ORIGINAL ARTICLE

Protection against Covid-19 by BNT162b2 Booster across Age Groups

Yinon M. Bar-On, M.Sc., Yair Goldberg, Ph.D., Micha Mandel, Ph.D., Omri Bodenheimer, M.Sc., Laurence Freedman, Ph.D., Sharon Alroy-Preis, M.D., Nachman Ash, M.D., Amit Huppert, Ph.D., and Ron Milo, Ph.D.

ABSTRACT

BACKGROUND

After promising initial results from the administration of a third (booster) dose of the BNT162b2 messenger RNA vaccine (Pfizer–BioNTech) to persons 60 years of age or older, the booster campaign in Israel was gradually expanded to persons in younger age groups who had received a second dose at least 5 months earlier.

METHODS

We extracted data for the period from July 30 to October 10, 2021, from the Israel Ministry of Health database regarding 4,696,865 persons 16 years of age or older who had received two doses of BNT162b2 at least 5 months earlier. In the primary analysis, we compared the rates of confirmed coronavirus disease 2019 (Covid-19), severe illness, and death among those who had received a booster dose at least 12 days earlier (booster group) with the rates among those who had not received a booster (nonbooster group). In a secondary analysis, we compared the rates in the booster group with the rates among those who had received a booster 3 to 7 days earlier (early postbooster group). We used Poisson regression models to estimate rate ratios after adjusting for possible confounding factors.

RESULTS

The rate of confirmed infection was lower in the booster group than in the nonbooster group by a factor of approximately 10 (range across five age groups, 9.0 to 17.2) and was lower in the booster group than in the early postbooster group by a factor of 4.9 to 10.8. The adjusted rate difference ranged from 57.0 to 89.5 infections per 100,000 person-days in the primary analysis and from 34.4 to 38.3 in the secondary analysis. The rates of severe illness in the primary and secondary analyses were lower in the booster group by a factor of 17.9 (95% confidence interval [CI], 15.1 to 21.2) and 6.5 (95% CI, 5.1 to 8.2), respectively, among those 60 years of age or older and by a factor of 21.7 (95% CI, 10.6 to 44.2) and 3.7 (95% CI, 1.3 to 10.2) among those 40 to 59 years of age. The adjusted rate difference in the primary and secondary analyses was 5.4 and 1.9 cases of severe illness per 100,000 person-days among those 60 years of age or older and 0.6 and 0.1 among those 40 to 59 years of age. Among those 60 years of age or older, mortality was lower by a factor of 14.7 (95% CI, 10.0 to 21.4) in the primary analysis and 4.9 (95% CI, 3.1 to 7.9) in the secondary analysis. The adjusted rate difference in the primary and secondary analyses was 2.1 and 0.8 deaths per 100,000 person-days.

CONCLUSIONS

Across the age groups studied, rates of confirmed Covid-19 and severe illness were substantially lower among participants who received a booster dose of the BNT162b2 vaccine than among those who did not.

From the Department of Plant and Environmental Sciences, Weizmann Institute of Science, Rehovot (Y.M.B.-O., R.M.), Technion–Israel Institute of Technology, Haifa (Y.G.), the Department of Statistics and Data Science, Hebrew University of Jerusalem (M.M.), and Israel Ministry of Health (O.B., S.A.-P., N.A.), Jerusalem, the Biostatistical and Biomathematical Unit, Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Ramat Gan (L.F., A.H.), and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv (L.F., A.H.) — all in Israel. Dr. Goldberg can be contacted at yairgo@technion.ac.il or at the Faculty of Industrial Engineering and Management, Technion–Israel Institute of Technology, Technion City, Haifa 3200003, Israel.

Mr. Bar-On and Dr. Goldberg and Drs. Huppert and Milo contributed equally to this article.

This article was published on December 8, 2021, at NEJM.org.

N Engl J Med 2021;385:2421-30.
DOI: 10.1056/NEJMoa2115926

After a resurgence of confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and severe coronavirus disease 2019 (Covid-19) illness in Israel,[1] Israeli authorities approved on July 30, 2021, the administration of a booster dose of the BNT162b2 messenger RNA vaccine (Pfizer–BioNTech) for persons 60 years of age or older who had received a second dose of vaccine at least 5 months earlier. Initial reports have indicated that the booster dose was effective in reducing the rates of confirmed infection and severe disease against the currently dominant B.1.617.2 (delta) variant in the elderly population.[2,3] Consequently, the booster campaign was extended to younger age groups in a stepwise manner: on August 13 for those 50 to 59 years of age, on August 20 for those 40 to 49 years of age, on August 24 for those 30 to 39 years of age, and on August 29 for all persons 12 years of age or older.

Although observational studies suggest that the booster dose is effective against both confirmed infection and severe disease in the elderly population, the extent of protection of an additional dose in younger age groups requires further clarification. Here, we quantified the booster effect on the adult population (≥16 years of age) relying on the analytical framework used to estimate the effectiveness of the booster dose in the population 60 years of age or older.[2] The results also extend our previous analysis of the effect of the booster dose among those 60 years of age or older with a longer follow-up time and with Covid-19–associated death as an outcome.

Methods

General Approach

Our methods are similar to those applied by Bar-On et al.[2] with minor modifications. Full details are provided in the Methods section in Bar-On et al.[2] and in the protocol of that study, available with the full text of that article at NEJM.org.

Study Population

Our analysis is based on data from the Israel Ministry of Health database; details about the database are provided in the Supplementary Methods 1 section in the Supplementary Appendix, available with the full text of this article at NEJM.org. Following the methods of Bar-On et al.,[2] we extracted on October 12, 2021, data regarding Israeli residents 16 years of age or older who had been fully vaccinated (i.e., received two doses of BNT162b2) at least 5 months before the end of the study and were alive on the date that their age group became eligible for the booster dose, totaling 5,065,502 persons. Similarly to Bar-On et al.,[2] we excluded from the analysis persons whose data did not include information regarding sex or area of residence; who had tested positive for SARS-CoV-2 on a polymerase-chain-reaction (PCR) assay before the date that their age group became eligible; who had received a booster dose before July 30, 2021; who had been abroad during the entire study period (persons were considered as being abroad in the period from 10 days before to 10 days after their return to Israel); or who had been fully vaccinated before January 16, 2021. A total of 4,696,865 persons met the inclusion criteria for the analysis (Fig. 1).

The extracted data included vaccination dates (first, second, and third doses); information regarding PCR testing (sampling dates and results); the date of any Covid-19–related hospitalization; demographic variables, such as age, sex, and area of residence; demographic group (general Jewish, Arab, or ultra-Orthodox Jewish population), as determined by the participant's statistical area of residence (similar to a census block)[4]; clinical status (mild or severe disease); and vital status. Severe disease was defined according to the National Institutes of Health Covid-19 treatment guidelines[5] as a resting respiratory rate of more than 30 breaths per minute, an oxygen saturation of less than 94% while breathing ambient air, or a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of less than 300.[6]

Study Design

Each participant's study period started on the date of becoming eligible to receive the booster dose — that is, when the booster became available for that participant's age group and more than 5 months had passed since receipt of the second dose (the latter of these two events). The end dates were chosen as October 10, 2021, for confirmed infection; October 5, 2021, for severe illness; and September 7, 2021, for death. The dates for confirmed infection, severe illness, and death were chosen to allow at least 2 days for the PCR result, 7 days for the development of severe illness, and 35 days for death. For participants who were abroad during part of the study period, we

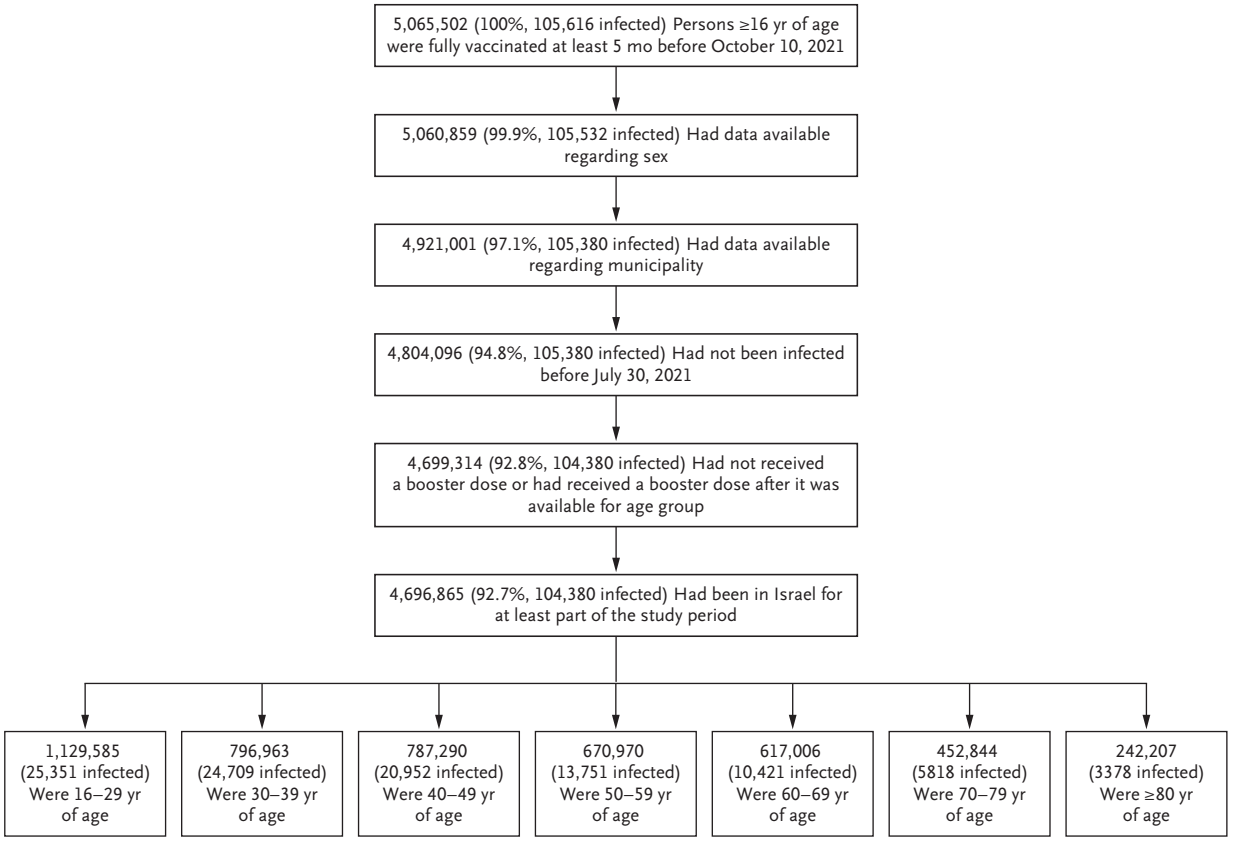

Figure 1. Study Population Derived from the Israel Ministry of Health Database.

excluded days at risk and Covid-19 outcomes during the period from 10 days before to 10 days after their return to Israel.

As in our previous study,[2] we calculated the rates of confirmed infection, severe illness, and death due to Covid-19 per person-days at risk in different dynamic groups: participants who had received a booster dose at least 12 days earlier (booster group) were compared with those who had not yet received the booster dose (nonbooster group) and, in a secondary analysis, with participants who had received a booster dose 3 to 7 days earlier (early postbooster group). The times of onset of severe Covid-19 and death were designated as the test date of confirmed infection.

OVERSIGHT

The study was approved by the institutional review board of the Sheba Medical Center. All the authors contributed to the writing and critical review of the manuscript, approved the final version, and made the decision to submit the manuscript for publication. The Israel Ministry of Health and Pfizer have a data-sharing agreement, but only the final results of this study were shared with Pfizer.

STATISTICAL ANALYSIS

We used the methods implemented by Bar-On et al.[2] with several modifications (details and comparisons with the original methods are provided in the Supplementary Analysis 2 section in the Supplementary Appendix). Briefly, we performed Poisson regression to estimate the rate of a specific outcome in a specific vaccination group, using the function for fitting generalized linear models in R statistical software.[7] These analyses were adjusted for the following covariates: sex, age group (16 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, 70 to 79 years, and ≥80 years), demographic group (general Jewish, Arab, and ultra-Orthodox Jewish population),[4] and the date of the second vaccine dose

(in half-month intervals). In addition, we accounted for environmental risk by including, as a time-varying covariate, a daily exposure risk index similar to that used by Goldberg et al.[8] based on the number of confirmed infections in the participant's area of residence during the past 7 days per 1000 residents. We categorized this quantity into 10 risk groups using the deciles of the variable. The 7-day moving average was chosen because the number of PCR tests typically drops on weekends.

We estimated adjusted rate ratios for confirmed infection, severe disease, and death due to Covid-19 between the booster group and the nonbooster group in different age groups by including interaction terms between age category and study group. The age categories for estimating the rate ratio were 16 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, and 60 or more years for confirmed infection; 40 to 59 years and 60 or more years for severe disease; and 60 or more years for death due to Covid-19. Grouping those 60 years of age or older allowed comparison with our previous estimates[2] (see the Supplementary Analysis 3 section and Tables S13 and S14 in the Supplementary Appendix for results involving a finer age subdivision). We restricted estimation of rate ratios to more limited age groups for severe disease (40 to 59 years and ≥60 years) and death (≥60 years) owing to smaller numbers of cases. Besides rate ratios, adjusted rate differences[9] were estimated between the various age groups (see the Supplementary Methods 2 section in the Supplementary Appendix). Uncertainty around rate ratio estimates was calculated by the exponent of the 95% confidence interval for the regression coefficient without adjustment for multiplicity.

In an additional analysis, we calculated the rate ratio of confirmed infection as a function of time after receipt of the booster dose. To this end, for each age group (16 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, and ≥60 years), we fitted a Poisson regression that included days after receipt of the booster dose as factors in the model. Each day until 12 days after receipt of the booster dose was considered as a separate factor, and days from day 12 onward were binned into intervals of 3 days (12 to 14 days, 15 to 17 days, and so on). The reference category comprised person-days before receipt of the booster dose.

As a sensitivity analysis, we analyzed the data using an alternative statistical method that relies on matching, similar to the method used by Dagan et al.[10] (see the Supplementary Analysis 1 section and Table S15 in the Supplementary Appendix). Briefly, each person who received a booster dose was matched with a person who had not yet received the booster and who shared a similar risk profile (on the basis of personal characteristics). The probabilities of confirmed infection during the period from day 12 after the booster dose until the end of the study were estimated for those receiving and those not receiving the booster dose with the use of the Kaplan–Meier method[10] and were compared.

RESULTS

STUDY POPULATION

Table 1 presents the characteristics of the participants in the booster, early postbooster (days 3 to 7), and nonbooster groups in terms of person-days at risk. We provide details on all model covariates in Table S3 and the same information within each age group in Tables S4 through S8.

The nonbooster group included approximately 98 million person-days, with 83,481 confirmed infections, 1171 cases of severe illness, and 298 deaths. The booster group included approximately 104 million person-days, with 6160 confirmed infections, 175 cases of severe illness, and 35 deaths. The early postbooster group included approximately 17 million person-days, with 8880 confirmed infections, 136 cases of severe illness, and 46 deaths. The percentage of person-days at risk was higher in the booster group than in the nonbooster group with respect to the general Jewish population (88.8% vs. 70.8%), an age of 70 years or older (28.6% vs. 11.2%), and receipt of a second vaccination dose in January 2021 (42.2% vs. 12.7%), and the percentage was lower in the booster group than in the nonbooster group with respect to an age younger than 40 years (18.5% vs. 46.9%). The early postbooster group was closer in its characteristics to the booster group, but the percentage of person-days at risk was higher in the booster group than in the early postbooster group with respect to an age of 70 years or older (28.6% vs. 18.6%) and receipt of a second vaccination dose in January 2021 (42.2% vs. 29.6%), and the percentage was lower in the booster group than in

Table 1. Demographic and Clinical Characteristics of the Study Population.*

Characteristic	Nonbooster Group				Booster Group				Early Postbooster Group			
	Person-days at Risk	Confirmed Infection	Severe Illness	Death	Person-days at Risk	Confirmed Infection	Severe Illness	Death	Person-days at Risk	Confirmed Infection	Severe Illness	Death
	percent	*number of cases*			*percent*	*number of cases*			*percent*	*number of cases*		
Sex												
Female	52.0	47,212	488	111	50.8	2995	68	12	51.2	4271	51	15
Male	48.0	36,269	683	187	49.2	3165	107	23	48.8	4609	85	31
Age distribution												
16–29 yr	27.2	22,441	10	0	9.3	317	0	0	18.4	1611	0	0
30–39 yr	19.7	21,452	16	1	9.2	842	1	0	14.5	1493	0	0
40–49 yr	16.9	16,885	49	2	13.8	1157	3	0	16.9	1794	3	0
50–59 yr	13.0	10,247	119	7	16.5	1011	5	1	15.8	1521	4	0
60–69 yr	12.0	7,037	233	44	22.6	1265	32	5	15.9	1274	20	4
70–79 yr	7.1	3,495	312	77	18.8	915	46	9	12.2	781	48	18
≥80 yr	4.1	1,924	432	167	9.8	653	88	20	6.4	406	61	24
Population												
General Jewish	70.8	61,584	923	252	88.8	5180	154	31	86.2	7558	125	43
Arab	23.6	14,293	188	33	7.1	536	11	1	9.6	617	7	2
Ultra-Orthodox Jewish	5.7	7,604	60	13	4.1	444	10	3	4.2	705	4	1
Vaccine period in 2021												
Jan. 16–31	12.7	9,598	449	135	42.2	2487	102	27	29.6	2615	84	33
Feb. 1–15	16.3	13,805	375	100	29.0	1802	53	5	25.5	2414	36	11
Feb. 16–28	14.9	14,330	116	27	14.5	1018	11	1	17.8	1855	9	2
Mar. 1–15	21.0	19,148	112	22	10.1	588	7	2	16.1	1341	4	0
Mar. 16–31	26.1	21,396	91	12	3.8	243	2	0	8.8	572	3	0
Apr. 1–15	7.0	4,456	23	2	0.4	20	0	0	1.7	76	0	0
Apr. 16–30	1.6	665	4	0	0.0	2	0	0	0.3	6	0	0
May 1–15	0.4	83	1	0	0.0	0	0	0	0.1	1	0	0

* The booster group includes participants who received the booster dose at least 12 days earlier, and the early postbooster group includes participants who received the booster dose 3 to 7 days earlier. The table presents the percentage of person-days at risk instead of the percentage of participants. Percentages may not total 100 because of rounding. Only person-days and events that were used in the main analysis are presented. Values are presented for the study period of July 30 to October 10, 2021. The number of person-days at risk was 98,112,120 in the nonbooster group, 104,202,554 in the booster group, and 16,978,846 in the early postbooster group.

Table 2. Poisson Regression Analysis of Confirmed Infections in Different Age Groups.*

Age	Nonbooster Group	Booster Group	Early Postbooster Group	Nonbooster Group vs. Booster Group		Early Postbooster Group vs. Booster Group	
	no. of confirmed infections (no. of person-days at risk)			Rate Ratio (95% CI)	Adjusted Rate Difference *events per 100,000 person-days*	Rate Ratio (95% CI)	Adjusted Rate Difference *events per 100,000 person-days*
≥60 yr	12,456 (22,803,132)	2833 (53,332,528)	2461 (5,844,835)	12.3 (11.8–12.8)	57.0	7.4 (7.0–7.8)	34.4
50–59 yr	10,247 (12,735,098)	1011 (17,239,405)	1521 (2,675,722)	12.2 (11.4–13.0)	69.0	7.2 (6.7–7.9)	38.3
40–49 yr	16,885 (16,560,386)	1157 (14,362,014)	1794 (2,866,033)	9.7 (9.2–10.3)	81.7	5.4 (5.0–5.8)	38.2
30–39 yr	21,452 (19,338,294)	842 (9,541,493)	1493 (2,470,306)	9.0 (8.4–9.7)	89.5	4.9 (4.5–5.3)	36.9
16–29 yr	22,441 (26,675,210)	317 (9,727,114)	1611 (3,121,950)	17.2 (15.4–19.2)	72.2	10.8 (9.6–12.2)	35.7

* For each group, we provide the number of confirmed infections, the total number of person-days at risk, and the estimated rate ratio and adjusted rate difference for the primary analysis (no booster vaccination relative to ≥12 days after booster vaccination) and the secondary analysis (3 to 7 days after booster vaccination relative to ≥12 days after booster vaccination). CI denotes confidence interval.

the early postbooster group with respect to an age younger than 40 years (18.5% vs. 32.9%). We adjusted for these substantial between-group differences by including these variables as covariates in the Poisson regression model.

EFFECT OF THE BOOSTER DOSE ACROSS AGE GROUPS

The detailed results of the Poisson regression analysis for confirmed infection, severe illness, and death are provided in Tables S9 through S12 and are summarized in Tables 2 and 3. The rate of confirmed infection was lower in the booster group than in the nonbooster group by a similar factor across age groups: 12.3 (95% confidence interval [CI], 11.8 to 12.8) among those 60 years of age or older, 12.2 (95% CI, 11.4 to 13.0) among those 50 to 59 years of age, 9.7 (95% CI, 9.2 to 10.3) among those 40 to 49 years of age, 9.0 (95% CI, 8.4 to 9.7) among those 30 to 39 years of age, and 17.2 (95% CI, 15.4 to 19.2) among those 16 to 29 years of age. The adjusted difference in the rate of confirmed infection between the nonbooster group and the booster group was 57.0 infections per 100,000 person-days among those 60 years of age or older, 69.0 among those 50 to 59 years of age, 81.7 among those 40 to 49 years of age, 89.5 among those 30 to 39 years of age, and 72.2 among those 16 to 29 years of age. The rate of confirmed infection at least 12 days after receipt of the booster dose was also substantially lower than the rate 3 to 7 days after receipt of the booster. The infection rate was lower by a factor of 7.4 (95% CI, 7.0 to 7.8) among those 60 years of age or older, by 7.2 (95% CI, 6.7 to 7.9) among those 50 to 59 years of age, by 5.4 (95% CI, 5.0 to 5.8) among those 40 to 49 years of age, by 4.9 (95% CI, 4.5 to 5.3) among those 30 to 39 years of age, and by 10.8 (95% CI, 9.6 to 12.2) among those 16 to 29 years of age.

The rate of severe illness was lower in the booster group than in the nonbooster group across the two age groups studied: by a factor of 17.9 (95% CI, 15.1 to 21.2) among those 60 years of age or older and by a factor of 21.7 (95% CI, 10.6 to 44.2) among those 40 to 59 years of age. The adjusted difference in the rate of severe illness between the nonbooster group and the booster group was 5.4 cases per 100,000 person-days among those 60 years of age or older and 0.6 cases per 100,000 person-days among those 40 to 59 years of age. In the secondary analysis,

Table 3. Poisson Regression Analysis of Severe Illness and Death Due to Coronavirus Disease 2019 in the Older Age Groups.*

Outcome	Age	Nonbooster Group	Booster Group	Early Postbooster Group	Nonbooster Group vs. Booster Group		Early Postbooster Group vs. Booster Group	
					Rate Ratio (95% CI)	Adjusted Rate Difference	Rate Ratio (95% CI)	Adjusted Rate Difference
	yr	*no. of cases (no. of person-days at risk)*				*events per 100,000 person-days*		*events per 100,000 person-days*
Severe illness	≥60	977 (22,135,011)	166 (46,668,795)	129 (5,733,307)	17.9 (15.1–21.2)	5.4	6.5 (5.1–8.2)	1.9
Severe illness	40–59	168 (27,599,399)	8 (25,890,717)	7 (5,141,634)	21.7 (10.6–44.2)	0.6	3.7 (1.3–10.2)	0.1
Death	≥60	288 (17,909,789)	34 (16,768,943)	46 (5,379,829)	14.7 (10.0–21.4)	2.1	4.9 (3.1–7.9)	0.8

* For each group and outcome, we provide the number of cases, the total number of person-days at risk, and the estimated rate ratio and adjusted rate difference for the primary analysis (nonbooster group relative to booster group) and the secondary analysis (early postbooster group relative to booster group).

the rate of severe illness 12 or more days after the booster was lower than the rate 3 to 7 days after the booster by a factor of 6.5 (95% CI, 5.1 to 8.2) among those 60 years of age or older and by a factor of 3.7 (95% CI, 1.3 to 10.2) among those 40 to 59 years of age. The rate of severe disease in the youngest age groups (16 to 29 and 30 to 39 years of age) was very low, and there were not enough cases to estimate the rate ratio reliably (26 cases in the nonbooster group, 1 case in the booster group, and no cases in the early postbooster group).

Among participants 60 years of age or older, the rate of Covid-19–associated death in the booster group was lower than in the nonbooster group by a factor of 14.7 (95% CI, 10.0 to 21.4). The adjusted rate difference between the nonbooster group and the booster group was 2.1 cases per 100,000 person-days. The rate of Covid-19–associated death 12 or more days after receipt of the booster dose was lower than the rate 3 to 7 days after receipt of the booster by a factor of 4.9 (95% CI, 3.1 to 7.9).

We also estimated the reduction in the rate of confirmed infection in the booster group as compared with the nonbooster group as a function of time after booster vaccination across the different age groups. As shown in Figure 2, a similar temporal pattern was seen in the different age groups: the rate of confirmed infection was lower in the booster group than in the nonbooster group by a factor of approximately 10. Of note, in all age groups, the rate of confirmed infection was lower in the early postbooster group than in the nonbooster group. We provide details on the possible source for this effect in the Discussion section.

The sensitivity analysis that used matching resulted in the following estimates (summarized in Table S15) for the factor by which the rate of confirmed infection in the booster group was lower than that in the nonbooster group: 9.5 (95% CI, 7.8 to 11.4) among those 60 years of age or older, 9.4 (95% CI, 5.2 to 13.0) among those 50 to 59 years of age, 8.4 (95% CI, 6.2 to 10.6) among those 40 to 49 years of age, 7.3 (95% CI, 5.7 to 8.7) among those 30 to 39 years of age, and 13.3 (95% CI, 5.9 to 18.8) among those 16 to 29 years of age. For severe illness, this approach yielded an estimated factor of 12.4 (95% CI, 4.3 to 30.4) among those 60 years of age or older.

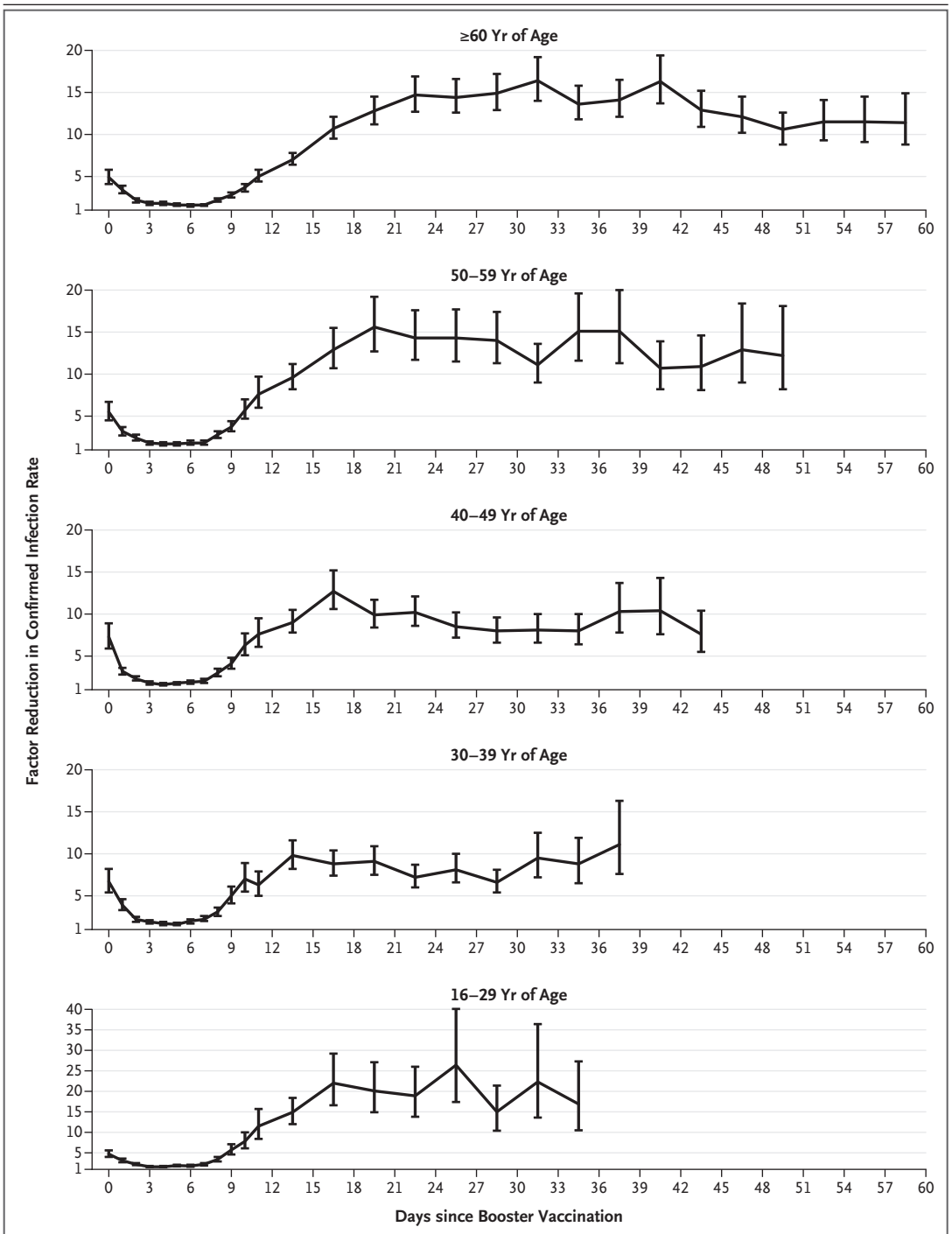

Figure 2. Reduction in Rate of Confirmed Infection in the Booster Group as Compared with the Nonbooster Group.
Shown is the factor reduction in the rate of confirmed infection among participants who received a third (booster) dose of the BNT162b2 vaccine as compared with those who did not receive a booster dose, according to the number of days after the administration of the booster dose, for different age groups. The I bars represent 95% confidence intervals, which have not been corrected for multiplicity.

DISCUSSION

We sought to determine whether the booster dose had a similar effect across different age groups and have indeed found that the booster dose reduced the rate of confirmed infection and severe illness by a similar factor in the age groups studied (although in the youngest age group, a larger reduction factor against confirmed infections was observed). The temporal pattern of the rate ratio between the booster group and the nonbooster group after booster vaccination was also similar across age groups. These findings are consistent with those of the phase 2–3 clinical trial of the BNT162b2 vaccine,[11] in which vaccine efficacy was similar across age groups.

Although in our primary analysis we attempted to address confounding and detection bias, some sources of bias may not have been measured or corrected adequately. These biases might include differences between booster recipients and those who chose not to receive the booster with respect to risk-avoidance behaviors and coexisting conditions, neither of which are recorded in the national database. Moreover, participants' risk-avoidance behavior and propensity to perform PCR tests are probably modified after receipt of the booster dose. In our secondary analysis, we tried to reduce the extent of confounding bias between the booster group and the nonbooster group by focusing solely on persons who received the booster dose and comparing rates during a period in which the booster was expected to have a small effect (days 3 to 7 after vaccination) with those during a period in which it had become effective (≥12 days after vaccination).

Although this type of analysis reduces confounding bias, because all participants potentially contribute days at risk to both groups, estimates of the rate ratio during the first days after vaccination could include the effect of transient biases. These potential biases include the "healthy vaccinee" bias,[12] in which people who feel ill tend not to get vaccinated in the following days, leading to a lower number of infections in the booster 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 PCR tests after booster vaccination is more pronounced just after receiving the dose (days 3 to 7) and that this bias declines over time. Thus, potential behavioral biases under this approach are expected to underestimate the true rate ratio. The secondary analysis showed a decrease in the rate of confirmed infection across age groups by a factor of approximately 5. Although the primary and secondary analyses were exposed to different biases and resulted in somewhat different estimates, both suggested a notable reduction in the rate of confirmed infections. With respect to severe illness in the booster group as compared with the nonbooster group (Table 3), the analysis shows decreased rates of severe Covid-19 in both age groups considered, but with wider confidence intervals owing to the lower number of cases of severe illness in those 40 to 59 years of age.

As compared with our previous analysis of the elderly population,[2] we made two methodologic modifications in the current analysis. First, instead of including indicators for calendar dates in order to adjust for exposure risk, we calculated a spatial–temporal index of risk according to the number of infections in each area of residence. This method better measures the exposure risk for each participant. Second, in our secondary analysis, we compared the rates 12 or more days after receipt of the booster with the rates 3 to 7 days after its receipt, instead of 4 to 6 days. This change was made to increase the number of person-days at risk in the early postbooster group and enabled us to apply the secondary analysis to severe Covid-19 as well.

Understanding the protective effect of the booster dose in younger age groups is key for forming public health policy. Booster vaccination programs may provide a way to control transmission without costly social-distancing measures and quarantines. Our findings provide evidence for the short-term effectiveness of the booster dose against the currently dominant delta variant in persons 16 years of age or older. Future studies will help determine the longer-term effectiveness of the booster dose against current and emerging variants.

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

We thank Ronen Fluss for productive feedback on an earlier version of the manuscript.

REFERENCES

1. Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity of the BNT162b2 vaccine: a nationwide study from Israel. August 30, 2021 (https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1). preprint.
2. Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. N Engl J Med 2021;385:1393-400.
3. Patalon T, Gazit S, Pitzer VE, et al. Short term reduction in the odds of testing positive for SARS-CoV-2; a comparison between two doses and three doses of the BNT162b2 vaccine. August 31, 2021 (https://www.medrxiv.org/content/10.1101/2021.08.29.21262792v1). preprint.
4. Muhsen K, Na'aminh W, Lapidot Y, et al. A nationwide analysis of population group differences in the COVID-19 epidemic in Israel, February 2020–February 2021. Lancet Reg Health Eur 2021;7:100130.
5. COVID-19 treatment guidelines: clinical spectrum of SARS-CoV-2 infection. Bethesda, MD: National Institutes of Health, 2021 (https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/).
6. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet 2021;397:1819-29.
7. R Core Team. The R project for statistical computing. The R Foundation, 2020 (https://www.r-project.org/).
8. Goldberg Y, Mandel M, Woodbridge Y, et al. Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: a three-month nationwide experience from Israel. April 24, 2021 (https://www.medrxiv.org/content/10.1101/2021.04.20.21255670v1). preprint.
9. Kleinman LC, Norton EC. What's the risk? A simple approach for estimating adjusted risk measures from nonlinear models including logistic regression. Health Serv Res 2009;44:288-302.
10. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384:1412-23.
11. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-15.
12. Remschmidt C, Wichmann O, Harder T. Frequency and impact of confounding by indication and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic review. BMC Infect Dis 2015;15:429.