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Tuberculosis Trends in the Post-COVID-19 Era: Is It Going to be a Global Concern?

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ABSTRACT

Background and Aims: Tuberculosis (TB), a leading cause of death from infectious diseases, faced considerable challenges during the coronavirus disease 2019 (COVID-19) pandemic. This review examines the impact of pandemic-related disruptions, including the diversion of healthcare resources, reduced access to TB diagnostics and treatment, and declining BCG vaccination rates, on TB trends. The aim is to forecast the post-COVID-19 TB burden, identify risk factors that exacerbate transmission, and propose strategies to prevent a global resurgence.

Methods: This narrative review incorporates epidemiological data, modeling research, and reports from the World Health Organization and national health systems. It examines TB trends before and after COVID-19, the outcomes of coinfection, and the pandemic's impact on immunology, socioeconomic factors, and health systems. The review also compares trends in India and South Africa—two countries facing significant challenges—to those observed during the COVID-19 pandemic.

Results: COVID-19 disruptions in healthcare led to an 18% decrease in TB notifications in 2020, resulting in delayed diagnoses, increased household transmission, and higher mortality. Immune dysregulation, including T-cell depletion and cytokine storms, contributed to a 12.3% mortality rate in COVID-19-TB coinfections. Models predict a 5%–15% rise in TB incidence and an additional 1.4 million deaths by 2025. Individuals with HIV, diabetes, and malnutrition were particularly vulnerable. Factors such as overcrowding, air pollution, and reduced Bacillus Calmette–Guérin (BCG) coverage in endemic regions have further heightened susceptibility to TB.

Conclusion: COVID-19 has undone years of progress in TB control, highlighting the need for a unified health strategy. Early diagnosis, treatment of latent TB, and BCG catch-up initiatives are crucial. Strengthening health systems, addressing socio-economic factors such as poverty and hunger, and utilizing pandemic advancements like telemedicine and vaccine research will be key to preventing a resurgence of TB. Continued financial support and international cooperation are essential to eliminating TB by 2030.

1 | Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*). According to the latest World Health Organization (WHO) reports, it is currently the 13th leading cause of death and the second leading cause of mortality from infectious diseases after coronavirus disease 2019 (COVID-19). It is estimated that around 25% of people are infected with TB worldwide, and eventually, 5%–10% of these infected individuals would develop symptoms and TB disease. TB is transmitted through close contact with cough and other mucous secretions of an ill person and is curable with antibiotic therapy. Due to its high prevalence and mortality as well as its preventable and curable nature of this disease, TB has always been important for health systems. In 2021, the highest prevalence of TB was reported in low-income countries, such as the South-East Asia region (46%), Africa region (23%), and the Western Pacific region (18%) [1, 2].

The COVID-19 pandemic had many health, economic, and social impacts worldwide. The impact of COVID-19 on the TB is still not clear. Quarantine effectively reduces the number of COVID-19 cases but increases the number of TB and diabetes cases. The challenging circumstances may be further exacerbated by additional health issues stemming from lifestyle changes associated with quarantine. Numerous systematic reviews have shown that, globally, quarantine measures implemented during the COVID-19 pandemic led to reduced physical activity, poorer dietary habits, and an increasingly sedentary lifestyle. These changes are linked to a higher risk of various comorbidities, including diabetes [3, 4]. Moreover, a separate systematic review reported that lockdowns were associated with worsening glycemic control in individuals with Type 2 diabetes mellitus (DM) [5]. Uncontrolled diabetes presents a significant risk factor for TB, contributing to poorer treatment outcomes and increased mortality. In the six countries with the highest TB incidence, approximately 10%–18% of TB cases are attributed to diabetes. Diabetes substantially increases the risk of developing active TB, with estimates ranging from a two- to fourfold increase [6]. To minimize these negative effects, increasing public awareness about the risks of TB transmission and implementing a healthy lifestyle should be considered the most effective strategies based on simulation. Considering the impact of COVID-19 on the deterioration of socio-economic conditions, the investigation of TB becomes even more important [2, 7]. Studies in different countries reported a decrease in incidence and mortality due to common infectious diseases during the COVID-19 pandemic [8–13]. The long-term effects of COVID-19 and its impact on the emergence of treatment-resistant species with high pathogenicity in the post-COVID-19 era is one of the current health concerns [14].

On one hand, long term consequences of COVID-19 and how the pandemic can affect other infectious disease trend in the post-COVID era are still unknown. On the other hand, exclusive clinical and epidemiological characteristics of TB make it a global concern. Therefore, this study aimed to review TB trends in the post-COVID-19 era.

2 | TB Risk Factors

Both exogenous and endogenous risk factors determine the likelihood of development from TB bacteria exposure to active disease. Awareness of these variables is critical for developing TB control measures [15]. Exogenous variables, such as sputum bacillary load and distance from a TB patient, are essential in accelerating the course from exposure to infection. Similarly, endogenous variables result in active TB disease infection. Along with well-known risk factors like human immunodeficiency viruses (HIV), malnutrition, and young age, new variables like diabetes, indoor air pollution, alcohol, immunosuppressive medications, and smoking also play a role [16]. *Below we discuss some of the most critical factors.*

2.1 | Immunodeficiency

The most significant immunosuppressive risk factor for active TB illness is HIV coinfection [17]. HIV/acquired immunodeficiency syndrome (AIDS) remains to be a significant health issue in South Africa, which not only has the highest number of people living with HIV globally and the fourth-highest adult HIV prevalence rate, but also the highest incidence of TB. Coinfection with HIV increases the likelihood of latent TB infection reactivating and speeds up the TB progression after initial or reinfection with TB [18–20]. According to studies conducted in countries with high HIV prevalence, TB incidence is highly correlated with geographical and temporal heterogeneity [21].

Genetic analysis of the host has provided several key insights. Certain acquired or inherited primary immunodeficiency diseases (PIDs) are associated with an increased risk of mycobacterial diseases, such as TB. Several monogenic disorders affecting IFN-γ immunity result in heightened susceptibility to mycobacterial infections. Moreover, specific mutations in genes linked to classical PIDs—such as hypomorphic variants of signal transducer and activator of transcription 1 (*STAT1*) and NF-kappa-B essential modulator *(NEMO)*, or cell-type–specific alterations like those in cytochrome B-245 beta chain (*CYBB*)—have been shown to confer a selective vulnerability to mycobacterial infections, including TB. These findings have established a foundational understanding of monogenic predisposition to severe TB and have paved the way for broader investigations using whole exome and whole genome sequencing. These approaches allow for the analysis and functional assessment of specific cells or molecules within their native biological contexts [22, 23].

At the immunological level, effective defense against mycobacteria involves T cells (as evidenced in AIDS), dendritic cells (e.g., deficiencies in *IRF8* and *GATA2*), and macrophages (e.g., *CYBB* deficiency), and requires IFN-γ for optimal activity, as seen in Mendelian susceptibility to mycobacterial disease (MSMD). Studies of MSMD have definitively shown that IFN-γ–mediated immunity in humans is a genetically regulated, continuous trait that significantly influences the outcome of mycobacterial infections [22].

2.2 | Malnutrition

There is a bidirectional link between TB and malnutrition: malnourished individuals are more susceptible to contracting TB, while TB, being a catabolic disease, can lead to or worsen malnutrition. Malnourished TB patients often experience worse outcomes, especially those with rifampicin-resistant (RR)/multidrug-resistant (MDR)-TB. Malnutrition weakens the immune system in various ways, which may contribute to some of the observed interactions [24, 25]. Additionally, malnutrition can affect the absorption and metabolism of drugs, potentially leading to treatment failure and increased treatment toxicity in TB patients [26].

2.3 | Young Age

Studies have indicated that the risk of TB infection is higher in children. While 60%–80% of individuals exposed to a source case with a positive sputum smear become infected, only 30%–40% of those exposed to a source case with a negative sputum smear are infected. Household sputum-positive cases remain a significant source of transmission, particularly for children up to the age of 5–10 [27, 28]. It is estimated that 7.5 million children are infected with *M. tuberculosis* each year, and 5%–10% of them may develop TB disease if they do not receive preventive treatment. The risk of developing TB disease after exposure is age-related, with the cumulative risk being higher in children under 5 years of age and adolescents (15–18 years), potentially due to increased time spent at home by young children. Contact with known TB cases, exposure to smoke, overcrowding in households, and poor living conditions are significant risk factors for pediatric TB. The public health implications of these findings underscore the need for ongoing monitoring and targeted interventions to achieve TB elimination by 2030 [29, 30]. This need has become even more urgent in the wake of the COVID-19 pandemic, which has revealed pediatric TB as a hidden threat. Recent data show that children have become more susceptible to TB than previously understood, with increased household transmission linked to stay-at-home measures and risk factors such as tobacco smoking [31, 32]. Additionally, co-infection with COVID-19 has led to worse prognoses, despite TB being both preventable and treatable. Ryckman et al. [33], in their review article on “Ending tuberculosis in a post-COVID-19 world,” emphasize that a person-centered, equity-oriented response—addressing the widened health disparities caused by the pandemic—is essential for moving forward. As global attention begins to return to other infectious diseases like TB, there is hope that the downward trends in TB control can stabilize and return to pre-pandemic progress [34].

2.4 | Diabetes

Active TB is linked to diabetes [35]. According to a systematic review of 13 studies on the link between diabetes and TB [36], diabetic patients are three times more likely to contract TB than those without diabetes. Diabetes-affected individuals also have poorer outcomes, according to studies. Alisjahbana et al. [37] showed that patients with TB and DM had a 22.2% smear-positive culture rate after treatment compared with only 6.9% of those without diabetes.

2.5 | Socioeconomic

Rapid urbanization [38], as seen in developing nations, and individuals’ socioeconomic level (SES), which has also been proven to increase infection vulnerability, are both factors to consider. The TB burden follows a robust socioeconomic gradient within and within countries, with the poorest at the highest risk [39]. People with lower socioeconomic status are more likely to be exposed to crowded and poorly ventilated environments. Marginalized people, particularly convicts, are more likely to contract TB [40].

In 2018, over 11 million people were incarcerated, reflecting a 24% increase since 2000, with growth observed in nearly all regions. Africa and Asia, which bear the highest burdens of TB and HIV, experienced a 29% and 38% rise in incarceration, respectively. Overcrowding in prisons, high individual-level risk factors, and limited access to diagnosis and treatment contribute to widespread TB transmission, placing prisoners at heightened risk, particularly for drug-resistant TB [41–43]. International guidelines and national programs prioritize case detection and prevention for high-risk groups such as HIV-positive individuals and household contacts of TB patients. However, incarcerated populations have received comparatively less attention. Studies consistently show a high TB burden in prisons, underscoring the need to prioritize incarcerated individuals in international recommendations and reporting metrics. To address the TB crisis in prisons and detention facilities, national TB control programs must invest in active case finding and preventive interventions. Nevertheless, significant gaps remain in understanding the global burden and transmission dynamics of TB among prisoners [40, 41, 44].

2.6 | Tobacco

Several systematic reviews [45–47] have assessed the smoking's effects on TB. According to Bates and colleagues, who analyzed 24 studies on tobacco's impact on TB, smokers had an increased risk of TB disease than nonsmokers. Smoking was clearly shown to remain a risk factor for TB infection and disease, including the risk of death in those with active TB [46]. Based on 15 studies, a higher risk of TB recurrence or relapse was observed among tobacco users compared to non-users. The risk ratios (RR) were as follows: ever using tobacco vs never using tobacco (RR = 1.78; 95% CI = 1.31–2.43; $I^2 = 85\%$), current tobacco use vs no tobacco use (RR = 1.95; 95% CI = 1.59–2.40; $I^2 = 72\%$), and former tobacco use vs never using tobacco (RR = 1.84; 95% CI = 1.21–2.80; $I^2 = 4\%$). For mortality, 38 studies were identified, with 13 reporting mortality during treatment. Ever using tobacco (RR = 1.55; 95% CI = 1.32–1.81; $I^2 = 0\%$) and current tobacco use (RR = 1.51; 95% CI = 1.09–2.10; $I^2 = 87\%$) significantly increased the likelihood of mortality during treatment in people with TB, compared to never using tobacco and not currently using tobacco, respectively [48].

2.7 | Gender

Biological sex is a crucial determinant of health, as differences in genetics, hormones, and epigenetic regulation influence the prevalence, manifestation, and treatment of diseases [49]. Recent studies on the gender epidemiology of TB highlight significant gender differences in the prevalence and notification rates, disease manifestation, progression, case-fatality rates, response to treatment, and throughout the continuum of TB pathogenesis and care [50, 51]. Men have a higher prevalence of TB and, in many settings, tend to remain infectious in the community for a longer period than women. As a result, men are likely to generate a greater number of secondary infections, and social mixing patterns suggest that men are primarily responsible for the majority of infections in men, women, and children [50, 52]. Potential risk factors for drug resistance may be more prevalent in one sex, particularly males, than the other. This could further exacerbate the existing differences in TB risk between the sexes [53].

Addressing the burden of disease and disparities in TB care for men is not only a matter of men's health but also crucial for broader TB prevention and care efforts. Given the compelling evidence, global discussions and policies on underserved populations must include a focus on men. Recommendations to address gender and TB cannot continue to prioritize the needs of women and girls while overlooking the inequities faced by men and boys, who bear the higher disease burden and often have less access to timely diagnosis and treatment. With a clear need and significant burden, improving diagnosis and treatment for men is essential to achieving the ambitious targets of the End TB Strategy [50].

Gender influences TB outcomes through a complex interplay of biological, behavioral, and social factors, and these disparities were further exacerbated by the COVID-19 pandemic. The pandemic not only heightened vulnerabilities and disrupted health services but also deepened existing social and gender inequalities—particularly in access to healthcare and exposure to gender-based violence. Although TB disproportionately affects men globally, many cases among men remain undiagnosed or unreported, undermining efforts in TB detection and control. A gender-sensitive approach is therefore crucial to address these disparities and to enhance TB prevention, diagnosis, and treatment—especially in the post-COVID-19 era, where these inequities have become even more evident [54].

2.8 | Alcohol

The use of alcohol is a significant risk factor for TB [55]. In a meta-analysis of risk factors associated with TB clustering, alcohol was found to be a risk factor for clustering (or recent TB transmission) both in high- and low-incidence countries [56]. This systematic review revealed that those who consume more than 40 g of alcohol daily and/or have an alcohol use problem are more likely to develop active TB [55]. Several studies have investigated the factors contributing to TB patient mortality [57–59]. These factors are similar to those associated with TB incidence.

In the context of high TB incidence and HIV prevalence, HIV positivity, progressive immunosuppression, smear-negative illness, and malnutrition are all risk factors for death. In areas with low TB and HIV prevalence, chronic comorbidities, positive sputum smears, and alcohol and drug abuse are risk factors [60]. In a systematic review of mortality risk factors in TB deaths, Nicholson et al. [61] found that malignancy, liver cirrhosis, renal failure, and military and pneumonic radiographic patterns predicted mortality. Their study found that 82.7% of deaths were not TB-related. In previous studies [62], aging and underlying comorbidities have been reported to be risk factors for TB deaths [63].

3 | Immunology, COVID-19, and TB

The immune system's deterioration was one of COVID-19's significant side effects during the pandemic. People who had the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were prone to subsequent infections, according to studies [64]. Through the reduction of T cells, B cells, and natural killer (NK) cells, COVID-19 impairs the immune system. With the destruction and reduction of the immunity level, the host body would not be able to destroy the invading pathogens, such as TB bacteria. People with severe COVID-19 infections had lower levels of CD4 expression [65, 66]. During the COVID-19 pandemic, the increase in TB cases was caused by the virus' effect on the immune system of the host. COVID-19 causes the excessive release of cytokines, which damages tissues and organs. This cytokine storm can also undermine the immune system of individuals, making them more vulnerable to contracting TB [17]. On the other hand, the recognition of several Mtb ligands by the host cell receptors activates the innate immune system. In addition to bacterial ligands, immune system cells can detect Mtb viability, which upregulates cytokine production and modifies the immunological response, potentially due to postmortem Mtb mRNA secretion [67]. Positive TB cases have reportedly sharply increased as the COVID-19 outbreak in South Africa has been controlled. Upon examining the pertinent information, the investigators determined that several factors were responsible for the 60% rise in TB cases during the quarantine period. These factors include a decline in the body's immunity following COVID-19 infection, increased population density as a measure to contain the pandemic, and the prevalence of food poverty in South Africa [68]. The WHO report states that one of the most important the primary risk factor for getting TB is the compromised immune system due to HIV. Various factors like inadequate diet, diabetes, and smoking can also hamper the immune system's functioning. Poor and insufficient diet can impact immunity levels and increase the likelihood of contracting TB. Individuals with elevated blood sugar levels are more vulnerable to diseases due to a weakened immune system [21, 69, 70]. The main mechanisms of immunity against TB are through cellular immunity and by T cells and mononuclear phagocytes. Of course, innate and humoral immunity also play a role against dealing with this bacterium [71, 72]. It was previously believed that antibodies were only effective against pathogens that existed outside of cells, as it was thought that they could not enter the cells to eliminate intracellular pathogens. However, it has

been more clear over the past few decades that antibodies also play a critical role in protecting against intracellular infections [73, 74].

3.1 | Impaired Innate Immune Response

Both innate and adaptive immunity are involved in the immune system's response to TB. The innate immune response, which activates macrophages and generates cytokines, chemokines, and interferons, plays a critical role during the early phases of an organism's entry into the body. According to studies, COVID-19 can interfere with the innate immune response. One of the earliest lines of protection against invasive infections is the innate immune response. a group of molecules and cells that work together to find and get rid of the pathogen. Interferons are a crucial component of the innate immune response [75, 76]. Under the impact of COVID-19, interferon synthesis can be impaired, which also disrupts the innate immune response. According to a study they carried out in 2020, Hadjadj et al. [77], it was discovered that patients with a more serious form of COVID-19 had considerably lower levels of Types 1 and 3 interferons than those with a milder form of COVID-19. According to a 2020 study by Major et al. [78], the SARS-CoV-2 virus can directly block the generation of Type I (IFN-α and IFN-β) and III (IFN-λ) interferons. In this study, the researchers discovered that the COVID-19 agent can prevent the activation of interferon-stimulated genes, which disrupts the interferon manufacturing process [78]. The innate immune response is interfered with in this illness by regulation of CD15 and CD16 in neutrophils and CD16 in NK cells, immature granulocytes, and monocyte [79]. There are a number of repercussions if the innate immune response is compromised by COVID-19. Interferon response impairment can cause the innate immune response to be delayed, allowing infections like Mtb to penetrate the defensive barrier. Additionally, this condition causes an overactive inflammatory response that could lead to immune cells attacking the body's healthy cells and tissues [75, 77, 78].

3.2 | Impaired Adaptive Immune Response

The amount of memory cells dropped in COVID-19 patients, according to a study by Kuri-Cervantes et al. [80] reported in 2020, and this could directly affect immune responses to subsequent illnesses. In individuals with severe COVID-19, this study found considerable changes in the leukocyte population, with monocytes, neutrophils, NK cells, and B and T lymphocytes being most affected. All these cases cause a disturbance in the immune response, which is one of the critical cases in the body's defense against Mtb [80]. In infections caused by viruses, T cells are activated [81, 82]. Increased CD4+ and CD8+ cell activation has reportedly been seen in severe COVID-19 cases. Of course, this activation of T cells in these patients was very heterogeneous compared to other viral infections [80]. B cells and antibodies play an important role in reducing the burden of Mtb and can control the disease in healthy people compared to people with impaired cellular immunity [83].

3.3 | Dysregulated Cytokine and Chemokine Production

Cytokines refer to small proteins that cells produce and use to affect the behavior of neighboring cells. These proteins include tumor necrosis factor, interleukins, and chemokines. Cytokines are versatile molecules because almost all cells with a nucleus can generate and react to them, making them essential to the body's balance and regulation [84]. Several studies have indicated that the failure to regulate the disease process can occur when certain cytokines are missing [85, 86]. The medical world is very interested in COVID-19's insufficient cytokine and chemokine production, since it is crucial in development of serious illnesses. Cytokines and chemokines are molecules that are generated by immune cells, which cause and regulate immune responses. When COVID-19 is present, the excessive and unregulated production of these molecules can cause a cytokine storm, which leads to a systemic inflammatory response, and can ultimately result in the failure of multiple organs and even death [87]. Numerous studies have demonstrated that individuals with severe COVID-19 have elevated levels of interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1), all of which are pro-inflammatory cytokines [75, 88] Immune cells including macrophages, monocytes, and T cells are stimulated by the virus to produce these cytokines. When individuals experience severe disease, their immune system response can become imbalanced, resulting in an excessive production of cytokines that can harm tissues and cause organ failure. Increased quantities of pro-inflammatory cytokines and chemokines can damage tissues and cause various organs to fail. Diseases like TB may appear as a result of this condition [87].

Acute COVID-19 in TB patients was associated with lower levels of IL-8, IL-13, TNF-α, and IP-10 compared to those with TB alone. This suggests a possible immunoregulatory effect of co-infection, as these cytokines are typically upregulated in both TB and COVID-19 patients compared to healthy individuals [89]. The study aligns with previous findings showing that COVID-19 co-infected patients had reduced *M. tuberculosis*-specific T-cell responses. Additionally, a recent study reported lower levels of Th1- and Th2-associated cytokines, including IP-10, in co-infected patients compared to those with TB alone [90]. However, this was not accompanied by a corresponding increase in innate inflammation. Variations in baseline inflammatory responses and pathogen genetics may contribute to this discrepancy. Since IP-10 is directly induced by IFN-γ, its reduction in co-infected patients may indicate regulation by Type I interferons, a pattern observed in other viral-microbial co-infections [91].

Studies have shown that immune cell dysregulation occurs following acute COVID-19, with patients experiencing prolonged depletion of dendritic cells and monocytes, as well as a sustained reduction in naïve and helper T-cells for several months post-infection [92, 93]. These immunological sequelae may explain the reduced cytokine expression observed in SARS-CoV-2 seropositive TB patients. In this context, myeloid cells primarily produce TNF-α, G-CSF, IL-1β, and IL-8, while T-cell subsets in TB patients release IP-10, IL-4, and IL-13 [94].

4 | Overview of TB Outbreaks

Outbreaks are defined as the sudden increase in the number of cases of a special illness. In most TB outbreaks, numerous persons were exposed to TB bacteria due to the delayed discovery of initial cases with long-lasting severe coughs. They were also affected by the initial cases socio-environmental characteristics, time and place of infection, and host factors, including immune state, infectivity, and/or pathogenicity of the bacteria [95]. To improve monitoring systems and strengthen general health systems, countries should collect and study TB outbreaks. Aside from this, outbreaks can provide excellent opportunities to gather key information about diseases. An analysis of Japanese TB outbreaks from 1993 to 2015 revealed 605 TB outbreaks involving 3491 TB cases [96]. However, according to the Japan TB Surveillance Center's *Annual Report 2022*, Japan, categorized as a medium-burden TB country, recorded 11,519 newly confirmed TB cases [97]. The majority of TB outbreaks took place in April and May, followed by healthcare infrastructure, schools, and welfare institutions. The highest number of TB patients were found in psychiatric hospitals and nursing homes per outbreak. In contrast, the highest number of latent TB cases was found in schools and jails. Another study examined TB outbreaks in the United States from 2022 to 2023 [98, 99]. This report revealed that in 2023, the number of cases increased by 1295, reflecting a 16% rise compared to 2022. Additionally, the incidence rate grew to 2.9 per 100,000 people, up from 2.5 in the previous year [99]. There was a greater likelihood that patients associated with major outbreaks had drug abuse, were homeless, or were diagnosed while in jail than all other TB patients. A majority of outbreaks were spread among family members and non-family members within households. Studying big outbreaks can guide focused measures to reduce TB morbidity associated with outbreaks.

An analysis of TB outbreaks in both Japan and the United States highlights the critical impact of delayed diagnosis, social determinants, and institutional settings on outbreak dynamics. In Japan, despite the presence of universal health coverage, delays in seeking care persist—particularly among individuals experiencing socioeconomic hardship, such as homelessness or precarious employment. These challenges contribute to prolonged periods before diagnosis, allowing ongoing transmission within communities and complicating efforts to control the spread of TB [100].

In the United States, TB cases reached their highest level in a decade in 2023, with over 9600 reported cases, representing a 16% increase from the previous year. This surge is attributed to factors such as increased migration and the reactivation of latent TB infections, particularly among individuals born abroad. The COVID-19 pandemic further exacerbated TB control efforts by straining public health services, resulting in delays in diagnosis and treatment. These insights are especially pertinent in the post-COVID era, where healthcare disruptions, reduced TB screening, and the diversion of public health resources have heightened the risk of delayed case detection. The pandemic has also impeded the timely identification and response to outbreaks, particularly in high-risk settings such as nursing homes, shelters, and correctional facilities, which were already under significant strain during COVID-19 [101].

By analyzing outbreak patterns before and after the pandemic, we can gain a clearer understanding of how COVID-19 has impacted TB transmission and detection. Applying these insights is essential for strengthening early detection and containment strategies moving forward.

5 | TB Trends in the Pre-COVID Era

Infectious pathogens are constantly growing due to demographic expansion, globalization of travel, and lifestyle changes. These factors have accelerated emergence of infectious diseases [102]. An additional focus needs to be placed on assessing the effects of superimposing viral epidemics [such as severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), and COVID-19] on long-standing diseases like TB, one of the most severe public health concerns worldwide, particularly in developing countries. Here, we focus on the pre-COVID-19 era. In 2019, TB remained the leading cause of death caused by infectious diseases causing morbidity and mortality. An estimated 10.0 million people contracted TB in 2019, with an estimated 1.2 million TB fatalities among HIV-negative individuals and an additional 208,000 deaths among HIV-positive individuals. Eighty percent of TB patients are adults, while 12% are children. A study by Zukowska [103] reviewed TB outbreaks between 2011 and 2020. This study identified TB outbreaks worldwide, on all continents, and in high- and low-incidence nations. The identified outbreaks typically contain five *M. tuberculosis* isolates. The strains that caused the outbreaks were mainly L4 and L2. Outbreak isolates are frequently drug-resistant [103].

The influence of sanitary isolation and Bacillus Calmette–Guérin (BCG) vaccination on TB incidence was apparent but difficult to measure, given the numerous other factors that played a role [104]. Most incidences were related to poverty alleviation. Three decades of successful chemotherapy, along with the belief that service integration would address care difficulties, caused a relaxation of public health restrictions in many nations in the 1980s [105]. In addition, other significant causes contributed to the rise of TB incidence in various countries at the same time: the HIV/AIDS epidemic, particularly in Africa; the emergence of MDR-TB in former Soviet Union nations after social and economic collapse; and continued migration from high-TB incidence settings to a lower-incidence country [106]. There were 2.9 million deaths related to TB in the 1990s, nearly 8 million new cases per year, and an estimated 1.7 billion people (one-third of the world's population) were infected. It became evident that only a comprehensive global TB control effort would be effective. A program called Direct Observation Therapy Short course or directly observed treatment short-course (DOTS), was developed. A lot depends on government commitment, surveillance, diagnosis, drug supply, and confirmation of treatment compliance. This has caused a 5%–6% annual drop in TB in the United States. DOTS has been adopted by all 22 nations with the highest TB burden, which accounts for 80% of all TB cases worldwide. The World Health Assembly has set a goal to increase the detection rate of infectious cases to 70% and the cure rate to 85% [107]. Following the implementation of the Stop TB Strategy in 2006,

further progress was made [108, 109]. Although there has been some progress, it has been delayed, and it is projected that the world will not achieve the End TB Strategy's goal of eliminating TB as a danger to public health globally by 2035. For instance, the 2020 global TB report shows that, even though the goal was to lower TB incidence by 20% between 2015 and 2020, there was only a 9% decrease in TB incidence, with an annual decline of approximately 2%. It also fell short of mortality reduction expectations, which was set at 35%, with only a 14% decrease in death rates between 2015 and 2020 [104]. TB response funding is one of the biggest obstacles. Research, prevention, and identification of TB patients, particularly drug-resistant TB patients, are crucial parts of this effort. Several factors, including the significant prevalence of the disease in South-east Asia, Africa, and the Western Pacific, make it challenging to eradicate the disease worldwide completely. Moreover, no recognized treatment for latent TB can be reactivated at any time. In addition, there is no effective vaccine for adults to confer herd immunity [110, 111]. However, the United Nations has not yet reached its target for TB-preventative therapy. Even minor achievements must be recognized and rewarded. According to the World Health Organization, 4.1 million people received TB prevention therapy in 2019 more than twice as many as in 2018 [112]. Notably, 85% of HIV patients who qualified for TB prophylactic therapy received it [113].

6 | TB and COVID-19 Pandemic

The COVID-19 era, spanning from March 18, 2020, to September 17, 2020, was a critical period during which the pandemic significantly impacted healthcare services and patient presentations. Understanding this timeframe is essential for assessing the pandemic's effects on medical practices, patient care, and the broader healthcare system. The insights gained from this period are vital for evaluating its impact on public health and healthcare delivery. The widespread outbreak of COVID-19 disrupted TB services like many other health services. The high prevalence of COVID-19 in sensitive and high-risk areas for TB, such as Africa, the Middle East, and Eastern Europe, increased the risk of TB incidence. According to the WHO report, TB diagnosis and treatment faced problems during the pandemic. The number of new TB cases in 2020 decreased by 1.3 million people in comparison with 2019, and the partial recovery cases in 2021 were 6.4 million, below pre-pandemic levels. The reduction of TB services by reducing the diagnosed and treated cases of TB causes an increase in mortality, and interpersonal transmission in the household and community, as well as an increase in the number of diagnosed cases after the COVID-19 pandemic. Another concern regarding TB was the reduction in budgets for TB services in many health systems worldwide to deal with COVID-19. In 2021, despite the pandemic and devoting a major part of the attention and budget of health systems to COVID-19, Bangladesh, Brazil, China, Uganda, and Zambia, as countries with the highest TB burden in the world, had the highest treatment coverage against TB. High treatment coverage against this disease in countries with a high burden of TB, considering the role of these countries in the spread of the disease and the emergence of drug-resistant species, is very important and shows the attention of health systems to this disease despite the conflict with COVID-19. Also, in 2020 compared to 2015, seven countries in the African Region including Ethiopia, Kenya, Lesotho, Namibia, South Africa, Republic of Tanzania, and Zambia had more than 20% reduction in new TB cases [114]. Also, In TB endemic nations like India, China, Indonesia, and the Philippines, reported TB cases decreased by 25%–30% in 2020 [115]. Based on the WHO global TB report 2022, the number of newly diagnosed cases was determined as a measure of the performance of health systems in preventing and treating TB. The incidence of TB increased worldwide from 2015 to 2019, but in 2020, 5.83 million new cases of TB (−18%) were reported. This decreasing pattern in 2020 was more evident in Region of Americas and South-East Asia Region. The highest percentage of TB incidence reduction in 2020 compared to 2019 was reported in India (41%), Indonesia (14%), Philippines (12%), China (8.1%), Bangladesh (4.8%), Pakistan (4.3%), Myanmar (2.4%), South Africa (1.4%), Russian Federation (1.1%), and Kenya (1%). In 2021, compared to 2020, new TB cases worldwide increased by 0.7 million. Only European Region and the Western Pacific Region continued their downward trend in 2021. In 2021, the countries of India (29%), China (21%), and Indonesia (19%) had the highest decrease in TB incidence compared to 2019 [110].

The delay in diagnosis increased TB transmission risk to household contacts, contributing to increased mortality [116]. Over one million people have been stopped from receiving TB treatment globally, setting the fight against TB back by a decade [116]. Patients with a severe COVID-19 infection are more likely to develop TB or reactivate their latent illness. Another complication is coinfection. A global cohort analysis of 49 patients revealed TB and COVID-19 coinfection. Co-infected patients had a higher mortality rate (12.3%) [117]. A meta-analysis of COVID-19 and TB coinfections showed a twofold increase in mortality, with many case-control studies correlating findings that corroborate the changed disease pathophysiology in coinfections [118].

Strict quarantine measures aimed at controlling the spread of the COVID-19 and caused disruptions to the regular provision and screening of TB services, including those with high rates of TB, particularly during the first wave of the pandemic [119, 120]. Due to the importance of continuous screening and treatment of TB in reducing the burden of this disease on the healthcare system, several studies were conducted in this field to evaluate the extent of this disruption and its outcome. In a study conducted in the first year of the COVID-19 in Nigeria, it was found that the diagnosis, evaluation and treatment services of TB in this country decreased. Although more than 70% of the centers providing TB services in this country were remained open during the quarantine. Also, the patients did not go to these centers due to the fear of COVID-19 infection [119]. Another study in Mexico revealed a 28.9% reduction in the monthly reported TB cases in the COVID-19 pandemic period, as compared to the corresponding period before the pandemic from March 2020 to February 2021 in four health area. But only in one facility, there was a notable rise of 150% in the reported cases during August, September, December,

and February between the pre-COVID-19 and COVID-19 phases. In addition, the study showed that TB treatment outcome rates were significantly lower than before the pandemic. The largest decrease was in January at the rate of −89.9%. Also, the overall rate of reduction was 46.7% in the four treatment centers studied. In general, all the four studied centers faced a decrease in the outcome of treatment, except for one center, which faced a 100% increase in April and October [121].

The start of the COVID-19 pandemic also had an impact on TB research and development (R&D) process. So that the focus in the fields of diagnosis, treatment, and prevention changed from endemic diseases such as TB to COVID-19 in all countries. In other words, governments' focus shifted from investing in these endemic diseases to COVID-19. Therefore, due to the progressive growth of TB in the coming years as mentioned in the previous section, as well as the increase in cases of Extensively Drug-Resistant TB (XDR-TB), there is still a need for financing to improve the diagnostic and treatment methods of this disease, from governments and donors [122, 123].

7 | TB in Post-COVID Era

Most individuals infected with COVID-19 are expected to recover fully within a few weeks. However, some may continue to experience symptoms for weeks or even months after their initial diagnosis. This condition is known as "long COVID," "post-acute sequelae of SARS-CoV-2," or "post-COVID-19 condition. According to the Centers for Disease Control and Prevention (CDC) report, the incidence rate of TB is gradually reverting to its levels before the COVID-19 pandemic. So, early diagnoses and accurate treatment of TB is crucial to prevent its transmission and tackle TB elimination efforts. Additionally, latent TB infection treatment is essential for preventing TB. Accordingly, the occurrence of TB in the United States had been decreasing and had reached a level of 2.2 cases per 100,000 individuals in 2019. But with the outbreak of the COVID-19 pandemic, this rate increased to 2.4 cases per 100,000 people in 2021. Furthermore, the rise in newly reported cases in 2022 in the US has sparked concerns regarding the potential escalation of TB prevalence. So that this rate reached 2.5 cases per 100,000 people, and the most reported cases in the United States were from Alaska [124]. It is also predicted that the incidence and mortality rate of TB will increase by 5%–15% in the next 5 years. In addition, studies have shown that during the COVID-19 period, the BCG vaccination rate decreased in TB endemic countries, which can increase the mortality rate caused by TB, especially in children [125]. Finally, the COVID-19 pandemic caused the reversal of the downward and controlled trend of TB and its subsequent mortality rate. WHO has reported that the COVID-19 pandemic has had negative impacts on the prevalence and management of TB globally. While the number of people receiving TB preventive treatment for individuals with HIV has exceeded the worldwide goal of 6 million between 2018 and 2022, surpassing 10 million within just 4 years. The majority of individuals who began preventive treatment in 2021 were from seven countries: India, South Africa, Zambia, Nigeria, Tanzania, Uganda, and Zimbabwe [114]. Also, WHO has stated that in 2021, the most reported cases of TB were in South-East Asia (46%), Africa (23%), and the Western Pacific (18%), respectively [1]. They published an updated list of countries with a high burden of TB in the 5-year period (2021–2025). Accordingly, among the 30 countries with high TB prevalence, Cambodia, Russia, and Zimbabwe were removed from this list, while Gabon, Mongolia, and Uganda were added to this list. On the basis of the latest updated list, the countries of Gabon and Brazil, Central Afr. Rep., Lesotho, Congo, Ethiopia, Kenya, Namibia, Thailand, Uganda, Tanzania, Angola, Bangladesh, DPR Korea, Pakistan, Papua New Guinea, Vietnam, and Sierra Leone are in the category of countries with high prevalence of TB [126]. According to the CDC report, among 2239 patients with TB in 2022, 30% were black, 26% were Hispanic, and 25% were non-Hispanic white. Also, among 6009 non-Americans diagnosed with TB in 2022, 44% were Asian, 37% were Hispanic, 10% were black, 5% were white, and 2% were Native Hawaiian or another Pacific Islander. Of all people with TB in the United States, the highest amount was observed in the ages higher than or equal to 65 years, 45–64 years, 25–44 years, 15–24 years, less than or equal to 4 years, and 5–14 years old, respectively [124]. In certain countries with a high incidence of TB, such as India and Vietnam, there have been distinct COVID-19 outbreaks that differ from those in other countries, according to research findings [127].

These lockdowns and mobility restrictions imposed during the COVID-19 era have had an impact on the consequences of TB. A study proposed that these restrictions during COVID-19 can increase TB incidence and mortality in the long-term period. While quarantine measures may lead to a 50% reduction in TB transmission temporarily, a 3-month pause in TB services followed by a 10-month recovery period to resume normal operations could result in the accumulation of undetected TB cases, leading to an increase of 1.19 million TB cases over the next 5 years [120]. Another study carried out in Spain discovered that the COVID-19 caused a reduction in the staff of TB wards, delays in laboratory test results and imaging, and the transformation of TB wards into COVID-19 wards. As a result, there were changes in the reported cases of TB. The study revealed that 169 patients were diagnosed with active TB in both 2019 and 2020. In 2019, the number of cases per 100,000 people was 10.25, while in 2020 it was 9.31. This means that the incidence rate was slightly higher in 2019 compared to 2020. During the lockdown phases, the number of cases was even higher in 2019 (12.9 per 100,000 people) compared to 2020 (8.57 per 100,000 people). However, in the post-lockdown period, the number of cases was similar in both years. Additionally, the study indicated that quarantine led to an increase in rates of latent TB in adults and active TB in children [31]. Also, in another study, it was calculated that the delay in the early diagnosis of new cases of TB during the COVID-19 period, led to a cumulative increase in death in India, Indonesia, Pakistan, and Kenya, respectively [128]. Finally, the modeling showed that this disruption will lead to an increase of 6.3 and 1.4 million new cases and death, respectively of TB in the 5-year period from 2020 to 2025 [122].

8 | Factors Contributing to Changes in TB Trends in the Post-COVID-19 Era

8.1 | COVID-19 Vaccination

Evidence suggests that COVID-19 vaccination may have a direct protective effect in reducing the risk of developing active TB. However, the exact mechanism of this interaction remains unclear at present [129]. The use of inactivated vaccines does not impact TB infection testing [130]. However, live vaccines, such as the measles, mumps, and rubella (MMR) vaccine, can slightly suppress the immune system, potentially lowering the response to TB tests. There is no conclusive information regarding the effects of mRNA vaccines on immune responses, and it remains uncertain how the COVID-19 mRNA vaccine might influence TB infection test results within the first 4 weeks after vaccination [129].

Inactivated vaccines, such as CoronaVac, have the potential to trigger both specific adaptive immune responses and non-specific innate immune responses [131]. Studies have shown that CoronaVac can stimulate innate immunity in mice, rats, and macaques [132, 133]. The overlapping transcriptomic responses of the host to COVID-19 and TB may offer some insight into our findings [134]. These study results could help clarify the observed dose-response relationship between COVID-19 vaccination and the risk of developing active TB [129]. This suggests the need for further investigation to understand the preventive mechanism, potentially advancing the development of TB vaccines in the future.

8.2 | Diabetes

Individuals with pre-existing health conditions, such as DM, are at a higher risk of developing COVID-19, experiencing more severe symptoms, and facing increased mortality rates [135–137]. The heightened vulnerability of people with DM to COVID-19 can be attributed to changes in innate immune functions, including chemotaxis, phagocytosis, and cytotoxicity, as well as alterations in T lymphocyte populations such as Th17, CD8, and Treg cells [138]. These immune changes, resulting from either COVID-19 or DM, suggest that individuals with poorly controlled glucose levels, especially those who have recently experienced or are currently battling COVID-19, may face an increased risk of TB. However, the exact impact of a COVID-19 episode on an individual's risk of developing TB is still not fully understood at the biological level. Several studies have reported cases of TB occurring shortly after or simultaneously with a COVID-19 episode [139, 140]. A study conducted by Calles-Cabanillas et al. [141] indicated that the likelihood of new TB cases was higher in individuals with a history of COVID-19 compared to controls, with statistical significance observed only in patients with DM (aOR 2.3). In individuals with DM, the risk of TB was 2.7 times greater in those who had not experienced COVID-19, and this risk increased to 7.9 times for those with a history of COVID-19. DM, in conjunction with previous COVID-19 infections, significantly raises the risk of developing TB. Therefore, it is recommended to perform latent TB screening in individuals with a history of COVID-19 and DM, and to initiate prophylactic treatment if the results are positive [141].

Future studies should explore whether having both COVID-19 and DM is a risk factor for TB, either due to its interaction with the immune system or as an indicator of immune system impairment. Since humans can develop immunity to COVID-19 through recurrent infections and the availability of second-generation vaccines, the impact of the pandemic on TB risk remains unclear [142]. Additionally, the emergence of new SARS-CoV-2 variants and limited access to annual COVID-19 vaccines in TB-endemic areas may further increase the risk of TB, particularly in individuals with poorly managed DM [141].

8.3 | Health System Factors

Since an increase in the epidemic wave of TB, especially due to more attention being given to COVID-19 in recent years, more resources are needed than expected for TB control [143]. For the fight against TB, reliable funding sources have been considered around the world. As long as adequate financial support is not provided, achieving TB control and elimination will remain challenging [144]. Most developed and developing countries have a plan to reduce TB patients in their health centers. TB could be controlled at the local level when DOTS is implemented [145]. The budget for additional interventions does not keep up with the demand as the number of HIV cases, immune deficiency disorders, and drug-resistant strains rises [146]. In 2011, suspension of the global funding program, the sole source of funds for programmatic management of drug-resistant TB (PMDT), hindered the fight against TB [144, 147]. Although many countries have increased their budgets, some still struggle to supply the cost of right drugs, and this has resulted in TB not being properly controlled [148]. Even after decades of struggle, TB is still considered a threat to the health of the global population. As a result, this epidemic is maintained at the global level by a complex interaction between multiple factors. The lack of sufficient funding allocated to research priorities in this field makes it difficult to discover these multiplex factors [149, 150]. A budget that was reviewed in 96 nations regulated by the WHO in the same year increased from $900 million to $1.5 billion despite a $300 million shortage [151].

8.4 | Social Determinants of Health

In recent years, more attention has been focused on the social aspects contributing to TB spread. These factors encompass various health-related elements, such as HIV infection, smoking, diabetes, alcohol consumption, malnourishment, overcrowding, substandard living conditions, and migration [152, 153]. Research has shown that a number of social and environmental factors can significantly increase an individual's chance of contracting the disease. For instance, individuals living in crowded and poorly ventilated conditions are more susceptible to TB, mainly due to higher exposure to the bacteria. Those who have compromised immune systems, such as those who have HIV, are also more susceptible to

getting TB after exposure [154]. The spread of TB can also be influenced by societal and environmental elements like poverty, malnutrition, and a lack of access to healthcare. Additionally, cultural beliefs and practices can influence the likelihood of contracting TB, such as a reluctance to seek medical care or traditional healing practices that may delay diagnosis and treatment [155]. Socioeconomic deprivation refers to the inadequate access to basic social and economic necessities. It encompasses a range of factors, including but not limited to low income, lack of education, unemployment, and overcrowding. The conditions in which individuals live, and the structural determinants of their environment contribute significantly to health disparities and an increased susceptibility to TB. Overall, socioeconomic deprivation is a complex issue with far-reaching implications for individual and population health [156]. The innovative socio-economic interventions against TB (ISIAT) project seeks to effectively combat TB by utilizing cutting-edge socio-economic strategies. By providing a range of psycho-social and economic solutions, the project seeks to increase awareness and reduce the prevalence of TB. The initiatives included in the project plan encompass public education and community awareness campaigns, poverty alleviation programs for affected communities, and education for family members of TB patients. The goal is to employ a multi-faceted approach that addresses the root causes of TB and ensures that affected individuals have access to the resources they need to effectively manage and recover from the disease [157]. As it is so important in determining the health outcomes of communities, the degree of social deprivation within a nation can have a substantial impact on the distribution of TB cases [158]. Inadequate nutrition in impoverished nations can lead to immune deficiencies and a decline in body mass index (BMI) among the population. Vitamin D deficiency is one factor that contributes to weakened immunity and is recognized as a risk factor for respiratory infections, such as TB [159]. In many regions of the world, particularly among older individuals with darker skin, a lack of vitamin D is prevalent. A healthy immune system depends on vitamin D, and low levels of this vitamin are linked to a higher risk of developing severe COVID-19 [160–163]. Improved comprehension of the diverse medical, social, and environmental components that contribute to the propagation of TB can lead to the creation of more precise and efficient prevention and control initiatives. Reducing the prevalence of TB in affected nations will depend heavily on addressing the underlying social determinants of health, enhancing access to quality healthcare, and putting policies in place to improve living conditions for vulnerable populations.

8.5 | Effects of COVID-19 on Smoking and Air Pollution

Numerous research looking at how tobacco affects TB have shown that smoking can cause the disease to go from being dormant and asymptomatic to being active and clinical [164]. Smoking can more than double the likelihood of acquiring this disease, according to a meta-analysis research. People who are heavy smokers have an up to 2.5 times increase in this number [165]. The immune system can be weakened by smoking, and it will be difficult for the body to fight the TB infection. In smokers, the level of cellular immunity decreases, and inflammatory mediators increase, which makes a person more susceptible to TB Smokers have a higher likelihood of undergoing TB treatment than ex-smokers. Therefore, it is advisable to incorporate quitting smoking program into TB disease control strategies. Giving up tobacco lessens the risk of additional smoking-related disorders while also improving general health [166].

Environmental air pollution is a potential risk of increasing TB incidence in relation to environmental damage. Exposure to outdoor air pollution has been shown to diminish airway resistance, affect epithelial permeability, and impair macrophages function, all of which can increase the chance of getting TB [167]. According to studies in the area of the connection between air pollution and the risk of TB, they have not yet been successful in establishing a direct link between these variables. Historical TB outbreaks in Western nations have been connected to coal consumption, suggesting that air pollution from coal burning may have had an impact. Some experts have also hypothesized that the recent TB epidemics in developing countries could be attributed to air pollution from coal use. To lessen the hazards connected with air pollution, it is crucial to address the potential health effects of coal burning and push toward cleaner more sustainable energy sources [168]. There are five types of pollutants commonly found in polluted air: carbon monoxide, ozone, nitrogen dioxide, sulfur dioxide, and suspended particles. These contaminants, which have been linked to an elevated risk of TB, are primarily produced by heavy traffic in large urban areas. To lessen the hazards to the public health brought on by air pollution, it is essential to address the sources of these pollutants and strive toward minimizing their emissions [169]. Although the COVID-19 pandemic has had a number of detrimental effects on public health, several TB risk factors, such smoking rates and air pollution levels, have improved as a result. To ascertain the long-term effects of these modifications on the prevalence of TB and other respiratory disorders, more research is necessary. Therefore, it is important to prioritize proceedings to reduce air pollution levels to minimize the potential risks to public health.

9 | TB and Other Infectious Disease Outbreaks: Lessons Learnt

The world has witnessed several epidemics and pandemics that affected both a large population and diseases, including SARS, MERS, HIV and, most recently, COVID-19. However, there are several studies that explore how epidemics and pandemics interact with TB. Herein, a brief review of this interaction examples has been provided. Their observations and experiences could help us in becoming well-prepared for the upcoming events.

9.1 | TB and SARS Outbreak

In 2002, the SARS coronavirus caused a global pandemic. The SARS outbreak exposed significant flaws in the country's public health systems, poor TB control, for example [170]. Several studies have documented TB coinfection in SARS patients in TB-endemic countries such as Singapore, China, and Taiwan

[171, 172]. TB had been confirmed in both SARS patients and TB acquired after recovering from SARS. Both circumstances were characterized by temporary immunosuppression [173], accompanied by impaired IgG antibody responses and delayed viral elimination in co-infected SARS patients. Additionally, steroid treatment for SARS exacerbated immunosuppression. SARS increased immunosuppression [171]. In a study of 83 SARS patients, three had TB coinfections. Two patients had TB and developed SARS; one later developed TB [174]. All three patients were taking steroid medication, which may have reduced their immunity to some viruses or TB infections and raised their chance of coinfection. Since CD4+ T-cells are essential for TB-specific immunity [175–177], TB development in the presence of SARS may result from CD4+ lymphopenia during viral infection [178]. Many precautions should had been taken to prevent disease spreading to naive patients during epidemics. For example, Chinese TB patients exposed to SARS in the same hospital ward developed the disease. Healthcare professionals in Taiwan were screened for TB during a SARS-related hospital screening in April 2003. Sixty TB cases were identified [179]. Another study showed that one TB patient contracted SARS coinfection due to an incorrect admission to a cohort of SARS patients [180]. This emphasizes the importance of watching for other infectious diseases, such as TB, even when epidemic or pandemic infections take up most of the news [181]. A study of infectious disease incidence in China after the SARS era revealed variations in incidence, mortality, and case-fatality rates of 45 infectious diseases from 2004 to 2013. During this period, Tb was the third most common infectious disease [182].

9.2 | TB and MERS Outbreak

MERS Coronavirus (CoV), which was discovered in Saudi Arabia in 2012 and currently affects 27 countries [183]. *M. tuberculosis* coinfection is especially critical since TB diagnosis may be ignored and overshadowed by concern about MERS-CoV infection, as occurred during the SARS outbreak [184]. Alfaraj et al. [185] reported MERS-CoV and TB coinfection in Riyadh. They looked into two cases where MERS-CoV and pulmonary TB coexisted. The first case was a 13-year-old boy who experienced fever, weight loss, coughing, and night sweats for 2 months. The second case was a 30-year-old female who had a cough, shortness of breath, and weight loss during the first few weeks of her condition. Both individuals had pulmonary TB and tested positive for MERS-CoV. Both experienced long-lasting symptoms that predicted their likelihood of contracting TB and MERS-CoV. This study emphasized the significance of thoroughly evaluating suspected MERS-CoV patients for other infectious disorders, such as TB, to avoid nosocomial transmission [186].

9.3 | TB and Ebola Virus (EBOV) Outbreak

WHO reported an EBOV outbreak in March 2014 in Guinea, a nation with a high incidence of TB and HIV [187]. The deadly EBOV outbreak in West Africa in 2014–2015 profoundly impacted various healthcare sectors, including TB prevention and control initiatives [188]. Ebola negatively impacted the healthcare workforce and services. During the peak of the Ebola outbreak, multiple staff members in all of those countries contracted the disease and died in Ebola treatment facilities. The impact of the Ebola epidemic's interruption of TB services in these nations will likely not be understood for several years. Still, it increased TB transmission, morbidity, death, and reduced patient adherence to TB treatment. International and regional failures to act quickly and effectively contributed to the Ebola outbreak [189, 190]. It was another reminder that health systems must be better prepared for infectious disease outbreaks in the international community, especially in Africa. It exposed African countries' shortcomings and vulnerabilities. As well as underscoring the need to strengthen and protect health services, the report also highlighted the inability to respond effectively to any new emerging or re-emerging infectious disease with pandemic potential [191]. The results of a retrospective cohort study comparing trends in TB incidences pre-, post-, and during the Ebola outbreak in 2014–2016 showed significant declines in TB rates. However, the outbreak did not affect TB patients' treatment outcomes [192].

9.4 | TB and HIV

As well known, TB and HIV are closely related. Patients with HIV/AIDS have a significantly higher risk of developing active TB than patients with healthy immune systems. TB occurs 10% of the time in HIV/AIDS patients [193, 194]. This heightened risk has led to the WHO recommending screening and preventative therapy for all HIV/AIDS patients [195]. There is an established risk of progression from latent TB infection to active TB infection when HIV is present [196]. TB has been affected by the global HIV epidemic in all aspects, including immunopathology, epidemiology, diagnosis, treatments, and preventative measures. Approximately one-quarter of the 42 million HIV-infected people worldwide are also infected with TB, and most of them live in African and Asian nations with inadequate healthcare [194]. TB disease progresses at a rate of 10% per year in HIV-infected people with immunosuppression [197]. HIV-coinfected patients have lower TB diagnostic sensitivity. Standard TB treatment regimens, particularly those without rifamycin throughout, may not be as effective. The treatment process is further complicated by toxicity, malabsorption, drug interactions, and unusual immune responses [198]. HIV pandemics in the early 1990s destabilized TB control in the United States; enormous political and financial resources were required to restore public health systems [199]. As a result of the dual burden of disease and insufficient resources, TB control in Africa and Asia is much more unstable [200]. When we consider the triple infection of HIV/TB/COVID-19, coinfection adversity increases. HIV coinfection with TB can aggravate TB pathogenesis, affecting the mortality rates of COVID-19/TB coinfected patients [201]. Despite the importance of T-cell-mediated immunity in controlling viral progression, COVID-19 efficiently depletes CD4+ T-cells [202]. A significant decrease in CD4+ T-cells reduces interleukin (IL)-2, IL-4, IL-5, and IL-13, which results in active TB illness [203, 204].

9.5 | TB and Measles

TB is one of the world's most serious diseases, particularly in developing countries. Measles also claimed 345,000 lives worldwide

in 2005 [205]. A latent TB infection may become active or exacerbated by measles [206]. By epidemiological findings [207, 208], delayed-type hypersensitivity can potentially suppress measles-induced hypersensitivity.

An analysis of the effects of measles prevalence and vaccination in African countries was conducted by Sato et al. [209] Using data from 46 African countries, they examined how measles infection and vaccination affected five major infectious diseases in Africa, including TB. It was found in this study that a rise in measles prevalence was associated with a rise in TB mortality and prevalence. In addition, they discovered that increased measles vaccination coverage reduces TB prevalence and death.

A measles outbreak also occurred in Korea in 2000–2001. Lee et al. [208] found that among 53,974 measles cases during the outbreak, 47 cases of TB were reported following measles, which was significantly lower than the incidence in the general population (standardized incidence ratio = 0.73; 95% CI = 0.54–0.96). This study found no evidence of an association between measles and TB. This contradicts the classic theory that measles activates TB.

9.6 | TB and Influenza

TB and influenza seem to have a bidirectional relationship in which TB may increase vulnerability to the flu and possible complications. In addition, influenza may do the same for TB. Patients with pre-existing respiratory disorders seem more susceptible to the flu. As a result of such pulmonary sequelae, patients may be predisposed to influenza infection and its complications, including mortality [65, 210]. Moreover, short-term immunosuppression brought on by TB may make patients more vulnerable to viral infection. In South Africa, an increased risk of death due to influenza, among TB patients with influenza has been reported [211]. Since influenza impairs immune function, it stands to reason that influenza might also encourage active TB in patients with latent TB infection [212]. However, proving a causal relationship between the two events is challenging since TB may manifest itself years or even decades after influenza. In Switzerland, pulmonary TB mortality increased during the influenza pandemics of 1889 and 1918 [213]. Also, Wuhan, China's summer influenza outbreak, may be responsible for the rise in TB cases [214]. On the other hand, a study from Thailand found no evidence of an adverse result for individuals with TB and influenza simultaneously [212]. The precise effects of TB and influenza co-infection are still unknown [215].

10 | Conclusion

Before COVID-19, TB was the leading cause of death among infectious diseases. Complications of these two respiratory disorders can be fatal, with serious public health consequences. The COVID-19 pandemic has adversely affected all TB eradication programs because of the enormous workload on healthcare facilities and the redirection of funding. TB eradication was hampered by these factors, which resulted in longer diagnosis delays. It is essential to recognize that TB is a multidimensional problem that requires a broader approach to solve. Further studies are recommended to follow the pattern and characteristics of TB in the post-pandemic era to become well-prepared for managing the possible outbreaks in the near and far future.

Author Contributions

All the authors had substantial contributions to the conception of the work. Drafting of the work was done by all the authors. All authors have read and approved the final version of the manuscript had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Transparency Statement

The lead author Abolfazl Fateh affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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