Accuracy of the QuantiFERON-TB Gold in Tube for diagnosing tuberculosis in a young pediatric population previously vaccinated with Bacille Calmette-Guérin

Acurácia do QuantiFERON-TB Gold in Tube no diagnóstico de tuberculose em uma população pediátrica jovem previamente vacinada com Bacille Calmette-Guérin

Precisión del quantiferon-tb gold in tube en el diagnóstico de tuberculosis en una población pediátrica joven previamente vacunada con Bacille Calmette-Guérin

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ABSTRACT

Objective: To evaluate the accuracy of an interferon-gamma release assay (QuantiFERON-TB Gold in Tube) for diagnosing Mycobacterium tuberculosis infection in a young pediatric population.

Methods: 195 children previously vaccinated with BCG were evaluated, being 184 healthy individuals with no clinical or epidemiological evidence of mycobacterial infection, and 11 with Mycobacterium tuberculosis infection, according to clinical, radiological, and laboratory parameters. A blood sample was obtained from each child and processed according to the manufacturer’s instructions. The assay performance was evaluated by a Receiver Operating Characteristic (ROC) curve.

Results: In the group of 184 non-infected children, 130 (70.6%) were under the age of four years (mean age of 35 months). In this group, 177 children (96.2%) had negative test results, six (3.2%) had indeterminate results, and one (0.5%) had a positive result. In the group of 11 infected children, the mean age was 58.5 months, and two of them (18%) had negative results. The ROC curve had an area under the curve of 0.88 (95% CI 0.82–0.92; p<0.001), disclosing a predictive positive value of 81.8% for the test (95% CI 46.3–97.4). The assay sensitivity was 81.8% (95% CI 48.2–97.2) and the specificity was 98.8% (95% CI 96–99.8).

Conclusions: In the present study, the QuantiFERON-TB Gold in Tube performance for diagnosing M. tuberculosis infection was appropriate in a young pediatric population.

Key-words: tuberculosis; interferon-gamma; interferon-gamma release tests.

RESUMO

Objetivo: Avaliar a acurácia de um teste de liberação de interferon-gama (QuantiFERON-TB Gold in Tube) para diagnosticar a infecção pelo Mycobacterium tuberculosis em uma população pediátrica.

Métodos: Avaliaram-se 195 crianças previamente vacinadas com BCG, sendo 184 sadias, sem evidência clínica ou epidemiológica de infecção pelo M. tuberculosis, e 11 com infecção, definida de acordo com critérios clínicos, radio-
lógica e laboratoriais. Obteve-se uma amostra de sangue de cada criança, processada conforme as instruções do fabricante. Avaliou-se o desempenho do ensaio por meio de uma curva de características operacionais (curva Receiver Operating Characteristic – ROC).

**Resultados**: No grupo de 184 crianças não infectadas, 130 (70,6%) eram menores de quatro anos (média de 35 meses). Nesse grupo, 177 crianças (96,2%) tiveram resultado negativo do teste, seis (3,2%) apresentaram resultado indeterminado e uma (0,5%) teve resultado positivo. No grupo de 11 crianças com infecção, a idade média era de 58,5 meses e duas (18%) apresentaram resultado positivo. A curva ROC determinou uma área sob a curva de 0,88 (IC95% 0,82–0,92; \( p<0,001 \)), evidenciando um valor preditivo positivo de 81,8% para o teste (IC95% 46,3–97,4). A sensibilidade do teste foi de 81,8% (IC95% 48,2–97,2) e a especificidade, de 98,8% (IC95% 96–99,8).

**Conclusões**: No presente estudo, o desempenho do QuantiFERON-TB Gold in Tube para o diagnóstico da infecção pelo *M. tuberculosis* foi adequado quando utilizado em uma população pediátrica jovem.

**Palavras-chave**: tuberculose; interferon gama; testes de liberação de interferon-gama.

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**RESUMEN**

**Objetivo**: Evaluar la precisión de una prueba de liberación de interferón gama (QuantiFERON-TB Gold in Tube) para el diagnóstico de la infección por el *Mycobacterium tuberculosis* en una población pediátrica.

**Métodos**: Se evaluaron 195 niños previamente vacunados con BCG, siendo 184 niños sanos sin evidencia clínica o epidemiológica de infección por el *M. tuberculosis*, y 11 niños con infección, definida conforme a criterios clínicos, radiológicos y laboratoriales. Se obtuvo una muestra de sangre de cada niño, que fue procesada conforme a las instrucciones del fabricante. El desempeño del ensayo fue evaluado mediante una curva de características operacionales (curva ROC).

**Resultados**: En el grupo de 184 niños no infectados, 130 (70,6%) tenían menos que cuatro años (promedio de 35 meses). En este grupo control, 177 niños (96,2%) tuvieron un resultado negativo de la prueba, mientras que 6 niños (3,2%) presentaron resultado indeterminado, y un niño (0,5%) tuvo un resultado positivo. En el grupo de 11 niños con infección, el promedio de edad era de 58,5 meses, y 2 niños (18%) presentaron resultado negativo. La curva ROC determinó un área bajo la curva de 0,876 (95%IC 0,82–0,92; \( p<0,001 \)), evidenciando un valor predictivo positivo del 81,8% para la prueba (95%IC 46,3–97,4). La sensibilidad de la prueba fue de 81,8% (95%IC, 48,2–97,2) y la especificidad de 98,8% (95%IC, 96–99,8).

**Conclusión**: En el presente estudio, el desempeño del QuantiFERON-TB Gold in Tube para el diagnóstico de la infección por el *M. tuberculosis* fue adecuado cuando utilizado en una población pediátrica joven.

**Palabras clave**: tuberculosis; interferón gama; pruebas de liberación de interferón gama.
system is: up to 25 points, tuberculosis is unlikely; from 30 to 35 points tuberculosis is possible, and above 40 points, tuberculosis is very likely. This scoring system has achieved sensitivity levels ranging from 58 to 88.9%, and specificity of 86.5 to 98%\textsuperscript{(8,9)}.

Laboratory assays based on the quantitation of interferon gamma (IFN-\(\gamma\)) release were developed in order to replace the tuberculin skin test for diagnosing \textit{Mycobacterium tuberculosis} infection. They are based on the observation that infection by mycobacteria induces a strong Th1 immune response\textsuperscript{(10-13)}.

The comparison of different mycobacterial genomes led to the identification of a differential region (RD1) that is present in \textit{Mycobacterium tuberculosis} and \textit{Mycobacterium bovis}, but is absent in BCG due to multiple passages in culture that the vaccine strain has experienced. The antigens encoded by this region form the basis of tests that measure the secretion of IFN-\(\gamma\) by T lymphocytes and which do not cross-react with BCG\textsuperscript{(11,14-16)}. In humans, two antigens were studied in greater detail, the Secretory Early Target 6 (ESAT-6) and the Culture Filtrate Protein 10 (CFP-10). The ESAT-6 antigen is encoded and expressed by \textit{Mycobacterium tuberculosis}, but is absent in BCG and other mycobacteria, excepting \textit{M. kansasii}, \textit{M. szulgai} and \textit{M. marinum}. CFP-10 is a specific protein from \textit{Mycobacterium tuberculosis}\textsuperscript{(14,15-17)}.

Currently, there are two commercial tests using a combination of ESAT-6 and CFP-10, based on a SPOT enzyme immunoassay technique (ELISPOT) called T-SPOT-TB (Oxford Immunotech, Abingdon, UK), or on an enzyme immune assay (QuantiFERON-TB Gold in Tube, Cellestis, Carnegie, Australia). The first kit was approved for use in Europe, and the second one in the USA for diagnosing either active or latent tuberculosis.

New diagnostic methods based on detection of IFN-\(\gamma\) released by T cells after \textit{in vitro} exposure to specific \textit{Mycobacterium tuberculosis} antigens offer potential advantages for the diagnosis of tuberculosis in children in comparison with TST, as the second generation of tests are not affected by previous BCG vaccination, and they do not require a second visit to determine the test result\textsuperscript{(10,18)}.

Nevertheless, some results are conflicting and there is limited information on the performance of these new tests in Brazilian pediatric patients\textsuperscript{(19,20)}.

The aim of this study was to determine the accuracy of a second generation IFN-\(\gamma\) release assay (QuantiFERON-TB Gold in Tube, Cellestis, Carnegie, Australia) for diagnosing \textit{Mycobacterium tuberculosis} infection in a young pediatric population previously vaccinated with BCG.

Method

This study was approved by the Research Review Board of the University of São Paulo. Children previously vaccinated with BCG who attended the clinical laboratory of the Instituto da Criança (Child’s Institute) do Hospital das Clínicas for routine blood sampling were included in the control group, after the informed consent of parents or legal guardians were obtained. Parents were thoroughly inquired on the children’s possible domiciliary contact with contagious tuberculosis patients, signs or symptoms compatible with tuberculosis, and previous BCG vaccination. Children with history of contact with a person with known or suspected tuberculosis, children who presented signs or symptoms compatible with the disease, those without a BCG scar or having any immune system disorder were excluded from the study.

Children referred to four different hospitals of the city of São Paulo with a recent diagnosis of \textit{Mycobacterium tuberculosis} infection were included in the infected group before the beginning of treatment. An informed consent was also obtained from parents or legal guardians. The initial diagnosis of tuberculosis infection was made by each child’s paediatrician. For the purposes of this study, children with definite and probable \textit{Mycobacterium} infection were included as a tuberculosis case if they had a) a positive microbiological identification of \textit{Mycobacterium tuberculosis}, either by bacilli observation on sputum smear or by standard culture isolation or b) a close contact with a bacilliferous adult presenting a Tuberculin Skin Test of 20 mm or more, with clinical or radiological abnormalities compatible with tuberculosis, and these children should have scored at least 40 points when evaluated by the diagnostic scoring system adopted by the Ministry of Health, Brazil\textsuperscript{(8,9)}. Children diagnosed as having a tuberculosis infection by the primary physician, presenting a close contact with a bacilliferous adult, with a positive tuberculin skin test, without unequivocal clinical or radiological abnormalities, for whom isoniazid prophylaxis was initiated based on hospital protocols, were also included in this study. Children who were already on treatment or chemoprophylaxis at the time of evaluation were not included in this study. A blood sample was obtained from each child enrolled in the study.

We performed the QuantiFERON-TB Gold In-Tube (QTF) assay according to the manufacturer’s instructions. Briefly, blood was collected and directly transferred into...
three separate tubes: the negative control tube containing only heparin, the positive control tube containing phytohemagglutinin as a mitogen, and a third tube containing M. tuberculosis-specific peptides ESAT-6, CFP-10 and TB7.7 (Rv2654). The tubes were incubated at 37°C for 18 hours, centrifuged to obtain plasma samples which were stored at -20°C until the ELISA test was performed. A calibration curve was plotted with the absorbance values (OD) defined by the IFN-γ produced in the three control tubes: with mitogen, negative control and with specific M. tuberculosis-antigens. Thereafter, the patients’ samples OD were measured and the corresponding levels of IFN-γ were calculated by means of the specific Cellestis software. Absolute values of IFN-γ were calculated by subtracting the OD of the tube with mitogens and the negative control from the absorbance of the tube containing M. tuberculosis-antigens. The result was considered indeterminate when the IFN-γ value of the negative control tube was ≥8.0IU/mL or the value after the subtraction of the negative-tube value from the mitogen-containing tube value was <0.5IU/mL.

The statistical software MedCalc® version 10.1.2 was used to obtain a Receiver Operating Characteristic Curve (ROC curve). The best cut-off value of the absolute IFN-γ level after stimulation by specific antigens was determined. The sensitivity, specificity, positive and negative predictive values of the newly established cut-off were calculated. The area under the curve (AUC) was used to assess the predictive accuracy of the test.

Results

From April to July 2008, 184 children with no clinical and epidemiological evidence of M. tuberculosis infection were enrolled in the study. There were 110 boys (59.7%), the mean age was 33 months, the median age was 35 months (3 months to 71 months). Six children (3.2%), all of them under the age of four, had an indeterminate result due to

Table 1 - Clinical characteristics of children considered infected with Mycobacterium tuberculosis

| Child | Gender | Age (months) | Infection      | TB contact | Clinical abnormalities | Radiological abnormalities | TST | TB Culture | QuantiFERON |
|-------|--------|--------------|----------------|------------|------------------------|---------------------------|-----|------------|-------------|
| 01    | F      | 59           | Latent TB      | Yes        | Neg                    | Neg                        | 18  | Sputum Negative | Positive    |
| 02    | F      | 120          | Latent TB      | Yes        | Neg                    | Neg                        | 15  | Sputum Negative | Positive    |
| 03    | F      | 8            | TB             | Yes        | +                      | Neg                        | NA  | Mycobacterium tuberculosis (cerebrospinal Fluid) | Positive |
| 04    | F      | 48           | Meningitis     | Yes        | Neg                    | Neg                        | 15  | Sputum Negative | Positive    |
| 05    | M      | 8            | Pulmonary TB   | Yes        | +                      | +                          | 23  | Sputum Negative | Negative    |
| 06    | M      | 31           | Pulmonary TB   | Yes        | +                      | +                          | 21  | Sputum Negative | Positive    |
| 07    | M      | 84           | Latent TB      | Yes        | Neg                    | Neg                        | 15  | Sputum Negative | Positive    |
| 08    | M      | 64           | Latent TB      | Yes        | Neg                    | Neg                        | 10  | Sputum Negative | Positive    |
| 09    | F      | 31           | Pulmonary TB   | Yes        | +                      | Neg                        | NA  | Mycobacterium tuberculosis (sputum) | Negative    |
| 10    | F      | 132          | TB             | Yes        | +                      | +                          | 10  | Sputum Negative | Positive    |
| 11    | F      | 59           | Latent TB      | Yes        | Neg                    | Neg                        | 11  | Sputum Negative | Positive    |

The diagnosis of latent tuberculosis or disease was based on attending physician criteria. A contact was considered positive if an adult with a positive sputum for Mycobacterium tuberculosis lived in the same house. Only clinical abnormalities related to tuberculosis are considered. The presence of a radiological abnormality was based on a chest X-ray exam result. F: Female; M: Male; TB: tuberculosis; Neg: Not present; +: present; TST: Tuberculin Skin Test; NA: Not available.
low mitogen responses. A second blood sample from these children to confirm these results was not obtained. One child (0.5%) with 23 months of age had an absolute IFN-γ value after stimulation with specific antigens higher than 0.35 IU/mL. This result was interpreted as being positive according to the manufacturer suggested cut-off for the test. This child remained in ambulatory follow-up and, after 10 months, did not show any clinical or radiological abnormalities suggestive of infection with *M. tuberculosis*, or had not any household contact identified with the disease. For the purposes of this study, this patient was considered as having a false positive result. The remaining 177 children (96.2%) had negative test results.

Eleven children with *M. tuberculosis* infection were selected, 4 boys (37%) and 7 girls (63%). The mean age was 58.5 months (8 to 132 months). Six children were diagnosed as having latent tuberculosis infection, 3 children had pulmonary disease, one child had *M. tuberculosis* meningitis and one child had *M. tuberculosis* pericarditis. Two children out of 11 had an absolute IFN-γ concentration after specific antigen stimulation <0.35 IU/mL so that these two test results were interpreted as being negative. One of these children was an eight months old boy with pulmonary disease, with clinical and radiological persistent abnormalities, a highly positive TST (23 mm), but with negative sputum smear and culture for *M. tuberculosis*. The other QTF-negative child was a 31 months old girl with pulmonary disease, with clinical and radiological persistent abnormalities and positive *M. tuberculosis* sputum culture (Table 1). Treatment with three drugs was indicated for both children.

The six children with indeterminate test results were excluded to plot the receiver operating characteristic (ROC) curve. The ROC curve (Figure 1) determined an area under the curve of 0.876 (95%CI 0.82–0.92; p<0.001), so that 0.305 IU/mL was established as the ideal cut-off for this population. This newly determined cut-off value is similar to that proposed by the manufacturer (0.350 IU/mL), unlike other studies that recommended a much lower cut off (0.2 IU/mL) in immune competent adult patients with active and untreated pulmonary tuberculosis (21). For this absolute IFN-γ concentration, the assay sensitivity found in the present study was 81.8% (95%CI 48.2–97.2) and the specificity was 98.8% (95%CI 96.0–99.8), meeting the requirements of the World Health Organization (WHO) regarding the sensitivity and specificity of immunological methods (greater than 80% and 95%, respectively). The positive predictive value was 81.8% (95% CI: 46.3–97.4), and the negative predictive value was 98.9% (95% CI 96.0–99.8).

**Discussion**

Interferon-γ release assays constitute an alternative for the diagnosis of latent infection in adults, as it is more accurate than TST (15). Only a few studies have evaluated the use of QFT in children, but the characteristics of the study populations are often heterogeneous. In two recent meta-analyses (22,23), the authors found that the overall accuracy of the QTF-G for the diagnosis of tuberculosis in children was good. In the review by Mandalakas (22), HIV coinfected or immunocompromised children were not excluded. For the assessment of sensitivity, definite (microbiologically confirmed) and probable tuberculosis was accepted. The authors found 17 studies that focused on the QTF-G sensitivity, with a pooled sensitivity of 83% (95%CI 75–92). For the assessment of QFT-G specificity six studies were selected with a pooled specificity of 91% (95%CI 78–100). Sun *et al.* (23) found nine studies assessing the QTF-G sensitivity for the diagnosis of active tuberculosis, resulting in a pooled sensitivity of 70% (95%CI 65–75), and when only culture-confirmed tuberculosis cases were considered, the
pooled sensitivity increased to 85%. They also found three studies assessing specificity, with a pooled specificity of 100% (95% CI 84–100) for QTF-G. For this meta-analysis, participants coinfected with HIV or other immune compromises and those who had received anti-tuberculosis treatment were excluded. It was also evident that the prevalence of tuberculosis in different settings may alter the performance of the assay, therefore justifying QFT-G evaluation in different populations. The great heterogeneity of studies with children makes them very difficult to compare. The population of our study represents more closely the conditions encountered in daily practice in our country: all children in our study had received BCG immunization and they were exposed to similar epidemiological conditions. In these conditions, our study found both, sensitivity and specificity of the test similar to those reported in the above mentioned meta-analyses.

QTF-G response is based on the release of IFN-γ by T lymphocytes previously sensitized with M. tuberculosis after exposure to two proteins present in the bacterial cell wall: ESAT-6 and CFP-10. Because these antigens are absent in BCG and most of the mycobacteria present in the environment, previous exposure to these bacteria and immunization with BCG does not induce a positive test result. In our study, all 184 children from the negative control group received the BCG vaccine, confirmed by the presence of scar. The median and the mean age were 35 months, not far from the recommended period for BCG immunization, and potentially more prone to interfere with the QTF-G test result due to recent vaccination. In the control group, all children but one had a negative QTF-G result, reinforcing the finding that immunization with BCG does not significantly interfere with the second generation QTF-G test results.

The rate of indeterminate results varies among different studies, raising a concern for a possible limitation of QTF-G use in children. Connell et al found 6% of indeterminate results, of which 4% were due to inadequate mitogen control values. Bergamini et al tested 315 children by QFT-G, and a higher rate of indeterminate results was found (21.5%), mainly in children under the age of four. The authors also reported that the concentration of mitogen-induced IFN-γ response had significantly increased with age. In another report, Lighter et al found a much lower rate of indeterminate results (1.5%) and, although the amount of IFN-γ released after stimulation with the mitogen was directly correlated with age, surprisingly, the proportion of indeterminate results was similar for all age groups. In the present study, we found indeterminate results in six children (3.2%), all of them under the age of four. Although this percentage seems not to have affected the QTF-G performance, in these cases it is advisable to repeat the test in a second sample, especially in young children. Due to the present study design, the evaluation of a second sample was not possible.

By means of a ROC curve, the best cut-off value for the studied population was 0.305 UI/mL, very similar to the one recommended by the QFT-G manufacturer (0.350 UI/mL). It is important to highlight that even in a young paediatric population the recommended cut off was the same as in adults.

Diagnosing tuberculosis in children is a very difficult task, and available tools are yet far from the ideal. In the present study, the performance of QuantiFERON-TB Gold in Tube for diagnosing M. tuberculosis infection in a predominant young paediatric population was appropriate. The main findings of this study were the high negative predictive value of the test, a useful parameter for the exclusion of tuberculosis in clinical practice, therefore reducing the prescription of unnecessary chemotherapy in children, and the surprisingly low percentage of indeterminate results (3.2%). Nevertheless, the sensitivity of 81.8%, although meeting the WHO criteria of at least 80%, does not recommend the QuantiFERON-TB Gold in Tube as a single laboratory parameter to define tuberculosis in children.

References

1. World Health Organization [homepage on the Internet]. WHO Global Tuberculosis Report 2012 [cited 2012 May 30]. Available from: http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf
2. Nelson LJ, Wells CD. Global epidemiology of childhood tuberculosis. Int J Tuberc Lung Dis 2004;8:636-47.
3. American Thoracic Society. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Am J Respir Crit Care Med 2000; 161:1376-95.
4. Lighter J, Rigaud M. Diagnosing childhood tuberculosis: traditional and innovative modalities. Curr Prob Pediatr Adolesc Health Care 2009;39:61-86.
5. Silva JB. Tuberculose: Guia de Vigilância Epidemiológica [apresentação]. J Bras Pneumol 2004;30 (Suppl 1):S57-86.
6. Conde MB, Melo FA, Marques AM, Cardoso NC, Pinheiro VG, Dalcín PT et al. III Diretrizes para Tuberculose da Sociedade Brasileira de Pneumologia e Tisiologia. J Bras Pneumol 2009;35:1018-48.
7. Joos TJ, Miller WC, Murdoch DM. Tuberculin reactivity in bacille Calmette-Guérin vaccinated populations: a compilation of international data. Int J Tuberc Lung Dis 2006;10:883-91.
8. Sant’Anna CC, Orfaliais CT, March MF. A retrospective evaluation of a score system adopted by the Ministry of Health, Brazil, in the diagnosis of pulmonary tuberculosis in childhood: a case control study. Rev Inst Med Trop S Paulo 2003;45:103-5.
9. Sant’Anna CC, Orfaliais CT, March Mde F, Conde MB. Evaluation of a proposed diagnostic scoring system for pulmonary tuberculosis in Brazilian children. Int J Tuberc Lung Dis 2006;10:463-5.
10. Lalvani A, Millington KA. T cell-based diagnosis of childhood tuberculosis infection. Curr Opin Infect Dis 2007;20:264-71.
11. Lighter J, Rigaud M, Eduardo R, Peng CH, Pollack H. Latent tuberculosis diagnosis in children by using the QuantiFERON-TB Gold In-Tube test. Pediatrics 2009;123:30-7.
12. Pai M, Riley LW, Colford JM Jr. Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review. Lancet Infect Dis 2004;4:761-76.
13. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med 2008;149:177-84.
14. Cho SN, Brennan PJ. Tuberculosis: diagnostics. Tuberculosis (Edinb) 2007;87 (Suppl 1):S14-7.
15. Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technol Assess 2007;11:1-196.
16. Nyendak MR, Lewinsohn DA, Lewinsohn DM. New diagnostic methods for tuberculosis. Curr Opin Infect Dis 2009;22:174-82.
17. Cho SN. Current issues on molecular and immunological diagnosis of tuberculosis. Yonsei Med J 2007;48:347-59.
18. Blanc P, Dubuc JC, Garnier JM, Bsdoure E, Minodier P. Que faut-il penser des tests sanguins in vitro pour le diagnostic de la tuberculose en pédiatrie? Arch Pediatr 2008;15:75-82.
19. Kampmann B, Whittaker E, Williams A, Walters S, Gordon A, Martinez-Alier N et al. Interferon-gamma release assays do not identify more children with active tuberculosis than the tuberculin skin test. Eur Respir J 2009;33:1374-82.
20. Bianchi L, Galli L, Moriondo M, Veneruso G, Becchioli L, Azzari C et al. Interferon-gamma release assay improves the diagnosis of tuberculosis in children. Pediatr Infect Dis J 2009;28:510-4.
21. Kanunfre KA, Leite OH, Lopes MI, Litvoc M, Ferreira AW. Enhancement of diagnostic efficiency by a gamma interferon release assay for pulmonary tuberculosis. Clin Vaccine Immunol 2008;15:1028-30.
22. Mandalakas AM, Detjen AK, Hesseling AC, Benedetti A, Menzies D. Interferon-gamma release assays and childhood tuberculosis: systematic review and meta-analysis. Int J Tuberc Lung Dis 2011;15:1018-32.
23. Sun L, Xiao J, Miao G, Feng WX, Wu XR, Yin QQ et al. Interferon gamma release assay in diagnosis of pediatric tuberculosis: a meta-analysis. FEMS Immunol Med Microbiol 2011;63:165-73.
24. Dheda K, van Zyl Smit R, Badri M, Pai M. T-cell interferon-gamma release assays for the rapid immunodiagnosis of tuberculosis: clinical utility in high-burden vs. low-burden settings. Curr Opin Pulm Med 2009;15:188-200.
25. Detjen AK, Keil T, Roll S, Hauer B, Mauch H, Wahn U et al. 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.
26. Connell TG, Ritz N, Paxton GA, Buttery JP, Curtis N, Ranganathan SC. A three-way comparison of tuberculin skin testing, QuantiFERON-TB gold and T-SPOT.TB in children. PLoS One 2008;3:e2624.
27. Bergamini BM, Losi M, Vaienti F, D’Amico R, Meccugni B, Meacci M et al. Performance of commercial blood tests for the diagnosis of latent tuberculosis infection in children and adolescents. Pediatrics 2009;123:e419-24.