



REVIEW PAPER

Tuberculosis epidemic in India – a systematic review

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ABSTRACT

Introduction and aim. India, accounting for approximately 26% of the global tuberculosis (TB) burden with a significant proportion of 0.11 million (6%) pediatric TB cases. The goal of this systematic review paper is to provide a thorough analysis of the TB epidemic in India, including information on the severity of the illness and challenges associated with diagnosis and treatment, the risk factors for transmission and progression of the disease, and the advancements and difficulties encountered in efforts to control at community level.

Material and methods. The terms “Tuberculosis in India,” “Drug-Resistant Tuberculosis,” “Tuberculosis and Associated Co-morbidities,” “Diagnosis of Tuberculosis,” “Prevention of Tuberculosis,” and “Treatment of Tuberculosis,” keywords were used to search in number of international electronic databases, including “Google Scholar,” “PubMed,” and “DOAJ.”

Analysis of the literature. Diagnosis and treatment of TB are significantly complicated by co-morbid condition such includes alcoholism, diabetes, HIV, undernutrition, diabetes and HIV. In addition, there may be treatment delays, and the extra-pulmonary or drug-resistant TB due to ignorance, misunderstandings, and lack of education among TB patients, and medical professionals, which ultimately increases morbidity and mortality.

Conclusion. Poverty, undernutrition, inadequate healthcare infrastructure, and co-morbidities, which frequently complicate TB diagnosis and treatment, must be addressed in addition to the critical need to prioritize TB research and development.

Keywords. drug-resistant tuberculosis, tuberculosis, undernutrition and tuberculosis

Introduction

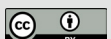
For decades, tuberculosis (TB), caused by the bacteria *Mycobacterium tuberculosis*, has been a major global concern. *M. tuberculosis* bacteria divide TB into two types based on the organs infected: pulmonary tuberculosis (PTB), which primarily affects the lungs, and extra-pulmonary tuberculosis (EPTB), which primarily affects other organs such includes pleura, lymph nodes, intestines, genitourinary tract, skin, bones and joints, and brain in the body.¹⁻⁴ TB is a highly contagious and transmissible disease that spreads naturally from person to person through sneezing or coughing in the vicinity.⁵⁻⁷ The World Health Organization (WHO) estimates that 10.6 million people worldwide

will have TB (in 2021), including 6 million men, 3.4 million women, and 1.2 million children.⁸ According to the Global Tuberculosis Report (2022) claimed that TB killed 1.6 million people and was difficult to diagnose and treat. Similar to this, in 2022 the high number of new cases (10.4 million) and fatalities (1.8 million) from TB, India’s leading cause of illness and mortality, is made worse by these statistics (Fig. 1).^{7,9,10} In the same vein TB is commonly prevalent in 0–9-year-old children in India, consisting 0.11 million pediatric cases especially among those who have immunological weaknesses.¹¹⁻¹⁵ The COVID-19 pandemic, on the other hand, has occasionally hampered the access to essential healthcare services, resulting in an increase

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in the incidence of various community-borne diseases, mortality, and morbidity.^{1,2}

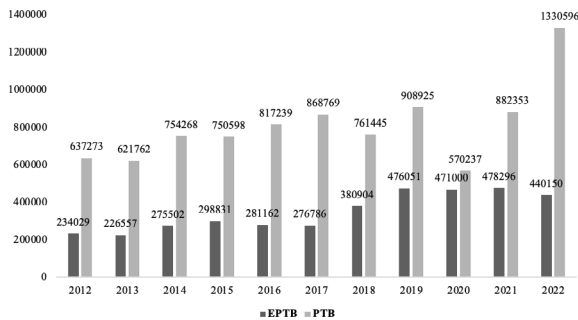


Fig. 1. Bacteriologically confirmed pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB) cases in India (Source: Global Tuberculosis Report 2022, India TB Report 2023)

India has more than 26% of the world's TB cases (in 2022), and undernutrition and poverty are major contributors to the disease's rising prevalence.^{1,2} As a result, treating TB is costly, time-consuming, and has a low success rate.^{1,2,16–22} Co-morbidities that weaken the immune system and increase the risks of TB infection in people over a short period of time include undernutrition, diabetes, HIV, tobacco use, smoking, and alcohol consumption.^{2,21–32} *M. tuberculosis* also has a diverse pattern of region-specific prevalence and susceptibility, genetic mutation over time, space, and environment.^{23,33,34} Nearly one in every two TB patients' household contacts has latent TB, and the severity of the infection is related to the age of the household contacts.^{28,35} Furthermore, old age group healthcare professionals are at a higher risk of developing a particularly latent TB infection due to their longer duration of employment and working in areas with high TB prevalence.^{5,35,36}

Aim

The objective of this study is to provide a concise and comprehensive summary of the TB epidemic in India, with a focus on the disease burden, challenges in diagnosis and treatment, risk factors for TB transmission and progression, and progress and challenges in TB control efforts.

Material and methods

A systematic literature review was conducted using a variety of international electronic databases, including Google Scholar, PubMed, DOAJ, and Government Database including India TB Report, Govt. of India Central TB Division with the search terms 'Tuberculosis in India', 'Drug-Resistant Tuberculosis', 'Tuberculosis and Associated Co-morbidities', 'Diagnosis of Tuberculosis', 'Prevention of Tuberculosis', and 'Treatment of Tuberculosis'. Relevant technical reports and government

databases were identified and reviewed according to predetermined inclusion criteria, which included descriptive studies, review articles, cross-sectional studies, and original survey studies. Government databases were utilized whenever required, along with the Global Tuberculosis Report (2022), to ensure comprehensive coverage of relevant literature and reports. This systematic review study covers literature and reports published between 20 May 2010 and 5 January 2023, and new studies were included during manuscript preparation and final revision. The search results were limited to full articles published in English, and a total of 216 publications, including titles, abstracts, and full texts, were initially identified using the present study's keywords and criteria. Duplicate scientific papers yielded from different search engines were excluded. The details of the literature search, inclusion, and exclusion are summarized in Fig. 2. A total of manuscripts (n=128) was identified and retrieved for detailed evaluation during the short-listing of published literature and manuscripts. Following a thorough review of the published research papers, and government database reports, n=80 were identified as appropriate and were considered for the present manuscript. The finalized manuscript, including both abstracts and full-length manuscripts, was downloaded to interpret the present study, revise it, and complete this review manuscript.

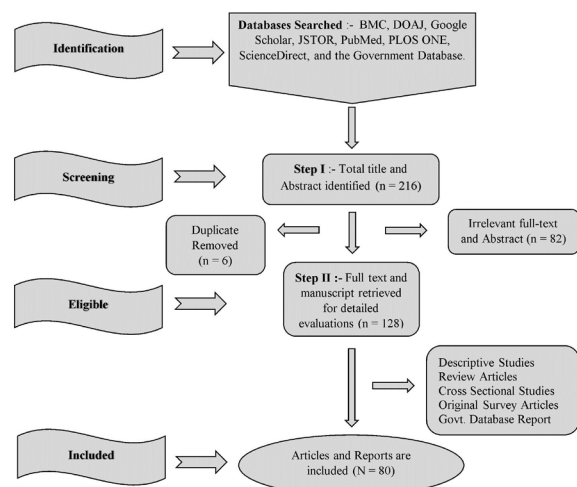


Fig. 2. Flow chart shows the research study selection process

Analysis of the literature

Occurrences of TB in India

The incidence of TB decreased by 18% from 2015 to 1.6 million cases in 2020, but following the COVID pandemic (in 2021), there was an 18% increase in cases to 2.14 million in India (Fig. 1), resulting in 40% of the population (1.9 million) having latent TB infection, with 10% of those cases expected to develop into active

TB.^{21,31,37} Despite the massive TB burden, India is actively spending \$23 billion a year to successfully reduce the global TB burden through the World Health Organization’s End Tuberculosis Strategy and the Revised National Tuberculosis Control Program (RNTCP), as well as by establishing “Nikshay,” an open web service that allows health organizations and medical councils to more easily track antibiotic use in real time as part of the Direct Observed Treatment Service.^{38–40} However, there are still a lot of gaps in the fight against TB because of a lack of information, a lack of awareness, a lot of myths and misconceptions, and the failure to pay fees to accredited social health activists (ASHA) workers.^{3,5,35} According to the National Family Health Survey-5 (NFHS-5) and several research investigations, certain social determinants are found to have the highest prevalence of TB (Fig 3).^{5,29,31,37,41,42} Although it is evident that rural and urban slums areas have a comparatively greater TB incidence, the prevalence has decreased as people’s socioeconomic position has improved.^{31,40–44}

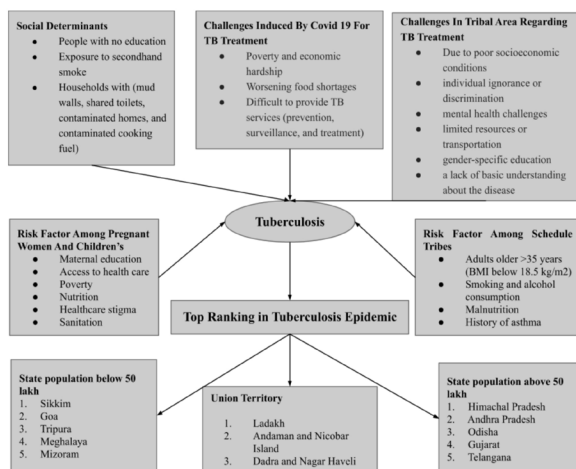


Fig. 3. Representing the risk factors, challenges and ranking (States and Union Territory) them with the tuberculosis epidemic in India

The burden of tuberculosis in different states of India

The vast geographic area and biological diversity of India have resulted in a number of epidemics that have harmed public health and caused catastrophic costs, such as TB, which accounts for a sizable portion of TB cases worldwide.^{11,34,45} Similar to this, the Seasonal Waves of Respiratory Disorders study discovered strong correlations between seasonal variation and a high prevalence of TB, with symptoms worsening slightly in the summer and exacerbating in the autumn as a result of climatic variations in various parts of India.⁴⁶ Similarly, research has revealed that atmospheric temperature is an important factor and has a significant association with the progression of TB during the summer and monsoon seasons (Fig. 4).⁴⁷

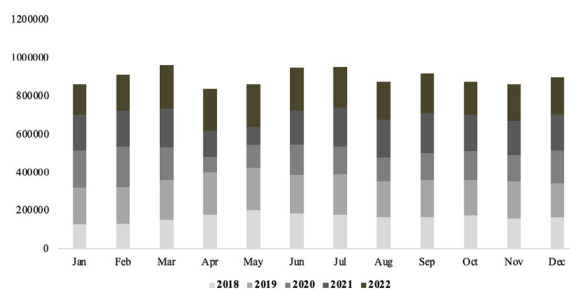


Fig. 4. Tuberculosis cases notified per month in the last five years (fluctuation of cases per month) (according to India TB Report 2019–2023)

According to the National Tuberculosis Reports (2022), (2023), the burden of TB in India is distributed across states, as shown in Fig. 5(a) and 5(b).^{48,49} As shown in Fig. 3, the report also identify the top five states and territories with the highest rankings. Despite this difficult situation, India is committed to eliminating TB by 2025, with the assistance of the National Tuberculosis Elimination Program (NTEP), which collects the majority of TB statistics in India and was previously called the RNTCP.^{22,48–53} According to the National Tuberculosis Report (2023), Kerala, Tamil Nadu, Assam, and Uttar Pradesh are the states that performed relatively better in terms of TB elimination than the majority of states in India in 2022.⁴⁹ Regarding performance Kerala created the System for Workplace Engagement to Eliminate and stop the spread of TB among employers in a variety of workplaces and industries.^{48,49,51–53}

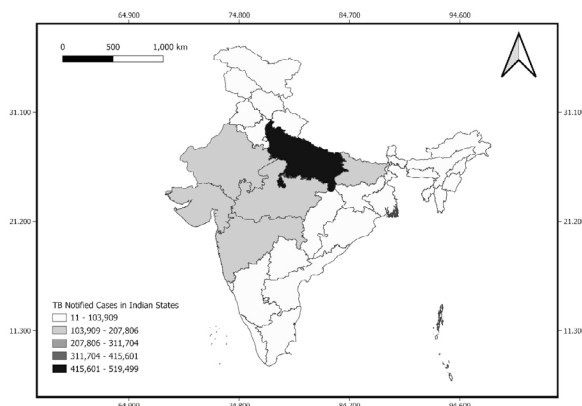


Fig. 5a. Distribution of the Tuberculosis Epidemic in Different States of India in 2021 (India TB Report 2022)

To understand the risk of TB among COVID patients and therefore help the program management design policies, the Tamil Nadu Post-COVID catch-up campaign was conducted.^{48,49,51–53} Intersectoral engagement with the Assam Branch of the Indian Tea Association was conducted in Assam to identify TB cases in tea gardens and the transgender community.^{48,49,51–53} In Uttar Pradesh, active case finding under the Dastak Abhi-

yan was carried out by going door to door to screen the community, eradicate communicable diseases, and inspire Gram Pradhan to actively participate in active case finding of TB.^{48,49,51–53}

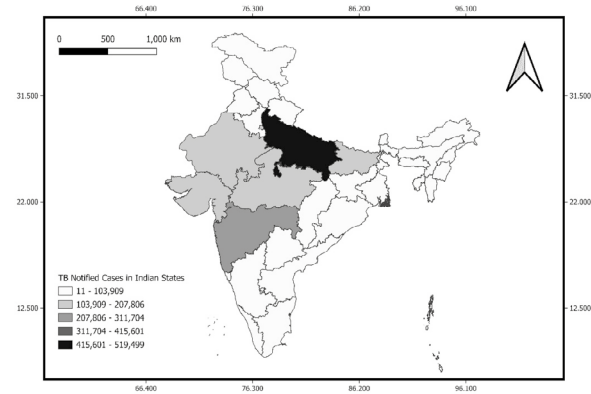


Fig. 5b. Distribution of the Tuberculosis Epidemic in Different States of India in 2022 (India TB Report 2023)

The scope of the TB epidemic in India was determined through prevalence studies. According to the National Tuberculosis Report (2023), men have a slightly higher prevalence of TB than women (1.37 million versus 0.78 million) (Fig. 6), which may be attributed to men’s more intense outdoor activities and women’s greater likelihood of accessing health services.^{1,3,4,20,38,41,46,54,55} In fact, many PTB patients used dangerous sputum disposal techniques, which are dominant in male and illiterate patients from lower socioeconomic groups.^{1,22,31,41–44,56}

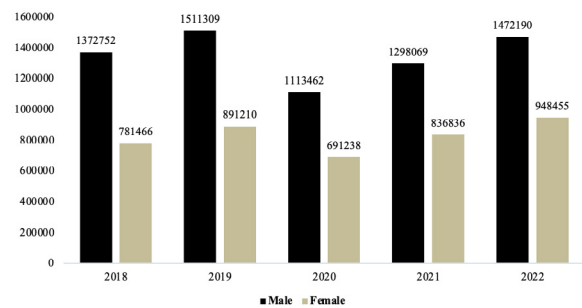


Fig. 6. Gender-specific data on TB-notified cases (India TB Annual Report 2019–2023)

TB is the most lethal infectious disease in the world, and genital TB is a common complication in infertile people who receive inadequate clinical care.^{30,57} When a pregnant TB patient cannot adequately protect, medications like isoniazid prophylaxis (3-6 months) or the Bacillus Calmette-Guerin (BCG) vaccine are administered to protect the neonates or newborns.^{11,57,58} Factors mentioned in Fig. 3 are the primary causes of an increase in risk factors among children and pregnant women, all of which contribute to the spread of TB.^{11,57,58}

In addition to gender differences in TB prevalence, mortality rates increased dramatically with age, being 17 times higher in children under 15 years and more than twice as common in adults 60 and older than in those between the ages of 15 and 59.^{1,3,4,10–12,20,28,38,41,43,46,59} Furthermore, the COVID-19 reaction-induced lockdown has resulted in poverty and economic hardship, worsening food shortages and making it more difficult to provide various TB services such as prevention, surveillance, and treatment to the vulnerable segment.^{13,22,31,44,60} Children with TB had significant implications or problems during the COVID epidemic, such as requiring more mechanical breathing, being hospitalized for longer periods of time, and having poorer outcomes.^{11,13,14}

Scheduled Tribes represent 8.6% of India’s population with having high TB prevalence (703 per 1,00,000) as compared to national TB average cases (256 per 1,00,000).^{6,15,16,22,61} Individual patients in tribal areas in India face major challenges due to poor socioeconomic conditions, socio-cultural variables, individual ignorance or discrimination, mental health challenges, limited resources or transportation, gender-specific education, a lack of basic understanding about the disease, and difficulty accessing the healthcare facility.^{1,3,22,43,60–63} According to studies by Rao et al.²⁹, Bhat et al.⁵⁵, and Thomas et al.¹⁶, PTB exposures were more prevalent among tribal groups, and 2.8 times higher prevalent among males than females.^{16,22,29,55,63}

Drug-resistant tuberculosis

According to current trends, drug-resistant tuberculosis (DR-TB), which is resistant to a variety of anti-tuberculosis drugs, is a serious problem in the Indian population, and as a result, it has become a new impediment to India’s efforts to combat the illness.^{33,36,45,56,59,64,65} The four first-line antibiotics for tuberculosis are rifampicin, isoniazid, pyrazinamide, and ethambutol. They are typically used in conjunction with other TB medications for the first 6 to 9 months of a patient’s treatment.^{5,19,33,65} Unfortunately, all TB vaccinations that were previously effective in preventing the disease are no longer effective, and multidrug-resistant tuberculosis (MDR-TB) has begun to emerge.^{56,59} There are number of factors, such as treatment failure, delayed diagnosis, financial difficulties, missed doses, drug side effects, dissatisfaction with services, lack of TB awareness, limited education and transportation, inconvenient clinic hours, prolonged treatment, non-adherence, alcoholism, illiteracy, other commitments during treatment, and insufficient support systems, have an impact on the spread of DR-TB.^{5,38,56,64} Additionally, traditional healers, a non-allopathic provider, a private physician, and independent practitioners have a significant role in delaying the prevention, detection, and treatment of TB in both rural and urban regions, which ultimately leads

to DR-TB.^{22,33–36,38} Furthermore, healthcare professionals can contribute to TB treatment failure due to various factors, including inadequate monitoring systems, a lack of courier services, insufficient knowledge and resources, increased workload, and a shortage of diagnostic kits.^{3,5,6,64,66,67}

Resistance to frequently given anti-tuberculosis medications results in extensively drug-resistant tuberculosis (XDR-TB) and MDR-TB.^{7,40,64} Furthermore, XDR-TB, a subtype of MDR-TB, is resistant to isoniazid, rifampicin, and any of three second-line injectable drugs (e.g., levofloxacin, moxifloxacin, and bedaquiline), whereas MDR is only resistant to drugs of the isoniazid and rifampicin types.^{33,36,45,59,64,65} Risk factors for MDR-TB include male gender, age over 60, living in crowded or congested environment using indigenous stove (Chulha), prior TB treatment, contact with an MDR patient, and being from a hilly region.^{40,45,59,68–70}

India is the country with the greatest rates of TB related morbidity and mortality, along with risk factors such as undernourishment, alcohol smoking, diabetes, and HIV infection (Fig. 7).^{2,9,10,23,24,26,27,29–32,54,56,71} Similarly, these co-morbidities act as a risk factors for the activation of latent TB into active TB.^{21,28,35,37,42} Moreover, misconceptions about TB transmission, such as the false beliefs regarding its spread through eating, sharing utensils, or touching patients, coupled with the social stigma faced more likely by women, contribute to social exclusion, avoidance, discrimination, rumors, verbal abuse, lost marriage prospects, and parental neglect.^{12,25,62}

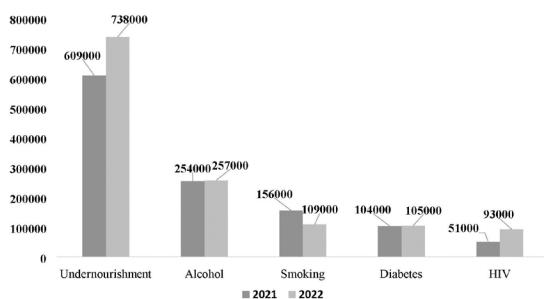


Fig. 7. Prevalence of tuberculosis-associated risk factors in India (Source: India TB Report 2022–2023)

Studies, highlighted that due to a lack of knowledge about TB, healthcare professionals either avoid dealing with TB patients or fear them, believing they will spread the disease, or lack trust and coordination with the government healthcare system.^{5,62,67,72} In contrast, mental health problems are also a major concern usually present in TB patients due to rumors and misconceptions among them, healthcare professionals, and society.^{5,12,62,67,72} Misconceptions about TB transmission, such as the false beliefs regarding its spread through eating, sharing utensils, or touching patients, coupled

with the social stigma faced more likely by women, contribute to social exclusion, avoidance, discrimination, rumors, verbal abuse, lost marriage prospects, and parental neglect.^{12,25,62}

Undernutrition and tuberculosis

Undernutrition, which affects 6.90 million people globally, is on the rise, negatively impacts people's immune systems, and is a risk factor in TB, although it is described as an individual's intake of insufficient calories and nutrients to meet their need to maintain good health.^{8,32,73,74} Several studies have found that adults aged 15–49 years with a low body mass index (BMI) (<18.50 kg/m²) are more likely to develop TB, experience poor treatment outcomes, and have a higher risk of death.^{9,28,31,37,38,41,73,74} Rural areas, scheduled castes and tribes, other socially and economically backward classes, states with higher levels of poverty, and migrant workers all have high rates of undernourishment, which increases their risk of developing TB.^{1,5,22,31,37,42} Nearly half of all active TB cases in women and all cases in males have undernutrition as a major risk factor.^{9,31,73}

Diabetes and tuberculosis

India faces a dual challenge of TB and diabetes. Diabetes is a metabolic disorder characterized by inadequate insulin production by the pancreas, leading to treatment failure and mortality and potentially contributing to the spread of TB.^{20,28,66,75} It is a fact that diabetes is a well-known major risk factor for more than 25% of TB patients, which also plays a major role in altering the disease pattern from PTB to EPTB or DR-TB (rifampin resistance) due to the weak immune system.^{3,20,23,30,32,71,75} Patients with PTB over 50, generally men with poor psychological status, who had a higher BMI, sedentary occupation, and positive family history of diabetes and were receiving Category II treatment were more likely to acquire diabetes and hypertension.^{62,66} Diabetes has been strongly associated with an increased risk of early mortality in TB patients and has created an enormous challenge for TB treatments.^{20,60,66,75}

Human immunodeficiency viruses (HIV) and tuberculosis

India has the highest number of HIV infections in Asia and the third-highest total number of infected people worldwide.^{16–20,54} Similarly, studies have revealed that participants' views toward people with HIV/AIDS were much more connected with their sentiments toward people with TB than with their attitudes toward people who act as sex workers.^{14,17} However, it was shown that HIV-positive status, a low BMI or undernutrition (<18.5 kg/m²), a male individual, and a history of prior TB treatment were substantially connected to PTB or EPTB and DR-TB.^{4,6,41,54,65,73} TB has become more difficult to

treat as MDR-TB and XDR-TB forms have emerged, as has HIV coinfection.^{2,58,76} The significant factors in the positive association of TB and HIV among sexually active age groups individuals is their poor knowledge of TB and its modes of transmission among.^{2,24,54,58,76} In several studies, it is noted that due to HIV epidemics, deficiency of vitamin D and C, and greater use of immunomodulating medications, EPTB is becoming more common.^{3,18–20,54,71}

Tobacco consumption and tuberculosis

In India, tobacco is a major health issue that contributes to a number of health problems, including mouth cancer, chronic bronchitis, and cardiovascular and lung disorders that ultimately cause millions of deaths annually.^{21,33,46,56,65,69,77} In the TB patient, tobacco smoking affects the efficacy of TB treatment and raises the risk of infection, which increases the likelihood of DR-TB and ultimately leads to mortality.^{28,33,65,77} Several studies revealed that smokers were four times more likely to get active or latent TB due to long-time of smoke exposure, not maintaining safe distance and following unhygienic lifestyle.^{21,69,77} There is a strong association between TB and tobacco use among males, lesser educated individuals, older people, alcoholics, and residents of rural and slum areas, mainly in thatched houses.^{29,69,71,77}

Alcohol consumption and tuberculosis

Alcohol consumption is observed as a serious public health concern on a global scale since it drastically raises morbidity and mortality as well as produces a variety of social issues and health concerns over the course of a lifetime.^{26–28,41,71} In a similar vein, numerous researchers have discovered a positive correlation between alcohol use and TB patients. Risky alcohol consumptions have also been associated to a delay in seeking treatment for TB as well as a poor treatment outcome that can lead to DR-TB.^{26,27,41,71} A father's history of alcohol consumption, residing in an area where illicit alcohol was being produced, and also belonging to a vulnerable segments of the population are all significant risk factors for consumption of alcohol and rising TB burden.^{26,40} However, in several studies have revealed that TB patient consume alcohol mainly due to anxiety, depression, family burden, social stigma and misconceptions of TB epidemic.^{12,25,62}

Adopted measures, challenges faced, and tuberculosis-related policies

According to the annual TB report, India is home to 26% of TB cases worldwide, and males are more likely to contract the disease than females (283 per 100,000 men versus 186 per 100,000 women) (162 per 100,000).^{20,48,49} Therefore, the total mortality rate due to TB is 0.20 individuals per 1000 every day. However, not all stra-

ta bear the same amount of the TB burden; the tribal community is one of the most severely impacted groups in the country.^{15,16,28,48,49,63} Additionally, several studies found that more than two-thirds of TB cases are observed in the economically productive age range (14–59 years).^{1,3,4,9,10,20,31,37,38,40,41,43,46,59,73,74} The international health community, which has established multiple 5-year targets for TB elimination, has proposed a method combining improved diagnostics, medications, and vaccinations to identify and treat both latent and active TB infections in order to meet the 2050 target.^{15,48,49,51} The Joint Effort for Tuberculosis Elimination Program, with TB professionals, NGOs, and private practitioners all playing crucial roles in assisting patients seeking TB treatment, has also proven successful in providing quality TB services and facilities to patients.^{5,60,62,72} Additionally, the President of India established the Pradhan Mantri TB Mukh Bharat Abhiyan to hasten the elimination of TB by 2025. Through community support and the use of Corporate Social Responsibility initiatives, Ni-kshay Mitra and Ni-kshay Digital Porat were introduced as part of this project to provide patient support and enhance the treatment outcomes for TB patients.^{48,49} In order to provide nutritional support for all TB patients, the Indian government introduced the direct benefit transfer (DBT) programme in March 2018.^{22,39,48,49,51–53} This includes depositing INR 500 (roughly \$7) into each TB patient's bank account, but delays were occurring in the DBT program due to the complexity of processes.^{5,22,39,61} However, NTEP is also continuously taking steps to increase awareness and improve TB services, but its implementation is difficult, particularly in rural areas, because in rural areas various community have their own distinctive ways of addressing health issues, which is one of the main reasons for postponing the diagnosis and appropriate treatment of TB.^{15,16,60,78} Additionally, studies have shown that social support is essential in order to improve the condition because patients with this chronic illness experience significant declines in their physical, social, economic, psychological, and emotional well-being even after therapy has ended.^{70,79}

It has been discovered that people with no prior experience of TB are strongly associated with improved treatment outcomes.^{4,40,79} But in the case of MDR-TB patients, they exhibited worse treatment results than the general TB patient and were unable to receive a proper diagnosis when tested at RNTCP diagnostic facilities.^{33,45,65,80} Additionally, household members are at high risk of infection when having close contacts with individuals having MDR-TB or during treatment.^{14,28,36}

The COVID-19 pandemic had a significant impact on TB notification methods, but several researchers have also reported that digital TB storytelling on Frequency Modulation radio has enhanced TB awareness

and knowledge. As a result, there has been an increase in active case-finding and better control of TB spread particularly among individuals belonging to vulnerable segments affected by poverty and undernutrition.^{12,31,70,78} Similar to this, the most popular sources of up-to-date information about TB and the RNTCP were the health education programme, textbook content, and especially the internet and television campaigns.^{12,31,70,78} However, despite people's awareness of TB diseases and knowledge of where to access free treatment and healthcare services provided by the government, there is still a lack of knowledge about the Directly Observed Treatment Service.^{12,49,67,79} This knowledge gap can be attributed to poverty and limited awareness of the importance of the Directly Observed Treatment Service.^{5,39,61}

Recommendations

Key measures should be implemented to reduce the prevalence of TB in India. First and foremost, there is a need for greater access to appropriate treatment and modern medical methods for diagnosis. Rapid and extremely sensitive testing processes, particularly in rural regions, should be expanded. Second, direct money transfers should be made available on a regular basis to TB patients registered on the Nikshay portal in order to provide financial assistance. Third, to address undernutrition among TB patients, enhanced distribution of resources and nutritional support should be ensured. Regular follow-ups with patients and social supports are also vital. Finally, thorough outreach campaigns utilizing traditional, and web-based forms should be established to improve knowledge of TB, its prevention, and treatment alternatives. These initiatives, particularly in impoverished areas, can assist to achieving TB eradication by 2025.

Conclusion

With a high case load and related problems, TB remains a major public health concern in India. Both genders are affected, with men having an admittedly higher occurrence. Undernutrition, diabetes, HIV, tobacco and alcohol usage, and mental health problems all contribute to the spread and progression of TB. Further, drug-resistant TB has emerged as a serious impediment to TB control efforts, worsening treatment outcomes even further. Despite the hurdles, India has introduced a variety of TB-fighting strategies and policies, such as enhanced diagnoses, treatments, Pradhan Mantri TB Mukh Bharat Abhiyan and nutritional support programmes.

Declarations

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Author contributions

Conceptualization, P.D. and N.M.; Methodology, P.D.; Software, P.D.; Validation, P.D. and N.M.; Formal Analysis, P.D. and N.M.; Resources, P.D.; Writing – Original Draft Preparation, P.D.; Writing – Review & Editing, N.M.; Visualization, N.M.; Supervision, N.M.; Funding Acquisition, P.D.

Conflicts of interest

Authors declare that there are no conflicts of interest.

Data availability

Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

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