

# Bacillus Calmette-Guérin as a Protective Factor for COVID-19?

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Worldwide, many national vaccination programs have included the bacillus Calmette-Guérin (BCG) vaccine during infancy as a protection from *Mycobacterium tuberculosis* infection [1]. BCG is an attenuated vaccine produced with *Mycobacterium bovis* that reduces to about half the risk of contracting tuberculosis disease [2,3]. With the reduction of tuberculosis prevalence, some countries, such as Spain and France, opted to vaccinate just people at high risk, while others like Russia and Ukraine, still indicate mass vaccination [4]. In Israel, the BCG vaccination was indicated generally to everyone until 1981, when it started to be administered just to populations at risk and immigrants from endemic countries [5].

## THE BCG VACCINATION AND COVID-19 MORTALITY

During the pandemic of the coronavirus disease-2019 (COVID-19), BCG vaccination has been proposed as a possible protective factor for the disease severity.

The correlation between BCG vaccination and COVID-19 low mortality rates is hard to make by simply comparing epidemiologic data from different countries since other important factors are simultaneously involved, such as discrepancy in socioeconomic situation, time of pandemic onset, availability and indication of diagnostic examinations, and political

strategies. However, a study comparing European countries with similar socioeconomic statuses showed lower mortality rates in countries with BCG policy [6]. An epidemiologic analysis of countries from around the world presented supporting findings that showed higher morbidity and mortality in those without BCG mass vaccination [7]. In Europe, a reduction of around 10% of the COVID-19 mortality rate was associated with a small increase (10%) with the BCG index [6]. Another observational study comparing BCG vaccinated European countries to non-vaccinated ones also found a statistically significant lower mortality rates in the first group, which supported this hypothesis [8].

In Europe a similar study found lower death rates in those countries that included BCG in their national vaccination routine. Interestingly, however, it was observed that some Northern European countries had low death rates regardless of universal BCG vaccination policy. They associated the reduced mortality in these regions with the consumption of aluminum chloride, a lysosomotropic agent, in their food habits [9].

A cross-sectional study [10] observed a lower incidence of COVID-19 in countries endemic for tuberculosis and in countries with BCG coverage when compared with countries without those features. However, a cohort study comparing COVID-19 incidence in BCG vaccinated and non-vaccinated patients in the Israeli population found no statistically significant difference in positive polymerase chain reaction test results

among symptomatic patients from either groups [11]. One could propose that the finding in the previously mentioned studies were due to confounding bias or simply that BCG reduces the severity of the disease but not the infection rate.

## HOW COULD BCG PROTECT AGAINST COVID-19?

The BCG vaccine is believed to directly protect against tuberculosis disease through stimulation of the cellular immune system since *M. tuberculosis* an intracellular pathogen [12]. However, it has also been shown to act in a non-specific way by enhancing the trained immunity and conferring a broad protection. For example, its success in combating vesical carcinoma by intravesical BCG therapy has been seen [13]. Trained immunity and its ability to confer broad protection is related to histone modifications, which leads to epigenetic changes and results in expression of numerous genes associated with better recognition of secondary infections agents by the innate immune system [14,15]. This mechanism was suggested as one of the pathways through which BCG could reduce COVID-19 complications [16].

BCG was previously associated with lower mortality rates unrelated to tuberculosis. In an animal model it was shown that mice that were inoculated with 1 mg of BCG had a higher resistance to numerous viruses when compared to the control group with statistically significant higher survival rate [17]. In fact, when compared to matched controls, it has been found that patients who received BCG had a higher

survival rate to respiratory viral infections [18] and fewer hospitalizations [19].

Countries with a national BCG vaccination policy have shown reduced mortality rates of COVID-19 compared to other countries. However, some of the confounding bias in the epidemiologic observations are hard to rule out and should be taken into consideration. Those factors include the discrepancy between countries in socioeconomic level, social distance policies, diagnostic test indications, and climate implications. Furthermore, BCG vaccination was previously shown to confer a higher survival rate for other diseases, including tuberculosis, and specifically viral infections, through enhancing the trained immune system, which could explain the protective feature in COVID-19.

### CONCLUSIONS

BCG has turned out to be a potential tool to prevent the COVID-19 complications. Clinical trials are needed to check the effectiveness of BCG as a protective role in COVID-19, its safety in older individuals and other possible adverse effects.

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### Capsule

## Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir

Understanding the inner workings of the virus that causes coronavirus disease-2019 (COVID-19) may help us to disrupt it. Yin et al. focused on the viral polymerase essential for replicating viral RNA. Replication of SARS-CoV-2 requires the viral RNA-dependent RNA polymerase (RdRp) enzyme, a target of the antiviral drug remdesivir. The authors report the cryo-electron microscopy structure of the SARS-CoV-2 RdRp, both in the apo form at 2.8-angstrom resolution and in complex with a 50-base template-primer RNA and remdesivir at 2.5-angstrom

resolution. The complex structure reveals that the partial double-stranded RNA template is inserted into the central channel of the RdRp, where remdesivir is covalently incorporated into the primer strand at the first replicated base pair, and terminates chain elongation. These structures provide insights into the mechanism of viral RNA replication and a rational template for drug design to combat the viral infection.

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