New hope for tuberculosis vaccines

The tuberculosis vaccine field has seen exciting new results over the past 12 months following decades of disappointing research. First, it was shown that, in adolescents uninfected with *Mycobacterium tuberculosis* in South Africa, re-vaccination with BCG (the vaccine recommended by WHO for use in neonates to prevent childhood tuberculosis) could protect against sustained *M tuberculosis* infection. An efficacy of 45·4% (95% CI 6·4–68·1; p=0·03) was shown against a secondary endpoint: sustained conversion of the QuantiFERON-TB gold in-tube test, which measures the host response to infection.[1] Second, an experimental subunit tuberculosis vaccine, M72/AS01$_E$, comprising only two antigens, Rv1196 and Rv0125, formulated with a potent adjuvant, showed 54·0% (90% CI 13·9–75·4; p=0 efficacy in protecting against development of pulmonary tuberculosis in adults with latent infection.[2] This vaccine was tested in a phase 2b efficacy trial in South Africa, Kenya, and Zambia over a 2-year follow-up period.[2] Both results represent major scientific breakthroughs in tuberculosis vaccine research and strongly indicate that it could be feasible to develop a tuberculosis vaccine to impact the global tuberculosis epidemic.

Tuberculosis has affected humanity for millennia and remains a serious threat to human health and wellbeing. The disease is the leading cause of death from a single infectious agent globally. It is estimated that 10 million people became ill with tuberculosis, and a staggering 1·6 million people died from the disease in 2017 alone.[3] Tuberculosis is responsible for a quarter of annual deaths associated with antimicrobial resistance and remains the primary cause of death in people with HIV.[3]

WHO, through the End TB Strategy, has set a target of 90% reduction in new tuberculosis cases by 2030. Neither optimal delivery of the existing diagnostic and treatment strategies nor economic development will allow the full achievement of this ambitious target. Intensified research that results in development of new tools is therefore needed, especially the development of a new tuberculosis vaccine that is safe, affordable, and more effective than BCG in protecting against pulmonary tuberculosis in adolescents, adults, and older people. Economic modelling has suggested that a new, effective tuberculosis vaccine can have a large impact; a tuberculosis vaccine targeting adolescents and adults in low-income countries with 60% efficacy against pulmonary tuberculosis over a 10-year duration could prevent 17 million cases of tuberculosis disease (range 11–24 million) by 2050.[4] The same modelling also showed extraordinary cost savings to health systems.

Considering the magnitude of the tuberculosis epidemic, global investments toward combatting the disease are surprisingly low. This underfunding is documented in the G-Finder report.[5] Although overall global funding for research in neglected infectious diseases in 2017 was the highest amount ever recorded, investments in tuberculosis research and development have remained stable, fluctuating around US$600 million annually over the past 10 years.[5] The underfunding of tuberculosis research is even more striking when considering disease burden: the world invested approximately $375 in research and development for each fatal tuberculosis case in 2017, while the corresponding amount for HIV/AIDS was $1337, and $1434 for malaria. Moreover, only about 12–13% of tuberculosis investments are currently allocated to vaccine research and development, despite the recognised benefits of vaccines in controlling infectious diseases.

The early efficacy results of BCG revaccination and M72/AS01$_E$ should give hope to communities affected by tuberculosis and give confidence to funders that tuberculosis vaccines can be developed and delivered from the current pipeline. We should build on these results and make sure that they are taken forward and translated without unnecessary delay. It must be shown that safety and protective effects are reproducible and would apply to diverse populations with broad geographical representation. Ultimately, we need a vaccine that protects younger and older adults, adolescents, children, infants, and people infected with HIV living in tuberculosis endemic countries.

However, no matter how promising an experimental vaccine candidate might appear in early human efficacy testing, these vaccines inevitably carry some risk of failure and it is therefore important to maintain a broad portfolio of vaccine candidates. Present funding for tuberculosis vaccine research is already too sparse and there is a risk of simple redirection of funds into clinical

trials of the frontrunners, leaving important funding gaps behind. Additional support should be mobilised for rational testing of the rich and diverse preclinical and clinical portfolio of tuberculosis vaccine candidates, as well as discovery of further novel candidates.

To achieve this ambitious, yet attainable goal, global coordination is needed to optimise resources, share data, and overcome technical obstacles. Traditional donors of tuberculosis vaccine research are called upon to increase their commitments in this time of hope, and governments of countries with the highest tuberculosis burden should make investments now to yield the potential benefits over the next decade to 2030.

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