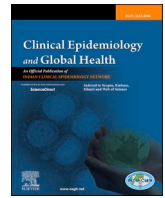




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# Is BCG associated with reduced incidence of COVID-19? A meta-regression of global data from 160 countries

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## ABSTRACT

**Background:** Global research is running towards to find a vaccine to stop the threat of the COVID-19. The Bacillus Calmette–Guérin (BCG) vaccine that prevents severe forms of tuberculosis is getting more attention in this scenario. The objective of our study was to determine the association between BCG vaccine coverage and incidence of COVID-19 at a national-level across the Globe.

**Methods:** The data of 160 countries were included in the study. Meta-regression was done to estimate the difference in the incidence of COVID-19 cases between countries with BCG vaccination coverage. BCG coverage was categorized as  $\leq 70\%$ ,  $>70\%$  and no vaccination. The analyses were carried out by adjusting for factors such as population density, income group, latitude, and percentage of the total population under age groups 15–64 and above 65 years of each country.

**Results:** The countries that had  $\leq 70\%$  coverage of BCG vaccine reported 6.5 (95% CI:  $-8.4$  to  $-4.5$ ) less COVID-19 infections per 10,000 population as compared to countries that reported no coverage. Those that had  $>70\%$  coverage reported 10.1 (95% CI:  $-11.4$  to  $-8.7$ ) less infections per 10,000 population compared to those with no BCG countries.

**Conclusion:** Our analysis suggests that BCG is associated with reduced COVID-19 infections if the BCG vaccine coverage is over 70%. The region-wise analyses also suggested similar findings, except the Middle East and North African region.

## 1. Introduction

There is evidence that the BCG (Bacillus Calmette Guerin) vaccine has been associated with beneficial, non-specific effects on the immune system.<sup>1</sup> Studies suggest that the BCG vaccine induces the innate immune response which might reduce viraemia after exposure, leading to less severe COVID-19 and more rapid recovery.<sup>2</sup> A randomized control trial suggests that BCG vaccine reduces mortality, attributable to protection against respiratory infections, as well as neonatal sepsis.<sup>3</sup> Data on BCG vaccination status when analysed at a national-level along with incident cases of COVID-19, can give us an ecological idea of a possible protective effect, if any. The objective of our study was to determine the association between BCG vaccine coverage and incidence of COVID-19 at a national-level across the Globe.

## 2. Methods

Country level data on COVID-19 confirmed cases were obtained from European Center for Disease Control & Prevention (ECDC).<sup>4</sup> Data on BCG vaccination coverage was obtained from the WHO Global Health Observatory.<sup>5</sup> The data related to other covariates were obtained from United Nations, Department of Economic and Social Affairs database.<sup>6</sup> We included 160 countries that reported official data on BCG vaccination coverage (%) and COVID-19 confirmed cases until May 31, 2020.

Meta-regression was done to estimate the difference in the incidence of COVID-19 cases between countries with BCG vaccination coverage. BCG coverage was categorized as  $\leq 70\%$ ,  $>70\%$  and no vaccination. We adjusted for population density, income group, latitude, and percentage of the total population under age groups 15–64 and above 65 years. The regression coefficients were presented in terms of number of cases per

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**Table 1**  
Results of meta-regression with incidence of COVID-19 as dependent variable by region & income group.

|   | Number of Countries (%) | Regression Coefficient (95% CI) for BCG (Per 10,000 Population) | P value |
|---|-------------------------|---|---------|
| <b>Global (160 Countries)</b>                 |                         |   |         |
| No BCG  | 20 (12.5)               | Ref   |         |
| ≤70% Coverage                                 | 9 (5.6)                 | −6.5 (−8.4 to −4.5)   | <0.001  |
| >70% Coverage                                 | 131 (81.9)              | −10.1 (−11.4 to −8.7)   | <0.001  |
| <b>Region Wise</b>                            |                         |   |         |
| <b>East Asia &amp; Pacific (18)</b>           |                         |   |         |
| No BCG  | 2 (11.1)                | Ref   |         |
| ≤70% Coverage                                 | 1 (5.6)                 | −4.0 (−6.7 to −1.2)   | 0.004   |
| >70% Coverage                                 | 15 (83.3)               | −4.2 (−6.7 to −1.6)   | 0.001   |
| <b>Europe &amp; Central Asia (40)</b>         |                         |   |         |
| No BCG  | 13 (32.5)               |   |         |
| ≤70% Coverage                                 | 1 (2.5)                 | 11.0 (−12.5 to 34.4)  | 0.359   |
| >70% Coverage                                 | 26 (65.0)               | −18.4 (−28.8 to −8.0)   | 0.001   |
| <b>Latin America &amp; the Caribbean (27)</b> |                         |   |         |
| No BCG  | 1 (3.7)                 | Ref   |         |
| >70% Coverage                                 | 26 (96.3)               | −14.3 (−28.8 to 0.2)  | 0.054   |
| <b>Middle East &amp; North Africa (18)</b>    |                         |   |         |
| No BCG  | 2 (11.1)                | Ref   |         |
| ≤70% Coverage                                 | 1 (5.6)                 | 254.4 (198.8 to 310.0)  | <0.001  |
| >70% Coverage                                 | 15 (83.3)               | 290.0 (231.9 to 348.1)  | <0.001  |
| <b>Income Group (World Bank)</b>              |                         |   |         |
| <b>Upper Middle Income (48)</b>               |                         |   |         |
| No BCG  | 2 (4.2)                 | Ref   |         |
| ≤70% Coverage                                 | 2 (4.2)                 | 0.5 (−9.8 to 10.7)  | 0.929   |
| >70% Coverage                                 | 44 (91.7)               | −3.2 (−10.5 to 4.2)   | 0.398   |
| <b>High Income (42)</b>                       |                         |   |         |
| No BCG  | 18 (42.9)               | Ref   |         |
| ≤70% Coverage                                 | 1 (2.4)                 | 16.7 (−12.2 to 45.7)  | 0.258   |
| >70% Coverage                                 | 23 (54.8)               | −17.7 (−27.2 to −8.1)   | <0.001  |

Note 1: Adjusted for population density, income group, latitude, and percentage of total population under age groups 15–64 and above 65 years.

Note 2: Estimates cannot be calculated for South Asia and Sub-Saharan African region (8 and 47 countries respectively) because all these countries have implemented BCG policy. North American countries are not implementing BCG policy.

10000 population with 95% confidence interval by inverse variance method with random effect model, using the DerSimonian-Laird estimator for  $\tau^2$ . Statistical analyses were performed using Stata software, version 16.0 (StataCorp LLC).

### 3. Results

Of the 160 countries for whom BCG vaccination coverage data is available, 20 (12.5%) did not use BCG, 5.6% had a coverage of ≤70% and 82% had >70% coverage (Table 1). The countries that had ≤70% coverage of BCG vaccine reported 6.5 (95% CI: −8.4 to −4.5) less COVID-19 infections per 10,000 population as compared to countries that reported no coverage ( $p < 0.001$ ). Those that had >70% coverage reported 10.1 (95% CI: −11.4 to −8.7) less infections per 10,000 population compared to those with no BCG countries ( $p < 0.001$ ).

Irrespective of the level of coverage, the East Asia and Pacific region countries reported 4 less infections per 10,000 population, as compared to countries without BCG vaccination strategy. Europe and Central Asian countries that had >70% coverage, had 18.4 (95% CI: −28.8 to −8.0) less infections per 10,000 population compared to no coverage

( $p < 0.001$ ). The Latin America and Caribbean countries that had >70% coverage reported 14.3 (95% CI: −28.8 to 0.2) per 10,000 less infections as compared to countries with no coverage.

The Middle East and North African countries, however, showed that those with >70% BCG coverage had a higher number of infections as compared to no coverage. High-income countries, with >70% coverage, had 17.7 (95% CI: −27.2 to −8.1) less number of infections per 10,000 population ( $p < 0.001$ ) as compared to no coverage.

### 4. Discussion

Randomized trials of BCG vaccine prophylaxis against COVID-19 would be ideal. The WHO clinical trials portal reveals 5 such ongoing trials (NCT04414267, NCT04417335, EUCTR2020-002448-21-GR, IRCT20200411047019N1 and NL8609). Till these trial results are available, our meta-regression of country level data will give policy makers some idea of potential benefit of BCG vaccination in preventing COVID-19.

Our analysis suggests that BCG is associated with reduced COVID-19 infections if the BCG vaccine coverage is over 70%. The region-wise analyses also suggested similar findings, except the Middle East and North African region. A large cohort from this region found no protective effect.<sup>7</sup> The spread of COVID-19 in the Middle East region is particularly alarming as these countries have continuously been considered as a hotspot for infectious diseases.<sup>8</sup> The countries in this region are having larger number of international travelers every year for tourism, business, and pilgrimage. This population by genetics has higher prevalence for diabetes and hypertension that are risk factors for COVID-19 disease.<sup>9</sup>

Concluding that BCG protects an individual against COVID-19 may be an ecological fallacy. But this study adds impetus for us to carefully study the data from the ongoing BCG trials for making any policy and programmatic decisions.

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### Ethical Approval

Not required.

### Declaration of competing interest

None of the authors have conflicts of interest to report.

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