Protection against COVID-19: beyond antibodies

Lancet Infect Dis 2021
Published Online
September 9, 2021
https://doi.org/10.1016/S1473-3099(21)00561-2

See Online/Articles
https://doi.org/10.1016/S1473-3099(21)00479-5

The COVID-19 pandemic has exposed the deep inequalities of our times. Differences in behaviour, political will, and technological capacity between affected countries have contributed to distinct outcomes.[1] 18 months after the COVID-19 pandemic began in China, mortality is highest among vulnerable populations without access to vaccination and those ideologically opposed to vaccination, in a way confirming that vaccines save lives.

In an unprecedented scenario, humankind timely developed safe and efficacious SARS-CoV-2 vaccines that have prevented thousands of deaths worldwide. In Chile, the UK, and the USA, all of which have licensed different vaccines, a decreasing number of COVID-19 deaths have correlated with vaccine rollout. Reductions in excess mortality have been observed in these countries, despite an increased number of cases, another clear indication that vaccines are effective.[2]

The first stages of vaccine development use basic science methods to carefully characterise the humoral and cellular immune responses induced. Subsequently, larger clinical trials are done, focused on assessing the protection conferred against infection, mild to moderate disease, and severe cases. When the effect of a vaccine is positive against any of these outcomes, it has the potential to save lives. Inactivated SARS-CoV-2 vaccines such as Sinovac's inactivated CoronaVac vaccine, which use well known vaccine technology,[3] were the first to be used in China and Latin America, contributing to a reduction in the number of deaths, albeit with modest protection against infection, especially among older individuals (aged >80 years).[4]

mRNA vaccines, based on a new technology, have been considered more robust than inactivated vaccines, and are thought to provide better protection against infection. Sterile protection is likely to be dependent on high levels of neutralising antibodies, whereas disease control seems to be dependent on T-cell responses.[5] However, the correlates of protection for SARS-CoV-2 vaccines are not fully described. In fact, for most vaccines used, the correlates of protection are unknown. Although the humoral and cellular responses induced by vaccines are well characterised, which aspect of the response is responsible for saving lives remains unclear.

Cellular and humoral immune responses can be assessed in the first stages of vaccine development; however, the surveillance of vaccine responses in large populations is only feasible through measurement of antibody responses, since the assessment of cellular responses is dependent on time-consuming, laborious, and expensive assays. Neutralising antibodies might represent the best humoral correlate, but their use for routine testing is unpractical due to technical requirements,[6] and they do not provide equal protection against all variants.[7] Thus, seroepidemiology is used to track vaccine rollout. However, antibody testing to evaluate COVID-19 vaccines has become routine, and misperceptions about the interpretation of this information among the general population has led to false understanding of vaccine effectiveness, contributing to vaccine hesitancy and increasing anxiety. Moreover, the absence of antibodies in routine tests might be explained by false-negative results.[6]

For more on **COVID-19 cases and mortality data** see https://ourworldindata.org/

One major practice that has hindered COVID-19 vaccination campaigns is that of self-testing for antibodies after vaccination. The general population does not understand that no specific level of antibodies exists as a clear cutoff for 100% protection. Therefore, although studies of humoral responses to vaccines in populations over time are necessary for the scientific community and vaccine developers, such studies need to be accompanied by clear messaging to the public that total antibody levels and protection might not be directly linked.

In *The Lancet Infectious Diseases*, Denis Sauré and colleagues[8] reported that people in Chile given Sinovac's inactivated CoronaVac vaccine had lower SARS-CoV-2 IgG seropositivity than those given Pfizer-BioNTech's mRNA BNT162b2 vaccine, as detected by rapid diagnostic tests after the first and second doses. 56 261 individuals were included in the analysis, contributing to narrow confidence intervals and compensating for certain biases, such as the accuracy of the rapid diagnostic tests in the field and selection bias. For CoronaVac, mean IgG positivity steadily declined after reaching a peak of 77·4% (95% CI 75·5–79·3) during week 3 after the second dose. By contrast, for the BNT162b2 vaccine, no decline in mean IgG positivity was observed after reaching a peak of 96·5% (95% CI 94·9–98·1).

Further investigation is needed to determine whether the decrease in IgG positivity after vaccination with CoronaVac parallels decreasing protection against severe disease. Effectiveness against intensive care unit (ICU) admission was 91·6% (95% CI 90·5–92·5) in Chile during the vaccine scaling-up campaign.[9] Decisions made by policy makers about the need for a third dose will benefit from seroepidemiology studies, but the most relevant information to assess vaccine effectiveness should be protection in terms of reduction of deaths and ICU admissions, especially considering new emerging variants. Equitable access to robust vaccines is the ideal scenario, but in reality the universal provision of any COVID-19 vaccine presents a challenge.

We declare no competing interests.

Marcus Vinícius Guimarães Lacerda, Daniel Youssef Bargieri
marcuslacerda.br@gmail.com

Instituto de Pesquisa Clínica Carlos Borborema, Fundação de Medicina Tropical Dr Heitor Vieira Dourado, Manaus, Brazil (MVGL); Fundação Oswaldo Cruz, Instituto Leônidas e Maria Deane, Manaus 69040-000, Brazil (MVGL); Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, Brazil (DYB)

1 Bambra C, Riordan R, Ford J, Matthews F. The COVID-19 pandemic and health inequalities. *J Epidemiol Community Health* 2020; **74:** 964–68.
2 Moghadas SM, Vilches TN, Zhang K, et al. The impact of vaccination on COVID-19 outbreaks in the United States. *Clin Infect Dis* 2021; published online Jan 30. https://doi.org/10.1093/cid/ciab079.
3 Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet* 2021; **398:** 213–22.
4 Ranzani OT, Hitchings MDT, Dorion M, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. *BMJ* 2021; **374:** n2015.
5 Tan AT, Linster M, Tan CW, et al. Early induction of functional SARS-CoV-2-specific T cells associates with rapid viral clearance and mild disease in COVID-19 patients. *Cell Rep* 2021; **34:** 108728.
6 Castro R, Luz PM, Wakimoto MD, Veloso VG, Grinsztejn B, Perazzo H. COVID-19: a meta-analysis of diagnostic test accuracy of commercial assays registered in Brazil. *Braz J Infect Dis* 2020; **24:** 180–87.
7 Alter G, Yu J, Liu J, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. *Nature* 2021; **596:** 268–72.
8 Sauré D, O'Ryan M, Torress JP, Zuniga M, Santelices E, Basso LJ. Dynamic IgG seropositivity after rollout of CoronaVac and BNT162b2 COVID-19 vaccines in Chile: a sentinel surveillance study. *Lancet Infect Dis* 2021; published online Sept 9. https://doi.org/10.1016/S1473-3099(21)00479-5.
9 Jara A, Undurraga EA, González C, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. *N Engl J Med* 2021; published online July 7. https://doi.org/10.1056/NEJMoa2107715.