DHS SCIENCE AND TECHNOLOGY

Master Question List for Monkeypox Virus (MPXV)

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Monkeypox Virus (MPXV) – Master Question List

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Foreword

This Master Question List (MQL) was developed by the Department of Homeland Security (DHS) Science and Technology Directorate (S&T) to present the current state of available information to government decision makers. This MQL quickly summarizes what is known and what additional information is needed to address fundamental questions such as, "What is the infectious dose?" and "How long does the virus persist in the environment?" The information provided is a succinct summary to allow structured and scientifically guided discussions across the Federal Government without burdening them with the need to review scientific reports, and to prevent duplication of efforts by highlighting and coordinating research.

Introduction

Monkeypox virus (MPXV) is a zoonotic virus (a virus that originates in animals) that causes the disease mpox, which has symptoms similar to, but less severe than smallpox, eradicated in 1980. MPXV has two distinct clades: Clade I and Clade II, with a higher case fatality rate associated with Clade I infection.[1] Outbreaks of MPXV have historically resulted from zoonotic spillover of Clade I MPXV in Central Africa and Clade II MPXV in West Africa and are considered endemic in different countries in the African continent. Some cases have occasionally been exported to Europe and North America. However, since May 13, 2022, mpox cases have been reported in multiple countries, including the United States. The virus involved in the 2022 outbreak, which is ongoing as of 2024, is Clade IIb, a member of the clade associated with less severe disease. Historically, this subgroup of MPXVs has not generally been associated with significant human-to-human transmission. However, this has not been the case in the current outbreak. To date, most, but not all, cases have been reported in men who have sex with men (MSM), and the location of the lesions suggests that sexual transmission has had a significant role in the spread of the disease. Clade IIb continues to circulate at low levels and cases continue to be reported worldwide.[2] Since late 2023, the Democratic Republic of the Congo (DRC) has been experiencing a large outbreak

that is linked to Clade Ib, which is associated with more severe disease. As of the preparation of this document, the fatality rate of Clade Ib appears to be lower than other Clade I viruses but still higher than Clade II viruses.

Key Updates

- Since late 2023, a large outbreak of mpox has been affecting the DRC. This outbreak is linked to a new subclade, Clade Ib, which was first identified in the Kamituga Health Zone located in the South Kivu Province in eastern DRC. [1, 3]
- Clade Ib has expanded to other African countries including Burundi, Kenya, Rwanda, and Uganda.[1]
- Clade Ib predominately affects young adults.[1, 3]
- Clade Ib has been detected outside of Africa with confirmed travel associated cases in Sweden[4-5] and Thailand.[6-7] No cases of Clade Ib have been reported in the U.S.[8]
- As of September 09, 2024, there have been 9,644 confirmed cases of mpox worldwide in 2024 (3449 Clade I and 6011 Clade II). [8]
- Estimated mortality rates by subclade are 5-10% (Clade Ia), 0.7% (Clade Ib), 0% (Clade IIa), and 0.2% (Clade IIb).[9]
- The U.S. Centers for Disease Control and Prevention (CDC) ceased updates on Clade IIb case counts in the U.S. as of January 10 , 2024, due to stabilized low levels of transmission.[2]

The cutoff date for information gathering related to this document was 09/09/2024.

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
BACKGROUND	• MPXV belongs to the same group of viruses as the Variola major virus, which causes the human disease known as smallpox and was declared eradicated in 1980. This group also includes vaccinia virus (an attenuated poxvirus used as the smallpox vaccine), horsepox virus, and cowpox virus. These viruses, known as orthopoxviruses (OPVs), are extremely large viruses with DNA genomes. • MPXV causes a disease similar to, but generally less severe than, smallpox. • There are two distinct MPXV clades: Clade I (formerly Congo Basin/Central African clade) and Clade II (formerly West African clade), with a higher case fatality rate associated with Clade I infection.
INFECTIOUS DOSE	• The infectious dose of MPXV in humans is unknown. • Based upon studies in non-human primates (NHPs), the infectious dose via inhalation is estimated to be between 10 and 10,000 infectious viral particles. Most of these studies were conducted with the Clade I MPXVs. • Clade II MPXVs have generally been found to be less infectious than Clade I MPXVs.
TRANSMISSIBILITY	• Four clades of MPXV are recognized, and modes of transmission vary between clades. Clades Ia and IIa viruses are associated with zoonotic transmission. Clade Ia viruses have been shown to exhibit limited human-to-human transmission, while Clade Ib and IIb viruses spread between humans more readily, particularly via sexual contact. Clade IIb viruses were predominantly associated with sexual transmission between MSM during the 2022-2023 outbreak. • The reproduction number (R_0) is a mathematical estimate of the average number of new individuals that a single infected individual will infect in a population without immunity. The R_0 of mpox across all clades is generally estimated to be between 0.57 to a maximum of 1.25. • The calculated R_0 for the Clade IIb outbreak is 1.10-2.40. • For the Clade I outbreak in the DRC between August 2023 and March 2024, the R_0 estimated for the total outbreak (predominately Clade Ia) is 1.2-1.3 and the estimated R_0 for the South Kivu region (predominately Clade Ib) is 1.4-1.6. Evidence suggests that the transmission rate of MPXV has increased over time due to declining immunity in the population after the end of smallpox vaccination.

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
HOST RANGE	• Mpox is a zoonotic disease and outbreaks are initiated by human contact with animals. • NHPs can be intermediate hosts but are not likely to be reservoir hosts. • The primary reservoir of the virus is unknown but is likely to be one or more species of rodent. • It is not known if rodent species native to the U.S. could serve as reservoir hosts, though several can become infected.
INCUBATION PERIOD	• The interval between exposure and the development of symptoms ranges from 1-31 days, with 7-17 days being the typical range. • Patients are contagious during the first week of the rash and may continue shedding the virus for weeks after symptoms have dissipated.
CLINICAL PRESENTATION	• Early presentation consists of fever, fatigue, headache, backache, mild to severe pulmonary lesions, anorexia, dyspnea, conjunctivitis, nasal discharge, swollen lymph nodes, chills and/or sweats, sore throat, cough, and shortness of breath. • Rash presents within 1-4 days upon onset of symptoms and lasts from 2-4 weeks. • Rash typically does not appear on the extremities but may appear on the palms and soles of feet. Lesions can develop on mucous membranes, in the mouth, on the tongue, and on the genitalia. • In the Clade IIb and Clade Ib outbreaks, lesions on the genitalia and the perianal region have been more common due to the role of sexual transmission. • Some patients in the Clade IIb and Clade Ib outbreaks have presented without fever.

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
CLINICAL DIAGNOSIS	• One U.S. Food and Drug Administration (FDA)-cleared test and eight Emergency Use Authorization (EUA) tests are approved for diagnosis of mpox in the U.S. All tests require swabs from lesions. • The current CDC case definition requires positive polymerase chain reaction (PCR), sequencing, or culture to be considered a confirmed case. • PCR based diagnostic testing in the U.S. is available through local, state, territorial or tribal health department and many large commercial laboratories. Outside of the U.S., testing is more limited, often with fewer than 50% of suspected cases tested in some African countries. • Culture-based diagnostics should only be performed by the CDC.
FATALITY RATE	• Estimated mortality rates by subclade are 5-10% (Clade Ia), 0.7% (Clade Ib), 0% (Clade IIa), and 0.2% (Clade IIb). • As of September 09, 2024, the fatality rate in the U.S. for Clade IIb is 0.2%, which is consistent with the global rate. • Data indicate that subpopulations, such as individuals with human immunodeficiency virus (HIV) and children, have increased likelihood for fatal outcomes. • Fetal mortality rates vary based on MPXV variant with Clade Ia exhibiting the highest rate at 75%.
MEDICAL TREATMENT	• Tecovirimat (also known as TPOXX or ST-246), cidofovir (Vistide), and brincidofovir (Tembexa) are antiviral medicines approved for the treatment of smallpox and have been shown to be effective against poxviruses. However, TPOXX does not appear to reduce the duration or impact mortality when used to treat Clade I mpox. • Vaccinia Immune Globulin Intravenous (VIGIV) is FDA approved for treatment of severe symptoms associated with Vaccinia vaccination. Efficacy against mpox has not been proven in humans; however, animal studies show cross-protection against OPVs, including MPXV. • TPOXX and VIGIV are in the Strategic National Stockpile (SNS). Brincidofovir was added to the SNS in October 2022, however tecovirimat should still be considered first for use.
VACCINES	• Two vaccines that were originally developed for smallpox have been licensed by the FDA for use against mpox and are maintained in the SNS (JYNNEOS and ACAM2000). Additional vaccines are available under an Investigational New Drug (IND) or internationally. • For post-exposure prophylaxis (PEP), following a known or

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
	presumed MPXV exposure, individuals can be vaccinated up to 4 days post-exposure for the best chance at protection. • The CDC does not recommend booster vaccinations (more than two doses) except for specific groups including healthcare professionals without proper personal protective equipment (PPE) working directly with infected patients and laboratory staff working directly with infected animals or cultures.
ENVIRONMENTAL STABILITY	• The median time of MPXV DNA persistence in various patient samples, like blood, urine, and skin lesions, is 5.7 days to 13.5 days. • MPXV, like other OPVs, can be stable in the environment for days to weeks under some circumstances. • MPXV can survive in scabs for months to years. • MPXV is resistant to desiccation in hot and cold environments. • Closely related OPVs may be stable for days to weeks in water, soil, and on refrigerated food. • MPXV is susceptible to inactivation under acidic conditions.
DECONTAMINATION	• U.S. Environmental Protection Agency (EPA) recommends bleach and a number of quaternary ammonium reagents for use against emerging viral pathogens. • Data demonstrating effectiveness against MPXV are not available for most common disinfectants, however testing with vaccinia virus (a close relative) suggests that bleach, Virkon, Dettol, and Sanytex are effective.
PERSONAL PROTECTIVE EQUIPMENT (PPE)	• Optimal PPE for clinicians caring for infected patients includes disposable gown and gloves, National Institute for Occupational Safety and Health (NIOSH)-certified N95 (or comparable) filtering disposable respirator, and face shield or goggles. • Additional PPE may be required for individuals working with samples or animals known or suspected to be infected with MPXV. • Laboratory studies with MPXV require Biosafety Level 2 or 3 (BSL-2 or BSL-3) precautions. These laboratories have enhanced safety precautions (such as the use of respirators) and higher levels of containment to avoid laboratory staff exposure or accidental release of a pathogen.
GENOMICS	• MPXV is a member of the Orthopoxvirus genus of the Poxviridae family of enveloped viruses, with a linear double-stranded DNA genome of around 200 kilobase pairs (kbp). • The distinct MPXV Clade Ib lineage linked to the Kamituga Health Zone in DRC was reveled through genomic analysis in

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
	January 2024. Clade Ib is divergent from previously sequenced Clade I strains. • Various genomic changes have been observed in both the Clade IIb and Clade Ib outbreaks that are associated with human-to-human transmission. • The increase in human-to-human transmission observed with both Clade IIb and Clade Ib may be due to increased editing by the host RNA editing enzyme APOBEC3.

Infectious Dose
How much agent will make a healthy individual ill?

What do we know?

The infectious dose of MPXV in humans by any route is unknown.[10]

- Cynomolgus macaques infected with MPXV are considered to currently be the best animal model for studying human mpox and its treatments, although no NHP model exists that perfectly represents human disease arising from OPV infection.[11]
- The estimated infectious dose (the dose required to cause any infection, not necessarily death) is $<10^1$-10^4 infectious viral particles (plaque forming units [PFUs]) in various animal models via intravenous, oral, intranasal, inhalation/aerosol, intradermal, and cutaneous routes. However, only aerosol infectious doses have been tested in NHPs. In this model, the median infectious dose is estimated to be 200 PFU via the aerosol route.[12-13]

The estimated median dose required to cause a lethal infection (median lethal dose or LD_{50}) is variable and has been estimated to be 10^5-10^7 PFU in NHPs, depending on route of exposure.[12-15]

- Across multiple animal models and exposure routes, the Clade I MPXV has generally been shown to have a lower lethal dose and higher mortality rate than Clade II MPXV. Exposure doses in these studies ranged from 10-10^7 PFU.[16]
- In an aerosol study with cynomolgus macaques, the inhalation LD_{50} for the Clade I ZaireV79-I-005 strain of MPXV was determined to be between 10^4 and 10^5 PFU.[17]

What do we need to know?

- What is the infectious dose in humans by relevant routes?
- What is the infectious dose of Clade Ib and Clade IIb MPXV in the NHP model?
- What is the correlation of animal models to human infection and disease? (Additional studies are needed to develop improved animal models).

Transmissibility
How does it spread from one host to another? How easily is it spread?

What do we know?

Four clades of MPXV are recognized, and modes of transmission vary between clades. Clade Ia and IIa viruses are associated with zoonotic transmission, with only Clade Ia viruses exhibiting limited human-to-human transmission. Clade Ib and IIb viruses spread between humans more readily, particularly via sexual contact. Clade IIb viruses were predominantly associated with sexual transmission between MSM during the 2022-2023 outbreak.[3, 18]

- Transmission of MPXV occurs when a person comes in contact with the virus from an animal,[19-21] human, or material contaminated with the virus. The virus may enter the body through broken skin, the respiratory tract, or other mucous membranes such as the rectum, eyes, genitals and oral cavity.[22-26] Transmission has been recorded from mother to fetus via placenta.[27-30]
    - Transmission by receptive anal, vaginal, or oral sexual contact is difficult to measure, as such exposure usually occurs in the context of sexual intercourse involving skin-to-skin contact. Live MPXV was found in seminal fluid samples, however no cases have been documented in which semen was the only method of MPXV transmission.[31-33]
- Humans can be contagious before a visible rash appears and can continue shedding the

virus weeks after symptoms have dissipated.[22-23, 34-38]

- Transmission in a healthcare setting is unlikely when infection control measures are taken.[39] Reported cases of infection following occupational exposure to MPXV have been predominately associated with needle stick injuries (67%) and fomites (22%).[40-42]

Since April 2022, Clade IIb MPXV has spread among humans who have not travelled to endemic areas and is credited to close, direct physical contact, which includes sexual transmission .[26, 32, 43-45] Human-to-human transmission has become the primary mode of transmission, raising concerns for unaccounted community spread.[44]

- Human-to-human transmission has been reported in previous outbreaks, but was not common.[46-48] Clade II infection has historically been rarely associated with human-to-human transmission.[48 22, 49-52;53]
- The mechanism for increased human-to-human spread is multifaceted and may include population-specific behaviors that increase risk.[37]
  - Direct contact among MSM has been cited as a source of a significant number of the infections in the Clade IIb outbreak.[44, 54]
  - Rates of droplet transmission in the Clade IIb outbreak do not appear to be different from prior outbreaks.[22-23, 34, 55]
- A case study of 129 pediatric households during the Clade IIb outbreak in California reported a secondary transmission rate of 7.1% for children < 9 that dropped to 0% for pediatric household contacts 10 or older.[45]

The R_0 of the Clade IIb outbreak is conservatively calculated to be 1.10-2.40 in countries like the U.S. with declining OPV immunity.[27, 56;23]

- R_0 is a mathematical estimate of the average number of new individuals that a single infected individual will infect in a population without immunity. If this number is less than one, the infection will quickly burn out. If it is greater than one, the infection can spread and cause an epidemic if not controlled.
- Several aspects of the Clade IIb outbreak, including transmission between MSM, are expected to complicate efforts to estimate R_0 and may make previous estimates unreliable for this outbreak.[37]
  - For the Clade IIb outbreak in Canada, the R_0 is estimated in the high-risk MSM population to be 1.464 and the low-risk population R_0 to be 0.0066.[57]

A record 14,626 cases of MPXV were recorded in the DRC for 2023.[58-60] A new subclade, Clade Ib, emerged in DRC in late 2023 and is associated with more sustained human-to-human transmission.[3]

- Based on available epidemiological data, Clade Ib has been spreading rapidly among adolescents and young adults, unlike Clade Ia.[58, 61-62] This could be a byproduct of the region where Clade Ib appears to have originated.
- The Clade Ib outbreak appears to be associated with sexual transmission. Most cases presented with genital lesions and in 29% of confirmed and suspected cases individuals indicated sex work as a profession.[3] This could be related to the concentration of sex workers associated with the mining industry in the region.[63-65]

For the Clade I outbreak in the DRC between August 2023 and March 2024, the R_0 estimated for the total outbreak (predominately Clade Ia) is 1.2-1.3 and the estimated R_0

for the South Kivu region (predominately Clade Ib) is 1.4-1.6[65]

What do we need to know?

- Is transmissibility affected by route of exposure? That is, would an individual infected via the aerosol route be more infectious than a person infected via direct contact?
- What is the ultimate impact of cessation of smallpox vaccination on the rate of human-to-human transmission?[20]
- What is the role of droplet/respiratory transmission in the current Clade Ib and Clade IIb outbreaks vs. other routes?

Host Range
How many species does it infect? Can it transfer from species to species?

What do we know?

Mpox is a zoonotic disease with transmission from animals (e.g., NHPs and rodents) to humans.[19, 66]

- The name monkeypox comes from the fact that the virus was first isolated from a monkey. NHPs are often intermediate hosts, exhibiting the same symptoms as humans,[67] however, and are not likely to be the reservoir.[47, 66, 68]
  - The primary reservoir is unknown, but small mammals (especially rodents) are likely to maintain the virus in environments of West and Central Africa[69] and are asymptomatic carriers.[67] The Gambian pouched rat, dormice, and sun and rope squirrels are of particular interest.[52, 66, 70-76]
  - Other potential hosts include multiple rodent species (prairie dogs, rabbits, porcupines, hamsters, shrews, chinchillas), opossums, marmots, groundhogs, anteaters, and hedgehogs.[19, 52, 68-69, 77-79]
- Contaminated body fluids from animals and eating undercooked meat in addition to eating wild game are all suspected of having the ability of spreading the virus to humans.[80]
- In 2003, humans became infected with Clade II MPXV after having contact with infected prairie dogs purchased as pets; these animals had been housed near a number of infected African rodents prior to being sold as pets.[81]
- CDC instructs veterinarians to consider all mammals susceptible to MPXV due to the wide variety of animals shown to exhibit mpox infection, and the lack of information regarding the types of animals that may become ill.[36]
- Relocation of animals from their natural habitats caused by humans moving to new environments, increasing travel from areas where the virus is endemic, and transporting laboratory animals or pets are all causes of increased incidence of mpox infection.[67]

What do we need to know?

- What is the potential for mpox to become an ongoing disease outside of West and Central Africa, such as by establishing a reservoir within native North American species?
- Which animal hosts (including new animal reservoirs) outside of Central Africa are capable of harboring disease and what is the ease of transmission?
- Is there a possibility of establishing new hosts of MPXV in household pets, agricultural

animals, or zoo animals?

Incubation Period
How long after infection do symptoms appear? Are people infectious during this time?

What do we know?

Typical incubation period in humans is 3-17 days, but can range from 1-31 days.[22, 46, 72, 82-83]

- Case studies from a 1980 surveillance program measured time intervals from exposure to fever onset ranges from 10-14 days, and from exposure to rash onset ranges from 12-16 days.[73]
- In the 2003 U.S. mpox outbreak (Clade II), the median incubation period was 12 days (range 2-26 days).[46, 84]
- In the 2017-2018 human mpox outbreak in Nigeria (Clade II), the time from first contact to disease onset ranged from 3-34 days (mean 13 days; median 9.5 days).[85]
- During the Clade IIb outbreak, the mean incubation period of 7.6 days (range from 3-20 days) was estimated from exposure to first symptom onset, and from exposure to rash onset was 8.7 days.[54, 86-87]
    - Given the different types of exposures and routes of transmission, the incubation period for mpox in the recent outbreak may also have a different duration.[88] During this period, a person does not have symptoms and may not appear ill. The severity of illness can depend upon the initial health of the individual and the route of exposure.[83]
- People who were exposed to the virus through non-invasive routes (i.e., petting infected animals) experienced slower illness progression with longer incubation period versus people with a complex exposure (i.e., scratch or bite from an infected animal).[86-87]

Patients are contagious during the first week of the rash,[72, 82] and direct contact should be prevented until lesions have completely healed.[89]

- In the Clade IIb outbreak, the median time from the development of the first skin lesion to the development of additional skin lesions was observed to be 5 days (range, 2-11 days).[32]
- Humans can be contagious before a visible rash appears and can continue shedding the virus weeks after symptoms have dissipated.[22-23, 34-38] It is usually a self-limiting disease with symptoms lasting 2-4 weeks.[90]
- In the Clade IIb outbreak, mpox has only been known to spread by people from the time symptoms start and up until the rash has fully healed and a fresh layer of skin has formed. However, MPXV has been detected in some samples taken from people who reported no symptoms.[91]

What do we need to know?

- What is the degree of infectivity of the host during the incubation period prior to onset of symptoms?
- What is the incubation period for Clade Ib?
- How should public health organizations intervene depending on incubation period?
- Are humans infectious via sexual fluids such as semen or vaginal secretions before symptom onset?

Clinical Presentation
What are the signs and symptoms of the infected person?
What do we know?

Human disease associated with Clade II MPXV infection is generally less severe than Clade I MPXV infection.[9, 48]

- Evidence suggests that the route of exposure may affect clinical presentation. Severity or location of lesions may correlate to how the virus is transmitted.[92]
- Recent multi-country studies showed that three men among 224 samples collected were serology confirmed MPXV exposure but without any symptoms.[88, 93]

The major clinical features of human mpox are similar to those of smallpox;[94-95] however, lymphadenopathy (lymph nodes with abnormal size, number, or consistency) is a key distinguishing feature of mpox.[82, 96]

- The disease typically presents with a short prodromal phase with influenza-like illness before classical mpox symptoms such as rash appear.[22, 47, 70, 82, 97-98]
    - Prodromal period (lasts 1-4 days): fever, fatigue, headache, backache, mild to severe pulmonary lesions, anorexia, dyspnea, conjunctivitis, nasal discharge, swollen lymph nodes, chills and/or sweats, sore throat, cough, and shortness of breath.[22, 47, 70, 82, 97-98]
    - In the Clade IIb outbreak, disease has not always been accompanied by classical prodromal symptoms and may present as a rash with typical lesions with or without perceptible fever.[37]
- Following the prodromal phase, mild to severe rash/lesions may appear, lasting 2-4 weeks. The rash may appear on the chest, face, genitals, hands/palms and feet. Lesions can develop on mucous membranes, in the mouth, on the tongue, and on the genitalia.[22, 47, 70, 82, 94, 98] The rash typically looks like blisters, pustules, or pimples and can be either itchy or painful.[94]
- Proctitis and tonsillitis have been more common in the Clade IIb outbreak due to the outsized role of sexual transmission.[37, 99-100]
- In a case study assessing primarily Clade Ib cases, skin rash, fever, headache, and swollen lymph nodes were the most common symptoms, having been reported by 88%, 74%, 72%, and 70% of patients, respectively. Additionally, two patients (one male and one female) reported being asymptomatic.[63] This is consistent with other MPXV clades.[101]
    - Males displayed symptoms of skin rash, chills or sweats, genital lesions, headache, and muscle pain more frequently than females.[63]

Atypical Presentation, Common Misdiagnoses, and Complications are associated with MPXV infection.

- Varicella is a common misdiagnosis for the mpox infection. The varicella rash is centripetal with lesions that appear superficial and have irregular borders, described as “dew drop on a rose petal.” This description differs from the mpox infection with a rash that follows a centrifugal pattern of distribution and lesions with defined borders that are deep and hard. Varicella also progresses rapidly at multiple stages, while mpox develops slowly with lesions at similar stages throughout the body. Lymphadenopathy is not observed in varicella.[102]
- Due to the genital and perianal presentation of lesions, in many cases, this may lead to a

misdiagnosis with sexually transmitted infections such as syphilis, chancroid, and herpes.[37, 100, 103-104]

- Patients with previous health concerns such as HIV or cancer may result in atypical clinical presentation of mpox, such as lesions appearing prior to systemic symptoms, dyspnea, and pharyngitis.[92, 105]
- Complications associated with MPXV infection includes ocular infections, which may result in corneal scarring and permanent vision loss.[25] Mpox can result in fatal outcomes for fetus in pregnancy.[106]
- Children, pregnant women, and immunocompromised individuals are at higher risk for serious complications and death from mpox.[95]
- Mpox related complications also include secondary infections such as bacterial skin infections in open lesions, dehydration or malnutrition caused by vomiting and diarrhea, pneumonia, or infections of the blood, brain, heart, or other organs.[95, 107]

What do we need to know?

- What rapid laboratory diagnostic would improve the ability of healthcare workers and others to differentiate mpox from other diseases caused by poxviruses, including smallpox?

Clinical Diagnosis
Are there tools to diagnose infected individuals? When during infection are they effective?

What do we know?

As of September 09, 2024, one FDA-cleared test and eight EUA tests have been approved for diagnosis of mpox in the U.S. All tests utilize swabs from lesions.[108]

- CDC's Non-Variola OPV Real-Time PCR Primer and Probe Set is the only FDA-cleared test.[108]
- Five of the EUA tests are performed via real-time PCR with multiple targets, two via real-time PCR with one target, and one is an at-home collection kit that is sent to Labcorp for testing.[109]

The current CDC case definition requires positive PCR, sequencing, or culture to be considered a confirmed case.[110]

- PCR-based diagnostics are the most reliable diagnostic tools for MPXV.[111]
  - PCR-based methods can be used on scab or vesicle material samples with or without virus isolation or propagation.[20, 70, 78, 112-115] PCR-based methods are effective during acute illness[21] and can differentiate between MPXV Clade I and Clade II strains.[116]
- PCR based diagnostic testing in the U.S. is available through local, state, territorial or tribal health department and many large commercial laboratories.[117] Outside of the U.S., the availability of testing is more limited, often with less than 50% of suspected cases tested in some African countries, though access is expanding.[118]
- Contact local or state health departments to inquire about diagnostic testing prior to contacting the CDC.[38, 111]

Antibody-based tests and electron microscopy are only sufficient for "probable" case status under the current case definition.[110]

- Enzyme-Linked Immunosorbent Assay (ELISA)-based serological diagnostics can be used to determine if exposure has occurred after a patient is PCR negative, but cannot

differentiate between clades, and may not be able to differentiate vaccinated from infected individuals.[119]

- Immunoglobulin M (IgM) titers may be positive as early as 2 days after rash onset; it is recommended that samples be collected at least 5 days after onset of rash.[119]
- IgG titers may be positive as early as 1-2 days after rash onset; it is recommended that samples be collected after 14 days following onset of rash.[119]

- PCR detection and diagnostic techniques remain effective for Clade Ib.[120]
- The CDC recommends that patients who travel from DRC receive Clade-specific testing.[121]

What do we need to know?

- In resource-limited settings, how can tests that detect MPXV without requiring virus isolation or amplification be improved?

Fatality Rate
How likely is it that some individuals will die from mpox?

What do we know?

Case fatality rate can range from 0-17%, depending on subclade, vaccination status, and age.[47, 51, 72-73, 112]

- Estimated mortality rates by subclade are 5-10% (Clade Ia), 0.7% (Clade Ib), 0% (Clade IIa), and 0.2% (Clade IIb).[9]
- The current case fatality rate in DCR estimated at 4.9%.[3,18]
- As of September 09, 2024, no deaths from Clade 1b have been reported in Rwanda, Kenya, or Uganda.[122]
- As of September 09, 2024, there are 2466 confirmed cases of Clade IIb, with seven deaths in all of 2024. The fatality rate so far in 2024 is 0.2%.[123] The case fatality rate in the U.S. at the height of the outbreak was 0.1%.[124]

Fetal fatality was studied in African countries and found data supporting that fatality rates vary based on MPXV variant. There are no data for fetal fatality regarding U.S. cases.

- Clade Ia has the most severe effects during pregnancy with a 75% fetal mortality rate.[28]
- During the Clade IIb outbreak, there were no confirmed cases of fetal infection.[125-126]
- In a cohort of eight pregnant women admitted to the hospital with Clade Ib MPXV, four had fetal losses—a fetal mortality rate of 50%[125]

Data indicate that subpopulations, such as individuals with HIV and children, have increased likelihood for fatal outcomes.

- A case study conducted on the Nigerian MPXV outbreak from 2017 to 2019 indicated that the risk of dying from mpox was nearly 14-fold higher in persons living with HIV compared with non-HIV coinfected cases.[127]
- The WHO reports a higher case fatality ratio in the current DRC outbreak for those under 5 years old (7.8%) than those over 5 years old (3%).[128]

What do we need to know?

- Are there demographic subpopulations who are more likely to have fatal outcomes, and if so, which groups are they?

- Do previous or existing medical issues increase likelihood of mpox mortality?

Medical Treatment
Are there effective treatments?

What do we know?

Tecovirimat (also known as TPOXX or ST-246), cidofovir (Vistide), and brincidofovir (Tembexa) are antiviral medicines approved for the treatment of smallpox or other therapeutic indications.[129-130] These antivirals have been shown to be effective against poxviruses in *in vitro* and *in vivo* studies.[131] However, TPOXX does not appear to reduce the duration or impact mortality when used to treat Clade I mpox.[132]

- TPOXX was approved in the U.S. only for the treatment of human smallpox; however, through a CDC Expanded Access-Investigational New Drug (EA-IND) protocol during the global outbreak of 2022, it was made available for certain mpox patients,[129] particularly for severe clinical symptoms or the immunocompromised.[131, 133]
    - A small study with confirmed MPXV-positive adults taking 600 mg oral TPOXX twice daily for 14 days resulted in no new lesions at median of 5 days after starting treatment.[134]
        - Oral TPOXX is available in the U.S. through enrollment in the ongoing STOMP (Study of Tecovirimat for mpox) clinical trial across the U.S. People who have been exposed or are symptomatic should contact their healthcare provider for enrollment.[130, 135-136] There is also an arm of the study for people who are immunocompromised, pregnant, lactating, have certain skin conditions, or are under 18.[129]
- Cidofovir is FDA approved for the treatment of cytomegalovirus retinitis in acquired immunodeficiency syndrome (AIDS) patients.[129] When used in animal studies, it was administered intravenously at 5 mg/kg on the day of infection to 2 days post-infection and provided complete protection from clinical mpox symptoms in NHPs.[137] However, this drug causes kidney damage.[131]
- Brincidofovir is a prodrug of cidofovir and is FDA approved for smallpox in adults and children.[129] It can be used in lower doses than cidofovir, so it is less toxic.[131] There are no efficacy data of brincidofovir in people, but *in vitro* and *in vivo* studies showed efficacy against OPVs. Brincidofovir would be given if the patient has a contraindication to tecovirimat or progresses to severe disease while on TPOXX.[129] However, MPXV can become resistant to brincidofovir.[131]
- VIGIV is FDA approved for treatment of severe symptoms associated with Vaccinia vaccination. Efficacy against mpox has not been proven in humans; however, animal studies show cross-protection against OPVs, including MPXV.[129, 138-139]
    - VIGIV at 6,000 U/kg may be administered for MPXV or complications of vaccination with live vaccina vaccines. This is used only in case-by-case basis. May need to re-dose, as half-life is 30 days, and may need to revaccinate for live viruses afterward.[140]
- TPOXX and VIGIV are in the SNS.[141] Brincidofovir was added to the SNS in Oct 2022, however, TPOXX should still be considered for use first. [129, 142]

What do we need to know?

- What is the efficacy of antiviral drugs against MPXV specifically?
- The JYNNEOS vaccine can be used as a PEP, what antiviral drugs or other treatments might be effective?

Vaccines
Are there effective vaccines?
What do we know?

Two vaccines that were originally developed for smallpox have been licensed by the FDA for use against mpox and are maintained in the SNS (JYNNEOS and ACAM2000). Additional vaccines are available under an IND or internationally.

- JYNNEOS (Bavarian Nordic A/S; known internationally as Imvamune or Imvanex) is a non-replicating Modified Vaccinia Ankara (MVA) vaccine. This vaccine is the dominant vaccine used for mpox in the U.S., and is licensed for MPXV by the FDA in addition to licensure for smallpox.[143] In April 2024, JYNNEOs was made commercially available in the U.S.[143]
  - A case-control study in the U.S. reporting on over 10,000 HIV+ patients showed full vaccination of those without immunocompromising conditions yielded 76.3% efficacy and 40.8% efficacy in partially vaccinated patients. The overall adjusted vaccine effectiveness was 66.0% when fully vaccinated, and 35.8% when partially vaccinated.[144]
  - Most post-vaccination breakthrough infections occur within two weeks of the first dose, prior to the second dose and before maximum protection is achieved.[145-146]
  - The vaccine is given in two doses, with the second dose four weeks after the first. Individuals are most protected two weeks after the second dose. While receiving the second dose four weeks after the first dose is the standard schedule, the second dose can be administered at any time.[147]
  - The duration of protection is not yet known[148]; however, no data to date indicate waning immunity.[143]
  - The most common side effects are pain, redness, or itching at the vaccination site, as well as fever, headache, tiredness, nausea, chills, and muscle aches.[148-149]
  - For PEP, following a known or presumed MPXV exposure, individuals can be vaccinated up to 4 days post-exposure for the best chance at protection. Vaccination can be considered up to 14 days following exposure but may be less effective. Once symptoms are present the vaccine will not be effective.[150]
  - There is limited data on vaccination with JYNNEOS in pregnant or lactating women. JYNNEOS can be given during pregnancy or nursing, but risks versus benefits should be discussed on a case-by-case basis.[151]
- **ACAM2000** (Emergent) is a live vaccinia virus vaccine licensed for smallpox and MPXV, which was initially made available for MPXV under EA-IND and received full approval in August 2024.[150, 152]
  - This vaccine is given as a single percutaneous dose.[153]
  - Greater risk of serious side effects have been found with this vaccine, and it should not be given to individuals who are immunocompromised or who have heart disease.[154] Not for use in pregnant or nursing women, infants, or young children.[155]
- Aventis Pasteur Smallpox Vaccine (APSV) is another live vaccinia vaccine that is in the SNS only for smallpox, but in rare circumstances could be used for mpox under an EUA or as an IND in an emergency, in cases where the other two vaccines weren't available or there are contraindications.[153, 156] Both JYNNEOS and ACAM2000 vaccines are in the SNS.[150]
- There has been a significant increase in human mpox cases over the decades following the

end of smallpox vaccinations in rural areas of DRC.[20, 37]

- Vaccination is not recommended for individuals who have recovered from a natural mpox infection, since reinfection is rare, occurring in less than 0.1% of patients.[143]
- Due to risk versus benefit, limited vaccine supply, and transmission through close or intimate contact, widespread mass vaccination is not recommended. Vaccination strategies focus on vaccinating high risk populations as well as PEP vaccination of individuals with known or suspected exposure through contact tracing.[150, 155]

The CDC does not recommend booster vaccinations (more than 2 doses) except for specific groups:[157]

- Vaccination is not recommended for healthcare professionals, or for clinical laboratory staff performing hematology, uranology, etc., unless sexual risk factors are present.[143, 157]
- Research laboratory staff who are investigating animal or human mpox cases and directly handle infected animals or cultures and typically work with much higher virulence stocks. These staff should get a booster between 2 and 10 years depending on the type of work.
- Healthcare workers who are caring for patients with mpox if appropriate PPE isn't available.

What do we need to know?

- Would it be advantageous to make the smallpox vaccine routinely available to those in MPXV-endemic regions with an increased risk of exposure?
- What is the duration or protection of the vaccines?
- Is there a higher incidence of breakthrough infection with vaccination versus recovery from natural infection?
- Are all treatments equally effective for each known strain in humans?

Environmental Stability
How long does the agent live in the environment?

What do we know?

- Poxviruses, like variola and vaccinia viruses, are known to remain infectious in sloughed scabs and unwashed bed linen for months to years, but MPXV may be less stable.[158-160] Viral OPV DNA present in lesion material is stable for a long period of time if kept in a relatively dark, cool environment.[161-162]

The median time of MPXV DNA persistence in various patient samples, like blood, urine, and skin lesions, was shown to be 5.7 days to 13.5 days.[160]

- MPXV DNA was detected on PPE, multiple surfaces, and an air sample taken during bedding change >1.5 meters from a patient's bed in the hospital. Viral isolation of the air sample resulted in an increase in viral DNA, but not cytopathic effects.[163]
- Live MPXV was recovered from multiple porous and non-porous surfaces in a patient's residence 15 days after the patient was admitted to the hospital.[164]
- MPXV-contaminated material including clothes, paper, and dust may remain contagious for years if not disinfected.[158]

As an OPV, MPXV is expected to be quite stable in the environment:[165]

- MPXV is relatively resistant to desiccation both in heat and cold.[165]
- Repeated freezing and thawing of undiluted MPXV-infected tissue culture fluid up to

12 times produced a 1.5- to 4-fold loss of infectious virus.[165]

- After 6 months of storage of infected tissue culture fluid at 4°C, the infectivity titer of stocks remained unchanged from the original; however, at -20°C there was a 100-fold loss of infectious virus, and at -70°C there was a 30-fold loss of infectious virus.[165]
- After 15 months of storage, the loss in viability was about 500-fold at 4°C, 1,000-fold at -70°C, and more than 10,000-fold at -20°C.[165]
- Vaccinia, another OPV, is stable for days to weeks in storm water and soil, lasting longer at cold temperatures.[159]

What do we need to know?

- How long does the virus remain viable in dried scabs on a patient?
- Does MPXV stability follow the same general trends as other OPVs?
  - If not, what is the stability of MPXV on various common surfaces and food items?

Decontamination
What are effective methods to kill the agent in the environment?

What do we know?

EPA lists emerging viral pathogens into Tiers (1-3), denoting increasing difficulty of inactivation. MPXV is Tier 1, meaning that it is among the easiest to destroy (chemically), with inactivation of virus upon destruction of its envelope.[166]

- List Q contains all EPA-registered disinfectants for use on emerging viral pathogens including MPXV.[166]
- Common household disinfectants on List Q include many with active ingredients of sodium hypochlorite (bleach) or quaternary ammonium (compounds).[166]
- List Q also identifies hospital-grade disinfectants.[166] Hospital disinfection is similar to above recommendations, with added notes to avoid sweeping, dry dusting, and vacuuming in the room of a patient with mpox.[166-167]

Effective means of home disinfection include standard laundry and dish washing methods, while using PPE and observing proper hand hygiene.[168]

- Hot water cycle achieving 140°F is recommended for laundering bed linens and clothing. Soiled laundry should not be shaken, as it may cause the virus to become airborne. [168]
- After removal of PPE, hands should be washed for at least 20 seconds with soap and water. If soap and water are not available, an alcohol based sanitizer with ≥ 60% alcohol is recommended.[169]

Vaccinia virus is commonly used as a surrogate for OPV inactivation.

- The disinfectants Virkon® and Dettol® were found to inactivate vaccinia virus. 5% Virkon completely inactivated the virus on contact while Dettol completely or near completely inactivated the virus on contact. Complete inactivation was achieved with contact time of 30 minutes [170]
- Formulations of 80% ethanol-based and 75% isopropanol-based disinfectants inactivated MPXV in tissue culture with a reduction factor of ≥6.7 when either were used a concentrations of 60% and 80% (vol/vol). A 30-second exposure with either formulation inactivated MPXV in tissue culture at concentrations above 30% (vol/vol).[171]

- Sanytex (3-10%) reduced vaccinia virus >10^4-fold in suspension containing protein after a 3-minute incubation. The higher concentration Sanytex was required to decontaminate higher protein concentrations in the suspension. Vaccinia virus (with protein) dried on a surface was reduced >10^4-fold with 30% Sanytex after 30 minutes.[172]
- Ultraviolet (UV) light at 254 nm for 20 seconds inactivates vaccinia virus in water.[159] Dried vaccinia was inactivated (>4 $\log_{10}$ reduction) in under 7 minutes with UV-C light (200-280 nm), which causes damage to the viral nucleic acids.[173]

What do we need to know?

- What viral titers of MPXV can be effectively decontaminated with sodium hypochlorite? (bleach), and how quickly does a prepared bleach solution lose effectiveness against MPXV?
- What is the minimum inhibitory concentration of decontaminating agent and duration of required contact time in samples relevant to MPXV (e.g., scabs and blood)?

Personal Protective Equipment (PPE)
What PPE is effective and who should be using it?

What do we know?

- Recommendations for the general public include avoiding skin contact with anyone that has mpox as well as their belongings, washing hands frequently, and getting vaccinated. Everyday use of PPE is not necessarily recommended but left to individual choice. For high-risk populations, masking may help prevent the spread of MPXV.[174-175]
- For clinicians, PPE should be donned before entering the patient's room and used for all patient contact. Optimal PPE includes disposable gown and gloves, NIOSH-certified N95 (or comparable) filtering disposable respirator, and face shield or goggles. All PPE should be disposed of prior to leaving patient's room.[167, 176]
- For dental care workers, NIOSH-certified N95 mask, particulate respirators (FFP3), fluid-resistant attire and eye protection are recommended.[177]
- All procedures involving handling potentially infectious material should be performed in laboratories utilizing BSL-2 or BSL-3 practices, depending on the risks involved in the procedure.[178]
- All persons working in or entering laboratory or animal care areas where activities with MPXV are being conducted may require additional PPE such as shoe covers and specialized gloves.
- Precautions should be taken against direct contact with lesions until the lesions have healed.[89] Cover open wounds and lesions. Use gown or sheet to cover lesions if transport is required, such as within hospital.[179]

What do we need to know?

- What additional precautions are required for immunosuppressed or other populations that may have prolonged contact with an infected individual?

Genomics
How does the disease agent compare to previous strains?

What do we know?

MPXV is a member of the Orthopoxvirus genus of the Poxviridae family of enveloped viruses, with a linear double-stranded DNA genome of around 200 kbp.[96, 180]

- On August 12, 2022, the World Health Organization (WHO) updated MPXV variant nomenclature to Clade I (formerly Congo Basin/Central African clade) and Clade II (formerly West African clade). Both clades are further divided into subclades a and b.[181]
- Like all OPVs, MPXV has an extremely low evolutionary rate, estimated at 6.5 x 10^{-6} substitutions/per site/per year,[182] which is approximately 2-3 orders of magnitude slower than RNA viruses like SARS-CoV-2 or Ebola virus.[183]

Historically, the strains belonging to Clade II tend to be less pathogenic and human-transmissible than Clade I strains.[112, 116, 184-185]

- Clade I MPXVs are regulated as U.S. Health and Human Services (HHS) Select Agents by the CDC Federal Select Agents Program. Clade II MPXVs are not Select Agents due to their lower severity/lethality.[186]
- A constellation of interdependent virulence factors appears to be responsible for the difference in virulence between Clade I and II viruses.[115, 187-189]

The 2022 global outbreak strain is a MPXV Clade IIb virus.[37, 190]

- The virus associated with the Clade IIb outbreak may have an accelerated evolutionary rate relative to other OPVs, potentially as much as an order of magnitude greater.[191]

The 2024 outbreak strain is a MPXV Clade Ib virus.[9]

- The distinct MPXV Clade Ib lineage linked to the Kamituga Health Zone in the DRC was revealed through genomic analysis in January 2024. Clade Ib is divergent from previously sequenced Clade I strains in DRC and increases the known diversity of Clade I by 54%.[3, 192]
- Clade Ib appears to be mutating at an accelerated rate as compared to Clade Ia, where the former has nearly 150 nucleotide substitutions compared to the 96 nucleotide substitutions for Clade Ia.[3]
- Clade Ib contains a large ~1 kbp deletion within a region typically used for identifying Clade I viruses.[3] PCR techniques remain effective for Clade Ib.[120]

Various genomic changes have been observed in both the 2022 Clade IIb and current (Clade Ib) outbreaks that are associated with human-to-human transmission.[3, 193-194]

- Four distinct lineages have been detected in Clade I, and a deletion that resulted in gene loss appears to correlate with human-to-human transmission.[112]
- The increase in human-to-human transmission observed with both Clade IIb[191, 195] and Clade Ib[3] may be due to increased editing by the host RNA editing enzyme APOBEC3.
- Loss of inverted repeats have also been reported in APOBEC3, indicative of evolutionary diversification.[196]
- Whole genome analysis of almost 2,000 samples from previous outbreaks revealed recent high mutation rates in MPXV regions relating to host cell attachment, potentiating transmissibility of the virus.[183]

What do we need to know?

- Are there changes due to genomic destabilization and gene loss/gain that may pose a potential threat for accelerated adaptation to humans?
- Has the progressive loss of non-essential genes enabled MPXV to adapt to human-to-human transmission? A study demonstrated that gene copy number variation might be a

crucial factor for modulating virus fitness.[112, 197]

- Could further adaptation of MPXV to humans occur through gene loss/gain or through nucleotide changes resulting in optimization of non-equivalent, redundant pathways (convergent evolution)?
- To determine more accurate genomic evolutionary rates, what is the phylogeny of MPXV in human populations prior to and including the Clade Ib and Clade IIb outbreaks?

Commonly Used Acronyms and Abbreviations

Acronym/Term	Definition	Description
AIDS	Acquired Immunodeficiency Syndrome	A chronic condition that compromises the immune system caused by HIV
APSV	Aventis Pasteur Smallpox Vaccine	Investigational vaccine with potential use under EUA or IND during smallpox emergency
BSL	Biosafety Level	N/A
CDC	Centers for Disease Control and Prevention	N/A
DHS S&T	U.S. Department of Homeland Security Science and Technology Directorate	N/A
DRC	Democratic Republic of the Congo	N/A
EA-IND	Expanded Access Investigational New Drug	Provisional FDA approval granted for use of investigational drug as clinical treatment
ELISA	Enzyme-Linked Immunosorbent Assay	Assay used to detect the presence of antibodies to a specific protein
EPA	U.S. Environmental Protection Agency	N/A
EUA	Emergency Use Authorization	Provisional FDA approval granted for pharmaceuticals and other medical products under emergency conditions
FDA	U.S. Food and Drug Administration	N/A
HHS	U.S. Department of Health and Human Services	N/A
HIV	Human Immunodeficiency Virus	N/A
Ig	Immunoglobulin	Antibodies (glycoprotein molecules produced by white blood cells)
IND	Investigational New Drug	FDA designation allowing for limited/controlled use of an unapproved pharmaceutical under specific conditions
LD_{50}	Median Lethal Dose	Dose required to cause a lethal effect in 50% of subjects
mpox	Monkeypox virus Disease	N/A
MPXV	Monkeypox Virus	N/A
MQL	Master Question List	N/A
MSM	Men who have Sex with Men	N/A
MVA	Modified Vaccinia Virus Ankara	Vaccina virus that cannot replicate in normal cells
NHP	Non-Human Primate	N/A
NIOSH	National Institute for Occupational Safety and Health	N/A
OPV	Orthopoxvirus	Group of viruses containing smallpox, monkeypox, vaccina virus, and others

Acronym/Term	Definition	Description
PEP	Post-Exposure Prophylaxis	N/A
PFU	Plaque Forming Unit	Unit representing a single infectious viral particle derived from viral quantification via plaque assay
PPE	Personal Protective Equipment	Equipment intended to protect individuals against hazardous environments
qPCR	Quantitative Polymerase Chain Reaction	Assay used to determine the number of RNA or DNA molecules representing a specific sequence target present in a sample
R_0	Basic Reproductive Number	Average number of new infections that each case is expected to generate in a population where all individuals are susceptible to infection
SNS	Strategic National Stockpile	Stockpile of drugs, tests, vaccines, and equipment maintained by the Federal Government for pandemic and biothreat response
$TCID_{50}$	Median Tissue Culture Infectious Dose	Dose necessary to infect 50% of tissue cells.; used as a standard measure of infectivity (e.g., it required 10^3 $TCID_{50}$ to produce clinical signs in exposed chickens)
TPOXX	Tecovirimat	N/A
UV	Ultraviolet	Light with wavelength in the 100-400 nm range
VIGIV	Vaccinia Immune Globulin Intravenous	Biologic regulated by the FDA for treatment of vaccinia and related complications; implicated for use in mpox
WHO	World Health Organization	N/A

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