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Zoonotic virus spillover: An Insight on Monkey pox virus Structural attributes Pathogenicity and Manifestations

Meenakshi Mehra [1], Kareena Jaswal [1], Sweta Joshi [2], Ramandeep Singh [1], Riya Mehra [3]

[1] *Himachal Institute of Pharmacy Paonta Sahib, Himachal Pradesh, 173025, India*
[2] *Devasthali College of Pharmacy, Rudrapur, Udham Singh Nagar, India*
[3] *G.B Pant University of Agriculture and Technology, Department of Food Science and Technology, Pantnagar, India*

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Correspondence
Meenakshi Mehra
E-mail*
(Corresponding Author)
mehrameenakshi1991@gmail.com

ABSTRACT

While mankind believed that they have reached unprecedented heights in every sphere of Technology and Civilization, the breakout of fatal pandemics in of late has broken that perception and served as a wakeup call. A slew of viruses has immersed in the environment imposing a serious threat to the survival of nearly all human beings on the planet. As the pandemic subsides, WHO declares the monkey box outbreaks as a public health emergency of international concern and lesson from COVID-19 geared up to deal with this outbreak. It is caused by clade IIb strain and the natural reserve virus is unknown whereas small mammals such a squirrels and monkeys are susceptible. This review encompasses compending encapsulation of molecular virology of virus their sign and symptoms, transmission, diagnosis and underlying pathogenesis, focuses on their mechanics. In addition, method for preventing and treating this viral infections. Current epidemiological overview is also taken into consideration.

1. INTRODUCTION

Monkeypox (Mpox) is a zoonotic viral disease caused by the Monkeypox virus (MPXV). The clinical presentation is similar to smallpox [1]. It is caused by an orthopoxvirus belonging to the family Poxviridae, subfamily Chordopoxvirinae that has been confirmed to have a highly differentiated double-stranded DNA [2].

Because it is a DNA virus, the monkeypox has better mechanisms of gene repair compared to RNA viruses like HIV and SARSCoV-2, meaning that its change takes more time [3]. The virus is divided into two clades: clade I, Congo basin, which originated in Central Africa, including Congo, and clade II, which is linked to West Africa.

With a case-fatality ratio of 10%, the former virus is more deadly and contagious, whereas, the later virus is more self-limited with a case-fatality ratio of 3-6%. As all zoonotic disease, the virus spreads endemically via animal human transmission. But most of the non-endemic spreads are mainly caused by contact with humans [4]. The disease develops about 2 weeks after the infection in humans and begins to manifest itself, with fever, headache, general malaise followed by swelling of lymph nodes. A rash of raised bumps appears in the face and body a few days later. The sickness gradually takes its course in two to four weeks, and patients eventually crust and peel off. The only goal of treatment is to reduce symptoms [5].

2. STRUCTURE AND GENOME

The MPXV particles, as measured under an electron microscope, were round brick and oval in shape and 200-250 nm in size. The virions has five different structures consisting of a core, membrane, lateral body, surface tubule and, nucleocapsid. It has a double-concave dumbbell-shaped core that is encircled by a two-layered lipoprotein membrane. Numerous RNA polymerase system-related enzymes that are crucial for the initial transcription of viral and structural genes are included in viral virions. They are more typically found in the M (mulberry) form of their proteins, which have regular 10 nm-long protrusions (tubules) on the surface, than in the C (capsule) form, which has a thick membrane and a smooth, uniform surface.

The essential receptor for MPXV entrance into host cells has not yet been identified, nevertheless [6]. Orthopoxvirus share more than 90% of their sequence with one another, making them antigenetically and genetically comparable to open reading frames (ORFs) [7]. Over 190 open reading frames (ORFs) larger than 60 amino acids are included in the 197 kb linear Human Monkeypox virus (hMPXV) DNA genome, which does not overlap [8]. From nucleotide locations 56,000 to 120,000, the central coding region (CRS) has a highly conserved sequence that is bordered by varied ends that include inverted terminal repeats (ITRs). The ITR sections of the hMPXV include at least four recognised ORFs [9].

3. TRANSMISSION

The monkey pox virus may spread in a variety of ways, but they are all assumed to entail close contact with infected people or animals. Transmission of an infection from infected animals to humans may occur via direct touch or exposure. The most prevalent causes are exudates from cutaneous or mucosal lesions, saliva, or respiratory excretions. Viral shedding via faeces is another possible method of exposure [10]. Compared to animal-to-human transmission, human-to-human transmission is less frequent although it may still happen when two people are in close proximity for a long time or come in touch with an infected person's lesions [11].

One example of contaminated objects or surfaces thought to increase the probability of viral transmission among household members is sharing a residence or using dishes that have been used by an infected individual. Another finding in the ongoing monkey pox epidemic is that men who have sex with other males are more likely to get the disease [12]. Similar to smallpox, the infectious process for monkey pox virus starts with the oropharyngeal or respiratory mucosa of the host.

The respiratory and oropharyngeal mucosa, which in the event of human-to-human transmission, serves as the site of inoculation, where the monkey pox virus multiplies after viral entrance. In primary viremia, the viral load increases and then spreads to neighbouring lymph nodes. Secondary viremia occurs when the virus has already disseminated via the bloodstream to other organs and tissues. The incubation phase is reflected throughout the entire process, which lasts anywhere from seven days to twenty-one days [13].

4. SIGNS AND SYMPTOMS

Mpox causes signs and symptoms which usually begin within a week but can start 1-21 days after exposure. Symptoms typically last 2-4 weeks but may last longer in someone with a weakened immune system. Bullous rash, high fever, chills, exhaustion, enlarged lymph nodes, muscular discomfort, and skin rash are all symptoms of monkey pox. All symptoms are present at the prodromal stage, but without rash.

The rash often occurs 4–5 days after the onset of the fever and lasts for 2–3 weeks. Although rash frequently emerges on the face, it may also be noticed on the palms and soles of the feet. Genital, anal, and oral mucosa involvement have been linked to recent instances [14]. The rash resembles 2 to 5 mm-diameter patches. Blisters and pustules are form from these areas and sores. With an umbilical cord-like depression in the centre. After around one to two weeks, these lesions finally form a crust, dry up, and peel off the skin. The rash may be uncomfortable while still developing, but it generally becomes irritating as it heals. Leukocytosis, thrombocytopenia, and abnormal liver function enzymes are only a few of the general laboratory abnormalities linked to monkey pox infection [15].

5. DIAGNOSIS

Conventional methods

The gold standard of diagnosis is PCR, which should be carried out initially. Additional tests specified in the table may be performed if the PCR test is negative but monkey pox infection is suspected. Following a positive monkey pox PCR result, all those have come into contact with the patient should be traced, tested, and, if at all feasible, immunised [16, 17].

Advanced method

Multiple cross displacement amplification (MCDA), a unique isothermal amplification approach that was developed more recently for nucleic acid detection, has been widely used to diagnose the presence of more than 50 pathogens, including bacteria, viruses, and fungi. The target sequences could be detected down to three copies using MCDA, which used a set of 10 primers to achieve nucleic acid amplification at a constant temperature (58-69°C) in 20–30 min. It also has distinct benefits on speed, sensitivity, high efficiency, and minimal equipment requirements.

In particular, nanoparticle-based biosensors (such as the lateral flow biosensor) have been developed and used to detect nucleic acid-based amplified products because they are quick, inexpensive, simple to use, and do not require sophisticated equipment or highly skilled personnel. Therefore, to diagnose MPXV infection and differentiate between West and Central African MPXV strains (MPXV-MCDA-LFB), the MCDA approach in combination with nanoparticle-based lateral flow biosensor (MCDA-LFB) is utilised [18].

6. PATHOGENESIS OF DISEASES

Although it is uncommon, droplet transfer is the most prevalent reason for transfer from person to person. This image displays both direct contact with mucocutaneous sores on sick patients and with contaminated objects or surfaces. The monkey pox virus spreads through contact with the patient's oropharyngeal or respiratory mucosa, as the smallpox virus does. Monkey pox viruses replicate at the injection site once they have gotten inside of the host. The oropharynx and respiratory mucosa serve as the routes of human-to-human transfer. Dissemination to the secondary lymph nodes follows viral replication in initial viremia. When a person has secondary viremia, the virus spreads to other lymph nodes and organs through the bloodstream transports in the body. The overall time needed is similar to the incubation phase, which may last up to 21 days but often lasts between 7 and 14 days.

It is not communicable during the incubation phase of monkeypox where the clinical signs are not present. This prodromal phase may also be associated with clinical signs and symptoms of monkey pox. Secondary viremia travels from lymphoid organs to the skin and tertiary organs such the lungs, eyes, and digestive systems during the prodromal stage. Humans are thought to be contagious during the prodromal period. The occurrence of lymphadenopathy, mucocutaneous lesions, and other nonspecific symptoms is mostly to blame. After one to two weeks, a person starts experiencing the typical nonspecific symptoms. The immune system-stimulating symptoms including fever, lymphadenopathy, and myalgia manifest without any apparent cause in the prodromal stage.

Due to their lack of specificity the first symptoms are often mistaken for the common cold or seasonal flu. The early activation of the immune system causes swelling of the lymph nodes in the maxillary, cervical, and inguinal regions, which also coincides with the development of fever. Before the outbreak of 2022, the rash often appeared 1–3 days after the first manifestation of systemic symptoms (fever, lymphadenopathy). The rash first appears on the face and then rapidly spreads to the rest of the body. The face and limbs are more often affected by lesions than the torso and mid-section which is referred to as a centrifugal distribution.

This illustration depicts typical oral lesions that obstruct the ability to eat, drink and stop an infected individual from doing so. A widespread bullous-pustular eruption is the hallmark of monkey pox. It has been discovered that the rash itself goes through a number of phases before reaching the desquamation stage, during which the scabs fall off. These distinctive lesions often appear as edematous, macular, and papular, followed by picture-perfect cases of vesicular and pustular lesions. In 2 to 3 weeks, these lesions ultimately crust. Lesions will form on the tongue and mouth before the rash manifests on the skin. These lesions are named Enanthem. The individual is no longer regarded as infectious when the crusted lesions peel off to show fresh skin underneath. In some cases, a scar may be left when the scab breaks off. Some individuals may even have areas of hyper-pigmentation and hypo-pigmentation where the rash was more concentrated.

Until then, the crust causes extreme itching. Epidermal necrosis is seen at the core of individual lesions during the early stages of lesion development in humans, along with initial expansion into the dermis' superficial layers. Non-human primates with monkey pox have also shown increased lesion pathology when pustules grow, including progressive ulceration, necrosis, and interstitial hyperplasia. Additionally, fluid and cellular debris collect in the intercellular gaps, where fissures form and oedema forms at the edges of the necrotic regions. Along with a preponderance of necrosis and inflammation in the superficial dermis, the loss of sebaceous glands and hair follicles is also noticeable. The combination of these characteristics caused the afflicted region to be described as a "partial wound," and lesions of this size should be carefully protected against consequences including subsequent bacterial infection and potential cellulitis [19].

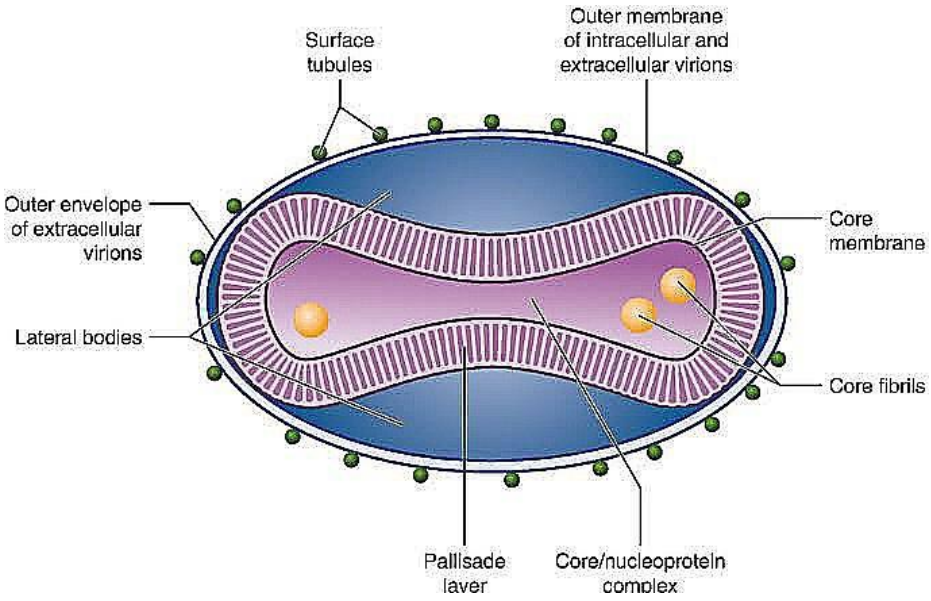

Fig.1 Structure of Monkey pox virus

Table 1. Diagnostic tests for Monkey pox

Tests	Description	Sample used
PCR	Based on NAAT. Real-timePCR is currently the gold standard for detection monkey pox DNA	Lesion Fluid
Viral Culture	Viruses are grown and isolated from patient samples	Lesion Fluid
Electron Microscopy	Electron microscopy is used morphologically identify small poxvirus	Biopsy specimen, Scab material, Vesicular fluid
Immuno Histochemistry	Test for the presence of orthopoxvirus-specific-antigen	Biopsy Specimen
Anti-orthopoxvirus IgG and IgM test	These tests can be used to access recent exposure to Orthopoxvirus.	Blood specimen

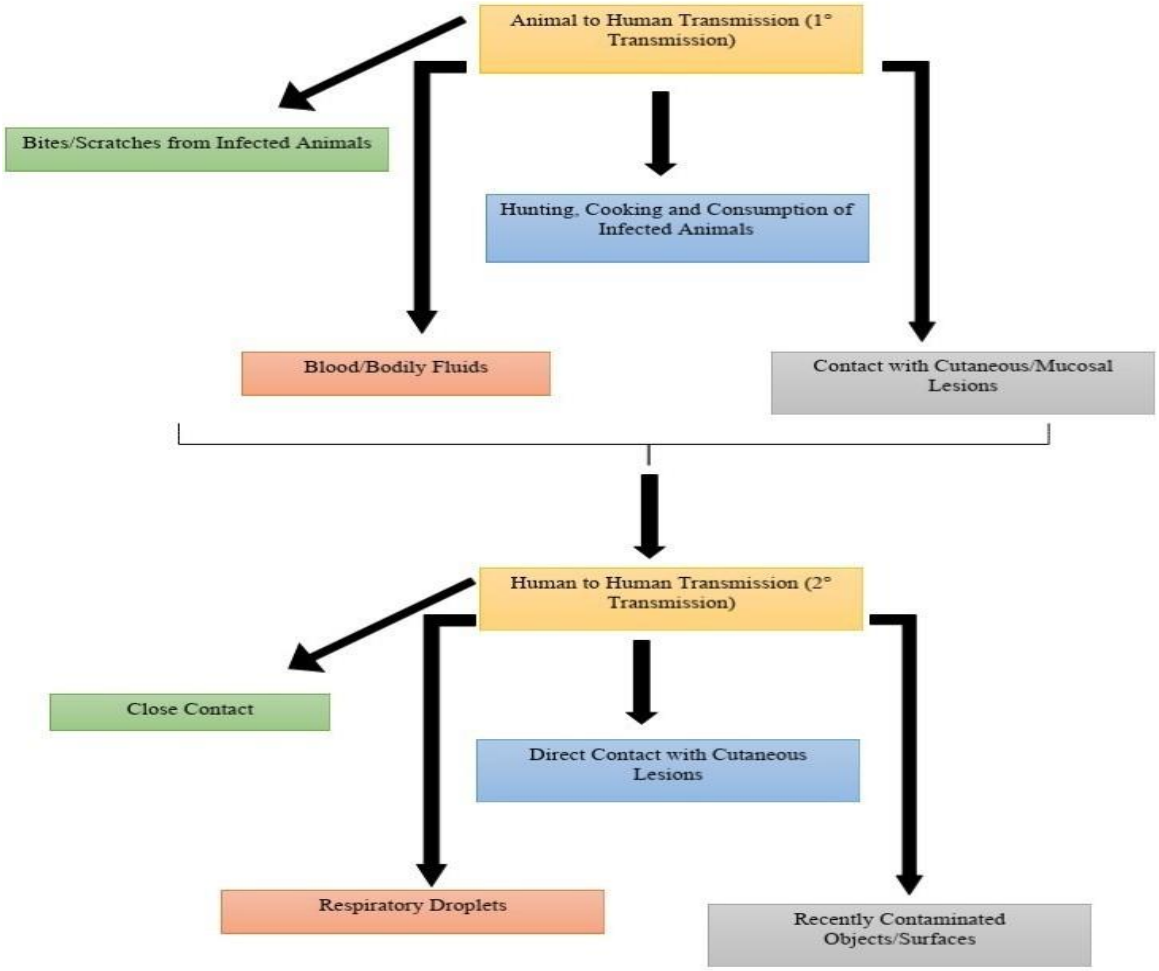

Fig. 2 Transmission of Monkeypox virus

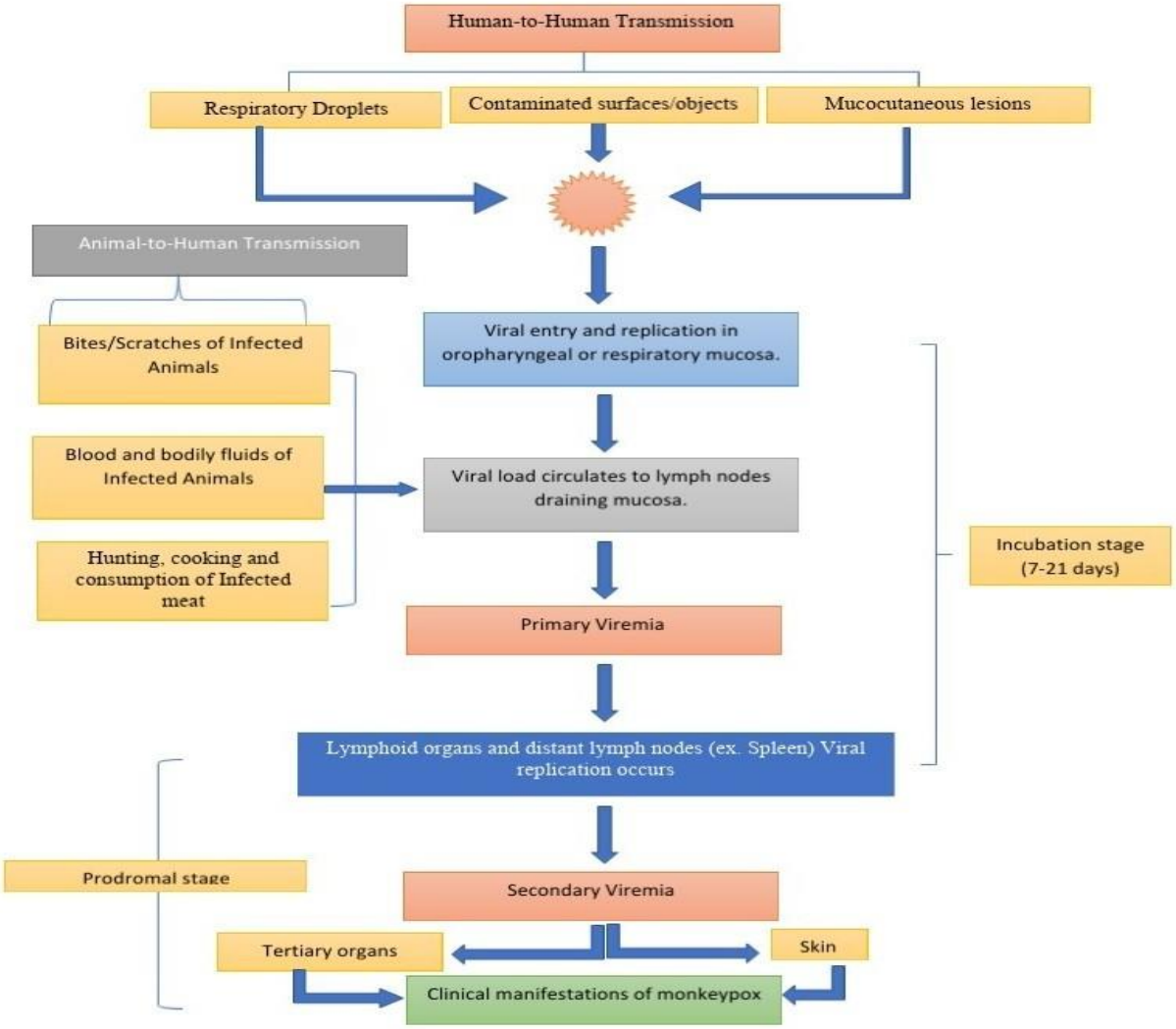

Fig. 3 Pathogenesis of monkey pox virus

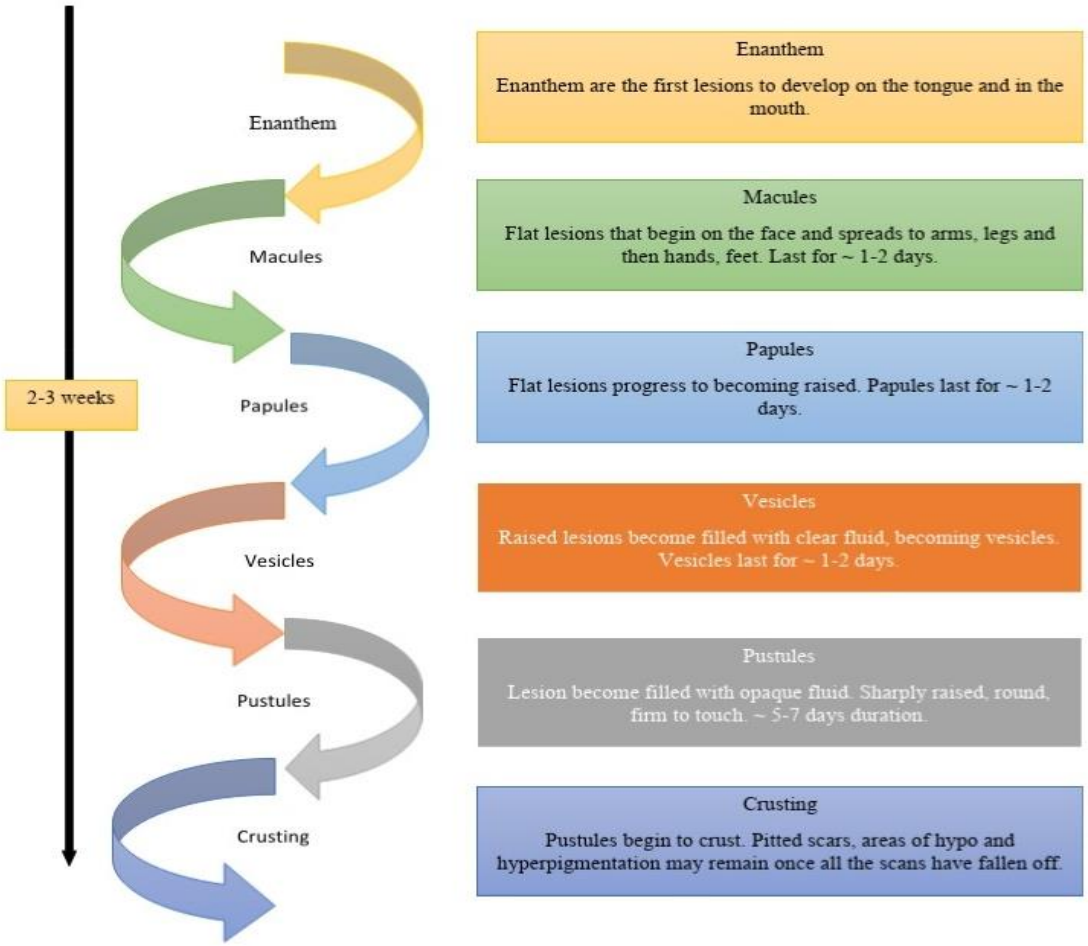

Fig. 4 Progression of Symptoms of Monkeypox virus

7. PREVENTION FROM SPREADING OF DISEASES

Step 1: Avoid near pores and skin contact with all of us who have monkey pox-like rash.

- This may include rashes, acne, blisters, or crusted skin.
- The rash may spread to other body areas, included the arms, legs, chest, face, and mouth, and may also manifest itself in the vaginal area (penis, testicles, labia, and vagina). Stay away from physical contact.
- Don't kiss, hug, cuddle, or intercourse with a person who has monkey pox.

Step 2: Do not use objects or materials used by monkey pox patients.

- Do not share cutlery or cups with monkey pox patients.
- Do not handle or touch a monkey pox patient's bedding, towels, or clothing.

Step 3: Wash your hands frequently.

- Wash your hands often using an alcohol-based hand sanitizer or washing one's hands thoroughly with soap and water, especially before touching one's face, eating, or using the bathroom, is recommended [20].

Step 4: Limit the trade in animals.

- Limiting the commerce in animals is another crucial element in the prevention of mpox that can also help to lower the disease's prevalence. A few nations across the world have passed laws that place limitations on the importation of non-human primates and rodents.

Step 5: Quarantine and monitor the infected animals.

- If captive animals are thought to have monkey pox, immediately quarantine from other animals and keep in isolation. Any animal that may have come into contact with an infected animal should be quarantined, handled carefully, and kept an eye out for symptoms of the measles for at least 30 days following the interaction [21].

8. TREATMENT OF DISEASES

Supportive care

Monkeypox treatment options include pain control and supportive care. In situations of monkeypox, painkillers such as non-steroidal anti-inflammatory medicines (NSAIDs), acetaminophen, or lidocaine may be used topically or intravenously. With caution regarding the adverse effects, gabapentin or opioids can be administered for severe pain. Oral /intravenous hydration is essential for patients having gastrointestinal symptoms (vomiting, diarrhoea, etc.) to prevent further fluid *loss.*

Antiviral agent

There is no currently FDA-approved antiviral treatment for monkeypox. However, antiviral medications for smallpox, such as tecovirimat, brincidofovir, Vaccinia Immunoglobulin Intravenous (VIGIV), and cidofovir, may also be helpful for curing monkeypox.

- **Tecovirimate** is the first antiviral medicine to be permitted by law to be used in smallpox therapy. TPOXX and ST-246 are two more popular brand names for people aged 18 years and older & in children weighing 3 kg or more, it is regarded as the preferred method. Patients with severely sick diseases may benefit from dual treatment with tecovirimate and brincidofovir. Tecovirimat blocks the viral coat protein VP37. Infected hosts are unable to produce more of the virus because VP37 hinders latter stages of viral development before discharge from infected cells. Animals treated with tecovirimate had less deadly monkey pox virus infection than animalstreated with a placebo at different phases of the illness. Strategic national stocks include Tecovirimat is available as an intravenous vial or an oral capsule.

- **Brincidofovir and Cidofovir** Since June 2021, brincidofovir has been legally prescribed in the United States for the treatment of smallpox. Cidofovir is an injectable medicine, but its oral analogue, brincidofovir, may have a more favourable safety profile. Therefore, it has a lower potential for nephrotoxicity. These drugs inhibit the critical enzyme required for viral DNA replication. Cidofovir'susefulness in treating human monkey pox has not been shown in clinical trials. Cidofovir is most effective when administered with an intravenous infusion of normal saline and probenecid. Liver function tests should be conducted before and throughout therapy with brincidofovir where it may raise serum transaminases and serum bilirubin. These procedures may be obtained with a EUA or IND [22].

- **Vaccinia Immunoglobulin (VIG)** In the United States, Vaccinia immunoglobulin verified plasma gamma globulins extracted from individuals immunised with live vaccinia virus vaccine, is approved for the treatment of smallpox vaccination sequelae.

- **ACAM2000 and MVA-BN Vaccines** ACAM2000 and MVA-BN vaccinations are available to combat the present outbreak. The Food and Drug Administration (FDA) has approved the use of ACAM2000 (Emergent Bio Solutions), a second-generation live, attenuated vaccinia virus vaccine, before or after exposure to monkeypox. Although successful, there is a chance of heart problems. Developed by Bavarian Nordic, MVA-BN is a third-generation live, attenuated, non-replicating, modified vaccinia Ankara vaccine [23].

9. Current Monkeypox scenario in world

- Since the latest situation report was issued on April 13, 2023, 183 additional cases of mpox (a 0.2% increase in the total cases) and 14 further deaths associated with them have been reported to WHO.

- Worldwide, the number of mpox cases reported each week is continuing to decline; however, the Western Pacific Region reported increase in cases (n = 62) over the past three weeks compared to the three weeks before (n = 46), which was caused by an outbreak of mpox that primarily affected men in Japan, the Republic of Korea, and China and had sustained local transmission.

- According to recent studies, the current multi-country outbreak of mpox has an incubation period of six to nine days. This scenario report offers in-depth knowledge about the subject.

- Through risk communication and community engagement initiatives, including those on social media, WHO continues to cooperate with Member States to manage and interrupt, prolonged person-to-person transmission of monkeypox [24].

10. CONCLUSION

The monkey-pox virus, which was formerly widespread in parts of Africa, is now spreading worldwide and has rarely been detected in the Western Hemisphere. Social seclusion and contact monitoring are essential since the virus is often transmitted via close contact with mucosal sores on infected patients. Middle-aged people have been reported to have monkey pox. This could be caused by the elderly losing their smallpox vaccination cross-immunity. As it develops into a primary viremia and multiplies inside the cytoplasm, the virus travels to nearby lymph nodes. Additionally, consequences from monkey pox infection include encephalitis, dehydration, bronchopneumonia, and shortness of breath. The corneal scarring that may result in vision loss is the issue that people are most afraid about. To reduce the danger of these problems as much as possible, it is critical to provide proper supportive care. Apply a wet occlusive dressing to the skin where the rash is very severe. The organization concentrates on how these instances emerge occasionally in Europe and the Western Hemisphere while monkey-pox cases continue to be verified across the planet. Understanding the exact amount of monkey pox symptoms, as well as the long-term impact of the virus and symptoms, is crucial, as is researching new therapies.

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Conflict of Interest Statement

The authors have declared that no competing interests exist.

Ethical approval

Not Applicable.

11. REFERENCES

1. **Mitja, O., Ogoina, D., Titanji, B.K., Galvan, C., Mayumbe, J.J., Marks, M., & Orkin, C.M. (2022).** Monkeypox. The Lancet. **401, 60-74**.
2. **Nawal, A., Zargham, H., Asmara, M., Asim, M., Uzna, I., Maria, F., Jahanzeb, M., & Amin, M. (2022).** Human monkeypox virus: An updated review. Medicine. **101, e30406**.
3. **Cohen, J. (2022).** Monkeypox outbreak questions intensify as cases soar. National Library of Medicine. **376, 902-903**.
4. **Chaudhari, S., Treffelsen, L., Virk, J., Parlkh, T., Ravikumar, N., Goti, M., Goyal, L., & YashiK. (2023).** The 2022 Monkeypox Epidemic and What Has Led to the Current State of the Disease in the US: A Systematic Review. Cureus. **15, e33515**.
5. **Britannica, The Editors of Encyclopaedia. (2023).** Monkeypox. Encyclopedia Britannica. https://www.britannica.com/science/monkey pox. Accessed **29 July 2023**.
6. **Choi, H., Lee, W., Roye, D., Bro, S., Urban, A., Entezari, A., & et al. (2023).** Corrigendum to "Effect modification of greenness on the association between heat and mortality: A multi-city multi-country study.eBiomedicine, Part of THE LANCET Discovery Science. **87, 104396**.
7. **Hendrickson, RC., Wang, C., Hatcher, EL., & Lefkowitz, EJ. (2010).** Orthopoxvirus genome evolution: the role of gene loss. Viruses. **2, 1933-67**.
8. **Shchelkunov, SN., Totmenin, AV., Babkin, IV., Safronov, PF., Ryazankina, OI., Petrov, NA., Gutorov, VV., Uvarova, EA., Mikheev, MV., Sisler, JR., Esposito, JJ., Jahrling, PB., Moss, B., & Sandakhchiev, LS. (2001).** Humanmonkeypox and smallpox viruses: genomic comparison. FEBS Lett. **509**, **66-70**.
9. **Kugelman, JR., Johnston, SC., Mulembakani, PM., Kisalu, N., Lee, MS., Koroleva, G., McCarthy, SE., & et al. (2014).** Genomic variability of monkeypox virus among humans, Democratic Republic of the Congo. Emerg Infect Dis.**20, 232-239**.

10. **Hutson, CL., Olson, VA., Carroll, DS., & et al. (2009).** A prairie dog animal model of systemic orthopoxvirus disease using West African and Congo Basin strains of monkeypox virus.Microbiology Society. **90, 323-333**.
11. **Simpson, K., Heymann, D., Brown, CS., & et al. (2020).** Human monkeypox - after 40 years, an unintended consequence of smallpox eradication. Vaccine.**38, 5077-81**.
12. **Okyay, RA., Bayrak, E., Kaya, E., & et al. (2022).** Another epidemic in the shadow of Covid 19 pandemic: a review of monkeypox. EJMO.**6, 95-99**.
13. **Moore, M., Rathish, B., & Zahra, F. (2023).** Mpox (Monkeypox). Stat Pearls, Treasure Island (FL). https://www.ncbi.nlm.nih.gov/books/NBK574519/.
14. **Thornhill, JP., Barkati, S., Walmsley, S., & et al. (2022).** Monkeypox virus infection in humans across 16 countries - April-June 2022. NEngl J Med. **387, 679-691**.
15. **Huhn, GD., Bauer, AM., Yorita, K., & et al. (2005).** Clinical characteristics of human monkeypox, and risk factors for severe disease. Clin Infect Dis.**41:1742–1751**.
16. **McCollum, AM., & Damon, IK. (2014).** Human monkeypox. Clinical Infectious Diseases. **58, 260–267**.
17. **Li, D., Wilkins, K., McCollum, AM., & et al. (2017).** Evaluation of the GeneXpert for human monkeypox diagnosis. Am J Trop Med Hyg. **96, 405-10**.
18. **Zhou, J., Xiao, F., Fu, J., Jia, N., Huang, X., Sun, C., Liu, C., Huan, H. (2023).** Rapid detection of monkeypox virus by multiple cross displacement amplification combined with nanoparticle-based biosensor platform. Journal of Medical Virology. **95, e28479**.
19. **Kaler, J., Hussain, A., Flores, G., & et al. (2022).** Monkeypox: A Comprehensive Review of Transmission, Pathogenesis, and Manifestation, Cureus. **14, e26531**.
20. **Gupta, A.K., Talukder, M., Rosen, T., & et al. (2023).** Differential Diagnosis, Prevention, and Treatment of mpox (Monkeypox): A Review for Dermatologists. Am J ClinDermatol. **24, 541-556**.
21. **Patel, M., Adnan, M., Aldarhami, A., Bazaid, A.S., Saeedi, N.H., Alkayyal, A.A., Saleh, F.M., Awadh, I.B., Saeed A, & Alshaghdali K. (2023).** Current Insights into Diagnosis, Prevention Strategies, Treatment, Therapeutic Targets, and Challenges of Monkeypox (Mpox) Infections in Human Populations. MDPI, Life. **13, 249**.
22. **Titanji, B.K., Tegomoh, B., Nemarollahi, S., Kimonos, M., & Kulkarni, P.A. (2022).** Monkeypox: A Contemporary Review for Healthcare Professionals. Open Forum Infectious Diseases. **9, ofac310**.
23. **Gessain, A., Nakoune, E., & Yazdanpanah, Y. (2022).** Monkeypox. The New England Journal of Medicine.**387, 1783-1793**.
24. **WHO. (2023).** Multi-country outbreak of mpox. External Situation Report **21**, published **27 April 2023**. Data as received by WHO national authorities by **17:00 CEST**, **24 April 2023.** Accessed from: World Health Organization. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20230427_mpox_external-sitrep-21.pdf?sfvrsn=91731cd2_3&download=true.