BCG as an adjunct or alternative vaccine to prevent COVID-19?

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Highlight

BCG vaccine may enhance the innate immune response as well as induce a specific immunity against SARS-CoV-2, which may potentially be associated with reduced severity of COVID-19, and may or may not necessarily be protective against SARS-CoV-2 infection. The effect from BCG vaccine was observed even decades after the vaccination.

Key words: Bacillus Calmette–Guérin; SARS-CoV-2; coronavirus; immunity; TB; Africa; pandemic

Coronavirus disease 2019 (COVID-19) has caused tremendous impact on many aspects of society globally and led to significant morbidity and mortality. There have been over 27 million confirmed cases globally, with over 906,000 deaths.[1] Limited treatment options have created a challenge in treating COVID-19. Vaccines are the ultimate solution to control the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus which causes COVID-19. While many new vaccines are in development, there is some evidence that existing vaccines may stimulate an immune response that could be protective against SARS-CoV-2. The Bacillus Calmette–Guérin (BCG) vaccine, an old vaccine which has existed for almost a century, may be a potential candidate in helping control the spread of the virus or reduce the impact of the disease. The BCG vaccine may enhance the general innate immune response, stimulating natural killer (NK) cells, monocytes and macrophages, and provide protection against other pathogens (i.e. SARS-CoV-2) that are unrelated to mycobacteria.[2,3] A recent study also showed that the BCG vaccination may induce a specific immunity against SARS-CoV-2 that targets the viral envelope protein that is essential for infectivity.[4] Several ecological studies found lower numbers of SARS-CoV-2 infections and reduced COVID-19 deaths in BCG-vaccinated regions, while our recent cohort study found lower hospitalization rates among BCG-vaccinated COVID-19 patients in the same communities in the Northeast Unites States even decades after vaccination.[5-7] These findings may indicate the potential of BCG vaccine in reducing the likelihood of severe COVID-19, and perhaps also the likelihood of acquiring infection.

The BCG vaccine is a live-attenuated strain derived from an isolate of *Mycobacterium bovis* and originally designed to prevent tuberculosis. It is estimated that over 130 million children were vaccinated with BCG every year in the world.[8] In addition to the specific effect against tuberculosis, BCG is known to elicit non-specific immune effects through the induction of the innate immune responses and the enhanced production of pro-inflammatory cytokines, such as IL-1β, tumor necrosis factor (TNF) and IL-6, to protect against a wide range of other infections.[2,9] A recent study by Nuovo *et al.* found that there is strong homology between a SARS-CoV-2 capsid protein and a *Mycobacterium bovis* protein. The authors suggested that BCG vaccination may induce a specific immunity directly against the SARS-CoV-2 envelope protein, which is essential to the infectivity of the virus.[4]

In addition to *in vitro* studies, several previous *in vivo* studies have suggested that BCG vaccination may have non-targeted protective effect against viral infections.[2] Yellow fever virus is a single-stranded positive-sense RNA virus, similar to the structure of SARS-CoV-2. In a randomized controlled trial (RCT), the BCG vaccine reduced yellow fever viremia by 71% (95% CI 6-91) in volunteers.[2] A case-control study suggested that the BCG vaccination may reduce the incidence of acute lower respiratory tract infections caused by respiratory syncytial virus (RSV).[10] The safety concern and possible adverse effects from BCG vaccine in the elderly are another important factor to consider. Previous RCTs and observational studies have provided evidence for the BCG vaccine in protecting against respiratory infections in both children and elder people.[2,3,11] A 60-year follow-up study by Aronson *et al.* found the BCG vaccine efficacy may persist for 50 to 60 years with a long duration of protection.[12] With the hypothesis that countries who continued BCG immunization programs would contain the spread of COVID-19 better than those that did not have or have ceased their national BCG vaccination programs,

recent ecological studies have shown lower numbers of SARS-CoV-2 infections and reduced COVID-19 deaths in BCG-vaccinated countries when compared with BCG-non-vaccinated countries.[6] Kinoshita and the colleagues found the prevalence of the SARS-CoV-2 infection was inversely associated with BCG vaccine coverage in Japan.[13] However, ecological studies were based on population rather than individual data and thus were likely to be biased by confounding factors.

In terms of SARS-CoV-2, a population-based study examining the cohort of Israeli adults aged 35-41 years found that BCG vaccination in childhood was associated with a similar rate of positive tests for SARS-CoV-2 compared with no vaccination (difference, 1.3%; 95% CI, −0.3% to 2.9%; $P = 0.09$).[7] This study showed that the BCG vaccine may not reduce the likelihood of acquiring SARS-CoV-2. We conducted a retrospective cohort study examining communities in the United States aged 18 years and older with the median age 39.5 years (IQR, 27.0–50.0) and found that COVID-19 patients with BCG vaccination were less likely to require hospital admission (3.7% vs 15.8%, $P = 0.019$), even decades after the vaccination.[5] In this study, COVID-19 patients who were admitted to the hospital might indicate presenting with more severe symptoms. Though there were several limitations to this study, such as small sample size, short study time frame, unknown BCG strain each patient received, unknown BCG booster status, a preponderance of female patients, and a predominately Latino/Hispanic population. However, these studies suggest that BCG vaccination may potentially be associated with reduced severity of COVID-19, but may or may not necessarily protective against infection.

Whether it is safe to give the general population BCG vaccine during the COVID-19 pandemic is another important consideration we have to make. To investigate the safety profile of BCG vaccine during the pandemic, Moorlag *et al.* compared COVID-19 and the associated

symptoms in the healthy volunteers who either received BCG in the last 5 years or did not. None of the BCG-vaccinated or control individuals were admitted to hospitals, suggesting that BCG vaccination might not be associated with increased risk of hospitalization during the pandemic in this population.[14] The results from the phase III ACTIVATE trial showed that BCG vaccination was safe and could protect the elderly against infections, especially respiratory tract infections of probable viral origin, in the, and no difference in the frequency of adverse effects was found between the BCG and placebo groups, while larger studies are needed to further access this.[3] Nonetheless, since BCG vaccine is a live-attenuated vaccine, a potentially lethal infection could be expected in HIV-infected or immunocompromised individuals.

There are currently RCTs underway or being planned in the Netherlands, Australia, Greece, United States, Germany, Denmark, France, Poland, Egypt, South Africa, India, Iran, Brazil, and Canada to assess BCG vaccine and VPM1002 vaccine (a genetically modified BCG vaccine) and their efficacy in COVID-19 prevention and/or severity reduction. (Table) However, the size of those trials are smaller than those of the SARS-CoV-2 specific vaccines and the results should be compared with caution. If the RCTs could further provide more solid evidence to support the hypothesis, which the induction of innate immune responses or even specific immunity directly against SARS-CoV-2 by BCG vaccine could provide protection against COVID-19, BCG vaccination may be able to serve as an adjunct or alternate and lower-cost option for COVID-19 as the supply and stock are sufficient.

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Table. Current clinical trials evaluating the efficacy of BCG vaccination in the prevention and severity reduction of COVID-19

Trial ID	Trial status	Interventions	Study type	Study design	Phase	Primary purpose	Enrollment	Age	Locations
NCT04379336	Recruiting	BCG vaccine vs. placebo	Interventional	Randomized	3	Prevention	500	≥18 years	South Africa
NCT04537663	Recruiting	BCG vaccine vs. placebo	Interventional	Randomized	4	Prevention	5200	≥60 years	Netherlands
NCT04475302	Recruiting	BCG vaccine (Freeze-dried)	Interventional	Non-randomized	3	Prevention	2175	60-80 years	India
NCT04369794	Recruiting	BCG vaccine vs. placebo	Interventional	Randomized	4	Treatment	1000	≥18 years	Brazil
NCT04414267	Recruiting	BCG vaccine vs. placebo	Interventional	Randomized	4	Prevention	900	≥50 years	Greece
NCT04327206	Recruiting	BCG vaccine vs. 0.9%NaCl	Interventional	Randomized	3	Prevention	10078	≥18 years	Australia
NCT04384549	Recruiting	BCG vaccine vs. placebo	Interventional	Randomized	3	Prevention	1120	≥18 years	France
NCT04348370	Recruiting	BCG vaccine vs. placebo	Interventional	Randomized	4	Prevention	1800	18-75 years	United States
NCT04439045	Recruiting	VPM1002 vs. placebo	Interventional	Randomized	3	Prevention	3626	≥18 years	Canada
NCT04387409	Recruiting	VPM1002 vs. placebo	Interventional	Randomized	3	Prevention	1200	≥18 years	Germany
NCT04435379	Recruiting	VPM1002 vs. placebo	Interventional	Randomized	3	Prevention	2038	≥60 years	Germany
U1111-1256-3892	Recruiting	BCG vaccine vs. placebo	Interventional	Randomized	N/A	Prevention	400	≥18 years	Brazil
IRCT20200411047019N1	Recruiting	BCG vaccine vs. 0.9%NaCl	Interventional	Randomized	3	Prevention	500	≥18 years	Iran
NL8547	Recruiting	BCG vaccine vs. placebo	Interventional	Randomized	3	Prevention	1600	≥60 years	Netherlands
EUCTR2020-001783-28-HU	Ongoing	BCG (Danish strain 1331) vs. placebo	Interventional	Randomized	-	Prevention	1000	≥18 years	Hungary
EUCTR2020-002111-22-PL	Ongoing	BCG-10 vs. placebo	Interventional	Randomized	-	Prevention	1000	18-64 years	Poland
NCT04534803	Not yet recruiting	BCG (Tokyo-172 Strain Solution) vs. placebo	Interventional	Randomized	3	Prevention	2100	≥70 years	-
NCT04362124	Not yet recruiting	BCG vaccine vs. placebo	Interventional	Randomized	3	Supportive care	1000	18-65 years	Colombia
NCT04350931	Not yet recruiting	Intradermal injection of BCG vaccine vs. placebo	Interventional	Randomized	3	Prevention	900	≥18 years	Egypt
NCT04461379	Not yet recruiting	BCG vaccine vs. placebo	Interventional	Randomized	3	Prevention	908	≥18 years	Mexico
NCT04373291	Not yet recruiting	BCG (Denmark) vs. saline	Interventional	Randomized	3	Prevention	1500	18-100 years	Denmark
ACTRN12620000707965	Not yet recruiting	VPM1002 vs. saline	Interventional	Randomized	3	Treatment	3468	≥18 years	Australia
U1111-1253-9610	Not recruiting	BCG vaccine vs. saline	Interventional	Randomized	3	Prevention	1000	18-75 years	Brazil

NCT04328441	Active, not recruiting	BCG vaccine vs. placebo	Interventional	Randomized	3	Prevention	1500	≥18 years	Netherlands
NCT04417335	Active, not recruiting	BCG vaccine vs. placebo	Interventional	Randomized	4	Prevention	2014	≥60 years	Netherlands
NCT04347876	Recruiting	Tuberculin test	Observational	Case-control	-	COVID-19 severity	100	12-80 years	Egypt

Data obtained from the U.S. National Library of Medicine Database and the World Health Organization Database (*clinicaltrials.gov*, accessed on September 6, 2020)