OPINION

Managing the COVID-19 pandemic: is BCG an alternative?

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An outbreak of a novel coronavirus disease (COVID-19) caused by the coronavirus (SARS-CoV-2) was first reported in Wuhan, China in December 2019, and soon spread rapidly across the globe causing a deadly pandemic. One of the earliest observations made was that there was a great variation in the susceptibility to infection and mortality rates in different parts of the world. It appeared that general BCG vaccination policies adopted by different countries may influence the transmission patterns, as well as COVID-19-associated morbidity and mortality. Large-scale clinical trials are needed to confirm the non-specific protective effects of BCG.

The ongoing COVID-19 pandemic caused by the 2019 novel coronavirus (SARS-CoV-2) continues to be one of the most serious threats to the human race. The infection was first reported in Wuhan, China, and soon spread rapidly across the world. As of 13 September 2021, 225,479,436 cases have been reported worldwide and there have been 4,644,176 deaths[1]. To date, there is no drug with proven efficacy which can be used against this disease. Though several vaccines have been developed, the vaccination process has not progressed with uniform rapidity in all countries, and a large proportion of people still remain unvaccinated. In this interim, alternate ways to mitigate the pandemic impact in some countries may be necessary.

One of the earliest observations made was that there was a variation in the susceptibility to infection and mortality rates in different countries. Social, geographical and ethnic differences no doubt play a role in this variation and it became important to understand the specifics of this variability which could contribute to mitigation of the spread of the virus. One of the explanations put forth to explain the difference in morbidity and mortality in different countries was related to the national policies on Bacillus Calmette-Guérin (BCG) vaccination.

BCG is a live attenuated strain derived from an isolate of *Mycobacterium bovis* used widely across the world as a vaccine against tuberculosis (TB). It was developed in the beginning of the 20th century at the Institut Pasteur in Paris and since then, almost 130 million children have been vaccinated every year. It confers protection against severe forms of *Mycobacterium tuberculosis* infection, but has a limited effect against pulmonary TB[2]. Many countries across the world, including Africa, Japan and China have a universal BCG vaccination policy for new-borns. Countries such as the United States and Canada have a policy only for selected populations and many countries in Europe, including Italy had a national policy for all in the past, but do not have one at present[3]. As the SARS-CoV-2 pandemic continued to rage around the world, it appeared that the spread of the virus was slower and recovery rates were better in countries which had mass immunization programmes with the BCG vaccine, suggesting that this vaccine may offer protection against COVID-19.

Many global epidemiological studies in vaccinated individuals have demonstrated the capacity of the BCG vaccine to protect against non-mycobacterial infections as well[4,5]. Vaccination with BCG provides non-specific protective effects against non-related infections and this protection is independent of T and B cells[6]. Childhood mortality decreased in Europe after 1920, which coincided with the period when BCG was introduced there. This was related to the ability of BCG to protect against unrelated infectious agents, such as pathogens causing respiratory-tract infections and sepsis.

The protective effect of BCG against SARS-CoV-2 may be due to the ability of the vaccine to induce a trained immune response, where the vaccinated individual can fight against other pathogens in addition to the tubercle bacillus.

Trained immunity is mediated by innate immune cells, leading to enhanced innate immune responses to different pathogens. This hyperactivation of the innate immune system occurs after exposure to certain stimuli and results in an augmented immune response to a secondary stimulus. It increases population immunity during a pandemic and is useful when a specific vaccine has not been developed. An important feature of trained immunity is immune memory related to the acquired immune response. In addition, innate stimuli lead to epigenetic reprogramming of innate immune cells such as monocytes, macrophages and natural killer cells[7,8]. When healthy individuals are given the BCG vaccine, they respond with an increased production of pro-inflammatory cytokines such as IL-1β, tumour necrosis factor (TNF) and IL-6. This is accompanied by a reprogramming of the innate immune cells with epigenetic changes of histone, which improves the effector functions of the cells. There are changes in cellular metabolism, particularly an increase in glycolysis, glutamine metabolism and oxidative phosphorylation[9]. While trained immunity has beneficial effects for the host, a persistent state of immune activation could also cause chronic inflammatory diseases[10]. It is possible that BCG vaccination may prevent or reduce the severity of COVID-19 disease because of its immunomodulatory effects. Countries and regions where BCG vaccination is mandatory, including middle and low-income countries with average health infrastructure, have shown a disproportionately smaller number of cases, thereby indicating that BCG vaccination may reduce the transmission of COVID-19 in the population. A study which analysed COVID-19 associated deaths relative to the size of the population has reported that the number of deaths was significantly lower in countries with a national BCG vaccination programme. In Europe there was a statistically significant difference in deaths/million between countries that had ceased vaccination in the last two decades (Norway, France, Finland, the UK and Germany) compared to those which had ceased vaccination in the last 3–4 decades (Austria, Belgium, Switzerland, Denmark, Spain, The Netherlands and Sweden), suggesting that BCG vaccination-induced protective effect could last ~20 years and could influence disease severity[11].

The link between BCG vaccination and severity of COVID-19 is, however, difficult to establish because of the difficulty in

comparing different locations with variations in demography and genetic make-up of populations, differences in disease diagnosis, reporting and management of patients, varying practice of interventions and different stages of the pandemic in different countries. It is not known for how long the pool of trained lymphocytes will be maintained in a vaccinated individual, and whether older people who may have received the BCG vaccine in childhood will be susceptible. According to some studies, the protective effect of BCG wanes with time and may disappear completely in 10–15 years (ref. 12). Randomized controlled trials with feasible primary end-points are urgently needed to confirm the hypothesis that BCG vaccination may protect against COVID-19. Trials to assess the efficacy of BCG vaccination in high-risk categories of individuals are currently being performed in several countries.

The risk of boosting innate immunity in a situation where the complication of the disease itself is an exaggerated cytokine response has also been considered[13]; however, deleterious effects are unlikely in healthy individuals. If the vaccine is capable of reducing viral loads, there would be less inflammation and consequently a disease which is less severe. Trained immunity itself is likely to become an important tool against emerging pathogens and would serve to bridge the gap until a specific vaccine is developed[14].

BCG vaccination may reduce the severity of COVID-19, and countries with a universal BCG policy have reported lower mortality rates[15]. However, definitive proof of this hypothesis depends on the results of clinical trials which are in progress in different countries across the world. As cases of COVID-19 cross 225 million, and new vaccines are still in different stages of clinical trials, the world hopes that a vaccine which is already in use, like BCG, can offer some protection or reduce the severity of disease outcomes, at least for people with comorbities, the elderly and high-exposure healthcare workers.

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