Utility of QuantiFERON Tuberculosis Gold-in-Tube Test for Detecting Latent Tuberculosis Infection among Close Household Contacts of Confirmed Tuberculosis Patients in Accra, Ghana

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Abstract

Objective/Background: Introduction of the interferon gamma (IFN-γ) release assays with their higher sensitivity and specificity over the traditional tuberculin skin test has improved testing for latent tuberculosis infection (LTBI). None of the IFN-γ release assays has ever been used to screen for LTBI in Ghana. This study set out to determine the utility of the QuantiFERON TB Gold-in-Tube (QFT-GIT) test for the diagnosis of LTBI among close household contacts of newly diagnosed sputum smear-positive tuberculosis (TB) patients in Accra, Ghana, and the associated risk factors for a positive QFT-GIT test. Materials and Methods: Close household contacts of newly diagnosed sputum smear-positive patients receiving anti-TB therapy from three hospitals in Accra were recruited, after providing written informed consent, between April 2012 and December 2014. In addition to demographic details, 2 mL of blood was collected from all participants for the QFT-GIT test for LTBI diagnosis. Results: Out of 112 eligible consenting participants, the QFT-GIT test was performed for 100 participants. The prevalence of LTBI (QFT-GIT positive) was 65%, with 32% being QFT-GIT negative and 3% indeterminate results. Contacts aged >15 years were more likely to be QFT-GIT positive than those aged <15 years, regardless of their Bacillus Calmette–Guerin status. There was significantly higher QFT-GIT test positivity in adult contacts who were parents, siblings, or spouses to index cases than in child contacts (P = 0.0016, P = 0.04, and P = 0.0003, respectively). Conclusion: The QFT-GIT test will be a useful tool for screening of TB contacts for LTBI in Ghana.

Keywords: Ghana, household contact, interferon gamma release assay, latent tuberculosis infection, QuantiFERON TB Gold-in-Tube test

Introduction

In 2013, 9 million people were newly diagnosed with tuberculosis (TB) and 1.5 million deaths were attributed to the disease.[1] Interestingly, TB disease develops in only 5%–10% of all those exposed to the pathogen; the remaining 90%–95%, if negative for human immunodeficiency virus (HIV), become latently infected for life without developing active TB.[2] (in people infected with HIV, the risk of latent TB reactivation is 20-fold[3]). This has led to an estimated 2 billion people living with latent TB infection (LTBI).[2] LTBI is a clinical state that is currently defined by immunological evidence of Mycobacterium tuberculosis infection accompanied by the absence of clinical and radiographic evidence of TB-related symptoms and pathology.[4,5] The anatomical location, number, and metabolic state in vivo of the infecting tubercle bacilli in LTBI remain debatable.[4,5] This huge reservoir (one-third of the world’s population) of latently infected individuals remains one of the major challenges of global TB control efforts. Mathematical modeling suggests that TB elimination cannot be reached by case finding and case management strategies alone,[6,7] and that more rapid progress in TB control requires implementation of additional interventions to target this huge reservoir.

Among major risk groups (HIV infected, migrants, prisoners, health workers, etc.), household contacts of active TB cases have been identified as one of the easiest targets for screening. Utility of the interferon gamma (IFN-γ) release assays with their higher sensitivity and specificity over the traditional tuberculin skin test has improved testing for latent tuberculosis infection (LTBI). None of the IFN-γ release assays has ever been used to screen for LTBI in Ghana. This study set out to determine the utility of the QuantiFERON TB Gold-in-Tube (QFT-GIT) test for the diagnosis of LTBI among close household contacts of newly diagnosed sputum smear-positive tuberculosis (TB) patients in Accra, Ghana, and the associated risk factors for a positive QFT-GIT test.

Materials and Methods:

Close household contacts of newly diagnosed sputum smear-positive patients receiving anti-TB therapy from three hospitals in Accra were recruited, after providing written informed consent, between April 2012 and December 2014. In addition to demographic details, 2 mL of blood was collected from all participants for the QFT-GIT test for LTBI diagnosis.

Results:

Out of 112 eligible consenting participants, the QFT-GIT test was performed for 100 participants. The prevalence of LTBI (QFT-GIT positive) was 65%, with 32% being QFT-GIT negative and 3% indeterminate results. Contacts aged >15 years were more likely to be QFT-GIT positive than those aged <15 years, regardless of their Bacillus Calmette–Guerin status. There was significantly higher QFT-GIT test positivity in adult contacts who were parents, siblings, or spouses to index cases than in child contacts (P = 0.0016, P = 0.04, and P = 0.0003, respectively).

Conclusion:

The QFT-GIT test will be a useful tool for screening of TB contacts for LTBI in Ghana.
transmission of TB. In families with a high crowding index (a large number of people sharing the same room), coupled with low socioeconomic status and poorly ventilated rooms, the risk of TB infection increases even after a short period of exposure to the infected person. The exact prevalence of LTBI among household contacts of TB cases in Ghana is not known. TB contact investigation is the best way of establishing this prevalence, and although this forms part of the National TB Control Program activities, the focus is more on identifying secondary cases of TB and not on LTBI detection. Diagnosing LTBI, although equally very important, has been challenging due to both logistical and operational difficulties of the 100-year-old tuberculin skin test (TST) used for LTBI diagnosis. The lack of highly trained health care workers who can accurately administer and read the test, the need for a return visit to read the test result, and the requirement of continuous refrigeration make the utility of the TST unattractive. The TST has other challenges including poor specificity, as a result of cross reactivity of Bacillus Calmette–Guerin (BCG) or environmental mycobacteria. During the past decade, two interferon gamma release assays (IGRAs), QuantiFERON TB Gold-in-Tube (QFT-GIT) test (Cellestis Ltd., Carnegie, Victoria, Australia) and T-SPOT-TB test (Oxford Immunotec, UK), have been introduced as novel assays for the detection of LTBI. The QFT-GIT test, an in vitro whole-blood interferon gamma (IFN-γ) assay based on M. tuberculosis-specific antigens (i.e., early secreted antigenic target 6 and culture filtrate protein 10), has been evaluated extensively for LTBI diagnosis. Numerous published reports clearly indicate that the QFT-GIT test is a more reliable marker of LTBI than TST, with higher sensitivity as well as specificity and a better correlation with exposure to M. tuberculosis. The IGRAs will, therefore, be a useful addition to screening of risk groups such as contacts of TB patients for TB infection. Immunocompetent adults with TST conversion after exposure to persons with infectious TB have a 5% risk of progression to active TB disease in the 2 years following exposure, with a further 5% residual lifetime risk of progression. In most low-burden regions, TB control policy targets recent contacts for preventive therapy on the basis of this 5% early risk. Several host factors, including age <5 years, HIV coinfection, diabetes mellitus, smoking, undernutrition, chronic renal failure, and iatrogenic immunosuppression, increase the risk of progression to active TB in remotely infected individuals to levels much higher than 5% over several decades.

However, in many developing countries including Ghana, LTBI is not treated; hence, screening will not be for the purpose of treatment, but for identifying people at risk of progressing to active TB for targeted intervention, for example, isoniazid preventive therapy (IPT) for children under 5 years who are contacts of active TB patients as well as HIV-positive individuals.

Despite its known advantage, none of the IGRAs has ever been used to screen for LTBI in a TB endemic country like Ghana. To the best of our knowledge, the present study was the first to investigate the diagnostic utility of the QFT-GIT test for determining the prevalence of LTBI in close household contacts of newly diagnosed sputum smear-positive TB patients in Accra, Ghana, and associated risk factors for QFT-GIT test positivity.

**Materials and Methods**

**Ethical approval**

This study was approved by the Institutional Review Board of the Noguchi Memorial Institute for Medical Research, University of Ghana, Legon/Accra (certified protocol number: 030/10-11). All participants were recruited after obtaining written informed consent from them.

**Recruitment of household contacts of tuberculosis index cases**

The participants were recruited from three health facilities in Accra/Ghana between April 2012 and December 2014. All household contacts of newly diagnosed sputum smear- or culture-positive TB index cases, aged 6 months or older, were invited to the same facility where the index cases were being treated, and informed about the study. Those who agreed to participate signed an informed consent form and were interviewed for demographic information, which included age, medical history, BCG vaccination status, and risk factors for TB (degree of closeness or proximity to the TB index case, smoking, and alcohol consumption). For minors (<18 years of age), parents/guardians signed parental consent and child ascent forms and responded on their behalf.

**Sample collection**

Blood samples were collected for the QFT-GIT test. One milliliter of blood was drawn into each of two tubes: One tube precoated with synthetic peptide antigens (early secreted antigenic target 6, culture filtrate protein 10, and TB7.7) and a second tube without antigens (negative control sample/NIL tube). The tubes were swirled several times to allow the blood to come into contact with the inner walls of the tubes. This ensured complete mixing of the blood and the antigens along the wall of the tube. Samples were transported the same day to the Noguchi Memorial Institute for Medical Research for incubation and further analysis.

**QuantiFERON TB Gold-in-Tube test**

The QFT-GIT test was performed following the manufacturer’s instructions. Briefly the tubes were incubated upright at 37°C overnight and then centrifuged at 2500 rpm for 10 min. The supernatant was harvested and stored at −20°C until ready for the IFN-γ enzyme-linked immunosorbent assay.

**QuantiFERON TB Gold-in-Tube interferon gamma enzyme-linked immunosorbent assay**

IFN-γ enzyme-linked immunosorbent assay was also performed according to the manufacturer’s instructions using IFN-γ standard for quantification. The quality of all laboratory analysis and calculation of the results were controlled using the accompanying QFT-GIT analysis software (version 2.62).
A sample was considered positive if it exceeded the standard cut-off value at 0.35 IU IFN-γ/mL. All positive results were confirmed by reanalysis of the same plasma sample before reporting it as positive. Samples with indeterminate results on the first run were rerun, and results were recorded as indeterminate if the second test was also indeterminate.

**Chest X-ray examination**
All QFT-GIT-positive participants were invited to the Korle-Bu Teaching Hospital, Accra, to undergo chest X-ray (CXR) examination by trained radiologists at the chest clinic.

**Statistical analysis**
Data were entered into Microsoft Excel 2010 (Microsoft Corp., Washington, USA) prior to analysis. Descriptive statistics such as frequency (percentage) was obtained for demographic, behavioral, and clinical factors measured on a nominal scale. For the QFT-GIT test, the accompanying software, Quantiferon-TB Gold IT Analysis software (version 2.17), was used to generate standard curves, which provided test results for each study participant. Participants were stratified by age, BCG vaccination status, sleeping proximity, and relation to index TB case. The QFT-GIT test result was treated as an outcome, and the proportion of positive cases corresponding to different levels of factors (covariates) was obtained using Fisher’s exact test.

**Results**

**Characteristics of tuberculosis contacts enrolled in the study**
Out of 112 eligible consenting participants, the QFT-GIT test was performed for 100 participants who provided 2 mL of blood required for the QFT-GIT test. Of these, 54% were females [Table 1]. The median age was 26.5 years, with 68% of the participants being 15 years or older (adults), 23% 5–15 years (children), and 9% <5 years (under 5 s).

More than half (70%) of the participants were BCG vaccinated as per the presence of BCG scar and/or vaccination records, while the BCG vaccination status of the rest could not be ascertained.

The majority of the participants (80%) could be classified as close household contacts, as they either shared the same bed, same room, or lived in the same house with the index TB cases. The rest lived in the same compound as the index case, but had a close contact with them on a daily basis.

Most (91%) of the participants were nuclear relations (parent, child, sibling, and spouse) of the index TB case, with parent-child relationship constituting 43% of these relations. In terms of proximity, 11%, 42%, 27%, and 20% of participants shared the same bed, same room, same house, and same compound, respectively, with the index TB case.

**QuantiFERON TB Gold-in-Tube test results**
Of the 100 TB contacts tested for LTBI with the QFT-GIT test, 65 (65%) had a positive QFT-GIT test result, 32 (32%) had a negative QFT-GIT test result, and three (3%) had an indeterminate test result even after a repeat run. To determine the possible risk factors for a positive QFT-GIT test result among the contacts of TB index cases, we looked at factors such as age, BCG vaccination status, sleeping proximity to the index case, and relation to the index case.

**Association between QuantiFERON TB Gold-in-Tube test positivity and age**
Of the 65 contacts who had positive QFT-GIT test results, 45 (69.2%) were aged ≥15 years, 13 (20%) 5–15 years, and 3 (4.6%) <5 years.

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**Table 1: Characteristics of tuberculosis contacts enrolled in the study**

|                        | All     | <5 years | 5-14 years | ≥15 years | P         |
|------------------------|---------|----------|------------|-----------|-----------|
| **Age**                |         |          |            |           |           |
| Median (IQR)           | 26.5 (2-86) | 3 (2-4) | 9 (5-14)  | 32 (15-86) | <0.0001   |
| Sex, n (%)             |         |          |            |           |           |
| Male                   | 46 (46.0) | 7 (77.8) | 12 (52.2)  | 27 (39.7) | 0.075     |
| Female                 | 54 (54.0) | 2 (22.2) | 11 (47.8)  | 41 (60.3) |           |
| **BCG status, n (%)**  |         |          |            |           |           |
| Yes                    | 70 (70.0) | 7 (77.8) | 18 (73.8)  | 45 (66.2) | 0.901     |
| No                     | 22 (22.0) | 2 (22.2) | 4 (17.4)   | 16 (23.5) |           |
| Unknown                | 8 (8.0)  | 0        | 1 (4.3)    | 7 (10.3)  |           |
| **Sleeping proximity, n (%)** |       |          |            |           |           |
| Same bed               | 11 (11.0) | 1 (11.1) | 0          | 10 (14.7) | 0.099     |
| Same room              | 42 (42.0) | 7 (77.8) | 12 (52.2)  | 23 (33.8) |           |
| Same house             | 27 (27.0) | 0        | 7 (30.4)   | 20 (29.4) |           |
| Same compound          | 20 (20.0) | 1 (11.1) | 4 (17.4)   | 15 (22.1) |           |
| **Relation to index case, n (%)** |       |          |            |           | 0.0001    |
| Parents                | 14 (14.0) | 0        | 0          | 14 (20.6) |           |
| Child                  | 29 (29.0) | 9 (100)  | 13 (56.5)  | 7 (10.3)  |           |
| Sibling                | 26 (26.0) | 0        | 7 (30.4)   | 19 (27.9) |           |
| Spouse                 | 22 (22.0) | 0        | 0          | 22 (32.4) |           |
| Other                  | 9 (9.0)  | 0        | 3 (13.1)   | 6 (8.8)   |           |

IQR: Interquartile range, BCG: *Bacillus* Calmette–Guérin
seven (10.8%) under 5 years [Table 2]. Although we observed an increase in the frequency of QFT-GIT test positivity with increasing age, the difference in the QFT-GIT test outcomes between the three age categories was not significant \((P = 0.46)\).

**Association between QuantiFERON TB Gold-in-Tube test positivity and Bacillus Calmette–Guerin vaccination status**

Generally, BCG-vaccinated children (age \(\leq 15\) years) were more likely to have a positive QFT-GIT test result than non-BCG-vaccinated children. The reverse was observed in the adult population (age >15 years), where BCG-vaccinated adults were less likely to have a positive QFT-GIT test result than non-BCG-vaccinated adults. This difference was, however, not statistically significant \((P = 0.27)\). However, non-BCG-vaccinated adult contacts were significantly more likely to have a positive QFT-GIT test result than children with no evidence of BCG vaccination \((P = 0.008)\). Among the adult contacts, those whose BCG vaccination status could not be determined had significantly \((P = 0.03)\) more positive QFT-GIT test results than their BCG-vaccinated and BCG-unvaccinated counterparts [Figure 1].

**Association between QuantiFERON TB Gold-in-Tube test positivity and sleeping proximity to tuberculosis index case**

Within the adult population (aged \(\geq 15\) years), the frequency of positive QFT-GIT test result was highest \((P = 0.06)\) in TB contacts sharing the same bed with index TB cases, whereas children sharing the same room with confirmed TB cases had the highest positive QFT-GIT test result. However, adults sharing the same house with an index TB case were significantly \((P = 0.03)\) more likely to have a positive QFT-GIT test result than children sharing the same house with the index case [Figure 2].

**Spouses and parents to index TB cases had the highest QFT-GIT test positivity among the adult population, while siblings had**
the highest QFT-GIT test positivity among the child TB contacts [Figure 3]. Among the two populations, there was significantly higher QFT-GIT test positivity in adult contacts who were parents, siblings or spouses to index cases than in children contacts \((P = 0.0016, 0.04, \text{and } 0.0003, \text{respectively})\). Although a similar trend was observed in contacts who were offspring and other relations (including grandparents, uncles, aunts, etc.) to index cases, the difference in QFT-GIT test positivity among the two age groups was not statistically significant \((P = 0.10)\).

**Chest X-ray results of QuantiFERON TB Gold-in-Tube-positive tuberculosis contacts**

Out of the 65 QFT-GIT-positive TB contacts expected to have their CXRs taken, only 24 availed themselves for the examination. Half \((12, 50\%)\) of these had a conclusive radiology result, which indicated a normal X-ray, and seven \((29.2\%)\) had an abnormal CXR, which required sputum smear and culture examinations to confirm the CXR findings (but all the seven were negative for *Mycobacterium* species). The others \((5, 20.8\%)\) had indeterminate results and were asked to repeat the CXR at a later time [Table 3].

**DISCUSSION**

In Ghana, TB contact investigation as part of the TB control strategy of the National TB Control Program is yet to be implemented fully. However, the National TB Control Program has been supportive of civil society groups engaged in such activity. These contact investigation programs utilize questionnaires to capture information on signs and symptoms of TB, followed by smear microscopy and/or culture for definitive TB diagnosis. This strategy, although effective in identifying secondary cases of TB among TB contacts, falls short of estimating or diagnosing LTBI among contacts of TB cases. The addition of a diagnostic tool such as the QFT-GIT test would not only provide information on LTBI situation among contacts of TB cases in Ghana, but also enhance contact investigation efforts. To the best of our knowledge, the present study is the first to use an IGRA for the diagnosis of LTBI among TB contacts in Ghana.

Our study demonstrated a high prevalence \((65\%)\) of LTBI among TB contacts, as has been reported in studies from other developing countries.\(^{[10,18-20]}\) In an attempt to identify risk factors for QFT-GIT test positivity among TB contacts in Ghana, we focused on some factors (age, BCG vaccination, duration of exposure, and proximity to index case) that have been demonstrated to be important in other studies.\(^{[9,21-23]}\) Although not significant, we observed a trend of increased QFT-GIT test positivity with “age” in our study. Age has been identified as a strong predictor for QFT-GIT test positivity in other studies.\(^{[10,24]}\) This could be as a result of accumulated exposure over time with increasing age or waning of protective effect of BCG with time in adults compared with children. In our study, adult contacts of confirmed TB cases were more likely to be positive for TB infection than contacts who are children, regardless of their BCG vaccination status and level of exposure (sleeping proximity and relation) to index TB cases.

However, with the vulnerability of children to infection due to their underdeveloped immune system, the likelihood of infection under such living conditions is high. In this study, children (up to 15 years of age) sharing the same room with confirmed TB cases had higher QFT-GIT test positivity compared with those sharing the same house or same compound with confirmed TB cases. This finding appears to confirm reports that adults, especially family members, are usually the major source of infection in children.\(^{[25]}\) In view of this, it is important that younger children, in particular, are protected against possible infections from active TB cases who they share such family ties with.

Our results also gives an insight into the possible family relations that could exacerbate the spread of infection, as we observed significantly high QFT-GIT test positivity in adult contacts who were parents, siblings, or spouses to confirmed TB cases.

![Figure 3: QuantiFERON TB Gold-in-Tube test positivity by age group according to relation to index tuberculosis case. Household tuberculosis contacts were categorized according to nature of relationship to the index case (parent, sibling, offspring/children, spouse, and other) and age group (<15 years or ≥15 years). Shown is the proportion of QuantiFERON TB Gold-in-Tube-positive individuals by age group with respect to the relationship to index tuberculosis cases.](image)

| Outcome     | n (%) | P     |
|-------------|-------|-------|
| Normal      | 12 (50)| 0.197 |
| Abnormal    | 7 (29.2)|       |
| Indeterminate| 5 (20.8)|       |

*All QFT-GIT-positive participants were invited for chest X-ray examination by trained radiologists using a digital X-ray system. Of the 65, only 24 availed themselves. Results were classified as normal, abnormal, and indeterminate: normal – clear lung shadows with no hilar lymphadenopathy; abnormal – hilar lymphadenopathy and patchy pulmonary opacities; indeterminate – unclear; therefore X-ray to be repeated at a later date. QFT-GIT: QuantiFERON TB Gold-in-Tube test.
TB cases, possibly due to their care-giving roles. Additionally, these individuals were living in overcrowded and poorly ventilated places, creating a conducive environment for transmission of the tubercle bacilli.[26]

Among the contacts, there was no association between QFT-GIT test positivity and CXR results, and active TB disease could not be established in any of these participants. It is, however, important that children below 5 years with a positive QFT-GIT test result and a normal CXR be put on IPT to prevent progression to active disease in the near future. In 2008, only an estimated 0.2% of eligible individuals globally received IPT.[27] Implementation of IPT has been hindered by the concerns over the reliability with which active TB can be excluded and the associated concerns over potential generation of isoniazid resistance.[11,28] Sensitization is required if the IPT policy is to be fully accepted and implemented.

**Conclusion**

In conclusion, our study demonstrated a high prevalence of LTBI in close household contacts of active TB cases. We also established the utility of the QFT-GIT test for detecting LTBI in Ghana. Given that the factors that trigger the development of active TB in people with LTBI are not fully understood, it would be important to include the QFT-GIT test in TB contact investigation activities. This will ensure that we are able to closely monitor TB contacts who have LTBI, as well as offer IPT to contacts under 5 years who are found to be uninfected.

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**Conflicts of interest**

There are no conflicts of interest.

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