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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study

Noam Barda*, Noa Dagan*, Cyrille Cohen, Miguel A Hernán, Marc Lipsitch, Isaac S Kohane, Ben Y Reis†, Ran D Balicer†

Summary

Background Many countries are experiencing a resurgence of COVID-19, driven predominantly by the delta (B.1.617.2) variant of SARS-CoV-2. In response, these countries are considering the administration of a third dose of mRNA COVID-19 vaccine as a booster dose to address potential waning immunity over time and reduced effectiveness against the delta variant. We aimed to use the data repositories of Israel’s largest health-care organisation to evaluate the effectiveness of a third dose of the BNT162b2 mRNA vaccine for preventing severe COVID-19 outcomes.

Methods Using data from Clalit Health Services, which provides mandatory health-care coverage for over half of the Israeli population, individuals receiving a third vaccine dose between July 30, 2020, and Sept 23, 2021, were matched (1:1) to demographically and clinically similar controls who did not receive a third dose. Eligible participants had received the second vaccine dose at least 5 months before the recruitment date, had no previous documented SARS-CoV-2 infection, and had no contact with the health-care system in the 3 days before recruitment. Individuals who are health-care workers, live in long-term care facilities, or are medically confined to their homes were excluded. Primary outcomes were COVID-19-related admission to hospital, severe disease, and COVID-19-related death. The third dose effectiveness for each outcome was estimated as 1–risk ratio using the Kaplan-Meier estimator.

Findings 1158 269 individuals were eligible to be included in the third dose group. Following matching, the third dose and control groups each included 728 321 individuals. Participants had a median age of 52 years (IQR 37–68) and 51% were female. The median follow-up time was 13 days (IQR 6–21) in both groups. Vaccine effectiveness evaluated at least 7 days after receipt of the third dose, compared with receiving only two doses at least 5 months ago, was estimated to be 93% (231 events for two doses vs 29 events for three doses; 95% CI 88–97) for admission to hospital, 92% (157 vs 17 events; 82–97) for severe disease, and 81% (44 vs seven events; 59–97) for COVID-19-related death.

Interpretation Our findings suggest that a third dose of the BNT162b2 mRNA vaccine is effective in protecting individuals against severe COVID-19-related outcomes, compared with receiving only two doses at least 5 months ago.

Funding The Ivan and Francesca Berkowitz Family Living Laboratory Collaboration at Harvard Medical School and Clalit Research Institute.

Copyright © 2021 Elsevier Ltd. All rights reserved.
Evidence before this study

No formal literature review was done. Several previous publications regarding the effectiveness of the third dose of the BNT162b2 mRNA COVID-19 vaccine have focused on antibody response, showing a pronounced humoral response after administration of the booster. Two recent studies from Israel have focused on clinical outcomes. The first reported a reduction of 90–96% in the risk for severe disease starting from day 12 after the booster dose, but did not adjust for pre-existing clinical conditions related to the risk of severe disease and did not evaluate the effectiveness within subgroups. The second found a reduction of 70–84% in the probability of testing positive for SARS-CoV-2 among vaccinated individuals, but did not estimate effectiveness for more severe outcomes.

Added value of this study

To our knowledge, the present study is the first to estimate the effectiveness of a third dose of an mRNA COVID-19 vaccine—BNT162b2 specifically—against severe outcomes with adjustment for various possible confounders, including comorbidities and behavioural factors, and within subgroups.

Our results suggest that that a third dose of the BNT162b2 vaccine is effective in preventing severe COVID-19–related outcomes. Compared with two doses of the vaccine administered at least 5 months ago, receiving a third dose was estimated to have an effectiveness of 93% in preventing COVID-19–related admission to hospital, 92% in preventing severe disease, and 81% in preventing COVID-19–related death.

Implications of all the available evidence

As of October, 2021, many countries are experiencing a resurgence of SARS-CoV-2 infections despite hitherto successful vaccination campaigns. This situation has been suggested to be caused by the greater infectiousness of the delta (B.1.617.2) variant of SARS-CoV-2, and by waning immunity as time passes from earlier vaccination. In the face of the current resurgence, several countries are planning to administer a third booster dose of mRNA COVID-19 vaccine. Our study suggests that a third vaccine dose is effective in reducing severe COVID-19–related outcomes for patients who have received two vaccine doses at least 5 months ago.

Methods

Study design and participants

This study was designed to emulate a target trial of the effects of a third dose of the BNT162b2 vaccine in a population of individuals who had already received two doses of the vaccine at least 5 months before recruitment. The study design is similar to our previous vaccine effectiveness studies conducted in the same population and setting, which have been described at length. Clalit Health Services is the largest of four integrated payer-provider health-care organisations providing mandatory health-care coverage in Israel, insuring over half of the Israeli population. Clalit Health Services information systems are fully digitised and feed into a central data warehouse, covering all aspects of care, including COVID-19. The study period was July 30, 2020, to Sept 23, 2021.

To be included in the study, an individual had to have received the second vaccine dose at least 5 months before the recruitment date, and have been eligible to receive the third vaccine dose as per the guidelines of the Israeli Ministry of Health on at least one of the days of the study period. For those aged 60 years or above, this meant individuals with recruitment potential on or after July 30, 2021; for ages 50–59 years, recruitment potential from Aug 12, 2021; for ages 40–49 years, recruitment potential from Aug 12, 2021; for ages 30–39 years from Aug 24, 2021; and for those aged at least 12 years, from Aug 30, 2021. Additional inclusion criteria were membership in the health organisation for at least 12 months, no previous documented SARS-CoV-2 infection, and no contact with the health-care system in the 3 days before the recruitment date.

Immunocompromised patients who received the third dose before July 30, 2021, were not included in the study, as the focus was on providing vaccine effectiveness estimates applicable to the general population. Individuals who are health-care workers, live in long-term care facilities, or are medically confined to their homes (irrespective of COVID-19) were excluded due to concerns of residual confounding. Individuals with

...
missing body-mass index or residential area data were also excluded. A complete definition of the study variables is provided in the appendix (pp 12–19).

This study was approved by the Clalit Health Services institutional review board and was exempt from requiring written informed consent. The protocol is included in the appendix (pp 3–11).

### Procedures

The target trial for this study would compare two treatment strategies: administration of the third dose at recruitment (third dose group) and no administration of the third dose at any time during follow-up (control group). To emulate this target trial, each day during the study period, eligible individuals who received the third dose on that day were matched to eligible controls who were previously vaccinated with two vaccine doses but had not yet received the third dose. Controls matched on a given day who received the third dose on a future date would become newly eligible to be recruited into the third dose group on that future date.

Individuals in the third dose group and the control group were exactly matched on a set of potential confounders: age ( categorised into 2-year bins), sex (male or female), place of residence, number of pre-existing chronic conditions considered to be risk factors for severe COVID-19 by the US Centers for Disease Control and Prevention (divided into six bins). The latter two matching variables were included as markers of health-seeking behaviour specifically related to vaccination against COVID-19, given that individuals who are more health conscious or concerned about the pandemic chose to be vaccinated sooner and did more PCR tests.

### Outcomes

Primary outcomes were hospital admission for COVID-19, severe COVID-19 disease (according to US National Institutes of Health criteria6), and COVID-19-related death. Each of these outcomes include the outcomes that precede it. These severe outcomes were chosen because of their greater public health importance.

---

**Table 1: Baseline characteristics**

|                  | Vaccinated with two doses | Vaccinated with three doses |
|------------------|---------------------------|-----------------------------|
| **Median age (IQR)** | 52 (37–68)                | 52 (37–68)                  |
| **Sex**          |                           |                             |
| Female           | 371 435 (51.0%)           | 371 435 (51.0%)             |
| Male             | 356 886 (49.0%)           | 356 886 (49.0%)             |
| **Population sector** |                        |                             |
| Jewish           | 612 006 (84.0%)           | 602 402 (82.7%)             |
| Arab             | 92 656 (12.7%)            | 102 067 (14.0%)             |
| Ultra-Orthodox Jewish | 23 659 (3.2%)          | 23 852 (3.3%)               |
| **CDC risk factor count** |                    |                             |
| 0                | 340 607 (46.8%)           | 340 607 (46.8%)             |
| 1                | 157 738 (24.1%)           | 157 738 (24.1%)             |
| 2                | 90 704 (12.5%)            | 90 704 (12.5%)              |
| ≥3               | 121 272 (16.7%)           | 121 272 (16.7%)             |
| **Number of SARS-CoV-2 PCR tests in the past 9 months** |             |                             |
| 0                | 407 815 (56.0%)           | 407 815 (56.0%)             |
| 1                | 134 016 (18.4%)           | 134 016 (18.4%)             |
| 2                | 84 832 (11.6%)            | 84 832 (11.6%)              |
| 3                | 41 962 (5.8%)             | 41 962 (5.8%)               |
| 4                | 21 553 (3.0%)             | 21 553 (3.0%)               |
| ≥5               | 38 143 (5.2%)             | 38 143 (5.2%)               |
| **CDC certain risk criteria** |                   |                             |
| Cancer           | 19 773 (2.7%)             | 20 621 (2.8%)               |
| Chronic kidney disease | 66 886 (9.2%)        | 68 982 (9.5%)               |
| Chronic obstructive pulmonary disease | 20 669 (2.8%)    | 22 249 (3.1%)               |
| Heart disease    | 71 428 (9.8%)             | 71 166 (9.8%)               |
| Solid organ transplant | 431 (<0.1%)          | 507 (<0.1%)                 |
| Obesity (ie, BMI 30–40) | 147 399 (20.2%)     | 145 022 (19.9%)             |
| Severe obesity (ie, BMI ≥40) | 13 438 (1.8%)   | 13 405 (1.8%)               |
| Pregnancy        | 45 888 (6.6%)             | 7442 (1.0%)                 |
| Sickle cell disease | 65 (<0.1%)           | 85 (<0.1%)                  |
| Smoking          | 115 250 (15.8%)           | 135 202 (18.6%)             |
| Type 2 diabetes  | 115 451 (15.9%)           | 115 733 (15.9%)             |

198 476 individuals appear in both groups, as they were first recruited as unvaccinated and then, following vaccination, re-recruited as vaccinated.

CDC—Centers for Disease Control and Prevention. BMI—body-mass index.

### Table 2: Effectiveness of the third vaccine dose versus two vaccine doses of the BNT162b2 mRNA COVID-19 vaccine

|                  | Vaccinated with two doses | Vaccinated with three doses | 1–risk ratio (95% CI) | Risk difference per 100 000 individuals (95% CI) |
|------------------|---------------------------|-----------------------------|-----------------------|-----------------------------------------------|
| Admissions to hospital | 231 220.8 | 29 14.4 | 93% (88–97) | 206.4 (146.1–275.1) |
| Severe disease | 157 158.9 | 17 12.9 | 92% (82–97) | 145.9 (93.1–207.7) |
| Death | 44 31.9 | 7 6.1 | 81% (59–97) | 25.8 (13.0–38.5) |

Estimates were obtained using the Kaplan-Meier estimator starting from day 7 after receipt of the third dose, in those who received it.

---

www.thelancet.com Vol 398 December 4, 2021

See Online for appendix
The dashed vertical line indicates day 7, on which the main analysis period begins. COVID-19 vaccine disease (B), and death (C) in individuals who received two versus three doses of the BNT162b2 mRNA vaccine.

For each outcome, matched pairs of individuals were followed from the start of follow-up until the earliest of: documentation of the outcome, end of the study calendar period (Sept 26, 2021), or death. We also ended the follow-up of a matched pair if the control individual received the third dose. Outcomes were ascertained in the period starting 7 days after receipt of the third dose in the vaccinated, similar to the period used to determine full vaccination after the second dose, and until the end of follow-up.

Statistical analysis
We used the Kaplan-Meier estimator to construct cumulative incidence curves and to estimate the risk for each outcome. The risks were compared via ratios and differences. We estimated the risk ratio for each outcome using only matched pairs in which both individuals were still at risk 7 days after receipt of the third vaccine dose in those vaccinated. We analysed outcomes in the full population and in subgroups defined by strata of age, sex, and number of comorbidities. 95% CIs were calculated using the nonparametric percentile bootstrap method with 1000 repetitions. The effectiveness of the third dose was estimated as 1-risk ratio. As a sensitivity analysis, vaccine effectiveness was also estimated as incidence rate ratio derived from a Poisson regression using the same dataset, with no further adjustment. Analyses were done using R software (version 4.0.4).

We conducted an ecological analysis in which we plotted daily incidence proportions of SARS-CoV-2 infection (ie, positive PCR test) among the at-risk population by age group around the time the third dose vaccination campaign started.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between July 30, 2020, and Sept 23, 2021, 1158 269 individuals were eligible to be included in the third dose group (appendix pp 20–21, 23). After matching, the third dose and control groups each included 728 321 individuals, with a median age of 52 years (IQR 37–68) and 51% were female (table 1). Baseline demographics were similar between the eligible population (ie, 1158 269 individuals) and the matched population included in the study. Total follow-up time was 12 632 473 days, with a median follow-up of 13 days (IQR 6–21) after the first 7 days in both groups, and a maximum follow-up time of 55 days.

Effectiveness of the third vaccine dose, compared with two doses only, was estimated to be 93% (95% CI 88–97; 231 events for two doses vs 29 events for three doses) against admission to hospital, 92% (82–97; 157 vs 17 events) against severe disease, and 81% (59–97; 44 vs seven events) against COVID-19-related death (table 2).

Figure 1: Cumulative incidence curves comparing COVID-19-related admission to hospital (A), severe disease (B), and death (C) in individuals who received two versus three doses of the BNT162b2 mRNA COVID-19 vaccine.

The dashed vertical line indicates day 7, on which the main analysis period begins.

and because they are less likely to be affected by biases stemming from a differential tendency to be tested that is expected to exist between the study groups.

Secondary outcomes were less severe: documented SARS-CoV-2 infection confirmed by positive PCR test and symptomatic infection.
Cumulative incidence curves for COVID-19-related admission to hospital began to diverge around 6 days after vaccination; for severe disease and COVID-19-related death, divergence was seen at around 8–9 days after vaccination (figure 1). The estimated third-dose vaccine effectiveness against admission to hospital and severe disease was similar between males and females, and between individuals aged 40–69 years and those aged at least 70 years (table 3). Third-dose vaccine effectiveness against documented SARS-CoV-2 infection was estimated to be 88% (95% CI 87–90; 6131 events for two doses vs 1135 events for three doses) and against symptomatic infection was 91% (89–92; 3345 vs 514 events; table 4). Individuals who received the third dose were tested less frequently for SARS-CoV-2 infection during follow-up than those who did not.

A sensitivity analysis defining booster effectiveness as 1–incidence rate ratio yielded similar results: 87% (95% CI 82–92) against admission to hospital, 89% (83–94) against severe disease, and 84% (67–93) against COVID-19-related death (appendix p 22).

Our ecological analysis showed that, shortly after the third-dose vaccination campaign was initiated in each age group, the incidence trend began to decline in the respective age groups when compared with that of age groups not yet eligible (figure 2).

**Discussion**

In this large observational study conducted using nationwide mass vaccination data in Israel, we estimated that a third dose of the BNT162b2 mRNA COVID-19 vaccine is effective in preventing severe COVID-19-related outcomes. Compared with two doses of the vaccine administered at least 5 months before, adding a third dose was estimated to be 93% effective in preventing COVID-19-related admission to hospital, 92% in preventing severe disease, and 81% in preventing COVID-19-related death, as of 7 or more days after the third dose.

Third-dose vaccine effectiveness against admission to hospital and severe disease was estimated to be similar between males and females, and between individuals aged 40–69 years and at least 70 years. In those aged...
The optimal time to achieve maximum protection against SARS-CoV-2-related outcomes after a third vaccine is unknown. In this study, we estimated effectiveness starting from day 7 after the third dose, which is similar to the period used to define full vaccination after the second dose. The choice of supported by high concentrations of antibodies in individuals 7 days after administration of the third dose. It is possible, however, that some degree of protection begins earlier. Although an increase in antibody production can be identified on days 3–5 after administration of the second dose of SARS-CoV-2 mRNA vaccines, for other vaccines (eg, influenza), antibodies and antibody-secreting cells are detected as early as day 2 after a booster dose. Moreover, a rapid response of the immune system can potentially prevent infections in individuals even if they were exposed to the virus shortly before the third dose. Such protection is termed the post-exposure effect and is well established in vaccinations for other pathogens, such as varicella, measles, and hepatitis A.

Our study has several limitations. First, differing testing frequencies between the groups do not allow unbiased estimates for the less severe secondary outcomes of documented infection and symptomatic infection. Second, as in any observational study, unmeasured confounding might exist. However, this concern is mitigated because our analysis was adjusted for various important possible confounders, including sociodemographic factors, clinical factors, and behavioural factors related to COVID-19. In addition, this study focuses on severe outcomes, which are less likely to be affected by differences in health-seeking behaviours or testing rates between groups. Third, due to the relative scarcity of events in individuals younger than 40 years, we could not evaluate vaccine effectiveness in this age group. Fourth, this vaccine effectiveness study did not explore potential adverse clinical events and excess health-care utilisation associated with the administration of a third dose. Finally, we excluded populations (health-care workers, those living in long-term care facilities, and those medically confined to their homes) that are likely to be targeted early to receive the booster dose.

There is an active debate surrounding the administration of third doses to individuals in some countries while other countries suffer from vaccine scarcity.
It is outside the scope of this epidemiological analysis to address the complex ethical issues involved in this debate, but there is an urgent need for increased vaccine production, distribution, and access worldwide. The present study was designed to use existing observational health data to study vaccine effectiveness in preventing specific COVID-19 outcomes, aiming to expand the scientific evidence base that might be useful in informing this broader discussion.

At the time of writing, many countries are experiencing a resurgence of SARS-CoV-2 infections despite hitherto successful vaccination campaigns, the cause of which is suggested to be the greater infectiousness of the delta variant and waning immunity as time passes from earlier vaccination. Regardless of the cause, these early findings suggest that a third dose of mRNA vaccine is effective in reducing severe COVID-19-related outcomes for patients who have received two doses at least 5 months before.

Declarations of interest
NB, ND, and RBD report institutional grants to Clalit Research Institute from Pfizer outside the submitted work and unrelated to COVID-19, with no direct or indirect personal benefits. MAH reports grants from the US National Institutes of Health (NIH) and US Department of Veterans Affairs, and personal fees from Cytel and ProPublica. ML reports grants from Pfizer, NIH, the UK National Institute for Health Research, the US Centers for Disease Control and Prevention, Open Philanthropy Project, the Wellcome Trust, and Pfizer; personal fees from Merck, Bristol Meyers Squibb, Sanofi Pasteur, and Janssen; and unpaid advice given on Covid vaccines or vaccine studies to One Day Sooner, Pfizer, AstrellaZeneca, Janssen, and COVAXX (United Biosciences), outside the submitted work. BYR reports grants from NIH outside the submitted work. All other authors declare no competing interests.

Data sharing
Due to data privacy regulations, the raw data of this study cannot be shared.

Acknowledgments
This study was funded by the Ivan and Francesca Berkowitz Family Living Laboratory Collaboration at Harvard Medical School and Clalit Research Institute. ML was supported by the Morris-Singer Fund.

References
1. Zipek D, Carbonare LD, Valentí MT, et al. Antibody response to BNT162b2 mRNA vaccination in naive versus SARS-CoV-2-infected subjects with and without waning immunity. *Rev Sa 2021*; published online April 30. https://doi.org/10.21283/rs.3.rs-440401/v1 (preprint).
2. Thompson RN, Hill EM, Grog JR. SARS-CoV-2 incidence and vaccine escape. *Lancet Infect Dis* 2021; 21: 913–14.
3. 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/10.1101/2021.08.18.21226217 (preprint).
4. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021; 385: 585–94.
5. Daouli D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. *Kidney Int* 2021; 100: 702–04.
6. Pfizer. Second quarter 2021 earnings teleconference. July 28, 2021. https://21l.pcdn.com/137678438/files/doc_financials/2021/q2/Q2-2021-Earnings-Charts-FINAL.pdf (accessed Oct 12, 2021).
7. Wu K, Choi A, Koch M, et al. Preliminary analysis of safety and immunogenicity of a SARS-CoV-2 variant vaccine booster. *medRxiv* 2021; published online May 6. https://doi.org/10.1101/2021.05.05.21256716 (preprint).
8. Fisher L. Vaccine booster shots for 32m to begin next month. Aug 1, 2021. https://www.telegraph.co.uk/politics/2021/08/01/ vaccine-booster-shots-32m-begin-next-month/ (accessed Aug 18, 2021).
9. Kar-gupta S. Ignoring WHO call, major nations stick to vaccine booster plans. Aug 5, 2021. https://www.reuters.com/world/europe/french-president-macron-third-covid-vaccine-doses-likely-elderly-vulnerable-2021-08-05/ (accessed Aug 18, 2021).
10. Restuccia A. Biden administration expected to call for COVID-19 vaccine booster shots. Aug 16, 2021. https://www.wsj.com/articles/biden-administration-to-call-for-COVID-19-vaccine-booster-shots-11629700011 (accessed Aug 18, 2021).
11. Kearns P, Siebert S, Willicombe M, et al. Examining the immunological effects of COVID-19 vaccination in patients with conditions potentially leading to diminished immune response capacity – the OCTAVE trial. SSRN 2021; published online Aug 23. https://doi.org/10.2139/ssrn.3900658 (preprint).
12. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes additional vaccine dose for certain immunocompromised individuals. Aug 12, 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-COVID-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised (accessed Aug 17, 2021).
13. Food and Drug Administration. FDA authorizes booster dose of Pfizer-BioNTech COVID-19 vaccine for certain populations. Sept 22, 2021. https://www.fda.gov/news-events/press-announcements/fda-authorizes-booster-dose-pfizer-biontech-COVID-19-vaccine-certain-populations (accessed Sept 29, 2021).
14. Hernàn MA, Robine JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol* 2016; 8: 758–64.
15. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021; 384: 1412–21.
16. Centers for Disease Control and Prevention. Certain medical conditions and risk for severe COVID-19 illness. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (accessed Dec 9, 2020).
17. National Institutes of Health. COVID-19 treatment guidelines. Oct 7, 2021. https://www.covid19treatmentguidelines.nih.gov/ (accessed Oct 12, 2021).
18. Kaplan EL, Mitty P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53: 457–81.
19. Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 vaccine booster against COVID-19 in Israel. *N Engl J Med* 2021; published online Sept 15. https://doi.org/10.1056/nejmoa214255.
20. Patalon T, Gazit S, Pitzer VE, Prunas O, Warren JI, Weinberger DM. Short term reduction in the odds of testing positive for SARS-CoV-2: a comparison between two doses and three doses of the BNT162b2 vaccine. *medRxiv* 2021; published online Aug 31. https://doi.org/10.1101/2021.08.29.21262792 (preprint).
21. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med* 2020; 383: 2603–15.
22. Ogata AF, Cheng CA, Desjardins M, et al. Circulating SARS-CoV-2 vaccine antigen detected in the plasma of mRNA-1273 vaccine recipients. *Clin Infect Dis* 2021; published online May 20. https://doi.org/10.1093/cid/ciaa465.
23. Brokstad KA, Cox RJ, Oldensohn J, Jonsson R, Haaheim LR. Parenteral influenza vaccination induces a rapid systemic and local immune response. *J Infect Dis* 1995; 171: 198–203.
24. Pyhälä R, Alanko S, Forsten T, et al. Early kinetics of antibody response to inactivated influenza vaccine. *Clin Diag Virol* 1994; 1: 271–78.
25. Gallagher T, Lipshitz M. Postexposure effects of vaccines on infectious diseases. *Epidemiol Rev* 2019; 41: 13–27.
26. Watson B, Seward J, Yang A, et al. Postexposure effectiveness of varicella vaccine. *Pediatrics* 2000; 105: 84–88.
27 Arciuolo RJ, Jablonski RR, Zucker JR, Rosen JB. Effectiveness of measles vaccination and immune globulin post-exposure prophylaxis in an outbreak setting—New York City, 2013. Clin Infect Dis 2017; 65: 1843–47.

28 Whelan J, Sonder GJ, Bovée L, Speksnijder A, van den Hoek A. Evaluation of hepatitis A vaccine in post-exposure prophylaxis, the Netherlands, 2004–012. PLoS One 2013; 8: e78914.

29 Mishra M. WHO calls for halting COVID-19 vaccine boosters in favor of unvaccinated. Aug 5, 2021. https://www.reuters.com/business/healthcare-pharmaceuticals/who-calls-moratorium-COVID-19-vaccine-booster-doses-until-september-end-2021-08-04/ (accessed Aug 18, 2021).