Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 72 / No. 9
March 3, 2023

Acute Kidney Injury Among Children Likely Associated with Diethylene Glycol–Contaminated Medications — The Gambia, June–September 2022

Parsa Bastani, PhD[1,2]; Anna Jammeh, MD[3,4]; Frederica Lamar, PhD[1,2]; Jason H. Malenfant, MD[1,5]; Peter Adewuyi, MD[6,7]; Alyson M. Cavanaugh, PhD[8]; Kimberly Calloway, DVM[1,8]; Carolyn Crisp, PhD[1,9]; Nuha Fofana, MPhil[3,10]; T. Christy Hallett, MD[9]; Amadou Jallow, MSPH[3,4]; Uzoamaka Muoneke, MD[11,12]; Momodou Nyassi, MD[3]; Jerry Thomas, MD[13]; Alyssa Troeschel, PhD[1,9]; Ellen Yard, PhD[2]; Michael Yeh, MD[9]; Mustapha Bittaye, MD[3]

On July 26, 2022, a pediatric nephrologist alerted The Gambia's Ministry of Health (MoH) to a cluster of cases of acute kidney injury (AKI) among young children at the country's sole teaching hospital, and on August 23, 2022, MoH requested assistance from CDC. CDC epidemiologists arrived in The Gambia, a West African country, on September 16 to assist MoH in characterizing the illness, describing the epidemiology, and identifying potential causal factors and their sources. Investigators reviewed medical records and interviewed caregivers to characterize patients' symptoms and identify exposures. The preliminary investigation suggested that various contaminated syrup-based children's medications contributed to the AKI outbreak. During the investigation, MoH recalled implicated medications from a single international manufacturer. Continued efforts to strengthen pharmaceutical quality control and event-based public health surveillance are needed to help prevent future medication-related outbreaks.

Investigation and Results

In July 2022, a pediatric nephrologist at the Edward Francis Small Teaching Hospital in The Gambia's capital city of Banjul alerted MoH to a cluster of AKI cases among children. Data on AKI incidence are not routinely collected in The Gambia; thus, the baseline AKI rate was unknown. However, the treating nephrologist expressed concern that the number of cases and deaths were well above baseline: through August 12, a total of 30 pediatric deaths among 37 AKI cases had been reported from facilities throughout the country (case fatality rate = 81%). In response to a request for assistance, a multidisciplinary CDC team, including an epidemiologist, an anthropologist, an infectious disease physician, and an environmental health scientist, arrived on September 16 to assist the Field Epidemiology Training Program (FETP) and MoH in characterizing the illness and identifying exposures. MoH collaborated separately with the World Health Organization (WHO) to test medications that might have been used by patients.

Active surveillance was conducted through reoccurring communication with the teaching hospital and other regional hospitals, inquiring about admissions of pediatric patients with kidney failure. As of September 29, 2022, MoH had identified 78 clinically suspected AKI cases. Among these patients, 66 (85%) had died. Most patients (75%) were aged <2 years, and 60% were male. Cases were reported from six of the country's

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seven health regions.* Among the 78 cases reported to MoH, symptom onset date was available for 67 (86%) (Figure).

CDC, MoH, and FETP investigators developed a standardized case report form to gather data about pediatric patients with AKI identified by MoH. Data collection consisted of a review of the patient's medical records and caregiver interview data. For this investigation, a confirmed case of pediatric AKI was defined as anuria (no urine output) of unknown etiology in a child aged ≤8 years, persisting for ≥24 hours, during June 21–September 29, 2022. June 21 was chosen as the start date because medications suspected to have possibly caused the AKI outbreak had been imported into the country on June 21. Investigators first reviewed the medical records of 52 (67%) of the 78 MoH-identified patients with suspected AKI who were treated by the teaching hospital. Next, interviews with at least one caregiver of each of 27 patients were conducted by investigators in local languages, including the caregivers of 20 patients whose children's hospital medical records were reviewed and seven patients whose medical records could not be located. Investigators selected a convenience sample of caregivers for interview based on their location of residence. Because of resource limitations and reluctance on the part of some caregivers to be interviewed, not all medical records could be located, and not all invited caregivers participated. In addition, interview data were collected in only two of the six health regions (Western Regions 1 and 2). This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.†

Caregivers were asked about the child's recent medical history, including disease course, experiences with the health care system, and possible exposures, including medications, foods, and experience of flooding, among others. All participating caregivers were interviewed in their homes. All four (15%) living patients whose caregivers were interviewed had been discharged at the time of interview. Among patients who had died, the mean interval between date of death and date caregivers were contacted for interview was 33 days. Information from medical records and interviews was used to determine whether patients on the MoH line list met the confirmed case definition. After data from the 27 caregiver interviews and 52 medical record reviews were combined, 59 case report forms were completed, representing 76% of the 78 cases reported to MoH, and 88% of the 67 patients with a symptom onset date. Among these 59 patients, 56 (95%) met the confirmed case definition and were included in the analysis.§

Among the 56 included patients, more than one half (54%) experienced fever as their first signs or symptoms, and 50%

*Cases were reported from Western Region 1, Western Region 2, Upper River Region, North Bank West Region, Lower River Region, and Central River Region. Cases were not reported from the North Bank East Region.

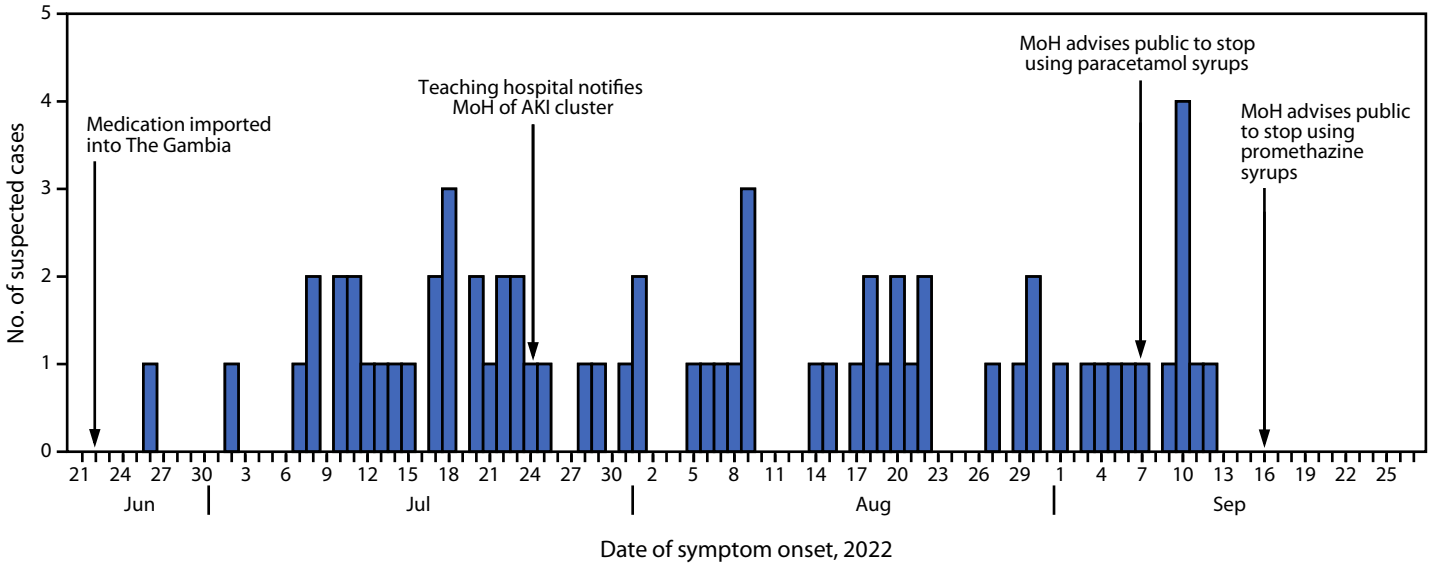
†45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

§The three patients who did not meet the case definition did not have documentation of anuria.

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

Suggested citation: [Author names; first three, then et al., if more than six.] [Report title]. MMWR Morb Mortal Wkly Rep 2023;72:[inclusive page numbers].

FIGURE. Date of first symptom onset for suspected cases of acute kidney injury of unknown etiology* among children (N = 67),† critical events in the outbreak investigation, and public health recommendations — The Gambia, June 12–September 29, 2022



Abbreviations: AKI = acute kidney injury; MoH = The Gambia's Ministry of Health.
* Baseline incidence of AKI not available. These data include cases from MoH Epidemiology and Disease Control Unit with reported date of initial symptom onset.
† Among 78 cases reported to MoH, symptom onset date was available for 67 (86%) patients.

experienced vomiting (Table 1). Approximately one third (34%) had diarrhea or loose stool as the first symptom. During the course of illness, all patients experienced anuria and fever, 95% experienced vomiting, and 73% experienced diarrhea. Nearly one half (48%) experienced anorexia or reduced feeding. The median interval from symptom onset to anuria was 5 days (IQR = 2–7 days); among the 26 patients who died, the median interval from onset of anuria to death was 6 days (IQR = 3–7 days).

Abnormal laboratory test results were received by 66%–100% of patients, including impaired renal and liver function, thrombocytosis, and mild to moderate anemia (Table 2). Fourteen patients underwent peritoneal dialysis, and one patient underwent hemodialysis; all 15 patients who received dialysis died.

Among the 26 patients with a caregiver interview, 100% of caregivers reported that the child consumed a prescription or over-the-counter syrup-based medication (including paracetamol, known in the United States as acetaminophen, commonly administered for fever) before the onset of anuria. Twelve patients (47%) had consumed four or more medications before being hospitalized. Although many caregivers were unable to recall the names of medications that they administered to their children, caregivers of 14 (54%) of these 26 patients identified the manufacturer name of at least one medication administered to their child before inpatient hospitalization. A single international manufacturer that produced a syrup-based medication was reported in eight of 14 (57%) interviews in which caregivers identified the manufacturer name of at least one medication administered to their child before inpatient hospitalization.

Public Health Response

Preliminary reports from the treating physicians at the teaching hospital indicated that caregivers had administered paracetamol and promethazine to their children before their development of AKI. Based on this information, MoH advised the public to suspend use of all paracetamol and promethazine syrups on September 7, 2022, and September 16, 2022, respectively (Figure). The laboratory analysis of 23 medication samples conducted by MoH and WHO confirmed that four products from Maiden Pharmaceuticals Limited (Haryana, India) contained diethylene glycol (DEG) and ethylene glycol (EG). Based on records from The Gambia's Medicines Control Agency, all medications that tested positive for DEG and EG were imported into The Gambia on June 21, 2022, shortly before the occurrence of the first AKI cases.

On October 4, 2022, MoH suspended the importation of all medications from this manufacturer and requested that health care providers stop prescribing, dispensing, and using medications produced by this manufacturer because of their possible contamination. On October 5, 2022, WHO issued a worldwide medical product alert for four syrup-based medications from Maiden Pharmaceuticals (*1*). In collaboration with WHO, UNICEF, ChildFund The Gambia, and The Gambia Red Cross Society, MoH supported a house-to-house recall and

TABLE 1. Signs and symptoms reported at the onset of illness and at any time during illness, intervals between onset of symptoms and onset of anuria, intervals between onset of anuria and death, and available medical records or caregiver interviews among pediatric patients with acute kidney injury (N = 56)* — The Gambia, June–September 2022

Symptoms and intervals until anuria or death	No. (%)†	No. of valid responses (median, [IQR])
First symptoms experienced		
Fever	30 (54)	NA
Vomiting	28 (50)	NA
Diarrhea/Loose stool	19 (34)	NA
Cough, runny nose, sneezing or unspecified cold symptom	7 (13)	NA
Anuria	2 (4)	NA
Anorexia	2 (4)	NA
Other§	5 (9)	NA
Symptoms ever experienced		
Anuria	56 (100)	NA
Fever	56 (100)	NA
Vomiting	53 (95)	NA
Diarrhea/Loose stool	41 (73)	NA
Reduced appetite/Decreased breastfeeding	27 (48)	NA
Difficulty breathing	22 (39)	NA
Cough, runny nose, sneezing or unspecified cold symptom	19 (34)	NA
Rash	6 (11)	NA
Abdominal pain	5 (9)	NA
Convulsions/Seizures	4 (7)	NA
Bloody diarrhea	1 (2)	NA
Jaundice	0 (—)	NA
Intervals from symptom onset to anuria (or death)¶		
First symptoms experienced to anuria, days	NA	31 (5 [2 to 7])
Vomiting onset to anuria, days	NA	25 (2 [1 to 6])
Loss of appetite/Refusal to breastfeed onset to anuria, days	NA	17 (1 [0 to 1])
Diarrhea onset to anuria, days	NA	17 (4 [2 to 6])
Difficulty breathing onset to anuria, days	NA	7 (0 [–3 to 1]**)
Onset of anuria to death, days	NA	26 (5.5 [3 to 7])

Abbreviation: NA = not available.

* A confirmed case of pediatric acute kidney injury was defined as anuria (no urine output) of unknown etiology in a child aged ≤8 years, persisting for ≥24 hours, during June 21–September 29, 2022.

† Percentages might sum to >100%, because multiple signs or symptoms could be reported for each patient.

§ Other reported symptoms included rash (one), headache (one), mouth ulcers (one), abdominal pain (one), and reduced urine output (one).

¶ Responses were considered valid if patients had the signs or symptoms of interest and had onset dates for both variables involved in the interval. For example, the interval vomiting onset to anuria was only calculated among patients who experienced vomiting and anuria and had recorded onset dates available for both symptoms.

** A negative value for this interval indicates that anuria preceded breathing difficulties.

collection of all products from this manufacturer in addition to all paracetamol, promethazine, and cough syrups. In conjunction with the recall, MoH promoted awareness about the contaminated medications through messaging on radio, television, social media, and in places of worship. MoH also commenced ongoing pharmacy spot checks to ensure that products from this manufacturer were not being sold. Surveillance officers were trained in case definitions, case report forms, following up with patients discharged from hospitals, and conducting active case finding in the community.

Discussion

This investigation strongly suggests that medications contaminated with DEG or EG imported into The Gambia led to this AKI cluster among children. AKI outbreaks associated with DEG-contaminated pharmaceutical products have been documented in Panama, Nigeria, India, and Haiti (*2*–*5*). Patients with DEG poisoning can experience a range of signs and symptoms, including altered mental status, headache, and gastrointestinal symptoms; however, the most consistent manifestation is AKI, characterized by oliguria (low urine output) or anuria, progressing over 1–3 days to renal failure (indicated by elevated serum creatinine and blood urea nitrogen) (*6*). In past DEG outbreaks, manufacturers have been suspected of substituting DEG in the place of more expensive, pharmaceutical-grade solvents (*3*,*7*). Medication testing supported contaminated medical syrups as the etiology of this cluster of AKI cases (*1*).

Further support for a toxic etiology includes the wide geographic distribution of cases in the country (six of seven health regions), a common pharmaceutical manufacturer of medications reported to have been used by many patients, and a low rate of intrahousehold spread. This intoxication appears to have only affected children, likely because medications in syrup form are most commonly used for children in The Gambia.

Factors that might have led to poor caregiver recall regarding medications administered to their children include the assumption by caregivers that medications would not harm their children, difficulty of parents of children who had died recalling administered medications owing to the interval between patients' deaths and the investigation, and the possibility of reduced reporting following the issuing of health alerts by MoH.

This likely poisoning event highlights the potential public health risks posed by the inadequate quality management of pharmaceutical exports. Among reports of AKI associated with DEG-contaminated medical products, this is the first in which DEG-contaminated medications were imported into a country, rather than being domestically manufactured. Inadequate regulatory structures make the sale of medications from international markets an especially high-risk activity in low-resource settings. Medications for export might be subject to less rigorous regulatory standards than those for domestic use (*8*). Simultaneously, low-resource countries might not have the human and financial resources to monitor and test imported drugs (*8*). In addition to improving pharmaceutical

TABLE 2. Laboratory test results among patients with acute kidney injury following medication exposures — Edward Francis Small Teaching Hospital, The Gambia, June–September 2022

Laboratory test	Normal reference range	Median patient value (IQR)	Abnormal test results	
			No./Total no. (%)	Direction of abnormality
Hemoglobin	11.5–16.5 g/dL	10.3 (9.0–11.5)	31/38 (82)	Low
Alanine transaminase	0–41 U/L	284.5 (135.0–473.0)	13/18 (72)	High
Alkaline phosphatase	45–135 U/L	272.5 (212.0–350.0)	14/14 (100)	High
Aspartate transferase	0–40 U/L	271.3 (176.5–610.5)	13/16 (81)	High
Blood urea nitrogen	1.7–8.3 mmol/L	29.8 (16.0–41.0)	37/41 (90)	High
Creatinine	44–123 μmol/L	711.0 (499.5–854.0)	34/38 (89)	High
Platelets	130–400 x 10^9/L	511.0 (388.0–598.0)	23/35 (66)	High

quality management, efforts should be made by MoH to strengthen event-based surveillance systems (*9*), which rely on unstructured information (e.g., reports, rumors, and other information) to detect unusual events that might signal an outbreak or other public health event. Event-based surveillance complements traditional reportable disease surveillance and has the potential to improve the ability to rapidly detect and respond to similar acute health events of unknown and unexpected etiologies. FETP-trained experts can provide valuable assistance in these and other efforts to help governments improve their capacities to detect and respond to outbreaks in the future.

Acknowledgments

World Health Organization; The Gambian Field Epidemiology Training Program; staff members at the Edward Francis Small Teaching Hospital, Banjul, The Gambia; CDC Organization of African Public Health Professionals; CDC Work Group on Health of Muslim Populations.

Corresponding author: Parsa Bastani, tqx2@cdc.gov.

[1]Epidemic Intelligence Service, CDC; [2]Division of Global Health Protection, Center for Global Health, CDC; [3]Ministry of Health, Banjul, The Gambia; [4]Epidemiology Disease Control Unit, Ministry of Health, Banjul, The Gambia; [5]Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, CDC; [6]The Gambian Field Epidemiology Training Program, Banjul, The Gambia; [7]African Field Epidemiology Network, Kampala, Uganda; [8]Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC; [9]Division of Environmental Health Science and Practice, National Center for Environmental Health, CDC; [10]Ghana Field Epidemiology and Laboratory Training Program, Accra, Ghana; [11]Department of Pediatrics, University of Nigeria, Nsukka, Enugu, Nigeria; [12]Department of Pediatrics, Edward Francis Small Teaching Hospital, Banjul, The Gambia; [13]Division of Laboratory Sciences, National Center for Environmental Health, CDC.

Summary

What is already known about this topic?

Diethylene glycol (DEG)–contaminated medications present a global health threat, especially in low-income countries.

What is added by this report?

A large cluster of acute kidney injury cases affecting children in The Gambia in 2022 was associated with case fatality rates >80%. The implicated syrup-based pediatric medications that had been administered to patients were imported from a single Indian manufacturer. This is one of the first documented DEG outbreaks in which contaminated medications were imported rather than being domestically manufactured.

What are the implications for public health practice?

DEG mass poisonings continue to occur worldwide, especially in low-resource settings. Strengthened international pharmaceutical regulatory structures and event-based surveillance systems can help prevent DEG-associated large-scale poisoning events.

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

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Cronobacter sakazakii Infections in Two Infants Linked to Powdered Infant Formula and Breast Pump Equipment — United States, 2021 and 2022

Julia C. Haston, MD[1,2]; Shanna Miko, DNP[1,2]; Jennifer R. Cope, MD[1]; Haley McKeel[1]; Cynney Walters[1]; Lavin A. Joseph, MS[1]; Taylor Griswold, MS[1]; Lee S. Katz, PhD[1]; Ashley A. Andújar, MHSA[1]; Laura Tourdot, MPH[3]; Joshua Rounds, MPH[3]; Paula Vagnone[3]; Carlota Medus, PhD[3]; JoAnn Harris, MD[4]; Robert Geist, MPH[5]; Daniel Neises, MPH[5]; Ashley Wiggington, MPH[6]; Trey Smith, MS[1]; Monica S. Im, MS[1]; Courtney Wheeler[1]; Peyton Smith, MS[1]; Heather A. Carleton, PhD[1]; Christine C. Lee, PhD[1,7]

Cronobacter sakazakii, a species of gram-negative bacteria belonging to the Enterobacteriaceae family, is known to cause severe and often fatal meningitis and sepsis in young infants. *C. sakazakii* is ubiquitous in the environment, and most reported infant cases have been attributed to contaminated powdered infant formula (powdered formula) or breast milk that was expressed using contaminated breast pump equipment (*1*–*3*). Previous investigations of cases and outbreaks have identified *C. sakazakii* in opened powdered formula, breast pump parts, environmental surfaces in the home, and, rarely, in unopened powdered formula and formula manufacturing facilities (*2*,*4*–*6*). This report describes two infants with *C. sakazakii* meningitis reported to CDC in September 2021 and February 2022. CDC used whole genome sequencing (WGS) analysis to link one case to contaminated opened powdered formula from the patient's home and the other to contaminated breast pump equipment. These cases highlight the importance of expanding awareness about *C. sakazakii* infections in infants, safe preparation and storage of powdered formula, proper cleaning and sanitizing of breast pump equipment, and using WGS as a tool for *C. sakazakii* investigations.

In September 2021, a state public health department reported an infant with *C. sakazakii* infection to CDC (patient A). In February 2022, a physician reported another case to CDC and a different state health department (patient B). CDC was invited to participate in the investigations and distributed case report forms to obtain detailed feeding information about the two cases. Patient isolates and environmental samples were sent to CDC, state public health laboratories, and other federal agencies for isolation, identification, and WGS analysis of *C. sakazakii*.

The first case occurred in September 2021 in a full-term (gestation of 40 weeks, 1 day) male infant (patient A) born to a healthy mother who had an uncomplicated pregnancy and spontaneous vaginal delivery. At age 14 days, the infant was evaluated at hospital A for fever, irritability, and excessive crying, oral candidiasis (thrush), and diaper dermatitis. Before his illness, he was fed both expressed breast milk and powdered formula. A lumbar puncture was performed, and *C. sakazakii* was isolated from the cerebrospinal fluid (CSF). The infant was admitted to the hospital and treated with intravenous antibiotics for 21 days; he made a full recovery with no apparent long-term sequelae (Table).

A *C. sakazakii* isolate from the CSF was analyzed by WGS. Samples of opened powdered formula and an opened bottled water container used for formula preparation in the patient's home were cultured in gram-negative enrichment broth followed by selective media. *C. sakazakii* isolates were recovered from both the powdered formula and the water container. WGS* was performed and identified two distinct strains of *C. sakazakii* (Figure). Sequence reads were cleaned,† assembled,§ and analyzed using high-quality single nucleotide polymorphism (SNP) analysis¶; results showed that the patient isolate was closely genetically related to an isolate from the powdered formula (0 SNPs apart).** A second isolate from the same can of powdered formula was closely genetically related to an isolate from the water container (within 4 SNPs).†† These two strains were not related to one another (>50,000 SNPs apart). Federal partners tested unopened powdered formula from the same lot as the powdered formula consumed by the patient; *C. sakazakii* was not detected.

The second case occurred in February 2022 in a preterm (gestation of 30 weeks, 6 days), hospitalized male infant (patient B) born by cesarean delivery because of breech presentation and the mother's worsening preeclampsia. At the time of illness onset, he was being treated in the neonatal intensive care unit for complications of prematurity but was stable, feeding, growing, and breathing without respiratory support. He was fed expressed breast milk fortified with liquid human milk fortifier primarily through an orogastric tube before becoming ill. At age 20 days, he experienced apneic and bradycardic episodes, temperature elevation, and a requirement for respiratory

* Genomic DNA was extracted and sequenced on MiSeq instruments (Illumina) following Nextera XT or DNA Prep library preparation.

† Sequence reads were cleaned using run_assembly_trumClean.pl. https://github.com/lskatz/CG-Pipeline.

§ Cleaned reads were assembled using SPAdes (version 3.14.0) https://github.com/ablab/spades.

¶ Lyve-SET (version 1.1.4f) was used for high-quality SNP analysis on reads https://github.com/lskatz/lyve-SET.

** *C. sakazakii* ATCC 29544 was used as the reference genome.

†† *C. sakazakii* isolated from the open formula (2021EL-1052c) was used as the reference genome.

TABLE. Patient characteristics and testing results in two infant cases of *Cronobacter sakazakii* infection — United States, 2021 and 2022

Characteristic	Patient A (2021)	Patient B (2022)
Age at illness onset	14 days	20 days
Gestational age at birth	40 wks 1 day	30 wks 6 days
Admitting hospital	Hospital A	Hospital B
Feeding source	Powdered infant formula and expressed maternal milk, by bottle	Expressed maternal milk with added liquid human milk fortifier, by orogastric tube
Disease manifestation	Meningitis	Meningitis and bacteremia
Outcome	Survived	Died
Environmental samples positive for *C. sakazakii*	Opened powered infant formula; opened water container	Breast pump parts
WGS analysis summary	Patient isolate (CSF) matched one strain identified in powdered formula Isolate from opened water container matched a separate strain identified in powdered formula	Patient isolates (CSF and blood) matched strain from breast pump
NCBI BioProject number	PRJNA420465	PRJNA420465
Biosample accession number	SAMN26725422 SAMN26725453 SAMN26725454 SAMN29506919	SAMN26725423 SAMN29506921 SAMN26725456

Abbreviations: CSF = cerebrospinal fluid; NCBI = National Center for Biotechnology Information; WGS = whole genome sequencing.

support. Seizures developed the following day. *C. sakazakii* was isolated from blood and CSF cultures. Despite treatment with intravenous antibiotics and repeat negative blood cultures, the patient died 13 days after illness onset.

Expressed milk samples, breast pump parts from two separate devices (one used in the hospital and one used in the mother's home), and liquid human milk fortifier samples from three lots were cultured in gram-negative enrichment broth followed by selective media; *C. sakazakii* was recovered from the breast pump parts used in the home. An interview revealed that these breast pump parts were cleaned in a household sink, sanitized, and sometimes assembled while still moist. No bacteria were recovered from the expressed milk samples, liquid human milk fortifier samples, hospital breast pump parts, or unopened powdered formula from the hospital. *C. sakazakii* isolates from the patient's blood and CSF, and those isolated from environmental samples, were analyzed by WGS,[§§] which indicated that the patient's CSF and blood isolates were closely genetically related to the isolate recovered from the home breast pump (0–1 SNPs).

Discussion

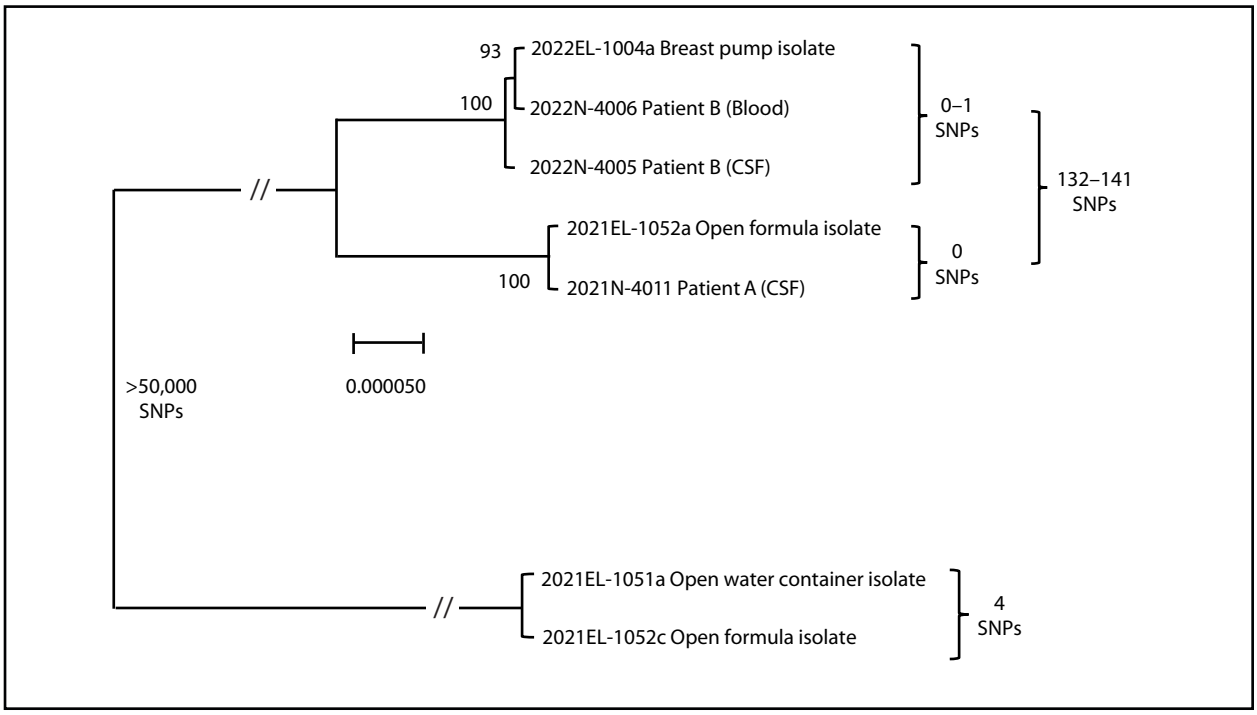
On the basis of the WGS analysis, these two cases of *C. sakazakii* infection in infants were not related. One case was likely transmitted by powdered formula prepared in the home, and the other through expressed milk contaminated by breast pump equipment. These cases illustrate the ubiquity of the pathogen in the environment, the importance of hygiene in preventing *C. sakazakii* infections, and the utility of WGS as a method for determining genetic relatedness and probable transmission sources. Understanding more about the sources of these infections can help educate clinicians and caregivers about ways to prevent *C. sakazakii* infections among infants.

C. sakazakii can cause meningitis and sepsis, most commonly in very young infants and those with a history of prematurity, possibly because of immaturity of their immune systems and gastrointestinal tracts (*7*). Although *C. sakazakii* infections are treatable with antibiotics, they often have devastating outcomes, with death occurring in nearly 40% of infants who develop meningitis (*2*). Many surviving infants also experience complications, including cerebral abscess and hydrocephalus, which can result in permanent neurologic sequelae (*2*). Because *C. sakazakii* infection is not a nationally notifiable condition, the actual incidence is unknown. However, it is estimated that approximately 18 cases of invasive *C. sakazakii* infection in infants occur annually in the United States, most of which are not associated with outbreaks but likely occur because of isolated instances of contamination of infant feeding products and equipment in the home (*2*,*8*).

Previous investigations have identified *C. sakazakii* in opened powdered formula because of its notable ability to survive in dry environments. However, it has also been recovered from many other environmental sources in the home, including kitchen sink surfaces, pacifiers, bottles, household utensils, vacuum cleaning bags, and other foods (*1*,*2*). Feeding utensils, such as scoops used for powdered formula, can become contaminated on countertops or in sinks and subsequently transfer *C. sakazakii* when reintroduced into the formula. Additional reports have linked *C. sakazakii* infections to contaminated

[§§] Methods for WGS analysis were identical to the investigation for patient A.

FIGURE. Maximum likelihood phylogeny from high quality single nucleotide polymorphism* analysis[†,§,¶] of *Cronobacter sakazakii* patient A and B isolates and environmental isolates — United States, 2021 and 2022



Abbreviations: CSF = cerebrospinal fluid; SNP = single nucleotide polymorphism; // = skip mark.
* SNP distances guide genetic relatedness between strains.
† Scale bar indicates the genomic distance of samples to right of skip mark.
§ Values at branch nodes indicate bootstrapping from 100 iterations. *C. sakazakii* isolates from patients A and B, in addition to environmental samples, form three distinct clusters in a maximum likelihood phylogeny.
¶ Skip mark indicates a truncation to capture the relationship between clusters.

expressed breast milk after recovering the organism from breast pump equipment (*3*–*5*). Phenotypic methods of identification and pulsed-field gel electrophoresis have previously been used to identify *Cronobacter* species and determine potential sources of transmission in cases of infant *C. sakazakii* infections in the United States. However, these methods were limited and could not definitively identify genetic relatedness. Analysis of WGS data from these two cases permitted more accurate determinations of relatedness among isolates. In future investigations, WGS can be used to guide public health practitioners and clinicians about potential outbreaks or sources of *C. sakazakii* related to illnesses.

The findings in this report are subject to at least three limitations. First, *C. sakazakii* infections are not nationally notifiable or reportable in most states, so associations with other strains and detection of potential outbreaks is currently limited. Second, standardized methods for identifying and characterizing *C. sakazakii* are not yet routine, further limiting wide-scale detection and surveillance efforts. Finally, on-site investigations were not performed, so the samples tested might not represent all potential sources of contamination (e.g., additional feeding products, equipment, or environmental surfaces).

Because of the widespread presence of *C. sakazakii* in the environment, caregivers of infants should follow safe hygiene, preparation, and storage practices, and learn steps to protect infants from infection. Clinicians providing care for infants aged <2 months or those who were born prematurely or are immunosuppressed should explain the risks of *C. sakazakii* infection to caregivers, especially if the infant is fed with powdered formula or expressed milk. Education should emphasize exploring alternatives to powdered formula for infants at highest risk and safe powdered formula preparation and storage (*9*). In addition, caretakers should be instructed to thoroughly clean and sanitize breast pump equipment (*10*). Hospitals caring for premature or critically ill infants might consider providing instructions and a dedicated basin for cleaning supplies at home upon hospital discharge to minimize the risk of contamination. Increased awareness of safe hygiene, preparation, and storage practices related to infant feeding products, enhanced understanding of *C. sakazakii* reservoirs, and ongoing public health messaging can help prevent infant *C. sakazakii* infections, complications, and deaths.

Summary

What is already known about this topic?

Infections caused by *Cronobacter sakazakii* are rare but can cause severe illness and death in infants.

What is added by this report?

Whole genome sequencing analysis was used to link one case of *Cronobacter sakazakii* infection in a full-term infant to an opened can of powdered infant formula, and another unrelated fatal case in a premature infant to contaminated breast pump equipment.

What are the implications for public health practice?

Increased awareness of the widespread presence of *Cronobacter* in the environment, along with promotion of safe preparation and storage of powdered infant formula, and careful cleaning and sanitization of breast pump equipment, could prevent potentially devastating infections.

Acknowledgments

Lori M. Gladney, Kelley Hise, Jordan Putney, Nancy Strockbine, Division of Foodborne, Waterborne, and Environmental Diseases, CDC; Division of Human and Animal Food West 1 Laboratory, Office of Regulatory Affairs (ORA), Food and Drug Administration (FDA); Office of Regulatory Science Laboratory, ORA, FDA; Kansas Department of Agriculture Laboratory.

Corresponding authors: Julia Haston, qdx2@cdc.gov; Christine Lee, pfx6@cdc.gov.

[1]Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC; [2]Epidemic Intelligence Service, CDC; [3]Minnesota Department of Health; [4]Hospital B; [5]Kansas Department of Health and Environment; [6]Missouri Department of Health and Senior Services; [7]Laboratory Leadership Service, CDC.

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

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Possible Undetected Mpox Infection Among Persons Accessing Homeless Services and Staying in Encampments — San Francisco, California, October–November 2022

Caroline J. Waddell, PhD[1,2]; Thomas D. Filardo, MD[1,2]; Namrata Prasad, PhD[1,2]; Gerald J. Pellegrini Jr.[1]; Neela Persad, MPH[1]; William C. Carson[1]; Terese Navarra[1]; Michael B. Townsend, PhD[1]; Panayampalli S. Satheshkumar, PhD[1]; David Lowe[1]; Deborah Borne, MD[3]; Julia Janssen, MD[3]; Nnenna Okoye, MD[3]; Anamaría Bejarano, MPH[3]; Grace E. Marx, MD[1,*]; Emily Mosites, PhD[1,*]

Monkeypox (mpox) is a disease caused by an *Orthopoxvirus.* The 2022 multinational outbreak, which began in May 2022, has spread primarily by close skin-to-skin contact, including through sexual contact. Persons experiencing homelessness have been disproportionately affected by severe mpox (*1*). However, mpox prevalence and transmission pathways among persons experiencing homelessness are not known, and persons experiencing homelessness have not been specifically recommended to receive mpox vaccine during the 2022 outbreak (*2*,*3*). During October 25–November 3, 2022, a CDC field team conducted an orthopoxvirus seroprevalence survey among persons accessing homeless services or staying in encampments, shelters, or permanent supportive housing in San Francisco, California that had noted at least one case of mpox or served populations at risk. During field team visits to 16 unique sites, 209 participants completed a 15-minute survey and provided a blood specimen. Among 80 participants aged <50 years who did not report smallpox or mpox vaccination or previous mpox infection, two (2.5%) had detectable antiorthopoxvirus immunoglobulin (Ig) G antibody. Among 73 participants who did not report mpox vaccination or previous mpox infection and who were tested for IgM, one (1.4%) had detectable antiorthopoxvirus IgM. Together, these results suggest that three possible undetected mpox infections occurred among a sample of persons experiencing homelessness, highlighting the need to ensure that community outreach and prevention interventions, such as vaccination, are accessible to this population.

During July–October 2022, the San Francisco Department of Public Health (SFDPH) identified cases of mpox among persons who were experiencing homelessness (Deborah Borne, MD, San Francisco Department of Public Health, personal communication, October 2022). SFDPH invited a CDC field team to conduct an orthopoxvirus seroprevalence survey among persons experiencing homelessness to better understand the prevalence of disease and possible transmission pathways. Existing collaboration between SFDPH and government- and community-based organizations serving persons experiencing homelessness facilitated site engagement in the project. Homeless service sites were prioritized for inclusion if they had provided services to at least one person with confirmed mpox or served persons at increased risk for mpox, including those identifying as lesbian, gay, bisexual, transgender, or queer; men who have sex with men; and persons who engage in sex work.

Participants provided oral consent to respond to a 15-minute orally administered survey and to provide a serum specimen. Persons aged ≥18 years were eligible to participate. The survey included questions about demographic characteristics and behaviors that could be related to mpox transmission in the context of homelessness, including frequency of sharing objects such as clothing and utensils as well as sexual activity and drug use in the preceding month. Surveys were conducted in person in English or Spanish or through a phone-based language interpreter if another language was requested. A trained phlebotomist performed venipuncture. When venipuncture was unsuccessful or when success was considered unlikely (e.g., because of needle aversion or inadequately visualized or damaged veins), participants were offered use of a microneedle device that passively collected capillary blood from the upper arm (*4*). Each participant received up to two $25 grocery store gift cards for participating in the survey and blood collection. This activity was reviewed and approved by CDC and conducted consistent with applicable federal law and CDC policy.[†]

Blood specimens were centrifuged in serum separator tubes and shipped to CDC for processing. All serum specimens were tested by enzyme-linked immunosorbent assay (ELISA) for presence of antiorthopoxvirus IgG. Those specimens with detectible IgG or from participants who reported higher mpox risk behaviors (sex work, multiple sexual partners, and persons assigned male at birth who identified as gay, bisexual, or transgender), were tested for IgM (*5*). Possible undetected mpox infection was defined as 1) detectable antiorthopoxvirus IgG (optical density minus cutoff value [OD-COV] ≥0.1) in a participant aged <50 years without reported smallpox

[*] These authors contributed equally to this report.

[†] 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.

or mpox vaccination or 2) detectable antiorthopoxvirus IgM (OD-COV ≥0.1) in a participant without reported mpox vaccination. Possible undetected infections identified by IgG testing were restricted to persons aged <50 years to avoid inclusion of participants who received smallpox vaccine during childhood. Participants who reported unknown vaccination history or previous mpox infection were not included as having possible undetected mpox infections. Descriptive analyses were performed, and outcomes were reported by vaccination history and serologic results.

The CDC field team recruited 284 participants from 16 unique sites (seven shelters, five service centers, two supportive housing locations, and two encampments); 11 (4%) participants were excluded from analysis because they reported living in their own private residence without accessing homeless services during the preceding month. Among the remaining 273 participants, 240 (88%) consented to blood collection, and blood was successfully collected from 209 (77%) (Table 1). Average participant age was 46 years; 69% reported male sex at birth, 59% reported male gender, and 9% were transgender. Most (77%) were heterosexual. The highest proportion of participants was non-Hispanic White (38%), followed by non-Hispanic Black or African American (32%); 70% were non-Hispanic. The most common recruitment sites were shelters (46%), followed by homeless service sites (33%).

A total of 207 participants were included in serologic analysis, after exclusion of two participants (1%) who reported both previous mpox infection and mpox vaccination (Table 2). Among these participants, 82 (40%) reported previous vaccination against smallpox, mpox, or both, including 50 (24%) who reported only smallpox vaccination, 22 (11%) who reported only mpox vaccination, and 10 (5%) who reported both. Neither smallpox nor mpox vaccination was reported by 117 (60%) participants; vaccination status of eight (4%) was unknown. Among the 32 participants who reported any mpox vaccination, 26 (81%) reported receiving 1 dose, and six (19%) reported receiving 2 doses.

Among 50 participants who reported only smallpox vaccination, antiorthopoxvirus IgG was detected in 19 (38%) and IgM in one (3%). Among 22 participants who reported only mpox vaccination, antiorthopoxvirus IgG was detected in 12 (55%) and IgM in four (21%). Among 80 participants aged <50 years who did not report smallpox or mpox vaccination, two (3%) had detectable antiorthopoxvirus IgG. Among 68 participants without reported mpox vaccination who were tested for antiorthopoxvirus IgM, one (1.5%) had detectable antibodies. These results yielded a total of three possible undetected mpox infections.

TABLE 1. Characteristics of persons experiencing homelessness or accessing homeless services who participated in an mpox seroprevalence survey (N = 209) — San Francisco, California, October–November 2022

Characteristic	No. (%)
Mean age, yrs (range)	46 (19–83)
Sex at birth	
Female	61 (29.2)
Male	145 (69.4)
Intersex	<5.0†
Unknown*	<5.0†
Gender	
Cisgender man	124 (59.3)
Cisgender woman	63 (30.1)
Nonbinary	<5.0†
Transgender man	0 (—)
Transgender woman§	19 (9.1)
Unknown*	0 (—)
Sexual orientation	
Bisexual	22 (10.5)
Gay or lesbian	14 (6.7)
Heterosexual	160 (76.6)
Pansexual	<5.0†
Unknown*	<5.0†
Other	8 (3.8)
Race	
American Indian or Alaska Native	10 (4.8)
Asian	9 (4.3)
Black or African American	66 (31.6)
Native Hawaiian or other Pacific Islander	<5.0†
White	80 (38.3)
Multiracial or other	38 (18.2)
Unknown*	5 (2.4)
Hispanic origin	
Hispanic or Latino	59 (28.2)
Non-Hispanic	147 (70.3)
Unknown*	3 (1.4)
Type of recruitment site	
Encampment	16 (7.7)
Permanent supportive housing	30 (14.3)
Service center	68 (32.5)
Shelter	95 (45.5)

* Survey responses were indicated as unknown if the participant declined to answer the question or answered that they did not know.

† The specific value for any cell with fewer than five participants is suppressed in accordance with data standards for the San Francisco Department of Public Health and are indicated within the cell as <5.0.

§ Among the 19 participants who identified as transgender women, 11 indicated that they were sexually oriented toward men (heterosexual), seven indicated that they were bisexual, gay or lesbian, or pansexual, and one declined to answer.

None of these three participants reported sexual contact during the preceding month, being transgender, being a gay or bisexual man, or having a rash at the time of the survey (Table 3). Among the three participants with possible undetected mpox infection, two reported that during the previous month they had shared unwashed utensils, spent time around and touched someone with a rash, and shared smoking devices.

TABLE 2. Self-reported smallpox and mpox vaccination history and antiorthopoxvirus serology results among persons experiencing homelessness or accessing homeless services, who participated in an mpox seroprevalence survey — San Francisco, California, October–November 2022

Self-reported vaccination history*	No. (row %)			
	All participants	IgG-positive result†,§	Received IgM test§	IgM-positive result†,¶
All participants	**207 (100.0)**	**48 (23.2)**	**102 (48.8)**	**5 (4.9)**
Any smallpox or mpox vaccination	**82 (39.6)**	38 (46.3)	60 (73.2)	5 (8.3)
Only smallpox vaccination	**50 (23.9)**	19 (38.0)	31 (62.0)	1 (3.2)
Only mpox vaccination	**22 (11.5)**	12 (54.5)	19 (86.3)	4 (21.1)
Both smallpox and mpox vaccination	**10 (4.8)**	7 (70.0)	10 (100.0)	0 (—)
Unknown vaccination history	**8 (3.8)**	2 (25.0)	5 (62.5)	0 (—)
No smallpox or mpox vaccination	**117 (56.0)**	10 (8.5)	37 (31.6)	0 (—)
No mpox vaccination	**167 (80.7)**	27 (16.1)	68 (40.4)	1 (1.5)
Age >50 yrs, no smallpox vaccination	**37 (17.7)**	8 (21.6)	17 (45.9)	0 (—)
Age ≤50 yrs, no smallpox or mpox vaccination	**80 (38.6)**	2 (2.5)	24 (30.0)	0 (—)

Abbreviations: IgG = immunoglobulin G; IgM = immunoglobulin M.
* Categories are not mutually exclusive.
† Optical density minus cutoff value ≥0.1.
§ Percentage of those with self-reported vaccination history.
¶ Percentage of participants who received antiorthopoxvirus IgM testing.

Discussion

Among 207 persons who were experiencing homelessness or accessing homeless services in San Francisco and voluntarily participated in an antiorthopoxvirus seroprevalence survey during a large multinational mpox outbreak, three possible undetected mpox infections were detected. Mpox infections might be undetected because of subclinical, atypical, or mild disease or because of barriers to seeking or accessing health care systems, which could have occurred among the participants in this survey. None of the participants with possible undetected mpox infections reported sexual contact during the preceding month, although some reported sharing utensils and smoking devices and spending time around or touching someone with a rash. However, the timing of mpox exposure among these three persons is not known and could have preceded the survey period. The transmission route for the three possible undetected mpox infections could not be determined; additional studies are needed to identify mpox transmission pathways among persons experiencing homelessness. In the current outbreak, mpox has primarily spread through sexual activity but can be spread through touching contaminated objects and through close personal contact outside of sexual activity, although this risk is considered to be lower (*6*).

Previous mpox vaccination was reported by 16% of survey participants. However, only 54% of participants reporting mpox vaccination had detectable antiorthopoxvirus IgG, and 21% had detectable IgM. A 2-dose mpox vaccination series is recommended to optimize immunity (*7*). Most participants who received mpox vaccine reported receiving a single dose, which might in part explain the lower seroprevalence (*2*,*7*). SFDPH and community partners collaborated to conduct pop-up vaccination events in San Francisco during September–December 2022 for persons experiencing homelessness; this active outreach approach can be further leveraged to better facilitate complete vaccination for eligible persons. A single mpox vaccine dose might still offer some protection against severe mpox-associated illness and hospitalization, for which persons experiencing homelessness (*1*,*7*,*8*) might be at higher risk.

The findings in this report are subject to at least seven limitations. First, participants were recruited as a convenience sample at prioritized locations; therefore, the findings are not generalizable to the entire population of persons experiencing homelessness or accessing homeless services in San Francisco. Second, the sample size was small because of time and resource limitations as well as logistical challenges associated with collecting blood samples from persons in encampments and at homeless service sites (*9*). Third, because of the small numbers of participants with potential undetected infection, statistical analyses could not be conducted to further refine possible transmission routes. Fourth, the survey ascertained frequency of behaviors during the preceding month to improve recall; however, it was not possible to determine whether behaviors that would increase mpox transmission risk were present outside that time frame. Fifth, the orthopoxvirus ELISA does not detect antibodies specific to *Monkeypox virus*; therefore, previous or acute mpox infection among the participants could not be distinguished from other orthopoxvirus infections or previous vaccination. Sixth, the survey relied on self-reported vaccination history and behaviors, which can be subject to recall and social desirability biases. Finally, it is possible for antibody testing to produce false-positive results. Efforts to improve specificity of possible mpox infection included restricting IgG results to persons aged <50 years to avoid inclusion of participants who received childhood smallpox vaccine,

TABLE 3. Behaviors reported during the preceding month, by persons experiencing homelessness or accessing homeless services, who participated in an mpox seroprevalence survey* — San Francisco, California, October–November 2022

Behavior and frequency	No. (%) All participants (N = 209)	No. (%) Possible undetected mpox infection† (n = 3)
Shared unwashed cups, spoons, or forks		
Never	**152 (72.7)**	1 (33.3)
A few times	**34 (16.3)**	2 (66.7)
Nearly every day	**8 (3.8)**	0 (—)
Every day	**15 (7.2)**	0 (—)
Unknown§	**0 (—)**	0 (—)
Shared unwashed clothing or bedding		
Never	**164 (78.5)**	3 (100.0)
A few times	**22 (10.5)**	0 (—)
Nearly every day	**7 (3.3)**	0 (—)
Every day	**16 (7.7)**	0 (—)
Unknown§	**0 (—)**	0 (—)
Shared unwashed personal care items¶		
Never	**185 (88.5)**	3 (100.0)
A few times	**15 (7.2)**	0 (—)
Nearly every day	**3 (1.4)**	0 (—)
Every day	**6 (2.9)**	0 (—)
Unknown§	**0 (—)**	0 (—)
Spent time around someone with a rash, lesion, or sore		
Never	**175 (83.7)**	1 (33.3)
A few times	**22 (10.5)**	2 (66.7)
Nearly every day	**5 (2.4)**	0 (—)
Every day	**7 (3.3)**	0 (—)
Unknown§	**0 (—)**	0 (—)
Touched someone with a rash, lesion, or sore		
Never	**195 (93.3)**	1 (33.3)
A few times	**10 (4.8)**	2 (66.7)
Nearly every day	**1 (<1.0)**	0 (—)
Every day	**2 (1.0)**	0 (—)
Unknown§	**1 (<1.0)**	0 (—)
Had a rash, lesion, or sore at the time of survey		
No	**181 (86.6)**	3 (100.0)
Yes	**28 (13.4)**	0 (—)
Unknown§	**0 (—)**	0 (—)
Injected drugs**		
Never	**160 (76.6)**	3 (100.0)
A few times	**16 (7.7)**	0 (—)
Nearly every day	**10 (4.8)**	0 (—)
Every day	**20 (9.6)**	0 (—)
Unknown§	**3 (1.4)**	0 (—)
Shared smoking devices††		
Never	**84 (40.2)**	1 (33.3)
A few times	**60 (28.7)**	1 (33.3)
Nearly every day	**16 (7.7)**	1 (33.3)
Every day	**47 (22.5)**	0 (—)
Unknown§	**2 (1.0)**	0 (—)
Had vaginal, anal, or oral sex		
No	**111 (53.1)**	3 (100.0)
Yes	**91 (43.5)**	0 (—)
Unknown§	**7 (3.3)**	0 (—)
Engaged in sex work§§		
No	**187 (89.5)**	3 (100.0)
Yes	**14 (6.7)**	0 (—)
Unknown§	**8 (3.8)**	0 (—)
Where slept most often		
Friend or family's house	**9 (4.3)**	1 (33.3)
Hotel or motel	**2 (1.0)**	0 (—)
Private residence	**12 (5.7)**	0 (—)
Permanent supportive housing	**37 (17.7)**	0 (—)
Shelter or navigation center	**99 (47.4)**	2 (66.7)
Unsheltered	**46 (22.0)**	0 (—)
Other	**2 (1.0)**	0 (—)
Unknown§	**2 (1.0)**	0 (—)

Abbreviations: IgG = immunoglobulin G; IgM = immunoglobulin M.

* Most surveys (198; 94.7%) were conducted in English, 10 (4.8%) in Spanish, and one (0.5%) in Mandarin.

† Possible undetected mpox infection was defined as detectable antiorthopoxvirus IgG antibody in a specimen from a person who did not report smallpox or mpox vaccination and was born after 1972 (aged <50 years), or in a specimen from a person with detectable antiorthopoxvirus IgM antibody who did not report mpox vaccination.

§ Survey responses are marked as unknown if the participant declined to answer the question or answered that they did not know.

¶ Based on response to the question, "In the last month have you shared unwashed personal care items (razors, toothbrushes, hairbrushes, etc.)?"

** Based on response to the question, "In the last month did you shoot up or inject any drugs - by shooting up, we mean using drugs with a needle, either by hitting a vein, skin popping, or muscling?"

†† Based on response to the question, "Have you shared bubbles/vapes/bongs/pipes/other smoking devices in the last month?"

§§ Based on responses to the following questions: 1) "Do you consider yourself to be a sex worker?" and 2) "In the last month did you have sex for money, drugs, food, housing, or other life needs?" Participants were classified as engaging in sex work if they responded affirmatively to either question.

asking about previous military service to avoid inclusion of participants who received smallpox vaccination in the service, and using a higher OD-COV in ELISA tests to reduce risk for false-positive results (*5*,*10*). However, participants close to the cutoff age of 50 years could have received childhood smallpox vaccine, as was the case of one participant without reported vaccination history who had detectable antiorthopoxvirus IgG.

These findings suggest that undetected mpox infections might have occurred among a small percentage of persons experiencing homelessness in San Francisco. It is still unknown whether unique mpox transmission pathways exist for persons experiencing homelessness. However, given that known and possible undetected mpox transmission occurred, and that severe mpox disease among persons experiencing homelessness is possible (*1*), accessible prevention measures are needed. Prioritization and inclusion in public health response planning, focused outreach, and on-site vaccination events can ensure that prevention measures reach persons experiencing homelessness.

Summary

What is already known about this topic?

During the 2022 multinational outbreak of monkeypox (mpox), transmission occurred primarily through skin-to-skin contact, including through sex. Persons experiencing homelessness have been disproportionately affected by severe mpox.

What is added by this report?

Among 209 surveyed persons accessing homeless services or staying in encampments in San Francisco, California, without self-reported vaccination or reported previous mpox infection during October 25–November 3, 2022, three had detectable antiorthopoxvirus immunoglobulin (Ig) G or IgM, consistent with possible undetected mpox infection.

What are the implications for public health practice?

Possible undetected mpox among persons experiencing homelessness during the 2022 mpox outbreak highlights the need for tailored outreach strategies that ensure interventions such as prevention messaging and vaccination reach persons experiencing homelessness.

Acknowledgments

Specimen Receiving Team, San Francisco Public Health Laboratory; participants described in this report and the community-based organizations or agencies that provided services for them; CDC Foundation; Lina Castro, Darlene Daevu, Thomas Knoble, Godfred Masinde, Mary Mercer, Frank Strona, Andi Tenner, Mpox Response Team, San Francisco Department of Public Health; San Francisco Department of Homelessness and Supportive Housing; Whole Person Integrated Care Street Medicine and Shelter Health teams, San Francisco Department of Public Health; Darpun Sachdev, California Department of Public Health; Ninnie Wynn, CDC Laboratory and Testing Task Force.

Corresponding authors: Emily Mosites, lwx7@cdc.gov; Grace Marx, lwx1@cdc.gov.

[1]CDC Mpox Emergency Response Team; [2]Epidemic Intelligence Service, CDC; [3]San Francisco Department of Public Health, San Francisco, California.

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

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Interim Clinical Treatment Considerations for Severe Manifestations of Mpox — United States, February 2023

Agam K. Rao, MD[1]; Caroline A. Schrodt, MD[1]; Faisal S. Minhaj, PharmD[1,2]; Michelle A. Waltenburg, DVM[3]; Shama Cash-Goldwasser, MD[2]; Yon Yu, PharmD[4]; Brett W. Petersen, MD[1]; Christina Hutson, PhD[1]; Inger K. Damon, MD, PhD[3]

Monkeypox (mpox) is a disease caused by infection with *Monkeypox virus* (MPXV), an *Orthopoxvirus* (OPXV) in the same genus as *Variola virus*, which causes smallpox. During 2022, a global outbreak involving mpox clade IIb was recognized, primarily among gay, bisexual, and other men who have sex with men.* Most affected patients have been immunocompetent and experienced ≤10 rash lesions (*1*). CDC has recommended supportive care including pain control.† However, some patients have experienced severe mpox manifestations, including ocular lesions, neurologic complications, myopericarditis, complications associated with mucosal (oral, rectal, genital, and urethral) lesions, and uncontrolled viral spread due to moderate or severe immunocompromise, particularly advanced HIV infection (*2*). Therapeutic medical countermeasures (MCMs) are Food and Drug Administration (FDA)–regulated drugs and biologics that are predominantly stockpiled by the U.S. government; MCMs developed for smallpox preparedness or shown to be effective against other OPXVs (i.e., tecovirimat, brincidofovir, cidofovir, trifluridine ophthalmic solution, and vaccinia immune globulin intravenous [VIGIV]) have been used to treat severe mpox. During May 2022–January 2023, CDC provided more than 250 U.S. mpox consultations. This report synthesizes data from animal models, MCM use for human cases of related OPXV, unpublished data, input from clinician experts, and experience during consultations (including follow-up) to provide interim clinical treatment considerations. Randomized controlled trials and other carefully controlled research studies are needed to evaluate the effectiveness of MCMs for treating human mpox. Until data gaps are filled, the information presented in this report represents the best available information concerning the effective use of MCMs and should be used to guide decisions about MCM use for mpox patients.

During May 2022, a global mpox outbreak was identified. A CDC clinical team began providing consultations§ to U.S. clinicians caring for patients with mpox, developing guidance and other online clinical resources for health care providers, and issuing health alerts¶ when emerging clinical concerns (e.g., severe infections in patients with advanced HIV infection) were detected. Before the 2022 outbreak, CDC experts in poxviruses and associated MCMs had evaluated efficacy data from animal models and reports of MCM use for a few human cases of related OPXV infections (e.g., vaccinia virus and cowpox virus). This information and unpublished data shared by intergovernmental partners guided initial clinical consultations; as more knowledge was acquired through clinical consultations, many of which involved repeated consultations and regular follow-up, CDC's approach to mpox cases was refined. Recurrent questions that would benefit from expert input were identified (e.g., management of ocular infections); input was solicited from external experts in infectious diseases (including HIV), immunology, neurology, ophthalmology, dermatology, and public health emergency response. Identified experts included leaders of professional societies and physicians experienced in treating mpox during the current outbreak. Partners from the Public Health Emergency Medical Countermeasures Enterprise,** a U.S. intragovernmental committee that optimizes preparedness for public health emergencies (e.g., through developing and stockpiling available MCMs), were also consulted. This report is a comprehensive synthesis of the compiled evidence and is intended to foster strategic decision-making rather than serve as a prescriptive treatment guideline. Clinical considerations were developed in the context of limited data about MCM effectiveness during the current outbreak, finite supplies of some MCMs (e.g., VIGIV and intravenous [IV] tecovirimat), and a need to incorporate evolving data and clinical observations into guidance that can be used to manage cases, including in future months if case counts increase. The rationale for specific guidance is included.

* https://www.cdc.gov/poxvirus/monkeypox/index.html
† https://www.cdc.gov/poxvirus/monkeypox/clinicians/pain-management.html
§ CDC offered an mpox clinical consultation service for the ongoing mpox outbreak. The existence of this service was widely publicized during CDC Clinician Outreach and Communication Activity calls, CDC's Health Alert Network messages, national conference presentations, and other communications. Health care providers seeking clinical consultations can continue to contact CDC mpox experts through the CDC Emergency Operations (770-488-7100) or by email (poxvirus@cdc.gov).
¶ https://emergency.cdc.gov/han/2022/han00475.asp
** https://aspr.hhs.gov/phemce/Pages/goals.aspx

MCMs Being Used to Treat Mpox and Indications for Use

MCMs for OPXV infections include antivirals (i.e., tecovirimat, brincidofovir, cidofovir, and trifluridine ophthalmic solution) and VIGIV. Tecovirimat, brincidofovir, and VIGIV are recommended based on efficacy data from experimental animal models involving exposure to diverse OPXVs (i.e., variola, mpox, vaccinia, ectromelia, and rabbitpox viruses), albeit via the respiratory route, which is different from the close skin and mucosal contact associated with the ongoing mpox outbreak. Cidofovir and trifluridine ophthalmic solution are recommended because of their successful use treating other viral infections; cidofovir is also recommended based on data on the effectiveness of brincidofovir. All four antivirals were sporadically used to treat severe manifestations of human OPXV infections before the 2022 global outbreak (*3*–*7*); VIGIV has been used to treat adverse events from live, replicating vaccinia virus vaccines that are licensed to prevent smallpox (e.g., progressive vaccinia after receipt of Dryvax[§§] or ACAM2000[¶¶]), and was used to treat smallpox disease before its 1980 worldwide eradication (*8*–*11*). Despite this real-world use, it is not known how often MCMs were associated with favorable outcomes and whether clinical improvements were due to MCMs, natural resolution of illness, or a combination of these.

MCMs have been widely used during the 2022 outbreak. As of February 2023, tecovirimat and VIGIV continue to be available through CDC-sponsored expanded access Investigational New Drug (IND) protocols; brincidofovir through an FDA–authorized single-patient emergency use IND; and cidofovir and trifluridine, commercially. To date, no data have shown whether MCMs are beneficial, including for pain control (irrespective of severity). Most persons recover with supportive care alone (including pain control[***]). MCMs (particularly tecovorimat) used without close monitoring could result in suboptimal drug levels and promote drug resistance,[†††] thereby reducing its effectiveness for the individual patient and others. In addition, the effectiveness of MCMs for the treatment of mpox has not been systematically evaluated. For these reasons, CDC strongly encourages enrollment in clinical trials (e.g., the National Institutes of Health (NIH)–funded Study of Tecovirimat for Human Mpox [STOMP] trial).[§§§]

Severe mpox might manifest as hemorrhagic disease, many confluent or necrotic lesions, severe necrotizing or obstructive lymphadenopathy (e.g., of the upper airway), obstructive edema (e.g., of the gastrointestinal tract), extradermatologic manifestation (e.g., pulmonary nodules, encephalitis, myopericarditis, and ocular infections), and sepsis (*12*). Some patients might not have severe mpox at the time of first health care interaction but are at risk for severe mpox because of underlying medical condition (e.g., severe or moderate immunocompromise)[¶¶¶] or presence of lesions on certain surfaces (e.g., penile foreskin, urethral meatus, or vulva). These might predispose patients to complications such as strictures or edema which could require procedures including urethral catheterization, colostomy, or surgical debridement. MCMs should be considered in these cases irrespective of patient immune status. Children and adolescents aged <18 years and pregnant persons have accounted for a small percentage (<0.3%) of total U.S. cases during the current outbreak, and when affected, have experienced mild illness (*13*,*14*); however, because these populations (particularly children aged <8 years) have historically experienced more severe clade I mpox infections, and because outcomes in pregnant women and neonates during the current outbreak might not be known for several months, case-by-case consideration of MCMs should be undertaken after weighing the potential benefits and harms.[****] Other populations might also benefit from case-by-case consideration of MCM use. Persons with a history of atopic dermatitis and eczema (both well-controlled and not) might experience uncontrolled viral spread, possibly as a result of associated defects in the innate or adaptive immune response (*15*). Persons with extensive breaks in the dermal barrier (e.g., from burns, impetigo, varicella zoster virus infections, herpes simplex virus infection, severe acne, severe diaper dermatitis with extensive denuded skin, psoriasis, and Darier disease [keratosis follicularis]) might also be at risk for severe manifestations of uncontrolled viral spread depending on the severity of the underlying condition (*16*).

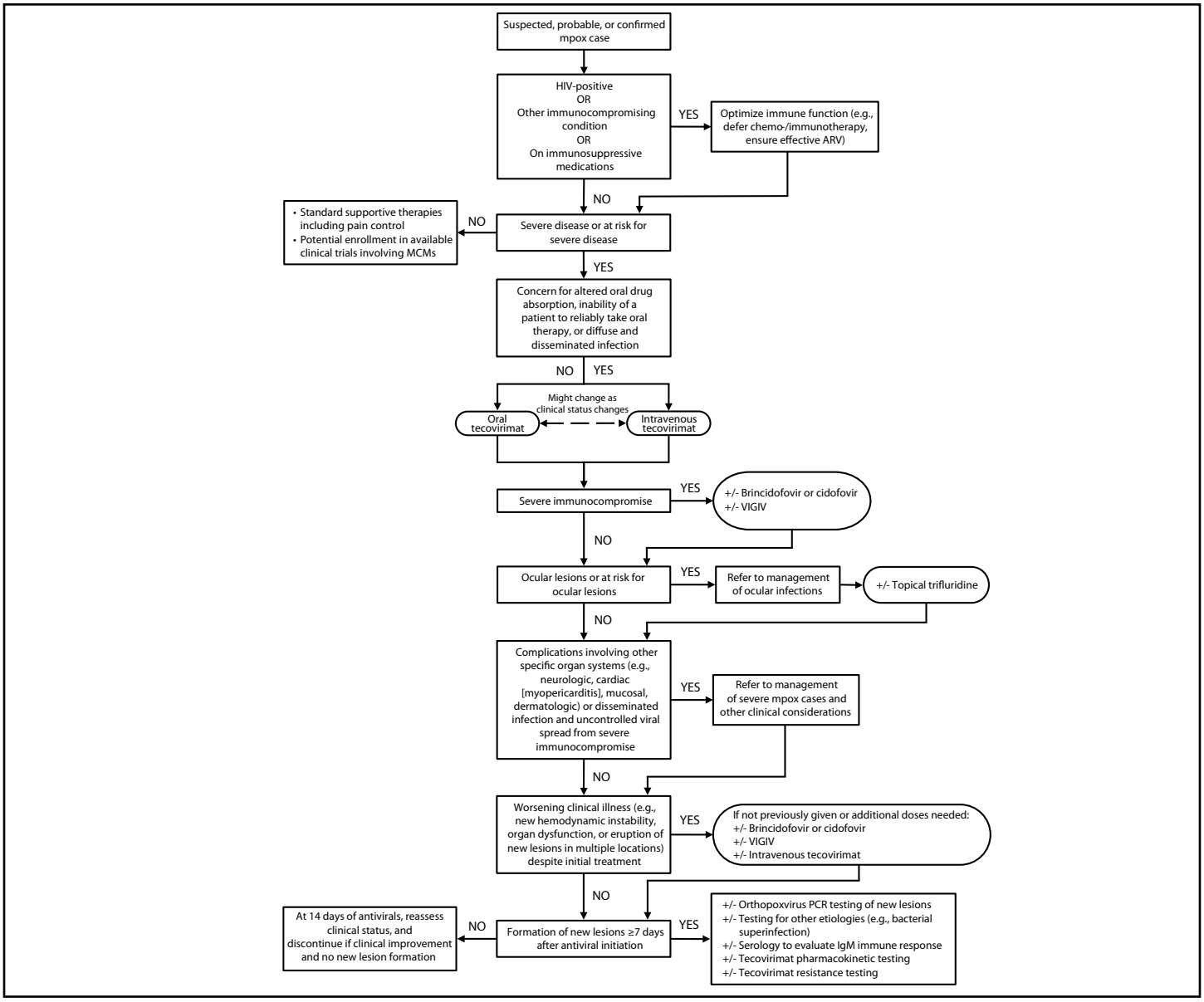
Approach to Using MCMs to Treat Mpox

Through iterative consultations, a management algorithm outlining the approach to patients with suspected, probable, or confirmed mpox has been developed to aid in decision-making regarding the earliest use of effective MCMs when indicated (Figure). Coinfections (e.g., with syphilis, herpes simplex, varicella zoster, or molluscum contagiosum) should be considered. All patients with suspected mpox should be evaluated for preexisting immunocompromising conditions and be tested for

[††] https://www.cdc.gov/poxvirus/monkeypox/about/science-behind-transmission.html
[§§] http://web.archive.org/web/20060117201021/http://www.fda.gov/cber/label/smalwye102502LB.pdf
[¶¶] https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert---ACAM2000.pdf
[***] https://www.cdc.gov/poxvirus/monkeypox/clinicians/pain-management.html
[†††] https://emergency.cdc.gov/han/2022/han00481.asp
[§§§] https://www.stomptpoxx.org/main

[¶¶¶] https://www.cdc.gov/poxvirus/monkeypox/clinicians/people-with-HIV.html
[****] https://www.cdc.gov/poxvirus/monkeypox/clinicians/pediatric.html; https://www.cdc.gov/poxvirus/monkeypox/clinicians/pregnancy.html

FIGURE. Approach to treatment*,†,§ of patients with severe¶ or at risk for severe manifestations of mpox†† — United States, February 2023§§**



Abbreviations: ARV = antiretroviral medications; GI = gastrointestinal; IgM = immunoglobulin M; MCM = medical countermeasure; PCR = polymerase chain reaction; VIGIV = vaccinia immune globulin intravenous.

* Treatment includes MCMs (i.e., tecovirimat, brincidofovir, cidofovir, VIGIV, and trifluridine) and supportive therapies, including pain management. https://www.cdc.gov/poxvirus/monkeypox/clinicians/pain-management.html

† Most immunocompetent patients should display signs of clinical improvement within 4 days of antiviral initiation (i.e., tecovirimat, brincidofovir, cidofovir, and trifluridine). Tecovirimat is expected to reach steady state concentrations by day 6 of dosing in healthy volunteers; therefore, worsening clinical illness after 7 days of treatment in patients with severe illness could prompt additional evaluations.

§ Concern for altered drug absorption includes the inability to tolerate or take oral therapy (e.g., nothing by mouth), or possibility that the oral drug absorption might be altered because of inability to consume a high-fat meal, severity of symptoms (e.g., systemic illness), comorbidities (e.g., history of gastric bypass or underlying GI disease), or other factors that might alter oral drug absorption.

¶ Hemorrhagic disease, a large number of confluent or necrotic lesions, severe lymphadenopathy that is necrotizing or obstructing (e.g., of the upper airway causing airway compromise or of the GI tract necessitating parenteral feeding), edema that is obstructing (e.g., of the lower GI tract), extradermatologic manifestations (e.g., pulmonary nodules, encephalitis, myopericarditis, or ocular infections), and sepsis. Detailed characteristics of severe disease are available at https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html#anchor_1655488137245.

** Persons with underlying medical conditions (e.g., severe or moderate immunocompromise [https://www.cdc.gov/poxvirus/monkeypox/clinicians/people-with-HIV.html]); bacterial superinfections; or complications including strictures, edema, and infections of the penile foreskin, vulva, urethral meatus, or anorectum, which could require procedural intervention (e.g., urethral catheterization, colostomy, or surgical debridement). This also includes those with or at risk for ocular lesions (i.e., presence of eyelid lesions, facial lesions near the eyes, or finger or hand lesions in patients unable to avoid touching their eyes [for whom autoinoculation is a concern]). Detailed characteristics of persons at risk for severe disease are available at https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html#anchor_1655488137245.

†† https://www.cdc.gov/poxvirus/monkeypox/clinicians/case-definition.html

§§ This figure is a comprehensive synthesis of heterogeneous evidence and is intended to foster strategic decision-making rather than serve as a prescriptive treatment guideline.

HIV. No antiviral MCMs for use against OPXVs are virucidal, and optimal immune function is essential to recovery, irrespective of whether multiple MCMs are administered. Antiviral MCMs might complement the immune response by reducing replication, maturation, or spread of OPXVs. VIGIV might provide some level of passive immunity to certain patients with moderate or severe immunocompromise until a patient's immune system is able to clear the virus. However, earliest optimization of immune function (e.g., by temporarily delaying or decreasing doses of chemotherapy and immunomodulatory therapies and by promptly initiating effective antiretroviral medications [ARVs] for treatment of HIV) is critical to favorable outcomes. Since August 2022, consultations with CDC have involved a large proportion of immunocompromised persons, particularly those with HIV and low CD4 cell counts (*12*). Comprehensive information about each MCM, including mechanism of action, safety, efficacy, and dosing should be reviewed along with the management algorithm when deciding about administration or cessation of MCMs (Table). Interactions with other medications including ARVs should also be considered (*17*).

Tecovirimat. Tecovirimat is administered two to three times daily (depending upon patient's weight), typically for 2 weeks. Based on the favorable safety and efficacy profile of tecovirimat compared with other MCMs, if only one MCM is administered, it should be tecovirimat, unless there is a contraindication such as a previous adverse event after receiving the drug. The pharmacokinetics of orally administered tecovirimat taken with a fatty meal compare favorably with those of IV tecovirimat. IV tecovirimat (which is currently available in limited supply) should be prioritized for patients who are unable to take oral medications or fatty meals with each dose, have gastrointestinal disease that might impair absorption (e.g., new or chronic diarrhea), or have diffuse and disseminated infection.[††††] For patients for whom IV tecovirimat is indicated, prepositioned oral tecovirimat should be administered until the IV formulation is obtained.

Patients with severe immunocompromise might benefit from extended treatment (i.e., >14 days) if new confirmed OPXV lesions occur or existing lesions worsen despite treatment. Data from animal studies suggest it might be safe to extend tecovirimat treatment (*18*). Clinicians should carefully consider the risks and benefits of extending treatment, and extensions of short, defined intervals should be used (e.g., an additional 3–7 days) with close monitoring for safety signals and clinical response. Tecovirimat resistance has been detected in a small number of patients with advanced HIV who received tecovirimat for periods of weeks to months (*19*). Resistance can also develop as the result of subtherapeutic levels of tecovirimat (e.g., because of medication noncompliance or because fatty meals are not taken with the oral formulation). Testing for tecovirimat resistance and pharmacokinetics[§§§§] for public health surveillance purposes is encouraged when any new lesions form after ≥7 days of treatment.

Brincidofovir and cidofovir. One of these drugs can be added to tecovirimat treatment for patients with (or at risk for) severe mpox. They are usually administered once weekly for 2 weeks. One animal study suggests that combined treatment (tecovirimat and brincidofovir, the prodrug of cidofovir) might have synergistic efficacy (*20*). Brincidofovir or cidofovir without tecovirimat should typically only be administered to patients in whom tecovirimat is contraindicated. Brincidofovir and cidofovir should not be used simultaneously or within 1 week of one another, because they form the same active metabolite (cidofovir diphosphate), which has a prolonged duration of action. Both drugs have FDA black box warnings and other safety considerations that require close monitoring. Diarrhea has been commonly reported in patients who receive brincidofovir[¶¶¶¶]; diarrhea of any etiology might impair absorption of orally administered tecovirimat and indicate a need for IV tecovirimat. In vitro studies suggest that brincidofovir might have superior antiviral activity to that of cidofovir against variola virus, likely because of better cellular uptake (*21*,*22*); however, because data are limited, side effect profiles should be prioritized when choosing between the two drugs. Development of resistance to brincidofovir or cidofovir is less likely to occur than is resistance to tecovirimat (*23*,*24*).

VIGIV. VIGIV administered as a single dose provides passive immunoglobulin (Ig) G antibodies against vaccinia virus, which might provide some cross-protection across the OPXV genus, including for MPXV. During the current outbreak, it has been recommended for mpox patients unable to mount a sufficiently robust immune response to clear the virus (e.g., because of HIV-related CD4 count <350 or after solid organ transplantation). Although its effectiveness for mpox is unknown, the safety profile is believed to be favorable; however, caution should be exercised when administering VIGIV to patients with ocular mpox involving the cornea because of a report of an animal study of vaccinia keratitis in which VIGIV was associated with persistent corneal scarring (*25*,*26*). VIGIV is available in limited supply. Subsequent dosing (i.e.,

[††††] https://www.cdc.gov/poxvirus/monkeypox/clinicians/obtaining-tecovirimat.html

[§§§§] https://www.cdc.gov/poxvirus/monkeypox/pdf/attachment-5-optional-pk-sample-testing.pdf

[¶¶¶¶] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000,214461s000lbl.pdf

TABLE. Summarized mechanisms of action, administration recommendations, adverse events, clinical considerations, and supporting data about medical countermeasures that can be used to treat mpox*— United States, February 2023

Consideration	Medical countermeasures				
	Tecovirimat (Tpoxx or ST-246)	**Brincidofovir (Tembexa or CMX001)**	**Cidofovir (Vistide)**	**VIGIV**	**Trifluridine (Viroptic)**
Description	An OPXV-specific antiviral with limited activity against unrelated RNA or DNA viruses	Lipid-conjugated analog of cidofovir with different properties compared with cidofovir	Monophosphate nucleotide analog used to treat viral infections including cytomegalovirus	Solvent- or detergent-treated, filtered sterile solution of purified immune globulin from human plasma of persons with antibodies to vaccinia virus	Nucleoside analog used to treat ocular viral infections including herpes simplex virus keratitis
Mechanism of action against OPXVs	Inhibits association of VP37 (a protein encoded by and highly conserved across the OPXV genus) with a cellular protein, preventing formation of egress-competent envelope virions necessary for cell-to-cell dissemination of virus	Once inside cells, the lipid ester linkage is cleaved to form cidofovir, which is then converted to CDP, which selectively inhibits OPXV DNA polymerase.	Intracellularly converted to CDP which selectively inhibits OPXV DNA polymerase	Provides passive antibody which might have cross-reactivity across the OPXV genus	Thymidine analog that interferes with DNA synthesis in cultured mammalian cells with selective toxicity to viral replication of OPXVs
Dose	600 mg†	200 mg§	5 mg/kg	6,000–9,000 units/kg¶	One drop into affected eyes
Route	Oral (capsules) or IV**	Oral (tablets or suspension)	IV	IV	Topical
Frequency	Twice daily (40 kg to <120 kg) Three times daily (>120 kg)	Once weekly	Once weekly	Single dose but can be repeated depending on duration of illness and severity of immunocompromise	Every 2 hrs when awake for the first 2 wks (maximum nine drops per eye per day) Then, four times daily for an additional 2 wks
Duration	2 wks unless indication to prolong††	2 wks unless indication to prolong††	2 wks unless indication to prolong††	NA	>4 wks
Potential adverse events	Headache, nausea, diarrhea, itching, and abdominal pain; labeled contraindication for IV administration when creatinine clearance is <30 mL/min§§	Abdominal pain, diarrhea, nausea, vomiting, and elevated liver enzymes	Nephrotoxicity, nausea, vomiting, and acidosis	Adverse events associated with infusion of immunoglobulins (e.g., headache, diaphoresis, erythema, anaphylaxis, thrombosis, acute kidney injury, and volume overload)	Adverse events associated with topical use (e.g., burning, stinging, or eyelid edema)
Warnings	Other warnings: Clearance of hydroxypropyl-β-cyclodextrin is dependent on glomerular filtration, and caution is advised in patients with mild to moderate renal impairment, and in pediatric patients <2 yrs.	BBW: Increased mortality seen in a 24-wk placebo-controlled trial for CMV prophylaxis in hematopoietic stem-cell transplant recipients. Prolonging therapy beyond 2 wks should be considered with caution, and currently requires FDA authorization on an individual patient basis through an emergency IND request. Other warnings: Neutropenia Potential human carcinogen, teratogen, and causing hypospermia	BBW: Severe nephrotoxicity resulting in dialysis or contributing to death. IV prehydration and administration of probenecid must be used with each infusion. Neutropenia Potential human carcinogen, teratogen, and causing hypospermia Other warnings: Decreased intraocular pressure, metabolic acidosis	Other warnings: Hypersensitivity, renal dysfunction, interference with blood glucose testing, thrombotic events, aseptic meningitis syndrome, hemolysis, transfusion-related acute lung injury, and transmission of infectious agents from human plasma	Other warnings: Continuous administration beyond the recommended duration might cause corneal epithelial toxicity.

See table footnotes on page 238.

TABLE. (*Continued*) Summarized mechanisms of action, administration recommendations, adverse events, clinical considerations, and supporting data about medical countermeasures that can be used to treat mpox*— United States, February 2023

Consideration	Medical countermeasures				
	Tecovirimat (Tpoxx or ST-246)	Brincidofovir (Tembexa or CMX001)	Cidofovir (Vistide)	VIGIV	Trifluridine (Viroptic)
Drug interactions	Might reduce levels of NNRTI rilpivirine Might increase concentration of blood glucose-lowering agent repaglinide Decrease concentration of midazolam	Protease inhibitors, cobicistat, and fostemsavir might increase brincidofovir concentration.	Cidofovir has limited interactions; however, it necessitates coadministration with probenecid which has numerous interactions (e.g., zidovudine, beta-lactam antimicrobials, diuretics, NSAIDs, and ACEi) that need to be monitored.	Vaccination with live virus vaccines (e.g., varicella, measles, mumps, and rubella) should be deferred for 3 mos after use.	NA
Data gleaned from selected animal studies¶¶	Cynomolgus macaques were lethally challenged IV with MPXV and treated on day 4, 5, and 6 postchallenge. Treatment with tecovirimat for 14 days resulted in statistically significant improvement in survival relative to placebo, except when given starting at day 6 postchallenge.	In a lethal rabbitpox and mousepox (ectromelia) model of infection, treatment with brincidofovir resulted in statistically significant improvement in survival relative to placebo, except when given starting at day 6 postchallenge in the mousepox study.	In a lethal dormouse model of MPXV, cidofovir-treated mice reduced mortality from 100% to 19%.	In a mouse-tail lesion model, VIGIV exerted a protective effect against vaccinia infection when compared with a negative control.	In a study of 56 rabbits with vaccinia keratitis, trifluridine significantly reduced clinical disease and viral culture positivity.
Data gleaned from use in humans before and during the 2022 outbreak	Of 255 patients treated during the current outbreak,*** the median interval to first subjective improvement was 3 days with limited adverse events reported.	Limited use as monotherapy; used (unsuccessfully) alternating with cidofovir for severe cowpox infection in a kidney transplant recipient	Limited use as a sole agent; used for ocular cowpox infection with unclear benefit and once (unsuccessfully) alternating with brincidofovir for severe cowpox infection in a transplant recipient	Evidence for smallpox prevention when given to high-risk contacts Mixed evidence for efficacy for treatment of progressive vaccinia	Used successfully off-label for ocular complications of vaccinia virus vaccination
Pregnancy, breastfeeding, and fertility considerations	Likely safe in pregnancy and breastfeeding without affecting fertility	Not recommended for pregnancy or breastfeeding Might cause irreversible infertility in males	Not recommended for pregnancy or breastfeeding Might cause irreversible infertility in males	Likely safe in pregnancy and breastfeeding without affecting fertility	Negligible systemic absorption when administered into the eye; likely safe in pregnancy and breastfeeding without affecting fertility
CNS considerations†††	Penetrates well	Penetrates to uncertain degree	Penetrates to limited degree	Penetrates to limited degree	NA
Resistance considerations	Single point mutation can confer resistance.§§§	Single point mutation can confer minor resistance; however, multiple mutations are needed for high-level resistance and the resultant virus becomes less virulent.	Single point mutation can confer minor resistance; however multiple mutations are needed for high-level resistance and the resultant virus becomes less virulent.	NA	Although in vitro resistance has not been reported, the possibility of resistance exists.

See table footnotes on page 238.

redosing) decisions should be made on a case-by-case basis in consultation with CDC. Clinical characteristics and laboratory results that might trigger consideration of additional doses of VIGIV include mpox lesions affecting a large percentage of a patient's body surface at the time of diagnosis, emergence of new mpox lesions (or expanding borders on existing lesions) several days after VIGIV, persistent severe immunocompromise (e.g., as evidenced by low CD4 values and undetectable OPXV IgM despite attempts to optimize immune function), lesions affecting mobility or that are concerning for long-term sequelae such as sexual dysfunction, and inability to maximally use other MCMs because of adverse events or contraindications.

Trifluridine. Trifluridine is an ophthalmic antiviral drug that has been shown to inhibit replication of several viruses,

TABLE. (*Continued*) Summarized mechanisms of action, administration recommendations, adverse events, clinical considerations, and supporting data about medical countermeasures that can be used to treat mpox*— United States, February 2023

Consideration	Medical countermeasures				
	Tecovirimat (Tpoxx or ST-246)	Brincidofovir (Tembexa or CMX001)	Cidofovir (Vistide)	VIGIV	Trifluridine (Viroptic)
Miscellaneous considerations	High-fat (approximately 600 calories and 25g fat) meal required with each oral dose| IV administration should be considered in those who are unable to take oral therapy, unable to consume a high-fat meal, have impaired gastrointestinal absorption (e.g., gastric bypass, diarrhea, or evidence of other gastrointestinal disfunction that might negatively affect drug absorption), or fail to improve on approximately 7 days of oral therapy.	Must be taken on an empty stomach or with a low-fat meal (approximately 400 calories with 25% of calories from fat) Might have superior antiviral activity to that of cidofovir because of increased cellular uptake Should not be administered within 1 wk of cidofovir because both form the same active metabolite (CDP), which has a prolonged duration of action	Must be given with probenecid to minimize nephrotoxicity Probenecid might have substantial drug interactions and consultation with a pharmacist is advised. Should not be administered within 1 wk of brincidofovir because both form the same active metabolite (CDP), which has a prolonged duration of action	Vaccinia-specific antibody, which might cross-react with MPXV Might interfere with endogenous antibody production and IgG antibody testing When used to treat vaccinia keratitis in rabbits, VIGIV resulted in prolonged scarring and stromal edema.	Can cause permanent limbal stem cell deficiency with prolonged use

Abbreviations: ACEi = angiotensin converting enzyme inhibitor; BBW = black box warning; CDP = cidofovir diphosphate; CMV = cytomegalovirus; CNS = central nervous system, EA-IND = expanded access - investigational new drug; FDA = Food and Drug Administration; IgG = immunoglobulin G; IND = investigational new drug; IV = intravenous; MPXV = *Monkeypox virus*; NA = not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NSAIDs = nonsteroidal anti-inflammatory drugs; OPXV = orthopoxvirus; VIGIV = vaccinia immune globulin intravenous.

* This table is a comprehensive synthesis of the heterogeneous evidence and is intended to foster strategic decision-making rather than serve as a prescriptive treatment guideline.

† Dosing for persons <40 kg and children is available at https://www.cdc.gov/poxvirus/monkeypox/pdf/tecovirimat-ind-protocol-cdc-irb.pdf.

§ Dosing for persons <48 kg and children is available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000,214461s000lbl.pdf.

¶ Data suggest that an aggressive early dosing regimen for patients with severe immunocompromise might be most beneficial; for this reason, a dose in the higher range (9,000 units/kg) early in the clinical course, potentially followed by an additional dose 3–4 days later, might help saturate viral antigens and halt viremia and viral replication.

** IV administration requires a syringe pump, a device that might not be easily accessible in all health care settings and has a slow infusion longer than 6 hours, irrespective of total infusion volume.

†† Per EA-IND the standard duration of tecovirimat treatment is 14 days, with clinical data being limited to a 14-day course. Based on individual patient risk-benefit assessment and disease progression, tecovirimat and cidofovir may be extended beyond 14 days, or shortened because of lack of virologic or clinical response or adverse event occurrence. Extension of brincidofovir currently requires FDA authorization on an individual patient basis through an emergency IND request secondary to concerns related to the BBW stated within the table.

§§ Secondary to potential accumulating of hydroxypropyl-β-cyclodextrin, an excipient in the IV tecovirimat formulation which is eliminated through glomerular filtration. Intravenous tecovirimat may be used with caution in patients with renal impairment (creatine clearance <30 mL/min) only if drug absorption via enteral administration is not anticipated to be dependable or feasible, and based on the risk-benefit assessment by the treating clinician that determines IV tecovirimat clinically necessary.

¶¶ Other animal studies examine the use of these agents; the studies noted within the table were used to gain FDA approval or provide evidence of efficacy for its off-label use.

*** https://www.cdc.gov/mmwr/volumes/71/wr/mm7137e1.htm?s_cid=mm7137e1_w

††† CNS penetration was determined based on available animal and human data. Well: data suggested that an MCM was able to cross the blood-brain barrier and enter intrathecal space at concentrations known to be effective; Uncertain: data suggested that an MCM can cross the blood-brain barrier, but unclear if at sufficient concentrations to be effective; Limited: evidence suggested that an MCM does not or would not cross the blood-brain barrier. The theoretical utility of any medical countermeasure in clearing MPXV from the central nervous system is unknown.

§§§ To date, <0.5% specimens (out of >5,000 specimens) sent to CDC for testing have been found to develop resistance within the current outbreak.

including vaccinia virus (*27*) and has demonstrated efficacy against ocular vaccinia virus infections in animal models (*25*,*28*) and humans (*28*,*29*). Continuous administration beyond the recommended 4-week duration of treatment should be avoided because of the risk for corneal epithelial toxicity (*30*).

Considerations in the Management of Severe Mpox Cases

Severe mpox (including ocular infections, neurologic complications, myopericarditis, mucosal lesion complications, and uncontrolled viral spread) have been reported. Manifestations of these complications, recommended MCMs, and other clinical considerations for each type of infection (e.g., involvement of specific clinical subspecialists) are summarized (Box).

Ocular infections. These can manifest as blepharitis, conjunctivitis, conjunctival lesions, keratitis, and vision loss. Ocular infections have occurred when MPXV infects the eye or periorbital area, usually via autoinoculation or local spread from nearby lesions (*31*).

Neurologic complications. Encephalitis and myelitis have been reported in some mpox patients (*32*). Whether these result from direct viral invasion of the central nervous system or autoimmune disease from antigenic stimulus is not known. Cases involving neurologic complications have rarely been reported to CDC, but have occurred in immunocompetent persons, despite resolving mpox skin lesions.

Myopericarditis. Myopericarditis cases have been reported among immunocompetent patients (*1*,*32*,*33*). The pathogenic mechanism is uncertain but might result from direct viral invasion or lymphocytic infiltration of the myocardium or pericardium, its sequelae (e.g., myonecrosis or myocardial fibrosis), or an autoimmune process.

Complications associated with some mucosal (oral, rectal, genital, and urethral) lesions. Certain mucosal surface lesions can cause strictures and other complications that impair activities of daily living (e.g., reduced oral intake, painful bowel movements, impaired urination, and airway obstruction).

Complications from uncontrolled viral spread in immunocompromised patients. Moderately or severely immunocompromised patients (e.g., advanced HIV and organ transplant recipients) have sometimes developed diffuse and disseminated lesions that have involved multiple organ systems, possibly because of persistent viremia or uncontrolled viral growth (*12*). Overwhelming systemic illness has resulted in death.

Other Clinical Considerations

Immune dysregulation. Earliest optimization of immune function is critical to favorable outcomes. Mpox patients with advanced HIV who have recently started ARVs and who then experience persistent or progressive lesions might manifest features commonly associated with immune reconstitution inflammatory syndrome; whether immune dysregulation is the cause of illness or the immune system is unable to effectively clear MPXV from infected cells is not known. Until definitive data are available, administration of systemic immunomodulators (including steroids) to patients with mpox should be undertaken with caution; models suggest that steroids are associated with severe illness and even death in OPXV-infected animals (*34*).

Lesions that persistently test positive. Positive OPXV and MPXV polymerase chain reaction (PCR) test results are expected until lesions resolve; therefore, serial testing of lesion specimens is not informative unless new lesions appear or lesions progress despite tecovirimat treatment. Test results do not guide duration of infection control policies because patients are considered infectious until all lesions have scabbed, the scabs have fallen off, and healthy tissue is visible underneath.

Prolonged occurrence of new lesions despite appropriate MCMs. If progressive lesions are noted, particularly after reversal of immunocompromise, diagnostic evaluation should include testing new lesions for OPXV and other infections, and evaluation for superinfections, noninfectious processes such as erythema multiforme, and immunologic function. Laboratories, such as CDC's poxvirus laboratory,***** can test for presence of viable virus from lesion specimens using culture techniques that might guide patient care. If viral culture is unavailable, evaluating trends in PCR cycle threshold values might be informative.

Knowledge Gaps and Next Steps

Knowledge gaps regarding optimal treatment of severe mpox are best addressed through data collected during randomized controlled trials and other carefully controlled research studies. Patients enrolled in well-designed studies might benefit from the close monitoring provided by these studies (e.g., effective adjustments of tecovirimat doses are made as part of the STOMP trial based on serially monitored pharmacokinetic parameters). Understanding the role of immune dysregulation in the clinical course of severely immunocompromised HIV patients started on ARVs was frequently recognized as a knowledge gap: CDC has partnered with NIH to study this (Virologic and Immunologic Characteristics of Severe Mpox Among Persons with Advanced HIV [VIRISMAP] study).†††††† Clinicians and health departments are encouraged to contact CDC when treating mpox in a patient recently started on ARVs. Controlled studies focused on understanding the impact of monotherapy or combination therapy on virus shedding, duration of illness, and clinical outcomes are needed, particularly for patients with severe immunocompromise. Public health laboratories, academic laboratories, and CDC continue to sequence the F13L gene (the tecovirimat target) to assess F13L viral mutations that might be associated with resistance. Phenotypic testing to evaluate resistance is also occurring at CDC.§§§§§ Analysis of anti-OPXV antibody levels and viral neutralization antibody levels are ongoing at CDC and are needed to develop guidance about redosing of VIGIV. Laboratories should consider examining T-cell and humoral responses to mpox in immunocompromised patients

***** CDC's poxvirus laboratory can be reached at poxvirus@cdc.gov and poxviruslab@cdc.gov.

†††††† https://www.cdc.gov/poxvirus/mpox/clinicians/treatment.html

§§§§§ https://www.cdc.gov/poxvirus/monkeypox/pdf/Optional-Lesion-Sample-to-CDC-for-Resistance-Testing.pdf

BOX. Important clinical considerations for management of severe mpox* — United States, February 2023

Ocular infections

- **Clinical manifestations:** Symptoms include eye pain, redness, drainage, foreign body sensation, vision changes or loss, or periorbital swelling. Involvement of the ocular surface can manifest as blepharitis, conjunctivitis, or keratitis; discrete lesions might be present. Lesions can also occur on external areas including the eyelids.
- **Diagnostic findings:** In a patient with known or suspected mpox, ocular infection can be confirmed by testing swabs from periorbital, lid or intraocular lesions for OPXV by PCR.
- **Treatment:** Prompt initiation of tecovirimat and topical administration of trifluridine should be considered. Trifluridine can also be used prophylactically in patients with mpox who are at high risk of ocular infection (e.g., lesions near the eye). Other systemic MCMs should be considered on a case-by-case basis. Lubricants and topical antibiotics may be considered for symptomatic management and prevention of complications.
- **Other considerations:** Obtain ophthalmology consultation.† Adverse events might occur from prolonged use of trifluridine. In addition, one animal study suggests increased risk of corneal scarring when VIGIV is administered in the setting of OPXV keratitis. Extensive use of agents that can further irritate the eye, such as topical povidone-iodine, might be avoided. Appropriate measures to prevent, diagnose, and treat ocular coinfections and superinfections should be taken.

Neurologic complications

- **Clinical manifestations:** Encephalitis and myelitis can occur. Severe headache, back or neck pain, altered mental status, seizures, or focal neurologic deficits in a patient with mpox or recently recovered from mpox should prompt suspicion for neurologic complications.
- **Diagnostic findings:** CSF might demonstrate a lymphocytic-predominant pleocytosis with protein elevation and normal glucose; availability of mpox-specific CSF testing is limited and consultation with CDC is suggested. MRI might show lesions in the brain or spinal cord which might or might not enhance.
- **Treatment:** Treatment of mpox-associated neurologic disease should involve MCMs and might involve immunomodulatory or immunosuppressive therapy (e.g., steroids, intravenous immunoglobulin, or plasmapheresis or plasma exchange). Clinicians treating mpox-associated neurologic disease should weigh the risks and benefits of immunosuppressive agents when direct viral neuroinvasion is a possibility. Data suggest tecovirimat penetrates the CNS well; although brincidofovir, cidofovir, and VIGIV might penetrate the CNS, the extent is either uncertain (brincidofovir) or limited (cidofovir and VIGIV).
- **Other considerations:** Consider neurology consultation. Neurologic disease related to mpox might be because of direct viral invasion of the CNS or resultant autoimmune disease from antigenic stimulus. Other neurologic diseases with similar presentations should be investigated (e.g., infectious diseases such as viral encephalitides and syphilis, and autoimmune, parainfectious, and vascular conditions).

Myopericarditis

- **Clinical manifestations:** New complaints of chest pain, shortness of breath, or palpitations in a patient with ongoing or recent mpox should prompt consideration of myopericarditis.
- **Diagnostic findings:** Similar findings to those associated with myopericarditis from etiologies other than mpox might be observed, including elevations in cardiac biomarkers, changes in electrocardiogram and on cardiovascular MRI, and pathologic changes of the myocardium.
- **Treatment:** Standard of care for myopericarditis should be considered; MCMs might also play a role by limiting viral spread to myocytes or decreasing the production of viral antigens responsible for the inflammatory response.
- **Other considerations:** Consider cardiology consultation. Other causes of myopericarditis should be investigated, including other viral infections or recent receipt of a vaccination that can be associated with myopericarditis.

See box footnotes on the next page.

BOX. (*Continued*) Important clinical considerations for management of severe mpox* — United States, February 2023

Complications associated with some mucosal (oral, rectal, genital, and urethral) lesions

- **Clinical manifestations:** Symptoms can include impaired activities of daily living (e.g., feeding, urination, or defecation) from painful or obstructing rectal, urinary tract, oral, and genital lesions, especially if associated with strictures, substantial edema, severe lymphadenopathy, or necrosis. Lesions might expose deep tissue including muscle or bone, and myonecrosis can occur. Healing might be slow, and scarring can result in strictures.
- **Diagnostic findings:** Complications associated with mucosal lesions can be diagnosed by physical examination in conjunction with other diagnostic testing; the diagnosis of mpox can be made by sampling mucosal or other lesions.
- **Treatment:** Prompt initiation of systemic MCMs should be considered. Some patients have required intubation, urinary catheterization, or placement of enteric tubes. Early and aggressive treatment might prevent such complications. Routine use of topical antimicrobial agents, particularly over-the-counter options, is not indicated and might cause irritation, contact dermatitis, or delayed wound healing.[§] Debridement is generally not recommended.
- **Other considerations:** Specialists (e.g., surgery, urology, or gastroenterology) should be consulted early in the clinical course. Symptomatic management, and especially pain control, is an important component of treatment. Coinfections and superinfections should be diagnosed and treated promptly. Sequelae are not fully known but can result in substantial morbidity (e.g., scarring leading to functional impairment, or necrosis necessitating surgical debridement, penectomy, or amputation of extremities).

Complications from uncontrolled viral spread in moderately to severely immunocompromised patients

- **Clinical manifestations**: Numerous, large, coalescing, or necrotic lesions of the skin can occur in patients with severe immunocompromise. Other organ systems (e.g., gastrointestinal tract, liver, lungs, brain, or adrenal glands) can be involved, resulting in signs and symptoms of organ dysfunction irrespective of severity of cutaneous lesions. Overwhelming systemic illness including sepsis can occur and might progress to death.
- **Diagnostic findings**: Uncontrolled viral spread can manifest as the appearance of new skin lesions or worsening of existing lesions. Involvement of other organ systems can result in a range of findings on physical exam and laboratory investigations (e.g., gastrointestinal obstruction, severe pneumonia, empyema, encephalitis, intractable hypotension, or transaminitis). Alternate or coinciding causes of severe illness should be investigated.
- **Treatment:** Immune function should be optimized through interventions such as effective HIV antiretrovirals and reduced immunomodulatory therapy as feasible. Prompt initiation of tecovirimat (potentially the intravenous formulation), and possible combination with either cidofovir or brincidofovir, and VIGIV, should be considered. Wound care is critical to ensure healing and prevent superinfection and autoinoculation.[§] Diffuse skin lesions might cause insensible fluid losses requiring intensive fluid management.
- **Other considerations**: Consider consultation with experts in infectious diseases, critical care, dermatology, wound care, gastroenterology, and surgery (e.g., general surgery, plastic surgery, and burn experts) as indicated. Administration of MCMs for extended durations (>14 days) might be reasonable if clinically indicated (e.g., new or progressive mpox lesions occur). The role of immune dysregulation in severe mpox illness is not known; there is no high-quality evidence to support or refute the use of steroids and other immunomodulators, and clinicians should weigh the risks and benefits of such therapies because optimal immune function aids recovery from mpox. Supportive care and close clinical monitoring for occurrence of complications such as secondary bacterial infections and sepsis can be critical in patients with severe mpox illness.

Abbreviations: CNS = central nervous system; CSF = cerebrospinal fluid; MCM = medical countermeasure; MRI = magnetic resonance imaging; OPXV = orthopoxvirus; PCR = polymerase chain reaction; VIGIV = vaccinia immune globulin intravenous.

* This report is a comprehensive synthesis of the heterogeneous evidence and is intended to foster strategic decision-making rather than serve as a prescriptive treatment guideline.

† Urgent ophthalmology consultation and management is particularly important for patients with eye pain, vision loss, or worsening ocular symptoms.

§ https://www.aad.org/public/diseases/a-z/monkeypox-self-care

Summary

What is already known about this topic?

During the 2022 global monkeypox (mpox) outbreak, some patients have experienced severe clinical manifestations. Medical countermeasures (MCMs) developed to treat smallpox have been used to treat mpox.

What is added by this report?

Data relevant to the use of tecovirimat, brincidofovir, cidofovir, trifluridine ophthalmic solution, and vaccinia immune globulin intravenous were reviewed. Animal models, MCM use for human cases of related orthopoxviruses, unpublished data, input from clinician experts, and experience during CDC mpox consultations were also evaluated to develop interim clinical treatment considerations.

What are the implications for public health practice?

Until data from controlled studies are available, these interim clinical considerations facilitate strategic decision-making about the use of MCMs to manage specific severe manifestations of mpox.

because immune response is crucial to viral clearance, and this data might facilitate development of improved clinical guidance (*35*).

Until data from controlled studies are available, observational data from patients treated under IND might provide insights into clinical outcomes. Providers administering MCMs under IND programs should complete and submit optional data collection forms to facilitate improved understanding of the role of MCMs. CDC will update guidance, as appropriate, as new data emerge.

Acknowledgments

James Chodosh, Department of Ophthalmology and Visual Sciences, University of New Mexico School of Medicine; Esther Freeman, George Hruza, American Academy of Dermatology Ad Hoc Task Force on Mpox Content; Susan Gorman, Administration for Strategic Preparedness and Response/Strategic National Stockpile; Michael Merchlinsky, Biomedical Advanced Research and Development Authority, U.S. Department of Health and Human Services; Daniel Pastula, Department of Neurology and Division of Infectious Diseases, University of Colorado School of Medicine; Gary Roselle, U.S. Department of Veterans Affairs; Irini Sereti, National Institute of Allergy and Infectious Diseases, National Institutes of Health; Steven Yeh, Truhlsen Eye Institute, University of Nebraska Medical Center/Nebraska Medicine; Jason Zucker, Division of Infectious Diseases, Columbia University School of Medicine; Robert Fisher, Michael Kennedy, Jennifer Reed, Rosemary Roberts, Dorothy Scott, Food and Drug Administration; William Bower, Kevin Chatham-Stephens, Jennifer R. Cope, Athena Kourtis, James Lee, Sara Luckhaupt, Janet McNicholl, Dana Meaney-Delman, Sapna Bamrah Morris, Elliot Raizes, P.S. Satheshkumar, James Sejvar, Michael Townsend, Kate Hendricks Walters, Patricia Yu, CDC; clinicians and health department personnel who consulted CDC for complicated cases of mpox and CDC clinical officers who performed (and continue to perform) consultations.

Corresponding author: Agam K. Rao, akrao@cdc.gov.

[1]Poxvirus and Rabies Branch, Division of High Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, CDC; [2]Epidemic Intelligence Service, CDC; [3]Office of the Director, Division of High Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, CDC; [4]Regulatory Affairs, Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, CDC.

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

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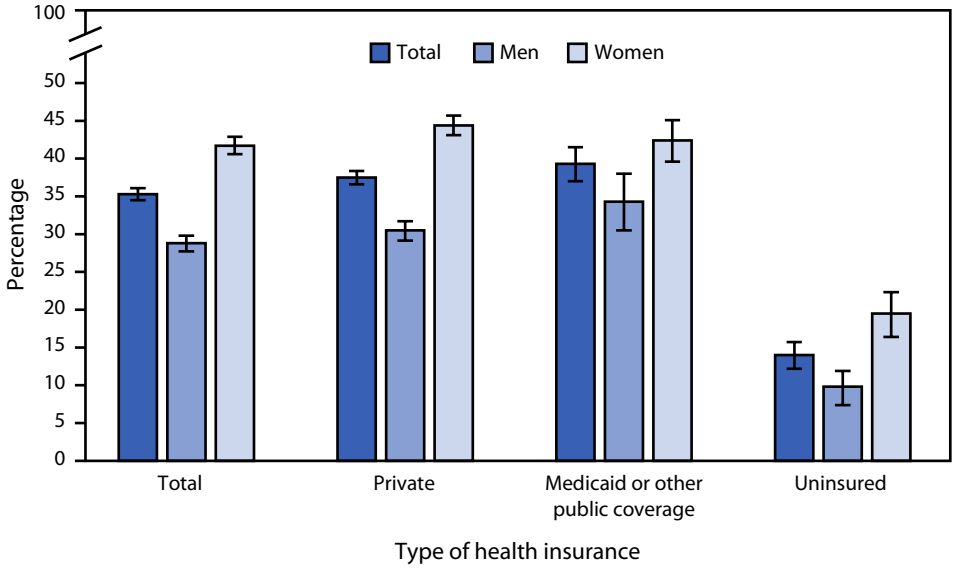
QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Percentage* of Adults Aged 18–64 Years Who Used Telemedicine in the Past 12 Months,† by Sex and Health Insurance Coverage§ — National Health Interview Survey, United States 2021¶



* With 95% CIs indicated by error bars.
† Based on a positive response to the question, "In the past 12 months, have you had an appointment with a doctor, nurse, or other health professional by video or phone?"
§ Health insurance coverage is based on reported status at the time of interview. Private insurance includes plans obtained through an employer, purchased directly, and received through local and community programs. Public coverage includes Medicaid or other state-sponsored health plans among adults without private insurance. In addition to adults without coverage, uninsured includes a very small percentage of adults who only have Indian Health Service coverage or a private plan that paid for only one type of service. Total includes other types of health insurance coverage not shown separately.
¶ Estimates are based on household interviews of a sample of the civilian, noninstitutionalized U.S. population.

Overall, in 2021, 35.3% of adults aged 18–64 years had a telemedicine visit with a health care professional in the past 12 months. The percentage was higher among women than men overall (41.7% versus 28.8%). Women were also more likely than were men to have had a telemedicine visit among those with private health insurance (44.4% versus 30.5%), Medicaid or other public coverage (42.4% versus 34.3%), and those who were uninsured (19.5% versus 9.8%). Adults with private health insurance (37.5%) or Medicaid or other public coverage (39.3%) were more likely to use telemedicine compared with uninsured adults (14.0%), and this pattern was seen for women and men.

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

Reported by: Jacqueline Lucas, MPH, jbw4@cdc.gov; Maria Villarroel, PhD; Robin Cohen, PhD.

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ISSN: 0149-2195 (Print)