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Epidemiological aspects of mpox (Monkeypox)

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Abstract

Monkeypox, lately known as mpox, is a zoonotic viral disease leading to an illness like smallpox in humans, but with lower mortality rates. Usually, the disease lasts between two and four weeks and occasionally results in death. The mpox virus (MPXV) is critical because it is widespread in Western and Central Africa and has spread throughout the Western Hemisphere due to international travel and the exotic pet trade. Mpox is now clinically significant due to the elimination of smallpox and the ensuing decline in vaccination efforts. Concern over the emergence of the human MPXV and its occasionally severe clinical manifestations has grown recently. The importation of diseased dogs to commercialize them as pet animals caused an outbreak of the MPXV in the United States of America. This heightened awareness of the potential for this disease to spread over the globe, either as a component of biological weapons in terrorist operations or as a result of the practice of importing wild animals as exotic pets. This review briefly describes the history, etiological agent, mode of transmission, clinical symptoms, diagnosis, treatment, and management of mpox, as well as vaccination and prevention of the disease.

Introduction

Mpox is a zoonotic viral disease-causing symptom quite similar to those of smallpox patients. The virus belongs to the *orthopoxvirus* genus within the *Poxviridae* family. Mpox virus (MPXV) has two clades and mostly presents in Central and West

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Africa, particularly in urban areas near tropical rainforests. The animal hosts of the virus are non-human primates and many rodent species (1, 2).

The mpox can transmit to humans through direct contact with the bodily fluids of diseased animals while hunting, chopping corpses for food, or playing with animals (3). Since 1981, the majority of cases have been reported in the Congo Basin in Central Africa. The bulk of yearly human mpox infections still occurs in this region. In the 1980s, the mortality rate among unvaccinated people in Central Africa was roughly 10%, but cases in West Africa had no mortalities due to a difference in the virus's virulence between the strains in Central and West Africa (4, 5). Following the importation of mpox-infected West African rodents from Ghana, an outbreak of the disease in the Midwestern United States of America (Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin) in 2003 marked the first human cases of mpox in the western hemisphere. The health hazards related to the international trade in exotic animals were recognized in part due to this outbreak (6). Immunity to mpox was previously attained by vaccination; however, mpox has become clinically significant due to the elimination of smallpox and the consequent decline in vaccination efforts (2). The introduction of the human MPXV and its occasionally severe clinical symptoms have recently caused concern. Furthermore, in recent years, mpox cases have increased in frequency and geographically expanded (7-9). Thus, the history, etiological agent, mode of transmission, clinical symptoms, diagnosis, treatment, and management of mpox, as well as vaccination and prevention, are all covered in this review.

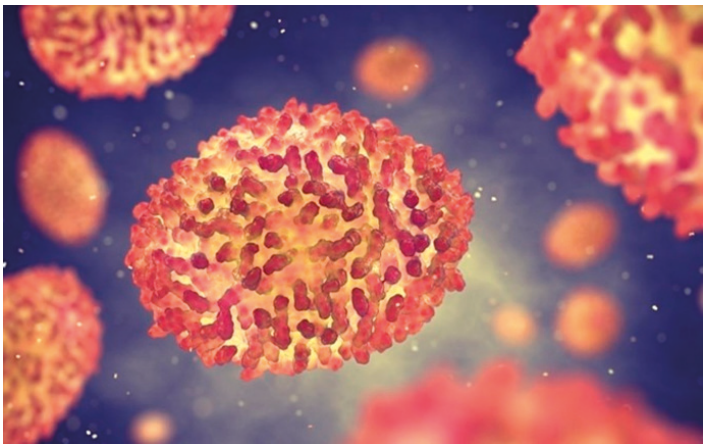

Fig. 1. The mpox virus is an orthopoxvirus from the same group of viruses as smallpox. Image Credit: nobeastsofierce / Shutterstock.com

History of mpox

An outbreak of fever and skin rashes in a group of cynomolgus monkeys at the State Serum Institute in Copenhagen in 1958 was initially attributed to the MPXV (10). Similar outbreaks were documented in American monkey colonies over the next few years. Mpox is no longer a rare, self-limiting illness seen only in endemic nations. Its constantly shifting transmission dynamics and epidemiology have raised the likelihood that it may become a much more dangerous virus (9). Mpox infection was brought to the Rotterdam Zoo in 1966 and numerous ape and monkey species were affected by the disease. The isolated viruses from the diseased animals were similar and belonged to an *orthopoxvirus* species that had not yet been identified prior to 1958 (2, 11).

The MPXV has caused a smallpox-like illness in humans in the Democratic Republic of the Congo

and Liberia in two different cases in 1970. In the African rainforest belt, especially in the Democratic Republic of the Congo, isolated cases have persisted (11). Based on the reports of the World Health Organization, thousands of confirmed cases of mpox have spread geographically over the past two years (12). Spain, France, Sweden, Saudi Arabia, Pakistan, Thailand, Kenya, Congo, Uganda, Rwanda, Burundi, South Africa, and other countries have reported many cases of the disease (12).

Etiology of mpox

The MPXV is an enveloped double-stranded DNA virus that belongs to the *Poxviridae* family's *Orthopoxvirus* genus (Figure 1). The MPXV is a zoonotic agent that can infect several hosts. Besides MPXV, the *Orthopoxvirus* (OPXV) genus contains the Vaccinia, Variola, and Cowpox viruses (8, 9, 13).

Orthopoxviruses induce immunological cross-protection which means that a smallpox vaccination or infection with one OPXV produces some level of protection against the other members of the genus. Individual virus strains vary greatly in virulence, with the Congo Basin strains consistently being more virulent than West African strains (4,5).

Mode of transmission

The MPXV's natural history is still unknown, and more research is required to pinpoint the precise reservoir or reservoirs and understand how the MPXV circulates in the wild (3). Direct contact with wild animals that have been killed for food, particularly squirrels and monkeys, can transmit the MPXV to humans. Rodents and nonhuman primates are the common hosts of the MPXV (13, 14). Consuming undercooked meat and other animal products from infected animals may also transfer the mpox to humans (13, 14). The infection can spread via the respiratory system, skin, or mucous membranes, through the bites and scratches of infected animals, or while handling infected materials. Therefore, hunting, skinning, preparing, and consuming infected rodents and monkeys are all factors in the infection's spread in African endemic areas (15). It is thought that the infection with mpox can disseminated from a diseased animal to another animal via biting or by close contact with its saliva, respiratory secretions, lesion exudate, or crust material. The disease can also be transmitted through oral abrasions of people who eat infected monkeys or squirrels. In addition, viral shedding through animal feces could be another source of exposure (13-15). Human-to-human transmission can occur via several methods. Close contact with lesions, bodily fluids, respiratory droplets, and contaminated bedding can spread the MPXV from one person to another (3, 4). Thus, there is a pressing need to learn more about mpox in both humans and animals. Furthermore, a clade I strain of mpox was most likely responsible for abortion in women who contracted the MPXV, which has sparked worries about the virus's vertical transmission and the consequences of infection in pregnant women (16, 17). Sexual contact was identified as a potentially new mode of transmission during the global mpox outbreak in 2022 (18). Currently, it is unclear whether sexual contact is solely an efficient way to make close contact with skin and mucous membranes or whether sexual transmission can also occur through reproductive fluids like semen. The importation of infected prairie dogs for commercializing them as pet animals recently caused an outbreak of mpox in the USA (19). This sparked worry and awareness of the potential for this agent to spread globally, either as part of biological weapons in terrorist attacks or as a result of the practice of importing wild animals as exotic pets due to the growing number of international travelers. Although research and evidence suggest that rodents are a likely reservoir, the precise species that carry MPXV and the details of viral dissemination in animal populations remain unclear. Many animal species are vulnerable to the MPXV. Rope squirrels, tree squirrels, dormice, non-human primates, Gambian pouched rats, and

other species are among them (20).

Clinical symptoms of mpox

In humans, the incubation period of mpox is typically 7 to 14 days. A fever, severe headache, lymphadenopathy, back pain, myalgia, severe asthenia, sore throat, and cough are the symptoms of the invasion stage of the disease, which lasts for 0-5 days. In the second stage, blister-like skin rashes typically start on the face before spreading to other areas of the body (8, 21) as shown in Figure 2. The blisters go through multiple stages before becoming crusty, scabbing over, and falling off (Figure 3). Rarely, mpox can result in death.

Fig. 2. Different stages of mpox in different regions of the human body. Images Credit: Nigeria Centre for Disease Control and https://www.cidrap.umn.edu

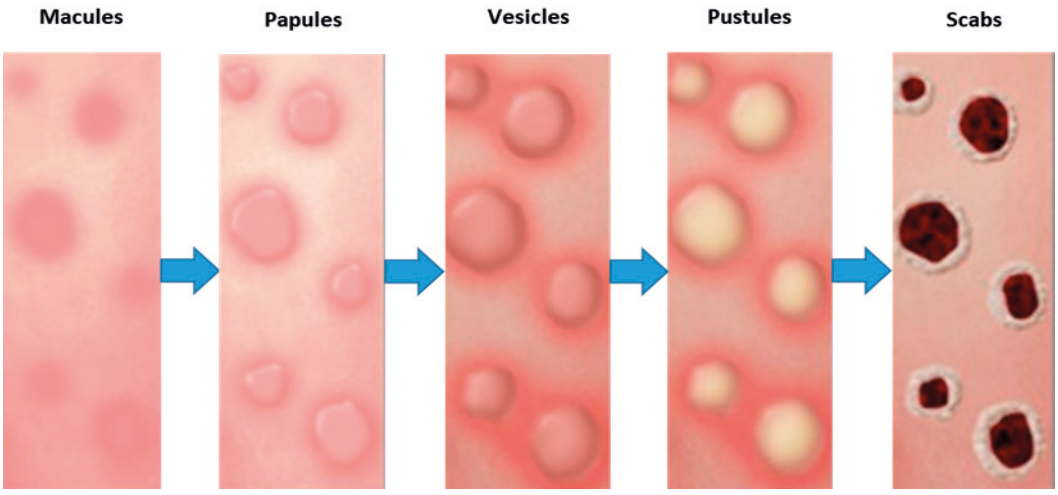

Fig. 3. Different stages of skin rash in humans with mpox disease. Images Credit: https://www.mountsinai.org

Typically, the skin eruptions start one to three days after the fever appears (20). Rather than the trunk, the rashes usually affect the face and limbs. In 95% of cases, it affects the face; in 75% of cases, it affects the palms of the hands and soles of the feet. Additionally, the disease can affect the cornea, genitalia (30%), conjunctivae (20%), and oral mucous membranes (70%) (22). Macules (flat-base lesions), papules (slightly elevated firm lesions), vesicles (lesions filled with clear fluid), pustules (lesions filled with pus), and crusts that dry up and fall off are the successive stages of the rash's development (Fig. 3). Lesions range in number from a few to several thousand. Lesions may clump together until sizable portions of skin peel off in extreme circumstances (23, 24).

In animals, the initial symptoms of mpox include fever, lack of appetite, lethargy, coughing, bloating, congested eyes, nasal secretions, and/or rashes. In severe cases, the affected animal can develop skin, tongue, and lip sores and die within 8-16 days (25).

Diagnosis of mpox

Mpox is diagnosed based on laboratory tests and clinical symptoms reported. Other rash conditions like chickenpox, measles, bacterial skin infections, scabies, syphilis, and medication-associated allergies are among the clinical differential diagnoses that need to be taken into account (26). One clinical characteristic that can be used to differentiate mpox from smallpox or chickenpox during the prodromal stage of illness is lymphadenopathy (23, 24)

Health professionals should gather the necessary samples and securely transport them to a laboratory equipped to handle them if mpox is suspected. Anti-orthopoxvirus IgM and IgG are found in serum taken from both index patients using enzyme-linked immunosorbent assays (ELISA). If the ELISA test yields a positive result, the serum samples are deemed to be positive for anti-orthopoxvirus IgG (27).

Clinical swabs obtained from cutaneous lesions are applied to identify distinct viral DNA sequences using real-time polymerase chain reaction (PCR) and/or sequencing in order to confirm the MPXV. Quantitative real-time PCR assays are used to screen for non-Variola virus Orthopoxviruses after DNA is extracted from the swabs (28). Because of its accuracy and sensitivity, PCR is the recommended laboratory test for diagnosis of the mpox. Specimens should be transported and packaged following both international and national regulations. Skin lesions, such as the roof or fluid from vesicles and pustules, as well as dry crusts, provide the best diagnostic samples for mpox. A biopsy is another choice if applicable. Lesion samples must be kept cold and in a sterile, dry tube without viral transport media. Due to the short duration of viremia in comparison to the timing of specimen collection after symptoms start, PCR blood tests are typically inconclusive and should not be routinely obtained from patients (29).

Because Orthopoxviruses are serologically cross-reactive, mpox-specific confirmation cannot be obtained using antigen and antibody detection techniques. Therefore, in situations where resources are scarce, serology and antigen detection techniques are not advised for diagnosis of the mpox. Furthermore, false positive results may result from recent or distant vaccination with a vaccine based on vaccinia (29).

Treatment and management of mpox

The targets of mpox clinical care are minimizing symptoms, controlling complications, and avoiding long-term effects and complications. The patients of mpox should be given sufficient amounts of food and fluids in order to maintain a sufficient nutritional status. Moreover, secondary bacterial infections should be controlled and treated (23).

Based on results obtained from studies on both humans and animals, the European Medical Association (EMA) licensed tecovirimat, an antiviral medication created for smallpox, for mpox in 2022 (8). Although

tecovirimat (ST-246, Tpoxx®) was approved by the USA Food and Drug Administration (FDA) in 2018 as the first antiviral medication specifically recommended for the treatment of smallpox disease in adults and children (30), it isn't widely accessible yet. By targeting the p37 protein of orthopoxviruses, tecovirimat prevents the formation of the viral envelope and the virus's egress (31, 32). Nevertheless, there is little evidence to support the effectiveness of antiviral treatment for mpox patients. There are ongoing clinical trials assessing tecovirimat's potential to cure mpox in humans (33).

Brincidofovir, also known by the brand name Tembexa, is a prodrug of cidofovir that is intended to release cidofovir intracellularly, increasing its anti-DNA virus activity and oral bioavailability while lowering plasma concentrations (34). Cidofovir has demonstrated efficacy against deadly MPXV challenge in animal models and has *in vitro* activity against MPXV. However, there is no clinical evidence to support its efficacy against mpox in humans, and using it may have major adverse effects, including nephrotoxicity (35, 36).

Many substances have been tested against poxviruses both *in vitro* and *in vivo*. Some acyclic nucleoside phosphonate derivatives have demonstrated strong and specific anti-poxvirus activity in addition to cidofovir (37, 38). Management of secondary bacterial superinfections is necessary during the treatment of mpox in humans to avoid complications. The patient should receive suitable antibiotics beside the antiviral therapy. Moreover, management of other complications such as balanitis, balanoposthitis, infected wounds or neurologic manifestations is crucial.

Vaccination against mpox

Several observational studies have shown that vaccination against smallpox is approximately 85% effective in preventing mpox (22). When an animal virus was used to vaccinate humans against smallpox, the history of vaccination began (39). Therefore, a previous smallpox vaccination may cause a less severe illness. The public no longer has access to the first-generation smallpox vaccinations. It's possible that some medical professionals or laboratory staff have a more recent smallpox vaccination to guard against occupational exposure to Orthopoxviruses (40, 41). To lower the chance of getting mpox, there are two Orthopoxvirus vaccinations available. Both the replication-competent smallpox and mpox vaccine (ACAM2000) and the non-replicating modified vaccinia Ankara (MVA) vaccine (JYNNEOS in the US, IMVANEX in the EU, and IMVAMUNE in Canada) are available. Regardless of clade, vaccination is anticipated to offer protection (42). In 2019, an even more recent vaccine against mpox was authorized, based on a modified attenuated vaccinia virus (Ankara strain). The availability of this two-dose vaccine is still restricted. Because of the cross-protection provided for the immune response to Orthopoxviruses, vaccines against smallpox and mpox are developed using formulations based on the vaccinia virus. The vaccine for smallpox protects against both. The length of immunity that the smallpox vaccine provides without periodic boosting is still up for debate (40, 41). Nonetheless, it is undeniable that having lifelong immunity to re-infection was a permanent reward for surviving smallpox (43).

Prevention of mpox

Educating people about risk factors and ways to reduce their exposure to the MPXV is the main strategy for preventing mpox. Research is currently underway to ascertain whether vaccination is a practical and appropriate means of mpox prevention and control. Some nations have policies in place or are developing policies to provide vaccines to people who might be at risk, such as laboratory employees, rapid response teams, and medical professionals (44, 45).

Reducing the risk of human-to-human transmission through surveillance and prompt case detection is

necessary to control the outbreaks. During human outbreaks, close contact with infected people is the most significant risk factor for catching the MPXV. Healthcare workers and household members are particularly vulnerable to infection. Healthcare workers who handle specimens from patients with suspected or confirmed MPXV infections should adhere to standard infection control protocols. The patient should ideally be treated by people who have been vaccinated against smallpox (45). The discovery of clusters of mpox cases in May 2022 in several non-endemic countries that have no direct travel connections to an endemic region is unusual. More research is being conducted to determine the infection's most likely source and prevent its spread. While investigating the cause of this outbreak, it is important to take into account all possible modes of transmission to safeguard public health (46). Reducing the likelihood of zoonotic transmission may also help prevent human mpox. Primary animal-to-human transmission has historically been the cause of the majority of human infections. Unprotected contact with wild animals, especially sick or dead ones, and their meat, blood, and other parts should be avoided. Furthermore, all foods containing animal parts or meat must be cooked through before consumption (44).

To support proper case management and public health response, as well as to enhance the disease research portfolio, there is an urgent need to greatly increase the quantity and quality of mpox data collected.

Conclusions

Although it is occasionally exported to other areas, the viral zoonotic disease mpox is mainly found in Central and West Africa's tropical rainforest regions. The illness is brought on by the MPXV, which is a member of the *Poxviridae* family's *Orthopoxvirus* genus. Compared to smallpox, mpox is less contagious and causes less severe illness. In addition, the symptoms usually disappear on their own within two to four weeks. Severe cases can occur, and the case fatality ratio has been roughly 3-6%. Close contact with contaminated bedding, bodily fluids, respiratory droplets, and lesions can expose humans to the MPXV. Like smallpox, mpox can result in some clinical manifestations, including fever, rashes, enlarged lymph nodes, and some health complications.

Vaccines used in the smallpox eradication program prevent mpox in humans. In addition, newer vaccines have been developed, one of which is approved to prevent mpox. An antiviral drug developed to treat smallpox can now be used to treat mpox.

There are still a lot of unanswered questions regarding MPXV epidemiology that need to be addressed by animal research. Therefore, there is an urgent need for major improvements in the amount and quality of data gathered about mpox in order to enhance the research portfolio, support appropriate case management, and aid in public health response.

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Ethical approval
Not applicable

Conflict of interest statement
The authors reported no potential conflict of interest.

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