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.
Durability of BNT162b2 vaccine against hospital and emergency department admissions due to the omicron and delta variants in a large health system in the USA: a test-negative case–control study

Sara Y Tartof, Jeff M Slezak, Laura Puzniak, Vennis Hong, Fagen Xie, Bradley K Ackerson, Srinivas R Valluri, Luis Jodar, John M McLaughlin

Summary

Background The duration of protection against the omicron (B.1.1.529) variant for current COVID-19 vaccines is not well characterised. Vaccine-specific estimates are especially needed. We aimed to evaluate the effectiveness and durability of two and three doses of the BNT162b2 (Pfizer–BioNTech) mRNA vaccine against hospital and emergency department admissions due to the delta (B.1.617.2) and omicron variants.

Methods In this case–control study with a test-negative design, we analysed electronic health records of members of Kaiser Permanente Southern California (KPSC), a large integrated health system in California, USA, from Dec 1, 2021, to Feb 6, 2022. Vaccine effectiveness was calculated in KPSC patients aged 18 years and older admitted to hospital or an emergency department (without a subsequent hospital admission) with a diagnosis of acute respiratory infection due to the omicron (B.1.1.529) variant since rapidly became the dominant SARS-CoV-2 variant of concern by WHO on Nov 26, 2021, and has been shown to correspond with similar escape potential.

Findings Analyses were done for 11123 hospital or emergency department admissions. In adjusted analyses, effectiveness of two doses of the BNT162b2 vaccine against the omicron variant was 41% (95% CI 21–55) against hospital admission and 31% (16–43) against emergency department admission at 9 months or longer after the second dose. After three doses, effectiveness of BNT162b2 against hospital admission due to the omicron variant was 85% (95% CI 80–89) at less than 3 months but fell to 55% (28–71) at 3 months or longer, although confidence intervals were wide for the latter estimate. Against emergency department admission, the effectiveness of three doses of BNT162b2 against the omicron variant was 77% (72–81) at less than 3 months but fell to 53% (36–66) at 3 months or longer. Trends in waning against SARS-CoV-2 outcomes due to the delta variant were generally similar, but with higher effectiveness estimates at each timepoint than those seen for the omicron variant.

Interpretation Three doses of BNT162b2 conferred high protection against hospital and emergency department admission due to both the delta and omicron variants in the first 3 months after vaccination. However, 3 months after receipt of a third dose, waning was apparent against SARS-CoV-2 outcomes due to the omicron variant, including hospital admission. Additional doses of current, adapted, or novel COVID-19 vaccines might be needed to maintain high levels of protection against subsequent waves of SARS-CoV-2 caused by the omicron variant or future variants with similar escape potential.

Funding Pfizer.

Copyright © 2022 Elsevier Ltd. All rights reserved.

Introduction

The SARS-CoV-2 omicron (B.1.1.529) variant was originally identified in Botswana and South Africa in November, 2021. Compared to the original SARS-CoV-2 strain (Wuhan-Hu-1), omicron (including BA lineages of B.1.1.529) has more than 30 mutations in its spike (S) protein. Many of these mutations are in the receptor-binding domain and have been shown to correspond with a high degree of transmissibility and neutralising antibody escape. Subsequently, omicron was declared a variant of concern by WHO on Nov 26, 2021, and has since rapidly become the dominant SARS-CoV-2 variant globally. Preliminary studies have shown that two doses of the BNT162b2 (Pfizer–BioNTech) mRNA vaccine do not sufficiently neutralise the omicron variant. Additionally, although levels of neutralisation against omicron after three doses of BNT162b2 are substantially higher than those seen after two doses, they are lower than those observed for the wild-type strain and for the delta (B.1.617.2) variant. However, early data suggest that T-cell responses induced by previous SARS-CoV-2 infection and by the BNT162b2 vaccine are not significantly altered against omicron. Although these findings suggest that protection against severe SARS-CoV-2 infection with omicron is likely to be better...
Articles

Research in context

Evidence before this study
We searched PubMed, medRxiv, and press coverage up to March 1, 2022, using the terms “BNT162b2”, “vaccin*”, “COVID-19”, “effective*”, “impact”, “model”, “omicron”, and “delta” for preprint and published studies, without applying any language restrictions. Due to the timing of publications, most reports were unable to describe vaccine effectiveness or durability against SARS-CoV-2 infection with the omicron (B.1.1.529) variant. Available data as of March 1, 2022, suggest that two doses of an mRNA vaccine provide reduced protection against the omicron variant and symptomatic COVID-19 compared with the delta (B.1.617.2) variant, and moderate protection against severe SARS-CoV-2 infection. The effectiveness of a third dose against infection with the omicron variant or symptomatic COVID-19 has been estimated to be higher than that of two doses, but with waning observed in the first few months. Only a few reports have estimated the effectiveness of a third dose against hospital admission due to the omicron variant, with an even smaller number evaluating the durability of a booster dose against severe outcomes. Studies evaluating the longer-term effectiveness of two and three doses of BNT162b2 against the omicron variant, especially for severe outcomes, are urgently needed.

Added value of this study
In this case–control study covering a large, diverse population in the USA, we show that in the first 3 months after receipt of a third dose, the BNT162b2 vaccine provided 85% protection against hospital admission due to the omicron variant but less protection thereafter. Three doses of BNT162b2 were also effective at preventing emergency department admissions due to the omicron variant (albeit slightly less effective than preventing hospital admissions); however, the protection afforded by three doses also waned over time for this milder form of SARS-CoV-2 infection. These are some of the earliest data showing the effectiveness of three doses of BNT162b2 against SARS-CoV-2 infection due to the omicron variant, while also highlighting that this protection is likely to wane after 3 months, even for hospital admissions.

Implications of all the available evidence
In the future, additional doses of current, adapted, or novel COVID-19 vaccines might be needed to maintain high protection against severe SARS-CoV-2 infection and maintain sufficient vaccine-induced pressure on future SARS-CoV-2 outbreaks.

preserved than that against less symptomatic infection in most individuals, the extent of the impact on vaccine effectiveness and potential waning is unclear.

Estimates of the real-world effectiveness of BNT162b2 (and other COVID-19 vaccines) against infection caused by the omicron variant are limited to data from South Africa and the US Centers for Disease Control and Prevention (CDC) and preprint reports from the UK, the USA, Canada, Qatar, and Denmark. Generally speaking, these data suggest that two doses of the mRNA vaccine are likely to provide only limited and short-lived protection against infection caused by the omicron variant and symptomatic COVID-19, and two doses have reduced effectiveness against hospital admission due to omicron compared to that seen for previous SARS-CoV-2 variants. Additionally, preliminary data suggest that three doses of the mRNA vaccine provide increased but modest protection against SARS-CoV-2 infection that wanes quickly, as well as increased protection against hospital admission in the first few months.

The effectiveness of a third (booster) dose of an mRNA vaccine against infection with the omicron variant or symptomatic COVID-19 has been estimated to be higher than that achieved after two doses, but with waning observed in the first few months. Only two published reports from the CDC and one non-peer-reviewed report have estimated the effectiveness of a third dose against hospital admission due to omicron. All studies reported vaccine effectiveness of roughly 90% soon after receipt of the third dose of an mRNA vaccine; however, none reported vaccine-specific estimates and only one provided long-term follow-up after receipt of a booster dose. Thus, studies evaluating the effectiveness of BNT162b2 against omicron in other robust health systems across the world, especially for severe outcomes and with sufficient follow-up, are urgently needed to inform public-health decision making about the need for (and timing of) additional boosters, improved COVID-19 vaccines tailored to target the omicron variant, or other effective COVID-19 vaccines. We aimed to evaluate the age-specific effectiveness and durability of two and three doses of BNT162b2 against hospital and emergency department admissions due to the omicron variant in a large integrated health system in the USA.

Methods

Study design and participants
This test-negative case–control study included members of Kaiser Permanente Southern California (KPSC), a large integrated health-care system in California, USA. KPSC membership includes more than 4·7 million members who are representative of the socioeconomic, racial, and ethnic diversity of the population of southern California. KPSC electronic health records integrate clinical data across all settings of care, including care delivered to members outside of the KPSC system. The study protocol was reviewed and approved by the KPSC institutional review board, which waived requirement for informed consent (number 12816).
All KPSC patients aged 18 years and older who were admitted to hospital or an emergency department from Dec 1, 2021 (date of the first laboratory-confirmed SARS-CoV-2 infection due to the omicron variant at KPSC), to Feb 6, 2022, with a diagnosis of acute respiratory infection based on ICD-10 codes (appendix pp 1–3) and who underwent a PCR test for SARS-CoV-2 were eligible for inclusion in this study. For inclusion in this study, patients were required to have at least 1 year of health plan membership (allowing a 45-day gap during previous membership to allow for potential delays in renewal) to determine comorbidities and medical history.

Specimens were included in the analysis if they were tested with the ThermoFisher TaqPath COVID-19 Combo Kit (ThermoFisher, Waltham, MA, USA), which can distinguish specimens with S protein target failure among positive specimens. Mutations in the S protein of omicron specimens cause a failure in PCR probes targeting the S gene, while the Orf1ab and nucleocapsid (N) probes retain sensitivity. S gene target failure (SGTF) is rare for the delta variant. An internal validation study of 1477 SARS-CoV-2 isolates that underwent whole genome sequencing resulted in confirmation of the omicron lineage in all SGTF samples (382 [100·0%] of 382) and the delta lineage was confirmed in 1092 (99·7%) of 1095 non-SGTF samples. Thus, samples with SGTF were characterised as omicron and those without as delta. We also included specimens not tested with the ThermoFisher TaqPath kit that were collected during periods when there was a 7-day rolling average with at least 95% predominance of a single variant lineage (ie, delta or omicron). Specifically, specimens collected from Dec 1, 2021, to Dec 9, 2021, were characterised as delta, and those from Dec 20, 2021, through to the end of the study period characterised as omicron (appendix pp 3–4). Specimens not tested on the ThermoFisher TaqPath COVID-19 Combo Kit or outside of our specified delta or omicron time periods were excluded from the analyses.

COVID-19 vaccines were provided at no cost to KPSC members following emergency use authorisation. Vaccinations administered outside of KPSC were captured via the California Immunization Registry, to which providers are required to report all COVID-19 vaccine administrations within 24 h. Being immunised with three doses of BNT162b2 was defined as receiving two doses of BNT162b2 at least 21 days after receiving two doses of BNT162b2, with at least 14 days elapsing after the third dose. Individuals who received a third dose less than 21 days after their second dose of BNT162b2, or had a hospital or emergency department admission up to and including 14 days since the third dose, or who received a third dose of a COVID-19 vaccine that was not BNT162b2 were excluded from the analysis. Immunisation with only two doses of BNT162b2 was defined as receiving two doses of BNT162b2, with at least 7 days elapsing after the second dose (and no third dose). Individuals with partial vaccination were excluded; partial vaccination was defined as receipt of only one dose of BNT162b2, receipt of a third dose less than 21 days after a second dose of BNT162b2, or having a hospital or emergency department admission up to and including 7 days since the second dose or 14 days since the third dose. Individuals were considered unvaccinated if they had never received BNT162b2 or any other COVID-19 vaccine.

Outcomes

Cases of hospital admission or an emergency department admission without a subsequent hospital admission were defined as those with a diagnosis of acute respiratory infection and a KPSC laboratory-confirmed positive SARS-CoV-2 PCR test from a sample collected within 14 days before the initial admission date through to 3 days after the admission. Controls were defined as those with a KPSC laboratory-confirmed negative SARS-CoV-2 PCR test collected within 14 days before a hospital or emergency department admission for acute respiratory infection to 3 days after the admission, and no laboratory-confirmed positive SARS-CoV-2 PCR tests within 90 days before the initial admission. Patients could contribute more than one event to the study if a subsequent event for the same patient occurred more than 30 days after the previous event.

Statistical analysis

We described the distribution of demographic and clinical characteristics of the study cohort by outcome status and COVID-19 vaccination status. Characteristics of cases and controls were compared by use of χ2 test for categorical variables and Fisher’s exact test for binary variables. Crude and adjusted vaccine effectiveness estimates following receipt of both two and three doses of BNT162b2 in the hospital and emergency department setting were constructed and compared with odds ratios (ORs) and 95% CIs from logistic regression models. Vaccine effectiveness was calculated as 1−OR multiplied by 100%, with corresponding 95% CIs calculated with the Wald method. Adjusted ORs and 95% CIs were estimated by adjusting for age (18–49, 50–64, and ≥65 years), sex (male and female), race or ethnicity (Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian or Pacific Islander, and other or unknown), body-mass index (<18·5 kg/m², 18·5–24·9 kg/m², 25·0–29·9 kg/m², 30·0–34·9 kg/m², >35·0 kg/m², and unknown), Charlson Comorbidity Index (0, 1, 2, 3, and ≥4), receipt of influenza vaccine in the year before admission (ever vs never), receipt of pneumococcal vaccine in the 5 years before admission (ever vs never), and documentation of previous SARS-CoV-2 infection (ever vs never) in multivariable logistic regression models. Analyses were done separately
for hospital and emergency department admissions. Analyses were further stratified by variant (delta vs omicron) and by age group (18–64 years vs ≥65 years). We also assessed vaccine effectiveness by time since vaccination (months since completion of a two-dose [only] or three-dose series).

All analyses were done with SAS Enterprise Guide statistical software (version 7.1). This study is registered with ClinicalTrials.gov (NCT04848584).

Role of the funding source

This study was sponsored by Pfizer. The study design was developed by KPSC but approved by Pfizer. KPSC alone collected and analysed the data. KPSC and Pfizer participated in the interpretation of data and the writing of the report.

Results

Between Dec 1, 2021, and Feb 6, 2022, there were 16,063 hospital admissions and 19,699 emergency department admissions across the KPSC health-care system with a documented SARS-CoV-2 PCR test. 3716 (23%) of 16,063 hospital admissions and 9367 (48%) of 19,699 emergency department admissions were for acute respiratory infection (figure 1). Of these, the final study population consisted of 11,123 encounters where patients were either SARS-CoV-2 negative, tested via the ThermoFisher TaqPath COVID-19 Combo Kit (and thus SGTF could be determined), or were assigned a variant lineage based on the time when the infection occurred (ie, when ≥95% of all infections were due to the delta or omicron variant). Among the final study population, 7361 (66%) of 11,123 patients with hospital encounters...
|                          | SARS-CoV-2 negative (n=3762) | Delta (B.1.617.2) variant (n=2838) | Omicron (B.1.1.529) variant (n=4523) | Total (n=11123) | p value |
|--------------------------|-----------------------------|-------------------------------------|--------------------------------------|-----------------|--------|
| Age, years               |                             |                                     |                                      |                 |        |
| 18−49                    | 1568 (42%)                  | 1579 (56%)                          | 2102 (47%)                          | 5249 (47%)      | <0.0001|
| 50−64                    | 709 (19%)                   | 774 (27%)                           | 1014 (22%)                          | 2497 (22%)      |        |
| ≥65                      | 1485 (40%)                  | 485 (17%)                           | 1407 (31%)                          | 3277 (30%)      |        |
| Sex                      |                             |                                     |                                      |                 |        |
| Male                     | 1607 (43%)                  | 1230 (43%)                          | 1885 (42%)                          | 4722 (43%)      | 0.34   |
| Female                   | 2155 (57%)                  | 1608 (57%)                          | 2638 (58%)                          | 6401 (58%)      |        |
| Race or ethnicity        |                             |                                     |                                      |                 |        |
| Asian                    | 362 (10%)                   | 204 (7%)                            | 351 (8%)                            | 917 (8%)        | <0.0001|
| Black                    | 489 (13%)                   | 298 (11%)                           | 701 (16%)                           | 1488 (13%)      |        |
| Hispanic                 | 1465 (39%)                  | 1425 (50%)                          | 2145 (47%)                          | 5035 (45%)      |        |
| Other or unknown         | 111 (3%)                    | 118 (4%)                            | 170 (4%)                            | 399 (4%)        |        |
| White                    | 1335 (36%)                  | 793 (28%)                           | 1156 (26%)                          | 3284 (30%)      |        |
| Body-mass index, kg/m²   |                             |                                     |                                      |                 |        |
| <18.5 (underweight)      | 133 (4%)                    | 28 (1%)                             | 97 (2%)                             | 258 (2%)        | <0.0001|
| 18.5–24.9 (normal or healthy weight) | 977 (26%) | 460 (16%) | 1002 (22%) | 2439 (22%) |        |
| 25.0–29.9 (overweight)   | 1054 (28%)                  | 859 (30%)                           | 1250 (28%)                          | 3161 (28%)      |        |
| 30.0–34.9 (obese, class 1) | 754 (20%) | 702 (25%) | 1032 (23%) | 2488 (22%) |        |
| ≥35.0 (obese, class 2–3) | 807 (22%)                  | 745 (26%)                           | 1071 (24%)                          | 2623 (24%)      |        |
| Unknown                  | 37 (1%)                     | 44 (2%)                             | 71 (2%)                             | 152 (1%)        |        |
| Comorbidities            |                             |                                     |                                      |                 |        |
| Hypertension             | 1658 (44%)                  | 686 (24%)                           | 1556 (34%)                          | 3900 (35%)      | <0.0001|
| Congestive heart failure | 568 (15%)                   | 88 (3%)                             | 361 (8%)                            | 1017 (9%)       | <0.0001|
| Myocardial infarction    | 230 (6%)                    | 52 (2%)                             | 157 (4%)                            | 439 (4%)        | <0.0001|
| Peripheral vascular disease | 1139 (30%) | 272 (10%) | 885 (20%) | 2296 (21%) | <0.0001|
| Cerebrovascular disease  | 245 (7%)                    | 60 (2%)                             | 205 (5%)                            | 510 (5%)        | <0.0001|
| Diabetes status          |                             |                                     |                                      |                 |        |
| Diabetes, unknown glycosylated haemoglobin | 55 (2%) | 37 (1%) | 76 (2%) | 168 (2%) | <0.0001|
| Diabetes, glycosylated haemoglobin <7.5 % | 625 (17%) | 249 (9%) | 539 (12%) | 1413 (12%) |        |
| Diabetes, glycosylated haemoglobin ≥7.5 % | 361 (10%) | 232 (8%) | 440 (10%) | 1033 (9%) |        |
| Chronic obstructive pulmonary disease | 1012 (27%) | 416 (15%) | 681 (15%) | 2129 (19%) | <0.0001|
| Renal disease            | 720 (19%)                   | 175 (6%)                            | 598 (13%)                           | 1493 (13%)      | <0.0001|
| Malignancy               | 339 (9%)                    | 96 (3%)                             | 231 (5%)                            | 666 (6%)        | <0.0001|
| Organ transplant         | 26 (1%)                     | 24 (1%)                             | 72 (2%)                             | 122 (1%)        | 0.0002 |
| Charlson Comorbidity Index | 0     | 1530 (41%) | 1744 (62%) | 2317 (52%) | 5611 (50%) | <0.0001|
| 1                        | 607 (16%)                   | 539 (19%)                           | 806 (18%)                           | 1952 (18%)      |        |
| 2                        | 383 (10%)                   | 245 (9%)                            | 405 (9%)                            | 1013 (9%)       |        |
| 3                        | 244 (7%)                    | 111 (4%)                            | 255 (6%)                            | 610 (6%)        |        |
| ≥4                       | 998 (27%)                   | 199 (7%)                            | 720 (16%)                           | 1917 (17%)      |        |
| Influenza vaccine year before admission | 2061 (55%) | 860 (30%) | 1752 (39%) | 4673 (42%) | <0.0001|
| Pneumococcal vaccine 5 years before admission | 916 (24%) | 460 (16%) | 883 (20%) | 2259 (20%) | <0.0001|
| Previous positive SARS-CoV-2 PCR test | 602 (16%) | 155 (6%) | 320 (7%) | 1077 (10%) | <0.0001|
| BNT162b2 vaccination status |                             |                                     |                                      |                 |        |
| Unvaccinated             | 1063 (28%)                  | 1748 (62%)                          | 2354 (52%)                          | 5165 (46%)      | <0.0001|
| Two doses (only) in the past ≥7 days and <3 months | 169 (5%) | 57 (2%) | 127 (3%) | 353 (3%) |        |
| Two doses 3 to <6 months ago | 304 (8%) | 176 (6%) | 319 (7%) | 799 (7%) |        |
| Two doses 3 to <9 months ago | 635 (17%) | 404 (14%) | 599 (13%) | 1638 (15%) |        |
| Two doses ≥9 months ago  | 417 (11%)                   | 217 (8%)                            | 557 (12%)                           | 1191 (11%)      |        |
| Three doses in the past ≥14 days and <3 months | 1022 (27%) | 188 (7%) | 430 (10%) | 1640 (15%) |        |
| Three doses ≥3 months ago | 152 (4%) | 48 (2%) | 137 (3%) | 337 (3%) |        |

Table 1: Characteristics of cases and test-negative controls among patients diagnosed with acute respiratory infection from Dec 1, 2021, to Feb 6, 2022
had a positive SARS-CoV-2 test, with 4523 (61%) of 7361 identified as omicron, and 2838 (39%) of 7361 identified as delta. Overall, 5165 (46%) of 11 123 patients were unvaccinated, 3981 (36%) of 11 123 were vaccinated with two doses only, and 1977 (18%) of 11 123 were vaccinated with three doses. The median age of the study population was 51 years (IQR 35–69). Compared to those who tested positive for SARS-CoV-2, those who tested negative tended to be older and White and more likely to have comorbidities and evidence of previous SARS-CoV-2 infection (table 1). Compared to patients who received three doses, unvaccinated patients were younger, more likely to be Black or Hispanic, less likely to have comorbidities, and less likely to have | Table 2: Characteristics by vaccination status among patients with a diagnosis of acute respiratory infection from Dec 1, 2021, to Feb 6, 2022

| Vaccination Status                        | Unvaccinated (n=5165) | Two doses (only) in the past ≥7 days (n=3981) | Three doses in the past ≥14 days (n=1977) | Total (n=11 123) | p value  |
|-------------------------------------------|-----------------------|-----------------------------------------------|------------------------------------------|-----------------|---------|
| Age, years                                |                       |                                               |                                          |                 |         |
| 18–49                                     | 464 (47%)             | 249 (47%)                                     |                                          |                 | <0.0001 |
| 50–64                                     | 2046 (52%)            | 1280 (49%)                                    |                                          |                 |         |
| ≥65                                       | 1104 (56%)            | 52 (5%)                                       |                                          |                 |         |
| Sex                                        |                       |                                               |                                          |                 |         |
| Male                                      | 2275 (44%)            | 1536 (53%)                                    | 911 (46%)                                | 4722 (43%)      | <0.0001 |
| Female                                    | 2890 (56%)            | 2445 (61%)                                    | 1066 (54%)                               | 6401 (58%)      |         |
| Race or ethnicity                          |                       |                                               |                                          |                 |         |
| Asian                                     | 246 (5%)              | 376 (9%)                                      | 295 (15%)                                | 917 (8%)        | <0.0001 |
| Black                                     | 794 (15%)             | 528 (12%)                                     | 166 (8%)                                 | 1488 (13%)      |         |
| Hispanic                                  | 2374 (46%)            | 1955 (49%)                                    | 706 (36%)                                | 5035 (45%)      |         |
| Other/Unknown                             | 200 (4%)              | 143 (4%)                                      | 56 (3%)                                  | 399 (4%)        |         |
| White                                     | 1551 (30%)            | 979 (25%)                                     | 754 (38%)                                | 3284 (30%)      |         |
| Body-mass index, kg/m²                    |                       |                                               |                                          |                 |         |
| <18·5 (underweight)                       | 116 (2%)              | 82 (2%)                                       | 60 (3%)                                  | 258 (2%)        | <0.0001 |
| 18·5–24·9 (normal or healthy weight)      | 1030 (20%)            | 867 (22%)                                     | 542 (27%)                                | 2439 (22%)      |         |
| 25·0–29·9 (overweight)                    | 1427 (28%)            | 1132 (28%)                                    | 604 (31%)                                | 3163 (28%)      |         |
| 30·0–34·9 (obese, class 1)                | 1198 (23%)            | 884 (22%)                                     | 406 (21%)                                | 2488 (22%)      |         |
| ≥35·0 (obese, class 2-3)                  | 1302 (25%)            | 967 (24%)                                     | 354 (18%)                                | 2623 (24%)      |         |
| Unknown                                   | 92 (2%)               | 49 (1%)                                       | 11 (1%)                                  | 152 (1%)        |         |
| Comorbidities                             |                       |                                               |                                          |                 |         |
| Hypertension                              | 1428 (28%)            | 1368 (34%)                                    | 1104 (56%)                               | 3900 (35%)      | <0.0001 |
| Congestive heart failure                  | 307 (6%)              | 386 (10%)                                     | 124 (16%)                                | 1017 (9%)       | <0.0001 |
| Myocardial infarction                     | 135 (3%)              | 167 (4%)                                      | 137 (7%)                                 | 439 (4%)        | <0.0001 |
| Peripheral vascular disease               | 712 (14%)             | 752 (19%)                                     | 832 (42%)                                | 2296 (21%)      | <0.0001 |
| Cerbrovascular disease                    | 188 (4%)              | 180 (5%)                                      | 147 (7%)                                 | 510 (5%)        | <0.0001 |
| Diabetes                                  |                       |                                               |                                          |                 |         |
| Diabetes; unknown glycated haemoglobin    | 95 (2%)               | 52 (1%)                                       | 21 (1%)                                  | 168 (2%)        |         |
| Diabetes; glycated haemoglobin <7·5%      | 466 (9%)              | 508 (13%)                                     | 439 (22%)                                | 1413 (13%)      | <0.0001 |
| Diabetes; glycated haemoglobin ≥7·5%      | 402 (8%)              | 393 (10%)                                     | 238 (12%)                                | 1033 (9%)       | <0.0001 |
| Chronic obstructive pulmonary disease      | 828 (16%)             | 739 (19%)                                     | 562 (18%)                                | 2129 (19%)      | <0.0001 |
| Renal disease                             | 468 (9%)              | 572 (13%)                                     | 503 (25%)                                | 1493 (13%)      | <0.0001 |
| Malignancy                                | 205 (4%)              | 215 (5%)                                      | 246 (12%)                                | 666 (6%)        | <0.0001 |
| Organ transplant                          | 23 (0·4%)             | 37 (1%)                                       | 62 (3%)                                  | 122 (1%)        | <0.0001 |
| Charlson Comorbidity Index                |                       |                                               |                                          |                 |         |
| 0                                         | 3000 (58%)            | 2046 (51%)                                    | 565 (29%)                                | 5611 (50%)      | <0.0001 |
| 1                                         | 943 (18%)             | 712 (18%)                                     | 297 (15%)                                | 1952 (18%)      | <0.0001 |
| 2                                         | 407 (8%)              | 358 (9%)                                      | 268 (14%)                                | 1033 (9%)       | <0.0001 |
| 3                                         | 215 (4%)              | 197 (5%)                                      | 198 (10%)                                | 610 (6%)        | <0.0001 |
| ≥4                                        | 600 (12%)             | 668 (12%)                                     | 649 (33%)                                | 1917 (17%)      | <0.0001 |
| Influenza vaccine year before admission    | 997 (19%)             | 1995 (50%)                                    | 1681 (85%)                               | 4673 (42%)      | <0.0001 |
| Pneumococcal vaccine 5 years before admission | 841 (16%)         | 794 (20%)                                     | 624 (32%)                                | 2259 (20%)      | <0.0001 |
| Previous positive SARS-CoV-2 PCR test      | 463 (9%)              | 452 (11%)                                     | 156 (8%)                                 | 1077 (10%)      | <0.0001 |
previously received influenza or pneumococcal vaccination (table 2).

Among the study population, 3275 (29%) of 11123 patients were admitted to the hospital and 7848 (71%) of 11123 were admitted to the emergency department (without a subsequent hospital admission). Of those admitted to the hospital with a positive SARS-CoV-2 test, 647 (33%) of 1949 were infected with the delta variant and 1302 (67%) of 1949 were infected with the omicron variant (figure 1). Of those admitted to the emergency department only, 2191 (40%) of 5412 were infected with the delta variant and 3221 (60%) of 5412 were infected with the omicron variant.

In adjusted vaccine effectiveness analyses, three doses of BNT162b2 restored immunity against hospital admission and emergency department admission (without a subsequent hospital admission) due to the delta variant to the level seen 3 months after the second dose, which waned 6 months after receipt of only two doses (figure 2; appendix p 5). Vaccine effectiveness against hospital admission due to the delta variant after two doses remained relatively consistent, at 84% (95% CI 74–90) less than 6 months after two doses and 73% (63–80) at least 6 months after two doses. The effectiveness of three doses against hospital admission due to the delta variant appeared to fall from 89% (95% CI 83–93) less than 3 months after three doses to 71% (40–86) from 3 months onwards, although the confidence intervals overlapped and were wide around the latter estimate. Against emergency department admission due to the delta variant, the effectiveness of two doses of BNT162b2 declined from 78% (95% CI 69–85) less than 3 months after the second dose to 57% (45–66) from 9 months onwards. Vaccine effectiveness against emergency department admission due to the delta variant was 84% (95% CI 80–87) less than 3 months after the third dose. Overall vaccine effectiveness after a third dose was 87% (95% CI 81–92) against hospital admission due to the delta variant (appendix p 5).

Immunity conferred by two or three doses of BNT162b2 was lower for the omicron variant than for the delta variant (figure 2; appendix p 5). The effectiveness of two doses against hospital admission due to the omicron variant was 68% (95% CI 48–80) at less than 3 months following a second dose and 41% (21–55) at 9 months onwards. The effectiveness of three doses

Figure 2: Adjusted vaccine effectiveness of mRNA COVID-19 vaccine BNT162b2 (Pfizer-BioNTech) against hospital and emergency department admission among individuals diagnosed with acute respiratory infection by variant of concern, from Dec 1, 2021, to Feb 6, 2022

Estimates adjusted for age, sex, race or ethnicity, body-mass index, Charlson comorbidity index, previous SARS-CoV-2 infection, previous influenza vaccination, and previous pneumococcal vaccination.
against hospital admission due to the omicron variant was 85% (95% CI 80–89) at less than 3 months following the third dose but fell to 55% (28–71) from 3 months onwards, although the confidence intervals were wide for this latter estimate. Protection against emergency department admission due to the omicron variant also appeared to wane after two doses, falling from 64% (95% CI 51–73) at less than 3 months after the second dose to 51% (43–59) at 6–9 months after the second dose and 31% (16–43) at 9 months onwards. The effectiveness of three doses against emergency department admission due to the omicron variant also waned, declining from 77% (95% CI 72–81) at less than 3 months following a third dose to 53% (36–66) at 3 months onwards (appendix p 5).

Overall, stratification of vaccine effectiveness by age group showed similar trends as with all ages, but revealed slightly higher vaccine effectiveness estimates among individuals aged 65 years and older versus those aged 18–64 years (appendix pp 6–8).

**Discussion**

In the first few months after receiving a booster dose of BNT162b2, it confers high protection (around 80–90%) against hospital and emergency department admission caused by the delta and omicron variants. Against the omicron variant, however, this protection is likely to wane significantly over time—even after a third dose. Specifically, in the present study, 3–5 months after receiving a booster dose of BNT162b2, effectiveness against hospital admission due to the omicron variant fell to 55% (95% CI 28–71), and effectiveness against emergency department admission due to the omicron variant (without subsequent hospital admission) fell to 53% (36–66), although confidence intervals were wide around the point estimate for hospital and emergency department admissions.

Our estimates of the effectiveness of three doses against hospital admission due to the omicron variant less than 3 months after the third dose (85% [95% CI 80–89]) were generally similar to those seen for hospital admission due to the delta variant (89% [83–93]) in the first 3 months following the third dose. Our vaccine effectiveness estimates against hospital admission due to the omicron variant less than 3 months after a third dose were also similar to those reported by the CDC (which reported effectiveness of around 90% for both mRNA vaccines) and the UK Health Security Agency (which reported effectiveness of approximately 85–90% for all vaccines used in the UK combined). Our study, to the best of our knowledge, is one of the first to report long-term follow-up outcomes after receipt of a booster dose, stratified by age. Similar to a recent CDC report showing waning effectiveness of mRNA COVID-19 vaccines after a third dose, we also detected early signs of waning against severe outcomes caused by the omicron variant from 3 months onwards after the receipt of a booster dose. More long-term follow-up data are needed, however, to fully understand the true magnitude of this decline.

Although waning was observed, effectiveness of two and three doses against hospital admission was generally higher than that seen for the less severe endpoint of emergency department admission across all timepoints. Previous reports have indicated that T-cell immunity might have a role in the prevention of severe SARS-CoV-2 infection, and laboratory results have suggested that T-cell epitopes have remained mostly unaltered for the omicron variant. The relationship between cell-mediated immunity and protection against severe infection, however, needs more research. It is also likely that trained innate immunity has an important role in durable protection, particularly against severe infection.

Unrelated live attenuated vaccines and adjuvanted vaccines can provide sustained protection against heterologous infections and severe outcomes, including COVID-19, possibly through induction of trained innate immunity, which mRNA vaccines also induce.

Our results showed waning effectiveness of two doses against emergency department admission for both the delta and omicron variants, consistent with previous evidence of waning effectiveness of BNT162b2 against the delta variant over time and with preliminary studies showing waning effectiveness against the omicron variant and symptomatic SARS-CoV-2 infection. After a third dose, effectiveness against emergency department admission increased to 84% (95% CI 80–87) for the delta variant and 77% (72–81) for the omicron variant. Waning of immunity against emergency department admission after three doses was moderate for the delta variant but was more pronounced for the omicron variant, falling to 53% (36–66) at 3 months or more after the third dose. This finding is consistent with early reports from the UK Health Security Agency suggesting that even after three doses, vaccine effectiveness against symptomatic SARS-CoV-2 infection due to the omicron variant wanes rapidly. Age-stratified analyses showed that effectiveness was generally higher in adults aged 65 years and older. However, this finding might reflect enhanced risk-mitigating behaviours, especially among vaccinated people in this age group, or the potential dilution of vaccine effectiveness among adults younger than 65 years.

There are two important implications of our findings. First, booster doses significantly improve protection against the omicron variant. Our data suggest that, in the first few months after their receipt, booster doses of BNT162b2 provide high levels of protection (around 80–90%) against hospital and emergency department admission due to the omicron variant—a level of protection not seen with only two doses. Thus, although booster doses were initially introduced to counteract waning immunity against infection during a period when the delta variant was predominant, in the omicron era three doses appear to be necessary to achieve high
levels of protection against severe COVID-19 outcomes. These findings are consistent with laboratory data reporting that neutralising antibody concentrations not only improved after a third dose (compared to after two doses) but also that the breadth of coverage against variants of concern seemed to increase.7

Second, although the initial effectiveness of a booster dose of BNT162b2 against the omicron variant was high, this protection waned after 3 months—even against a severe outcome such as hospital admission. Although more data are needed about the precise magnitude of this effect, this finding suggests that additional doses of current, adapted, or novel COVID-19 vaccines, which are currently in development, might be necessary in the future. Thus far, studies have shown that heterologous boosting with adenoviral vector vaccines does not improve the cellular response or the breadth of protection after priming with mRNA;42–45 however, continual evaluation of booster strategies will be needed in the future. Preliminary data from Israel have shown improved protection against SARS-CoV-2 infection with the omicron variant and severe COVID-19 in individuals who received a fourth dose of BNT162b2 compared to those who had received only three doses at least 4 months ago.46 However, data describing the durability of additional booster doses (beyond the third dose) are needed.

Our study is not without limitations. As this was an observational study, there might be residual confounding driven by differences in the likelihood of exposure to SARS-CoV-2 between vaccinated and unvaccinated individuals. Although we controlled for key socio-demographic and clinical characteristics, we were not able to capture data on occupation or behaviours, and sample size limitations precluded inclusion of all potentially confounding variables in adjusted analyses. Moreover, although vaccinated individuals might be more likely to seek care or testing for SARS-CoV-2 (thus biasing vaccine effectiveness results downwards), the test-negative design of the study, particularly in the hospital setting where there is universal testing, helps mitigate against this bias caused by differences in health-care-seeking behaviour—including the propensity to test—between groups or high-risk groups. Furthermore, due to the rapid influx of at-home antigen tests and increasing variation in clinic-based testing practices, we were not able to assess long-term durability of the third dose or to provide vaccine effectiveness estimates specific to age groups or high-risk groups. Additionally, in the emergency department admission.

In conclusion, BNT162b2 provided 85% protection against hospital admission due to the omicron variant in the first 3 months after receipt of a third dose but less protection thereafter. Three doses of BNT162b2 were also effective at preventing emergency department admission due to the omicron variant (although slightly less effective than at preventing hospital admission), however, protection also waned for this milder form of infection. These findings reiterate the need to continue the development of additional strategies to ensure long-term protection against severe SARS-CoV-2 infection caused by the omicron variant or future variants that stem from this variant of concern. In the future, additional doses of current, adapted, or novel COVID-19 vaccines might be needed to maintain high protection against severe infection and sufficient vaccine pressure on future waves of SARS-CoV-2 infection.
Articles

Contributors
SYT, JMS, LJ, and JMM conceived this study. JMS, VH, and FX analysed the data, and SYT, VH, JMS, and FX had raw data to validate the data. SYT, JMS, JMM, BKA, SRV, and LP wrote the first draft of the protocol. SYT and JMM wrote the first draft of the manuscript. All authors contributed to the study design, drafting the protocol, and edited the manuscript for important intellectual content. All authors gave final approval of the version to be published and had final responsibility for the decision to submit for publication.

Declaration of interests
SRV, LJ, VP, and JMM are employees of and hold stock or stock options, or both, in Pfizer. SYT, JMS, VH, FX, and BKA received research support from Pfizer during the conduct of this study that was paid directly to KPSC. BKA received research support for work unrelated to this study, provided by Pfizer, Moderna, Dynavax, Sequirus, GlaxoSmithKline, and Genentech. JMS received research support from ALK-Abelló, Dynavax, and Novavax for work unrelated to this study. SYT received research support from Genentech for work unrelated to this study.

Data sharing
Anonymised data that support the findings of this study can be made available from the investigative team in the following conditions: agreement to collaborate with the study team on all publications; provision of external funding for administrative and investigator time necessary for this collaboration; demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections; and agreement to abide by the terms outlined in data use agreements between institutions.

Acknowledgments
We thank Timothy Frankland, Harpreet S Takhar, Oluwaseye A Ogun, Donald McCarthy, Erin Lopez, Joann M Zamparo, Kajie Pan, and Sharon Gray for assistance with management and data support on this study. We thank Michael Aragones, Soon Kyu Choi, Lee Childs, Julie Stern, Joy Gelfond, Kortney Kottman, Ana Acededo, Jonathan Arguello, Samantha Quinones, Samantha Baluyot, and Elmer Apaya for their technical and laboratory support processing SARS-CoV-2 specimens. We thank Deborah Malden for graphic assistance. We acknowledge Üğur Şahin and Özlem Türeci from BioNTech, the holder of the emergency use authorisation for BNT162b2 in Israel; BNT162b2 is produced with BioNTech proprietary mRNA technology and was developed by BioNTech and Pfizer.

References
1. Viana R, Mayo S, Amsako DG, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. Nature 2022; 603: 679–86.
2. WHO. COVID-19 weekly epidemiological update, edition 74. Published Jan 11, 2022. https://apps.who.int/iris/bitstream/handle/10665/350466/CoV-WeeklySitrep1Jan22-Eng.pdf?sequence=1&isAllowed=y (accessed March 18, 2022).
3. Pfizer. Pfizer and BioNTech provide update on omicron variant. Dec 28, 2021. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-update-on-omicron-variant (accessed January 5, 2022).
4. Cele S, Jackson L, Khoury DS, et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. Nature 2022; 602: 564–56.
5. Nemert I, Kikler L, Lustig Y, et al. Third BNT162b2 vaccination neutralization of SARS-CoV-2 omicron infection. N Engl J Med 2022; 386: 492–94.
6. Schmidt F, Muecksch F, Wesblum Y, et al. Plasma neutralization of the SARS-CoV-2 omicron variant. N Engl J Med 2022; 386: 599–601.
7. Mui A, Liu BG, Ballisich AK, et al. Neutralization of SARS-CoV-2 Omicron by BNT162b2 mRNA vaccine-vaccinated human sera. Science 2022; 375: 678–80.
8. De Marco I, D’Orso S, Pirroirno M, et al. Preserved T cell reactivity to the SARS-CoV-2 Omicron variant indicates continued protection in vaccinated individuals. bioRxiv 2021; published online Dec 30. https://doi.org/10.1101/2021.12.30.474453 (preprint).
9. GeurtzvanKessel CH, Geers D, Schmitz KS, et al. Divergent SARS-CoV-2 omicron-reactive T and B cell responses in COVID-19 vaccine recipients. Sci Immunol 2022; 7: eaba2202.
10. Liu J, Chandrashekar A, Sellers D, et al. Vaccines elicit highly cross-reactive cellular immunity to the SARS-CoV-2 omicron variant. medRxiv 2022; published online Jan 3. https://doi.org/10.1101/2022.01.02.22268634 (preprint).
11. Tarke A, Coelho CH, Zhang Z, et al. SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from alpha to omicron. Cell 2022; 185: 847–59.
12. Keeton R, Tincho MB, Ngomti A, et al. T cell responses to SARS-CoV-2 spike cross-recognize Omicron. Nature 2022; 603: 488–92.
13. Collie S, Champion J, Moultrie H, Bekker L-G, Gray G. Effectiveness of BNT162b2 vaccine against omicron variant in South Africa. N Engl J Med 2021; 386: 494–96.
14. Thompson MG, Natarajan K, Irving SA, et al. Effectiveness of a third dose of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance – VISION Network, 10 States, August 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022; 71: 255–63.
15. Ferrándiz M, Rao S, Dixon BF, et al. Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance — VISION Network, 10 States, August 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022; 71: 255–63.
16. Danza P, Koo TH, Hadidi M, et al. SARS-CoV-2 infection and hospitalization among adults aged ≥18 years, by vaccination status, before and during SARS-CoV-2 B.1.1.529 (omicron) variant predominance — Los Angeles County, California, November 7, 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022; 71: 177–81.
17. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England. Technical Briefing 34: update on hospitalisation and vaccine effectiveness for Omicron VOC-21NOV-01 (B.1.529). Dec 31, 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1044481/Technical-Briefing-31-Dec-2021-Omicron-severity_update.pdf (accessed Jan 15, 2022).
18. Tsieng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and delta variants. N Engl J Med 2022; published online Feb 21. https://doi.org/10.1056/s Ian12/012-07573-y.
19. Buchan SA, Chung H, Brown KA, et al. Effectiveness of COVID-19 vaccines against Omicron or Delta infection. medRxiv 2022; published online Jan 1. https://doi.org/10.1101.2021.12.30.21268563 (preprint).
20. Chemaitelly H, Ayyoub FH, AlMukdad S, et al. Duration of protection of BNT162b2 and mRNA-1273 COVID-19 vaccines against symptomatic SARS-CoV-2 Omicron infection in Qatar. medRxiv 2022; published online Feb 8. https://doi. org/10.1101/2022.02.07.22270568 (accessed March 18, 2022).
21. Hansen CH, Schelde AB, Moutsen-Helm IR, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: a Danish cohort study. medRxiv 2021; published online Dec 22. https://doi.org/10.1101/2021.12.20.21267966 (preprint).
22. Accorsi ER, Britton A, Fleming-Dutra KE, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 omicron and delta variants. JAMA 2022; 327: 639–51.
23. Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. N Engl J Med 2022; published online March 2. https://doi.org/10.1056/ NEJMoa219451.
24. UK Health Security Agency. Effectiveness of 3 doses of COVID-19 vaccines against symptomatic COVID-19 and hospitalisation in adults aged 65 years and older, Jan 7, 2022. https://www.gov.uk/guidance/monitoring-reports-of-the-effectiveness-of-covid-19-vaccination (accessed Jan 10, 2022).
25. Koenbick C, Langer-Gould AM, Gould MK, et al. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. Perm J 2022; 16: 37–41.
26. Wolter N, Wasilla Jassat, Sibongile Walaza, et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. Lancet 2022; 399: 437–46.
27 Scott L, Hsiao NY, Moyso S, et al. Track Omicron’s spread with molecular data. Science 2021; 374: 1454–55.

28 Tartof SY, Slezak JM, Fischer H, et al. Safety and efficacy of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet 2021; 398: 1407–16.

29 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.

30 Turner JS, O’Halloran JA, Kalaidina E, et al. SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses. Nature 2021; 596: 109–13.

31 Arunachalam PS, Scott MKD, Hagan T, et al. Systems vaccinology of the BNT162b2 mRNA vaccine in humans. Nature 2021; 596: 410–16.

32 Teijaro JR, Farber DL. COVID-19 vaccines: modes of immune activation and future challenges. Nat Rev Immunol 2021; 21: 195–97.

33 Bruvoort KJ, Ackerson B, Sy LS, et al. Recombinant adjuvanted zoster vaccine and reduced risk of COVID-19 diagnosis and hospitalization in older adults. J Infect Dis 2021; published online Dec 28. https://doi.org/10.1093/infdis/jiaa633.

34 Pozzetto B, Legros V, Djebali S, et al. Immunogenicity and efficacy of heterologous ChAdOx1-BNT162b2 vaccination. Nature 2021; 600: 701–06.

35 Parry H, Bruton R, Stephens C, et al. Differential immunogenicity of BNT162b2 or ChAdOx1 vaccines after extended-interval homologous dual vaccination in older people. Immun Ageing 2021; 18: 34.

36 Barros-Martins J, Hammerschmidt SI, Cossmann A, et al. Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. Nat Med 2021; 27: 1525–29.

37 Liu X, Shaw RH, Stuart ASV, et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. Lancet 2021; 398: 856–69.

38 Munro APS, Janani L, Cornelius V, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet 2021; 398: 2258–76.

39 Atmar RL, Lyke KE, Deming ME, et al. Homologous and heterologous Covid-19 booster vaccinations. N Engl J Med 2022; 386: 1046–57.

40 GeurtsvanKessel CH, Geers D, Schmitz KS, et al. Divergent SARS-CoV-2 Omicron-reactive T- and B cell responses in COVID-19 vaccine recipients. Sci Immunol 2022; published online Feb 3. https://doi.org/10.1126/sciimmunol.abo2202.

41 Bar-On Y, Goldberg Y, Mandel M, et al. Protection by 4th dose of BNT162b2 against Omicron in Israel. medRxiv 2022; published online Feb 1. https://doi.org/10.1101/2022.02.01.22270232 (preprint).

42 De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. Euro Surveill 2013; 18: 20583.

43 Haber M, An Q, Foppa IM, Shay DK, Ferdinands JM, Orenstein WA. A probability model for evaluating the bias and precision of influenza vaccine effectiveness estimates from case-control studies. Epidemiol Infect 2015; 143: 1417–26.

44 Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine 2013; 31: 2165–68.

45 Lipstitch M, Jha A, Simonsen L. Observational studies and the difficult quest for causality: lessons from vaccine effectiveness and impact studies. Int J Epidemiol 2016; 45: 2060–74.

46 Juliano AD, Brunkard JM, Boehmer TK, et al. Trends in disease severity and health care utilization during the early omicron variant period compared with previous SARS-CoV-2 high transmission periods - United States, December 2020-January 2022. MMWR Morb Mortal Wkly Rep 2022; 71: 146–52.