

the primary analysis is unfortunately common. In early phase studies in a pandemic, little is known for certain, and it seems biologically plausible that treating patients earlier could be more effective. Nonetheless, as well as being vigilant against overinterpretation, we need to ensure that hypotheses generated in efficacy-based trials, even in subgroups, are confirmed or refuted in subsequent adequately powered trials or meta-analyses.

We have already seen how different interpretations will be put on these results, with the unintended early release of this study's results on the WHO website.¹¹ This underlines how labelling of trials is mistaken as positive or negative—equating a $p > 0.05$ with no evidence of benefit. There has been a welcome discussion of p value limitations recently.¹² An absence of statistical significance in an underpowered trial means that the findings are inconclusive. The particular challenges of delivering pandemic trials underline the importance of data sharing, allowing rapid curation of relevant datasets for individual patient data meta-analyses.¹³ With each individual study at heightened risk of being incomplete, pooling data across possibly several underpowered but high-quality studies looks like our best way to obtain robust insights into what works, safely, and on whom. We eagerly await the ongoing trials.

I am employed by University of Edinburgh and by the UK Medical Research Council/National Institutes of Health Research as Chair of the Efficacy and Mechanisms Evaluation Funding Committee.

John David Norrie
j.norrie@ed.ac.uk

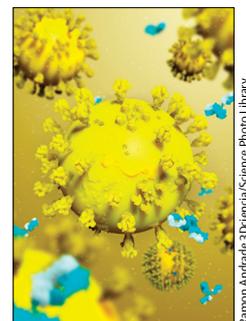
Edinburgh Clinical Trials Unit, Usher Institute, Edinburgh EH16 4UX, UK

- 1 Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; published online April 29. [https://doi.org/10.1016/S0140-6736\(20\)31022-9](https://doi.org/10.1016/S0140-6736(20)31022-9).
- 2 WHO. COVID-19 therapeutic trial synopsis. Geneva: World Health Organization, Feb 18, 2020. https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf (accessed April 25, 2020).
- 3 Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020; **382**: 929–36.
- 4 Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med* 2020; published online April 10. DOI:10.1056/NEJMoa2007016.
- 5 Ford I, Norrie J. Pragmatic Trials. *N Engl J Med* 2016; **375**: 454–63.
- 6 Tang W, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomised, controlled trial. medRxiv 2020; published online April 14. <https://doi.org/10.1101/2020.04.10.20060558> (preprint).
- 7 Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalised with severe COVID-19. *N Engl J Med* 2020; published March 18. DOI:10.1056/NEJMoa2001282.
- 8 Cook JA, Julious SA, Sones W, et al. DELTA² guidance on choosing the target difference and undertaking and reporting the sample size calculation for a randomised controlled trial. *BMJ* 2018; **363**: k3750.
- 9 Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000; **355**: 1064–69.
- 10 Sleight P. Debate: subgroup analyses in clinical trials: fun to look at—but don't believe them! *Curr Control Trials Cardiovasc Med* 2000; **1**: 25–27.
- 11 BBC. Hopes dashed as coronavirus drug remdesivir 'fails first trial'. April 23, 2020. www.bbc.co.uk/news/world-52406261 (accessed April 25, 2020).
- 12 Wasserstein RL, Schirm AL, Lazar NA. Moving to a world beyond “ $p < 0.05$ ”. *Am Stat* 2019; **73**: 1–19.
- 13 Simmonds MC, Higgins JPT, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials* 2005; **2**: 209–17.

What policy makers need to know about COVID-19 protective immunity

About a third of the world is under lockdown as a public health measure to curb the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). Policy makers are increasingly pressed to articulate their rationales and strategies for moving out of lockdown; the process of re-emergence is already cautiously starting in Austria, Switzerland, Denmark, Wuhan, and some US states. As the counterpoise between further disease spread and socioeconomic costs is debated, it is essential that policy makers in all affected countries have the best possible data and understanding to inform any course of action.

Strategies in various countries that aim to stagger return to work on the basis of disease severity risk and age do not take account of how exposing even lower-risk individuals, such as young people with no comorbidities, to the virus so as to increase herd immunity can still result in pandemic spread. The only selective pressure on SARS-CoV-2 is transmission—stop transmission and you stop the virus. The linchpin for a strategy to move out of lockdown seemingly rests on increased testing and contact tracing, possible return-to-work permits based on immune status,¹ repurposed or new therapeutics,² and, finally, vaccination.^{3,4} This approach is broadly



Ramon Andrade/3DScientific/Science Photo Library

Published Online
April 27, 2020
[https://doi.org/10.1016/S0140-6736\(20\)30985-5](https://doi.org/10.1016/S0140-6736(20)30985-5)

sensible, yet immunology is a complex branch of molecular medicine and policy makers need to be alerted to important aspects of immunology in relation to COVID-19. There is no certainty as to the immunological correlates of antiviral protection or the proportion of the population who must attain them, making it impossible to identify a point when this level of immunity has been reached.

Current discussion, for example, addresses the notion that scaled up antibody testing will determine who is immune, thus giving an indication of the extent of herd immunity and confirming who could re-enter the workforce. There are questions to be addressed about the accuracy of tests and practicalities of implementation of laboratory-based versus home-use assays.⁵ For any country contemplating these issues, another crucial question is how solid is the assumption that antibodies to SARS-CoV-2 spike protein equate to functional protection? Furthermore, if presence of these antibodies is protective, how can it be decided what proportion of the population requires these antibodies to mitigate subsequent waves of cases of COVID-19?

Any discussions should be informed by consideration of correlates of protection. Initially proposed by Stanley Plotkin,^{6,7} this concept rests on the notion of empirically defined, quantifiable immune parameters that determine the attainment of protection against a given pathogen. Caution is needed because total measurable antibody is not precisely the same as protective, virus-neutralising antibody. Furthermore, studies in COVID-19 show that 10–20% of symptomatically infected people have little or no detectable antibody.⁸ In some cases of COVID-19, low virus-binding antibody titres might correlate with lethal or near-lethal infection, or with having had a mild infection with little antigenic stimulation. Importantly, scientists must not only identify correlates of protection but also have a robust understanding of the correlates of progression to severe COVID-19, since knowledge of the latter will inform the former.

The route to certainty on the degree and nature of the immunity required for protection will require evidence from formal proofs using approaches such as titrated transfers of antibodies and T lymphocytes to define protection in non-human primate models, as used, for example, in studies of Ebola virus.⁹

A study of survivors of SARS showed that about 90% had functional, virus-neutralising antibodies and around 50% had strong T-lymphocyte responses.¹⁰ These observations bolster confidence in a simple view that most survivors of severe COVID-19 would be expected to have protective antibodies. A caveat is that most studies, either of SARS survivors or of COVID-19 patients, have focused on people who were hospitalised and had severe, symptomatic disease. Similar data are urgently needed for individuals with SARS-CoV-2 infection who have not been hospitalised.

How long is immunity to COVID-19 likely to last? The best estimate comes from the closely related coronaviruses and suggests that, in people who had an antibody response, immunity might wane, but is detectable beyond 1 year after hospitalisation.^{10–12} Obviously, longitudinal studies with a duration of just over 1 year are of little reassurance given the possibility that there could be another wave of COVID-19 cases in 3 or 4 years. Specific T-lymphocyte immunity against Middle East respiratory syndrome coronavirus, however, can be detectable for 4 years, considerably longer than antibody responses.¹³

Some of the uncertainty about COVID-19 protective immunity could be addressed by monitoring the frequency of reinfection with SARS-CoV-2. Anecdotal reports of reinfection from China and South Korea should be regarded with caution because some individuals who seemed to have cleared SARS-CoV-2 infection and tested negative on PCR might nevertheless have harboured persistent virus. Virus sequencing studies will help to resolve this issue and in cases of confirmed reinfection it will be important to understand if reinfection correlates with lower immunity.

Policy briefings in the UK and other countries have rightly emphasised the imperative to collect seroprevalence data.¹⁴ This approach has sometimes been construed in a narrow sense as testing that would allow people back to work. However, seroprevalence data can show what proportion of a population has been exposed to and is potentially immune to the virus, and is thus wholly distinct from the snapshot of people who accessed PCR testing. How can one determine how much herd immunity is sufficient to mitigate subsequent substantial outbreaks of COVID-19? This calculation depends on several variables,¹⁵ including the calculated basic reproduction

number (R_0), currently believed to be about 2.2 for SARS-CoV-2.¹⁶ On the basis of this estimated R_0 , the herd immunity calculation suggests that at least 60% of the population would need to have protective immunity, either from natural infection or vaccination.¹⁷ This percentage increases if R_0 has been underestimated.

Most of the available COVID-19 serology data derive from people who have been hospitalised with severe infection.^{8,18} In this group, around 90% develop IgG antibodies within the first 2 weeks of symptomatic infection and this appearance coincides with disappearance of virus,¹⁸ supporting a causal relationship between these events. However, a key question concerns antibodies in non-hospitalised individuals who either have milder disease or no symptoms. Anecdotal results from community samples yield estimates of under 10% of tested “controls” developing specific IgG antibodies. We await larger seroprevalence datasets, but it seems likely that natural exposure during this pandemic might, in the short to medium term, not deliver the required level of herd immunity and there will be a substantial need for mass vaccination programmes.

There are more than 100 candidate COVID-19 vaccines in development, with a handful in, or soon to be in, phase 1 trials to assess safety and immunogenicity.⁴ Candidate vaccines encompass diverse platforms that differ in the potency with which immunity is stimulated, the specific arsenal of immune mediators mobilised, the number of required boosts, durability of protection, and tractability of production and supply chains.^{3,4} Safety evaluation of candidate COVID-19 vaccines will need to be of the highest rigour. Some features of the immune response induced by infection, such as high concentrations of tumour necrosis factor and interleukin 6, which could be elicited by some candidate vaccines, have been identified as biomarkers of severe outcome.¹⁹

Researchers should be commended for decades of iterative efforts, bringing us to a point where there are many candidate vaccines in development against a novel virus first sequenced in January, 2020. Delivery of efficacious vaccines is not a competitive race to the finish, but a considered evaluation of a safe, potent, global response.⁴ Few would disagree that science should guide the clinical therapeutic approach to an infected

person. Science must also guide policy decisions. Reliance on comprehensive seroprevalence data and a solid, research-based grasp of correlates of protection will allow policy to be guided by secure, evidence-based assumptions on herd immunity, rather than optimistic guesses.

We declare no competing interests.

*Daniel M Altmann, Daniel C Douek, Rosemary J Boyton
d.altmann@ic.ac.uk

Department of Immunology and Inflammation (DMA) and Department of Infectious Diseases (RJB), Faculty of Medicine, Hammersmith Hospital, Imperial College London, London W12 0NN, UK; Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA (DCD); and Lung Division, Royal Brompton & Harefield NHS Foundation Trust, London, UK (RJB)

- 1 Studdert DM, Hall MA. Disease control, civil liberties, and mass testing—calibrating restrictions during the COVID-19 pandemic. *N Engl J Med* 2020; published online April 9. DOI:10.1056/NEJMp2007637.
- 2 Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. *Antimicrob Agents Chemother* 2020; **64**: e00399–20.
- 3 Amanat F, Krammer F. SARS-CoV-2 vaccines: status report. *Immunity* 2020; **52**: 583–89.
- 4 Thanh Le T, Andreadakis Z, Kumar A, et al. The COVID-19 vaccine development landscape. *Nat Rev Drug Discov* 2020; published online April 9. DOI:10.1038/d41573-020-00073-5.
- 5 Adams ER, Anand R, Andersson M, et al. Evaluation of antibody testing for SARS-Cov-2 using ELISA and lateral flow immunoassays. *bioRxiv* 2020; published online April 20. <https://doi.org/10.1101/2020.04.15.20066407> (preprint).
- 6 Plotkin SA. Vaccination against the major infectious diseases. *CR Acad Sci III* 1999; **322**: 943–51.
- 7 Plotkin SA. Immunologic correlates of protection induced by vaccination. *Pediatr Infect Dis J* 2001; **20**: 63–75.
- 8 Tan W, Lu Y, Zhang J, et al. Viral kinetics and antibody responses in patients with COVID-19. *medRxiv* 2020; published online March 26. <https://doi.org/10.1101/2020.03.24.20042382> (preprint).
- 9 Stanley DA, Honko AN, Asiedu C, et al. Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge. *Nat Med* 2014; **20**: 1126–29.
- 10 Li CK, Wu H, Yan H, et al. T cell responses to whole SARS coronavirus in humans. *J Immunol* 2008; **181**: 5490–500.
- 11 Temperton NJ, Chan PK, Simmons G et al., Longitudinally profiling neutralizing antibody response to SARS coronavirus with pseudotypes. *Emerg Infect Dis* 2005; **11**: 411–16.
- 12 Choe PG, Perera RAPM, Park WB, et al. MERS-CoV antibody responses 1 year after symptom onset, South Korea, 2015. *Emerg Infect Dis* 2017; **23**: 1079–84.
- 13 Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to respiratory coronaviruses. *Immunol Res* 2014; **59**: 118–28.
- 14 Department of Health and Social Care, UK Government. Government begins large-scale virus infection and antibody test study. April 23, 2020. <https://www.gov.uk/government/news/government-begins-large-scale-virus-infection-and-antibody-test-study> (accessed April 24, 2020).
- 15 Anderson RM, May RM. Vaccination and herd immunity to infectious diseases. *Nature* 1985; **318**: 323–29.
- 16 Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020; **382**: 1199–207.
- 17 Guerra FM, Bolotin S, Lim G, et al. The basic reproduction number (R_0) of measles: a systematic review. *Lancet Infect Dis* 2017; **17**: e420–28.
- 18 Wu F, Wang A, Liu M, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. *bioRxiv* 2020; published online April 20. <https://doi.org/10.1101/2020.03.30.20047365>.
- 19 Feldmann M, Maini RN, Woody JN, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet* 2020; published online April 9. [https://doi.org/10.1016/S0140-6736\(20\)30858-8](https://doi.org/10.1016/S0140-6736(20)30858-8).