Tuberculosis vaccines: time to reset the paradigm?

Ajit Lalvani,1 Saranya Sridhar,1 C Fordham von Reyn2

ABSTRACT
Development of a more effective tuberculosis vaccine is a global public health priority. The first clinical efficacy trial of a new tuberculosis vaccine candidate in over 45 years recently reported its results. Unfortunately, the vaccine, MVA85A, showed no improved efficacy over BCG in preventing tuberculosis disease or infection in 2797 infants. This disappointing result has far-reaching ramifications because the majority of TB vaccine candidates in clinical trials broadly aim to induce the same type of immune responses as MVA85A. This compels close re-examination of the immunological paradigm underpinning the development of most new tuberculosis vaccines. Progress will require frank appraisal of the gaps in our understanding of protective immunity and appropriate use and interpretation of the available animal models. Identifying correlates of protection by dissecting immune responses induced by existing partially effective vaccines may be a good place to focus renewed efforts.

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 (Mtbc) 85A antigen, is designed to improve on the currently available vaccine Bacillus Calmette-Guerin (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.1 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 13 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 Mtbc protein antigens. This is based on solid evidence of the necessity of these T cells in mediating protection against Mtbc in numerous animal models. In humans, while Th1 T cells are necessary in controlling Mtbc (as evidenced by the HIV-TB co-infection epidemic) they are not sufficient for protection and do not correlate with vaccine-induced protection.2 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 Mtbc, 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.3 4 Unlike the small animal models which offer pragmatic advantages to evaluate vaccines, other animal models like the non-human primate (NHP) and bovine model using Mycobacterium bovis resemble human tuberculosis infection more closely and offer key complementary advantages over small animal models. NHPs can be infected with a physiological low-dose aerosol concentration and manifests latent infection and reactivation like humans. Cattle infected with M. bovis, the only natural host-pathogen animal model, show granulomatous and cell-mediated immune responses very similar to human tuberculosis and provide a natural transmission model unlike mice, rabbits or guinea pigs that do not transmit tuberculosis efficiently. It is notable that only 1 of the 14 vaccine candidates in clinical trials has shown efficacy superior to BCG in either the primate or bovine models (table 1). Another critical component in the demonstration of vaccine efficacy in animal models is the choice of the comparator. For example, in the NHP and bovine models MVA85A demonstrated efficacy compared with naive unvaccinated controls, but no greater efficacy than BCG, as in the Phase IIb clinical trial.5 6 Although it has now been proposed to advance vaccines only if they show efficacy in at least two animal models,7 the choice of these animal models needs to be predefined depending on the proposed action of the candidate vaccines.
<table>
<thead>
<tr>
<th>Clinical trial status</th>
<th>Vaccine name</th>
<th>Description</th>
<th>Type of vaccine</th>
<th>Mono/Pauci/Poly antigen</th>
<th>Proposed use</th>
<th>Clinical end-points</th>
<th>Efficacy tested in NHP and/or Bovine models</th>
<th>Efficacy greater than BCG in NHP/Bovine models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III</td>
<td>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&lt;sup&gt;16&lt;/sup&gt;</td>
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<tr>
<td>Phase Iib</td>
<td>MVA85A/AERAS-485</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>No&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phase Iib</td>
<td>AERAS-402/ Crucell Ad35</td>
<td>Adenoviral vector expressing antigen 85A, 85A, TB10.4</td>
<td>Viral vector</td>
<td>Pauciantigen</td>
<td>Boost BCG</td>
<td>Prevention of infection and disease</td>
<td>No</td>
<td>–</td>
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<tr>
<td>Phase II</td>
<td>VPM 1002</td>
<td>Recombinant BCG strain expressing listeriolysin and carrying a urease deletion mutation</td>
<td>Recombinant live attenuated mycobacteria</td>
<td>Polyantigen</td>
<td>Boost/Replace BCG</td>
<td>Prevention of infection and disease</td>
<td>No</td>
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<tr>
<td>Phase II</td>
<td>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>No</td>
<td>–</td>
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<td>Phase II</td>
<td>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>
<td>NHP</td>
<td>Yes&lt;sup&gt;17&lt;/sup&gt;</td>
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<tr>
<td>Phase II</td>
<td>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>No</td>
<td>–</td>
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<tr>
<td>Phase I</td>
<td>AdAg85A</td>
<td>Recombinant adenoviral vector expressing antigen 85A</td>
<td>Viral vector</td>
<td>Monoantigen</td>
<td>Replace BCG</td>
<td>Prevention of infection and disease</td>
<td>Bovine</td>
<td>No&lt;sup&gt;5&lt;/sup&gt;</td>
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<tr>
<td>Phase I</td>
<td>rBCG30</td>
<td>Recombinant BCG strain expressing Mtb antigen 85B</td>
<td>Recombinant protein</td>
<td>Pauciantigen</td>
<td>Boost BCG</td>
<td>Prevention of infection and disease</td>
<td>No</td>
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<td>Phase I</td>
<td>H4-IC31</td>
<td>Recombinant fusion protein of Mtb antigens 85B, TB10.4 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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<td>Phase I</td>
<td>H1-CAF01</td>
<td>Recombinant fusion protein of Mtb antigens 85B, ESAT-6 with CAF01 adjuvant</td>
<td>Recombinant protein</td>
<td>Pauciantigen</td>
<td>Boost/Replace BCG</td>
<td>Prevention of infection and disease</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Phase I</td>
<td>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&lt;sup&gt;18&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>Mtb</sup>, Mycobacterium tuberculosis; <sup>NHP</sup>, non-human primate; <sup>BCG</sup>, Bacillus Calmette-Guerin.
Priming vaccines designed to improve on BCG were required to improve on the efficacy of BCG in reducing bacillary burden in the murine model. Thus, vaccine testing was over-reliant on small animal models in which a reduction in bacillary burden could be easily measured. Since 2005, when BCG was shown to protect against \textit{Mtb} infection,\textsuperscript{8} vaccine candidates have begun to include prevention of infection as a clinical end point. However, this has not resulted in the concomitant adaptation of preclinical vaccine evaluation to routinely include 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.\textsuperscript{4,9}

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. Immunoepidemiological studies have revealed that natural infection with non-tuberculous mycobacteria (NTM) or contained latent \textit{Mtb} infection reduce the risk of disease on subsequent exposure to \textit{Mtb}.\textsuperscript{10,11} Vaccine-induced protection against \textit{Mtb} in humans has been demonstrated following immunisation with live mycobacteria such as BCG and \textit{Mycobacterium microti}, as well as by immunisation with inactivated whole-cell vaccines such as \textit{M. bovis} and vaccines derived from NTM.\textsuperscript{12,11} Thus, all documented instances of immune protection against tuberculosis in humans have involved polyantigenic exposure or vaccination with whole mycobacteria.\textsuperscript{12} 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.\textsuperscript{14} The only new TB vaccine to have demonstrated efficacy in a Phase III trial is an inactivated whole-cell NTM vaccine (DAR-901).\textsuperscript{15} Collectively these observations suggest that polyantigenic mycobacterial responses, including responses to secreted, cell wall and cysytolic 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, ranging from viral vectored, to recombinant BCG, to inactivated whole-cell vaccines. These vaccines are designed to work by preventing infection, disease, or reactivation or by improving response to treatment.

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.’

\textbf{Correction notice} This article has been corrected since it was published Online First. The Corresponding author’s address has been updated.

\textbf{Contributors} All authors were involved in the intellectual design and writing of the manuscript.

\textbf{Competing interests} AL is inventor of patents relating to \textit{T} cell-based diagnosis, prognosis, monitoring and vaccination of TB.

\textbf{Provenance and peer review} Commissioned; internally peer reviewed.

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Thorax published online June 7, 2013

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