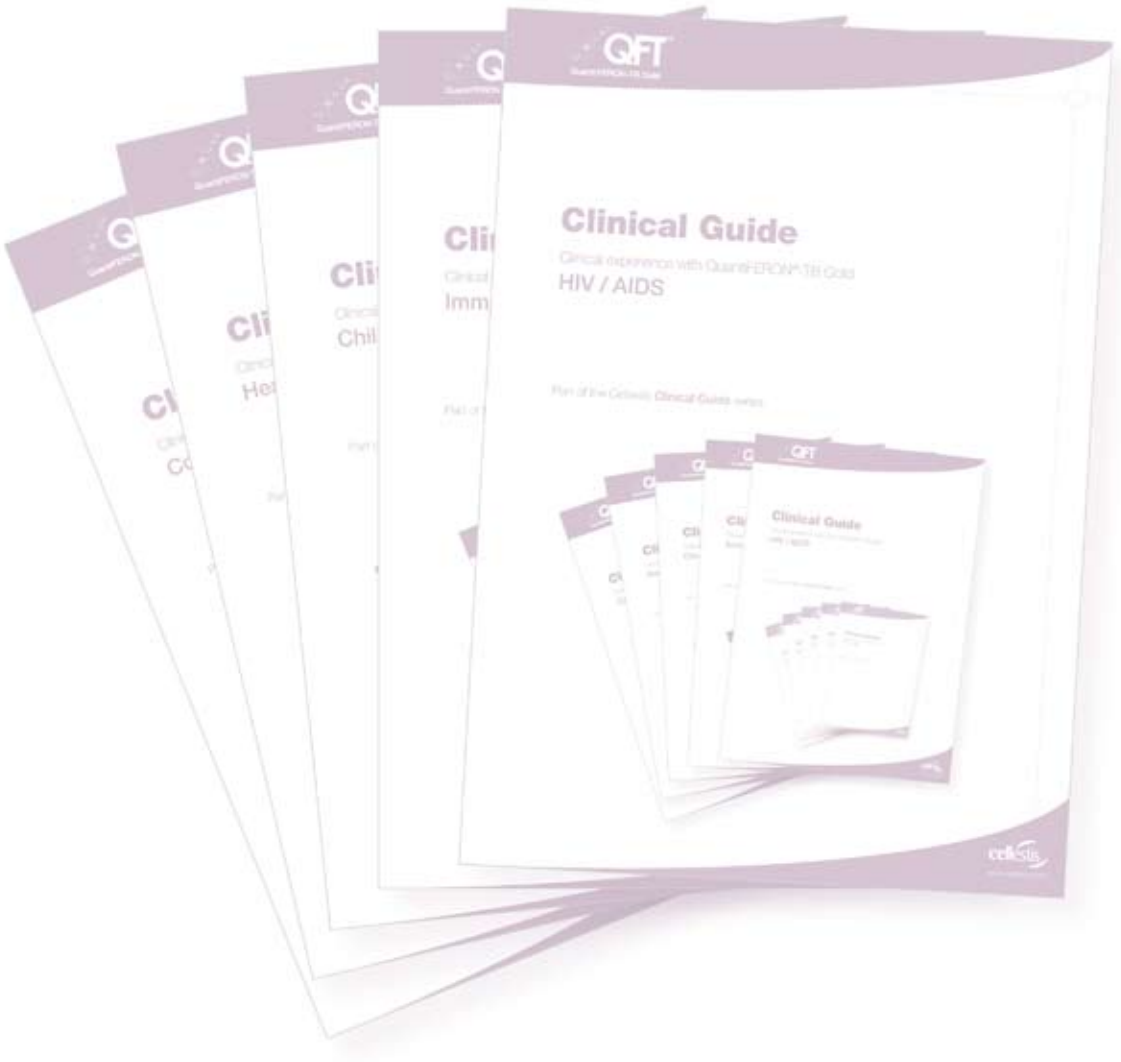
QFT™
QuantiFERON-TB Gold

Clinical Guide

Clinical experience with QuantiFERON®-TB Gold

Paediatrics



Cellestis Clinical Guide series 2008

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This clinical guide is intended to provide healthcare professionals with an overview of current clinical information on the use of QuantiFERON®-TB Gold (QFT™) for detecting tuberculosis (TB) infection in **children**.

Common Questions

What is the risk of TB in children?

Childhood tuberculosis represents a sentinel event in a community—suggesting recent transmission from an infectious adult. Children exposed to adults with smear positive TB have a high risk for infection, and this risk increases with the degree of contact.[1,2]

In children, up to 50% of untreated infants and 15% of older children with latent TB infection will develop disease within two years of being infected.[3] Accurately identifying those who are latently infected is difficult as they remain asymptomatic. In countries with a high incidence of TB, risk of infection among children in contact with adults with TB is as high as 50%.[4]

What difficulties occur in trying to diagnose TB in children?

Children often present with vague, non-specific signs and symptoms. The diagnosis of tuberculosis in children is traditionally based on chest radiography, tuberculin skin testing, and mycobacterial staining/culture—although these investigations may not always be positive in children with TB. Tuberculosis is less often bacteriologically confirmed in children than in adults. This is due to the difficulty in obtaining suitable specimens, as a large number of cases of childhood TB are extrapulmonary and young children rarely produce sputum—resulting in the use of invasive procedures to collect sample material.[5,6,7,8]

When available, culture results are frequently negative; in most patients that test positive, the results come too late to serve initial case management. Consequently, few children treated for TB are treated on the basis of a microbiological diagnosis.[3,7] QFT is a simple blood test and in most cases provides a next day result. This simple and speedy diagnostic procedure can assist in the initial assessment of children for whom there is clinical suspicion of TB infection.

What are the limitations of the TST in detecting LTBI in children? Does QFT overcome these limitations?

TST reactions are common in healthy children vaccinated with BCG or infected with environmental mycobacteria.[9,10,11] Children suffering from malnutrition, measles and HIV often have false negative reactions.[12] The TST is also subject to boosting, reader variability, and false-negative results in immune compromised.[12] This combination of systematic non-specificity, and lack of sensitivity, combine to produce responses that more often produce confusion than provide clarity.

QFT is an innovative blood test that measures the cell-mediated immune response of TB-infected individuals. The test uses specially designed blood collection tubes that are coated with *M. tuberculosis* specific antigens (ESAT-6, CFP-10 and TB7.7(p4)), along with negative and positive control tubes. These TB-specific antigens are encoded within two regions of the *M. tuberculosis* genome that are deleted from all BCG strains and are absent in most non-tuberculous mycobacterial (NTM) species—except *M. marinum*, *M. szulgai* and *M. kansasii*. As a result, QFT is not affected by BCG vaccination [13] or reactivity to non-tuberculous mycobacteria (except *M. marinum*, *M. szulgai* and *M. kansasii*).[14] Clinical studies have shown that QFT has higher specificity in children than the TST.[14,16] The specificity of QFT in children has been shown as 100%, compared to 58% for the TST.[14] In addition, QFT has been shown to be effective in malnourished children.[15] As the test produces a numerical result it is not subject to reader variability.

How sensitive is QFT in children?

QFT has been shown to be effective in children less than 6 months of age and in children with bacteriologically confirmed TB (the sensitivity of QFT was 93%).[14] The sensitivity of TST in children with active TB can be low, and is even lower in children with disseminated TB, malnutrition, or HIV infection—which are all common in regions with a high prevalence of TB.[17,18,19] In a study of children who lived in close contact with smear-positive adult TB patients, QFT detected more children infected with TB than did the TST. Positive QFT results showed significant correlation with smear status of the infected adults, whereas TST did not.[16]

How often does QFT yield an indeterminate QFT result, and what do such results mean?

Indeterminate results occur very infrequently with QFT. In clinical studies that included young children (< 4 years old) and malnourished children, the indeterminate rate of QFT ranged from 0–4.1%.[13,15,20]

However, an indeterminate QFT is meaningful, suggesting possible anergy and does not indicate a failed test. By including an internal positive control (phytohemaglutinin tube), the QFT test enables the distinction between indeterminate results and those that are truly QFT negative. The phytohemaglutinin positive control can be affected by blood mishandling, and should not be used as the sole assessment of immune status. In contrast, a negative TST does not differentiate between those individuals who are anergic and those who have a truly negative TST.

To date, over 130 independent papers have been published on the use of QFT. There is now strong clinical evidence supporting the use of QFT in children—the volume of published evidence supporting that QFT provides a major improvement in the detection of childhood TB is rapidly growing.

> "QFT can be a substitute for TST in detecting latent TB infection in childhood contacts aged ≤ 5 years, especially in those who may have a false-positive TST due to BCG vaccination or non-tuberculous mycobacterial infection".[13]

Summary of Published Studies

Publication	Main Finding
Nakaoka H, Lawson L, Squire SB, Coulter B, Ravn P, Brock I, Hart CA, Cuevas LE. Risk for tuberculosis among children. *Emerg Infect Dis 2006; 12:1383–8.*	A Nigerian study that assessed the risk of TB infection using QFT and the TST in 207 children (mean age 7.4 years) in 3 different risk groups. In the highest risk group (children with close contact to adults with smear positive TB), QFT detected more children infected with TB than the TST—showing the superior sensitivity of QFT. A clear correlation with smear status was seen, with 45% (4/11), 80% (16/20), 68% (15/22), and 90% (17/19) of children in contact with adults with scanty, +, ++, and +++ AFB, respectively showing positive results from the QFT test ($p = 0.03$). Unlike TST, positive QFT results were related to increasing age, indicating accuracy, as young children have a lower lifetime risk of infection. In children with no household exposure to adults with infectious TB, QFT showed superior specificity. Positive rates were lower with QFT (10%) compared to TST (13%), and similar rates were observed in contacts of smear negative cases.
Dogra S, Narang P, Mendiratta DK, Chaturvedi P, Reingold AL, Colford JM Jr, Riley LW, Pai M. Comparison of a whole blood interferon-gamma assay with tuberculin skin testing for the detection of tuberculosis infection in hospitalized children in rural India. *J Infect 2007; 54:267–76.*	An Indian study that compared QFT to the TST in 105 children who were suspected of having TB, or had contact with an index case. In this study 11 children (10.5%) were QFT positive, whereas the TST was positive in 15 (15%) at ≥5mm, 11 (10.5%) at ≥10mm, or 4 (4%) at ≥15mm. Concordance of TST with QFT was high (95%) at the 10mm TST cut-off. All ≥15mm TST subjects were QFT positive. There were no indeterminate QFT results, despite 40% of the children being <4 years old and 57% of them being malnourished.
Detjen AK, Keil T, Roll S, Hauer B, Mauch H, Wahn U, Magdorf K. Interferon-gamma release assays improve the diagnosis of tuberculosis and nontuberculous mycobacterial disease in children in a country with a low incidence of tuberculosis. *Clin Infect Dis 2007; 45:322–8.*	Comparison of QFT to Elispot and TST in 73 children—28 with bacteriologically confirmed TB, 23 with bacteriologically confirmed non-tuberculous mycobacterial (NTM) lymphadenitis and 22 with other respiratory tract infections. In this study both tests had equal sensitivity (93%) and QFT slightly higher specificity than Elispot (100% vs. 98% respectively). Children with NTM lymphadenitis were all QFT negative, whereas 78% were TST positive. This study shows that QFT is effective in children <3 years old as 54% of the children in this study were <3 years old.
Okada K, Mao TE, Mori T, Miura T, Sugiyama T, Yoshiyama T, Mitarai S, Onozaki I, Harada N, Saint S, Kong KS, Chhour YM. Performance of an interferon-gamma release assay for diagnosing latent tuberculosis infection in children. *Epidemiol Infect 2007; 8:1–9 [Epub ahead of print].*	A Cambodian study that compared QFT with the TST in children ≤5 years old who were household contacts (≥1 month) of an index case. QFT was positive in 17% of cases while the TST was positive in 24% of cases. In this trial 88% of the children were BCG vaccinated and this did not affect QFT results. There was a low rate of indeterminate QFT results–4.1% (9 of 217).

Publication	Main Finding
Mori M, Kurosawa R, Imagawa T, Katakura S, Mitsuda T, Aihara Y, Yokota S. Usefulness of interferon-gamma based diagnosis of Mycobacterium tuberculosis infection in childhood tuberculosis. *Kansenshogaku Zasshi 2005; 79:937–44.*	A Japanese study that evaluated the usefulness of QFT in diagnosing primary TB. In 5 children who presented with signs and symptoms of TB infection, QFT was positive and these children were subsequently confirmed as having TB disease. In 3 asymptomatic cases that did not have abnormalities on diagnostic imaging, QFT was positive—one of these cases subsequently developed TB. In 12 other children, QFT was negative and after 12 months of follow-up, none of these children developed TB disease.
Connell T, Bar-Zeev N, Curtis N. Early detection of perinatal tuberculosis using a whole blood interferon-gamma release assay. *Clin Infect Dis 2006; 42:82–5.*	A case report of QFT use in 2 infants (<6 months old), suspected of having perinatal TB. Both had negative TST results, however the chest x-ray was suggestive of milliary TB and QFT was positive in both infants. Based on these results both children were promptly started on antituberculosis treatment and culture of gastric aspirates revealed MTB 6 weeks later.
Connell TG, Curtis N, Ranganathan SC, Buttery JP. Performance of a whole blood interferon gamma assay for detecting latent infection with Mycobacterium tuberculosis in children. *Thorax 2006; 61:616–20.*	An Australian study that compared the performance of QFT with TST in detecting LTBI and TB disease in 101 children. In the LTBI risk group (n=42, median age 9.2 years) 26% were QFT positive, while 70% were TST positive. However QFT was positive in all 9 children with TB disease (median age 3.9 years), while TST results were only available for 6 of these 9 children and was positive for 4 of 6 (at ≥10mm).
Domínguez J, Ruiz-Manzano J, De Souza-Galvão M, Latorre I, Milà C, Blanco S, Jiménez MA, Prat C, Lacoma A, Altet N, Ausina V. Comparison of two commercially available interferon-gamma blood tests for immunodiagnosis of tuberculosis infection. *Clin Vaccine Immunol 2007; Oct 31 [Epub ahead of print].*	This study evaluated Elispot and QFT for detecting TB in 626 adults and children with active TB and latent infection. In this study 9 children had active TB and both tests produced similar results in this group—QFT and Elispot were positive in 67% of cases (6 of 9).
Tsiouris SJ, Austin J, Toro P, Coetzee D, Weyer K, Stein Z, El-Sadr WM. Results of a tuberculosis-specific IFN-gamma assay in children at high risk for tuberculosis infection. *Int J Tuberc Lung Dis 2006; 10:939–41.*	This was the first study that compared QFT to the TST in 184 South African children aged 5–15 years old, who had no prior history of TB—but had current and/or prior contact with TB. QFT and TST (at ≥10mm) were positive in 33.2% and 43.5% of children, respectively ($p<0.001$) indicating that QFT may be more specific than the TST. There were no indeterminate QFT results reported.

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References

1. Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. *Bull Int Union Tuberc 1975; 50:90–106.*
2. Loudon RG, Williamson J, Johnson JM. An analysis of 3,485 tuberculosis contacts in the city of Edinburgh during 1954–1955. *Am Rev Tuberc 1958; 77:623–43.*
3. Shingadia, D, Novelli V. Diagnosis and treatment of tuberculosis in children. *Lancet Infect Dis 2003; 3:624-32.*
4. Almeida LM, Barbieri MA, Da Paixao AC, Cuevas LE. Use of purified protein derivative to assess the risk of infection in children in close contact with adults with tuberculosis in a population with high Calmette-Guérin bacillus coverage. *Pediatr Infect Dis J 2001; 20:1061–5.*
5. Nelson LJ, Wells CD. Tuberculosis in children: considerations for children from developing countries. *Semin Pediatr Infect Dis. 2004; 15:150-4.*
6. Gie RP, Beyers N, Schaaf HS, Goussard P. The challenge of diagnosing tuberculosis in children: a perspective from a high incidence area. *Paediatr Respir Rev 2004; 5 (Suppl. A):S147-9.*
7. Hesseling AC, Schaaf HS, Gie RP, Starke JR, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. *Int J Tuberc Lung Dis 2002; 6:1038-45.*
8. Zar HJ, Tannenbaum E, Apolles P, Roux P, Hanslo D, Hussey G. Sputum induction for the diagnosis of pulmonary tuberculosis in infants and young children in an urban setting in South Africa. *Arch Dis Child 2000; 82:305–8.*
9. Wang L, Turner MO, Elwood RK, Schulzer M, FitzGerald JM. A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements. *Thorax 2002; 57:804–9.*
10. Fine PE, Sterne JA, Ponnighaus JM, Rees RJ. Delayed-type hypersensitivity, mycobacterial vaccines and protective immunity. *Lancet 1994; 344:1245–9.*
11. Black GF, Weir RE, Floyd S, Bliss L, Warndorff DK, Crampin AC, Ngwira B, Sichali L, Nazareth B, Blackwell JM, Branson K, Chaguluka SD, Donovan L, Jarman E, King E, Fine PE, Dockrell HM. BCG-induced increase in interferon-gamma response to mycobacterial antigens and efficacy of BCG vaccination in Malawi and the UK: two randomised controlled studies. *Lancet 2002; 359:1393–401.*
12. Huebner RE, Schein MF, Bass JB Jr. The tuberculin skin test. *Clin Infect Dis 1993; 17:968–75.*
13. Okada K, Mao TE, Mori T, Miura T, Sugiyama T, Yoshiyama T, Mitarai S, Onozaki I, Harada N, Saint S, Kong KS, Chhour YM. Performance of an interferon-gamma release assay for diagnosing latent tuberculosis infection in children. *Epidemiol Infect 2007; 8:1-9 [Epub ahead of print].*
14. Detjen AK, Keil T, Roll S, Hauer B, Mauch H, Wahn U, Magdorf K. Interferon-gamma release assays improve the diagnosis of tuberculosis and nontuberculous mycobacterial disease in children in a country with a low incidence of tuberculosis. *Clin Infect Dis 2007; 45:322-8.*
15. Dogra S, Narang P, Mendiratta DK, Chaturvedi P, Reingold AL, Colford JM Jr, Riley LW, Pai M. Comparison of a whole blood interferon-gamma assay with tuberculin skin testing for the detection of tuberculosis infection in hospitalized children in rural India. *J Infect 2007; 54:267-76.*
16. Nakaoka H, Lawson L, Squire SB, Coulter B, Ravn P, Brock I, Hart CA, Cuevas LE. Risk for tuberculosis among children. *Emerg Infect Dis 2006; 12:1383-8.*
17. Donald PR. Childhood tuberculosis: out of control? *Curr Opin Pulm Med 2002; 8:178–82.*
18. Mukadi YD, Wiktor SZ, Coulibaly IM, Coulibaly D, Mbengue A, Folquet AM, Ackah A, Sassan-Morokro M, Bonnard D, Maurice C, Nolan C, Kreiss JK, Greenberg AE. Impact of HIV infection on the development, clinical presentation, and outcome of tuberculosis among children in Abidjan, Côte d'Ivoire. *AIDS 1997; 11:1151–8.*
19. Madhi SA, Huebner RE, Doedens L, Aduc T, Wesley D, Cooper PA. HIV-1 co-infection in children hospitalised with tuberculosis in South Africa. *Int J Tuberc Lung Dis 2000; 4:448–54.*
20. Tsiouris SJ, Austin J, Toro P, Coetzee D, Weyer K, Stein Z, El-Sadr WM. Results of a tuberculosis-specific IFN-gamma assay in children at high risk for tuberculosis infection. *Int J Tuberc Lung Dis 2006; 10:939-41.*

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