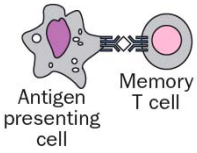
LTBI-Tuberculin skin test

PPD

~200 antigens

Skin

Presentation of mycobacterial antigens

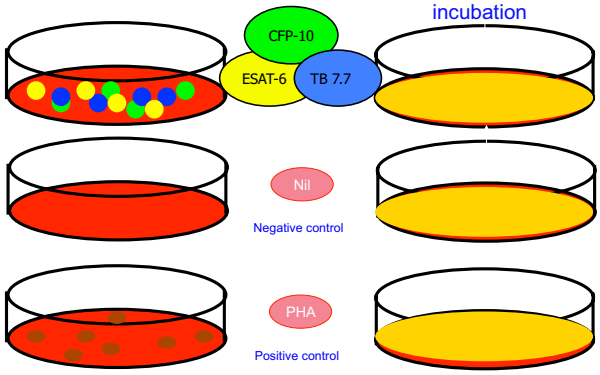


QuantiFERON®-TB Gold In Tube

ELISA

3 ml blood

16-24 hour incubation



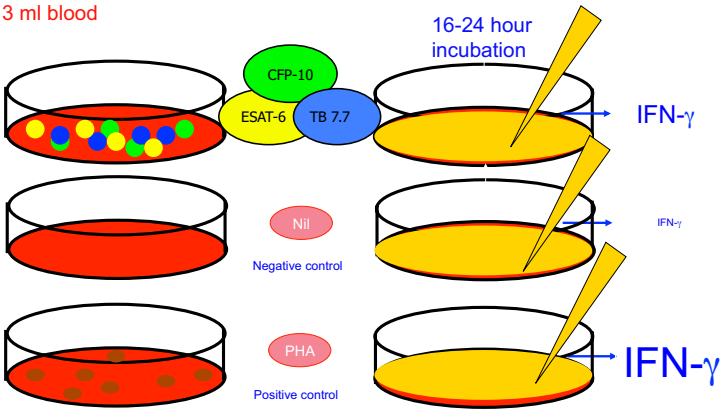
Andersen et al Lancet 2000;356:1099-1104

QuantiFERON®-TB Gold In Tube

ELISA

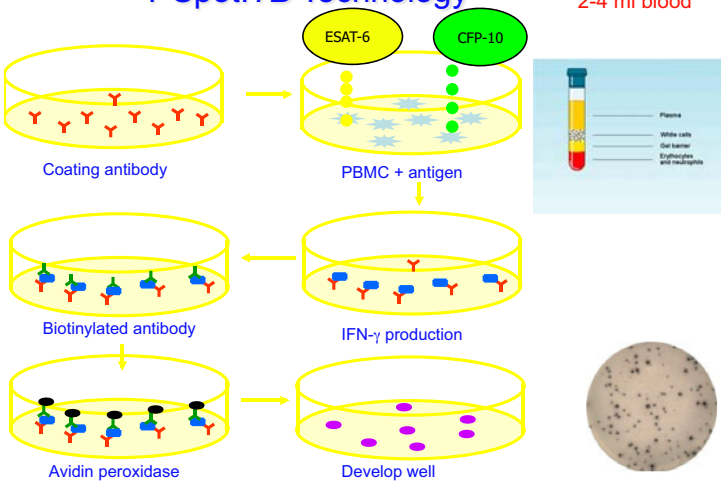
3 ml blood

16-24 hour incubation



T-Spot.*TB* Technology

2-4 ml blood

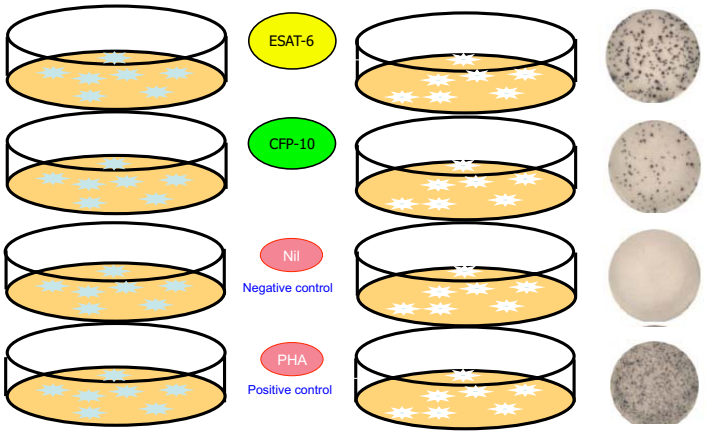


Measurement of IFN-γ secreted by antigen specific T cells

T-SPOT.*TB*®

Overnight incubation

ELISPOT



MAJOR ARTICLE

Clinical Infectious Diseases 2006; 42:e82–5

Early Detection of Perinatal Tuberculosis Using a Whole Blood Interferon-γ Release Assay

Tom Connell,[1,2] Naor Bar-Zeev,[3] and Nigel Curtis[1,2]
[1]Infectious Diseases Unit, Department of General Medicine, and [2]Department of Paediatrics, University of Melbourne, Royal Children's Hospital Melbourne, Parkville, Australia

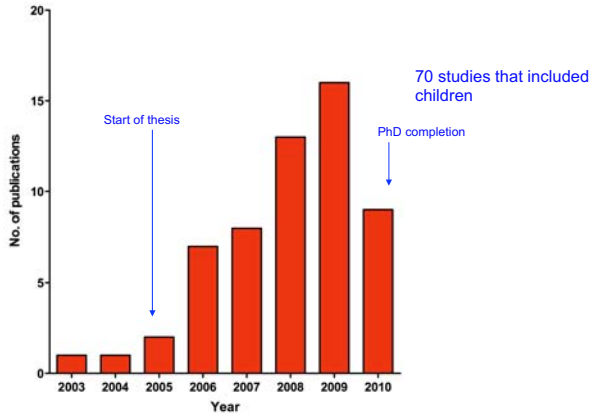
13 week old

- Poor weight gain, cough, abnormal CXR
- TST negative/IGRA+
- TB culture positive

18 day old

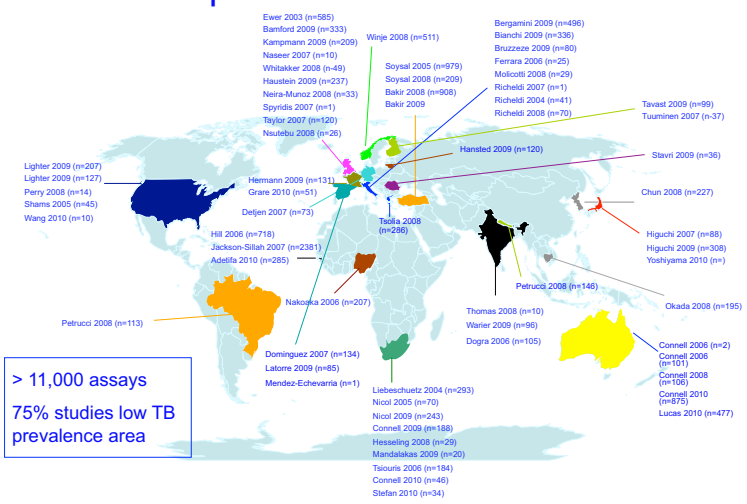
- 24 hour history of vomiting and lethargy
- CXR- disseminated TB
- TST negative/IGRA+

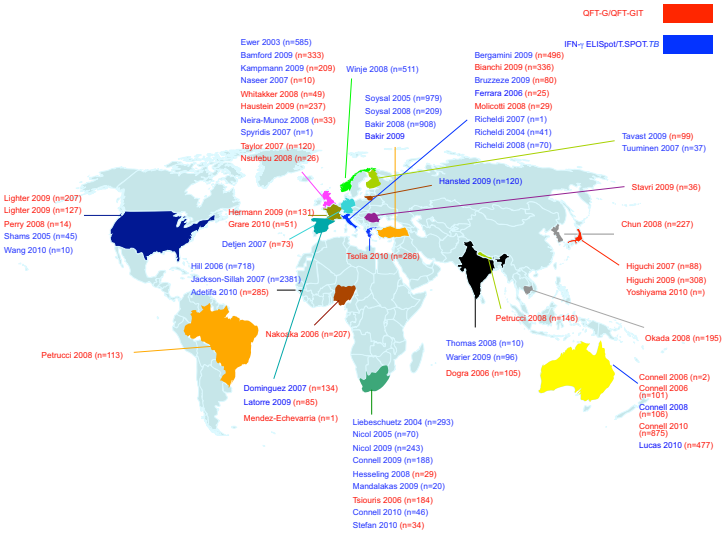
IGRA publications in children



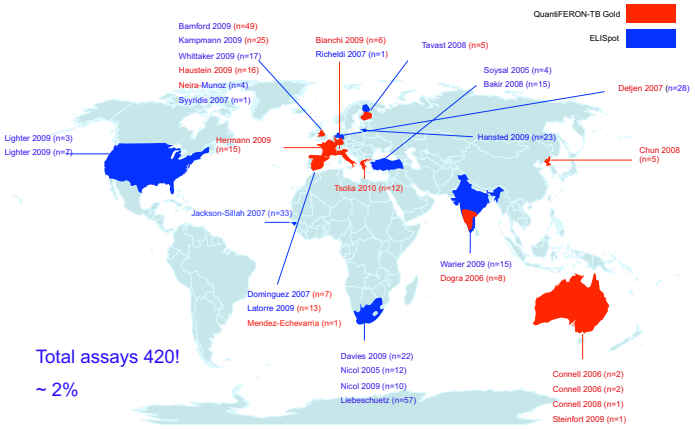
World Map of IGRA studies in children

World Map of IGRA studies in children

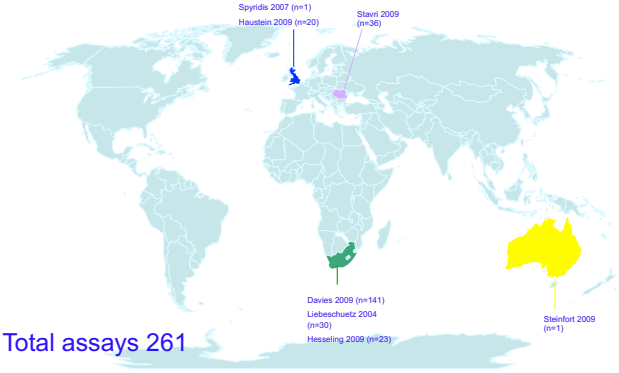




IGRA and culture confirmed TB in children



World map of IGRA studies HIV-infected children



How to evaluate IGRA in children?

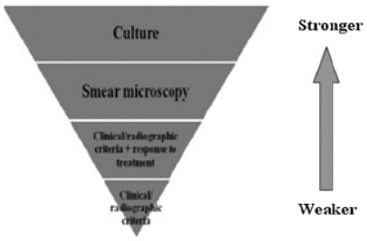
TB disease

-Sensitivity

Children with culture confirmed TB

-Specificity

Children in whom TB has been excluded/alternative diagnosis

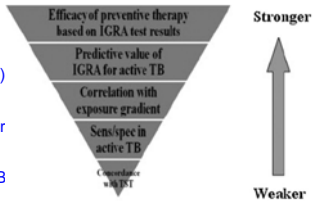


Ling et al Paed Resp Rev 2011;12(1):9-15

How to evaluate IGRA for LTBI?

Latent TB infection

- No gold standard
- Assessment of sensitivity/specificity problematic
- Compare results with TST and assess influence of different factors on test results (BCG, TB contact)
- Sensitivity
  - Correlate test results with the degree of exposur
- Specificity
  - Assess in populations with low prevalence of TB



Ling Paed Resp Rev 2011;12(1):9-15

Thorax ONLINE

Performance of a whole blood interferon gamma assay for detecting latent infection with Mycobacterium tuberculosis in children

T G Connell, N Curtis, S C Ranganathan and J P Buttery

Thorax 2006;61:616-620; originally published online 6 Apr 2006;

Aim

Comparison of **QuantiFERON-TB Gold** IGRA with **TST**

Patients

Children with high risk of LTBI or TB disease

- close contact with adult with infectious TB
- clinical suspicion of TB disease
- immigrated within 5 years from high TB prevalence country

Tuberculin skin test

10 IU tuberculin (PPD 100 IU/ml) *CSL*

Positive TST

induration > 15 mm (prior BCG)
induration > 10 mm (without prior BCG and no TB contact)
induration > 5 mm known TB contacts (irrespective of BCG)

Table 1 Demographic and clinical details of study subjects

	Diagnosis		
	Latent TB (n=42)	TB disease (n=9)	Uninfected (n=50)
Demographic data			
Median age in years (range)	9.2 (0.6–17.9)	3.9 (1.2–17.1)	6.8 (0.4–16.9)
Male	23 (55%)	6 (67%)	32 (64%)
Born in high TB prevalence area	37 (88%)	7 (78%)	48 (96%)
TB contact			
Household†	24 (60%)	5 (56%)	6 (12%)
Non-household	0 (0%)	0 (0%)	1 (2%)
Unknown	7 (14%)	1 (11%)	8 (16%)
None	11 (26%)	3 (33%)	35 (70%)
Clinical			
BCG			
Scar present	19 (45%)	3 (33%)	27 (54%)
History but no scar	2 (5%)	0	2 (4%)
No evidence of prior BCG	21 (50%)	6 (67%)	21 (42%)
Fevers	1 (2%)	7 (78%)	0
Night sweats	0 (0%)	6 (66%)	0
Cough >2 weeks	0 (0%)	6 (66%)	0
Tuberculin skin test			
0–5 mm	0 (0%)		37 (74%)
>5–10 mm	9 (22%)	2 (22%)*	9 (18%)
>10–15 mm	11 (26%)	1 (11%)	4 (8%)
>15 mm	22 (52%)	3 (33%)	0
Chest radiograph			
Normal	38 (90%)	3 (33%)	12 (24%)
Abnormal	0 (0%)	6 (66%)	0
Not done/unavailable	4 (10%)		38 (76%)

*Three children with TB disease did not have TST.
†34 with pulmonary TB; 1 with lymph node TB.

91% from TB endemic countries

60% latent TB were close contacts

Connell et al Thorax 2006;61:616-20

Table 2 Results of whole blood IFN-γ assay by diagnostic group

Diagnosis (based on TST)	Whole blood IFN-γ assay result			
	Negative	Positive	Failed	Total
Uninfected	38 (76%)	0	12 (24%)*	50 (100%)
Latent TB	26 (62%)	11 (26%)	5 (12%)†	42 (100%)
TB disease	0	9 (100%)‡	0	9 (100%)
Total	64	20	17	101

*Nine high negative control; three inadequate mitogen control.
†Three high negative control; two inadequate mitogen control.
‡Three patients did not have a TST.

Poor correlation between TST & QFT-G for latent TB

QFT-G negative in 26/37 (70%) patient with (TST-defined) LTBI
(κ=0.38 (95%CI 0.24-0.38)

Connell et al Thorax 2006;61:616-20

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Total	64	20	17	101

*Nine high negative control; three inadequate mitogen control.
†Three high negative control; two inadequate mitogen control.
‡Three patients did not have a TST.

False positive TST?
=> QFT-G higher specificity?

? Unlikely

60% household TB contact

Large TST induration (median 17.5 mm)

No effect of BCG on TST

Connell et al Thorax 2006;61:616-20

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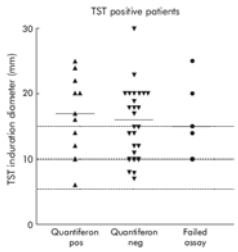
Total	64	20	17	101

*Nine high negative control; three inadequate mitogen control.
†Three high negative control; two inadequate mitogen control.
‡Three patients did not have a TST.

False negative QFT-G?
=> QFT-G poor sensitivity?

? More likely

- QFT-G **positive** in 8/24 (33%) children with TB household contact
- QFT-G **negative** in 50% of children with TST > 15 mm



Connell et al Thorax 2006;61:616-20

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Total	64	20	17	101

*Nine high negative control; three inadequate mitogen control.
†Three high negative control; two inadequate mitogen control.
‡Three patients did not have a TST.

High 'failure' rate: 17% assays inconclusive result

? Laboratory error: Unlikely: experienced lab (> 3000 assays/yr for over 2 yrs)

PostScript

Whole blood IFN-γ assay for detecting TB in children

Connell *et al*[1] uses the QuantiFERON-TB Gold

A J Radford, J S Rothel, G Sberna
Cellestis Ltd, 1046A Dandenong Road, Victoria, Australia 3163

Connell et al Thorax 2006;61:616-20
Radford et al Thorax 2006; 61(10):920-1
Curtis et al Thorax 2006;61 (10) 920-1 author reply

OPEN ACCESS Freely available online PLoS one

A Three-Way Comparison of Tuberculin Skin Testing, QuantiFERON-TB Gold and T-SPOT.*TB* in Children

Tom G. Connell[1,2,3*], Nicole Ritz[1,2,3*], Georgia A. Paxton[4], Jim P. Buttery[1,2,3], Nigel Curtis[1,2,3*], Sarath C. Ranganathan[1,2,5]

Aim

Compare **QFT-GIT**, **T.SPOT.*TB*** with **TST**

Patients

Children with high risk of LTBI or TB disease
- close contact with adult with infectious TB
- clinical suspicion of TB disease
- immigrated within 5 years from high TB prevalence country

Connell TG, Ritz N et al PlosOne 2008;3:7:e2624

Table 2. Results of QuantiFERON-TB gold in-Tube and T-SPOT.*TB* assays in each diagnostic category.

		QuantiFERON-TB gold In-Tube: Positive	Negative	Indeterminate	T-SPOT.*TB*: Positive	Negative	Indeterminate
All patients (n = 100)	Latent TB (n = 38)	18 (47%)	20 (53%)	(0)	15 (39%)	19 (50%)	4 (10%)*
	TB disease (n = 9)	8 (89%)	1 (11%)	0	9 (100%)	0	0
	Uninfected (n = 49)	2 (4%)	44 (90%)	3 (6%)†	1 (2%)	38 (78%)	10 (20%)‡
	No TST result (n = 4)	1 (25%)	3 (75%)	0	0	4 (100%)	0
Patients with TB contact (n = 44)	Latent TB (n = 22)	13 (59%)	9 (41%)	0	10 (46%)	10 (46%)	2 (9%) §
	TB disease (n = 9)	8 (89%)	1 (11%)	0	9 (100%)	0	0
	Uninfected (n = 11)	1 (9%)	8 (73%)	2 (18%) ‖	1 (9%)	5 (45%)	5 (45%)**
	No TST result (n = 2)	1 (50%)	1 (50%)	0	0	2 (100%)	0

Moderate agreement between TST & QFT-GIT and T.SPOT.*TB* overall

Good agreement between QFT-GIT and T.SPOT.*TB*

QFT-GIT and TST (κ=0.50 (95%CI 0.34-0.56)
T.SPOT.TB and TST (κ=0.51 (95%CI 0.35-0.55)
QFT-GIT and T.SPOT.*TB* (κ=0.83 (95%CI 0.65-0.91)

Connell TG, Ritz N et al PlosOne 2008;3:7:e2624

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	Uninfected (n = 49)	2 (4%)	44 (90%)	3 (6%)†	1 (2%)	38 (78%)	10 (20%)‡
	No TST result (n = 4)	1 (25%)	3 (75%)	0	0	4 (100%)	0
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	TB disease (n = 9)	8 (89%)	1 (11%)	0	9 (100%)	0	0
	Uninfected (n = 11)	1 (9%)	8 (73%)	2 (18%) ‖	1 (9%)	5 (45%)	5 (45%)**
	No TST result (n = 2)	1 (50%)	1 (50%)	0	0	2 (100%)	0

False positive TST?
=> QFT-G/T.SPOT.*TB* higher specificity?

42% household TB contact

Median (range) TST induration 15 (12-22) mm

No effect of BCG on TST

Connell TG, Ritz N et al PlosOne 2008;3:7:e2624

Table 2. Results of QuantiFERON-TB gold in-Tube and T-SPOT.*TB* assays in each diagnostic category.

		QuantiFERON-TB gold In-Tube			T-SPOT.*TB*		
		Positive	Negative	Indeterminate	Positive	Negative	Indeterminate
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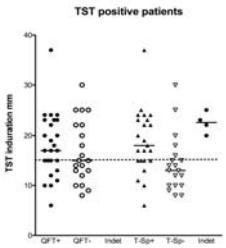
	TB disease (n = 9)	8 (89%)	1 (11%)	0	9 (100%)	0	0
	Uninfected (n = 49)	2 (4%)	44 (90%)	3 (6%)†	1 (2%)	38 (78%)	10 (20%)‡
	No TST result (n = 4)	1 (25%)	3 (75%)	0	0	4 (100%)	0
Patients with TB contact (n = 44)	Latent TB (n = 22)	13 (59%)	9 (41%)	0	10 (46%)	10 (46%)	2 (9%) ¶
	TB disease (n = 9)	8 (89%)	1 (11%)	0	9 (100%)	0	0
	Uninfected (n = 11)	1 (9%)	8 (73%)	2 (18%) ‖	1 (9%)	5 (45%)	5 (45%)**
	No TST result (n = 2)	1 (50%)	1 (50%)	0	0	2 (100%)	0

False negative IGRA?
=> QFT-G/T.SPOT.*TB* lower sensitivity?

QFT-GIT and T.SPOT.*TB* positive in less than 60% of household TB contacts.

Median TST induration 15 (11-37) mm



TB in Cape Town

Incidence rates > 1600/100,000 in adults

Annual rate of infection estimated to be 3%

MDR-TB ~7% of cases

Majority of children who develop TB disease co-infected with HIV

TB meningitis is one of the most common forms of meningitis at Red Cross Children's Hospital

Hesseling et al CID 2009; 48(1):108-14
Rangaka et al AJRCCM 2007;175(5):514-20
Van Rie et al ADC 1999;80(5):433-7

Active TB disease in HIV-infected children

HIV-infected children are more vunerable to TB
- RR active TB HIV-infected 24.2 (95% CI 17-34) vs. HIV uninfected
- 9 m pre-ART 53 cases/100 children vs. 6.4 cases/100 on ART

TB is a frequent cause of death in HIV-infected children
- 8-15% of cases of pneumonia in hospitalised children
- Autopsy studies-up to 20% of cases
- Mortality higher in HIV-infected children compared to HIV uninfected

TB and HIV - the 'cursed duet'
- Up to 50% of children with TB are co-infected with HIV
- As HIV incidence increased -TB incidence increased x 2.5

Braitstein el al PIDJ 2009;28(7):626-32
Walters et al BMC Paediatr 2008;8,1
Zar et al BMJ 2007;334(7585):136-139
Hesseling et al CID 2009;48(1):108-114
Marais et al JID 2004;Suppl 1:S76-85
Palme et al PIDJ 2002;21(11):1053-61
Mukadi et al AIDS 1997;11:1151-8
UNAIDS:2008
Corbett et al Arch Int Med 2003;163(9):1009
Zar et al Acta Paediatr 2001;90(2):119-125
Lawn et al CID 2006; 42:1040-7
Harries et al IJTLD 1997;1:346-51
Jeena et al IJTLD 2002;6(8):672-8

Detection of tuberculosis in HIV-infected children using an enzyme-linked immunospot assay

Mary-Ann Davies[a,f,*], Tom Connell[b,c,d,e,*], Christine Johannisen[a], Kathryn Wood[a,e], Sandy Pienaar[a], Katalin A. Wilkinson[e,g], Robert J. Wilkinson[e,g,h], Heather J. Zar[a], Brian Eley[a], David Beatty[a], Nigel Curtis[b,c,d] and Mark P. Nicol[a,e,i]

AIDS 2009 May 15;23(8):961-9

Aims

To compare the diagnostic sensitivity and specificity of an **IFN-γ ELISpot assay with TST**

To investigate the effect of age, nutritional status and HIV on IFN-γ ELISpot assay and TST

Patients

HIV-infected children with symptoms suggestive of TB

HIV-infected children with an alternate diagnosis

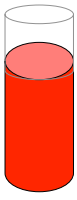
HIV-uninfected children without TB

Tuberculin skin test

➢5 mm induration in HIV-infected children

➢10 mm induration HIV-uninfected children

Minimum of 1 induced sputum or 2 Gastric aspirates



4-5 ml of blood for IFN-γ ELISpot assay

Antigens ESAT-6, CFP-10, PPD

Blood taken for CD4

Zar et at ADC 2000;82:305-8
Zar et al Lancet 2005;365:13-04

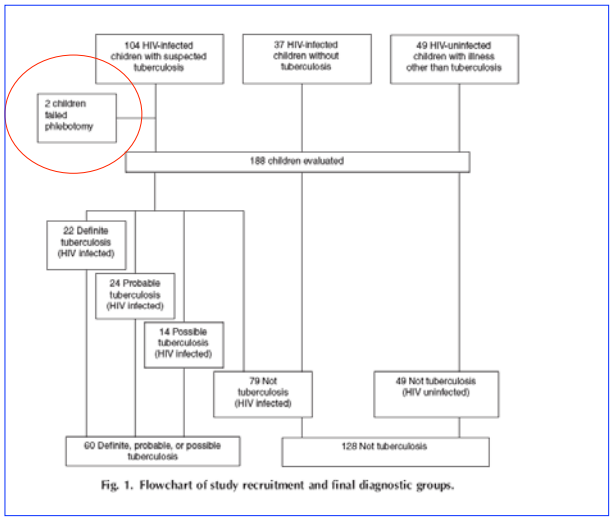


Fig. 1. Flowchart of study recruitment and final diagnostic groups.

Connell, Davies et al AIDS 2009; May 15;23(8):961-9

Table 3. Number of children (%) positive to *Mycobacterium tuberculosis*-specific antigens by diagnostic group.

	Definite TB	Probable TB	Possible TB	Not TB	
Response rates	HIV-positive ($n=22$)[a]	HIV-positive ($n=24$)[b]	HIV-positive ($n=14$)	HIV-positive ($n=79$)[c]	HIV-negative ($n=49$)[d]
ESAT-6	10 (48)	9 (50)	4 (28)	14 (19)	3 (7)
CFP-10	13 (62)	9 (50)	3 (21)	18 (24)	7 (16)
ESAT-6/CFP-10	14 (66)	11 (61)	4 (28)	20 (27)	7 (16)
TST	5/15 (33)[e]	5/19 (26)[f]	0/9 (0)[h]	7 (15)[g]	1 (10)

CFP-10, culture filtrate protein-10; ESAT-6, early secreted antigenic target-6; TB, tuberculosis; TST, tuberculin skin test.
[a]One assay deemed indeterminate (high-negative control).
[b]Six assays deemed indeterminate (six high-negative control).
[c]Five assays deemed indeterminate (three high-negative control, one positive control, one technical).
[d]Five assays deemed indeterminate (three high-negative control; two low cell count).
[e]Four children failed to return for TST reading. Three children did not have TST.
[f]Five children failed to return for TST reading.
[g]Seven children failed to return for TST reading; 24 children did not have TST.
[h]Three children failed to return for TST reading.

IFN-γ ELISpot assay positive 25/39 (64%) vs. TST 10/34 (29%), p=0.005

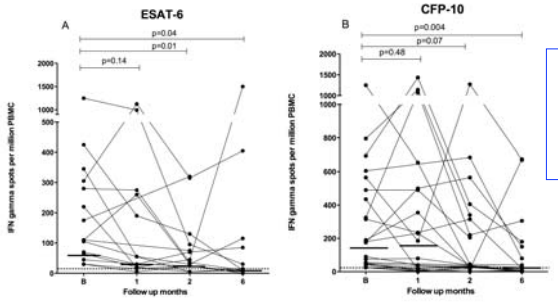
< 24 mths 3/19 TST + vs. 11/19 ELISpot +
CD4% < 15 0/12 TST + vs. 8/12 ELISpot +

Connell, Davies et al AIDS 2009; May 15;23(8):961-9

RESEARCH ARTICLE Open Access

Reversion and conversion of *Mycobacterium tuberculosis* IFN-γ ELISpot results during anti-tuberculous treatment in HIV-infected children

Tom G Connell[*1,2,3,4], Mary-Ann Davies[3,5,6], Christine Johannisen[5], Kathryn Wood[1,5], Sandy Pienaar[5], Katalin A Wilkinson[1,7], Robert J Wilkinson[1,8,7], Heather J Zar[5], David Beatty[5], Mark P Nicol[1,5,9], Nigel Curtis[1,2,3,4] and Brian Eley[5]



Magnitude of responses lower but
<50% reversion

Connell et al BMC Infectious Disease 2010;10:138

Performance of QFT-G or QFT-GIT in young children

Performance of Commercial Blood Tests for the Diagnosis of Latent Tuberculosis Infection in Children and Adolescents

Barbara Maria Bergamini, MD[a], Monica Losi, PhD[a], Francesca Vaienti, MD[a], Roberto D'Amico, PhD[a], Barbara Meccugni, BSc[a], Marisa Meacci, BSc[a], Donatella De Giovanni, MD[a], Fabio Rumpianesi, MD[a], Leonardo M. Fabbri, MD[a], Fiorella Balli, MD[a], Luca Richeldi, MD, PhD[a]

Pediatrics 2009;e419-2424

Use in routine clinical practice of two commercial blood tests for diagnosis of infection with *Mycobacterium tuberculosis*: a prospective study

Giovanni Ferrara, Monica Losi, Roberto D'Amico, Pietro Roversi, Roberto Piro, Marisa Meacci, Barbara Meccugni, Ilaria Marchetti Dori, Alessandro Andreani, Barbara Maria Bergamini, Cristina Mussini, Fabio Rumpianesi, Leonardo M Fabbri, Luca Richeldi

Lancet 2006;367:1328-34

Results: Two hundred thirty-seven tests from 237 children were included in the analysis. Fifty-nine children (25%) were immunocompromised by our definition. An indeterminate test result was obtained in 83 children (35%). The likelihood of an indeterminate test result was inversely correlated with age ($P < 0.001$) for children who were not known to be immunocompromised, and decreased by 13% per year of age. Impaired

:669-673

LETTERS TO THE EDITOR

Indeterminate Interferon-γ Release Assay Results in Children

To the Editors:

the diagnosis of *Mycobacterium tuberculosis* infection in children correlates with age and immune status.[1] This report adds to recent publications that question the performance of current interferon-γ (IFN-γ) release assays (IGRA) for the diagnosis of tuberculosis (TB) tained with the QuantiFERON-TB (QFT) Gold In-Tube assay (35% of the study population). Notably, indeterminate test results were over-represented in children younger than 5 years of age, and those with immunodeficiencies or medical conditions asso-

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Hypotheses

Age influences the magnitude of the positive control IFN-γ response in the QFT-G and QFT-GIT assays

A higher number of indeterminate assay results are seen in younger children

Methods

Results of positive control IFN-γ response in all QFT-G and QFT-GIT assays from children attending the RCH (2003-2008)

Positive control IFN-γ response correlated with age

Children stratified by age into three groups (0-5 yrs, 5-10 yrs, >10 yrs)

Results

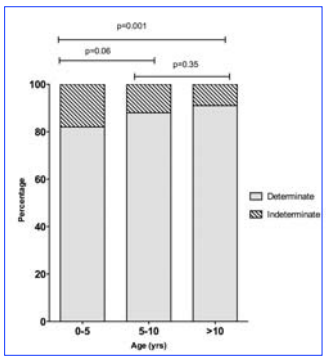
Results of 875 assays from 783 children available for analysis

Median age of children 9.1 yrs (range 25 days to 18 yrs)

118 (13%) assays indeterminate

89 (79%) failed positive control response

24 (21%) high negative (nil) control



Summary of results

Younger children (< 5 yrs) have a higher number of indeterminate assays results compared to older children

? Functionally immature immune system

? Assay related phenomenon

Whole blood assay vs. PBMC (T.SPOT.*TB*)

Frenkel et al J Peds 1987;111(1):97-100
Miyawaki et al Clin Exp Immun 1985;59 (2):505-11
Vigano et al Biol Neonate 1999;75 (1):1-8

How to evaluate IGRA in children?

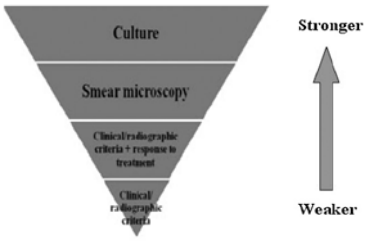
TB disease

-Sensitivity

Children with culture confirmed TB

-Specificity

Children in whom TB has been excluded/alternative diagnosis



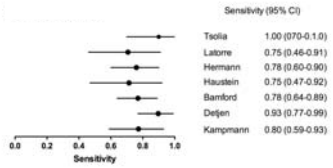
Ling et al Paed Resp Rev 2011;12(1):9-15

Sensitivity non-HIV

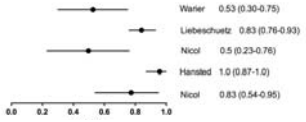
Connell, Curtis et al *unpublished*

QFT-G/QFT-GIT

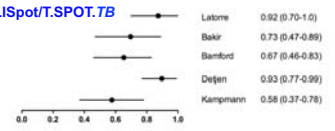
Low TB prevalence

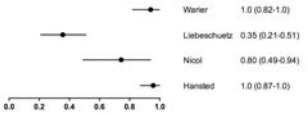


High TB prevalence

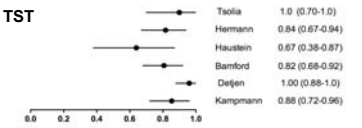


ELISpot/T.SPOT.*TB*



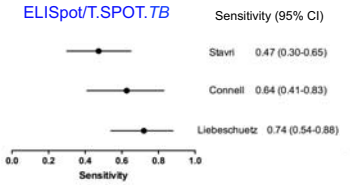


TST

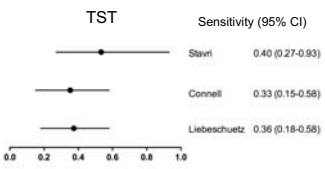


Sensitivity HIV

ELISpot/T.SPOT.*TB*



TST

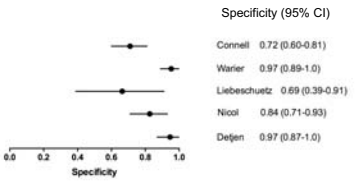


Stavri et al 2009;68(1):14-9

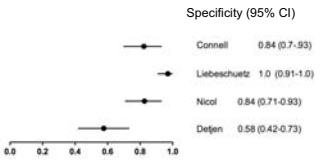
Connell, Davies et al AIDS 2010;23:961-969

Specificity

IGRA



TST



Connell, Davies et al AIDS 2010;23:961-969

Detjen et al 2007 CID;45(3):322-8

Nicol et al 2005 CID; 40(9):1301-8

Liebeschuetz et al Lancet 2004;364(9452):2196-203

Warier et al Indian Paeds 2009;47 (1):90-2

TB disease summary

IGRA

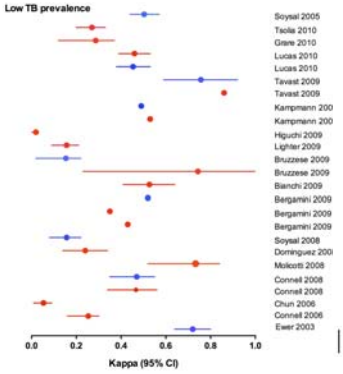
- Cannot distinguish between LTBI and TB disease

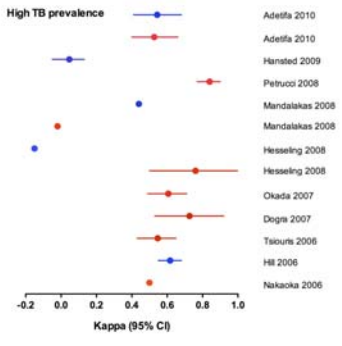
Sensitivity not high enough for rule out test

Specificity will be low in high TB prevalence countries (older children)

Sensitivity similar to TST (except in HIV+)

Agreement between TST and IGRA





IGRA and LTBI

Comparison studies with TST in screening/contact investigations

- Poor to moderate agreement with TST
- Most TST+/IGRA-
- Influence of prior BCG on TST not consistent

Good agreement between both IGRA

Management dilemmas in routine practice

IGRA in resource limited settings?

REVIEW

Interferon-gamma release assays (IGRAs) in high-endemic settings: could they play a role in optimizing global TB diagnostics? Evaluating the possibilities of using IGRAs to diagnose active TB in a rural African setting

Roos E. Barth, Tania Mudrikova, Andy I.M. Hoepelman*

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Received 15 February 2008; accepted 25 March 2008

EXPERT REVIEWS

Diagnosis of pulmonary tuberculosis in children: new advances

Expert Rev. Anti Infect. Ther. 8(3), 277–288 (2010)

Heather J Zar†, Tom G Connell and Mark Nicol

The global burden of childhood pulmonary TB has been underappreciated, in part due to difficulties in obtaining microbiological confirmation of disease. Most HIV-uninfected children can be diagnosed using a combination of clinical and epidemiological features, tuberculin skin

T-cell interferon-γ release assays for the rapid immunodiagnosis of tuberculosis: clinical utility in high-burden vs. low-burden settings

Keertan Dheda[a,b,c], Richard van Zyl Smit[a], Motasim Badri[a] and Madhukar Pai[d]

NO

Barth et al IJID 2008;12(6)e1-6
Zar et al Exp Rev anti Infect 2010;8(3):277-288
Dheda et al Curr Opin Pulm Med 2009;15:188-200

Do IGRA have a future?

Improve quality of studies

- Majority of studies cross-sectional reporting sensitivity and specificity
- Understanding of immunology underlying discordant results
- Need more studies to assess the IMPACT of tests

Stage-specific antigens or cytokines to differentiate TB disease from latent TB infection

Pai et al Curr Opin Pulm Med 2010;16 (3):271-84
Connell, Curtis et al PIDJ 2010;29 (3):285-6
Harari et al Nature Med 2011;17(3):372-6

World Health Organization

Session 4. Diagnostics policies (B): use of commercial IGRAs in low-income and middle-income countries

STAG-TB:

- Acknowledges the large body of work and compelling evidence base demonstrating the poor performance of current commercial IGRAs in low-income and middle-income countries (typically high-TB[1] settings and/or high HIV-burden settings) and the adverse impact of misdiagnosis and wasted resources on patients and health services when using these tests for the diagnosis of active TB disease;
- Acknowledges the large body of work and compelling evidence base to discourage the use of IGRAs for the detection of latent TB infection (LTBI) in adults, children, health-care workers, contacts and those involved in outbreak investigations in low-income and middle-income countries (typically high-TB[1] settings and/or high-HIV burden settings), acknowledging the difficulty in obtaining high-quality data on the diagnosis of LTBI in the absence of a reference standard;
- Endorses the findings of the WHO Expert Group[2] land supports the strategic approach to develop "negative" WHO policy recommendations to discourage the use of commercial IGRAs in low-income and middle-income countries (typically high-TB[3] settings and/or high-HIV burden settings).

How do I use IGRA in clinical practice?

REVIEW 10.1111/j.1469-0691.2011.03555.x

Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion?

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