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Efficiency of restricting participation in tuberculosis vaccine trials to interferon-gamma release assay-positive participants

Frank Cobelens[1,2], Puck T Pelzer[3], Richard G White[4]

[1]*Department of Global Health, Amsterdam University Medical Centers, University of Amsterdam, Netherlands;* [2]*Amsterdam Institute for Global Health & Development, Amsterdam, Netherlands;* [3]*Epidemiology, IAVI, Amsterdam, Netherlands;* [4]*Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, UK*

Background: One approach to reducing sample sizes for late-stage TB vaccine trials is to increase the expected TB case accrual rate by restricting enrolment to infected participants. This requires pre-enrolment testing, while its efficiency is unknown.

Methods: We modelled a population in which we estimated the prevalence of QuantiFERON (QFT, cut-off ≥ 0·35 IU/ml) positivity by age for an annual risk of TB infection (ARTI) of 4% (range, 2-6%), and based on these the expected TB incidence among QFT-positive (QFT+) and QFT-negative individuals, with and without taking QFT reversion, partial protection afforded by previous infection and increasing ARTI during adolescence (age varied ARTI) into account. We then modelled 3-year vaccine trials enrolling participants 15-44 years and calculated the ratio of TB case accrual in the placebo group in a QFT+ participant-only trial population, versus that in a mixed trial population of participants without prior QFT testing ('efficiency').

Results: Preliminary results suggest TB case accrual is considerably higher in QFT+ compared to QFT-negative participants among adolescents and young adults, but much less so at later ages. This effect is exacerbated by partial protection and age varied ARTI. In a model including QFT reversion, partial protection, and age varied ARTI, a QFT+ only trial had no more than 1.1 times higher case accrual than a mixed trial. This was largely unaffected by assumptions about parameter values, duration of disease progression following QFT conversion and dynamics of QFT reversion, but strongly sensitive to the ARTI. At 2% ARTI, a QFT+ only trial had considerably higher case accrual than a mixed trial population, whereas at 6% ARTI, accrual was similar or even lower for a QFT+ only trial.

Conclusions: For TB vaccine trials in high-incidence populations there may be limited or no efficiency of pre-enrolment QFT screening. High incidences in QFT+ adolescents cannot be simply extrapolated to older ages.

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Conflicts of Interest
None