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.

Interplay of infection and vaccination in long-term protection from COVID-19

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The SARS-CoV-2 omicron variant has rapidly spread throughout the world, including in countries with high vaccination rates. As populations increasingly include individuals with both vaccination-driven and infection-driven immunity, it becomes important to understand the differential protection associated with diverse immune histories. Although studies assessing long-term immunity after omicron infection are not yet possible, population-wide studies done in the context of previous variants of concern can be highly informative.

In *The Lancet Infectious Diseases*, Peter Nordström and colleagues[1] use Swedish national infection and vaccination registers to assess population-wide protection from SARS-CoV-2 infection up to October, 2021. Using a cohort of more than 2 million individuals, they showed that infection-associated immunity was 95% protective against subsequent reinfection during 20 months of follow-up compared with no immunity (adjusted hazard ratio [aHR] 0·05 [95% CI 0·05–0·05] p<0·001). In comparison, convalescent individuals who received one dose of a COVID-19 vaccine exhibited a further 58% lower risk of reinfection (aHR 0·42 [95% CI 0·38–0·47]; p<0·001), albeit it with some degree of waning over the next 9 months of follow-up. Convalescent individuals receiving two doses of a vaccine benefitted from only marginally greater protection (aHR 0·34 [95% CI 0·31–0·39]; p<0·001) than those who received one dose (aHR 0·42 [95% CI 0·38–0·47]; p<0·001), with a 66% lower risk of reinfection than those in the infection-only cohort.

These data show, in a large cohort, the added protective benefit of vaccination among individuals recovered from COVID-19. Although the difference in protection between the one-dose and two-dose vaccine groups was reasonably small, Nordstrom and colleagues found some evidence for greater waning of protection among the single-dose group than the two-dose group. In both cases, there was at least 90% reduction in the risk of COVID-19-associated hospitalisation compared with the convalescent cohort. A substantial benefit related to the large sample size of this population-wide study is the ability to also assess the risk of reinfection among specified subgroups. In particular, protection from previous infection was weaker in individuals aged 65 years and older, suggesting that vaccination might be particularly important in some high-risk populations; this is probably particularly true for protection against omicron, in which a third vaccine dose is key to eliciting cross-reactive neutralising antibodies.[2,3] On balance, these data clearly show the benefits of two-dose vaccination for convalescent individuals, both in terms of the durability of immunity and protection from severe disease.

The data also show the long-term protective effect of SARS-CoV-2 infection alone, which was stable for 20 months of follow-up. This level of protection was notable, considering the wide range of neutralising antibody titres generated by mild COVID-19.[4,5] The authors note that, given these results, infection history should be accounted for when so-called immunity passports are required for individuals to partake in wider societal activities. Although these analyses cannot take into account the effect of vaccination on viral transmission to others, immune profiles should, at the very least, be informative in assessing an individual's risk of subsequent reinfection, regardless of the nature of previous antigen exposure.

As the pandemic continues to evolve, the nature of population-wide immunity against SARS-CoV-2 will become increasingly complex. Due to the immune evasion of the omicron variant driving an increasing number of breakthrough infections, combined with varying recommendations for third or fourth vaccine doses,[6] many populations will exhibit a mixture of infection-elicited and vaccine-elicited immunity. Although Nordstrom and colleagues focus on the protection associated with infection followed by vaccination, many individuals will now have vaccination followed by infection. A recent study,[7] however, showed that regardless of whether infection occurs before or after vaccination, the quantity, quality, and breadth of the humoral immune response were vastly improved. This finding further supports the notion that infection histories should be an important consideration in determining whether individuals are protected against SARS-CoV-2. Future studies will be required to assess whether infection by distinct viral

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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1 Nordström P, Ballin M, Nordström A. Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden. *Lancet Infect Dis* 2022; published online March 31. https://doi.org/10.1016/S1473-3099(22)00143-8.

2 Gruell H, Vanshylla K, Tober-Lau P, et al. mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 omicron variant. *Nat Med* 2022; published online Jan 19. https://doi.org/10.1038/s41591-021-01676-0.

3 Cheng SMS, Mok CKP, Leung YWY, et al. Neutralizing antibodies against the SARS-CoV-2 omicron variant BA.1 following homologous and heterologous CoronaVac or BNT162b2 vaccination. *Nat Med* 2022; published online Jan 20. https://doi.org/10.1038/s41591-022-01704-7.

4 Chia WN, Zhu F, Ong SWX, et al. Dynamics of SARS-CoV-2 neutralising antibody responses and duration of immunity: a longitudinal study. *Lancet Microbe* 2021; **2:** e240–49.

5 Harrington WE, Trakhimets O, Andrade DV, et al. Rapid decline of neutralizing antibodies is associated with decay of IgM in adults recovered from mild COVID-19. *Cell Rep Med* 2021; **2:** 100253.

6 Regev-Yochay G, Gonen T, Gilboa M, et al. 4th Dose COVID mRNA vaccines' immunogenicity and efficacy against omicron VOC. *medRxiv* 2022; https://doi.org/10.1101/2022.02.15.22270948 (preprint).

7 Bates TA, McBride SK, Leier HC, et al. Vaccination before or after SARS-CoV-2 infection leads to robust humoral response and antibodies that effectively neutralize variants. *Sci Immunol* 2022; **7:** eabn8014.

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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