A number of COVID-19 vaccine candidates have shown promising results, but substantial uncertainty remains regarding their effectiveness and global roll-out. Boosting innate immunity with Bacillus Calmette Guerin (BCG) or other live attenuated vaccines may also play a role in the fight against the COVID-19 pandemic. BCG has long been known for its non-specific beneficial effects, most likely explained by epigenetic and metabolic reprogramming of innate immune cells, termed trained immunity. In this issue of the JCI, Rivas et al. add to these arguments by showing that BCG-vaccinated healthcare providers from a Los Angeles healthcare organization had less COVID-19 diagnosis and serology, compared to unvaccinated individuals. Prospective clinical trials are thus warranted to explore BCG effects in COVID-19. We posit that beyond COVID-19, vaccines that elicit trained immunity, such as the BCG, may mitigate the impact of emerging pathogens in future pandemics.
BCG vaccination in healthcare providers and the protection against COVID-19

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COI Statement:
MGN has patents, (US18/61935, titled “Targeted nanoimmunotherapy to increase trained immunity” and US18/61939, titled “Targeted nanoimmunotherapy for inhibition of trained immunity” and is a scientific founder of Trained Therapeutix and Discovery. He received unconditional research grants from ViiV HealthCare.
Abstract

A number of COVID-19 vaccine candidates have shown promising results, but substantial uncertainty remains regarding their effectiveness and global roll-out. Boosting innate immunity with Bacillus Calmette Guerin (BCG) or other live attenuated vaccines may also play a role in the fight against the COVID-19 pandemic. BCG has long been known for its non-specific beneficial effects, most likely explained by epigenetic and metabolic reprogramming of innate immune cells, termed trained immunity. In this issue of the JCI, Rivas et al. add to these arguments by showing that BCG-vaccinated healthcare providers from a Los Angeles healthcare organization had less COVID-19 diagnosis and serology, compared to unvaccinated individuals. Prospective clinical trials are thus warranted to explore BCG effects in COVID-19. We posit that beyond COVID-19, vaccines that elicit trained immunity, such as the BCG, may mitigate the impact of emerging pathogens in future pandemics.
The time between SARS-CoV-2 emergence and an effective vaccine

Approximately one year ago a new type of respiratory infection emerged in Wuhan, China. Shortly thereafter, the etiologic agent of this disease was described as a new coronavirus (SARS-CoV-2), closely related to the agent of severe acute respiratory syndrome (SARS), and the disease was termed coronavirus disease 2019 (COVID-19). The clinical spectrum of COVID-19 is heterogeneous, with approximately 40% of infected individuals being asymptomatic, some others suffer a mild upper respiratory tract infection, while a notable minority develops severe pneumonia with ARDS, respiratory insufficiency, and even death (1). Although aggressive containment measures have been initiated by many countries, the pandemic could not be contained, with many countries in the Northern Hemisphere experiencing a second infection wave in the autumn-winter of 2020. It is expected that SARS-CoV-2 infection will become endemic, with regular outbreaks occurring either when quarantine measures are relaxed, or in the cold seasons in future years. Vaccination remains the most realistic hope to curb the spread of the virus. A number of vaccines have been recently reported to be effective against COVID-19, but it will take several months till enough doses can be produced and distributed to the population of the developed countries, and much longer to vaccinate the entire world population. In the time between the emergence of the virus and an effective worldwide vaccination, COVID-19 will have caused immense suffering and deaths among millions of people, and disastrous economic consequences.

Because of the very high morbidity and mortality burden caused by COVID-19, alternative approaches for the prevention of the disease have been proposed. One approach is the repurposing of existing drugs, such hydroxychloroquine, lopinavir/ritonavir, remdesivir or interferon-beta, all of which have shown, unfortunately, disappointing effectiveness (2). Another interesting strategy proposed is to use the long-known, but mostly neglected, property of some vaccines to induce cross-protection against infections outside the target disease (3). Especially vaccines that contain live-attenuated microorganisms, such as Bacillus Calmette Guerin (BCG), measles-containing vaccines (such as MMR), and oral polio vaccine (OPV) have such properties, as they improve mortality in children beyond the protection against their respective target diseases (4).

**BCG-induced protection**

BCG was developed against tuberculosis at the beginning of the 20th century at the Institute Pasteur in Paris, and since then it has been one of the most used vaccines in the world. After its introduction in various countries around the world during the decades following, epidemiological surveys found that BCG vaccination strongly reduced infant mortality, an effect that could not be explained by reduction in tuberculosis alone (reviewed in 5).
Interestingly, BCG-induced protection appeared to be due to effects against respiratory tract infections, in particular (6), an observation later confirmed also in randomized trials in adults (7,8). These clinical trials have been complemented by experimental studies that investigated the mechanisms through which BCG induces these protective effects. Spencer et al. showed that BCG vaccination reduced viral titers of influenza A virus in mice, an effect dependent on macrophages (9), suggesting strong effects on the innate immunity. This hypothesis was strengthened by studies demonstrating increased monocyte function after BCG vaccination in human volunteers (10). Subsequently, it was discovered that the monocyte functional changes are accompanied by transcriptional, epigenetic, and metabolic reprogramming of the myeloid cells progenitors in BCG-vaccinated individuals (11) (Figure 1A, B). The long-term changes in the innate immune cell phenotype after BCG vaccination amount to a de facto induction of innate immune memory, a phenomenon that we have termed trained immunity. There is evidence that induction of trained immunity is, at least in part, the mechanism through which BCG vaccination provides its beneficial effects, also against viral infections (12). Based on these arguments, it was, therefore, hypothesized that BCG vaccination is effective as a preventive measure against SARS-CoV-2 infection and may also reduce disease severity.

**BCG-COVID-19 prevention hypothesis**

This BCG-COVID-19 prevention hypothesis receives a boost by an elegant study published in this issue of the *JCI* by Rivas and colleagues (13). The authors assessed morbidity due to SARS-CoV-2 infections in a large cohort of healthcare professionals from a multi-site Los Angeles healthcare organization. Almost one third of the volunteers participating in the study had received earlier BCG vaccination, which was accompanied by a marked decrease (by approximately 30-40%) of self-reported COVID-19 diagnoses, self-reported positive COVID-19 RT-PCR tests, and anti-SARS-CoV-2 specific serology. BCG vaccinations were shown to be associated with lower COVID-19 incidence, despite the fact that the vaccinated group was slightly older and had more co-morbidities. Symptoms associated with COVID-19 were also notably less severe in the BCG-vaccinated compared to the unvaccinated individuals. Interestingly, internal controls showed that such positive effects were not induced by other vaccinations such as those against influenza, meningococcus or pneumococcus, so the effect seems to be pertained to BCG immunization. It must be said, however, that the number of individuals not vaccinated against influenza was too small to draw strong conclusions (13).

These data are important, as they seem to support several epidemiological studies that suggest that countries with a BCG vaccination program have a lower number of COVID-19 infections and a reduced mortality (13, 14,15). However, demographic, ethnic and genetic differences of populations in different countries, as well as differences in the social distancing
measures and population compliance, in diagnosing and reporting the COVID-19 cases, all induce bias in such analyses, despite great efforts to correct for them. In addition, studies investigating vaccinated and non-vaccinated cohorts of individuals from countries that have stopped their BCG vaccination policy in recent years have found that the number of COVID-19 diagnoses did not differ, and hence early-life BCG vaccination is unlikely to provide protection (16). While these studies have provided important arguments cautioning against the conclusion that BCG vaccination at birth can protect against COVID-19, they do not reject the idea that BCG would be protective when given later in life, and especially shortly before the emergence of SARS-CoV-2. While the study of Rivas et al. unfortunately did not collect data regarding the time of BCG vaccination, it is conceivable that the protective effect may have been due to more recent vaccinations. In line with recent vaccination protection, a recent observational survey of individuals vaccinated with BCG in the last 2 years (17), and one clinical study in healthcare personnel offered BCG vaccination during the first phase of the pandemic (18), have both suggested protective effects of BCG against SARS-CoV-2 infection.

Conclusions and considerations
There is compelling support for BCG vaccination as a way to prevent COVID-19, and the study of Rivas and colleagues (13) provides an important piece in this puzzle. However, in order to be fully convinced that BCG vaccination can have such protective effects, randomized controlled trials are needed, which could provide the highest level of proof for the hypothesis that BCG vaccination protects against COVID-19. As more than 20 clinical trials are currently assessing the efficacy of BCG vaccination against COVID-19, we expect a clear answer soon.

Two RNA-based vaccines from BioNtech/Pfizer and Moderna have been recently reported to give more than 90% protection against COVID-19, including in the elderly. A third vaccine based on an adenovirus platform from Oxford/Astra-Zeneca seems to provide also at least 60% protection. Should BCG studies continue, given the high effectiveness of specific vaccines? There are several important arguments for why studies on the effects of the BCG vaccine (and other live attenuated vaccines) against COVID-19 are needed. Firstly, it is yet unknown how long COVID-19 specific vaccines could provide protection, and one may hypothesize that a combination of BCG with a COVID-19 specific vaccine would induce lasting protection. Secondly, although it has been claimed that the new vaccines are protective in the elderly, we do not know the extent to which comorbidities, medication, and frailty affect the vaccine response. Combination of the COVID-19 specific vaccine with BCG may aid the specific immune response. Thirdly, next year will be characterized by a shortage of the new COVID-19 vaccines, especially in the developing countries. The availability of BCG, which does not necessitate storage at very low temperatures, could provide an important tool against
the pandemic in areas where cooling facilities are in shortage. Finally, and maybe the most
important reason, it is crucial to learn whether live attenuated vaccines such as BCG protect
against the spread of a severe infection during a pandemic: such a trained immunity-based
vaccination may prove powerful in future pandemics against the uncontrolled spread of an
emerging pathogen. BCG, and maybe other live-attenuated vaccines, could represent a bridge
vaccination during the period between the emergence of a new pathogen and the
development of a specific vaccine, to diminish the suffering of the population from both the
disease itself and its economic consequences (Figure1C).

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Figure 1. Model for trained immunity mechanisms that improve the anti-viral host defense. 

A. Trained immunity is mediated by metabolic and epigenetic rewiring in the innate immune cells, leading to increased gene transcription and host defense against heterologous pathogens. 

B. Following a first exposure to live or live/attenuated challenge, the innate immune response increases, becoming poised via trained immunity to increase substantially following a second infection. 

C. Trained immunity can be used as a tool for enhancing population immunity during a pandemic.
References