ORIGINAL ARTICLE

BNT162b2 Protection against the Omicron Variant in Children and Adolescents

A.M. Price, S.M. Olson, M.M. Newhams, N.B. Halasa, J.A. Boom, L.C. Sahni, P.S. Pannaraj, K. Irby, K.E. Bline, A.B. Maddux, R.A. Nofziger, M.A. Cameron, T.C. Walker, S.P. Schwartz, E.H. Mack, L. Smallcomb, J.E. Schuster, C.V. Hobbs, S. Kamidani, K.M. Tarquinio, T.T. Bradford, E.R. Levy, K. Chiotos, S.S. Bhumbra, N.Z. Cvijanovich, S.M. Heidemann, M.L. Cullimore, S.J. Gertz, B.M. Coates, M.A. Staat, M.S. Zinter, M. Kong, B.M. Chatani, J.R. Hume, K.V. Typpo, M. Maamari, H.R. Flori, M.W. Tenforde, L.D. Zambrano, A.P. Campbell, M.M. Patel, and A.G. Randolph, for the Overcoming Covid-19 Investigators*

ABSTRACT

BACKGROUND

Spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.1.529 (omicron) variant, which led to increased U.S. hospitalizations for coronavirus disease 2019 (Covid-19), generated concern about immune evasion and the duration of protection from vaccines in children and adolescents.

METHODS

Using a case–control, test-negative design, we assessed vaccine effectiveness against laboratory-confirmed Covid-19 leading to hospitalization and against critical Covid-19 (i.e., leading to receipt of life support or to death). From July 1, 2021, to February 17, 2022, we enrolled case patients with Covid-19 and controls without Covid-19 at 31 hospitals in 23 states. We estimated vaccine effectiveness by comparing the odds of antecedent full vaccination (two doses of BNT162b2 messenger RNA vaccine) at least 14 days before illness among case patients and controls, according to time since vaccination for patients 12 to 18 years of age and in periods coinciding with circulation of B.1.617.2 (delta) (July 1, 2021, to December 18, 2021) and omicron (December 19, 2021, to February 17, 2022) among patients 5 to 11 and 12 to 18 years of age.

RESULTS

We enrolled 1185 case patients (1043 [88%] of whom were unvaccinated, 291 [25%] of whom received life support, and 14 of whom died) and 1627 controls. During the delta-predominant period, vaccine effectiveness against hospitalization for Covid-19 among adolescents 12 to 18 years of age was 93% (95% confidence interval [CI], 89 to 95) 2 to 22 weeks after vaccination and was 92% (95% CI, 80 to 97) at 23 to 44 weeks. Among adolescents 12 to 18 years of age (median interval since vaccination, 162 days) during the omicron-predominant period, vaccine effectiveness was 40% (95% CI, 9 to 60) against hospitalization for Covid-19, 79% (95% CI, 51 to 91) against critical Covid-19, and 20% (95% CI, –25 to 49) against noncritical Covid-19. During the omicron period, vaccine effectiveness against hospitalization among children 5 to 11 years of age was 68% (95% CI, 42 to 82; median interval since vaccination, 34 days).

CONCLUSIONS

BNT162b2 vaccination reduced the risk of omicron-associated hospitalization by two thirds among children 5 to 11 years of age. Although two doses provided lower protection against omicron-associated hospitalization than against delta-associated hospitalization among adolescents 12 to 18 years of age, vaccination prevented critical illness caused by either variant. (Funded by the Centers for Disease Control and Prevention.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Patel can be contacted at aul3@cdc.gov or at the Influenza Division, Centers for Disease Control and Prevention, 1600 Clifton Rd. NE, H24-7, Atlanta, GA 30329-4027.

*A list of the Overcoming Covid-19 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

Ms. Price, Ms. Olson, Dr. Patel, and Dr. Randolph contributed equally to this article.

This article was published on March 30, 2022, at NEJM.org.

N Engl J Med 2022;386:1899-909.
DOI: 10.1056/NEJMoa2202826

A Quick Take is available at NEJM.org

In the United States, the messenger RNA (mRNA) vaccine BNT162b2 (Pfizer–BioNTech) is currently authorized for use in persons 5 to 18 years of age.[1,2] Real-world evaluations have shown the BNT162b2 vaccine to be highly effective at reducing the risk of hospitalization and death from coronavirus disease 2019 (Covid-19) among adolescents 12 to 18 years of age, but data on its effectiveness among children 5 to 11 years of age are limited.[3-8] Moreover, the studies involving adolescents have been limited to measuring effectiveness for approximately 3 months after vaccination, and they preceded circulation of the B.1.1.529 (omicron) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Studies in adult populations indicate that the effectiveness of two vaccine doses against Covid-19 wanes and is lower against the omicron variant than against the B.1.617.2 (delta) variant.[9-11]

The durability of protection against severe Covid-19 after full vaccination (i.e., after receipt of two doses of BNT162b2) is uncertain but is important to understand as time since vaccination increases. Furthermore, the recent emergence of the omicron variant, against which the neutralization efficiency of BNT162b2 is reduced, coupled with increases in Covid-19 hospitalizations among children, has prompted concerns about immune evasion.[12] In this analysis, we examined the duration of protection among adolescents 12 to 18 years of age during the delta-predominant period, as well as protection against omicron variant–associated hospitalizations among children and adolescents 5 to 18 years of age. We also evaluated the effectiveness of two doses of BNT162b2 vaccine against Covid-19 leading to hospitalization and against Covid-19 leading to receipt of life-supporting interventions or to death among adolescents 12 to 18 years of age during the period from July 1, 2021, through February 17, 2022, in the United States.

Methods

Study Design

We used a case–control, test-negative design to assess vaccine effectiveness against Covid-19 leading to hospitalization and against critical Covid-19 (i.e., leading to life-supporting interventions or death). In this design, vaccine effectiveness is estimated by comparing the odds of antecedent vaccination among hospitalized case patients who have laboratory-confirmed Covid-19 and control patients without Covid-19.[13-17] The dates of emergency use authorization for BNT162b2 varied among the age groups of 16 to 18 years (December 2020), 12 to 15 years (May 2021), and 5 to 11 years (October 2021). Because the time since vaccination was longer among adolescents 12 to 18 years of age than in the other age groups, we assessed duration of protection by comparing effectiveness from 2 to 22 weeks and more than 23 weeks after full vaccination among patients admitted to the hospital during the delta-predominant period (defined as July 1, 2021, to December 18, 2021) or during the period of omicron-variant circulation (defined as December 19, 2021, to February 17, 2022).[11,18-20] For the age group of 5 to 11 years, estimation of effectiveness was possible only during the omicron period because vaccination had only recently been approved for this age group.

The surveillance protocol, available with the full text of this article at NEJM.org, was reviewed by the Centers for Disease Control and Prevention (CDC) and other participating institutions and was determined to be public health surveillance and not subject to informed-consent requirements; this review was conducted in accordance with applicable federal laws and CDC policy.[21] The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

Study Population

Participants included in this study were identified through active surveillance for Covid-19–associated hospitalizations in 31 pediatric hospitals across 23 states in the CDC-funded Overcoming Covid-19 Network.[4,22] Case patients were identified through review of hospital admission logs or electronic medical records and included those hospitalized with Covid-19 as the primary reason for admission or with a clinical syndrome consistent with acute Covid-19 (one or more of the following: fever, cough, shortness of breath, loss of taste, loss of smell, gastrointestinal symptoms, receipt of respiratory support, or new pulmonary findings on chest imaging). All case patients had to have had a positive SARS-CoV-2 reverse-transcriptase–polymerase-chain-reaction (RT-PCR) or antigen test result within 10 days after symptom onset or within 72 hours after hospital admission.

We classified control patients as hospitalized patients with a negative SARS-CoV-2 RT-PCR or

antigen test result, with or without Covid-19–associated symptoms.[4,5] Each matched control patient was selected from among the patients who were hospitalized within the same institution as the case patient, were in the same age category as the case patient (5 to 11 years, 12 to 15 years, or 16 to 18 years), and were hospitalized within 4 weeks before or after the date of admission for the case patient.

We excluded patients who received the SARS-CoV-2 test result more than 10 days after illness onset or more than 72 hours after the admission date, those who were partially vaccinated, those who were vaccinated 0 to 13 days before symptom onset, those whose vaccination status was unknown, and those who had received the mRNA-1273 (Moderna) or Ad26.COV2.S (Johnson & Johnson–Janssen) vaccine, neither of which was authorized for adolescents younger than 18 years of age during the study period. Patients admitted for reasons not related to Covid-19 (e.g., trauma or suicide attempt) who had a positive SARS-CoV-2 test during admission were identified by the enrolling site and excluded from the analysis. Patients who had received a third dose of BNT162b2 were also excluded from the analytic data set because the sample size (12 case patients and 30 control patients) was insufficient for an evaluation of booster-dose protection.

DATA COLLECTION

Demographic characteristics, clinical information about the current illness, and SARS-CoV-2 testing history were obtained through interviews with the patients' parents or guardians and review of electronic medical records. Parents or guardians were asked about Covid-19 vaccination history, including vaccination dates, the number of doses of vaccine, whether the most recent dose occurred in the last 14 days, the location where vaccination occurred, the vaccine manufacturer, and the availability of a Covid-19 vaccination card. Study personnel searched state immunization information systems, electronic medical records, and other sources (including documentation from pediatricians) to verify reported or unknown vaccination status.

VACCINATION STATUS

For this analysis, patients were considered to be vaccinated against Covid-19 on the basis of source documentation or plausible reporting by the patient's parents or guardians if vaccination dates and location were provided at the time of the interview. Patients were categorized as unvaccinated if BNT162b2 had not been received before illness onset and were categorized as fully vaccinated if the second dose of BNT162b2 had been administered at least 14 days before illness onset.

CHARACTERIZATION OF COVID-19 SEVERITY

To evaluate vaccine protection against a gradient of disease severity, we distinguished patients with critical Covid-19 (i.e., Covid-19 leading to life-supporting interventions or death) during their hospital stay. Life-supporting interventions were defined as noninvasive mechanical ventilation (bilevel positive airway pressure or continuous positive airway pressure), invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation during the hospital stay.

STATISTICAL ANALYSIS

Vaccine effectiveness against Covid-19–associated hospitalization was estimated with the use of logistic regression, comparing odds ratios of antecedent vaccination (fully vaccinated vs. unvaccinated) in case patients as compared with controls with the following equation: vaccine effectiveness = 100 × (1 − odds ratio) (Tables S1, S2, and S3 and the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org). We adjusted models a priori for U.S. Census region, calendar time of admission (biweekly intervals), age, sex, and race and ethnic group.[4,15,23] Using a change-in-estimate approach, we assessed other potential confounding factors (the presence of any 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%.[15,24] We also adjusted the standard error for clustering according to hospital, an analysis that did not substantially alter the results. Time-varying vaccine effectiveness models (a priori) were then constructed by adding a categorical term (2 to 22 weeks vs. >22 weeks, dichotomized on the basis of the median time since vaccination among case patients) for interval from receipt of the second vaccine dose and illness onset.[18,20] Unvaccinated patients were assigned a value of 0 weeks since vaccination.

To assess vaccine effectiveness against a gradient of disease severity, we conducted analyses

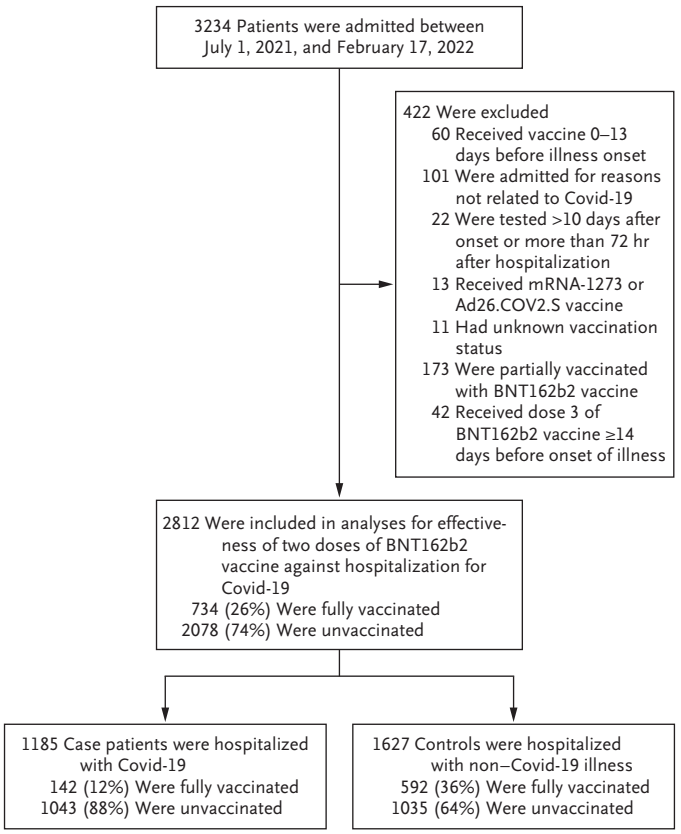

Figure 1. Study Enrollment and Outcomes (July 1, 2021–February 17, 2022).
Covid-19 denotes coronavirus disease 2019.

of subgroups defined according to receipt of life-supporting interventions or death in the hospital, with separately constructed models. In addition, models evaluating vaccine effectiveness during the delta period and the omicron period were generated for adolescents 12 to 18 years of age who were age-eligible for vaccination and had sufficient vaccination uptake during both periods. For children 5 to 11 years of age, vaccine effectiveness was calculated only for the omicron period, since these children were not eligible for vaccination until October 29, 2021. Subgroup analyses of time-varying vaccine effectiveness and severity were not possible for children 5 to 11 years of age because of sample-size limitations.

The widths of the confidence intervals were not adjusted for multiplicity, and therefore the intervals should not be used to infer vaccine effectiveness for the subgroup analyses. Statistical analyses were conducted with R software, version 4.0.2 (R Foundation for Statistical Computing), and SAS software, version 9.4 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

Among the 3234 eligible patients enrolled during the period from July 1, 2021, to February 17, 2022, a total of 422 (13%) were excluded (Fig. 1). Our analysis involving adolescents included 918 case patients and 1357 control patients who were between 12 and 18 years of age and were admitted to the hospital during the delta period (684 case patients) or omicron period (234 case patients). Among these case patients, the median age was 16 years, and 78% had at least one underlying health condition (Table 1). Among control patients, the median age was 15 years, and 67% had at least one underlying condition. Among the 918 adolescent case patients, 122 (13%) were fully vaccinated and 796 (87%) were unvaccinated. In contrast, among the 1357 adolescent control patients, 542 (40%) were fully vaccinated and 815 (60%) were unvaccinated.

We enrolled 267 case patients and 270 control patients who were children 5 to 11 years of age, all whom were admitted during the omicron period. Among case patients in this age group, the median age was 8 years, and 82% had at least one underlying health condition. Among the control patients, the median age was 8 years, and 73% had at least one underlying condition. Among the 267 case patients, 20 (7%) were fully vaccinated and 247 (93%) were unvaccinated (Table 1). Among 270 control patients, 50 (19%) were fully vaccinated and 220 (81%) were unvaccinated.

CLINICAL SEVERITY OF COVID-19 CASES

Among the 1185 case patients overall, 291 (25%) had critical Covid-19, including 14 who died. Among the 918 case patients who were 12 to 18 years of age, 249 (27%) had critical Covid-19, including 22 (2%) patients who received extracorporeal membrane oxygenation and 13 (1%) who died (Table 2). Among the 249 adolescents with critical Covid-19, 232 (93%) were unvaccinated.

Among the 267 children 5 to 11 years of age with Covid-19, 42 (16%) had critical Covid-19, including 2 patients who received extracorporeal membrane oxygenation and 1 who died. Among the 42 children 5 to 11 years of age with critical Covid-19, 38 (90%) were unvaccinated.

VACCINE EFFECTIVENESS DURING CIRCULATION OF THE DELTA AND OMICRON VARIANTS

Vaccine effectiveness during the delta and omicron periods combined was similar in the group of patients who were 12 to 15 years of age and the group of patients who were 16 to 18 years of age (83% [95% CI, 77 to 88] and 82% [95% CI, 74 to 88], respectively) (Fig. 2). Effectiveness against Covid-19–associated hospitalization among adolescents 12 to 18 years of age was higher during the delta period than during the omicron period (92% [95% CI, 89 to 95] vs. 40% [95% CI, 9 to 60]).

In the analysis in which time since vaccination was taken into account, vaccine effectiveness against hospitalization for Covid-19 during the delta period among adolescents 12 to 18 years of age was 93% (95% CI, 89 to 95) during the 2 to 22 weeks after full vaccination and 92% (95% CI, 80 to 97) in the 23 to 44 weeks after full vaccination. In contrast, during the omicron period, vaccine effectiveness against hospitalization for Covid-19 was similar during the 2 to 22 weeks and 23 to 44 weeks after full vaccination (43% [95% CI, –1 to 68] and 38% [95% CI, –3 to 62], respectively).

Among children 5 to 11 years of age, vaccine effectiveness was 68% (95% CI, 42 to 82) against Covid-19–associated hospitalization during the omicron period. The interval from vaccination to Covid-19 hospitalization during the omicron period was longer among participants 12 to 18 years of age than among those 5 to 11 years of age (median, 162 days vs. 34 days).

VACCINE EFFECTIVENESS ACCORDING TO DISEASE SEVERITY AMONG ADOLESCENTS

During the delta period, vaccine effectiveness against critical Covid-19 among adolescents 12 to 18 years of age was 96% (95% CI, 90 to 98), as compared with 91% (95% CI, 86 to 94) against hospitalization without life support. During the omicron period, vaccine effectiveness was 79% (95% CI, 51 to 91) against critical Covid-19, as compared with 20% (95% CI, –25 to 49) against noncritical Covid-19 (Fig. 3). Sample sizes were insufficient for subgroup analysis involving children 5 to 11 years of age.

DISCUSSION

In a multicenter network made up of 31 pediatric hospitals covering 23 states, in which 1185 hospitalized case patients with Covid-19 who were 5 to 18 years of age and 1627 control patients of similar age without Covid-19 were enrolled during the period from July 2021 through February 2022, the effectiveness of two doses of the BNT162b2 vaccine against hospitalization for Covid-19 was sustained through the period of delta-variant circulation. However, during the omicron period, the effectiveness of two doses of BNT162b2 against hospitalization for Covid-19 decreased to 40% among adolescents 12 to 18 years of age, with similar point estimates of effectiveness among those in whom Covid-19 developed within 2 to 22 weeks after vaccination (43%; 95% CI, –1 to 68) or at least 23 weeks after vaccination (38%; 95% CI, –3 to 62). Among adolescents, the estimated effectiveness against omicron-related critical illness was 79% (95% CI, 51 to 91), as compared with 20% (95% CI, –25 to 49) against hospitalization for less-severe illness. For children 5 to 11 years of age, who had only recently been authorized to receive the vaccine and on average had been vaccinated 1 month earlier (median, 34 days), vaccination reduced the risk of hospitalization for Covid-19 during the period of omicron circulation by 68%.

Several studies have shown that the BNT162b2 vaccine was highly effective at reducing the risk of hospitalization and life-threatening illness in adolescents during the delta period,[3-7,17] but data on duration of protection, protection against omicron, and protection among children 5 to 11 years of age have been limited. A recent study showed a decline in effectiveness against emergency department and urgent care Covid-19 visits among adolescents 12 to 18 years of age, but effectiveness improved with a booster dose among those 16 to 17 years of age.[8] The study was not powered to assess effectiveness against hospitalization for Covid-19 during the omicron period alone. In adult populations, the protection conferred by two vaccine doses against Covid-19 wanes (more against milder infection than against severe disease) and is lower for omicron than for delta.[9-11] However, a booster dose increases protection, including protection against omicron.

In our analysis involving adolescents 12 to 18 years of age, during the period of delta-variant circulation in the United States, we did not find a decline in protection from two BNT162b2 vaccine doses against hospitalization for Covid-19 for more than 6 months after vaccination. In con-

Table 1. Characteristics of Hospitalized Case Patients and Controls from 31 Pediatric Hospitals in 23 States, July 2021–February 2022.*

Characteristic	Overall (5–18 Yr)		5–11 Yr		12–18 Yr	
	Case Patients (N=1185)	Control Patients (N=1627)	Case Patients (N=267)	Control Patients (N=270)	Case Patients (N=918)	Control Patients (N=1357)
Median age (IQR) — yr	15 (12–17)	15 (14–17)	8 (6–10)	8 (7–10)	16 (14–17)	15 (14–17)
Female sex — no. (%)	574 (48)	787 (48)	115 (43)	121 (45)	459 (50)	666 (49)
Race and ethnic group — no. (%)†						
White, non-Hispanic	433 (37)	679 (42)	89 (33)	98 (36)	344 (37)	581 (43)
Black, non-Hispanic	304 (26)	336 (21)	63 (24)	61 (23)	241 (26)	275 (20)
Hispanic, any race	302 (25)	400 (25)	74 (28)	80 (30)	228 (25)	320 (24)
Other, non-Hispanic	69 (6)	114 (7)	18 (7)	14 (5)	51 (6)	100 (7)
Unknown	77 (6)	98 (6)	23 (9)	17 (6)	54 (6)	81 (6)
Median Social Vulnerability Index (IQR)‡	0.6 (0.4–0.9)	0.6 (0.2–0.8)	0.6 (0.3–0.8)	0.6 (0.1–0.8)	0.7 (0.4–0.9)	0.6 (0.2–0.8)
Census region — no. (%)						
Northeast	135 (11)	156 (10)	43 (16)	35 (13)	92 (10)	121 (9)
Midwest	300 (25)	442 (27)	57 (21)	97 (36)	243 (26)	345 (25)
South	488 (41)	604 (37)	104 (39)	74 (27)	384 (42)	530 (39)
West	262 (22)	425 (26)	63 (24)	64 (24)	199 (22)	361 (27)
Month of admission — no. (%)						
July 2021	46 (4)	60 (4)	—	—	46 (5)	60 (4)
August 2021	175 (15)	218 (13)	—	—	175 (19)	218 (16)
September 2021	196 (17)	334 (21)	—	—	196 (21)	334 (25)
October 2021	107 (9)	292 (18)	—	—	107 (12)	292 (22)
November 2021	96 (8)	181 (11)	—	—	96 (10)	181 (13)
December 2021	197 (17)	189 (12)	65 (24)	59 (22)	132 (14)	130 (10)
January 2022	326 (28)	295 (18)	180 (67)	175 (65)	146 (16)	120 (9)
February 2022	42 (4)	58 (4)	22 (8)	36 (13)	20 (2)	22 (2)

Underlying health conditions — no./total no. (%)						
At least one underlying condition, including obesity	901/1145 (79)	1089/1598 (68)	207/251 (82)	182/250 (73)	694/894 (78)	907/1348 (67)
Respiratory, including asthma	414/1144 (36)	455/1592 (29)	99/251 (39)	101/250 (40)	315/893 (35)	354/1342 (26)
Cardiovascular	135/1144 (12)	124/1617 (8)	45/251 (18)	16/248 (6)	90/893 (10)	108/1341 (8)
Neurologic or neuromuscular	243/1144 (21)	314/1594 (20)	91/251 (36)	49/250 (20)	152/893 (17)	265/1344 (20)
Immunosuppression or autoimmune	102/1145 (9)	156/1596 (10)	42/251 (17)	22/250 (9)	60/834 (7)	134/1346 (10)
Endocrine, including diabetes	178/1143 (16)	150/1593 (9)	35/250 (14)	15/247 (6)	143/893 (16)	135/1346 (10)
Diabetes	102/1140 (9)	90/1592 (6)	11/249 (4)	9/247 (4)	91/891 (10)	81/1345 (6)
Other chronic conditions§	592/1144 (52)	640/1594 (40)	136/251 (54)	95/250 (38)	456/893 (51)	545/1344 (41)
In-person school attendance — no./total no. (%)¶	463/727 (64)	683/983 (69)	80/155 (52)	120/170 (71)	383/572 (67)	563/813 (69)
Previous hospitalizations in past year — no./total no. (%)¶	261/746 (35)	333/999 (33)	80/150 (53)	60/163 (37)	181/596 (30)	273/836 (33)
Vaccination status — no. (%)‖						
Unvaccinated	1043 (88)	1035 (64)	247 (93)	220 (81)	796 (87)	815 (60)
Fully vaccinated	142 (12)	592 (36)	20 (7)	50 (19)	122 (13)	542 (40)
If fully vaccinated, median days from second vaccine to illness onset (IQR)**	145 (81–201)	99 (55–152)	34 (23–52)	39 (25–48)	162 (111–206)	106 (64–156)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race and ethnic group were reported by the patients or by their parents or guardians or were extracted from the medical record.
‡ Data were missing for 6 patients (2 case patients and 4 controls). 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 at https://www.atsdr.cdc.gov/placeandhealth/svi/index.html. The median scores on the Social Vulnerability Index were based on 2018 data.
§ Other chronic conditions included, but were not limited to, 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.
¶ In-person school attendance and previous hospitalization in the past year were based on information reported by parent or guardian.
‖ Patients were defined as unvaccinated if they had not received any coronavirus disease 2019 (Covid-19) vaccine before illness onset. Patients were defined as fully vaccinated if they had received both doses of a two-dose BNT162b2 vaccination regimen, with the second dose received at least 14 days before illness onset.
** Dates are based on patients with documented vaccination (138 case patients and 577 controls), not plausible self-report. We used the date of illness onset for case patients and controls with Covid-19–like illness with median value imputed if missing. For controls without Covid-19–like illness, we used the date of admission as the date of illness onset.

Table 2. Clinical Outcomes and Severity among Children and Adolescents Hospitalized with Covid-19.*

Characteristic	Children 5–11 Yr			Adolescents 12–18 Yr		
	Total (N = 267)	Unvaccinated (N = 247)	Fully Vaccinated (N = 20)†	Total (N = 918)	Unvaccinated (N = 796)	Fully Vaccinated (N = 122)†
ICU admission — no./total no (%)	60/262 (23)	55/244 (23)	5/18 (28)	326/912 (36)	306/790 (39)	20/122 (16)
Critical Covid-19 — no./total no. (%)‡	42/259 (16)	38/241 (16)	4/18 (22)	249/910 (27)	232/789 (29)	17/121 (14)
Invasive mechanical ventilation	18/259 (7)	17/241 (7)	1/18 (6)	96/905 (11)	88/784 (11)	8/121 (7)
Noninvasive mechanical ventilation	26/258 (10)	24/240 (10)	2/18 (11)	195/907 (21)	182/786 (23)	13/121 (11)
Vasoactive infusion	11/259 (4)	9/241 (4)	2/18 (11)	75/908 (8)	69/787 (9)	6/121 (5)
Extracorporeal membrane oxygenation	2/259 (1)	2/241 (1)	0/18	22/907 (2)	21/786 (3)	1/121 (1)
Death before discharge from hospital	1/249 (<1)	1/232 (<1)	0/17	13/879 (1)	11/765 (1)	2/114 (2)
Median hospital length of stay (IQR) — days§	2 (1–5)	2 (1–5)	3 (1–3)	4 (2–7)	4 (2–8)	3 (2–5)

* ICU denotes intensive care unit.
† 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.
‡ Critical Covid-19 was defined as Covid-19 leading to life support (i.e., noninvasive mechanical ventilation [bilevel positive airway pressure or continuous positive airway pressure] or invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation) or death.
§ Data on length of hospital stay were missing for 20 children 5 to 11 years of age (17 unvaccinated and 3 fully vaccinated) and for 58 adolescents 12 to 18 years of age (47 unvaccinated and 11 fully vaccinated).

trast, effectiveness declined during the omicron period. The lower effectiveness among adolescents 12 to 18 years of age was temporally associated with both a longer time since vaccination and the emergence of the omicron variant. However, the sustained protection in the analysis according to time since vaccination during the delta and omicron periods among adolescents 12 to 18 years of age, with an overall lower effectiveness during the omicron period, suggests that evasion of immunity contributed more to the decline in protection than waning immunity. During the omicron period, effectiveness was also relatively lower among children 5 to 11 years of age than was expected on the basis of an efficacy of 91% against infection, which was observed in a randomized, controlled trial before the omicron variant emerged.[25] Reduced neutralization efficiency of the BNT162b2 vaccine against the recently emerged omicron variant has been observed.[12,26] Ongoing surveillance and future analyses of time since vaccination as more omicron-associated hospitalizations accumulate will help to address whether protection against severe disease is sustained during the omicron period. Evaluations of vaccine effectiveness can also address whether observed declines are related to waning protection that would be bolstered by booster doses of current vaccines (or increasing antigen content) or are instead related to immune evasion, which might require other strategies, such as updates to the vaccine strain.

Our study provides strong evidence for the benefits of vaccination in preventing the most severe forms of disease related to the delta and omicron variants in children and adolescents. During the omicron period, vaccine protection among adolescents 12 to 18 years of age was higher against critical illness (79%) than against noncritical illness (20%). Breakthrough infections can occur in persons who have been vaccinated against respiratory viruses such as SARS-CoV-2 and influenza because sterilizing immunity providing lifelong protection against infection is untenable; variants can emerge against which vaccine-induced antibodies have reduced neutralization efficiency, and preexisting antibodies wane with time.[27,28] However, these breakthrough infections would be expected to invoke memory B- and T-cell responses, which can limit the progression of disease.[29-31] Our findings support the premise that vaccination-induced immunity at-

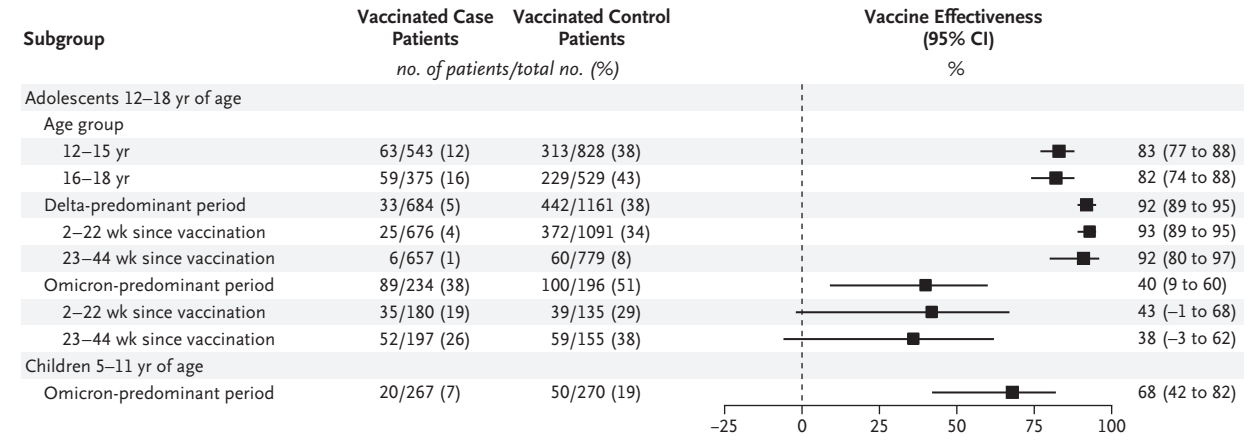

Figure 2. Effectiveness of the BNT162b2 Vaccine against Hospitalization for Covid-19, Stratified According to Age and Variant.

The delta-predominant period was defined as July 1, 2021, through December 18, 2021. The omicron-predominant period was defined as December 19, 2021, to February 17, 2022. For children 5 to 11 years of age, evaluation was limited to the omicron period because of the recent introduction of vaccination in this group (on October 29, 2021). For the subgroup analysis of time since vaccination, 4 case patients were not included because of missing dates of vaccination. Vaccine effectiveness was calculated as (1 – adjusted odds ratio) × 100, where the odds ratio is the odds of vaccination in case patients as compared with controls.

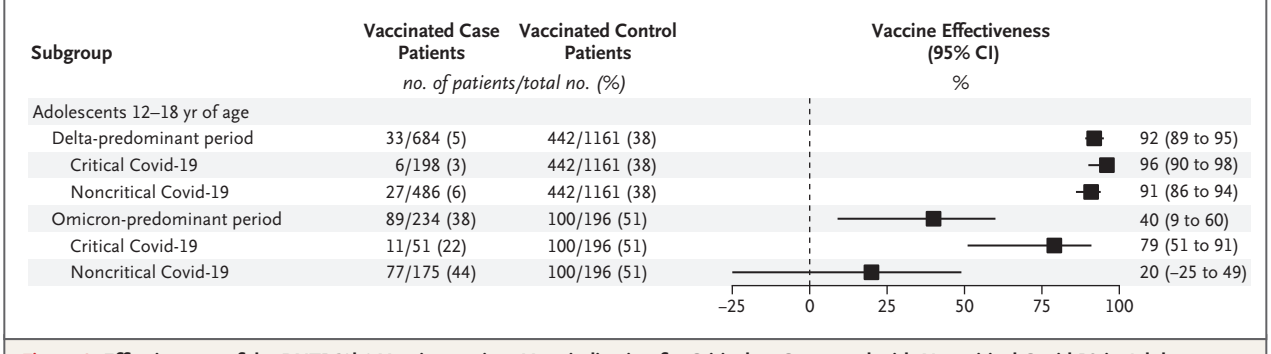

Figure 3. Effectiveness of the BNT162b2 Vaccine against Hospitalization for Critical as Compared with Noncritical Covid-19 in Adolescents 12 to 18 Years of Age, Stratified According to Variant.

Numbers were insufficient to stratify the analysis according to disease severity among children 5 to 11 years of age. In this analysis, only subgroups of case patients were based on disease severity; the entire control group (regardless of disease severity) served as the basis for comparison. Critical Covid-19 was defined as Covid-19 leading to life support (i.e., noninvasive mechanical ventilation [bilevel positive airway pressure or continuous positive airway pressure] or invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation) or death. Information on this outcome was missing for 8 case patients admitted during the omicron period. Vaccine effectiveness was calculated as (1 – adjusted odds ratio) × 100, where the odds ratio is the odds of vaccination in case patients as compared with controls.

tenuated Covid-19 disease severity without fully eliminating the risk of breakthrough infections in vaccinated children and adolescents. Although no such previous data are available for children, studies evaluating Covid-19 in vaccinated as compared with unvaccinated adults have shown similar disease attenuation.[10,32] With waning protection against infection and recurrent emergence of variants that evade immunity, ongoing monitoring is necessary to ensure that Covid-19 vaccines provide sustained attenuation of illness severity and prevent life-threatening disease.

Our analysis has some limitations. We estimated effectiveness only for the BNT162b2 vaccine, which was widely available for adolescents 12 to 18 years of age in the United States. Because of the recent authorization of the BNT162b2 vaccine for children 5 to 11 years of age in the United

States, the sample and the duration of follow-up since full vaccination were limited. As the pandemic evolves, additional analyses with longer durations of follow-up since vaccination will be important to assess the durability of protection against Covid-19–associated hospitalization, critical illness, and death. Misclassification due to reduced sensitivity of the SARS-CoV-2 assay cannot be ruled out, especially because the use of antigen assays was permitted, although in most case patients (94%) Covid-19 was diagnosed by RT-PCR. Finally, we could not evaluate vaccine effectiveness after a booster dose because eligibility for booster doses was not expanded to include adolescents 12 to 15 years of age until January 2022, and only a small number of patients received a booster dose during the surveillance period in this analysis.

The effectiveness of two doses of BNT162b2 against any hospitalization for Covid-19 was lower during the omicron period than during the delta period in adolescents 12 to 18 years of age, but vaccination prevented most life-threatening Covid-19 in both periods. Vaccination also reduced the risk of hospitalization for Covid-19 among children 5 to 11 years of age by two thirds during the omicron period, and most children with critical Covid-19 were unvaccinated. Continued monitoring of vaccine effectiveness against severe Covid-19 will be important to inform vaccination strategies as the time since vaccination increases or if new SARS-CoV-2 variants emerge.

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

Supported by the Centers for Disease Control and Prevention (CDC) under a contract with Boston Children's Hospital.

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

APPENDIX

The authors' full names and academic degrees are as follows: Ashley M. Price, M.P.H., Samantha M. Olson, M.P.H., Margaret M. Newhams, M.P.H., Natasha B. Halasa, M.D., Julie A. Boom, M.D., Leila C. Sahni, Ph.D., M.P.H., Pia S. Pannaraj, M.D., M.P.H., Katherine Irby, M.D., Katherine E. Bline, M.D., Aline B. Maddux, M.D., Ryan A. Nofziger, M.D., Melissa A. Cameron, M.D., Tracie C. Walker, M.D., Stephanie P. Schwartz, M.D., Elizabeth H. Mack, M.D., Laura Smallcomb, M.D., Jennifer E. Schuster, M.D., Charlotte V. Hobbs, M.D., Satoshi Kamidani, M.D., Keiko M. Tarquinio, M.D., Tamara T. Bradford, M.D., Emily R. Levy, M.D., Kathleen Chiotos, M.D., M.S.C.E., Samina S. Bhumbra, M.D., Natalie Z. Cvijanovich, M.D., Sabrina M. Heidemann, M.D., Melissa L. Cullimore, M.D., Shira J. Gertz, M.D., Bria M. Coates, M.D., Mary A. Staat, M.D., Matt S. Zinter, M.D., Michele Kong, M.D., Brandon M. Chatani, M.D., Janet R. Hume, M.D., Katri V. Typpo, M.D., M.P.H., Mia Maamari, M.D., Heidi R. Flori, M.D., Mark W. Tenforde, M.D., Ph.D., Laura D. Zambrano, Ph.D., M.P.H., Angela P. Campbell, M.D., M.P.H., Manish M. Patel, M.D., and Adrienne G. Randolph, M.D.

The authors' affiliations are as follows: the Covid-19 Response Team, Centers for Disease Control and Prevention (A.M.P., S.M.O., M.W.T., L.D.Z., A.P.C., M.M.P.), the Center for Childhood Infections and Vaccines of Children's Healthcare of Atlanta and the Department of Pediatrics, Emory University School of Medicine (S.K.), and the Division of Critical Care Medicine, Department of Pediatrics, Emory University School of Medicine, Children's Healthcare of Atlanta (K.M.T.) — all in Atlanta; the Department of Anesthesiology, Critical Care, and Pain Medicine, Boston Children's Hospital (M.M.N., A.G.R.), and the Departments of Anaesthesia and Pediatrics, Harvard Medical School (A.G.R.) — both in Boston; the Division of Pediatric Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville (N.B.H.); the Department of Pediatrics, Baylor College of Medicine, Immunization Project, Texas Children's Hospital, Houston (J.A.B., L.C.S.), and the Department of Pediatrics, Division of Critical Care Medicine, University of Texas Southwestern, Children's Medical Center, Dallas (M.M.); the Division of Infectious Diseases, Children's Hospital Los Angeles and Departments of Pediatrics and Molecular Microbiology and Immunology, University of Southern California, Los Angeles (P.S.P.), the Division of Pediatric Hospital Medicine, UC San Diego–Rady Children's Hospital, San Diego (M.A.C.), the Division of Critical Care Medicine, UCSF Benioff Children's Hospital, Oakland (N.Z.C.), and the Department of Pediatrics, Divisions of Critical Care Medicine and Allergy, Immunology, and Bone Marrow Transplant, University of California, San Francisco, San Francisco (M.S.Z.) — all in California; Section of Pediatric Critical Care, Department of Pediatrics, Arkansas Children's Hospital, Little Rock (K.I.); the Division of Pediatric Critical Care Medicine, Nationwide Children's Hospital Columbus (K.E.B.), the Division of Critical Care Medicine, Department of Pediatrics, Akron Children's Hospital, Akron (R.A.N.), and the Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati (M.A.S.) — all in Ohio; the Department of Pediatrics, Section of Critical Care Medicine, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora (A.B.M.); the Department of Pediatrics, University of North Carolina at Chapel Hill Children's Hospital, Chapel Hill (T.C.W., S.P.S.); the Division of Pediatric Critical Care Medicine (E.H.M.) and the Department of Pediatrics (L.S.), Medical University of South Carolina, Charleston; the Division of Pediatric Infectious Diseases, Department of Pediatrics, Children's Mercy Kansas City, Kansas City, MO (J.E.S.); the Departments of Pediatrics and Microbiology, Division of Infectious Diseases, University of Mississippi Medical Center, Jackson (C.V.H.); the Department of Pediatrics, Division of Cardiology, Louisiana State University Health Sciences Center and Children's Hospital of New Orleans, New Orleans (T.T.B.); the Divisions of Pediatric Infectious Diseases and Pediatric Critical Care Medicine, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester (E.R.L.), and the Division of Pediatric Critical Care, University of Minnesota Masonic Children's Hospital, Minneapolis (J.R.H.) — both in Minnesota; the Division of Critical Care Medicine, Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Philadelphia (K.C.); the Ryan White Center for Pediatric Infectious Disease and Global Health, Department of Pediatrics, Indiana University School of Medicine, Indianapolis (S.S.B.); the Division of Pediatric Critical Care Medicine, Children's Hospital of Michigan, Central Michigan University, Detroit (S.M.H.), and the Division of Pediatric Critical Care Medicine, Department of Pediatrics, Mott Children's Hospital and University of Michigan, Ann Arbor (H.R.F.); the Division of Pediatric Critical Care, Department of Pediatrics, Children's Hospital and Medical Center, Omaha, NE (M.L.C.); the Division of Pediatric Critical Care,

Department of Pediatrics, Cooperman Barnabas Medical Center, Livingston, NJ (S.J.G.); the Division of Critical Care Medicine, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago (B.M. Coates); the Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Alabama at Birmingham, Birmingham (M.K.); the Division of Pediatric Infectious Diseases, Department of Pediatrics, UHealth Holtz Children's Hospital, Miami (B.M. Chatani); and the Department of Pediatrics and Banner Children's at Diamond Children's Medical Center, University of Arizona, Tucson (K.V.T.).

REFERENCES

1. Food and Drug Administration. FDA approves first COVID-19 vaccine. August 23, 2021 (https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine).
2. Food and Drug Administration. FDA authorizes Pfizer-BioNTech COVID-19 vaccine for emergency use in children 5 through 11 years of age. October 29, 2021 (https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age).
3. Glatman-Freedman A, Hershkovitz Y, Kaufman Z, Dichtiar R, Keinan-Boker L, Bromberg M. Effectiveness of BNT162b2 vaccine in adolescents during outbreak of SARS-CoV-2 delta variant infection, Israel, 2021. Emerg Infect Dis 2021;27:2919-22.
4. Olson SM, Newhams MM, Halasa NB, et al. Effectiveness of BNT162b2 vaccine against critical Covid-19 in adolescents. N Engl J Med 2022;386:713-23.
5. Olson SM, Newhams MM, Halasa NB, et al. Effectiveness of Pfizer-BioNTech mRNA vaccination against COVID-19 hospitalization among persons aged 12–18 years — United States, June–September 2021. MMWR Morb Mortal Wkly Rep 2021;70:1483-8.
6. Reis BY, Barda N, Leshchinsky M, et al. Effectiveness of BNT162b2 vaccine against delta variant in adolescents. N Engl J Med 2021;385:2101-3.
7. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet 2021;398:1407-16.
8. Klein NP, Stockwell MS, Demarco M, et al. Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA vaccination in preventing COVID-19-associated emergency department and urgent care encounters and hospitalizations among nonimmunocompromised children and adolescents aged 5–17 years — VISION Network, 10 States, April 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:352-8.
9. Collie S, Champion J, Moultrie H, Bekker L-G, Gray G. Effectiveness of BNT162b2 vaccine against omicron variant in South Africa. N Engl J Med 2022;386:494-6.
10. Lauring AS, Tenforde MW, Chappell JD, et al. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ 2022;376:e069761.
11. Thompson MG, Natarajan K, Irving SA, et al. Effectiveness of a third dose of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance — VISION Network, 10 States, August 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:139-45.
12. Nemet I, Kliker L, Lustig Y, et al. Third BNT162b2 vaccination neutralization of SARS-CoV-2 omicron infection. N Engl J Med 2022;386:492-4.
13. Chua H, Feng S, Lewnard JA, et al. The use of test-negative controls to monitor vaccine effectiveness: a systematic review of methodology. Epidemiology 2020;31:43-64.
14. Dean NE, Hogan JW, Schnitzer ME. Covid-19 vaccine effectiveness and the test-negative design. N Engl J Med 2021;385:1431-3.
15. Tenforde MW, Patel MM, Ginde AA, et al. Effectiveness of SARS-CoV-2 mRNA vaccines for preventing Covid-19 hospitalizations in the United States. Clin Infect Dis 2021 August 6 (Epub ahead of print).
16. Treanor JJ. Influenza vaccination. N Engl J Med 2016;375:1261-8.
17. Olson SM, Newhams MM, Halasa NB, et al. Vaccine effectiveness against life-threatening influenza illness in US children. Clin Infect Dis 2022 January 13 (Epub ahead of print).
18. Feng S, Chiu SS, Chan ELY, et al. Effectiveness of influenza vaccination on influenza-associated hospitalisations over time among children in Hong Kong: a test-negative case-control study. Lancet Respir Med 2018;6:925-34.
19. Ferdinands JM, Gaglani M, Martin ET, et al. Waning vaccine effectiveness against influenza-associated hospitalizations among adults, 2015-2016 to 2018-2019, United States hospitalized adult influenza vaccine effectiveness network. Clin Infect Dis 2021;73:726-9.
20. Tenforde MW, Self WH, Naioti EA, et al. Sustained Effectiveness of Pfizer-BioNTech and Moderna vaccines against COVID-19 associated hospitalizations among adults — United States, March–July 2021. MMWR Morb Mortal Wkly Rep 2021;70:1156-62.
21. Office of the Federal Register. Title 45. In: Code of federal regulations: a point in time eCFR system. February 22, 2022 (https://www.ecfr.gov/cgi-bin/text-idx?SID=fc043bd2812f0775fa80066558a6bbcf&mc=true&node=pt45.1.46&rgn=div5#se45.1.46_1102).
22. Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children — initial therapy and outcomes. N Engl J Med 2021;385:23-34.
23. Patel MK, Bergeri I, Bresee JS, et al. Evaluation of post-introduction COVID-19 vaccine effectiveness: summary of interim guidance of the World Health Organization. Vaccine 2021;39:4013-24.
24. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol 1993;138:923-36.
25. Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. N Engl J Med 2022;386:35-46.
26. Garcia-Beltran WF, St Denis KJ, Hoelzemer A, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. Cell 2022;185(3):457.e4-466.e4.
27. Lipsitch M, Krammer F, Regev-Yochay G, Lustig Y, Balicer RD. SARS-CoV-2 breakthrough infections in vaccinated individuals: measurement, causes and impact. Nat Rev Immunol 2022;22:57-65.
28. Patel MM, York IA, Monto AS, Thompson MG, Fry AM. Immune-mediated attenuation of influenza illness after infection: opportunities and challenges. Lancet Microbe 2021;2(12):E715-E725 (https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00180-4/fulltext).
29. Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 2021;371(6529):eabf4063.
30. Goel RR, Painter MM, Apostolidis SA, et al. mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern. Science 2021;374(6572):abm0829.
31. Liu J, Chandrashekar A, Sellers D, et al. Vaccines elicit highly conserved cellular immunity to SARS-CoV-2 Omicron. Nature 2022 January 31 (Epub ahead of print).
32. Tenforde MW, Self WH, Adams K, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA 2021;326:2043-54.