



HEALTH SCIENCES

Current Pandemic in the World: Monkeypox from Past to Present

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Abstract: Monkeypox is a zoonotic viral infection that was first identified in humans in 1970 in the Democratic Republic of Congo. The cases seen again in early May 2022 have reached 78.000 as of today. On July 23, 2022, the World Health Organization decided that the monkeypox outbreak represents a public health emergency. For the early diagnosis and effective treatment of monkeypox, inter-individual transmission routes, disease symptoms, factors affecting the course of the disease, presence of another infection, prognosis, pharmacological agents used in the prophylactic treatment, and their effects, populations at risk, waste disposal protocol should be known. For this reason, our aim is to reveal the sources of transmission of the monkeypox virus from past to present, what are the signs and symptoms in patients after infection, ways of protection from the virus, the mutation status of the virus, and treatment approaches.

Key words: diagnosis, Monkeypox, outbreak, treatment, vaccine.

INTRODUCTION

Monkeypox (MPX) disease is a zoonotic viral infection transmitted from animals to humans, caused by a member of the Orthopoxvirus genus of the Poxviridae family. The virus, which is the causative agent of the disease, was isolated from monkeys in Denmark in 1958 and proved to be transmitted to humans in 1970 in the Democratic Republic of Congo (DRC) (Arita et al. 1980, Magnus et al. 1959). MPX virus was approved as an orthopox virus by the World Health Organization (WHO) in 1980. In the 2000s, cases were reported, especially in the DRC and different African regions, and in 2018-2019, in Israel, Singapore, and the United Kingdom, after the trips to Nigeria, and in 2020, 4594 suspected cases were detected in the DRC (Cimerman et al. 2022, Erez et al. 2019, Vaughan et al. 2018, Yong et al. 2020).

In early May 2022, a case of MPX was confirmed in a patient who had recently traveled to Nigeria

in the UK, and as of 21 May, WHO had reported 92 MPX cases, 28 of which were suspected, in 12 countries where the disease was not normally present. A total of 219 cases were seen all over the world as of May 25, 71 were distributed in the United Kingdom, 51 in Spain, 37 in Portugal, 15 in Canada, 9 in the USA, and the remaining 36 mostly in European countries. While the number of confirmed cases in June was around 700, it increased rapidly, reaching 16,000 in July and 78,000 in November. It was determined that 98% of the cases with an average age of 41 were male. Countries with 3000 or more cases are given in Fig 1 (Cimerman et al. 2022, Global.Health / Map 2022).

While the epidemic of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) continues in the world, the possibility of another epidemic occurring in approximately 55 countries is a cause for concern all over the World (Europe, 2022). However, thought that MPX

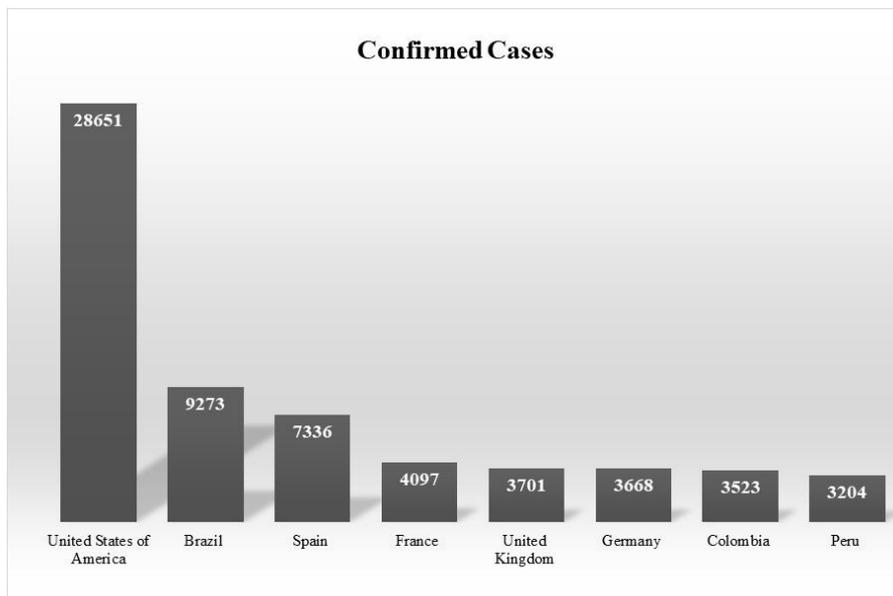


Figure 1. Countries with the highest number of Monkeypox cases by November 2022.

is not a new disease in the scientific world and the clinical course of the disease can progress more controlled with sufficient knowledge. In this review, our aim is to reveal the sources of transmission of the MPX virus from past to present, what are the signs and symptoms in patients after infection, ways of protection from the virus, the mutation status of the virus, and treatment approaches.

MATERIALS AND METHODS

A systematic literature search was conducted using PubMed databases from May 2022 to November 2022. The keywords used were “monkeypox, monkeypox smallpox, monkeypox treatment, monkeypox vaccines” (Table I). After examining the titles and abstracts of the articles or reviews selected according to the search results, joint works of literature were removed (n=232). The literature sources, which were examined in detail as full text, were deemed suitable for inclusion in this systematic review.

MPX virus type and virulence

MPX virus is divided into 2 different phylogenetic species as West African and Central African. The

West African type is a less virulent form and the severity of the disease is less common in this form. West African species are seen in Spain as of 2022. It has been reported that the Central African species escaped from the immune system by preventing cytokine production and T cell-mediated immunity in patients who had previously been in contact with the MPX virus. The presence of complement enzyme-inhibiting strains in Central African species, which are not found in West African species, also contributes to the more virulent form of Central African species. In addition, the Central African species down-regulates the immune response in the host through apoptotic cell death, causing suppression of genes that provide the immune response. Unlike other viruses such as Influenza or SARS-CoV-2, viruses in the Poxviridae family have been reported to have a much lower ability

Table I. Literature numbers by keywords.

Keywords	Total	2022
Monkeypox	1973	1082
Monkeypox smallpox	679	183
Monkeypox treatment	584	258
Monkeypox vaccines	536	249

to mutate, but have a greater genetic makeup in terms of their virulence and ability to suppress the immune system (Bunge et al. 2022, Smith et al. 2013).

MPX virus reservoir and transmission routes

The main source of disease for the MPX virus is thought to be an infection in African rodents. animal-to-human transmission can occur by scratching, biting, and direct or indirect contact with bodily fluids or lesion material. It has been reported that the virus can enter the human body through the respiratory tract, skin, or mucous membranes (eyes, nose, or mouth) as a result of skin lesions of infected animals, body fluids, and contact via droplets (ECDC 2022).

The MPX virus is transmitted from person to person through close contact of an infected person with contaminated respiratory droplets, bodily fluids, skin lesions, lesion materials, or contaminated objects such as bedding. The virus enters the body through damaged skin tissue, respiratory tract, or mucous membranes (eyes, nose, or mouth) (Sah et al. 2022). Respiratory droplets can be transmitted by sneezing and coughing, but respiratory droplets cannot move more than a few meters. Therefore, prolonged face-to-face contact is usually required for transmission to occur. This poses a greater risk to healthcare workers and family members of their contacts. Most cases occur in men who have sexual intercourse with men, and who have genital lesions suggesting that transmission occurs through close physical contact (Adalja & Inglesby 2022, Mahase 2022). In some cases, there is also a history of contact with animals. Neonatal MPX cases show that it can be transmitted from mother to fetus through the placenta (Miura et al. 2022).

Clinical findings of MPX disease

Clinical manifestations of the MPX virus appear after the incubation period. The incubation period generally ranges from 7-14 days, with a maximum of 21 days (Ilic et al. 2022). Clinical manifestations are related to the degree of exposure to the virus, the patient's health status, and complications and may vary. In general, flu-like symptoms such as fever, muscle, and headache are seen at the beginning, while a skin appearance similar to a rash, syphilis, or herpes occurs on the skin later on (Arita et al. 1980). MPX complications can also include deep abscesses and secondary infections. In some cases, proctitis or pharyngitis with minimal or no skin lesions was detected. Cases often apply to health institutions with characteristic lymphadenopathy in the groin. Complaints may be accompanied by a series of complications such as secondary bacterial infection, respiratory distress, bronchopneumonia, encephalitis, corneal infection, vomiting, and dehydration due to diarrhea.

The symptoms of the MPX virus are similar to other smallpox diseases and show some differences. The disease is accompanied by fever and headache, fatigue, and swollen lymph nodes (Damon 2011). The main difference between smallpox and the MPX virus is lymphadenopathy, that is, enlargement of the lymph nodes. Rash development and 1-4 mm diameter maxillary, cervical, and inguinal lymphadenopathies are present. Enlarged lymph nodes are hard and painful. The fever generally lasts for 3 days until the onset of the rash. The rash first begins as macules (flat lesions), progresses to papules (slightly raised firm lesions), vesicles (lesions filled with clear fluid), and pustules (raised lesions filled with yellowish fluid), eventually ending with crusts that dry and flake off. Lesions, which can number from a few to thousands, are usually more intense on the

face and extremities (95%), but can be seen on the palms and soles (75%), oral mucosa (70%), genitals (30%) and conjunctiva (20%). In severe cases, the lesions may coalesce and turn into patches of skin. Lesions seen in the oral cavity may cause nutritional disorders in the future (Ježek et al. 1987).

Mortality and morbidity for MPX

The symptoms and course of the disease in cases vaccinated against smallpox differ significantly from that of unvaccinated subjects. Secondary bacterial infections of lesions occurring on the skin are especially seen in unvaccinated MPXs (Petersen et al. 2022). Serum antibodies can be detected within two weeks of exposure. The mortality rate due to MPX has been reported to range from 1% to 10%, but severe cases are more common among children and the mortality rate is around 15% in this patient group.

Whether the MPX virus is sexually transmitted is controversial. However, according to the cases, the disease is more common in homosexual men. According to reports from Portugal and Italy, fifty percent of the cases are HIV (+), causing HIV cases to be among the risk factors for the disease (Petersen et al. 2022). Considering the hospitalization rates among MPX cases, it was stated that it was higher in those with HIV infection (Curran et al. 2022). For this reason, it is necessary to raise awareness about potential sexually transmitted infections. Naming viruses such as SARS-CoV-2 and the Chinese virus creates a stigmatizing effect on countries, people, and the economy. For the MPX virus, there is a stigma in the form of men who have sexual intercourse with men. This situation may cause discrimination in society and may prevent individuals infected with the virus from applying to health institutions. Failure to treat infected individuals or being late may result in an increase in the number of cases. For this

reason, it is necessary to make denominations that do not stigmatize any population or ethnic origin. Thus, hesitations about the correct determination of the number of cases and sharing the information can be eliminated (Europe 2022, Nitsche et al. 2004).

MPX virus diagnosis methods and risk groups

The factors affecting the early diagnosis and effective treatment of MPX are as follows:

- transmission status during the incubation period,
- inter-individual transmission routes,
- factors affecting the transmission period,
- disease symptoms,
- primarily affected organs,
- factors affecting the course of the disease,
- presence of another infection (sexually transmitted infections),
- prognosis,
- pharmacological agents used in the prophylactic treatment and their effects/side effects,
- isolation protocol,
- populations at risk,
- virus viability outside the host,
- waste disposal protocol.

It is important to detect the MPX virus at an early stage and to prevent the course of the disease and the epidemic situation. Virus isolation studies have shown that MPX strains show more virulence than Variola or Vaccinia strains, form large plaques in the Vero cell line, and are more proliferative at 39.0 °C. Histopathology studies stated that it is difficult to distinguish because it shows necrotic structures similar to smallpox (Martín-Delgado et al. 2022). In addition, due to the fear of using Orthopoxvirus species as biological weapons in the past, there is a need for rapid diagnosis and risk assessment. Therefore, the use of targeted RT-PCR has been defined as an extremely fast,

safe, sensitive, and reliable method (Noe et al. 2022).

In cases where MPX is suspected recommended that healthcare personnel wear protective glasses, respirator masks, gloves, and fully protective clothing. A detailed history should be taken by asking about age, gender, the onset date of symptoms, when skin lesions started to occur, whether there was a sexually transmitted infection in the past, whether there was a recent trip to risk areas, and other risk factors. Afterward, swap samples containing especially skin lesions should be taken and sent to the laboratory by taking safety precautions similar to SARS-CoV-2.

Detection of non-variola zoonotic Orthopoxvirus species (monkeypox, racoonpox, camelpox, and vaccinia) can be made by RT-PCR method from DNA samples obtained from serum, rectal or cutaneous swabs or mucosal structures with lesions. One of the most common kits used in scanning is the RealStar Zoonotic Orthopoxvirus kit, released by Altona Diagnostics in June 2022 (Raccagni et al. 2022). After detecting non-variola zoonotic Orthopoxvirus species with the kit in which Cowpox virus is used as a positive control, definitive results can be reached in the diagnosis with MPX virus-specific kits (Bio Perfectus Technologies, Creative Biogene Biotechnology, Altona Diagnostics, and Runmei Gene Technology).

After cases are confirmed, individuals with high-risk contacts, contacts, or low-risk contacts should be identified. Those who are in physical contact with the case or who are less than one meter away in the same environment are at high risk; Those who come into contact with the towels, bedspreads, and clothes infected by the case or who are in the same environment during the contagion period are at risk; those other than these can be grouped as low risk. Risk groups may be informed about the symptoms

expected to be seen in MPX disease, and they may be asked to observe themselves for a period of 21 days and to apply to a health institution, especially if there is a lesion on the skin. People in the high-risk group may be asked to isolate themselves for a while, reduce contact with their environment, and use masks (Homepage | European Centre for Disease Prevention and Control 2022). In terms of public health, each individual should be considered in the low-risk group and especially those who will travel to different countries (such as those who will go to Hajj and Umrah, and those who will attend Qatar FIFA World Cup 2022) should be informed about MPX (Tambo & Al-Nazawi 2022).

Prophylactic treatment approach

ACAM-2000 and MVA-BN smallpox vaccines are recommended prophylactically for people at risk of exposure to MPX. Those who have the smallpox vaccine (usually born before 1970) have been shown to reduce MPX disease symptoms and spread (Fine et al. 1988, Halani et al. 2022, Rizk et al. 2022). According to 2022 data, it has been reported that ACAM2000 and JYNNEOS (also called IMVAMUNE, IMVANEX, and MVA-BN) vaccines can be used (Chan-Tack et al. 2019). A comparison of ACAM-2000 and JYNNEOS vaccines is given in Table II. Both ACAM2000 and JYNNEOS vaccines have been reported to have a protective effect against the MPX viruses (Niaz et al. 2022).

Pharmacological treatment approaches for MPX

It has been reported that hospitalization rates are low in the treatment of MPX disease and antiviral treatments can be applied with tecovirimat, cidofovir, or brincidofovir drugs (Fine et al. 1988). The most recommended tecovirimat (ST-246) is a low molecular weight therapeutic agent used in the treatment of smallpox and monkeypox

Table II. Comparison of ACAM-2000 and JYNNEOS vaccines.

	ACAM-2000	JYNNEOS
Licensing	FDA; August 2007	FDA; September 2019
Vaccine viability and type	Replication-competent vaccinia virus	Replication-deficient modified vaccinia Ankara virus
Approved diseases for use	Smallpox	Smallpox
Contraindications	Pregnancy Cardiac diseases Suppression of immunity Vaccine allergy	Vaccine allergy
Serious side effects	Myopericarditis Encephalitis	-
Drug dose and route of administration	Single dose Percutaneously by the multiple puncture technique	Two doses 28 days apart Subcutaneously

caused by Orthopoxvirus species. It was approved by the FDA in July 2018 to treat smallpox caused by the variola virus. It has been reported that it inhibits virus-induced cytopathic activity and plaque formation in cell culture studies (Russo et al. 2020). It showed strong antiviral activity against MPX, cowpox, and variola strains (EC50 values of 0.014, 0.050, and 0.046 respectively) in antiviral activity studies conducted on different virus strains in the Orthopoxviridae family. In experimental animal studies, it has been shown that it reduces the infection caused by the disease, provides protective immunity against the new virus agent, and causes the prevention of major morbidity. Although up to 23 times the recommended dose in humans was administered in mice, no serious side effects were observed (Chan-Tack et al. 2019, Jordan et al. 2010). Tecovirimat showed protective activity against mortality in Orthopoxvirus strains tested in different experimental animal models. In clinical studies, no serious side effects have occurred and no deaths have been reported due to the use of tecovirimat. Oral administration of Tecovirimat at 600mg twice a day for 14 days has been recommended. Although the side effects that occur as a result of treatment are at low

rates, headaches or nausea may occur (Jordan et al. 2010). VP37 (also known as F13), a highly conserved protein in Orthopoxvirus species, plays a role in its mechanism of action (Russo et al. 2020). The VP37 protein ensures that the virus is enveloped and spread throughout the body with a double membrane layer produced from endosomes or Golgi. Tecovirimat targets the VP37 protein, preventing the virus from spreading in the host (Jordan et al. 2010). The pharmacological properties of TPOXX containing the active ingredient Tecovirimat are shown in Table III (Tecovirimat: Uses, Interactions, Mechanism of Action | DrugBank Online [25.07.2022], TPOXX (Tecovirimat) Dosing, Indications, Interactions, Adverse Effects, and More [25.07.2022]). Tecovirimat has been approved by the FDA for emergency cases (such as those taking immunosuppression therapy, and pregnant women) after showing positive results in MPX treatment. Following preclinical studies with Tecovirimat, safety studies were also conducted in randomized controlled trials. In the study, in which side effects similar to the placebo group were observed, it caused headache and abdominal pain when administered orally, and erythema and swelling at the infusion site in

Table III. Pharmacological properties of the most recommended therapeutic agent in MPX treatment.

Active ingredient	Tecovirimat
Prescription products	Tpoxx, Tecovirimat Siga
Chemical taxonomy	Organic compounds: Organoheterocyclic compounds: Isoindolines
Chemical formula	$C_{19}H_{15}F_3N_2O_3$
Predicted properties	Water Solubility: 0.021 mg/mL, melting point (°C): 196
Dosage forms	200 mg capsule
Recommended use	30 minutes after meal
Adults dosage	600 mg twice daily for 14 days
Pediatrics dosage	13 kg-25 kg: 200 mg twice daily for 14 days 25 kg- 40 kg: 400 mg twice daily for 14 days 40 kg>: 600 mg twice daily for 14 days
Adverse reaction	Headache and nausea
Drug-drug interaction	Repaglinide: hypoglycemia Midazolam
Pregnancy and lactation	No adequate a clinic studies. Benefit and harms balance should be considered. Pregnancy category: C
Absorption	Peak plasma time: 4-6 hr Minimum plasma concentration: 587 ng/mL
Distribution	Bound to human plasma proteins: 77-82% Blood-to-plasma ratio: 0.62-0.90
Metabolism	Hydrolysis *substrate of UGT1A1 and UGT1A4. *inhibitor of CYP2C8 and CYP2C19. *inducer of CYP3A4.
Elimination	Half-life: 20 hr (600 mg orally administration) Excretion: 73% urine (predominantly as metabolites); 23% feces (predominantly as parent drug)

addition to headache when administered intravenously (Niaz et al. 2022).

CONCLUSIONS

MPX disease, which resurfaced in May 2022, was detected in more than 70 countries as of November. The SARS-CoV-2 epidemic, which we are still struggling with around the world, has changed the perspective of all people towards diseases and made them more conscious. Therefore, despite the rapidly increasing

number of cases, we think that MPX disease can be controlled by increasing awareness and rapid detection of cases. We propose to prevent the spread of the disease as a result of international cooperation in countries struggling with poverty, especially in Africa, to create a different perception in order to eliminate stigma and to investigate the mechanisms of action of pharmacological agents used in treatment.

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