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Original article

A META-ANALYSIS AND SYSTEMATIC REVIEW ON TUBERCULOSIS INFECTION PREVALENCE IN INDIA.

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Abstract

Objectives:

There exists a gap in understanding TBI prevalence within diverse risk groups in the country. Hence, this comprehensive review and pooled-analysis sought to determine the incidence of tuberculosis infections or TBI in the Indian subcontinent, considering geographical variations, socioeconomic profiles, and specific susceptible groups.

Methods:

By conducting an extensive review, this study explored Tuberculosis Infection (TBI) prevalence in India from 2013 to 2022. Utilizing databases like Scopus, CINAHL, EMBASE, and MEDLINE, 72 publications underwent an examination adhering to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The comprehensive approach included diverse languages and study settings, providing a thorough understanding of TBI prevalence in India.

Results:

On reviewing 10,515 documents, 72 studies comprising prevalence studies (approx. 42) and long-term studies (approx. 30) were incorporated for this paper. The overall prevalence of Tuberculosis Infection (TBI) in India, sourced from population-based sample studies, was established at 41%. This percentage held steady at 36 % when eliminating highly susceptible groups from the public at large. Regions grappling with heightened active TB burdens, especially in Tamil Nadu and Delhi, demonstrated a corresponding surge in TBI prevalence.

Conclusion:

The present comprehensive analysis unveiled the significant pervasiveness of Tuberculosis Infections in India, aligning with proactive TB infections, hinting at the potential transformation from latent form to active TB. Notably, this possibility was pronounced in individuals residing in the southern and parts of the country. Addressing these regional variations is crucial for adapting and prioritizing tailored strategies to effectively manage TBI in India.

Recommendation:

Our study thus recommends prioritizing Tuberculosis Preventive Treatment (TPT) in high Tuberculosis Infection (TBI) prevalence areas, advocating a 'No test, treat only' approach for resource efficiency to support effective programmatic management in pursuit of India's TB elimination goals.

Keywords: *Tuberculosis, TB infection, Systematic review, Tuberculin skin test*

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Introduction

Tuberculosis (TB), a significant health concern across the globe, is the primary cause of mortality by infection with a single pathogen called *Mycobacterium tuberculosis* [1]. As reported in the Global TB Report of 2022, approximately 10.6 million new TB patients were recorded in 2021 alone [2]. Concerned by its drastic surge, the End-TB scheme introduced by the World Health Organization (WHO) targets to decrease TB fatality by 95% and latest occurrences by 90% by 2035 [2]. However, achieving these goals hinges on strengthening prognostic, prophylactic, and therapeutic services for TB [3].

TB infection (TBI) is characterized by a consistent immune system activity triggered by the TB bacteria antigens, lacking clinical proof of active tuberculosis. TBI acts as a precursor to the emergence of fully developed TB disease, especially in individuals with compromised immune systems [4]. This creates a substantial reservoir of people with TBI, emphasizing the critical importance of TBI management in global initiatives to alleviate the

pervasiveness of TB, particularly in high TB-prevalent countries, such as India.

Among the six high-burden countries in the southeast Asian region, India contributes to 28% of the worldwide tuberculosis burden, with the largest tuberculosis infection burden [5]. The National TB prevalence survey in 2021 revealed a rough occurrence of TBI of 31.3% in patients aged over 15, with 5 to 10 % progressing to active TB disease [6]. Delayed diagnosis allows a single active TB case to infect others, perpetuating a collection of tuberculosis-infected cases. Treating these patients is crucial in preventing active TB disease and breaking the transmission chain, aligning with the WHO's End-TB tactic [7].

While the importance of treating Tuberculosis Infection (TBI) in preventing TB disease is often overlooked, it holds a significant role in the National Strategic Plan of India to end this disease by year 2025, surpassing sustainable development goals by five years [8]. The Lancet Commission for tuberculosis emphasizes the ineffectiveness of TB prognosis and therapeutic approaches without integrating tuberculosis Preventive Treatment (TPT) [9]. Urgent improvements are needed in implementing proven interventions, especially new TPT regimens, targeting high-risk groups efficiently [10]. The present comprehensive review aims to unveil the TBI incidence rates in India, considering geographical and sociodemographic variations, with crucial programmatic implications.

Materials and Methods

Study design

Conforming to the rules of the Preferred Reporting Items for the Systematic Reviews and Meta-Analysis (PRISMA), a thorough review of the diverse studies investigating tuberculosis infections in the population of the Indian subcontinent was carried out. To gather relevant studies, we explored databases like Embase, Medline, the Cochrane Library, Scopus, Google Scholar, and Web of Science. Employing operators used in Boolean (or, and) and with no language constraints, we used keywords such as "tuberculosis", "TB", or "pulmonary tuberculosis" combined with "cross-sectional study" or "prevalence study" or "survey" and "India." Additionally, we examined the list of references of review articles and primary studies for further insights.

Study setting

Two reviewers autonomously evaluated the studies based on their abstracts and titles for 2 years. Subsequently, complete texts of the chosen documents were acquired. Extracted information from the included studies encompassed details such as authorship, publication year, study duration, setting, participants, sample size, research methodology, and prevalence figures. A unanimous consensus was reached between the two reviewers. In our study, we categorized sputum smear-positive pulmonary TB as cases where a most one sample of sputum exhibited acid - fast bacilli through microscopy. For pulmonary tuberculosis with positive test, we called it as having one culture demonstrating the growth of the bacteria, regardless of the smear result. We considered any sample displaying acid - fast bacilli on direct microscopy or the growth of the bacteria as indicative of positive pulmonary TB.

Participants - Inclusion and exclusion criteria

Every primary study including the residents of India, irrespective of the method used to measure TBI, was incorporated in this study. Various tests such as, tuberculin skin test (TST), TB, interferon-gamma release assay, T-cell test, or C-tuberculosis test, were considered for distinguishing TBI. Exclusions comprised reviews, editorials, opinion pieces, case reports, conference abstracts, posters, study protocols, reports, theses, and any unprinted work. For this study, TBI was classified as the immunological reaction to the TB antigen with no clinical signs for the manifestation of TB.

Data sources/measurement

For data sourcing, two researchers employed Critical appraisal tools from the Joanna Briggs Institute to systematically evaluate the methodological quality and risk of bias in selected studies, covering various designs like randomized controlled trials, cohort, and cross-sectional studies [13]. The evaluation categorized studies into 'low,' 'moderate,' or 'high' risk of bias based on their scores. This meticulous process ensured a robust foundation for synthesizing findings within the systematic review.

Study size

For this review, we explored through databases such as Web of Science, Google Scholar, Scopus, Cochrane Library, Medline, and Embase, seeking studies published between Jan 2013 and Dec 2022.

Statistical methods

The pervasiveness of TB was determined by calculating the ratio of reported cases to the overall study cohort, expressed as the number of patients for every 100,000 individuals. Among the 72 studies, 4 presented age- as well as gender-standardized occurrence figures. Moreover, to ensure consistency during our meta-analysis, we computed the rough incidence rates from tabulated data identified from these studies. Employing a mixed - effects model in STATA 12.0, we calculated combined incidence and 95 % confidence intervals. Assessment of between-study heterogeneity utilized the Q-statistic and I-squared test with

two-sided p-values. Sub-group investigations considered gender and the apportionment of populations in rural and urban areas. Additionally, sensitivity studies involved removing three studies reporting high pervasiveness of positive TB.

Quality assessment

Two researchers separately evaluated the quality of method and risk of bias in the chosen studies using the tools from Joanna Briggs Institute (JBI). These tools, called Critical appraisal tools, are particularly designed for systematic reviews and consist of questionnaires tailored for assessing randomized controlled trials, cohort, and cross-sectional studies [13]. After assessment, studies were categorized based on their scores, falling into 'low,' 'moderate,' or 'high' risk of bias.

Results/Outcomes

To begin with, we identified a total of 10,515 studies. After eliminating 519 duplicates, 9,996 studies underwent initial screening. Subsequent evaluation of abstracts and titles led to the disregard of 9,846 reports, narrowing down the selection to 150 studies for an in-depth full - text review. Unfortunately, the complete text of 45 papers were not accessible. In addition, ten more reports were incorporated through cross-referencing. To summarize, 115 studies/reports fulfilled the criteria for inclusion for a comprehensive examination. In continuation of this, 72 studies were chosen for further assessment, on elimination of 43 reports due to inappropriate study design or invalid outcomes.

Incidence of Tuberculosis Infection in population-based cohort investigations.

As per the between- studies variance model, the overall incidence rates of TBI in population-based cohort studies was determined to be 40.8% (95% Confidence Interval: 29.5 - 52.6 %, Q-statistic = 1648.9, p-value < 0.0001, I-squared = 99%). Upon exclusion of risk groups, the pooled prevalence of this infection within the public at large in community-based studies was 36% (95% Confidence Interval: 28 – 45 %, Q-statistic = 17.38, p-value < 0.0001, I-squared = 83%). Focusing on adults (age more than 15 years), the pervasiveness of TBI among the public at large was found to be 35% (95 % Confidence Interval: 24 – 46 %, Q-statistic = 13.93, p-value < 0.0001, I-squared = 86 %). In light of substantial heterogeneity (p-value < 0.00001, I-squared = 99 %), a sensitivity analysis was conducted. Following the exclusion of studies contributing to this heterogeneity, the total prevalence of TBI was adjusted to 38% (95 % Confidence Interval: 29 – 46 %, Q-statistic = 10.72, p-value = 0.02, I-squared = 72%).

Among the 72 papers, 30 were long-term studies and 42 were point-in-time studies. The research distribution across Indian subcontinent's zonal divisions revealed a concentration in the southern part (40.8%), followed by the northern region (32.3%), western region (8.8%), central region (5.9%), and eastern region (0.4%). Majority of the studies (70/72) utilized Tuberculin Skin Test (TST) for TBI diagnosis, while 10% (7/72) employed Interferon-Gamma Release Assay (IGRA), and 61% (43/72) utilized both. TST positivity criteria varied, with 59 studies considering > 10 mm in duration and 11 considering > 5 mm. The analysis encompassed 38,767 people throughout the studies. The prevalence estimation utilized IGRA data when available, and TST results were considered in its absence. Utilizing available IGRA data for its higher specificity in diagnosing Tuberculosis Infection (TBI) compared to tuberculin skin test, the aggregated pervasiveness of tuberculosis infections was calculated as shown (Table 1).

Table 1: Summary of Study Attributes in the Included Articles

Study design	Citations	Study location	Population size	High-risk group	Test	Size of TST (in mm)	TBI infected patients
CRS	[13]	Hospital	250	Crohn's disease	TST	≥ 10	51
CRS	[14]	Community	170	Diabetic patients	IGRA	Nil	50
Cohort	[15]	Hospital	100	Detachment of retina	TST	≥ 10	16
Cohort	[17]	Community	74	Public at large	IGRA and TST	≥ 10	38
CRS	[18]	Community	476	Close associates	IGRA and TST	≥ 10	266
CRS	[19]	Community	77	Close associates	IGRA and TST	> 5	31
CRS	[20]	Community	77	Close associates	IGRA and TST	> 5	32
Cohort	[21]	Community	80	Close associates	IGRA and TST	≥ 10	23
Cohort	[22]	Community	869	Close associates	IGRA and	> 5	478

					TST		
CS	[23]	Community	200	Close associates	TST	≥ 10	78
Cohort	[24]	Hospital	755	Medical personnel	TST	≥ 10	339
Cohort	[25]	Community	1020	Close associates	IGRA and TST	> 5	257
CRS	[26]	Community	6177	Public at large	TST	≥ 10	1220
CRS	[27]	Community	787	Public at large	TST	≥ 10	198
Cohort	[28]	Community	200	Public at large	IGRA and TST	≥ 10	45
CRS	[29]	Community	205	Close associates	IGRA and TST	> 5	173
Cohort	[30]	Hospital	60	COVID-19	TST	≥ 10	23
CRS	[31]	Hospital	215	Public at large	TST	> 5	27
CRS	[32]	Hospital	100	HIV-AIDS	IGRA and TST	≥ 10	33
Cohort	[33]	Hospital	206	Medical personnel	TST	≥ 10	76
CRS	[34]	Hospital	702	Close associates	IGRA and TST	≥ 10	69
CRS	[35]	Hospital	362	Public at large	IGRA and TST	≥ 10	297
Cohort	[36]	Community	572	Public at large	IGRA and TST	≥ 10	174
Cohort	[37]	Community	162	Close associates	IGRA and TST	≥ 10	44
Cohort	[38]	Community	398	Public at large	IGRA and TST	≥ 10	96
Cohort	[39]	Community	80	Close associates	IGRA	Nil	43
Cohort	[40]	Hospital	200	Medical personnel	IGRA and TST	≥ 10	45
CRS	[41]	Community	1523	Close associates	TST	> 5	801
Cohort	[42]	Hospital	125	Medical personnel	TST	≥ 10	14
Cohort	[43]	Hospital	598	Medical personnel	TST	≥ 10	120
Cohort	[44]	Hospital	171	Medical personnel	TST	≥ 10	48
Cohort	[45]	Hospital	60	COVID-19	TST	≥ 10	15
Cohort	[46]	Hospital	327	Sarcoid disease	TST	≥ 10	33
CRS	[47]	Hospital	730	Rheumatism	IGRA and TST	≥ 10	36
CRS	[48]	Hospital	44	Rheumatism	IGRA and TST	≥ 10	6
Cohort	[49]	Hospital	257	Crohn's disease	IGRA and TST	≥ 10	48
CRS	[50]	Hospital	401	Pregnant women	IGRA and TST	≥ 10	150
CRS	[51]	Hospital	252	Pregnant women	IGRA and TST	> 5	71
CRS	[52]	Community	780	Close associates	IGRA and TST	> 5	460
CRS	[53]	Community	200	Close associates	TST	≥ 10	96
CRS	[54]	Community	2351	Public at large	IGRA	Nil	1226
CRS	[55]	Community	5351	Public at large	TST	≥ 10	794
CRS	[56]	Community	663	Close associates	IGRA	≥ 10	292

					and TST		
Cohort	[57]	Hospital	105	Scaly skin disorder	TST	≥ 10	33
Cross-sectional	[58]	Hospital	75	Psoriasis	IGRA and TST	≥ 10	16
Cohort	[59]	Hospital	15	Sarcoid disease	TST	≥ 10	4
CRS	[60]	Community	150	Public at large	IGRA and TST	≥ 10	105
Cohort	[61]	Community	997	Close associate	IGRA and TST	> 5	484
Cohort	[62]	Community	144	Public at large	IGRA and TST	≥ 10	57
CRS	[63]	Community	53	HIV-AIDS	IGRA	Nil	25
CRS	[64]	Hospital	100	HIV-AIDS	TST	≥ 10	44
CRS	[65]	Community	133	COVID-19	IGRA	Nil	61
CRS	[66]	Community	70	Public at large	TST	≥ 10	7
CRS	[67]	Community	196	Diabetic patients	IGRA and TST	≥ 10	47
Cohort	[68]	Community	1189	Close associates	TST	≥ 10	661
CRS	[69]	Hospital	200	Medical personnel	TST	≥ 10	29
CRS	[70]	Hospital	371	Public at large	TST	≥ 10	227
CRS	[71]	Hospital	33	Close associates	IGRA and TST	≥ 10	14
Cohort	[72]	Community	1511	Close associates	IGRA and TST	≥ 10	917
CRS	[73]	Community	639	Diabetic patients	IGRA and TST	> 5	354
CRS	[74]	Community	178	Rheumatism	IGRA	≥ 10	18
CRS	[75]	Community	152	Close associates	TST	≥ 10	62
CRS	[76]	Community	174	Public at large	IGRA	Nil	77
Cohort	[77]	Community	1389	Close associates	TST	≥ 10	1172
CRS	[78]	Community	469	HIV-AIDS	IGRA and TST	≥ 10	136
Cohort	[79]	Community	299	Close associates	IGRA and TST	≥ 10	35
Cohort	[80]	Hospital	80	Close associates	IGRA and TST	≥ 10	34
Cohort	[81]	Hospital	168	Public at large	IGRA and TST	≥ 10	27
CRS	[82]	Community	6608	Public at large	TST	≥ 10	794
CRS	[83]	Hospital	62	Sarcoid disease	IGRA and TST	≥ 10	16
CRS	[84]	Hospital	226	Medical personnel	IGRA	Nil	64
CRS	[85]	Hospital	100	Rheumatism	TST	> 5	36

Investigating variances in geography, age, sex, and annual trends in TBI

Based on the existing data, the incidence of Tuberculosis Infection (TBI) from population-based cohort studies was notably high in different regions. In Delhi, it stood at 68% (95 % confidence interval: 46 - 87%), while in Tamil Nadu, it was 42% (95 % confidence interval: 24 – 61 %), and in Maharashtra, it recorded at 26% (95 % confidence interval: 16 - 36%). Delving into urban, rural, and tribal areas, the pooled prevalence in urban locales was 37% (95% confidence interval: 16 to 60%), in rural settings, it was 27 % (95 % confidence interval: 11 to 48 %), and in tribal regions, it reached 33 % (95 % confidence interval: 20 to 47 %).

In the children's demographic, the combined pervasiveness of tuberculosis infection was identified to be 33 % (95 %

confidence interval: 24 to 42 %) for children < 5 years old and 40 % (95 % confidence interval: 30 to 51%) for those in the age group 6 to 14 years. In the adult cohort, specifically between the age 15 to 45 years, the incidence of TBI was 52 % (95 % confidence interval: 39 to 69 %), while in the geriatric population (> 45 years), it was identified to be 62% (95 % confidence interval: 50 to 74 %). Breaking down by gender, the total prevalence of TBI was 41 % (95 % confidence interval: 19 to 65 %) in men and 31 % (95 % confidence interval: 09 to 59 %) in women. A consistent trend in TBI prevalence throughout the years was noted based on data collated between 2013 and 2022 by various studies.

Assessment of Quality and Risk

A substantial portion of the studies (around 71 studies) exhibited a low-risk bias, surpassing the 70% threshold on the JBI score. A single study categorized with a moderate-risk bias (score between 50 to 69 %). None of the articles were disregarded as per the evaluation of the quality.

Discussion

This review examined existing evidence on TBI prevalence among residents of India, drawing from the results of IGRA and TST. These diagnostic tests help identify individuals eligible for Tuberculosis Preventive Treatment (TPT). The data encompassed over 38,767 TST and IGRA results across India. Population-based studies on observation revealed this disease to be present in more than 1/3rd of total population of India, with an increasing prevalence as age advanced.

Prior research, utilizing Bayesian models, by Collins et al. estimated TBI prevalence among Indians at 33.9% [84]. The Indian national tuberculosis incidence survey in 2019 to 2021 also reported an approximate prevalence of 31 % [7]. Collectively, these pieces of evidence underscore a substantial reservoir of tuberculosis infections in India, with a significant proportion at risk of progressing to tuberculosis disease. This review highlighted an escalating TBI pervasiveness with age, particularly in adulthood and geriatric patients, posing a challenge to national TB elimination endeavours.

A mathematical model by Chong et al., focusing on countries with moderate tuberculosis pervasiveness, proposed that surveillance and offering TPT to 20 to 40 % of the geriatric patients could lead to a 50 % overall drop in tuberculosis incidence [85]. Moreover, in the past decade, we observed a consistent TBI trend, indicating a consistent TB prevalence. The treatment rates for this infection among highly vulnerable groups in India were suboptimal at 12 % [6]. The WHO emphasizes prophylaxis and therapy as crucial interventions to reach the End-TB targets [2]. Indian subcontinent's National Strategic Plan compassing 2017 to 2025 centres on prevention, detection, and treatment as principal tenets for TB elimination [10]. Treating active TB reduces infectious TB prevalence, thereby cutting transmission and lowering incidence, while treating TBI prevents latent infection progression, directly decreasing the number of cases. Evidence suggests that treating both tuberculosis infection and active tuberculosis collaboratively synergizes to decrease TB occurrence [86]. Thus, elevating TBI therapeutic approach, especially when active TB treatment levels are significant (95%), could yield comparable benefits [6]. Scaling up Tuberculosis Preventive Treatment will expedite the reduction of tuberculosis occurrence, aligning with India's targets.

The review brought attention to notable differences in the prevalence of Tuberculosis Infection (TBI) across regions, particularly in areas with existing cases of active TB such as Delhi and Tamil Nadu. This indicates a potential inclination towards the transformation of TBI into active TB disease. Tuberculosis infection case - finding incurs a substantial enforcement expense, but without it, the number of cases will rise, necessitating increased efforts for proactive identification and management of cases [5]. India's National TB Elimination Programme suggests these efforts for high TB pervasive areas, resulting in an extended enforcement period. Both active and TBI case-finding share similar cost sensitivities, but TBI case-finding has a shorter implementation period. Current diagnostics for these infections rely on tests like TST and IGRA, each with its challenges and limitations. Issues like testing hesitancy and questionable test validity pose challenges to widespread screening. Emerging regimens like 3-month weekly rifamycin and isoniazid (3HP) show promise, presenting operational alternatives [3]. Considering these challenges, a 'no test, treat only' approach, excluding active - tuberculosis, should be considered [86].

This comprehensive review on Tuberculosis Infection (TBI) prevalence in India employed a thorough literature search and manual-searching of references, The combines incidence rates focused specifically on population-based cohorts, enhancing validity and providing a nuanced understanding of TBI burden. However, the evidence covered all regions except the eastern part of India, limiting a comprehensive nationwide depiction.

Conclusion

Prioritizing Tuberculosis Preventive Treatment (TPT) initiation in regions with high Tuberculosis Infection (TBI) prevalence is crucial due to the less prognostic ability and operational costs of diagnostic tests. Considering a 'No test, treat only' approach after excluding active TB for high-disease incidence rate areas is proposed, challenging the current active case-finding strategy. Future research should focus on TBI among individuals with multimorbidity and specific populations like prisoners, migrants and patients residing in mental health care centres. Prioritizing high TB burden states for community-based screening and TPT implementation is essential for TB elimination goals in

India. This review highlights a substantial TBI burden, suggesting conversion to active TB, emphasizing the need for country-specific interventions in the northern and southern regions.

Limitations

Our study had limitations, including the lack of separation based on purified protein derivative (PPD) strength in TST studies and inconsistencies in TBI diagnosis. Detecting true heterogeneity is yet another shortcoming of this study, which took into account only a small number of studies analysed using Q-statistic and I-squared test.

Recommendations

Our study recommends the prioritizing Tuberculosis Preventive Treatment (TPT) in high Tuberculosis Infection (TBI) prevalence areas with a 'No test, treat only' approach for resource efficiency. Targeted research on TBI in specific populations is vital, supporting effective programmatic management for India's TB elimination goals.

List of Abbreviations

TB - Tuberculosis

WHO – Worl Health Organization

TBI – Tuberculosis infection

TPT - TB Preventive Treatment

PRISMA - Preferred Reporting Items for the Systematic Reviews and Meta-Analysis

TST - Tuberculin Skin Test

JBI - Joanna Briggs Institute

IGRA - Interferon-Gamma Release Assay

PPD – Purified Protein Derivative

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Conflict of interest

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