ORIGINAL ARTICLE

# Protection by a Fourth Dose of BNT162b2 against Omicron in Israel

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## ABSTRACT

### BACKGROUND

On January 2, 2022, Israel began administering a fourth dose of BNT162b2 vaccine to persons 60 years of age or older. Data are needed regarding the effect of the fourth dose on rates of confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and of severe coronavirus disease 2019 (Covid-19).

### METHODS

Using the Israeli Ministry of Health database, we extracted data on 1,252,331 persons who were 60 years of age or older and eligible for the fourth dose during a period in which the B.1.1.529 (omicron) variant of SARS-CoV-2 was predominant (January 10 through March 2, 2022). We estimated the rate of confirmed infection and severe Covid-19 as a function of time starting at 8 days after receipt of a fourth dose (four-dose groups) as compared with that among persons who had received only three doses (three-dose group) and among persons who had received a fourth dose 3 to 7 days earlier (internal control group). For the estimation of rates, we used quasi-Poisson regression with adjustment for age, sex, demographic group, and calendar day.

### RESULTS

The number of cases of severe Covid-19 per 100,000 person-days (unadjusted rate) was 1.5 in the aggregated four-dose groups, 3.9 in the three-dose group, and 4.2 in the internal control group. In the quasi-Poisson analysis, the adjusted rate of severe Covid-19 in the fourth week after receipt of the fourth dose was lower than that in the three-dose group by a factor of 3.5 (95% confidence interval [CI], 2.7 to 4.6) and was lower than that in the internal control group by a factor of 2.3 (95% CI, 1.7 to 3.3). Protection against severe illness did not wane during the 6 weeks after receipt of the fourth dose. The number of cases of confirmed infection per 100,000 person-days (unadjusted rate) was 177 in the aggregated four-dose groups, 361 in the three-dose group, and 388 in the internal control group. In the quasi-Poisson analysis, the adjusted rate of confirmed infection in the fourth week after receipt of the fourth dose was lower than that in the three-dose group by a factor of 2.0 (95% CI, 1.9 to 2.1) and was lower than that in the internal control group by a factor of 1.8 (95% CI, 1.7 to 1.9). However, this protection waned in later weeks.

### CONCLUSIONS

Rates of confirmed SARS-CoV-2 infection and severe Covid-19 were lower after a fourth dose of BNT162b2 vaccine than after only three doses. Protection against confirmed infection appeared short-lived, whereas protection against severe illness did not wane during the study period.

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During late December 2021, with the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.1.529 (omicron) variant, the prevalence of confirmed infection rose sharply in Israel. Some of the contributing factors were increased immune evasion by the variant[1] and the passage of more than 4 months since most adults had received their third vaccine dose. In an effort to address the challenges presented by the omicron variant and to reduce the load on the health care system, on January 2, 2022, Israeli authorities approved the administration of a fourth dose of the BNT162b2 vaccine (Pfizer–BioNTech) to persons who were 60 years of age or older, as well as to high-risk populations and health care workers, if more than 4 months had passed since receipt of their third dose. The real-world effectiveness of the fourth dose against confirmed infection and severe illness remains unclear. In this study, we used data from the Israeli Ministry of Health national database to study the relative effectiveness of the fourth dose as compared with only three doses against confirmed infection and severe illness among older persons in the Israeli population.

## Methods

### Study Population

For this analysis, we included persons who, on January 1, 2022, were 60 years of age or older and had received three doses of BNT162b2 at least 4 months before the end of the study period (March 2). We excluded the following persons from the analysis: those who had died before the beginning of the study period (January 10); those for whom no information regarding their age or sex was available; those who had had a confirmed SARS-CoV-2 infection before the beginning of the study, determined with the use of either a polymerase-chain-reaction (PCR) assay or a state-regulated rapid antigen test; those who had received a third dose before its approval for all older residents (i.e., before July 30, 2021); those who had been abroad for the entire study period (January 10 to March 2; persons were considered to be abroad 10 days before traveling until 10 days after their return to Israel); and those who had received a vaccine dose of a type other than BNT162b2.

For persons who met the inclusion criteria, we extracted information on March 4, 2022, regarding SARS-CoV-2 infection (confirmed either by state-regulated rapid antigen test or by PCR) and severe Covid-19 (defined with the use of the National Institutes of Health definition[2] as a resting respiratory rate of >30 breaths per minute, an oxygen saturation of <94% while breathing ambient air, or a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of <300) during the 14 days after confirmation of infection. During the study period, infections were overwhelmingly dominated by the omicron variant.[3] We also extracted data regarding vaccination (dates and brands of first, second, third, and fourth doses) and demographic variables such as age, sex, and demographic group (general Jewish, Arab, or ultra-Orthodox Jewish), as determined by the person's statistical area of residence (similar to a census block[4]).

### Study Design

The study period started on January 10, 2022, and ended on March 2, 2022, for confirmed infection and ended on February 18, 2022, for severe illness. The starting date was set to 7 days after the start of the vaccination campaign (January 3, 2022) so that at least the first four-dose group (days 8 to 14 after vaccination) would be represented throughout the study period (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The end dates were chosen to minimize the effects of missing outcome data due to delays in reporting PCR or antigen test results and to allow time for the development of severe illness.

The design of the study was similar to that of a previous study in which we assessed the protection conferred by the third vaccine dose as compared with the second dose.[5] We calculated the total number of person-days at risk and the incidence of confirmed infection and of severe Covid-19 during the study period defined for each outcome. For persons who received the fourth dose, treatment groups were defined according to the number of weeks that had passed since receiving that dose, starting from the second week (8 to 14 days after vaccination). These four-dose groups were compared with two control groups. The first control group included persons who were eligible for a fourth dose but had not yet received it (three-dose group). Because persons who received the fourth dose

might have differed from those who had not according to unmeasured confounding variables, a second control group was defined as persons who had received a fourth dose 3 to 7 days earlier (internal control group). This control group included the same persons as the four-dose groups, but during a period in which the fourth dose was not expected to affect the rate of confirmed infection or severe illness. The membership in these groups was dynamic, and participants contributed risk days to different study groups on different calendar days, depending on their vaccination status.

### OVERSIGHT

The study was approved by the institutional review board of the Sheba Medical Center. All the authors contributed to the conceptualization of the study, critically reviewed the results, approved the final version of the manuscript, and made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data in this report. The Israeli Ministry of Health and Pfizer have a data-sharing agreement, but only the final results of this study were shared.

### STATISTICAL ANALYSIS

Using quasi-Poisson regression, we estimated the rates of confirmed infection and severe Covid-19 per 100,000 person-days for each study group (included as factors in the model), with adjustment for the following demographic variables: age group (60 to 69 years, 70 to 79 years, or ≥80 years), sex, and demographic group (general Jewish, Arab, or ultra-Orthodox Jewish). Because incidences of both confirmed infection and severe illness increased rapidly during January 2022, the risk of exposure at the beginning of the study period was lower than at the end of the study period. Moreover, the fraction of the population in each study group changed throughout the study period (Fig. S1). Therefore, we included calendar date as an additional covariate to account for changing exposure risk.[6] The end of the study period for severe Covid-19 was set to 14 days before the date of data retrieval (March 4), allowing at least 14 days of follow-up time for the development of severe illness. To ensure the same follow-up time for severe Covid-19 in all persons, we considered only cases of severe illness that developed within 14 days after confirmation of infection. The date used for counting events of severe Covid-19 was defined as the date of the test confirming the infection that subsequently led to the severe illness.

Persons who received four doses were assigned to groups according to the numbers of weeks that had passed since receipt of the fourth dose; for each outcome, we estimated the incidence rate in each of these four-dose groups and in the two control groups. We calculated two rate ratios for each treatment group and each outcome: first, the ratio of the rate in the three-dose group to that in each four-dose group; and second, the ratio of the rate in the internal control group to that in each four-dose group. Note that the higher this rate ratio is, the greater the protection conferred by the fourth dose of vaccine. In addition, adjusted rate differences per 100,000 person-days during the study period were estimated with a method similar to that used in our previous analysis.[7] Confidence intervals were calculated by exponentiating the 95% confidence intervals for the regression coefficients, without adjustment for multiplicity. Thus, the confidence intervals should not be used to infer differences between study groups.

To check for possible biases, we performed several sensitivity analyses. First, we estimated the rate ratios for confirmed infection using an alternative statistical method that relied on matching (similar to that used by Dagan et al.[8]), as described in detail in the Supplementary Appendix; this approach could not be applied to the analysis of severe Covid-19 because of the small case numbers. Second, we examined the results of using data on infections confirmed only by PCR testing and excluding data on those confirmed by state-regulated antigen testing. Third, we repeated the analyses with data from the general Jewish population only. Fourth, we analyzed the data while accounting for the exposure risk over time in each person's area of residence. Fifth, we analyzed the data while accounting for the time of vaccination since the third dose. Further details of the sensitivity analyses are provided in the Supplementary Appendix.

## RESULTS

### STUDY POPULATION

A total of 1,252,331 persons met the criteria for inclusion in the study (Fig. 1). The total number of events and person-days at risk in each of the

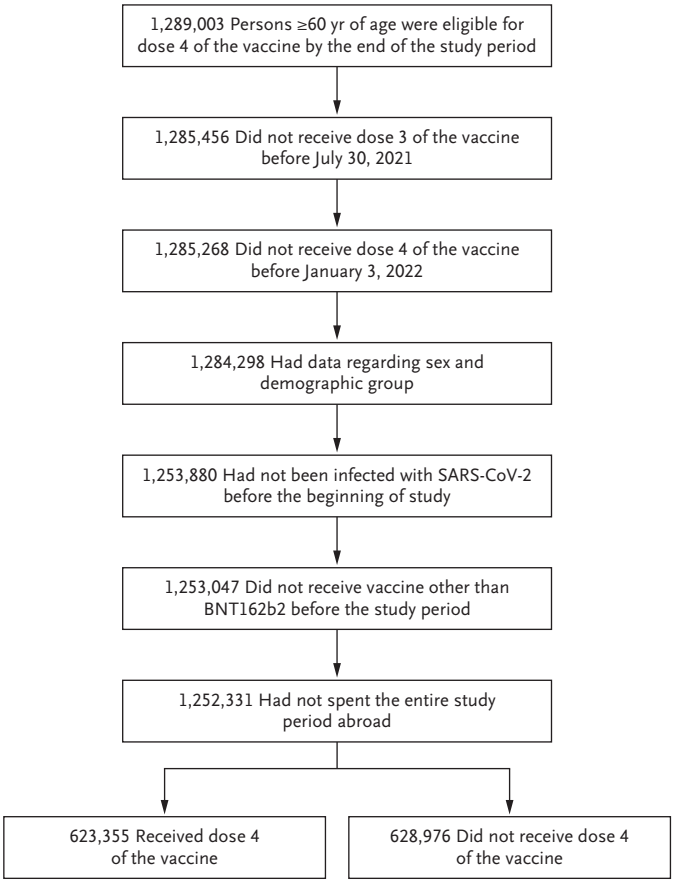


**Figure 1. Study Population.**

The study included persons who were 60 years of age or older who had not been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before the study period, were eligible for the fourth dose of the BNT162b2 vaccine by the end of the study period, had available data regarding sex and demographic group, had not stayed abroad for the entire study period, and had not received a coronavirus disease 2019 (Covid-19) vaccine other than BNT162b2 before the study period.

study groups, along with the distribution of covariates used in the analysis, are shown in Table 1, which provides statistics aggregated across weeks since receipt of the fourth dose from the second week onward. The information for each treatment group according to the week since receipt of the fourth dose is provided in Table S1. Overall, the distributions of covariates in the aggregated treatment groups are similar to those in the internal control group. As compared with the three-dose group, the aggregated four-dose groups and the internal control group included more person-days over the age of 80 years (24.9% and 25.1%, respectively, vs. 16.2%) and more person-days from the general Jewish population (94.2% and 93.7% vs. 84.4%). Those in the three-dose group had a larger number of risk days than did those in the aggregated four-dose groups (31.0 million person-days vs. 23.9 million person-days) but had more confirmed infections (111,780 vs. 42,325) and more severe cases (1210 vs. 355).

### PROTECTION CONFERRED BY THE FOURTH DOSE

As shown in Table 1, the unadjusted rate of confirmed infection was 177 cases per 100,000 person-days in the aggregated four-dose groups, 361 cases per 100,000 person-days in the three-dose group, and 388 cases per 100,000 person-days in the internal control group. The unadjusted rate of severe Covid-19 was 1.5 cases per 100,000 person-days in the aggregated four-dose groups, 3.9 cases per 100,000 person-days in the three-dose group, and 4.2 cases per 100,000 person-days in the internal control group.

The results of the quasi-Poisson regression analysis are summarized in Table 2 for confirmed infection and in Table 3 for severe illness. Figure 2 provides a graphical representation of the results for both confirmed infection and severe illness.

The adjusted rate of confirmed infection was lower in the four-dose groups than in the two control groups. The adjusted rate among persons in the fourth week (22 to 28 days) after receipt of the fourth dose was lower by a factor of 2.0 (95% confidence interval [CI], 1.9 to 2.1) than that in the three-dose group and was lower by a factor of 1.8 (95% CI, 1.7 to 1.9) than that in the internal control group. The adjusted rate of confirmed infection (after rounding) in the fourth week after the fourth dose was 171 cases per 100,000 person-days (95% CI, 165 to 177), as compared with 340 cases per 100,000 person-days (95% CI, 337 to 343) in the three-dose group and 308 cases per 100,000 person-days (95% CI, 299 to 317) in the internal control group (Table S2). In the analysis of adjusted rate differences, the group in the fourth week after the fourth dose had 170 fewer confirmed infections per 100,000 person-days (95% CI, 162 to 176) than the three-dose group, and 137 fewer confirmed infections per 100,000 person-days (95% CI, 125 to 148) than the internal control group. From the fifth week (29 to 35 days) onward, the rate ratio for confirmed infection started to decline. The adjusted rate of infection in the eighth week after

**Table 1. Demographic and Clinical Characteristics of the Persons in the Study Groups.***

| Population | Aggregated Four-Dose Groups† | | | Three-Dose Group‡ | | | Internal Control Group§ | | |
|---|---|---|---|---|---|---|---|---|---|
| | % Person-Days at Risk | No. of Infections (Cases per 100,000 Person-Days) | No. of Severe Cases (Cases per 100,000 Person-Days) | % Person-Days at Risk | No. of Infections (Cases per 100,000 Person-Days) | No. of Severe Cases (Cases per 100,000 Person-Days) | % Person-Days at Risk | No. of Infections (Cases per 100,000 Person-Days) | No. of Severe Cases (Cases per 100,000 Person-Days) |
| Total | 100 | 42,325 (177) | 355 (1.5) | 100 | 111,780 (361) | 1210 (3.9) | 100 | 10,531 (388) | 114 (4.2) |
| Women | 51.8 | 20,646 (166) | 154 (1.2) | 55.1 | 62,531 (366) | 499 (2.9) | 52.6 | 5,135 (360) | 54 (3.8) |
| Men | 48.2 | 21,679 (188) | 201 (1.7) | 44.9 | 49,249 (354) | 711 (5.1) | 47.4 | 5,396 (419) | 60 (4.7) |
| Age group | | | | | | | | | |
| 60–69 yr | 32.5 | 16,701 (214) | 41 (0.5) | 52.0 | 69,198 (429) | 193 (1.2) | 33.6 | 4,302 (471) | 8 (0.9) |
| 70–79 yr | 42.5 | 16,349 (161) | 102 (1.0) | 31.8 | 30,817 (313) | 363 (3.7) | 41.3 | 3,965 (353) | 33 (2.9) |
| ≥80 yr | 24.9 | 9,275 (155) | 212 (3.6) | 16.2 | 11,765 (235) | 654 (13.0) | 25.1 | 2,264 (332) | 73 (10.7) |
| Population | | | | | | | | | |
| General Jewish | 94.2 | 39,886 (177) | 319 (1.4) | 84.4 | 95,708 (366) | 965 (3.7) | 93.7 | 9,688 (381) | 98 (3.9) |
| Ultra-Orthodox Jewish | 2.7 | 1,119 (176) | 12 (1.9) | 4.6 | 5,262 (372) | 67 (4.7) | 2.7 | 500 (676) | 5 (6.8) |
| Arab | 3.1 | 1,320 (176) | 24 (3.2) | 11.1 | 10,810 (315) | 178 (5.2) | 3.6 | 343 (349) | 11 (11.2) |

* Percentages of person-days at risk (in the analysis of confirmed infections) are shown instead of numbers of persons, since persons could move among the study groups. Days at risk and rates of infection were calculated for the study period January 10 to March 2, 2022. Severe cases were defined as cases of severe coronavirus disease 2019 (Covid-19) occurring within 14 days after confirmation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the period January 10 to February 18, 2022.
† The total number of person-days at risk in the aggregated four-dose groups (i.e., persons who had received a fourth dose of BNT162b2 vaccine at least 8 days earlier) was 23,935,905.
‡ The total number of person-days at risk in the three-dose group (i.e., persons who were eligible for a fourth dose of BNT162b2 but had not yet received it) was 31,000,299.
§ The total number of person-days at risk in the internal control group (i.e., persons who had received a fourth dose of BNT162b2 only 3 to 7 days earlier) was 2,673,874.

**Table 2.** Results of the Quasi-Poisson Regression Analysis of Confirmed SARS-CoV-2 Infection.*

| Group (Days since Dose 4) | No. of Confirmed Infections (Person-Days at Risk) | Adjusted Rate Ratio (95% CI) | | Adjusted Rate Difference (95% CI) | |
|---|---|---|---|---|---|
| | | Comparison with Three-Dose Group | Comparison with Internal Control Group | Comparison with Three-Dose Group | Comparison with Internal Control Group |
| | | | | *cases/100,000 person-days at risk* | |
| Three-dose group | 111,780 (31,000,299) | Reference | — | Reference | — |
| Internal control group (3–7) | 10,531 (2,717,489) | 1.1 (1.1 to 1.1) | Reference | 33 (23 to 42) | Reference |
| Four-dose groups | | | | | |
| Week 2 (8–14) | 12,840 (4,181,768) | 1.5 (1.5 to 1.6) | 1.4 (1.3 to 1.4) | 115 (109 to 121) | 82 (72 to 93) |
| Week 3 (15–21) | 8,926 (4,041,309) | 2.1 (2.0 to 2.1) | 1.9 (1.8 to 1.9) | 175 (169 to 181) | 142 (132 to 152) |
| Week 4 (22–28) | 7,225 (3,883,824) | 2.0 (1.9 to 2.1) | 1.8 (1.7 to 1.9) | 170 (162 to 176) | 137 (125 to 148) |
| Week 5 (29–35) | 5,611 (3,701,580) | 1.7 (1.6 to 1.7) | 1.5 (1.4 to 1.6) | 136 (127 to 145) | 103 (90 to 115) |
| Week 6 (36–42) | 3,686 (3,479,549) | 1.5 (1.4 to 1.6) | 1.4 (1.3 to 1.5) | 116 (103 to 127) | 83 (68 to 100) |
| Week 7 (43–49) | 2,666 (3,040,564) | 1.2 (1.2 to 1.3) | 1.1 (1.0 to 1.2) | 67 (50 to 83) | 35 (15 to 53) |
| Week 8 (50–56) | 1,304 (1,547,985) | 1.1 (1.0 to 1.2) | 1.0 (0.9 to 1.1) | 22 (–10 to 52) | –10 (–43 to 20) |

* Rate ratios and rate differences were calculated for the three-dose group or internal control group as compared with the indicated groups in the left-hand column. For example, the rate ratio in the three-dose group as compared with the four-dose group at 4 weeks after the fourth dose was 2.0, indicating that the rate of confirmed infection was lower in the fourth week after the fourth dose by a factor of 2.0. CI denotes confidence interval.

the fourth dose was very similar to those in the control groups; the rate ratio for the three-dose group as compared with the four-dose group was 1.1 (95% CI, 1.0 to 1.2), and the rate ratio for the internal control group as compared with the four-dose group was only 1.0 (95% CI, 0.9 to 1.1).

The rate ratios comparing the control groups with the four-dose groups were larger and longer-lasting for severe Covid-19. For persons in the fourth week after receipt of the fourth dose, the adjusted rate of severe illness was lower by a factor of 3.5 (95% CI, 2.7 to 4.6) than that in the three-dose group and was lower by a factor of 2.3 (95% CI, 1.7 to 3.3) than that in the internal control group. The adjusted rate of severe Covid-19 (after rounding) in the fourth week after the fourth dose was 1.6 cases per 100,000 person-days (95% CI, 1.2 to 2.0), as compared with 5.5 cases per 100,000 person-days (95% CI, 5.2 to 5.9) in the three-dose group and 3.6 cases per 100,000 person-days (95% CI, 3.0 to 4.5) in the internal control group (Table S2). The adjusted rate differences were 3.9 fewer cases per 100,000 person-days (95% CI, 3.4 to 4.5) and 2.1 fewer cases per 100,000 person-days (95% CI, 1.4 to 3.0) than the three-dose group and the internal control group, respectively. Severe illness continued to occur at lower rates in the four-dose groups than in the control groups in later weeks after receipt of the fourth dose, and no signs of waning were evident by the sixth week after receipt of the fourth dose (Fig. 2).

### SENSITIVITY ANALYSES

The results of the matched analysis of confirmed infection were similar to the results obtained in the main analysis (Fig. S3). In addition, restricting the quasi-Poisson regression analysis to the general Jewish population, adding as a covariate the exposure risk over time in each individual's area of residence, or adding as a covariate the time since administration of the third dose did not substantially change the results of the main analysis (Figs. S4 and S5).

As described in the Supplementary Appendix, the testing policy in Israel was changed in early January 2022 (before the study period) for persons younger than 60 years of age. Even though the testing policy for the study population (persons ≥60 years of age) did not change, we tested the possible effect of the type of diagnostic test used to confirm infection by repeating the analysis

counting only infections confirmed by positive PCR tests. This resulted in only very minor changes to the estimated level of protection conferred by the fourth dose (Figs. S4 and S5). In addition, we compared the testing rate and test type (PCR or antigen) among persons who received the fourth dose as compared with those who received only three doses and found the differences to be of limited extent (Fig. S2).

## DISCUSSION

The omicron variant is genetically divergent from the ancestral SARS-CoV-2 strain for which the BNT162b2 vaccine was tailored. The results presented here indicate that as compared with three vaccine doses given at least 4 months earlier, a fourth dose provides added short-term protection against confirmed infections and severe illness caused by the omicron variant. The incidence rate for confirmed infection was lower by a factor of 2 and the rate of severe disease lower by a factor of 3 among persons in the fourth week after receiving the fourth dose than among eligible persons who did not receive the fourth dose.

Comparing the rate ratio over time since the fourth dose (Fig. 2) suggests that the protection against confirmed infection with the omicron variant reaches a maximum in the fourth week after vaccination, after which the rate ratio decreases to approximately 1.1 by the eighth week; these findings suggest that protection against confirmed infection wanes quickly. In contrast, protection against severe illness did not appear to decrease by the sixth week after receipt of the fourth dose. More follow-up is needed in order to evaluate the protection of the fourth dose against severe illness over longer periods.

Although our analysis attempts to address biases such as confounding, some sources of bias may not have been measured or adequately controlled for — for example, behavioral differences between persons who received the fourth dose and those who did not. For severe illness, differences in the prevalence of coexisting conditions could potentially have affected the results; however, this information is not recorded in the national database, and therefore we did not adjust for such differences. Differences in coexisting conditions could also be associated with differential treatment with antiviral drugs such as ritonavir-boosted nirmatrelvir, which could have

**Table 3. Results of the Quasi-Poisson Regression Analysis of Severe Covid-19.***

| Group (Days from Vaccination) | No. of Severe Cases (Person-Days at Risk) | Adjusted Rate Ratio (95% CI) | | Adjusted Rate Difference (95% CI) | |
|---|---|---|---|---|---|
| | | Comparison with Three-Dose Group | Comparison with Internal Control Group | Comparison with Three-Dose Group | Comparison with Internal Control Group |
| | | | | *cases/100,000 person-days at risk* | |
| Three-dose group | 1210 (24,857,976) | Reference | — | Reference | — |
| Internal control group (3–7) | 114 (2,673,746) | 1.5 (1.2–1.9) | Reference | 1.8 (0.9–2.6) | Reference |
| Four-dose groups | | | | | |
| Week 2 (8–14) | 125 (4,073,168) | 2.4 (2.0–2.9) | 1.6 (1.2–2.1) | 3.2 (2.7–3.7) | 1.3 (0.6–2.2) |
| Week 3 (15–21) | 99 (3,868,314) | 2.9 (2.3–3.6) | 1.9 (1.4–2.6) | 3.6 (3.1–4.2) | 1.7 (1.0–2.7) |
| Week 4 (22–28) | 66 (3,639,393) | 3.5 (2.7–4.6) | 2.3 (1.7–3.3) | 3.9 (3.4–4.5) | 2.1 (1.4–3.0) |
| Week 5 (29–35) | 47 (3,277,662) | 3.4 (2.5–4.7) | 2.3 (1.6–3.3) | 3.9 (3.3–4.5) | 2.0 (1.2–3.0) |
| Week 6 (36–42) | 18 (2,133,014) | 4.3 (2.6–7.1) | 2.8 (1.6–4.9) | 4.2 (3.4–4.9) | 2.4 (1.3–3.4) |

* Rate ratios and rate differences were calculated for the three-dose group or internal control group as compared with the indicated groups in the left-hand column. For example, the rate ratio in the three-dose group as compared with the four-dose group at 4 weeks after the fourth dose was 3.5, indicating that the rate of severe Covid-19 was lower in the fourth week after the fourth dose by a factor of 3.5.

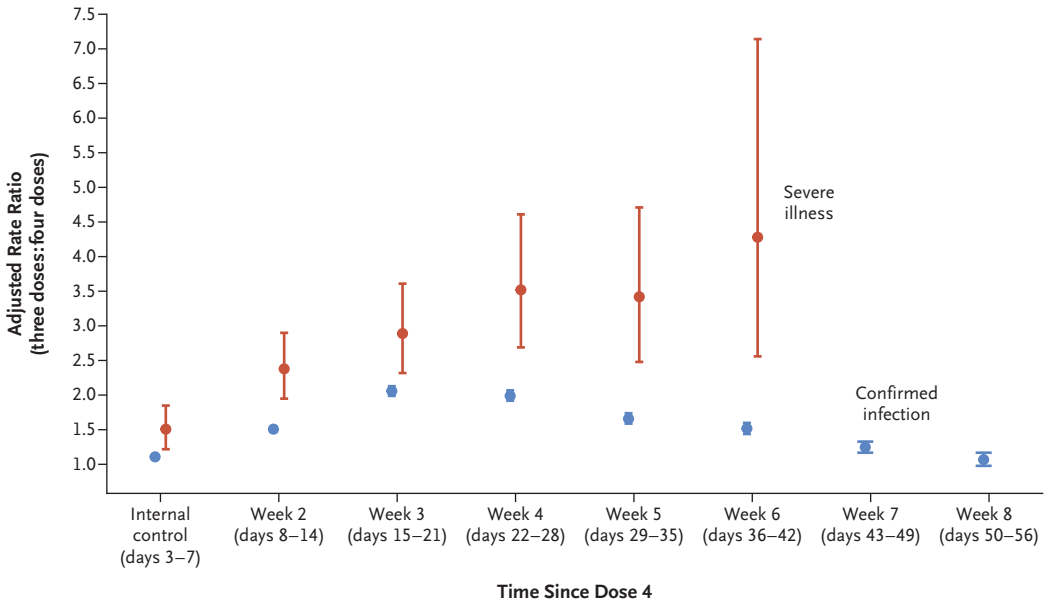


**Figure 2. Adjusted Rate Ratios for Confirmed Infection and Severe Illness.**

Shown are adjusted rate ratios for confirmed SARS-CoV-2 infection and severe Covid-19 in the group of persons eligible for a fourth dose who had not yet received it (three-dose group) as compared with those who had received a fourth dose, as a function of time since the fourth dose (the higher the rate ratio, the greater the protection conferred by the fourth dose of vaccine). Persons in the internal control group had received a fourth dose 3 to 7 days earlier (a period in which the fourth dose was not expected to affect the rate of confirmed infection or severe illness). Because of the 14-day follow-up period for severe Covid-19, the study period for this outcome was 2 weeks shorter than that for confirmed infection, and therefore the estimates of the adjusted rate ratio for severe illness end at week 6 instead of week 8.

affected the results. To address some of these biases, we compared the rate of confirmed infection and severe illness within the group of people who received the fourth dose. Estimates of the rate ratio during the first days after vaccination could include the effect of transient biases (Fig. S6). These potential biases include the "healthy vaccinee" bias,[9] in which people who feel ill tend not to get vaccinated in the following days, which leads to a lower number of confirmed infections and severe disease in the four-dose group during the first days after vaccination. Moreover, one would expect that detection bias due to behavioral changes, such as the tendency to perform fewer tests after vaccination, is more pronounced shortly after receipt of the dose.

Thus, we compared the rates of confirmed infections and severe illness at different weeks after the fourth dose, from the second week onward, with the rates on days 3 to 7 after its receipt, a period during which the transient biases would have diminished but before the vaccine would be expected to have affected the rate of the outcomes of interest.[6] The rate ratios obtained for confirmed infections were very similar to those obtained when comparing the treatment groups with the persons who did not receive a fourth dose. For severe illness, the rate ratios relative to the internal control group were lower than the rate ratios relative to the three-dose group. Even when the internal control group was the basis for comparison, the rate ratios for severe illness were still higher than those for confirmed infection and did not show signs of waning immunity.

In addition, several sensitivity analyses were performed to assess the robustness of the results to further potential biases. First, we performed the analyses using data only from the general Jewish population, since the participants in that group are more common in the population that received the fourth dose. Second, we included in the model the risk of exposure in the person's area of residence. The results of these analyses were similar to the results of the main analysis.

Overall, these analyses provided evidence for the effectiveness of a fourth vaccine dose against severe illness caused by the omicron variant, as compared with a third dose administered more than 4 months earlier. For confirmed infection, a fourth dose appeared to provide only short-term protection and a modest absolute benefit. Several reports have indicated that the protection against hospital admission conferred by a third dose given more than 3 months earlier is substantially lower against the omicron variant than the protection of a fresh third dose against hospital admission for illness caused by the B.1.617.2 (delta) variant.[1,10,11] In our study, a fourth dose appeared to increase the protection against severe illness relative to three doses that were administered more than 4 months earlier.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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