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Trajectories of tuberculosis-specific interferon-gamma release assay responses among medical and nursing students in rural India

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Abstract *Background:* Interferon gamma release assays (IGRAs) have been shown to be highly dynamic tests when used in serial testing for TB infection. However, there is little information demonstrating a clear association between TB exposure and IGRA responses over time, particularly in high TB incidence settings.

Objectives: To assess whether QuantiFERON-TB Gold In-Tube (QFT) responses are associated with occupational TB exposures in a cohort of young health care trainees in India.

Methods: All medical and nursing students at Mahatma Gandhi Institute of Medical Sciences were approached. Participants were followed up for 18 months; QFT was performed 4 times, once every 6 months. Various modeling approaches were used to define IFN-gamma trajectories and correlations with TB exposure.

Results: Among 270 medical and nursing trainees, high rates of conversions (6.3–20.9%) and reversions (20.0–26.2%) were found depending on the definitions used. Stable converters were more likely to have had TB exposure in hospital pre-study.

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Recent occupational exposures were not consistently associated with QFT responses over time.

Conclusion: IFN-gamma responses and rates of change could not be explained by occupational exposure investigated. High conversion and subsequent reversion rates suggest many health care workers (HCWs) would revert in the absence of treatment, either by clearing the infection naturally or due to fluctuations in the underlying immunological response and/or poor assay reproducibility. QFT may not be an ideal diagnostic test for repeated screening of HCWs in a high TB incidence setting.

1. Introduction

India accounts for one fifth of the global TB burden [1–3], and as such, Indian health care workers (HCWs) are consistently at an increased risk of occupational exposure to TB, development of latent TB infection (LTBI) and active disease [4–7].

In 2009, the World Health Organization (WHO) released guidelines on TB infection control (TBIC) in resource-limited settings and is now actively promoting TBIC in high TB burden countries [8]. The emergence of multi-drug resistance (MDR) [9] and extensively drug-resistant (XDR-TB) [10] strains has heightened the necessity for TBIC measures, and reinforces the importance of protecting the health care work force [10].

Annual screening of HCWs for LTBI is a critical element in TBIC programs in developed countries and is now gaining some attention in resource-limited countries as well [11]. Traditionally, screening HCWs for LTBI was performed with the tuberculin skin test (TST), but interferon-gamma release assays (IGRAs) are now available as an alternative [12,13]. IGRAs have logistical advantages which make them attractive for use in serial testing of HCWs, and systematic reviews have shown both tests (TST and IGRAs) estimate similar rates of positivity in high TB incidence settings such as India [14].

Screening HCWs for LTBI in high TB incidence settings poses many challenges, including a high level of repeated exposures, re-infection, and limited resources to carry out screening or offer isoniazid preventive therapy (IPT) when necessary. Early serial testing studies suggest IGRA results may be highly variable over time, resulting in higher frequencies of conversions and spontaneous reversions than seen with the conventional TST [15]; many groups are now exploring alternative IGRA conversion definitions or the use of a borderline zone for values close to the cut-off that might better correlate with true instances of new infection [16,17]. However, these analyses have been conducted largely in low TB incidence settings, and data are still lacking as to the extent to which IGRA conversions or rates of change are associated with TB exposure (as a proxy for the likelihood of TB infection) in a high TB incidence setting.

1.1. Study objectives

Study objectives were firstly to estimate rates of QuantiFERON-TB Gold In-Tube (QFT) conversions and reversions in Indian health care trainees, during six-month intervals, over four test points. Secondly, rates of TB exposure were estimated by type of health care trainee, and evaluated whether QFT conversions were associated with TB exposures, and QFT reversions with treatment. HCWs were categorized by patterns of QFT responses, to assess whether different patterns were associated with exposure. Secondary objectives were to assess what occupational TB exposure factors (if any) were associated with change in IFN-gamma response over the four time points.

2. Materials and methods

2.1. Study setting and population

This study was conducted at the Mahatma Gandhi Institute of Medical Sciences (MGIMS), Sevagram, a teaching hospital located in central India. The hospital sees an average of 300 smear positive TB cases per year, two thirds of which are treated as in-patients. As MGIMS is a referral center, most smear positive patients are seriously ill when they reach the hospital and require hospitalization. Approximately three quarters of all smear positive in-patients are diagnosed only during in-patient evaluation.

TB infection control measures are limited, screening for LTBI is not routinely performed and personal respirators are not routinely provided (and when available not routinely employed by HCWs when interacting with patients with active