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Interim Estimates of 2021–22 Seasonal Influenza Vaccine Effectiveness — United States, February 2022

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In the United States, annual vaccination against seasonal influenza is recommended for all persons aged ≥6 months except when contraindicated (*1*). Currently available influenza vaccines are designed to protect against four influenza viruses: A(H1N1)pdm09 (the 2009 pandemic virus), A(H3N2), B/Victoria lineage, and B/Yamagata lineage. Most influenza viruses detected this season have been A(H3N2) (*2*). With the exception of the 2020–21 season, when data were insufficient to generate an estimate, CDC has estimated the effectiveness of seasonal influenza vaccine at preventing laboratory-confirmed, mild/moderate (outpatient) medically attended acute respiratory infection (ARI) each season since 2004–05. This interim report uses data from 3,636 children and adults with ARI enrolled in the U.S. Influenza Vaccine Effectiveness Network during October 4, 2021–February 12, 2022. Overall, vaccine effectiveness (VE) against medically attended outpatient ARI associated with influenza A(H3N2) virus was 16% (95% CI = −16% to 39%), which is considered not statistically significant. This analysis indicates that influenza vaccination did not reduce the risk for outpatient medically attended illness with influenza A(H3N2) viruses that predominated so far this season. Enrollment was insufficient to generate reliable VE estimates by age group or by type of influenza vaccine product (*1*). CDC recommends influenza antiviral medications as an adjunct to vaccination; the potential public health benefit of antiviral medications is magnified in the context of reduced influenza VE. CDC routinely recommends that health care providers continue to administer influenza vaccine to persons aged ≥6 months as long as influenza viruses are circulating, even when VE against one virus is reduced, because vaccine can prevent serious outcomes (e.g., hospitalization, intensive care unit (ICU) admission, or death) that are associated with influenza A(H3N2) virus infection and might protect against other influenza viruses that could circulate later in the season.

To derive these interim 2021–22 VE estimates, seven study sites of the U.S. Influenza Vaccine Effectiveness Network (California, Michigan, Pennsylvania, Tennessee, Texas, Washington, and Wisconsin) prospectively enrolled patients

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aged ≥6 months who had ARI with cough, fever or feverishness, or loss of taste or smell seeking outpatient medical care (i.e., telehealth, primary care, urgent care, or emergency department) or clinical testing for SARS-CoV-2 ≤10 days after illness onset. Inclusion criteria included age ≥6 months on September 1, 2021, enrollment after local influenza circulation was identified,* and no treatment with an influenza antiviral medication (e.g., oseltamivir or baloxavir) during this illness. After informed consent, participants or their guardians were interviewed to collect demographic data, information on general and current health status and symptoms, and 2021–22 influenza vaccination status. A clinical or research upper respiratory specimen for influenza and SARS-CoV-2 molecular testing was collected from eligible patients. Participants who require 2 vaccine doses during their first vaccination season (including children aged <9 years) were considered vaccinated if they received ≥1 dose of any seasonal influenza vaccine ≥14 days before illness onset, according to medical records and registries (Wisconsin site); medical records and self-report (California, Pennsylvania, Tennessee, Texas, and Washington sites); or self-report only (Michigan site). VE against all influenza A viruses and against influenza A(H3N2) viruses was estimated using the test-negative design as 100% x (1 – adjusted odds ratio [OR]).† Using logistic regression, estimates were adjusted for study site, age group, days from illness onset to enrollment, and month of illness onset. This study was reviewed and approved by CDC and U.S. Influenza Vaccine Effectiveness Institutional Review Boards.§

Among the 3,636 children and adults with ARI enrolled at the seven study sites during October 4, 2021–February 12, 2022, a total of 194 (5%) received a positive test result for influenza A virus infection by real-time reverse–transcription polymerase chain reaction; none received a positive test result for influenza B virus infection. Among 178 influenza A viruses subtyped, one was A(H1N1)pdm09 and 177 were A(H3N2) viruses (Table 1); 11 patients received positive test results for both influenza A and SARS-CoV-2 viruses. The proportion of patients with influenza differed by study site, age group, and days from illness onset to enrollment. The percentage of ARI patients with reported or documented receipt of 2021–22

* U.S. Influenza Vaccine Effectiveness Network sites and the dates of the first influenza-positive case by site are the University of Michigan School of Public Health (in partnership with University of Michigan Health System [Ann Arbor, Michigan] and the Henry Ford Health System [Detroit, Michigan]) (October 4, 2021); Vanderbilt University Medical Center, (Nashville, Tennessee) (November 2, 2021); Kaiser Permanente Washington (Seattle, Washington) and Kaiser Permanente Southern California (Los Angeles, California) (November 9, 2021); Baylor Scott & White Health (Temple, Texas) (November 21, 2021); Marshfield Clinic Research Institute (Marshfield, Wisconsin) (November 24, 2021); and University of Pittsburgh Schools of the Health Sciences (in partnership with the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania) (November 29, 2021).

† 100% x (1 – OR [ratio of odds of being vaccinated among outpatients who received positive test results to CDC's real-time reverse–transcription polymerase chain reaction influenza test to the odds of being vaccinated among outpatients who received influenza-negative test results]).

§ 45 C.F.R. part 46; 21 C.F.R. part 56.

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TABLE 1. Selected characteristics for enrolled patients with medically attended acute respiratory infection, by influenza test result status and seasonal influenza vaccination status* — U.S. Influenza Vaccine Effectiveness Network, United States, October 4, 2021–February 12, 2022

Characteristic	Test result status			Vaccination status*		
	Influenza-positive no. (%)	Influenza-negative no. (%)	P-value†	Total no. of patients	Vaccinated no. (%)	P-value†
Overall	**194 (5)**	**3,442 (95)**	**NA**	**3,636**	**1,817 (50)**	**NA**
Study site						
California	3 (1)	438 (99)	<0.001	441	263 (60)	<0.001
Michigan	11 (4)	268 (96)		279	178 (64)	
Pennsylvania	16 (5)	325 (95)		341	147 (43)	
Tennessee	46 (9)	441 (91)		487	251 (52)	
Texas	14 (3)	476 (97)		490	151 (31)	
Washington	4 (1)	405 (99)		409	235 (57)	
Wisconsin	100 (8)	1,089 (92)		1,189	592 (50)	
Age group						
6 mos–8 yrs	30 (8)	356 (92)	<0.001	386	214 (55)	<0.001
9–17 yrs	51 (11)	403 (89)		454	163 (36)	
18–49 yrs	87 (5)	1,699 (95)		1,786	793 (44)	
50–64 yrs	19 (3)	653 (97)		672	393 (58)	
≥65 yrs	7 (2)	331 (98)		338	254 (75)	
Illness onset to enrollment, days						
<3	112 (6)	1,614 (94)	0.01	1,726	888 (51)	0.28
3–4	55 (5)	1,129 (95)		1,184	578 (49)	
5–7	27 (4)	699 (96)		726	351 (48)	
Influenza test result						
Negative	NA	3,442	NA	3,442	1,738 (50)	NA
Influenza A positive	194 (100)	NA		194	79 (41)	
A (H1N1)pdm09	1 (0.5)	NA		1	0 (—)	
A (H3N2)	177 (91)	NA		177	69 (39)	
A subtype pending	16 (8)	NA		16	10 (63)	
Influenza B positive	0 (—)	NA	NA	0	0 (—)	NA

Abbreviation: NA = not applicable.

* Defined as having received ≥1 doses of influenza vaccine ≥14 days before illness onset. A total of 101 participants who received the vaccine ≤13 days before illness onset were excluded from the study.

† Pearson's chi-square test was used to assess differences between the numbers of persons with influenza-negative and influenza-positive test results in the distribution of enrolled patient and illness characteristics and in differences between groups in the percentage vaccinated.

TABLE 2. Number and percentage of persons receiving 2021–22 seasonal influenza vaccine among 3,636 outpatients with acute respiratory infection, by influenza test result status and vaccine effectiveness* against all influenza A and against virus type A(H3N2) — U.S. Influenza Vaccine Effectiveness Network, United States, October 4, 2021–February 12, 2022

Influenza type, all ages	Influenza-positive		Influenza-negative		VE*	
	Total	Vaccinated no. (%)	Total	Vaccinated no. (%)	Unadjusted % (95% CI)	Adjusted % (95% CI)†
Influenza A	**194**	79 (41)	**3,442**	1,738 (50)	32 (10 to 50)	14 (–17 to 37)
Influenza A/H3N2	**177**	69 (39)	**3,174**	1,564 (49)	34 (11 to 52)	16 (–16 to 39)

Abbreviations: OR = odds ratio; VE = vaccine effectiveness.

* VE was estimated using the test-negative design as 100% x (1 – OR [ratio of odds of being vaccinated among outpatients who received influenza-positive test results to odds of being vaccinated among outpatients who received influenza-negative test results]); ORs were estimated using logistic regression. https://www.cdc.gov/flu/vaccines-work/us-flu-ve-network.htm

† Adjusted for study site, age group, number of days from illness onset to enrollment, and month of illness using logistic regression.

influenza vaccine ranged from 31% to 64% among study sites and differed by age group.

Among participants with a positive influenza test result, 41% had received the 2021–22 seasonal influenza vaccine, compared with 50% of influenza test result–negative participants (Table 2). VE against outpatient medically attended ARI associated with influenza A virus types was 14% (95% CI = –17% to 37%). VE for all ages combined was 16% (95% CI = –16% to 39%) against outpatient medically attended ARI associated with influenza A(H3N2) virus infection.

As of February 12, 2022, CDC had genetically characterized 65 influenza A(H3N2) viruses from U.S. Influenza Vaccine Effectiveness Network participants; all viruses belonged to genetic clade 3C.2a1b subclade 2a.2. This viral subclade has been identified in >99% of genetically characterized A(H3N2) viruses submitted to CDC from U.S. public health laboratories nationwide to date during the 2021–22 influenza season. Post-infection ferret antisera raised against the cell-propagated 2021–22 vaccine reference virus A/Cambodia/e0826360/2020 poorly neutralized the majority of circulating A(H3N2) viruses from subclade 2a.2 (*3*).

Discussion

This interim estimate of 2021–22 influenza VE suggests that influenza vaccination did not significantly reduce the risk of outpatient medically attended illness with influenza A(H3N2) viruses that have predominated so far this season. These findings are consistent with previous evidence of low to no protection against outpatient infection with A(H3N2) subclade 2a.2 viruses from an investigation of an influenza outbreak on a university campus during October–November 2021 (*4*). These VE estimates underscore the need for ongoing diagnostic testing for influenza, influenza antiviral treatment and prophylaxis when indicated, and everyday preventive measures (*4*,*5*). CDC continues to recommend influenza vaccination when VE against outpatient illness is reduced because a growing body of evidence suggests that influenza vaccination can avert serious outcomes, including hospitalization, ICU admission, and death, among persons who are vaccinated but still become infected (*6*). In addition, vaccination is likely to prevent illness or serious complications of infection with other influenza viruses that might circulate later in the season, including influenza A(H1N1)pdm09 and B viruses (*6*).

Compared with influenza vaccination during 2020–21, influenza vaccination coverage is lower so far this season in certain groups, including some groups who are at high risk for severe influenza or complications from influenza, such as persons who are pregnant, infants, and preschool-aged children, as well as persons from racial and ethnic minority groups (*7*). Persons aged ≥6 months who have not yet been vaccinated this season should be vaccinated.

This influenza VE estimate is the first since the 2019–20 season; effectiveness of 2020–21 influenza vaccines could not be assessed because influenza virus circulation was historically low. Cumulative rates of laboratory-confirmed influenza hospitalizations so far this season have also been substantially lower than in recent A(H3N2)-predominant seasons (*7*). During the 2021–22 influenza season, clinical laboratory data reported to CDC showed increased influenza virus circulation beginning in November 2021 and continuing through mid-December 2021. From late December 2021 through late January 2022, during the rapid rise in SARS-CoV-2 B.1.1.529 (Omicron) variant positivity, influenza activity declined; however, during the first 2 weeks of February 2022, a slight increase in the percentage of specimens testing positive for influenza at clinical laboratories was reported. Influenza activity is difficult to predict and may continue for multiple weeks.

On February 25, 2022, the World Health Organization issued recommendations that the 2022–23 influenza vaccines for the northern hemisphere include updates to A(H3N2) reference viruses representing the 2a.2 subclade of A(H3N2) clade 3C.2a1b, as well as updates to the B/Victoria lineage vaccine component (*3*). Predicting circulation of virus subtypes and predominant clades within subtypes remains challenging. Evolution of circulating viruses has required frequent updates to the composition of influenza vaccines. Efforts to develop influenza vaccines that provide broader coverage of the diversity among circulating viruses are ongoing.

The findings in this report are subject to at least four limitations. First, because of low influenza test positivity, VE estimates were limited to all ages combined against influenza A overall and against A(H3N2); VE can vary by virus type or subtype (*8*), vaccine formulation, and antigenic match between circulating viruses and vaccine components (*9*,*10*).¶ End-of-season VE estimates could change as enrollment continues or if other influenza viruses predominate later in the season. Second, vaccination status at six of seven sites included self-report, which might result in misclassification of influenza vaccination status for some patients. Third, health care seeking behavior has changed during the COVID-19 pandemic and enrollment of patients with outpatient illness from COVID-19 testing sites might have affected results. The test-negative design for estimating influenza VE requires validation when influenza test-negative controls include patients with COVID-19 and receipt of influenza and COVID-19 vaccines are correlated. Finally, VE estimates in this report are specific to the prevention of outpatient illness rather than to more severe illness outcomes (e.g., hospitalization or death); data from studies measuring VE against more severe outcomes this season will be available at a later date.

Although influenza virus circulation and laboratory-confirmed influenza associated hospitalizations declined from late December 2021 through January 2022, some regions of the United States have seen increases in influenza activity since that time.** Influenza activity is difficult to predict, and strategies to prevent influenza illness remain important to reduce strain on health care services. Vaccination against seasonal influenza might protect against other influenza viruses that could circulate later in the season and their potentially serious complications. Clinicians should consider diagnostic testing for patients with ARI, especially among hospitalized patients and those at increased risk for complications. All hospitalized patients and all outpatients at higher risk for serious complications

¶ Sample sizes to achieve an adequate number of influenza cases to estimate a significant VE with 95% CIs that do not include 0 were estimated for the following age groups: 6 months–17 years, 18–49 years, and ≥50 years. Sample size calculations were based on a type I error probability of 5% and a type II error probability of 20% (power 80%) to detect 40% VE against any influenza and 30% VE against influenza A(H3N2). Assumptions about vaccination coverage varied by age group: 50% for 6 months–17 years, 30% for 18–49 years, and 50% for ≥50 years.

** https://www.cdc.gov/flu/weekly/index.htm

Summary

What is already known about this topic?

Annual vaccination against seasonal influenza is recommended for all persons in the United States aged ≥6 months. Effectiveness of seasonal influenza vaccine varies by influenza season.

What is added by this report?

Based on data from 3,636 children, adolescents, and adults with acute respiratory infection during October 4, 2021–February 12, 2022, seasonal influenza vaccination did not reduce the risk for outpatient respiratory illness caused by influenza A(H3N2) viruses that have predominated so far this season.

What are the implications for public health practice?

CDC recommends influenza vaccination for as long as influenza viruses are circulating. Vaccination can prevent serious influenza-related complications caused by viruses that might circulate later in the season, including 2009 pandemic A(H1N1) and influenza B viruses.

from influenza should be treated as soon as possible with a neuraminidase inhibitor medication if influenza is suspected (*5*). Physicians should not wait for confirmatory influenza laboratory testing, and the decision to use antiviral medication should not be influenced by patient influenza vaccination status. Clinicians should be aware that influenza activity might continue or increase, and influenza should be considered as a possible diagnosis in all patients with ARI.

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Characteristics and Adverse Events of Patients for Whom Nifurtimox Was Released Through CDC-Sponsored Investigational New Drug Program for Treatment of Chagas Disease — United States, 2001–2021

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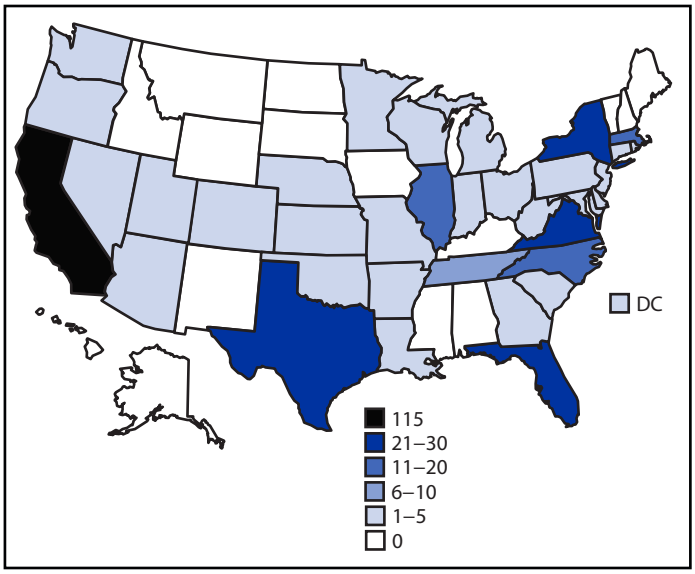
Chagas disease, or American trypanosomiasis, is caused by the parasite *Trypanosoma cruzi*. Chagas disease is endemic in rural areas of Latin America, but *T. cruzi*, triatomine vectors, infected mammalian reservoir hosts, and rare cases of autochthonous vector borne transmission have been reported in the United States (*1*). Possible modes of transmission include the following: vector borne via skin or mucosal contact with feces of infected triatomine bugs, congenital, blood transfusion, organ transplantation, or laboratory accident. Chagas disease can be treated with benznidazole (commercially available since May 14, 2018) or nifurtimox (*2*). Before January 25, 2021, nifurtimox (Lampit) had been exclusively available through CDC under an Institutional Review Board–approved Investigational New Drug (IND) treatment protocol, at which time it became reasonably accessible to health care providers outside of the program. This report summarizes CDC Drug Service reports for selected characteristics of and adverse events reported by 336 patients for whom nifurtimox was requested under the CDC IND program during January 1, 2001–January 25, 2021. Of the 336 patients, 34.2% resided in California. Median age of patients was 37 years (range = 1–78 years). Most patients were aged ≥18 (91.8%; 305 of 332) and Hispanic (93.2%; 290 of 311). Among the patients with available information, 91.4% (222 of 243) reported an adverse event. Among those with information about the severity of their adverse events, 20.5% reported a severe event. On August 7, 2020, the Food and Drug Administration (FDA) announced approval of a nifurtimox product, Lampit (Bayer), for treatment of Chagas disease in patients aged <18 years weighing ≥5.5 lbs (≥2.5 kg). Lampit became commercially available during October 2020. Physicians should take frequency of adverse events into consideration when prescribing nifurtimox and counseling patients.

Patient characteristics and reported adverse events were recorded for the purpose of drug release under the CDC program. The information was provided by the physicians who requested nifurtimox to treat their patients and monitored the patients during and after treatment. Age groups were created based on Chagas disease treatment recommendations (*1*). Data were excluded for releases made under FDA individual IND authorizations, separate from the CDC protocol. In some situations, the process for release of nifurtimox was initiated but never finalized; data from those incomplete requests were also excluded. If multiple releases of the drug were for treatment of the same patient, the associated data were combined. The prevalence of patient characteristics, reported adverse events, and severity of adverse events are reported. Fisher's exact test was used to assess statistical significance ($p<0.05$). All analyses were performed using R (version 4.0.2; R Foundation) and QGIS (version 3.10; QGIS Association). This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.*

From January 1, 2001, until patient enrollment was discontinued on January 25, 2021, CDC released nifurtimox under the IND for treatment of 336 patients, 22 (6.5%) of whom did not start treatment. Patients for whom information was available but who did not begin treatment did not differ substantially from the group as a whole. The state with the highest number of patients for whom drug was released was California (115; 34.2%) followed by New York (29; 8.6%) (Figure). The median age of 332 patients with reported age was 37 years (range = 1–78 years), with 27 (8.1%) aged <18 years,

* 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

FIGURE. Number of nifurtimox releases for treatment of Chagas disease for 336 unique patients, by state — United States, 2001–2021



Abbreviation: DC = District of Columbia.

246 (74.1%) aged 18–50 years, and 59 (17.8%) aged >50 years. Among the 27 patients aged <18 years, five were aged <15 years.

Approximately one half of patients were female (58.9%; 196 of 333) and most identified as Hispanic (93.2%; 290 of 311). Among 315 patients reporting country of exposure,† the three most commonly reported countries were El Salvador (109; 34.6%), Mexico (99; 31.4%), and Bolivia (37; 11.7%) (Table 1).

Information on adverse events was available for 243 (77.4%) of the 314 persons who started treatment; among those, 222 (91.4%) reported at least one adverse event; a total of 1,155 adverse events were reported. The median number of adverse events reported per person was four (range = 0–17). Most adverse events were reported for the following categories: gastrointestinal (68.7%), neurologic (60.5%), and constitutional (46.5%). The most common adverse events reported were nausea (50.6%), anorexia (46.1%), weight loss (35.0%), headache (33.3%), and abdominal pain (23.1%) (Table 2). At least 90% of patients aged <18, 18–50, and >50 years reported adverse events. There was no statistically significant difference between the percentage of females and males reporting adverse events (93.6% and 88.2%, respectively; p = 0.17).

Information on severity of adverse events was available for 210 (94.6%) persons who reported an adverse event and 1,042 (90.2%) adverse events. Among those 1,042 events, 680 (65.3%) were described as mild, 254 (24.4%) as moderate, and 108 (10.4%) as severe. Forty-three patients reported a severe adverse event; the most frequent were depression (22.6%), peripheral neuropathy (18.5%), paresthesia (17.9%), and dizziness/vertigo (17.2%) (Table 2). The percentage of patients with at least one adverse event classified as severe was higher among patients aged >50 years (31.8%) than among those aged 18–50 years (18.1%; odds ratio = 2.1; p = 0.06). Two (13.3%) adolescents, both aged 17 years, reported severe adverse events. The percentage of females and males reporting severe adverse events was similar (22.0% and 17.4%, respectively; p = 0.48).

† Country of exposure was reported by the physician caring for the patient.

TABLE 1. Demographic characteristics of patients for whom nifurtimox was released through CDC-sponsored Investigational New Drug treatment program for Chagas disease — United States, 2001–2021

Characteristic	No. (%) of patients	
	For whom nifurtimox was released	Reporting country of exposure
Age group, yrs (n = 332)		
0–17	27 (8.1)	NA
18–50	246 (74.1)	NA
>50	59 (17.8)	NA
Sex (n = 311)		
Female	196 (58.9)	NA
Male	137 (41.1)	NA
Country of exposure* (n = 315)		
El Salvador	NA	109 (34.6)
Mexico	NA	99 (31.4)
Bolivia	NA	37 (11.7)
United States	NA	16 (5.1)
Honduras	NA	15 (4.8)
Brazil	NA	11 (3.5)
Guatemala	NA	11 (3.5)
Argentina	NA	10 (3.2)
Colombia	NA	9 (2.9)
Nicaragua	NA	4 (1.3)
Peru	NA	4 (1.3)
Paraguay	NA	3 (1.0)
Chile	NA	2 (0.6)
Costa Rica	NA	2 (0.6)
Belize	NA	1 (0.3)

Abbreviation: NA = not applicable.
* Patients might have had more than one country of exposure.

TABLE 2. Adverse events and their severity reported by patients treated for Chagas disease with nifurtimox through CDC-sponsored Investigational New Drug treatment program — United States, 2001–2021

Characteristic	No. of patients reporting an adverse event (%) n = 243	No. of patients reporting a severe adverse event/No. of patients reporting the adverse event with data on severity (%)
Gastrointestinal	**167 (68.7)**	—*
Nausea	123 (50.6)	11/117 (9.4)
Anorexia	112 (46.1)	7/106 (6.6)
Abdominal pain	56 (23.1)	6/53 (11.3)
Vomiting	41 (16.9)	4/38 (10.5)
Diarrhea	6 (2.5)	—†
Other§	12 (4.9)	—*
Neurologic	**147 (60.5)**	—*
Headache	81 (33.3)	9/79 (11.4)
Memory loss	53 (21.8)	2/51 (3.9)
Drowsiness	41 (16.9)	3/37 (8.1)
Dizziness/Vertigo	34 (14.0)	5/29 (17.2)
Paresthesia	28 (11.5)	5/28 (17.9)
Peripheral neuropathy	28 (11.5)	5/27 (18.5)
Disorientation	22 (9.1)	1/20 (5.0)
Tremors	18 (7.4)	2/16 (12.5)
Blurry vision	10 (4.1)	—†
Other¶	9 (3.7)	—*
Constitutional	**113 (46.5)**	—*
Weight loss	85 (35.0)	5/81 (6.2)
Fatigue	22 (5.9)	1/17 (5.9)
Weakness	9 (3.7)	—†
Fever	8 (3.3)	1/6 (16.7)
Allergy	7 (2.9)	1/5 (20.0)
Malaise	5 (2.1)	1/5 (20.0)
Other**	6 (2.5)	—*
Psychiatric	**84 (34.6)**	—*
Anxiety	51 (21.0)	7/47 (14.9)
Insomnia	51 (21.0)	6/49 (12.2)
Depression	32 (13.2)	7/31 (22.6)
Mood swings	5 (2.1)	1/4 (25.0)
Other††	6 (2.5)	—*

See table footnotes on the next page.

Discussion

CDC was the sole provider of nifurtimox in the United States for the 20 years before the drug became commercially available; this report represents the most complete description of the patients treated and adverse events reported during that time. CDC provided information on adverse events to FDA annually and before the drug's approval. Providers should be aware of the frequency and profile of adverse events when counseling patients and prescribing nifurtimox.

Most patients for whom CDC released nifurtimox under the IND were adults aged 18–50 years. Twenty-seven (8.1%) patients were aged <18 years, the group for which FDA has approved the use of nifurtimox (Lampit). However, FDA-approved drugs can be used for nonapproved indications (i.e., off-label use), in accordance with the practice of medicine. The frequency of adverse events in adults and the most common adverse events and systems affected in children, adolescents, and adults were consistent with those reported in previous studies (*3*–*7*). The clinical study cited in the FDA approval of nifurtimox (Lampit) did not include adults but found that adverse events were more frequent in adolescents (aged 12 to <18 years) compared with younger age groups (*8*). Children and adolescents treated under the CDC IND were older (median age = 17 years) and reported more adverse events than in that study (90% versus 64.5%) (*8*). Among all age groups, the percentage of severe adverse events was higher than that described in other reports (10.4% versus 3.2%–5.1%) (*5*,*6*), including among children (13.3% versus 0.9%–1.6%) (*3*,*8*). These differences might be because of the way in which adverse events were reported, treatment dose differences, and older ages of children treated with nifurtimox under CDC's protocol. The high frequency and types of adverse events reported in adults and older children under the CDC IND is important information for providers prescribing nifurtimox and could be included in discussions with patients during treatment decisions and counseling. However, most adverse events reported were mild, as reported in other studies, and in some studies, symptomatic treatment, dose reductions and temporary suspensions of treatment were employed to enable completion of a full 60-day treatment course (*4*,*6*).

Considerable variation was observed in the number of nifurtimox releases by state. Provider awareness and the availability of Chagas disease–focused health care services likely contributed to these differences. Although California has the highest estimated number of persons with Chagas disease and the most patients treated with nifurtimox, the majority of nifurtimox requests were from a single medical center in that state (*9*). Similarly, although the estimated number of patients with Chagas disease in New York is lower than that in Texas or Florida, more nifurtimox requests originated in New York, and many were for patients treated at a single New York City medical center with a large immigrant patient population where patients were actively tested for Chagas disease.

The findings in this report are subject to at least two limitations. First, 23% of patient reports lacked data on adverse events, and 10% of the adverse events recorded lacked information on severity. This might have led to overestimations of adverse events and severity if providers were more likely to report adverse events and adverse events of high severity. Second, adverse events and their severity were defined by patients and their physicians. CDC did not conduct investigations into any adverse events. Severity was not standardized; therefore, adverse events might be reported differently, leading to misclassification.

TABLE 2. (*Continued*) Adverse events and their severity reported by patients treated for Chagas disease with nifurtimox through CDC-sponsored Investigational New Drug treatment program — United States, 2001–2021

Characteristic	No. of patients reporting an adverse event (%) n = 243	No. of patients reporting a severe adverse event/No. of patients reporting the adverse event with data on severity (%)
Musculoskeletal	**68 (28.0)**	—*
Arthralgia	42 (17.3)	3/39 (7.7)
Myalgia	42 (17.3)	2/39 (5.1)
Chest pain	9 (3.7)	—†
Other§§	5 (2.1)	—*
Dermatologic	**35 (14.4)**	—*
Rash	28 (11.5)	2/27 (7.4)
Pruritis	6 (2.5)	—†
Other¶¶	5 (2.1)	—*
Cardiovascular	**8 (3.3)**	—*
Tachycardia/ Palpitations	6 (2.5)	1/3 (33.3)
Other***	3 (1.2)	—*
Miscellaneous†††	**20 (8.2)**	—*
None	**21 (8.6)**	**NA**

Abbreviation: NA = not applicable.

* Patients could have both severe and nonsevere adverse events in each category, therefore not calculated.

† None reported as severe.

§ Other includes abdominal discomfort (three), abnormal taste (three), dry mouth (three), hepatitis (two), dysphagia (one), and constipation (one).

¶ Other includes confusion (three), seizure (two), excessive blinking (one), forgetfulness (one), leg weakness (one), poor balance (one), and stuttering (one).

** Other includes chills (two), hot flashes (two), diaphoresis (one), and irritation (one).

†† Other includes crying spells (two), hallucinations (two), morbid thoughts (one), and nightmares (one).

§§ Other includes whole body pain (two), back pain (two), and leg cramps (one).

¶¶ Other includes flushing (two), dry skin (one), hair loss (one), and jaundice (one).

*** Other includes syncope (one), affliction from the heart (one), and high blood pressure (one).

††† Miscellaneous includes urinary symptoms (four), sexual dysfunction (three), cough (three), shortness of breath (three), hypoglycemia (three), facial swelling (two), hypersensitivity pneumonitis (one), itchy eyes (one), left-sided neck vein throbbing (one), runny nose (one), elevated alanine aminotransferase (one), and eosinophilia (one).

Summary

What is already known about this topic?

Nifurtimox is used to treat Chagas disease. During 2001–2021, CDC sponsored an Investigational New Drug protocol, which made nifurtimox available for treatment of Chagas disease in the United States.

What is added by this report?

CDC released nifurtimox to 336 patients, 34.2% of whom were in California. Most patients were aged ≥18 years (91.8%; 305 of 332) and Hispanic (93.2%; 290 of 311). Among 243 treated patients reporting information about adverse events, 91.4% (222 of 243) experienced at least one adverse event.

What are the implications for public health practice?

Nifurtimox is now commercially available as Lampit (Bayer) and is no longer distributed by CDC. Physicians should be aware of the frequency of adverse events when prescribing nifurtimox.

FDA approval and commercial availability of a nifurtimox product (Lampit) and benznidazole are anticipated to improve access to therapy for the approximately 300,000 estimated persons with *T. cruzi* infection living in the United States (*10*). Although CDC no longer distributes nifurtimox or benznidazole, CDC provides reference diagnostic testing for *T. cruzi* infection (https://www.cdc.gov/dpdx) and teleconsultative services regarding Chagas disease. Health care providers and U.S. health departments with questions about Chagas disease can contact CDC Parasitic Diseases Branch Inquiries by telephone (404-718-4745) or email (parasites@cdc.gov) or review CDC's website https://www.cdc.gov/parasites/chagas.

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Evaluation of Serologic Cross-Reactivity Between Dengue Virus and SARS-CoV-2 in Patients with Acute Febrile Illness — United States and Puerto Rico, April 2020–March 2021

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The diagnosis of dengue disease, caused by the dengue virus (DENV) (a flavivirus), often requires serologic testing during acute and early convalescent phases of the disease. Some symptoms of DENV infection, such as nonspecific fever, are similar to those caused by infection with SARS-CoV-2, the virus that causes COVID-19. In studies with few COVID-19 cases, positive DENV immunoglobulin M (IgM) results were reported with various serologic tests, indicating possible cross-reactivity in these tests for DENV and SARS-CoV-2 infections (*1*,*2*). DENV antibodies can cross-react with other flaviviruses, including Zika virus. To assess the potential cross-reactivity of SARS-CoV-2, DENV, and Zika virus IgM antibodies, serum specimens from 97 patients from Puerto Rico and 12 U.S.-based patients with confirmed COVID-19 were tested using the DENV Detect IgM Capture enzyme-linked immunosorbent assay (ELISA) (InBios International).* In addition, 122 serum specimens from patients with confirmed dengue and 121 from patients with confirmed Zika virus disease (all from Puerto Rico) were tested using the SARS-CoV-2 pan-Ig Spike Protein ELISA (CDC).† Results obtained for DENV, Zika virus IgM, and SARS-CoV-2 antibodies indicated 98% test specificity and minimal levels of cross-reactivity between the two flaviviruses and SARS-CoV-2. These findings indicate that diagnoses of dengue or Zika virus diseases with the serological assays described in this report are not affected by COVID-19, nor do dengue or Zika virus diseases interfere with the diagnosis of COVID-19.

Persons infected with SARS-CoV-2 can be asymptomatic or experience a range of illnesses from mild fever to life-threatening respiratory disease. In mildly symptomatic patients with fever, COVID-19 might be confused with other diseases that have similar symptoms, including dengue and Zika virus diseases. Dengue, caused by four antigenically distinct dengue virus serotypes (DENV-1–4) transmitted by *Aedes spp.* mosquitoes, is usually a mild febrile illness but might evolve into severe dengue disease resulting in life-threatening conditions, such as dengue hemorrhagic fever and dengue shock syndrome. Dengue disease is a major public health problem throughout tropical and subtropical regions, causing approximately 400 million infections per year, 25% of which are clinically apparent (*3*). DENV-1–4 transmission has been reported in the Americas during the current COVID-19 pandemic, causing concerns about persons with COVID-19 antibodies being misdiagnosed based on results from a flavivirus antibody test because of antibody cross-reactivity.

Laboratory diagnosis of dengue disease focuses on the detection of viral RNA by real-time reverse transcription–polymerase chain reaction (RT-PCR) or nonstructural protein 1 (NS1) antigen tests in blood specimens. These tests identify a large percentage of cases during the first few days of illness (*4*). After 5 days of illness, DENV-1–4 RNA and NS1 decline with the rise in antibody response; therefore, IgM antibody detection by ELISA becomes the primary option for diagnosing recent DENV-1–4 infections (*4*). Serologic cross-reactivity between DENV and Zika virus is an important limitation in the diagnosis of these diseases. In light of the overlapping symptoms associated with dengue disease and COVID-19, patients in areas where DENV-1–4 and SARS-CoV-2 circulate could be infected with either one of these viruses while they still have detectable levels of antibodies against the other. Patients might also have DENV-1–4 and SARS-CoV-2 coinfections. In addition, depending on the specificity of each test, a false positive serologic test result for one of the diseases is more likely during a period of low incidence if incidence of the other disease is high.

Recent reports indicated possible cross-reactivity in serologic (IgM) tests for DENV in specimens from confirmed COVID-19 cases (*1*,*2*). In a study of dengue disease cases detected before the COVID-19 pandemic, some specimens returned a false-positive result when tested for SARS-CoV-2 IgG or IgM. A study of 32 COVID-19 cases found no cross-reactivity with DENV, whereas only two of 44 dengue disease cases indicated cross-reactivity on a SARS-CoV-2 IgM ELISA (*3*). A more extensive evaluation of 11 SARS-CoV-2 immunochromatographic antibody tests indicated specificity in panels of 20–40 dengue specimens ranging from 85% to 100%, indicating variability of test performance (*5*). In another study, no cross-reactivity of dengue specimens in a SARS-CoV-2 IgM ELISA was observed, but cross-reactivity for SARS-CoV-2 in five of 26 confirmed Zika virus specimens did occur (*6*).

* http://inbios.com/wp-content/uploads/2016/05/900106-07-IVD-DENV-Detect-IgM-Capture-ELISA-Insert.pdf
† https://www.biorxiv.org/content/10.1101/2020.04.24.057323v2

The purpose of this study was to assess the potential cross-reactivity of SARS-CoV-2 IgM antibodies in the DENV Detect IgM Capture ELISA, a Food and Drug Administration-approved ELISA test frequently used for the diagnosis of DENV-1–4 infections with demonstrated high sensitivity in the acute and early convalescent phases of the disease (*1*). A secondary aim was to determine whether Zika virus and DENV-1–4 IgM antibodies cross-react with the SARS-CoV-2 pan-Ig Spike Protein ELISA (*7*). Five serum specimen panels were evaluated; these included two panels from COVID-19 patients, one from dengue disease patients, one from Zika virus disease patients, and one from Zika virus and DENV-negative patients with acute febrile illness.

Since 2012, the Sentinel Enhanced Dengue Surveillance System in Puerto Rico has maintained a repository of serum and nasal swab specimens collected from febrile patients evaluated at several hospital-based acute febrile illness surveillance sites (*8*). A panel of 97 serum specimens obtained 4–9 days after illness onset from patients with confirmed COVID-19 (based on SARS-CoV-2 real-time RT-PCR positive test results)[§] was prepared from specimens collected in Puerto Rico during April 2020–March 2021. A second panel consisted of 12 convalescent serum specimens from COVID-19 patients with high SARS-CoV-2 antibody titers collected in the United States during 2020–2021[¶] and tested using the SARS-CoV-2 pan-Ig Spike Protein ELISA (*7*). To assess whether specimens from COVID-19 patients were cross-reactive with DENV IgM, these specimens were tested using the DENV Detect IgM Capture ELISA according to the manufacturer's instructions. The remaining panels consisted of 365 specimens[**] collected from patients with acute febrile illness in Puerto Rico before 2017; these specimens were evaluated as 1) DENV IgM-positive by the DENV Detect IgM Capture ELISA (122 specimens), 2) Zika virus IgM-positive by Zika virus MAC-ELISA (CDC) (122 specimens), and 3) both Zika virus and DENV IgM-negative (121 specimens). The DENV specimens were collected during 2012–2014; the Zika virus and acute febrile illness specimens were obtained during the 2016 Zika virus disease epidemic. Serum specimens were tested for SARS-CoV-2 antibodies using SARS-CoV-2 pan-Ig Spike Protein ELISA, as previously described (*7*), and were considered positive, negative, or equivocal according to their optical density ratio. All serum specimens used in this study were deidentified. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.[††]

Summary

What is already known about this topic?

In studies with few COVID-19 cases, positive dengue virus (DENV) immunoglobulin M results were reported with various serologic tests, indicating possible cross-reactivity in serologic tests for DENV and SARS-CoV-2 infections.

What is added by this report?

In a large cohort of febrile patients in Puerto Rico (where DENV is endemic) with recently confirmed SARS-CoV-2, DENV, or Zika virus infections, the specificity of DENV and SARS-CoV-2 enzyme-linked immunosorbent assays was ≥98%.

What are the implications for public health practice?

These findings indicate that diagnoses of dengue or Zika virus diseases with the serological assays described in this report are not affected by COVID-19, nor do dengue or Zika virus diseases interfere with the diagnosis of COVID-19.

None of the 97 specimens from COVID-19 patients collected in Puerto Rico tested positive for anti-DENV IgM; 95 specimens tested negative and two returned equivocal results, indicating a 100% specificity during the period of symptomatic disease when most patients with dengue disease or Zika virus disease are usually tested (Table). The convalescent serum specimens collected from 12 U.S. confirmed COVID-19 patients all tested negative. Among the 122 DENV IgM-positive specimens, two specimens returned positive anti–SARS-COV-2 pan-Ig test results. Similarly, two of 122 Zika virus IgM-positive and two of 121 negative specimens returned positive results, indicating a 98% specificity of the anti–SARS-CoV-2 Spike Protein pan-Ig ELISA.

Discussion

The results obtained for DENV and Zika virus IgM and SARS-CoV-2 antibodies evaluated with the tests described in this study indicated high specificity and minimal levels of cross-reactivity between the two flaviviruses (DENV and Zika virus) and SARS-CoV-2. A previous study reported a similar test specificity of the SARS-CoV-2 pan-Ig Spike Protein ELISA assay (99%) for pathogens unrelated to those evaluated in this study (*7*), and similarly high levels of specificity (97%) have been reported for the DENV Detect IgM Capture ELISA (*9*).

The findings in this report are subject to at least three limitations. First, the study was conducted with tests used at CDC laboratories for reference testing and do not constitute a direct assessment of other available tests. In addition, selection of specimens from acute and early convalescent phases of disease is

[§] Confirmed COVID-19 cases were based on tests conducted by Dengue Branch, Division of Vector-Borne Diseases, CDC.

[¶] Twelve convalescent serum specimens from U.S. COVID-19 patients were tested at Microbial Pathogenesis and Immune Response Laboratory, CDC.

[**] These 365 specimens collected from patients with acute febrile illness in Puerto Rico before 2017 were evaluated at Dengue Branch, Division of Vector-Borne Diseases, CDC.

[††] 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

TABLE. Cross-reactivity of SARS-CoV-2 in the DENV Detect IgM Capture ELISA* and of dengue virus and Zika virus in the CDC SARS-CoV-2 pan-Ig Spike Protein ELISA† — United States and Puerto Rico, April 2020–March 2021

Pathogen or syndrome	Location and collection time frame	Test	Analyte	No. of specimens	No. positive or reactive	No. negative or nonreactive	No. equivocal	% Specificity (95% CI)
SARS-CoV-2	Puerto Rico Dec 2020–Jan 2021	DENV Detect IgM Capture ELISA	Anti-DENV IgM	97	0	95	2	100 (96–100)
SARS-CoV-2	United States 2020–2021	DENV Detect IgM Capture ELISA	Anti-DENV IgM	12	0	12	0	100 (74–100)
DENV	Puerto Rico 2012–2014	SARS-CoV-2 pan-Ig Spike Protein ELISA	Anti-SARS-CoV-2 and total human antibodies	122	2	120	NA	98 (94–100)
Zika virus	Puerto Rico 2016	SARS-CoV-2 pan-Ig Spike Protein ELISA	Anti-SARS-CoV-2 and total human antibodies	122	2	120	NA	98 (94–100)
Acute febrile illness	Puerto Rico 2016	SARS-CoV-2 pan-Ig Spike Protein ELISA	Anti-SARS-CoV-2 and total human antibodies	121	2	119	NA	98 (94–100)

Abbreviations: DENV = dengue virus; ELISA = enzyme-linked immunosorbent assay; IgM = immunoglobulin M; NA = not applicable.
* http://inbios.com/wp-content/uploads/2016/05/900106-07-IVD-DENV-Detect-IgM-Capture-ELISA-Insert.pdf
† https://www.biorxiv.org/content/10.1101/2020.04.24.057323v2

based on the recommended time for dengue disease diagnosis; therefore, this study does not address cross-reactivity after day 9 of symptoms, when antibody levels might be higher than those detected during disease. The study did not assess cross-reactivity from COVID-19 vaccine-elicited antibodies. Finally, sampling in this study does not address the contribution of previously acquired IgG antibodies to the specificity of these tests.

These findings indicate that in a cohort of patients in Puerto Rico, where dengue disease is endemic, the serologic diagnosis of dengue disease with a commonly used IgM test is not affected by antibodies to SARS-CoV-2, nor do Zika virus and DENV IgM antibodies interfere with SARS-CoV-2 antibody detection. These results suggest that previously reported cross-reactivity between these viruses appears to be nonspecific and not a result of actual cross-reactivity from shared or similar epitopes. A possible explanation for these apparent cross-reactive results might be the presence of antibodies from a recent flavivirus infection in COVID-19 patients in areas of co-endemicity. Therefore, routine testing algorithms established for dengue and Zika diseases with the assays described in this report can proceed with the understanding that the chances of misdiagnosis of dengue or Zika virus diseases are not augmented by COVID-19, nor do dengue or Zika virus diseases interfere with the diagnosis of COVID-19.

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COVID-19 Vaccine Provider Access and Vaccination Coverage Among Children Aged 5–11 Years — United States, November 2021–January 2022

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On October 29, 2021, the Pfizer-BioNTech pediatric COVID-19 vaccine received Emergency Use Authorization for children aged 5–11 years in the United States.† For a successful immunization program, both access to and uptake of the vaccine are needed. Fifteen million doses were initially made available to pediatric providers to ensure the broadest possible access for the estimated 28 million eligible children aged 5–11 years, especially those in high social vulnerability index (SVI)§ communities. Initial supply was strategically distributed to maximize vaccination opportunities for U.S. children aged 5–11 years. COVID-19 vaccination coverage among persons aged 12–17 years has lagged (*1*), and vaccine confidence has been identified as a concern among parents and caregivers (*2*). Therefore, COVID-19 provider access and early vaccination coverage among children aged 5–11 years in high and low SVI communities were examined during November 1, 2021–January 18, 2022. As of November 29, 2021 (4 weeks after program launch), 38,732 providers were enrolled, and 92% of U.S. children aged 5–11 years lived within 5 miles of an active provider. As of January 18, 2022 (11 weeks after program launch), 39,786 providers had administered 13.3 million doses. First dose coverage at 4 weeks after launch was 15.0% (10.5% and 17.5% in high and low SVI areas, respectively; rate ratio [RR] = 0.68; 95% CI = 0.60–0.78), and at 11 weeks was 27.7% (21.2% and 29.0% in high and low SVI areas, respectively; RR = 0.76; 95% CI = 0.68–0.84). Overall series completion at 11 weeks after launch was 19.1% (13.7% and 21.7% in high and low SVI areas, respectively; RR = 0.67; 95% CI = 0.58–0.77). Pharmacies administered 46.4% of doses to this age group, including 48.7% of doses in high SVI areas and 44.4% in low SVI areas. Although COVID-19 vaccination coverage rates were low, particularly in high SVI areas, first dose coverage improved over time. Additional outreach is critical, especially in high SVI areas, to improve vaccine confidence and increase coverage rates among children aged 5–11 years.

To facilitate equitable access to pediatric COVID-19 vaccine for all children aged 5–11 years, doses were distributed through vaccination partners from state and local health departments, including Vaccines for Children¶ (VFC) program providers and other providers (jurisdictions),** the Federal Retail Pharmacy Program†† (FRPP), and federal entities.§§ Vaccination program operations considered vaccine supply, packaging, shelf life, site training, ability to vaccinate children aged 5–11 years, demand,

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† https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age

§ Fifteen SVI indicators: 1) percentage of persons with incomes below poverty threshold, 2) percentage of civilian population (aged ≥16 years) who is unemployed, 3) per capita income, 4) percentage of persons aged ≥25 years with no high school diploma, 5) percentage of persons aged ≥65 years, 6) percentage of persons aged ≤17 years, 7) percentage of civilian noninstitutionalized population with a disability, 8) percentage of single-parent households with children aged <18 years, 9) percentage of persons who are racial/ethnic minorities (i.e., all persons except those who are non-Hispanic White), 10) percentage of persons aged ≥5 years who speak English "less than well," 11) percentage of housing in structures with ≥10 units (multiunit housing), 12) percentage of housing structures that are mobile homes, 13) percentage of households with more persons than rooms (crowding), 14) percentage of households with no vehicle available, and 15) percentage of persons in group quarters. The 15 indicators are categorized into four themes: 1) socioeconomic status (indicators 1–4), 2) household composition and disability (indicators 5–8), 3) racial/ethnic minority status and language (indicators 9 and 10), and 4) housing type and transportation (indicators 11–15). Overall SVI includes all 15 indicators as a composite measure and a final score is ranked from lowest (0) to highest (1) vulnerability. https://www.atsdr.cdc.gov/placeandhealth/svi/index.html

¶ VFC is a federally funded program that provides routine childhood vaccines through VFC participating providers (i.e., private physicians' offices and public health clinics) at no cost to children who might not otherwise be vaccinated because of inability to pay. Federally Qualified Health Centers, the Rural Health Clinics program, and state and local health departments are also VFC/primary care providers. https://www.cdc.gov/vaccines/programs/vfc/index.html

** Jurisdiction partners consisted of 62 states, territories, and cities, including the 50 states, District of Columbia, three cities (Chicago, Illinois; New York, New York; Philadelphia, Pennsylvania), five U.S. territories (American Samoa, Guam, Northern Mariana Islands, Puerto Rico, and U.S. Virgin Islands), and three freely associated states (Federated States of Micronesia, Marshall Islands, and Palau).

†† Pharmacy partners include 21 retail and independent pharmacy networks across the United States. https://www.cdc.gov/vaccines/covid-19/retail-pharmacy-program/index.html

§§ Federal entity partners that received direct allocations of COVID-19 pediatric vaccine include U.S. Department of Defense, U.S. Department of State, Indian Health Service, Veterans Health Administration, and the Health Resources & Services Administration. A complete list of federal entity partners receiving direct allocation of COVID-19 vaccine can be found at https://www.cdc.gov/vaccines/imz-managers/downloads/Covid-19-Vaccination-Program-Interim_Playbook.pdf.

and equity in the distribution strategy and selection of initial vaccine providers.[¶¶]

COVID-19 vaccine administration data reported to the U.S. Department of Health and Human Services (HHS) and CDC by partners via immunization information systems, the Vaccine Administration Management System, or direct data submission, and county-level SVI data were analyzed.[***] Active providers were defined as those who received shipments or administered ≥1 BNT162b2 (Pfizer-BioNTech) pediatric COVID-19 vaccine dose in the preceding 28 days or reported inventory in the preceding 7 days. COVID-19 vaccination coverage was defined as the number of children who received ≥1 dose, or who received 2 doses (primary series completion), during November 1, 2021–January 18, 2022, divided by county population totals for those aged 5–11 years. Data reported to CDC by January 28, 2022, were included in the analysis. Total county pediatric population denominators used to create vaccination coverage estimates were obtained from the U.S. Census Bureau 2019 population estimates.[†††] WorldPop 2020 data were used for the mapped population.[§§§] SVI data were obtained from CDC's 2018 SVI database. County-level SVI rankings were used; geospatial analysis used census tract–level SVI.[¶¶¶] Provider county was used to determine provider SVI, and recipients' county was used for vaccine recipient SVI. SVI rank cutoffs of 0–0.5 for low and >0.5–1 for high SVI were used.[****]

The number and geographic distribution of active providers by November 29, 2021, and January 18, 2022 (4 and 11 weeks, respectively, after the COVID-19 vaccination program launch on November 1, 2021) were assessed for children aged 5–11 years by SVI area. Data are presented at 4 weeks to illustrate the situation during the early program launch, and at 11 weeks, after peak demand, and during which the most recent data were available. The proportion of children who lived within 5 miles of an active provider was estimated, and the percentage of doses administered and total vaccination coverage rates by 4 and 11 weeks after the program launch were calculated by high and low SVI areas. RRs were calculated with corresponding 95% CIs to evaluate coverage rates between high and low SVI areas with generalized estimating equation models using binomial regression and log link.[††††] Statistical analyses were conducted using Stata (version 16; StataCorp); CIs that excluded 1.0 were considered statistically significant. Maps were generated using QGIS (version 3.24; QGIS Association). This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.[§§§§]

By 4 and 11 weeks after launch of the pediatric COVID-19 vaccination program, there were 38,732 and 39,786 active providers, respectively (Table) (Figure 1). Overall, and in high SVI areas, 92% of children aged 5–11 years lived within 5 miles (8 km) of an active provider, and in low SVI areas, 89% of children aged 5–11 years lived within 5 miles (8 km) of an active provider (Figure 2). Across states, 73%–100% of children aged 5–11 years lived within 5 miles (8 km) of an active provider, overall and in high SVI areas. By 11 weeks

[¶¶] The new pediatric formulation was packaged in 10-dose vials with a minimum order requirement of 100 doses (300 doses during the first week) and has a shorter shelf life (6 months) than the adult formulation (9 months), risking higher wastage. Partners considered the following in their site selection: provider type, site training and ability to vaccinate younger age groups, geographic access, provider ability to store and administer vaccine given limited shelf life, provider throughput, and community level demand to minimize wastage of initial limited supply. Initially 15 million doses were made available to partners to order and by 11 weeks 39 million doses were made available. https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/pfizer-bioNTech-children-adolescents.html

[***] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/distributing/about-vaccine-data.html

[†††] https://www.census.gov/programs-surveys/popest.html (Accessed January 28, 2022).

[§§§] https://www.worldpop.org/project/categories?id=3 (Accessed January 28, 2022).

[¶¶¶] Geospatial analyses to produce maps were done only on the geographic boundaries of the 50 states and District of Columbia using Census tract–level SVI with populations aggregated at the state level. WorldPop age-specific raster files from 2020 using 5-mile [8-km] buffer zones around active provider coordinates were used to estimate pediatric proximity and coverage, overall and limited to children residing in high SVI areas.

[****] https://covid.cdc.gov/covid-data-tracker/#vaccination-equity (Accessed January 28, 2022).

[††††] State fixed effects and robust variance were also used.

[§§§§] 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

TABLE. Active pediatric COVID-19 vaccine providers* for children aged 5–11 years at 4 and 11 weeks after launch of pediatric COVID-19 vaccination program,† by county-level social vulnerability index§ and provider type — United States, November 1, 2021–January 18, 2022

Characteristic	No. (%) of providers	
	4 weeks after program launch	11 weeks after program launch
SVI area		
High SVI areas	20,625 (53.2)	21,480 (54.0)
Low SVI areas	18,092 (46.7)	18,293 (46.0)
Total	**38,732 (100)**	**39,786 (100)**
Provider type		
VFC	12,171 (31.4)	13,164 (33.1)
FRPP	17,064 (44.1)	17,581 (44.2)
Federal entities	923 (2.4)	854 (2.1)
Other	8,574 (22.1)	8,187 (20.6)

Abbreviations: FRPP = Federal Retail Pharmacy Program; SVI = social vulnerability index; VFC = Vaccines for Children.

* Active providers included from 62 jurisdiction partners, 21 pharmacy partners, and five federal entity partners.

† As of November 1, 2021.

§ SVI is composed of ranks from lowest (0) to highest (1) vulnerability. Rank cutoffs of 0–0.5 for low SVI and >0.5–1 for high SVI were used. https://www.atsdr.cdc.gov/placeandhealth/svi/index.html

after launch, 54.0% of active providers were in high SVI areas, 44.6% and 32.7% of whom were FRPP and VFC providers, respectively (Supplementary Table 1, https://stacks.cdc.gov/view/cdc/114935). At 4 and 11 weeks after launch, 39.3% and 43.1% of first doses were administered in high SVI areas, respectively (Supplementary Table 2, https://stacks.cdc.gov/view/cdc/114935).

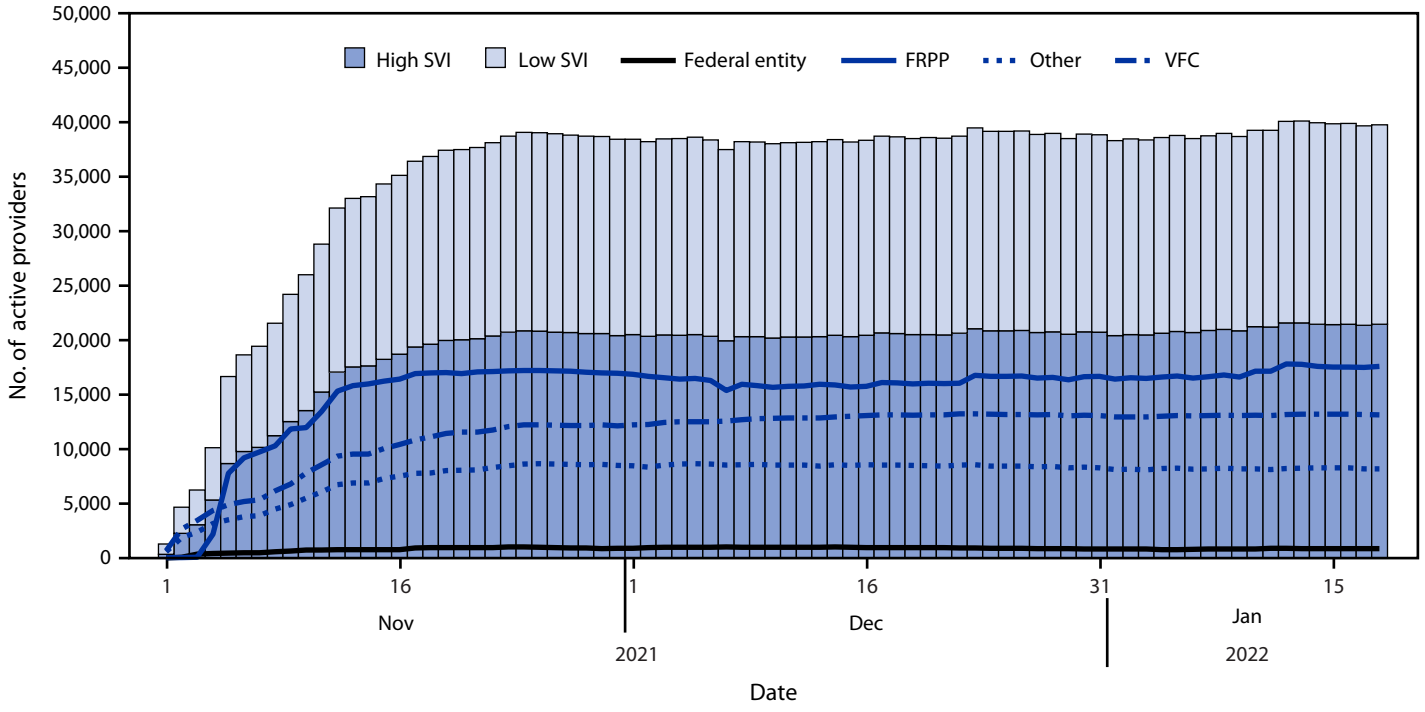
First dose coverage at 4 weeks after launch was 15.0% (10.5% and 17.5% in high and low SVI areas, respectively; RR = 0.68; 95% CI = 0.60–0.78) and at 11 weeks after launch was 27.7% (21.2% and 29.0% in high and low SVI areas, respectively; RR = 0.76; 95% CI = 0.68–0.84). Overall series completion at 11 weeks after launch was 19.1% (13.7% and 21.7% in high and low SVI areas, respectively; RR = 0.67; 95% CI = 0.58–0.77). Among all provider types, FRPP providers administered the highest percentage of all doses in both high SVI areas (48.7%) and low SVI areas (44.4%) (Supplementary Table 3, https://stacks.cdc.gov/view/cdc/114935).

Discussion

To maximize pediatric vaccination opportunities, federal, state, local, and pharmacy partners developed a robust network of providers trained to serve pediatric populations and best manage the vaccine given product and supply considerations, with particular attention focused on ensuring access in the most underserved communities at risk for COVID-19–related illness and death.[¶¶¶¶] By 4 weeks after program launch, an active COVID-19 vaccine provider was within 5 miles (8 km) of the residence of >90% of children aged 5–11 years. An estimated 27.7% of all children aged 5–11 years received a first dose of COVID-19 vaccine by 11 weeks after the program began, similar to the coverage trends reached after launch of the COVID-19

[¶¶¶¶] A successful vaccination program requires substantial planning, including vaccine development and evaluation, adequate vaccine production and supply to meet anticipated demand, a predictable and stable network of administration sites, public demand and trust, and strategic vaccine delivery to best reach the eligible population. Like other COVID-19 vaccine program launches (i.e., initiation of adolescent vaccination and booster vaccination), sites expected a higher demand during the initial weeks of the program. Site selection balanced vaccine access with expected demand to avoid distributing supply across too many providers, potentially decreasing vaccination opportunities at high demand sites, and increasing vaccine wastage at low demand sites. COVID-19 vaccine provider sites were expected to have trained staff members specialized in vaccinating children. Providers were asked to consider vial size (10 doses) and 6-hour time frame when scheduling children for vaccination, especially early in the program to minimize waste and optimize use of supply. https://www.cdc.gov/vaccines/covid-19/downloads/Pediatric-Planning-Guide.pdf

FIGURE 1. Active pediatric COVID-19 vaccine providers,* by social vulnerability index,† provider type, and date — United States, November 1, 2021–January 18, 2022



Abbreviations: FRPP = Federal Retail Pharmacy Program; SVI = social vulnerability index; VFC = Vaccines for Children.
* Active providers included 62 jurisdiction partners, 21 pharmacy partners, and five federal entity partners.
† SVI is a composite measure of resilience, and includes socioeconomic status, household composition and disability, minority status and English language facility, and housing type and transportation. SVI is composed of ranks from lowest (0) to highest (1) vulnerability. Rank cutoffs of 0–0.5 for low SVI and >0.5–1 for high SVI were used. https://www.atsdr.cdc.gov/placeandhealth/svi/index.html

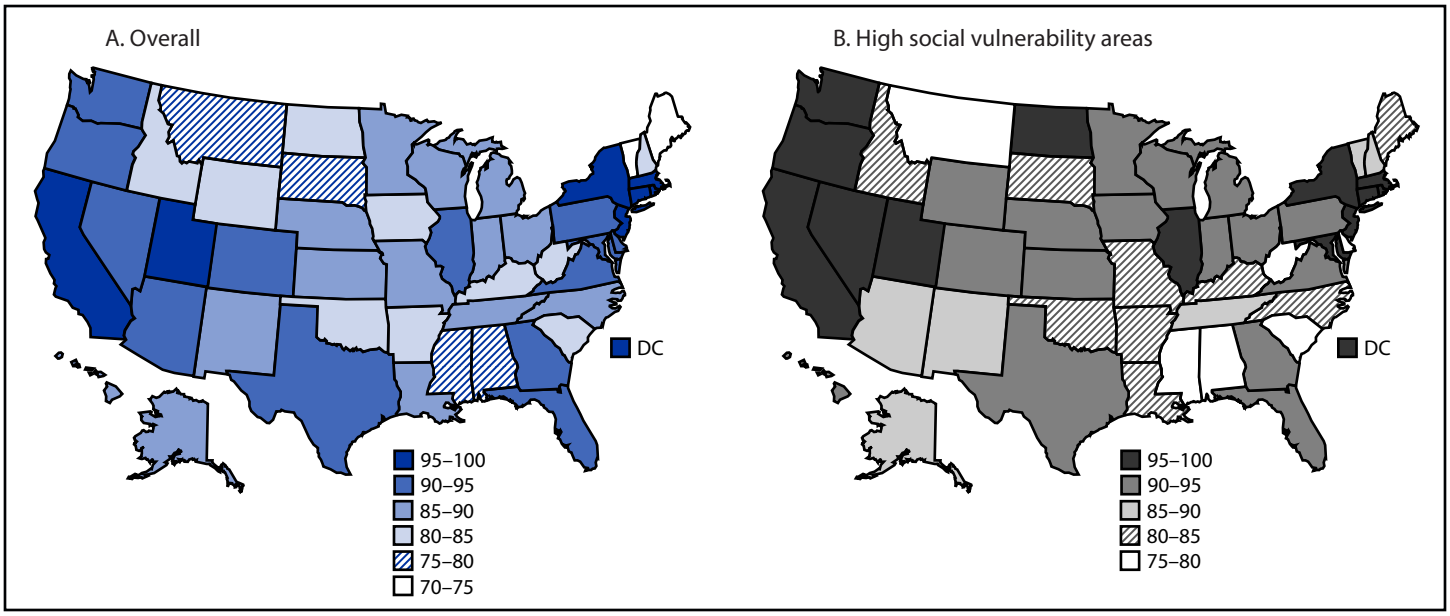
vaccination program for persons aged 12–15 years (*1*). At 11 weeks, despite 54.0% of vaccine providers being in high SVI areas, the series completion rate was approximately 33.0% lower in high than in low SVI areas, underscoring the importance of strengthening strategies (e.g., education, culturally and linguistically relevant outreach, and engagement of trusted providers) to improve vaccination coverage in these communities (*2*).

The expansion of legal authorities for the COVID-19 emergency response***** to allow pharmacists to vaccinate children and adolescents aged 3–18 years helped increase available providers and vaccine access for children aged 5–11 years. Pharmacy providers were critical in addressing high initial demand for COVID-19 vaccine among this age group, including during evenings, weekends, and over holidays, when other providers might be less available. Pharmacists also played a larger role in provision of COVID-19 vaccine to children aged 5–11 years compared with administration of routine vaccines: 46.4% of all COVID-19 pediatric vaccine doses were administered by pharmacy partners, whereas 12.3% of pediatric seasonal influenza vaccine doses were administered to children aged 5–12 years in pharmacies during 2020–21 (*3*). Pharmacies might also be important for vaccination of children aged 3–4 years if vaccine becomes available for this age group.

Likely contributors to low vaccination coverage include vaccine hesitancy among parents and caregivers and potential need for alternative convenient, trusted vaccine access points (*2*). With pediatric COVID-19 vaccine readily available in most communities, ongoing strategies to improve coverage could focus on improving vaccine confidence among caregivers through provision of information from trusted messengers, such as faith and community leaders, about the impact of

***** On August 24, 2020, the Public Readiness and Emergency Preparedness Act amendment resulted in the HHS Secretary amending the Declaration to identify state-licensed pharmacists (and pharmacy interns acting under their supervision if the pharmacy intern is licensed or registered by their state board of pharmacy) as qualified persons under section 247d–6d(i)(8)(B) to administer vaccine to persons aged 3–18 years. This act covers all Advisory Committee on Immunization Practices recommended vaccines. These requirements are consistent with those in many states that permit licensed pharmacists to administer vaccines to children and adolescents. Expansion was in response to an identified decline in routine pediatric vaccine coverage indicating that U.S. children and adolescents and their communities face increased risks for outbreaks of vaccine-preventable diseases. CDC reports suggested that decreases in rates of routine childhood vaccinations were because of changes in health care access, decrease in well-child visits, increased physical distancing, and other COVID–19 prevention strategies. https://www.govinfo.gov/content/pkg/FR-2020-08-24/pdf/2020-18542.pdf

FIGURE 2. Percentage* of children aged 5–11 years living within 5 miles (8 km) of an active pediatric COVID-19 vaccine provider,† by state, 4 weeks after pediatric vaccination program launch, overall (A) and in high social vulnerability§ areas (B) — United States, November 1, 2021–January 18, 2022



Abbreviations: DC = District of Columbia; SVI = social vulnerability index.

* Maps depict geographical distance of the population to a provider offering vaccine for children aged 5–11 years. States where vaccine access is lower (<81% of the population lives within a within a 5 mile [8 km] radius of a vaccination site) might be because of various factors including rurality, lower number of active jurisdictional providers, and in rare instances jurisdictional plans had lower number of vaccination providers but still had high vaccine coverage by implementing additional efforts (e.g., Maine and Vermont).

† Active providers included from 50 states and District of Columbia among jurisdiction partners, 21 pharmacy partners, and three federal entity partners (Health Resources & Services Administration, U.S. Department of Defense, and Veterans Health Administration) within those geographic areas.

§ SVI is composed of ranks from lowest (0) to highest (1) vulnerability. Rank cutoffs of 0–0.5 for low SVI and >0.5–1 for high SVI were used. In low SVI areas, 89% of children aged 5–11 years lived within 5 miles (8 km) of an active pediatric COVID-19 provider at 4 weeks after program launch. https://www.atsdr.cdc.gov/placeandhealth/svi/index.html

Summary

What is already known about this topic?

Successful vaccination coverage requires access to vaccine and uptake. COVID-19 vaccination coverage in children is low.

What is added by this report?

At 11 weeks after launch of the pediatric COVID-19 vaccination program, 92% of children aged 5–11 years lived within 5 miles (8 km) of a pediatric vaccine provider; 44% of providers were pharmacies. COVID-19 first-dose vaccination coverage rates were low, particularly in high social vulnerability index (SVI) areas, but improved over time.

What are the implications for public health practice?

Broad vaccine access should be maintained while critical outreach efforts continue to improve vaccine coverage among children aged 5–11 years, especially in high SVI areas. If COVID-19 vaccine is recommended for children aged <5 years, similar efforts to strategically maximize access and coverage might be considered.

COVID-19 among children (*4*–*7*) and the safety and effectiveness of COVID-19 vaccination (*8*,*9*) in culturally relevant and accessible formats to address community-level concerns (*10*).

The findings in this report are subject to at least four limitations. First, SVI metrics do not include all population characteristics that could be used to identify disparities and are measured at the county level rather than a lower administrative level such as zip code. Second, analyses of vaccine administration data were at the recipient level, with approximately 12% of data missing or suppressed because of small administration numbers, possibly having a larger effect on high SVI areas and potentially underestimating coverage in these areas. Third, spatial analysis does not consider ability to travel to the site using established transportation infrastructure, which could over- or underestimate accessibility. Finally, some private practice providers might not offer vaccine to children not already established as patients in their practice, resulting in overestimates of provider accessibility.

Initial vaccine distribution for children aged 5–11 years successfully provided vaccination opportunities within 5 miles (8 km) of most children, with 54.0% of providers located in high SVI areas. COVID-19 first-dose vaccination coverage rates were low, particularly in high SVI areas, but showed improvement over time: at 4 weeks after the program launch, first-dose vaccination coverage was 32.0% lower in children in high than in low SVI counties, and at 11 weeks after the program launch, this gap between high and low SVI area coverage was reduced to 24.0%. Ongoing efforts are critical to improving vaccination coverage among all children aged 5–11 years and reducing coverage disparities. Experiences gained through this program can be used to guide COVID-19 vaccine planning for children aged <5 years pending expansion of COVID-19 vaccine recommendations for this age group. Specifically, planning could consider vaccine supply, vaccine formulation (i.e., shelf life or doses per vial), fewer vaccinations provided in pharmacies, preferred vaccination locations in communities, community risk, vulnerability, and geography.

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SARS-CoV-2 Incidence in K–12 School Districts with Mask-Required Versus Mask-Optional Policies — Arkansas, August–October 2021

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Masks are effective at limiting transmission of SARS-CoV-2, the virus that causes COVID-19 (*1*), but the impact of policies requiring masks in school settings has not been widely evaluated (*2–4*). During fall 2021, some school districts in Arkansas implemented policies requiring masks for students in kindergarten through grade 12 (K–12). To identify any association between mask policies and COVID-19 incidence, weekly school-associated COVID-19 incidence in school districts with full or partial mask requirements was compared with incidence in districts without mask requirements during August 23–October 16, 2021. Three analyses were performed: 1) incidence rate ratios (IRRs) were calculated comparing districts with full mask requirements (universal mask requirement for all students and staff members) or partial mask requirements (e.g., masks required in certain settings, among certain populations, or if specific criteria could not be met) with school districts with no mask requirement; 2) ratios of observed-to-expected numbers of cases, by district were calculated; and 3) incidence in districts that switched from no mask requirement to any mask requirement were compared before and after implementation of the mask policy. Mean weekly district-level attack rates were 92–359 per 100,000 persons in the community* and 137–745 per 100,000 among students and staff members; mean student and staff member vaccination coverage ranged from 13.5% to 18.6%. Multivariable adjusted IRRs, which included adjustment for vaccination coverage, indicated that districts with full mask requirements had 23% lower COVID-19 incidence among students and staff members compared with school districts with no mask requirements. Observed-to-expected ratios for full and partial mask policies were lower than ratios for districts with no mask policy but were slightly higher for districts with partial policies than for those with full mask policies. Among districts that switched from no mask requirement to any mask requirement (full or partial), incidence among students and staff members decreased by 479.7 per 100,000 ($p<0.01$) upon implementation of the mask policy. In areas with high COVID-19 community levels, masks are an important part of a multicomponent prevention strategy in K–12 settings (*5*).

COVID-19 incidence among K–12 students and staff members in Arkansas public school districts with different mask policies was investigated during August 23–October 16, 2021. Mask policies were defined as follows: 1) full (universal mask requirement for all students and staff members)†; 2) partial (masks required in certain settings [e.g., in classrooms but not in gym or music class], among certain populations [e.g., only certain grades, only students or staff members, or only unvaccinated persons], or if specific criteria [e.g., physical distancing ≥6 feet]) could not be met); and 3) none (masks not required in the school setting). Consistent with a Federal Order in place during the investigation period, all persons were required to wear masks while on school buses (*6*).

District-level data were compiled from the Arkansas Department of Health's (ADH's) COVID-19 surveillance database and immunization registry, Arkansas Center for Health Improvement's mask policy database, and Arkansas Department of Education's 2021–22 enrollment and 2019 free or reduced-cost school lunch databases. Four districts (2%) were excluded, including three serving special needs populations (blind, deaf, and incarcerated persons) and 1 year-round district.§

Data were analyzed using three different approaches: 1) IRRs and 95% CIs were used to compare districts with full or partial mask requirements to those with no mask

* Community attack rates were based on the weekly number of cases in the school district, minus the weekly number of cases among staff members or students during the same period. Denominators were calculated based on the population for each school district, minus the district student and staff member 2021–22 enrollment.

† Outdoor mask use requirements and mask requirements for student athletes who were actively participating in extracurricular sports were not considered when categorizing school district mask policies into full, partial, or none. Arkansas Department of Health guidance during the investigation period stated that outdoor masking was "not generally necessary" unless conditions were crowded.

§ Schools that serve blind, deaf, and incarcerated populations generally offer or require boarding, which might increase the risk for SARS-CoV-2 transmission. The year-round school district was excluded because its schedule was not comparable with other public school districts in Arkansas.

requirements[¶]; 2) ratios of observed-to-expected numbers of cases were estimated by district (given the underlying weekly community COVID-19 incidence)[**] using negative binomial generalized estimating equation models with autoregressive correlation structure; and 3) associations between mask policy and COVID-19 incidence were estimated using a comparative interrupted time series model among students and staff members in a subset of 26 districts[††] that began the school year without a mask requirement and subsequently transitioned to full or partial mask requirements.[§§]

District-level mask policies[¶¶] (the exposure) were included in analyses based on the policy in place 1 week before school-associated COVID-19 incidence (the outcome) was measured.[***] IRRs and ratios of observed-to-expected case numbers were adjusted for district-wide weekly COVID-19 non–school-associated (community) attack rates, district-wide weekly staff member and student vaccination coverage,[†††] and the proportion of students receiving free or reduced-cost school lunches (as a proxy for socioeconomic status and educational disadvantage) (*7*). Weekly district-level vaccination coverage rates among students and staff members were calculated from the ADH immunization registry, which was matched to school district enrollment and staffing data based on name and date of birth. Sensitivity analyses were also conducted to evaluate the impact of varying lag times between the exposure and outcome and to investigate variations by grade level and vaccine eligibility.[§§§] Statistical analyses were completed with SAS (version 9.4; SAS Institute). Statistical significance was defined as p<0.05. This project was reviewed and approved by ADH and CDC and was conducted consistent with applicable federal law and CDC policy.[¶¶¶]

During the investigation, statewide COVID-19 community transmission levels declined from substantial to moderate, and vaccination coverage increased.[****] Among 233 included public school districts, 30%, 21%, and 48% had full, partial, or no mask policies, respectively, at baseline (August 22–28, 2021). Mean weekly district-level COVID-19 incidence among students and staff members was consistently higher than community incidence and decreased over time from 745 per 100,000 (August 29–September 4) to 137 per 100,000 (October 10–16); mean weekly school district level student and staff member vaccination coverage increased from 13.5% to 18.6% during the same period. COVID-19 incidence among students and staff members was 23% lower in districts with full

[¶] Models used an autoregressive correlation structure of order 1 with a log population offset. The negative binomial generalized estimating equation model for the effect of mask policy (A) on COVID-19 incidence rates (C^s_{ij}/N^s_i) among students/staff members, adjusted for confounders is $ln(C^s_{ij}) = ln(N^s_i) + \beta_0 + \beta_1 A_{1,i,j-1} + \beta_2 A_{2,i,j-1} + \beta_3 J + \beta_4 lnR^c_{i,j-1} + \beta_5 V_{i,j-1} + \beta_6 L_i$ where school district $i = 1, 2, 3, ..., 233$; week $j = 2, 3, ..., 8$; observed cases in school district i and week j are given by C^s_{ij} ; community incidence rate in school district i and week j is given by R^c_{ij}; N^s_i is school district staff member and student population for school district i; A_1 and A_2 are full and partial mask policies; V is a vector representing categorical weekly vaccination coverage among students and staff members; L is a vector representing time-fixed categorical proportions of students receiving free or reduced-cost lunches during 2019.

[**] The expected number of cases for school district i during week j was estimated as follows: community cases in school district i and week j are given by C^c_{ij}; population estimates for the school district and community are given by N^s_{ij}, and N^c_{ij}, respectively. The expected number of cases for school district i and week j is given by $E^s_{ij} = N^s_{ij}\ (((C^c_{ij-1} + C^c_{ij})/2)/N^c_{ij})$, where the community cases for a given week is a 2-week moving average of cases during the same week as the school cases and cases during the preceding week. The estimates of observed-to-expected numbers of cases by school district i and week j for modeling are given by $\gamma^s_{ij} = C^s_{ij}/E^s_{ij}$. The base model is given by $ln(C^s_{ij}) = ln(E^s_{ij}) + \beta_0 + \beta_1 A_{1,i,j-1} + \beta_2 A_{2,i,j-1} + \beta_3 J + \beta^5 V_{i,j-1} + \beta_6 L_i$.

[††] Twenty-six included districts represented urban and rural counties and were from each of Arkansas' five public health regions, with an average enrollment of 1,130 students.

[§§] School weeks were standardized to align the comparative interrupted time series (CITS) cut point (time zero) with the transition of mask policy from no masks required to a full or partial mask requirement. The cut point represents the week that any mask requirement was implemented, and the first weekly incidence under a mask requirement policy was measured during the following week. CITS first estimates baseline (i.e., before mask policy) linear trends in the dependent variable (weekly school-associated COVID-19 incidence) and separately, weekly community incidence. CITS then compares post-mask implementation policy period deviations for each group from those baseline trends. Consistent with models 1 and 2, an autoregressive (order 1) covariance structure was specified to incorporate 1-week lags between mask policy and COVID-19 incidence. Formally, the following regression specification was estimated using ordinary least-squares and standard errors: $y_t = \beta_0 + \beta_1 \tau_t + \beta_2 Post_t + \beta_3 (\tau_t \times Post_t) + \beta_4 Treat + \beta_5 (\tau_t \times Treat) + \beta_6 (Treat \times Post_t) + \beta_7 (\tau_t \times Treat \times Post_t) + \varepsilon_t$ where y_t is the COVID-19 infection rate per 100k during standardized week τ_t, where t is an index for equally spaced time point. *Treat* is an indicator that is equal to 1 for the school (i.e., the treatment group) and zero for the community; *Post* is an indicator for post-mask policy implementation. The interaction term $(\tau_t \times Treat)$ is a group-specific time trend that establishes separate baseline linear trends for school-associated and community COVID-19 incidence. The interaction term $(\tau_t \times Post_t)$ is a change in postintervention time trend that differentiates linear trends pre- and postimplementation of mask requirement policy. Finally, the interaction terms $(Treat \times Post_t)$ provide estimates of changes in incidence rates between mask policy implementation weeks in the sample and baseline trends. These three interaction terms were used to determine whether pre- to postimplementation period changes in incidence rates differed for those who were directly affected by the policy change (i.e., staff members and students) and those who resided in the same community but were not directly affected by the mask policy.

[¶¶] Some school boards based mask policies on locally available COVID-19 data. Policies were reevaluated weekly, monthly, or on an ad hoc basis, depending on the district.

[***] For districts with mask policies that changed midweek, if the policy change occurred on Wednesday or later, the change was applied to the following week.

[†††] District-wide weekly COVID-19 non–school-associated (community) attack rates and student and staff member vaccination rates varied from week to week. Variables included in the analysis were based on the measurement the week before weekly student and staff member COVID-19 incidence (the outcome) was measured.

[§§§] Analyses were stratified by vaccine eligibility because vaccination coverage data were not available at the school level.

[¶¶¶] 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C.0 Sect.552a; 44 U.S.C. Sect. 3501 et seq.

[****] COVID-19 incidence declined during the investigation period across the state, from a 7-day average high of 74.3 per 100,000 (substantial transmission = 50–99.99 cases per 100,000) on August 25, 2021, to 19.7 (moderate transmission = 10–49.99 cases per 100,000) on October 16, 2021. Vaccination rates across the state increased during the investigation period from 40% to 46.8%. https://covid.cdc.gov/covid-data-tracker/#datatracker-home

mask policies than in districts with no mask policy (IRR = 0.77 [95% CI = 0.66–0.88]), 24% lower among staff members only (IRR = 0.76 [95% CI = 0.64–0.90]), and 23% lower among students only (IRR = 0.77 [95% CI = 0.66–0.89]) (Table). IRRs comparing districts with partial mask policies with those with no mask policy were not statistically significant (IRR = 0.88 [95% CI = 0.77–1.01] for students and staff members, 0.85 [95% CI = 0.71–1.02] for staff members only, and 0.89 [95% CI = 0.77–1.03] for students only).

Ratios comparing observed-to-expected cases among students and staff members exceeded 1.0 for all groups (students only, staff members only, and combined students and staff members) and mask policies (Figure 1) (Supplementary Figure, https://stacks.cdc.gov/view/cdc/115046). The ratios of observed-to-expected cases for school districts with full mask policies for students only (1.50; 95% CI = 1.33–1.70); staff members only (1.69; 95% CI = 1.35–2.07) and combined students and staff members (1.52; 95% CI = 1.35–1.72) were lower than the ratios for no mask policy (students only: 2.06 [95% CI = 1.86–2.26]; staff members only: 2.44 [95% CI = 2.02–2.90]; combined students and staff members: 2.10 [95% CI = 1.92–2.30]. Observed-to-expected ratios for school districts with partial mask policies were also lower than ratios for no mask policies, but slightly higher than those in districts with full mask policies.

Among 26 districts that switched from no mask policy to any policy (full or partial) during the investigation, COVID-19 incidences for student and staff members were higher than those in the community during the period with no mask policy (estimated difference at baseline = 891.8 per 100,000, p<0.01). However, a week after implementation of a mask policy, the incidence among students and staff members decreased significantly (estimated point reduction in incidence = 479.7 per 100,000; p<0.01). Although the incidence among community members decreased at the same time (estimated point reduction in community incidence = 104.6 per 100,000, p<0.01), there was a significantly higher rate of reduction in incidence among students and staff members compared with that in community members (estimated difference in point reduction = 375.0 per 100,000; p<0.01) (Figure 2).

Sensitivity analyses demonstrated consistent findings. Analyses with 0-, 2-, and 3-week lag times were consistent with the initial analysis. Stratification by school level (grades K–5, 6–8, and 9–12) did not change the main results (Table). Adjusted student estimates stratified by vaccine-eligible (grades 7–12) and -ineligible (K–6) grade levels did not significantly differ from the unstratified estimates. Among vaccine eligible-grades, IRRs decreased with increasing student vaccination coverage. IRRs standardized to the surrounding community incidence were consistent with reported IRRs.

TABLE. Estimated incidence rate ratios comparing weekly COVID-19 case incidence in kindergarten through grade 12 school districts with mask requirements to those without mask requirements — 233 school districts, Arkansas, August–October 2021

Group/School district mask policy	Adjusted IRR (95% CI)
Overall*	
None†	Ref.
Full†	0.77 (0.66–0.88)
Partial†	0.88 (0.77–1.01)
Among staff members*	
None	Ref.
Full	0.76 (0.64–0.90)
Partial	0.85 (0.71–1.02)
Among students*	
None	Ref.
Full	0.77 (0.66–0.89)
Partial	0.89 (0.77–1.03)
Grades K–5§	
None	Ref.
Full	0.78 (0.66–0.92)
Partial	0.88 (0.75–1.03)
Grades 6–8§	
None	Ref.
Full	0.69 (0.57–0.83)
Partial	0.83 (0.69–1.01)
Grades 9–12§	
None	Ref.
Full	0.68 (0.57–0.83)
Partial	0.79 (0.65–0.95)
School district student vaccination coverage, % (N)¶,**	
<10 (6–30)	Ref.
10–19 (29–101)	1.08 (0.80–1.46)
20–29 (72–75)	1.03 (0.77–1.39)
30–39 (22–69)	0.80 (0.58–1.11)
≥40 (8–54)	0.62 (0.44–0.87)

Abbreviations: IRR = incidence rate ratio; K = kindergarten; Ref. = reference group.

* Models were adjusted for week of school, COVID-19 incidence in the community during the preceding week, staff member and student vaccination rate in the previous week, and percentage of students in the district receiving free or reduced-cost lunch in 2019.

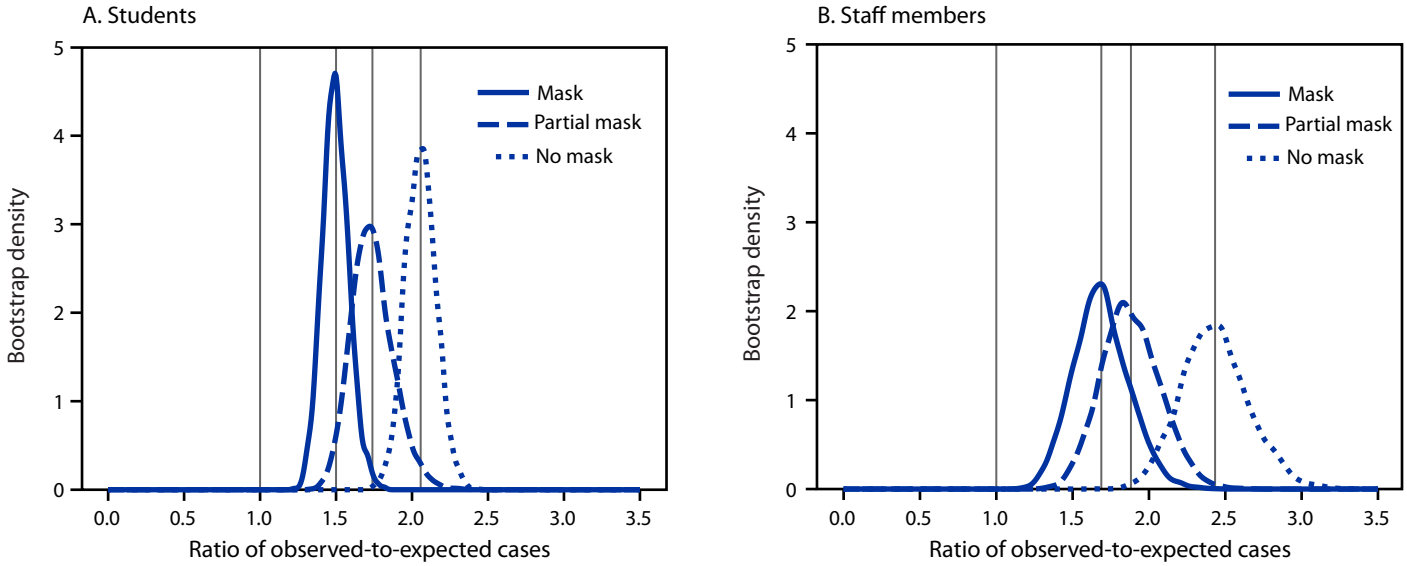
† Mask policies were defined as follows: 1) full (universal mask requirement for all students and staff members); 2) partial (masks required in certain settings [e.g., in classrooms but not in gym or music class], among certain populations [e.g., only certain grades, only students or staff members, or only unvaccinated persons], or if specific criteria [e.g., physical distancing >6 feet] could not be met); and 3) none (masks not required in the school setting).

§ Models were adjusted for week of school, COVID-19 incidence in the community during the preceding week, and percentage of students in the district receiving free or reduced-cost lunch during 2019. Grade level–stratified models were not adjusted for vaccination coverage because students in grades K–5 were not eligible for vaccination, and estimates were stratified to allow for comparison across grade levels.

¶ Number of districts in each category varied over time, and N is shown as range over the course of the investigation.

** Among students in vaccine-eligible grades only (grades 7–12). Compared with <10% of district students vaccinated as the referent category. Models adjusted for mask policy, week of school, COVID-19 incidence in the community during the preceding week, and percentage of students in the district receiving free or reduced-cost lunch during 2019.

FIGURE 1. Mean estimates* of the ratio of observed school district cases to expected school district cases among students (A) and staff members (B), based on surrounding community incidence, by mask requirement status — 233 school districts, Arkansas, August–October 2021



* The mean estimates were calculated by drawing 5,000 random bootstrap samples from the dataset and averaging over all school districts with the same mask policy within each sample. The reference line at 1.0 implies that the school district incidence equals the community incidence. Vertical lines for each mask policy are the means for the 5,000 bootstrap samples and illustrate the difference of the group's mean relative to the reference line. For example, the student and staff member mask group means are 1.50 and 1.69, which indicates that the mean incidences among students and staff members in school districts with mask requirements are 50% and 69% higher, respectively, than the mean incidence in their surrounding communities.

Discussion

During August–October 2021, public school districts in Arkansas with full or partial mask requirements had lower incidences of COVID-19 among students and staff members than did districts without mask requirements. Strengths of this investigation include the use of multiple analyses, and sensitivity analyses, with the protective effect of mask use holding across all analyses, including within districts that switched from no mask policy to any mask policy during the investigation period. Universal mask use, in coordination with other prevention strategies such as vaccination of students and staff members in K–12 schools, remains an important tool for preventing SARS-CoV-2 transmission (*8*).

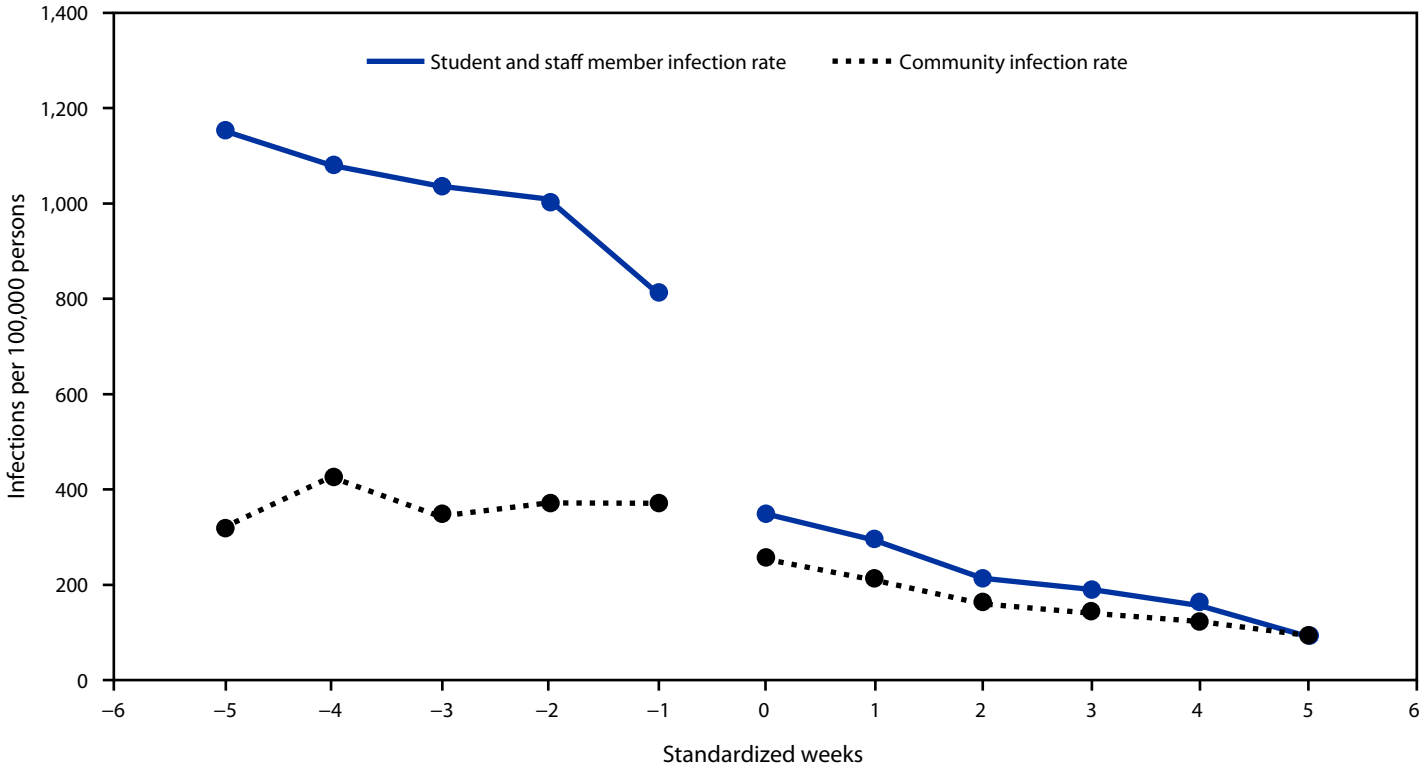
On average, in the studied school districts, weekly COVID-19 incidences among students and staff members were higher than those in the surrounding communities; observed numbers of student and staff member cases were higher than expected based on community incidences for all mask policies. This highlights the potential for incidence within schools to be higher than that in communities in settings where community transmission levels are moderate to substantial and where the majority of students are unvaccinated. Expected numbers of school cases were calculated based on the assumption that cases in the wider community were as likely to be identified and reported as were those among students and staff members. Testing access was similar across the state, and there were no school-based testing programs in place during the investigation period.[††††]

The findings in this report are subject to at least five limitations. First, this was an ecologic study, and data on ventilation and other community and school-based prevention efforts were not available for inclusion in the analysis. However, surrounding community incidence was included in all analyses as a proxy for community-level factors (such as testing intensity) that could influence transmission or case identification that were not otherwise accounted for. Second, compliance with an existing mask policy was not directly observed or otherwise evaluated; however, noncompliance with mask policies would bias results toward the null. Third, quarantine rules differed for schools with and without mask requirements.[§§§§]

[††††] Arkansas Department of Health recommended that exposed or symptomatic persons (including students and school staff members) get tested during the investigation period. However, there were no school surveillance testing programs nor test to stay programs in place during this time.

[§§§§] Close contacts were defined as persons who were within 6 feet of a person with confirmed COVID-19 for ≥15 minutes within a 24-hour period. According to state guidance, school-associated close contacts were not required to quarantine if the person with COVID-19 and the close contact were masked during exposure, or if the close contact was fully vaccinated or had been infected with COVID-19 within the past 90 days. The close contact definition and the quarantine policy did not change during the investigation period.

FIGURE 2. Student and staff member and community SARS-CoV-2 infection rates before and after* implementation of school mask requirement — 26 school districts, Arkansas, August–October 2021



* Weeks were standardized to align the time before (negative values) and after (positive values) the district changed from no mask requirement to partial or full mask requirement. Time zero indicates the week the policy changed from none to full or partial mask requirement, and the first weekly incidence under a mask requirement policy was measured during the following week. Upon implementation of the mask policy, the incidence among students and staff members decreased by 479.7 per 100,000. Incidence among community members decreased at the same time by 104.6 per 100,000, a difference of 375.0 per 100,000.

Students in schools with mask requirements were less likely to be quarantined than were their unmasked counterparts, also potentially biasing IRRs toward the null. Fourth, the pre- and postimplementation of mask policy analysis in a subset of 26 school districts could not separately investigate the impact of full and partial mask policies because of small sample sizes. Finally, data were obtained during a period of B.1.617.2 (Delta) variant predominance and might not be reflective of the current period of B.1.1.529 (Omicron) variant predominance; similar investigations could be beneficial as new variants arise.

This investigation indicates that school mask policies were associated with lower COVID-19 incidence in areas with moderate to substantial community transmission. Masks remain an important part of a multicomponent approach to preventing COVID-19 in K–12 settings, especially in communities with high COVID-19 community levels (*5*).

Summary

What is already known about this topic?

Masks are an important part of a multicomponent prevention strategy to limit transmission of SARS-CoV-2. Some school jurisdictions required masks in K–12 schools for fall 2021, while others did not.

What is added by this report?

In Arkansas during August–October 2021, districts with universal mask requirements had a 23% lower incidence of COVID-19 among staff members and students compared with districts without mask requirements.

What are the implications for public health practice?

Masks remain an important part of a multicomponent approach to prevent COVID-19 in K–12 settings, especially in communities with high levels of COVID-19.

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Notes from the Field

Congenital Varicella Syndrome Case — Illinois, 2021

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On April 8, 2021, a newborn was delivered at 24 weeks' gestation with congenital varicella syndrome, after maternal varicella was diagnosed at 12 weeks' gestation. At 22 weeks' gestation, an ultrasound identified a multitude of fetal abnormalities (Box); congenital varicella syndrome was confirmed by a positive varicella-zoster virus (VZV) polymerase chain reaction test of the amniotic fluid. Because the prognosis of the fetus was poor, a decision was made to induce labor. At delivery, the newborn had a heart rate of 60 beats/minute, an Apgar score of 1, and weighed 526 g; the newborn died approximately 15 minutes after delivery. After birth, neither additional VZV testing nor an autopsy was performed.

The mother, aged 27 years, was born outside the United States and had no documented history of varicella disease or vaccination. She was healthy with no remarkable past medical history. She initiated routine prenatal care at 5 weeks and 6 days' gestation; serum collected at that time was VZV immunoglobulin (Ig) G equivocal. At 12 weeks and 5 days' gestation, she developed a maculopapulovesicular rash and received a diagnosis of varicella from her health care provider. Serologic testing for VZV IgM was positive. The source of exposure was unknown. The mother worked in a large retail store. Her older child, a boy aged 2 years, had received 1 dose of varicella vaccine in 2019 at age 1 year. He did not have a known rash near the time his mother developed varicella. Birth of this older child occurred in a different state, and records were not available for review. It is not known whether the mother was assessed for varicella immunity during her previous pregnancy.

Before the introduction of routine childhood varicella vaccination in 1995, approximately 4 million cases, 10,500–13,500 hospitalizations, and 100–150 deaths from varicella occurred annually in the United States (*1*). The U.S. varicella vaccination program has reduced the incidence of varicella by >90%, as well as community transmission of VZV.* However, this case illustrates that severe consequences of VZV infection might occur and underscores the importance of vaccination. Congenital varicella syndrome can lead to severe birth defects, including hypoplasia of an extremity, microcephaly, skin and ocular abnormalities, intellectual disability, and low birth weight (*1*). This syndrome is estimated to occur among 0.4%–2.0% of newborns born to women who develop varicella during the first or second trimester of pregnancy (*1*). Because most women of childbearing age are immune to VZV, congenital varicella syndrome is rare. Before introduction of the varicella vaccine, approximately 44 cases of congenital varicella syndrome were estimated to have occurred annually in the United States (*1*). This is the third reported case of congenital varicella syndrome in the United States since the varicella vaccination program started in 1995 (*2*) (J Leung and M Marin, CDC, unpublished data, 2021); however, underreporting is possible because congenital varicella cases are not nationally notifiable. An Australian study documented reduction in the incidence of congenital varicella syndrome after implementation of universal varicella vaccination of children at age 18 months (*3*).

This case reaffirms current Advisory Committee on Immunization Practices recommendations for preventing varicella that all adults be assessed for varicella immunity, and that those who do not have evidence of immunity† should receive 2 doses of varicella vaccine, with special emphasis for adult groups at high risk, including nonpregnant women of childbearing age (*1*). Among non–U.S.-born adults, birth before 1980 is not considered evidence of varicella immunity because of the higher likelihood of these adults to be susceptible to varicella, especially those from tropical climates (*1*,*4*). All pregnant women should have prenatal assessment for varicella evidence of immunity, and postpartum vaccination should be recommended for susceptible women. It is important to assess and assure documentation of evidence of immunity with each pregnancy, in advance of future pregnancies. If susceptible pregnant women are exposed to VZV, varicella-zoster immune globulin (VariZIG) is recommended to prevent severe maternal disease and should be administered within 10 days of exposure (*5*); whether this step modifies infection in the fetus is uncertain although some evidence suggests that it might be beneficial for the fetus. This intervention is effective only if an exposure is identified.

This case of congenital varicella syndrome is a reminder that varicella during pregnancy can cause severe outcomes and underscores the importance of assessing varicella immunity in adults, vaccinating nonimmune persons, as well as prenatal assessment and postpartum vaccination of susceptible women against varicella.

* https://www.cdc.gov/vaccines/pubs/surv-manual/chpt17-varicella.html (Accessed March 25, 2021).

† Evidence of immunity to varicella includes 1) documentation of age-appropriate varicella vaccination, 2) laboratory evidence of immunity or confirmation of disease, 3) diagnosis or verification of a history of varicella or herpes zoster by a health care provider, and 4) birth in the United States before 1980. The last criterion is based on serologic evidence of VZV infection documented in most U.S. adults born before 1980. Birth in the United States before 1980 is not adequate evidence of immunity for health care workers, pregnant women, or persons with weakened immune system; these persons need to meet one of the other criteria for evidence of immunity.

BOX. Timeline for congenital varicella syndrome case, by date and gestational age* — Illinois, 2021

December 2, 2020 (gestational age: 5 weeks, 6 days)
- Pregnant woman (patient) initiated routine prenatal care.
- Baseline maternal laboratory test result showed serology for VZV IgG antibodies was equivocal (value <135 [reference value for positive VZV >185]), rubella immune, and the rapid plasma reagin was non-reactive.
- Genetic screening results were negative for trisomy 13, 18, 21, and sex chromosome aneuploidy.

December 3, 2020 and December 17, 2020 (gestational age: 6 weeks, 0 days and 8 weeks, 0 days)
- Ultrasound was performed to estimate gestational age because of discrepancy with LMP.
- Estimated delivery date using LMP was June 30, 2021 and by ultrasound was July 29, 2021.
- There was no information collected on fetal characteristics from either ultrasound.

January 19, 2021 (gestational age: 12 weeks, 5 days)
- Patient reported onset of skin rash.
- There was no evidence of household contacts with rash illness or known source of transmission.

January 21, 2021 (gestational age: 13 weeks, 0 days)
- Patient visited her primary care provider and was clinically diagnosed with varicella. She had a generalized maculopapulovesicular rash with 250–499 lesions on arms, face, head, trunk, and legs; no complications were noted. It is unknown whether the patient visited an obstetrician at this time.
- Symptomatic treatment was provided; no antivirals were administered.
- Serology test result for VZV IgM was positive.

February 9, 2021 (gestational age: 15 weeks, 5 days)
- Patient visited obstetrician for routine appointment; varicella skin lesions had resolved.

March 8, 2021 (gestational age: 19 weeks, 4 days)
- Ultrasound showed incomplete visualization of fetal anatomy.

March 25, 2021 (gestational age: 22 weeks, 0 days)
- Patient consulted a maternal fetal medicine specialist because of her diagnosis of varicella during pregnancy.
- Ultrasound result showed fetal abnormalities, including abnormal profile (small chin and suspected orbit anomaly), absent cavum septum pellucidum, left orbit/lens abnormality, abnormal flexion of arms and legs with no movement, complex cardiac defect, and echogenic bowel; the fetus's abdominal cord insertion and sex identification was suboptimal. The estimated fetal weight was low at 408 g (13th percentile).
- Amniocentesis result showed amniotic fluid specimen was positive for VZV by polymerase chain reaction. Test results were negative for cytomegalovirus, toxoplasmosis, and parvovirus.
- No genetic studies were performed at patient's request because of amniocentesis confirming congenital varicella syndrome.

April 8, 2021 (gestational age: 24 weeks, 0 days)
- Labor was induced.
- Infant was born with a heart rate of 60 beats/minute, an Apgar score of 1, and weighing 526 g; newborn died approximately 15 minutes after delivery.
- Antibody screening showed newborn was negative for direct antiglobulin IgG.
- Placenta pathology results showed fetal membranes with mild chronic subchorionic inflammation, singleton placental disc (131g); premature/second trimester chorionic villi with scattered intervillous fibrin aggregates and associated mild chronic lymphocytic and mononucleate infiltrates, which focally extended to the adjacent villi.
- No additional laboratory testing nor autopsy was performed on the newborn after birth.

Abbreviations: LMP = last menstrual period; IgG = immunoglobin G; IgM = immunoglobin M; VZV = varicella-zoster virus.
*Gestational age estimated using an estimated delivery date of July 29, 2021, based on ultrasound.

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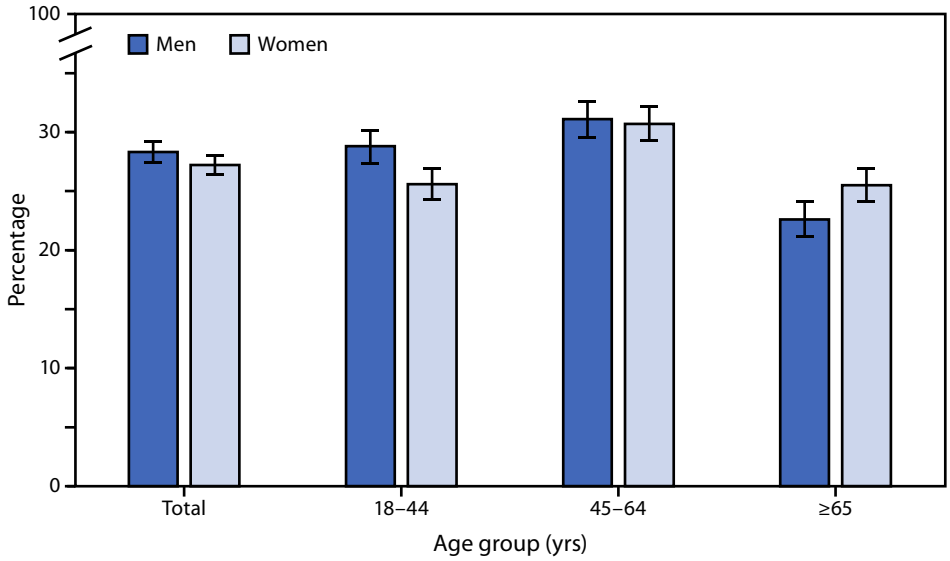
QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Percentage* of Adults Aged ≥18 Years Who Sleep <7 Hours on Average in a 24-Hour Period,† by Sex and Age Group — National Health Interview Survey,§ United States, 2020



* With 95% CIs indicated by error bars.
† Determined by the number of hours indicated in respondents' answers to the questionnaire item asking, "On average, how many hours of sleep do you get in a 24-hour period?" Respondents were instructed to round to the nearest whole hour.
§ Estimates are based on household interviews of a sample of the civilian, noninstitutionalized U.S. population.

Overall, 28.3% of men and 27.2% of women aged ≥18 years slept <7 hours on average within a 24-hour period. Among persons aged 18–44 years, men (28.8%) were more likely to sleep <7 hours compared with women (25.6%). Among adults aged 45–64 years, the percentage was similar for men (31.1%) and women (30.7%). However, among those aged ≥65 years, women (25.5%) were more likely than men (22.6%) to sleep <7 hours.

Source: National Center for Health Statistics, National Health Interview Survey, 2020. https://www.cdc.gov/nchs/nhis/index.htm

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