Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 71 / No. 31
August 5, 2022

Outbreaks of Acute Gastrointestinal Illness Associated with a Splash Pad in a Wildlife Park — Kansas, June 2021

Samaria K. Aluko, MPH[1,2,*]; Syed S. Ishrati, MD[3,*]; David C. Walker, MS[1]; Mia C. Mattioli, PhD[1]; Amy M. Kahler, MS[1]; Kayla L. Vanden Esschert, MPH[1]; Kaylee Hervey, MPH[4]; Justin Rokisky Jr., MPH[2,5]; Mary E. Wikswo, MPH[6]; Joseph P. Laco, MSEH[5]; Sonalli Kurlekar, MPH[4]; Adrienne Byrne, MS[4]; Noelle-Angelique Molinari, PhD[1]; Michelle E. Gleason, MPH[1]; Christine Steward, MPH[4]; Michele C. Hlavsa, MPH[1]; Daniel Neises, MPH[3]

In June 2021, Kansas state and county public health officials identified and investigated three cases of shigellosis (a bacterial diarrheal illness caused by *Shigella* spp.) associated with visiting a wildlife park. The park has animal exhibits and a splash pad. Two affected persons visited animal exhibits, and all three entered the splash pad. Nonhuman primates are the only known animal reservoir of *Shigella*. The splash pad, which sprays water on users and is designed so that water does not collect in the user area, was closed on June 19. The state and county public health codes do not include regulations for splash pads. Thus, these venues are not typically inspected, and environmental health expertise is limited. A case-control study identified two distinct outbreaks associated with the park (a shigellosis outbreak involving 21 cases and a subsequent norovirus infection outbreak involving six cases). *Shigella* and norovirus can be transmitted by contaminated water; in both outbreaks, illness was associated with getting splash pad water in the mouth (multiply imputed adjusted odds ratio [aOR_{MI}] = 6.4, p = 0.036; and 28.6, p = 0.006, respectively). Maintaining adequate water disinfection and environmental health expertise and targeting prevention efforts to caregivers of splash pad users help prevent splash pad–associated outbreaks. Outbreak incidence might be further reduced when U.S. jurisdictions voluntarily adopt CDC's Model Aquatic Health Code (MAHC) recommendations and through the prevention messages: "Don't get in the water if sick with diarrhea," "Don't stand or sit above the jets," and "Don't swallow the water."†

On June 18, 2021, the Kansas Department of Health and Environment (KDHE) notified CDC of three cases of shigellosis associated with visiting the wildlife park. Because splash pads are not typically regulated, and thus not inspected, the capacity to identify factors contributing to outbreaks associated with such venues is also limited. KDHE and Sedgwick County Health Department (SCHD) consulted with CDC on the outbreak investigation, which included a case-control study that identified 21 shigellosis cases in respondents who visited the wildlife park on June 11 and six norovirus infection cases in respondents who visited the park 1 week later, on June 18.

INSIDE

Continuing Education examination available at https://www.cdc.gov/mmwr/mmwr_continuingEducation.html

*These authors contributed equally to this report.
† https://www.cdc.gov/healthywater/swimming/swimmers/water-play-areas-interactive-fountains.html

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Clinical Laboratory and Epidemiologic Investigation

In Kansas, shigellosis is reportable, and patients are interviewed using standard case investigation forms. The initial investigation identified eight patients with shigellosis who reported entering the splash pad on June 11 and who all experienced signs and symptoms 12–73 hours later. Two of the eight patients had stool cultures positive for *Shigella flexneri* type 1; whole genome sequencing found no base pair differences between the two isolates. The remaining six patients had stool specimens tested using multiplex polymerase chain reaction and were positive for the *Shigella*/enteroinvasive *Escherichia coli* target (*ipaH* gene). Two of these six patients also had specimens that tested positive for the Shiga toxin target (stx_1/stx_2 genes); however, neither stool culture yielded Shiga toxin–producing *E. coli*.

KDHE and the wildlife park, through press releases and Facebook posts, encouraged patrons who visited the park during the period from the seasonal opening day (May 28) through June 19 to voluntarily complete an online outbreak questionnaire during July 12–August 4. The questionnaire requested information on demographic characteristics, activities during wildlife park visits, and signs and symptoms of respondents who experienced gastrointestinal illness (case-patients). Participants who did not experience gastrointestinal illness were considered control respondents.

Summary statistics and bivariate analyses assessed potential exposures. Where item nonresponse was present, missing values were multiply imputed[§] (*1*,*2*). Unadjusted and adjusted odds ratios and CIs were estimated using Firth penalized maximum likelihood logistic regression (*3*), which can mitigate bias due to rare events. Multiply imputed analyses were compared with complete case analyses. All statistical analyses were conducted in R (version 4.1.3, R Foundation). This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.[¶]

Analysis of data from 404 respondents who only visited the park once during May 28–June 19 identified two distinct outbreaks (Figure 1). Among 72 respondents[**] who visited on June 11, 21 (29%) experienced illness meeting the shigellosis case definition (three or more loose stools in 24 hours with onset 12–73 hours after visiting the wildlife park on June 11).

[§] Missing values were multiply imputed 60 times using chained equations. CIs were calculated using penalized profile likelihood for complete case analysis and a combination of likelihood profiles for multiply imputed analyses.

[¶] 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.

[**] Data were excluded from analysis for respondents when the question asking respondents if they became ill after visiting the wildlife park was unanswered (five); they became ill after visiting the wildlife park but did not know if they experienced gastrointestinal symptoms (two); or the illness was determined to be a secondary case (one). One patient, who entered the splash pad on June 11 and had at least supportive laboratory evidence of *Shigella* detection, did not participate in the case-control study.

The *MMWR* series of publications is published by the Center for Surveillance, Epidemiology, and Laboratory Services, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30329-4027.

Suggested citation: [Author names; first three, then et al., if more than six.] [Report title]. MMWR Morb Mortal Wkly Rep 2022;71:[inclusive page numbers].

The median ages of shigellosis case-patients and controls[††] were 5 years (range = 1–15 years) and 11 years (range = 1–70 years), respectively (p<0.01).[§§] Both case-patients and controls were predominantly female (62% and 67%, respectively). Playing in the splash pad water was not associated with illness; however, getting splash pad water in the mouth was associated with illness (multivariate complete case adjusted odds ratio [aOR_C] = 10.2, p = 0.007; aOR_{MI} = 6.4, p = 0.036) (Table) (Figure 2). Touching or feeding lemurs (the only nonhuman primates available for patron interaction) was not associated with illness. Three case-patients were hospitalized for an average of 3 days; no deaths were reported.

Among 27 respondents[¶¶] who visited the wildlife park on June 18, six (22%) experienced illness meeting the norovirus infection case definition (vomiting or three or more loose stools in 24 hours with onset 12–56 hours after visiting the wildlife park on June 18). Responses for three case-patients indicated a health care provider diagnosed norovirus infection. The median ages of norovirus infection case-patients and controls[***] were 5 years (range = 1–38 years) and 20 years (range = 3–63 years), respectively (p = 0.04). Case-patients and controls were predominantly female (83% and 68%, respectively). All six case-patients played in the splash pad water and got the splash pad water in their mouths (Figure 2). Getting splash pad water in the mouth was associated with illness (aOR_C = 24.1, p = 0.007; aOR_{MI} = 28.6, p = 0.006). One case-patient was hospitalized for 1 day; no deaths were reported.

Environmental Microbiology Laboratory and Environmental Health Investigation

The wildlife park's unregulated splash pad included jets, tipping buckets, and slides. SCHD worked with the splash pad operator and CDC to identify potential factors contributing to the outbreaks. Water stood in the collection tank (into which water drains after spraying users and before it is filtered, disinfected, and resprayed) overnight instead of being continuously recirculated, filtered, and chlorinated. The

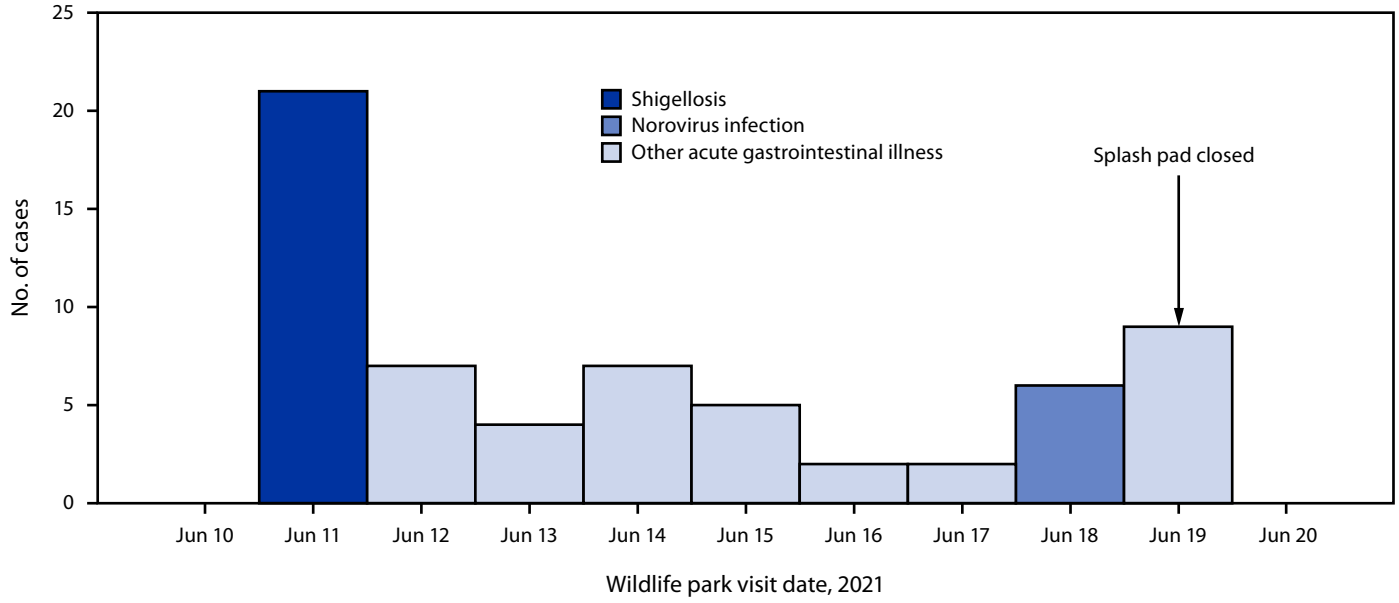
[††] Controls for shigellosis cases were defined as respondents who did not experience gastrointestinal symptoms (i.e., diarrhea, bloody diarrhea, abdominal pain, nausea, or vomiting) after visiting the wildlife park on June 11.

[§§] Case-patient and control age data were compared using the Mann-Whitney U test.

[¶¶] Data were excluded from analysis for respondents who became ill after visiting the wildlife park but did not know if they experienced gastrointestinal symptoms (one) or the illness onset date was not reported (one). Two patients, who entered the splash pad on June 18 and had laboratory-confirmed norovirus infection, did not participate in the case-control study.

[***] Controls for cases of norovirus infection were defined as respondents who did not experience gastrointestinal symptoms after visiting the wildlife park on June 18.

FIGURE 1. Cases of acute gastrointestinal illness (N = 63)* among study respondents,[†] by wildlife park visit date — Kansas, June 2021



* A case of shigellosis was defined as diarrhea (three or more loose stools in 24 hours) with onset 12–73 hours after visiting the wildlife park on June 11 (n = 21). A case of norovirus infection was defined as vomiting or diarrhea (three or more loose stools in 24 hours) with onset 12–56 hours after visiting the wildlife park on June 18 (n = 6). A case of other acute gastrointestinal illness was defined as diarrhea (three or more loose stools in 24 hours) with onset 12–73 hours after visiting the wildlife park on June 12, 13, 14, 15, 16, 17, or 19 (n = 36). For these visit dates, no case-patients had clinical laboratory evidence supporting detection of the same pathogen.

† One patient, who entered the splash pad on June 11 and had at least supportive laboratory evidence of *Shigella* detection, did not participate in the case-control study. Two patients, who entered the splash pad on June 18 and had laboratory-confirmed norovirus infection, did not participate in the case-control study.

splash pad did not have an automated controller to measure and help maintain the free chlorine concentration needed to prevent pathogen transmission. In addition, no staff member had documentation of having completed standardized operator training. Splash pad water samples were collected on June 19 from the four sand filters, seven pumps, and collection tank. CDC tested the samples for *Shigella* and fecal indicator bacteria.[†††] Total coliforms were detected in three of the seven pumps feeding the splash pad features; *E. coli* was detected in one of the coliform-positive pumps.

Public Health Response

After the splash pad was closed, CDC drafted operation and management guidance for reopening, based on the 2018 MAHC (*4*). SCHD finalized the recommendations and shared them with the splash pad operator. On July 24, the operator reopened the splash pad to the public after voluntarily addressing gaps and implementing best practices, including continuously recirculating, filtering, and disinfecting water (MAHC 5.7.1.1.1 and 5.7.3.1);[§§§] using an automated controller (MAHC 5.7.3.7.1); and completing operator training (MAHC 6.1.2). After these interventions were implemented, no additional splash pad–associated illnesses were identified.

[†††] https://www.standardmethods.org/doi/10.2105/SMWW.2882.194

Discussion

Pathogens that cause gastrointestinal illness can be transmitted when water contaminated with feces from infected persons is ingested. Splash pads are intended for young children, aged <5 years. Young children are more likely to experience acute gastrointestinal illness including shigellosis and norovirus infection (*5*,*6*), and, because of inadequate toileting and hygiene skills, are more likely to contaminate the water. Swim diapers do not prevent contamination of water (*7*). Children also ingest more recreational water than do adults (*8*). One study of splash

[§§§] For reference purposes, MAHC elements discussed in this report are followed by the specific section number that corresponds to that element.

TABLE. Potential exposures among case-patients and control study respondents who visited a wildlife park — Kansas, June 2021

Potential exposures*,†,§	No./Total no. (%)		Bivariate complete case analysis		Multivariate complete case analysis		Bivariate multiply imputed analysis		Multivariate multiply imputed analysis	
	Case patients	Control participants	aOR_C¶ (95% CI)**	P-value	aOR_C¶ (95% CI)**	P-value	aOR_{MI}¶ (95% CLIP)**	P-value	aOR_{MI}¶ (95% CLIP)**	P-value
Jun 11, 2021										
Shigella††,§§										
Played in splash pad water	**21/21 (100)**	**35/43 (81)**	10.3 (1.2– 1,356.0)	0.032	—¶¶	—¶¶	10.3 (1.2–1,356.0)	<0.001	2.6 (0.1–406.2)	0.502
Got splash pad water in the mouth	**13/15 (87)**	**7/19 (37)**	9.0 (2.0–56.4)	0.003	10.2 (1.8–109.5)	0.007	10.0 (1.5–83.5)	0.008	6.4 (1.1–65.2)	0.036
Drank water from drinking fountain	**3/17 (18)**	**3/41 (7)**	2.7 (0.5–14.0)	0.237	3.0 (0.4–41.9)	0.318	3.3 (0.6–17.1)	0.143	3.1 (0.4–33.4)	0.187
Touched or fed lemurs	**4/19 (21)**	**12/42 (29)**	0.7 (0.2–2.3)	0.580	1.2 (0.2–9.0)	0.886	0.8 (0.2–2.5)	0.637	0.9 (0.2–4.6)	0.876
Jun 18, 2021										
Norovirus***,†††										
Played in splash pad water	**6/6 (100)**	**13/19 (68)**	6.3 (0.6–863.0)	0.149	—¶¶	—¶¶	6.3 (0.6–378.0)	0.149	0.7 (0.003–140.0)	0.866
Got splash pad water in the mouth	**6/6 (100)**	**5/12 (42)**	17.7 (1.5–2,501.5)	0.018	24.1 (2.2–4,042.2)	0.007	32.3 (3.0–4,494.9)	0.002	28.6 (2.3–3,584.8)	0.006
Drank water from drinking fountain	**0/6 (—)**	**2/18 (11)**	0.5 (0.003–7.5)	0.656	0.1 (0.001–1.8)	0.130	0.42 (0.003–6.0)	0.560	0.1 (0.001–2.0)	0.148

Abbreviations: aOR_C = adjusted odds ratio, complete case; aOR_{MI} = adjusted odds ratio, multiply imputed; CLIP = combination of likelihood profiles.

* Sex (male or female) was not found to be associated with illness.

† Age was found to be associated with illness but was removed from the model because of its high correlation with getting splash pad water in the mouth.

§ Among those who visited on June 11 or June 18, self-reporting indicated 21% (15 of 73) wore the same shoes in the animal area and splash pad; 7% (five of 69) used indoor showers before entering the splash pad, and 59% (24 of 41) always used hand sanitizer or washed hands with soap after touching or feeding animals. None of these behaviors were associated with illness in initial analyses and were removed from consideration before multivariate modeling.

¶ aORs calculated using Firth penalized likelihood logistic regression, pooled estimates for multiply imputed analysis.

** CIs calculated using penalized profile likelihood, intervals by CLIP for multiply imputed analysis.

†† Case-patients (21) were respondents who experienced diarrhea (three or more loose stools in 24 hours) with onset 12–73 hours after visiting the wildlife park on June 11.

§§ Control participants (43) were respondents who did not experience gastrointestinal signs or symptoms (i.e., diarrhea, bloody diarrhea, abdominal pain, nausea, or vomiting) after visiting the wildlife park on June 11.

¶¶ Among persons completing responses, all case-patients played in splash pad water; because there was no variation, an aOR for this variable cannot be estimated in the complete case analysis.

*** Case-patients (six) were respondents who experienced vomiting or diarrhea (three or more loose stools in 24 hours) with onset 12–56 hours after visiting the wildlife park on June 18.

††† Control participants (19) were respondents who did not experience gastrointestinal symptoms after visiting the wildlife park on June 18.

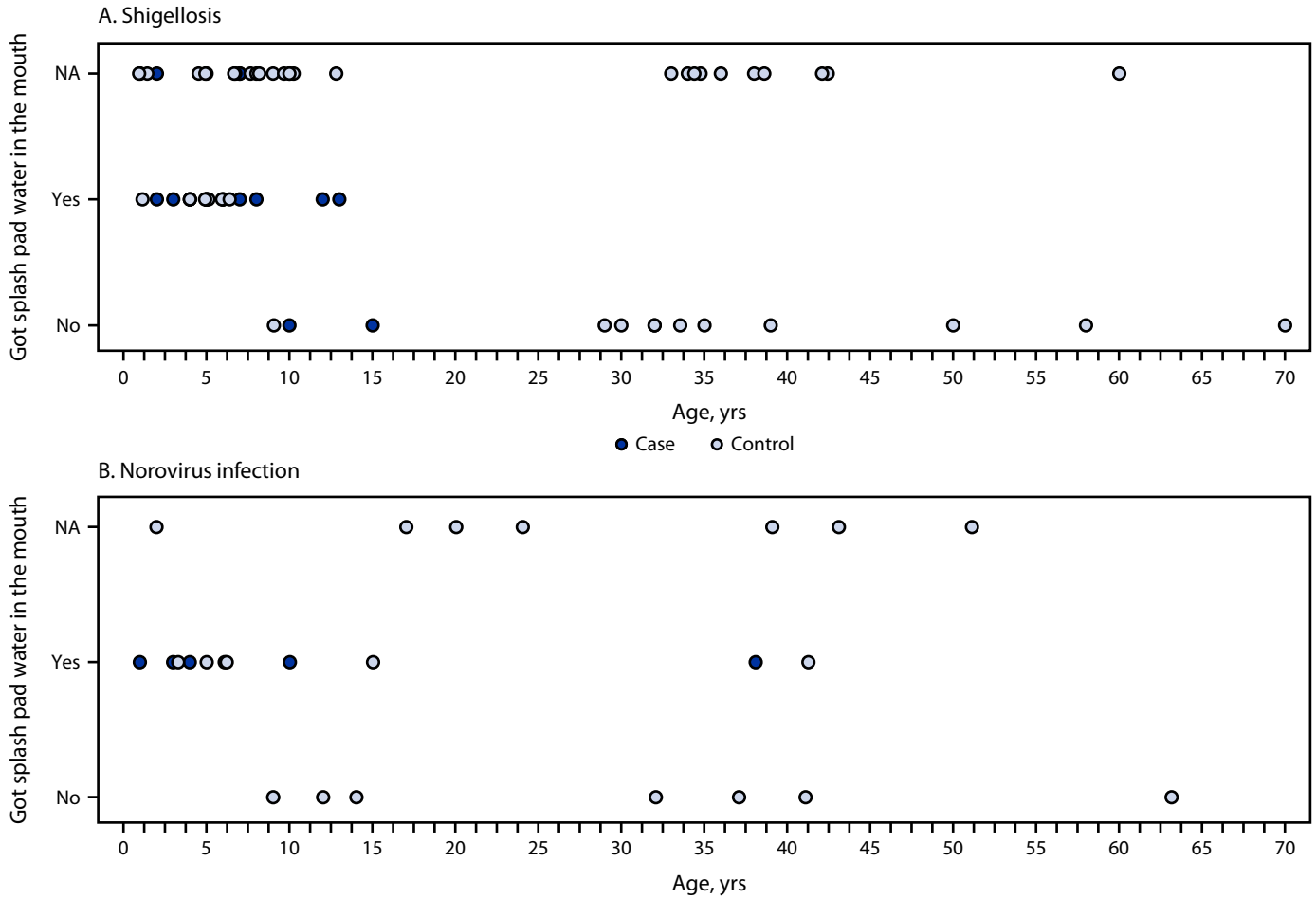
pad behaviors documented children wearing diapers, sitting on water jets, and placing their open mouths to the water (*9*). When splash pads jet or spray water, aerosolization depletes the free chlorine concentration, making it more difficult to maintain the minimum concentration necessary to prevent pathogen transmission. These two splash pad outbreaks were caused by pathogens readily inactivated by free chlorine,¶¶¶ indicating that the outbreaks might have been prevented by maintaining water disinfection. The environmental health investigation findings elucidated why these outbreaks occurred; no additional cases were identified after the operator implemented reopening guidance, suggesting that pathogen transmission can be prevented.

Splash pads typically do not have standing water in the user area. Thus, they might not meet a jurisdiction's definition of a treated recreational water venue (e.g., pool) open to the public, which can exempt them from regulation under public health codes. In 1997, the first reported splash pad–associated outbreak also occurred near animals**** (*10*). Although neither the investigation of the 1997 outbreak nor this shigellosis outbreak found evidence of waterborne zoonotic pathogen transmission, they highlight the potential for such transmission. In public animal settings with splash pads, using

¶¶¶ At 1 ppm free chlorine, the minimum concentration recommended by CDC and typically required in U.S. jurisdictions for treated recreational water venues open to the public, most pathogens are inactivated within minutes at pH of 7.2–7.8 and temperature of 77°F (25°C). pH will determine the relative amounts of hypochlorous acid (HOCl, a very active chlorine disinfectant) and hypochlorite ion (OCl^-, a less active chlorine disinfectant).

**** In the 1997 Minnesota outbreak, children soaked themselves in the recirculated water by standing on grates above the jets. The jets were 50 yds (46 m) away from ruminants (animal reservoirs of the outbreak etiology, *Cryptosporidium*, a parasite that causes diarrhea).

FIGURE 2. Age distribution of shigellosis (A) and norovirus infection (B) case-patients and control study respondents, by wildlife park visit date* and whether got splash pad water in the mouth — Kansas, June 2021



Abbreviation: NA = not applicable.
* Shigellosis outbreak associated with park visit on June 11 and norovirus infection outbreak associated with park visit on June 18.

the splash pad before entering animal areas or changing shoes before entering the splash pad could prevent the introduction and transmission of zoonotic pathogens.

The findings in this report are subject to at least five limitations. First, daily overall wildlife park and splash pad patron counts were not available, and respondent representativeness was not assessed. Second, case-patient and control respondent counts were small, and analyzing data by wildlife park visit date further limited statistical power. However, for visit dates other than June 11 or 18, no case-patients had clinical laboratory evidence supporting detection of the same pathogen. Missing data were multiply imputed to partially address limited statistical power. Third, wording of one response choice lacked clarity[††††] and might have increased error in exposure observations resulting in increased SE and reduced significance in the association between the splash pad and illness. Fourth, small samples can cause rare events to be overrepresented, leading to bias. Statistical techniques, including Firth penalized logistic regression, were employed to account for this. Finally, the time elapsed from splash pad entry until study response could have led to recall bias.

By identifying factors contributing to outbreaks, environmental health specialists provide data central to developing effective mitigation and prevention strategies for outbreaks associated with treated recreational water venues open to the public. As splash pad use increases, exempting splash pads from regulation under public health codes needs to be reconsidered. CDC's MAHC recommendations can be voluntarily adopted by U.S. jurisdictions. Environmental health specialists also enforce public health codes through inspections and serve as healthy and safe swimming resources for operators.[§§§§] To further promote healthy and safe swimming, environmental health specialists can partner with the aquatics sector to engage the public and increase awareness of the importance of healthy swimming steps. Efforts to prevent splash pad–associated outbreaks need to be targeted to caregivers, with prevention messages that include "Don't get in the water if sick with diarrhea," "Don't stand or sit above the jets," and "Don't swallow the water."

[††††] The question asked if respondents went into the wildlife park splash pad area and provided the following answer choices: 1) Yes, went and played in the splash park, 2) Yes, went to the splash park area but did not play in the water, and 3) No, did not go into the splash park area.

[§§§§] https://www.cdc.gov/healthywater/swimming/swimmers/splash-pad-operation-and-management.html

Summary

What is already known about this topic?

Splash pads jet or spray water on users.

What is added by this report?

Two outbreaks were associated with a Kansas wildlife park: one caused by *Shigella* and involving 21 cases in study respondents who visited on June 11 and the other caused by norovirus and involving six cases in respondents who visited on June 18. Getting splash pad water in the mouth was associated with illness on both days. Outbreak contributing factors included inadequate disinfection, equipment, and training.

What are the implications for public health practice?

Maintaining adequate water disinfection and environmental health expertise and targeting prevention efforts to caregivers of children help prevent splash pad–associated outbreaks.

Acknowledgments

Megan E. Gerdes, Haley J. McKeel, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC.

Corresponding author: Michele Hlavsa, acz3@cdc.gov.

[1]Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC; [2]Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee; [3]Kansas Department of Health and Environment; [4]Sedgwick County Health Department, Wichita, Kansas; [5]Division of Environmental Health Science and Practice, National Center for Environmental Health, CDC; [6]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, CDC.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

References

1. Van Buuren S, Groothuis-Oudshoorn CGM. Flexible multivariate imputation by MICE. Leiden, Netherlands: TNO Prevention and Health; 1999.
2. Heinze G, Ploner M, Beyea J. Confidence intervals after multiple imputation: combining profile likelihood information from logistic regressions. Stat Med 2013;32:5062–76. PMID:23873477 https://doi.org/10.1002/sim.5899
3. Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1993;80:27–38. https://doi.org/10.1093/biomet/80.1.27
4. CDC. The model aquatic health code (MAHC). Atlanta, GA: US Department of Health and Human Services, CDC; 2022. https://www.cdc.gov/MAHC
5. Burke RM, Mattison CP, Marsh Z, et al. Norovirus and other viral causes of medically attended acute gastroenteritis across the age spectrum: results from the medically attended acute gastroenteritis study in the United States. Clin Infect Dis 2021;73:e913–20. PMID:34398953 https://doi.org/10.1093/cid/ciab033
6. CDC. National enteric disease surveillance: *Shigella* annual report, 2016. Atlanta, GA: US Department of Health and Human Services, CDC; 2018. https://www.cdc.gov/nationalsurveillance/pdfs/LEDS-Shig-2016-REPORT-508.pdf

7. Amburgey JE, Anderson JB. Disposable swim diaper retention of *Cryptosporidium*-sized particles on human subjects in a recreational water setting. J Water Health 2011;9:653–8. PMID:22048425 https://doi.org/10.2166/wh.2011.063
8. Dufour AP, Behymer TD, Cantú R, Magnuson M, Wymer LJ. Ingestion of swimming pool water by recreational swimmers. J Water Health 2017;15:429–37. PMID:28598347 https://doi.org/10.2166/wh.2017.255
9. Nett RJ, Toblin R, Sheehan A, Huang WT, Baughman A, Carter K. Nonhygienic behavior, knowledge, and attitudes among interactive splash park visitors. J Environ Health 2010;73:8–14. PMID:21133310
10. CDC. Outbreak of cryptosporidiosis associated with a water sprinkler fountain—Minnesota, 1997. MMWR Morb Mortal Wkly Rep 1998;47:856–60. PMID:9790661

Interim Recommendation of the Advisory Committee on Immunization Practices for Use of the Novavax COVID-19 Vaccine in Persons Aged ≥18 years — United States, July 2022

Evelyn Twentyman, MD[1]; Megan Wallace, DrPH[1]; Lauren E. Roper, MPH[1]; Tara C. Anderson, DVM, PhD[1]; Amy B. Rubis, MPH[1]; Katherine E. Fleming-Dutra, MD[1]; Elisha Hall, PhD[1]; Joy Hsu, MD[2]; Hannah G. Rosenblum, MD[1]; Monica Godfrey, MPH[1]; W. Roodly Archer, PhD[3]; Danielle L. Moulia, MPH[1]; Laura Daniel, MPH[1]; Oliver Brooks, MD[4]; H. Keipp Talbot, MD[5]; Grace M. Lee, MD[6]; Beth P. Bell, MD[7]; Matthew Daley, MD[8]; Sarah Meyer, MD[1]; Sara E. Oliver, MD[1]

The NVX-CoV2373 (Novavax) COVID-19 vaccine is a recombinant spike (rS) protein nanoparticle vaccine with Matrix-M adjuvant to protect against infection with SARS-CoV-2, the virus that causes COVID-19. On July 13, 2022, the Food and Drug Administration (FDA) issued Emergency Use Authorization (EUA) for the Novavax vaccine for primary COVID-19 immunization of unvaccinated adults aged ≥18 years, administered as 2 doses (5 μg rS and 50 μg Matrix-M adjuvant in each dose) 3 weeks apart (*1*). On July 19, 2022, the Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation for use of the Novavax vaccine in persons aged ≥18 years for the prevention of COVID-19.* In the per-protocol† efficacy analysis, vaccine efficacy (VE) against reverse transcription–polymerase chain reaction (RT-PCR)–confirmed symptomatic COVID-19 was 89.6% (95% CI = 82.4%–93.8%). The Alpha variant (B.1.1.7) of SARS-CoV-2 was the predominant circulating variant during the period of case accrual for VE assessments. Cases of myocarditis or pericarditis were reported in temporal association with vaccination, suggesting a possible causal relationship. The ACIP recommendation for the use of the Novavax COVID-19 vaccine is interim and will be updated as additional information becomes available. The adjuvanted, protein subunit-based Novavax COVID-19 vaccine provides an additional option for unvaccinated adults, increasing flexibility for the public and for vaccine providers. Vaccination is important for protection against COVID-19.

Since June 2020, ACIP has convened 31 public meetings to review data relevant to the epidemiology of COVID-19 and considerations for the use of COVID-19 vaccines, including the Novavax vaccine.§ The ACIP COVID-19 Vaccines Work Group (Work Group), comprising experts in adult and pediatric medicine, infectious diseases, vaccinology, vaccine safety, public health, and ethics, has held weekly meetings to review COVID-19 surveillance data, evidence for VE, postauthorization effectiveness, safety, and implementation considerations for COVID-19 vaccines. To guide its deliberations regarding recommendations for use of these vaccines, ACIP used the Evidence to Recommendation (EtR) Framework¶ and incorporated a Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach** (*2*). Within the EtR Framework, ACIP considered the importance of COVID-19 as a public health problem, as well as population values and preferences, acceptability, feasibility, resource use, and equity regarding use of the Novavax COVID-19 vaccine among persons aged ≥18 years. After conducting systematic reviews of published and unpublished evidence for benefits and harms, the Work Group used the GRADE approach to independently assess the certainty of evidence for outcomes related to the Novavax COVID-19 vaccine, rated on a scale of type 1 (high certainty) to type 4 (very low certainty)†† (*2*). Work Group conclusions regarding evidence for use of the Novavax COVID-19 vaccine among persons aged ≥18 years were presented to ACIP at a public meeting on July 19, 2022.

Summary of Evidence for Use of the Novavax COVID-19 Vaccine in Persons Aged ≥18 Years

The body of evidence regarding efficacy of the Novavax COVID-19 vaccine among persons aged ≥18 years consisted of data from one randomized, double-blind, placebo-controlled phase III clinical trial (2019nCoV-301), based in the United States and Mexico, in which 29,945 participants aged ≥18 years were enrolled and randomized 2:1 to receive 2 intramuscular doses of either Novavax COVID-19 vaccine (5 μg rS and 50 μg Matrix-M adjuvant) or saline placebo, separated by an interval of 3 weeks (*3*). Upon completion of the assigned study arm (i.e., receipt of either 2 doses of vaccine or 2 doses of placebo), trial participants were offered the opportunity to cross over in a blinded fashion ("blinded crossover") from their originally assigned study arm. Therefore, all trial participants had the opportunity to receive trial vaccine in either the precrossover

* On July 19, 2022, ACIP voted 12 to 0 (three members absent) in favor of the interim recommendation for use of the Novavax COVID-19 vaccine for persons ≥18 years.

† The per-protocol efficacy analysis population was defined as participants who were randomized, received both doses as assigned, had no evidence of SARS-CoV-2 infection before dose 1, and did not have a COVID-19 event at any time before 7 days after dose 2.

§ https://www.cdc.gov/vaccines/acip/meetings/index.html

¶ https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-novavax-etr.html

** https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-novavax.html

†† https://www.cdc.gov/vaccines/acip/recs/grade

or postcrossover period, while remaining blinded throughout. Efficacy and safety data are available from the precrossover period (December 27, 2020–September 27, 2021) of this trial, and these data comprise the basis of the assessment made using the GRADE approach. Data from additional sources were considered in assessment of benefits and harms, as guided by the EtR Framework. These sources included additional safety data available from the postcrossover period of 2019nCoV-301, safety data from three additional Novavax clinical trials based in the United Kingdom (2019nCoV-302), South Africa (2019nCoV-501), and Australia (2019nCoV-101), postmarketing safety data submitted to FDA by Novavax summarizing administration of 744,235 doses of Novavax COVID-19 vaccine globally as of April 30, 2022 (*4*), and publicly available data pertaining to the administration of 160,000 Novavax COVID-19 vaccine doses in Australia as of June 26, 2022 (*5*).

The primary efficacy endpoint was diagnosis of RT-PCR–confirmed symptomatic COVID-19 ≥7 days after receipt of the second dose in the 2-dose primary series of Novavax COVID-19 vaccine arm compared with that in the placebo arm. Per the manufacturer's trial protocol, COVID-19 cases were only included in the efficacy analysis if they were RT-PCR–confirmed by a designated central laboratory. The primary efficacy endpoint was assessed until a participant received the first blinded crossover vaccination or until the data cutoff date of September 27, 2021, whichever occurred earlier. The per-protocol VE analysis population included 17,272 Novavax COVID-19 vaccine recipients and 8,385 placebo recipients with a median 2.5 months of blinded follow-up after receipt of dose 2. VE[§§] against RT-PCR–confirmed symptomatic COVID-19, observed during the period of Alpha variant predominance, was 89.6% (95% CI = 82.4%–93.8%) in persons aged ≥18 years without evidence of previous SARS-CoV-2 infection.[¶¶] This estimate was based on symptomatic illness in 17 vaccine recipients and 79 placebo recipients, none of whom was hospitalized. VE against severe COVID-19[***] was 100%, based on four severe cases in the placebo group and none in the vaccine group. Subgroup analyses by age demonstrated VE against RT-PCR–confirmed symptomatic COVID-19 of 90.3% (95% CI = 83.1%–94.4%) among participants aged 18–64 years and 76.3% (95% CI = 29.1%–95.7%) among participants aged ≥65 years. A post hoc analysis of VE[†††] among participants aged 50–64 years demonstrated VE of 90.7% (95% CI = 72.9%–96.8%) against RT-PCR–confirmed symptomatic COVID-19. Additional evidence pertaining to potential VE in persons aged ≥65 years was provided through immunobridging. The measure of immune response to 2 doses of Novavax COVID-19 vaccine in persons aged ≥65 years without evidence of previous SARS-CoV-2 infection was slightly lower than that observed in persons aged 50–64 years, with a geometric mean ratio (GMR) for day 35 neutralizing antibody titer of 0.91 (95% CI = 0.68–1.2) for persons aged ≥65 years, demonstrating estimates that would have met FDA's usual success criterion for immunobridging noninferiority.[§§§] Subgroup analyses of VE against RT-PCR–confirmed symptomatic COVID-19 by ethnicity and race demonstrated that most estimates by ethnicity and race (when calculable from the data) were comparable to the per-protocol VE overall, but VE in participants of Hispanic or Latino (Hispanic) ethnicity was lower (75.7%; 95% CI = 46.0%–89.1%).

Among vaccine recipients aged ≥18 years, reactogenicity, defined as solicited local and systemic reactions during the 7 days after vaccination, was reported frequently. Following dose 2, 78.6% of participants reported any local reactions, and 69.3% reported any systemic reactions. Most solicited reactions were mild to moderate and lasted 1–3 days; all were reported more frequently after dose 2 than after dose 1 among vaccine recipients. Severe solicited reactions (grade 3 or higher, defined as interfering with daily activity) were more common in vaccine (16.3%) than placebo (4.0%) recipients. Severe solicited local reactions occurred in 1.1% of vaccine recipients after dose 1 and in 6.7% after dose 2, compared with 0.2% and 0.3%, respectively, in placebo recipients. Severe solicited systemic

[§§] For GRADE evidence assessment, relative risks (RRs) were calculated from numerators and denominators available in the body of evidence. VE estimates were defined as 100% x (1 – RR). Manufacturer VE estimates were calculated from a log-linear model using modified Poisson regression.

[¶¶] In 2019nCoV-301, 6.5% of vaccine recipients and 8.4% of placebo recipients in the precrossover period had evidence of previous infection with SARS-CoV-2 at baseline, as assessed by serology before vaccination.

[***] Because no COVID-19–associated hospitalizations occurred in the per-protocol trial efficacy analysis, severe COVID-19 was used as a surrogate measure for COVID-19–associated hospitalization in GRADE assessments. Severe COVID-19 was defined as a COVID-19 case associated with one or more of the following conditions: tachypnea (≥30 breaths per minute at rest), tachycardia (resting heart rate ≥125 beats per minute), hypoxemia (oxygen saturation ≤93% on room air or ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen <300 mmHg), high-flow oxygen therapy or noninvasive ventilation/noninvasive positive pressure ventilation, mechanical ventilation or extracorporeal membrane oxygenation, or one or more major organ system dysfunction or failure, including any of the following conditions: acute respiratory distress syndrome, acute renal failure, acute hepatic failure, acute right or left heart failure, septic or cardiogenic shock (systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg), acute stroke (ischemic or hemorrhagic), acute thrombotic event, requirement for vasopressors, systemic corticosteroids, hemodialysis, admission to an intensive care unit, or death.

[†††] Post hoc VE was based on manufacturer VE estimate.

[§§§] Noninferiority is declared if the lower bound of the two-sided 95% CI for the GMR is >0.67, and the point estimate of GMR is ≥0.8.

reactions occurred in 2.4% of vaccine recipients after dose 1 and in 12.1% after dose 2, compared with 2.1% after each dose among placebo recipients. Reported reactions varied with age and were more common among vaccine recipients aged 18–64 years than among those aged ≥65 years. Among vaccine recipients aged 18–64 years, the most common reactions associated with any vaccine dose included injection site pain or tenderness (82.2%), fatigue (62.0%), muscle pain (54.1%), and headache (52.9%). In participants aged ≥65 years, the most common vaccine-associated reactions associated with any dose included injection site pain or tenderness (63.4%), fatigue (39.2%), muscle pain (30.2%), and headache (29.2%). The most common grade 3 or higher local reaction reported by vaccine recipients after dose 2 was pain or tenderness at the injection site (6.3%). The most common grade 3 or higher systemic reaction reported by vaccine recipients after dose 2 was fatigue (10.5%). Reports of unsolicited serious adverse events[¶¶¶] were comparable between vaccine (1.0%) and placebo (1.1%) recipients in the precrossover period and among participants who crossed over to receive Novavax COVID-19 vaccine (1.4%) and placebo (1.2%) in the postcrossover period.

Cases of myocarditis or pericarditis were detected in Novavax clinical trials. Among a total of 41,546 vaccine recipients aged ≥16 years, including within both precrossover and postcrossover vaccine arms in 2019nCoV-301, as well as all vaccine recipients in 2019nCoV-302, 2019nCoV-501, and 2019-nCoV101 combined, six cases of myocarditis or pericarditis were detected; five occurred within 20 days of vaccination. Among these five, four did not have likely alternative etiologies, suggesting a possible causal relationship with vaccine. Cases of myocarditis or pericarditis have also been detected in global postauthorization surveillance; during a period in which 744,235 doses of Novavax COVID-19 vaccine were administered in Australia, Canada, the European Union, New Zealand, and South Korea, 35 reports (representing 36 adverse events) were identified among 20 male and 15 female vaccine recipients with a median age of 34 years (range = 23–62 years): 29 reports of pericarditis, including five in persons with a history of pericarditis after mRNA COVID-19 vaccine; four myocarditis cases; two myopericarditis cases; and one case of carditis, not otherwise specified. A postmarketing analysis from Australia identified three cases of myocarditis and 12 cases of pericarditis reported during a period in which 160,000 Novavax COVID-19 vaccine doses were administered (*5*).

[¶¶¶] Serious adverse events are defined as death, life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, important medical event, or congenital anomaly or birth defect. Five participants in the vaccine arm experienced serious adverse events that the investigator considered to be related to vaccination. Among these, FDA considered one event of angioedema as being potentially related to vaccination.

In addition to the myocarditis or pericarditis cases detected in Novavax clinical trials, one case of angioedema (2019nCoV-301) and one case of Guillain-Barré syndrome (2019nCoV-302) were also considered to be potentially related to vaccination. A detailed summary of safety data, including information on reactogenicity, is available at https://www.cdc.gov/vaccines/covid-19/info-by-product/novavax/reactogenicity.html.

From GRADE evidence assessment, the level of certainty for the benefits of Novavax COVID-19 vaccination among persons aged ≥18 years was type 1 (high certainty) for the prevention of symptomatic laboratory-confirmed COVID-19 assessed using direct efficacy. Evidence was type 3 (low certainty) for prevention of COVID-19–associated hospitalization. No COVID-19–associated hospitalizations were present in the per-protocol trial efficacy analysis; therefore, the outcome was evaluated using severe COVID-19 as a surrogate measure. Concerns of imprecision arose because of the small number of severe COVID-19 events. Regarding potential harms after vaccination, evidence was type 1 (high certainty) for serious adverse events and reactogenicity of grade 3 or higher. No data were available to assess other GRADE benefits, including prevention of death due to COVID-19 or prevention of asymptomatic SARS-CoV-2 infection.

Recommendations for Use of the Novavax COVID-19 Vaccine in Persons Aged ≥18 Years

Data reviewed within the EtR Framework supported use of the Novavax COVID-19 vaccine in persons aged ≥18 years. COVID-19 remains a major public health problem in the United States. As of July 14, 2022, approximately 89 million COVID-19 cases have occurred in the United States, and outcomes have been most severe among adults: of 4,936,004 COVID-19–related hospitalizations in the United States during August 1, 2020–July 10, 2022, most (4,798,764; 97.2%) were among persons aged ≥18 years; and >99% of 1,015,431 COVID-19–related deaths in the United States through July 13, 2022, were among persons aged ≥18 years (*6*,*7*). COVID-19 continues to expose longstanding health inequities in the United States, as racial and ethnic minority populations continue to experience a disproportionate incidence of COVID-19 (*8*).

The benefits of receiving a primary COVID-19 vaccination series with authorized or approved vaccines are clear (*1*,*3*,*9*). Outcomes of COVID-19 among persons who are not vaccinated against COVID-19 are significantly worse than those among persons who have received at least a primary vaccination series; in April 2022, among persons aged ≥5 years, unvaccinated persons had six times the risk of dying from COVID-19 compared with those who had received a primary COVID-19 vaccination series (*9*). However, the benefits of Novavax

COVID-19 vaccine in the context of currently circulating SARS-CoV-2 variants is unknown because VE was assessed during the period of Alpha predominance. Direct evidence of efficacy against the Omicron variant or any of its sublineages is not yet available; evaluation of Novavax COVID-19 VE, including the subgroups in which VE in the trial appeared to have been potentially relatively lower (persons aged ≥65 years and persons of Hispanic ethnicity), will be based on postauthorization surveillance.

In evaluation of potential harms, cases of myocarditis or pericarditis were detected during Novavax COVID-19 vaccine clinical trials; in addition, reports of myocarditis or pericarditis were identified during postauthorization use of Novavax COVID-19 vaccine in countries outside the United States (*1*). These reports underscore the critical importance of ongoing vaccine safety surveillance in the United States and internationally to help assess the possible risk for Novavax COVID-19 vaccine-associated myocarditis or pericarditis, in addition to ongoing monitoring of myocarditis or pericarditis after receipt of mRNA COVID-19 vaccines and continued communication with health care providers.

As of May 2022, an estimated 13.9% of persons aged ≥18 years in the United States remained unvaccinated against COVID-19 (*10*). The availability of a COVID-19 vaccine that uses more traditional vaccine technology provides an additional option for unvaccinated persons. Recent data reflect some interest in protein-based adjuvanted vaccines such as the Novavax COVID-19 vaccine (*2*). A survey designed to assess vaccination intentions for adjuvanted or nonadjuvanted protein-based COVID-19 vaccines among unvaccinated Americans conducted during January–February 2022 found that 16.0% of unvaccinated adults said that they "probably" or "definitely" would get an adjuvanted protein-based vaccine, with significantly lower intent among non-Hispanic White persons (9.6%) than among non-Hispanic Black or African American (20.1%) and Hispanic persons (19.5%), and with significantly higher intent among men (21.8%) than among women (11.9%) (*2*).

Although uncertainty remains in the valuation of the vaccine by all populations, it was determined that for most populations, the desirable effects of Novavax COVID-19 vaccine outweigh any potential undesirable effects. The Novavax COVID-19 vaccine is likely acceptable, and implementation of vaccination feasible, particularly in the context of knowledge gained over the course of >1.5 years of distribution and administration of COVID-19 vaccines.

Before vaccination, the EUA Fact Sheet should be provided to vaccine recipients and their caregivers. Novavax COVID-19 vaccine is authorized as a 2-dose primary series separated by 3 weeks. Some studies with mRNA COVID-19 vaccines (*11*) have indicated that the small risk of myocarditis or pericarditis might be reduced with a longer interval between doses; however, no data currently exist for Novavax COVID-19 vaccine. Consequently, based on evidence of benefits of an extended interval in persons receiving mRNA COVID-19 vaccines, an 8-week interval between Novavax doses may be selected to potentially reduce the risk for myocarditis or pericarditis after vaccination. Development of myocarditis or pericarditis after a dose of an mRNA COVID-19 vaccine or Novavax COVID-19 vaccine is a precaution to a subsequent dose of any COVID-19 vaccine. Additional clinical guidance is available at https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html. ACIP will continue to review additional data as they become available.

Summary

What is already known about this topic?

On July 13, 2022, the Food and Drug Administration issued Emergency Use Authorization for the NVX-CoV2373 (Novavax) COVID-19 vaccine.

What is added by this report?

On July 19, 2022, the Advisory Committee on Immunization Practices made an interim recommendation for use of the Novavax vaccine in persons aged ≥18 years as a primary 2-dose series vaccination for the prevention of COVID-19.

What are the implications for public health practice?

The adjuvanted, protein subunit–based Novavax COVID-19 vaccine provides an additional option for unvaccinated adults, increasing flexibility for the public and for vaccine providers. Vaccination is important for protection against COVID-19.

Reporting of Vaccine Adverse Events

Adverse events that occur after receipt of any COVID-19 vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS). Vaccination providers are required by FDA to report vaccine administration errors, serious adverse events, cases of multisystem inflammatory syndrome, and cases of COVID-19 that result in hospitalization or death after administration of COVID-19 vaccine under EUA. Reporting is encouraged for any clinically significant adverse event even if it is uncertain whether the vaccine caused the event. Information on how to submit a report to VAERS is available at https://vaers.hhs.gov/index.html or 1-800-822-7967. In addition, CDC has established v-safe, a voluntary smartphone-based active surveillance system that monitors adverse events occurring after COVID-19 vaccination. Reports to v-safe indicating a medically significant health impact are followed up by CDC's v-safe call center to collect additional information, and complete a VAERS report, if indicated. Information on v-safe is available at https://www.cdc.gov/vsafe.

Acknowledgments

Karen Broder, Mary Chamberland, LeAnne Fox, Megan Freedman, Julianne Gee, Ruth Link-Gelles, Susan Goldstein, Valerie Morelli, Tamara Pilishvili, Edwin Shanley, David Shay, Tom Shimabukuro, John Su, Naomi Tepper, JoEllen Wolicki, CDC. Voting members of the Advisory Committee on Immunization Practices: Kevin A. Ault, University of Kansas Medical Center; Lynn Bahta, Minnesota Department of Health; Beth P. Bell, University of Washington; Oliver Brooks, Watts HealthCare Corporation and past president, National Medical Association; Wilbur Chen, University of Maryland School of Medicine; Sybil Cineas, Warren Alpert Medical School of Brown University; Matthew Daley, Kaiser Permanente Colorado; Camille N. Kotton, Massachusetts General Hospital and Harvard Medical School; Grace M. Lee, Lucile Packard Children's Hospital and Stanford University School of Medicine; James Loehr, Cayuga Family Medicine; Sarah Long, Drexel University College of Medicine; Veronica V. McNally, Franny Strong Foundation; Katherine A. Poehling, Wake Forest School of Medicine; Pablo J. Sánchez, The Research Institute at Nationwide Children's Hospital; H. Keipp Talbot, Vanderbilt University. Members of the Advisory Committee on Immunization Practices COVID-19 Vaccines Work Group (in addition to listed authors): Edward Belongia, Center for Clinical Epidemiology & Population Health, Marshfield Clinic Research Institute; Henry Bernstein, Cohen Children's Medical Center, Zucker School of Medicine at Hofstra/Northwell; Dayna Bowen Matthew, George Washington University Law School; Uzo Chukwuma, Indian Health Service; Marci Drees, Society for Healthcare Epidemiology of America; Jeffrey Duchin, Infectious Diseases Society of America; Doran Fink, Food and Drug Administration; Sandra Fryhofer, American Medical Association; Jason M. Goldman, American College of Physicians; Michael Hogue, American Pharmacists Association; Denise Jamieson, American College of Obstetricians and Gynecologists; Jeffrey Kelman, Centers for Medicare & Medicaid Services; David Kim, U.S. Department of Health and Human Services; Kathy Kinlaw, Center for Ethics, Emory University; Susan Lett, Council of State and Territorial Epidemiologists; Lauri Markowitz, CDC; Kendra McMillan, American Nurses Association; Kathleen Neuzil, Center for Vaccine Development and Global Health, University of Maryland School of Medicine; Sean O'Leary, American Academy of Pediatrics; Christine Oshansky, Biomedical Advanced Research and Development Authority; Stanley Perlman, Department of Microbiology and Immunology, University of Iowa; Marcus Plescia, Association of State and Territorial Health Officials; Chris Roberts, National Institutes of Health; William Schaffner, National Foundation for Infectious Diseases; Rob Schechter, Association of Immunization Managers; Kenneth Schmader, American Geriatrics Society; Bryan Schumacher, U.S. Department of Defense; Peter Szilagyi, University of California, Los Angeles; Jonathan Temte, American Academy of Family Physicians; Matthew Tunis, National Advisory Committee on Immunization Secretariat, Public Health Agency of Canada; Melinda Wharton, CDC; Matthew Zahn, National Association of County and City Health Officials; Rachel Zhang, Food and Drug Administration.

Corresponding author: Evelyn Twentyman, ydj2@cdc.gov.

[1]National Center for Immunization and Respiratory Diseases, CDC; [2]National Center for Environmental Health, CDC; [3]Center for Global Health, CDC; [4]Watts HealthCare Corporation, Los Angeles, California; [5]Vanderbilt University School of Medicine, Nashville, Tennessee; [6]Stanford University School of Medicine, Stanford, California; [7]University of Washington, Seattle, Washington; [8]Institute for Health Research, Kaiser Permanente Colorado, Denver, Colorado.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

References

1. Food and Drug Administration. Novavax COVID-19 vaccine, adjuvanted. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2022. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/novavax-covid-19-vaccine-adjuvanted
2. Twentyman E. Evidence to Recommendation Framework: Novavax COVID-19 vaccine in adults. Presented at the Advisory Committee on Immunization Practices meeting, Atlanta, GA; July 19, 2022. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-07-19/05-COVID-Twentyman-508.pdf
3. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee meeting June 7, 2022: FDA briefing document, Novavax COVID-19 vaccine. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2022. https://www.fda.gov/media/158912/download
4. Food and Drug Administration. FDA review of effectiveness and safety of Novavax COVID-19 vaccine in adults ≥18 years of age: Emergency Use Authorization request. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2022. https://www.fda.gov/media/159004/download
5. Department of Health and Aged Care, Australian Government. COVID-19 vaccine safety report – 30-06-2022. Woden, Canberra: Australian Government, Department of Health and Aged Care; 2022. https://www.tga.gov.au/periodic/covid-19-vaccine-safety-report-30-06-2022#section-1865
6. CDC. COVID data tracker. COVID-19 cases and deaths in the United States. Atlanta, GA: US Department of Health and Human Services, CDC; 2022. Accessed July 18, 2022. https://covid.cdc.gov/covid-data-tracker/#trends_dailycases
7. National Center for Health Statistics. Weekly updates by select demographic and geographic characteristics. Atlanta, GA: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2022. Accessed July 18, 2022. https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#AgeAndSex
8. CDC. COVID data tracker: health equity data. Atlanta, GA: US Department of Health and Human Services, CDC; 2022. Accessed July 18, 2022. https://covid.cdc.gov/covid-data-tracker/#health-equity-data
9. CDC. COVID data tracker: rates of COVID-19 cases and deaths by vaccination status. Atlanta, GA: US Department of Health and Human Services, CDC; 2022. Accessed July 18, 2022. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status
10. CDC. For immunization managers: COVID-19 vaccination coverage and confidence among adults. Atlanta, GA: US Department of Health and Human Services, CDC; 2022. Accessed July 18, 2022. https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/adults.html
11. Moulia D. Myocarditis and COVID-19 vaccine intervals: international data and policies. Presented at the Advisory Committee on Immunization Practices meeting, Atlanta, GA; February 4, 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/11-COVID-Moulia-508.pdf

Post–COVID-19 Symptoms and Conditions Among Children and Adolescents — United States, March 1, 2020–January 31, 2022

Lyudmyla Kompaniyets, PhD[1]; Lara Bull-Otterson, PhD[1]; Tegan K. Boehmer, PhD[1]; Sarah Baca[1,2]; Pablo Alvarez, MPH[1,2]; Kai Hong, PhD[1]; Joy Hsu, MD[1]; Aaron M. Harris, MD[1]; Adi V. Gundlapalli, MD, PhD[1]; Sharon Saydah, PhD[1]

Post–COVID-19 (post-COVID) symptoms and conditions* are new, recurring, or ongoing health problems that occur 4 or more weeks after infection with SARS-CoV-2 (the virus that causes COVID-19). Previous studies have characterized and estimated the incidence of post-COVID conditions among adults (*1*,*2*), but data among children and adolescents are limited (*3*–*8*). Using a large medical claims database, CDC assessed nine potential post-COVID signs and symptoms (symptoms) and 15 potential post-COVID conditions among 781,419 U.S. children and adolescents aged 0–17 years with laboratory-confirmed COVID-19 (patients with COVID-19) compared with 2,344,257 U.S. children and adolescents without recognized COVID-19 (patients without COVID-19) during March 1, 2020–January 31, 2022. The analysis identified several symptoms and conditions with elevated adjusted hazard ratios among patients with COVID-19 (compared with those without). The highest hazard ratios were recorded for acute pulmonary embolism (adjusted hazard ratio [aHR] = 2.01), myocarditis and cardiomyopathy (1.99), venous thromboembolic event (1.87), acute and unspecified renal failure (1.32), and type 1 diabetes (1.23), all of which were rare or uncommon in this study population. Conversely, symptoms and conditions that were most common in this study population had lower aHRs (near or below 1.0). Patients with COVID-19 were less likely than were patients without to experience respiratory signs and symptoms, symptoms of mental conditions, muscle disorders, neurological conditions, anxiety and fear-related disorders, mood disorders, and sleeping disorders. COVID-19 prevention strategies, including vaccination for all eligible children and adolescents, are critical to prevent SARS-CoV-2 infection and subsequent illness, including post-COVID symptoms and conditions (*9*).

CDC analyzed linked medical claims and commercial laboratory data for persons with a health care encounter possibly related to COVID-19.† Analyses were restricted to children and adolescents aged 0–17 years who were continuously enrolled in a health insurance plan during March 1, 2019–January 31, 2022. Children and adolescents aged 0–17 years with laboratory-confirmed COVID-19 and those without recognized COVID-19§ were matched 1:3 based on age at encounter, sex, and month of index date.¶ Patients were followed for a minimum of 60 days and a maximum of 365 days or until January 31, 2022, whichever occurred first. Scientific literature on symptoms and conditions associated with post-COVID illness among children or adults was reviewed (*1*–*5*). Symptoms and conditions were identified by the first occurrence and classified based on the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM)

* CDC defines post-COVID conditions as new, returning, or ongoing health problems occurring ≥4 weeks after being infected with SARS-CoV-2. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html

† This analysis used CDC-licensed HealthVerity, Inc. medical claims data linked to SARS-CoV-2 commercial laboratory data (May 2022 release). Patients were eligible for inclusion in CDC licensed data if they had a health care encounter (diagnosis, procedure, treatment, or laboratory test) possibly related to COVID-19 on or after December 1, 2019.

§ A retrospective cohort of children and adolescents aged 0–17 years with continuous enrollment in an insurance plan during March 1, 2019–January 31, 2022, was identified within a subset of CDC-licensed HealthVerity data that included persons with a health care encounter possibly related to COVID-19. Patients with COVID-19 were selected from among patients with a positive SARS-CoV-2 test result during March 2020–November 2021 or an ICD-10-CM code of B97.29 (other coronavirus as the cause of diseases classified elsewhere) during March–April 2020 or U07.1 code (COVID-19, virus-identified [laboratory-confirmed]) during April 2020–November 2021 (https://www.cdc.gov/nchs/data/icd/Announcement-New-ICD-code-for-coronavirus-3-18-2020.pdf). Patients without COVID-19 were selected after excluding patients who had any ICD-10-CM codes related to COVID-19 (A41.89, B34.2, B97.21, B94.8, J12.81, J12.82, J12.89, M30.3, M35.81, U07.1, or U07.2), a positive SARS-CoV-2 test result, or received treatment for COVID-19 (casirivimab/imdevimab, etesevimab/bamlanivimab, sotrovimab, bebtelovimab, nirmatrelvir, molnupiravir, or remdesivir) at any point during the study period. Vaccination status of patients was not included for this analysis.

¶ The index date for the group of patients with COVID-19 was the date of either the first claim with a COVID-19 diagnosis code or the first positive SARS-CoV-2 test result (whichever occurred first). The index date for patients without COVID-19 in the main analysis was the date of a randomly selected claim during the month in which the patient without COVID-19 was matched to a patient with COVID-19. The index date for patients without COVID-19 in the sensitivity analysis was the date of the first negative SARS-CoV-2 test result, first health care encounter possibly related to COVID-19 (associated with an ICD-10-CM code of B97.89, Z86.16, R05, R06.02, R50.9, R19.7, R53.8, R09.3, R04.2, R09.2, J00–J06, J09–J11, J12.9, J13–J18, or J80), or the first claim during the pandemic period if other dates were not available.

codes documented 31–365 days after the index date but not during the 7–365 days preceding the index date.**

The incidences (occurrence per 100,000 person-years) of nine potential post-COVID symptoms and 15 potential post-COVID conditions among children and adolescents aged 0–17 years were calculated. Separate Cox proportional hazards models were used to estimate aHRs for each symptom and condition, after excluding persons with that particular symptom or condition during the 7–365 days preceding the index date.†† All models were adjusted for age, sex, race, U.S. Census Bureau region, payor type, previous medical complexity (*10*), and previous hospitalization.§§ The same models were estimated separately for three age groups (2–4, 5–11, and 12–17 years).¶¶ A sensitivity analysis was performed to assess the incidences of potential post-COVID symptoms and conditions among children and adolescents aged 0–17 years who had not experienced any of the 24 assessed symptoms or conditions before the index date.*** Finally, incidence of each symptom and condition among patients with COVID-19 was plotted against aHRs from the main analysis. Analyses were conducted using R software (version 4.1.0; R Foundation); p-values <0.05 were considered statistically significant. This activity was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.†††

During March 1, 2020–January 31, 2022, a total of 781,419 patients aged 0–17 years with COVID-19 and 2,344,257 patients aged 0–17 years without COVID-19 were identified (Table 1). The median age of both patients with and without COVID-19 was 12 years, and 50.0% in both groups were female; 72.2% of patients with COVID-19 were enrolled in Medicaid managed care, compared with 70.6% of patients without COVID-19. Patients without COVID-19 had a higher prevalence of previous hospitalization (4.5%) and complex chronic disease (15.6%), than did patients with COVID-19 (3.6% and 11.7%, respectively).

Patients with COVID-19 were significantly more likely than were those without to develop the following assessed post-COVID symptoms: smell and taste disturbances (aHR = 1.17), circulatory signs and symptoms (1.07), malaise and fatigue (1.05), and musculoskeletal pain (1.02) (Table 2). Patients with COVID-19 were also more likely than were those without to develop the following assessed post-COVID conditions: acute pulmonary embolism (2.01), myocarditis and cardiomyopathy (1.99), venous thromboembolic event (1.87), acute and unspecified renal failure (1.32), type 1 diabetes (1.23), coagulation and hemorrhagic disorders (1.18), type 2 diabetes (1.17), and cardiac dysrhythmias (1.16). Patients with COVID-19 were less likely than were those without to experience respiratory signs and symptoms (0.91), symptoms of mental conditions (0.91), sleeping disorders (0.91), neurological conditions (0.94), anxiety and fear-related

** Potential post-COVID conditions were selected from a range of body systems and were assessed by the first occurrence of at least one of the following ICD-10-CM codes documented 31–365 days after the index date but not during the 7–365 days preceding the index date: 1) circulatory system disorders: acute pulmonary embolism (I26), myocarditis and cardiomyopathy (A36.81, B33.20, B33.22, B33.24, B58.81, I25.5, I40, I41, I42.0–I42.5, I42.8, I42.9, I43, I51.4, J10.82, J11.82, and O90.3), cerebrovascular disease (G46 and I67–I68 [except I67.0 and I67.4]), venous thromboembolic event (I82.40, I82.49, I82.4Y, I82.4Z, I82.62, I82.50, I82.59, I82.5Y, I82.5Z, and I82.72), cardiac dysrhythmias (I47, I48.0, I48.19, I48.21, I48.3–I48.9, and I49.1–I49.9); 2) endocrine, nutritional, and metabolic disorders: type 1 diabetes (E10), type 2 diabetes (E11); 3) digestive system disorders: gastrointestinal and esophageal disorders (K20, K21, K22.0–K22.6, K22.89, K22.9, K23, K58, K59.0–K59.2, K59.89, K59.9, and K92.9); 4) musculoskeletal and connective tissue disorders: muscle disorders (M60.0, M60.1, M60.8, M60.9. M61, M62, and M63); 5) mental, behavioral, and neurodevelopmental disorders: anxiety and fear-related disorders (F06.4, F40.0, F40.1, F40.228, F40.230, F40.231, F40.232, F40.233, F40.240, F40.248, F40.8, F40.9, F41, and F93.0), mood disorders (F06.30, F34.8. F34.9, and F39); 6) nervous system disorders: neurological conditions (F05, R40.0, R41, R44, A85, A86, G04, G05, R29, R26, R27, G26, and G50–G65); 7) respiratory system disorders: asthma (J45); 8) genitourinary disorders: acute renal failure (N17 and N19), chronic kidney disease (N18 and R88.0); 9) blood system disorders: coagulation and hemorrhagic disorders (D47.3, D65, D68.3–D68.9, D69, D75.82, D75.83, and M36.2); 10) other symptoms, signs and abnormal clinical and laboratory findings: malaise and fatigue (G93.3, R53.1, and R53.8), respiratory signs and symptoms (R04–R09), smell and taste disturbances (R43.8 and R43.9), symptoms of mental conditions (F30.4, F31.70, F31.72, F31.74, F31.76, F31.78, F32.5, F33.40, F33.42, R45.0–R45.7, R45.8 [except R45.851 and R45.88], and R46), sleeping disorders (G47 and R06.3), circulatory signs and symptoms (R00, R01, R03.0, and R09.89), dizziness and syncope (I95.1, G90.9, R42, and R55), and musculoskeletal pain (M25.5, M25.6, M54.6, M54.8, M54.9, M79.1, M79.6, and M79.7).

†† Proportional hazards assumption was tested for every Cox proportional hazards model. In some models, proportionality assumption for certain variables was rejected, and the Schoenfeld residuals and survival curves were visually examined. Although slopes were not always parallel, the survival curves did not cross in any cases, indicating that the nonproportionality might not lead to severe bias in the results. The estimated aHRs from Cox models were compared against aHRs from Weibull models (estimated using "SurvRegCensCov" R package) and average aHRs from weighted Cox models (estimated using "coxphw" R package) and were found to be very close in magnitude and significance level.

§§ Previous hospitalization was defined by a presence of an inpatient claim during the 7–365 days before the index date. Previous medical complexity was defined using the validated pediatric medical complexity algorithm as presence of complex chronic disease (at least one claim with a progressive condition, at least one claim with malignant neoplasms, or at least one claim per body system for two different body systems), presence of noncomplex chronic disease (at least one claim for a single body system not flagged as progressive), or absence of chronic disease (reference category; none of the previously described encounters) during the 7–365 days before the index date.

¶¶ Age-stratified analyses were only performed when there were at least 10 patients with COVID-19 and at least 10 patients without COVID-19 in that age group with the specific symptom or condition. Each model was adjusted for age as a continuous covariate (to account for age differences within each age group), sex, race, U.S. Census Bureau region, payor type, previous medical complexity, and previous hospitalization.

*** The maximum possible matching ratio was used. For the main analysis, patients without COVID-19 were matched 3:1 to patients with COVID-19. For the analysis of a cohort of patients with no previous symptoms or conditions of interest, patients without COVID-19 were matched 2:1 to patients with COVID-19.

††† 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 1. Characteristics of children and adolescents aged 0–17 years with and without COVID-19 — HealthVerity medical claims database, United States, March 1, 2020–January 31, 2022

Characteristic*	No. (%)			
	All patients†		Patients without previous symptoms or conditions†	
	Patients without COVID-19§	Patients with COVID-19§	Patients without COVID-19§	Patients with COVID-19§
Total	**2,344,257**	**781,419**	**792,672**	**396,336**
Sex				
Female	1,172,481 (50.0)	390,827 (50.0)	394,536 (49.8)	197,268 (49.8)
Male	1,171,776 (50.0)	390,592 (50.0)	398,136 (50.2)	199,068 (50.2)
Age group, yrs				
Median (IQR)	12 (8–15)	12 (8–15)	12 (8–15)	12 (8–15)
<2	2,952 (0.1)	984 (0.1)	564 (0.1)	282 (0.1)
2–4	155,190 (6.6)	51,730 (6.6)	48,550 (6.1)	24,275 (6.1)
5–11	904,284 (38.6)	301,428 (38.6)	316,010 (39.9)	158,005 (39.9)
12–17	1,281,831 (54.7)	427,277 (54.7)	427,548 (53.9)	213,774 (53.9)
Race¶				
Asian	74,943 (3.2)	23,241 (3.0)	26,039 (3.3)	12,213 (3.1)
Black or African American	566,891 (24.2)	196,887 (25.2)	198,705 (25.1)	101,839 (25.7)
White	1,178,288 (50.3)	382,371 (48.9)	381,841 (48.2)	189,895 (47.9)
Other	73,401 (3.1)	24,648 (3.2)	26,044 (3.3)	12,889 (3.3)
Unknown or unavailable	450,734 (19.2)	154,272 (19.7)	160,043 (20.2)	79,500 (20.1)
Payor type				
Commercial	666,068 (28.4)	214,371 (27.4)	244,047 (30.7)	118,300 (29.8)
Medicaid	1,655,886 (70.6)	563,860 (72.2)	541,415 (68.3)	276,422 (69.7)
Medicare Advantage	13,466 (0.6)	1,277 (0.2)	4,415 (0.6)	676 (0.2)
Unknown or unavailable	8,837 (0.4)	1,911 (0.2)	2,795 (0.4)	938 (0.2)
U.S. Census Bureau region**				
Northeast	283,916 (12.1)	86,436 (11.1)	79,015 (10.0)	44,770 (11.3)
Midwest	527,527 (22.5)	132,879 (17.0)	167,233 (21.1)	68,471 (17.3)
South	1,160,472 (49.5)	448,844 (57.4)	397,624 (50.2)	217,886 (55.0)
West	372,342 (15.9)	113,260 (14.5)	148,800 (18.8)	65,209 (16.5)
Hospitalization during 7–365 days preceding index date				
Yes	104,768 (4.5)	28,294 (3.6)	8,030 (1.0)	4,007 (1.0)
No	2,239,489 (95.5)	753,125 (96.4)	784,642 (99.0)	392,329 (99.0)
Medical complexity during 7–365 days preceding index date				
No chronic disease	1,328,582 (56.7)	506,026 (64.8)	672,355 (84.8)	333,882 (84.2)
Non-complex chronic disease	649,710 (27.7)	184,188 (23.6)	95,337 (12.0)	50,980 (12.9)
Complex chronic disease	365,965 (15.6)	91,205 (11.7)	24,980 (3.2)	11,474 (2.9)

Abbreviation: ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*.

* Categories might not sum to 100% because of rounding or missing values.

† Columns 2 and 3 describe the main cohort: patients with COVID-19 and patients without COVID-19 who were matched 1:3 based on age, sex, and month of the index date (for patients with COVID-19, the date of either the first claim with a COVID-19 diagnosis code or the first positive SARS-CoV-2 test result, whichever occurred first; for patients without COVID-19, the date of a randomly selected claim during the month in which the patient without COVID-19 was matched to a patient with COVID-19). Columns 4 and 5 describe a cohort of patients with none of the 24 assessed symptoms or conditions during 7–365 days before the index date; patients with COVID-19 and patients without COVID-19 were matched 1:2 based on age, sex, and month of the index date (for patients with COVID-19, the date of either the first claim with a COVID-19 diagnosis code or the first positive SARS-CoV-2 test result, whichever occurred first; for patients without COVID-19, the date of the first negative SARS-CoV-2 test result, first health care encounter possibly related to COVID-19, or the first claim during the pandemic period if other dates were not available).

§ The cohort consisted of children and adolescents aged 0–17 years with continuous enrollment in an insurance plan during March 1, 2019–January 31, 2022, identified within a subset of CDC-licensed HealthVerity data that included persons with a health care encounter possibly related to COVID-19. Patients with COVID-19 were selected from patients who received a positive SARS-CoV-2 test result during March 2020–November 2021 or an ICD-10-CM code of B97.29 during March–April 2020 or U07.1 code during April 2020–November 2021. Patients without COVID-19 were selected after excluding patients who had an ICD-10-CM code related to COVID-19 (A41.89, B34.2, B97.21, B97.29, B94.8, J12.81, J12.82, J12.89, M30.3, M35.81, U07.1, or U07.2), a positive SARS-CoV-2 test result, or received treatment for COVID-19 (casirivimab/imdevimab, etesevimab/bamlanivimab, sotrovimab, bebtelovimab, nirmatrelvir, molnupiravir, or remdesivir) at any point during the study period. Vaccination status of patients was not included for this analysis.

¶ Analysis did not include ethnicity.

** U.S. Census Bureau regions: *Northeast*: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; *Midwest*: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; *South*: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia; *West*: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming.

disorders (0.85), mood disorders (0.78), and muscle disorders (0.94); no significant associations were found for the remaining five symptoms and conditions.

In age-stratified analysis of three age groups (2–4, 5–11, and 12–17 years), the unadjusted incidences of symptoms and conditions differed by age group (Supplementary Table, https://stacks.cdc.gov/view/cdc/118760). Among children aged 2–4 years, the highest aHRs for patients with COVID-19 compared with patients without COVID-19 were for myocarditis and cardiomyopathy (aHR = 2.39), acute and unspecified renal failure (1.52), and coagulation and hemorrhagic disorders (1.47) (Table 3). Unlike other age groups, children aged 2–4 years had higher rates of asthma diagnosis (1.12) and respiratory signs and symptoms (1.07) after COVID-19. Among children aged 5–11 years, the highest aHRs for patients with COVID-19 compared with those without were for myocarditis and cardiomyopathy (2.84), venous thromboembolic event (2.69), and acute and unspecified renal failure (1.38). Among patients aged 12–17 years, the highest aHRs for those with COVID-19 compared with those without were for acute pulmonary embolism (2.03), myocarditis and cardiomyopathy (1.66), and venous thromboembolic event (1.52).

TABLE 2. Incidence* and adjusted hazard ratios of selected potential post–COVID-19 symptoms and conditions among children and adolescents aged 0–17 years with and without COVID-19 — HealthVerity medical claims database, United States, March 1, 2020–January 31, 2022

	All patients†			Patients without previous symptoms or conditions†		
	No. (incidence)*			No. (incidence)*		
Outcome	Patients without COVID-19	Patients with COVID-19	aHR (95% CI)§	Patients without COVID-19	Patients with COVID-19	aHR (95% CI)§
Symptom						
Smell and taste disturbances	5,028 (296)	1,924 (340)	1.17 (1.11–1.24)¶	1,173 (205)	715 (250)	1.21 (1.11–1.33)¶
Circulatory signs and symptoms	80,900 (5,092)	27,207 (5,126)	1.07 (1.05–1.08)¶	18,729 (3,334)	10,518 (3,727)	1.12 (1.09–1.14)¶
Malaise and fatigue	74,908 (4,659)	24,970 (4,648)	1.05 (1.03–1.06)¶	15,712 (2,784)	8,964 (3,168)	1.13 (1.10–1.16)¶
Musculoskeletal pain	201,899 (14,819)	67,744 (14,800)	1.02 (1.02–1.03)¶	62,417 (11,647)	34,460 (12,662)	1.09 (1.07–1.10)¶
Dizziness and syncope	48,976 (2,993)	15,731 (2,876)	1.01 (0.99–1.03)	10,890 (1,923)	5,630 (1,980)	1.03 (0.99–1.06)
Gastrointestinal and esophageal disorders	94,395 (6,195)	30,266 (5,898)	1.01 (0.99–1.02)	22,411 (4,021)	11,686 (4,151)	1.03 (1.00–1.05)
Sleeping disorders	51,227 (3,203)	14,011 (2,588)	0.91 (0.90–0.93)¶	9,138 (1,616)	4,238 (1,488)	0.92 (0.89–0.95)¶
Respiratory signs and symptoms	283,139 (23,456)	85,279 (20,948)	0.91 (0.91–0.92)¶	80,364 (15,200)	47,690 (17,796)	1.16 (1.14–1.17)¶
Symptoms of mental conditions	47,138 (2,906)	12,944 (2,364)	0.91 (0.89–0.93)¶	9,268 (1,637)	4,529 (1,591)	0.97 (0.94–1.00)
Condition						
Acute pulmonary embolism	224 (13)	131 (23)	2.01 (1.62–2.50)¶	43 (8)	36 (13)	1.74 (1.12–2.72)¶
Myocarditis and cardiomyopathy	1,172 (69)	692 (122)	1.99 (1.81–2.19)¶	224 (39)	264 (92)	2.34 (1.96–2.79)¶
Venous thromboembolic event	315 (18)	164 (29)	1.87 (1.54–2.26)¶	51 (9)	37 (13)	1.48 (0.97–2.26)
Acute and unspecified renal failure	2,116 (124)	788 (139)	1.32 (1.22–1.43)¶	347 (61)	223 (78)	1.30 (1.10–1.54)¶
Type 1 diabetes	2,080 (123)	792 (140)	1.23 (1.13–1.33)¶	641 (112)	349 (122)	1.10 (0.96–1.25)
Coagulation and hemorrhagic disorders	4,454 (263)	1,582 (280)	1.18 (1.12–1.25)¶	849 (148)	537 (188)	1.26 (1.14–1.41)¶
Type 2 diabetes	6,197 (366)	2,170 (384)	1.17 (1.11–1.23)¶	1,210 (212)	729 (255)	1.19 (1.09–1.31)¶
Cardiac dysrhythmias	13,031 (774)	4,595 (817)	1.16 (1.12–1.20)¶	2,391 (419)	1,442 (504)	1.20 (1.13–1.28)¶
Cerebrovascular disease	441 (26)	149 (26)	1.20 (1.00–1.45)	67 (12)	28 (10)	0.84 (0.54–1.30)
Chronic kidney disease	1,105 (65)	321 (57)	1.07 (0.95–1.22)	171 (30)	81 (28)	0.99 (0.76–1.29)
Asthma	82,105 (5,625)	27,327 (5,557)	1.00 (0.99–1.01)	26,470 (4,785)	12,751 (4,533)	0.93 (0.91–0.95)¶
Muscle disorders	23,655 (1,424)	6,807 (1,222)	0.94 (0.91–0.96)¶	4,075 (715)	2,109 (738)	1.03 (0.98–1.09)
Neurological conditions	64,436 (4,077)	18,681 (3,485)	0.94 (0.92–0.95)¶	12,954 (2,298)	6,513 (2,295)	0.99 (0.96–1.02)
Anxiety and fear-related disorders	112,234 (7,686)	31,274 (6,107)	0.85 (0.84–0.86)¶	28,624 (5,166)	13,016 (4,634)	0.90 (0.88–0.91)¶
Mood disorders	23,108 (1,406)	5,248 (944)	0.78 (0.75–0.80)¶	3,656 (642)	1,531 (535)	0.83 (0.78–0.88)¶

Abbreviation: aHR = adjusted hazard ratio.

* Occurrences per 100,000 person-years.

† Columns 2, 3, and 4 represent analyses of incidences and aHRs obtained after 1:3 matching of patients with COVID-19 and patients without COVID-19. Incidences and aHRs for each symptom or condition were calculated after excluding patients who had that particular symptom or condition during 7–365 days before the index date (for patients with COVID-19, the date of either the first claim with a COVID-19 diagnosis code or the first positive SARS-CoV-2 test result, whichever occurred first; for patients without COVID-19, the date of a randomly selected claim during the month in which the patient without COVID-19 was matched to a patient with COVID-19). Columns 5, 6, and 7 represent incidences and aHRs obtained after 1:2 matching of patients with COVID-19 and those without who had not experienced any of the 24 assessed symptoms or conditions during 7–365 days before the index date (for patients with COVID-19, the date of either the first claim with a COVID-19 diagnosis code or the first positive SARS-CoV-2 test result, whichever occurred first; for patients without COVID-19, the date of the first negative SARS-CoV-2 test result, first health care encounter possibly related to COVID-19, or the first claim during the pandemic period if other dates were not available).

§ Each aHR was obtained from a single Cox proportional hazards model, with the specific symptom or condition as the outcome and the following covariates: presence of COVID-19, age group, sex, race, U.S. Census Bureau region, payor type, previous medical complexity, and previous hospitalization.

¶ P-value <0.05.

The sensitivity analysis of 396,336 patients with COVID-19 and 792,672 matched patients without COVID-19 (without previous symptoms or conditions of interest) found that patients in both groups were healthier at baseline than their counterparts in the main cohort; 84.2% of persons with COVID-19 and 84.8% patients without COVID-19 had no previous documentation of chronic disease, compared with 64.8% and 56.7%, respectively in the main cohort (Table 1). Higher rates of five symptoms and six conditions among patients with COVID-19 compared with those without were found in the sensitivity analysis, whereas the main analysis found higher rates of four symptoms and eight conditions. In the sensitivity analysis, aHRs for type 1 diabetes and venous thromboembolic event were not statistically significant, and the aHR for respiratory signs and symptoms was elevated (1.16) (Table 2).

Analysis of the relationship between incidence rates among patients with COVID-19 and aHRs found that five post-COVID conditions with the highest aHRs had low incidence rates, ranging from 23 (acute pulmonary embolism) to 140 (type 1 diabetes) per 100,000 person-years (Supplementary Figure, https://stacks.cdc.gov/view/cdc/118761). Conversely, this analysis found that five symptoms and conditions with the highest incidence rates among patients with COVID-19 had lower aHRs (near or below 1.0): respiratory signs and symptoms (0.91), musculoskeletal pain (1.02), anxiety and fear-related disorders (0.85), gastrointestinal and esophageal disorders (1.01), and asthma (1.00).

Discussion

This analysis found increased incidence rates of several symptoms and conditions during the 31–365 days after a diagnosis of COVID-19 among children and adolescents aged 0–17 years. The highest aHRs were associated with potentially serious conditions, such as acute pulmonary embolism, myocarditis and cardiomyopathy, venous thromboembolic event, acute and unspecified renal failure, and type 1 diabetes. These conditions with the highest aHRs were rare or uncommon among children and adolescents in this analysis. Some of the study's findings are consistent with previous evidence of elevated risk for new onset of diabetes (*5*), myocarditis (*6*), and certain symptoms (*4*), whereas other conditions (acute

TABLE 3. Adjusted hazard ratios of selected potential post–COVID-19 symptoms and conditions among children and adolescents aged 2–17 years with and without COVID-19, by age group — HealthVerity medical claims database, United States, March 1, 2020–January 31, 2022

Outcome	Adjusted hazard ratio (95% CI)*		
	Aged 2–4 yrs	Aged 5–11 yrs	Aged 12–17 yrs
Symptom			
Smell and taste disturbances	1.22 (0.70–2.15)	0.94 (0.83–1.07)	1.23 (1.16–1.31)†
Circulatory signs and symptoms	1.17 (1.12–1.23)†	1.11 (1.08–1.13)†	1.04 (1.02–1.06)†
Malaise and fatigue	1.13 (1.05–1.22)†	1.08 (1.05–1.12)†	1.03 (1.01–1.04)†
Musculoskeletal pain	1.16 (1.10–1.21)†	1.06 (1.04–1.07)†	1.00 (0.99–1.01)
Dizziness and syncope	1.08 (0.90–1.29)	1.03 (0.99–1.08)	1.00 (0.98–1.02)
Gastrointestinal and esophageal disorders	1.15 (1.10–1.20)†	1.02 (1.00–1.04)†	0.97 (0.95–0.99)†
Sleeping disorders	0.99 (0.93–1.06)	0.89 (0.86–0.92)†	0.91 (0.89–0.94)†
Respiratory signs and symptoms	1.07 (1.04–1.10)†	0.93 (0.92–0.94)†	0.88 (0.87–0.89)†
Symptoms of mental conditions	1.03 (0.97–1.10)	0.92 (0.90–0.95)†	0.89 (0.86–0.91)†
Condition			
Acute pulmonary embolism	—§	—§	2.03 (1.61–2.56)†
Myocarditis and cardiomyopathy	2.39 (1.57–3.65)†	2.84 (2.39–3.37)†	1.66 (1.48–1.88)†
Venous thromboembolic event	—§	2.69 (1.73–4.19)†	1.52 (1.22–1.91)†
Acute and unspecified renal failure	1.52 (1.07–2.14)†	1.38 (1.16–1.63)†	1.27 (1.15–1.40)†
Type 1 diabetes	1.01 (0.57–1.78)	1.31 (1.13–1.53)†	1.20 (1.09–1.33)†
Coagulation and hemorrhagic disorders	1.47 (1.20–1.80)†	1.28 (1.15–1.43)†	1.10 (1.03–1.19)†
Type 2 diabetes	1.24 (0.85–1.81)	1.14 (1.02–1.28)†	1.18 (1.11–1.24)†
Cardiac dysrhythmias	1.44 (1.22–1.70)†	1.23 (1.14–1.32)†	1.12 (1.08–1.17)†
Cerebrovascular disease	1.66 (0.85–3.23)	1.14 (0.79–1.64)	1.18 (0.93–1.48)
Chronic kidney disease	0.86 (0.54–1.36)	1.04 (0.83–1.31)	1.12 (0.96–1.31)
Asthma	1.12 (1.07–1.18)†	1.02 (1.00–1.05)†	0.96 (0.94–0.98)†
Muscle disorders	0.87 (0.77–0.98)†	0.86 (0.82–0.91)†	0.96 (0.93–0.99)†
Neurological conditions	0.98 (0.93–1.04)	0.96 (0.93–0.98)†	0.91 (0.89–0.93)†
Anxiety and fear-related disorders	0.91 (0.83–1.00)	0.86 (0.83–0.88)†	0.84 (0.82–0.85)†
Mood disorders	0.82 (0.62–1.08)	0.73 (0.69–0.77)†	0.80 (0.77–0.83)†

* Each adjusted hazard ratio was obtained from a single Cox proportional hazards model stratified by age group, with the specific symptom or condition as the outcome and the following covariates: presence of COVID-19, age (continuous variable), sex, race, U.S. Census Bureau region, payor type, previous medical complexity, and previous hospitalization.

† P-value <0.05.

§ Age-stratified analyses were only performed when there were at least 10 patients with COVID-19 and at least 10 patients without COVID-19 in that age group with the specific symptom or condition.

pulmonary embolism, venous thromboembolic event, acute renal failure, coagulation and hemorrhagic disorders, and cardiac dysrhythmias) have not been previously reported as post-COVID conditions among children and adolescents.

Several symptoms and conditions (respiratory signs and symptoms, mental health symptoms and conditions, neurological conditions, muscle disorders, and sleeping disorders) were less likely to occur among patients with COVID-19 than among patients without COVID-19. Reasons for these observed associations are likely multifactorial, and might be, in part, because patients without COVID-19 were selected from a cohort of patients with a health care encounter possibly related to COVID-19 and were less healthy than were patients with COVID-19 at baseline. Although most of the symptoms and conditions selected for the analysis were based on those observed in previous post-COVID studies, they are not unique to patients with a history of COVID-19, and many are common among children and adolescents. A United Kingdom study found a high prevalence of poor mental health and well-being among all children and adolescents aged 11–17 years during the pandemic, but no difference among those with positive and negative SARS-CoV-2 test results (*7*). Respiratory signs and symptoms were less likely to occur among patients with COVID-19 than among those without in the main cohort. The opposite result was found in a subset of children aged 2–4 years and in a cohort of children and adolescents with no previous symptoms or conditions of interest; new respiratory signs and symptoms were more likely to occur among children and adolescents who had COVID-19, compared with those without a history of COVID-19.

The findings in this report are subject to at least seven limitations. First, the definitions of potential post-COVID symptoms and conditions are subject to misclassification bias because the symptoms and conditions were defined by a single ICD-10-CM code and no information on laboratory assessments or degree of severity was available. Second, because the incidence date of a symptom or a condition was based on the first occurrence of the ICD-10-CM code, the actual incidence date of that symptom or condition might have occurred prior to COVID-19. Third, patients infected with SARS-CoV-2 without a documented COVID-19 diagnosis or positive test result might have been misclassified as not having had COVID-19, potentially reducing the magnitude of observed associations. Fourth, the aHR estimates might be reduced because patients without COVID-19 were patients with a health care encounter possibly related to COVID-19. Fifth, because patients' vaccination status was likely underreported in this dataset, this analysis was not adjusted for previous receipt of COVID-19 vaccines. Sixth, although this study relied on statistical significance for interpreting the increased rates of symptoms and conditions, further understanding of the clinical significance of the observed associations, including whether these symptoms and conditions are transient or chronic, is necessary. Finally, generalizability might be limited because the analysis was restricted to children and adolescents aged 0–17 years included in a medical claims database, approximately 70% of whom were enrolled in Medicaid managed care; therefore, findings are not necessarily representative of all children and adolescents with COVID-19 or of those who do not seek health care.

These findings can be used to apprise health care professionals and caregivers about new symptoms and conditions that occur among children and adolescents in the months after SARS-CoV-2 infection. COVID-19 prevention strategies, including vaccination for all eligible persons aged ≥6 months, are critical for preventing SARS-CoV-2 infection and subsequent illness and for reducing the public health impact of post-COVID symptoms and conditions.

Summary

What is already known about this topic?

Children and adolescents might be at risk for certain post-COVID symptoms and conditions.

What is added by this report?

Compared with patients aged 0–17 years without previous COVID-19, those with previous COVID-19 had higher rates of acute pulmonary embolism (adjusted hazard ratio = 2.01), myocarditis and cardiomyopathy (1.99), venous thromboembolic event (1.87), acute and unspecified renal failure (1.32), and type 1 diabetes (1.23), all of which were rare or uncommon in this study population.

What are the implications for public health practice?

COVID-19 prevention strategies, including vaccination for all eligible persons aged ≥6 months, are critical to preventing SARS-CoV-2 infection and subsequent illness, and reducing the public health impact of post-COVID symptoms and conditions among persons aged 0–17 years.

Acknowledgments

Members of the Data, Analytics, and Visualization Task Force, CDC COVID-19 Emergency Response Team; Matthew Oster, Center on Birth Defects and Developmental Disabilities, CDC; John R. Pleis, Division of Research and Methodology, National Center for Health Statistics, CDC.

Corresponding author: Lyudmyla Kompaniyets, opt4@cdc.gov.

[1]CDC COVID-19 Emergency Response Team; [2]GAP Solutions Inc, Herndon, Virginia.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

References

1. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature 2021;594:259–64. PMID:33887749 https://doi.org/10.1038/s41586-021-03553-9
2. Chevinsky JR, Tao G, Lavery AM, et al. Late conditions diagnosed 1–4 months following an initial coronavirus disease 2019 (COVID-19) encounter: a matched-cohort study using inpatient and outpatient administrative data—United States, 1 March–30 June 2020. Clin Infect Dis 2021;73(Suppl 1):S5–16. PMID:33909072 https://doi.org/10.1093/cid/ciab338
3. Kikkenborg Berg S, Dam Nielsen S, Nygaard U, et al. Long COVID symptoms in SARS-CoV-2-positive adolescents and matched controls (LongCOVIDKidsDK): a national, cross-sectional study. Lancet Child Adolesc Health 2022;6:240–8. PMID:35143771 https://doi.org/10.1016/S2352-4642(22)00004-9
4. Hernandez-Romieu AC, Carton TW, Saydah S, et al. Prevalence of select new symptoms and conditions among persons aged younger than 20 years and 20 years or older at 31 to 150 days after testing positive or negative for SARS-CoV-2. JAMA Netw Open 2022;5:e2147053. PMID:35119459 https://doi.org/10.1001/jamanetworkopen.2021.47053
5. Barrett CE, Koyama AK, Alvarez P, et al. Risk for newly diagnosed diabetes >30 days after SARS-CoV-2 infection among persons aged <18 years—United States, March 1, 2020–June 28, 2021. MMWR Morb Mortal Wkly Rep 2022;71:59–65. PMID:35025851 https://doi.org/10.15585/mmwr.mm7102e2
6. Boehmer TK, Kompaniyets L, Lavery AM, et al. Association between COVID-19 and myocarditis using hospital-based administrative data—United States, March 2020–January 2021. MMWR Morb Mortal Wkly Rep 2021;70:1228–32. PMID:34473684 https://doi.org/10.15585/mmwr.mm7035e5
7. Stephenson T, Pinto Pereira SM, Shafran R, et al; CLoCk Consortium. Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLoCk): a national matched cohort study. Lancet Child Adolesc Health 2022;6:230–9. PMID:35143770 https://doi.org/10.1016/S2352-4642(22)00022-0
8. Magnusson K, Skyrud KD, Suren P, et al. Healthcare use in 700 000 children and adolescents for six months after covid-19: before and after register based cohort study. BMJ 2022;376:e066809. PMID:35039315 https://doi.org/10.1136/bmj-2021-066809
9. Taquet M, Dercon Q, Harrison PJ. Six-month sequelae of post-vaccination SARS-CoV-2 infection: a retrospective cohort study of 10,024 breakthrough infections. Brain Behav Immun 2022;103:154-162. PMID:35447302 https://doi.org/10.1016/j.bbi.2022.04.013
10. Simon TD, Haaland W, Hawley K, Lambka K, Mangione-Smith R. Development and validation of the pediatric medical complexity algorithm (PMCA) version 3.0. Acad Pediatr 2018;18:577–80. PMID:29496546 https://doi.org/10.1016/j.acap.2018.02.010

Notes from the Field

Increase in Pediatric Intracranial Infections During the COVID-19 Pandemic — Eight Pediatric Hospitals, United States, March 2020–March 2022

Daliya Khuon[1,2]; Sara Ogrin[3]; Julie Engels[4]; Aileen Aldrich[1,2,5]; Rosemary M. Olivero[1,2]

During the first 2 years of the U.S. COVID-19 pandemic, pediatric centers anecdotally reported increased rates of intracranial bacterial infections, many of which were diagnosed during or immediately after an infection with SARS-CoV-2, the virus that causes COVID-19 (*1*,*2*). Although intracranial bacterial infections occur as a rare complication of partially treated or untreated bacterial rhinosinusitis in adolescents as well as mastoiditis in children of all ages (*3*), a 236% increase in cases among children was observed at a Michigan children's hospital (Aldrich A and Ogrin S, Helen DeVos Children's Hospital of Spectrum Health, unpublished data, 2022). Most of these cases were in infants and children aged <12 years and associated with a diversity of identified pathogens, including a range of *Streptococcus* species with more severe disease requiring extended intensive care unit admission and multiple surgical interventions; many of the cases had recent or concurrent SARS-CoV-2 infection. To ascertain whether a similar trend occurred nationally during the first 2 years of the COVID-19 pandemic, a survey was conducted through the Emergency Infections Network (EIN) of the Infectious Diseases Society of America, a provider-based network of approximately 2,800 infectious diseases specialists primarily based in North America. The initial survey was sent to all EIN participants in February 2022 and queried respondents about whether they had observed an increase in intracranial infections or an increase in invasive *Streptococcus* spp. infections in patients aged ≤18 years during the first 2 years of the COVID-19 pandemic, irrespective of a recent or concurrent COVID-19 infection. The initial survey included 109 respondents, 47 (43%) of whom reported observing an increase in intracranial infections. A follow-up survey was conducted among 64 EIN respondents who expressed interest in further participation, eight of whom were able to query their electronic medical records to determine case rates before the pandemic (January 1, 2018–January 1, 2020) and during the early pandemic (March 1, 2020–March 1, 2022) using *International Classification of Diseases, Tenth Revision* codes (Supplementary Box, https://stacks.cdc.gov/view/cdc/119620). Data were provided by eight institutions, representing all four U.S. Census Bureau regions (Northeast, Midwest, South, and West). Descriptive statistics, including number of diagnoses by infection type, were used (Supplementary Table, https://stacks.cdc.gov/view/cdc/119803). Percent change was calculated for each infection category for each institution, and mean percent change was calculated across institutions. Percent change was used rather than raw numbers because of the wide variability in numbers of cases among institutions. Statistical significance could not be calculated because of the low number of survey respondents. No demographic or COVID-19 vaccination data were collected on individual patients. This activity was reviewed by CDC and was conducted with applicable federal law and CDC policy.*

During the early COVID-19 pandemic, isolated intracranial abscess increased in the participating institutions by a mean of 100.9% (SD = 133%), and sinusitis complicated by intracranial abscess increased by a mean of 76.7% (SD = 97%). Orbital cellulitis, sinusitis, and mastoiditis all decreased on average by 14.5% (SD = 31%), 31.9% (SD = 17%), and 24.7% (SD = 31%), respectively (Figure). Mastoiditis complicated by intracranial abscess decreased by 116.7% (SD = 96%).

The findings in this report are subject to at least three limitations. Because participation in the EIN surveys was voluntary, the results are not representative of intracranial infections throughout the United States. Second, the response rate was low, and response bias possibly affected the findings. Finally, only limited data were collected, and the cross-sectional nature of this analysis precludes inference of causation.

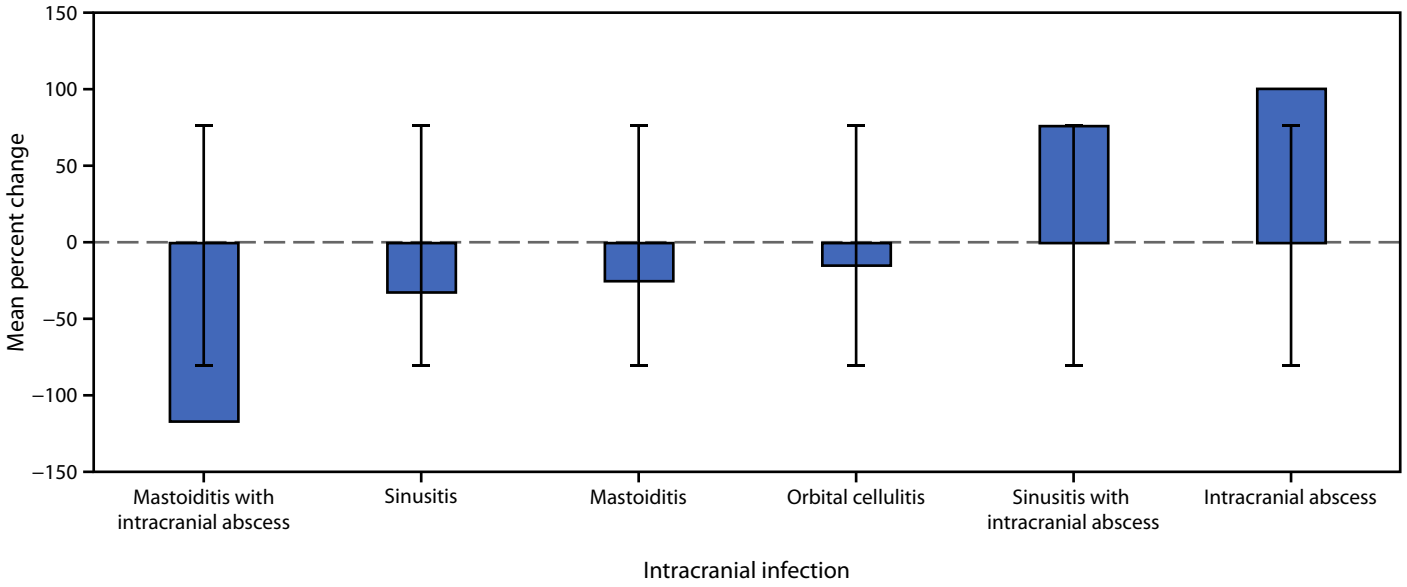
On June 8, 2022, CDC asked health care providers and health departments to report the occurrence of brain abscess, epidural empyema, or subdural empyema in persons aged ≤18 years without a previous history of neurosurgical procedures or head trauma, hospitalized on or after June 1, 2021, and to retain associated clinical specimens and isolates. To report possible cases,† health care providers should contact their health department and email CDC (CDCStrepInquiry@cdc.gov).

This initial investigation suggests a possible increase in some forms of intracranial infections in persons aged ≤18 years living in the United States during March 2020–March 2022, coinciding with the first 2 years of the COVID-19 pandemic. Further characterization of affected patients, disease course,

* 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.

† CDC is asking health care providers and health departments to report the occurrence of brain abscess, epidural empyema, or subdural empyema in persons aged ≤18 years without a previous history of neurosurgical procedures or head trauma, hospitalized on or after June 1, 2021. Health care providers and health departments are encouraged to report cases that are 1) associated with streptococcal infection, 2) because of other bacterial pathogens, 3) polymicrobial, or 4) have no pathogen identified.

FIGURE. Mean percent change* in number of intracranial bacterial infections† among children and adolescents aged ≤18 years from before the COVID-19 pandemic through the early pandemic — eight U.S. children's hospitals, January 2018–March 2022



* Mean percent change was calculated across participating institutions for each infection type from the prepandemic (January 1, 2018–January 1, 2020) to the early pandemic (March 1, 2020–March 1, 2022) periods. SD shown by error bars.
† Intracranial abscess count does not include counts from sinusitis with intracranial abscess or mastoiditis with intracranial abscess.

temporal association with COVID-19 infection (as well as predominant variants circulating at the time of diagnosis), microbiology of cases, and morbidity and mortality associated with this observation are needed, because the factors causing this possible increase in intracranial infections are not fully understood at this time. Intracranial infections require prompt and intensive medical management; therefore, defining the pathogenesis, relation to SARS-CoV-2 infection, and other risk factors, can both raise public awareness and help medical providers diagnose and appropriately manage affected patients.

Acknowledgment

Susan Beekman, Emerging Infections Network.

Corresponding author: Rosemary M. Olivero, Rosemary.olivero@helendevoschildrens.org, 312-515-6007.

[1]Pediatric Infectious Diseases, Helen DeVos Children's Hospital of Spectrum Health, Grand Rapids, Michigan; [2]Department of Pediatrics and Human Development, College of Human Medicine, Michigan State University, Grand Rapids, Michigan; [3]Department of Pharmacy, Helen DeVos Children's Hospital of Spectrum Health, Grand Rapids, Michigan; [4]Spectrum Health Hospital Group, Grand Rapids, Michigan; [5]Department of Pediatrics, College of Osteopathic Medicine, Michigan State University, Grand Rapids, Michigan.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

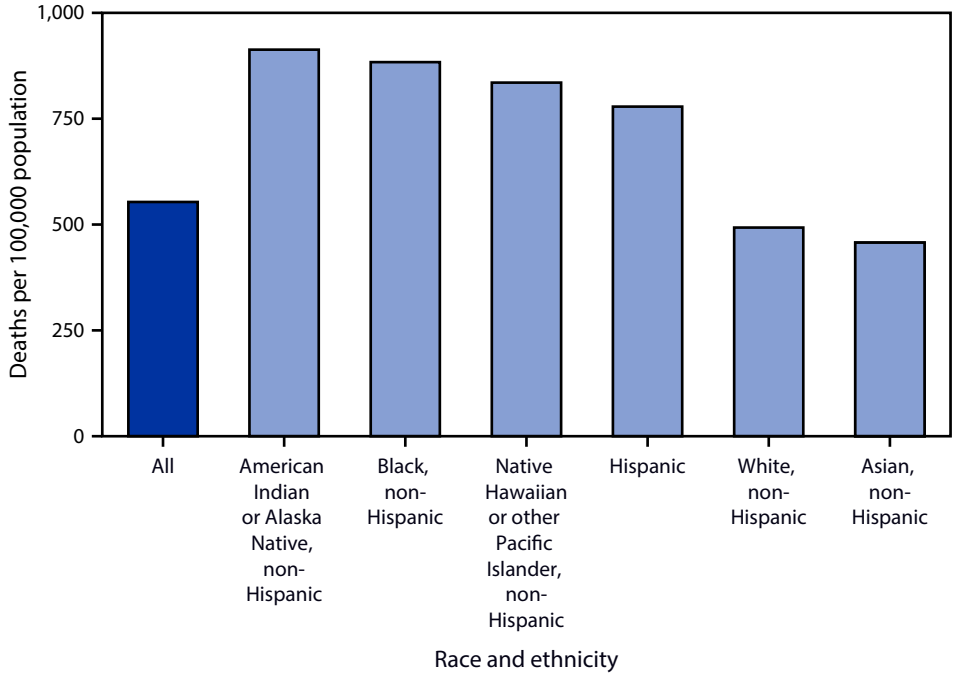
References

1. Arteaga AA, Tran J, Frey H, Lewis AF. Rapidly progressive complicated acute bacterial sinusitis in the setting of severe pediatric SARS-CoV-2 infection. Ann Otol Rhinol Laryngol 2021. Epub October 27, 2021. PMID:34706569 https://doi.org/10.1177/00034894211055337
2. Turbin RE, Wawrzusin PJ, Sakla NM, et al. Orbital cellulitis, sinusitis and intracranial abnormalities in two adolescents with COVID-19. Orbit 2020;39:305–10. PMID:32419568 https://doi.org/10.1080/01676830.2020.1768560
3. Milinis K, Thompson N, Atsmoni SC, Sharma SD. Sinogenic intracranial suppuration in children: systematic review and meta-analysis. Otolaryngol Head Neck Surg 2021. Otolaryngol Head Neck Surg 2022;167:215–23. PMID:34491863 https://doi.org/10.1177/01945998211043847

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Age-Adjusted Death Rates* from Diabetes Mellitus† Among Adults Aged ≥65 Years, by Single Race and Hispanic Origin — National Vital Statistics System, United States, 2020



* Deaths per 100,000 population, age-adjusted to the 2000 U.S. standard population.
† Deaths with diabetes mellitus as underlying or contributing cause were identified using the *International Classification of Diseases, Tenth Revision* multiple cause of death codes E10–E14.

In 2020, the age-adjusted death rate from diabetes mellitus as the underlying or contributing cause of death for adults aged ≥65 years was 553.4 per 100,000 population. The rates were higher for non-Hispanic American Indian or Alaska Native (913.6), non-Hispanic Black (884.1), non-Hispanic Native Hawaiian or other Pacific Islander (835.4), and Hispanic adults (778.5) compared with non-Hispanic White (493.3) and non-Hispanic Asian adults (457.7). Rates were lower among Hispanic than among non-Hispanic American Indian or Alaska Native and non-Hispanic Black adults, and rates were lower among non-Hispanic Asian compared with non-Hispanic White adults.

Source: National Vital Statistics System, 2020. https://www.cdc.gov/nchs/nvss/deaths.htm

Reported by: Yelena Gorina, MS, MPH, yag9@cdc.gov, 301-458-4241.

The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format. To receive an electronic copy each week, visit *MMWR* at https://www.cdc.gov/mmwr/index.html.

Readers who have difficulty accessing this PDF file may access the HTML file at https://www.cdc.gov/mmwr/index2022.html. Address all inquiries about the *MMWR* Series to Editor-in-Chief, *MMWR* Series, Mailstop V25-5, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30329-4027 or to mmwrq@cdc.gov.

ISSN: 0149-2195 (Print)