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Impact of prior SARS-CoV-2 infection on incidence of hospitalization and adverse events following mRNA SARS-CoV-2 vaccination: A nationwide, retrospective cohort study

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ABSTRACT

Background: Previous studies evaluated the SARS-CoV-2 vaccine safety or compared adverse events following vaccination to those from infection. Limited data about the impact of prior infection on post-vaccine adverse events are available. The objective of this study was to evaluate the impact of prior SARS-CoV-2 infection on outcomes shortly after vaccination using a longitudinal design.

Methods: Nationwide, multicenter, retrospective cohort study of hospitalization, death, and pre-specified adverse event rates among Veterans who received mRNA vaccines within the Veterans Health Administration between 12/11/2020 and 8/31/2021. Daily incidence rates were compared before and after vaccine doses, stratified by history of microbiologically-confirmed SARS-CoV-2.

Results: 3,118,802 patients received a first dose and 2,979,326 a second, including 102,829 with a history of SARS-CoV-2 infection. Daily incident hospitalization rates were unchanged before and after the second dose among patients without previous infection (28.8/100,000 post-dose versus 28.6/100,000 pre-dose, $p = 0.92$). In previously-infected patients, the hospitalization rate increased above baseline one day following vaccination (158.2/100,000 after dose 2 versus 57.3/100,000 pre-dose, $p < 0.001$), then returned to baseline. Chart review indicated vaccine side effects, such as fever, constitutional symptoms, weakness, or falls, as the definite (39%) or possible (18%) cause of hospitalization. Affected patients had mean age 75, and 90% had at least one serious comorbidity. Hospitalizations were brief (median 2 days), with rapid return to baseline health. Worse baseline health among previously-infected patients prevented conclusions about mortality risk.

Conclusions: Two-dose mRNA vaccine regimens are safe in a population with many comorbidities. Transient increased risks of hospitalization were identified among patients with prior SARS-CoV-2, absolute risk ~1:1000. Findings support additional study regarding the optimal dosing schedule in this population.

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1. Introduction

In early 2020, as the spread of SARS-CoV-2 evolved into a pandemic, an unprecedented global effort began to develop and administer vaccines to control the spread and severity of SARS-CoV-2. Three vaccines are currently approved in the United States

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(Pfizer-BioNTech's BNT162b2, Moderna's mRNA-1273 and Janssen/Johnson & Johnson's Ad26.COV2.S) [1].

The most commonly reported adverse events (AEs) of vaccine administration are local injection site reactions, fatigue, headache, dizziness, nausea, fevers, and myalgias [2]. Minor adverse events were also reported among placebo groups in clinical trials [3–5]. Prior studies have reported specific syndromes associated with particular vaccines, such as the thrombosis with thrombocytopenia syndrome with adenovirus-vector vaccines and myocarditis following receipt of mRNA vaccines [6–9]. Rates of anaphylaxis are estimated at 2–11 cases per million after receipt of Moderna and Pfizer vaccines. Recent studies reporting on pre-specified vaccine-related adverse events reported no increase following vaccination, and that adverse event rates following vaccination with BNT162b2 were lower than those caused by natural infection, however, patients with a history of infection were excluded, thus it is not clear if these post-surveillance studies generalize to those with existing immunity. [10,11]

Natural infection confers lasting immunity [12] and multiple studies demonstrate robust immune responses to a single dose of mRNA vaccine in previously infected patients [13–19]. Critical questions remain about best practices for vaccinating previously infected patients, who might develop more vaccine-related adverse events due to their pre-existing immunity. Thus, the objective of this large, multicenter, retrospective cohort study was to determine whether hospitalization, specific adverse events reported in the literature or listed in the Vaccine Adverse Event Reporting System (VAERS) database, or death occurred more frequently after vaccination than at the expected rate for the population, and to evaluate the impact of prior SARS-CoV-2 on the relationship.

2. Methods

2.1. Cohort creation

A longitudinal cohort of all patients who received an mRNA COVID-19 vaccine (BNT162b2 or mRNA-1273) within the Veterans Affairs Healthcare System (VA) during the period from 12/11/2020 to 8/31/2021 was created. The small number of patients who received the Janssen vaccine were excluded.

Data extracted included acute care hospitalization and the primary diagnosis associated with that hospitalization (ICD-10 codes), emergency room visits, demographic information (e.g., age, sex, race, ethnicity), laboratory data from the VA COVID-19 shared data resource [20], which includes history of laboratory-confirmed COVID-19, defined by any prior positive PCR or antigen test at a VA facility or some positive tests performed at non-VA facilities but reported to a VA provider, and patient frailty index using previously described methods [21]. Data on diagnostic codes associated with emergency department visits was extracted from the VA Emergency Department Information System (EDIS). Vital status was obtained from the National Death Index. All analyses were stratified by SARS-CoV-2 infection history and by mRNA vaccine type.

2.2. Hospitalizations

The primary outcome measure was the daily incidence rate of acute care hospitalization at a VA or non-VA hospital per 100,000 vaccinated patients. Hospitalizations either within or reimbursed by the VA healthcare system were captured. Admissions to a psychiatric facility or unit, a VA community living center, or a VA domiciliary were excluded. The daily incident hospitalization rates for the longitudinal cohort during the period from 56 days prior to vaccination and 56 days after vaccination were calculated, and confidence intervals and changes relative to the vaccination date evaluated using bootstrapping with the percentile method. Findings were calculated for the entire population and stratified by history of SARS-CoV-2 infection. The primary diagnoses (ICD-10 codes) associated with hospitalizations at a VA hospital during the periods 7–14 days before vaccination and 0–7 days after the first dose of vaccine were compared. Analysis before versus after dose 2 was not performed, out of concern that the pre-dose comparator for dose 2 would be close to the time of the post-dose data for dose 1. A random sample of 80 acute-care hospitalizations that occurred the day after vaccine receipt underwent manual review to determine the reason for hospitalization and whether it was associated with vaccine receipt (yes, no, or probable/possible, based on the symptoms leading to hospitalization, timing of onset and resolution, and objective findings and treatment).

2.3. Specific adverse events

Specific adverse events reported to be associated with vaccination were identified using diagnostic codes based on published research (for arterial and venous thrombotic events and hypersensitivity reactions) and adverse event reports from VAERS (Supplementary File 1). Frequency of use of these codes was compared during hospitalizations pre and post vaccination. Similarly, use of these codes during emergency department visits (per 1,000,000 vaccinated patients) was calculated daily relative to the day of vaccination, and trends were evaluated in patients with and without a history of SARS-CoV-2 infection.

2.4. Mortality

Trends in daily incident mortality (per 1,000,000 vaccinated patients) relative to the day of vaccination were determined in patients with and without a history of SARS-CoV-2 infection. All deaths within 48 h of either vaccine dose underwent manual review to determine the cause and location of death (e.g., at home versus in the hospital), major medical problems, and to assess if the death was expected (e.g., patient on hospice) and/or potentially linked to vaccine receipt.

2.5. Sensitivity analysis

All of the analyses described above were repeated in a subset of patients who met criteria for regular use of the VA, defined as veteran patients with at least one diagnostic code each year during the two years prior to the first dose of COVID-19 vaccination and who had not had incident hospitalization within 30 days of the first dose. Plots were also made stratifying by the vaccine product used (Pfizer or Moderna).

2.6. Statistical analysis

Daily rates of acute care hospitalization, death, and coding for adverse events up to 56-days prior to the first dose of vaccine and up to 56-days following the second dose were plotted, both for the entire cohort and stratified by SARS-CoV-2 history. Rates were censored 21 days following the first dose of the Pfizer vaccine and 28 days following the first dose of the Moderna vaccine. Confidence intervals (95%) for daily rates were calculated using 200 times of random sampling with replacement of the cohort. This bootstrapping strategy was performed using the R-boot package (version 1.3–28). [22,23] Separate plots and calculations were made relative to the first and second doses of the mRNA vaccine. All analyses were completed using R version 4.0.2.

Analysis of proportions of hospitalizations before and after the second vaccine dose, or of pre-specified adverse events leading to hospitalization before and after the first vaccine dose, were performed using Fisher's exact test.

2.7. Ethical considerations

The study was approved as an exempt study by the VA Boston Healthcare System Research and Development Committee (#3328-X) prior to data collection and analysis with a waiver of informed consent.

3. Results

During the period from 12/11/2020 to 8/31/2021, 3,118,802 Veteran patients at 129 different VA facilities received one dose of a SARS-CoV-2 mRNA vaccine and 2,979,326 received two doses (1,389,401 Pfizer, 1,589,925 Moderna). 102,829 had a prior SARS-CoV-2 infection.

Baseline demographics are presented in Table 1. The median age was 66.96 (SD = 14.88), and 91.5% were male. 102,829 (3.3%) had a history of laboratory-confirmed SARS-CoV-2 prior to vaccine receipt. Prior to vaccination, patients with a history of SARS-CoV-2 had higher proportions of mild, moderate and severe frailty (19.1%, 10.2% and 8.9% respectively) compared to patients with no documented history of prior infection (14.2%, 5.7% and 3.4% respectively).

3.1. Acute care hospitalizations

Incidence of acute care hospitalizations is shown in Fig. 1. The increasing incidence of hospitalization shortly before dose 1, which is particularly evident in patients without a history of infection, reflects the policy of a minority of facilities to vaccinate inpatients. Among the entire cohort, without stratification for infection history, no clear increase above the baseline rate of hospitalization was identified, nor was there an identified difference between the two mRNA vaccines (Supplementary Fig. 1). After stratification, the baseline rate of hospitalization appeared to be higher in the previously-infected group, consistent with the higher rate of frailty. No attempt to identify specific clinical or demographic variables that might explain this difference was undertaken.

Among the 2,979,326 patients in the entire cohort who received the second dose of vaccine, 880 were hospitalized on the day of vaccination (day 0) and 982 were hospitalized during the 1-day period following vaccination, corresponding to hospitalization rates of 29.5/100,000 prior to vaccination and 33.0/100,000 following ($p = 0.019$). After stratifying by history of SARS-CoV-2 infection, there was no change above baseline among patients without prior infection (baseline rate 28.6/100,000 versus 28.8/100,000 following vaccination, $p = 0.92$). A substantial increase was found among patients with a prior infection, particularly following the second dose (baseline rate prior to vaccination 57.3/100,000, versus 158.2/100,000 following vaccination, $p < 0.001$). Identifying a similar peak after the first dose was made challenging by the peak beginning to rise before the first dose, due to facility-level vaccination policies. A sensitivity analysis limited to regular VA users who were not hospitalized in the 30 days prior to the first dose confirmed the peak after dose 2 and supported the likelihood of a smaller peak after dose 1 (Supplementary Fig. 2) and also did not reveal a difference between vaccine types (Supplementary Fig. 3).

Manual review of a random sample (n = 80) of previously-infected patients hospitalized the day after dose 2 found that 31 (38%) developed new symptoms, such as fever or weakness typical of post-vaccine side effects (Table 2) severe enough for them to be hospitalized within 24 h. All but 3 (10%) of these patients had at least 1 of 8 pre-specified serious medical conditions, and mean age was 75. Recovery was typically rapid, with mean hospitalization for 2.7 days. Thirty-five of the 80 patients reviewed (44%) had illnesses pre-dating vaccination, and in 14 cases (18%), the

Table 1
Baseline Characteristics of the Cohort, Stratified by History of SARS-CoV-2 Infection.

	Overall	No Documented SARS-CoV-2 Infection	History of SARS-CoV-2 Infection
N (%)	3,118,802	3,015,973 (96.7)	102,829 (3.3)
Age (mean (standard deviation))	66.96 (14.88)	67.07 (14.87)	63.70 (14.80)
Gender (%)			
Female	266,110 (8.5)	255,826 (8.5)	10,284 (10.0)
Male	2,852,692 (91.5)	2,760,147 (91.5)	92,545 (90.0)
Race (%)			
Black	582,355 (18.9)	555,852 (18.7)	26,503 (26.1)
White	2,167,744 (70.5)	2,102,236 (70.7)	65,508 (64.4)
Other or unknown	326,577 (10.6)	316,915 (10.7)	9662 (9.5)
Ethnicity (%)			
Hispanic or Latinx	216,079 (7.4)	205,683 (7.3)	10,396 (10.5)
Not Hispanic or Latinx	2,692,137 (92.6)	2,603,498 (92.7)	88,639 (89.5)
Rural status (%)			
Rural	201,831 (25.3)	174,397 (25.1)	27,434 (27.1)
Urban	594,732 (74.7)	520,807 (74.9)	73,925 (72.9)
Unknown	72 (0.0)	67 (0.0)	5 (0.0)
Region (%)			
Continental	529,756 (17.0)	510,868 (16.9)	18,888 (18.4)
Midwest	639,994 (20.5)	616,188 (20.4)	23,806 (23.2)
North Atlantic	705,066 (22.6)	683,076 (22.6)	21,990 (21.4)
Pacific	557,088 (17.9)	540,957 (17.9)	16,131 (15.7)
Southeast	686,898 (22.0)	664,884 (22.0)	22,014 (21.4)
Frailty (%)*			
Non-frail	313,913 (10.1)	310,501 (10.3)	3412 (3.3)
Pre-frail	2,064,069 (66.2)	2,003,983 (66.4)	60,086 (58.4)
Mild	446,978 (14.3)	427,306 (14.2)	19,672 (19.1)
Moderate	181,915 (5.8)	171,408 (5.7)	10,507 (10.2)
Severe	111,927 (3.6)	102,775 (3.4)	9152 (8.9)

* Defined according to previously defined frailty index.

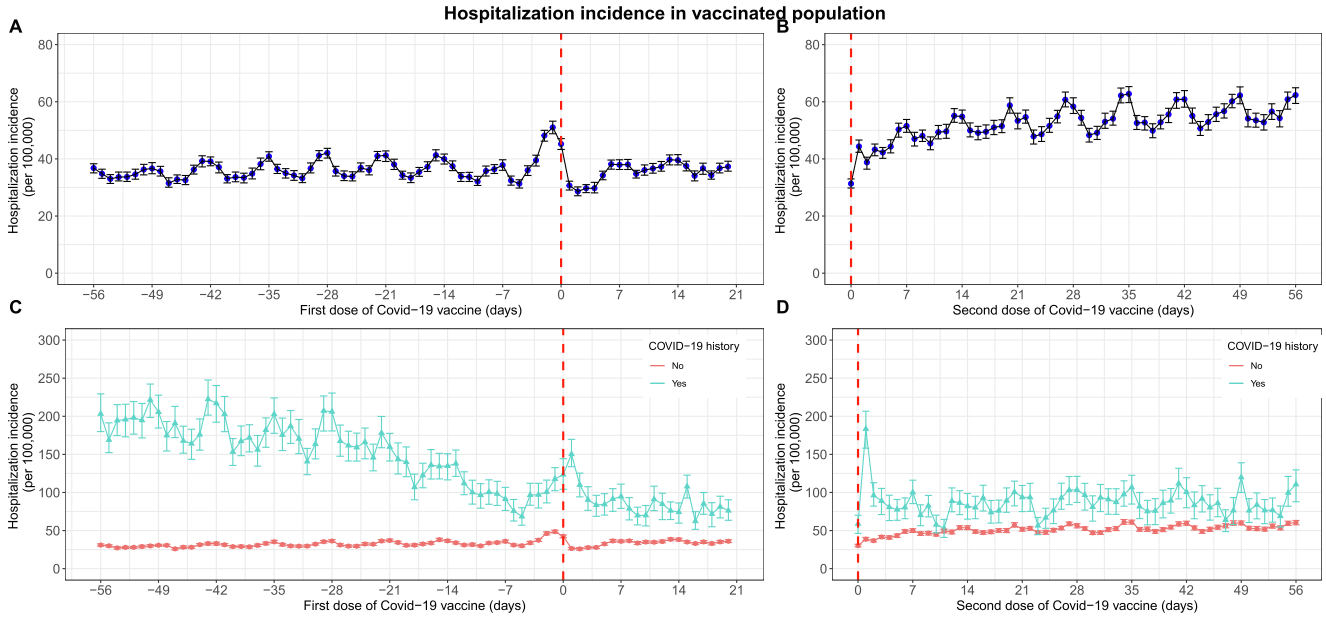

Fig. 1. Daily incidence of hospitalization per 100,000 Veteran patients during the period from 56 days prior to vaccination and 56 days after vaccination. Panels A and B are for the combined cohort of patients following the first (Panel A) and second (Panel B) doses of vaccine. Panels C and D present the analysis stratified by history of documented SARS-CoV-2 infection within the VA healthcare system following the first (Panel C) and second (Panel D) doses of vaccine. In panels C and D, patients with a history of SARS-CoV-2 infection are represented in blue and patients without a history of SARS-CoV-2 infection are represented in orange. Day 0 is the date of vaccination. Confidence intervals are calculated using a bootstrapping methodology. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Summary of Cases of Previously Infected Patients Hospitalized Following Vaccination for Vaccine-Related Adverse Events.

	Number of cases (out of 31, %)
Co-morbidities	
Chronic obstructive pulmonary disease (COPD)	7 (23)
Coronary Artery Disease	11 (35)
Heart Failure	5 (16)
Diabetes	16 (52)
Cirrhosis	2 (6)
Chronic kidney disease	7 (23)
Cancer, not in remission	4 (13)
Dementia	2 (6)
None	3 (10)
Symptoms/Reason for Admission	
Constitutional	30 (97)
Shortness of breath or hypoxemia	8 (26)
Altered mental status	10 (32)
Gastrointestinal complaints	4 (13)
Fall	8 (26)

timing suggested illness may have been exacerbated by vaccination, but attribution could not be determined because of chronic poor health and frequent hospitalizations.

3.2. VAERS and literature-defined specific adverse events

The causes of hospitalization in the total cohort were similar during the period from 14 to 7-days before the first dose to 0 to 7 after the first dose (Supplementary File 2). In the pre-specified list derived from a combination of VAERS, thromboembolic events, and hypersensitivity reactions, no individual code was used more or less often before and after the first vaccine dose (all $p > 0.05$), including venous thromboembolic events (pre- 84 vs post- 81, $p = 0.89$), major cardiac adverse events (pre- 244 vs post-, 258, $p = 0.53$), or myocarditis or pericarditis (pre- 5 vs post- 2, $p = 0.45$).

Rates of the same list of pre-specified adverse events associated with emergency department visits during the period from 56 days prior to the first dose of vaccine to 56 days after the second dose are presented in Fig. 2. No increase in specific adverse events was detected in the whole cohort without stratification for prior infection. After stratification, the baseline rate of coding for adverse events of interest appeared to be higher in the previously infected group, as with hospitalizations and with the same caveats. There was a suggestion in the graph that peaks of increased incidence might have occurred one day after each vaccine dose, which were more evident in analysis limited to regular VA users not hospitalized in the 30 days before dose 1 (Supplementary Fig. 4). However, absolute case numbers were too small (fewer than 10 per day) to allow definitive conclusions, or to assess for differences between the Pfizer and Moderna vaccines (Supplementary Figs. 5 and 6).

3.3. Mortality

Trends in daily mortality rates, with or without stratification by SARS-CoV-2 infection history, are presented in Fig. 3. The gradual upward trend, which appears identical after the first or second dose, likely reflects patients being less likely to choose to be vaccinated while seriously ill, I.e. a "healthy vaccinee" effect. In addition to there being no difference in the trends after the first versus the second dose, trends were similar for the two different vaccines (Supplementary Fig. 7), and when the cohort was limited to regular VA users with no recent hospitalizations (Supplementary Fig. 8).

The trends in mortality rates in previously infected patients appeared to differ from that in uninfected patients solely by absence of the gradual rise over the first few days after vaccination, suggesting the absence of a "healthy vaccinee" effect in a population that was sicker overall. The small number of events prevented a rigorous comparison between mortality in previously infected and uninfected patients.

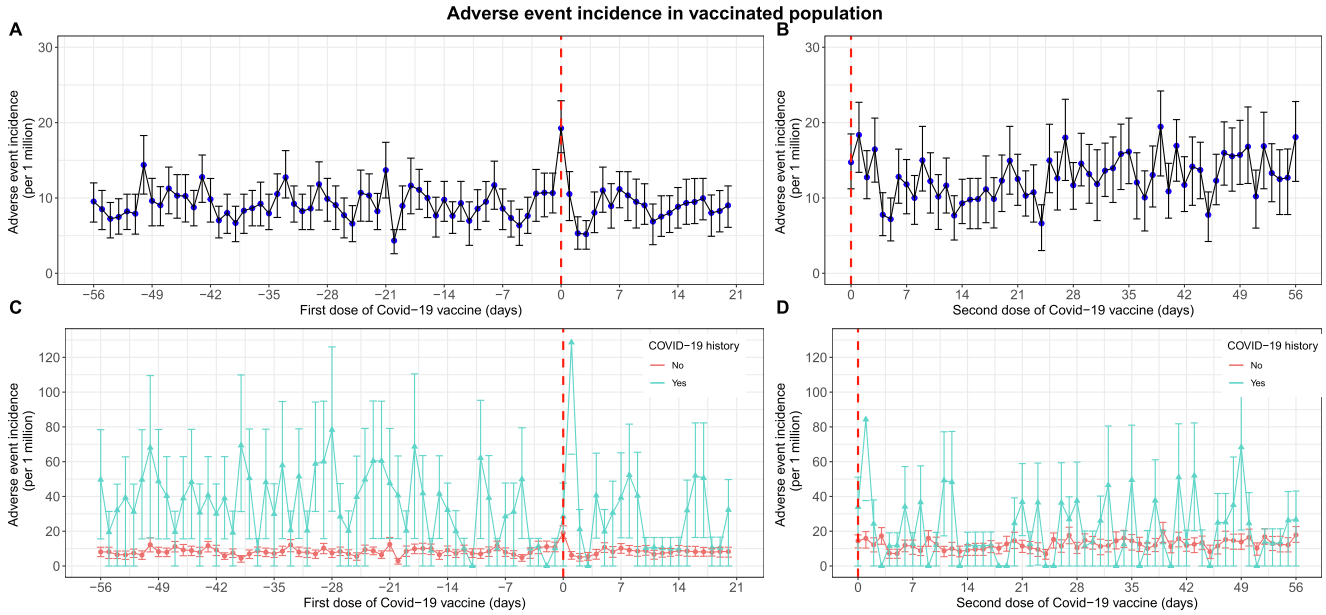

Fig. 2. Daily incidence of specific adverse events determined *a priori* to be of interest, recorded at emergency department visits per 1,000,000 Veteran patients during the period from 56 days prior to vaccination and 56 days after vaccination. Panels A and B are for the combined cohort of patients following the first (Panel A) and second (Panel B) doses of vaccine. Panels C and D present the analysis stratified by history of documented SARS-CoV-2 infection within the VA healthcare system following the first (Panel C) and second (Panel D) doses of vaccine. In panels C and D, patients with a history of SARS-CoV-2 infection are represented in blue and patients without a history of SARS-CoV-2 infection are represented in orange. Day 0 is the date of vaccination. Confidence intervals are calculated using a bootstrapping methodology. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

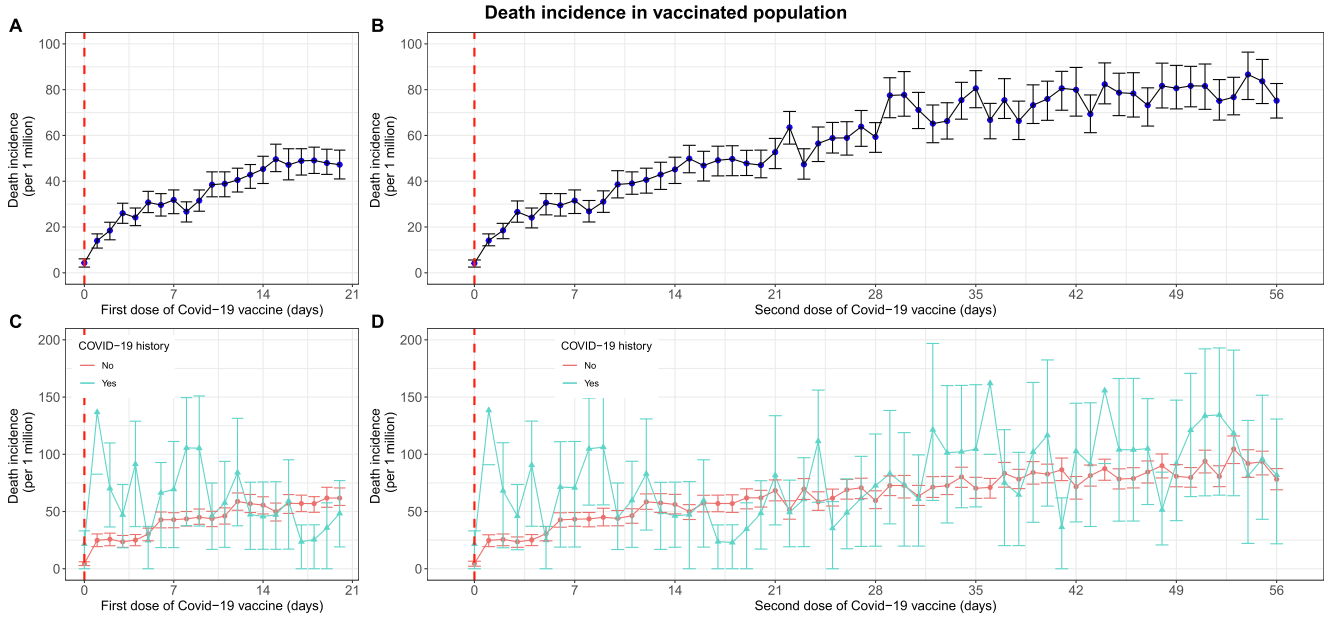

Fig. 3. Daily incidence of death per 1,000,000 Veteran patients during the period from the date of vaccination until 56 days after vaccination. Panels A and B are for the combined cohort of patients following the first (Panel A) and second (Panel B) doses of vaccine. Panels C and D present the analysis stratified by history of documented SARS-CoV-2 infection within the VA healthcare system following the first (Panel C) and second (Panel D) doses of vaccine. In panels C and D, patients with a history of SARS-CoV-2 infection are represented in blue and patients without a history of SARS-CoV-2 infection are represented in orange. Day 0 is the date of vaccination. Confidence intervals are calculated using a bootstrapping methodology. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Findings from the detailed manual review of all deaths within 48-hours following vaccination (N = 262/3,118,802, 0.008%) are summarized in Table 3.

4. Discussion

In this multicenter, nationwide retrospective cohort study of 3,344,749 Veterans who received SARS-CoV-2 mRNA vaccines, the risk of hospitalization following vaccination is low, and substantially lower than reported rates from natural infection, which may be as high as 10% in very frail patients. Across the longitudinal cohort, we found no excess mortality and no increase in the specific adverse events reported to VAERS, similar to findings from other recently published post-approval safety studies [10,11]. There was a small but significant increase in hospitalization rate among patients with a history of SARS-CoV-2 infection, particularly after

Table 3
Summary of manual review of all patients who died within 48 h of receiving a dose of an mRNA COVID-19 vaccine.

Category	Number of cases (%)*	Lab confirmed SARS-COV-2 History	Died at home or in ED	Died in hospital or nursing facility	Median age (range)	Details
Outpatient - clinician concern for adverse reaction	6 (2.3%, 5.0%)	0	6/6	0/6	73 (66–83)	Outpatient received a dose of vaccine, explicitly was noticed by family or clinician to be feeling worse afterwards, and died shortly after; includes a case of anaphylaxis
Inpatient or facility – clinical concern for adverse reaction	7 (2.7% 5.8%)	3	0/7	7/7	80 (64–87)	Patient was hospitalized, in rehab, or known to be sick with serious medical conditions, was felt to overall be stable or on the way to discharge, then decompensated
Died at home, no other information	69 (26.5%, 57.5%)	11	69/69	0/69	76 (43–99)	Outpatient otherwise felt to be clinically stable died at home
Not enough information	114** (43.1%, NA)	14	n/a	n/a	77 (33–96)	No information surrounding circumstances of death
Plausible alternative explanation for death	38 (14.6%, 31.7%)	2	18/45	27/45	75 (28–97)	Plausible alternative explanation based on chart review, e.g. sepsis, procedural complication, acute bleed, cancer complication, CVA, COVID pneumonia (1 case)
Patient already in hospice	28 (10.8%, NA)	4	n/a	n/a	81 (49–97)	Patient was enrolled in hospice at the time of vaccine
Total Number of Cases	**262***	**34**			**77 (28–99)**	

* The first percentage is of the total deaths within 48 h (262). The second percentage is based on the 120 deaths that did not occur in hospice or did not have enough information to make any assessment. NA = not applicable.
** Two patients had an uncertain time of death but were estimated to have died within 48 h. They are included under "Not enough information."

receipt of the second dose of either mRNA vaccine, with an absolute increased risk of 1:1000. Reassuringly, among patients with no history of infection, we found no evidence for any excess mortality associated with vaccine receipt. The sample size of patients with a recent or prior infection who died is too small to allow conclusions, since comparison to patients without infection would require adjustment for multiple confounding variables. These findings strongly support vaccine safety but raise questions about the optimal vaccination schedule in patients with a confirmed infection history. Additional research is needed to inform the best strategy for previously infected patients, who might benefit from a single-dose vaccination regimen, a delayed second-dose strategy, or simple interventions to prevent post-vaccine fever and dehydration if the standard vaccination schedule is used.

Trends that deviate from flat lines are worth additional discussion. First, the gradual upward trend in mortality in the uninfected group (Fig. 3) undoubtedly reflects the fact that patients not only must be alive to be vaccinated but also received vaccination at times of relatively stable health. The same phenomenon was also observed to a lesser extent for hospitalization after dose 2 (Fig. 1). This "healthy vaccinee" effect probably also explains the downward trend in incident hospitalizations in the previously infected group prior to dose 1 (Fig. 1). The absolute rate of incident hospitalizations the day after dose 2 was no higher than the absolute rate 21–56 days prior to dose 1. However, we contend that a convincing short-term change in a local trend is the most relevant to the specific research question we addressed.

Our findings are consistent with those from other large post-vaccination surveillance studies and support the safety of mRNA vaccines. Studies of 6–11 million individuals through the Vaccine Safety Datalink did not find any increased rate of adverse events following vaccination [11], and found lower mortality compared to unvaccinated persons [24]. Another study of 21,000 nursing home residents also found reduced mortality and no increase in pre-specified adverse events compared to unvaccinated persons [25]. A study of 30 million individuals did find a slightly increased risk of thromboembolism and stroke following vaccination, although significantly less risk for these adverse events than occurs after SARS-CoV-2 infection [10].

These previously published investigations addressed different questions using different designs and controls than ours; most published analyses of adverse events compare vaccinated persons to unvaccinated controls, which is an important clinical question, but one distinct from the focus of this study; our study was novel in comparing vaccination among those with previous infection to uninfected controls. Another innovative aspect was the use of each individual as his or her own control, which allows us to make conclusions about the impact of a specific event, in this case vaccination, on an individual patient, although specific time-related trends in health and behaviors are limitations of this approach. Incident hospitalizations and emergency room visits are commonly used adverse event detection triggers that are often included in patient safety monitoring tools, including the outpatient Institute for Healthcare Improvement trigger toolkit [26–30]. Combining specific adverse event reporting surveillance with the general trigger tools approach to surveillance, we did not find an increase in the specific adverse events that have been reported to VAERS following a vaccination event, but we did see an increase in general adverse events in the subpopulation of patients with an infection history, as evidenced by 24-hour hospitalization rates following vaccination.

Based on the inflammatory nature of the disease and a number of studies demonstrating immunity induced by natural infection [12–19,31–34], we hypothesized that patients with prior SARS-CoV-2 infection might be at higher risk of adverse outcomes following vaccination due to immune memory and inflammatory reactions. Our study is consistent with this hypothesis, since the spectrum of related symptoms and objective findings such as weakness, muscle aches, fever, mental status changes, falls, dehydration and acute kidney injury were transiently increased especially after the second dose. No patients in our cohort had received a third dose of the vaccine, but our study raises questions about whether higher adverse event rates will be identified with increasing exposure to SARS-CoV-2 antigens in at-risk and frail

populations. Additional studies are needed to characterize whether the severity of prior infection impacts post-vaccine adverse event severity. We did not distinguish between laboratory SARS-CoV-2 infection and symptomatic COVID-19 pneumonia, and responses may differ between these groups.

Although the benefit for the population is clear, our results raise the question of whether patients who have a history of SARS-CoV-2 infection should be considered for a more personalized vaccination schedule based on frailty, comorbidities, and other factors. Studies of natural immunity suggest that prior SARS-CoV-2 infection confers protection against severe outcomes from future infections, although duration and durability of this immunity is unknown. In a large Israeli study, breakthrough infections in vaccinated individuals were more common than reinfections in previously infected individuals, and a single dose of vaccine in a previously infected individual decreased reinfection risk [35]. Antibody titers increase markedly after a single vaccine dose in this population (10-fold to 140-fold) [13,15,36]. The relationship between SARS-CoV-2 infection, timing of vaccination, and adverse events, should also be evaluated, as it is possible that a non-standardized vaccination dosing schedule, for example by increasing the time between the two doses, would minimize adverse events while maximizing prevention of infection. Along these lines, the Norwegian Medicines Agency investigated the deaths of frail elderly patients after vaccination and advised caution in this subpopulation [37].

Strengths of our study include the large, national sample of patients geographically spanning numerous institutions across the entire United States engaged in a closed healthcare system, therefore maximizing data capture. We included VA and non-VA fee-basis admissions in the hospitalization assessment, thus maximizing case ascertainment. Mortality assessments in VA data, and especially the National Death Index, are highly accurate, maximizing ability to determine cause and location of death. [38] Additionally, a random sample of persons with prior infection who were hospitalized following vaccine receipt and every death within 48 h underwent detailed manual review to validate and enhance database findings with detailed clinical information. This is a major strength of the study, as it focuses on accurately measured, clinically significant outcomes as a means of surveillance, rather than self-reporting of adverse events from clinicians and patients.

Other post-vaccine safety studies have used a control matching strategy to compare the risk of specific adverse events among vaccinated individuals and those who developed natural infection. In our study, we calculated the daily baseline risk of hospitalization for the longitudinal cohort and stratified by infection history, which inherently balances potential confounding variables, and used the baseline risk of hospitalization and specific adverse events to examine trends above the expected rate. This strategy of using the expected rates from the cohort and then using the cohort as its own control is a highly robust method for isolating the risk of hospitalization and death following a specific event exposure that is not subject to the limitations of control matching procedures present in other analyses. Additionally, our study was not reliant on self-report of temporally associated adverse events, but rather an evaluation of changes in rates associated with vaccine administration as an isolated event and exposure.

4.1. Limitations

Our study has several limitations. The study was conducted in the national VA healthcare system, which has a large population of older, male patients, limiting generalizability of conclusions to other populations, particularly women and children. This likely impacted our ability to detect certain adverse events, such as myocarditis following vaccination, which appear to be concentrated among demographic groups (young and adolescent men) with limited or no representation in the VA population [8,11]. Due to limited distribution within the VA, we were not able to assess the safety profile of the Janssen adenovirus-based vaccine [7]. In addition, VA patients frequently receive care at multiple health systems and we were not able to fully account for the reasons for non-VA admissions, thus it is possible that an increase in specific diagnoses was missed. Some patients may primarily receive care outside of the VA or have received their SARS-CoV-2 diagnosis outside of the VA, or a vaccine outside of the VA, and this missing data may have biased findings in unpredictable ways. However, we attempted to address this limitation through a sensitivity analyses limited to patients identified as regular VA users using criteria used in many previous studies, which revealed similar findings to those from the complete longitudinal cohort.

4.2. Conclusions

Our findings strongly support the safety of the mRNA vaccines. In contrast to prior research, we focused on the risk of adverse events after vaccination in patients with and without prior history of infection, rather than comparing adverse events in vaccinated versus infected populations. The increase in hospitalizations among patients with a history of SARS-CoV-2 is dwarfed by the protection provided against severe COVID-19. As governments and public health organizations develop the optimal schedule for timing and number of doses of SARS-CoV-2 vaccines, it is increasingly important to identify risk factors and comorbidities that maximize immunization safety and protection from severe disease.

Data sharing

Patient level data cannot be shared due to privacy laws. Code underlying the data will be made available upon request to the authors.

Transparency statement

The authors affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Patient consent / ethical approval

This study was approved by the VA Boston Research and Development committee as an exempt study prior to data collection and analysis with a waiver of informed consent.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This study was unfunded. The VA played no role in the design of the study, data collection, analysis, writing, or submission of the article for publication. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work other than that detailed above, no other relationships or activities that could appear to have influenced the submitted work.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.01.026.

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