# Prevalence and factors associated with tuberculosis infection in India

Sriram Selvaraju a, Banurekha Velayutham a, Raghuram Rao b, Kiran Rade c, Kannan Thiruvengadam a, Smita Asthana d, Rakesh Balachandar e, Sampada Dipak Bangar f, Avi Kumar Bansal g, Jyothi Bhat h, Vishal Chopra i, Dasarathi Das j, Shantha Dutta k, Kangjam Rekha Devi l, Gaurav Raj Dwivedi m, Arshad Kalliath n, Avula Laxmaiah o, Major Madhukar p, Amarendra Mahapatra j, Suman Sundar Mohanty q…Balram Bhargava

This passage describes a sub-analysis conducted on data from a recent **National TB prevalence survey in India**. The focus is on individuals aged over 15 years who were tested for tuberculosis (TB) infection using a specific test called the **QuantiFERON-TB Gold Plus (QFT-Plus) assay**. Here’s a breakdown of the key points:

### **1. TB Infection Testing**

* **Target Group**: The analysis was conducted on individuals aged **over 15 years**.
* **Test Used**: The test used to detect TB infection was the **QuantiFERON-TB Gold Plus (QFT-Plus) assay**. This is a blood test that measures the immune system's response to TB bacteria.
* **Definition of TB Infection**: A person was considered to have a TB infection if their **QFT-Plus test result** was **greater than 0.35 IU/ml**. This value is a threshold used to determine if the test is positive.

### **2. Statistical Estimates**

* **Prevalence**: The study calculated the **prevalence** of TB infection, which refers to the proportion of people in the study who tested positive for TB.
* **Prevalence Ratio (PR)**: The **prevalence ratio** was calculated to compare the prevalence of TB infection between different groups within the study. The PR tells us how much more or less common TB infection is in one group compared to another.
* **Adjusted Risk Ratio (aRR)**: The **adjusted risk ratio** was also calculated. This statistic adjusts for various factors that might influence the risk of TB infection, giving a clearer picture of the relationship between these factors and TB infection. For example, it might adjust for age, gender, or other variables.
* **Confidence Intervals (CIs)**: The results are presented with **95% confidence intervals**. This means the researchers are 95% confident that the true value lies within the interval range provided.

### **Summary:**

The sub-analysis focused on individuals over 15 years old from a national TB survey in India, who were tested for TB infection using the QuantiFERON-TB Gold Plus assay. A positive TB infection was defined by a test result greater than 0.35 IU/ml. The analysis calculated the prevalence of TB infection, comparing it across different groups, and adjusted for various factors to better understand the risk, all while providing confidence intervals to indicate the reliability of these estimates.

This passage provides results from an analysis of 16,864 individuals who were tested for tuberculosis (TB) infection. Here’s a breakdown of the key points:

### **1. Prevalence of TB Infection**

* **Total Individuals Analyzed**: The study included **16,864 individuals**.
* **Prevalence of TB Infection**: Among these individuals, **22.6%** were found to have a TB infection. This means that out of every 100 people tested, about 23 had a TB infection.
* **Confidence Interval (CI)**: The prevalence estimate is given with a **95% confidence interval** of **19.4% to 25.8%**, indicating that the true prevalence of TB infection in the population is likely to fall within this range.

### **2. Factors Associated with Higher Risk of TB Infection**

The study identified several factors that are more likely to be associated with a higher risk of TB infection. These are expressed as **adjusted risk ratios (aRR)**, which account for other variables in the analysis.

* **Age > 30 Years**:
  + **Risk**: Individuals over 30 years old are **1.49 times** more likely to have a TB infection compared to those 30 years or younger.
  + **95% CI**: The confidence interval for this risk ratio is **1.29 to 1.73**, meaning the increased risk is statistically significant.
* **Being Male**:
  + **Risk**: Men are **1.26 times** more likely to have a TB infection compared to women.
  + **95% CI**: The confidence interval is **1.18 to 1.34**, indicating a reliable association between being male and a higher risk of TB infection.
* **Residing in an Urban Location**:
  + **Risk**: Individuals living in urban areas are **1.58 times** more likely to have a TB infection compared to those living in rural areas.
  + **95% CI**: The confidence interval is **1.03 to 2.43**, showing a significant but wider range, which means the effect is more variable but still significant.
* **Past History of TB**:
  + **Risk**: People with a past history of TB are **1.49 times** more likely to have a TB infection again.
  + **95% CI**: The confidence interval is **1.26 to 1.76**, showing a strong association between past TB and current infection risk.

### **Summary:**

In this study of 16,864 individuals, 22.6% were found to have a TB infection. The analysis identified that people over 30, men, those living in urban areas, and individuals with a past history of TB are more likely to be infected. These associations were statistically significant, with the adjusted risk ratios and confidence intervals providing insight into how much more likely these groups are to have TB infection compared to others.

About one fourth (22.6%) of the individuals were infected with TB in India. Individuals aged > 30 years, males, residing in urban location, and those with past history of TB were more likely to have TB infection. Targeted interventions for prevention of TB and close monitoring are essential to reduce the burden of TB in India.

Tuberculosis (TB) is the major cause of mortality and morbidity among the communicable diseases. Globally, an estimated 10 million people develop TB and over a million deaths occur annually [[1]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib1). India accounts for about 25% of global TB burden, with an estimated TB incidence of 2.77 million in 2022 [[2]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib2). India is committed to end TB by 2025 [[3]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib3). In this context, it becomes imperative to address Latent [TB infection](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tuberculosis) (LTBI) which is the immune response to stimulation by [Mycobacterium tuberculosis](https://www.sciencedirect.com/topics/medicine-and-dentistry/mycobacterium-tuberculosis) antigens in the [absence](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/epileptic-absence) of clinically active TB [[4]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib4). A mathematical modelling study estimated 1.7 billion with LTBI globally in 2014 [[5]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib5). Individuals with TB infection can subsequently break down to TB disease. The lifetime risk of developing TB in healthy individuals is 5–10% which however increases in the presence of co-existing conditions such as HIV, undernutrition, diabetes and habits which include smoking and alcohol use [[4]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib4), [[6]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib6). Annual risk of TB infection in India by [Tuberculin](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tuberculin) skin test (TST) surveys has been reported as 1.5% in 2005 [[7]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib7). Studies in India have quantified the magnitude of TB infection in high-risk groups for TB which include household contacts, diabetes mellites, [rheumatoid arthritis](https://www.sciencedirect.com/topics/medicine-and-dentistry/rheumatoid-arthritis), refugees, [health care](https://www.sciencedirect.com/topics/medicine-and-dentistry/health-care) workers [[8]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib8), [[9]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib9), [[10]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib10), [[11]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib11), [[12]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib12), [[13]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib13), [[14]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib14). In a TB endemic country like India, it is essential to understand the current burden of TB infection at the population level. A critical component of End TB strategy is treatment of LTBI to prevent active TB disease [[15]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib15). The objective of the present analysis is to estimate the prevalence of TB infection among general population in India. The factors associated with TB infection were explored.

## Methods

Individuals who were tested for [TB infection](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tuberculosis) by [Interferon Gamma](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/interferon-gamma) Release Assay (IGRA) in the National TB prevalence survey in India were included in this sub-group analysis. In brief, the TB prevalence survey which was a cross-sectional study was conducted in 443 clusters across India during the period 2019–2021 to estimate the prevalence of microbiologically confirmed [pulmonary TB](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-tuberculosis) in those aged > 15 years. Participants willing for the study were interviewed using a semi-structured interview schedule after obtaining [informed consent](https://www.sciencedirect.com/topics/medicine-and-dentistry/informed-consent). Data on demographic profile, social habits, co-morbid conditions, health-seeking behaviour, [TB treatment](https://www.sciencedirect.com/topics/medicine-and-dentistry/tuberculosis-treatment), symptoms were collected. Chest x-ray was taken for all survey participants except those bed-ridden or pregnant. [Body weight](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/body-weight) (Kg) and height (cm) was recorded. Point of care blood test for blood sugar and haemoglobin was done. Study participants were eligible for [sputum](https://www.sciencedirect.com/topics/medicine-and-dentistry/sputum) collection if they had symptoms suggestive of TB, if on current TB treatment or with a past history of TB or with abnormal chest x-ray. CBNAAT, liquid culture and smear microscopy was done in the sputum specimen. Chest x-ray reading was done by Medical Officer and by Tele radiologist.

### Blood test for IGRA

IGRA testing was planned in 52 clusters which were proportionately distributed based on the total number of clusters in the National TB prevalence survey in each of the 20 State groups. Within each State group, the clusters were randomly selected for IGRA testing. Out of the 52 clusters, we were able to conduct IGRA testing in 26 clusters at the National level due to COVID-19 pandemic, covering atleast one cluster in every state group. The distribution of Districts with clusters tested for TB infection by IGRA across India is illustrated in [Fig. 1](https://www.sciencedirect.com/science/article/pii/S1876034123003362#fig0005). The Quantiferon -TB Gold Plus (QFT-Plus) assay was done as per the Manufacturers protocol by trained personnel. The cut-off value was 0.35 IU/ml [[16]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib16).

### Operational definitions

TB Infection – Individuals positive by QFT-Plus assay (value >0.35 IU/ml) [[16]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib16).

TB uninfected - Individuals negative by QFT-Plus assay.

TB disease - Bacteriological evidence for TB by two tests (CBNAAT/smear/liquid culture) Or in one test and Chest x-ray abnormality.

Smoker – History of smoking in the past or current.

Alcohol user – History of alcohol use in the past or current.

Diabetes – Self reported or having random blood sugar ≥ 200 mg/dl.

Below Poverty Line (BPL) - Self reported based on availability of BPL card issued by the Government.

This passage describes the statistical methods used to analyze the data from a study on TB infection. Here's a breakdown of the key points:

### **1. Data Preparation**

* **Verification and Validation**: Before analysis, the data was checked for:
  + **Duplication**: Ensuring that no participant was counted more than once.
  + **Outliers**: Identifying and assessing any data points that were unusually high or low compared to the rest of the data.
  + **Logical Validation**: Ensuring that the data made sense and followed expected patterns (e.g., ages within a realistic range).

### **2. Statistical Software**

* The analysis was conducted using **Stata16**, a statistical software package from Stata Corporation.

### **3. Descriptive Analysis**

* **Summarizing Participant Characteristics**: The characteristics of the survey participants (like age, gender, etc.) were summarized using percentages and rates per 100.
* **Confidence Intervals**: These percentages and rates were presented with **95% Confidence Intervals (CIs)**, which provide a range within which the true values are likely to fall.
* **Exact Binomial Formula**: This formula was used to calculate the confidence intervals, which is appropriate when working with proportions or percentages.

### **4. Post-Hoc Analysis**

* **Identifying Factors Associated with TB Infection**:
  + A **post-hoc analysis** was conducted, meaning it was done after the initial analysis to explore further insights.
  + **Generalized Linear Models**: These models were used to identify relationships between different variables and TB infection.
  + **Binomial and Poisson Regression**: These specific types of regression models were used to analyze the data. Both models are used when dealing with count data or binary outcomes (e.g., whether or not someone has TB).
  + **Log Link Functions**: These were applied to the models to help linearize the relationship between variables, making it easier to interpret the results.

### **5. Variable Selection**

* **Choosing Variables**:
  + Variables associated with TB infection were selected based on **data availability** and **literature review**.
  + Additional variables were identified through **exploratory data analysis**, which involves examining the data to uncover patterns or relationships that weren't initially apparent.

### **6. Estimates Calculation**

* **Prevalence, Prevalence Ratio (PR), and Adjusted Risk Ratio (aRR)**:
  + These estimates were calculated to quantify the occurrence of TB infection and the strength of association between various factors and TB infection.
  + **Prevalence**: The proportion of the population found to have TB infection.
  + **Prevalence Ratio (PR)**: A measure comparing the prevalence of TB infection across different groups.
  + **Adjusted Risk Ratio (aRR)**: Similar to PR but adjusted for other variables that might influence the relationship.
  + **Stata “svy” Commands**: These commands were used to adjust for the **design effect** of the study, which accounts for how the survey was conducted (e.g., sampling methods).

### **7. Statistical Significance**

* **Two-Sided Analysis**: The statistical tests considered both directions of an effect (e.g., whether a factor increased or decreased the risk of TB infection).
* **Type I Error (Alpha = 0.05)**: The threshold for determining statistical significance was set at 0.05, meaning there is a 5% risk of concluding that there is an effect when there is none.

### **Summary:**

The statistical analysis involved verifying and validating the data before using Stata16 for analysis. Descriptive statistics were calculated with confidence intervals, and advanced models like binomial and Poisson regression were used to identify factors associated with TB infection. Variables were selected based on data availability, literature, and exploratory analysis. Prevalence, prevalence ratio, and adjusted risk ratio were estimated, with adjustments for the study design. All analyses were conducted with a 5% significance level.

Verbatim:

## Discussion

The present analysis has provided an estimate of 226 per 1000 (22.6%) for the burden of TB infection in India for population aged > 15 years. The recent [systematic review](https://www.sciencedirect.com/topics/medicine-and-dentistry/systematic-review) and meta-analysis concluded 24.8% global prevalence of LTBI based on IGRA [[17]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib17). The IGRA based LTBI prevalence for the South East Asia region was reported as 36% (95%CI: 25.3 – 46.7) [[17]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib17). A population-based study among 1319 individuals aged > 15 years in Vietnam documented LTBI of 36.8% (95%CI 33.4–40.3) [[18]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib18). Population based studies which have reported LTBI based on IGRA include China 24.3% (n = 2169), Saudi Arabia 9.1% (n = 1369) and United States 4.8% (n = 6083) [[19]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib19), [[20]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib20), [[21]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib21). Our findings that about one-fourth of the population has TB infection in India is a matter of concern and needs to be addressed in the context of TB elimination.

Males were more likely to have TB infection as observed in our analysis. Higher TB infection rates among males has been reported in earlier studies [[18]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib18), [[19]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib19). This possibly could be attributed to sociological factors [[19]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib19). A meta-analysis which included 2.2 million from 56 TB prevalence surveys over 28 countries concluded that TB prevalence is higher among men than women [[22]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib22). These findings imply that active case finding to be strengthened in men for detection of TB.

The prevalence of TB infection increased as age advanced in the present analysis. This observation has been reported in previous studies too [[18]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib18), [[19]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib19). Similar observation has been reported from an earlier study in household contacts which documented LTBI prevalence of 77% in individuals aged 15–18 years and 85% in persons aged > 45 years [[9]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib9). Increased frequency of social contacts and use of public transits leading to increased exposure could be contributing to higher LTBI prevalence with advancing age [[9]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib9). These findings suggest that older age groups need to be sensitized about TB, TB case detection be actively undertaken and be considered for intervention with TB preventive therapy.

Geographical differences in the prevalence of TB infection were observed in the current analysis. This could be attributed to the geographical differences in the prevalence of TB which is mirrored by TB infection. States especially those with high TB infection rates (>30%) which include Delhi, Telangana, Uttar Pradesh, Punjab, Chandigarh, Karnataka have to identify the possible reasons and plan appropriate targeted interventions. Individuals residing in urban location were more likely to have TB infection in the present analysis. Annual risk of TB infection of 2.2% in the urban compared to 1.3% in the rural areas has been reported in an earlier study from India [[7]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib7). This could be attributed to overcrowding, slums, migrant population in urban settings. Advocacy, Communication and Social Mobilisation (ACSM) activities pertaining to TB and active case finding has to be strengthened in urban settings.

Individuals with past history of TB were more likely to have TB infection in this analysis. This is anticipated since prior sensitization with *M.tuberculosis* is likely to be IGRA positive. This enforces that individuals with past history of TB have to be closely evaluated by active case finding periodically and considered for TB preventive strategies.

[Body mass index](https://www.sciencedirect.com/topics/medicine-and-dentistry/body-mass-index) was not associated with TB infection in the present analysis. Undernutrition leads to poor immune response and tests for LTBI are likely to be negative. Undernutrition fuelling the TB burden is well documented and WHO estimated that globally, 1.9 million TB cases are attributed to undernutrition [[23]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib23). Cognizant of the burden of undernutrition and TB, the TB programme of India has introduced Direct Benefit Transfer (DBT) for nutritional support to TB patients (Ni-kshay Poshan Yojana) [[24]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib24). Individuals with low BMI in the community have to be counselled for appropriate nutritional intake, periodically screened for TB for early case detection and if required offered TB preventive strategies which warrants further evaluation.

We observed that smoking and or alcohol use not to be associated with TB infection. Nevertheless, it has been reported that alcohol use disorders and smoking attribute 0.74 and 0.73 million TB cases respectively worldwide [[23]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib23). TB programme of India offers counselling, linkage to de-addition centres and tobacco cessation services including social support systems to TB patients with smoking and alcohol use [[24]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib24). ACSM activities for community sensitization on the [adverse effects](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/adverse-event) of smoking and alcohol use needs to be strengthened along with providing relevant information on interventions available for quitting.

Diabetes is a potential risk factor for TB and WHO has estimated 0.37 million TB cases to be attributed to diabetes [[23]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib23). In the present analysis we did not observe diabetes mellites to be associated with TB infection or disease. HIV being a potent risk factor for TB could not be analysed since status of HIV was unknown in 95.2% of the population in our study.

Irrespective of subclinical or symptomatic TB in those diagnosed with TB in the survey, 27% of their household contacts had TB infection. An earlier systematic review of 95 studies from low and middle- income countries documented 51.5% (95%CI: 47.1–55.8%) [latent TB](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/latent-tuberculosis) infection among contacts of TB patients [[25]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib25). This underscores the importance of TB preventive therapy (TPT) in contacts of TB patients as recommended by the TB program of India [[26]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib26). Individuals with subclinical TB could contribute substantially to the ongoing transmission of *M.tb* [[27]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib27). More than half of the TB patients diagnosed in the survey had subclinical TB which is [absence](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/epileptic-absence) of TB symptoms but abnormal [chest radiograph](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography) and or bacteriological evidence of TB. Though this was a cross-sectional analysis and the number of contacts tested for TB infection is small, the possibility that subclinical TB is transmissible cannot be ruled out. Our observation that transmissibility of subclinical TB is similar to symptomatic TB needs to be explored in future studies.

This analysis has inherent limitations. The numbers may not be sufficient for sub-group analysis of factors associated with TB infection. The findings have to be interpreted considering this limitation. Information on potential factors for TB infection such as contact with TB patient, duration of exposure, biomass fuel use, HIV status and other [immunosuppressive](https://www.sciencedirect.com/topics/medicine-and-dentistry/immunosuppressive-drug) conditions was not available. Moreover, information on the time of infection – recent / past could not be elucidated.

Our analysis has shown that in India, about one fourth (22.6%) of the individuals were infected with TB. Geographical variation in the prevalence of TB infection was observed. Those aged > 30 years, being male, residing in urban location, and with past history of TB were more likely to have TB infection. Individuals with TB infection are reservoirs of future TB disease. Recent evidence from modelling study suggest the possibility of self-clearance of *M.tb* infection in 24.4% of individuals within 10 years of infection and 73.1% over a lifetime [[28]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib28). Further, the lifetime risk of TB in those retaining the viable infection is 17%. The self-clearance of *M.tb* infection was least in India compared to China and Japan [[28]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib28). The target of the END TB Strategy of the World Health Organisation (WHO), is to reduce the incidence of TB by 90% by 2035 while India is committed to eliminate TB by 2025 [[1]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib1), [[3]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib3). In the context of TB elimination in India, it is essential to map the population vulnerable to TB infection and provide primordial prevention by means of ACSM activities and improving the awareness on TB prevention. The National TB Elimination Programme (NTEP) in India has been [scaling up](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/scale-up) the implementation of “Guidelines for Programmatic Management of Tuberculosis Preventive Treatment in India, 2021″ by a comprehensive ‘cascade of care’ approach as a core strategy to deliver TPT services across the country [[26]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib26). This guideline is implemented across all the states to systematically reach out and screen all target populations (PLHIV, household contacts, and other groups at risk of developing TB disease) after ruling out TB and provide TPT as a part of the continuum of care. Scaling up of the comprehensive TB prevention strategy is a critical component of the India’s National Strategic Plan 2017–25 and would hasten the decline of TB incidence in India. The testing for TB infection by indra-dermal skin test (Cy-TB) offers wider scope of its use under programmatic settings [[29]](https://www.sciencedirect.com/science/article/pii/S1876034123003362#bib29). It is essential to also address determinants of TB disease which include malnutrition, social habits and co-morbid conditions. Targeted interventions which include TB preventive therapy and active screening for early detection of disease in high-risk groups for TB is essential to reduce the burden of TB in India.