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# Comparative COVID-19 Vaccine Effectiveness Over Time in Veterans

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***Background.*** Comparative effectiveness of coronavirus disease 2019 (COVID-19) vaccines across patient subgroups is poorly understood and essential to precisely targeting vaccination strategies.

***Methods.*** We used the US Department of Veterans Affairs COVID-19 Shared Data Resource to identify veterans who utilize VA health care and had no documented severe acute respiratory syndrome coronavirus 2 infection before December 11, 2020. Using a test-negative case–control design (TND), we used conditional logistic regression with adjustment for covariates to estimate vaccine effectiveness (VE) over time for veterans who received 2 doses of mRNA vaccines or 1 dose of Ad26.Cov2.S.

***Results.*** We identified 4.8 million veterans with a mean age of 64 years, of whom 58% had ≥1 chronic disease. Vaccine effectiveness for symptomatic infections, hospitalizations, and ICU admission or death declined over time and varied by the type of vaccine ($P < 0.01$). VE estimates against symptomatic infection during months 1 and 7 for mRNA-1273 compared with BNT162b2 were 89.7% (95% CI, 84.4%–93.0%) and 57.3% (95% CI, 48.4%–64.7%) vs 81.6% (95% CI, 75.9%–85.9%) and 22.5% (95% CI, 7.2%–35.2%) for individuals age <65 years and 78.4% (95% CI, 71.1%–83.9%) and 36.2% (95% CI, 27.7%–43.6%) vs 66.3% (95% CI, 55.7%–74.4%) and −23.3% (95% CI, −40.5% to −8.2%) in subjects age ≥65 years; against hospitalization 92.0% (95% CI, 76.1%–97.3%) and 83.1% (95% CI, 66.8%–91.4%) vs 85.6% (95% CI, 72.6%–92.4%) and 57.0% (95% CI, 31.2%–73.2%) in subjects age <65 years and 66.1% (95% CI, 45.3%–79.0%) and 64.7% (95% CI, 55.2%–72.3%) vs 61.0% (95% CI, 41.3%–74.2%) and 1.7% (95% CI, −22.0% to 20.8%) in those age ≥65 years; against ICU admission or death 89.2% (95% CI, 49.5%–97.7%) and 84.4% (95% CI, 59.0%–94.1%) vs 87.6% (95% CI, 61.0%–96.1%) and 66.4% (95% CI, 7.7%–87.8%) in subjects age <65 years and 75.4% (95% CI, 51.7%–87.5%) and 73.8 (95% CI, 62.9%–81.5%) vs 67.4% (95% CI, 32.6%–84.3%) and 29.3% (95% CI, 2.3%–48.9%) in subjects age ≥65 years, respectively ($P_{interaction} < .01$ for all comparisons). Similarly, mRNA-1273 was more effective than BNT162b2 in veterans with >1 chronic disease.

***Conclusions.*** mRNA-1273 was more effective than BNT162b2 in older veterans and those with chronic diseases.

***Keywords.*** COVID-19; TND; vaccine effectiveness; waning immunity.

Three coronavirus disease 2019 (COVID-19) vaccines have received Emergency Use Authorization or full approval by the Food and Drug Administration (FDA) in the United States. These vaccines reported high efficacy and effectiveness in early studies in preventing symptomatic infection and severe disease, and increased use of these vaccines initially led to a sharp reduction in severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) cases [1–4]. However, cases are surging again with the introduction of new variants, and breakthrough infections have been reported in fully vaccinated individuals.

Current guidelines by the FDA and Centers for Disease Control and Prevention (CDC) recommend vaccination of

eligible persons with 1 of the 3 vaccines, without preference for any specific vaccine. Recent studies using data from the Veterans Health Administration (VA) and other cohorts suggest that the mRNA-1273 (Moderna) vaccine may be more effective compared with the BNT162b2 (Pfizer-BionTech) vaccine [5, 6], but these studies are limited by the lack of comparative effectiveness of vaccines among patient subgroups. In addition, previously published studies yielded somewhat contradictory results, with 1 reporting VE across vaccines and the other differential waning of effectiveness between vaccines over time [5, 6]. Rather than a one-size-fits-all approach to vaccination, tailoring vaccination and subsequent boosters based on individual patient characteristics may be more efficient from an individual and societal perspective.

We used data from the VA, the largest integrated health care system in the United States, with >9 million beneficiaries, to assess and compare effectiveness of the mRNA-1273, BNT162b2, and Ad26.COV2.S (Janssen) vaccines. We tested 2 hypotheses—vaccine effectiveness decreases over time for

individual vaccines and effectiveness varies across vaccines, particularly in older veterans and those with chronic diseases.

## METHODS

### Data Sources

In response to the SARS-CoV-2 pandemic, the VA rapidly created a national COVID-19 Shared Data Resource. This resource contains information on all veterans with a laboratory-confirmed diagnosis of SARS-CoV-2 infection and receipt of vaccine within the VA. Information of veterans tested or vaccinated outside the VA is captured by patient self-report (presentation of a vaccination card) or through claims data. The VA COVID-19 Shared Data Resource is updated regularly and contains extensive demographic, clinical characteristics, including preexisting chronic conditions as captured by the Charlson Comorbidity Index (CCI), receipt of a vaccine, laboratory data, vital signs, and clinical outcome information derived from multiple validated sources [1, 7]. The study was approved by the Institutional Review Board at the VA Pittsburgh Healthcare System. A waiver of informed consent was granted for the study.

### Study Population

To identify a homogenous group of veterans with similar immune status with regards to COVID-19, our analysis cohort included veterans with the following characteristics in the VA COVID-19 Shared Data Resource: those with least 2 primary care appointments in the preceding 18 months of vaccine rollout, because these individuals were more likely to receive care through the VA, and no documentation of infection before December 11, 2020, the start of vaccine rollout within the VA.

### Study Design

We used the test-negative case–control design (TND) to assess VE over time for individual vaccines and to compare effectiveness across different vaccines [8]. The TND design is recommended by the World Health Organization (WHO) for studying the VE of COVID-19 vaccines and has been used by our group in prior work [1, 7, 9]. In brief, VE is calculated as $1 - OR_V$, where $OR_V$ reflects the ratio of the odds of being a case in vaccinated vs unvaccinated study subjects.

### Matching

We matched veterans based on age, geographic region, and calendar time. We chose age because vaccination was rolled out in a staged manner, prioritizing elderly veterans. We also selected geographic regions at the individual county level and calendar time because temporal changes in SARS-CoV-2 transmission may vary across geographic regions, particularly for emerging variants, due to differences in social distancing, mask utilization, other nonpharmaceutical interventions, varying uptake of the vaccine, and varying average social-economic status.

We merged counties with <500 veterans that were within a 100-mile distance.

In the primary analysis estimating VE, we matched veterans who ever tested positive at least once (cases) to those who never tested positive in the study period (controls). The testing date for those ever testing positive was the date of the first positive test, while the testing date for the rest was the date of the first negative test. Cases were matched to controls in the same age category (<40, 40–64, 65–79, and >80 years), geographic region, and testing date (10-day windows).

### Comparative Effectiveness Analysis

We also modified the TND design to estimate the comparative effectiveness (CE) of the 2 more common vaccines, mRNA-1273 and BNT162b2. In this design, cases and controls were restricted to having been vaccinated by 1 of these 2 vaccines before their test date. Cases were matched to controls based on geographic region, race, and date of testing.

### Ascertainment of Vaccination

Individuals received 1 of the 3 following COVID-19 vaccines: mRNA-1273, BNT162b2, or Ad26.COV2.S. We considered a person to be fully vaccinated 14 days after 1 dose of the Ad26.COV2.S vaccine or after 2 doses of the mRNA-1273 and BNT162b2 vaccines, based on WHO guidelines [10].

### Case Definition or Outcomes

Following WHO guidelines [10], we assessed 3 outcomes from December 11, 2020, to October 31, 2021: symptomatic infection (defined as presence of symptoms consistent with flu-like illness and a PCR-positive swab), hospitalization with COVID-19 (the subset of those with a symptomatic infection who were hospitalized between −14 and +2 days of a positive test for SARS-COV-2), and intensive care unit (ICU) admission or fatal case of COVID-19 (the subset of those hospitalized who required admission to the ICU or died within 28 days of a SARS-COV-2-positive test) [11].

### Statistical Analysis

We described sociodemographic and clinical characteristics of the analysis cohort and different matched groups with the use of frequency distributions and measures of central tendency. For the TND design estimating VE, the adjusted odds ratio $(OR_{adj})$, comparing the odds of case status among vaccinated and unvaccinated, and its associated 95% CI were derived using a conditional logistic regression model that accounted for matching and adjusted for gender, race, and number of chronic conditions (as ≤1 or >1). VE at monthly time intervals was estimated as $1 - OR_{adj}$. In the modified TND design for estimating CE between mRNA-1273 and BNT162b2, we estimated adjusted ORs comparing odds of case status between being vaccinated with mRNA-1273 and being vaccinated with
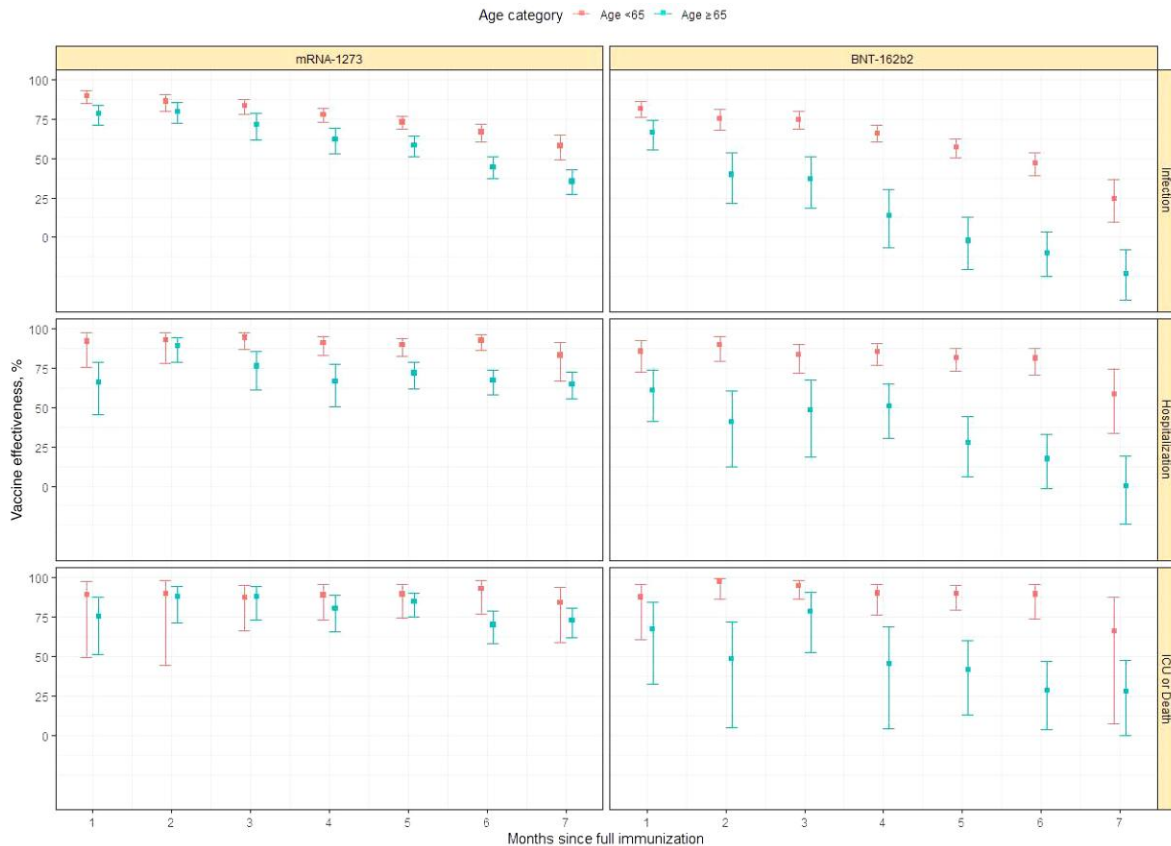
**Figure 1.** Vaccine effectiveness against symptomatic infection, hospitalization, ICU admission, or death over time for 2 mRNA vaccines stratified by age. Abbreviation: ICU, intensive care unit.

BNT162b2. These models were also conditional logistic regression models accounting for matching, number of months between vaccination and testing, gender, age, and number of chronic conditions.

To test hypotheses that VE or CE depended on time since vaccination, individual vaccines, and patient characteristics, we conducted likelihood ratio tests comparing models with and without the corresponding terms in the model. We compared vaccines over time using 2 approaches. First, we calculated VE estimates for individual vaccines by comparing vaccinated and unvaccinated persons and then compared VE estimates across vaccines. Second, we calculated ORs comparing mRNA-1273 and BNT162b2 vaccines because these vaccines accounted for >90% of vaccines administered in the VHA. We estimated VE using 4 subgroups based on age (<65 and ≥65 years) and burden of chronic disease (Charlson Comorbidity Index ≤1 and >1). We selected these subgroups based on the results of prior studies showing waning VE among older individuals and those with a chronic disease [5, 6, 12].

All analyses were performed using R 4.0.5, and a *P* value of ≤.05 was considered statistically significant. We did not adjust for multiple comparisons.

## RESULTS

The clinical characteristics of the 4.8 million veterans in our analysis cohort, from which the subsequent matched cohorts were constructed, are included in Supplementary Table 1. The mean age (SD) was 64 (16) years, and 2 042 637 (42.5%) and 680 958 (14.2%) were ≥65 and ≥80 years, respectively. Approximately 58% (n = 2 786 910) of veterans had ≥1 documented chronic disease, 36.4% (n = 1 750 890) had ≥2 chronic diseases, and 21.3% (n = 1 022 369) had ≥3 chronic diseases.

Between December 11, 2020, and October 31, 2021, 2 457 733 (51.1%) were vaccinated and 2 348 209 (48.9%) remained unvaccinated. Among vaccinated veterans, 971 750 (39.5%), 1 289 639 (52.5%), and 196 344 (8.0%) received the BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines, respectively. The numbers of vaccinated subjects over time for each vaccine are shown in Supplementary Figure 1.

Overall, 341 786 (7.1%) were tested for SARS-CoV-2 infection between December 11, 2020, and October 31, 2021, at least once; of these, 78 613 (23%) were fully immunized and 240 860 (70%) were unvaccinated at the time of testing (Supplementary Figure 2). Of those tested, symptoms of flu-like

**Table 1. Vaccine Effectiveness of mRNA-1273 and BNT162b2 Vaccines Against Symptomatic Infection by Age**

Symptomatic Infection

| | mRNA-1273 | | | | | | BNT162b2 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age <65 y | | | Age ≥65 y | | | Age <65 y | | | Age ≥65 y | | |
| | Controls | Cases | VE (95% CI) | Controls | Cases | VE (95% CI) | Controls | Cases | VE (95% CI) | Controls | Cases | VE (95% CI) |
| Unvaccinated | 16089 | 19252 | n/a | 11886 | 12643 | n/a | 16572 | 20185 | n/a | 11485 | 12914 | n/a |
| Month | | | | | | | | | | | | |
| 1 | 260 | 38 | 89.7 (84.8–93.0) | 300 | 96 | 78.4 (71.1–83.9) | 334 | 85 | 81.6 (75.9–85.9) | 228 | 112 | 66.3 (55.7–74.4) |
| 2 | 211 | 41 | 86.2 (79.8–90.6) | 221 | 66 | 79.8 (72.2–85.3) | 264 | 94 | 75.0 (67.6–80.7) | 167 | 123 | 39.8 (21.6–53.8) |
| 3 | 317 | 84 | 83.3 (78.2–87.2) | 205 | 86 | 71.3 (61.9–78.5) | 375 | 133 | 74.8 (68.8–79.7) | 159 | 117 | 37.7 (19.5–51.8) |
| 4 | 508 | 170 | 77.8 (73.1–81.7) | 290 | 147 | 61.7 (52.4–69.1) | 606 | 310 | 65.9 (60.2–70.8) | 203 | 203 | 12.8 (−7.9 to 29.5) |
| 5 | 652 | 278 | 73.1 (68.4–77.1) | 583 | 319 | 58.2 (51.2–64.2) | 712 | 444 | 56.7 (50.5–62.1) | 330 | 383 | −2.4 (−20.4 to 12.9) |
| 6 | 531 | 270 | 66.9 (60.9–71.9) | 837 | 587 | 44.9 (37.6–51.3) | 598 | 442 | 47.2 (39.3–54.1) | 552 | 645 | −10.6 (−25.9 to 2.8) |
| 7 | 337 | 212 | 57.3 (48.4–64.7) | 829 | 633 | 36.2 (27.7–43.6) | 303 | 306 | 22.5 (7.2–35.2) | 521 | 682 | −23.3 (−40.5 to −8.2) |

P < 0.001 for VE by age category.
Abbreviation: VE, vaccine effectiveness.

**Table 2. Vaccine Effectiveness of mRNA-1273 and BNT162b2 Vaccines Against Hospitalization by Age**

Hospitalization

| | mRNA-1273 | | | | | | BNT162b2 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age <65 y | | | Age ≥65 y | | | Age <65 y | | | Age ≥65 y | | |
| | Controls | Cases | VE (95% CI) | Controls | Cases | VE (95% CI) | Controls | Cases | VE (95% CI) | Controls | Cases | VE (95% CI) |
| Unvaccinated | 2409 | 3248 | n/a | 4197 | 4798 | n/a | 2599 | 3498 | n/a | 4223 | 5091 | n/a |
| Month | | | | | | | | | | | | |
| 1 | 42 | 5 | 92.0 (76.1–97.3) | 89 | 39 | 66.1 (45.3–79.0) | 62 | 15 | 85.6 (72.6–92.4) | 94 | 51 | 61.0 (41.3–74.2) |
| 2 | 41 | 6 | 92.7 (78.0–97.6) | 77 | 19 | 89.0 (78.8–94.3) | 64 | 14 | 89.8 (79.6–94.9) | 75 | 56 | 41.0 (12.2–60.3) |
| 3 | 60 | 9 | 95.3 (88.1–98.1) | 79 | 32 | 76.4 (61.4–85.5) | 95 | 24 | 83.4 (71.7–90.2) | 50 | 35 | 48.5 (18.7–67.3) |
| 4 | 100 | 17 | 90.8 (83.2–94.9) | 93 | 48 | 66.7 (50.7–77.5) | 120 | 31 | 85.4 (76.8–90.9) | 99 | 67 | 50.8 (30.5–65.2) |
| 5 | 114 | 24 | 89.8 (82.6–94.0) | 201 | 85 | 71.9 (62.2–79.1) | 152 | 57 | 81.8 (73.3–87.6) | 150 | 146 | 26.7 (4.7–43.6) |
| 6 | 96 | 22 | 92.5 (86.1–95.9) | 284 | 144 | 67.2 (58.4–74.2) | 117 | 43 | 80.9 (70.5–87.7) | 238 | 238 | 16.4 (−2.7 to 32.0) |
| 7 | 42 | 25 | 83.1 (66.8–91.4) | 278 | 160 | 64.7 (55.2–72.3) | 56 | 41 | 57.0 (31.2–73.2) | 200 | 247 | 1.7 (−22.0 to 20.8) |

P < 0.001 for VE by age category.
Abbreviation: VE, vaccine effectiveness.

ICU Admission or Death

| | mRNA-1273 | | | | | | BNT162b2 | | | | | |
| | Age <65 y | | | Age ≥65 y | | | Age <65 y | | | Age ≥65 y | | |
| | Controls | Cases | VE (95% CI) | Controls | Cases | VE (95% CI) | Controls | Cases | VE (95% CI) | Controls | Cases | VE (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Unvaccinated | 942 | 1315 | n/a | 2049 | 2586 | n/a | 999 | 1400 | n/a | 2023 | 2712 | n/a |
| **Month** | | | | | | | | | | | | |
| 1 | 16 | 2 | 89.2 (49.5–97.7) | 47 | 24 | 75.4 (51.7–87.5) | 26 | 6 | 87.6 (61.0–96.1) | 41 | 20 | 67.4 (32.6–84.3) |
| 2 | 17 | 3 | 89.7 (44.8–98.1) | 37 | 13 | 87.9 (71.4–94.8) | 28 | 4 | 97.2 (86.4–99.4) | 34 | 24 | 48.6 (5.2–72.1) |
| 3 | 32 | 8 | 87.6 (66.7–95.3) | 46 | 15 | 88.1 (73.5–94.6) | 52 | 6 | 94.9 (86.6–98.1) | 34 | 8 | 78.8 (52.4–90.6) |
| 4 | 37 | 7 | 89.0 (72.9–95.5) | 61 | 28 | 80.5 (66.1–88.8) | 44 | 13 | 90.1 (76.2–95.9) | 36 | 33 | 45.5 (4.8–68.8) |
| 5 | 40 | 8 | 89.5 (74.7–95.7) | 106 | 36 | 84.7 (75.6–90.5) | 52 | 20 | 89.9 (79.2–95.1) | 75 | 66 | 42.5 (14.8–61.2) |
| 6 | 38 | 6 | 93.2 (77.0–98.0) | 143 | 82 | 70.8 (59.1–79.1) | 39 | 13 | 89.6 (74.1–95.8) | 116 | 117 | 28.6 (3.7–47.2) |
| 7 | 24 | 11 | 84.4 (59.0–94.1) | 146 | 70 | 73.8 (62.9–81.5) | 14 | 9 | 66.4 (7.70–87.8) | 99 | 98 | 29.3 (2.3–48.9) |

P < 0.001 for VE by age category.

Abbreviations: ICU, intensive care unit; VE, vaccine effectiveness.

illness and a positive PCR were reported in 87 010 (25%) veterans. Of these, 66 547 (76%) occurred among unvaccinated veterans and 16 232 (19%) among veterans who were fully vaccinated. A total of 22 529 veterans were hospitalized with symptoms consistent with COVID-19; of these, the proportions who were unvaccinated and fully vaccinated were 75% (n = 16 864) and 18% (n = 4155), respectively. A total of 7881 veterans were admitted to the ICU or died within 28 days of a SARS-CoV-2-positive test; of these, the proportions who were unvaccinated and fully vaccinated were 76% (n = 5991) and 18% (n = 1430), respectively.

**Varying Comparative Effectiveness of Vaccines Over Time**

Consistent with prior studies, VE for symptomatic SARS-CoV-2 infection, hospitalization, and ICU admission or death decreased over time ($P < 0.001$ for all 3 outcomes) (Supplementary Figure 3 and Supplementary Table 2).

As the number of veterans who received an Ad26.COV2.S vaccine and experienced 1 of the 3 outcomes was small, these individuals were excluded in subsequent analyses. Vaccine effectiveness for symptomatic infections over time varied by the type of vaccine ($P < 0.001$) (Supplementary Table 2 and Supplementary Figure 3). Effectiveness was higher for mRNA-1273 (84.6% and 46.6% for months 1 and 7) compared with BNT162b2 (76.1% and 0.1% for months 1 and 7). Vaccine effectiveness for hospitalizations due to symptomatic COVID-19 over time also varied by vaccine type ($P < 0.001$), and effectiveness was higher for mRNA-1273 (76.6% and 71.3% for months 1 and 7) compared with BNT162b2 (72.9% and 19.8% for months 1 and 7). Similarly, monthly VE for ICU admission or death was higher for mRNA-1273 compared with BNT162b2 ($P < 0.001$; 80.5% and 77.2% vs 74.7% and 39.5% at months 1 and 7, respectively). The differences in VE for all 3 outcomes were small in the initial 4 months and more pronounced in the subsequent 3 months.

**Comparative Vaccine Effectiveness Across Subgroups**

The differences in VE over time for symptomatic infection, hospitalization, and ICU admission or death between mRNA-1273 and BNT162b2 vaccines varied by age and chronic disease ($P_{interaction} < .001$ for most comparisons) (Figure 1; Supplementary Figure 4 and Supplementary Table 3) and were least pronounced for severe disease, including hospitalizations and ICU admission or death. Both mRNA vaccines were effective for nearly all time points in veterans who were younger or had no or only 1 chronic disease (Figure 1; Supplementary Figure 4; Tables 1–3; Supplementary Tables 4–6). For example, in patients <65 years of age, VE was largely preserved for hospitalizations (month 1 and 7 VEs were 92.0% and 83.1% for mRNA-1273 and 85.6% and 57.0% for BNT162b2, respectively) and ICU admission or death (month 1 and 7 VEs were 89.2% and 84.4% mRNA-1273 and 87.6% and

**Table 4. Comparative Effectiveness TND Study Comparing Odds Ratios for Time to Each Outcome Between mRNA-1273 and BNT162b2 for Each Month Since Vaccination, Separately for Veterans Aged <65 and ≥65 Years**

| | Age <65 y | | | | | Age ≥65 y | | | | | P Value for Time Interaction (Age*Time Interaction) |
| | Controls | | Cases | | | Controls | | Cases | | | |
| | mRNA-1273 | BNT162b2 | mRNA-1273 | BNT162b2 | OR (95% CI) | mRNA-1273 | BNT162b2 | mRNA-1273 | BNT162b2 | OR (95% CI) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Symptomatic infections | | | | | | | | | | | 0.001 (0.027) |
| 1 | 77 | 104 | 34 | 77 | 0.475 (0.27–0.83) | 96 | 113 | 84 | 81 | 0.839 (0.51–1.37) | |
| 2 | 140 | 124 | 40 | 101 | 0.36 (0.22–0.58) | 107 | 131 | 58 | 107 | 0.473 (0.2–1.14) | |
| 3 | 127 | 210 | 93 | 138 | 0.899 (0.63–1.29) | 111 | 162 | 93 | 108 | 0.428 (0.19–0.94) | |
| 4 | 279 | 424 | 189 | 343 | 0.694 (0.54–0.89) | 213 | 181 | 151 | 173 | 0.39 (0.2–0.78) | |
| 5 | 412 | 507 | 320 | 512 | 0.608 (0.49–0.75) | 501 | 350 | 330 | 364 | 0.39 (0.21–0.74) | |
| 6 | 341 | 460 | 376 | 445 | 1.043 (0.84–1.3) | 679 | 447 | 602 | 632 | 0.249 (0.13–0.47) | |
| 7 | 293 | 243 | 244 | 327 | 0.628 (0.48–0.82) | 708 | 508 | 651 | 698 | 0.436 (0.23–0.83) | |
| Hospitalizations | | | | | | | | | | | 0.434 (0.016) |
| 1 | 20 | 27 | 5 | 14 | 0.615 (0.15–2.47) | 37 | 39 | 37 | 39 | 0.876 (0.37–2.08) | |
| 2 | 18 | 29 | 6 | 13 | 0.744 (0.17–3.19) | 32 | 66 | 17 | 52 | 0.18 (0.02–1.71) | |
| 3 | 21 | 52 | 9 | 21 | 0.586 (0.19–1.8) | 30 | 34 | 31 | 31 | 0.786 (0.12–5.29) | |
| 4 | 47 | 86 | 13 | 26 | 0.595 (0.22–1.59) | 52 | 57 | 54 | 61 | 0.651 (0.11–4.03) | |
| 5 | 92 | 155 | 26 | 52 | 0.565 (0.28–1.12) | 138 | 118 | 86 | 142 | 0.387 (0.08–1.94) | |
| 6 | 63 | 108 | 23 | 39 | 0.803 (0.38–1.68) | 143 | 119 | 147 | 248 | 0.33 (0.07–1.63) | |
| 7 | 67 | 47 | 29 | 38 | 1.057 (0.46–2.45) | 189 | 135 | 178 | 246 | 0.317 (0.06–1.65) | |
| ICU or death | | | | | | | | | | | 0.126 (0.499) |
| 1 | 11 | 7 | 2 | 8 | 0.171 (0.02–1.66) | 20 | 15 | 24 | 13 | 1.774 (0.49–6.47) | |
| 2 | 8 | 16 | 2 | 4 | 1.903 (0.2–17.94) | 17 | 11 | 11 | 23 | 0.027 (0–0.93) | |
| 3 | 15 | 20 | 7 | 6 | 1.165 (0.23–6.01) | 20 | 15 | 13 | 8 | 0.18 (0.01–4.24) | |
| 4 | 25 | 50 | 6 | 10 | 1.134 (0.28–4.59) | 30 | 29 | 33 | 33 | 0.139 (0.01–2.25) | |
| 5 | 40 | 55 | 9 | 19 | 0.721 (0.24–2.15) | 56 | 36 | 39 | 64 | 0.052 (0–0.71) | |
| 6 | 22 | 44 | 6 | 13 | 0.492 (0.12–1.96) | 61 | 54 | 86 | 112 | 0.247 (0.02–3.58) | |
| 7 | 23 | 20 | 12 | 10 | 0.472 (0.11–1.96) | 66 | 42 | 82 | 107 | 0.125 (0.01–1.95) | |

Abbreviations: ICU, intensive care unit; OR, odds ratio; TND, test-negative design; VE, vaccine effectiveness.

66.4% for BNT162b2, respectively). Similar findings were observed for patients with a low burden of chronic diseases (Supplementary Figure 4, Supplementary Tables 4–6). In contrast, VE differed over time in older veterans and those with >1 chronic disease. For example, VE for mRNA-1273 for hospitalizations and ICU admission or death was >70% for most time points in elderly veterans ≥65 years of age and subjects with >1 chronic health condition. In contrast, effectiveness for BNT162b2 for the same outcomes in these patients declined below 50% after the second month, though confidence intervals were wide for many time points.

Models comparing mRNA-1273 with BNT162b2 in the modified TND confirmed statistically significant heterogeneity in the protective effect of mRNA-1273 across age groups for both symptomatic infections ($P = 0.001$) and hospitalizations ($P = 0.016$). Increased protection of mRNA-1273 compared with BNT162b2 was especially observed more than 5 months following vaccination (Table 4). For example, whereas in veterans aged <65 years the OR comparing vaccines for symptomatic infection was 1.04 (95% CI, 0.84–1.30) in month 6, in older veterans the OR was 0.25 (95% CI, 0.13–0.47). A similar trend was observed for symptomatic infections among veterans with chronic conditions, but the $P$ value for heterogeneity of CE odds ratios between chronic disease subgroups over time was not significant ($P = 0.057$) (Supplementary Table 7). Sample sizes precluded statistically significant comparisons for the ICU or death outcome.

## DISCUSSION

Our results suggest that vaccine effectiveness was higher for the mRNA-1273 vaccine when compared with the BNT162b2 vaccine, particularly in older veterans and those with chronic diseases. The effectiveness for BNT162b2 was <50% in these veterans, and therefore, the mRNA-1273 vaccine may be preferred in older adults with multiple chronic diseases. Overall, our findings suggest that the type of vaccine and perhaps the timing of booster doses may have to be precisely targeted based on age and chronic diseases.

Higher effectiveness was observed for mRNA-1273 compared with BNT162b2 in younger veterans and those with a low burden of chronic diseases, but these differences were small, and the 95% CIs overlapped. Thus, the clinical relevance of this finding is unclear. However, the differences in VE, particularly for hospitalizations, among older veterans and those with high burden of chronic diseases were large with nonoverlapping confidence intervals. More importantly, VE for BNT162b2 for symptomatic infection and hospitalization in these patients was <50% for most time points.

Collectively, these findings may favor the mrNA-1273 vaccine over BNT162b2 in older adults. Of note, the average age of participants in the international randomized controlled trial and subsequent real-world studies for the BNT162b2 vaccine was ~50 years, and the proportion of subjects with comorbidities was low or not known [2, 3, 13, 14]. Thus, the discrepant findings between our and prior studies for BNT162b2 vaccine may be due to differences in participant characteristics. We performed comparative VE analyses over 7 months in distinct subgroups of veterans who were matched on age, location, and socioeconomic status, which may explain the differences between our results and recently published data [5, 12].

Our study has several strengths, including a large sample size of US residents across 50 states, data being collected from multiple sources in one of the largest integrated health care systems, and adjustment for several confounding variables. Additionally, our estimates for effectiveness over time for the BNT162b2 vaccine among younger persons are similar to estimates from recent studies [15, 16]. Our findings are consistent with studies showing that mRNA-1273 was more effective compared with BNT162b2 vaccine to reduce risk of symptomatic infection and hospitalization and to increase levels of antibodies [11–13]. Finally, our results showing that VE varies by age and chronic diseases were consistent in using different approaches.

Limitations include the lack of generalizability of our findings to nonveterans, women, and small sample sizes of persons who received the Ad26.COV2.S vaccine, and for some of the subgroup analyses for the mRNA-1273 and BNT162b2 vaccines, and potential for residual confounding despite adjusting for multiple covariates. In addition, we did not perform chart review to confirm that deaths within 28 days of a SARS-CoV-2-positive test were caused by COVID-19, which could have resulted in misclassification bias. However, this bias would have applied to all 3 vaccines and therefore should not have affected our comparative vaccine effectiveness analysis. Also, our study period does not include the period of Omicron predominance, a variant characterized by overall lower vaccine effectiveness.

In conclusion, the mRNA-1273 vaccine had higher effectiveness for symptomatic SARS-COV2 infection, hospitalization, and ICU admission or death compared with BNT162b2, particularly for older veterans and those with a higher burden of chronic disease. If validated in future studies, individualized vaccination strategies based on type of vaccine, variant subtype, and individual patient characteristics may be necessary.

## References

1. Butt AA, Omer SB, Yan P, Shaikh OS, Mayr FB. SARS-CoV-2 vaccine effectiveness in a high-risk national population in a real-world setting. Ann Intern Med **2021**; 174:1404–8. doi:10.7326/M21-1577
2. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA COVID-19 vaccine in a nationwide mass vaccination setting. New Engl J Med **2021**; 384:1412–23. doi:10.1056/NEJMoa2101765
3. 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**; 27:1614–21. doi:10.1038/s41591-021-01446-y
4. 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**; 27:2136–43. doi:10.1038/s41591-021-01583-4
5. Dickerman BA, Gerlovin H, Madenci AL, et al. Comparative effectiveness of BNT162b2 and mRNA-1273 vaccines in U.S. veterans. New Engl J Med **2021**. 386:105–15. doi:10.1056/NEJMoa2115463
6. Cohn BA, Cirillo PM, Murphy CC, Krigbaum NY, Wallace AW. SARS-CoV-2 vaccine protection and deaths among US veterans during 2021. Science **2021**; 375:331–6. doi:10.1126/science.abm0620
7. Butt AA, Yan P, Shaikh OS, Mayr FB, Omer SB. Rate and risk factors for severe/critical disease among fully vaccinated persons with breakthrough SARS-CoV-2 infection in a high-risk national population. Clin Infect Dis. **In press**. doi:10.1093/cid/ciab1023
8. Butt AA, Chemaitelly H, Khal AA, et al. SARS-CoV-2 vaccine effectiveness in preventing confirmed infection in pregnant women. J Clin Invest **2021**; 131:e153662. doi:10.1172/JCI153662
9. Butt AA, Yan P, Shaikh OS, Mayr FB. Outcomes among patients with breakthrough SARS-CoV-2 infection after vaccination in a high-risk national population. EClinicalMedicine **2021**; 40:101117. doi:10.1016/j.eclinm.2021.101117
10. World Health Organization. Evaluation of COVID-19 vaccine effectiveness. **2021**. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1. Accessed September 15, 2021.
11. Agrawal U, Katikireddi SV, McCowan C, et al. COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2·57 million people in Scotland (EAVE II): a prospective cohort study. Lancet Respir Med **2021**; 9:1439–49. doi:10.1016/S2213-2600(21)00380-5
12. Young-Xu Y, Korves C, Roberts J, et al. Coverage and estimated effectiveness of mRNA COVID-19 vaccines among US veterans. JAMA Netw Open **2021**; 4: e2128391. doi:10.1001/jamanetworkopen.2021.28391
13. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. New Engl J Med **2020**; 383:2603–15. doi:10.1056/NEJMoa2034577
14. Thomas SJ, Moreira ED, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine through 6 months. New Engl J Med **2021**; 385: 1761–73. doi:10.1056/NEJMoa2110345
15. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. New Engl J Med **2021**; 385:e83. doi:10.1056/NEJMoa2114114
16. Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 vaccine in Israel. New Engl J Med **2021**; 385:e85. doi:10.1056/NEJMoa2114228