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HIV and Sexually Transmitted Infections Among Persons with Monkeypox — Eight U.S. Jurisdictions, May 17–July 22, 2022

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High prevalences of HIV and other sexually transmitted infections (STIs) have been reported in the current global monkeypox outbreak, which has affected primarily gay, bisexual, and other men who have sex with men (MSM) (*1*–*5*). In previous monkeypox outbreaks in Nigeria, concurrent HIV infection was associated with poor monkeypox clinical outcomes (*6*,*7*). Monkeypox, HIV, and STI surveillance data from eight U.S. jurisdictions* were matched and analyzed to examine HIV and STI diagnoses among persons with monkeypox and assess differences in monkeypox clinical features according to HIV infection status. Among 1,969 persons with monkeypox during May 17–July 22, 2022, HIV prevalence was 38%, and 41% had received a diagnosis of one or more other reportable STIs in the preceding year. Among persons with monkeypox and diagnosed HIV infection, 94% had received HIV care in the preceding year, and 82% had an HIV viral load of <200 copies/mL, indicating HIV viral suppression. Compared with persons without HIV infection, a higher proportion of persons with HIV infection were hospitalized (8% versus 3%). Persons with HIV infection or STIs are disproportionately represented among persons with monkeypox. It is important that public health officials leverage systems for delivering HIV and STI care and prevention to reduce monkeypox incidence in this population. Consideration should be given to prioritizing persons with HIV infection and STIs for vaccination against monkeypox. HIV and STI screening and other recommended preventive care should be routinely offered to persons evaluated for monkeypox, with linkage to HIV care or HIV preexposure prophylaxis (PrEP) as appropriate.

Eight health departments matched probable and confirmed cases of monkeypox† diagnosed through July 22, 2022, and occurring among persons aged ≥18 years, to local HIV and STI surveillance data using individually established methods that included various personal identifiers (e.g., name,

*Eight state and city or county jurisdictions independently funded for HIV surveillance: California (including Los Angeles County and San Francisco), District of Columbia, Georgia, Illinois (including Chicago), and New York (excluding New York City).

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

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soundex,[§] date of birth, address, and telephone number). Matched data were deidentified and securely transmitted to CDC for analysis.

Among persons with monkeypox, prevalence of diagnosed HIV infection, determined through local HIV surveillance matches,[¶] was calculated. HIV surveillance data were used to assess receipt of HIV care,[**] HIV viral suppression (an indication of antiretroviral therapy use),[††] most recent CD4 count,[§§] and time since HIV diagnosis (*8*). STI surveillance data were used to assess chlamydia, gonorrhea, and syphilis diagnoses. Monkeypox signs, symptoms, and outcomes were compared according to HIV infection status. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.[¶¶]

Among 1,969 persons aged ≥18 years with monkeypox diagnosed during May 17–July 22, 2022, in eight participating jurisdictions, 755 (38%) had received an HIV diagnosis, 816 (41%) had another reportable STI diagnosed in the preceding year, and 363 (18%) had both; 1,208 (61%) persons had either (Table 1) (Table 2).[***] Since May 1, 2022, 19 (1%) persons with monkeypox had received an HIV diagnosis, and 297 (15%) had received an STI diagnosis. Persons with monkeypox and HIV infection more commonly had received an STI diagnosis in the preceding year (48%) than had those without HIV infection (37%).

Among persons with monkeypox, the weekly percentage with concurrent HIV infection increased over time (31%–44% by July). The percentage of persons with monkeypox who had HIV infection was higher in older age groups: among persons aged 18–24 years, HIV prevalence was 21%, and among those aged ≥55 years, was 59%. HIV prevalence among persons with monkeypox also varied by race and ethnicity, ranging from a high of 63% among non-Hispanic Black or African American (Black) persons, to 41% among Hispanic or Latino (Hispanic) persons, 28% among non-Hispanic White persons, and 22% among non-Hispanic Asian persons.

Among 755 persons with monkeypox and HIV infection, 713 (94%) received HIV care in the preceding year, 618 (82%) were virally suppressed, and 586 (78%) had CD4

[§] Soundex is a phonetic algorithm for indexing names by sound. https://www.archives.gov/research/census/soundex

[¶] Persons with self-reported HIV infection whose records were not located in local HIV surveillance data were excluded from all analyses.

[**] Receipt of HIV care was defined as at least one HIV viral load or CD4 test since May 1, 2021; tests conducted during evaluation for monkeypox might have been included.

[††] HIV viral suppression was defined as the most recent HIV viral load <200 copies/mL since May 1, 2021.

[§§] Recent CD4 count was defined as the most recent CD4 count since May 1, 2021.

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

[***] Thirty-nine persons had a self-reported HIV diagnosis in monkeypox surveillance records that could not be confirmed with local HIV surveillance data and were thus excluded from analyses.

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TABLE 1. Demographic characteristics of persons with monkeypox and HIV infection* — eight U.S. jurisdictions,† May 17–July 22, 2022

Characteristic	No. of persons with monkeypox	No. of persons with monkeypox and diagnosed HIV infection	HIV prevalence among persons with monkeypox (row %)
Total	**1,969**	**755**	**38**
Age, median, yrs (IQR)	35 (30–42)	38 (32–45)	—
Age group, yrs			
18–24	106	22	21
25–34	801	246	31
35–44	670	291	43
45–54	278	131	47
≥55	105	62	59
Missing	9	3	33
Sex assigned at birth			
Male	1,466	548	37
Female	10	0	—
Missing or declined to answer	493	207	42
Gender identity			
Man	1,888	730	39
Woman	7	1	14
Transgender man or woman	8	0	—
Another gender identity	14	2	14
Missing or declined to answer	52	22	42
Race and ethnicity			
Asian, non-Hispanic	89	20	22
Black or African American, non-Hispanic	409	256	63
Hispanic or Latino§	158	64	41
Other¶	169	61	36
White, non-Hispanic	919	255	28
Missing	225	99	44
Monkeypox report date**			
May 15–Jun 4	24	3	13
Jun 5–11	35	9	26
Jun 12–18	64	13	20
Jun 19–25	110	32	29
Jun 26–Jul 2	201	65	32
July 3–9	331	104	31
Jul 10–16	498	196	39
Jul 17–23	596	264	44
Missing	110	69	63

* Persons with self-reported HIV infection who did not match to local HIV surveillance data (39) were excluded from the analysis.
† Eight state and city or county jurisdictions independently funded for HIV surveillance: California (including Los Angeles County and San Francisco), District of Columbia, Georgia, Illinois (including Chicago), and New York (excluding New York City).
§ Hispanic or Latino persons can be of any race.
¶ Other includes persons who identify as Native Hawaiian and other Pacific Islander, American Indian or Alaska Native, or multiracial, and persons who declined to report.
** Report date includes either date of specimen collection, *Orthopoxvirus* test, monkeypox diagnosis by clinician, illness onset, or rash onset. Report date shown by epidemiologic week; the first 3 weeks of the outbreak are combined because of small numbers.

count ≥350/μL. The median interval since HIV diagnosis was 10 years (IQR = 6–15 years). Data on HIV PrEP use were available for 172 (14%) persons without HIV infection, 115 (67%) of whom reported current PrEP use.

Compared with persons with monkeypox who did not have HIV infection, those with HIV infection were more likely to report rectal pain (34% versus 26%), tenesmus (20% versus 12%), rectal bleeding (19% versus 12%), purulent or bloody stools (15% versus 8%), and proctitis (13% versus 7%), but were less likely to report lymphadenopathy (48% versus 53%) (Figure). The prevalence of other signs and symptoms was similar among persons with monkeypox with and without HIV infection. Among 564 persons with monkeypox, HIV, known HIV viral load values, and signs and symptoms data, the 51 persons with unsuppressed HIV viral load were more likely than were the 513 with suppressed viral load to have lymphadenopathy (59% versus 46%), generalized pruritis (59% versus 42%), rectal bleeding (25% versus 18%), and purulent or bloody stools (22% versus 14%). Compared with persons with CD4 counts ≥350/μL, those with CD4 counts <350/μL more commonly experienced fever (69% versus 59%) and generalized pruritis (53% versus 42%).

Among 1,308 (66%) persons with information on hospitalization, the proportion of persons hospitalized with monkeypox was lower among those without HIV infection (3%, 26 of 798) than among those with HIV infection (8%, 42 of 510). Among

TABLE 2. Monkeypox hospitalization, sexually transmitted infections, and HIV prevention and care characteristics, by HIV infection status* — eight U.S. jurisdictions,† May 17–July 22, 2022

Characteristic	No. (%) of persons with monkeypox§	No. (%) of persons without diagnosed HIV infection§	No. (%) of persons with diagnosed HIV infection§
Total	**1,969**	**1,214**	**755**
Hospitalization during monkeypox illness			
Hospitalized for monkeypox¶	68 (5)	26 (3)	42 (8)
Duration of hospitalization, median, days (range)**	3 (0–10)	3 (0–10)	2 (0–7)
History of STIs			
Reportable STI diagnosis during preceding yr	816 (41)	453 (37)	363 (48)
Gonorrhea	546 (28)	307 (25)	239 (32)
Chlamydia	489 (25)	278 (23)	211 (28)
Syphilis	165 (8)	69 (6)	96 (13)
STI diagnosis since May 1, 2022	297 (15)	166 (14)	131 (17)
No. of STIs diagnosed during preceding yr			
1	396 (20)	220 (18)	176 (23)
2	222 (11)	117 (10)	105 (14)
≥3	198 (10)	116 (10)	82 (11)
HIV prevention and care characteristic			
Received HIV care in preceding yr††	NA	NA	713 (94)
Suppressed HIV viral load§§	NA	NA	618 (82)
Recent CD4 count cells/μL, median (IQR)¶¶	NA	NA	639 (452–831)
CD4 count <350 cells/μL	NA	NA	91 (12)
CD4 count <200 cells/μL	NA	NA	25 (3)
Yrs since HIV diagnosis, median (IQR)	NA	NA	10 (6–15)
HIV diagnosis since May 1, 2022	NA	NA	19 (3)
Current HIV PrEP use***	NA	115 (67)	NA

Abbreviations: NA = not applicable; PrEP = preexposure prophylaxis; STI = sexually transmitted infection.

* Persons with self-reported HIV infection who did not match to local HIV surveillance data (39) were excluded from the analysis.

† Eight state and city or county jurisdictions independently funded for HIV surveillance: California (including Los Angeles County and San Francisco), District of Columbia, Georgia, Illinois (including Chicago), and New York (excluding New York City).

§ Row percentages calculated using nonmissing data.

¶ Overall, 1,308 persons had data available for hospitalization, including 798 persons without diagnosed HIV infection and 510 persons with diagnosed HIV infection.

** Overall, 48 hospitalized persons had data available for hospitalization duration, including 18 persons without diagnosed HIV infection and 30 persons with diagnosed HIV infection.

†† Receipt of HIV care was defined as at least one HIV viral load or CD4 test since May 1, 2021; tests conducted during evaluation for monkeypox might have been included.

§§ HIV viral suppression was defined as the most recent HIV viral load <200 copies/mL since May 1, 2021.

¶¶ Recent CD4 count was defined as the most recent CD4 count since May 1, 2021.

*** Among persons without diagnosed HIV infection, 172 persons had data available for current HIV PrEP use.

45 persons with monkeypox and HIV infection who were not virally suppressed, 12 (27%) were hospitalized, and among 61 with a CD4 count <350 cells/μL, nine (15%) were hospitalized.

Discussion

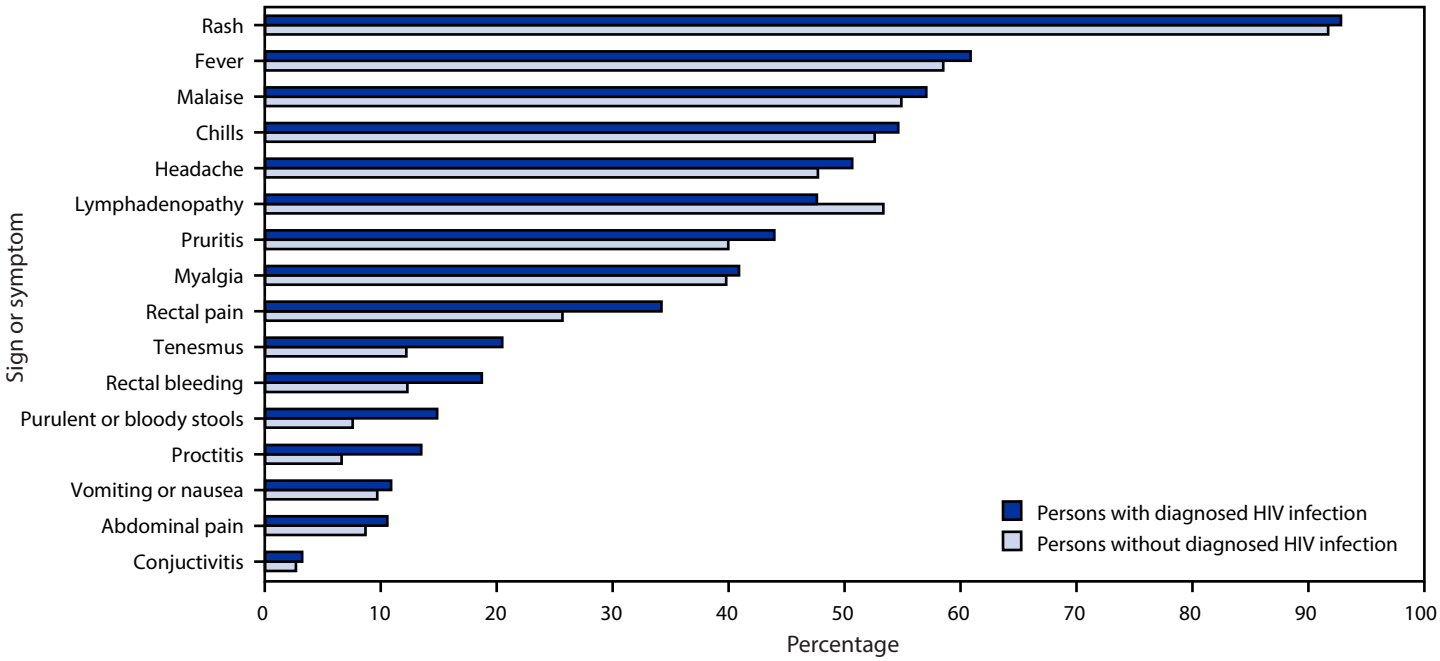
Among persons with monkeypox in eight U.S. jurisdictions, prevalences of concurrent HIV infection and reportable STI diagnoses within the preceding 12 months were high, consistent with previous reports (*1*–*5*). To date, most U.S. monkeypox cases have occurred among MSM (*4*), who have higher prevalences of HIV infection and STIs than the general population. However, in this analysis, the percentage of persons with monkeypox who had HIV infection (38%) was higher than national HIV prevalence estimates for U.S. MSM (23%); this finding was also true when comparing *Monkeypox virus* and HIV coinfection among Black persons (63%), Hispanic persons (41%), and persons aged ≥55 years (59%) to overall HIV prevalences among Black MSM (39%), Hispanic MSM (19%), and MSM aged 50–60 years (32%), respectively (*9*). Increasing HIV prevalence among persons with monkeypox over time suggests that monkeypox might be increasingly transmitted among networks of persons with HIV infection, underscoring the importance of leveraging HIV and STI care and prevention delivery systems for monkeypox vaccination and prevention efforts.††† Consideration should be given to prioritizing persons with HIV infection and STIs for vaccination and other prevention efforts. HIV and STI screening and other recommended preventive care§§§ should be routinely offered to persons evaluated for monkeypox, with linkage to HIV care or HIV PrEP, as appropriate.

The proportion of persons with *Monkeypox virus* and HIV coinfection who received HIV care (94%) exceeded the overall percentage of persons with diagnosed HIV infection who received care in 2020 (74%) (*8*). Approximately two thirds of

††† https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/overview.html

§§§ https://www.cdc.gov/std/treatment-guidelines/default.htm

FIGURE. Signs and symptoms of monkeypox,*,† by HIV infection status§ — eight U.S. jurisdictions,¶ May 17–July 22, 2022



* Persons with self-reported HIV infection who did not match to local HIV surveillance data (39) were excluded from the analysis.
† Signs and symptoms were not mutually exclusive.
§ Percentages calculated using nonmissing data. Overall, 1,707 persons had data available for signs and symptoms except proctitis, including 1,082 persons without diagnosed HIV infection and 625 persons with diagnosed HIV infection. For proctitis, data were available for 393 persons without diagnosed HIV infection and 304 persons with diagnosed HIV infection.
¶ Eight state and city or county jurisdictions independently funded for HIV surveillance: California (including Los Angeles County and San Francisco), District of Columbia, Georgia, Illinois (including Chicago), and New York (excluding New York City).

Summary

What is already known about this topic?

In the current global monkeypox outbreak, HIV infection and sexually transmitted infections (STIs) are highly prevalent among persons with monkeypox.

What is added by this report?

Among 1,969 persons with monkeypox in eight U.S. jurisdictions, 38% had HIV infection, and 41% had an STI in the preceding year. Among persons with monkeypox, hospitalization was more common among persons with HIV infection than persons without HIV infection.

What are the implications for public health practice?

It is important to leverage systems for delivering HIV and STI care and prevention and prioritize persons with HIV infection and STIs for vaccination. Screening for HIV and other STIs and other preventive care should be considered for persons evaluated for monkeypox, with HIV care and HIV preexposure prophylaxis offered to eligible persons.

persons with monkeypox without HIV infection for whom data were available reported HIV PrEP use, whereas nationally, an estimated 25% of eligible persons received an HIV PrEP prescription in 2020 (*8*). Moreover, 41% of persons with monkeypox had received a diagnosis of another reportable STI in the preceding year. These findings suggest that reported monkeypox cases are occurring among persons with recent access to HIV and sexual health services. Referral bias might partially explain these findings, as persons with monkeypox signs and symptoms who have established connections with HIV or sexual health providers might be more likely to seek care (*2*), and these providers might be more likely to recognize and test for *Monkeypox virus*. Monkeypox signs and symptoms might have led persons with HIV infection who have not been in HIV care to reengage in care. Persons with monkeypox signs and symptoms who are not engaged in routine HIV or sexual health care, or who experience milder signs and symptoms, might be less likely to have their *Monkeypox virus* infection diagnosed. To ensure appropriate diagnosis and treatment, it is important that health care providers who do not specialize in HIV or sexual health become familiar with the clinical guidance for monkeypox diagnosis and treatment.¶¶¶

The higher prevalence of rectal signs and symptoms among persons with HIV infection could be related to differences in site of exposure, increased biologic susceptibility, or other factors. Rectal signs and symptoms did not vary by HIV immune status (CD4 count <350/μL versus ≥350 μL), supporting differences in

¶¶¶ https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html

site of exposure as a likely explanation. In a prospective cohort in Spain, MSM with monkeypox who engaged in receptive anal sex were more likely to report proctitis and systemic signs and symptoms preceding rash (*3*). When evaluating patients with rectal signs and symptoms, care providers should consider monkeypox and the possibility of concurrent rectal STIs. Understanding whether rectal signs and symptoms can precede rash onset or occur when rash is absent or unrecognized (because of anatomic site or small number of lesions) will help inform guidance for *Monkeypox virus* testing and new diagnostic approaches.

Limited data suggest that persons with HIV infection, particularly those with low CD4 counts or without HIV viral suppression, were more commonly hospitalized during their monkeypox illness than were persons without HIV infection. However, because data on reason for hospitalization are incomplete, it is not known whether this represents more severe monkeypox illness. Ongoing monitoring of outcomes of monkeypox by HIV infection status is important (*7*).

The findings in this report are subject to at least five limitations. First, this analysis was limited to diagnosed and reported monkeypox cases in eight jurisdictions and might not be generalizable to all U.S. monkeypox cases. Second, incomplete data on clinical signs and symptoms and hospitalization might affect the associations observed by HIV infection status. Third, some persons with undiagnosed HIV infection might have been misclassified as not having HIV, which could reduce differences in outcomes by HIV infection status. Fourth, local matching might have underestimated the prevalences of HIV infection and STIs by not including diagnoses reported in other jurisdictions or recent diagnoses. Finally, this analysis did not assess the relative contribution of structural, social, behavioral, or biologic factors to higher HIV infection and STI prevalences among persons with monkeypox. Further studies could improve understanding of such factors, monkeypox outcomes, and the impact of vaccination and treatment.

Public health efforts should continue to ensure equitable access to monkeypox screening, prevention, and treatment, particularly among MSM. It is important that systems for delivering HIV and STI care and prevention be leveraged for monkeypox evaluation, vaccination and other prevention interventions, and treatment (*10*). Data on diagnosis of HIV infections and STIs in close temporal association to monkeypox diagnosis reinforce the importance of offering recommended testing, prevention, and treatment services for HIV, STIs, and other syndemic conditions to MSM and other persons evaluated for monkeypox.**** Routine matching of monkeypox, HIV, and STI surveillance data to monitor trends and clinical characteristics of persons with coinfections can further inform public health interventions.

**** https://www.cdc.gov/msmhealth/index.htm

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References

1. European Centre for Disease Prevention and Control; World Health Organization Regional Office for Europe. Joint ECDC-WHO Regional Office for Europe monkeypox surveillance bulletin. Stockholm, Sweden: European Centre for Disease Prevention and Control; 2022. https://monkeypoxreport.ecdc.europa.eu
2. Thornhill JP, Barkati S, Walmsley S, et al.; SHARE-net Clinical Group. Monkeypox virus infection in humans across 16 countries—April–June 2022. N Engl J Med 2022;387:679–91. PMID:35866746 https://doi.org/10.1056/NEJMoa2207323
3. Tarín-Vicente EJ, Alemany A, Agud-Dios M, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. Lancet 2022;400:661–9. PMID:35952705 https://doi.org/10.1016/S0140-6736(22)01436-2
4. Philpott D, Hughes CM, Alroy KA, et al.; CDC Multinational Monkeypox Response Team. Epidemiologic and clinical characteristics of monkeypox cases—United States, May 17–July 22, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1018–22. PMID:35951487 https://doi.org/10.15585/mmwr.mm7132e3
5. UK Health Security Agency. Investigation into monkeypox outbreak in England: technical briefing 6. London, England: United Kingdom Health Security Agency; 2022. https://www.gov.uk/government/publications/monkeypox-outbreak-technical-briefings/investigation-into-monkeypox-outbreak-in-england-technical-briefing-6
6. Ogoina D, Iroezindu M, James HI, et al. Clinical course and outcome of human monkeypox in Nigeria. Clin Infect Dis 2020;71:e210–4. PMID:32052029 https://doi.org/10.1093/cid/ciaa143
7. Yinka-Ogunleye A, Aruna O, Dalhat M, et al.; CDC Monkeypox Outbreak Team. Outbreak of human monkeypox in Nigeria in 2017–18: a clinical and epidemiological report. Lancet Infect Dis 2019;19:872–9. PMID:31285143 https://doi.org/10.1016/S1473-3099(19)30294-4
8. CDC. HIV surveillance report. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data United States and 6 dependent areas, 2020. Atlanta, GA: US Department of Health and Human Services, CDC; 2022. Accessed August 21, 2022. https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-27-no-3/index.html
9. CDC. HIV surveillance report. HIV infection risk, prevention, and testing behaviors among men who have sex with men—National HIV Behavioral Surveillance, 23 U.S. cities, 2017. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Accessed August 21, 2022. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-special-report-number-22.pdf
10. O'Shea J, Filardo TD, Morris SB, Weiser J, Petersen B, Brooks JT. Interim guidance for prevention and treatment of monkeypox in persons with HIV infection—United States, August 2022. MMWR Morb Mortal Wkly Rep 2022;71:1023–8. PMID:35951495 https://doi.org/10.15585/mmwr.mm7132e4

Detection of a Highly Divergent Type 3 Vaccine-Derived Poliovirus in a Child with a Severe Primary Immunodeficiency Disorder — Chongqing, China, 2022

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Oral poliovirus vaccine (OPV) has proven to be highly effective in the global effort to eradicate poliomyelitis because of its ability to induce both humoral and intestinal immunity, ease of administration, and low cost (*1*). Sabin-strain OPV contains live attenuated virus and induces immunity by replicating in the intestinal tract, triggering an immune response that clears the vaccine virus. However, among undervaccinated communities and persons with immunodeficiency, OPV mutations that arise during prolonged replication can result in the emergence of genetically divergent, neurovirulent vaccine-derived polioviruses (VDPVs). In addition, OPV has resulted in rare cases of vaccine-associated paralytic poliomyelitis (VAPP) among vaccine recipients or their close contacts (*1*). Identification of circulating polioviruses relies on surveillance of acute flaccid paralysis (AFP) and environmental surveillance of wastewater (i.e., sewage). In 2022, type 3 VDPV (VDPV3) was detected in stool specimens from an infant with primary immunodeficiency disorder (PID) through a pilot surveillance program to identify VDPVs in children with PIDs. Integrated AFP, environmental, and immunodeficiency-associated VDPV (iVDPV) surveillance is critical to detecting and containing all polioviruses and achieving the goal of global polio eradication.

In 2016, the year after the Global Polio Eradication Initiative (GPEI) Global Certification Commission* certified the eradication of type 2 wild poliovirus (WPV2) (*2*), China joined a global, synchronized effort to cease the use of type 2 oral poliovirus vaccine (OPV2). At that time, the routine polio vaccination schedule was changed from 3 doses of trivalent OPV (which contains Sabin strain types 1, 2 and 3) to 1 dose of injectable inactivated polio vaccine (IPV) (which contains inactivated 1, 2, and 3 poliovirus serotypes) followed by 3 doses of bivalent OPV (bOPV) (which contains Sabin strain types 1 and 3). In 2020, the schedule was changed to 2 doses of IPV followed by 2 doses of bOPV to increase protection against type 2 poliovirus.

Although China was declared free of all indigenous wild poliovirus (WPV) transmission by the GPEI's Regional Certification Commission in 2000,† the country continues to face two substantial threats to its polio-free status, namely the risk for importation of WPV from a country with endemic transmission and the emergence of circulating VDPVs because of ongoing domestic use of OPV. Sensitive, nationwide AFP surveillance§ is effective in detecting children paralyzed by WPVs and VDPVs. The National Polio Laboratory Network of China supports environmental surveillance to detect polioviruses excreted from infected persons or circulating in a community, even if not detected by AFP surveillance.

Prolonged excretion of iVDPVs can potentially seed community transmission of genetically divergent infectious polioviruses, threatening polio eradication efforts. Children with PIDs are susceptible to recurrent, severe enterovirus infections. Because their immune systems cannot clear replicating live vaccine virus, these children are at increased risk for paralysis when exposed to OPV (*3*). Sensitive AFP surveillance detects iVDPV–infected persons with paralysis; however, persons who excrete iVDPV might not develop paralysis in the short-term, (*4*) and wastewater analysis in China is geographically limited in scope because not all areas of the country conduct environmental surveillance. These limitations of poliovirus surveillance mean that a substantial number of iVDPVs cases might not be routinely detected.

In response to World Health Organization (WHO) recommendations to extend poliovirus surveillance to persons with PIDs, the Chinese Center for Disease Control and Prevention (CCDC) launched a pilot iVDPV surveillance program in 2021. Five children's hospitals located in Beijing, Shanghai, Zhengzhou, and Chongqing participate in the program, which recruits children who receive a new diagnosis of primary antibody deficiency or combined immunodeficiency disorder to provide stool specimens for poliovirus testing.

In March 2022, VDPV3 was detected in stool specimens from an infant who had received a new diagnosis of PID and was hospitalized in Children's Hospital of Chongqing Medical University (CHCMU). CCDC and partners in Chongqing investigated the case. This study was reviewed and approved by the institutional review board of the Chinese Center for Disease Control and Prevention.

* https://polioeradication.org/tools-and-library/policy-reports/certification-reports/global-certification-commission/

† https://www.who.int/china/health-topics/poliomyelitis-(polio)#:~:text=In%202000%20China%20was%20declared,the%20WHO%20Western%20Pacific%20Region

§ AFP surveillance comprises identification and reporting of children with AFP and transporting of stool specimens to a certified laboratory for analysis. Isolated polioviruses are further characterized to determine a strain's origin. https://polioeradication.org/polio-today/polio-now/surveillance-indicators/

Summary

What is already known about this topic?

Surveillance of acute flaccid paralysis (AFP) and wastewater (environmental) are critical to polio eradication efforts. Children with primary immunodeficiency disorders (PIDs) can excrete vaccine-derived polioviruses (VDPVs), which can hamper eradication efforts.

What is added by this report?

In March 2022, a type 3 VDPV was detected in stool specimens from an infant with PID who was hospitalized in Children's Hospital of Chongqing Medical University, China. Surveillance for poliovirus in PID patients has increased detection of immunodeficiency-related (iVDPV) cases.

What are the implications for public health practice?

Integrated systematic poliovirus surveillance, including AFP, environmental, and iVDPV surveillance, is critical to the detection and containment of all polioviruses and achievement of global polio eradication.

The patient, a boy aged 1 year, was born in Guizhou province. He was initially admitted to CHCMU's immunology division at age 6 months with persistent diarrhea, daily fevers, diffuse red papular rash, and lymphadenitis. He received a diagnosis of severe combined immunodeficiency (SCID) with heterozygous mutations in the ZAP70 gene, which is a rare autosomal recessive form of SCID caused by abnormal T-cell receptor signaling. Lymph node biopsy and culture found disseminated mycobacterial disease. He had received the recommended Bacille Calmette-Guérin vaccine (BCG) on the first day of life and subsequently developed recurrent localized abscesses and ulcers at the BCG vaccination site. His parents reported having sought treatment at a local hospital at this time; however, no documentation of any evaluation was available. The patient had also received 2 IPV doses at ages 2 and 3 months (May 24 and June 29, 2021, respectively) and the first bOPV dose at age 4 months (July 29, 2021), as recommended. Shortly after receipt of the first bOPV dose, he experienced left axillary lymphadenitis that ultimately involved right axillary, occipital, and cervical lymph nodes. He later acquired *Klebsiella pneumoniae* and developed *Pneumocystis yersini* pneumonia. He died of respiratory failure in the CHCMU intensive care unit on May 3, 2022, at age 13 months.

During the patient's hospitalization, stool specimens were obtained on February 28 and March 1, 2022, and sent to the CCDC polio laboratory for testing in accordance with WHO recommendations (*5*). Four isolates obtained and tested by real-time reverse transcription–polymerase chain reaction were identified as type 3 poliovirus. Genetic sequencing of viral capsid VP1 coding region indicated that the four isolates diverged from type 3 Sabin strain by 22, 23, 22, and 24 nucleotides (2.4%–2.7%) and shared 15 nucleotide substitutions.

Discussion

The first identified iVDPV case was reported in the United Kingdom in 1962; as of May 2020, only 149 cases have been reported worldwide (*6*). Most patients with iVDPV develop paralysis before they receive a diagnosis of immune deficiency and are typically detected through AFP surveillance. Other iVDPV cases have been detected through stool cultures obtained to diagnose enterovirus infection in children with suspected or confirmed PID. Among the three types of poliovirus, 56% of iVDPVs were type 2, 23% were type 3, 17% were type 1, and 4% were heterotypic mixtures (*6*). The incidence of iVDPV2 detection declined markedly after the global removal of OPV2 from routine immunization in 2016. Eleven cases of iVDPV were detected in China by AFP surveillance through 2021, before the case described in this report; among these previous cases, four patients died and seven stopped excreting poliovirus.

Children with PID are affected by a range of inherited disorders that result in developmental defects or dysfunction of immune system components (*7*). Live vaccines are usually contraindicated in children with PID because of their risk for causing disease. Although prenatal screening programs can identify some PIDs, identification and diagnosis of PID requires consultation with specialists including clinical immunologists. Infants with PID might therefore receive BCG or OPV before receiving a diagnosis of PID, increasing the risk for disseminated mycobacterial disease and iVDPV infection. ZAP70 gene deficiency is very rare and manifests with typical clinical features of SCID early in life (*8*). Approximately one half of BCG-vaccinated SCID patients have developed BCG-associated manifestations (*9*). Therefore, dissemination after BCG vaccination might be the initial clinical sign of PID, after which, receipt of live, attenuated vaccines is contraindicated.

As the global initiative progresses toward polio eradication, identification of patients with PID is increasing in importance, because iVDPVs can jeopardize polio eradication efforts through long-term excretion by PID patients. To identify non-paralyzed iVDPV cases, GPEI has proposed augmenting AFP and environmental surveillance with poliovirus surveillance in children with PID diagnoses and is supporting implementation of iVDPV surveillance in several countries (*6*).

The findings in this report are subject to at least one limitation. The infant's death precluded collection of additional stool specimens to further assess virus mutations. The infant described in this report never experienced paralysis. Among known patients who excrete iVDPVs, approximately 30% do not experience paralysis (*4*).

Surveillance among patients with PID has increased detection of iVDPVs in patients without paralysis (*6*). This early

finding of a nonparalyzed iVDPV patient in the PID pilot project supports the development of a long-term plan and guidance for iVDPV surveillance in China. Comprehensive iVDPV surveillance requires awareness among clinical immunologists that children who receive a new diagnosis of PID should have stool specimens tested for poliovirus by contacting their local public health authorities. Currently, antiviral treatment of iVDPV infections is under development (*10*). Effective treatment clears prolonged or chronic infection among patients with PIDs and removes a potential source of poliovirus transmission. Integrated systematic poliovirus surveillance including AFP, environmental, and iVDPV surveillance is critical to detecting and containing all polioviruses and helping to achieve and sustain a world free of polio.

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References

1. Wang HB, Luo HM, Li L, et al. Vaccine-derived poliovirus surveillance in China during 2001–2013: the potential challenge for maintaining polio free status. BMC Infect Dis 2017;17:742–9. PMID:29197328 https://doi.org/10.1186/s12879-017-2849-z
2. Bigouette JP, Wilkinson AL, Tallis G, Burns CC, Wassilak SGF, Vertefeuille JF. Progress toward polio eradication—worldwide, January 2019–June 2021. MMWR Morb Mortal Wkly Rep 2021;70:1129–35. PMID:34437527 https://doi.org/10.15585/mmwr.mm7034a1
3. Pethani AS, Kazi Z, Nayyar U, et al. Poliovirus excretion among children with primary immune deficiency in Pakistan: a pilot surveillance study protocol. BMJ Open 2021;11:e045904. PMID:34321293 https://doi.org/10.1136/bmjopen-2020-045904
4. Shaghaghi M, Soleyman-Jahi S, Abolhassani H, et al. New insights into physiopathology of immunodeficiency-associated vaccine-derived poliovirus infection; systematic review of over 5 decades of data. Vaccine 2018;36:1711–9. PMID:29478755 https://doi.org/10.1016/j.vaccine.2018.02.059
5. World Health Organization. Polio laboratory manual. 4th ed. Geneva, Switzerland: World Health Organization; 2004. https://apps.who.int/iris/bitstream/handle/10665/68762/WHO_IVB_04.10.pdf?sequence=1&isAllowed=y
6. Macklin G, Diop OM, Humayun A, et al. Update on immunodeficiency-associated vaccine-derived polioviruses—worldwide, July 2018–December 2019. MMWR Morb Mortal Wkly Rep 2020;69:913–7. PMID:32673297 https://doi.org/10.15585/mmwr.mm6928a4
7. Mohanty MC, Madkaikar MR, Desai M, et al. Poliovirus excretion in children with primary immunodeficiency disorders, India. Emerg Infect Dis 2017;23:1664–70. PMID:28930011 https://doi.org/10.3201/eid2310.170724
8. Santos A, Dias A, Cordeiro A, et al. Severe axillary lymphadenitis after BCG vaccination: alert for primary immunodeficiencies. J Microbiol Immunol Infect 2010;43:530–7. PMID:21195982 https://doi.org/10.1016/S1684-1182(10)60082-5
9. Marciano BE, Huang CY, Joshi G, et al. BCG vaccination in patients with severe combined immunodeficiency: complications, risks, and vaccination policies. J Allergy Clin Immunol 2014;133:1134–41. PMID:24679470 https://doi.org/10.1016/j.jaci.2014.02.028
10. Sutter RW, Modlin JF, Zaffran M. Completing polio eradication: the case for antiviral drugs. J Infect Dis 2017;215:333–4. PMID:27932609 https://doi.org/10.1093/infdis/jiw547

Detection of Higher Cycle Threshold Values in Culturable SARS-CoV-2 Omicron BA.1 Sublineage Compared with Pre-Omicron Variant Specimens — San Francisco Bay Area, California, July 2021—March 2022

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Before emergence in late 2021 of the highly transmissible B.1.1.529 (Omicron) variant of SARS-CoV-2, the virus that causes COVID-19 (*1*,*2*), several studies demonstrated that SARS-CoV-2 was unlikely to be cultured from specimens with high cycle threshold (Ct) values[§] from real-time reverse transcription–polymerase chain reaction (RT-PCR) tests (suggesting low viral RNA levels) (*3*). Although CDC and others do not recommend attempting to correlate Ct values with the amount of infectious virus in the original specimen (*4*,*5*), low Ct values are sometimes used as surrogate markers for infectiousness in clinical, public health, or research settings without access to virus culture (*5*). However, the consistency in reliability of this practice across SARS-CoV-2 variants remains uncertain because Omicron-specific data on infectious virus shedding, including its relationship with RNA levels, are limited. In the current analysis, nasal specimens collected from an ongoing longitudinal cohort[¶] (*6*,*7*) of nonhospitalized participants with positive SARS-CoV-2 test results living in the San Francisco Bay Area[**] were used to generate Ct values and assess for the presence of culturable SARS-CoV-2 virus; findings were compared between specimens from participants infected with pre-Omicron variants and those infected with the Omicron BA.1 sublineage. Among specimens with culturable virus detected, Ct values were higher (suggesting lower RNA levels) during Omicron BA.1 infections than during pre-Omicron infections, suggesting variant-specific differences in viral dynamics. Supporting CDC guidance, these data show that Ct values likely do not provide a consistent proxy for infectiousness across SARS-CoV-2 variants.

As part of an ongoing longitudinal cohort study, persons with documented SARS-CoV-2 infection (based on a positive clinical real-time RT-PCR test result) and their household members were recruited within 5 days of the first symptom onset in the household (or first RNA-positive test result if the infected person was asymptomatic). All participants self-collected nasal swab specimens once daily for 2 weeks from the first onset in the household; some participants also provided a serum specimen at enrollment to identify evidence of previous infection.[††] In a single laboratory, real-time RT-PCR targeting SARS-CoV-2 nucleocapsid (*N*) and envelope protein (*E*) genes[§§] (*8*) was used to detect RNA and to determine Ct values, whole genome sequencing was used to identify the infecting variant strain and sublineage, and the presence or absence of culturable virus was assessed by cytopathic effect observed in tissue culture.[¶¶] Enrollment sera were tested for the presence or absence of anti-N immunoglobulin G (IgG) per manufacturer (Abbott) instructions at a clinical laboratory at the University of California, San Francisco.

Participants with confirmed infection (based on having at least one nasal specimen test positive by real-time RT-PCR for both

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§ Ct values reflect the number of amplification cycles necessary to detect viral RNA. Ct values are inversely related to the amount of viral RNA present in a specimen and are sometimes used as a proxy for viral RNA levels or loads, with low Ct values indicating high viral RNA levels and high Ct values low viral RNA levels. Ct value of 40 was assigned to negative real-time RT-PCR results because the PCR was run for 40 cycles without detecting any signal.

¶ In brief, study enrollment began during September 2020. Eligible persons with positive SARS-CoV-2 RT-PCR test results are identified from local outpatient or public health COVID-19 data sources and contacted to ask about interest in the study. Persons are eligible if they can be enrolled within 5 days of their illness onset (or first positive test result, if asymptomatic), and have at least one household member who is also willing to enroll and is not yet known to be infected themselves; if a household member is already known to be infected, that household can still be eligible if household members can be enrolled within 5 days of that household member's illness onset (or first positive test result, if asymptomatic). At enrollment, participants provide an optional blood specimen that is taken to a biorepository that same day for processing as serum, aliquoting, and long-term storage at −112°F (−80°C).

** The San Francisco Bay Area consists of nine counties (Alameda, Contra Costa, Marin, Napa, San Francisco, San Mateo, Santa Clara, Solano, and Sonoma) and 101 municipalities in California.

†† Participants are instructed on how to collect (daily) and store nasal specimens; daily specimens are collected regardless of symptom status. Once collected, nasal specimens are stored at −4°F (−20°C) in the participant's household until transferred on dry ice to a biorepository for processing, aliquoting, and long-term storage at −112°F (−80°C).

§§ Detection of these targets is not affected by the viral genome sequences of the variants, such as Omicron. The *E* gene is not mutated between Omicron and pre-Omicron genomes, and the only mutation in the targeted sequence of the real-time RT-PCR probe of the Omicron *N* gene does not perturb its efficient detection.

¶¶ Cytopathic effect (CPE) was assessed in Vero cells stably overexpressing the human TMPRSS-2 and ACE-2 genes. Briefly, 200 μL of nasal specimen (3 mL total specimen, previously aliquoted and frozen at −112°F [−80°C]) were added to a well of a 96-well plate and serially diluted twofold with 2.5x104 cells per well. Vero-TMPRSS2-hACE2 cells form characteristic syncytia (fused cells) upon SARS-CoV-2 infection, enabling rapid and specific visual evaluation for CPE, which was assessed after 2 and 5 days. Cells from wells with CPE were then processed for RNA extraction and real-time RT-PCR to confirm SARS-CoV-2 infection.

N and *E*) were included, and the analysis was limited to specimens collected within 14 days of onset for each participant (for symptomatic patients, onset was defined as the first day of symptoms,*** and for asymptomatic participants, as the first RNA-positive specimen [i.e., positive for both *N* and *E* real-time RT-PCR targets]). Participants aged ≥18 years were classified as adults, and those aged <18 years were classified as children and adolescents. Vaccination status was classified as fully vaccinated††† (completion of a primary COVID-19 vaccination series) or unvaccinated; no participants were partially vaccinated, and no participants had received a booster dose ≥14 days before either symptom onset or enrollment. Ct values of Omicron specimens were compared with those of pre-Omicron specimens among all specimens, among RNA-positive specimens, and among specimens with viable virus detected in tissue culture (virus-positive specimens). With *E*-specific Ct value as the main outcome and variant group (Omicron versus pre-Omicron) as the main exposure, mixed linear regression models were used to account for clustering of multiple specimens per participant, and to control for potential confounding by age group and vaccination status. When Ct values among all or RNA-positive specimens were compared, an interaction term of the product of variant and infectiousness (i.e., virus-positivity) was included; this interaction term was excluded when Ct values within virus-positive specimens were assessed. Longitudinal sampling of infected participants resulted in some subsequently negative real-time RT-PCR specimens (no target detected); these were included in the all-specimen models and were assigned a Ct value of 40 for analysis. Sensitivity analyses were conducted with comparable models using *N*-specific Ct values as the outcome. All statistical analyses were performed using Stata Software (version 16.1; StataCorp). This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.§§§

A total of 1,147 nasal swab specimens from 124 participants were analyzed; among 17 participants infected with Omicron variants (all BA.1 sublineages) and 107 infected with pre-Omicron variants,¶¶¶ 149 and 998 specimens, respectively, were collected (Table). Timing of specimen collection after onset (in each participant) was similar in both groups (median = 8 days; IQR = 6–11 days). Among the 17 participants with Omicron BA.1 infections, nine (53%) were adults and 10 (59%) were fully vaccinated. Among 107 participants with pre-Omicron infections, 92 (86%) were adults and 35 (33%) were fully vaccinated. Nearly all participants were symptomatic (16 of 17 participants with Omicron BA.1 infection and 100 of 107 with pre-Omicron infection). No participants reported previous infection, and among 58 participants with available sera, none had detectable anti-N IgG at enrollment.

Accounting for age group and vaccination status, *E*-specific Ct values in all specimens were significantly higher in Omicron specimens than in pre-Omicron specimens (Ct difference = 4.45, p<0.001).**** When analysis was limited to RNA-positive specimens, a similar trend was observed (Ct difference = 3.90, p<0.001).†††† Despite these higher

TABLE. Characteristics of participants infected with SARS-CoV-2 pre-Omicron variants and Omicron BA.1 sublineage and nasal swab specimens evaluated for real-time reverse transcription–polymerase chain reaction cycle threshold values — San Francisco Bay Area, California, July 2021–March 2022

Participant and specimen	No. (%)		Change in *E*-specific Ct value between pre-Omicron and Omicron variants
	Pre-Omicron	Omicron	
All participants (N = 124)	**107 (100)**	**17 (100)**	—
Adults aged ≥18 yrs	92 (86)	9 (53)	—
Fully vaccinated*	35 (33)	10 (59)	—
Symptomatic†	100 (93)	16 (94)	—
Culturable virus detected	76 (71)	13 (76)	—
All specimens (N = 1,147)	**998 (100)**	**149 (100)**	**4.45§**
RNA-positive specimens¶	539 (53)	72 (48)	3.90§
Virus-positive specimens¶	298 (30)	39 (26)	5.77§
Median duration of virus detection after onset, days (IQR)	6 (5–8)	6 (5–8)	—
Median interval from onset to specimen collection, days (IQR)	8 (6–11)	8 (6–11)	

Abbreviations: Ct = cycle threshold; *E* = envelope gene.

* Fully vaccinated participants were defined as those who had received all recommended doses of a Food and Drug Administration–authorized or approved primary vaccine series (2 mRNA vaccine doses or a single dose of Johnson & Johnson [Janssen] vaccine) ≥14 days before either symptom onset or enrollment (whichever occurred earlier).

† Participants were considered symptomatic if they reported one or more COVID-19 signs or symptoms consistent with those listed by CDC, including fever, chills, shortness of breath, fatigue, muscle or body aches, headache, loss of taste, loss of smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhea. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

§ p<0.001.

¶ RNA-positive specimens are positive for both SARS-CoV-2 nucleocapsid and envelope gene real-time RT-PCR targets. Virus-positive specimens contain viable SARS-CoV-2 virus detected in tissue culture.

*** Participants were considered symptomatic if they reported one or more COVID-19 signs or symptoms consistent with those listed by CDC, including fever, chills, shortness of breath, fatigue, muscle or body aches, headache, loss of taste, loss of smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhea. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

††† Fully vaccinated participants were defined as those who had received all recommended doses of a Food and Drug Administration–authorized or approved primary vaccine series (2 mRNA vaccine doses or a single dose of Johnson & Johnson [Janssen] vaccine) ≥14 days before either symptom onset or enrollment (whichever occurred earlier).

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

¶¶¶ Pre-Omicron infections included 40 B.1.617.2 (Delta) and 67 pre-Delta infections.

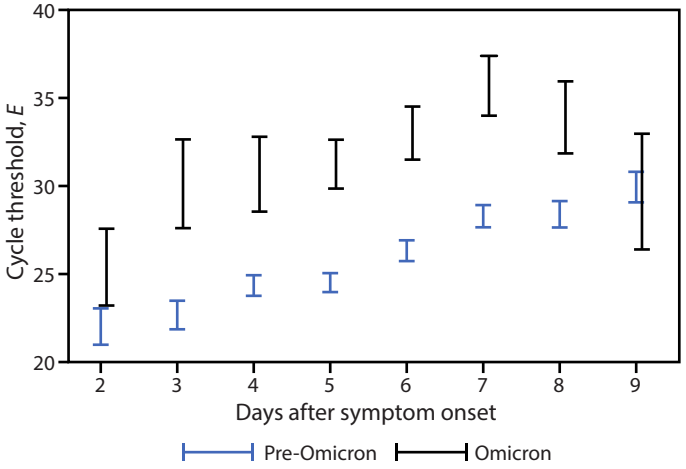
**** Among all specimens, *N*-specific Ct values were also significantly higher in Omicron versus pre-Omicron infections (Ct difference = 3.84, p<0.001).

†††† Among RNA-positive specimens, *N*-specific Ct values were also significantly higher in Omicron versus pre-Omicron infections (Ct difference = 3.27, p<0.001).

Ct values in Omicron than in pre-Omicron specimens, culturable virus was detected in specimens from a similar percentage of participants in both variant groups (Omicron = 76%; pre-Omicron = 71%), a similar percentage of total specimens (Omicron = 26%; pre-Omicron: 30%), and was detected for a similar duration following onset (median = 6 days, IQR = 5–8 days for both Omicron and pre-Omicron specimens). Among virus-positive specimens, *E*-specific Ct values were significantly higher in Omicron specimens than pre-Omicron specimens (Ct difference = 5.77, p<0.001).[§§§§] This difference was observed as early as day 3 after onset through day 8 after onset (Figure 1). When stratified by age group or vaccination status (Figure 2), virus-positive Omicron specimens were associated with higher *E*-specific Ct values than were virus-positive pre-Omicron specimens (p<0.01). Similar findings were observed in the *N*-specific analysis (p<0.001).

[§§§§] Among virus-positive specimens, *N*-specific Ct values were also significantly higher in Omicron versus pre-Omicron infections (Ct difference = 3.84, p<0.001). Further, no difference was detected in either *E*- or *N*-specific Ct values over time between Delta and pre-Delta specimens (*E*: Ct difference = −1.86, p = 0.25; *N*: Ct difference = −2.35, p = 0.14). Although not statistically significant, in the case of Delta infections, *E*- and *N*-specific Ct values were lower (suggesting higher viral RNA levels) compared with pre-Delta infections, hence the negative difference between Delta and pre-Delta specimens.

FIGURE 1. Pre-Omicron and Omicron BA.1 envelope gene–specific* cycle threshold values among nasal specimens with culturable SARS-CoV-2 virus,[†,§] by days after illness onset — San Francisco Bay Area, California, July 2021–March 2022

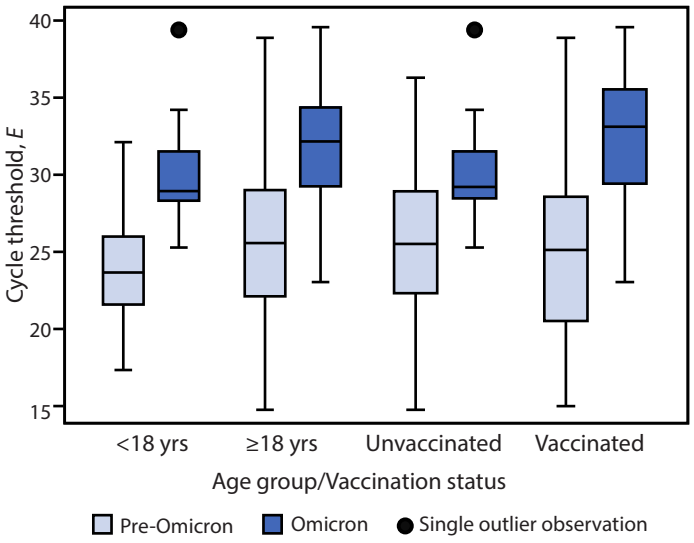


Abbreviation: *E* = envelope gene.
* Nucleocapsid-specific real-time reverse transcription–polymerase chain reaction results were similar.
† Included 33 Omicron specimens and 256 pre-Omicron specimens.
§ Displayed as 95% CIs. The mixed model used in this analysis included an interaction term between variant and time after symptom onset.

Discussion

In this study, and consistent with other published findings (*9*), Ct values detected in nasal specimens were higher (suggesting lower RNA levels) in those obtained from participants infected with SARS-CoV-2 Omicron BA.1 sublineage than in those from participants infected with pre-Omicron variants. However, despite these higher Ct values, culturable virus was detected from a similar proportion of participants in both variant groups, and for a similar duration following onset; consistent with a recent report (*10*), participants infected with Omicron BA.1 had detectable culturable virus for a median of 6 days after onset. Notably, among these virus-positive (i.e., potentially infectious) specimens, Ct values were higher than were those for pre-Omicron specimens, especially during the first week of illness. In addition, these differences between Omicron and pre-Omicron infections were observed in adults and in children and adolescents and were irrespective

FIGURE 2. Pre-Omicron and Omicron BA.1 envelope gene–specific* cycle threshold values among nasal specimens with culturable SARS-CoV-2 virus,[†] by age group[§] and by primary COVID-19 vaccination status[¶,] — San Francisco Bay Area, California, July 2021–March 2022**



Abbreviation: *E* = envelope gene.
* Nucleocapsid-specific real-time reverse transcription–polymerase chain reaction results were similar.
† Displayed as 95% CIs. The mixed model used in this analysis included an interaction term between variant and time after symptom onset.
§ Adults aged ≥18 years included 21 Omicron and 273 pre-Omicron specimens. Children and adolescents aged <18 years included 18 Omicron and 25 pre-Omicron specimens.
¶ Fully vaccinated included 18 Omicron and 81 pre-Omicron specimens. Unvaccinated included 21 Omicron and 217 pre-Omicron specimens.
** Boxplots display the median, lower, and upper quartiles and 1.5 times above or below the lower and upper quartiles.

Summary

What is already known about this topic?

Before emergence of the SARS-CoV-2 B.1.1.529 (Omicron) variant, infectious SARS-CoV-2 was unlikely to be cultured at high cycle threshold (Ct) values. Based on this, low Ct values, which are suggestive of high RNA levels, are sometimes used as surrogate markers for infectiousness.

What is added by this report?

In a longitudinal study including daily nasal swabbing, although Omicron BA.1 sublineage infections exhibited higher Ct values than did pre-Omicron infections, culturable Omicron virus was still detected. Among virus-positive specimens, Ct values were higher for Omicron than for pre-Omicron specimens, especially during the first week of illness.

What are the implications for public health practice?

Supporting CDC guidance, these data show that Ct values likely do not provide a consistent proxy for infectiousness across SARS-CoV-2 variants.

of vaccination status. Presence of culturable Omicron BA.1 in nasal specimens, despite high Ct values, might contribute to the high levels of Omicron transmission observed in other studies (*2*). Further, these findings highlight variant-specific differences in viral dynamics, specifically, differences in the relationship between RNA and shedding of infectious virus.

Strengths of this study include the robust prospective longitudinal nature of nasal swab specimen collection. Similar findings were observed from two distinct real-time RT-PCR targets, both of which have been shown to reliably amplify both Omicron and pre-Omicron variants.

The findings in this report are subject to at least three limitations. First, this is a single-site study with a small number of participants infected with the Omicron BA.1 sublineage; thus, these findings might not be representative of all infected persons. Replication of these findings with additional participants is necessary and is ongoing. Second, approximately one half of the participants did not provide an enrollment serum specimen; thus, it was not possible to comprehensively assess the incidence of previous infection. Finally, duplication was not carried out on multiple real-time RT-PCR platforms across laboratories.

Virus-positive (i.e., potentially infectious) specimens from participants infected with SARS-CoV-2 Omicron variants had significantly higher Ct values than did virus-positive specimens from participants infected with pre-Omicron variants. Supporting CDC guidance (*4*), these data highlight that Ct values likely do not provide a reliable or consistent proxy for infectiousness across SARS-CoV-2 variants.

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References

1. Lambrou AS, Shirk P, Steele MK, et al.; Strain Surveillance and Emerging Variants Bioinformatic Working Group; Strain Surveillance and Emerging Variants NS3 Working Group. Genomic surveillance for SARS-CoV-2 variants: predominance of the Delta (B.1.617.2) and Omicron (B.1.1.529) variants—United States, June 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:206–11. PMID:35143464 https://doi.org/10.15585/mmwr.mm7106a4
2. Araf Y, Akter F, Tang YD, et al. Omicron variant of SARS-CoV-2: genomics, transmissibility, and responses to current COVID-19 vaccines. J Med Virol 2022;94:1825–32. PMID:35023191 https://doi.org/10.1002/jmv.27588
3. Platten M, Hoffmann D, Grosser R, et al. SARS-CoV-2, Ct-values, and infectivity-conclusions to be drawn from side observations. Viruses 2021;13:1459. PMID:34452325 https://doi.org/10.3390/v13081459
4. CDC. Frequently asked questions about coronavirus (COVID-19) for laboratories. Atlanta, GA: US Department of Health and Human Services, CDC; 2021. https://www.cdc.gov/coronavirus/2019-ncov/lab/faqs.html
5. Binnicker MJ. Can testing predict SARS-CoV-2 infectivity? The potential for certain methods to be surrogates for replication-competent virus. J Clin Microbiol 2021;59:e0046921. PMID:34346713 https://doi.org/10.1128/JCM.00469-21
6. Kelly JD, Lu S, Anglin K, et al. Magnitude and determinants of SARS-CoV-2 household transmission: a longitudinal cohort study. Clin Infect Dis. Epub July 5, 2022. https://doi.org/10.1093/cid/ciac545
7. Garcia-Knight M, Anglin K, Tassetto M, et al. Infectious viral shedding of SARS-CoV-2 Delta following vaccination: a longitudinal cohort study. medRxiv [Preprint posted online May 19, 2022]. https://doi.org/10.1101/2022.05.15.22275051
8. Bei Y, Vrtis KB, Borgaro JG, Langhorst BW, Nichols NM. The Omicron variant mutation at position 28,311 in the SARS-CoV-2 N gene does not perturb CDC N1 target detection. medRxiv [Preprint posted online December 17, 2021]. https://doi.org/10.1101/2021.12.16.21267734
9. Sentis C, Billaud G, Bal A, et al.; The Covid-Diagnosis HCL Study Group. SARS-CoV-2 Omicron variant, lineage BA.1, is associated with lower viral load in nasopharyngeal samples compared to Delta variant. Viruses 2022;14:919. PMID:35632661 https://doi.org/10.3390/v14050919
10. Boucau J, Marino C, Regan J, et al. Duration of shedding of culturable virus in SARS-CoV-2 Omicron (BA.1) infection. N Engl J Med 2022;387:275–7. PMID:35767428 https://doi.org/10.1056/NEJMc2202092

Orthopoxvirus Testing Challenges for Persons in Populations at Low Risk or Without Known Epidemiologic Link to Monkeypox — United States, 2022

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Since May 2022, approximately 20,000 cases of monkeypox have been identified in the United States, part of a global outbreak occurring in approximately 90 countries and currently affecting primarily gay, bisexual, and other men who have sex with men (MSM) (*1*). *Monkeypox virus* (MPXV) spreads from person to person through close, prolonged contact; a small number of cases have occurred in populations who are not MSM (e.g., women and children), and testing is recommended for persons who meet the suspected case definition* (*1*). CDC previously developed five real-time polymerase chain reaction (PCR) assays for detection of orthopoxviruses from lesion specimens (*2*,*3*). CDC was granted 510(k) clearance for the nonvariola-orthopoxvirus (NVO)–specific PCR assay by the Food and Drug Administration. This assay was implemented within the Laboratory Response Network (LRN) in the early 2000s and became critical for early detection of MPXV and implementation of public health action in previous travel-associated cases as well as during the current outbreak (*4*–*7*). PCR assays (NVO and other *Orthopoxvirus* laboratory developed tests [LDT]) represent the primary tool for monkeypox diagnosis. These tests are highly sensitive, and cross-contamination from other MPXV specimens being processed, tested, or both alongside negative specimens can occasionally lead to false-positive results. This report describes three patients who had atypical rashes and no epidemiologic link to a monkeypox case or known risk factors; these persons received diagnoses of monkeypox based on late cycle threshold (Ct) values ≥34, which were false-positive test results. The initial diagnoses were followed by administration of antiviral treatment (i.e., tecovirimat) and JYNNEOS vaccine postexposure prophylaxis (PEP) to patients' close contacts. After receiving subsequent testing, none of the three patients was confirmed to have monkeypox. Knowledge gained from these and other cases resulted in changes to CDC guidance. When testing for monkeypox in specimens from patients without an epidemiologic link or risk factors or who do not meet clinical criteria (or where these are unknown), laboratory scientists should reextract and retest specimens with late Ct values (based on this report, Ct ≥34 is recommended) (*8*). CDC can be consulted for complex cases including those that appear atypical or questionable cases and can perform additional viral species- and clade-specific PCR testing and antiorthopoxvirus serologic testing.

The three patients described in this report were not MSM, and all had an atypical rash (i.e., without the characteristic progression over 2–4 weeks from pustular to deep-seated, umbilicated lesions). The patients initially received positive *Orthopoxvirus* real-time PCR test results, with high Ct values (≥34); the positive PCR results were followed by implementation of clinical and public health recommendations for monkeypox, including antiviral treatment and PEP.† This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.§

Description of Patients

Patient A, a healthy pregnant woman (estimated 37 weeks' gestation) was evaluated for labor and was noted to have a pruritic erythematous rash on her arms, abdomen, upper back, calves, and shins. Her lesions, not typical for monkeypox, had irregular borders, and were different sizes and in different stages of development (i.e., tan papules, crusted papules, pustules, and hyperpigmented macules) in the same anatomic locations, with reported onset 5 weeks earlier. No genital lesions were present. She did not report typical prodromal signs or symptoms of monkeypox (e.g., body aches, lymphadenopathy, fever, or chills). A household member was reported to have a similar rash, with onset 4 days before that in patient A; that person's rash resolved within 1 week, and no testing was performed; no epidemiologic link to a person with monkeypox was identified. Patient A had no interstate or international travel during the 3 weeks preceding rash onset. She reported varicella infection and receipt of smallpox vaccination as a child. Tests for varicella-zoster virus, syphilis, herpes simplex virus, cryptococcosis, and histoplasmosis were performed, all

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

† https://www.cdc.gov/poxvirus/monkeypox/health-departments/vaccine-considerations.html

§ 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.

with negative results. A swab from a pustular forearm lesion, obtained 53 days after rash onset yielded a positive NVO test result (Table). Two days after receiving the result, the woman had an uncomplicated vaginal delivery of a healthy neonate. The state health department and CDC clinicians recommended several measures until lesions resolved: 1) initiation of monkeypox infection-control precautions[¶] in the hospital, 2) precautions to prevent skin-to-skin contact between mother and infant,[**] 3) designation of another household member as the primary caregiver, 4) delay of breastfeeding, and 5) disposal of breast milk. Because of concern for congenital or perinatal transmission, vaccinia immune globulin intravenous (VIGIV) was administered to the neonate under a single patient emergency Investigational New Drug application. Further testing with a Clade II (i.e., West African) MPXV–specific real-time PCR LDT was inconclusive. Because of the discordant results, serum from patient A obtained on day 42 after rash onset was sent to CDC for serologic analysis; no antiorthopoxvirus antibodies were detected, arguing against orthopoxvirus infection (*9*). The recommendations restricting contact with the baby and for delaying breastfeeding were discontinued after rash resolution when the infant was aged 21 days (Figure). The patient's skin lesions were most likely attributable to bed bugs, which was a diagnosis that the clinical care team considered initially but set aside upon receipt of the positive NVO result.

[¶] https://www.cdc.gov/poxvirus/monkeypox/clinicians/infection-control-healthcare.html

[**] https://www.cdc.gov/poxvirus/monkeypox/clinicians/pregnancy.html

Patient B is an elementary school–aged, previously healthy child (Table). The child developed influenza-like symptoms followed 2 days later by raised lesions on the face. The next day, lesions had spread to the trunk, back, and arms. The lesions were initially papulopustular, and over the course of 2 days became ulcerated and crusted. No epidemiologic link to a person with monkeypox was identified. A swab of a facial lesion tested positive by an orthopoxvirus generic LDT. Treatment with tecovirimat was started because the child had periorbital lesions and because of concern for potential ocular autoinoculation and development of sight-threatening disease. The child lived with four other persons and had engaged in a contact sport when the rash was present. The child isolated at home, and all family members received PEP with JYNNEOS vaccine; PEP for teammates was held pending reextraction and retesting of the original specimen (Figure). The subsequent result was negative, and the child was released from isolation. Enterovirus PCR testing was positive, suggesting a diagnosis of hand, foot, and mouth disease.

Patient C is an infant who visited the United States with both parents for approximately 1 month and subsequently traveled to another country with four other families for vacation. During that trip, the infant experienced diarrhea followed by lymphadenopathy, and 2 days later, after returning to the United States, developed fever and a rash (Table). The rash was described as maculopapular and vesicular, and started on the arms and legs progressing to the earlobe, chest, scalp, and lower abdomen; the rash scabbed over 2 weeks later. One abdominal lesion tested positive by NVO and an orthopoxvirus

TABLE. Characteristic of and testing, interventions, and treatment given to persons initially receiving monkeypox diagnoses based on a false-positive test result— United States, 2022

Patient	Patient characteristic	Symptoms	Initial real-time PCR test result*	Additional MPXV, NVO, or OPXV real-time PCR test result*	IgM[†]	Treatment administered	Total no. of contacts who received PEP[§] (adults, children)	Suspected alternative diagnosis
A	Pregnant woman, 37 weeks' gestation	Rash, pruritus	Pos NVO Ct: 34.30	MPXV: inconclusive[¶]	Neg	Tecovirimat to patient A, VIGIV to neonate	1 (1, 0)	Bed bugs
B	Elementary school-aged child	Rash, fatigue, headache, decreased appetite, fever	Pos NVO Ct: 35.82	Neg NVO Ct: >40**	NP	Tecovirimat	4 (2, 2)	Hand, foot, and mouth disease
C	Infant	Diarrhea, lymphadenopathy, fever, rash	Pos NVO Ct: 34.67 OPVX Ct: 36.71	MPXV: Inconclusive[¶] Neg OPXV Ct: >40 Neg NVO Ct >40	Neg	Tecovirimat	19 (12, 7)	Pending

Abbreviations: Ct = cycle threshold; IgM = immunoglobulin M; MPXV = *Monkeypox virus*; Neg = negative; NP = not performed; NVO = non-variola *Orthopoxvirus*; OPXV = *Orthopoxvirus*; PCR = polymerase chain reaction; PEP = postexposure prophylaxis; Pos = positive; VIGIV = vaccinia immune globulin intravenous.

* Real-time PCR assays for testing of orthopoxviruses and *Monkeypox virus*–specific assays have varying Ct cutoffs depending on assay used. Cutoffs can range from approximately 37 to 40.

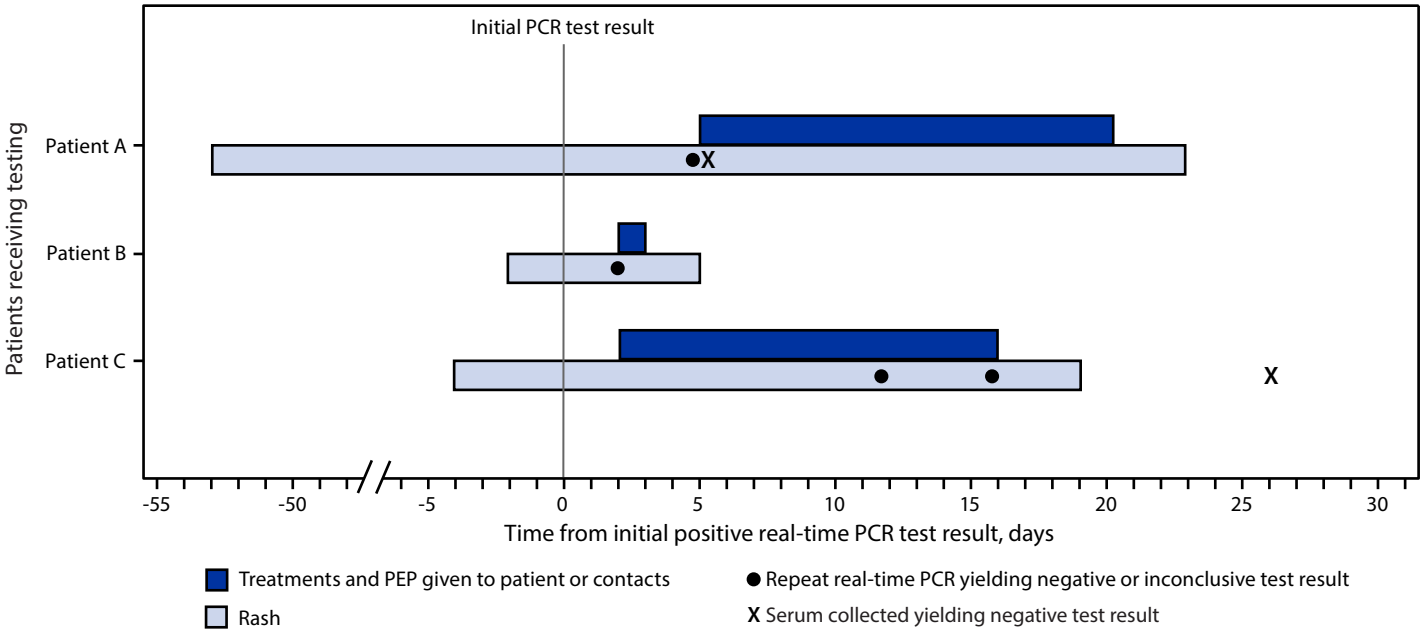
† Antiorthopoxvirus IgM antibody is expected to be detectable 4–56 days after rash onset in patients with monkeypox.

§ JYNNEOS vaccine.

¶ Test results from duplicate swab from the initial lesion, inconclusive based on internal control indicating inadequate specimen collection.

** Test results from a reextraction and retesting of the initial lesion swab.

FIGURE. Timeline of patient testing and public health interventions for false-positive *Monkeypox virus* test results — United States, 2022



Abbreviations: PCR = polymerase chain reaction; PEP = postexposure prophylaxis.

Summary

What is already known about this topic?

Testing for *Monkeypox virus*, using Food and Drug Administration 510(k)–cleared non-variola *Orthopoxvirus* real-time polymerase chain reaction (PCR) test and laboratory developed real-time PCR tests, is critical for diagnosis of suspected cases.

What is added by this report?

Three persons with atypical rashes, uncharacteristic illnesses, and absence of risk factors or an epidemiologic link to a known monkeypox case received false-positive real-time PCR test results; late cycle threshold values were all ≥34.

What are the implications for public health practice?

When testing specimens from patients with atypical signs and symptoms or without epidemiologic links or risk factors or where these are unknown, laboratories should reextract and retest specimens with real-time PCR Ct values that are high (≥34) to avoid unnecessary medical treatment and expenditure of public health resources.

generic LDT; two other lesions tested negative. The infant was treated with oral tecovirimat. No epidemiologic link to a person with monkeypox was identified. Over a 15-day period starting on the second day of the vacation, five of 11 children (including patient C) and four of 14 adults from the families who vacationed with the infant experienced rashes that varied in appearance. Among some of the children, the rash looked like insect bites and not consistent with monkeypox; among others, the rash was vesicular or pustular involving the arms, legs, feet, fingers, or face, and eventually scabbing over. Results of NVO testing of lesions on four children and four adults were negative or inconclusive. A multijurisdictional investigation was launched to determine potential exposures and administer PEP to all family members. Twelve adults and seven children (aged 0–14 years) received PEP with JYNNEOS. Because of the ongoing investigation, multiple families changed travel plans, and patient C's family postponed travel back to their country of residence for approximately 4 weeks. Serum from two adults and four children (including patient C) obtained 3–31 days after rash onset did not detect the presence of anti-orthopoxvirus antibodies (Figure).

Discussion

Evaluation of these three patients for monkeypox highlights the need for caution in interpreting single laboratory test findings in patients with a low pretest probability of infection; this includes lack of an epidemiologic link, non-MSM populations (e.g., women and children, who currently account for <2% of confirmed monkeypox cases), and signs, symptoms, or rash progression inconsistent with monkeypox. This approach is similar to the caution recommended in evaluating other laboratory tests when pretest probability is low (e.g., D-dimer results for a deep vein thrombosis or serology for Lyme disease)[††] (*10*). Multiple clinical features in each of these three patients were inconsistent with monkeypox, including an atypical rash that

[††] https://www.cdc.gov/lyme/resources/pdfs/lyme-1532_poster_prior-pretest-probability-testing_digital-508.pdf

was inconsistent with the characteristic progression of monkeypox lesions, as well as the absence of an epidemiologic link to a known case of monkeypox. The Ct values of all initial positive test results were high (≥34) indicating a low level of viral DNA. Cautious interpretation of test results is warranted when the pretest probability of monkeypox is low. As monkeypox testing has expanded, CDC recommends that laboratory professionals verify positive diagnostic results (*8*) for *Orthopoxvirus* or MPXV DNA in specimens with high Ct values, especially from persons who do not meet epidemiologic risk criteria for monkeypox or for whom lesions do not progress as expected. Molecular tests (e.g., real-time PCR tests) are highly specific and sensitive; however, when epidemiologic criteria are absent or unknown and the Ct value is high (generally ≥34), CDC recommends reextraction and retesting of the specimen.

Monkeypox currently occurs predominantly among MSM, although infection can occur in any person after close physical contact with persons with monkeypox or items that have been in contact with lesions, such as clothing or bedding. Because the positive predictive value in populations with low disease incidence is lower than that in populations with a higher disease incidence, laboratory results in persons with low pretest probability of infection should be carefully examined and reviewed, and other plausible diagnoses (e.g., hand, foot, and mouth disease; varicella; molluscum contagiosum) should be considered. The clinical course of illness should be reviewed, including documenting the lesions with photographs. CDC can be consulted for atypical or questionable cases and can perform additional viral-specific and clade-specific PCR testing and antiorthopoxvirus serology.

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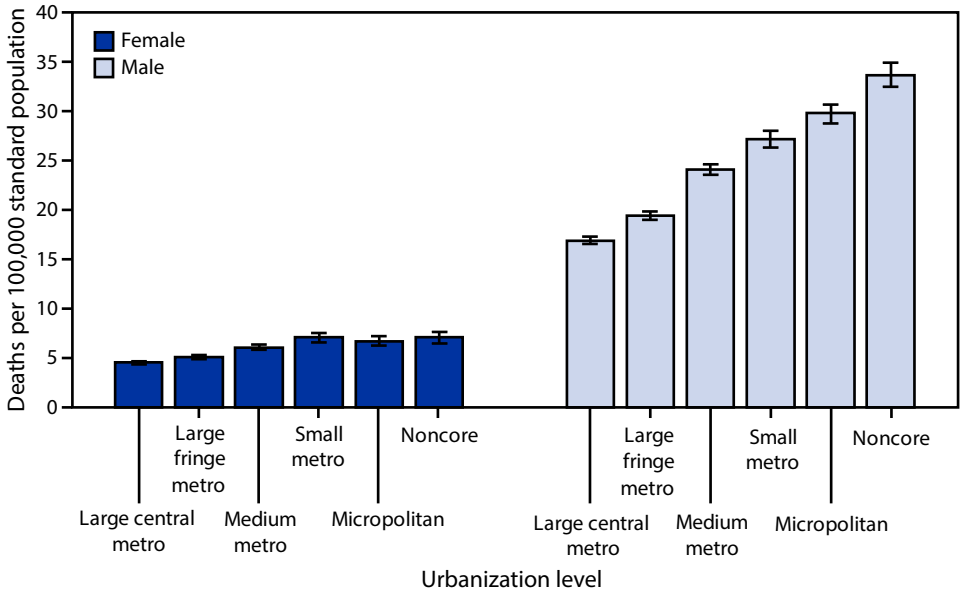
References

1. Philpott D, Hughes CM, Alroy KA, et al.; CDC Multinational Monkeypox Response Team. Epidemiologic and clinical characteristics of monkeypox cases—United States, May 17–July 22, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1018–22. PMID:35951487 https://doi.org/10.15585/mmwr.mm7132e3
2. Li Y, Olson VA, Laue T, Laker MT, Damon IK. Detection of *Monkeypox virus* with real-time PCR assays. J Clin Virol 2006;36:194–203. PMID:16731033 https://doi.org/10.1016/j.jcv.2006.03.012
3. Li Y, Zhao H, Wilkins K, Hughes C, Damon IK. Real-time PCR assays for the specific detection of monkeypox virus West African and Congo Basin strain DNA. J Virol Methods 2010;169:223–7. PMID:20643162 https://doi.org/10.1016/j.jviromet.2010.07.012
4. Minhaj FS, Rao AK, McCollum AM. Imported monkeypox from international traveler, Maryland, USA, 2021. Emerg Infect Dis 2022;28:1738. PMID:35798002 https://doi.org/10.3201/eid2808.220726
5. Minhaj FS, Ogale YP, Whitehill F, et al.; Monkeypox Response Team 2022. Monkeypox outbreak—nine states, May 2022. MMWR Morb Mortal Wkly Rep 2022;71:764–9. PMID:35679181 https://doi.org/10.15585/mmwr.mm7123e1
6. Rao AK, Schulte J, Chen TH, et al.; July 2021 Monkeypox Response Team. Monkeypox in a traveler returning from Nigeria—Dallas, Texas, July 2021. MMWR Morb Mortal Wkly Rep 2022;71:509–16. PMID:35389974 https://doi.org/10.15585/mmwr.mm7114a1
7. Aden TA, Blevins P, York SW, et al. Rapid diagnostic testing for response to the monkeypox outbreak—Laboratory Response Network, United States, May 17–June 30, 2022. MMWR Morb Mortal Wkly Rep 2022;71:904–7. PMID:35834423 https://doi.org/10.15585/mmwr.mm7128e1
8. CDC. Laboratory Outreach Communication System, lab advisory: *Monkeypox virus* testing considerations to prevent false positive test results. (Accessed August 23, 2022). https://www.cdc.gov/locs/2022/08-23-2022-Lab-Advisory-Monkeypox_Virus_Testing_Considerations_Prevent_False_Positive_Test_Results.html
9. Karem KL, Reynolds M, Braden Z, et al. characterization of acute-phase humoral immunity to monkeypox: use of immunoglobulin M enzyme-linked immunosorbent assay for detection of monkeypox infection during the 2003 North American outbreak. Clin Diagn Lab Immunol 2005;12:867–72. PMID:16002637
10. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003;349:1227–35. PMID:14507948 https://doi.org/10.1056/NEJMoa023153

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Age-Adjusted Suicide* Rates,† by Urbanization Level§ and Sex — National Vital Statistics System, 2020



* Suicides were identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes U03, X60–X84, and Y87.0.
† Age-adjusted suicide rates are per 100,000 standard population; 95% CIs are indicated by error bars.
§ Urbanization level is based on county of residence using the National Center for Health Statistics Urban-Rural Classification Scheme for Counties. https://www.cdc.gov/nchs/data/series/sr_02/sr02_166.pdf

In 2020, age-adjusted suicide rates among females increased as the level of urbanization declined, from 4.6 per 100,000 population in large central metropolitan areas to 7.1 in small metropolitan areas, but were similar for small metropolitan, micropolitan, and noncore areas. Rates among males were lowest in large central areas (16.9) and increased as the level of urbanization declined to 33.7 in noncore areas. Males had higher death rates than females for each corresponding urbanization level.

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

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For more information on this topic, CDC recommends the following link: https://www.cdc.gov/suicide

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