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Tuberculosis: A Review on Its Novel Advancement on Its Elimination

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ABSTRACT

Tuberculosis, caused by Mycobacterium tuberculosis, remains a global public health issue. Latent TB is an airborne chronic disease; 46% of the world's population is thought to be infected with LTB. It is most prevalent in the lungs (pulmonary TB) but can also affect other organs (extrapulmonary TB). Immunocompromised individuals, such as HIV-positive individuals, are at much greater risk for active TB.M. tuberculosis is an aerobic, non-motile rod whose high levels of lipids make it difficult to diagnose and thus avoid the immune system. It is transmitted via aerosol droplets, where the bacteria infect the lungs and can then remain in granulomas for years. One of the major obstacles to TB control is the advent of drug-resistant strains, such as multidrug-resistant TB, which are not effective when compared to the best first-line agents. Toxic treatment, lack of quality drugs, or improper medicine contribute to its growth. High levels of diagnostic variability hinder progress, and an estimated 4 million undiagnosed cases a year fuel transmission. WGS can be applied in various ways, but its use has a limited impact. A financial constraint also severely limits TB control efforts. Future strategies to combat TB will include better vaccines, new drugs and rapid point-of-care diagnostics. Controlling the disease requires focused screening practices, diagnosis intervention, adequate funding, and drug resistance, along with ethical principles of informed consent and patient agency in research and care.

Keywords: Mycobacterium tuberculosis, drug-resistant, novel drug discovery, TB preventive therapy and screening practices

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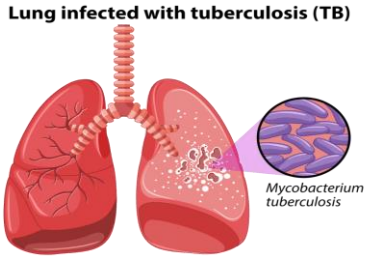
INTRODUCTION

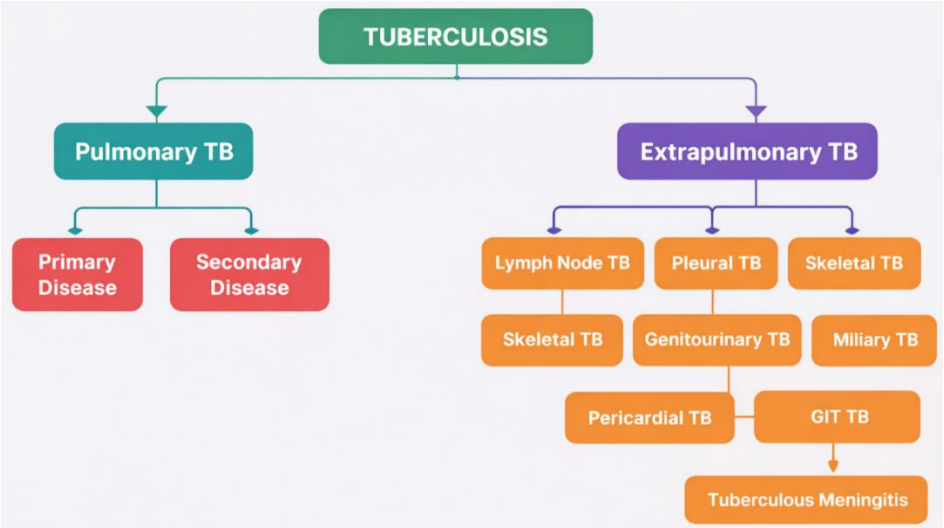
M. tuberculosis was identified by Robert Koch in 1882. Since then, the worldwide tuberculosis load has gone undetected and spread across continents. Tuberculosis (TB) is an exceedingly infectious airborne infection that is one of the main causes of death [1]. Although pulmonary tuberculosis is most common in the lungs, it can move to other organs and cause extrapulmonary tuberculosis.

M. tuberculosis can remain dormant in the human body for years without showing symptoms, leading to many asymptomatic carriers of latent TB infection (LTBI). The WHO 2022 report reports that almost a quarter of the world's population, some 2 billion people, suffer from latent TB. For those with LTBI, the lifetime risk of reactivation is estimated to be 5–10% [2]. It is more likely that drug-resistant bacteria will reinfect those with weak immune systems, particularly those co-infected with HIV. Among 38 million HIV-positive people, the risk of active TB is approximately 18 times higher. Once activated, bacterial replication is initiated, leading to symptomatic TB disease. [3]



Types:

Tuberculosis is a typical infectious disease that affects the lungs; it's called pulmonary TB. Tuberculosis outside of the lung is called extra pulmonary TB. [4]



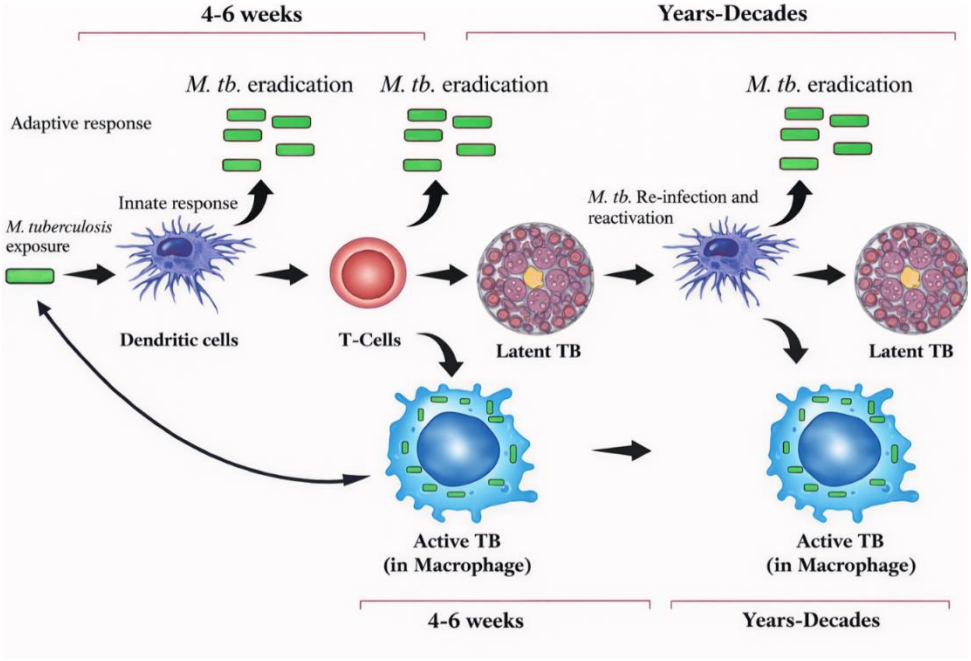
Etiology:

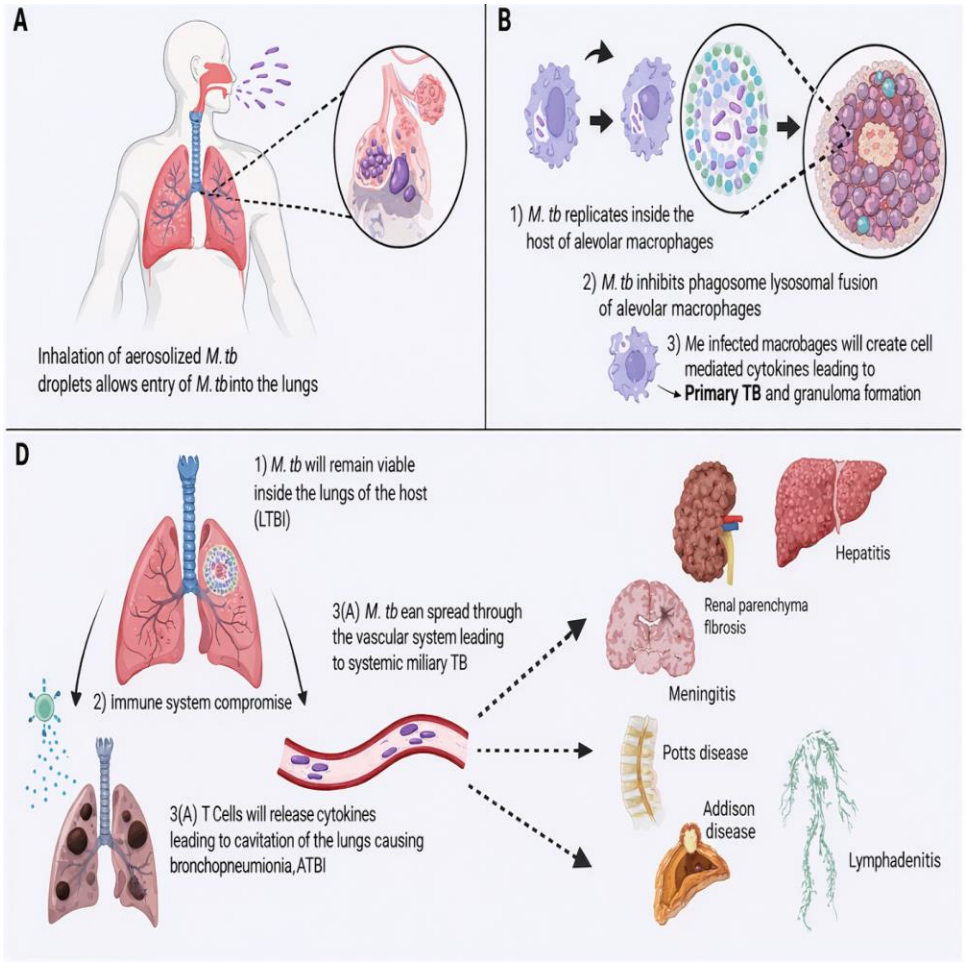
- The M Tb complex includes M. tuberculosis. M. bovis, M. africanum, and M. canettii, which can infect humans.
- These are aerobic, non-spore-forming, nonmotile rods (bacilli).
- These cells are characterized by a high lipid content, which in turn increases their acid-fast staining ability as well as their ability to control the immune system and cause diseases.
- M tb is slow to form and generates only after about 20 hours, whereas visible colonies on solid media take 3 to 8 weeks to appear, which complicates diagnosis.
- M. tuberculosis is a major vector in humans, although it can also be spread to some animals.
- Virulence of M tb strains may be influenced by genetic variability across nations. [5]

Pathogenesis:

Tuberculosis (TB) spreads through tiny airborne droplets that contain Mycobacterium tuberculosis (M. tb). These droplets are released when an infected person coughs, sneezes, or talks.[6] Once inhaled, the bacteria go to the lungs, where alveolar macrophages engulf them as part of the body's immune response. If these macrophages can't destroy the bacteria, M. tb survives and grows inside them, spreading to other macrophages. This process draws in lymphocytes and leads to the formation of a granuloma, which is a structured cluster of immune cells trying to contain the infection. At this stage, the host usually shows no symptoms, and the infection can either be cleared or become latent. Granulomas help limit bacterial spread in people with strong immune systems, but M. tb can persist for years by escaping immune defences, especially by preventing phagolysosome fusion. [7]. This leads to latent TB infection (LTBI), which is not infectious but hard to treat. As the disease progresses, granulomas change both structurally and functionally. Macrophages transform into lipid-rich, foamy macrophages due to M. tb disrupting host lipid metabolism and the effect of mycolic acids, which aid the bacteria in surviving. The centre of the granuloma may undergo necrosis, creating caseum that holds dormant bacilli [8]. When the immune system weakens due to factors like HIV infection, malnutrition, diabetes, immunosuppressive therapy, or other chronic illnesses—the caseous core can liquefy and form cavities. This reactivates bacterial growth and leads to active TB. The result is lung damage, a high bacterial load, and the spread of bacteria within the lungs and to other organs through the bloodstream. Granulomas range from solid to necrotic to caseous forms,

indicating a shift from latent to active disease, with reactivation closely linked to granuloma breakdown and immune failure.



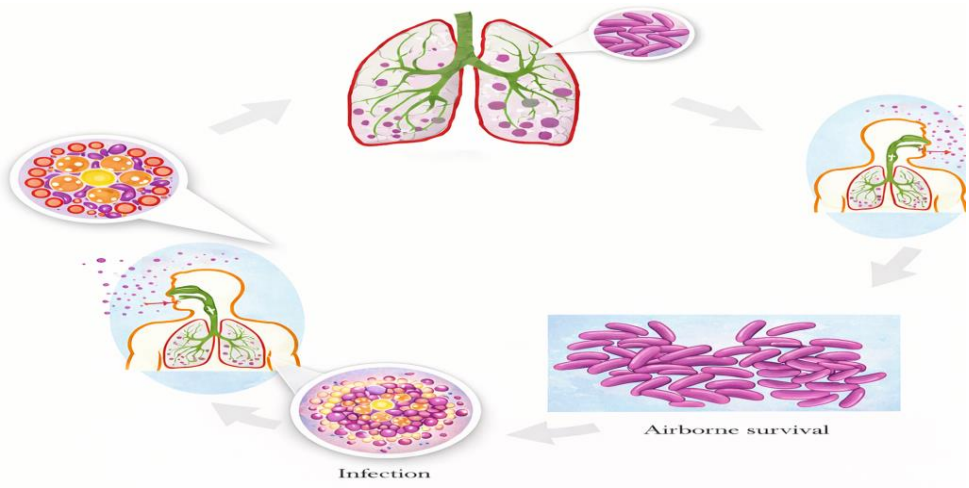


Transmission Of TB:

Aerosol transmission:

The transmission of airborne viruses includes two steps: aerosol production by a source, transporting the aerosols through the air and depositing them on an infected host. The pathogen should be able to overcome environmental stressors. This is why M. tuberculosis is an example of the disease, as it is transmitted via small particles (<5 μm) that accumulate in poorly ventilated spaces.

Aerosol production is mediated by activities such as coughing, sneezing, singing, speaking, and breathing. Staphs may contain either culturable or nonculturable bacteria. M. tuberculosis cannot infect the terminal airways of the lung, whereas SARS-CoV-2 can infect the nasal and proximal airway mucosal surfaces.[10]



Transmission of drug-resistant in tuberculosis:

Transmission is key to the development of drug-resistant tuberculosis because DR-TB mostly originates in people who have never had tuberculosis. DR-TB strains exhibit varying fitness levels due to their diverse epidemic ages and mutations. [11]. Studies indicate that more transmissible strains will evolve. It is noteworthy that patients with drug-susceptible tuberculosis and DR-TB did not differ significantly in infectiousness. Although less contagious DR strains may not be as prevalent, delayed treatment initiation often leads to greater transmission risk. Drug-resistant strains could spawn and adapt through compensatory alterations due to inadequate drug susceptibility testing.[12] In some cases, these changes may improve transmission and may affect overall strain fitness in cases of ineffective therapy.

Genomic transmission tracking:

WGS technology in the last few years has increased its utility for disease surveillance, including in the case of the COVID pandemic, where it was used to detect SARS-CoV-2 mutations. WGS

has provided important insights into the dynamics of tuberculosis transmission and is much more successful in identifying case clusters than before.[13] Using routine WGS in low-risk areas of tuberculosis can lead to finding new intervention targets, public health interventions and local transmission events. But, while there are still constraints such as pre-culture, cost and infrastructure needs, COVID-19's increased use of WGS provides an interesting opportunity to further the control of tuberculosis. The World Health Organization has proposed efforts to expand access to genomics in the world, but implementation is still elusive.[14]

GAPS In Diagnosis and Screening:

TB remains a major public health issue in countries with high levels of disease burden, such as India. In 2022, India screened 94% of TB patients' home contacts compared to 84% globally. [15] However, many asymptomatic patients are not included in the existing symptom-based screening tools and thus need to be addressed early in the process. Artificial intelligence, chest X-rays and approved quick molecular tests could help to speed up case diagnosis and treatment.[16]

A key issue is the estimated 4 million cases of tuberculosis undiagnosed each year, which increases transmission risk.[17] This is complicated by a lack of identification and diagnosis of index cases, barriers to access to diagnostic services, and social stigma. New screening interventions are needed to close the gap in detection and equal access to preventive care based on community participation.

Financial constraints significantly constrain efforts to fight TB. By 2023, TB-related programs in low and middle-income countries were funded for $5.7 billion, although there was little from India to contribute domestically. The addition of the USAID funding cut has added further pressure on resources, leading to questions about whether TB programs will survive in the long run. Without improved funding, there will be 10.6 million additional cases and 2.2 million TB-related deaths in 2030.[18] For TB prevention, more funding from domestic and foreign sources is required for long-term control. To combat tuberculosis, screening, diagnosis, and funding must be addressed. A concerted effort will be needed to accelerate the detection of these cases, reduce the cost of preventive medical care, and obtain funding.

DRUG RESISTANT IN TB:

Drug-Resistant TB: Resistance was first identified in the 1940s when streptomycin was used as a monotherapy for tuberculosis. Most TB patients were treated with isoniazid in 1952, and rifampin in 1970 allowed treatment interventions to use various regimens to reduce the resistance to drugs.

But, during the mid-1990s, MDR-TB epidemics in the U.S., Spain, Italy, Argentina and Russia erupted due to combination therapy. [19] The time period saw patterns of outbreaks that reflected the epidemiology of the HIV epidemics, especially in those countries where patients and screening were most lacking.

Tuberculosis with Multiple Drug Resistance:

For example, tuberculosis drugs may lead to TB bacteria becoming resistant. TB non-responsive to isoniazid or rifampicin, the two most effective anti-TB drugs, is called MDR-TB. The multi-drug resistance persists due to a combination of two factors: the incorrect use of TB drugs and the transmission of the TB virus from person to person. As with many TB patients, this usually takes place over six months with monitoring and supports [20].

Drug Resistance Types and Tuberculosis Management Techniques:

Tuberculosis is resistant to drugs in two forms: acquired and primary. The cases where drugs bind in patients who have not received anti-tubercular treatment are called primary drug resistance. Conversely, those already receiving chemotherapy exhibit drug resistances [21]. This resistance in a patient who has already had chemotherapy is known as "acquired drug resistance"

Drug discovery and development:

The conventional method of discovering new drugs is costly and time-consuming. To overcome resistance, new drugs that target distinct modes of action against Mycobacterium tuberculosis are crucial. [22]

Table :1 Drug discovery and development

Drug	Drug class	Mechanism	Current dosage and mode of administration	Trail phase
Bedaquiline	Diarylquinoline	By blocking its ATP synthase, bedaquiline stops Mycobacterium TB from generating energy, which results in bacterial cell death	Oral, 400 mg per day for 2 weeks, 200 mg three times per week for 22 weeks	Pivotal trials in DR-TB have shown significant efficacy, and it is approved for usage
Delamanid	Nitro - dihydro - imidazooxazole	Delamanid suppresses mycobacterial growth and inhibits the synthesis of mycolic acid, which is essential for the bacterial cell wall.	Oral, 100 mg per day for 2 months, then 200 mg per day for 4 months	Approved; ongoing studies are evaluating long-term safety and efficacy

Pretomanid	Nitroimidazole	Pretomanid interferes with the development of cell walls and generates reactive nitrogen species, which both contribute to bacterial death	Oral, 100-200 mg per day	Accepted; key trials (Nix-TB study) have shown considerable success rates for DR-TB patients
Clofazimine	Riminophenazine	Clofazimine prevents growth by interfering with the mycobacterial membrane's ability to produce lipids	Oral,50 mg soft gelatin capsules	It is authorized and typically taken in conjunction with other drugs
Thioridazine	Phenothiozine	Thioridazine may disrupt the metabolism and activity of bacteria	Oral,50 mg to 100 mg three times per day	Not frequently used to cure tuberculosis; only in the early stages of research

Prevention and control:

TB prevention strategies are a vital part of decreasing the burden on the individual and community. These techniques are intended to prevent new TB infections, especially those in high-risk populations, and to prevent latent forms of infection from turning into active diseases. Plus, prevention of TB seeks to control the population transmission of tuberculosis. Below are some of the major components of tuberculosis prevention: [23] [24]

Vaccination: In some countries, BCG is administered to prevent severe tuberculosis in children. While not 100% effective in preventing tuberculosis, the BCG vaccine may be useful for preventing severe forms of the disease (such as tuberculous meningitis and miliary tuberculosis) in young children.

Screening and testing: Populations can be detected ahead of time by focused testing and screening programmes that target latent TB infection. Early detection and treatment will stop the disease from progressing to active tuberculosis. People who are most at risk, such as those who have close contact with TB patients and those who are immunocompromised, are typically tested.

Latent tuberculosis infection (LTBI) treatment: In fact, providing preventive medication to individuals with LTBI significantly lowers their risk of developing active TB illness. Isoniazid and rifapentine are two anti-TB drugs that are frequently used to treat LTBI since they have been demonstrated to be successful in stopping the development of active TB.[25]

National goals for Tb elimination:

The MoHFW, Government of India, introduced this plan in 2017. It is the government's proposal to eradicate tuberculosis in India, including the actions and interventions that will significantly

and successfully alter the disease's incidence, prevalence, and mortality. This is on top of what was previously practiced.

The objectives of NSP 2017–2025

- Increasing and improving drug resistance testing and early identification of tuberculosis.
- To properly treat tuberculosis to stop the spread of the disease by preventing the development of medication resistance
- Increasing the ability to monitor continuously
- Preventing latent tuberculosis infection (LTBI) and the onset of TB.
- Eradicating tuberculosis in India [26]

CHALLENGES:

Health system-related challenges:

Infrastructure and human resources are impediments to the efficient delivery of TPT services. Also, inadequate supply and procurement of TPT drugs rob patients of their treatment continuity. Lack of readily available diagnostic tools to identify TBI is complicating TPT delivery. Also, data entry and system administration issues hinder the evaluation and monitoring of TPT programs [27].

Community-related challenges:

Reaching and involving all members of the enormous population in need of TPT services has logistical challenges. Furthermore, the stigma associated with tuberculosis persists, producing prejudice and fear, limiting community participation and collaboration. Healthcare professionals frequently refuse contact tracing visits due to privacy concerns and the stigma associated with tuberculosis. The community's lack of information about TPT has a further impact on service adoption [28].

Tuberculosis preventive treatment eligible population-related challenges

Treatment outcomes are impacted by TPT non-adherence, which is frequently caused by extended treatment regimens. Furthermore, isoniazid resistance makes TPT less effective, especially when used in monotherapy regimens. Reservations about starting TPT may also be expressed by TB contacts or the eligible population, particularly if they are asymptomatic or ignorant of the advantages. TPT coverage and service access are further impacted by private health care providers' reluctance [29].

Strategies and approaches to address present challenges:

Cost-effective drugs that meet the different epidemiology of tuberculosis in the country will be needed for the next phase of the eradication of tuberculosis in India.

Handling health sector issues:

However, to address such issues, various strategies such as implementing a centralized procurement mechanism for TPT medicines, thus ensuring continuous access, may be employed. Continuous capacity development, such as training support for health facilities involved in TPT programs, may enhance the provision of health services. Additionally, the implementation of effective surveillance tools is valuable for monitoring TPT elements and improving any errors created within the systems [30]. There is a need for partnership among various players, including the public as well as private entities, health departments, NGOs, academics, as well

Advancements in Tuberculosis (TB) research:

Tuberculosis is the second-highest infectious cause of death from one infectious agent, and with increasing numbers of drug-resistant cases, it has become a global threat to public health. Early and effective treatment is critical for preventing the development of drug-resistant pathogens. This requires timely and reliable point-of-care diagnostic tools to efficiently handle cases. The most applied tests for tuberculosis and their diagnosis are clinical, immunological, microscopic examination, radiography, and bacterial culture.

In addition, recent advances in molecular diagnostic methods, including:

- MTBDRplus
- loop- medicated isothermal amplification (LAMP)
- line probe assay (LPA)
- GeneXpert
- whole genome sequencing (WGS)

This has been used to diagnose and characterize tuberculosis. These approaches can detect both Mycobacterium tuberculosis (MTB) and mutations associated with commonly used anti-TB medicines. In this paper, we examine the utilization of currently available diagnostic tools and strategies for detecting MTB in clinical settings, ranging from conventional to recently deployed next-generation sequencing (NGS) technologies.[31]

Conventional TB diagnostic techniques:

Innovative approaches that can provide same-day results for tests and identify multiple drug-resistant mutants are needed to ensure that unmet requirements in TB diagnostics are met at the point of care, such as rapidity, affordability, simplicity, precision and high sensitivity. Across a

broad spectrum of disciplines such as molecular biology, nanotechnology, biosensors, VLSI, and so on, this has led to fast developments in the ability to make the whole process available on a single page.

Biosensing techniques for TB detection:

Most of the non-biosensing methods for MTB detection discussed above are not performed in a laboratory, requiring highly trained staff members and sophisticated equipment found in large-scale laboratory facilities. To prevent tuberculosis infections and reliably detect them early, it is necessary to develop a sensitive, real-time, fast, and portable system (Griffiths and Hall, 1993; Owen, 1994). Biosensing technology has shown promise in defeating this deadly disease. Biosensors have been effective.

Developments in device platforms for point-of-care (POC) TB detection:

Innovative methodologies that can produce test results on the same day and identify various drug-resistant mutants need to be developed to meet the TB diagnostic demands of rapidity, affordability, simplicity, precision and high sensitivity at the point-of-care. The emergence of such rapid developments in molecular biology, nanotechnology, biosensors, VLSI, etc., has allowed us to combine all these processes into a single unit.[32]

Ethical consideration:

Etiquette considerations for tuberculosis research include ensuring that the studies meet high scientific and ethical standards, that vulnerable groups are protected, and that the potential benefits outweigh the risks [33]. Researchers also need to consider how the dissemination of their findings may affect public health, practice, and policy. Questions about ethics are central to clinical and research on tuberculosis because they inform decisions that affect patient populations and global public health care. For all TB-related research studies, diagnostic procedures, treatment plans, and public health interventions, informed consent, justice, patient autonomy, and privacy should guide all activities. Finding a balance between personal rights and public health needs may be difficult, but we need to uphold the ethical practice of tuberculosis care and research.

Future prospects:

Despite the difficulties of TB prevention, global efforts must be taken in many directions:

1. **Research and Development:** This includes developing sensitive, specific, and user-friendly point-of-care diagnostic tests, implementing AI for quick screening and CRISPR/Cas-based assays for improving detection.

2. **Vaccine Research:** Investing in new vaccine antigens and vaccine delivery systems is crucial, especially for populations at high risk. It is important to promote candidates like M72/AS01E and new platforms such as mRNA vaccines.
3. **Surveillance and Drug-Resistant TB Treatment:** New anti-TB drugs need robust surveillance and research. Shorter, effective treatment plans for drug-resistant TB are needed along with strong infection control measures.
4. **Community-Based Programs:** Promoting awareness, disseminating stigma and promoting access to care are important initiatives. Taking measures against social causes of poverty and malnutrition is a key to disease prevention.
5. **Health Systems Strengthening:** There is a need for sustainable funding and improvement of healthcare systems, such as infrastructure and workers' training to fight TB.
6. **Collaboration with Other Organizations:** Global collaboration, such as the Stop TB Partnership, is an essential ingredient in ensuring equal access to diagnostics, drugs, and vaccines. [34]

CONCLUSION:

Tuberculosis is a major global health condition that persists frequently with high rates of asymptomatic cases and high rates of mortality. Even though M. tuberculosis has long been identified, millions of undiagnosed cases, multidrug-resistant TB (MDR-TB), and funding limitations limit the elimination of the disease. To overcome these hurdles, an international strategy must be pursued that focuses on developing effective vaccines, new drugs and accessible diagnostics, particularly in resource-limited contexts. Strategies must also address social health risk factors and adopt integrated care models for TB treatment in combination with co-infections such as HIV, while maintaining ethical standards for patient rights. Research, screening, and funding are the most important things to commit to to prevent and combat TB.

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