

Background immunity: How important is it for SARS-CoV-2?

Dear Editor,

While waiting for a safe and effective vaccine against *Severe acute respiratory syndrome-related coronavirus 2* (SARS-CoV-2), the etiologic agent of coronavirus disease-2019 (COVID-19), much has been speculated about the relationship between pre-existing immunity and SARS-CoV-2 infections. In line with this concern, here we discuss the importance and potential implications of background immunity, specifically the hygiene hypothesis, innate immunity training and cross-immunity, in the transmission of SARS-CoV-2 and/or severity of COVID-19.

Briefly, the hygiene hypothesis suggests that children raised in poor hygiene conditions, with frequent exposure to environmental antigens and targets of continuous infections (mainly by helminths), would be less susceptible to diseases resulting from immunity imbalance, such as allergic and autoimmune diseases.¹ Since the clinical course of COVID-19 seems to be somehow related to an imbalance of the immune response, it would be conceivable that hygiene (within the above perspective), could influence the severity of SARS-CoV-2 infections. In addition, massive exposure to numerous antigens during childhood could contribute to the development of immunity, especially proinflammatory responses, which would be useful in a nonspecific control of various infectious agents, including SARS-CoV-2. This idea overlaps that of innate immunity training, discussed later.

Although the relationship between the hygiene hypothesis and protection against COVID-19 seems theoretically plausible, this association has not yet been clearly demonstrated. A preprint study performed with economic and socio-demographic determinants found weak evidence for the hygiene hypothesis as a protection factor for COVID-19.² On the other hand, an ecological study conducted with all confirmed cases of COVID-19 in Brazil until May 6, 2020, reported a positive association between the incidence rate of COVID-19 and the Social Vulnerability Index, which includes deficiency in water supply, sewage, and garbage collection.³

Innate immunity training, which corresponds to long-term epigenetic changes in innate immune cells after exposure to infection-related antigens, such as those delivered by live vaccines (e.g., *Bacillus Calmette-Guérin* [BCG] and measles vaccines), has also been considered a potential tool against SARS-CoV-2, at least until effective and specific vaccines are available. These epigenetic changes result in an increased production of proinflammatory cytokines, which are not antigen-specific and, thus, may contribute to protection against heterologous infections.⁴

Although the role of trained immunity in protecting against non-related infections has been reported by systematic review⁵ and experimental studies⁶, its influence on COVID-19 remains uncertain.

Several studies have suggested an association between BCG immunization and reduced transmission, severity, and/or deaths from COVID-19.⁷ This association could explain the difference in incidence and severity of COVID-19 among different age groups and among countries with different BCG vaccination policies. Other studies, however, have not found a significant relationship between positive tests for SARS-CoV-2 and BCG vaccination,⁸ or between BCG and the outcome of COVID-19.⁹ Although apparently conflicting, these findings were obtained from epidemiological-based studies and, thus, perhaps reflect the multifactorial nature of the virus-host relationship, as well as the different variables and analytical methods adopted.

To clarify this issue, there are at least 17 clinical trials, at different stages, aiming to assess the protection of BCG immunization against SARS-CoV-2.¹⁰ These studies will certainly provide considerable insights in the near future. Experimental studies carried out with suitable animal models, which could reveal which (and how) the immunological mechanisms stimulated by BCG vaccine could be useful against SARS-CoV-2, would also be timely. Interestingly, *in silico* analyzes have found some homology between BCG and SARS-CoV-2 proteins, which could have possible implications for the induction of memory B-cells.¹¹

In addition to the above, Grifoni et al.¹² reported a probable background immunity against SARS-CoV-2: TCD4 cells from about 40%–60% individuals not previously exposed to SARS-CoV-2 can cross-react to SARS-CoV-2 proteins. Additional studies capable of evaluating the influence of this pre-existing cross-immunity on SARS-CoV-2 infection and/or on the severity of COVID-19 would be interesting. In addition to providing information on population immunity, these studies may generate insights regarding the virus-host interaction, as well as being useful for the development of effective vaccine strategies.

Importantly, even if future studies prove that hygienic conditions, innate immunity training and the cross-response of T cells to other human coronaviruses may contribute to the prevention and/or outcome of COVID-19, these issues should be considered beyond the immunological perspective, paying attention to the combined influence of the several aspects of the host, the virus, and the environment. In other words, the importance of these mechanisms, alone or combined, must be considered according to the history and environmental characteristics of the target population.

Moreover, even if these hypotheses are eventually confirmed, these findings should not discourage the implementation of containment measures, nor the development of vaccines or anti-SARS-CoV-2 drugs. On the contrary, this deepening of knowledge about the virus-host interaction would be very useful to adapt strategies against COVID-19. Finally, it must be emphasized that if background immunity

was sufficient in itself, COVID-19 probably would not have reached its pandemic status—nature can help us, but it does not work alone.

José Valter Joaquim Silva Júnior^{1,2,3} 

Thaís Regina Rocha Lopes^{1,3}

Rudi Weiblen³

Eduardo Furtado Flores³

¹*Virology Sector, Laboratory of Immunopathology Keizo Asami, Federal University of Pernambuco, Pernambuco, Brazil*

²*Department of Microbiology and Parasitology, Federal University of Santa Maria, Santa Maria, Brazil*

³*Virology Sector, Department of Preventive Veterinary Medicine, Federal University of Santa Maria, Santa Maria, Brazil*

Correspondence

Eduardo Furtado Flores, Setor de Virologia, Departamento de Medicina Veterinária Preventiva, Universidade Federal de Santa Maria, Av. Roraima, 1000, Camobi, Santa Maria, Rio Grande do Sul 97105-900, Brazil.

Email: eduardofurtadoflores@gmail.com

ORCID

José Valter Joaquim Silva Júnior  <https://orcid.org/0000-0001-5932-0971>

REFERENCES

- Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clin Exp Immunol*. 2010; 160:1-9.
- Sethi T, Kedia S, Awasthi R, Lodha R, Ahuja V. A counterfactual graphical model reveals economic and sociodemographic variables as key determinants of country-wise COVID-19 burden. *medRxiv*. 2020.
- Freire de Souza CD, Machado MF, Feliciano do Carmo R. Human development, social vulnerability and COVID-19 in Brazil: A study of the social determinants of health. *Infect Dis Poverty*. 2020;9:124. <https://idpjournal.biomedcentral.com/articles/10.1186/s40249-020-00743-x>
- Netea MG, Giamarellos-Bourboulis EJ, Domínguez-Andrés J, et al. Trained Immunity: a tool for reducing susceptibility to and the severity of SARS-CoV-2 infection. *Cell*. 2020;181:969-977.
- Higgins JPT, Soares-Weiser K, López-López JA, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ*. 2016;355:i5170.
- 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.
- Sharma AR, Batra G, Kumar M, Mishra A, Singla R, Singh A, Singh RS, Medhi B. BCG as a game-changer to prevent the infection and severity of COVID-19 pandemic? *Allergol Immunopathol (Madr)*. 2020; 48(5):507-517.
- Hamiel U, Kozer E, Youngster I. SARS-CoV-2 rates in BCG-vaccinated and unvaccinated young adults. *JAMA*. 2020;323:2340-2341.
- Szigeti R, Kellermayer D, Trakimas G. BCG epidemiology supports its protection against COVID-19? A word of caution. *PLoS One*. 2020;15: e0240203. <https://journals.plos.org/plosone/article/related?id=10.1371/journal.pone.0240203>
- Bacillus Calmette Guerin and COVID*; 2020. <https://clinicaltrials.gov/ct2/results?cond=BCG+SARS-CoV-2&term=&cntry=&state=&city=&dist=>. Accessed October 1, 2020.
- Strongin AY, Sloutsky A, Cieplak P. A Note on the potential BCG vaccination—COVID-19 molecular link. *Coronaviruses*. 2020;1:4-6.
- Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell*. 2020;181(7):489-501.