Archives of Academic Emergency Medicine. 2024; 12(1): e70

REVIEW ARTICLE

Monkeypox: A Comprehensive Review of Virology, Epidemiology, Transmission, Diagnosis, Prevention, Treatment, and Artificial Intelligence Applications

Erfan Rahmani[1], Ziba Bayat[2], Mehrdad Farrokhi[3]*, Shiva Karimian[2], Reza Zahedpasha[4], Hamed Sabzehie[5], Sepehr Ramezani Poor[2], Parisa Jafari Khouzani[6], Solmaz Aminpour[7], Mohammad Karami[8], Omid Afsharjahanshahi[9], Maryam Sharifi[10], Behnaz Dalvandi[2], Reza Dalvandi[2], Amirhossein Esfahani[2], Maryam Alaei[2], Mahtab Mirbolouk[11], Fateme Moradi[2], Amitis Nozari[2], Seyed Mohammad Shahab Mirabedini[2], Mahrokh Janmohamadi[2], Sara Moghimi[12], Farzaneh Nikfarjam[2], Faezeh Jalayer Sarnaghy[2], Amirhossein Mirbolook[2], Mohammad Pirouzan[2], Mozhdeh Mohammadi Virsoudi[2], Atousa Moghadam Fard[2], Mehdi Nikandishnobar[13], Hossein Boustani Hezarani[14], Mohammadreza Fadavighafari[2], Masoud Farrokhi[2]

1. School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
2. ERIS Research Institute, Tehran, Iran.
3. Student Research Committee, Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
4. Department of Radiology, School of Medicine, 5th Azar Hospital, Gorgan, Golestan, Iran.
5. Kocaeli Health and Technology University, Kocaeli, Turkey.
6. Graduated, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
7. Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland.
8. Student, Nanjing Medical University, International School (SIE), Nanjing, China.
9. Atilim University Faculty of Medicine, Ankara, Turkey.
10. City Dental College and Hospital, Dhaka University, Dhaka, Bangladesh.
11. School of Pharmacy, Cyprus International University, Nicosia, North Cyprus.
12. Department of Physiology, Tulane School of Medicine, Tulane University, New Orleans 70112, Louisiana, U.S.A.
13. Faculty of Medicine, Atilim University, Ankara, Turkey.
14. Azerbaijan Medical University, Baku, Azerbaijan.

Received: July 2024; Accepted: August 2024; Published online: 17 September 2024

Abstract: Monkeypox (Mpox), an uncommon zoonotic Orthopoxvirus, is commonly manifested by blisters on the skin and has a mortality rate of approximately 0-10%. Approximately two decades after the cessation of global smallpox vaccination, the number of confirmed cases of Mpox has been growing, making it the most common Orthopoxvirus infection. Therefore, in this narrative review, we aimed to shed light on recent advancements in the pathophysiology, transmission routes, epidemiology, manifestations, diagnosis, prevention, and treatment of Mpox, as well as the application of artificial intelligence (AI) methods for predicting this disease. The clinical manifestations of Mpox, including the onset of symptoms and dermatologic characteristics, are similar to those of the infamous smallpox, but Mpox is clinically milder. Notably, a key difference between smallpox and Mpox is the high prevalence of lymphadenopathy. Human-to-human, animal-to-human, and animal-to-animal transmission are the three main pathways of Mpox spread that must be considered for effective prevention, particularly during outbreaks. PCR testing, as the preferred method for diagnosing Mpox infection, can enhance early detection of new cases and thereby improve infection control measures. JYNNEOS and ACAM2000 are among the vaccines most commonly recommended for the prevention of Mpox. Brincidofovir, Cidofovir, and Tecovirimat are the primary treatments for Mpox cases. Similar to other viral infections, the best approach to managing Mpox is prevention. This can, in part, be achieved through measures such as reducing contact with individuals displaying symptoms, maintaining personal safety, and adhering to practices commonly used to prevent sexually transmitted infections.

Keywords: Artificial Intelligence; Mpox; Monkeypox virus; Outbreak; Prevention; Transmission; Treatment

Cite this article as: Rahmani E, Bayat Z, Farrokhi M, et al. Monkeypox: A Comprehensive Review of Virology, Epidemiology, Transmission, Diagnosis, Prevention, Treatment, and Artificial Intelligence Applications. Arch Acad Emerg Med. 2024; 12(1): e70. https://doi.org/10.22037/aaem.v12i1.2491.

1. Introduction

Monkeypox (Mpox), an uncommon zoonotic Orthopoxvirus, is commonly manifested by blisters on the skin and has a mortality rate of 0-10% (1). Mpox was first reported in primates and rodents, and in 1958, an outbreak manifested by blisters on the skin of monkeys was found in Africa (2). Mpox, caused by a double-stranded DNA virus, is native to Central and West Africa but was first identified during polio vaccine-related investigations in Denmark (3). Two genetic clades have been identified for Mpox: Clade I, or the Congo Basin Clade, and Clade II, or the West African Clade. Clade I is frequently found in Central and Southern Cameroon, while Clade II is commonly identified in the Sierra Leone region and Western Cameroon (4, 5). Patients with Clade I Mpox showed a higher mortality rate (10%) compared to those with Clade II Mpox (1%) (6, 7). The manifestations of Mpox are mainly similar to those reported in cases of smallpox, though the severity of symptoms in Mpox is milder than in smallpox (8). The first confirmed case of Mpox in a human was identified in a nine-month-old child in the Democratic Republic of Congo (9). After this patient, cases of Mpox were found in Nigeria in 1971, some of which had no history of smallpox vaccination (10). Since 2017, a large outbreak with numerous suspected and confirmed cases of Mpox has been ongoing in Nigeria. In May 2022, the first confirmed case of Mpox was found in a traveler returning from Nigeria to the United Kingdom, who then transmitted the disease to their family members.

(11). The World Health Organization (WHO) reported Mpox as a Public Health Emergency of International Concern (PHEIC) following an increase in the number of human cases in non-endemic regions starting in May 2022 (12-15). Although in May 2023, the WHO stated that Mpox was no longer a PHEIC, on August 14, 2024, due to an increase in Mpox cases in several African countries, particularly the Democratic Republic of the Congo (DRC), the WHO once again declared Mpox a PHEIC (16). Approximately two decades after the cessation of global smallpox vaccination, the number of confirmed cases of Mpox has been growing, making it the most common Orthopoxvirus infection (17). Therefore, in this narrative review, we aimed to shed light on recent advancements in the pathophysiology, transmission routes, epidemiology, manifestations, diagnosis, prevention, and treatment of Mpox, as well as the application of artificial intelligence (AI) methods for predicting this disease.

2. Methods

A comprehensive search was conducted across three databases: Medline, Web of Science, and Scopus. The aim was to identify the most recent and relevant studies related to Mpox infection. To ensure a thorough search, we used the search terms "Mpox" and "Monkeypox" within the Title/Abstract fields of these databases.

2.1. Virology and Pathophysiology

Mpox is an enveloped, double-stranded linear DNA virus with characteristics such as lateral bodies and a dumbbell-shaped core, similar to those of the Orthopoxvirus genus. Vaccinia virus, camelpox, smallpox, ectromelia (mousepox), and cowpox are other members of this family with similar morphological features. Monkeypox, with an approximate length of 220–450 nm and a diameter of 140–260 nm, uses the cytoplasm of its host to complete its life cycle (18, 19). Depending on the type of host cell and species, several proteins are required to initiate the replication cycle of Mpox. Furthermore, the infection process becomes more complex as the virus evolves new mechanisms to evade the immune system.

However, Karler et al. (20) showed that four distinct types of proteins are used by the Mpox virus for binding to the host cell. There are mainly three processes for the entry of the Mpox virus into the host cell, including endocytosis, micropinocytosis, and fusion. Interactions between the Mpox virus and host cells are carried out by the termini of the genomes, while virus assembly and transcription are conducted by the genome's central region. It has been estimated that the incubation period and the length of manifestations are 5-21 days and 2-5 weeks, respectively (21, 22). Results from investigations on nonhuman primates infected with other orthopoxviruses constitute the majority of knowledge regarding the etiology and pathogenesis of the Mpox virus in humans. Replication of the Mpox virus in fibroblasts and keratinocytes following respiratory or skin-to-skin contact is the main mechanism of Mpox infection (23-25). Animal models of aerosolized Mpox infection have revealed that the tonsils, mediastinal, and mandibular lymph nodes are the first sites to be involved during the pathogenesis of Mpox infection. Lymphatic distribution of the virus can lead to the spread of lesions and dissemination to other organs, such as the spleen, heart, kidneys, and cerebrospinal fluid (CSF) (26). Type I and II interferon signaling pathways, immune responses from natural killer cells, and serologic immunity constitute the main defensive mechanisms of the body against the Mpox virus (27-29). Gamma delta T cells located in infected tissues may also play a partial role in the immune response against Mpox infection (30). Investigations on lethal infections in nonhuman primates have shown that the adaptive immune system, through B cell–derived neutralizing antibodies, is critical for protection against the Mpox virus (31). The Th1 response by T cells, with the expansion of CD4+ and CD8+ cells, is another aspect of the immune response against the Mpox virus (29).

*Corresponding Author: Mehrdad Farrokhi; Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: drfarrokhi@gmail.com, Phone number: +989365035851, ORCID: https://orcid.org/0000-0002-1559-2323.

2.2. Epidemiology

In the initial reports of human Mpox infection in Zaire, 282 cases were identified between 1980 and 1985. Unvaccinated patients showed a fatality rate of approximately 11%, which was higher than the 15% found in children, while vaccinated cases had no mortality (32). The first case of Mpox from a nonendemic region after the Mpox outbreak in the USA was a British traveler who returned to the UK from Nigeria with a rash in 2022. In that year, the UK Health Security Agency (UKHSA) reported several other confirmed cases of Mpox infection in the country (33). Moreover, in May 2020, Spain, Portugal, the USA, and Canada reported seven, fourteen, one, and thirteen Mpox cases, respectively (34). Similarly, the Netherlands, Austria, France, Germany, Italy, Belgium, Sweden, Israel, Mexico, the United Arab Emirates, and several other European countries also reported their first confirmed case of Mpox during this month (33, 35, 36).

Since 2022, the Democratic Republic of the Congo has seen a sharp increase in the rate of infected cases and deaths due to Mpox infection. Person-to-person spread of the clade Ib offshoot of clade I of Mpox has also been reported in some regions of the Democratic Republic of the Congo. Other countries have also experienced this clade since mid-2024. Between January 2022 and August 2024, more than 100,000 laboratory-confirmed cases of Mpox infection and over 220 deaths due to these infections have been reported from over 120 countries (37, 38). The top 10 countries with the most reported Mpox cases, from lowest to highest, are Germany (n = 3,886), Peru (n = 3,939), the United Kingdom (n = 4,018), Mexico (n = 4,132), Colombia (n = 4,256), France (n = 4,283), the Democratic Republic of the Congo (n = 4,385), Spain (n = 8,104), Brazil (n = 11,841), and the United States of America (n = 33,556). These 10 countries accounted for 80% of the cases reported (37).

2.3. Clinical Manifestations

The clinical manifestations of Mpox, including the onset of symptoms and dermatologic characteristics, are similar to those of the infamous smallpox, but Mpox is clinically milder (39, 40). Notably, a key difference between smallpox and Mpox is the high prevalence of lymphadenopathy (90%) in Mpox cases (21, 39). Additionally, the clinical characteristics of Mpox resemble those of varicella zoster virus (VZV), and accumulating evidence has shown cases of co-infection with both diseases (41, 42). As previously mentioned, the incubation period, which typically lasts 5-21 days, may be accompanied by myalgia, cephalgia, lethargy, and pyrexia (21, 39). Discrimination between Mpox and smallpox cases with these symptoms is based on the presence of either unilateral or bilateral lymphadenopathy, which may involve the inguinal, cervical, axillary, submandibular, and postauricular regions (21, 43). One to two days after lymphadenopathy, short-lived rashes, beginning with an enanthem similar to that seen in smallpox, appear on the tongue or in the mouth of Mpox cases. After one day, a macular rash develops on the face and spreads caudally to other parts of the body (21, 44). In non-human primates, the initial clinical signs of Mpox include epidermal plaques and papules progressing to crusts and pustules. Smallpox pustules are frequently found on the extremities and face, but they can present anywhere (45). In previous outbreaks, the perioral and anogenital regions were commonly the first affected areas, while the extremities and trunk had fewer lesions. Necrotic crusts and paraphimosis were also reported in male cases. Pain and proctitis can result from rectal lesions as primary manifestations (46). Accumulating evidence has revealed that the duration and severity of symptoms are associated with the density of dermatologic lesions (47). Ocular involvement, secondary dermatologic infections, pneumonia, and encephalitis are severe complications that may occur in some cases (48, 49). High-risk cases, such as immunocompromised patients, pregnant women, and neonates, may experience severe complications (50, 51). Approximately 35% of Mpox cases require clinical treatment (48, 52).

2.4. Diagnosis

Confirmation of Mpox diagnosis based solely on the signs and symptoms of patients is impossible, as their manifestations are not distinguishable from infections caused by other members of the poxvirus family (22). Therefore, diagnostic laboratory technologies for the early detection of Mpox cases are crucial. Some current laboratory investigations for identifying the Mpox virus include Polymerase Chain Reaction (PCR) of viral DNA, immunohistochemistry, culture evaluation of rash specimens, electron microscopy assessment, and serological antibody testing (22). The WHO recommends PCR testing as the preferred method for diagnosing Mpox infection. The best specimen collection for laboratory evaluation of Mpox involves scraping scabs, discharge, or vesicular lesions, which should be kept cold in a sterile setting. Viral culture for laboratory evaluation can be conducted using nasopharyngeal or oropharyngeal swabs. Sampling from vesiculopustular rashes or vesicular lesions on the skin can assist in achieving a more accurate diagnosis (21). Several laboratory techniques may be required simultaneously to rule out smallpox in some cases (53). Active cases of Mpox can be diagnosed based on the detection of DNA or genetic material of the Mpox virus in skin lesions (54). Detection of viral DNA requires that specimens of lesion material be stored in a dark, cool tube (55). The main disadvantages of this diagnostic technique are its relatively high cost and the need for expert technicians (56). Serologic antibody assessment using enzyme-linked immunosorbent assay (ELISA) is also used for diagnosing active cases. In contrast to PCR, conducting ELISA can be done with minimal training and at a lower cost. However, due to cross-reactivity among orthopoxviruses and the fact that ELISA does not specifically detect the Mpox virus, the results of this test cannot confirm a diagnosis of Mpox infection (57). Therefore, serologic evaluation and ELISA for antibody detection are not typically rec-

ommended for diagnosing Mpox (56, 58).

2.5. Transmission

Human-to-human, animal-to-human, and animal-to-animal are the three main pathways of Mpox transmission (Figure 1). Direct contact with fluids and secretions from infected animals is the most common method of animal-to-human transmission (20). Therefore, the rate of Mpox infection in humans is influenced by the number of animal contacts. Due to the presence of different sources of animal contact, it is difficult to determine the exact source of infection for a specific patient (18). West Africa and Nigeria have primarily reported cases of human-to-human transmission of Mpox (17). Using contaminated objects from Mpox patients and living with them in the same place can lead to human-to-human transmission. Large respiratory droplets and direct contact are other modes of Mpox virus transmission (18). However, human-to-human transmission played a lesser role in the 2022 Mpox outbreak in Europe, as most cases involved the West African clade of the virus (59-61).

Investigations have also detected Mpox virus in semen samples (4). Indeed, genital fluids, including vaginal fluid and seminal fluid, from infected cases consistently contain the Mpox virus (62, 63). In some patients, Mpox virus DNA was detected in seminal fluid even a long time after the onset of clinical manifestations (64). Moreover, urethral and anal swabs from infected cases can be used to culture viable Mpox virus (65).

These sexual transmission characteristics of Mpox virus have led some researchers to investigate the possibility of classifying Mpox infection as a sexually transmitted infection (29, 66). There are few studies on vertical transmission of Mpox infection, but there is some findings that show this type of transmission (67, 68). Due to the susceptibility of children and pregnant women, greater caution must be exercised to prevent vertical transmission (67, 69). In recent years, most confirmed cases of Mpox during outbreaks have been reported in bisexual or homosexual men. In this regard, an investigation also showed that 98% of Mpox patients were bisexual or homosexual men, with 41% co-infected with human immunodeficiency virus (HIV) (70, 71).

2.6. Prevention

As previously discussed, sexual and physical transmission from infected individuals to healthy people are two main routes of infection spread.

Therefore, reducing contact with those who have symptoms of Mpox infection, considering personal safety, and following practices commonly used for sexually transmitted infections can help prevent human-to-human transmission of Mpox. Regular handwashing with appropriate hand rub and ensuring a safe environment for respiratory habits can also reduce Mpox transmission (72). Public education on the routes of Mpox transmission, risk factors, and safety measures plays a pivotal role in controlling the disease in society. Early identification of outbreaks and implementing appropriate measures are effective in preventing the rapid spread of infection. Vaccination is another critical component of prevention programs currently under investigation and will be discussed in the next section (73). Furthermore, it is estimated that reducing the number of sexual partners, particularly in regions with a high rate of infection, can lower the possibility of Mpox transmission. Healthcare personnel who have contact with infected individuals are considered a high-risk group. They are advised to follow safety measures and use effective personal protective equipment, such as respirator masks, disposable gloves, face shields, and long-sleeved gowns (74, 75).

2.7. Vaccines

Some evidence suggests that smallpox vaccines may also offer cross-protection against monkeypox (76). Vaccines activate a cascade of cellular and biomarker mechanisms that result in the removal of infected cells by cytotoxic T cells, which are activated by antibodies secreted from B lymphocytes. Most people worldwide did not receive the smallpox vaccine, as the disease was eradicated long ago. As a result, the likelihood of resistance to Orthopoxvirus is low. The WHO has suggested that the most effective preventive measure may be further research into vaccines against the Mpox virus (77). Due to the limited number of companies producing or researching Mpox vaccines, ensuring sufficient supply for the global population is a significant challenge. Considering the above-mentioned limitations, future research may focus on improving available smallpox vaccines for use against Mpox. Orthopoxviruses share similar genetic characteristics, suggesting that vaccines against one Orthopoxvirus may offer cross-protection against others (78). The WHO has recommended that if a person has been in contact with an infected patient, vaccination should be administered within 4 days. Moreover, vaccination can be given up to two weeks after exposure if the individual does not show symptoms of Mpox infection (38). For individuals over the age of 18, JYNNEOS (modified vaccinia virus Ankara (MVA)), a replication-deficient vaccine, was approved by the Food and Drug Administration (FDA) to prevent Mpox infection (79, 80). Additionally, further investigations are being conducted to confirm its efficacy and safety for pediatric subjects. High-risk populations, such as HIV patients, can also safely receive this vaccine. (79, 81-83). ACAM2000, a replication-competent vaccine for the prevention of Mpox infection, was approved by the FDA in 2007 (84). However, this vaccine has some side effects, including myopericarditis, encephalitis, eczema vaccinatum, and progressive vaccinia (83, 85).

2.8. Treatment

Similar to other infections by other Orthopoxviruses, prevention from infection sequela, reducing complications, and alleviation of symptoms are the main aims of optimal treatment of Mpox infection (86). Brincidofovir as an orally ad-

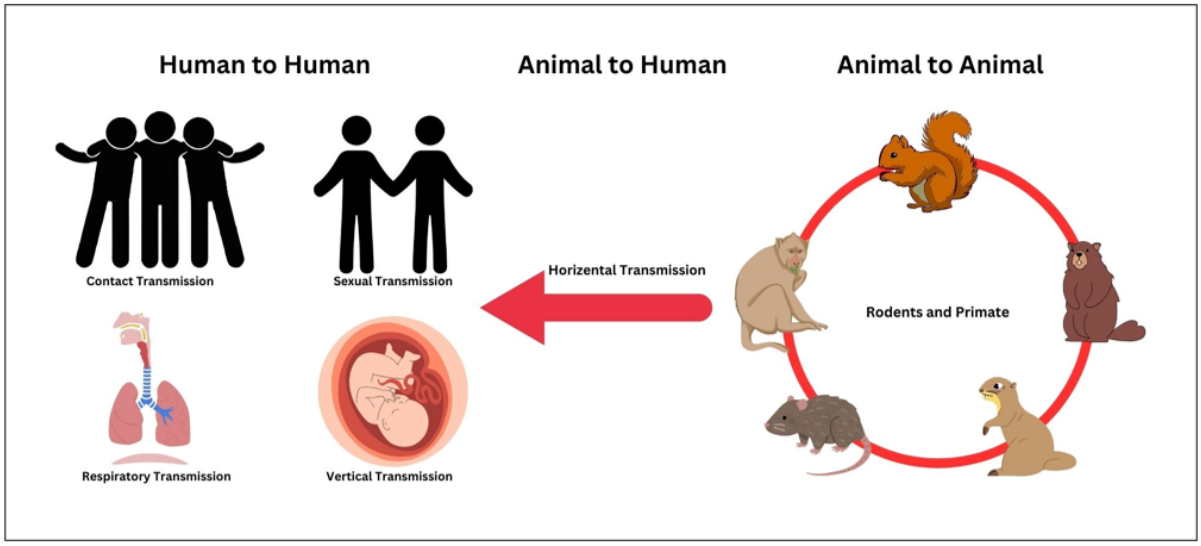

Figure 1: Three main types of Mpox transmission including animal to animal, animal to human, and human to human.

ministered drug and Cidofovir as an intravenously administer drug are two antiviral treatments against Orthopoxvirus (18, 19). US FDA's animal rule confirmed tecovirimat which is an inhibitor of the release of intracellular viruses applied for the treatment of smallpox. Tecovirimat was also approved for the management of Mpox by European Medical Association (EMA) in 2022 (18, 87). Release of the Mpox virus from infected cells mediated by the VP37 viral protein can be suppressed by Tecovirimat (88). Tecovirimat is available in two forms: intravenous vial and oral capsule (85). Its efficacy has been demonstrated in animals, but its effectiveness in humans is still under further investigation (87, 89). Brincidofovir, a lipid conjugate of cidofovir, is an inhibitor of viral DNA polymerase and was approved for the treatment of cytomegalovirus retinitis in AIDS (90). Severe cases of Mpox infection can be treated with both brincidofovir and tecovirimat together (19, 85). During the management of Mpox infection, early detection and treatment of secondary bacterial infections should be considered (56). Although some cases manifest severe symptoms of Mpox infection with a 3 to 10% fatality rate, the infection is typically self-limiting, and the symptoms of the majority of patients will improve without treatment (91, 92).

Supportive care, such as reducing mucosal and dermatologic complications, managing gastrointestinal symptoms including diarrhea and vomiting to control fluid loss, and providing appropriate nutrition and hydration, plays a crucial role in the clinical management of Mpox infection (22).

2.9. Public Health Measures

The potential for a disease to affect a large proportion of a population or geographical region within a specific time frame is known as an epidemic, which should also be considered for Mpox infection. Sometimes, even a single case of infection can result in an epidemic in a particular region at a given time. Nowadays, one case of Mpox infection can pose a critical public health threat to a region. Therefore, suspected cases of Mpox infection must be promptly evaluated and reported by clinicians to public health authorities. Additionally, the WHO must be informed of confirmed cases of Mpox infection according to the International Health Regulations (IHR) (91). Prevention of Mpox spread through isolation of infected cases and monitoring of previous contacts should be carried out by healthcare providers. Investigations into the most common modes of Mpox transmission in the region should be conducted to aid in further planning for effective preventive measures (75). Genomic sequencing of the Mpox virus to identify the clade responsible for epidemics may also be helpful for understanding the epidemiology of the infection in the region (93).

2.10. Application of Artificial Intelligence Techniques for Monkeypox management

Recently, a systematic review by Chadaga et al. (94) was conducted using a comprehensive search of electronic databases, including Medline, Scopus, Web of Science, and publisher archives, as well as search engines like Google Scholar and PubMed. They searched for eligible studies using keywords related to monkeypox and AI, which resulted in the inclusion of 34 studies that met the inclusion criteria. Overall, their findings revealed that AI has been applied in various aspects of research on the Mpox virus, including treatments, vaccine and drug design and production, epidemiological modeling of infection, diagnosis of infected cases, and media risk management. It has also been proposed that AI can combine recent findings from regenerative medicine, gene therapy, and pharmacology to provide novel treatments for Mpox infection. Predicting future outbreaks of Mpox, detecting disease clusters, and monitoring patients were also reported as effective applications of AI (95).

However, studies on the applications of AI in various aspects of Mpox management are limited, and further investigations

in this field will be required to improve disease control.

3. Conclusion

Human-to-human, animal-to-human, and animal-to-animal transmission are the three main pathways of Mpox spread that must be considered for effective prevention, particularly during outbreaks. PCR testing, as the preferred method for diagnosing Mpox infection, can enhance early detection of new cases and thereby improve infection control measures. JYNNEOS and ACAM2000 are among the vaccines most commonly recommended for the prevention of Mpox. Brincidofovir, Cidofovir, and Tecovirimat are the primary treatments for Mpox cases. Similar to other viral infections, the best approach to managing Mpox is prevention. This can, in part, be achieved through measures such as reducing contact with individuals displaying symptoms, maintaining personal safety, and adhering to practices commonly used to prevent sexually transmitted infections. These strategies can help mitigate human-to-human transmission of Mpox.

4. Declarations

4.1. Acknowledgments

The authors thank all those who contributed to this study.

4.2. Funding/Support

None.

4.3. Conflict of interest

None.

4.4. Authors' contribution

All authors contributed to study design, data collection, and writing the draft of the study. All authors read and approved final version of manuscript.

4.5. Data Availability

Not applicable.

4.6. Using Artificial Intelligence Chatbots

None.

References

1. Ladnyj I, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. Bulletin of the World Health Organization. 1972;46(5):593.
2. Okyay RA, Bayrak E, Kaya E, Şahin AR, Koçyiğit BF, Taşdoğan AM, et al. Another epidemic in the shadow of Covid 19 pandemic: a review of monkeypox. proteins. 2022;7(10):10.14744.
3. von Magnus P, Andersen EK, Petersen KB, Birch Andersen A. A pox-like disease in cynomolgus monkeys. 1959.
4. Thornhill JP, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison LB, et al. Monkeypox Virus Infection in Humans across 16 Countries - April-June 2022. N Engl J Med. 2022;387(8):679-91.
5. Saijo M, Ami Y, Suzaki Y, Nagata N, Iwata N, Hasegawa H, et al. Virulence and pathophysiology of the Congo Basin and West African strains of monkeypox virus in non-human primates. J Gen Virol. 2009;90(Pt 9):2266-71.
6. Likos AM, Sammons SA, Olson VA, Frace AM, Li Y, Olsen-Rasmussen M, et al. A tale of two clades: monkeypox viruses. J Gen Virol. 2005;86(Pt 10):2661-72.
7. Levitt CV, Tran QK, Hraky H, Mazer-Amirshahi M, Pourmand A. Emergency department approach to monkeypox. World J Emerg Med. 2023;14(5):341-8.
8. Abdelaal A, Serhan HA, Mahmoud MA, Rodriguez-Morales AJ, Sah R. Ophthalmic manifestations of monkeypox virus. Eye. 2023;37(3):383-5.
9. Marennikova S, Šeluhina EM, Mal'Ceva N, Čimiškjan K, Macevič G. Isolation and properties of the causal agent of a new variola-like disease (monkeypox) in man. Bulletin of the World Health Organization. 1972;46(5):599.
10. Elsheikh R, Makram AM, Vasanthakumaran T, Tomar S, Shamim K, Tranh ND, et al. Monkeypox: A comprehensive review of a multifaceted virus. Infectious Medicine. 2023;2(2):74-88.
11. Zumla A, Valdoleiros SR, Haider N, Asogun D, Ntoumi F, Petersen E, et al. Monkeypox outbreaks outside endemic regions: scientific and social priorities. The Lancet Infectious Diseases. 2022;22(7):929-31.
12. Capobianchi MR, Di Caro A, Piubelli C, Mori A, Bisoffi Z, Castilletti C. Monkeypox 2022 outbreak in non-endemic countries: Open questions relevant for public health, nonpharmacological intervention and literature review. Front Cell Infect Microbiol. 2022;12:1005955.
13. Ranjan S, Vashishth K, Sak K, Tuli HS. The Emergence of Mpox: Epidemiology and Current Therapeutic Options. Curr Pharmacol Rep. 2023;9(3):144-53.
14. Tehranchinia Z, Robati RM, Moravvej H, Memariani M, Memariani H. Monkeypox Disease with a Focus on the 2022 Outbreak; a Narrative Review. Arch Acad Emerg Med. 2023;11(1):e19.
15. Alavi-Moghaddam M. Monkeypox Outbreak in Non-Endemic Areas: Will it Cause a New Pandemic? a Letter to Editor. Arch Acad Emerg Med. 2022;10(1):e60.
16. WHO WHO. WHO Director-General declares mpox outbreak a public health emergency of international concern 2024 [Available from: https://www.who.int/news/item/14-08-2024-who-director-general-declares-mpox-outbreak-a-public-health-emergency-of-international-concern.
17. Sklenovská N, Van Ranst M. Emergence of Monkeypox as the Most Important Orthopoxvirus Infection in Humans. Front Public Health. 2018;6:241.
18. McCollum AM, Damon IK. Human monkeypox. Clin Infect Dis. 2014;58(2):260-7.

19. Elsheikh R, Makram AM, Vasanthakumaran T, Tomar S, Shamim K, Tranh ND, et al. Monkeypox: A comprehensive review of a multifaceted virus. Infect Med (Beijing). 2023;2(2):74-88.
20. Kaler J, Hussain A, Flores G, Kheiri S, Desrosiers D. Monkeypox: A Comprehensive Review of Transmission, Pathogenesis, and Manifestation. Cureus. 2022;14(7):e26531.
21. 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.
22. Nyame J, Punniyakotti S, Khera K, Pal RS, Varadarajan N, Sharma P. Challenges in the treatment and prevention of monkeypox infection; A comprehensive review. Acta Trop. 2023;245:106960.
23. Zaucha GM, Jahrling PB, Geisbert TW, Swearengen JR, Hensley L. The pathology of experimental aerosolized monkeypox virus infection in cynomolgus monkeys (Macaca fascicularis). Lab Invest. 2001;81(12):1581-600.
24. Lum FM, Torres-Ruesta A, Tay MZ, Lin RTP, Lye DC, Rénia L, et al. Monkeypox: disease epidemiology, host immunity and clinical interventions. Nat Rev Immunol. 2022;22(10):597-613.
25. Nagata N, Saijo M, Kataoka M, Ami Y, Suzaki Y, Sato Y, et al. Pathogenesis of fulminant monkeypox with bacterial sepsis after experimental infection with West African monkeypox virus in a cynomolgus monkey. Int J Clin Exp Pathol. 2014;7(7):4359-70.
26. Tree JA, Hall G, Pearson G, Rayner E, Graham VA, Steeds K, et al. Sequence of pathogenic events in cynomolgus macaques infected with aerosolized monkeypox virus. J Virol. 2015;89(8):4335-44.
27. Al-Musa A, Chou J, LaBere B. The resurgence of a neglected orthopoxvirus: Immunologic and clinical aspects of monkeypox virus infections over the past six decades. Clin Immunol. 2022;243:109108.
28. Song H, Josleyn N, Janosko K, Skinner J, Reeves RK, Cohen M, et al. Monkeypox virus infection of rhesus macaques induces massive expansion of natural killer cells but suppresses natural killer cell functions. PLoS One. 2013;8(10):e77804.
29. Thornhill JP, Gandhi M, Orkin C. Mpox: The Reemergence of an Old Disease and Inequities. Annu Rev Med. 2024;75:159-75.
30. Shao L, Huang D, Wei H, Wang RC, Chen CY, Shen L, et al. Expansion, reexpansion, and recall-like expansion of Vgamma2Vdelta2 T cells in smallpox vaccination and monkeypox virus infection. J Virol. 2009;83(22):11959-65.
31. Edghill-Smith Y, Golding H, Manischewitz J, King LR, Scott D, Bray M, et al. Smallpox vaccine-induced antibodies are necessary and sufficient for protection against monkeypox virus. Nat Med. 2005;11(7):740-7.
32. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. J Infect Dis. 1987;156(2):293-8.
33. Araf Y, Nipa JF, Naher S, Maliha ST, Rahman H, Arafat KI, et al. Insights into the Transmission, Host Range, Genomics, Vaccination, and Current Epidemiology of the Monkeypox Virus. Vet Med Int. 2024;2024:8839830.
34. WHO WHO. Mpox (monkeypox) 2023 [Available from: https://www.who.int/en/news-room/fact-sheets/detail/monkeypox.
35. Yahoo is part of the Yahoo family of brands 2022 [Available from: https://www.yahoo.com/news/austrias-first-case-monkeypox-confirmed-153959022.html.
36. Mpox (monkeypox) 2022 [Available from: https://www.france24.com/en/europe/20220520-france-germany-belgium-report-first-monkeypox-cases-amid-unusual-spread-in-europe.
37. 2022-24 Mpox (Monkeypox) Outbreak: Global Trends 2024 [Available from: https://worldhealthorg.shinyapps.io/mpx_global/.
38. Mpox 2024 [Available from: https://www.who.int/news-room/fact-sheets/detail/mpox.
39. Kumar N, Acharya A, Gendelman HE, Byrareddy SN. The 2022 outbreak and the pathobiology of the monkeypox virus. J Autoimmun. 2022;131:102855.
40. Quarleri J, Delpino MV, Galvan V. Monkeypox: considerations for the understanding and containment of the current outbreak in non-endemic countries. Geroscience. 2022;44(4):2095-103.
41. Meyer H, Perrichot M, Stemmler M, Emmerich P, Schmitz H, Varaine F, et al. Outbreaks of disease suspected of being due to human monkeypox virus infection in the Democratic Republic of Congo in 2001. J Clin Microbiol. 2002;40(8):2919-21.
42. Rimoin AW, Kisalu N, Kebela-Ilunga B, Mukaba T, Wright LL, Formenty P, et al. Endemic human monkeypox, Democratic Republic of Congo, 2001-2004. Emerg Infect Dis. 2007;13(6):934-7.
43. O'Neill M, LePage T, Bester V, Yoon H, Browne F, Nemec EC. Mpox (Formally Known as Monkeypox). Physician Assist Clin. 2023;8(3):483-94.
44. How to Report Test Results | Mpox | Poxvirus | CDC 2024 [Available from: https://www.cdc.gov/poxvirus/Mpox/lab-personnel/report-results.html.
45. Anwar F, Haider F, Khan S, Ahmad I, Ahmed N, Imran M, et al. Clinical Manifestation, Transmission, Pathogenesis, and Diagnosis of Monkeypox Virus: A Comprehensive Review. Life (Basel). 2023;13(2).
46. Sharma A, Prasad H, Kaeley N, Bondalapati A, Edara L, Kumar YA. Monkeypox epidemiology, clinical presentation, and transmission: a systematic review. Int J Emerg Med. 2023;16(1):20.
47. Gessain A, Nakoune E, Yazdanpanah Y. Monkeypox. N Engl J Med. 2022;387(19):1783-93.
48. Benites-Zapata VA, Ulloque-Badaracco JR, Alarcon-

Braga EA, Hernandez-Bustamante EA, Mosquera-Rojas MD, Bonilla-Aldana DK, et al. Clinical features, hospitalisation and deaths associated with monkeypox: a systematic review and meta-analysis. Ann Clin Microbiol Antimicrob. 2022;21(1):36.
49. Learned LA, Reynolds MG, Wassa DW, Li Y, Olson VA, Karem K, et al. Extended interhuman transmission of monkeypox in a hospital community in the Republic of the Congo, 2003. Am J Trop Med Hyg. 2005;73(2):428-34.
50. Mitjà O, Alemany A, Marks M, Lezama Mora JI, Rodríguez-Aldama JC, Torres Silva MS, et al. Mpox in people with advanced HIV infection: a global case series. Lancet. 2023;401(10380):939-49.
51. Ogoina D, Iroezindu M, James HI, Oladokun R, Yinka-Ogunleye A, Wakama P, et al. Clinical Course and Outcome of Human Monkeypox in Nigeria. Clin Infect Dis. 2020;71(8):e210-e4.
52. Silva S, Kohl A, Pena L, Pardee K. Clinical and laboratory diagnosis of monkeypox (mpox): Current status and future directions. iScience. 2023;26(6):106759.
53. Kannan S, Shaik Syed Ali P, Sheeza A. Monkeypox: epidemiology, mode of transmission, clinical features, genetic clades and molecular properties. Eur Rev Med Pharmacol Sci. 2022;26(16):5983-90.
54. Wawina-Bokalanga T, Sklenovska N, Vanmechelen B, Bloemen M, Vergote V, Laenen L, et al. An accurate and rapid Real-time PCR approach for human Monkeypox virus diagnosis. medRxiv. 2022:2022.06.23.22276033.
55. Kanji JN, Dieu P, Wong A, Pabbaraju K, Shokoples S, Smyczek P, et al. Retrospective testing for the presence of monkeypox virus in a high-risk population from February-June 2022 in Alberta, Canada. J Assoc Med Microbiol Infect Dis Can. 2023;8(1):85-9.
56. Rabaan AA, Al-Shwaikh SA, Alfouzan WA, Al-Bahar AM, Garout M, Halwani MA, et al. A Comprehensive Review on Monkeypox Viral Disease with Potential Diagnostics and Therapeutic Options. Biomedicines. 2023;11(7).
57. Doshi RH, Guagliardo SAJ, Doty JB, Babeaux AD, Matheny A, Burgado J, et al. Epidemiologic and Ecologic Investigations of Monkeypox, Likouala Department, Republic of the Congo, 2017. Emerg Infect Dis. 2019;25(2):281-9.
58. 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).
59. Dye C, Kraemer MUG. Investigating the monkeypox outbreak. Bmj. 2022;377:o1314.
60. Alakunle EF, Okeke MI. Monkeypox virus: a neglected zoonotic pathogen spreads globally. Nat Rev Microbiol. 2022;20(9):507-8.
61. Karagoz A, Tombuloglu H, Alsaeed M, Tombuloglu G, Al-Rubaish AA, Mahmoud A, et al. Monkeypox (mpox) virus: Classification, origin, transmission, genome organization, antiviral drugs, and molecular diagnosis. J Infect Public Health. 2023;16(4):531-41.
62. Peiró-Mestres A, Fuertes I, Camprubí-Ferrer D, Marcos M, Vilella A, Navarro M, et al. Frequent detection of monkeypox virus DNA in saliva, semen, and other clinical samples from 12 patients, Barcelona, Spain, May to June 2022. Euro Surveill. 2022;27(28).
63. Antinori A, Mazzotta V, Vita S, Carletti F, Tacconi D, Lapini LE, et al. Epidemiological, clinical and virological characteristics of four cases of monkeypox support transmission through sexual contact, Italy, May 2022. Euro Surveill. 2022;27(22).
64. Lapa D, Carletti F, Mazzotta V, Matusali G, Pinnetti C, Meschi S, et al. Monkeypox virus isolation from a semen sample collected in the early phase of infection in a patient with prolonged seminal viral shedding. Lancet Infect Dis. 2022;22(9):1267-9.
65. Moschese D, Pozza G, Mileto D, Giacomelli A, Cutrera M, Cossu MV, et al. Isolation of viable monkeypox virus from anal and urethral swabs, Italy, May to July 2022. Euro Surveill. 2022;27(36).
66. Allan-Blitz LT, Gandhi M, Adamson P, Park I, Bolan G, Klausner JD. A Position Statement on Mpox as a Sexually Transmitted Disease. Clin Infect Dis. 2023;76(8):1508-12.
67. Kisalu NK, Mokili JL. Toward Understanding the Outcomes of Monkeypox Infection in Human Pregnancy. J Infect Dis. 2017;216(7):795-7.
68. Fahrni ML, Priyanka, Choudhary OP. Possibility of vertical transmission of the human monkeypox virus. Int J Surg. 2022;105:106832.
69. Huang Y, Mu L, Wang W. Monkeypox: epidemiology, pathogenesis, treatment and prevention. Signal Transduct Target Ther. 2022;7(1):373.
70. Del Rio C, Malani PN. Update on the Monkeypox Outbreak. Jama. 2022;328(10):921-2.
71. Aden D, Zaheer S, Kumar R, Ranga S. Monkeypox (Mpox) outbreak during COVID-19 pandemic-Past and the future. J Med Virol. 2023;95(4):e28701.
72. McAndrew T, Majumder MS, Lover AA, Venkatramanan S, Bocchini P, Besiroglu T, et al. Early human judgment forecasts of human monkeypox, May 2022. Lancet Digit Health. 2022;4(8):e569-e71.
73. Costello V, Sowash M, Gaur A, Cardis M, Pasieka H, Wortmann G, et al. Imported Monkeypox from International Traveler, Maryland, USA, 2021. Emerg Infect Dis. 2022;28(5):1002-5.
74. Lai CC, Hsu CK, Yen MY, Lee PI, Ko WC, Hsueh PR. Monkeypox: An emerging global threat during the COVID-19 pandemic. J Microbiol Immunol Infect. 2022;55(5):787-94.
75. 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):782-5.
76. Parker S, Nuara A, Buller RM, Schultz DA. Human monkeypox: an emerging zoonotic disease. Future Microbiol.

2007;2(1):17-34.
77. Smallpox: post-eradication vigilance continues. WHO Chron. 1982;36(3):87-91.
78. Miller L, Richter M, Hapke C, Stern D, Nitsche A. Genomic expression libraries for the identification of cross-reactive orthopoxvirus antigens. PLoS One. 2011;6(7):e21950.
79. Rao A, Mena LA, Petersen B. Monkeypox: updates about clinical diagnosis and treatment. 2022.
80. Petersen E, Zumla A, Hui DS, Blumberg L, Valdoleiros SR, Amao L, et al. Vaccination for monkeypox prevention in persons with high-risk sexual behaviours to control ongoing outbreak of monkeypox virus clade 3. Int J Infect Dis. 2022;122:569-71.
81. Asadi Noghabi F, J GR, Makkar D, Roozbeh N, Ghelichpour S, Zarei A. Managing Monkeypox Virus Infections: A Contemporary Review. Iran J Med Sci. 2024;49(1):1-9.
82. Radix M, Hoffmann CJ, Gonzalez CJ. Monkeypox Vaccination in Adults With HIV. 2022.
83. Rao AK, Petersen BW, Whitehill F, Razeq JH, Isaacs SN, Merchlinsky MJ, et al. Use of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Nonreplicating) for Preexposure Vaccination of Persons at Risk for Occupational Exposure to Orthopoxviruses: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(22):734-42.
84. Greenberg RN, Kennedy JS. ACAM2000: a newly licensed cell culture-based live vaccinia smallpox vaccine. Expert Opin Investig Drugs. 2008;17(4):555-64.
85. Rizk JG, Lippi G, Henry BM, Forthal DN, Rizk Y. Prevention and Treatment of Monkeypox. Drugs. 2022;82(9):957-63.
86. Wang J, Shahed-Ai-Mahmud M, Chen A, Li K, Tan H, Joyce R. An Overview of Antivirals against Monkeypox Virus and Other Orthopoxviruses. J Med Chem. 2023;66(7):4468-90.
87. Grosenbach DW, Honeychurch K, Rose EA, Chinsangaram J, Frimm A, Maiti B, et al. Oral Tecovirimat for the Treatment of Smallpox. N Engl J Med. 2018;379(1):44-53.
88. Sliva K, Schnierle B. From actually toxic to highly specific–novel drugs against poxviruses. Virol J. 2007;4:8.
89. Quenelle DC, Buller RM, Parker S, Keith KA, Hruby DE, Jordan R, et al. Efficacy of delayed treatment with ST-246 given orally against systemic orthopoxvirus infections in mice. Antimicrob Agents Chemother. 2007;51(2):689-95.
90. Xiang Y, White A. Monkeypox virus emerges from the shadow of its more infamous cousin: family biology matters. Emerg Microbes Infect. 2022;11(1):1768-77.
91. 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.
92. Poland GA, Kennedy RB, Tosh PK. Prevention of monkeypox with vaccines: a rapid review. Lancet Infect Dis. 2022;22(12):e349-e58.
93. Shapovalova V. Monkeypox Virus – New Challenges of Modernity: Experimental Organizational and Legal, Clinical and Pharmacological Studies. SSP Modern Pharmacy and Medicine. 2022;2(3):1-15.
94. Chadaga K, Prabhu S, Sampathila N, Nireshwalya S, Katta SS, Tan RS, et al. Application of Artificial Intelligence Techniques for Monkeypox: A Systematic Review. Diagnostics (Basel). 2023;13(5).
95. Patel M, Surti M, Adnan M. Artificial intelligence (AI) in Monkeypox infection prevention. J Biomol Struct Dyn. 2023;41(17):8629-33.