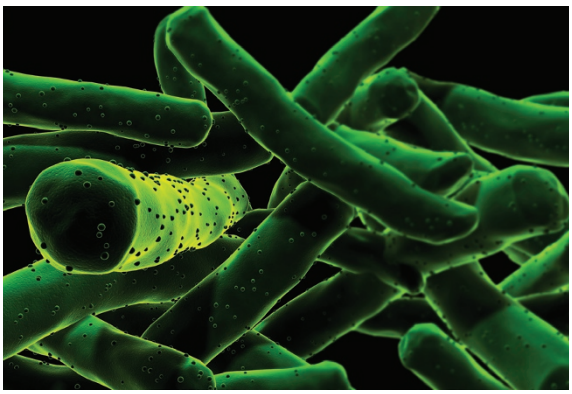
Bettering BCG: a tough task for a TB vaccine?

Despite the existence of the BCG (Bacille Calmette-Guerin) vaccine, tuberculosis remains a substantial global health problem. One issue with BCG is that although it effectively protects against disseminated tuberculosis in young children, it shows only variable protection against pulmonary tuberculosis. Thus, there is an ongoing quest for new tuberculosis vaccines that can improve upon BCG. One of these candidates, MVA85A, consisting of a modified vaccinia Ankara virus expressing the immunodominant *Mycobacterium tuberculosis* protein, has recently been tested in a phase 2b trial in South African infants previously vaccinated with BCG[1]. Although the primary objective of this trial was to assess vaccine safety, the efficacy of MVA85A against tuberculosis was only 17.3%, and there was no evidence for protection against *M. tuberculosis* infection. We asked the experts to comment on what this trial tells us about the actions of MVA85A and how the lessons learned can be extended to future trials of tuberculosis vaccines.



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Despite the inability of MVA85A to protect recipients from infection with *M. tuberculosis*, the trial represents a major milestone for clinical research in South Africa and for tuberculosis vaccine research around the world[1]. The failure of this vaccine to confer protection, while being substantially immunogenic, highlights the need for further research into true correlates of tuberculosis immunity.

MVA85A successfully elicited antigen-specific T helper type 1 (T_H1) and T_H17 $CD4^+$ T cell responses in vaccine recipients[2] that were predicted to be protective. However, these responses were not effective in preventing *M. tuberculosis* infection[1]. Thus, the identification of early biomarkers of the protective immunity against *M. tuberculosis* remains an important goal. High-throughput screening of leukocyte mRNAs and soluble immunomodulatory molecules in plasma from individuals vaccinated with MVA85A may help identify indicators of protection. Patient samples collected throughout the MVA85A trial should help inform future vaccine studies and may also aid in the identification of such biomarkers.

Additional insights may come from studying tuberculosis resisters—people who do not become infected with *M. tuberculosis* despite chronic exposure to the bacteria. Situating such studies in zones of elevated transmission risk within tuberculosis-endemic areas may aid in identifying these individuals. For example, work at the University of Cape Town has already begun to model zones of elevated transmission risk of tuberculosis on public transport by monitoring exhaled CO_2

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The World Health Organization estimates that there are 8.7 million new tuberculosis cases and 1.4 million deaths from tuberculosis annually. The emergence of multidrug-resistant forms of tuberculosis is devastating to patients, especially HIV-positive individuals, and to healthcare providers. The only tuberculosis vaccine, BCG, which was discovered in 1908 and is given to about 100 million children each year, prevents the most severe forms of tuberculosis in children, but it has only variable efficacy, ranging from 0–77%, in protecting adults[1].

> "We learned that without clear-cut protection it is not possible to fill the most challenging gap in our knowledge, namely identifying biomarkers of protection."

There are great expectations for a new vaccine that could boost the limited protection provided by BCG. The MVA85A vaccine had been found to produce some protection in mouse models of tuberculosis. However, a recent trial of this vaccine in 2,800 BCG-vaccinated children in South Africa revealed that, although it could prime for interferon-γ (IFN-γ) production and polyfunctional T cells, it failed to prevent either tuberculosis infection or disease[1], a disappointment for many.

All vaccines have historically

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concentrations as a proxy for air exchange[3].

Ongoing integration of translational and basic science research in tuberculosis-endemic settings represents a synergistic approach to improving our understanding of this disease, and it is crucial for progression toward an effective vaccine. The successful execution of the MVA85A vaccine trial in South Africa, brought about through substantial local and international collaboration, signifies a great achievement for the global tuberculosis community. Conducting high-quality research at the heart of the epidemic reflects a growing trend in the field, placing diseases that disproportionately affect the developing world at the top of the global agenda.

"The successful execution of the MVA85A vaccine trial in South Africa, brought about through substantial local and international collaboration, signifies a great achievement."

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derived from iterative processes. No vaccine trial, in my view, is a failure if we learn something important. Here we learned, as in mouse experiments, that IFN-γ is necessary but not sufficient for protection. We learned that the viral delivery system, which should have induced both T_H cells and cytotoxic T lymphocytes (CTLs), in this trial failed to induce a strong $CD4^+$ response or any $CD8^+$ T cell response, and perhaps that infants are not the best group on whom to initially test a new vaccine. We learned that without clear-cut protection it is not possible to fill the most challenging gap in our knowledge, namely identifying biomarkers of protection, which can only be derived from human protection trials. Perhaps we will relearn that mice are not great models for predicting protection in humans. Humans show very different pathology in *M. tuberculosis* infection, and human macrophages use a vitamin D–dependent mechanism to produce antimicrobial peptides not found in mice[4,5]. Recent data indicating that an IFN-β signature correlates with active disease[6] and that IFN-β inhibits the antimicrobial mechanism of human macrophages induced *in vitro* by IFN-γ[7] raise the question of whether viral vectors will be optimal for boosting tuberculosis protection in humans. Perhaps the most encouraging lesson from this study is that a large-scale and beautifully designed and implemented trial against tuberculosis can be carried out in a major disease-endemic country in Africa.

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The world urgently needs an efficient tuberculosis vaccine. Therefore, the recently published lack of efficacy in the phase 2b trial of the MVA85A vaccine[1] is very disappointing and has stimulated reflections in the tuberculosis vaccine community on what we potentially should do differently from now on.

When discussing lessons learned from this trial, it is important to bear in mind what a new, improved tuberculosis vaccine needs to achieve. The classical BCG vaccine protects children efficiently against disseminated disease, and this is probably the most convincing argument for its use. It is therefore clear that targeting BCG-vaccinated children, as in the recent MVA85A trial, may be neither the easiest nor the most urgently needed indication in the battle against tuberculosis. Observations from animal models have demonstrated that when BCG is at its best, there is only a relatively small window for improvement by a booster vaccine[8,9]. Therefore BCG's main limitation seems to be the fact that immunity only lasts 10–15 years, with the result that tuberculosis lung disease affects mostly the adult population. So, in light of this, why were infants chosen as a target for the first efficacy trial of a tuberculosis vaccine since the introduction of BCG 80 years ago? One answer is that the high prevalence of latent *M. tuberculosis* and the chronicity of the infection render clinical testing of candidate vaccines in the adult population much more logistically demanding, lengthy and costly.

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There is a strong pipeline of other leading tuberculosis vaccines that are currently in clinical trials. These vaccines promote immune responses that differ from MVA85A in both their specificity and quality and may still show efficacy in the infant population. However, given the negative outcome of the MVA85A trial in children, we now need to focus a considerable effort on understanding the requirements for a booster vaccine for the adult or adolescent population, taking into consideration that the majority of this population would be already latently infected with *M. tuberculosis*. There is still room for optimism, as the data from other age groups and other leading tuberculosis booster vaccines with a strong preclinical track record in animals with and without latent *M. tuberculosis* will start emerging in the coming years.

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