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Current Approaches of Tuberculosis and Its Future Prospectives

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ABSTRACT

Tuberculosis is a major global health issue, with approximately 10 million people falling ill and 1.4 million dying yearly. One of the most significant challenges to public health is the emergence of drug-resistant tuberculosis. For the last half-century, treating tuberculosis has adhered to a uniform management strategy in most patients. However, treatment ineffectiveness in some individuals with pulmonary tuberculosis presents a major challenge to the global tuberculosis control initiative. Unfavorable outcomes of tuberculosis treatment (including mortality, treatment failure, loss of follow-up, and unevaluated cases) may result in increased transmission of tuberculosis and the emergence of drug-resistant strains. Treatment failure may occur due to drug-resistant strains, non-adherence to medication, inadequate absorption of drugs, or low-quality healthcare. Identifying the underlying cause and adjusting the treatment accordingly to address treatment failure is important. This is where approaches such as artificial intelligence, genetic screening, and whole genome sequencing can play a critical role. In this review, we suggest a set of particular clinical applications of these approaches, which might have the potential to influence decisions regarding the clinical management of tuberculosis patients.

Keywords- Tuberculosis, Health, Drug resistant, Treatment.

I. INTRODUCTION

In 1882, Robert Koch discovered the tubercle bacillus, usually referred to as Mycobacterium tuberculosis (M. tb), as the causative agent of tuberculosis (TB) [1]. Since its discovery, the TB epidemic appears to be relentless, proliferating in every region of the world. Tuberculosis (TB) is an extremely infectious illness that spreads through the air and is among the leading causes of death globally [2]. Pulmonary TB primarily targets the lungs, but it can potentially metastasize to other areas of the body, resulting in extrapulmonary TB. Mycobacterium tuberculosis (M. tb) has the ability to remain in a dormant state for extended periods of time within the body, without causing any symptoms of sickness. This can lead to individuals becoming asymptomatic carriers of tuberculosis, often known as inactive TB. Based to the 2022 report from the World Health Organization (WHO) [2], approximately 2 billion people, which is almost one fourth of the global population, are latently infected with M. tb (Figure 1). The estimated lifetime risk for TB reactivation in individuals with latent TB infections (LTBI) is 5-10% [2]. Undoubtedly, the inactive mycobacteria have the potential to become active (known as active TB), especially in individuals with weakened immune systems, such as those who are simultaneously infected with the human immunodeficiency virus (HIV). The incidence of tuberculosis (TB) is estimated to be 18 times greater in those with HIV compared to those without HIV, among the approximately 38 million persons living with HIV [2,4]. When the stalemate is resolved, the reactivation of TB occurs and the amount of bacteria increases significantly, resulting in the onset of symptoms of the disease [5]. Timely detection and effective management

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of tuberculosis (TB) is essential in order to halt the transmission of the germs and the emergence of drug-resistant strains [6]. Various diagnostic approaches are frequently used, such as immunological, radiographical, microscopical, bacterial culture, and clinical methods. Immunological assays, such as QuantiFERON-TB Gold (QFT) and Tuberculin skin test (Mantoux test), are primarily employed to screen for and exclude tuberculosis (TB) infection [6]. Similarly, radiography, specifically Chest X-rays, is employed as a screening method for diagnosing current pulmonary tuberculosis. However, it is not effective in identifying latent tuberculosis infection. Sputum smear microscopy is a highly effective and often employed technique for diagnosing tuberculosis. It involves staining the TB bacteria with Ziehl-Neelsen stain. However, this method has limitations in terms of its low sensitivity and inability to distinguish between M. tb and other acid-fast bacilli. Sputum culture is a diagnostic procedure for tuberculosis that is very specific and sensitive. It involves using Löwenstein-Jensen medium to culture the TB bacteria. Unlike smear spectroscopy, sputum culture is a more precise and accurate way for diagnosing TB. Due to the slow growth of M. tb, it often requires a minimum of two weeks (sometimes 6-8 weeks) for the colonies to become visible. This delay in colony appearance further hinders the process of diagnosing and treating the infection. Ultimately, a small proportion of patients infected with tuberculosis (TB), approximately 5-10%, experience the emergence of various signs and symptoms that enable a clinical diagnosis to be made [6]. The symptoms of active pulmonary tuberculosis may include pleuritic chest pain, low-grade fever, prolonged productive cough, hemoptysis, exhaustion, loss of appetite, night sweats, and weight loss [6,7] (Figure 1). In terms of geography, the WHO South-East Asian area had the highest proportion of individuals who contracted TB in 2021, accounting for 45% of cases. This was followed by the WHO African region with 23% and the WHO Western Pacific region with 18%. More than 50% of the global burden of tuberculosis (TB) is attributed to four countries: India (28%) and Indonesia (9.2%) in the WHO South-East Asian region, and China (7.4%) and the Philippines (7.0%) in the WHO Western Pacific region. The user's text is "[2]." While the proportion of individuals with latent tuberculosis infection (LTBI) who are at risk of developing active tuberculosis (TB) may appear to be minimal, it is important to note that around 10 million people have been diagnosed with TB each year since at least 2000 [2]. Furthermore, between 2000 and 2021, the annual death toll from TB ranged from 1.4 to over 2 million individuals, with the most significant mortality rates observed during the period from 2000 to 2010. The most recent 2022 World Health Organisation (WHO) study has recorded that in 2021, tuberculosis (TB) caused the deaths of over one million individuals globally. This includes an estimated 1.4 million deaths among those who are HIV-negative and 0.2 million fatalities among those who are HIV-positive. Prior to the COVID-19 pandemic, tuberculosis (TB) caused more deaths than any other infectious agent, including HIV/AIDS [2]. Regrettably, there is now no efficacious vaccine accessible for the prevention of TB disease in adults, whether it is prior to or following exposure to M. tb [2,4]. However, the sole authorised tuberculosis (TB) vaccine, bacille Calmette-Guérin (BCG), which was created almost a century ago, can provide a limited level of protection in infants and children, particularly against severe types of TB such as miliary TB and TB meningitis. Although tuberculosis can affect anyone regardless of their location, the majority of individuals (about 90%) who get active tuberculosis are adults. Furthermore, there is a higher prevalence of tuberculosis among men compared to women [2,4]. Thus, it is imperative to develop a more effective vaccine that can confer immunity against all types of tuberculosis in individuals of various age groups. Furthermore, there is an urgent need for novel anti-TB medications that surpass the present treatment alternatives in terms of effectiveness, tolerance, and duration of treatment in order to effectively treat and control the spread of tuberculosis. This review article will provide an overview of TB pathophysiology, current treatment regimens, obstacles in global TB control, and current TB therapeutic targets along with their respective drug candidates.

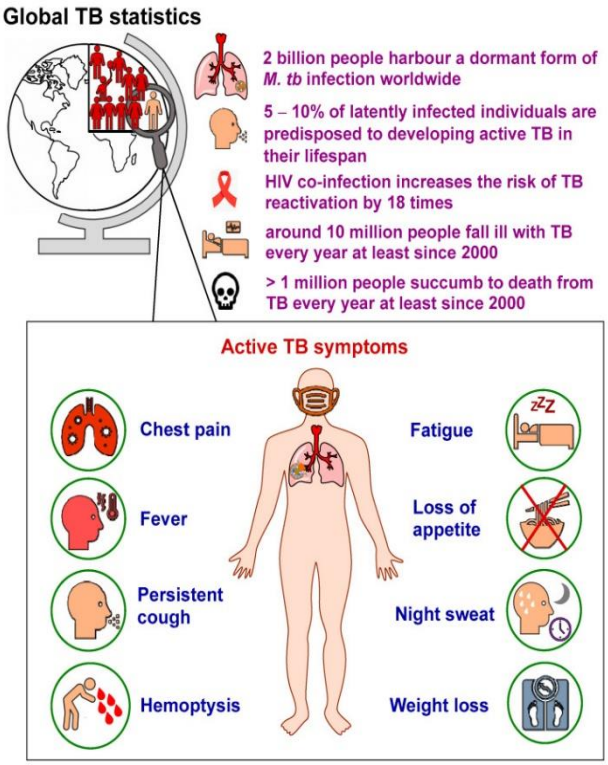

Figure 1: illustrates general tuberculosis (TB) statistics and the primary symptoms of pulmonary TB.

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II. EPIDEMIOLOGY

Following the upheaval created by the COVID-19 epidemic, there is a glimmer of optimism emerging in the battle against tuberculosis (TB). The research indicates that in 2022, a total of 7.5 million individuals received a diagnosis of tuberculosis, marking the greatest number documented since the World Health Organisation commenced worldwide tuberculosis monitoring in 1995. Despite likely encompassing a significant number of individuals who contracted tuberculosis in prior years, this data indicates that countries across the globe are regaining the ability to provide and access healthcare treatments. India, Indonesia, and the Philippines, which collectively contributed to more than 60% of the worldwide decline in newly diagnosed TB cases between 2017 and 2021, all experienced a recovery beyond the levels seen in 2018 by 2022.

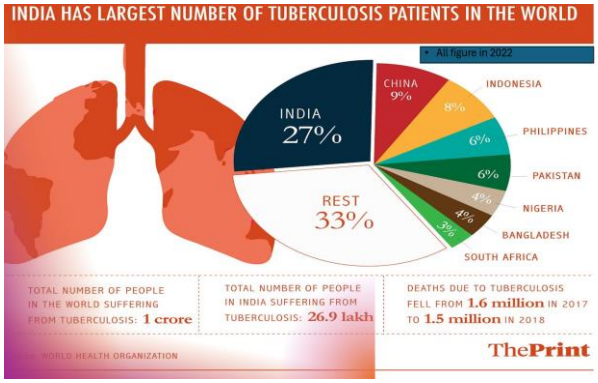

Fig: 2 TB cases largest in India in 2022

The global incidence of tuberculosis (TB) in 2021 was anticipated to be 10.6 million persons (95% uncertainty interval [UI]: 9.9–11 million), which represents a 4.5% increase from the 10.1 million cases (95% UI: 9.5–10.7 million) reported in 2020. This marks a reversal of the previous trend of gradual decline over several years (see Figure 3, left panel). Moreover, the predicted TB incidence rate, which represents the number of new cases per 100,000 population per year, has witnessed a 3.6% increase from 2020 to 2021.

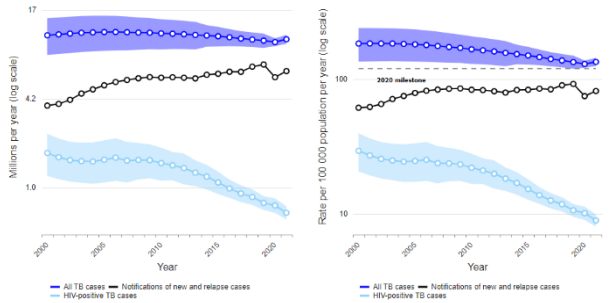

Fig: 3 lobal trends in the estimated number of incident TB cases (left) and the incidence rate (right), 2000–2021

The facility was characterised by the absence of any chemotherapeutic medicines, the lack of diagnostic x-ray capabilities, and the absence of any tuberculosis control programme. This time spanned approximately the mid-20th century. During this era, due to the lack of viable medications or drug combinations for treating TB, a push to establish sanatoriums emerged in Europe and rapidly expanded globally. The prevailing justification for the establishment of sanatoria was based on the belief that a strict routine of rest, proper nourishment, exposure to clean outdoor air, and residing at high altitudes provided the most favourable conditions for the patient's immune system to isolate and contain areas of pulmonary tuberculosis (TB) infection. In 1863, Hermann Brehmer established the first sanatorium in the world, called Brehmerschen Heilanstalt für Lungenkranke, in the city of Gerbers'd (Sokolowski), Silesia (now Poland), specifically for the treatment of tuberculosis. The user's text is "[15]".

Tuberculosis has been referenced in the ancient Indian texts known as the Vedas and the Ayurvedic traditions. The fight against tuberculosis (TB) in India can be divided into three distinct periods from a historical perspective. The early period predates the discoveries of x-ray and chemotherapy. The post-independence period saw the initiation and implementation of nationwide TB control programs. The current period is characterized by the ongoing TB control program, which is supported by the World Health Organization (WHO).

III. EARLY PERIOD OF TB CONTROL

The establishment of the first open-air sanatorium for the treatment and isolation of tuberculosis patients in India took place in 1906 in Tiluania, near the city of Ajmer in Rajasthan. This was followed by the opening of the first tuberculosis facility in Bombay in 1917.The user's text is "[16]". Starting in 1925, chest radiography began to have a diagnostic function in identifying the presence of tuberculosis consolidation in deep-seated locations. By 1945, the functionality of this device was improved to include the MMR (mass miniature radiography) version. The initial breakthrough in combating tuberculosis was achieved with the development of a successful immunization against the disease. BCG (bacillus of Calmette and Guerin) was created in 1906 by Albert Calmette and Camille Guerin. It is derived from a weakened strain of tuberculosis found in cows. On July 18, 1921, BCG was administered to people for the first time in France. In 1948, WHO and UNICEF collaborated to establish a BCG vaccination production facility in Guindy, Madras (now Chennai). In 1951, India initiated a large-scale BCG campaign with the aim of managing tuberculosis. This marked the inaugural statewide campaign against tuberculosis (TB)[17]. It was a significant milestone in India's history, as it was the first instance where the message of

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health and disease prevention was disseminated to the most remote regions of the country.

District TB program

The Indian government formulated the District Tuberculosis Program in 1961, with the Anantapur district in Andhra Pradesh state being established as the inaugural model district TB center (DTC). The objective of this program was to integrate TB control strategies with the current government health services in order to economically minimize the TB issue in the community. The user's text is enclosed in tags. Soon after the establishment of the Anantapur DTC, it became clear that while it was easy to identify cases of TB anywhere, the main challenge in combating the disease was ensuring that patients remained on treatment until they were completely cured.The user's text is "[19]". In 1962, the Indian government initiated the National TB Control Programme (NTCP) based on the district TB centre model.

Era of short-course chemotherapy

During the mid-20th century, approximately around the time when India achieved independence in 1947, very efficient medications for treating tuberculosis began to emerge. These medications include Streptomycin (1944), PAS (1946), Thiacetazone (1950), Isoniazid (1952), and Rifampicin (1966). The user's text is "[20]". In 1956, the Indian government founded the Tuberculosis Research Centre (TRC) in Chennai with the support of the Indian Council of Medical Research (ICMR), the government of Chennai state, the World Health Organization (WHO), and the British Medical Research Council (BMRC). The advent of Rifampicin and Pyrazinamide in the 1970s brought about significant advancements in the chemotherapy treatment for tuberculosis, as these medications were both extremely effective and well-tolerated. These medications facilitated the use of short-course chemotherapy (SCC), enabling treatment to be streamlined and its duration to be shortened. The discovery of Rifampicin in 1967 is widely regarded as a significant milestone in the development of anti-TB medications. Despite ongoing research, no new medicine has surpassed Rifampicin in terms of effectiveness against TB since its initial discovery.

Current WHO-assisted ongoing TB control program

In 1992, the Government of India, in collaboration with the WHO and the Swedish International Development Agency (SIDA), assessed the national program and determined that it had managerial deficiencies, insufficient funding, excessive dependence on x-ray, nonstandard treatment plans, low rates of treatment adherence and completion, and a lack of organized data on treatment results. The user's text is "[22]". In 1993, the World Health Organization (WHO) classified tuberculosis (TB) as a worldwide emergency and developed the Directly Observed Treatment, Short-course (DOTS) plan. WHO also advised all nations to use this strategy. This strategy was developed based on five essential components, namely, political dedication and consistent financial support for tuberculosis control programs, diagnosis through sputum smear examinations, uninterrupted provision of high-quality anti-tuberculosis medications, supervised drug intake, and precise reporting and documentation of all registered cases.

The World Bank acknowledged that the DOTS plan was the most cost-effective health intervention and agreed to give credit support for the NTCP. Initially, the aid was intended to cover a population of 271 million people, but this was later altered to cover a population of 730 million people. Currently, the program is receiving valuable support from various bilateral and multilateral agencies, including the Danish International Development Agency (DANIDA), Department for International Development (DFID), US Agency for International Development (USAID), Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria (GFATM), Global Drug Facility (GDF), and the World Health Organization (WHO). The Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria is the primary and largest provider of external financial resources for the management and prevention of tuberculosis. The user's text is "[23]".

In 1997, the Revised National TB Control Program (RNTCP) was created to rejuvenate and strengthen the NTCP, with support from the international agencies indicated above. The user's text is "[24]". The internationally approved DOTS strategy was devised and adopted in order to revitalize the TB control program in India. This method is considered the most systematic and cost-effective technique. The emphasis was placed on the political and administrative dedication to guarantee the delivery of well-structured and comprehensive tuberculosis (TB) control services. This includes ensuring reliable and early diagnosis through smear microscopy, a continuous supply of high-quality anti-TB drugs, effective and patient-friendly treatment using short-course chemotherapy (SCC) administered under direct observation, and accountability through accurate reporting, recording, and effective supervision. The user's text is "[25]". Currently, India's DOTS program holds the title for being the most rapidly increasing and largest program globally in terms of patients who have started treatment. It also ranks as the second largest program in terms of the number of people it covers.

TB Drug Targets

In 1998, the complete genome sequencing of *M. tb* (approximately 4000 genes) was unveiled, which advanced our understanding of the molecular biology of the bacterium [41]. Knowledge of the whole-genome *M. tb* sequence enabled researchers to identify a subset of genes that are essential in vitro and in vivo [42]. This revelation in turn contributed to the discovery of new targets for novel compounds via identifying the mutated genes of the strains resistant to these compounds. The

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gene knockdown techniques, whereby the gene of a specific target is depleted, has also facilitated the validation process of several *M. tb* drug targets [42]. The TB drug discovery approaches can be classified into target-based and phenotypic screening [43,44] (Fig 4). The genome-derived target-based approach (target-to-drug) involves the identification of a specific cellular target in advance but without giving any information about its druggability (drug penetration or efflux) [43]. Indeed, it has been a difficult conundrum to translate a good bacterial enzyme inhibition into a potent whole-cell *M. tb* inhibitory activity because of the difficulty to penetrate the highly impermeable waxy cell wall of *M. tb* [35]. In addition, several inhibitors, which were identified against essential targets, were lacking drug-like properties. Therefore, no anti-TB drug has emerged from this strategy to date [35,43,44].

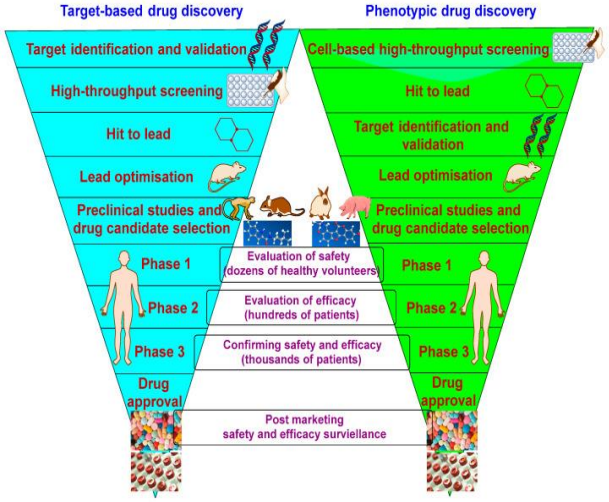

Fig : 4 A simplified diagram illustrating the cascade of target-based and phenotypic drug development approaches for tuberculosis (TB).

IV. TB DIAGNOSIS

A precise and prompt diagnosis of tuberculosis helps decrease mortality and premature death. The increasing instances of medication resistance pose a significant challenge to the objective of eliminating tuberculosis. Significant progress has been made in laboratory diagnostic methods for detecting infections. These solutions can either enhance or substitute the current conventional approaches. Conventional techniques for detection include Acid-fast bacillus smear microscopy and microbial culture. In contrast, sophisticated approaches such as CRISPR Cas, Gene Expert, and LAMP are used. The traditional methods are characterised by a laborious and time-consuming process, yet they remain prevalent in nations with a high prevalence of tuberculosis. The absence of state-of-the-art sophisticated methods for detecting Mycobacterial infection can be ascribed to insufficient financing, limited sensitivity and specificity, and inadequate availability in the peripheral healthcare system where patients seek treatment. This situation poses a risk to the eradication and control of the infection. Figure 5 presents a compilation of diagnostic techniques employed for the detection of active, latent, and multi-drug resistant cases.

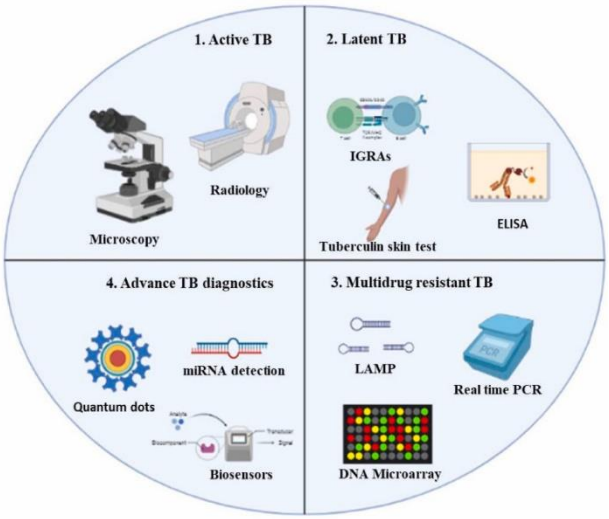

Figure: 5 illustrates many techniques used to diagnose tuberculosis infection.

The prompt identification of tuberculosis (TB) entails two primary techniques: microscopy, which enables the observation of live bacilli through a microscope, and radiography, which includes analysing chest X-rays to detect any irregularities (1). Latent tuberculosis (TB) infection is detected by the tuberculin skin test, enzyme-linked immunosorbent assay (ELISA), and interferon-gamma release assay (IGRA). The tests depend on the host's inflammatory reaction in the presence of the MTBC pathogen (2). To detect multi-drug resistant tuberculosis, it is important to do more precise and sensitive tests such as RT-PCR, DNA microarray, and LAMP. These methods definitively identify the changes in the genes, allowing for the detection of drug resistance (3). The application of nanoparticles, miRNA, and CRISPR-Cas in diagnostics has resulted in notable progress in tuberculosis (TB) diagnosis, leading to a groundbreaking impact.

V. CONCLUSION

Based on the preceding debate, it is clear that we have made significant progress in our battle against this lethal illness. However, in the words of renowned English poet Robert Frost, "we still have a considerable distance to cover before we can declare this planet free of tuberculosis." The World Health Organization (WHO), under its "STOP TB" plan, has set a goal to eradicate tuberculosis as a public health issue worldwide by the year 2050. To enhance our efforts in combating

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this lethal illness, it is imperative that we enhance our surveillance programmes to precisely assess the prevalence of various forms of tuberculosis, including children TB, HIV/TB, and MDR-TB. It is crucial to establish regulations for the appropriate and logical use of first- and second-line anti-TB medications. They should unequivocally not be marketed as non-prescription medications. In India and other developing nations, it is imperative for local governments to actively promote and invest in the domestic production of anti-TB medications. This will lead to improved oversight and adherence to manufacturing and quality control standards. Monitoring product quality in the marketplace should include recognising defective products resulting from substandard manufacturing techniques, products that have deteriorated due to insufficient distribution and storage, and products that have been adulterated, tampered with, or counterfeited due to vested interests. Numerous studies have extensively recorded the prevalence of counterfeit and inferior medications, particularly antimalarials, in poor nations. If counterfeit pharmaceuticals of this kind are present in the markets, it is reasonable to conclude that counterfeit anti-TB drugs are also available in same markets.

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