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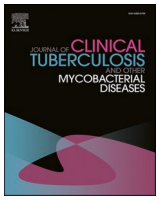

Tuberculin test using Indian indigenous purified-protein derivative (PPD) shows only moderate agreement with international standard PPD

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ABSTRACT

Background: In India, the prevalence of Latent TB infection (LTBI) is estimated to be around 40%. Various formulations of PPD(Purified protein derivative) are available, for diagnosis of LTBI, which may give variable responses. The commercially available PPD in India is by Arkray Healthcare (TST-Arkray). It is unclear if this product may have a similar sensitivity compared to other internationally accepted tuberculins (TST-Tubersol).
Objectives: To assess the performance of the two TSTs compared to Quantiferon-Gold Plus (QFT-Plus).
Methodology: A blood sample was collected for the QFT-Plus test. Both the TSTs were placed in the right and the left volar aspect of the forearms and 48 hrs later, the subjects came back to the study site for reading.
Results: Among the 512 participants who were recruited, 326 subjects were healthcare professionals and 186 subjects were household contacts of patients with tuberculosis. They were tested with both TST-Tubersol and TST-Arkray, 139(27 %) participants tested positive for TST-Tubersol (≥10 mm), whereas 203 participants (40.1 %)tested positive for TST-Arkray. There was moderate agreement between the two tests with k = 0.58. Also, there was only poor agreement between both the TSTs with QFT Plus(kappa = 0.19 for Tubersol and 0.17 for Arkray). With QFT-Plus as gold standard, the sensitivity, specificity, PPV and NPV of TST-Tubersol, ast an induration cut-off of 10 mm was 46.8 %,76.3 %,31.8 % and 85.8 %. respectively and TST- Arkray; 60.6 %, 64 %, 28.5 % and 87.2 % respectively.
Conclusion: The Indian TST (Arkray Diagnostics) has shown moderate agreement with the internationally accepted Tubersol. Additionally, there was poor agreement between the TSTs and QFT plus test.

1. Introduction

Tuberculosis (TB) is a major cause of ill health and disability, one of the top ten causes of mortality worldwide, and the leading cause of death from a single infectious agent (ranking above HIV/AIDS since 2007) until the coronavirus (COVID-19) pandemic [1]. The COVID-19 pandemic has reversed the years of progress in providing essential TB services and reducing the TB disease burden. Global TB targets are mostly off-track, with reduced access to TB diagnosis and treatment, increasing TB deaths [2]. India has the largest burden of global TB,

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accounting for one-quarter of the total number of cases reported. The countries that contributed most to the global reduction in TB notifications between 2019 and 2020 were India (41 %), Indonesia (14 %), the Philippines (12 %) and China (8 %) [1]. Reductions in the reported number of people diagnosed with TB in 2020 and 2021 suggest that the number of people with undiagnosed and untreated TB has grown, resulting first in an increased number of TB deaths and more community transmission of infection and then, with some lag-time, increased numbers of people developing TB. [1] Latent tuberculosis infection (LTBI) is defined by the detection of a specific immune response to Mycobacterium tuberculosis complex (MTC) antigens in a healthy person (i.e., with no symptoms or signs of active TB) [3]. The diagnosis of LTBI is difficult and it depends on the indirect measurements of immune reactivity to antigenic challenge. [4] There is no gold standard test available for the diagnosis of LTBI. Hence the global LTBI prevalence is also not certain. On average, 10 % of immune-competent hosts with LTBI will develop active disease during their lifetime, and this risk increases in immune-deficient hosts [5]. In India, the prevalence of LTBI is estimated to be about 40% [5].

The Tuberculin Skin Test (TST) is one of two methods recommended by WHO for the diagnosis of LTBI and is the most common test used in high-burden countries. Either TST or IGRA (Interferon Gamma Release Assay) can be used to test for LTBI in high-income and upper-middle-income countries with an estimated TB incidence of less than 100 per hundred thousand [6].IGRAs are more expensive and technically complex to perform than TST. Given the comparable performance and the cost, replacing the TST with IGRAs as a public health intervention in resource-constrained settings like in India is not recommended [7–9]. However, various formulations of tuberculin are available for the TST, which may give variable responses when administered in different populations [7,8]. Purified protein derivative (PPD) tuberculin is a precipitate of species-nonspecific molecules obtained from filtrates of sterilized, concentrated cultures. The commercially available tuberculin in India is manufactured by SPAN Diagnostics/ Arkray Healthcare, (PPD-RT 23; TST-Arkray), which is a PPD calibrated against WHO approved standard preparation (RT23). This antigen solution was made available in 2003 and it provided the Revised National TB Control Programme (RNTCP) and researchers in India with a locally sourced option for LTBI testing. Several studies in India are now using this tuberculin formulation, but it is unclear if its accuracy is similar to other internationally accepted tuberculin formulations, and we are not aware of any published validation of this Indian product.

This study was designed to determine the degree of agreement of the TST-Arkray (PPD-RT 23; Arkray Diagnostics; 5 TU) with a validated and internationally used Tubersol (Tuberculin CT68, Sanofi Pasteur Ltd; 5 TU) -TST-Tubersol. Tubersol is a tuberculin preparation from a large Master Batch Connaught Tuberculin (CT68) and is a cell-free purified protein fraction obtained from a human strain of Mycobacterium tuberculosis grown on a protein-free synthetic medium and inactivated. Both these were also compared with QuantiFERON-TB Gold Plus (QFT-Plus), an IGRA that measures the cell-mediated immune response to specific TB antigens in whole blood.

2. Methodology

2.1. Study population

The study was performed under the aegis of the Regional Prospective Observational Research for Tuberculosis (RePORT) India consortium, an Indo-US collaborative effort, to perform observational research in Tuberculosis. It was established in 2013, jointly by the Department of Science & Technology (DST) India and the National Institute of Allergy and Infections (NIAID), USA, under the Indo-US Vaccine Action Program (VAP).

Our study population was recruited from two tertiary care teaching hospitals: the Christian Medical College, Vellore and the Jawaharlal Institute of Postgraduate Medical, Education and Research (JIPMER), Pondicherry. We included household contacts of people with pulmonary TB and healthcare personnel (HCP). We excluded people less than or equal to 17 years of age, people with presumptive TB, those with known or suspected immunosuppressive states or autoimmune disorders, those on treatment with steroids or other immune-suppressive agents and those who refused to provide informed consent.

2.2. Methodology

The study protocol was approved by the Institutional review board with IRB No.9632 dated 23.09.2015. After obtaining informed consent, the following details were obtained: demographic characteristics, history of exposure to TB, and history of BCG vaccination. Subsequently, the presence/absence of the BCG scar was verified. BCG vaccination results in reactive tuberculin skin tests (TSTs) in many recipients, thereby creating the potential for confusion in interpretation; there is no reliable method to distinguish a true-positive TST due to infection versus a false-positive test from prior vaccination [10]. A blood specimen was collected for QFT plus test in the appropriate tubes. Both the TSTs (TST-Tubersol & TST- Arkray) were placed and 48 hrs later, the participants were asked to come back to the study site for reading. Both the person placing the TST and the person who measured the induration were blinded to the tuberculin formulation used. Participants who did not have TST placed did not come for TST reading or had indeterminate QFT-Plus results were excluded from the analysis.

2.3. Tuberculin skin test (TST)

0.1 mL of PPD for both the study TSTs was injected into the volar aspect of the forearms. The placement of each test was standardized using a measuring tape to be 10 mm below the crook of the elbow. The test reagents were injected intra-dermally with a tuberculin syringe, with the needle bevel facing upward, to produce a wheal of between 6 and 10 mm in diameter [11].

2.4. QFT –Plus(Quantiferon Gold Plus)

The 4th generation Quantiferon test (QFT-Plus) was performed on a blood sample by ELISA method as per the manufacturer's recommendations. QFT-Plus was positive if the response to the TB antigens minus the negative control was $>$ 0.35 IU/ml and 0.25 % of negative control [7].

2.5. Positive TST and QFT-Plus results

All participants with test results that are positive for latent TB by either or both the TST tests and or QFT- plus were screened for symptoms of active TB and referred for further evaluation, including a chest x-ray, according to prevailing programmatic guidelines [12].

2.6. Sample size calculation and statistical methods

The agreement between the two TSTs is considered satisfactory if the true kappa could be concluded to be at least 0.70 [13]. The test of kappa was two-sided at the 5 % significance level and the test should show significance with a power of 90 % if the true kappa was 0.75. The expected proportion of tests with positive TST was assumed to be 40 %, the required sample size is 1600.

We estimated the kappa and the corresponding 95 % CI for the Kappa statistics to determine the agreement between the two tests. We used the Kappa value interpretation according to Landis & Koch et al., [14]: $<$0- No agreement, 0 – 0.20 Slight, 0.21 – 0.40 Fair, 0.41 – 0.60 Moderate, 0.61 – 0.80 Substantial and 0.81–1.0 Perfect. Sensitivities specificities, positive and negative predictive values of the two TST induration thresholds were measured against QFT- plus result as reference standard

and analysis was done using the SPSS version 19. software.

3. Results

The baseline characteristics of the study population are provided in Table 1. Out of the 512 participants who were recruited, 326 subjects were healthcare professionals and 186 subjects were household contacts of TB patients. Sixteen participants did not come for follow-up and were excluded. Among 496 participants who qualified for final analysis, the median age was 21.3 years (IQR 20.3,22.5 years), 194(39 %) subjects were males, 30(6 %) gave history of diabetes and 55(11.1%) history of chronic respiratory disorders. A vast majority (474, 95.5%) of the participants had a BCG scar. The interpretation of the TSTs was documented with induration at three cut-offs, 5 mm, 10 mm and 15 mm, as per the Centre for disease control recommendations(CDC) [11].

The results of both TSTs are compared in Table 2. At an induration cut-off of 5 mm, 229 (46.2 %) participants tested positive for the TST-Tubersol, while 247 (49.7 %) tested positive for the TST-Arkray (Table 2). There was substantial agreement (kappa = 0.77) between the two TSTs.

Using the standard induration cut-off of 10 mm, 139 (28.1 %) participants tested positive for TST-Tubersol, while 203 (40.1 %) participants tested positive for TST-Arkray. There was only moderate agreement (kappa = 0.58). Using an induration cut-off of 15 mm, 68 (13.7 %) participants tested positive with the TST-Tubersol test, while 121 (24.4 %) subjects tested positive with TST-Arkray, the agreement was moderate(kappa = 0.47).

The agreement of both TST tests with QFT-plus results at various cut-offs is tabulated in Table 3. At an induration cut-off of 5 mm, the agreements of TST- Tubersol and TST- Arkray with QFT– plus were (kappa = 0.16 and 0.14, respectively). At an induration cut-off of 10 mm, the agreements of TST- Tubersol and TST- Arkray with QFT – Plus were (kappa = 0.19 and 0.17, respectively). At an induration cut-off of 15 mm, the agreements of TST -Tubersol and TST- Arkray with QFT – Plus were (kappa = 0.28 and 0.23, respectively). Therefore, the agreements between the TSTs and QFT – plus were poor at all induration cut-offs.

There was poor agreement between TST and QFT-plus. With the standard cut-off of ≥ 10 mm,94 participants who tested positive for TST-Tubersol and 143 participants who tested positive for TST-Arkray, tested negative by QFT-plus. Likewise, with a higher cut-off of ≥ 15 mm, 32 participants who tested positive for TST-Tubersol and 88 participants for TST-Arkray, tested negative by QFT-plus (Table 3).

With QFT-Plus as gold standard, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of TST-Tubersol, at an induration cut-off of 10 mm was 46.8 %, 76.3 %, 31.8 % and 85.8 % respectively(Table 3). Whereas, TST Arkray, at the same induration cut-off showed sensitivity of 60.6 %, specificity of 64 %, PPV of 28.5 % and NPV of 87.2 %(Table 4).

Table 1
Baseline characteristics: N = 496 participants (Health care professionals = 326, Household contacts = 186).

Variable	Frequency(N)	Percentage
Age		
<= 22 Years	304	60.94
> 22 Years	192	39.06
Males	194	39.45
Smokers	10	2.15
Presence of BCG scar	474	95.5
Not aware of BCG status	20	5.66
Diabetics	25	5.86
Chronic respiratory disorders	50	10.74

Table 2
Positivity of TST-Tubersol and TST- Arkray at various indurations.

TST-Tubersol		TST-Arkray		Agreement	Kappa
Cut-off 5 mm					
<5mm	≥5mm	<5mm	≥5mm	88.7	0.77
267 (53.8 %)	229 (46.16 %)	249 (50.2 %)	247 (49.7 %)		
Cut-off 10 mm				Agreement	Kappa
<10 mm	≥10 mm	<10 mm	≥10 mm	88.1	0.58
357 (71.9 %)	139 (28.1 %)	293 (59.1 %)	203 (40.1 %)		
Cut-off 15 mm				Agreement	Kappa
<15 mm	≥15 mm	<15 mm	≥15 mm	87.6	0.47
428 (86.2 %)	68 (13.7 %)	375 (75.6 %)	121 (24.4 %)		

4. Discussion

PPD-RT 23 (TST-Arkray) is the most used PPD formulation in India. To authorize the use of a new PPD formulation [15], a trial validating the new formulation with the international benchmark must be performed. We are unaware of any study validating TST-Arkray. We have shown that using the standard induration cut-off of 10 mm, 28.1 % tested positive with TST-Tubersol while 40.1 % tested positive with TST-Arkray. Thus, the TST-Arkray reported more positives compared to the TST-Tubersol. Of the 200 participants who were reported as positive by TST-Arkray at an induration cut-off of 10 mm, only 57 participants tested positive by the QFT-Plus test, which explains the poor agreement between the two tests(K = 0.17). Therefore, there is a risk of over-diagnosis of LTBI by the TST in a high TB prevalence setting. At the standard cut-off of 10 mm, we found only a moderate degree of agreement between TST-Arkray and the TST-Tubersol (K = 0.58).

There are various studies where other formulations of PPD were compared and their efficacy was studied. Villarino et al [16], compared the two PPD formulations, Aplisol and Tubersol with tuberculin PPD –S1- which is used to standardize commercial PPD reagents- in a population with minimal risk for pulmonary tuberculosis, with no previous history of TB, no exposure and no previous BCG vaccination. Tubersol did produce a slightly smaller reaction than Aplisol and PPD-S1, however, the specificities of both were as high as 98 % and were comparable with the PPD-S1.

In our study, we reported that the agreement of both the TSTs –TST-Tubersol and TST-Arkray with the QFT plus was poor. In high-burden countries like India, most studies have shown lower agreement between TST and IGRAs. This has been attributed to BCG vaccination, which can produce false-positive TST results. In an Indian cohort of nursing students, we had previously reported the prevalence of LTBI to be 40 % based on TST results and 17.3 % based on IGRA [17]. High proportions of discrepant results between the two tests have been noted in other studies [18,19]. In our cohort, BCG scar was noted in 97 % of the subjects, which could have contributed to false positive TST.

Interferon-Gamma release assays (IGRA), detects TB Ag-specific (ESAT-6, CFP-10 and TB7.7) circulating effector memory T cells, through IFN-gamma secretion as measured by ELISA. The MTB antigens used in IGRAs are absent from BCG and non-tuberculous mycobacteria, thus decreasing the incidence of false-positive results, compared to TST.

Several studies compared the performance of the Tuberculin skin test (TST) and the Quantiferon Plus test for the diagnosis of LTBI [9,17,18]. These comparisons have been performed in various high-risk groups like health care workers, army personnel, cancer patients, and paediatric populations. In our cohort, we found only poor agreement between the TSTs & QFT plus. For the recommended cut-off of 10 mm induration, the agreements of TSTs with QFT plus were; TST-Tubersol (K = 0.196) and TST-Arkray (K = 0.172). A study in Iran compared the prevalence of LTBI among 177 lab staff and non-lab staff, using 2 TSTs (Razi Vaccine and Serum Research Institute, Karaj, Iran;5 TU) and the QFT test. The estimated prevalence of LTBI detected by both the TSTs and the QFT was

Table 3
Diagnostic yield of TST-Tubersol and agreement with QFT-plus results:

TST-Tubersol	QFT-plus		Kappa	Sensitivity 95 % CI	Specificity 95 % CI	PPV 95 % CI	NPV 95 % CI
	Negative	Positive					
<5mm(Negative)	232	32		66 %	58.4 %	27.3 %	87.8 %
≥5mm(Positive)	165	62	0.158	(55.4 %-75.4 %	(53.4 %-63.3 %)	(23.7–31.2 %)	(84.3–90.6 %)
<10 mm(Negative)	303	50	0.196	46.8 %	76.3 %	31.8 %	85.8 %
≥10 mm(Positive)	94	44		(36.4–57.3 %)	(71.8 %-80.4 %)	(26.1 %-38.2 %)	(83.2–88.1 %)
<15 mm(Negative)	365	63	0.285	33 %	92 %	49.2 %	85.2 %
≥15 mm(Positive)	32	31		(23.6–43.4 %)	(88.8 %-94.4 %)	(38.4–60.1 %)	(83.3 %-87 %)

Table 4
Diagnostic yield of TST-Arkray and agreement with QFT-plus results:

TST-Arkray	QFT-plus		Kappa	Sensitivity 95 % CI	Specificity 95 % CI	PPV 95 % CI	NPV 95 % CI
	Negative	Positive					
<5mm(Negative)	216	30	0.139	68.1 %	54.4 %	26.1 %	87.8 %
≥5mm(Positive)	181	64		(57.6 %-77.3 %)	(49.3 %-59.3 %)	(22.8 %-29.6 %)	(84 %-90.7 %)
<10 mm Negative)	254	37	0.172	60.6 %	64 %	28.5 %	87.2 %
≥10 mm(Positive)	143	57		(50 %-70.5 %)	(59 %-68.7 %)	(24.4 %–33 %)	(84.1 %-90 %)
<15 mm(Negative)	309	48	0.231	48.9 %	72.50 %	34.33 %	82.86 %(79.7 % −85.6 %)
≥15 mm(Positive)	88	46		(38.4 %-59.5 %)	(67.3 % − 77.3 %)	(28.5 % −40.71 %)	

similar, but the agreement was poor (K = 0.19) [20]. In a moderate incidence setting, a study done among 149 adult cancer patients from 2 tertiary care hospitals in Columbia, the results showed moderate agreement between TST and QFT (K = 0.43) [21]. A *meta*-analysis in hemodialysis patients was conducted by Ferguson et al. to evaluate the diagnostic accuracy of the tests for LTBI [22]. TST had a pooled sensitivity of 31 % and specificity of 63 % compared to QFT-Plus and T Spot TB test. In addition, the pooled sensitivity and specificity of the QFT-Plus (Quantiferon-TB Gold plus) tests were 53 % and 69 %, respectively. Their results suggest that the QFT test was more sensitive than TST, but they did not estimate agreement between the two tests.

In the previous systematic review [22], which included only studies in which head-to-head comparison was made between TST and IGRA, it was concluded that both these tests have their advantages and disadvantages and neither of them could be considered better than the other.

Ruhwald and colleagues [23] reported an assessment of C-Tb (Statens Serum Institute, Copenhagen, Denmark), a diagnostic skin test for LTBI. This test is based on the Mycobacterium tuberculosis-specific RD1 antigens ESAT-6 and CFP10 that are used in IGRAs. These authors compared C-Tb with the QuantiFERON-TB Gold In-Tube (QFT GIT) and the TST in 979 people, separated into subgroups of people with varying degrees of risk of infection with M. tuberculosis. A trend was found towards positivity with an increased risk of infection, with concordant results seen between C-Tb and QFT in 785 (94 %) of 834 participants. This could prove to be a simpler and more reliable test that could be used in high-burden countries with high BCG vaccination status, like India. However, this study has reported concordance and not agreement.

5. Limitations

The sample size calculated was 1600 participants, however, there was a shortage of TST-Tubersol production, which made procurement very difficult. Thus, the sample size was not met.

6. Conclusion

The indigenous TST used in India, the TST-Arkray (PPD-RT 23) shows only moderate agreement with the internationally accepted TST-Tubersol (Tuberculin CT 68). TST-Arkray seems to overdiagnose LTBI and this is concerning, as it may lead to unwarranted treatment for LTBI, in a resource-limited country. As already known, there was poor agreement between both the TSTs and QFT-Plus. Efforts should be made by the manufacturers to ensure that the indigenous PPDs are bio-equivalent to the products that conform to international standards. Adequate quality assurance systems should be in place before regulatory approval for any new PPD formulation, which is being planned for use in practice.

Credit authorship contribution statement

Devasahayam J. Christopher: Conceptualization, Methodology, Validation, Supervision, Project administration, Funding acquisition, Review and editing of draft. **N. Priya:** Data curation, Writing – original draft, Writing – review & editing, Visualization. **Deepa Shankar:** Methodology, Data curation, Software, Investigation. **Barney Isaac:** Methodology, Validation, Formal analysis. **Andrea DeLuca:** Conceptualization, Methodology, Validation. **Sonali Sarkar:** Methodology, Validation. **Senbagavalli Prakash Babu:** Methodology, Validation, Project administration. **Prasanna Samuel:** Formal analysis. **Adithya Cattamanchi:** Validation, Review and editing of draft. **Amita Gupta:** Conceptualization, Methodology, Validation. **Jerrold Ellner:** Conceptualization, Methodology, Validation. **Sudha Srinivasan:** Methodology, Validation. **Samyra Cox:** Methodology, Validation. **Balamugesh Thangakunam:** Conceptualization, Methodology, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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