

Original Articles

Interferon-gamma Release Assays in Childhood Tuberculosis: A Systematic Review

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Abstract

Objective and methods: To evaluate interferon-gamma release assays (IGRA) in childhood tuberculosis, a systematic review was conducted by searching MEDLINE. **Results:** Seventeen relevant articles were included, all using surrogate measures (positive rate in culture-confirmed tuberculosis and negative rate among low-risk subjects) for tuberculosis infection. Only one paper contained data for estimating likelihood ratios for the tuberculin skin test (TST) and IGRA among predominantly BCG-unvaccinated paediatric subjects. The positive and negative likelihood ratios (95% confidence interval) were, respectively, 5.5 (2.3-13.2) and 0.44 (0.28-0.71) for TST with 15 mm cut-off; 74.9 (4.8-1181) and 0.09 (0.03-0.29) for QuantiFERON-TB Gold in-Tube; and 37.1 (5.3-258) and 0.07 (0.02-0.28) for T-SPOT.TB tests. Predictive values varied in different clinical and epidemiological settings. Unlike TST, test performance of IGRA was not affected by BCG vaccination status. **Conclusion:** TST may still play an important role in targeted contact investigation and clinical management, although IGRA may outperform TST in some settings.

Key words

Child; Interferon-gamma; review; Tuberculin test; Tuberculosis

Introduction

Untreated tuberculosis (TB) disease carries significant morbidity and mortality. The diagnosis of TB disease among infants and children has been challenging owing to the often non-specific presentation of TB at this age range, the practical difficulty in obtaining specimens for definitive diagnosis, and the lack of simple and accurate culture-independent tests. There is also a need for making an accurate diagnosis of latent TB infection in the appropriate clinical context to reduce the risk of developing TB disease

among infants and young children who are more prone to develop disseminated forms of TB disease than adults, possibly as a result of relatively immature host immunity.

In 2004, childhood TB accounted for 10% of all new cases in Africa and 2% in the established market economies.¹ Data on HIV-related TB in children are insufficient and conflicting.² Studies have reported an increasing proportion of children with TB-HIV coinfection, and higher mortality rates were observed among these patients.^{3,4} In Hong Kong, out of a total of 5766 TB notifications in 2006, the number of cases among children aged <5, 5-9, and 10-14 years were 5, 10, and 33 respectively, with the corresponding notification rates of 2.4, 3.2, and 8.0 per 100000 person-years.⁵ Despite a relatively low incidence of disease among these age groups, contact investigation among infants and schoolchildren has been a major public health concern, especially when a large number of them were exposed to a potentially infectious case in a congregate setting.

Before the advent of interferon-gamma release assays (IGRA), clinicians have relied on the time-honoured tuberculin skin tests (TST) for making a diagnosis of TB

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infection. However, TST shows cross-reactivity to BCG and nontuberculous mycobacteria. Its sensitivity is also lower among infants, young children, severely malnourished and the immunocompromised. Unlike IGRA, it is also necessary to consider the booster phenomenon in interpreting TST response.

With the advance in mycobacteriology and immunology, a number of antigens have been discovered in the pathogenic *Mycobacterium tuberculosis complex*. These antigens, which are absent in all BCG strains and most environmental mycobacteria (with the exception of the opportunistic pathogens *Mycobacterium szulgai*, *Mycobacterium marinum*, *Mycobacterium flavescens*, and *Mycobacterium kansasii*), are located in the region of difference (RD-1) and the two antigens commonly used are the CFP-10 (culture filtrate protein 10) and ESAT-6 (early secretory antigen target 6). The fact that these antigens are largely restricted to the MTB, and their ability to stimulate T cells, form the basis for novel assays that assess the presence of tuberculosis infection, by detection of the release of interferon-gamma (IFN- γ) when previously sensitised T cells are incubated with these antigens *in vitro*. These tests are collectively known as IGRA. Table 1 summarises the comparison between TST and IGRA.

QuantiFERON-TB Gold (QFT-G), QuantiFERON-TB Gold in-Tube (QFT-G-IT) (Cellestis Limited, Carnegie, Victoria, Australia) and the T-SPOT.TB test (Oxford Immunotec, Oxford, UK) are the commercially available IGRA formats. The QuantiFERON-TB Gold measures the level of IFN- γ in the supernatant of the antigen stimulated cells by enzyme linked immunoassay (ELISA). The T-SPOT.TB test enumerates IFN- γ secreting T cells by enzyme linked immunospot technique (ELISPOT). The technical details of the two IGRA are shown in Figure 1. The inclusion of TB7.7, which is another *M. tuberculosis*-specific RD1 antigen, in QFT-G-IT would theoretically enhance sensitivity without reducing specificity, in comparison with using only CFP-10 and ESAT-6.

QuantiFERON-TB Gold tests have been approved by US Food and Drug Administration for the diagnosis of active TB as well as latent TB infection.⁶ T-SPOT.TB tests have been approved in the UK.⁷ Approval for diagnostic use have also been obtained throughout the European Union⁸ and the Canadian settings for both IGRA.⁹

Most studies of IGRA have been done in adults. Owing to the lack of a gold standard for TB infection, many studies have examined the sensitivity of IGRA using TB disease

Table 1 Comparison of the tuberculin skin test and interferon-gamma release assays

	Tuberculin skin tests	Interferon-gamma release assays
Test administration	<i>In vivo</i> test requiring no laboratory support	<i>In vitro</i> blood tests requiring laboratory support
Immune response	Type 4 delayed hypersensitivity reaction	TH-1 immune response
Reagents	Purified protein derivative	Reagents containing CFP-10 and ESAT-6
Timing of the tests	Needs two visits 48-72 hours apart	Only one visit; results available after one day
Outcome measurement	Skin induration	QuantiFERON-TB Gold: level of gamma-interferon produced T-SPOT.TB test: no of T cells producing gamma-interferon (spot forming cells)
Interpretation of results	More subjective and operator-dependent	Less subject to inter- and intra-observer bias
Booster response	Yes	No
Cost	Low	High
Patient acceptability	Usually well tolerated in patients	Obtaining 8 ml of blood sample may not be acceptable to some patient groups especially children
Internal positive and negative controls	Absent	Phytohemagglutinin and saline are used as positive and negative controls, respectively. Indeterminate results (e.g. lack of mitogen response) may suggest anergy in immunocompromised subjects.

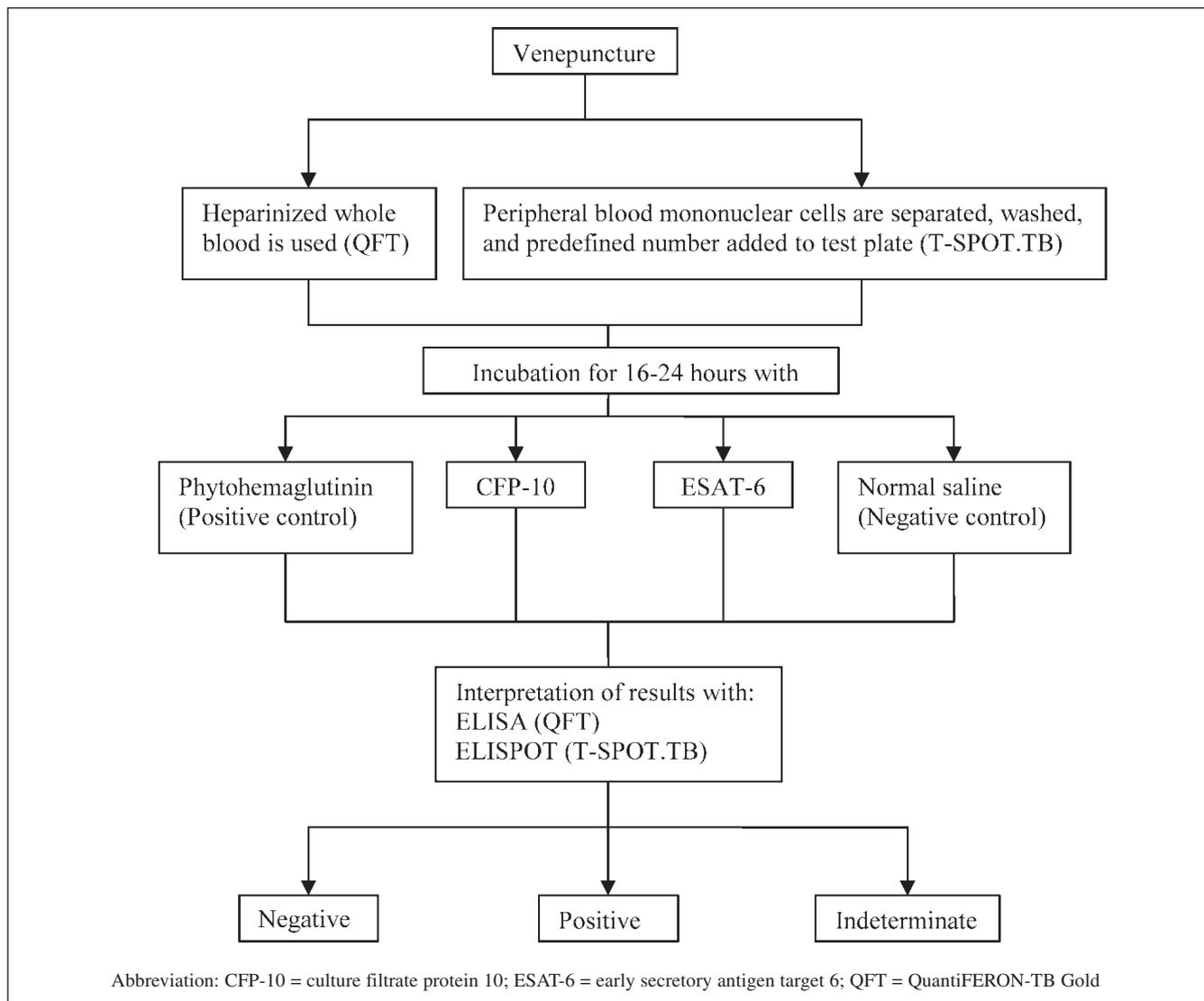


Figure 1 Schematic diagram of procedures in QuantiFERON-TB Gold and T-SPOT.TB.

as a surrogate. The performance of IGRA has also been evaluated by correlating test results with TB exposure factors and BCG status. In general, studies have demonstrated similar levels of specificity for the two IGRA and independence from BCG status.^{10,11} The sensitivity of IGRA has been shown to be at least equivalent to that of TST and superior with T-SPOT.TB among HIV-infected children, severely malnourished, and children under three years. Besides theoretical advantages, IGRA have operational advantages over TST: completed in one visit, results available in 24 hours, absence of inter- and intra-observer divergence, detection of potential immunodepression and avoidance of boosting by repeat testing. However, it is noteworthy that IGRA, like TST, cannot tell

recent from remote TB infection. Currently, there are scanty data on their ability to predict the risk of developing TB disease, especially in endemic settings. Literature on the application of interferon-gamma assays in children is still in its infancy. Their application has also been hampered by cost considerations.

Objectives

The current review aimed at examining test characteristics of IGRA in comparison with TST for the diagnosis of latent TB infection and TB disease among immunocompetent children.

Methods

We searched the MEDLINE through 26 October 2008 for English articles related to IGRA and tuberculosis in children by combining with the Boolean operator "AND" the following search phrases: (1) Interferon-gamma release assay*[tiab] OR Interferon-gamma release assay*[tiab] OR Interferon-gamma assay*[tiab] OR IGRA[tiab] OR Interferon* assay*[tiab] OR IFN* assay*[tiab] OR Interferon-gamma response*[tiab] OR quantiferon*[tiab] OR QFT*[tiab] OR enzyme-linked immunospot assay*[tiab] OR ELISPOT[tiab] OR T-SPOT.TB[tiab] OR T cell-based assay[tiab]; (2) Tuberculosis*[tiab] OR TB*[tiab] OR tuberculous[tiab]; and (3) child*[tiab] OR paediatric*[tiab] OR pediatric*[tiab] OR school*[tiab] or adolescent*[tiab].

The literature search was supplemented by relevant studies from a recent systematic review.¹⁰ An article was included for this review only if (1) the paper contained original data for estimating sensitivity or specificity of TST or IGRA, or (2) if the study compared the agreement of TST with IGRA with or without reference to TB risk factors, or (3) the study contained data for evaluating the prognostic value of IGRA. An article was excluded if non-commercial interferon-gamma assays with gross deviation in methodology from commercial assays were used. Only data involving immunocompetent subjects were included for analysis as far as practicable.

Likelihood ratios (LR), the ratios between the pre-test and post-test odds, were calculated for each study with concurrent data on sensitivity and specificity. The term "odds" refers to the chance of presence versus the chance of absence. The positive LR [$\text{sensitivity}/(1-\text{specificity})$] tells us the proportional increase in the odds of the diagnosis if the test is positive, while the negative LR [$(1-\text{sensitivity})/\text{specificity}$] tells us the proportional decrease in such odds if the test is negative. A good test should have a high positive LR and a low negative LR. Summary measures for LR would be generated in a random effects model only if concurrent data on sensitivity and specificity were available from at least three sets of data in the absence of significant threshold effect, which was assessed by the Spearman's correlation coefficient and defined as significant when the p-value was 0.1 or above. Predictive values were estimated by reference to LR under three hypothetical values for prevalence of TB infection (Pr-LTBI) (0.1, 0.3, and 0.5) that are compatible with the range of risk of infection among household contacts of tuberculosis.¹²⁻¹⁵ MetaDiSc version 1.4 and Microsoft Excel 2002 were used for computation.

Results

A total of 86 English articles were identified from MEDLINE. After excluding 64 articles that were irrelevant, one article that did not compare IGRA with TST, one article that involved a non-commercial whole-blood interferon-gamma assay with prolonged incubation,¹⁶ one article that involved HIV-infected children,¹⁷ and two articles that involved an ELISPOT assay using different methods from T-SPOT.TB assay,^{18, 19} 17 articles were included for further analysis. One article that involved TST, QFT-G, and T-SPOT.TB tests²⁰ with low-risk adolescents as the comparator groups was identified by a recent systematic review¹⁰ but missed by the current literature review. The article was, however, excluded from the current review because cases with TB disease were largely adults rather than paediatric subjects.

Test Characteristics

Table 2 shows the test performance of TST, QuantiFERON-TB Gold/Gold in-Tube assays, and T-SPOT.TB assays among children in the included studies. Only one paper from Germany contained data for estimating likelihood ratios for TST and IGRA among predominantly BCG-unvaccinated paediatric subjects.²¹ Data were thus insufficient for generating summary measures of likelihood ratios for TST and IGRA.

Predictive Values

Only one German study²¹ contained concurrent data on sensitivity and specificity for estimating positive predictive values (PPV) and negative predictive values (NPV).

Assuming a Pr-LTBI of 10%, the PPV [95% confidence interval (CI)] of QFT-G-IT, T-SPOT.TB test, and TST with cut-off values at 15 mm, 10 mm and 5 mm would be, respectively, 89% (35%-99%), 80% (37%-97%), 38% (20%-59%), 21% (16%-28%) and 19% (15%-24%), whereas the corresponding NPV (95% CI) would be 99% (97%-100%), 99% (97%-100%), 95% (93%-97%), 100% (95%-100%) and 100% (95%-100%), respectively. Increasing the Pr-LTBI from 10% to 30% would increase the corresponding PPV (95% CI), respectively, to 97% (67%-100%), 94% (70%-99%), 70% (49%-85%), 51% (42%-60%) and 47% (40%-55%); and decrease the corresponding NPV (95% CI) to 96% (89%-99%), 97% (89%-99%), 84% (77%-89%), 99% (84%-100%) and 99% (82%-100%), respectively. If Pr-LTBI is 50%, the corresponding PPV (95% CI) would be, respectively, 99% (83%-100%), 97% (84%-100%), 85% (69%-93%), 71%

Table 2 Best-estimated values of sensitivity and specificity of tuberculin skin tests and interferon-gamma release assays among children

References	Country	Age in years	BCG ^a	TST ^b cut-off (mm)	Active TB	Test positive	Sens (%) (95% CI)	Controls	Test negative	Spec (%) (95% CI)	LR+ (95% CI)	LR- (95% CI)
TST												
Dominquez, 2008 ²²	Spain	Range <5-18 (largely 5-18)	No	5	9	9	100.0 (66.4-100.0)					
Detjen, 2007 ²¹	Germany	Range 4/12-15	No	5	28	28	100.0 (87.7-100.0)	45	24	53.3 (37.9-68.3)	2.1 (1.5-2.9)	0.03 (0.00-0.51)
Winje, 2008 ³⁶	Norway	Range 14-15	No	6				29712	29432	99.1 (98.9-99.2)		
Winje, 2008 ³⁶	Norway	Range 14-15	No	10				29712	29563	99.5 (99.4-99.6)		
Detjen, 2007 ²¹	Germany	Range 4/12-15	No	10	28	28	100.0 (87.7-100.0)	45	27	60.0 (44.3-74.3)	2.4 (1.7-3.5)	0.03 (0.00-0.46)
Detjen, 2007 ²¹	Germany	Range 4/12-15	No	15	28	17	60.7 (40.6-78.5)	45	40	88.9 (75.9-96.3)	5.5 (2.3-13.2)	0.44 (0.28-0.71)
Winje, 2008 ³⁶	Norway	Range 14-15	No	15				29712	29673	99.9 (99.8-99.9)		
Winje, 2008 ³⁶	Norway	Range 14-15	Yes	6				5887	5651	96.0 (95.5-96.5)		
Soysal, 2008 ³⁸	Turkey	Range 6-10	Yes	10				14833	12854	86.7 (86.1-87.2)		
Winje, 2008 ³⁶	Norway	Range 14-15	Yes	10				5887	5731	97.4 (96.9-97.7)		
Liebeschuetz, 2004 ³⁷	South Africa	Interquartile range 2-7	Yes	15	91	64	70.3 (59.8-79.5)					
Winje, 2008 ³⁶	Norway	Range 14-15	Yes	15				5887	5820	98.9 (98.6-99.1)		
QFT-G-IT												
Dominquez, 2008 ²²	Spain	Range <5-18	No		9	6	66.7 (29.9-92.5)					
Detjen, 2007 ²¹	Germany	Range 4/12-15	No		28	26	92.9 (76.5-99.1)	40 ^c	40	100.0 (91.2-100.0)	74.9 (4.8-1181)	0.09 (0.03-0.29)
T-SPOT.TB test												
Dominquez, 2008 ²²	Spain	Range <5-18 (largely 5-18)	No		9	6	66.7 (29.9-92.5)					
Liebeschuetz, 2004 ³⁷	South Africa	Interquartile range 2-7	Yes		103	88	85.4 (77.1-91.6)					
Detjen, 2007 ²¹	Germany	Range 4/12-15	No		28	26	92.9 (76.5-99.1)	40 ^c	39	97.5 (86.8-99.9)	37.1 (5.3-258)	0.07 (0.02-0.28)

Abbreviations: CI = confidence interval; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; QFT-G-IT = QuantiFERON-TB Gold in-Tube; Sens = sensitivity; Spec = specificity; TB = tuberculosis; TST = tuberculin skin test

^a Predominant BCG vaccination status

^b Two units of purified protein derivative (PPD) RT23 were used for the tuberculin skin test in all studies except for two^{21,38} that used other batches of PPD with potency equivalent to 5 Tuberculin Units of PPD-S.

^c Indeterminate results (n=5) were excluded from analysis.

(63%-78%) and 68% (61%-74%); whereas the corresponding NPV (95% CI) would be 92% (78%-97%), 93% (78%-98%), 69% (59%-78%), 97% (69%-100%) and 97% (66%-100%), respectively.

Comparison of Performance

Table 3 summarises findings of studies that have compared the performance of TST with IGRA. In one study using 5 mm as cut-off for TST, agreement with TST was

Table 3 Studies that have compared the performance of QuantiFERON-TB Gold assays and T-SPOT.TB tests with the tuberculin skin test

References	Study design or setting, country	IGRA besides TST	TST cut-off (mm)	Agreement between TST and IGRA	Agreement between IGRA	Correlation with TB exposure	Tests affected by BCG
Hesseling, 2008 ²³	Household contact, South Africa	T-SPOT.TB, QFT-G	10	T-SPOT.TB: poor (k=-0.15) QFT-G: good (k=0.78)	Poor (k=-0.03)	T-SPOT.TB probably better than QFT-G	No comment
Connell 2008 ²⁴	Case-control, Australia	T-SPOT.TB, QFT-G-IT	15: BCG within 5 years and moderate risk 10: BCG within 5 years and high risk 5: active TB suspected	QFT-G-IT: moderate (k=0.50) T-SPOT.TB: moderate (k=0.51)	High (k=0.83)	Both IGRA probably similar but better than TST	No comment
Okada, 2008 ²⁵	Household contact, Cambodia	QFT-G	10	Good (k=0.63)	NA	QFT-G probably better than TST	None
Dominguez, 2008 ²²	Subjects with active TB or TB contact or screening of LTBI, Spain	T-SPOT.TB, QFT-G-IT	5	Non-vaccinated: poor T-SPOT.TB: k=0.33 QFT-G-IT: k=0.24 BCG-vaccinated: poor T-SPOT.TB: k=0.12 QFT-G-IT: k=0.08	Good (k=0.79 for non-vaccinated; k=0.68 for BCG-vaccinated)		TST, but not for both IGRA
Nakaoka, 2006 ²⁶	Household contact, Nigeria	QFT-G-IT	10	Low-risk group: poor (k=0.246) High-risk group: moderate (k=0.498)	NA	Both IGRA and TST correlated with TB exposure	No comment
Dogra, 2007 ²⁷	Subjects with suspected TB disease or TB contact, India	QFT-G-IT	10	Overall: good (k=0.73) BCG scar-negative: k=1.0 BCG scar-positive: k=0.63	NA	No comment	None
Connell, 2006 ³⁰	Subjects with high risk of LTBI or TB disease, Australia	QFT-G	15: BCG vaccinated 5: TB contact 10: others	Poor (k=0.3)	NA	No comment	Not for QFT-G; no comment for TST
Brock 2004 ²⁸	Contact investigation in Denmark, largely BCG-unvaccinated	QFT-G	10	Good (k=0.866)	NA	No comment	Not for QFT-G; no comment for TST
Liebeschuetz, 2004 ³⁷	Children with suspected TB, South Africa	ELISPOT (similar to T-SPOT.TB)	>0: HIV+ 15: others	Poor (k=0.09)	NA	No comment	No comment
Ewer, 2003 ²⁹	School TB outbreak, UK	ELISPOT (similar to T-SPOT.TB)	By Heaf test 15: BCG-vaccinated 5: BCG-unvaccinated	Good (k=0.72)	NA	ELISPOT better correlated than TST	TST, but not for ELISPOT

Abbreviations: IGRA = interferon-gamma release assays; k = kappa statistic; LTBI = latent tuberculosis infection; NA = not available; QFT-G = QuantiFERON-TB Gold; QFT-G-IT = QuantiFERON-TB Gold in-Tube; TST = tuberculin skin test

poor for both QFT-G-IT ($k=0.24$ for non-vaccinated and 0.08 for BCG-vaccinated) and T-SPOT.TB tests ($k=0.33$ for non-vaccinated subjects and 0.12 for BCG-vaccinated subjects).²² Most studies using 10 mm or above as the cut-off for TST showed moderate to good agreement with IGRA.²³⁻²⁹ One study using 10 mm as cut-off for TST showed poor agreement with T-SPOT.TB.²³ Two studies using 10 mm as cut-off showed poor agreement between TST and QFT-G-IT among low-risk subjects and between TST and QFT-G among all subjects, respectively.^{26,30} Four studies suggested IGRA correlated better with TB exposure than TST.^{23-25,29} One study suggested that T-SPOT.TB tests correlated better with TB exposure than QFT-G.²³ Six studies showed that test performance of IGRA was not affected by BCG vaccination status.^{22,25,27-30}

Prognostic Value

Four longitudinal studies that evaluated the prognostic values of IGRA were identified. One reported that TB contacts with positive ELISPOT results had a similar incidence of TB as that of contacts with positive TST results.³¹ One study involving an expectedly high proportion of schoolchildren with positive TST with no known risk factors for TB infection showed that all tested negative by QFT-G and none developed active TB.³² Another study that described a contact investigation in a newborn nursery and maternity ward suggested that QFT-G was useful in identifying subjects for preventive treatment of latent TB infection.³³ A study that described the long-term outcome of the 91 students for 3.5 years showed that students who were TST-positive but QFT-G-negative did not develop active TB.³⁴

Discussion

The current review corroborates one recent Canadian guideline⁹ and two recent meta-analyses^{10,11} about the scarcity of evidence-base for using IGRA in children. There have been relatively few evaluation studies of TST and IGRA among immunocompetent children and adolescents. Data in the published literature were not sufficient for generating summary measures of LR for IGRA and TST. The single German study that contained data compared paediatric patients with TB disease with those having non-tuberculous disease or other respiratory infections.²¹ Given the low background prevalence of TB infection among paediatric subjects, the LR as derived in that study may be equally applicable in evaluating the role of IGRA and TST

for the diagnosis of both latent TB infection and TB disease in geographic locations with low or intermediate TB burden.

Test Characteristics

The best single parameter for assessing test characteristics is probably the LR, which considers sensitivity and specificity concurrently. These parameters can be used to estimate positive and negative predictive values under different values of pre-test odds. Systematic reviews and a recent guideline on IGRA have focused on sensitivity and specificity rather than LR.⁹⁻¹¹ As there is often a trade-off between sensitivity and specificity, it may be misleading to examine sensitivity and specificity in isolation with no regard to threshold effects.

Among BCG-unvaccinated children, positive LR (95% CI) of TST increased from 2.1 (1.5-2.9) to 2.4 (1.7-3.5) and 5.5 (2.3-13.2) whereas negative LR (95% CI) increased from 0.03 (0.00-0.51) to 0.03 (0.00-0.46) and 0.44 (0.28-0.71) as the cut-off value increased from 5 mm to 10 mm and 15 mm, respectively.

Although IGRA is less affected by inter- and intra-observer bias than TST, the frequency of indeterminate results may render IGRA less attractive. In general, indeterminate results are uncommon with T-SPOT.TB assays, but relatively common with QFT-G/QFT-G-IT, which could be as high as 17%³⁰ and 32%.³⁵ A recent study also showed that 16 (27.6%) of 58 positive first QFT-G-IT results were negative on confirmatory analysis of the same plasma samples.³⁶ Repeating a test may reduce indeterminate results at the expense of additional costs.

Clinical Implications

In interpretation of TST and IGRA, it is important to note the following points:

1. These tests depend on the host's immunological reaction to infection by the tubercle bacillus.
2. Clinically manifest disease only develops in a minority of infected subjects after a highly variable latent period.
3. None of these tests are able to distinguish between latent infection and active disease.
4. The prevalence of background infection varies greatly between different places and settings, depending on past disease incidence and exposure pattern.
5. Remote infection generally carries a much lower risk of disease development than recent infection.
6. None of these tests are able to distinguish satisfactorily between recent and remote infection, or between untreated and treated infection/disease.

7. BCG vaccination practices also vary, and the specificity of TST may be affected by BCG vaccination, particularly for vaccination after infancy or revaccination.

Whether TST or IGRA is better for the diagnosis of latent TB infection depends on both the clinical context and purpose of the tests. If it is not affordable to miss a case, the attending physician should choose a sensitive test with a high NPV for ruling out the condition. If it is important not to over diagnose, the physician should choose a specific test with a high PPV.

Contact Investigation

During targeted TB contact investigation of immunocompetent children and adolescents, as the risk of developing disease may be relatively low, it may be more important not to over-diagnose. When the risk of infection is low around 10%, neither TST nor IGRA is sufficiently good for ruling in latent TB infection. This also partly explains why targeted screening should be restricted to close contacts with relatively high risk of infection. When the risk of infection is moderate to high, TST with a cut-off value at 15 mm shows satisfactory and comparable PPV as IGRA. Cost consideration and more evidence about the prognostic value of TST may lend support to using TST at cut-off of 15 mm in areas with a high background prevalence of infection. However, a caveat is the reportedly inferior sensitivity of TST relative to T-SPOT.TB tests among HIV-infected children, those younger than three years, and the severely malnourished children.³⁷ Sensitivity is a major issue, when there is a higher risk of progression from infection to disease. Sensitivity could be poor for TST among the immunocompromised regardless of the choice of cut-off.³⁷ IGRA, especially T-SPOT.TB tests, might perform better in such scenario, although further studies are necessary to establish their role in the targeted screening of latent TB infection among such patients.

Diagnosis of TB Disease

Untreated active TB disease carries very substantial morbidity and mortality at all ages. In managing a sick child who may be suffering from a potentially serious disease, it may be more important to rule out than rule in. Although neither TST nor IGRA are designed specifically for diagnosis of TB disease, the fact that infection must precede disease may form the rationale of using IGRA to assist in the diagnosis of TB disease. Although positive evidence of infection, by either a TST with a suitable cut-off or IGRA,

is not sufficient to rule in TB disease, a negative test makes such a diagnosis much less likely. QFT-G-IT, T-SPOT.TB tests and TST using a low cut-off value of 5 to 10 mm may all be used to rule out TB infection with reasonably high NPV. There are however a few caveats. First, estimated values of NPV in this review were based on one single German study of predominantly BCG-unvaccinated subjects. The NPV of a negative TST among BCG vaccinated subjects is not entirely certain. It is also likely that NPV will be reduced in the presence of other factors such as young age below 3 years, malnutrition, and immunosuppression.³⁷ Second, while these aforementioned factors may exert lesser influence on the sensitivity of T-SPOT.TB tests,³⁷ it is uncertain whether QFT-G-IT performs equally well in the presence of these factors. It would be prudent to await corroboration of such findings by further evidence. Thus, although it is possible that T-SPOT.TB tests or QFT-G-IT may be better than TST for ruling out TB infection, a negative test must be interpreted with caution within the whole clinical context. Further workup is generally required when significant symptoms persist, and diagnosis is still pending.

Limitations of Current Review

The current review did not include infants, neonates, and immunocompromised subjects. Our literature search might not have included all articles related to evaluation of IGRA in children. This might have been partially remedied by supplementing missing articles with the help of a recent systematic review. Publication bias is one potential source of error, which may be further accentuated by restricting literature search to English articles in MEDLINE. The scarcity of publication may render it difficult to apply findings from this review to all clinical scenarios and public health settings indiscriminately.

Conclusions

Available evidence suggests that the time-honoured TST with appropriate cut-off values may still play an important role for targeted TB contact investigation and clinical management, although IGRA, especially QFT-G-IT and T-SPOT.TB tests, may outperform TST to different extent in some public health and clinical settings. When the risk of infection is very high and it is important to rule out TB disease, hardly any test can substitute for clinical acumen.

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