Title: What's next for BCG revaccination to prevent tuberculosis?

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Early this year, the world will have the confirmatory phase 2b trial results on whether Bacillus Calmette–Guérin (BCG) revaccination prevents tuberculosis (TB) infection, or more accurately, whether it prevents conversion to a positive interferon-gamma release assay (IGRA) test sustained over 6 months [1]. Unfortunately, despite rigorous analysis [2], BCG revaccination's ability to prevent TB infection is not a reliable indicator of whether BCG revaccination would prevent TB disease.

"No problem, just run a phase 3 prevention of disease randomised controlled trial" we hear you say. That would be ideal, but that trial is expected to be prohibitively expensive since the vaccine is thought only to work if given to TB-uninfected individuals, and few initially-TB-uninfected people would develop TB disease, requiring very large numbers to be enrolled and followed up for many years.

So, what could, or should, the world do with the results from this multi-million dollar confirmatory phase 2b trial, early this year?

If the confirmatory trial suggests that BCG revaccination prevents infection, a phase 3 randomised controlled prevention of disease trial in IGRA-negative individuals could be carried out. The advantage of this approach would be, that this would be the definitive test of whether BCG revaccination does indeed prevent disease in a IGRA-negative general population. The cons would include the extremely high cost and a long wait. A phase 3 prevention of disease study in IGRA-negatives could cost over $1.5 billion, far higher than the $550 million cost of the smaller M72 trial in IGRA-positive individuals [3] which itself was extremely difficult to raise funding for. Also, a phase 3 prevention of disease study among IGRA-negative individuals would likely take more than five years to implement, although potentially this duration could be reduced [4].

Of course, given BCG is already licensed, an evaluation of the programmatic rollout of BCG revaccination (aka a phase 4 study) could also be carried out. The advantage of that approach would be that, if the vaccine works, it would start saving lives years earlier. The cons include that rigorous evaluation of programmatic rollouts is difficult, so it may not generate sufficient evidence for the WHO policy change that would be needed for global uptake. Also, if BCG revaccination does not prevent disease, it would have been a large waste of resources and would have exposed large numbers of people to potential adverse effects, including the potential for disseminated disease in individuals with untreated HIV. Interestingly, the Indian government has just been reported to be planning a 'programme implementation' of BCG revaccination in 23 states, which may be evaluated over the first 2 years [5].

On the other hand, if the confirmatory trial shows that BCG revaccination does not prevent infection, in theory, a phase 3 RCT prevention of disease trial could still be carried out, because BCG revaccination's ability to prevent TB infection is not currently a reliable indicator of whether BCG revaccination would prevent TB disease [2]. However, previous trials of BCG revaccination, carried out in TB-infected and TB-uninfected individuals, failed to show protection [6, 7], and if raising funds for a phase 3 with a positive prevention of infection signal is considered unlikely, then with a negative prevention of infection signal this approach is likely to be dead in the water. The other approach, of course, would be to drop further evaluation entirely. The advantages would include that these resources could be used elsewhere, and the cons could include that we may be throwing away a cheap, safe and readily available strategy that does in fact prevent disease.

Whether we have a positive or negative signal from the confirmatory BCG revaccination trial early this year, the path forward will not be easy. Governments, funders and regulatory agencies should weigh these factors and be prepared to act decisively and rapidly when the results come. What we cannot do is suffer the long delays that beset M72 TB vaccine development [8].

To that end, we very much welcome the recent launch of the WHO TB Vaccine Accelerator Council [9] to coordinate funders and governments to prepare to deliver new TB vaccines. These BCG revaccination results will be this groups first real test to see if they can indeed co-ordinate to use these important data to accelerate TB vaccine development, and inform policy decision-making.

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Refs

1. Gates Medical Research Institute. *A randomized, placebo-controlled, observer-blind, phase IIb study to evaluate the efficacy, safety, and immunogenicity of BCG revaccination in healthy adolescents for the prevention of sustained infection with Mycobacterium tuberculosis. Available from: available at https://clinicaltrials.gov/ct2/show/NCT04152161*. 2021.
2. Pelzer, P., *BCG prevention of TB infection endpoints and tuberculosis disease: a comprehensive individual-participant meta-analysis of trials and observational studies*, in *World Conference on Lung Health 2023*. 2023.
3. Bill and Melinda Gates Foundation. *Wellcome and the Gates Foundation to Fund Late-Stage Development of a Tuberculosis Vaccine Candidate That Could Be the First in 100 Years If Proven Effective*. 2023 [cited 2023 2023_12_15]; Available from: https://www.gatesfoundation.org/ideas/media-center/press-releases/2023/06/funding-commitment-m72-tb-vaccine-candidate.
4. Hill, P.C., et al., *An aspiration to radically shorten phase 3 TB vaccine trials.* The Journal of Infectious Diseases, 2023.
5. Prasad, R. *BCG revaccination study in adults to begin in 23 states*. The Hindu 2023 [cited 2023 2023_12_15]; Available from: https://www.thehindu.com/sci-tech/bcg-revaccination-study-in-high-risk-adults-to-begin-in-23-states/article67594580.ece.
6. Rodrigues, L.C., et al., *Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial.* The Lancet, 2005. **366**(9493): p. 1290-1295.
7. Karonga Prevention Trial Group, *Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi.* The Lancet, 1996. **348**(9019): p. 17-24.
8. ProPublica. *How a Big Pharma Company Stalled a Potentially Lifesaving Vaccine in Pursuit of Bigger Profits*. 2023 [cited 2023 2023_12_15]; Available from: https://www.propublica.org/article/how-big-pharma-company-stalled-tuberculosis-vaccine-to-pursue-bigger-profits.
9. WHO. *Tuberculosis Vaccine Accelerator Council*. 2023 [cited 2023 2023_12_15]; Available from: https://www.who.int/initiatives/tuberculosis-vaccine-accelerator-council.