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Review Article

Monkeypox (mpox) in animals and humans – A comprehensive review

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Abstract

Multi-nation 2022 monkeypox (mpox) outbreak has shaken the world, which was just recuperating in the aftermath of Covid-19. The outbreak occurred in various non-African regions along with the reports of human-to-human transmission. The cases have been occasionally reported in India, but the number is on rise in the country. The present manuscript has comprehensively reviewed the various aspects of monkeypox virus and its disease in humans and animals.

Keywords: Animal host, Human infection, Monkeypox, Orthopox

Highlights

- Mpox is an emerging zoonosis globally.
- 'One Health' concept should be strengthened to elucidate epidemiology and prevent future outbreaks.

INTRODUCTION

Multi-nation 2022 monkeypox outbreak has shaken the world, which was just recuperating in the aftermath of Covid-19. The outbreak occurred in various non-African regions along with the reports of human-to-human transmission. The cases have been occasionally reported in India, but the number is on rise in the country. The present manuscript has comprehensively reviewed the causative agent, epidemiology of monkeypox in animals and humans, modes of transmission, clinical signs, diagnosis, control and prevention of disease in humans. Recently, World Health Organization (WHO) has recommended use of "mpox" name instead of monkeypox for the disease to prevent any social stigmas associated with name 'monkeypox' (https://www.who.int/news/item/28-11-2022-who-recommends-new-name-for-monkeypox-disease), therefore in this manuscript, 'mpox' name has been used in place of monkeypox.

The virus characteristics

Mpox is a viral disease caused by a poxvirus, which are large viruses of size 200-250 nm with double helix DNA genome and lipoprotein membrane envelope (Condit *et al*., 2006). Poxviruses belong to *Poxviridae* family, an ancient virus family reported in vertebrates and non-vertebrates (Barrett and McFadden, 2008). *Poxviridae* has two subfamilies: *Chordopoxvirinae* and *Entomopoxvirinae*; *Chordopoxvirinae* includes poxviruses of vertebrates, and *Entomopoxvirinae* has poxviruses of insects (Kabuga and El Zowalaty, 2019). *Chordopoxvirinae* subfamily has ten genera and numerous unclassified species. Monkeypox virus (MPXV) belongs to *Orthopox* genus of *Chordopoxvirinae* subfamily. The other important species of *Orthopox* genus are variola major virus (responsible for smallpox infections of human in the past), variola minor or vaccinia virus (smallpox vaccine strain), cowpox virus, camelpox virus, raccoon pox virus, skunk pox virus among others (Chen *et al.*, 2022). Orthopoxviruses are supposed to be descended from rodent-borne ancestors with some orthopoxviruses such as mpox and cowpox viruses retaining rodents as reservoir hosts (Xiang and White, 2022). Orthopoxviruses are genetically and antigenically closely related, and thus infection with one species of orthopoxvirus provides cross-protection to other species of the genus (Xiang and White, 2022).

Poxviruses have linear double stranded genome having about ~200 kilobases comprising ~200 genes. About half of the genes are conserved and are essential for viral replication. The genome of poxviruses has all the genes for viral replication, transcription, assembly and exit, but it needs host ribosomes to translate mRNA (Hraib *et al.*, 2022). The conserved genes are in the central region of genome. The non-conserved genes (accessory genes) are located in inverted terminal repeats (ITRs) at ends which play important roles in virus-host interactions; this provides host specificity to poxviruses (Senkevich *et al.*, 2021).

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Mpox outbreaks: History to present

In 1958, mpox was isolated for the first time from nonfatal outbreaks among cynomolgus macaques (*Macaca fascicularis)* in the University of Copenhagen, Denmark imported from Singapore. The macaques had developed vesiculopapular rash over the body (Parker and Buller, 2013). In the subsequent years, similar outbreaks among captive monkeys were reported in USA (1959 and 1962) and Netherlands (1964) (Magnus *et al.*, 1959; Cho and Wenner, 1973; Parker and Buller, 2013). The first isolation from humans was in 1970 from a 9 months old baby in Democratic Republic of Congo (DRC) during a smallpox surveillance programme (Brown and Leggat, 2016). Subsequently, cases in other African countries (1 in Liberia, 1 in Sierra Leone, 1 in Ivory Coast and 2 in Nigeria) were reported. From DRC, human mpox cases have been reported since 1970 (Bunge *et al.*, 2022). Cameroon reported its first case in 1979 (2 in number), Central African Region in 1984 and Gabon in 1987 (Durski *et al.*, 2018). From 1970 to the end of the 20th century, globally <1000 laboratory confirmed human mpox cases were reported, mostly from DRC and the rest from other seven African countries of central and west Africa (Xiang and White, 2022). In the 21st century, the number of cases in DRC increased dramatically along with the geographical expansion globally (Sklenovská and van Ranst, 2018). Subsequently, Republic of Congo reported its first human case in 2003 (Learned *et al.*, 2005) and South Sudan in 2005 (Formenty *et al.*, 2010). In countries viz., Central African Republic, Sierra Leone, Liberia, Cameroon and Nigeria, human mpox re-emerged with a gap of 3 or 4 decades (Xiang and White, 2022). In Nigeria, it occurred in 2017 after a gap of 39 years, and since then, the cases have been reported in the country (Kabuga and El Zowalaty, 2019).

The first emergence of human mpox outside of Africa occurred in USA in 2003 and was attributed to the import of wild Gambian pouched rats (*Cricetomys gambianus*) from Ghana (West African country) to United States. The infection spilled from the rodents to the prairie dogs in a pet distribution center and further to the owners of prairie dogs (Brown and Leggat, 2016). Forty-seven cases from six states were reported. Interestingly, mpox was never reported in Ghana beforehand (https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html). In Nigeria in 2017, a major outbreak of human mpox occurred, and from September 2018 to November 2021, sporadic human mpox infections were reported in non-African countries and all were associated with travel to Nigeria (in Israel in September 2018; in UK in September 2018, December 2019 and May 2021; in Singapore in May 2019; in USA July 2021, November 2021) (Bonilla-Aldana and Rodriguez-Morales, 2022).

In May 2022, multiple cases of mpox were identified in several non-endemic countries with the first case identified in UK on 7 May 2022. It was followed by detection of two more cases in the country on 14 May 2022. Although the first victim (related to the clinical case of 7 May 2022) travelled from Nigeria, the cases of 14 May neither have any such history nor any contact with an infected person (Mukherjee *et al.*, 2022). The definite theory of this outbreak has yet to be discovered. Since May 2022, the cases of mpox have been pouring from countries known to be non-endemic for mpox. Many of these cases are among homosexual males, probably indicating the transmission through direct contact with pox lesions of body (Hraib *et al.*, 2022). The present outbreak has witnessed simultaneous occurrence of mpox cases in endemic and non-endemic countries has been a first. This led to a declaration of mpox as Public Health Emergency of International Concern by the World Health Organization (WHO) on 23 July 2022. (https://www.who.int/europe/news/item/23-07-2022-who-director-general-declares-the-ongoing-monkeypox-outbreak-a-public-health-event-of-international-concern).

In the present outbreak, till 23 December 2022, globally 83,497 confirmed cases from 110 countries were reported. There have been 72 deaths with case fatality ratio of 0.086%. The 10 most affected countries are USA (n=29,542), Brazil (n=10,398), Spain (n=7,496), France (n=4,110), Colombia (n=3,971), United Kingdom (n=3,730), Germany (n=3,676), Peru (n=3,629), Mexico (n=3,509) and Canada (n=1,459) having 85.7% of total number of cases globally.

In the African region, during this outbreak, the highest number of mpox cases were reported from Nigeria (n=753), followed by DRC (n=277) and Ghana (n=116). Other African countries have a smaller number of cases (WHO, 2022).

In South East Asia region, India reported the first case on 14 July 2022. Till 23 December 2022, country has a toll of 23 mpox cases (WHO, 2022). The first reported cases of Kerala state had a history of international travel to United Arab Emirates, while the cases reported from New Delhi didn't reflect any such history (Sah *et al.*, 2022).

Clades of MPXV

MPXV has two distinct clades, *viz.*, West African and Congo Basin (Central Africa) which differ genetically and have distinct epidemiological and clinical features. The two clades differ by about 5% genotypically. Central African has higher virulence and consequently, a higher case fatality rate (~10%) than

West African clade (1-3%). The present outbreak is of West African clade (Chakraborty *et al.*, 2022).

Recently, to prevent any cultural and social offense associated with existing names of clades, WHO has renamed the clades as clade I and clade II; Congo Basin clade is clade I and West African clade is clade II, which is further divided into clade IIa and clade IIb. The present outbreak strains have been grouped as clade IIb (https://www.cdc.gov/poxvirus/monkeypox/about/index.html). As per a recent study, lineage B.1 of clade IIb is the most circulating lineage in 2022 outbreak (Chakraborty *et al.*, 2022).

Life cycle of Poxviruses in the host

Poxviruses can infect all mammalian cell types, and the infectivity among different species is not mediated through receptors of cell entry. Rather, it depends upon the mechanisms to circumvent the host antiviral responses (Xiang and White, 2022). Similarly, MPXV can also infect wide range of cells. However, based on histological findings of Zaucha *et al*. (2001) on *Macaca fascicularis*, lymphoid tissues are the principal targets of MPXV (Zaucha *et al.*, 2001). In the study, MPXV antigens were detected in salivary epithelium, follicles, and sebaceous tissues of lips along with many other tissues. Osorio *et al*. (2009) detected MPXV antigens in ovaries, brain, heart, kidney, liver, pancreas and lungs in immunodeficient mice (Osorio *et al.*, 2009).

In their life cycle, Poxvirus produces two types of distinct stages *viz*., intracellular mature virion and extracellular enveloped virus. Mature virions have a single membrane with about 20 proteins in the membrane and are released by cell lysis. Enveloped virions are mature virions with a lipid membrane wrapped around them (having eight unique proteins and derived from Golgi apparatus or endosomes) and released by exocytosis. Both mature virions and enveloped virions are infectious in nature. Within the cell, MPXV replicates in the cytoplasm (Gong *et al.*, 2022).

Host range

Unlike smallpox virus which infects only humans, MPXV is reported from various mammalian species especially wild rodents (Gong *et al*., 2022). Notably, apart from the 1958 outbreak in Danish laboratory, in natural conditions the isolation of virus has been successful in only two instances - from *Funisciurus anerythrus* (rope squirrel) in DRC in 1985 (Khodakevich *et al*., 1986) and *Cercocebus atys* (sooty mangabey monkey) at Tai National Park of Cote d'Ivoire in 2012 (Radonić *et al.*, 2014). Therefore, the identified host range of MPXV has been on the basis of serological tests and laboratory infections (Parker and Buller, 2013). Seropositivity has been reported in *Funisciurus* (rope squirrels), *Heliosciurus* (sun squirrels), *Oenomys* (rufousnosed rat), *Graphiurus* (dormice) and *Cricetomys* (African giant pouched rats) (Parker and Buller, 2013). Among nonhuman primates of Africa region, crowned monkey (*Cercopithecus pogonias*), white-nosed monkeys (*Cercopithecus petaurista*), western colobus monkey (*Colobus badius*) had anti-MPXV antibodies (Breman *et al*., 1977; Parker and Buller, 2013). Laboratory infections have been successfully established in rabbits, opossums, prairie dogs and ground squirrels (Hutson and Damon, 2010). The outbreaks of MPXV in chimpanzees of various wild sanctuaries of Cameroon (2014 and 2016) and Cote d'Ivoire were reported (Guagliardo *et al.*, 2020; Patrono *et al.*, 2020). More than 40 animal species have been found to be infected with MPXV naturally or experimentally (Parker and Buller, 2013).

Among domestic animals in DRC, infections have been reported in domestic pig (*Sus scrofula*) (Hutin *et al.*, 2001) and Italian Greyhound (Seang *et al.*, 2022). Of domestic pigs, serum samples were positive for mpox virus neutralization test during a human outbreak investigation conducted in DRC during 1996-1997 (Hutin *et al.*, 2001). The detection in Italian Greyhound was based on DNA detection in June 2022; the dog contacted the infection from MPXV positive owner and developed skin lesions after 12 days of the owner's symptoms (Seang *et al.*, 2022).

Host range determination among Orthopoxviruses

Among Orthopoxviruses, MPXV and cowpoxvirus have broad host range (Hutson *et al.*, 2007), while species such as variola virus and camelpox have only one host (Xiang and White, 2022). The host range determination in OPXV has been highly influenced by the presence of accessory non-conserved regions located at each end of genome owing to their role in virus-host interactions (Senkevich *et al.*, 2021). Evolutionary, the OPXV have descended from a common ancestor with the lineage-specific loss of accessory genes. The ancestral virus is believed to be full of accessory genes and has a broad host range (Hendrickson *et al.*, 2010). For reference, among OPXV, smallpox virus has the smallest genome and only one host species (Xiang and White, 2022). Among these accessory genes, various genes viz., E3L, K3L, K1L, C7L, CP77 and C16L have been identified which affect the host range by interacting with host antiviral proteins (Xiang and White, 2022). E3L and K3L are associated with Protein Kinase R, while K1L, C7L and CP77 (independently) are linked to Mammalian Sterile Alpha Motif Domain-containing 9 (SAMD9) and its paralog SAMD9L. C16L inhibits human Zinc-finger

(Xiang and White, 2022).

Poxviruses are double stranded viruses, and mutation rates in their genome are pretty low, i.e. 2×10^{-6}–1×10^{-5} nucleotide substitution/site/year, which is much lower than SARS-CoV (SARS-CoV has ssRNA genome with ~6.58×10^{-3} substitutions per site per year). It equates to around 1-2 nucleotides change in the genome in a year. Further, their DNA polymerase has 3'-5' exonuclease activity as proofreader (Xiang and White, 2022). However, the genome of poxviruses has many other happenings. Gene loss is one of the important evolutionary characteristics of poxviruses. It has been seen that loss of accessory genes has been attributed to a narrower host range, while full set of accessory genes leads to a wider host range. In West African strains of mpox virus, there has been a loss of 17% of accessory genes from 2008-2007 with the concurrent expansion in human-to-human transmission (Kugelman *et al.*, 2014). Further, gene recombination due to large sizes of poxviruses may help in acquiring of host range genes. Moreover, poxviruses can make copies of accessory genes and may result in change in host range (Xiang and White, 2022). It indicates the potential of mpox virus to establish in new hosts including animals and humans.

Genomic basis of virulence differences among West African and Central African strains

Among West African and Central African strains, Central African strains have higher virulence than West African strains. The virulence differences have been associated with the few gene orthologs, viz. BR-203, BR-209 and COP-C3L (Mukherjee *et al*., 2022). BR-203 encodes a protein with 221 amino acids, which is full length in Central African strains but shorter (51 amino acids) in West African strains. The full-length protein with its C-terminal sequence helps in viral propagation in the host cell by avoiding apoptosis of infected lymphocytes. BR-209 is an interleukin-1β (IL-1β) binding protein and, therefore, prevents binding of IL-1β to IL-1 receptors. IL-1 is responsible for inflammatory response to infection by release of tumor necrosis factor and other cytokines. There are differences in amino acids fragments of BR-209 in both clades, although the significance of differences in the virulence of clades is yet to be ascertained (Mukherjee *et al*., 2022). COP-C3L is a complement control protein that inhibits the host complement system's activation. The gene is absent in West African strains (Mukherjee *et al*., 2022).

Transmission

Animals to animals: The modes of transmission of MPXV among animals are not clear. Close contact with the infected animals is probably the most important route as was evident during 2003 outbreak of USA (Guarner *et al.*, 2004). Before the outbreak, about 500 prairie dogs were housed with infected small mammals followed by infection and amplification in prairie dogs. There has been detection of virus in the lungs of prairie dogs indicating the possible transmission through close contact with respiratory droplets (Guarner *et al.*, 2004).

Animals to humans: MPX in humans is primarily a zoonotic disease and is transmitted from animals to humans through direct and indirect contact with infected animals, their body excretions, lesions and respiratory secretions (Martín-Delgado *et al.*, 2022). The transmission by bites of infected animals and eating improperly cooked meat of infected animals is reported (Ellis *et al.*, 2012; Ihekweazu *et al.*, 2020). The majority of infections in the previous outbreaks in the African region are associated with exposure to animals (Martín-Delgado *et al*., 2022).

Human to human: In the current outbreak, a large number of cases are among homosexual men indicating the transmission among humans through infected semen as MPXV has been detected in semen (Lapa *et al.*, 2022). Transmission may also be due to long-term direct close contact with respiratory droplets, secretions and excretions of infected individuals (The vaccinia virus used in smallpox vaccination is also known to be transmitted through sexual contact) (Hraib *et al*., 2022). The congenital infection of foetus through placenta is also possible (Dashraath *et al.*, 2022). MPXV has been detected in faecal samples of humans also (Peiro-Mestres *et al.*, 2022); however, replication-competent virus has not been isolated from faecal samples (https://www.cdc.gov/poxvirus/monkeypox/about/science-behind-transmission.html). Nosocomial transmission of MPX among healthcare workers through needle injury has occurred in Brazil (Carvalho *et al.*, 2022). In an outbreak in the Republic of Congo involving 11 persons, six sequential human-to-human transmissions were reported (Learned *et al.*, 2005).

Smallpox vaccination is believed to have the protective effects against mpox as there is cross-reaction among species of Orthopoxvirus genus. For reference, smallpox was declared 'eradicated' in 1980 and smallpox vaccinations were stopped globally. Incidentally, the number of mpox cases in Africa increased dramatically after 2000. In individuals non-vaccinated with smallpox vaccine, the secondary attack rate of mpox infection is estimated to be 9.3% (Damon, 2011).

Symptoms

In animals: In natural conditions, nonhuman primates have been found to be very susceptible to MPXV. The disease is manifested like humans involving

rash over the body followed by scab formation and scab falloff. Mortality in various nonhuman primates is also reported. Prairie dogs involved in the 2003 outbreak in the USA were also susceptible and acted as amplifying hosts during that outbreak. Therefore, prairie dogs are currently used as laboratory animal models for MPXV studies (Hutson *et al.*, 2011). The wild rodent reservoirs are believed to not to manifest any symptoms of MPXV (Parker and Buller, 2013).

In humans: Human mpox disease exhibit similar, but milder, symptoms as that of smallpox infection. The incubation period ranges from 5 days to 3 weeks followed by prodromal stage. During prodromal stage (lasting for 0-2 days), a person has high fever, fatigue, headache and lymphadenopathy. Lymphadenopathy is a distinguishing feature of mpox from smallpox and chickenpox (McCollum and Damon, 2014). Lymphadenopathy is commonly seen in neck, groin and submandibular areas. Prodromal phase is followed by rash phase (lasting for 7-21 days). Rash usually develops within 1-5 days after fever and involves face, trunk, palms, soles and oral mucosa but may involve other areas such as genitalia and conjunctiva. Rash begins as the macules and progresses to papular, vesicular and pustular lesions, followed by crusting and falling off. Rash lesions are infectious in nature, and patient is contagious when rash appears. Secondary bacterial infections may lead to complications such as sepsis, gastroenteritis, bronchopneumonia, encephalitis, keratitis and dehydration due to vomiting and diarrhoea. Symptoms may last from 2-5 weeks. The most notable disease for differential diagnosis is chickenpox, which has clinically similar symptoms. Others to differentiate are Rickettsial diseases, Staphylococcus infections and syphilis (Hraib *et al*., 2022). Although mpox is a self-limiting disease, death may happen especially in immune-compromised individuals such as HIV patients, children and cases with secondary bacterial infections (Yinka-Ogunleye *et al.*, 2019). Smallpox vaccination has a major impact on the clinical severity of human mpox as evident in many epidemiological studies. 1980-1990 studies observed the mpox manifestations to be less severe with lower mortality in smallpox vaccinated group (Hraib *et al*., 2022).

Detection and diagnosis

Globally, detection and diagnosis of mpox have been mainly confirmed through quantitative polymerase chain reaction. Widely used targets are C3L, TNFR and E9L (Mukherjee *et al*., 2022). C3L and TNFR are used in differentiation of Central African and West African strains (Mukherjee *et al*., 2022). Because of technical difficulties and cost prohibitions, the application is not possible in resource limited countries. Serological detection in humans has been mainly employed through Orthopox genus-based ELISA; thus, their interpretation requires careful consideration of epidemiological settings where employed. IgM-based ELISA along with clinical case pictures and epidemiological data may help in case of outbreak settings in resource limited countries (Hraib *et al*., 2022). Other tests such as virus neutralization tests, immunohistochemistry and electron microscopy have been used in many research investigations. As high virus load is found in the skin samples and a human becomes infectious on rash development, skin samples are routinely used in viral DNA studies.

Prevention and control

As multiple rodent species are considered as the reservoirs of mpox and transmission have been documented through contact with these animals, mpox is a suitable candidate to be considered as a zoonosis. Further, human- to-human transmission has been documented in the current outbreak (Martín-Delgado *et al*., 2022). In this regard, the prevention and control of disease necessitates the inter-sectoral collaboration between human medicine and veterinary medicine under the umbrella of 'One Health' approach.

As, in the past, the major transmission episodes have occurred through contact with animals, the contact with the animal reservoirs, especially small mammals, should be taken seriously. The awareness among endemic areas and occupational groups may pave the way in this regard. Surveillance studies in domestic animals for determination of host range should be conducted.

In humans, vaccination with smallpox vaccines has been prescribed in the USA as smallpox vaccination is known to provide 85% protection against mpox (Fine *et al.*, 1988). USA has approved two smallpox vaccines, viz. JYNNEOS and ACAM2000 for mpox prevention. JYNNEOS is a replication impaired odified vaccinia Ankara stain used mainly in the outbreak (Xiang and White, 2022). The antiviral drugs used in the therapeutic applications in mpox patients are cidofovir, brincidofovir and tecovirimat (Mukherjee *et al*., 2022). Cidofovir and brincidofovir inhibit DNA synthesis by inhibiting DNA polymerase 3'-5' activity (Siegrist and Sassine, 2022). Tecovirimat inhibits F13L protein required for exocytosis of enveloped proteins (Siegrist and Sassine, 2022). Also, vaccinia immunoglobulins are being used in the USA to treat mpox patients (Rizk *et al.*, 2022).

The emergence of new or previously occurring diseases has seen a substantial rise in recent decades. To tackle such situations, the surveillance of diseases is of paramount importance especially in developing

countries like India where the resources are limited. Mpox is not an exception. The strengthening of infrastructure and creation of facilities for diagnosis will pave the way for the control of endemic as well as emerging diseases. The awareness of stakeholders on emerging diseases will further strengthen these aims and should be prioritized. The awareness among people regarding clinical signs and modes of transmission will help the public to make sound decisions. All these involve multiple sectors that should coordinate for the effective control of mpox to set an example under 'One Health' umbrella.

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