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PERSPECTIVES

An aspiration to radically shorten phase 3 TB vaccine trials

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A new tuberculosis (TB) vaccine is a high priority. However, the classical development pathway is a major deterrent. Most TB cases arise within two years after *M. tuberculosis* exposure, suggesting a three-year trial period should be possible if sample size is large to maximise the

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number of early exposures. Increased sample size could be facilitated by working alongside optimised routine services for case ascertainment, with strategies for enhanced case detection and safety monitoring. Shortening enrolment could be achieved by simplifying screening criteria and procedures and strengthening site capacity. Together, these measures could enable radically shortened phase 3 TB vaccine trials.

Key words: tuberculosis, vaccine, trial

MAIN POINT

A new tuberculosis vaccine is urgent but licensure requires clinical trials that take many years. Options for an accelerated phase 3 TB vaccine prevention of disease trial through increasing trial sample size and shortening the enrolment period are discussed.

Tuberculosis (TB) is responsible for over 1.5 million deaths annually(1). The BCG vaccine is inadequate to facilitate TB elimination, but there are only three new TB vaccines (VPM1002; M72/AS01E; MTBVAC) currently entering phase 3 prevention of disease (POD) trials. Recently, stakeholders emphasized the need to explore innovative TB vaccine designs and build trial capacity in high-incidence countries (2). In addition, careful selection of trial endpoints is important to optimise trial efficiency (3).

Lessons from COVID-19 include conducting human trials and phases in parallel, mobilisation of large-scale funding, harmonisation of efforts and use of efficient designs(4). For *M. tuberculosis*, the annual risk of infection is estimated to average only 2% in TB endemic settings (5), rarely reaching up to 10% (6). Furthermore, fewer than 10% of those with new *M. tuberculosis* infection progress to TB disease in five years (7). Phase 2b TB vaccine trials recruit around three thousand participants with up to three years of follow-up (8, 9). Phase 3 trials then randomise tens of thousands of individuals with around five years of follow-up.

However, noting that the majority of those who progress to TB disease do so within two years after *M. tuberculosis* exposure (10), a robust phase 3 adolescent/adult POD TB vaccine trial may only need two to three years of follow-up if a sufficient number of participants are exposed to *M. tuberculosis* early after receiving vaccination/placebo. Here we consider options to achieve a shortened trial in relation to study size, participant characteristics and enrolment procedures.

STUDY SIZE AND PARTICIPANTS

a) One (more standard) approach to accrue the required number of TB cases without having to increase the study size is to focus enrolment on high-risk sub-populations, such as people with directly impaired immunity (eg. people with HIV have an up to 37-fold increased risk of developing TB (11) and

people with Diabetes a two times increase(12)), a positive Interferon Gamma Release Assay (IGRA; two times increased risk versus a negative test(13)), or contacts of TB cases in the first two years after exposure.

- An advantage of this approach is that the higher incidence of disease will accrue endpoints more quickly.

- The limitations include that these populations may be of small size and not representative of those to which the vaccine will eventually be given. In addition, those with immunocompromise have relatively weak immune responses, potentially leading to an underestimate of vaccine efficacy. Further, TB case contacts can be considered for post-, but not pre-exposure vaccine trials. Finally, TB preventive treatment (TPT) is indicated in people with HIV and young children (plus older children and adults in some settings) who are household contacts of a TB case.

b) Another approach, which could enable a larger study size, is to work alongside and optimise routine health services for case detection. This is usually reserved for post-licensure phase 4 evaluations, but was part of the case-finding strategy of the Chingleput BCG trial in India (14). Such an approach should aim to maximize case capture as well as support increased capacity to detect cases, while still requiring and ensuring robust case confirmation ascertainment according to the protocol.

- An advantage of this approach is that the cost per study participant may be reduced, enabling enrolment of a larger number of individuals within a short timeframe. Improved routine passive case detection systems would strengthen the health system with better standardisation of indications and diagnostic processes and quality assurance capacity building. The use of routine services would support generalizability of trial findings to real life conditions.
- A limitation of this approach is that use of routine services for case capture may lead to a reduced incidence of endpoints accrued and identify cases that would be in general more severe. However, possible late or under- diagnosis is likely to be non-differential, and vaccine efficacy estimates would not be affected, as high diagnostic specificity would be maintained. Extra sample collection and processing may be challenging with this design, limiting study of, for example, immunological correlates of protection.

There could be four additional enhancements to such a trial design:

i) For licensure, a minimum number of participants, consecutively enrolled from the beginning, could have active follow-up for safety and TB disease through regular clinic attendance. A planned early interim safety analysis could be done. The remaining participants could be monitored using an intensified Adverse Drug Event reporting system, supported by providing participants access to phone/web-based safety monitoring. These systems could also remind them to present to clinics for diagnosis when unwell.

ii) Routine case detection could be supplemented with active case finding among contacts of incident TB cases found during follow-up. If a high proportion of a defined population participates in the trial, then a high proportion of cases diagnosed during follow-up will have contacts who had been enrolled and received vaccine or placebo. These could be actively investigated as a 'high-risk' sub-population. Case contact recruitment can also support assessment of vaccine efficacy against *M. tuberculosis* transmission.

iii) An end-of-trial TB prevalence survey in those enrolled could be conducted based on both chest X-ray and symptom driven GeneXpert sputum testing (15). A prevalence survey was used in the BCG trial in Chingleput, which followed 90,000 individuals (14).

iv) Follow-up of all participants could continue until the last person randomised completes 2 years of follow-up, as has been done in other trials (16), and provides a median participant follow-up period of approximately 2 ½ years.

- Advantages of these enhancements include that active case-finding of household contacts of identified TB cases engages a high-risk group and a prevalence survey addresses the potential problems associated with cases being missed by passive detection. A secondary endpoint of asymptomatic, subclinical, X-ray positive TB disease could also be introduced.

- Limitations include that active case finding in household contacts may add only a small percentage increase to diagnosed case accrual. Also, fewer incident index TB cases in the intervention arm potentially will lead to fewer households undergoing active case finding than in the placebo arm, which may require an adjusted statistical analysis. Further, a prevalence survey adds significant costs and one assumes that pathology in missed cases persists until the end of follow-up.

REDUCING ENROLMENT TIME

Reducing enrolment time to increase the numbers able to be recruited might be achieved in a number of ways:

a) Trial enrolment may be quicker if results from pre-enrolment testing for *M. tuberculosis* infection are not required to determine eligibility.

- The advantages of this approach include quicker recruitment. The study population may also be more consistent with the population in which the vaccine will eventually be rolled out. Local populations will most likely be well characterised pre-trial, through observational studies of *M. tuberculosis* infection and disease.

- The limitations of this approach include the lack of testing for *M. tuberculosis* infection. However, batch IGRA testing could still be carried out, enabling stratification of efficacy and safety results by infection status. Furthermore, the benefit may be negated by the turnaround times of other tests required at screening.

b) Pre-enrolment testing for TB disease could be limited to symptom screen and GeneXpert sputum testing; this approach could also be used during the trial for case capture, in participants first screened for TB symptoms. Testing for TB disease would then identify clinical TB disease in need of treatment. Sputum culture could be done in those who are GeneXpert positive, to study the influence of strain on efficacy (17).

- The advantages of this approach include that chest x-ray and sputum culture could be avoided at enrolment, with little reduction to sensitivity to detect clinical TB disease (15).

- A limitation of this approach is that if the vaccine does not protect against subclinical disease, observed vaccine efficacy would be reduced. Incident TB cases occurring in the first few months of trial follow-up could be excluded to address this (9).

c) Trial enrolment may be quicker if the number of trial sites is increased.

- An advantage of this approach includes that larger numbers of trial participants can be enrolled and randomised within a short period.

- The limitations include that increasing the number of trial sites might increase the administrative complexity and cost.

CONCLUSION

A phase 3 adolescent/adult POD trial of three years' duration requires both a short enrolment time and a very large study population to maximise the number of early *M. tuberculosis* exposures post-vaccination. Such a design would have the added benefit of increased generalisability (figure). Important considerations such as costs, combining phases 2b and 3, and formal sample size calculations should be explored. Operational research could explore feasibility, speed, and efficiency gains. Trial simulation modelling could help prioritise design components. Formal observation beyond the trial period could help understand longer term effectiveness and safety, as done for COVID-19 and Hepatitis B vaccines (18, 19). Consensus-building consultations may be needed with regulators, local authorities and country TB programmes. Pre-trial capacity strengthening and epidemiological studies would be important. Domestic and international funders, policy and regulatory bodies should come together to achieve this aspiration, and accelerate the time to potential availability of a new TB vaccine.

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Table. Advantages and limitations of proposed approaches to phase 3 clinical POD tuberculosis vaccine trial design

Proposed approaches	Advantages	Limitations
Traditional design		
Enrol high-risk populations	Higher number of endpoint accruals per population over the study period	Non-representative of ultimate target population

		May have weak immune responses leading to an underestimate of vaccine efficacy
		Due to known high-risk, preventive therapy may be mandatory
Alternative design		
Enhanced routine passive case detection	Cost per TB case detected is likely to be much lower	Cases detected by routine health services may be more advanced clinically
	May more accurately measure 'real-world' effect of vaccine	Risk of reduced case capture and under-diagnosis of incident TB cases
Non-reliance on TST/IGRA testing at screening	More representative of target population	Study may be sub-optimally balanced in relation to the proportions with and without *M. tuberculosis* infection
	TST/IGRA testing can be performed late, in batches efficacy estimates generated according to baseline infection status	Potential source of bias if vaccine efficacy is different according to baseline infection status
Limit pre-enrollment testing to symptoms and Xpert	Sensitivity to detect clinical TB will remain high despite reduction in testing	May affect ability to estimate vaccine efficacy against subclinical TB
Increase site capacity	Required number of participants can be enrolled within a short period	Increased cost and logistical challenges

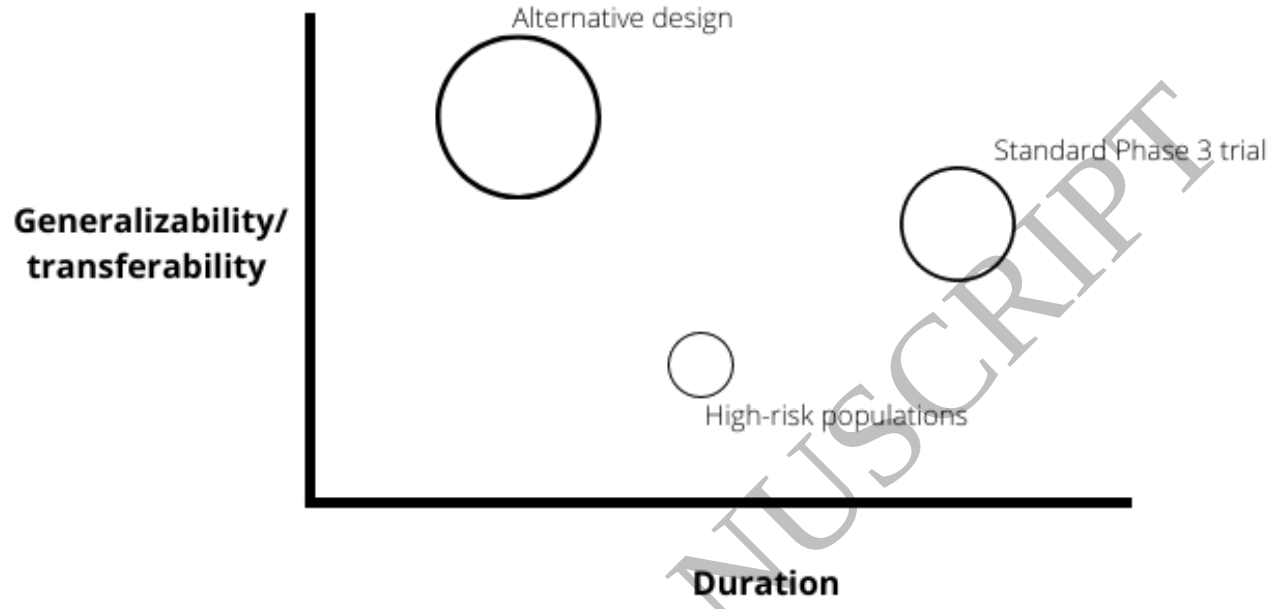

Figure. Expected changes to generalizability/transferability and study duration of three basic phase 3 Prevention of Disease phase 3 tuberculosis vaccine trial designs. The size of the circles reflects the different size of the study populations required.

Notes. Alternative design: This includes measures to increase study size and reduce enrolment time ; High risk populations: These can include, for example, people with HIV, people with diabetes, and TB case contacts.