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Debate on Bacille Calmette-Guérin vaccination against COVID-19: Is it worth performing clinical trials?

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ABSTRACT

The non-specific beneficial effects of Bacille Calmette-Guérin (BCG) vaccination suggest that this vaccine might play a role in protecting individuals against severe coronavirus disease 2019 (COVID-19). Several studies propose that BCG vaccination may increase the body's immunity, thereby preventing respiratory infections caused by other respiratory pathogens. As the number of deaths due to COVID-19 is increasing rapidly and there is no specific treatment available to date, scientists are evaluating the effectiveness of already approved drugs as therapies against COVID-19, and the results were found to vary widely: from no significant effect being observed to a reduction in the time taken for clinical improvement. This study thus aims to evaluate whether it is worth performing clinical trials to examine the effects of the BCG vaccine on COVID-19. We herein emphasize the need to conduct phase III randomized controlled trials with adequate sample size and quality to investigate the effects of the BCG vaccine on COVID-19. In the event that BCG vaccination provides non-specific protection against COVID-19, administering it could be helpful in controlling the transmission of COVID-19 and other infectious diseases during future pandemics.

Bacille Calmette-Guérin (BCG) is a live attenuated bacterial vaccine that is most commonly used to protect humans against tuberculosis [1]. BCG is one among a group of unique vaccines that can stimulate a broad immune response by epigenetic reprogramming of innate immune cells (e.g., monocyte/macrophages), whereas most conventional vaccines produce only specific responses following the introduction of vaccine-related antigens [2]. Thus, BCG vaccination leads to increased cytokine production in response to non-related pathogens, which is termed "trained immunity" [3]. Additionally, the BCG vaccine induces a sustained change in the immune system by producing heterologous T helper 1 (Th1) (interferon-γ) and Th17 (Interleukin (IL)-17 and IL-22) immune responses to non-mycobacterial stimulation, which remain strongly elevated even one year after BCG vaccination [4]. Therefore, these non-specific beneficial effects of BCG vaccination suggest that the vaccine could play a role in protecting individuals against severe coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5].

In March 2020, the World Health Organization declared COVID-19 a pandemic as it had spread to more than 210 countries and territories. The existing healthcare systems of even some of the most developed countries failed to control the disease. Although the SARS-CoV-2 virus mostly causes fever and cough in affected individuals, it can lead to fatal respiratory symptoms in severe cases. Further, no approved treatment for COVID-19 is available to date. The number of deaths from COVID-19 continues to increase rapidly, prompting scientists to discover an easy curative or preventive intervention that can have an instant global impact by saving thousands of lives. Evaluating the effectiveness of already approved drugs as therapies against COVID-19 is one of the strategies currently employed in this regard. The results published vary widely and range from no significant effects being observed to results indicating a reduction in time for clinical improvement [6]. Therefore, this manuscript aims to evaluate whether performing clinical trials to examine the efficacy of BCG vaccination against COVID-19 is worthwhile.

Debate on BCG vaccination against COVID-19

Once researchers observed higher frequencies of cases and mortalities from COVID-19 in certain countries than in others [7], a debate on the efficacy of the BCG vaccine sparked. Scientists then compared data from countries with and without mandatory BCG vaccination policies in their routine immunization programs in an attempt to account for this difference. In a paper published in *JAMA*, Hamiel et al. analyzed data from Israel, where BCG vaccination was part of routine immunization until 1982. The results of the analysis did not support the theory that BCG vaccination in childhood had a protective effect against COVID-19 in adulthood. However, the

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investigators of the study did not reach any conclusion about the association between BCG vaccination status and the severity of COVID-19 due to few numbers of severe cases [8]. Moreover, researchers also noticed a trend of slower transmission of the virus in countries with a national vaccination policy that requires BCG vaccination [9]. Another study found that the incidence and mortality rates were significantly lower among residents of countries with current universal BCG vaccination policies than in residents of countries without or with discontinued BCG vaccination policies [10]. Nevertheless, it is unclear whether BCG vaccination can decrease COVID-19 incidence. Additionally, although these results show interesting trends, they are prone to significant bias because of the presence of confounders such as unknown vaccination status [8] and inconsistences in testing rates and reporting between countries [11]. Therefore, it is difficult to draw any conclusion about the efficacy of the BCG vaccine against COVID-19 without conducting further controlled clinical trials.

Reasons for evaluating BCG vaccination against COVID-19

A controlled study to evaluate the efficacy of BCG vaccination in protecting against COVID-19 is warranted for several reasons, the most important of which is the non-specific preventive effects of the BCG vaccine against other respiratory and viral infections. Some of the other reasons are as follows:

a. Several randomized controlled trials (RCTs) conducted among infant, adults, and elderly people between 2005 and 2015 have shown a reduction in infant mortality due to pneumonia, sepsis, and respiratory infection following BCG vaccination [12];
b. BCG vaccination has been found to decrease the risk of pneumonia in people aged >65 years who have comorbidities, and it was also found to significantly prevent acute upper respiratory tract infections [13];
c. BCG vaccination shows enhanced immunogenicity in response to the A(H1N1) strain of the 2009 pandemic trivalent influenza vaccine but not to the A(H3N2) and A(H7N9) vaccine strains, for unknown reasons [14]
d. BCG vaccination has reduced viremia following yellow fever infection, which is correlated with IL-1b production [15].

These findings suggest that as the BCG vaccine exerts non-specific effects on cytokine responses following infection by some unrelated viral pathogens, it may be able to increase the body's immunity, resulting in the prevention of respiratory infections caused by other pathogens.

Historically, healthcare systems in developing countries have had a critical shortage of trained healthcare workers in comparison to the vast numbers of patients. To maintain an effective healthcare system, it is necessary to safeguard healthcare workers as they confront COVID-19. Given the lack of curative measures for COVID-19, the most effective strategy against the disease is prevention. One of the simplest options could be to boost the immune system of healthcare workers with a safe, low-cost, and easily available BCG vaccine in the interim period while COVID-19 vaccine clinical trials are underway. A fast-tracked clinical trial examining the effects of BCG vaccination on COVID-19 to generate solid evidence for the preventive effects of the BCG vaccine against COVID-19 is necessary and could be beneficial. As the BCG vaccine is already licensed, administering this vaccine would save time by bypassing the time-consuming pre-clinical animal studies as well as the Phase I and Phase II trials, which are crucial stages in the development of a new vaccine. Hence, a BCG vaccination trial could provide an opportunity to obtain efficacy data against COVID-19 quickly, as phase III trials could directly be initiated in the presence of an adequate sample size.

Considering the possibility of vaccine scarcity during a pandemic, it is wise to target high-risk groups such as healthcare workers and older people first. Studies are underway to evaluate the effects of the BCG vaccine given to healthcare workers directly involved in taking care of patients with COVID-19 (NCT04328441, NCT04327206, NCT04362124, NCT04379336, NCT04347876, NCT04348370, NCT04350931, NCT04373291, NCT04384549, and NCT04387409). However, until there is further clear evidence, sufficient local supplies of the BCG vaccine should be ensured for neonatal vaccination to prevent disease and deaths from tuberculosis. Production of the BCG vaccine would need to increase to meet the new demand if evidence shows the effectiveness of the BCG vaccine against COVID-19.

Finally, in addition to the Phase III trials that are currently underway, more RCTs with adequate sample size and quality could be conducted to investigate the effects of BCG vaccination against COVID-19. Given the limited production of the BCG vaccine, scientists could also consider initiating studies using new TB vaccine candidates that are in Phase II of clinical trials and have been shown to confer an immunity similar to that conferred by the traditional BCG vaccine [16]. If any of those vaccines provide non-specific protection, they may be used to bridge the gap before a COVID-19-specific vaccine is developed, which could be a significant means to control the transmission of COVID-19 and similar infectious diseases during future pandemics.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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