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Unprecedented Outbreak of West Nile Virus — Maricopa County, Arizona, 2021

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West Nile virus (WNV) is a mosquitoborne disease primarily transmitted through bites of infected *Culex* species mosquitos (*1*). In the United States, WNV is the leading domestically acquired arboviral disease; it can cause severe illness affecting the brain and spinal cord with an associated case fatality rate of 10% (*2*,*3*). On September 2, 2021, Maricopa County Environmental Services Department, Vector Control Division (MCESD-VCD) notified the Maricopa County Department of Public Health (MCDPH) and the Arizona Department of Health Services (ADHS) that the WNV vector index (VI), a measure of infected Culex mosquitoes, was substantially elevated. By that date, at least 100 WNV cases had already been reported among Maricopa County residents to MCDPH by health care providers and laboratories. Within 2 weeks, the VI reached its highest ever recorded level (53.61), with an associated tenfold increase in the number of human disease cases. During 2021, a total of 1,487 human WNV cases were identified; 956 (64.3%) patients had neuroinvasive disease, and 101 (6.8%) died. MCESD-VCD conducted daily remediation efforts to mitigate elevated VI and address mosquito-related complaints from residents (i.e., large numbers of outdoor mosquitoes from an unknown source and unmaintained swimming pools potentially breeding mosquitoes). MCDPH increased outreach to the community and providers through messaging, education events, and media. This was the largest documented focal WNV outbreak in a single county in the United States (*4*). Despite outreach efforts to communities and health care partners, clinicians and patients reported a lack of awareness of the WNV outbreak, highlighting the need for public health agencies to increase prevention messaging to broaden public awareness and to ensure that health care providers are aware of recommended testing methods for clinically compatible illnesses.

Investigation and Results

WNV, an arthropod-borne arbovirus, is primarily transmitted through bites of infected Culex mosquitoes and is the leading cause of domestically acquired arbovirus infections in the United States (*1*). Transmission is also possible through blood transfusions; since 2005, the Food and Drug Administration has recommended WNV nucleic acid testing of minipools consisting of combined individual blood donation samples, with an automatic switch to individual donation testing upon detection of a positive result (*5*). Persons with a WNV-positive

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reverse transcription–polymerase chain reaction (RT-PCR) or immunoglobulin M (IgM) blood or cerebrospinal fluid (CSF) test result are reported to public health. Health care providers are required to report patients within 5 working days of detection, diagnosis, or treatment of a suspected or confirmed WNV infection; laboratories are required to report positive WNV test results within the same period. WNV case reports are stored within the Arizona Medical Electronic Disease Surveillance Intelligence System.*,† MCDPH investigates reports of positive WNV laboratory test results, classifies them according to national case definitions (*6*), and regularly communicates with health care providers via a mass notification system (SurvAlert) regarding community health threats. MCDPH responds to WNV outbreaks in partnership with MCESD-VCD, with support from ADHS.

No vaccine or specific therapy exists for WNV; thus, treatment is supportive. The case fatality rate in persons with neuroinvasive disease is 10% (*2*,*3*). The frequency and location of outbreaks vary annually and are challenging to predict (*1*). In Arizona, WNV was first detected in 2003 (12 cases); the majority of cases occurred among Maricopa County residents (*2*). The largest outbreak previously recorded in Maricopa County occurred in 2004 (355 cases).

MCESD-VCD conducts vector surveillance and abatement§ based on resident complaints of mosquito abundance and routine mosquito trap deployments in specific locations throughout the county.¶ When mosquitoes are found in traps, MCESD-VCD organizes them into groups (pools) of up to 50 female *Culex* spp. mosquitoes to be tested as one sample. Each pool is then tested for WNV using RT-PCR; a positive mosquito pool is one in which the sample is WNV-positive. From this testing, MCESD-VCD calculates a VI (the estimated proportion of infected mosquitoes of a particular species in a specific area collected during weekly mosquito surveillance). The highest VI previously recorded in Maricopa County was 19.4 in 2019 (*7*). When the VI exceeds 3.0 (based on analysis of data from previous seasons), MCESD-VCD notifies MCDPH that an increase in human WNV cases is anticipated within 2–3 weeks. Laboratory processing and notification of VI to MCDPH lags throughout the season (approximately 1–2 weeks). ADHS coordinates confirmatory human WNV testing with the Arizona State Public Health Laboratory and CDC, monitors WNV surveillance data statewide, provides resources, and issues health alert notifications (HANs).

On May 4, 2021, MCESD-VCD notified MCDPH of the first 2021 WNV-positive mosquito pool. MCESD-VCD

* https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/communicable-disease-reporting/reportable-diseases-list.pdf
† https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/communicable-disease-reporting/lab-reporting-requirements.pdf

§ https://codes.findlaw.com/az/title-36-public-health-and-safety/az-rev-st-sect-36-601.html.
¶ https://www.maricopa.gov/632/Vector-Control

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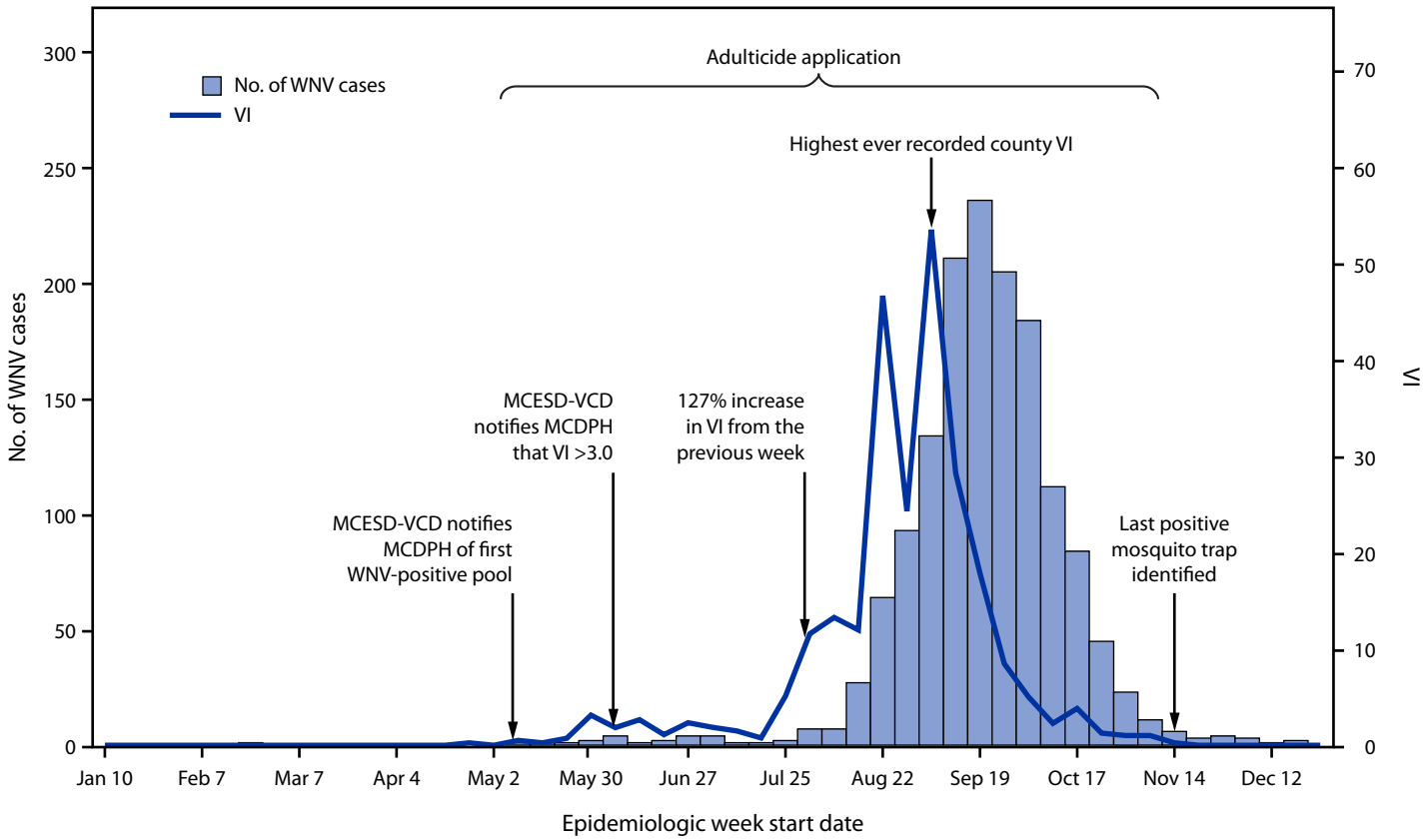
continued mosquito surveillance and commenced application of adulticides based on WNV-positive pools. On June 11, MCESD-VCD notified MCDPH that the VI had exceeded 3.0 (Figure). MCDPH enhanced routine surveillance by forwarding WNV IgM-positive serum and CSF specimens collected from persons with suspected WNV cases to the Arizona State Public Health Laboratory (ASPHL) for confirmatory testing. WNV-positive RT-PCR samples are considered confirmatory tests and were not forwarded to ASPHL. On August 12, the VI had increased by approximately 127% from the previous week (from 5.11 to 11.57). By September 2, the WNV VI was 46.72, peaking the week of September 11 at 53.61; the highest level ever recorded in the county. A VI peak this late in the season (i.e., in September) has occurred twice before in Maricopa County, in 2014 (VI = 9.6) and 2018 (VI = 7.9).

During 2021, MCDPH identified 1,487 confirmed or probable human WNV cases and an additional 78 asymptomatic viremic blood donors. The majority (95%) of persons with WNV had illness onset during a 12-week period during August 15–November 6, 2021. On September 25, the outbreak peaked at 236 cases reported in a single week. The last adulticide application occurred November 9. The last positive mosquito trap was identified the week of November 14; adulticide was not applied because the temperatures had decreased to <50°F (<10°C); according to manufacturer instructions, the material cannot be applied at these temperatures.**,††

Among the 1,487 WNV cases, 956 (64.3%) were classified as neuroinvasive disease, and 101 (6.8%) patients died; all deaths occurred among patients with neuroinvasive disease (Table). In addition to the 78 asymptomatic WNV reports identified through routine blood donation screening, 25 of the 1,487 WNV cases were identified as blood donors with symptomatic WNV; one of these symptomatic patients was

** https://www3.epa.gov/pesticides/chem_search/ppls/008329-00109-20180110.pdf
†† https://www3.epa.gov/pesticides/chem_search/ppls/002724-00791-20131118.pdf

FIGURE. Number of West Nile virus cases (N = 1,487),§ vector indices,* and public health responses, by epidemiologic week start date† — Maricopa County, Arizona, 2021



Abbreviations: MCDPH = Maricopa County Department of Public Health; MCESD-VCD = Maricopa County Environmental Services Department, Vector Control Division; VI = vector index; WNV = West Nile virus.
* The VI is the estimated proportion of infected mosquitoes of a particular species in a specific area collected during weekly mosquito surveillance.
† The number of persons with WNV each week is based on date of symptom onset; VI data are based on date of mosquito collection, which lags from MCDPH notification date by approximately 1-2 weeks.
§ Neuroinvasive and nonneuroinvasive cases are shown.

TABLE. Characteristics of residents with West Nile virus (N = 1,487), by clinical syndrome* — Maricopa County, Arizona, 2021

Characteristic	No. (%)							
	Neuroinvasive disease, clinical syndrome*						Nonneuroinvasive disease¶	Total cases
	All	Encephalitis†	Meningitis†	GBS	AFP†	Not specified†,§		
Total (%)	**956 (64.3)**	618 (64.6)	319 (33.4)	1 (<1.0)	1 (<1.0)	17 (1.8)	531 (35.7)	**1,487**
Age, yrs, median (IQR)	70 (58–78)	73 (63–80)	61 (48–71)	79 (NA)	59 (NA)	67 (57–72)	59 (48–69)	**66 (53–75)**
Sex								
Female	393 (41.0)	250 (40.5)	139 (43.6)	1 (100)	0 (—)	3 (17.6)	247 (46.5)	**640 (43.0)**
Male	563 (58.9)	368 (59.5)	180 (56.4)	0 (—)	1 (100)	14 (82.4)	284 (53.5)	**847 (57.0)**
Race**								
AI/AN	2 (<1.0)	2 (<1.0)	0 (—)	0 (—)	0 (—)	0 (—)	1 (<1.0)	**3 (<1.0)**
Asian	6 (<1.0)	1 (<1.0)	5 (1.6)	0 (—)	0 (—)	0 (—)	6 (1.1)	**12 (<1.0)**
Black or African American	16 (1.7)	10 (1.6)	6 (1.9)	0 (—)	0 (—)	0 (—)	1 (<1.0)	**17 (1.1)**
NH/OPI	1 (<1.0)	1 (<1.0)	0 (—)	0 (—)	0 (—)	0 (—)	0 (—)	**1 (<1.0)**
White	814 (85.1)	518 (83.8)	282 (88.4)	0 (—)	1 (100)	13 (76.5)	345 (65.0)	**1,159 (77.9)**
Other	18 (1.9)	12 (1.9)	6 (1.9)	0 (—)	0 (—)	0 (—)	13 (2.4)	**31 (2.1)**
Unknown	99 (10.4)	74 (12.0)	20 (6.3)	1 (100)	0 (—)	4 (23.5)	165 (31.1)	**264 (17.8)**
Ethnicity††								
Hispanic or Latino	58 (6.1)	33 (5.3)	24 (7.5)	0 (—)	0 (—)	1 (5.9)	19 (3.6)	**77 (5.2)**
Not Hispanic or Latino	787 (82.3)	501 (81.1)	272 (85.3)	0 (—)	1 (100)	13 (76.5)	346 (65.2)	**1,133 (76.2)**
Unknown	111 (11.6)	84 (13.6)	23 (7.2)	1 (100)	0 (100)	3 (17.6)	166 (31.3)	**277 (18.6)**
Hospitalized	923 (96.5)	600 (97.1)	309 (96.9)	1 (100)	1 (100)	12 (70.6)	91 (17.1)	**1,014 (68.2)**
Length of stay, days, median (IQR)	7 (4–11)	9 (6–13)	5 (3–7)	9 (NA)	16 (NA)	4 (2–7)	4 (2–6)	**6 (4–10)**
Deaths§§	101 (10.6)	99 (16.0)	2 (0.6)	0 (—)	0 (—)	0 (—)	0 (—)	**101 (6.8)**
Decedent age, yrs, median (IQR)	79 (71–83)	79 (71–83)	76 (65–86)	NA	NA	NA	NA	**79 (71–83)**

Abbreviations: AFP = acute flaccid paralysis; AI/AN = American Indian or Alaska Native; GBS = Guillain-Barré syndrome; NA = not applicable; NH/OPI= Native Hawaiian or other Pacific Islander.

* The constellation of physical symptoms associated with a person's illness. https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/mosquito-borne/wnv-sle-case-classification-algorithm.pdf

† Percentages of cases of encephalitis, meningitis, GBS, AFP, and unspecified neurologic signs or symptoms are percentages of neuroinvasive cases.

§ Not specified encompasses other neurologic or neuroinvasive clinical syndromes not covered under the categories of encephalitis, meningitis, GBS, or AFP.

¶ Nonneuroinvasive case classification indicates an acute systemic febrile illness with absence of neuroinvasive disease.

** Race is a mutually exclusive category self-reported by the patient. The Other category includes those who did not identify with the provided options.

†† Ethnicity is a mutually exclusive category self-reported by the patient.

§§ Deaths from West Nile virus are deaths for which West Nile virus was listed as a contributing or underlying cause of death on the death certificate.

diagnosed with neuroinvasive disease. The median age among all patients was 66 years (IQR = 53–75 years), and among those who died, the median age was 79 years (IQR = 71–83 years). Most cases occurred in persons who were White (78%), non-Hispanic or Latino (76%), and male (57%). In total, 1,014 (68.2%) patients were hospitalized, with 91% of hospitalizations occurring among persons with neuroinvasive disease. The median length of hospitalization for persons with neuroinvasive disease was 7 days (IQR = 4–11 days), compared with 4 days (IQR = 2–6 days) for those with nonneuroinvasive disease. During the investigation, cross-reactivity with mumps IgM testing was reported for 11 cases. MCDPH clinical staff members reviewed patient clinical courses, including symptoms, comorbidities, and potential exposures to determine compatibility with WNV and mumps; all patients' clinical illnesses were considered to be more consistent with WNV than with mumps.

Public Health Response

After identification of the first confirmed human case during the 2021 WNV transmission season, MCDPH issued a SurvAlert on June 25, advising health care providers to consider WNV and other arboviruses in patients with clinical signs or symptoms compatible with WNV neuroinvasive disease.[§§] MCDPH also alerted local blood banks to trigger individual donor screening rather than pooled screening. MCESD-VCD continued applying pesticide and larvicides, conducting mosquito surveillance, and responding to resident complaints of large quantities of mosquitoes or unmaintained swimming pools. In August, in anticipation of an increase in mosquitos during the Arizona monsoon

§§ Provider messaging advised that clinicians consider testing in the following scenarios: all cases of viral encephalitis; all cases of acute flaccid paralysis or Guillain-Barré syndrome of unknown etiology, with or without presence of viral meningitis or viral encephalitis; and cases of aseptic meningitis, especially those with at least one of the following: altered mentation, profound muscle weakness, flaccid paralysis, spastic paralysis, Guillain-Barré syndrome, or seizure.

season (June 15–September 30),[¶] MCDPH increased social media messaging regarding mosquito breeding and WNV prevention strategies after each rain. In September, MCDPH added the local social networking service for neighborhoods, Nextdoor.com, to their social media outreach targeting populations at higher risk. ADHS worked with community partners, including the Arizona office of AARP and the Arizona Geriatric Society, to prioritize outreach to persons aged ≥60 years, who are at increased risk for WNV-associated morbidity and mortality (*3*).

On September 1, MCDPH issued a press release regarding the first death in a patient with confirmed WNV. Based on the substantially elevated VI, MCESD-VCD, MCDPH, and ADHS coordinated an enhanced response including distribution of insect repellent and information packets and participated in interviews across multiple media platforms to increase public awareness. ADHS also issued a HAN notifying providers of the record-breaking season. On October 13, MCDPH, MCESD-VCD, ADHS, and CDC met to discuss outbreak response strategies, including issuing a SurvAlert reiterating the unprecedented number of WNV cases and recommending that providers test the serum and CSF of patients being evaluated for suspected WNV. Throughout the 2021 season, MCESD-VC fogged >400,000 acres with adulticide (twice the 10-year per-acre average), applied larvicide to approximately 25,000 sites, and received approximately 9,500 mosquito abundance or green pool complaints (40% more than average).

Discussion

The largest recorded WNV outbreak in a U.S. county occurred during May–December 2021 in Maricopa County, Arizona, and included more than four times the number of cases reported (355) in the previous largest outbreak in the county during 2004 (*8*). The reason for the unprecedented 2021 WNV outbreak is unknown, but is likely multifactorial, potentially related to increased rain (*9*), recent population growth and housing development, and changes in health care-seeking behavior during the COVID-19 pandemic. In response to this large number of human cases, local and state public health and vector agencies worked together to increase public and health care provider awareness, reinforce prevention messaging, and expand vector control activities.

The majority of identified cases resulted in neuroinvasive disease and occurred among older adults (aged ≥60 years). More than 1,000 patients required hospitalization, taxing a health care system that was already stressed as a result of the COVID-19 pandemic. Although COVID-19 cases exceeded WNV cases in Maricopa County (19,656 COVID-19 patients were hospitalized during May–December 2021) (*8*), health care facilities anecdotally reported intensive care units at full capacity with approximately one half of patients infected with SARS-CoV-2 and one half with WNV.

Summary

What is already known about this topic?

West Nile virus (WNV) is endemic in Maricopa County, Arizona. Since WNV was first detected in 2003, four outbreaks have occurred.

What is added by this report?

In 2021, Maricopa County experienced its fifth, and largest, WNV outbreak reported in the county: 1,487 cases, 1,014 (68%) hospitalizations, and 101 (7%) deaths, taxing a stressed health care system during the COVID-19 pandemic.

What are the implications for public health practice?

Clinicians should consider WNV testing in serum and cerebrospinal fluid in patients with a clinically compatible illness. Public health agencies should continually review messaging to improve awareness. Human and mosquito surveillance is essential to mounting a rapid, coordinated response and limiting further spread.

In spite of increased community and health care partner outreach through social and other media and health care provider messaging, anecdotally, clinicians and patients reported a lack of awareness of the WNV outbreak, highlighting the need for a more effective messaging strategy to increase public and provider awareness, case diagnosis, and WNV prevention. Based on provider reports, public health reminders to clinicians to consider WNV testing of both serum and CSF for ill patients are needed, especially among those patients with possible neuroinvasive disease. In addition, providers should be aware of potential cross-reactivity with other flaviviruses (e.g., St. Louis encephalitis and dengue) and potential false-positive results of the mumps IgM test; this has not been described previously and requires further evaluation.

The findings in this report are subject to at least three limitations. First, most cases identified were neuroinvasive disease, suggesting underrecognition of nonneuroinvasive disease, either because of mild illness, consideration of alternative etiologies (e.g., COVID-19), or low provider awareness about WNV. Previous estimates indicate that approximately 30–70 nonneuroinvasive cases occur for every neuroinvasive case identified (*10*); thus, surveillance data likely underestimate the true magnitude of this outbreak. Second, it was not possible to determine receipt of public messaging to ensure outreach to all areas of the county. Health education messaging materials developed for previous WNV outbreaks might be outdated; local, state, and federal agencies are currently partnering to update media campaigns. Finally, delays in laboratory testing affected timeliness of case investigation and implementation

[¶] https://www.weather.gov/fgz/Monsoon

of prevention measures, slowed identification of response thresholds, and delayed the public health response.

WNV continues to cause serious illness and affects health care capacity, especially when outbreaks co-occur with other diseases, such as COVID-19. Increasing temperatures might extend the period during which mosquitos can multiply, potentially prolonging the WNV season in relation to the local environmental conditions (*9*). Analyses are underway to identify data thresholds for increased public and provider messaging on prevention, diagnosis, and testing. Timely and coordinated mosquito and human case surveillance are critical to identifying outbreaks and guiding prevention efforts.

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Rapid Analysis of Drugs: A Pilot Surveillance System To Detect Changes in the Illicit Drug Supply To Guide Timely Harm Reduction Responses — Eight Syringe Services Programs, Maryland, November 2021–August 2022

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A record number of 2,912 drug overdose deaths occurred in Maryland during the 12-month period July 1, 2020–June 30, 2021. Illicitly manufactured fentanyl, fentanyl analogs, or both* were involved in 84% of these deaths.† Timely identification of illicit drug market changes (e.g., fentanyl rapidly replacing heroin) could improve the public health response, specifically communications about risks for novel psychoactive substances. During November 19, 2021–August 31, 2022, the National Institute of Standards and Technology (NIST)§ tested 496 deidentified drug paraphernalia samples that staff members collected at eight Maryland syringe services programs (SSPs), also known as needle exchange programs,¶ in partnership with the Maryland Department of Health Center for Harm Reduction Services (CHRS).** All test results were available within 48 hours. Among the 496 paraphernalia samples collected, 367 (74.0%) tested positive for an opioid, and 364 (99.2%) of these samples contained fentanyl or fentanyl analogs. Approximately four fifths of fentanyl-positive samples also tested positive for the veterinary medicine xylazine, a sedative that when combined with opioids might increase the potential for fatal respiratory depression and soft tissue infections when injected (*1*). For 248 of the 496 samples, SSP participants also completed a questionnaire about the drugs they had intended to purchase. Among the 212 participants who had intended to buy an opioid, 87.7% were exposed to fentanyl, fentanyl analogs, or both, and 85.8% were unknowingly exposed to xylazine. Results improved awareness of fentanyl and xylazine among SSP staff members and galvanized efforts to enhance SSPs' wound care services for participants experiencing soft tissue injuries possibly associated with injecting xylazine. Rapid analysis of drug paraphernalia can provide timely data on changing illicit drug markets that can be used to mitigate the harms of drug use more effectively.

In June 2021, CHRS, which oversees SSPs in Maryland, and NIST implemented the Rapid Analysis of Drugs (RAD) program to address the need for rapid, comprehensive, and reliable identification of illicit drugs. Twelve pilot sites were selected based on each site's capacity and proximity to drug trafficking routes identified by law enforcement partners. In August 2021, eight of the 12 SSPs that were contacted agreed to participate.†† Staff members attended a virtual training covering RAD's legal context and processes, including how to collect samples as safely as possible from used paraphernalia. Program staff members then sampled multiple types of drug paraphernalia, excluding syringes.

RAD involves a four-step process. First, wearing gloves, SSP staff members wipe or swab used drug paraphernalia received from registered SSP participants. Each individual wipe or swab is then placed into a small paper envelope that is collected in a larger mailing envelope (*2*). Program staff members administered a deidentified questionnaire simultaneously with paraphernalia sample collection and linked the questionnaire and sample with a unique barcode number.§§ Second, samples are mailed to NIST in accordance with U.S. Postal Service regulations. Third, samples are extracted and analyzed using direct analysis in real time mass spectrometry (DART-MS), a rapid ambient ionization mass spectrometry screening technique capable of analyzing a sample in seconds and detecting more than 1,100 drugs, cutting agents, and related substances¶¶ (*3*). Fourth, within 48 hours, NIST reports substances identified in each sample to CHRS and SSPs.*** SSPs are then responsible

* Fentanyl analogs, also known as fentanyl-related substances, vary in potency and are synthetic opioids similar in chemical structure to fentanyl but modified to produce distinct substances. Fentanyl analogs include acetyl fentanyl, acryl fentanyl, butyryl fentanyl, despropionyl fentanyl, and 4-fluorofentanyl.

† https://beforeitstoolate.maryland.gov/oocc-data-dashboard

§ https://www.nist.gov

¶ https://www.cdc.gov/ssp/index.html

** https://health.maryland.gov/phpa/Pages/accessharmreduction.aspx

†† The four SSPs that did not participate cited political pushback and insufficient capacity to implement RAD. Capacity issues included inadequate staffing and safety concerns about handling the paraphernalia on-site because SSPs typically only collect syringes for off-site disposal using biohazard containers that require no contact with staff members. As of January 10, 2023, Maryland had 22 active SSPs.

§§ Responses were documented into a webform accessible by CHRS staff members.

¶¶ Data are interpreted using libraries, specifically the NIST and National Institute of Justice DART-MS Data Interpretation Tool and NIST DART-MS Forensics Database (version 1.5; Firefly), enabling identification of more than 1,100 drugs, cutting agents, and related substances (https://data.nist.gov/od/id/mds2-2448). DART-MS cannot differentiate some isomers from one another.

*** NIST shares sample results with CHRS virtually via Google Workspace. CHRS merges the NIST results with the questionnaire responses and makes the deidentified data available to all participating SSPs also using Google Workspace.

for sharing individual results back to the participant who submitted the sample. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.†††

During November 19, 2021–August 31, 2022, staff members from eight SSPs asked program participants for permission to collect a sample from their used paraphernalia for drug testing and to complete a questionnaire about the drugs they had intended to purchase. A total of 496 paraphernalia samples were collected. For 248 (50.0%) of these samples, the program participant completed the questionnaire. No overdoses occurred on-site during sampling. The five most common types of paraphernalia tested, accounting for 95.7% of samples, were plastic bags (54.8%), cookers (16.3%), capsules (11.7%), vials (6.9%), and pipes or straws (6.0%). Among the 496 samples, one or more opioids were detected in 367 (74.0%) and cocaine in 77 (15.5%); none of the screened drugs were detected in 26 (5.2%) samples. Among the 367 opioid-positive samples, 363 (98.9%) contained fentanyl, 23 (6.3%) fluorofentanyl, and six (1.6%) fentanyl carbamate. One sample contained fluorofentanyl only; all other fentanyl analogs (e.g., fluorofentanyl and fentanyl carbamate) were also detected with fentanyl. Nonfentanyl opioids were detected infrequently: heroin (1.9%), tramadol (1.6%), methadone (0.5%), and protonitazene (0.3%). Among samples positive for fentanyl or a fentanyl analog (364), 84.4% had at least one other stimulant, sedative, or benzodiazepine detected: 293 (80.5%) had xylazine, 23 (6.3%) cocaine, 10 (2.7%) synthetic cathinones, six (1.6%) benzodiazepines, and three (0.8%) amphetamines (Figure).

Questionnaires were submitted for 248 (50.0%) samples.§§§ Among 212 respondents who reported opioid purchases,¶¶¶ 50.9% intended to purchase both heroin and fentanyl, or "fentanyl and/or heroin,"**** 46.7% sought fentanyl alone, and 2.4% sought heroin alone (Table). Eighty-one percent of samples matched the participant's intentions but contained one or more additional substances, 13.2% did not include the substance the participant intended to purchase, and 5.7% matched participant intentions without other substances present. When the participant reported intent to buy heroin, no sample tested positive for heroin, and 1.9% of samples tested positive for heroin when the participant reported buying "fentanyl and heroin." When participants reported intent to buy "fentanyl" or "fentanyl and heroin," 97.0% and 79.6% of the samples, respectively, tested positive for fentanyl. When participants intended to buy "fentanyl" or "fentanyl and/or heroin," xylazine was detected in 90.9% and 84.3% of samples, respectively. The questionnaire did not indicate xylazine in the list of drugs that participants might have intended to purchase; if they wanted to purchase xylazine, they would have needed to write it in an "other" drug category, and none of the participants did.

Discussion

RAD supported Maryland's public health response to overdose deaths by quickly identifying the broad adulteration of fentanyl with xylazine and documenting the dominance of fentanyl (including samples mixed with fluorofentanyl) (*4*) and absence of heroin. Because of the success of the eight RAD pilot sites, CHRS expanded RAD to all Maryland SSPs during 2022; as of April 2023, 14 programs are participating.

Xylazine's pervasiveness as an adulterant was unexpected by CHRS, program staff members, and participants, but aligned with observational evidence about an increase in injection-related wounds observed in other reports on xylazine (*1*). Wounds might appear outside the area of injection and might also occur when xylazine is smoked or snorted. Documenting the widespread adulteration of fentanyl with xylazine facilitated stronger communication about the risk for injection-related wounds with participants. CHRS is investing in wound care training and certification for nurses working in harm-reduction settings, creating standards of care for wound treatment in low-resourced settings, and pursuing quantitative data analysis opportunities to corroborate the relationship between statewide incidence of skin and soft tissue infections and the drug supply revealed through RAD.

Co-use of xylazine with fentanyl might increase the chance of fatal overdose.†††† The effects of xylazine are not reversed by naloxone and might require medical care; however, naloxone does reverse the effects of fentanyl and other opioids even when co-used with xylazine and should be administered for any suspected overdose (*1*,*5*). In response to these findings, CHRS and SPPs updated overdose response training to include managing xylazine-involved overdoses.

More than one half of questionnaire respondents intending to purchase opioids thought heroin might be present with fentanyl in the drugs they purchased, whereas heroin was present in fewer than 2% of samples. Because fentanyl is fast-acting and potent, it might lead to rapid onset of overdose (*6*). This finding reinforces the continued importance

††† 5 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.

§§§ Questionnaire responses that reported sampled paraphernalia being used more than once were excluded from analysis on intended purchased substance.

¶¶¶ Four instances of intended purchase of opioid pills were excluded from analysis because of inability to ascertain which opioid was the intended purchase.

**** Some participants who selected the response categories "heroin" and "fentanyl" might have been trying to indicate that they did not know if the drug product was solely heroin or fentanyl.

†††† https://www.dea.gov/sites/default/files/2022-12/The%20Growing%20Threat%20of%20Xylazine%20and%20its%20Mixture%20with%20Illicit%20Drugs.pdf

of fentanyl-specific overdose education efforts in Maryland. This instruction includes injecting slowly, not using drugs when alone, using fentanyl test strips, carrying naloxone, and seeking and accepting medical attention for an overdose.[§§§§]

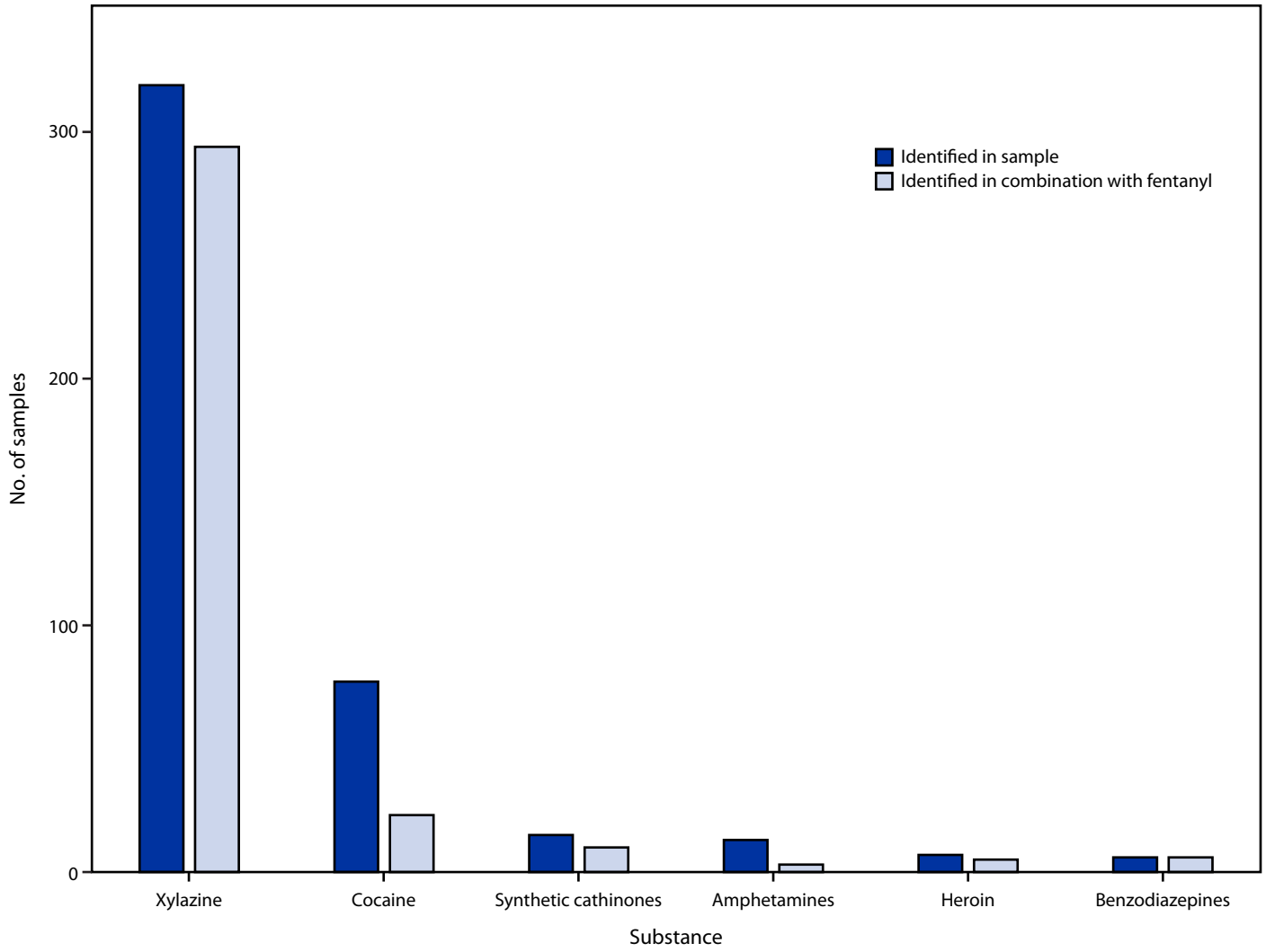
The findings in this report are subject to at least three limitations. First, drug paraphernalia were conveniently sampled from eight SSPs that primarily serve persons who use opioids and inject drugs; results are not necessarily generalizable to all persons using drugs or in other geographic regions. Second, syringes were not included in RAD because of sampling safety. Finally, DART-MS analysis is not quantitative, and substance purity was not measured.

Timely data about the illicit drug supply have been limited, retrospective, and often anecdotal. This report provides critical information on fentanyl and xylazine exposures among a population at high risk for overdose and related harm. In some areas, fentanyl is adulterated with emerging substances such as xylazine (*7*). Also, heroin-involved overdoses have substantially declined in some places as fentanyl-involved overdoses have become more dominant.[¶¶¶¶] RAD can provide timely data on the rapid increase of common illicit drugs (e.g., fentanyl)

[§§§§] https://www.goslow.org; https://www.samhsa.gov/find-help/harm-reduction

[¶¶¶¶] https://www.chicagohan.org/documents/14171/234367/2021_MidYr_Opioid_Report_AUg2021.pdf; https://www.hamiltoncountyhealth.org/wp-content/uploads/2021Snapshot_HCARC_20221014-6.pdf; https://www.nyc.gov/assets/doh/downloads/pdf/epi/databrief133.pdf; https://ocme.dc.gov/sites/default/files/dc/sites/ocme/Opioid%20related%20Overdoses%20Deaths%208.18.22%20FINAL.pdf

FIGURE. Samples tested (N = 496) and found to contain selected substances* and number of instances the selected substance was found in combination with fentanyl — eight syringe services programs, Maryland, November 2021–August 2022



* Samples were analyzed using direct analysis in real time mass spectrometry (DART-MS).

TABLE. Concordance between actual* and intended drug purchases among study participants intending to purchase opioids (N = 212) — eight syringe services programs, Maryland, November 2021–August 2022

DART-MS analysis findings	Total no. with questionnaire indicating participant intended to purchase any opioid (%) (N = 212)	Type of opioid participant intended to purchase, no. (%)		
		Fentanyl only (n = 99)	Heroin only (n = 5)	Fentanyl and heroin (n = 108)
Substance identified				
Any opioid detected	**188 (88.7)**	96 (97.0)	4 (80.0)	88 (81.5)
Fentanyl or fentanyl analogs	**186 (87.7)**	96 (97.0)	4 (80.0)	86 (79.6)
Heroin	**6 (2.8)**	4 (4.0)	0 (—)	2 (1.9)
Tramadol†	**2 (0.9)**	2 (2.0)	0 (—)	0 (—)
Stimulants, excluding caffeine				
Cocaine	**15 (7.1)**	8 (8.1)	0 (—)	7 (6.5)
Methamphetamine or amphetamine	**1 (0.5)**	0 (—)	0 (—)	1 (0.9)
Drugs other than opioids and stimulants				
Xylazine	**182 (85.8)**	90 (90.9)	1 (20.0)	91 (84.3)
Other substances§	**6 (2.8)**	1 (1.0)	2 (40.0)	3 (2.8)
Match between participant's intention and DART-MS analysis				
DART-MS results matched intention and no extra substances found	**12 (5.7)**	5 (5.1)	0 (—)	7 (6.5)
DART-MS results matched intention and extra substances found	**172 (81.1)**	91 (91.9)	0 (—)	81 (75.0)
DART-MS results did not match intention	**28 (13.2)**	3 (3.0)	5 (100.0)	20 (18.5)

Abbreviation: DART-MS = direct analysis in real time mass spectrometry.
* Identified by DART-MS.
† Tramadol is the only opioid other than fentanyl, fentanyl analogs, and heroin that was detected in samples with survey responses.
§ Other substances include anabolic steroids, anticonvulsants, benzodiazepines, and delta-9-tetrahydrocannabinol.

Summary

What is already known about this topic?

Illicitly manufactured fentanyl was involved in 84% of 2,912 drug overdose deaths in Maryland during July 2020–June 2021.

What is added by this report?

Among 364 samples from drug paraphernalia collected at eight syringe services programs during November 2021–August 2022 that tested positive for fentanyl or fentanyl analogs, 80% also contained xylazine (an animal sedative). Heroin was rarely detected. Results were available within 48 hours. Sample test results did not always differ from participant expectations and were used to enhance harm reduction efforts.

What are the implications for public health practice?

Rapid analysis of drug paraphernalia can provide timely data on changing illicit drug markets that can be used to mitigate the harms of drug use more effectively.

as well as influx of emerging substances (e.g., xylazine) that can help harm reduction programs mitigate the health impact more effectively. This in turn might strengthen participants' trust in SSPs, which might increase participants' likelihood of seeking treatment and reducing their drug use (*8*). Providing persons who use drugs with timely data on the drugs they are using versus what they intended to use might also reduce public health harms (*9*,*10*).

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Maryland Syringe Services Program staff members and participants.

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Effectiveness of Monovalent mRNA COVID-19 Vaccination in Preventing COVID-19–Associated Invasive Mechanical Ventilation and Death Among Immunocompetent Adults During the Omicron Variant Period — IVY Network, 19 U.S. States, February 1, 2022–January 31, 2023

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As of April 2023, the COVID-19 pandemic has resulted in 1.1 million deaths in the United States, with approximately 75% of deaths occurring among adults aged ≥65 years (*1*). Data on the durability of protection provided by monovalent mRNA COVID-19 vaccination against critical outcomes of COVID-19 are limited beyond the Omicron BA.1 lineage period (December 26, 2021–March 26, 2022). In this case-control analysis, the effectiveness of 2–4 monovalent mRNA COVID-19 vaccine doses was evaluated against COVID-19–associated invasive mechanical ventilation (IMV) and in-hospital death among immunocompetent adults aged ≥18 years during February 1, 2022–January 31, 2023. Vaccine effectiveness (VE) against IMV and in-hospital death was 62% among adults aged ≥18 years and 69% among those aged ≥65 years. When stratified by time since last dose, VE was 76% at 7–179 days, 54% at 180–364 days, and 56% at ≥365 days. Monovalent mRNA COVID-19 vaccination provided substantial, durable protection against IMV and in-hospital death among adults during the Omicron variant period. All adults should remain up to date with recommended COVID-19 vaccination to prevent critical COVID-19–associated outcomes.

Monovalent mRNA COVID-19 vaccination has been shown to prevent hospitalization and critical outcomes, including IMV and death, during SARS-CoV-2 Alpha, Delta, and early Omicron variant periods (*2*,*3*). However, rapid waning of COVID-19 VE against infection, outpatient illness, and hospitalization has been observed during Omicron variant predominance (*4*). Understanding the durability of protection provided by monovalent mRNA vaccination against critical outcomes is vital. Although a bivalent mRNA dose was recommended on September 1, 2022, for all persons who had completed a primary COVID-19 vaccination series, bivalent vaccination coverage among adults aged ≥18 years is 20%, and most adults have only received monovalent mRNA vaccines (*1*,*5*). In addition, COVID-19 VE against hospitalization might be artificially reduced by routine testing for SARS-CoV-2 at admission, which can detect SARS-CoV-2 infection in patients admitted for reasons other than COVID-19 (*4*,*6*,*7*). VE against critical outcomes might be less susceptible to this bias and is therefore needed to help guide COVID-19 vaccination policy regarding revaccination intervals.

Data from the Investigating Respiratory Viruses in the Acutely Ill (IVY) Network[§] were used to conduct a case-control analysis measuring the effectiveness of monovalent mRNA COVID-19 vaccination against COVID-19–associated IMV and in-hospital death. During February 1, 2022–January 31, 2023, adults aged ≥18 years admitted to 24 hospitals in 19 U.S. states who met a COVID-19–like illness case definition[¶] and received SARS-CoV-2 testing were enrolled. IVY Network methods have been described previously (*2*,*3*). Briefly, case-patients were defined as those who received a positive SARS-CoV-2 reverse transcription–polymerase chain reaction (RT-PCR) or antigen test result within 10 days of illness onset and within 3 days of hospital admission, and either received IMV or died in the hospital within 28 days of admission. Control patients were defined as those who received negative SARS-CoV-2 and influenza test results by RT-PCR within 10 days of illness onset and within 3 days of hospital admission. Patients who received positive influenza test results were excluded from the analysis because of potential correlation between COVID-19 and influenza vaccination behaviors (*8*).

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[§] https://www.cdc.gov/flu/vaccines-work/ivy.htm
[¶] COVID-19–like illness was defined as including any one of the following signs and symptoms: fever, cough, shortness of breath, new or worsening findings on chest imaging consistent with pneumonia, or hypoxemia defined as SpO2 <92% on room air or supplemental oxygen to maintain SpO2 ≥92%. For patients on chronic oxygen therapy, hypoxemia was defined as SpO2 below baseline or an escalation of supplemental oxygen to maintain a baseline SpO2.

Demographic and clinical data, including receipt of IMV and in-hospital death within 28 days of admission, were collected through electronic medical record (EMR) review and patient or proxy interview. COVID-19 vaccination history was ascertained from state or jurisdictional registries, EMRs, vaccination cards, and self-report. Patients were included in the analysis if they 1) received zero COVID-19 vaccines doses (unvaccinated) or 2) received 2, 3, or 4 monovalent mRNA COVID-19 vaccine doses (monovalent-vaccinated), with the last dose received ≥14 days before illness onset for a primary series dose or ≥7 days before illness onset for a booster dose. Patients were excluded from the analysis if they were immunocompromised,** received a non-mRNA COVID-19 vaccine dose, received only 1 monovalent mRNA COVID-19 vaccine dose, received a bivalent mRNA COVID-19 vaccine dose, or for other reasons†† that made the patient ineligible.

VE against IMV and in-hospital death was calculated using logistic regression, in which the odds of monovalent mRNA vaccination (versus being unvaccinated) were compared between COVID-19 case-patients and control patients. Logistic regression models were adjusted for U.S. Department of Health and Human Services region, calendar time in biweekly intervals, age, sex, and self-reported race and Hispanic ethnicity. VE was calculated as (1 – adjusted odds ratio) x 100%. Results were stratified by age group, time since receipt of last monovalent mRNA vaccine dose, and number of monovalent mRNA vaccine doses received.§§ Differences between VE point estimates with nonoverlapping 95% CIs were considered statistically significant. Analyses were conducted using SAS (version 9.4; SAS Institute). This activity was determined to be public health surveillance by each participating site and CDC and was conducted in a manner consistent with all applicable federal laws and CDC policy.¶¶

During February 1, 2022–January 31, 2023, a total of 6,354 immunocompetent control patients and COVID-19 case-patients with IMV or in-hospital death were enrolled in the IVY Network. After exclusion of 1,933 patients,*** 4,421 (70%) were included in the analysis (362 case-patients and 4,059 control patients). Patients were most commonly excluded because of receipt of a bivalent mRNA COVID-19 vaccine dose (446 [23% of excluded patients]), receipt of a non-mRNA COVID-19 vaccine (392 [20%]), or receipt of only 1 monovalent mRNA COVID-19 vaccine dose (260 [13%]). Among included patients, the median age was 64 years (IQR = 53–75 years) (Table 1). Ninety-one percent of patients had one or more chronic condition, and 20% had a previous self-reported or documented SARS-CoV-2 infection. Among 362 case-patients with IMV or in-hospital death, 146 (40%) were unvaccinated, 216 (60%) were monovalent-vaccinated, 293 (81%) received IMV, and 156 (43%) died in the hospital within 28 days of admission. Among 4,059 control patients, 979 (24%) were unvaccinated, and 3,080 (76%) were monovalent-vaccinated.

Among monovalent-vaccinated patients, the median interval from receipt of last dose to illness onset was 248 days (IQR = 138–378 days) (Table 2). When compared with unvaccinated patients, the VE of 2–4 monovalent mRNA vaccine doses against IMV and in-hospital death was 62%. VE was 57% among patients aged 18–64 years and 69% among patients aged ≥65 years. When stratified by interval since receipt of last monovalent dose, VE against IMV and in-hospital death was 76% at 7–179 days, 54% at 180–364 days, and 56% at ≥365 days. Within each interval since receipt of last monovalent dose, VE estimates did not differ significantly by number of doses received. VE point estimates were higher 7–179 days since last dose compared with ≥180 days since last dose, although 95% CIs overlapped.

Discussion

Among immunocompetent adults aged ≥18 years admitted to 24 hospitals in the IVY Network in 19 U.S. states, receipt of 2–4 monovalent mRNA COVID-19 vaccine doses provided substantial protection against COVID-19–associated IMV and in-hospital death during the Omicron variant period.

** Immunocompromising conditions were defined as active solid tumor or hematologic cancer (i.e., newly diagnosed cancer or cancer treatment within the previous 6 months), solid organ transplant, bone marrow/stem cell transplant, HIV infection, congenital immunodeficiency syndrome, use of an immunosuppressive medication within the previous 30 days, splenectomy, or another condition that causes moderate or severe immunosuppression.

†† Other reasons for exclusion: 1) illness onset after hospital admission, 2) enrollment >7 days after hospital admission, 3) receipt of a SARS-CoV-2–positive test result >3 days after hospital admission, 4) case-patient with co-infection with influenza or respiratory syncytial virus, 5) control patient with receipt of a positive influenza test result, and 6) participant withdrawal.

§§ VE estimates comparing recipients of 4 monovalent mRNA vaccine doses with unvaccinated patients were restricted to adults aged ≥50 years admitted during April 5, 2022–January 31, 2023, consistent with CDC recommendations regarding eligibility for a second monovalent mRNA booster dose. https://www.cdc.gov/media/releases/2022/s0328-covid-19-boosters.html (Accessed March 26, 2023).

¶¶ 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.

*** A total of 1,933 immunocompetent patients were excluded from the analysis for the following reasons (not mutually exclusive): illness onset occurred after hospital admission (82), patient enrolled >7 days after hospital admission (239), inability to obtain an upper respiratory sample for central laboratory testing among controls (149), SARS-CoV-2 test >3 days after hospital admission (33), SARS-CoV-2 testing indeterminate (65), case-patient received a positive influenza test result (21), control patient received a positive influenza test result (29), influenza testing indeterminate or not done (83), case-patient received a positive respiratory syncytial virus test result (27), verified and self-reported vaccination history missing so that vaccination status could not be assigned (57), non-mRNA vaccine received (392), partial vaccination (260), bivalent vaccination (446), received COVID-19 vaccines outside of CDC guidelines (144), last monovalent dose received <14 days before illness onset if primary series or <7 days before illness onset if booster (55), and withdrew (12).

TABLE 1. Characteristics of COVID-19 case-patients who received invasive mechanical ventilation or died in the hospital and COVID-19 test-negative control patients among immunocompetent adults aged ≥18 years — IVY Network, 24 hospitals,* 19 U.S. states, February 1, 2022–January 31, 2023

Characteristic	No. (%) Total (N = 4,421)	COVID-19 case-patients with IMV or death (n = 362)	COVID-19 test-negative control patients (n = 4,059)
Vaccination status			
Unvaccinated	**1,125 (25)**	146 (40)	979 (24)
2–4 Monovalent mRNA doses	**3,296 (75)**	216 (60)	3,080 (76)
2 Monovalent mRNA doses	**1,148 (26)**	87 (24)	1,061 (26)
3 Monovalent mRNA doses	**1,642 (37)**	108 (30)	1,534 (38)
4 Monovalent mRNA doses	**506 (11)**	21 (6)	485 (12)
Female sex	**2,202 (50)**	141 (39)	2,061 (51)
Median age, yrs (IQR)	**64 (53–75)**	66 (55–79)	64 (52–75)
Age group, yrs			
18–64	**2,258 (51)**	163 (45)	2,095 (52)
≥65	**2,163 (49)**	199 (55)	1,964 (48)
Race and ethnicity			
Black or African American, non-Hispanic	**938 (21)**	40 (11)	898 (22)
White, non-Hispanic	**2,616 (59)**	238 (66)	2,378 (59)
Hispanic or Latino, any race	**535 (12)**	48 (13)	487 (12)
Other race, non-Hispanic†	**155 (4)**	18 (5)	137 (3)
Other§	**177 (4)**	18 (5)	159 (4)
HHS region*			
1	**783 (18)**	74 (20)	709 (17)
2	**284 (6)**	18 (5)	266 (7)
3	**150 (3)**	5 (1)	145 (4)
4	**775 (18)**	76 (21)	699 (17)
5	**608 (14)**	45 (12)	563 (14)
6	**473 (11)**	18 (5)	455 (11)
7	**297 (7)**	19 (5)	278 (7)
8	**674 (15)**	53 (15)	621 (15)
9	**153 (3)**	14 (4)	139 (3)
10	**224 (5)**	40 (11)	184 (5)

TABLE 1. (*Continued*) Characteristics of COVID-19 case-patients who received invasive mechanical ventilation or died in the hospital and COVID-19 test-negative control patients among immunocompetent adults aged ≥18 years — IVY Network, 24 hospitals,* 19 U.S. states, February 1, 2022–January 31, 2023

Characteristic	No. (%) Total (N = 4,421)	COVID-19 case-patients with IMV or death (n = 362)	COVID-19 test-negative control patients (n = 4,059)
No. of chronic medical condition categories¶			
0	**423 (10)**	36 (10)	387 (10)
1	**1,095 (25)**	113 (31)	982 (24)
2	**1,304 (30)**	95 (26)	1,209 (30)
≥3	**1,599 (36)**	118 (33)	1,481 (36)
Previous SARS-CoV-2 infection**			
Any previous SARS-CoV-2 infection	**868 (20)**	31 (9)	837 (21)
Previous Omicron variant infection	**471 (11)**	21 (6)	450 (11)

Abbreviations: HHS = U.S. Department of Health and Human Services; IMV = invasive mechanical ventilation.

* Hospitals by HHS region included *Region 1*: Baystate Medical Center (Springfield, Massachusetts), Beth Israel Deaconess Medical Center (Boston, Massachusetts), and Yale University (New Haven, Connecticut); *Region 2*: Montefiore Medical Center (New York, New York); *Region 3*: Johns Hopkins Hospital (Baltimore, Maryland); *Region 4*: Emory University Medical Center (Atlanta, Georgia), University of Miami Medical Center (Miami, Florida), Vanderbilt University Medical Center (Nashville, Tennessee), and Wake Forest University Baptist Medical Center (Winston-Salem, North Carolina); *Region 5*: Cleveland Clinic (Cleveland, Ohio), Hennepin County Medical Center (Minneapolis, Minnesota), Henry Ford Health (Detroit, Michigan), The Ohio State University Wexner Medical Center (Columbus, Ohio), and University of Michigan Hospital (Ann Arbor, Michigan); *Region 6*: Baylor Scott & White Medical Center (Temple, Texas) and Baylor University Medical Center (Dallas, Texas); *Region 7*: Barnes-Jewish Hospital (St. Louis, Missouri) and University of Iowa Hospitals (Iowa City, Iowa); *Region 8*: Intermountain Medical Center (Murray, Utah) and UCHealth University of Colorado Hospital (Aurora, Colorado); *Region 9*: Stanford University Medical Center (Stanford, California) and Ronald Reagan UCLA Medical Center (Los Angeles, California); and *Region 10*: Oregon Health & Science University Hospital (Portland, Oregon) and University of Washington (Seattle, Washington).

† Other race, non-Hispanic includes American Indian or Alaska Native, Asian, and Native Hawaiian or other Pacific Islander categories, which were combined because of small counts.

§ Other includes patients who self-reported their race and ethnicity as "Other" and those for whom race and ethnicity were unknown.

¶ Chronic medical condition categories include autoimmune, cardiovascular, endocrine, gastrointestinal, hematologic, neurologic, pulmonary, and renal diseases.

** Previous SARS-CoV-2 infection was defined as any self-reported or documented previous SARS-CoV-2 infection. Previous Omicron infection was defined as any self-reported or documented previous SARS-CoV-2 infection that occurred during December 26, 2021–January 31, 2023.

Protection was highest during the first 6 months after the last monovalent dose, with persistent residual protection remaining after 6 months and sustained at 1–2 years. Monovalent mRNA vaccination also provided substantial protection against COVID-19–associated IMV and death among adults aged ≥65 years, the age group that remains at highest risk of severe COVID-19 (*1*). These findings underscore the importance of staying up to date with COVID-19 vaccination to prevent critical outcomes of COVID-19, including optional, additional bivalent mRNA booster doses for persons at highest risk of severe disease.†††

A previous analysis from the IVY Network showed high effectiveness of monovalent mRNA COVID-19 vaccination against COVID-19–associated IMV and death during the Delta and early Omicron variant periods (*2*). The current analysis expands on these findings by reporting monovalent mRNA COVID-19

††† https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html?ACSTrackingID=USCDC_2120-DM104004&ACSTrackingLabel=Updated%20Guidance%3A%20Interim%20Clinical%20Considerations%20for%20Use%20of%20COVID-19%20Vaccines&deliveryName=USCDC_2120-DM104004 (Accessed April 24, 2023).

TABLE 2. Effectiveness of monovalent mRNA COVID-19 vaccination against COVID-19–associated invasive mechanical ventilation or in-hospital death among immunocompetent adults aged ≥18 years — IVY Network, 24 hospitals,* 19 U.S. states, February 1, 2022–January 31, 2023

Group	Case-patients who received IMV or died, no. of monovalent-vaccinated†/total no. (%)	Control patients, no. of monovalent-vaccinated†/ total no. (%)	Median interval from last monovalent mRNA vaccine dose to illness onset (IQR), days	Adjusted VE against IMV and death % (95% CI)§
Overall	**216/362 (60)**	**3,080/4,059 (76)**	**248 (138–378)**	**62 (52–70)**
Age group, yrs				
18–64	85/163 (52)	1,421/2,095 (68)	263 (144–380)	57 (39–70)
≥65	131/199 (66)	1,659/1,964 (84)	238 (133–375)	69 (57–78)
Interval from last monovalent mRNA vaccine dose to illness onset, days				
7–179	63/209 (30)	1,112/2,091 (53)	109 (68–145)	76 (66–83)
180–364	95/241 (39)	1,110/2,089 (53)	269 (220–317)	54 (37–66)
≥365	58/204 (28)	858/1,837 (47)	455 (402–549)	56 (36–69)
Interval from last monovalent mRNA vaccine dose to illness onset, by no. of doses received				
≥7 days before illness onset				
2 doses	87/233 (37)	1,061/2,040 (52)	395 (292–512)	53 (37–65)
3 doses	108/254 (43)	1,534/2,513 (61)	210 (129–313)	65 (54–74)
4 doses¶	19/95 (20)	461/968 (48)	118 (66–169)	83 (70–91)
7–179 days before illness onset				
2 doses	6/152 (4)	108/1,087 (10)	114 (72–153)	—**
3 doses	42/188 (22)	633/1,612 (39)	116 (75–147)	70 (55–81)
4 doses¶	15/91 (16)	353/860 (41)	94 (55–135)	84 (69–92)
≥180 days before illness onset				
2 doses	81/227 (36)	953/1,932 (49)	418 (326–531)	50 (32–64)
3 doses	66/212 (31)	901/1,880 (48)	292 (235–366)	59 (42–72)
4 doses¶	4/80 (5)	108/615 (18)	223 (197–258)	—**

Abbreviations: IMV = invasive mechanical ventilation; VE = vaccine effectiveness.

* https://www.cdc.gov/flu/vaccines-work/ivy.htm

† Monovalent-vaccinated patients received 2–4 monovalent mRNA COVID-19 vaccine doses and zero bivalent mRNA COVID-19 vaccine doses.

§ VE was estimated by comparing the odds of monovalent mRNA vaccination among case-patients and control patients, calculated as VE = 100 × (1 − odds ratio). Logistic regression models were adjusted for date of hospital admission (biweekly intervals), U.S. Department of Health and Human Services region (10 regions), categorical age (18–49, 50–64, and ≥65 years), sex, and race and ethnicity (Black or African American, non-Hispanic; White, non-Hispanic; Hispanic or Latino, any race; Other race, non-Hispanic; and Other, unknown) unless otherwise noted. Logistic regression models for age group–specific VE estimates were adjusted for continuous age.

¶ Logistic regression models for VE of 4 monovalent doses were restricted to patients aged ≥50 years admitted during April 5, 2022–January 31, 2023, and were adjusted for continuous age.

** VE estimate was not reported because of insufficient sample size.

VE against IMV and in-hospital death for a full year during the Omicron variant period. These results suggest some waning of protection against IMV and death after 6 months from receipt of the last dose but demonstrate clinically meaningful levels of protection for ≥1 year (median = 455 days). In stratified analyses, VE appeared to correlate more closely with time since last dose than with total number of doses received. These findings are consistent with evidence from the United Kingdom showing that among adults aged ≥65 years, VE of monovalent COVID-19 vaccination against COVID-19–associated mortality during the Omicron variant period was 49.7% for 2 doses and 56.9% for 3 doses after 40 weeks (280 days) from vaccination (*9*). Together, these results suggest maximal benefit of COVID-19 vaccination during the first 6 months after receipt, which should be considered along with trends in COVID-19 incidence and risk factors for severe disease when planning COVID-19 revaccination schedules.

The findings in this report are subject to at least four limitations. First, the sample size was insufficient to generate VE estimates for each Omicron lineage period separately or to calculate some VE estimates stratified by both time since last monovalent mRNA dose and number of doses received. Second, although case-patients had evidence of acute respiratory illness and received a positive SARS-CoV-2 test result, inclusion of case-patients who died or required IMV for reasons other than COVID-19 could have reduced VE because of misclassification. Third, previous SARS-CoV-2 infection was infrequently reported or documented among patients in this analysis, which prevented evaluation of the impact of previous infection on VE against critical outcomes. Finally, although VE estimates were adjusted for patient-level demographic characteristics, calendar time, and geographic region, residual confounding, including from COVID-19 antiviral treatment, cannot be excluded.

Since the start of the COVID-19 pandemic, approximately 1.1 million COVID-19–associated deaths have occurred in the United States, with the majority occurring among patients aged ≥65 years. Monovalent mRNA COVID-19 vaccination provided substantial, durable protection against COVID-19–associated IMV and death during the Omicron variant period,

Summary

What is already known about this topic?

Waning of monovalent mRNA COVID-19 vaccine effectiveness against COVID-19–associated hospitalization among adults is recognized; however, little is known about the durability of protection provided by these vaccines against COVID-19–associated invasive mechanical ventilation (IMV) and in-hospital death during the Omicron variant period.

What is added by this report?

Monovalent mRNA vaccination was 76% effective in preventing COVID-19–associated IMV and death <6 months after the last dose and remained 56% effective at 1–2 years.

What are the implications for public health practice?

Monovalent mRNA COVID-19 vaccines provided substantial, durable protection against COVID-19–associated IMV and death. All adults should remain up to date with recommended COVID-19 vaccination to prevent critical outcomes of COVID-19.

including among older adults. Protection against these critical outcomes appeared to correlate more closely with time since last dose than with total number of doses received. On April 18, 2023, bivalent mRNA vaccines became the only mRNA COVID-19 vaccines authorized for use in the United States.[§§§] Only 42% of adults aged ≥65 years have received a bivalent mRNA COVID-19 vaccine dose and are up to date with COVID-19 vaccination (*1*). CDC recommends that all adults remain up to date with COVID-19 vaccination, including the updated bivalent vaccine, to prevent critical outcomes of COVID-19.

[§§§] https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccines (Accessed April 25, 2023).

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Notes from the Field

Shiga Toxin-Producing *Escherichia coli* O157:H7 Linked to Raw Milk Consumption Associated with a Cow-Share Arrangement — Tennessee, 2022

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Shiga toxin-producing *Escherichia coli* (STEC) causes foodborne illness that can result in life-threatening kidney failure from hemolytic uremic syndrome (HUS). On August 9, 2022, the Tennessee Department of Health (TDH) identified two cases of STEC infection in two infants aged 10 months who experienced diarrhea on July 25 and August 1. Stool specimens from both infants tested positive for STEC by polymerase chain reaction. One infant developed HUS requiring hemodialysis and hospitalization for 27 days. The second infant was hospitalized for 1 day and did not develop HUS. Both lived in households that consumed raw milk acquired from the same cow-share program, and at least one infant had reportedly consumed raw milk.*

To determine STEC source, TDH initiated an outbreak investigation, including a site visit to the cow-share dairy farm. Because the owner lived in a rural area without phone service or electricity, a TDH employee first visited the dairy farm to inform the owner of the investigation and collect a list of cow-share participants. On August 15, a site investigation and environmental assessment were conducted. The dairy farm included seven to 10 cows that were hand-milked daily. Observations identified possible routes of fecal contamination during milking and possible milk storage at temperatures higher than recommended, with cooling facilitated by mechanical circulation of cool spring water followed by immersion of milk containers in ice-filled coolers. Samples were taken from eight sites including a milk filter, a collection pail, barn posts, and four manure locations, as well as a sample of raw milk.

TDH conducted case finding among cow-share participants. The cow-share list included 125 participants from Georgia, Tennessee, and North Carolina. TDH obtained telephone numbers for 109 participants and successfully reached 50 participants (40% of total) from households that included 112 persons. Three probable cases from a single household were identified based on exposure and self-described resolved clinical symptoms that began on July 20, without laboratory confirmation.† The two households with the two index cases in infants did not participate in the cow-share but obtained raw milk from participants. In total, five cases with two confirmed in hospitalized infants were identified; no deaths were reported.

The Tennessee Department of Health Laboratory Services (TDHLS) isolated STEC O157:H7 in the second index patient's stool specimen. STEC was not isolated in the first index patient's stool because of delayed specimen collection for testing by TDHLS. A U.S. Department of Agriculture laboratory identified two isolates of STEC O157:H7 from a single cattle manure sample in the dairy farm's milking barn. Whole genome sequencing conducted by TDHLS demonstrated that human and cattle stool isolates were highly related, with zero allele differences detected.§

In Tennessee, direct sale of raw milk is prohibited, and TDH advises against raw milk consumption; however, sharing of raw milk through cow-share arrangements is legally permitted.¶ Because the cow-share intends to continue raw milk distribution, TDH requested the University of Tennessee Extension's Agriculture and Natural Resources Team visit the dairy farm on August 30 to provide education concerning best practices to reduce risk for milk contamination. Households participating in the cow-share were also mailed an educational letter about the risk for foodborne illness associated with raw milk.**

Raw milk consumption is associated with outbreaks and sporadic cases of foodborne illness (*1*,*2*). Children aged <5 years, adults aged ≥65 years, and persons with weakened immune systems are at greatest risk for severe illness. Although pasteurization reduces the risk of illness, raw milk regulation varies by state and point of sale.†† Environmental sampling is a useful tool for public health investigations; it permitted illness in this outbreak to be linked with STEC on the dairy farm. This outbreak highlights the risk for severe illness associated with cow-share arrangements, especially among young children,

* A cow-share program allows persons to purchase a share of a milk cow or dairy herd. Cow-share participants can use the milk obtained through the arrangement for personal use.

† A confirmed case was defined as illness in a person who consumed or had access to raw milk from the cow-share, became ill with diarrheal illness, and received a positive STEC test result on a specimen collected after July 1, 2022. A probable case was defined as illness in a person who consumed or had access to raw milk from the cow-share and became ill with diarrheal illness, without laboratory confirmation.

§ TDHLS performed testing on human stool samples using culture and polymerase chain reaction. The U.S. Department of Agriculture laboratory performed testing on environmental samples using brilliant green agar, anti-O157 immunomagnetic beads, and CHROMagar O157. Whole genome sequencing (cgMLST) was performed using CDC's PulseNet standard operating procedure to determine *E. coli* serotype and BioNumerics (version 7.60; Biomérieux) for bioinformatics analysis.

¶ TN Code Sect. 53–3-119.

** https://www.cdc.gov/foodsafety/pdfs/raw-milk-infographic2-508c.pdf

†† https://realrawmilkfacts.com/raw-milk-regulations

who are at increased risk for STEC-related HUS. The outbreak also demonstrated that households not formally participating in cow-share arrangements can be affected. Increasing awareness of inherent health risks of raw milk products in Tennessee could prevent further morbidity.

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Notes from the Field

Posttreatment Lesions After Tecovirimat Treatment for Mpox — New York City, August–September 2022

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Monkeypox virus is an orthopoxvirus that can cause substantial morbidity due to skin and mucosal lesions (*1*). During the 2022 multinational Monkeypox (mpox) outbreak, tecovirimat, an antiviral medication approved for the treatment of smallpox, was used as an investigational treatment for severe mpox. However, efficacy and optimal treatment duration are still being investigated (*1*,*2*). In a late 2022 assessment of the use of tecovirimat for treatment of mpox under the expanded access Investigational New Drug protocol, three patients were found to have developed new lesions after completing treatment (*3*). This report describes a series of patients in New York City (NYC) with mpox who also developed new lesions after completing tecovirimat treatment, suggesting that posttreatment lesions might occur more commonly than previously reported.

A case of posttreatment mpox lesions was defined as the occurrence of new skin or mucosal lesions in an NYC resident with probable or confirmed mpox (*4*), emerging ≤30 days after completing the recommended 14-day tecovirimat treatment course, after improvement or resolution of initial mpox lesions. During August–September 2022, health care providers voluntarily reported 10 such cases to the NYC Department of Health and Mental Hygiene (DOHMH). Providers were asked to complete a survey detailing patient demographic and clinical characteristics and illness course. Descriptive analyses were performed on the nine surveys submitted.

The median patient age was 33 years (range = 23–46 years); eight were men, and one was a transgender woman (Table). Among eight patients with race reported, four were Black or African American, and four were White. Two patients reported Hispanic or Latino ethnicity. HIV status was known for all nine patients. Five had HIV, including four who were taking antiretrovirals at the time of mpox diagnosis (CD4 count >350 cells/mm^3 and viral load <200 copies/mL), and one who was not taking antiretrovirals (CD4 count <200 cells/mm^3 and viral load unknown).

No patient received JYNNEOS vaccine* before experiencing mpox. Initial lesions tested positive for *Orthopoxvirus* using polymerase chain reaction testing. The median initial symptom severity score was 8 out of a possible 23 points (range = 6–13), assessed using the mpox severity score†. Six patients were tested for sexually transmitted infections (STIs) at the time of mpox diagnosis; one received a positive gonorrhea test result and was treated.§

The median interval from mpox symptom onset to tecovirimat initiation was 9 days (range = 6–16 days). All patients received outpatient treatment from their health care provider with weight-appropriate oral dosing of tecovirimat, and all completed the recommended 14-day course with self-reported full adherence. No patient reported an adverse reaction, and providers assessed all patients' mpox lesions as improved after treatment completion.

New lesions appeared a median of 13 days after completion of tecovirimat treatment (range = 2–30 days). In eight patients, posttreatment lesions were rated by the provider to be less severe than initial lesions (median severity score = 3 [range = 3–7]). Among six patients for whom orthopoxvirus testing of posttreatment lesions was conducted, one received a positive result. Two patients received repeat STI testing; one received a positive syphilis test result. The immunocompromised patient with untreated HIV received both the positive posttreatment orthopoxvirus and the positive syphilis test results.¶ Tecovirimat was restarted for two patients (one treated for 7 additional days and one treated for 14 additional days), both of whom had resolution of their lesions. Among the seven patients who did not receive a second course of tecovirimat, six had resolution of lesions, and one was lost to follow-up.

The findings in this report are subject to at least three limitations. First, because active surveillance for posttreatment lesions was not conducted, the number of cases reported here likely represents an underestimate of the actual prevalence. Second, not all posttreatment lesions were tested for *Orthopoxvirus* or other potential etiologies. Finally, analyses relied on provider-reported data, which can be subjective.

Further research is needed to understand the etiology of new lesions in patients with mpox after completion of tecovirimat therapy. One possibility is that *Monkeypox virus*,

* https://www.fda.gov/vaccines-blood-biologics/jynneos

† Mpox severity score was developed by researchers at Columbia University, Cornell University, University of North Carolina, and CDC. Scores can range from 0 to 23. For this report, authors calculated each patient's severity score on the basis of provider survey responses. https://mpoxseverityscore.com/

§ STI testing included gonorrhea and chlamydia (six patients), syphilis (four patients), and herpes simplex virus (one patient).

¶ Posttreatment lesions were treated with 14 days of additional tecovirimat with eventual lesion resolution. Patient received a diagnosis of suspected secondary syphilis and received a positive rapid plasma regain (RPR) blood test result; previous RPR test results were negative. Syphilis treatment was initiated after lesions resolved.

TABLE. Summary of demographic information, clinical features, and outcomes among nine adults with posttreatment lesions after completing tecovirimat treatment for mpox* (N = 9) — New York City, August–September 2022

Characteristic	No. (%)
Total no. of cases	**9 (100)**
Median age, yrs (range)	33 (23 to 46)
Gender	
Man	8 (89)
Transgender woman	1 (11)
Race	
Black or African American	4 (44)
White	4 (44)
Unknown	1 (11)
Ethnicity	
Hispanic or Latino	2 (22)
Not Hispanic or Latino	6 (67)
Unknown	1 (11)
HIV-positive patients	**5 (56)**
Receiving ART at time of mpox diagnosis†	4 (80)§
Not receiving ART at time of mpox diagnosis¶	1 (20)§
Reasons for tecovirimat initiation**	
Proctitis	5 (56)
HIV	3 (33)
Facial lesions	1 (11)
Oral lesions	2 (22)
Urethral lesions	2 (22)
Rectal pain	1 (11)
Dysphagia	1 (11)
Result of treatment with initial tecovirimat course	
Worsening lesions	0 (—)
No change in lesions	0 (—)
Mild improvement of lesions	1 (11)
Significant improvement of lesions	3 (33)
Complete resolution of lesions	5 (56)
Difference between initial and posttreatment lesion severity score, median (range)	−4 (−10 to 1)
Outcome of posttreatment lesions, by treatment	
Tecovirimat treatment given (n = 2)††	
Lesions resolved	2 (100)
Additional lesions did not resolve	0 (—)
No additional tecovirimat treatment given (n = 7)	
Lesions resolved	6 (86)
Lesions did not resolve	0 (—)
Lost to follow-up	1 (14)

Abbreviation: ART = antiretroviral therapy.
* Reported to the New York City Department of Health and Mental Hygiene.
† These patients had CD4 count >350 cells/mm^3 and viral load <200 copies/mL.
§ Percentage of HIV-positive patients.
¶ This patient was immunocompromised (CD4 <200 cells/mm^3).
** Providers could report multiple reasons.
†† One patient was treated with tecovirimat for an additional 7 days, and the other was treated for an additional 14 days.

like other viruses (e.g., SARS-CoV-2), can recur (*5*), but the recurrent viral load might be too low for test detection. Immunocompetent patients might not require additional tecovirimat, because most posttreatment lesions in this analysis resolved without further treatment. However, the clinical course in immunocompromised patients might be more complicated. The proportions of patients not tested for STIs, at initial mpox diagnosis and at the assessment of posttreatment lesions, represent missed opportunities to identify potential coinfections or alternative diagnoses.

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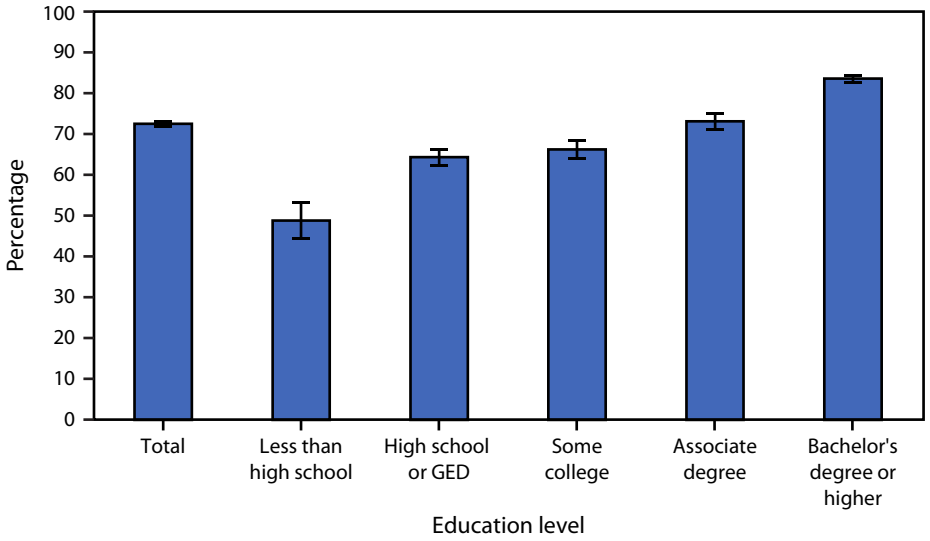
QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Percentage* of Currently Employed Adults Aged ≥18 Years Who Have Paid Sick Leave,† by Education Level — National Health Interview Survey, 2021§



Abbreviation: GED = general educational development certificate.
* With 95% CIs indicated by error bars.
† Based on responses to a question that asked, "When you last worked is paid sick leave available if you needed/need it?"
§ Estimates were based on household interviews of a sample of adults aged ≥18 years who were working last week, were not working last week because they were temporarily absent, or who performed seasonal or contract work. Self-employed respondents or respondents performing unpaid work at family businesses were not included.

In 2021, 72.5% of employed adults had paid sick leave. The percentage with sick leave was highest among workers with a bachelor's degree or higher (83.6%), followed by workers with an associate degree (73.2%). The percentage of sick leave was similar for workers with some college (66.3%) and those with a high school diploma or GED (64.4%). The lowest percentage of sick leave occurred among workers with less than a high school education (48.8%).

Source: National Center for Health Statistics, National Health Interview Survey, 2021. https://www.cdc.gov/nchs/nhis.htm

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