Original Article

Prevalence of Tuberculosis Infection among Adults of Thiruvananthapuram District of Kerala as Measured by Interferon Gamma Release Assay – A Cross-Sectional Study

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Abstract

Background: To achieve the goals of the end tuberculosis (TB) strategy, strategies for management of TB infection (TBI) have to be expanded. The first step to devise policies is to understand the distribution and determinants of TBI in the community. The objectives of the study were to estimate the prevalence of TBI using Interferon Gamma Release Assay (IGRA) and its determinants among the adult population of Thiruvananthapuram district, Kerala. **Materials and Methods:** A community-based, cross-sectional study using the stratified cluster sampling was carried out among the adults. TBI was detected using IGRA conducted on whole blood sample. Data on determinants were collected using a structured questionnaire by the face-to-face interview. The prevalence of TBI was estimated. Univariate and multivariate analysis was conducted to identify the determinants. **Results:** Age standardized prevalence of TBI among 396 adults was 20.5% (95% confidence interval [CI] 16.52–24.48). On adjusting for the possible confounders, increasing age (adjusted odds ratio [OR] 1.028; 95% CI 1.008–1.048; $P = 0.005$), history of contact with active TB disease (adjusted OR 7.61; 95% CI 4.43–13.05; $P < 0.001$), childhood contact (adjusted OR 8.20; 95% CI 3.14–21.41; $P < 0.001$), and household contact (adjusted OR 10.12; 95% CI 5.39–18.98; $P < 0.001$) were found to be the determinants of TBI in this population. **Conclusion:** The present study observed that nearly one-fifth of the adult population in the Thiruvananthapuram district has TBI. For the programmatic management, factors such as increasing age and contact history may be considered for the elimination of TBI in the state.

Keywords: Kerala, prevalence, risk factors, tuberculosis, tuberculosis infection

Introduction

Tuberculosis (TB) is one of the top ten causes of death worldwide.[1] Even though being the highest burden country, India has committed achieving the sustainable development goals (SDG) related to ending TB by 2025, 5 years ahead of the global targets. To achieve the same, the National Strategic Plan for TB elimination 2017–2025, which was built on 4 Strategic pillars of "Detect-Treat-Prevent-Build," was brought out. One of the main components of "Prevent" strategy is to address TB infection (TBI).

WHO defines TBI as a state of the persistent immune response to stimulation by *Mycobacterium* TB antigens without evidence of clinically manifested active TB. Estimates show that about one-third of the world's population is infected with TB.[2] However, studies show that around 5%–10% of those who are infected will develop active disease during their lifetime and usually within the first 5 years of initial infection.[2] Studies show that up to 17% fall in the annual incidence of cases can be achieved through community-based TB preventive therapy.[3] Hence, along with active case detection and effective treatment, reservoir shall be reduced either through preventive drug therapy or through vaccination to achieve the ambitious targets of TB elimination at the national and global levels.

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There are limited population-based studies undertaken in recent times to estimate the prevalence of TBI among the general population in India. Changes in demography, disease burden, and advances in public health mandate the need to estimate the prevalence of TBI for planning robust public health interventions.

Tuberculin skin test (TST) and Interferon Gamma Release Assay (IGRA) are the two currently available WHO recommended tests for the diagnosis of TBI. According to the WHO, standard Tuberculin faces a global shortage and IGRA has a better sensitivity and specificity when compared to the TST,[4] especially in a population that receives Bacille Calmette-Guérin vaccine extensively. Furthermore for a field level survey, IGRA is a better choice compared to TST since it requires only single visit. Hence, the Government of India has also endorsed IGRA for the detection of TBI for programmatic management of TB preventive therapy, although it is compartively expensive.

Since the State of Kerala in India shows a clear evidence of declining transmission of TB and lower rates of drug-resistant TB in the state, the State Government has declared its commitment to achieve SDG related to Ending TB earlier than the rest of India. The state has notified 68 incident TB cases per 100,000 population in 2019 compared to the national figure of 159 per 100,000 population. In this background, the current study aims to estimate the prevalence of TBI among the adult population of Thiruvananthapuram district in Kerala, India using WHO-approved IGRA.

Materials and Methods

A community-based cross-sectional study was conducted in Thiruvananthapuram district, the state capital of Kerala between the period of January 2019 and June 2020. About 9% of the total population of the State resides in the southernmost district of the State making it the second most populous district in the State with the highest population density[5] with a sex ratio of 1088 females per 1000 males and in the third stage of demographic transition with a more aging population. The study participants were adults aged 18 years and above who have been residing in the district for the past 5 years continuously. Persons who were either known cases of TB or have taken anti-TB treatment were excluded from the study.

Assuming the prevalence of TBI as 33%,[2] with 20% relative precision, 5% level of significance, and a design effect of 2, and 5% nonresponders, the sample size was estimated as 426. A stratified cluster sampling method was used. Out of 1299 rural wards and 237 urban wards, 13 rural and 7 urban wards (lowest political division) were selected using simple random sampling from the list of all wards after considering the proportional distribution of the total population in urban and rural wards. From each ward (cluster), 22 participants were included. In selected wards, a junction was selected based on the map where a bottle was rotated. The street toward which the cap of the bottle pointed was selected for the survey. First house was selected randomly based on the last two digits of a currency note. Households were selected continuously till 22 eligible participants are recruited from the ward. Only one participant was recruited per household using the lottery method. The survey was conducted on holidays to ensure the participation of college students and the working population.

The protocol was approved by the Institutional Ethics Committee (No May 13, 2018/MCT). After obtaining informed consent, data on sociodemographic and clinical history were collected using a semi-structured questionnaire. Socioeconomic status was assessed using the Modified Kuppuswamy Scale.[6] 5 ml of whole blood sample for IGRA test was collected by a trained medical practitioner and transported to the designated laboratory within 8 h of sample collection following standard operating procedures. QuantiFERON-TB GOLD testing was performed and analyzed according to manufacturer instructions (QIAGEN, Germany). A sample was considered positive if the quantity of the interferon-gamma in TB Antigen tube minus Nil tube was ≥0.35 IU/ml and >25% of Nil value.

History of contact with a case of TB was enquired in detail to each participant and based on the setting where the exposure occurred, the contacts have been further classified into three categories, viz i) household contact who shared the same enclosed living space as the case for one or more nights or frequent or extended daytime periods during the 3 months before initiation of treatment of index case, (ii) neighborhood contact who had contact with a case of TB in the neighborhood any time during 3 months before the start of the treatment but never shared an enclosed space with the index case and (iii) workplace contact who shared the same enclosed space at the place of work as the case for one or more days any time during the 3 months before the start of treatment of index case. Any known history of contact was also assessed further to understand the age at which the participant got exposed to a case of TB and labeled as a childhood contact if the participant was exposed to a case of TB before the age of 12 years.

2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. IBM Corp. Released was used for descriptive, bivariable, and multivariable data analysis. The prevalence of TBI with 95% confidence interval was estimated using Cochran's method with DESCRIBE-WINPEPI program (version 3.16) to account for clustering in the study design, variation of the number of participants tested in each cluster, between cluster variability and uncertainty in estimating standard error. Difference between categorical variables was tested using the Chi-square test of independence and Fisher's exact test. The odd's ratio and 95% confidence interval (CI) were used as a measure of strength of association. Directed Acyclic Graphs were drawn to identify potential cofounders. Binary logistic regression was then performed

with TBI status as the dependant variable and by entering age, known history of contact, household contact, childhood contact, gender, urban-rural stratification, and socioeconomic status as independent variables. Adjusted odds ratio (OR) and confidence interval for the factors associated with TBI were estimated. "$P < 0.05$" was considered statistically significant.

Results

After the process of sampling, 21 persons did not consent to the study, and 5 persons were excluded since they were known cases of TB or were on anti-TB treatment. Out of 406 participants who consented to the study, 10 had indeterminate results and were not included in statistical analysis. The mean standard deviation age of 396 study participants was 46.68 (14.5) years and ranged from 18 to 90 years. One hundred and forty (35.4%) participants were male and 256 (64.6%) were female.

The prevalence of TBI among study participants was estimated to be 22.47 (95% CI 17.24–27.71). The age-standardized prevalence was estimated using 2011 census data to adjust for the right-sided skewness observed in the age of the participants and was assessed to be 20.5% (95% CI 16.52–24.48). The characteristics of the study population and the proportion with TBI among each study groups are shown in Table 1 and results of final logistic regression model in Table 2.

Discussion

The present study found the proportion of TBI among the adult population of Thiruvananthapuram district to be 22.47% (17.24%–27.71%) and age-standardized prevalence to be 20.5% (95% CI 16.52–24.48). Population studies conducted to estimate the burden of TBI in India dates back to the 1960s which estimated a prevalence of 33%.[7] Another study conducted in Tumkur district of Mysore using TST in 1960–1961 showed a TBI prevalence of 38.3% among the general population.[8] The prevalence estimated in the present study is also lower when compared to the 30.8% (28.3%–34.8%) estimated for the South-East Asian Region using mathematical modeling in 2016.[9] Nation-wide tuberculin survey conducted in 2000, estimated annual risk of TBI in South Zone of India is 1.0% which was lower compared to the national value of 1.7%.[10] A study conducted in 2006 among 4821 school children in Kerala aged between 5 and 9 years also concluded that the transmission rate is low in Kerala.[11] The lower TBI prevalence among the adult population in this study could be attributed to the better social development indicators of Kerala, especially in health and education sectors gained over the decades.

The present study shows that a person with a known history of contact with a case of TB is at higher risk for infection when compared to a person with no known history of contact (adjusted OR = 7.61, 95%CI 4.43–13.06, $P < 0.001$) especially the household contacts (adjusted OR = 10.11, 95%CI 5.39–18.98, $P < 0.001$). A study[12] conducted in India showed that infection prevalence among household contacts of pulmonary TB was 47% at <6 years, 53% between 6 and 14 years, and 78% between 15 and 45 years while the present study showed a prevalence of 64.1% among the household contacts ≥18 years and 63.6% among those participants who were exposed to a case of TB at an age <12 years. The present study also demonstrated that exposure to an active case of TB during childhood is a risk factor for infection (adjusted OR 8.20; 95% CI 3.14–21.41; $P < 0.001$).

In the present study, the prevalence of TBI was found to be increasing with increasing age groups. A study[13] conducted among health care workers also showed a similar trend of increase in prevalence with increasing age; i.e., the age groups 35–44 years (OR = 2.43; 95% CI 1.45–4.06; $P = 0.0007$) and 45–60 years (OR = 4.81; 95% CI 2.72–8.52) are at increased risk for TBI. This increased risk for TBI with advancing age can be attributed to the increased social interaction patterns of older people and higher chance of exposure to a TB case during their childhood when disease prevalence was higher.

The present study showed that the prevalence is more in urban areas (24.68% [14.59–34.78]) when compared to rural areas (18.81% [13.35–24.26]) which is in consistent with the findings of the nationwide survey of 1955-58[14] and 2000.[10] Study concluded that prevalence of infection is higher among males (25.7%) when compared to female sex (20.7%) similar to a study conducted using TST.[15] Failure to establish a significant difference could be due to inadequate power of the present study to establish the causation between these factors and infection, which was not the primary objective of the present study. Due to the same reason present study couldn't establish a statistical significance on either socioeconomic status of participant or tobacco smoking status, though these factors are widely quoted as risk factors for infection.[1,16] Also there are studies[17-19] showing healthcare workers are at higher risk for TBI which could not be determined in the present study due to an insufficient number of participants belonging to that category.

The study ensured proper sampling of the study participants from the community. Data and sample collection were done by a single qualified investigator which reduced the chances of errors. Sample were processed and results were interpreted by experienced microbiologists from a tertiary care setting. Appropriate planning and execution of field level activities adhering to the protocols ensured internal validity. Sample size was estimated based on the primary objective and so the study was not powered enough to study many of the determinants.

Conclusion

To summarise, the prevalence of TBI was 22.47% (95% CI 17.24–27.71) among the adult population of Thiruvananthapuram district. Increasing age and history of contact were found out as factors associated with TBI. Being a resource constraint setting, State might not be in a position to address the burden of latent TBI as a community-based approach, instead, policies can be tailored

Table 1: Characteristics of study population and proportion of tuberculosis infection across various categories (*n*=396)

Variable	Number of participants	Number of participants with positive IGRA results, *n* (%)	Univariate analysis		
			OR value	95% CI	*P*
Age group (years)					
18-35	96	11 (11.5)	1	-	0.006
36-58	211	51 (24.2)	2.46	1.22-4.97	
>58	89	27 (30.3)	3.37	1.55-7.29	
Gender					
Male	140	36 (25.7)	1.33	0.82-2.15	0.25
Female	256	53 (20.7)	1	-	
Socioeconomic class					
Upper class	11	4 (36.4)	1	-	
Upper middle class	59	12 (20.3)	0.44	0.11-1.78	0.15
Lower middle class	121	25 (20.7)	0.45	0.12-1.68	
Upper lower class	199	44 (22.1)	0.49	0.14-1.77	
Lower class	6	4 (66.7)	3.5	0.43-28.4	
Geographical location					
Urban area	179	44 (26.8)	1.57	0.97-2.52	0.06
Rural area	217	41 (18.9)	1	-	
Overcrowding					
Yes	126	9 (17.6)	0.71	0.33-1.52	0.37
No	80	80 (23.2)	1	-	
BCG scar					
Present	312	67 (21.5)	0.77	0.44-1.34	0.56
Absent	84	22 (26.2)	1	-	
Diabetes mellitus					
Present	70	20 (28.6)	1.49	0.83-2.67	0.17
Absent	326	69 (21.2)	1	-	
Habit of smoking					
Yes	35	8 (22.9)	1.02	0.45-2.34	0.95
No	361	81 (22.4)	1	-	
Health-care worker					
Yes	21	1 (4.8)	0.16	0.02-1.23	0.05
No	375	88 (23.5)	1	-	
Known history of contact with TB					
Yes	111	57 (51.4)	8.35	4.95-14.08	<0.001
No	285	32 (11.2)	1	-	
Childhood contact					
Yes	22	14 (63.6)	6.98	2.82-17.24	<0.001
No	374	75 (20.1)	1	-	
Household contact					
Yes	64	41 (64.1)	10.55	5.82-19.13	<0.001
No	332	48 (14.5)	1	-	
Neighborhood contact					
Yes	46	15 (32.6)	1.8	0.93-3.52	0.08
No	350	74 (21.1)	1	-	
Workplace contact					
Yes	1	1 (100)			
No	395	88 (22.3)	-		

IGRA: Interferon gamma release assay, TB: Tuberculosis, OR: Odd's ratio, CI: Confidence interval, BCG: Bacillus -calmette-guerin vaccine

to focus on high-risk groups like household contacts and old age population. Henceforward a program inclusive of meticulous contact tracing, risk assessment, and effective preventive therapy can reduce the burden of TB at a faster rate shortly.

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Conflicts of interest

There are no conflicts of interest.

Table 2: Sociodemographic and clinical characteristics of participants and predictors of tuberculosis infection: Results of binary logistic regression analysis

Variable	Multivariate analysis		
	OR	Percentage CI	*P*
Age	1.028	1.008-1.048	0.005
Known history of contact	7.61	4.435-13.056	<0.001
Household contact	10.116	5.391-18.983	<0.001
Childhood contact	8.198	3.139-21.408	<0.001
Female gender	0.762	0.437-1.327	0.336
Rural area	0.678	0.389-1.183	0.171
Lower socioeconomic status	0.736	0.426-1.274	0.274

OR: Odds ratio, CI: Confidence interval

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