



# Monkeypox: A Re-emerging Viral Zoonotic Infection

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Received 2022 July 01; Revised 2022 October 24; Accepted 2022 November 01.

## Abstract

**Context:** Monkeypox virus (MPXV) infection is a zoonotic disease, endemic in sub-Saharan Africa, but recently has re-emerged outside Africa and caused some concerns.

**Evidence Acquisition:** The current study aimed to briefly present a narrative mini-review on different features of MPXV. Data were gathered from Google Scholar, ScienceDirect, and PubMed databases and also WHO and CDC websites, using "Monkeypox", "Variola", "Bioterrorism", and "Bioweapon" keywords.

**Results:** Monkeypox virus is categorized into two genetic clades with different outcomes. The incubation period of infection is 5 - 21 days, and infection by Central African clade may lead to a clinical representation similar to smallpox with about 10% mortality rate. Monkeypox virus can infect a wide range of mammals, and its natural reservoir is almost unknown. It is endemic in sub-Saharan Africa and is rarely seen outside Africa. Its most reliable detection is based on nucleic acid amplification tests (NAATs). Treatment is mainly supportive, and some selective drugs are developed for severe cases. Avoiding close contact with wild animals and infected patients is the first line of prevention. Prior vaccination with smallpox or MPX vaccines is also protective. Due to similar symptoms of human monkeypox and smallpox, it may be a candidate for bioterrorism. However, there is no evidence of recent intentional spread of MPXV.

**Conclusions:** This study has tried to provide a summary of MPXV infection. Despite recent concerns, there is still a very low risk of the MPXV pandemic. However, it is recommended to be alert for such infection and provide essential readiness against it.

**Keywords:** Monkeypox Virus, Smallpox, Bioterrorism, Pandemics

## 1. Context

Monkeypox virus (MPXV) infection is a re-emerging zoonotic disease caused by a member of the Orthopoxvirus genus. It is endemic in sub-Saharan Africa, although its recent emergence outside Africa has concerned governments and healthcare professionals. Monkeypox virus (MPXV) was first isolated from cynomolgus monkeys (*cynomolgus macaques*) in 1958 in Copenhagen, Denmark (1). This genus belongs to the Poxviridae family. They are large dsDNA viruses that replicate in the host cell's cytoplasm. Multiple poxvirus genera members can infect humans in a zoonotic manner which may be identified by the history of animal exposure and geographic location. The smallpox virus is the only human selective pathogen in this group that was declared to be eradicated in 1980 by the World Health Organization (WHO). Cowpox and vaccinia

are the other important viruses in this genus (2).

## 2. Evidence Acquisition

The recent emergence of the monkeypox virus outside Africa has attracted the attention of healthcare professionals and also general population all over the world. The current article aimed to represent a narrative mini-review of monkeypox virus in different criteria. The literature was gathered from major textbooks and also by searching in Google Scholar, ScienceDirect, and PubMed databases using "Monkeypox", "Variola", "Bioterrorism", and "Bioweapon" keywords. The studied papers had no time limit; however, latest articles were preferred. The World Health Organization (WHO) and centers for disease control and prevention (CDC) websites were also surfed for the latest news about monkeypox.

### 3. Results

#### 3.1. Genetic Clades of Monkeypox Virus

Monkeypox virus has been categorized into two genetic clades with geographical, epidemiological, and clinical differences: The west African and the central African clade. The case fatality rate of the West African clade is lower than 1%, and no human-human transmission has been seen up to now. In contrast, the central African clade (or Congo basin clade) represents a case fatality rate of up to 11% and human-human transmission (3).

#### 3.2. Epidemiology

Monkeypox virus can infect a broad taxonomic range of mammalian species. However, its natural host is not confidently understood and was so-called monkeypox due to its first detection in infected monkeys. Monkeypox virus has also been isolated from wild animals such as rope squirrels (*Funisciurus congicus*) and sooty mangabey (*Cercocebus atys*) in Africa (2, 3). It is endemic in sub-Saharan Africa. Monkeys, like humans, are believed to be accidental hosts, and their natural reservoir is still unknown. By the elimination of smallpox in the 1970s, monkeypox was recognized as a human pathogen in Zaire [currently the democratic republic of Congo (DRC)] (4). Transmission usually occurs through close contact with infected animals and body fluids. Human-to-human transmission happens via respiratory droplets and close contact over a relatively long period of time, although its occurrence is very low (5).

Several cases of human MPXV infection have been increasingly reported from western and central African countries, where the disease is endemic, with more outbreaks in the past few years. Nevertheless, it was not seen outside Africa until 2003. The accidental transition of infected rodents from Africa to the US led to the first human monkeypox outbreak in a non-African country. Seventy-one cases of human MPXV infection were reported to the CDC in the 2003 outbreak, including 35 laboratory-confirmed cases (2, 6).

Interestingly, from 13 May 2022 to 2 June 2022, 780 confirmed cases were reported in 27 non-endemic countries. Most cases did not represent a history of traveling to endemic areas. The cases increased to 75348 until 21 October 2022, of which 74457 were from non-endemic areas (7). Genetic studies showed that the west African clade of MPXV infected all the analyzed cases. Notably, most reported cases were homosexual men (8).

#### 3.3. Clinical Representation

The incubation period of MPXV is 5 to 21 days. The first common sign of systemic MPXV infection is fever, followed by rash 3 - 5 days later. The rash evolves classically from macular to papular, vesicular, and finally, pustular phases. The clinical features of Central African clade infection are similar to smallpox, with lymphadenopathy as the most noticeable difference affecting sublingual, submandibular, and cervical regions. Other common signs are sore throat, respiratory distress, bronchopneumonia, gastrointestinal complications, dehydration, sepsis, encephalitis, corneal infection, and secondary bacterial infections. Unvaccinated children are the most prone group to infection. The approximate mortality rate is about 10%, and all deaths have occurred in unvaccinated children (2, 6, 9).

#### 3.4. Diagnosis

Up to now, the most common and reliable laboratory method for poxvirus diagnosis is based on nucleic acid amplification tests (NAATs) that include polymerase chain reaction (PCR) and consequent sequencing in some cases. Samples should be taken from the skin lesions, dry crusts, or skin biopsy and stored in a dry, sterile tube to be taken to the laboratory concerning cold chain supply. Other diagnostic methods include viral culture (isolation), electron microscopy, Immunohistochemistry, and detection of specific antibodies (IgG and IgM) in blood samples. However, due to close serologic similarities and immunologic cross-reactions among orthopoxviruses, serology-based tests are unreliable for early diagnosis and may be used in epidemiologic surveys or to study prior vaccination history or infection (2, 6, 9, 10).

#### 3.5. Treatment

Most monkeypox cases represent mild symptoms and do not need particular medical intervention. Only patients with other risk factors may need to be hospitalized, and severe cases need intensive care until recovery of the infection. Poxvirus infection treatments are mainly supportive and should be taken to prevent secondary bacterial infections. There is no specific approved drug against MPXV. However, some therapeutics have been candidates for topical or systemic administration against Orthopoxviruses. The majority of such compounds are DNA polymerase inhibitors. Some nucleoside analogs formerly used against the herpes virus, such as Acyclovir, do not affect poxviruses. Other anti-herpes compounds, 5-iodo-2'-deoxyuridine, adenine arabinoside, and trifluorothymidine, are effective on

poxviruses; however, due to systemic toxicity, they can only be topically used on ocular infections.

Some phosphonate-nucleoside analogs, such as cidofovir, show activity against orthopoxviruses in vitro or in animal models, but they have renal toxicity and cannot be used for human treatment. Tecovirimat and brincidofovir are orally administered agents approved by the FDA for the treatment of smallpox in 2018 and 2021, respectively. Tecovirimat targets the orthopoxvirus vaccinia F13 protein homologs, playing a crucial role in the viral release from the host cell. It is effective in animal models infected by MPXV and may also be effective in humans. It can be prophylactically used after exposure to infection or therapeutically administered after the onset of symptoms. Brincidofovir is a cidofovir analog that can be orally used. Animal models show its effectiveness against orthopoxviruses; however, there is limited data about its usage for treating MPXV infection (2, 6, 9, 11-14).

### 3.6. Prevention

The first line of prevention in endemic areas is to avoid close contact with wildlife, especially rodents, primates, and their body fluids or raw meat. At least six weeks of quarantine are required after exposure to infected animals. Human patients should be hospitalized in an isolated room, preferably with negative air pressure equipment. Standard personal protective equipment (PPE) is recommended for healthcare workers and family members of infected patients to avoid human-human transmission. Physical distancing is also recommended to avoid infective respiratory droplets of the patient (15).

Previous smallpox vaccination with vaccinia virus significantly protects against monkeypox virus infection and inhibits severe symptoms. However, due to smallpox eradication since 1981, most individuals (especially youth) are not vaccinated with the smallpox vaccine and are also susceptible to monkeypox. Imvamune (Jynneos), a modified Vaccinia Ankara (MVA) vaccine, was approved for immunization against both smallpox and monkeypox viruses in 2019. Up to now, mass vaccination for monkeypox is not recommended (8). Administration of the MVA vaccine would be effective for prophylaxis after exposure to MPXV (post-exposure prophylaxis) within four days after contact (16).

Vaccinia immune globulin (VIG), which is used for treating orthopoxvirus-related disorders, can be considered prophylactic for immune-deficient patients with a history of exposure to the monkeypox virus (4).

### 3.7. Risk of Bioterrorism

Concerns about using biological agents in warfare have been increasing in recent years. Vaccination against smallpox has been stopped since its' worldwide eradication, and the majority of population are susceptible to orthopoxvirus-related infections. Smallpox, along with anthrax, botulism, plague, tularemia, and viral hemorrhagic fevers, is in the A category of the CDC list of bioterrorism agents, meaning it is the highest priority with the most adverse outcome in individuals and populations by the ease of transmission and high mortality rates, leading to public panic (2). Albeit the smallpox virus is not currently available to terrorist groups, the monkeypox virus, which may represent similar symptoms, can be achieved from natural reservoirs (3). There are some reports that at least one country (former Soviet Union) tried to adapt MPXV to use as a biological weapon (17, 18). There is no evidence of the bio-terroristic spread of the monkeypox virus up to now. However, as MPXV is also considered a serious pathogen leading to important public health diseases, there is an immediate demand to provide appropriate prevention, readiness, and response activities. Hence, as a precaution against bioterrorism, governments should supply vaccines and effective antiviral treatments against such a virus (19-22).

## 4. Conclusions

This study has tried to briefly summarize the different features of monkeypox virus infection. Although the recent incidence of monkeypox outside Africa has concerned governments and health authorities in different countries, there is still a very low risk of the MPXV pandemic. However, it is recommended to keep an eye on such an infection and provide essential readiness to supply vaccines, treatment facilities, and preventive measures against a potential outbreak.

## Footnotes

**Authors' Contribution:** Study concept and design, Seyyed-Javad Hosseini-Shokouh and Mohammad Barati; Drafting of the manuscript, Hamed Naghoosi and Mohammad Gholami.

**Conflict of Interests:** This study was conducted in the Infectious Diseases Research Center at Aja University of Medical Sciences. The authors have no conflict of interest.

**Funding/Support:** The study has not any funding.

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