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-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. 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 to evaluate vaccines, other animal models have been shown to protect against tuberculosis. Immunoepidemiological 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 vaccination or vaccination with whole mycobacteria. A recent longitudinal study from Tanzania indicates that HIV-infected adults immunised with BCG at birth who have polyantigenic
**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/ Poly antigenic</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</td>
</tr>
<tr>
<td>Phase IIb</td>
<td>MVAg85A/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</td>
</tr>
<tr>
<td>Phase IIb</td>
<td>AERAS-402/ Crucell Ad35</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>No</td>
<td>–</td>
</tr>
<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>
<td>–</td>
</tr>
<tr>
<td>Phase II</td>
<td>RUTI</td>
<td>Liposomes fragments of Mtb</td>
<td>Whole cell vaccine</td>
<td>Polyantigen</td>
<td>Adjunct to LTBI INH prophylaxis/ Boost BCG</td>
<td>Prevention of infection, disease and reactivation</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Phase II</td>
<td>M72</td>
<td>Recombinant fusion protein of Mtb antigens RV1196 and Rv0125 with A501 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</td>
</tr>
<tr>
<td>Phase II</td>
<td>H1-IC31</td>
<td>Recombinant fusion protein of Mtb antigens 85A, 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>
</tr>
<tr>
<td>Phase I</td>
<td>AdAg85A</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>No</td>
</tr>
<tr>
<td>Phase I</td>
<td>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>No</td>
<td>–</td>
</tr>
<tr>
<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>
<td>No</td>
<td>–</td>
</tr>
<tr>
<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</td>
</tr>
</tbody>
</table>

*Mtb,* Mycobacterium tuberculosis; NHP, non-human primate; BCG, Bacillus Calmette-Guerin.

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.’

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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