Safety of COVID-19 Vaccination in United States Children Ages 5 to 11 Years

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abstract

BACKGROUND AND OBJECTIVES: Limited postauthorization safety data for the Pfizer-BioNTech coronavirus disease 2019 vaccination among children ages 5 to 11 years are available, particularly for the adverse event myocarditis, which has been detected in adolescents and young adults. We describe adverse events observed during the first 4 months of the United States coronavirus disease 2019 vaccination program in this age group.

METHODS: We analyzed data from 3 United States safety monitoring systems: v-safe, a voluntary smartphone-based system that monitors reactions and health effects; the Vaccine Adverse Events Reporting System (VAERS), the national spontaneous reporting system comanaged by the Centers for Disease Control and Prevention and Food and Drug Administration; and the Vaccine Safety Datalink, an active surveillance system that monitors electronic health records for prespecified events, including myocarditis.

RESULTS: Among 48 795 children ages 5 to 11 years enrolled in v-safe, most reported reactions were mild-to-moderate, most frequently reported the day after vaccination, and were more common after dose 2. VAERS received 7578 adverse event reports; 97% were nonserious. On review of 194 serious VAERS reports, 15 myocarditis cases were verified; 8 occurred in boys after dose 2 (reporting rate 2.2 per million doses). In the Vaccine Safety Datalink, no safety signals were detected in weekly sequential monitoring after administration of 726 820 doses.

CONCLUSIONS: Safety findings for Pfizer-BioNTech vaccine from 3 United States monitoring systems in children ages 5 to 11 years show that most reported adverse events were mild and no safety signals were observed in active surveillance. VAERS reporting rates of myocarditis after dose 2 in this age group were substantially lower than those observed among adolescents ages 12 to 15 years.

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Drs Hause and Shay conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Klein conceptualized and designed the Vaccine Safety Datalink (VSD) study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content; Dr Abara conducted the review of medical

WHAT'S KNOWN ON THIS SUBJECT: Safety findings for the Pfizer-BioNTech coronavirus disease 2019 vaccination among children ages 5 to 11 years from preauthorization trials of ~3000 children and in early surveillance from United States postauthorization safety monitoring during the first 6 weeks of vaccination in this age group were reassuring.

WHAT THIS STUDY ADDS: Analyses from 3 United States safety monitoring systems during 4 months of the Pfizer-BioNTech vaccine administration confirmed findings from preauthorization trials and early postauthorization surveillance and provided insight on rare adverse events; rates of postvaccination myocarditis were substantially lower than in older children.

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On October 29, 2021, the Food and Drug Administration (FDA) amended the Emergency Use Authorization (EUA) for Pfizer-BioNTech (BNT-162b2) messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccine to include children ages 5 to 11 years, administered as 2 doses, 21 days apart. In preauthorization trials of children ages 5 to 11 years, most reactions were mild-to-moderate and no serious adverse events related to vaccination were reported.[1]

Early postauthorization safety findings from v-safe, a voluntary smartphone-based surveillance system, and the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system, obtained during the first 6 weeks of BNT-162b2 vaccination among children ages 5 to 11 years were similar to those from preauthorization trials.[2] During these weeks, 8.7 million vaccine doses were administered, 42 504 children enrolled in v-safe, and 4249 VAERS reports were submitted. Initial safety findings, while generally reassuring, reflected data for a brief period and included few data after dose 2.

As of February 27, 2022, >16 million BNT-162b2 vaccine doses had been administered to children ages 5 to 11 years.[3] We analyzed postauthorization safety surveillance data from v-safe and VAERS,[2] to include substantial data on dose 2, and included findings from an additional system, the Vaccine Safety Datalink (VSD), which uses electronic health records to sequentially monitor for safety signals among prespecified adverse events.

METHODS

Design, Setting, and Participants

Centers for Disease Control (CDC) established v-safe (https://vsafe.cdc.gov) to monitor health effects after COVID-19 vaccination. Parents and guardians can enroll children in v-safe after any dose. Health surveys are sent to parents or guardians via text messages that link to web-based surveys on days 0 to 7 after vaccination; then weekly through 6 weeks after vaccination; and then 3, 6, and 12 months after vaccination. Health surveys sent in the first week include questions about injection site and systemic reactions and health impacts; injection site and systemic reactions can be further described by severity as mild, moderate, or severe (Supplemental Information). CDC's v-safe call center contacts a parent or guardian when a report indicates that a child received medical care after vaccination and encourages completion of a VAERS report, if indicated.

VAERS is a United States spontaneous reporting system comanaged by CDC and FDA that accepts reports of adverse events after vaccination from any source, including health care providers, vaccine manufacturers, and members of the public.[4] Under COVID-19 vaccine EUAs, vaccination providers are required to report adverse events, including hospitalizations and deaths temporally associated with vaccination.[5] Symptoms, signs, and diagnostic findings in VAERS reports are assigned Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.[6] More than 1 MedDRA preferred term may be assigned to a report; these terms do not necessarily correspond to medically verified diagnoses. VAERS reports are classified as serious using the US federal regulatory definition: if hospitalization, prolongation of hospitalization, life-threatening illness, permanent disability, congenital anomaly or birth defect, or death are reported.[7] VAERS staff follow-up on serious reports to obtain additional information, including medical records. Death certificates and autopsy reports are obtained for reports of death, if available. CDC and FDA physicians assessed all serious reports, including reports of death, to form a clinical impression based on available information; each report was only assigned 1 impression on the basis of consensus opinion.

Reports to VAERS of multisystem inflammatory syndrome in children (MIS-C) after receipt of BNT-162b2 vaccine were adjudicated using methods similar to those previously described, which included input from CDC's Clinical Immunization Safety Assessment Project (Supplemental Information).[8] The Brighton Collaboration case definitions for anaphylaxis and seizure were used to identify and classify reports coded for these conditions (Supplemental Information).[9,10] Reports to VAERS of myocarditis after receipt of BNT-162b2 vaccine were identified by searching for selected MedDRA preferred terms (Supplemental Information), as well as reported symptom text indicating "myocarditis" or "increased/abnormal troponins." CDC attempted to collect records and confirm information from health care providers to determine if the CDC myocarditis case definition (Supplemental Information) was met.[8]

CDC's VSD uses rapid cycle analysis (RCA) to conduct near real-time sequential monitoring for prespecified adverse events.[11] RCA monitoring of COVID-19 vaccines began in December 2020, and when the BNT-162b2 EUA was extended to include children ages 5 to 11 years, monitoring began in this age group. The participating VSD sites included: Denver Health, HealthPartners, Kaiser Permanente (Colorado, Northern California,

Northwest, Southern California, and Washington) and Marshfield Clinic. A description of COVID-19 vaccine surveillance has been published.[12] In addition to the outcomes being tested sequentially, we monitored for records of acute respiratory distress syndrome, anaphylaxis, MIS-C, and narcolepsy, conditions for which comparator groups were not available. We reviewed medical records and adjudicated cases of anaphylaxis, MIS-C, and myocarditis (Supplemental Information) to verify diagnosis and assess timing of symptom onset.

It is possible for persons to be included in >1 safety monitoring system; for example, an adverse event identified in VSD may also be reported to VAERS. We are not able to identify or remove possible duplications because of deidentification procedures used by the systems. However, the 3 monitoring systems include surveillance for different outcomes and multiple reports of adverse outcomes in a single individual would not affect the interpretation of findings from any of the systems.

Data Analysis

Data collected from v-safe and VAERS from November 3, 2021 to February 27, 2022 and from VSD from October 31, 2021 to February 26, 2022, among children ages 5 to 11 years who received BNT-162b2 COVID-19 vaccine were analyzed.

We described reactions and health impacts reported in v-safe health surveys for children who had at least 1 health check-in survey on days 0 to 7 by frequency and reaction severity.

We described nonserious and serious reports to VAERS by MedDRA preferred terms and clinical impressions, respectively. Reporting rates for myocarditis were calculated for VAERS reports that met the CDC case definition for myocarditis (Supplemental Information), by using doses administered as the denominator, and stratified by sex and dose number.[3]

We compared outcome rates in VSD data during a risk interval 1 to 21 days after vaccination to rates on the same calendar days among persons who were then in a comparison interval 22 to 42 days after vaccination.[12] Vaccinees contributed person-time to each analysis in a 21 day risk interval after dose 1 or 2; they later contributed person-time as comparators in an interval 22 to 42 days after the most recent dose. We used Poisson regression to estimate rate ratio and 95% confidence interval (CI) adjusted for age, sex, calendar day, site, and race and ethnicity groups. We conducted weekly 1-sided sequential tests of the null hypothesis that vaccination did not affect risk during a 1- to 21-day risk interval, using a 1-sided $P <$ .0061 to account for 1 year of planned weekly analyses. Because of a lack of appropriate comparators, we conducted descriptive analyses only for anaphylaxis and MIS-C. SAS software (version 9.4; SAS Institute) was used to conduct all analyses; Lucidchart was used to create the flowchart.

These surveillance activities were reviewed by CDC and conducted consistent with applicable federal law and CDC policy (45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.); VSD RCA surveillance was approved by the institutional review boards of each participating site with a waiver of informed consent.

RESULTS

v-safe

There were 48 795 children ages 5 to 11 years who received BNT-162b2 vaccination enrolled in v-safe after dose 1 from November 3, 2021 to February 27, 2022; the median age was 8 years, 24 243 (49.7%) were girls (Table 1), and information for dose 2 was available for 39 416. Most registrants reported BNT-162b2 vaccine was administered alone, without other vaccinations (96.4% and 99.3% for dose 1 and 2, respectively). Seasonal

TABLE 1 Selected Demographic Characteristics for Children Ages 5 to 11 y Who Completed at Least 1 v-safe Health Check-in Survey on Days 0 to 7 After Receiving Dose 1 BNT-162b2 COVID-19 Vaccine (N = 48 795) in the United States From November 3 to February 27, 2022

Characteristic	Total (%)
Sex	
Female	24 243 (49.7)
Male	24 392 (50.0)
Unknown	160 (0.3)
Age range, y (median)	5–11 (8)
Ethnicity	
Hispanic	7082 (14.5)
Not Hispanic	40 116 (82.2)
Unknown	1597 (3.3)
Race	
American Indian	275 (0.6)
Asian	3554 (7.3)
Black	2765 (5.7)
Native Hawaiian or Other Pacific Islander	145 (0.3)
White	35 169 (72.1)
Multiracial	3930 (8.1)
Other	1567 (3.2)
Unknown	1390 (2.8)

influenza vaccine was the most frequently simultaneously administered (Supplemental Table 10).

Injection site reactions (Table 2) were more frequently reported in the week after dose 2 (22 396; 56.8%) than dose 1 (26 778; 54.9%); likewise, systemic reactions were more frequently reported in the week after dose 2 (16 161; 41.0%) than dose 1 (17 214; 35.3%). For both doses, reactions were most frequently reported the day after vaccination. Injection site pain, fatigue, headache, fever, and myalgia were among the most frequently reported reactions and were mostly mild to moderate in severity (Table 3).

Health impacts, including inability to perform normal daily activities, inability to attend school, and receipt of medical care, were more frequently reported in the week after dose 2 than dose 1. Health impacts were most frequently reported the day after vaccination. ~7.6% of parents reported that their child was unable to perform normal daily activities on the day after receipt of dose 2, 9.0% reported their child was unable to attend school, and 0.3% reported their child received medical care. In the weeks after dose 1 and dose 2, a visit to an outpatient clinic visit was the most common type of care sought (328; 0.7% and 235; 0.6%, respectively). Hospitalization in the week after vaccination was reported for 10 (0.02%) and 6 (0.02%) children after dose 1 and 2, respectively. Staff members from v-safe's call center attempted to contact the parents or guardians of all hospitalized children; 5 said the report was made in error or hospitalization was unrelated to vaccination. Information regarding reason for hospitalization was available for 8 children and included appendicitis (2), respiratory infection (2), vomiting and dehydration (1), acute febrile illness (1), MIS-C (1) and retropharyngeal cellulitis (1).

VAERS

From November 3, 2021 to February 27, 2022, VAERS received and processed 7578 reports of adverse events for children ages 5 to 11 years who received BNT-162b2 vaccine; the median age was 8 years, and 3558 (47.0%) reports were for girls (Table 4). Most reports indicated BNT-162b2 vaccine was administered alone (7403; 97.7%); seasonal influenza vaccine was the most frequently simultaneously

TABLE 2 Reactions Reported for Children Ages 5 to 11 y ($N = 48\,795$) Who Completed at Least 1 v-safe Health Check-in Survey on Days 0 to 7 After Receiving Pfizer BioNTech COVID-19 Vaccine in the United States From November 3 to February 27, 2022

	% of v-safe Enrollees Reporting Reaction or Health Impact																	
	Dose 1 (48 795)									Dose 2 (39 416)								
Event	Days 0–7[a]	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 0–7[a]	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Any injection site reaction	54.9	43.2	58.1	27.0	10.9	5.3	3.2	2.0	1.5	56.8	43.4	62.7	33.4	13.8	5.9	3.2	2.1	1.7
Itching	3.9	1.4	2.0	1.7	1.2	0.9	0.7	0.5	0.4	3.8	1.2	1.7	1.7	1.4	1.0	0.7	0.4	0.4
Injection site pain	52.7	41.8	56.4	24.9	9.2	4.1	2.2	1.4	1.0	55.0	42.4	61.4	31.4	11.9	4.4	2.2	1.4	1.2
Redness	4.0	1.7	2.7	2.0	1.1	0.8	0.4	0.2	0.2	4.7	1.7	3.2	2.8	1.7	1.0	0.6	0.4	0.3
Swelling	4.2	1.8	3.8	2.0	0.9	0.5	0.4	0.2	0.1	5.2	1.8	4.3	3.2	1.6	0.9	0.5	0.2	0.2
Any systemic reaction	35.3	14.2	26.2	17.2	11.5	8.9	7.5	6.6	6.5	41.0	11.5	40.4	21.9	11.8	7.9	6.2	5.2	5.3
Abdominal pain	5.2	1.1	2.6	1.9	1.6	1.1	1.0	0.9	0.9	6.6	0.8	5.1	2.5	1.4	1.0	0.9	0.7	0.8
Myalgia	7.7	2.5	5.6	3.3	1.8	1.3	1.0	0.8	0.8	10.6	1.8	10.8	4.7	2.0	1.1	0.7	0.7	0.6
Chills	4.2	1.1	2.6	1.6	1.1	0.7	0.7	0.5	0.4	6.9	1.0	7.6	2.2	0.9	0.4	0.4	0.3	0.4
Diarrhea	2.7	0.3	1.1	1.0	0.8	0.6	0.6	0.5	0.5	2.4	0.2	1.0	1.0	0.7	0.6	0.5	0.3	0.3
Fatigue	20.4	7.8	15.4	9.1	5.8	4.2	3.4	2.9	2.7	25.7	6.6	26.1	11.9	5.7	3.6	2.8	2.3	2.3
Fever	8.5	1.8	5.3	3.6	2.3	1.7	1.5	1.4	1.3	13.9	1.9	14.8	5.0	1.9	1.2	0.9	0.8	1.0
Headache	14.4	4.3	9.4	6.2	4.1	3.1	2.7	2.3	2.2	19.7	3.5	19.0	9.2	4.4	2.8	2.2	1.9	1.8
Joint pain	2.4	0.5	1.5	0.9	0.6	0.4	0.4	0.3	0.3	3.1	0.4	2.7	1.4	0.6	0.3	0.3	0.3	0.3
Nausea	5.1	1.2	2.7	2.1	1.4	1.0	0.8	0.8	0.7	7.0	1.1	6.1	2.5	1.4	0.8	0.7	0.6	0.6
Rash	1.3	0.2	0.4	0.5	0.5	0.5	0.4	0.4	0.4	1.1	0.2	0.3	0.4	0.3	0.3	0.3	0.3	0.3
Vomiting	2.5	0.4	1.1	0.8	0.6	0.4	0.5	0.4	0.4	2.9	0.3	2.0	0.9	0.5	0.4	0.3	0.3	0.3
Any health impact	11.4	2.0	6.1	4.5	3.5	2.9	2.7	2.5	2.3	15.4	1.8	13.9	6.1	2.9	2.1	1.9	1.8	1.9
Unable to perform normal daily activities	5.4	1.2	3.1	2.1	1.4	1.0	0.9	0.9	0.9	7.8	1.1	7.6	2.8	1.1	0.8	0.6	0.6	0.6
Unable to attend school	8.2	0.9	4.0	3.1	2.5	2.2	2.1	1.9	1.6	10.9	0.9	9.0	4.2	2.1	1.6	1.5	1.4	1.4
Needed medical care	1.2	0.1	0.2	0.3	0.4	0.3	0.4	0.3	0.3	1.2	0.1	0.3	0.3	0.3	0.3	0.3	0.3	0.2
Telehealth	0.3	0.01	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.3	0.02	0.1	0.1	0.1	0.1	0.1	0.05	0.05
Clinic	0.7	0.1	0.1	0.1	0.2	0.2	0.3	0.2	0.2	0.6	0.04	0.1	0.1	0.2	0.1	0.2	0.2	0.1
Emergency visit	0.1	0.004	0.02	0.03	0.1	0.03	0.03	0.03	0.02	0.1	0	0.03	0.03	0.02	0.02	0.02	0.04	0.03
Hospitalization	0.02	0	0.003	0.01	0.003	0.003	0.02	0.01	0.01	0.02	0	0	0.004	0	0.004	0	0.01	0.01

[a] Percentage of enrollees who reported a reaction or health impact at least once during days 0 to 7 postvaccination.

TABLE 3 Most Frequently Reported Solicited Reactions Reported for Children Ages 5 to 11 y Who Completed at Least 1 v-safe Health Check-in Survey on days 0 to 7 After Receiving BNT-162b2 COVID-19 ($N = 48\,795$) in the United States From November 3 to February 27, 2022

	% of v-Safe Enrollees Reporting Reaction[a]							
	Dose 1 (48 795)				Dose 2 (39 416)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Injection site pain	42.0	10.2	0.5	52.7	40.9	13.4	0.7	55.0
Fatigue	12.1	7.3	1.0	20.4	13.7	10.5	1.5	25.7
Headache	8.9	4.8	0.7	14.4	11.2	7.5	1.0	19.7
Myalgia	4.4	2.9	0.4	7.7	5.6	4.5	0.4	10.6
Chills	2.4	1.5	0.2	4.2	3.8	2.8	0.4	6.9
Fever[b]	1.5	0.9	0.8	3.2	2.5	1.6	0.9	5.1

[a] Percentage of enrollees who reported a reaction or health impact at least once during days 0 to 7 postvaccination. Parents and guardians who participate in v-safe use the following definitions to describe the severity of a child's symptoms: mild (noticeable, but not problematic), moderate (limit normal daily activities), or severe (make daily activities difficult or impossible).

[b] The number of registrants who reported having a fever may differ from the total who entered information about temperature. Severity of fever was defined as: mild (38.0 to 38.4°C), moderate (38.5 to 38.9°C), and severe (≥40.0°C). Registrants were not required to enter temperature.

administered vaccine (148; 2.0%) (Supplemental Table 11).

Most VAERS reports were classified as nonserious (7379; 97.4%) (Table 5). Among the most commonly reported nonserious events were those related to an administration error, including product preparation issue (1434; 19.4%), incorrect dose administered (1361; 18.4%), product storage error (417; 5.7%), underdose (388; 5.3%), and expired product administered (246; 3.3%). Each report could include several terms related to an administration error; for example, the terms "incorrect dose administered" and "underdose" could both appear in a report. Terms related to an administration error were often accompanied by a term specifying "no adverse event" (1651; 22.4%). Other frequently reported nonserious events included those related to syncope (371; 5.0%), including dizziness (387; 5.2%), systemic reactions known to be associated with the vaccine (fever [541; 7.3%], vomiting [541; 7.3%], headache [465; 6.3%], nausea [330; 4.5%]), urticaria [312; 4.2%], and rash [311; 4.2%]).

TABLE 4 Adverse Event Reports Among Children Ages 5–11 y Who Received BNT-162b2 COVID-19 Vaccine, by Selected Demographic Characteristics ($N = 7578$) – Vaccine Adverse Event Reporting System (VAERS), United States, November 3 to February 27, 2022

Characteristic	Total (%)
Sex	
Female	3558 (47.0)
Male	3547 (46.8)
Unknown	473 (6.2)
Age range, yrs (median)	5–11 (8)
Ethnicity	
Hispanic[a]	1067 (14.1)
Not Hispanic	3016 (39.8)
Unknown	3495 (46.1)
Race	
American Indian	66 (0.9)
Asian	328 (4.3)
Black	419 (5.5)
Native Hawaiian or Other Pacific Islander	20 (0.3)
White	2984 (39.4)
Multiracial	163 (2.2)
Other	747 (9.9)
Unknown	2846 (37.6)

[a] Includes persons reported as of Hispanic ethnicity, but of unreported or unknown race.

Among the 194 serious reports to VAERS, the most common clinical impressions included MIS-C (26; 13.4%), seizure (21; 10.8%), myocarditis (19; 9.7%), appendicitis (13; 6.7%), and allergic reaction (8; 4.1%). Of the 26 reports identified as possible MIS-C, 23 have been reviewed and adjudicated; 3 were under review. Of the 23 adjudicated, 21 met the CDC MIS-C case definition (Fig 1), 19 had laboratory evidence of past or recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Supplemental Information). All were discharged from the hospital. There were 126 reports of seizure with symptom onset on days 0 to 21 after vaccination, of which 21 were serious. Of these 21, 15 met the Brighton Collaboration case definition; 10 confirmed seizure cases were new-onset seizures, including 2 patients with potential evolving seizure disorders who had evidence of seizures before vaccination. There were 7 preliminary reports of anaphylaxis with symptom onset during days 0 to 7 after vaccination (Table 6); 2 were serious. Of these 7 reports, 2 met the Brighton Collaboration case

TABLE 5 Reports of Nonserious and Serious Events to Vaccine Adverse Event Reporting System (VAERS) for Children Ages 5 to 11 y After Receipt of BNT-162b2 COVID-19 Vaccine ($N = 7578$) in the United States From November 3 to February 27, 2022

Reported Events	Number (%) Reporting
Nonserious VAERS reports	7379 (100)
Symptom, sign, diagnostic result, or condition (MedDRA PT[a])	
No adverse event[b]	1651 (22.4)
Product preparation issue	1434 (19.4)
Incorrect dose administered	1361 (18.4)
Pyrexia	541 (7.3)
Vomiting	541 (7.3)
Headache	465 (6.3)
Product storage error	417 (5.7)
Underdose	388 (5.3)
Dizziness	387 (5.2)
Syncope	371 (5.0)
Fatigue	336 (4.6)
Nausea	330 (4.5)
Urticaria	312 (4.2)
Rash	311 (4.2)
Expired product administered	246 (3.3)
Serious VAERS reports[c,d,e]	194 (100)[f]
Clinical impression	
Multisystem inflammatory syndrome in children (MIS-C)	26 (13.4)
Seizure[g]	21 (10.8)
Myocarditis[h]	19 (9.8)
Appendicitis	13 (6.7)
Allergic reaction	8 (4.1)
COVID-19	7 (3.6)
Abdominal pain	6 (3.1)
Diabetes mellitus type 1	5 (2.6)
Death	4 (2.1)
Immune thrombocytopenic purpura	4 (2.1)
Asthma	3 (1.5)
Ataxia	3 (1.5)
Kawasaki disease	3 (1.5)
Kawasaki disease, incomplete	3 (1.5)
Migraine	3 (1.5)
Altered mental status	2 (1.0)
Anaphylaxis[i]	2 (1.0)
Chest pain	2 (1.0)
Gastrointestinal infection	2 (1.0)
Nephrotic syndrome	2 (1.0)
Panic attack	2 (1.0)
Pneumonia	2 (1.0)
Reactive arthritis	2 (1.0)
Tachycardia	2 (1.0)

[a] Signs and symptoms in VAERS reports are assigned MedDRA preferred terms (PTs) by VAERS staff members. Each VAERS report might be assigned more than one MedDRA PT, which can include normal diagnostic findings. A MedDRA PT does not indicate a medically confirmed diagnosis.

[b] Reports of no adverse event were often accompanied by product preparation issue, incorrect dose administered, product storage error, underdose, or expired product administered.

[c] VAERS reports are classified as serious if any of the following are reported: hospitalization, prolongation of hospitalization, life-threatening illness, permanent disability, congenital anomaly or birth defect, or death.

[d] Serious reports to VAERS were reviewed by CDC and FDA physicians to form a clinical impression; each report was only assigned 1 impression. The clinical impression of the event does not establish a causal role with vaccination. Reports of myocarditis were identified using a combination of MedDRA PTs; in some cases, reports of myocarditis (identified by fulfilling criteria of the CDC working case definition of myocarditis) did not have the MedDRA PT "myocarditis" assigned to them. https://www.meddra.org/how-to-use/basics/hierarchy

[e] Cells with fewer than 2 reports were suppressed. The clinical impressions of these reports included: Allergic angioedema, anxiety disorder, arrythmia (ventricular), arthritis (aseptic), arterial-venous malformation, autoimmune hemolytic anemia, Bell's palsy, bursitis, cardiopulmonary arrest, dehydration, dizziness, encephalitis or meningitis, encephalomyelitis, erythema multiforme, existing heart disease, facial paralysis, febrile illness, gastrointestinal bleeding, Guillain-Barre Syndrome, head trauma, headache, hearing loss, heart failure (congenital heart disease), hemolytic anemia, Henoch Schoenlein purpura, Herpes zoster, hypotension, insect bite, lethargy, loss of taste, lower extremity weakness, lymphadenopathy (cervical), mesenteric adenitis, mood disorder, myalgia, myoclonus, myositis, obsessive compulsive disorder, pancreatitis, pericarditis, radial neuropathy, rash, syncope, systemic lupus erythematosus, tachypnea, vomiting, and vomiting and diarrhea.

[f] Five reports that were duplications were removed from this list.

[g] There were 126 preliminary reports of seizure; 21 were considered serious, including 2 reports of febrile seizure, and 2 reports of potentially evolving seizure disorder.

[h] There were 45 preliminary reports of myocarditis during the 0 to 21 d after vaccination. On review, 23 were considered reports of myocarditis; 19 were considered serious. Three reports of myocarditis indicated the patient had COVID-19.

[i] There were 7 preliminary reports of anaphylaxis; 2 were considered serious.

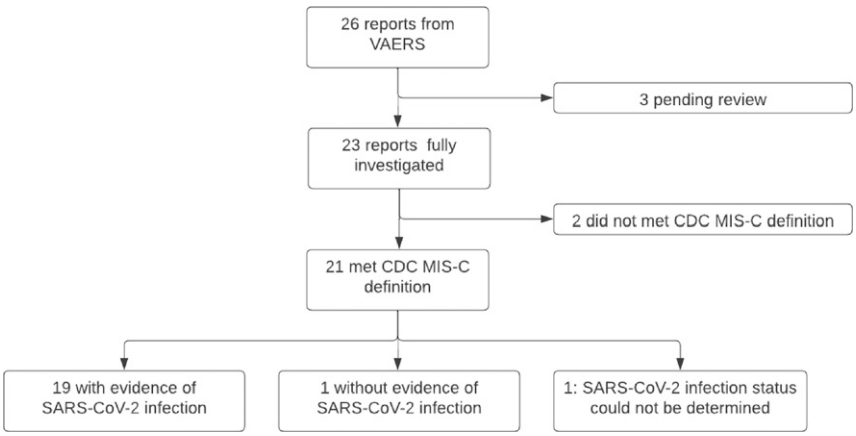

FIGURE 1
Investigation of reports of multisystem inflammatory syndrome in children (MIS-C) among children ages 5 to 11 years in the United States from November 3 to February 27, 2022. For this investigation, only SARS-CoV-2 serology results from serum obtained before IVIG administration were used to meet the serology component of the CDC MIS-C definition.

definition, 1 did not meet the case definition, 1 remains under review, and 3 lacked enough information to confirm anaphylaxis. Assuming the unconfirmed reports met the Brighton Collaboration case definition, the estimated reporting rate of anaphylaxis would be 0.30 cases per million doses administered.

Forty-five preliminary reports of myocarditis with symptom onset during days 0 to 21 after vaccination were identified. On review, 23 were classified as reports of myocarditis; 19 met the regulatory definition of serious (Table 5), of which 17 (37.8%) were verified by health care provider interview or medical record review to meet the CDC case definition for myocarditis. Among the 17 verified cases, 12 were male, and 15 were hospitalized. As of April 22, 2022, 13 had recovered symptomatically and 2 were recovering. When using the generally accepted risk interval of 0 to 7 days postvaccination, the reporting rate for verified vaccine-associated myocarditis after BNT-162b2 was greater among boys than girls and greater after dose 2 (Table 7). Among boys, the reporting rate of verified myocarditis during days 0 to 7 after dose 2 was 2.2 per 1 million doses administered.

TABLE 6 Frequency and Reporting Rates of Selected Adverse Events of Special Interest Reported Within 0 to 21 d After Vaccination to Vaccine Adverse Event Reporting System (VAERS) for Children Ages 5 to 11 y Who Received BNT-162b2 COVID-19 vaccine in the United States From November 3 to February 27, 2022

Reports of Adverse Events of Special Interest[a]	*n*	Reports per Million Doses Administered
Acute disseminated encephalomyelitis	1	0.1
Acute respiratory distress syndrome	1	0.1
Anaphylaxis (0–7 d interval)	7	0.4
Anaphylaxis (0–1 d interval)	6	0.4
Appendicitis	15	0.9
Bell's palsy	16	1.0
Cerebral venous sinus thrombosis	0	0
Disseminated intravascular coagulation	0	0
Encephalitis, myelitis, or encephalomyelitis	1	0.1
Guillain-Barré syndrome (0–42 d interval)	1	0.1
Immune thrombocytopenia	2	0.1
Kawasaki disease	5	0.3
Myocarditis	45	2.7
Myocarditis (0–7 d)	39	2.4
Narcolepsy or cataplexy	0	0
Pulmonary embolism	0	0
Seizure	126	7.6
Stroke, hemorrhagic	0	0
Stroke, ischemic	0	0
Thrombosis with thrombocytopenia syndrome	0	0
Thrombotic thrombocytopenic purpura	0	0
Transverse myelitis	0	0
Venous thromboembolism	2	0.1

[a] These represent reports, not verified by case definition. The risk window is 0 to 21 d after vaccination unless otherwise indicated.

VAERS received 4 reports of death after vaccination during the analytic period. Two occurred in girls, ages 5 and 6 years, who had complex medical histories, including autonomic instability and frequent admissions to pediatric intensive care; autopsy was not performed for either decedent. One death occurred in a girl aged 7 years; on autopsy, evidence of influenza infection was documented. One death occurred in an 8-year-old boy, 8 days after dose 2. He experienced nausea and vomiting the night before his death; an autopsy was performed and results are pending. The available information for these reports did not support a causal association between vaccination and death for any of the decedents.

VSD

From October 31, 2021 to February 26, 2022, 726 820 doses of BNT-162b2 vaccine (384 905 dose 1 341 915 dose 2) were administered in a cohort of 889 263 children ages 5 to 11 years enrolled

TABLE 7 Reporting Rates (per 1 Million Doses Administered) of Verified Reports to the Vaccine Adverse Event Reporting System (VAERS) of Myocarditis[a] Among Children Ages 5 to 11 y During Days 0 to 7 After BNT-162b2 Vaccination in the United States From November 3 to February 27, 2022

	Dose 1			Dose 2		
	Cases[b]	Doses Administered	Rate per 1 Million Doses	Cases[b]	Doses Administered	Rate per 1 Million Doses
Boys	<5	4 674 922	<1	8	3 677 341	2.2
Girls	<5	4 560 861	<1	<5	3 589 292	<1

[a] VAERS reports of myocarditis were identified using a combination of MedDRA preferred terms, with symptom onset during day of vaccination through day 6 after vaccination and verified to meet case definition by clinician interview with a care provider, or clinician review of the medical record.
[b] Cells with fewer than five persons were suppressed and indicated as "<5" for confidentiality. For 1 case, sex was not reported.

in the participating sites. Forty-three percent of children in this age group received at least 1 vaccine dose; 38% received 2 doses. For dose 1, the median age was 8 years and 49.3% were girls (Table 8). Inactivated influenza vaccines were the type most commonly administered together with BNT-162b2 vaccine (5.6%) (Supplemental Table 12). The number of cases of prespecified outcomes during the 21-day risk interval ranged from 0 for 13 of 19 outcomes (eg, Kawasaki disease) to 40 for appendicitis (1 per 1000 person-years) (Table 9). None of the analyses comparing outcomes in the risk versus comparison intervals approached the criterion for a statistical signal (1-sided $P < .0061$).

Seven potential cases of myocarditis were identified among children ages 5 to 11 years during days 1 to 21 after vaccination. After medical record review and adjudication, 4 of the 7 cases were confirmed as myocarditis; 2 occurred during the 7 days after dose 2 vaccination. Three cases that were not confirmed had a history of myocarditis, congenital heart defect, or chest pain without laboratory findings consistent with myocarditis. Three cases of anaphylaxis were identified in electronic health records during days 0 to 1 after vaccination after dose 1. After medical record review and adjudication, 2 met the Brighton Collaboration case definition and 1 did not (5.2 [95% CI, 0.6–18.7] cases per million dose 1 vaccinations and 2.78 [95% CI, 0.3–9.9] per million total doses). Five potential cases of MIS-C were identified and 4 were confirmed after medical record review and adjudication. All confirmed cases had both documented COVID-19 infection and COVID-19 vaccination before a diagnosis of MIS-C.

TABLE 8 Selected Demographic Characteristics for Children Ages 5–11 y in the Vaccine Safety Datalink Who Received Dose 1 BNT-162b2 COVID-19 Vaccine ($N = 384\,905$) in the United States From October 31, 2021 to February 26, 2022

Characteristic	Total (%)
Sex	
Female	189 634 (49.3)
Male	195 271 (50.7)
Age range, yrs (median)	5–11 (8)
Ethnicity	
Hispanic	101 685 (26.4)
Not Hispanic	236 683 (61.5)
Unknown	46 537 (12.1)
Race	
American Indian	1055 (0.3)
Asian	78 841 (20.5)
Black	19 121 (5.0)
Native Hawaiian or Other Pacific Islander	2728 (0.7)
White	116 957 (30.4)
Multiracial	17 981 (4.7)
Unknown	46 537 (12.1)

DISCUSSION

We describe safety findings from 3 surveillance systems, v-safe, VAERS, and VSD, during a period when approximately 16 million doses of BNT-162b2 vaccine were administered to United States children ages 5 to 11 years.[3] Known and expected systemic reactions were less frequently reported for children ages 5 to 11 years (35.3% in the week after dose 1 and 41.0% in the week after dose 2) than for older children (48.9% in the week after dose 1 and 63.4% in the week after dose 2).[1,2,13] It is possible that systemic reactions are less frequently reported for younger children because they receive a smaller amount of mRNA (10 μg) than persons aged ≥12 years (30 μg).[1] Administration errors were among the most frequently reported events to VAERS, perhaps because of confusion about the recommended dosage for this age group. Importantly, most reports classified as administration errors did not include any mention of an adverse health event.

Similar to systemic reactions, health impacts were more frequently reported to v-safe in the week after dose 2 than dose 1. In the week after dose 2, inability to complete daily activities was less frequently reported for children ages 5 to 11

TABLE 9 Events Among Children Ages 5 to 11 y in a 21-d Risk Interval After BNT-162b2 Vaccination Compared to Events on the Same Calendar Day Among Children Ages 5 to 11 y in a 22–42-d Interval After Their Most Recent Vaccination, Vaccine Safety Datalink, Oct 31, 2021 to Feb 26, 2022

Outcome	Events in Risk Interval (Events per Million Person-Years)	Events in Comparison Interval (Events per Million Person-Years)	Adjusted Rate Ratio (95% Confidence Interval)	*P*		Signal, 1-sided $P < .0061$
				2-sided	1-sided	
Acute disseminated encephalomyelitis	0 (0)	0 (0)	N/A	N/A	N/A	No
Acute myocardial infarction	0 (0)	0 (0)	N/A	N/A	N/A	No
Appendicitis	40 (995.2)	21 (1044.9)	0.94 (0.51–1.76)	.844	.639	No
Bell's palsy	3 (74.6)	1 (49.8)	2.55 (0.27–67.7)	.464	.378	No
Cerebral venous sinus thrombosis	0 (0)	0 (0)	N/A	N/A	N/A	No
Disseminated intravascular coagulation	0 (0)	0 (0)	N/A	N/A	N/A	No
Encephalitis, myelitis, or encephalomyelitis	0 (0)	0 (0)	N/A	N/A	N/A	No
Guillain-Barré syndrome	0 (0)	0 (0)	N/A	N/A	N/A	No
Immune thrombocytopenia	1 (24.9)	1 (49.8)	0.65 (0.02–27.0)	0.796	.849	No
Kawasaki disease	0 (0)	0 (0)	N/A	N/A	N/A	No
Myocarditis or pericarditis[b]	4 (99.5)	1 (49.8)	0.5 (0.05–15.6)	.595	.903	No
Pulmonary embolism[a]	0 (0)	0 (0)	N/A	N/A	N/A	No
Seizure	13 (323.5)	8 (398.0)	0.93 (0.35–2.55)	.874	.659	No
Stroke, hemorrhagic	0 (0)	0 (0)	N/A	N/A	N/A	No
Stroke, ischemic	1 (24.9)	0 (0)	Not calculable	.926	0.926	No
Thrombosis with thrombocytopenia syndrome	0 (0)	1 (49.8)	0 (0–2.15)	.874	.659	No
Thrombotic thrombocytopenic purpura	0 (0)	0 (0)	N/A	N/A	N/A	No
Transverse myelitis	0 (0)	0 (0)	N/A	N/A	N/A	No
Venous thromboembolism[a]	0 (0)	0 (0)	N/A	N/A	N/A	No

Table includes all identified cases and analyses were not limited to chart-confirmed cases. There were 40 192 person-years of follow-up in the risk interval and 20098.1 person-years in the comparison interval. Overall estimate from Poisson regression models stratified by site, age in years, sex, race and ethnicity, and calendar date. One-sided $P < .0061$ required for a signal alert. This threshold keeps the probability of a false-positive signal (ie, a signal due to chance alone) below 0.05 for a 1-y period of weekly surveillance. N/A, not applicable.

[a] Incident outcome definition was first event recorded.

[b] Incident outcome definition was first event in 60 d.

years (7.8%) than for adolescents ages 12 to 15 years (23.1%).[13] Inability to attend school and receipt of medical care in the week after dose 2 were more frequently reported for children ages 5 to 11 years (10.9% and 1.2%, respectively) than for adolescents ages 12 to 15 years (6.1% and 0.8%).[13] Hospitalization in the week after vaccination was uncommon among both age groups; among the 16 children ages 5 to 11 years who were reportedly hospitalized, information was available for 8 and did not indicate a causal association with vaccination.[13]

There were 2 confirmed cases of anaphylaxis in the VSD, for a rate of 5.2 per million dose 1 vaccinations and 2.7 per million total doses administered. These findings are consistent with an estimated rate of confirmed anaphylaxis among persons aged ≥12 years of 5.0 (95% CI, 3.5–6.9) per million BNT-162b2 total doses.[14]

VAERS accepts all reports regardless of biological or clinical plausibility for a causal association between a reported outcome and vaccination.[7] Four deaths after BNT-162b2 vaccination were reported to VAERS; no evidence of a causal association between vaccination and death was found. VAERS received 26 reports of MIS-C and of those adjudicated, nearly all had evidence of past or recent SARS-CoV-2 infection. Similarly, in the VSD, all confirmed cases of MIS-C after vaccination had documented COVID-19 infection before a diagnosis of MIS-C. The results of enhanced surveillance for MIS-C in children aged 5 to 11 years who had onset within 90 days of their last COVID-19 vaccine dose is ongoing; a more detailed report is forthcoming. Among persons aged 12 to 20 years, the overall reporting rate for MIS-C after COVID-19 vaccination was 1.0 case per million persons who received ≥1 dose and most had evidence of past or recent SARS-CoV-2 infection. The potential contribution of vaccination, if any, to these illnesses is unknown.[8]

Myocarditis is a rare adverse event associated with mRNA-based COVID-19 vaccination.[15,16] The reporting rate of verified myocarditis during days 0 to 7 after dose 2 was lower among boys ages 5 to 11 years (2.2 per 1 million doses administered) than boys ages 12 to 15 years (45.7 per 1 million doses administered).[17] In weekly sequential analyses of VSD data, no signal for an increased risk of myocarditis after vaccination was found.

Simultaneous vaccination with BNT-162b2 and other vaccines among children ages 5 to 11 years was not common in our data. Current CDC clinical guidance states that COVID-19 vaccines may be administered without regard to timing of other vaccines, including simultaneous

administration of COVID-19 vaccine and other vaccines.[18]

The findings in this report are subject to several limitations. Data from each of these surveillance systems may not be representative of the vaccinated United States population. V-safe is a new, voluntary system and may be more likely to include data from vaccinated persons who experience an adverse event than those who do not. VAERS is subject to reporting biases, especially underreporting of nonserious events. VSD includes insured populations with ready access to health care. The nature of the passive surveillance data from VAERS means findings from this system generally cannot be used to establish causality.[4] Data from each surveillance system are preliminary. Data collection, including review of myocarditis reports, is ongoing in each system. Our priority was to summarize the most salient available safety data and make it available for timely risk-benefit assessments regarding use of BNT-162b2 vaccine in US children ages 5 to 11 years.

The Advisory Committee on Immunization Practices and the American Academy of Pediatrics currently recommend BNT-162b2 vaccination for children ages 5 to 11 years to prevent COVID-19 and its potentially serious complications.[19,20] However, as of March 7, 2022, only ~26% of children ages 5 to 11 years have received 2 doses of COVID-19 vaccine.[3] The updated safety findings presented here, collected during the administration of ~16 million doses of BNT-162b2 vaccine to children ages 5 to 11 years, are consistent with previous findings for this age group and demonstrate a favorable safety profile. Myocarditis after BNT-162b2 vaccination for children ages 5 to 11 years was rarely reported and reporting rates were lower than for older children. Serious allergic reactions were rare and occurred at a rate similar to that observed in other age groups. Systemic reactions are relatively common among children ages 5 to 11 years but usually are clinically mild and resolve quickly.

ABBREVIATIONS

BNT-162b2: Pfizer-BioNTech mRNA COVID-19 vaccine
CDC: Centers for Disease Control and Prevention
CI: confidence interval
COVID-19: coronavirus disease 2019
EUA: Emergency Use Authorization
FDA: Food and Drug Administration
MedDRA: Medical Dictionary for Regulatory Activities
MIS-C: multisystem inflammatory syndrome in children
mRNA: messenger RNA
RCA: rapid cycle analysis
RR: rate ratios
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
VAERS: Vaccine Adverse Events Reporting System
VSD: Vaccine Safety Datalink

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