

Household contact investigation for the detection of active tuberculosis and latent tuberculosis: A comprehensive evaluation in two high-burden provinces in Iran

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Abstract

Background: Systematic evaluation of household contacts of persons with pulmonary tuberculosis (TB) in low- and middle-income countries is recommended by the World Health Organization (WHO). This study recruited adult household contacts of diagnosed TB patients in two high burden provinces of Iran to estimate the prevalence and incidence of active disease and latent TB infection (LTBI) among individuals exposed to TB cases.

Methods: We conducted a cohort study among adults in household contact with a pulmonary TB index case. All subjects were assessed for active disease through evaluation of symptoms. Tuberculin skin test (TST) and QuantiFERON®-TB Gold Plus (QFT-Plus) were used to define LTBI. These tests were performed at the time of the index TB case diagnosis and repeated if the previous result was negative, at three-, 12-, and 18-months post recruitment. In addition, interferon- γ -induced protein-10 (IP-10) concentrations were measured in QFT-Plus supernatants for all participants three months after diagnosing the index case.

Results: A total of 451 individuals who had close contact with 95 active TB patients were enrolled in this study. Five (1.1%) contacts were diagnosed with active TB and 285 (63.2%) were identified with LTBI during our study. The incidence rate of LTBI among adult household contacts of TB index cases was 0.44 per person per year.

Conclusion: The overall rate of LTBI was high. Systematic screening of all household contacts of pulmonary TB should be expanded in Iran to make the timely achievement of the global end TB strategy feasible.

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Keywords: Household contact investigation, interferon-, interferon- γ -induced protein-10, latent tuberculosis, tuberculin skin test

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Introduction

Tuberculosis (TB), a contagious disease caused by *Mycobacterium tuberculosis* (*Mtb*), is one of the top ten causes of death worldwide with an estimated 10 million new cases and 1.5 million deaths in 2018 [1]. The World Health Organization (WHO) end TB strategy targets a 4–5% annual decline in the incidence of TB worldwide [1]. According to current trends, this goal is unlikely to be attained without a substantial increase

in efforts to find and treat, as well as prevent TB cases from different geographical locations of the world [2]. In high TB burden countries with limited resources, passive TB case finding is the norm, consisting of the screening and evaluation of symptomatic patients presenting to healthcare facilities [3]. This model does not detect individuals with minimal symptoms of active TB or those with latent TB infection (LTBI) and can lead to delayed diagnosis and management of TB cases [4].

The WHO recommends active case finding strategies in order to identify and treat patients earlier, reducing the period of infectiousness and therefore transmission, including in low- and middle-income countries with a high incidence of the disease [5]. Household contacts (people who live in the same housing unit) of TB patients have a high risk of becoming infected with *M. tuberculosis* compared to the members of general population [6]. A systematic review conducted by Fox et al. has reported an average active TB prevalence of 3.1% and an average LTBI prevalence of 51.5% among household contacts of TB patients in low- and middle-income countries [6]. According to the WHO recommendations, active and systematic screening of household contacts that are exposed to an index case of TB can be an efficient, targeted approach to intensified TB case finding that is within the purview of TB control programs in low- and middle-income countries [7].

Contact tracing and active case finding in household TB contacts has been implemented for decades in high-income countries, where the incidence of TB in the community is low [8]. Ideally, a thorough contact investigation should include clinical evaluation, chest radiological assessment, microbiological examination of sputum, and the use of tests to detect LTBI, such as the tuberculin skin test (TST) or an interferon- γ release assay (IGRA) [9]. In addition, the IFN- γ inducible protein 10 (IP-10) has been found to be increased in the plasma of TB patients and is expressed in high levels following Mtb antigen-specific stimulation in both active TB and LTBI, suggesting its potential as a biomarker for TB [24,25].

There has been an increasing roll-out of contact investigations in high TB burden countries as national programs seek new methods for improving case finding. To date, studies investigating TB contacts in high burden TB districts in Iran have been insufficient and inadequate and were limited to the evaluation of close contacts of pulmonary TB cases that were less than five years or those with an immunodeficiency [10]. Therefore, the current study recruited household contacts of diagnosed TB patients in two high TB burden provinces of Iran to estimate the baseline prevalence of active disease and LTBI among individuals exposed to TB in their household and subsequent incidence of active TB disease and LTBI during follow up. In this survey we focused on adult contacts (≥ 18 years), as

the evaluation of child household contacts has been explored in a separate study.

Material and methods

Study setting and target population

This study was conducted in various districts of two high-burden TB provinces in Iran, including Golestan and Sistan–Baluchestan. The population of this study was adult household contacts of pulmonary TB patients. A household contact was defined as an individual who shared the same enclosed living space for at least seven consecutive days during the 3 months prior to the diagnosis of TB in the index case. Index case identification was performed through the regional reference centers for TB in the Golestan and Sistan–Baluchestan provinces from July 2017 to August 2019. The list of adults with a history of cough >2 weeks who had a diagnosis of sputum smear and/or culture-positive TB was provided from Iran's Ministry of Health and Medical Education. The confirmed TB cases were questioned about any household contacts aged 18 years and older. Household contacts > 18 years of age were verbally invited to participate in our study and were invited to attend their local health centers for clinical and laboratory evaluation. The study was undertaken at an outpatient level and all household contacts were followed up for 18 months after enrolment.

Ethics statement

This study was approved by the Ethical Committee of Shahid Beheshti University of Medical Sciences, (approval number: IR.NIMAD.REC.1395.039). The index cases as well as household contact participants provided signed informed consent forms for inclusion in the study.

Clinical and microbiological evaluation for active TB cases

All household contacts were clinically evaluated at the time of the index TB case diagnosis for active TB and LTBI. The household contacts in this study were categorized as two groups: retrospective and prospective. The retrospective cohort included household contacts of TB indexes that had a diagnosis of pulmonary TB until six months before the beginning this study. The prospective cohort included household contacts of TB indexes that were diagnosed with pulmonary TB during our study. Investigations for LTBI were repeated at three-, 12-, and 18- months if the previous LTBI test was negative. Household contacts were evaluated for active TB using symptoms, signs, and chest radiology. All chest X-rays

were examined by two radiologists, blinded to clinical details. A scale of severity was assigned as described by Petruccioli et al.; 0: normal chest X-ray; 1: mild grade; 2: intermediate grade; 3: high grade [11]. Sputum smear examination and culture on Lowenstein Jensen media were performed for those with abnormal chest radiograph or respiratory symptoms exceeding two weeks in duration.

Investigation of LTBI cases

QFT-Plus and TST were performed to diagnose LTBI cases among the contacts. The QFT-Plus assay was carried out according to the manufacturer's instructions (QIAGEN, Germantown, MD, USA). Briefly, whole blood was added into four QFT-Plus tubes, including Nil control tube (blank), TBI tube (comprising mycobacterial antigens derived from ESAT-6 and CFP-10 proteins of *M. tuberculosis* that stimulate CD4 T-cells), TB2 tube (containing *M. tuberculosis* specific antigens that stimulate CD8 T-cells in addition to CD4 T-cells), and Mitogen control tube (containing non-specific mitogen phytohemagglutinin [PHA]), respectively. All tubes were incubated at 37°C for 20 hours, then, the samples were centrifuged, and the plasma supernatants were analyzed to measure the concentration of IFN-γ using ELISA. IFN-γ was measured using a QFT-Plus Analysis Software (www.quantiferon.com) in a Bio-Rad (Hemel Hempstead, UK) plate reader (model 550) at 450 nm. QFT-Plus tests were considered positive if the antigen-stimulated response of IFN-γ (TBAg-Nil) was ≥ 0.35 IU/mL, negative if the mitogen-stimulated response (Mitogen-Nil) was ≥ 0.5 IU/mL and the antigen-stimulated response was < 0.35 IU/ml, or indeterminate if both mitogen-stimulated and antigen-stimulated responses were < 0.35 IU/ml and un-stimulated response (Nil) was ≥ 0.8 IU/mL.

After QFT-Plus blood sampling, TST was performed using the Mantoux technique by trained personnel following standard procedures. Accordingly, all participants were injected intradermally (ID) with 5 units of purified protein derivative (PPD) and the immunological response was measured as the horizontal diameter of induration at 48–72 h. TST results were interpreted as negative (< 5 mm), and positive (≥ 5 mm) [12]. LTBI was defined as the presence of a positive QFT-Plus result and/or positive TST result in the absence of clinical signs/radiological evidence of active TB disease. In addition, in our study, household contacts without clinical or radiological evidence of active disease that were negative for both QFT-Plus and TST were considered healthy contacts.

In addition, an IP-10 assay was performed for all participants as an additional marker for LTBI detection. Accordingly, IP-10 concentrations were measured in QFT-Plus supernatant plasma using a commercially available Enzyme Linked Immunoassay (ELISA) kit (Antigenix America Inc, New York, US).

The results were analyzed and interpreted as positive or negative according to a receiver operating characteristic (ROC) curve as previously described by Yassin et al. [13].

Statistical analysis

All statistical analysis was performed using SPSS v.22 (IBM Corp, New York, USA) and Prism 7 software (Graphpad Software 6.0, San Diego, USA). ROC analysis was carried out to define cut-off values between those with LTBI and healthy contacts. The significant area under curve (AUC) for LTBI and healthy contacts was compared to determine whether IP-10 could distinguish between the two conditions. The Kruskal–Wallis test and Mann–Whitney U test were used for comparisons and a Bonferroni correction was applied. Statistical tests were considered significant if *P* values were < 0.05 .

Results

Baseline characteristics of the participants

We identified 149 index patients with pulmonary TB with an average of five contacts per index case. A total of 439 individuals who had close contact with the index cases agreed to participate in the study. The participants were categorized into two groups, referred to as the retrospective and prospective groups. The retrospective group ($n = 168$) was defined as the household contacts that had been exposed to an index case in the last six months and the prospective group consisted of those who were recruited prospectively as new index cases were diagnosed ($n = 283$). Of the 439 household contacts analyzed, 299 (68.1%) were female and 140 (31.9%) were male. The median age of the contacts was 36 (range 18–90) years. Demographic characteristics and symptoms recorded at the time of screening are reflected in Table 1.

Active TB among household contacts

Clinical evaluation showed 16 (3.6%) of the contacts reported cough and chest pain, of which 12 (75%) had a productive cough. All these 16 symptomatic contacts had sputum collected for microbiological examination with smear and culture, among whom four (25%) had smear- and culture-positive results. Moreover, one patient was diagnosed with active TB based on the chest X-ray, clinical evaluation, and TST and QFT-Plus results, despite negative microbiology. One household contact was diagnosed with active TB at baseline and four contacts were diagnosed 18 months after the diagnosis of the index case.

LTBI among household contacts

Of the TB contacts included in this study, 100 (22.8%), 41 (12.5%), 40 (14 %) and 23 (9.3%) showed positive TST results

(≥ 5 mm induration), respectively, at the baseline, three months, 12 months, and 18 months after beginning the survey. Accordingly, a total of 204 (46.4%) of household contacts enrolled in our study showed a positive TST reaction.

In total, 237 (58.8%) of the household contacts showed positive IFN- γ responses by the QFT-Plus results. Our findings indicated that 168 (41.7%) of the participants were positive at the baseline, in which 85 individuals were in the retrospective cohort and 83 individuals were followed prospectively. Among contacts with negative baseline QFT-Plus results and valid follow-up QFT-Plus data, 51 (12.7%), 13 (3%) and 5 (1.1%) had become positive after three, 12, and 18 months, respectively.

A total of 285 (64.9%) subjects were defined as LTBI during our study. Our findings revealed that 204 (46.4%) of the household adult contacts were considered as LTBI at the baseline (which could be considered as the prevalence of LTBI at the starting point of the study). Accordingly, of the subjects without evidence of LTBI at baseline, 50 (11.4%), 21 (4.8%) and 10 (2.3%) were diagnosed as LTBI after three-, 12-, and 18-months, respectively. The LTBI incidence rate was calculable only in the prospective cohort and was 0.44 per person per year.

In addition to TST and QFT-Plus, we also measured IP-10 levels using ELISA in supernatants of whole blood samples stimulated with TB-specific-antigens. IP-10 levels were higher in contacts with LTBI (Mean \pm standard error of the mean (SEM): 3621 \pm 303.5 for TB1 and 4075 \pm 333.8 for TB2) compared to healthy contacts (TST-/QFT-) (Mean \pm SEM: 112.4 \pm 87.51 for TB1 and 217.1 \pm 146.9 for TB2) in response to both TB1 and TB2 stimulation (Fig. 1). To define IP-10 results as positive or negative, a cut-off value for IP-10 was calculated using the ROC curve between the LTBI and healthy contacts. For TB1 a cut-off of 26.0 pg/mL identified LTBI with 74.5% sensitivity (69.1%-79.2%) and 85.9% specificity (78.9%-90.9%); similarly, for TB2, an IP-10 level >16.15 pg/mL predicted LTBI with 75.9% sensitivity (70.6%-80.5%) and 86.7% specificity (79.8%-91.5%). Accordingly, 75.4% (215/285) of LTBI contacts and 14% (19/136) of healthy contacts were considered as IP-10-TB1-positive, respectively. In addition, the proportion of LTBI and healthy subjects with positive IP-10-TB2 were, respectively, 77.2% (220/285) and 18.4% (25/136).

Detection of suspicious predisposing factors for positive latent TB patients was performed using binary logistic regression with positive/negative LTBI as outcome and age, gender, smoking, BMI, size of family as predictors. The result showed higher number of family member significantly increases the risk of positive LTBI during the time ($OR = 1.12$). Other mentioned factor did not affect the risk of infection (Table 2).

Detection of suspicious predisposing factors for positive latent TB patients was performed using binary logistic

TABLE 1. Demographic and clinical characteristics of the Iranian household contacts of tuberculosis cases

Demographic and clinical characteristics (n = 439)	N (%)
Gender	
Male	140 (31.9)
Female	299 (68.1)
Age categories	
Age 18–24	82 (12.3)
Age 25–34	120 (18)
Age 35–44	108 (16.2)
Age 45–54	67 (10)
Age 56–64	30 (4.5)
Age ≥ 65	30 (4.5)
Region	
Golestan	
Gorgan	111 (25.3)
Agh'ghala	35 (8)
Gonbad Kavous	57 (13)
Aliabad	27 (6.2)
SistansBaluchestan	
Zabol	64 (14.6)
Zahak	63 (14.4)
Hirmand	33 (7.5)
Hamoun	49 (11.2)
Relationship with index case	
Spouse	83 (18.9)
Sibling	27 (6.2)
Offspring	156 (35.5)
Parents	36 (8.2)
Other (e.g., aunt, uncle, etc.)	134 (30.5)
Had a history of TB	
Yes	8 (1.8)
No	431 (96.6)
Symptoms at entry to the study	
Cough	16 (3.5)
Haemoptysis	12 (2.7)
Unintentional weight loss	5 (1.1)
Fever	3 (0.7)
Chest pain	8 (1.8)
Night sweats	3 (0.7)
Current smoker	16 (3.6)
Tuberculosis prophylaxis	11 (2.5)

regression with positive/negative LTBI as outcome and age, gender, smoking, BMI, size of family members predictors. The result showed higher number of family member significantly increases the risk of positive LTBI during the time ($OR = 1.12$). Other mentioned factor did not affect the risk of infection (Table 3). The study actually was designed as a longitudinal multiple cross sectional study to assess the incidence rate of active and latent TB tuberculosis by household contact. Additionally, a case cohort design was performed to investigate predisposing factor for these two outcomes. Therefore similar to other case cohort studies we considered an internal control group inside the followed population (individuals who did not infected) which are comparable with patients who experienced the outcomes (Infected patients). A logistic regression was used to determine which factor may affect the chance of infection during the follow up period.

Discussion

Household contacts exposed to patients with pulmonary TB, in a variety of settings, are at substantial risk of active TB and

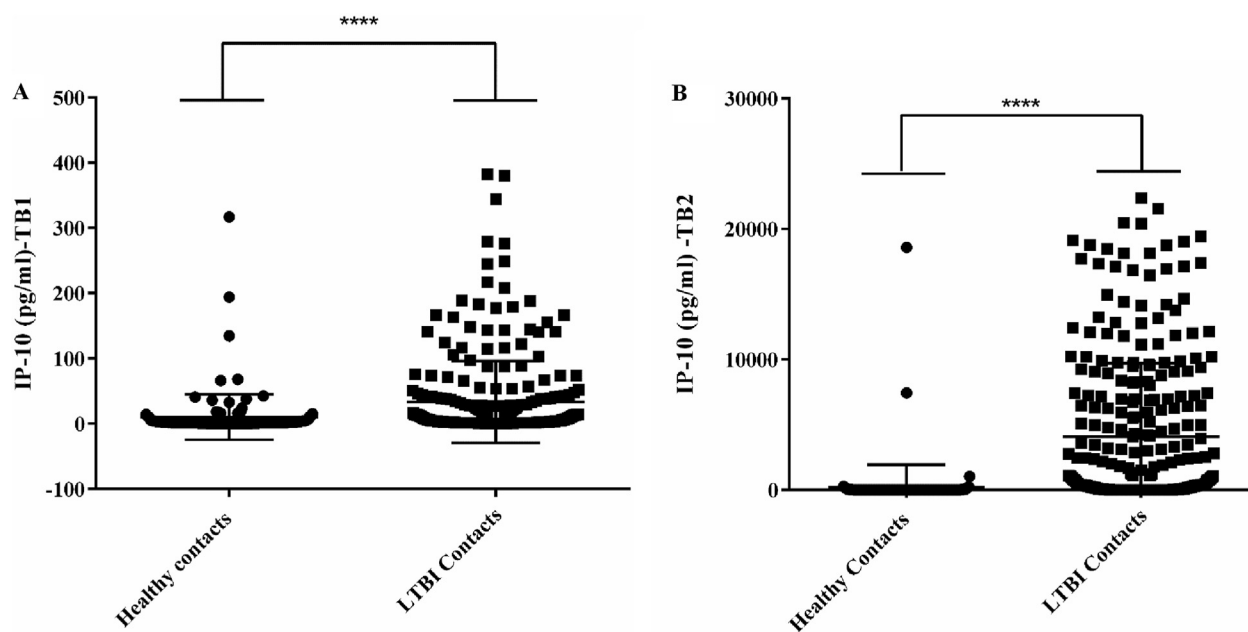


FIG. 1. Significantly increased IP-10 levels in LTBI contacts compared to healthy contacts. A) IP-10 levels in response to TB1 and B) TB2 stimulation. ELISA was carried out with QFT-Plus supernatants and IP-10 was expressed as pg/mL. The horizontal lines represent the median; statistical analysis was performed using the Mann–Whitney test with Bonferroni correction and **** represents P -value < 0.0001 . Footnotes: IP-10: IFN- γ inducible protein 10; LTBI: latent tuberculosis infection.

LTBI. Although the prevalence of LTBI is higher in low- and middle-income countries compared to high-income countries on a population level, there is no significant difference in the prevalence among household contacts of TB patients [6]. Therefore, household contact investigation should be a critical part of the public health response to TB in all contexts. Previously, Beyanga et al. described that an active case finding approach led to a TB detection rate about twenty times higher than the detection rate achieved by passive diagnosis [14]. Non-targeted household investigations in high TB burden regions with weak healthcare systems tend to demonstrate a lower yield [15]. For instance, investigations in Ghana and South Africa reported a low prevalence of TB cases among the household contacts of TB index cases when non-targeted household contact evaluation was implemented [16,17]. To the best of our knowledge, this is the first active case finding of adult household contacts of patients with active TB in Iran.

Using active case finding among household contacts of confirmed adult pulmonary TB cases in two high burden provinces of Iran, we found, on average, 11.4 adults with active TB per 1000 household contacts screened. Our systematic implementation and standardized follow-up of the household contacts indicated that four contacts were diagnosed with active disease after 18 months, thus the incidence of new active TB cases among contacts was 9.1 per 1000. The prevalence

obtained in this study were lower than active case findings in high-burden countries such as Nigeria and Tanzania, which reported about 65 active TB cases per 1000 household contacts [14,18]. Most household contacts in the current study did not have any clinical manifestations of active TB.

Diagnosing LTBI among household contacts and recognizing the potential risk factors for progression to active disease is critical towards reducing TB incidence [19]. Unlike previous studies investigating the prevalence of LTBI in Iran, both TST and IGRA results were available for each subject in our study. Using both TST and QFT-Plus we found that 64.9% of household contacts enrolled in this investigation had LTBI at both baseline and follow-up, which is lower than that reported by Alavi et al. in Ahvaz [20]. However, the prevalence found in our study was higher compared to another study from Tehran [20], which can be justified partly by the high incidence of TB in the regions of our study.

At baseline, the prevalence of TST and QFT-Plus positivity among adult household contacts was 39.5% and 23.5%, respectively. The overall prevalence of TST-positivity among household contacts in our study was higher than found in previous studies in Iran (42.8%) [10,21]. However, the overall prevalence of LTBI found in our study is much lower than the results recently reported in Iraqi Kurdistan [22,23]. Our findings were also in line with other reports in high-incidence, low-resource settings, in which a high prevalence and incidence of

TABLE 2. Analysis of suspicious predisposing factors for positive latent TB patients

	Beta	S.E.	Sig.	Exp(B)	95% CI	
					Lower	Upper
Age	.010	.011	.320	1.011	.990	1.032
Gender	.216	.324	.505	1.241	.658	2.341
Previous Hx of TB	-.737	1.273	.563	.479	.039	5.808
Family size	.114	.057	.044	1.120	1.003	1.252
Smoking	.203	.556	.716	1.225	.412	3.644
BMI	.004	.005	.493	1.004	.993	1.014
Constant	-.163	2.621	.950	.850		

LTBI have been described among household contacts of TB cases [24,25]. The prevalence of LTBI at baseline in our study was 47.3%, as defined by either positive IGRA or TST. The overall prevalence of LTBI among household contacts of TB patients varies between studies, reaching up to 93% in countries with high TB-burden and limited resources [26].

This investigation is, to our knowledge, the first study to actively screen adult household contacts for LTBI in Iran. Our follow-up data indicated that the prevalence of LTBI among household contacts of TB index cases was 46.4% and 58.8% by TST and QFT-Plus, respectively, which is similar to other studies in high-incidence countries [27–29]. In contrary the incidence rate of LTBI was higher than those reported in Iraq (10.6% and 16.3% by TST and QFT-Plus, respectively) [22]. The high prevalence of LTBI among household contacts of pulmonary TB patients in our study suggests the need for ongoing screening of this population. This is in keeping with multiple guidelines [30–32].

In the present study, the positivity rate of IGRA was lower than TST in contacts of pulmonary TB patients at the baseline. However, the overall positivity rate in both IGRA and TST tests were nearly similar (55.4% vs 58.7%, respectively). These findings could suggest that positive IGRA results may be achieved later than TST. It is also possible that cross reactivity of TST with previous BCG vaccination as well as non-tuberculous mycobacteria infections could give rise to more individuals with

TABLE 3. Other mentioned factor did not affect the risk of infection

	Beta	S.E.	Sig.	Exp(B)	95% CI	
					Lower	Upper
Age	.010	.011	.320	1.011	.990	1.032
Gender	.216	.324	.505	1.241	.658	2.341
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BMI	.004	.005	.493	1.004	.993	1.014
Constant	-.163	2.621	.950	.850		

positive TST at baseline [33]. It could also be that the TST at baseline provides a boosting phenomenon that leads to IGRA positivity at subsequent visits. Although the study of Leyten et al. revealed that boosting of QFT-GIT response is rare. [34].

It has been previously described that IGRAs could be more reliable than TST for identification of LTBI cases among household contacts of TB patients in countries, where BCG vaccination is mandatory [34]. Moreover, although conversion of the TST is known to occur within 2–12 weeks, the interval for positive conversion of the IGRA following exposure to a patient with active TB is unclear [35]. We claim that doing both tests together increase the sensitivity for detecting LTBI.

IP-10 assay was previously thought to have significant advantages over IGRAs, including the possibility to use smaller blood volumes and to be detected in urine samples. It is also possible to measure IP-10 in dried plasma spots using filter paper, allowing cheap and simple transportation at room temperature [36–39]. Therefore, an IP-10 assay would be useful as an uncomplicated and inexpensive alternative test for LTBI diagnosis in child household contacts of TB cases, especially in low-resource settings. However, in our study IP-10 assay showed a low specificity and sensitivity to identify those with LTBI (as defined by IGRA and TST).

Of note, previous studies have shown the combination of the IGRAs and IP-10 assay has been reported to increase sensitivity, suggesting there may be a role for IP-10 in a combination test [40].

There were some limitations in our study. First, the social barrier might be the reason household contacts refused to participate. Second, inter-observer variability among health care professionals could lead to misinterpretation of TST results. Finally, the immune response in QFT-Plus negative subjects was not investigated, which may attribute to false negative results. We have considered that the study was done in only one country so the generalizability should be concerned. In addition, we have to mention that we have collected limited clinical data so evaluation of the relationship between clinical and demographic characteristics of contacts and LTBI positivity was not possible to evaluate precisely.

Neither we nor others can differentiate the exact source of infection in a person in endemic countries unless they use foot prints of microbes like PFGE (although Iran is not categorized as endemic yet, but the incidence is considerable). It is the limitation of our study.

Through systematic active case finding among adult household contacts of TB patients and by using both TST and QFT-Plus, the overall rate of LTBI was found to be high in two high TB-burden provinces in Iran. It is recommended that systematic screening for LTBI be expanded to all age groups of household contacts of pulmonary TB cases in Iran. This would help to achieve the global

End TB Strategy and elimination goal feasible, particularly in Golestan and Sistan-Baluchestan provinces. Standardizing the household contact investigation procedures would make implementation and monitoring by health services easier. This will also facilitate the treatment of LTBI cases and would assist Iran in achieving the goals set by the End TB Strategy.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Shahid Beheshti University of Medical Sciences, (approval number: IR.NIMAD.REC.1395.039). The patients provided signed informed consent forms for inclusion in the study.

Consent for publication

Not applicable.

Author contributions

Conceptualization: RMG and AK.

Data curation: RMG, AK, and MN.

Formal analysis: SMHA.

Investigation: APM and MS.

Methodology: RMG, AK, and MN.

Resources: MN and SMHA.

Software: LA.

Supervision: RMG, MN, SMHA, APM, and MS.

Validation: SRT and FF.

Visualization: RMG and SMHA.

Writing – original draft: RMG, SMHA, JAS, and SRT.

Writing – review & editing: RMG, RMG, and JAS.

Transparency declaration

The authors declare that there is no conflict of interest. Researcher Grant Committee under award number [942732] from the National Institutes for Medical Research Development (NIMAD), Tehran, Iran.

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Abbreviations

BCG	Calmette-Guérin bacillus vaccine
CI	Confidence interval
IGRAs	Interferon- γ release assays
IP-10	interferon- γ -induced protein-10
IQR	Interquartile range
HIV	Human immunodeficiency virus
LTBI	Latent tuberculous infection
Mtb	<i>Mycobacterium tuberculosis</i>
PHA	phytohemagglutinin
PPD	Purified proteinderivatives
QFT	QFT-Plus, QuantiFERON®-TB Gold Plus
TB	Tuberculosis
TST	Tuberculin Skin Test
WHO	World Health Organization

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