Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

recommended in the UK, on the duration of protection needs to be further assessed. The effects of the waning of immunity, currently considered pivotal in the risk of breakthrough infections, could not be assessed with such short follow-up. Finally, the study was unable to investigate whether a second dose of vaccine diminished the risks of breakthrough disease for older people, those with comorbid conditions, or for other risk factors.

With probable waning of protection against infection, and possibly against severe outcomes, use of a booster (third) dose is being considered. Some countries have recommended wide use of boosters to enhance population protection and reduce transmission. Global vaccine shortage and concerns regarding global vaccine equity prompted WHO to recommend against boosting.[10] Restricting booster doses to populations at the highest risk for severe disease will allow maximisation of booster dose benefits, with a minimised effect on global vaccine distribution. The findings reported by Agrawal and colleagues[6] allow identification and prioritisation of at-risk populations to be considered for boosting. Additionally, characterising the risks, or lack thereof, of delayed dosing schedules can aid policy makers in considering viable alternatives to standard dosing schedules in settings where vaccine availability is limited.

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1 Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet* 2021; **397:** 1646–57.
2 Hall VJ, Foulkes S, Saei A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. *Lancet* 2021; **397:** 1725–35.
3 Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* 2021; **397:** 2461–62.
4 Mizrahi B, Lotan R, Kalkstein N, et al. Correlation of SARS-CoV-2 breakthrough infections to time-from-vaccine; preliminary study. *medRxiv* 2021; published online July 31. https://doi.org/10.1101/2021.07.29.21261317 (preprint).
5 Shrotri M, Navaratnam AMD, Nguyen V, et al. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. *Lancet* 2021; **398:** 385–87.
6 Agrawal U, Katikireddi SV, McCowan C, et al. COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2·57 million people in Scotland (EAVE II): a prospective cohort study. *Lancet Respir Med* 2021; published online Sept 29. https://doi.org/10.1016/S2213-2600(21)00380-5.
7 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584:** 430–36.
8 Aveyard P, Gao M, Lindson N, et al. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. *Lancet Respir Med* 2021; **9:** 909–23.
9 Pouwels KB, Pritchard E, Matthews PC, et al. Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *medRxiv* 2021; published online Aug 24. https://doi.org/10.1101/2021.08.18.21262237 (preprint).
10 The Lancet Infectious Diseases. COVID-19 vaccine equity and booster doses. *Lancet Infect Dis* 2021; **21:** 1193.

Waning immunity to SARS-CoV-2: implications for vaccine booster strategies

Jim West/Science Photo Library

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As we approach the end of the second year of the COVID-19 pandemic, of the many challenges facing immunologists and vaccinologists, one of the toughest has been the characterisation of the durability of protective immunity. The duration of immune protection has crucial implications for the implementation of booster vaccination programmes[1]—including the need for and timing of additional doses—which are a source of intense debate among both scientists and policy makers. In a Personal View in *The Lancet Respiratory Medicine*,[2] Gregory Milne and colleagues review emerging data on cellular and humoral immunity to SARS-CoV-2, in response to natural infection and vaccination, and offer their views on what the evidence means in terms of the longevity of protective immunity. Health policy makers have the unenviable task of developing strategies to reduce the burden of disease in the face of many points of uncertainty and controversy, including those related to the emergence of SARS-CoV-2 variants of concern and the equitable distribution of vaccines.

Booster programmes require adequate vaccine stocks, national supply and implementation logistics, and a rationale for age or risk-group prioritisation, but also the challenge of yet more uncharted immunology for which the existing evidence base is thin: in a world in which booster recipients will be drawn from those with variable prior immunity—which might be based on previous infection, often overlaid with vaccination with

an mRNA or adenovirus vector-based spike vaccine—what form should a booster dose take, and when might it most advantageously be given?

Added to this is consideration of the substantial geopolitical and ethical implications of booster vaccination programmes, including the questions of whether it is appropriate to give what has been described as an extra life jacket to the privileged few, when many in the world have yet to receive any life jacket at all.[3] The intricacy of these deliberations is demonstrated by the divergent booster programme strategies of countries such as the UK (cautious, stratified booster roll-out), Israel (hard-line revision of the green passport approach, which affords full social access specifically and only to those who have received a third dose), and the USA (ongoing reappraisals, but moving towards a highly targeted booster programme).

The basic immunology evidence base that underpins the current deliberations is evaluated by Milne and colleagues.[2] As with so much that we have had to confront in the pandemic, decisions on booster programmes represent real-life choices that sit at the interface between immunological research and epidemiology data on SARS-CoV-2-related morbidity and mortality. Until recently, we had no clear consensus on the serum half-life of protective, neutralising antibodies after either natural infection or vaccination. Initial assumptions were that the poor durability of protective antibodies following seasonal infection by the human common cold coronaviruses might be replicated with SARS-CoV-2[4]—the fact that we succumb to winter colds caused by the same viruses year after year is a stark warning about the possibility of rapidly waning protection. The underlying mechanism of reinfection with common cold coronaviruses is generally thought to involve coronavirus adaptations that subvert innate pathways such as those leading to production of type I interferons. As longitudinal data have emerged from cohorts infected by SARS-CoV-2, interpretation of findings on waning immunity has become a source of ongoing debate. There is substantial heterogeneity between individuals in antibody levels after infection.[5,6] However, with estimates of a serum half-life for neutralising antibodies of more than 200 days, along with evidence of well sustained T-cell and B-cell memory[6] and an improving B-cell repertoire due to affinity maturation (the concept that the immune response develops through a progressively more focused and tightly binding antibody repertoire),[7] immune protection might be expected to last for about 1–2 years after infection.

Since the end of 2020, data on immunity from countries with vaccination programmes have been overlaid with the effects of diverse spike vaccine platforms, each with distinct profiles of mean decline in neutralising antibodies and vaccine response kinetics. During this time, variants of concern have also emerged, notably the increasing dominance of the delta variant, which is associated with a 5–10-times fall in neutralising antibodies.[8] Although basic immunology findings predict that the vast majority of people would nevertheless have sufficient protection to avert any risk of infection,[9] real-world data have been more salutary. Data from individuals who received the Pfizer–BioNTech mRNA vaccine BNT162b2, especially those over the age of 60 years, who were vaccinated early in the programme, show susceptibility to breakthrough infection caused by the delta variant. Breakthrough infections are correlated with diminished antibody titres, especially at 6 months or more after the second vaccine dose.[1,10] A third booster dose is sufficient to flatten the curve of breakthrough cases, even in areas where the delta variant is dominant.[10] On the one hand, this can be read as a good news story, of calm, determined, rational immune monitoring managing to largely mitigate the next public health disaster. On the other hand, it is a sobering reminder of what a formidable pathogen we face, such that all traditional, textbook immunology assurances that T-cell and B-cell memory priming will provide lasting protection look a little thin.

Finally, there is a need to confront the detail of protective immune repertoires and immune imprinting. It is already known that the immune response elicited by first-generation vaccines results in wide variability in neutralisation of current variants of concern, and that imprinting of the immune repertoire by previous exposure to the virus can differentially shape the protective response.[11] Decoding these patterns and optimising protection against future variants will depend on fine mapping of cross-protective epitopes and making informed choices about which spike sequences to adopt for future booster dose programmes. The optimum COVID-19 vaccination strategy for the next few years is currently far from

obvious, but probably not just a matter of using the sequence of the most recent variant of concern.

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1 Dolgin E. COVID vaccine immunity is waning — how much does that matter? *Nature* 2021; **597:** 606–07.
2 Milne G, Hames T, Scotton C, et al. Does infection with or vaccination against SARS-CoV-2 lead to lasting immunity? *Lancet Respir Med* 2021; published online Oct 21. https://doi.org/10.1016/S2213-2600(21)00407-0.
3 The Irish Times. Science uncertain about need for vaccine boosters, WHO says. Aug 18, 2021. https://www.irishtimes.com/news/health/science-uncertain-about-need-for-vaccine-boosters-who-says-1.4650435 (accessed Oct 6, 2021).
4 Edridge AWD, Kaczorowska J, Hoste ACR, et al. Seasonal coronavirus protective immunity is short-lasting. *Nat Med* 2020; **26:** 1691–93.
5 Reynolds CJ, Swadling L, Gibbons JM, et al. Discordant neutralizing antibody and T cell responses in asymptomatic and mild SARS-CoV-2 infection. *Sci Immunol* 2020; **5:** eabf3698.
6 Cohen KW, Linderman SL, Moodie Z, et al. Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells. *Cell Rep Med* 2021; **2:** 100354.
7 Muecksch F, Weisblum Y, Barnes CO, et al. Affinity maturation of SARS-CoV-2 neutralizing antibodies confers potency, breadth, and resilience to viral escape mutations. *Immunity* 2021; **54:** 1853–68.e7.
8 Mlcochova P, Kemp S, Dhar MS, et al. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. *Nature* 2021; published online Sept 6. 10.1038/s41586-021-03944-y.
9 Altmann DM, Boyton RJ, Beale R. Immunity to SARS-CoV-2 variants of concern. *Science* 2020; **371:** 1103–04.
10 Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. *N Engl J Med* 2021; **385:** 1393–400.
11 Aydillo T, Rombauts A, Stadlbauer D, et al. Immunological imprinting of the antibody response in COVID-19 patients. *Nat Commun* 2021; **12:** 3781.

Charting a course for the management of long COVID


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It is difficult to think beyond the immediate crisis, when wave after wave of the COVID-19 pandemic has repeatedly overwhelmed health systems and resulted in high rates of mortality and severe disruption to normal life. However, the recognition of a syndrome of prolonged, multisystem disability in survivors of COVID-19[1–3]—commonly referred to as long COVID or the post-COVID-19 condition—has made obtaining knowledge of its pathogenesis, prognosis, and management an important competing priority. A comprehensive, coordinated global research strategy for the post-acute sequelae of COVID-19, rather than a piecemeal approach, is clearly required, although difficult to achieve in the midst of a pandemic.

For this reason, the Position Paper from the UK-based International COVID-19 Airways Diseases Group in *The Lancet Respiratory Medicine*,[4] presenting research priorities for the long-term effects of COVID-19 in the context of airways disease, is to be welcomed. The consensus recommendations, which are both broad and insightful, will inform future research efforts.

The highest-ranked research priorities, identified by the group using the Child Health and Nutrition Research Initiative (CHNRI) prioritisation method, include investigation of whether prognostic scores and clinical or radiological features at hospital admission predict post-discharge morbidity in groups of patients with and without pre-existing airways disease. This strategy allows targeted follow-up and management of patients who are at risk of greatest morbidity from long COVID within overstretched health-care systems, where resourcing will inevitably be constrained. This priority is based in part on evidence that, for long COVID, there is a risk gradient that increases according to the severity of the acute SARS-CoV-2 infection.[2] However, evaluation of prediction scores in those not admitted to hospital will also be important, as long COVID can also occur in both adults and children who have had mild acute SARS-CoV-2 infection.[2,3] Indeed, the greatest total burden of disease from long COVID is likely to occur in the vast majority of those with SARS-CoV-2 infection who are not admitted to hospital.

The broad focus on comparisons of patients with and without pre-existing airways disease is sound, as many of the pulmonary and extrapulmonary symptoms of long COVID and airways disease are shared. Similarly, the recommendation to extend assessments of the effects of long COVID to extrapulmonary organs is warranted, because although acute SARS-CoV-2 infection primarily affects the lungs, COVID-19 is a multisystem disease,