



COMMENTARY

Possible Correlation between Bacillus Calmette Guérin (BCG) Vaccination Policy and SARS-Cov-2 Transmission, Morbidity and Mortality Rates: Implications for the African Continent

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Abstract

Since its discovery in the Huanan Seafood Market, Hubei province, Wuhan, China, in December 2019, the 2019-novel Coronavirus has evolved rapidly into a global pandemic of devastating proportions. With the most developed health systems of the world struggling to contain the spread, there have been concerns raised about the relatively lower case and mortality figures coming out of the African continent, especially in the earlier days of the outbreak. While most institutions are quick to raise the obvious resource and diagnostic limitations as an explanation for this situation, recently a series of ecological studies have suggested a possible correlation between BCG vaccination policy and COVID-19 transmission and mortality rates, opening a case for an alternative or additional explanation for why Africa as a continent is reacting less violently to the SARS-CoV-2 virus. In this commentary, we rapidly present the key findings from these studies and highlight what implications such a correlation could have on African healthcare systems, should it be true.

Keywords

BCG, Vaccination, Global health, COVID-19, SARS-CoV-2

Abbreviations

BCG: Bacillus Calmette Guérin; CFR: Case-Fatality Ratio; COVID-19: Coronavirus Disease 2019; NSE: Non-specific Effects; RCTs: Randomised Controlled Trials; HCWs: Healthcare Workers

Introduction

By May 30, 2020, the ravaging COVID-19 pandemic had spread to 188 countries, infecting 5,945,737 people, causing 365,368 fatalities (CFR = 6.15%) [1], there have however been curious variations in its transmission patterns as well as associated morbidity and mortality rates across geographical regions. While these variations have been attributed to differences in cultural norms, health systems and response efforts, recently four epidemiological studies have proposed an alternative explanation using the universal BCG vaccination policies adopted by different countries. In this commentary, we discuss the findings of these studies, briefly review the literature on the non-mycobacterial effects of the BCG vaccine and highlight the response of the scientific community to the studies establishing the correlation. We then speak on the scientific efforts in motion to prove the theory and outline the possible implications such a correlation may have on healthcare in Africa.

The Correlation

The first study by Miller, et al. [2] found that nations with long-standing universal BCG vaccination policies have had significantly lower mortality rates (deaths per million) and transmission rates (case per million), compared with nations that had no such policy in place. Further, they were able to demonstrate that the earlier this policy was instituted, the lower the COVID-19

mortality rate in the elderly population. Similarly, Hegarty, et al. [3], after analyzing COVID-19 case and mortality data over a 15-day period showed that nations with long-standing or recently abolished BCG vaccination policy had a significantly lower COVID-19 incidence compared with those without such policies (38.4 vs. 358.4 cases per million). To further support this correlation, Dayal and Gupta hypothesised that nations with recent BCG revaccination policies would have a lower SARS-CoV-2 case-fatality ratio (CFR) than those without such policies, and rightly so, as contained in their short report [4], they observed a significant difference (5.2% vs. 0.6% CFR). Finally, in a paper published in the Journal of Infectious Diseases and Epidemiology, Dolgikh [5] showed that there was a clear epidemiological correlation between COVID-19 case and fatality figures and BCG vaccination policy, and the correlation may depend strongly on the age of administration of the vaccine, with early vaccination seemingly providing more effective protection.

The Non-Mycobacterial Effect of BCG

Evidence exists in literature to explain the possible effect of the BCG vaccine on SARS-CoV-2, which may be due to certain heterologous or non-specific effects (NSE) the vaccine produces on immune cells, conferring some protection against non-mycobacterial pathogens. For example, Mathurin, et al. [6] in 2009, reported that mice having the BCG vaccine were resistant to infection by the vaccinia virus due to a CD4+ T-cell immune response. This concept was later termed trained immunity, and has been explained to be a result of certain epigenetic and metabolic changes to the immune cells, causing promotion of the genetic loci encoding pro-inflammatory cytokines [7]. The findings of these four studies have however drawn fierce reactions from the scientific community due to fears that they may be used to push a narrative that BCG vaccination could indeed be a 'cure' for COVID-19 and falsely inform policy decisions. In a critical review, Kirov highlighted that these studies did not sufficiently accommodate for other confounding factors such as: population age, race, chronic diseases, income levels and time from community spread, establishing indeed that median population age had a more significant influence on COVID-19 mortality rate than BCG vaccination policy [8]. In another critique, Emily MacLean, a PhD candidate at the McGill University International Tuberculosis Centre, succinctly presented the many confounding factors that could render this correlation inaccurate in a Nature feature [9].

The BCG/COVID-19 Clinical Trials

These criticisms however are a call for Randomised Control Trials (RCTs) to be conducted towards either establishing or debunking the hypothesis that BCG confers some protection against SARS-CoV-2, and determining how long such protection lasts if it does exist. Two of such trials have recently been launched, involving

healthcare workers (HCWs) in Australia (BRACE) [10] and the Netherlands (BCG-CORONA) [11]. While the BRACE study in Australia will enroll over 4,000 HCWs, half of whom will receive the BCG vaccination and the other half unvaccinated, after which the incidence of COVID-19 in both groups will be compared after 6 months, the BCG-CORONA study in the Netherlands will recruit 1,500 HCWs, who will be separated into 2 groups (one group receiving the BCG vaccine and the other group being unvaccinated), and would then compare the rates of unplanned absenteeism due to COVID-19 or ill health between the two groups.

Africa's BCG Situation

According to the latest edition of the BCG World Atlas (available at www.bcgatlas.org) all African countries have an existing universal BCG vaccination policy in place as at 2017, except South Sudan for which no data was available (probably owing to the fact that it used to be a part of Sudan). Should it be proven that BCG does offer protection against SARS-CoV-2, many African nations with scarce financial and human resources to fight the pandemic head-on may have in retrospect benefitted immensely from implementing this policy intervention several years ago. There have been concerns about the relatively lower case and fatality rate of COVID-19 pandemic in Africa, which currently stands at 135,292 and 3,922 respectively [12], with underreporting due to diagnostic limitations being blamed for such small numbers. However, in light of this new evidence, an alternative explanation worth considering could be the presence of long-standing BCG vaccination policies in African countries.

Implications of the Correlation on Healthcare in Africa

In a recent statement, the Treatment Action Group revealed an important consequence of the possible effect of BCG against SARS-CoV-2. Should it be confirmed by ongoing studies that BCG does have an effect on COVID-19 incidence and morbidity/mortality rates, the ensuing increase in demand for the vaccine by nations who ordinarily do not require large quantities of the drug, could result in a shortfall in vaccine supply to many African countries [13]. As many African nations remain heavily reliant on this vaccine for curtailing *Mycobacterium tuberculosis* which remains endemic on the continent, such a shortfall may render parts of the continent susceptible to an outbreak, if not sufficiently prepared for. Similar incidents have already been recorded in this pandemic with chloroquine supplies falling globally [14], due to an astronomical 3,000% increase in demand in March 2020 [15], following emergence of evidence that it could be effective in the treatment of COVID-19 cases [16]. There are very valid fears that a similar occurrence with BCG vaccine supply could result in a double tragedy for the fragile health systems of many African nations, who may have to battle an outbreak of tuber-

culosis simultaneously with SARS-CoV-2. It is therefore imperative that while we are optimistic about the protection BCG could offer against this novel virus, we are not blinded to the possible consequences it could have on the many years of progress we have gained as a continent over our familiar foes.

Conclusion

With a COVID-19 vaccine being at least 18 months away [17], BCG presents the option of using an existing, safe alternative to boost the immune system against SARS-CoV-2, and this is an alternative that deserves every form of scientific consideration, however, as a continent, Africa should not remain oblivious to the potential implications of this, if it does receive the world's endorsement.

Competing Interests

The authors declare no competing interest.

Conflict of Interest

None.

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None.

Authors' Contributions

OAA conceived and designed the study, reviewed the literature and prepared the manuscript. IGE reviewed the manuscript for scientific content. All authors have read and approved the final manuscript.

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