GLOBAL APPROACHES TO IMMUNITY AND EPIDEMIOLOGICAL STUDIES OF SARS-COV-2: DOES UNIVERSAL BCG VACCINATION POLICY PLAY A ROLE ?'

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Keywords: SARS-CoV-2; Universal BCG vaccination policy; COVID-19; Coronavirus; Morbidity; Mortality

It has been observed that countries without universal policies of BCG vaccination are more severely affected compared to countries with long-established BCG vaccination policies. This has led researchers to investigate the possible relation between BCG and COVID-19. The authors have evaluated the current research regarding the role of the universal *Bacille Calmette Guerin* (BCG) vaccination policy of a country to the morbidity and mortality due to COVID-19/ SARS-CoV-2 in that country. It is believed that the BCG vaccine trains the immune system of the human body for non-mycobacterial pathogens through non-specific immunotherapeutic mechanisms. Most of the epidemiological studies point towards a positive correlation but barring a few, and they tend to ignore factors like lower testing rates in countries having universal BCG policy. BCG vaccination policy cannot be seen in isolation as the factors like climatic conditions, nutritional habits, genetic and ethnic aspects, social and cultural influence and age distribution also are responsible for the varied morbidity and mortality due to COVID-19. Multiple-dose BCG vaccine repurposing for SARS-CoV-2, however, should be explored. Clinical trials of the BCG vaccine to test its efficacy on SARS-CoV-2 are urgently needed before deducing unidirectional correlations.

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INTRODUCTION

World Health Organisation (WHO) recognized SARS Cov-2 /COVID-19 as a potential global health threat due to its high mortality, extraordinary basic reproduction number and lack of clinically approved drugs and vaccines.[1]

It has been observed that countries without universal policies of BCG vaccination like Italy, Spain, UK, Netherland and USA are more severely affected compared to countries with long-established BCG vaccination policies. This has led to scientists and researchers all across the globe turning their attention to this vaccine. Does BCG provide partial herd immunity? Is it possible that in a country where BCG vaccination has already taken place, the transmission of COVID-19 from a partially immune person to another individual with the same immune status due to BCG vaccination policy of the country make COVID-19 slowly less and less virulent after each transmission? Is there a likely association between the existence of universal BCG vaccine policies and the morbidity and mortality associated with COVID-19 infections? Can that lead to the protection of the whole population in the long run? We tried to find the answers to these questions by examining and reviewing data and information in the literature about this hypothesis.

BCG VACCINE AND TRAINED IMMUNITY

BCG is a live attenuated strain derived from an isolate of *Mycobacterium bovis* and is used widely across the world as a vaccine for Tuberculosis (T.B.).[2] Many nations like Japan, India and China, have a universal BCG vaccination policy in newborns. On the other hand, many countries like France, Switzerland and Spain have withdrawn their universal vaccine policies. These counties have discontinued the BCG vaccination policy because of the low risk for developing tuberculosis infections and the doubtful efficacy of the BCG vaccine. Countries like the United States of America, Italy, and the Netherlands have not adopted universal vaccine policies.[3] One reason for the effectiveness of BCG is its positive heterologous or non-specific immune effects.[4] It leads to enhanced response against other non-mycobacterial pathogens through non-specific immunotherapeutic mechanisms. This protective effect of BCG on unrelated infections is called trained immunity.[5] Metabolic and epigenetic changes and chromatin remodeling through histone modifications in innate immune cells that promote genetic regions encoding for pro-inflammatory cytokines are responsible for trained immunity. BCG vaccination increases the secretion of pro-inflammatory cytokines, specifically interleukin 1β (IL-1β), leading to trained immunity.[6] There are some examples in the literature of the broad benefits of BCG.

A study conducted in West-African country Guinea Bissau suggested that during the administration of BCG to LBW, there was a tendency for lower mortality already during the first three days after BCG vaccination. A 17 % reduction in infant mortality was observed and the mortality level halved during the trial compared with the pre-trial level.[6] Another study designed to assess the heterologous protective effects of BCG vaccination against respiratory infection (R.I.) and sepsis that occur because of reasons not due to T.B. in children born in Spain. A total of 464 611 hospitalization episodes from 1992 to 2011 were analysed and it was found that BCG vaccination at birth may decrease hospitalization, due to R.I. and sepsis, not related to tuberculosis, through heterologous protection.[7] BCG vaccinations in the elderly (60 –75 years old), once a month

for three consecutive months, significantly prevent the acute upper respiratory tract infection and can increase the IFN-γ level as Th1 response and IL-10 as Treg response. [8,9] In another study, it was shown that if the BCG vaccine is administered before the influenza vaccine, the antibody titer to the influenza vaccine is considerably improved. Also, it was found that there was improved pro-inflammatory leukocyte response, more rapid seroconversion, and even modulation of cytokine responses against unrelated pathogens after the BCG vaccination.[10]

According to a report published by the World Health Organization, BCG has beneficial off-target effects, but more trials of the vaccine against a wider range of infections need to be done [11]. It is to be noted that WHO does not recommend the promotion of BCG vaccination for COVID-19 prevention but asks for a more cautious approach.[12,13]

BCG AND SARS-CoV-2: WHAT DOES EPIDEMIOLOGICAL STUDIES SAY?

The analysis of the data from various countries points to the fact that the countries which did not implement the universal vaccination policy have much more morbidity and mortality due to SARS-CoV-2 compared to countries that have universal BCG vaccination policy in place. For example, countries lacking universal BCG vaccination policies like Italy, the Netherland, and the USA have been more severely affected compared to countries with universal BCG policies like India and Japan. At the time of writing this paper, India and Japan are consistently maintaining a low mortality rate. India and Japan have been implementing universal BCG vaccination policies since 1948 and 1947, respectively.[14] Compare this to Italy, where universal BCG vaccination was never implemented and the mortality due to COVID-19 is very high. China also had a universal BCG vaccination policy in place. Initially, the scale of mortality was very large in China, but now the spread is contained.[14] It had also found that the earlier a country established a BCG vaccination policy, the stronger the reduction in their number of deaths per million inhabitants.[15] This is also proven from the example of Iran, where BCG vaccination policy started late (in 1984), so their elderly population is not protected. In fact, anyone who is over 36 has the risk of contracting this disease if the hypothesis of BCG providing non-specific immunity is correct. This can also point to the fact that there is a higher blanket immunity among the young that could be reducing infections among the old, thus reducing the overall mortality rates.[16] Analysing data from 210 countries with respect to compulsory vaccination with BCG vaccine showed that the number of COVID-19 positive and death cases per million of the population was significantly higher in nations not using childhood BCG vaccination than those that are still using it.[17]

In one of the studies, again, it was inspected whether national programs that use BCG vaccination could be the reason for the differential incidence and mortality observed in COVID-19 between different nations. According to the analysis of the data by authors, current national programs of BCG vaccination exist in 131 countries, 21 countries have no current program of national BCG vaccination, and for 26 countries, status is unknown. Countries with the national program of whole population BCG vaccination appear to have a lower incidence and death rate from COVID-19.[18] A simple linear regression maximum slope over five days analysis of the daily COVID-19 case and death statistics showed a correlation with national BCG vaccination policies. In another study, a comparison between the impact of COVID-19 in terms of case fatality rates (CFR) between countries with high disease burden and those with BCG revaccination policies was made. A significant difference in the case fatality rate between the two groups of countries was observed, supporting the view that universal BCG vaccination has a shielding effect on the course of COVID-19, maybe, preventing advancement to severe disease and death.[19]

Very little evidence was found in the literature about BCG vaccination not affecting the morbidity and mortality due to SARS-CoV-2. But this should be taken with a pinch of salt as one cannot ignore factors like population density, median age, T.B. incidence, urban population, and, most significantly, CoV-2 testing rates. A study found that if only countries with high testing rates are analysed, then there was no longer a significant association between the number of COVID-19 cases per million inhabitants and the BCG vaccination policy.[20] The developing countries that are showing less morbidity and mortality can be because of less and questionable testing. In one such study, country-age-level case statistics were merged with the start/termination years of BCG vaccination policy and a regression discontinuity and difference-in-difference analysis was performed. The results did not support the BCG hypothesis. But authors quoted certain limitations to their analysis, so further studies need to be done to corroborate the results.[21] It would be too simplistic to attribute the difference in mortality and morbidity because of BCG vaccination. Many factors are responsible, like inherent population constitution, e.g., genetics, age, underlying co-morbidities, different inherent virulence and pathogenicity of SARS-CoV-2 virus strains in different regions.[22] Iceland is a very good example where measures like effective social distancing and use of personal protective equipment (PPE) are the only epidemiologic measures that were taken and the spread of the pandemic was averted in spite of having no universal BCG vaccination policy. Also, political and economic variations between countries significantly influence COVID-19 testing rates.[23]

Mortality data from the COVID-19 pandemic for the top 100 countries ranked by mortality per capita and normalized in time at 0.1 deaths per million for each country was done, which showed that BCG vaccination is correlated with protection from death from COVID-19. This correlation was linked to existing information signifying that trained immunity may be an important mechanism in individuals demonstrating protection from the lethal effects of COVID-19.[24.]

CONCLUSION

In the current scenario, when there is a race to find a cure for COVID-19, it is very tempting to hail the BCG vaccine as the 'miracle drug', but extreme caution is required and one must not make simplistic conclusions. Our analysis does reveal an association between universal BCG vaccination policy and reduced morbidity and mortality due to COVID-

19 in a country. Factors like genetics, age, co-morbidities, the difference in virulence and pathogenicity of SARS-CoV-2 virus strains also should be taken into account and studies need to be carried out incorporating these dimensions. Also, we should base our understating on solid empirical evidence. For that, there is an urgent need for clinical trials of the BCG vaccine. Clinical trials are already underway across the globe for studying the efficacy of the BCG vaccine against COVID-19. Scientists at the University of Melbourne and Murdoch Children's Research Institute, Australia, are administering the BCG vaccine/placebo to thousands of physicians, nurses, respiratory therapists and other health care workers. A clinical trial of 1,000 health care workers in the Netherlands, Radboud University Medical Centre in Nijmegen is also underway. Hopefully, these will make the picture clearer in the days to come. However, one thing is clear. Even in countries where BCG vaccination is in place, response to COVID-19 has been very different across different countries. This is attributed to marked variation in the BCG stocks used around the world and differences in the virulence of the strains of Mycobacterium tuberculosis. BCG has its own share of controversies, with questions being raised about its efficacy in preventing infection from even Mycobacterium tuberculosis, let alone COVID-19. Hopefully, the results of the clinical trials will show away. Developing economies that have very weak health infrastructure will be most benefited if the BCG vaccine proves out to be effective against SARS-CoV-2.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this work.

ACKNOWLEDGEMENT

The authors thank their respective institutions for administrative and moral support.

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This paper was presented at the International Conference "

CONFERENCE ON MOLECULAR STRUCTURE & INSTRUMENTAL APPROACHES"

at RK University, Rajkot (Gujarat-India) on 26-27th November 2020

Received: 10.12.2020.
Accepted: 04.01.2021.