

ORIGINAL ARTICLE

Effectiveness of BNT162b2 Vaccine against Critical Covid-19 in Adolescents

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ABSTRACT

BACKGROUND

The increasing incidence of pediatric hospitalizations associated with coronavirus disease 2019 (Covid-19) caused by the B.1.617.2 (delta) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the United States has offered an opportunity to assess the real-world effectiveness of the BNT162b2 messenger RNA vaccine in adolescents between 12 and 18 years of age.

METHODS

We used a case–control, test-negative design to assess vaccine effectiveness against Covid-19 resulting in hospitalization, admission to an intensive care unit (ICU), the use of life-supporting interventions (mechanical ventilation, vasopressors, and extracorporeal membrane oxygenation), or death. Between July 1 and October 25, 2021, we screened admission logs for eligible case patients with laboratory-confirmed Covid-19 at 31 hospitals in 23 states. We estimated vaccine effectiveness by comparing the odds of antecedent full vaccination (two doses of BNT162b2) in case patients as compared with two hospital-based control groups: patients who had Covid-19–like symptoms but negative results on testing for SARS-CoV-2 (test-negative) and patients who did not have Covid-19–like symptoms (syndrome-negative).

RESULTS

A total of 445 case patients and 777 controls were enrolled. Overall, 17 case patients (4%) and 282 controls (36%) had been fully vaccinated. Of the case patients, 180 (40%) were admitted to the ICU, and 127 (29%) required life support; only 2 patients in the ICU had been fully vaccinated. The overall effectiveness of the BNT162b2 vaccine against hospitalization for Covid-19 was 94% (95% confidence interval [CI], 90 to 96); the effectiveness was 95% (95% CI, 91 to 97) among test-negative controls and 94% (95% CI, 89 to 96) among syndrome-negative controls. The effectiveness was 98% against ICU admission and 98% against Covid-19 resulting in the receipt of life support. All 7 deaths occurred in patients who were unvaccinated.

CONCLUSIONS

Among hospitalized adolescent patients, two doses of the BNT162b2 vaccine were highly effective against Covid-19–related hospitalization and ICU admission or the receipt of life support. (Funded by the Centers for Disease Control and Prevention.)

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*A list of the Overcoming Covid-19 investigators is provided in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org).

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UNDERSTANDING THE ROLE OF VACCINATION in the prevention of hospitalization for coronavirus disease 2019 (Covid-19), including life-threatening illness, among children can inform vaccination decisions and efforts to improve vaccination coverage. In May 2021, the Food and Drug Administration expanded the emergency use authorization for use of the BNT162b2 messenger RNA (mRNA) vaccine (Pfizer–BioNTech) to include adolescents between 12 and 15 years of age.¹ This expansion was based on a randomized, placebo-controlled trial that showed a vaccine efficacy of 100% (95% confidence interval [CI], 75 to 100) against symptomatic Covid-19 among adolescents.² However, in that trial, cases of severe Covid-19 were not observed, given the relatively rare nature of this outcome. In early September 2021, the incidence of pediatric hospitalization caused by the B.1.617.2 (delta) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reached the highest level during the pandemic.^{3,4} This surge provided an opportunity to evaluate the real-world effectiveness of the BNT162b2 vaccine against severe Covid-19 in adolescents.

In the Overcoming Covid-19 investigation, we recently reported the interim findings of high effectiveness (93%) for the BNT162b2 vaccine against Covid-19 hospitalization among adolescents between 12 to 18 years of age among 179 case patients at 19 sites in 16 states.⁵ Since the time of that report, we expanded surveillance to 31 sites in 23 states and enrolled an additional 266 patients who had been hospitalized with Covid-19. With a substantial increase in the sample size, we now extend those findings to report the effectiveness of two doses of the BNT162b2 vaccine among adolescents against Covid-19 hospitalization resulting in admission to an intensive care unit (ICU) or in the receipt of other life-supporting interventions.

METHODS

STUDY DESIGN

We used a case–control, test-negative design to assess the effectiveness of vaccination against Covid-19 resulting in hospitalization, ICU admission, or life-supporting interventions by comparing the odds of antecedent vaccination among laboratory-confirmed case patients and hospitalized controls without Covid-19.^{2,6,7} Evaluations of

vaccine effectiveness have commonly used test-negative controls to reduce bias from health care–seeking behavior and to improve logistics.^{8–11} Estimates of vaccine effectiveness that are generated by the case–control or test-negative design are expressed as percentages and can be interpreted as the fraction of the specified outcome prevented in association with vaccination.^{7,8,12} The surveillance protocol and the statistical analysis plan (in the Supplementary Appendix, both available with the full text of this article at NEJM.org) were reviewed by the Centers for Disease Control and Prevention (CDC) and by the other participating institutions as public health surveillance; this review was conducted in accordance with applicable federal laws and CDC policy.¹³ CDC technical staff members served as coinvestigators and were involved in the study design, participated in the data collection and analysis and in the preparation of the manuscript, and were involved in the decision to submit the manuscript for publication.

ENROLLMENT OF CASE PATIENTS AND CONTROLS

To identify case patients and controls, we conducted active surveillance of adolescents between 12 and 18 years of age who had been admitted to 31 hospitals in 23 states in the CDC-funded Overcoming Covid-19 Network.^{14,15} The network was funded to evaluate vaccine effectiveness against severe Covid-19 and multisystem inflammatory syndrome in children (MIS-C) in vaccine-eligible participants. After the CDC contract had been awarded, 39 referral health centers for pediatric patients were approached on the basis of their previous experience in the enrollment of patients with Covid-19 or in conducting evaluations of vaccine effectiveness against influenza.^{15,16} Representatives at 31 centers agreed to participate during this period.

During the surveillance period at each study site, investigators attempted to capture all cases that met the inclusion criteria. All case patients and controls were enrolled regardless of the availability of information regarding their vaccination status. During the period from May 30 through October 25, 2021, investigators began screening for potentially eligible patients through a review of hospital admission logs and electronic medical records. For this report, the hospitalization date of the first enrolled case patient was July 1, when the percentage of fully vacci-

nated adolescents surpassed 20% in the United States and thus was sufficient for an evaluation of vaccine effectiveness.^{10,17} The onset of enrollment varied depending on local incidence and ethics approval at the site.

Case patients were selected among adolescents who were hospitalized with Covid-19 as the primary reason for admission or who had a clinical syndrome consistent with acute Covid-19 (one or more symptoms of fever, cough, shortness of breath, loss of taste, loss of smell, gastrointestinal symptoms, respiratory support, or new pulmonary findings on chest imaging). All case patients had positive results for SARS-CoV-2 on reverse transcriptase–polymerase-chain-reaction (RT-PCR) assay or on antigen testing within 10 days after symptom onset or within 72 hours after hospitalization. Results of documented positive tests before admission were accepted in 28 case patients. We excluded 23 adolescents who had received a diagnosis of MIS-C during their current hospitalization (Table S1 in the Supplementary Appendix).

Because of potential biases related to the selection of controls,¹⁸⁻²⁰ we included two groups of hospitalized patients as controls: those who had negative results for SARS-CoV-2 on RT-PCR assay or antigen testing (test-negative) but who had Covid-19–like symptoms; and those without Covid-19–like symptoms who may or may not have undergone SARS-CoV-2 testing (syndrome-negative). At each site, investigators targeted a case-to-control ratio of approximately 1:1 for each of the two control groups. Eligible controls were selected from among patients in closest proximity to the ward where the case patients were hospitalized within 3 weeks after the case patient's hospitalization date.

DATA COLLECTION

The parent or guardian of each participant was approached by trained study personnel or electronic medical records on all case patients and controls were reviewed to collect data regarding demographic characteristics, clinical information about the current illness, and SARS-CoV-2 testing history. Parents or guardians were asked about the patient's Covid-19 vaccination history, including the number of doses and whether the most recent administration had occurred during the previous 14 days, the location where vaccination had occurred, the vaccine manufacturer,

and the availability of a Covid-19 vaccination card. Study personnel searched sources, including state vaccination registries, electronic medical records, or other sources (including documentation from pediatricians), to verify reported or unknown vaccination status.

VACCINATION STATUS

Patients were considered to have received Covid-19 vaccination based on source documentation or by plausible self-report if vaccination dates and location were provided by a parent or guardian at the time of the interview. Because the mRNA-1273 vaccine (Moderna) and Ad26.COV2.S vaccine (Johnson & Johnson–Janssen) had not been authorized for use in adolescents at the time of study initiation, patients who had received those vaccines were excluded. Patients were categorized as being unvaccinated (no receipt of the BNT162b2 vaccine before illness onset) or vaccinated if the most recent dose (first or second dose of the BNT162b2 vaccine) had been administered at least 14 days before illness onset. Adolescents who had received only one dose of vaccine or who had received a second dose less than 14 days before illness onset were considered to have been partially vaccinated; those who had received two doses at least 14 days before illness onset were considered to have been fully vaccinated. Patients who had received only one dose less than 14 days before illness onset were excluded from the analysis.²

OUTCOMES

The prespecified primary outcomes were Covid-19 resulting in hospitalization, ICU admission, the receipt of life-supporting interventions, or death. Life support was defined as the receipt of non-invasive or invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation.

STATISTICAL ANALYSIS

We first conducted bivariate analyses to assess for between-group differences in characteristics on the basis of case status (case patients vs. controls) and vaccination status (fully vaccinated vs. unvaccinated). We then constructed logistic-regression models for the prespecified primary outcomes to calculate odds ratios of antecedent vaccination (fully or partially vaccinated vs. unvaccinated) in case patients as compared with con-

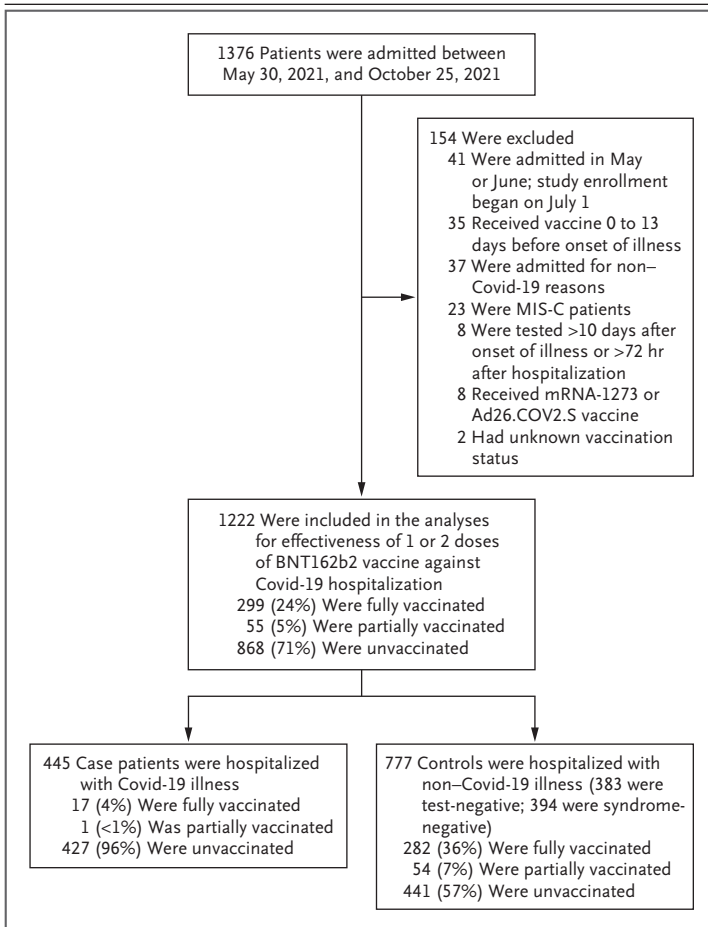


Figure 1. Study Enrollment and Outcomes (July 1–October 25, 2021).

Among the case patients between 12 and 18 years of age who were hospitalized with coronavirus disease 2019 (Covid-19), 37 patients who had a positive result on SARS-CoV-2 testing but were admitted to the hospital for a non-Covid-19 reason were excluded from the analyses. Patients were described as having been fully vaccinated if they had received a second dose of the BNT162b2 vaccine at least 14 days before the onset of illness. Patients were described as having been partially vaccinated if they had received the first dose of the BNT162b2 vaccine at least 14 days before illness onset. Among the 777 control patients, 383 had received negative results on SARS-CoV-2 testing (test-negative) and 394 had no Covid-19 symptoms (syndrome-negative).

controls, with associated 95% confidence intervals. A priori, we adjusted models for the U.S. Census region, calendar date of admission, age, sex, and race or ethnic group.^{6,10} To evaluate clustering according to hospital, we also included the hospital as a random effect in mixed-effects regression models, an analysis that did not substantially alter the results. Using a change-in-estimate approach, we assessed other potential confounding factors (the presence of underlying health

conditions, specific underlying conditions, and the score on the Social Vulnerability Index) that were not included in the final models because these factors did not change the odds ratio for vaccination by more than 5%.^{6,21}

We calculated vaccine effectiveness against the primary outcomes by comparing the odds of full vaccination against Covid-19 among case patients and controls using the equation for vaccine effectiveness of $(1 - \text{adjusted odds ratio}) \times 100$, as determined from logistic-regression models. We used Firth logistic regression (a penalized likelihood-based method) for models with fewer than five vaccinated case patients.²² Preplanned subgroup analyses included effectiveness against Covid-19 hospitalization according to age group (12 to 15 years vs. 16 to 18 years) and protection of partial vaccination with the BNT162b2 vaccine against Covid-19 hospitalization. We computed effectiveness separately with each control group and overall with the two control groups combined. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer vaccine effectiveness for the subgroup analyses. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

Between May 30 and October 25, 2021, a total of 1376 eligible case patients and controls underwent screening; of these patients, 154 were excluded. Exclusions included 41 patients who were admitted to the hospital in May or June when vaccination coverage was low, 35 who had received the first dose of vaccine less than 14 days before illness onset, 37 with a positive SARS-CoV-2 test who were admitted for reasons other than Covid-19 symptoms (Table S2), 23 who had received a diagnosis of MIS-C, 8 who had undergone SARS-CoV-2 testing more than 10 days after illness onset or more than 72 hours after hospitalization, 2 who had unknown vaccination status, and 8 who had received a non-BNT162b2 vaccine (Fig. 1).

The primary analysis included 1222 vaccinated and unvaccinated patients (445 case patients and 777 controls). Among the controls, 383 (49%) were test-negative for SARS-CoV-2, and 394 (51%) were syndrome-negative. Among the case patients,

the median age was 16 years, 74% had at least one underlying condition (including obesity), and 70% attended an in-person school (Table 1). Among the controls, the median age was 15 years, 70% had at least one underlying condition, and 70% attended an in-person school. Case patients more frequently resided in areas with higher scores on the Social Vulnerability Index (median score, 0.64) than controls (median score, 0.58). (The Social Vulnerability Index ranges from 0 to 1.0, with higher scores indicating greater social vulnerability.) Underlying conditions, which included obesity, were common, both among adolescents who were vaccinated (73%) and those who were unvaccinated (71%). Respiratory and endocrine disorders were more prevalent among case patients (33% and 16%, respectively) than among controls (23% and 11%, respectively); neurologic or neuromuscular disorders and immunosuppressive or autoimmune disorders were more prevalent among controls (22% and 12%, respectively) than among case patients (13% and 5%, respectively).

Of the 299 case and control patients who were classified as having been fully vaccinated, 288 (96%) had verified documentation of full vaccination. Among the 445 case patients with available vaccination data, only 17 (4%) had been fully vaccinated, 1 (<1%) had been partially vaccinated, and 427 (96%) were unvaccinated. In contrast, among 777 controls with available vaccination data, 282 (36%) had been fully vaccinated, 54 (7%) had been partially vaccinated, and 441 (57%) were unvaccinated (Fig. 1).

Of the 445 case patients, 180 (40%) were admitted to the ICU, and 127 (29%) critically ill case patients received life-supporting interventions during hospitalization, including 13 patients (3%) who received extracorporeal membrane oxygenation and 7 (2%) who died (Table 2). Two case patients who were admitted to the ICU (1 who had an immunosuppressive disorder and 1 who was healthy) had been fully vaccinated. The remaining 178 case patients who were admitted to the ICU, including 126 of 127 patients who required life-supporting interventions and the 7 who died, were unvaccinated. Among 425 case patients with available hospital discharge data, the median length of hospital stay was 5 days (interquartile range [IQR], 2 to 7) among unvaccinated case patients and 4 days (IQR, 1 to 5) among vaccinated case patients.

VACCINE EFFECTIVENESS

The effectiveness of the BNT162b2 vaccine against Covid-19 hospitalization was 94% (95% CI, 90 to 96) in analyses involving both control groups combined; the effectiveness was 95% (95% CI, 91 to 97) in the analysis involving test-negative controls and 94% (95% CI, 89 to 96) in the analysis involving syndrome-negative controls (Fig. 2). The vaccine effectiveness was 98% (95% CI, 93 to 99) against Covid-19 requiring ICU care and 98% (95% CI, 92 to 100) against Covid-19 requiring life support. In subgroup analyses, the effectiveness of two doses of the vaccine against Covid-19 hospitalization was similar in various age groups: 95% (95% CI, 88 to 97) among 251 case patients between 12 and 15 years of age and 94% (95% CI, 88 to 97) among 193 case patients between 16 and 18 years of age.

The effectiveness of partial vaccination was 97% (95% CI, 86 to 100). However, it is important to note that the median time between the last vaccine dose and the onset of Covid-like symptoms in case patients was 30 days in 1 partially vaccinated adolescent and 90 days (IQR, 53 to 126 days) among fully vaccinated adolescents. The effectiveness against hospitalization among patients with a positive SARS-CoV-2 test who did not have Covid-19 as the primary cause for hospitalization was 78% (95% CI, 48 to 91) (Table S4).

DISCUSSION

In this multicenter evaluation conducted in 31 hospitals across 23 U.S. states, we compared 445 case patients between 12 and 18 years of age who were hospitalized with Covid-19 with 777 control patients without Covid-19. Despite eligibility for Covid-19 vaccination, 96% of the patients who were hospitalized with Covid-19 and 99% of those who received life support had not been fully vaccinated. We found that vaccination with two doses of the BNT162b2 mRNA vaccine reduced the risk of hospitalization from Covid-19 by 94% among adolescents between 12 and 18 years of age in the United States. Vaccination averted nearly all Covid-19 cases requiring life support and leading to death in this cohort of hospitalized adolescents. Of the 13 patients who received extracorporeal membrane oxygenation and 7 who died, all were unvaccinated.

These findings are consistent with efficacy

Table 1. Characteristics of Hospitalized Case Patients and Controls and Vaccination Status at Baseline.*

Characteristic	Case Patients (N = 445) [†]		Control Patients (N = 777) [‡]		Vaccination Status [§]		
			Test-Negative (N = 383)	Syndrome-Negative (N = 394)	Fully Vaccinated (N = 299)	Partially Vaccinated (N = 55)	Unvaccinated (N = 868)
Age							
Median (IQR) — yr	16 (14–17)	15 (14–17)	15 (14–17)	15 (14–17)	16 (14–17)	15 (13–17)	15 (14–17)
Distribution — no. (%)							
12–15 yr	252 (57)	225 (59)	225 (59)	237 (60)	164 (55)	36 (65)	514 (59)
16–18 yr	193 (43)	158 (41)	158 (41)	157 (40)	135 (45)	19 (35)	354 (41)
Female sex — no. (%)	231 (52)	191 (50)	191 (50)	183 (46)	156 (52)	27 (49)	422 (49)
Race or ethnic group — no. (%) [¶]							
Non-Hispanic White	171 (38)	159 (42)	159 (42)	171 (43)	121 (40)	22 (40)	358 (41)
Non-Hispanic Black	106 (24)	73 (19)	73 (19)	86 (22)	58 (19)	10 (18)	197 (23)
Hispanic	110 (25)	94 (25)	94 (25)	81 (21)	79 (26)	15 (27)	191 (22)
Other	31 (7)	31 (8)	31 (8)	38 (10)	31 (10)	7 (13)	62 (7)
Unknown	27 (6)	26 (7)	26 (7)	18 (5)	10 (3)	1 (2)	60 (7)
Median score on Social Vulnerability Index (IQR)	0.64 (0.40–0.85)	0.56 (0.26–0.82)	0.56 (0.26–0.82)	0.60 (0.31–0.82)	0.52 (0.20–0.75)	0.65 (0.37–0.88)	0.62 (0.37–0.84)
U.S. Census region — no. (%)							
Northeast	16 (4)	22 (6)	22 (6)	22 (6)	25 (8)	1 (2)	34 (4)
Midwest	84 (19)	72 (19)	72 (19)	55 (14)	36 (12)	6 (11)	169 (19)
South	250 (56)	206 (54)	206 (54)	211 (54)	140 (47)	31 (56)	496 (57)
West	95 (21)	83 (22)	83 (22)	106 (27)	98 (33)	17 (31)	169 (19)
Month of admission in 2021 — no. (%)							
July	43 (10)	27 (7)	27 (7)	28 (7)	14 (5)	1 (2)	83 (10)
August	148 (33)	89 (23)	89 (23)	99 (25)	57 (19)	17 (31)	262 (30)
September	178 (40)	169 (44)	169 (44)	146 (37)	124 (41)	24 (44)	345 (40)
October	76 (17)	98 (26)	98 (26)	121 (31)	104 (35)	13 (24)	178 (21)

Underlying health condition — no. (%)**								
At least one underlying condition, including obesity	328 (74)	278 (73)	267 (68)	217 (73)	38 (69)	618 (71)		
Respiratory, including asthma	147 (33)	125 (33)	50 (13)	74 (25)	7 (13)	241 (28)		
Cardiovascular	38 (9)	28 (7)	30 (8)	24 (8)	3 (5)	69 (8)		
Neurologic or neuromuscular	56 (13)	84 (22)	84 (21)	69 (23)	10 (18)	145 (17)		
Immunosuppression or autoimmune	23 (5)	44 (11)	46 (12)	43 (14)	6 (11)	64 (7)		
Endocrine, including diabetes	73 (16)	47 (12)	39 (10)	31 (10)	10 (18)	118 (14)		
Diabetes	46 (10)	30 (8)	24 (6)	19 (6)	9 (16)	72 (8)		
Other chronic condition, including obesity	239 (54)	182 (48)	148 (38)	133 (44)	25 (45)	411 (47)		
Other characteristic — no./total no. (%)††								
In-person school attendance	159/227 (70)	151/214 (71)	156/225 (69)	144/194 (74)	20/33 (61)	302/439 (69)		
Hospitalization in past yr	57/255 (22)	76/221 (34)	58/236 (25)	60/198 (30)	9/34 (26)	122/480 (25)		

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† Among the 445 hospitalized case patients, 28 had received a positive test result at an outside hospital.

‡ Among the 394 syndrome-negative controls, 31 (8%) did not undergo testing for coronavirus disease 2019 (Covid-19).

§ Patients were described as being fully vaccinated if they had received a second dose of the BNT162b2 vaccine at least 14 days before the onset of illness. Patients were described as being partially vaccinated if they had received the first dose of the BNT162b2 vaccine at least 14 days before illness onset.

¶ Race or ethnic group was reported by the patients or their parents or guardians or was extracted from the medical record.

|| Scores on the Social Vulnerability Index range from 0 to 1.0, with higher scores indicating greater social vulnerability. Details regarding this index are available on the website of the Agency for Toxic Substances and Disease Registry of the Centers for Disease Control and Prevention at <https://www.atsdr.cdc.gov/placeandhealth/svi/index.html>. The median scores on the Social Vulnerability Index for case patients and controls are based on 2018 data.

** Some patients had more than one underlying health condition. Listed under the category of “other chronic condition” are obesity, rheumatologic or autoimmune disorder, hematologic disorder, renal or urologic dysfunction, gastrointestinal or hepatic disorder, metabolic or confirmed or suspected genetic disorder, and atopic or allergic condition.

†† Data regarding in-person school attendance and hospitalization during the past year were reported by the parent or guardian.

Table 2. Clinical Outcomes and Covid-19 Severity among Hospitalized Case Patients, According to Vaccination Status.*

Variable	Unvaccinated (N = 427)	Fully or Partially Vaccinated (N = 18)
Severe Covid-19 — no. (%)†	194 (45)	2 (11)
ICU admission — no. (%)	178 (42)	2 (11)
Life-threatening illness with life support — no. (%)‡	126 (30)	1 (6)
Invasive mechanical ventilation — no./total no. (%)	48/425 (11)	1/18 (6)
Noninvasive mechanical ventilation (BiPAP or CPAP) — no./total no. (%)	90/423 (21)	1/18 (6)
Vasoactive infusions — no./total no. (%)	38/426 (9)	1/18 (6)
Extracorporeal membrane oxygenation — no./total no. (%)	13/425 (3)	0
Patients with discharge data — no./total no. (%)	407/427 (95)	18/18 (100)
Median length of hospital stay (IQR)§	5 (2–7)	4 (1–5)
Death before discharge — no./total no. (%)	7/407 (2)	0

* BiPAP denotes bilevel positive airway pressure, CPAP continuous positive airway pressure, and IQR interquartile range.

† Severe Covid-19 illness was defined as admission to the intensive care unit (ICU) or life-threatening illness.

‡ Life-threatening Covid-19 was defined as illness leading to invasive or noninvasive mechanical ventilation, the use of vasopressors or extracorporeal membrane oxygenation, or illness resulting in death.

§ Data regarding the length of the hospital stay were not available for 28 unvaccinated patients.

data from the BNT162b2 clinical trial involving adolescents between 12 and 15 years of age, which showed vaccine efficacy of 100% (95% CI, 75 to 100) against nonhospitalized Covid-19 illness (i.e., any infection in which patients were not hospitalized).² In that trial, efficacy was based on the detection of no Covid-19 cases among 1005 participants who had received the BNT162b2 vaccine, as compared with 16 cases in 978 participants (1.6%) who had received placebo. No children with severe cases or cases resulting in hospitalization were observed in either group in the trial, which meant that the trial did not have sufficient power to assess vaccine efficacy against Covid-19 hospitalization or severe Covid-19. Post-marketing evaluations from Israel also showed that the BNT162b2 vaccine was highly effective against SARS-CoV-2 infection and nonhospitalized Covid-19 in adolescents between 12 and 18 years of age, but the data did not include sufficient cases to examine the effectiveness against Covid-19 hospitalization or severe disease.^{23,24} A U.S. cohort study involving participants from Kaiser Permanente Southern California showed effectiveness against Covid-19 hospitalization of 81% for fully vaccinated patients between 12 and 15 years of age; however, that study was conducted through August 2021 and assessed only 45 cases, which resulted in wide 95% confidence intervals (–55 to 98).²⁵

The high vaccine efficacy against infection in the BNT162b2 clinical trial in children between the ages of 12 and 15 years suggests that vaccination should also prevent postinfection disease progression leading to hospitalization. However, postauthorization monitoring of effectiveness is also necessary as vaccines are introduced in order to understand vaccine performance in real-world settings.¹⁹ Vaccine protection may differ in adolescents with underlying medical conditions, who are overrepresented in hospitalized settings and are often excluded from clinical trials.²⁶ Vaccine efficacy against new variants²⁴ and according to the interval since vaccination²⁷ could also vary. In our current study, a high percentage of case patients had underlying conditions (74%), but it is important to note that 26% were previously healthy. A disproportionate number of patients were Black (24%) or Hispanic (25%), populations that are at higher risk for Covid-19 than White children in the United States.^{26,28} Patients with underlying conditions and those from minority populations were underrepresented in the BNT162b2 clinical trial among adolescents between 12 and 15 years of age.² Despite these differences in the characteristics of patients and the high prevalence of underlying medical conditions (including obesity) in our study cohort, we observed that vaccination was associated with an overall risk reduction of 94% for Covid-19

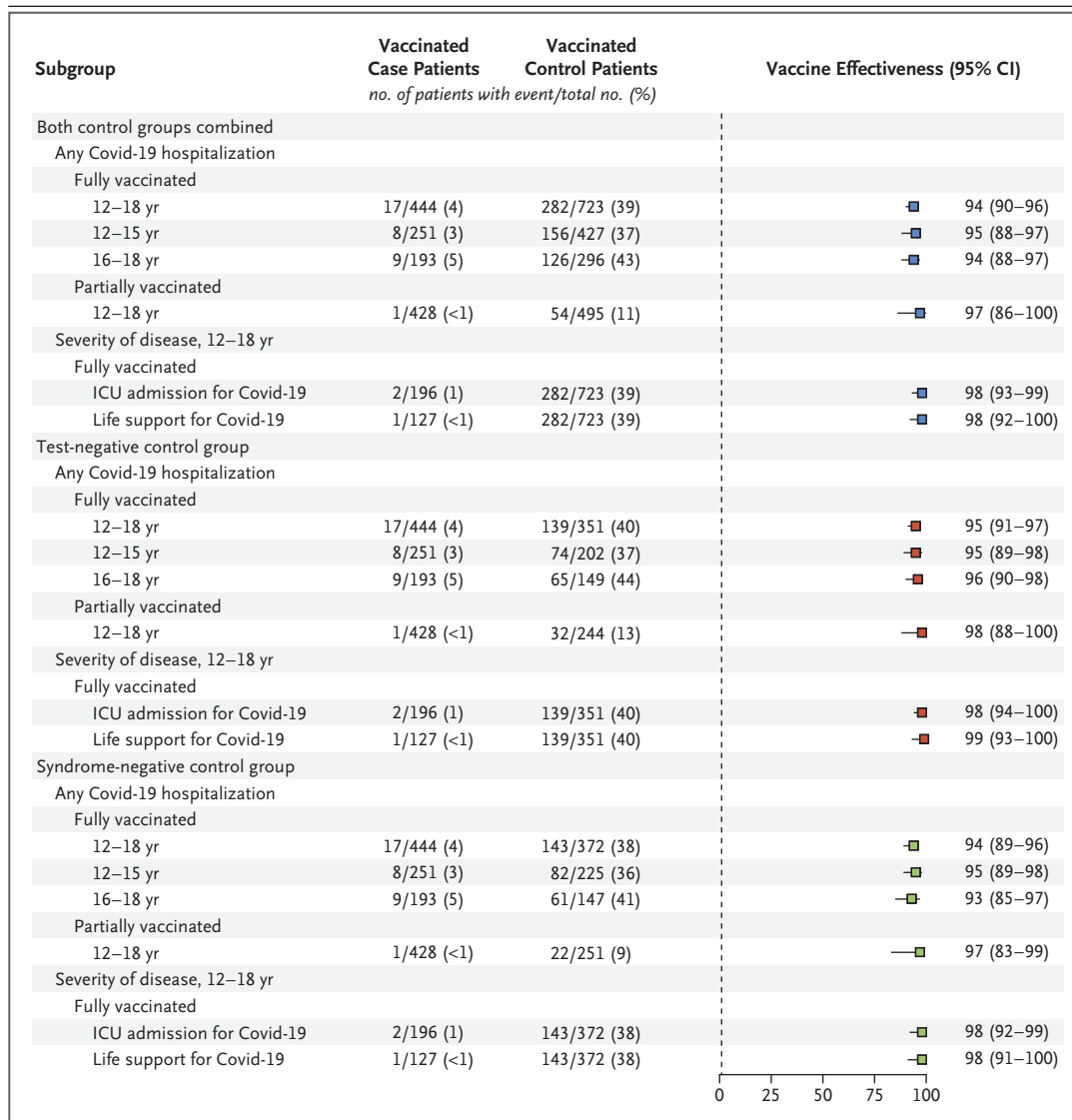


Figure 2. Effectiveness of the BNT162b2 Vaccine against Covid-19 Hospitalization in the Study Population.

Shown is the effectiveness of the BNT162b2 vaccine against Covid-19 hospitalization in all the case patients as compared with each of the two control groups (test-negative and syndrome-negative) and in the two control groups combined. Vaccine effectiveness was calculated as $(1 - \text{adjusted odds ratio}) \times 100$, in which the odds ratio is the odds of vaccination (fully or partially vaccinated vs. unvaccinated as referent group) in Covid-19 case patients as compared with control patients.

hospitalization and 98% for ICU admission or life-threatening Covid-19 illness. In addition, the median duration of follow-up in this analysis was longer (90 days) than that in the earlier BNT162b2 clinical trial (60 days). Despite the high level of protection afforded by vaccination² and the documented severity of Covid-19 in adolescents,²⁶ only 39% of the controls in our study were fully vaccinated against Covid-19. These

data suggest that efforts to improve vaccination coverage among all adolescents, especially those at highest risk for severe Covid-19,^{28,29} could markedly decrease the risk of severe Covid-19 among adolescents in the United States.

Our study has certain limitations. We did not have sufficient sequencing results to assess vaccine effectiveness directly against specific variants; however, more than 96% of the circulating

variants during the evaluation period were delta.³⁰ Findings from urban health centers in this study may not be generalizable to patients with less severe disease who may present at nonurban hospitals. We also observed a high percentage of case patients (56%) from the southern United States, where Covid-19 transmission was high during this period. This study only assessed the effectiveness of the BNT162b2 vaccine, which was most widely available for adolescents in the United States during the study period. The effectiveness of a single dose of vaccine was high, but the duration of protection from one dose is unknown. It should be noted that the effectiveness of partial versus full vaccination in this study cannot be directly compared because of the between-group differences in the interval since vaccination. In case patients, the median interval between the first dose and illness onset was only 30 days (as compared with 90 days after the second dose), which indicates that most

partially vaccinated adolescents were hospitalized between dose 1 and 2. Finally, because the vaccination of children between 12 and 15 years of age was initiated in May 2021, an evaluation of the duration of protection was not possible.

In this real-world evaluation of the effectiveness of the BNT162b2 mRNA vaccine in adolescents between 12 and 18 years of age in the United States, when the delta variant was predominant, we found that the vaccine was highly effective against Covid-19 hospitalization and critical illness, including among patients with underlying risk factors for severe illness. Vaccination averted nearly all life-threatening Covid-19 illness in this age group.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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

APPENDIX

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