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MAJOR ARTICLE

Hospitalized Patients With Severe Coronavirus Disease 2019 During the Omicron Wave in Israel: Benefits of a Fourth Vaccine Dose

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Background. Waning immunity and an increased incidence of coronavirus disease 2019 (COVID-19) during the Omicron outbreak led the Israeli Ministry of Health to recommend a fourth vaccine dose for high-risk individuals. In this study, we assessed its effect for hospitalized patients with severe breakthrough COVID-19.

Methods. In this multicenter cohort study of hospitalized adults with severe COVID-19 in Israel, from 15 to 31 January 2022, cases were divided according to the number of vaccinations received. Poor outcome was defined as mechanical ventilation or in-hospital death and was compared between 3- and 4-dose vaccinees using logistic regression.

Results. Included were 1049 patients, median age 80 years. Among them, 394 were unvaccinated, 386 and 88 had received 3 or 4 doses, respectively. The 3-dose group was older, included more males, and immunosuppressed patients but with similar outcomes, 49% vs 51% compared with unvaccinated patients ($P = .72$). Patients who received 4 doses were similarly older and immunosuppressed but had better outcomes compared with unvaccinated patients, 34% vs 51% ($P < .01$). We examined independent predictors for poor outcome in patients who received either 3 or 4 doses a median of 161 days or 14 days before diagnosis, respectively. Receipt of the fourth dose was associated with protection (odds ratio, 0.51; 95% confidence interval, .3–.87), as was remdesivir. Male sex, chronic renal failure, and dementia were associated with poor outcomes.

Conclusions. Among hospitalized patients with severe breakthrough COVID-19, a recent fourth dose was associated with significant protection against mechanical ventilation or death compared with 3 doses.

Keywords. COVID-19; BNT162b2; vaccine; booster; fourth dose.

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a significant change in the response to coronavirus disease 2019 (COVID-19) since the end of 2020. Nevertheless, due to waning immunity [1–3], a third dose given as a booster became an essential countermeasure during the Delta variant wave approximately 5 months later [4, 5]. The spread of the Omicron variant, which began in mid-November 2021, has challenged even the most vaccinated populations with lower vaccine effectiveness (VE) and high rates of breakthrough infections [6–8]. On 2 January 2022, the Israeli Ministry of Health recommended a fourth dose (second booster) for individuals aged ≥60 years, immunocompromised patients, and healthcare personnel at least 4 months after receipt of the third dose, anticipating a benefit in the prevention of severe outcomes. Since then, several population studies have shown the benefit of a fourth dose in preventing severe COVID-19, hospitalization, or death [9–11].

Based on national data, by 15 January 2022, 487 211 Israelis aged ≥60 years had received a fourth dose of vaccine, constituting 31% of the eligible population. Another 108 643 (7%) individuals had received a fourth dose by 31 January 2022. There were no prioritizations of specific populations other than by age.

In this study, we assessed the benefit of a fourth vaccine dose compared with 3 doses for hospitalized patients with severe or critical breakthrough COVID-19.

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METHODS

This multicenter, cohort study included adult patients hospitalized in 14 participating hospitals due to severe or critical COVID-19 from 15 January 2022 to 31 January 2022. All hospitalized patients with COVID-19 are reported to the Israeli Ministry of Health according to severity. Electronic medical records of adult patients reported to have polymerase chain reaction–confirmed severe or critical COVID-19 during their stay were reviewed by an infectious diseases specialist. COVID-19 severity was defined according to the National Institutes of Health guidelines [12]. Vaccination data were retrieved from the medical records if clearly stated or by linking patient information from their health maintenance organization databases. Patients without valid data regarding previous vaccinations or who lacked clinical data and patients who did not have severe or critical COVID-19 upon retrospective case review were excluded. Cases were divided into cohorts according to the number of vaccine doses received at least 7 days prior to diagnosis. The vaccine type was not recorded, but 99% of all vaccine doses given in Israel were BNT162b2 (Pfizer) [13]. The primary composite outcome of the study was mechanical ventilation (MV) or in-hospital death, defined as "poor outcome." For intergroup comparisons, patients who received no or only 1 dose were considered unvaccinated, were grouped together, and were compared separately to vaccinated patients who received 3 or 4 doses.

To assess the benefit of the fourth dose for the 3-dose population, we performed an outcome analysis on the entire group of patients who had received 3 or 4 doses.

When available, we recorded the results of SARS-CoV-2 RNA sequencing. The national sequencing data showed that the most common circulating variant during the study period was Omicron, constituting 90%–99% of sequenced isolates [14].

Statistical Analyses

Variables were compared among vaccinated groups and between patients with good or poor outcomes. Categorical variables were compared using χ^2 or Fisher exact tests, and continuous variables were compared using the Mann–Whitney test. Multivariate analysis of risk factors for poor outcome was performed with logistic regression on vaccine doses and other clinically meaningful possible confounders and on variables with $P < .1$ on univariant analysis using the enter method. All tests were 2-tailed. IBM SPSS-27 was used for all analyses.

Ethics Approval

The study was approved by the institutional research ethics boards of each participating hospital and, overall, by the Assuta-Ashdod Hospital Board. Due to the retrospective design, informed consent was not required.

RESULTS

During the study period, 2602 patients were hospitalized in Israel with severe or critical COVID-19. Among them, 862 were unvaccinated and 106, 393, 947, and 294 had received 1, 2, 3, or 4 doses, respectively, at least 7 days before their admission.

From 15 January 2022 to 31 January 2022, 1237 cases reported with severe or critical COVID-19 in the participating hospitals were reviewed. After excluding 188 patients, 1049 patients with verified severe COVID-19 and a known vaccination

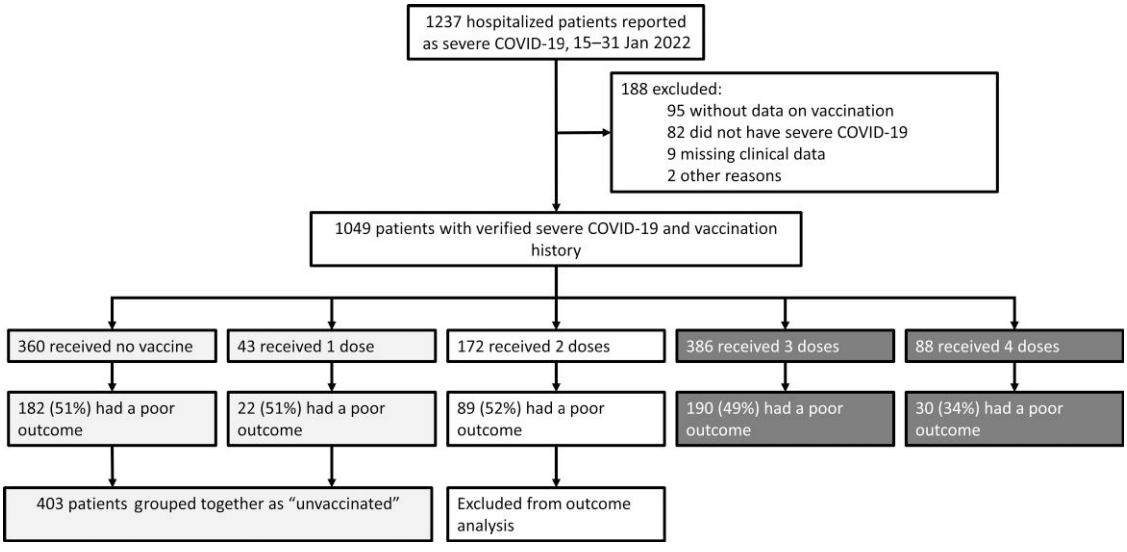

Figure 1. Study population flowchart displaying the inclusion of patients and selection of cohorts according to vaccination status. Light-gray boxes contain the unvaccinated groups (no or 1 vaccine dose). Dark-gray boxes contain the fully vaccinated groups (3 or 4 doses). Abbreviation: COVID-19, coronavirus disease 2019.

history were analyzed (Figure 1). These constituted 40% of the nationally reported cases during the study period (R. Singer, Ministry of Health, written personal communication, 4 April 2022). Groups included 360 (42% of national data) unvaccinated patients, 43 (41%) after 1 dose, 172 (44%) after 2 doses, 386 (41%) after 3 doses, and 88 (30%) after 4 doses. The median age was 80 years (interquartile range [IQR], 69–87), 535 (51%) were males, and 28 (2.7%) had a history of previous COVID-19. Among the 138 (13%) patients with a viral RNA sequencing result, all were the Omicron variant.

We compared unvaccinated patients (no vaccination or only 1 dose) to fully vaccinated patients with 3 or 4 doses. The 172 patients who received only 2 doses were not included in the analysis as they were deemed to have partial immune status, with a median time from the second dose of 326 days (IQR, 255–360). The 3-dose group had received their third dose a median of 161 days (IQR, 147–168) before admission, while the 4-dose group had received the fourth dose a median of 14 days (IQR, 10–18) before admission ($P < .01$). Seventeen patients were still hospitalized at the time of data collection, of whom 15 were mechanically ventilated and, therefore, reached the primary poor outcome.

Table 1 compares unvaccinated patients to those with 3 doses. The 3-dose vaccinees were older; had a higher frequency of long-term care facility (LTCF) residence, hypertension, chronic renal failure, cancer, and immunosuppression; had a lower rate of previous COVID-19; and had received fewer treatments with baricitinib and more convalescent plasma therapy. The rates of death and MV were similar between groups (49% vs 51%, $P = .72$). After adjusting for the differences between patients in these 2 groups, the risk for a poor outcome remained similar: odds ratio (OR), 0.77 and 95% confidence interval (CI), .57–1.04 (Supplementary Table 1).

Next, we compared the unvaccinated patients to the 4-dose vaccinated patients (Table 1). The 4-dose vaccinated cohort were older, more lived in LTCFs and were immunosuppressed,

Table 1. Comparison Between Unvaccinated and 3- or 4-Dose Vaccinated Hospitalized Patients With Severe or Critical Coronavirus Disease 2019

Variable	Unvaccinated (0/1 Doses)	Received 3 Doses	*P* Value (0 vs 3)	Received 4 Doses	*P* Value (0 vs 4)
N	403	386		88	
Time from last vaccine dose (IQR), days	NA	161 (147–168)	NA	14 (10–18)	NA
Age, median (IQR), years	78 (67–86)	81 (70–88)	**.03**	83 (74–88)	**<.01**
Male sex, n (%)	190 (47)	206 (53)	.09	49 (56)	.16
Long-term care facility residence, n (%)	53 (13)	73 (19)	**.03**	34 (39)	**<.01**
Comorbidities, n (%)					
Diabetes mellitus	178 (45)	178 (46)	.67	38 (43)	.91
Hypertension	261 (65)	278 (72)	**.03**	63 (72)	.26
Body mass index >30 kg/m^2	110/358 (31)	78/335 (23)	**.03**	18/74 (24)	.33
Ischemic heart disease	124 (31)	122 (32)	.82	30 (34)	.61
Congestive heart failure	125 (31)	125 (32)	.7	20 (23)	.16
Chronic renal failure	99 (25)	122 (32)	**.03**	26 (30)	.34
Chronic liver disease	15 (4)	9 (2)	.3	2 (2)	.56
Chronic lung disease	94 (23)	96 (25)	.62	25 (29)	.34
Dementia	135 (34)	109 (28)	.12	33 (38)	.54
Cancer	50 (12)	79 (21)	**<.01**	20 (23)	**.01**
Immunosuppression, n (%)	33 (8)	79 (21)	**<.01**	31 (36)	**<.01**
Past COVID-19, n (%)	15 (4%)	3 (1%)	**<.01**	0 (0%)	.09
Treatment before severe COVID-19, n (%)					
Nirmaltrevir/ritonavir	5 (1)	8 (2)	.41	4 (5)	.06
Molnupiravir	5 (1)	3 (1)	.73	2 (2)	.61
Treatment during admission, n (%)					
Oxygen	388 (96)	376 (97)	.42	85 (97)	1.0
High-flow nasal canula	148 (37)	130 (35)	.5	24 (27)	.11
Mechanical ventilation	83 (20)	85 (22)	.66	14 (16)	.38
Extracorporeal membrane oxygenation	7 (2)	3 (1)	.34	1 (1)	1.0
Steroids	375 (93)	357 (93)	.79	82 (93)	1.0
Remdesivir	201 (50)	182 (47)	.43	55 (63)	**.04**
Anti-interleukin 6	21 (5)	21 (6)	1.0	3 (3)	.6
Baricitinib	44 (11)	25 (7)	**.03**	7 (8)	.45
Convalescent plasma	1 (<1)	8 (2)	**.02**	2 (2)	.09
Death, n (%)	188 (47%)	170 (44%)	.48	26 (30%)	**<.01**
Hospital stay, median (IQR), days	6 (4–9)	6 (3–10)	.31	5 (3–10)	.36
Poor outcome (death or mechanical ventilation), N (%)	204 (51%)	190 (49%)	.72	30 (34%)	**<.01**

Bold values emphasize value < = .05.
Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range.

Table 2. Univariate Comparison of Patients Who Were Vaccinated With 3 or 4 Doses With Favorable vs Poor Outcome, Defined as Death or Mechanical Ventilation

Variable	Favorable Outcome	Poor Outcome	*P* Value
N	254	220	
Age, median (interquartile range), years	81 (70–88)	82 (70–88)	.82
Male sex, n (%)	122 (48)	133 (61)	**.01**
Long-term care facility residence, n (%)	49 (19)	58 (26)	.08
Comorbidities, n (%)			
Diabetes mellitus	109 (43)	107 (49)	.23
Hypertension	179 (71)	162 (74)	.54
Ischemic heart disease	80 (32)	72 (33)	.84
Congestive heart failure	74 (29)	71 (32)	.49
Chronic renal failure	65 (26)	83 (38)	**<.01**
Chronic liver disease	4 (2)	7 (3)	.36
Chronic lung disease	78 (31)	43 (20)	**<.01**
Dementia	62 (24)	80 (36)	**<.01**
Cancer	52 (21)	47 (22)	.82
Immunosuppression, n (%)	54 (22)	56 (26)	.33
Past coronavirus disease 2019, n (%)	1 (<1%)	2 (1%)	.6
Remdesivir treatment, n (%)	144 (57%)	93 (42%)	**<.01**
Received 4 vaccine doses, n (%)	58 (23%)	30 (14%)	**.01**

Bold values emphasize value < = .05.

and more received remdesivir treatment. The rate of death or MV was significantly lower for 4-dose patients (34% vs 51%, respectively; $P < .01$).

As a significant difference in the primary outcome was shown only for the 4-dose patients, we evaluated the risk factors for a poor outcome within the fully vaccinated patient group (3 or 4 doses) using univariate analysis (Table 2) followed by multivariate regression analysis (Figure 2). Receipt of a fourth dose was shown to confer significant protection against a poor outcome compared with 3 doses, with an OR of 0.51 (95% CI, .3–.87). Other variables associated with protection from a poor outcome were chronic lung disease and remdesivir treatment, while male sex, dementia, and chronic renal failure were detrimental. Immunosuppression showed a trend for a worse outcome (OR, 1.58; 95% CI, .98–2.54; $P = .06$). Age was not associated with outcome in this fully vaccinated group. Three sensitivity analyses were done: one with death as a sole outcome (Supplementary Tables 2, 3), the second with LTCF residence replacing dementia (Supplementary Table 4), and the third excluding patients residing in LTCF from the analysis (Supplementary Table 5). In all analyses, the fourth dose was associated with protection against either death or composite poor outcome.

DISCUSSION

In this study, we analyzed clinical data from 1049 adult patients with severe or critical COVID-19 who were admitted to 14 general hospitals in Israel over a 2-week period in January 2022 during a COVID-19 wave when the Omicron variant was predominant. Fully vaccinated adults with either 3 or 4 vaccines were older and more were immunocompromised compared with the unvaccinated patients. A fourth vaccine (received a median of 2 weeks before infection) provided significant protection from death or MV (OR, 0.51; 95% CI, .3–.87) to the older, immunocompromised patient population compared with 3 vaccine doses (last dose received a median of 23 weeks prior).

VE against various clinical outcomes was shown to decrease during the Omicron wave due to the antigenic distance of this variant and waning immunity. VE against symptomatic infection was at best 67.2% shortly after a third BNT162b2 dose and declined to 47.5% after 10 or more weeks [6]. VE against hospitalization after a 3-dose BNT162b2 vaccination schedule decreased from 91% within 2 months of vaccination to 78% beyond 4 months [8]. VE against MV or death was 94% after 3 doses during the Omicron period in another study [7], but the median time from the third dose was only 60 days.

The waning immunity after 3 doses and the fact that most of the older Israeli population was more than 4–5 months after their third dose at the onset of the Omicron wave led the Israeli Ministry of Health to recommend a fourth dose to individuals aged ≥60 years, those with comorbidities, and healthcare personnel on 2 January 2022. Since then, several studies have shown high protection afforded by a fourth dose against severe disease and death. Compared with individuals who received 3 doses, those who received a fourth dose had a 3.5-fold lower rate of severe disease during a 6-week follow-up in a national observational study [9]. VE against infection was modest and declined rapidly. In 2 other studies that compared 4- to 3-dose recipients, VE of 64%–73% against severe disease was reported at a 4- to 9-week follow-up after dose 4 [10, 11] and 88% against mortality during a 10-week follow-up after dose 4 [15]. Our findings show another added benefit from the fourth dose. Even after failure of that dose to prevent infection and progression to severe disease, it was associated with greater protection from the most severe outcomes.

In a previous study on breakthrough infections during the Delta wave in Israel, we showed that although vaccinated patients were considerably older and more immunocompromised, poor outcome, once hospitalized, was not different between vaccinated and unvaccinated patients [16]. In that study, the vaccinated cohort included patients who had received 2 doses of BNT162b2 approximately 6 months earlier. Those results echo those of our present study in the subgroup of patients who received 3 doses 5 months before infection. This is not to imply that vaccination did not have an effect on disease outcomes. It prevented hospitalization of the younger and healthier population, as can be seen by the differences in age and comorbidities between the unvaccinated and 3-dose

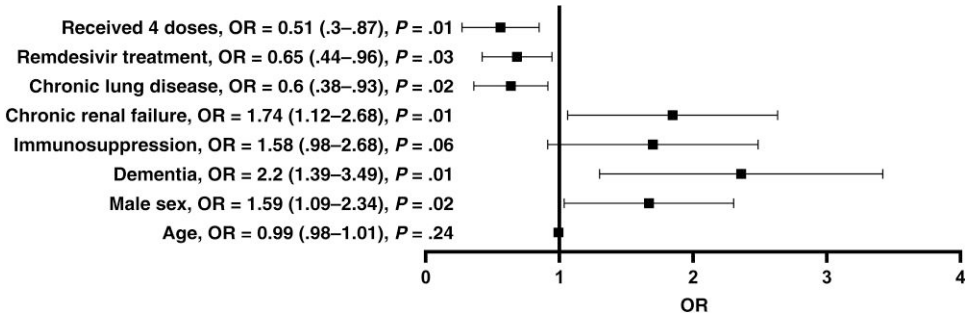

Figure 2. Risk factors for poor outcome within vaccinated patients. Box-and-whisker plot displaying a regression analysis of risk factors for a poor composite outcome of death or mechanical ventilation within the population of vaccinated (3 or 4 doses) patients with severe coronavirus disease 2019. Blocks and whiskers signify OR (poor vs good outcome) and 95% confidence intervals. Abbreviation: OR, odds ratio.

vaccinees. Recent vaccination was highly protective against severe disease and death after the primary 2-dose series [17–19] and shortly after the third dose [4, 5]. The current study enabled us to compare fully vaccinated patients with a breakthrough infection from a single variant with various intervals from their last booster. The data presented here suggest that the observed benefit of this additional dose might not be due to a specific immunogenicity of a fourth dose but to its temporal proximity to infection.

Other independent variables associated with protection against poor outcomes were treatment with remdesivir and chronic lung diseases. Improved outcomes with remdesivir were expected [20, 21]. More surprising was improved outcomes of patients with chronic lung infection. A possible explanation is low baseline oxygenation, wrongfully diagnosed as severe COVID-19. A sensitivity analysis that excluded patients with chronic lung disease did not significantly change the results (data not shown). Age was not found to correlate with poor outcomes, but the cohort was composed of a fairly homogenous group of older patients, limiting this analysis.

The strengths of this study are its multicenter design, thorough record review by experienced specialists, and its representation of the Israeli population, as it contains approximately 40% of severe COVID-19 patients reported nationally. As cases with clinical disease onset less than 7 days after dose 4 were not included in the 4-dose cohort, their proportion was lower (30%) compared with the national registry that does not contain these data.

Since only patients with verified severe or critical disease were included, the rate of adverse outcomes was high (poor outcomes in approximately 50% of unvaccinated or 3-dose cohorts and 34% after 4 doses), allowing comparative analysis with a limited number of patients with significant findings. Nevertheless, some limitations should be noted. The retrospective design might lead to several biases due to inherent differences between patient populations who received varying numbers of vaccine doses. These were adjusted for in the multivariate analyses, but some unknown differences might not have been accounted for. In addition, we excluded patients without valid vaccination records, although these accounted for only 7% of the entire cohort. The cohort that received 4 doses was relatively small, comprised of 88 patients, which limited the strength of the analysis. A possible censoring bias was limited by collection of information on patients' outcomes at least 4 weeks after the end of the study period, with only 2 patients still hospitalized without reaching the combined outcome. Last, disease onset might be hard to assess, especially in older patients with dementia. Onset could have been less than 7 days after vaccination in some patients who received a recent (fourth) dose. Nevertheless, this would be expected to bias results toward decreasing the effectiveness of the fourth dose.

CONCLUSIONS

Despite good protection afforded by a 3-dose vaccination schedule against COVID-19, breakthrough infections in vulnerable older populations during an Omicron variant wave resulted in significant morbidity and mortality. Within a population of hospitalized patients with severe or critical COVID-19, recent receipt of a fourth dose resulted in significantly lower probability of death or MV, in the short term. These findings suggest that administration of a fresh booster dose should be considered for at-risk individuals facing a new COVID-19 wave.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. T. B.-N. and M. C. conceptualized the study and performed the data analysis. All authors took part in data acquisition,

interpretation, critical revision of the manuscript, and its final approval and are accountable for its integrity and accuracy.

Potential conflicts of interest. T. B.-N. reports receiving honoraria from Reckitt Benckiser for lectures. B. C. reports receiving honoraria and/or lecture fees from Pfizer, MSD, Gilead, Tradis Gat, Dexell, AstraZeneca, and Reckitt Benkiser. Y. M. reports receiving a quality grant, unrelated to coronavirus disease 2019 (COVID-19) vaccines, from Pfizer paid to the institution (Wolfson Medical Center); honoraria for lectures unrelated to COVID vaccines from Pfizer and MSD; and consulting fees from MSD for serving on an advisory board. G. R. reports receiving honoraria and/or lecture fees from Pfizer (honoraria for lectures, unrelated to COVID-19 vaccines), MSD (honoraria for lectures, unrelated to COVID-19 vaccines), and Asetllas; consulting fees from MSD and Gilead; and travel fees from MSD; none of these fees are related to the study. T. B. N., K. H., Y. M., and O. Z. are members of the Israeli National Advisory Board on COVID-19 Management and Vaccination. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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