Prospects and challenges of a new live tuberculosis vaccine

An effective vaccine against tuberculosis is urgently needed. In this issue, Michele Tameris and colleagues report the results of a randomised, double-blind, dose-escalation trial of a new tuberculosis vaccine, MTBVAC, compared with BCG in a small group of adults and infants in South Africa. By contrast with most other novel tuberculosis vaccines, MTBVAC is a live vaccine based on an attenuated strain of Mycobacterium tuberculosis. With around 4000 genes and a broad functional armamentarium, ranging from dormancy and intracellular survival to immune escape, M tuberculosis has successfully infected humans for thousands of years. Thus, it is not surprising that around 25% of the world’s population is infected with this pathogen, which is transmitted via respiratory droplets. Although tuberculosis is now the deadliest infectious disease caused by a single pathogen, more than 90% of ostensibly immunocompetent individuals with M tuberculosis can successfully contain their infection, remain asymptomatic, and never develop the disease. Experimental results in non-human primates and epidemiological data from humans provide evidence that previous M tuberculosis infection protects against new infection. By analogy, one would hope that MTBVAC, in which two crucial M tuberculosis virulence genes (phoP and fadD26) have been deleted, could induce an immune state similar to latent tuberculosis infection and reduce the risk of subsequent active infection and disease.

The available BCG vaccine, which is based on an attenuated Mycobacterium bovis strain, was developed at the beginning of the 20th century. Several regions of difference, comprising hundreds of virulence genes, were deleted in BCG. These deletions afforded remarkable safety but could have compromised immunogenicity and protective efficacy. Even though BCG vaccination can lead to modest (around 19%) prevention of M tuberculosis infection and protects against the development of disseminated disease in early childhood, around 1 million children develop intrathoracic tuberculosis yearly in regions where the vaccine is administered. Furthermore, the BCG vaccine has variable and inadequate efficacy against pulmonary tuberculosis later in life.

After decades of research, a phase 2b trial in which BCG-vaccinated South African infants were boosted with MVA85A, a modified Vaccinia Ankara virus expressing antigen 85A, was unsuccessful. Subsequently, two other phase 2 trials of tuberculosis vaccines have provided highly promising results. Re-vaccination of M tuberculosis-uninfected South African adolescents with BCG (who had also received the vaccine as infants) had around 45% efficacy against sustained M tuberculosis infection. A novel subunit vaccine, M72/AS01e, which contains a fusion protein (comprising Mtb32A and Mtb39A), had vaccine efficacy of 54% against the development of microbiologically proven tuberculosis in adults infected with M tuberculosis in three African countries. Although these results are highly promising, the question remains: can they be improved upon?

In Tameris and colleagues’ trial, three doses of MTBVAC, which is given subcutaneously, were tested: 2.5 × 10⁴ colony-forming units (CFU), 2.5 × 10⁵ CFU, and 2.5 × 10⁶ CFU. The high dose, 2.5 × 10⁷ CFU, induced stronger durable, polyfunctional T-helper-1 CD4 cell responses than an equivalent dose of BCG. Although the protective efficacy against M tuberculosis infection and tuberculosis disease in both children and adults has yet to be established, these immunological data are encouraging. Tameris and colleagues report one case of probably viral aseptic meningitis in an MTBVAC-vaccinated adult with newly acquired HIV infection. Among the 28 MTBVAC-vaccinated infants, they report one death (likely to have been due to viral pneumonia), one case of unlikely tuberculosis, and one case of unconfirmed tuberculosis and two cases of pneumonia—an incidence consistent with previous observations in the same community. A high, dose-related frequency of positive interferon-γ release assay (IGRA) results (which were reported in seven of the nine infants who received the highest dose of MTBVAC), although unexpected based on the findings of a previous MTBVAC safety study in Swiss adults uninfected with M tuberculosis, suggests that the conversions were MTBVAC induced. If MTBVAC induces positive results, the diagnostic utility of IGRA as a blood test for M tuberculosis infection would be compromised in vaccine recipients. Because the risk of developing tuberculosis is highest within the first years after infection, IGRA conversion typically prompts initiation of preventive treatment with isoniazid or other drug combinations. The IGRA quantifies interferon-γ generated by CD4 lymphocytes in response...
to the immunogenic M tuberculosis proteins ESAT-6 and CFP-10, which are encoded by crucial virulence genes deleted from BCG but present in MTBVAC.\textsuperscript{5,12} Notably, the deletion of the transcription factor PhoP in MTBVAC reduces secretion (but not expression) of ESAT-6, but CFP-10 secretion is unaffected. Deletion of the ESAT-6 and CFP-10 genes in a modified MTBVAC strain resulted in decreased protective efficacy in mice, and thus both proteins are crucial to the vaccine’s immunogenicity.\textsuperscript{12}

In addition to safety, especially in immunocompromised recipients, the challenge in future trials will be to distinguish the effects of MTBVAC from natural M tuberculosis infection in vaccinated children. Because MTBVAC is a live vaccine, preventive therapy with isoniazid or other tuberculous drugs could plausibly reduce the immunogenicity and efficacy of the vaccine. However, withholding preventive therapy from infants with post-vaccination IGRA conversion in settings with a high incidence of tuberculosis would pose an ethical conundrum. The results of an analysis\textsuperscript{13} of quantitative IGRA values in South African children enrolled in the MVA85A TB vaccine trial might help to address this challenge. In that study, compared with non-convertors, convertors with IGRA values higher than 4-0 international units (IU) of interferon-γ per mL did not have a significantly increased risk of tuberculosis, whereas those within 0-35–4-0 IU/mL did not have a significantly increased risk of tuberculosis. Ideally, alternate IGRA independent of CFP-10 will be developed to diagnose new natural M tuberculosis infection in MTBVAC recipients. Until then, management of post-vaccination IGRA converters with more than 4 IU/mL interferon-γ (a concentration that was reported in only one of nine infants in both the 2·5 × 10⁴ CFU and 2·5 × 10⁵ CFU MTBVAC groups), would have to be individualised. Withholding of isoniazid or other anti-tuberculous preventive therapy in MTBVAC recipients with IGRA conversion but interferon-γ concentrations of less than 4-0 IU/mL, combined with clinical monitoring, seems unlikely to put children at risk. Furthermore, withholding of preventive therapy in this group would reduce the risk of side-effects of anti-tuberculous drugs and the risk of potentially jeopardising vaccine efficacy. Such management would also allow appropriate assessment of MTBVAC-induced correlates of protection against tuberculosis, the investigation of which should include all immune arms. The full spectrum of immune responses, mechanisms, and antigens involved, and their likely differential roles in prevention of M tuberculosis infection and disease development, are still not fully understood. Further studies of the promising live-attenuated MTBVAC vaccine could help to unravel the complex interplays that underlie the multiplicity of protective mechanisms needed to safeguard against tuberculosis.

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I declare no competing interests.


