Tuberculosis vaccines: time to reset the paradigm?

Ajit Lalvani, Saranya Sridhar, C Fordham von Reyn

The recent publication of a Phase IIb efficacy trial of the tuberculosis vaccine candidate MVA85A represents the long awaited outcome of the hopes and investment of a global research endeavour seeking a giant leap in tuberculosis control. MVA85A, a modified vaccinia virus expressing the *Mycobacterium tuberculosis* (*Mtb*) 85A antigen, is designed to improve on the currently available vaccine Bacillus Calmette-Guérin (BCG) and is the first among a number of novel vaccine candidates to enter a Phase IIb efficacy trial in infants. Given that the immunological rationale underpinning the development of MVA85A is shared by 9 out of 14 vaccines in clinical trials, the lack of efficacy in this recent pivotal trial is a significant setback to the tuberculosis vaccine community. The results of this trial therefore have far reaching implications for the current dominant approach to vaccine development and highlight several gaps in the current strategy.

In a randomised placebo-controlled trial, 2797 BCG vaccinated infants at a trial site in South Africa were enrolled between 4–6 months of age and administered either one intradermal dose of MVA85A or a placebo. The participants were actively followed every 3 months to identify tuberculosis infection or disease for a median of 24 months. Although, MVA85A induced strong antigen-specific CD4 multicytokine-secreting T cell responses 28 days after vaccination, there was no evidence of increased efficacy against tuberculosis disease or infection over and above that of BCG. The disappointment in the failure of this vaccine in infants, which has been 15 years in the making, needs to be tempered by the opportunity to learn lessons and consider alternative strategies. In the words of Winston Churchill, ‘Success consists of going from failure to failure without loss of enthusiasm.’

The immunological rationale for MVA85A and other similar vaccines is the induction of a high frequency of CD4 and CD8 Th1 cytokine-secreting T cells specific for a single or a few immunodominant *Mtb* protein antigens. This is based on solid evidence of the necessity of these T cells in mediating protection against *Mtb* in numerous animal models. In humans, while Th1 T cells are necessary in controlling *Mtb* (as evidenced by the HIV-TB co-infection epidemic) they are not sufficient for protection and do not correlate with vaccine-induced protection. Yet, MVA85A and 8 of 14 TB vaccine candidates in clinical trials are primarily designed to induce these T cells whose induction has long been taken as a marker of protective efficacy. The lack of a correlate of protective immunity thus currently bedevils tuberculosis vaccine development and evaluation and is the first gap that needs to be bridged by the tuberculosis vaccine community.

The second knowledge gap relates to the appropriate choice of animal models in the preclinical vaccine development pathway. Animal challenge models of *Mtb*, especially rodents and rabbits used to evaluate vaccine immunogenicity and efficacy have shortcomings and cannot replicate the susceptibility, pathophysiology or spectrum of disease observed in humans. Unlike the small animal models which offer pragmatic advantages over small animal models, such as the bovine model, in which protection against infection can be robustly assessed. Therefore, it is critical for each vaccine candidate to match the intended site of action in the natural history of tuberculosis to the appropriate animal model during preclinical testing.

The third gap is the insufficient attention in tuberculosis vaccine development accorded to the extensive examples of human immune protection against tuberculosis. Both natural mycobacterial infection and several types of mycobacterial vaccines have been shown to protect against tuberculosis. Immunopathological studies have revealed that natural infection with non-tuberculous mycobacteria (NTM) or contained latent *Mtb* infection reduce the risk of disease on subsequent exposure to *Mtb*. Vaccine-induced protection against *Mtb* in humans has been demonstrated following immunisation with live mycobacteria such as BCG and *Mycobacterium microti*, as well as by immunisation with inactivated whole-cell vaccines such as *M. bovis* and vaccines derived from NTM.

Thus, all documented instances of immune protection against tuberculosis in humans have involved polyantigenic exposure or vaccination with whole mycobacteria. A recent longitudinal study from Tanzania indicates that HIV-infected adults immunised with BCG at birth who have polyantigenic
responses to mycobacteria at baseline have a reduced risk of subsequent tuberculosis compared with those with pauciantigenic responses. The only new TB vaccine to be tested in large-scale clinical trials is an inactivated whole-cell NTM vaccine (DAR-901). Collectively these observations suggest that polyantigenic mycobacterial responses, including responses to secreted, cell wall and cytosolic antigens, may induce the necessary innate and adaptive immune mechanisms required for protection against tuberculosis in humans. Studies to identify a surrogate marker for vaccine-induced protection, another crucial gap in tuberculosis vaccine development, should focus not only on responding cell phenotypes and cytokines but also on the breadth of mycobacterial antigens to which responses are induced.

There are currently 14 candidate vaccines in clinical trials and over 40 next-generation candidates in preclinical testing. Table 1 summarises the range of vaccine types in clinical trials and over 40 next-generation vaccines in preclinical testing. The table includes information on the type of vaccine, proposed use, clinical endpoints, and efficacy in NHP and/or BCG models.

### Table 1: Tuberculosis vaccine candidates in clinical trials

<table>
<thead>
<tr>
<th>Clinical trial status</th>
<th>Vaccine name</th>
<th>Description</th>
<th>Type of vaccine</th>
<th>Mono/Pauci/Polymantigen</th>
<th>Proposed use</th>
<th>Clinical end-points</th>
<th>Efficacy tested in NHP and/or BCG</th>
<th>Efficacy greater than BCG in NHP and/or BCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III DAR-901</td>
<td>Whole cell non-tuberculous mycobacteria</td>
<td>Inactivated mycobacteria</td>
<td>Polyantigen</td>
<td>Boost BCG</td>
<td>Prevention of tuberculosis disease in adolescents and adults</td>
<td>Bovine</td>
<td>No</td>
<td></td>
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<tr>
<td>Phase IIb MV Ag85A</td>
<td>Modified Vaccinia Ankara vector expressing antigen 85A</td>
<td>Viral vector</td>
<td>Monoantigen</td>
<td>Boost BCG</td>
<td>Prevention of infection, disease and reactivation</td>
<td>NHP and Bovine</td>
<td>No6</td>
<td></td>
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<tr>
<td>Phase IIb AERAS-402/</td>
<td>Adenoviral vector expressing antigen 85A, 85B, TB10.4</td>
<td>Viral vector</td>
<td>Pauciantigen</td>
<td>Boost BCG</td>
<td>Prevention of infection and disease</td>
<td></td>
<td></td>
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<tr>
<td>Crucell Ad35</td>
<td>Phase I H1-CAF01 Recombinant fusion protein</td>
<td>Recombinant live attenuated mycobacteria</td>
<td>Polyantigen</td>
<td>Boost/Replace BCG</td>
<td>Prevention of infection and disease</td>
<td></td>
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<tr>
<td>Phase II VPM 1002</td>
<td>Recombinant BCG strain expressing listeriolysin and carrying a urease deletion</td>
<td>Recombinant protein</td>
<td>Polyantigen</td>
<td>Replace BCG</td>
<td>Prevention of infection and disease</td>
<td>NHP</td>
<td>Yes17</td>
<td></td>
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<tr>
<td>Phase II RUTI</td>
<td>Liposomed fragments of Mtb</td>
<td>Whole cell vaccine</td>
<td>Polyantigen</td>
<td>Adjunct to LTB INH prophylaxis/Boost BCG</td>
<td>Prevention of infection, disease and reactivation</td>
<td></td>
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<tr>
<td>Phase II M72</td>
<td>Recombinant fusion protein of Mtb antigens RV1196 and RV0125 with AS01 adjuvant</td>
<td>Recombinant protein</td>
<td>Pauciantigen</td>
<td>Replace BCG</td>
<td>Prevention of infection and disease</td>
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<tr>
<td>Phase II H1-IC31</td>
<td>Recombinant fusion protein of Mtb antigens 85B, ESAT-6 with IC31 adjuvant</td>
<td>Recombinant protein</td>
<td>Pauciantigen</td>
<td>Boost/Replace BCG</td>
<td>Prevention of infection and disease</td>
<td></td>
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<tr>
<td>Phase I AdAg8SA</td>
<td>Recombinant adenoviral vector expressing antigen 85A</td>
<td>Viral vector</td>
<td>Monoantigen</td>
<td>Boost/Replace BCG</td>
<td>Prevention of infection and disease</td>
<td>Bovine</td>
<td>No5</td>
<td></td>
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<tr>
<td>Phase I AERAS-422</td>
<td>Recombinant BCG strain expressing mutation PBoA and Mtb antigens 85B, 85B and TB10.4</td>
<td>Recombinant live attenuated mycobacteria</td>
<td>Polyantigen</td>
<td>Replace BCG</td>
<td>Prevention of infection and disease</td>
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<tr>
<td>Phase I rBCG30</td>
<td>Recombinant BCG strain expressing Mtb antigen 85B</td>
<td>Recombinant protein</td>
<td>Polyantigen</td>
<td>Boost BCG</td>
<td>Prevention of infection and disease</td>
<td></td>
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<tr>
<td>Phase I ID93/GLA-SE</td>
<td>Recombinant fusion protein of Mtb antigens RV2608, RV3619, RV3620 and RV1813 with GLA-SE adjuvant</td>
<td>Recombinant protein</td>
<td>Polyantigen</td>
<td>Boost/Replace BCG</td>
<td>Prevention of infection and disease</td>
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<tr>
<td>Phase I H4-IC31</td>
<td>Recombinant fusion protein of Mtb antigens 85B, 1B1.0.4 with IC31 adjuvant</td>
<td>Recombinant protein</td>
<td>Pauciantigen</td>
<td>Boost BCG</td>
<td>Prevention of infection and disease</td>
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<tr>
<td>Phase I H1-CAF01</td>
<td>Recombinant fusion protein of Mtb antigens 85B, ESAT-6 with CAFO1 adjuvant</td>
<td>Recombinant protein</td>
<td>Pauciantigen</td>
<td>Boost/Replace BCG</td>
<td>Prevention of infection and disease</td>
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<tr>
<td>Phase I H56-IC31</td>
<td>Recombinant fusion protein of Mtb antigens 85B, ESAT-6 and RV2660 with IC31 adjuvant</td>
<td>Recombinant protein</td>
<td>Pauciantigen</td>
<td>Boost/Replace BCG</td>
<td>Prevention of infection, disease and reactivation</td>
<td>NHP</td>
<td>No</td>
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</table>

*Mtb, Mycobacterium tuberculosis; NHP, non-human primate; BCG, Bacillus Calmette-Guerin.*
While the result of the MVA85A efficacy trial is a sobering reminder of the biological complexity of human tuberculosis, we are now compelled to identify and explore new alternative strategies for improved TB vaccines. It is critically important that as new clinical trial data become available we continue to dissect the nature of the immune responses in recipients of both effective and ineffective vaccines. Progress in the field of vaccinology is often an iterative process and we must maintain momentum by continuing to study promising vaccine candidates while simultaneously feeding back the knowledge gleaned from these trials to develop and improve immunisation strategies. At this key moment in the history of tuberculosis vaccine research, we might do well to heed the words of Francis Bacon: ‘From a closer and purer league between these two faculties, the experimental and the rational (such as has never been made), much may be hoped.’

Correction notice This article has been corrected since it was published Online First. The Corresponding author’s address has been updated and the abstract removed.

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