Monkeypox Virus Transmission: Review of the Scientific Evidence

Introduction
Since early 2022, the monkeypox virus has spread rapidly around the world. As with any infectious disease outbreak, the methods of transmission determine which protective measures are needed. Many pathogens spread via multiple transmission methods at the same time, requiring multiple layers of protective measures to contain spread.

Where there is scientific uncertainty, the precautionary principle states that the highest level of protection should be chosen in order to prioritize protecting people’s health. This document summarizes the current scientific evidence—and unanswered questions—regarding the transmission modes of the monkeypox virus.

About the Monkeypox Virus
Human monkeypox is a zoonotic viral disease caused by the monkeypox virus, which belongs to the same family of viruses as smallpox. The first human case was identified in 1970.\(^1\) Monkeypox is considered a re-emerging disease that has caused multiple localized outbreaks since 2017. The monkeypox virus is now spreading rapidly in many countries that have not historically had cases.

- **Animal-to-Human Transmission**

While the natural reservoir for the monkeypox virus has yet to be determined, the virus has a wide range of animal hosts, including prairie dogs, squirrels, wild chimpanzees, shrews, monkeys, dogs, and Gambian pouched rats.\(^{ii,iii,iv,v}\) Monkeypox-infected animals can have similar clinical manifestations to humans infected with the virus, including respiratory signs of varying severity and skin lesions that range from one to several. Studies have also shown that saliva, urine, and feces from infected animals can contain viable monkeypox virus.\(^{vii,viii}\) Animal-to-human transmission of monkeypox has been documented through contact and airborne transmission routes.\(^{ix}\) For example, occupationally transmitted infections occurred in several veterinary staff during the 2003 U.S. monkeypox outbreak while handling or caring for monkeypox-infected prairie dogs within six feet.\(^x\)

- **Human-to-Human Transmission**

Human-to-human transmission of the monkeypox virus, including nosocomial and household transmission, has been well documented.\(^{xi,xii,xiii}\) For example:
• Health care workers were infected during the 2017-18 outbreak in humans in Nigeria.\textsuperscript{xiv}
• Between 2018 and 2021, seven monkeypox cases were identified in the UK, two of whom were infected in a household cluster with a travel-associated case and the other was a health care worker who was infected after caring for the patient without PPE.\textsuperscript{xv}

➢ Human-to-Animal Transmission

Human-to-animal transmission of monkeypox has also been identified during the 2022 outbreak. A pet dog developed lesions and tested positive for the virus, twelve days after its owners developed symptoms of monkeypox.\textsuperscript{xvi} The dog shared a bed with both owners but had not had contact with other pets or other humans.

Evidence on Transmission Modes of Monkeypox Virus

➢ Contact Transmission

Main points:
• Most patients infected with monkeypox virus present with infectious skin lesions.
• Monkeypox virus can remain infectious in the environment at least 15 days, possibly longer, primarily on porous surfaces (e.g., bedding and clothing).
• Monkeypox virus has been detected on many surfaces in houses and hospital rooms of positive patients.

Contact transmission of the monkeypox virus is well established. Infection with the monkeypox virus typically results in skin lesions, with 95 percent of patients presenting with rash.\textsuperscript{xvii} Research has shown that 99 percent of skin lesion swabs were positive for monkeypox,\textsuperscript{xviii} and that skin lesions had the highest positivity rate and viral load of specimens tested.\textsuperscript{xix,xx} Contact with lesions of an infected patient is thought to be one primary transmission mode for the monkeypox virus. The virus can enter the body through mucous membranes and broken skin.

The monkeypox virus is an orthopoxvirus, which has exceptional ability to remain infectious in the environment.\textsuperscript{xix} Viable (infectious) monkeypox virus has been found on surfaces from households where an individual with monkeypox left up to 15 days prior to sampling. Viable virus was detected primarily on porous surfaces, such as bedding and clothing.\textsuperscript{xxii,xxiii}

Research has documented extensive environmental contamination with the monkeypox virus.\textsuperscript{xxiv,xxv} For example, patients with monkeypox infections were isolated in hospital rooms and viral contamination was found on sink handles, soap dispensers, toilet seats, chair surfaces, mobile phones, cabinet doors, fabrics used by the patients, gloved hands of the investigators, and all hand-contact points in the anteroom.\textsuperscript{xxvi} Infectivity was demonstrated for some surfaces, including gloves, after handling contaminated fabrics.

During the 2003 monkeypox outbreak in the United States, researchers found that human monkeypox cases were likely associated with daily exposure to infected prairie dogs through touching and/or cleaning cages and soiled bedding.\textsuperscript{xxvii} This study highlights that
potential exposure to excretions and secretions of an infected prairie dog (e.g., urine, feces, and saliva) could have led to transmission.

**Unanswered questions:**
- What is the viral load required to cause an infection?
- Can patients without lesions shed infectious virus? How?
- Can transmission occur via other bodily fluids (e.g., urine, feces, saliva, semen, vaginal fluid, blood, etc.)?
- Can infection occur via inoculation in the eye? Via ingestion?

➢ **Airborne/Aerosol Transmission**

**Main points:**
- Studies show that airborne/aerosol transmission of monkeypox is possible and has likely occurred, though it is unclear how often it happens.
- Monkeypox virus is stable suspended in aerosols for at least 90 hours.
- Monkeypox virus can be aerosolized when contaminated objects, such as bedding and clothing, are moved and shaken.

Monkeypox virus can be aerosolized during viral shedding in the respiratory tract and/or through lesions of the mouth or throat during breathing, speaking, coughing, or sneezing. Airborne/aerosol transmission potential of the monkeypox virus is also well established. While the scientific literature indicates that airborne/aerosol transmission may not be the predominant or most frequent mode of transmission for the monkeypox virus, scientific evidence shows that it is possible and has occurred. Therefore, measures to prevent airborne/aerosol transmission of the monkeypox virus are necessary.

There are two primary ways that the monkeypox virus may become airborne:

1. Infectious virus that is present on objects, such as bedding and clothing, can become aerosolized when the object is moved, especially if it is shaken.

2. People who are infected with the monkeypox virus shed virus in their respiratory tracts and can have lesions in their throats and mouth. Virus can become aerosolized when people breathe, speak, cough, sneeze, laugh, or sing.

Like other orthopoxviruses, the monkeypox virus has an exceptional ability to remain infectious in the environment for long periods of time. One study found that the virus was viable (infectious) after 90 hours suspended in an aerosol.xxxviii

Infectious monkeypox virus that is present on objects, such as bedding and clothing, can become aerosolized when the object is moved, especially if it is shaken.

Objects, such as bedding and clothing, can become contaminated with infectious monkeypox virus (see section on Contact Transmission), and this virus can be aerosolized when the object is moved. A majority (75 percent) of air samples were positive and 50 percent were viable (infectious) during a bed linen change in a hospital isolation room where a patient with monkeypox was isolated.xxx At least one case has been documented
where a health care worker was infected while changing the bedding and clothing of a patient with monkeypox.xxx Because the patient had not yet been identified as having monkeypox, the health care worker was wearing only a disposable apron and gloves, with no respirator. Similarly, in the 2003 outbreak in the United States, a study found that cleaning the cages or bedding of monkeypox-infected animals was associated with acquiring monkeypox.xxxi

Airborne transmission during PPE doffing is of particular concern for health care workers. One study found positive contamination in the breathing zone of a worker while doffing PPE, including a powered air purifying respirator (PAPR), isolation gown, inner and outer gloves, and boot covers, in addition to contamination on the skin on the hands and wrists.xxxii While a trained observer and doffing assistant were utilized, contamination was observed on every subject to a certain extent.

*People who are infected with the monkeypox virus shed virus in their respiratory tracts and can have lesions in their throats and mouth. Virus can become aerosolized when people breathe, speak, cough, sneeze, laugh, or sing.*

Animals and humans infected with monkeypox and other poxviruses can generate respiratory aerosols. Monkeypox can cause lesions in the respiratory tract, including on the tongue, in the mouth, and in the throat. Data indicate that about 30 percent of patients have oropharyngeal mucosal lesions.xxxiii

Individuals infected with monkeypox can also shed virus in their respiratory tracts, even in the absence of lesions.xxxiii,xxxiv,xxxv A majority of patients (60 percent) were positive for monkeypox virus on oropharyngeal swabs.xxxvi One study noted that most positive oropharyngeal swabs did not come from patients with visible lesions in the throat at the time of testing.l

Environmental contamination of surfaces unlikely to have been touched by patients was documented in a hospital.l Samples that were positive for monkeypox virus included the air vent above the door between the bedroom and the bathroom, “suggesting non-contact contamination possibly via respiratory droplets or re-aerosolization from activities such as changing bed linen.”

This means that individuals infected with monkeypox can release viral particles when breathing, speaking, coughing, singing, or laughing. Respiratory symptoms, including cough and nasal congestion, can occur with a monkeypox infection.li A primer on aerosol transmission of respiratory viruses published in the journal *Science* states:lii

Respiratory droplets and aerosols can be generated by various expiratory activities. Advances in aerosol measurement techniques, such as aerodynamic and scanning mobility particle sizing, have shown that the majority of exhaled aerosols are smaller than 5 μm, and a large fraction are <1 μm for most respiratory activities, including those produced during breathing, talking, and coughing. Exhaled aerosols occur in multiple size modes that are associated with different generation sites and production mechanisms in the respiratory tract.
... Aerosols produced by an infected individual may contain infectious viruses, and studies have shown that viruses are enriched in small aerosols (<5 µm). The transport of virus-laden aerosols is affected by the physicochemical properties of aerosols themselves and environmental factors, including temperature, relative humidity, ultraviolet radiation, airflow, and ventilation. Once inhaled, virus-laden aerosols can deposit in different parts of the respiratory tract. Larger aerosols tend to be deposited in the upper airway; however, smaller aerosols, although they can also be deposited there, can penetrate deep into the alveolar region of the lungs.

... Although both aerosols and droplets can be produced by infected individuals during expiratory activities, droplets fall quickly to the ground or surfaces within seconds, leaving an enrichment of aerosols over droplets. The airborne pathway likely contributes to the spread of other respiratory viruses whose transmission was previously characterized as droplet driven.


Evidence from animal studies further elucidates airborne/aerosol transmission of the monkeypox virus. For example, studies conducted by U.S. Centers for Disease Control and Prevention (CDC) scientists found that caged prairie dogs infected with monkeypox infected others in separate nearby cages, and authors concluded that respiratory transmission is possible for monkeypox, though it may not occur at high rates.

Studies have found that non-human primates can be systemically infected with the monkeypox virus when exposed via the respiratory tract to aerosols containing infectious virus and that there is no difference in systemic illness based on inoculation route. Another study cultured infectious virus from nasal discharge and oropharynx samples in prairie dogs up to 22 days after infection.
In a 2003 outbreak related to infected prairie dogs in the United States, seven people were infected occupationally and had NOT handled a prairie dog, indicating airborne/aerosol transmission occurred. Five people reported having been within three feet of a prairie dog, one in the same room but not within three feet, and one person was in the same facility only within 48 hours of the death of an infected prairie dog.

An outbreak at the Rotterdam Zoo indicates that aerosol transmission was likely at play. Giant anteaters became ill twelve days after arriving at the zoo. Subsequently, animals housed nearby but in separate cages became infected, including orangutans, African gorillas, chimpanzees, Asian gibbons, and others.

It is worth noting that, when airborne/aerosol transmission is possible, ruling out the role of airborne/aerosol transmission requires extensive contact tracing and data collection. For example, a recently published case report of a 20-year-old male demonstrated monkeypox infection without sexual exposure and with both possible contact and airborne exposures. The patient developed symptoms and tested positive for monkeypox about 14 days after attending a large, outdoor crowded event in the U.K. The patient did not wear a mask or a respirator during the event. No sexual contact was reported during his travel or in the preceding three months. The crowded event was the largest exposure risk for the individual, where transmission could have occurred via close contact or airborne/aerosol transmission. The report also notes that transmission could have occurred via fomites in a hotel or through any route during travel.

Unanswered questions:
- How often does the monkeypox virus transmit via airborne/aerosol transmission?
- How much virus do people with monkeypox emit via respiratory events such as breathing, speaking, and coughing?
- Can the monkeypox virus be transmitted by people who are infected but who have not yet developed or who do not experience symptoms?

Transmission in the Absence of Symptoms

Main points:
- Asymptomatic monkeypox infections have been documented, but it is not clear how often they occur or whether or how often transmission can result.
- Some individuals with monkeypox may shed virus before or after lesions and other symptoms occur, but it is unclear whether or how often transmission can result.

Asymptomatic monkeypox infections have been documented, however, it is unclear how common asymptomatic monkeypox infections are. Three asymptomatic cases were identified in previously smallpox-vaccinated individuals after exposure to monkeypox-infected prairie dogs.

Asymptomatic cases have also been identified during the current 2022 monkeypox outbreak. One study in Belgium found evidence of asymptomatic infections in three
individuals that had positive anorectal monkeypox PCR results after retrospective sexually transmitted infection (STI) screening.\textsuperscript{lxvi}

Another study also found monkeypox virus in anorectal swabs in asymptomatic individuals collected as part of a routine STI screening in France. Of the 200 asymptomatic individuals who were screened and were negative for *N. gonorrhoeae* and *C. trachomatis*, 6.5 percent were PCR positive for monkeypox, two of whom later developed symptoms\textsuperscript{lxvii}

Transmission from asymptomatic monkeypox cases has not yet been documented. Contact tracing has been limited during the 2022 global outbreak, which means that data required to study asymptomatic transmission is not being effectively gathered. Some scientists hypothesize that asymptomatic transmission could be an explanation for why the virus has begun to spread so much more rapidly between humans compared to prior outbreaks.\textsuperscript{lxviii}

The CDC currently states that the infectious period begins with the onset of rash and ends when all scabs have fallen off and a fresh layer of intact skin as formed.\textsuperscript{lxix} Data on this topic is extremely limited. Epidemiologic data indicates that only a proportion of cases in the current outbreak are experiencing a prodrome prior to rash.\textsuperscript{lxx} Some data indicates that viral shedding may begin prior to symptom onset and/or continue after lesions have healed.\textsuperscript{lxxi} Researchers found that Cynomolgus Macaques shed monkeypox virus in nasal and oral swabs concomitantly even prior to the presence of lesions – which suggests that humans infected with monkeypox could also shed or transmit the virus prior to showing clinical signs.\textsuperscript{lxxii}

Other studies have detected virus in multiple body fluids, such as saliva, blood, and semen, and lesions for four to 16 days after symptom onset.\textsuperscript{lxxiii} One study reported that a patient was negative on lesion swabs but positive on oropharyngeal, anal, and plasma samples on day five after symptom onset.\textsuperscript{lxxiv}

**Unanswered questions:**
- How frequently do asymptomatic infections occur?
- Can transmission happen from asymptomatic infections? How often? Under what circumstances?
- Can transmission occur before onset of symptoms? How often and through what routes/body fluids?
- Can transmission occur after lesions have healed? How often and through what routes/body fluids?

**Other Transmission Modes**

**Main points:**
- Sexual transmission may be occurring with monkeypox, though it is unclear whether or how often at this point.
- Monkeypox virus has been detected in multiple body fluids (blood, saliva, semen, and vaginal fluid), but it is unclear whether or how often transmission can occur via these routes.
• The presence of genital lesions does not necessarily indicate site of inoculation.
• Maternal-to-fetal transmission and negative outcomes have been documented, though not much is known about monkeypox virus and pregnancy.
• Ocular transmission may be possible.

➢ Sexual Transmission

It is not yet clear whether sexual transmission is occurring with the monkeypox virus or whether this is a major transmission route for the virus.

Monkeypox virus particles have been detected in bodily fluids, such as blood, saliva, semen, and vaginal fluid; however, it remains unclear whether transmission can occur from these fluids. A recent study from Spain found high viral loads in most skin pustules, saliva, rectal swabs, semen, urine, and fecal samples from monkeypox cases. Another study isolated infectious monkeypox virus from a semen sample of an infected patient living with HIV, and the authors concluded, “semen collected in the acute phase of infection (day 6 after symptom onset) might contain a replication-competent virus and represent a potential source of infection.” While sexual transmission of monkeypox virus may be one possible mode of transmission, contact and airborne transmission must not be ignored as the clinical presentation of the virus can manifest in various ways.

Unfortunately, public health agencies, including the U.S. CDC, have heavily focused their messaging on monkeypox on sexual transmission, particularly among men who have sex with men, which has contributed to stigmatization related to the virus and has also led many individuals to incorrectly believe that monkeypox is sexually transmitted only among men who have sex with men and that they are not at risk for infection.

While the virus was introduced into communities of men who have sex with men and is seriously impacting LGBTQ people, the virus is not a health risk limited to those communities. The available data do not currently allow for delineation between sexual transmission and transmission from close contact with lesions of infected individuals or airborne/aerosol transmission. The CDC does not currently post detailed data on monkeypox cases, including sex, gender, sexual orientation, race/ethnicity, age, or occupation. Other reporting, such as in the CDC’s Morbidity and Mortality Weekly Report, indicates that the CDC has detailed data on just 41 percent of reported monkeypox cases, indicating that the CDC has drawn conclusions about transmission based on epidemiologic data for less than half of confirmed cases.

Some are arguing that, because many patients are presenting with genital lesions, the genitals must be the site of inoculation, but this is not driven by the available data. Orthopoxvirus infections, such as monkeypox, cause mucosal lesions on different parts of the body in animals and humans, including but not limited to the genital and rectal areas. For example:

• Horsepox, a poxvirus disease of horses, often causes lesions on the face, vulva, and other body parts.
• In a study of aerosolized monkeypox virus infection in Cynomolgus monkeys, the rectum was most frequently affected.\textsuperscript{lxxx}

• Skin rashes or lesions on the genitalia have also been documented in human cases of monkeypox infections prior to the current 2022 outbreak.\textsuperscript{lxix}

• Lesions on the external genitalia were reported on a pediatric patient with severe monkeypox virus infection associated with the 2003 U.S. monkeypox outbreak. Transmission may have occurred after the monkeypox-infected prairie dog licked her fingers through the cage; no other direct contact was reported (also raising the question of airborne/aerosol transmission).\textsuperscript{lxxi}

• A 2018 study documented a 38-year-old man who was likely infected with monkeypox after exposure to two dead rodents in Nigeria a few days before travelling back home to Israel. His lesions started on his penis shaft; no sexual contact was documented in the report.\textsuperscript{lxxii}

• Angelo et al. also documented two U.K. travelers not known to be epidemiologically linked to one another, each reported a rash that started in the groin; no sexual contact was documented in the report. One traveler reported contact with an ill individual at a family gathering and bushmeat consumption.\textsuperscript{lxxiv}

➢ Maternal-to-Fetal Transmission

Data on maternal monkeypox virus infection are limited, including susceptibility to or severity of disease. However, adverse pregnancy outcomes have been reported, including congenital monkeypox virus infection, spontaneous miscarriage, and fetal death.\textsuperscript{lxxv, lxxvi} A 2017 study demonstrated generalized lesions on a stillborn fetus and high viral loads detected in several fetal tissues (umbilical cord and placenta),\textsuperscript{lxxvii} confirming vertical transmission of monkeypox virus during pregnancy or to the newborn by close contact during and after birth.\textsuperscript{lxxviii}

➢ Ocular Transmission

Ocular exposure to monkeypox virus may also be a potential route of transmission. Monkeypox lesions on eyelids and conjunctiva have been documented both prior to and during the 2022 outbreak.\textsuperscript{lxxix, xc, xci} One study found similar viral loads on conjunctival and eye secretions-compared with cutaneous lesions from a monkeypox-infected individual,\textsuperscript{xci} raising the possibility of transmission through ocular secretions.

Unanswered questions:

• What body fluids can transmit the monkeypox virus? Under what circumstances and how often?
• What are the risk factors for and impacts of the monkeypox virus on pregnancy?
• Can inoculation occur through the eye?

Additional Considerations for Transmission

Main points:

• Certain conditions can increase the risk of infection and/or severe disease with monkeypox.
• The route of inoculation may influence severity of illness, though there is limited data on this topic.
• Co-infection with other pathogens can increase the risk of infection and/or severe disease with monkeypox.

➢ **Conditions that Can Increase Risk of Infection and/or Severe Disease with Monkeypox**

Monkeypox virus can enter the body through broken skin (bodily fluids), mucous membranes (eyes, nose, or mouth), or the respiratory tract. Because of this, individuals with a history of atopic dermatitis (or eczema) and other skin conditions may be at increased risk of severe monkeypox disease.\textsuperscript{xciii}

➢ **Route of Inoculation May Influence Severity of Illness**

Route of orthopoxvirus infection, such as smallpox and monkeypox, may influence the clinical manifestations and severity of disease. For example, a 2012 review of smallpox transmission found that dermal and nasal exposures tended to produce less extensive spread of smallpox around the body compared with infection via lower respiratory tract deposition.\textsuperscript{xciv} Similarly, severe inflammation of the lung was observed in a 2011 study of Cynomolgus Macaques infected with monkeypox virus, suggesting that the lung is a major target organ of the virus.\textsuperscript{xcv} Researchers also found that Cynomolgus Macaques shed monkeypox virus in nasal and oral swabs concomitantly even prior to the presence of lesions – which suggests that humans infected with monkeypox could also shed or transmit the virus prior to showing clinical signs.\textsuperscript{1}

A 2006 study of human monkeypox cases associated with monkeypox-infected prairie dogs found that individuals who had been bitten or scratched by the animals experienced more pronounced systemic symptoms and were significantly more likely to have been hospitalized compared with those who had noninvasive exposures (e.g., touched an infected animal, cleaned an infected animal’s cage, and/or stood within 6 feet of an infected animal).\textsuperscript{xcvi}

➢ **Co-Infections with Other Pathogens**

Evidence of co-infections with other pathogens have been documented and can also impact clinical severity. A case report in Germany documented a severe monkeypox virus infection of a 40-year-old patient who was concomitantly infected with syphilis and advanced HIV infection, with monkeypox lesions on the nasal area that progressed to necrosis.\textsuperscript{xcvii} Given the ongoing, unabated Covid-19 pandemic around the world, individuals infected with monkeypox could also be co-infected with SARS-CoV-2. Researchers recently reported on a Covid-vaccinated patient who tested positive for monkeypox virus, SARS-CoV-2, and HIV infection. Notably, despite resolution of symptoms, the patient’s monkeypox oropharyngeal swab still tested positive after 20 days, suggesting that monkeypox-infected individuals may still be contagious for several days even after remission of symptoms.\textsuperscript{xcviii} Additionally,
the impacts of long Covid or post-acute Covid-19 syndrome (PASC) dysregulating the immune system could place some individuals at higher risk of monkeypox infection with an exposure and/or more severe disease.\textsuperscript{xcix}

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