OPTIMIZATION AND INTERPRETATION OF SERIAL QUANTIFERON TESTING TO MEASURE ACQUISITION OF *M. TUBERCULOSIS* INFECTION

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Background
Conversion from a negative to positive QuantiFERON-TB test is indicative of *Mycobacterium tuberculosis* (*M.tb*) infection, which predisposes to tuberculosis disease. Interpretation of serial tests is confounded by immunological and technical variability.

Objectives
To improve consistency of serial QuantiFERON-TB testing algorithms and provide a data-driven definition of conversion.

Methods
Sources of QuantiFERON-TB variability were assessed and optimal procedures identified. Distributions of IFNγ response levels were analysed in healthy adolescents, *M.tb*-unexposed controls, and pulmonary tuberculosis patients.

Results
Individuals with no known *M.tb* exposure had IFNγ values <0.2 IU/mL. Among individuals with IFNγ values <0.2, 0.2-0.34, 0.35-0.7, and >0.7 IU/mL, tuberculin skin test positivity was 15%, 53%, 66% and 91% ($p<0.005$), respectively. Together, these findings suggest that values <0.2 IU/mL were true negatives. In short-term serial testing, "uncertain" conversions, with at least one value within the uncertainty zone (0.2-0.7 IU/mL), were partly explained by technical assay variability. Individuals who had a change in QuantiFERON-TB IFNγ values from <0.2 to >0.7 IU/mL had 10-fold higher tuberculosis incidence rates than those who maintained values <0.2 IU/mL over 2 years ($p=0.0003$). By contrast, "uncertain" converters were not at higher risk than non-converters ($p=0.229$). Eighty-seven percent of active TB patients had IFNγ values >0.7 IU/mL, suggesting that these values are consistent with established *M.tb* infection.

Conclusions
Implementation of optimized procedures and a more rigorous QuantiFERON-TB conversion definition, an increase from IFNγ <0.2 to >0.7 IU/mL, would allow more definitive detection of recent *M.tb* infection and potentially improve identification of those more likely to develop disease.