Science Brief: Detection and Transmission of Mpox (Formerly Monkeypox) Virus During the 2022 Clade IIb Outbreak

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Executive Summary

Knowledge regarding how mpox virus spreads continues to evolve. During the current outbreak, people have been infected mostly during sexual activity from contact with mpox lesions on the skin or mucosal surfaces, such as the throat, anus, or rectum, of a person with mpox. A few infections have resulted from injury with a sharp instrument used in a clinical situation to sample skin lesions, a practice that CDC recommends against. Mpox has also been transmitted through skin piercing and tattooing as well as occupationally to healthcare workers in the absence of sharps exposure; the precise means of transmission for these cases remain unknown. Risk of infection through contact with contaminated surfaces, or objects (i.e., fomites, or passive vectors) is considered low. Some cases have reported sexual contact with an infected partner before that partner had developed rash, lesions, or other signs or symptoms of illness (i.e., contact with a partner with presymptomatic infection). No cases of transmission have been definitively linked to exposure to infected people who never developed signs or symptoms of illness (i.e., asymptomatic infection). As new scientific evidence and other information about mpox virus infection become available, this brief will be updated.

Affected Populations and Clinical Presentation

Most mpox virus infections during the current outbreak have been transmitted through close, intimate contact with symptomatic people, primarily during sexual contact. The majority of infections have been transmitted among men during male-to-male sexual contact; however, heterosexual sexual transmission, transmission to children through close non-sexual skin-to-skin contact with a caregiver, transmission through needlestick with a skin lesion-contaminated sharp, through body piercing and tattooing, and occupational exposures in absence of full or sufficiently effective personal protective equipment (PPE) have also been reported.
Skin rash often with anogenital or oropharyngeal/perioral mucosal lesions has been the predominate symptom of mpox virus infection at diagnosis [1, 4-6, 13, 27-37]. Fever, chills, headache, and lymphadenopathy have also been frequently reported by patients; however, in contrast to previous outbreaks where these symptoms usually preceded rash onset (i.e., prodromal), in the current outbreak up to half of patients report rash as their first symptom [1, 4, 5, 27, 38]. The estimated incubation period from infection to illness onset averages seven days with an upper range at approximately three weeks [1, 5, 13, 39-43]. Currently, evidence indicates all persons are infectious with the onset of illness (i.e., rash or other related symptoms), but that some people can also transmit the virus to others up to four days before they develop signs or symptoms (i.e., while presymptomatic) [41, 42, 44, 45]. There is no evidence at this time that persons who are infected but eventually clear the infection without developing illness (i.e., asymptomatically infected) have transmitted mpox virus.

**Mpxo Virus in Human Samples other than Skin Rash Lesions and Implications for Transmission**

Detection of mpxo virus by polymerase chain reaction (PCR) using swabs (not sharps) of skin lesions (e.g., vesicles, ulcers) is the recommended method to confirm infection in symptomatic people because skin lesions contain the highest concentration of virus (Figure) and are most likely to yield positive results [31, 34, 46-52]. Concentrations of viral DNA in clinical swab samples have correlated with the amount of replication-competent virus present, indicating that greater viral burden as assessed by PCR predicts greater potential for infectivity [53]. Viral DNA has been detected by PCR in a wide variety of samples (Table); however, replication-competent (i.e., potentially infectious) virus has been isolated only from skin lesion swabs, oropharyngeal swabs, anorectal swabs, urethral swabs, conjunctival swabs, and semen (Table). Viral DNA typically remains detectable no longer than about 3 weeks from illness onset [47, 54-60] although specimens with cycle threshold (Ct) values >35 (i.e., low viral burden) have been reported beyond this time in upper respiratory tract swabs (up to 41 days and possibly 73 days) [54], saliva (up to 76 days) [58], and semen (up to 54 days) [58]. In a single study, replication-competent virus was detected only in samples within the first 3 weeks after illness onset in skin lesion swabs, anorectal swabs, oropharyngeal swabs, or semen [34]. No infections have been reported from exposures to persons with mpxo whose skin and mucosal lesions are fully healed.

**Oropharynx and saliva:**

The clinical presentation of mpxo illness in the current outbreak is notable for the high prevalence of oropharyngeal and perioral lesions at diagnosis [1, 4-6, 27]. Oropharyngeal mucosa can exhibit lesions typical of mpxo virus infection [1] and multiple studies have detected mpxo virus DNA by PCR in nasopharyngeal and oropharyngeal swabs [9, 29, 34, 38, 51, 55, 61-67]. Oropharyngeal swabs can include both virus from swabbed mucosal lesions and from saliva. At least two reports describe recovery of replication-competent virus from such specimens [34, 55]. Transmission has also been documented where the source of infection was oral contact (kissing) with a person who had a crusted oral lesion [68]. Mpxo virus DNA has also been detected by PCR of saliva of patients both with and without oropharyngeal lesions [38, 52, 61, 66, 69, 70]; however, there have been no reports definitively describing isolation of replication-competent virus from saliva alone in the absence of oropharyngeal lesions. In some cases, concentrations of viral DNA in saliva have been comparable to those observed in paired samples from skin lesions (i.e., saliva and skin lesions collected at the same time) [38, 69]. As a whole, this evidence indicates that exposure to the oropharynx and saliva can transmit infection; however, data are insufficient to determine if an oral lesion needs to be present at time of exposure.

**Anorectum:**

The clinical presentation of mpxo illness in the current outbreak is also notable for the high prevalence of anal and perianal lesions at diagnosis [1, 4-6, 27]. Anal mucosa can also exhibit lesions typical of mpxo virus infection [1, 71, 72] and multiple studies have detected mpxo virus DNA by PCR in anorectal swabs, including anorectal swabs collected from persons without visible external perianal lesions or without proctitis [34, 45, 55, 61, 62, 67, 69, 73]. In two reports, swabs have yielded replication-competent virus [34, 72]. Transmission via exposure to anal mucosa such as through insertive anal contact (e.g., penis or finger) or through anilingus is particularly challenging to assess since such exposure typically occurs in the context of other intimate physical contact during sex that includes skin-to-skin contact. No report has yet been able to establish exposure to anorectal mucosa as the sole source of infection. However, the presence of mucosal lesions in the anorectum characteristic of mpxo and the ability to recover replication-competent virus in anorectal swabs, which can have concentrations of viral DNA comparable to skin lesions [48] (Figure) that in at least one report were comparable from skin and anorectal swabs collected at the same time (i.e., paired samples) [31], support anorectal exposure can transmit infection.
Semen:
Mpx virus DNA has been detected by PCR in semen of infected men \[^{34, 38, 59, 66, 67, 69, 74-76}\]. In three reports, semen has yielded replication-competent virus \[^{34, 59, 76}\], but there have been no cases reported to date where exposure to semen has been implicated as the only possible mode of mpx virus transmission (e.g., use of semen for \textit{in vitro} fertilization). Transmission via exposure to semen such as through receptive anal, vaginal, or oral sexual contact is particularly challenging to assess since such exposure typically occurs in the context of sex that includes skin-to-skin contact. Concentrations of viral DNA in semen have been lower than those observed from skin lesions \[^{38, 69, 74}\] \textbf{(Figure)}. Epidemiologic data presently indicate that exposure to semen might plausibly transmit infection, but at this time data are insufficient to definitively support this exposure as a source of infection.

Urine and urethral mucosa:
Several studies have detected mpx virus DNA by PCR in urine or urethral swabs \[^{9, 52, 62, 63, 65, 67, 69, 75}\]. In one case, a urethral swab has also yielded replication-competent virus; no urethral lesion was present \[^{62}\]. There have been no cases of transmission epidemiologically linked to exposure to urine and, when assessed, concentrations of viral DNA have been lower than those observed from skin lesions \textbf{(Figure)} including samples from paired skin lesions \[^{9, 65}\]. Epidemiologic data presently indicate that exposure to urine or urethral mucosa might plausibly transmit infection, but at this time data are insufficient to definitively support this exposure as a source of infection.

 Conjunctiva or ocular uid:
Mpx virus DNA has been detected by PCR in conjunctival swabs or swabs of eyelid lesions as well as in the corneal epithelium from people with evidence of ocular mpx virus infection \[^{61, 65, 77-80}\]. In one case, a conjunctival swab yielded replication-competent virus \[^{65}\]; however, to date no transmissions have been epidemiologically linked to exposure to conjunctival fluids or ocular tissues. In one case, concentrations of viral DNA in a conjunctival swab from a person with conjunctivitis but no lesion on the eyelid or conjunctiva has been comparable to a paired skin lesion \[^{77}\]. Thus, exposure to conjunctivae or ocular fluids might plausibly transmit infection, especially in the presence of conjunctivitis, but at this time data are insufficient to definitively support this exposure as a source of infection.

Blood:
Mpx virus DNA is readily detected by PCR in specimens of blood plasma and serum \[^{9, 29, 34, 38, 44, 55, 59, 60, 63, 65, 67, 75}\]. However, no studies have thus far detected the presence of replication-competent virus in blood or blood products, albeit few investigators have tried to culture virus due to the very low concentrations of DNA typically detected \textbf{(Figure)}. To date, there have been no cases of transmission attributable to exposure to blood or blood products. Concentrations of viral DNA when assessed have been lower than those observed from skin lesions and from samples from other exposure sources \textbf{(Figure)} including with paired skin lesions \[^{9, 55, 63, 65}\] or paired scabs/crusts \[^{38}\]. Epidemiologic data are presently insufficient to support exposure to blood as a source of infection.

Feces:
Two studies have reported detection of mpx virus DNA by PCR in feces \[^{38, 69}\]; however, replication-competent virus has not been isolated from feces and transmission has not been linked epidemiologically to exposure to feces. Epidemiologic data are presently insufficient to support exposure to feces as a source of infection.

Vagina:
Among cisgender women who most likely acquired mpx virus through sexual contact, the clinical presentation of illness in the current outbreak is notable for the high prevalence of genital lesions at diagnosis \[^{8, 13, 34, 81-84}\]. Three studies have reported detection of mpx virus DNA by PCR in vaginal swabs \[^{13, 34}\] as well as vulvar and cervical lesions \[^{85}\]. Replication-competent virus has not been isolated from vaginal mucosa or fluids. Transmission via exposure to vaginal fluids through vaginal or oral sexual contact is particularly challenging to assess since such exposure typically occurs in the context of sex that includes
skin-to-skin contact. However, despite the lack of definitive evidence epidemiologically linking vaginal exposure to transmission, indirect evidence from two cases [8] is consistent with the plausible hypothesis that mpox is sexually transmissible via exposure to vulvovaginal tissues and fluids.

Breastmilk:

At this time, available data are insufficient to estimate the extent to which mpox virus DNA or replication-competent virus may be present in breastmilk. No epidemiologic data are presently available to support exposure to breastmilk as a source of infection. Establishing transmission via exposure to breastmilk will be particularly challenging to assess since such exposure typically includes skin-to-skin contact.

Contaminated sharp injury as well as piercing and tattooing:

In the current outbreak, there have been at least four documented cases of healthcare workers infected with mpox virus through a skin-penetrating injury from a non-bloody sharp used to sample a skin lesion; in all cases the healthcare worker's first or only lesion after infection appeared at the inoculation site [18-21]. CDC recommends against the use sharps to sample lesions. The sharps involved were contaminated with vesicular or pustular material; however, the sharps were not tested for the presence of viral DNA or for replication-competent virus.

Multiple reports document that mpox virus can be transmitted in the context of receiving piercings and tattoos in both adults and children [16, 22-24]. Investigation of a cluster of 20 cases implicated poor aseptic measures leading to exposure to tattoo and piercing materials contaminated by a source patient. Viral DNA was detected on equipment (e.g., sharps, other work instruments such as tweezers and scissors) and surfaces (e.g., chairs, workshop surfaces) [23]. However, in none of these reports has either the presence of replication-competent virus nor definitive epidemiological evidence sufficiently explained precisely how transmission occurred although initial rash lesions tended to first appear at the site of piercing or tattoo [22-24].

Detection of Mpox Virus on Surfaces, Materials, and Objects

During the current outbreak, while widespread surface contamination of mpox virus has been detected in households and in hospital rooms of people with symptomatic mpox [86-89], concentrations of virus have been generally low when assessed (i.e., Ct values >30 in reported studies) both on surfaces [89] and in air samples [90]. Despite multiple attempts to isolate replication-competent virus, the only objects yielding culturable virus are those that would be expected to have been most heavily contaminated. For example, in one hospital-based study of isolation rooms of patients these objects included a glove used by a healthcare provider after examining a patient, the soap dispenser operating lever in a patient's bathroom, and a towel on one patient's bed [88]. In another hospital-based study the samples that yielded replication-competent virus included an air sample taken during a bed linen change in a patient's room and a floor swab from the area where PPE of providers caring for patients was donned and doffed [86]. No cases of transmission during the current outbreak have been documented due to exposure to surfaces, materials, or other objects among persons who have followed recommended precautions when caring for a person with mpox in the home or in the healthcare setting. A case of mpox during 2018 was attributed to exposure to a patient's soiled bedding; however, in this case the worker was not wearing full PPE (i.e., only wearing disposable apron and gloves) [91]. Other possible cases of occupationally acquired mpox where sharps exposures were ruled out have been attributed to mpox exposures in absence of full or sufficiently effective PPE [25, 26].

Detection and Transmission of Mpox in the Absence of Illness Signs or Symptoms

Emerging evidence indicates that some patients can transmit mpox virus before they develop recognizable signs or symptoms of illness (i.e., presymptomatic transmission). Although mpox virus DNA has been detected at low levels in samples from some people who never developed symptoms, there is no evidence at this time that such persons are infectious to others. Larger studies and modeling are needed to learn how many cases of mpox may have resulted from people who spread the virus before symptoms appeared, and to determine to what extent, if at all, some persons assessed as having transmitted mpox virus to others presymptomatically may have had paucisymptomatic infection.
Presymptomatic infection

Comparisons of the incubation period (i.e., time to develop illness after infection) for mpox with its serial interval (i.e., the time between illness onset in the index case and illness onset in the secondary case) are consistent with the possibility that people infected with mpox virus can transmit the virus before signs and symptoms of illness appear. Mpox virus DNA has been detected in anorectal swabs, urethral swabs, genital swabs, oropharyngeal swabs, and saliva from people who at the time of sample collection neither demonstrated evident signs nor reported symptoms of illness. Some of these samples have also yielded replication-competent virus from anorectal swabs and urethral swabs, and some of these patients demonstrated new serologic evidence of orthopoxvirus exposure when tested in the weeks following initial sample collection. Epidemiological investigation with sufficient data to definitively assess the timing of transmission and illness onset has confirmed sexual transmission of mpox virus has occurred from 1-4 days prior to illness onset.

Infection in the absence of any symptoms

There have been documented cases of people exposed to mpox virus who never develop signs or symptoms of illness but whose samples (i.e., anorectal swabs, oropharyngeal swabs, genital swabs, saliva) have had viral DNA detected at low concentrations near the limit of detection of the assay. However, none of the samples were assessed for replication-competent virus due to the high Ct values (i.e., low concentrations of viral DNA). Most of these people had received smallpox vaccination in childhood or as post-exposure prophylaxis. Among the remainder who were unvaccinated, none showed clear evidence of seroconversion. To date, no cases of transmission have been definitively linked to exposure to infected people who never developed signs or symptoms of illness (i.e., asymptomatic infection).

Figure. Mpxo Virus Concentrations According to Sampled Exposure Source (From Palich et al.)
Footnote: In this study, clinical samples found to be weakly positive (35≤Ct<40) or negative (Ct≥40) using PCR were excluded for this analysis. All samples were the first specimens collected after diagnosis, which was a median of 5 days (IQR 3-6) after illness onset. Specimens were not tested by culture to confirm presence of infectious virus. Notably, at 14 days after initial diagnosis, the majority of specimens were PCR negative for mpox virus. To more fully understand potential infectivity at different stages of illness, prospectively collected data assessing specimen positivity over time are needed. Results are given as box plots in which red lines represent median Ct. Ct=cycle threshold. MPXV=mpox virus.

Table. Mpox Virus in Human Samples and Implications for Transmission

<table>
<thead>
<tr>
<th>Exposure source</th>
<th>Mpxo virus DNA detected by PCR</th>
<th>Replication-competent virus detected/isolated</th>
<th>Epidemiologically supported source of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Oropharynx and saliva</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes†</td>
</tr>
<tr>
<td>Anorectum</td>
<td>Yes</td>
<td>Yes</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Semen</td>
<td>Yes*</td>
<td>Yes</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Urine/urethra</td>
<td>Yes</td>
<td>Yes</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Conjunctivae or ocular fluid</td>
<td>Yes</td>
<td>Yes</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Blood/plasma/serum</td>
<td>Yes</td>
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<td>Insufficient data</td>
</tr>
<tr>
<td>Feces</td>
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</tr>
<tr>
<td>Vagina</td>
<td>Yes</td>
<td>Insufficient data</td>
<td>Insufficient data†</td>
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<tr>
<td>Breastmilk</td>
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<td>Insufficient data</td>
<td>Insufficient data</td>
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<tr>
<td>Contaminated sharp‡</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* DNA has been detected at Ct values <35 in recovered patients more than 30 days after illness onset in an upper respiratory tract swab, saliva, and semen.
† The preponderance of existing data support exposure to anorectal and vulvovaginal tissues and fluids as capable of transmitting infection; however, it is difficult with current evidence to definitively isolate these exposures from other concomitant exposures (see text).
‡ Includes body modification with piercings and tattooing.

References


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