Epidemiology of Human Monkeypox about the 2022 Outbreak: A Narrative Review

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ABSTRACT

Abstract: Human Monkeypox is a zoonotic disease caused by 2 distinct clades of human monkeypox virus (MPXV). MPXV infections can cause several clinical symptoms including fever, skin rash, back pain, and lymphadenopathy in humans. Even though MPXV infections are generally self-limiting, death is possible and fatality due to MPXV infections in humans is 3-6 percent. While the disease is endemic to Africa, its potential to cause outbreaks in other continents has been observed. The natural reservoir of MPXV in Africa and the full host range of the virus are not known, but rodents are suggested to be the reservoirs. The transmission of MPXV occurs via close contact and the prevention strategies include avoiding close contact and post-exposure prophylactic vaccination of people at risk with smallpox vaccines. In this study, the most recent information about the epidemiology of MPXV about the latest research on the 2022 outbreak of MPXV has been reviewed.

Keywords: Monkeypox, monkey poxvirus, epidemiology, zoonoses

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Introduction

Human Monkeypox is a zoonotic disease first discovered in 1970 in the Democratic Republic of Congo when the regional elimination of smallpox revealed the sporadic cases of a disease with similar clinical presentation (1). Human Monkeypox primarily occurs in remote villages in the tropical rainforests of West and Central Africa (2). However, the disease outbreaks have occurred in multiple countries worldwide from Europe to the US with the 2022 outbreak, in which cases have been confirmed from North and South America, Africa, Europe, Australia, and the Middle East (3). The potential of spreading to non-endemic countries along with its clinical severity, possessing case fatality rates (CFR) of approximately 3-6 percent, and being zoonotic has made the World Health Organization (WHO) consider human Monkeypox a moderate threat globally and a high-risk for the European region in 2022 (4, 5). Due to the importance of the disease, the investigation of the epidemiology of human Monkeypox is necessary. The current review aimed to gather and summarize the current information regarding the epidemiology of human Monkeypox with a focus on epidemiological characteristics of the outbreak in 2022.

Methods

In this review, the articles published between January 01, 2017, and September 01, 2022, from the databases of Google Scholar and PubMed, and fact sheets from WHO, Centers for Disease Control (CDC), and European Centre for Disease Prevention and Control were used. The keyword "Monkeypox" was used to find relevant articles.

Results

Aetiology

The aetiological agent of Monkeypox is Monkeypox virus (MPXV), a member of the genus Orthopoxvirus and the family of Poxviridae, and is a DNA virus (6, 7). MPXV was first isolated in 1958 in Denmark from captive non-human primates. However, the first confirmed human infections were discovered in the Democratic Republic of Congo in 1970 (8). It has been thought that MPXV similar to other orthopoxviruses is in circulation in animal hosts. MPXV shares similar virulence factors modulating the host immune system with the Variola virus (9).

There are 2 distinct MPXV clades including West African (WA) and Congo Basin (CB) clades. The CB MPXV causes about 10 percent of mortality and human-to-human transmissions up to 6 CB sequential inter-human transmission events have been recorded in an outbreak in Africa, whereas the WA clade is associated with milder clinical disease and lower morbidity and mortality (10, 11). In a study, it has been shown that MPXV isolates that belong to the CB clade generally differ from each other by only single nucleotides. The viral gene encoding for interleukin-1β receptors has been identified as one of the less conserved genes between CB and WA clades. The protein produced by the mentioned gene prevents cytokines from binding to the IL-1 receptors, which are involved in the inflammatory response during infection. This gene is thought to be a cause for the difference observed between the virulence of isolates of the CB and WA clades (12). Moreover, the O1L gene has been associated with the host range of the virus (13).

The outbreak of 2022 is thought to have a single origin and its phylogenomic characterizations suggest that the causative agent is an MPXV belonging to the clade 3, which was formerly designated as a WA clade (14).

Epidemiology

Hosts

The natural reservoir of MPXV in Africa has not been discovered. Neither its full host range nor how the virus is maintained in nature is known. However, it has been suggested that sylvatic rodent species particularly African rope squirrels might be its reservoir. The virus has been isolated from captive crab-feeding macaques (*Macaca fascicularis*), chimpanzees living in rainforest, a sooty mangabey monkey in Thailand, southern opossum (*Didelphis marsupialis*), rope squirrels, sun squirrels, pet prairie dogs, mice, Gambian-

pouched rat (*Cricetomys gambianus*), rabbits, hamsters, groundhogs, porcupines, African hedgehogs (Atelerix sp.), and humans. Moreover, under experimental or captive conditions, a broad range of mammalians have been observed to be susceptible to MPXV including rabbits, ant-eaters, and ground squirrels (15-17).

Moreover, viable virus has been isolated from maggots in the corpses of chimpanzees, in the flies collected around the corpse, and from the leaves where flies had regurgitated or defecated near the corpse.

During the current outbreak, MPXV has been isolated from a greyhound dog that belonged to 2 infected patients, providing evidence that dogs may also be infected with monkeypox and manifest clinical symptoms resembling human cases (18).

Transmission

For humans, the means of MPXV transmission are animal-human and human-human transmission. The human-human transmission occurs through close contact with skin lesions of an infected person, via fomites, or by being exposed to infectious large respiratory droplets (19). During the 2022 outbreak, Antinori *et al.*, have studied 4 Monkeypox male cases who had sex with men in Italy and suggested that since the majority of the lesions were observed on the anus and the genital area of the patients, the close contact during sexual activity is possibly another means of human-human transmission (20). Even though the sexual transmission of MPXV has never been confirmed, the virus DNA has been detected in 29 out of 32 the seminal fluids of cases that were analyzed during the 2022 outbreak (21). Animal-human transmission is presumed to happen through direct or indirect contact through animal handling, bites, scratches, and virus-contaminated materials such as bodily fluids, cutaneous legions, and mucosal lesions of the infected animals. The virus is presumed to enter the body through broken skin, respiratory tract, or mucous membranes in these cases (22). Moreover, there are reports of nosocomial outbreaks of MPXV in which healthcare personnel were infected (23). Also, in a study, it was observed that all the surfaces that were touched by the patients' hands contained viral contaminations with the highest load being detected in the hospital room's bathroom (24).

In a study conducted on rope squirrels, it has been suggested that rope squirrels may also be infected through infectious aerosols or fomites (25). However, the mechanisms of animal-animal, animal-human, and human-human transmission of MPXV have not been fully discovered (26, 27).

Current situation

From 1st January through 4th September 2022, 52 996 laboratory-confirmed cases of Monkeypox and 18 deaths have been reported to the WHO from 102 countries/territories/areas in all six WHO regions. The majority of cases were reported in America and Europe. The first case of Monkeypox has been confirmed in Iran on August 14, 2022 (28).

Attack rate

MPXV outbreaks are typically characterized by a high secondary attack rate (SAR) among close contacts (29).

The overall SAR of MPXV has been estimated to have a range of 0-11 percent in a systematic review and meta-analysis of scientific papers and grey documents published between 1972 and 2018 (30).

Case Fatality Rate

The CFR has been reported to be approximately 3-6 percent by the WHO. However, CFR is different between WA and CB clades. The CFR of WA clade viruses is about 3.6 percent (95% CI: 1.7-6.8), while the CFR of CB clade viruses is approximately 10.6 percent (95% CI: 8.4-13.3) (31).

Basic Reproduction number (R0)

R0 is described as the mean number of secondary cases of an infectious disease arising from a typical case in a completely susceptible population (32). For Human Monkeypox, the R0 has been reported to be between 1.10 and 2.40, suggesting that each MPXV-infected individual has the capability of infecting 1 or 2 susceptible individuals (33).

Table 1. Summary of morbidity and mortality measures for MPXV infections

No.	Measure	Clade (%)		Overall range (%)
		West African	Congo Basin	
1	SAR	-	-	0-11
2	R0	-	-	1.10-2.40
3	CFR	3.6 (95% CI: 1.7-6.8)	10.6 (95% CI: 8.4-13.3)	3-6

Risk factors

Unprotected contact with the skin, mucous membranes, lesions, the bodily fluids of an infected individual, and fomites have been identified as the important risk factors in the 2022 MPXV outbreak (34, 35). Moreover, activities including oral, anal, and vaginal sex, touching the genitals or the anus of an infected patient, hugging, massage, kissing, and prolonged face-to-face contact can transmit the virus (36).

Close contact with animals including markets that sell bush meats, wildlife parks, zoos, farms, and owning imported pets such as prairie dogs, and traveling to areas where MPXV is endemic have been considered to be risk factors in the previous MPXV outbreaks (37-39).

Given that MPXV infection can cause severe congenital infections, pregnancy loss, and maternal mortality and morbidity, pregnant women are considered a high-risk sub-group (40). In addition, the majority of MPXV cases during the current outbreak are men who had sex with men (41).

Incubation period and clinical signs

Generally, the incubation period of MPXV can range from 5 to 21 days (Mean=13) (42-44). However, it is speculated that the duration of the incubation period of MPXV may depend on the transmission route. For instance, based on the data from the 2003 MPXV outbreak in the US, it was observed that people who had been exposed to the virus by non-invasive routes like petting infected animals had undergone slower disease progression and longer incubation periods seen in the aforementioned cases in comparison with the cases who had complex exposures such as being bitten or scratched by an infected animal resulting in the breaking of the skin surface (45).

During the 2022 outbreak, in a study conducted on MPXV-confirmed cases in the Netherlands, the average incubation period was estimated to be 8.5 days with a 95 percent credible interval of 4.2-17.3 days by using a lognormal distribution (46). However, in the study conducted by Charniga et al. in which the data of probable and confirmed cases in the US was pooled with the data of Miura et al., the estimated average incubation period was 7.6 days with a 95 percent credible interval of 6.2-9.7, whereas the median incubation period was estimated to be 6.4 days (95%Crl: 5.1-7.9) (45). Moreover, in a study conducted on PCR-confirmed cases of Monkeypox in Italy, the average incubation period was estimated to be 9.1 days (95% Confidence Interval of the mean: 6.5-10.9; 5th and 95th percentiles of the distribution: 1-24) (47).

MPXV and variola virus (the causative agent of smallpox) lead to similar symptoms, but the symptoms of Monkeypox are more temperate, and initial symptoms are fever, headache, muscle pain, and fatigue. Lymphadenopathy is specific to Monkeypox, whereas Chickenpox and Smallpox do not cause any lymphadenopathy (48).

The MPXV infection is usually self-limited within 2 to 4 weeks without requiring treatment (49). However, this disease can occur severely in some patients, such as children, pregnant women, or people with immune deficiency (50). The infection period consists of two parts including the invasion period and the skin eruption period. The invasion period is between 0 and 5 days, characterized by fever, severe headache, chills, tiredness, asthenia, lymphadenopathy (inflammation of lymph nodes), back pain, and myalgia. Usually, 1 to 3 days after the appearance of fever, skin rash begins (skin eruption period). Skin rash usually first appears on the face and spreads quickly centrifugally all over the body. The face and limbs are affected by skin

complications more than other areas. The prevalence of clinical symptoms in the face, palms of hands and soles of feet, mucous membranes of the mouth, genital system, and conjunctiva and cornea have been reported in 95%, 75%, 70%, 30%, and 20% of cases, respectively (51). The appearance of Monkeypox lesions evolves from macules (smooth-based lesions) to papules (hard, slightly raised lesions), vesicles (clear fluid-filled lesions), pustules (yellow fluid-filled lesions), and crusts which dry up and fall. Each of these steps takes 1 to 2 days. The number of lesions varies from a few to several thousand (52, 53). Other symptoms reported in Monkeypox include secondary infections, respiratory distress, bronchopneumonia, sepsis, encephalitis, vision loss due to corneal infection, gastrointestinal involvement, vomiting, and diarrhea with dehydration (54, 55).

Diagnosis

Epidemiological and clinical characteristics are essential in the diagnosis of Monkeypox. A history of traveling to an endemic country in the past 21 days or contact with animals and infected patients is common in these patients. However, most cases since May 2022 have been reported in non-endemic countries and did not have any history of traveling to endemic countries.

The most common specimens for laboratory validation of MPXV are skin lesion samples, such as swabs from the surface, exudate, or roof of a lesion/lesions, or crusts. Nasopharyngeal swabs and saliva are also important diagnostic samples, whilst blood samples are usually not used for diagnostic purposes.

The diagnostic methods used for the confirmation of Monkeypox infection are:

1. Molecular examinations: Real-time or conventional PCR is used as a primary detection method to detect specific MPXV viral DNA sequences.

2. Serological tests: MPXV-specific IgM and IgG in serum are used to diagnose the disease in acute and convalescent periods, but this method should not be used independently for diagnosis. It is also important that there is an antigenic cross-reaction between MPXV and other orthopoxviruses.

3. Microscopic tests: Smallpox virus can be identified in a sample using an electron microscope, but this method cannot differentiate MPXV from smallpox virus. However, due to more economic costs, more complicated technical processes, and low sensitivity, it is not considered preferable to other methods.

4. Viral isolation: It is known as the standard diagnostic method of infection and has high sensitivity and specificity. However, due to the requirement for special facilities and special skills, this method is not used as a routine diagnostic method (56).

Prevention

Vaccination has been recommended as a post-exposure prophylactic measure for health workers at risk, clinical lab personnel, and others who might be at risk (57). Vaccines that were used during the small eradication campaign have been shown to protect MPXV and may improve the clinical manifestation of Monkeypox. The available vaccines are JYNNEOS™, a non-replicative live vaccine with circa 85 percent effectiveness against MPXV, and ACAM2000®, a replication-competent live vaccine. The adverse effects of ACAM2000® include major cutaneous reactions and eczema vaccinatum, progressive vaccinia in immunocompromised patients, fetal vaccinia which may cause the death of the fetus and the newborn, myocarditis, and post-vaccine encephalitis (58). Neither JYNNEOS™ nor ACAM2000® are currently approved for use during pregnancy (59).

For healthcare professionals, wearing protective equipment including N-95 masks, disposable gowns and gloves, and disposable headgear has been recommended (60).

The avoidance of having close, skin-to-skin contact with people who have a rash that resembles Monkeypox rash, the avoidance of having contact with objects and materials touched by an MPXV-infected patient, and washing hands with water and

soap or an alcohol-based hand sanitizer frequently and particularly before eating, touching one's face, and after using the bathroom are the recommended preventive measures by CDC (61).

Treatment

MPXV infections are usually mild and self-limiting. Therefore, in most cases, supportive treatment including antipyretics for pyrexia, analgesics for pain, or antibiotics to prevent secondary bacterial infections is often sufficient (62).

There are currently no treatments specifically for MPXV infections (63). However, it has been recommended that antivirals such as tecovirimat may be used in patients who are more likely to have severe manifestations like immunocompromised cases (64).

Conclusion

Human Monkeypox is a zoonotic disease and possesses considerable potential for spawning outbreaks in lands in which it is not endemic (1, 4). The outbreak of 2022 is thought to have a single origin with phylogenomic characterizations, suggesting that the causative agent is an MPXV belonging to clade 3, formerly designated as a WA clade (14). The majority of cases since May 2022 are reported in non-endemic countries without any history of traveling to endemic countries (56) with the majority being reported in the Americas and the European region (28). Despite the majority of the cases of the current outbreak being reported to be men who had sex with men, other subgroups are also susceptible to the disease (40, 41). Important risk factors identified in the 2022 outbreak are unprotected contact with the skin, mucous membranes, lesions, the bodily fluids of an infected individual, and fomites (34, 35). MPXV is often a self-limiting condition; however, severe outcomes such as death can happen (31). The prevention of MPXV infections relies on post-exposure prophylaxis for people at risk (57), wearing protective equipment for healthcare professionals (60), and the avoidance of close skin-to-skin contact, and contact with materials and objects touched by infected patients (61). Although there are no treatments for MPXV infections, currently (63), because most infections are mild and self-limiting, supportive treatment is usually sufficient (62). Tecovirimat may be used in severe cases such as immunocompromised patients (64). It is necessary to focus on research studies on the epidemiology of the disease and its prevention strategies.

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Conflict of interest

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Ethical Considerations

Not Applicable.

Code of Ethics

A code of ethics was not obtained.

Author Contribution

A. FD and H. A: Conceptualization, A. FD and P. A: Writing, H. A: Review. All authors have read and agreed to the submitted version of the manuscript.

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