ORIGINAL ARTICLE

Safety and Efficacy of a Third Dose of BNT162b2 Covid-19 Vaccine

Edson D. Moreira, Jr., M.D., Ph.D., Nicholas Kitchin, M.D., Xia Xu, Ph.D., Samuel S. Dychter, M.D., Stephen Lockhart, D.M., Alejandra Gurtman, M.D., John L. Perez, M.D., Cristiano Zerbini, M.D., Michael E. Dever, M.D., Timothy W. Jennings, D.O., Donald M. Brandon, M.D., Kevin D. Cannon, M.D., Michael J. Koren, M.D., Douglas S. Denham, D.O., Mezgebe Berhe, M.D., M.P.H., David Fitz-Patrick, M.D., Laura L. Hammitt, M.D., Nicola P. Klein, M.D., Ph.D., Haylene Nell, M.D., Georgina Keep, B.Sc., Xingbin Wang, Ph.D., Kenneth Koury, Ph.D., Kena A. Swanson, Ph.D., David Cooper, Ph.D., Claire Lu, Ph.D., Özlem Türeci, M.D., Eleni Lagkadinou, M.D., Ph.D., Dina B. Tresnan, D.V.M., Ph.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., William C. Gruber, M.D., and Kathrin U. Jansen, Ph.D., for the C4591031 Clinical Trial Group*

ABSTRACT

BACKGROUND

Active immunization with the BNT162b2 vaccine (Pfizer–BioNTech) has been a critical mitigation tool against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the coronavirus disease 2019 (Covid-19) pandemic. In light of reports of waning protection occurring 6 months after the primary two-dose vaccine series, data are needed on the safety and efficacy of offering a third (booster) dose in persons 16 years of age or older.

METHODS

In this ongoing, placebo-controlled, randomized, phase 3 trial, we assigned participants who had received two 30-μg doses of the BNT162b2 vaccine at least 6 months earlier to be injected with a third dose of the BNT162b2 vaccine or with placebo. We assessed vaccine safety and efficacy against Covid-19 starting 7 days after the third dose.

RESULTS

A total of 5081 participants received a third BNT162b2 dose and 5044 received placebo. The median interval between dose 2 and dose 3 was 10.8 months in the vaccine group and 10.7 months in the placebo group; the median follow-up was 2.5 months. Local and systemic reactogenicity events from the third dose were generally of low grade. No new safety signals were identified, and no cases of myocarditis or pericarditis were reported. Among the participants without evidence of previous SARS-CoV-2 infection who could be evaluated, Covid-19 with onset at least 7 days after dose 3 was observed in 6 participants in the vaccine group and in 123 participants in the placebo group, which corresponded to a relative vaccine efficacy of 95.3% (95% confidence interval, 89.5 to 98.3).

CONCLUSIONS

A third dose of the BNT162b2 vaccine administered a median of 10.8 months after the second dose provided 95.3% efficacy against Covid-19 as compared with two doses of the BNT162b2 vaccine during a median follow-up of 2.5 months. (Funded by BioNTech and Pfizer; C4591031 ClinicalTrials.gov number, NCT04955626.)

The authors' affiliations are listed in the Appendix. Dr. Dychter can be contacted at samuel.dychter@pfizer.com.

*A complete list of the C4591031 Clinical Trial Group investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 23, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2200674

The coronavirus disease 2019 (COVID-19) pandemic remains a global public health emergency, and vaccination is a critical mitigation tool.[1] The BNT162b2 vaccine (Pfizer–BioNTech) contains a nucleoside-modified messenger RNA encoding the spike glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] The BNT162b2 vaccine has been licensed for immunization of persons 16 years of age or older in the United States and has been issued emergency use authorization (EUA) by the Food and Drug Administration (FDA) for immunization of children between the ages of 5 and 15 years.[3,4] Globally, the BNT162b2 vaccine has been authorized in 117 countries across North and South America, the United Kingdom, Europe, Africa, Asia, and Oceania.[5]

In an ongoing pivotal clinical trial (C4591001) involving healthy children and adults who were 12 years of age or older, two doses of the BNT162b2 vaccine (30 μg) were safe, immunogenic, and at least 95% efficacious in preventing Covid-19 from 7 days until approximately 2 months after the second injection.[6-8] After the second dose, vaccine efficacy against Covid-19 had waned to 90% within 2 to 4 months and to 84% within 4 to 6 months.[9] Similar estimates have been reported from real-world effectiveness and surveillance studies.[10-12]

The emergence of the B.1.617.2 (delta) variant of SARS-CoV-2, which coincided with breakthrough cases among vaccinated persons,[13,14] raised the question as to whether the reduced effectiveness of the initial vaccine regimen was due to the emergence of the delta variant or simply to declining efficacy over time. Although protection against infection and mild disease appeared to wane in the months after vaccination, the effectiveness against severe disease and hospital admission remained high.[10,11,15] Waning immunity and the potential for continued circulation of additional SARS-CoV-2 variants suggested the need for a third (booster) dose of the BNT162b2 vaccine. A third BNT162b2 dose that was administered 7 to 9 months after the primary two-dose series was shown to increase the magnitude and breadth of the immune response in a small group of participants from the pivotal trial.[16]

On the basis of immunogenicity data from the primary series and from the booster dose, on December 9, 2021, the FDA authorized a third BNT162b2 dose in persons 16 years of age or older who had received the primary BNT162b2 series at least 6 months earlier.[17] Here, we report safety and efficacy results from an ongoing, placebo-controlled, randomized, phase 3 clinical trial (C4591031) that assessed the administration of a third BNT162b2 dose in more than 10,000 healthy participants who had received the primary two-dose series in the pivotal trial.

Methods

Trial Objectives, Participants, and Oversight

All the trial participants were a least 16 years of age and had previously received two doses of the BNT162b2 vaccine administered 19 to 42 days apart in the ongoing pivotal trial. Participants had received the second vaccine dose at least 175 days (approximately 6 months) earlier and had received no previous clinical or microbiologic diagnosis of Covid-19. Additional inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org, along with the protocol. All the participants provided written informed consent; in adolescents younger than 18 years of age, written informed consent was provided by a parent or guardian.

Pfizer was responsible for the design and conduct of the trial; for the collection, analysis, and interpretation of the data; and for the writing of the manuscript. Both Pfizer and BioNTech manufactured the vaccine and placebo that were used in the trial. BioNTech was the regulatory sponsor and contributed to interpretation of the data and the writing of the manuscript. All aggregated analyses of the data were available to all the authors, who vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol.

Procedures

Using an interactive Web-based response system, we randomly assigned the participants in a 1:1 ratio to receive an intramuscular injection of a third dose of the BNT162b2 vaccine or saline placebo. All the participants and site personnel were unaware of the trial-group assignments, except for staff members who prepared, dispensed, or administered the injections. The trial design originally called for all the participants to remain unaware of their assigned group until after a prespecified interim analysis. This planned analysis was to occur 2 months after the third dose, with subsequent review by the data and safety

monitoring committee. In anticipation of recommendations by regulatory authorities that booster doses be made available, we revised the protocol to allow for the unblinding of the trial-group assignments before the 2-month cutoff. During the interim analysis, the data monitoring committee also recommended that participants be made aware of their trial-group assignments to allow those in the placebo group to receive a third vaccine dose. This recommendation was made in consideration of the observation of waning effectiveness after two doses, the observed benefit of the third dose, and the recommendation for boosters in some countries. On September 24, 2021, on the basis of FDA issuance of the EUA for a BNT162b2 booster and at the discretion of the sponsor, participants in the placebo group were offered the opportunity to receive the BNT162b2 vaccine.

SAFETY

The incidence of adverse events and serious adverse events was the primary safety end point. Data regarding unsolicited adverse events, including reactogenicity, were collected from the time that informed consent was provided through 1 month after the administration of dose 3. We collected assessments of reactogenicity and other adverse events by telephone follow-up. The collection of reports of serious adverse events was ongoing from the time that informed consent was provided through 6 months after dose 3.

EFFICACY

The primary efficacy end point was the effectiveness of the BNT162b2 vaccine against laboratory-confirmed Covid-19 beginning at least 7 days after the administration of dose 3. This end point was analyzed both in participants who had no evidence of previous SARS-CoV-2 infection and in all participants. The efficacy of the BNT162b2 vaccine against severe Covid-19 was determined according to the definitions used by the FDA and the Centers for Disease Control and Prevention (CDC).[18,19] The methods that were used for identifying SARS-CoV-2 infection and Covid-19 are summarized in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size was chosen to provide a relatively large database to assess safety, with the intent of accruing sufficient Covid-19 cases to assess vaccine efficacy. The number of participants was not based on a projected between-group difference. We determined that the enrollment of 10,000 participants would provide 4250 participants with data that could be evaluated in each group, assuming a loss of follow-up of 15%. Included in the primary analyses were all the participants who had undergone randomization and received either a third dose of the BNT162b2 vaccine or placebo with no important deviations from the protocol.

We calculated safety end points as counts, percentages, and associated Clopper–Pearson two-sided 95% confidence intervals in the safety population (Table S1 in the Supplementary Appendix). Adverse events and serious adverse events are presented according to the terms used in the *Medical Dictionary for Regulatory Activities*, version 24.0. Between-group differences in percentages of participants who reported having adverse events are presented with associated two-sided Miettinen–Nurminen 95% confidence intervals for adverse events with an incidence of at least 1% in either group.

Interim efficacy analyses were performed after all the participants had reached 2 months of blinded follow-up and through the data-cutoff date; these data were reviewed by the data monitoring committee. Data from participants who were made aware of trial-group assignments before the first interim analysis because of the regulatory decision were censored at the time of the unblinding of the trial group. Details regarding the procedures that were used to determine the relative efficacy of the third dose of vaccine as compared with placebo are provided in the Supplementary Appendix.

We calculated two-sided Clopper–Pearson 95% confidence intervals for relative vaccine efficacy after adjustment for surveillance time. Confidence intervals were not adjusted for multiplicity and thus cannot be used to infer effects. Instead, the trial was designed to provide information to assist policymakers in deciding whether to recommend a third dose of vaccine, as well as the timing of this dose if recommended. Missing efficacy data (e.g., the report of a symptom without laboratory testing data) were not imputed.

RESULTS

PARTICIPANTS

From July 1 to August 10, 2021, a total of 10,136 participants who had received two doses of the BNT162b2 vaccine in the pivotal trial underwent

randomization at 123 sites in the United States, South Africa, and Brazil. Overall, 5081 participants received a third BNT162b2 dose and 5044 received placebo (Fig. 1). A larger number of participants in the placebo group than in the vaccine group withdrew from the trial in order to receive a third dose of vaccine owing to pending changes in national recommendations.

The demographic characteristics of the participants were well balanced in the two groups (Table 1) and were generally representative of the expected participant population (Table S2). The median age was 53.0 years, 23.3% of participants were 65 years of age or older, and 1% were 16 or 17 years of age; 49.1% were male; and 79.0% were White, 9.2% were Black, 5.5% were Asian, and 14.9% were Hispanic or Latinx. Almost half the participants (48.7%) had coexisting conditions, including obesity (in 35.9%), chronic pulmonary disease (in 9.2%), and diabetes without chronic complications (in 8.3%); 5.4% had evidence of current or previous SARS-CoV-2 infection at baseline. The median interval between dose 2 and dose 3 was 10.8 months (range, 5.0 to 12.6) in the vaccine group and 10.7 months (range, 5.0 to 12.8) in the placebo group. The median follow-up from dose 3 to the data-cutoff date (October 5, 2021) was 2.5 months (range, 0.3 to 3.5).

SAFETY

Within 1 month after the administration of dose 3, adverse events were more frequent in the vaccine group than in the placebo group (Fig. 2A and Table 2). Injection-site pain was the most frequently reported adverse event in the two groups and was reportedly more often in the vaccine group (risk difference, 11.3 percentage points) (Fig. 2B). From dose 3 through the data-cutoff date, serious adverse events were reported by slightly more participants in the placebo group than in the vaccine group (0.5% vs. 0.3%) (Table S3). In a blinded investigation, serious adverse events were considered by the investigator to be related to either the vaccine or placebo in 3 participants who had received the BNT162b2 vaccine and in 2 participants who had received placebo.

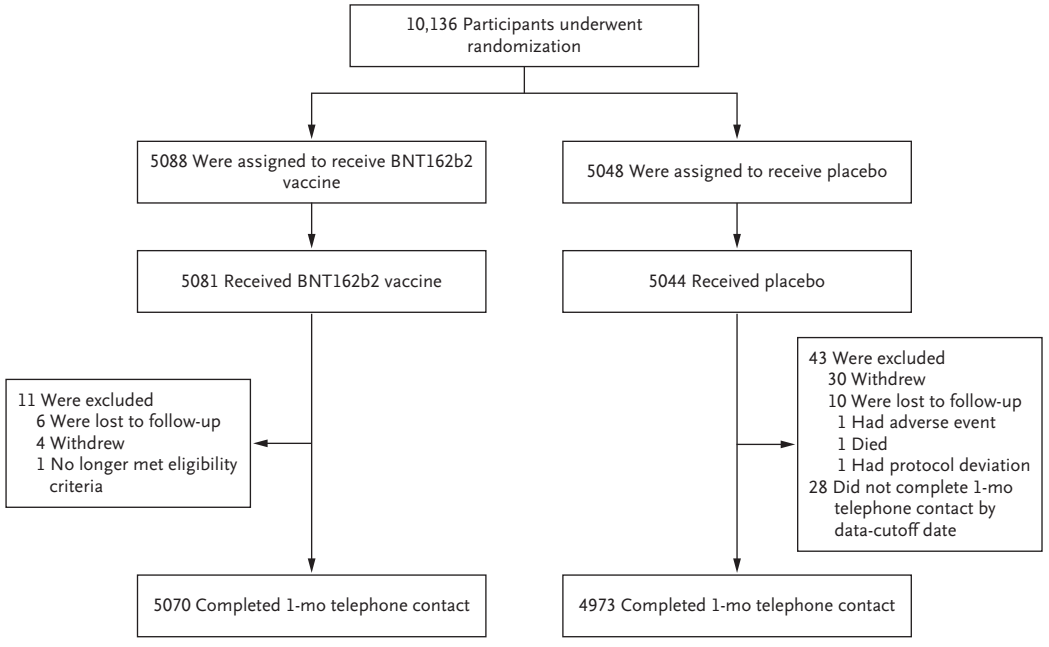

Figure 1. Enrollment and Randomization.

Participants who were included in the withdrawal category discontinued their participation in the trial before the data-cutoff date of October 5, 2021. Because of the early unblinding of the trial results, some of the participants became aware of the trial-group assignments before the 1-month telephone contact. One participant who was assigned to receive the BNT162b2 vaccine actually received placebo and was included in the analysis of the placebo group.

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	BNT162b2 (N = 5081)	Placebo (N = 5044)	Total (N = 10,125)
Age — yr			
Mean ±SD	51.8±15.2	51.7±15.3	51.7±15.3
Median (range)	53.0 (16–86)	53.0 (16–87)	53.0 (16–87)
Distribution — no. (%)			
16–55 yr	2823 (55.6)	2797 (55.5)	5620 (55.5)
>55 yr	2258 (44.4)	2247 (44.5)	4505 (44.5)
≥65 yr	1175 (23.1)	1188 (23.6)	2363 (23.3)
Sex — no. (%)			
Male	2457 (48.4)	2518 (49.9)	4975 (49.1)
Female	2624 (51.6)	2526 (50.1)	5150 (50.9)
Race or ethnic group — no. (%)†			
White	3997 (78.7)	4002 (79.3)	7999 (79.0)
Black	472 (9.3)	460 (9.1)	932 (9.2)
American Indian or Alaska Native	86 (1.7)	91 (1.8)	177 (1.7)
Asian	288 (5.7)	269 (5.3)	557 (5.5)
Native Hawaiian or other Pacific Islander	8 (0.2)	11 (0.2)	19 (0.2)
Multiracial	207 (4.1)	196 (3.9)	403 (4.0)
Other or not reported	23 (0.5)	15 (0.3)	38 (0.4)
Hispanic or Latinx ethnic group — no. (%)†			
Yes	760 (15.0)	748 (14.8)	1508 (14.9)
No	4309 (84.8)	4288 (85.0)	8597 (84.9)
Not reported	12 (0.2)	8 (0.2)	20 (0.2)
Country — no. (%)			
United States	4367 (85.9)	4326 (85.8)	8693 (85.9)
Brazil	580 (11.4)	584 (11.6)	1164 (11.5)
South Africa	134 (2.6)	134 (2.7)	268 (2.6)
SARS-CoV-2 status — no. (%)‡			
Positive	284 (5.6)	261 (5.2)	545 (5.4)
Negative	4789 (94.3)	4775 (94.7)	9564 (94.5)
Unknown	8 (0.2)	8 (0.2)	16 (0.2)
Body-mass index — no. (%)§			
Underweight: <18.5	57 (1.1)	49 (1.0)	106 (1.0)
Normal weight: ≥18.5–24.9	1431 (28.2)	1459 (28.9)	2890 (28.5)
Overweight: ≥25.0–29.9	1768 (34.8)	1725 (34.2)	3493 (34.5)
Obese: ≥30.0	1823 (35.9)	1811 (35.9)	3634 (35.9)

* Results are for the safety population. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the participants.
‡ Positive status with respect to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was defined as a positive result on N-binding antibody testing or nucleic acid amplification testing at the first vaccination visit or a medical history of coronavirus disease 2019 (Covid-19).
§ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data regarding body-mass index were missing for 2 participants.

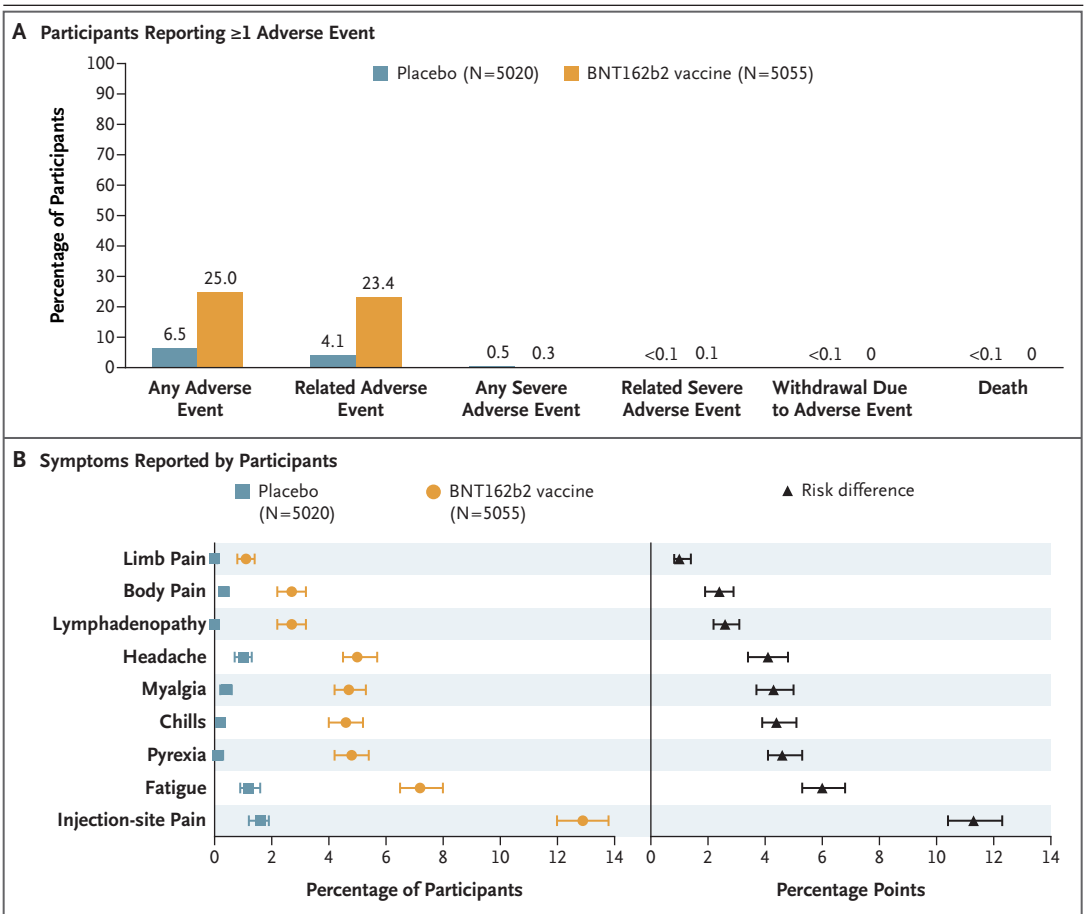

Figure 2. Adverse Events.

Panel A shows the percentage of participants who reported having at least one adverse event after the receipt of a third dose of the BNT162b2 vaccine or placebo. Data regarding any adverse events and adverse events that were deemed by the investigator to be related to either the BNT162b2 vaccine or placebo were collected within 1 month after receipt of the third dose; data regarding severe adverse events, withdrawal, or death were reported before the data-cutoff date of October 5, 2021. Panel B shows adverse events that were reported in the safety population, with the exclusion of participants with stable human immunodeficiency virus infection, who were evaluated separately. The graph on the left shows the percentage of participants with adverse events, and the graph on the right shows the between-group difference (BNT162b2 vaccine minus placebo) in these events as measured in percentage points. The error bars indicate 95% confidence intervals calculated with the Clopper–Pearson method for adverse events and the Miettinen–Nurminen method for risk difference.

In the vaccine group, these serious adverse events were tachycardia in 1 participant (7 days after dose 3) and increased hepatic enzyme levels in 2 participants (4 and 48 days after dose 3). Among the participants with increased hepatic enzyme levels, 1 had a medical history of Gilbert's syndrome and both reported the use of concomitant medications (paracetamol, atorvastatin calcium, and butalbital). In the placebo group, serious adverse events that were considered to be related to placebo were myocardial infarction (8 days after the injection) and chest pain (5 days after the injection). One adverse event leading to withdrawal in a participant who had received placebo (metastatic cancer) was not considered by the investigator to be related to placebo. One death from pulmonary embolism 51 days after the injection of placebo was deemed to be unrelated to placebo. No cases of myocarditis or pericarditis were reported.

EFFICACY

Interim analyses were conducted at 2 months and on the data-cutoff date. Among the participants without evidence of previous SARS-CoV-2 infection who had an onset of Covid-19 within 7 days to 2 months after the receipt of the third dose, 5 cases were observed in the vaccine group and 109 in the placebo group, which corresponded to a relative vaccine efficacy of 95.6% (95% confidence interval [CI], 89.3 to 98.6). In the corresponding analysis conducted at the data-cutoff date, Covid-19 was identified in 6 participants in the vaccine group and in 123 in the placebo group, which corresponded to a relative vaccine efficacy of 95.3% (95% CI, 89.5 to 98.3) (Fig. 3 and Table 3).

Among all the participants regardless of previous infection within 7 days to 2 months after receipt of the third dose, 6 cases were observed in the vaccine group and 110 cases in the placebo group, for a relative vaccine efficacy of 94.7% (95% CI, 88.2 to 98.1). In the analyses performed through the data-cutoff date, Covid-19 was identified in 7 participants in the vaccine group and in 124 in the placebo group, for a relative vaccine efficacy of 94.6% (95% CI, 88.5 to 97.9). Increased protection started within 7 days after the third dose of the BNT162b2 vaccine but was maximal after 7 days. Severe Covid-19 as defined according to the FDA criteria[18] (but not the CDC criteria) was reported in no participants in the vaccine group and in 2 participants in the placebo group. The FDA definition was based solely on the peripheral-blood oxygen saturation level, and the 2 participants with lower levels were not hospitalized. Although the trial was not designed to assess efficacy according to subgroup, the relative vaccine efficacy among subgroups as defined by age, sex, race, ethnicity, geographic location, and the presence or absence of obesity or other coexisting illness was generally consistent with that observed in the overall population (Tables S4 and S5).

DISCUSSION

Data from the phase 2–3 portion of the ongoing pivotal trial of the BNT162b2 vaccine showed that although overall vaccine efficacy was more than 90% for the period from 7 days to 6 months after the second dose, efficacy decreased with increasing time after the second dose.[9] In addition, real-world data suggested that the humoral immune response and protection against SARS-CoV-2 infection and nonsevere disease appeared to wane in the months after vaccination; these trends were particularly evident in the elderly and in those with immunosuppression.[14,20-22] However, the effectiveness of the BNT162b2 primary immunization series against severe disease, hospitalization, or death remained high.[11,15,21,22]

Although data on waning effectiveness against infection after the primary two-dose series are still emerging, particularly in the face of emerging SARS-CoV-2 variants such as the B.1.1.529 (omicron) variant,[10,14,23] data from the phase 1 study of a third BNT162b2 dose showed that neutralization geometric mean titers against the delta variant increased after a booster dose administered approximately 8 months after the second dose.[16] In consideration of these data and immunologic and safety findings for a booster dose from the pivotal trial, Covid-19 booster vaccinations have been implemented in some countries.[24-28] Consequently, it is important that data from prospective, randomized clinical trials regarding the safety, immunogenicity, and efficacy of booster doses be generated in a timely manner.

In our phase 3 trial, which included more than 10,000 participants, a third 30-μg dose of BNT162b2 administered a median of 10.8 months after the second dose was safe and effective. The safety profile was consistent with the results of previous trials, and reactogenicity was similar to that after the second dose.[6,9] No new safety signals were identified, and no cases of myocarditis or pericarditis were reported.

At a median follow-up of 2.5 months, the relative vaccine efficacy of the third BNT162b2 dose against Covid-19 was 95.3% (95% CI, 89.5 to 98.3) among participants without evidence of previous SARS-CoV-2 infection. Multiple subgroup analyses showed that efficacy was generally consistent regardless of age, sex, race, ethnicity, or the presence of coexisting conditions. These efficacy results were observed when the delta variant was the predominant circulating SARS-CoV-2 strain globally, although other variants were also circulating during the trial (e.g., the P.1 [gamma] variant in Brazil).[13,29] No cases of severe Covid-19 were observed in BNT162b2 recipients through the data-cutoff date. Among the protocol-defined cases of Covid-19 in the placebo group, none re-

Table 2. Adverse Events.*

Adverse Event	BNT162b2 (N = 5055)	Placebo (N = 5020)
	number of participants (percent)	
Blood or lymphatic system disorder		
Any	140 (2.8)	2 (<0.1)
Lymphadenopathy	135 (2.7)	2 (<0.1)
Cardiac disorder	8 (0.2)	4 (0.1)
Ear or labyrinth disorder	3 (<0.1)	1 (<0.1)
Endocrine disorder	1 (<0.1)	0
Eye disorder	7 (0.1)	2 (<0.1)
Gastrointestinal disorder		
Any	83 (1.6)	41 (0.8)
Nausea	48 (0.9)	16 (0.3)
Diarrhea	25 (0.5)	13 (0.3)
Vomiting	11 (0.2)	2 (<0.1)
General disorder or injection-site condition		
Any	1061 (21.0)	154 (3.1)
Injection site		
Pain	651 (12.9)	78 (1.6)
Erythema	22 (0.4)	0
Swelling	21 (0.4)	1 (<0.1)
Fatigue	365 (7.2)	61 (1.2)
Pyrexia	242 (4.8)	7 (0.1)
Chills	233 (4.6)	9 (0.2)
Pain	135 (2.7)	15 (0.3)
Malaise	35 (0.7)	4 (0.1)
Axillary pain	13 (0.3)	1 (<0.1)
Asthenia	8 (0.2)	1 (<0.1)
Hepatobiliary disorder	2 (<0.1)	2 (<0.1)
Immune system disorder	0	3 (0.1)
Infection or infestation	24 (0.5)	26 (0.5)
Injury, poisoning, or procedural complication	15 (0.3)	23 (0.5)
Investigations	32 (0.6)	11 (0.2)
Increased body temperature	30 (0.6)	3 (0.1)
Metabolism or nutrition disorder	15 (0.3)	11 (0.2)
Decreased appetite	9 (0.2)	0
Musculoskeletal or connective-tissue disorder	340 (6.7)	40 (0.8)
Myalgia	239 (4.7)	20 (0.4)
Arthralgia	42 (0.8)	13 (0.3)
Limb pain	54 (1.1)	1 (<0.1)
Neck pain	9 (0.2)	2 (<0.1)
Benign, malignant, or unspecified neoplasm†	5 (0.1)	8 (0.2)

Table 2. (Continued)

Adverse Event	BNT162b2 (N = 5055)	Placebo (N = 5020)
	number of participants (percent)	
Nervous system disorder	284 (5.6)	62 (1.2)
Headache	255 (5.0)	48 (1.0)
Lethargy	12 (0.2)	3 (0.1)
Dizziness	9 (0.2)	3 (0.1)
Psychiatric disorder	10 (0.2)	9 (0.2)
Renal or urinary disorder	6 (0.1)	0
Reproductive system or breast disorder	6 (0.1)	4 (0.1)
Respiratory, thoracic, or mediastinal disorder	10 (0.2)	10 (0.2)
Skin or subcutaneous tissue disorder	22 (0.4)	10 (0.2)
Surgical or medical procedure	1 (<0.1)	0
Vascular disorder	5 (0.1)	7 (0.1)

* Adverse events during the first month after administration of the third dose of the BNT162b2 vaccine or placebo are reported according to the system organ class among participants with at least one adverse event in either group. Data are reported as preferred terms if the event was reported by at least 0.2% of the participants in either group and as such may not add up to the number of events in each body system. Results are for the safety population; data for participants with stable human immunodeficiency virus infection were analyzed separately. The data-cutoff date was October 5, 2021.

† This category includes cysts and polyps.

sulted in hospitalization, a finding that supported the durable protection against severe Covid-19 after the two-dose primary series of the BNT162b2 vaccine.

In this trial, the prevention of Covid-19 by a third dose of the BNT162b2 vaccine was shown by the relative vaccine efficacy of more than 95% on top of any residual protection from the two-dose series. Thus, the absolute vaccine efficacy of the third dose relative to a hypothetical unvaccinated population would be even higher. The high efficacy of a third BNT162b2 dose has important potential benefits beyond reducing illness, such as preventing Covid-19 sequelae after breakthrough infections,[30] and early data suggest it may be critical to improving efficacy against the omicron variant.[23] A third dose may also reduce workplace absenteeism and transmission to those who have not been vaccinated, as suggested from the primary two-dose series.[31-33]

Real-world data on booster effectiveness are limited. However, in a trial involving Israeli adults who were 60 years of age or older, a third BNT162b2 dose administered at least 5 months after the two-dose primary series resulted in an incidence of SARS-CoV-2 infection that was 11.3 times lower than that in participants who had not received a booster and an incidence of severe Covid-19 that was 19.5 times lower.[24] Also in Israel, an observational study involving participants who were 12 years of age or older and were eligible to receive a booster according to the Israeli Ministry of Health guidelines showed that the effectiveness of a third BNT162b2 dose administered at least 5 months after the second dose was 93% against hospital admission, 92% against severe Covid-19, and 81% against death as compared with two doses.[34] Another database study from Israel involving approximately 850,000 adults 50 years of age or older showed that those who had received a BNT162b2 booster dose at least 5 months after the second dose had 90% lower Covid-19–associated mortality than those who had not received the additional dose.[35] In the United Kingdom, the relative vaccine effectiveness of a BNT162b2 booster given at least 140 days after a second dose was 84.4% against symptomatic disease in adults 50 years of age or older, which

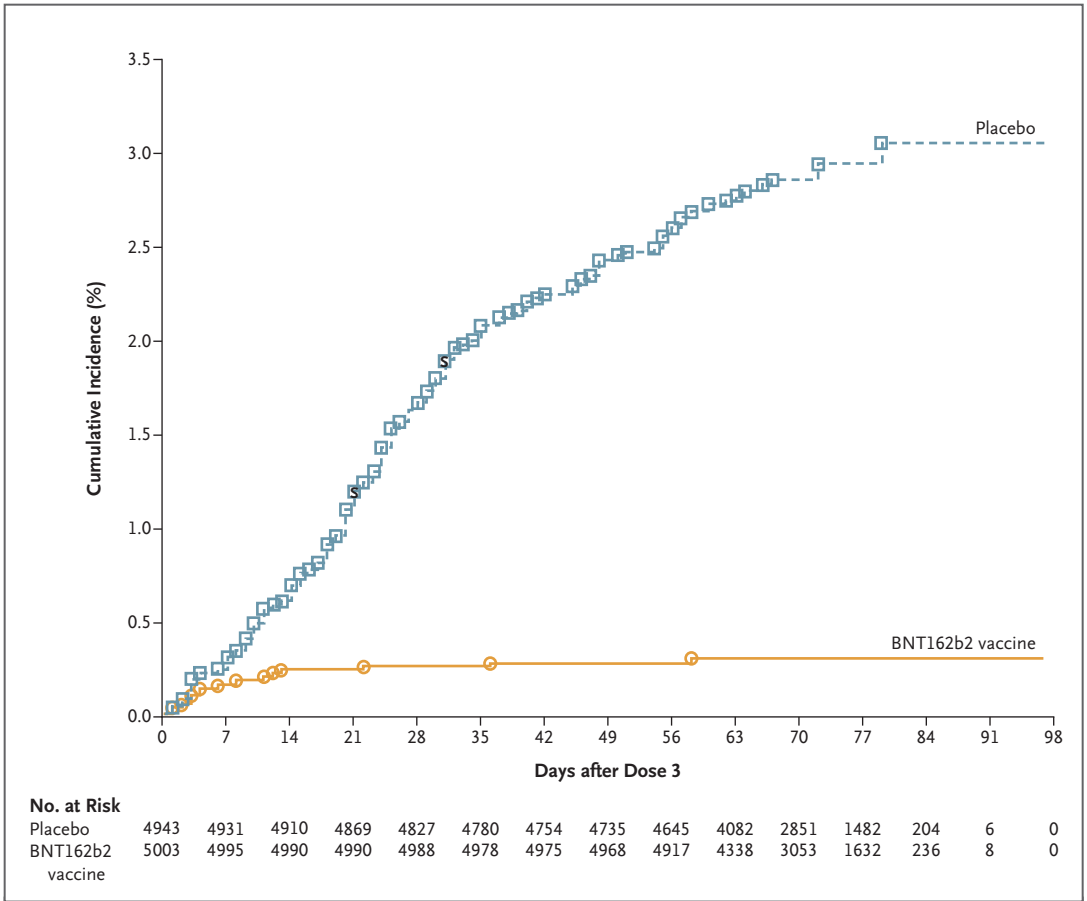

Figure 3. Cumulative Incidence of Covid-19 after a Third Dose of BNT162b2.

Shown is the cumulative incidence curve of the first Covid-19 occurrence after dose 3 in the total efficacy population, as calculated by means of the Kaplan–Meier method (Table S1 in the Supplementary Appendix). Each symbol represents the onset of a Covid-19 case; symbols with an S represent severe Covid-19 cases.

corresponded to an absolute vaccine effectiveness of 94.0% as compared with unvaccinated participants.[36]

Limitations of our current trial include the lack of data regarding participants who had received a third BNT162b2 dose after a primary series with a longer interval between doses and regarding long-term protection against SARS-CoV-2 infection. In addition, follow-up of placebo recipients was limited because of the unblinding of the trial in some cases to allow for receipt of a third dose of BNT162b2. Longer-term follow-up from this ongoing trial will continue to provide data, since the participants will be followed for 1 year to assess the duration of protection after a third dose of BNT162b2. Although we did not evaluate the booster protection after a primary series with different Covid-19 vaccines, early data from a study of heterologous primary–booster schedules suggest that BNT162b2 was also safe and immunogenic when it was administered after a primary series with the adenoviral vector vaccine ChAdOx1.[37] In addition, U.S. participants accounted for most of the Covid-19 cases in the efficacy assessment. However, the likelihood that vaccine efficacy would differ across countries appears to be low, even though this trial was not powered for comparisons between countries. Finally, we did not evaluate the incidence of asymptomatic infection or assess vaccine efficacy against transmissibility. It is anticipated that forthcoming clinical data on an omicron-based Covid-19 vaccine will clarify whether this new formulation will increase vaccine efficacy against severe disease, affect transmissibility, or improve the duration of protection.

Overall, the data from the C4591031 clinical trial strongly support the administration of a

Table 3. Relative Vaccine Efficacy against Covid-19.*

Efficacy End Point	BNT162b2		Placebo		Relative Vaccine Efficacy (95% CI)†
	no./total no.	*surveillance time (no. at risk)‡*	*no./total no.*	*surveillance time (no. at risk)‡*	%
Efficacy population with complete data					
First Covid-19 occurrence ≥7 days after dose 3					
Without evidence of infection <7 days after dose 3§	6/4695	0.82 (4659)	123/4671	0.79 (4614)	95.3 (89.5 to 98.3)
With or without evidence of infection <7 days after dose 3	7/4993	0.87 (4934)	124/4952	0.84 (4863)	94.6 (88.5 to 97.9)
Total efficacy population					
First Covid-19 occurrence after dose 3	15/5056	0.98 (5003)	141/5019	0.94 (4943)	89.8 (82.6 to 94.4)
≤7 days	8/5056	0.10 (5003)	15/5019	0.10 (4943)	47.3 (–32.3 to 80.7)
7 days to <2 mo	6/5056	0.67 (4995)	112/5019	0.64 (4928)	94.8 (88.4 to 98.1)
2 mo to <4 mo	1/5056	0.21 (4891)	14/5019	0.20 (4616)	93.3 (56.1 to 99.8)

* Details regarding the populations that were evaluated for vaccine efficacy are provided in Table S1 in the Supplementary Appendix.
† The 95% confidence interval for the relative vaccine efficacy was calculated with the Clopper–Pearson method after adjustment for surveillance time.
‡ Shown is the total surveillance time per 1000 person-years for the given end point across all the participants in each group at risk for the end point. The time period for Covid-19 case accrual was from 7 days after dose 3 to the end of the surveillance period.
§ Participants without evidence of infection had no serologic or virologic evidence of SARS-CoV-2 infection within 7 days after the receipt of dose 3. No evidence of infection was defined as a negative result on N-binding antibody testing or on nucleic acid amplification testing (NAAT) of a nasal swab at the first vaccination visit or negative results on NAAT at any unscheduled visit within 7 days after the administration of dose 3.

third dose of the BNT162b2 vaccine in persons who are 16 years of age or older and confirm the increased protection against Covid-19 provided by the primary immunization series.

Supported by BioNTech and Pfizer.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the participants who volunteered for this trial and the personnel at the trial centers for their contributions; Sheena Hunt, Tricia Newell, and Allison Gillies of ICON, who wrote the first draft of the manuscript under direction from the authors; the members of the C4591031 data and safety monitoring board — Jonathan Zenilman, Kathryn Edwards, Robert Belshe, Lawrence Stanberry, Steve Self, Robert Phillips Heine, and Heather S. Lipkind — for their dedication and diligent review of the data; Pfizer colleagues Greg Adams, Alexa Asher, Ayman Ayoub, Patricia Banchero, Pauline Baur, Mark Boaz, Salim Bouguermouh, Christopher Bowen, Donna Boyce, Sarah Burden, Adriana Cahill, William Carey, Patrick Caubel, Andrea Cawein, Prajakta Chivate, Darren Cowan, Kimberly Ann Cristall, Steven De Beukelaer, Carmel Devlin, Jeoff Duran, Ashraf El Fiky, Ye Feng, Gary Friedman, Jason Quan Gong, Cynthia Ingerick-Holt, Luis Jodar, Joshua Jones, Connie Liu, Rod MacKenzie, Robert Maroko, Susan Mather, Jason McKinley, Donald McVinnie, Xiao Yu Mo, Farheen Muzaffar, Elizabeth Paulukonis, Malathi Pitchai, Kellie Lynn Richardson, Karen Rosenzweig, Harpreet Seehra, Janaki Shankaran, Helen Smith, Sandip Suryawanshi, Dana Tielemans, Svitlana Tonkovyd, Elisa Harkins Tull, Sarah Tweedy, Venerando Umali, Erica Weaver, Chris Webber, Jenah West, David Whritenour, Caitlin Wright, Helen Yang, Gabriel Zegrean, and Rong Zhang; the members of the Pfizer Vaccines Clinical Assay Team and the Pfizer Vaccines Assay Development Team and all the other Pfizer colleagues who contributed to the success of this trial; and BioNTech colleagues Elizabeth Adams, Rene Bartz, Meghan Bushway, Alexandra Kemmer Brück, Zakaria Khondker, Kimberly Krüger, Christian Miculka, Orkun Orzhelvaci, Ruben Rizzi, Svetlana Shpyro, and Anna Sokolowska.

APPENDIX

The authors' affiliations are as follows: Associação Obras Sociais Irmã Dulce and the Oswaldo Cruz Foundation, Bahia (E.D.M.), and Centro Paulista de Investigação Clinica, São Paulo (C.Z.) — both in Brazil; Vaccine Research and Development, Pfizer, Hurley, United Kingdom (N.K., S.L., G.K.); Vaccine Research and Development, Pfizer, Collegeville, PA (X.X., J.L.P., X.W.); Vaccine Research and Development, Pfizer (S.S.D.), and California Research Foundation (D.M.B.), San Diego, and Kaiser Permanente Vaccine Study Center, Oakland (N.P.K.) — all in California; Vaccine Research and Development, Pfizer, Pearl River, NY (A.G., K.K., K.A.S., D.C., C.L., P.R.D., W.C.G., K.U.J.); Clinical Neuroscience Solutions, Orlando (M.E.D.), and Jacksonville Center for Clinical Research, Jacksonville (M.J.K.) — both in Florida; Clinical Research Professionals, Chesterfield, MO (T.W.J.); Accellacare, Wilmington, NC (K.D.C.); Clinical Trials of Texas, San Antonio (D.S.D.), and North Texas

Infectious Diseases Consultants, Dallas (M.B.); East-West Medical Research Institute, Honolulu (D.F.P.); Johns Hopkins Bloomberg School of Public Health, Baltimore (L.L.H.); Tiervlei Trial Centre, Karl Bremer Hospital, Cape Town, South Africa (H.N.); BioNTech, Mainz, Germany (Ö.T., E.L., U.Ş.); and Worldwide Safety, Safety Surveillance and Risk Management, Pfizer, Groton, CT (D.B.T.).

REFERENCES

1. World Health Organization. Statement on the ninth meeting of the International Health Regulations (2005) Emergency Committee regarding the Coronavirus disease (COVID-19) pandemic. October 26, 2021 (https://www.who.int/news/item/26-10-2021-statement-on-the-ninth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic).
2. Sahin U, Muik A, Vogler I, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature 2021;595:572-7.
3. Food and Drug Administration. FDA approves first COVID-19 vaccine. August 23, 2021 (https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine).
4. Food and Drug Administration. FDA authorizes Pfizer-BioNTech COVID-19 vaccine for emergency use in children 5 through 11 years of age. October 29, 2021 (https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age).
5. McGill COVID19 Vaccine Tracker Team. Pfizer/BioNTech: comirnaty (https://covid19.trackvaccines.org/vaccines/6/).
6. 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.
7. Frenck RW Jr, Klein NP, Kitchin N, et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. N Engl J Med 2021;385:239-50.
8. BioNTech. Comirnaty (BNT162b2): summary of product characteristics (https://biontech.de/sites/default/files/2020-12/Comirnaty_5735_Product_Information.pdf).
9. Thomas SJ, Moreira ED Jr, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med 2021;385:1761-73.
10. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. N Engl J Med 2021;385:585-94.
11. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet 2021;398:1407-16.
12. 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.
13. Centers for Disease Control and Prevention. COVID data tracker: variant proportions (https://covid.cdc.gov/covid-data-tracker/#variant-proportions).
14. Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med 2021;385(24):e85.
15. Tenforde MW, Self WH, Naioti EA, et al. Sustained effectiveness of Pfizer-BioNTech and Moderna vaccines against COVID-19 associated hospitalizations among adults — United States, March–July 2021. MMWR Morb Mortal Wkly Rep 2021;70:1156-62.
16. Falsey AR, Frenck RW Jr, Walsh EE, et al. SARS-CoV-2 neutralization with BNT162b2 vaccine dose 3. N Engl J Med 2021;385:1627-9.
17. Food and Drug Administration. Coronavirus (COVID-19) update: FDA expands eligibility for Pfizer-BioNTech COVID-19 booster dose to 16- and 17-year-olds. December 9, 2021 (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-pfizer-biontech-covid-19-booster-dose-16-and-17).
18. US Food and Drug Administration. COVID-19: developing drugs and biological products for treatment or prevention guidance for industry. February 2021 (https://www.fda.gov/media/137926/download).
19. US Centers for Disease Control and Protection. People with certain medical conditions (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people--with-medical-conditions.html).
20. Levin EG, Lustig Y, Cohen C, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. N Engl J Med 2021;385(24):e84.
21. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. N Engl J Med 2021;385(24):e83.
22. Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 cases and hospitalizations among adults, by vaccination status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1306-11.
23. Andrews N, Stowe J, Kirsebom F, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. December 14, 2021 (https://www.medrxiv.org/content/10.1101/2021.12.14.21267615v1). preprint.
24. 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.
25. Centers for Disease Control and Protection. COVID-19 vaccine booster shots (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html#print).
26. National Health Service UK. How to get a booster dose of the coronavirus (COVID-19) vaccine (https://www.nhs.uk/conditions/coronavirus-covid-19/coronavirus-vaccination/coronavirus-booster-vaccine/).
27. Ministry of Health Singapore. COVID-19 vaccination (https://www.moh.gov.sg/covid-19/vaccination).
28. Federal Government Germany. The most important questions and answers about the coronavirus vaccination (https://www.bundesregierung.de/breg-de/themen/coronavirus/coronavirus-vaccination-faq-1959802).
29. GISAID Initiative. Tracking of variants (https://www.gisaid.org/hcov19-variants/).
30. Ledford H. Do vaccines protect against long COVID? What the data say. Nature 2021;599:546-8.
31. Maltezou HC, Panagopoulos P, Sourri F, et al. COVID-19 vaccination significantly reduces morbidity and absenteeism among healthcare personnel: A prospective multicenter study. Vaccine 2021;39:7021-7.
32. Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of vaccination on household transmission of SARS-CoV-2 in England. N Engl J Med 2021;385:759-60.
33. Shah ASV, Gribben C, Bishop J, et al. Effect of vaccination on transmission of SARS-CoV-2. N Engl J Med 2021;385:1718-20.
34. Barda N, Dagan N, Cohen C, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet 2021;398:2093-100.
35. Arbel R, Hammerman A, Sergienko R, et al. BNT162b2 vaccine booster and mortality due to Covid-19. N Engl J Med 2021;385:2413-20.
36. Andrews N, Stowe J, Kirsebom F, Gower C, Ramsay M, Bernal JL. Effectiveness of BNT162b2 (Comirnaty, Pfizer-BioNTech) COVID-19 booster vaccine against covid-19 related symptoms in England: test negative case-control study. November 15, 2021 (https://www.medrxiv.org/content/10.1101/2021.11.15.21266341v1). preprint.
37. Munro APS, Janani L, Cornelius V, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet 2021;398:2258-76.