Editorial

# BCG vaccination and Covid-19 protection

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The **coronavirus pandemic**, is an ongoing pandemic of coronavirus disease 2019 (**COVID-19**) caused by severe acute respiratory syndrome coronavirus-2 (**SARS-CoV-2**)[1]. The World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern on 30 January 2020, and a pandemic on 11 March 2020[2,3]. Antiviral medications are under investigation for COVID-19, as well as medications targeting the immune response. None has yet been shown to be clearly effective on mortality in published randomized controlled trials.

In the absence of a specific vaccine the medical community investigates existing vaccines for potential general immunity augmentation, the so-called **trained immunity**. The antituberculous vaccine Bacille Calmette-Guérin vaccine (BCG) contains a live, weakened strain of *Mycobacterium bovis*, a cousin of *M. tuberculosis*. The vaccine is named after French microbiologists Albert **Calmette** and **Camille Guérin**, who developed it in the early 20th century. First used in humans in **1921,** BCG is now one of the most widely used vaccines in infants and neonates, in whom its main utility is in the prevention of tuberculous meningitis and disseminated tuberculosis[4]. Importantly, BCG is also used as adjuvant immunotherapy for patients with non-muscle-invasive **bladder cancer**[5] BCG, has been used in **Greece** by the Greek Red Cross since 1925, the vaccine being produced by the Greek Pasteur Institute in Athens[6]. It prevents about 60% of tuberculosis (TB) cases in children on average, with large differences between countries. BCG vaccination has been suggested to have nonspecific beneficial effects in children from developing countries, reducing morbidity and mortality caused by unrelated pathogens[7].

## NON-SPECIFIC EFFECTS OF VACCINES: CURRENT EVIDENCE AND POTENTIAL IMPLICATIONS

### How it works

Several mechanisms by which BCG provides non-specific protection against respiratory infections have been a subject of active investigation. In general, when a pathogen enters the body, white blood cells of the "**innate**" immune system attack it first. The innate immune system, composed of white blood cells such as macrophages, natural killer cells, and neutrophils, was supposed to have no memory[8]. If these cells fail, they call in the "**adaptive**" immune system, and *T cells and antibody-producing B cells* start to divide to fight. Key to this is that certain T cells or antibodies are **specific**

to the pathogen. Once the pathogen is eliminated, a small portion of these pathogen-specific cells transform into memory cells that speed up T cell and B cell production the next time the same pathogen attacks. Vaccines are based on this mechanism of immunity[9-13].

Molecular similarity between BCG antigens and viral antigens could lead, after BCG vaccination, to a population of memory B and T cells that recognize both BCG and respiratory pathogens. In addition, BCG could lead to antigen-independent activation of bystander B and T cells, a mechanism that has been termed **heterologous immunity**[9-14]. Finally, BCG could lead to long-term activation and reprogramming of innate immune cells. This last mechanism, which has been the subject of much interest in the past decade, has been called **trained immunity**[5,9].

This process can explain the rapid effects of BCG vaccination and has been suggested to be mediated by **epigenetic programming of monocytes or macrophages**[10,11]. Monocytes undergo histone modification at promoter sites of genes encoding inflammatory cytokines, leading to long-term changes in their ability to respond to novel stimuli and resulting in an increasingly active immune response when they are reactivated. Monocytes from adults who receive BCG vaccination exhibit increased expression of various surface markers related to activation and produce cytokines, such as IL-1β, IL-6, IFNγ and TNF, in response to infection with various pathogens[9-14].

## Evidence

The idea that BCG offers protection against the novel coronavirus, or SARS-CoV-2, seems to stem from the vaccine's ability to induce trained immune response, where the immune system of someone vaccinated with BCG, produces the ability to fight off other pathogens, including parasites and viruses[15,16]. There is weak evidence, but some previous studies have shown that the BCG-induced response can actually improve our ability to fight some unrelated viruses as well. It could **prevent up to 30** per cent of all known infections, not only from viruses. The vaccine has demonstrated that it can protect against other viral infections of the respiratory tract such as **influenza**[17]. In a randomized placebo-controlled study published in 2018, the team showed that BCG vaccination protects against experimental infection with a weakened form of the yellow fever virus**,** which is used as a vaccine[13].

## Debate

At the moment, there is **no evidence** that those who have been administered the BCG vaccine have any immunization against Covid-19. It is debated that BCG, which is administered to children under one year of age, offers protection more than 15 years, and any effect might be just a **correlation.** The studies published have been criticized for their methodology[18-22].

On 11 April 2020, WHO updated its ongoing evidence review of the major scientific databases and clinical trial repositories, observed that countries that routinely used the vaccine in neonates had **less reported cases** of COVID-19 to date. However, WHO believes that "such ecological studies are prone to significant **bias** from many **confounders**, including differences in national demographics and disease burden, testing rates for COVID-19, and the stage of the pandemic in each country".

Recently, in a research letter in JAMA in a cohort of Israeli adults aged 35 to 41 years, BCG vaccination in childhood was associated with a **similar rate** of positive test results for SARS-CoV-2 compared with no vaccination. Because of the small number of severe cases, no conclusion about the association between BCG status and severity of disease can be reached[23].

In the absence of convincing evidence, WHO does not recommend BCG vaccination for the prevention of COVID-19[24].

## Ongoing trials

Studies are in progress to determine whether BCG vaccination could protect against COVID-19 infection. Several trials involving BCG vaccination have commenced in Netherlands, Australia, Germany, and Greece[19,20]. **Netherlands** will recruit 1000 health care workers in eight Dutch hospitals who will either receive BCG or a placebo. Giamarellos has set up an open study in **Greece** to see whether BCG can increase resistance to infections overall in elderly people. The researchers will be blinded to which arm of the study—vaccine or placebo—a person is in. A research group in **Melbourne** and another at the **University of Exeter** are setting up a BCG study among health care workers. It is possible that BCG-Tokyo would be preferable to BCG-Danish. A team at the **Max Planck Institute** for Infection Biology will start a similar trial with VPM1002, a genetically modified version of BCG that has not yet been approved for use against TB. However, BCG vaccine is already in short supply, and indiscriminate use could jeopardize the supply needed to protect children against tuberculosis in high-risk areas or could engender a false sense of security. In addition, there is a possibility that up-regulation of immunity by BCG will exacerbate COVID-19 in a minority of patients with severe disease[21].

## UNANSWERED QUESTIONS

- First, how long does the heterologous immunity engendered by BCG last after vaccination?
- Second, what is the optimal time to vaccinate?
- Third, can it bridge the gap before a disease-specific vaccine is developed?
- Fourth, will the use of BCG to prevent COVID-19 affect its use to treat bladder cancer?

In **conclusion**, the vaccine probably won't eliminate infections with the new coronavirus completely, but is likely to diminish its effect on individuals. The vaccine may confront textbook knowledge of how immunity works.

## CONFLICT OF INTEREST

None.

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