ORIGINAL ARTICLE

Exploring the Potential Correlation Between BCG Coverage and Covid-19 Related Mortality

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ABSTRACT

Background: The lower COVID-19 related mortality observed in countries with a universal Bacillus Calmette-Guérin (BCG) vaccination policy led to the belief that the vaccine potentially has a protective role COVID-19. This study estimated the effect of the mean percentage of BCG vaccination coverage among infants, from 2010 to 2018, on the change in the mean weekly number of COVID-19 related deaths per million population whilst considering for the confounders of population density, elderly and urban proportions of the population.

Methods: The mean weekly number of COVID-19 related deaths per million population in 52 countries was regressed against the mean percentage of BCG coverage among infants from 2010 to 2011, population density per km2, percentages of urban and elderly (above 65-year of age) population in those countries in a multiple linear regression analysis.

Results: A significant regression model (F (4, 46)= 3.0941, p= 0.02) with an R^2 of 0.319 was calculated. The mean number of weekly COVID-19 related deaths decreased by 0.179 with every 1% increase in the mean BCG coverage among infants from 2010 to 2018 (p=0.018) and increased by 0.013 (p=0.506), 0.189 (p=0.593), and 0.113 (p=0.469) when the mean number of people living per km2, percentage of elderly population, and percentage of urban population increased by 1 respectively.

Conclusions: There seems to be a statistically significant correlation between BCG vaccination coverage among infants and reduced COVID-19 related mortality. However, this relationship in no way represents conclusive scientific evidence and further detailed studies are warranted before the BCG can be recommended as protective against COVID-19

INTRODUCTION

In December 2019, the world came across an unprecedented medical calamity in the form of a pandemic, triggered by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] Starting in the Wuhan City of China, the abrupt unfolding of the Coronavirus disease 2019 (COVID-19) pandemic to the rest of the world rendered most of the researchers unable to come up with effective solutions in a timely manner. Severe human and economic losses were met whilst life came to an almost standstill. Being the most logical approach to the problem, many entities around the world started to work on the rapid development of a vaccine against the COVID-19. One of the drawbacks of this approach was the length of time required to establish the safety and efficacy of a new vaccine.[2] Hence, an exploration of the already established medicines and vaccines, by reason of their easy accessibility and known safety profile, was proposed as a potential alternative solution to the ongoing crisis. Among those suggested and advocated to be possibly curative and protective against the COVID-19 was also the Bacillus Calmette-Guérin (BCG) vaccine.[3-5]

In 1908, a French physician Leon Charles Albert Calmette and a veterinarian Jean-Marie Camille Guerin, while working at the Institut Pasteur de Lille in France, noted that repeated sub-culturing of the mycobacterium tuberculosis resulted in successively lesser virulent strains of the bacillus. Consequently, the now avirulent BCG strain was made possible after sub-culturing the bacillus 239 times over a period of 13 years. After proving to be safe in animal studies, the first human trials of the vaccine were then conducted in 1921.[6] The vaccine, however, has remained less effective against the common respiratory form of the tuberculosis but more effective against the more severe disseminated form of the disease.[7]

Several types of the BCG vaccine have been developed over time, each with a different concentration of live particles and a reactogenicity profile. According to World Health Organization (WHO) the major strains used globally are: Pasteur 1173 P2, Danish 1331, Glaxo 1077, Tokyo 172-1, Russian BCG-I and Moreau RDJ strains. According to The BCG World Atlas the Pasteur 1173 P2 strain has been in use mainly in Iran, Colombia and Tunisia, Danish 1331 in Mexico, South Africa, South Korea and some of the European countries, Tokyo-172 in Japan, Taiwan and Kuwait, Russian BCG-I in Russia and Moreau in Brazil, Croatia and Czech Republic. Where as in other countries multiple concurrent strains of the vaccine are in utility.[8-9]

BCG vaccine coverage among infants in different countries around the world, from 2010 to 2018, has been constituted in TABLE 1. During this period, the mean BCG vaccine coverage among infants in the United States of America (USA), Spain, United Kingdom (UK), Italy, France, Germany, Canada, Belgium, Netherlands, Switzerland, Israel, Austria, Denmark, Czechia, Norway, Australia and Finland remained at zero percent, where as it was observed to be above 90% in Russia, Brazil, Turkey, Iran, Peru, Saudi Arabia, Mexico, Chile, Ecuador, Qatar, Belarus, United Arab Emirates (UAE), Poland, Bangladesh, Japan, Romania, South Korea, Dominican Republic, Serbia, Egypt, Panama, Malaysia, Morocco, Argentina and

Algeria. Mean BCG coverage among infants (from 2010 to 2018) was noted to be 89.89% in India, 83.78% in Pakistan, 58% in Portugal, 24.89% in Sweden, 39.78% in Ireland, 77.67% in Ukraine, 85.11% in Indonesia, 87.56% in Colombia, 84% in Philippines and 83.33% in South Africa.[9-10]

Studies have revealed increased survival rate in children when immunized with live attenuated vaccines, which can not be explained by immunity against the vaccine specific infection alone. It is believed that this non-specific cross immunity is induced through epigenetic reprogramming, the process of mitotically heritable alteration in gene expression with an unchanged genomic sequence, leading to what is known as trained immunity.[11,12]This trained immunity, hypothesized to be a function of the innate immunity, is believed to play a role in protecting against non-specific infections such as the Influenza virus, Respiratory Syncytial Virus (RSV) and Herpes Simplex Virus 2 (HSV-2).[13-15] However, there have been no conclusive evidence to date to prove if the BCG vaccine can induce such non-specific immunity against the SARS-CoV-2.[16]

BCG vaccine can induce non-specific cross immunity and besides being partially effective against the tuberculosis, studies have also demonstrated some therapeutic and protective effect against bladder cancer and viral respiratory infections.[13, 17] Perhaps it was for this reason along with the observation of lower COVID-19 related mortality in countries with a higher BCG coverage that the idea of BCG being possibly protective against the COVID-19 was put forward. However, most of the studies on the subject so far remain theoretical and without the consideration for many of the confounding factors that may have been spuriously causing the observed correlation.[18,19]

In this study we have tried to estimate the effect of mean BCG coverage among infants, from 2010 to 2018, on the mean weekly COVID-19 related mortality while considering for the confounders of population density, elderly (above 65-year of age) and urban proportion of the population along with the course of the pandemic in a country.

MATERIALS AND METHODS

Data concerning mean BCG coverage among infants in 54 countries around the world, from 2010 to 2018 (for 9 years), was derived from two sources: WHO and The BCG World Atlas.[9,10] Mean BCG coverage in a country during this nine year period was estimated by dividing the total sum of the percentages of the BCG coverage from 2010 to 2019 by the total number of years involved. Population density per km^2 in a country along with the percentages of above 65-year olds and urban population were obtained from online data sources: The World Bank and Worldometer.[20-22] Mean number of weekly COVID-19 related deaths per million population, for the next 6 weeks after excluding the first 30 days since the announcement of an index case in a country, was calculated using the online COVID-19 database Worldometer by dividing the total number of COVID-19 related deaths per million population in those six weeks by 6.[23] Dates of index cases were derived by conducting Wikipedia search with the phrase "COVID-19 pandemic in [country name]".[24] The entire formulated data used in our analysis has been illustrated in TABLE 1.

Table 1: Data on population density per kilometer square, percentage of elderly population (>65-year olds), percentage of urban population, index cases, mean BCG coverage among infants from 2010 to 2018 and mean weekly COVID-19 related mortality per million population from 54 countries

Adapted from WHO, The BCG World Atlas, The World Bank, Worldometer and Wikipedia. [9,10,20,21,22,23,24] (BCG: Bacillus Calmette-Guérin, COVID-19: Coronavirus Disease 2019, USA: United States of America, UK: United Kingdom, N/A: Not available)

Country	Density (per km^2)	>65- year olds (%)	Urban population (%)	Index Case of COVID-19	Mean BCG Coverage among infants (2010-2018)	Mean weekly COVID-19 related mortality per million population
USA	36	16	83	1/20/2020	0	3.2195
Spain	94	19	80	1/31/2020	0	61.3449
Russia	9	15	74	1/31/2020	95.6667	0.1485
UK	281	18	83	1/31/2020	0	30.1609
Italy	206	23	69	1/31/2020	0	54.7398
France	119	20	82	1/24/2020	0	20.6235
Germany	240	21	76	1/27/2020	0	4.6727
Brazil	25	9	88	2/25/2020	96	7.1439
Turkey	110	8	76	3/11/2020	95.6667	6.4620
Iran	52	6	76	2/19/2020	99	9.2428
India	464	6	35	1/30/2020	89.8889	0.0348
Canada	4	17	81	1/27/2020	0	1.8856
Peru	26	8	79	3/6/2020	90.6667	12.9656
Belgium	383	19	98	2/4/2020	0	69.8470
Netherlands	508	19	92	2/27/2020	0	46.5231
Saudi Arabia	16	3	84	3/2/2020	98.1111	1.2304
Mexico	66	7	84	2/28/2020	96.667	4.3136
Pakistan	287	4	35	2/26/2020	83.7778	0.4437
Chile	26	12	85	3/3/2020	95.1111	3.0515

Ecuador	71	7	63	2/29/2020	91	19.6772
Switzerland	219	19	74	2/25/2020	0	31.1587
Portugal	111	22	66	3/2/2020	58	16.1490
Sweden	25	20	88	1/31/2020	24.8889	14.8361
Qatar	248	1	96	2/27/2020	97	0.6942
Belarus	47	15	79	2/28/2020	98.2222	2.3106
Argentina	17	11	93	3/3/2020	96.7778	1.1690
Finland	18	22	86	1/29/2020	0	1.4439
Singapore	700	11	N/A	1/23/2020	98.8889	0.1709
Ireland	72	14	63	2/29/2020	39.7778	47.6934
UAE	118	1	86	1/29/2020	95.2222	0.2696
Poland	124	18	60	3/4/2020	93	3.6815
Bangladesh	1265	5	39	3/8/2020	98.7778	0.3572
Ukraine	75	16	69	3/3/2020	77.6667	1.6539
Austria	109	19	57	2/25/2020	0	10.3630
Japan	347	28	92	1/16/2020	94.2222	0.0672
Romania	84	18	55	2/26/2020	96.4444	7.7712
Indonesia	151	6	56	3/2/2020	85.1111	0.5307
Colombia	46	8	80	3/6/2020	87.5556	1.7655
Philippines	368	5	47	1/30/2020	84	0.3742
South Africa	49	5	67	3/5/2020	83.3333	0.7082
South Korea	527	14	82	1/20/2020	98.1111	0.5364
Dominican Republic	225	7	85	3/1/2020	98.8889	5.3927
Denmark	137	20	88	2/27/2020	0	13.2650
Kuwait	240	3	N/A	2/24/2020	98.3333	1.6391
Serbia	100	18	56	3/6/2020	98	8.7374
Egypt	103	5	43	2/14/2020	95.3333	0.5130
Panama	58	8	68	3/9/2020	98.4444	8.6525
Czechia	139	19	74	3/1/2020	0	10.7090
Norway	15	17	83	2/26/2020	0	6.1179
Australia	3	16	86	1/25/2020	0	0.2941
Malaysia	99	7	78	1/25/2020	98.7778	0.3192
Morocco	83	7	64	3/2/2020	99	0.6728
Algeria	18	6	73	2/17/2020	99	1.6609

Data from each of the 52 countries (after excluding Kuwait and Singapore due to the non-availability of data on urban population) was utilized to form four independent scale variables: mean percentage of BCG coverage among infants from 2010 to 2018, population density per km^2, percentage of above 65-year old population and percentage of urban population along with one dependent scale variable concerning the mean number of weekly COVID-19 related deaths per million population. A multiple linear regression analysis, with robust standard errors calculated using the covariance estimator HC3 (to make up for the heteroscedasticity in the data), was computed using the IBM Statistical Package for Social Sciences (SPSS) for Windows, Version 24.0.

RESULTS

Assumptions of multiple linear regression were tested for and are reported in TABLE 2.

Table 2: Assumptions of multiple linear regression
(Q-Q plot: Qunatile-Quantile plot, VIF: Variance Inflation Factor, HC3: Heteroskedasticity Consistent 3)

Assumption	Criteria	Model
Linearity	Scatter plot inspection	Satisfied
Multivariate Normality	Q-Q plot	Satisfied
Multicollinearity	Tolerance < 0.02, VIF < 3	Satisfied
Autocorrelation	Durbin Watson value 1.5 to 2.5	1.729
Homoscedasticity	Scatter plot inspection	Heteroscedasticity was detected: hence, robust standard errors were calculated using the covariance estimator HC3

A multiple linear regression was calculated to project the change in the mean number of COVID-19 related deaths per week per million population based on changes in population density, BCG vaccine coverage among infants, elderly (above 65-year of age) population and urban population. A significant regression was found (F (4,

46)= 3.0941, p= 0.02) with an R^2 of 0.319. Predicted change in the mean number of COVID-19 related deaths per week per million population was equal to 8.895 - 0.179 (BCG coverage among infants) + 0.013 (population density per km^2) + 0.189 (elderly population above 65-year of age) + 0.113 (urban population) where population density is measured as total population divided by total land in kilometers and BCG coverage, elderly population (above 65-year of age) and urban population as percentages within the range of 0% to 100%. Mean number of COVID-19 related deaths per week per million population decreased by 0.179 with every 1% increase in the mean BCG coverage of infants from 2010 to 2011, and increased by 0.189 and 0.113 with every 1% increase in elderly population (above 65-year of age) and urban population respectively. Similarly, the mean number of COVID-19 related deaths per week per million population increased by 0.013 when the total population divided by total land in kilometers increased by 1. Only BCG coverage among infants was found to be a significant predictor of the mean number of COVID-19 related death per week per million population (p= 0.018) where as population density, elderly population (above 65-year of age) and urban population were the insignificant predictors in our analysis (p= 0.506, p= 0.596 and p= 0.469 respectively). Co-efficients of our multiple linear regression analysis, along with robust standard errors calculated via the covariance estimator HC3, have been constituted in TABLE 3.

Table 3: Coefficients of regression with robust standard errors calculated using covariance estimator HC3
Predicted variable = mean number of deaths per week per million population (BCG: Bacillus Calmette-Guérin, HC3: Heteroskedasticity Consistent 3)

Model: Predictors	**B**	**SE (HC3)**	**T**	**P**
Mean BCG coverage among infants from 2010 to 2018 (%)	-0.179	0.073	-2.452	0.018
Population above the age of 65 years (%)	0.189	0.351	0.538	0.593
Population density per km^2	0.013	0.019	0.670	0.506
Urban Population (%)	0.113	0.154	0.729	0.469

DISCUSSION

COVID-19 continues to remain a major global health crisis claiming hundreds of thousands of lives and causing social and economical restrictions. Unfortunately, no effective treatment or vaccine is available yet to cure or protect against the COVID-19. The BCG vaccine, due to its boosting effect on the trained immunity, was also among the various solutions proposed to be possibly effective against the COVID-19.[13,14] Hence this study tried to estimate the effect of the mean BCG coverage among infants, from 2010 to 2018 in 52 countries around the world on the mean number of weekly COVID-19 related deaths per million population whilst taking into consideration the population density per km^2, percentage of elderly population (above 65-year of age) and percentage of urban population.

An overall trend of a relatively lower COVID-19 related mortality was observed in countries with a higher BCG coverage leading to several authors comparing COVID-19 related mortality with whether or not the country has a universal BCG vaccination policy in place.In one such article Masayuki Miyaska invited attention to whether if BCG was casually related to reduced COVID-19 mortality and that if the different strains of BCG provided different levels of protection against the COVID-19.[3] A study conducted by Ozdemir C etal. found that mean of cases per population ratio in BCG-vaccinated countries (n= 138) than BCG non-vaccinated countries (n= 37) was 0.0147 ± 0.027 vs 0.1892 ± 0.244 respectively with p <0.0001 while the mean of deaths per cases ratio was 3.4232 ± 3.688 vs 5.3429 ± 4.830 respectively with p <0.05.[4] Similar results were produced in our analysis showing a statistically significant 0.179 decrease in the mean number of deaths per week per million population with every 1% increase in the mean BCG coverage among infants from 2010 to 2018 (p= 0.018).

Japan happens to have a distinctly lower COVID-19 related mortality in the world despite having a highly dense and elderly population. Iwasaki A etal. speculated that besides the inherently suited culture for social distancing (no hand shaking, hugging or kissing) and the use of masks, BCG could also have been one of the reasons why Japan has a much lower COVID-19 related mortality than the rest of the world. They further speculated that the Tokyo-172, being one of the original strains, could be more effective than the rest in conferring protection against the COVID-19 as Japan also happens to has lower COVID-19 related morality among the countries that have a universal BCG vaccination policy in place.[5, 25] Our study found that increase in the percentages of elderly population (above 65-year of age) and urban population or increase in the mean number of people per km^2 were insignificant predictors of the mean number of COVID-19 related deaths per week per million population (p= 0.593, p= 0.469 and p= 0.506 respectively).

Other authors have raised the issue of the non-consideration of confounders stating that the differences in the death rates of COVID-19 could be attributed to the changing demographics and the course of the pandemic in different countries around the world.[18,19] In our study we included the confounders of population density, elderly population (above 65-year of age) and urban population, all of which were found to be statistically insignificant predictors of COVID-19 related mortality. To make up for the confounder of the course of the pandemic the inclusion criteria was designed to analyze only the next 6 weeks worth of data after excluding the first 30 days since the announcement of an index COVID-19 case in a particular country. However, other confounders such as: co-morbidities, health care quality and many others still remain to be addressed.

All the studies so far on the correlation between BCG vaccination and protection against COVID-19 have been

hypothetical and speculative and hence the World Health Organization (WHO) has advised against the use of BCG vaccine for the purpose of producing immunity against the COVID-19 until any clear supporting evidence is available. Currently, there are three ongoing clinical trials that aim to look for the protective role of BCG vaccine against COVID-19 in healthcare workers. These clinical trials based in Australia, USA and Netherlands are looking for different outcomes like incidence of COVID-19, severity of symptoms (Australia, USA) and absenteeism from work (Netherlands).[16] However, there still remains the need for more focused, comprehensive and conclusive clinical trials before, and if at all, the BCG vaccine could be confidently used on a large scale as a protection against the SARS-CoV-2 infection.

CONCLUSIONS

With hundreds of thousands of fatalities so far, COVID-19 remains one of the most pre-eminent health issues leading to dreadful social and economic constraints around the globe. Currently, there is no clearly effective treatment regimen or vaccine available against the COVID-19. Besides the development of a safe and effective COVID-19 specific vaccine, some authors have also suggested a probe into the pre-existing vaccine BCG as a possible solution to the ongoing crisis of COVID-19 due to its enhancing effect on the trained immunity which can confer protection against other non-specific infections besides tuberculosis. This analysis found a statistically significant decrease in the mean weekly number of COVID-19 related deaths per million population with increase in the mean BCG coverage among infants from 2010 to 2018. Population density along with the elderly and urban proportions of the population was found to be statistically insignificant predictors of the mean weekly number of COVID-19 related deaths per million population.

Studies conducted on the BCG vaccine being potentially protective against COVID-19 have been largely theoretical and unproven thus far. As pointed out by the WHO, thorough and definitive clinical trials are essential before BCG can be recommended for protection against the SARS-CoV-2 infection.

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