

## Estimating the prevalence of Positive Tuberculin Skin Test Reactions in General Population and High-risk Groups: A Meta-analysis

### Abstract

Results of tuberculin skin test (TST) surveys among different populations have been reported in many studies as a method for detecting primary *Mycobacterium tuberculosis* infection. Combining these results provides reliable estimates of primary latent tuberculosis (TB) infection for health policymakers. This study aims to estimate the prevalence of latent TB infection in general and high-risk populations in Iran. National and international databanks were searched using specific keywords. After restricting the search strategy, duplicates exclusion, reviewing titles, abstracts and full texts, and quality assessment, eligible papers were selected. The heterogeneity between the results was assessed according to Cochrane and I-squared indices. The prevalence of positive TST reactions was estimated using fixed and random effect models. Totally, 33 papers were entered into the meta-analysis reporting the TST results in 12693 people aged over 18. The prevalence (95% confidence intervals) of positive TST reactions in all groups, general population, health staff, medical students, household close contacts, patients with TB, immunocompromised patients, HIV/AIDS patients, and those with risky behaviors was 26.2% (19.6–32.8), 25.4% (4.8–46.1), 38.9% (27.4–50.9), 13.4% (9.9–16.7), 35.9% (16.4–55.5), 13.7% (8.4–18.9), 29.4% (21.2–37.7), and 14.6% (3.9–25.3), respectively. Our study showed great varieties of positive TST results among different Iranian subpopulations. Furthermore, the prevalence of latent TB infection among health professionals and family members of TB patients was considerably different from that of the other subgroup. Since TB control programs such as active case finding are routinely conducted among household close contacts and HIV/AIDS cases, other high-risk groups including health-care workers and immunocompromised patients should be taken into consideration in these preventive programs.

**Keywords:** Latent tuberculosis, purified protein derivative, tuberculin skin test, tuberculosis

### Introduction

In 2016, tuberculosis (TB) is still one of the most important fatal infectious diseases in the world.<sup>[1,2]</sup> In the recent years, due to population changes, inappropriate health coverage, immunodeficiencies, unsuccessful control of the disease, HIV/AIDS epidemic, income imbalances, spread of the poverty, and psychological problems in Asian and African countries, TB has been taken into consideration.<sup>[3–6]</sup>

Approximately 9.6 million people developed TB during 2015, 1.5 million of which were died. One-third of the world population is at risk of developing TB infection.<sup>[7–10]</sup> It is estimated that the prevalence of TB will be three folds of that in 2010.<sup>[11]</sup> The incidence rate of TB in Iran in 2014 was 16.75 per 100,000 populations which were 1.38 folds than that in 2005.<sup>[5,7,9]</sup>

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Latent TB infection is defined as the asymptomatic presence of *Mycobacterium tuberculosis* (MBT) in an infected person leading to a tuberculin skin test (TST) reaction.<sup>[12,13]</sup> In most cases, MBT is controlled by the immune system, and only a latent TB infection is occurred. This infection is not harmful but can potentially lead to an active disease according to the situation of patient. Therefore, reduction in the number of latent infection sources can ensure the human health and prevent the transmission of the infection in the future.<sup>[12,13]</sup>

TST is a reliable and standard method widely used for diagnosis of latent TB infection. It is also useful in the evaluation of those suspected to TB with negative MBT cultures. In this test, 0.1 ml of an antigen including purified protein derivatives (PPD) is injected intradermal into the anterior forearm. The size of the skin reaction (induration) is measured after 48–72 h.<sup>[14]</sup>

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Many TST surveys have been carried out in Iran to estimate the latent TB infection among different subpopulations such as general population, health workers, medical students, and high-risk and immunocompromised patients. Systematic combining the results of these studies using meta-analysis<sup>[15-17]</sup> provides reliable evidences required for TB control programs. This study aims to estimate the frequency of positive TST reactions in general and high-risk populations (health and treatment staffs, medical students, household close contacts, immunocompromised patients, HIV/AIDS cases, and people with high-risk behavior) in Iran.

## Procedure

### Search strategy

Iranian and international databanks such as SID, MAGIran, Medlib, PubMed, Google Scholar, Scopus, and ScienceDirect were searched to find electronic papers published from 1990 to 31 January 2016. The search was conducted during 24 February to 11 March 2016 by two independent researchers using the following keywords and their Farsi equivalents:

“Prevalence,” “Frequency,” “Percent,” “Latent Tuberculosis Infection,” “Tuberculin Skin Test,” “TST,” “LTBI,” “LTI,” “Purified Protein Derivative” “PPD,” “Tuberculin test,” “Latent tuberculosis,” “Cross-sectional study,” “descriptive study,” “Longitudinal study,” “cohort study,” “Iran,” and “Not children.”

To increase the number of eligible articles, references of these studies as well as nonelectronic articles were investigated. Moreover, some research centers and experts in the field of infectious diseases were interviewed. The search results were evaluated by a third researcher for detecting any ignored relevant article.

### Study selection

Full texts or abstracts of all studies identified during the advanced search were extracted. After excluding duplicates, we investigated the remained articles reviewing titles, abstracts, and full texts. We also reviewed the findings of the articles to prevent reprint bias.

### Quality assessment

The articles selected during the above steps were quality assessed using STROBE checklist.<sup>[18]</sup> This checklist contains 22 questions including different aspects of methodology. The total quality score of each paper varied between 0 and 44 classified into low quality (<15.5), moderate quality (15.5–29.5), and high quality (30–44). Low-quality studies were excluded from the meta-analysis.

### Data extraction

Titles, first author name, date of study conduction, sample size and sampling method, study design, study language,

study subgroups, mean age and age range of participants, cutoff point for diagnosis of latent TB infection, time of reading the TST results, frequency of TST reaction sizes (0–5, 6–9, above 10, and above 15 mm) were extracted from each study and entered into the Excel spreadsheet.

### Inclusion criteria

Studies written in English or Persian reporting the sample size and prevalence of positive PPD test (>5 mm for HIV/AIDS cases and >10 mm for others) among Iranian population aged >18 years and achieved enough quality scores were included into the meta-analysis.

### Exclusion criteria

Studies did not report the sample size and frequency of cases with positive TST, case reports, case-control and experimental studies, studies carried out among populations under 18, and those with low-quality scores (<15.5) were excluded from the meta-analysis.

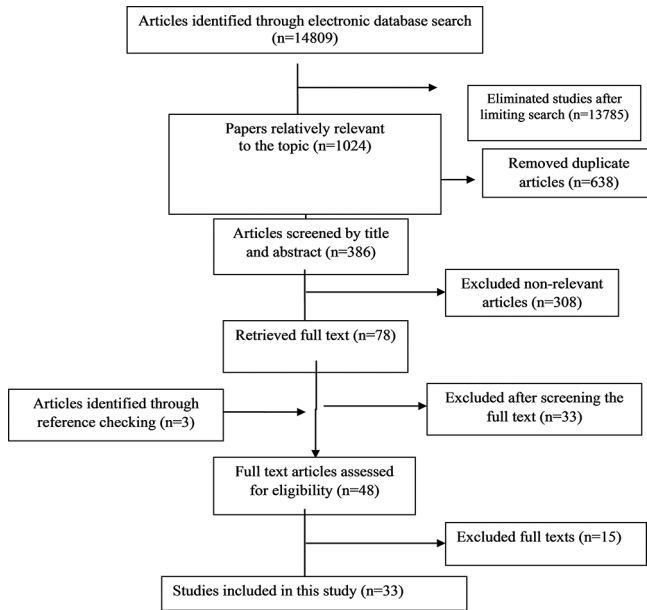
### Statistical analysis

All statistical analyses were performed by Stata version 11 package (StataCorp, College station, TX, USA). Standard error of the frequency of TST results was calculated based on binomial distribution rule. The heterogeneity between the results was assessed using Cochrane and I-squared ( $I^2$ ) indices with  $P < 0.1$  as significant heterogeneity. The  $I^2$  index <25%, 25%–75%, and >75% were considered low, moderate, and high heterogeneity.<sup>[19]</sup> Based on the results of the heterogeneity studies, random or fixed effect models were applied for combining the primary estimates. Some of the suspected factors for heterogeneity were assessed using meta-regression models. Furthermore, subgroup analyses were performed based on publication date, study groups, and publication language. In addition, sensitivity analysis was conducted to assess the effect of each primary study on the total estimates. Publication bias was conducted with Egger test. Point and pooled estimates of TST results as well as their 95% confidence intervals (CIs) were illustrated by forest plots.

## Results

During the primary search, 14,809 evidences reporting the results of Iranian TST surveys were identified which were reduced to 386 after restricting the search strategy as well as duplicate exclusion. Investigating the titles and abstracts, 308 irrelevant articles were detected, and reviewing full texts, 33 irrelevant studies were removed. In addition, three new studies were detected eligible and added to the search results. During the investigation of inclusion/exclusion criteria and quality assessment, 15 papers were omitted and 33 papers were remained for the final meta-analysis [Figure 1].

The publication dates of the primary studies varied from 1996 for the study conducted by Sadeghi reported the

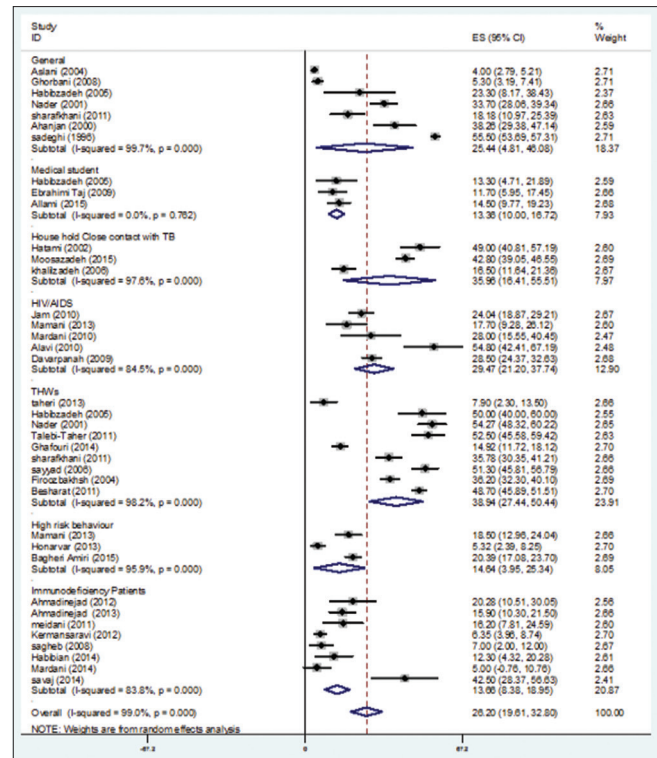


**Figure 1: Literature search and review flowchart for selection of primary studies**

prevalence of positive PPD among general population to 2015 for the study conducted by Moosazadeh reporting the prevalence of latent TB infection as of 42.8% among family members of TB cases [Table 1]. The study populations were general population (four studies), health staff (six studies), medical students (two studies), household close contacts (three studies), immunocompromised patients (eight studies including six studies among hemodialysis patients, one study among diabetic patients, and one study among lung and cardiac transplant candidates), HIV/AIDS cases (four studies), populations with risky behaviors (two studies), general population plus medical students and staff (one study), HIV/AIDS cases plus those with risky behaviors (one study), and general population plus health workers (two studies) [Table 2].

TST results were read after 48 h (four studies) or 72 h (29 studies). The cutoff point for detecting latent TB infection had been considered 5 mm for HIV/AIDS cases and >10 mm for other groups.

Minimum and maximum frequencies of positive TST reactions were 4% in the study conducted by Aslani among general population in 2004 and 55.5% in the study conducted by Sadeghi among general population in 1996, respectively [Table 1]. As illustrated in Figure 2, the prevalence of positive (>10 mm) TST reactions among Iranian people aged over 10 using random effect model was estimated as of 26.2% (95% CI: 19.6–32.8). Frequency of >15 mm TST reactions was reported in six studies varied between 2.5% among general population in Ahanjan study and 30.1% among health staff in Nader study. Based on random effect model, the total frequency of >15 mm TST reaction was estimated as of 11.2% (95% CI: 10.01–12.4).



**Figure 2: Frequency of the positive tuberculin skin test by subgroup according to the Iranian studies entered into the meta-analysis**

Meta-regression models showed that publication date ( $P = 0.007$ ) and study groups ( $P = 0.04$ ) had significant influence on the heterogeneity [Table 3]. Subgroup analysis indicated that health staffs (38.9%) and household close contacts (35.9%) had the most prevalence of positive TST, while medical students had lower latent TB infection rates than the other groups (13.4%). The total prevalence of latent TB infection according to the studies carried out before and after 2007 was estimated as of 35.5% (18.9–51.9) and 26.2% (19.6–32.8), respectively.

Out of the studies entered into the meta-analysis, 20 papers had been written in English and 13 papers written in Persian. The total estimates of positive TST according to these studies were 25.1% (15.6–34.6) and 27.6% (19.3–35.8), respectively. There were no significant differences between the results based on the publication language.

Results of the sensitivity analysis showed that Besharat, Sadeghi, and Aslani studies had considerable influence on the total estimate [Figure 3]. Egger test results showed no evidence of publication bias ( $\beta = 4.3, P = 0.144$ ).

## Discussion

Our study estimated the total prevalence (95% CIs) of positive TST among all study groups, general population, health staffs, medical students, household close contacts, immunocompromised patients, HIV/AIDS cases, and people with risky behaviors as of 26.2% (19.6–32.8), 25.4 (4.8–46.1), 38.9% (27.4–50.4), 13.4% (9.9–16.7),

**Table 1: Characteristics of the studies entered into the meta-analysis**

Id	First author	Publication year	Population	Sample size total	PPD	
					>10 (%)	>15 (%)
1	Habibzadeh	2005	THWs	96	50	-
2	Habibzadeh	2005	Medical student	60	13.3	-
3	Habibzadeh	2005	General	30	23.3	-
4	Ahanjan	2000	General	115	38.26	2.5
5	Aslani	2004	General	1000	4	-
6	Ebrahimi Taj	2009	Medical student	120	11.7	-
7	Ghafouri	2014	THWs	476	14.92	5.3
8	Hatami	2002	Household close contact with TB	143	49	-
9	Kermansaravi	2012	Immunodeficiency patients (diabetic)	400	6.35	-
10	Meidani	2011	Immunodeficiency patients (hemodialysis)	74	16.2	-
11	Nader	2001	General	270	33.7	7.7
12	Nader	2001	THWs	269	54.27	30.1
13	Sayyad	2006	THWs	318	51.3	-
14	Sharafkhani	2011	General	110	18.18	-
15	Sharafkhani	2011	THWs	299	35.78	-
16	Ahmadinejad	2012	Immunodeficiency patients (kidney failure)	65	20.28	-
17	Allami	2015	Medical student	213	14.5	-
18	Besharat	2011	THWs	1212	48.7	24.6
19	Davarpanah	2009	HIV/AIDS	459	28.5	-
20	Habibian	2014	Immunodeficiency patients (hemodialysis)	65	12.3	-
21	Jam	2010	HIV/AIDS	262	24.04	-
22	Mamani	2013	HIV/AIDS	79	17.7	-
23	Mamani	2013	High-risk behavior group (injecting drug users)	189	18.5	-
24	Moosazadeh	2015	Household close contact with TB	668	42.8	-
25	Sadeghi	1996	General	2899	55.5	-
26	Sagheb	2008	Immunodeficiency patients (hemodialysis)	100	7	-
27	Taheri	2013	THWs	89	7.9	10.11
28	Alavi	2010	HIV/AIDS	62	54.8	-
29	Ghorbani	2008	General	433	5.3	-
30	Ahmadinejad	2013	Immunodeficiency patients (kidney failure)	164	15.9	-
31	Bagheri Amiri	2015	High-risk behavior group (homeless people)	569	20.39	-
32	Honarvar	2013	High-risk behavior group (opiate drug users)	226	5.32	-
33	Khalilzadeh	2006	Household close contact with TB	224	16.5	-
34	Mardani	2010	HIV/AIDS	50	28	-
35	Savaj	2014	Immunodeficiency patients (hemodialysis)	47	42.5	-
36	Talebi-Taher	2011	THWs	200	52.5	-
37	Mardani	2014	Immunodeficiency patients (lung and heart transplant candidates)	55	5	-
38	Firoozbakhsh	2004	THWs	583	36.2	-

TB=Tuberculosis, HIV=Human immunodeficiency virus, PPD=Purified protein derivatives THWs= Treatment and Health Workers

35.9% (16.4–55.5), 13.7% (8.4–18.9), 29.4% (21.2–37.7) and 14.6% (3.9–25.3), respectively.

The prevalence of latent TB infection among general population in China<sup>[20]</sup> and the USA<sup>[21]</sup> has been estimated as of 19.98% (2015) and 4.4% (2016), respectively. Both of these estimates were lower than that estimated in the current meta-analysis.

According to the results of a study carried out in Malaysia in 2011, the prevalence of latent TB infection among health-care workers was 10.6% (8.6–12.6), which was considerably lower than that estimated in the current meta-analysis. The observed difference might be partially

due to the effect of false-positive results following previous BCG vaccination and exposure to the none TB *Mycobacterium*. The situations of TB infection/disease as well as health development status are similar in the two countries. Moreover, the above-mentioned findings in Malaysia are estimated by a single primary study and maybe some other surveys provide different results while the estimate of our study has been obtained by combination of the results of multiple surveys.<sup>[22]</sup>

Another study conducted in western Kenya in 2015 showed the prevalence of positive TST among health-care workers as of 60%, which might be due to the high prevalence of

**Table 2: Estimating the prevalence of Positive Tuberculin Skin Test Reactions by subgroup**

Subgroup	Number primary studies*	Sample size	Frequency		Heterogeneity		
			Percentage	95% CI	I <sup>2</sup>	Q	P
General	7	4857	25.4	4.8-46.1	99.7	2350.4	<0.001
Treatment and health workers	9	3542	38.9	27.4-50.4	98.2	436.6	<0.001
Medical students	3	393	13.4	9.9-16.7	0	0.54	0.762
Household close contact with TB	3	1035	35.9	16.4-55.5	97.6	83.4	<0.001
Immunodeficiency patients	8	970	13.7	8.4-18.9	83.8	43.2	<0.001
HIV/AIDS	5	912	29.4	21.2-37.7	84.5	25.8	<0.001
High-risk behavior	3	984	14.6	3.9-25.3	95.9	49.4	<0.001
Pooled estimate (total)	38	12693	26.2	19.6-32.8	99	3813.9	<0.001

\*Number of the primary studies carried out among common subgroups. TB=Tuberculosis, HIV=Human immunodeficiency virus, CI=Confidence interval

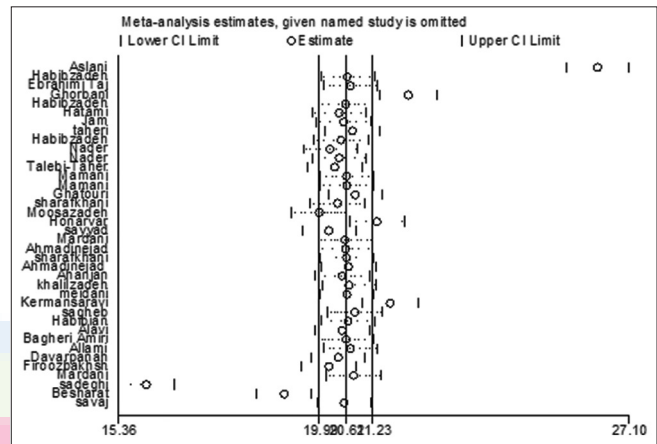
**Table 3: The associations between suspected factors for heterogeneity of the results**

Variables	B	P
Publication year	-1.5	0.007
Population group	-2.8	0.043
Age mean	-0.2	0.528

HIV/AIDS in this area. It should be noted that 22% of the population living in this region were HIV positive.<sup>[23]</sup> Results of a meta-analysis<sup>[24]</sup> showed that the prevalence of latent TB infection among medical and nursing students in the low- and middle-income countries was 12%, which is similar to that observed in the current meta-analysis. That study reported the risk of TB infection among health-care workers as of 25–5361 per 100,000 population. In South Africa, the prevalence of latent TB infection among medical students was reported as of 26.6%, which was higher than our estimates.<sup>[25]</sup>

Fox *et al.* in 2013 combined the results of 76 studies carried out among 60,557 household close contacts with TB cases in low- and middle-income countries and reported the prevalence of latent TB infection as of 51.5% (47.1–55.8), which was higher than Iran's estimate. They also estimated the prevalence in high-income countries combining the results of 92 TST surveys as of 28.1% (24.2–32.4), which was lower than that of Iran. Therefore, it seems that the TB infection rate among Iranian household close contacts is in the middle of that among low- and high-income countries. Obviously, there is a great heterogeneity between the incidence and prevalence of TB and HIV/AIDS as well as vaccination status in low- and high-income countries.<sup>[26]</sup>

In Shanghai, the prevalence of TB infection (17.2%) was lower than that of Iran; however, the survey was conducted among people other than close contacts.<sup>[27]</sup> Latent TB infection among household close contacts in Korea (38%) in 2014<sup>[28]</sup> was similar to the rates observed in Iran, while the corresponding rate in Australia (31.4%) was higher than Iran.<sup>[29]</sup> In northern parts of Iran, latent TB infection rate was the same among male and female close contacts (41.8% vs. 43.7%, respectively).<sup>[13]</sup>



**Figure 3: Sensitivity analysis for assessing the effect of each primary study on the total estimates**

Deiss *et al.* conducted a systematic review in 2009 and showed that latent TB infection among IV drug users varied between 10% and 59% as similar to the rates represented in the current meta-analysis. The addiction not only weakens the immune system but also leads to other socioeconomic problems such as homelessness, imprisonment, and poor socioeconomic and sanitary status.<sup>[30]</sup> Another study in Taiwan in 2013 showed that 85% of addicts under methadone replacement therapy were positive for TST which is expectable in such groups.<sup>[31]</sup> Mamani *et al.* reported that the prevalence of latent TB infection among Iranian intravenous drug users was 18.3%, which was similar in both genders.<sup>[32]</sup> Selwyn<sup>[33]</sup> found that the results of TST survey among HIV-positive patients were in keeping with the results of our meta-analysis.

Based on the results of TST studies conducted by Foster *et al.*,<sup>[34]</sup> Manuel *et al.*,<sup>[35]</sup> Seyhan *et al.*,<sup>[36]</sup> and Bartalesi *et al.*,<sup>[37]</sup> the prevalence of latent TB infection among patients undergoing hemodialysis was estimated as of 13%, 24.2%, 34%, and 19%, respectively.

There are different reasons for the heterogeneity between the results of Iranian surveys with those conducted in other countries such as prevalence of TB infection/disease, time duration of close contact with active TB cases, non-TB

*Mycobacterium*, dose and quality of PPD injected, the level of the immune responses, BCG vaccination coverage, and study age group among different countries.

It should be mentioned that in a region with 90% TB infection prevalence, the positive predictive value for TST is 99%. This value is 15% in a region with 1% infection prevalence.<sup>[38]</sup> It causes high false-positive results.

A systematic review<sup>[39]</sup> combined the results of 22 TST surveys carried out among pregnant women in the USA, China, Tanzania, and Chile. Such subgroups were not considered in the Iranian TST surveys.

The significant heterogeneity observed between the results of the primary studies was one of the limitations in the current meta-analysis which was not changed after subgroup analysis based on population subgroups and publication date. It might be due to other potential factors influenced the heterogeneity such as area of residence and methodology. We did not investigate the effect of these factors due to the lack of relevant data in the primary studies. Another limitation of our meta-analysis was that the primary evidences were collected from only 13 provinces, most of which were conducted in the capital of Iran. While, among the most affected areas such as Sistan and Baluchestan (southeast Iran) and Golestan (northern Iran), only one TST survey had been carried out which met our inclusion criteria.

## Conclusions

Our meta-analysis showed that there is a great variation in the results of TST among different population groups in Iran. We also found that health-care workers and household close contacts (family members of TB cases) were more infected than the other study groups. Since TB control programs such as active case finding are routinely conducted among household close contacts, HIV/AIDS cases, and immunocompromised patients, other high-risk groups including health-care workers should be taken into consideration in these preventive programs.

In addition, due to the above-mentioned variation in the TB infection estimates in different provinces, further studies are recommended to be carried out with more precise methodologies among all subgroups in geographical areas with different endemicities.

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## Conflicts of interest

There are no conflicts of interest.

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