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LETTER

Anticipated reduction in COVID-19 mortality due to population-wide BCG vaccination: evidence from Germany

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ABSTRACT

Bacillus Calmette-Guérin (BCG) vaccine is known to have "bystander benefits" in protecting against heterologous infections; interim analysis of the "ACTIVATE" trial shows protection against respiratory infections in the elderly population. Epidemiologic studies suggest a potential benefit of BCG vaccination on COVID-19 outcomes. Differential past BCG vaccination policies between the former East and West German states provides a unique natural experiment to assess the potential effect of prior BCG vaccination on COVID-19. We estimated a 5% heterologous vaccine efficacy in the highly vaccinated former East Germany using the COVID-19 International Modeling (CoMo) Consortium model. A comparable BCG vaccination campaign undertaken prior to the pandemic in former West Germany, instituted along with known country-wide transmission reduction measures, is associated with a 37% decrease in projected mortality by mid-summer, 2020. These findings support a combined heterologous vaccine and non-pharmaceutical interventions (HVI+NPI) approach to mitigate the SARS-CoV-2 pandemic until SARS-CoV-2 specific vaccines are widely distributed.

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Bacillus Calmette-Guérin (BCG) vaccination has been used for over 80 years to protect against Mycobacterium tuberculosis infection. Some countries still have national vaccination programs for children, but others provide vaccination only to high-risk individuals.[1] While prescribed to prevent infection against one pathogen, BCG appears to have a "bystander benefit" in protecting against other heterologous infections, thought to be through a process of boosting natural and innate immunity by epigenetically reprogramming or "training" of innate immune cells.[2] Epidemiological observations suggest sustained beneficial effects in older children and adults, BCG administered during childhood have been associated with lower mortality from natural causes during almost 40 years of follow-up[3] and lower risk of pneumonia in people with 65 y or more.[4] These nonspecific beneficial effects of BCG vaccine do not only include protection against other heterologous infections but also are associated with prolonged reduced risk of lymphomas and leukemia, up to 30 years after vaccination.[5] Recently Cirovic et al. provided the biological mechanism for the persistent effects of BCG vaccination demonstrating transcriptional and functional changes at the level of human bone marrow-resident hematopoietic stem and progenitor cells.[6]

The recent phase III ACTIVATE trial assessed whether BCG vaccination also had similar protective heterologous effects in the elderly population; its interim analysis showed that BCG vaccination significantly increased the time to the first infection, compared to placebo, with most of the protection against respiratory tract infections of likely viral origin.[7] In the context of the current pandemic, a number of epidemiological studies have shown that BCG vaccination is associated with a lower number of COVID-19 cases and reduced mortality, but these studies are complex due to inherent biases and multiple confounders.[8] In a recent study, Escobar and colleagues aimed to mitigate potential confounding variables by including countries that fulfilled the criteria of the stage of: COVID-19 epidemic, development, rurality, population density, and age structures.[9] They reported that for every 10% increase in their BCG index, there was a 10.4% reduction in COVID-19 mortality in Europe. They then analyzed data from Germany because of the differences in the BCG vaccination policies in states of the former East Germany and those of the former West Germany, which together comprise modern-day Germany, and concluded that BCG vaccination had a beneficial effect on COVID-19 mortality. Their study showed that the average COVID-19 mortality rate in the former West Germany was 2.9-fold higher than in the former East Germany.[9] Hauer and colleagues had similar results and emphasized that the population with a greater risk of death due to COVID-19 was higher in the former East Germany because of its large proportion of elderly people.[10] However, these studies did not account for the potential effects of non-pharmaceutical interventions (NPIs) on reducing SARS-CoV-2 infection and thus COVID-19 deaths. We investigated these factors in a comprehensive modeling environment capable of representing both vaccination and NPIs.

We first estimated current BCG vaccination coverage in >65 y in Germany (Figure 1A). In states of the former East Germany, individuals 45 to 84 years old today were vaccinated with approximately 85% coverage.[11] In states of the

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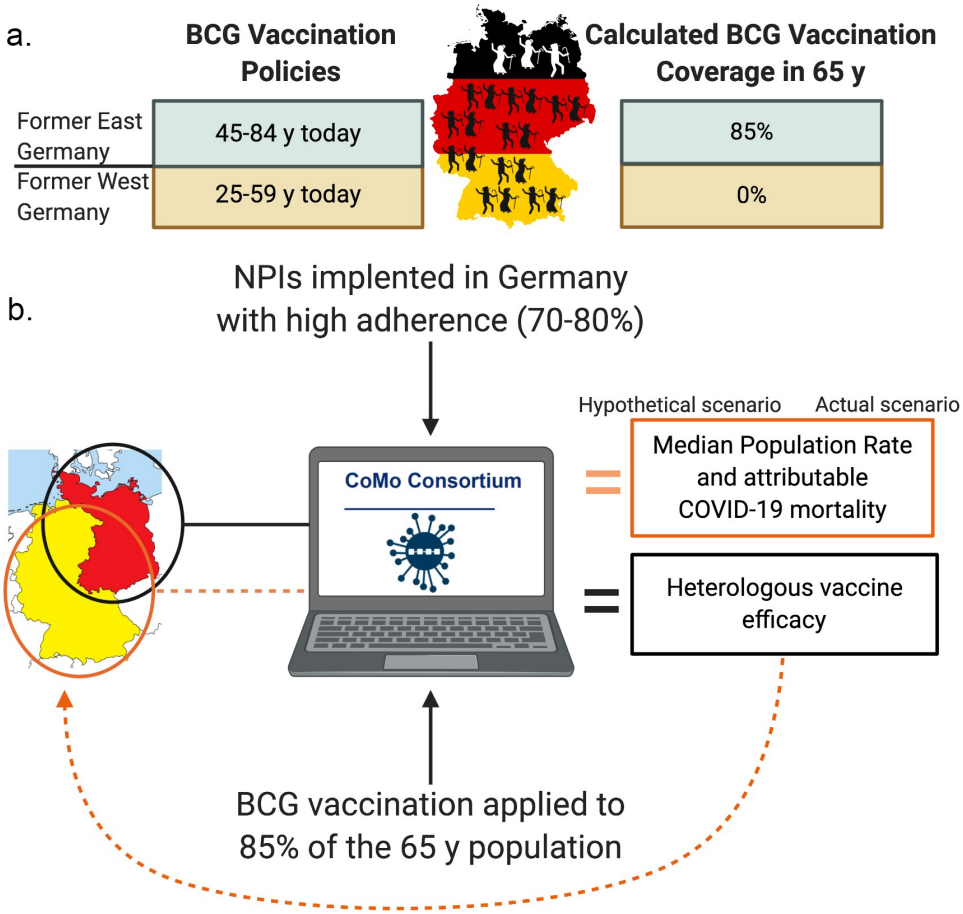

Figure 1. Methodology. (a). Calculated BCG vaccination coverage in people with 65 y or more based on Germany's population data in the States of Former East and West Germany. (b). Algorithm implemented with the CoMo model to calculate first the Heterologous Vaccine efficacy of BCG in former East Germany in the context of NPIs and then to simulate a scenario in former West Germany incorporating a BCG campaign before the onset of the pandemic.

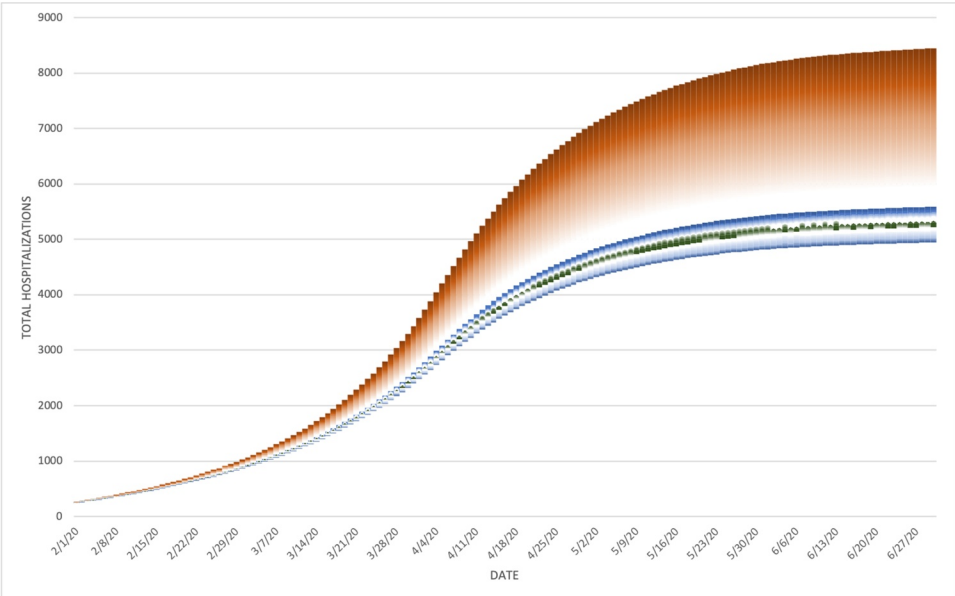

Figure 2. Projected COVID-19 mortality reduction in former West German states with hypothetical preexisting BCG-vaccine coverage of ≥ 65 y population equivalent to former East German states (assuming 5% heterologous-efficacy and 85% coverage). Red = modeled actual COVID-19 mortality data (median); Green = modeled hypothetical COVID-19 mortality (median); Blue = 25th, 75th quantiles for modeled hypothetical mortality (with 0.01 SD "Gaussian noise" for key parameters).

former West Germany, individuals 22 to 59 years old today were vaccinated, resulting in 0% of coverage. Using the Oxford-Cornell-founded COVID-19 International Modeling (CoMo) Consortium model,[12] we simulated publicized NPIs implemented across Germany, incorporating handwashing, physical-distancing, school-closures, working at home, self-isolation if symptomatic, international travel ban, and shielding the elderly.[13] We introduced BCG vaccination as an intervention in the model by applying it to 85% of the >65 y population. Assuming a relatively high adherence to NPIs (70–80%), we found that a 5% heterologous vaccine efficacy fit available case and mortality data in former East German states. We then simulated what the combination of a comparably efficacious BCG vaccination campaign instituted prior to the onset of the SARS-CoV-2 pandemic, along with an identical suite of NPIs, would have produced in former West German states up to June 2020 (Figure 1B). Without BCG, the model calculated a median population infection rate in former West German states of 5.2% through the end of June 2020 (interquartile range using 0.01 SD Gaussian "noise" around key parameters of 4.8% and 5.6%), and a median attributable COVID-19 mortality of 8,466 (7,890, 9,141). With East German-like BCG coverage, the corresponding median infection rate decreased by 40% to 3.1% (2.8, 3.3) and the median mortality decreased by 37% to 5,281 (4,932, 5,577) (Figure 2).

The implication of our model-based experiment is that BCG vaccination prior to exposure to SARS-CoV-2 may be associated with substantial decreases in COVID-19-related hospitalizations and deaths, even with modest heterologous vaccine efficacy. Along with published interim data from the double-blinded, placebo-controlled, ACTIVATE trial of BCG vaccination in the elderly showing benefit against respiratory viral infections, our model supports a combined heterologous vaccination intervention (HVI) and NPI approach to mitigate the SARS-CoV-2 pandemic until SARS-CoV-2 specific vaccines are available and widely distributed.

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Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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