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MAJOR ARTICLE

Assessing the Diagnostic Performance of New Commercial Interferon-γ Release Assays for *Mycobacterium tuberculosis* Infection: A Systematic Review and Meta-Analysis

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Background. We compared 6 new interferon-γ release assays (IGRAs; hereafter index tests: QFT-Plus, QFT-Plus CLIA, QIAreach, Wantai TB-IGRA, Standard E TB-Feron, and T-SPOT.TB/T-Cell Select) with World Health Organization (WHO)–endorsed tests for tuberculosis infection (hereafter reference tests).

Methods. Data sources (1 January 2007–18 August 2021) were Medline, Embase, Web of Science, Cochrane Database of Systematic Reviews, and manufacturers' data. Cross-sectional and cohort studies comparing the diagnostic performance of index and reference tests were selected. The primary outcomes of interest were the pooled differences in sensitivity and specificity between index and reference tests. The certainty of evidence (CoE) was summarized using the GRADE approach.

Results. Eighty-seven studies were included (44 evaluated the QFT-Plus, 4 QFT-Plus CLIA, 3 QIAreach, 26 TB-IGRA, 10 TB-Feron [1 assessing the QFT-Plus], and 1 T-SPOT.TB/T-Cell Select). Compared to the QFT-GIT, QFT Plus's sensitivity was 0.1 percentage points lower (95% confidence interval [CI], −2.8 to 2.6; CoE: moderate), and its specificity 0.9 percentage points lower (95% CI, −1.0 to −.9; CoE: moderate). Compared to QFT-GIT, TB-IGRA's sensitivity was 3.0 percentage points higher (95% CI, −.2 to 6.2; CoE: very low), and its specificity 2.6 percentage points lower (95% CI, −4.2 to −1.0; CoE: low). Agreement between the QFT-Plus CLIA and QIAreach with QFT-Plus was excellent (pooled κ statistics of 0.86 [95% CI, .78 to .94; CoE: low]; and 0.96 [95% CI, .92 to 1.00; CoE: low], respectively). The pooled κ statistic comparing the TB-Feron and the QFT-Plus or QFT-GIT was 0.85 (95% CI, .79 to .92; CoE: low).

Conclusions. The QFT-Plus and the TB-IGRA have very similar sensitivity and specificity as WHO-approved IGRAs.

Keywords. tuberculosis; IGRAs; tuberculin skin test; interferon-gamma; infection.

One of the most effective tuberculosis (TB) preventive strategies is the treatment of high-risk individuals with *Mycobacterium tuberculosis* (*Mtb*) infection (TBI) [1]. To this end, the World Health Organization (WHO) recommends performing either the tuberculin skin test (TST) or interferon-gamma (IFN-γ) release assays (IGRAs) [2]. IGRAs are blood-based tests that measure IFN-γ production by T lymphocytes after their in vitro exposure to *Mtb* antigens [3]. The first IGRAs endorsed by WHO included the QuantiFERON-Gold (QFT-G, Qiagen), the QuantiFERON-TB Gold In-Tube (QFT-GIT, Qiagen), and the T-SPOT.TB (Oxford Immunotec) assays. Early studies assessing their diagnostic performance confirmed a higher specificity relative to the TST, although their sensitivity was similar [4,5].

In 2015 Qiagen launched the QuantiFERON-TB Gold Plus (QFT-Plus), which added a new stimulation tube (TB2) using the same ESAT-6 and CFP-10 antigens but designed to induce a $CD8^+$-specific response to increase its sensitivity [6]. In 2021, a chemiluminescence immunoassay analyzer (Liaison XL) was adapted to the QFT-Plus to fully automate IFN-γ quantification (QFT-Plus CLIA, Qiagen/Diasorin) [7]; furthermore, in 2021 Qiagen also released the QIAreach, which uses the same TB2 tube from the QFT-Plus but dropped positive and negative controls and includes digital fluorescence lateral flow nanoparticle technology to quantify IFN-γ [8,9]. The Wantai TB-IGRA

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(TB-IGRA, Beijing Wantai Biological Pharmacy Enterprise) and the Standard E TB-Feron (TB-Feron, SD Biosensor) were released in 2011 and 2018, respectively [10,11]; both include positive and negative test controls plus a tube with *Mtb*-specific antigens (ESAT-6 and CFP-10) [10–13]. Finally, in 2021, Oxford Immunotec released the T-Cell Select, a reagent kit that automatically isolates mononuclear cells from blood samples stored for up to 54 hours at room temperature using a magnetic bead–based cell separation system (the rest of the procedure being the same as with the T-SPOT.TB) [14].

To determine whether new or updated IGRAs could be included under current WHO recommendations for IGRA testing, we conducted a systematic review and meta-analysis to compare the diagnostic performance of the above-mentioned new tests (QFT-Plus, QIAreach, QFT-Plus CLIA, TB-IGRA, TB-Feron, and T-SPOT.TB with T-Cell Select) with the WHO-endorsed IGRAs (QFT-G, QFT-GIT, or T-SPOT.TB). Partial results from this review for QFT-Plus, QIAreach, TB-IGRA, TB-Feron, and T-SPOT.TB with T-Cell Select were presented to a WHO technical advisory group in October 2021.

METHODS

Data Sources and Searches

With the aid of a librarian (Dr Genevieve Gore), we searched Medline, Embase, Web of Science, the Cochrane Database of Systematic Reviews, and the International Clinical Trials Registry Platform from 1 January 2007 (3 years before the earliest release date of all index IGRAs) to 18 August 2021, using no language restrictions (Supplementary Table 1 [Supplementary Material part A]). We considered 4 additional data sources: (1) all references of included studies; (2) a hand search of the *International Journal of Tuberculosis and Lung Disease* (as this focuses on clinical and epidemiologic TB-related studies); (3) manufacturers' data submitted to regulatory authorities, including published or unpublished studies; and (4) a public call for data coordinated by WHO on 23 August 2021. The last date for evaluating these additional sources was 27 October 2021.

Study Selection

We included cross-sectional and cohort studies, with any number of participants, both published and unpublished, conducted by independent investigators or the manufacturer, comparing any selected new IGRA with WHO-endorsed tests or with the QFT-Plus in the same subjects. Both tests were performed simultaneously, and technicians were blinded to the results of the other tests. Eligible studies assessed sensitivity in patients with newly diagnosed active TB, and specificity in healthy individuals, ideally at low risk of TBI, although because we estimated the difference in specificity between 2 tests in the same population, we included studies conducted in general population samples in countries with intermediate TB incidence rates (10–120 cases per 100 000/year), as well as low TB incidence rates (<10 cases per 100 000/year), as long as the participants did not have additional risk factors for exposure. Included studies estimated agreement in any population provided tests were simultaneous. Studies assessing the predictive ability for incident TB or reproducibility were also included. Four reviewers (L. A., S. L.-C., T. M., E. O.-B.) screened titles and abstracts independently and in duplicate. Discordance at this stage meant the study was included for full-text review. The same 4 reviewers screened full texts for eligibility; at this stage, discordance was solved by consensus or with the help of D. M. Full eligibility criteria are shown in Supplementary Table 2.

Data Extraction and Quality Assessment

Four reviewers (L. A., S. L.-C., T. M., E. O.-B.) extracted data independently and in duplicate using a standardized form designed for this study. Information retrieved included the characteristics of the study population, sampling methods, tests being compared, diagnostic outcomes, potential conflicts of interest, and results from contingency tables. If data were missing, the corresponding authors were contacted via email. Four reviewers (L. A., S. L.-C., T. M., E. O.-B.) assessed the risk of bias (RoB) of the included studies in duplicate for each diagnostic outcome using the Quality Assessment of Diagnostic Accuracy Studies–comparative tool (QUADAS-C) tailored to the needs of this review (Supplementary Tables 3–5) [15]. Overall study RoB was classified as follows: (1) low: if all comparison domains were considered at low RoB; (2) high: if ≥ 1 comparison domain was considered at high RoB; or (3) unknown: if ≥ 1 comparison domain was considered as at unknown RoB but none was considered at high RoB.

Data Synthesis and Analysis

The primary outcomes of interest were the pooled differences in sensitivity and specificity between the new IGRAs and any WHO-endorsed tests. Because Qiagen replaced QFT-GIT with the QFT-Plus in 2019, some studies used the latter as a reference. The primary analysis was restricted to published independent studies fulfilling all our inclusion criteria and allowing the reconstruction of contingency tables with paired comparisons. In this context, ignoring the correlated nature of observations may lead to an overestimation of variability and wider confidence intervals (CIs) [16,17]. We conducted 3 secondary analyses in which we added studies to those included in the primary analysis: (1) adding unpublished reports while still making paired comparisons; (2) adding published studies that did not have contingency tables and, therefore, were analyzed making parallel (unpaired) comparisons; (3) making parallel comparisons of all data (published and unpublished studies). We pooled results when 2 or more studies were available;

otherwise, we provided results from individual studies. For the agreement outcome, our primary analysis included only studies from peer-reviewed literature that fulfilled all our inclusion criteria; data from unpublished studies were incorporated in a secondary analysis.

We conducted all meta-analyses in R (version 4.1.0) using the following packages: meta, version 4.19-2 [18]; MKinfer, version 0.6 [19]; metafor, version 3.0–2 [20]; and psych, version 2.1.9 [21]. The sensitivity and specificity from individual studies were pooled using random-effects meta-analysis with generalized linear mixed-effects models and logit-transformed proportions [22]. When information from contingency tables was available, we estimated differences in sensitivity and specificity and their 95% CIs from individual studies using the Wilson method for paired comparisons with a continuity correction; otherwise, we used the Wilson method for independent binomial proportions [17]. Approximate standard errors for differences in sensitivity and specificity were obtained by dividing the absolute difference between the upper and lower limits of the 95% CIs by 3.92. We pooled these estimates via random-effects meta-analysis using the inverse variance method with the Sidik-Jonkman estimator [23]. We used Knapp-Hartung adjustments to estimate 95% CIs of pooled effects [24]. For the agreement outcome, we calculated the Cohen kappa (κ) statistic from individual studies [25]; 95% CIs were estimated using the Fleiss, Cohen, and Everitt method [26]. Then, approximate standard errors were obtained by dividing the absolute difference between the upper and lower limits of the 95% CI by 3.92. We pooled these estimates via random-effects meta-analysis using the inverse variance method with the DerSimonian-Laird estimator [27]. All results are presented in tables and using Forest plots; we also report the I^2 statistic for all meta-analyses [28]. Finally, the certainty of evidence was summarized using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) as recommended elsewhere [29].

Role of the Funding Source

This study was funded by the WHO Global TB Programme to inform its policy development activities. Two of its members (A. K. and N. I.) are included as co-authors of this publication because they contributed significantly to the project's conception, assisted with the acquisition of data, provided critical revisions to the manuscript, and approved its final version. The review protocol was developed for and approved by the WHO in July 2021.

RESULTS

Studies Included in the Review

We identified 5895 unique titles from databases and registries; of these, 5475 and 367 were excluded after screening and full-text review, respectively (Supplementary Figure 1; for reasons of exclusion after full-text review, see Supplementary Table 6). We retrieved 147 additional reports from other sources; of these, we excluded 9 and 104 after screening and full-text review, respectively (Supplementary Figure 2). Among 87 reports included, 48 evaluated the QFT-Plus; of these, 44 assessed the QFT-Plus with enzyme-linked immunosorbent assay (ELISA) (12 of them assessing sensitivity [30–40] including 1 unpublished evaluation supplied by Qiagen; 9 specificity [31–37,41] including 1 unpublished evaluation supplied by Qiagen; 33 agreement [31,33,36–39,41–66] including 1 unpublished evaluation supplied by Qiagen; 3 predictive ability [67–69]; and 3 reproducibility [57,70,71]), and 4 evaluated the QFT-Plus with CLIA (all 4 agreement [7,72–74]); 3 reports evaluated the QIAreach (all 3 agreement [9,75] including 1 unpublished evaluation supplied by Qiagen); 26 reports evaluated the TB-IGRA (26 sensitivity [12,76–99] including 1 unpublished evaluation supplied by Beijing Wantai; 16 specificity [12,76–79,83–86,92,93,95–98] including 1 unpublished evaluation supplied by Beijing Wantai; and 8 agreement [12,78,79,87,89,98,99] including 1 unpublished evaluation supplied by Beijing Wantai); 10 reports evaluated the TB-Feron (3 sensitivity [100–102]; 2 specificity [100,101]; 10 agreement [13,66,100–102], 1 of them also assessing the QFT-Plus [66], and unpublished independent evaluations by the Duzen Lab [Turkey], the National Mycobacteria Reference Laboratory [Greece], the Korean National Tuberculosis Association [Korea; 2 separate evaluations], and the Université de Lille [France]); and 1 report evaluated the T-SPOT.TB with T-Cell Select (agreement [1 unpublished evaluation supplied by Oxford Immunotec]) (Figure 1). As part of our search, we identified 11 additional commercial IGRAs that have been developed and undergone some evaluation but were not included in this review since the review protocol, and especially the search strategy, did not consider them. These tests are listed in Supplementary Table 39 (Supplementary Material Part D).

QFT-Plus, QFT-Plus CLIA, and QIAreach

As seen in Supplementary Table 7 (Supplementary Material Part B), none of the studies assessing QFT-Plus sensitivity were considered to have low RoB. In our primary analysis (paired comparisons of published studies) including 505 subjects, the sensitivity of the QFT-Plus was 0.1 percentage points lower than that of the QFT-GIT (95% CI, −2.8 to 2.6) (Table 1). In our secondary analysis (parallel comparisons of published studies), including 252 subjects, the sensitivity of the QFT-Plus was 5.8 percentage points higher than that of the T-SPOT.TB (95% CI, −22.2 to 33.8); findings were similar in 1 study allowing paired comparisons of these tests [33]. As seen in Supplementary Table 8, 1 of 9 studies assessing QFT-Plus specificity was classified at low RoB. In parallel comparisons of published studies including 529 subjects, the

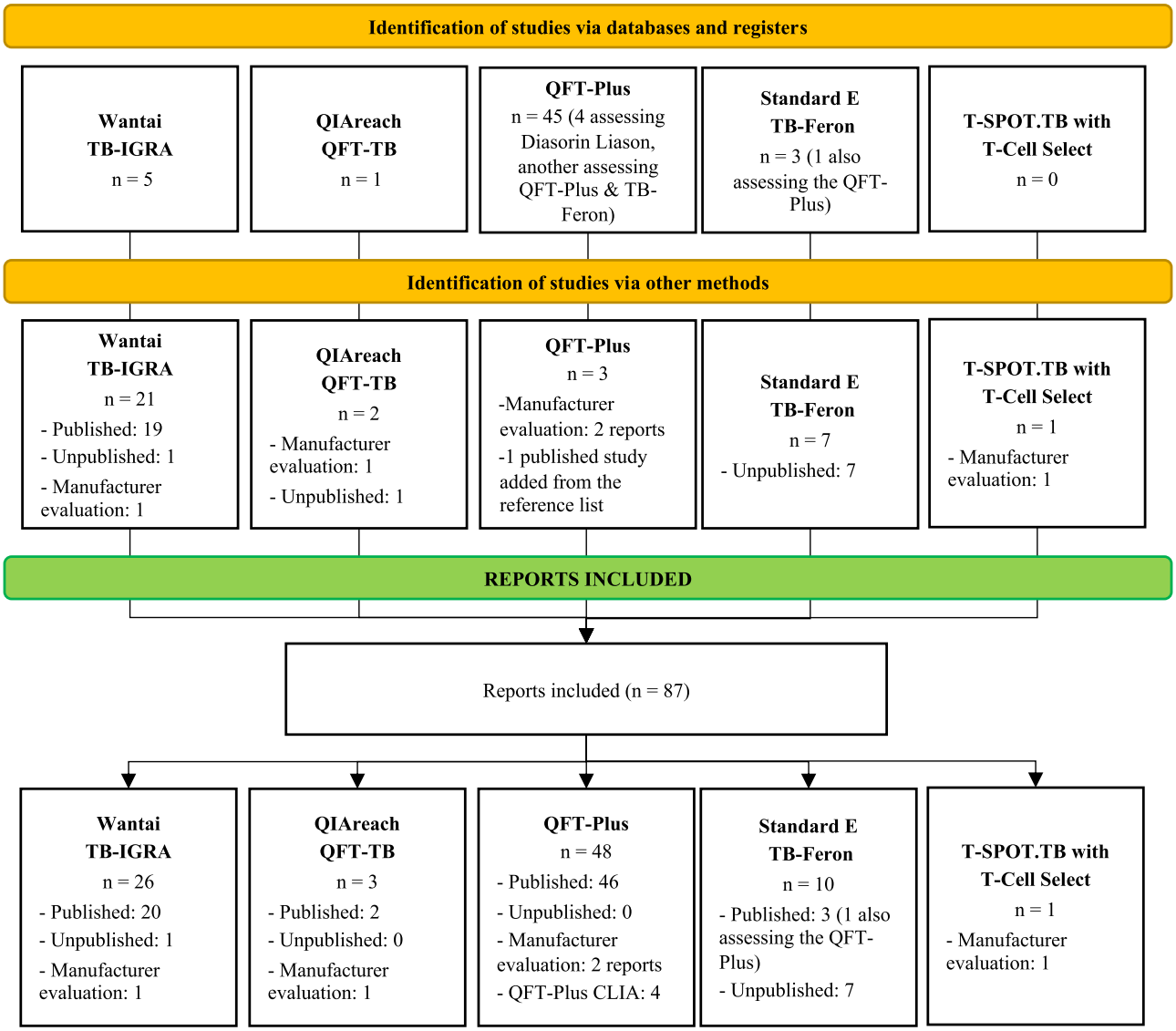

Figure 1. Flow diagram of the studies included according to their sources. The complete search is shown in Supplementary Figures 1 and 2.

specificity of the QFT-Plus was 0.9 percentage points lower than that of the QFT-GIT (95% CI, −1.0 to −.9); findings were similar in 1 study allowing paired comparisons of these tests' specificities [41]. In parallel comparisons of all studies, including 156 subjects, the specificity of the QFT-Plus was 0.6 percentage points lower than that of the T-SPOT.TB (95% CI, −12.0 to 10.9); findings were similar in the 1 study allowing paired comparisons of these tests' specificity (Table 1).

Of the 33 studies assessing the agreement between QFT-Plus and the WHO-endorsed tests, 21 (63.6%) were classified at low RoB (Supplementary Table 9). In our primary analyses, the pooled κ statistics comparing the QFT-Plus against the QFT-GIT and the T-SPOT.TB were 0.82 (95% CI, .78 to .85; N = 6586 subjects) and 0.72 (95% CI, .57 to .86; N = 3139 subjects), respectively (Table 2). On the other hand, the pooled κ statistic comparing the QFT-Plus and the TST was 0.32 (95% CI, .20 to .44; N = 1312 subjects). Of the studies assessing the agreement of the QFT-Plus CLIA and the QIAreach with the QFT-Plus, 25% (1/4) and 33.3% (1/3) were classified at low RoB, respectively (Supplementary Tables 10 and 11). In our primary analyses, the pooled κ statistics comparing the QFT-Plus CLIA and the QIAreach with the QFT-Plus were 0.86 (95% CI, .78 to .94; N = 1173 samples) and 0.96 (95% CI, .92 to 1.00; N = 289 samples), respectively (Table 2). As summarized in Supplementary Tables 20 and 21, we found very limited information regarding QFT-Plus reproducibility or its predictive ability for incident TB.

Wantai TB-IGRA

As seen in Supplementary Table 22 (Supplementary Material Part C), only 1 of 26 studies assessing the sensitivity of the

Table 1. Summary of Differences in Sensitivity and Specificity Between the QuantiFERON-TB Gold Plus and the QFT-GIT or the T-SPOT.TB Assays

Comparator/ Outcome	Analysis	Studies, No.	Subjects Tested, No.	Correctly Classified (QFT-Plus), No.	Correctly Classified (Comparator), No.	Pooled Estimate QFT-Plus, % (95% CI); I^2	Pooled Estimate Comparator, % (95% CI); I^2	Difference in Sensitivity or Specificity[a] (QFT-Plus – Comparator), % Points (95% CI); I^2	Certainty of the Evidence (GRADE)
QFT-GIT as comparator									
Sensitivity	Paired comparisons (published studies)[b]	5	505	432	431	90.1 (76.6–96.2); 90%	89.4 (76.7–95.6); 92%	–0.1 (–2.8 to 2.6); 11%	Moderate[c] ⊕⊕⊕◯
	Paired comparisons (all studies)	7	972	861	864	90.8 (82.4–95.4); 90%	90.6 (82.4–95.2); 92%	–0.5 (–1.9 to 0.9); 10%	
	Parallel comparisons (published studies)	9	903	792	787	90.3 (84.2–94.2); 86%	89.3 (83.1–93.4); 88%	0.5 (–1.6 to 2.6); 12%	
	Parallel comparisons (All studies)	12	1397	1244	1244	90.4 (85.8–93.6); 84%	90 (85.4–93.3); 87%	0.0 (–1.5 to 1.5); 11%	
Specificity	Paired comparisons (published studies)[b]	1	211	207	209	98.1 (95.2–99.5); NA	99.1 (96.6–99.9); NA	–0.9 (–3.5 to 1.1); NA	Moderate[c] ⊕⊕⊕◯
	Paired comparisons (all studies)	6	1137	1101	1113	97.1 (92.6–98.9); 75%	98.6 (94.4–99.7); 72%	–1.0 (–2.0 to 0.1); 26%	
	Parallel comparisons (published studies)	3	529	518	523	97.9 (96.3–98.8); 0%	98.9 (97.5–99.5); 0%	–0.9 (–1.0 to –0.9); 0%	
	Parallel comparisons (all studies)	9	1505	1461	1476	97.3 (94.9–98.6); 65%	98.5 (96.5–99.4); 62%	–0.9 (–1.5 to –0.3); 11%	
T-SPOT.TB as comparator									
Sensitivity	Paired comparisons[b] (published studies)	1	99	98	96	99.0 (94.5–100); NA	97.0 (91.4–99.4); NA	2.0 (–2.4 to 7.4); NA	Low[c,e] ⊕⊕◯◯
	Paired comparisons (all studies)[d]	1	99	98	96	99.0 (94.5–100); NA	97.0 (91.4–99.4); NA	2.0 (–2.4 to 7.4); NA	
	Parallel comparisons (published studies)	3	252	238	223	95.1 (87.5–98.2); 63%	90.8 (75.4–97.0); 89%	5.8 (–22.2 to 33.8); 84%	
	Parallel comparisons (all studies)[d]	3	252	238	223	95.1 (87.5–98.2); 63%	90.8 (75.4–97.0); 89%	5.8 (–22.2 to 33.8); 84%	
Specificity	Paired comparisons[b] (published studies)	0	…	…	…	…	…	…	Low[c,e] ⊕⊕◯◯
	Paired comparisons (all studies)	1	50	49	50	98.0 (89.4–99.9); NA	99.0 (92.9–100); NA	–2.0 (–10.5 to 5.3); NA	
	Parallel comparisons (published studies)	1	106	104	104	98.1 (93.4–99.8); NA	98.1 (93.4–99.8); NA	0.0 (–4.9 to 4.9); NA	
	Parallel comparisons (all studies)	2	156	153	154	98.1 (94.2–99.4); 0%	98.7 (95–99.7); 0%	–0.6 (–12.0 to 10.9); 1%	

A summary of each analysis, including information from individual studies, is shown in Supplementary Material Part B, Supplementary Tables 12–15 (sensitivity) and Supplementary Tables 16–19 (specificity). Forest plots of pooled sensitivities and specificities are shown in in Supplementary Material Part B, Supplementary Figures 10–12 and 13–14, respectively. For a summary of the risk of bias assessment, please refer to Supplementary Figures 3–6. In line with the GRADE approach, the certainty of evidence (CoE) is categorized into four levels: very low (⊕◯◯◯), low (⊕⊕◯◯), moderate (⊕⊕⊕◯), and high (⊕⊕⊕⊕).

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not available.

[a]Pooled differences in sensitivity or specificity do not match exactly to the differences in the pooled sensitivities or specificities since they correspond to different meta-analytical approaches.

[b]Primary analysis.

[c]Downgraded because most studies were considered at unclear risk of bias.

[d]No unpublished studies were included in this analysis; results are repeated from the analysis including only published studies.

[e]Downgraded because CIs are very wide and hence consistent with both an appreciable gain and appreciable loss in diagnostic accuracy.

Table 2. Summary of Agreement Between the New or Updated Interferon-γ Release Assays and the World Health Organization–Endorsed Tests or the Tuberculin Skin Test

Index Test/Comparator	Studies Included	Studies, No.	Subjects Tested, No.	Total Concordant, No.	Agreement Pooled κ Statistic (95% CI); I^2	Certainty of the Evidence (GRADE)
QFT-Plus						
QFT-GIT	Published studies	22	6586	6204	0.82 (.78–.85); 67.4%	High ⊕⊕⊕⊕
	All studies	23	7187	6799	0.82 (.79–.86); 75.4%	
T-SPOT.TB	Published studies[a]	7	3139	2767	0.72 (.57–.86); 97.5%	Moderate[b] ⊕⊕⊕◯
TST	Published studies[a]	7	1312	914	0.32 (.20–.44); 81.2%	Moderate[b] ⊕⊕⊕◯
QFT-Plus CLIA[c]						
QFT-Plus	Published studies[a,d]	4	1173	1039	0.86 (.78–.94); 74.8%	Low[e] ⊕⊕◯◯
QIAreach[c]						
QFT-Plus	Published studies[d]	2	289	279	0.96 (.92–1.00); 24.9%	Low[e] ⊕⊕◯◯
	All studies[d]	3	529	498	0.95 (.92–.98); 0.0%	
Wantai TB-IGRA						
QFT-GIT	Published studies	3	1127	950	0.79 (.64–.94); 92.1%	Very low[b,f,g] ⊕◯◯◯
	All studies	4	2355	2043	0.79 (.70–.88); 90.6%	
T-SPOT.TB	Published studies[a]	3	340	320	0.87 (.81–.93); 0.0%	Low[f,g] ⊕⊕◯◯
TST	Published studies[a]	2	141	103	0.37 (.05–.69); 51.6%	Very low[d,f,g] ⊕◯◯◯
TB-Feron ELISA[c]						
QFT-Plus or QFT-GIT	Published studies	4	1062	1001	0.85 (.79–.92); 62.0%	Low[f,g] ⊕⊕◯◯
QFT-Plus or QFT-GIT or QFT-Gold	All studies	10	2454	2326	0.88 (.84–.93); 73.2%	Low[f,g] ⊕⊕◯◯

Forest plots of each agreement analysis included in this table are shown in the following figures: Supplementary Material Part B: Supplementary Figures 15–18 (QFT-Plus), Supplementary Figure 19 (QFT-Plus CLIA), Supplementary Figures 20 and 21 (QIAreach); Supplementary Material Part C: Figures 39–42 (Wantai TB-IGRA); and Supplementary Material Part D: Supplementary Figures 48 and 49 (TB-Feron). Only the manufacturer evaluation of the T-SPOT.TB with T-Cell Select was identified/included in this study; results are summarized in Supplementary Material Part D, Supplementary Figure 50 and Supplementary Table 38. For a summary of the risk of bias assessment, please refer to Supplementary Figures 7–9 (QFT-Plus), 28–30 (TB-IGRA), and 43–45 (TB-Feron). In line with the GRADE approach, the certainty of evidence (CoE) is categorized into four levels: very low (⊕◯◯◯), low (⊕⊕◯◯), moderate (⊕⊕⊕◯), and high (⊕⊕⊕⊕).

Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

[a]No unpublished studies assessing this comparison were identified/included.

[b]Downgraded because of the wide CIs.

[c]Insufficient studies were identified that assessed sensitivity or specificity of these tests. Hence, only measures of agreement could be pooled and are shown.

[d]Three studies assessing QFT-Plus CLIA [73], [7], [74] and 1 study assessing the QIAreach [75] reported results by number of samples instead of per patient.

[e]Downgraded because 3 of 4 QFT-Plus CLIA studies and 2 of 3 QIAreach studies were considered at high risk of bias.

[f]Downgraded because most studies were considered at either unclear or high risk of bias.

[g]Downgraded because of the risk of publication bias.

TB-IGRA was considered to have low RoB. In parallel comparisons of published studies including 1600 subjects, the sensitivity of the TB-IGRA was 3.0 percentage points higher than that of the QFT-GIT (95% CI, −.2 to 6.2); (Table 3). In parallel comparisons of published studies including 1288 subjects, the sensitivity of the TB-IGRA was 1.6 percentage points lower than that of the T-SPOT.TB (95% CI, −4.2 to 1.0); we did not find any significant differences between these tests' sensitivities in 1 study allowing paired comparisons [99]. As seen in Supplementary Table 23, only 1 of 16 studies assessing TB-IGRA's specificity was classified as having low RoB. In parallel comparisons of published studies, the specificity of the TB-IGRA was 2.6 percentage points lower than that of the QFT-GIT (95% CI, −4.2 to −1.0; N = 818 subjects) and 10.3 percentage points lower than the T-SPOT.TB (95% CI, −17.2 to −3.4; N = 185 subjects) (Table 3). As seen in Supplementary Table 24, 1 of 8 studies assessing TB-IGRA agreement was considered to have low RoB. In our primary analyses, the pooled κ statistics comparing the TB-IGRA against the QFT-GIT and T-SPOT.TB were 0.79 (95% CI, .64 to .94; N = 1127 subjects) and 0.87 (95% CI, .81 to .93; N = 340 subjects), respectively (Table 2).

TB-Feron ELISA

The characteristics of the studies assessing the sensitivity, specificity, and agreement of the TB-Feron are shown in Supplementary Tables 33–35 and Supplementary Figures 46–

Table 3. Summary of Pooled Differences in Sensitivity and Specificity Between the Wantai TB-IGRA and the QFT-GIT or the T-SPOT.TB

Comparator/ Outcome	Analysis	Studies, No.	Subjects Tested, No.	Correctly Classified (Wantai TB-IGRA), No.	Correctly Classified (Comparator), No.	Pooled Estimate Wantai TB-IGRA, % (95% CI); I^2	Pooled Estimate Comparator, % (95% CI); I^2	Difference in Sensitivity or Specificity[a] (Wantai TB-IGRA – Comparator), % Points (95% CI); I^2	Certainty of the Evidence (GRADE)
QFT-GIT as comparator									
Sensitivity	Paired comparisons (published studies)[b]	0	…	…	…	…	…	…	Very low[c,d,e] ⊕OOO
	Paired comparisons (all studies)	1	43	31	35	72.1 (56.3–84.7); NA	81.4 (66.6–91.6); NA	−9.3 (−21.5 to 2.7); NA	
	Parallel comparisons (published studies)	5	1600	1373	1321	86.4 (81.5–90.2); 87%	83.2 (76.3–88.4); 93%	3.0 (−.2 to 6.2); 32%	
	Parallel comparisons (all studies)	7	2429	2041	1966	84.5 (79.8–88.4); 85%	82.2 (76.8–86.6); 90%	2.8 (−.3 to 5.9); 57%	
Specificity	Paired comparisons (published studies)[b]	0	…	…	…	…	…	…	Low[c,e] ⊕⊕OO
	Paired comparisons (all studies)	0	…	…	…	…	…	…	
	Parallel comparisons (published studies)	4	818	714	733	85.9 (77.1–91.6); 90%	88.7 (77.7–94.7); 91%	−2.6 (−4.2 to −1.0); 2%	
	Parallel comparisons (all studies)	6	1093	927	958	84.3 (77.0–89.7); 87%	86.8 (78.0–92.4); 87%	−2.8 (−4.7 to −.8); 17%	
T-SPOT.TB as comparator									
Sensitivity	Paired comparisons (published studies)[b]	1	68	66	66	97.1 (89.8–99.6); NA	97.1 (89.8–99.6); NA	.0 (−7.0 to 7.0); NA	Very low[c,d,e] ⊕OOO
	Paired comparisons (all studies)[f]	1	68	66	66	97.1 (89.8–99.6); NA	97.1 (89.8–99.6); NA	.0 (−7.0 to 7.0); NA	
	Parallel comparisons (published studies)	6	1288	1065	1092	87.7 (80.9–92.3); 89%	88.7 (83–92.7); 87%	−1.6 (−4.2 to 1.0); 16%	
	Parallel comparisons (all studies)[f]	7	1332	1104	1132	87.8 (81.9–91.9); 88%	88.9 (83.8–92.6); 85%	−1.6 (−3.9 to .6); 11%	
Specificity	Paired comparisons (published studies)[b]	0	…	…	…	…	…	…	Very low[c,d,e] ⊕OOO
	Paired comparisons (all studies)	0	…	…	…	…	…	…	
	Parallel comparisons (published studies)	1	185	151	170	81.6 (75.3–86.9); NA	91.9 (87–95.4); NA	−10.3 (−17.2 to −3.4); NA	
	Parallel comparisons (all studies)	3	285	241	261	85.5 (77.3–91.1); 45%	91.6 (87.7–94.3); 0%	−5.6 (−20 to 8.7); 33%	

A summary of each analysis, including information from individual studies, is shown in Supplementary Material Part C, Supplementary Tables 25–29 (sensitivity) and Supplementary Tables 30–32 (specificity). Forest plots of pooled sensitivities and specificities are shown in Supplementary Material Part C, Supplementary Figures 31–34 and 35–38, respectively. For a summary of the risk of bias assessment, please refer to Supplementary Figures 22–27. In line with the GRADE approach, the certainty of evidence (CoE) is categorized into four levels: very low (⊕OOO), low (⊕⊕OO), moderate (⊕⊕⊕O), and high (⊕⊕⊕⊕).

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not available.

[a]Pooled differences in sensitivity or specificity do not match exactly to the differences in the pooled sensitivities or specificities since they correspond to different meta-analytical approaches.

[b]Primary analysis.

[c]Downgraded because most studies were considered at either unclear or high risk of bias.

[d]Downgraded because CIs are very wide, and consistent with both an appreciable gain and appreciable loss in diagnostic accuracy.

[e]Downgraded because of the risk of publication bias.

[f]No unpublished studies were included in this analysis; results are repeated from the analysis including only published studies.

49 (Supplementary Material Part D). In paired comparisons of all studies including 139 subjects, the sensitivity of the TB-Feron was 3.7 percentage points higher (95% CI, −18.5 to 25.9) than that of the QFT-G or QFT-Plus (Supplementary Table 36). In our primary analysis including 327 subjects, the specificity of the TB-Feron was 5.4 percentage points lower than that of the QFT-Plus (95% CI, −15.3 to 4.4) (Supplementary Table 37). In our primary analyses including 1062 subjects, the pooled κ statistic comparing the TB-Feron and the QFT-Plus or QFT-GIT was 0.85 (95% CI, .79 to .92) (Table 2).

T-SPOT.TB With T-Cell Select

We only identified 1 report in which the manufacturer assessed the agreement of T-SPOT.TB when processing samples with T-Cell Select from 0 to 58 hours after blood collection (divided into 4 time points) versus without T-Cell Select within 8 hours. Overall agreement within 0–8 hours was 96.5% (95% CI, 94.7%–97.8%) and did not change significantly up to 48–55 hours (Supplementary Table 38 and Supplementary Figure 50).

DISCUSSION

In this review, we identified and summarized studies comparing the diagnostic performance of 6 new commercial IGRAs (ie, Qiagen's QFT-Plus, QIAreach, and QFT-Plus CLIA; Wantai's TB-IGRA; the Standard E TB-Feron; and Oxford Immunotec's T-SPOT.TB with T-Cell Select) against IGRAs that have previously been endorsed by the WHO. According to our results, the QFT-Plus and the TB-IGRA have similar diagnostic performance as their comparators; studies assessing other new tests are too limited to make valid conclusions.

Pooled differences in sensitivity and specificity between the QFT-Plus and its predecessor, the QFT-GIT, ranged within 1 percentage point, while their agreement was almost perfect. These results confirm findings from previous studies suggesting these tests are equivalent, with no apparent improvement in sensitivity [103]. Agreement between the QFT-Plus and the T-SPOT.TB was substantial; nevertheless, studies comparing their diagnostic accuracy were scarce. Notably, the studies assessing QFT-Plus sensitivity incorporated in this review included only 8 individuals with HIV, and none was focused on children. In both subgroups, $CD8^+$-specific immune responses have a major role against *Mtb* [104–106]. Hence, studies focusing on these subpopulations with an appropriate study design are required. Although reports estimating the predictive ability for incident TB of QFT-Plus are limited, we would not expect major differences between them, given the excellent agreement of QFT-Plus with QFT-GIT.

We did not find clinically meaningful differences in sensitivity or specificity between the TB-IGRA and the QFT-GIT, and we found almost perfect agreement between the TB-IGRA and the T-SPOT.TB, although we found few studies comparing these tests. Inferences about the accuracy of the TB-IGRA are limited by the low quality of most reports, due to incomplete description of key methodologic aspects and missing data, precluding full assessment of their RoB. Most publications were identified by the manufacturer since they were not listed in the databases and registries included in our electronic search. We could not assess potential conflicts of interest for most studies due to a lack of information. Finally, the generalizability of results with TB-IGRA (and even availability of the test itself) to other settings and populations is uncertain as almost all studies were conducted in 1 country (China).

On the other hand, we found only fair agreement between the TST and the QFT-Plus or the TB-IGRA (Table 2), consistent with previous systematic reviews assessing the agreement of the TST with previous versions of the QFT or the T-SPOT.TB in healthcare workers (pooled κ = 0.28 [95% CI, .22 to .35]) [107]; people immigrating from high to low TB-incidence settings (individual κ values ranged from 0.32 to 0.56) [108]; and people with HIV (pooled κ = 0.37 [95% CI, .28 to .46]) [109].

The included studies assessing the remaining IGRAs (ie, QFT-Plus CLIA, QIAreach, TB-Feron, and T-SPOT.TB with T-Cell Select) were mainly limited to the evaluation of agreement with reference tests. The QIAreach and the TB-Feron are entirely new tests; therefore, independent evaluations of their sensitivity and specificity are needed before these can be adopted. On the other hand, the T-SPOT.TB with T-Cell Select and the QFT-Plus with CLIA are modifications of previously validated tests; nevertheless, independent evaluation of these tests would be desirable before widespread use. Finally, our search identified 11 additional commercial IGRAs for the diagnosis of TBI (Supplementary Table 39); however, most of these were described in a single publication, and our search was not designed specifically for these other tests. This would be needed to adequately assess their diagnostic accuracy.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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(foundation grant paid to institution) from the Canadian Institutes of Health Research prior to the conduct of this review. D. M. also reports unpaid participation as a member of Scientific Advisory Committee for TB CHAMP (pediatric TB studies in South Africa). All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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