MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

The BCG Vaccine & COVID-19

OVERVIEW

The bacillus Calmette-Guérin (BCG) vaccine, best known for its role in helping to prevent tuberculosis infection, also appears to protect recipients from a variety of non-tuberculosis-related infections, including respiratory infections, as seen in global studies. Further, two recent studies suggest that the impact of COVID-19 is more severe—with more illness and more death—in countries that do not routinely administer the BCG vaccination to their populations. For this reason, the BCG vaccine is now being investigated in Australia and Europe to protect individuals at high-risk of serious COVID-19 infection, such as the elderly and healthcare workers. A trial in Boston is also underway to test BCG in healthcare workers at risk for COVID-19 infection.

WHAT IS THE BCG VACCINE?

BCG is a live, attenuated ("weakened") bacterial vaccine. It contains a strain of bacteria called *Mycobacterium bovis* (a relative of the bacteria responsible for tuberculosis in humans) that has been weakened so that it cannot cause disease in people with a healthy immune system. Instead, it prompts the immune system to prepare for a protective response against future infection. BCG has historically been given as a vaccination to prevent tuberculosis infection. Since the introduction of the BCG vaccine in 1921, it has been the most widely administered vaccine in the history of medicine. BCG is typically considered to be very safe. It is on the World Health Organization's Model List of Essential Medicines for both adults and children, and it is given to roughly 100 million children per year globally, typically in places where there may be a high risk of tuberculosis.

WHY DO WE THINK BCG COULD PROTECT FROM COVID-19 INFECTION AND COMPLICATIONS?

A large body of data suggests that BCG vaccination may have broad benefits beyond the prevention of tuberculosis, including protection from respiratory infections that are unrelated to tuberculosis, as well as a reduced risk of death from such infections. In addition, new and very preliminary data suggests that large-scale BCG vaccination may have a role in preventing COVID-19 illness and death, and may explain the variability in COVID-19 infection and outcomes seen across borders and age groups (Figure 1).

Collectively, these studies highlight the potential of the BCG vaccine to protect against diverse diseases, including, possibly, COVID-19.

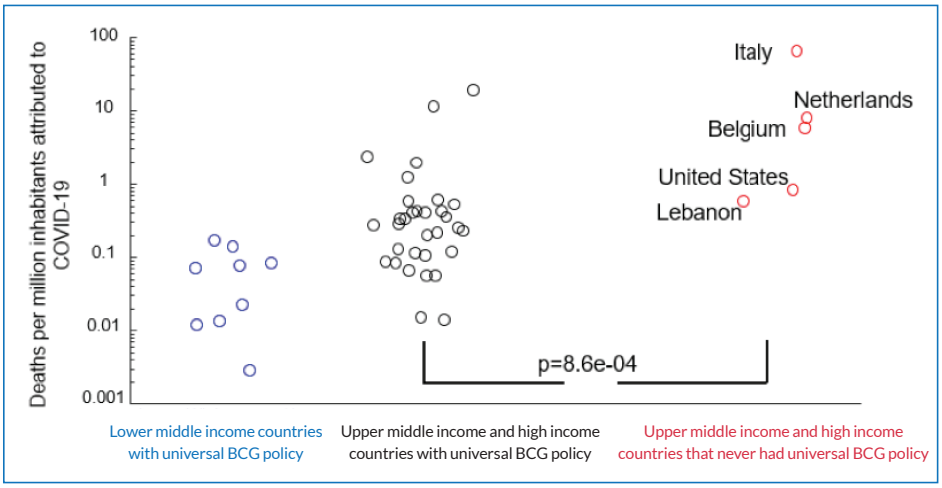

Figure 1. Association between BCG vaccination and death from COVID-19. Countries that have not had a universal BCG policy currently have the highest number of COVID-19 cases and deaths per million inhabitants. Deaths per million inhabitants are shown here. (Source: Miller A, et al. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. MedRxiv. 2020. Reprinted with permission.)

BCG WORKS DIFFERENTLY THAN VACCINES BEING DESIGNED TO TARGET COVID-19 DIRECTLY

Historically, vaccine design has involved the identification of the "perfect" antigen that generates long-term, infection-specific immune responses and provides protective immunity upon reencounter with the same disease-causing agent later. However, this approach can take months to years to develop, and has yet to lead to a successful vaccine against coronaviruses. Another approach may be to more broadly boost the immune system to fight infection, by triggering a form of "non-specific" immune memory, called trained immunity, which can arm cells against broad range of infectious diseases.

BCG appears to trigger this form of immunity. Multiple clinical trials have demonstrated the beneficial "off target" effects of BCG as it relates to infections. For example, in a randomized study, BCG vaccination induced trained immunity in healthy adults who were exposed to an attenuated strain of the yellow fever virus. In newborn children, BCG vaccination provides protection not only against tuberculosis, but also against viral infections of the respiratory tract and against neonatal sepsis—while also significantly reducing mortality. BCG vaccination also has been shown to alter the immune system so that it produces white blood cells that provide enhanced protection against pulmonary infection.

EVIDENCE OF HETEROLOGOUS PROTECTIVE EFFECTS OF BCG AGAINST VIRAL INFECTIONS IN HUMANS.

Virus	Setting	Example	Comments
RSV *(Respiratory syncytial virus)*	Guinea-Bissau	Fewer RSV infections in BCG-vaccinated children	Children 0-5 years old
Influenza	Netherlands	Enhanced antibody titers against the 2009 pandemic influenza A (H1N1) vaccine strain	Healthy adult volunteers
Unspecified respiratory viruses	Spain	Fewer hospitalizations due to respiratory infections and sepsis	Children 0-15 years old
COVID-19	Global	Fewer cases in countries with longstanding universal BCG vaccination policies	All ages

Long-term effects of vaccines on innate immune function. Upon vaccination, the innate immune system becomes activated by the vaccine. The stimulation of innate immunity can lead to long-term effects leading to an increase response to a (nonrelated) infection. For example, BCG vaccination leads to training of innate immunity and a more effective host immune response, accompanied by a reduced mortality, as a result of nonrelated infections.

CONCLUSIONS

BCG's safety profile, ease of administration and demonstrated potential to prevent respiratory infections make it an ideal candidate to test as an agent for protection against COVID-19 infection and subsequent complications. Multiple clinical trials as well as retrospective studies of BCG and COVID-19 are underway. The data from these trials will help us understand the role of BCG in current and future pandemics.

REFERENCES

A full list of references can be found at www.bcgandautoimmunity.org

CONTACT INFORMATION

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