

Questions and Answers on Tuberculosis Vaccines

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What is the current status of tuberculosis vaccine development?

The only existing vaccine against tuberculosis (TB), Bacille Calmette-Guérin (BCG), created in 1921, has variable protective efficacy. WHO recommends vaccinating HIV-uninfected infants with BCG as it provides protection against severe extrapulmonary (non-lung) forms of paediatric TB¹. However, BCG is unreliable in protecting against pulmonary TB, which accounts for most of the disease burden worldwide. A safe, effective and affordable TB vaccine would represent a major advance in the control of the disease. Several vaccine candidates are currently at different stages of preclinical or clinical development². The most advanced candidate, a poxvirus (“Modified Vaccinia Ankara”, MVA)-vectored vaccine expressing the immune-dominant Mycobacterium tuberculosis antigen 85A, developed by Oxford-Emergent consortium, has recently been evaluated in an infant phase IIb “Proof-of-concept” (PoC) trial in South Africa.

What were the design and the main objectives of the infant study in South Africa?

The study population included in the analysis consisted of 2794 BCG-vaccinated, HIV-negative infants aged 4–6 months, with both study arms almost equally sized. 1399 infants have received one dose of MVA85A, while 1395 infants in the control arm received placebo (Candin, a *C.albicans*-derived skin test antigen). Follow-up was up to 37 months. The primary objective of the study was to assess the safety of MVA85A in these infants. The secondary objectives were to evaluate efficacy of the vaccine against (a) the disease and (b) *M. tuberculosis* infection. This distinction is important as infection only leads to formal TB disease in a small minority of immune-competent individuals. Additional objectives included the evaluation of immunogenicity. Safety, efficacy and immunogenicity results are described in a recent publication.³

What conclusions can be drawn from the results of the PoC phase IIb trial ?

This is the first clinical trial conducted to evaluate the efficacy of a new TB vaccine candidate against clinical TB or *M. tuberculosis* infection, and results are therefore of considerable interest to the vaccine research as well as the public health communities.

In this trial, MVA85A appears to be safe and well tolerated, confirming similar findings from previous phase I and phase IIa clinical trials using this vaccine. None of the observed serious adverse events (or deaths) observed in the study arm were assessed by the sponsors as being related to the vaccine and only one serious adverse event involving brief hospitalization occurred in the placebo group.

The efficacy analysis is based on the number of TB cases amongst the vaccinated versus control subjects. In the vaccine arm, there were 32 cases, while in the placebo arm there were 39 cases. Based on this, the calculated vaccine efficacy is 17.3% (95% CI: -31.9% to 48.2%) for the primary TB case definition, which is not statistically significant. Moreover, there was no evidence of protection against *M. tuberculosis* infection: using the Quantiferon-TB Gold assay as the read-out, 349 out of 2792 infants became infected, respectively 178 in the vaccine arm and 171 in the placebo arm, a calculated vaccine efficacy of – 3.8% (95% CI: -28.1% to 15.9%).

What are the implications for future studies of this and other TB vaccine candidates?

Phase IIb PoC trials are designed to allow “triage” of vaccine candidates and target populations, in order to decrease the risk for entering into hugely complex and resource consuming phase III trials. Current regulatory rules require a phase IIb PoC trial to be corroborated in larger phase III trials before a vaccine can be licensed. Over-interpretation of phase IIb trial results should therefore be avoided.

So, what can be drawn from the absence of a significant efficacy of the vaccine, as shown in this infant trial ?

- First, it is important to remember that this vaccine was given months after all the infants had received BCG vaccine. It is therefore possible that BCG may have provided a plateau level of protection, with very little, if anything to be added on by MVA85A.
 - Second, South Africa, and in particular the Western Cape province, has exceptionally high rates of TB in all age groups, including young children, which may be difficult to address by any vaccine. Therefore, one cannot assume that similar results would have been obtained in different populations.
 - Third, adults may be a better target population for this vaccine, as immunogenicity might be better than in infants. Not least, adults are the primary source of transmission as they more likely develop the contagious form of the disease and represent the major part of the burden of TB disease worldwide. It must be noted, in this regard, that this vaccine is currently being evaluated in HIV-infected adults in South Africa and Senegal, using a 2-dose regimen.
 - Finally, there are several other TB vaccine candidates in the clinical pipeline which differ from MVA85A both in their antigenic composition and in the way these antigens are delivered.
- For all these reasons, results of this trial should not be considered as providing any definitive answer to the question of whether a new TB vaccine can provide better protection than BCG alone, and further studies of this and other vaccines are therefore urgently needed.

How is WHO involved in tuberculosis vaccine research efforts?

The role of WHO is to advise and guide the TB vaccine development activities of the global research community. This includes scientific consensus-building, guidance on vaccine evaluation, and assessment of the evidence base for policy recommendations on vaccine introduction and use. WHO also provides guidance to national regulatory agencies on approaches and methodologies related to the assessment, licensure and surveillance of vaccines. In addition, the mechanism of WHO prequalification ensures that vaccines supplied to countries through UN agencies meet international standards for quality, safety and efficacy and are appropriate for the target population. More information on TB-vaccine development and TB in general is available at http://www.who.int/vaccine_research/development/tuberculosis/en/index1.html , and <http://www.who.int/topics/tuberculosis/en/>.

References

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