Does the BCG Vaccine Offer Any Protection Against Coronavirus Disease 2019?

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Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-COV2), shares features with diseases caused by other coronaviruses such as influenza, the Severe Acute Respiratory Syndrome (SARS) outbreak of 2003, and the Middle East Respiratory syndrome (MERS) outbreak of 2012. COVID-19 has been a challenging and devastating pandemic, resulting in death rates of more than 1%, testing nations both rich and poor, and outlining the importance of strong public health programs. Social distancing, masking and hand washing have become the new norm. Healthcare professionals are on the front lines, risking their lives. Those with pre-existing health conditions or older individuals face a significant risk for complications.

As scientists race to understand this deadly virus and find a cure to protect millions, an unlikely ally may come in a vaccine created over 100 years ago. The Bacillus Calmette-Guérin or BCG vaccine was created in 1921 to protect against tuberculosis (TB). At the time, tuberculosis was widespread, and the BCG vaccine was quickly implemented globally. However, as tuberculosis rates declined, developed countries such as the United States and many European countries discontinued widespread BCG administration. This change in vaccination policy was due to the supply of the vaccine and concerns for its efficacy. On the other hand, countries such as India, Pakistan, Indonesia, Vietnam, Russia, Ethiopia, and many others have continued widespread administration of the BCG vaccine. Many of these countries still have high rates of tuberculosis infections, as well as a large percentage of their population live in poverty (1). When COVID-19 started to emerge as a pandemic, global leaders and public health officials feared this pandemic would have catastrophic effects on these countries, overwhelming their healthcare systems, and killing millions. Interestingly, the opposite outcome was observed as these countries reported low rates of COVID-19. Instead, Europe became the world's first epicenter outside of mainland China, followed by the United States, both of which reported large infection rates and death tolls due to COVID-19. The hardest hit countries had a similarity in that, they did not require widespread neonatal BCG vaccination. Ultimately, it is possible that the key difference between rates of COVID-19 infections in nations lies in neonatal BCG immunization rates amongst the populations. However, these conclusions are subject to confounding variables, such as the strength of the public health programs, and testing and reporting rates for COVID-19. An interesting outlier is Iran, which implemented a nationwide BCG vaccination program late in 1984, for children less than 6 years of age, using the

Pasteur strain (2). With the high rates of COVID-19 cases in Iran, further research needs to examine this outlier, to see if there is any association with the type of vaccine used, administration at a later age, or the fact that currently middle-aged and elderly Iranians are not universally vaccinated.

Another interesting observation comes from the COVID-19 racial/ethnic distribution in the United States. The Centers for Disease Control and Prevention (CDC) released the race/ethnicity data for 580 lab-confirmed COVID-19, hospitalized patients on April 8, 2020 (3). In this data, African Americans constituted 33% of patients (when compared to 18% in the catchment populations) while Asians constituted 5.5% of the patients (proportion of Asians in the catchment population was not described). In certain states, Asian American populations showed higher disease and death rates for COVID-19, when compared to the general population (4). Interpretation of this data is, however, subject to confounding variables. The racial category for the Asian population is reported differently throughout the nation. Many states have differing definitions for the Asian race, certain states fail to divide the Asian population into different subgroups, and others combine Asian populations with 'other' racial groups (5). Furthermore, because the US does not have a widespread COVID-19 testing program, certain communities lack access to tests, and disparities for groups may be hidden. Once comprehensive data is available, it would be interesting to examine if the Asian subgroups consisting of individuals who received the BCG vaccine from a BCG administering country, before immigrating to the US show better outcomes against COVID-19, when compared to other Asian American subgroups.

The BCG vaccine was created by Albert Calmette and Camille Guérin against a live attenuated strain of Mycobacterium bovis, a mycobacterium that is similar to the one that causes tuberculosis. The vaccine creates both specific immunity to that mycobacterium, as well as nonspecific immunity against other pathogens that cause respiratory tract infections. In a study conducted on mice, researchers found that when subjecting mice to infectious viruses such as the A0 and A2 influenza viruses, herpes simplex virus, as well as other highly infectious viruses, mice inoculated with BCG were found to exhibit a significantly higher resistance to these infections compared to control mice (6). An explanation for this finding may lie in the fact that the BCG vaccine results in innate immune memory in the host. This trained immunity works by reprogramming a host's bone marrow hematopoietic stem cells and multipotent progenitors through epigenetic/metabolic changes, resulting in greater variability of the differentiated innate immune cells response following a pathogen (7). Ultimately, this may result in the host's immune system being able to successfully fight off large numbers of respiratory tract infections, including possibly SARS-CoV-2.

The World Health Organization (WHO) stands firm on the stance that there is no scientific evidence as to whether the BCG vaccine actually protects against COVID-19. Furthermore, WHO mentions that BCG vaccination is particularly important for children in countries with high prevalence of tuberculosis, and if local supplies are diverted, these children will face an increase in disease and death from tuberculosis (8).

As more scientific research is being conducted, the preliminary findings may indicate BCG as a potential safeguard against COVID-19. This may be explained through the lower rates of infection in countries with widespread neonatal BCG vaccination policies. Furthermore, immigrants who come from BCG administering countries may also have this advantage against COVID-19. Currently, the US Government is working to release a racial/ethnic breakdown of COVID-19 cases. As more data is published on race and ethnicities, it will be useful to examine if fewer COVID-19 cases and deaths occur amongst immigrant populations from BCG-administering parent countries, after adjusting for confounders.

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