Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

RESURGENCE OF MONKEYPOX: TRANSMISSION, CLINICAL FEATURES WITH EMPHASIS ON COUNTERMEASURES AND TREATMENT

Fathimath Ina Shareef[1], Mariyam Luba Abdulla[1], Aminath Efa Ibrahim[1], Kannan Subbaram[1]*

1. School of Medicine, The Maldives National University, Male', Maldives.

ARTICLE INFO

Received:
07 Sep 2022
Received in revised form:
14 Dec 2022
Accepted:
16 Dec 2022
Available online:
28 Dec 2022

Keywords: Monkeypox, Outbreak, Modes of transmission, Clinical features, Vaccines, Antiviral drugs

ABSTRACT

Monkeypox virus is a DNA virus classified under the family Poxviridae and the genus Orthopoxvirus. Monkeypox is usually restricted to the Central and Western zones of the African continent. In 2022, many monkeypox cases were reported from non-endemic countries in North America, Europe, Asia, and Australasia. On 23rd July 2022, the Chief of the World Health Organization (WHO) declared the 2022 monkeypox epidemic as a public health emergency of international concern (PHEIC). It announced recommendations to curb the transmission of the disease around the globe. Monkeypox is a zoonotic disease, but human-to-human transmission can occur through direct or indirect contact with body fluids, skin lesions, and respiratory droplets. The recent outbreak was noticed commonly in homosexual men. A pregnant mother infected with monkeypox resulted in congenital monkeypox, resulting in miscarriage. Clinical manifestation of monkeypox lesions follows four stages: macules, papules, vesicles, and pustules, followed by crusts/scabs. There have been some cases of complications like septicemia, bronchopneumonia, ocular involvement, and central nervous system manifestations. There are effective antiviral agents like tecovirimat (TPOXX), cidofovir, and brincidofovir, which are all available for treatment. The vaccines which are administered for monkeypox are LC16, MVA-BN (JYNNEOS in the United States of America), and ACAM2000.

To Cite This Article: Shareef FI, Abdulla ML, Ibrahim AE, Subbaram K. Resurgence of Monkeypox: Transmission, Clinical Features with Emphasis on Countermeasures and Treatment. Pharmacophore. 2022;13(6):42-9. https://doi.org/10.51847/4ubxVhhdMa

Introduction

After the eradication of smallpox in West Africa and Central Africa, monkeypox (MPX) infections in humans were discovered in these regions in the early 1970s [1]. Prior to this, it was first found in captive monkeys in 1958. While there is no primary reservoir for the virus, it can be found in various types of rodents, shrews, and small mammals [2]. This initial case was found in Bukenda, the Democratic Republic of Congo, in a 9-month-old baby with a vesicular eruption. Between 1970-1971, cases were found in Ivory Coast, Liberia, Sierra Leone, as well as Nigeria.

The most cases have been reported from the Democratic Republic of Congo with 6000 cases, and Nigeria with 3000 cases. Since September 2017, there have been many monkeypox cases reported in Nigeria. Before this, Nigeria's last confirmed case was in 1978 [3].

Outside of Africa, an outbreak occurred in May 2003 in the USA in the Midwest, where 72 cases were found in 2 months, 42 of which were confirmed cases. It was believed to have been passed on from prairie dogs that were with an animal distributor to whom several African rodents had been imported from Ghana. A ban on importing and breeding African rodents was then put into place, as genomic analysis showed identical sequences from a person, a prairie dog, and two rodents [4].

The monkeypox virus (MPXV) is classified under the genus Orthopoxvirus of the subfamily Chordopoxvirinae and the family Poxviridae. It is closely related to other Orthopoxviruses, mainly variola, which causes smallpox. Both diseases show similar symptoms and are difficult to distinguish through laboratory tests. The main structural elements in the monkeypox virus are the core, lateral bodies, outer membrane, and envelope [5]. The core contains viral DNA and proteins, and lateral bodies are

Corresponding Author: Kannan Subbaram; School of Medicine, The Maldives National University, Male', Maldives. E-mail: Kannan.subbaram@mnu.edu.mv.

on either side of the core **(Figure 1)**. They are enclosed within an outer membrane with a ridged surface. The virions are enveloped by a lipoprotein membrane, which includes polypeptides such as orthodox hemagglutinin.

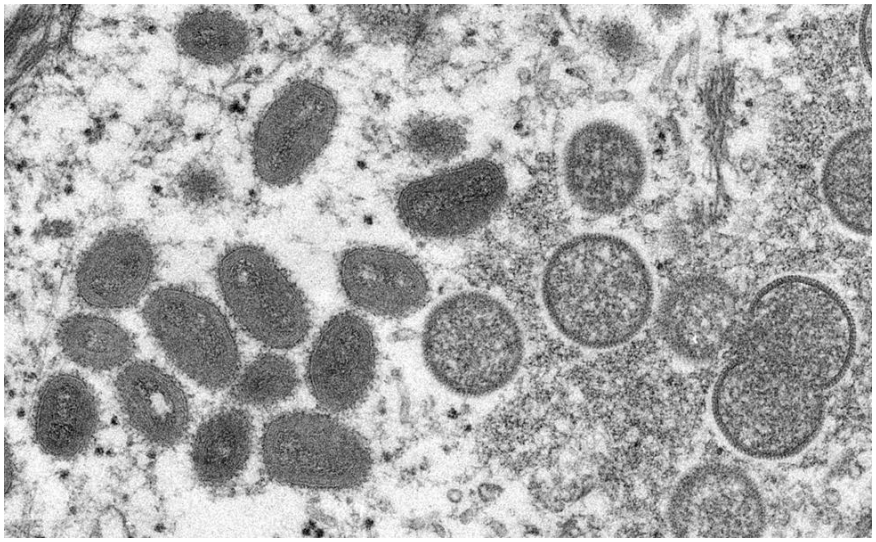

Figure 1. Electron micrograph of monkeypox virus particles – CDC

Monkeypox Epidemic in 2022

In early May 2022, along with the usual reports of cases of Monkeypox from endemic countries, cases started being reported from various geographical areas which were not endemic to it [1] **(Figure 2)**. Most of such confirmed cases had a travel history to countries in Europe and North America. Men who have sex with men were mainly affected, and most cases were identified through primary and secondary healthcare facilities during sexual health services and other health services. Although it is not a sexually transmitted disease, this raises the possibility of transmission during intercourse due to direct contact, as the rash often involves the anogenital region.

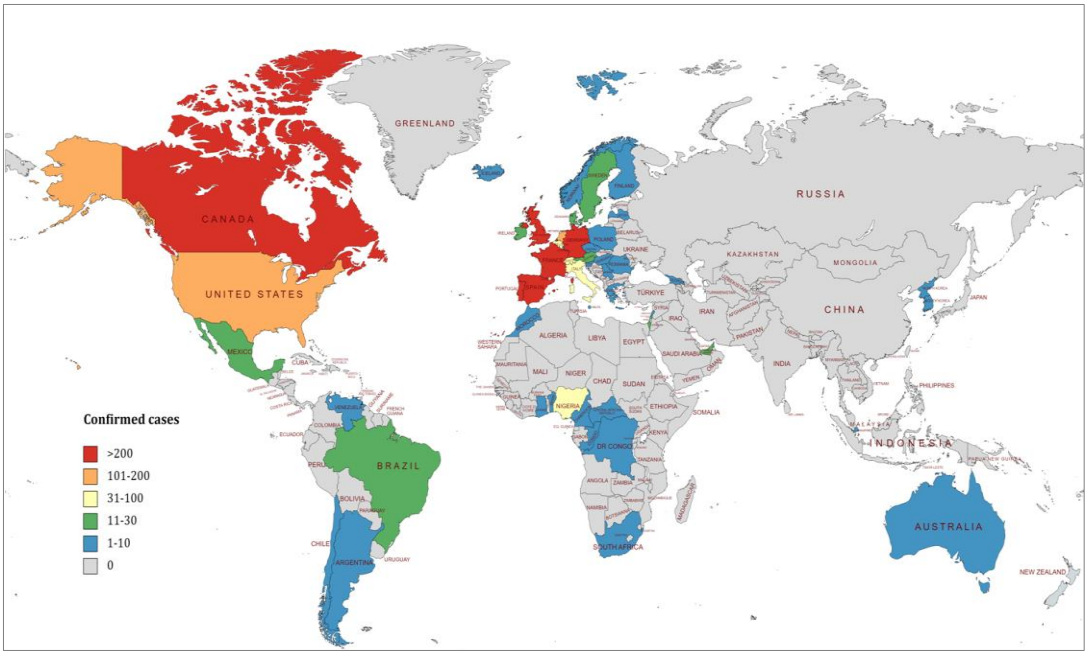

Figure 2. Countries affected by monkeypox virus in the current epidemic - adapted from WHO

According to the latest update by WHO on 27th June 2022, there were a total of 3413 confirmed cases and one death from 50 different countries. The European region was the most severely affected, with 86% of cases, followed by the Region of Americas (11%), African region (2%), Eastern Mediterranean Region (<1%), and Western Pacific Region (<1%). The death was reported in Nigeria [6].

The sudden spread of Monkeypox to non-endemic areas is peculiar, raising several questions about why it is spreading now. One proposed theory is that the lockdowns enforced due to the COVID-19 pandemic may have controlled the spread. As travel

bans were lifted, international travel to endemic areas may have facilitated the spread to non-endemic areas [7]. Another contributing factor could be diminishing herd immunity to smallpox as vaccination rates fall.

Monkeypox Variants

There are two distinct clades of the monkeypox virus; the Congo Basin and the West African clade. The Congo Basin is centered in the Democratic Republic of Congo, while the West African clade lies mostly between the Equator and the South of the Sahara [8]. The former Congo Basin (Central African) clade is now referred to as Clade one (I), and the former West African clade is referred to as Clade two (II), which consists of two subclades; Clade IIa and Clade IIb. Clade I is known to cause more severe diseases and is more contagious. There is ongoing research to identify the genes responsible for this. One of the differences between Clade I and II is the N2R, and N3R deletion, responsible for human-to-human transmission, observed in Clade I. Clade IIb is the variant largely circulating in the 2022 global outbreak [9].

Modes of Transmission

Although the exact mode of transmission is not established, based on other poxviruses, it is suggested that animal-to-human transmission may be from infected animals, such as non-human primates, terrestrial rodents, antelope, gazelle, or tree squirrel, biting or scratching humans. It may also be transmitted through humans eating uncooked, infected meat [10].

Human-to-human transmission may occur through respiratory droplets, direct or indirect contact with bodily fluids, skin lesions, or recently contaminated surfaces or material. The respiratory droplets are more than 5mm, making them heavy. Hence, it requires close contact for the transmission of these virus particles [8]. The virus can cross the placenta, resulting in vertical transmission. They may result in miscarriages in the first trimester. Newborns may also be infected during delivery or soon after birth [11]. Many cases have been reported in men who have sex with men, which suggests direct contact with lesions during sexual contact.

Clinical Features

The incubation period lasts for 6 to 13 days. The clinical manifestation of monkeypox appears in two stages [12]. In the first stage, which lasts up to 5 days, the patient may suffer from fever, intense headache, backache, myalgia, severe asthenia, and cervical, axillary, and inguinal lymphadenopathy. The second stage starts one to three days after the onset of fever, in which exanthema and a typical poxviral lesion develop [13] **(Figure 3)**. The lesions seen in monkeypox are firm or rubbery, well-circumscribed, deep-seated, and often develop umbilication, which resembles a dot on the top of the lesion [14]. The clinical presentation in the ongoing epidemic is atypical and unusual, characterized by anogenital lesions and rashes that relatively spare the face and extremities. In previous outbreaks, itchy and painful lesions are reported mostly in the face, limbs, and oral mucosa [15]. The lesions progress through four stages, macular, papular, vesicular, and pustular, before it starts scabbing over and desquamation occurs [16] **(Figure 4)**. This process is self-limiting within 4-6 weeks. Only around 2% of the cases need to be hospitalized [17].

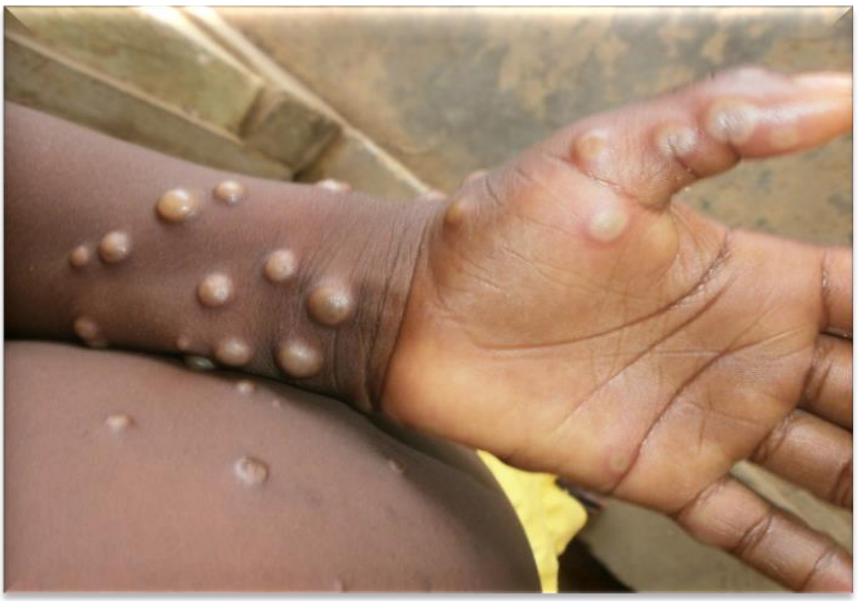

Figure 3. Skin lesions of monkeypox – courtesy from WHO

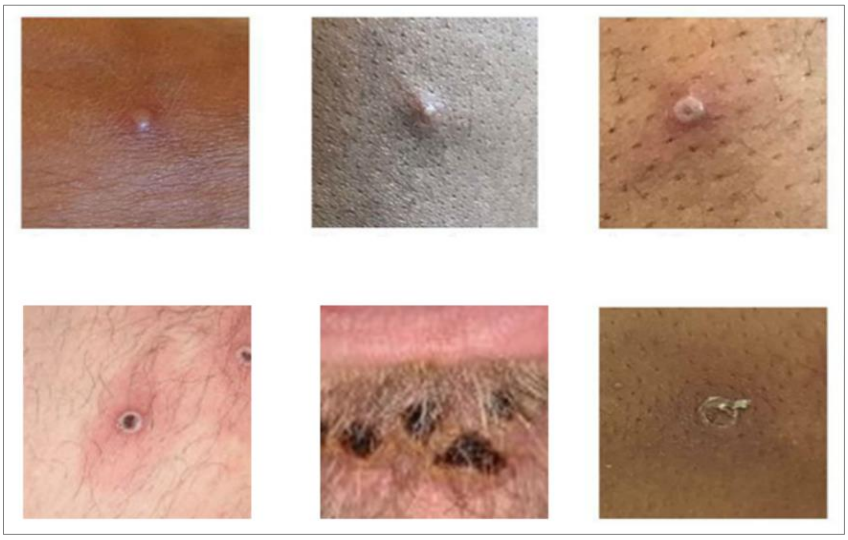

Figure 4. Stages of monkeypox rashes - UK Health Security Agency

Complications

Complications may include secondary infections due to bacterial colonization of the open lesions; septicemia, from a systemic spread of secondary bacteria; bronchopneumonia, as the frequent entry route is respiratory [18]. Around 20% of patients were also affected by conjunctivitis and corneal lesions, which may lead to scarring and blindness [19]. CNS manifestations of monkeypox are most commonly a generalized or frontal headache associated with asthenia, myalgia, and neuralgia. Although rarely, monkeypox can also lead to encephalitis, along with seizures. Three such cases have been reported during the current outbreak [20].

Treatment Options Available for Monkeypox

Currently, no treatment is specifically approved for the monkeypox virus. However, antiviral drugs that have been developed for the treatment of smallpox have been licensed to be used against monkeypox as well [21, 22]. Tecovirimat, TPOXX, is an antiviral that acts by inhibiting the activity of the orthopoxvirus VP37 protein, which blocks its interaction with the cellular Rab9 GTPase and TIP47, preventing the formation of virions required for the dissemination of the virus [23]. Tecovirimat is approved to be used in adults and pediatric populations weighing a minimum of 3 kg, although TPOXX injection is contraindicated in patients with severe renal impairment, with a creatinine clearance below 30 mL/min [24]. The most common adverse reactions reported with TPOXX capsules were headaches, nausea, abdominal pain, and vomiting, while those administered with TPOXX injection reported administration site reactions and headaches [25]. The European Medicines Agency first licensed TPOXX for the use of monkeypox in January 2022 [26]. As data is unavailable on the effectiveness of Tecovirimat in patients with monkeypox, the Centers for Disease Control and Prevention allows the use of stockpiled tecovirimat to treat monkeypox during an outbreak under the New Investigational Drug protocol.

Cidofovir is an antiviral medication used to treat cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. CDC currently holds an expanded protocol that allows the use of stockpiled cidofovir for treating orthopoxviruses, including the monkeypox virus, in an outbreak [27].

Brincidofovir is a lipid conjugate of cidofovir, which is designed to resemble a natural lipid, resulting in endogenous uptake by the cells. Endogenous Brincidofovir is cleaved to produce phosphorylated cidofovir to yield the active antiviral. This is incorporated into multiplying DNA chains, resulting in a reduction in the rate of DNA synthesis. Brincidofovir is approved by the FDA for use in patients with smallpox. Although data on the effectiveness against monkeypox in humans has not been demonstrated, it is shown to be effective against orthopoxviruses in vitro and animal studies. CDC is developing an EA-IND to facilitate this drug's use for monkeypox treatment [28].

Treatment Using Immunoglobulins

FDA has approved two preparations of vaccinia immunoglobulins; VIGIV Cangene and VIGIV Dynport [29]. It is prepared with purified IgG antibodies extracted from the plasma of healthy individuals that have been immunized with a live vaccinia virus, using an anion-exchange column chromatography method. Minimal amounts of IgA can also be found in the solution. They are followed by sterilization and stabilization. Vaccinia immunoglobulins are used to counteract the adverse effects, such as progressive vaccinia seen after smallpox vaccination or in those who are contraindicated to get the smallpox vaccinations before or after exposure. The efficacy data for use against smallpox is limited, but small studies have shown favorable pharmacokinetic profiles [30]. They have been shown to cause anaphylactic reactions and some local stiffness, nausea & headaches. This is contraindicated for those with vaccinia keratitis due to the risk of corneal scarring, a history of systemic reactions to any parenteral immunoglobulin preparations, and those with a history of IgA hypersensitivity.

Vaccines

Vaccination is one of the public health measures currently being implemented against monkeypox [31]. Three vaccines have been approved for use against monkeypox- LC16, MVA-BN (JYNNEOS in the United States of America) & ACAM2000. The former two are newer generations of the smallpox vaccine that have been developed to be safer & are also believed to be efficacious against monkeypox. Unfortunately, data on the efficacy of these vaccines are limited, especially in the context of the current outbreak. Vaccines are not recommended for the whole population but for those at risk, with priority given to those at higher risk of infection, determined through thorough case investigation & contact tracing [32].

High-risk groups are recommended to have primary preventive (or pre-exposure) vaccination include, but are not limited to, men who have sex with men, individuals with multiple sexual partners, research laboratory personnel that handle cultures or animals that can cause infection in humans, and designated response team members [33]. Post-exposure preventive vaccination is recommended for those with high or medium exposure risk. High risk for exposure is defined as direct exposure of the skin or mucous membranes to skin or respiratory secretions, body fluids, or potentially infectious material of a person with confirmed, probable, or suspected monkeypox. In contrast, the medium risk is posed with a proximity in the same room or indoor physical space as a symptomatic patient with confirmed monkeypox if they were not wearing appropriate personal protective equipment.

Vaccine - X; JYNNEOS

MVA-BN or JYNNEOS is a live, non-replicating vaccine. This means that the vaccine contains an attenuated form of the pox virus that can mimic the infection caused by the virus to train the body's immune system to fight future infections [34]. This vaccine is administered subcutaneously or intradermally (for those who are 18 years or older) in 2 doses, 28 days apart. It is preferred that the second dose is completed no more than 35 days after the first one. The efficacy of only one dose of the vaccine is unknown. Subcutaneous administration can be painful, whereas intradermal is less so. However, the latter can cause side effects of redness, firmness, itching & swelling at the site of injection [35]. Live vaccines are usually contraindicated for the immunosuppressed; nevertheless, they have also been deemed safe for immunocompromised individuals. Due to a lack of data, safety is not confirmed for pregnant & lactating individuals as well as pediatric populations; however, its use can be considered based on clinical judgment. FDA has approved its use for those under the age of 18 years [36].

Vaccine - Y; ACAM2000

ACAM2000 is a live replicating vaccine with more known side effects and contraindications than JYNNEOS. It contains the vaccinia virus that, is of the same family as the smallpox virus & hence can provide immunity against it [37]. This vaccine is administered percutaneously in a single dose with a special two-pronged needle that pricks the skin multiple times. A localized infection will follow this at the site of inoculation called a "take." It is normal for this sore to take multiple weeks to heal.

Side effects of this vaccine include pain & swelling at the inoculation site, lymphadenitis & symptoms such as malaise, fever, myalgia & headache, as well as urticaria & folliculitis. Myocarditis, pericarditis, progressive vaccinia & post vaccinal encephalitis have also been reported as possible adverse events [38]. This vaccine is contraindicated for anyone who is immunosuppressed, pregnant or lactating, under the age of 1 year or has cardiac conditions, skin conditions such as eczema and psoriasis, and a history of allergic reactions to the vaccine. Those who cannot isolate themselves from those with the conditions mentioned above should also not get the vaccine.

Results and Discussion

Clade IIb is currently the predominant variation of Monkeypox circulating in the 2022 global outbreak. Although it is less severe and the transmission rate is low, healthcare workers still need to be vigilant about the disease, as it can lead to severe neurological and ocular complications and septicemia [16]. Stricter screening policies before travel to & from endemic areas to non-endemic areas is a possible, important step that can be taken to control & prevent future outbreaks. This is because some international spread has been attributed to people who traveled to endemic regions or animals imported from these areas [4].

There is a lot of room for further development of antivirals that can be used to manage those infected with the virus while minimizing side effects & increasing availability. The primary, secondary & tertiary preventive measures for smallpox should be available to everyone at increased risk of infection [39]. The implementation of vaccination as a public health measure is limited for the population due to a lack of data on efficacy and side effects. Clinical trials on an international level are required to use immunization as effectively as possible [40]. This is an important step as one of the causes of the recent outbreak may have been due to diminishing herd immunity to smallpox. While a suitable solution for vaccination is sought, educating the public about preventive measures is integral to preventing future outbreaks. This may include limiting contact with those affected by isolation, ensuring that meat is properly cooked before ingesting, as well as using personal protective equipment such as masks. Regular screening programs targeted toward those at high risk may also prove to be beneficial [41]. The diagram depicting clinical features, complications, treatment, and prophylaxis is given **(Figure 5)**.

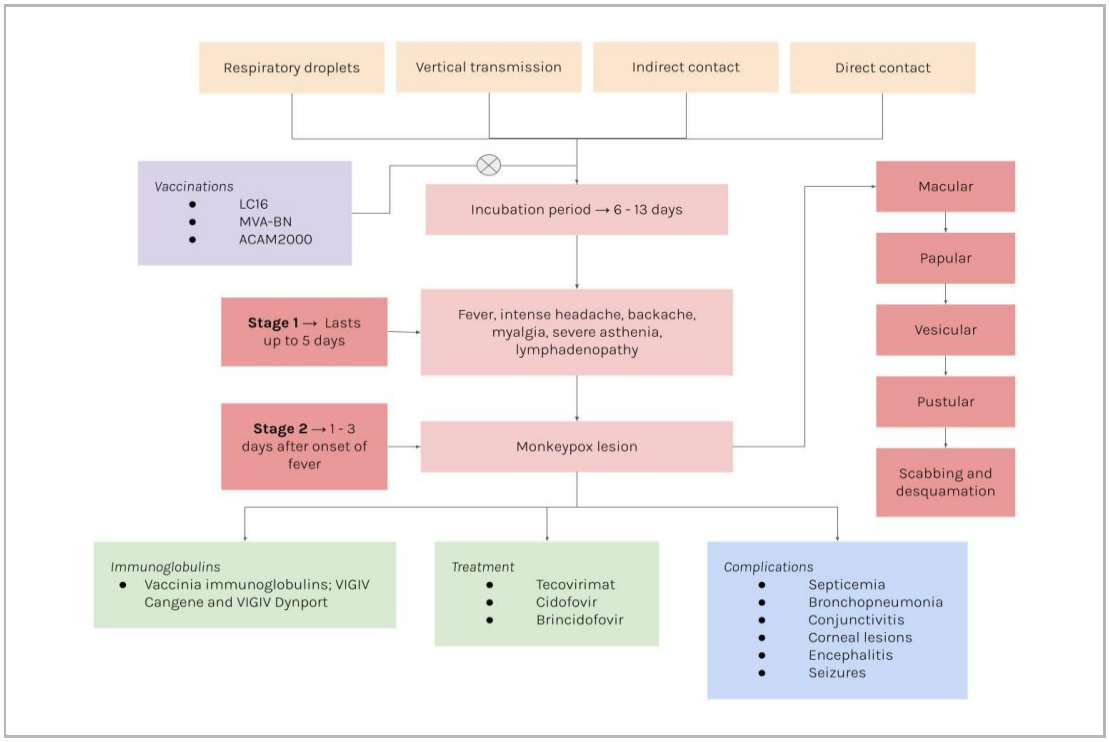

Figure 5. Clinical features, complications, treatment, and prophylaxis

Conclusion

Monkeypox, an endemic in certain parts of Africa, exhibited an exponential rise in cases in 50 countries in 2022. The infection that is believed to be transmitted among humans through the respiratory route as well as direct & indirect with bodily fluids has a Clade I & Clade II variant, with the latter being further divided into Clade IIa & IIb. Infected persons can have manifestations that happen in 2 stages. The first one has systemic manifestations such as fever, headaches & lymphadenopathy, while the second one presents with the skin lesions characteristic of the monkeypox infection. The infection can progress to cause septicemia, pneumonia, conjunctivitis, corneal scarring, encephalitis, and other CNS manifestations as well. The infection can be treated with antivirals such as Tecovirimat, which has been approved for smallpox infections, as well as cidofovir & brincidofovir. Vaccinations have been developed for pre-exposure prophylaxis as well as post-exposure prophylaxis & they are LC-16, JYNNEOS & ACAM2000. Passive immunity with vaccinia immunoglobulins is also one available option currently.

Acknowledgments: The authors acknowledge the School of Medicine, The Maldives National University academic staff for their help in proofreading and grammar correction.

Conflict of interest: None

Financial support: None

Ethics statement: Ethical guidelines are duly followed for informed consent as per the declaration of Helsinki.

References

1. Peter OJ, Kumar S, Kumari N, Oguntolu FA, Oshinubi K, Musa R. Transmission dynamics of Monkeypox virus: a mathematical modelling approach. Model Earth Syst Environ. 2022;8(3):3423-34. doi:10.1007/s40808-021-01313-2
2. Bunge EM, Hoet B, Chen L, Lienert F, Weidenthaler H, Baer LR, et al. The changing epidemiology of human monkeypox—A potential threat? A systematic review. PLoS Negl Trop Dis. 2022;16(2):e0010141. doi:10.1371/journal.pntd.0010141
3. Silva NIO, de Oliveira JS, Kroon EG, Trindade G de S, Drumond BP. Here, there, and everywhere: The wide host range and geographic distribution of zoonotic orthopoxviruses. Viruses. 2020;13(1):43. doi:10.3390/v13010043
4. Whitehouse ER, Bonwitt J, Hughes CM, Lushima RS, Likafi T, Nguete B, et al. Clinical and Epidemiological Findings from Enhanced Monkeypox Surveillance in Tshuapa Province, Democratic Republic of the Congo during 2011-2015. J Infect Dis. 2021;223(11):1870-8. doi:10.1093/infdis/jiab133

5. Harapan H, Setiawan AM, Yufika A, Anwar S, Wahyuni S, Asrizal FW, et al. Knowledge of human monkeypox viral infection among general practitioners: a cross-sectional study in Indonesia. Pathog Glob Health. 2020;114(2):68-75. doi:10.1080/20477724.2020.1743037
6. Hutson CL, Gallardo-Romero N, Carroll DS, Salzer JS, Ayers JD, Doty JB, et al. Analgesia during monkeypox virus experimental challenge studies in prairie dogs (cynomys ludovicianus). J Am Assoc Lab Anim Sci. 2019;58(4):485-500. doi:10.30802/AALAS-JAALAS-18-000036
7. Sood A, Sui Y, McDonough E, Santamaría-Pang A, Al-Kofahi Y, Pang Z, et al. Comparison of multiplexed immunofluorescence imaging to chromogenic immunohistochemistry of skin biomarkers in response to monkeypox virus infection. Viruses. 2020;12(8):787. doi:10.3390/v12080787
8. Vaughan A, Aarons E, Astbury J, Brooks T, Chand M, Flegg P, et al. Human-to-human transmission of monkeypox virus, United Kingdom, October 2018. Emerg Infect Dis. 2020;26(4):782. doi:10.3201/eid2604.191164
9. Patrono LV, Pléh K, Samuni L, Ulrich M, Röthemeier C, Sachse A, et al. Monkeypox virus emergence in wild chimpanzees reveals distinct clinical outcomes and viral diversity. Nat Microbiol. 2020;5(7):955-65. doi:10.1038/s41564-020-0706-0
10. Davi SD, Kissenkötter J, Faye M, Böhlken-Fascher S, Stahl-Hennig C, Faye O, et al. Recombinase polymerase amplification assay for rapid detection of Monkeypox virus. Diagn Microbiol Infect Dis. 2019;95(1):41-5. doi:10.1016/j.diagmicrobio.2019.03.015
11. Sadeuh-Mba SA, Yonga MG, Els M, Batejat C, Eyangoh S, Caro V, et al. Monkeypox virus phylogenetic similarities between a human case detected in Cameroon in 2018 and the 2017-2018 outbreak in Nigeria. Infect Genet Evol. 2019;69:8-11. doi:10.1016/j.meegid.2019.01.006
12. Tregubchak TV, Bauer TV, Maksyutov RA, Gavrilova EV. Cases of Orthopoxviral Infections around the World over a Period of 2008-2018. Probl Osobo Opasnykh Infektsii. 2021;(3):33-9. doi:10.21055/0370-1069-2021-3-33-39
13. Falendysz EA, Lopera JG, Doty JB, Nakazawa Y, Crill C, Lorenzsonn F, et al. Characterization of Monkeypox virus infection in African rope squirrels (Funisciurus sp.). PLoS Negl Trop Dis. 2017;11(8):e0005809. doi:10.1371/journal.pntd.0005809
14. Reynolds MG, Doty JB, McCollum AM, Olson VA, Nakazawa Y. Monkeypox re-emergence in Africa: a call to expand the concept and practice of One Health. Expert Rev Anti Infect Ther. 2019;17(2):129-39. doi:10.1080/14787210.2019.1567330
15. Petersen BW, Kabamba J, McCollum AM, Lushima RS, Wemakoy EO, Muyembe Tamfum JJ, et al. Vaccinating against monkeypox in the Democratic Republic of the Congo. Antiviral Res. 2019;162:171-7. doi:10.1016/j.antiviral.2018.11.004
16. Sklenovská N, Van Ranst M. Emergence of Monkeypox as the Most Important Orthopoxvirus Infection in Humans. Front Public Health. 2018;6:241. doi:10.3389/fpubh.2018.00241
17. Tumewu J, Wardiana M, Ervianty E, Anggraeni S, Widia Y, Amin M, et al. An adult patient with suspected of monkeypox infection differential diagnosed to chickenpox. Infect Dis Rep. 2020;12(s1):8724. doi:10.4081/idr.2020.8724
18. Alakunle E, Moens U, Nchinda G, Okeke MI. Monkeypox virus in Nigeria: Infection biology, epidemiology, and evolution. Viruses. 2020;12(11):1257. doi:10.3390/v12111257
19. Petersen E, Abubakar I, Ihekweazu C, Heymann D, Ntoumi F, Blumberg L, et al. Monkeypox — Enhancing public health preparedness for an emerging lethal human zoonotic epidemic threat in the wake of the smallpox post-eradication era. Int J Infect Dis. 2019;78:78-84. doi:10.1016/j.ijid.2018.11.008
20. Harapan H, Setiawan AM, Yufika A, Anwar S, Wahyuni S, Asrizal FW, et al. Physicians' willingness to be vaccinated with a smallpox vaccine to prevent monkeypox viral infection: A cross-sectional study in Indonesia. Clin Epidemiol Glob Health. 2020;8(4):1259-63. doi:10.1016/j.cegh.2020.04.024
21. Beer EM, Bhargavi Rao V. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. PLoS Negl Trop Dis. 2019;13(10):e0007791. doi:10.1371/journal.pntd.0007791
22. Reshetnikova TI, Zenkin AS, Krylova TG. The Histological Structure of Pig Organs and Tissues during the Experimental Use of the Triazavirin Antiviral Drug. J Biochem Technol. 2020;11(4):1-7.
23. Guagliardo SAJ, Doshi RH, Reynolds MG, Dzabatou-Babeaux A, Ndakala N, Moses C, et al. Do monkeypox exposures vary by ethnicity? Comparison of aka and Bantu suspected monkeypox cases. Am J Trop Med Hyg. 2020;102(1):202. doi:10.4269/ajtmh.19-0457
24. Yinka-Ogunleye A, Aruna O, Dalhat M, Ogoina D, McCollum A, Disu Y, et al. Outbreak of human monkeypox in Nigeria in 2017–18: a clinical and epidemiological report. Lancet Infect Dis. 2019;19(8):872-9. doi:10.1016/S1473-3099(19)30294-4
25. Petersen E, Kantele A, Koopmans M, Asogun D, Yinka-Ogunleye A, Ihekweazu C, et al. Human Monkeypox: Epidemiologic and Clinical Characteristics, Diagnosis, and Prevention. Infect Dis Clin North Am. 2019;33(4):1027-43. doi:10.1016/j.idc.2019.03.001
26. Besombes C, Gonofio E, Konamna X, Selekon B, Gessain A, Berthet N, et al. Intrafamily transmission of monkeypox virus, Central African Republic, 2018. Emerg Infect Dis. 2019;25(8):1602. doi:10.3201/eid2508.190112

27. Doty JB, Malekani JM, Kalemba LN, Stanley WT, Monroe BP, Nakazawa YU, et al. Assessing monkeypox virus prevalence in small mammals at the human–animal interface in the democratic republic of the congo. Viruses. 2017;9(10):283. doi:10.3390/v9100283
28. Reynolds MG, McCollum AM, Nguete B, Lushima RS, Petersen BW. Improving the care and treatment of monkeypox patients in low-resource settings: Applying evidence from contemporary biomedical and smallpox biodefense research. Viruses. 2017;9(12):380. doi:10.3390/v9120380
29. Mucker EM, Wollen-Roberts SE, Kimmel A, Shamblin J, Sampey D, Hooper JW. Intranasal monkeypox marmoset model: Prophylactic antibody treatment provides benefit against severe monkeypox virus disease. PLoS Negl Trop Dis. 2018;12(6):e0006581. doi:10.1371/journal.pntd.0006581
30. Wilson ME, Hughes JM, McCollum AM, Damon IK. Human monkeypox. Clin Infect Dis. 2014;58(2):260-7. doi:10.1093/cid/cit703
31. Berhanu A, Prigge JT, Silvera PM, Honeychurch KM, Hruby DE, Grosenbach DW. Treatment with the smallpox antiviral tecovirimat (ST-246) alone or in combination with ACAM2000 vaccination is effective as a postsymptomatic therapy for monkeypox virus infection. Antimicrob Agents Chemother. 2015;59(7):4296-300. doi:10.1128/AAC.00208-15
32. Usman S, Isa Adamu I. Modeling the Transmission Dynamics of the Monkeypox Virus Infection with Treatment and Vaccination Interventions. J Appl Math Phys. 2017;5(12):2335. doi:10.4236/jamp.2017.512191
33. Russo AT, Berhanu A, Bigger CB, Prigge J, Silvera PM, Grosenbach DW, et al. Co-administration of tecovirimat and ACAM2000TM in non-human primates: Effect of tecovirimat treatment on ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge. Vaccine. 2020;38(3):644-54. doi:10.1016/j.vaccine.2019.10.049
34. Rice AD, Adams MM, Lampert B, Foster S, Lanier R, Robertson A, et al. Efficacy of CMX001 as a prophylactic and presymptomatic antiviral agent in new zealand white rabbits infected with rabbitpox virus, a model for orthopoxvirus infections of humans. Viruses. 2011;3(2):63-82. doi:10.3390/v3020063
35. Iizuka I, Ami Y, Suzaki Y, Nagata N, Fukushi S, Ogata M, et al. A single vaccination of nonhuman primates with highly attenuated smallpox vaccine, LC16m8, provides long-term protection against monkeypox. Jpn J Infect Dis. 2017;70(4):408-15. doi:10.7883/yoken.JJID.2016.417
36. Earl PL, Americo JL, Wyatt LS, Eller LA, Whitbeck JC, Cohen GH, et al. Immunogenicity of a highly attenuated MVA smallpox vaccine and protection against monkeypox. Nature. 2004;428(6979):182-5. doi:10.1038/nature02331
37. Hooper JW, Custer DM, Thompson E. Four-gene-combination DNA vaccine protects mice against a lethal vaccinia virus challenge and elicits appropriate antibody responses in nonhuman primates. Virology. 2003;306(1):181-95. doi:10.1016/S0042-6822(02)00038-7
38. Abrahams BC, Kaufman DM. Anticipating smallpox and monkeypox outbreaks: Complications of the smallpox vaccine. Neurologist. 2004;10(5):265-74. doi:10.1097/01.nrl.0000138998.11209.88
39. Simpson K, Heymann D, Brown CS, Edmunds WJ, Elsgaard J, Fine P, et al. Human monkeypox – After 40 years, an unintended consequence of smallpox eradication. Vaccine. 2020;38(33):5077-81. doi:10.1016/j.vaccine.2020.04.062
40. Nakazawa Y, Mauldin MR, Emerson GL, Reynolds MG, Lash RR, Gao J, et al. A phylogeographic investigation of African monkeypox. Viruses. 2015. doi:10.3390/v7042168
41. Fuller T, Thomassen HA, Mulembakani PM, Johnston SC, Lloyd-Smith JO, Kisalu NK, et al. Using remote sensing to map the risk of human monkeypox virus in the Congo basin. Ecohealth. 2011;8(1):14-25. doi:10.1007/s10393-010-0355-5