Comparison of Moderna versus Pfizer-BioNTech COVID-19 vaccine outcomes: A target trial emulation study in the U.S. Veterans Affairs healthcare system

George N. Ioannou,[a,b]* Emily R. Locke,[b] Pamela K. Green,[b] and Kristin Berry[b]

[a]Division of Gastroenterology, Veterans Affairs Puget Sound Healthcare System and University of Washington, 1660 S. Columbian Way, Seattle, WA 98108, USA
[b]Research and Development, Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA

eClinicalMedicine 2022;45: 101326
Published online 5 March 2022
https://doi.org/10.1016/j.eclinm.2022.101326

Summary

Background mRNA COVID-19 vaccines manufactured by Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) have been shown to be efficacious but have not been compared in head-to-head clinical trials.

Methods We designed this observational study to emulate a target trial of COVID-19 vaccination by BNT162b2 versus mRNA-1273 among persons who underwent vaccination in the national U.S. Veterans Affairs (VA) healthcare system from 11/12/2020 to 25/03/2021 using combined VA and Medicare electronic health records. We identified the best matching mRNA-1273 recipient(s) for each BNT162b2 recipient, using exact/coarsened-exact matching (calendar week, VA integrated service network, age buckets and Charlson comorbidity index buckets) followed by propensity score matching. Vaccine recipients were followed from the date of first vaccine dose until 25/08/2021 for the development of SARS-CoV-2 infection, SARS-CoV-2-related hospitalization or SARS-CoV-2-related death.

Findings Each group included 902,235 well-matched vaccine recipients, followed for a mean of 192 days, during which 16,890 SARS-CoV-2 infections, 3591 SARS-CoV-2-related hospitalizations and 381 SARS-CoV-2-related deaths were documented. Compared to BNT162b2, mRNA-1273 recipients had significantly lower risk of SARS-CoV-2 infection (adjusted hazard ratio [aHR] 0.736, 95% CI 0.696−0.779) and SARS-CoV-2-related hospitalization (aHR 0.633, 95% CI 0.562−0.713), which persisted across all age groups, comorbidity burden categories and black/white race. The differences between mRNA-1273 and BNT162b2 in risk of infection or hospitalization were progressively greater when the follow-up period was longer, i.e. extending to March 31, June 30 or August 25, 2021. These differences were more pronounced when we analyzed separately the outcomes that occurred during the follow-up period from July 1 to August 25, 2021 when the Delta variant became predominant in the U.S. (aHR for infection 0.584, 95% CI 0.533−0.639 and aHR for hospitalization 0.387, 95% 0.311−0.482). SARS-CoV-2-related deaths were less common in mRNA-1273 versus BNT162b2 recipients (168 versus 213) but this difference was not statistically significant (aHR 0.808, 95% CI 0.592−1.103).

Interpretation In conclusion, although absolute rates of infection, hospitalization and death in both vaccine groups were low regardless of the vaccine received, our data suggests that compared to BNT162b2, vaccination with mRNA-1273 resulted in significantly lower rates of SARS-CoV-2-infection and SARS-CoV-2-related hospitalization. These differences were greater with longer follow-up time since vaccination and even more pronounced in the Delta variant era.

Funding U.S. Department of Veterans Affairs, grant numbers COVID19−8900−11 and C19 21−278.

Introduction

The US Food and Drug Administration (FDA) issued Emergency Use Authorization (EUA) for the two-dose mRNA COVID-19 vaccines manufactured by Pfizer-BioNTech (BNT162b2) on 12/11/2020 and by Moderna (mRNA-1273) on 12/18/2020. The effectiveness of each vaccine against infection, hospitalization and death has been demonstrated in randomized controlled trials and

*Corresponding author at: Division of Gastroenterology, Veterans Affairs Puget Sound Healthcare System and University of Washington, 1660 S. Columbian Way, Seattle, WA 98108, USA.
E-mail addresses: georgei@medicine.washington.edu, george.ioannou@va.gov (G.N. Ioannou).

Research in context

Evidence before this study

We searched PubMed for studies published since February 2020 by searching all fields for ("BNT162b2" or "mRNA-1273" or "COVID-19 vaccine"), with no language restrictions. The two mRNA COVID-19 vaccines (BNT162b2 and mRNA-1273) have differences in dosing, interval between doses and composition of the lipid nanoparticle vehicles. Randomized controlled trials comparing the effectiveness of the two vaccines have not been performed.

Added value of this study

To our knowledge, our study is the largest target trial emulation study comparing 902,235 BNT162b2 vaccine recipients and their matched counterparts who received mRNA-1273 with a long period of follow-up (mean follow-up 192 days) extending into the period of predominance of the Delta variant. Compared to BNT162b2, vaccination with mRNA-1273 resulted in significantly lower rates of SARS-CoV-2-infection (adjusted hazards ratio 0.736, 95% CI 0.696–0.779) and SARS-CoV-2-related hospitalization (aHR 0.633, 95% CI 0.562–0.713). These differences were greater with longer follow-up time since vaccination and even more pronounced in the Delta variant era.

Implications of all the available evidence

Primary series vaccination with two doses mRNA-1273 appears to be superior to BNT162b2 against infection and hospitalization related to the Alpha and Delta SARS-CoV-2 variants. Future studies should also compare "booster" doses of the two vaccines and extend the observation to the time period of Omicron variant predominance.

observational studies.[1–8] However, it is unclear if one vaccine is superior to the other, especially against the B.1.617.2 (Delta) variant, or as more time from vaccination accrues. Differences in effectiveness between these two vaccines would have important clinical and public health implications and might also inform the composition and dosing of future mRNA vaccines. Although both vaccines include full-length, Spike protein-encoding mRNAs, they have different doses of mRNA content (100 μg for mRNA-1273 versus 30 μg for BNT162b2), interval between doses (28 days for mRNA-1273 versus 21 days for BNT162b2), and composition of the lipid nanoparticle vehicles. It has been suggested that vaccination with mRNA-1273 may elicit greater immune responses than BNT162b2.[9] Some studies suggested a greater drop in vaccine effectiveness over time in BNT162b2 than in mRNA-1273 vaccine recipients[9] and slightly lower vaccine effectiveness against infection[10] and hospitalization.[8–11]

The Veterans Affairs (VA) healthcare system, the largest national, comprehensive healthcare system in the U.S., has vaccinated a very large proportion of its enrollees using both of the mRNA vaccines across the country. It is unlikely that a randomized controlled trial comparing the two vaccines will ever be performed. Therefore, we used target trial emulation design[12] to compare the two mRNA vaccines in the VA healthcare system with respect to risk of infection, hospitalization and death.

Methods

Study setting and data sources

The VA provides care at 171 medical centers and 1112 outpatient clinics throughout the country. It employs a nationwide electronic health records (EHR) system enabling accurate ascertainment of relevant baseline characteristics and potential confounders. We used data from the VA's Corporate Data Warehouse (CDW), a relational database of VA enrollees' comprehensive EHR, including the VA COVID-19 Shared Data Resource, which includes analytic variables provisioned by the VA Informatics and Computing Infrastructure (VINCI) on all VA enrollees who were tested for, or vaccinated against SARS-CoV2 and detailed clinical outcomes for those who tested positive.[13] We also used Medicare data obtained through the VA Information Resource Center (VIReC)[14] to identify any additional VA enrollees diagnosed with COVID-19 or hospitalized for COVID-19 through Medicare-covered services

The study was approved by the VA Puget Sound Institutional Review Board (protocol # 01,885), which waived the requirement for informed consent because this was a retrospective study based on electronic health records.

Specification and emulation of target trial: eligibility criteria and study population

We designed this observational study to emulate a target randomized controlled trial of COVID-19 vaccination by BNT162b2 versus mRNA-1273 in the national VA healthcare system with a recruitment period between December 11, 2020 and March 25, 2021 and with the primary endpoints being time from vaccination to SARS-CoV-2 infection, SARS-CoV-2-related hospitalization or SARS-CoV-2-related death.[12] To facilitate target trial emulation and determine the target trial population, we created a cohort of all VA enrollees aged 18 years or older who were alive as of 11 December 2020 (the date of emergency use authorization for BNT162b2) and had an inpatient or outpatient encounter in the VA health care system in the preceding 12 months (n = 5 766 638) (Figure 1). Among these, we identified those who received at least one dose of BNT162b2 or mRNA-

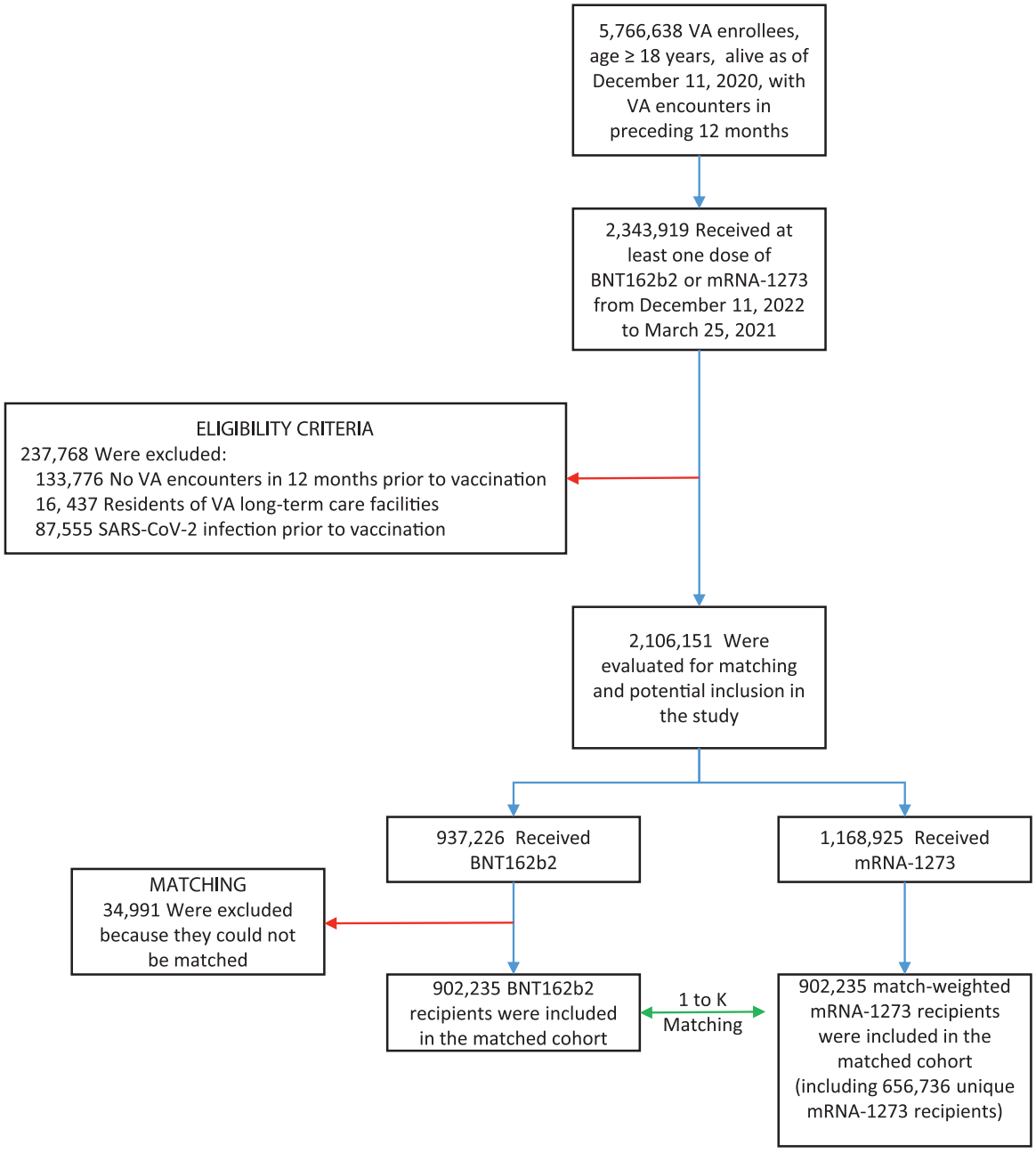

Figure 1. Eligibility criteria and matching process resulting in the selection of a study population for the emulation of a target trial comparing the effectiveness of BNT162b and mRNA-1273 COVID-19 vaccines in the national Veterans Affairs healthcare system.

Abbreviations: VA denotes the U.S. Department of Veterans Affairs and SARS-CoV-2 the severe acute respiratory syndrome coronavirus 2.

1273 between December 11, 2020 and March 25, 2021 (n = 2343,919), either administered within VA and documented in VA pharmacy records (84.9%) or administered outside the VA but with the type and date of vaccination documented in VA records (15.1%). We then applied the target trial's three eligibility criteria to exclude ineligible persons as follows. We excluded 133,776 who did not have an outpatient or inpatient encounter in the VA healthcare system in the preceding 12 months prior to vaccination, 16,437 who were living in VA long-term care facilities, and 87,555 with evidence of SARS-CoV-2 infection prior to the vaccination date either in VA or Medicare date (because they have a high rate of protection against re-infection[15] thereby masking

the effect of vaccination). The remaining 2106,151 persons who received at least one dose of mRNA vaccine including 937,226 with BNT162b2 and 1168,925 with mRNA-1273 were eligible to be included in the emulation of the target trial.

Specification and emulation of target trial: treatment assignment

We aimed to emulate a target trial that would randomize eligible participants after stratification by the following characteristics: calendar week of vaccination, VA Integrated Service Network (or VISN, the 19 administrative regions of VA[16]), age (6-year buckets) and Charlson Comorbidity Index (CCI) (3-point buckets). Calendar week and VISN were selected as stratification variables because of the well-described temporal and geographic variability in risk of SARS-CoV-2 infection. Age and CCI were chosen because these are the two characteristics most strongly associated with development of SARS-CoV-2 infection, hospitalization or death in VA patients.[17–20] We emulated this stratification strategy by matching mRNA-1273 to BNT162b2 recipients by these characteristics. To further reduce any residual confounding that might be present after this exact/coarsened-exact matching step, we executed an additional propensity score matching step ultimately aiming to identify the best mRNA-1273 recipient match(es) for each BNT162b2 recipient. This strategy of exact matching (calendar week, VISN), coarsened exact matching (age, CCI) and propensity score matching was implemented using STATA's kmatch command[21] (StataCorp, College Station, TX. USA). Each BNT162b2 recipient was matched to mRNA-1273 recipient(s) with replacement and in a 1:K variable ratio, where K varied based on the number of propensity score ties. We included all ties to avoid imbalance due to random pruning. Entropy balancing of means in all matching characteristics was included as a refinement in the matching process. The characteristics used in the propensity score logistic regression model were selected *a priori* and were characteristics associated with the likelihood of getting vaccinated by BNT162b2 versus mRNA-1273 (the exposure) and the risk of developing SARS-CoV-2 infection, hospitalization or death (the outcomes) in the VA population,[17,18,20,22] and categorized as shown in Table 1. These characteristics were: age, sex, self-reported race and ethnicity, urban/rural residence (based on zip codes, using data from the VA Office of Rural Health,[23] which uses the Secondary Rural-Urban Commuting Area [RUCA] for defining rurality), VISN, CCI, body mass index (BMI, calculated using measured weight and height), diabetes, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) and the Care Assessment Need (CAN) score. The CAN score is a validated measure of 1-year mortality in VA enrollees calculated using

	Matched Cohorts who received COVID-19 vaccination with	
	Pfizer-BioNTech (BNT162b2) *N* = 902,235	**Moderna (mRNA-1273) *N* = 902,235**
Date of vaccination		
13/12/20–12/19/20	41(0.0)	41(0.0)
12/20/20–12/26/20	2684(0.3)	2684(0.3)
12/27/20- 1/2/21	8715(1.0)	8715(1.0)
1/3/21- 1/9/21	24,788(2.7)	24,788(2.7)
1/10/21- 1/16/21	63,766(7.1)	63,766(7.1)
1/17/21- 1/23/21	95,983(10.6)	95,983(10.6)
1/24/21- 1/30/21	113,362(12.6)	113,362(12.6)
1/31/21- 2/6/21	95,311(10.6)	95,311(10.6)
2/7/21- 2/13/21	73,261(8.1)	73,261(8.1)
2/14/21- 2/20/21	52,119(5.8)	52,119(5.8)
2/21/21- 2/27/21	83,154(9.2)	83,154(9.2)
2/28/21- 3/6/21	91,393(10.1)	91,393(10.1)
3/7/21- 3/13/21	82,521(9.1)	82,521(9.1)
3/14/21- 3/25/21	115,137(12.8)	115,137(12.8)
Sex (%)		
Female	7.8	7.1
Male	92.2	92.9
Age (years), mean ±SD	67.5 ± 13.3	67.5 ± 13.3
Age (years), median (IQR)	71.0 (61.0,75.0)	71.0 (61.0,75.0)
Age Group (%)		
18 to 49	10.5	10.5
50 to 59	12.6	12.6
60 to 64	10.0	10.0
65 to 69	12.7	12.3
70 to 74	25.7	25.9
75 to 79	14.2	14.3
80 to 84	6.7	6.7
85 to 89	5.0	5.0
≥90	2.7	2.7
Race (%)		
White	69.1	70.5
Black	19.9	19.0
Asian	1.3	1.2
American Indian/Alaska Native	0.7	0.6
Pacific Islander/ Native Hawaiian	0.9	0.8
Declined/Unknown/Missing	8.0	7.8
Ethnicity (%)		
Non-Hispanic	88.3	89.0
Hispanic	6.3	5.7
Declined/Unknown/Missing	5.5	5.3
Urban/Rural (%)		
Rural/Highly rural	39.8	39.8
Urban	59.5	59.6
Missing	0.7	0.6
VA Integrated Service Network (VISN) (%)		
1	4.5	4.5
2	4.7	4.7
4	5.2	5.2
5	3.1	3.1
6	6.0	6.0
7	6.1	6.1
8	11.8	11.8
9	3.2	3.2
10	6.3	6.3
12	5.4	5.4
15	3.5	3.5
16	5.9	5.9
17	5.1	5.1
19	3.8	3.8
20	4.8	4.8
21	5.9	5.9
22	8.2	8.2
23	6.4	6.4

Table 1 *(Continued)*

	Matched Cohorts who received COVID-19 vaccination with	
	Pfizer-BioNTech (BNT162b2) *N* = 902,235	**Moderna (mRNA-1273) *N* = 902,235**
Body Mass Index (kg/m^2), mean ±SD	30.0 ± 5.6	29.9 ± 5.5
Body Mass Index (kg/m^2), median (IQR)	29.3 (26.4,32.7)	29.3 (26.5,32.6)
Body Mass Index (kg/m^2), group (%)		
<18.5	0.7	0.5
18.5 to <25	15.7	15.3
25 to <30 (Overweight)	32.9	33.2
30 to <35 (Obese I)	24.5	25.4
35 to <40 (Obese II)	10.7	10.2
≥40 (Obese III)	5.3	4.9
Missing	10.2	10.5
Charlson Comorbidity Index, mean ± SD	2.6 ± 2.8	2.6 ± 2.8
Charlson Comorbidity Index, median (IQR)	2.0 (0.0,4.0)	2.0 (0.0,4.0)
Charlson Comorbidity Index group (%)		
0	28.1	28.1
1	17.4	17.8
2	13.1	13.3
3	11.6	11.1
4	8.1	8.2
5–6	11.1	11.0
7–8	5.9	5.8
≥9	4.7	4.7
Diabetes (%)		
No	68.7	68.8
Yes	31.3	31.2
Chronic Kidney Disease (%)		
No	89.1	89.6
Yes	10.9	10.4
Congestive heart failure (%)		
No	95.1	95.5
Yes	4.9	4.5
Chronic Obstructive Pulmonary Disease (%)		
No	86.7	87.3
Yes	13.3	12.7
CAN Score† for mortality w/in 1 year, mean ± SD	54.7 ± 26.0	54.5 ± 25.9
CAN Score† for mortality w/in 1 year, median (IQR)	60.0 (35.0,75.0)	60.0 (35.0,75.0)
CAN Score† for mortality w/in 1 year group (%)		
0–30	21.4	21.4
31–55	26.2	26.2
56–75	22.7	22.6
76–90	17.0	16.9
91–95	1.1	1.0
96–98	3.2	3.1
99	0.9	0.9
Missing	7.4	7.9
Immunosuppressant medications* (%)	6.4	6.4

***Table 1*: Baseline sociodemographic and clinical characteristics of persons who received COVID-19 vaccination between December 11, 2020 and March 25, 2021 in the VA healthcare system with Pfizer-BioNTech (BNT162b2) vaccines and their matched counterparts who received Moderna (mRNA-1273) vaccines.**

† CAN score is the Care Assessment Needs score a validated measure of 1-year mortality in VA enrollees, presented as a percentile of all VA enrollees.

* Immunosuppressant medications prescribed in the previous year (see list of immunosuppressant medications in Supplementary Appendix-Supplementary Methods 2).

socio-demographics, clinical diagnoses, vital signs, medications, laboratory values, and health care utilization data from VA's national EHR.[17,24] Diabetes, CHF, COPD and CKD were defined by international classification of disease, tenth revision (ICD-10) codes documented in VA EHR in the 2-year period prior to vaccination. Lists of ICD-10 codes defining each of these conditions were developed by the VA Centralized Interactive Phenomics Resource or CIPHER (see Supplementary Appendix for these ICD10 codes and for CCI calculation method). We additionally extracted immunosuppressant medications (see Supplementary Appendix) prescribed in the prior year to confirm comparability in the matched groups.

The end result of executing STATA's kmatch procedure was to assign each person who received the first dose of BNT162b2 to up to K persons who received the first dose of mRNA-1273 during the same calendar week and within the same VISN, who also had the same age bucket and CCI bucket and had a nearest-neighbor propensity score within a caliper of 0.019 (0.2 times the standard deviation of the propensity score).

Target trial follow-up period and primary endpoints: SARS-CoV-2 infection, SARS-CoV-2-related hospitalization and SARS-CoV-2-related death

Follow-up of eligible vaccine recipients for the study's three primary endpoints extended from first vaccine dose to August 25, 2021 resulting in a minimum potential follow-up of 5 months and maximum of 8.5 months. Vaccine recipients were censored at the time of death unrelated to COVID-19, or on August 25, 2021.

Vaccine recipients who tested positive for SARS-CoV-2 RNA in a respiratory specimen within the VA system based on polymerase chain reaction (PCR) tests as well as those with such tests performed outside the VA but documented in VA records were identified by the VA National Surveillance Tool. The earliest date of a documented positive test was taken as each patient's date of infection. We also identified any additional vaccine recipients who had a diagnosis of COVID-19 recorded in CMS-Medicare records obtained through VIReC[14] based on ICD-10 codes. The earliest date of documentation was taken as the date of infection. Medicare records do not include the results of SARS-CoV-2 tests.

The majority (75.49%) of incident infections were found only in VA data, 18.43% only in Medicare data and 6.07% in both data sources.

SARS-CoV-2-related hospitalization was defined as hospitalization on or within 30 days after a positive test or COVID-19 diagnosis. We used both VA and CMS-Medicare data to identify these hospitalizations, of which 64.1% were recorded in VA data, 34.6% in Medicare data and 1.3% in both.

SARS-CoV-2-related death was defined as death from any cause within 30 days of a positive test or COVID-19

diagnosis.[17,18,20,22] Deaths occurring both within and outside the VA are comprehensively captured in CDW from a variety of VA and non-VA sources including VA inpatient files, VA Beneficiary Identification and Records Locator System (BIRLS), Social Security Administration (SSA) death files, and the Department of Defense.[25]

Statistical analysis

We used Cox proportional hazards regression to compare BNT162b2 recipients versus matched mRNA-1273 recipients with respect to time to development of SARS-CoV-2 infection, hospitalization or death starting from the date of receipt of the first vaccine dose and extending up to August 25, 2021. We calculated an unadjusted HR as well as a HR adjusted for all the baseline characteristics listed in Table 1. All analyses were weighted to account for variable-ratio matching and matching with replacement. A robust sandwich-type variance estimator was used to account for clustering within matched group, clustering within subjects, and clustering in the cross-classification of the matched and within subject clusters.[26]

We also estimated the absolute risk of each outcome derived from the Kaplan-Meier estimator for a period of 24 weeks since vaccination and 24-week risk differences and risk ratios comparing BNT162b2 versus mRNA-1273 groups. The 95% confidence intervals for risks were calculated using a robust sandwich-type variance estimator. We chose nonparametric bootstrapping with 500 samples to calculate 95% confidence intervals for risk difference and ratio due to the lack of closed form solutions to the variance estimators.

Subgroup analysis determined *a priori* were based on age, CCI categories and black/white race.

To investigate whether any differences between mRNA-1273 versus BNT162b2 recipients were more pronounced with longer follow-up since vaccination we performed analyses with follow-up extending to March 31 or June 30 as well as August 25,2021. In an exploratory analysis that is subject to "depletion of susceptibles" bias,[27] we analyzed separately outcomes that occurred after July 1, 2021, in order to determine whether any differences between the two vaccines were pronounced against the Delta variant, which became the predominant variant in the U.S. after July 1, 2021, including among VA enrollees.[8] The analysis of outcomes that occurred after July 1, 2021 was limited to matched pairs who were still alive and uninfected as of that date with a time of origin of July 1, 2021.

Negative outcome control. We used a negative outcome control[28] to verify there was no uncontrolled residual confounding or unsuspected source of selection bias after matching. We chose as a negative outcome control the incidence of SARS-CoV-2 infection in the ten days following the first vaccine dose, since there is no expectation of protective effect immediately after vaccination.

Missing values. We chose not to impute missing values in BMI and CAN score (shown in Table 1), but rather modeled them with a missing category as part of the propensity score logistic regression model, because "missingness" is these two variables is informative and meaningful, and matching for "missingness" would result in better matching. Missing BMI is an in indicator of VA enrollees who had not had their weight measured in the prior year, while missing CAN score is an indicator of VA enrollees who did not have a primary care provider because it is calculated only in those assigned to a VA primary care provider.

Role of the funding source

The funding source did not have any involvement in study design, data collection, data analysis, data interpretation or in writing of the article. All four co-authors had access to the data and agreed with the decision to submit for publication.

Results

Baseline characteristics of BNT162b2 recipients and their matched counterparts who received mRNA-1273

All baseline characteristics were well balanced between the two matched cohorts (n = 902,235 in each group, Table 1). Baseline characteristics of BNT162b2 and mRNA-1273 vaccine recipients before matching are shown in Supplementary Appendix-Supplementary Table 1. Comparison of the standardized mean differences and variance ratios of baseline characteristics and the cumulative distribution of propensity scores between persons vaccinated with BNT162b2 and mRNA-1273 shown for the raw and matched data demonstrate balance after matching (Figure 2). Prior to matching the absolute standardized difference in baseline characteristics between BNT162b2 and mRNA-1273 recipients ranged from 0.000 to 0.297 with a median of 0.039 (IQR: 0.010–0.079). After matching the absolute standardized differences ranged from 0.000 to 0.021 with a median of 0.006 (IQR: 0.001–0.010). The BNT162b2 recipients consisted of 902,235 unique persons who were matched 1:K to 656,736 unique mRNA-1273 recipients. Matching with replacement allowed the matching of ~96% of the BNT162b2 to ~56% of the mRNA-1273 recipients. mRNA-1273 recipients were reused as matches up to 120 times with a median of 2 BNT162b2 recipients (inter-quartile range (IQR): 1–4). BNT162b2 vaccine recipients had up to 136 tied matches with a median of 1 (IQR: 1–2).

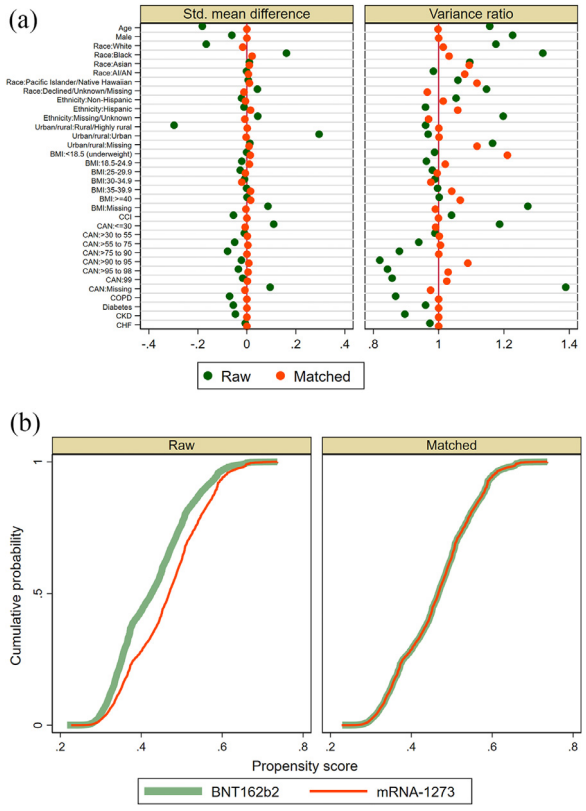

Figure 2. Comparison of baseline characteristics in Moderna (mRNA-1273) versus Pfizer-BioNTech (BNT162b2) vaccine recipients demonstrated balance after matching.

a. Absolute standardized mean difference and variance ratio of baseline characteristics between mRNA-1273 versus BNT162b2 recipients.

The green dots show the raw results and the orange dots the results after matching. The results demonstrate that all measured variables were well-balanced between the two vaccine groups after matching.

Abbreviations: AI/AN: American Indian/Alaska Native; BMI: Body Mass Index; CAN: Care Assessment Need score; CHF: Congestive Heart Failure; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease.

b. Cumulative distribution of propensity score between mRNA-1273 versus BNT162b2 recipients shown for the raw and matched data.

The green line demonstrates the propensity score distribution for BNT162b2 and the orange line for mRNA-1273. The figure demonstrates almost complete overlap of the propensity score distributions in the two vaccine groups after matching.

By design, an identical number of match-weighted persons initiated vaccination in the mRNA-1273 and BNT162b2 groups each week from 12/13/21 to 3/25/21 (Table 1). Both BNT162b2 and mRNA-1273 groups were predominantly male (92.2% vs. 92.9%), had advanced mean age (67.5 yrs in both groups), diverse racial/ethnic distribution (e.g. Black 19.0% vs. 19.0%, Hispanic 6.3% vs. 5.7%) and a substantial comorbidity burden (mean CCI 2.6 in both groups) and similar CAN score (54.7 vs. 54.5) with a similar proportion not having an assigned primary care team as evidenced by missing CAN score (7.4% vs. 7.9%). Major comorbid conditions such as diabetes, CHF, COPD and CKD and exposure to immunosuppressant medications were common and nearly equally distributed in the two groups.

Compliance with second vaccine dose

A second vaccine dose was administered to a very similar proportion of mRNA-1273 (96.5%) and BNT162b2 (97.3%) vaccine recipients. The second dose was administered within ±4 days of the recommended date (i.e. 21 ± 4 days for BNT162b2 and 28 ± 4 days for mRNA-1273 after the first dose) in a similarly high proportion of mRNA-1273 (93.5%) and BNT162b2 (94.4%) vaccine recipients. Detailed information on distribution of mRNA-1273 and BNT162b2 vaccines in the VA system during this time period was recently published by our group.[29]

SARS-CoV-2 infection in BNT162b2 versus mRNA-1273 recipients

During a mean follow-up of 192 days, identical in the BNT162b2 and mRNA-1273 groups, 16,890 SARS-CoV-2 infections, 3591 SARS-CoV-2-related hospitalizations and 381 SARS-CoV-2-related deaths were documented.

Compared to BNT162b2 recipients, mRNA-1273 recipients had a ~26% lower risk of SARS-CoV-2 infection (adjusted hazard ratio [aHR] 0.736, 95% CI 0.696−0.779), an association that persisted in a similar magnitude across all age (18 to <65, 65 to <75, ≥75) and CCI sub-groups (0−1,2−3, ≥4) and for both black and white persons (Table 2 and Figure 3a). The difference between mRNA-1273 and BNT162b2 recipients was progressively greater when follow-up was longer, i.e. extending to March 31, 2021 (mean follow-up 45 days, aHR 0.913, 95% CI 0.838−0.994), or ~9% lower risk), versus June 30, 2021 (mean follow-up 135 days, aHR 0.851, 95% CI 0.793−0.913 or ~15% lower risk) versus the main analysis, which extended to August 25, 2021 (mean follow-up 192 days, 26% lower risk). The Kaplan-Meier curves also demonstrated an increasing rate of infection and an increasing gap between mRNA-1273 and BNT162b2 recipients as follow-up extended from 150 to 220 days from vaccination (Figure 3a). The difference between mRNA-1273 and BNT162b2 recipients was greater when we analyzed separately the outcomes that occurred in the time period after July 1, 2021 (aHR 0.584, 95% CI 0.533−0.639) − when the Delta variant was predominant - than in the time period before July 1, 2021 (aHR 0.851, 95% CI 0.793−0.913).

SARS-CoV-2-related hospitalization in BNT162b2 versus mRNA-1273 recipients

Compared to BNT162b2 recipients, mRNA-1273 recipients had a ~37% lower risk of SARS-CoV-2-related

Type ofCOVID-19 vaccination	N	Person-days	SARS-CoV-2 infectionsN	SARS-CoV-2 infections Incidence rate per 1000 person-days	Unadjusted Hazard Ratio(95% CI)	Adjusted Hazard Ratio†(95% CI)
All Persons, Follow-up extending for 10 days only (negative outcome control)						
BNT162b2	902,235	9017,808	1158	0.128	1	1
mRNA-1273	902,235	9017,753	1114	0.123	0.962 (0.841−1.100)	0.966 (0.841−1.110)
All Persons, Follow-up extending to 3/31/21						
BNT162b2	902,235	41,094,639	3503	0.085	1	1
mRNA-1273	902,235	41,013,742	3173	0.077	0.908 (0.834−0.989)	0.913 (0.838−0.994)
All Persons, Follow-up extending to 6/30/21						
BNT162b2	902,235	122,692,177	5546	0.045	1	1
mRNA-1273	902,235	122,688,660	4697	0.038	0.847 (0.789−0.908)	0.851 (0.793−0.913)
All Persons, Follow-up extending to 8/25/21						
BNT162b2	902,235	172,770,241	9751	0.056	1	1
mRNA-1273	902,235	172,858,651	7139	0.041	0.732 (0.691−0.774)	0.736 (0.696−0.779)
SUB-GROUPS, Follow-up extending to 8/25/21						
Age 18 to <65						
BNT162b2	298,557	52,942,252	2907	0.055	1	1
mRNA-1273	299,272	53,084,087	2170	0.041	0.745 (0.666−0.834)	0.749 (0.670−0.838)
Age 65 to <75						
BNT162b2	346,354	67,361,564	3706	0.055	1	1
mRNA-1273	344,323	66,924,615	2606	0.035	0.707 (0.646−0.775)	0.711 (0.649−0.779)
Age ≥ 75						
BNT162b2	257,324	52,466,425	3138	0.060	1	1
mRNA-1273	258,640	52,849,949	2362	0.045	0.746 (0.680−0.819)	0.752 (0.685−0.824)
CCI 0−1						
BNT162b2	410,655	77,037,408	3122	0.041	1	1
mRNA-1273	413,690	77,551,674	2378	0.031	0.757 (0.666−0.859)	0.758 (0.668−0.859)
CCI 2−4						
BNT162b2	296,033	57,316,422	3240	0.057	1	1
mRNA-1273	293,610	56,930,653	2454	0.043	0.762 (0.692−0.839)	0.767 (0.696−0.845)
CCI ≥ 5						
BNT162b2	195,547	38,416,411	3389	0.088	1	1
mRNA-1273	194,935	38,376,324	2307	0.060	0.682 (0.628−0.741)	0.687 (0.633−0.747)
White persons						
BNT162b2	623,437	120,248,394	6903	0.057	1	1
mRNA-1273	636,466	122,750,739	5074	0.041	0.721 (0.674−0.772)	0.728 (0.680−0.779)
Black persons						
BNT162b2	179,805	33,697,219	1933	0.057	1	1
mRNA-1273	171,451	32,065,194	1363	0.043	0.740 (0.653−0.838)	0.743 (0.656−0.842)
Follow-up time period 07/ 01/2021 to 08/25/2021						
BNT162b2	884,960	49,476,555	4156	0.084	1	1
mRNA-1273	884,960	49,510,381	2411	0.049	0.579 (0.530−0.633)	0.584 (0.533−0.639)

***Table 2*: Comparison of Pfizer-BioNTech (BNT162b2) versus Moderna (mRNA-1273) vaccine recipients with respect to the risk of developing documented SARS-CoV-2 infection.**

*Adjusted for sex, age, race, ethnicity, urban/rural residence, CCI, diabetes, COPD, CKD, CHF, BMI and CAN score and stratified by VA region [VISN]. "Stratification" using STATA's strata option allows the baseline hazard function to differ by VISN under the constraint that the coefficients are equal across VISNs.

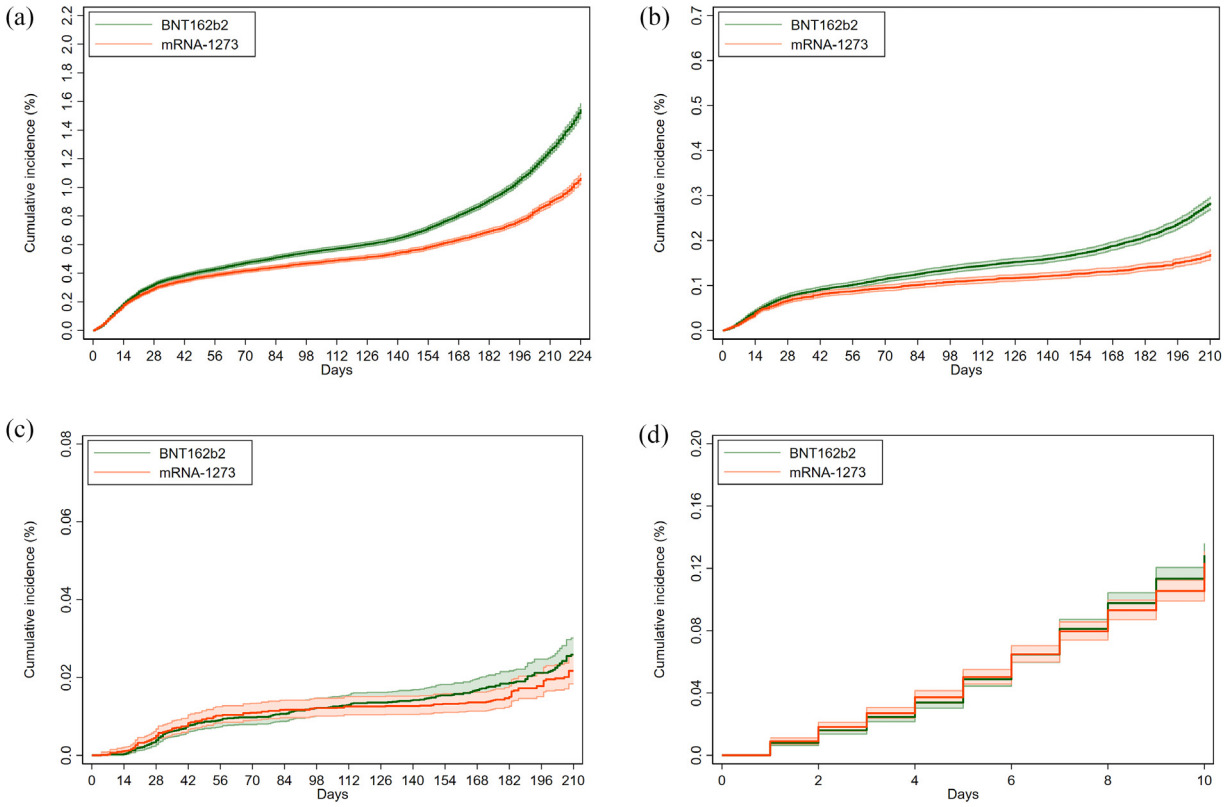

Figure 3. Kaplan-Meier curve showing cumulative incidence (%) and 95% confidence intervals of SARS-CoV-2 infections (a), SARS-CoV-2-related hospitalizations (b) SARS-CoV-2-related deaths (c) and SARS-CoV-2 infections in the first 10 days after the first vaccine dose as a negative control outcome (d) in persons who received Pfizer-BioNTech (BNT162b2) versus Moderna (mRNA-1273) COVID-19 vaccination.

a. SARS-CoV-2 Infection
b. SARS-CoV-2 related hospitalization
c. SARS-CoV-2-related death
d. SARS-CoV-2 infection in the first 10 days after the first vaccine dose (negative outcome control)

The green lines show cumulative incidence and 95% confidence intervals for BNT162b2 and the orange lines for mRNA-1273. The Figures show lower cumulative incidence of infection (a) and hospitalization (b) in the nRNA-1273 versus the BNT162b2 vaccine recipients and also an increasing gap between mRNA-1273 and BNT162b2 vaccine recipients as follow-up extended from 150 to 220 days. The cumulative incidence curves for mortality (c) appear very similar for the two vaccine groups with overlapping confidence intervals Figure 3.d shows that the cumulative incidence of SARS-CoV-2 infection in the first 10 days following first vaccine dose (used as a negative outcome control) was almost identical in the mRNA-1273 and BNT162b2 groups suggesting absence of uncontrolled residual confounding.

hospitalization (adjusted hazard ratio [aHR] 0.633, 95% CI 0.562–0.713); this association persisted in a similar magnitude across all subgroups of age and CCI and in both Black and White persons (Table 3 and Figure 3b). The difference between mRNA-1273 and BNT162b2 recipients was progressively greater when follow-up was longer, i.e. extending to March 31, 2021 (aHR 0.888, 95% CI 0.744–1.059), or ~11% lower risk), versus June 30, 2021 (aHR 0.767, 95% CI 0.666–0.884 or ~23% lower risk) versus the main analysis which extended to August 25, 2021 (37% lower risk). The Kaplan-Meier curves also demonstrated an increasing rate of SARS-CoV-2-related hospitalization and an increasing gap between mRNA-1273 and BNT162b2 recipients as follow-up extended from 150 to 220 days (Figure 3b). The difference between mRNA-1273 and BNT162b2 recipients was greater when we analyzed separately the outcomes that occurred in the time period after July 1, 2021 (aHR 0.387, 95% CI 0.311–0.482) – when the Delta variant was predominant - than in the time period before July 1, 2021 (aHR 0.767, 95% CI 0.666–0.884).

SARS-CoV-2-related mortality in BNT162b2 versus mRNA-1273 recipients

SARS-CoV-2-related mortality was lower in the mRNA-1273 group (168 SARS-CoV-2-related deaths, 0.097 per 100,000 person-days) than in the matched BNT162b2

group (213 SARS-CoV-2-related deaths, 0.123 per 100,000 person-days) with an aHR of 0.808 (95% CI 0.592–1.103) and a 95% confidence interval that crossed one and therefore did not reach "statistical significance" (Table 4 and Figure 3c). There was also no significant difference in SARS-CoV-2-related mortality between the two vaccination groups when limited to subgroups of age, CCI or White/Black race, or for follow-up periods extending to earlier dates or when analyzing separately outcomes that occurred before or after July 1, 2021.

Comparison of BNT162b2 versus mRNA-1273 at 24 weeks after vaccination: risk difference and risk ratio

Calculation of risk differences at 24 weeks after vaccination confirmed lower absolute risk in the mRNA-1273 group compared to the BNT162b2 group in SARS-CoV-2 infection (−1.729 events/1000 persons), hospitalization (−0.559 events/1000 persons) and death (−0.032 events/1000 persons) (Table 5). Risk ratios at 24 weeks also confirmed lower risk of SARS-CoV-2 infection, hospitalization and death in mRNA-1273 versus BNT162b2. Detailed subgroup analyses of risk differences and risk ratios are shown in Supplementary Appendix-Supplementary Tables 2–4.

Results of negative outcome control: SARS-CoV-2 infection in the 10 days following first vaccine dose

Cumulative incidence of SARS-CoV-2 infection in the first 10 days following first vaccine dose was almost identical in the mRNA-1273 and BNT162b2 groups (Figure 3d and Table 1) suggesting absence of uncontrolled residual confounding.

Discussion

Our target trial emulation study performed in the national VA healthcare system comparing 902,235 BNT162b2 vaccine recipients and their matched counterparts who received mRNA-1273 with follow-up extending to August 25, 2021 demonstrated that mRNA-1273 recipients had a ~26% reduction in the risk of SARS-CoV-2 infection (aHR 0.736, 95% CI 0.696–0.779) and a ~37% reduction in the risk of SARS-CoV-2-related hospitalization (aHR 0.633, 95% CI 0.562–0.713) compared to BNT162b2 recipients. The magnitudes of these effects were similar across all age groups, comorbidity burden categories and white/black racial groups. The differences between mRNA-1273 and BNT162b2 in risk of infection or hospitalization were progressively greater when the follow-up period was longer, i.e. extending to March 31, versus June 30, versus August 25, 2021. These differences were even more pronounced when we analyzed separately the outcomes that occurred during the follow-up period from July 1 to August 25, 2021 when the Delta variant became predominant in the U.S. (aHR for infection 0.584, 95% CI 0.533–0.639 and aHR for hospitalization 0.387, 95% 0.311–0.482). SARS-CoV-2-related mortality was also lower in mRNA-1273 versus BNT162b2 recipients with an aHR of 0.808 (95% CI 0.592–1.103); however, this estimate had a broad confidence interval that crossed one. The absolute risks of all outcomes were low regardless of the vaccine received.

Our findings complement and extend those of a recent comparative effectiveness target trial emulation study of BNT162b2 versus mRNA-1273 by Dickerman et al.,[10] which was also conducted using VA data, with some notable differences. First, we supplemented VA EHR data with Medicare data on additional SARS-CoV-2 infections (18.4%) and hospitalizations (34.6%) in VA enrollees that were not documented in VA data while Dickerman et al. did not. This would be expected to result in underestimation of absolute risk differences between mRNA-1273 and BNT162b2 in infection and hospitalization rates reported by Dickerman et al. Additionally, participants with SARS-CoV-2 infection prior to vaccination recorded only in Medicare data would not have been identified and appropriately excluded by Dickerman et al. The eligibility criteria and matching methods that we employed resulted in a much greater number of vaccine recipients retained as participants in the emulated trial (902,235/group versus 219,842/group) and a much greater number of outcomes during follow-up (16,890 versus 2016 infections, 3591 versus 411 hospitalizations and 381 versus 81 SARS-CoV-2-related deaths) compared to Dickerman et al. This was achieved without sacrificing the comparability of the matched comparison groups in baseline characteristics or negative outcome controls. This makes our results more generalizable and more precise, as well as enabling precise estimates among subgroups of age, CCI and race. We compared effectiveness over progressively longer follow-up periods and indeed showed greater differences between mRNA-1273 and BNT162b2 with longer follow-up, which was not addressed by Dickerman et al. (although this can be seen in the risk curves they provided). Our follow-up period for persons vaccinated up to March 25, 2021 extended to August 25, 2021 versus July 1, 2021 in Dickerman et al. This provided longer mean follow-up in our study (192 days versus 126 days) and also enabled assessment extending into the Delta predominant period (which began after July 1, 2021) for persons who were vaccinated many months before. A notable advantage of Dickerman et al. is that they conducted a second target trial with recruitment between July 1 to September 20 to specifically address the comparative effectiveness of the two vaccines against the Delta variant. It is reassuring that the two emulation studies that were performed completely independently both reported superiority of mRNA-1273 with regards to SARS-CoV-2-related infection and hospitalization.

Type ofCOVID-19 vaccination	N	Person-days	SARS-CoV-2 hospitalizations N	SARS-CoV-2 hospitalization rate per 10,000 person-days	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio* (95% CI)
All Persons, Follow-up extending to 3/31/21						
BNT162b2	902,235	41,195,498	863	0.209	1	1
mRNA-1273	902,235	41,109,129	758	0.184	0.880 (0.737−1.051)	0.888 (0.744−1.059)
All Persons, Follow-up extending to 6/30/21						
BNT162b2	902,235	123,115,891	1427	0.116	1	1
mRNA-1273	902,235	123,067,603	1084	0.088	0.760 (0.659−0.875)	0.767 (0.666−0.884)
All Persons, Follow-up extending to 8/25/21						
BNT162b2	902,235	173,484,192	2210	0.127	1	1
mRNA-1273	902,235	173,474,589	1381	0.080	0.625 (0.554−0.704)	0.633 (0.562−0.713)
SUB-GROUPS, Follow-up extending to 8/25/21						
Age 18 to <65						
BNT162b2	298,557	53,140,418	335	0.063	1	1
mRNA-1273	299,272	53,258,698	175	0.033	0.520 (0.378−0.718)	0.531 (0.384−0.733)
Age 65 to <75						
BNT162b2	346,354	67,633,501	854	0.126	1	1
mRNA-1273	344,323	67,151,830	565	0.084	0.667 (0.550−0.809)	0.673 (0.554−0.816)
Age ≥ 75						
BNT162b2	257,324	52,710,273	1021	0.194	1	1
mRNA-1273	258,640	53,064,061	642	0.121	0.623 (0.524−0.740)	0.634 (0.534−0.753)
CCI 0−1						
BNT162b2	410,655	77,290,745	356	0.046	1	1
mRNA-1273	413,690	77,782,511	224	0.029	0.626 (0.408−0.961)	0.627 (0.412−0.956)
CCI 2−4						
BNT162b2	296,033	57,568,903	643	0.112	1	1
mRNA-1273	293,610	57,152,968	443	0.077	0.693 (0.555−0.865)	0.700 (0.561−0.875)
CCI ≥ 5						
BNT162b2	195,547	38,624,544	1211	0.314	1	1
mRNA-1273	194,935	38,539,111	714	0.185	0.592 (0.510−0.687)	0.600 (0.517−0.697)
White persons						
BNT162b2	623,437	120,768,609	1528	0.127	1	1
mRNA-1273	636,466	123,188,668	987	0.08	0.634 (0.548−0.733)	0.647 (0.559−0.747)
Black persons						
BNT162b2	179,805	33,822,490	481	0.142	1	1
mRNA-1273	171,451	32,178,733	253	0.079	0.553 (0.427−0.715)	0.568 (0.437−0.738)
Follow-up time period 07/01/ 2021 to 08/25/2021						
BNT162b2	896,776	50,199,666	780	0.155	1	1
mRNA-1273	896,776	50,208,942	295	0.058	0.378 (0.306−0.469)	0.387 (0.311−0.482)

***Table 3*: Comparison of Pfizer-BioNTech (BNT162b2) versus Moderna (mRNA-1273) vaccine recipients with respect to the risk of developing SARS-CoV-2-related hospitalization.**

* Adjusted for sex, age, race, ethnicity, urban/rural residence, CCI, diabetes, COPD, CKD, CHF, BMI and CAN score and stratified by VA region [VISN]. "Stratification" using STATA's strata option allows the baseline hazard function to differ by VISN under the constraint that the coefficients are equal across VISNs.

Type ofCOVID-19 vaccination	N	Person-days	SARS-CoV-2 death N	SARS-CoV-2 mortality per 100,000 person-days	Unadjusted Hazard Ratio(95% CI)	Adjusted Hazard Ratio† (95% CI)
All Persons, Follow-up extending to 3/31/21						
BNT162b2	902,235	41,226,694	77	0.187	1	1
mRNA-1273	902,235	41,138,339	79	0.192	1.028 (0.661−1.599)	1.044 (0.673−1.620)
All Persons, Follow-up extending to 6/30/21						
BNT162b2	902,235	123,250,161	129	0.105	1	1
mRNA-1273	902,235	123,178,624	115	0.093	0.893 (0.613−1.301)	0.905 (0.622−1.318)
All Persons, Follow-up extending to 8/25/21						
BNT162b2	902,235	173,707,988	213	0.123	1	1
mRNA-1273	902,235	173,648,487	168	0.097	0.790 (0.578−1.079)	0.808 (0.592−1.103)
SUB-GROUPS, Follow-up extending to 8/25/21						
Age 18 to <65						
BNT162b2	298,557	53,169,648	11	0.021	1	1
mRNA-1273	299,272	53,272,454	16	0.030	1.452 (0.369−5.716)	1.433 (0.317−6.483)
Age 65 to <75						
BNT162b2	346,354	67,714,989	71	0.105	1	1
mRNA-1273	344,323	67,225,166	44	0.066	0.626 (0.359−1.089)	0.633 (0.360−1.111)
Age ≥ 75						
BNT162b2	257,324	52,823,351	131	0.248	1	1
mRNA-1273	258,640	53,150,868	108	0.203	0.816 (0.553−1.205)	0.843 (0.573−1.240)
CCI 0−1						
BNT162b2	410,655	77,331,262	27	0.035	1	1
mRNA-1273	413,690	77,813,768	21	0.026	0.756 (0.099−5.779)	0.764 (0.102−5.697)
CCI 2−4						
BNT162b2	296,033	57,634,580	38	0.066	1	1
mRNA-1273	293,610	57,207,944	41	0.72	1.093 (0.580−2.061)	1.143 (0.597−2.188)
CCI ≥ 5						
BNT162b2	195,547	38,742,146	148	0.382	1	1
mRNA-1273	194,935	38,626,775	106	0.275	0.721 (0.503−1.033)	0.739 (0.515−1.060)
White persons						
BNT162b2	623,437	120,923,057	172	0.142	1	1
mRNA-1273	636,466	123,313,424	140	0.113	0.799 (0.570−1.120)	0.823 (0.587−1.153)
Black persons						
BNT162b2	179,805	33,869,909	31	0.092	1	1
mRNA-1273	171,451	32,210,019	22	0.069	0.751 (0.230−2.455)	0.765 (0.234−2.500)
Follow-up time period 07/01/ 2021 to 08/25/2021						
BNT162b2	899,986	50,393,838	84	0.167	1	1
mRNA-1273	899,986	50,394,587	53	0.105	0.631 (0.366−1.089)	0.657 (0.371−1.162)

***Table 4*: Comparison of Pfizer-BioNTech (BNT162b2) versus Moderna (mRNA-1273) vaccine recipients with respect to the risk of developing SARS-CoV-2-related death.**

*Adjusted for sex, age, race, ethnicity, urban/rural residence, CCI, diabetes, COPD, CKD, CHF, BMI and CAN score and stratified by VA region [VISN]. "Stratification" using STATA's strata option allows the baseline hazard function to differ by VISN under the constraint that the coefficients are equal across VISNs.

SARS-CoV-2 Outcome	No. of Events		24-wk Risk (95% CI)		Risk Difference (95% CI)	Risk Ratio (95% CI)
	BNT162b2	mRNA-1273	BNT162b2	mRNA-1273		
			Events/1000 persons		*Events/1000 persons*	
Documented infection	7206	5682	8.079	6.351	−1.729	0.786
			(7.864 to 8.300)	(6.026 to 6.692)	(−1.960 to −1.498)	(0.761 to 0.811
Hospitalization	1679	1185	1.878	1.319	−0.559	0.702
			(1.781 to 1.980)	(1.181 to 1.473	(−0.672 to −0.446)	(0.652 to 0.753)
Death	150	122	0.168	0.136	−0.032	0.809
			(0.141 to 0.200)	(0.101 to 0.182)	(−0.067 to 0.003)	(0.620 to 0.999)

***Table 5*: Comparison of Pfizer-BioNTech (BNT162b2) versus matched Moderna (mRNA-1273) vaccine recipients (*n* = 902,235 in each group) with respect to the risk of developing SARS-CoV-2 infection, SARS-CoV-2-related hospitalization and SARS-CoV-2-related death over a 24-week time period since vaccination.**

A number of test-negative, case-control studies of vaccine effectiveness in hospitalized patients suggested slightly lower vaccine effectiveness against SARS-CoV-2-related hospitalization for BNT162b2 than mRNA-1273.[8,9,11] For example, among 1175 U.S. Veterans hospitalized at 5 VA medical centers from February 1 to August 6, 2021, vaccine effectiveness was 83.4% (95% CI 74.0−89.4) for BNT162b2 and 91.6% (95% CI 83.5 −95.7) for mRNA-12738; among 14,636 patients hospitalized across nine U.S. states during June-August 2021, vaccine effectiveness was 80.0% (95% CI 73−85) for BNT162b2 and 95% (95% CI 92−97) for mRNA-127311; and among 3689 patients hospitalized at 21 U.S. hospitals across 18 states during March 11-August 15, 2021, vaccine effectiveness was 88% (95% CI 85−91), for BNT162b2 and 93% (95% CI 91−95) for mRNA-1273.9 Our target trial emulation study design has the advantage of being able to directly compare the two vaccines with respect to risk of infection, hospitalization and death (rather than just hospitalization) and would be expected to more closely reflect the results of the randomized study that it explicitly attempted to emulate. Furthermore, the large study population and large number of outcomes allowed us to confirm that the difference between the two vaccines persisted across all age groups and comorbidity burden categories.

A critical finding of our study is the widening gap between BNT162b2 and mRNA-1237 recipients with respect to risk of infection and hospitalization that was observed as the follow-up period extended from the time of vaccination until March 31 or June 30 or August 25, 2021(Tables 2 and 3). This widening gap may reflect a greater decline in protection over time after vaccination in BNT162b2 than in mRNA-1237 recipients, as was reported in a case-control study in which vaccine effectiveness against hospitalization of BNT162b2 dropped from 91% to 77% after 4 months but that of mRNA-1237 dropped only from 93% to 92%.[9] Alternatively, this may also reflect a greater difference between mRNA-1237 and BNT162b2 in protection against the Delta variant (predominant after July 1) than the Alpha (B.1.1.7) variant (predominant before July 1). Indeed, the differences between mRNA-1273 and BNT162b2 in risk of infection or hospitalization were much greater when we analyzed separately the outcomes that occurred during the follow-up period after than before July 1, 2021. However, a test-negative, case-control study performed in the UK reported only a small decline in the effectiveness of BNT162b2 against symptomatic disease among persons with the Delta variant (88%, 95% CI 85.3 −90.1) than persons with the Alpha variant (93.7%, 95% CI 91.6−95.3).[7]

Each dose of mRNA-1273 contains >3 times the dose of mRNA than BNT162b2 (100 μg versus 30 μg), which may elicit greater or longer-lasting immune responses. Recipients of mRNA-1273 had greater anti-receptor binding domain IgG levels than recipients of BNT162b2, although levels of anti-Spike IgG were similar.[9] Differences between the two mRNA vaccines in dosing interval (28 days for mRNA-1273 and 21 days for BNT162b2) and composition of the lipid nanoparticles that protect and deliver the mRNA may also result in different levels of immunogenicity. These differences may inform the design of future mRNA vaccines for COVID-19, other viruses or other conditions, if indeed the two vaccines are further proven to have different effectiveness.

Our study has several limitations. Despite a sophisticated matching methodology and adjustment for potential confounders, residual confounding (e.g. by geographic region smaller than VISN level) cannot be completely excluded in a non-randomized study. However, health seeking behaviors and prophylactic measures (masking, physical distancing, avoiding congregate settings) would be expected to be very similar when comparing matched groups of recipients of two different vaccines (rather than comparing vaccinated versus unvaccinated persons). In addition, our analysis of a negative outcome control suggested little confounding. While some additional infections (diagnosed or undiagnosed) and even hospitalizations undoubtedly occurred and were not captured in our analysis, we would expect

this outcome misclassification to be nondifferential between the matched groups of BNT162b2 and mRNA-1273 vaccine recipients. Also, some hospitalizations and deaths that occurred following SARS-CoV-2 infection may have been unrelated to the infection. This outcome misclassification would also be expected to be nondifferential. Nondifferential outcome misclassification would be expected to produce bias towards the null, with minimal influence on relative measures of effect such as the aHRs that we reported. Our study population is predominantly male, which may limit the generalizability of our findings to women. Our analysis of outcomes limited to the time period of Delta predominance (July 1 to August 25, 2021) is potentially biased because it is limited to persons who remained alive and uninfected as of July 1, many months after "randomization". However, if anything this would be expected to result in an attenuation in the difference between mRNA-1273 and BNT162b2 due to greater "depletion of susceptibles" in the less effective BNT162b2 group in the time period before July 1[27].

In conclusion, although absolute rates infection, hospitalization and death in both vaccine groups were low, our findings suggest that vaccination with mRNA-1273 results in significantly lower rates of SARS-CoV-2-infection and SARS-CoV-2-related hospitalization than vaccination with BNT162b2, and these differences become more pronounced as time from vaccination accrues. The comparative effectiveness and safety of the two mRNA vaccines should continue to be studied, especially comparisons of "booster" doses of the two vaccines with observation extending to the time period of Omicron variant predominance, as they may inform decisions made by governments, healthcare systems and individuals regarding vaccine choices.

Contributors

GNI and KB designed the study.

GNI and KB drafted the manuscript including figures and tables and ERL and PKG helped edit and revise the manuscript. All authors reviewed and agreed on the final version and all authors had access to the data.

PKG and ERL acquired the data and curated analytic variables.

ERL was responsible for project administration.

KB was responsible for statistical analysis.

GNI and KB interpreted the analyses and had final responsibility for the decision to submit for publication.

Declaration of interests

None of the authors has any conflicts of interest to disclose.

Funding

U.S. Department of Veterans Affairs, Grant Nos. COVID19–8900–11 and C19 21–278.

Data sharing statement

The data that support the findings of this study are available from the VA. VA data are made freely available to researchers behind the VA firewall with an approved VA study protocol. More information is available at https://www.virec.research.va.gov or by contacting the VA Information Resource Center (VIReC) at VIReC@va.gov.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101326.

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):2603–2615.
2 Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. *N Engl J Med*. 2020;383(20):1920–1931.
3 Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403–416.
4 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):1819–1829.
5 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.
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 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. *N Engl J Med*. 2021;385(7):585–594.
8 Bajema KL, Dahl RM, Prill MM, et al. Effectiveness of COVID-19 mRNA vaccines against COVID-19-associated hospitalization - five Veterans Affairs medical centers, United States, February 1-August 6, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(37):1294–1299.
9 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(38):1337–1343.
10 Dickerman BA, Gerlovin H, Madenci AL, et al. Comparative effectiveness of BNT162b2 and mRNA-1273 vaccines in U.S. veterans. *N Engl J Med*. 2021.
11 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 B1.617.2 (Delta) variant predominance - Nine States, June-August 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(37):1291–1293.
12 Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758–764.
13 Veterans Affairs Corporate Data Warehouse. Available at: http://www.hsrd.research.va.gov/for_researchers/vinci/cdw.cfm Last accessed on 03/22/21.
14 VA Information Resource Center (VIReC) Medicare Data. Available at: https://vaww.virec.research.va.gov/VACMS/Medicare/Data.htm Last accessed 05/30/2021.
15 Hall VJ, Foulkes S, Charlett A, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care

workers in England: a large, multicentre, prospective cohort study (SIREN). *Lancet*. 2021;397(10283):1459–1469.
16 List of Veterans Affairs medical facilities. https://en.wikipedia.org/wiki/List_of_Veterans_Affairs_medical_facilities Last accessed: May 7, 2021.
17 Ioannou GN, Green P, Fan VS, et al. Development of COVIDVax model to estimate the risk of SARS-CoV-2-related death among 7.6 Million US veterans for use in vaccination prioritization. *JAMA Netw Open*. 2021;4:(4) e214347.
18 Ioannou GN, Locke E, Green P, et al. Risk factors for hospitalization, mechanical ventilation, or death among 10131 US veterans with SARS-CoV-2 infection. *JAMA Netw Open*. 2020;3:(9) e2022310.
19 Fan VS, Dominitz JA, Eastment MC, et al. Risk Factors for testing positive for SARS-CoV-2 in a national US healthcare system. *Clin Infect Dis*. 2020.
20 King JT, Yoon JS, Rentsch CT, et al. Development and validation of a 30-day mortality index based on pre-existing medical administrative data from 13,323 COVID-19 patients: the Veterans Health Administration COVID-19 (VACO) Index. *PLoS ONE*. 2020;15:(11) e0241825.
21 Jann B. *KMATCH: Stata module Module For Multivariate-Distance and Propensity-Score matching, Including Entropy balancing, Inverse Probability weighting, (coarsened) Exact matching, and Regression adjustment. Statistical Software Components S458346*. Boston College Department of Economics; 2020. revised 19 Sep.
22 Ioannou GN, O'Hare AM, Berry K, et al. Trends over time in the risk of adverse outcomes among patients with SARS-CoV-2 infection. *Clin Infect Dis*. 2021.
23 Veterans Health Administration, Office of Rural Health. Available at: https://vaww.vashare.vha.va.gov/sites/ruralhealth/GSOD/default.aspx Last accessed 03/28/2021.
24 Osborne TF, Veigulis ZP, Arreola DM, Roosli E, Curtin CM. Automated EHR score to predict COVID-19 outcomes at US department of Veterans Affairs. *PLoS ONE*. 2020;15:(7) e0236554.
25 Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the department of Veterans Affairs. *Popul Health Metr*. 2006;4:2.
26 Austin PC, Cafri G. Variance estimation when using propensity-score matching with replacement with survival or time-to-event outcomes. *Stat Med*. 2020;39(11):1623–1640.
27 Lipsitch M, Goldstein E, Ray GT, Fireman B. Depletion-of-susceptibles bias in influenza vaccine waning studies: how to ensure robust results. *Epidemiol Infect*. 2019;147:e306.
28 Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology*. 2010;21(3):383–388.
29 Ioannou GN, Green P, Locke ER, Berry K. Factors associated with early receipt of COVID-19 vaccination and adherence to second dose in the Veterans Affairs healthcare system. *PLoS ONE*. 2021;16:(12) e0259696.