Effectiveness of Universal BCG Immunisation in Reducing the Incidence and Mortality of COVID-19: A Secondary Data Analysis

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Abstract

Background: Bacillus Calmette-Guérin (BCG) vaccine's immunomodulatory properties can protect against respiratory infections due to its nonspecific trained immunity of innate immune cells. The objective of the study is to assess the effectiveness of BCG in reducing incidence and morality of ongoing COVID-19 pandemic.

Methodology: The present study is a secondary data analysis to compare the incidence and mortality of COVID 19 among countries who had BCG vaccine in their national immunisation schedule with other group of countries who did not have. Twenty six countries with BCG vaccinations and eleven countries without BCG vaccinations were included in the analysis. The analysis was performed using the glmer() function in R and a random effects logistic model to study the determinants of incidence and mortality.

Results: The association between the BCG vaccination and number of cases of COVID-19 was significant in the univariate analysis ($p = 0.002$), upon statistical adjustment; the random effects model shows there was no association between countries with BCG vaccine included in the national immunization schedule and the number of cases ($p = 0.377$). Similarly, BCG was not statistically associated with mortality (case fatality rate > 5%) with a p value of 0.443.

Conclusion: Considering single variable BCG vaccine, the incidence and mortality of COVID-19 was found to be significantly higher in non BCG vaccinated countries while no significant association was observed when other determinants were included affecting the epidemiology of COVID-19. Additional research is recommended, to study the relationship between BCG and COVID-19.

Key words: BCG, COVID-19; Cases Per Million; Lockdown; Air Connectivity Index.

Introduction

A century old live attenuated vaccine Bacillus Calmette-Guérin commonly known as BCG had a controversial tag all through the history. BCG vaccine was developed from a less virulent bacteria called M. bovis by French bacteriologists Albert Calmette and Camille Guérin, after a research of 13 years, from 1908 to 1921. (1) Soon after World War II BCG gained popularity since the use was encouraged, stimulated in particular by UNICEF, by the fledgling World Health Organization (WHO), and by Scandinavian Red Cross Societies. Even when the safety of the vaccine is unquestionable even after 100 years of use, the efficacy of the vaccine to protect from tuberculosis is still a controversy. (2) To date, BCG remains as the most widely used vaccine worldwide and has been given to more than 4 billion individuals with astonishing safety records. (3)

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Different immunogenetic mechanisms of BCG are being discussed recently. The most common mechanism for any vaccination is the humoral immunity, which acts though generating antibodies against specific antigen in the vaccine. The most extensively studied in case of BCG is the cell-mediated immunity, which acts through macrophages, neutrophils and dendritic cells. Lately 100 year old BCG vaccine was found to have the ability to induce non-specific cross-protection against pathogens that might be unrelated to the tuberculosis. This ability is attributed to epigenetic reprogramming through changes in methylation pattern of histone associated with specific genes in circulating monocytes (part of innate immunity).(4)

Randomized controlled trials have provided evidence that the BCG vaccine's immunomodulatory properties can protect against respiratory infections.(5) In high-mortality settings like Guinea-Bissau, BCG-Danish is found to reduce all-cause neonatal mortality by 38% (95% CI 17–54), which was three fold higher than the neonatal tuberculosis incidence rate, mainly because there were fewer deaths from pneumonia and sepsis.(6) Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a single-stranded positive-sense RNA virus, and the role of BCG vaccine in reducing the viremia has been already established in other viral diseases. (7) It can be argued that BCG vaccine might be protective against many unrelated pathogens due its nonspecific trained immunity of innate immune cells. The ongoing coronavirus disease 2019 (COVID-19) pandemic has renewed academic and clinical interest in a 100 year old BCG vaccine, Bacillus Calmette–Guérin (BCG). Randomized controlled trials are underway in the Netherlands and Australia to assess whether BCG-Danish reduces the incidence and severity of Corona Virus Disease-19 (COVID-19) in health-care workers (NCT04327206, NCT04328441). (8), (9) This study highlights evidence of any significant association between BCG vaccine and protection against COVID -19.

Material And Methods

Study Design

The present study is a cross-sectional secondary data analysis to compare the incidence and mortality of COVID 19 among countries all around the world in two groups to observe the association of BCG vaccination in reducing the COVID-19 incidence and mortality.

Study Groups

One group included the countries who had BCG vaccine in their national immunisation schedule and other group was the countries who did not have BCG vaccine in their national immunisation schedule.

Data extraction

The data about COVID-19 incidence in different countries were collected from WHO COVID-19 situation report of 4th May, 2020 and current BCG status of the country was collected from world BCG atlas for a secondary analysis. (10) (11) The current population density was collected from the latest *World Bank data.* (12) Classification of countries on the basis of economy was done by using the World Bank Report data (World Bank Country and Lending Groups). (13) Air Connectivity Index was extracted from the World Bank Data. (14) Date of lock down or partial lock down was collected from the website of National response to COVID-19 pandemic by country and territory. (15) Day to reach 500 cases was assessed from WHO COVID-19 situation report. (10)

Sample size

Due to lack of prior studies on similar terms, using various simulations we found that sample size of 10 countries without BCG and 30 countries with BCG vaccine in their national immunisation program will give more than 90% power. To maximize statistical power and precision, a ratio of 1:3 was adopted as number of countries without BCG vaccine was limited. A purposive sampling was done among both the groups of countries to select the most populous 10 and 30 countries among the "No BCG" in national immunisation schedule group and "Regular BCG" vaccination in national immunisation schedule, respectively.

Outcome variable

Our primary outcome was cases per million, but since cases per million is directly affected by the testing capacity of the individual county, other secondary outcomes compared between two groups were deaths per million and case fatality rate of each countries. Other secondary outcome variables to compare between two groups were, testing per million, Air Connectivity Index, population density and days till 500 cases.

Statistical Analysis

We considered a random effects logistic model to study the determinants of incidence and mortality of COVID-19 in various countries. This model was chosen due to the fundamental assumption that the factors influencing incidence and mortality of COVID-19 would be inherently diverse across different countries. The analysis was performed using the glmer() function in the lme4 package in R. (16) (17) The glmer() function takes in arguments which specify the dependent variable, list of explanatory variables and a variable that specifies the random effect. For the multilevel random effects logistic model, we considered a dichotomous variable for cases per million (>1000 cases per million) as the dependent variable and used a reduced model with the country as the random effect variable. Logit link function was used to estimate the odds ratios and the confidence intervals were estimated using the profiling method. For assessment of mortality, we dichotomized the case fatality rate variable (CFR ≤ 5% & CFR > 5%).

This study did not need approval from the Ethical committee and the requirement for informed consent was waived because only registry and reported data was used. This study doesn't involve any human or animal experiments. Informed consent was not required.

Results

Out of total countries, 26 countries with BCG vaccinations and eleven countries without BCG vaccinations as per National Immunization Schedule were included in the analysis according to inclusion criteria. Proportion of Non BCG countries were significantly higher in high income countries. Air Connectivity Index and days since reaching 500 confirmed cases, confirmed cases per million, deaths per million, tests performed per million and case fatality rate was significantly higher in non BCG countries as compared to BCG countries using univariate model (table1).

In the results of the univariable analysis, high income countries were associated with higher incidence of COVID-19 cases, after adjusting for air connectivity index, population density, enforcement of lockdown measures and the random effects by country, this association was found not to be statistically significant.

As shown in Table 2, though the association between the BCG vaccination and number of cases of COVID-19 was significant in the univariate analysis (p = 0.002), upon statistical adjustment; the random effects model shows there was no association between countries with BCG vaccine included in the national immunization schedule and the number of cases (p = 0.377). Similarly, BCG was not statistically associated with mortality (case fatality rate > 5%) with a p value of 0.443 (Table 3).

Each country is represented by a bubble, with y-axis showing the number of confirmed cases per million and tests performed per million on the x-axis. The size of the bubble is reflected by the case fatality rate of the country while the color represents the income category. It is interesting to note that countries with high income tend to cluster around the extreme x and y axis and also have high case fatality rate (bubble size) as compared to countries in the lower spectrum of the income category (Figure 1).

Table 1: Summary table based on status of BCG vaccine in immunization schedule

Dependent: BCG in NIS		BCG	Non BCG	p
Income Category	High Income	6 (23.1)	10 (90.9)	0.001
	Low & Middle Income	20 (76.9)	1 (9.1)	
Population Density	Mean (SD)	158.6 (234.2)	165.8 (146.4)	0.926
Air Connectivity Index	Mean (SD)	4.1 (1.7)	10.3 (5.5)	<0.001
Days to reach 500 confirmed cases	Mean (SD)	32.7 (18.4)	37.6 (12.6)	0.427
Days since reaching 500 confirmed cases	Mean (SD)	40.1 (10.6)	54.0 (6.6)	<0.001
Lockdown before 500 cases	Enforced	13 (50.0)	2 (18.2)	0.151
	Not Enforced	13 (50.0)	9 (81.8)	
Confirmed cases per million	Mean (SD)	506.3 (692.2)	2318.7 (1463.6)	<0.001
Deaths per million	Mean (SD)	23.8 (54.5)	291.5 (220.0)	<0.001
Tests performed per million	Mean (SD)	7015.0 (9655.1)	24424.3 (11257.3)	<0.001
Case Fatality Rate	Mean (SD)	3.9 (2.8)	10.0 (5.7)	<0.001

Table 2: Association between confirmed cases per million and characteristics of the selected countries by univariate and random effects model

Explanatory Variables		Cases per million		Odds Ratio	
		< 1000	≥ 1000	Univariate Model	Random Effects Model
Income Category	High Income	6 (26.1)	10 (71.4)	-	-
	Low & Middle Income	17 (73.9)	4 (28.6)	0.14 (0.03-0.58, p=0.010)	199.79 (0.62-64726.36, p=0.072)
BCG in NIS	BCG	21 (91.3)	5 (35.7)	-	-
	Non BCG	2 (8.7)	9 (64.3)	18.90 (3.59-154.04, p=0.002)	3.49 (0.22-55.60, p=0.377)
Lockdown before 500 cases	Enforced	12 (52.2)	3 (21.4)	-	-
	Not Enforced	11 (47.8)	11 (78.6)	4.00 (0.95-21.31, p=0.073)	0.05 (0.00-3.22, p=0.162)
Days since reaching 500 confirmed cases	Mean (SD)	38.8 (9.8)	53.1 (8.1)	1.25 (1.11-1.48, p=0.003)	1.72 (0.99-2.99, p=0.053)
Population Density	Mean (SD)	177.6 (247.5)	133.1 (130.4)	1.00 (0.99-1.00, p=0.539)	1.00 (0.98-1.01, p=0.526)
Days to reach 500 confirmed cases	Mean (SD)	35.7 (18.2)	31.6 (14.7)	0.99 (0.94-1.03, p=0.471)	0.98 (0.91-1.06, p=0.633)

Table 3: Association between case fatality rate and characteristics of the selected countries by univariate and random effects model

Explanatory Variables		Case Fatality Rate		Odds Ratio	
		≤ 5%	> 5%	Univariate Model	Random Effects Model
Income Category	**High Income**	7 (31.8)	9 (60.0)	-	-
	Low & Middle Income	15 (68.2)	6 (40.0)	0.31 (0.07-1.19, p=0.094)	3.43 (0.15-80.44, p=0.443)
BCG in NIS	**BCG**	19 (86.4)	7 (46.7)	-	-
	Non BCG	3 (13.6)	8 (53.3)	7.24 (1.61-41.10, p=0.014)	4.13 (0.38-44.29, p=0.242)
Lockdown before 500 cases	**Enforced**	11 (50.0)	4 (26.7)	-	-
	Not Enforced	11 (50.0)	11 (73.3)	2.75 (0.70-12.46, p=0.162)	0.63 (0.08-5.23, p=0.668)
Days since reaching 500 confirmed cases	**Mean (SD)**	39.9 (10.7)	50.5 (9.7)	1.12 (1.04-1.25, p=0.013)	1.15 (0.99-1.34, p=0.074)
Population Density	**Mean (SD)**	166.6 (249.2)	152.1 (141.4)	1.00 (1.00-1.00, p=0.835)	1.00 (0.99-1.01, p=0.871)
Days to reach 500 confirmed cases	**Mean (SD)**	32.5 (18.9)	36.7 (13.6)	1.02 (0.98-1.06, p=0.458)	1.03 (0.98-1.08, p=0.300)

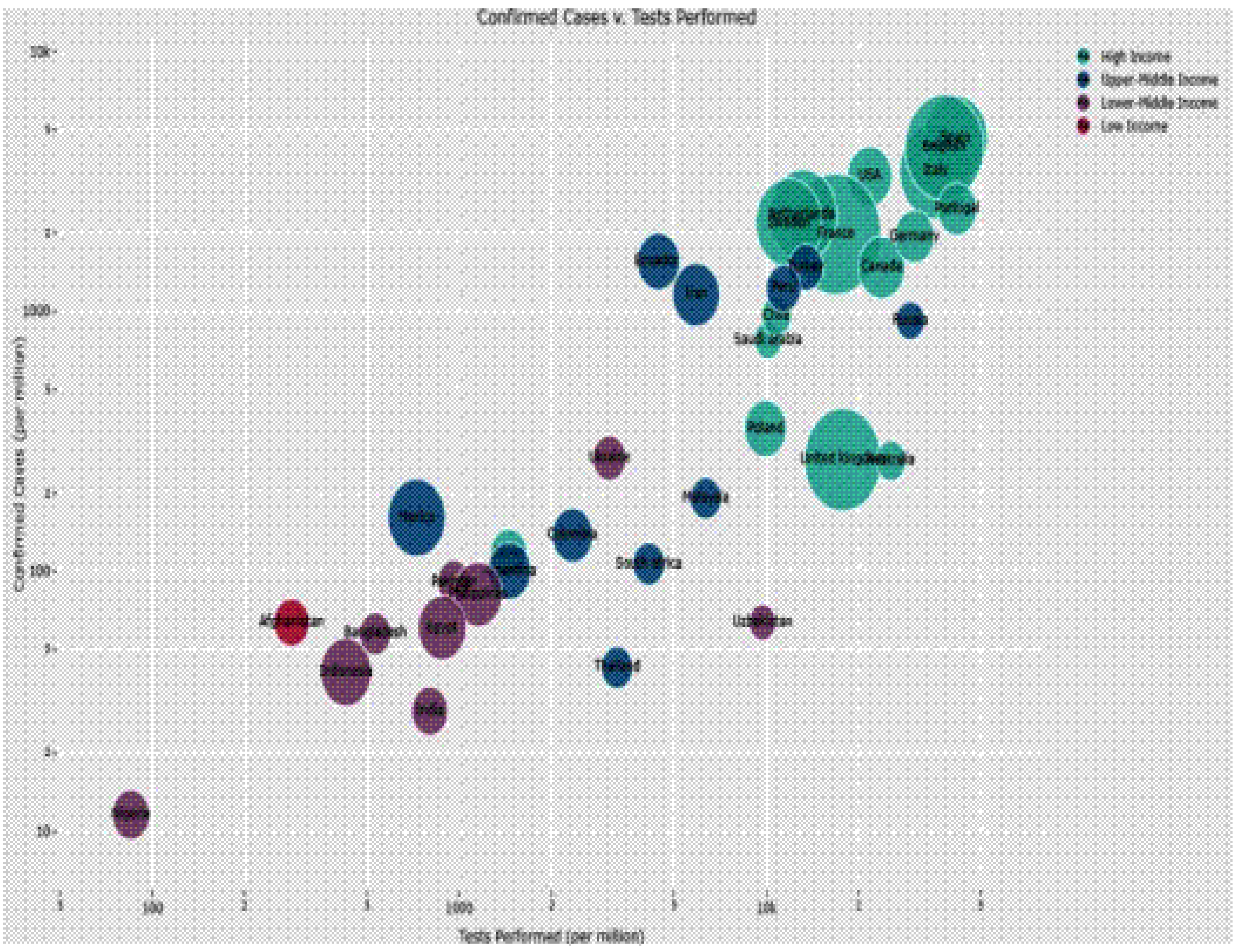

Figure 1: Confirmed cases compared with income.

Discussion

Our study was a secondary analysis of data to study the determinants of incidence and mortality of COVID-19 on various countries to evaluate the effect of BCG vaccine in incidence and mortality of COVID -19. The factors affecting the incidence and mortality is inherently diverse and will depend on several factors other than the BCG vaccine.

Priyadarsini SL et al identified Social distancing and community consciousness, age, air temperature, airflow and ventilation, population density and humidity were identified as the driving or key factors in the epidemiology of COVID-19.(17) Univariate analysis of BCG will compare only one variable (BCG in NIS) among the two groups without considering the other factors affecting the epidemiology. The univariate analysis of the secondary data comparing countries with and without BCG in NIS, showed significant difference in cases per million as well as case fatality rate. But considering the non-random selection of countries for evaluation and multifactorial nature of disease epidemiology and other confounding factors, a multifactorial analysis done by adjusting for few known factors e.g. Air Connectivity Index, population density, enforcement of lockdown measures and using a random effect logit model showed no significant difference between the BCG vaccinated and BCG non vaccinated countries.

Other than BCG vaccine in the national immunisation schedule (BCG in NIS), the two groups compared were found significantly different in income, Air Connectivity Index, confirmed cases per million, deaths per million, tests performed per million, case fatality rate. BCG in NIS group mainly constituted low income countries but had significantly lower cases per million and deaths per million of COVID-19. This is in contrast to the expectation of low-income countries to perform worser than high income countries in tackling a pandemic. While BCG can be argued as the factor behind this, it cannot be considered confirmatory as Non – BCG vaccinated countries have performed three times more tests compared to BCG vaccinated countries.(18) But it can be argued that a significant reduction in case fatality rate of covid-19 in BCG immunised countries cannot be solely attributed to low number of testing. Case fatality rate might underestimate mortality in the initial phase of an outbreak, therefore comparing case fatality rate at this stage might not be appropriate.(19) The Air Connectivity Index of Non-BCG vaccinated countries are also significantly higher than the BCG vaccinated countries, suggesting the difference in climate and air quality can also be a factor in higher cases of COVID-19 in non – BCG vaccination countries.

Comparing countries with cases per million > 1000 and < 1000 with multivariate analysis BCG in NIS had no significant effect on difference in cases per million. This means that, when other factors like income, population density etc. were taken into consideration BCG, in NIS was not offering any additional protection to the countries in fighting COVID- 19. On further comparison of countries with case fatality rate more than 5% and less than 5%, it revealed also showed BCG in NIS was not reducing mortality due to COVID- 19.

We also considered several factors like lockdown before 500 cases to compare between two groups of countries and found that enforcing lockdown before

500 cases did not confer any significant protection in reducing the incidence or mortality. A conceptual modelling by Vega D et al suggested that an extensive initial lockdown followed by gradual return into normal activities will reduce the contacts to a maximum of 40% of the contacts they had before the quarantine.(20) The findings from our study is suggesting early lockdown before 500 cases was not very effective, but since it was not the primary objective of the study, further research is required to assess the efficiency of lockdown in controlling the pandemic.

Even when few countries was successful in keeping the COVID incidence and mortality in check, none of the measures taken were effective in making a significant change in number of days to reach 500 confirmed cases. The mean number of days to reach 500 cases in countries with less than 1000 cases per million was 35.7 and countries with more than1000 cases per million was 31.6 and not significantly different in both the groups. This suggests that the first wave of COVID-19 is progressing in every country in a similar trend even with different types of strategies. While days after 500 cases were significantly different in two groups of high and low number of cases per million, which again suggests the successful containment of COVID-19 happened after the first wave of 500 cases in countries with a smaller number of cases of COVID-19.

Strengths

Our study first systematically reviewed the data and scientifically analyzed the association of BCG vaccine and COVID-19 incidence. Previously WHO reviewed three preprints (manuscripts posted online before peer-review), which compared the incidence of COVID-19 cases in countries where the BCG vaccine is used with countries where it is not used and observed that countries that routinely used the vaccine in neonates had less reported cases of COVID-19 to date. WHO bulletin also states that "Such ecological studies are prone to significant bias from many confounders, including differences in national demographics and disease burden, testing rates for COVID-19 virus infections, and the stage of the pandemic in each country". (21) In our study we adjusted for other confounding variables using random effects model, therefore reducing the chances of bias.

Limitations

The list of countries chosen for this analysis is not comprehensive therefore the findings and inferences made may be flawed. Also, the authors would like to point out that due to the novel nature of COVID-19, there may explanatory variables that may not have been included in this analysis.

Conclusion

In the present study, it has been observed that when we considered only one variable that i.e. BCG vaccine, the incidence and mortality of COVID-19 was found to be significantly different in BCG vaccinated countries and non BCG vaccinated countries. However, when considered other factors such as Air Connectivity index, population density, tests per million etc. there was no significant association with incidence and mortality of COVID-19. Therefore emphasis has to be made for further clinical trials to ensure effectiveness of BCG vaccine against COVID-19.

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Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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