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

Elisa Nemes1*, Virginie Rozot1*, Hennie Geldenhuys1, Nicole Bilek1, Simbarashe Mabwe1, Deborah Abrahams1, Lebohang Makhethe2, Mzwandile Erasmus1, Alana Keyser2, Asma Toefy7, Yolundi Cloete1, Frances Ratangee3, Thomas Blauenfeldt2, Morten Ruhwald2, Gerhard Walzl3, Bronwyn Smith3, Andre G. Loxton3, Willem A. Hanekom1, Jason R. Andrews4, Maria D. Lempicki5, Ruth Ellis5, Ann M. Ginsberg5, Mark Hatherill1**, Thomas J. Scriba** and the C-040-404 Study Team† and ACS Study Team‡

1South African Tuberculosis Vaccine Initiative, Institute of Infectious Disease and Molecular Medicine & Division of Immunology, Department of Pathology, University of Cape Town, Cape Town, South Africa.
2Statens Serum Institut, Artillerivej 5, 2300 Copenhagen, Denmark
3South Africa Department of Science and Technology–National Research Foundation Centre of Excellence for Biomedical Tuberculosis Research, South African Medical Research Council Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
4Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, California, USA
5AERAS, Rockville, MD, USA

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.