

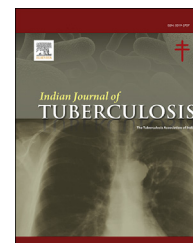


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Short communication

Is the tuberculosis vaccine BCG an alternative weapon for developing countries to defeat COVID-19?

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ARTICLE INFO

Article history:

Received 10 October 2020

Accepted 22 October 2020

Available online 4 November 2020

Keywords:

Bacille Calmette-Guérin vaccine (BCG)

COVID-19

SARS-CoV-2 virus

Morbidity

Mortality

ABSTRACT

Background: Coronavirus disease (COVID-19) is a new respiratory infectious disease, and there is no vaccine currently. Previous studies have found that BCG vaccination can provide extensive protection against respiratory infectious diseases.

Methods: Herein, we obtained the latest data from the World Health Organization (WHO) as of August 12, 2020, and determined the relationship between three parameters (including the BCG vaccination coverage, human development index (HDI), and transmission classifications) and the incidence rate and mortality of COVID-19.

Results: The results showed that the morbidity and mortality of COVID-19 in countries with BCG vaccination recommendation were significantly lower than these in countries without BCG vaccination recommendation, and countries with lower HDI have lower morbidity and mortality. In addition, we also found that the mode of virus transmission is also related to the morbidity and mortality of COVID-19.

Conclusions: Although our data supports the hypothesis that BCG vaccination is beneficial in reducing the morbidity and mortality of COVID-19, the data supporting this result may be inaccurate due to many confounders such as PCR testing rate, population characteristics, and protection strategies, the reliability of this result still needs to be verified by clinical trials.

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Abbreviations: BCG, Bacille Calmette-Guérin vaccine; COVID-19, coronavirus disease; HDI, human development index; IL, interleukin; LDCs, least developed countries; LLDCs, landlocked developing countries; PCR, polymerase chain reaction; SIDs, small island developing states; TB, tuberculosis; TNF, tumor necrosis factor; WHO, World Health Organization.

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<https://doi.org/10.1016/j.ijtb.2020.10.012>

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1. Background

The coronavirus disease (COVID-19) has been spread globally for eight months, people's lives and health are under unprecedented threat. Vaccination is considered to be the most effective way to stop the spread of the pandemic. As of 3 September 2020, there are 321 candidate vaccines for COVID-19 in preclinical evaluation, and 33 candidate vaccines for COVID-19 in clinical trials.¹ Of the 33 COVID-19 vaccines in clinical trials, six vaccines have been in phase III clinical trials.¹ The protection efficiency and safety of these vaccines are still under investigation. Recently, the Russian Ministry of Health has announced the approval of the world's first COVID-19 vaccine, but its safety and effectiveness have been questioned because the vaccine skipped Phase III clinical trials (<http://www.chinadaily.com.cn/a/202008/11/WS5f325c7aa31083481725fa58.html>). Besides, the pandemic has severely resulted in a shortage of personal protective equipment, biomedical equipment, and diagnostic reagents in more and more countries. Developing countries, especially the least developed countries (LDCs), landlocked developing countries (LLDCs), and small island developing states (SIDS) are at an absolute disadvantage in this vaccine race and the battle for medical supplies. Those countries are suffering from long-term impediments to sustainable development.

Fortunately, most developing countries have carried out a wide range of Bacille Calmette-Guérin vaccine (BCG) vaccination strategies. Studies have found that the prevalence of COVID-19 is relatively mild in these countries,^{2,3} which may be due to the trained immunity induced by the BCG vaccine⁴, such as enhanced production of tumor necrosis factor (TNF), interleukin 1 β (IL-1 β), and IL-6.³ However, there are contradictory reports on whether BCG can effectively prevent COVID-19.^{5,6} In May 2020, Dr. Matteo Riccò et al claimed that BCG might not avoid SARS-CoV-2 infection based on a meta-analysis including 13 studies (12 papers are preprints that have not been peer-reviewed).⁶ Therefore, it is very urgent to clarify the effect of BCG vaccination on COVID-19 prevention by analyzing the latest data of confirmed cases and deaths of COVID-19 in various countries, which will provide a reference for formulating efficient and scientific prevention strategies.

2. Main text

2.1. The BCG coverage and human development index (HDI) are associated with the morbidity and mortality of COVID-19

Herein, we obtained the global COVID-19 pandemic data from the official website of the World Health Organization (WHO) on 12 August 2020. According to the coverage rate of BCG, all countries were divided into three levels. We found that the COVID-19 incidence rate of countries with BCG recommendation was significantly lower than that of countries without BCG recommendation (Fig. 1A), and the COVID-19 mortality rate of countries with BCG coverage of ≥ 90 was also significantly lower (Fig. 1B). These data indicated that higher BCG coverage might have a significant effect on reducing the incidence rate

and mortality of COVID-19. According to the data released by WHO, most countries nationally recommend BCG vaccination are LDCs, LLDCs, and SIDS, but the HDI of these countries is generally low. In order to verify the relationship between HDI and the incidence rate and mortality of COVID-19, we divided all the countries into four levels according to the Human Development Report 2019 released by the United Nations Development Programme. The data indicated that countries with a lower HDI had lower COVID-19 incidence (Fig. 1C) and mortality (Fig. 1D). Countries with low HDI are mainly concentrated in LDCs, while the BCG vaccination rate in LDCs is generally higher than 90%. This result once again shows that increasing the coverage of BCG can effectively reduce the morbidity and mortality of COVID-19.

2.2. Transmission classifications have a influence on the development of the COVID-19

Furthermore, the transmission classifications play an important role in affecting the development direction of the COVID-19 pandemic, which reflects the quality of a country's prevention strategy for COVID-19. We proposed a hypothesis that the transmission of COVID-19 is mainly classified as clustered or sporadic cases in countries with good prevention strategies, while the transmission is classified as community transmission in countries with poor prevention strategies. To test this hypothesis, we analyzed the impact of different transmission classifications on the incidence rate and mortality of COVID-19. Our analysis showed that the COVID-19 morbidity (Fig. 1E) and mortality (Fig. 1F) of countries with clustered or sporadic cases were significantly lower than those of countries with community transmission.

2.3. Data and reality: confounders that cannot be ignored

It should be pointed out that although the current data seem to support the hypothesis that the BCG vaccine induced protection from COVID-19 infection, some confounding factors behind the data may affect the accuracy of the data. First, international comparisons of COVID-19 epidemiology are difficult because the ways in which countries record COVID-19 cases and deaths differ depending on the polymerase chain reaction (PCR) results or clinical judgment.⁷ Second, population characteristics of countries such as population density, median age and urban population, and mainly SARS-CoV-2 test rates are the main confounders that can lead to a misinterpretation of the BCG vaccination policy as protective against COVID-19. Test rates are low in less developed countries, which also affects the incidence of COVID-19.

2.4. Developing countries are facing severe challenges

Although our data support the hypothesis that BCG vaccination can reduce the morbidity and mortality of COVID-19, this hypothesis needs more clinical trials to verify. It is encouraging that at least five clinical trials are currently evaluating the role of BCG in the prevention and treatment of COVID-19

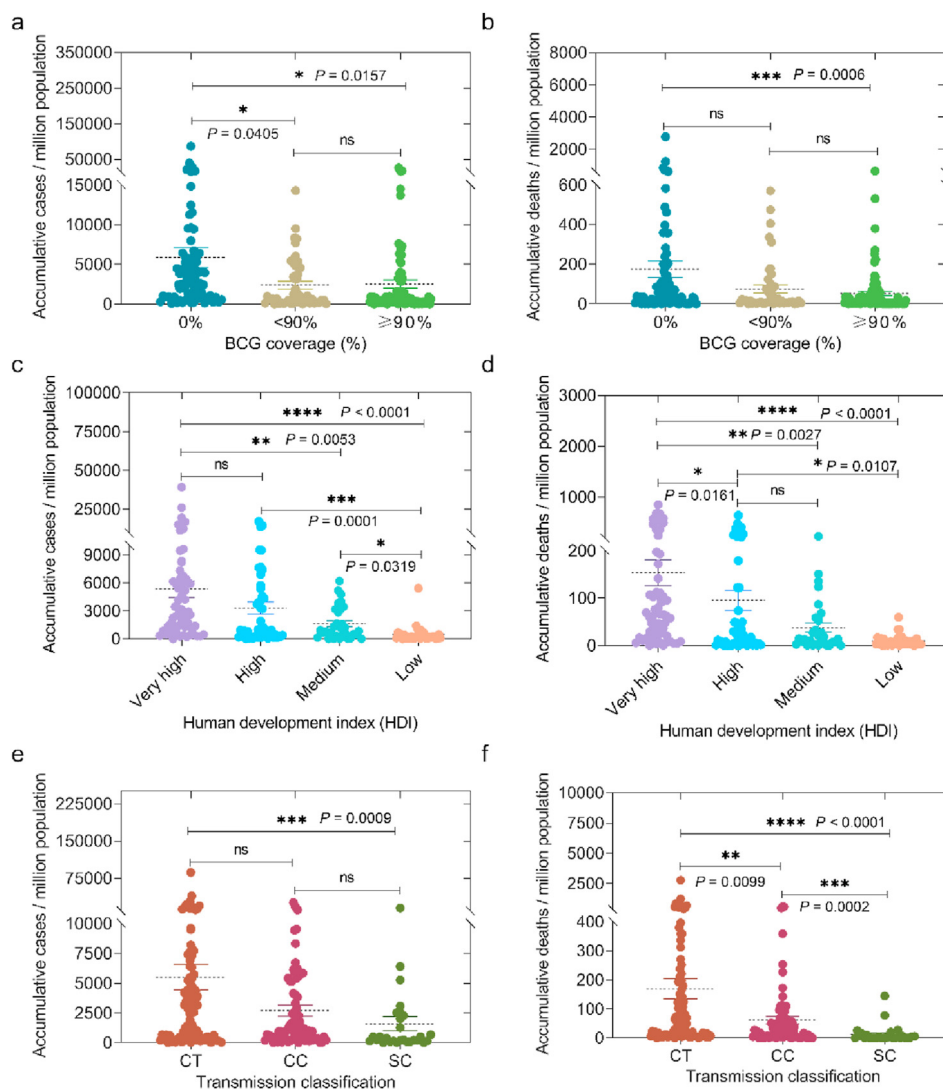


Fig. 1 – The relationships between BCG coverage (a and b), HDI (c and d), or transmission classification (e and f) and incidence rate and mortality of COVID-19. All of the results in this study were performed by using a GraphPad Prism 8 software (San Diego, CA, USA). The data were expressed as confirmed cases or deaths per 1 million population and compared with one-way analysis of variance (ANOVA) or Kruskal–Wallis test according to the data normality and homogeneity of variances. All data were shown as mean +SEM ($n = 6$ or 7). $P < 0.05$ was considered significantly different. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$; ns, no significance. CT, community transmission; CC, clusters of cases; SC, sporadic cases. All the original data used in this study can be obtained from the [Supplementary Material Table S1](#).

in different countries.⁸ However, the advantages of widespread BCG vaccination will not allow developing countries to achieve a decisive victory in this epidemic. Even more worryingly, an editorial comment published in the journal Nature warned that COVID-19 might accelerate the spread of tuberculosis (TB) in developing countries, especially in LDCs.⁹ The population of 47 LDCs accounted for 12% of the world's total population, but their total GDP accounted for only 2% of the world.¹⁰ These countries are not only suffering from infectious diseases such as COVID-19, tuberculosis, and AIDS, but are also facing the risk of food shortages and humanitarian crises.

2.5. Open and cooperation are the magic weapon to defeat the COVID-19 pandemic

It is therefore our hope that this study will give people in a gloomy world a ray of light and confidence in defeating the epidemic, provide an alternative vaccine for high-risk population (such as health care workers, the elderly, etc.), and win time for the development of COVID-19 vaccines. Moreover, routine preventive measures such as keeping social distance, wearing masks, and washing hands frequently should be strengthened to prevent the spread of COVID-19. Here, we recommend that more countries disclose their vaccines as

public products, which will not only help developing countries (especially LDCs, LLDCs, and SIDs) overcome the COVID-19, but will also lay the foundation for the global eradication of the SARS-CoV-2 virus.

3. Conclusions

In countries where the government recommends BCG, the high coverage of the BCG vaccination reduces the morbidity and mortality of COVID-19. However, this result may be inaccurate due to many confounders such as PCR testing rate, population characteristics, and protection strategies. The role of BCG in COVID-19 should be confirmed by clinical trials. Furthermore, we still need to increase investment in human, material, and financial resources to accelerate the development of effective and safe COVID-19 vaccines.

Ethics approval and consent to participate

Not applicable.

Funding

This study was funded by the National Natural Science Foundation of China (Grant No. 81801643), Beijing Municipal Science & Technology Commission (Grant No. Z181100001718005 and 19L2152), and Chinese PLA General Hospital (Grant No. QNC19047).

Authors' contributions

Conceptualization: XQW and WPG; Data curation: WPG; Formal analysis: WPG; Funding acquisition: WPG; Methodology: WPG; Software: WPG; Writing - original draft: WPG; Writing - review & editing: WPG and XQW.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Conflicts of interest

The authors have none to declare.

Acknowledgments

We would like to thank the tireless contributions of the staff in the Institute for Tuberculosis Research, and Editage (www.editage.cn) for English language editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijtb.2020.10.012>.

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