Supplementary Appendix

Supplement to: Muñoz FM, Sher LD, Sabharwal C, et al. Evaluation of BNT162b2 Covid-19 vaccine in children younger than 5 years of age. N Engl J Med 2022;387:621-34. DOI: 10.1056/NEJMoa2211031

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

SUPPLEMENTARY APPENDIX

List of Investigators

Name	Institute	Location
Acevedo, Armando	Acevedo Clinical Research Associates	Miami, FL, USA
Adkinson, Rachel*	Johns Hopkins University Center for Immunization Research	Baltimore, MD, USA
Anderson, Evan	Emory Children's Center Illness POD	Atlanta, GA, USA
	Emory University School of Medicine	Atlanta, GA, USA
Armiñana, Angels Ulied	EAP Centelles	Barcelona, Spain
Arora, Samir	Aventiv Research Inc	Columbus, OH, USA
Baker, Jeffrey	Clinical Research Prime	Idaho Falls, ID, USA
Barnett, Elizabeth	Boston Medical Center	Boston, MA, USA
Bocchini, Claire†	Texas Children's Hospital and Baylor College of Medicine	Houston, TX, USA
Bollyky, Jenna‡	Clinical & Translational Research Unit (CTRU) & Spectrum BioBank, Stanford University	Palo Alto, CA, USA
Boppana, Suresh	University of Alabama at Birmingham - School of Medicine	Birmingham, AL, USA
Caserta, Mary	University of Rochester Medical Center	Rochester, NY, USA
Casey, Janet	Rochester Clinical Research, Inc	Rochester, NY, USA
Chalhoub, Fadi	Clinical Neuroscience Solutions, Inc	Jacksonville, FL, USA
Conejo, Pablo Rojo	Hospital Universitario 12 de Octubre	Madrid, Spain
Czajka, Hanna	Centrum Badań Klinicznych Jagiellońskie	Krakow, Poland
Davis, Christopher	Tribe Clinical Research, LLC	Greenville, SC, USA
Day, J Chris (replaced Pahud, Barbara)	Children's Mercy Hospital	Kansas City, MO, USA
De Valle, Oscar	West Houston Clinical Research Service	Houston, TX, USA
Dever, Michael	Clinical Neuroscience Solutions	Orlando, FL, USA
Domachowske, Joseph	SUNY Upstate Medical University	Syracuse, NY, USA
Eder, Frank	Meridian Clinical Research, LLC	Binghamton, NY, USA
Englund, Janet	Seattle Children's Hospital	Seattle, WA, USA
Feijoo, Brittany‡	Johns Hopkins University Center for Immunization Research	Baltimore, MD, USA
Fergie, Jaime	Driscoll Children's Hospital	Corpus Christi, TX, USA
Frenck Jr, Robert‡	Cincinnati Children's Hospital Medical Center	Cincinnati, OH, USA
Guasch, Clàudia Fortuny	Hospital Sant Joan de Déu	Barcelona, Spain
Hand, Jonathan (previously Garcia-Diaz, Julia)	Ochsner Clinic Foundation	New Orleans, LA, USA
Hartman, Aaron	Virginia Research Center	Midlothian, VA, USA
Kantele, Anu	Meilahti Vaccine Research Center (MeVac)	Helsinki, Finland
Klein, Terry	Alliance for Multispecialty Research, LLC	Wichita, KS, USA
Kokko, Satu	Tampere University/Oulu Vaccine Research Clinic	Oulu, Finland

Kopinska, Elzbieta	MICS Centrum Medyczne Torun	Torun, Poland
Korbal, Piotr	In-Vivo Społka Z Ograniczoną	Bydgoszcz, Poland
Korkowski, Sarah‡	Seattle Children's Hospital	Seattle, WA, USA
Koski, Susanna	Tampere University/Helsinki South Vaccine Research Clinic	Helsinki, Finland
Li, Simon	Rutgers University	New Brunswick, NJ, USA
López, José García-Sicilia	Hospital Universitario HM Montepríncipe	Madrid, Spain
Majda-Stanisławska, Ewa	GRAVITA Diagnostyka i Leczenie nieplodnosci	Lodz, Poland
Maldonado, Yvonne	Clinical & Translational Research Unit (CTRU) & Spectrum BioBank, Stanford University	Palo Alto, CA, USA
Marshall, Gary	Novak Center for Children's Health	Louisville, KY, USA
Martinón-Torres, Federico	CHUS - Hospital Clínico Universitario de Santiago	Santiago de Compostela, Spain
Meyer, Jay	Meridian Clinical Research, LLC	Lincoln, NE, USA
Mirani, Gayatri†	Texas Children's Hospital and Baylor College of Medicine	Houston, TX, USA
Montañà, Josep-Lluís Arimany	Hospital Universitari General de Catalunya	Barcelona, Spain
Muñoz, Flor	Texas Children's Hospital - Clinical Research Center	Houston, TX, USA
Nachman, Sharon	Advanced Specialty Care	Commack, NY, USA
	Clinical Research Center	East Setauket, NY, USA
	Stony Brook University	Stony Brook, NY, USA
Natalini Martínez, Silvina	Hospital HM Puerta del Sur	Mostoles, Spain
Ogbuagu, Onyema	Yale Center for Clinical Investigation	New Haven, CT, USA
Paavola, Pauliina	Tampere University/Kokkola Vaccine Research Clinic	Kokkola, Finland
Patel, Nehali	St. Jude Children's Research Hospital	Memphis, TN, USA
Paulsen, Grant	Cincinnati Children's Hospital Medical Center	Cincinnati, OH, USA
Ramchandra, Mahalakshmi	Bay Colony Pediatrics	Dickinson, TX, USA
Riesenberg, Robert	Atlanta Center for Medical Research	Atlanta, GA, USA
Ruedebusch, Paula‡	Seattle Children's Hospital	Seattle, WA, USA
Senders, Shelly	Senders Pediatrics	South Euclid, OH, USA
Seppa, Ilkka	Tampere University/Turku Vaccine Research Clinic	Turku, Finland
Seppa, Ilkka (previously Sipila, Marjaana)	Tampere University/Tampere Vaccine Research Clinic	Tampere, Finland
Sexter, Joanna	Meridian Clinical Research	Washington, DC, USA
Sharp, Stephan	Clinical Research Associates Inc	Nashville, TN, USA
Sher, Lawrence	Peninsula Research Associates	Rolling Hills Estates, CA, USA
Simonsen, Kari	Children's Hospital & Medical Center	Omaha, NE, USA
Slechta, Stacy	Alliance for Multispecialty Research, LLC	Newton, KS, USA

Smith, Michael‡	Duke Vaccine and Trials Unit	Durham, NC, USA
Smith, Yvonne	Rophe Adult and Pediatric Medicine/SKYCRNG	Union City, GA, USA
Stryczynska-Kazubska, Joanna	Rodzinne Centrum Medyczne LUBMED	Lubon, Poland
Suryadevara, Manika‡	SUNY Upstate Medical University	Syracuse, NY, USA
Talaat, Kawsar	Johns Hopkins University Center for Immunization Research	Baltimore, MD, USA
Ukkonen, Benita	Tampere University/Espoo Vaccine Research Clinic	Espoo, Finland
Valdivieso, Mariano Miranda	Hospital de Antequera	Antequera, Spain
Vanchiere, John	LSUHSC-Shreveport Clinical Trials Office	Shreveport, LA, USA
Walter, Emmanuel	Duke Vaccine and Trials Unit	Durham, NC, USA
Wiedermann, Bernhard	Children's National Medical Center	Washington, DC, USA
Wisman Jr, Paul	Pediatric Associates of Charlottesville, PLC	Charlottesville, VA, USA
	Pediatric Research of Charlottesville, LLC	Charlottesville, VA, USA
Yudovich, Martin	Pediatric Associates	Houston, TX, USA
Zerbini, Cristiano	CEPIC – Centro Paulista de Investigação Clínica e Serviços Médicos Ltda	São Paulo, Brazil

* Site coordinator
† Co-investigator
‡ Sub-investigator

Eligibility Criteria

The study included healthy participants; those with pre-existing stable disease (ie, disease not requiring a significant change in therapy or hospitalization for worsening disease in the 6 weeks before enrolment) could be included. Exclusion criteria in the phase 1/2/3 portions of the study included receipt of treatments to prevent COVID-19, previous or current multisystem inflammatory syndrome in children (MIS-C) diagnosis, history of severe adverse reaction with a vaccine or any component of the study intervention, and immunodeficiency, autoimmune disease, or conditions associated with prolonged bleeding. In the phase 1 portion of the study, exclusion criteria additionally included past clinical (based on COVID-19 symptoms/signs alone if a SARS-CoV-2 nucleic acid amplification test [NAAT] result was unavailable) or virologic (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) COVID-19 diagnosis, as well as known HIV or hepatitis C or B virus infection.

Ethical Conduct of the Study

This study was conducted in accordance with the study protocol and with consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences Ethical Guidelines, International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable laws and regulations, including applicable privacy laws. The study protocol and any amendments, informed consent documents, and other relevant documents were approved by institutional review board/ethics committees (IRB/EC) before the study was initiated. Before any study activity, written informed consent was obtained from the participants' parents/legal guardians.

Phase 1 Review of Safety Data and Stopping Rules

An Internal Review Committee (IRC) reviewed safety and immunogenicity data to permit dose level escalation in each age group, and to select the dose level to proceed to phase 2/3.

Stopping rules were applied to all phase 1 participants based on review of adverse event (AE) and reactogenicity (electronic diary) data, until the start of phase 2/3 or 30 days after the last dose in phase 1 in each age group. These data were continuously monitored by the investigators and sponsor to allow prompt identification of any event contributing to the stopping rule.

The stopping rule criteria for each BNT162b2 dose level included: (1) if a participant developed a serious AE as assessed by the investigator as possibly related to the vaccine or for which there was no

alternative, plausible, attributable cause; (2) if a participant developed a grade 4 local reaction or systemic event as assessed as possibly related by the investigator, or for which there was no alternative, plausible, attributable clause; (3) if any participant developed a fever >40 ºC for ≥1 daily measurement after vaccination as assessed as possibly related by the investigator, or for which there was no alternative, plausible, attributable cause; (4) if two participants within the same age group reported the same or similar severe AEs after vaccination as assessed by the investigator as possibly related to the vaccine or for which there was no alternative, plausible, or attributable cause; and (5) if any participant died or required intensive care unit (ICU) admission because of SARS-CoV-2 infection.

If a stopping rule was met, the IRC was to consider all data; randomization and vaccine administration for all dose levels in the affected age group were to be paused; and the Data Monitoring Committee was to review all appropriate data. All other routine study conduct activities were to continue for all vaccinated participants.

Seroresponse Definition

Seroresponse was defined as an increase in titer of ≥4 times that of baseline (before dose 1), or by titer ≥4 times the lower limit of quantitation (LLOQ) if the baseline measurement was <LLOQ.

Immunobriding Analysis

Post-dose 2 immunobridging assessment

The pediatric post-dose 2 immunobridging subset included approximately 300 participants in the BNT162b2 group and 150 participants in the placebo group for each pediatric age group (ie, 6 months–<2 years and 2–4 years of age). Comparator data were from a randomly selected subset of participants 16–25 years of age from Study C4591001 and included approximately 300 participants in the BNT162b2 group and 50 in the placebo group. Different sets of 16–25-year-old participants were selected for each of the pediatric age group immunobridging analyses.

Post-dose 3 immunobridging assessment

The pediatric post-dose 3 immunobridging subset included the first approximately 200 participants in each pediatric age group (ie, 6 months–<2 years and 2–4 years of age) who received dose 3 of BNT162b2 3-µg and 100 who received placebo, completed the 1 month after dose 3 visit, and had 1 month after dose 3 blood sample collection (this included a non-overlapping group of participants relative to the prior post-dose 2 immunobridging analyses). The comparator group of young adults

16–25 years of age from Study C4591001 included a random subset of 200 participants who received dose 2 of BNT162b2 30-μg and 50 who received placebo (this included a different group of young adults relative to the prior post-dose 2 immunobridging analyses).

Additional Procedures for Monitoring of Potential Myocarditis or Pericarditis

Any study participant who reported acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks after a study vaccination was evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis.

Determination of SARS-CoV-2 Infection, COVID-19, and MIS-C

Surveillance for potential COVID-19 and MIS-C cases occurred throughout a participant's involvement in the study. Participants who developed an acute illness were considered to have potential COVID-19. In this circumstance, assessments were to include nasal (anterior nares) swab sample collection by site staff personnel or a participant's parent/guardian, which were tested at a central laboratory using the reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid) or other equivalent nucleic acid amplification–based test (NAAT), to detect SARS-CoV-2. Clinical information and results from local standard-of-care tests were also assessed. The case definition used the central laboratory NAAT result. If no central laboratory result was available, 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 [≥3 loose stools per day], vomiting, and inability to eat/poor feeding) 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 using an acceptable test) and which triggered a potential COVID-19 illness visit.

Diagnosis of severe COVID-19 included the US Centers for Disease Control and Prevention (CDC) definition (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-

medicalconditions.html), and the protocol-defined definition of confirmed COVID-19, which required the presence of ≥1 of the following that triggered a potential COVID-19 illness visit:

(1) clinical signs at rest indicative of severe systemic illness (eg, respiratory rate and heart rate as shown in the following table, SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mmHg)

Participant age	Respiratory rate	Heart rate
6–<9 months	>61	>168
9–<12 months	>58	>161
12–<18 months	>53	>156
18–<24 months	>46	>149
2–<3 years	>38	>142
3–<4 years	>33	>136
4–<6 years	>29	>131

(2) respiratory failure (ie, needing high-flow oxygen, including continuous positive airway pressure, bilevel positive airway pressure, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation)

(3) evidence of shock or cardiac failure (ie, systolic blood pressure <70 + [age in years × 2] mmHg for age up to 10 years or requiring vasoactive drugs to maintain blood pressure in the normal range)

(4) significant acute renal failure (ie, serum creatinine ≥2 × upper limit of normal [ULN] for age or 2-fold increase in baseline creatinine

(5) significant gastrointestinal/hepatic failure (ie, total bilirubin ≥4 mg/dL or alanine transaminase 2 × ULN for age)

(6) significant neurological dysfunction (ie, Glasgow Coma Scale score ≤11 or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline)

(7) intensive care unit admission

(8) death

Confirmed MIS-C was per the CDC MIS-C case definition (available from: www.cdc.gov/mis-c/hcp/ [accessed August 29, 2022]).

Calculation of Immunogenicity Parameters

Geometric mean titers (GMTs) were derived by exponentiating the mean in logarithmically transformed neutralizing titer values. Geometric mean ratios (GMRs) were derived by exponentiating the mean of the difference (6-months–<2-year-olds minus 16–25-year-olds, and 2–4-year-olds minus 16–25-year-olds), in logarithmically transformed neutralizing titer values. Associated 2-sided 95% CIs for GMTs and GMRs were obtained by calculating confidence limits for the transformed values

based on the Student *t* distribution and then exponentiating the limits. Geometric mean fold rises (GMFRs) were calculated for participants with non-missing values at both time points by exponentiating the mean of the difference (later time point minus earlier time point) of logarithmically transformed assay results. Associated 2-sided 95% CIs were obtained using the Student *t* distribution for the mean difference and exponentiating the confidence limits.

Sample Size Calculations

A sample size of 225 evaluable participants in each age group would provide 90.4% power to demonstrate immunobridging based on GMR and 92.6% power based on seroresponse rate after dose 2. A sample size of 130 evaluable BNT162b2 recipients in each age group would provide 93.3% power to demonstrate immunobridging based on GMR and 90.4% power based on seroresponse rate after dose 3.

Dose 3 Evaluable Immunogenicity Population and Timing of Dose 3 Administration

The dose 3 evaluable immunogenicity population included 204 participants 2–4 years of age who received three BNT162b2 doses and 92 who received placebo, of whom 143 and 59, respectively, were without evidence of prior SARS-CoV-2 infection ≤1 month after dose 3. In participants 6 months–<2 years of age, 132 and 67 received three BNT162b2 and placebo doses, respectively, of whom 82 and 49 were without evidence of prior SARS-CoV-2 ≤1 month after dose 3. The comparator group of young adults included 183 participants in the BNT162b2 30-μg group and 45 participants in the placebo group of the Study C4591001 dose 2 evaluable immunogenicity population, of whom 170 and 38 participants, respectively, were without evidence of prior SARS-CoV-2 infection ≤1 month PD2. All children 6 months–4 years of age in the immunobridging subset received all three 3-μg doses of BNT162b2. All comparator young adults 16–25 years of age received two 30-μg doses of BNT162b2. Most pediatric and young adults (>85%) received dose 2 within the protocol defined window of 19−23 days after dose 1. In children 6 months–<2 years of age, the median (range) timing of dose 3 administration after dose 2 of BNT162b2 was 12.9 (8.6–20.0) and of placebo was 12.2 (8.4–20.0) weeks. In children 2–4 years of age, the median (range) timing of dose 3 administration after dose 2 of BNT162b2 was 10.7 (8.1–15.6) weeks and of placebo was 10.7 (8.6–16.0) weeks.

Figure S1. Participant flow in the phase 1 study among participants (A) 6 months–<2 years of age and (B) 2–4 years of age

The phase 1 study was conducted at 7 US sites.

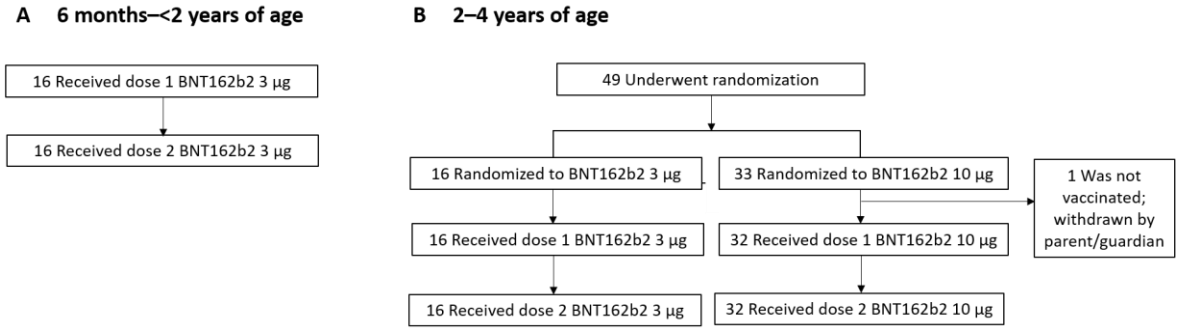

Figure S2. Local reactions and systemic events in participants (A) 6 months–<2 years of age and (B) 2–4 years of age reported 7 days after administration of BNT162b2 in the phase 1 study

The age-specific severity scales and descriptions for reactogenicity events for both age groups are summarized in **Table S4**. Fever categories are designated in the key. Error bars are the 95% CIs. The numbers above the bars show the percentage of participants in each group with the specified local reaction or systemic event. 3 µg=3 µg BNT162b2; 10 µg=10 µg BNT162b2; PD1=after dose 1; PD2=after dose 2.

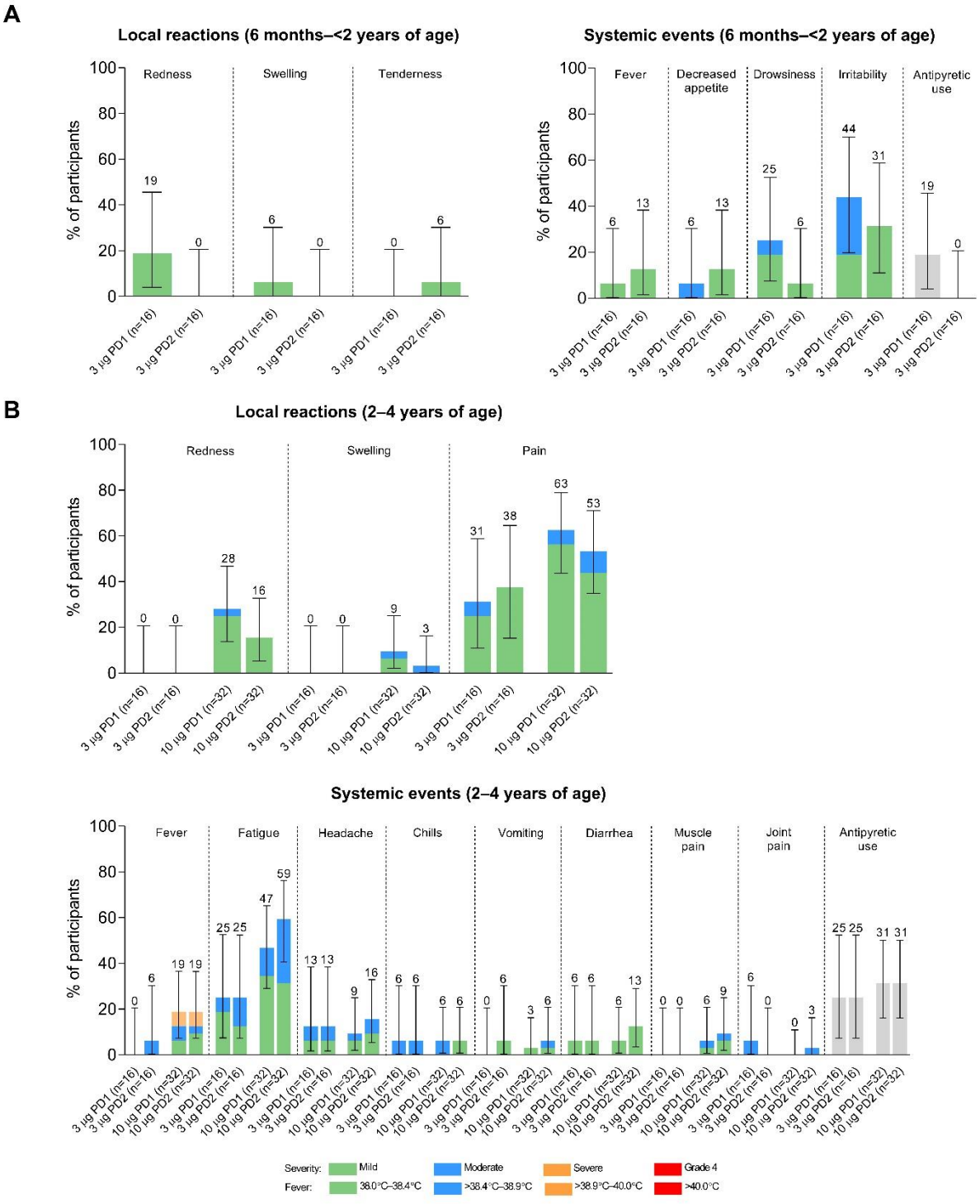

Figure S3. Geometric mean and 95% CI for ancestral strain SARS-CoV-2 neutralizing titers 7 days after dose 2 in phase 1 participants 6 months–11 years of age and 1 month after dose 2 for participants 12–25 years of age from a previous phase 2/3 study

Results are for the all-available immunogenicity population (**Table S1**).

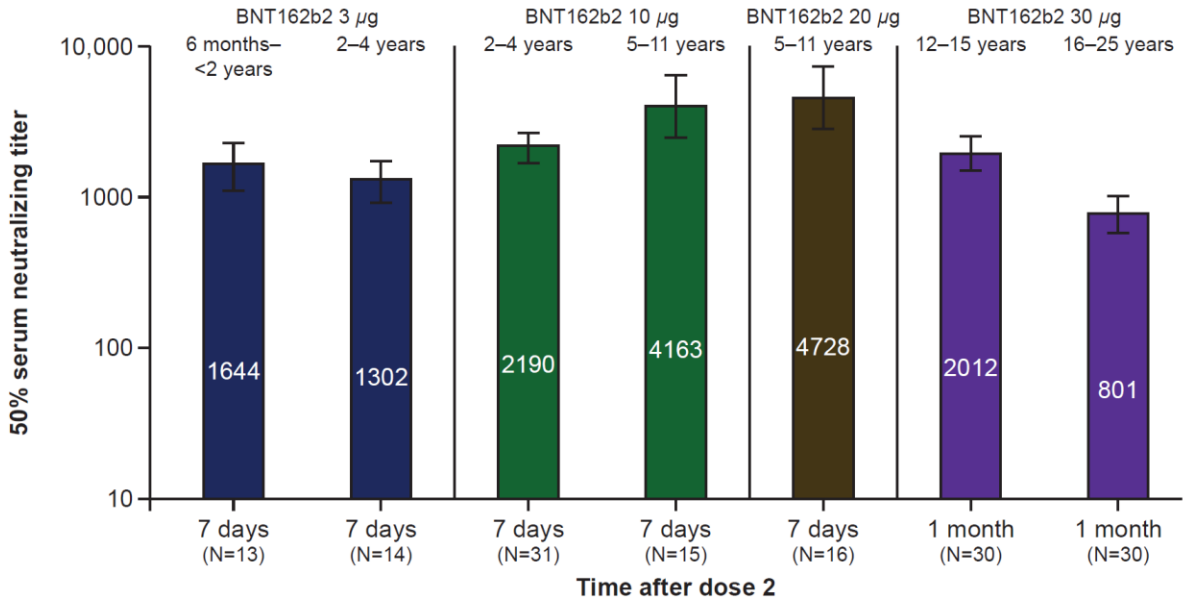

Figure S4. Geometric means of ancestral strain SARS-CoV-2 neutralizing titers for participants 6 months–4 years and 16–25 years of age among BNT162b2 recipients

The 50% neutralizing titers were determined in a validated microneutralization assay against ancestral SARS-CoV-2 strain (USA-WA1/2020). Results are for participants in the immunobridging subset of the dose 3 (for participants 6 months–4 years of age) and dose 2 (for participants 16–25 years of age) evaluable immunogenicity populations (**Table S1**) who had no serological or virological evidence of SARS-CoV-2 infection before the 1 month after dose 3 (for participants 6 months–4 years of age) or dose 2 (for participants 16–25 years of age) blood sample collection, and who had no COVID-19 medical history. Values within the bars are GMTs (95% CIs). The GMFR from before vaccination to 1 month after dose 3 (for all age groups) and from before to after dose 3 (for participants 6 months–<2 years and 2–4 years of age) are shown above the bars. 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. Corresponding GMTs for placebo recipients were 21–24 across timepoints and age groups. D1=dose 1; D3=dose 3; GMFR=geometric mean fold rise; GMT=geometric mean titer; LLOQ=lower limit of quantitation; PD2=after dose 2; PD3=after dose 3.

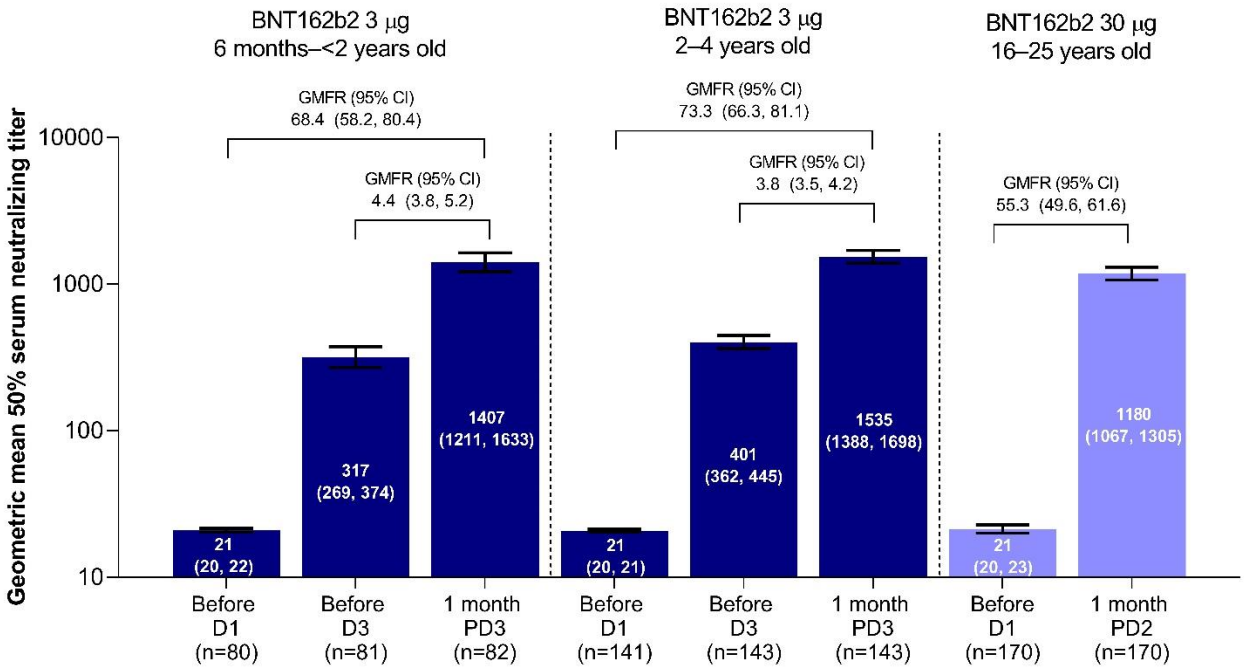

Figure S5. Serum SARS-CoV-2 neutralization titers for the Omicron BA.1 sublineage after dose 3 in participants 6 months–<2 years, 2–4 years, and 18–50 years of age without evidence of prior SARS-CoV-2 infection who received dose 3 approximately 3 months after dose 2

The 50% serum neutralizing titers against the Omicron BA.1 sublineage are shown. Values within the bars are GMTs (95% CIs). Assay results below the LLOQ were set to 0.5 × LLOQ. Results are in the Omicron neutralization subset (**Table S1)** and are based on an unvalidated fluorescent focus reduction neutralization test. Samples were tested contemporaneously for comparability. The adult reference group included participants 18–50 years of age from Study C4591017 (NCT04713553) who had received a third 30-µg BNT162b2 dose at a median (range) of 13.0 (11.9–14.3) weeks after dose 2 and were without evidence of prior SARS-CoV-2 infection (ie, having negative N-binding antibody and negative nucleic acid amplification test results at dose 1, 1 month after dose 2, dose 3, and 1 month after dose 3 study visits). Dose 3 was administered at a median (range) of 12.9 (8.6–20.0) and 10.6 (8.6–13.7) weeks after dose 2 among participants 6 months–<2 years and 2–4 years of age, respectively. GMT=geometric mean titer; LLOQ=lower limit of quantitation; PD3=after dose 3.

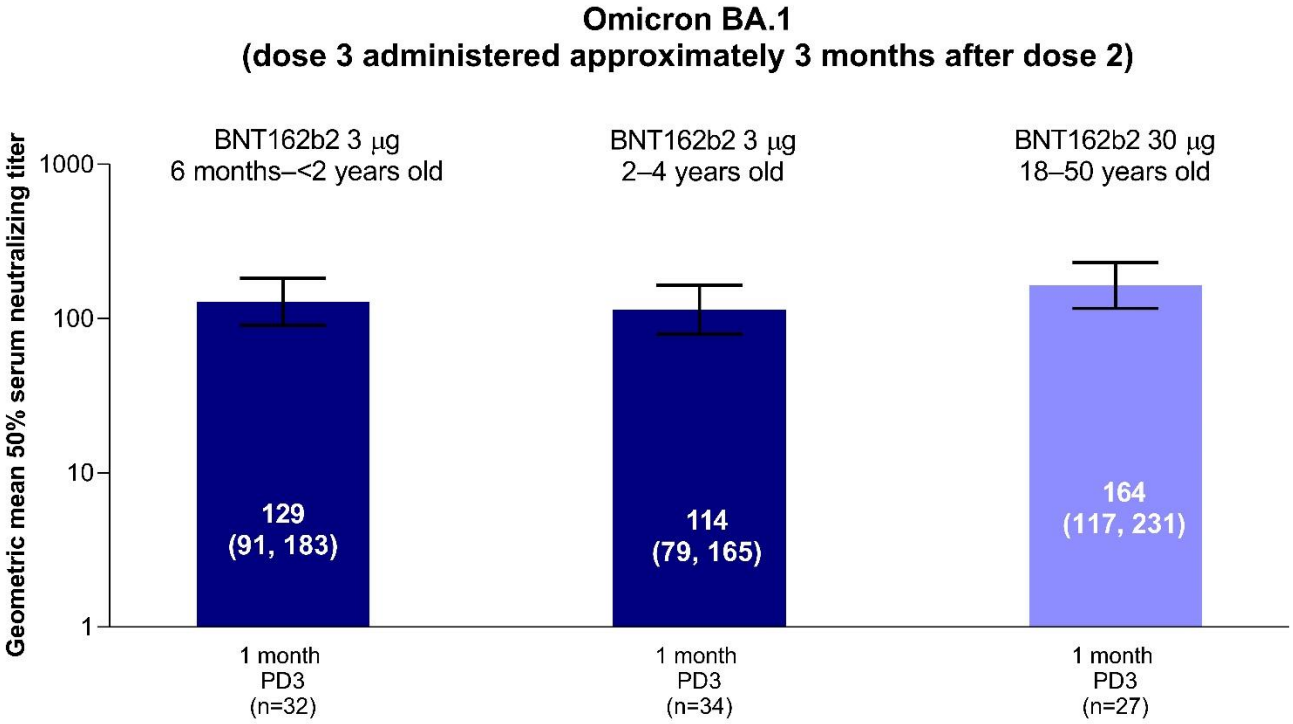

Table S1. Study populations

Population	Description
Enrolled	All participants who provided informed consent
Randomized	All participants who were assigned a randomization number
Dose 2 evaluable immunogenicity	All eligible randomized participants who received two doses of the vaccine at the same dose level to which they were randomized, with dose 2 received within the predefined window (within 19–42 days after dose 1), having ≥1 valid and determinate immunogenicity result after dose 2 from the blood sample collected within an appropriate window after dose 2 (within 6–8 days after dose 2 for phase 1 and within 28–42 days after dose 2 for phase 2/3), and having no other important protocol deviations as determined by the clinician
Dose 3 evaluable immunogenicity	All eligible randomized participants who received three doses of the vaccine at the same dose level to which they were randomized, with dose 2 received within the predefined window (within 19–42 days after dose 1), with dose 3 received within the predefined window (≥60 days after dose 2), having ≥1 valid and determinate immunogenicity result after dose 3 from the blood sample collected within an appropriate window after dose 3 (within 28–42 days after dose 3), and having no other important protocol deviations as determined by the clinician
All-available immunogenicity	Dose 2 all-available: all randomized participants who received 2 doses of the vaccine with ≥1 valid and determinate immunogenicity result after dose 2 from the blood sample collected at 1 month after dose 2 visit regardless of visit window
	Dose 3 all-available: all randomized participants who received 3 doses of the vaccine with ≥1 valid and determinate immunogenicity result after dose 3
Omicron neutralization subset	For each of the pediatric groups, included ~40 BNT162b2 3-µg recipients randomly selected from the post-dose 3 immunobridging subset (see definition in Immunobriding Analysis section of **Supplementary Appendix**) who had received 3 vaccine doses and had sufficient blood volume for testing at dose 3 and 1 month after dose 3
	The adult reference group was from the C4591017 study and included ~30 participants 18–50 years of age who had received a third 30-µg BNT162b2 dose approximately 3 months after dose 2
Safety	All participants who received ≥1 dose of the study intervention
Evaluable efficacy	Dose 2 evaluable efficacy: all eligible randomized participants who received all vaccination(s) at the same dose level to which they were randomized, with dose 2 received within the predefined window (within 19–42 days after dose 1), and having no other important protocol deviations as determined by the clinician on or before 7 days after dose 2
All-available efficacy	Dose 1 all-available efficacy: all randomized participants who received ≥1 vaccination
	Dose 2 all-available efficacy: all randomized participants who completed 2 vaccination doses
	Dose 3 all-available efficacy: all randomized participants who completed 3 vaccination doses

Table S2. Demographic characteristics of phase 1 participants*

Characteristic	6 months–<2 years of age	2–4 years of age		
	BNT162b2 3 µg (N=16)	BNT162b2 3 µg (N=16)	BNT162b2 10 µg (N=32)	Total (N=48)
Age at vaccination				
Mean (SD)	15.4 (6.30) months	3.0 (0.73) years	3.1 (0.75) years	3.1 (0.74) years
Median (range)	15.5 (6–23) months	3.0 (2–4) years	3.0 (2–4) years	3.0 (2–4) years
Male, n (%)	10 (62.5)	9 (56.3)	19 (59.4)	28 (58.3)
Race, n (%)				
White	14 (87.5)	12 (75.0)	26 (81.3)	38 (79.2)
Black or African American	0	0	2 (6.3)	2 (4.2)
American Indian or Alaska Native	0	0	1 (3.1)	1 (2.1)
Asian	1 (6.3)	1 (6.3)	2 (6.3)	3 (6.3)
Mutiracial	1 (6.3)	2 (12.5)	1 (3.1)	3 (6.3)
Not reported	0	1 (6.3)	0	1 (2.1)
Hispanic/Latinx, n (%)	3 (18.8)	0	1 (3.1)	1 (2.1)
Country, n (%)				
United States	16 (100.0)	16 (100.0)	32 (100.0)	48 (100.0)

* Results are for the safety population **(Table S1)**.

Table S3. Representativeness of phase 2/3 study participants*

Category	Details
Disease, problem, or condition under investigation	COVID-19 in children younger than 5 years
Special considerations related to	
Sex and gender	COVID-19 rates are similar between male and female children <5 years of age.[1] Limited data are available on the relationship between gender identity and COVID-19.[2]
Age	COVID-19 cases are generally of similar prevalence across age groups.[1] However, in the first 2 weeks of 2022, which corresponded to the peak of the omicron variant wave in the United States, there were 1009 weekly cases per 100,000 population in those 0–4 years of age compared with 1705 weekly cases per 100,000 in the general population and 768 weekly cases per 100,000 population of those ≥75 years of age.[3] However, the US COVID-19-incident deaths were highest in older populations (51 per 100,000 population ≥75 years of age) and lower in young children (0.14 per 100,000 population <5 years of age).[3]
Race or ethnic group	While COVID-19 affects all races and ethnicities, racial and ethnic minority populations are at increased risk for COVID-19-associated hospitalization and mortality.[1,4] Among children <5 years of age, the highest weekly cases in the first 2 weeks of 2022 were in American Indian/Alaska Native populations (771 per 100,000 population) and the lowest in White populations (530 per 100,000 population).[3]
Geography	COVID-19 cases have been reported worldwide, although the number of cases and deaths have varied by country/region.[5] As of June 15, 2022, the number of COVID-19 cases and attributed deaths in the United States were >84 million and >1 million, respectively.
Other considerations	Not applicable
Overall representativeness of this trial	The participants included in this study were younger than 5 years. The proportion of male and female children was 50:50. The study disproportionately included White participants (79%), with 4% and 13% of participants of Black/African American and Hispanic/Latinx race/ethnicity, respectively. The study was conducted in Brazil, Finland, Poland, Spain, and the United States, with 81% of participants from the United States, which has reported high numbers of COVID-19 cases and deaths.

1. US Centers for Disease Control and Prevention. Risk for COVID-19 infection, hospitalization, and death by age group. Updated November 22, 2021. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html. Accessed May 18, 2022.
2. Morgan et al. Front Sociol. 2021;6:650729.
3. US Centers for Disease Control and Prevention. COVID Data Tracker. COVID-19 Weekly Cases and Deaths per 100,000 Population by Age, Race/Ethnicity, and Sex. https://covid.cdc.gov/covid-data-tracker/#demographicsovertime. Accessed May 18, 2022.
4. Khanijahani et al. Int J Equity Health. 2021;20:248.
5. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/. Accessed June 16, 2022.

* A literature search of PubMed and government sources was conducted to determine the representativeness of the participant population to the population of individuals with COVID-19.

Table S4. Severity scale for local reactions and systemic events

	Mild	Moderate	Severe	Grade 4
Local reaction				
<2 years of age				
Tenderness	Hurts if gently touched (eg, whimpers, winces, protests, or withdraws)	Hurts if gently touched with crying	Causes limitation of limb movement	ER visit or hospitalization
Redness	1–4 caliper units (0.5–2.0 cm)	5–14 caliper units (>2.0–7.0 cm)	>14 caliper units (>7 cm)	Necrosis/exfoliative dermatitis
Swelling	1–4 caliper units (0.5–2.0 cm)	5–14 caliper units (>2.0–7.0 cm)	>14 caliper units (>7 cm)	Necrosis
2–4 years of age				
Pain	Does not interfere with activity	Interferes with activity	Prevents daily activity	ER visit or hospitalization
Redness	1–4 caliper units (0.5–2.0 cm)	5–14 caliper units (>2.0–7.0 cm)	>14 caliper units (>7 cm)	Necrosis/exfoliative dermatitis
Swelling	1–4 caliper units (0.5–2.0 cm)	5–14 caliper units (>2.0–7.0 cm)	>14 caliper units (>7 cm)	Necrosis
Systemic event				
<2 years of age				
Decreased appetite (loss of appetite)	Decreased interest in eating	Decreased oral intake	Refusal to eat	ER visit or hospitalization
Drowsiness (increased sleep)	Increased or prolonged sleep bouts	Slightly subdued interfering with daily activity	Disabling; not interested in usual daily activity	ER visit or hospitalization
Irritability (fussiness)*	Easily consolable	Requiring increased attention	Inconsolable; crying cannot be comforted	ER visit or hospitalization
2–4 years of age				
Vomiting	1–2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	ER visit or hospitalization
Diarrhea	2–3 loose stools/24 hours	4–5 loose stools/24 hours	≥6 loose stools/24 hours	ER visit or hospitalization
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalization
Fatigue/tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalization
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalization
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalization
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalization

ER=emergency room; IV=intravenous.

For the fever scale, refer to the legend and scale of **Figure 2** and **Figure S2**.

*Synonymous with restless sleep or decreased sleep.

Table S5. Phase 1 participants reporting ≥1 adverse event from dose 1 to 1 month after dose 2

	6 months–<2 years of age	2–4 years of age	
Adverse event	**BNT162b2 3 µg (N†=16) n‡ (%)**	**BNT162b2 3 µg (N†=16) n‡ (%)**	**BNT162b2 10 µg (N†=32) n‡ (%)**
Any event	2 (12.5)	4 (25.0)	12 (37.5)
Related§	1 (6.3)	2 (12.5)	7 (21.9)
Severe	0	0	0
Life-threatening	0	0	0
Any serious adverse event	0	0	0
Any adverse event leading to discontinuation	0	0	0
Death	0	0	0

Results are for the safety population (**Table S1**).

† 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 the investigational product.

Table S6. Phase 2/3 participants reporting ≥1 adverse event from dose 1 to 1 month after dose 3

Adverse event	6 months–<2 years of age		2–4 years of age	
	BNT162b2 3 µg (N*=1178) n† (%)	Placebo (N*=598) n† (%)	BNT162b2 3 µg (N*=1835) n† (%)	Placebo (N*=915) n† (%)
Any adverse event	355 (30.1)	162 (27.1)	344 (18.7)	171 (18.7)
Related‡	55 (4.7)	21 (3.5)	37 (2.0)	18 (2.0)
Severe	12 (1.0)	10 (1.7)	9 (0.5)	6 (0.7)
Life-threatening	0	1 (0.2)§	0	0
Any serious adverse event	17 (1.4)	14 (2.3)	12 (0.7)	8 (0.9)
Related‡	0	1 (0.2)	1 (0.1)	0
Severe	8 (0.7)	9 (1.5)	5 (0.3)	3 (0.3)
Life-threatening	0	1 (0.2)§	0	0
Any adverse event leading to withdrawal	3 (0.3)	0	3 (0.2)	1 (0.1)
Related‡	3 (0.3)	0	2 (0.1)	1 (0.1)
Serious	0	0	1 (0.1)	0
Severe	1 (0.1)	0	1 (0.1)	1 (0.1)
Life-threatening	0	0	0	0
Death	0	0	0	0

Results are for the safety population (**Table S1)**.

* 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 the investigational product.

§ Grade 4 adverse event (thermal burn).

Table S7. Vaccine efficacy by variant of concern in phase 2/3 participants based on first COVID-19 occurrence from 7 days after dose 3

Variant of concern	BNT162b2 (N=873*)		Placebo (N=381*)		Vaccine efficacy (95% CI)
	n1†	Surveillance time‡ (n2§)	n1†	Surveillance time‡ (n2§)	
Overall	13	0.124 (794)	21	0.054 (351)	73.2% (43.8, 87.6)
Omicron	13	0.124 (794)	20	0.054 (351)	71.8% (40.5, 87.1)
Omicron BA.1.1	0	0.124 (794)	1	0.054 (351)	100.0% (–1591.3, 100.0)
Omicron BA.2	2	0.124 (794)	8	0.054 (351)	89.2% (45.7, 98.9)
Omicron BA.2.10	0	0.124 (794)	1	0.054 (351)	100.0% (–1591.3, 100.0)
Omicron BA.2.12.1	6	0.124 (794)	9	0.054 (351)	71.1% (9.1, 91.5)
Omicron BA.2.21	1	0.124 (794)	0	0.054 (351)	Undefined
Omicron BA.4	2	0.124 (794)	1	0.054 (351)	13.3% (–5016.9, 95.5)
Omicron BA.5	2	0.124 (794)	0	0.054 (351)	Undefined
Unknown	0	0.124 (794)	1	0.054 (351)	100.0% (–1591.3, 100.0)

Cutoff date was June 17, 2022. Data are for participants without evidence of SARS-CoV-2 infection before 7 days after dose 3 in the evaluable efficacy population **(Table S1)**. Two-sided 95% CI for vaccine efficacy was derived based on the Clopper and Pearson method adjusted for surveillance time.

* Number of participants in the specified group.

† Number of participants meeting the specified endpoint.

‡ 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 7 days after dose 3 to the end of the surveillance period.

§ Number of participants at risk for the endpoint.

Results are for the evaluable efficacy population in participants without evidence of previous SARS-CoV-2 infection (**Table S1**). Two-sided 95% CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

* Number of participants in the specified group.

† 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.

§ Number of participants at risk for the endpoint.

‖ COVID-19 cases missing sequencing data were assigned as Delta variant if illness onset date was before December 20, 2021, or Omicron variant if illness onset date was on or after December 20, 2021.