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.

attention: 27 trials were completed and included in a meta-analysis, which suggested an overall benefit of IL-6 blockade, probably driven by the large RECOVERY and REMAP-CAP trials.[8] However, a clearly notable factor differentiating these trials from the COV-AID trial is the 28-day mortality in the standard-of-care group, which exceeded 25% compared with only 10% in the COV-AID trial.[8]

This low mortality in the COV-AID trial reflects historical trends, which make it ever more difficult to reveal incremental benefits in patients with COVID-19 treated with biologic agents in randomised trials. Of note, the COV-AID study was designed to reveal a large treatment effect; it was not designed to show moderate treatment effects. It is worth remembering that the moderate clinical effectiveness of dexamethasone, which contributed to saving innumerable lives, required a massive nationwide investigation to be revealed.[9] Thereby, writing off potential therapeutic options (ie, cytokine inhibitors) on the basis of the negative results of relatively small trials only powered to detect large clinical effects is not advisable.

Two important messages can be taken from this investigation and instruct further use of cytokine inhibitors in COVID-19. First, this study adds to the zeitgeist that universal treatment of COVID-19 with cytokine inhibitors is neither a suitable nor a sustainable option. Consequently, patient selection is crucial, and the severity of the individual's inflammatory response is the main criterion for eligibility to treatment. Indeed, a patient-level meta-analysis indicated that the benefit of anakinra treatment in COVID-19 is maximum for patients with serum C-reactive protein concentrations greater than 100 mg/L,[10] whereas the SAVE-MORE trial found that early identification of candidate patients with suPAR followed by treatment with anakinra resulted in a 55% relative decrease in mortality, which reached 80% for patients with cytokine storm. Screening of individuals on the basis of molecular taxonomy of inflammatory responses is not always practical. Still, it is a necessary and feasible leap to transition from blanket therapeutic attempts, which are bound to yield mixed or disappointing results, to refined and appropriate management strategies.

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Severe breakthrough COVID-19 infections in Scotland—implications for immunisation programmes

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Clinical trials of the BNT162b2 mRNA (Pfizer–BioNTech) and ChAdOx1 nCoV-19 adenoviral (Oxford–AstraZeneca) vaccines showed high efficacy against symptomatic infection; however, evidence continues to emerge regarding protection against severe disease, hospitalisation, and death under real-world conditions. In December, 2020, the vaccines were approved in Scotland and rolled out, starting with health-care workers and the most vulnerable populations. At the time, the UK vaccination programme advised an

extended dosing interval of 8–12 weeks, rather than the shorter 3-week interval used in the trials, to maximise coverage with a first dose quickly amid restricted vaccine supply. Since their introduction, early evaluations of COVID-19 vaccines, albeit with short follow-up, have shown excellent effectiveness in preventing severe outcomes.[1] Breakthrough infections (in vaccinated people) were rare.[2] Later assessments, since the surge in cases associated with the Delta variant, have reported increasing infection rates and breakthrough infections.[3,4] Factors such as waning immunity and strain-specific decline in vaccine effectiveness (immune escape) might contribute to breakthrough infections.[4,5] Overall risk for severe outcome comprises the risk of becoming infected (higher in health-care workers with greater exposure, for example) and the risk of deteriorating upon infection (higher with increasing age). Characterising people at the greatest risk of severe breakthrough infections, hospitalisation, and death is critical to promote targeted interventions, aimed at enhancing protection of vulnerable populations. Moreover, establishing the risks associated with alternative dosing schedules can support the adoption of such schedules in other countries that aim to maximise population-level protection given a restricted number of available vaccine doses.

In *The Lancet Respiratory Medicine*, Utkarsh Agrawal and colleagues report results from Scotland's nationwide platform, EAVE II, assessing risk factors and frequency of hospitalisation and death in people who have received COVID-19 vaccines.[6] Between Dec 8, 2020, and April 18, 2021, 2 572 008 individuals received their first dose of vaccine—841 090 (32·7%) received BNT162b2 and 1 730 918 (67·3%) received ChAdOx1. Overall, substantially lower rates of COVID-19 hospitalisation or death were reported in vaccinated individuals compared with unvaccinated individuals (4·6 events per 1000 person-years *vs* almost 8·6 events per 1000 person-years, respectively), despite the unvaccinated group being younger and at lower risk. Severe outcome 14 days or more after the first dose of vaccine was documented in 1196 (<0·1%) vaccinated individuals. 883 individuals were admitted to hospital and 541 people died with COVID-19 14 days or more after the first vaccination, 228 of whom died after admission to hospital. Severe COVID-19 outcomes were associated with older age, comorbidities, hospitalisation in the previous 4 weeks, having a high-risk occupation, residing in a care home, socio-economic deprivation, being male, and being an ex-smoker. However, a history of COVID-19 infection before vaccination was protective against severe outcomes.

Pascal Bachelet/BSIP/Science Photo Library

The study findings were consistent with previously described risk factors for severe outcomes in unvaccinated people.[7] An important novel finding was the substantial protective effect of previous infection against severe infection in vaccinated people. This finding suggests that there remains a protective effect of immunity from previous COVID-19 episodes that goes beyond the protection conferred by vaccination. Indeed, this effect might be underestimated in this study,[6] since the investigators only had data on previous confirmed COVID-19, not all SARS-CoV2 infections (some of which might have been undetected). Other findings include a lack of association between asthma or heart failure and increased risk for severe outcomes in people vaccinated with BNT162B2. Vaccines remain critical to reduce risk in people with chronic cardiorespiratory conditions as previous evaluations identified an increased risk for severe disease in people with pre-existing cardiorespiratory disease.[7,8]

The study findings should be interpreted in the context of several limitations. A comparison between BNT162b2 and ChAdOx1 vaccines was not feasible because of different deployment dates and target populations. Interestingly, a lower risk of severe outcomes was associated with a longer time since receipt of the first vaccine. This observation might have been driven by an inclination towards healthy behaviours in those who received early vaccines or by people receiving the second dose during follow-up. Short follow-up (median 55 days and 19 days after receipt of the first dose and second dose, respectively) might further limit the applicability of the findings. Studies indicate a potential time-dependent decline in antibody levels, which might contribute to breakthrough infections;[4,5] however, there are few data on the waning of protection against severe disease. Preliminary data from Israel, where most people were vaccinated with BNT162b2 using the standard 3-week dosing interval, show higher rates of breakthrough infections in the early-vaccinated population compared with those who were vaccinated later.[4] Data from the UK, where a longer dosing interval was used, also suggest lower vaccine efficacy against infection, but not severe disease, with the Delta variant.[9] The effect of a longer interval between the doses, as

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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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