The COVID-19 pandemic (caused by the SARS-CoV-2 virus) has caused over 1.6 million deaths globally in 2020\(^1\). Early responses to address this crisis have involved the development of vaccines and rearranging existing drugs. Interestingly, however, some epidemiological studies linked Bacillus-Calmette-Guérin (BCG) - one of the world’s oldest vaccines - to the protection of humans against nonspecific pathogens such as SARS-CoV-2\(^3\). It comprises an attenuated, less virulent strain of Mycobacterium bovis, and years of data support its protective efficacy against tuberculosis, ie: its intended target. Nonspecific targets that BCG elicits protective effects ranging from Mycobacteria that causes leprosy through to non-mycobacterial prokaryotes including Staphylococcus aureus, and viruses including respiratory syncytial virus (RSV)\(^4\) and those causing viral warts\(^7\,8\) and recurrent aphthous stomatitis\(^9\). BCG vaccine has been associated with a reduction in respiratory tract infections of vulnerable patient groups including neonates and the elderly, which has raised hopes that BCG may offer protection against COVID-19 during the second wave of epidemics\(^3\).

**Epidemiological and clinical evidence of BCG-mediated protection against nonspecific pathogens**

Although little specific evidence suggested that BCG protected against the coronaviruses that caused the 2003 severe acute respiratory syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) epidemics (SARS-CoV-1 and MERS-CoV, respectively), several observations suggested that it might offer protection against COVID-19. Countries routinely conducting mass vaccination programmes that included BCG have seen significantly lower mortality rates from COVID-19 than countries that administer the vaccine on a case-by-case basis following a positive Mantoux test result\(^3\,10\,12\). One study suggested that case-by-case BCG vaccinating countries (Italy, the USA, the Netherlands, Belgium) had 265 cases per million population compared with 60 in low-income countries that applied mass vaccinations\(^13\).
Although one study did not prove a protective effect of BCG against COVID-19\(^1\), the authors acknowledged that their observations may be confounded by reporting biases. Generally, opinion leaders believe that continued investigation is required until a consensus is reached\(^3,10,11\). Data from several eagerly awaited randomised clinical trials will determine how BCG affects COVID-19 infection. The BCG-CORONA (the Netherlands) and BRACE (Australia) placebo-controlled trials are studying the effects of BCG on 1500 and 10,078 healthcare workers, respectively exposed to COVID-19 patients\(^{15-17}\). Additionally, a study in the USA reported a statistically significant reduction in the number of COVID-19 disease related to hospital admissions in BCG-vaccinated participants (although the authors did not indicate when they were vaccinated)\(^{18}\). This suggests that BCG vaccination deployment may reduce COVID-19 cases, hospitalisations, and deaths, a view shared by many opinion leaders.

**How BCG mediates protection against nonspecific pathogens**

There are several mechanisms for this putative protective effect. BCG reportedly triggers a form of nonspecific innate immune cell memory by epigenetic reprogramming - known as trained memory. PBMCs from vaccines stimulated with nonspecific pathogens produce elevated levels of proinflammatory cytokines IFN-\(\gamma\), TNF-\(\alpha\), and IL-1\(\beta\), which were also linked to the protection of T-cell- and B-cell-deficient BCG-vaccinated SCID mice against non-mycobacterial pathogens\(^{19}\). This process was accompanied by methylation of these genes\(^{19}\). Additionally, BCG-recipients subsequently vaccinated with the yellow fever vaccine had lower levels of viremia than those not unvaccinated which was also correlated with epigenetic reprogramming within proinflammatory cytokine genes\(^{20}\). Taken all together, these findings strongly implicate the presence of trained memory in BCG-mediated protection against nonspecific pathogens.

Adaptive immunity may also be playing a role. A clinical trial showed that BCG vaccination followed by influenza vaccination increased antibody titres against the latter (correlating with the protective efficacy), suggesting that it may increase B-cell responses against nonspecific respiratory viral pathogens in some settings in 2009\(^{21}\). Additionally, the elevated proinflammatory cytokines driven by BCG were postulated to increase heterologous responses of CD4+ and CD8+ Th1 and Th17 cells\(^{10,22}\). If such responses are directed against SARS-CoV-2, it would be likely to have protective effects.

**CONCLUSION**

The combination of epidemiological data from the countries who apply mass vaccination backed up by strong immunological evidence that BCG vaccine protects against a wide range of non-tuberculous mycobacteria, makes a strong case that BCG could help to control COVID-19. Consensus will be reached out and confirmed if the imminent further clinical trials will be carried to support this premise.

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