituberculosis drugs. The classification of DR-TB is based on the pattern and extent of resistance:

- **Hr-TB (Isoniazid-Resistant TB):** Resistance is confined to isoniazid, with rifampicin susceptibility maintained.
- **RR-TB (Rifampicin-Resistant TB):** Resistance exists solely to rifampicin, regardless of isoniazid susceptibility.

- **MDR-TB (Multidrug-Resistant TB):** Defined by resistance to at least both rifampicin and isoniazid, the two most potent first-line agents.
- **Pre-XDR-TB (Pre-Extensively Drug-Resistant TB):** Refers to MDR-TB with additional resistance to either a fluoroquinolon or a second-line injectable drug (e.g., amikacin, kanamycin, or capreomycin).
- **XDR-TB (Extensively Drug-Resistant TB):** MDR-TB strains exhibiting additional resistance to rifampicin, isoniazid, any fluoroquinolon, and at least one Group A drug (bedaquiline, linezolid, or pretomanid) or Group B drug (clofazimine or cycloserine).
- **TDR-TB (Totally Drug-Resistant TB):** Although not officially recognized by the World Health Organization (WHO), this term is occasionally used to describe strains resistant to all first- and second-line drugs, also referred to as pan-resistant TB.

Mechanisms of Resistance

Drug resistance in TB can be categorized based on its origin:

- **Primary resistance:** Occurs when an individual is infected with a drug-resistant strain without prior TB treatment.
- **Acquired resistance:** Develops during treatment, typically as a result of inadequate, incomplete, or inappropriate therapy.

Accurate diagnosis of drug resistance requires confirmation via molecular diagnostic techniques (e.g., Xpert MTB/XDR, targeted gene sequencing) and phenotypic drug susceptibility testing (DST) in culture-based systems.

Treatment Outcome Definitions in Tuberculosis

Standardized definitions for treatment outcomes are essential for monitoring TB control programs:

- **Cured:** A patient with bacteriologically confirmed pulmonary TB who is smear- or culture-negative in the final month of treatment and on at least one previous occasion.