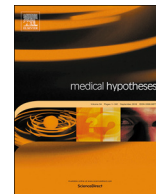




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Letter to Editors

BCG vaccination and COVID-19: Much ado about nothing?



We read with great interest the article “Relation between BCG coverage rate and COVID-19 infection worldwide” by Macedo et al. [1], which provides a worldwide overview of vaccination programmes and COVID-19 burden in different countries, and postulates that BCG may protect from COVID-19.

By relying on speculation more than on evidence the current scientific debate seems to value the idea of a BCG-related lower susceptibility to COVID-19 [2]. As a *proof of concept*, different authors reported a limited COVID-19 burden in BCG vaccinated countries [2–5]. The hypothesis is certainly supported by a strong immunological rationale. In fact, BCG vaccination may contribute to polarize the physiological immune reaction toward a Th1 pattern and exert an additional protective role against viruses [6].

However, when looking at the different distribution of COVID-19 outbreak worldwide according to BCG coverage, several confounding factors should be considered.

The low temperature facilitates the virus spread. The most affected countries experienced the COVID-19 pandemic during their wintertime [7], which could explain the difference between the northern and southern hemisphere besides BCG vaccination.

Furthermore, depending on the local health care system, case identification resources, including COVID-19 swabs, may vary in different countries, which is relevant when sizing the impact of a viral infection.

In Europe, where the above-mentioned variables are quite homogeneous, COVID-19 outbreak is still lower where BCG vaccination is regularly provided [8]. It is the case of Eastern Countries (except Portugal). However, the population mean age in BCG unvaccinated states is significantly higher in comparison to vaccinated ones (respectively 40.9-SD 3.1- vs 37.8-SD 5.7- years; *t*-test: $p = 0.031$), as well as the mean life expectancy (respectively 81.6-SD 1.7 vs 75.0-SD 2.6 years; *t*-test: $p < 0,001$) [8]. This evidence is not negligible when considering that most of COVID-19 fatal cases were registered in patients older than 70.

Furthermore, the population's density is significantly higher in BCG unvaccinated countries (median 127.6 [IQR: 83,1 – 230.5] inhabitants/Km² vs 73.7 [IQR: 45.0 – 101.0]; Mann-Whitney test: $p = 0.003$). The difference is remarkable when considering its relevance in facilitating the infection from human to human [9]. The same effect can be exerted by the international commercial exchanges and air traffic, which is much more relevant in European Western Countries, primarily interested by the COVID-19 outbreak.

In the light of the above-mentioned determinants, the hypothetical relevance of BCG-vaccination as a protection from COVID-19, although fascinating, remains quite controversial and further focused research is required besides speculation.

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Conflict of interest statement

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