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Effectiveness of various COVID-19 vaccine regimens among 10.4 million patients from the National COVID Cohort Collaborative during Pre-Delta to Omicron periods – United States, 11 December 2020 to 30 June 2022

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ABSTRACT

Objective: This study reports the vaccine effectiveness (VE) of COVID-19 vaccine regimens in the United States, based on the National COVID Cohort Collaborative (N3C) database.
Methods: Data from 10.4 million adults, enrolled in the N3C from 11 December 2020 to 30 June 2022, were analyzed. VE against infection and death outcomes were evaluated across 13 vaccine regimens in recipient cohorts during the Pre-Delta, Delta, and Omicron periods. VE was estimated as (1-odds ratio) × 100% by multivariate logistic regression, using the unvaccinated cohort as reference.
Results: Natural immunity showed a highly protective effect (70.33%) against re-infection, but the mortality risk among the unvaccinated population was increased after re-infection; vaccination following infection reduced the risk of re-infection and death. mRNA-1273 full vaccination plus mRNA-1273 booster showed the highest anti-infection effectiveness (47.59%) (95% CI, 46.72–48.45) in the overall cohort. In the type 2 diabetes cohort, VE against infection was highest with BNT162b2 full vaccination plus mRNA-1273 booster (61.19%) (95% CI, 53.73–67.75). VE against death was also highest with BNT162b2 full vaccination plus mRNA-1273 booster (89.56%) (95% CI, 85.75–92.61). During the Pre-Delta period, all vaccination regimens showed an anti-infection effect; during the Delta period, only boosters, mixed vaccines, and Ad26.COV2.S vaccination exhibited an anti-infection effect; during the Omicron period, none of the vaccine regimens demonstrated an anti-infection effect. Irrespective of the variant period, even a single dose of mRNA vaccine offered protection against death, thus demonstrating survival benefit, even in the presence of infection or re-infection. Similar patterns were observed in patients with type 2 diabetes.
Conclusions: Although the anti-infection effect declined as SARS-CoV-2 variants evolved, all COVID-19 mRNA vaccines had sustained effectiveness against death. Vaccination was crucial for preventing re-infection and reducing the risk of death following SARS-CoV-2 infection.

1. Introduction

Vaccination against coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), has been a major factor in controlling the pandemic. As of June 28, 2023, variants of SARS-CoV-2, known as Alpha, Beta, Gamma, Delta, and Omicron, have caused over 103 million confirmed COVID-19 cases and more than 1 million deaths in the United States (US) [1]. Although

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reports of the effectiveness of some vaccination regimens are available for specific cohorts, regions and countries [2–4], vaccine effectiveness (VE) of various vaccination regimens on a large national cohort in the US against different variants of SARS-CoV-2 has not previously been reported. Moreover, clinical trials evaluating COVID-19 vaccines largely excluded individuals with diabetes, and limited data are available about the effectiveness of COVID-19 vaccines in diabetic population [5–7]. Considering the high risk of severe COVID-19 in type 2 diabetes patients [8–11] and their inability to mount robust immune responses following vaccination [12], whether or not COVID-19 vaccines are equally effective among patients with and without type 2 diabetes is still unclear.

In this study, we address the effectiveness of various COVID-19 vaccine regimens against SARS-CoV-2 infection and mortality using data from the National COVID Cohort Collaborative (N3C), the largest longitudinal electronic health record repository of COVID-19 patients across 74 sites in the US [13], over an 18-month long-term period from December 11, 2020 to June 30, 2022, to assess the effectiveness of 13 vaccine regimens against the Pre-Delta, Delta, and Omicron variants of SARS-CoV-2, using a non-vaccination cohort as reference. We evaluated the VE based on the different variant-dominant periods, heterogenous or homologous vaccination, and prior infection. Because our study population comprises more than 10% type 2 diabetes patients, we also provide additional evidence of VE in this sub-population.

2. Methods

2.1. Study enrollment and variant-dominant periods

A detailed description of the data source and eligible enrollment is given in the Supplementary Methods section. De-identified information from adults (≥18 years old), who had clinic visit records and/or who received at least one dose of a COVID-19 vaccine between December 11, 2020 and June 30, 2022, was extracted from the N3C database. Based on reports from the Centers for Disease Control and Prevention (CDC) of dominant SARS-CoV-2 variants (greater than50%) in the US [14,15], the Pre-Delta period was December 11, 2020 to June 25, 2021; the Delta period was from June 26, 2021 to December 24, 2021; and the Omicron period was from December 25, 2021 to June 30, 2022. Each variant-dominant period had a similar observation duration of about 6 months. The VE over time was calculated by month within the six-month observation of each variant-dominant period. To avoid the effect of re-infection on VE, the patients with COVID-19 infection enrolled in the Pre-Delta period were excluded from enrollment in the other periods, so the patients enrolled in the Delta period were considered first time infected with SARS-CoV-2, and the same approach applied for patients enrolled in the Omicron period. Also, considering that the patients' vaccination status might change during time, and to avoid repeated enrollment, we only enrolled the patients in the partial vaccination cohort if the patients received only one dose of the mRNA vaccination and they were not counted in the fully vaccinated and booster cohorts; in the booster cohort, subjects were both fully vaccinated and received one more vaccine booster dose.

Based on this classification, 1,945,155 COVID-19 patients were enrolled in this study, including 431,369 patients who became infected and 3.49% of whom (15,045) died after infection within the six months during the pre-Delta period; 788,935 patients became infected and 1.58% (12,453) died after infection within the six months during the Delta period; and 724,851 patients became infected and 1.18% (8,560) died after infection within the six months during the Omicron period. The distribution of the 13 vaccine regimens and non-vaccination is illustrated in Supplementary Figure S1.

2.2. Case definition, vaccination status and outcomes

According to the N3C diagnostic definition [13,16], COVID-19 patients including first time infection and re-infection were those who recorded a positive COVID-19 test in either the measurement or condition table in the N3C Data Enclave. Type 2 diabetes patients were defined as those diagnosed before COVID-19 or non-COVID patients with type 2 diabetes in the condition table.

The vaccination regimens included three SARS-CoV-2 vaccines authorized by the Food and Drug Administration (FDA): two mRNA vaccines from Pfizer-BioNTech [BNT162b2] and Moderna [mRNA-1273] and one viral vector vaccine from Johnson & Johnson/Janssen [Ad26.COV2.S]. Patients with clinical visit records and/or first positive SARS-CoV-2 test records during the Pre-Delta, Delta, and Omicron periods were categorized into 13 vaccine regimen- recipient cohorts based on the number of doses and type of vaccines. The details are shown in the Supplementary Methods section and Supplementary Figure S1.

The primary outcome was the first positive SARS-CoV-2 test after 14 days of the most recent vaccination. The secondary outcome was all mortality within the six months after the SARS-CoV-2 infection. Survival status was collected from any cause of death after COVID-19 infection, from each follow-up month for COVID-19 positive cases until the observation end point of each period.

2.3. Statistical analysis

Categorical variables were summarized as the number with percentage and analyzed by Chi-square test. Descriptive statistics were used to compare infection and death rates among participants based on age, gender, race/ethnicity, and US geographical region. To account for potential covariates associated with COVID-19 and vaccine uptake, we conducted multivariable logistic regression models to estimate the odds ratio of infection by comparing the odds of vaccination in test-positive cases with the odds of non-vaccination in test-positive cases, as well as the odds ratios of death in test-positive cases, adjusted by age, gender, US geographical region, race, and prior infection. We calculated vaccination effectiveness against SARS-CoV-2 infection and death using the following formula: adjusted VE = (1- adjusted odds ratio) × 100%. Additional details can be found in the Supplementary Methods section.

To examine the VE trend of different vaccinations over a six-month observation duration for each variant-dominant period, we calculated the VE against infection for each month (1st, 2nd, 3rd, 4th, 5th, 6th month) following the most recent vaccination and the VE against death for each month after the infection occurred. The results are presented in Supplementary Figures S4–S6 and Tables S6-S8 for infection, as well as Figures S9–S11 and Tables S12-S14 for death, encompassing both the overall cohort and diabetes and non-diabetes cohorts.

All the analyses described in this publication were conducted with data or tools accessed through the NCATS N3C Data Enclave. Statistical significance was set at two-sided $p < 0.05$.

3. Results

3.1. Study participants

As shown in Fig. 1, after exclusion criteria were applied, our study cohort comprises 10,412,853 adults, of whom 1,398,176 (13.43%) were diabetics and 9,014,677 were non-diabetics. Participants were categorized into 14 vaccination status, of which 7,921,297 (76.07%) were unvaccinated. The vaccination rate was lower than the US national rate, which may due to the patients included in the N3C with multiple comorbities and immune dysfunction [13,17], including diabetes, renal disease, liver disease, pulmonary disease, heart failure, cancers, etc. [16].

The characteristics, infection and death rate of the enrolled participants are summarized in Table 1 and Table S1. Overall, 1,945,155 (18.68%) were diagnosed with COVID-19 and 1.85% (36,058) died after infection. Compared with females, males had a lower infection rate (17.50%), but higher death rate after infection (2.61%) ($P < 0.00001$). Young adults (<30 years old) showed a higher infection rate (20.14%)

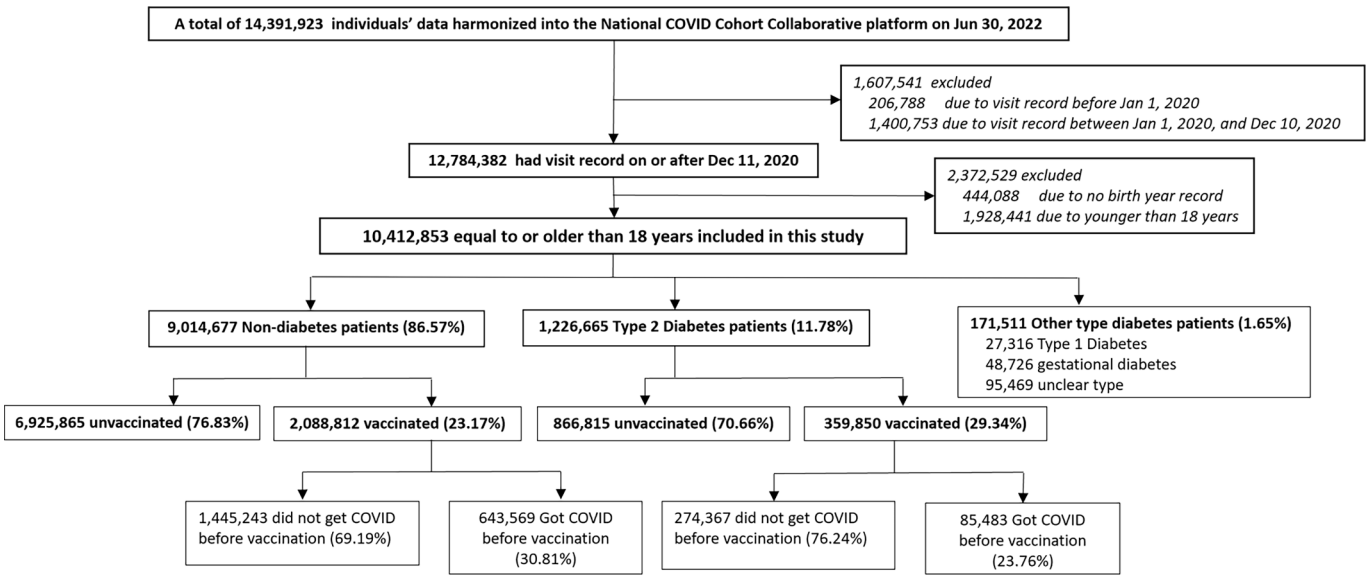

Fig. 1. Study enrollment (December 11, 2020 to June 30, 2022). We used December 11, 2020, the date that the US Food and Drug Administration approved the SARS-CoV-2 vaccines for general use as the beginning of the study period. The end of the observation period was June 30, 2022. COVID-19 patients were defined as patients who took the COVID test and were recorded as positive in the measurement table or patients who were recorded as COVID-19 positive in the condition table from the N3C Data Enclave. Non-diabetes patients were defined as patients who did not have any type of diabetes. Diabetes patients were defined as patients who were diagnosed with diabetes before COVID-19 or non-COVID-19 patients recorded with diabetes in the condition table from the N3C Data Enclave. When studying the diabetes cohort, we only focused on type 2 diabetes patients since they constituted the vast majority (1,226,665/1,398,176, 87.73%) of the diabetes patients and had more accurate and complete information.

but with the lowest death rate (0.10%), while those greater than 65 years old showed the lowest infection rate (15.82%), but the highest death rate after infection (6.58%) ($P < 0.00001$). Whites had the highest infection rate (20.31%), Black/African Americans had the highest death rate (2.09%), Asians the lowest infection rate (12.68%) and Hispanic/Latinos the lowest death rate (1.35%) ($P < 0.00001$). Unvaccinated participants had a significantly higher death rate (2.11%) than those with any type of vaccination (0.96%) ($P < 0.0001$). Patients with type 2 diabetes comprise most of the diabetes cohort and exhibited high risk of death after infection (5.64%).

3.2. Benefit of Covid-19 vaccination after prior infection

As of June 30, 2022, there were 23.93% (2,491,556/10,412,853) vaccinated participants in the N3C Data Enclave. Notably, 22.44% (2,336,406) of the whole cohort acquired SARS-CoV-2 infection before their first dose of vaccination. This percentage was relatively lower in type 2 diabetes cohort (14.67%, 179,927), and higher in non-diabetes cohort (23.67%, 2,133,838). We compared the infection and mortality risk among unvaccinated participants without prior infection, unvaccinated with prior infection (natural immunity), vaccinated without prior infection, and vaccinated with prior infection (hybrid immunity) in the whole cohort, and type 2 diabetes and non-diabetes subgroups (Fig. 2).

For all three cohorts, the re-infection rate of the natural immunity group was significantly lower than the unvaccinated population without prior infection (9.33% vs. 21.54% in the whole cohort, 14.95% vs. 19.33% in the type 2 diabetes cohort, 8.91% vs. 21.87% in the non-diabetes cohort) ($P < 0.0001$) (Fig. 2A). The infection rate of the vaccinated group was similar to the unvaccinated group (21.14% vs. 21.54% in the whole cohort, 16.05% vs. 19.33% in type 2 diabetes cohort, and 22.16% vs. 21.87% in non-diabetes cohort). Notably, the hybrid immunity group had the lowest SARS-CoV-2 infection rates in all the three cohorts: 6.99% in the whole cohort, 7.94% in type 2 diabetes cohort, and 6.82% in non-diabetes cohort (Fig. 2A). Contrary to re-infection rate, the death rate was significantly higher in the natural immunity group compared to the unvaccinated without prior infection group (3.52% vs. 1.96% in the whole cohort, 7.63% vs. 6.35% in the type 2 diabetes cohort, 3.07% vs. 1.38% in the non-diabetes cohort) ($P < 0.0001$) (Fig. 2B). Vaccination significantly decreased the mortality risk compared to the unvaccinated without prior infection group (0.90% vs. 1.96% in the whole cohort, 2.97% vs. 6.35% in the type 2 diabetes cohort, 0.60% vs. 1.38% in the non-diabetes cohort) (Fig. 2B). Although the death rate of the natural immunity group was highest in all three cohorts (3.52% in the whole cohort, 7.63% in the type 2 diabetes cohort, 3.07% in the non-diabetes cohort), vaccination after infection decreased the death rates as low as the vaccinated without prior infection group: 1.04% vs. 0.90% in the whole cohort, 3.03% vs. 2.97% in type 2 diabetes cohort, and 0.70% vs. 0.60% in non-diabetes cohort (Fig. 2B). The type 2 diabetes cohort had a significantly higher re-infection rate (14.95%) than the whole (9.33%) and non-diabetes (8.91%) cohorts. However, vaccination after infection reduced the re-infection rate (7.94%) similar to the whole (6.99%) and non-diabetes (6.82%) cohorts (Fig. 2A).

Table S2 showed the protection against infection and death regarding prior infection and vaccination status by adjusting for age, gender, race/ethnicity, and region. Natural immunity showed an anti-reinfection protection effect in the three cohorts (70.33%, 95% CI 70.14–70.52 in the whole cohort; 31.68%, 95% CI 30.22–33.11 in the type 2 diabetes cohort; 72.52%, 95% CI 72.34–72.71 in the non-diabetes cohort), and vaccination after infection increased the anti-reinfection effect to 81.78% (95% CI 81.59–81.96) in the whole cohort, 70.81% (95% CI 69.97–71.63) in the type 2 diabetes cohort, and 83.06% (95% CI 82.88–83.24) in the non-diabetes cohort. Vaccination provided an anti-death effect of 57.15% (95% CI, 55.51–58.73) in the whole cohort, 54.74% (95% CI, 51.85–57.46) in the type 2 diabetes cohort, and 58.98% (95% CI, 56.94–60.93) in the non-diabetes cohort. Natural immunity alone did not show any anti-death effect in the three cohorts (VE < 0); however, vaccination after prior infection provided a high anti-death effect of 53.61% (95% CI, 49.04–57.78) in the whole cohort, 55.12% (95% CI, 47.66–61.53) in the type 2 diabetes cohort, and 54.03% (95% CI, 48.05–59.33) in the non-diabetes cohort.

3.3. Vaccine effectiveness against infection

Effectiveness of different vaccine regimens against infection in the

Table 1
Characteristics, SARS- CoV-2 infection and death rates of the enrolled patient participants during the study period*.

Variables	Total (N)	Percentage (%)	Infection† (N_1)	Death¶ (N_2)	Infection† rate (%)	Death rate rate (%)	P-value for Infection	P-value for Death
Overall	10,412,853		1,945,155	36,058	18.68	1.85		
Gender							<0.00001	<0.00001
Male	4,426,520	42.51	774,423	20,210	17.50	2.61		
Female	5,979,567	57.42	1,169,652	15,847	19.56	1.35		
Other/unknown	6,766	0.06	1,080	<20	15.96	–		
Age (year)							<0.00001	<0.00001
18 to 30	1,873,961	18.00	377,465	381	20.14	0.10		
30 to 50	3,454,028	33.17	696,521	2,738	20.17	0.39		
50 to 65	2,795,308	26.84	508,954	9091	18.21	1.79		
>65	2,289,556	21.99	362,215	23,848	15.82	6.58		
Race/Ethnicity							<0.0001	<0.00001
White	6,485,202	62.28	1,317,174	25,424	20.31	1.93		
Black/African American	1,418,948	13.63	236,975	4,955	16.70	2.09		
Hispanic/ Latino	1,106,041	10.62	180,152	2,437	16.29	1.35		
Asian	286,272	2.75	36,312	586	12.68	1.61		
Other/unknown	1,116,390	10.72	174,542	2,656	15.63	1.52		
US Region							<0.0001	<0.00001
Midwest	3,772,621	36.23	991,144	15,765	26.27	1.59		
South	2,152,775	20.67	297,166	7,623	13.80	2.57		
Northeast	1,810,579	17.39	264,562	5,706	14.61	2.16		
West	956,448	9.19	129,555	2,140	13.55	1.65		
Other/unknown	1,720,430	16.52	262,728	4,824	15.27	1.84		
Diabetes status							<0.001	<0.0001
Non-diabetes	9,014,677	86.57	1,696,050	22,872	18.81	1.35		
Type 1 diabetes	27,316	0.26	5,275	70	19.31	1.33		
Type 2 diabetes	1,226,665	11.78	215,857	12,167	17.60	5.64		
Gestational diabetes	48,726	0.47	8,877	<20	18.22	–		
Vaccination Status§							<0.0001	<0.0001
Unvaccinated	7,921,297	76.07	1,511,118	31,890	19.08	2.11		
Any COVID-19 Vaccination	2,491,556	23.93	434,037	4,168	17.42	0.96		
BNT162b2								
BNT162b2_partial	593,337	5.70	109,649	1,082	18.48	0.99		
BNT162b2_full	706,377	6.78	149,611	1,252	21.18	0.84		
BNT162b2_full + BNT162b2_booster	285,441	2.74	34,599	214	12.12	0.62		
BNT162b2_full + mRNA-1273_booster	18,563	0.18	1,775	<20	9.56	–		
mRNA-1273								
mRNA-1273_partial	216,360	2.08	31,366	411	14.50	1.31		
mRNA-1273_full	357,714	3.44	75,257	888	21.04	1.18		
mRNA-1273_full + mRNA-1273_booster	216,193	2.08	19,307	158	8.93	0.82		
mRNA-1273_full + BNT162b2_booster	25,709	0.25	2,673	<20	10.40	–		
Ad26.COV2.S								
Ad26.COV2.S_full	31,066	0.30	5,402	103	17.39	1.91		
Ad26.COV2.S_full + BNT162b2_booster	4,081	0.04	270	<20	6.62	–		
Ad26.COV2.S_full + mRNA-1273_booster	2,819	0.03	83	<20	6.49	–		
Mix (BNT162b2 + mRNA-1273)								
Mix_full	17,128	0.16	1,938	<20	11.31	–		
Mix_full + any booster	1,691	0.02	179	<20	10.59	–		
Variant Period							<0.0001	<0.0001
Pre-Delta	7,205,581	69.20	431,369	15,045	5.99	3.49		
Delta	8,980,373	86.24	788,935	12,453	8.79	1.58		
Omicron	9,192,549	88.28	724,851	8,560	7.89	1.18		

* Cells with participant count<20 are labeled as "<20" since the proportion is too small to quantitatively report.

† The number of infection (N_1) was based on the first positive SARS-CoV-2 PCR test after 14 days of the most recent vaccination. The infection rate was calculated by the number of participants infected (N_1) dividing the total number of participants (N).

¶ The number of death (N_2) was based on the mortality after the SARS-CoV-2 infection. The death rate was calculated by the number of patients who died after the SARS- CoV-2 infection (N_2) within six months dividing the number of infected patients (N_1).

§ Partial BNT162b2 and mRNA-1273 Vaccine cohorts were patients who took only one dose of each vaccine. Full BNT162b2 and mRNA-1273 Vaccine cohorts were patients who took two doses of each vaccine, with the second dose 21 days or later after the first dose. Full Ad26.COV2.S cohort was defined as patients who took one dose of Ad26.COV2.S Vaccine. BNT162b2, mRNA-1273, and Ad26.COV2.S plus BNT162b2 Booster and mRNA-1273 Booster cohorts were patients who took full vaccination plus a third dose of each vaccine after Aug 12, 2021 and 90 days (mRNA vaccines)/60 days (Ad26.COV2.S) later than the full vaccination. Mix full cohort was patients who took only two doses of mRNA vaccines and the second dose was 21 days or later than the first dose with BNT162b2 and mRNA-1273 each. Mix full plus any booster was patients who took Mixed full vaccination plus have taken the third dose of BNT162b2 or mRNA-1273 after Aug 12, 2021 and 90 days later than the second dose. Due to a limitation of data, we did not include the fourth vaccine dose in this study.

whole cohort during different variant-dominant periods were estimated by adjusting for age, gender, race, region, and prior infection (Fig. 3 and Table S3). During the study period, the VE against infection ranged from 47.59% (95% CI, 46.72–48.45) for mRNA-1273 full vaccination plus mRNA-1273 booster, to 46.19% (95% CI, 43.28–48.99) for BNT162b2 full vaccination plus mRNA-1273 booster, to 42.00% (95% CI, 39.38–44.54) for mRNA-1273 full vaccination plus BNT162b2 booster, and to 36.98% (95% CI, 36.20–37.76) for BNT162b2 full vaccination plus BNT162b2 booster. For the four different full vaccination regimens, only mixed full vaccination (one dose of BNT162b2 plus one dose of mRNA-1273) and Ad26.COV2.S full vaccination showed protection against infection, 35.17% (95% CI, 31.71–38.50) for mixed full vaccination, 25.08% (95% CI, 22.39–27.68) for Ad26.COV2.S full vaccination. For the two partial vaccination regimens, one dose mRNA-1273

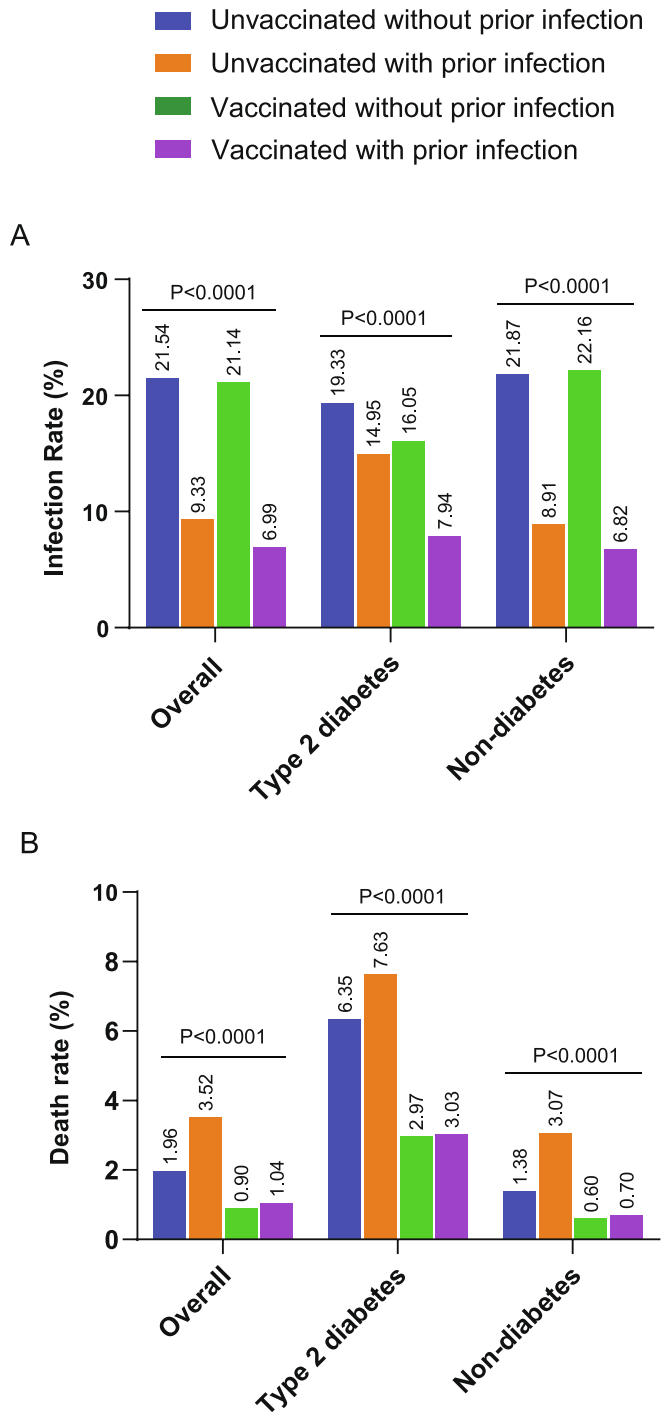

Fig. 2. Comparison of Infection and death rates with prior infection and vaccination status. At the beginning of the analysis, the participants were assigned to one of the four cohorts: 1) unvaccinated participants with no history of SARS-CoV-2 infection before the study period; 2) unvaccinated participants with prior SARS-CoV-2 infection before the study period; 3) vaccinated participants with no history of SARS-CoV-2 infection before the study period; and 4) vaccinated participants with prior SARS-CoV-2 infection before the study period. Then, the infection and related mortality rate among the unvaccinated without prior infection, unvaccinated with prior infection (natural immunity), vaccinated without prior infection, and vaccinated with prior infection (hybrid immunity) were compared in the whole cohort as well as the type 2 diabetes and non-diabetes cohorts.

and one dose BNT162b2, no anti-infection effect (VE < 0) was observed (Fig. 3A and Table S3).

During the Pre-Delta period, there was no booster vaccination, and all partial and full vaccination regimens showed high VE against infection, from the highest to lowest were 85.85% (95% CI, 85.14–86.54) for mRNA-1273 full vaccination, 81.43% (95% CI, 78.40–84.16) for Ad26.COV2.S full vaccination, 78.88% (95% CI, 66.64–87.65) for heterologous full vaccination (one dose of BNT162b2 plus one dose of mRNA-1273), and 77.86% (95% CI, 77.18–78.52) for BNT162b2 full vaccination. For the two partial vaccination regimens, the VE against infection of one dose mRNA-1273 was 67.99% (95% CI, 66.41–69.52), which was similar to one dose BNT162b2 vaccination – 67.70% (95% CI, 66.85–68.54) (Fig. 3B and Table S3).

During the Delta period, VE against infection from the highest to lowest were 47.64% (95% CI, 45.47–49.73) for mRNA-1273 full vaccination plus mRNA-1273 booster, 45.11% (95% CI, 43.55–46.63) for BNT162b2 full vaccination plus BNT162b2 booster, 36.15% (95%CI, 29.02–42.56) for mRNA-1273 full vaccination plus BNT162b2 booster, and 34.19% (95% CI, 26.21–41.30) for BNT162b2 full vaccination plus mRNA-1273 booster. Among different full vaccination (without booster) regimens, only Ad26.COV2.S (32.95%) (95% CI, 29.16–36.53) showed protection against infection (Fig. 3C and Table S3).

During the Omicron period, for the whole cohort, only one dose of mRNA-1273 vaccination showed protection against infection (15.66%) (95% CI, 13.78–17.51) (Fig. 3D and Table S3).

A similar pattern of VE against infection was found among the type 2 diabetes (Figure S2 and Table S4) and non-diabetes (Figure S3 and Table S5) cohorts during the different variant-dominant periods.

3.4. *Vaccine effectiveness against infection over time*

The VE against infection declined over time comparing the VE of different regimens in the whole cohort (Figure S4 and Table S6). Overall, BNT162b2 partial vaccination showed protection only at the first month (7.42%) (95% CI, 5.64–9.15). BNT162b2 full vaccination showed the highest VE at the first month (47.26%) (95% CI, 46.04–48.47), then fell to 7.92% (95% CI, 5.82–9.97) at the second month, an overall decline of 39.34 percentage points. Heterologous booster (BNT162b2 full vaccination with mRNA-1273 booster) showed stronger protection against infection than homologous booster (BNT162b2 full vaccination with BNT162b2 booster) across the entire study period. The adjusted VE of BNT162b2 full vaccination with mRNA-1273 booster ranged from 36.25% (95% CI, 19.67–49.39) at the fourth month to 10.83% at the sixth month (Fig. S4A and Table S6).

Fig. S4B and Table S6 show the comparison of VE against infection of different mRNA-1273 vaccination regimens in the whole cohort. The mRNA-1273 full vaccination had the highest VE against infection compared to BNT162b2 and Ad26.COV2.S full vaccination (64.69%) (95% CI, 63.29–66.04) at the first month, falling to 37.05% (95% CI, 34.62–39.41) at the second month and 16.96% (95% CI, 14.02–19.83) at the third month. Similar to BNT162b2 vaccination, heterologous booster (mRNA-1273 full vaccination with BNT162b2 booster) showed stronger protection against infection than homologous booster (mRNA-1273 full vaccination with mRNA-1273 booster). mRNA-1273 full vaccination with BNT162b2 booster showed stronger protection than mRNA-1273 full vaccination with mRNA-1273 booster, from 37.10% (95% CI, 22.82–48.73) at the fourth month to 10.03% at the sixth month.

As shown in Fig. S4C, Ad26.COV2.S full vaccination had the highest VE against infection in the whole cohort at the first month (30.82%) (95% CI, 23.51–37.44), and showed protection against infection until the fourth month (14.62%) (95% CI, 4.50–23.74). The VE of Ad26.COV2.S vaccine against infection declined less over time than the mRNA vaccines, but it offered lower overall protection, which was also confirmed in other studies [16].

Similar patterns were found in type 2 diabetes (Figure S5 and

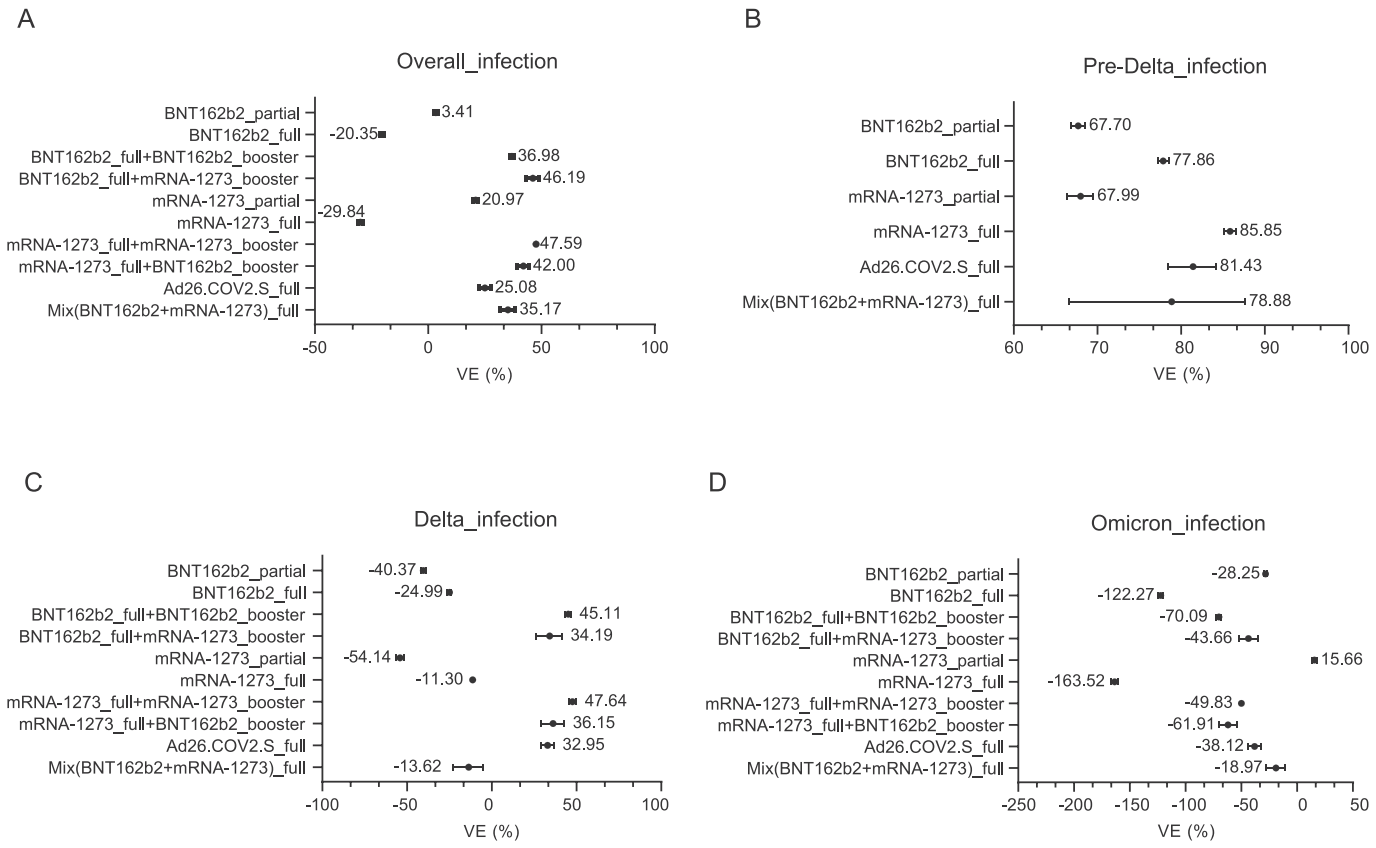

Fig. 3. Effectiveness of different vaccine regimens against SARS-CoV-2 infection, stratified according to variant-dominant periods in the whole cohort, after adjusting for age, gender, region, race, and prior infection. A) Adjusted VE against SARS-CoV-2 infection during the Overall study period (December 11, 2020 to June 30, 2022); B) Adjusted VE against SARS-CoV-2 infection during the Pre-Delta period (December 11, 2020 to June 25, 2021). During the Pre-Delta period, there was no booster vaccination; C) Adjusted VE against SARS-CoV-2 infection during the Delta period (June 26, 2021 to December 24, 2021); D) Adjusted VE against SARS-CoV-2 infection during the Omicron period (December 25, 2021 to June 30, 2022).

Table S7) and non-diabetes (Figure S6 and Table S8) cohorts.

3.5. Vaccine effectiveness against death

As shown in Fig. 4 and Table S9, VE against death in the whole cohort ranged from 89.56% (95% CI, 85.75–92.61) for BNT162b2 full vaccination plus mRNA-1273 booster, to 85.83% (95% CI, 82.49–88.70) for mRNA-1273 full vaccination plus BNT162b2 booster, to 84.74% (95% CI, 83.75–85.70) for mRNA-1273 full vaccination plus mRNA-1273 booster, and 84.43% (95% CI, 83.50–85.32) for BNT162b2 full vaccination plus BNT162b2 booster. For the different primary vaccination regimens, Ad26.COV2.S full vaccination did not show any protection against death (VE < 0); whereas all the mRNA vaccination regimens showed an anti-death effect: 74.56% (95% CI, 68.95–79.44) for heterologous mixed full vaccination, 58.07% (95% CI, 56.88–59.23) for BNT162b2 full vaccination, and 46.22% (95% CI, 44.47–47.93) for mRNA-1273 full vaccination. For the two partial vaccination regimens, VE against death of one dose mRNA-1273 was 58.25% (95% CI, 56.47–59.98), which was slightly higher than one dose BNT162b2 (56.15%, 95% CI, 54.90–57.38) (Fig. 4A and Table S6).

During the Pre-Delta period, the highest VE was 50.66% (95% CI, 48.78–52.48) for BNT162b2 partial vaccination, compared to 43.14% (95% CI. 40.96–45.23) for BNT162b2 full vaccination, 38.09% (95% CI, 34.49–41.49) for mRNA-1273 partial and 34.05% (95% CI, 31.20–36.74) for mRNA-1273 full (Fig. 4B and Table S6).

During the Delta period, partial and full vaccination all showed protection against death, except for Ad26.COV2.S full vaccination. The mRNA-1273 full vaccination showed 40.07% (95% CI 38.06–42.02) which was the lowest VE against death and mixed full vaccination showed 70.44% (95% CI, 62.17–76.92) which was the highest. Since this period, vaccine boosters were available, the effectiveness of a booster increased to 81.48% (95% CI, 79.93–82.92) in BNT162b2 full plus BNT162b2 booster, 91.87% (95% CI, 84.88–95.63) in BNT162b2 full plus mRNA-1273 booster, 81.09% (95% CI, 79.17–82.85) in mRNA-1273 full plus mRNA-1273 booster, 83.99% (95% CI, 77.19–88.76) in mRNA-1273 full vaccination plus BNT162b2 booster (Fig. 4C and Table S6). Against Omicron infection, all vaccination regimens that included boosters remained highly effective, similar to findings in the Delta period (Fig. 4D and Table S6).

Similar patterns of VE against death were also found among the type 2 diabetes (Figure S4 and Table S7) and non-diabetes (Figure S5 and Table S8) cohorts.

3.6. Vaccine effectiveness against death over time

Compared with the VE against infection, the VE against death showed less substantial attenuation over time (Figures S9–S11, Tables S12-S14). VE against death of mRNA partial and full vaccination was significantly decreased at the fifth or sixth months. The heterologous booster vaccination regimens showed higher VE against death than homologous booster regimens during the two-month observation period after vaccination, while the homologous booster vaccination maintained protection during the six-month observation period in the whole cohort (Table S12).

Overall, the VE against death for BNT162b2 partial was 51.53% (95% CI, 44.18–57.94) during the first month and 77.59% (95% CI, 72.00–82.06) at the third month, then decreased to 48.43% (95% CI, 35.08–59.06) at the sixth month. The VE against death of BNT162b2 full

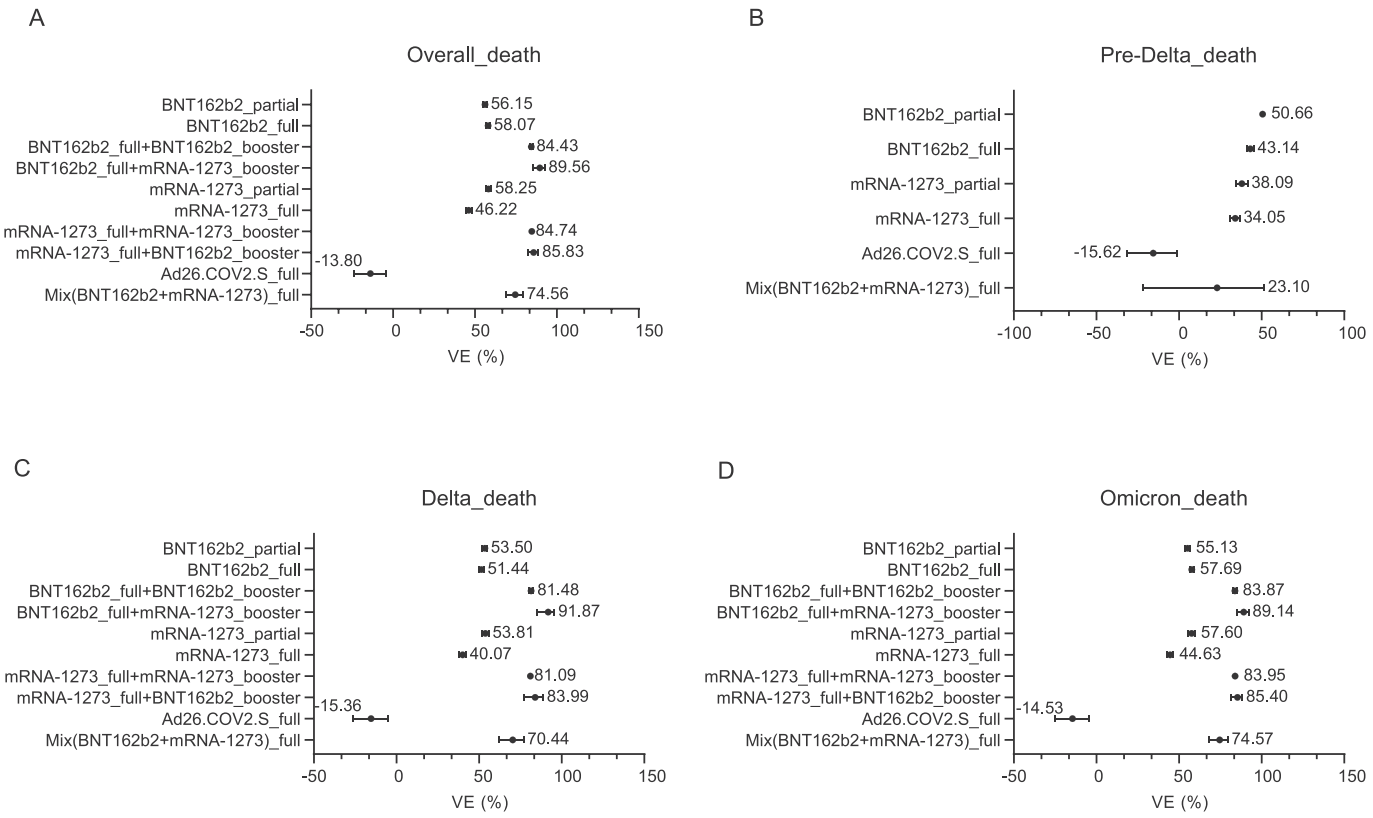

Fig. 4. Effectiveness of different vaccine regimens against death after SARS-CoV-2 infection, stratified according to variant-dominant periods in the whole cohort, after adjusting for age, gender, region, race, and prior infection. A) Adjusted VE against death after SARS-CoV-2 infection during the Overall study period (December 11, 2020 to June 30, 2022); B) Adjusted VE against death after SARS-CoV-2 infection during the Pre-Delta period (December 11, 2020 to June 25, 2021). During the Pre-Delta period, there was no booster vaccination; C) Adjusted VE against death after SARS-CoV-2 infection during the Delta period (June 26, 2021 to December 24, 2021); D) Adjusted VE against death after SARS-CoV-2 infection during the Omicron period (December 25, 2021 to June 30, 2022).

vaccination started at 64.60% (95%CI 56.74–71.00) at the first month, dropped to 71.76% (95% CI, 64.55–77.51) at the third month, before falling to 42.12% (95% CI, 30.16–52.05) at the sixth month. The VE against death for BNT162b2 full plus BNT162b2 booster started at 83.35% (95% CI, 77.69–87.58) at the first month and then fell to 73.15% (95% CI, 58.48–82.66) at the fifth month. The VE against death for BNT162b2 full plus mRNA-1273 booster was 94.06% (95% CI, 57.56–99.17) at the first month and then fell to 85.10% (95% CI, 39.83–96.31) at the second month (Figure S9A and Table S12).

The mRNA-1273 VE against death had less substantial attenuation over time compared to BNT162b2. Among those who received one dose of mRNA-1273, VE against death was 51.57% (95% CI, 40.79–60.39) at the first month, rose to 74.28% (95% CI, 63.18–82.04) at the third month, and then fell back to 53.76% (95% CI, 32.70–68.21) at the sixth month. For mRNA-1273 full vaccination, VE against death started at 68.18% (95% CI, 56.87–76.52) at the first month and then dropped to 27.20% (95% CI, 7.78–42.48) at the fifth month. The mRNA-1273 full vaccination plus mRNA-1273 booster showed similarly strong protection compared to mRNA-1273 full vaccination plus BNT162b2 booster, from 78.75% (95% CI, 71.66–84.07) at the first month, dropping to 70.26% (95% CI, 49.24–82.59) at the fifth month (Figure S9B and Table S12).

Among participants who received mixed mRNA vaccination (one dose of BNT162b2 plus one dose of mRNA-1273) as the primary course, the VE against death was 71.30% (95% CI, 29.88–88.25), showing higher protection and less substantial attenuation over time than either two doses of BNT162b2 or mRNA-1273. Although Ad26.COV2.S full vaccination had some effectiveness against infection (Fig. S4C and Table S6), it did not have any protection against death after infection at all intervals after vaccination (Figure S9C and Table S12).

The type 2 diabetes (Figure S10 and Table S13) and non-diabetes (Figure S11 and Table S14) cohorts showed similar VE changes over time as for the whole cohort.

4. Discussion

Data on VE against infection with SARS-CoV-2 variants and death from COVID-19 between various COVID-19 vaccine regimens in the US are still under investigation. With more people now exposed to SARS-CoV-2 [18], there is a higher chance of re-infection. Previous studies reported the natural infection with SARS-CoV-2 elicits strong protection against re-infection with the Alpha, Beta, and Delta variants [19–22]. Based on the N3C data, natural immunity lowered the re-infection risk, but if unvaccinated, re-infection brought higher death risk to all three cohorts, which might be due to the weak immune system of these individuals. Our study showed that vaccination could significantly decrease the death risk if natural immunity is coupled with subsequent vaccination, indicating that the immunity induced by vaccines might be much stronger than natural immunity.

During the overall study period, the VE of mRNA-1273 full vaccination plus mRNA-1273 booster against SARS-CoV-2 infection among all the vaccination types was the highest in the whole cohort, while BNT162b2 full vaccination plus mRNA-1273 booster showed the highest VE in the type 2 diabetes cohort. Among all the full vaccination regimens, the mixed vaccination of two mRNA vaccines showed the highest VE against infection in our three study cohorts. This could be due to mRNA-1273 eliciting more robust neutralizing antibody responses and anti-infection effect than BNT162b2 [23,24].

During the Pre-Delta period, all types of vaccination showed more than 66% effectiveness against infection in the three cohorts. During the

Delta period, booster vaccination showed a strong anti-infection effect, while partial and full vaccines almost no anti-infection effect except Ad26.COV2.S full and mixed full vaccination which showed marginal anti-infection effect in the whole cohort. This result reflects the necessity for booster administration during the Delta-dominant period.

During the Omicron period, all vaccination regimens, except mRNA-1273 partial vaccination, were not effective in protecting against infection. This result could be due to the Omicron variant harboring multiple mutations that can mediate immune evasion and spread more easily than the original strain, even in fully vaccinated people [19,25].

Our results showed that during the three variant-dominant periods, VE against infection declined, but vaccination still provided anti-death effectiveness. As the vaccines were generated based on the original virus, during these later time periods, immune cells may not fully recognize the mutated variants, and thus, boosters are necessary or updated vaccines are required to tackle newly emergent variants. Although the vaccines had limited anti-infection effect during the Omicron period, the two mRNA vaccines maintained strong anti-death protection, indicating that due to the mutation, the circulating antibodies generated by the vaccines might not be able to neutralize the mutated viruses to prevent infection, but memory B cells are still likely to recognize them and undergo new rounds of affinity maturation, resulting in new neutralizing antibodies to prevent a severe outcome caused by the mutated variants [25].

Ad26.COV2.S vaccination showed an anti-infection effect during the Pre-Delta and Delta periods, but did not show any anti-death effect during any of the variant-dominant periods. One possible reason is Ad26.COV2.S may have yielded lower antibody concentrations, as evidenced by previously reported undetectable neutralization titers [24]. For recipients of the Ad26.COV2.S primary dose, heterologous boosting with BNT162b2 or mRNA-1273 vaccines has been shown to increase cellular and humoral immunity [26], resulting in increased effectiveness compared to homologous boosting [27].

Our results, as well as those of other studies [28–30], identified that heterologous booster regimens (BNT162b2 full vaccination plus mRNA-1273 booster, mRNA-1273 full vaccination plus BNT162b2 booster) showed stronger protection than homologous booster regimens (BNT162b2 full vaccination plus BNT162b2 booster, mRNA-1273 full vaccination plus mRNA-1273 booster) across the study period in all three cohorts.

The present study has some limitations. First, given the available data in the study period, we were unable to include the fourth vaccine dose and thus compare the VE of the new bivalent booster against the Omicron variant. Second, survival status was routinely collected from each follow-up month's COVID-19 positive cases until the observation end point; the time for mortality ascertainment should be sufficiently long to capture delayed deaths for partial and full vaccination. Since, the observation periods for the booster vaccination were limited, the period following booster administration may be too short to capture delayed deaths. Third, as an observational study, there may be residual confounding for which could not account. For example, some vaccinated individuals may be included within the non-vaccination report due to differing completeness of the electronic health records. Moreover, the participants included in this study were patients with multiple comorbities and immune dysfunction, which may have resulted in the lower vaccination rate observed than the national vaccination rate. Considering these limitations, the reported VE may have some bias toward lower values than that would be expected in the general population with less co-morbidity.

Of note, this is one of the most extensive studies performed on a nationwide cohort and included an 18-month long-term period, encompassing the Pre-Delta to the Omicron periods. In addition to estimating the VE of diverse vaccination regimens in the US, we also evaluated a series of factors, such as different variant-dominant periods, heterogenous and homologous vaccination, and previous infection before vaccination. Further, few studies have studied VE in type 2 diabetes patients. This study identified similar VE patterns in type 2 diabetes patients. Compared with the whole cohort and non-diabetes group, type 2 diabetes patients with prior infection showed a higher re-infection and death risk. Importantly, vaccination after prior infection provided strong anti-reinfection and anti-death protection, reinforcing the perspective that it is critical for type 2 diabetes patients (especially those with prior COVID-19 infection) to get vaccinated. Due to the high infection rate during the Omicron-dominant period, the regimens of full vaccination plus boosters needs to be promoted to reduce infection/re-infection and mortality. The results of our study provide evidence of VE against infection and death among COVID-19 patients, especially those with pre-existing type 2 diabetes.

Author contribution

Authorship was determined using the International Committee of Medical Journal Editors recommendations. YD designed and supervised the study. YF and KW extracted the data and searched the literature. YF and KW contributed equally. YF and ZW processed and conducted data analyses and interpretation. YF drafted the manuscript and prepared the figures. ZW, HY, YC, LW, HW, RY, and JRH contributed to editing the manuscript and interpreting the data, and all authors reviewed and approved the final version for publication. YD and YF directly accessed and verified the data reported in the manuscript and are responsible for the integrity of the data and the accuracy of the analyzed data.

Ethical approval

The National COVID Cohort Collaborative (N3C) is a national electronic health record repository supported and managed by the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH). The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol No. IRB00249128. To conduct the study using the de-identified data from the N3C Data Enclave, this project has been approved under the authority of the NIH Review Board and N3C Data Access Committee with the de-identified data access (NCATS N3C DATA ENCLAVE INSTITUTIONAL DATA USE AGREEMENT) (DUR ID: RP-8B3D84).

Declaration of Competing Interest

All the authors declare no competing interest, except LW provided consulting service to Pupil Bio Inc. and received honorarium.

Data Availability

All the analyses described in this publication were conducted with data or tools accessed through the N3C Data Enclave and approved by the N3C Publication Committee and Download Request Committee. The N3C Data Enclave is managed under the authority of the NIH; information can be found at https://ncats.nih.gov/n3c/resources. Data can be shared by contacting with the N3C Data Access Committee.

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Appendix A. Supplementary data

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