

## Revaccination with BCG: Does it work?

In 2022, 1.5 million people died of tuberculosis (1). There is just one licensed vaccine, live attenuated *Mycobacterium bovis* BCG. BCG protects infants against disseminated disease but the majority of people who have tuberculosis have pulmonary disease and live in low- and middle-income countries where the efficacy of BCG is very limited (2). One obvious strategy to enhance the effect of BCG is to administer it again as a homologous boost. This is self-evidently important: if BCG revaccination can improve the protective efficacy of this 100-year-old vaccine, we would have an inexpensive, readily deployable tool to help improve TB control globally. However, the evidence to date on the value of BCG revaccination has been conflicting and it is not currently recommended by the WHO.

In this edition of The Lancet Infectious Diseases, new light is shed on when and how BCG revaccination might be beneficial (REF). The phase 3 multicentre BRACE trial was designed to evaluate whether vaccination with BCG confers 'off-target' protection against COVID-19 disease (3). Dos Santos and colleagues took the opportunity to embed a nested RCT within BRACE by adding tuberculosis-related outcomes in the three Brazilian BRACE trial sites. In this highly cost-efficient way they were able to determine whether BCG revaccination provides any protection against *M. tuberculosis* infection. The definitions of infection used were based on initial and sustained interferon-gamma release assay conversion using the QuantiFERON-TB Gold Plus test. The results were disappointing: there was no protective effect of BCG revaccination against either initial or sustained QFT Plus conversion; conversion was observed in 3.4% (34/996) and 3.2% (32/989) of participants in the BCG and placebo groups, respectively.

The first reported Prevention-of-Infection (POI) trial, conducted in South African adolescents, reported a statistically significant 45.3% reduction in sustained QFT conversion after BCG revaccination as a secondary endpoint (11.6% and 6.7% in the placebo and BCG-re-vaccination groups respectively) (4). This result was unexpected as a previous cluster randomised study, REVAC, in more than 200,000 Brazilian school children had shown no effect of BCG revaccination on reducing the incidence of tuberculosis disease (5).

So why was there an effect of BCG revaccination in the South African study but not REVAC or BRACE? First, the absolute rates may be important. The force of infection was much higher in the South African study, with 15% 2-year QFT conversion in the placebo group compared with the 1-year 3% QFT conversion in the placebo group in BRACE. Second, it is worth noting that the REVAC study was not resoundingly negative: a subgroup analysis suggested a signal of efficacy in the urban but not the rural setting (6). This would be consistent with the idea, advocated by Dye, that BCG revaccination might be most effective in those without prior mycobacterial sensitization (7). Exposure to non-tuberculous mycobacteria is thought to be greater closer to the equator and in rural settings.

Third, the endpoint in these studies was different: immunity against *M. tuberculosis* infection may not be the same as immunity against tuberculosis disease. Recent correlates work has demonstrated that immune correlates of tuberculosis disease in South African infants are not associated with risk of *M. tuberculosis* infection in the same population (8).

A larger repeat POI trial is underway in South Africa to replicate the original POI result, and is scheduled to report in 2024. If the original results are replicated, then this should drive practice, at least in South Africa.

We must take every opportunity to design and conduct studies with BCG and candidate vaccines that inform this field, and find ways to do these studies more cost-effectively. Tuberculosis vaccine

efficacy trials are large and expensive. The planned phase III trial for M72/AS01e, an adjuvanted protein vaccine candidate which demonstrated 49.7% efficacy in a phase IIb trial, is currently estimated to need to enrol 28,000 subjects and cost US\$550m (9). Opportunities like the BRACE study do not come along frequently. Dos Santos and colleagues are to be congratulated for their creativity and tenacity in seeing this nested trial through to completion and its clear result: unfortunately, the relatively simple approach of BCG revaccination will not be applicable in all geographical areas, even if it is shown to be effective in some.

TB is a highly successful, well-evolved pathogen. Drug and vaccine efficacy trials are long and expensive. Progress has been slow but the quality of the trials has been high so, as each one reports, there is a sense of solid knowledge building. Continuing the momentum of the last two decades will be needed if it is not to take us another 100 years to licence and deploy a more effective vaccine.

## References

1. Global Tuberculosis Report 2023 [Internet]. [cited 2024 Jan 6]. Available from: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023>
2. Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PEM, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis* [Internet]. 2014 Feb 15 [cited 2024 Jan 6];58(4):470–80. Available from: <https://pubmed.ncbi.nlm.nih.gov/24336911/>
3. Pittet LF, Messina NL, Orsini F, Moore CL, Abruzzo V, Barry S, et al. Randomized Trial of BCG Vaccine to Protect against Covid-19 in Health Care Workers. *New England Journal of Medicine* [Internet]. 2023 Apr 26;388(17):1582–96. Available from: <https://doi.org/10.1056/NEJMoa2212616>
4. Nemes E, Geldenhuys H, Rozot V, Rutkowski KT, Ratangee F, Bilek N, et al. Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination. *N Engl J Med* [Internet]. 2018 Jul 12 [cited 2024 Jan 6];379(2):138–49. Available from: <https://pubmed.ncbi.nlm.nih.gov/29996082/>
5. Rodrigues LC, Pereira SM, Cunha SS, Genser B, Ichihara MY, De Brito SC, et al. Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet* [Internet]. 2005 Oct 8 [cited 2024 Jan 6];366(9493):1290–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/16214599/>
6. Barreto ML, Pilger D, Pereira SM, Genser B, Cruz AA, Cunha SS, et al. Causes of variation in BCG vaccine efficacy: Examining evidence from the BCG REVAC cluster randomized trial to explore the masking and the blocking hypotheses. *Vaccine*. 2014 Jun 24;32(30):3759–64.
7. Dye C. Making wider use of the world's most widely used vaccine: Bacille Calmette-Guerin revaccination reconsidered. *J R Soc Interface* [Internet]. 2013 Oct 6 [cited 2024 Jan 6];10(87). Available from: <https://pubmed.ncbi.nlm.nih.gov/23904584/>
8. Satti I, Wittenberg RE, Li S, Harris SA, Tanner R, Cizmeci D, et al. Inflammation and immune activation are associated with risk of Mycobacterium tuberculosis infection in BCG-vaccinated infants. *Nat Commun* [Internet]. 2022 Dec 1 [cited 2024 Jan 6];13(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/36329009/>

9. Press Release: Funding Late-Stage Development of M72 TB Vaccine Candidate | Bill & Melinda Gates Foundation [Internet]. [cited 2024 Jan 6]. Available from: <https://www.gatesfoundation.org/ideas/media-center/press-releases/2023/06/funding-commitment-m72-tb-vaccine-candidate>