

EDITORIALS



Added Benefit of Covid-19 Vaccination after Previous Infection

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More than 2 years into the Covid-19 pandemic, persons who have recovered from primary SARS-CoV-2 infection make up an increasing proportion of the global population. Persons with infection-induced immunity appear to have greater protection against reinfection and severe Covid-19 than those without previous infection.¹⁻⁴ However, little is known about how much protection is gained by vaccination in previously infected persons. Two studies in this issue of the *Journal* — one by Hammerman et al.⁵ and the other by Hall et al.⁶ — deliver persuasive evidence that among persons with infection-induced immunity, Covid-19 vaccination provides substantial added protection against SARS-CoV-2 reinfection.

Using medical records from a large health care organization in Israel, Hammerman et al. retrospectively evaluated 149,032 patients who had recovered from previous SARS-CoV-2 infection, 56% of whom subsequently received the BNT162b2 vaccine (Pfizer–BioNTech). The authors compared reinfection rates among patients who were vaccinated with those among patients who were not vaccinated between March and November 2021, which included the period when the B.1.617.2 (delta) variant was predominant in Israel. Vaccine effectiveness against reinfection was estimated at 82% among patients who were 16 to 64 years of age and 60% among those 65 years of age or older. It is surprising that reinfection rates among older patients were substantially lower than those among younger patients (regardless of vaccination status). These lower rates may reflect additional safety measures taken

by patients in the older age group to guard against reinfection.

Hall et al. evaluated the duration of infection-induced immunity among 9488 persons with documented previous SARS-CoV-2 infection in a prospective cohort of health care workers in the United Kingdom who had undergone testing every 2 weeks. The authors estimated the effectiveness of the BNT162b2 vaccine against reinfection in this population. In unvaccinated persons, the estimated protection against reinfection was 86% within a year after the initial infection and 69% beyond a year. In vaccinated persons, vaccination more than 1 year after the primary infection increased protection to approximately 94%, a level at which it remained for more than 6 months. Notably, 95% of the participants in the cohort had received two doses of vaccine by the end of the study period (September 21, 2021), which limited the amount of follow-up time available. Nevertheless, this study shows that although infection had offered protection against reinfection before the participants were vaccinated, this protection had waned. Vaccination provided increased, longer-lasting protection to previously infected participants, and it gave them greater than 90% protection against reinfection more than 18 months after the primary infection. The authors did not report how long protection remained at this high level after vaccination.

These studies offer compelling evidence of additional protection conferred by vaccination against reinfection with SARS-CoV-2, and they strengthen the rationale for vaccination for every-

one, regardless of previous infection status. Although countries differ in the specifics of their recommendations for persons who have been previously infected with SARS-CoV-2 (e.g., with respect to the timing of vaccination after infection and the number of doses), the clear message from these studies is that subsequent vaccination increases protection against reinfection.

The protection conferred by vaccination has important clinical relevance and policy implications. Some observers may assert that 69% protection more than 1 year after previous infection — without vaccination — is good enough. Although neither study directly assessed protection against reinfection during the period when the B.1.1.529 (omicron) variant had been predominant, in the context of the global spread of this highly infectious variant, increasing protection to approximately 95% in a large segment of the population can avert a substantial number of reinfections, including those that result in severe disease. Given recent evidence of decreased vaccine effectiveness against the omicron variant,^{7,8} it will be important to monitor the added benefit of vaccination after previous infection during surges involving newly identified variants.

It will also be critical to learn more about the duration of protection conferred by infection- and vaccine-induced immunity, regardless of whether vaccination or infection occurs first, whether the duration varies according to the number of doses, or whether Covid-19 vaccines other than the BNT162b2 vaccine perform similarly. Hammerman et al. suggest that one dose of vaccine after SARS-CoV-2 infection may be sufficient, but their limited amount of follow-up provided only weak evidence for this conclusion. If protection wanes after both infection and vaccination, determination of whether a continued benefit may be derived from additional booster doses will be needed in order to inform decisions regarding the most appropriate vaccination schedules and numbers of booster doses. Until data show that the ceiling for the level of protection has been reached, it appears probable

that even small increases in protection with additional doses will be clinically meaningful.

These two studies have addressed important questions about vaccinating the increasing number of persons who have recovered from Covid-19, and they have shown that vaccination provides better protection against subsequent reinfection than previous infection alone. However, a critical question is how much boosting after natural immunity will be needed. To answer that question, ongoing monitoring is warranted.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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