



Treatment Action Group

Treatment Action Group Information Note on BCG and SARS-CoV-2/COVID-19

More research required to determine if century-old tuberculosis (TB) vaccine protects against SARS-CoV-2/COVID-19

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Topline Messages

Widespread media reports¹ that baccille Calmette–Guérin (BCG), the existing vaccine used against TB, may be protective against SARS-CoV-2/COVID-19 need to be read with caution until results become available from recently begun randomized controlled [clinical trials](#). While this research is underway, governments must ensure adequate and uninterrupted supply of BCG to protect children against TB. Healthcare workers addressing Covid-19 should only be (re)vaccinated with BCG in the context of clinical research until ongoing studies return results justifying the wider application of BCG against SARS-CoV-2/COVID-19 outside of research settings. This information note from Treatment Action Group (TAG) provides background on the use of BCG for COVID-19; overviews ongoing clinical trials; discusses BCG supply concerns; and highlights how other experimental COVID-19 vaccines are benefitting from investments in TB research.

BCG and TB

First introduced into human use in 1921, BCG is a live attenuated form of *Mycobacterium bovis*, the organism that causes TB in cattle. BCG is the most widely administered vaccine in the world and protects young children against the most severe forms of TB, including TB meningitis and disseminated TB. This protective effect wanes over time, and BCG does not appear to confer significant protection against pulmonary TB, the most common form of the disease, in adolescents or adults. A [recently completed phase II clinical trial](#) showed that South African adolescents revaccinated with BCG were less likely to acquire TB infection (as measured by sustained conversion on a type of test called an interferon-gamma release assay, which detects the body's immune response to TB infection but does not measure infection directly).² This finding is now being confirmed in a follow-on study supported by the Gates Medical Research Institute.³

BCG and COVID-19

An ecological study published on March 28, 2020 on medRxiv pre-peer review has generated outsized optimism in many media outlets for suggesting that differences in BCG vaccination policies and practices may partially explain different mortality rates from COVID-19 between countries with universal BCG vaccination programs and those without.⁴ The study makes use of the [BCG World Atlas](#), a compendium of BCG vaccination policies in over 180 countries compiled by McGill University. Emily MacLean, a doctoral candidate at McGill International TB Centre, has published an elegant dissection of the study's limitations and flaws. TAG shares MacLean's view that "with further research, it may emerge that the BCG vaccine does confer protection against COVID-19; however, with the current state of knowledge we cannot state this with any degree of certainty, and an ecological study does not provide sufficient evidence."⁵

There are valid scientific reasons to think that BCG may help protect against SARS-CoV-2/COVID-19. Megan Murray of the Harvard T.H. Chan School of Public Health wrote a concise summary of evidence on the so-called “non-specific effects” that BCG may have against illnesses other than TB.⁶ Several observational studies and randomized controlled trials have shown that BCG reduces the occurrence and severity of infectious diseases other than TB, in particular the acute lower respiratory infections that are a leading cause of death in children under five years of age in developing countries.⁷ Immunologically speaking, these non-specific effects might represent heterologous immunity, whereby immunity to one pathogen provides cross-protection against others. Another non-exclusive possibility is trained immunity, whereby BCG alters the expression of genes involved in pathogen recognition and immune response.

Based on these ideas, several countries have initiated clinical trials of BCG in healthcare workers to see whether the vaccine reduces the incidence of SARS-CoV-2/COVID-19 or results in less severe disease. In Australia, the [BRACE](#) trial will recruit over 4000 healthcare workers; half will receive a single dose of BCG and half will remain unvaccinated (no intervention).⁸ The study will compare incidence of COVID-19 and severe COVID-19 between the two groups six months post-randomization (secondary outcomes will follow participants out to 12 months). In the Netherlands, the [BCG-CORONA](#) study will randomize up to 1500 healthcare workers to receive either BCG or placebo and compare rates of unplanned absenteeism from work (measured biweekly).⁹ This unplanned absenteeism endpoint is meant to be highly pragmatic; the idea is that healthcare workers vaccinated with BCG will be less likely to miss work due to COVID-19 or ill health, thus relieving burden on the healthcare workforce.

Several other research institutes are looking into studies of BCG and SARS-CoV-2/COVID-19, including a possible study in France by the French National Institute of Health and Medical Research (INSERM).¹⁰ Scientists associated with INSERM have also discussed the possibility of studying BCG against SARS-CoV-2/COVID-19 in African countries. This proposal drew strong public rebuke when a clip from a television interview with Camille Loch (INSERM) and Jean Paul Mira (Paris’s Cochin Hospital) quoted Mira saying that African countries would make a good setting for clinical trials because participants there would have less access to other protective measures against SARS-CoV-2/COVID-19.¹¹ INSERM subsequently issued a statement that the quote was taken from a shortened clip and was mis-interpreted; however the French Embassy in South Africa quickly denounced the remarks: “We are deeply shocked by these comments, that of course, do not reflect the position of the French authorities.”¹² World Health Organization (WHO) Director-General Tedros Adhanom Ghebreyesus condemned the remarks “in the strongest terms possible,” saying: “When we need solidarity, these kinds of racist remarks do not help [...] Africa cannot and will not be a testing ground for any vaccine.” Tedros went on to say that protocols must treat people equally wherever they participate in research. “The hangover from the colonial mentality has to stop,” concluded Tedros.

TAG takes this opportunity to issue a strong reminder to all trial funders and sponsors that any medical research conducted in communities at risk of SARS-CoV-2/COVID-19—which are often communities facing other forms of present and historical marginalization and deprivation—must meaningfully and respectfully engage community representatives in all matters related to research design and conduct. The obligation to engage communities as more than clinical trial participants is an ethical and human rights imperative in keeping with the Declaration of Helsinki, the human right to participate in and enjoy the benefits of scientific progress, the Denver Principles, and Good Participatory Practice guidelines for biomedical research.¹³

Risks to Global BCG Supply

Should trials of BCG and SARS-CoV-2/COVID-19 prove successful, global demand for BCG will increase rapidly. Although the vaccine is cheap, made by multiple suppliers, and unfettered by intellectual property barriers, the annual supply is limited; BCG is an old, unprofitable product, useful for TB, but otherwise taken for granted. If a sudden increase in demand catches BCG manufacturers unprepared, there is a real risk of seeing shortages that would stymie efforts to confront COVID-19 and undermine childhood TB vaccination programs.

This risk of supply shortages is a frightening possibility. From 2013 to 2015, many countries experienced recurrent shortages of BCG for childhood immunization (with some countries experiencing shortages as far back as 2005). Multiple factors drove these shortages, including the small number of quality-assured suppliers and the exit of key suppliers from the market.¹⁴ These shortages resulted in increased rates of childhood TB and lost lives. One modelling exercise estimates that at current coverage levels, BCG prevents nearly 120,000 TB deaths in the first 15 years of life. Every 10% drop in coverage (or 26 million dose shortfall) would cause over 11,000 additional TB deaths in a given birth cohort in the first 15 years of life.¹⁵ Real world data from South Africa indicate that an uptick in TB meningitis among children seen around this time was related to BCG shortages.¹⁶

For the moment, there is sufficient BCG supply to meet forecasted demand for TB programs. In 2017, a WHO analysis found that available supply of BCG (500 million doses) was 1.5 times greater than expected demand (350 million doses).¹⁷ At the time, manufacturers reported a capacity to increase BCG supply by 35 percent (up to 700 million doses). However, the WHO has warned that serious structural risks to BCG availability and accessibility remain unresolved.¹⁸ Two manufacturers account for a majority of global supply, many countries have only one locally registered BCG product, and most suppliers have not invested in modernizing and strengthening manufacturing protocols.

TAG believes it is critically important for manufacturers to start preparing now to increase supply of BCG to meet the demand expected if clinical trials demonstrate the vaccine protects healthcare workers against SARS-CoV-2 or lessens COVID-19 disease severity or speeds recovery times. Without immediate steps to increase BCG supply, there is a real risk that some countries may reencounter supply disruptions for critical childhood TB immunization programs. TAG calls on all governments to ensure that childhood immunization programs receive sufficient and predictable supplies of BCG while trials are ongoing and afterward in the event that BCG is widely picked up as a tool against SARS-CoV-2. No child should have their life or life prospects cut short by preventable, severe forms of TB. While research is ongoing, TAG encourages healthcare workers who wish to receive BCG to do so in the context of clinical research.

Beyond BCG for COVID-19

Additionally, TAG points out that BCG is just one of several TB vaccine platforms now being studied for utility against SARS-CoV-2/COVID-19. An experimental TB vaccine closely related to BCG called VPM1002 will soon be tested against COVID-19 in elderly patients and healthcare workers in German hospitals.¹⁹ MTBVAC, a live-attenuated form of *Mycobacterium tuberculosis* developed by the University of Zaragoza in Spain, may soon be tested against SARS-CoV-2 in animal models in preparation for future trials in humans.²⁰ Other COVID-19 vaccine candidates make use of vaccine strategies previously studied for TB, including the delivery of antigens using viral vectors including Ad5 and ChAdOx1.^{21,22} Together, these

projects suggest that research for a SARS-CoV-2/COVID-19 vaccine has benefitted tremendously from the last two decades of investment in TB vaccine research and development. More information on these and other TB vaccine candidates can be found in TAG's 2019 [TB Vaccine Pipeline Report](#).

Parting Thoughts

Despite using BCG for nearly 100 years, the global scientific and public health community is just beginning to understand its full potential against TB and a host of other pathogens and conditions. Well-designed, randomized controlled trials on BCG and COVID-19 should continue, and governments must take steps to ensure an adequate supply of BCG for everyone in need. Today, this means young children who need protection against TB. Tomorrow, that group may also include healthcare workers, elderly, first responders such as delivery workers, grocery employees, firefighters, and other populations vulnerable to COVID-19.

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¹ See, for example, coverage in the [New York Times](#), [Bloomberg](#), and [Forbes](#).

² Nemes E, Geldenhuys H, Rozot V, et al. Prevention of *M. tuberculosis* infection with H4:IC31 vaccine or BCG revaccination. *N Engl J Med*. 2018;379(2):138–149. doi: 10.1056/NEJMoa1714021.

³ See p. 17 of Frick M. The TB vaccine pipeline—M72/AS01E: between nature and licensure. New York: Treatment Action Group; 2020. <https://www.treatmentactiongroup.org/resources/pipeline-report/2019-pipeline-report/>

⁴ Among other claims, the study found lower COVID-19 mortality in 55 middle- and high-income countries with universal BCG vaccination policies compared to 5 countries that never had universal BCG vaccination. See: Miler A, Reandelar MJ, Fasciglione K, et al. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medRxiv. 28 March 2020. doi: 10.1101/2020.03.24.20042937.

⁵ MacLean E. Universal BCG vaccination and protection against COVID-19: critique of an ecological analysis. *Nature Microbiology Community*. 1 April 2020. <https://naturemicrobiologycommunity.nature.com/users/36050-emily-maclean/posts/64892-universal-bcg-vaccination-and-protection-against-COVID-19-critique-of-an-ecological-study>

⁶ Murray M. Could BCG vaccination/revaccination protect against SARS-CoV-2 disease? [Blog]. March 2020. <https://ghresearch.org/COVID-19/could-bcg-vaccination-revaccination-protect-against-sars-cov-2-disease/>

⁷ See, for example: Hollm-Delgado MG, Stuart EA, Black RE. Acute lower respiratory infection among Bacille Calmette–Guérin (BCG)-vaccinated children. *Pediatrics*. 2014;133(1):e73–81. doi: 10.1542/peds.2013-2218.

⁸ ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier: NCT04327206, BCG vaccination to protect healthcare workers against COVID-19 (BRACE). Last updated: 7 April 2020. <https://clinicaltrials.gov/ct2/show/record/NCT04327206>

⁹ ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier: NCT04328441, Reducing health care workers absenteeism in COVID-19 pandemic through BCG vaccine (BCG-CORONA). Last updated 3 April 2020. <https://clinicaltrials.gov/ct2/show/record/NCT04328441>

¹⁰ Could TB vaccine protect medics from COVID-19? Agence France-Presse. 03 April 2020. <https://www.france24.com/en/20200403-could-tb-vaccine-protect-medics-from-COVID-19>

¹¹ Jean-Paul Mira of Cochin Hospital stated: "If I can be provocative, shouldn't we do this study in Africa where there are no masks, no treatment, no intensive care? A bit like we did in some studies on AIDS. We tried things on prostitutes because they are highly exposed and do not protect themselves."

¹² 'Deeply shocked.' French embassy in SA on proposal to test vaccine on poor Africans. *Business Insider South Africa*. 5 April 2020. <https://www.businessinsider.co.za/french-africans-test-vaccine-2020-4>

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- ¹³ World Health Organization. Good Participatory Practice for Trials of Emerging Pathogens. Geneva: World Health Organization; 2016. <https://www.avac.org/resource/good-participatory-practice-guidelines-trials-emerging-and-re-emerging-pathogens%C2%A0-are>.
- ¹⁴ Cernuschi T, Malvoti S, Nickels E, Friede M. Bacillus Calmette-Guérin (BCG) vaccine: A global assessment of demand and supply balance. *Vaccine*. 2018;36(4):498–506. doi: 10/1016/j.vaccine.2017.12.010.
- ¹⁵ Harris R, Dodd P, White R. The potential impact of bCG vaccine supply shortages on global pediatric tuberculosis mortality. *BMC Med*. 14(1):138;2016. doi: 10.1186/s12916-016-0685-4.
- ¹⁶ du Preez K, Seddon J, Schaaf H, et al. Global shortages of BCG vaccine and tuberculosis meningitis in children. *Lancet Glob Health*. 2019;7(1):e28–29. doi: 10.1016/S2214-109X(18)30474-1.
- ¹⁷ Cernuschi T, et al. BCG vaccine: A global assessment of demand and supply balance.
- ¹⁸ World Health Organization. Global market update: BCG vaccine. Geneva: World Health Organization; 2017. https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/WHO_BCG_vaccine_global_market_update.pdf.
- ¹⁹ VPM1002 is a live recombinant form of BCG developed by the Max Planck Institute for Infection Biology and Vakzine Projekt Management in Germany and licensed to the Serum Institute of India. See: Max Planck Institute. Immune boost against the coronavirus. 20 March 2020. <https://www.mpg.de/14608782/corona-virus-studie>
- ²⁰ MTBVAC is being developed to protect against pulmonary TB in newborns and adults and is undergoing two phase IIa trials in South Africa. Experiments in mice have shown that MTBVAC can protect against *Streptococcus pneumoniae*, raising the possibility that if BCG protects against COVID-19, MTBVAC could do the same. Martin, Carlos (University of Zaragoza, Zaragoza, Spain). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 8 April 2020.
- ²¹ Ad5 has been studied for TB in the vaccine candidate Ad5.Ag85A by CanSino and McMaster University and against COVID-19 in the Ad5-nCoV supported by CanSino (and also studied by CanSino against Ebola). See: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier: NCT04313127, A phase I clinical trial in 18–60 adults (APICHT). Last updated 31 March 2020. <https://clinicaltrials.gov/ct2/show/record/NCT04328441>
- ²² ChAdOx1 is being studied for TB in a the prime-boost regimen ChAdOx1.85A + MVA85A developed at the University of Oxford and against COVID-19 in ChAdOx1 n-CoV-19. See: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier: NCT04324606, A study of a candidate COVID-19 vaccine (COV001). Last updated 6 April 2020. <https://clinicaltrials.gov/ct2/show/record/NCT04328441>