# Toward superhuman SARS-CoV-2 immunity?

To the Editor - If asked, many scientists would probably agree with the statement 'Natural infection gives better immunity than vaccination'. Indeed, if one survives the infection, there are certainly many pathogens for which natural infection induces stronger immune responses and more long-lived immunity than does vaccination. Measles is prototypic of this[1]. While there was a clear risk, after infection, of death, encephalitis and pneumonia before there was a vaccine, survivors gained lifelong immunity. Vaccination against measles, on the other hand, requires two shots and may not offer lifelong complete protection but has proven to be good enough to keep the disease in check when widely implemented.

In contrast to the measles virus, there are a number of pathogens for which vaccination generates stronger immune responses and more-effective protection against disease than does natural infection. In these cases, the man-made vaccine is 'superhuman'; that is, it gives humans immune responses superior to those generated in response to infection. The bacterium that causes tetanus is a notable example of this. Infection with this pathogen results in production of the highly potent tetanus toxin in small amounts that are sufficient to cause severe disease but not enough to generate a strong immune, particularly antibody, response. On the other hand, vaccination with an inactivated form of the toxin (tetanus toxoid) generates antibody responses sufficient to provide protection against the toxin for a decade and probably longer[2]. Hence, vaccination is recommended even for those who have been infected with the bacterium that causes tetanus and have shown clinical symptoms, as well as those who have been merely potentially exposed.

Another example from the bacterial world is *Haemophilus influenza* type b (Hib). Hib causes a variety of serious conditions, including meningitis, pneumonia and septicemia. The surface of the bacterium is protected by a coating of sugars, which typically induce rather poor antibody responses. However, the responses can be greatly enhanced by linkage of the sugars to a protein in a vaccine in preparations known as 'glycoconjugates'[3]. The typical responses to vaccination are therefore greatly enhanced relative to the responses to natural infection. The vaccine is now given to children under the age of 2 years in many developed countries in particular and has greatly reduced the incidence of meningitis due to Hib.

Among viruses, two classic cases in which vaccines generate immunity superior to that generated by natural infection are varicella zoster virus, which can lead to shingles, and human papillomavirus (HPV), some strains of which cause various malignancies, including cervical, penile and oropharyngeal cancer. Varicella zoster virus typically causes chickenpox in children and young adults and is resolved but rendered latent so that when re-activated in later life, it can lead to shingles. Immunity arising from the primary infection does not prevent the disease in those who develop shingles. However, the recently developed vaccines Zostavax and Shingrix do offer protection against shingles. Shingrix protects around 90% vaccinees across all age groups, and it is suggested for an extended time period[4]. Protection seems to be antibody based but with important contributions from $CD4^+$ T cells.

The quintessential example of immunity superior to that induced by infection is the vaccine against HPV. The HPV strains that cause genital cancers enter the body via genital mucosal surfaces, and the antibody responses induced are low and take a long time to develop—more than 8 months in one study[5]. In contrast, two or three sequential intramuscular injections of one of the vaccines against HPV induce potent neutralizing antibody responses that have been shown directly in an animal model to prevent entry of the virus into target cells and the establishment of infection[6]. The vaccines against HPV are based on the incorporation of a single viral surface protein into virus-like particles. They have been shown to offer complete protection against cervical cancer.

Where does the coronavirus SARS-CoV-2 lie along the spectrum of natural infection versus vaccine-induced protective efficacy? The answer to this question will be known only as more data are collected from ongoing natural infection and vaccine studies; the initial results from interim analyses by Pfizer/BioNTech and Moderna of mRNA vaccines against SAR-CoV-2 showing a reduction in infections of around 95% are very encouraging[7]. There are a number of other promising signs for vaccines. Protection against infection and disease has been associated with neutralizing antibodies in both vaccine studies and passive-antibody-transfer studies in animal models[8]. Furthermore, passive antibodies seem to have beneficial effects on established early SARS-CoV-2 infection in humans, which suggests that they can contribute to protection[9]. Many of the current vaccines in clinical trials[10] induce high levels of neutralizing antibodies that animal model studies predict would provide protection. Furthermore, even if the levels reached do not provide complete sterilizing immunity and are insufficient to prevent the upper-respiratory-tract symptoms typical of the common cold, they may prevent serious lower-respiratory-tract disease. The disadvantage of such an outcome is that the vaccine probably would not prevent ongoing transmission from an infected vaccinee. In contrast to many of the vaccines, natural infection induces highly variable levels of neutralizing antibodies, a proportion of which may not provide immunity. At the patient level, there are isolated reports of re-infection with SARS-CoV-2 associated with an insufficient initial antibody response. A second likely contributor to protection against SARS-CoV-2 is cellular immunity[11], although the data on its importance are not yet clear. A number of vaccines are expected to induce substantial cellular immune responses. One important unknown factor in the context of both natural infection and vaccination is the durability of immune responses. Multiple longitudinal cohort studies of antibody levels after COVID-19 have shown that they are variable, with some showing durability over several months and others showing some 'fall-off'. The durability of antibody responses is likely to be 'tweakable' through judicious choice of vaccines. In general, extensive molecular studies of SARS-CoV-2 and neutralizing antibody responses will be of value should rational design strategies be needed to generate optimal vaccines[12].

Overall, we are optimistic, given the number of platforms being investigated and the huge ongoing efforts, that a vaccine (or vaccines) against COVID-19 with immune responses and protection superior to that achieved through natural infection is an achievable goal. ❐

Dennis R. Burton[1,2]✉ and Eric J. Topol[1,3]✉

[1]*The Scripps Research Institute, La Jolla, CA, USA.* [2]*Ragon Institute of MGH, Harvard and MIT, Cambridge, MA, USA.* [3]*Scripps Translational Research Institute, La Jolla, CA, USA.*
✉*e-mail: burton@scripps.edu; etopol@scripps.edu*

Published online: 30 November 2020
https://doi.org/10.1038/s41591-020-01180-x

## References

1. Amanna, I. J. & Slifka, M. K. *Curr. Top. Microbiol. Immunol.* **428**, 1–30 (2020).
2. Hammarlund, E. et al. *Clin. Infect. Dis.* **62**, 1111–1118 (2016).
3. Rappuoli, R., De Gregorio, E. & Costantino, P. *Proc. Natl Acad. Sci. USA* **116**, 14–16 (2019).
4. Cunningham, A. L. et al. *J. Infect. Dis.* **217**, 1750–1760 (2018).
5. Carter, J. J. et al. *J. Infect. Dis.* **174**, 927–936 (1996).
6. Day, P. M. et al. *Cell Host Microbe* **8**, 260–270 (2010).
7. Cohen, J. *Science* https://www.sciencemag.org/news/2020/11/just-beautiful-another-covid-19-vaccine-newcomer-moderna-succeeds-large-scale-trial (2020).
8. Klasse, P. J., Nixon, D. F. & Moore, J. P. *Preprints* **2020**, 2020090166 (2020).
9. DeFrancesco, L. *Nat. Biotechnol.* **38**, 1242–1252 (2020).
10. Krammer, F. *Nature* **586**, 516–527 (2020).
11. Lipsitch, M., Grad, Y. H., Sette, A. & Crotty, S. *Nat. Rev. Immunol.* **20**, 709–713 (2020).
12. Burton, D. R. & Walker, L. M. *Cell Host Microbe* **27**, 695–698 (2020).

## Acknowledgements

D.R.B. receives financial support from The National Institute of Allergy and Infectious Diseases, the Bill & Melinda Gates Foundation, Ragon Institute, The International AIDS Vaccine Initiative and the Pendleton Trust. Funding for E.J.T. was provided by the Clinical and Translational Science Award (CTSA grant UL1TR002550) from the National Center for Advancing Translational Sciences of the US National Institutes of Health.

## Author contributions

D.R.B. and E.J.T. conceived of the idea and wrote the piece together.

## Competing interests

The authors declare no competing interests.