31 | MPOX, FORMERLY MONKEYPOX

31.1 | Disease agent

- Monkeypox virus (MPV, MPXV or hMPXV)

31.2 | Disease agent characteristics

- Family: *Poxviridae*; Subfamily: *Chordopoxvirinae*; Genus: *Orthopoxvirus*.
- Virion morphology and size: Enveloped, generally brick-shaped viruses about 200 × 200 × 250 nm in size.
- Nucleic acid: linear, double-stranded DNA genome (approximately 186–223 kb) with covalently closed ends.
- Physicochemical properties: Resistant to common phenolic disinfectants; inactivated with polar lipophilic solvents, such as chloroform, and at low pH. Complete inactivation of the closely related vaccinia virus occurs in 2–3 h at 60°C or within minutes following exposure to 20 nM caprylate at 22°C; however, MPV is more resistant than vaccinia to solvent-detergent treatment. Benzalkonium chloride, with or without alcohol, sodium hypochlorite (bleach) and ≥60% ethanol are examples of active environmental disinfectants. Hand sanitizers with 60% alcohol also are beneficial in preventing spread of the virus. Washing clothes, linens, towels, and bedding with detergents can be effective in preventing transmission.

31.3 | Disease name

- Mpox (formerly monkeypox)

31.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical
- Public perception and/or regulatory concern regarding blood safety: Very low
- Public concern regarding disease agent: Low to very low at time of 2003 United States (US) outbreak and 2021 imported US cases. Increasing public concern to moderate levels with the 2022 outbreak.

31.5 | Background

- 1958—MPV first identified in laboratory monkeys at State Serum Institute in Copenhagen.
- 1970—First human case of mpox was detected in Zaire (Democratic Republic of the Congo—DRC) after smallpox eradication in the country.
- June 2003—First case of mpox in the Western Hemisphere was in the United States. The source of this single outbreak was Gambian pouched rats imported from West Africa. Prairie dogs housed in pet stores in close proximity to these became infected and transmitted the infection to humans.
- July 2021—imported case of mpox diagnosed in Dallas, Texas in returning traveler from Nigeria. No subsequent transmission documented.
- Other members of the *Orthopoxvirus* genus include variola virus (smallpox virus), vaccinia virus (smallpox vaccine virus), ectromelia virus, camelpox virus, and cowpox virus.
- Two clades are recognized and have been renamed during the 2022 global epidemic:
  - Clade I: The Central African (Congo Basin) clade present in Gabon, Cameroon, Republic of Congo, Central African Republic, and the Democratic Republic of Congo
  - Clade II: The West African clade, less virulent than clade I, is present in Nigeria, Sierra Leone, Ivory Coast, Liberia, and the US (ex-Ghana) during the 2003 outbreak (designated clade IIa). The 2022 international outbreak is designated clade IIb.
- A global mpox outbreak began in spring 2022. On August 4, 2022, the US Department of Health and Human Services declared the US mpox outbreak to be a public health emergency. Among the cases, 99% were among men; among men with available information, 94% reported male-to-male sexual (MSM) or close intimate contact during the 3 weeks before symptom onset. By the end of 2022, over 30,000 cases had occurred, and the epidemic appeared to be waning.

31.6 | Common human exposure routes

- Animal-to-human transmission occurs by a bite, scratch, direct contact with body fluids or lesion material or indirect contact (e.g., contaminated bedding) or through preparation and/or consumption of bushmeat.
- During the 2022 outbreak, human-to-human transmission is thought to have occurred primarily through direct (i.e., skin-to-skin) contact, including that associated with sexual activity.
- Contamination of the inanimate environment, esp. clothing and linens, with virus from skin lesions can also occur, particularly among caregivers.

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31.7 | Likelihood of secondary transmission

- Before 2022, the risk of human-to-human transmission was considered low, but the 2022 outbreak appeared to be driven by direct contact with an infected patient.
- Droplet transmission requires prolonged face-to-face contact (e.g., within a 6-foot radius for >3 h) but does not appear to be a major route of transmission.
- Extent of exposure (e.g., complex bite wound vs simple touching) can influence disease severity.
- Period of human-to-human transmission is from the onset of symptoms until scabs are dry, separated and lesions epithelialized. It remains unclear if transmission can occur prior to the appearance of symptoms.
- MPV is known to persist in a household environment for at least 15 days.

31.8 | At-risk populations

- In Africa, people in contact with infected animals including bushmeat.
  - Historically, risk was very low outside endemic areas, based on animal import controls.
- Transmission during the 2022 outbreak has been concentrated in MSM sexual networks in which multiple and anonymous contacts are common.
- Concerns that extensive transmission to other cohorts as the epidemic evolves have not been realized and the epidemic appears to be waning, although a few cluster outbreaks in urban areas are still occurring.

31.9 | Vector and reservoir involved

- Animal vectors include rodents and squirrels. All mammals are considered potentially susceptible to infection. Despite its name, monkeys are not considered an important reservoir.
  - The potential for establishment of an animal reservoir(s) in historically nonendemic countries was an important concern during the 2022 epidemic.

31.10 | Blood phase

- In a 2003 outbreak in the Republic of Congo, 2 of 3 peripheral blood samples from 3 probable/confirmed patients were PCR positive (1 of 5 samples positive on day 33 after rash onset).
- Among US samples from 2003, 3 of 12 peripheral blood samples were PCR positive and one was equivocal within 21 days of rash onset; none were positive/equivocal beyond 21 days after onset.
- Among 7 patients in the United Kingdom between 2018 and 2021, 6 of 7 had a positive blood PCR at some point after rash onset, with the latest detected at day 30 after onset.
- Animal models demonstrate infectious viremia and parenteral transmission in nonhuman primates.
- Asymptomatic infectious viremia has not been well studied.

31.11 | Survival/persistence in blood products

- Unknown

31.12 | Transmission by blood transfusion

- There have been no reports of transmission of MPV through blood transfusion.
- Parenteral transmission has been demonstrated in animal models.

31.13 | Cases/frequency in population

- Precise surveillance is not available, but in a Nigerian outbreak since 2017 there have been 200 confirmed cases with 500 suspected.
- Sporadic outbreaks have occurred in other Central and West African countries usually close to tropical rain forests where humans have frequent contact with infected animals.
- The 2003 outbreak in the United States, as a result of virus introduction through infected exotic pets, resulted in 47 laboratory-confirmed cases.
- As of 25 May 2023, 87,543 cases have been reported globally including 30,194 in the United States from a peak of 3,000 or more cases daily in August 2022. Starting in May 2023, there has been <1 case/day reported in the United States. Incidence for males in rural areas was only 4% of those in urban areas.
- The risk for reintroduction is inversely related to the proportion of MSM with prior immunity via infection or vaccination. CDC estimates predict communities with 50%–100% immunity have a low probability of sustained reintroduction; those with <50% are at risk for linear to exponential increases in cases.

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31.14 | Incubation period

- Mean of 12 days, range of 5–21

31.15 | Likelihood of clinical disease

- A high percentage of exposed individuals develop clinical disease.
- In addition, serological evidence of infection has been reported in about 3% of asymptomatic household contacts of mpox symptomatic individuals studied between 1980 and 1984 in the DRC.
  - Asymptomatic infection has been reported from during the 2022 epidemic, but its extent and any association with infectious viremia is not yet characterized.
  - NAT of gonorrhea/chlamydia clinical samples from sexually transmitted disease clinics of clients with no apparent mpox infection during the 2022 epidemic has identified as many as 6.5% MPV-positive samples.

31.16 | Primary disease symptoms

- Most patients demonstrate characteristic prodromal illness for 2 days before the onset of rash with fever, malaise, and lymphadenopathy that is prominent in the inguinal and cervical areas (uncommon in smallpox). The prodrome may be milder and even absent among infections during the 2022 outbreak.
- Typical mpox rash, which can be intensely painful, begins as maculopapular lesions of 2–5 mm in diameter; the rash becomes generalized in distribution in most cases, spreading in centrifugal pattern although more limited skin disease appears to be a feature of the 2022 epidemic
- Skin lesions progress from macules to papules to firm, deep seated vesicles and pustules followed by umbilication, scabbing, and desquamation over a period of 14–21 days.
- Lesions are observed on mucous membranes, including the mouth, on the tongue, and on genitalia.
- Lesions in atypical locations are prominent during the 2022 outbreak, for example, the genital skin and anorectal mucosa, and anorectal and oral infections have been a cause of substantial morbidity.

31.17 | Severity of clinical disease

- In addition to skin lesions, extracutaneous manifestations, such as secondary skin and/or soft-tissue infection (19% of cases), pneumonitis (12%), ocular complications (4%–5%), and encephalitis (<1%), are also observed.
- No hemorrhagic form of mpox has been described in humans, in contrast to smallpox.
- Among individuals with smallpox vaccination history, the rash is milder and more likely to be pleomorphic.
- Pediatric and immunocompromised patients are more likely to suffer severe infection and complications.
- A high proportion of 2022 cases are in HIV-infected patients, but the illness does not seem more severe if HIV is well managed with antiretroviral therapy.

31.18 | Mortality

- In Africa, the reported mortality rate differs between clades I and II.
- Clade IIa has a case fatality rate of 1%–3.6% versus 10.6% for clade I. This compares to a 30% mortality with smallpox.
  - Reported mortality in locales with access to advanced medical care is substantially lower.
  - Mortality during 2022 from the IIb strain is much lower than historic case fatality rates in endemic countries with 140 deaths reported worldwide.

31.19 | Chronic carriage

- Not recognized

31.20 | Treatment available/efficacious

- Preexposure immunization may be recommended for individuals with a very high risk of exposure to the virus including high-risk cohorts and laboratory workers.
- No proven treatment for humans but animal studies suggest effectiveness with tecovirimat, that has been approved for treatment of smallpox.
  - It has protected nonhuman primates from fatal MPV infection. Supplies are available in the United States Strategic National Stockpile and available under IND. Availability elsewhere may vary.
  - Cidofovir and brincidofovir (used to treat serious CMV infections) have *in vitro* activity but clinical data are limited to a few case reports for cidofovir.
- In animals, treatment with antiviral compounds is more effective in reducing mortality than is the therapeutic use of smallpox vaccine.

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- Postexposure immunization with vaccinia vaccines may be effective for mpox prevention or mitigation of disease severity and is recommended for high-risk, exposed individuals.
- Data are not available on the effectiveness of vaccinia immune globulin (VIG) for treatment of mpox complications. It is administered under an IND but has no proven benefit in the treatment of smallpox complications. It is unknown whether a person with severe mpox will benefit from treatment with VIG; however, its use may be considered in such instances.
  - VIG can be considered for prophylactic use in an exposed person with severe immunodeficiency in T-cell function for which smallpox vaccination following exposure to mpox is contraindicated.

31.21 | Agent-specific screening question(s)

- No specific question is in use.
- Not indicated because transfusion transmission has not been demonstrated.
- No sensitive or specific question is feasible.

31.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists; however, research-based NAT assays are in development.
- A PCR-based algorithm is recommended for diagnostic use for the 2022 outbreak. A reactive generic orthopox virus screening test is confirmed using an MPV-specific PCR assay when available. If an MPV-specific PCR (preferable) is not available, an *Orthopoxvirus*-positive PCR can be considered confirmation in non-endemic countries. PCR can be used alone, or in combination with sequencing.
- Serological tests are not useful for the diagnosis of acute infection.

31.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.
- Prudent practice would be to defer infected donors at least until all lesions are fully resolved and a minimum of 21 days after the onset of symptoms.
- Based on the incubation period, CDC has recommended that asymptomatic close contacts of infected people or animals be placed under fever surveillance for 21 days. The 21 days would be a minimum donor deferral if such contact has occurred.
- Receipt of JYNNEOS, the live, nonreplicating smallpox/mpox vaccine, in wide use for mpox in the United States, does not require donor deferral. By contrast, the ACAM2000 live, replication-competent vaccine requires a 21-day donor deferral.
- The need for specific interventions to minimize a theoretical risk of transfusion transmission of MPV during the 2022 epidemic is undetermined.
  - Donors must be well on the day of donation, undergo a limited skin examination, and have their temperature taken in the donor room.
  - Since 2020 in the United States, MSM have been specifically deferred for 3 months after the most recent such contact to reduce the risk of collecting donations from recently HIV-infected donors. This interval is believed to be well beyond the duration of a putative MPV infectious viremia and high adherence to this donor criterion effectively mitigates any risk where donors continue to be directly questioned about MSM activity.
    - The US policy was changed by the FDA in May 2023 with most blood collection organizations planning to implement the change to an individual donor assessment by summer-fall 2023. According to the new policy, any individual with a new sexual partner or multiple partners, either engaging in anal sex within the prior 3 months, will be deferred for 3 months.
    - In much of the world, the MSM deferral has been discarded and replaced by individual donor assessments.

31.24 | Impact on blood availability

- Agent-specific health question (s): Not applicable
- Laboratory test(s) available: Not applicable

31.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

31.26 | Leukoreduction efficacy

- Unknown

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31.27 | Pathogen reduction efficacy for plasma derivatives

- Multiple pathogen reduction steps used in the fractionation process have been shown to be robust in removal of enveloped viruses.
- Pasteurization has been effectively used for inactivation of vaccinia virus and may be useful for MPV. In contrast, vaccinia virus was relatively resistant to inactivation by solvent/detergent treatment of blood products.
- Nanofiltration of plasma may be effective in the removal of MPV.

31.28 | Other prevention measures

- Avoidance of contact with potential animal sources, infected patients and contaminated materials (e.g., bedding), careful hand hygiene, and personal protective equipment are key.
- Extensive DNA sequence and amino acid homology among poxviruses give rise to cross-immunity against various poxviruses, explaining a protective effect of vaccinia virus vaccines used for smallpox for mpox. With the eradication of smallpox and the cessation of near-universal vaccination, population immunity has likely declined in younger age cohorts and susceptibility to mpox is increasing.
- A very safe, live, non-replicating, smallpox vaccine (JYNNEOS™) appears very effective for preexposure prevention of human mpox. It is FDA-approved for prevention of mpox, and CDC recommends its use preexposure and for up to 14 days after the exposure. Historic data from Africa suggest it is at least 85% effective, preventing illness when administered within 4 days of exposure and may ameliorate symptoms after infection when given beyond that window.
  - Early data using two doses of JYNNEOS in the 2022 epidemic are consistent with this level of effectiveness. One dose provides variable immunity and of shorter duration.
- ACAM-2000, an attenuated, replicating smallpox vaccine, is also available in the strategic national stockpile but side effects and risks of secondary transmission to immune-compromised individuals are more likely than with the non-replicating JYNNEOS vaccine and would be useful only for contacts with contraindications to JYNNEOS. Recipients of ACAM2000 require a 21-day deferral.
- Donor room infection control
  - Risk in donor rooms should be minimal given the requirement for intimate and prolonged contact for transmission
    - Donors must be healthy
    - Afebrile
    - Routine cleaning procedures should be sufficient
  - Infected collection facility personnel should follow public health recommendations for isolation and quarantine.
  - Potentially exposed collection facility personnel may continue to work as long as they remain asymptomatic.

31.29 | Other comments

- Waning immunity after the discontinuation of routine smallpox vaccination may lead to concern that MPV might be used as a bioweapon.

SUGGESTED READING

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