Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study

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Abstract

COVID-19 has spread to most countries in the world. Puzzlingly, the impact of the disease is different in different countries. These differences are attributed to differences in cultural norms, mitigation efforts, and health infrastructure. Here we propose that national differences in COVID-19 impact could be partially explained by the different national policies respect to Bacillus Calmette-Guérin (BCG) childhood vaccination. BCG vaccination has been reported to offer broad protection to respiratory infections. We compared large number of countries BCG vaccination policies with the morbidity and mortality for COVID-19. We found that countries without universal policies of BCG vaccination (Italy, Nederland, USA) have been more severely affected compared to countries with universal and long-standing BCG policies. Countries that have a late start of universal BCG policy (Iran, 1984) had high mortality, consistent with the idea that BCG protects the vaccinated elderly population. We also found that BCG vaccination also reduced the number of reported COVID-19 cases in a country. The combination of reduced morbidity and mortality makes BCG vaccination a potential new tool in the fight against COVID-19.

Introduction

The COVID-19 pandemic originated in China and it has quickly spread over all continents affecting most countries in the world. However, there are some striking differences on how COVID-19 is behaving in different countries. For instance, in Italy there has been strong curtailing of social interactions and COVID-19 mortality is still high. In contrast, Japan had some of the earlier cases, but the mortality is low despite not having adopted some the more restrictive social isolation measurements. These puzzling differences have been adjudicated to different cultural norms as well as differences in medical care standards. Here we propose an alternative explanation: that the country-by-country difference in COVID-19 morbidity and mortality can be partially explained by national policies on Bacillus Calmette-Guérin (BCG) vaccination.

BCG is a live attenuated strain derived from an isolate of *Mycobacterium bovis* used widely across the world as a vaccine for Tuberculosis (TB), with many nations, including Japan and China, having a universal BCG vaccination policy in newborns [1]. Other countries such as Spain, France, and Switzerland, have discontinued their universal vaccine policies due to comparatively low risk for developing *M. bovis* infections as well as the proven variable effectiveness in preventing adult TB; countries such as the United States, Italy, and the Netherlands, have yet to adopt universal vaccine policies for similar reasons.

Several vaccines including the BCG vaccination have been shown to produce positive "heterologous" or non-specific immune effects leading to improved response against other non-mycobacterial pathogens. For instance, BCG vaccinated mice infected with the vaccinia virus were protected by increased IFN-Y production from CD4+ cells[2]. This phenomenon was named

'trained immunity' and is proposed to be caused by metabolic and epigenetic changes leading to promotion of genetic regions encoding for pro-inflammatory cytokines[3]. BCG vaccination significantly increases the secretion of pro-inflammatory cytokines, specifically IL-1B, which has been shown to play a vital role in antiviral immunity[4] . Additionally, a study[5] in Guinea-Bissau found that children vaccinated with BCG were observed to have a 50% reduction in overall mortality, which was attributed to the vaccine's effect on reducing respiratory infections and sepsis.

Given our current understanding of the BCG vaccine's nonspecific immunotherapeutic mechanisms and by analyzing current epidemiological data, this investigation aims to identify a possible correlation between the existence of universal BCG vaccine policies and the morbidity and mortality associated to COVID-19 infections all over the world.

Methods

We collected the BCG vaccination policies across countries from the BCG World Atlas [6], available form http://www.bcgatlas.org/. We complemented the database in respect to dates of initiation of BCG vaccination. The additional references are in the adjunct table. Data of COVID-19 cases and death per country were obtained from https://google.org/crisisresponse/covid19-map on the morning (EST) of March 21st, 2020. Data were analyzed using Matlab scripts.

Results

Initially, we compared countries that never had in place a universal BCG vaccination policy (Italy, USA, Lebanon, Nederland, and Belgium), with countries that have a current universal BCG vaccination policy. We included only countries with more than 1 million inhabitants. The mortality rate might be influenced by multiple factors including a country's standard of medical care. In order to account for that, we classified countries according to their GNI per capita in 2018 using the World Bank data (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups). Countries were divided in three categories: low income (L) with an annual income of 1,025 dollars or less, lower middle income with an income between 1,026 and 3,995 dollars, and middle high and high income countries, which included countries with annual incomes over 3,996 dollars. In order to determine if BCG vaccination was protective for COVID-19 infections, we used the number of deaths per million inhabitants per country attributed to COVID-19 (see attached table). Most of the countries with low-income levels (17/18) reported zero deaths attributed to COVID-19 and have universal BCG policies in place consistent with a protective role of BCG vaccination. However, this might be because of underreporting and we have excluded them from the analysis. Middle high and high- income countries that have a current universal BCG policy (55 countries) had 0.78± 0.40 (mean±s.e.m) deaths per million people (see **Figure 1**). In contrast, middle high and high income countries that never had a universal BCG policy (5 countries) had a larger mortality rate, with 16.39 ± 7.33 deaths per million people. This difference between countries was highly significant (p=8.64e-04, Wilcoxon rank sum test).

Middle high and high-income countries that have a universal BCG policy have some variability in the mortality rate. COVID-19 has increased lethality with age[7]. We wondered if countries that established a universal BCG policy earlier would have a reduced mortality rate, as older people that are more severely affected by COVID-19 would be protected. We analyzed the data from 28 countries where we had access to the start of the universal BCG vaccination policy. There was a positive significant correlation (ρ=0.44, p=0.02, linear correlation) between the year of the

establishment of universal BCG vaccination and the mortality rate, consistent with the idea that the earlier that a policy was established, the larger fraction of the elderly population would be protected (see **Figure 2, left panel**). For instance, Iran has a current universal BCG vaccination policy but it just started in 1984, and has an elevated mortality with 19.7 deaths per million inhabitants. In contrast, Japan started its universal BCG policy in 1947 and has around 100 times less deaths per million people, with 0.28 deaths. Brazil started universal vaccination in 1920 and also has an even lower mortality rate of 0.0573 deaths per million inhabitants.

As the numbers of tuberculosis cases dropped in the late 20th century, several middle high and high-income countries in Europe dropped the universal BCG policy between years 1963 and 2010. We hypothesized that although these countries do not have a universal current vaccination policy, they would also show a trend where the earlier they started their universal policy, the larger fraction of the elderly population would be covered, and the lower the death rate per million people. We analyzed 17 countries that dropped their universal BCG policy. There was also a positive significant correlation (ρ=0.54, p=0.02, linear correlation) between the year of the establishment of universal BCG vaccination and the mortality rate (see **Figure 2, right panel**). For instance, Spain started their universal policy in 1965 and lasted until 1981 (16 years) and has a high mortality rate (29.5 deaths per million inhabitants). In contrast, Denmark started their policy in 1946 and ended in 1986 (40 years) and has almost 10 times less deaths per million inhabitants with 2.3 deaths.

We have found evidence that BCG vaccination is correlated with reduced mortality rates produced by COVID-19. Mortality rates are a robust measure that has less dependence to the levels of COVID-19 testing. However, mortality rates per country relate to both the number of cases present in a country as well as the dead probability for individual cases. We wondered if BCG vaccination would also affect the spread of disease with the caveat that the number of reported COVID-19 cases is going to depend strongly on the number of tests performed per country.

The countries with low-income levels (18) reported few number of cases of COVID-19 per million inhabitants: 0.32 ± 0.09. However, the issue of underreporting might be more critical for estimating the number of cases and we have excluded the low income countries from further analysis. Middle high and high-income countries that have a current universal BCG policy (55 countries) had 59.54± 23.29 (mean±s.e.m) cases per million inhabitants (see **Figure 3**). Consistent with a role of BCG in slowing spread of COVID-19, middle high and high income countries that never had a universal BCG policy (5 countries) had about 4 times the number of cases per million inhabitants, with 264.90± 134.88. This difference between countries was significant (p=0.0064, Wilcoxon rank sum test), suggesting that broad BCG vaccination along with other measures could slow the spread of COVID-19.

We also wondered if the middle high and high-income countries that have current universal vaccination policies (28 countries) would show a relationship between the number of cases and the year that the universal vaccination started. Interestingly, there was no significant correlation (r=0.21, p=0.27) between the year that vaccination started and the total number of COVID-19 cases, suggesting that early vaccination of the elderly population was not a factor in reducing the number of cases (see **Figure 4**).

Discussion

We have shown epidemiological evidence indicating that some of the differences in morbidity and mortality produced by COVID-19 across countries might be partially explained by a country's BCG

vaccination policy. Italy, where the COVID 19 mortality is very high, never implemented universal BCG vaccination. On the other hand, Japan had one of the early cases of COVID-19 but it has maintained a low mortality rate despite **not** implementing the most strict forms of social isolation[8]. Japan have been implementing BCG vaccination since 1947. Iran had also been heavily hit by COVID-19 and it started its universal BCG vaccination policy only in 1984 potentially leaving anybody over 36 years old unprotected.

Why did COVID-19 spread in China despite having a universal BCG policy since the 1950's? During the Cultural Revolution (1966-1976), tuberculosis prevention and treatment agencies were disbanded and weakened[9]. We speculate that this could have created a pool of potential hosts that would be affected by and spread COVID-19. Currently, however, the situation in China seems to be improving.

Our data suggests that BCG vaccination seem to significantly reduce mortality associated with COVID-19. We also found that the earlier that a country established a BCG vaccination policy, the stronger the reduction in their number of deaths per million inhabitants, consistent with the idea that protecting the elderly population might be crucial in reducing mortality. However, there is still not proof that BCG inoculation at old age would boost defenses in elderly humans, but it seems to do so in Guinea pigs against M. tuberculosis [10].

BCG vaccination has been shown to produce broad protection against viral infections and sepsis[11], raising the possibility that the protective effect of BCG might be not directly related to actions on COVID-19 but on associated co-occurring infections or sepsis. However, we also found that BCG vaccination was correlated with a reduction in the number of COVID-19 reported infections in a country suggesting that BCG might confer some protection specifically against COVID-19. The broad use of the BCG vaccine across a population could reduce the number of carriers, and combined with other measures could act to slow down or stop the spread of COVID-19.

Different countries use different BCG vaccination schedules[6], as well as different strains of the bacteria[12]. We have not divided the data depending on the strain used to determine which strains are better at stopping spread of infection, as well as reducing mortality in the elderly population. As each country used the same strain for the whole population, difference in strains for different purposes should be gathered in randomized control trials with different subjects from the same population tested with different strains.

USA and other countries like Italy without a universal vaccination policy but with high fraction of immigrants from countries with different universal BCG policies and using different strains offer the possibility to perform epidemiological studies to determine vaccination schedules and strains that would optimize protection against COVID-19.

The correlation between the beginning of universal BCG vaccination and the protection against COVID-19 suggests that BCG might confer long-lasting protection against the current strain of coronavirus. However, randomized controlled trials using BCG are required to determine how fast an immune response develops that protects against COVID-19. BCG is generally innocuous with the main side effect the development of inflammation at the site of injection. However, BCG is contraindicated in immune compromised people as well as pregnant women[13], so care should be taken when applying these possible intervention for COVID-19.

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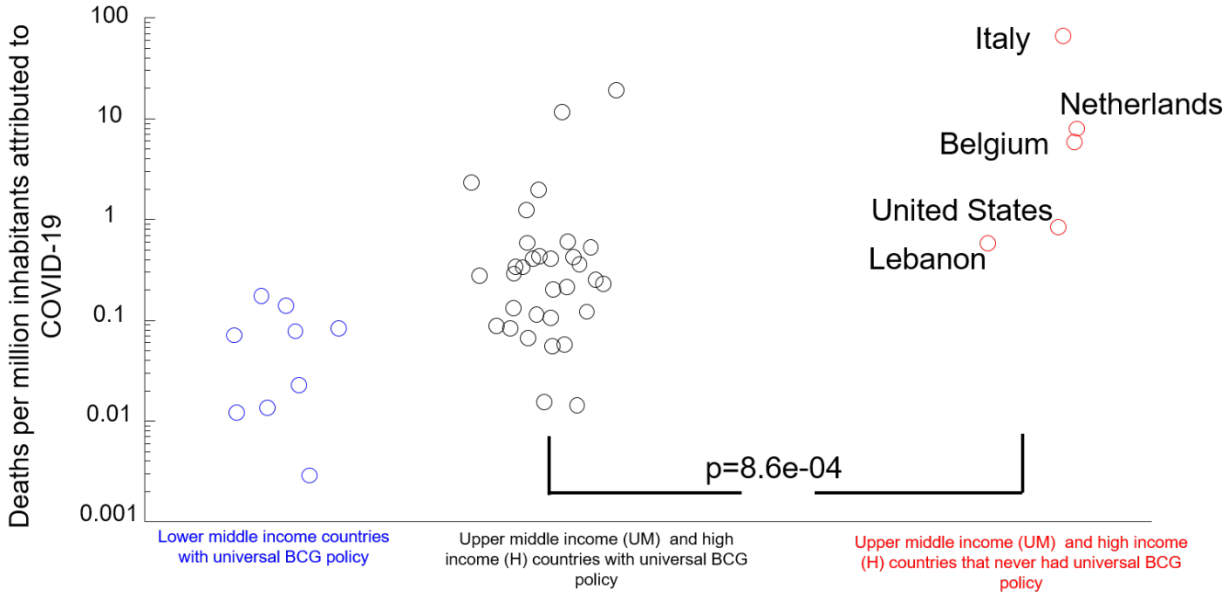

Figure 1: Higher death rates were presented in countries that never implemented a universal BCG vaccination policy.

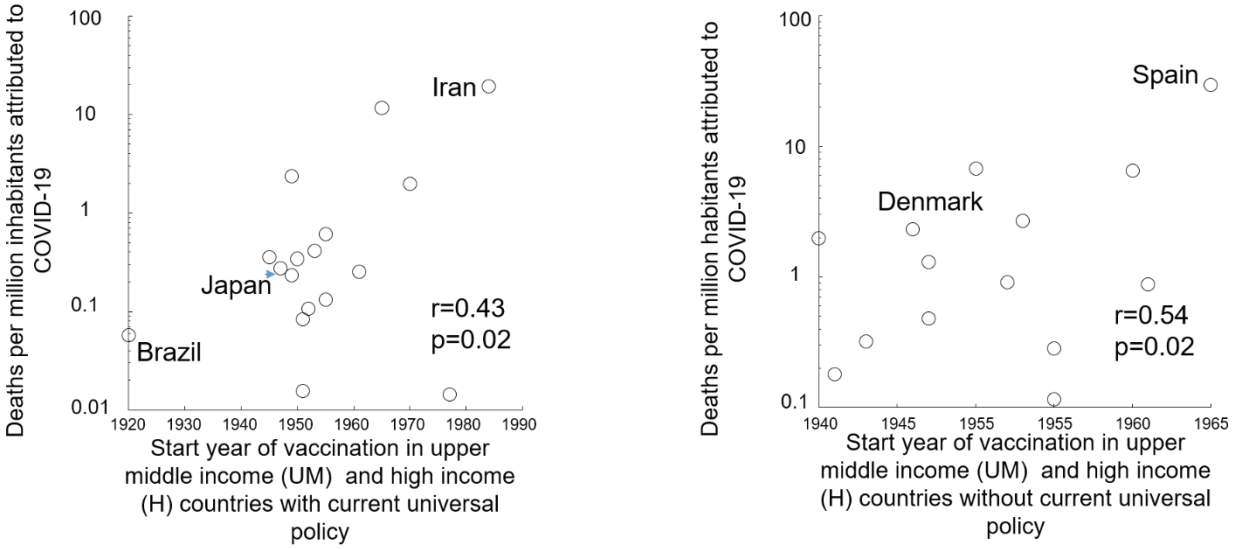

Figure 2: Earlier date of the start of vaccination reduces the mortality rate. Left panel correspond to upper middle income and high income countries with current universal BCG vaccination policy. The right panel correspond to countries that do not have a current universal vaccination policy.

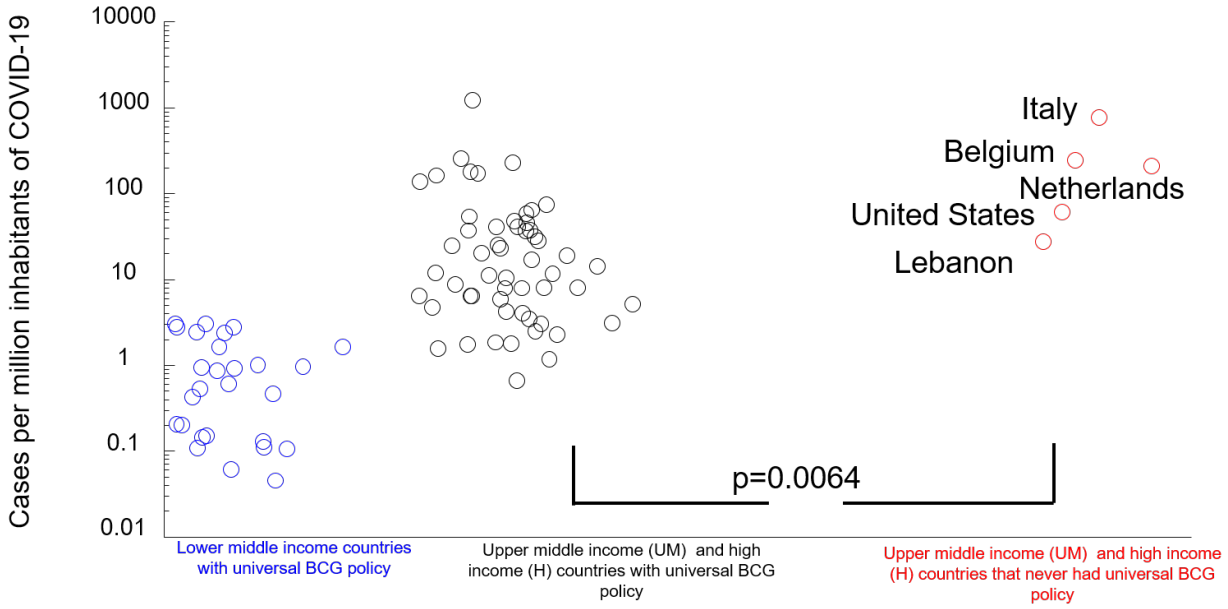

Figure 3: Higher number of COVID-19 cases were presented in countries that never implemented a universal BCG vaccination policy.

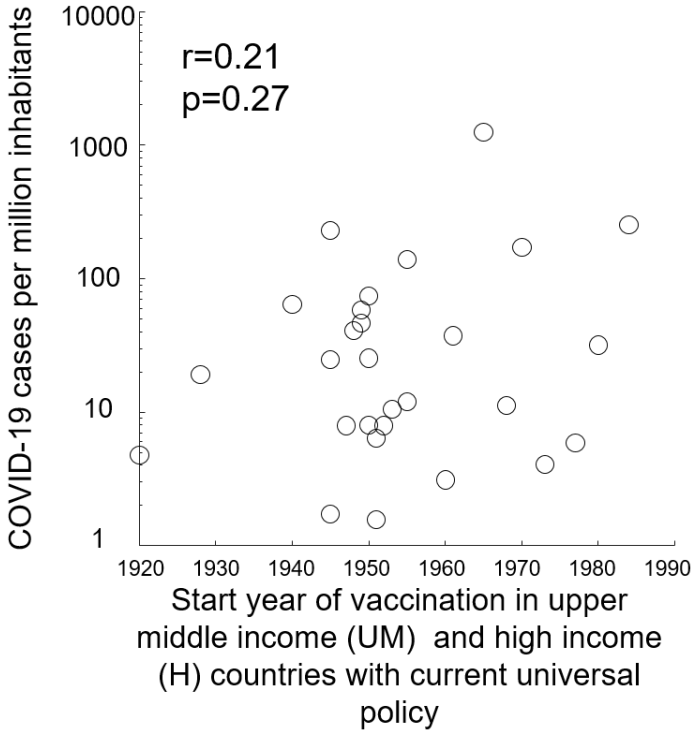

Figure 4: Later start of BCG vaccination policy did not correlate with number of COVID-19 cases.