RESEARCH LETTER

Odds of Hospitalization for COVID-19 After 3 vs 2 Doses of mRNA COVID-19 Vaccine by Time Since Booster Dose

Vaccination with a booster dose of COVID-19 mRNA vaccine has been associated with decreased risk of developing severe COVID-19 compared with no vaccination. However, among individuals already fully vaccinated with the primary series of an mRNA vaccine, less is known about how much protection is added by a booster and how long that protection lasts. We assessed the association between COVID-19 mRNA booster immunization compared with vaccination with the primary mRNA vaccination series alone and the odds of hospitalization for COVID-19.

Methods | This study included adults who received either 2 or 3 doses of an mRNA COVID-19 vaccine and were hospitalized between October 1, 2021, and July 26, 2022, within the Providence health care network in 6 western US states. This study was approved by the Providence institutional review board, with a waiver of informed consent.

We performed a case-control study using methods previously described. Cases were individuals admitted to the hospital for COVID-19, which was defined as having a final coded diagnosis of COVID-19 or a positive nucleic acid amplification test (NAAT) for symptomatic SARS-CoV-2 and receiving treatment with remdesivir or dexamethasone. Each case was matched with 4 controls who were admitted to the hospital nonelectively for reasons other than COVID-19 within 3 days in the same geographic region as cases and received their second dose of COVID-19 vaccine (ie, completed their primary series) within 7 days of the case. We collected demographics, comorbidities, COVID-19 vaccination data, and history of prior COVID-19 (positive SARS-CoV-2 NAAT in the presence of symptoms) from electronic medical records. We determined if hospitalization occurred when the Omicron variant accounted for more than 50% of community COVID-19 cases based on US Centers for Disease Control and Prevention regional estimates.

We used multivariable conditional logistic regression to identify factors associated with hospitalization for COVID-19. We calculated the odds of hospitalization for COVID-19 among individuals who received 3 vs 2 doses of mRNA vaccine by time since receiving a booster dose. R version 4.1.2 (R Foundation for Statistical Computing) was used for the statistical analysis, with a 2-sided $P < .05$ defining statistical significance.

Results | There were 3062 cases (mean age, 70.8 [SD, 15.4] years; 52.6% were men; and 34.7% were boosted) and 12,248 matched controls (mean age, 67.1 [SD, 18.2] years; 46.7% were men; and 49.3% were boosted) included (Table). Factors associated with an increased odds of hospitalization included age of 70 years or older, male sex, cognitive disease, chronic obstructive pulmonary disease, diabetes, immunodeficiency, obesity, rheumatologic disease, transplant, and BNT162b2 (Pfizer-BioNTech) vaccine.

In the multivariable analysis, booster vaccination was associated with decreased odds of hospitalization for COVID-19 in the same geographic region as cases and received their second dose of COVID-19 vaccine (ie, completed their primary series) within 7 days of the case. We collected demographics, comorbidities, COVID-19 vaccination data, and history of prior COVID-19 (positive SARS-CoV-2 NAAT in the presence of symptoms) from electronic medical records. We determined if hospitalization occurred when the Omicron variant accounted for more than 50% of community COVID-19 cases based on US Centers for Disease Control and Prevention regional estimates.

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### Table. Characteristics of Cases and Controls and the Results of the Multivariable Analysis for the Outcome of Hospitalization for COVID-19

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 3062)</th>
<th>Matched controls (n = 12,248)</th>
<th>Multivariable analysisa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR (95% CI)</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Age group, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤69 y</td>
<td>70.8 (15.4)</td>
<td>67.1 (18.2)</td>
<td>1 [Reference]</td>
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<tr>
<td>70-79 y</td>
<td>883 (28.8)</td>
<td>3005 (24.5)</td>
<td>1.47 (1.31-1.64)</td>
</tr>
<tr>
<td>≥80 y</td>
<td>963 (31.5)</td>
<td>3370 (27.5)</td>
<td>1.57 (1.38-1.78)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1452 (47.4)</td>
<td>6523 (53.3)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Male</td>
<td>1610 (52.6)</td>
<td>5725 (46.7)</td>
<td>1.32 (1.21-1.44)</td>
</tr>
<tr>
<td>Race and ethnicity, No. (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>African American/Black</td>
<td>117 (3.8)</td>
<td>509 (4.2)</td>
<td>0.94 (0.76-1.17)</td>
</tr>
<tr>
<td>Asian</td>
<td>157 (5.1)</td>
<td>763 (6.2)</td>
<td>0.84 (0.70-1.01)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>440 (14.4)</td>
<td>1584 (12.9)</td>
<td>1.13 (0.99-1.29)</td>
</tr>
<tr>
<td>White</td>
<td>2092 (68.3)</td>
<td>8459 (69.1)</td>
<td>1 [Reference]b</td>
</tr>
<tr>
<td>Otherc</td>
<td>256 (8.4)</td>
<td>933 (7.6)</td>
<td>1 [Reference]b</td>
</tr>
</tbody>
</table>

(continued)
The odds of hospitalization varied based on time since booster: less than 50 days (adjusted OR, 0.24 [95% CI, 0.18-0.30]), 50 to 100 days (adjusted OR, 0.24 [95% CI, 0.18-0.30]), 100 to 150 days (adjusted OR, 0.47 [95% CI, 0.38-0.58]), and longer than 150 days (adjusted OR, 0.72 [95% CI, 0.61-0.84]). The Figure displays the odds of hospitalization for COVID-19 based on time from the booster dose.

Discussion | In a large US population, mRNA boosters were associated with decreased odds of hospitalization compared with the mRNA vaccine primary series alone, with the magnitude of the association attenuated with more time since the booster dose.

Studies comparing COVID-19 rates among boosted individuals vs unvaccinated individuals have found 55% to 99% lower odds of COVID-19 among those who are boosted.1,2,4 By matching cases with controls based on the date of second mRNA dose, this study was able to measure the added benefit of a booster dose to the primary series. This study’s findings are similar to the hazard ratio of 0.48 for hospitalization for COVID-19 associated with boosters that was found in a study with shorter follow-up.5 Because the 2-dose primary series reduces long-term risk for hospitalization,3 even if the magnitude of the association attenuated over time after 3 vs 2 vaccine doses, the overall risk for hospitalization among vaccinated individuals remains low.
Limitations include possible booster vaccination at outside facilities; however, Providence hospitals routinely capture outside vaccination data upon admission. Some cases or controls may have been misclassified. The predominant SARS-CoV-2 variant changed over the course of the study, with 81% of participants hospitalized when Omicron predominated, and these findings may not apply to future variants.

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Author Contributions: Dr Robicsek had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ridgway, Tideman, Wright, Diaz, Robicsek.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ridgway, Tideman, Wright, Robicsek.
Critical revision of the manuscript for important intellectual content: Tideman, French, Wright, Parsons, Diaz, Robicsek.
Statistical analysis: Tideman, French, Wright, Robicsek.
Obtained funding: Robicsek.
Administrative, technical, or material support: Tideman, Parsons, Diaz, Robicsek.
Supervision: Parsons, Robicsek.

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