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Odds of Testing Positive for SARS-CoV-2 Following Receipt of 3 vs 2 Doses of the BNT162b2 mRNA Vaccine

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➕ Supplemental content

IMPORTANCE With the evidence of waning immunity of the mRNA vaccine BNT162b2 (Pfizer-BioNTech), a nationwide third-dose (booster) vaccination campaign was initiated in Israel during August 2021; other countries have begun to administer a booster shot as well.

OBJECTIVE To evaluate the initial short-term additional benefit of a 3-dose vs a 2-dose regimen against infection of SARS-CoV-2.

DESIGN, SETTING, AND PARTICIPANTS This preliminary retrospective case-control study used 2 complementary approaches: a test-negative design and a matched case-control design. Participants were included from the national centralized database of Maccabi Healthcare Services, an Israeli healthcare maintenance organization covering 2.5 million members. Data were collected between March 1, 2020, and October 4, 2021, and analyses focused on the period from August 1, 2021, to October 4, 2021, because the booster dose was widely administered from August 1 onward.

EXPOSURES Either 2 doses or 3 doses of the BNT162b2 vaccine.

MAIN OUTCOMES AND MEASURES The reduction in the odds of a positive SARS-CoV-2 polymerase chain reaction (PCR) test at different time intervals following receipt of the booster dose (0-6, 7-13, 14-20, 21-27, and 28-65 days) compared with receiving only 2 doses.

RESULTS The study population included 306 710 members of Maccabi Healthcare Services who were 40 years and older (55% female) and received either 2 or 3 doses of the BNT162b2 vaccine and did not have a positive PCR test result for SARS-CoV-2 prior to the start of the follow-up period. During this period, there were 500 232 PCR tests performed, 227 380 among those who received 2 doses and 272 852 among those who received 3 doses, with 14 989 (6.6%) and 4941 (1.8%) positive test results in each group, respectively. Comparing those who received a booster and those who received 2 doses, there was an estimated odds ratio of 0.14 (95% CI, 0.13-0.15) 28 to 65 days following receipt of the booster (86% reduction in the odds of testing positive for SARS-CoV-2).

CONCLUSION AND RELEVANCE Previous studies have demonstrated that vaccine-derived protection against SARS-CoV-2 wanes over time. In this case-control analysis, we showed an association between receipt of the booster dose and a reduction in the odds of testing positive for SARS-CoV-2, potentially countering waning immunity in the short term. Further monitoring of data from this population is needed to determine the duration of immunity following the booster.

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The short-term effectiveness of a 2-dose regimen of the mRNA vaccine BNT162b2 (Pfizer-BioNTech) against SARS-CoV-2 was demonstrated both in clinical trials[1,2] and real-world settings.[3,4] However, long-term effectiveness remains undetermined, and there is evidence of waning immunity in terms of antibody dynamics[5-7] and protection against infection.[8]

The Delta variant of SARS-CoV-2 was the dominant strain in Israel during the summer of 2021 (responsible for >99% of cases) and caused a rapidly growing number of cases, many in vaccinated individuals.[9] A national third-dose (booster) vaccination campaign was initiated in Israel on August 1, 2021. As of August 24, 2021, a booster dose was recommended for everyone 30 years and older, as well as for high-risk populations.[10] Current guidelines state that a minimum interval of 5 months since receipt of the second dose is required to be eligible for the booster dose, and the booster was introduced in older age groups first. By October 4, 2021, more than 3.6 million individuals had received a booster dose.[9] Boosters are also now recommended in other countries, including the US.

Few studies on a third-dose regimen have been published to date, and most are in high-risk populations, such as patients who have undergone solid organ transplant.[11,12] These studies reported adequate antibody responses, though follow-up time was short and cohort sizes were small. Another nationwide study from Israel indicated a reduction in infections and hospitalizations following receipt of the booster.[13] However, they were unable to adjust for chronic health conditions or changes in testing practice.

To this end, we conducted a preliminary retrospective study aimed at evaluating the additional protection afforded to those receiving a third booster dose of the BNT162b2 vaccine compared with those receiving a 2-dose regimen over the short term. These analyses leveraged data from Maccabi Healthcare Services (MHS), Israel's second-largest health maintenance organization, which covers 2.5 million members.

In this case-control study, we hypothesized that receipt of the booster dose would be associated with a decreased risk of SARS-CoV-2 infection compared with receiving 2 doses and that this would be evident within a couple of weeks of receipt of the booster. We used 2 complementary approaches to evaluate the marginal benefit of the third dose, both previously undertaken to evaluate the effectiveness of vaccines against SARS-CoV-2 and each with its own limitations: a test-negative design and a matched case-control design.

Methods

Data Collection and Study Population

Maccabi Healthcare Services is a 2.5 million–member, not-for-profit health maintenance organization. It is the second-largest health fund in Israel and covers 26% of the population. The study population consisted of MHS members who were 40 years and older and received either 2 or 3 doses of the BNT162b2 vaccine. Anonymized electronic medical records were retrieved from MHS's centralized computerized database. Analyses focused on the period from August 1, 2021 (when the booster dose was first

Key Points

Question What is the additional reduction in the odds of infection with SARS-CoV-2 in people receiving a third dose (booster) of the BNT162b2 (Pfizer-BioNTech) vaccine compared with those receiving 2 doses?

Findings In this case-control study that included 306 710 Israeli adults 40 years and older, there was an estimated significant reduction in the odds of SARS-CoV-2 infection within a few weeks of receiving the booster compared with receiving just the 2 primary doses. Those receiving the booster also had lower odds of hospitalization.

Meaning The findings of this study suggest that the waning of vaccine-induced protection against SARS-CoV-2 infection seems to be counteracted in the short-term by a third dose and further monitoring is needed to determine the duration of immunity following the booster.

widely administered among eligible individuals), to October 4, 2021. Only those who had received their second dose of the vaccine at least 150 days prior (ie, those eligible for a booster) were included in the analysis. Participants were excluded from the study if they disengaged from MHS for any reason prior to March 2020 or if they tested positive for COVID-19 by a polymerase chain reaction (PCR) test before the start of the follow-up period. A person could not have a documented positive test and then contribute another test (positive or negative) in the future.

Individual-level data for the study population included age (in 10-year age categories), biological sex, socioeconomic status (SES) index, and a coded geographical statistical area (the smallest geostatistical unit assigned by Israel's Central Bureau of Statistics, which corresponds to neighborhoods). The SES index was measured on a scale from 1 (lowest) to 10 (highest) based on several parameters, including household income, educational qualifications, household crowding, and car ownership. Data collected also encompassed the last documented body mass index (BMI; calculated as weight in kilograms divided by height in meters squared, where obesity was defined as BMI ≥30) and information on chronic diseases from MHS's automated registries, including cardiovascular diseases (CVDs),[14] hypertension,[15] diabetes,[16] chronic kidney disease,[17] chronic obstructive pulmonary disease, and immunocompromised conditions, as well as data on cancer from the National Cancer Registry.[18] The definitions of these comorbidities in this data set have been previously described and validated.[14-17] The registry of immunosuppressed individuals includes those with immunocompromised conditions, such as recipients of hematopoietic stem cells, patients who have undergone solid organ transplant, patients receiving immunosuppressive therapy, asplenic individuals, and those with chronic kidney failure. COVID-19–related information included dates of the first, second, and third doses of the vaccine (if received) and results of any PCR tests for SARS-CoV-2, including tests performed outside of MHS. For those hospitalized with COVID-19, the database also contained the date of hospital admission. For individuals with multiple recorded hospital admissions, we only counted the first instance.

This study was approved by the MHS institutional review board. Owing to the retrospective design of the study, patient informed consent was waived by the institutional review board, and all identifying details of the participants were removed before computational analysis.

Statistical Analysis

Primary Analysis: Test-Negative Design

For the main analysis, we used a test-negative design,[19,20] in which *cases* were defined as those who had a positive PCR test result for SARS-CoV-2 and *controls* were those with negative test results. Individuals could contribute multiple negative test results to the analysis but were excluded once they tested positive. If multiple tests were conducted within a 5-day period, the day of test was considered to be the last day of that test series. In sensitivity analyses, we included all tests regardless of serial testing or defined the day of the test to be the first in the series; the results were unchanged. The analysis sought to estimate the reduction in the odds of a positive test result at different time intervals following receipt of the booster (third) dose (0-6, 7-13, 14-20, 21-27, and 28-65 days) compared with those receiving only 2 doses. The 7- and 14-day cutoffs for the third dose were chosen based on second-dose research.[3,4] We did not expect the vaccine to induce an immune response during the first 7 days following its receipt; therefore, this served as a negative control period.

We used backward selection to identify covariates to include in the final model, starting with the available variables and removing nonsignificant ones. The final model included the 10-year age category, biological sex, and certain comorbidities (diabetes, immunosuppression status, BMI ≥30, CVD). The SES category, chronic obstructive pulmonary disease, hypertension, and chronic kidney disease were included in the full initial model but were not significant and not included in the final model; their inclusion and/or exclusion did not influence the estimates of the effect of the booster dose. An additional covariate consisted of the number of positive tests performed on that day throughout the population (log-transformed) to adjust for variability in level of exposure at different time points. In sensitivity analyses, we evaluated 2 alternative ways to adjust for time-varying infection risk, by using a covariate consisting of the number of positive tests per day stratified by socioeconomic level, or by using a series of dummy variables representing a calendar week. These alternatives yielded estimates of vaccine effectiveness that were similar to the results presented in the main analysis.

A generalized estimating equation logistic regression model was fit to the data. The marginal benefit of the third dose (compared with receiving 2 doses) was calculated as 100% × [1 − (odds ratio)] for each of the booster dose time categories. This is analogous to a standard vaccine effectiveness estimate but adjusting for vaccination history. The odds ratio should approximate the risk ratio for these analyses. Importantly, this quantity provides a measure of the relative benefit of the booster dose compared with the 2-dose regimen but not the total effectiveness (compared with no vaccine). The generalized estimating equation model accounts for repeated samples collected from the same individual over time and assumed an exchangeable correlation structure.

While we were unable to determine the reason a person was tested (eg, whether they were symptomatic or being tested for workplace screening), we did have data on the frequency with which individuals were tested. We repeated the analysis for individuals who had no tests during June and July and for individuals who had at least 1 test during June and July to identify those who were tested regularly.

Secondary Analysis: Matched Case-Control Design

As a complementary analysis, we used a matched case-control design.[21,22] Cases were defined as individuals with a positive PCR test result occurring after August 1, 2021, among those 40 years and older who did not have a previous positive test recorded and who received at least 2 doses of the vaccine. Up to 20 controls per case were drawn from the entire population (58% of the population were matched to 20 controls, 78% of the population had at least 10 controls, and 88% of the population had at least 5 controls). Eligible controls were individuals who had not tested positive before the date when the case was tested and who had received at least 2 doses of the vaccine. Controls were matched by 10-year age category, residential SES, biological sex, and the month when the second dose was administered. A conditional logistic regression model was fit to the data,[23] adjusting for the same set of comorbidities as in the test-negative analysis (diabetes, immunosuppression status, BMI ≥30, CVD) and for the number of positive tests performed on that day.

Secondary Analysis: Matched Case-Control Analysis for Hospitalization

Similar to the analysis of infections, we performed a matched case-control analysis for hospitalization with COVID-19. Cases were individuals with at least 2 doses of the vaccine who were hospitalized after August 1, 2021. Eligible controls were individuals who had not tested positive prior to the date of hospitalization of the case. Matching was performed as for the infection case-control analysis. Up to 20 controls per case were drawn from the entire population (48% of the population were matched to 20 controls, 70% of the population had at least 10 controls, and 81% of the population had at least 5 controls). A conditional logistic regression was fit to the data, adjusting for comorbidities (diabetes, immunosuppression status, BMI ≥30, CVD).

Analyses were performed using R, version 4.0.5 (R Foundation). The analysis conforms to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

Results

From August 1, 2021, when the booster dose became widely available, through October 4, 2021, 500 232 PCR tests were performed among 306 710 MHS members 40 years and older (55% female) who did not have a previous documented SARS-CoV-2 infection. Baseline characteristics of the participants are summarized in **Table 1**. During the period when the booster was available, 227 380 total tests with 14 989 positive results (6.6%) were conducted in the 2-dose group, and 272 852 total tests with 4941 positive results (1.8%) were conducted in the 3-dose group. The positive per-

Table 1. Demographic Characteristics Associated With Tests Among Individuals With at Least 2 Doses of the BNT162b2 Vaccine Who Were Tested August 1-October 4, 2021[a]

Characteristics	Individuals receiving 2 doses (n = 227 380)	Individuals receiving 3 doses (n = 272 852)
Age, mean (SD), y	53.0 (10.6)	59.0 (12.5)
Age group, y		
40-49	106 264 (46.7)	71 143 (26.1)
50-59	72 752 (32.0)	80 839 (29.6)
60-69	27 696 (12.2)	64 604 (23.7)
70-79	13 773 (6.1)	35 689 (13.1)
≥80	6895 (3.0)	20 577 (7.5)
Sex		
Male	97 058 (42.7)	127 281 (46.6)
Female	130 322 (57.3)	145 571 (53.4)
SES Index, mean (SD) (range, 1-10)	6.80 (1.85)	7.04 (1.84)
Comorbidities		
Cardiovascular disease	3247 (1.4)	7497 (2.7)
Obesity (BMI ≥30)	49 901 (21.9)	65 383 (24.0)
Immunosuppression	6028 (2.7)	9314 (3.4)
Diabetes	19 993 (8.8)	38 733 (14.2)
Chronic kidney disease	23 182 (10.2)	52 048 (19.1)
Hypertension	49 012 (21.6)	89 696 (32.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SES, socioeconomic status.

[a] Data are related to the number of tests; individuals can be counted more than once for these calculations.

Table 2. Testing Results Among Those With at Least 2 Doses of the BNT162b2 Vaccine at Different Time Points, August 1-October 4, 2021

	No.		
Time after booster receipt	Positive test	Total tests	% Positive
No booster	14 989	227 380	6.6
0-6 d	1886	31 308	6.0
7-13 d	1297	42 756	3.0
14-20 d	485	43 896	1.1
21-27 d	423	40 556	1.0
28-65 d	850	114 336	0.7

Table 3. Marginal Measure of Effectiveness of 3 vs 2 Doses of the BNT162b2 Vaccine

	% (95% CI)[a]	
Time after booster, d	Test-negative analysis	Matched case-control
0-6	12 (8-17)	50 (47-52)
7-13	58 (56-61)	71 (69-73)
14-20	85 (83-86)	87 (85-88)
21-27	85 (83-86)	85 (84-87)
28-65	86 (85-87)	83 (82-85)

[a] Data are reported as the percentage (95% CI) reduction in the odds of testing positive for SARS-CoV-2.

centage was highest among those who had not received a booster and among those who had received a booster in the previous 7 days, and was lowest among individuals who had received the booster more than 2 weeks prior (**Table 2**).

The marginal measure of effectiveness of the third dose compared with the second dose increased over time following receipt of the booster, with a small reduction in the odds of testing positive in the first 7 days (12%; 95% CI, 8%-17%), moderate marginal measure of effectiveness in days 7 through 13 (58%; 95% CI, 56%-61%), and high marginal measure of effectiveness in days 14 through 20 and beyond (85%; 95% CI, 83%-86%) (**Tables 3** and

4 and eFigure 1 in the Supplement). After repeating this analysis for each age group individually, the estimates for the marginal effect were consistent for all age groups after the first 2 weeks (eFigure 2 in the Supplement). Likewise, the estimates were similar regardless of the presence of the recorded comorbidities (eFigure 3 in the Supplement).

Because it takes time for the booster to induce an immune response, a measure of effectiveness was not expected in the first week after receipt of the booster. It was hypothesized that the small association with decreased SARS-CoV-2 infection observed in some age groups during the first 7 days following receipt of the booster was because of a bias in testing behavior around time of receipt of the booster. After stratifying the analysis based on whether the individual had previously been tested in June and July, it was determined that individuals who had previously been tested had no detectable immune response in days 0 through 6 postbooster, while individuals without a previous test during that period did have a statistically significant reduction (eFigure 4 in the Supplement). After excluding individuals who were not tested in June and July from the analysis, there was no association of the booster dose with infection of SARS-CoV-2 in days 0 through 6 for any of the age groups, except the group who was 80 years and older (eFigure 5 in the Supplement). Importantly, the estimated vaccine effects were comparable regardless of test his-

tory after the first 2 weeks, suggesting that this is a short-term bias that is not associated with the main conclusions.

Similar to the results from the test-negative analysis, the matched case-control analysis estimated that the marginal measure of effectiveness of the booster dose compared with the second dose increased from 50% (95% CI, 47%-52%) 6 days after the booster to 71% (95% CI, 69%-72%) 7 to 13 days after the booster, and 87% (95% CI, 85%-88%), 85% (95% CI, 84%-87%), and 83% (95% CI, 82%-85%) at 14 to 20, 21 to 27, and 28 to 65 days, respectively, after the booster (Table 3 and eTables 1 and 2 in the Supplement). Baseline characteristics of the participants are given in eTable 2 in the Supplement.

Finally, the odds of hospitalization among those who received the booster vs those who had received 2 doses but had not yet received the booster were evaluated (eTable 3 in the Supplement). After 14 days, the odds of hospitalization among those who received a booster dose were 92% to 97% lower than those who had received just 2 doses (eTable 4 in the Supplement). The interpretation of these estimates for hospitalization is challenging; however, the apparent immune response of the booster was evident as soon as a few days after its receipt (87% measure of effectiveness at 0-6 days).

Discussion

In this study, we found that a third dose of the mRNA vaccine BNT162b2 provided additional protection against detected SARS-CoV-2 infection. Across the test-negative and matched case-control analyses, we estimated an 83% to 87% reduction in the odds of testing positive for SARS-CoV-2 after at least 2 weeks following receipt of the booster compared with receiving 2 doses. These numbers should be interpreted as the reduction in the odds of infection in a person receiving the booster dose compared with a person receiving only the 2 primary doses. This reduction comes on top of the reduction in the risk conferred by the first 2 doses.

This analysis also suggests that individuals who received the booster dose have a lower odds of hospitalization than those receiving 2 doses. However, these results should be interpreted with caution because a reduction in the odds of hospitalization was already evident in the first week after receipt of the booster when an effect would not be expected. This association with reduction in the first week could occur if individuals who are already infected and symptomatic with COVID-19 are less likely to seek a booster dose. This bias would make it appear that those with a booster dose are less likely to be hospitalized and would explain why the estimated effect was strongest at 0 to 6 days postbooster. However, the bias would most likely be short lived, so it is possible that estimates of the effect of the booster against hospitalization are more reliable at least 2 weeks after receipt of the booster.

Limitations

This study has the inherent limitation of being short term and preliminary. The total benefit of the vaccine program will depend on the long-term effectiveness of the first 2 doses of the vaccine against infection and severe disease. Waning will erode these benefits to varying degrees over time, but the booster

Table 4. Odds Ratios for SARS-CoV-2 Infection, Demographics and Comorbidities, Test-Negative Design, and Vaccination Status

Category	OR (95% CI)
Vaccination status	
2 Doses	1 [Reference]
3 Doses	
Days 0-6	0.88 (0.83-0.92)
Days 7-13	0.42 (0.39-0.44)
Days 14-20	0.15 (0.14-0.17)
Days 21-27	0.15 (0.14-0.17)
Days 28-65	0.14 (0.13-0.15)
Age group, y	
40-49	1 [Reference]
50-59	0.85 (0.82-0.88)
60-69	0.78 (0.74-0.82)
70-79	0.74 (0.7-0.79)
≥80	0.60 (0.55-0.66)
Sex	
Male	1 [Reference]
Female	0.82 (0.79-0.84)
Comorbidities	
Obesity (BMI ≥30)	1.23 (1.19-1.28)
Diabetes	1.26 (1.20-1.32)
Immunosuppression	1.11 (1.02-1.21)
Cardiovascular disease	1.19 (1.07-1.33)
Time-varying risk of exposure	
Log (No. of community infections)	2.09 (1.99-2.21)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); OR, odds ratio.

can restore some of the effectiveness. However, it will also be important to monitor waning of effectiveness following receipt of the booster dose.

There are methodological limitations to these analyses as well. As in every observational study, there is a potential bias relating to health care–seeking behavior in terms of PCR testing behaviors around the time of vaccine receipt. Related work from Israel demonstrates that this change in testing behavior was most pronounced in the week after receipt of the booster dose.[13] In an attempt to address this, we performed a stratified analysis based on whether the individual had been previously tested. We found that there was no association of the booster dose with decreased SARS-CoV-2 infection in the first week following receipt (as expected) among those who had been previously tested in June and July, while those who had not been previously tested exhibited a potential bias. The difference between these groups largely disappeared after 2 weeks. Those who had been previously tested could include individuals who undergo more common screening tests and thus might be less susceptible to changes in behavior related to vaccination. The change in testing behavior had a stronger influence on the matched case-control analysis. This could be because the test-negative analysis adjusts for the decline in testing volume. Studies limited to symptomatic cases could further mitigate this bias but would not allow investigation of protection against asymptomatic infection. Given that chronically ill patients were prioritized for booster vaccination, uncontrolled

confounding by indication is possible. However, the matching and adjustment performed renders residual confounding by unmeasured factors less likely.

We use odds ratios as an approximation of the relative risk and marginal measure of effectiveness of the third dose, which is a reasonable approximation given that outcome is relatively rare over the time frame of the analysis. Another limitation stems from the fact that the Delta variant was the dominant strain in Israel at the time of study; thus, the risk reduction against other strains cannot be inferred.

Conclusions

In this case-control study, analyses show that a third dose of the BNT162b2 vaccine was associated with a lower odds of SARS-CoV-2 infection and hospitalization. Other studies have demonstrated that protection against SARS-CoV-2 wanes over time. Further monitoring of data from this population is needed to determine the duration of immunity following the booster dose.

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