

CAN WE ERADICATE TUBERCULOSIS?

A Review of Obstacles to Eliminate the Disease

Incidence per 100,000 population



Rafael Laniado-Laborín

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Can We Eradicate Tuberculosis? A Review of Obstacles to Eliminate the Disease

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FOREWORD

Integrity. It is a word that is used for specific purposes in medical and public health research. The term defines a set of guiding values, including rigor, transparency, open communication, respect, and accountability [1]. At its core is the practice of honesty in how we think about health conditions. Integrity forms the foundation of the work undertaken by Dr. Rafael Laniado-Laborin in this book, *Can We Eradicate Tuberculosis? A Review of Obstacles to Eliminate the Disease*.

Dr. Laniado-Laborin explores an invisible killer that has devastated humanity for thousands of years. *Mycobacterium tuberculosis*—the bacterium that causes the disease known as “TB”—has been found in prehistoric mummies [2], leaving an ancient archeological record of suffering. And while the world we live in has radically changed in those same centuries, TB continues to persist as one of the deadliest and most challenging diseases known to humankind. The latest data from the World Health Organization, published in 2024, quantifies some of the global misery caused by TB [3]. It estimates that more than 10 million people became sick with TB in 2023, a number that has failed to decline despite numerous promises to end the disease within the next decade. While emphasizing these commitments to eradicating TB, the WHO document reports that we still have a long way to go. TB has once again become the leading infectious killer of adults worldwide. Yet, on page 6, the report optimistically notes that: “there are several positive trends following strong post-COVID recovery efforts that continued in 2023. These include: the global rise in the number of people falling ill with TB each year has slowed and started to stabilize; the global number of people dying from TB each year continues to fall; the WHO African and European regions have made good progress towards the 2025 milestones for reductions in the TB incidence rate and the number of deaths caused by TB; the globally reported number of people newly diagnosed with TB reached a new high in 2023; the treatment success rate for people with drug-susceptible TB has been sustained at a high level and continues to improve for people with drug-resistant TB; the coverage of TB preventive treatment has been sustained for people living with HIV and continues to improve for household contacts of people diagnosed with TB.”

There has indeed been some remarkable progress in the fight against this deadly disease. But we have come up far short when it comes to stopping this formidable foe. The focus on these achievements glosses over the immeasurable human suffering that continues to be caused by TB each year. Dissecting these statistics reveals that of the 10 million people who became sick with TB in 2023, almost 2.7 million were not diagnosed or started on treatment. More than a million people died in one year from a condition that has been treatable and preventable for decades. There seems to be little to celebrate in these grim numbers. Yet victory narratives continue to guide much of the discourse on global approaches to TB. Continuing to focus on how far we have come often distracts us from what else we need to do. It is a disconnect that has been paid for with people’s lives.

Integrity. When used colloquially, the term refers to having strong moral principles. Such ethical principles are at the heart of Dr. Laniado-Laborin’s new book. They guide him to be brave enough to ask a critical question: why has TB continued to plague people around the world? His powerful truth-telling springs from years of dedicated service to people living with the disease. He is an international expert with deep roots in the Tijuana community. His years working as a physician alongside and listening to people impacted by TB bring to this book a rich and exceptional perspective, allowing him to sensitively explore the corners of humanity where TB has a stranglehold. With a keen eye for connection, he links the dots

between the current TB pandemic and other human misfortunes, revealing that the causes of TB's persistence are as much social as they are biological [4]. *Mycobacterium tuberculosis* is spread through the air and can theoretically make any person who breathes sick, a common trait for all humanity. Yet the burden of suffering caused by TB is not commonly shared. More so than many other diseases, TB exposes the fault lines in how humans relate to one another. Dr. Laniado-Laborin thoughtfully exposes how TB capitalizes on these created inequalities, turning them to its advantage.

Can We Eradicate Tuberculosis? analyzes how TB impacts the most vulnerable in society. It shines a light on TB in vulnerable populations, bringing to the forefront people who have substance use disorder, people who are incarcerated, and people on the move. These are populations that most societies would rather forget about. Dr. Laniado-Laborin has made them the central players in both his service work and in his book. His scholarly endeavor, however, goes beyond merely exposing these social woes. The book also brings a lens of compassionate determination to address the myriad problems facing these populations. The essence of *Can We Eradicate Tuberculosis?* is a deep compassion grounded in the foundations of human rights. It exemplifies another meaning of integrity—the state of being whole—in situating TB within the larger context in which the disease continues to occur.

This book is timely, badly needed in an era when the very foundations of medical care and public health are under attack by powerful nations. The United States government has significantly reduced investment in TB services [5]—in an approach to global health that appears to lack integrity. The possibility that millions more lives will be unnecessarily lost or compromised by this age-old disease—and human indifference to it—has never been so great. However, these current threats to TB also offer an opportunity to reset how we, as a community of concern, approach the disease. Dr. Laniado-Laborin's insightful solutions, eloquently shared in this book, offer an ideal place to recenter and reinvigorate the global fight against TB.

The noted author John Green—whose recent book “Everything is Tuberculosis” also aims to change the paradigm by which we address humanity's most notable infectious killer—emphasizes that the integrity contained in a humanistic response to TB can spark “virtuous cycles.” In a chapter of this same name, he states, “Vicious cycles are common. Injustice and unfairness permeate every aspect of human life. But virtuous cycles are also possible” [6]. This book by Dr. Laniado-Laborin is poised to set in motion a more ethical, moral, and sustainable approach to TB. The noted physician, anthropologist, and TB advocate, Dr. Paul Farmer, would often refer to the lasting positive effects that can result from these virtuous cycles as “collateral benefits” [7]. That is, by choosing to tackle a disease like TB with integrity and in a dignified way that prioritizes the humanity of each person, society gains in unanticipated positive ways. In our divided world, such virtuous acts are badly needed. *Can We Eradicate Tuberculosis?* offers a roadmap not just for halting the onslaught of TB but also for restoring the integrity required to collectively heal the injustices that seem to define our current world.

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PREFACE

Tuberculosis remains a leading cause of death worldwide, especially in developing countries. Understanding the reasons behind its persistence can help prevent its spread across national borders, which is crucial for global health security. The lack of tuberculosis control increases the risk of further international transmission.

The failure to globally eradicate tuberculosis can be explained by the almost exclusively biological approach to this disease instead of a holistic approach that takes into consideration multiple sociocultural factors.

It is essential to identify gaps in health systems and understand why national tuberculosis control programs have struggled to identify weaknesses in these areas, including diagnosis, treatment adherence, financing, and infrastructure. This information is crucial for developing more effective strategies to combat the disease. Efforts to control tuberculosis require significant funds and resources. By analyzing why previous strategies have not been as successful, it will be possible to allocate resources where they are needed most, whether in diagnosis, treatment, or public health education. Discussing the failure to control tuberculosis raises awareness about the disease, its challenges, and the urgency of taking adequate measures. Public awareness can help garner support for policy changes, funding, and community-level interventions.

Social determinants have been relegated to the background, allocating the vast majority of funding to the biological approach to the disease. Tuberculosis thrives almost exclusively in areas with poverty, overcrowding, malnutrition, and inadequate health care. Discussing the failure of global efforts highlights the social and economic factors that exacerbate the spread of the disease, and these must be addressed to prevent future outbreaks.

One of the consequences of the failure to control tuberculosis has been the increase in drug-resistant strains of tuberculosis. A deeper understanding of the factors that contribute to drug resistance (such as community transmission dynamics, inadequate treatment, incomplete courses, or lack of access to second-line medications) can guide the development of better policies to combat resistant strains.

Governments and international organizations can use analysis of past failures to make more informed decisions and develop more targeted, sustainable tuberculosis control programs. These decisions may involve international collaborations, improvements in diagnostic methods, the development of vaccines or new medications for more effective and less toxic treatments that can be administered for increasingly shorter periods. Discussing the failure to control tuberculosis will raise awareness about the disease, its associated challenges, and the enormous urgency to take action. Public awareness can help garner support for policy changes, funding, and community-level interventions.

The primary objective of this book is to examine the reasons behind the failure of global tuberculosis control, which is crucial for enhancing healthcare strategies, combating drug resistance, and ultimately reducing the burden of this deadly disease.

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CHAPTER 1

Introduction

If you do what you've always done, you'll get what you've always gotten.

Albert Einstein (1879-1955)

Abstract: *Mycobacterium tuberculosis* may have killed more people than any other microbial pathogen. All modern members of the *M. tuberculosis* complex likely share a common African ancestor, dating back approximately 35,000 to 15,000 years ago. The history of tuberculosis underwent a radical shift when Robert Koch delivered his famous presentation, “*Die Aetiologie der Tuberculose*,” to the Berlin Physiological Society. In the 19th century, tuberculosis was treated by prolonged interment in tuberculosis sanatoriums, where patients were hospitalized for long periods; unfortunately, the cure rates did not differ significantly from the spontaneous cure of the disease. The prognosis of tuberculosis patients changed dramatically with the introduction of effective chemotherapy in the 1940s. However, the purely biomedical approach to the disease has only managed to turn tuberculosis into a curable disease, but one that frequently leaves extensive after-effects affecting the quality of life of survivors. There are multiple factors that, unfortunately, will prevent us from reaching the goals proposed by the World Health Organization, since this would require reducing the current rate by 1,000 times in less than 25 years.

Keywords: Elimination, Koch, *Mycobacterium tuberculosis*, Tuberculosis, WHO.

INTRODUCTION

Tuberculosis is a scourge that has devastated humanity since prehistoric times. *Mycobacterium tuberculosis* may have killed more people than any other microbial pathogen [1].

Modern molecular genetic techniques and the genome sequencing of several *M. tuberculosis* strains enable a more rigorous estimate of the origin of mycobacteria, facilitated by the low mutation rate of *M. tuberculosis*. It has been concluded that an early progenitor of *M. tuberculosis* was present in East Africa 3 million years ago and may have infected early hominins at that time. However, it is likely that all modern members of the *M. tuberculosis* complex, including its African variants — *Mycobacterium africanum* and *Mycobacterium canettii* — as well as

Mycobacterium bovis —shared a common African ancestor approximately 35,000 to 15,000 years ago [2, 3].

Tuberculosis was already well known in classical Greece, where it was referred to as consumption. The Greek physician Galen wrote about tuberculosis and recommended fresh air, milk, and sea travel as treatments for the condition. In the 19th century, René Théophile Hyacinthe Laennec elucidated the pathogenesis of tuberculosis, which had emerged throughout Europe with mortality rates in London, Stockholm, and Hamburg of 800–1,000/100,000 per year. The history of tuberculosis underwent a radical shift on March 24, 1882, when Robert Koch delivered his famous presentation, “Die Aetiologie der Tuberculose,” to the Berlin Physiological Society [1].

This was followed by treatment in tuberculosis sanatoriums, where patients were hospitalized for long periods, and the cure rates did not differ significantly from the spontaneous cure of the disease [4]. However, this strategy was the first to impact public health by reducing disease transmission to the community.

The history and prognosis of tuberculosis patients changed dramatically with the introduction of effective chemotherapy in the 1940s [5]. They raised the hope that, coupled with advances in diagnostic methods, it would finally be possible to eliminate this disease. However, the purely biomedical approach to the disease during the second half of the last century and part of this one has only managed to turn tuberculosis into a curable disease (although it continues to kill 10-15% of cases), but one that frequently leaves extensive after-effects affecting the quality of life of survivors. Worse still, after a significant drop in disease rates attributable to public health measures before the era of effective chemotherapy, in the present century, the global incidence of tuberculosis remains greater than 100 cases per 10⁵ population (134 cases per 10⁵ population in 2023) [6].

There are multiple factors that, unfortunately, will prevent us from reaching the goals proposed by the World Health Organization (WHO), including the elimination of tuberculosis by 2050 (by reaching the figure of less than one case per million), since this would require reducing the current rate 1,000 times in less than 25 years [7].

CONCLUSION

Tuberculosis has once again become the leading cause of death from a single infectious agent. Despite the availability of excellent diagnostic methods and effective treatment regimens, the global incidence of this disease remains unaddressed, currently exceeding 100 cases per 100,000 people. In the following

chapters, the various obstacles that continue to impede the eradication of this disease will be examined.

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CHAPTER 2

Epidemiology of Tuberculosis

Epidemiology is like a bikini: what is revealed is interesting; what is concealed is crucial.

Albert Einstein (1879-1955)

Abstract: Tuberculosis claims the highest death toll in history, with an estimated 1 billion lives lost, and still now causes 10 million cases and one and a half million deaths annually. While TB occurs worldwide, its incidence varies significantly between regions and countries. Low- and middle-income countries bear a disproportionate burden, with a high percentage of cases and deaths concentrated in these areas. The World Health Organization's Southeast Asia and African regions account for the largest proportion of global TB cases. The global TB incidence rate was 134 per 100,000 population in 2023. The goal for TB elimination is to reduce the annual incidence to less than one case per million inhabitants by 2050. A reduction of 1,000 times the current incidence is required in just 25 years to achieve this goal.

Keywords: Epidemiology, Incidence, Mortality, Prevalence, Tuberculosis, WHO global report.

INTRODUCTION

Global Epidemiology

The World Health Organization (WHO) publishes an annual global report on tuberculosis, based on information requested from 215 countries and geographic areas. In 2024, only 178 of the organization's 194 member countries reported data.

The global number of tuberculosis cases was 10.8 million (95% uncertainty interval [UI]: 10.1–11.7 million) in 2023, representing a slight increase from 10.7 million in 2022. However, this was still almost half a million more cases than in 2021 and 700,000 more cases than in 2020.

The global TB incidence rate (new cases per 10⁵ population) in 2023 was 134 (95% UI: 125–145). While the global rate is worryingly high, 87% of cases in 2023 were reported by the 30 countries with the highest burden. More than half

(56%) of cases were reported by just five countries: India (26%), Indonesia (10%), China (6.8%), the Philippines (6.8%), and Pakistan (6.3%) [1].

In 2023, 55% of people who developed TB were men, 33% were women, and 12% were children and young adolescents.

TB caused an estimated 1.25 million deaths (95% UI: 1.13–1.37 million) in 2023, including 1.09 million among HIV-negative people and 161,000 among people with HIV. The total was down from the best estimates of 1.32 million in 2022, 1.42 million in 2021, and 1.40 million in 2020 [1].

The WHO estimates that in 2023, there were 400,000 cases (95% CI: 360,000–440,000 cases) of rifampicin-resistant or multidrug-resistant tuberculosis (including isoniazid- and rifampicin-resistant cases); however, only 175,923 cases were reported and treated during that year, which represents less than half of the estimated cases [1].

The global treatment success rate for susceptible tuberculosis in 2023 was 88% (the goal is to achieve a cure rate of greater than 90%); in contrast, only two out of three patients (68%) with RR/MDR tuberculosis achieved a cure or completed treatment.

Financial costs are one of the main obstacles to closing the gaps in tuberculosis diagnosis and treatment. It is estimated that more than half of TB patients incur catastrophic costs (including direct medical costs, non-medical costs, and indirect costs such as lost income due to inability to work) [2]. Catastrophic costs are those that equal or exceed 20% of annual household income. The WHO set a target of 0% catastrophic costs by 2020 as one of its three main objectives for the End TB Strategy. By 2023, it was estimated that 49% of TB cases would still incur catastrophic costs [1] (Fig. 1).

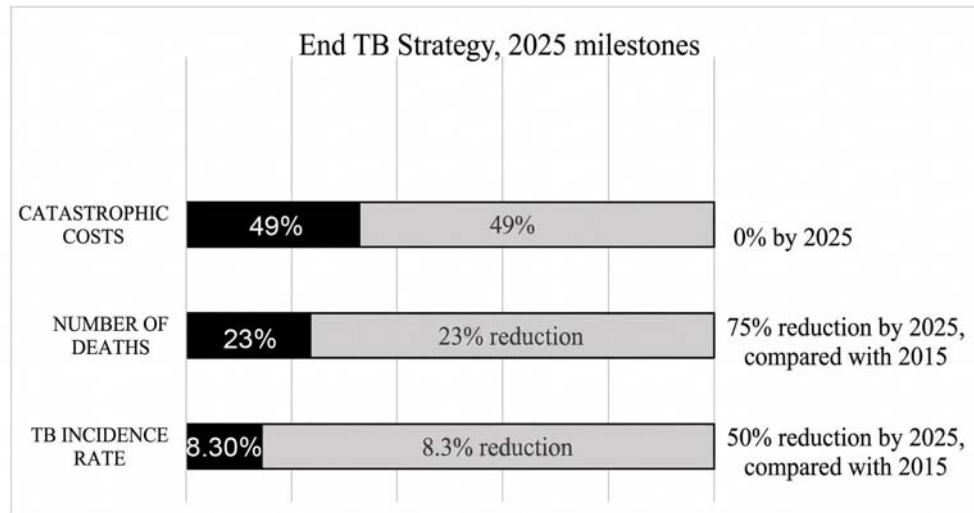


Fig. (1). World Health Organization End TB strategy 2025 milestones [1].

During the United Nations High-Level Meeting in 2023, new goals were established, which can be summarized as follows:

1. Diagnostic coverage with rapid molecular tests in 100% of newly diagnosed cases; in 2023, only 48% of cases globally received a rapid molecular test.
2. Treatment coverage of 90%; in 2023, only 3 out of 4 diagnosed patients received treatment.
3. Preventive treatment coverage of 90% in high-risk populations. In 2023, only one in five household contacts received preventive treatment, and only just over half (56%) of people living with HIV received preventive treatment.
4. A funding target of US\$22 billion was set for prevention, diagnosis, and treatment services. In 2023, only US\$5.7 billion (26%) was invested in these areas.
5. A funding target of US\$5 billion was set for TB research; in 2022, only US\$1 billion was used to fund research projects.

The goal for TB elimination is to reduce the annual incidence to less than one case per million inhabitants by 2050 [1]. A reduction of 1,000 times the current incidence is required in just 25 years to achieve this goal.

CONCLUSION

The global number of people falling ill with tuberculosis in 2023 was 10.8 million, a figure much higher than the 10.1 million in 2020. The global TB

CHAPTER 3

The Evolution of Tuberculosis Elimination Paradigms: A History of Failed Strategies

We won't Get Fooled Again.

The Who. British rock band, 1971.

Abstract: Tuberculosis is a millennial disease against which humans have implemented various control strategies that, unfortunately, have failed to achieve the ultimate goal- the elimination of the disease. Tuberculosis continues to cause millions of cases globally and more than a million deaths annually. Throughout history, multiple paradigms have been established regarding its control, including tuberculosis sanatoriums, control through BCG vaccination, the achievement of cure through pharmacological treatment, and, more recently, the assignment of responsibility to health systems, culminating in the current paradigm of the strategy to end tuberculosis. While these efforts have saved millions of lives over recent decades, tuberculosis continues to wreak havoc in various regions, almost exclusively in those with socioeconomic underdevelopment.

Keywords: Control, Elimination, End TB, Paradigms, Tuberculosis.

INTRODUCTION

The genus *Mycobacterium* is considered to have originated more than 150 million years ago. Egyptian mummies dating back to 2,400 BC reveal skeletal deformities typical of vertebral tuberculosis, and these lesions were clearly illustrated in works of art from that period. However, there is no description of tuberculosis in Egyptian papyri [1]. The first written documents describing tuberculosis, from India, date back approximately 3,300 years. Regarding treatment, there was not much to offer; for example, during the Roman Empire, Galen, personal physician to Emperor Marcus Aurelius, recommended fresh air and milk as a successful treatment for tuberculosis [2]. There are no reports on the cure rate of this treatment, but we can reasonably assume it was not very high. In the Middle Ages, cervical lymph node tuberculosis, known as scrofula, was believed to be the

king's evil and was thought to be cured if the king touched the lesion [3]. There are no reports of the success rate of that treatment strategy either.

In Italy during the 18th century, mandatory notification and isolation of TB patients were implemented, prohibiting their entry into public hospitals and establishing designated areas for their treatment [4]. However, it was not until the 20th century that the first effective antituberculosis drug was discovered with the isolation of streptomycin in 1944 [5]. Since the 1940s, with the discovery of the first effective antituberculosis drug and the goal of eradicating the disease by 2050, we have pursued various supposedly valid paradigms that, unfortunately, have failed to eliminate the disease [6].

The Sanatoria Paradigm

The fact that Robert Koch established tuberculosis as an airborne disease in the late 1880s, along with the hypothesis that cities were breeding grounds for the disease, served as the basis for developing and justifying the tuberculosis sanatorium [7].

Sanatoria had to be situated in natural surroundings, ideally in the dry air of an unspoiled mountain region; this, combined with good nutrition and rest, would benefit the patients with the disease. The sanatoria movement proved to be a significant milestone in treating tuberculosis by isolating infectious patients and reducing community transmission [8].

The first sanatorium to treat tuberculosis was established in Silesia in central Europe. It prompted many successors, and by the end of the 19th century, a sanatorium movement had taken place in Europe. However, sanatorium treatment proved less successful than initially hoped, and by the late 1890s, a search for alternatives to treat the disease began. Sanatorium treatment was costly and unaffordable for poor patients, who constituted most cases. With the advent of effective chemotherapy in the 1950s, sanatorium treatment became unnecessary and gradually declined [9].

The Prevention Paradigm

Humans have been infected with *M. tuberculosis* for millennia, and after centuries of useless treatment regimens, tuberculosis suddenly became a potentially preventable disease with the introduction of a vaccine. To date, BCG has been given to more than 4 billion individuals. The French immunologists Albert Calmette and Camille Guérin, working at the Pasteur Institute in Lille from 1900 to 1921, finally developed a vaccine from a virulent *M. bovis* strain by attenuating it through cultivation in a bile-containing substrate and subculturing it 230 times.

This strain failed to produce progressive tuberculosis when injected into test animals. At Guérin's suggestion, the vaccine was named *Bacillus Calmette-Guérin*, now known as BCG [10].

In 1921, the first human trial of the BCG vaccine was conducted at the Charité Hospital in Berlin. BCG proved to be a safe vaccine, but the question of its effectiveness remained unanswered. In 1930, a tragic disaster shattered the confidence of BCG. In Lübeck, Germany, 250 infants were vaccinated with BCG provided by the Pasteur Institute. After a year, among 250 vaccinated infants, there were 73 tuberculosis-related deaths, and another 135 children were infected but recovered. After 20 months, an investigation report exonerated BCG as the cause of the disaster, attributing it to negligent vaccine contamination with virulent tubercle bacilli in the Lübeck laboratory [11].

BCG is currently the only clinically available TB vaccine. While BCG has demonstrated significant effectiveness in several populations, protection has not been consistent against all forms of TB and in all age groups. The BCG vaccine has a documented protective effect against meningitis and disseminated TB in children. Still, it does not prevent primary infection, and more importantly, it does not prevent the reactivation of latent pulmonary disease, the principal source of bacillary spread in the community. The impact of BCG vaccination on the transmission of *M. tuberculosis* is therefore limited [12].

The Chemotherapy Paradigm

The effective treatment of tuberculosis started in 1944 with the discovery of streptomycin by Schatz *et al.* [13], and it became a reality in 1952 with the discovery of isoniazid. However, it was quickly learned that monotherapy with any of the available drugs (streptomycin, isoniazid, or PAS) was associated with the rapid development of drug-resistant strains of *M. tuberculosis*. This led to an axiom of treatment that still stands: never treat active tuberculosis with a single drug. Effective medications for treatment have made it possible to eliminate the need for hospitalization, as studies have demonstrated the non-inferiority of outpatient treatment at a lower cost and with greater accessibility. The main problem with outpatient treatment was the lack of treatment supervision. A regimen with streptomycin, isoniazid, and PAS, administered for one year, was highly effective. Still, the loss-to-follow-up rate was high due to its long duration, and at that time, the high cost of the drugs limited its use to wealthier countries [14].

The discovery of rifampin, an antibiotic isolated from *Streptomyces mediterranei*, marked a significant milestone in tuberculosis treatment, as it enabled a reduction in treatment duration from 12 months to six months when combined with isoniazid and pyrazinamide, due to the bactericidal and sterilizing properties of

CHAPTER 4

Poverty and Tuberculosis: The Grim Reaper?

Tuberculosis is the perfect expression of an imperfect civilization.

The white death. Thomas Dormandy, 2000

The opposite of poverty is justice.

Bryan Stevenson, social justice activist (1959-)

Abstract: According to World Bank estimates for 2022, 45.5% of the world's population lived in poverty (living on ≤ 6.85 US dollars per day). Tuberculosis is not only a product of poverty, but it also creates poverty. It is a disease influenced by social determinants in direct relation to cycles of poverty and social exclusion. Therefore, effectively combating tuberculosis requires addressing the implications of existing health vulnerabilities, including social protection as an indispensable component of the human right to health. Social protection is a nationally defined set of basic social guarantees that secure protection to prevent or alleviate poverty, vulnerability, and social exclusion. It has been demonstrated that countries that allocate a substantial portion of their gross domestic product (GDP) to social protection programs exhibit lower rates of tuberculosis morbidity and mortality compared to countries that do not. Modeling studies report that if a country increases its investment in social protection from 0% to 1% of its GNP, investing just 1% of its GDP in social protection programs, this is associated with reductions of 18.3 prevalent cases per 10^5 , 8.16 incident cases per 10^5 , and 5.48 TB deaths per 10^5 population.

Keywords: Barriers, Health, Immunocompromise, Policies, Poverty, Social protection, Tuberculosis.

INTRODUCTION

According to World Bank estimates for 2022, 9% (712 million) of the world's population lived in extreme poverty (extreme poverty defined as living on less than \$2.15 US per day). Overall, 45.5% of the world's population (3.619 billion) lived in poverty (US\$6.85 per day) [1]. Despite scientific and socioeconomic advances, a high global burden and mortality from tuberculosis persists to this day, mainly affecting the poor and vulnerable populations [2].

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The transmission and development of active tuberculosis are driven primarily by socioeconomic factors such as poverty and malnutrition. In fact, in some regions, declines in disease burden were observed long before the introduction of effective chemotherapy, which is likely attributable, at least in part, to improvements in living standards and the implementation of public health measures. Since the discovery of the first anti-tuberculosis drugs in the 1940s, the primary approach to combating tuberculosis has been biomedical. The burden of the disease declined rapidly in the early 1950s, coinciding with the introduction of effective anti-tuberculosis drugs; however, the reduction in incidence since the 1960s has been slow and uneven [3]. Despite the importance of social determinants in the genesis of tuberculosis, efforts during the last decades have focused almost exclusively on biomedical solutions that emphasize the development and implementation of new diagnostic methods and treatment regimens, and not sufficient attention has been paid to the characteristics of patients, the nature of their demands, and the broader context in which tuberculosis programs are developed and implemented.

Tuberculosis is undoubtedly a disease of poverty. There is a close symbiotic relationship between tuberculosis and poverty. Tuberculosis is not only a product of poverty, but it also creates poverty. It is a disease influenced by social determinants in direct relation to cycles of poverty and social exclusion. Poverty increases the risk of tuberculosis among socially disadvantaged populations, which exacerbates social inequalities and disparities in health care [4, 5]. Understanding the relationship between tuberculosis and poverty is essential to breaking this cycle. The greater the poverty in a community, the greater the probability of being infected with *Mycobacterium tuberculosis* and the greater the risk of developing the disease. The lack of basic health services to diagnose or treat patients, a common finding in poor communities, the presence of malnutrition that weakens the immune system, increasing the chances of infection and active TB, and the inadequate living conditions in overcrowded environments make TB transmission more likely and amplify its impact on a community. The lack of good-quality services to diagnose or treat patients leads to greater delays in diagnosis and treatment, perpetuating the spread of the disease.

Most research aimed at understanding disparities in the TB burden has focused on individual-level risk factors, including low body mass, human immunodeficiency virus (HIV) infection, diabetes, tobacco use, alcohol use, and indoor air pollution; most of these risk factors are more prevalent among people experiencing poverty [6]. Poverty is associated with a longer duration of disease due to reduced healthcare access, with more prolonged community transmission, and people experiencing poverty have a higher effective contact rate due to crowding and poorly ventilated living conditions [7]. Tuberculosis will exacerbate existing

poverty by affecting income-earning capacity, especially if catastrophic costs are incurred [8].

Among the many fundamental human rights proposed by the UN (including access to adequate nutrition, decent housing, safe and reasonably paid work conditions, and free education) is the right to health, which encompasses the health sector's response to providing optimal care for those affected by tuberculosis. Therefore, effectively combating tuberculosis requires addressing the implications of existing health vulnerabilities, including social protection as an indispensable component of the human right to health [4]. Social protection is defined as the set of policies, programs, and measures designed to reduce poverty and the vulnerability of individuals by providing income security, access to essential services (such as health, education, or housing), and support in the face of social risks such as unemployment, illness, old age, disability, or maternity. It includes various components such as social security (pension system, health insurance, unemployment insurance), social assistance (support for people in poverty or vulnerability), and regulations that promote fair working conditions. Its main objectives are the reduction of poverty and inequality and the promotion of social inclusion. Therefore, it is urgent to implement policies that guarantee the right to health by strengthening health systems, particularly for socially vulnerable populations [4, 9]. As already mentioned, social protection is designed to protect people from poverty and social exclusion, including job security and a decent income, and thus food security [10, 11]. Therefore, it is vitally important that any strategy developed to eliminate tuberculosis goes beyond the biomedical approach and includes a comprehensive vision of the human risks encompassed within what is defined as social protection, to achieve a significant impact on the struggle against this disease [4].

Slow progress in the control of tuberculosis since the 1990s is due at least in part to programmatic gaps that include, among others, reliance on sputum microscopy for diagnosis and lack of implementation of drug-susceptibility testing in laboratory networks and unsupervised treatment, but more importantly because of the failure to address the social drivers of tuberculosis such as poverty, overcrowding among increasingly urbanized populations [12], malnutrition [13], diabetes mellitus [14], alcoholism, illicit drug addiction [15], and factors such as stigma and social isolation [16]. The recent WHO Stop TB Strategy emphasized the delivery of tuberculosis services, including new diagnostics and treatment regimens. It is an approach focused on testing and treating strategies that should have paid more attention to patient needs and demands.

CHAPTER 5

Uncontrolled Comorbidities and Tuberculosis: The Relationship among Tuberculosis, diabetes, and HIV

The biggest public health challenge is rebuilding the health systems.

Paul Farmer (1959-2022)

Abstract: Epidemiological studies estimate that by 2045, almost 800 million adults will be living with Type 2 Diabetes Mellitus (T2DM). Diabetes mellitus is an independent risk factor for tuberculosis by increasing susceptibility to the infection. Hyperglycemia and insulin resistance impair the function of the host's innate and adaptive immune cells, resulting in a decline in the immune system's ability to eliminate and kill *Mycobacterium tuberculosis*. The association between T2DM and active TB is well established. Data from multiple studies showed that patients with T2DM had a 2- to 4-fold increased risk of active tuberculosis. Furthermore, diabetes also increases the severity of TB infection, and it is associated with higher rates of drug-resistant tuberculosis. T2DM is associated with significantly more mutations conferring resistance to isoniazid and ethionamide (Rv1482c-*fabG1*) and fluoroquinolone (*gyrA*), as well as a trend towards more mutations for rifampicin (*rpoB*) resistance.

Globally, 39.9 million [36.1–44.6 million] people were living with HIV at the end of 2023, and 630,000 people died with HIV during 2023, which is equivalent to one death due to HIV/AIDS every minute. An estimated 1.3 million people acquired HIV during 2023 (range 1.0-1.7 million), including 1.2 million adults 15+ years, and 120,000 children under 15 years. In patients with HIV and tuberculosis (TB) coinfection, the interaction between HIV and TB accelerates the progression of both diseases since TB favors a rapid increase in HIV replication, worsening the progression of immunosuppression, and, simultaneously, HIV infection increases the risk of progression to active disease in people with TB infection. At the end of 2023, 23% of people living with HIV did not have access to antiretroviral therapy.

Keywords: Antiretrovirals, Coinfection, Diabetes, HIV, Insulin resistance, Tuberculosis.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is an endocrine and metabolic disorder characterized by elevated blood glucose levels resulting from insufficient insulin secretion or increased insulin resistance. Epidemiological studies have shown that over the past 30 years, the incidence of Type 2 Diabetes Mellitus (T2DM) has increased from 3.5% to 5.0% in women and from 3.9% to 6.0% in men. In 2021, 536 million adults were living with Type 2 Diabetes Mellitus (T2DM), a figure that is expected to increase to 783 million in 2045. Furthermore, it is estimated that in 2021, T2DM was responsible for 6.7 million deaths worldwide, that is, one death every 5 seconds [1]. In 2019, the number of people with diabetes in Latin America was estimated to be 31.6 million. By 2030, the number is expected to increase to 40.2 million and 49.1 million by 2045 [2].

Due to its multi-organ and multi-system impact, diabetes has been associated with both acute and long-term complications that affect healthcare needs, costs, well-being, and productivity [3]. As an independent risk factor for tuberculosis (TB), T2DM increases TB susceptibility, and patients with T2DM are more likely to develop TB than non-diabetic patients. Furthermore, T2DM also increases the severity of TB infection, and it is also associated with higher rates of specific anti-tuberculosis drug-related side effects. Of the ten countries with the highest number of T2DM patients worldwide, six are also classified as “high burden” for TB by the WHO, meaning they contribute to 80% of tuberculosis (TB) cases worldwide. Approximately 95% of TB and 75% of the T2DM cases live in low- and middle-income countries [4]. Hyperglycemia and insulin resistance impair the function of the host’s innate and adaptive immune cells, leading to a decline in the immune system’s ability to remove and kill *Mycobacterium tuberculosis* (*M. tuberculosis*) [5]. There is now ample evidence that T2DM predisposes individuals to develop active TB and that its contribution to global TB prevalence will increase further with the rise of T2DM prevalence. The association between T2DM and active TB is well established. Data from multiple studies showed that patients with T2DM had a 2- to 4-fold increased risk of active tuberculosis [6 - 11]. The WHO estimates approximately 350,000 TB cases were attributable to T2DM in 2019 [12].

Resistance to anti-tuberculosis drugs is a public health menace, with 410,000 reported cases of TB resistant to one of the most potent TB drugs, rifampicin. Of those, almost 80% also had resistance to isoniazid, known as multidrug-resistant TB (MDR-TB). Research evidence has linked T2DM with an increased risk of MDR-TB. Regarding TB-T2DM and drug-resistant TB, a meta-analysis that included 24 observational studies from 15 different countries revealed that T2DM has a significant positive association with MDR-TB (OR = 1.97, 95% CI.: 1.58-

2.45; $p: 0.031$) regardless of the level of income of the country, how tuberculosis was diagnosed, or the design of the primary studies [13].

IMPAIRMENT OF IMMUNITY IN TB-T2DM

Metabolic changes in T2DM cause neutrophils, macrophages, natural killer cells, and other cells related to innate immunity to function less effectively. Alveolar macrophages phagocytose mycobacteria in the lungs, inducing the activation of the body's innate immunity [14]. Neutrophils reach the site of infection first and cause the accumulation of other cells by secreting cell-signaling proteins, specifically cytokines and chemokines. Normally, interferon-gamma activates macrophages, but T2DM impairs the activation of alveolar macrophages with interferon-gamma by reducing the release of IL-1 β , IL-12, and IL-18 from antigen-presenting cells [15]. T helper 1 (Th1) cells play a crucial role in host-acquired immunity. Among its functions is the generation of gamma interferon. The growth and multiplication of Th1 require the presence of the cytokine IL-2. In individuals affected by T2DM, Th1 activity is diminished, which explains their increased susceptibility to MTB infection. The increased production of IL-4-secreting Th2 cells in patients with tuberculosis and diabetes has a detrimental effect on Th1 cell production [16].

Type 2 Diabetes Mellitus (T2DM) is characterized by insulin resistance and the progressive loss of beta cell mass and/or function, leading to chronic hyperglycemia [17]. Critchley *et al.* showed that T2DM patients with poor glycemic control (HbA1c >11%) had an elevated risk for hospitalization from TB. Optimal control of blood glucose (HbA1c $\leq 5.7\%$) reduces the risk of hospitalization. However, even well-controlled T2DM patients remain at a higher risk than matched controls without T2DM, suggesting that metabolic factors other than hyperglycemia contribute to the increased susceptibility to infections in T2DM [18]. T2DM patients who develop active TB frequently have more severe disease, longer delay in culture conversion, and higher bacterial load [19]. A higher mycobacterial load in patients with TB-T2DM suggests that TB patients with TB-T2DM are more infectious than TB patients without T2DM. Patients with dysglycemia are more likely to transmit MTB in a household contact setting [20].

TB-DM is associated with more symptoms, such as fever, cough, and hemoptysis, a higher frequency of positive smear microscopy at the time of diagnosis, and an increased incidence of lung cavitations and parenchymal lesions compared with patients with TB without DM [21]. Bilateral pulmonary involvement and extensive pulmonary disease can also be found on CT scans in TB-T2DM patients [22].

CHAPTER 6

Tuberculosis in Prisons: An Uncontrolled Source

Contracting TB in prison is most certainly not part of a prisoner's sentence.

World Health Organization.

Abstract: Tuberculosis represents a public health problem in prisons. Tuberculosis notifications in penitentiary institutions have increased by more than 250% since the year 2000. In developing countries, prison TB prevalence rates are 5 to 10 times the national average; TB outbreaks and an increase in both case rates and drug resistance rates are not uncommon; in some of those areas, approximately 50% of the inmates with TB have strains of *Mycobacterium tuberculosis* that are drug-resistant. The prevalence of tuberculosis was greater than 1,000 per 100,000 prisoners in all global regions except for North America and the Western Pacific.

Prisons are favorable environments for the transmission of *Mycobacterium tuberculosis*. During incarceration, prisoners face living conditions, such as overcrowding, absence or precariousness of basic services and housing infrastructure, malnutrition, poor ventilation, and difficulty accessing health services. The significant turnover of the prison population, combined with long periods of tuberculosis infection latency, results in a considerable proportion of people (in some reports, greater than 40%) contracting tuberculosis infection during their incarceration but developing the disease years after they are released.

Furthermore, it is essential to establish periodic evaluation mechanisms to identify areas for improvement and adapt control strategies to the changing needs of the prison population. Ongoing training for health personnel and custodians in outbreak management and the efficient use of available resources is also essential. Promoting intersectoral collaboration between health authorities, international organizations, and civil society can strengthen the comprehensive response and ensure that the human rights and dignity of persons deprived of liberty are always respected.

Keywords: Drug resistance, Incarceration, Overcrowding, Prisons, Screening, Tuberculosis.

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INTRODUCTION

According to the latest edition of the World Prison Population List (WPPL), published in May 2024 by the Institute for Crime & Justice Policy Research (ICPR) at Birkbeck, University of London, approximately 11.5 million people are held in penal institutions worldwide.

Tuberculosis represents a public health problem in prisons [1]. Tuberculosis notifications in penitentiary institutions have increased by more than 250% since the year 2000, an increase that is largely driven by increasing incarceration rates. Prisons have also been implicated in outbreaks of multidrug-resistant and extensively drug-resistant tuberculosis in multiple countries [2].

In developing countries, prison TB prevalence rates are 5 to 10 times the national average. TB outbreaks and an increase in both case rates and drug resistance rates are not uncommon; in some of those areas, approximately 50% of the inmates with TB have strains of *Mycobacterium tuberculosis* that are drug-resistant. Unfortunately, this is not a problem limited to some distant third-world countries; outbreaks of MDR-TB have already been reported in correctional facilities in developed countries [3, 4].

Tuberculosis incidence rates were consistently much higher in prisons than in the general population. The overall pooled incidence of *M. tuberculosis* infection among prisoners was 15.0 (95% credible interval [CrI] 3.8–41.6) per 100 person-years. The incidence of tuberculosis (per 100,000 person-years) among prisoners was highest in studies from the WHO African (2,190 [95% CrI 810–4840] cases) and South-East Asia (1,550 [240–5300] cases) regions and in South America (970 [460–1860] cases), and lowest in North America (30 [20–50] cases) and the WHO Eastern Mediterranean region (270 [50–880] cases). The prevalence of tuberculosis was greater than 1,000 per 100,000 prisoners in all global regions except North America and the Western Pacific, with the highest rates in the WHO South-East Asia region (1,810 [95% CrI 670–4000] cases per 100,000 prisoners). The incidence rate ratio between prisons and the general population was much higher in South America (26.9; 95% CrI 17.1–40.1) than in other regions but was nevertheless higher than 10 in the WHO African (12.6; 6.2–22.3), Eastern Mediterranean (15.6; 6.5–32.5), and South-East Asia (11.7; 4.1–27.1) regions [5]. Tuberculosis prevalence rates in prisons in some countries are very high. For example, the prevalence rates in Brazil, Thailand, the Russian Federation, and China are reported as 2,527 cases per 10⁵ prisoners, 2,096 per 10⁵, 1,259 per 10⁵, and 1,156 per 10⁵ respectively [6].

High rates of tuberculosis transmission in prisons hinder efforts to eliminate tuberculosis in the general population. Prison-acquired infections put inmates at

high risk for tuberculosis after release. Genomic epidemiological studies in several countries have documented that *Mycobacterium tuberculosis* strains circulating in prisons spread to surrounding communities (transmitted by released prisoners, prisoner visitors, or prison staff); therefore, in practice, prisons act as amplifiers of the disease through community transmission of tuberculosis [7].

Prisons are favorable habitats for the transmission of *Mycobacterium tuberculosis* [8]. During incarceration, prisoners face living conditions, such as overcrowding, absence or precariousness of basic services and housing infrastructure, malnutrition, poor ventilation, and difficulty accessing health services, which make the penitentiary system an environment with potential for transmission and development of tuberculosis [9]. The main reason for the high risk of *M. tuberculosis* infection and active tuberculosis in prisons is the disproportionate number of inmates with factors that expose them to the microorganism or, if infected, that favor the development of active disease. These risk factors include malnutrition, HIV infection, hepatitis B and C virus infection, ongoing substance abuse, a high proportion of inmates belonging to racial and ethnic minorities (often recent immigrants from countries with a high incidence of tuberculosis), and belonging to a population with low socioeconomic status and inadequate access to medical care [3, 10]. In addition to these individual and demographic risk factors, the physical and social environment of prisons plays a critical role in facilitating the spread of tuberculosis. Overcrowded living conditions, poor ventilation, limited access to sunlight, and the frequent movement and turnover of inmates further compound the problem. Delays in diagnosing active tuberculosis, combined with inadequate infection control measures, can lead to the rapid transmission of the disease within confined settings. These challenges make prisons particularly vulnerable to tuberculosis outbreaks, underscoring the need for targeted public health interventions and improved healthcare infrastructure within correctional facilities.

Frequent contact between the prison population and the community through guards and family visits facilitates the spread of *M. tuberculosis* to the general population [7, 10]. When prisoners are released and return to the community, they present a 5.5 times greater risk of active TB than the general population [9].

The significant turnover of the prison population, combined with long periods of tuberculosis infection latency, results in a considerable proportion of people (in some reports greater than 40%) contracting tuberculosis infection during their incarceration but developing the disease years after they are released [11]. However, even those who develop active tuberculosis in prison may not be diagnosed until after leaving prison due to underdetection in prisons. A study from Thailand found that formerly incarcerated TB patients were 4.7 times more

CHAPTER 7

Tuberculosis in Vulnerable Populations: A Problem that no one Genuinely Wants to Acknowledge

The true measure of any society can be found in how it treats its most vulnerable members.

Mahatma Gandhi (1869-1948)

Abstract: Vulnerable populations refer to individuals who have limited access to healthcare, receive substandard care, and experience poor health outcomes. Vulnerable populations include patients who are racial or ethnic minorities, children, the elderly, socioeconomically disadvantaged, underinsured, or those with certain medical conditions. Vulnerable populations are at risk for unequal healthcare access and outcomes because of economic, cultural, ethnic, or health characteristics. Tuberculosis primarily affects people of low socioeconomic status and vulnerable groups who face social exclusion, increased risk of exposure, and difficulties accessing quality health services. Recent studies from South America identified the following factors as associated with unsuccessful treatment for tuberculosis: homelessness, substance abuse, and HIV coinfection. Substance use disorders, including alcohol consumption, are prevalent in patients with tuberculosis and are believed to increase the incidence and mortality of tuberculosis and promote delay in seeking health care and poor adherence to tuberculosis treatment.

Keywords: Alcoholism, Homelessness, Migrants, Substance abuse, Tuberculosis, Vulnerable populations.

INTRODUCTION

Vulnerable populations refer to individuals who have limited access to healthcare, receive substandard care, and experience poor health outcomes. The term vulnerable is often used interchangeably with other terms, including marginalized, disadvantaged, disenfranchised, underprivileged, at-risk, underserved, and hard-to-reach. Vulnerable populations are at risk for unequal healthcare access and outcomes because of economic, cultural, ethnic, or health characteristics. Vulnerable populations include patients who are racial or ethnic minorities,

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children, the elderly, socioeconomically disadvantaged, underinsured, or those with certain medical conditions. Members of vulnerable populations often have health conditions that are exacerbated by unnecessarily inadequate healthcare [1].

Three dimensions can be utilized as criteria for identifying vulnerable populations: a) the socioeconomic positions of individuals (assessed by income, occupation, ethnicity, gender, sexual orientation, and migration status), b) the risk of tuberculosis infection and disease (assessed by tuberculosis risk factors identified in epidemiological studies), and c) the access to health systems (assessed by the ability to perceive, seek, reach and pay for health services) [2].

Although the global rate of tuberculosis is declining by 2% annually, the disease's distribution is heterogeneous, primarily affecting people of low socioeconomic status and those in situations of social exclusion. The epidemiology of tuberculosis depends on socioeconomic factors and health risks that make certain groups more vulnerable.

Tuberculosis has been defined as a disease of poverty, and few diseases better reflect and express the magnitude of social inequalities that influence its distribution and outcomes. Vulnerable groups such as immigrants, refugees, homeless people, and people with low social status remain the most affected, with a higher risk of loss to follow-up and worse treatment outcomes. Furthermore, poverty creates an ecosystem in which tuberculosis becomes more prevalent, more deadly, and difficult to treat. Poverty and its related factors increase the risk of *M. tuberculosis* infection, as well as the probability of progression to active disease and greater severity of disease, also hindering access to quality medical care.

Vulnerable groups, such as immigrants, refugees, homeless people, and those with low social status, are the most affected by tuberculosis due to longer delays in accessing health care and diagnosis, a higher risk of being lost to follow-up care, and consequently worse treatment outcomes. Poverty favors the spread of the disease and hinders both access to medical care and effective treatment. These vulnerable groups face social barriers that limit their access to adequate health services. A recent review confirms that tuberculosis is highly prevalent among these populations due to social factors, including incarcerated people, Indigenous peoples, and those with substance use disorders, unlike other groups with biomedical or epidemiological risks [3, 4].

Improved integration of these groups is needed, including targeted efforts to identify them, specific screening and prevention measures, and treatment support. Prevalence rates were often more than 25 times higher among homeless people,

incarcerated people, refugees, asylum seekers, and people with HIV, compared to the general population [3, 4].

In addition to other interventions aimed at tuberculosis control, it is necessary to achieve treatment success since patients with a history of noncompliance with treatment or relapse of infection have a higher risk of developing resistant and multidrug-resistant tuberculosis. However, therapeutic success may be hindered by the sociodemographic characteristics of the population, such as sex, age, economic condition, vulnerability, and ethnicity, leading to a loss of follow-up due to difficulties in patient care and their work schedules, adverse events from medications, fragile support systems, problems in the doctor-patient relationship, poor education, and lack of use of culturally adapted technologies.

A recent study from Colombia sought to identify clinical, sociodemographic, and programmatic differences in patients previously treated for tuberculosis. The following independent variables were identified as associated with unsuccessful treatment for tuberculosis: homelessness (aOR = 2.45; CI_{95%}=1.54-3.89), substance abuse (aOR=1.95; CI_{95%}=1.24-3.05), having tuberculosis/HIV coinfection (aOR = 1.69; CI_{95%}=1.00- 2.86) or diabetes (aOR =1.89; CI_{95%} =1.29-2.77) [5].

A large retrospective study from Brazil, which included more than 40,000 TB patients, reported an unfavorable treatment outcome in 17% of the cases. Homelessness (aOR 3.03, CI_{95%} = 2.07-4.42), HIV (aOR 2.89, CI_{95%} = 2.45-3.40), and illicit drug use (aOR 2.22, CI_{95%} = 1.93-2.55) were the primary factors associated with unfavorable treatment outcomes [6].

SUBSTANCE USE DISORDERS

Substance Use Disorders (SUD), including alcohol consumption, are prevalent in patients with tuberculosis and are believed to increase the incidence and mortality of tuberculosis and promote delay in seeking health care and poor adherence to tuberculosis treatment [7].

Several factors contribute to the increased TB risk among persons with SUD; a common comorbidity associated with SUD is the Human Immunodeficiency Virus (HIV) infection, which carries its own increased susceptibility to TB. In addition to HIV-associated immunosuppression, direct impairment of the cell-mediated immune response due to exposure to alcohol and drugs such as cannabis and opiates facilitates the acquisition of tuberculosis infection and the development of the disease. On the other hand, frequent incarceration, social deprivation, and inadequate housing conditions, all common characteristics of drug users, contribute as risk factors for tuberculosis [8].

CHAPTER 8

Tuberculosis Infection: When will we Pay Attention to it?

An ounce of prevention is worth a pound of cure.

Benjamin Franklin (1706-1790).

Abstract: Inequalities in tuberculosis (TB) preventive treatment (TPT) are due to many factors, including poverty, lack of resources, and poor access to care, especially in countries with a high TB burden, where the vast majority of resources are allocated to the diagnosis and treatment of active disease. Recent estimates of the global burden of latently infected persons with *Mycobacterium tuberculosis* suggest that a third of the worldwide population, or about 1.7 billion people, harbor this infection. The current strategy recommended by the World Health Organization (WHO) to end TB includes detecting and treating Tuberculosis Infection (TBI) in subjects who are contacts of an infectious pulmonary TB case as a priority to eliminate tuberculosis by 2035. However, according to the WHO 2024 World Report, the global TB preventive treatment coverage target for 2027 is 90% among household contacts, whereas the current global coverage stands at only 21%. The relatively high costs of TBI diagnosis and preventive therapy, and the need to prioritize curing active cases, explain why preventive therapy is not a priority in tuberculosis control strategies in developing countries.

Keywords: Chest x-rays, Contact tracing, IGRA, Infection, Treatment, Tuberculin, Tuberculosis.

INTRODUCTION

Inequalities in Tuberculosis (TB) Preventive Treatment (TPT) are due to many factors, including poverty, lack of resources, and poor access to care [1]. TPT remains a secondary objective in most countries with a high tuberculosis burden, where the vast majority of resources are allocated to the diagnosis and treatment of active disease. The average provision of TPT for household contacts in the 30 countries with the highest tuberculosis burden is only 22% [2].

Despite notable variations in the risk of progressing to active TB, Tuberculosis Infection (TBI) represents the breeding ground for future TB cases [3]. Therefore,

eliminating TB is theoretically unattainable unless the burden of TBI is addressed through TPT [4]. Recent estimates of the global burden of latently infected persons with *Mycobacterium tuberculosis* suggest that 23% (95% uncertainty interval 20.4%-26.4%) of the worldwide population, or about 1.7 billion people, harbor this infection, with about 1% of the global population estimated to have been infected in the previous two years [5]. By 2030, this large pool of latently infected persons will generate 16.3 cases of active TB per 100,000 population [6].

The current strategy recommended by the World Health Organization (WHO) to end TB includes detecting and treating TBI in subjects who have been in contact with an infectious pulmonary TB case as a priority to eliminate tuberculosis by 2035. Systematic detection and treatment of TBI are essential elements of the WHO End Tuberculosis strategy [7]. Several theoretical modeling studies suggest that combining screening and treatment for tuberculosis infection with the current strategy for treating active disease could achieve a reduction in tuberculosis incidence that is close to the WHO's End TB by 2035 target [8 - 10]

However, according to the WHO 2024 World Report, the global TB preventive treatment coverage target for 2027 is 90% among household contacts, whereas the current global coverage stands at only 21%. The relatively high costs of TBI diagnosis and preventive therapy, and the need to prioritize curing active cases, explain why preventive therapy is not a priority in tuberculosis control strategies in developing countries, or is half-hearted at best [1, 10]. However, failing to implement tuberculosis contact investigation and TPT will incur a significant burden of avertable illness and mortality in the coming decades [11] (Fig. 1).

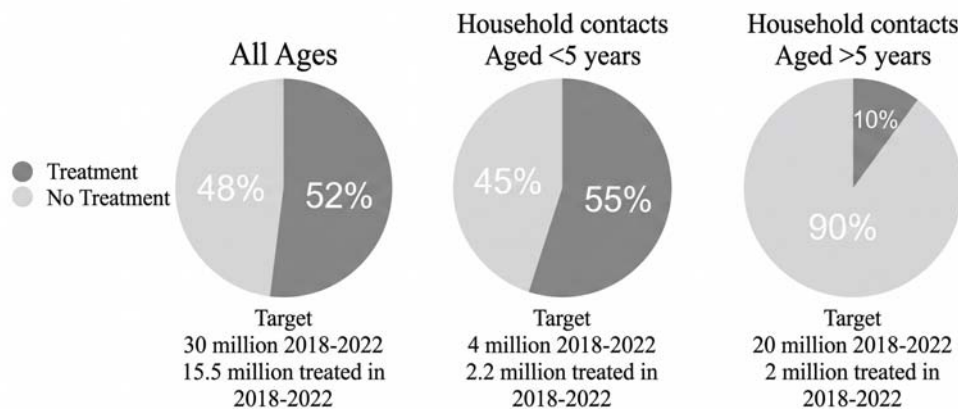


Fig. (1). Global numbers of people provided with TB preventive treatment (TPT) between 2018-2022 compared with targets set at the 2018 UN high-level-meeting.

During the First United Nations High-Level Meeting (UNHLM) on TB in 2018, the assembly set TBI targets for 2018-2022. The first target was to treat tuberculosis infection in 30 million people, of which only 15.5 million received treatment during that period (52%). For people living with HIV, the target was to treat 6 million, and 11.3 million received treatment (188%); for household contacts aged under 5 years, the target was 4 million, and only 2.2 million (55%) were treated. Finally, the target for household contacts 5 years and older was to treat 20 million subjects; only 2 million in this group received treatment (10%). During the 2023 United Nations General Assembly's second high-level meeting, the targets were even more ambitious, set at 45 million people to be treated for TB infection, including 30 million household contacts of people with tuberculosis, including children and 15 million people living with HIV for the period between 2023 and 2027 [1].

Although there has been progress in preventive therapy for people living with HIV, only 17 million of the estimated 39 million in 2022 initiated PTT between 2005 and 2022. Household contact coverage is even lower, with only 17.5% of the 2022 UN target met, at 4.2 million. Reaching the new target of 45 million by 2027 is unlikely [8 - 12].

Other groups at risk of progressing from TBI to active disease include people who require treatment with biological agents for autoimmune diseases, people receiving dialysis, those preparing for an organ or hematological transplant, or those who have silicosis. For these groups, systematic testing and provision of TPT for those who test positive are also strongly recommended. Additionally, systematic TB infection testing and treatment are conditionally recommended for prisoners, health workers, immigrants from countries with a higher TB burden than the host country, homeless people, and people who use drugs [13].

Populations that are also at higher risk of TB but for whom systematic testing for TB infection and TPT is currently not recommended by the WHO [14] include undernourished people, alcoholics, cigarette smokers, and people with diabetes mellitus.

There is empirical evidence that systematic detection and treatment of tuberculosis infection can positively impact the burden of active tuberculosis cases. A multicenter cohort study in Spain demonstrated a significant decline in TB incidence over two decades following the implementation of a TPT program. In 2002, the Basque Country's Department of Health reported 26.2 tuberculosis cases per 100,000 people. After implementing a TB control program in 2003, which included nurse case managers and a unified electronic records system, the rate fell to 8.6 per 100,000 by 2023 [15]. Treating TBI on a large scale has

CHAPTER 9

BCG: Is it the Best we can Offer for Prevention?

There is no vaccine against stupidity.

Albert Einstein (1879-1995).

Abstract: The only vaccine available for over a century against tuberculosis (TB) is the BCG vaccine, which has been administered to over four billion people, making it the most widely used vaccine. Controlled trials in different parts of the world have shown that its effectiveness in preventing pulmonary tuberculosis (PTB) varies between 0% and 80%. However, trials worldwide have shown that BCG effectiveness is 60 to 80 percent against childhood tuberculous meningitis and disseminated tuberculosis, and protection lasts for up to 10 years, partly justifying its use. A more consistently effective vaccine than BCG is urgently needed for adolescents and adults to achieve the World Health Organization's 'End TB strategy'. Currently, 19 vaccine candidates are in clinical development, with many others in preclinical stages. Numerous variants of new recombinant vaccine strains and subunit vaccines are currently being actively developed. International funding for TB research and development was US\$1.2 billion in 2023, up from US\$1.03 billion in 2022, but less than one-quarter of the \$5 billion annual target agreed upon by countries at the UN High-Level Meeting (HLM) on TB in 2023.

Keywords: Attenuated, BCG, Live, Masking, *M. bovis*, *M. vaccae*, Vaccination.

INTRODUCTION

Vaccination would be the most economically efficient method for preventing and managing TB, serving as a crucial approach toward realizing the WHO's Global End TB Strategy by 2035 [1]. The only vaccine available for over a century against tuberculosis (TB) is the BCG vaccine, with over four billion doses administered, making it the most widely used vaccine [2].

The BCG vaccine is an attenuated strain of *Mycobacterium bovis*, which was developed after it was accidentally observed that *M. bovis* lost its virulence when grown in bile. It was hypothesized that exposure to a nonvirulent strain would increase host immunity to infection by a virulent strain of an immunologically similar organism. *M. bovis* was further attenuated by passing it through 230 serial

cultures in potato, glycerol, and bile medium. Subsequently, various controlled trials in different parts of the world have revealed that its effectiveness in preventing pulmonary tuberculosis (PTB) varies between 0% and 80% [3]. However, trials worldwide have shown that BCG effectiveness is 60 to 80 percent against childhood tuberculous meningitis and disseminated tuberculosis, and protection lasts for up to 10 years, partly justifying its use [4 - 8]. Several studies on the BCG vaccine have shown that BCG vaccination cannot develop varied, diversified, and distinct cell-mediated immune responses in humans, which could eradicate MTB infection [9]. BCG shares epitopes with nontuberculous mycobacteria (NTM), providing a mechanism for cross-protection against infections from NTM [10]. This might explain, at least in part, why there has been an increase in NTM disease in developed countries where routine BCG vaccination has been discontinued [11].

FACTORS THAT EXPLAIN THE VARIABILITY OF BCG PROTECTION EFFICACY

It has been hypothesized that factors likely to be associated with the variable efficacy of BCG in different geographic areas are as follows:

1. One factor is masking. Environmental mycobacterial infections have been associated with reduced protection against tubercle bacillus infection; therefore, BCG vaccination does not increase naturally acquired protection. This could mask, wholly or partially, any protection provided by the BCG vaccine [12 - 14].
2. Another factor is blockade. Pre-existing natural immunity resulting from exposure to nontuberculous mycobacteria may impede the replication of the BCG strain within the host, thus affecting the development of an optimal immune response to BCG vaccination. Supporting evidence includes observations that the prevalence of environmental mycobacterial infection declines, while BCG efficacy improves, with increasing distance from the equator [13, 15 - 17].
3. Diminishing BCG-induced immunity over time is also a factor.
4. Influence of socioeconomic, psychological factors, and nutritional status [18] is crucial.
5. The original BCG strain, developed by Calmette and Guérin, is no longer available; instead, various substrains (such as French Pasteur 1173 P2, Danish 1331, Glaxo 1077, and Tokyo 172) are maintained by different laboratories using diverse methodologies. These substrains now differ from both each other and the original strain. Variations in preparation (*e.g.*, cultivation techniques) and genetic differences among BCG strains globally have been proposed as

contributing factors to the observed variability in vaccine efficacy [19 - 21]. However, a recent meta-analysis showed no relationship between the estimated vaccine efficacy and the different BCG strains used in clinical trials over different years [22].

6. Variable BCG efficacy may be due to host factors, such as cultural practices, genetics, and environmental exposures, which vary by region. Testing these factors in humans and even animal models has been challenging until recently [23]. Some countries have stopped using BCG; discontinuation is recommended if:
 1. The annual rate of sputum smear-positive pulmonary TB has been less than 5 per 100,000 for the past 3 years.
 2. TB meningitis in children under five averages less than 1 case per 10 million people over 5 years.
 3. The annual tuberculosis infection risk is below 0.1% [24].

BCG VACCINE CANDIDATES

The ideal vaccine strategy for TB should encompass three key components: preventing primary infection and disease after exposure, preventing the reactivation of latent infection, and utilizing an immunotherapeutic adjuvant to enhance standard TB treatment and promote patient recovery [25]. It must also have a high-security profile and be developed and administered using low-cost technology [26].

The stages in the development of a vaccine include the identification and study of potential molecules, the implementation of studies in animal models, preclinical development, the initial clinical stage, safety, immunogenicity, and clinical trials that require prolonged follow-up of thousands of participants and their regulatory approvals; All of this in total takes 10 to 15 years, involving the investment of enormous monetary resources, which, combined with the risk of failure, makes projects aimed at developing a vaccine unattractive for the industry [27].

A more consistently effective vaccine than BCG is urgently needed for adolescents and adults to achieve the 'End TB strategy' set by the World Health Organization [18]. The poor efficacy of BCG in preventing pulmonary tuberculosis has led various research groups to develop alternative candidates for years, either to improve it or to replace it completely. There are currently at least 19 vaccine candidates in different stages of clinical development, and even more in preclinical stages.

Globally, for many years, advanced variants of anti-tuberculosis vaccines have been developed that offer greater immunogenicity than BCG and alternative vaccines based on other species of mycobacteria. Thanks to the development of

Pediatric tuberculosis: The Forgotten Plague

The time has come for the hidden epidemic of childhood tuberculosis to emerge from the shadow of adult tuberculosis.

Peter Donald, pediatrician.

Abstract: Tuberculosis is one of the leading causes of death in children under 5 years of age worldwide. More than 80% of children who die from tuberculosis are under 5 years of age, and 96% of them die without being diagnosed and receiving adequate treatment. In 2023, of the global number of people who developed TB, 12% were children and young adolescents (aged 0–14 years), with 1.3 million cases. Of the global number of deaths caused by TB among HIV-negative people in 2023, 166,000 were children and young adolescents (aged <15 years), equivalent to 15% of the total. For decades, children and adolescents have been ignored by global and national programs, decision-makers, researchers, and companies that produce diagnostic equipment and anti-tuberculosis drugs. Now is the time to act and end these unnecessary and preventable pediatric deaths from tuberculosis. Children have the same rights as adults regarding tuberculosis care and research. It is time to put these words into action, and eliminating tuberculosis depends on it.

Keywords: Child, Diagnosis, Pediatric, Treatment, Tuberculosis.

INTRODUCTION

Tuberculosis is one of the leading causes of death in children under 5 years of age worldwide. More than 80% of children who die from tuberculosis are under 5 years of age, and 96% of them die without being diagnosed and receiving adequate treatment. The most recent WHO guidelines for pediatric tuberculosis care offer clear recommendations on evidence-based approaches to diagnosing and treating children with drug-sensitive and drug-resistant tuberculosis.

During the United Nations High-Level Meeting in 2018, the following goals were set for the period 2018-2022:

1. To treat at least 3.5 million children with TB. Only 2.5 million (71%) were treated.
2. To treat 115 thousand children with RR/MDR TB. Only 21,600 (19%) were treated.
3. To treat 4 million children under 5 years of age who were household contacts of TB cases. Only 2.2 million (55%) were treated [1].

In 2023, of the global number of people who developed TB, 12% were children and young adolescents (aged 0–14 years), with 1.3 million cases. Of the global number of deaths caused by TB among HIV-negative people in 2023, 166,000 were children and young adolescents (aged <15 years), equivalent to 15% of the total. Of the global deaths from TB among people with HIV, 25,000 were children and young adolescents (16% of the total) [2]. Even worse, according to the World Health Organization (WHO), only about one-third of the cases are recorded and reported [3]. Most TB deaths in children occur from a lack of diagnosis and treatment [4].

Traditionally, children have not been considered a source of infection and hence do not contribute to community transmission of the disease. Children are usually not considered a significant factor in the persistence of tuberculosis endemicity. Furthermore, due to the nonspecific clinical presentation, the difficulty in obtaining sputum samples in young children, and the fact that the disease is usually paucibacillary, it is more difficult to confirm the disease than in adults.

For decades, children and adolescents have been ignored by global and national programs, decision-makers, researchers, and companies that produce diagnostic equipment and anti-tuberculosis drugs. The current goal is to identify all pediatric cases, which will require innovative diagnostic methods specific to this age group and the urgent need to implement WHO recommendations in primary care, where most children and adolescents are treated. The most recent WHO guidelines for pediatric tuberculosis care offer clear recommendations on evidence-based approaches to diagnosing and treating children with drug-sensitive and drug-resistant tuberculosis. The lack of emphasis on children in the global strategy for tuberculosis control means that the pediatric prevalence of tuberculosis infection, morbidity, and mortality from tuberculosis remains largely unknown. Now is the time to act and end these unnecessary and preventable pediatric deaths from tuberculosis [5]. Children have the same rights as adults regarding tuberculosis care and research. It is time to put these words into action, and eliminating tuberculosis depends on it.

Two factors primarily account for the deficiencies in pediatric tuberculosis care. Bacteriological confirmation of drug-resistant tuberculosis disease is more

difficult to attain in children than in adults. Young children are more likely to have paucibacillary and extrapulmonary disease and frequently cannot provide a lower respiratory sample. Another problem is that all diagnostic tests, whether phenotypic or genotypic, have poor sensitivity in pediatrics. Under program conditions, the sensitivity of smear microscopy in children is less than 5%. Unfortunately, in resource-limited countries, which are those with the highest disease burden, diagnosis is primarily based on smear microscopy. A worrying aspect is that the majority of reported childhood tuberculosis cases are smear microscopy-positive, indicating the enormous gap between the actual incidence of pediatric tuberculosis and the reported incidence [6, 7]. Chest X-rays facilitate clinical diagnosis but are not always accessible, especially in economically underdeveloped countries. Digital X-rays with artificial intelligence interpretation are already routine tools for diagnosing tuberculosis in adults; however, this technology is not yet available for diagnosing tuberculosis in children.

The advent of new drugs in the last 15 years has enabled, based on high-quality evidence, the transformation of treatment for drug-resistant tuberculosis, shortening it from 18-24 months to just 6 months, which is the current World Health Organization recommendation for adults. However, patients under the age of 14 cannot benefit from this treatment, as they are excluded from clinical trials due to the unknown safety in this age group [8]. This again proves the urgent need to include children in clinical trials [9].

Another significant gap in pediatric tuberculosis is the lack of integration of pediatric tuberculosis programs into primary health care. Urgent investment is needed to access new rapid molecular diagnostic point-of-care methods and to research and develop strategies for non-sputum samples in resource-limited regions. Training primary care providers to diagnose and treat pediatric tuberculosis is also necessary [10].

An aspect of pediatric tuberculosis that has been neglected in countries with a high disease burden is the treatment of tuberculosis infection in children and adolescents in contact with active cases of pulmonary tuberculosis, especially those under 5 years of age. Studies have found that contact tracing is cost-effective in countries with high TB incidence [11]. A recent modeling study showed that routine screening for tuberculosis among young children combined with contact tracing and preventive treatment would have a significant public health impact and be cost-effective in preventing pediatric tuberculosis deaths in high-incidence settings [12].

Infection tracing in pediatric contacts is traditionally limited to household contacts, based on the assumption that children spend more time exposed to adults

CHAPTER 11

Concluding remarks

*The definition of insanity is doing the same thing
yet expecting different results.*

Anonymous.

Abstract: We will not achieve the World Health Organization's (WHO) proposed goal of eliminating tuberculosis globally by 2035, and likely not even by 2050. The goal for TB elimination is to reduce the annual incidence to less than one case per million inhabitants by 2050. Achieving this goal requires a reduction of 1,000 times the current incidence in just 25 years. Responding in part to a lack of political will to address TB, the WHO introduced the End TB Strategy in 2015. Ending the TB epidemic might be possible, but several conditions must be met: optimization of current strategies for TB care and prevention; universal access to TB care through universal health coverage and social protection by addressing social determinants of TB, including poverty and inequality; and investment in research on diagnostic tools, drugs, and prevention. The elimination of tuberculosis requires genuine political commitment, adequate funding, and effective management from governments at all levels.

Keywords : Elimination, End TB strategy, Goals, Poverty, Tuberculosis.

INTRODUCTION

The World Health Organization's (WHO) goal of eliminating tuberculosis globally by 2035 is unlikely to be achieved, and even 2050 may be out of reach. The failure to achieve the goals set by the WHO in its End TB Strategy should prompt a reevaluation of the strategy's implementation, particularly given the current focus on a biomedical approach and the relegation of the social determinants of tuberculosis to purely theoretical consideration. Tuberculosis (TB) has long been considered a 'disease of poverty'. Social, political, and economic conditions associated with poverty facilitate TB transmission and are linked to chronic underinvestment in the development and implementation of innovative technologies, including diagnostics, medicines, and vaccines [1].

Every patient with tuberculosis should have access to innovative diagnostic methods that allow for rapid diagnosis and treatment with new, shortened, all-oral regimens, as a matter of social justice.

Responding in part to this lack of political will to address TB, the World Health Organization (WHO) introduced the End TB Strategy in 2015.

As proposed by the WHO, ending the TB epidemic requires a combination of biomedical, public health, and socioeconomic interventions, along with research and innovation. The WHO End TB strategy [2] has three pillars: patient-centered care, bold policies, and intensified research and innovation. It is possible to end the TB epidemic, but there are several provisos:

1. Optimization of current strategies for TB care and prevention
2. Achieving universal access to TB care through universal health coverage and social protection
3. Addressing social determinants of TB, including poverty and inequality
4. Investing in research on diagnostic tools, drugs, and the prevention of TB.

The three 2035 targets proposed by the WHO for the End TB Strategy are:

1. A 95% reduction in the number of TB deaths compared with 2015.
2. A 90% reduction in the TB incidence rate compared with 2015.
3. Zero percent of TB-affected families experiencing catastrophic costs due to TB.

The WHO has also proposed 10 performance indicators to assist in implementing the strategy to achieve these goals (Table 1).

Table 1. Key performance indicators for the End TB strategy.

No.	Performance indicator	Target (%)
1	TB treatment coverage	≥90
2	TB treatment success rate	≥90
3	Percentage of TB-affected households that experience catastrophic costs due to TB	0
4	Percentage of newly notified TB patients diagnosed using WHO-recommended rapid tests	≥90
5	Latent TB infection treatment coverage	≥90
6	Contact investigation coverage	≥90
7	Drug susceptibility coverage for TB patients	100
8	Treatment coverage, new TB drugs	≥90

(Table 1) *cont....*

No.	Performance indicator	Target (%)
9	Documentation of HIV status among TB patients	≥90
10	Case fatality ratio	≤5

*Modified from Matteelli *et al.* [3].

Despite the availability of new anti-TB drugs and rapid diagnostic methods for the first time in decades, access to essential treatment and care remains woefully inadequate in high-incidence, low-income countries. If current conditions persist, the spread of drug-resistant TB is expected to increase and ultimately undermine the End TB Strategy goals.

At high-level meetings sponsored by the United Nations, calls have begun for countries to strengthen their solidarity in actions against TB, recognizing that controlling the pandemic will require a global effort. Even if developed countries with a low disease burden believe they are on the path to eradicating the disease, the infectious nature of TB and the high mobility of human beings will likely prevent tuberculosis elimination, even in these low-burden countries.

The factors perpetuating tuberculosis that require urgent attention are as follows:

Political Commitment, Funding, and Stewardship

Progress against tuberculosis has stalled in most countries, and deficiencies in treatment and prevention persist. The goal of ending tuberculosis by 2035 requires a political commitment that goes beyond rhetoric and is translated into concrete actions and investments. Achieving this goal requires developing a national TB strategy that is integrated into health and social sector plans, including social protection benefits for individuals affected by TB, as well as access to universal health coverage and equitable TB services for all. Politicians must ensure the allocation of a sufficient budget for TB management and TB research under government stewardship. Political commitment requires a willingness to act and active participation; passive empathy is useless.

The elimination of tuberculosis requires real political commitment, funding, and management from governments at all levels (national, state, and municipal). To ensure case reporting and successful treatment in line with international recommendations, the participation of the nongovernmental health sector is vital, but it must be linked to the national tuberculosis program's activities.

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