

The way forward for TB vaccines

Tuberculosis (TB) is now the largest single-pathogen cause of global adult mortality ¹; more than 10 million incident cases of disease occur worldwide every year. In 2018, global TB prevention, diagnosis and treatment efforts were estimated to cost US\$10.4 billion ². With such a high global burden, and a current average annual incidence rate decline of only 1.8%, new efficacious vaccines are urgently needed to accelerate progress towards the World Health Organization 'End TB' and elimination goals ¹.

The year 2018 was particularly uplifting for the field of TB vaccine development, as unprecedented results were reported from two proof of concept efficacy trials. *Van Der Meeren* and colleagues reported that the GSK subunit vaccine M72/AS01_E, consisting of *Mtb* antigens and monophosphoryl lipid A and QS21 formulated in liposomes as adjuvant, prevented pulmonary TB disease in adults already-infected with *Mycobacterium tuberculosis* (*Mtb*) ³. The vaccine efficacy in this phase IIB trial was 54% (95% CI, 3-78). *Nemes* and colleagues reported that bacille Calmette–Guérin (BCG) revaccination of previously-uninfected adolescents protected against *Mtb* infection, as defined by sustained conversion of the Quantiferon Gold In Tube test ⁴. The BCG revaccination vaccine efficacy was 45% (95% CI, 6-68) for this secondary study endpoint.

These results could translate into a significant breakthrough for TB prevention if the protective effects against pulmonary disease could be confirmed (for M72/AS01_E) or demonstrated (for BCG revaccination), and shown to be generalisable. For example, in India, preliminary mathematical modelling has suggested that a vaccine rolled out in 2025 with characteristics similar to those demonstrated for M72/AS01_E in the phase IIB trial, and with a duration of efficacy of 10 years, could, as a single intervention, reduce TB incidence in 2050 by around 40% ⁵.

For M72/AS01_E, a larger confirmatory trial, powered to improve the accuracy of efficacy estimates, is now needed. This trial could also explore whether age and gender affect protection, as suggested in secondary analyses based on a limited number of cases ³. Further investigations should also include examining protection in *Mtb*-uninfected persons and in high risk groups such as HIV-infected persons, and on what the duration of vaccine protection could be. Involving multiple geographies would be required to support generalisability of the findings. Investments are not only needed for the next phase of clinical trials, but also to ensure sustainable and affordable supply of vaccine antigens and adjuvant. Preparatory work on licensure and policy pathways, equitable access, and delivery should be initiated early to allow rapid implementation, should phase III trial results be positive.

The observation that adolescent BCG revaccination may prevent sustained *Mtb* infection also requires further investigation, for multiple reasons. The estimate of effect should be generated in trials with more precision, as the confidence intervals were wide ⁴. Then, whether prevention of *Mtb* infection translates into protection against TB disease should be characterized, as ultimately a policy recommendation for adolescent BCG revaccination by the WHO would likely require demonstration of prevention of pulmonary TB disease ⁶. At this stage, evidence appraisal would need to take into account previous studies of BCG revaccination showing little, or no, impact on prevention of tuberculosis disease ^{7–10}. Even if

confirmed, obstacles to delivery of BCG would include the current contra-indication of the vaccine in HIV-infected persons.

Multiple other TB vaccine candidates are currently in clinical development, mostly for prevention of adolescent/adult TB disease. Some candidates are being developed for BCG replacement in neonates, although this strategy is likely to have lower population level impact before 2050, than efficacious vaccination at older ages ¹¹. Three vaccines have entered, or are about to enter, efficacy trials for prevention of adult TB disease: two inactivated nontuberculous mycobacterial vaccines, *Vaccae* (Anhui Zhifei Longcom, contains *Mycobacterium vaccae*) and Immunovac (Cadila Pharmaceuticals, contains *Mycobacterium w*, aka *M. indicus pranii*), and a recombinant BCG vaccine (VPM-1002, Serum Institute India, contains a listeriolysin insertion and urease deletion). Three vaccines will be tested for ability to prevent recurrence of adult TB disease after successful cure: VPM-1002 and 2 novel subunit vaccines, ID-93/GLA-SE (IDRI, contains two *Mtb* antigens and glucopyranosyl lipid formulated in a stable emulsion as adjuvant) and H56/IC31 (States Serum Institut, contains three *Mtb* antigens and an 11-mer antibacterial peptide and a synthetic oligodeoxynucleotide as adjuvant). Vaccines that are currently being, or will soon be, tested for ability to prevent *Mtb* infection include DAR-901 (Dartmouth, contains inactivated *Mycobacterium obuense*) and ID-93. Prevention of infection trials have the advantage of requiring relatively small sample sizes, but then require prevention of disease confirmation. Multiple other viral vectored, subunit and whole cell vaccine candidates are in earlier clinical trials, including a recombinant *Mtb*, MTBVAC (Biofabri), which has two mutations rendering the organism at least as safe as BCG in animal models.

Among preclinical advances in 2018, a recombinant, attenuated cytomegalovirus (CMV) vaccine which expresses 6-9 *Mtb* antigens demonstrated the best protection against pulmonary *Mtb* challenge ever reported in non-human primates ¹². This vector induces immunity in this animal model regardless of pre-existing CMV exposure, and may have a mechanism of action that is distinct from most other TB vaccination approaches, by inducing effector T cells that are widely distributed in all organs, including the lung, and which are continuously replenished due to ongoing antigen expression (most T cell targeted vaccines induce a long-lived central memory T cell response). Human testing of this candidate is under intense preparation.

The TB vaccine field needs to move forward with a sense of urgency, and in a strategic, data-driven way. The current funding available for TB vaccines ¹³ will be insufficient to drive rapid progress, and therefore an increase and diversification of resources is required. Some of these resources should be used to increase clinical trial capacity, and to continue the discovery and advanced development of early pipeline candidates.

A better understanding of protective immunity against TB is critical. Toward this goal, samples available from the two recent efficacy trials ^{3,4} could now be examined to identify mechanisms and correlates of protection, which, in turn, may contribute to accelerate clinical testing of candidates and guide future vaccine discovery.

Models of vaccine use-case, in diverse geographical settings, should be developed to inform vaccine development strategies that could deliver most impact. Further modelling and health-economic research, into the public health impact and value of TB vaccines would

support rational prioritisation of investments. Last, but no means least, we need to prepare for success; prompt implementation of successful vaccination strategies will be critical to help prevent the more than 4000 deaths due to TB each and every day.

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