# Monkeypox: Facts about the Disease

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## Abstract

Monkeypox is a zoonotic disease caused by the monkeypox virus of the genus *Orthopoxvirus* genus and Poxiviridae family. Many animal species, including rodents and monkeys, can transmit the virus. However, the natural reservoir is unknown yet. It can be transmitted to humans via close contact with infected animal or person, or contaminated materials. Monkeypox virus was first detected in 1958 among cynomolgus monkey's colony in Denmark. The first human case of monkeypox was reported in September 1970 in a 9-month-old child with smallpox-like vesicular skin lesions. This virus usually affects humans and animals living in Central and West Africa, yet it led to several outbreaks previously out of Africa since its discovery. Since 7 May 2022, monkeypox started to appear again in non-endemic countries. By 29 July 2022 at 9:00 PM (GMT), 22485 confirmed cases were recorded worldwide. This review focuses on monkeypox virus structure, transmission, symptoms, diagnosis methods, treatment and prevention.

**Keywords**: monkeypox, transmission, symptoms, diagnosis, treatment.

## Introduction

Monkeypox virus was detected in 1958 in the Statens Serum Institute in Copenhagen, Denmark when two non-fatal outbreaks of pox-like disease were ascertained in cynomolgus monkey's colony, hence the name monkeypox. The Institute was continuously receiving monkeys from Singapore back then for research purposes concerning polio vaccine [1, 2 & 3].

The first human case of monkeypox was reported in September 1970 in Equateur Region, Zaire (now called Democratic Republic of Congo) in a 9-month-old child with smallpox-like vesicular skin lesions [4, 5, 6&7]. Later on, similar human cases were recorded in 11 African countries across Central and West Africa: Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo (Congo-Kinshasa), Gabon, Cote d'Ivoire, Liberia, Nigeria, the Republic of the Congo (Congo-Brazzaville), Sierra Leone and South Sudan [6, 8 & 9]. Since 2017, Nigeria has experienced a large outbreak, with more than 200 confirmed cases and over 500 suspected cases and approximately 3% fatality rate [9&10].

Monkeypox is a disease with a global health concern, as it not only affects west and central African countries, but the rest of the world. The first monkeypox outbreak outside of Africa was in the USA in 2003 and was linked to contact with infected pet prairie dogs that had been kept with imported Gambian pouched rats and dormice from Ghana [9, 11, 12&13]. It`s noteworthy that no fatalities were recorded in that outbreak [12&14].

With time, monkeypox continued to be reported among travellers from Nigeria to several non-endemic countries, such as occupied Palestine (September 2018), the United Kingdom (September 2018, December 2019, May 2021 and May 2022), Singapore (May 2019), and the USA (July and November 2021) [3&9].

Monkeypox virus belongs to the Poxviridae family (Poxviruses) [12], which are considered an ancient virus family that must have existed in a discernable "pox" form prior to invertebrates and vertebrates divergence [7&15]. Poxviridae is classified into two subfamilies: Chordopoxvirinae (poxviruses of vertebrates) and Entomopoxvirinae (poxviruses of insects) [7, 16&17]. Chordopoxvirinae contains 10 genera including *Orthopoxvirus* [16&17].

Monkeypox virus is one of the five *Orthopoxvirus* species pathogenic for humans, together with variola virus, camelpox virus, cowpox virus and vaccinia virus [3&10]. All *Orthopoxvirus* species are zoonotic pathogens (have animal reservoirs), except for variola virus which is an exclusively human pathogen [18].

**Monkeypox virus structure**

Like other poxviruses, monkeypox virus is considered one of the largest and most complex viruses. The virions are brick-like shaped with slightly rounded edge particles reaching 220 - 450 nm in length and 140 - 260 nm in width [3,12&18]; therefore, this virus is large enough to be detectable using a light microscope [12, 16&18]. However, electron microscope`s higher magnification is needed to distinguish ultrastructure [12 16&18].

The orthopox virion consists of four main elements: core, lateral bodies, outer membrane and the outer lipoprotein envelope. The central core contains the viral double-stranded DNA and core fibrils, and it is surrounded by a layer of rod-shaped structures called the palisade layer. As for the outer membrane, it is composed of many surface tubules, and often encloses the central core, palisade layer and the lateral bodies (Fig. 1). The outer lipoprotein envelope is found in the spontaneously released virions, while it is absent in virions released by cellular disruption [18].

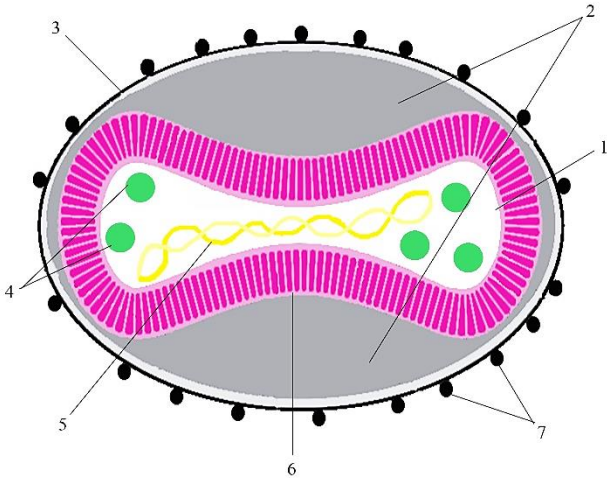


Fig. 1: A poxvirus particle

1: Core, 2: Lateral bodies, 3: Outer membrane, 4: Core fibrils, 5: viral double-stranded DNA, 6: Palisade layer, 7: surface tubules

The monkeypox genome is among the largest of all viral genomes. It is a large (197 kbp) single linear molecule of double-stranded DNA [12&16]. The genome contains of about 190 nonoverlapping open reading frames (>180 bp long) with 60 or more amino acid residues. The guanine and cytosine content of monkeypox viral DNA is low (31.1%) [18&19].

There are two distinct genetic clades of monkeypox virus: the Central African and the West African [3, 11, 18&20]. The Central African clade (also known as Congo Basin clade) is characterized by its high virulence, efficient human-to-human transmission and by having a high fatality rate (1.5 -10%), while the West African clade is less pathogenic and less virulent with fatality rate <1% [3&21].

**Reservoir and Transmission**

The natural reservoir of monkeypox is still unknown. Yet, many animals are suspected to harbour the virus, including squirrels, rats, striped mice, dormice and monkeys [2 &22].

Primary transmission (animal-to-human) can happen via direct or indirect contact with bodily fluids or cutaneous or mucosal lesions of an infected animal through handling, scratches or bites [2 & 9].

Secondary transmission (human-to-human) can occur through close contact with respiratory secretions, skin lesions of an infected person or recently contaminated objects [2, 9 &23]. Of note, transmission via respiratory droplet requires prolonged face-to-face contact, which means that health workers and family members of active cases at greater risk [9&24].

In addition, transmission may also happen through the placenta from mother to fetus (congenital monkeypox) or during close contact during and after birth [9].

The researchers advise constantly monitoring the fetus for infection and performing regular ultrasounds (every 2-4 weeks) to confirm the placenta integrity and suitable growing of the fetus. The fetus monitoring should also include its measurements, detailed assessment of its organs and the amniotic fluid [25]. After birth, the baby should be isolated until infection is gone [25].

**Geographical Distribution of monkeypox cases in 2022**

Once again, health officials began reporting an outbreak of monkeypox in several regions outside Africa early in May 2022 [23]. World health organization (WHO) implied that the virus is behaving differently compared to past outbreaks, and is also affecting wider range of countries [26].

On 7 May 2022, WHO was informed of a confirmed case of monkeypox in a person who came from Nigeria [27]. The patient had a rash on 29 April 2022 and arrived to the United Kingdom on 4 May 2022 [27].

Since then, multiple cases were identified in several non-endemic countries. By 29 July 2022 at 9:00 PM (GMT), 22485 confirmed cases were reported worldwide in 79 countries (Table 1, Fig. 2) [28]. As for the fatalities, WHO recorded 75 deaths until 24 July 2022, and those incidences were noticeably confined to some African countries. [29]

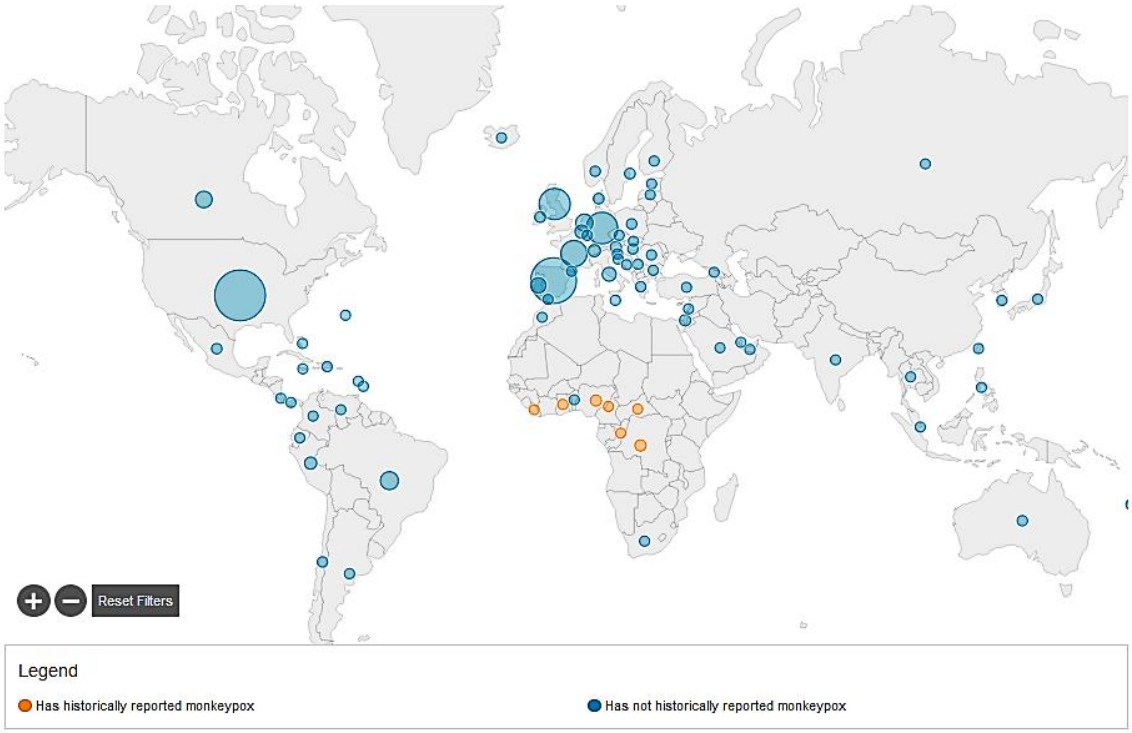


Fig. 2: Geographical Distribution of monkeypox cases until 29 July 2022 [28]

Officials from the Centre for Disease Control and Prevention (CDC) declared that at least two strains of monkeypox are currently spreading in the USA only. Actually, most cases in the USA share the same strain that has been circulating in Europe, but recent studies detected

another variant. Both variants apparently evolved from strains present in Nigeria since 2017 at least [30].

Today, WHO is working with a group of experts on changing the name of monkeypox virus, its clades and the disease it causes. This is due to the recent criticism for the current name by many scientists who described it as discriminating, stigmatizing and inaccurate. As for the proposed name, scientists suggest starting with hMPXV, to denote the human version of the monkeypox virus. Besides, they suggest using letters and numbers, based on order of discovery, instead of geographic locations. Accordingly, the current international outbreak lineage would be called B.1 [26].

**Symptoms**

The incubation period of monkeypox is usually from 6 -13 days but may range from 5 - 21 days [9].

The infection can be divided into two phases:

- The prodromal stage (0–5 days) with manifestations of fever, chills, headache, backache, lymphadenopathy (1–4 cm in diameter), myalgia and exhaustion [9,31&32].
- The skin eruption usually begins within 1–3 days of fever. The rash is usually more concentrated on the face and extremities. It may affect the oral mucous membranes, cornea, conjunctivae as well as the genitalia. The rash typically evolves within several phases: macules, papules, vesicles, pustules then crusts that dry up and fall off [9&32]. The number of lesions normally range from a few to thousands [9 &31].

The mokeypox is generally self-limited disease, as the symptoms last from 2 - 4 weeks [9, 14 &30].

Complications of monkeypox may include secondary bacterial infections, sepsis, bronchopneumonia, encephalitis and cornea infection with vision loss [9,12,14,21&23]. Hospitalization may be necessary in more severe cases [14].

Of note, infants and young children are the main candidates for developing severe symptoms, despite the fact that they are rarely fatal [25].

**Diagnosis**

**Clinical diagnosis:** Many diseases may develop rashes like chickenpox, syphilis, measles, scabies, bacterial skin infections and medication-associated allergies. Therefore, those illnesses must be considered when diagnosing monkeypox [9]. Clinical differentiation of monkeypox from smallpox and chickenpox may be difficult [33]. Nevertheless, lymphadenopathy during the prodromal stage of disease can be an important clinical feature to distinguish monkeypox from smallpox or chickenpox [9,17&34].

**Laboratory diagnosis:** Confirmation of monkeypox infection depends on the sample`s type and quality along with the type of laboratory test. Thus, samples should be packaged carefully and shipped according to the national and international requirements [9].

- Polymerase chain reaction (PCR) test is the preferred laboratory test because of its accuracy and sensitivity [9]. This method allows the detection of monkeypox DNA [7]. Furthermore, PCR can discriminate the two clades of this virus [35]. For this, ideal diagnostic specimens for monkeypox are from skin lesions – the roof or fluid from vesicles and pustules, and dry crusts [9].

  PCR blood tests are usually doubtful given the short duration of viremia relative to the timing of sample collection after the beginning of symptoms [9].

- Biopsy is an option, when it is possible. Lesion samples should be stored in a dry sterile tube (without viral transport media) and kept cold [9].
- Serology and antigen detection methods are not recommended for diagnosis or case investigation. Antigen and antibody detection methods don`t provide a confirmation for monkeypox infection, because orthopoxviruses are serologically cross-reactive [9].
- Blood tests are not recommended when diagnosing monkeypox, because the virus doesn`t stay in the blood for long. Consequently, they are not accurate tests for diagnosing this disease [36].

It`s noteworthy that recent or remote vaccination with a vaccinia-based vaccine might give false positive results [9].

It is crucial to provide full patient information with the samples, in order to interpret test results correctly, including [9]:

- Patient`s age.
- Date of fever onset.
- Date of rash onset.
- Date of sample collecting.
- Current condition of the patient (stage of rash).

**Treatment**

Currently there is no particular treatment approved for monkeypox. Yet, antivirals developed for smallpox treatment may be efficient [37].

Tecovirimat (also known as TPOXX) is an approved antiviral agent by the United States Food and Drug Administration (FDA) in 2018 for smallpox treatment [38] and by the European Medicines Agency (EMA) for monkeypox in 2022 based on animal and human studies [9]. Tecovirimat is available as oral (200 mg capsule) and injection for intravenous formulations [37]. This drug interferes with a viral protein (p37) that is necessary for producing new mature enveloped virions [39].

Of note, CDC holds an Expanded Access Investigational New Drug Protocol (EA-IND) that allows the usage of Tecovirimat for non-variola orthopoxviruses treatment, along with the following medications [37]:

- Cidofovir (known as Vistide), which was first licenced by the FDA in 1996 as an antiviral drug to cure cytomegalovirus retinitis in acquired immunodeficiency syndrome (AIDS) patients [37&40].
- Vaccinia Immune Globulin Intravenous (VIGIV), which was licensed by FDA in 2005 to treat the complications of vaccinia vaccination [37&41].
- Brincidofovir (known as Tembexa), which was approved by the FDA on 4 June 2021 as an antiviral medication to treat smallpox in adult and children, including neonates [42].

**Prevention**

There are number of precautions that can be taken to prevent monkeypox:

- Avoid contact with animals that could harbour the virus, or any contaminated materials by a sick animal [43].

- Infected patients are considered contagious until all scabs have fallen off [23&44]. Thus, it is crucial to take appropriate precautions and isolate patients to prevent the spread of the disease [44].
- Close contacts of active cases should observe the development of their symptoms up to three weeks from their recent exposure to the virus. They also should not donate blood, organs or bone marrow during that time [45].
- Healthcare workers should wear proper personal protective equipment (FFP2 masks, gloves and water-resistant gowns) when working with confirmed or suspected cases. Laboratory staff should also take cautions to avoid exposure to virus [45].

As for vaccination, smallpox and monkeypox vaccines are developed from vaccinia virus because of the cross-protection provided for the immune response to orthopoxviruses [9]. Moreover, data indicated that smallpox vaccines could protect people against monkeypox, with 85% affectivity. Thus, prior smallpox vaccination might lead to milder disease [9, 11, 46&47]. However, people younger than 40 -50 years old might be more susceptible to monkeypox because of ceasing the smallpox vaccination campaigns worldwide after eradication of the disease [9].

ACAM200 and JYNNEOS™ (also known as Imvamune or Imvanex) are the currently licensed vaccines in the USA to prevent smallpox [46].

JYNNEOS™

JYNNEOS™ is a non-replicating live virus approved from FDA since 2019 to prevent monkeypox [23&48]. It is administered as two 0.5 ml subcutaneous injections preferably into

the upper arm (deltoid), with four weeks interval. It can be given to adults >18 years old [48&49].

JYNNEOS™ should be kept frozen at -25 to -15ºC in its original package to protect it from light. Once melted, it may be refrigerated at 2-8ºC up to 12 hours [48&49].

Some side effects can be noted when taking JYNNEOS™, including:

- In the injection site effects: pain, redness, itching, induration and swelling [49].
- Systemic effects: fever, chills, headache, muscle pain, fatigue and nausea [49].

It`s noteworthy that human data are inadequate to inform vaccine-associated risks to pregnant women [49].

ACAM2000

ACAM2000 is administered as a live virus preparation [50]. It was approved from FDA since 2007. A droplet (0.0025 ml) of ACAM2000 should be administered by the percutaneous route (scarification) via 15 jabs of a bifurcated needle by the subcutaneous, intradermal intramuscular, or intravenous route. It can be given to adults >16 years old [50].

After reconstitution, ACAM2000 vaccine can be stored at room temperature (20-25°C) for 6 - 8 hours, or in a refrigerator (2-8°C) for no longer than 30 days [50].

Some sides effects can be noted when taking ACAM2000, including:

- In the injection site effects: pain, redness, itching and swelling [51].
- Systemic effects: fever, rash, enlarged lymph nodes, shortness of breath, malaise, fatigue, muscle pain, headache, arm soreness, nausea, vomiting, diarrhea, and constipation [51].

It`s worth mentioning that ACAM2000 has not been studied in pregnant or nursing women[50].

## Conclusion

Monkeypox virus is one of the Orthopoxvirus spieces. It causes in monkeypox disease, which emerged once again in non-endemic regions early in May 2022. Human monkeypox clinical symptoms mimic those of smallpox lesions and need a differential diagnostic with similar infections. In this context, PCR test is the most reliable diagnostic method. Precautions should be done in order to prevent the disease from spreading, including patients isolation, close contacts monitoring and wearing personal protective equipment when caring for patients. Today, one vaccine (JYNNEOS$^{TM}$) and one drug (tecovirimat) were approved in 2019 and 2022 respectively for monkeypox, and investigations are ongoing in this area.

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Table 1: Monkeypox cases worldwide until 29 July 2022 [28]

| **Country** | **Cases** |
|---|---|
| United States of America | 4906 |
| Spain | 4298 |
| Germany | 2595 |
| United Kingdom | 2546 |
| France | 1955 |
| Brazil | 978 |
| Netherlands | 879 |
| Canada | 803 |
| Portugal | 633 |
| Italy | 479 |
| Belgium | 393 |
| Peru | 269 |
| Switzerland | 264 |
| Democratic Republic of the Congo * | 163 |
| Occupied Palestine | 133 |
| Nigeria * | 133 |
| Austria | 124 |
| Sweden | 88 |
| Ireland | 85 |
| Denmark | 81 |
| Mexico | 59 |
| Poland | 59 |
| Norway | 51 |
| Australia | 45 |
| Chile | 45 |
| Hungary | 37 |
| Slovenia | 33 |
| Greece | 32 |
| Ghana * | 30 |
| Luxembourg | 28 |
| Romania | 21 |
| Argentina | 20 |
| Czechia | 19 |
| Finland | 17 |
| Malta | 17 |
| United Arab Emirates | 16 |
| Colombia | 12 |
| Croatia | 12 |

| | |
|---|---|
| Singapore | 11 |
| Serbia | 10 |
| Iceland | 9 |
| Central African Republic * | 8 |
| Cameroon * | 7 |
| Estonia | 6 |
| Slovakia | 6 |
| Gibraltar | 5 |
| Bulgaria | 4 |
| India | 4 |
| Lebanon | 4 |
| Andorra | 3 |
| Benin | 3 |
| Costa Rica | 3 |
| Dominican Republic | 3 |
| Ecuador | 3 |
| Latvia | 3 |
| Saudi Arabia | 3 |
| South Africa | 3 |
| Jamaica | 2 |
| Japan | 2 |
| New Zealand | 2 |
| Qatar | 2 |
| Republic of the Congo * | 2 |
| Taiwan | 2 |
| Thailand | 2 |
| Bahamas | 1 |
| Barbados | 1 |
| Bermuda | 1 |
| Bosnia and Herzegovina | 1 |
| Georgia | 1 |
| Liberia * | 1 |
| Martinique | 1 |
| Morocco | 1 |
| New Caledonia | 1 |
| Panama | 1 |
| Philippines | 1 |
| Russia | 1 |
| South Korea | 1 |
| Turkey | 1 |
| Venezuela | 1 |

| | |
|---|---|
| **Total** | **22485** |

* Country has historically reported monkeypox