Title:

Six-month effectiveness of BNT162b2 mRNA COVID-19 vaccine in a large US integrated health system: a retrospective cohort study

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Summary

Background

Vaccine effectiveness (VE) studies have not differentiated the impact of Delta from potential waning immunity on recent observed reductions in effectiveness against SARS-CoV-2 infections. We evaluated overall and variant-specific effectiveness of BNT162b2 against SARS-CoV-2 infections and COVID-19-related hospitalizations by time since vaccination among members of a large US healthcare system.

Methods

In this retrospective cohort study, we analyzed electronic health records from Kaiser Permanente Southern California (KPSC) between Dec 14, 2020 – Aug 8, 2021 to assess BNT162b2 VE against SARS-CoV-2 infections and COVID-19-related hospitalization. Effectiveness calculations were based on hazards ratios from adjusted Cox models.

Findings

For fully vaccinated individuals, effectiveness against SARS-CoV-2 infections was 73% (95%CI: 72–74) and against COVID-19-related hospitalizations was 90% (89–92). Effectiveness against infections declined from 88% (86–89) during the first month after full vaccination to 47% (43–51) after ≥5 months. Among sequenced infections, VE against Delta was lower compared to VE against other variants (75% [71–78] *vs* 91% [88–92]). VE against Delta

infections was high during the first month after full vaccination (93% [85–97]) but declined to 53% [39–65] at ≥4 months. VE against hospitalization for Delta for all ages was high overall (93%).

Interpretation

Our results confirm high effectiveness of BNT162b2 against hospitalizations through roughly six months after being fully vaccinated, even in the face of widespread dissemination of Delta. Reductions in effectiveness against SARS-CoV-2 infections over time are likely primarily due to waning rather than Delta escaping vaccine protection.

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Introduction

In a pivotal randomized controlled trial (RCT), the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine showed ≥95% efficacy against symptomatic and severe disease due to SARS-CoV-2 infection.[1] In the first months following rapid nationwide uptake of the vaccine in Israel, BNT162b2 was also shown to be highly effective in the real-world setting and to have large public health impact on reducing infections, hospitalizations, and deaths at a time when Alpha was the predominant strain.[2-4] Similar evidence of real-world vaccine effectiveness of BNT162b2 in the United States,[5-8] Canada,[9] the United Kingdom,[10-16] and other locations[17,18] in the early months following vaccine introduction has since been published.

The continual emergence of SARS-CoV-2 variants has raised concern that COVID-19 vaccines could have reduced effectiveness against new viral strains. However, BNT162b2 has shown high levels of neutralizing antibody against many variants of concern (VOC), including Alpha (B.1.1.7 lineage), Gamma (P.1 lineage), and Delta (B.1.617.2 lineage). Neutralizing antibody levels against Beta (B.1.351 lineage) and Kappa (B.1.617.1 lineage) were somewhat reduced, but still showed robust neutralizing activity.[19-21] Confirmatory, real-world studies have shown high effectiveness of two doses of BNT162b2 against COVID-19, especially severe disease, caused by VOCs Alpha,[3,17] Beta,[17,22] and Delta[9,14-16,23,24] in a variety of settings.

After global transmission of the Delta variant in June and July of 2021, reports describing reduced effectiveness of BNT162b2 (and other COVID-19 vaccines) against SARS-CoV-2 infections caused by Delta began to surface from Israel,[25] the United States,[26,27] and Qatar.[23] The Israel Ministry of Health published data through mid-July 2021 that showed BNT162b2

effectiveness against SARS-CoV-2 infections declined from ≥90% in the period prior to widespread dissemination of Delta to <40% in the time period when Delta accounted for the vast majority of infections.[25] The US Centers for Disease Control and Prevention (CDC) published similar data[24,26,27] and has expressed new concerns that vaccinated individuals may be more susceptible to Delta and that, even if effectiveness against severe disease remains high, vaccinated people could be transmitting the virus even if to a lesser degree than the unvaccinated.[28,29]

The introduction of Delta, however, may not be the primary driver of recently-reported declines in effectiveness against SARS-CoV-2 infections and increasing rates of breakthrough infections among persons who are fully vaccinated.[23] In Israel, the United States, and Qatar for example, widespread dissemination of Delta also coincided with the time period during which many of the high-risk individuals who were first fully vaccinated (e.g., healthcare workers, the immunocompromised, and the elderly) were approaching six months since the receipt of their second dose. Thus, waning of vaccine-induced immunity is an important factor in recently reported declines in effectiveness. Data from the pivotal RCT showed that efficacy of BNT162b2, during a period before Delta was circulating, declined from 96% (95% confidence interval [CI]: 93–98%) in the first two months after the second dose to 84% (95%CI: 75–90%) four to six months after being fully vaccinated.[30] Thus, waning was observed independently of the introduction of Delta. Additionally, effectiveness against Delta infections has been shown to be high among individuals who were fully vaccinated with BNT162b2 in the previous 2–3 months, including young children in Israel[31] and adults in the United Kingdom[10-16] and Canada[9].

Vaccine effectiveness (VE) studies in the setting of widespread Delta activity to date, however, have not adequately differentiated the impact of Delta from potential waning immunity

on observed reductions in effectiveness against SARS-CoV-2 infections. This distinction is critical to inform policy regarding the need for booster doses and what the antigenic composition of future vaccines should be. To help answer this urgent public-health question, we evaluated overall and variant-specific real-world effectiveness of BNT162b2 against SARS-CoV-2 infections and COVID-19-related hospitalizations by time since vaccination among members of a large integrated healthcare system in the United States.

Methods

Study design and population

In this retrospective cohort study, we analyzed electronic health records (EHRs) from the Kaiser Permanente Southern California (KPSC) healthcare system between Dec 14, 2020 – Aug 8, 2021 to assess the effectiveness of the BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19-related hospitalization. The study population consisted of all KPSC members ≥12 years of age. The start of the study period corresponded to the date the first doses of BNT162b2 were administered to KPSC members.

KPSC is an integrated healthcare organization with ≥4·7 million members representative of the socioeconomic and racial/ethnic diversity of the area's population.[32] KPSC EHRs integrate clinical data including diagnostic, pharmacy, laboratory, and vaccination history information across all settings of care. Care delivered to members outside of the KPSC system is also captured, as outside providers must submit detailed claims to KPSC for reimbursement by the health plan.

Participants were required to have ≥1 year of prior membership (allowing a 31-day gap any time during the prior membership period to allow for potential delays in membership renewal) to determine comorbidities and medical history. Patients with documentation requesting

removal from all research studies were excluded (n=17). The study protocol was reviewed and approved by the KPSC institutional review board, which waived requirement for informed consent (IRB#12816).

BNT162b2 vaccination

COVID-19 vaccines were provided to KPSC members at no cost following emergency use authorization (EUA). COVID-19 vaccines administered to KPSC members outside of the KPSC system during the study period were captured using batch queries to the California Immunization Registry (CAIR). California providers are required by law to report all COVID-19 vaccine administrations to CAIR every 24 hours. KPSC followed the state of California guidance in rolling out COVID-19 vaccines, first making vaccines available to healthcare workers in Dec 2020. Vaccines were then progressively made available to the elderly, individuals with underlying health conditions, and essential workers. By April 2021, anyone ≥16 years of age was eligible to receive the vaccine. Those 12–15 years of age became eligible in May 2021.

The primary exposure was being fully vaccinated with BNT162b2, defined as receiving 2 doses of BNT162b2 with ≥7 days after the second dose. Individuals were considered partially vaccinated if they received only one dose with ≥14 days after the first dose or if they received 2 doses with <7 days after the second dose. Patients were considered unvaccinated until receipt of their first dose of BNT162b2, or until censoring at disenrollment, death, or receipt of another COVID-19 vaccine.

Outcomes

Outcomes included i) SARS-CoV2 infection defined as testing positive for SARS-CoV-2 via a polymerase chain reaction (PCR) test from any sample (i.e., bronchial lavage, nasopharyngeal or

nasal swab, oropharyngeal swab, throat swab, saliva, sputum, or tracheal aspirate) in any clinical setting regardless of the presence of symptoms (see Appendix Table 1 for assay), and ii) COVID-19-related hospitalization defined as a hospitalization with a positive SARS-CoV-2 PCR test that was conducted between 14 days prior to 3 days after the date of hospital admission.

Variant identification

All PCR-positive SARS-CoV-2 laboratory specimens collected between March 4, 2021 and July 21, 2021 were processed for whole genome sequencing (WGS) and viral lineage designation (see Appendix Table 1 for details). A small number of archived specimens (n=148) collected prior to Mar 4, 2021 were also included.

Statistical analysis

Using descriptive statistics, we described the distribution of demographic and clinical characteristics of the study cohort by BNT162b2 vaccination status and history of SARS-CoV-2 infection. Among those who tested positive for SARS-CoV-2, we described study population characteristics by infecting strain (i.e., Delta *vs* other variant). Median time since being fully vaccinated was also described. Incidence rate ratios comparing rates of SARS-CoV-2 infection and COVID-19-related hospitalizations among fully- and partially-vaccinated individuals to the unvaccinated were estimated using the hazard ratios (HR) with 95% CIs from an unadjusted Cox model. BNT162b2 vaccination status was categorized as time-varying, with all participants entering the cohort as unvaccinated. 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, or receipt of >2 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 prior to being vaccinated or censored. To assess durability,

vaccine effectiveness (VE) was estimated at monthly intervals after being fully vaccinated with BNT162b2. Calendar time was included in all models (crude and adjusted) as the underlying time scale to adjust for changes in vaccine eligibility, testing practices, non-pharmaceutical intervention and lockdown requirements, disease activity, and potential changes in COVID-19 treatment over time.

Adjusted HRs and 95%CIs were estimated by including all measured covariates in the Cox proportional hazards regression models. Variables included in the multivariable model included age, sex, race/ethnicity, BMI, cardiac disease, organ transplant, diabetes (by A1C), chronic obstructive pulmonary disease, renal disease, malignancy, hypertension, Charlson index, healthcare utilization in year prior to index date (outpatient, virtual, ED, inpatient), influenza and pneumococcal vaccinations in year prior, neighborhood deprivation index (NDI)[33], and prior infection with SARS-CoV-2 as indicated by PCR or serology. Robust variance was computed to account for clustering introduced by including NDI in the model. For all models, VE was calculated as (1–HR) * 100%. Due to limitations in sample size, variant-specific VE analyses were not stratified by age, were estimated only out to ≥4 months for SARS-CoV-2 infections, and were not stratified by month for COVID-19-related hospitalization.

Results

As of Dec 14, 2020 there were 3 436 957 members age ≥12 years of age with ≥1 year prior membership who were included in the study cohort. Median age was 45 years (IQR=29–61), and 40·5% were Hispanic, 32·3% White, 11·6% Asian/Pacific Islander, and 8.0% Black. In the year prior to study start date, 2·2% (74 284 / 3 436 957) had ≥1 positive SARS-CoV-2 PCR test, and 15·8% (543 628 / 3 436 957) had ≥1 prior negative PCR test.

206 During the study period, 5·4% (184 041 / 3 436 957) were SARS-CoV-2-infected (Dec
207 14, 2020 – Aug 8, 2021), among whom 6·6% (12 130 / 184 041) were hospitalized for COVID-
208 19. SARS-CoV-2-infected, compared to uninfected, were younger (median age: 42 years *vs* 45
209 years, *P* = <0·001), more likely to be Hispanic (57·7% *vs.* 39·5%, *P* = <0·001), and obese
210 (43·9% *vs*. 32·7%, *P* = <0·001). Among SARS-CoV-2-infected, those who were hospitalized for
211 COVID-19, compared with those not hospitalized, were older, more likely to be male, have
212 comorbidities, and have higher prior healthcare utilization (Table 1; Appendix Table 2).

213 Of 9147 specimens sent for WGS, 55·2% (5050 / 9147) had a sequence determined.
214 Specimens for which a sequence could not be determined were more likely to have high cycle
215 threshold (Ct) values (Appendix Table 3). The median Ct values of sequenced N, ORF1ab, and S
216 genes were 30·8, 32·4, and 28·8 *vs*. median Ct values of 23·0, 23·3, and 23·4, respectively, for
217 specimens for which sequence could not be determined. Over the study period, 28·4% of
218 specimens for which a sequence could be determined were Delta. The proportion of sequenced
219 specimens that were Delta increased from 0·6% (7 / 1202) in Apr 2021 to 86·6% (933 / 1077) in
220 Jul 2021 (Figure 1). Those infected with Delta were more likely to be Black (18·8% of Delta
221 cases *vs* 10·8% of other sequenced variants, *P* = <0·001). The distribution of comorbidities and
222 prior utilization was generally consistent between the variant groups (Appendix Table 4).

223 By Aug 8, 2021, 33% (1 146 768 / 3 436 957) of cohort members received ≥1 dose of
224 BNT162b2 (1 010 516 received ≥1 dose of mRNA-1273, 109 911 Ad26.COV2.S, 2972 other
225 COVID-19 vaccines or mixed regimens, and 1 166 790 remained unvaccinated). Of these, 91·0%
226 (n=1 043 289) patients were fully vaccinated, and 6·6% (n=76 205) were partially vaccinated
227 with BNT162b2 (Table 1). Mean time since being fully vaccinated (7 days after second dose)

was 3·4 months; 72·1% (752 562 / 1 043 289) of the fully vaccinated were fully vaccinated ≥3 months previously.

Fully vaccinated individuals had an adjusted VE of 73% (95%CI:72–74) against SARS-CoV-2 infections and 90% (89–92) against COVID-19-related hospitalizations (Appendix Tables 5a & 5b). Stratified by age groups, the fully-vaccinated VE against infection was highest for those 12-15 years of age (91% [88–93]) and lowest for those ≥65 years of age (61% [57–65]) (Appendix Table 5a). The age stratified VE against hospitalizations was 92% (88–95) for those 16-44 years, and 86% (82–88) for those ≥65 years of age (Appendix Table 5b).

VE against infection for the fully vaccinated decreased with increasing time since vaccination, declining from 88% (86–89) during the first month after full vaccination to 47% (43–51) after ≥5 months (≥157 days after second dose) (Figure 2a; Appendix Table 6a). Individuals ≥65 years of age had lower overall effectiveness against infections but declined at a similar rate (VE at <1 month after being fully vaccinated: 80% [73–85]; VE at ≥5 months: 43% [30–54]) (Figure 2a; Appendix Table 6a).

Among fully vaccinated persons of all ages, protection against COVID-19-related hospitalization did not wane over time, with overall adjusted VE estimates of 87% (82–91) at < 1 month after being fully vaccinated, and 88% (82–92) at ≥5 months after full vaccination (Figure 2b; Appendix Table 6b).

Overall VE against Delta infections for the fully vaccinated was lower compared to VE against other variants (75%, [71–78] *vs* 91% [88–92]) (Appendix Table 6). While estimates against both Delta and other variants were high at <1 month after full vaccination (VE against Delta: 93% [85–97] and VE against other variants: 97% [95–99]), VE against Delta infections

declined to a greater extent at ≥ 4 months after full vaccination (VE against Delta: 53% [39–65] and VE against other variants: 67% [45–80]), although CIs overlapped. For specimens where a sequence could not be determined, adjusted VE after full vaccination declined from 84% [78–88]) at <1 month to 47% (30–59) after ≥ 4 months (Figure 3; Appendix Tables 7&8).

Among the fully vaccinated, VE against hospitalization was high for both Delta (VE=93% [84–96]) and for other variants (VE=95% [90–98]). Effectiveness against hospitalization was lower among specimens that failed sequencing (VE=77% [67–85]) (Appendix Table 7).

Discussion

This retrospective cohort study conducted in large integrated healthcare system showed that individuals who were fully vaccinated with BNT162b2 had 73% (95%CI: 72–74) overall effectiveness against SARS-CoV-2 infections and 90% (89–92) effectiveness against COVID-19-related hospitalizations after a mean follow-up of 3.4 months. Effectiveness against SARS-CoV-2 infections waned during the six months of this study, falling from 88% (86–89) within one month after being fully vaccinated to 47% (43–51) ≥5 months after being fully vaccinated. Effectiveness against hospitalization in all age groups did not wane over the duration of the study. These findings are consistent with preliminary reports from the Israel Ministry of Health and US CDC showing reductions in effectiveness of BNT162b2 against infections ≥5 months after being fully vaccinated, but consistently high estimates against COVID-19-related hospitalizations and severe disease through July 2021.[24-27] The most recent report from Israel, however, suggests that some reduction in effectiveness against hospitalization has been observed among the elderly roughly six months after receiving the second dose of BNT162b2.[31] Thus,

long-term effectiveness data against severe outcomes should be continuously monitored in our study population and globally.

Effectiveness of BNT162b2 against infections caused by Delta, which became the predominant strain in KPSC by July 2021, was 75% (95%CI: 71–78) over the study period. This was somewhat lower than overall effectiveness against infections caused by other (non-Delta) strains for which sequencing information was available, estimated at 91% (95%CI: 88–92). Effectiveness against Delta infections at one month after being fully vaccinated was high at 93% (85–97) but fell to 53% (39–65) ≥4 months after being fully vaccinated. Thus, waning effectiveness against infection may be more pronounced against Delta compared to other variants, however, waning was observed for both Delta and non-Delta variants and CIs overlapped. Effectiveness against Delta-related hospitalizations over the entire study period was high, at 93% (84–96) and was comparable to effectiveness against hospitalization for other (non-Delta) variants. These findings are consistent with recent reports from the United States[24,26,27] and Qatar,[23] but provide a clearer picture that reductions in VE over time are likely primarily due to waning rather than Delta escaping vaccine protection.

In context with our findings, studies from the United Kingdom[14,15] and Canada[9] have shown high effectiveness of BNT162b2 against symptomatic COVID-19 caused by Delta in a vaccine schedule that separates the first and second doses by two to three months instead of three weeks. This longer interval between doses may lead to higher immunological responses,[34,35] however, duration of follow-up in these studies (<3 months)[9,14,15] was insufficient to determine the effects of waning. Moreover, given the lower effectiveness after only one dose observed in our study and in other reports of one-dose effectiveness against VOCs like Beta or Delta,[14,17,23] delaying the second dose is not without risk.

Our results reiterate in a real-world US setting that vaccination with BNT162b2 remains a critical tool for preventing COVID-19, especially COVID-19-associated hospitalization, caused by all current VOCs. Our finding that BNT162b2 effectiveness against SARS-CoV-2 infections significantly waned over the six-month study period, especially as transmission of Delta increased, has important implications for clinical development and vaccination policy. Along with other emerging evidence,[9,14-16,23] our results suggest that despite early effectiveness of BNT162b2 against Delta and other VOCs, effectiveness erodes steadily in the months following receipt of the second dose. Waning effectiveness and an increased number of infections six to 12 months after the second dose—along with the potential need for booster doses—was expected given that lower neutralizing antibody titers during this time period have been observed in immunogenicity studies.[36-38] Waning has been observed for both mRNA-based COVID-19 vaccines,[26,27] and is consistent with studies of other coronaviruses.[39] Reassuringly, early Phase 1 data demonstrate that a third booster dose of the current BNT162b2 vaccine given six months after the second dose elicited neutralizing antibody titers against the original SARS-CoV-2 wild-type strain, Beta, and Delta that were several fold higher than after two primary doses.[36,37] Modeling studies have predicted that these increases in neutralizing antibody titers will restore high levels of effectiveness.[38] Moreover, early unpublished data from an Israeli health maintenance organization suggest that a third booster dose is highly effective in a setting where Delta accounts for nearly all cases.[40] These findings suggest that boosting with the current BNT162b2 vaccine rather than a Delta-specific construct is likely to be a robust public health strategy to ensure continued high levels of vaccine protection.

Israel has already begun a booster program for older adults and the immunocompromised who were previously fully immunized—a program that is expect to be expanded to the entire

vaccine-eligible population.[41] Additionally, top health officials in the United States[42] and the Joint Committee on Vaccination and Immunisation (JCVI) in the United Kingdom[43] both recently announced that comprehensive booster programs will be started in September 2021. For policymakers, considerations of when and to whom to provide booster doses must also be viewed within the global context of vaccine supply, namely that many countries remain without adequate supply of COVID-19 vaccines.

Our study has potential limitations. Vaccinated individuals are different in many ways from those that remain unvaccinated. Though we controlled for demographics, comorbidities, and neighborhood-level variables that may reflect differences in socioeconomic status, we were unable to control for other potentially confounding factors that could impact infection rates, such as occupation, adherence to masking guidelines, testing behaviors, social interactions, and other factors. Rather than use convenience or biased sampling, we systematically collected and submitted all PCR-positive specimens for sequencing, however, we were unable to determine the sequence for 45% of samples. Effectiveness was lowest for PCR-positive specimens for which a sequence could not be determined. These specimens had higher Ct values than other PCR-positive specimens which likely corresponded to milder or asymptomatic infections. Thus, our VE estimates against SARS-CoV-2 infections could be muted by very mild or asymptomatic infections and are not directly comparable to other estimates of effectiveness against symptomatic disease. Contrastingly, sequencing was more likely to fail among the vaccinated due to lower viral loads, which could lead to an overestimate of variant-specific effectiveness. Furthermore, our study only evaluated short-term outcomes and further research is needed to determine the potential effectiveness against long-term sequalae of COVID-19, such as its association with persistent cognitive deficits, including the acceleration of Alzheimer's disease [44]

Finally, while the KPSC EHR may miss some vaccinations administered outside of the health system, our data capture through CAIR minimized this impact.

Our results confirm high effectiveness of BNT162b2 against hospitalizations through roughly six months after being fully vaccinated, even in the face of widespread dissemination of Delta. These findings underscore the importance of continuing to prioritize improving COVID-19 vaccination rates, even in hard-to-reach communities. Effectiveness against infections was high early on, both for Delta and other VOCs, but waned over the study period. While waning effectiveness against hospitalization was not observed in our study population to date, this should be carefully monitored as preliminary data from Israel suggest that reduced effectiveness against severe disease could eventually follow observed reductions in effectiveness against SARS-CoV-2 infections.[31] Our findings indicate that policymakers will need to continue to monitor vaccine effectiveness over time and may need to consider recommendations for booster doses to restore initial high-levels of protection observed early in the vaccination program, and to help control heightened transmission of Delta as we enter the upcoming fall/winter viral respiratory season.

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Role of the Funding Source

The study design was developed by KPSC but approved by Pfizer. KPSC collected and analyzed the data; Pfizer did not participate in the collection or analysis of data. KPSC and Pfizer participated in the interpretation of data, in the writing of the report; and in the decision to submit the paper for publication.

Contributors

SYT, FJA, LJ, and JMM conceived this study. JMS, HF, VH, and ONR conducted the analysis. SYT, FJA, JMS, HF, and JMM 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.

Declaration of interests

JMZ, SG, KP, FJA, LJ, and JMM are employees of and hold stock and/or stock options in Pfizer Inc. TBF holds stock in Pfizer Inc. SYT received research support from Pfizer during the conduct of this study. All other authors report no conflicts.

Data Sharing

Individual-level testing and clinical outcomes data reported in this study are not publicly shared. Individuals wishing to access disaggregated data, including data reported in this study, should

submit requests for access to SYT (sara.y.tartof@kp.org). Deidentified data (including, as applicable, participant data and relevant data dictionaries) will be shared upon approval of analysis proposals with signed data-access agreements in place.

Figure Titles and Legends

Figure 2. Adjusted* vaccine effectiveness, with 95% confidence intervals, against SARS-CoV-2 infection (panel a), and hospitalizations (panel b), by age group and number of months since being fully vaccinated with BNT162b2, Kaiser Permanente Southern California, December 14 2020 – August 8, 2021

a.) Against SARS-CoV-2 infection

b.) COVID-19 Hospitalization

Figure 2 footnote:

*VE estimates and 95% confidence intervals calculated via Cox regression models adjusted for: age, sex, race/ethnicity, prior PCR positive SARS-CoV-2, prior healthcare utilization (inpatient, outpatient, emergency department, virtual), BMI, acute myocardial infarction, congestive heart failure, cerebrovascular disease, peripheral vascular disease, organ transplant, diabetes mellitus, malignancy, renal disease, chronic obstructive pulmonary disease, hypertension, Charlson index, influenza vaccination year prior to index date, pneumococcal vaccination 5 years prior to index date, neighborhood deprivation index

** BNT162b2 authorized for 12 to <16-year-olds in March 2021, limiting follow up time for this age group

Figure 3. Adjusted* vaccine effectiveness, with 95% confidence intervals, against SARS-CoV-2 infection by variant, and number of months since being fully vaccinated with BNT162b2, Kaiser Permanente Southern California, December 14 2020 – August 8, 2021

Figure 3 footnote:

*VE estimates and 95% confidence intervals calculated via Cox regression models adjusted for: age, sex, race/ethnicity, prior PCR positive SARS-CoV-2, prior healthcare utilization (inpatient, outpatient, emergency department, virtual), BMI, acute myocardial infarction, congestive heart failure, cerebrovascular disease, peripheral vascular disease, organ transplant, diabetes mellitus, malignancy, renal disease, chronic obstructive pulmonary disease, hypertension, Charlson index, influenza vaccination year prior to index date, pneumococcal vaccination 5 years prior to index date, neighborhood deprivation index

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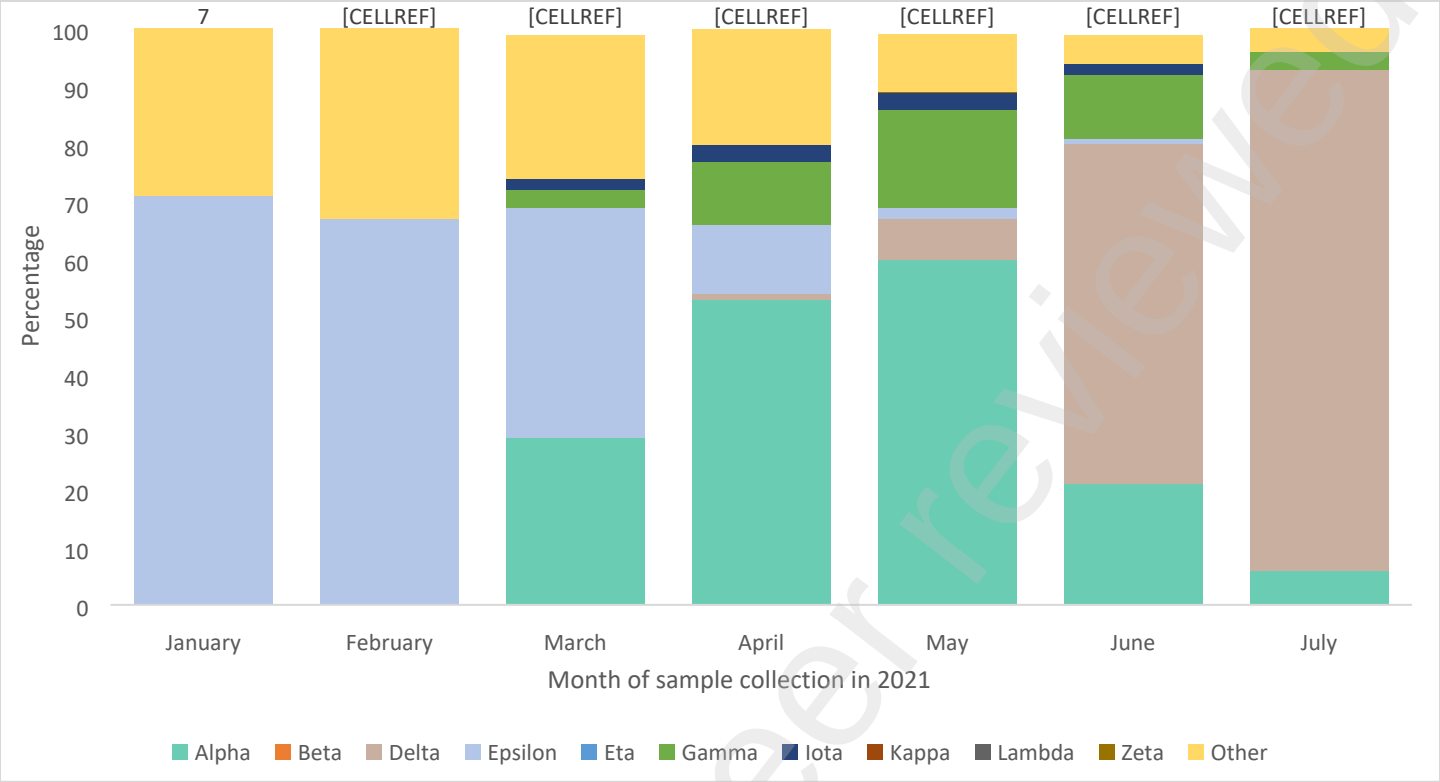
Table 1. Select Characteristics of Kaiser Permanente Southern California members age ≥12 years (n=3 436 957), by BNT162b2 vaccination status (as of Aug 8, 2021), and by SARS-CoV-2 outcomes (Dec 14, 2020 to Aug 8, 2021)

	BNT162b2 Vaccination Status				SARS-CoV-2 Outcomes			
	Unvaccinated * (N=2 290 189)	1 dose <14 days*** (N=27 274)	1 dose >= 14 days or 2 doses <7 days (N=76 205)	2 doses >=7 days (N=1 043 289)	Uninfected (N=3 252 916)	SARS-CoV-2 infection (N=184 041)	COVID-19-hospitalization (N=12 130)	Total (N=3 436 957)
Age (Dec 14, 2020)								
12-15	104 918 (4·6%)	7164 (26·3%)	10 697 (14%)	78 843 (7·6%)	192 999 (5·9%)	8623 (4·7%)	45 (0·4%)	201 622 (5·9%)
16-44	1 038 609 (45·4%)	12 943 (47·5%)	35 876 (47·1%)	420 393 (40·3%)	1 417 518 (43·6%)	90 303 (49·1%)	2366 (19·5%)	1 507 821 (43·9%)
45-64	709 815 (31%)	5808 (21·3%)	20 709 (27·2%)	314 911 (30·2%)	990 866 (30·5%)	60 377 (32·8%)	4302 (35·5%)	1 051 243 (30·6%)
65+	436 847 (19·1%)	1359 (5%)	8923 (11·7%)	229 142 (22%)	651 533 (20%)	24 738 (13·4%)	5417 (44·7%)	676 271 (19·7%)
Mean, Median	45·4, 45	32·1, 29	38·9, 37	45·8, 46	45·4, 45	43·3, 42	60·4, 62	45·3, 45
Sex								
Male	1 115 148 (48·7%)	12 694 (46·5%)	36 843 (48·3%)	472 709 (45·3%)	1 552 606 (47·7%)	84 788 (46·1%)	6608 (54·5%)	1 637 394 (47·6%)
Female	1 174 921 (51·3%)	14 579 (53·5%)	39 355 (51·6%)	570 540 (54·7%)	1 700 146 (52·3%)	99 249 (53·9%)	5522 (45·5%)	1 799 395 (52·4%)
Other/unknown	120 (0%)	1 (0%)	7 (0%)	40 (0%)	164 (0%)	4 (0%)	0 (0%)	168 (0%)
Race/ethnicity								
Hispanic	924 696 (40·4%)	14 683 (53·8%)	35 991 (47·2%)	415 217 (39·8%)	1 284 467 (39·5%)	106 120 (57·7%)	6691 (55·2%)	1 390 587 (40·5%)
Black	197 993 (8·6%)	3465 (12·7%)	6350 (8·3%)	68 391 (6·6%)	262 682 (8·1%)	13 517 (7·3%)	1201 (9·9%)	276 199 (8%)
White	759 438 (33·2%)	5563 (20·4%)	19 422 (25·5%)	324 033 (31·1%)	1 066 792 (32·8%)	41 664 (22·6%)	2752 (22·7%)	1 108 456 (32·3%)
Asian/PI	226 149 (9·9%)	1734 (6·4%)	8355 (11%)	162 948 (15·6%)	385 995 (11·9%)	13 191 (7·2%)	1268 (10·5%)	399 186 (11·6%)
Other	52 505 (2·3%)	602 (2·2%)	1906 (2·5%)	25 431 (2·4%)	76 892 (2·4%)	3552 (1·9%)	117 (1%)	80 444 (2·3%)
Unknown	129 408 (5·7%)	1227 (4·5%)	4181 (5·5%)	47 269 (4·5%)	176 088 (5·4%)	5997 (3·3%)	101 (0·8%)	182 085 (5·3%)
BMI								
Underweight (<18·5)	62 618 (2·7%)	2127 (7·8%)	3953 (5·2%)	38 136 (3·7%)	103 360 (3·2%)	3474 (1·9%)	132 (1·1%)	106 834 (3·1%)
Normal or healthy weight (18·5-24·9)	607 399 (26·5%)	8366 (30·7%)	22675 (29·8%)	307 811 (29·5%)	907 630 (27·9%)	38 621 (21%)	1750 (14·4%)	946 251 (27·5%)
Overweight (25·0-29·9)	687 057 (30%)	7167 (26·3%)	21 499 (28·2%)	318 164 (30·5%)	978 156 (30·1%)	55 731 (30·3%)	3436 (28·3%)	1 033 887 (30·1%)
Obese, class 1 (30·0-34·9)	439 367 (19·2%)	4634 (17%)	13 359 (17·5%)	191 486 (18·4%)	605 962 (18·6%)	42 884 (23·3%)	3101 (25·6%)	648 846 (18·9%)
Obese, class 2 (35·0-39·9)	203 208 (8·9%)	2272 (8·3%)	6232 (8·2%)	86 551 (8·3%)	276 414 (8·5%)	21 849 (11·9%)	1803 (14·9%)	298 263 (8·7%)
Obese, class 3 (≥40·0)	137 456 (6%)	1497 (5·5%)	3854 (5·1%)	54 839 (5·3%)	181 492 (5·6%)	16 154 (8·8%)	1691 (13·9%)	197 646 (5·8%)
Unknown	153 084 (6·7%)	1211 (4·4%)	4633 (6·1%)	46 302 (4·4%)	199 902 (6·1%)	5328 (2·9%)	217 (1·8%)	205 230 (6%)
Comorbidities								
Congestive heart failure	43 875 (1·9%)	218 (0·8%)	995 (1·3%)	20 120 (1·9%)	61 451 (1·9%)	3757 (2%)	1357 (11·2%)	65 208 (1·9%)
Coronary artery disease	26 661 (1·2%)	120 (0·4%)	568 (0·7%)	12 379 (1·2%)	37 662 (1·2%)	2066 (1·1%)	613 (5·1%)	39 728 (1·2%)
Peripheral vascular disease	179 305 (7·8%)	539 (2%)	3538 (4·6%)	96 772 (9·3%)	268 007 (8·2%)	12 147 (6·6%)	3316 (27·3%)	280 154 (8·2%)
Cerebrovascular disease	34 513 (1·5%)	147 (0·5%)	846 (1·1%)	16 661 (1·6%)	49 626 (1·5%)	2541 (1·4%)	730 (6%)	52 167 (1·5%)

Organ transplant	3111 (0·1%)	18 (0·1%)	63 (0·1%)	1638 (0·2%)	4408 (0·1%)	422 (0·2%)	160 (1·3%)	4830 (0·1%)
Diabetes with unknown A1c	25 942 (1·1%)	195 (0·7%)	725 (1%)	9648 (0·9%)	34 427 (1·1%)	2083 (1·1%)	329 (2·7%)	36 510 (1·1%)
Diabetes with A1c<7·5	157 336 (6·9%)	814 (3%)	3693 (4·8%)	81 669 (7·8%)	229 185 (7%)	14 327 (7·8%)	2566 (21·2%)	243 512 (7·1%)
Diabetes with A1c≥7·5	86 318 (3·8%)	644 (2·4%)	2254 (3%)	38 732 (3·7%)	117 845 (3·6%)	10 103 (5·5%)	1966 (16·2%)	127 948 (3·7%)
COPD	204 050 (8·9%)	2338 (8·6%)	6298 (8·3%)	101 486 (9·7%)	295 394 (9·1%)	18 778 (10·2%)	2209 (18·2%)	314 172 (9·1%)
Renal disease	106 351 (4·6%)	420 (1·5%)	2137 (2·8%)	53 200 (5·1%)	154 006 (4·7%)	8102 (4·4%)	2579 (21·3%)	162 108 (4·7%)
Malignancy	52 934 (2·3%)	288 (1·1%)	1194 (1·6%)	27 092 (2·6%)	77 528 (2·4%)	3980 (2·2%)	792 (6·5%)	81 508 (2·4%)
Hypertension	465 109 (20·3%)	2637 (9·7%)	10 930 (14·3%)	231 754 (22·2%)	673 564 (20·7%)	36 866 (20%)	6227 (51·3%)	710 430 (20·7%)
Charlson Index								
0	1 685 257 (73·6%)	22 609 (82·9%)	60 171 (79%)	743 248 (71·2%)	2 379 993 (73·2%)	131 292 (71·3%)	4460 (36·8%)	2 511 285 (73·1%)
1	303 977 (13·3%)	3213 (11·8%)	9266 (12·2%)	149 201 (14·3%)	437 558 (13·5%)	28 099 (15·3%)	2171 (17·9%)	465 657 (13·5%)
2	126 645 (5·5%)	713 (2·6%)	3047 (4%)	62 764 (6%)	182 559 (5·6%)	10 610 (5·8%)	1499 (12·4%)	193 169 (5·6%)
3	57 517 (2·5%)	254 (0·9%)	1240 (1·6%)	30 419 (2·9%)	85 034 (2·6%)	4396 (2·4%)	885 (7·3%)	89 430 (2·6%)
4+	116 793 (5·1%)	485 (1·8%)	2481 (3·3%)	57 657 (5·5%)	167 772 (5·2%)	9644 (5·2%)	3115 (25·7%)	177 416 (5·2%)
Prior positive SARS-CoV-2 PCR								
1	47 993 (2·1%)	668 (2·4%)	1681 (2·2%)	18 356 (1·8%)	68 258 (2·1%)	440 (0·2%)	71 (0·6%)	68 698 (2%)
2+	3827 (0·2%)	53 (0·2%)	116 (0·2%)	1590 (0·2%)	5537 (0·2%)	49 (0%)	6 (0%)	5 586 (0·2%)
Prior positive SARS-CoV-2 serology								
1	2466 (0·1%)	41 (0·2%)	56 (0·1%)	1231 (0·1%)	3764 (0·1%)	30 (0%)	4 (0%)	3 794 (0·1%)
2+	69 (0%)	0 (0%)	0 (0%)	45 (0%)	113 (0%)	1 (0%)	0 (0%)	114 (0%)

*Unvaccinated group includes those not vaccinated with BNT162b2 as of Aug 8, and those vaccinated with COVID-19 vaccines· Those vaccinated with COVID-19 vaccines other than BNT162b2 are censored in the VE modeling at vaccination date·

Figure 1. Distribution of Variants from January 2021 through July 2021 (n=5,050)



	January	February	March	April	May	June	July
	N (%)						
Alpha	0 (0%)	0 (0%)	385 (28·84%)	640 (53·24%)	393 (60·28%)	160 (21·16%)	60 (5·57%)
Beta	0 (0%)	0 (0%)	2 (0·15%)	5 (0·42%)	2 (0·31%)	1 (0·13%)	1 (0·09%)
Delta	0 (0%)	0 (0%)	0 (0%)	7 (0·58%)	48 (7·36%)	446 (58·99%)	933 (86·63%)
Epsilon	5 (71·43%)	14 (66·67%)	534 (40%)	140 (11·65%)	11 (1·69%)	4 (0·53%)	0 (0%)
Eta	0 (0%)	0 (0%)	2 (0·15%)	2 (0·17%)	1 (0·15%)	1 (0·13%)	0 (0%)
Gamma	0 (0%)	0 (0%)	40 (3%)	132 (10·98%)	109 (16·72%)	86 (11·38%)	33 (3·06%)
Iota	0 (0%)	0 (0%)	25 (1·87%)	33 (2·75%)	17 (2·61%)	17 (2·25%)	1 (0·09%)
Kappa	0 (0%)	0 (0%)	1 (0·07%)	1 (0·08%)	0 (0%)	0 (0%)	0 (0%)
Lambda	0 (0%)	0 (0%)	1 (0·07%)	4 (0·33%)	3 (0·46%)	0 (0%)	1 (0·09%)
Zeta	0 (0%)	0 (0%)	6 (0·45%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other variants	2 (28·57%)	7 (33·33%)	339 (25·39%)	238 (19·8%)	68 (10·43%)	41 (5·42%)	48 (4·46%)
All	7 (100%)	21 (100%)	1335 (100%)	1202 (100%)	652 (100%)	756 (100%)	1077 (100%)