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BCG Vaccination strategy for preventaion against COVID-19: Hype or Hope?

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Abstract

The Bacillus Calmette-Guerin vaccine (BCG vaccine) designed to prevent tuberculosis in children has been shown to induce a trained immune response in the body to fight against bacteria as well as other parasites and viruses. This knowledge has been reciprocated to generate the idea that this vaccine can also offer protection against severe acute respiratory syndrome coronavirus-2 (SARS-COV-2). Some recent pre-print articles have highlighted that countries with mass BCG immunizations seems to have a lower incidence of coronavirus disease 2019 (COVID-19) compared to those without BCG immunization. There are yet no experimental proof of any such association and the world health organisation (WHO) is currently testing the theory with clinical trials on selected cohorts. Epidemiologists and other scientific experts has expressed both their hope and concern simultaneously regarding the success theory of BCG vaccination to prevent COVID-19. Though its still not verified in any way whether the BCG vaccination can actually prevent COVID-19 or not but we believe a thorough analytical research in this regard is indeed worth a shot.

1. Introduction

The whole world, currently, is combating the COVID-19, which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It is posing a significant threat to global health as well as the economy. The medium of the spread of this novel virus is primarily through respiratory droplets, close and physical contact. With a non-uniform pattern of development, in its first three months, this novel virus has infected more than 3,00,000 individuals and caused more than 13,000 deaths (1) . The figures keep on increasing.

SARS-CoV-2 belongs to Coronaviridae family, possessing a positive-sense single-stranded RNA genome (2-4). It is the seventh type of coronavirus to infect humans and cause ailments. The other six members of the coronaviridae family-like SARS-CoV or MERS-CoV (Middle East Respiratory Syndrome Coronavirus) are also known for their pathogenicity with comparatively higher mortality rate than that of SARS-CoV-2 (5).

Currently, not a single antiviral or antimicrobial treatment has been proven to be useful for COVID-19. Combining more than three antivirals are not recommended. At the moment, treatment options are primarily based on the previous encounters and results showing benefits in the treatment of SARS, Ebola, MERS influenza, and other viral infections (6).

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1.1. BCG vaccine and its antiviral role

Bacillus Calmette-Guerin (BCG) vaccine is basically used for the treatment of tuberculosis (TB) and it was introduced in 1921. It is a live attenuated strain obtained from *Mycobacterium bovis* isolate. Relevant studies retrieved from PubMed and clinicaltrial.gov, suggested that some strains of BCG vaccine not only prevented the propagated types of TB, but also induced protection against infections with other non-mycobacterial pathogens or non-related causative agents (7). In case of humans, evidences obtained from laboratory and clinical experiments and studies suggests that BCG vaccination may have non-specific preventive results against viral infections (8). For example, in the BCG-vaccinated mice, enhanced production of interferon gamma (IFN-γ) from the CD4+ cells took place in order to prevent the infection from the vaccinia virus (9). This phenomenon of stimulation of CD4+ cells for overproduction of IFN-γ for prevention of viral infection was termed as 'trained immunity'.

Various metabolic as well as epigenetic changes are responsible for causing trained immunity. Due to this trained immunity caused by these metabolic and epigenetic changes, various genetic regions are promoted for encoding of pro-inflammatory cytokines (10) . Pro-inflammatory cytokines like Interleukin-1B (IL-1B), also known as leukocytic pyrogen have an enhance in their secretions on BCG vaccination. IL-1B is known to have a crucial role in immunity against viruses (11).

A study conducted in West-African country Guinea Bissau suggested that BCG vaccinated children experienced a reduction of 50% in overall mortality. It was inferred that this reduction in overall mortality was due to BCG vaccine which reduced sepsis and further, respiratory infections (12).

1.2. Epidemiological studies

Various epidemiological studies arrived at a similar conclusion that the countries which adopted the universal BCG vaccination policy had a reduced mortality rate (Table 1) due to COVID-19 compared to the countries which did not implement the policy (1, 13). It was hypothesised that protection offered by BCG vaccination against COVID-19 was due vaccine's non-specific effects. These non-specific effects caused a reduction in respiratory tract infections in children, reduced viremia and antiviral effects in experimental animals (7).

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1.3. BCG vaccine: non-specific effects

Since 1970s BCG vaccines are known to have non-specific immune effects. BCG showed improved immunity against influenza and listeria in murine models (14, 15). Recent studies exhibited the mechanism of BCG vaccine and its non specific effects at molecular level. These unspecific benefits of the vaccine are primarily due to NOD2 and mTOR arbitrated changes in the immune cell's epigenetic landscape (10, 16-18).

There is a persistant change induced in the conformation of chromatin in adaptive and innate immune cells due to the BCG priming. These changes help the immune cells in improving immunity against bacterial, fungal, mycobacterial and viral infections (10, 16, 17, 19-22).

2. BCG vaccine: hope or hype?

BCG vaccinated healthcare workers involved in the care of patients suffering from COVID-19 were studied as subjects and clinical trials were run on them using two registered protocols which aimed at observing whether the vaccine was enhancing their immunity against SARS-CoV-2 (23, 24).

At present, due to the unavailability of any concrete evidences stating the fact that BCG vaccine prevents the infection of SARS-CoV-2, WHO does not approve of using the vaccine for treatment of COVID-19. Inspite the fact that studies and experiments conducted both on humans and animals have suggested the NSEs (non-specific effects) of BCG vaccine on immune system, the clinical relevance and proper classification of these effects are still not known. Epidemiological studies, that indicate less reported cases of COVID-19 in BCG vaccinated neonates, are influenced by various factors including the burden of disease and differences in demographics of the country, testing rates for COVID-19 virus infections and phase of the pandemic in each country.

3. Conclusion

Although BCG is known to possess the NSEs (non-specific effects) and also known to augment the immune system against viral infection, yet there are no strong clinical evidences suggesting that it might be a solution to cure COVID-19. WHO does not recommend the promotion of BCG vaccination for COVID-19 prevention, however WHO still continues to recommend BCG vaccination for newborns in areas with high occurences of tuberculosis.

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Further experimental work needs to be conducted for clarification of the fact whether BCG vaccine is a hype or a hope amidst the pandemic.

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Disclosure statement

The authors report no conflicts of interest

Abbreviations	
COVID-19	Coronavirus Disease 2019
SARS-CoV-2S	Severe Acute Respiratory Syndrome Coronavirus 2 Spike Protein
BCG	Bacille Calmette-Guérin
WHO	World Health Organization
MERS-CoV	Middle East Respiratory Syndrome coronavirus
NSEs	Non-specific effects
IL-1B	Interleukin-1B
IFN-γ	Interferon gamma

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Table 1.

	Incidence (per million)	**Death rate (per million)**
Countries with BCG vaccination policy.	38.4	4.28
Countries without BCG vaccination policy.	358.4	40

Table 1: Depicting that countries with BCG vaccination policy have lower infection due to COVID-19 and mortality rates compared to those that do not have the policy.

Figure 1:

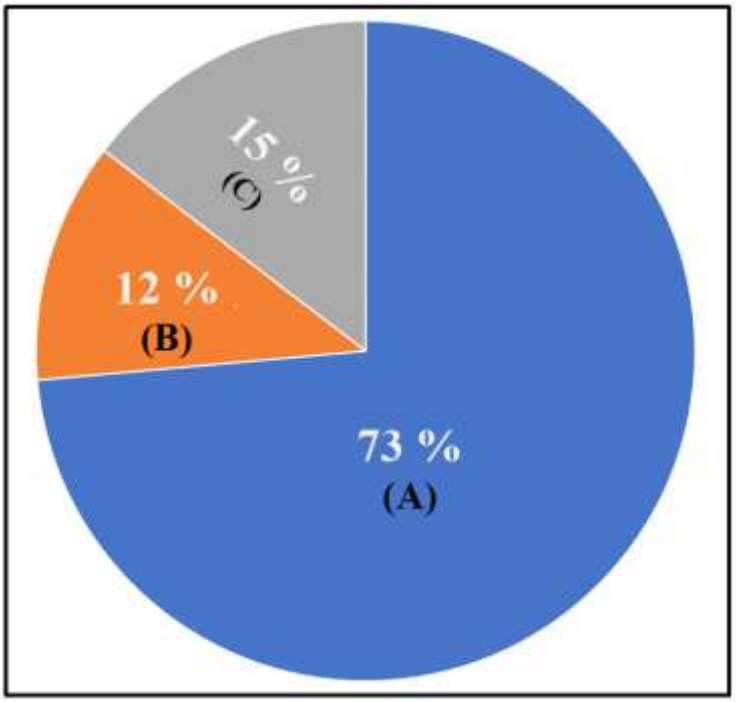

Figure 1: Global implementation of BCG vaccination policy. The pi chart was plotted based on study conducted in 178 countries (1) (A) % of countries with BCG vaccination policy (B) % of countries without BCG vaccination policy (C) Unclear whether they had this policy