Prevalence of latent tuberculosis infection in household contacts of pulmonary tuberculosis, time to treat

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Key words: tuberculosis; latent tuberculosis infection, Mantoux, chest X-ray.

Contributions: VSCS, SJ, VS, DA, PK, JC, helped in the treatment of the patients, retrieved the data and conceived the content of the manuscript; VSCS, SJ, drafted the manuscript. All authors read and revised the manuscript critically for important intellectual concepts and VS, DA, PK, JC, approved the final version of the manuscript.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: the study protocol was reviewed and approved by the Institutional Ethics Committee of Government Medical College and Hospital (No.GMCH/IEC/2019/142/).

Informed consent: written informed consent for the use of data was obtained from the index cases during the study.

Funding: none.

Availability of data and materials: data and materials are available from the corresponding author upon request.

Received: 23 February 2023.
Accepted: 12 May 2023.
Early view: 22 May 2023.

Monaldi Archives for Chest Disease 2024; 94:2563
doi: 10.4081/monaldi.2023.2563

Abstract

Treatment of latent pulmonary tuberculosis (TB) in household contacts has been included in the National Tuberculosis Elimination Program to achieve the target of TB elimination by the Government of India by 2025. However, there are no clear estimates of the prevalence of latent TB among the contacts that could suggest the impact of this intervention. The study was conducted to determine the prevalence of and factors predicting latent TB among household contacts with pulmonary TB. All microbiologically confirmed pulmonary TB patients registered between January 2020 and July 2021 and their household contacts were enrolled. All contacts underwent Mantoux testing to determine the prevalence of latent TB. All symptomatic patients also underwent chest radiographs and sputum examinations to diagnose active pulmonary TB. Thereafter, different demographic and clinical factors were evaluated to find predictors of latent TB using a logistic regression model.

A total of 118 pulmonary TB cases and their 330 household contacts were enrolled. The prevalence of latent TB and active TB among the contacts was found to be 26.36% and 3.03%, respectively. The female gender of index TB cases was independently associated with a high proportion of latent TB cases in the family (adjusted odds ratio 2.32; 95% confidence interval 1.07-5.05; p=0.03). Neither the higher sputum smear positivity nor the severity of the chest radiograph of index TB cases had any association with the number of contacts being diagnosed as latent TB or active TB. The results showed a significant prevalence of latent TB among household contacts with pulmonary TB. The severity of the disease in the index patient had no association with the prevalence of latent TB.

Introduction

Tuberculosis (TB), caused by the bacteria *Mycobacterium tuberculosis*, is one of the leading causes of death worldwide [1,2]. Depending on the host's immunity, the disease may present with a varying degree of severity, ranging from asymptomatic infection (termed latent TB) to progressive disease (active TB). An active case of pulmonary TB coughs out the infectious droplet nuclei, which can cause infection to others who come in contact with him unless the patient is detected early and started on treatment [3]. So, it is important to diagnose and treat such cases as soon as possible.

Recently, the Government of India reframed the revised National Tuberculosis Control Program and renamed it the National Tuberculosis Elimination Program, with the aim of eliminating TB from India by 2025. In line with it, the National Strategic Plan 2017-

2025 was devised, integrating the four strategic pillars of "DETECT-TREAT-PREVENT-BUILD", defining four key areas of action [4]. Under the "PREVENT" pillar, the program is planned to include treatment of latent TB in the contacts of bacteriologically confirmed index cases and in individuals who are at high risk of getting TB disease [4]. This is an echo of the World Health Organization's End TB Strategy, which has incorporated the detection and treatment of latent TB as the key component to meet the targets.

Approximately one-fourth of the world population has been estimated to have latent TB [5]. The prevalence of latent TB has been highly variable across different geographical regions. This variability is partly explained by the difference in the methods used to diagnose latent TB, the population screened, and partly by bacterial, host, and environmental factors. There are no clear figures on the prevalence of latent TB in India, which is one of the countries with the highest TB burden in the world. Few studies done across small geographical areas in India have yielded a prevalence figure between 43-52% [6,7]. Hence, this study was conducted to evaluate the prevalence of latent and active TB through screening of the contacts of sputum-positive TB patients from this geographical area and to evaluate various predictors of latent TB.

Materials and Methods

This cross-sectional study was conducted in the Department of Pulmonary, Critical Care and Sleep Medicine, Government Medical College and Hospital, Chandigarh, India, over one and a half years, from January 2020 to July 2021. The subjects were microbiologically confirmed pulmonary TB cases and their household contacts. Informed consent was obtained from all the index cases as well as their household contacts. The study was approved by the institutional ethics committee of the Government Medical College and Hospital.

An index case was defined as a microbiologically confirmed pulmonary TB (drug-sensitive/drug-resistant) patient, and "a household contact" was defined as a person living with the index case and sharing food from the same kitchen for a minimum of three months before the diagnosis of TB disease in the index case [8]. Among the index cases, extrapulmonary TB and those who did not give consent were excluded from the study. Among the household contacts, those who had a past history of treated TB as well as those who did not give consent were excluded from the study.

All index cases were evaluated for demographic data, their baseline symptoms, smoking habits, chulha exposure, sputum smear grading for acid-fast bacilli (AFB) and/or sputum cartridge based nucleic acid amplification test (CBNAAT), and chest X-rays. The baseline chest X-rays of the index patients were classified into non-extensive disease and extensive disease. The extensive disease was defined by the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography [9].

All household contacts of index cases were selected by verbal questioning with the index case. Their demographic profile, symptoms, and signs were noted using a structured questionnaire along with their clinical examination. Additionally, details about their known co-morbidities, immunocompromised states or therapy, and smoking/alcohol use were noted. For the identification of presumptive TB, four symptoms suggestive of TB, *i.e.*, productive cough of any duration, fever/night sweats, loss of weight, and hemoptysis, were asked as defined by the World Health Organization [4].

After clinical assessment, all contacts underwent the Mantoux test. Latent TB was defined by a Mantoux test reading of >10 mm induration measured after 48-72 hours of administration [10]. All symptomatic contacts also underwent chest X-rays posterior-anterior view, and sputum examinations to evaluate for active TB disease. Chest radiography findings that were considered suggestive of active TB included infiltrates/consolidation, any cavitary lesion, any nodule with poorly defined margins, pleural effusion, hilar or mediastinal lymphadenopathy, and military pattern [10,11]. In the case of pediatric household contacts (<12 years), screening was done in the pediatric outpatient department by Mantoux test, chest X-rays, and gastric lavage as per the advice of the pediatrician. Appropriate tests like fine needle aspiration of fluid/pus were sent for cytology and CBNAAT in suspected extra-pulmonary TB. Active TB was confirmed in the contacts either based on sputum smear microscopy/CBNAAT (microbiologically confirmed TB) or based on relevant clinico-radiological findings (clinically diagnosed TB) [4]. Finally, the number of cases diagnosed as active TB and latent TB among the household contacts was analyzed in terms of their prevalence as well as for any association with different demographic and clinical factors like sputum smear grade and disease extent on the X-rays of the index patient.

Results

A total of 118 freshly diagnosed pulmonary TB patients and 330 household contacts were enrolled in the study.

Clinical profile of the index cases

The mean age of the index cases was 40.02+18.6 years, with 39 (33%) patients presenting in the age group of 20-40 years. In contrast, 46% of contacts were in the age group of 20-40 years. Males comprised 62% of the TB patients, in contrast to 54% of the household contacts. Smoking, diabetes, and hypertension were more common among the index cases as compared to contacts. Among 118 TB patients, sputum high bacillary load and extensive involvement on X-rays were seen in 51 (43.2%) and 43 (36.4%) patients, respectively (Table 1). Approximately one-fourth (23%) of the contacts were symptomatic at baseline. Cough was the most common symptom (13.0%), followed by fever/night sweats (4.2%) and significant weight loss (3.9%). Chest X-ray findings suggestive of TB were seen in 33 patients.

Comparison of contacts with and without latent tuberculosis

Out of 320 household contacts, 87 (26.4%) subjects had a positive Mantoux test and were categorized as having latent TB; 10 patients (3%) were diagnosed with pulmonary TB based on a positive sputum AFB smear. There was no statistically significant difference in age, gender, or smoking prevalence between contacts with or without latent TB (Table 2).

Association of latent tuberculosis with the tuberculosis among index cases

Out of 118 index patients, 41 had >50% of their household contacts diagnosed with latent TB, and 77 (65.3%) had <50% of their contacts suffering from latent TB. Out of different demographic and clinical parameters, the female gender was independently associated with the higher (>50%) proportion of household contacts suffering from latent TB [adjusted odds ratio (OR) 2.32; 95% confidence interval (CI) 1.07-5.05; p=0.034) (Table 3).

Discussion

The present study evaluated the prevalence of latent TB among household contacts of microbiologically proven pulmonary TB cases. The results showed that more than one-fourth of the contacts had latent TB, which was independently associated with the female gender of index TB cases. The global prevalence of latent TB has been estimated to be around 25% [5]. In India, there are no estimated figures on the prevalence of latent TB. However, given the high TB burden in India, it is likely that the figure will be higher than the global estimate. The present study showed the prevalence of latent TB to be 26.4% among household contacts with pulmonary TB, which is lower than the global estimate. These lower figures need to be interpreted in light of the fact that they represent the data from a small geographical region and do not represent a country's prevalence. This prevalence was also found to be comparable to studies from California (30%) and Scotland (31.2%) [11,12], but lower than the studies from India (52.6%) and Malawi (66%) that have a high TB burden [6,13]. The possible reasons for reduced prevalence may be differences in disease severity, socioeconomic status, smaller sample size, and differences in the measurement tools used. Apart from the modifiable factors, Mantoux positivity significantly depends on the host's immune response to tubercular protein. Hence, the Mantoux induration will be affected in immunocompromised states like diabetes, HIV, malnutrition, and patients on immunosuppressive therapy. The present study included subjects from household contacts of index patients, which might also have created some selection bias.

Nevertheless, a relatively lower prevalence of latent TB found among household contacts in the present study undermines the contribution of seroconversion, secondary to exposure to fresh TB patients, to the prevalence of latent TB. In contrast to our results, a Chinese study from Shanghai showed a much lower prevalence of latent TB infection (17.2%) in their study [14]. This is possibly because Shanghai, being one of China's biggest cities, is inhabited by people with better socioeconomic status, greater awareness, better housing, less overcrowding, and better health infrastructure.

The present study tried to find a causal association between latent TB and different demographic and clinical parameters of index patients as well as contacts. The results showed that latent TB had no association with the age and smoking status of either of the subject groups (p>0.05). Also, there was no gender difference in the

Table 1. Demographic and clinical characteristics of sputum smear-positive index cases (n=118).

S. no	Variable		Index cases (n=118)	Household contacts (n=320)
1	Age (years)		40.02±18.6	31.90±16.44
2	Males (%)		73 (61.9)	176 (53.3)
3	Smoking (%)		42 (35.6)	56 (17)
4	Chulha exposure (%)		13 (11)	37 (11.2)
5	Diabetes (%)		19 (16.1)	8 (2.4)
6	Hypertension (%)		9 (7.6)	19 (5.8)
7	Previous TB (%)		33 (28)	
8	Sputum smear grading	Negative/Scanty/1+ (%) 2+/3+/4+ (%)	67 (56.8) 51 (43.2)	
9	Chest X-ray findings	Extensive disease (%) Non extensive disease (%)	43 (36.4) 75 (63.3)	

TB, tuberculosis.

Table 2. Comparison of different characteristics between contacts with and without latent tuberculosis.

	Latent TB (n=87)	Normal (excluding active TB) (n=233)	p value
Age (years)	32.8±14.4	31.6±17.1	0.55
Male (%)	45 (51.7)	127 (54.5)	0.70
Smoking	19	33	0.10
Chulha exposure (%)	6 (16.7)	30 (83.3)	0.13
Comorbidity (%)	10 (37.0)	17 (63.0)	0.23

TB, tuberculosis.

Table 3. Association of latent tuberculosis with demographic and clinical parameters of index tuberculosis cases.

	Independent variable	Univariate analysis OR (95% CI)	p value	Multivariate analysis aOR (95% CI)	p value
1	Age	0.98 (0.96-1.003)	0.08		
2	Female gender	2.32 (1.07-5.05)	0.034	2.32 (1.07-5.05)	0.034
3	High AFB group	0.66 (0.31-1.43)	0.29		
4	Extensive disease on chest radiographs	1.18 (0.54-2.6)	0.67		

OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; AFB, acid-fast bacilli.

prevalence of latent TB. However, it was seen that the female gender of index TB cases had a positive association with the higher proportion of household contacts being found to have latent TB (adjusted OR 2.32; 95% CI 1.07-5.05; p=0.03). This association could be explained by the fact that the majority of the female patients were homemakers, remaining at home throughout the day, resulting in prolonged exposure to the index patients, leading to Mantoux positivity. In contrast, a study by Nair *et al*. found that male gender and being siblings of the index case (adjusted OR 3.4; 95% CI 1.2-9.7) were important risk factors for an abnormal chest X-ray finding among the household contacts screened [8].

In the present study, the prevalence of active TB among household contacts was 3.03%. This was lower than the studies in Chattisgarh (10.1%) [15], and Chennai (5.3%) [8] in India and Tanzania (6.4%) [16], Turkey (5.4%) [17], and Mandalay in Myanmar, where a high prevalence of 13.8% active TB was found [18]. However, in other studies from India and California, a much lower prevalence rate (1% and <1%, respectively) was found [11,19]. The wide difference in the prevalence rates seen in different studies could be due to the difference in the sample size of the contacts screened, ranging from 174 in Myanmar to 1556 in Chattisgarh [15,18]. The methods of screening also varied, and even Gene Xpert was used in the studies conducted in Myanmar and Tanzania [16,18]. The studies from South Africa and Tanzania used sputum cultures for screening of the contacts [16,20].

The severity of TB is usually described based on the grade of sputum positivity and the extent of involvement on X-rays. In the present study, 51 (43.2%) index cases had a higher sputum grading of >2+. However, on logistic regression analysis, higher sputum grading had no association with higher latent TB prevalence among the contacts. (OR 0.66; 95% CI 0.31-1.43; p=0.29). In the case of active TB among contacts, 90% of the cases were the contacts of the index cases whose sputum smear was negative/scanty or 1+ (p=0.03). This is in contrast to a study conducted by Xu *et al.,* where they found that the rate of active pulmonary TB among the contacts was positively associated with the amount of bacteria discharged in the sputum of the index cases (r=0.99, p<0.01) [21].

In the present study, chest X-rays showed extensive disease in 43 (36.4%) index TB patients. This was similar to the study in Chennai, where the proportion of index cases with cavitary lesions on chest X-rays was 33% (n=91) [8]. In our study, the extensive disease on chest X-rays in the index case was not a significant determinant of both latent TB (OR 1.18; 95% CI 0.54-2.6; p=0.67) and active TB among contacts. However, in a study from Malawi, there was an association between cavitary disease and the amount of lung field affected on the chest X-rays of the index case and the tuberculin skin test positivity of the child contacts [13]. The difference in the findings could be attributed to the difference in the population groups included in the contact population.

The present study results showed a high prevalence of latent TB among household contacts with microbiologically confirmed pulmonary TB. A sample of 330 contacts provided adequate power for the results. The results suggest that the duration of exposure to the index case may be more important than the severity of the disease in determining latent TB. However, the study was conducted in a hospital setting among the contacts of those index cases who presented in the in-patient or out-patient department and hence is not representative of the general population. Genotyping of the index cases and the contacts was not done to confirm whether the transmission had actually occurred in the household contacts leading to their Mantoux conversion or otherwise. Various challenges were also faced during the study, including getting consent from the index cases to screen their contacts. This was due to the lack of awareness among the population about the need for early screening. Moreover, due to the ongoing COVID pandemic, the socio-economic and household conditions of the index cases were not studied, which may also have a strong influence on the prevalence of latent TB.

Conclusions

Latent TB is multi-factorial in origin. Hence, its prevalence has been highly variable across different studies, both within and outside the same geographical region. Nevertheless, the high prevalence, as has been seen in this study, highlights the need to actively diagnose and treat this form of TB. The same has been incorporated into the National Strategic Plan 2017-2025 by the Government of India. Active management of latent TB has been initiated in a phased manner in India to achieve the TB elimination goal by 2025. Nevertheless, screening is a dynamic process, and the programs should regularly formulate decisions on when and how to screen and which high-risk groups to prioritize for management.

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