

More than 100 years after the first TB vaccine, why are we still waiting for a second?

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It has been more than 100 years since the first and only tuberculosis (TB) vaccine—the Bacillus Calmette–Guérin (BCG) vaccine—was used

for the first time medically in 1921. With an estimated 1.6 million people dying from TB in 2021, there is an urgent need for new vaccines to help stem the never-ending pandemic.

There are more than 10 TB vaccines currently in development, with some now in the later stages of the clinical trials process. In a presentation in one of the preliminary pre-ECCMID days of this year's European Congress on Clinical Microbiology & Infectious Diseases (ECCMID 2023, Copenhagen, April 15-19) Frank Cobelens, Professor of Global Health at the University of Amsterdam and the Amsterdam Institute for Global Health and Development (AIGHD), Netherlands, will discuss the frontrunners among the [candidate vaccines](#), and the challenges facing TB [vaccine](#) development.

"In order to reach the WHO's target of ending TB as a global health problem, we desperately need an effective and safe vaccine for use in adults and adolescents," explains Prof Cobelens.

"However, TB vaccine research and development is hampered by our limited knowledge of protective immune responses, poor prediction of efficacy in humans by animal models and lack of correlates of protection (the immune response required to give protection), all leading to a high-risk pipeline that includes large trials of long duration. Essentially, we don't know if vaccines will work until they are at the end of the clinical trials process—meaning high-risk, high cost."

Despite this, for the first time since decades there are several promising new TB vaccine candidates entering phase 3 trials (efficacy testing in humans), even though 2 of the 4 (VPM1002 and MTBVAC) are still live-attenuated vaccines just as BCG is— and for which the added value in terms of protection and safety over BCG is yet to be established.

"However, the current need for long trials implies that licensure of any

of these candidates will take at least several years," says Prof Cobelens. He adds that a key issue for WHO in licensing any new TB vaccine is evidence of prevention of disease (POD)—however many of the current trials are looking at prevention of infection (POI) or prevention of recurrence (POR) in those with latent infection—which are not quite the same as POD.

Prof Cobelens will highlight that, for the first time in decades there is a different platform candidate that has shown protection in adults and adolescents in a phase II trial: M72/AS01E (an adjuvanted subunit vaccine). This is also important because it allows the field to identify correlates of protection. In a trial of some 3500 participants in Kenya, South Africa, and Zambia, the vaccine demonstrated 50% protection against TB infection after three years follow-up. It was also safely tested in 400 people living with HIV.

This vaccine, licensed by pharmaceutical company GlaxoSmithKline to the Bill & Melinda Gates Medical Research Institute, is now going to enter a phase III trial in high-incidence settings across Africa, with an estimated 26,000 participants. It will include people never infected with TB and those with latent TB to see if they are protected from TB disease. But as the trial will require three years for recruitment and five for follow up, it is unlikely to provide results until the start of the 2030s.

Other vaccines considered frontrunners include the Russian Vaccine GamTBVac, currently in a phase 3 trial with 7000 participants expected to report in or around 2025. Also considered promising is the VPM1002 (live recombinant BCG), which is about report on trials on prevention of infection in babies and prevention of recurrence in adults in the next two years (delayed due to COVID pandemic)—while a further phase 3 trial, to test prevention of infection in adult household contacts of primary infected persons, is currently underway.

Another genetically modified live-attenuated vaccine, MTBVAC, has just begun a BCG-controlled phase 3 trial in babies in South Africa and Madagascar, while a phase 3 trial in BCG-vaccinated and unvaccinated adults is in its planning stages. Results from these trials are likely to be announced at the end of this decade.

"We have waited more than a century for a new effective TB vaccine, and unfortunately that wait is set to last at least several more years," concludes Prof Cobelens.

"However, there are promising new approaches that include alternative routes of delivery for BCG-vectored vaccines that will hopefully enter the development pipeline soon. We are also in the early stages of harnessing the vaccine innovation that emerged during the COVID pandemic—which could open the door on other new routes to a successful TB vaccine."

More information: [2022 Global TB report](#)

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