Hospitalization Rates Following mRNA SARS-CoV-2 Booster Vaccination among Patients with and without Prior SARS-CoV-2 Infection: A Nationwide, Retrospective Cohort Study

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Abstract

Background

We previously reported a transient increased risk of hospitalization after mRNA vaccination among patients with prior SARS-CoV-2, absolute risk ~ 1:1000. Here, we extend and expand this analysis to evaluate the impact of prior infection on hospitalization after a third (booster) dose.

Methods

Nationwide, retrospective cohort study of hospitalization among US Veterans who received a third dose of mRNA vaccine between 7/1/2021-2/28/2022. Daily rates of incident hospitalization were compared before and after booster doses, stratified by history of SARS-CoV-2.

Results

1,632,806 patients received a third dose, including 90,174 with a history of SARS-CoV-2 infection. Hospitalization rates were unchanged before and after the booster dose among patients with (112.3/100,000 post-dose versus 100.2/100,000 pre-dose, p = 0.24) or without previous infection (32.1/100,000 post-dose versus 31.3/100,000 pre-dose, p = 0.71). Among 241 patients hospitalized after receipt of the initial vaccination, 90 received a booster, and none of these 90 patients were hospitalized.

Conclusions

There was not convincing evidence for increased hospitalizations shortly after booster vaccines, including in patients with a history of SARS-CoV-2 infection who required hospitalization after their initial vaccine. The size and design of the study prevent strong conclusions about absence of risk.

Introduction

The mRNA vaccines BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) frequently cause transient side effects reflecting systemic inflammation, such as fever, myalgia, and fatigue. Although recovery is typical within 2 days, such symptoms may lead to inpatient admissions, particularly among frail patients. We recently reported, using a nationwide cohort of US Veterans receiving care within the Veterans Health Administration, that among patients with a history of documented SARS-CoV-2 infection, the risk of hospitalization 1 day after the second dose in a standard 2-dose initial vaccination regimen increased by approximately 1:1000 and returned to baseline within 2 days;\(^1\) no increase in hospitalization rate following receipt of vaccination was found in the much larger cohort of patients with no known history of infection. Patients for whom chart review indicated vaccine side effects as the cause of hospitalization
had mean age 75, and 90% had at least 1 of 8 pre-specified serious medical conditions. Recovery was
typically rapid, with mean hospitalization for 2.7 days.

After multiple studies starting in the summer of 2021 suggested waning immunity after an initial vaccine
series, additional studies indicated that a 3rd ("booster") increased protection against severe Covid-19, at
least in older patients. Subsequent studies found reduced risk of severe infection after booster
vaccination during periods when the delta and omicron variants have been dominant. The US Food and
Drug Administration approved a booster shot for all adults as of November 18, 2021, after having
approved boosters previously for patients with risk factors for severe disease, including age > 65.
Additional input about patients with a history of SARS-CoV-2 infection, and how that might impact risks
and benefits of additional vaccine doses, was not provided.

In light of the poor tolerance of common vaccine side-effects we observed in some older men with
chronic medical problems who had a history of prior SARS-CoV-2 infection before the primary vaccination
series, we evaluated the daily rates of hospitalization before and after an additional dose of vaccine,
again stratifying by history of SARS-CoV-2 infection since that group was at risk in our previous study.
Our hypothesis was that risk would be lower, likely low enough to prevent detection in a large population,
due to the greater time between immunologic exposures. However, anticipating that patients hospitalized
the day after completing the initial vaccine series might be at particularly high risk of hospitalization after
a booster, we also determined whether any such patients were re-hospitalized one day after the booster.

Methods

Cohort creation:

A longitudinal cohort of all Veteran patients who received a third dose of an mRNA COVID-19 vaccine
(BNT162b2 or mRNA-1273) within the Veterans Affairs Healthcare System (VA) during the period from
7/1/2021 – 2/28/2022 was created. The small number of patients who received the Janssen vaccine were
excluded. We did not attempt to distinguish 3rd doses considered to complete an initial vaccination series
in immunocompromised patients from boosters given to the general population and will refer to any third
dose as a booster.

Data extracted included vaccination data, acute care hospitalization, demographic information (e.g., age,
sex, race, ethnicity), and laboratory data from the VA Corporate Data Warehouse and VA COVID-19 Shared
Data Resource, 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. A frailty index was calculated using a previously described method. The subset of
previously-infected patients who had been hospitalized 1 day after their second dose of mRNA vaccine,
38–56% of them for vaccine side effects as we reported previously, was also evaluated for receipt of a
booster and for hospitalization again 1 day after the booster.
Hospitalizations:
The primary outcome measure was the daily incidence rate of acute care hospitalization (new admissions) 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 boosting and 21 days after boosting 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 at any time before receipt of the booster dose. A sensitivity analysis was performed using a subcohort from which patients with incident hospitalization within 30 days before receipt of the booster were excluded.

We used the primary ICD-10 code associated with a hospitalization as the best surrogate for the reason for hospitalization, in order to compare these reasons in the 21 days before to the 21 days after boosting, and to compare reasons 1, 2, and 3 days after boosting in patients with a history of SARS-CoV-2 infection.

Statistical Analysis:
Daily rates of incident acute care hospitalization (i.e. only new admissions) up to 56-days prior to the booster dose of vaccine and up to 21 days afterward were plotted, both for the entire cohort and stratified by SARS-CoV-2 history. In order to visualize the differences in variability associated with different numbers of cases being graphed, confidence intervals (95%) for daily rates were calculated using 500 times of random sampling with replacement of the cohort. This bootstrapping strategy was performed using the R-boot package (version 1.3–28).\textsuperscript{8,9} All analyses were completed using R version 4.0.2.

Analysis of proportions of hospitalizations before (day 0) and after (day 1) the booster vaccine dose were performed using the prop.test function in R, which is a test of proportions in 2x2 tables. Tracings of daily hospitalization rates over the 11 weeks of data collection were examined qualitatively to ensure that the hypothesis could be tested in this simple manner, and to look for unexpected findings that might require analysis. No attempt was made to compare between the groups with and without a documented history of infection before boosting, due to numerous potential confounders, as we noted previously.\textsuperscript{1}

To ensure that our previous finding among all vaccinated VA patients also characterized the boosted subset studied here, we determined incident hospitalization rates before (day 0) and after (day 1) the second dose of mRNA vaccine, stratified by whether patients had documented SARS-CoV-2 infection before dose 1.

Frequency of use of ICD-10 codes was analyzed by T-tests, with P values adjusted for multiple comparisons through the Bonferroni method. Because different ICD-10 codes can be used for similar
syndromes, we also grouped these qualitatively into categories but did not formally analyze those categories, since the categories are not validated.

**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.

**Results**

During the period from 7/1/2021 to 2/28/2022, 1,632,806 Veteran patients at 131 different VA facilities received a third dose of a SARS-CoV-2 mRNA vaccine (812,891 Pfizer, 819,915 Moderna). The median age was 71 (SD = 13), and 91.7% were male (Table 1, Demographics). 90,174 had a prior SARS-CoV-2 infection. 95,355 patients received the booster before 9/24/2022, the date at which boosting was routinely recommended for all persons age 65 or older or with chronic medical conditions.

**Acute Care Hospitalizations:**

Among the 1,632,806 patients in the entire cohort who received the booster dose, 605 were hospitalized on the day of the booster (day 0), and 629 were hospitalized during the 1-day period following the booster, corresponding to hospitalization rates of 34.9/100,000 on the day of boosting and 36.3/100,000 one day afterward (p = 0.51). Daily incident hospitalization rates before and after booster doses, stratified by prior infection, are presented in Fig. 1. Among patients without prior SARS-CoV-2 infection, the baseline rate was 31.3/100,000, versus 32.1/100,000 after the booster (p = 0.71). Among patients with a prior infection, the baseline rate was 100.2/100,000, versus 112.3/100,000 after boosting (p = 0.24). Although hospitalization rates both before and after vaccination appeared to be higher in the group with prior infection, as we observed in our first study, we did not attempt to compare these groups, due to numerous potential confounders, as the group with prior infection was consistently more frail than patients without documentation of prior infection (45.2% of patients in the group with previous infection had a frailty index calculated as mild, moderate, or severe, compared to 28.7% in the uninfected group, see Table 1).

A secondary analysis was done excluding patients who had not had incident hospitalizations within 30 days prior to boosting, in order to enrich for outpatients who had not recently been severely ill. Visually, among the whole cohort or patients without known prior infection, incident hospitalizations were similar one day after boosting as they were subsequently (Fig. 2). However, the trend was less clear among patients with previous infection: the hospitalization rate was higher one day after boosting than in the next three days, but the rates for those days were among the lowest for the entire observation period. We therefore examined the primary ICD-10 diagnostic codes associated with hospitalizations beginning on days 1, 2, and 3 after boosting. Although numbers were much too small to allow conclusions to be drawn, there were more admissions on day 1 for systemic (fever, weakness, malaise) or neurologic...
(encephalopathy, altered mental status, dementia) symptoms on day 1 (6 and 6 patients) than on day 2 (2 and 0 patients) or day 3 (1 and 2 patients) (Supplementary Tables 1 and 2). If true, data showing 10 excess cases of hospitalizations for systemic or neurologic symptoms would indicate an absolute risk of approximately 1 in 9,000 patients in this population.

ICD-10 codes were also used to compare hospitalizations before (1–21 days) and after (21 days) boosting in the previously infected group. The only code that differed significantly, after adjustment for multiple comparisons, was related to alcohol withdrawal. After grouping codes related to similar organ systems or symptoms, only substance use more broadly was clearly increased before vaccination, and no organ system or symptom complex was clearly increased after boosting (Supplementary Tables 3 and 4).

We also determined whether the boosted cohort was representative of the much larger vaccinated cohort from our previous study, considering hospitalization shortly after the initial vaccine series. Among all patients who received the booster dose, 542 had been hospitalized on the day of the second dose of the original vaccine series (day 0), and 566 had been hospitalized during the 1-day period following the second dose, corresponding to hospitalization rates of 31.6/100,000 before boosting and 33.0/100,000 afterward (p = 0.49). Among patients without prior SARS-CoV-2 infection, the baseline rate was 30.8/100,000 before versus 29.6/100,000 after the second dose (p = 0.55). Among patients with a history of infection prior to initial vaccination, the baseline rate was 56.6/100,000 before versus 132.0/100,000 after the second dose (p < 0.001), i.e. a transient increase in hospitalizations had occurred previously in the cohort used in this follow-up study.

Among the 241 patients with prior infection in this study who had been hospitalized 1 day after their second dose of mRNA vaccine, 90 (37%) received a booster dose, and none were hospitalized 1 day afterward.

**Discussion**

Among 1,632,806 US Veterans who received an mRNA vaccine series, including the pre-specified subset of 90,174 with a documented prior history of infection, receipt of a booster dose of mRNA vaccine was not definitively associated with a transient increased risk of hospitalization, as was seen previously after the second dose of an initial vaccine series, a finding confirmed to have also characterized the population in this study.¹ In addition, the 90 patients previously hospitalized 1 day after receiving the second dose did not require hospitalization shortly after a booster. Although this study cannot rule out a small risk of severe adverse reactions after booster shots, the data are reassuring that booster shots are sufficiently well-tolerated by patients with a history of infection, and even patients who required hospitalization after the second dose that boosting should not be discouraged.

The reasons for these findings are unknown. The longer interval between doses is likely to be a contributing factor, as longer intervals between doses may reduce post-vaccination adverse events. An alternative, but also reassuring, explanation is that patients with prior adverse reactions were able to take precautions such as hydration, anti-pyretic medications, or closer monitoring. It is also possible that
patients who suffered the most severe effects and were at the highest risk of another severe reaction differentially opted not to get a booster dose. Considering the comorbidities seen among the patients hospitalized in our first study, patients with adverse reactions attributable merely to poor tolerance of common and short-term side effects of mRNA vaccines should be encouraged to receive booster shots, with appropriate education, monitoring, and precautions.

The most important limitation is that that the study only provides “absence of evidence” rather than “absence of evidence,” for 2 reasons. First, although all comparisons are within-cohort, the characteristics of the patients undoubtedly changed somewhat over time, and statistical adjustment with numerous time-varying covariates and unmeasurable confounders is not feasible. Second, we cannot rule out occurrence of vaccine-related adverse events at a low enough frequency to be indistinguishable from noise, and our examination of ICD-10 codes were consistent with a risk of 1 in 9,000 hospitalizations for systemic or neurologic symptoms, but numbers were far too low to analyze or use to draw conclusions. Other limitations are similar to those acknowledged in our initial paper evaluating the risk of hospitalization following the initial vaccination series, and include the retrospective nature of the data and the predominantly older, male population which may not be generalizable to women, children, and young and adolescent males. Missing data leading to misclassification is a concern with all retrospective datasets, but the VA has a closed healthcare system with a rich electronic health record, and the simple outcome of hospitalization is also captured in the numerous hospital systems that contract with the VA for reimbursement. The study was designed to minimize problems with missing data: the cohort of interest is defined by having data on 4 required exposures (1 infection and 3 vaccine doses) and is evaluated within-group over time in reference to the last of those exposures, rather than by comparison to another group. Finally, the study does not provide a detailed assessment of a broad range of adverse events related to vaccination and was not intended to.

In conclusion, in this large, national retrospective cohort, we did not see the same increase in hospitalizations following booster doses among patients with a history SARS-CoV-2 infections that was found when we evaluated adverse events following the primary vaccination series. These data support the safety of additional doses of the mRNA vaccine in previously infected and previously uninfected patient populations.

**Declarations**

**Competing interests and funding:**

This study was unfunded but co-authors receive research funding support from the VA Office of Research and Development. 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/doi_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.
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.

References


Tables
### Table 1
Baseline Demographics of Cohort

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<th>Overall</th>
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<th>With COVID-19 History</th>
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<td>68.63 (12.97)</td>
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<td>1570809 (91.7)</td>
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<td>Region (%)</td>
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### Table

<table>
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<th>Overall</th>
<th>Without COVID-19 History</th>
<th>With COVID-19 History</th>
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<td>Vaccine type (%)</td>
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<td>PFIZER</td>
<td>812891 (47.5)</td>
<td>767604 (47.3)</td>
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### Figures

![Graph](image.png)

**Figure 1**

Daily incidence of hospitalization per 100,000 Veteran patients during the period from 56 days before booster vaccination to 21 days after vaccination among patients with and without a documented history of SARS-CoV-2 infection within the VA healthcare system. 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. Both groups are shown on one graph for brevity; the apparent differences in baseline hospitalization rates were not analyzed, due to many potential sources of confounding. Day 0 is the date of booster vaccination. Confidence intervals were calculated using a bootstrapping methodology. The hypothesis was related to comparing day 1 to day 0; tracings for weeks before and after were made to qualitatively assess stability of baseline rates both close and more distant in time from vaccination.
Figure 2

Daily incidence of hospitalization per 100,000 Veteran patients during the period from 56 days before booster vaccination to 21 days after vaccination among patients with and without a documented history of SARS-CoV-2 infection within the VA healthcare system. Patients with incident hospitalization within 30 days prior to boosting were excluded. 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. Both groups are shown on one graph for brevity; the apparent differences in baseline hospitalization rates were not analyzed, due to many potential sources of confounding. Day 0 is the date of booster vaccination. Confidence intervals were calculated using a bootstrapping methodology. The hypothesis was related to comparing day 1 to day 0; tracings for weeks before and after were made to qualitatively assess stability of baseline rates both close and more distant in time from vaccination.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AEBooster16Feb2023forRSuppltables.docx