Effectiveness of a third dose of BNT162b2 mRNA COVID-19 vaccine in a large US health system: A retrospective cohort study

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Summary

Background Globally, recommendations are expanding for third (booster) doses of BNT162b2 (Pfizer–BioNTech). In the United States, as of November 19, 2021, boosters were recommended for all adults aged 18 years and older. We evaluated the effectiveness of a third dose of BNT162b2 among adults in a large US integrated health system.

Methods In this retrospective cohort study, we analyzed electronic health records from Kaiser Permanente Southern California between Dec 14, 2020 and Dec 5, 2021 to assess vaccine effectiveness (VE) of two and three doses of BNT162b2 against SARS-CoV-2 infections (without hospital admission) and COVID-19-related hospital admission. VE was calculated using hazards ratios from adjusted Cox models.

Findings After only two doses, VE against infection declined from 85% (95% CI 83–86) during the first month to 49% (46–51) ≥ 7 months following vaccination. Overall VE against hospitalization was 90% (95% CI 86–92) within one month and did not wane, however, effectiveness against hospitalization appeared to wane among immunocompromised individuals but was not statistically significant (93% [72–98] at 1 month to 74% [45–88] after ≥ 7 months; p=0.490). Three-dose VE (median follow-up 13 months [SD 6]) was 88% (95% CI 86–89) against infection and 97% (95–98) against hospitalization. Effectiveness after three doses was higher than that seen one month after receiving only two doses for both outcomes. Relative VE of three doses compared to two (with at least six months after the second dose) was 75% (95% CI 71–78) against infections and 70% (48–83) against hospital admissions.

Interpretation These data support the benefit of broad BNT162b2 booster recommendations, as three doses confers comparable, if not better, protection against SARS-CoV-2 infections and hospital admission as was seen soon after receiving two doses.

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Introduction

BNT162b2 mRNA vaccine (tozinameran, Pfizer–BioNTech) has been shown to be highly effective in both clinical and real-world settings. By June and July 2021, five to six months after the introduction of the vaccine across the globe, the SARS-CoV-2 delta variant became
Research in context

Evidence before this study
Following the introduction of a BNT162b2 booster program in Israel, several studies have shown that a third dose of the vaccine improves protection against SARS-CoV-2 infections and severe disease, compared to individuals who received only two doses of the vaccine at least 5 months ago. Data about the effectiveness of BNT162b2 booster campaigns in the United States and elsewhere, however, are limited.

Added value of this study
We evaluated the effectiveness of a third dose of BNT162b2 in a large United States integrated health system. Our results confirm that effectiveness wanes after receipt of two doses of BNT162b2 and that being immunised with a third dose of BNT162b2 confers comparable, if not better, protection against SARS-CoV-2 infections and COVID-19 hospital admissions as was seen in the first few months after receiving two doses. Importantly, these findings confirm that three doses confer high protection against the delta variant, which accounted for >99% of infections in the United States during the time when third doses were administered in our study. Unlike prior studies, however, we further provide effectiveness estimates for three doses compared to unvaccinated individuals to provide helpful context and support the interpretation of our findings. Compared to the unvaccinated, effectiveness of being immunised with a third dose of BNT162b2 was 88% (95% CI 86–89) against infections not requiring hospital admission, 90% (88–92) against symptomatic COVID-19 not requiring hospital admission, and 97% (95–98) against COVID-19-related hospital admissions among all adults aged ≥18 years.

Implication of all the available evidence
Data from this study, combined with the improved immunogenicity, high efficacy, and tolerable safety profile of a third BNT162b2 dose observed in the clinical trial setting and with preliminary real-world data from the BNT162b2 booster program in Israel, support the benefit of broad age-based recommendations for third doses—especially in the context of the delta variant and introduction of the highly transmissible omicron variant. Additional studies evaluating the real-world effectiveness of both two and three doses of BNT162b2 against the newly emerged omicron variant are still needed.

In a recent publication we showed that reductions in BNT162b2 effectiveness over time were primarily due to waning immunity rather than the delta variant escaping vaccine protection. We, thus, proposed that third (booster) doses of BNT162b2 would likely be needed to restore initial high levels of protection. Clinical studies demonstrating improved immunogenicity and efficacy following a third dose of BNT162b2 subsequently informed Emergency Use Authorization for third dose use and supported global recommendations for booster doses. Israel was the first country to implement a widespread BNT162b2 third dose programme and by August 30, all Israeli citizens ≥12 years of age were eligible. Early estimates showed that a third dose of BNT162b2 restored high levels of protection and led to significantly lower rates of SARS-CoV-2 infection, symptomatic COVID-19, and severe illness compared to individuals who only had two doses.

On August 12, 2021, the US Food and Drug Administration (FDA) amended the emergency use authorization for BNT162b2 to allow the use of a third dose in immunocompromised individuals. On September 22, 2021, FDA authorized third doses for all adults aged 65 years and older and for adults 18–64 years of age at high-risk of severe disease or institutional and/or occupational exposure. FDA and CDC expanded eligibility for a third dose to all individuals aged 18 years and older on November 19 and to everyone aged 16 years and older on December 15, 2021.

Despite early encouraging data from Israel, real-world data about the effectiveness of BNT162b2 booster campaigns in the United States and elsewhere are limited. We evaluated the vaccine effectiveness (VE) of a third dose of BNT162b2 in a large United States integrated health system.

Methods

Study design and participants
In this retrospective cohort study, we analyzed electronic health records from the Kaiser Permanente Southern California (KPSC) health-care system (CA, USA) to assess effectiveness of a third dose of BNT162b2 against SARS-CoV-2 infections and COVID-19-related hospital admissions. KPSC is an integrated health-care organization with more than 4.7 million members, representative of the socioeconomic, racial, and ethnic diversity of the area’s population. KPSC electronic health records integrate clinical data across all settings of care, including care delivered to members outside of the KPSC system.

The study population consisted of all KPSC members aged 18 years and older with at least 1 year of membership (allowing a 31-day gap during previous membership to allow for potential delays in renewal) to the predominant strain worldwide. Subsequently, reports describing reduced effectiveness of BNT162b2 (and other COVID-19 vaccines) against SARS-CoV-2 infections began to surface and there was concern that infections with delta could evade vaccine-induced immunity.
determine comorbidities and medical history. Patients with a documented request to be removed from all research studies were excluded. The start of the study period (December 14, 2020) corresponded to the date the first doses of BNT162b2 were administered to KPSC members. The study protocol was reviewed and approved by the KPSC institutional review board which waived requirement for informed consent (number 12816).

Procedures
COVID-19 vaccines were provided to KPSC members free-of-charge. COVID-19 vaccines administered to members outside of the KPSC system during the study period were captured using batch queries to the California Immunisation Registry. California providers are required by law to report all COVID-19 vaccine administriations to the registry every 24 h.

The primary exposure was being immunised with three doses of BNT162b2, defined as receiving a third dose of BNT162b2 at least 21 days after receiving two doses of BNT162b2 with at least 14 days after the third dose. Only individuals vaccinated with a third dose of BNT162b2 after August 12, 2021 (the first FDA authorization) were included in the third dose analysis. Individuals who received a third dose of BNT162b2 prior to this date, who had a third dose < 21 days after their second dose of BNT162b2, or who received a COVID-19 vaccine third dose that was not BNT162b2 were censored from the analysis. Immunisation with only two doses of BNT162b2 was defined as receiving two doses of BNT162b2 with 7 days or more after the second dose (and no third dose). This was consistent with our previous definition and the pivotal randomized clinical trial definition of “fully vaccinated.” Individuals were considered unvaccinated until receipt of their first dose of BNT162b2, or censoring at disenrollment, death, or receipt of another COVID-19 vaccine.

Outcomes
Similar to our previous analysis, our two main outcomes (which were mutually exclusive) were (i) SARS-CoV-2 infection defined as testing positive for SARS-CoV-2 via a PCR test from any sample regardless of the presence of symptoms and without hospital admission, and (ii) COVID-19-related hospital admission defined as a hospital admission with a positive SARS-CoV-2 PCR test that was conducted between 14 days before and 3 days after the date of hospital admission.

Statistical analysis
Using descriptive statistics, we detailed the distribution of demographic and clinical characteristics of the study cohort by BNT162b2 vaccination status and history of SARS-CoV-2 infection. Median time since being immunised with three doses and with only two doses as well as the time between receipt of second and third doses of BNT162b2 was also described. Hazard ratios (HRs) with 95% CIs from Cox models with time-varying covariates were estimated comparing rates of SARS-CoV-2 infection and COVID-19 hospital admissions among individuals who were immunised with three doses or two doses compared to those who were unvaccinated. Further, among a population restricted to individuals immunised with at least two doses at least six months ago (i.e., eligible for a third dose in the United States), we estimated HRs for relative effectiveness of a third BNT162b2 dose versus two BNT162b2 doses, as has been done in other studies.

BNT162b2 vaccination status was categorized as time-varying, with all participants entering the cohort as unvaccinated. As participants received vaccines over time, their vaccination exposure status changed accordingly, contributing person-time to the partially vaccinated category after their first dose, the fully vaccinated with two doses category ≥ 7 days following their second dose, and so on. Follow-up time was censored at the time of disenrollment from KPSC, death, receipt of any other newly licensed or investigational COVID-19 vaccine or prophylactic agent other than BNT162b2, receipt of a third dose of BNT162b2 prior to August 12, 2021 or < 21 days after a second dose of BNT162b2, receipt of a non-BNT162b2 COVID-19 vaccine, or receipt of more than three doses of BNT162b2. Unexposed person-time consisted of follow-up time of those never vaccinated against COVID-19, as well as time contributed by participants before being vaccinated or censored. Calendar time was included in all models to allow the baseline hazard to vary flexibly as vaccine eligibility, testing practices, non-pharmaceutical interventions, lockdown requirements, disease activity, and COVID-19 treatment changed over time. As done previously, we assessed durability of VE of 2 doses at monthly intervals for individuals who were immunised with two doses of BNT162b2. Effectiveness over time was not assessed for third doses since the recommendation was only recently made available in the United States and thus there was insufficient follow-up time to determine durability of a third dose protection.

Adjusted HRs and 95% CIs were estimated by including all measured covariates in the Cox models with time-varying vaccination status. Variables included in the multivariable models are shown in Table 1. Participants who had immunocompromised conditions or received immunosuppressive medications in the year prior to index date were defined as having immunocompromised status using an algorithm modified slightly from that described in a landmark study from Greenberg and colleagues (Appendix Table 1a–c). Robust variance was computed to account for clustering introduced by including neighbourhood deprivation index in the model. For all models, VE was calculated
### BNT162b2 vaccination status

| Unvaccinated (n=1 959 271) | Partially vaccinated (n=68 667) | Two doses (only) plus ≥7 days (n=829 100) | Three doses plus ≥14 days (n=276 037) |
|---------------------------|---------------------------------|------------------------------------------|----------------------------------------|
| Age, years                |                                 |                                          |                                        |
| 18–44                     | 887400 (45.3%)                  | 36100 (52.6%)                            | 432092 (52.1%)                         |
| 45–64                     | 653633 (33.4%)                  | 28850 (33.3%)                            | 286114 (34.5%)                         |
| ≥65                       | 418238 (21.3%)                  | 9717 (14.2%)                             | 110894 (13.4%)                         |
| ≥75                       | 166750 (8.5%)                   | 3508 (5.1%)                              | 43008 (5.2%)                           |
| Sex                       |                                 |                                          |                                        |
| Male                      | 1004582 (51.3%)                 | 35126 (51.2%)                            | 454281 (54.8%)                         |
| Female                    | 954589 (48.7%)                  | 33535 (48.8%)                            | 374782 (45.2%)                         |
| Race/ethnicity            |                                 |                                          |                                        |
| Asian                     | 1900286 (9.7%)                  | 7198 (10.5%)                             | 99906 (1.2%)                           |
| Black                     | 163439 (8.3%)                   | 5868 (8.5%)                              | 62887 (7.6%)                           |
| Hispanic                  | 761359 (38.9%)                  | 29905 (43.6%)                            | 365712 (44.1%)                         |
| Other                     | 443356 (2.3%)                   | 1629 (2.4%)                              | 20127 (2.4%)                           |
| Normal or healthy weight (18.5-24.9) | 494391 (25.2%)                 | 18044 (26.3%)                            | 214061 (25.8%)                         |
| Overweight (25.0-29.9)    | 608290 (31%)                    | 21205 (30.9%)                            | 258305 (31.2%)                         |
| Obese, class 1 (30.0-49)  | 391103 (20%)                    | 13311 (19.4%)                            | 166114 (20%)                           |
| Obese, class 2-3 (>35.0)  | 304321 (15.5%)                  | 10291 (15%)                              | 128566 (15.5%)                         |
| Unknown                   | 132618 (6.8%)                   | 4740 (6.9%)                              | 49916 (6%)                             |
| Comorbidities             |                                 |                                          |                                        |
| Hypertension              | 438234 (22.4%)                  | 11763 (17.1%)                            | 144328 (17.4%)                         |
| Congestive heart failure  | 42092 (2.1%)                    | 1090 (1.6%)                              | 11772 (1.4%)                           |
| Myocardial infection      | 25531 (1.3%)                    | 651 (1%)                                 | 7065 (0.9%)                            |
| Peripheral vascular disease| 172295 (8.8%)                   | 3961 (5.8%)                              | 46259 (5.6%)                           |
| Cerebrovascular disease   | 32907 (1.7%)                    | 921 (1.3%)                               | 9965 (1.2%)                            |
| Diabetes with unknown glycated haemoglobin | 23933 (1.2%)                     | 794 (1.2%)                               | 8499 (1%)                              |
| Diabetes with glycated haemoglobin <7.5% | 148609 (7.6%)                  | 3893 (5.7%)                              | 47919 (5.8%)                           |
| Diabetes with unknown glycated haemoglobin ≥7.5% | 80550 (4.1%)                     | 2373 (3.5%)                              | 27921 (3.4%)                           |
| Chronic obstructive pulmonary disease | 178711 (9.1%)                     | 5625 (8.2%)                              | 66461 (8%)                             |
| Renal disease             | 101925 (5.2%)                   | 2414 (3.5%)                              | 27817 (3.4%)                           |

### SARS-COV-2 outcomes

| Uninfected (n=919 754) | SARS-CoV-2 infection (n=197 535) | COVID-19 hospital admission (n=15 786) | Total (N=3 133 075) |
|-------------------------|---------------------------------|----------------------------------------|----------------------|
| Age, years              |                                 |                                        |                      |
| 18–44                   | 1297716 (44.4%)                 | 104848 (52.9%)                         | 3361 (21.3%)         |
| 45–64                   | 976165 (33.4%)                  | 69311 (35.1%)                         | 5767 (36.5%)         |
| ≥65                     | 654873 (22.1%)                  | 23740 (12%)                           | 6658 (42.2%)         |
| ≥75                     | 254515 (8.7%)                   | 7487 (3.8%)                           | 3436 (21.8%)         |
| Sex                     |                                 |                                        |                      |
| Male                    | 1534845 (52.6%)                 | 108696 (55%)                          | 7268 (46%)           |
| Female                  | 1384766 (47.4%)                 | 88834 (45%)                           | 8518 (54%)           |
| Race/ethnicity          |                                 |                                        |                      |
| Asian                   | 332683 (11.4%)                  | 12271 (6.2%)                          | 1306 (8.3%)          |
| Black                   | 236484 (8.1%)                   | 14341 (7.3%)                          | 1625 (10.3%)         |
| Hispanic                | 1119807 (38.4%)                 | 107989 (54.6%)                        | 8264 (52.4%)         |
| Other                   | 67398 (2.3%)                    | 3910 (2%)                             | 188 (1.2%)           |
| Pacific Islander        | 21892 (0.7%)                    | 1362 (0.7%)                           | 71496 (2.3%)         |
| Unknown                 | 158423 (5.4%)                   | 6872 (3.5%)                           | 165483 (5.3%)        |
| Body-mass index, kg/m²  |                                 |                                        |                      |
| Underweight (<18.5)     | 43187 (1.5%)                    | 1718 (0.9%)                           | 156 (1%)             |
| Normal or healthy weight (18.5-24.9) | 761462 (26.1%)                 | 39150 (19.8%)                         | 2212 (14%)           |
| Overweight (25.0-29.9)  | 917361 (31.4%)                  | 62065 (31.4%)                         | 4436 (28.1%)         |
| Obese, class 1 (30.0-49) | 574903 (19.7%)                  | 47460 (24%)                           | 4052 (25.7%)         |
| Obese, class 2-3 (>35.0) | 437537 (15%)                    | 41064 (20.8%)                         | 4606 (29.2%)         |
| Unknown                 | 185104 (6.3%)                   | 6078 (3.1%)                           | 324 (2.1%)           |
| Comorbidities           |                                 |                                        |                      |
| Hypertension            | 665045 (22.8%)                  | 37226 (18.8%)                         | 7721 (48.9%)         |
| Congestive heart failure | 60720 (2.1%)                    | 2832 (1.4%)                           | 1600 (10.1%)         |
| Myocardial infection    | 37243 (1.3%)                    | 1731 (0.9%)                           | 750 (4.8%)           |
| Peripheral vascular disease | 265294 (9.1%)                  | 10650 (5.4%)                          | 4047 (25.6%)         |
| Cerebrovascular disease | 49015 (1.7%)                    | 2182 (1.1%)                           | 868 (5.5%)           |
| Diabetes with unknown glycated haemoglobin | 33689 (1.2%)                     | 2074 (1%)                             | 425 (2.7%)           |
| Diabetes with glycated haemoglobin <7.5% | 226152 (9.1%)                  | 13888 (7%)                            | 3135 (19.9%)         |
| Diabetes with unknown glycated haemoglobin ≥7.5% | 152321 (5.2%)                  | 6539 (3.3%)                           | 3102 (19.7%)         |

Table 1 (Continued)
as: (1−HR) multiplied by 100%. Aligning with evolving BNT162b2 third dose recommendations in the United States, we ran stratified analyses of VE for age groups 18–64 years, 65 years and older, and by immunocompromising status. Given that some studies have suggested BNT162b2 effectiveness against hospital admission may be lower or have more pronounced waning in individuals 75 years and older,39 we also ran stratified analyses for this age group. Statistical comparisons of VE by time since vaccination were made using Wald $\chi^2$ tests for contrasts within Cox models. All analyses were performed using SAS Enterprise Guide statistical software, version 7.1 Table 2.

This study was registered with ClinicalTrials.gov, NCT04848584.

Role of the funding source
The funder of the study approved the study design, participated in data interpretation, and writing of the report.

Results
The study period ran from December 14, 2020 to December 5, 2021. As of December 5, 2021, of 3 606 667 individuals assessed for eligibility, 3 133 075 (86.9%) members met the inclusion criteria. Median age was 45 years (IQR 33–62) and 1 482 118 (47.3%) participants were male. 1 235 969 (39.4%) participants were Hispanic, 1 037 984 (33.1%) were white, 346 260 (11.1%) were Asian, and 252 450 (8.1%) Black, and 260 412 (8.3%) were Pacific Islander, Native American, or ‘Other’. In the year before the study start date, 70 976 (2.3%) of 3 133 075 participants had one or more positive SARS-CoV-2 PCR tests (Table 1).

During the study period, 197 535 (6.3%) of 3 133 075 participants were infected with SARS-CoV-2, among whom 15 786 (8.6%) were admitted to hospital. A higher proportion of the individuals infected with SARS-CoV-2 were younger (median age 44 years vs 48 years), and obese (> 30 kg/m²; 44.8% vs 34.6%) than those who were not infected. Among those infected with SARS-CoV-2, a higher proportion of those who were admitted to hospital for COVID-19 were older, male, had comorbidities, had Charlson Index score ≥ 4, and had greater previous health-care utilisation than those not admitted to hospital (Tables 1, Appendix 2). Based on unpublished but internally validated natural language processing algorithms to detect COVID-related symptoms, 91% of both positive SARS-CoV-2 infections and hospital admissions were symptomatic.

By December 5, 2021, 1 173 804 (37.5%) of 3 133 075 cohort members had received one or more doses of BNT162b2 (1 063 877 received ≥ 1 dose of mRNA-1273 [Moderna], 129 490 Ad26.COV2.S [Janssen], 533 other COVID-19 vaccines or mixed regimens, and 765 371
| Unvaccinated | Immunized with 2 doses with ≥6 mos after 2nd dose | Immunized with 3 doses | Adjusted VE of 3 doses relative to unvaccinated | Adjusted VE of 3 doses relative to ≥6 mos after 2nd dose |
|--------------|-----------------------------------------------|------------------------|----------------------------------|----------------------------------|
| Cases | Person Years | Rate per 100 000 person-years | Cases | Person Years | Rate per 100 000 person-years | Cases | Person Years | Rate per 100 000 person-years | Cases | Person Years | Rate per 100 000 person-years |
| SARS-CoV-2 infection |
| Age, years | | | | | | | | | | | |
| ≥18 | 166671 | 1254548 | 13285.3 | 4070 | 108473 | 3752.1 | 183 | 26406 | 693.0 | 88 (86-89) | 75 (71-78) |
| 18 – 64 | 148151 | 1068390 | 13866.8 | 3230 | 77789 | 4152.3 | 96 | 11378 | 843.7 | 89 (87-91) | 77 (71-81) |
| ≥65 | 18520 | 186158 | 9948.5 | 840 | 30683 | 2737.7 | 87 | 15028 | 578.9 | 89 (86-91) | 78 (72-82) |
| ≥75 | 5724 | 68547 | 8350.5 | 257 | 12845 | 2000.8 | 33 | 5776 | 571.3 | 86 (79-90) | 70 (56-79) |
| Immunocompromised | 4169 | 28151 | 14809.4 | 129 | 2997 | 4304.3 | 22 | 1892 | 1162.8 | 84 (75-90) | 68 (49-80) |
| Non-immunocompromised | 162502 | 1226398 | 13250.3 | 3941 | 105476 | 3736.4 | 161 | 24513 | 656.8 | 88 (86-90) | 76 (72-79) |
| COVID-19 hospital admission |
| Age, years | | | | | | | | | | | |
| ≥18 | 13910 | 1315744 | 1057.2 | 172 | 113490 | 151.6 | 14 | 27163 | 51.5 | 97 (95-98) | 70 (48-83) |
| 18 – 64 | 8291 | 1125783 | 736.5 | 52 | 81993 | 63.4 | 6 | 11809 | 50.8 | 95 (89-98) | 28 (-68-69) |
| ≥65 | 5619 | 189962 | 2958.0 | 120 | 34198 | 381.0 | 8 | 15354 | 52.1 | 97 (95-99) | 83 (64-92) |
| ≥75 | 2812 | 69427 | 4050.3 | 80 | 13083 | 611.5 | 4 | 5864 | 68.2 | 97 (92-99) | 86 (62-95) |
| Immunocompromised | 998 | 29276 | 3408.9 | 22 | 3125 | 704.0 | 6 | 1941 | 309.1 | 87 (70-95) | 55 (-11-82) |
| Non-immunocompromised | 12912 | 1286468 | 1003.7 | 150 | 110365 | 135.9 | 8 | 25222 | 31.7 | 98 (96-99) | 79 (56-90) |

Table 2: Relative vaccine effectiveness (VE) of BNT162b2 of three doses versus unvaccinated, and three doses versus two doses at least 6 months prior.

Note: Regression models were adjusted for all variables described in Table 1.
remained unvaccinated). Of these, 829 100 (26.5%) of 3 133 075 were immunised with only two doses of BNT162b2, and 276 037 (8.8%) were immunised with three BNT162b2 doses after August 12, 2021 (Table 1). Only 3.5% (10 035 / 276 037) were vaccinated with a third dose less than 6 months after receipt of the second dose. Median time since being immunised with three doses (14 days after third dose) was 1.3 months (SD 0.6). Median time since being immunised with only two doses (7 days after second dose) was 7.1 months (SD 2.4). Among individuals who received three doses, median time between receipt of the second and third dose was 7.4 months (SD 1.1).

Similar to our previous analysis, among those who were immunised with only two doses of BNT162b2, VE against infection decreased with increasing time since vaccination, declining from 85% (95% CI 81–86) during the first month after being immunised (7 to 36 days after the second dose) to 49% (46–51) after 27 months (217 days after second dose, p<0.0001; Figures 1a, Appendix 1a, Appendix Table 3a). Effectiveness of immunisation with only two doses waned for individuals aged 18–64 years and 65 years and older (Figure 2a and c, Appendix Table 3a) and for both immunocompromised and non-immunocompromised groups (Figure 3a and c, Appendix Table 3c).

Among all adults who were immunised with only two doses, overall adjusted VE estimates for COVID-19 hospital admissions were 90% (95% CI 86–92) within 1 month, and 88% (85–90) at ≥27 months, showing no significant waning (p=0.004; Figures 2b, Appendix 1b, Appendix Table 3b). For immunocompromised patients, VE fell from 93% (95% CI 72–98) at 1 month after being immunised with two doses to 74% (45–88) after ≥27 months, however, this finding was not statistically significant (p=0.490; Figure 3b, Appendix Table 3c).

Individuals who were immunised with three doses of BNT162b2 had an adjusted VE of 88% (95% CI 86–89) against SARS-CoV-2 infections and 97% (95–98) against COVID-19-related hospital admissions (Figures 1a and b; Appendix 1a and b, Appendix Table 3a and b). Estimates of three-dose VE against infections were similar across age groups and immunocompromising status, with VE ranging from 84 to 89% (Figures 2, 3, Appendix Table 3a and c). Among adults aged 65 years and older, VE against infections after three doses (89% [95% CI 86–91]) was higher than VE in the first month after being immunised with only two doses (85% [95% CI 74–85], p <0.001; Figure 2c, Appendix Table 3a). Estimates of three-dose VE against hospital admission was similar across age groups (VE of 97% for age groups 18 years and older, 65 years and older, and 75 years and older; Figures 1e, Appendix Table 3b) and slightly lower for immunocompromised patients versus those who were not (87% [95% CI 70–95] vs 98% [96–99]; Figure 3b and d, Appendix Table 3c). Among all adults, VE against hospitalization with three doses (97% [95% CI 95–98]) was higher compared to VE one month after only two doses (90% [86–92], p =0.002). Given that 91% of all infections were symptomatic, we did not see a notable difference in adjusted effectiveness of three doses against symptomatic COVID-19 (90% [95% CI 88–92]) and all SARS-CoV-2 infections (88% [86–89]). Similarly, effectiveness against hospital admission with COVID-19 symptoms mirrored that of effectiveness for all admissions with a positive SARS-CoV-2 test. VE against hospital admission with COVID-19 symptoms was 91% (95% CI 88–93) one month after being immunized with two doses and 97% (95–98) after three doses.

The relative VE comparing adults immunised with three doses to those who had only two doses of BNT162b2 with at least 6 months since receipt of the second dose was 75% (95% CI 71–78) and 70% (48–83) against infections and hospital admissions, respectively (Appendix Table 3a and b). Relative VE of a third dose versus two doses was highest for preventing hospital admissions among the elderly (65 years and older: 83% [95% CI 64–92]; 75 years and older: 86% [95% CI 62–95]; Tables 2, Appendix 3b).

Discussion

Waning of vaccine-induced immunity after two doses of BNT162b2 has been demonstrated in a variety of settings and against several SARS-CoV-2 outcomes, and was further supported by the data in this study. Further, we found that a third (booster) dose of BNT162b2, now recommended by CDC for all US individuals aged 16 years and older, restored high levels of protection against SARS-CoV-2 infections and COVID-19 hospital admissions in a large population of US adults aged 18 years and older.

In an extension to our previous analysis, our results showed that among all adults aged 18 years and older, VE of only two doses of BNT162b2 against infection fell from 85% (95% CI 81–86) at 1 month to 49% (46–51) after ≥27 months. However, after being immunised with a third dose, VE against infections was restored to 88% (95% CI 86–89) over a median follow-up time of 13 months after being fully immunised with a third dose. This trend was seen across age groups and regardless of immunocompromising status. Among adults aged 65 years and older, VE against infections with three doses (85% [95% CI 86–91]) was higher than the VE in the first month after being immunised with only two doses (80% [95% CI 74–85]).

The public health impact of a third dose to prevent severe disease is substantial. We estimated that the rate of hospital admission among all adults aged 18 years and older at least 6 months after their second dose was 154 per 100,000 person-years, and that for those with 3 doses was 52 per 100,000 person-years. Therefore, among all adults, the absolute rate reduction for
Figure 1. Vaccine effectiveness of 2- and 3-doses of BNT162b2 against (A) SARS-CoV-2 infections and (B) COVID-19 hospital admissions — December 14, 2020 to December 5, 2021.

*Blue circles represent 2-dose VE estimates, and the yellow circles represent 3-dose VE estimates. The bars represent 95% confidence intervals. Estimates are adjusted for age, sex, race/ethnicity, body mass index, comorbidities, Charlson comorbidity index, previous SARS-CoV-2 PCR, previous positive SARS-CoV-2 serology, influenza vaccine in year prior, pneumococcal vaccine in prior 5 years, neighborhood deprivation index, prior healthcare utilization (Tables 1, Appendix 2).
Figure 2. Vaccine effectiveness (VE) of 2- and 3-doses of BNT162b2 against SARS-CoV-2 infections and COVID-19 hospital admissions by age group — December 14, 2020 to December 5, 2021. (A) VE against infections among individuals aged 18–64 years; (B) VE against hospital admissions among individuals aged 18–64 years; (C) VE against infections among individuals aged 65 years and older; (D) VE against hospital admissions among individuals aged 65 years and older; (E) VE against infections among individuals aged 75 years and older; (F) VE against hospital admissions among individuals aged 75 years and older.

*Blue circles represent 2-dose VE estimates, and the yellow circles represent 3-dose VE estimates. The bars represent 95% confidence intervals. Estimates are adjusted for age, sex, race/ethnicity, body mass index, comorbidities, Charlson comorbidity index, previous SARS-CoV-2 PCR, previous positive SARS-CoV-2 serology, influenza vaccine in year prior, pneumococcal vaccine in prior 5 years, neighborhood deprivation index, prior healthcare utilization (Tables 1, Appendix 2).

Figure 3. Vaccine effectiveness (VE) of 2- and 3-doses of BNT162b2 against SARS-CoV-2 infections and COVID-19 hospital admissions by immunocompromising status — December 14, 2020 to December 5, 2021. (A) VE against infections among immunocompromised; (B) VE against hospital admissions among immunocompromised; (C) VE against infections among non-immunocompromised; (D) VE against hospital admissions among non-immunocompromised.

*Blue circles represent 2-dose VE estimates, and the yellow circles represent 3-dose VE estimates. The bars represent 95% confidence intervals. Estimates are adjusted for age, sex, race/ethnicity, body mass index, comorbidities, Charlson comorbidity index, previous SARS-CoV-2 PCR, previous positive SARS-CoV-2 serology, influenza vaccine in year prior, pneumococcal vaccine in prior 5 years, neighborhood deprivation index, prior healthcare utilization (Tables 1, Appendix 2).
The estimated relative effectiveness of a third dose observed in our study (which represents the relative further reduction in rates of SARS-CoV-2 infections and COVID-19 infections when giving a booster dose to individuals who were immunized with only two doses at least 6 months ago) was 70 to 78% against infections and 70 to 86% against hospital admissions across age groups. These estimates of relative effectiveness are slightly higher than those observed in an unpublished study of US Veterans, and slightly lower than those observed in the randomized clinical trial setting and in reports from Israel. Differences in estimated relative VE observed in our study versus the clinical trial are likely primarily explained by the fact that the average time between receipt of the second and third doses in our study was around 7 months but was longer (around 10 months; i.e., more waning after the second dose) in the clinical trial. In addition, we measured effectiveness against SARS-CoV-2 infections (both symptomatic and asymptomatic illness), while the clinical trial evaluated effectiveness against symptomatic COVID-19 only, where the impact of vaccination may be larger. In Israel, more healthy young individuals have received a booster dose compared to the US booster program which primarily targeted the elderly and high-risk during the time our study was conducted. Thus, subtle differences in relative VE across studies are likely explained by differences in study populations and endpoints, time since receipt of the second dose, and disease activity at the time of study conduct. Importantly, all studies that have evaluated relative VE of a third dose—including ours—have shown a meaningful improvement in VE against a broad range of SARS-CoV-2 outcomes. Unlike prior studies, however, we further provide estimates for three doses compared to unvaccinated individuals to provide helpful context and support the interpretation of our findings.

VE against hospital admission after two doses did not wane to the same extent as VE against infection waned. Waning of VE against hospital admission over 7 months was not observed in our combined overall estimate. However, VE against hospital admission appeared to wane from the first month to up to 8 months for immunocompromised patients (93% to 74%), although this finding was not statistically significant. Notably, among all adults, VE against hospitalization after being immunized with a third dose (97% [95% CI 95–98]) was significantly higher than VE in the first month after being immunized with only two doses (90% [86–92]). High VE after a third dose against both SARS-CoV-2 infections and COVID-19 hospital admissions seen in our study corresponds to a time when the delta variant accounted for ≥ 99% of all SARS-CoV-2 infections at KPSC and the United States. Thus, our third dose VE estimates can be interpreted as delta-specific and, similar to early studies from Israel, provides reassurance that a third dose of BNT162b2 restores high levels of protection against the delta variant of concern (VOC). This is consistent with clinical data showing that neutralizing antibody levels not only improved after a third dose (compared to post-dose two), but also that the breadth of coverage against variants of concern seemed to increase, as neutralizing antibody levels against the wild-type strain versus beta and delta variants were much more comparable after receiving a third dose compared to a second dose. This has also been observed for the recently characterized omicron variant, and preliminary laboratory data using a pseudovirus neutralization assay suggest that while two primary doses may not elicit robust neutralizing antibody responses, three doses do. Preliminary omicron-specific VE estimates from Public Health England confirm this, showing that while two doses may only provide limited protection against omicron infection, three doses improve protection from 70 to 75%. However, as the prevalence of omicron continues to increase, additional studies evaluating the effectiveness and durability of booster doses will be required, to continue to inform the utility of third doses and the potential need for additional vaccine doses overtime to combat the omicron and other emerging VOCs.

As this study was observational, unmeasured confounding cannot be ruled out. Unmeasured differences between vaccinated and unvaccinated individuals and between those who choose to receive a third dose versus those who did not could impact our VE estimates. For example, we did not have information about adherence to masking guidelines, social interactions, and occupation, which are related to likelihood of testing for SARS-CoV-2 either when experiencing symptoms or routinely as a preventive measure. However, testing was widely available and provided free of charge in KPSC during the study period. Moreover, our Cox models controlled for important sociodemographic and clinical characteristics including time, age, sex, race/ethnicity, neighborhood deprivation index, history or SARS-CoV-2 testing and healthcare utilisation, and history of underlying comorbidities and/or immunocompromising conditions. Thus, our comparisons are well-balanced across these known potential confounders. Although history of comorbidities and immunocompromising status were not time-varying, they were based on recent health records in the year prior to the patient’s index date. Another limitation is that we relied on KPSC electronic health records to ascertain vaccination status, and some vaccinations administered outside of the health system could be missed. However, KPSC supplements their medical record information with vaccination history data from the California Immunisation Registry to minimize this risk of bias. Similarly, SARS-CoV-2 infection
was based on positive tests captured in the KPSC system and may not be reflective of all infections, including those for which testing was not sought and those not reported to KPSC.

In summary, our results suggest that being immunised with a third dose of BNT162b2 confers comparable, if not better, protection against SARS-CoV-2 infections and COVID-19 hospital admissions as was seen in the first few months after receiving two doses. Importantly, these findings confirm that three doses ensure high protection against the delta variant, which accounted for > 90% of infections in the United States during the time when third doses were administered in our study.23 These data, combined with the improved immunogenicity, high efficacy, and tolerable safety profile of a third BNT162b2 dose observed in the clinical trial setting1,24 and with preliminary real-world data from the BNT162b2 booster program in Israel,26,32–34 support the benefit of broad age-based recommendations for third doses—especially in the context of the delta variant and the expansion of the highly transmissible omicron variant. Finally, preliminary immunogenicity and real-world effectiveness data suggest that third doses of BNT162b2 will likely help confer protection against omicron.49 However, additional studies evaluating the real-world VE of both two and three doses of BNT162b2 against this emerging variant are still needed.

Contributors
SYT, JMS, LJ, and JMM conceived this study. JMS and VH conducted the analysis. SYT, JMS, JMM, 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.

Data sharing statement
Anonymized data that support the findings of this study may be made available from the investigative team in the following conditions: (1) agreement to collaborate with the study team on all publications, (2) provision of external funding for administrative and investigator time necessary for this collaboration, (3) demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and (4) agreement to abide by the terms outlined in data use agreements between institutions.

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Declaration of interests
JMZ, SG, SRV, KP, LJ, LP, and JMM are employees of and hold stock and/or stock options in Pfizer Inc. TBF holds stock in Pfizer Inc. SYT, JMS, VH, BA, HT, TF, SRS, and OO received research support from Pfizer during the conduct of this study that was paid directly to KPSC. All other authors report no conflicts.

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Supplementary materials
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References
1 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2569–2625.
2 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(15):1412–1423.
3 Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021;397(10287):819–829.
4 Haas EJ, McLaughlin JM, Khan F, et al. Infections, hospitalisations, and deaths averted via a nationwide vaccination campaign using the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine in Israel: a retrospective surveillance study. Lancet Infect Dis. 2021. https://doi.org/10.1016/S1473-3099(21)00566-1. ISSN 1473-3099.
5 Britton A, Jacobo Silska KM, Edens C, et al. Effectiveness of the Pfizer-BioNTech COVID-19 vaccine among residents of two skilled nursing facilities experiencing COVID-19 Outbreaks - Connecticut, December 2020-February 2021. MMWR Morb Mortal Wkly Rep. 2021;70(11):406–410.
6 Thompson MG, Burgess JL, Naleway AL, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers - Eight U.S. Locations, December 2020-March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(13):495–500.
7 Nanduri S, Plishivtch T, Derado G, et al. Effectiveness of Pfizer-BioNTech and Moderna vaccines in preventing SARS-CoV-2 infection among nursing home residents before and during widespread circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant - National...
Healthcare Safety Network. March 1-August 1, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(19):513-516.

Tenforde MW, Olson SM, Self WH, et al. Effectiveness of Pfizer-BioNTech and Moderna vaccines against COVID-19 among hospitalized adults Aged ≥65 Years - United States, January-March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(18):574-579.

Nastre S, He S, Chung H, et al. Effectiveness of COVID-19 vaccines against variants of concern in Ontario, Canada 2021.

Hall VJ, Foukles S, Saei A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multi-centre, cohort study. Lancet. 2021;397(10309):1725-1735.

Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Pfizer-BioNTech Vaccine against the Delta (B.1.617.2) Variant. N Engl J Med. 2021;385(7):59-59.

Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test-negative case-control study. BMJ. 2021;373:n1088.

Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet. 2021;397(10309):1634-1637.

Lopez Bernal J, Gower C, Andrews N. Public health England delta variant vaccine effectiveness study E. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021;385(7):59-59.

Stowe J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant media. tghn.org/articles/2021 2022.

Alu-Raddad LF, Chemaitelly H, Butt AA. National Study Group for C.V. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med. 2021;385(2):187–189.

Chemaitelly H, Yassine HM, Benslimane FM, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med. 2021;27(12):1624-1627.

Tang P, Hasan MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nat Med. 2021.

Tenforde MW, Self WH, Nasani EA, et al. Sustained effectiveness of Pfizer-BioNTech and Moderna Vaccines against COVID-19 associated hospitalizations among adults - United States, March-July 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1156-1162.

Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021;397(10293):2460-2462.

ImoHCC-VCE. C Vaccine Effectiveness data on a cohort of persons vaccinated by Jan-2021 al. Two February 2021. Presented at Israel Ministry of Health COVID-19 Vaccine Campaign Effectiveness Committee Meeting on 20-Jul-2021. www.gov.il/BiPFolder/reports/ vaccine-efficacy-safetylevel-up-committee/he/files_publication s/corona_two-dosevaccination-data.pdf 2021.

Rosenberg ES, Holtrage DR, Dorabawila V, et al. New COVID-19 cases and hospitalizations among adults, by Vaccination Status - New York. May 3-July 25, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(37):1306-1311.

Tartof SY, Sleuzak JM, Fischer H, et al. Effectiveness 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(10319):1407-1416.

Evaluation of a Booster Dose (Third Dose) Vaccines and Related Biological Products Advisory Committee Briefing Document [cited Vaccines and Related Biological Products Advisory Committee [cited; Available from: https://www.fda.gov/advisory-committees/advisory-committee-calend ar/vaccines-related-biological-products-advisory-committee-sep tember-17-2021-meeting-announcement#event_materials. 2022.

Gibbs M, Mandelboim O, Indenbaum V, et al. Early immuno- nogenicity and safety of the third dose of BNT162b2 mRNA Covid-19 vaccine among adults older than 60 years; real world experience. J Infect Dis. 2021.

Barda N, Dagan N, Cohen C, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet. 2021;398(10315):4005-4010.

Sacik M, Ketter J, Shamir Stein N, Elka Zohar A. Effectiveness of a third dose of BNT162b2 mRNA vaccine. J Infect Dis. 2022;225(1):30-33. https://doi.org/10.1093/infdis/jiaa556.

US. Comirnaty and Pfizer-BioNTech COVID-19 Vaccine . In: Drug UPA-editor. 2021.

(JCVI). U$Cov. JCVI interim advice: potential COVID-19 booster vaccine programme winter 2021 to 2022. 2021.

(SAHPR) SAHPRA. Approval of booster dosing with the Pfizer Comirnaty from 15 December 2021. 2021.

Health IMo. Third dose of the COVID-19 vaccine 2021.

Bar-On YM, Goldberg Y, Mandel M, et al. Protection against Covid-19 by BNT162b2 Booster across Age Groups. N Engl J Med. 2021;385(24):2430. https://doi.org/10.1056/NEJMoa2126926.

Cho D. CBER Assessment of booster dose of Pfizer-BioNTech COVID-19 Vaccine (0.3 mL) administered following a primary COVID-19 immunization series in individuals 18 years of age and older. 2021.

Gruber M. Emergency use authorization (EUA) for an unapproved product review memorandum: extended population 2021. Available from: https://www.fda.gov/media/134421/download.

Koehnck 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(4):216.

Greenberg JA, Hohmann SF, Hall JB, Kress JP, David MZ. Validation of a method to identify immunocompromised patients with severe sepsis in administrative databases. Ann Am Thorac Soc. 2016;13(12):2355-2359.

Grannis SJ, Rowley EA, Ong TC, et al. Interim estimates of COVID-19 vaccine effectiveness against COVID-19-associated emergency department or urgent care clinic encounters and hospitalizations among adults during SARS-COV-2 B.1.1.7 (Delta) Variant Predominance - Nine States, June-August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(27):1291-1293.

Rosenberg ES, Doralabwila V, Easton D, et al. COVID-19 vaccine effectiveness by product and timing in New York state medRxiv 2021. Available from: 10.1101/2021.01.05.21254935.

Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 or mRNA-1273 vaccine for preventing post-vaccination COVID-19 infection: an observational study medRxiv2021. Available from: https://www.medrxiv.org/content/10.1101/2021.11.29.21266777v1.

Koebnick 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(4):216.

Lin DY, Gu Y, Wheeler B, et al. Effectiveness of Covid-19 vaccines in the United States over 9 months: surveillance data from the State of North Carolina 2021. Available from: 10.1101/ 2021.05.23.21265304.

Israel A, Merzon E, Schaffer A, et al. Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection in a large cohort medRxiv 2021. Available from: https://doi.org/10.1101/2021.05.03.21260496.

Self WH, Tenforde MW, Rhoads JP, et al. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 hospitalizations among adults without immunocompromising conditions - United States, March-August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(15):1137-1145.

Sharma A, Oda G, Holdoryny M. Effectiveness of a third dose of BNT162b2 or mRNA-1273 vaccine for preventing post-vaccination COVID-19 infection: an observational study medRxiv2021. Available from: https://www.medrxiv.org/content/10.1101/2021.12.03.21266771v1.

Pfizer and BioNTech provide update on omicron variant [press release]. businesswire, December 8, 2021 2021.

Andrews N, Stowe J, Kirsebom F, et al. Effectiveness of COVID-19 vaccines against the B.1.1.529 variant of concern medRxiv2021. Updated December 14, 2021. Available from: https://doi.org/10.1101/ 2021.12.14.21267615.