Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: 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. DOI: 10.1056/NEJMoa2107456

SUPPLEMENTARY APPENDIX

List of Investigators

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Ethical Conduct of the Study

This study was conducted in accordance with the study protocol and principles within the International Conference on Harmonisation Guidelines for Good Clinical Practice, the Declaration of Helsinki, and Council for International Organizations of Medical Sciences International Ethical Guidelines. All applicable laws and regulations were followed and the study protocol, informed consent documents, and other relevant documents were prospectively approved by institutional review board/ethics committees (IRB/EC) at each study site. Before any study activity, written informed consent was obtained from participants, or their parents/legal guardians. When consent was obtained from a parent/legal guardian, affirmative agreement from the participant was subsequently obtained when in the capacity to provide assent, as determined by the IRB/EC.

Study Responsibilities

Pfizer was responsible for the design, study conduct, data collection, data analysis, data interpretation, and writing of this manuscript. Both Pfizer and BioNTech manufactured clinical trial material. BioNTech was the sponsor of the study and contributed to data interpretation and writing of the manuscript. All study data were available to all authors who vouch for its accuracy and adherence of the study to the protocol.

Determination of SARS-CoV-2 Infection and COVID-19 Illness

Surveillance for potential cases of COVID-19 was undertaken throughout the study. A participant was considered to have potential COVID-19 illness if the participant developed acute respiratory illness. In this circumstance, the participant was to be assessed using a nasal (midturbinate) swab, which was tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid Xpert Xpress SARS-CoV-2), or other equivalent nucleic acid amplification-based test (NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests were assessed. The central laboratory NAAT result was used for the case definition. If no result was available from the central laboratory, a local NAAT result could be used if it was obtained using either the Cepheid Xpert Xpress SARS-CoV-2, Roche cobas SARS-CoV-2 real-time RT-PCR test, or the Abbott Molecular/RealTime SARS-CoV-2 assay.

SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases were documented (for both, the onset date of the case was the date that symptoms were first experienced by the participant; if new symptoms were reported within 4 days after resolution of all previous symptoms, they were considered as part of a single illness). The definition of confirmed COVID-19 included the presence of ≥1 symptom (ie, fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, vomiting) and being SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period (either at the central laboratory or at a local testing facility and using an acceptable test).

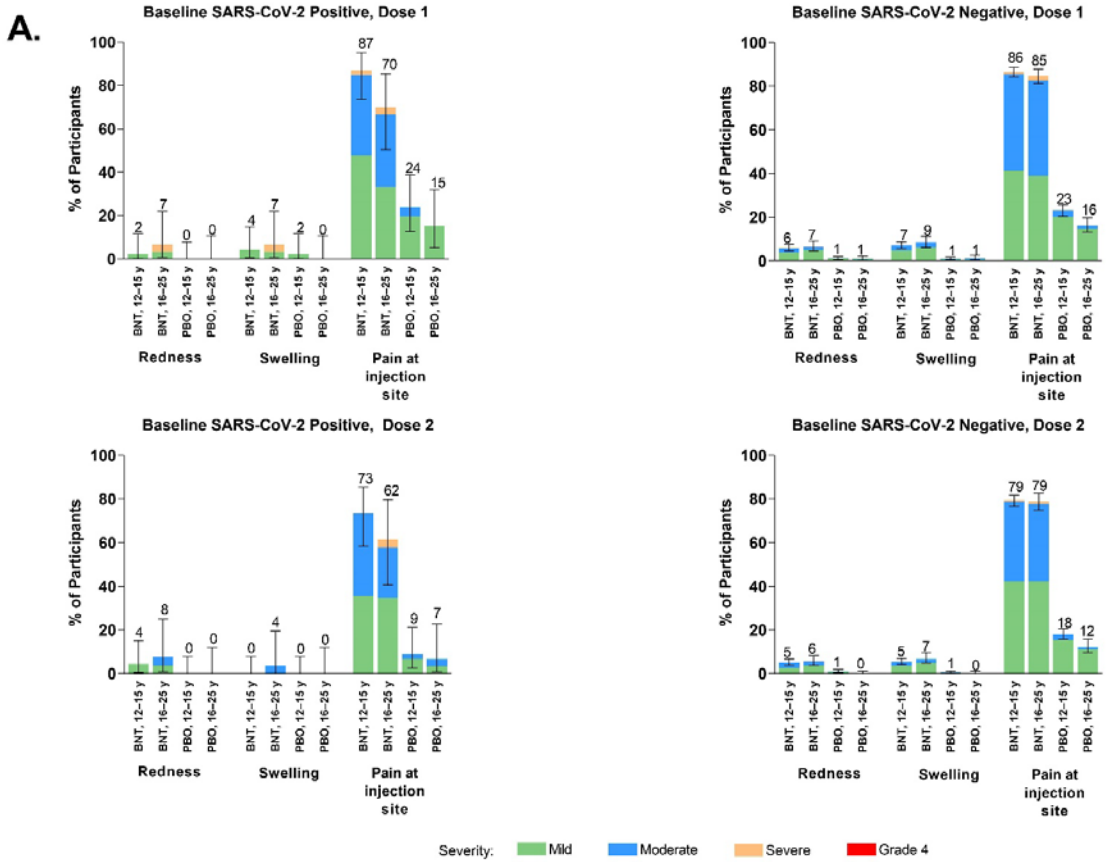
Diagnosis of severe COVID-19 included confirmed COVID-19 and the presence of ≥1 of the following: (1) clinical signs at rest indicative of severe systemic illness (eg, respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mmHg; (2) respiratory failure (ie, needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation); (3) evidence of shock (ie, systemic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors); (4) significant acute renal, hepatic, or neurologic dysfunction; (5) intensive care unit (ICU) admission; or (6) death. Severe COVID-19, as defined by the US Centers for Disease Control and Prevention (CDC), includes: 1) hospitalization; 2) admission to the ICU; 3) intubation or mechanical ventilation; or 4) death (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions [accessed April 25, 2021]).

Calculation of Immunogenicity Parameters

The GMR and associated 2-sided 95% CI were derived by calculating differences in means (12–15-year-olds minus 16–25-year-olds) and CIs on the natural log scale of the titers based on the Student's *t* distribution and then exponentiating results. A sample size of 225 evaluable participants (or 280 vaccine recipients) per age group was estimated to provide 90.8% power for declaring noninferiority (95% CI lower limit for the GMR >0.67). Due to a testing laboratory supply limitation of the qualified viral lot used during the validation of the assay and clinical testing of samples, immunogenicity analyses were performed only on participants who had the required tests completed using the same available viral reagent lot. SARS-CoV-2 neutralizing GMTs were derived by calculating and then exponentiating the mean of the assay results; the associated 2-sided CIs were determined from the natural log scale of the results using the Student's *t* distribution and then exponentiating the confidence limits. GMFRs were calculated by exponentiating the mean of the difference of logarithmically transformed assay results; associated 2-sided CIs were obtained using the Student's *t* distribution for the mean difference and exponentiating the confidence limits. GMFRs were only calculated for participants with nonmissing values before the first dose and at the postvaccination timepoint.

Figure S1. Local reactions and systemic events reported within 7 days after administration of BNT162b2 or placebo, according to age group and baseline SARS-CoV-2 status

Panel A shows local reactions after dose 1 and dose 2 and panel B shows systemic events after dose 1 and 2 in participants 12–15 and 16–25 years old. Results are for the reactogenicity subset of the safety population, which included all participants in the 12–15 years old group and the subset of participants in the 16–25 years old group who had electronic diary data. Baseline SARS-CoV-2 positive included a positive N-binding antibody result at Visit 1, a positive nucleic acid amplification test (NAAT) result at Visit 1, or a medical history of COVID-19. Participants whose baseline SARS-CoV-2 status could not be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis. Severity categories for local reactions and systemic events are described in **Figure 2** and fever categories are designated in the key. The numbers above the bars show the overall percentage of participants in each group who reported the specified local reaction or systemic event. Error bars are the 95% CI. BNT=BNT162b2; PBO=placebo; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.



B.

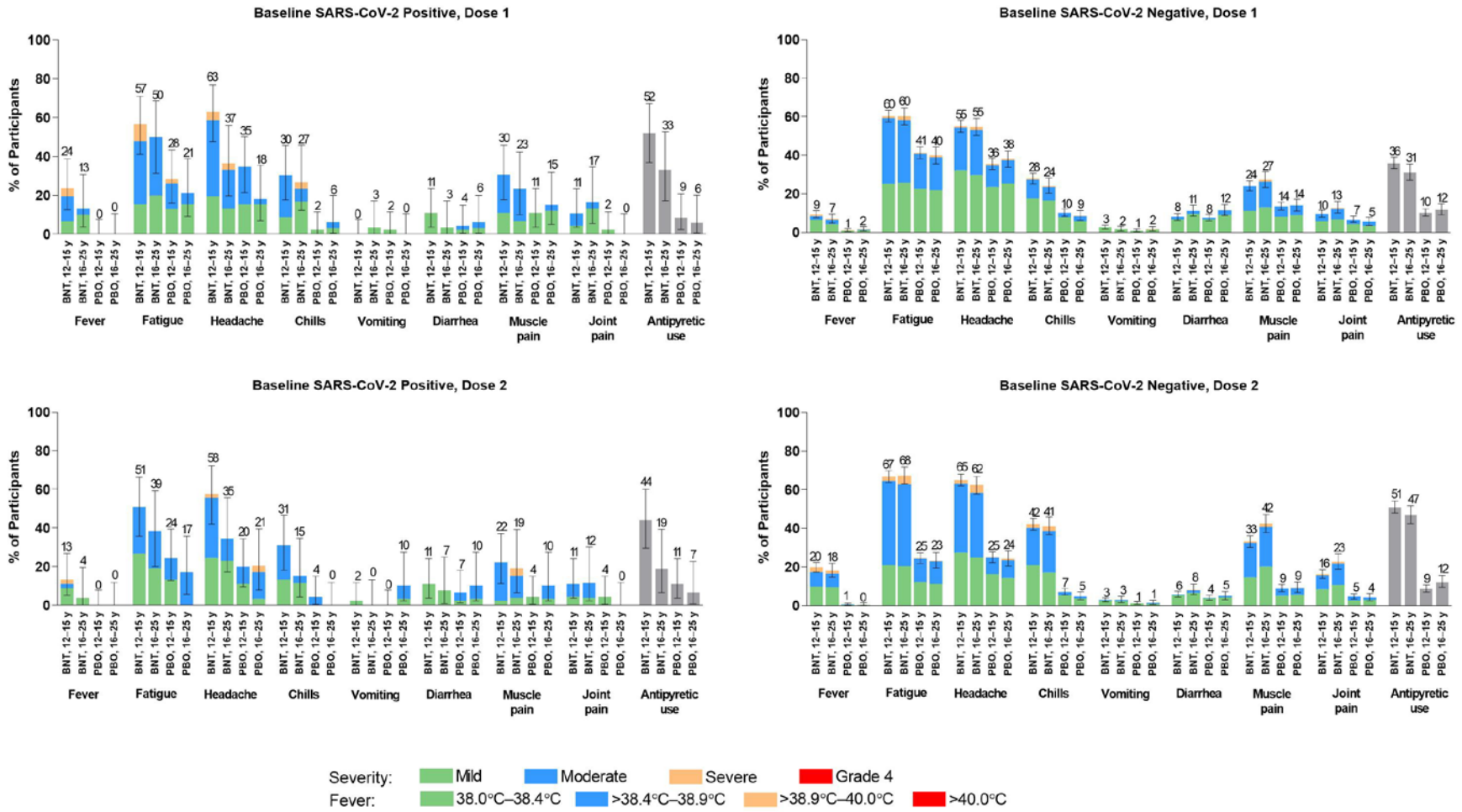

Baseline SARS-CoV-2 Positive, Dose 1
Baseline SARS-CoV-2 Negative, Dose 1
Baseline SARS-CoV-2 Positive, Dose 2
Baseline SARS-CoV-2 Negative, Dose 2
% of Participants
BNT, 12–15 y
BNT, 16–25 y
PBO, 12–15 y
PBO, 16–25 y
Fever
Fatigue
Headache
Chills
Vomiting
Diarrhea
Muscle pain
Joint pain
Antipyretic use
Severity: Mild Moderate Severe Grade 4
Fever: 38.0°C–38.4°C >38.4°C–38.9°C >38.9°C–40.0°C >40.0°C

Figure S2. Geometric mean titers and geometric mean fold rises of SARS-CoV-2 50% neutralizing titers for participants 12–15 years old and 16–25 years old

Results are for the dose 2 evaluable immunogenicity population, irrespective of baseline SARS-CoV-2 infection status.
Error bars are the 95% CI. The data within the bars are the GMTs with 95% CI. n=154–207 for the BNT162b2 12–15 years old group, n=135–185 for the BNT162b2 16–25 years old group, n=29–36 for the placebo 12–15 years old group, and n=24–32 for the placebo BNT162b2 16–25 years old group.
GMTs, GMFRs, and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers or fold rises and the corresponding CIs (based on the Student *t* distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
GMFR=geometric mean fold rise; GMT=geometric mean titer; LLOQ=lower limit of quantitation; NT50=50% neutralizing titer; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

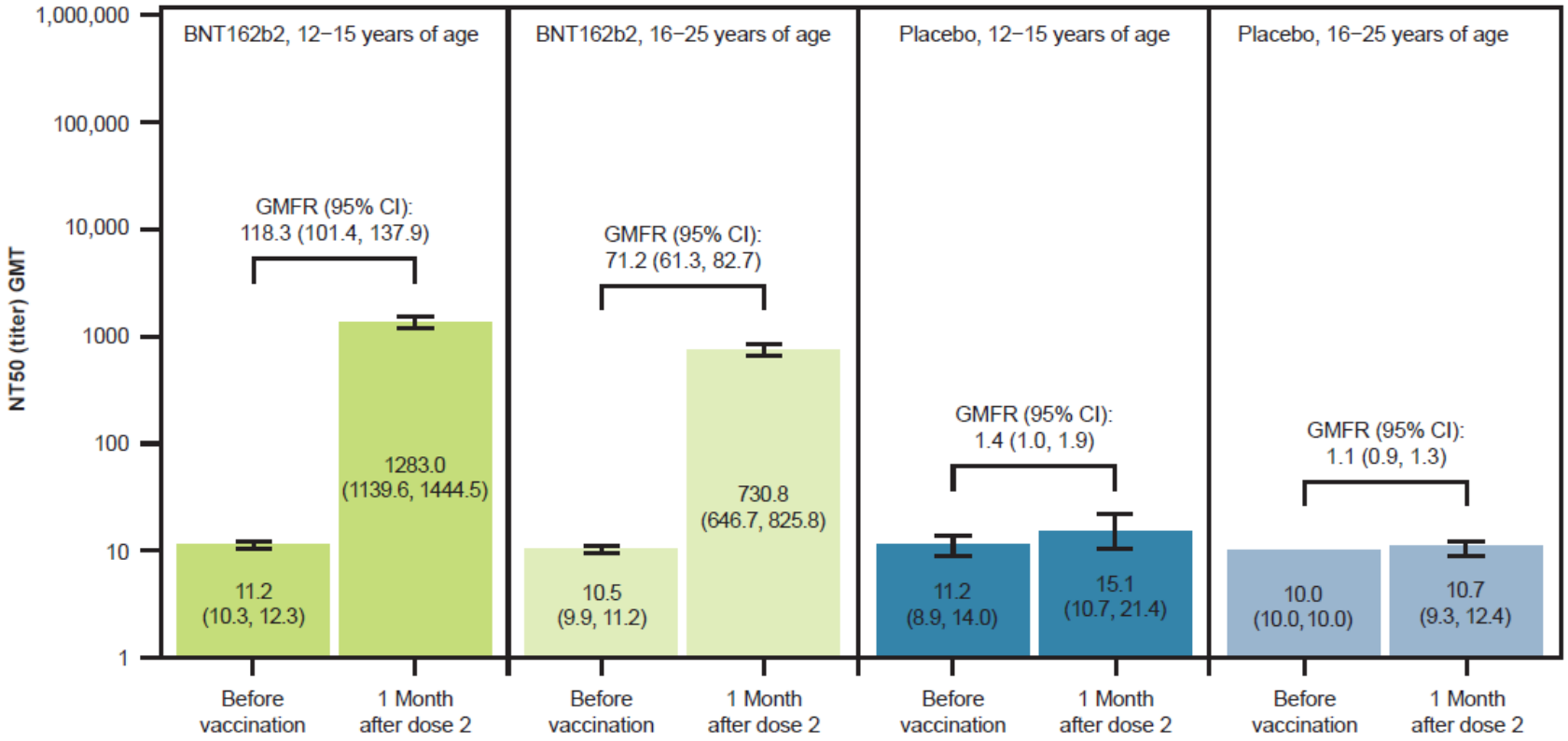


Table S1. Explanation of populations for various analyses

Figure/table number	Figure/table title	Population(s) and sample size*
Figure 1	Disposition of participants 12–15 years old (A), and 16–25 years old (B)	All randomized participants 12–15 years old (N=2264) and 16–25 years old (N=3788)
Figure 2	Local reactions and systemic events reported within 7 days after administration of BNT162b2 or placebo, according to age group	Reactogenicity subset of the safety population, which included all participants in the 12–15 years old group (N=2260) and the subset of participants in the 16–25 years old group who had electronic diary data (N=1097)†
Table 1	Demographic characteristics of the participants	Reactogenicity subset of the safety population, which included all participants in the 12–15 years old group (N=2260) and the subset of participants in the 16–25 years old group who had electronic diary data (N=1098)
Table 2	Geometric mean ratio of 50% neutralizing titers 1 month after dose 2 of participants 12–15 years old and 16–25 years old without evidence of infection up to 1 month after dose 2	The subset of the dose 2 evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection of 12–15 year olds (N=190) and 16–25 year olds (N=170); ie, participants who had no serologic or virologic evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at vaccination visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at vaccination visits 1 and 2, and had negative NAAT [nasal swab] at any unscheduled visit up to 1 month after dose 2)
Table 3	Vaccine efficacy in participants 12–15 years old	Evaluable efficacy population, which included all eligible 12–15-year-old participants (without evidence of infection prior to 7 days after dose 2: N=1983; with or without evidence of infection prior to 7 days after dose 2: N=2229) who received 2 doses of BNT162b2 or placebo as randomized, with dose 2 received within the predefined window, and had no major protocol deviations
Table S2	Participants 12–15-years-old and 16–25-years-old reporting at least 1 adverse event from dose 1 through 1 month after dose 2	Reactogenicity subset of the safety population, which included all participants in the 12–15 years old group (N=2260) and the subset of participants in the 16–25 years old group who had electronic diary data (N=1097)
Table S3	Vaccine efficacy in participants 12–15 years old at time points from after dose 1 to 2 to <4 months after dose 2 (adjusted for surveillance time)	All-available efficacy population, which includes all 12–15-year-old participants (N=2260) who received 1 or 2 doses
Figure S1	Local reactions and systemic events reported within 7 days after administration of BNT162b2 or placebo, according to age group and baseline SARS-CoV-2 status	Reactogenicity subset of the safety population, which included all participants in the 12–15 years old group (N=2260) and the subset of participants in the 16–25 years old group who had electronic diary data (N=1097)†
Figure S2	Geometric mean titers and geometric mean fold rises of SARS-CoV-2 50% neutralizing titers of participants 12–15 years old and 16–25 years old	Dose 2 evaluable immunogenicity population, irrespective of baseline SARS-CoV-2 infection status ▪ Participants 12–15 years old: N=184 (before vaccination) and N=243 (1 month after dose 2) for geometric mean titers; N=183 for geometric mean fold rises ▪ Participants 16–25 years old: N=160 (before vaccination) and N=217 (1 month after dose 2) for geometric mean titers; N=159 for geometric mean fold rises

*N values include BNT162b2 and placebo recipients combined where applicable.
†One participant 16–25 years old was HIV positive; this participant was included in the disposition and demographic summary, but not in the safety, efficacy, and immunogenicity analyses.

Table S2. Participants 12–15-years-old and 16–25-years-old reporting at least 1 adverse event from dose 1 through 1 month after dose 2

Adverse event	BNT162b2		Placebo	
	12–15 years old (N*=1131) n† (%)	16–25 years old (N*=536) n† (%)	12–15 years old (N*=1129) n† (%)	16–25 years old (N*=561) n† (%)
Any event	68 (6.0)	58 (10.8)	67 (5.9)	45 (8.0)
Related‡	33 (2.9)	33 (6.2)	21 (1.9)	12 (2.1)
Severe	7 (0.6)	9 (1.7)	2 (0.2)	3 (0.5)
Life-threatening	1 (0.1)	0	1 (0.1)	0
Any serious adverse event	4 (0.4)	2 (0.4)	1 (0.1)	2 (0.4)
Related‡	0	0	0	0
Severe	2 (0.2)	2 (0.4)	0	1 (0.2)
Life-threatening	0	0	1 (0.1)	0
Any adverse event leading to discontinuation	2 (0.2)	1 (0.2)	0	2 (0.4)
Related‡	1 (0.1)	1 (0.2)	0	0
Severe	1 (0.1)	1 (0.2)	0	0
Life-threatening	1 (0.1)	0	0	0
Death	0	0	0	0

Results are for the reactogenicity subset of the safety population, which included all participants in the 12–15 years old group and a subset of participants in the 16–25 years old group.

*Number of participants in the specified group. This value is the denominator for the percentage calculations.

†Number of participants reporting ≥1 occurrence of the specified event category. For 'any event', n=the number of participants reporting ≥1 occurrence of any event.

‡Assessed by the investigator as related to investigational product.

Table S3. Vaccine efficacy in participants 12–15 years old at time points from after dose 1 to 2 to <4 months after dose 2 (adjusted for surveillance time)

Efficacy endpoint subgroup	BNT162b2 (N=1131)		Placebo (N=1129)		VE (95% CI[§])
	n1[*]	Surveillance time[†] (n2[‡])	n1*	Surveillance time[†] (n2[‡])	
First COVID-19 occurrence after dose 1	3	0.257 (1120)	35	0.250 (1119)	91.6% (73.5, 98.4)
After dose 1 to before dose 2	3	0.065 (1120)	12	0.065 (1119)	75.1% (7.6, 95.5)
After dose 1 to <11 days after dose 1	3	0.034 (1120)	4	0.034 (1119)	25.1% (–342.6, 89.0)
≥11 days after dose 1 to before dose 2	0	0.032 (1117)	8	0.031 (1115)	100.0% (41.6, 100.0)
Dose 2 to 7 days after dose 2	0	0.021 (1114)	5	0.021 (1105)	100.0% (–8.1, 100.0)
≥7 days after dose 2	0	0.170 (1113)	18	0.164 (1100)	100.0% (78.0, 100.0)
≥7 days after dose 2 to <2 months after dose 2	0	0.137 (1113)	16	0.134 (1100)	100.0% (74.8, 100.0)
≥2 months after dose 2 to <4 months after dose 2	0	0.031 (654)	2	0.029 (624)	100.0% (–399.9, 100.0)

Results are for the all-available efficacy population, which includes all 12–15-year-old participants who received 1 or 2 doses.
*Number of participants meeting the endpoint definition.
[†]Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from dose 1 to the end of the surveillance period for overall row and from the start to the end of the range stated for each time interval.
[‡]Number of participants at risk for the endpoint.
[§]95% CI for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
VE=vaccine efficacy.