




Letter to the Editor

Coronavirus disease 2019 (COVID-19) hospitalization metrics that do not account for disease severity underestimate protection provided by severe acute respiratory coronavirus virus 2 (SARS-CoV-2) vaccination and boosting: A retrospective cohort study

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To the Editor—Vaccination with severe acute respiratory coronavirus virus 2 (SARS-CoV-2) reduces the risk of severe coronavirus disease 2019 (COVID-19), as has typically been assessed using the simple metric of hospitalization contemporaneous with a positive test for SARS-CoV-2. In Fillmore et al,¹ we demonstrated that simple hospitalization metrics overestimated the number of severe cases among vaccinated US veterans prior to widespread recommendations for additional vaccine doses.

On the basis of reports of waning immunity and partial cross protection against the SARS-CoV-2 delta and omicron variants, the Centers for Disease Control and Prevention (CDC) issued recommended additional doses of vaccine, initially for high-risk patients, in August 2021. The recommendation was subsequently expanded to include all adults in mid-November 2021.^{2–4} CDC expands eligibility for COVID-19 booster shots to all adults.

Owing to the new variant and widespread availability of booster doses, we update our analysis to re-examine trends in COVID-19 severity among hospitalized patients, stratifying by vaccination status (ie, unvaccinated, vaccinated but not boosted, or boosted).

Methods

Methods have been previously described in detail.¹ All inpatient admissions to a Veterans' Affairs (VA) hospital between March 1, 2020, and February 15, 2022, with a laboratory-confirmed diagnosis of SARS-CoV-2 up to 14 days prior to or during the admission were included for visualization of trends. For the updated analysis focused on the impact of booster doses, the start time was chosen as the date at which 10 patients who had received booster vaccinations (referred to as “boosted” patients) had been

hospitalized (September 26, 2021). During the period from September 26, 2021, to November 30, 2021, the SARS-CoV-2 δ (delta) variant was defined as the predominant strain, with a shift to SARS-CoV-2 (omicron) predominance December 1, 2021–February 15, 2022. Data were extracted electronically from the VA Corporate Data Warehouse and the VA COVID-19 Shared Data Resource.^{4,5}

Patients were considered fully vaccinated if ≥ 14 days had elapsed after receipt of a single dose of an adenovirus vaccine or after receipt of a second dose of either mRNA-1273 (Moderna) or BNT162b2 (Pfizer) vaccines. Patients were considered to be fully boosted 7 days after receiving an additional dose of any of the available vaccines. Demographic variables were collected and a measurement of frailty calculated among patients hospitalized September 2, 2021–February 15, 2022.⁶

As in our previous manuscript, moderate-to-severe COVID-19 was defined as receipt of any oxygen supplementation ≥ 0.5 L per minute or any documented oxygen saturation (SpO₂) $< 94\%$ during an inpatient admission at any time between 1 day before and 2 weeks after the positive SARS-CoV-2 test.⁷ Severe COVID-19 was defined as oxygen supplementation ≥ 2 L per minute or any documented SpO₂ $< 90\%$. Receipt of dexamethasone or remdesivir during the SARS-CoV-2 hospitalization were also assessed, as surrogate markers for COVID-19 with respiratory compromise.

The total numbers of SARS-CoV-2-associated admissions and the numbers meeting criteria for moderate-to-severe or severe disease were plotted over time. The proportions of admissions meeting different criteria were then calculated and plotted over time. The changing proportions of admissions meeting criteria were modeled as smooth functions of time using penalized splines in Poisson regression and were then stratified by vaccination status. The study was approved by the VA Boston R&D committee with a waiver for informed consent (protocol no. 3328-X).

Results

Between September 26, 2021, and February 16, 2022, 4,751 admissions representing 3,962 unique patients at 113 unique VA

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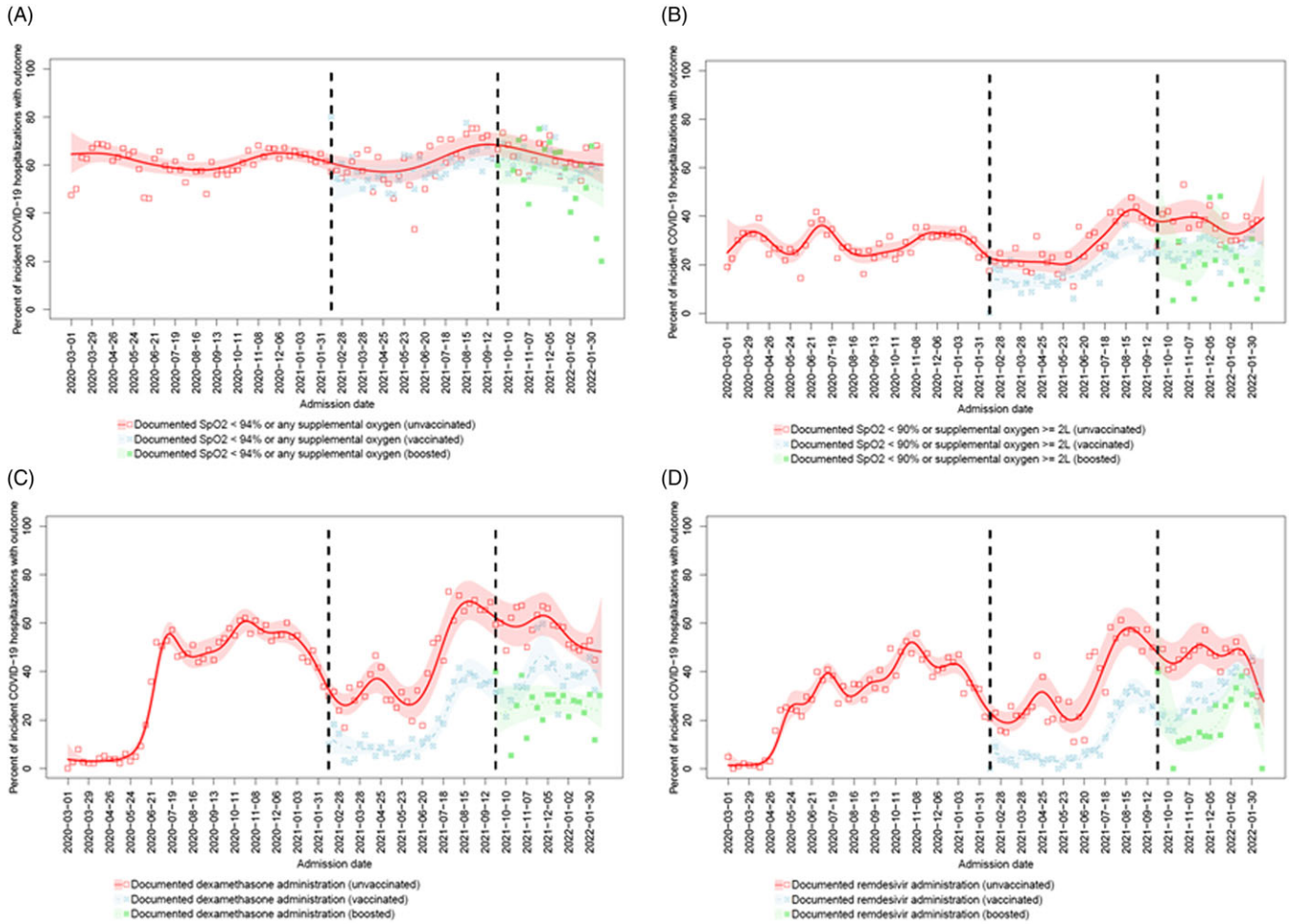


Fig. 1. Trends in metrics of severity of SARS-CoV-2 infection over time in patients hospitalized contemporaneous with a positive test, stratified by vaccination status (unvaccinated, vaccinated but not boosted, or boosted). The period of predominance of the SARS-CoV-2 δ (delta) variant was approximately July 1, 2021, to November 30, 2021, and that of the SARS-CoV-2 (omicron) variant beginning December 1, 2021. (A) Minimum oxygen saturation (SpO_2) < 94% or supplementary oxygen at any level (cf, minimum used is ≥ 0.5 L/minute). (B) Minimum SpO_2 < 90% or supplementary oxygen ≥ 2 L/minute. (C) Use of dexamethasone during hospitalization. (D) Use of remdesivir during hospitalization.

facilities occurred contemporaneously with laboratory-confirmed SARS-CoV-2. Mean age and frailty were highest among boosted patients, followed by vaccinated patients, and then unvaccinated patients (Supplementary Table 1 online). The numbers and proportions of patients meeting the criteria for moderate-to-severe hypoxemia, severe hypoxemia, and use of dexamethasone or remdesivir, stratified by vaccination status and by predominant strain are shown in Supplementary Table 2 (online).

The trends in COVID-19 hospitalization in the VA have continued to track with the national data from CDC COVID-Net (Supplementary Figs. 1–3 online).⁸ The proportions of patients who met the criteria related to hypoxemia or medication use, stratified by vaccination status, are shown in Figure 1.

Estimates of severe disease based on medication use were consistently lower than estimates based on definitions of moderate-to-severe hypoxemia and consistently higher than estimates using severe hypoxemia definitions. When comparing medications as a measure of disease severity, dexamethasone receipt was slightly higher than remdesivir receipt and captured slightly more facilities (101 of 113 facilities had any dexamethasone receipt vs 98 of 113 with any remdesivir receipt), although the 2 measures were strongly correlated (Supplementary Fig. 4 online).

The proportions of patients meeting criteria for moderate-to-severe hypoxemia did not differ comparing vaccinated (but not boosted) patients to unvaccinated patients ($P = .11$) nor comparing boosted to vaccinated patients ($P = .36$). However, the proportions who met the criteria for severe hypoxemia, dexamethasone use, or remdesivir use were lower among boosted patients than vaccinated patients ($P = .03$; $P < .001$; $P < .001$, respectively) and were lower among vaccinated patients than unvaccinated patients ($P < .001$; $P < .001$; $P < .001$, respectively). Proportions appeared similar before and after the omicron variant became predominant.

Discussion

Among patients hospitalized and positive for SARS-CoV-2 infection during periods with predominance of the delta and omicron variants, a third (ie, booster) vaccination reduced the likelihood of the patient having severe COVID-19, as measured by either severe hypoxemia or by use of dexamethasone or remdesivir. These findings support the effectiveness of additional doses of vaccine in protecting against severe disease and reinforce the need for metrics among hospitalized patients that include measures of disease severity to avoid underestimating vaccine effectiveness, to improve

hospital capacity forecasting and resource allocation, to understand severity of illness from the current variant, and to improve transparency of data reporting.

This study had several limitations. Data regarding prior infection, which could reduce risk of severe disease in any group, were not included due to the likelihood of missing data and complexity of analysis. Data regarding booster doses were also more likely to be missing than data on initial vaccination. However, both factors should underestimate the benefit of boosters. Additionally, the VA population is mostly male with high proportions of patients who are older and have chronic medical problems, which affects the generalizability of our findings.

None of the metrics for severity is a perfect measure. The use of minimal supplemental oxygen at any point during a hospitalization overestimates severity, and the choice of any cutoff for the degree of supplementation trades sensitivity for specificity. Medication administration data may slightly underestimate cases of severe disease. In the VA data, dexamethasone captures more cases and more facilities, and its specificity during the pandemic coupled with a requirement for a positive test for SARS-CoV-2 should be very high. The fact that use of dexamethasone, which was adopted as the proxy metrics for hospitalization due to COVID-19 in Massachusetts on January 20, 2022, falls between our hypoxemia-based definitions of moderate-to-severe and severe disease is reassuring regarding its value as a surrogate marker for measuring trends in disease severity.

In conclusion, COVID-19 hospitalization metrics that do not account for underlying disease severity lead to systemic biases in evaluating vaccine effectiveness. Simple metrics that encompass assessments of hypoxemia or medication administration can be used to improve pandemic surveillance.

Supplementary material. To view supplementary material for this article, please visit <https://doi.org/10.1017/ice.2022.79>

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References

1. Fillmore NR, La J, Zheng C, *et al.* The COVID-19 hospitalization metric in the pre- and post-vaccination eras as a measure of pandemic severity: a retrospective, nationwide cohort study. *Infect Control Hosp Epidemiol* 2021. doi: [10.1017/ice.2022.13](https://doi.org/10.1017/ice.2022.13).
2. Fast HE, Zell E, Murthy BP, *et al.* Booster and additional primary dose COVID-19 vaccinations among adults aged ≥ 65 years—United States, August 13, 2021–November 19, 2021. *Morb Mortal Wkly Rep* 2021; 70:1735.
3. Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. Centers for Disease Control and Prevention website. <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>. Update April 21, 2022. Accessed May 17, 2022.
4. COVID-19 shared data resource. US Department of Veterans' Affairs website. https://www.hsrdr.research.va.gov/for_researchers/cyber_seminars/archives/3810-notes.pdf. Published 2020. Accessed May 17, 2022.
5. Guidebook on COVID-19 Testing v1.2 27 (2021). US Department of Veterans Affairs (Internal Guidance and Recommendations).
6. Cheng D, DuMontier C, Yildirim C, *et al.* Updating and validating the US Veterans' Affairs frailty index: transitioning from ICD-9 to ICD-10. *J Gerontol A* 2021;76:1318–1325.
7. Clinical spectrum of SARS-CoV-2 infection. National Institutes of Health website. <https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/>. Updated September 3, 2021. Accessed September 6, 2021.
8. Coronavirus disease 2019 (COVID-19)–Associated Hospitalization Surveillance Network (COVID-NET). Centers for Disease Control and Prevention website. <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html>. Published 2020. Accessed May 17, 2022.