

ORIGINAL ARTICLE

Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents

Robert W. Frenck, Jr., M.D., Nicola P. Klein, M.D., Ph.D., Nicholas Kitchin, M.D., Alejandra Gurtman, M.D., Judith Absalon, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Emmanuel B. Walter, M.D., Shelly Senders, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Hua Ma, Ph.D., Xia Xu, Ph.D., Kenneth Koury, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Timothy Jennings, D.O., Donald M. Brandon, M.D., Stephen J. Thomas, M.D., Özlem Türeci, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

ABSTRACT

BACKGROUND

Until very recently, vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had not been authorized for emergency use in persons younger than 16 years of age. Safe, effective vaccines are needed to protect this population, facilitate in-person learning and socialization, and contribute to herd immunity.

METHODS

In this ongoing multinational, placebo-controlled, observer-blinded trial, we randomly assigned participants in a 1:1 ratio to receive two injections, 21 days apart, of 30 µg of BNT162b2 or placebo. Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants was an immunogenicity objective. Safety (reactogenicity and adverse events) and efficacy against confirmed coronavirus disease 2019 (Covid-19; onset, ≥7 days after dose 2) in the 12-to-15-year-old cohort were assessed.

RESULTS

Overall, 2260 adolescents 12 to 15 years of age received injections; 1131 received BNT162b2, and 1129 received placebo. As has been found in other age groups, BNT162b2 had a favorable safety and side-effect profile, with mainly transient mild-to-moderate reactogenicity (predominantly injection-site pain [in 79 to 86% of participants], fatigue [in 60 to 66%], and headache [in 55 to 65%]); there were no vaccine-related serious adverse events and few overall severe adverse events. The geometric mean ratio of SARS-CoV-2 50% neutralizing titers after dose 2 in 12-to-15-year-old participants relative to 16-to-25-year-old participants was 1.76 (95% confidence interval [CI], 1.47 to 2.10), which met the noninferiority criterion of a lower boundary of the two-sided 95% confidence interval greater than 0.67 and indicated a greater response in the 12-to-15-year-old cohort. Among participants without evidence of previous SARS-CoV-2 infection, no Covid-19 cases with an onset of 7 or more days after dose 2 were noted among BNT162b2 recipients, and 16 cases occurred among placebo recipients. The observed vaccine efficacy was 100% (95% CI, 75.3 to 100).

CONCLUSIONS

The BNT162b2 vaccine in 12-to-15-year-old recipients had a favorable safety profile, produced a greater immune response than in young adults, and was highly effective against Covid-19. (Funded by BioNTech and Pfizer; C4591001 ClinicalTrials.gov number, NCT04368728.)

From Cincinnati Children's Hospital, Cincinnati (R.W.F.); Kaiser Permanente Vaccine Study Center, Oakland (N.P.K.), and the California Research Foundation, San Diego (D.M.B.) — both in California; Vaccine Research and Development, Pfizer, Hurler, United Kingdom (N.K., S.L., R.B.); Vaccine Research and Development, Pfizer, Pearl River (A.G., J.A., K.A.S., K.K., W.V.K., D.C., P.R.D., K.U.J., W.C.G.), and SUNY Upstate Medical University, Syracuse (S.J.T.) — both in New York; Vaccine Research and Development (J.L.P., H.M., X.X.) and Worldwide Safety, Safety Surveillance and Risk Management (S.M.), Pfizer, Collegeville, PA; Duke Human Vaccine Institute, Durham, NC (E.B.W.); Senders Pediatrics, South Euclid, OH (S.S.); Clinical Research Professionals, Chesterfield, MO (T.J.); BioNTech, Mainz, Germany (Ö.T., U.Ş.); and Worldwide Safety, Safety Surveillance and Risk Management, Pfizer, Groton, CT (D.B.T.). Address reprint requests to Dr. Gurtman at Vaccine Research and Development, Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965, or at alejandra.gurtman@pfizer.com.

*The members of C4591001 Clinical Trial Group are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on May 27, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2107456

Copyright © 2021 Massachusetts Medical Society.

AS OF MAY 21, 2021, THE CORONAVIRUS disease 2019 (Covid-19) pandemic has caused more than 165 million infections across all ages globally, as well as more than 3.4 million deaths.¹ BNT162b2 (Pfizer–BioNTech) is a Covid-19 vaccine containing nucleoside-modified messenger RNA encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein.² In healthy adults, two 30- μ g doses of BNT162b2 elicited high neutralizing titers and robust, antigen-specific CD4+ and CD8+ T-cell responses against SARS-CoV-2.^{3,4} In the phase 2–3 part of an ongoing global, phase 1–2–3 randomized, controlled trial involving participants 16 years of age or older, BNT162b2 had a favorable safety profile characterized by transient mild-to-moderate injection-site pain, fatigue, and headache and was 95% effective in preventing Covid-19 from 7 days after dose 2.⁵ On the basis of these findings, BNT162b2 received emergency use authorization from the Food and Drug Administration on December 11, 2020, for Covid-19 prevention in persons 16 years of age or older.⁶ On May 10, 2021, the emergency use authorization was expanded to include persons 12 years of age or older on the basis of data presented in this report.⁷ Other vaccines against SARS-CoV-2 are authorized for emergency use^{1,8–10}; however, BNT162b2 is the only one currently authorized for use in persons younger than 16 years of age.

Although children and adolescents generally have milder Covid-19 than adults, severe illness can occur in this population, especially in those with underlying medical conditions.¹¹ Adolescents may play an important role in SARS-CoV-2 transmission.^{12,13} Thus, their vaccination may prevent disease and contribute to herd immunity. Furthermore, with immunization of older persons, younger persons account for an increased proportion of Covid-19 infections.^{14,15} The pandemic has interrupted the education and social development of students and has simultaneously burdened caregivers.^{16–18} Safe, efficacious vaccines for younger populations are therefore paramount.

METHODS

OBJECTIVES, PARTICIPANTS, AND OVERSIGHT

We conducted a randomized, placebo-controlled, observer-blinded, phase 3 trial as part of a phase 1–2–3 trial assessing BNT162b2 safety, immuno-

genicity, and efficacy in healthy persons 12 years of age or older. This report presents findings from 12-to-15-year-old participants enrolled in the United States, including descriptive comparisons of safety between participants in that age cohort and those who were 16 to 25 years of age and an evaluation of the noninferiority of immunogenicity in the 12-to-15-year-old cohort to that in the 16-to-25-year-old cohort. Data were collected through the cutoff date of March 13, 2021.

Eligible participants were healthy or had stable preexisting disease (including hepatitis B, hepatitis C, or human immunodeficiency virus infection). Persons with a previous clinical or virologic Covid-19 diagnosis or SARS-CoV-2 infection, previous coronavirus vaccination, diagnosis of an immunocompromising or immunodeficiency disorder, or treatment with immunosuppressive therapy (including cytotoxic agents and systemic glucocorticoids) were excluded.

The ethical conduct of the trial is summarized in the Supplementary Appendix, available with the full text of this article at NEJM.org. Additional details of the trial are provided in the protocol, available at NEJM.org. Pfizer was responsible for the trial design and conduct, data collection, data analysis, data interpretation, and writing of the manuscript that was submitted. Both Pfizer and BioNTech manufactured the vaccine and placebo. BioNTech was the regulatory sponsor of the trial and contributed to data interpretation and writing of the manuscript. All data were available to the authors, who vouch for their accuracy and completeness and for the adherence of the trial to the protocol.

PROCEDURES

Randomization was conducted with the use of an interactive Web-based response system. Participants were assigned in a 1:1 ratio to receive two intramuscular injections of 30 μ g of BNT162b2 or placebo (saline) 21 days apart. For evaluation of immediate vaccine-associated reactions, participants were observed in the clinic for 30 minutes after vaccination.

SAFETY

Safety objectives included the assessment of local or systemic reactogenicity events, which were recorded by the participants in an electronic diary (e-diary) for 7 days after each dose. Unsolicited adverse events (i.e., those reported by the partici-

pant without e-diary prompting) and serious adverse events were also recorded from receipt of the first dose through 1 month and 6 months after dose 2, respectively.

IMMUNOGENICITY

Immunogenicity assessments (SARS-CoV-2 serum neutralization assay and receptor-binding domain [RBD]–binding or S1-binding IgG direct Luminex immunoassays) were performed before vaccination and 1 month after dose 2, as described previously.³ The immunogenicity objective was to show noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants. Noninferiority was assessed among participants who had no evidence of previous SARS-CoV-2 infection with the use of the two-sided 95% confidence interval for the geometric mean ratio of SARS-CoV-2 50% neutralizing titers in 12-to-15-year-old participants as compared with 16-to-25-year-old participants 1 month after dose 2. BNT162b2 immunogenicity was evaluated in participants with and those without serologic or virologic evidence of previous SARS-CoV-2 infection. Corresponding end points were the geometric mean SARS-CoV-2 neutralizing titers at baseline (i.e., immediately before receipt of the first injection) and 1 month after dose 2 and geometric mean fold rises (GMFRs) in titers from baseline to 1 month after dose 2.

EFFICACY

The efficacy of BNT162b2 against confirmed Covid-19 with an onset 7 or more days after dose 2 was summarized in participants who did not have evidence of previous SARS-CoV-2 infection, as well as in all vaccinated participants. Surveillance for potential Covid-19 cases was undertaken throughout the trial; if acute respiratory illness developed in a participant, the participant was tested for SARS-CoV-2. Methods for identifying SARS-CoV-2 infections and Covid-19 diagnoses are summarized in the Supplementary Appendix.

STATISTICAL ANALYSIS

The safety population included all participants who received at least one dose of BNT162b2 or placebo. The reactogenicity subset included all 12-to-15-year-old participants and a subset of 16-to-25-year-old participants (those who received

an e-diary to record reactogenicity events). Safety end points are presented descriptively as counts, percentages, and associated Clopper–Pearson two-sided 95% confidence intervals, with adverse events and serious adverse events described according to terms in the *Medical Dictionary for Regulatory Activities*, version 23.1, for each group.

Immunogenicity was assessed in a random subset of participants in each age cohort with the use of a simple random-sample selection procedure. For immunogenicity assessments, all participants in both age cohorts were from U.S. sites. The dose 2 immunogenicity population that could be evaluated included participants who underwent randomization and received two BNT162b2 doses in accordance with the protocol, received dose 2 within the prespecified window (19 to 42 days after dose 1), had at least one valid and determinate immunogenicity result from a blood sample obtained within 28 to 42 days after dose 2, and had no major protocol deviations. Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants was assessed on the basis of the geometric mean ratio of SARS-CoV-2 50% neutralizing titers. A sample of 225 BNT162b2 recipients who could be evaluated (or 280 BNT162b2 recipients overall) in each age cohort was estimated to provide 90.8% power for declaring noninferiority (defined as a lower limit of the 95% confidence interval for the geometric mean ratio of >0.67). A testing laboratory supply limitation of the qualified viral lot used for assay validation and clinical testing resulted in the trial having fewer participants than anticipated for the immunogenicity analyses. Calculations of the geometric mean ratios, geometric mean titers, and GMFRs are described in the Supplementary Appendix.

Although the formal evaluation of efficacy was to be based on the overall results obtained across all age cohorts, the statistical analysis plan specified that descriptive efficacy summaries would be provided for each age cohort (the stratification factor). The efficacy analysis for the 12-to-15-year-old cohort was planned as a descriptive analysis because the number of cases that would occur in the age subgroups was unknown. The efficacy population that could be evaluated included all eligible 12-to-15-year-old participants who underwent randomization and

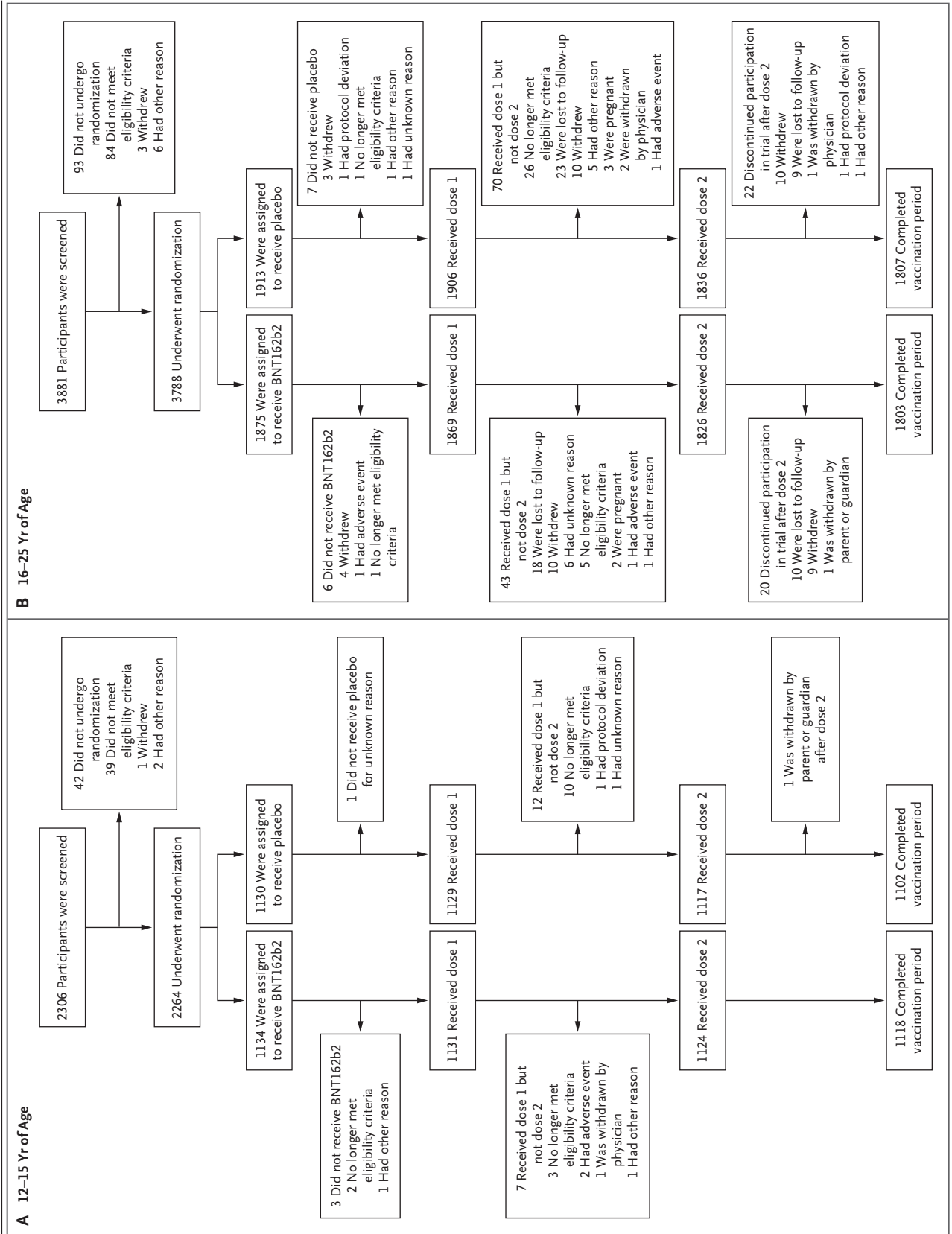


Figure 1 (facing page). Screening, Randomization, and Vaccine and Placebo Administration.

Participants who received dose 1 but not dose 2 could continue to be evaluated for safety. Participants were considered to have completed the vaccination period if they had completed the follow-up visit 1 month after dose 2 as of the data-cutoff date. As of the data-cutoff date, some participants had not yet completed their 1-month follow-up visit after dose 2. Some participants became eligible for a vaccine according to local or national recommendations before the 1-month follow-up visit after dose 2. These participants could choose to be made aware of their randomly assigned injection, and those who had received placebo could then choose to receive BNT162b2. Participants who had originally received placebo and chose to receive BNT162b2 as part of the trial would then follow a different visit schedule.

received two doses of BNT162b2 or placebo, received dose 2 within the prespecified window (19 to 42 days after dose 1), and had no major protocol deviations. The all-available efficacy population included all participants who received one or two doses. Vaccine efficacy was defined as $100 \times (1 - \text{IRR})$, where IRR is the ratio of the rate of a first confirmed Covid-19 illness in the BNT162b2 group to the corresponding rate in the placebo group. Two-sided Clopper–Pearson 95% confidence intervals were calculated (not adjusted for multiple comparisons). Because the number of participants who reported symptoms but were missing a valid polymerase-chain-reaction test result was small, data for these participants were not imputed in the analysis.

RESULTS

PARTICIPANTS

Between October 15, 2020, and January 12, 2021, a total of 2306 adolescents 12 to 15 years of age were screened for inclusion, and 2264 underwent randomization across 29 U.S. sites; 2260 participants received injections, with 1131 receiving BNT162b2 and 1129 receiving placebo (Fig. 1). More than 97% of the BNT162b2 recipients received dose 2. In the reactogenicity subset, all the 12-to-15-year-old participants were from the United States and the 16-to-25-year-old participants were recruited globally (Table 1). Although documented previous Covid-19 was an exclusion criterion, approximately 5% of the participants were SARS-CoV-2–positive at baseline, possibly

because of previous asymptomatic infection. In the immunogenicity subset, all the participants in both age cohorts were from the United States. Among the 2260 participants who were 12 to 15 years of age, 51% were male, 86% were White, and 12% were Hispanic or Latinx. Overall, 1308 participants (58%) had at least 2 months of follow-up after their second vaccine dose. The trial populations are summarized in Table S1 in the Supplementary Appendix.

SAFETY

Reactogenicity

In both age cohorts, BNT162b2 recipients reported more local and systemic events than placebo recipients (Fig. 2). Local and systemic events were generally mild to moderate in severity, reported at similar frequencies in both age cohorts, and typically resolved within 1 or 2 days. In both age cohorts, injection-site pain was the most common local reaction. Severe injection-site pain after any BNT162b2 dose was reported in 1.5% of 12-to-15-year-old participants and in 3.4% of 16-to-25-year-old participants; no severe pain was reported after placebo administration.

In both age cohorts, headache and fatigue were the most frequently reported systemic events. After BNT162b2 injection, severe headache and severe fatigue were reported in a lower percentage of 12-to-15-year-old participants than of 16-to-25-year-old participants. Fever (oral body temperature, $\geq 38^\circ\text{C}$) occurred after dose 2 of BNT162b2 in 20% of 12-to-15-year-old recipients and in 17% of 16-to-25-year-old recipients. The use of antipyretic agents was slightly more frequent among BNT162b2 recipients who were 12 to 15 years of age than among those who were 16 to 25 years of age (37% vs. 32% after dose 1, and 51% vs. 46% after dose 2). Fever with a temperature higher than 40°C occurred in 1 (0.1%) of the 12-to-15-year-old participants 1 day after BNT162b2 dose 1. In general, systemic events were reported more often after BNT162b2 dose 2 than after dose 1. No differences in reactogenicity were noted between participants who were SARS-CoV-2–positive at baseline and those who were SARS-CoV-2–negative at baseline (Fig. S1).

Adverse Events

Among 12-to-15-year-old participants, adverse events occurring from dose 1 through 1 month after dose 2 were reported by 6% of BNT162b2

Table 1. Demographic Characteristics of the Participants.*

Characteristic	BNT162b2		Placebo	
	12–15 Yr (N=1131)	16–25 Yr (N=537)	12–15 Yr (N=1129)	16–25 Yr (N=561)
Male sex — no. (%)	567 (50.1)	255 (47.5)	585 (51.8)	269 (48.0)
Race or ethnic group — no. (%)†				
White	971 (85.9)	445 (82.9)	962 (85.2)	466 (83.1)
Black or African American	52 (4.6)	47 (8.8)	57 (5.0)	50 (8.9)
American Indian or Alaska Native	4 (0.4)	7 (1.3)	3 (0.3)	1 (0.2)
Asian	72 (6.4)	22 (4.1)	71 (6.3)	21 (3.7)
Native Hawaiian or other Pacific Islander	3 (0.3)	3 (0.6)	0	1 (0.2)
Multiracial	23 (2.0)	12 (2.2)	29 (2.6)	19 (3.4)
Not reported	6 (0.5)	1 (0.2)	7 (0.6)	3 (0.5)
Hispanic or Latinx ethnic group — no. (%)†				
Hispanic or Latinx	132 (11.7)	112 (20.9)	130 (11.5)	105 (18.7)
Non-Hispanic or non-Latinx	997 (88.2)	423 (78.8)	996 (88.2)	456 (81.3)
Not reported	2 (0.2)	2 (0.4)	3 (0.3)	0
Country — no. (%)				
Argentina	0	20 (3.7)	0	28 (5.0)
Brazil	0	24 (4.5)	0	19 (3.4)
Germany	0	11 (2.0)	0	20 (3.6)
South Africa	0	34 (6.3)	0	45 (8.0)
Turkey	0	12 (2.2)	0	15 (2.7)
United States	1131 (100)	436 (81.2)	1129 (100)	434 (77.4)
Age at vaccination — yr				
Mean	13.6±1.11	19.4±3.26	13.6±1.11	19.6±3.33
Median (range)	14.0 (12–15)	18.0 (16–25)	14.0 (12–15)	19.0 (16–25)
Baseline SARS-CoV-2 status — no. (%)‡				
Positive	46 (4.1)	30 (5.6)	47 (4.2)	34 (6.1)
Negative	1028 (90.9)	497 (92.6)	1023 (90.6)	522 (93.0)
Missing	57 (5.0)	10 (1.9)	59 (5.2)	5 (0.9)

* Plus–minus values are means ±SD. Results are for the reactogenicity subset of the safety population, which included all participants in the 12-to-15-year-old cohort and a subset of participants in the 16-to-25-year-old cohort. Percentages may not total 100 because of rounding.

† Race and ethnic group were reported by the participants.

‡ A positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) status required a positive N-binding antibody result at vaccination visit 1, a positive nucleic acid amplification test (NAAT) result at vaccination visit 1, or a medical history of coronavirus disease 2019 (Covid-19).

and placebo recipients; slightly more BNT162b2 recipients than placebo recipients reported related adverse events (3% vs. 2%) (Table S2). Among 16-to-25-year-old BNT162b2 recipients, 11% reported any adverse event and 6% had vaccine-

related adverse events. Among BNT162b2 recipients, severe adverse events were reported in 0.6% of those who were 12 to 15 years of age and in 1.7% of those who were 16 to 25 years of age.

One BNT162b2 recipient in the 12-to-15-year-

old cohort discontinued vaccination because of a vaccine-related adverse event: a temperature greater than 40°C (described above) in a 14-year-old boy who was SARS-CoV-2–negative at baseline, had no reported medical history, and had no other symptoms. He received BNT162b2 dose 1 and had fever (temperature, 40.4°C) 1 day after vaccination, which resolved 2 days later. The participant did not receive dose 2 but remained in the trial for safety follow-up. One BNT162b2 recipient in the 16-to-25-year-old cohort discontinued vaccination because of severe vaccine-related injection-site pain and headache, both of which were reported 1 day after dose 1 and resolved within 1 day. Lymphadenopathy was reported in 9 of 1131 BNT162b2 recipients (0.8%) and in 2 of 1129 placebo recipients (0.2%) who were 12 to 15 years of age, as compared with in 1 of 536 BNT162b2 recipients (0.2%) and in no placebo recipients who were 16 to 25 years of age. Appendicitis was reported in 2 participants: 1 BNT162b2 recipient in the 16-to-25-year-old cohort and 1 placebo recipient in the 12-to-15-year-old cohort. No thromboses or hypersensitivity adverse events or vaccine-related anaphylaxis was seen. Few participants in any cohort ($\leq 0.4\%$ through 1 month after dose 2) had serious adverse events, and none were considered by the investigators to have been vaccine-related. No deaths were reported.

IMMUNOGENICITY

The immune response to BNT162b2 in 12-to-15-year-old adolescents was noninferior to that observed in 16-to-25-year-old young adults. The geometric mean ratio of the BNT162b2 neutralizing geometric mean titer in 12-to-15-year-old participants to that in 16-to-25-year-old participants 1 month after dose 2 was 1.76 (95% confidence interval [CI], 1.47 to 2.10) (Table 2), which met the noninferiority criterion (i.e., a lower boundary of the two-sided 95% confidence interval of >0.67). The lower boundary of the two-sided 95% confidence interval for the geometric mean ratio was greater than 1, indicating a greater response in adolescents than in young adults.

Among all participants regardless of serologic evidence of previous SARS-CoV-2 infection, the serum-neutralizing geometric mean titer 1 month after BNT162b2 dose 2 was 1283.0 in the 12-to-15-year-old cohort and 730.8 in the 16-to-25-year-old cohort (Fig. S2). The corresponding geometric mean titers at 1 month among placebo recipients

were 15.1 and 10.7. Substantial increases in the 50% neutralizing titer from baseline were observed, with GMFRs from baseline to 1 month after dose 2 of 118.3 among 12-to-15-year-old participants and 71.2 among 16-to-25-year-old participants. The corresponding GMFRs among placebo recipients were 1.4 and 1.1.

EFFICACY

Among the 1983 participants in the 12-to-15-year-old cohort who could be evaluated and did not have evidence of previous SARS-CoV-2 infection, no cases of Covid-19 with an onset of 7 or more days after dose 2 were observed among BNT162b2 recipients and 16 cases were observed among placebo recipients, which corresponded to an observed vaccine efficacy of 100% (95% CI, 75.3 to 100) (Table 3). Similarly, in the group that included all 2229 participants in the 12-to-15-year-old cohort who could be evaluated, regardless of whether they had evidence of previous SARS-CoV-2 infection, vaccine efficacy from 7 days after dose 2 was 100% (95% CI, 78.1 to 100), with no Covid-19 cases observed among BNT162b2 recipients and 18 cases observed among placebo recipients. After dose 1 and before dose 2, there were 3 Covid-19 cases noted (within 11 days after dose 1) among BNT162b2 recipients, as compared with 12 cases among placebo recipients (vaccine efficacy, 75%; 95% CI, 7.6 to 95.5) (Table S3). No cases of severe Covid-19 were observed in this age cohort.

DISCUSSION

A two-dose regimen of 30 μg of BNT162b2 administered 21 days apart to adolescents 12 to 15 years of age was safe and immunogenic and resulted in an observed vaccine efficacy of 100% against Covid-19 from 7 days after dose 2. BNT162b2 elicited a high immune response in adults,³ which translated to a 95% vaccine efficacy among participants in the phase 2–3 trial who were 16 years of age or older.⁵ Noninferiority of immunogenicity in 12-to-15-year-old adolescents, as shown in our trial, was initially planned as the primary assessment of vaccine effectiveness through “immunobridging,” an approach in which the effectiveness of a vaccine is inferred from immunogenicity data. The efficacy analysis was descriptive because a sufficient number of Covid-19 cases was not anticipated. However,

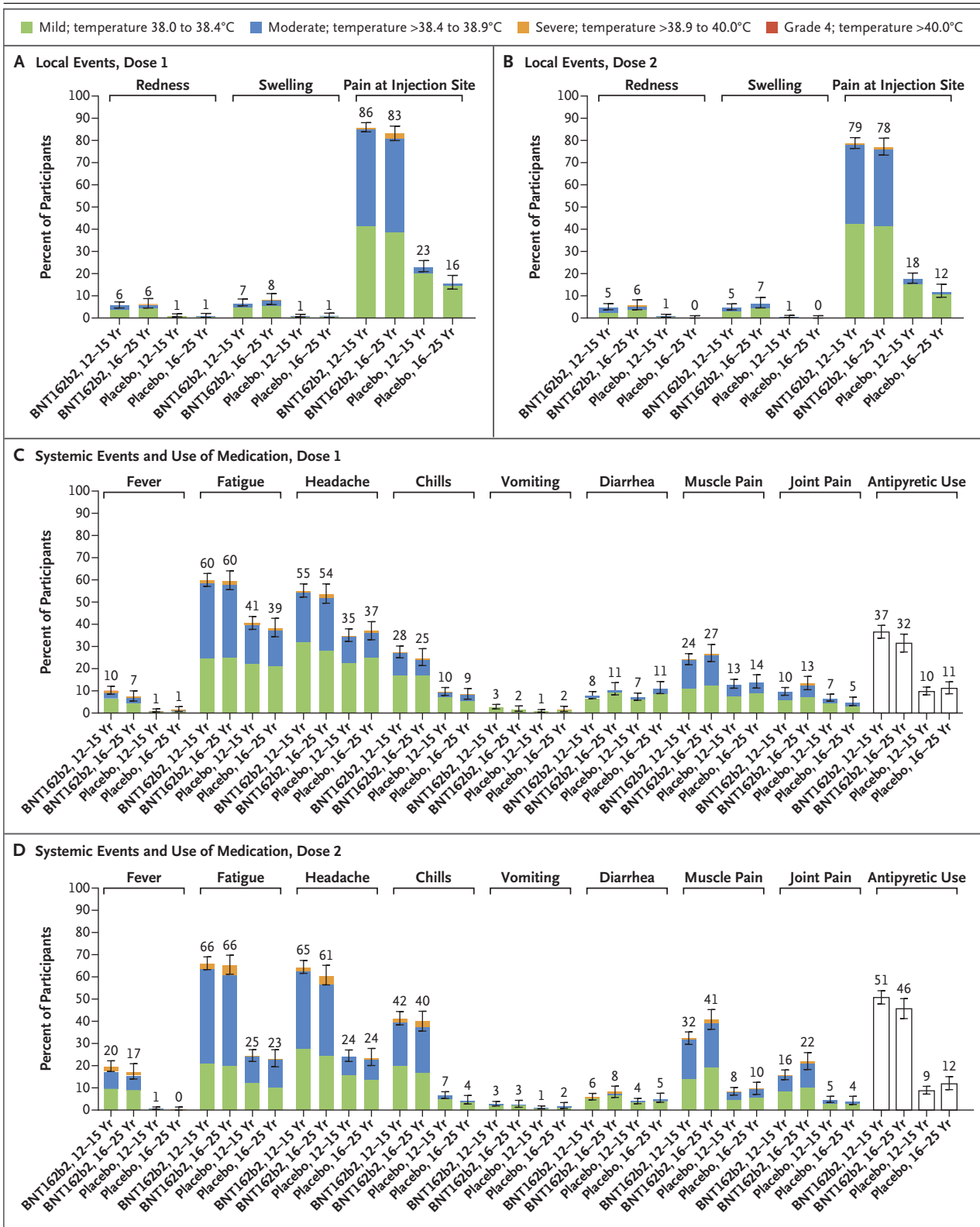


Figure 2 (facing page). Local Reactions and Systemic Events Reported within 7 Days after Administration of BNT162b2 or Placebo.

The results shown are for the reactogenicity subset of the safety population, which included all participants in the 12-to-15-year-old cohort and the subset of participants in the 16-to-25-year-old cohort who had electronic diary data available. Pain at the injection site was graded as mild (does not interfere with activity), moderate (interferes with activity), severe (prevents daily activity), or grade 4 (led to an emergency department visit or hospitalization). Redness and swelling were graded as mild (>2.0 to 5.0 cm in diameter), moderate (>5.0 to 10.0 cm in diameter), severe (>10.0 cm in diameter), or grade 4 (necrosis or exfoliative dermatitis for redness and necrosis for swelling). Fever categories are designated in the key. Fatigue, headache, chills, new or worsened muscle pain, and new or worsened joint pain were graded as mild (does not interfere with activity), moderate (some interference with activity), or severe (prevents daily routine activity). Vomiting was graded as mild (one or two times in 24 hours), moderate (more than two times in 24 hours), or severe (requires intravenous hydration), and diarrhea as mild (two or three loose stools in 24 hours), moderate (four or five loose stools in 24 hours), or severe (six or more loose stools in 24 hours). Grade 4 for all systemic events indicated an emergency department visit or hospitalization. I bars indicate 95% confidence intervals. The numbers above the I bars are the overall percentages of the participants in each group who reported the specified local reaction or systemic event. No participant had a grade 4 local reaction. With regard to systemic events, there was one incident of fever with a temperature higher than 40°C in a 12-to-15-year-old participant after dose 1 of BNT162b2.

given the number of cases and the precision of vaccine efficacy estimates, the vaccine efficacy in this trial provides a high level of certainty about the efficacy results. The lower limit of the 95% confidence interval for vaccine efficacy, which was greater than 75%, provides substantial evidence of efficacy in this age group and is consistent with the high efficacy previously reported in participants 16 years of age or older.⁵ Although BNT162b2 is a two-dose regimen, early protection after a single dose has been reported in clinical trials and on the basis of real-world data.^{5,19,20} It is reassuring that early protection is also observed in this age group, given the important public health implications for pandemic control.

Evaluation of BNT162b2 in younger adolescents was undertaken for several reasons. The incidence of Covid-19 is reported to be higher among 12-to-17-year-old adolescents than among younger children.²¹ In addition, children, especially from low-income families, have been negatively affected by the lack of in-person learning during the pandemic.^{17,18} Therefore, a demonstration of efficacy and safety in 12-to-15-year-old adolescents is important in order to expand the emergency use authorization to include children 12 years of age or older and make a critical step toward achieving herd immunity. Finally, the favorable safety and side-effect profile and high efficacy, along with the acceptable risk-to-benefit ratio in ado-

Table 2. SARS-CoV-2 Serum Neutralization Assay Results 1 Month after Dose 2 of BNT162b2 among Participants without Evidence of Infection.*

Age Group	No. of Participants	Geometric Mean 50% Neutralizing Titer (95% CI)†	Geometric Mean Ratio (95% CI), 12 to 15 Yr vs. 16 to 25 Yr‡
12–15 yr	190	1239.5 (1095.5–1402.5)	1.76 (1.47–2.10)
16–25 yr	170	705.1 (621.4–800.2)	—

* Results are for the subset of participants in the dose 2 immunogenicity population that could be evaluated (i.e., participants who underwent randomization and received two BNT162b2 doses in accordance with the protocol, received dose 2 within the prespecified window, had at least one valid and determinate immunogenicity result from a blood sample obtained within 28 to 42 days after dose 2, and had no major protocol deviations) who had no evidence of previous SARS-CoV-2 infection. Participants without evidence of previous infection were those who had no serologic or virologic evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (i.e., 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 results (nasal swab) at any unscheduled visit up to 1 month after dose 2.

† Geometric mean titers and two-sided 95% confidence intervals were calculated by exponentiating the mean logarithm of the titers and the corresponding confidence intervals (based on the Student's *t* distribution). Assay results below the lower limit of quantitation were set to 0.5 times the lower limit of quantitation.

‡ The geometric mean ratio and two-sided 95% confidence intervals were calculated by exponentiating the mean difference of the logarithms of the titers (the 12-to-15-year-old cohort minus the 16-to-25-year-old cohort) and the corresponding confidence intervals (based on the Student's *t* distribution). The noninferiority criterion was met, since the lower boundary of the two-sided confidence interval for the geometric mean ratio was greater than 0.67.

Table 3. Vaccine Efficacy against Covid-19 in Participants 12 to 15 Years of Age.*

Efficacy End Point†	BNT162b2		Placebo		% Vaccine Efficacy (95% CI)‡
	No. of Participants with Event/ Total No.§	Surveillance Time (No. at Risk)¶	No. of Participants with Event/ Total No.§	Surveillance Time (No. at Risk)¶	
Covid-19 occurrence at least 7 days after dose 2 in participants without evidence of previous infection	0/1005	0.154 (1001)	16/978	0.147 (972)	100 (75.3–100)
Covid-19 occurrence at least 7 days after dose 2 in participants with or without evidence of previous infection	0/1119	0.170 (1109)	18/1110	0.163 (1094)	100 (78.1–100)

* Results are for the efficacy population that could be evaluated, which included all eligible 12-to-15-year-old participants who received two doses of BNT162b2 or placebo as randomly assigned, with dose 2 received within the prespecified window, and had no major protocol deviations.

† Participants without evidence of previous infection were those who had no serologic or virologic evidence of past SARS-CoV-2 infection before 7 days after dose 2 (i.e., N-binding antibody testing [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 results (nasal swab) at any unscheduled visit before 7 days after dose 2.

‡ The 95% confidence interval for vaccine efficacy was derived on the basis of the Clopper–Pearson method with adjustment for surveillance time.

§ The number of participants with a first occurrence of Covid-19 at 7 or more days after dose 2 and the total number of participants with data are shown.

¶ Total surveillance time in 1000 person-years for the given end point across all participants within each group of participants who were at risk for the end point is shown. The period for Covid-19 case accrual was from 7 days after dose 2 to the end of the surveillance period.

lescents, now justify vaccine evaluation in younger age groups.²²

The favorable safety profile of BNT162b2, which was seen in adults in the pivotal trial and through ongoing pharmacovigilance after vaccine introduction, was also observed in 12-to-15-year-old recipients.^{5,23} Adherence was high, with more than 97% of BNT162b2 recipients receiving dose 2. As previously reported for vaccine recipients 16 years of age or older, systemic events in 12-to-15-year-old BNT162b2 recipients were reported more often after dose 2 than after dose 1.⁵ Antipyretic use after both doses was slightly higher in the 12-to-15-year-old cohort than in the 16-to-25-year-old cohort. This favorable safety profile is important, because a precedent exists for vaccines being increasingly reactogenic when administered to younger people. In the small percentage of participants who were SARS-CoV-2–positive at baseline, no differences in reactogenicity from those who were SARS-CoV-2–negative at baseline were noted, which supports immunization without screening for evidence of previous SARS-CoV-2 infection.

These results have several implications. Vaccination of adolescents is likely to confer the direct benefit of preventing disease along with indi-

rect benefits, including community protection.²⁴ Although children generally have a lower burden of symptomatic Covid-19 than adults, schools, youth sports, and other community gatherings may represent important sources of ongoing outbreaks and transmission, despite high rates of adult immunization.^{13,14,25} Vaccination of adolescents will allow them to reintegrate into society and resume in-person learning safely, which are especially important outcomes given the severe mental health effects of the Covid-19 pandemic on this group.^{18,22,26} Recent real-world data suggest that BNT162b2 prevents asymptomatic infection.^{19,27} Given the observed immunogenicity and efficacy, it is likely that vaccination will also prevent asymptomatic infection in children, thereby broadening community protection.

This analysis has some limitations. The efficacy analysis was prespecified as descriptive because an accurate sample size to assess vaccine efficacy could not be calculated before the start of the trial, given uncertainties about the incidence of SARS-CoV-2 infection. Therefore, the primary basis for the establishment of efficacy in 12-to-15-year-old adolescents was a neutralizing antibody response that was found to be noninferior to that in vaccine recipients 16 years

of age or older, for whom efficacy had been shown.⁵ This report includes safety data through 1 month of follow-up after dose 2 for some participants. Data on longer-term safety and the duration of efficacy and antibody responses in children are not yet available.

Although racial and ethnic diversity was lower among the 12-to-15-year-old participants than among those who were 16 years of age or older, vaccine efficacy in the latter age cohort is consistent among racial and ethnic subgroups,⁵ and a similar pattern is likely in the younger cohort. All 12-to-15-year-old participants in this trial were enrolled at U.S. sites, whereas the 16-to-25-year-old participants were recruited globally. In the immunogenicity subset, however, all participants in both age cohorts were from the United States. The testing laboratory supply limitation resulted in fewer than anticipated participants in the immunogenicity analyses; however, even with the smaller sample size and lower power, the trial still established noninferiority of the immune response. Although some participants received other vaccinations during the trial period, we did not formally examine concomitant vaccination with BNT162b2 and other vaccines received during adolescence. These results do not determine whether BNT162b2 vaccination prevents asymptomatic infection or transmission of SARS-CoV-2; asymptomatic surveillance is ongoing in this age group.

Given the safety, immune response, and efficacy of the BNT162b2 vaccine in adolescents

12 to 15 years of age reported in this analysis, studies are ongoing to evaluate these measures in younger children and in other special populations, such as pregnant women.

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 Sheena Hunt, who wrote the first draft of the manuscript under direction from the authors, and Tricia Newell and Philippa Jack (all from ICON) for medical writing and editorial assistance with an earlier version of the manuscript, which was funded by Pfizer; all the participants who volunteered for this trial; the members of the data and safety monitoring committee — Jonathan Zenilman, Kathryn Edwards, Lawrence Stanberry, Robert Belshe, and Steven G. Self — who have been reviewing the trial safety data on a weekly basis; Greg Adams, Negar Aliabadi, Mohanish Anand, Fred Angulo, Ayman Ayoub, Melissa Bishop-Murphy, Mark Boaz, Christopher Bowen, Salim Bouguerrou, Donna Boyce, Sarah Burden, Andrea Cawein, Patrick Caubel, Darren Cowen, Kimberly Ann Cristall, Michael Cruz, Daniel Curcio, Carmel Devlin, Niesha Foster, Luis Jodar, Stephen Kay, Esther Ladipo, Marie-Pierre Hellio Le Graverand-Gastineau, Juleen Gayed, Jacqueline Lowenberg, Rod MacKenzie, Robert Maroko, Jason McKinley, Tracey Mellelieu, Brendan O'Neill, Jason Painter, Sohil Patel, Elizabeth Paulukonis, Allison Pfeffer, Katie Puig, Kimberly Rarrick, Balaji Prabu Raja, Kellie Lynn Richardson, Elizabeth Rogers, Melinda Rottas, Charulata Sabharwal, Vilas Satishchandran, Harpreet Sehra, Judy Sowards, Helen Smith, Uzma Sarwar, David Swerdlow, Elisa Harkins Tull, Sarah Tweedy, Erica Weaver, John Wegner, Jenah West, David C. Whritenour, Fae Wooding, Emily Worobetz, Nita Zalavadia, Liping Zhang, and Lefteris Zolotas, all from Pfizer, for their contributions to this work; the Pfizer Vaccines Clinical Assay Team, the Pfizer Vaccines Assay Development Team, and all of the Pfizer colleagues not named here who contributed to the success of this trial; Corinna Rosenbaum, Christian Miculka, Andreas Kuhn, Ferdia Bates, Paul Strecker, Ruben Rjzzi, Martin Bexon, Eleni Lagkadinou, and Alexandra Kemmer-Brück (all from BioNTech); and Dietmar Katinger and Andreas Wagner (both from Polymun).

REFERENCES

- World Health Organization. Coronavirus disease (COVID-19) dashboard. 2021 (<https://covid19.who.int/>).
- Pfizer Manufacturing Belgium NV. Pfizer-BioNTech COVID-19 vaccine: fact sheet for healthcare providers administering vaccine (vaccination providers). 2021 (<http://labeling.pfizer.com/ShowLabeling.aspx?id=14471>).
- Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med* 2020;383:2439-50.
- Sahin U, Muik A, Vogler I, et al. BNT162b2 induces SARS-CoV-2-neutralising antibodies and T cells in humans. December 11, 2020 (<https://www.medrxiv.org/content/10.1101/2020.12.09.20245175v1>). preprint.
- 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.
- FDA takes key action in fight against COVID-19 by issuing emergency use authorization for first COVID-19 vaccine. News release of the Food and Drug Administration, Silver Spring, MD, December 11, 2020 (<https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19>).
- Coronavirus (COVID-19) update: FDA authorizes Pfizer-BioNTech COVID-19 vaccine for emergency use in adolescents in another important action in fight against pandemic. News release of the Food and Drug Administration, Silver Spring, MD, May 10, 2021 (<https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use>).
- World Health Organization. Status of COVID-19 vaccines within WHO EUL/PQ evaluation process. March 23, 2021 (https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_23March2021_0.pdf).
- European Medicines Agency. Authorised COVID-19 vaccines. 2021 (<https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised#authorised-covid-19-vaccines-section>).
- Food and Drug Administration. COVID-19 vaccines. 2021 (<https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines>).

11. Tsabouri S, Makis A, Kosmeri C, Siomou E. Risk factors for severity in children with coronavirus disease 2019: a comprehensive literature review. *Pediatr Clin North Am* 2021;68:321-38.
12. Romain B, Schneiderman M, Geliebter A. Prevalence of COVID-19 in adolescents and youth compared with older adults in states experiencing surges. *PLoS One* 2021;16(3):e0242587.
13. Szablewski CM, Chang KT, Brown MM, et al. SARS-CoV-2 transmission and infection among attendees of an overnight camp — Georgia, June 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1023-5.
14. The White House. Press briefing by White House COVID-19 response team and public health officials. April 5, 2021 (<https://www.whitehouse.gov/briefing-room/press-briefings/2021/04/05/press-briefing-by-white-house-covid-19-response-team-and-public-health-officials-24/>).
15. Centers for Disease Control and Prevention. COVID data tracker. 2021 (https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases).
16. Buonsenso D, Roland D, De Rose C, et al. Schools closures during the COVID-19 pandemic: a catastrophic global situation. *Pediatr Infect Dis J* 2021;40(4):e146-e150.
17. Masonbrink AR, Hurley E. Advocating for children during the COVID-19 school closures. *Pediatrics* 2020;146(3):e20201440.
18. Townsend E. Debate: the impact of school closures and lockdown on mental health in young people. *Child Adolesc Ment Health* 2020;25:265-6.
19. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021;384:1412-23.
20. Thompson MG, Burgess JL, Naleway AL, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers — eight U.S. locations, December 2020–March 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:495-500.
21. Leeb RT, Price S, Sliwa S, et al. COVID-19 trends among school-aged children — United States, March 1–September 19, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1410-5.
22. Cooper DM, Afghani B, Byington CL, et al. SARS-CoV-2 vaccine testing and trials in the pediatric population: biologic, ethical, research, and implementation challenges. *Pediatr Res* 2021 February 24 (Epub ahead of print).
23. Gee J, Marquez P, Su J, et al. First month of COVID-19 vaccine safety monitoring — United States, December 14, 2020–January 13, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:283-8.
24. Kao CM, Orenstein WA, Anderson EJ. The importance of advancing severe acute respiratory syndrome coronavirus 2 vaccines in children. *Clin Infect Dis* 2021;72:515-8.
25. Russell FM, Greenwood B. Who should be prioritised for COVID-19 vaccination? *Hum Vaccin Immunother* 2021;17:1317-21.
26. Jones EAK, Mitra AK, Bhuiyan AR. Impact of COVID-19 on mental health in adolescents: a systematic review. *Int J Environ Res Public Health* 2021;18:2470.
27. Tande AJ, Pollock BD, Shah ND, et al. Impact of the COVID-19 vaccine on asymptomatic infection among patients undergoing pre-procedural COVID-19 molecular screening. *Clin Infect Dis* 2021 March 10 (Epub ahead of print).

Copyright © 2021 Massachusetts Medical Society.