

## Evaluation of State-Led Surveillance of Neonatal Abstinence Syndrome — Six U.S. States, 2018–2021

Shahla M. Jilani, MD<sup>1</sup>; Kristina West, MS, LLM<sup>2</sup>; Laura Jacobus-Kantor, PhD<sup>2</sup>; Mir M. Ali, PhD<sup>2</sup>; Alice Nyakeriga, PhD<sup>3</sup>; Heather Lake-Burger, MS, MPH<sup>4</sup>; Meagan Robinson<sup>5</sup>; A. Elise Barnes, MPH<sup>6</sup>; Tracey Jewell, MPH<sup>7</sup>; Shayne Gallaway, PhD<sup>8,9</sup>

Opioid use disorder (OUD) is a significant public health problem in the United States, which affects children as well as adults. During 2010–2017, maternal opioid-related diagnoses increased approximately 130%, from 3.5 to 8.2 per 1,000 hospital deliveries, and neonatal abstinence syndrome (NAS) increased 83%, from 4.0 to 7.3 per 1,000 hospital deliveries (1). NAS, a withdrawal syndrome, can occur among infants following in utero exposure to opioids and other psychotropic substances (2). In 2018, a study of six states with mandated NAS case reporting for public health surveillance (2013–2017) found that mandated reporting helped quantify NAS incidence and guide programs and services (3). To review surveillance features and programmatic development in the same six states, a questionnaire and interview with state health department officials on postimplementation efforts were developed and implemented in 2021. All states reported ongoing challenges with initial case reporting, limited capacity to track social and developmental outcomes, and no requirement for long-term follow-up in state-mandated case reporting; only one state instituted health-related outcomes monitoring. The primary surveillance barrier beyond initial case reporting was lack of infrastructure. To serve identified needs of opioid- or other substance-exposed mother-infant dyads, state health departments reported programmatic successes expanding education and access to maternal medication for opioid use disorder (MOUD), community and provider education or support services, and partnerships with perinatal quality collaboratives. Development of additional infrastructure is needed for states aiming to advance NAS surveillance beyond initial case reporting.

A 2018 study (3) identified six states (Arizona, Florida, Georgia, Kentucky, Tennessee, and Virginia) with laws mandating NAS case reporting by applying specific criteria focusing on laws across all 50 states and the District of Columbia that

explicitly named “neonatal abstinence syndrome” in disease and conditions reporting laws. Although each state reported distinct pathways for law enactment, state officials consistently indicated that the purpose for mandating NAS reporting was to characterize both NAS incidence and impact in the state and to identify more severely affected communities and opportunities for programmatic development. One of the main findings from that study indicated that mandated reporting helped quantify NAS incidence and guide programs and services.

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Accordingly, the overarching aim of the current study was to review surveillance features and program development by the same six states, after the enactment of state laws, to better understand NAS surveillance beyond initial case reporting. Thus, this qualitative study was designed to examine longer-term surveillance and programs developed postimplementation as a primary objective, and changes since the 2018 study in data collection and quality assurance practices as a secondary objective. Epidemiologists and birth defects program managers from all six states completed the 34-item questionnaire and semistructured follow-up telephone interview during February–April 2021. Questionnaire and interview data were analyzed for similarities and differences in initial case reporting (timeliness, reporting criteria, and completeness) and features beyond initial case reporting (outcomes follow-up, quality assurance measures, and resources used) and, although not directly linked to surveillance programs, subsequent programmatic development since enactment of state-mandated NAS case reporting. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.\*

A review of the programs indicated both differences and similarities across the six states' surveillance features (Table 1). Important distinctions centered around data timeliness, with

\*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.

some additional variation in state-specified reporting criteria, and the least amount of variance in case follow-up and in use of reports. Case reporting typically occurs within 30 to 66 days in Georgia, Kentucky, and Virginia, with the shortest reporting time noted by Tennessee (28 days) and the longest by Florida (180 days). As in the 2018 study, all six states reported that clinical diagnosis, regardless of whether treatment was given, prompted NAS case reporting (reporting varies from state to state). However, both Georgia and Tennessee reported transitioning to implementation of the NAS case definition recommended by the Council of State and Territorial Epidemiologists (CSTE) to standardize use in provider reporting with clinical record documentation and administrative claims-based data (4). Most states estimated receiving reports for approximately 75% of total NAS cases diagnosed by clinicians; Arizona receives reports for 50% to 75% of total cases. Consistent with the 2018 study, states collectively use case reporting to determine 1) incidence of NAS, 2) substance exposure patterns within different geographic and demographic communities, and 3) program development within the respective states. Kentucky also uses case reporting to characterize hospital discharge disposition for mother and infant.

Alongside information on surveillance extending beyond initial case reporting, states also noted numerous ongoing case reporting challenges (Table 2). These include collecting missing information (e.g., race or ethnicity, toxicology data, and substance exposure history) for mother or infant; assessing

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TABLE 1. Features of neonatal abstinence syndrome case reporting — six states,\* 2018–2021†

State (yr) <sup>§</sup>	Reporting timeliness, <sup>¶</sup> days	Reporting criteria: clinician diagnosis <sup>**</sup>	Case follow-up <sup>††</sup>	Estimated completeness of case capture, <sup>§§</sup> %	Use of case reports	
					To determine NAS incidence, community substance use patterns, and guide program development	To characterize mother-infant hospital discharge disposition
Arizona (2017)	Unknown <sup>¶¶</sup>	Yes	None	50–75	Yes	No
Florida (2014)	180	Yes	None	>75	Yes	No
Georgia (2017)	51	Yes: infant toxicology positive. <sup>***</sup> Transitioning to CSTE case reporting definition. <sup>†††</sup>	None	>75	Yes	No
Kentucky (2014)	66	Yes	None	>75	Yes	Yes
Tennessee (2017)	28	Yes: transitioning to CSTE case reporting definition. <sup>†††</sup>	None	>75	Yes	No
Virginia (2017)	30	Yes	None	>75	Yes	No

**Abbreviations:** CSTE = Council of State and Territorial Epidemiologists; NAS = neonatal abstinence syndrome.

\* Arizona, Florida, Georgia, Kentucky, Tennessee, and Virginia.

† The six states that implemented mandatory NAS reporting during 2013–2017 were invited for voluntary participation in a follow-up questionnaire and telephone interview to review NAS case reporting and surveillance from May 2018 to February 2021.

§ Year legal NAS case reporting mandate became effective; Florida had passive NAS case reporting system from the Agency for Health Care Administration within 6 months of diagnosis.

¶ Average number of days from the time of NAS diagnosis to case report.

\*\* Medical provider diagnosis regardless of whether infant required or was given specific treatment.

†† System or standard operating procedure in place for follow-up of infants with diagnosed NAS or their families once state health department has been notified of the case.

§§ Capture of total case incidence rate via case reporting compared with hospital discharge records.

¶¶ Timeliness is unknown because state-level resources to analyze and monitor completeness received limited NAS case reports.

\*\*\* For Georgia, infants with positive toxicology or clinician diagnosis of NAS are reported.

††† [https://cdn.ymaws.com/www.cste.org/resource/resmgr/2019ps/final/19-MCH-01\\_NAS\\_final\\_7.31.19.pdf](https://cdn.ymaws.com/www.cste.org/resource/resmgr/2019ps/final/19-MCH-01_NAS_final_7.31.19.pdf)

data accuracy from electronic health records, claims data, and medical record abstraction; sharing reports with other agencies; and de-duplicating data received from multiple sources. To reduce missing data, Kentucky and Tennessee instituted mandatory data fields and linkage of case reporting to vital records. Georgia noted that providing reporter education on case reporting best practices and partnering with national laboratories for electronic reporting of positive infant toxicology were helpful to initial case reporting efforts.

States were asked about resources most and least helpful to surveillance efforts. Georgia and Tennessee noted that partnership with reporting hospital personnel and the use of free web-based reporting tools were helpful. Arizona officials noted that using an existing state disease reporting system streamlined hospital-based case reporting but noted that their state's NAS case definition only accounted for opioids. Georgia reported that even after transitioning to the CSTE case definition, opportunities for improvement remain, including case definition implementation by medical provider and facilities to continue standardizing reporting using clinical and administrative data sources. Florida, Georgia, Kentucky, Tennessee, and Virginia reported that partnering with perinatal quality collaboratives was helpful for ongoing surveillance efforts offering improvement opportunities for 1) case reporting, data collection, and data quality; 2) clinician education on resources

### Summary

#### What is already known about this topic?

Increasing diagnoses of maternal opioid use disorder and neonatal abstinence syndrome (NAS) continue to affect U.S. communities. During 2018, a study of six states with mandated NAS case reporting for public health surveillance (2013–2017) found that mandated reporting helped quantify NAS incidence and inform programs and services.

#### What is added by this report?

A follow-up study of these states found continued advantages in determining NAS incidence and community exposure patterns to guide state program development. However, persistent data collection challenges and infrastructural gaps influence states' capacity for longer-term surveillance beyond initial case reporting.

#### What are the implications for public health practice?

States considering surveillance beyond initial case reporting might benefit from understanding opportunities and challenges related to necessary infrastructure and resource development to facilitate longer-term public health follow-up.

for opioid and substance-exposed infants and mothers, and 3) health outcomes tracking.

States were also asked about monitoring health-, social services-, and developmental-related outcomes. No states reported available capacity to follow up on use of social

**TABLE 2. Features of state-led surveillance of neonatal abstinence syndrome in states with mandated reporting\* — six states, 2018–2021**

Program feature	Surveillance findings reported by health officials <sup>†</sup>	States implementing surveillance feature
<b>Ongoing challenges with initial case reporting<sup>§</sup></b>		
Resource-intensive activities (surveillance-related activities requiring the most state resources)	Collecting missing information (infant)	Arizona, Georgia, Tennessee, Virginia
	Collecting missing information (mother)	Arizona, Georgia, Tennessee, Virginia
	Assessing data accuracy (medical record abstraction)	Florida
	Sharing reports with local, state, and federal agencies	Tennessee
	Deduplicating data received from multiple facilities and medical providers	Georgia, Kentucky, Virginia
	Tracking and reconnecting with families of infants relocating within state	Arizona, Virginia
	Barriers to initial case reporting	Lack of capacity to carry out medical record abstractions
	Limited awareness of surveillance efforts by facilities, medical providers, or staff turnover	Georgia, Kentucky
	Variability in case identification and reporting by facility	Georgia
	Passive surveillance registry limits timeliness, accuracy, and data completeness	Florida
	Challenges with criteria or implementation of NAS case definition	Arizona, Georgia
<b>Activities beyond initial case reporting<sup>†</sup></b>		
Health-related outcomes <sup>¶</sup> (e.g., maternal OUD or SUD, initiation or retention in MOUD program, infant hospitalization rates and comorbidities)	Monitoring comorbidities in infants with NAS	Kentucky
	Monitoring infant hospitalization rates	Kentucky
	Monitoring rates of infant preventative health maintenance visit, vaccine information	Kentucky
Social services-related outcomes <sup>¶</sup> (e.g., linkage to housing, transportation, food or nutrition, child welfare, legal assistance, or juvenile courts services)	N/A	None
Development-related outcomes <sup>¶</sup> (e.g., linkage or retention in Head Start, early intervention, home nursing visitation services)	N/A	None
Program development or improvement activities informed by state NAS surveillance** (to serve identified needs of opioid or substance-exposed mother-infant dyads)	OUD education campaign (e.g., stigma reduction) for providers and families	Arizona, Kentucky, Tennessee
	Expand MOUD programs for pregnant or postpartum women	Arizona, Florida
	Educational outreach to local MOUD providers and jails for expanded access to contraception for persons voluntarily seeking contraception	Tennessee
	Educational or training outreach to hospitals participating in quality improvement program initiative to improve care management for NAS	Georgia
	Teleconsultation program for providers on maternal substance use prevention and treatment	Virginia
	Plan of Safe Care program designed specifically to identify OUD in pregnancy and link to MOUD	Florida
	Expand reimbursement for OUD screening or intervention	Florida
Policy enactment informed by state NAS surveillance** (to address needs of opioid or substance-exposed mother-infant dyads)	Broadened same-day long-term contraception availability through state Medicaid program	Tennessee
Barriers to follow-up of initial case reports	Lack of infrastructure within agency to conduct follow-up with families of infants with reported cases of NAS	Arizona, Florida, Georgia, Tennessee, Virginia
	Lack of infrastructure at outside agencies that provide services to families of infants	Arizona, Virginia
	Lack of access to necessary infrastructure or services in rural communities	Kentucky, Tennessee

See table footnotes on the next page.

services or developmental-related outcomes. With the exception of Kentucky, states reported that they did not monitor health-related outcomes. Kentucky has instituted state-level monitoring of infant hospitalization and comorbidity rates, and preventive health maintenance and vaccination rates, facilitated by direct linkage and data-sharing with their state Medicaid program. Overall, officials reported a lack of infrastructure (personnel, resources, and data linkages) within state health departments and outside agencies as primary reasons for limited long-term surveillance of NAS. Florida described

their passive case reporting system as limiting timeliness, accuracy, and data completeness, and consequently, affecting downstream follow-up and surveillance.

### Discussion

The current study was designed to review NAS surveillance beyond initial case reporting and program development after implementation of state-mandated NAS case reporting; however, none of the six states report follow-up of infants or families beyond the initial NAS case report. Notably, initial

TABLE 2. (Continued) Features of state-led surveillance of neonatal abstinence syndrome in states with mandated reporting\* — six states, 2018–2021

Program features	Surveillance findings reported by health officials <sup>†</sup>	States implementing surveillance feature
<b>Quality assurance measures and resources as reported by health officials<sup>§,††</sup></b>		
Institution of required data fields	+ Collecting missing data	Kentucky, Tennessee
Link case report data to vital records	+ Collecting missing data	Kentucky, Tennessee
Health official review of reported cases	– Requiring more resources to carry out activity	Kentucky, Tennessee
Request additional or missing information	– Collecting missing data; burdensome, inefficient	Georgia, Tennessee
Reporter education on best practices to complete case report	+ Collecting missing data and data quality	Georgia, Tennessee
Partnering with national laboratories to receive positive toxicology for infant via ELR	+ Enabling confirmation of select reported results and identification of cases that may have been otherwise missed – Laborious to set up	Georgia
Tools or resources used (local or community or state-level resources used in conducting surveillance)	+ Partnering with reporting hospital staff + Using web-based electronic reporting tools  – Faxing reports + Partnering with state perinatal quality collaborative  + Using existing state disease reporting system streamlines hospital reporting + State mandate for NAS public health reporting	Georgia, Tennessee Georgia, Kentucky, Tennessee Kentucky Florida, Georgia, Kentucky, Tennessee, Virginia Arizona  Arizona, Georgia, Tennessee, Virginia

**Abbreviations:** ELR = electronic laboratory reporting; MOUD = medication for opioid use disorder; NAS = neonatal abstinence syndrome; OUD = opioid use disorder; SUD = substance use disorder; + = most helpful; – = least helpful.

\* Arizona, Florida, Georgia, Kentucky, Tennessee, and Virginia.

<sup>†</sup> Surveillance findings listed are summarized from responses to questionnaires and semistructured interviews completed by state health departments.

<sup>§</sup> Including and extending beyond initial case reporting; surveillance features listed are summarized from question items detailed in both questionnaire and semistructured interview completed by state health departments.

<sup>¶</sup> Monitoring of specified outcomes since enactment of state-mandated NAS case reporting.

\*\* Programs developed or policies enacted since institution of state-mandated NAS case reporting.

<sup>††</sup> Quality assurance measures enacted to improve completeness of case reporting.

state reporting mandates were intended to improve short-term timeliness of NAS epidemiologic data collection, not necessarily long-term follow-up or surveillance. Consequently, most reporting programs were not initially linked to existing health, social services, or developmental follow-up programs within states, explaining the significant data-sharing gap. Only one state has been able to monitor infant health-related outcomes and, despite ongoing interest in long-term outcomes, none of the six states has been able to track use of social services or development-related outcomes. The states cited critical infrastructure gaps as limiting their ability to conduct longer-term surveillance and reported distinct care access gaps in rural communities (e.g., geographic and internet bandwidth limitations). This limitation is concerning given 2004–2017 data showing disparities in OUD and NAS incidence across rural versus urban regions and remote rural counties (1,5,6). Considerations for infrastructure development to support long-term surveillance include capacity-building measures for 1) sufficient personnel (e.g., epidemiologist, data or information technology manager, or developmental specialist), 2) technical architecture (electronic system for housing longer-term surveillance data or data linkages to other state systems), and 3) legislative pathways to address potential

confidentiality barriers regarding data-sharing between state health departments and other state agencies.

Despite state health department-reported infrastructural limitations in surveillance beyond initial case reporting, the six states with mandated NAS reporting have been able to achieve several noteworthy programmatic developments to serve identified needs of opioid and substance-exposed mother-infant dyads. Many of these developments focus on educational programs for medical providers and families to serve identified needs of opioid and substance-exposed infants and families, including stigma reduction (Arizona, Kentucky, and Tennessee). Georgia has implemented a quality improvement initiative centering around hospital educational outreach to improve NAS care management. Tennessee conducted educational outreach to providers of MOUD and local jails to expand access to contraception for persons voluntarily seeking access. Virginia provides educational teleconsultation to medical providers on OUD prevention and treatment. Florida is in the process of applying the Plan of Safe Care model for infants and families to a parallel program identifying pregnant women with OUD to link to MOUD, essential for a mother-infant dyad care model (7,8). With respect to policy enactment, Tennessee has broadened voluntary long-acting reversible contraception

availability through Medicaid, a policy partially informed by state-mandated NAS case reporting.

The findings in this report are subject to at least two limitations. First, because this analysis relies largely on qualitative data, it cannot quantify the impact of NAS surveillance in the six states. Second, this study is a follow-up of six states with mandated NAS case reporting implemented during 2013–2017; other states with reporting statutes and regulations not meeting the search criteria from the 2018 study are not included (9). As such, study findings from these six states might not be generalizable.

Although mandated NAS case reporting offers opportunities for short-term epidemiologic data collection, continued case reporting and infrastructural challenges limit the breadth of short- and long-term surveillance. With resource- and capacity-building assessments and responding actions, state health departments might be better prepared to bridge the gap between initial case reporting and longer-term needs analysis and support for affected infants and families.

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Corresponding author: Shahla M. Jilani, shahla.jilani@hhs.gov, 202-815-1970.

<sup>1</sup>Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services, Washington, DC; <sup>2</sup>Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services, Washington, DC; <sup>3</sup>Tennessee State Department of Health; <sup>4</sup>Florida Department of Health; <sup>5</sup>Virginia Department of Health; <sup>6</sup>Georgia Department of Public Health; <sup>7</sup>Kentucky Department for Public Health; <sup>8</sup>Arizona Department of Health Services; <sup>9</sup>Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion, CDC.

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## Trends in Breast Cancer Incidence, by Race, Ethnicity, and Age Among Women Aged $\geq 20$ Years — United States, 1999–2018

Taylor D. Ellington, MPH<sup>1,2</sup>; Jacqueline W. Miller, MD<sup>1</sup>; S. Jane Henley, MSPH<sup>1</sup>; Reda J. Wilson, MPH<sup>1</sup>; Manxia Wu, MD<sup>1</sup>; Lisa C. Richardson, MD<sup>1</sup>

Breast cancer is commonly diagnosed among women, accounting for approximately 30% of all cancer cases reported among women.\* A slight annual increase in breast cancer incidence occurred in the United States during 2013–2017 (1). To examine trends in breast cancer incidence among women aged  $\geq 20$  years by race/ethnicity and age, CDC analyzed data from U.S. Cancer Statistics (USCS) during 1999–2018. Overall, breast cancer incidence rates among women decreased an average of 0.3% per year, decreasing 2.1% per year during 1999–2004 and increasing 0.3% per year during 2004–2018. Incidence increased among non-Hispanic Asian or Pacific Islander women and women aged 20–39 years and decreased among non-Hispanic White women and women aged 50–64 and  $\geq 75$  years. The U.S. Preventive Services Task Force currently recommends biennial screening mammography for women aged 50–74 years (2). These findings suggest that women aged 20–49 years might benefit from discussing potential breast cancer risk and ways to reduce risk with their health care providers. Further examination of breast cancer trends by demographic characteristics might help tailor breast cancer prevention and control programs to address state- or county-level incidence rates<sup>†</sup> and help prevent health disparities.

USCS includes incidence data from central cancer registries reporting to CDC's National Program of Cancer Registries and National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.<sup>§</sup> All malignant cases of breast cancer<sup>¶</sup> diagnosed in women during 1999–2018 were selected from registries with high quality data covering 97% of the U.S. population.\*\* Trends in breast cancer incidence per 100,000 U.S. 2000 standard population were examined for women aged  $\geq 20$  years by race/ethnicity for five mutually exclusive groups (non-Hispanic American Indian or Alaska Native, non-Hispanic Asian or Pacific Islander, non-Hispanic Black, Hispanic, and non-Hispanic White) and age group (20–39, 40–49, 50–64, 65–74, and  $\geq 75$  years). Annual percent change (APC) and average annual percent change (AAPC) in incidence were estimated using joinpoint regression, with

a maximum of three joinpoints (up to four-line segments) allowed.<sup>††</sup> Two-sided statistically significant differences from zero were determined using a *t*-test for APCs and AAPCs from linear regressions with zero joinpoints and a *z*-test for AAPCs from linear regressions with one or more joinpoints. APC and AAPC were considered to be  $>0$  or  $<0$  if  $p < 0.05$ , otherwise, rates were considered stable. Incidence rates were calculated with SEER\*Stat software (version 8.3.8; National Cancer Institute) and APC and AAPC were calculated in Joinpoint software (version 4.6.00; National Cancer Institute).<sup>§§</sup> This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.<sup>¶¶</sup>

During 1999–2018, breast cancer incidence among women aged  $\geq 20$  years decreased an average of 0.3% per year, decreasing 2.1% per year during 1999–2004 and increasing 0.3% per year during 2004–2018 (Table). Incidence trends varied by racial and ethnic group (Figure 1). Incidence among non-Hispanic White women, among whom rates were highest, decreased an average of 0.3% per year from 198.0 to 186.5 per 100,000 population, decreasing 2.3% per year during 1999–2004 and increasing 0.4% per year during 2004–2018. Incidence among non-Hispanic Black women did not change significantly during 1999–2018. Incidence among Hispanic women decreased an average of 1.6% per year during 1999–2004, then increased an average of 0.4% per year during 2004–2018. Incidence among non-Hispanic American Indian or Alaska Native women increased an average of 1.4% per year during 1999–2016 then stabilized during 2016–2018. Among non-Hispanic Asian or Pacific Islander women, incidence was stable during 1999–2005 and increased 1.4% per year during 2005–2018, increasing an average of 0.8% per year during 1999–2018.

Among women aged  $< 50$  years, breast cancer incidence increased 0.7% per year during 2010–2018 among those aged 20–39 years and 0.4% per year during 2002–2018 among those aged 40–49 years (Table). In contrast, incidence among women aged 50–64 years stabilized during 2005–2018 after

\* <https://www.cdc.gov/cancer/dataviz>

† <https://gis.cdc.gov/Cancer/USCS/#/StateCounty/>

§ <https://www.cdc.gov/cancer/uscs/index.htm>

¶ [http://www.iacr.com.fr/index.php?option=com\\_content&view=category&layout=blog&id=100&Itemid=577](http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577)

\*\* [https://www.cdc.gov/cancer/uscs/technical\\_notes/criteria/registries.htm](https://www.cdc.gov/cancer/uscs/technical_notes/criteria/registries.htm)

†† Annual percent change and average annual percent change calculated in Joinpoint software (version 4.6.00; National Cancer Institute).

§§ Incidence and death rates calculated in SEER\*Stat software (version 8.3.8; National Cancer Institute).

¶¶ 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. Number, rate, and change in rate\* of breast cancer incidence<sup>†</sup> among women aged ≥20 years, by race/ethnicity<sup>§</sup> and age group — United States, 1999–2018**

Characteristic	No.	1999 rate*	2018 rate*	Absolute change in rate	Year range	APC	AAPC 1999–2018
<b>Overall</b>	<b>4,290,123</b>	<b>189.3</b>	<b>177.8</b>	<b>–11.5</b>	<b>1999–2004</b> <b>2004–2018</b>	<b>–2.1<sup>¶</sup></b> <b>0.3<sup>¶</sup></b>	<b>–0.3<sup>**</sup></b>
<b>Race/Ethnicity</b>							
AI/AN, non-Hispanic	20,325	121.4	127.3	5.9	1999–2016 2016–2018	1.4 <sup>¶</sup> –6.6	0.6
A/PI, non-Hispanic	145,751	122.4	143.5	21.1	1999–2005 2005–2018	–0.4 1.4 <sup>¶</sup>	0.8 <sup>**</sup>
Black, non-Hispanic	451,788	167.4	174.0	6.6	1999–2005 2005–2008 2008–2015 2015–2018	–0.1 2.2 0.5 –1.3	0.3
Hispanic	305,075	136.3	134.0	–2.3	1999–2004 2004–2018	–1.6 <sup>¶</sup> 0.4 <sup>¶</sup>	–0.1
White, non-Hispanic	3,341,855	198.0	186.5	–11.5	1999–2004 2004–2018	–2.3 <sup>¶</sup> 0.4 <sup>¶</sup>	–0.3 <sup>**</sup>
<b>Age group, yrs</b>							
20–39	204,345	27.0	28.1	1.1	1999–2010 2010–2018	0.1 0.7 <sup>¶</sup>	0.3 <sup>**</sup>
40–49	659,045	154.1	160.5	6.4	1999–2002 2002–2018	–1.1 0.4 <sup>¶</sup>	0.2
50–64	1,524,658	310.2	267.8	–42.4	1999–2005 2005–2018	–2.8 <sup>¶</sup> 0.0	–0.9 <sup>**</sup>
65–74	995,279	444.4	445.5	1.1	1999–2004 2004–2013 2013–2018	–2.8 <sup>¶</sup> 1.5 <sup>¶</sup> 0.0	0.0
≥75	906,796	460.5	406.9	–53.6	1999–2004 2004–2009 2009–2018	–2.4 <sup>¶</sup> 0.6 –0.4 <sup>¶</sup>	–0.7 <sup>**</sup>

**Abbreviations:** AAPC = average annual percent change; AI/AN = American Indian or Alaska Native; APC = annual percent change; A/PI = Asian or Pacific Islander.

\* Per 100,000 population; overall rates were age-adjusted to the 2000 U.S. standard population. AAPC and APC were calculated using joinpoint regression, which allowed different slopes for four periods; the year at which slopes changed could vary by age and race/ethnicity.

<sup>†</sup> Cancer incidence data were compiled from cancer registries that meet U.S. Cancer Statistics data quality criteria (<https://www.cdc.gov/cancer/npcr/standards.htm>), covering 97% of the U.S. population.

<sup>§</sup> Mutually exclusive racial/ethnic groups are based on information about race/ethnicity that was collected separately and combined for this report. Race/ethnicity were grouped as non-Hispanic AI/AN, non-Hispanic A/PI, non-Hispanic Black, Hispanic, and non-Hispanic White. Hispanic persons can be any race. Data are not presented for those with unknown or other race or unknown ethnicity (n = 25,329).

<sup>¶</sup> APC was significantly different from zero at the  $\alpha = 0.05$  level.

\*\* AAPC was significantly different from zero at the  $\alpha = 0.05$  level.

decreasing 2.8% per year during 1999–2005. Incidence among women aged 65–74 years decreased 2.8% per year during 1999–2004, increased 1.5% per year during 2004–2013, then stabilized during 2013–2018. Incidence among women aged ≥75 years decreased 2.4% per year during 1999–2004, was stable during 2004–2009, then decreased 0.4% per year during 2009–2018.

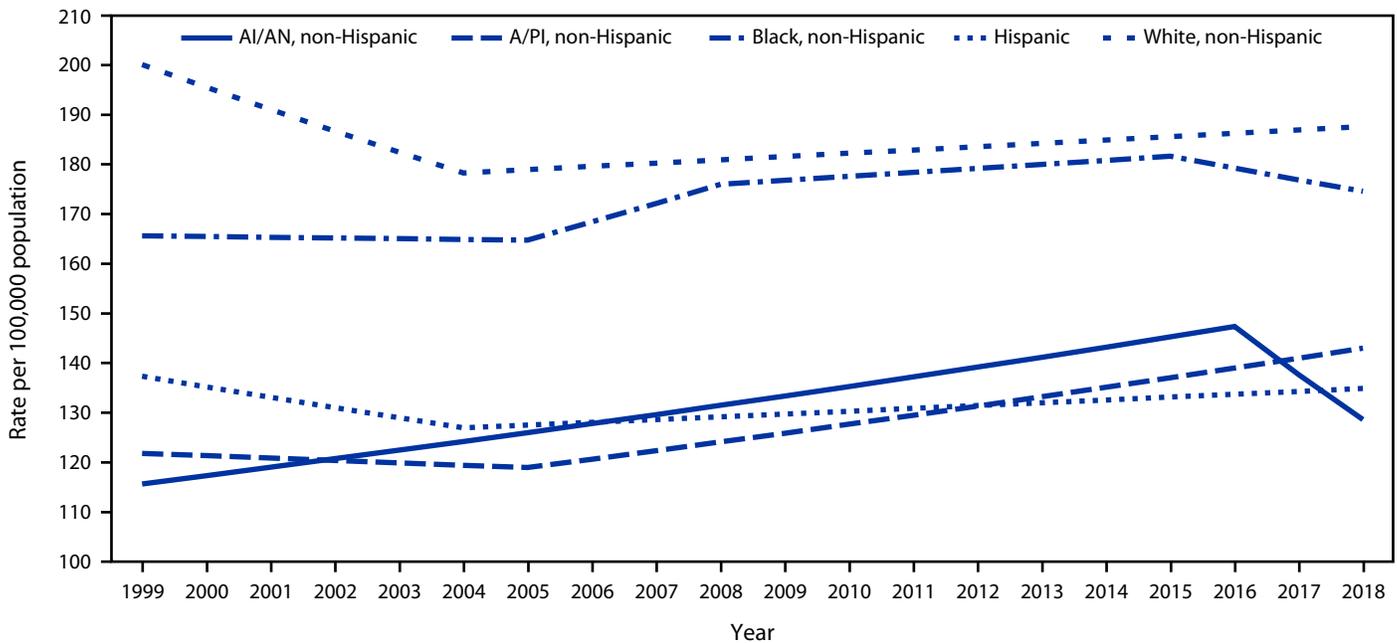
Among women aged 20–39 and 40–49 years, incidence was stable among non-Hispanic Black and Hispanic women but increased for other racial and ethnic groups (Figure 2). Incidence among non-Hispanic White women aged 50–64 years decreased an average of 0.8% per year, the largest decrease among any race/ethnicity and age group. Incidence among non-Hispanic American Indian or Alaska Native

women aged 40–49 years increased an average of 1.9% per year, the largest increase among any racial/ethnic and age group.

## Discussion

The findings in this report indicate that breast cancer incidence among women aged ≥20 years decreased during 1999–2004 but increased during 2004–2018. During 1999–2018, incidence increased among non-Hispanic Asian or Pacific Islander women and women aged 20–39 years but decreased among non-Hispanic White women and women aged 50–64 and ≥75 years.

A previous study found that breast cancer incidence increased during 2004–2013 among Asian or Pacific Islander women, driven by a significant increase among those aged 45–49 years

FIGURE 1. Trends\* in breast cancer incidence<sup>†</sup> among women aged  $\geq 20$  years, by race/ethnicity<sup>§,¶</sup> — United States, 1999–2018

**Abbreviations:** AAPC = average annual percent change; AI/AN = American Indian or Alaska Native; A/PI = Asian or Pacific Islander.

\* Trends were estimated using joinpoint regression, with a maximum of three joinpoints (up to four-line segments allowed); the year at which slopes changed could vary by age and race/ethnicity. Data displayed are the modeled age-adjusted rates.

<sup>†</sup> Cancer incidence data were compiled from cancer registries that meet U.S. Cancer Statistics data quality criteria (<https://www.cdc.gov/cancer/npcr/standards.htm>), covering 97% of the U.S. population.

<sup>§</sup> Mutually exclusive racial/ethnic groups are based on information about race/ethnicity that was collected separately and combined for this report. Race/ethnicity were grouped as non-Hispanic AI/AN, non-Hispanic A/PI, non-Hispanic Black, Hispanic, and non-Hispanic White. Hispanic persons can be any race. Data are not presented for those with unknown or other race or unknown ethnicity.

<sup>¶</sup> AAPC was significantly different from zero at the  $\alpha = 0.05$  level for non-Hispanic A/PI and non-Hispanic White persons.

(3). Another study found that among women aged  $<45$  years born in California, breast cancer risk among Asian or Pacific Islander women exceeded that among White women (4). Further examination of breast cancer incidence by detailed Asian or Pacific Islander race groups, age, cancer stage, and migration status might help further explain the increase in observed rates.

Results of this study also show that breast cancer incidence during 2010–2018 increased among women aged 20–49 years. Age and genetic, hormonal, and reproductive factors contribute to breast cancer risk. Modifiable risk factors for breast cancer include excess body weight (among postmenopausal women), physical inactivity, alcohol use, and hormone replacement therapy use.\*\*\* During 2017–2018, approximately 39.7% of women aged 20–39 years in the United States had obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>), compared with 20.7% during 1988–1994, and a similar increase was observed during this period among women aged 40–59 and  $\geq 60$  years (5). The Community Preventive Services Task Force recommends

evidence-based strategies to create social and physical environments that support healthy behaviors, such as reduced excessive alcohol use and increased physical activity (6). CDC's National Comprehensive Cancer Control Program assists programs to help support and promote these strategies in communities.††† CDC's Bring Your Brave campaign provides information about breast cancer to women aged  $<45$  years.§§§

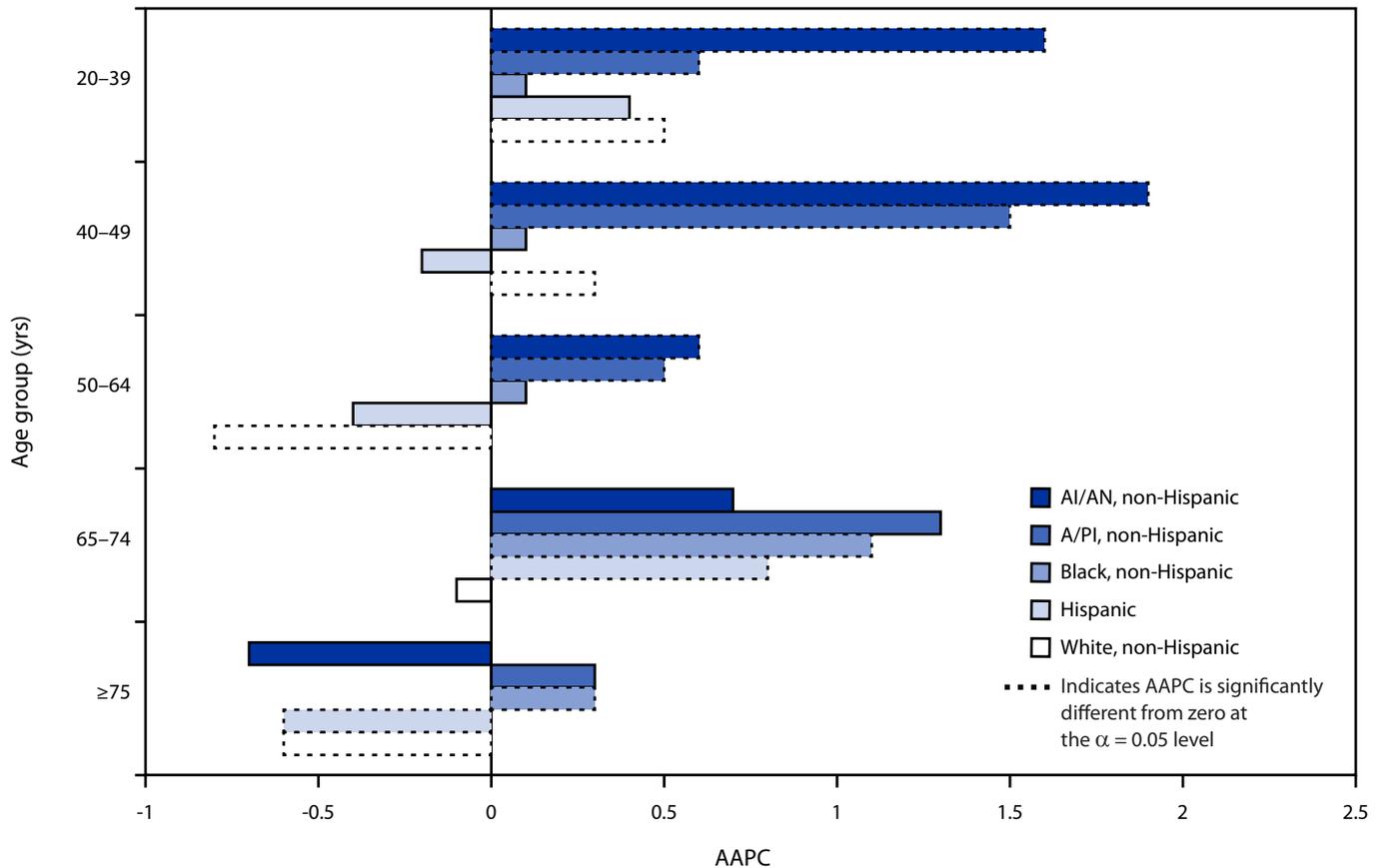
Some forms of hormone replacement therapy taken for  $>5$  years during menopause can raise breast cancer risk. Previous studies have associated the observed decrease in breast cancer incidence, specifically in the early 2000s, to be temporally related to the first report of the Women's Health Initiative (7). The report found an increased risk of breast cancer associated with hormone replacement therapy followed by a decrease in the use of hormone replacement therapy among postmenopausal women in the United States (7). In 2017, the North American Menopause Society announced that “for women aged younger than 60 years or who are within

††† <https://www.cdc.gov/cancer/ncccp/>

§§§ [https://www.cdc.gov/cancer/breast/young\\_women/bringyourbrave/take\\_action/index.htm](https://www.cdc.gov/cancer/breast/young_women/bringyourbrave/take_action/index.htm)

\*\*\* [https://www.cdc.gov/cancer/breast/basic\\_info/risk\\_factors.htm](https://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm)

**FIGURE 2. Average annual percent change\* in breast cancer incidence† among women aged ≥20 years by race/ethnicity§ and age group — United States, 1999–2018**



**Abbreviations:** AAPC = average annual percent change; AI/AN = American Indian or Alaska Native; A/PI = Asian or Pacific Islander.

\* AAPC is the weighted average of the annual percent change during 1999–2018. To determine whether AAPC was significantly different from zero, a t-test was used if the joinpoint regression model had zero joinpoints, and a z-test was used if the joinpoint regression model had  $\geq 1$  joinpoint.

† Cancer incidence data were compiled from cancer registries that meet U.S. Cancer Statistics data quality criteria (<https://www.cdc.gov/cancer/npcr/standards.htm>), covering 97% of the U.S. population.

§ Mutually exclusive racial/ethnic groups are based on information about race/ethnicity that was collected separately and combined for this report. Race/ethnicity were grouped as non-Hispanic AI/AN, non-Hispanic A/PI, non-Hispanic Black, Hispanic, and non-Hispanic White. Hispanic persons can be any race. Data are not presented for those with unknown or other race or unknown ethnicity.

10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome vasomotor symptoms and for those at elevated risk for bone loss or fracture” (8). Women who receive hormone therapy for >5 years might need to monitor any symptoms associated with breast cancer and consult with their health care provider if any symptoms of breast cancer are noticed.

From 2008 to 2015, breast cancer screening increased slightly among Hispanic women but declined among other groups, including >10% in some groups, including Asian women (9). The U.S. Preventive Services Task Force recommends that women aged 50–74 years who are at average risk for breast cancer get a mammogram every 2 years (2). Women aged 40–49 years, particularly those who have a known first-degree relative (i.e., parent, child, or sibling) with breast cancer, should

talk to their physician or other health care professionals about starting screening with mammography (2). CDC’s National Breast and Cervical Cancer Early Detection Program provides breast and cervical cancer screenings and diagnostic services to low-income, uninsured, and underinsured women across the United States.”

The findings of this report are subject to at least two limitations. First, analyses based on race/ethnicity might be biased if race/ethnicity were systematically misclassified. However, ongoing efforts are made to ensure that this information is as accurate as possible.\*\*\*\* Finally, delays in cancer reporting might result in an underestimation of incidence.

“““ <https://www.cdc.gov/cancer/nbccedp/screenings.htm>

\*\*\*\* [https://www.cdc.gov/cancer/uscs/technical\\_notes/interpreting/race.htm](https://www.cdc.gov/cancer/uscs/technical_notes/interpreting/race.htm)

**Summary****What is already known about this topic?**

Breast cancer accounts for 30% of all cancers diagnosed in women.

**What is added by this report?**

During 1999–2018, breast cancer incidence among women aged  $\geq 20$  years decreased an average of 0.3% per year, decreasing 2.1% per year during 1999–2004 and increasing 0.3% per year during 2004–2018. Incidence increased among non-Hispanic Pacific Islander women and women aged 20–39 years but decreased among non-Hispanic White women and women aged 50–64 and  $\geq 75$  years.

**What are the implications for public health practice?**

The U.S. Preventive Services Task Force currently recommends biennial mammography screening for women aged 50–74 years. Women aged 20–49 years might benefit from discussing potential breast cancer risk and ways to reduce risk with their health care providers.

In this report, trends in breast cancer incidence differed by demographic characteristics, suggesting that breast cancer prevention and control programs be tailored to address state- or county-level incidence rates and help prevent health disparities. Breast cancer risk can be reduced with healthy behaviors, including maintaining a healthy weight, engaging in regular physical activity, and reducing alcohol use. The U.S. Preventive Services Task Force currently recommends biennial screening mammography for women aged 50–74 years (2); in addition, these findings suggest women aged 20–49 years might benefit from discussions with their health care providers about potential breast cancer risk and ways to reduce risk.

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State and regional cancer registry and health department personnel.

Corresponding author: Taylor D. Ellington, [tellington@cdc.gov](mailto:tellington@cdc.gov), 404-498-2258.

<sup>1</sup>Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, CDC; <sup>2</sup>Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee.

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## Impact of the DREAMS Program on New HIV Diagnoses in Adolescent Girls and Young Women Attending Antenatal Care — Lesotho, 2015–2020

Andrew R. Pelletier, MD<sup>1</sup>; Josip Derado, PhD<sup>1</sup>; Limpho Maela, MPH<sup>2</sup>; Thabiso Lekhotsa, MPH<sup>3</sup>; Masechache Sechache, MPA<sup>3</sup>; Konosoang Nkuatsana<sup>4</sup>

Lesotho is a small, landlocked country in southern Africa with a population of approximately 2 million persons, approximately two thirds of whom live in rural areas (1). Lesotho has the second highest prevalence of HIV infection in the world (2). In 2017, 25.6% of persons aged 15–59 years living in Lesotho were HIV-positive (3). Strategies implemented in recent years to control HIV include efforts to reduce mother-to-child transmission and improve coverage with antiretroviral therapy, as well as increasing testing for HIV. Among persons aged 15–24 years, the HIV prevalence among females in 2017 (11.1%) was approximately three times that among males (3.4%) (3). The Determined, Resilient, Empowered, AIDS-Free, Mentored, and Safe (DREAMS)\* program in Lesotho was started during October 2016 in two districts. DREAMS comprises a package of biomedical, behavioral, and structural interventions to address factors that make adolescent girls and young women vulnerable to HIV acquisition (4). The goal of the DREAMS program was to decrease HIV incidence among adolescent girls and young women by 25% after 1 year and by 40% after 2 years (4). After 3.5 years of program implementation in Lesotho, new HIV diagnoses among adolescent girls and young women attending antenatal care (ANC) decreased 71.4% in the two districts that implemented DREAMS compared with a reduction of 48.4% in three comparison districts without the program ( $p = 0.002$ ). During 2016–2020, reductions in new HIV diagnoses among adolescent girls and young women attending ANC in Lesotho have been substantial, both in districts that have and have not implemented the DREAMS program (DREAMS and non-DREAMS districts). Apart from the DREAMS program, the decrease in new HIV diagnoses might be a result of the reduction in viral load in the population because more persons living with HIV infection became virally suppressed while on antiviral therapy, as well as other interventions such as preexposure prophylaxis, voluntary medical male circumcision, behavior change, and increased HIV diagnostic coverage.

During U.S. government fiscal years 2016–2020, the Elizabeth Glaser Pediatric AIDS Foundation was the single treatment partner funded by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) for all districts in Lesotho

(except for the first two quarters of fiscal year 2020 when mothers2mothers<sup>†</sup> [M2M] replaced the Elizabeth Glaser Pediatric AIDS Foundation in two non-DREAMS districts). PEPFAR treatment partners reported quarterly on monitoring, evaluation, and reporting indicators, and provided data on the number of pregnant adolescent girls and young women who were tested for HIV at ANC by two age groups (15–24 years and  $\geq 25$  years) for each of the districts. Adolescent girls and young women were defined as females aged 15–24 years. HIV test results were categorized as negative, previously known positive, and newly test-positive. In keeping with Office of the Global AIDS Coordinator (OGAC) methodology, the new HIV diagnosis rate was calculated using the formula ( $[\text{new ANC test-positives}] / [\text{total ANC clients tested} - \text{known ANC positives}]$ ) (5).

For this report, aggregate data for adolescent girls and young women in the two adjacent DREAMS districts (Berea and Maseru) were compared with aggregate data for adolescent girls and young women in three non-DREAMS districts (Leribe, Mafeteng, and Mohale's Hoek). Data for women aged  $\geq 25$  years in the two DREAMS districts were also examined. Data from the first quarter of fiscal year 2016 (October 2015–December 2015) served as the baseline for comparison with the first 3.5 years of DREAMS implementation (October 2016–March 2020). A Poisson log-linear regression model was used to determine rates of decline in new HIV diagnoses among adolescent girls and young women and women aged  $\geq 25$  years attending ANC by quarter and to compare rates of decline between groups, with  $p < 0.05$  considered statistically significant. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.<sup>§</sup>

The number of adolescent girls and young women attending ANC in each district varied little from year to year (Table). Among adolescent girls and young women in the two DREAMS districts, the percentage of new HIV diagnoses decreased from 11.4% in the first quarter of fiscal year 2016 to 3.3% in the second quarter of fiscal year 2020, for a total reduction of 71.4% ( $p < 0.001$ ) (Figure). A decline of 48.4% occurred among adolescent girls and young women in the three

\* <https://www.state.gov/pepfar-dreams-partnership/>

<sup>†</sup> <https://m2m.org/>

<sup>§</sup> 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.

**TABLE. Number and percentage of new HIV diagnoses among adolescent girls and young women attending antenatal care, by district DREAMS implementation status and age group — Lesotho, fiscal years 2016–2020**

Fiscal year and quarter	Females aged 15–24 years attending antenatal care				Women aged ≥25 years attending antenatal care	
	DREAMS districts*		non-DREAMS districts†		DREAMS districts*	
	No. of new HIV diagnoses (%)	No. tested	No. of new HIV diagnoses (%)	No. tested	No. of new HIV diagnoses (%)	No. tested
FY2016 Q1	158 (11.4)	1,392	93 (7.7)	1,215	171 (16.6)	1,033
FY2016 Q2	153 (9.4)	1,623	111 (7.3)	1,516	205 (16.2)	1,267
FY2016 Q3	155 (9.0)	1,715	100 (6.7)	1,489	183 (16.0)	1,147
FY2016 Q4	130 (7.9)	1,647	76 (5.7)	1,341	157 (12.9)	1,214
FY2017 Q1	105 (7.3)	1,444	66 (6.2)	1,063	138 (13.8)	1,003
FY2017 Q2	144 (8.3)	1,741	83 (5.7)	1,450	150 (12.0)	1,253
FY2017 Q3	112 (7.3)	1,531	73 (5.4)	1,358	108 (10.4)	1,041
FY2017 Q4	101 (6.5)	1,545	74 (5.2)	1,415	119 (9.8)	1,217
FY2018 Q1	80 (5.9)	1,346	56 (5.2)	1,087	117 (12.0)	976
FY2018 Q2	107 (5.9)	1,823	60 (4.2)	1,419	137 (11.2)	1,228
FY2018 Q3	95 (5.6)	1,703	55 (3.8)	1,466	120 (10.4)	1,152
FY2018 Q4	106 (6.1)	1,745	68 (5.1)	1,335	137 (11.0)	1,242
FY2019 Q1	69 (4.4)	1,553	56 (4.8)	1,179	109 (9.7)	1,126
FY2019 Q2	92 (5.0)	1,837	60 (4.1)	1,454	131 (9.3)	1,403
FY2019 Q3	81 (4.9)	1,657	48 (3.6)	1,340	109 (9.1)	1,198
FY2019 Q4	64 (3.8)	1,679	50 (3.6)	1,377	104 (8.4)	1,233
FY2020 Q1	53 (3.7)	1,437	44 (4.0)	1,109	73 (7.3)	994
FY2020 Q2	56 (3.3)	1,723	55 (4.0)	1,392	101 (7.5)	1,344

**Abbreviations:** DREAMS = Determined, Resilient, Empowered, AIDS-Free, Mentored and Safe; FY = fiscal year; Q = quarter.

\* Bera and Maseru.

† Leribe, Mafeteng, and Mohale's Hoek.

non-DREAMS districts, from 7.7% to 4.0% ( $p < 0.001$ ). The difference in the percentage reduction among adolescent girls and young women in DREAMS versus non-DREAMS districts was statistically significant ( $p = 0.002$ ). When restricting the analysis to women aged ≥25 years in the two DREAMS districts, the percentage new HIV diagnoses decreased 54.6%, from 16.6% to 7.5% ( $p < 0.001$ ).

### Discussion

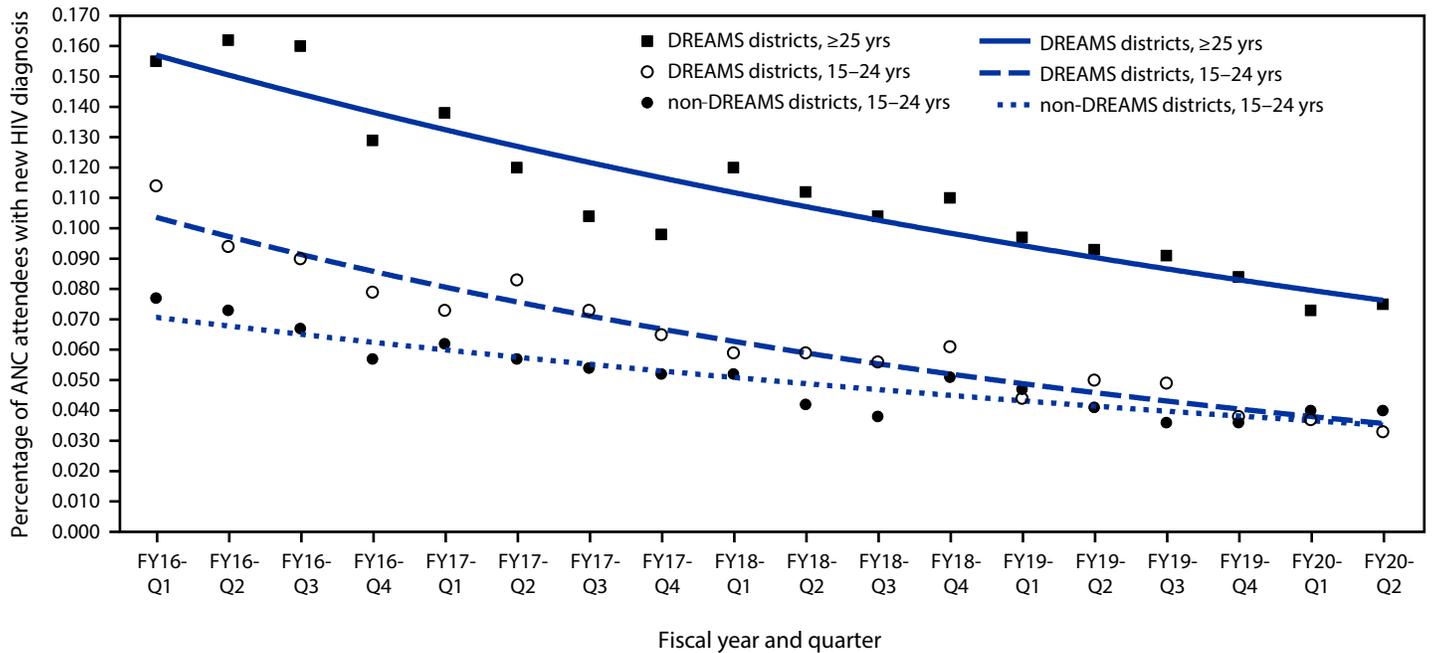
Results of the first 3.5 years of the DREAMS program implementation in Lesotho showed a substantial reduction in new diagnoses of HIV infection among adolescent girls and young women in both DREAMS and three non-DREAMS districts. This occurred at a time when the national HIV treatment program in Lesotho had begun universal initiation of antiretroviral therapy for all HIV-positive persons regardless of CD4 count, and the country had demonstrated good progress toward the United Nations Programme on HIV and AIDS (UNAIDS) 90–90–90 goals (90% of persons living with HIV know their status, 90% of those with HIV who know their status are receiving treatment, and 90% of those receiving treatment are virally suppressed) (6). The Lesotho Population-Based HIV Impact Assessment (LePHIA), conducted during November 2016–May 2017, found that 81% of persons living with HIV infection knew their status, 92% of those who knew their status were on treatment, and 88% of those on treatment were virally

suppressed (3). However, the results for adolescent girls and young women (61%–90%–76%) were cause for concern (7).

The concurrent reduction in new HIV diagnoses among adolescent girls and young women attending ANC in two DREAMS and three non-DREAMS comparison districts might have resulted from an overall reduction in viral load in the population because more persons living with HIV infection became virally suppressed. Other factors, including preexposure prophylaxis, voluntary medical male circumcision, behavior change, and increased HIV diagnostic coverage might have also played a role. The reductions in new HIV diagnoses at ANC among adolescent girls and young women in the three non-DREAMS comparison districts and among women aged ≥25 years in the two DREAMS districts suggests that much of the decline was attributable to factors other than DREAMS, because these women were not eligible for the program, either because of where they lived or their age.

The findings in this report are subject to at least five limitations. First, changes in new HIV diagnoses among adolescent girls and young women attending ANC might be an inaccurate measure of changes in HIV incidence. Reporting of new HIV diagnoses could be affected by multiple factors related to surveillance efforts (e.g., nonuniversal ANC attendance and incomplete HIV testing during ANC). However, the LePHIA indicated that 97.1% of pregnant women aged 15–49 years had attended ANC at least once, and 95.6% knew their HIV

**FIGURE. New HIV diagnoses\* among adolescent girls and young women attending antenatal care, by district DREAMS implementation status and age group — Lesotho, fiscal years 2016–2020**



**Abbreviations:** ANC = antenatal care; DREAMS = Determined, Resilient, Empowered, AIDS-Free, Mentored, and Safe; FY = fiscal year; Q = quarter.  
\* Trend lines derived from Poisson regression model.

status (3). Second, data for HIV testing at ANC were obtained from implementing partners rather than from the database maintained by OGAC. This was done because the Elizabeth Glaser Pediatric AIDS Foundation data were more complete and contained fewer values considered to be outliers. Third, the five districts (including the two DREAMS and three non-DREAMS districts) might differ in ways that affect a direct comparison between DREAMS and non-DREAMS districts. However, the population of Lesotho is largely homogenous, and there are few obvious differences among the five districts where 73% of the population resides (1). Fourth, this assessment was based on an ecologic analysis. Data were not available for individual adolescent girls and young women in DREAMS districts to compare outcomes of those participating in the program with those of nonparticipants. Data were also not available to assess what percentage of the eligible population received a complete suite of program services. Finally, data from Lesotho might not be representative of data from the other nine countries in Africa that were part of the original DREAMS program.

The second LePHIA was completed in March 2020. Although HIV incidence has declined among persons aged ≥15 years, marked disparities still exist in incidence and prevalence between women and men (8). LePHIA was not designed to provide a specific incidence estimate for adolescent girls and young women at the district level. Therefore, LePHIA results cannot be used to directly assess the impact of the DREAMS program in Lesotho. However, the results of the second LePHIA indicate that substantial work remains to address gender disparities. Conducting similar analyses of ANC data in other countries implementing DREAMS could determine whether the results from Lesotho are generalizable and complement the findings of a recent evaluation of DREAMS on HIV incidence among adolescent girls and young women in Kenya and South Africa (9). Results of these studies might better clarify the impact of DREAMS and help guide future decisions on how best to reduce HIV incidence among adolescent girls and young women in Africa.

**Summary****What is already known about this topic?**

During 2016–2017, HIV prevalence among adolescent girls and young women in Lesotho was approximately three times that among young men. The Determined, Resilient, Empowered, AIDS-Free, Mentored, and Safe (DREAMS) program was established in 2016 to decrease HIV incidence among young women.

**What is added by this report?**

New HIV diagnoses among adolescent girls and young women attending antenatal care decreased significantly in both DREAMS and non-DREAMS districts, although reductions were greater in DREAMS districts.

**What are the implications for public health practice?**

Apart from DREAMS, the decrease in new HIV diagnoses might be a result of the reduction in viral load in the population because more persons living with HIV infection became virally suppressed while on antiviral therapy, preexposure prophylaxis, voluntary medical male circumcision, behavior change, and increased HIV diagnostic coverage.

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Corresponding author: Andrew R. Pelletier, arp1@cdc.gov, 404-553-7438.

<sup>1</sup>Division of Global HIV and TB, Center for Global Health, CDC; <sup>2</sup>Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC; <sup>3</sup>United States Agency for International Development, Washington, DC; <sup>4</sup>Lesotho Ministry of Health, Maseru, Lesotho.

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# Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12–18 Years — United States, July–December 2021

Laura D. Zambrano, PhD<sup>1,\*</sup>; Margaret M. Newhams, MPH<sup>2,\*</sup>; Samantha M. Olson, MPH<sup>1</sup>; Natasha B. Halasa, MD<sup>3</sup>; Ashley M. Price, MPH<sup>1</sup>; Julie A. Boom, MD<sup>4</sup>; Leila C. Sahni, PhD<sup>4</sup>; Satoshi Kamidani, MD<sup>5</sup>; Keiko M. Tarquinio, MD<sup>6</sup>; Aline B. Maddux, MD<sup>7</sup>; Sabrina M. Heidemann, MD<sup>8</sup>; Samina S. Bhumbra, MD<sup>9</sup>; Katherine E. Blin, MD<sup>10</sup>; Ryan A. Nofziger, MD<sup>11</sup>; Charlotte V. Hobbs, MD<sup>12</sup>; Tamara T. Bradford, MD<sup>13</sup>; Natalie Z. Cvijanovich, MD<sup>14</sup>; Katherine Irby, MD<sup>15</sup>; Elizabeth H. Mack, MD<sup>16</sup>; Melissa L. Cullimore, MD<sup>17</sup>; Pia S. Pannaraj, MD<sup>18</sup>; Michele Kong, MD<sup>19</sup>; Tracie C. Walker, MD<sup>20</sup>; Shira J. Gertz, MD<sup>21</sup>; Kelly N. Michelson, MD<sup>22</sup>; Melissa A. Cameron, MD<sup>23</sup>; Kathleen Chiotos, MD<sup>24</sup>; Mia Maamari, MD<sup>25</sup>; Jennifer E. Schuster, MD<sup>26</sup>; Amber O. Orzel, MPH<sup>2</sup>; Manish M. Patel, MD<sup>1</sup>; Angela P. Campbell, MD<sup>1,†</sup>; Adrienne G. Randolph, MD<sup>2,27,†</sup>; Overcoming COVID-19 Investigators

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Multisystem inflammatory syndrome in children (MIS-C) is a severe postinfectious hyperinflammatory condition, which generally occurs 2–6 weeks after a typically mild or asymptomatic infection with SARS-CoV-2, the virus that causes COVID-19 (1–3). In the United States, the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine is currently authorized for use in children and adolescents aged 5–15 years under an Emergency Use Authorization and is fully licensed by the Food and Drug Administration for persons aged ≥16 years (4). Preliminary randomized trials in persons aged ≥5 years documented high vaccine efficacy and immunogenicity (5),<sup>§</sup> and real-world studies in persons aged 12–18 years demonstrated high vaccine effectiveness (VE) against severe COVID-19 (6). Recent evidence suggests that COVID-19 vaccination is associated with lower MIS-C incidence among adolescents (7); however, VE of the 2-dose Pfizer-BioNTech regimen against MIS-C has not been evaluated. The effectiveness of 2 doses of Pfizer-BioNTech vaccine received ≥28 days before hospital admission in preventing MIS-C was assessed using a test-negative case-control design,<sup>¶</sup> among hospitalized patients aged 12–18 years at 24 pediatric hospitals in 20 states\*\* during July 1–December 9, 2021, the period when most MIS-C patients could be temporally linked to

SARS-CoV-2 B.1.617.2 (Delta) variant predominance. Patients with MIS-C (case-patients) and two groups of hospitalized controls matched to case-patients were evaluated: test-negative controls had at least one COVID-19–like symptom and negative SARS-CoV-2 reverse transcription–polymerase chain reaction (RT-PCR) or antigen-based assay results, and syndrome-negative controls were hospitalized patients without COVID-19–like illness. Among 102 MIS-C case-patients and 181 hospitalized controls, estimated effectiveness of 2 doses of Pfizer-BioNTech vaccine against MIS-C was 91% (95% CI = 78%–97%). All 38 MIS-C patients requiring life support were unvaccinated. Receipt of 2 doses of the Pfizer-BioNTech vaccine is associated with a high level of protection against MIS-C in persons aged 12–18 years, highlighting the importance of vaccination among all eligible children.

This study used a test-negative case-control design, commonly used for postauthorization VE evaluations (6,8). Patients were hospitalized at 24 participating sites in the Overcoming COVID-19 Network, a collaboration between CDC and approximately 70 pediatric hospitals nationwide to assess COVID-19 complications in children and young adults.<sup>††</sup> Given that children aged 5–11 years were not recommended to receive the Pfizer-BioNTech vaccine until November 2, 2021,<sup>§§</sup> this analysis focused on persons aged 12–18 years.<sup>¶¶</sup> VE was assessed by comparing the odds of antecedent vaccination between MIS-C patients and hospitalized controls without evidence of SARS-CoV-2 infection during July 1–December 9, 2021. Case-patients met CDC criteria for MIS-C,<sup>\*\*\*</sup> which

\* These authors contributed equally to this report.

† These senior authors contributed equally to this report.

§ <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine>

¶ In this context, the test-negative case-control design was used to compare the odds of previous Pfizer-BioNTech vaccine receipt among inpatients without evidence of SARS-CoV-2 infection with case-patients hospitalized for MIS-C. These control patients included those with respiratory virus infection who received a negative test result for SARS-CoV-2 infection (test-negative) or patients without symptoms compatible with COVID-19 (syndrome-negative), including fever, cough, shortness of breath, loss of taste, loss of smell, gastrointestinal symptoms, use of respiratory support for the acute illness, or new pulmonary findings on chest imaging consistent with pneumonia.

\*\* This investigation included patients enrolled from 24 pediatric hospitals in 20 states: Alabama, Arkansas, California, Colorado, Georgia, Illinois, Indiana, Louisiana, Massachusetts, Michigan, Mississippi, Missouri, Nebraska, New Jersey, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, and Texas.

†† <https://overcomecovid.org/>

§§ CDC recommendation for pediatric COVID-19 vaccine for children aged 5–11 years: <https://www.cdc.gov/media/releases/2021/s1102-PediatricCOVID-19Vaccine.html>

¶¶ The lower age bound for the study population was set at 12 years and 49 days to allow for the first vaccine dose on the patient's 12th birthday, a second dose 21 days thereafter, and a 28-day window between the patient's second dose and hospitalization for MIS-C.

\*\*\* CDC case definition criteria for MIS-C are available at <https://www.cdc.gov/mis/mis-c/hcp/index.html>. For the purposes of this analysis, all MIS-C case-patients were required to have laboratory evidence of current or recent infection (RT-PCR, antigen-, or antibody-based testing).

included a clinically severe illness requiring hospitalization, temperature  $\geq 100.4^{\circ}\text{F}$  ( $38^{\circ}\text{C}$ ) for  $\geq 24$  hours or subjective fever, evidence of inflammation (demonstrated by elevated levels of inflammatory markers), involvement of two or more organ systems, no alternative plausible diagnosis, and current or recent SARS-CoV-2 infection, indicated by a positive result from an RT-PCR test, serologic test, or antigen test. Two hospitalized control groups included 1) patients with one or more symptoms consistent with COVID-19, but with a negative result from a SARS-CoV-2 RT-PCR or antigen test (test-negative) and 2) patients without symptoms compatible with COVID-19 who might or might not have received SARS-CoV-2 testing (syndrome-negative).<sup>†††</sup> Eligible controls were matched to case-patients by site, age group (12–15 years and 16–18 years), and case-patient hospitalization date (within plus or minus approximately 3 weeks).

Vaccination status was verified through searches of state immunization information systems, electronic medical records, or other sources, including documentation from pediatricians or patient immunization cards. For this analysis, persons were categorized as unvaccinated or fully vaccinated on or before the case-patient hospitalization date. Patients were considered unvaccinated if they had received no doses of the Pfizer-BioNTech vaccine; full vaccination in terms of expected protection against MIS-C was defined as receipt of 2 doses of Pfizer-BioNTech COVID-19 vaccine, with receipt of the second dose  $\geq 28$  days before hospital admission. The 28-day window was selected because a person is considered fully vaccinated against COVID-19  $\geq 14$  days after receipt of the second dose, and MIS-C generally occurs approximately 2–6 weeks after SARS-CoV-2 infection, with most cases occurring by the fourth week (1–3). Patients were excluded based on the following conditions: 1) receipt of only 1 vaccine dose; 2) receipt of the second dose within 28 days of hospital admission; 3) age 12–15 years and admission before July 1, 2021 (given that vaccination was not expanded to this age group until May 12, 2021); and 4) receipt of any COVID-19 vaccine other than Pfizer-BioNTech.

Demographic characteristics, clinical information related to the current illness, and SARS-CoV-2 testing history were obtained through parent or guardian interview conducted by trained study personnel or review of electronic medical

records.<sup>§§§</sup> Descriptive statistics were used to compare characteristics of case-patients and hospitalized controls, and Fisher's exact or Wilcoxon rank-sum tests were used for categorical and continuous variables, respectively. VE against MIS-C was calculated by comparing the odds of full COVID-19 vaccination among MIS-C case-patients and controls using the equation  $VE = 100 \times (1 - \text{adjusted odds ratio})$ . Adjusted odds ratios were calculated using multivariable logistic regression models with Firth penalization to reduce bias contributed by sparse data. Models were adjusted for U.S. Census region, age, sex, and race/ethnicity (8). To account for potential residual confounding by calendar time related to increasing vaccination coverage, the case-patient hospitalization date was used as a reference point for comparing antecedent vaccination in case-patients and controls. Other factors (underlying health conditions and social vulnerability index) were assessed, but not included in the final model if they did not alter the odds ratio estimate by  $>5\%$ . Sensitivity analyses were conducted to evaluate VE against MIS-C among patients with serologic evidence of previous infection (because non-MIS-C acute COVID-19 patients might have a positive RT-PCR assay in the absence of serology) and to evaluate whether VE differed by control group. Statistical analyses were conducted using SAS (version 9.4; SAS Institute); statistical significance was defined as  $p < 0.05$ . This activity was reviewed by CDC and other participating institutions and was conducted consistent with applicable federal law and CDC policy.<sup>¶¶¶</sup>

During July 1–December 9, 2021, among 117 MIS-C case-patients aged 12–18 years, 15 were excluded from the analysis, including six patients who received only 1 dose by the date of hospitalization, four who received their second vaccine dose within 28 days of hospital admission, and five patients aged 12–15 years who were hospitalized before July 1, 2021. The 283 patients in the primary analysis included 102 MIS-C case-patients and 181 controls (90 [50%] test-negative and 91 [50%] syndrome-negative) (Table 1). The median age among all case-patients and controls was 14.5 years, and 58% had at least one underlying condition (including obesity). COVID-19 vaccination coverage was approximately 5% among case-patients and 36% among controls.

Among the 70 children in this analysis who were fully vaccinated (with 2 doses), one syndrome-negative control patient

<sup>†††</sup> Vaccine effectiveness studies in the context of respiratory viruses most commonly include test-negative controls. Because of potential biases related to the selection of controls, including the potential for misclassification of test-negative patients due to false-negative tests, syndrome-negative controls were also included as a separate control group. Among the 91 syndrome-negative controls, 18 (20%) had no record of SARS-CoV-2 testing. The remaining syndrome-negative controls had a record of SARS-CoV-2 testing by RT-PCR or antigen and received negative test results.

<sup>§§§</sup> Among the 102 MIS-C case-patients and 181 controls enrolled, 50 (49%) and 113 (62%), respectively, had information obtained through a combination of parent interview and medical records abstraction, while 52 (51%) case-patients and 68 (38%) control patients had information obtained solely through medical records abstraction.

<sup>¶¶¶</sup> 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.

had received a third dose. Among 102 MIS-C case-patients, five (5%) were fully vaccinated with 2 doses  $\geq 28$  days before hospitalization, and 97 (95%) were unvaccinated (Table 2). Overall, 91 (89%) case-patients had cardiovascular involvement, 84 (82%) had gastrointestinal involvement, and 68 (67%) had hematologic involvement. Sixty-two (61%) were admitted to an intensive care unit, and 38 (37%) received life support during hospitalization, including invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation (ECMO). All 38 MIS-C patients requiring life support were unvaccinated; among these, nine patients required invasive mechanical ventilation, 35 received vasoactive infusions and one required ECMO. No deaths among these patients were reported. Hospital length of stay was similar among vaccinated and unvaccinated MIS-C patients (median = 5 days).

VE against MIS-C was 91% (95% CI = 78%–97%) (Table 3).\*\*\*\* In a sensitivity analysis excluding patients with positive RT-PCR or antigen-based SARS-CoV-2 test results and no positive serologic test, VE was 90% (95% CI = 75%–96%). VE against MIS-C was similar, irrespective of control group (test-negative controls: 92%, 95% CI = 77%–97%; syndrome-negative controls: 89%, 95% CI = 70%–96%); therefore, the pooled VE estimate using both control populations was deemed acceptable.

### Discussion

During July–December 2021, a period of Delta variant predominance, a real-world evaluation of VE in 24 U.S. pediatric hospitals found that receipt of 2 doses of the Pfizer-BioNTech vaccine was associated with a high level of protection against MIS-C among patients aged 12–18 years who received their second vaccine dose  $\geq 28$  days before hospitalization. Most (95%) patients aged 12–18 years hospitalized with MIS-C were unvaccinated. No fully vaccinated patients with MIS-C required respiratory or cardiovascular life support, as opposed to 39% of unvaccinated MIS-C patients who did. A recent Overcoming COVID-19 hospital network investigation reported high VE (93% [95% CI = 83%–97%]) against COVID-19–related hospitalizations in persons aged 12–18 years (6). The current findings contribute to the growing body of evidence that vaccination is likely effective in preventing severe COVID-19–related complications in children, including MIS-C.

\*\*\*\* VE against MIS-C was also assessed comparing the odds of antecedent vaccination with the second dose of the Pfizer-BioNTech vaccine  $\geq 14$  days before hospital admission. Point estimates did not significantly differ from the primary analysis presented in this report. (VE after 14 days: 86%; 95% CI = 70%–93%.)

The findings in this report are subject to at least seven limitations. First, VE was not assessed against MIS-C attributed to specific variants; however, >99% of COVID-19 cases reported during July–December 2021 resulted from infections with the Delta variant (9). Second, VE against MIS-C attributed to the B.1.1.529 (Omicron) variant could not be assessed, given the timing of hospital admission of included patients relative to emergence of this variant in the United States. Third, timing of initial SARS-CoV-2 infection relative to vaccination could not be inferred, and this investigation cannot differentiate between protection from acquisition of SARS-CoV-2 infection versus protection against development of MIS-C after infection. Fourth, the timing at which protection against MIS-C is conferred after 2 doses of vaccine is unknown; some protection might be possible within 28 days of vaccination, and this investigation had insufficient power to evaluate VE for 1 dose of vaccine. Fifth, this analysis examines VE against MIS-C conferred only by the Pfizer-BioNTech vaccine. Sixth, although the hospital sites participating in this investigation covered a broad geographic area, the results of this analysis are not generalizable to the entire U.S. pediatric population. Finally, given the short time frame of enrollment, this analysis was not designed to evaluate waning immunity or duration of protection against MIS-C.

As of December 13, 2021, 52.3% of eligible U.S. children and adolescents aged 12–17 years had received the primary Pfizer-BioNTech 2-dose series (10). In a multistate hospital network, this real-world investigation found that receipt of 2 doses of Pfizer-BioNTech vaccine was strongly associated with prevention of MIS-C among adolescents. Children aged 5–11 years, who are now authorized to receive the Pfizer-BioNTech vaccine, represent the age group at highest risk for MIS-C (1,3). This analysis lends supportive evidence that vaccination of children and adolescents is highly protective against MIS-C and COVID-19 and underscores the importance of vaccination of all eligible children.

### Overcoming COVID-19 Investigators

Meghan Murdock, Children's of Alabama, Birmingham, Alabama; Mary Glas Gaspers, University of Arizona, Tucson, Arizona; Katri V. Typo, University of Arizona, Tucson, Arizona; Connor P. Kelley, University of Arizona, Tucson, Arizona; Ronald C. Sanders, Arkansas Children's Hospital, Little Rock, Arkansas; Masson Yates, Arkansas Children's Hospital, Little Rock, Arkansas; Chelsea Smith, Arkansas Children's Hospital, Little Rock, Arkansas; Kathryn Crane, Rady Children's Hospital, San Diego, California; Geraldina Lionetti, University of California, San Francisco Benioff Children's Hospital Oakland, Oakland, California; Juliana Murcia-Montoya, University of California, San Francisco Benioff Children's Hospital Oakland, Oakland, California; Matt S. Zinter, University of California,

**TABLE 1. Characteristics of multisystem inflammatory syndrome in children case-patients and controls aged 12–18 years — 24 pediatric hospitals, 20 U.S. states,\* July 1–December 9, 2021**

Characteristic	No. (%)			p-value†
	Total (N = 283)	MIS-C case-patients (n = 102)	Controls (n = 181)	
<b>Median age, yrs (IQR)</b>	14.5 (13.4–15.9)	14.2 (13.0–15.9)	14.7 (13.6–15.9)	0.06
<b>Age group, yrs</b>				
12–15	221 (78.1)	81 (79.4)	140 (77.3)	0.77
16–18	62 (21.9)	21 (20.6)	41 (22.7)	
<b>Sex</b>				
Female	132 (46.6)	30 (29.4)	102 (56.4)	<0.01
<b>Race/Ethnicity</b>				
White, non-Hispanic	105 (37.1)	32 (31.4)	73 (40.3)	0.39
Black, non-Hispanic	99 (35.0)	42 (41.2)	57 (31.5)	
Asian, non-Hispanic	8 (2.8)	1 (1.0)	7 (3.9)	
Hispanic, any race	51 (18.0)	19 (18.6)	32 (17.7)	
Multiple/Other, non-Hispanic	10 (3.5)	4 (3.9)	6 (3.3)	
Unknown	10 (3.5)	4 (3.9)	6 (3.3)	
<b>SVI,<sup>§</sup> median (IQR)</b>	0.60 (0.30–0.80)	0.64 (0.43–0.78)	0.56 (0.27–0.81)	0.09
<b>U.S. Census region*</b>				
Northeast	8 (2.8)	3 (2.9)	5 (2.8)	0.98
Midwest	75 (26.5)	28 (27.5)	47 (26.0)	
South	159 (56.2)	56 (54.9)	103 (56.9)	
West	41 (14.5)	15 (14.7)	26 (14.4)	
<b>Month of admission</b>				
June	1 (0.4)	0 (—)	1 (0.6)	0.35
July	9 (3.2)	5 (4.9)	4 (2.2)	
August	49 (17.3)	16 (15.7)	33 (18.2)	
September	82 (29.0)	35 (34.3)	47 (26.0)	
October	85 (30.0)	30 (29.4)	55 (30.4)	
November	48 (17.0)	15 (14.7)	33 (18.2)	
December	9 (3.2)	1 (1.0)	8 (4.4)	
<b>Underlying health condition<sup>¶</sup></b>				
At least one underlying condition (including obesity)	164 (58.0)	40 (39.2)	124 (68.5)	<0.01
Asthma	49 (17.3)	15 (14.7)	34 (18.8)	0.42
Cardiovascular system disorder	23 (8.1)	3 (2.9)	20 (11.0)	0.02
Neurologic/Neuromuscular disorder	45 (15.9)	7 (6.9)	38 (21.0)	<0.01
Active or previous oncologic disorder	9 (3.2)	1 (1.0)	8 (4.4)	0.16
Nononcologic immunosuppressive disorder	13 (4.6)	2 (2.0)	11 (6.1)	0.14
Endocrine disorder	16 (5.7)	4 (3.9)	12 (6.6)	0.43
Diabetes	9 (3.2)	2 (2.0)	7 (3.9)	0.50
<b>Other chronic conditions**</b>	97 (34.3)	21 (20.6)	76 (42.0)	<0.01

See table footnotes on the next page.

San Francisco Benioff Children's Hospital, San Francisco, California; Denise Villarreal-Chico, University of California, San Francisco Benioff Children's Hospital, San Francisco, California; Adam L. Skura, Children's Hospital Los Angeles, Los Angeles, California; Harvey Peralta, Children's Hospital Los Angeles, Los Angeles, California; Justin M. Lockwood, Children's Hospital Colorado, Aurora, Colorado; Emily Port, Children's Hospital Colorado, Aurora, Colorado; Imogene A. Carson, Children's Hospital Colorado, Aurora, Colorado; Brandon M. Chatani, Holtz Children's Hospital, Miami, Florida; Laila Hussaini, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, Georgia; Nadine Baida, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, Georgia; Bria M. Coates, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; Courtney M. Rowan, Riley Hospital for Children, Indianapolis, Indiana; Mary Stumpf, Riley Hospital for Children, Indianapolis, Indiana; Marla S. Johnston, Children's Hospital of New Orleans, New Orleans, Louisiana; Benjamin J. Boutselis, Boston Children's Hospital, Boston, Massachusetts; Suden

Kucukak, Boston Children's Hospital, Boston, Massachusetts; Sabrina R. Chen, Boston Children's Hospital, Boston, Massachusetts; Edie Weller, Boston Children's Hospital, Boston, Massachusetts; Laura Berbert, Boston Children's Hospital, Boston, Massachusetts; Jie He, Boston Children's Hospital, Boston, Massachusetts; Heidi R. Flori, University of Michigan CS Mott Children's Hospital, Ann Arbor, Michigan; Janet R. Hume, University of Minnesota Masonic Children's Hospital, Minneapolis, Minnesota; Ellen R. Bruno, University of Minnesota Masonic Children's Hospital, Minneapolis, Minnesota; Lexie A. Goertzen, University of Minnesota Masonic Children's Hospital, Minneapolis, Minnesota; Emily R. Levy, Mayo Clinic, Rochester, Minnesota; Supriya Behl, Mayo Clinic, Rochester, Minnesota; Noelle M. Drapeau, Mayo Clinic, Rochester, Minnesota; Lora Martin, Children's Hospital of Mississippi, Jackson, Mississippi; Lacy Malloch, Children's Hospital of Mississippi, Jackson, Mississippi; Cameron Sanders, Children's Hospital of Mississippi, Jackson, Mississippi; Kayla Patterson, Children's Hospital of Mississippi, Jackson, Mississippi; Anita Dhanrajani, Children's Hospital of

**TABLE 1. (Continued) Characteristics of multisystem inflammatory syndrome in children case-patients and controls aged 12–18 years — 24 pediatric hospitals, 20 U.S. states,\* July 1–December 9, 2021**

Characteristic	No. (%)			p-value <sup>†</sup>
	Total (N = 283)	MIS-C case-patients (n = 102)	Controls (n = 181)	
<b>Laboratory test results<sup>††</sup></b>				
RT-PCR or antigen-positive, antibody not performed	11 (3.9)	11 (10.8)	0 (—)	<0.01
RT-PCR or antigen-positive, antibody-positive	12 (4.2)	12 (11.8)	0 (—)	
Antibody positive only	76 (26.9)	76 (74.5)	0 (—)	
Pre-admission results available only	3 (1.1)	3 (2.9)	0 (—)	
<b>Fully vaccinated<sup>§§</sup></b>	<b>70 (24.7)</b>	<b>5 (4.9)</b>	<b>65 (35.9)</b>	<b>&lt;0.01</b>
Median interval from receipt of second vaccine dose to reference hospitalization date, days (IQR) <sup>¶¶</sup>	84 (51–122)	63 (48–89)	88 (52–122)	0.37

**Abbreviations:** MIS-C = multisystem inflammatory syndrome in children; RT-PCR = reverse transcription-polymerase chain reaction; SVI = social vulnerability index.

\* Patients included vaccinated and unvaccinated persons aged 12–18 years enrolled from 24 pediatric hospitals in 20 states. *Northeast:* Boston Children's Hospital (Massachusetts), Children's Hospital of Philadelphia (Pennsylvania), and Saint Barnabas Medical Center (New Jersey); *Midwest:* Akron Children's Hospital (Ohio), Children's Hospital and Medical Center: Nebraska (Nebraska), Children's Hospital of Michigan (Michigan), Children's Mercy Kansas City (Missouri), Cincinnati Children's Hospital Medical Center (Ohio), Lurie Children's Hospital of Chicago (Illinois), Mayo Clinic (Minnesota), Nationwide Children's Hospital (Ohio), and Riley Children's Hospital (Indiana); *South:* Arkansas Children's Hospital (Arkansas), Children's of Alabama (Alabama), Children's Healthcare of Atlanta (Georgia), Children's Hospital of New Orleans (Louisiana), Medical University of South Carolina Children's Health (South Carolina), Monroe Carell Jr. Children's Hospital at Vanderbilt (Tennessee), Texas Children's Hospital (Texas), University of Mississippi Medical Center (Mississippi), University of North Carolina at Chapel Hill Children's Hospital (North Carolina), and University of Texas Southwestern Medical Center (Texas); *West:* Children's Hospital Colorado (Colorado), Children's Hospital Los Angeles (California), University of California San Diego-Rady Children's Hospital (California), and University of California San Francisco Benioff Children's Hospital Oakland (California).

<sup>†</sup> Testing for statistical significance was conducted using Fisher's exact test to compare categorical variables or Wilcoxon rank-sum test for medians to compare continuous data. Statistical significance was defined as  $p < 0.05$ .

<sup>§</sup> CDC/ATSDR SVI documentation is available at <https://www.atsdr.cdc.gov/placeandhealth/svi/index.html>. Median SVI for case-patients and controls are based on U.S. 2018 SVI data.

<sup>¶</sup> Underlying conditions with a missing response (yes/no) were assumed not to be present.

<sup>\*\*</sup> Other chronic conditions included rheumatologic/autoimmune disorder, hematologic disorder, renal or urologic dysfunction, gastrointestinal/hepatic disorder, metabolic or confirmed or suspected genetic disorder (including obesity), or atopic or allergic condition.

<sup>††</sup> With the exception of the "pre-admission results available only" category, all other test results were obtained after hospital admission.

<sup>§§</sup> COVID-19 vaccination status included the following two categories: 1) unvaccinated, defined as no receipt of any SARS-CoV-2 vaccine before hospitalization for current illness and 2) fully vaccinated, defined as receipt of both doses of a 2-dose Pfizer-BioNTech vaccination  $\geq 28$  days before illness onset.

<sup>¶¶</sup> Dates are based on those with documented vaccination, not plausible self-report. For controls without COVID-19-like illness, a reference date was set to the admission date of their matched case-patient to account for residual confounding by hospital admission date relative to expanding vaccination coverage.

Mississippi, Jackson, Mississippi; Shannon M. Hill, Children's Mercy Hospital, Kansas City, Missouri; Abigail Kietzman, Children's Mercy Hospital, Kansas City, Missouri; Valerie H. Rinehart, Children's Hospital & Medical Center, Omaha, Nebraska; Lauren A. Hoody, Children's Hospital & Medical Center, Omaha, Nebraska; Stephanie P. Schwartz, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Angelo G. Navas, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Paris C. Bennett, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Nicole A. Twinem, Akron Children's Hospital, Akron, Ohio; Merry L. Tomcany, Akron Children's Hospital, Akron, Ohio; Mary Allen Staat, Cincinnati Children's Hospital, Cincinnati, Ohio; Chelsea C. Rohlf, Cincinnati Children's Hospital, Cincinnati, Ohio; Amber Wolfe, Nationwide Children's Hospital, Columbus, Ohio; Rebecca L. Douglas, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Kathlyn Phengchomphet, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Megan M. Bickford, Medical University of South Carolina Children's Health, Charleston, South Carolina; Lauren E. Wakefield, Medical University of South Carolina Children's Health, Charleston, South Carolina; Laura Smallcomb, Medical University of South Carolina Children's Health, Charleston, South Carolina; Laura S. Stewart, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee; Meena Golchha, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee; Jennifer N. Oates, Texas Children's Hospital, Houston, Texas; Cindy Bowens, University of Texas Southwestern, Children's Medical Center Dallas, Dallas, Texas.

Corresponding author: Laura D. Zambrano, [lzambrano@cdc.gov](mailto:lzambrano@cdc.gov).

<sup>1</sup>CDC COVID-19 Response Team; <sup>2</sup>Department of Anesthesiology, Critical Care, and Pain Medicine, Boston Children's Hospital, Boston, Massachusetts; <sup>3</sup>Division of Pediatric Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee; <sup>4</sup>Department of Pediatrics, Baylor College of Medicine, Immunization Project, Texas Children's Hospital, Houston, Texas; <sup>5</sup>The Center for Childhood Infections and Vaccines of Children's Healthcare of Atlanta and the Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia; <sup>6</sup>Division of Critical Care Medicine, Department of Pediatrics, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, Georgia; <sup>7</sup>Department of Pediatrics, Section of Critical Care Medicine, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado; <sup>8</sup>Department of Pediatrics, Children's Hospital of Michigan, Central Michigan University, Detroit, Michigan; <sup>9</sup>The Ryan White Center for Pediatric Infectious Disease and Global Health, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana; <sup>10</sup>Division of Pediatric Critical Care Medicine, Nationwide Children's Hospital Columbus, Ohio; <sup>11</sup>Division of Critical Care Medicine, Department of Pediatrics, Akron Children's Hospital, Akron, Ohio; <sup>12</sup>Department of Pediatrics, Department of Microbiology, Division of Infectious Diseases, University of Mississippi Medical Center, Jackson, Mississippi; <sup>13</sup>Department of Pediatrics, Division of Cardiology, Louisiana State University Health Sciences Center and Children's Hospital of New Orleans, New Orleans, Louisiana; <sup>14</sup>Division of Critical Care Medicine, UCSF Benioff Children's Hospital Oakland, Oakland, California; <sup>15</sup>Section of Pediatric Critical Care, Department of Pediatrics, Arkansas Children's Hospital, Little Rock, Arkansas; <sup>16</sup>Division of Pediatric Critical Care Medicine, Medical University of South Carolina, Charleston, South Carolina; <sup>17</sup>Division of Pediatric Critical Care, Department of Pediatrics, Children's Hospital and Medical Center, Omaha, Nebraska; <sup>18</sup>Division of Infectious Diseases, Children's Hospital Los Angeles and Departments of Pediatrics and

**TABLE 2. Clinical outcomes and severity among multisystem inflammatory syndrome in children case-patients aged 12–18 years, by vaccination status\* — 24 pediatric hospitals, 20 U.S. states,† July–December 2021**

Characteristic	No. (%)		
	Total (N = 102)	Unvaccinated (n = 97)	Fully vaccinated ≥28 days before hospitalization (n = 5)
<b>Organ system involvement<sup>§</sup></b>			
Cardiovascular	91 (89.2)	86 (88.7)	5 (100.0)
Respiratory	29 (28.4)	28 (28.9)	1 (20.0)
Hematologic	68 (66.7)	66 (68.0)	2 (40.0)
Gastrointestinal	84 (82.4)	79 (81.4)	5 (100.0)
Neurologic	9 (8.8)	8 (8.2)	1 (20.0)
Dermatologic	36 (35.3)	34 (35.1)	2 (40.0)
Renal/Urologic	35 (34.3)	33 (34.0)	2 (40.0)
<b>Intensive care unit admission</b>			
<b>Critically ill patients on life support</b>			
Invasive mechanical ventilation	9 (8.8)	9 (9.3)	0 (—)
Vasoactive infusions	35 (34.3)	35 (36.1)	0 (—)
Extracorporeal membrane oxygenation	1 (1.0)	1 (1.0)	0 (—)
<b>Patients with discharge data</b>			
Hospital length of stay, median (IQR)	5 (4–8)	5 (4–8)	5 (2–6)

**Abbreviation:** BNP = brain natriuretic peptide.

\* COVID-19 vaccination status included the following two categories: 1) unvaccinated, defined as no receipt of any SARS-CoV-2 vaccine before hospitalization for current illness and 2) fully vaccinated, defined as receipt of both doses of a 2-dose Pfizer-BioNTech vaccination ≥28 days before illness onset.

† Patients included vaccinated and unvaccinated persons aged 12–18 years enrolled from 24 pediatric hospitals in 20 states. *Northeast:* Boston Children's Hospital (Massachusetts), Children's Hospital of Philadelphia (Pennsylvania), and Saint Barnabas Medical Center (New Jersey); *Midwest:* Akron Children's Hospital (Ohio), Children's Hospital and Medical Center: Nebraska (Nebraska), Children's Hospital of Michigan (Michigan), Children's Mercy Kansas City (Missouri), Cincinnati Children's Hospital Medical Center (Ohio), Lurie Children's Hospital of Chicago (Illinois), Mayo Clinic (Minnesota), Nationwide Children's Hospital (Ohio), and Riley Children's Hospital (Indiana); *South:* Arkansas Children's Hospital (Arkansas), Children's of Alabama (Alabama), Children's Healthcare of Atlanta (Georgia), Children's Hospital of New Orleans (Louisiana), Medical University of South Carolina Children's Health (South Carolina), Monroe Carell Jr. Children's Hospital at Vanderbilt (Tennessee), Texas Children's Hospital (Texas), University of Mississippi Medical Center (Mississippi), University of North Carolina at Chapel Hill Children's Hospital (North Carolina), and University of Texas Southwestern Medical Center (Texas); *West:* Children's Hospital Colorado (Colorado), Children's Hospital Los Angeles (California), University of California San Diego-Rady Children's Hospital (California), and University of California San Francisco Benioff Children's Hospital Oakland (California).

§ Organ system involvement was defined with the following criteria: 1) Cardiovascular (e.g., shock, elevated troponin, BNP, N-terminal-pro hormone BNP, abnormal echocardiogram, or arrhythmia); 2) Respiratory (e.g., pneumonia, acute respiratory distress syndrome, and pulmonary embolism); 3) Renal (e.g., acute kidney injury or renal failure); 4) Gastrointestinal (e.g., abdominal pain, vomiting, diarrhea, elevated bilirubin, or elevated liver enzymes); 5) Neurologic (e.g., cerebrovascular accident, aseptic meningitis, or encephalopathy); 6) Hematologic (e.g., elevated D-dimers, thrombophilia, or thrombocytopenia); 7) Dermatologic (e.g., rash, erythema, or peeling).

**TABLE 3. Effectiveness\* of 2 doses of Pfizer-BioNTech vaccine against multisystem inflammatory syndrome in children among hospitalized patients aged 12–18 years — 24 pediatric hospitals, 20 U.S. states,† July–December 2021**

Control groups	No. vaccinated <sup>§</sup> /Total (%)		
	MIS-C case patients	Control patients	Adjusted VE, % (95% CI)
<b>All controls</b>	5/102 (4.9)	65/181 (35.9)	91 (78–97)
Test-negative	5/102 (4.9)	34/90 (37.8)	92 (77–97)
Syndrome-negative	5/102 (4.9)	31/91 (34.1)	89 (70–96)
<b>Sensitivity analysis</b>			
MIS-C case patients with serologic evidence present <sup>¶</sup>	5/88 (5.7)	61/161 (37.9)	90 (75–96)

**Abbreviations:** MIS-C = multisystem inflammatory syndrome in children; VE = vaccine effectiveness.

\* VE estimates were based on odds of antecedent vaccination in MIS-C case-patients versus controls adjusted for U.S. Census region, continuous age in years, sex, and race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic multiple race/other, Hispanic of any race, or unknown). Firth penalized regression was used for models with six or fewer vaccinated cases.

† Patients included vaccinated and unvaccinated persons aged 12–18 years enrolled from 24 pediatric hospitals in 20 states. *Northeast:* Boston Children's Hospital (Massachusetts), Children's Hospital of Philadelphia (Pennsylvania), and Saint Barnabas Medical Center (New Jersey); *Midwest:* Akron Children's Hospital (Ohio), Children's Hospital and Medical Center: Nebraska (Nebraska), Children's Hospital of Michigan (Michigan), Children's Mercy Kansas City (Missouri), Cincinnati Children's Hospital Medical Center (Ohio), Lurie Children's Hospital of Chicago (Illinois), Mayo Clinic (Minnesota), Nationwide Children's Hospital (Ohio), and Riley Children's Hospital (Indiana); *South:* Arkansas Children's Hospital (Arkansas), Children's of Alabama (Alabama), Children's Healthcare of Atlanta (Georgia), Children's Hospital of New Orleans (Louisiana), Medical University of South Carolina Children's Health (South Carolina), Monroe Carell Jr. Children's Hospital at Vanderbilt (Tennessee), Texas Children's Hospital (Texas), University of Mississippi Medical Center (Mississippi), University of North Carolina at Chapel Hill Children's Hospital (North Carolina), and University of Texas Southwestern Medical Center (Texas); *West:* Children's Hospital Colorado (Colorado), Children's Hospital Los Angeles (California), University of California San Diego-Rady Children's Hospital (California), and University of California San Francisco Benioff Children's Hospital Oakland (California).

§ COVID-19 vaccination status included the following two categories: 1) unvaccinated, defined as no receipt of any SARS-CoV-2 vaccine before hospitalization for current illness and 2) fully vaccinated, defined as receipt of both doses of a 2-dose Pfizer-BioNTech vaccination ≥28 days before illness onset.

¶ Analysis excluded 14 MIS-C case-patients who were positive by reverse transcription-polymerase chain reaction only with no serologic evidence of previous infection and 20 controls matched to these patients, given potential misclassification of patients with severe acute COVID-19.

Molecular Microbiology and Immunology, University of Southern California, Los Angeles, California; <sup>19</sup>Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama; <sup>20</sup>Department of Pediatrics, University of North Carolina at Chapel Hill Children's Hospital, Chapel Hill, North Carolina; <sup>21</sup>Division of Pediatric Critical Care, Department of Pediatrics, Saint Barnabas Medical Center, Livingston, New Jersey; <sup>22</sup>Division of Critical Care Medicine, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; <sup>23</sup>Division of Pediatric Hospital Medicine, UC San Diego-Rady Children's Hospital, San Diego, California; <sup>24</sup>Division of Critical Care Medicine, Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; <sup>25</sup>Department of Pediatrics, Division of Critical Care Medicine, University of Texas Southwestern, Children's Medical Center Dallas, Dallas, Texas; <sup>26</sup>Division of Pediatric Infectious Diseases, Department of Pediatrics, Children's Mercy Kansas City, Kansas City, Missouri; <sup>27</sup>Departments of Anesthesia and Pediatrics, Harvard Medical School, Boston, Massachusetts.

## References

## Summary

## What is already known about this topic?

The Pfizer-BioNTech vaccine, currently authorized for persons aged  $\geq 5$  years, provides a high level of protection against severe COVID-19 in persons aged 12–18 years. Vaccine effectiveness against multisystem inflammatory syndrome in children (MIS-C), which can occur 2–6 weeks after SARS-CoV-2 infection, has remained uncharacterized.

## What is added by this report?

Estimated effectiveness of 2 doses of Pfizer-BioNTech vaccine against MIS-C was 91% (95% CI = 78%–97%). Among critically ill MIS-C case-patients requiring life support, all were unvaccinated.

## What are the implications for public health practice?

Receipt of 2 doses of Pfizer-BioNTech vaccine is highly effective in preventing MIS-C in persons aged 12–18 years. These findings further reinforce the COVID-19 vaccination recommendation for eligible children.

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## 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

Catherine E. Barrett, PhD<sup>1,2</sup>; Alain K. Koyama, ScD<sup>1,2</sup>; Pablo Alvarez, MPH<sup>1</sup>; Wilson Chow<sup>1</sup>; Elizabeth A. Lundeen, PhD<sup>1,2</sup>; Cria G. Perrine, PhD<sup>1</sup>; Meda E. Pavkov, MD, PhD<sup>2</sup>; Deborah B. Rolka, MS<sup>2</sup>; Jennifer L. Wiltz, MD<sup>1</sup>; Lara Bull-Otterson, PhD<sup>1</sup>; Simone Gray, PhD<sup>1</sup>; Tegan K. Boehmer, PhD<sup>1</sup>; Adi V. Gundlapalli, MD<sup>1</sup>; David A. Siegel, MD<sup>1</sup>; Lyudmyla Kompaniyets, PhD<sup>1</sup>; Alyson B. Goodman, MD<sup>1</sup>; Barbara E. Mahon, MD<sup>1</sup>; Robert V. Tauxe, MD<sup>1</sup>; Karen Remley, MD<sup>1</sup>; Sharon Saydah, PhD<sup>1</sup>

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The COVID-19 pandemic has disproportionately affected people with diabetes, who are at increased risk of severe COVID-19.\* Increases in the number of type 1 diabetes diagnoses (1,2) and increased frequency and severity of diabetic ketoacidosis (DKA) at the time of diabetes diagnosis (3) have been reported in European pediatric populations during the COVID-19 pandemic. In adults, diabetes might be a long-term consequence of SARS-CoV-2 infection (4–7). To evaluate the risk for any new diabetes diagnosis (type 1, type 2, or other diabetes) >30 days<sup>†</sup> after acute infection with SARS-CoV-2 (the virus that causes COVID-19), CDC estimated diabetes incidence among patients aged <18 years (patients) with diagnosed COVID-19 from retrospective cohorts constructed using IQVIA health care claims data from March 1, 2020, through February 26, 2021, and compared it with incidence among patients matched by age and sex 1) who did not receive a COVID-19 diagnosis during the pandemic, or 2) who received a prepandemic non-COVID-19 acute respiratory infection (ARI) diagnosis. Analyses were replicated using a second data source (HealthVerity; March 1, 2020–June 28, 2021) that included patients who had any health care encounter possibly related to COVID-19. Among these patients, diabetes incidence was significantly higher among those with COVID-19 than among those 1) without COVID-19 in both databases (IQVIA: hazard ratio [HR] = 2.66, 95% CI = 1.98–3.56; HealthVerity: HR = 1.31, 95% CI = 1.20–1.44) and 2) with non-COVID-19 ARI in the prepandemic period (IQVIA, HR = 2.16, 95% CI = 1.64–2.86). The observed increased risk for diabetes among persons aged <18 years who had COVID-19 highlights the importance of COVID-19 prevention strategies, including vaccination, for all eligible persons in

this age group,<sup>§</sup> in addition to chronic disease prevention and management. The mechanism of how SARS-CoV-2 might lead to incident diabetes is likely complex and could differ by type 1 and type 2 diabetes. Monitoring for long-term consequences, including signs of new diabetes, following SARS-CoV-2 infection is important in this age group

Retrospective cohorts were constructed using two U.S. medical claims databases: IQVIA<sup>¶</sup> and HealthVerity.<sup>\*\*</sup> Patients who were aged <18 years on their index encounter date and who were continuously enrolled in a closed payor system throughout the study period<sup>††</sup> were followed from their index date<sup>§§</sup> until the end of the study period. Patients were excluded from the analysis if they had preexisting diabetes, defined as one or more

<sup>§</sup> As of January 7, 2021, children aged ≥5 years are eligible for COVID-19 vaccination. <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>

<sup>¶</sup> IQVIA PharMetrics Plus (<https://www.iqvia.com>) is a database of adjudicated health care claims from closed U.S. health plans, including claims from primarily commercial health plans (preferred provider and health maintenance) used to provide a complete view of patient care across all care settings. During January 2013–March 2021, PharMetrics Plus had approximately 163 million enrollees. IQVIA data (2021 Quarter 3 2021 data release) were extracted using the E360 Software-as-a-Service Platform. <https://www.iqvia.com/solutions/real-world-evidence/platforms/e360-real-world-data-platform>

<sup>\*\*</sup> HealthVerity (<https://healthverity.com/>) provides access to patient-level linked data from 70 different commercial health data sources using privacy-preserving record linkage to generate a comprehensive and longitudinal patient history. During 2014–2021, there were medical claims of approximately 150 million patients. This study used CDC-licensed HealthVerity (November 2021 data release) closed payor claims data linked to SARS-CoV-2 laboratory testing and hospital chargemaster data for patients with any health care encounter possibly related to COVID-19.

<sup>††</sup> In IQVIA, the study period was 2 years and 2 months (January 29, 2019–March 31, 2021) for the pandemic period groups or January 29, 2016–March 31, 2018 for the prepandemic period groups. In HealthVerity, the study period was December 1, 2018–July 31, 2021.

<sup>§§</sup> The index date for the COVID-19 group was the first outpatient claim or hospital discharge date with a COVID-19 diagnosis (IQVIA, HealthVerity) or a positive SARS-CoV-2 test result (HealthVerity). The index date for the non-COVID-19 group was the date of a randomly selected claim during the month in which the patient was matched to a COVID-19 group patient (IQVIA and HealthVerity). Because of a lack of ARI cases in winter months comparable to COVID-19, the index dates for the ARI and non-ARI groups were defined based on a randomly chosen ARI or non-ARI claim during the prepandemic study period (IQVIA).

\* <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html>

<sup>†</sup> CDC defines post-COVID-19 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>

*International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) diagnosis codes for diabetes (E08–E13) in the 1–13 months preceding their index date.

In the IQVIA database, patients with a COVID-19 diagnosis (ICD-10-CM codes B97.29 or U07.1)<sup>¶¶</sup> during March 1, 2020–February 26, 2021, were defined as having COVID-19. Patients with COVID-19 were matched by age and sex to pandemic and pre-pandemic period comparison groups.<sup>\*\*\*</sup> The pandemic period non-COVID-19 group comprised patients without COVID-19-related ICD-10-CM codes during March 1, 2020–February 26, 2021.<sup>†††</sup> The pre-pandemic period ARI group comprised patients with a diagnosis of ARI<sup>§§§</sup> (Supplementary Table 1, <https://stacks.cdc.gov/view/cdc/113062>) during March 1, 2017–February 26, 2018. A pre-pandemic non-ARI group consisted of those in this age group whose records did not include ARI ICD-10-CM codes during March 1, 2017–February 26, 2018.

In HealthVerity, the COVID-19 group comprised patients aged <18 years whose record included an ICD-10-CM diagnosis code for COVID-19 or a positive SARS-CoV-2 polymerase chain reaction (PCR) test result during March 1, 2020–June 28, 2021. The pandemic period non-COVID-19 group consisted of those who had a negative SARS-CoV-2 PCR test result and no record of COVID-19 diagnosis codes or positive SARS-CoV-2 test results during the same period. Both groups were identified within a subset of CDC-licensed HealthVerity data that includes patients with a health care encounter possibly related to COVID-19 (Supplementary Table 2, <https://stacks.cdc.gov/view/cdc/113062>). There was no pre-pandemic comparison period for the HealthVerity data.

Incident diabetes was defined as one or more health care claims with a diabetes diagnosis (ICD-10-CM codes E08–E13) occurring >30 days after the index date (excluding cases of transient, resolved hyperglycemia). Frequencies of incident

diabetes codes on, and DKA codes on or before, the date of the incident diabetes encounter were calculated.<sup>¶¶¶</sup> Cox regression models were used to estimate HRs for diabetes risk. HRs were also estimated by age group and sex. Age and sex effect modifications were assessed using interaction terms. SAS (version 9.4; SAS Institute) and PANDAS (version 1.3.0; PANDAS Community) software were used to conduct all analyses. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.<sup>\*\*\*\*</sup>

Among 80,893 patients with COVID-19 in the IQVIA database, the mean age was 12.3 years, 50.1% were female, and 0.7% were hospitalized at their index COVID-19 encounter (Table 1). Among 439,439 patients with COVID-19 in HealthVerity, the mean age was 12.7 years, 50.1% were female, and 0.9% were hospitalized at their index encounter. Diabetes was coded in 0.08% (IQVIA) and 0.25% (HealthVerity) of claims for patients with COVID-19, with the majority of diabetes diagnoses for type 1 or type 2 (IQVIA, 94.1%; HealthVerity, 94.0%). In comparison, 0.03% (IQVIA) and 0.19% (HealthVerity) diabetes cases were coded among those without COVID-19. DKA was reported in 48.5% (IQVIA) and 40.2% (HealthVerity) of patients with COVID-19 and diabetes; these proportions were higher than DKA reported in patients with diabetes without COVID (IQVIA: non-COVID 13.6%; ARI 22.0%; non-ARI 27.5%; HealthVerity: 29.7%).

In the IQVIA database, diabetes incidence was 316 per 100,000 person-years in the COVID-19 group, 118 per 100,000 person-years in the pandemic period non-COVID-19 group, 126 per 100,000 person-years in the pre-pandemic ARI group, and 125 per 100,000 person-years in the pre-pandemic non-ARI group (Table 2). Diabetes risk was 166% higher in the COVID-19 group than in the non-COVID-19 group (HR = 2.66, 95% CI = 1.98–3.56) and 116% higher than in the pre-pandemic ARI group (HR = 2.16, 95% CI = 1.64–2.86) (Figure). Diabetes incidence did not significantly differ between the pre-pandemic ARI and non-ARI groups (HR = 0.99, 95% CI = 0.84–1.15). In the HealthVerity database, diabetes incidence was 31% higher among patients aged <18 years with COVID-19 (399 per 100,000 person-years) than among those without COVID-19 (304 per 100,000 person-years; HR = 1.31, 95% CI = 1.20–1.44).

In the IQVIA database, risk for diabetes was similar across age groups and by sex. In the HealthVerity database, there

¶¶ ICD-10-CM B97.29 code (other coronavirus as the cause of diseases classified elsewhere) between March–April 2020 and U07.1 code (COVID-19, virus identified [laboratory-confirmed]) beginning April 2020. <https://www.cdc.gov/nchs/data/icd/Announcement-New-ICD-code-for-coronavirus-3-18-2020.pdf>

\*\*\* The maximum possible matching ratio was used in each comparison. In IQVIA, the non-COVID-19 and ARI groups were both matched 5:1 to the COVID-19 group and the non-ARI group was matched 2:1 to the ARI group. In HealthVerity, the non-COVID-19 group was matched 1:1 to the COVID-19 group.

††† ICD-10-CM diagnoses related to COVID-19 and multisystem inflammatory syndrome in children (MIS-C) that were used to exclude possible COVID-19 in non-COVID-19 groups include B97.29, U07.1, B34.2, B97.2, B97.21, J12.82, U07.2, A41.89, J12.81, J12.89, M35.8, B94.8, M30.3, and M35.81.

§§§ Among those with ARI, the most common ARI codes were acute pharyngitis (J02, 38.3%), acute upper respiratory infection of multiple and unspecified sites (J06, 22.1%), acute sinusitis (J01, 11.8%), influenza due to unidentified influenza virus (J10, 4.8%), influenza due to other identified influenza virus (J11, 4.5%), acute bronchitis (J20, 4.3%), acute tonsillitis (J03, 3.1%), and acute nasopharyngitis (common cold) (J00, 2.7%).

¶¶¶ Frequencies of incident diabetes codes within the following categories were calculated: type 1 diabetes or type 2 diabetes (E10–E11), diabetes due to underlying condition or other diabetes (E08, E13), and drug or chemical induced diabetes (E09). DKA was defined as E08.1, E09.1, E10.1, E11.1, and E13.1 coded before or including the incident diabetes encounter.

\*\*\*\* 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.

**TABLE 1. Characteristics of matched pediatric groups with and without evidence of COVID-19 or acute respiratory infection and number of new diabetes diagnoses, by age, sex, and preceding COVID-19 or acute respiratory infection diagnosis — IQVIA PharMetrics Plus and HealthVerity claims databases, United States, March 1, 2020–June 28, 2021\***

Database/Characteristic	No. (%)				
	Pediatric overall	COVID-19	Non-COVID-19	ARI	Non-ARI
<b>IQVIA</b>					
Total no. of patients	1,698,753	80,893	404,465	404,465	808,930
Age, mean (SD), yrs	12.3 (4.3)	12.3 (4.3)	12.3 (4.3)	12.3 (4.3)	12.3 (4.3)
<b>Age group, yrs</b>					
0–4	124,530 (7.3)	5,930 (7.3)	29,650 (7.3)	29,650 (7.3)	59,300 (7.3)
5–11	483,273 (28.4)	23,013 (28.4)	115,065 (28.4)	115,065 (28.4)	230,130 (28.4)
12–15	592,830 (34.9)	28,230 (34.9)	141,150 (34.9)	141,150 (34.9)	282,300 (34.9)
16–17	498,120 (29.3)	23,720 (29.3)	118,600 (29.3)	118,600 (29.3)	237,200 (29.3)
Female sex	850,857 (50.1)	40,517 (50.1)	202,585 (50.1)	202,585 (50.1)	405,170 (50.1)
Hospitalized at index encounter	6,473 (0.4)	566 (0.7)	614 (0.2)	1,602 (0.4)	3,691 (0.5)
<b>New diabetes diagnosis<sup>†</sup></b>					
Overall	<b>937 (0.06)</b>	<b>68 (0.08)</b>	<b>132 (0.03)</b>	<b>227 (0.06)</b>	<b>510 (0.06)</b>
<b>DM type (% of all newly diagnosed diabetes)<sup>§</sup></b>					
Type 1 or Type 2	891 (95.1)	64 (94.1)	124 (93.9)	210 (92.5)	493 (96.7)
Due to underlying condition/Other	31 (3.3)	3 (4.4)	6 (4.5)	8 (3.5)	14 (2.7)
Drug or chemical induced	15 (1.6)	1 (1.5)	2 (1.5)	9 (4.0)	3 (0.6)
DKA (% of all newly diagnosed diabetes) <sup>¶</sup>	241 (25.7)	33 (48.5)	18 (13.6)	50 (22.0)	140 (27.5)
<b>HealthVerity</b>					
Total no. of patients	878,878	439,439	439,439	—**	—
Age, mean (SD), yrs	12.7 (3.8)	12.7 (3.8)	12.7 (3.8)	—	—
<b>Age group, yrs</b>					
0–4	28,532 (3.2)	14,266 (3.2)	14,266 (3.2)	—	—
5–11	321,496 (36.6)	160,748 (36.6)	160,748 (36.6)	—	—
12–15	319,458 (36.3)	159,729 (36.3)	159,729 (36.3)	—	—
16–17	209,392 (23.8)	104,696 (23.8)	104,696 (23.8)	—	—
Female sex	440,024 (50.1)	220,012 (50.1)	220,012 (50.1)	—	—
Hospitalized at index encounter	13,118 (3.0)	7,510 (0.9)	5,608 (1.3)	—	—
<b>New diabetes diagnosis</b>					
Overall	<b>1,973 (0.22)</b>	<b>1,120 (0.25)</b>	<b>853 (0.19)</b>	—	—
<b>DM type (% of all newly diagnosed diabetes)</b>					
Type 1 or type 2	1,871 (94.8)	1,053 (94.0)	818 (95.9)	—	—
Due to underlying condition/Other	67 (3.4)	42 (3.8)	25 (2.9)	—	—
Drug or chemical induced	35 (1.8)	25 (2.2)	10 (1.2)	—	—
DKA (% of all newly diagnosed diabetes)	703 (35.6)	450 (40.2)	253 (29.7)	—	—

**Abbreviations:** ARI = acute respiratory infection; DKA = diabetic ketoacidosis; DM = diabetes mellitus; ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*.

\* Groups in IQVIA included patients aged <18 years with or without COVID-19 (COVID-19; non-COVID-19, respectively) and patients aged <18 years with or without ARI (ARI; non-ARI, respectively), during March 1, 2020–February 26, 2021, determined using presence or absence of ICD-10-CM codes for COVID-19 and ARI. The non-COVID-19 group was matched 5:1 to the COVID-19 group by age, sex, and month of encounter. The ARI group was matched 5:1 to the COVID-19 group by age and sex, and a random encounter date was selected. The non-ARI group was matched 2:1 to the ARI group by age and sex, and a random encounter date was selected. In HealthVerity, among patients aged <18 years, those with COVID-19 (COVID), determined by ICD-10-CM code or by a positive SARS-CoV-2 test result during March 1, 2020–June 28, 2021, were matched 1:1 to those with a negative SARS-CoV-2 test result (non-COVID-19) during the same period.

<sup>†</sup> New diabetes diagnosis could occur >30 days after the index encounter and included ICD-10-CM codes E08 (diabetes due to underlying condition), E09 (drug or chemical induced diabetes), E10 (type 1 diabetes), E11 (type 2 diabetes), and E13 (other specified diabetes).

<sup>§</sup> The denominator was patients aged <18 years who received a new diabetes diagnosis. Diabetes ICD-10-CM codes at the new diabetes encounter were grouped into any type 1 or type 2 code (E10, E11), diabetes due to underlying condition (E08) or other specified diabetes (E13) codes, or drug induced diabetes (E09).

<sup>¶</sup> The denominator was patients aged <18 years with a new diabetes diagnosis. DKA was defined as E08.1, E09.1, E10.1, E11.1, and E13.1 coded any time before and including the index encounter.

\*\* Dashes indicate no prepandemic data available for ARI and non-ARI in the HealthVerity database.

was no association with diabetes in children aged <12 years, although a significantly increased risk was observed among all other age and sex groups. However, no age group or sex interaction terms were statistically significant.

## Discussion

New diabetes diagnoses were 166% (IQVIA) and 31% (HealthVerity) more likely to occur among patients with COVID-19 than among those without COVID-19 during the pandemic and 116% more likely to occur among those

TABLE 2. Incidence of new diabetes diagnoses by age group and sex — IQVIA PharMetrics Plus and HealthVerity claims databases, United States, March 1, 2020–June 28, 2021\*

Database/ Characteristic	COVID-19			Non-COVID-19			ARI			Non-ARI		
	No. of DM cases	Person- years	Diabetes incidence <sup>†</sup> (95% CI)	No. of DM cases	Person- years	Diabetes incidence <sup>†</sup> (95% CI)	No. of DM cases	Person- Years	Diabetes incidence <sup>†</sup> (95% CI)	No. of DM cases	Person- years	Diabetes incidence <sup>†</sup> (95% CI)
<b>IQVIA</b>												
Overall	68	21,563	316 (241–391)	132	111,418	118 (98–139)	227	180,436	126 (109–142)	510	407,741	125 (114–136)
Age group, yrs												
0–11	20	7,662	261 (146–375)	30	39,512	76 (49–103)	56	65,810	85 (63–107)	148	147,255	101 (84–117)
12–17	48	13,886	346 (248–443)	102	71,906	142 (114–169)	171	114,626	149 (127–172)	362	260,486	139 (125–153)
Sex												
Female	34	10,849	313 (208–419)	69	56,112	123 (94–152)	125	90,835	138 (113–162)	252	203,209	124 (109–139)
Male	34	10,699	318 (211–425)	63	55,306	114 (86–142)	102	89,601	114 (92–136)	258	204,532	126 (111–142)
<b>HealthVerity</b>												
Overall	1120	280,767	399 (376–423)	853	281,072	304 (284–324)	— <sup>§</sup>	—	—	—	—	—
Age group, yrs												
0–11	240	113,575	211 (186–239)	214	113,642	188 (164–214)	—	—	—	—	—	—
12–17	880	167,192	526 (492–562)	639	167,430	381 (353–412)	—	—	—	—	—	—
Sex												
Female	602	140,844	427 (394–462)	478	141,018	339 (310–370)	—	—	—	—	—	—
Male	518	139,914	370 (339–403)	375	140,045	268 (242–296)	—	—	—	—	—	—

**Abbreviations:** ARI = acute respiratory infection; DM = diabetes mellitus, ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*.

\* Groups in IQVIA included patients aged <18 years with or without COVID-19 (COVID-19; non-COVID-19, respectively) and patients aged <18 years with or without ARI (ARI; non-ARI, respectively), during March 1, 2020–February 26, 2021, determined using presence or absence of ICD-10-CM codes for COVID-19 and ARI. The non-COVID-19 group was matched 5:1 to the COVID-19 group by age, sex, and month of encounter. The ARI group was matched 5:1 to the COVID-19 group by age and sex, and a random encounter date was selected. The non-ARI group was matched 2:1 to the ARI group by age and sex, and a random encounter date was selected. In HealthVerity, among patients aged <18 years, those with COVID-19 (COVID), determined by ICD-10-CM code or by a positive SARS-CoV-2 test result during March 1, 2020–June 28, 2021, were matched 1:1 to those with a negative SARS-CoV-2 test result (non-COVID-19) during the same period by age, sex, and month of encounter.

<sup>†</sup> Cases per 100,000 person-years.

<sup>§</sup> Dashes indicate no prepandemic data available for ARI and non-ARI in the HealthVerity database.

with COVID-19 than among those with ARI during the prepandemic period. Non-SARS-CoV-2 respiratory infection was not associated with diabetes. These findings are consistent with previous research demonstrating an association between SARS-CoV-2 infection and diabetes in adults (4–7). The inclusion of only patients aged <18 years with a health care encounter possibly related to COVID-19 in the non-COVID-19 HealthVerity group could account for the lower magnitude of increased diabetes risk in this group compared with risk in the IQVIA group. In addition, patients without COVID-19 in HealthVerity had higher hospitalization rates than did those in IQVIA, suggesting more severe disease at the index encounter in the HealthVerity comparison group.

The observed association between diabetes and COVID-19 might be attributed to the effects of SARS-CoV-2 infection on organ systems involved in diabetes risk. COVID-19 might lead to diabetes through direct attack of pancreatic cells expressing angiotensin converting enzyme 2 receptors, through stress hyperglycemia resulting from the cytokine storm and alterations in glucose metabolism caused by infection, or through precipitation of prediabetes to diabetes (8). A percentage of these new diabetes cases likely occurred in persons

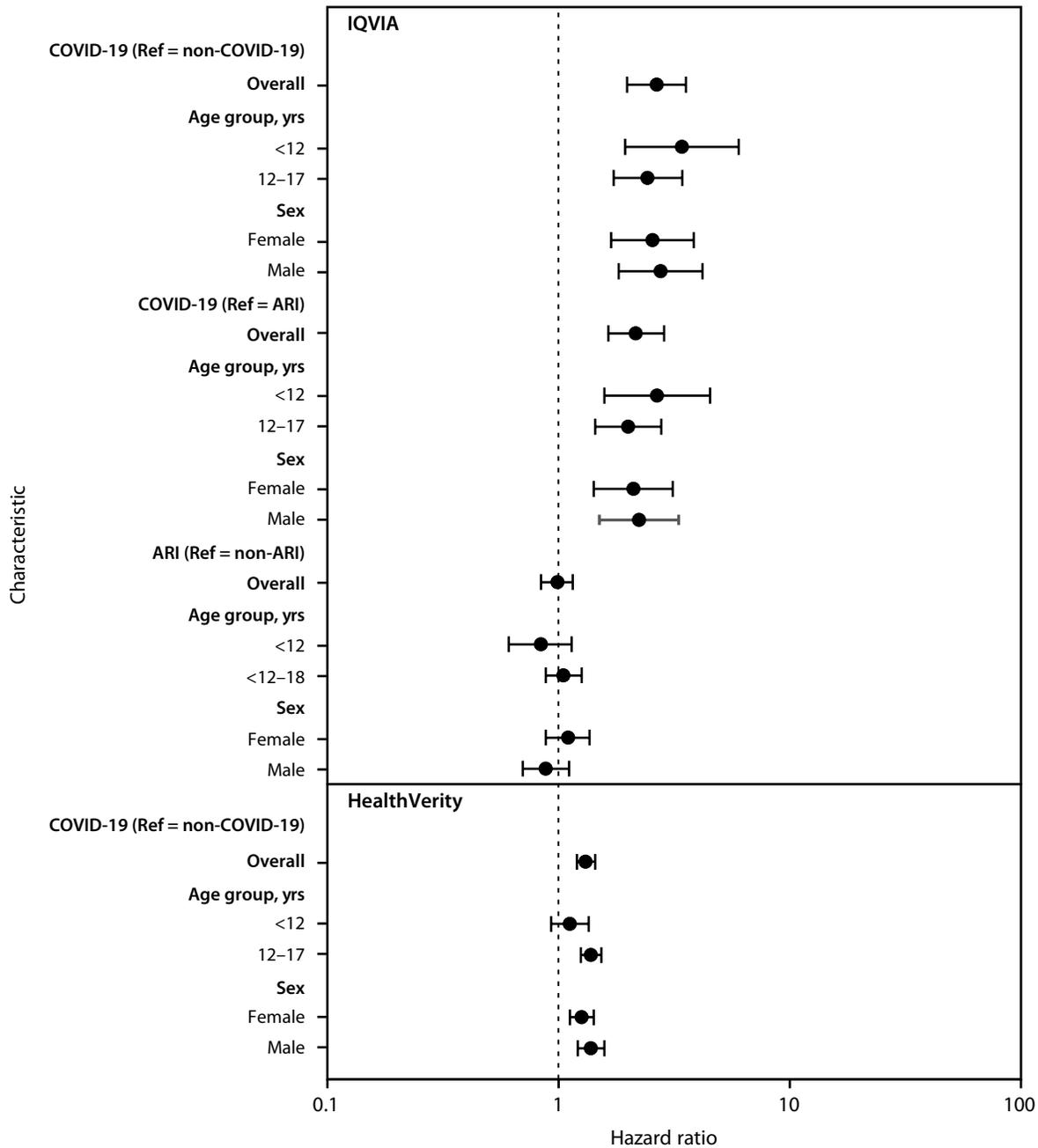
with prediabetes, which occurs in one in five adolescents in the United States.<sup>†††</sup> Steroid treatment during hospitalization might lead to transient hyperglycemia; however, only 1.5%–2.2% of diabetes codes were for drug- or chemical-induced diabetes, with the majority of codes being for type 1 or type 2 diabetes. Alternatively, COVID-19 might have indirectly increased diabetes risk through pandemic-associated increases in body mass index,<sup>§§§§</sup> a risk factor for both serious COVID-19 illness and diabetes. Future studies addressing the role of comorbidities and increases in body mass index in post-COVID-19 diabetes are warranted. Although this study can provide information on the risk for diabetes following SARS-CoV-2 infection, additional data are needed to understand underlying pathogenic mechanisms, either those caused by SARS-CoV-2 infection itself or resulting from treatments, and whether a COVID-19-associated diabetes diagnosis is transient or leads to a chronic condition.

Evidence of increased pediatric type 1 diabetes has been reported during the COVID-19 pandemic (1,2). Among

<sup>††††</sup> <https://www.cdc.gov/media/releases/2019/p1202-diabetes.html>

<sup>§§§§</sup> [https://www.cdc.gov/mmwr/volumes/70/wr/mm7037a3.htm?s\\_cid=mm7037a3\\_w](https://www.cdc.gov/mmwr/volumes/70/wr/mm7037a3.htm?s_cid=mm7037a3_w)

FIGURE. Hazard ratio for the association between COVID-19 or acute respiratory infection and new diabetes diagnosis among patients aged <18 years, by age group and sex — IQVIA PharMetrics Plus and HealthVerity claims databases,\* United States, March 1, 2020–June 28, 2021†,§,¶



**Abbreviations:** ARI = acute respiratory infection; HR = hazard ratio, ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*; Ref = referent.

\* <https://www.iqvia.com/>; <https://healthverity.com/>

† 95% CIs indicated by error bars.

§ Groups in IQVIA included patients aged <18 years with or without COVID-19 (COVID-19; non-COVID-19, respectively) and patients aged <18 years with or without ARI (ARI; non-ARI, respectively), during March 1, 2020–February 26, 2021, determined using presence or absence of ICD-10-CM codes for COVID-19 and ARI. The non-COVID-19 group was matched 5:1 to the COVID-19 group by age, sex, and month of encounter. The ARI group was matched 5:1 to the COVID-19 group by age and sex, and a random encounter date was selected. The non-ARI group was matched 2:1 to the ARI group by age and sex, and a random encounter date was selected. In HealthVerity, among patients aged <18 years, those with COVID-19 (COVID), determined by ICD-10-CM code or by a positive SARS-CoV-2 test result during March 1, 2020–June 28, 2021, were matched 1:1 to those with a negative SARS-CoV-2 test result (non-COVID-19) during the same period by age, sex, and month of encounter.

¶ Hazard ratios are plotted on a logarithmic scale.

persons aged <18 years with COVID-19 and new diabetes diagnoses in this study, nearly one half had DKA at or around the time of diagnosis. This number was higher than that in comparison groups, and higher than previous reports of DKA among incident type 1 diabetes cases before the pandemic (28%) (9). Increased frequency of DKA at time of diagnosis of type 1 diabetes during the pandemic has previously been reported and was thought to be due to delayed care-seeking for diabetes (3). However, the observed association of increased risk for diabetes diagnosis following SARS-CoV-2 infection would not be explained solely by delayed care. COVID-19 has disproportionately affected racial/ethnic minority groups, and those aged <18 years in these groups are also at increased risk for type 2 diabetes (10). An association between COVID-19 and new pediatric diabetes diagnoses might disproportionately affect racial/ethnic minority groups. Race/ethnicity data were unavailable in the present data sets; however, future studies should address racial and ethnic disparities in COVID-19 and diabetes, and whether persons aged <18 years who are at risk for COVID-19 are also those at risk for delaying medical care.

Health care providers should screen for diabetes symptoms in persons aged <18 years with a history of SARS-CoV-2 infection. These symptoms can include frequent urination, increased thirst, increased hunger, weight loss, tiredness or fatigue, stomach pain, and nausea or vomiting.<sup>¶¶¶</sup>

The findings in this report are subject to at least four limitations. First, the definition of diabetes might have low specificity because it used a single ICD-10-CM code, did not include laboratory data at the time of diagnosis, and could not reliably distinguish between type 1 and type 2 diabetes. Second, patients infected with SARS-CoV-2 without a COVID-19 diagnosis or documented positive test result might be misclassified as not having COVID-19. Third, the present analyses lacked information on covariates that could have affected the association between COVID-19 and incident diabetes, including prediabetes, race/ethnicity, and obesity status. Finally, estimated associations are only representative of persons aged <18 years seeking care included in these commercial claims databases and not of pediatric populations with SARS-CoV-2 infection without commercial health insurance or who do not seek health care.

These data suggest an increased risk for diabetes among persons aged <18 years with COVID-19, which is supported by independent studies in adults (4–7). These findings underscore the importance of COVID-19 prevention among all

## Summary

### What is already known about this topic?

SARS-CoV-2 infection is associated with worsening of diabetes symptoms, and persons with diabetes are at increased risk for severe COVID-19. SARS-CoV-2 infection might also induce newly diagnosed diabetes.

### What is added by this report?

Persons aged <18 years with COVID-19 were more likely to receive a new diabetes diagnosis >30 days after infection than were those without COVID-19 and those with prepandemic acute respiratory infections. Non-SARS-CoV-2 respiratory infection was not associated with an increased risk for diabetes.

### What are the implications for public health practice?

The increased diabetes risk among persons aged <18 years following COVID-19 highlights the importance of COVID-19 prevention strategies in this age group, including vaccination for all eligible persons and chronic disease prevention and treatment.

age groups, including vaccination for all eligible children and adolescents, and chronic disease prevention and treatment. Public health messages highlighting the risks associated with COVID-19 among the pediatric population are especially important to inform clinicians and parents about possible sequelae of COVID-19. SARS-CoV-2 infection might lead to type 1 or type 2 diabetes through complex and differing mechanisms. Partner agencies and clinicians in the field should be aware of long-term consequences and monitor persons aged <18 years in the months following a SARS-CoV-2 infection for new diabetes onset. Long-term follow-up studies of COVID-19 are warranted to further define the potential association between COVID-19 and increased diabetes risk among those in this age group.

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Corresponding author: Sharon Saydah, [ssaydah@cdc.gov](mailto:ssaydah@cdc.gov).

<sup>1</sup>CDC COVID-19 Emergency Response Team; <sup>2</sup>Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, CDC.

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<sup>¶¶¶</sup> <https://www.cdc.gov/diabetes/basics/symptoms.html>

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## Notes from the Field

### HIV Outbreak During the COVID-19 Pandemic Among Persons Who Inject Drugs — Kanawha County, West Virginia, 2019–2021

Rebecca B. Hershow, PhD<sup>1,2</sup>; Suzanne Wilson, MPH<sup>3</sup>; Robert A. Bonacci, MD<sup>1,2</sup>; Molly Deutsch-Feldman, PhD<sup>1,4</sup>; Olivia O. Russell, MPH<sup>5</sup>; Sherri Young, DO<sup>6</sup>; Shannon McBee, MPH<sup>3</sup>; Erica Thomasson, PhD<sup>3</sup>; Shawn Balleydier<sup>3</sup>; Miracle Boltz, MHCA<sup>3</sup>; Vicki Hogan, MPH<sup>3</sup>; Amy Atkins, MPA<sup>3</sup>; Nancy Worthington, PhD<sup>7</sup>; Robert McDonald, MD<sup>8</sup>; Monica Adams, PhD<sup>2</sup>; Anne Moorman, MPH<sup>9</sup>; Danae Bixler, MD<sup>9</sup>; Stephen Kowalewski<sup>8</sup>; Melinda Salmon<sup>8</sup>; R. Paul McClung, MD<sup>2</sup>; Alexandra M. Oster, MD<sup>2</sup>; Kathryn G. Curran, PhD<sup>2</sup>

During October 2019, the West Virginia Bureau for Public Health (WVBPH) noted that an increasing number of persons who inject drugs (PWID) in Kanawha County received a diagnosis of HIV. The number of HIV diagnoses among PWID increased from less than five annually during 2016–2018 to 11 during January–October 2019 (Figure). Kanawha County (with an approximate population of 180,000\*) has high rates of opioid use disorder and overdose deaths, which have been increasing since 2016,<sup>†</sup> and the county is located near Cabell County, which experienced an HIV outbreak among PWID during 2018–2019 (1,2). In response to the increase in HIV diagnoses among PWID in 2019, WVBPH released a Health Advisory<sup>§</sup>; and WVBPH and Kanawha-Charleston Health Department (KCHD) convened an HIV task force, conducted care coordination meetings, received CDC remote assistance to support response activities, and expanded HIV testing and outreach.

After suspension of the KCHD syringe services program (SSP) in March 2018 and a community-based SSP in April 2021 (because of concerns about program administration), a state law<sup>¶</sup> and a Charleston City Council ordinance\*\* enacted stricter SSP requirements. No new SSPs have opened in Kanawha County since the legislation passed. During 2020–2021, the COVID-19 pandemic affected HIV response activities and in-person services for PWID (e.g., curtailment of partner services,<sup>††</sup> limitation in outreach testing, and closure

of drop-in centers). In April 2021, WVBPH requested partner services surge support, and in May 2021 requested CDC assistance with an HIV outbreak investigation; CDC provided surge and investigation support during April–August 2021.

An HIV outbreak case was defined as a confirmed HIV diagnosis on or after January 1, 2019 in a PWID living in Kanawha County at the time of diagnosis. Investigators conducted qualitative interviews with 26 PWID and 45 community partners (including service providers),<sup>§§</sup> and for 65 PWID with HIV, abstracted medical records for 496 health care encounters beginning 1 year before HIV diagnosis through June 18, 2021.<sup>¶¶</sup> This activity was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.<sup>\*\*\*</sup>

As of October 27, 2021, 85 persons met the HIV outbreak case definition; 54 (52%) patients were male, 67 (79%) were aged 20–39 years at diagnosis, and 77 (91%) were non-Hispanic White. Forty patients (47%) had experienced unstable housing during the past year, and 73 (86%) had previous or current hepatitis C infection. Among 80 living persons, 20 (25%) had an HIV care visit during the preceding 90 days,<sup>†††</sup> and 26 (33%) were virally suppressed based on last test results.<sup>§§§</sup> Among 25 persons with available HIV molecular sequencing data, 19 (76%) were molecularly clustered (i.e., had an HIV sequence that was closely related to the HIV sequence of one or more other persons), indicating recent HIV transmission. Fifteen (79%) persons were in one molecular cluster, unrelated to the cluster identified during the Cabell County outbreak investigation (2).

Interview and medical record data indicated that methamphetamines and heroin were the most frequently injected drugs, and polysubstance use was common (57 [88%] of 65 patients). PWID reported reusing or sharing syringes, mainly because of limited access to sterile syringes after SSP closures. PWID expressed medical mistrust because of

§§ Interview topics for persons who inject drugs included substance use, sexual behavior, barriers to engagement in medical and social services, and strategies to improve engagement in HIV prevention and treatment. Interview topics for community partners included unmet medical and social service needs for persons who inject drugs, barriers to providing HIV and substance use services for persons who inject drugs, and strategies to address the HIV outbreak and improve engagement in HIV prevention and treatment.

¶¶ As of June 18, 2021, 65 persons met the case definition and had one or more health care encounters at sites participating in the medical records abstraction.

\*\*\* 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.

††† Engagement in HIV care was defined as receiving a laboratory test result (CD4, viral load, or genotype test results), documented medical care visit, or antiretroviral treatment prescription in the past 90 days.

§§§ These patients had an HIV-1 viral load test result of <200 HIV RNA copies/mL.

\* <https://www.census.gov/quickfacts/kanawhacountywestvirginia> (Accessed January 10, 2021).

† <https://dhhr.wv.gov/office-of-drug-control-policy/datadashboard/Pages/default.aspx>

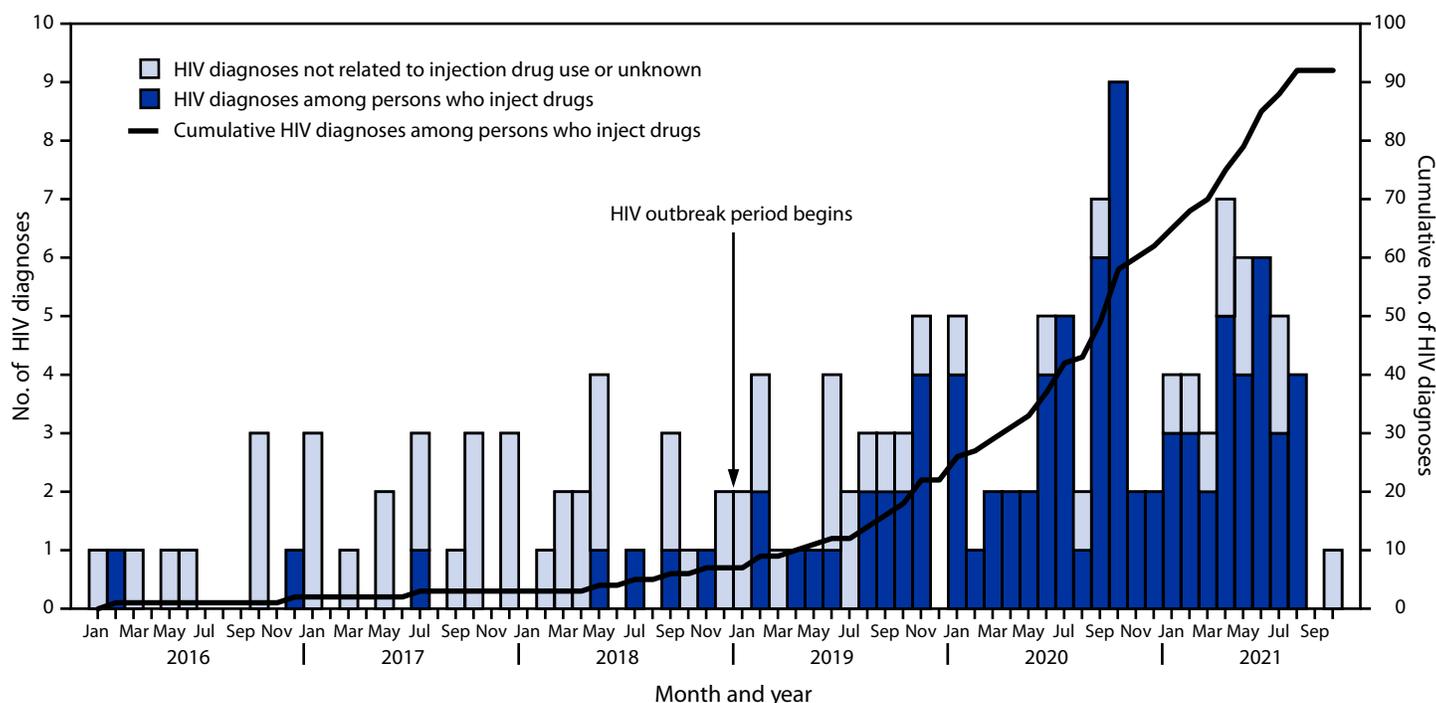
§ [https://oeps.wv.gov/healthalerts/documents/wv/WVHAN\\_162.pdf](https://oeps.wv.gov/healthalerts/documents/wv/WVHAN_162.pdf)

¶ [https://www.wvlegislature.gov/Bill\\_Text\\_HTML/2021\\_SESSIONS/RS/signed\\_bills/senate/SB334%20SUB1%20ENR\\_signed.pdf](https://www.wvlegislature.gov/Bill_Text_HTML/2021_SESSIONS/RS/signed_bills/senate/SB334%20SUB1%20ENR_signed.pdf)

\*\* [https://library.municode.com/wv/charleston/ordinances/code\\_of\\_ordinances?nodeId=1080097](https://library.municode.com/wv/charleston/ordinances/code_of_ordinances?nodeId=1080097)

†† Partner services refers to efforts to interview persons with a new diagnosis of HIV and their sexual or needle-sharing partners to offer HIV prevention and treatment and other services. <https://www.cdc.gov/hiv/effective-interventions/diagnose/partner-services/index.html>

FIGURE. Diagnoses of HIV infection, by injection drug use category — Kanawha County, West Virginia, January 2016–October 2021



experiences of stigma and discrimination in health care settings. Medical record abstraction revealed that HIV screening tests were performed at fewer than one third of health care encounters before diagnosis, and none of the patients had been prescribed preexposure prophylaxis (PrEP). Prescriptions of naloxone for overdose prevention and medications for opioid use disorder were documented at fewer than a quarter of opioid-related health care encounters.<sup>\*\*\*</sup> Service providers described challenges reaching PWID, including COVID-19 restrictions (e.g., drop-in center closures and outreach activity restrictions) and low SSP access because of some community opposition to evidence-based SSPs and new legislation restricting SSPs.

Recommendations based on investigation findings and HIV surveillance data are guiding response activities.<sup>\*\*\*\*</sup> WVBPH and KCHD are expanding HIV and hepatitis C testing and PrEP access with partners, training service providers on HIV and stigma reduction, and enhancing care coordination by improving linkage to HIV and substance use services and hiring additional partner services staff members. Stigma and discrimination and low SSP access have posed challenges to engaging PWID in HIV prevention and treatment; these challenges have been exacerbated by the COVID-19 pandemic (3).

<sup>\*\*\*</sup> Opioid-related health care encounters included all encounters in which a person was documented to be using opioids by a clinician, had a positive toxicology screen for opioids, or received syringe services.

<sup>\*\*\*\*</sup> [https://oeps.wv.gov/hiv-aids/documents/data/EpiAid\\_Report.pdf](https://oeps.wv.gov/hiv-aids/documents/data/EpiAid_Report.pdf)

Increasing access to comprehensive harm reduction services (e.g., SSPs) through expansion of mobile services, street outreach, and telehealth encounters led by patient-trusted staff members might improve delivery of important health and social services to PWID (4,5).

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Corresponding author: Rebecca B. Hershow, [qdt8@cdc.gov](mailto:qdt8@cdc.gov), 404-718-1597.

<sup>1</sup>Epidemic Intelligence Service, CDC; <sup>2</sup>Division of HIV Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC; <sup>3</sup>West Virginia Bureau for Public Health, West Virginia Department of Health and Human Resources; <sup>4</sup>Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC; <sup>5</sup>DLH Corporation, Atlanta, Georgia; <sup>6</sup>Kanawha-Charleston Health Department, Charleston, West Virginia; <sup>7</sup>Division of Overdose Prevention, National Center for Injury Prevention and Control, CDC; <sup>8</sup>Division of STD Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC; <sup>9</sup>Division of Viral Hepatitis, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC.

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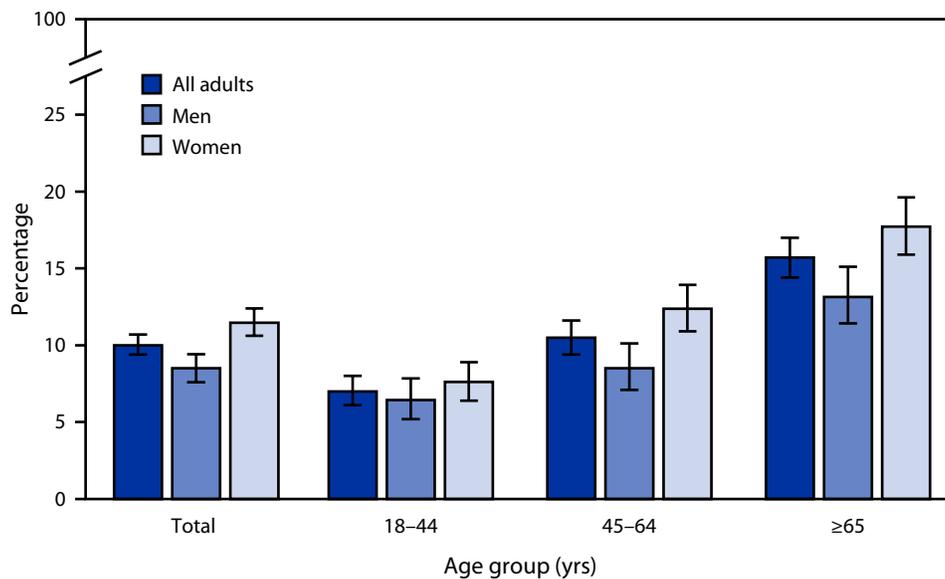
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## QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

## Percentage\* of Adults Aged $\geq 18$ Years Who Received Care at Home From a Friend or Family Member in the Past 12 Months,<sup>†</sup> by Sex and Age Group — National Health Interview Survey,<sup>§</sup> United States, July–December 2020



\* With 95% CIs indicated with error bars.

<sup>†</sup> Based on a response to the question, "During the past 12 months, did you receive care at home from a friend or family member?" The definition of care was left up to respondent interpretation in most cases, but if asked, the interviewer could clarify that care encompasses a wide range of activities with which a person might need help, including personal and household tasks.

<sup>§</sup> Estimates are based on household interviews of a sample of the civilian, noninstitutionalized U.S. population.

During July–December 2020, 10.0% of adults aged  $\geq 18$  years received care at home from a friend or family member in the past 12 months. Among both men and women, the percentage of adults who received care in the past 12 months increased with age. Women were more likely than men to receive care among those aged  $\geq 18$  years (11.5% and 8.5%, respectively), 45–64 years (12.4% and 8.5%, respectively), and  $\geq 65$  years (17.7% and 13.2%, respectively).

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

**Reported by:** Amanda E. Ng, MPH, [qkd2@cdc.gov](mailto:qkd2@cdc.gov), 301-458-4587; Anjel Vahratian, PhD.





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