



A Review Article On: Monkeypox Virus

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ABSTRACT

Monkeypox a viral zoonosis, is a disease caused by the monkeypox virus. The first case of Monkeypox occurred in a 9-month-old child in the Democratic Republic of the Congo in 1970. In this review the overall information about monkeypox disease, their causes, symptoms, treatment and comparison between monkeypox and smallpox was studied.

Keywords

Transmission, Monkeypox, Treatment, Vaccine

INTRODUCTION:

Monkeypox, a viral zoonosis, is a disease caused by the monkeypox virus, which remained a neglected tropical illness in sub-Saharan Africa for decades. It wasn't until May 2022, when an initial cluster of infections was reported in the United Kingdom, that global attention was drawn to this disease. According to the World Health Organization, the virus is an emerging zoonotic infection, primarily transmitted from animals to humans. The monkeypox virus belongs to the orthopoxviral genus in the Poxviridae family, with a double-stranded DNA genome. While it was once confined to endemic areas in Africa, the virus has increasingly spread to other parts of the world, partly due to changes in global environmental factors, human activities, and the cessation of smallpox vaccination programs after eradication in 1980.

Monkeypox has been observed to transmit through direct contact with infected animals, humans, or contaminated materials. Populations in forested regions, healthcare workers, and individuals in close contact with infected persons or animals are at higher risk. Vulnerable groups, such as children, pregnant women, and immunocompromised individuals, are particularly susceptible. The virus shares structural features with other Ortho poxviruses, and its genome is 96.3% similar to that of the variola virus, the cause of smallpox. Though the monkeypox virus has a lower-case fatality rate (3.4% to 10%), it poses a significant threat in certain settings.

The emergence and spread of monkeypox are further exacerbated by global environmental changes, including deforestation, land use changes, and increased human-animal interactions due to tourism and trade. These disruptions create new opportunities for the virus to spread, further highlighting the need for preparedness in both endemic and non-endemic regions. Recent outbreaks in non-endemic areas, such as the 2003 outbreak in the United States, illustrate the global reach of the virus. As travel becomes increasingly interconnected, isolated outbreaks can quickly evolve into larger global epidemics, making monkeypox a growing public health concern.¹

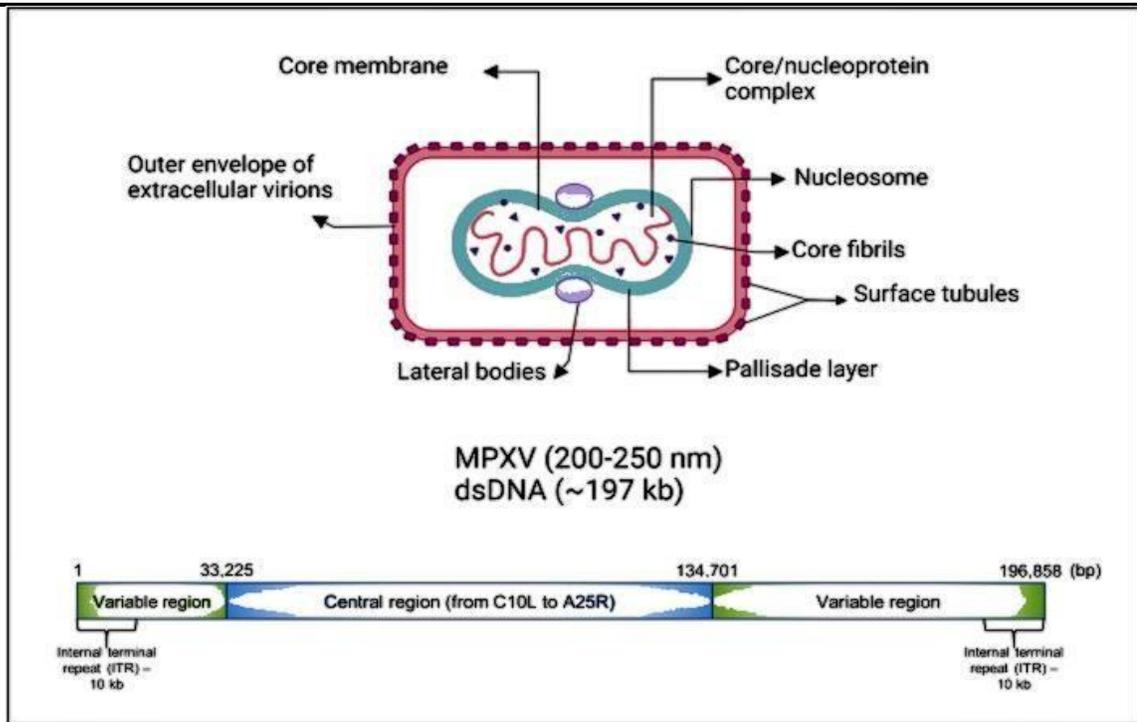
History.

The first case of Monkeypox occurred in a 9-month-old child in the Democratic Republic of the Congo in 1970. The virus gained substantial Prominence in 2003–2004, following an outbreak in the United States.² Clinical manifestations following monkeypox infection is similar to Smallpox,^{3,4} However, Monkeypox is typically less lethal. The global Attention to Monkeypox rose in the 1970s, following the eradication of Smallpox, as the incidence of the virus increased due to the cessation of Smallpox vaccination programs. The virus was named after its initial Observation in macaque monkeys, though it is not actually transmitted By these primates. Instead, transmission is believed to occur through Various rodent and small mammal species, although the exact origin of The virus remains uncertain. Prior to 1970, the occurrence of the virus Was only documented in non-human hosts. However, this perception Was revised following the 2003 out Case in a returning traveler from Nigeria in May reack in the United States The 2003 Monkeypox outbreak in the United State Resrevealed an increased level of Transmissibility among human hosts, as well as a higher level of viremia in infected patients.

Table – 1:- Comparing different vaccine that are currently used in different countries by type, route of administration, target group and recommended number of doses^{5,8}

NUMBER	VACCINE	TYPE	ROUTE OF ADMINISTRATION	RECOMMENDED No. Of DOSE
1.	ACAM2000	Live attenuated (2nd generation)	Percutaneously	Single dose
2.	JYNNEOSTM / MVA - BN	Vaccinia virus (Ankara strain) containing MPX antigen	Subcutaneously	2 doses within 28 days
		(3 Rd generation)		
3.	LC - 16	Live attenuated (3 Rd generation)	Percutaneously	2 doses within 28 days

Singapore reported one suspected Case in a returning traveler from Nigeria in May 2019^{9,10} three



relatives from the same family Who had traveled from Nigeria to the United Kingdom (UK) were also confirmed infected in May 2021.¹¹ An additional case of a man who Moved from Nigeria to Texas, USA and developed human monkeypox was reported in July 2021.¹² at that same time infection was identified in another patient who had recently moved From Nigeria to Maryland, USA, that same year ¹⁵Transmission and risk factors of MPVX

Monkeypox can spread through multiple routes:

1. Animal to Human Transmission:

Direct Contact with Infected Animals: Humans can contract the virus by handling animals, especially rodents, monkeys, and squirrels, or by consuming undercooked meat from infected animals.

Animal Products: The handling of materials contaminated with animal body fluids, or direct contact with skin or blood of infected animals, is a risk factor.

2. Human to Human Transmission:

Respiratory Droplets: Prolonged face-to-face contact or exposure to respiratory droplets from an infected person can facilitate transmission. **Skin-to-Skin Contact:** Direct contact with lesions, bodily fluids, or contaminated surfaces (like bedding and clothing) can transmit the virus.

Vertical Transmission: Transmission from a pregnant woman to the fetus via the placenta is also possible.

3. Fomites:

Contaminated objects like clothing, bedding, and other surfaces that have been in contact with infected individuals can serve as a medium for transmission.

4. Sexual Transmission:

Recent data suggests that sexual contact can also be a mode of transmission, particularly during close physical interactions such as intercourse, due to skin lesions or bodily fluids.¹⁶Risk Factors for Monkeypox Infection

Several factors increase the likelihood of infection:

Geographic Location: People living in or traveling to endemic regions, especially parts of central and West Africa, are at higher risk of animal-to-human transmission.

Exposure to Infected Animals:

Handling or consuming bushmeat, or coming into contact with animal carcasses, is a risk factor in endemic areas.

Human-to-Human Contact:

Close Contact: Those living in close quarters with infected individuals or healthcare workers attending to symptomatic patients are at higher risk of transmission.

Household and Social Contact: Shared living spaces with infected persons increase the likelihood of catching the virus.

Healthcare Settings: Lack of proper personal protective equipment (PPE) for healthcare workers increases the risk of nosocomial transmission.

Immune Status:

Immunocompromised Individuals: Those with weakened immune systems (due to conditions like HIV/AIDS, cancer, or due to immunosuppressive treatments) are at a higher risk of severe disease and complications.

Age and Vaccination History:

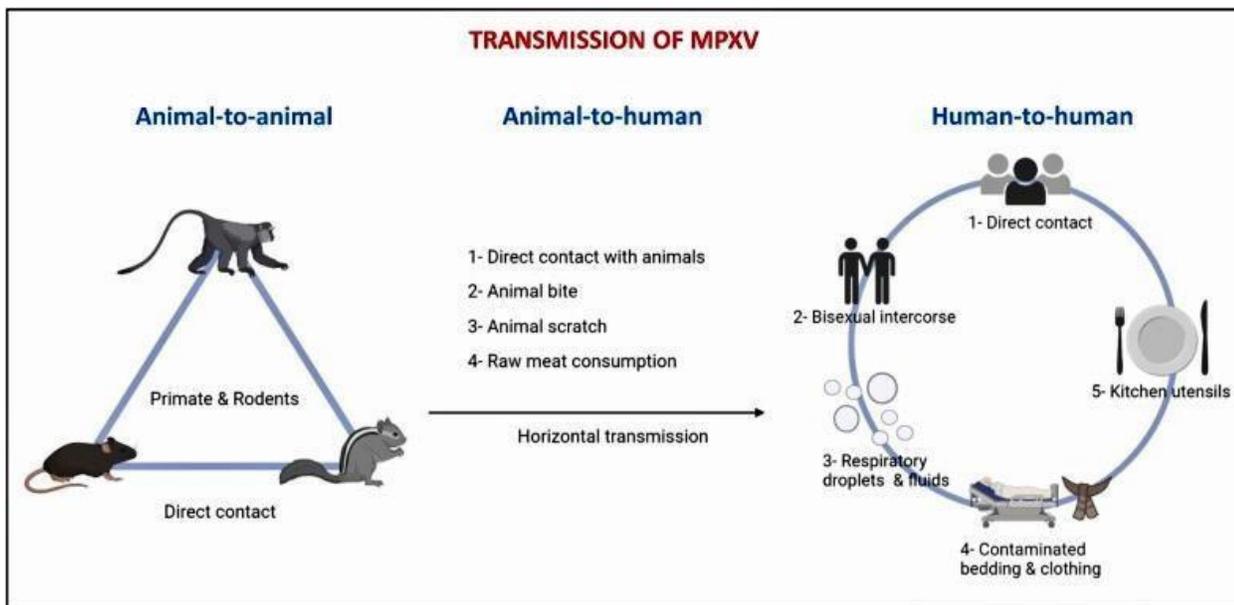
Older Individuals: Adults born before the widespread use of the smallpox vaccine (which also provides some immunity to monkeypox) are at increased risk.

Unvaccinated Individuals: People who have not been vaccinated against smallpox are at a higher risk of severe infection.

Exposure to Infected Individuals:

Sexual Contacts: Recent outbreaks have shown that men who have sex with men (MSM) are at higher risk, though the virus can be transmitted to anyone through close contact.

1. Travel to areas with ongoing outbreaks or endemic regions significantly increases the risk of infection, as recent outbreaks have shown that monkeypox can spread rapidly across borders.^{17,18}



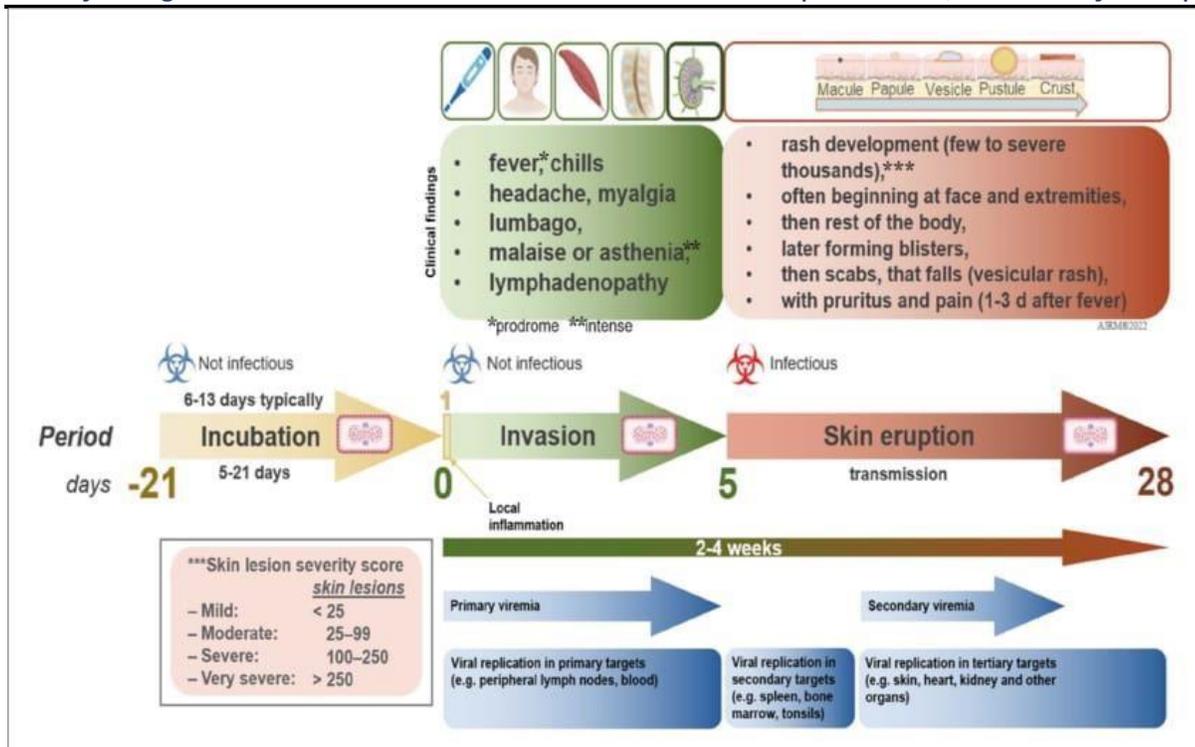
The risk of transmission of MPXV by substances of human origin (SOHO) for recipients in the EU/EEA area has been evaluated by the European Center for Disease Control,¹⁹ While it recognises that monkeypox virus is likely to be transmissible through SOHOs, the overall risk is estimated to be low, for reasons of a historical absence of documented transmission of this virus from such sources, uncertainty about the duration of viremia and a lack of data on the duration and viral loads of MPXV in asymptomatic patients. In the UK, the UK Standing Advisory Committee on Transfusion Transmitted Infections (SACTTI) has produced a position statement on MPXV infection in donors and its potential transmissibility. The Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) have subsequently issued guidance on donor selection, specifically that donors with recently diagnosed MPXV infections cannot donate within 28 days nor can close contacts of individuals with MPXV infection within the last 21 days.

Clinical features

The incubation period has been estimated at 5 to 21 days, and duration of symptoms and signs at 2 to 5 weeks. The illness begins with nonspecific symptoms and signs that include fever, chills, headaches, lethargy, asthenia, lymph node swellings, back pain, and myalgia (muscle ache) and begins with a fever before rashes appear. Within 1 to 5 days after the onset of fever, rashes of varying sizes appear, first on the face (Fig. 3), The rash undergoes several stages of evolution from macules, papules, vesicles (fluid-filled blisters) (see Fig. 3)



The clinical presentation of monkeypox includes symptoms and lesions that are difficult to distinguish from smallpox.^{20,21,22,23} Although the clinical manifestations of monkeypox are milder than smallpox, the disease can prove fatal, death rates ranging from 1% to 10%. Mortality is higher among children and young adults and the course is more severe in immunocompromised individuals.²⁴ A range of complications has been reported, such as secondary bacterial infections, respiratory distress, bronchopneumonia, encephalitis, corneal infection with ensuing loss of vision, gastrointestinal involvement, vomiting, and diarrhea with dehydration. Case fatality rates have varied between 1% and 10% in outbreaks, deaths occurring mostly among young adults and children. Particularly those with immunosuppression are at risk of severe disease. Lymphadenopathy is seen in up to 90% of patients and appears to be a clinical feature distinguishing human monkeypox from smallpox. Monkeypox is a self-limiting disease, and the duration of symptoms is approximately 2 to 4 weeks.²⁵ The incubation period of monkeypox is usually 6-13 days but can range from 5 to 21 days in Some cases (Figure 4). Short after the incubation Period, monkeypox infection undergoes two Phases or periods (Figure 4); the invasion phase and skin eruption (rash phase) Initial clinical findings of human monkeypox



are Very alike those of smallpox, chickenpox, and Measles. It begins with a prodromal phase, that Can include fever, headache, myalgia, and severe asthenia (Table 2). Early in the disease, lymphad-Enopathy caused by monkeypox is what differ-Entiates it from smallpox.

Splenomegaly and he-Patomegaly can also be found in these patients, As MPXV replicates in different lymphatic tissues and other organs (Figure 4) ^{26,27}. The vesicular-pustular rash is the clinical hallmark Feature of monkeypox, largely impacting the in-Fected individual (Table 2) (Figure 4)

Table: - Reported clinical findings in monkeypox and smallpox

Characteristics	Monkeypox	Smallpox
• Period		
Incubation phase	Often 6 – 13 days	Usually 6 – 13 days
Prodromal phase	1 – 3 days	1 – 3 days
Rash phase	14 – 28 days	14 – 28 days
• Sign and symptoms		
Fever	Usually between 38.5°C and 40.5°C	Usually, < 40° C
Muscle pain, severity	Moderate	Moderate
Lymphadenopathy	Moderate	No
Headache, severity	Moderate	Severe
• Skin lesions		

Depth (mm)	Superficial to deep; 4 – 6 days	Deep, 4-6 days
Distribution	Centrifugal; mainly	Centrifugal
Evaluation	Homogeneous rash	Homogeneous rash
Lesions appearance	Hard will- circumscribed, deep and umbilicated	Hard will-circumscribed, deep and umbilicated
Lesions progression	Slow progression, each stage lasts about 1-2 days	Slow progression, each stage lasts about 1-2 days

Diagnosis:

1. Clinical presentation

The early diagnosis of monkeypox is based on clinical signs and epidemiological links.^{28,29} According to WHO recommendations, any individual meeting with a suspected case, that is, a person of any age who presents in a non-MPX endemic country with an unexplained acute rash and one or more of the following signs or symptoms for which the common causes of acute eruption do not explain the clinical presentation, should be tested for the presence of MPX. Asthenia, headache, sudden start of fever over 38.5°C, lymphadenopathy, myalgia, and back discomfort should all be evaluated^{29,30}

2. Laboratory tests

Cell culture, polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), immunohistochemistry, electron microscope, or Western blot analysis or sequencing are currently available diagnostic tests for MPXV detection, with PCR being used for definitive diagnosis.^{31,32}

Lesion fluid, lesion roof, scab/crust, oropharyngeal tissue or nasopharyngeal tissue swab, tonsillar tissue, punch biopsy kit, whole blood, and acute and convalescent phase sera are all required for laboratory diagnosis.³² The lesion samples must be stored in a dry, sterile tube in a cool environment.³⁰ During specimen collection, standard contact and droplet precautions must be implemented, and any potentially contaminated samples with the MPXV must be handled in Biosafety level 2 facilities.²⁹

3. Polymerase chain reaction (PCR)

Nucleic acid amplification testing (NAAT), which uses real-time or conventional PCR to detect unique sequences of viral DNA, is used to confirm monkeypox infection. Positive results from an OPXV PCR assay followed by monkeypox confirmation via PCR and/or sequencing, or positive results from a monkeypox PCR

assay in suspected cases, indicate monkeypox infection³¹ To detect MPXV DNA from clinical and veterinary specimens, as well as MPXV infected cell cultures, reverse-transcription polymerase chain reaction (RT-PCR) targets conserved regions of the extracellular-envelope protein gene (B6R), DNA polymerase gene, E9L, DNA-dependent RNA polymerase subunit 18, rpo18, and F3L gene are usually considered as targets. In conjunction with sequencing, RT-PCR is the technique of choice for routine diagnosis of MPXV.¹⁸ The PCR test is considered the gold standard laboratory test for its specificity and sensitivity, and it is best performed in a Biosafety level-three facility.

4. Immunologic assay

Immunological methods for detecting IgG and IgM antibodies, as well as immunohistochemistry for viral antigen detection, can be used to detect OPXV DNA.¹⁸ Unfortunately, because OPXVs are serologically cross-reactive, none of these tests provide MPX-specific confirmation.³⁰ Positive IgM capture enzyme-linked immunosorbent assay (ELISA) results indicate recent exposure to OPXV in both unvaccinated and vaccinated individuals, whereas positive IgG capture ELISA results indicate previous exposure to OPXV via vaccination or natural infection.²⁸ IgM and IgG antibodies are detected in serum 5 to 8 days after the onset of the rash, respectively. Immunochemistry analysis can be used to distinguish between OPXV infection and herpes virus infection.^{28,30}

5. Electron microscope

Electron microscopy with negative staining can be used to examine biopsy specimens from lymph nodes or scab material, vesicular fluid, blood specimens, or viral cultures.³² MPXV studies, and phase I human trials are available for clinical use and should be considered for individuals with more severe manifestations of the disease or for postexposure prophylaxis in high-risk situations^{33,34}. Novel Drugs, as well as those that are approved for other indications, have been investigated as Potential therapeutic agents in this regard.

Cidofovir. :-

Cidofovir [(s)-1(3-hydroxy-2-phosphonylmethoxypropyl)cytosine] (HPMPC), a nucleotide analog of cytosine monophosphate that was approved by the U.S. Food and Drug Administration (FDA) in 1996 for the treatment of cytomegalovirus retinitis in Patients with HIV, demonstrates potent activity against other herpesviruses and orthopoxvirus^{33,36} This agent inhibits viral replication by binding to poxvirus DNA Polymerase^{33,38} Cidofovir preexposure prophylaxis has been shown to protect Cynomolgus monkeys against intravenous infection with monkeypox virus, while cidofovir treatment of infected monkeys results in lower peripheral blood viral loads and Skin lesion counts if administered within 48 h of inoculation^{33,39}. Cidofovir treatment within 24 h of infection appears to be more effective than postexposure smallpox vaccination in preventing death of primates after lethal intratracheal challenge With monkeypox virus^{39,40} However, concurrent administration of cidofovir

with Smallpox vaccine may result in an attenuated humoral immune response following Monkeypox virus challenge. Combination therapy with cidofovir and the chemotherapeutic agent mitoxantrone has been shown to have modest synergistic activity against monkeypox virus, based on a mouse model⁴². Overall, these observations imply that for cidofovir therapy to be effective against human monkeypox infection, treatment may need to be initiated prior to the onset of the skin rash, which would require early diagnostic consideration and detection of viral DNA in peripheral blood samples during the prodrome phase. The standard adult human treatment dose of Cidofovir (administered intravenously) is 5 mg/kg weekly for 2 weeks followed by 5 mg/kg biweekly (34). To mitigate the risk of nephrotoxicity, cidofovir must be coadministered with oral probenecid, which prevents the intracellular uptake of the drug by proximal renal tubular epithelial cells and requires intravenous prehydration with 1 to 2 liters of normal saline with or without additional fluid hydration post-cidofovir administration³³. The adult dose of probenecid is 2 g given 3 h prior to cidofovir administration,

Brincidofovir: -

Brincidofovir (hexadecyloxypropyl-cidofovir, also known as HDP-cidofovir or CMX001), is an orally bioavailable and less nephrotoxic lipid analog of cidofovir with demonstrated effectiveness in the treatment of orthopoxvirus infections, including Monkeypox virus, based on animal models^{33,34,44,46}. Brincidofovir is converted to cidofovir intracellularly, although it is not a substrate of the organic anion transporter in proximal renal tubular epithelial cells⁴⁷. Brincidofovir demonstrates greater in vitro potency than cidofovir by achieving higher intracellular concentrations of the active form of the drug, cidofovir diphosphate⁴⁷. Experience with brincidofovir for the treatment of human monkeypox infection has been limited.

Tecovirimat

One of the most promising antivirals for the treatment of human monkeypox infection is tecovirimat {ST-246, or TPOXX; 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2-(1H)-yl)carboxamide}, a small molecule that was discovered and codeveloped by SIGA Technologies (New York, USA) and the U.S. Government following high-throughput screening studies for drugs with activity against Variola virus⁴⁹⁻⁵¹.

Prevention and Control: -

a. Public Awareness and Education

Inform the public about how monkeypox spreads (via contact with infected individuals, animals, or contaminated materials). Promote early recognition of symptoms such as fever, rash, and swollen lymph nodes.

b. Hygiene Practices

Wash hands frequently with soap and water or use hand sanitizer. Avoid close contact with individuals showing symptoms of monkeypox.

c. Safe Handling of Animals

Avoid handling or consuming raw or undercooked meat from wild animals, especially in endemic regions. Implement regulations to limit trade and handling of wild animals that can carry monkeypox.

2. Control Measures

a. Isolation and Contact Tracing

Isolate confirmed and suspected cases to prevent further transmission. Conduct contact tracing to identify and monitor individuals exposed to the virus.

Vaccination

a. Use vaccines like the JYNNEOS (Immune or Imvanex) vaccine, which is FDA approved for monkeypox prevention. Prioritize vaccination for high-risk groups, including healthcare workers and close contacts of infected individuals.

b. Infection Control in Healthcare Settings

Use personal protective equipment (PPE) such as gloves, masks, and gowns. Disinfect surfaces and equipment that may be contaminated. Community Engagement Work with local communities, especially in endemic regions, to enhance understanding and collaboration in control efforts.^{52,53,54}

One Health Approach: Monkeypox

Taking into consideration that most emerging infectious diseases reported globally (especially those declared as PHEIC) are zoonotic diseases, prevention should target breaking the transmission chain both from animal-to-human and human-to-human.^{55,56,57,58} Therefore, the collaboration between health and veterinary professionals, along with the environmental or ecological professionals, is crucial in infection prevention and control (IPC) for zoonoses.⁵⁹ The cooperation between human, animal, and ecological sectors is called the One Health concept. The goal of One Health is to improve population health by recognizing that human and animal health are interdependent and tied to the ecosystem. The key principle of One Health is "to improve the coordination between public health, veterinary, and environmental services. For example, an application of One Health in monkeypox control is when epidemiologists and veterinarians collaborate in an outbreak investigation, identifying the animal reservoir of monkeypox, and ecologists explore the ecological change or conditions favorable to the emergence of monkeypox. In short, cooperation under one health principle is essential to advance knowledge and capacity in the prevention, detection, and response to emerging diseases.

Global Response and Challenges: -

Epidemiology of Human Monkeypox in the Global Outbreak in 2022. Since early May 2022, for the first time, many outbreaks of human monkeypox have been reported in countries in the European Region, where the disease is not endemic^{60,61}. First, between 13 and 16 May 2022, the

UK reported six cases of human monkeypox, without any epidemiological links with travel to Africa or imported animals, and with all cases self-identifying as gay, bisexual, or other men who have sex with men. Most confirmed cases of human monkeypox reported a history of travel to countries in Europe and North America. Besides, human monkeypox cases in endemic countries continue to be reported.

Since early May 2022 and as of 19 September, over 62,000 cases of human monkeypox have been reported worldwide, among them almost all in non-endemic countries⁶². As of 19 September, 44 European countries have reported 24,017 cases, representing 38.5% of all cases reported worldwide in the current outbreak: the largest number was recorded in Spain (6947), followed by France (3898), Germany (3563), and the UK (3552), while one case each was recorded in Turkey and Ukraine. In this outbreak, the largest number of cases (23,892) was reported in the US, representing 38.3% of all reported cases worldwide. Differences in the number of human monkeypox cases by country may be partly explained by differences in population and size of the at-risk populations, socio-economic status, underdiagnosis, and/or underreporting.

Ongoing research into monkeypox (mpox) focuses on understanding its transmission, improving diagnostics, and developing effective treatments and vaccines. The global outbreaks in 2022 and 2024 highlighted the disease's pandemic potential, sparking a renewed interest in controlling it.

Key Research Areas:

1. **Genetic Evolution and Surveillance:** Recent studies show significant genetic variations in the monkeypox virus (MPXV), including changes that may impact transmission and immune evasion. Continuous genomic monitoring is critical to detect new variants and assess their potential health impacts^{63,64}.
2. **Vaccine Development:** Advances include mRNA-based, DNA-based, and multivalent vaccines targeting diverse Ortho poxvirus strains. Current vaccines, such as modified vaccinia Ankara (MVA), are being optimized for efficacy and broader protection. Novel immunostimulatory adjuvants and delivery methods are also under investigation to improve safety and accessibility⁶³.
3. **Therapeutic Interventions:** Antiviral drugs like tecovirimat, initially developed for smallpox, are being evaluated for mpox treatment. Research is also exploring drugs targeting the virus's immune-modulating mechanisms⁶⁴.

4. Epidemiological Trends: Studies are mapping mpox's spread, especially in endemic regions, and identifying high-risk populations (e.g., immunocompromised individuals). Efforts focus on strengthening public health responses and increasing global vaccine distribution.
5. Future Directions: - Integrated Disease Management: Collaborative strategies for surveillance, vaccination, and therapeutic interventions aim to mitigate outbreaks in endemic and non-endemic regions.

Zoonotic Research: Further studies are needed on animal reservoirs and environmental factors driving the virus's spillover to humans. Global Preparedness: Strengthening health systems to respond rapidly to emerging outbreaks will be crucial in managing future mpox cases.

CONCLUSION

This review concluded that, monkeypox is a transmitted disease. The treatment must be taken in early phase. To avoid the spread of monkeypox (mpox), prioritize vaccination if recommended, avoid close contact with individuals exhibiting a rash that looks like mpox, and practice good hygiene, including frequent handwashing and disinfecting surfaces.

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