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BCG Vaccine Induces Immunity and Protects Against COVID-19?

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Materials and Method: We searched various databases like PubMed, Medline, and Google scholar for articles explaining the effect of BCG against respiratory disease and COVID-19. The keywords used were "BCG vaccine" AND "COVID- 19" OR "BCG Vaccine against Respiratory Infections" AND "COVID-19 disease".

Results: Our results showed that BCG vaccination induces trained immunity against several viral infections. Some studies consider that BCG vaccination is a protective factor for COVID-19. Because countries without long-standing BCG vaccination policy have been more severely affected with COVID-19 than countries with such policy.

Conclusion: Thus, we conclude that BCG can have protective action against COVID-19, but more clinical trials needed to confirm the hypothesis.

Keywords: COVID-19, BCG vaccination, Trained immunity, SARS-CoV-2, Respiratory tract infection.

I. Introduction

Coronavirus disease is a respiratory infection originated in central China and quickly spread into many countries, which may lead to complications like Severe Pneumonia and Acute Respiratory Distress Syndrome (ARDS) (O'Neill & Netea, 2020). The disease is reported to be caused by a new strand in coronavirus family, namely Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Coronaviruses (CoVs) belong to the subfamily Orthocoronavirinae in the family Coronaviridae, Order Nidovirales. There are four genera within the subfamily Orthocoronavirinae, namely Alpha coronavirus (α-CoV), Beta coronavirus (β-CoV), Gamma coronavirus (γ-CoV) and Delta coronavirus (δ-CoV) (Banerjee et al., 2019). The CoV genome is an enveloped, positive-sense, single-stranded RNA with a size varying between 26 kb and 32 kb, the largest genome of known RNA viruses (Banerjee et al., 2019).

Bacillus – Calmette–Guerin (BCG) is a live attenuated vaccine developed against Tuberculosis at the beginning of the 20th century at the Institute Pasteur in Paris. Since then, it is referred to be the most used vaccine in the world, with around 130 million children vaccinated every year. Many randomized control trials have reported 50% reduction of mortality among young infants vaccinated with BCG (Aaby et al., 2011). This reduction appears to be due to the protective action of BCG against unrelated infectious agents, especially respiratory tract infections and neonatal sepsis (O'Neill & Netea, 2020).

COVID-19 has caused large number of deaths with tens of thousands of cases confirmed worldwide, thus posing a serious threat to Global Public Health (Li et al., 2020). However, currently there are no clinically proven vaccines or specific therapeutic drugs available to control or contain the disease spread (Aaby et al., 2011).

Thus, considering the protective action of BCG vaccine against major respiratory infections in general, we aimed to study its effect in inducing immunity against COVID-19.

II. Methods

Various articles reporting the effectiveness of BCG vaccination against respiratory diseases were searched in database like PUBMED, MEDLINE, and GOOGLE SCHOLAR. The keywords used were "BCG vaccine" AND "COVID 19" OR ""BCG Vaccine against Respiratory Infections" AND "COVID-19 disease".

III. Results

a) BCG Induced Trained Immunity against COVID-19

In general, everyone is aware that the BCG vaccine is the most used vaccine worldwide, with around 130 million children vaccinated every year. But many epidemiological studies have reported that the BCG vaccine has reduced the infant mortality globally (O'Neill & Netea, 2020). Everyone well knows that virus pathogen is the most common cause of respiratory tract infection and mortality in children and BCG, an effective

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vaccine against TB, with protective action against all respiratory infections, can be concluded as the reason for the reduction in mortality among children affected by respiratory diseases.

A community-based case-control study from Guinea Bissau has showed that BCG vaccine reduces the incidence of respiratory syncytial virus infection (Stensballe et al., 2005). BCG vaccination significantly increases the secretion of pro-inflammatory cytokines, specifically IL-1B and plays a vital role in antiviral immunity (Kleinnijenhuis et al., 2014). A recent randomized, placebo-controlled human challenge study has also showed that BCG vaccination induced genome-wide epigenetic reprogramming of monocytes and protected against an attenuated yellow fever virus vaccine strain (Arts et al., 2018). These study findings thus strengthen the fact that inducing trained immunity by BCG vaccine results in significant protection against several viral infections.

b) *Does BCG vaccination policy reduce morbidity and mortality of COVID-19?*

BCG, a live attenuated vaccine used worldwide against Tuberculosis including many nations like Japan and China, have a universal BCG vaccination policy among newborns (*Correlation between Universal BCG Vaccination Policy and Reduced Morbidity and Mortality for COVID-19: An Epidemiological Study | MedRxiv*, n.d.-a). A recent epidemiological study showed that the countries without long-standing BCG policy had been more severely affected with COVID -19 than countries with such policy (*Correlation between Universal BCG Vaccination Policy and Reduced Morbidity and Mortality for COVID-19: An Epidemiological Study | MedRxiv*, n.d.-a).

They classified the countries into three categories low-income, low-middle income, and high-income based on GNI per capita in 2018. The study reported that the low-income countries showed less number of deaths attributed to COVID-19 due to long-standing BCG policy, than low-middle income and high-income countries (Italy, Belgium, Netherlands, United States, and Lebanon). In Italy with no universal vaccination policy, the COVID-19 case mortality is very high in spite of implementing preventive measures like social distancing and strict Isolation.

On the other hand, countries like Japan with no strict isolation measures, managed to maintain reduced mortality rate. This may be due to their long-standing BCG policy and this can be considered as an evidence that the BCG vaccination policy can be a protective factor against COVID-19 infection.

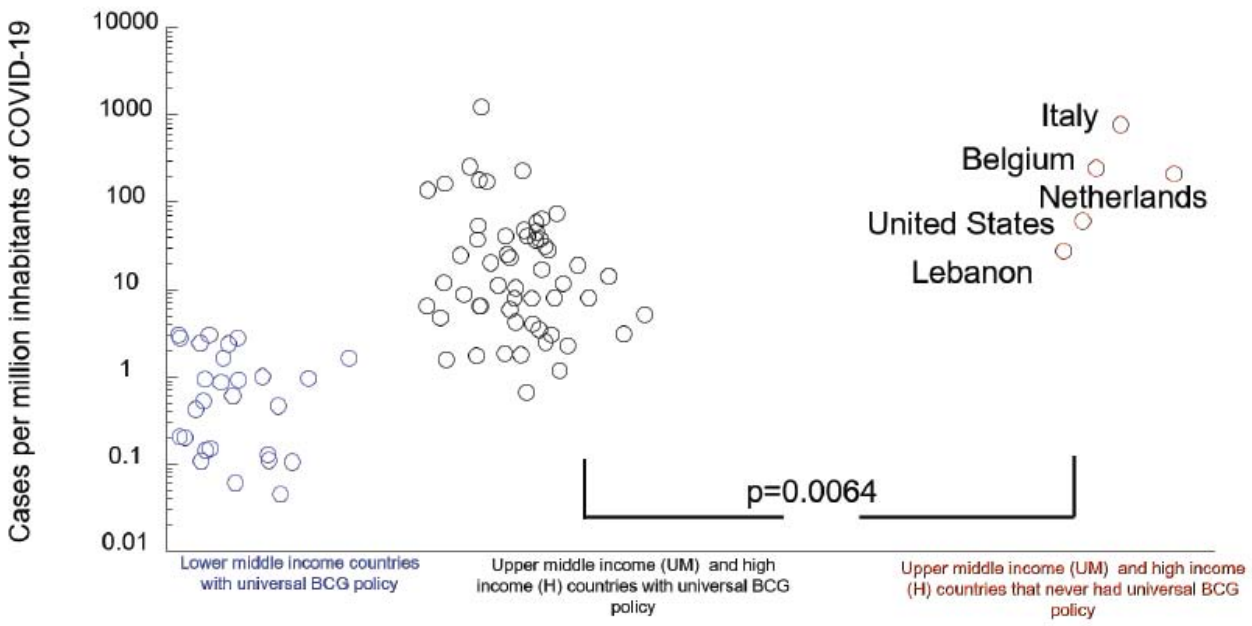

Figure 1: Numbers of COVID 19 cases in countries that never implemented a universal BCG vaccination policy(*Correlation between Universal BCG Vaccination Policy and Reduced Morbidity and Mortality for COVID-19: An Epidemiological Study | MedRxiv*, n.d.-b).

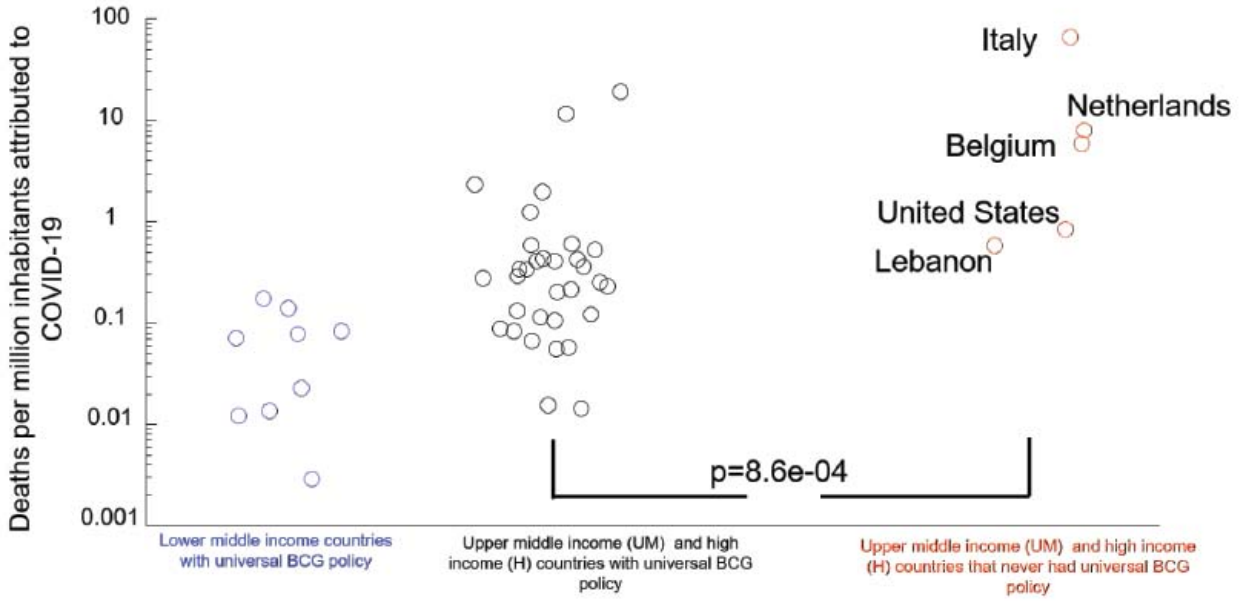

Figure 2: Higher death rate in countries that never implemented a universal BCG vaccination policy(*Correlation between Universal BCG Vaccination Policy and Reduced Morbidity and Mortality for COVID-19: An Epidemiological Study | MedRxiv*, n.d.-b).

The recent ecological study examined the effects of BCG vaccination on countries affected with COVID-19, based on cases and deaths of people due to the disease and exponential growth factors over specific periods of the Pandemic (Sala et al., 2020). The results of the study suggested that BCG vaccination and exposure to tuberculosis may induce non-specific protection against the novel SARS-CoV-2 infection. However, these findings can neither be hastily dismissed nor taken as ultimate evidence and this brings up the need more clinical trial to confirm the hypothesis.

c) Confounding factors

Most studies though showed supportive evidences for the hypothesis that BCG has protective action against COVID-19, were still affected by potential confounding factors like –the different phases of the outbreak, mean age of the affected population, management of the pandemic, administration of number of tests, definitions of COVID-19–related deaths, or underreporting.

A recent cohort study in Israeli tried to remove these confounding factors. In Israeli, between the period of 1955 to 1982, BCG vaccinations were included as a national immunization program and covered 90% of population. After 1982, the use of vaccine was restricted to be administered only to immigrants from countries with a high prevalence of Tuberculosis (Hamiel et al., 2020a). This change allowed comparison of infection rates (Table 1) and proportions with severe COVID-19 disease in 2 similar populations with differing BCG status-Individuals born during the three years before and three years after cessation of the universal BCG vaccine programme (Hamiel et al., 2020a).

Table 1: Results of SARS-CoV-2 PCR Testing by Age Group(Hamiel et al., 2020b)

	Birth Year		Difference (95% CI)	P-value
	1979-1981 (BCG vaccinated)	1983-1985 (BCG unvaccinated)		
Total population	297340	301600		
Immigrants in total population, No. (%) [a]	14 569 (4.9)	13 873 (4.6)		
No. of test	3064	2869		
Proportion of population tested, %	1.02	0.96		

Men tested, No. (%)	1509 (49.2)	1458 (50.8)		.29
Positive results				
No. (%)	361 (11.7)	299 (10.4)	1.3 (−0.3 to 2.9)	.09
No. per 100 000 population in age group[b]	121	100	21 (−10 to 50)	.15
Men with positive result, No (%)	181 (50)	152 (51)		.87
No. with severe disease	1	1		

Abbreviations: PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

a. Number of immigrants from countries with BCG vaccination policy and in their total population included in different birth-year groups.

b. Rates per 100 000 population do not represent the positivity rate in the population because the persons

The result of the study showed that there was no statistically significant difference in the proportion of positive test results in the BCG-vaccinated group (361 [11.7%]) vs the unvaccinated group (299 [10.4%]; difference, 1.3%; 95%CI, 0.3%to 2.9%; P = .09) (Hamiel et al., 2020a).

Thus, the study does not conclude any supportive evidence to accept the hypothesis that BCG vaccination in childhood has a protective effect against COVID 19 in childhood. The strength of the study is a large population-based cohort and the comparison of two similar groups with limiting the confounding to the minimum (Hamiel et al., 2020a).

IV. Discussion

SARS-CoV first appeared in 2002 and rapidly spread to 32 countries and regions, after which the world experienced the then MERS-CoV outbreak in 2012(Li et al., 2020). SARS-CoV-2 has spread rapidly in multiple countries causing severe illness, and sustained human-to-human transmission, making it a serious public-health threat to be concerned (Li et al., 2020). The disease since its first outbreak, has been a major challenge for public health authorities to control and there is currently no officially approved vaccine to protect from the disease.

Many ecological studies have tried to prove that BCG vaccination induces immunity and protection against COVID-19. But these studies are affected by bias from various confounding factors such as differences in national demographics and disease burden, testing rates for COVID-19 virus infections, and the stage of the pandemic in each country. Some cohort studies tried to limit these confounders and conclude with supportive evidences, still failed.

The studies aimed to state that countries with BCG vaccination policy showing reduced morbidity and mortality makes the vaccine, a potential new tool to fight against COVID-19. But without doing any clinical trial, we can neither accept nor eliminate this hypothesis.

WHO reported that there is no evidence that the Bacillus – Calmette-Guérin vaccine (BCG) protects the people fromCOVID-19 infection. This lead to two clinical trials to address this question which are underway, and the WHO will evaluate the evidence when it is available (*Bacille Calmette-Guérin (BCG) Vaccination and COVID-19*, n.d.).

Thus, in the absence of evidence, BCG is not recommended as a prevention against COVID-19 (*Bacille Calmette-Guérin (BCG) Vaccination and COVID-19*, n.d.). In the meantime, the factual theory of protective effect of BCG against respiratory infections in general can be considered as a supportive evidence in its conclusion.

V. Conclusion

Thus, as the whole world is looking for preventive vaccination for COVID-19, any study findings that prove that BCG vaccination induces immunity and protection against COVID-19 cannot be carelessly eliminated. However, they can neither be taken as ultimate supportive evidence, hence raising the need for more clinical trials to confirm the hypothesis.

Compliance with Ethical Standards

Conflict of interest: The authors have no competing interests to declare.

Ethical approval and informed consent: Not applicable

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