

Systematic Review: T-Cell–based Assays for the Diagnosis of Latent Tuberculosis Infection: An Update

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Background: Interferon- γ -release assays (IGRAs) are alternatives to the tuberculin skin test (TST). A recent meta-analysis showed that IGRAs have high specificity, even among populations that have received bacille Calmette–Guérin (BCG) vaccination. Sensitivity was suboptimal for TST and IGRAs.

Purpose: To incorporate newly reported evidence from 20 studies into an updated meta-analysis on the sensitivity and specificity of IGRAs.

Data Sources: PubMed was searched through 31 March 2008, and citations of all original articles, guidelines, and reviews for studies published in English were reviewed.

Study Selection: Studies that evaluated QuantiFERON-TB Gold, QuantiFERON-TB Gold In-Tube (both from Cellestis, Victoria, Australia), and T-SPOT.TB (Oxford Immunotec, Oxford, United Kingdom) or its precommercial ELISpot version, when data on the commercial version were lacking. For assessing sensitivity, the study sample had to have microbiologically confirmed active tuberculosis. For assessing specificity, the sample had to comprise healthy, low-risk individuals without known exposure to tuberculosis. Studies with fewer than 10 participants and those that included only immunocompromised participants were excluded.

Data Extraction: One reviewer abstracted data on participant characteristics, test characteristics, and test performance from 38 studies; these data were double-checked by a second reviewer. The original investigators were contacted for additional information when necessary.

Data Synthesis: A fixed-effects meta-analysis with correction for overdispersion was done to pool data within prespecified subgroups. The pooled sensitivity was 78% (95% CI, 73% to 82%) for QuantiFERON-TB Gold, 70% (CI, 63% to 78%) for QuantiFERON-TB Gold In-Tube, and 90% (CI, 86% to 93%) for T-SPOT.TB. The pooled specificity for both QuantiFERON tests was 99% among non-BCG-vaccinated participants (CI, 98% to 100%) and 96% (CI, 94% to 98%) among BCG-vaccinated participants. The pooled specificity of T-SPOT.TB (including its precommercial ELISpot version) was 93% (CI, 86% to 100%). Tuberculin skin test results were heterogeneous, but specificity in non-BCG-vaccinated participants was consistently high (97% [CI, 95% to 99%]).

Limitations: Most studies were small and had limitations, including no gold standard for diagnosing latent tuberculosis and variable TST methods and cutoff values. Data on the specificity of the commercial T-SPOT.TB assay were limited.

Conclusion: The IGRAs, especially QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube, have excellent specificity that is unaffected by BCG vaccination. Tuberculin skin test specificity is high in non-BCG-vaccinated populations but low and variable in BCG-vaccinated populations. Sensitivity of IGRAs and TST is not consistent across tests and populations, but T-SPOT.TB appears to be more sensitive than both QuantiFERON tests and TST.

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The tuberculin skin test (TST) was formerly the only test for detecting latent tuberculosis infection; however, interferon- γ -release assays (IGRAs) have emerged as attractive alternatives. Two IGRAs, QuantiFERON-TB Gold (Cellestis, Carnegie, Australia) and T-SPOT.TB (Oxford Immunotec, Oxford, United Kingdom), are now commercially available, and their use is expanding. Although IGRAs are intended for diagnosing latent tuberculosis infection, active tuberculosis is used as a surrogate standard to estimate accuracy in the absence of a gold standard for latent tuberculosis infection.

In a recent meta-analysis (1), Menzies and colleagues showed that IGRAs have high specificity, especially in populations who have received bacille Calmette–Guérin (BCG) vaccination. However, the sensitivity of both TST and IGRAs was suboptimal, and none of these tests could distinguish between latent tuberculosis and active disease. Since the publication of this meta-analysis, the evidence base for IGRAs has rapidly grown with publication of several guidelines and statements (2–6). We present an updated meta-analysis that will provide helpful information

for clinicians and for agencies developing updated guidelines.

METHODS

Study Selection and Eligibility

Using the same search strategy as that published elsewhere (1), we searched PubMed for new studies through 31 March 2008 that reported data on the sensitivity and specificity of commercial IGRAs. We reviewed citations of all original articles, guidelines, and reviews for studies published in English.

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Appendix Tables

Conversion of graphics into slides

Context

Tuberculin skin tests (TSTs) and new interferon- γ -release assays (IGRAs) are alternative tests for detecting latent tuberculosis.

Contribution

This updated meta-analysis of 38 studies found that sensitivity of IGRAs and TST was not consistent across tests and populations, but TSPOT.TB seemed to be more sensitive than QuantiFERON tests and TST. Both the TST and IGRAs had high specificity (>95%) for tuberculosis in populations not vaccinated with bacille Calmette–Guérin (BCG). The specificity of IGRAs was also high in populations vaccinated with BCG, whereas TST specificity was low and highly variable.

Caution

The studies had many limitations, including small sample sizes and no reference standard test for diagnosing latent tuberculosis.

Implication

The specificity of IGRAs for detecting latent tuberculosis is good and seems unaffected by BCG vaccination status.

—The Editors

The inclusion criteria for this update were narrower than for the original meta-analysis, which included research, in-house, or commercial versions of QuantiFERON or enzyme-linked immunospot (ELISpot) tests that used early-secreted antigenic target 6, with or without culture filtrate protein 10 and with or without TB7.7 antigens. For the update, we restricted the studies to QuantiFERON-TB Gold (also known as QFT-2G), QuantiFERON-TB Gold In-Tube (also known as QFT-3G) (both from Cellestis, Victoria, Australia), and T-SPOT.TB (Oxford Immunotec, Oxford, United Kingdom) or its pre-commercial ELISpot version, when data on the commercial version were lacking. Unlike the original meta-analysis, we excluded studies with fewer than 10 participants, studies that included only immunocompromised populations, and studies that used only early-secreted antigenic target 6.

For studies assessing sensitivity, the study sample had to comprise participants with microbiologically confirmed active tuberculosis, but not include only immunocompromised participants. For studies assessing specificity, the sample had to comprise healthy, low-risk individuals without known exposure to tuberculosis who were from countries with a low tuberculosis incidence rate.

Two independent reviewers performed searches and selected articles meeting the inclusion criteria. One reviewer abstracted data on participant characteristics and test characteristics and performance, and a second reviewer double-checked these data. When necessary, we contacted the original investigators for additional information.

Data Synthesis

For each study, we calculated sensitivity or specificity and 95% CIs and summarized the results in forest plots. To pool estimates across the studies, we did a fixed-effects meta-analysis with correction for overdispersion to account for between-study variability by using MetaDiSc software, version 1.4 (Hospital Ramón y Cajal, Madrid, Spain; www.hrc.es/investigacion/metadisc_en.htm). We evaluated heterogeneity by using the chi-square and I^2 tests. Because we found heterogeneity, we performed subgroup analyses; we analyzed each commercial test (and test version, in the case of QuantiFERON) separately and evaluated BCG-vaccinated and nonvaccinated groups separately for specificity studies. When data on the sensitivity and specificity of concurrently done TSTs were reported, we extracted and summarized the data in tables and forest plots.

Role of the Funding Source

The Canadian Institutes of Health Research and the Fonds de la recherche en santé du Québec had no role in the design, conduct, and analysis of the study or the decision to submit the manuscript for publication.

RESULTS

A total of 38 articles (7–44) met our inclusion criteria, 20 of which (comprising 1879 participants) were new articles not included in our previous meta-analysis. Of these, 15 included QuantiFERON-TB Gold or QuantiFERON-TB Gold In-Tube and 9 included T-SPOT.TB.

Eight articles in the original meta-analysis (1) were excluded from this update because they included noncommercial assays (45–48), had fewer than 10 participants (49, 50), included only immunocompromised populations (51), or used only early-secreted antigenic target 6 as the antigen (45).

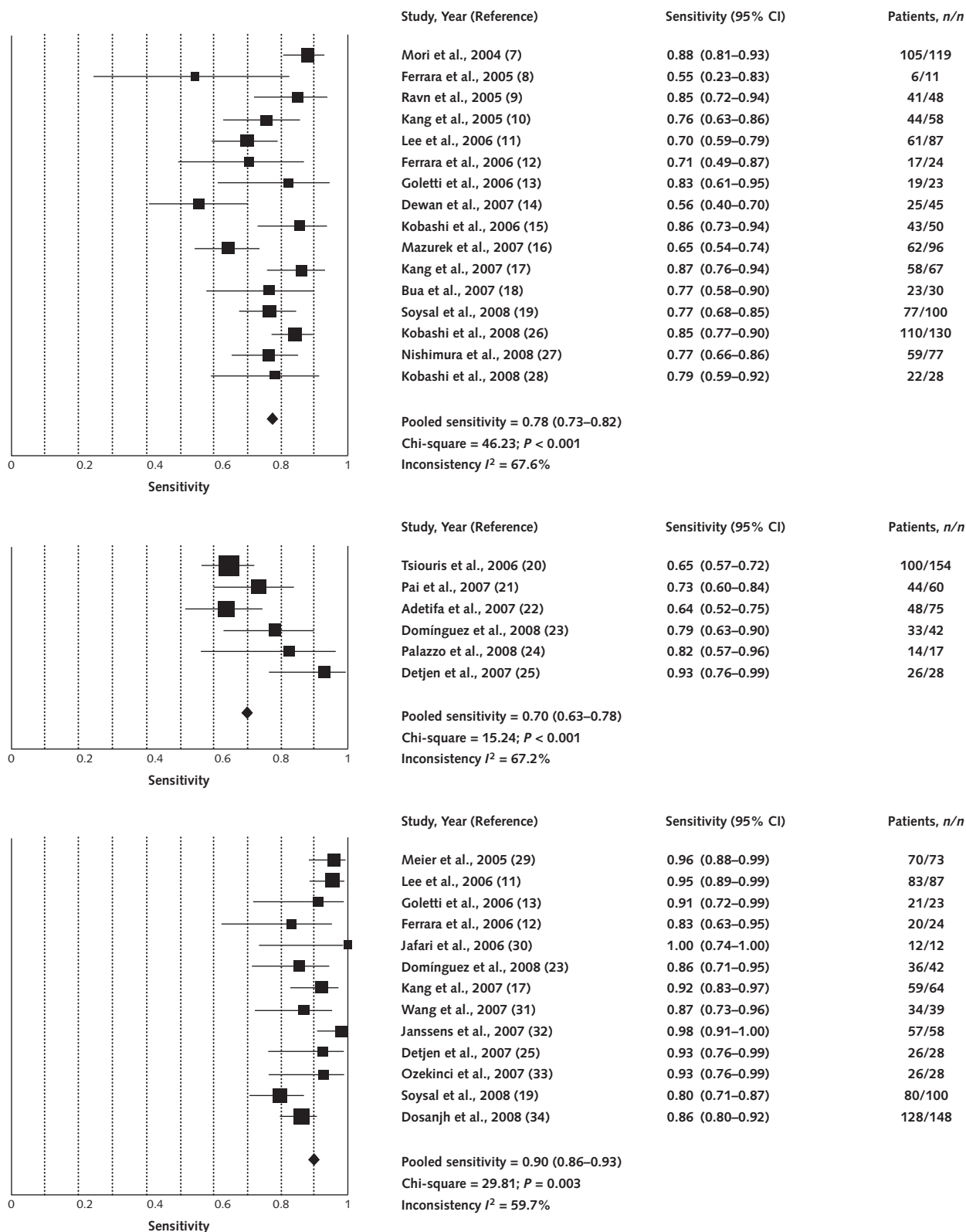
Appendix Tables 1 through **4** (available at www.annals.org) provide details on the included studies. All studies were cross-sectional. Of the 38 studies, 21 (55%) had some sort of industry involvement or support, such as sponsorship, donation of test kits, participation in advisory boards, involvement of test developers, or ownership of patents.

Sensitivity of Interferon- γ -Release Assays

We identified 22 studies of QuantiFERON tests, comprising 1369 participants (**Appendix Table 1**), and 13 studies of T-SPOT.TB, comprising 726 participants (**Appendix Table 2**). Active tuberculosis was confirmed by culture in most cases, and most studies included participants without HIV infection. Three of the QuantiFERON studies were from countries with a high rate of tuberculosis incidence, whereas none of the T-SPOT.TB studies was from a high-incidence country. Almost all of the sensitivity studies included only adults.

Figure 1 shows the forest plot and pooled sensitivity estimates. The pooled sensitivity of all 22 QuantiFERON

Figure 1. Forest plot of studies estimating sensitivity of interferon- γ -release assays in patients with active tuberculosis as a surrogate for latent tuberculous infection.



Point estimates for sensitivity and 95% CIs are shown along with pooled estimates. **Top.** QuantiFERON-TB Gold (16 studies). **Middle.** QuantiFERON-TB Gold In-Tube (6 studies). **Bottom.** T-SPOT.TB (13 studies).

studies was 76% (95% CI, 72% to 80%) (plot not shown). Pooled sensitivity was 78% (CI, 73% to 82%) for QuantiFERON-TB Gold, 70% (CI, 63% to 78%) for QuantiFERON-TB Gold In-Tube, and 90% (CI, 86% to 93%) for T-SPOT.TB (Figure 1). Although we found no obvious differences in sensitivity between QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube, the non-overlapping CIs suggest that the pooled sensitivity of T-SPOT.TB was higher than that of either QuantiFERON-TB test.

Seven studies (Appendix Table 5) reported head-to-head comparisons of T-SPOT.TB and QuantiFERON sensitivity. In 6 of those studies, T-SPOT.TB had a higher sensitivity than QuantiFERON-TB Gold, with difference ranging from 3% to 25%. One study reported identical sensitivity estimates for both assays. Studies that used QuantiFERON-TB Gold showed lower sensitivity relative to T-SPOT.TB than did studies that used QuantiFERON-TB Gold In-Tube.

Specificity of Interferon- γ -Release Assays

We identified 16 studies of QuantiFERON tests, 8 of BCG-vaccinated and 8 of non-BCG-vaccinated samples, comprising 1624 participants (Appendix Table 3). None of the specificity studies was from a country with a high rate of tuberculosis incidence. Almost all of the specificity studies included only adults. The BCG vaccination policies in the study countries varied; for example, Japan and South Korea have a policy of repeated BCG vaccinations, whereas the United States and the Netherlands do not recommend BCG vaccination.

We identified 2 studies that used the commercial T-SPOT.TB assay and 4 studies that used the precommercial ELISpot version, with a combined total of 290 participants. Appendix Table 4 summarizes these 6 studies. Figure 2 presents the forest plot and pooled estimates. The pooled specificity was 98% (CI, 96% to 99%) for all QuantiFERON studies, 99% (CI, 98% to 100%) for QuantiFERON among non-BCG-vaccinated populations, and 96% (CI, 94% to 98%) for QuantiFERON among BCG-vaccinated populations (Figure 2). The pooled specificity of T-SPOT.TB/ELISpot was 93% (CI, 86% to 100%) (Figure 2). All but 1 T-SPOT.TB study included BCG-vaccinated participants. When only the 2 commercial T-SPOT.TB studies were pooled, the specificity was 87% (CI, 80% to 92%).

Sensitivity and Specificity of Tuberculin Skin Test

Figure 3 shows the forest plot of TST sensitivity and specificity estimates. Sensitivity estimates (20 studies with 1193 participants) were heterogeneous, with a pooled estimate of 77% (CI, 71% to 82%). Specificity in non-BCG-vaccinated populations (6 studies with 847 participants) was consistently high, with a pooled estimate of 97% (CI, 95% to 99%). Specificity in BCG-vaccinated populations (6 studies with 551 participants) was low and highly heterogeneous.

DISCUSSION

This updated meta-analysis includes the results of 20 new studies and synthesizes a substantial body of new IGRA literature. Our results confirm that IGRAs have excellent specificity that is unaffected by BCG vaccination. In particular, we found that both QuantiFERON tests have excellent specificity on the basis of a large number of consistent studies. In contrast, data on the specificity of the commercial T-SPOT.TB assay are limited. Further research is needed to better define the specificity of the T-SPOT.TB assay and to assess the trade-offs between sensitivity and specificity.

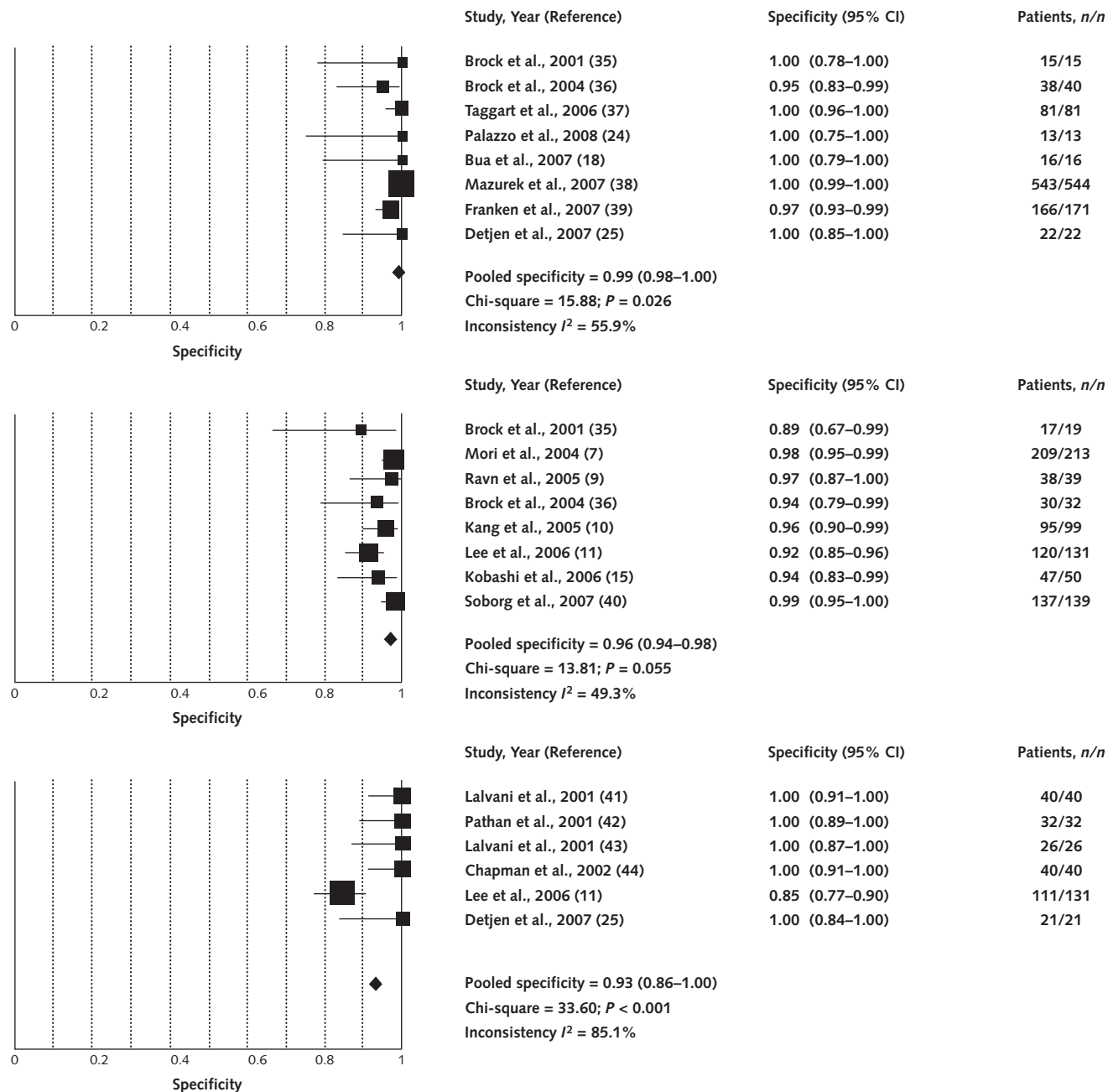
Our results suggest that TST specificity is high in non-BCG-vaccinated populations but low and highly variable in BCG-vaccinated populations. Overall, the high specificity of IGRAs, especially QuantiFERON, might prove to be useful in BCG-vaccinated individuals, particularly in settings where TST specificity is compromised by BCG vaccination after infancy or by multiple BCG vaccinations (52). Specificity estimates for IGRAs were highly consistent across studies, which may be because almost all specificity studies were conducted in settings with a low rate of tuberculosis incidence and test methods and cutoff values are better standardized than for the TST.

The sensitivity of IGRAs and the TST was not consistent across the tests and samples. This may have been because of the spectrum (case-mix) and severity of tuberculosis cases included in various studies, the varying background rates of tuberculosis and HIV across countries, or the inherent differences among the various test formats. For example, 3 studies of QuantiFERON-TB Gold In-Tube in countries with a high rate of tuberculosis incidence showed lower sensitivity than studies in countries with a low rate of incidence. Persons with tuberculosis in high-incidence countries often have advanced disease and are likely to be infected with HIV or malnourished. Anergy due to advanced disease, malnutrition, and HIV-associated immune suppression may lower the sensitivity of IGRAs.

The pooled T-SPOT.TB sensitivity was higher than that of the QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube assays. This finding should be carefully interpreted, however, because it is not based on direct head-to-head comparison studies. Seven studies (5 that used QuantiFERON-TB Gold and 2 that used QuantiFERON-TB Gold In-Tube) that did provide head-to-head comparisons showed higher sensitivity for T-SPOT.TB, although the difference ranged from 0% to 25% (median, 7%). Tuberculin skin test sensitivity results are hard to interpret because of the heterogeneity; however, the pooled estimate of 77% suggests that TST is probably as sensitive as QuantiFERON but less sensitive than T-SPOT.TB.

The higher sensitivity of T-SPOT.TB may be clinically useful in evaluating high-risk populations with immunosuppressive conditions. However, the diagnosis of active tuberculosis rests on microbiological detection of *Mycobac-*

Figure 2. Forest plot of studies estimating specificity of interferon- γ -release assays in populations at very low risk for latent tuberculous infection.



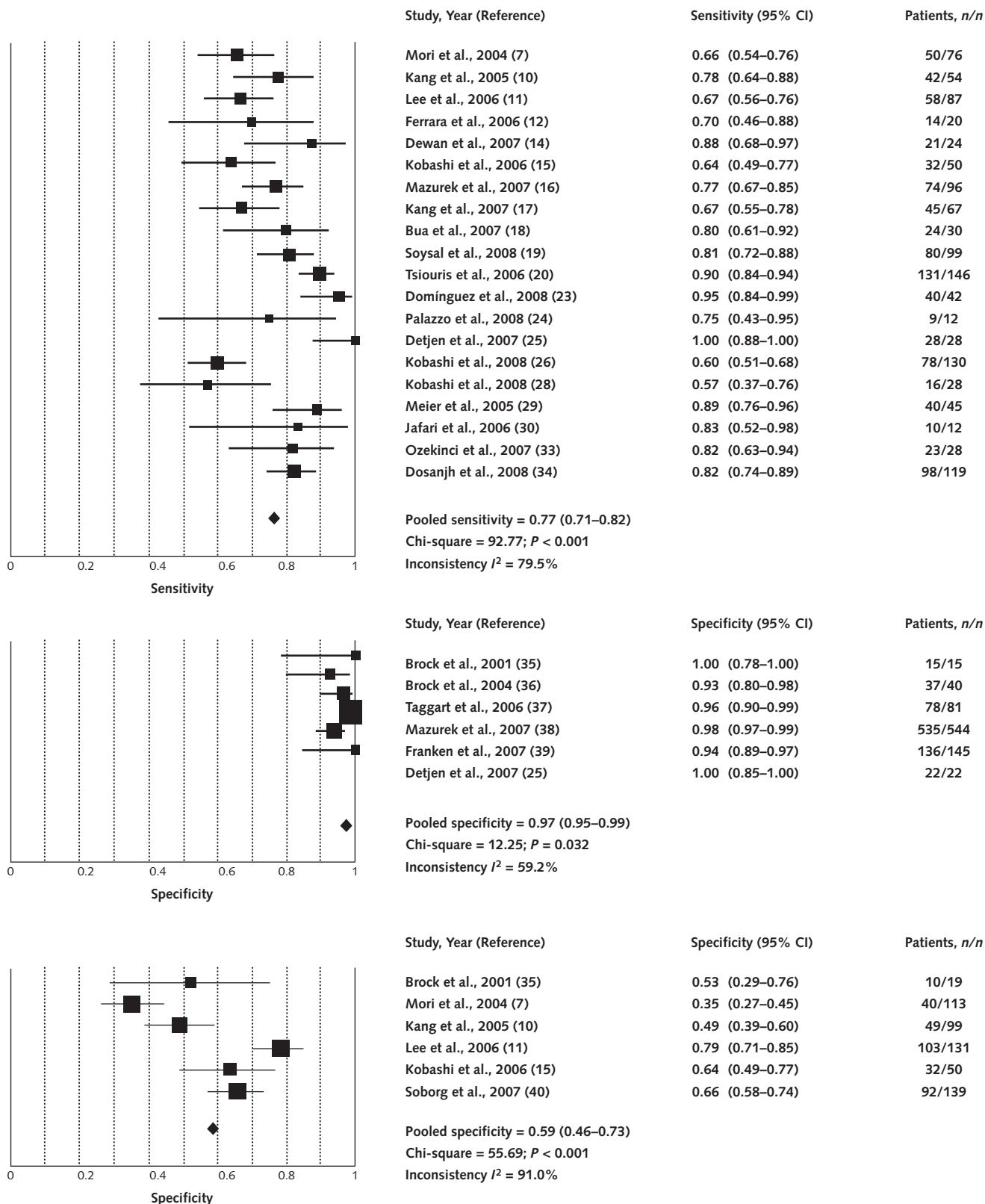
Point estimates for specificity and 95% CIs are shown along with pooled estimates. **Top.** QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube (braille Calmette–Guérin [BCG] nonvaccinated; 8 studies). **Middle.** QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube (BCG vaccinated; 8 studies). **Bottom.** T-SPOT.TB (predominantly BCG vaccinated; 6 studies).

terium tuberculosis. Immune-based tests, such as IGRAs and TST, do not directly detect *M. tuberculosis*; they merely indicate a cellular immune response to recent or remote sensitization with *M. tuberculosis*. In settings with high tuberculosis incidence, in which latent infection is widespread, a positive IGRA result may not necessarily indicate active tuberculosis (53, 54). Furthermore, a negative

IGRA result would not conclusively rule out active disease in an individual suspected to have tuberculosis (53, 54); this also applies to the TST.

Our meta-analysis has limitations. Most studies were small and had limitations, including no gold standard for diagnosing latent tuberculosis infection and variable TST methods, cutoff values, and results. Our meta-analysis of

Figure 3. Forest plot of studies estimating sensitivity and specificity of the tuberculin skin test.



Point estimates for sensitivity and specificity and 95% CIs are shown along with pooled estimates. **Top.** Sensitivity (20 studies). **Middle.** Specificity in non–bacille Calmette–Guérin-vaccinated populations (6 studies). **Bottom.** Specificity in bacille Calmette–Guérin-vaccinated populations (6 studies).

TST accuracy did not include all the available literature on TST; we included only TST studies that also included a comparison of IGRAs. Thus, several older studies on TST were not eligible for inclusion.

Although sensitivity and specificity are useful and easily measured test characteristics, they have limitations (55). Given the lack of a gold standard, sensitivity and specificity for active tuberculosis may not translate to accuracy for latent tuberculosis (which cannot be directly estimated). Also, studies that reported sensitivity did not always report specificity and vice versa. Thus, the trade-offs between these test characteristics are not easy to interpret. Furthermore, the sensitivity and specificity of single tests do not provide information on their incremental or added value.

Despite the substantial body of literature on IGRAs, several questions remain unanswered (56), including the prognostic ability of these tests to accurately identify individuals with latent infection who are at the highest risk for progressing to active tuberculosis and therefore most likely to benefit from preventive therapy (57–59). The IGRAs appear to have dynamic characteristics that increase the likelihood of conversions and reversions over time (60). Data on high-risk populations, such as children and immunocompromised persons, are limited. Ongoing studies should resolve these issues within the next few years and inform evidence-based guidelines on how to implement IGRAs in clinical practice.

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Appendix Table 1. Sensitivity of QuantiFERON-TB Gold (QFT) among Patients with Active Tuberculosis (TB)

Study, Year (Reference)	Industry Supported?*	Sample	Setting	Patients with Active (Culture-Confirmed) TB, n (%)	HIV-Positive Patients, %	QFT Result, n (%)			Sensitivity of TST	
						Positive	Negative	Indeterminate†	Cutoff Value	Patients, n/n (%)
Mori et al., 2004 (7)	Yes	Predominantly adults	Japan	119 (100)	0	105 (88)	13 (11)	1 (1)	5 mm	50/76 (66)
Ferrara et al., 2005 (8)	No	Predominantly adults	Italy	11 (45)	0	6 (55)	3 (27)	2 (18)	Risk stratified	3/9 (33)
Ravn et al., 2005 (9)	Yes	Predominantly adults	Denmark	48 (56)	6	41 (85)	7 (15)	0 (0)	NR	NR
Kang et al., 2005 (10)	Yes	Adults	South Korea	58 (100)	0	44 (76)	10 (17)	4 (7)	10 mm	42/54 (78)
Lee et al., 2006 (11)	Yes	Predominantly adults	South Korea	87 (63)	0	61 (70)	18 (21)	8 (9)	10 mm	58/87 (67)
Ferrara et al., 2006 (12)	Yes	Predominantly adults	Italy	24 (NR)	NR	17 (71)	6 (25)	1 (4)	Risk stratified	14/20 (70)
Goletti et al., 2006 (13)	Yes	Predominantly adults	Italy	23 (100)	0	19 (83)	4 (17)	0 (0)	NR	NR
Dewan et al., 2007 (14)	No	Adults	United States	45 (82)	7	25 (56)	17 (38)	3 (7)	5 mm	21/24 (88)
Kobashi et al., 2006 (15)	No	Predominantly adults	Japan	50 (100)	0	43 (86)	2 (4)	5 (10)	NR	32/50 (64)
Mazurek et al., 2007 (16)	Yes	Adults	United States	96 (72)	11	62 (65)	24 (25)	10 (10)	5 mm	74/96 (77)
Kang et al., 2007 (17)	Yes	Adults	South Korea	67 (100)	0	58 (87)	7 (10)	2 (3)	10 mm	45/67 (67)
Bua et al., 2007 (18)	NR	Adults	Italy	30 (NR)	7	23 (77)	2 (7)	5 (17)	NR	24/30 (80)
Soysal et al., 2008 (19)	NR	Predominantly adults	Turkey	100 (100)	0	77 (77)	22 (22)	1 (1)	5 mm	80/99 (81)
Tsiouris et al., 2006 (20)	Yes	Adults	South Africa	154 (100)	17	100 (65)	31 (20)	23 (15)	Risk stratified	131/146 (90)
Pai et al., 2007 (21)	No	Adults	India	60 (97)	5	44 (73)	16 (27)	0 (0)	NR	NR
Adetifa et al., 2007 (22)	Yes	Adults	The Gambia	75 (100)	9	48 (64)	27 (36)	0 (0)	NR	NR
Domínguez et al., 2008 (23)	Yes	Adults and children‡	Spain	42 (NR)	0	33 (79)	9 (21)	0 (0)	5 mm	40/42 (95)
Palazzo et al., 2008 (24)	NR	Predominantly adults	Italy	17 (100)	0	14 (82)	3 (18)	0 (0)	NR	9/12 (75)
Detjen et al., 2007 (25)	No	Children	Germany	28 (100)	0	26 (93)	2 (7)	0 (0)	10 mm	28/28 (100)
Kobashi et al., 2008 (26)	NR	Adults (including elderly)	Japan	130 (100)	0	110 (85)	6 (5)	14 (10)	5 mm	78/130 (60)
Nishimura et al., 2008 (27)	NR	Adults	Japan	77 (80)	0	59 (77)	18 (23)	0 (0)	NR	NR
Kobashi et al., 2008 (28)	NR	Adults	Japan	28 (100)	0	22 (79)	2 (7)	4 (14)	5 mm	16/28 (57)

NR = not reported; TST = tuberculin skin test.

* "Industry support" refers to any industry involvement or support (e.g., sponsorship, donation of test kits, participation in advisory boards, and involvement of test developers or ownership of patents).

† Indeterminate results were not excluded in calculating sensitivity estimates.

‡ Children formed 27% of the sample.

Appendix Table 2. Sensitivity of T-SPOT.TB among Patients with Active Tuberculosis (TB)

Study, Year (Reference)	Industry Supported?*	Sample	Setting	Patients with Active (Culture-Confirmed) TB, n (%)	HIV-Positive Patients, %	T-SPOT.TB Result, n (%)			Sensitivity of TST	
						Positive	Negative	Indeterminate†	Cutoff Value	Patients, n/n (%)
Meier et al., 2005 (29)	Yes	Adults	Germany	73 (86)	2	70 (97)	2 (3)	1 (1)	NR	40/45 (89)
Lee et al., 2006 (11)	Yes	Predominantly adults	South Korea	87 (63)	0	83 (95)	4 (5)	0 (0)	10 mm	58/87 (67)
Goletti et al., 2006 (13)	Yes	Predominantly adults	Italy	23 (100)	0	21 (91)	2 (9)	0 (0)	NR	NR
Ferrara et al., 2006 (12)	No	Predominantly adults	Italy	24 (NR)	NR	20 (83)	4 (17)	0 (0)	Risk stratified	14/20 (70)
Jafari et al., 2006 (30)	Yes	Predominantly adults	Germany	12 (67)	NR	12 (100)	0 (0)	0 (0)	10 mm	10/12 (83)
Domínguez et al., 2008 (23)	Yes	Adults and children‡	Spain	42 (NR)	0	36 (86)	3 (7)	3 (7)	5 mm	40/42 (95)
Kang et al., 2007 (17)	Yes	Adults	South Korea	64 (100)	0	59 (92)	5 (8)	0 (0)	10 mm	45/67 (67)
Wang et al., 2007 (31)	NR	Predominantly adults	Taiwan	39 (95)	7	34 (87)	5 (13)	0 (0)	NR	NR
Janssens et al., 2007 (32)	No	Adults	Switzerland	58 (100)	0	57 (98)	1 (2)	0 (0)	NR	NR
Detjen et al., 2007 (25)	No	Children	Germany	28 (100)	0	26 (93)	2 (7)	0 (0)	10 mm	28/28 (100)
Ozekinci et al., 2007 (33)	No	Adults	Turkey	28 (NR)	NR	26 (93)	2 (7)	0 (0)	10 mm and 15 mm	23/28 (82)
Soysal et al., 2008 (19)	NR	Predominantly adults	Turkey	100 (100)	0	80 (80)	16 (16)	4 (4)	5 mm	80/99 (81)
Dosanjh et al., 2008 (34)	Yes	Adults	United Kingdom	148 (100)	5	128 (86)	20 (14)	0 (0)	10 mm	98/119 (82)

NR = not reported; TST = tuberculin skin test.

* "Industry support" refers to any industry involvement or support (e.g., sponsorship, donation of test kits, participation in advisory boards, and involvement of test developers or ownership of patents).

† Indeterminate results were not excluded in calculating sensitivity estimates.

‡ Children formed 27% of the sample.

Appendix Table 3. Specificity of QuantiFERON-TB Gold (QFT) in Bacille Calmette–Guérin (BCG)–Vaccinated and Non-BCG-Vaccinated Patients with an Expected Low Prevalence of Tuberculous Infection*

Study, Year (Reference)	Industry Supported?†	Sample	Setting	Not BCG Vaccinated or Predominantly Nonvaccinated						BCG Vaccinated or Predominantly Vaccinated					
				Patients, n	QFT		TST		Patients, n	QFT		TST			
					False-Positive Result, n	Specificity, %	False-Positive Result, n	Specificity, %		False-Positive Result, n	Specificity, %	False-Positive Result, n	Specificity, %		
Brock et al., 2001 (35)	Yes	Predominantly adults	Denmark	15	0	100	0	100	19	2	89	9	53		
Mori et al., 2004 (7)	Yes	Predominantly adults	Japan	–	–	–	–	–	213	4	98.1	73/113	35		
Ravn et al., 2005 (9)	Yes	Predominantly adults	Denmark	–	–	–	–	–	39	1	97	NR	NR		
Brock et al., 2004 (36)	Yes	Adults and children	Denmark	40	2	95	3	93	32	2	94	NR	NR		
Kang et al., 2005 (10)‡	Yes	Adults only	South Korea	–	–	–	–	–	99	4	96	50	49§		
Taggart et al., 2006 (37)	NR	Adults only	United States	81	0	100	3	96	–	–	–	–	–		
Lee et al., 2006 (11)‡	Yes	Predominantly adults	South Korea	–	–	–	–	–	131	11	91.6	28	78.6§		
Kobashi et al., 2006 (15)	No	Predominantly adults	Japan	–	–	–	–	–	50	3	94	18	64		
Palazzo et al., 2008 (24)	NR	Predominantly adults	Italy	13	0	100	–	–	–	–	–	–	–		
Bua et al., 2007 (18)	NR	Adults only	Italy	16	0	100	–	–	–	–	–	–	–		
Mazurek et al., 2007 (38)	Yes	Adults only	United States	544	1	99.8	9	98.4§	–	–	–	–	–		
Franken et al., 2007 (39)	NR	Adults only	The Netherlands	171	5	97.1	9/145	93.8§	–	–	–	–	–		
Soborg et al., 2007 (40)	Yes	Adults only	The Netherlands	–	–	–	–	–	139	2	98.6	47	66.2		
Detjen et al., 2007 (25)	No	Children only	Germany	22	0	100	0	100§	–	–	–	–	–		

NR = not reported; TST = tuberculin skin test.

* Participants were healthy volunteers from the general population, students, or recruits with no history of exposure to tuberculosis.

† “Industry support” refers to any industry involvement or support (e.g., sponsorship, donation of test kits, participation in advisory boards, and involvement of test developers or ownership of patents).

‡ Because South Korea is an intermediate-incidence country, some of the low-risk participants may have been latently infected.

§ Cutoff value ≥10 mm.

|| Cutoff value ≥12 mm.

Appendix Table 4. Specificity of Enzyme-Linked Immunospot (ELISpot) and T-SPOT.TB in Bacille Calmette–Guérin (BCG)–Vaccinated and Non-BCG-Vaccinated Participants with an Expected Low Prevalence of Tuberculous Infection*

Study, Year (Reference)	Industry Supported?†	Sample	Setting	Test (Antigens)	Not BCG-Vaccinated or Predominantly Nonvaccinated						BCG-Vaccinated or Predominantly Vaccinated								
					No	ELISpot/T-SPOT.TB		TST		No	ELISpot/T-SPOT.TB		TST						
						False-Positive Result, n	Specificity, %	False-Positive Result, n	Specificity, %		False-Positive Result, n	Specificity, %	False-Positive Result, n	Specificity, %					
Lavani et al., 2001 (41)	Yes	Adults	United Kingdom	ELISpot (ESAT-6)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Pathan et al., 2001 (42)	Yes	Adults	United Kingdom	ELISpot (ESAT-6)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Lavani et al., 2001 (43)	Yes	Adults	United Kingdom	ELISpot (ESAT-6)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Chapman et al., 2002 (44)	Yes	Adults	United Kingdom	ELISpot (ESAT-6/CFP-10)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Lee et al., 2006 (11)‡	Yes	Adolescents	South Korea	T-SPOT.TB (ESAT-6/CFP-10)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Detjen et al., 2007 (25)	No	Children only	Germany	T-SPOT.TB (ESAT-6/CFP-10)	21	0	100	0	100	–	–	–	–	–	–	–	–	–	–

CFP-10 = culture filtrate protein 10; ESAT-6 = early-secreted antigenic target 6; NR = not reported; TST = tuberculin skin test.

* Participants were healthy volunteers from the general population, students, or recruits with no history of exposure to tuberculosis.

† “Industry support” refers to any industry involvement or support (e.g., sponsorship, donation of test kits, participation in advisory boards, and involvement of test developers or ownership of patents).

‡ Because South Korea is an intermediate-incidence country, some of the low-risk participants may have been latently infected.

|| Cutoff value ≥10 mm.

Appendix Table 5. Head-to-Head Comparisons of Sensitivity of QuantiFERON-TB (QFT) Gold versus T-SPOT.TB among Patients with Active Tuberculosis (TB)

Study, Year (Reference)	Industry Supported?*	Sample	Setting	Patients with Active (Culture-Confirmed) TB, n (%)	Sensitivity†			Difference between T-SPOT.TB and QFT Gold Sensitivity, percentage points
					Patients with Positive QFT Gold Result, n (%)		Patients with Positive T-SPOT.TB Result, n (%)	
					Patients with Positive QFT Gold Result, n (%)	Patients with Positive T-SPOT.TB Result, n (%)	Patients with Positive T-SPOT.TB Result, n (%)	
Lee et al., 2006 (11)	Yes	Predominantly adults	South Korea	87 (63)	61 (70)‡	83 (95)	25	
Ferrara et al., 2006 (12)	Yes	Predominantly adults	Italy	24 (NR)	17 (71)‡	20 (83)	12	
Goletti et al., 2006 (13)	Yes	Predominantly adults	Italy	23 (100)	19 (83)‡	21 (91)	8	
Kang et al., 2007 (17)	Yes	Adults	South Korea	67 (100)	58 (87)‡	59 (92)	5	
Soysal et al., 2008 (19)	NR	Predominantly adults	Turkey	100 (100)	77 (77)‡	80 (80)	3	
Domínguez et al., 2008 (23)	Yes	Adults and children§	Spain	42 (NR)	33 (79)	36 (86)	7	
Detjen et al., 2007 (25)	No	Children	Germany	28 (100)	26 (93)	26 (93)	0	

NR = not reported.

* “Industry support” refers to any industry involvement or support (e.g., sponsorship, donation of test kits, participation in advisory boards, and involvement of test developers or ownership of patents).

† Indeterminate results were not excluded in calculating sensitivity estimates.

‡ QFT Gold.

§ Children formed 27% of the sample.

|| QFT Gold In-Tube.