DHS SCIENCE AND TECHNOLOGY

Master Question List for Monkeypox Virus (MPXV)

December 2023

For comments or questions related to the contents of this document, please contact the DHS S&T Hazard Awareness & Characterization Technology Center at HACTechnologyCenter@hq.dhs.gov.

Science and Technology

DHS Science and Technology Directorate | MOBILIZING INNOVATION FOR A SECURE WORLD

Monkeypox Virus (MPXV) – Master Question List

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Foreword

The following Master Question List (MQL) was developed by the Department of Homeland Security (DHS) Science and Technology Directorate (S&T) to provide government decision makers with up-to-date information that will enable them to appropriately respond to outbreaks caused by monkeypox virus. This MQL summarizes what is known and what knowledge gaps exist 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 facilitate 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.

Situation Overview

The Monkeypox virus (MPXV) is a zoonotic virus (a virus that originates in animals) that causes symptoms similar to, but less severe than smallpox, which was eradicated in 1980. The virus is native to Africa, but cases are occasionally exported to Europe and North America. Since May 13, 2022, mpox (the disease caused by MPXV) cases have been reported in multiple countries, including the United States. The virus causing the present outbreak is a member of a subgroup of MPXVs associated with less severe disease than other groups of MPXVs. 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. There is reason to suspect that this previously unseen mode of transmission may be contributing to increased transmission rates. As of the preparation of this document, mpox cases are in decline in the United States and globally, although some transmission is still occurring.

The cutoff date for information gathering related to this document was 02/16/2023.

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, which was declared eradicated in 1980. This group also includes vaccinia virus (an attenuated poxvirus used in 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 at least two broad groups (clades) of MPXVs. • Virologists use the term "clade" to describe a group of viruses that have extremely similar genetic sequences and are different enough from other viruses of the same species that they form a distinct genetic cluster. • Clade I (formerly Congo Basin clade) is found in Central Africa. About 10% of cases are fatal. • Clade II (formerly West African clade) includes the virus responsible for the current outbreak, and is associated with a lower death rate, about 1%. In the past, viruses of this clade have also been less transmissible than Clade I viruses.
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	• The virus enters the body through broken skin, the respiratory tract, and other non-respiratory mucous membranes. • Human-to-human transmission is thought to occur primarily through respiratory droplets, direct contact with body fluids/lesion material, and fomites contaminated with lesion material. • Rates of droplet transmission in this outbreak appear similar to prior outbreaks. • The current outbreak strain may have accumulated mutations that increase its transmissibility. However, there is not yet enough evidence to suggest that these dramatically increase the basic reproductive number (R_0) of the virus. • 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 current outbreak is 1.10-2.40. This may be related to novel mutations accumulated during prolonged human-to-human transmission. • 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. • Direct contact among MSM currently has been cited as a source

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
	of a significant number of the infections in the current outbreak.
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. • Domesticated animals in MPXV-positive households have been infected with MPXV by owners. • It is not known if rodent species native to the United States could serve as reservoir hosts, though several can become infected.
INCUBATION PERIOD	• The interval between exposure and the development of symptoms ranges from 1 to 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 to 4 weeks. • Rash is typically confined to the trunk 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 current outbreak, lesions on the genitalia and the perianal region have been more common due to the role of sexual transmission, and early presentation has not always included fever or other typical early symptoms of mpox. • Some patients in the current outbreak have presented without fever. • These unusual presentations can lead to misdiagnosis as a common sexually transmitted infection such as syphilis, chancroid, or herpes. • Swollen lymph nodes (lymphadenitis) are a feature of mpox disease not seen in smallpox.
CLINICAL DIAGNOSIS	• One U.S. Food and Drug Administration (FDA)-cleared test and seven Emergency Use Authorization (EUA) tests are approved for diagnosis of mpox in the United States. All tests require swabs from lesions. • The current Centers for Disease Control and Prevention (CDC) case definition requires positive polymerase chain reaction (PCR), sequencing, or culture to be considered a confirmed case. • Culture-based diagnostics should only be performed by the CDC.
FATALITY RATE	• As of 02/15/2023, the fatality rate in the United States for the

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
	current outbreak is 0.1%, which is consistent with the global rate.
MEDICAL TREATMENT	• There are currently no MPXV-specific antiviral drugs. • Tecovirimat (TPOXX) is approved for smallpox and mpox. • Brincidofovir (Tembexa), cidofovir (VISTIDE), and vaccinia immune globulin intravenous (VIGIV) are potential treatment options. • Tecovirimat and VIGIV are in the Strategic National Stockpile (SNS). • For post-exposure prophylaxis (PEP), smallpox and JYNNEOS vaccines can be administered at 3 and 4 days post-exposure, respectively. Both vaccines are effective in reducing clinical symptoms up to 14 days post-exposure.
VACCINES	• Vaccination with smallpox vaccine (vaccinia virus) is reported to provide protection against 85% of MPXV infections. • JYNNEOS (Bavarian Nordic A/S) is specifically licensed for MPXV by the FDA in addition to licensure for smallpox. JYNNEOS is a two-dose, non-replicating Modified Vaccinia Virus Ankara (MVA) vaccine that can be given to people for whom live vaccina vaccines are not safe. • ACAM2000 (Emergent) is a live vaccinia virus vaccine licensed for smallpox, made available for MPXV under Expanded Access Investigational New Drug (EA-IND) by the FDA. • ACAM2000 and JYNNEOS are maintained in the SNS, along with Aventis Pasteur Smallpox Vaccine (APSV), another live vaccinia vaccine that would be used under an EUA or as an IND in an emergency.
ENVIRONMENTAL STABILITY	• The median time of MPXV DNA persistence in various patient samples, like blood, urine, and skin lesions, is from 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.

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
PERSONAL PROTECTIVE EQUIPMENT (PPE)	• Optimal personal protective equipment (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 (e.g., high-efficiency particulate air [HEPA] filtration of all exhaust air) to avoid laboratory staff exposure or accidental release of a pathogen.
GENOMICS	• MPXV is a DNA virus with a genome more than 10 times larger than that of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). • In August 2022, the World Health Organization (WHO) updated clade nomenclature in which the Congo Basin/Central African clade has been renamed Clade I, and the West African clade was renamed Clade II, with subclades IIa and IIb. • Like related viruses, MPXV evolves slowly. Its genome changes 100-1,000 times slower than that of SARS-CoV-2. • Research conducted in 2022 suggests that the virus responsible for the latest outbreak may be evolving slightly faster than normal, but still significantly slower than other viruses like influenza and SARS-CoV-2. • This faster evolutionary rate may be due to accumulated mutations that enhance transmission of the virus, but more work is needed to clearly demonstrate this finding. • Clade I MPXVs are regulated as U.S. Department of 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.

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.[1]

- 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.[2]
- 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.[3-4]

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.[3-6]

- 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 to 10^7 PFU.[7]
- In an aerosol study with cynomolgus macaques, the inhalation LD_{50} for the ZaireV79-I-005 strain (Clade I) of MPXV was determined to be between 10^4 and 10^5 PFU.[8]

What do we need to know?

- What is the infectious dose in humans by relevant routes?
- 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?

Transmission of MPXV occurs when a person comes in contact with the virus from an animal, 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.[9-13] Humans can be contagious before a visible rash appears and can continue shedding the virus weeks after symptoms have dissipated.[9-10, 14-18]

- Human-to-human transmission is thought to occur primarily through respiratory droplets, direct contact with body fluids or lesion material, and indirect contact with lesion material via contaminated fomites.[9-11] Transmission has been recorded from mother to fetus via placenta.[19]
  - Rates of droplet transmission in this outbreak do not appear to be different from prior outbreaks.[9-10, 14, 20]
- Person-to-person transmission has been reported in previous outbreaks, but was not common.[21-23]
  - Clade II (formerly West African clade) MPXV infection has historically been rarely associated with human-to-human transmission.[23] However, up to six sequential person-to-person Clade I (formerly Congo Basin clade) MPXV transmissions have been documented prior to this outbreak.[9, 24] Approximately 0-11% of mpox household contacts have been infected in prior outbreaks.[25-29]

Since April 2022, MPXV has spread among humans who have not travelled to endemic areas and is credited to sexual transmission.[13, 30-32] Human-to-human transmission has become the primary mode of transmission, raising concerns for unaccounted community spread.[32]

- The mechanism for increased person-to-person spread is multifaceted and may include population-specific behaviors that increase risk.[17]
  - Direct contact among MSM has been cited as a source of a significant number of the infections in the current outbreak.[32-33]
- A case study of 81 healthcare workers (with 57 of 81 participating in the survey) reported no signs or symptoms consistent with mpox following exposure to infected patients, indicating transmission in a healthcare setting is unlikely when infection control measures are undertaken.[34]
- Sources of laboratory-acquired infections include exposure to aerosols, environmental samples, naturally or experimentally infected animals, infectious cultures, or clinical samples, including lesion fluid or crusted scabs, tissue specimens, excretions, and respiratory secretions.[35]

MPXV can be spread by direct contact between animals and humans.[36-38]

- Humans may become infected following a bite, scratch, or handling of an infected animal and exposure to excretion, secretion, or fomites such as bedding from an infected animal.[32, 39]
- A 2017-2018 mpox epidemic in Nigeria was most likely caused by transmission of MPXV from rodents to humans.[19]
- Transmission to domesticated animals by MPXV-infected humans has been observed in the current outbreak via close contact such as petting, cuddling, hugging, kissing, licking, sharing sleeping areas, and sharing food.[19, 40]
  - Evidence of first human-to-dog transmission of MPXV was published June 2022. Owner and dog were reported co-sleeping. The dog presented skin lesions around the abdomen and anal area. Owner and dog viruses showed 100% sequence homology.[41;29]

The R_0 of the current outbreak is conservatively calculated to be 1.10-2.40 in countries like the United States with declining OPV immunity.[19, 42;10]

- 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.
- It is believed that the transmission rate of mpox has increased through time, coincident with reductions in the fraction of the population with vaccine-derived immunity to smallpox.[10]
  - A maximum R_0 value of 1.25 was estimated from data on smallpox cross-immunity in the Democratic Republic of the Congo.[10]
- Mutations have been identified in the current outbreak strain that may enhance transmissibility relative to previous Clade II (formerly West African clade) viruses, but these mutations are unlikely to dramatically increase the R_0 of the virus.[43]
- Several aspects of the current outbreak, including transmission between MSM, are expected to complicate efforts to estimate R_0 and may make previous estimates unreliable for this outbreak.[17]

What do we need to know?

- How is the R_0 of the current outbreak impacted by the association with the MSM community?
- 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?

- Is the apparent increase in person-to-person transmission in the current outbreak related to genomic changes in the virus, sociological factors, or both?
- Do these factors impact decisions about the types of public health interventions needed to stop an outbreak?
- What is the ultimate impact of cessation of smallpox vaccination on the rate of person-to-person transmission?[37]
- What is the role of droplet/respiratory transmission in the current outbreak vs. other routes?
- How can we improve surveillance and epidemiological analysis to better assess public health burden and develop strategies to reduce widespread disease?
- Is there a clade-dependent difference in transmission?

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.[36, 44]
  - The name monkeypox comes from the fact that the virus was first isolated from a monkey. NHPs are often intermediate hosts and are not likely to be the reservoir.[22, 44-45]
  - The primary reservoir is unknown, but small mammals (especially rodents) are likely to maintain the virus in environments of West and Central Africa.[40] The Gambian pouched rat, dormice, and sun and rope squirrels are of particular interest.[28, 39, 44, 46-51]
  - Other potential hosts include multiple rodent species (prairie dogs, rabbits, porcupines, hamsters, shrews, chinchillas), opossums, marmots, groundhogs, anteaters, and hedgehogs.[28, 36, 40, 45, 52-54]
- 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.[55]
- CDC instructs veterinarians to consider all mammals susceptible to MPVX 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.[16]

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?
- Does wild animal trade pose a risk to spillover accidental infections creating new hosts?
- Due to the most recent outbreak, what is the possibility of humans harboring a genital reservoir of the virus?[32]
- 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 is 3-17 days, but can range from 1 to 31 days).[9, 21, 47, 56-57]
  - Case studies from a 1980 surveillance program measured time intervals from exposure to fever onset ranges from 10 to 14 days, and from exposure to rash onset ranges from 12 to 16 days.[48]
  - In the 2003 U.S. mpox outbreak (Clade II), the median incubation period was 12 days (range 2-26 days).[21, 58]

  - In the 2017-2018 human mpox outbreak in Nigeria (Clade II), the time from first contact to disease onset ranged from 3 to 34 days (mean 13 [SD 9]; median 9.5 days).[59]
  - During the most recent outbreak (data collected between May and June 2022), the mean incubation period of 7.6 days (range from 3 to 20 days) was estimated from exposure to first symptom onset, and from exposure to rash onset was 8.7 days.[33, 60-61]
  - 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.[62] 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.[57]
- 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).[60-61]
- Patients are contagious during the first week of the rash,[47, 56] and direct contact should be prevented until lesions have completely healed.[63]
  - In the most recent 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).[30]
  - Humans can be contagious before a visible rash appears and can continue shedding the virus weeks after symptoms have dissipated.[9-10, 14-18] It is usually a self-limiting disease with symptoms lasting 2-4 weeks.[64]
  - Animals such as black-tailed prairie dogs infected via intranasal and intradermal routes with MPXV at $10^{4.5}$ PFU continued shedding viable virus for up to 21 days post-infection.[46]
- In the current global 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.[65]

What do we need to know?

- What is the degree of infectivity of the host during the incubation period prior to onset of symptoms?
- 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 less severe and is associated with <1% mortality, whereas Clade I MPXV infection has a 10% case fatality rate in unvaccinated individuals.[23] Case fatality rate can range from 0 to 17%, depending on vaccination status and age.[22, 27, 47-48, 66]
- In prior outbreaks, children less than 10 years of age made up the majority of cases (83-86%).[22, 25]
- Evidence suggests that the route of exposure may affect clinical presentation. Severity or location of lesions may correlate to how the virus is transmitted, via pustule or skin versus semen. Transmission of the virus via semen may result in more severe and prolonged symptoms, including myopericarditis.[67]

Symptoms

- The major clinical features of human mpox are similar to those of smallpox;[22] however, lymphadenopathy (lymph nodes with abnormal size, number, or consistency) is a key

distinguishing feature of mpox.[56, 68] Early onset of fever can also be a sign of illness.[12]

- The disease typically presents with a short prodromal phase with influenza-like illness before classical mpox symptoms such as rash appear.[9, 22, 39, 56, 69-70]
  - 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.[9, 22, 39, 56, 69-70]
  - In the current 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.[17]
- Following the prodromal phase, mild to severe rash/lesions may appear, lasting 2-4 weeks. The rash is typically confined to the trunk 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.[9, 22, 39, 56, 70]
- Proctitis and tonsillitis have been more common in the current outbreak due to the outsized role of sexual transmission.[17, 71-72]

Atypical Presentation, Common Misdiagnoses, and Complications

- 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.[73]
- In combination with 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.[17, 71]
- Patients with previous health concerns such as human immunodeficiency virus (HIV) or cancer may result in atypical clinical presentation of mpox, such as lesions appearing prior to systemic symptoms, dyspnea, and pharyngitis.[67, 74]
- Complications associated with MPXV infection includes ocular infections, which may result in corneal scarring and permanent vision loss.[12] Mpox can result in fatal outcomes for fetus in pregnancy.[75]

What do we need to know?

- Can the current mpox case definition be refined to 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?

Since June 2022 and as of 02/16/2023, one FDA-cleared test and seven EUA tests have been approved for diagnosis of mpox in the United States. All tests utilize swabs from lesions.[76]

- CDC’s Non-Variola OPV Real-Time PCR Primer and Probe Set (K221834) is the only FDA-cleared test.[76]
- All seven EUA tests are performed via real-time PCR with multiple targets:[77]
  - Alinity m MPXV by Abbott Molecular, Inc.
  - Quest Diagnostics Monkeypox Virus Qualitative Real-Time PCR by Quest Diagnostics
  - TaqPath Monkeypox/Orthopox Virus DNA Kit by Life Technologies (part of Thermo Scientific)

  - cobas MPXV for use on the cobas 6800/8800 Systems (cobas MPXV) by Roche Molecular Systems, Inc.
  - VIASURE Monkeypox Virus Real-Time PCR Reagents for BD MAX System by Beckton, Dickinson & Company (BD)
  - QuantiVirus MPXV Test Kit by DiaCarta, Inc.
  - Xpert Mpox by Cepheid

The current CDC case definition requires positive PCR, sequencing, or culture to be considered a confirmed case.[78]

- PCR-based diagnostics are the most reliable diagnostic tools for MPXV.[79]
  - PCR-based methods can be used on scab or vesicle material samples with or without virus isolation or propagation.[37, 39, 53, 66, 80-82] PCR-based methods are effective during acute illness[38] and can differentiate between MPXV Clade I and Clade II strains.[83]
- Culture-based diagnosis should only be attempted by the CDC.[18, 79]
- Contact local or state health departments to inquire about diagnostic testing prior to contacting the CDC.[18, 79]

Antibody-based tests and electron microscopy are only sufficient for "probable" case status under the current case definition.[78]

- 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.[84]
  - 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.[84]
  - 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.[84]
  - IgM ELISA can distinguish between recent MPXV infection and previous smallpox vaccination.[84]
  - MPXV-specific IgG was detected in human serum for as long as a year after the initial infection.[38]
- Confirmation is possible through MPXV isolation and immunohistochemistry from human[39] and animal samples.[85-86]
- Intracellular cytokine staining analysis has been used to quantify OPV-specific CD4+ and CD8+ T-cell responses based on gamma interferon and tumor necrosis factor-α production.[38]
- Confirmation possible through morphological identification consistent with an OPV by electron microscopy.[39]

What do we need to know?

- How quickly does a patient become PCR positive after exposure to MPXV?
- 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?

- As of 02/15/2023, confirmed cases in the current outbreak of mpox in the United States was 30,193, with 32 deaths[20]. The fatality rate is 0.1%.
- This rate is consistent with the global fatality rate of 0.1%. As of 02/18/2023, there have been 86,019 confirmed mpox cases in the current outbreak worldwide, with 96 total deaths.[87]
  - Global fatality rate is the same when United States data is subtracted (55,826 cases, 64

deaths).

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?

Antiviral Drugs

- There are currently no MPXV-specific antiviral drugs.[88]
- TPOXX, cidofovir, and brincidofovir (Tembexa) are effective against poxviruses in *in vitro* and *in vivo* studies.
  - Tecovirimat was approved in the United States for treatment of human smallpox and mpox, particularly for severe clinical symptoms or the immunocompromised.[88]
    - A small study with confirmed MPXV-positive adults taking 600 mg oral tecovirimat twice daily for 14 days resulted in no new lesions at median of 5 days after starting treatment.[89]
  - Cidofovir administered intravenously at 5 mg/kg on the day of infection to 2 days post-infection provided complete protection from clinical mpox symptoms in NHPs.[90] However, this drug causes kidney damage.[88]
  - Brincidofovir is less toxic, can be used in lower doses, and is approved in the United States to treat smallpox in children and adults.[88] MPXV can become resistant to brincidofovir.[88]
- TPOXX and VIGIV are in the SNS.[91] Brincidofovir (Tembexa) inclusion into SNS is expected.

Post-Exposure Prophylaxis (PEP)

- Smallpox vaccines should be administered within 3 days post-exposure to provide maximal benefit, but may still attenuate the disease and prevent death when given up to 2 weeks post-exposure.[35, 55, 86, 92-93]JYNNEOS is suitable for use as a post-exposure vaccination, ideally within 4 days of exposure and can be used up to 14 days post-exposure.[94] While the live vaccinia virus vaccine may cause serious complications in those who are immunocompromised, studies of the JYNNEOS vaccine show no severe adverse events in those with HIV or atopic dermatitis.[95]
- 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 redose, as half-life is 30 days, and may need to revaccinate for live viruses afterward.[96]

What do we need to know?

- What is the efficacy of antiviral drugs against MPXV specifically?
- What is the efficacy of JYNNEOS vaccine compared to the live vaccinia vaccine when used as PEP?

Vaccines
Are there effective vaccines?

What do we know?

The CDC recommends pre-exposure vaccination every 3 years for several groups:[35, 56]

- Persons who are investigating animal or human mpox cases.
- Healthcare workers who are caring for patients with mpox.
- Anyone who has direct contact with suspected MPXV-infected animals.
- Laboratory workers who handle specimens that may contain MPXV.
- Vaccination with smallpox vaccine (vaccinia virus) is reported to provide protection against

85% of MPXV infections. CDC recommends revaccination every 3-10 years for individuals with likely exposure.[28, 97]

Three vaccines originally developed for smallpox, which could be used for mpox, are maintained in the SNS (JYNNEOS, ACAM2000 and APSV), the first two of which are licensed by the FDA for use in the United States. Additional vaccines are available internationally.

- JYNNEOS (Bavarian Nordic A/S; known internationally as Imvamune or Imvanex;[95]) is a non-replicating Modified Vaccinia Virus Ankara (MVA) vaccine that is appropriate for use in individuals for whom the live vaccine is contraindicated. This vaccine is specifically licensed for MPXV by the FDA in addition to licensure for smallpox.[98]
  - Data in the United States from July-Oct 2022 in a study of 18-49 year-old males showed mpox incidence was 10 times as high in unvaccinated individuals than those who were fully vaccinated.[99-100] Another real-world retrospective study of males in 2022 in Israel showed 86% efficacy with a single subcutaneous dose[101] Most post-vaccination breakthrough infections occur within 2 weeks of the first dose, prior to the second dose and before maximum protection is achieved.[102-103]
  - The vaccine is given in two doses, with the second dose 4 weeks after the first. Individuals are most protected 2 weeks after the second dose. The duration of protection is not yet known.[104] A booster dose at 2 or 10 years is recommended for individuals at continued risk of exposure.[98]
  - Dosing was historically by subcutaneous injection at a 0.5-mL dose to at-risk adults 18 years and older.[105] As of August 2022, the FDA issued an EUA that JYNNEOS can be given subcutaneously to individuals under 18, and can be given to adults 18 and over by intradermal injection at a 0.1-mL dose, which increases the number of doses available for use 5-fold.[106-109] Dosing subcutaneously or intradermally appears to be equally efficacious.[104, 110]
  - 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.[98, 104]
  - 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. Risk versus benefit for vaccination after 14 days should be reviewed on an individual basis. Once symptoms are present, the vaccine will not be effective.[94]
- ACAM2000 (Emergent) is a live vaccinia virus vaccine licensed for smallpox, made available for MPXV under EA-IND by the FDA.[94]
  - This vaccine is given as a single percutaneous dose.[95]
  - 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.[111] Not for use in pregnant or nursing women, infants, or young children.[112]
- APSV is another live vaccinia vaccine that would be used under an EUA or as an IND in an emergency.[95]
- LC16 m8 is a live replicating attenuated vaccine derived from vaccinia and licensed in Japan.[112-113]
- Both JYNNEOS and ACAM2000 vaccines are in the SNS.[94]
- There has been a significant increase in human mpox cases over the decades following the end of smallpox vaccinations in rural areas of the Congo.[17, 37]
- 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.[94, 112]

What do we need to know?

- Which vaccine provides the best protection and carries the least health burden on the patient?
- Would it be advantageous to make the smallpox vaccine routinely available to those in MPXV-endemic regions with an increased risk of exposure?
- Is there a value in conducting preclinical and clinical trials of live vaccinia smallpox vaccines for human MPXV to better establish efficacy and obtain specific FDA licensure for MPXV.

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.[114-116] Viral OPV DNA present in lesion material is stable for a long period of time if kept in a relatively dark, cool environment.[117-118]

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 according to Weibull regression models fitted with data from 2018 and 2019 cases and the 2022 outbreak.[116]

- 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.[119]
- 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.[120]
- MPXV-contaminated material including clothes, paper, and dust may remain contagious for years if not disinfected.[114]

As an OPV, MPXV is expected to be quite stable in the environment:[121]

- MPXV is relatively resistant to desiccation both in heat and cold.[121]
- 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.[121]
- 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.[121]
- 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.[121]
- MPXV-infected tissue culture fluid adjusted to pH 2 completely inactivated 10^5 PFU/mL virus; 10-fold loss was observed when starting fluid was adjusted to pH 10.[121]
- Vaccinia, another OPV, is stable for days to weeks in storm water and soil, lasting longer at cold temperatures.[115]
- After 14 days of storage at 4°C, vaccinia virus was detected via PCR on food at titers of 200-300 median tissue culture infectious dose ($TCID_{50}$)/100 µL.[115] Under the same conditions and methods, vaccinia was also observed on gauze at ~200 $TCID_{50}$/100 µL.[115]

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?

- Effective means of home disinfection include standard laundry and dish washing methods,

while using PPE and observing proper hand hygiene. Hot water cycle achieving 140°F is recommended for laundering bed linens and clothing.[122] Soiled laundry should not be shaken, as it may cause the virus to become airborne. Surfaces should be cleaned and disinfected with EPA-registered chemicals with an emerging viral pathogens claim. This is a category of disinfectants that have been validated against a wide range of viruses, including difficult to inactivate viruses, that the EPA has approved for use against viruses for which we have little to no information about disinfectant efficacy.[123-125]

- 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.[125]
  - List Q contains all EPA-registered disinfectants for use on emerging viral pathogens.[125]
  - Common household disinfectants on List Q include many with active ingredients of sodium hypochlorite (bleach) or quaternary ammonium (compounds).[125]
  - List Q also identifies hospital-grade disinfectants.[125] 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.[124-125]
- Ultraviolet (UV) light at 254 nm for 20 seconds inactivates vaccinia virus in water.[115] 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.[126]
- Heating MPXV for 20 minutes at 40°C caused no significant loss of infectivity, while heating for 20 minutes at 50 or 56°C resulted in significant (87%) or complete loss of infectivity.[121]
- Similarly, MPXV was inactivated (>4 $\log_{10}$ reduction) by heating viral transport media or fetal bovine serum (FBS) spiked with MPXV for 5 minutes at 70°C or for 15 minutes at 60°C.[127]
- Vaccinia virus is commonly used as a surrogate for OPV inactivation. The disinfectants Virkon® and Dettol® were found to inactivate vaccinia virus (starting titers 10^9-10^{10} $TCID_{50}$/mL).[128]
  - 5% Virkon (disinfectant containing potassium peroxymonosulfate, sodium dodecylbenzenesulfonate, sulfamic acid, and inorganic buffers) completely inactivated the virus on contact in presence and absence of FBS.[128]
  - Dettol (household disinfectant containing 4.8% chloroxylenol and isopropanol and castor oil soap) completely or near completely inactivated the virus on contact. Complete inactivation was achieved with contact time of 30 minutes in presence or absence of FBS.[128]
- 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 at 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).[129]
- Sanytex (3-10%) (a non-corrosive commercial solution containing quaternary ammonium, aldehydes, alcohol, and detergent) 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.[130]

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; and 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.[131-132]
- 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.[124, 133]
- 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.[35]
- 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.[63] Cover open wounds and lesions. Use gown or sheet to cover lesions if transport is required, such as within hospital.[134]

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 DNA virus with a 197 kb genome.[68]
- On August 12, 2022, WHO updated MPXV variant nomenclature to Clade I (formerly Congo Basin/Central African clade) and Clade II (formerly West African clade). Clade II is further divided into Subgroups IIa and IIb.[135]
- The strains belonging to Clade II tend to be less pathogenic and human-transmissible than Clade I strains.[66, 83, 136-137]
  - The current outbreak strain is a MPXV Clade IIb virus.[17, 138]
  - 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.[66]
  - A constellation of interdependent virulence factors appears to be responsible for the difference in virulence between Clade I and II viruses.[82, 139-141]
- Like all OPVs, MPXV has an extremely low evolutionary rate, estimated at 6.5×10^{-6} substitutions/per site/per year,[142] which is approximately 2-3 orders of magnitude slower than RNA viruses like SARS-CoV-2 or Ebola virus.[143]
  - This rate is so low that the inherent error rate of some sequencing technologies can create artifact that may artificially inflate apparent evolutionary rates.[43]
  - Evolutionary rate may be affected by recombination between strains during coinfections.[144]
- Clade I MPXVs are regulated as HHS Select Agents by the CDC Federal Select Agents Program. Clade II MPXVs are not Select Agents due to their lower severity/lethality.[145]
- The virus associated with the latest outbreak may have an accelerated evolutionary rate relative to other OPVs, potentially as much as an order of magnitude greater.[43]
- This enhanced evolutionary rate appears to have led to accumulation of mutations that

would be expected to enhance the transmissibility of the virus.[43]

- The result of the extensive human-to-human transmission experienced by this strain may be due to increased editing by the host RNA editing enzyme APOBEC3.[43] Loss of inverted repeats have also been reported in APOBEC3, indicative of evolutionary diversification.[146]
- Whole genome analysis of almost 2,000 samples from previous and current outbreaks revealed recent high mutation rates in MPXV regions relating to host cell attachment, potentiating transmissibility of the virus.[143]

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.[66, 147]
- 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 2022-2023 outbreak?

Commonly Used Acronyms and Abbreviations

Acronym/Term	Definition	Description
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
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
FBS	Fetal Bovine Serum	Media additive used in tissue culture to facilitate cell growth
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 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
PEP	Post-Exposure Prophylaxis	N/A

Acronym/Term	Definition	Description
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
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2	N/A
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

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