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Contact investigation in a primary school using a whole blood interferon-gamma assay

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Summary *Objectives:* To evaluate the usefulness of QuantiFERON®-TB Gold (QFT-G) for children.
Methods: Students in a primary school exposed to a tuberculosis patient were investigated using the tuberculin skin test (TST), chest X-ray examination and sequential QFT-G tests.
Results: The first QFT-G test was conducted one month after the end of exposure for 308 of the 313 children, with 6 (1.9%) positive. TST results were obtained from 306 of the students at 2 months after exposure, and 200 (65.4%) had induration $\geq$5 mm. A second QFT-G test, a further month later, and a third QFT-G test, six months after exposure, found an additional 2 positive and one weakly positive, respectively. Overall, the rate of QFT-G positivity was 9.8% (4/41) for close contact children ($\geq$90 h exposure), significantly higher than for casual contacts ($\leq$18 h exposure; 1.8%, 5/272; $p = 0.020$), whereas there was no significant difference in TST positive rates ($p = 0.078$).
Conclusions: These data suggest that QFT-G has the same performance characteristics in BCG vaccinated children as it does in adults. The observation that none of the 297 students who were QFT-G negative had developed active TB after 3 years of follow-up suggests that QFT-G has a very high negative predictive value.

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Introduction

Tuberculosis (TB), which is caused by infection with *Mycobacterium tuberculosis* complex (MTB), is still a major human health problem, especially in developing countries.[1] It has been estimated that third of the world's population is latently infected with MTB,[2] providing a large reservoir for future transmission. In developed countries, contact investigations are a major component of TB control activities, with those identified as having latent TB infection (LTBI) generally indicated for preventive chemotherapy.[3,4] Until recently, the tuberculin skin test (TST) and chest X-ray examination have been the main tools used for contact investigations. However, chest X-ray examination does not detect LTBI. Moreover, the TST is known to be confounded by prior BCG vaccination or reactivity to non-tuberculous mycobacteria (NTM) due to cross-reactivity between the PPD used for the TST and antigens of BCG and NTM.[5] Thus, identification of contacts with LTBI has been problematic, especially in countries where BCG vaccination is widely conducted.

Identification of the highly specific RD1 region of the MTB genome has enabled development of new diagnostics for MTB infection, interferon-gamma release assays (IGRAs), which distinguish MTB infection from effects of prior BCG vaccination or reactivity to the majority of NTM.[6] The clinical performance of one of these tests, QuantiFERON®-TB Gold (QFT-G), has been extensively investigated by our group and others,[7–13] and QFT-G is now routinely used for contact investigations in several countries including Japan. Although there have been some studies reporting good performance of QFT-G in children,[14–18] available data in this population group are limited. In the present study, we used the QFT-G test in a contact investigation in a primary school to further evaluate its usefulness in children.

Subjects and methods

The index case

The index case was a 46 years old male teacher in a primary school. Feeling discomfort in his throat in September 2005 and developing a severe cough in early October 2005, he initially visited an otolaryngologist, but TB was not detected. On 17 November he attended a clinic after producing sputum containing blood and chest X-ray revealed cavitary lesions in his lung's left middle quadrant. Due to suspicion of pulmonary TB, a CT scan was performed and based on the findings he was admitted to a specialist TB hospital. Sputum smear for AFB was 2+ positive, and he was diagnosed with active pulmonary TB on November 21, 2005. His sputum culture was positive, and the isolate was susceptible to the first-line anti-TB drugs.

Contact investigation

The main focus of the contact investigation was students in the primary school. A total of 313 students were evaluated using QFT-G, TST and chest X-ray. According to extent of contact with the index case, students were divided into two groups (Table 1). The close contact group consisted of 41 children, mean age 8.6 years (range 8–9), who were students in the class where the index case was the teacher in charge. These students had contact every weekday until the index case was diagnosed with TB; an aggregate of at least 90 h. Other students attending the same school ($n = 272$; mean age 9.8 years; range 8–12) were categorized as casual contacts and had contact for a total of 18 h or less.

Table 1 Characteristics of each group.

Close contact group	Casual contact group
$n = 41$	$n = 272$
Mean age (range): 8.6 years old (8–9)	Mean age (range): 9.8 years old (8–12)
Sex (M/F): 20/21	Sex (M/F): 137/135
BCG: 100%	BCG: 98.5%
QFT-G-positives: 4	QFT-G-positives: 5
Rate of QFT-G-positives: 9.8%	Rate of QFT-G-positives: 1.8%
Rate of TST positivity (5 mm): 52.6%	Rate of TST positivity (5 mm): 67.2%
Rate of TST positivity (10 mm): 34.2%	Rate of TST positivity (10 mm): 28.7%

The initial contact investigation was carried out in the middle of December 2005, one month after the end of exposure, using QFT-G only. A subsequent investigation was conducted in late January/early February 2006 using the TST for 307 of the students, which was approximately 8 weeks after the index case was reported. A third round of testing was carried out in late February 2006, employing the QFT-G test for those who had been negative in the first QFT-G test. A further evaluation was conducted in June 2006 using QFT-G for those with negative responses in the previous rounds of testing. Finally, a chest X-ray was performed for all subjects one year after the index case was reported. The study was approved by ethics committees in the Health and Welfare Center, Miyamae Ward Office. Written informed consent was obtained for all subjects.

QFT-G assay

The QFT-G assay was performed using QFT-G kits (Cellestis Ltd., Carnegie, Australia) according to the manufacturer's instructions. IFN-γ responses to either ESAT-6 and/or CFP-10 that are greater than or equal to 0.35 IU/ml above the value for the respective Nil control are indicative of MTB infection. If a person's response (corrected for the Nil control) is less than 0.35 IU/ml for both TB-specific antigens and their response to the mitogen-positive control is above 0.5 IU/ml, they are considered test negative. No test result ("Indeterminate") is recorded if the Nil-corrected IFN-γ response for an individual is less than 0.35 IU/ml for the MTB-specific antigens and less than 0.5 IU/ml for the mitogen positive control.

Tuberculin skin test

The TST was performed using the defined standard test dose of tuberculin PPD (containing 0.05 mcg PPD in 0.1 ml, Nippon BCG Manufacturing Co. Ltd), which is equivalent to