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.

variants imparts differing levels of protective immunity, and to better understand the epidemiological effect of infection across different variant waves.

Looking forward, the incorporation of infection history in an immune profile of an individual, although justified, brings into question how future booster regimens should be planned for. For instance, are individuals with infection-associated immunity required to obtain two further doses to have the level of immunity observed in individuals with no previous infection but receiving three doses? Regardless, SARS-CoV-2 infection is clearly an important contributor to protective immunity, and its interplay with vaccination warrants further longitudinal studies, ultimately providing insights to drive proactive health policies and measures for optimal population-wide immunity in this pandemic.

We declare no competing interests.

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Effectiveness of SARS-CoV-2 vaccines in the post-natural infection world

Natural viral infections provide immunity from subsequent infection through a repertoire of memory T cells and B cells, except when the virus mutates to an extent that it evades recognition by memory cells.[1] Vaccines are designed to represent the virus either in the form of an inactivated or attenuated whole virus or an immunogenic subunit such as the spike protein in the case of SARS-CoV-2.[2] After a natural infection, the immune system assesses the virus in multiple ways and provides both antibody-mediated and cellular protection.[3,4] As the SARS-CoV-2 pandemic has relentlessly progressed, with multiple waves, the immune landscape of the global population has transformed from being immune naive to having natural infection-induced immunity. Although vaccinating the naive population is logical, an important question arises of whether to vaccinate those who were previously infected with SARS-CoV-2. The need for boosting natural immunity, through vaccination, comes from the waning of immunity, with declining antibody titres, and the emergence of SARS-CoV-2 variants with immune-evasion properties.

In *The Lancet Infectious Diseases*, Thiago Cerqueira-Silva and colleagues have addressed the issue of vaccine effectiveness among individuals who were previously infected.[5] For this study, the authors used national COVID-19 notification, hospitalisation, and vaccination datasets from Brazil to assess effectiveness against symptomatic infection, hospitalisation, and death for the four vaccines in use in the country during the study period: CoronaVac (Sinovac), ChAdOx1 nCoV-19 (Oxford-AstraZeneca), Ad26.COV2.S (Janssen), and BNT162b2 (Pfizer-BioNtech). Of the people who had previous confirmed SARS-CoV-2 infection, the authors included 22 566 symptomatic individuals with RT-PCR-positive reinfection and 145 055 negative RT-PCR tests from 68 426 symptomatic matched controls in a test-negative case-control study. After adjusting for important confounders, vaccine effectiveness against symptomatic infection 14 days or more from complete vaccination after a previous natural infection was 39·4% (95% CI 36·1–42·6) for CoronaVac, 56·0% (51·4–60·2) for ChAdOx1 nCoV-19, 44·0% (31·5–54·2) for Ad26.COV2.S (single-dose vaccine), and 64·8% (54·9–72·4) for

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BNT162b2. Vaccine effectiveness against hospitalisation or death after complete vaccination was more impressive: 81·3% (75·3–85·8) for CoronaVac, 89·9% (83·5–93·8) for ChAdOx1 nCoV-19, 57·7% (–2·6 to 82·5) for Ad26.COV2.S, and 89·7% (54·3–97·7) for BNT162b2.

The study has some major strengths. First, the linkage of three national databases for SARS-CoV-2 testing, disease surveillance for COVID-19, and immunisation. This showcases the importance of population-level data and the power of big-data analysis. Second, the comprehensive evaluation of vaccine effectiveness of four vaccines used globally. And third, the study of the dose–response relationship. However, an important missing piece of information is the SARS-CoV-2 variants against which vaccine effectiveness estimates are reported. This absence is important in view of variable vaccine effectiveness against different variants.[6]

The vaccine effectiveness estimates in the study by Cerqueira-Silva and colleagues are generally lower than those in naive populations reported earlier.[6,7] However, this discrepancy is expected given that Cerqueira-Silva and colleagues' estimates were for additional protection provided by vaccination over and above that offered by immunity resulting from natural infection. Natural infection might act as a priming or booster dose; in a previous study,[8] protection against reinfection was maintained at greater than 90% for more than 6 months after vaccination among participants with natural immunity who were subsequently vaccinated, even in those who were infected more than 12 months before vaccination. Protection as high as 82%, similar to two vaccine doses, was shown in individuals previously infected who had received a single dose of vaccine.[9] These clinical findings are corroborated by in-vitro immunological studies showing that humoral and cellular immune responses are high after the multiple antigen exposure provided by natural infection and vaccination.[10,11] In addition to antibody-mediated immunity, cellular T-cell responses provide protection against severe disease, hospitalisation, and death.[6]

The results of Cerqueira-Silva and colleagues' study and other recent studies challenge the concept of population-level herd immunity through natural infection alone against SARS-CoV-2 and suggest that vaccinating individuals who were previously infected provides further protection, particularly against severe disease. These data should help guide policy decisions and mitigate vaccine hesitancy among people who have previously had SARS-CoV-2 infection.

However, some clinical and immunological questions remain to be answered. Primary exposure to an antigen leads to epitope-specific B-cell memory known as immune imprinting. Barring the ancestral virus infection, subsequent SARS-CoV-2 infections during multiple waves caused by variants have led to heterologous exposure to virus antigens. How immune imprinting by the first exposure, either by the virus or vaccine, affects the durability and breadth of immune responses remains to be studied. What additional protection does natural infection provide to vaccinated individuals and how durable is this protection? And what is the optimal timing of vaccination after natural infection? These questions are important in view of the large swath of the global population who have been exposed to natural infections caused by delta (B.1.617.2) and omicron (B.1.1.529) variants.

Hybrid immunity due to exposure to natural infection and vaccination is likely to be the norm globally and might provide long-term protection even against emerging variants. Besides vaccination, continued surveillance for further emergence of variants for their immune evasiveness and pathogenicity should continue.

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COVID-19 mRNA vaccine safety during the first 6 months of roll-out in the USA

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A primary mission of the US vaccination campaign, which began in December, 2020, following emergency use authorisation (EUA) of the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) COVID-19 mRNA vaccines, was ensure vaccine benefit while monitoring vaccine safety.[1,2] This mission was facilitated by both the enormity of the roll-out and mRNA COVID-19 vaccine distribution and the administration by the US Government of all doses, giving an unprecedented opportunity to measure vaccine safety. As of Feb 28, 2022, over 530 million doses of mRNA COVID-19 vaccines had been administered in the USA.

In *The Lancet Infectious Diseases*, Hannah Rosenblum and colleagues[3] from the US Centers for Disease Control and Prevention report the first 6 months (Dec 14, 2020, to June 14, 2021) of safety monitoring of mRNA COVID-19 vaccines, in individuals aged at least 16 years, during which time over 50% of the eligible US population received at least one vaccine dose and more than 298 million doses were administered.

Post-EUA safety data were accrued through the Vaccine Adverse Event Reporting System (VAERS), a passive and spontaneous reporting system that was established in 1990, and active surveillance through the smartphone-based system v-safe.[4] V-safe was developed in 2020 to actively monitor mRNA COVID-19 vaccine safety, reactogenic symptoms, and health effects.[5] Reporting rates for adverse events were calculated using the number of doses of mRNA vaccines administered during the 6 months as a denominator.[6]

Of the 340 522 VAERS reports submitted following both mRNA vaccines, 313 499 (92·1%) were non-serious, 246 085 (72·3%) were from female recipients, and 154 171 (45·3%) were from those aged 18–49 years. The most common Medical Dictionary for Regulatory Activities (MedDRA) terms assigned to non-serious reports were headache, fatigue, and pyrexia, and to severe reports were dyspnoea, death, and pyrexia. Deaths comprised 4496 serious reports (1·3% of all reports to VAERS). 4471 reports were verified as unique deaths after review, of which more than 80% were reported in individuals aged 60 years and older. Of 808 (18·1%) reports for which death certificates or autopsy reports were available, 376 (46·5%) deaths were attributed to heart disease and 102 (12·6%) to COVID-19.

7 914 583 individuals enrolled in v-safe and completed at least one health survey 0–7 days after mRNA COVID-19 vaccination during the study period following dose one or two. Adverse events were mild, non-serious, more common after dose two than after dose one, and included injection-site pain, fatigue, and headache. More reactogenic symptoms were reported in female than in male recipients and in individuals younger than 65 years than in older recipients. Health effects, including the inability to do everyday activities, work, or seek medical care, were also greater after dose two than after dose one and affected female recipients more than male recipients.

Reassuringly, the 6-month VAERS data suggest that although approximately one in 1000 vaccinated individuals might have an adverse event, most events are non-serious. No unusual patterns emerged in causes of death or serious adverse events among VAERS reports. Deaths predictably were most common in those older than 65 years, which includes those who were most at risk of death before vaccination. The reactogenicity findings from v-safe following mRNA COVID-19 immunisation support those reported from clinical trials and a large population study in the UK.[1,2,7]