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Association of Receipt of the Fourth BNT162b2 Dose With Omicron Infection and COVID-19 Hospitalizations Among Residents of Long-term Care Facilities

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IMPORTANCE The administration of a fourth BNT162b2 COVID-19 vaccine dose was approved in Israel in December 2021 for individuals 60 years or older who were vaccinated with a third dose 4 months previously or earlier to control the substantial surge of the SARS-CoV-2 Omicron variant. Nonetheless, the association between receipt of the fourth dose and protection against infection remains elusive.

OBJECTIVE To determine the association of the fourth BNT162b2 dose with protection against SARS-CoV-2–related infections, hospitalizations, and deaths during the Omicron surge in long-term care facility (LTCF) residents.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study was conducted in Israel between January 10 and March 31, 2022 and included LTCF residents 60 years or older.

EXPOSURES Vaccination with the fourth dose of BNT162b2 vs 3 doses that were administered 4 months previously or earlier.

MAIN OUTCOMES AND MEASURES Cumulative incidences of SARS-CoV-2 infections, hospitalizations, and deaths during the Omicron surge. The follow-up was initiated more than 7 days after receipt of the fourth dose, which was matched to the follow-up initiation date of those who had received 3 doses of vaccine in each facility. We obtained hazard ratios and 95% confidence intervals from multivariable Cox regression models.

RESULTS The data of 43 775 residents (mean [SD] age, 80.1 [9.4] years; 29 679 women [67.8%]) were analyzed, of whom 24 088 (55.0%) and 19 687 (45.0%) received the fourth and third dose (4 months previously or earlier), respectively. The median follow-up time was 73 days (4-dose group: IQR, 6 days; 3-dose group: IQR, 56 days). More than 7 days postvaccination with the fourth dose, SARS-CoV-2 infection was detected among 4058 fourth-dose vs 4370 third-dose recipients (cumulative incidence, 17.6% vs 24.9%). The corresponding incidences of hospitalizations for mild-to-moderate COVID-19, severe illness, and mortality were 0.9% and 2.8%, 0.5% and 1.5%, and 0.2% and 0.5%, respectively. The adjusted protections were 34% (95% CI, 30%-37%), 64% (95% CI, 56%-71%), and 67% (95% CI, 57%-75%) against overall infection, hospitalizations for mild-to-moderate illness, and severe illness, respectively, and 72% (95% CI, 57%-83%) against related deaths.

CONCLUSIONS AND RELEVANCE The results of this cohort study suggest that receipt of a fourth BNT162b2 dose conferred high protection against COVID-19 hospitalizations and deaths among LTCF residents during a substantial Omicron variant surge, but protection was modest against infection. These findings are relevant to the control of COVID-19 pandemic globally, especially among the population of LTCFs.

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Supplemental content

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Regarding the rapid dissemination of the SARS-CoV-2 Delta variant of concern and waning vaccine-acquired immunity,[1,2] in July 2021, Israel was the first country to introduce a third vaccine dose 5 months or more following the second vaccine dose,[3] which was associated with high protection against overall SARS-CoV-2 infection, COVID-19 hospitalizations, and deaths in the general population.[4-6] Elderly residents of long-term care facilities (LTCFs) are at risk for severe and fatal COVID-19,[7-9] with reduced immunity following vaccination with COVID-19 messenger RNA vaccines and rapid decline in the immune response after 2 vaccine doses.[10,11] To protect this population, the Israeli government launched a designated task force, Senior Shield, which was responsible for preventing and controlling COVID-19 in LTCFs, including providing personal protective equipment, screening and early detection of health care workers and residents with SARS-CoV-2 infection, and COVID-19 vaccination.[12,13]

The vaccination campaign with the third BNT162b2 dose among LTCF residents in August 2021 was associated with high vaccine uptake and rapid declines in the incidence of SARS-CoV-2 infection and COVID-19 hospitalizations.[13] The protection of the third dose (compared with the second dose administered 5 or more months earlier) was 89% against infection, 92% to 93% against COVID-19 hospitalization, and 96% against COVID-19 deaths during the Delta variant surge.[14]

The Omicron variant, first identified in Israel in November 2021, became the dominant variant in January 2022.[15] By the beginning of December 2021, a marked rise in SARS-CoV-2 infections was observed, which was also found among fully vaccinated persons.[16] To contain this substantial surge, the Israeli Ministry of Health approved administration of a fourth BNT162b2 dose on December 31, 2021, which was initially designated for LTCF residents and later for the general population 60 years or older. The goal was to provide cross-protection against Omicron infection, including associated hospitalization and severe illness, by increasing antibody levels to the original Wuhan strain. Indeed, among the general Israeli population 60 years or older, the protection granted by the fourth BNT162b2 dose was estimated at 45% to 50% against SARS-CoV-2 infection and 62% to 71% against severe COVID-19 during the period of 1 to 4 weeks after vaccination compared with vaccination with 3 doses 4 months or more earlier.[17,18] In this article, we assessed the association of receipt of a fourth BNT162b2 dose with protection against overall SARS-CoV-2 infection and COVID-19 hospitalizations and deaths among LTCF residents during the substantial rise in COVID-19 incidence owing to the Omicron variant.

Key Points

Question What is the association of receiving the fourth dose of BNT162b2 vaccine with Omicron variant infection among residents of long-term care facilities?

Findings In this cohort study of 24 088 recipients of a fourth dose of vaccine and 19 687 individuals who received a third dose only (4 months previously or earlier), receipt of the vaccine dose was associated with 34% protection against infection, 64% to 67% against hospitalizations for mild-to-moderate and severe illness, and 72% against deaths.

Meaning The study results suggest that a fourth BNT162b2 dose was associated with high protection against COVID-19 hospitalizations and deaths among residents of long-term care facilities during a surge associated with the Omicron variant.

Methods

Study Design and Ethics Approval

A prospective cohort study was undertaken between January 10 and March 31, 2022, within the framework of Senior Shield routine SARS-CoV-2 infection surveillance. The study protocol was approved by the institutional review board of the Soroka University Medical Center (Beer-Sheva, Israel). Exemption for participants from signing a written informed consent was provided given the retrospective study design.

Study Population

The LTCFs varied in their bed size, funding sources, and characteristics of the resident populations (functional status, disabilities, and needs). This included state-funded chronic geriatric facilities, acute geriatric care facilities funded by sick funds, welfare facilities, and others (eMethods in the Supplement).

On December 31, 2021, Israeli authorities approved the administration of a fourth BNT162b2 dose to all LTCF residents who had received a third dose at least 4 months earlier. Vaccination was conducted in the LTCFs in collaboration with Israel's national emergency medical services organization. Vaccination was conducted rapidly in parallel in multiple facilities and regions across the country, prioritizing facilities with high-risk residents and aiming to achieve maximal coverage for the LTCF population. The vaccines were obtained from a central warehouse and transported to the LTCFs by well-trained medics. Documentation of vaccination was transferred to the Senior Shield database. The current study analyzed data of residents who received the fourth BNT162b2 dose within a collective vaccination week at their facility (the fourth dose group) and residents who received only 3 doses of the vaccine (the comparison group). Individuals with prior COVID-19 were at risk for reinfection. The policy in Israel is that persons who had a prior laboratory-confirmed SARS-CoV-2 infection should be vaccinated with 1 BNT162b2 dose. This group would have hybrid immunity that was induced by natural exposure to the virus (ie, via multiple antigens) and vaccine-induced immunity to just the spike antigen. It was shown that hybrid immunity was associated with more significant protection against SARS-CoV-2 reinfection than vaccine-induced immunity.[19-21] Therefore, to minimize confounding, we excluded individuals with previous infection from the analysis.

Data Sources

Information was retrieved via the Senior Shield database on COVID-19 vaccination status, dates, numbers and results of

SARS-CoV-2 reverse-transcription–polymerase chain reaction (RT-PCR) tests, COVID-19 hospitalizations, disease severity, vital status, and demographic characteristics. During the Omicron wave, the screening for SARS-CoV-2 in LTCFs included weekly RT-PCR tests of the staff and screening of the residents every 2 weeks. Once an individual received a positive result, all residents and staff of the facility were tested every 3 days until each had 2 negative results. The screening tests were performed using an RT-PCR assay, but some facilities (comprising 3708 residents [8.5%]), used a rapid SARS-CoV-2 antigen detection assay in addition to the RT-PCR assay. These results were included in the analysis of overall infection.

End Points

Given the high transmissibility of the Omicron variant, we postulated that the fourth dose might not confer significant protection against infection. Therefore, we considered COVID-19 hospitalizations as the primary end point and SARS-CoV-2 infection as a secondary end point. The incidence of SARS-CoV-2 infection was defined as a documentation of positive test result (mostly by RT-PCR) in the Senior Shield system. The screening policy for RT-PCR did not change throughout the study. COVID-19 hospitalization and related deaths were defined based on the documentation in the Senior Shield database, including RT-PCR testing.

Follow-up

Most facilities vaccinated residents during 5 consecutive days, referred to as a *collective vaccination week*, in which a facility reached its maximal vaccination rate. The follow-up start date was more than 7 days following the administration of the fourth BNT162b2 dose given that the vaccine was administrated during the collective vaccination week. The count of follow-up days began on day 8 postvaccination. The starting follow-up timing was determined a priori assuming that the effect of a booster reaction would be evident 1 week after vaccination. For residents who received 3 doses only, the follow-up start date was set as 7 days after the midpoint of the collective vaccination week in their facility; thus, we created a common calendar follow-up. The facility was a fixed effect. The earliest follow-up start date was January 10, 2022. The study groups were followed until the earliest of the following: SARS-CoV-2 infection, COVID-19 hospitalization, COVID-19–related death, receipt of the fourth dose for those in the 3-dose group, death owing to illness other than COVID-19, or end of follow-up on March 31, 2022. We also considered a follow-up start date of more than 14 days postvaccination with the 4-dose group (and a matched date for the 3-dose group) considering that the conferred protection might increase with time after vaccination.[17]

Independent Variable

The administration of the fourth BNT162b2 dose (a dichotomous variable) was defined as yes vs recipient of 3 doses only. The third dose was administered 4 months previously or earlier.

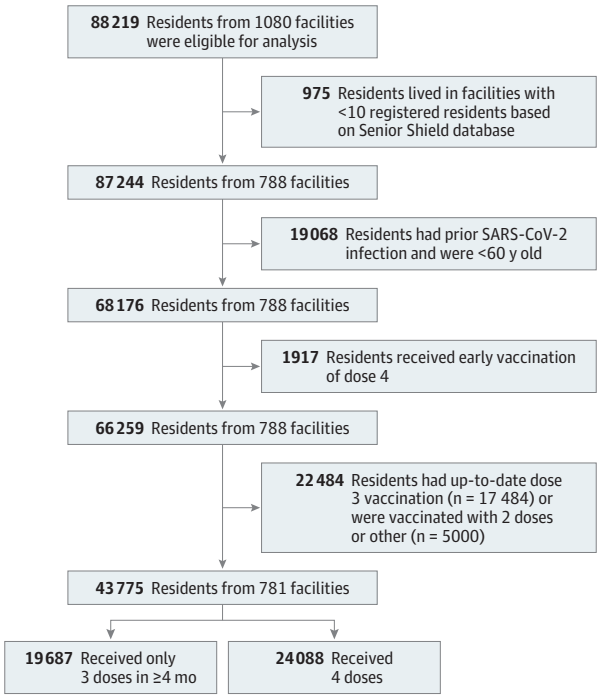
Covariates

Covariates included age (years), sex, facility, population group (defined based on the location of residents in towns with a predominant general Jewish population, ultraorthodox Jewish population, or Arab population), and socioeconomic status based on the resident's address.[22] We defined the resident's functional status based on the documentation in the Senior Shield database as residents who needed maximum or total assistance in performing activities of daily living, those who needed some assistance, and independent residence in performing daily living activities.

Statistical Analysis

We described the baseline characteristics of the study groups using means and standard deviations for continuous variables and counts and percentages for categorical variables. Using a Kaplan-Meier survival analysis, we created cumulative incidence curves of SARS-CoV-2 infection, COVID-19 hospitalizations, and related deaths among the study groups. The log-rank test was used to compare the curves between the study groups. Cox proportional hazard regression models[23] with follow-up days used as the time scale were constructed to calculate the hazard ratios (HRs) and 95% CIs for the study end points. The independent variables were administration of the fourth BNT162b2 dose, age, sex, socioeconomic status, population group, and functional status. The facilities were analyzed as strata (ie, the variable facility was treated as a fixed effect). We calculated an HR for vaccination with the fourth dose compared with recipient of the third vaccine dose 4 months previously or earlier. The amount of protection associated with receipt of the fourth vaccine dose was calculated as (1 − HR) × 100. The analyses were performed for initiating the follow-up date more than 7 days or 14 days postvaccination with the fourth dose. A sensitivity analysis was performed while including only residents who received 75% or more of SARS-CoV-2 tests during the follow-up period. The proportional hazards assumption was tested using the Schoenfeld residuals without violation. Multicollinearity was assessed using a variance inflation factor, with values of 2.6 or less in all analyses suggesting no multicollinearity. Missing data were low, expect for functional status, for which data were available for 29 585 residents (67.6%). Individuals with missing data on this variable were assigned a missing category and were included in the complete-case analysis. A 2-sided P value of <.05 was considered statistically significant without adjustment for multiplicity. We assessed the robustness of the HRs to potential unmeasured confounders using the E-value,[24] which is the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both vaccinations and the outcome to fully explain away the specific vaccination-outcome associations, which were conditional on the measured covariates. A large E-value indicated that considerable unmeasured confounding would be needed to explain away an effect estimate, whereas a small E-value suggested that little unmeasured confounding would be needed to explain away an effect estimate.[24] We calculated the number needed to receive vaccination as 1/(cumulative incidence in the 3-dose group − the cumulative incidence in the 4-dose group). Analyses were conducted using R, version 4.1.0 (R Foundation).

Figure 1. Flowchart of Selection of Study Groups



During step 1, we excluded from the analysis very small facilities that had fewer than 10 residents per facility, resulting in the exclusion of 975 residents from 292 very small facilities. The mean number of residents per facility before the exclusion of these facilities was 96 (median, 37 residents) and after the exclusion of these facilities was 132 (median, 80 residents).

Results

The Senior Shield database included 88 219 residents from 1080 facilities; of these, 43 775 (mean [SD] age, 80.1 [9.4] years; 29 679 women [67.8%]) from 781 facilities were eligible for the analysis (**Figure 1**). Most residents (39 601 [90.5%]) were Jewish individuals from the general ; 26 331 residents (60.2%) belonged to geriatric facilities, followed by welfare facilities of statutory accommodation (6427 [14.7%]) and elderly day-care facilities (6426 [9.4%]). The study groups comprised 24 088 recipients (55.0%) of the fourth dose and 19 687 recipients (45.0%) of 3 doses 4 months previously or earlier; of these, 3834 (8.8%) were censored because they received the fourth dose of the vaccine later. The fourth dose recipients, compared with those who received 3 doses, were older (mean [SD] age, 82.3 [8.7] vs 77.3 [9.5] years), more often belonged to high socioeconomic status communities (44.5% vs 30.1%), included more individuals who lived in welfare statutory accommodation (20.5% vs 7.6%), and less often included individuals who regularly attended elderly day-care centers (6.7% vs 12.8%). The proportion of residents who needed maximum or total assistance in performing activities of daily living was similar between the groups (16.3% vs 15.3%) (**Table 1**).

Association of Vaccination With the Fourth BNT162b2 Dose With SARS-CoV-2 Infection, COVID-19 Hospitalizations, and Deaths

After initiating the count of the follow-up duration at more than 7 days postvaccination, the follow-up duration ranged between 1 and 80 days for the recipients of the fourth BNT162b2 dose (median, 73 days; IQR, 6 days). The follow-up duration for the 3-dose group ranged between 1 and 78 days (median, 73 days; IQR, 56 days).

The incidence of overall SARS-CoV-2 infection was lower among the 4-dose vs 3-dose recipients (**Figure 2**A). SARS-CoV-2 infection was detected among 4058 residents who received the fourth dose of the vaccine vs 4370 among residents who received 3 doses, yielding cumulative incidences of 17.6% vs 24.9%. There were 217 hospitalizations for COVID-19 of mild-to-moderate severity among the 4-dose recipients compared with 493 among the 3-dose recipients (Figure 2B), yielding cumulative incidences of 0.9% and 2.8%, respectively. The corresponding numbers of COVID-19 hospitalizations for severe illness were 108 and 259 (Figure 2C), and the respective cumulative incidences were 0.5% and 1.5%. There were 39 COVID-19 related deaths among the fourth dose recipients vs 85 deaths among the 3-dose recipients, yielding a cumulative mortality of 0.2% vs 0.5% (Figure 2D).

Significant inverse associations were found between vaccination with the fourth dose and each of the study end points, which were strengthened in multivariable models that controlled for age, sex, population group, socioeconomic status, and functional status. Considering the period of more than 14 days after the fourth dose yielded point estimates of greater magnitude, although confidence intervals were overlapping with those for the period more than 7 days after the fourth dose (**Table 2**).

Association of Vaccine Dose With Positive Outcomes

The adjusted protection that vaccination conferred was 34% (95% CI, 30%-37%) against overall SARS-CoV-2 infection. For COVID-19 hospitalizations for mild-to-moderate illness, severe illness, and COVID-19 related deaths, the level of protection conferred was 64% (95% CI, 56%-71%), 67% (95% CI, 57%-75%), and 72% (95% CI, 54%-83%), respectively, at 7 days or more postvaccination with the fourth dose. These estimates were higher when considering the period of more than 14 days after fourth dose administration (**Figure 3**). The number needed to receive vaccination for overall infection, hospitalization for mild-to-moderate COVID-19, severe illness, and death were 14, 53, 100, and 333, respectively.

Sensitivity Analysis

Limiting the analysis to 26 698 residents from 746 facilities who underwent 75% or more of the tests during follow-up (9887 [37.0%] received 3 doses and 16 811 [63.0%] received 4 doses) (eFigure and eTable 1 in the Supplement) showed comparable results. This also yielded slightly stronger point estimates (eTable 2 in the Supplement).

Analysis of E-Value

The E-value for HR (and of the corresponding CI) of the end point of infection was 2.0 (1.88). The respective E-value of the

Table 1. Characteristics of the Study Groups

Characteristic	No. (%)	
	3 Doses only (n = 19 687)	4 Doses (n = 24 088)
Sex		
Female	13 235 (67.2)	16 464 (68.3)
Male	6435 (32.7)	7595 (31.5)
Missing	17 (0.1)	29 (0.1)
Age, mean (SD), y	77.3 (9.5)	82.3 (8.7)
Socioeconomic status		
Low	3556 (18.1)	3771 (15.7)
Medium	8456 (43.0)	7899 (32.8)
High	5926 (30.1)	10 714 (44.5)
Missing	1749 (8.9)	1704 (7.1)
Population group		
Arab	747 (3.8)	604 (2.5)
General Jewish population	17 500 (88.9)	22 101 (91.8)
Ultraorthodox Jewish population	928 (4.7)	837 (3.5)
Missing	512 (2.6)	546 (2.3)
Starting follow-up epidemiological week, median (IQR)[a]	4 (1)	4 (1)
Vaccination with the fourth dose at the facility level[b]		
0%-59%	15 130 (76.9)	12 972 (53.9)
60%-69%	3027 (15.4)	5458 (22.7)
70%-79%	1219 (6.2)	4270 (17.7)
80%-100%	311 (1.6)	1388 (5.8)
No. of SARS-CoV-2 tests during the study period		
0	4382 (22.3)	2404 (10.0)
1-3	7290 (37.0)	6092 (25.3)
4-7	4499 (22.8)	7081 (29.4)
8-11	1930 (9.8)	4395 (18.2)
≥12	1586 (8.1)	4116 (17.1)
Performed SARS-CoV-2 rapid antigen detection assay	2114 (10.7)	1594 (6.6)
Facility type[c]		
Mental health	418 (2.1)	259 (1.1)
Geriatric facilities	11 969 (60.8)	14 362 (59.6)
Elderly day-care facilities	2515 (12.8)	1613 (6.7)
Welfare: statutory accommodation (independent)	1495 (7.6)	4932 (20.5)
Welfare: nursing homes (frail)	937 (4.8)	1628 (6.8)
Welfare: disabilities	578 (2.9)	371 (1.5)
Other	1695 (8.6)	923 (3.8)
Functional status		
Need maximum or total assistance in activities of daily living	3009 (15.3)	3938 (16.3)
Need some assistance in activities of daily living	1461 (7.4)	1682 (7.0)
Independent	7219 (36.7)	10 175 (42.2)
Other	786 (4.0)	1315 (5.5)
Missing	7212 (36.6)	6978 (29.0)

[a] More than 7 days after vaccination with the fourth dose and a matching index week for the recipients of 3 doses only.

[b] Vaccination with the fourth dose at the facility level; this variable was defined as the proportion of residents who were vaccinated with the fourth dose of the BNT162b2 vaccine in a certain facility among all residents registered in the same facility.

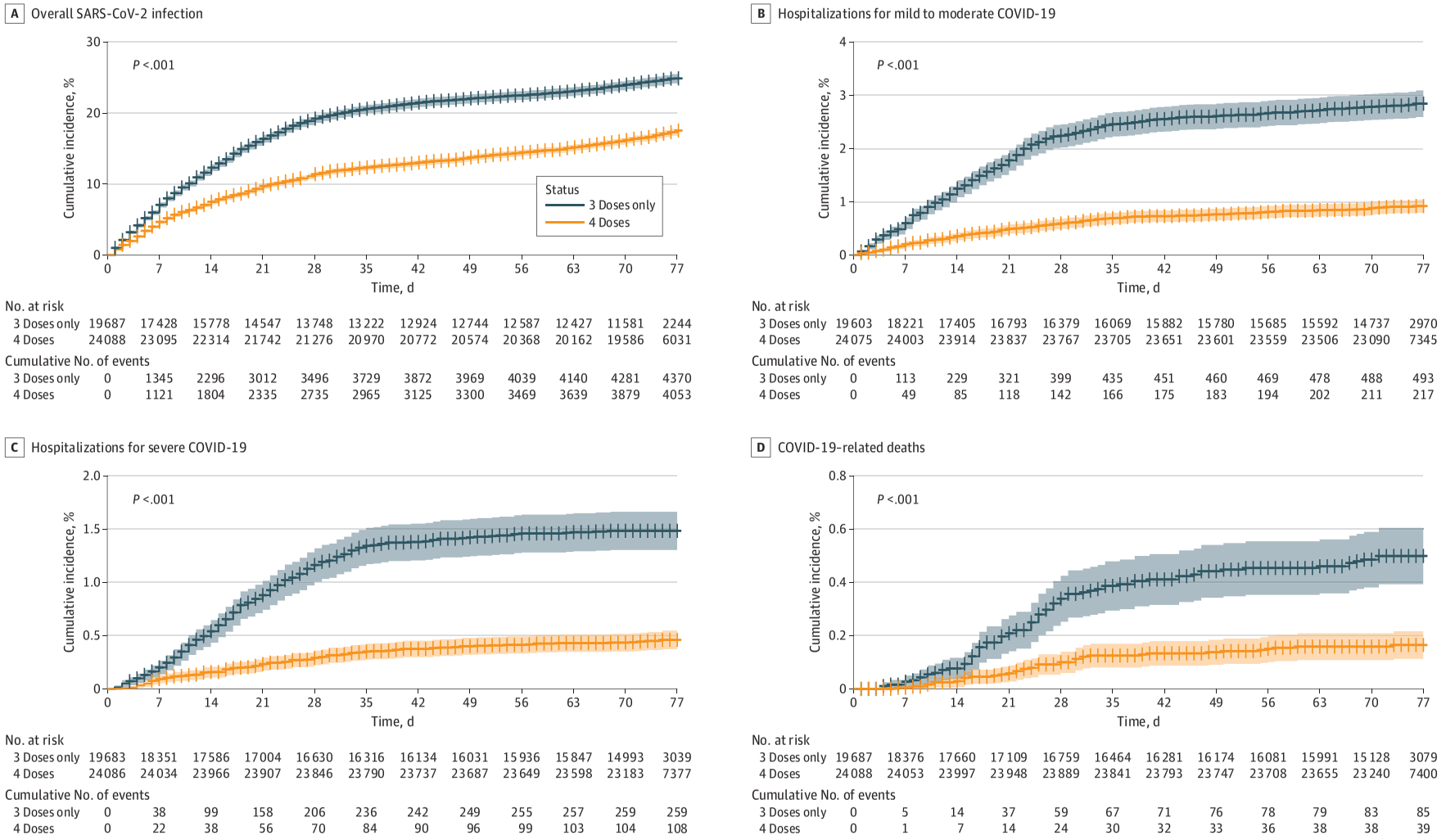
[c] The geriatric facilities include long-term facilities and a few acute care facilities. Facilities that were classified as *welfare disabilities* included individuals with mental/cognitive and physical disabilities. The welfare nursing homes serve a population that needs some help and supervision in performing activities of daily living. Welfare statutory accommodation serves independent individuals in terms of their ability to perform activities of daily living. Elderly day-care facilities serve individuals who live in their own homes but are transported to these facilities 2 to 3 times a week; they vary in their needs and functional status.

HR for hospitalization owing to mild-to-moderate COVID-19 was 5.0 (3.97), 5.5 (4.08) for severe disease), and 6.6 (3.77) for COVID-19 related deaths.

Discussion

The results of this cohort study suggest a strong association of receipt of a fourth BNT162b2 dose with increased protection compared with 3 doses administered 4 months previously or earlier among LTCF residents against COVID-19 hospitalizations and deaths during the Omicron surge in Israel. The fourth dose was also associated with a moderate degree of protection against overall SARS-CoV-2 infection. These findings may be of global importance given the substantial burden associated with the Omicron variant, waning of vaccine-acquired immunity, and importance of protecting populations. Unlike prior variants, such as Alpha, Beta and Delta, that

Figure 2. Cumulative Incidence of the Study End Points by Study Group



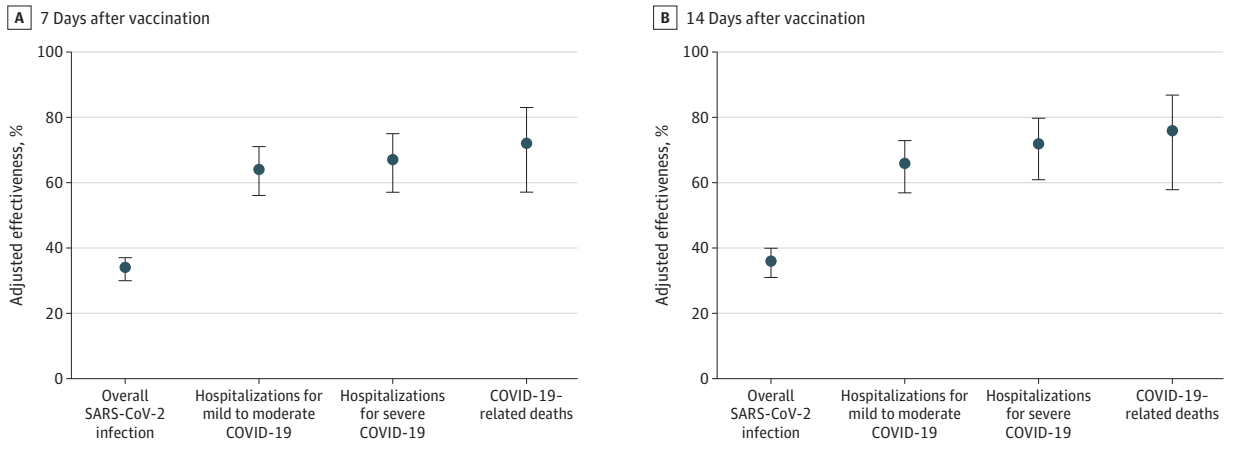
Shaded lines represent 95% CIs. The follow-up began more than 7 days after vaccination with the fourth dose and a matching facility-specific starting follow-up date for the recipients of the 3 doses. *P* values were obtained by the log-rank test.

Table 2. Associations of Administration of the Fourth Dose of BNT162b2 Vaccine With SARS-CoV-2 Infection, COVID-19 Hospitalizations, and Deaths

Characteristic	No. of residents	No. of cases	Cumulative incidence, %	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
>7 d Following vaccination with the fourth dose							
Confirmed SARS-CoV-2 infection							
3 Doses of the BNT162b2 vaccine	19 687	4370	24.9	1 [Reference]	<.001	1 [Reference]	<.001
4 Doses of the BNT162b2 vaccine	24 088	4058	17.6	0.67 (0.64-0.71)		0.66 (0.63-0.70)	
Mild/moderate COVID-19 hospitalization							
3 Doses of the BNT162b2 vaccine	19 603	493	2.8	1 [Reference]	<.001	1 [Reference]	<.001
4 Doses of the BNT162b2 vaccine	24 075	217	0.9	0.40 (0.33-0.48)		0.36 (0.29-0.44)	
Severe COVID-19 hospitalization							
3 Doses of the BNT162b2 vaccine	19 603	259	1.5	1 [Reference]	<.001	1 [Reference]	<.001
4 Doses of the BNT162b2 vaccine	24 075	108	0.5	0.37 (0.28-0.48)		0.33 (0.25-0.43)	
COVID-19–related death							
3 Doses of the BNT162b2 vaccine	19 687	85	0.5	1 [Reference]	<.001	1 [Reference]	<.001
4 Doses of the BNT162b2 vaccine	24 088	39	0.2	0.32 (0.20 – 0.49)		0.28 (0.17-0.46)	
>14 d Following vaccination with the fourth dose							
Confirmed SARS-CoV-2 infection							
3 Doses of the BNT162b2 vaccine	17 212	3035	19.1	1 [Reference]	<.001	1 [Reference]	<.001
4 Doses of the BNT162b2 vaccine	22 929	2937	13.6	0.66 (0.62-0.70)		0.64 (0.60-0.69)	
Mild/moderate COVID-19 hospitalization							
3 Doses of the BNT162b2 vaccine	17 143	339	2.1	1 [Reference]	<.001	1 [Reference]	<.001
4 Doses of the BNT162b2 vaccine	22 908	151	0.7	0.39 (0.31-0.48)		0.34 (0.27-0.43)	
Severe COVID-19 hospitalization							
3 Doses of the BNT162b2 vaccine	17 209	194	1.2	1 [Reference]	<.001	1 [Reference]	<.001
4 Doses of the BNT162b2 vaccine	22 927	96	0.3	0.32 (0.23-0.44)		0.28 (0.20-0.39)	
COVID-19–related death							
3 Doses of the BNT162b2 vaccine	17 212	65	0.4	1 [Reference]	<.001	1 [Reference]	<.001
4 Doses of the BNT162b2 vaccine	22 929	26	0.1	0.25 (0.15-0.43)		0.24 (0.13-0.42)	

Abbreviation: HR, hazard ratio.

Figure 3. Adjusted Association of BNT162b2 Fourth Dose Vaccination With Protection Against Omicron



Adjusted association (filled circles) and 95% CIs (error bars) of the administration of a fourth dose of BNT162b2 vaccine with protection against overall SARS-CoV-2 infection, COVID-19 hospitalizations, and related deaths at 7 days (A) and 14 days (B) after vaccination compared with vaccination with 3 doses four months previously or earlier.

carried approximately 10 variations in the spike protein, the Omicron variant has more than 30 variations,[25] including multiple variations in the receptor-binding domain, the main factor targeted by current COVID-19 vaccines.[26] The Omicron variant exhibits a higher transmissibility than prior SARS-CoV-2 variants[27] as well as the capability to evade naturally ac-

quired and vaccine-induced immunity.[26,28-31] A study from South Africa suggested that the protection conferred with the BNT162b2 vaccine was 70% against hospitalization during the Omicron period vs 93% during the preceding period in which the Delta variant was dominant.[32] Despite initial hesitation, a decision to administer a fourth BNT162b2 dose to risk group for severe COVID-19 who had received 3 doses 4 months previously or earlier was made in Israel with the assumption that the fourth dose was likely to boost the levels of neutralizing antibodies, which might provide cross-protection against the Omicron variant.[33] This study's findings support the notion of cross-protection against the Omicron variant using the original formulation of the BNT162b2 vaccine. Additionally, this booster might enhance protection, likely because of increasing the cross-reacting neutralizing antibody levels and enhancing cross-reactive cellular immunity against SARS-CoV-2 variants, including Omicron.[33,34] The associations found in this study between the fourth BNT162b2 dose among LTCF residents with protection against severe COVID-19, hospitalization, and death are comparable with the findings reported in the general Israeli population 60 years or older.[17,18]

The estimated effectiveness of the fourth dose against the Omicron variant found in the current study is lower than that found for the third dose against the Delta variant (89% against infection and 92%-96% against COVID-19 hospitalization and deaths),[14] likely owing to the high immune escape of the Omicron variant.

Strengths and Limitations

This study had limitations. We adjusted for known and measured confounders. Nonetheless, we cannot rule out residual confounding. We did not have information on comorbidities and the reasons for opting not to be vaccinated with the fourth dose. The sensitivity analysis using the E-value showed that the HR for the association between vaccination with the fourth dose and infection was moderately robust. The associations of vaccination with the fourth dose and COVID-19–related hospitalizations and deaths were strongly robust to unmeasured confounders, and only strong unmeasured confounders associated with vaccination and each of these outcomes could explain away the observed HRs for these outcomes.

Information on the symptoms of individuals with SARS-CoV-2 who were not hospitalized were not systematically collected. Therefore, we cannot assess the association of fourth dose vaccination with protection against asymptomatic vs symptomatic infection. Notably, the lack of information on symptoms was not associated with vaccination status. We did not have information on diagnosis codes on hospital admission or discharge records. Some hospitalizations or deaths might have occurred for reasons other than COVID-19 concurrent to SARS-CoV-2 infection. These cases are expected to occur similarly among the recipients of 3 and 4 doses of the vaccine; thus, such potential nondifferential misclassification is not expected to affect the estimates.

Healthy vaccinee bias or effect is likely of less concern in this study because SARS-CoV-2 testing was conducted within the framework of the Senior Shield program regardless of vaccination history and the vaccine was recommended strongly to all residents. The uptake of testing was higher among the 4-dose group than the 3-dose group. Limiting the analysis to those who underwent 75% of more of the tests during the follow-up period showed consistent findings.

An additional potential limitation is the heterogeneity of the LTCF population. While most of the study population comprised residents of geriatric facilities, the Senior Shield taskforce provides services to all types of LTCFs across the country (Table 1).

The strengths of this study include the use of national-level data that were collected within the framework of the Senior Shield COVID-19 surveillance program, in which SARS-CoV-2 PCR testing was undertaken systematically using a standardized protocol that was not associated with the individual's vaccination history. The large sample size with various types of facilities increases the generalizability of the study findings. Our analytical approach reduced confounding associated with characteristics of the facility by considering the facility as a fixed effect. Moreover, we evaluated the association of fourth dose vaccination with positive outcomes against multiple outcomes of various degrees of severity and considered 2 follow-up periods (7 or 14 days after vaccination), showing consistent findings.

Conclusions

The results of this cohort study suggest a strong association between receipt of a fourth BNT162b2 dose with protection against COVID-19–related hospitalizations, severe disease, and deaths during the Omicron surge. It also found the presence of moderate protection against overall SARS-CoV-2 infection among LTCF elderly residents.

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