

Could anti-tubercular vaccination protect against COVID-19 infection?

Correspondence to the letter entitled: Is BCG vaccination effecting the spread and severity of COVID-19? ALLERGY, 24 April 2020.

We have read with great attention the kind contribution by C. Ozdemir et al, about the possible effects of tuberculosis vaccine with Calmette-Guérin Bacillus (BCG) on the course of COVID-19 pandemics.¹ We agree, because our group has been working for the last few months on this hypothesis, with a different approach, over the ability of BCG to provide protection against COVID-19. Several studies, as also reported by Redelman-Sidi, G., are currently ongoing to determine the effect of BCG vaccination on outcomes from COVID-19, including in two high-risk populations.² The countries without

universal vaccination policies (ie, Italy, Netherlands, United States) would seem to be hit more severely against COVID-19, than in countries with universal vaccination policies and for a long time with BCG. Since 1975, BCG vaccination policy in Sweden changed from routine vaccination of all newborn infants to selective vaccination of groups at higher risk,³ and Spain did the same, but not Portugal (Figure 1). To this epidemiological observation, detectable in open access databases of global BCG vaccination policy and practices, the so-called one Iberian Peninsula paradox must be added.⁴⁻⁶ Indeed, it seems that the citizens of Portugal would be less susceptible to COVID-19, at least in the severe form, while Spanish citizens would have a

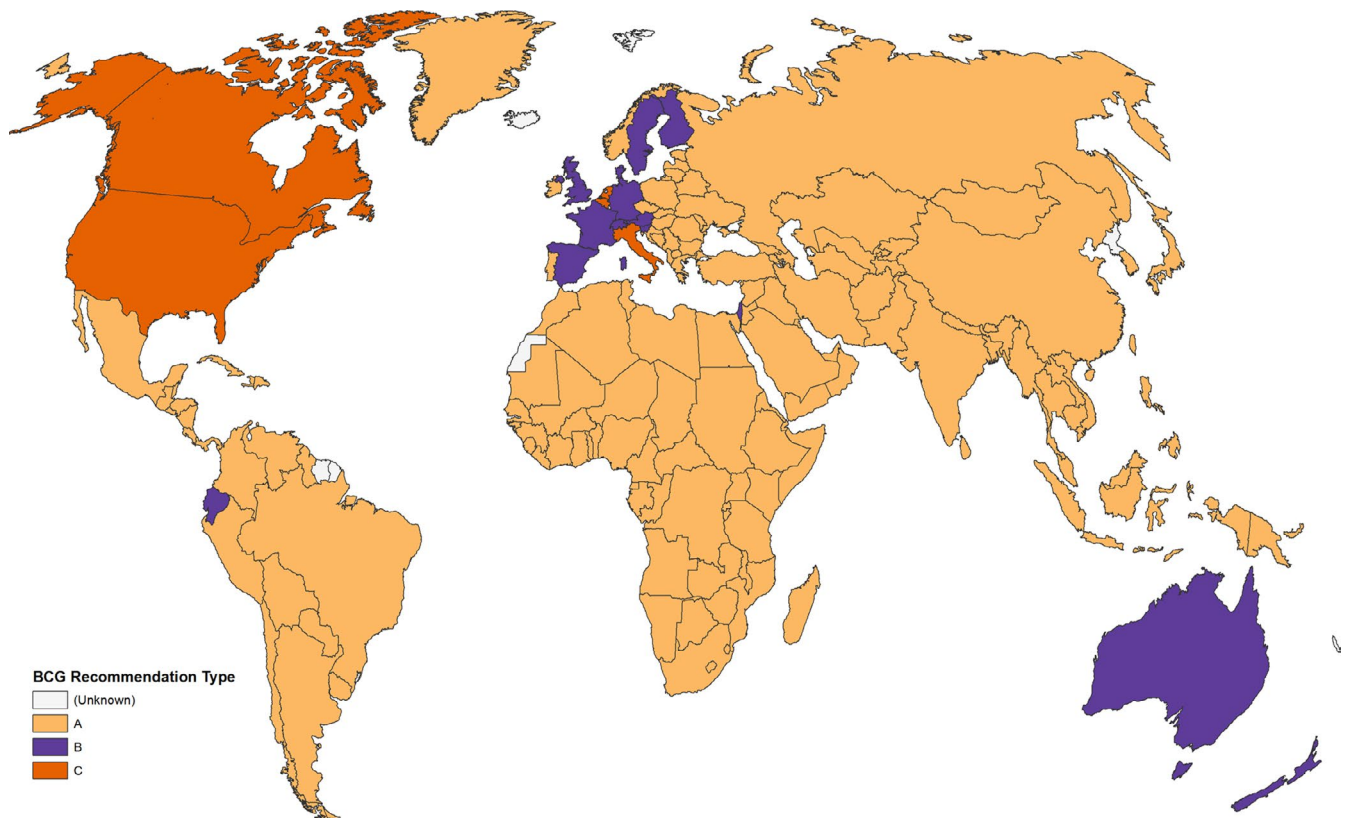


FIGURE 1 Map displaying BCG vaccination policy by country. A, Countries with universal BCG vaccination program; (B) countries that used to recommend BCG vaccination for everyone, but currently are not recommending it; and (C) countries that never had universal BCG vaccination programs (modified figure from by Zwerling A, et al 2011⁴)

COVID-19 CASES PORTUGAL VS SPAIN (11th March – 27th April)

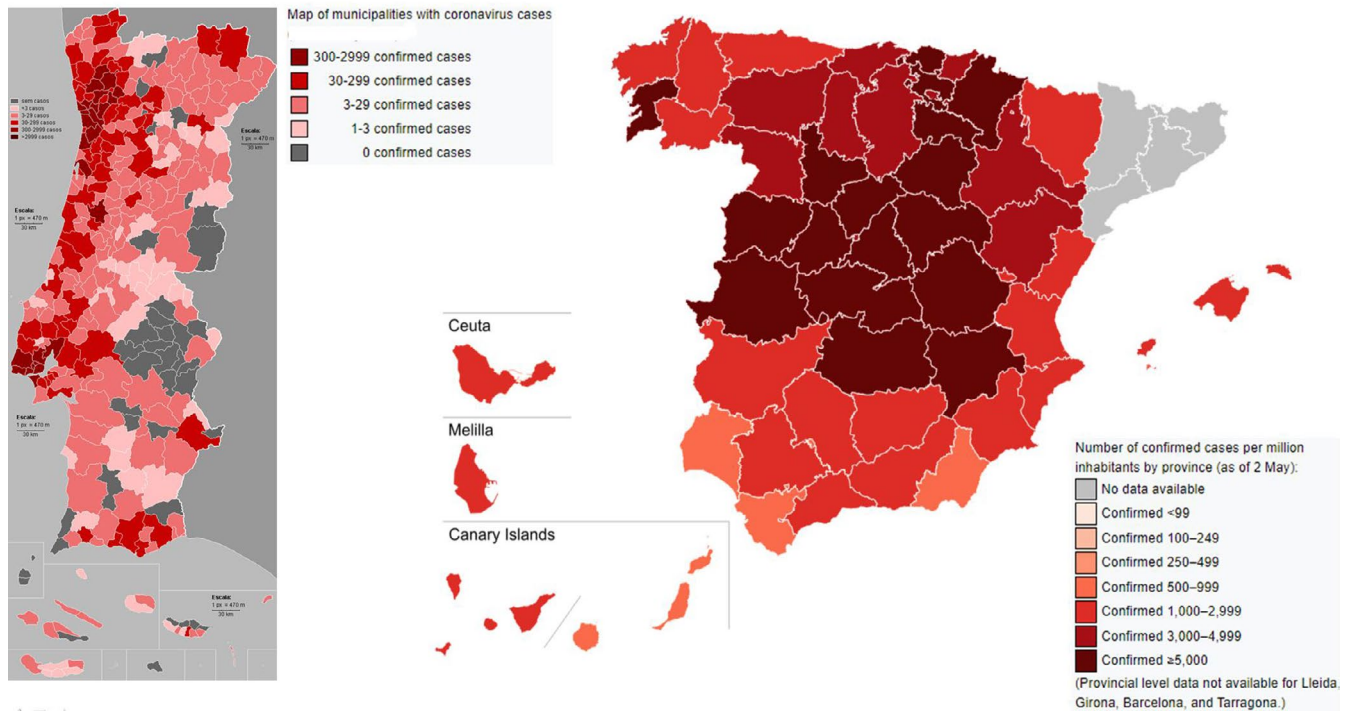


FIGURE 2 Differences in numbers of COVID-19 cases and deaths per million detected in Portugal versus Spain (data: Wikipedia.org), from March 11 to April 27, 2020. Citizens of Portugal (figure on the left) seem to be less susceptible to coronavirus (COVID-19) infections, at least in the severe form, while Spanish citizens (figure on the right) would have a high mortality rate from COVID-19 infections, as protective vaccination against BCG is mandatory in Portugal while in Spain it is not. Sources: Portugal Directorate-General of Health (press conferences/website) for Portugal, and Sources: ISCIII regular updates from the Ministry of Health, for Spain

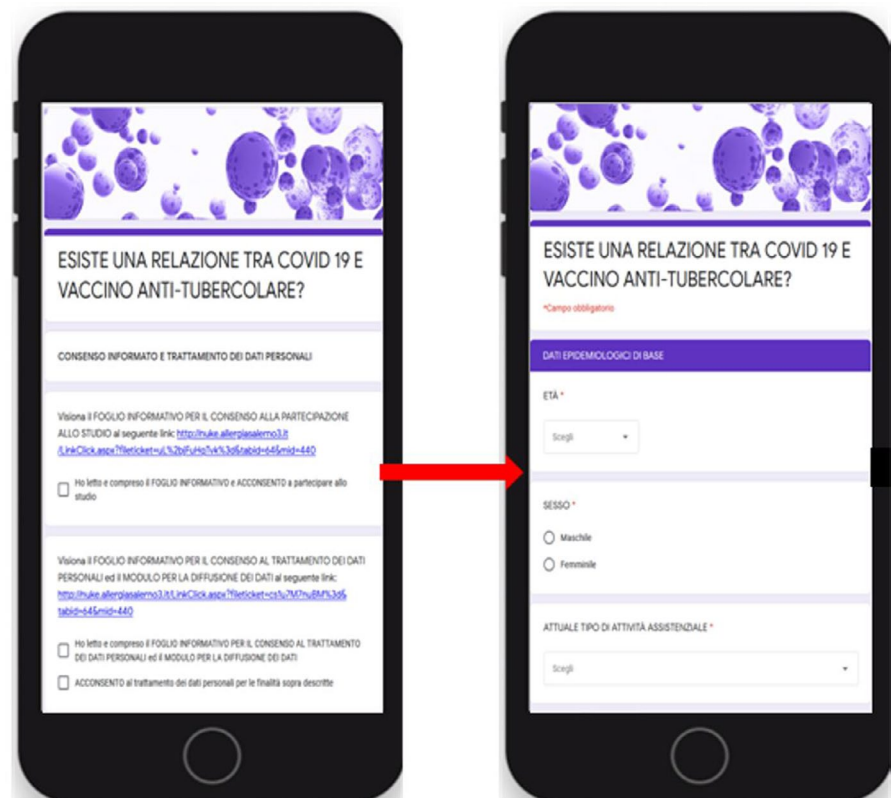


FIGURE 3 When regulatory and disclosure screens are filled in, the app asks the questions to get, in unnamed, the data of BCG vaccination in doctor population

high mortality rate from COVID-19, as protective vaccination against BCG is mandatory in Portugal while in Spain it is not (Figure 2). In order to respond to their question about BCG vaccination effecting the spread and severity of COVID-19, we argue that the BCG vaccination seems to induce an immune response also against other infectious agents,⁷ acting as an immune enhancer of innate immune system components. This immunological phenomenon was extensively studied, especially the induction of "non-antigen-specific immunological memory" in innate immunity cells as macrophages, monocytes, and NK cells. After BCG stimulation, these cells undergo an epigenetic reprogramming of some transcription factors; promoters of cytokine genes are de-phased or de novo created. Excluding any influence due to pollution and/or climate change,⁸ this epigenetic remodeling is maintained even after the disappearance of the primary stimulus ("nonspecific immunological memory of the antigen"), giving the cell the ability to respond more powerfully to the next stimulus, although not related to previous stimuli.

In SARS-CoV infection (to verify for SARS-CoV-2 infection), type I interferons, by macrophages/monocytes, represent a fundamental mechanism of protection from viral infections; they induce the secretion of antiviral molecules and place uninfected cells in a transient antiviral state. This type of defense is useful and decisive especially in the early phase of the infection, but in the late phase an excessive interferon response should induce to the cytokine release syndrome. It is therefore conceivable that the epigenetic upgrade of monocyte-macrophage line may favor a more effective interferon response, with an immediate resolution of the infectious process. Another of the escape mechanisms of SARS-CoV2 should seem to be the inhibition of the natural killer cells, with consequent decrease of Th1 response (reduction of IL-12, IL-15, IL-18) and with reduction of the direct cytotoxic action of the infected cells.

The improved response capacity of these enhanced cells seems to be linked essentially to specific cytokine secretion profiles that promote a more effective elimination of any infection; in particular, IL-1 β has been identified as main cytokine effecting to reduce viremia in case of secondary viral stimuli.⁹


We identified the Italian Medical Class as a study cohort because they underwent BCG vaccination for regulatory devices, and in parallel is the subject most exposed to infection. Therefore, an observational study aimed at understanding whether there is an epidemiological relationship between vaccination with BCG and COVID-19 was approved on March 31, 2020, by an independent Ethical Committee. The aim of this study is to assess the ability and readiness to respond to viral infection by doctors who have been vaccinated against TB, in relation to their degree of occupational exposure, age, gender, year of vaccination, and subspecialists in different disciplines.

Through a survey on all physicians belonging to Professional Orders, we will evaluate possible COVID-19 contagion, severity of infection, and BCG vaccination (Figure 3). Pending the ongoing trials (NCT04327206, NCT04328441), as reported by Curtis N. et al, there are four main reasons why it is very important to adhere to WHO recommendation, that in the absence of evidence it does not

recommend BCG vaccination for the prevention of COVID-19.¹⁰ This study could serve as an easy, quick, and low-cost research tool to evaluate the protective effect of BCG against COVID-19 worldwide, and how a greater number of years since the vaccination could be correlated with an increased risk of infection and with a greater severity of clinical picture during Cytokines Release Syndrome by COVID-19.

CONFLICT OF INTEREST

The authors have no conflict of interests to declare related to this work, nor financial associations that could have influenced the outcome of the findings here detailed.

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REFERENCES

- Ozdemir C., Kucuksezer U.C., Tamay Z.U. Is BCG vaccination effecting the spread and severity of COVID-19? *Allergy*. 2020;75:1824-1827. <https://doi.org/10.1111/all.14344>.
- Redelman-Sidi G. Could BCG be used to protect against COVID-19? *Nat Rev Urol*. 2020;17(6):316-317.
- Romanus V. Selective BCG vaccination in a country with low incidence of tuberculosis. *Euro Surveill*. 2006;11(3):14-17.
- Zwerling A., Behr M.A., Verma A., Brewer T.F., Menzies D., Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. *PLoS Med*. 2011;8(3):e1001012.
- Marta Rodriguez Martinez & Euronews with AP, AFP. Has the key to a coronavirus vaccine been staring us in the face for a century?. <https://www.euronews.com/2020/04/06/has-the-key-to-a-coronavirus-vaccine-been-staring-us-in-the-face-for-a-century>. Accessed April 10, 2020.
- Miller A., Reandelar M.J., Fasciglione K., Roumenova V., Li Y., Otazu G.H. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. *medRxiv*. 2020. <https://doi.org/10.1101/2020.03.24.20042937>.

7. Biering-Sørensen S., Aaby P., Napirna B.M., et al. Small randomized trial among low-birthweight children receiving bacillus Calmette-Guérin vaccination at first health center contact. *Pediatr Infect Dis J* 2012;31:306-308.
8. Patella V., Florio G., Magliacane D., et al. Air Pollution and Climate Change Task Force of the Italian Society of Allergology, Asthma and Clinical Immunology (SIAAIC). Urban air pollution and climate change: "The Decalogue: Allergy Safe Tree" for allergic and respiratory diseases care. *Clin Mol Allergy*. 2018;16:3.
9. Arts RJW, Moorlag SJCFM, Novakovic B., et al. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. *Cell Host Microbe* 2018;23:89-100.
10. Curtis N., Sparrow A., Ghebreyesus T.A., Netea M.G. Considering BCG vaccination to reduce the impact of COVID-19. *Lancet*. 2020;395(10236):1545-1546.