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What Tool for Diagnosis of Latent Tuberculosis Infection in Developing Country with Tuberculosis High Burden: Interferon Gamma Release Assays *versus* Tuberculin Skin Test in Burkina Faso

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Abstract

Background: The diagnosis and treatment of active tuberculosis and the detection/management of latent tuberculosis infection (LTBI) cases are the two main strategies for the TB control, particularly in endemic countries. Tuberculin skin test (TST) and Interferon Gamma Release Assays (IGRAs) are tools for detection of LTBI. The objective of this study was to evaluate the performance of the TST and QuantiFERON-TB Gold Plus® (QTF-Plus) and to identify a threshold for TST in best agreement with QTF-Plus for LTBI detection in a high TB burden setting. **Methods:** In July 2020, a cross-sectional analytical study was performed for QFT-Plus using blood samples and TST in 101 individuals with a high risk of TB living in Bobo-Dioulasso, Burkina Faso. A crude comparison between both tests was done and receiver operating characteristic curve was generated to determine TST's threshold. TST sensi-

tivity, specificity, predictive values and accuracy were calculated. Adjusted agreement between TST and QFT-Plus was evaluated. **Results:** With the minimum threshold of positivity set at 5 mm for TST, the overall agreement between the latter and QFT-Plus was poor with a Kappa coefficient (κ) rated at 0.319 (95% CI: 0.131 - 0.508). This cut-off yielded a sensitivity of 94.12% (95% CI: 88.53 - 99.71), and very poor specificity of 36.4% (95% IC: 25.0 - 47.80). However, an adjusted cut-off set at 11 mm gave a better specificity of 72.73% (95% CI: 62.1 - 83.30) of TST and improved the PPV (86%). Moreover, concordance between both tests was improved with κ at 0.56 (95% CI: 0.385 - 0.728) and 80.20% of accuracy. Factors associated with discordance between TST (11 mm) and QFT-Plus results were BCG vaccination, OR = 7.53 (95% CI: 1.43 - 139.25), p = 0.05 and chronic cough, OR = 5.07 (95% CI: 1.27 - 20.43), p = 0.01. **Conclusions:** This study showed that using a minimal cut-off of 11mm for TST significantly improved the concordance between QTF-Plus (IGRA) and TST. Using the cut-off TST of 11 mm would be ideal in low-income countries with a high TB burden, taking into account factors that could contribute to the discrepancy of results.

Keywords

LTBI Diagnosis, IGRA, TST Threshold, Concordance, Burkina Faso

1. Introduction

Latent tuberculosis infection (LTBI) is a *Mycobacterium tuberculosis* complex infection status without evidence of clinical or radiological symptoms or signs of active tuberculosis and it is non-transmissible [1] [2]. A third of the world's population has been exposed to tuberculosis (TB), estimating 1.7 billion LTBI cases among the world's population [3]. Most of these cases remain undiagnosed and therefore constitute a major challenge in the control of tuberculosis [1]. According to the World Health Organization (WHO), the diagnosis and treatment of LTBI are one of the strategies recommended by the World Health Organization (WHO) to combat TB worldwide [4] [5]. This challenge needs the availability of efficient diagnosis tools, especially in populations with a higher risk of exposure to TB disease.

To date, only the tuberculin skin test (TST) and interferon gamma release assays (IGRA) remain the most widely used tools in the screening of LTBI [6]. These tests are all based on the principle of cell-mediated immunity [7] [8].

The TST measures the delayed-type hypersensitivity response to intradermal injection of a mixture of purified protein that derivatives from many mycobacterial antigens, including *M. tuberculosis*, *M. bovis BCG*, and non-tuberculous mycobacteria (NTM) [9]. However, this test is characterized by a high rate of false positive in high TB burden settings and in immunocompromised subjects [10] [11] [12]. Furthermore, this test requires a second visit within 48 hours to

72 hours for result reading and interpretation [13]. However, it remains the most widely used in low-income countries principally due to its low cost, its accessibility and does not require any particular infrastructure [13] [14].

IGRA evaluates in vitro the response of lymphocytes after stimulation by specific antigens of the tubercle bacillus (ESAT-6 and CFP-10). Among the currentavailable IGRA tests, QFT-GIT, QFT-Plus and T-SPOT. TB are the most widely used, FDA-approved IGRAs [12] [15]. These tests show a significant reduction in false-positive results because the synthetic peptides used are absent in BCG vaccine strains and most NTM infections. Additionally, these tests require only a single patient visit and results are available within 24 hours after testing [13] [15]. However, although efficient, the IGRAs remain almost inaccessible in low-income countries thus limiting their routine use [15].

For low-income countries with high TB burden such as Burkina Faso, it will be important to look for a low-cost, accessible, and reliable method whose performance would be similar to IGRA tests.

Many studies comparing IGRAs and TST have been performed and reported inconsistent agreement [11] [16], but there is no data available in Burkina Faso. Although TST has limits, it remains possible to set a different threshold of positivity depending on whether we want to increase its sensitivity or specificity according to the screening context [6]. Indeed, a Receiver Operating Characteristic (ROC) curve established from the continuous values of the TST would make it possible to predict a cut-off, whose results are equivalent to those of the QFT-Plus [17] to improve access to high-quality and low-cost diagnostics. In this study, we conducted for the first time in the country a two-step screening of LTBI for comparing the performance of TST with the IGRA, QuantiFERON-TB® Gold Plus (QTF-Plus) and we identified an appropriate cut-off of TST in agreement with QTF-Plus from peoples known to be at risk for TB.

2. Material and Methods

2.1. Study Site

A cross-sectional analytical study was conducted with population exposed to tuberculosis from March to July 2020 living Bobo-Dioulasso city (Burkina Faso).

2.2. Study Population and Sample Collection

In several localities, studies have reported that population groups such as health professionals, contacts of index TB cases and slaughterhouse workers, are at risk of latent tuberculosis because of the profession or proximity to suspected tuberculosis cases [18] [19] [20] [21] [22]. In this way, our population consisted in exposed to tuberculosis including: 1) household contacts of TB index cases, 2) health care workers (HCWs) and 3) slaughterhouses workers (SWs) who gave their consent to participate to the study.

From each participant, sociodemographic data as well as 4 mL of blood samples were collected as well as stools and urines. In addition, TST has been ap-

plied. All whole blood samples were brought to the laboratory of Centre MURAZ, the host institute for QTF-Plus analyses.

2.3. Tests Carried Out

2.3.1. QuantiFERON-TB Gold Plus® (QFT-Plus) Method

Before performing the TST, 4 mL of venous blood was drawn in heparinized tube to determine interferon gamma response to ESAT-6 and CFP-10 antigens using QFT-Plus test (Qiagen, Hiden, Germany).

The QFT-Plus includes new antigens designed to increase the sensitivity of the test comparatively to the previous IGRA tool (QTF-GIT). Briefly, 1 mL of blood was drawn directly into 4 separate tubes identified as the Nil control (negative control), the mitogen control (positive control containing phytohemagglutinin), TB1 (containing *M. tuberculosis* complex specific antigens ESAT-6 and CFP-10 modified for eliciting CD4+ T-cell responses) and TB2 (containing *M. tuberculosis* complex specific antigens ESAT-6 and CFP-10 modified for eliciting CD8+ T-cell responses). After filling each tube, they were inverted slowly 10 times each to coat the sides of the tubes and placed into a 37˚C incubator for 16 to 24 h. All the tubes were centrifuged at 3000 × g for 15 minutes to separate the plasma and were stored at −20˚C before analyses. The QFT-Plus IFN-γ ELISA was performed on an automated ELISA processor the EVOLIS machine (BIO-RAD, France), an automated ELISA processor. Results were calculated using QFT-Plus analysis software version 2.71.2 as described by the manufacturer [23] [24].

Results of LTBI were defined as positive for IFN-γ concentration ≥ 0.35 IU/mL (calculated as either TB1 or TB2 antigen minus nil) per the manufacturer's guideline. If antigen-nil was <0.35 IU/mL or <25% of the nil value, when the mitogen was ≥0.5 IU/mL, the result was considered negative. If 1) nil was >8 IU/mL or 2) antigen-nil ≥ 0.35 IU/mL and <25% of the nil value when the nil was ≤8.0 IU/mL and the mitogen was <0.5 IU/mL, the results were considered indeterminate [24].

2.3.2. Tuberculin Skin Test (TST)

TST was performed with a 0.1 mL intradermal injection of tuberculin equivalent to 5 IU TUBERTEST® (Sanofi Pasteur, France) in anterior forearm, followed by the measure of the diameter of the indurated area range from 48 h to 72 h later [25]. Test is positive when the indurated area was ≥5 mm as indicated the manufacturer.

2.3.3. Parasitological Tests

Each stool sample was prepared and treated using the Kato-Katz and formol ether concentration methods, as well as the direct saline/iodine method, in order to diagnose infections with intestinal parasites. In addition, urine samples were examined qualitatively to screen for *Schistosoma spp.* using the urinary sediment method, and by rapid point-of-care circulating cathodic antigen (POC-CCA) cassette test (batch numbers 191031120, ICT INTERNATIONAL, Noordhoek, South Africa) according to the manufacturer's instructions on the day of the

sample collection.

2.4. Statistical Analysis

Collected data from questionnaires and results of tests carried out were entered first using Microsoft Excel 2016, then cleaned and exported to Stata 14 software (Stata Corp., College Station, Texas, USA) for statistical analyses. Concordance between TST and QFT-Plus results were assessed using Cohen's kappa (κ) values. Kappa values < 0.4 indicated weak agreement, values between 0.41 - 0.60 good agreements, and values > 0.6 strong agreement as previously described by Bergot *et al.* [7]. The cut-off points for TST were determined using a Receiver Operating Characteristic (ROC) curve and based on the Youden index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were generated at various cut-off points. Odds ratios (ORs) for factors associated with discordant results were estimated by logistic regression. A p-value under 0.05 was considered statistically significant.

2.5. Ethical Considerations

The protocol of the study was approved by the "*Comité d'Ethique pour la Recherche en Santé du Burkina Faso*" (CERS)—Reference: 2017-07-106/CERS. Data collection authorizations were provided by the Ministry of Health and the *Haut Bassins* regional directors of health and regional director of Animal and Fisheries Resources. All participants provided informed written consent after the study procedure, risks, and benefits were explained to them.

3. Results

3.1. Sociodemographic Characteristics of Study Population

Baseline characteristics of the 101 participants with reliable QTF-Plus and TST results are shown in the Table 1. Among them, 42 were HCWs, 31 were SWs and 28 were household contacts of TB index cases. The average age was 38.52 ± 12.01 years. Male constituted 66.34% of the study population and sex ratio (M/F) was 1.97. Most of the participants (76.24) were BCG vaccinated, 19.80% were smoking, 31.68% have experience with alcoholism and 9.90% have had some chronic cough.

Table 1. Sociodemographic characteristics of study population.

Variables	Category	No.	Proportion (%)
Sex	Male	67	66.34
	Female	34	33.66
Age	*Mean*	*38.52*	-
	SD	*12.01*	-
Type of participants	Healthcare	42	41.58
	Household	28	27.72
	Slaughterhouse	31	30.69

Continued

BCG Scars	Yes	77	76.24
	No	23	22.77
	Unknown	01	0.99
Smoking	Yes	20	19.80
	No	81	80.20
Alcoholism	Yes	32	31.68
	No	69	68.32
Chronic cough	Yes	10	9.90
	No	91	90.10

SD: Standard deviation, BCG: Bacillus Calmette-Guerin.

3.2. Assessment of the Internal Quality of QFT-Plus Results

The QFT-Plus was used as gold standard for tests comparison. Following the manufacturer's instructions, a result is positive if the concentration of IFN-$\gamma \geq$ 0.35 IU/mL, calculated from either that of TB1 or TB2 antigen minus Nil). In the Figure 1, the correlation coefficient (r) was 0.944, $p < 0.001$ indicating a strong correlation between the TB1-Nil and TB2-Nil interferon-γ response and testifying to the reliability of the QTF-Plus to be used as gold standard for comparison with the TST.

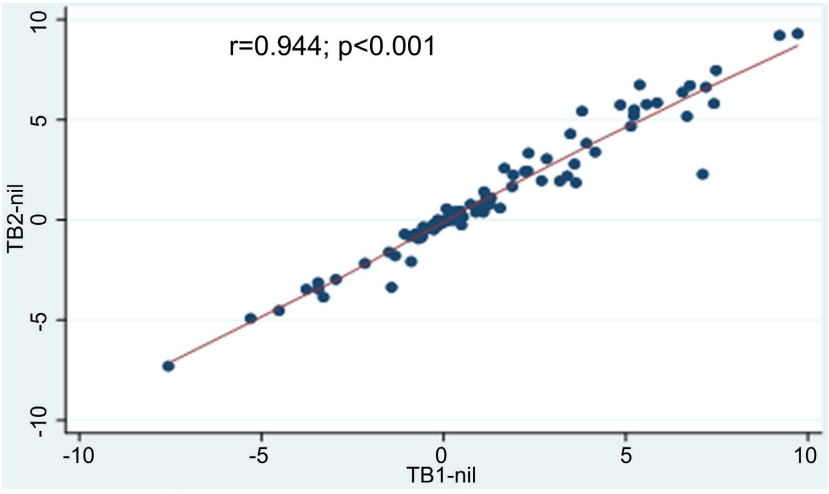

Figure 1. Correlation between TB1-Nil and TB2-Nil and showing association of IFN-γ responses in the TB1 and TB2 tubes.

3.3. Agreement between QFT-Plus and TST

The TST positivity rate was higher compared to QFT-Plus (85.14% *versus* 67.33%). We found 26 (25.75%) discordant results, distributed across 22 cases of TST+/QFT-Plus—and 4 samples QFT-Plus+/TST−. Both assays gave the same results in 63.36% of positive cases and 10.89% of negative cases. The crude degree of agreement between QFT-Plus and TST was 74.26% with a weak concor-

dance kappa (κ) = 0.31; (95% CI: 0.13 - 0.51; p-value < 0.001, Table 2). The agreements between the two tests, depending on the types of participants in the study, were relatively low also with 61.90%, kappa (κ) = 0.29 for health care workers, 96.77%, κ = 0.96 for abattoir workers and 67.86%, κ = 0.29 for household contact of TB index cases (Table 4).

Table 2. Comparison between QFT-Plus and TST.

Tuberculin skin Test results	QuantiFERON TB Gold Plus results		Total
	Positive n (%)	Negative n (%)	
Positive	64 (63.36)	22 (21.78)	86 (85.14)
Negative	4 (3.97)	11 (10.89)	15 (14.86)
Total	68 (67.33)	33 (32.67)	101 (100.00)

Kappa Cohen test, κ = 0.31, 95% CI (0.13 - 0.51); p < 0.001.

3.4. Appropriate Cut-Off Points from TST in Accord with High Agreement with QFT-Plus in LTBI Detection and Factors Associated with Discordance for Both Tests

The ROC curve from the continuous values of TST predicted with more accuracy the result of QFT-Plus test than its outcomes (positive or negative) according to the cut-off given by the manufacturer, with a significant area under the curve (AUC) = 0.820, p < 0.001 (Figure 2).

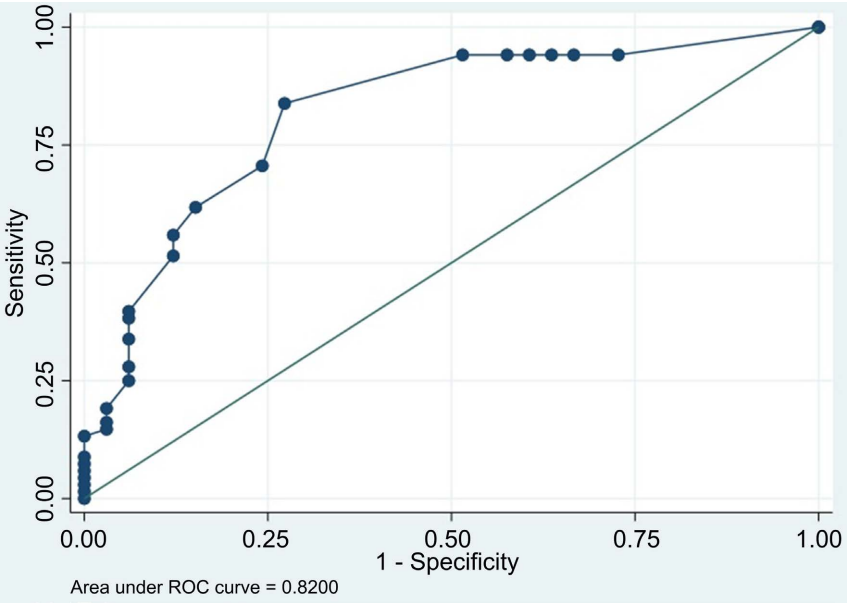

Figure 2. Receiver operating characteristic (ROC) curve for determination of TST cut-off point (in millimetres) in continue value.

By the Youden index, minimal cut-off of 11 mm yielded more reliable results than the 5 mm (from the manufacturer) and others designed cut-off (10 mm or 12 mm). This should be a reconciling threshold for interpretation of the two

tests. Indeed, by adjusting the cut-off to 11 mm, the number of TST results initially positive at the 5 mm cut-off (TST+/QFT-Plus−: 22 (21.78%)) was reduced in favour of the QFT-Plus (TST−/QFT-Plus+: 11 (10.89%)). The overall discrepancy (TST−/QFT-Plus+; TST+/QFT-Plus−) has been reduced from 25.74% to 19.75%. The number of true negatives (QFT-Plus−/TST−) also increased (11, 10.89% (5 mm) to 24, 23.76% (11 mm)). Sum of all above, the agreement between the TST (threshold at 11 mm) and QFT-Plus results was more significant 80.2% with good kappa value (k = 0.56; 95% IC: 0.38 - 0.73, p < 0.001) compared to other cut-offs (Table 3).

Table 3. Comparison between QFT-Plus and TST following gradual cut-offs of TST (5 mm, 10 mm, 11 mm).

	5 mm	TST 10 mm	TST 11 mm
Participant size	n = 101 (%)	n = 101 (%)	n = 101 (%)
QFT−/TST−	11 (10.89)	16 (15.84)	24 (23.76)
QFT+/TST+	64 (63.36)	64 (63.36)	57 (56.43)
QFT−/TST+	22 (21.78)	17 (16.83)	9 (8.91)
QFT+/TST−	4 (3.96)	4 (3.96)	11 (10.89)
All discordant (%)	26 (25.74)	21 (20.79)	20 (19.80)
Concordance, %	74.26%	79.21%	80.20%
kappa (95% CI)	0.32 (0.13 - 0.51)	0.47 (0.29 - 0.66)	0.56 (0.38 - 0.73)
Fisher, p-value	<0.001	0.013	<0.001

The comparison of the results according to the type of participants, reported that the cut-off adjusted of 11 mm would remain more effective compared to the commercial cut-off (5 mm). Indeed, the kappa coefficient of concordance was 0.33, 1.00 and 0.55 among Health workers, Slaughterhouse workers and Contact of TB index cases respectively (Table 4).

Table 4. Comparison between QFT-Plus and TST following gradual cut-offs of TST (5 mm, 10 mm, 11 mm) according the type of participants.

	TST 5 mm	TST 10 mm	TST 11 mm
Health workers	**n = 42**	**n = 42**	**n = 42**
QFT−/TST−	6 (14.28)	8 (19.04)	15 (35.71)
QFT+/TST+	20 (47.61)	20 (47.61)	13 (30.95)
QFT−/TST+	15 (35.71)	13 (30.95)	6 (14.28)
QFT+/TST−	1 (2.38)	1(2.38)	8 (19.04)
All discordant (%)	16 (38.10)	14 (33.33)	14 (33.33)
Concordance, %	61.90	66.67	66.67
Kappa	0.29	0.33	0.33
Fisher, p-value	0.0192	0.0042	0.0150

Continued

Slaughterhouse workers	n = 31	n = 31	n = 31
QFT−/TST−	0 (0.00)	1 (3.23)	1 (3.23)
QFT+/TST+	30 (96.77)	30 (96.77)	30 (96.77)
QFT−/TST+	1 (3.23)	0 (0.0)	0 (0.00)
QFT+/TST−	0 (0.00)	0 (0.00)	0 (0.00)
All discordant (%)	1 (3.23)	0 (0.00)	0 (0.00)
Concordance, %	96.77	100.00	100.00
kappa,	0.98	1.00	1.00
Fisher, p-value	0.03	<0.001	<0.001
Household contact of TB index cases	**n = 28**	**n = 28**	**n = 28**
QFT−/TST−	5 (17.85)	7 (25.00)	8 (28.57)
QFT+/TST+	14 (50.0)	14 (50.0)	14 (50.0)
QFT−/TST+	6 (21.42)	4 (14.28)	3 (10.71)
QFT+/TST−	3 (10.71)	3 (10.71)	3 (10.71)
All discordant (%)	9 (32.14)	7 (25.00)	6 (21.43)
Concordance, %	67.86	75.00	78.57
kappa	0.29	0.47	0.55
Fisher, p-value	0.056	0.0066	0.0018

Elsewhere, the commercial cut-off showed a high sensitivity of 94.12% with a low specificity of 33.33% and a low accuracy of 74.26%. With a new cut-off at 10 mm, the sensitivity remains unchanged, but the specificity is improved slightly to 48.5% as well as the precision to 79.21%. Good specificity and accuracy were achieved by slightly increasing the cut-off to 11 mm (cut-off using Youden index). Indeed, this cut-off brought 83.82% as sensitivity, 72.73% as specificity, 79.1% as PPV, 80% as NPV, and 80.2% as accuracy (Table 5). Unlike a 12.5 mm cut-off, the specificity is significantly increased around 84.85% to the detriment of the sensitivity around 61.76%, which is not desirable for a diagnostic test (because high sensitivity is needed). The diagnosis using the diameter measurements from ROC curve and "Youden index" gave better accuracy to TST and improved the positive predictive value as well as the specificity.

Table 5. Sensitivity, specificity, PPV, NPV and accuracy for the different TST cut-offs points in predicting LTBI.

TST (mm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
≥5	94.12	33.33	74.42	73.33	74.26
≥10	94.12	48.48	79.01	80	79.21
≥11	83.82	72.73	86.36	68.57	80.2
≥12	70.59	75.76	85.71	55.56	72.28

NPV: Negative predictive value, PPV: Positive predictive value, TST: Tuberculin skin test.

Considering the overall discordance observed in this study at the 11 mm cut-off, we found that the factors associated with this situation were the presence of BCG vaccination with an OR = 7.53 (95% CI: 1.43 - 139.25), p = 0.05 and chronic cough with an OR = 5.07 (95% CI: 1.27 - 20.43), p = 0.01, from the participants (Table 6).

Table 6. Principal factors associated with discordant test results: cut-off: TST ≥ 11 mm versus QFT-Plus positive results.

Variables	Concordants n (%)	Discordants n (%)	OR (95% CI)	p-Value
Age				
15 - 30 years	23 (82.1)	5 (17.9)	1	
31 - 46 years	39 (84.8)	7 (15.2)	0.83 (0.24 - 3.07)	0.76
47 - 62 years	19 (70.4)	8 (29.6)	1.94 (0.55 - 7.35)	0.30
Sex				
Male	55 (82.1)	12 (17.9)	1	
Female	26 (76.5)	8 (23.5)	1.41 (0.50 - 3.84)	0.50
Type of Participant				
Health care workers	28 (66.7)	14 (33.3)	1	
Slaughterhouses workers	31 (100.0)	0 (0.0)	0.00 (NA-)	0.99
Household contacts of TB index cases	22 (78.6)	6 (21.4)	0.55 (0.17 - 1.60)	0.28
BCG Scars				
	23 (95.8)	1 (4.2)	1	
	58 (75.3)	19 (24.7)	7.53 (1.43 - 139.25)	0.05
Smoking				
	63 (77.8)	18 (22.2)	1	
	18 (90.0)	2 (10.0)	0.39 (0.06 - 1.53)	0.23
Alcoholism				
	54 (78.3)	15 (21.7)		
	27 (84.4)	5 (15.6)	0.67 (0.20 - 1.93)	0.47
Chronic Cough				
	76 (83.5)	15 (16.5)	1	
	5 (50.0)	5 (50.0)	5.07 (1.27 - 20.43)	0.01
Parasite Infection				
Protozoa	28 (71.8)	11 (28.2)	1	
	53 (85.5)	9 (14.5)	0.43 (0.16 - 1.16)	0.09
Helminth	69 (80.2)	17 (19.8)	1	
	12 (80.0)	3 (20.0)	1.01 (0.21 - 3.64)	0.98

4. Discussion

People with LTBI are at risk for active tuberculosis. So, about 5% - 10% among

them probably develop active tuberculosis [2]. Burkina Faso counts about 46 cases of TB per 100,000 inhabitants [26]. WHO implemented the End TB strategy by integrating the approach of early diagnosis and treatment of persons at risk for active tuberculosis [27]. Although there are no data relating to LTBI in the general population, the need of using adequate and low-cost diagnostic tool is essential. The objective of this study was to compare the results of the IGRA (QFT-Plus) and TST and to establish a reliable threshold between the two tests in the early diagnosis of LTBI in people known to be at risk for TB.

In this study, participants (n = 101) were screened for LTBI using the QFT-Plus and the TST to allow for the comparison of the results. The TST gave more positive results (85.14%) than QFT-Plus (67.33%). With the manufacturer's cut-off (5 mm), 25.75% of results were discordant. Indeed, the crude degree of agreement between both assays was 74.26% with a weak concordance $\kappa = 0.31$; 95% CI: 0.13 - 0.51; p-value < 0.001. Similar results have been found in high TB incidence countries with $\kappa = 0.38$ in a recent meta-analysis [28] and in the Republic of South Korea regarding the comparison of both tests, $\kappa = 0.33$ [6] [29]. The discrepancy was observed in a quarter of the results with a high trend in the TST (QFT−/TST+), this could be explained by the false-positive results which are common in TST due to cross-reaction with the BCG vaccine or environmental non-tuberculous mycobacteria [11].

ROC curves obtained from continuous values of TST predict more accurately the result of QTF-Plus test than its positive or negative outcomes according to the manufacturer's cut-off, with an area under the curve (AUC) = 0.820, $p < 0.001$. Using threshold from ROC curves, it becomes possible to establish good concordance between the TST and the QFT-plus. Also, it improves the positive predictive value (86.36%) from a cut-off ≥ 11 mm as well as the specificity (72.73%).

Regarding the concordance between both tests, the discrepancy rate with the threshold 11 mm was reduced to 19.75% compared to the commercial cut-off (25.75%). Indeed, this cut-off brought a good agreement between the TST and QFT-Plus, 80.2% (kappa = 0.58), $p < 0.001$ compared to other cut-offs (5 mm and 10 mm). Similar results were reported in South Korea after increasing the TST cut-off which increased the agreement from $\kappa = 0.38$ to $\kappa = 0.56$ between TST and IGRA [6] [30]. However, as Ferreira *et al.* in Brazil reported, decreasing the cut-off to 5 mm would increase the diagnostic sensitivity of the TST [17] but not the specificity and concordance.

In addition, we observed strong association between discordant results and a history of BCG vaccination as well as having chronical cough. BCG may have a larger effect on TST in populations with a greater number of people vaccinated. On this way understanding disagreement between tests for tuberculosis infection may help clinicians avoid diagnostic errors.

The results of this study indicate that the 11 mm threshold increased specificity, predictive values, and accuracy of TST. Previous studies suggest that increasing the cut-off of the TST leads to an increase in sensitivity and a decrease in the specificity of the test [31]. The specificity was significantly improved to

72.73% versus around 33.65% for the manufacturer set and thus sparing the false positive test. However, by increasing the positivity threshold to 12.5 mm, the specificity increased to 84.85% at the expense of the sensitivity ~61.76%, which is not desirable for a diagnostic test because high sensitivity is needed.

In choosing a diagnostic tool for LTBI as an advanced strategy for fighting tuberculosis, several aspects must be considered. These aspects include the cost and effectiveness of the test. The IGRA tests, despite having very high sensitivity and specificity are difficult to be utilized in low-resource settings because they are expensive, time-consuming, and require specialized equipment and skilled personnel [15]. TST appears to be the most viable option tool because of its low cost [17] [32] and it is possible to set different cut-offs of positivity depending on whether one wants to increase its sensitivity or specificity according to the screening context [6] and targeted risk group. Furthermore, the results obtained in our study argue in favour of the use of TST with an adjusted cut-off in our country. Previous studies focusing on cost effectiveness concluded that TST was the most cost-effective strategy than using IGRA [33] [34] [35]. In our context using 11 mm as cut-off from TUBERTEST® (Sanofi-Pasteur, France) not only yields result superimposable to those of the IGRA (QFT-Plus) but would also lead to more people being screened compared to the QFT-test.

Our study contains limitations which are among others the small size of the study sample, the non-inclusion of TB cases which would serve as reference to better compare both tests and the lack of data on chest X-rays of the participants. In addition, we did not test a booster with a second TST test, so we could not prove whether it correlated better with QFT-Plus [36]. However, the establishment of the ROC curve made it possible for the first time to assess the concordance between the TST and QFT-Plus and to identify a diagnostic cut-off threshold that reconciles the two tests in the country. This can contribute considerably to aiding therapeutic decision-making to prevent active forms of the disease, with the effect of reducing morbidity and mortality due to TB in Burkina Faso.

5. Conclusion

In this study, we reported a weak concordance (k = 0.31) between the TST for its commercial cut-off and the IGRA, QuantiFERON-TB® Gold Plus (QTF-Plus) in people known to be at risk for tuberculosis. However, after adjusting the cut-off of TST to 11 mm, the study showed an improved concordance between the two tests k = 0.58. Use of the cut-off TST of 11 mm would be ideal in low-income countries with a high TB burden, but consideration should be given to factors such as chronic cough or the presence of BCG scarring that could contribute to discrepant results with the IGRA test. In addition, additional longitudinal data on a large scale are needed, in order to validate this threshold of 11 mm.

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Author Contributions

Diakourga Arthur Djibougou, Gloria Ivy Mensah, Potiandi Serge Diagbouga conceived and designed the study. Diakourga Arthur Djibougou conducted the field study. Diakourga Arthur Djibougou performed field data collection and performed the lab analysis. Diakourga Arthur Djibougou and Tibila Kientega analyzed the data. Diakourga Arthur Djibougou, Gloria Ivy Mensah, Potiandi Serge Diagbouga, Tibila Kientega, Leon Tinnoaga Sawadogo, Clément Ziemlé Meda, Hervé Hien, Roch Konbobr Dabiré, Bassirou Bonfoh, Roch Konbobr Dabiré, Kennedy Kwasi Addo and Bassirou Bonfoh critically revised the manuscript. All authors read and approved the final manuscript.

Conflicts of 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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Ethics Approval and Consent to Participate

The protocol of the study was approved by the Ethics Committee for Health Research of Burkina Faso known as *Comité d'éthique pour la recherche en Santé* (CERS)–Reference: 2017-07-106/CERS. The study was conducted in accordance with the declaration of Helsinki. Data collection authorizations were provided by the Ministry of Health and the Regional Directors of Health of the Hauts-Bassins and of Animal and Fisheries Resources. All participants and or their parents/legal guardians provided informed written consent after the study procedure, risks, and benefits were explained to them.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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Abbreviations

AUC: area under the curve; BCG: Bacillus Calmette-Guérin; CI: Confidence interval; ELISA: Enzym Linked Immuno-Sorbent Assay; HCWs: Healthcare Workers; IFN-γ: Interferon γ; IGRAs: Interferon Gamma Release Assays; IU: International Unity; LTBI: Latent Tuberculosis Infection; NPV: Negative predictive value; NTM: non-tuberculous mycobacteria; SD: Standard deviation; QFT-Plus: QuantiFERON TB Gold-Plus; TB: Tuberculosis; PPV: Positive predictive value; ROC: receiver operating characteristic; TST: Tuberculin Skin Test; WHO: World Health Organization