Analytic Preparation to Support a Trial of "TB Step Change" in Karachi
September 23, 2022

Background

Existing trials of interventions designed to reduce the population-level burden of TB have primarily used one of two approaches, namely population-based prevalence surveys and cross-sectional surveys of infection (e.g., TST or IGRA) in young children. Both of these approaches are problematic, for different reasons.

Prevalence surveys give an accurate portrayal of TB prevalence, but (a) are resource-intensive to carry out [because the prevalence of TB is generally <1%]; and (b) cannot be performed without actually treating those people diagnosed as having TB (i.e., represent an intervention themselves). Thus, one must either perform an intervention – a pre-trial prevalence survey – in the control arm of the trial, or lack a pre-trial baseline against which the primary outcome can be assessed. Furthermore, a pre-trial prevalence survey is itself a case-finding intervention – one that may have a large but temporary impact on TB prevalence, making it difficult to disentangle the impact of the primary intervention from that of the pre-trial prevalence survey.

An alternative approach that could be carried out on a sufficiently small scale so as not to "contaminate" the effect of the primary intervention is a TST/IGRA conversion study (i.e., measurement of TST/IGRA response, with longitudinal follow-up of those who are TST/IGRA-negative at baseline). TST/IGRA surveys are used to measure the prevalence of latent TB infection (LTBI), and TST/IGRA conversion is a common outcome in trials of TB vaccines. Since individuals exposed to TB will generally convert their TST/IGRA result before progressing to TB disease, measurement of TST/IGRA positivity can give an indication of the level of ongoing transmission in the population.

A related question is the appropriate size of geographic regions over which interventions can be implemented and surveys of epidemiologically meaningful outcomes can be carried out. This relates to the appropriate unit of randomization (and thus, study power) for any clinical trial.

Proposal

We propose to explore the following quantity as the primary outcome of a potential "TB Step Change" trial: the **annual rate of IGRA (or skin test) conversion**. This quantity would be estimated by performing a relatively small, population-based IGRA survey in the intervention and control arms before the onset of the trial. This would likely happen in "rolling" fashion – in other words, study clusters would be allocated to different waves. Those in Wave 1 would first have the pre-intervention IGRA survey performed. Then, while the intervention clusters in Wave 1 receive the intervention, the pre-intervention IGRA survey would move to Wave 2, etc. One year after the pre-intervention survey in each wave, the survey team would return to those clusters (intervention and control) for the post-intervention survey. In this fashion, all clusters in the trial would receive a pre-intervention and post-intervention survey, one year apart – thereby enabling an estimate the annual risk of TB infection in the two arms and of the difference between arms. We would then link these estimates to a mathematical model of TB transmission to project future changes in TB incidence and mortality over a longer (e.g., 5- and 10-year) time horizon.

The endpoint of IGRA conversion has been widely used in studies of candidate TB vaccines (e.g., Nemes et al, NEJM 2018; 379:138; Munseri et al, Vaccine 2020; 38:7239) and also in trials of individual-level prevention of infection (e.g., Dias de Oliveira et al, AJTMH 2020;103:1466), but to our knowledge has not been used in studies of population-level TB interventions such as the one proposed. It is therefore important to lay the analytical groundwork for evaluation of this outcome as a potential primary trial outcome for – including its role in modeling analyses to project the longer-term impact of the trial intervention.

Approach

Our proposed approach over the six-month planning phase (October 2022 through March 2023) would be as follows:

1. Review the scientific literature to inform a likely range of possible IGRA/skin-test conversion (and reversion) rates and appropriate IGRA cutoff values in the study area.
2. Use a simple mathematical model to estimate the levels of reduction in conversion rates that would likely correspond to a 25% reduction in incidence and mortality over 5 years (comparing the intervention to the control arm), as well as the appropriate timing of outcome measurement to correlate to this effect.
3. Based on the results of (1) and (2) above, perform sample size calculations to inform the size of a serial IGRA/skin-test survey that would be required to detect a difference corresponding to a 25% reduction in incidence and mortality.
4. Convene (virtually) a panel of TB experts and statisticians to obtain external review of our assumptions and methods. This would include one pre-analysis call (in November) to obtain initial thoughts on the approach, and one post-analysis call (in January) for review of calculations and estimates.
5. Provide the framework for a more detailed model of TB transmission (expanding on the simple model in step 2 above) that could use observed reductions in IGRA/skin-test conversion to project longer-term reductions in TB incidence and mortality.
6. In consultation with IRD, GiveWell, and other external consultants, identify secondary outcomes (e.g., changes in TB mortality, post-trial TB prevalence) that could bolster confidence in our primary outcomes and link with the model outlined in step 5 above.
7. Develop the outline of a Statistical Analysis Plan for a “TB Step Change” trial, including input on the appropriate geographic scale of randomization and analysis.

Timeline and Deliverables

Our proposed timeline and deliverables would include:

Oct 31, 2022: Document summarizing literature estimates of likely rates of IGRA/skin-test conversions and approach to estimate the likely conversion rate in the study area
November 2022: Initial panel held (including development of introductory materials)
Jan 15, 2023: Draft report, including results of simple model designed to estimate minimum important difference in IGRA/skin-test conversion rate and sample size estimates for the trial
January – February 2023: Follow-up panel held (structured around the draft report above)
Mar 31, 2023: Final report, including framework for a transmission model to project longer-term outcomes from IGRA/skin-test conversion rates and outline of a Statistical Analysis Plan

Budget and Justification

Our proposed budget includes funding for salaries, external consultants, and indirect costs. Please note that JHU applies a federally negotiated 63.75% indirect cost rate to all research-related grants. However, if a funding organization has a written policy on indirect costs that pre-dates the awarding of this grant, JHU will generally accept the terms of that policy for an award of this size. The budget below is crafted in anticipation that a funding agency might have a policy of no more than 10% indirect costs. However, this is contingent on receipt of a written policy – if no such policy exists, then the 63.75% level will apply, and we may need to reduce the volume of deliverables accordingly.

David Dowdy, PI: $14,405 (10% effort for 6 months; salary $215,000; 34% fringe)
Sourya Shrestha, Assistant Scientist: $7,571 (10% effort; salary $113,000; 34% fringe)
Tess Ryckman, Assistant Scientist: $61,417 (83.3% effort; salary $110,000; 34% fringe)
External Consultants: $10,000 (5 members, 2 meetings, $1000 per meeting)
Indirect Costs (10%): $9,339
Total Budget: $102,732

Dr. Dowdy will be responsible for team management and oversight of the project and will take final responsibility for all deliverables. Dr. Shrestha will oversee the modeling efforts, including construction of simple transmission models to link IGRA conversion rates to anticipated reductions in incidence/mortality and project the longer-term impact of the intervention (steps 2 and 5 above). Dr. Ryckman will perform the literature review, prepare materials for the external panel, write the model code, perform sample size calculations, and write the first draft of all reports. External consultants will be offered $1000 per meeting to compensate them for their time in reviewing materials, attending a two-hour virtual meeting, and providing written recommendations on the basis of that meeting.