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REVIEW ARTICLE

Outbreaks of human monkeypox during the COVID-19 pandemic: a systematic review for healthcare professionals

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ABSTRACT

The ongoing 2022 multicountry monkeypox epidemic has drawn worldwide attention. Human monkeypox is a virus that spreads from animals to humans. It is an endemic disease in the rain forests of Central and West Africa. However, the disease recently emerged in India, and also in United States through imported wild rodents from Africa, even though the world is still struggling to escape from the clutches of the COVID-19 pandemic. Monkeypox is one of the contagious zoonotic diseases caused by the monkeypox virus (MPXV), transmitted to humans by direct contact with an infected person or animal or contact with virus-contaminated material. Its lesions are similar to smallpox in humans with various medical complications including flu-like symptoms, fever, malaise, back pain, headache, and a characteristic rash. Public health experts around the world are very concerned about the rapid spread of the infection, which has intensified efforts to find the source and cause of this phenomenon. Several viral infections with epidemic potential threaten global health security. Early recognition of cases and timely intervention of potential transmission chains are necessary to contain further outbreaks. At this early stage of monkeypox outbreaks, the current review provides updated information on the current worldwide monkeypox outbreak status, disease aetiology, clinical presentation, therapy, and preventive measures worldwide. Our review will also provide useful information to health professionals and the general public.

Keywords: Orthopoxvirus; Monkeypox; Human; Re-emergence; Vaccination; Diagnosis; Treatment; Prevention; Healthcare professionals; Outbreak

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INTRODUCTION

The World Health Organization (WHO) included "monkeypox" in its list of infectious diseases caused by viruses that have the potential to become endemic or pandemic, along with Crimean-Congo hemorrhagic fever, Ebola virus disease, Hendra virus infection, influenza, Lassa fever, Marburg virus disease, MERS-CoV, SARS-CoV, Nipah virus infection, smallpox, yellow fever, Zika virus disease, and SARS-CoV. The prevalence of these infections is rising globally and typically cause neurological symptoms (1). The largest non-endemic outbreak of the monkeypox virus (MPXV) has occurred recently. Unlike earlier outbreaks, there is no clear association between infected people or a common source of exposure to the virus (such as travel to endemic areas or contact with infected animals). It is still unclear how the disease spreads. According to the World Health Organization (WHO), infection with MPXV now poses the greatest threat to public health (2). In the present taxonomy of MPXV genetic diversity, only two MPXV clades are recognized: "West African" and "Central African" or "Congo Basin" (1). These historical MPXV clade names, however, oppose the best practice of avoiding geographic locations in naming illnesses and disease groupings (3, 4). The recent and prompt example of SARS-CoV-2 implementation should be the standard (3). Recent papers and conferences, such as the WHO, and Research and Development (R&D) symposium, have shown that the current worldwide pandemic is caused by MPXV of the West African clade which has a recorded 1% death rate (2, 5). In the past, the illness was relatively uncommon outside of Africa, with occasional endemics mainly in the Democratic Republic of the Congo (DRC) and Nigeria (5). Considering the recent spread of monkeypox in light of the ongoing COVID-19 pandemic and the possibility of a coincidence between SARS-CoV-2 and the monkeypox virus is important. This can result in changes related to infection pattern, severity, management, or response to vaccination in one or both the diseases (6). On May 7th, 2022 the World Health Organization (WHO) received a report of a case of monkeypox in which the patient had a previous history of travelling from the United Kingdom to Nigeria and back where the Zoonotic monkeypox disease is endemic in Central and Western Africa (2, 5). The monkeypox virus (MPXV), a virus belonging to the genus Orthopoxvirus, which also includes variola that is the causative agent of smallpox, causes the illness and resembles smallpox symptoms (6, 7). As of 22 July 2022, about 21,000 laboratory-confirmed cases of monkeypox and five deaths have been reported to WHO from 75 countries/territories/areas in all six WHO Regions (8). As more cases in the current epidemic are being reported, it is essential for professionals worldwide to update their awareness about this zoonotic virus, including its prevention, clinical care, prophylaxis, and fundamentals of infection control, to fully understand the more enormous implications of the outbreak. In this article, we provide a general overview of monkeypox virus infection as a reference for medical professionals who might encounter this condition in their profession.

Review methods

Databases including the NCBI Database, Web of Science, CrossRef, Scopus, Medline, PubMed and Google Scholar were searched for study inclusion and exclusion criteria. Search procedures were carried out through essential keywords on outbreaks, Healthcare Professionals, clinical manifestations of the monkeypox virus, and other orthopoxviruses.

Virology

Orthopoxviruses (OPXV) are giant, brick-shaped viruses that range in size from 140-450 nm and have a 200-500 kbp genome that codes for more than 200 genes (9-11). Poxviridae is a double-stranded deoxyribonucleic acid virus that can infect many animals, such as birds, reptiles, insects, and mammals (9). Monkeypox virus has long been able to spread among wild animals, and due to the large number of potential hosts, it can occasionally infect humans through spill over events (10). The family includes two subfamilies, Entomopoxvirinae (with 18 genera and 52 species) and Cordopoxvirinae (with 4 genera and 30 species). Monkeypox is a member of the family Poxviridae, of the subfamily Cordopoxvirinae, and belongs to the Orthopoxvirus genus (11, 12). Human infection is associated with molluscum contagiosum, cowpox, monkeypox, vaccinia, camelpox, alaskapox, yaba monkey tumour virus, tenapox virus, ORF virus, pseudocowpox virus, and Variola (smallpox). Molluscum contagiosum and Variola viruses have humans as their primary and reservoir hosts (12).

Interestingly, orthopoxvirus (OPXV) exhibits immunological cross-reactivity and cross-protection, and infection with any species of the genus provides significant resistance to diseases caused by any other species of the same genus (13, 14). Still, they play essential roles in the host antiviral response, and poxviruses complete their replication cycle inside the cytoplasm of infected cells through various molecular pathways, which are massive (15). However, its clinical features are comparable to those of poxviruses; the MPXV genome is double-stranded linear DNA (197 kb) composed of hairpin loops, open reading frames, and tandem repeats. Similarly, the inverted terminal repeat (ITR) consists of tandem repeats, hairpin loops, and open reading frames (ORFs) (Fig. 1) (16). There is a misunderstanding about the importance of the disease due to the rarity, careless handling, and limited documentation of monkeypox outbreaks worldwide. Although smallpox is currently considered the second most harmful pox virus after the re-emerging MPX, proper care is not being taken to stop it from spreading like wildfire.

The replication cycle of Poxviruses sheds light on how the monkeypox virus replicates. Like other viruses, Poxviruses contain proteins that facilitate the virus's attachment to a cell, fusion with the cell's membrane, and entrance into the host cell. Before the union, the mature virion (MV), which has a single membrane, and the extracellular enveloped virion (EV), which has a second outer membrane, are broken in the case of the poxvirus (17). The four viral proteins connected to the MV help the virus adhere to a host cell by attaching to laminin or glycosaminoglycans (17, 18). Glycosaminoglycans are found on the surface of all mammalian cells and are essential for binding viruses to cell membranes, although not all cellular receptors have been fully characterized (18). Widely abundant glycosaminoglycans such as chondroitin and heparin sulfates, as well as laminin, play a role in cellular attachment of other poxviruses (Fig. 2). The fusing of the virus to the host cell relies on 11 to 12 non-glycosylated transmembrane proteins ranging in size from 4 to 43 kDa, regardless of whether the MV or EV mediates infection (19). EVs have a delicate outer membrane and are specially tailored for escaping the intact cell and spreading inside the host, in contrast to MVs, which are relatively stable and hypothesized to facilitate transmission across host animals (17, 19). Poxviruses DNA replication occurs inside cytoplasmic structures known as Guarnieri bodies but is now often referred to as factories (20). Each factory originates from an infectious particle. In the first stage of infection, they are small DNA-containing structures

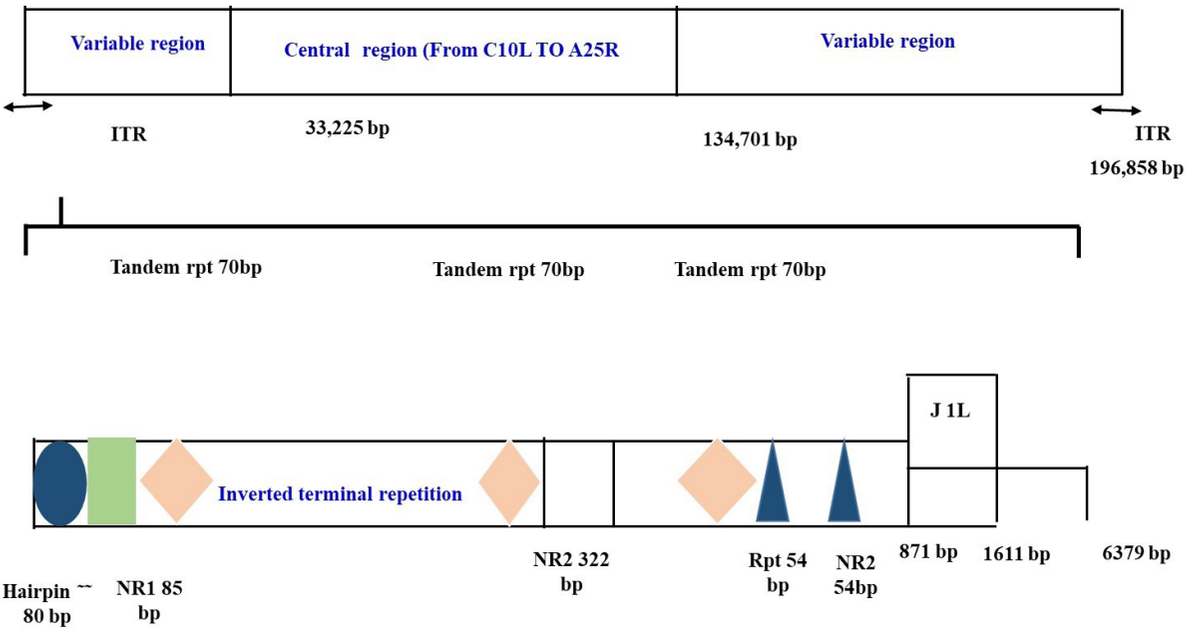

Fig. 1. Shows the structure of the genome of the monkeypox virus (MPXV). The MPXV genome is approximately 197 kb long, and the region at the centre is 101,476 base pairs (bp) long. Both ends have an inverted terminal repeat (ITR) of 6379 (bp), a hairpin of 80 (bp), 54 (bp) of short tandem repeats, NR1 and NR2 regions, and a coding region.

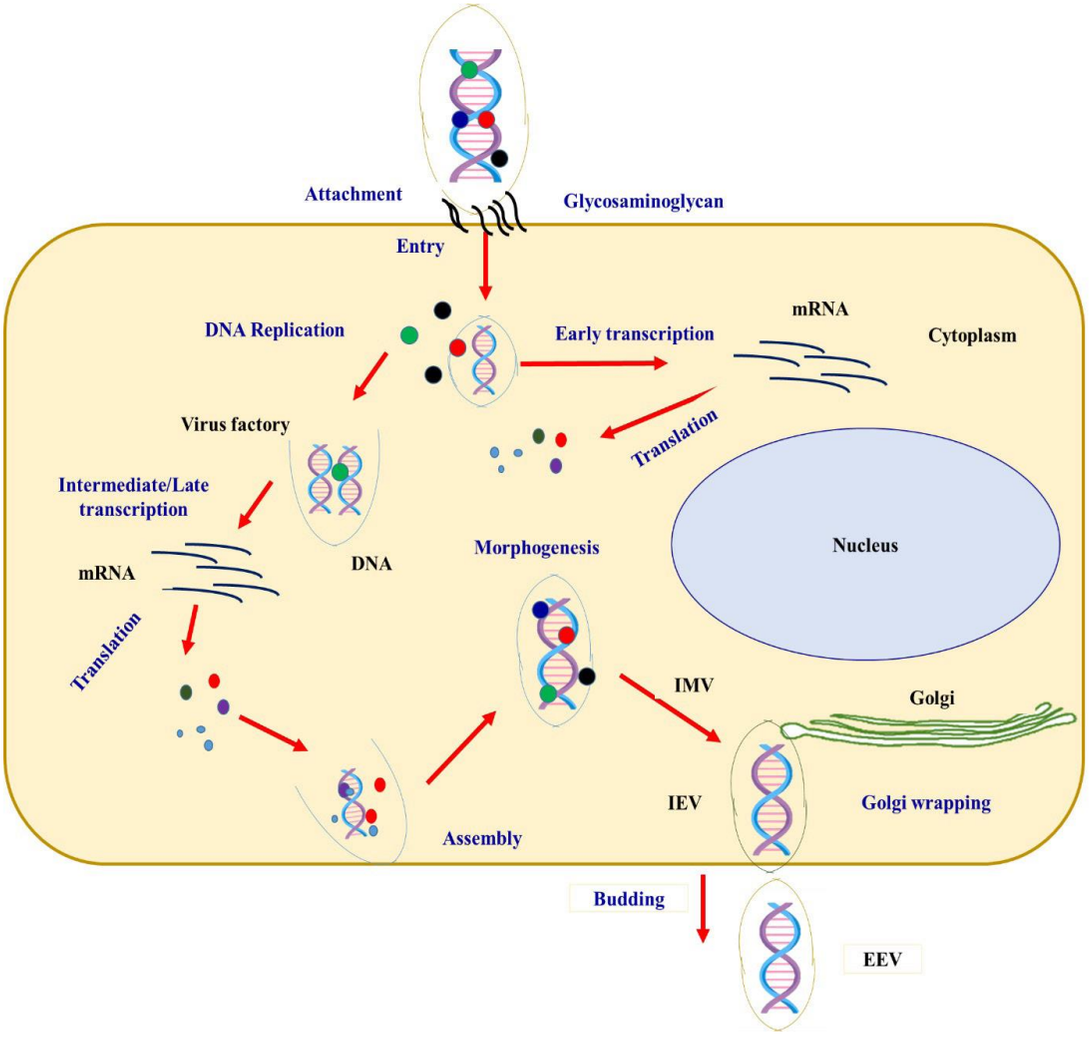

Fig. 2. Shows the replication cycle of a poxvirus. Key events are outlined: attachment (1), entry (2), early viral gene transcription and translation (3), DNA replication (4), intermediate and late transcription and translation (5), assembly (6), morphogenesis (7), envelopment by intracellular membranes (8) and budding (10). For further more detail information see the pox virus replication.

surrounded by membranes that are generated by the cell's rough endoplasmic reticulum (RER) (19, 20). As DNA synthesis continues, these factories will enlarge and eventually begin to collide and fuse to an irregular shape as cavities filled with viral mRNA and host translation factors develop (20, 21). In the late stages of the replication cycle, a group of viral membrane-building proteins and a group of late gene products work together to disrupt the endoplasmic reticulum membrane in the region and form crescent structures as substrates for assembling immature virions (IV) (21). While the majority of mature virions remain inside of the cell (IMV), some are transported via microtubules and become enveloped by two ER or Golgi-derived membranes. The most prevalent infectious species, MV, is created by processing IV (20, 21). By associating with the cytoplasmic membrane, these MVs will exit the cell. The following sections attempt to compile all publicly accessible data on instances of the human monkeypox outbreak from the first case in 1970 until 2022. Both official and unofficial reports are included in this information.

Human monkeypox outbreaks in the past and present (2022)

The overview of the monkeypox virus epidemic includes all cases reported via official means through research articles, reviews, books, and WHO reports. We further illustrated the historical timeline of out-

breaks of the human monkeypox virus until 2022 in Fig. 3 (22). Rashes, fever, chills, adenopathy, headaches, and myalgia are typical signs and symptoms of sickness (23). According to the World Health Organization and the Centres for Disease Control and Prevention, the clinical picture of monkeypox closely resembles that of smallpox. However, the fundamental distinction between monkeypox and smallpox is the rapid lymph node swelling in monkeypox infection that occurs before the development of fever. A rash generally starts 1-3 days following the beginning of fever and lymphadenopathy, with lesions emerging simultaneously and progressing at the same pace (24). In addition to secondary bacterial infections, respiratory distress, bronchopneumonia, gastrointestinal involvement, dehydration, sepsis, encephalitis, and corneal infection with subsequent vision loss, patients might have various other consequences. Currently, there is no particular therapy for a monkeypox virus infection; instead, patients are handled with supportive care and symptomatic medication (25). It is known that the monkeypox virus may infect a variety of primates and rodent species (22). Due to interaction with infected pet Prairie dogs imported from Ghana, the first MPX cases in humans were identified in the United States in 2003, resulting in an outbreak that resulted in more than 70 cases (23). People can get the monkeypox virus from infected pet animals, and infected people may be able to spread it to pet animals through close contact, such as petting, cuddling, hugging, kissing, licking, sharing sleeping areas, and sharing food. All mammals should be considered vulnerable since the species of animals that may get monkeypox are presently unknown (26). Contact with both living and deceased animals, as well as intake of wild game or bushmeat, are recognized risk factors. The development of a new rash, which has so far been seen on the belly and anus, is one of the signs of monkeypox in dogs. As a consequence of MPXV exports from Africa, human MPX cases were later reported in Israel (2018), the United Kingdom (2018, 2019, 2021, and 2022), Singapore (2019), and the United States (2021) (27, 28). Due to its importance in the current scenario, Human MPX activity is troubling, especially before the current wave in many African countries and in non-endemic countries outside Africa. Between January 1st, 2022 and July 22nd, 2022, 21,000 laboratory-confirmed cases of monkeypox and five deaths have been reported to WHO from 75 countries/territories/areas in all six WHO Regions. A major human MPX epidemic brought on by the West African clade

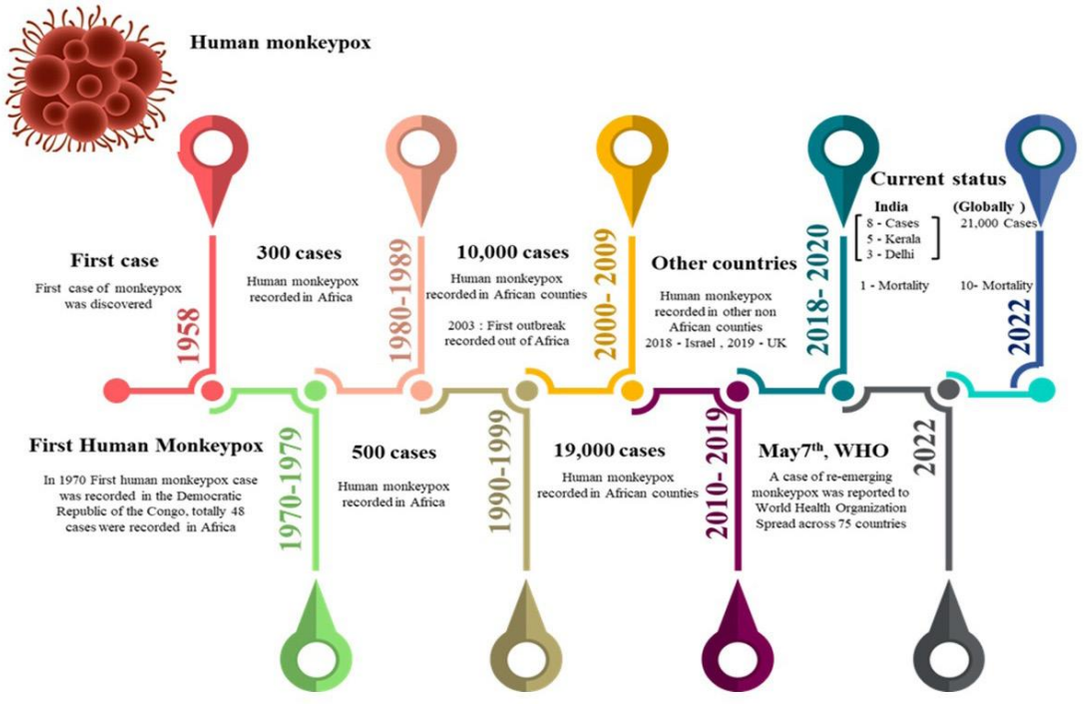

Fig. 3. Timeline of reported human monkeypox outbreaks in the World from 1958 till 2022. Source: based on data from the Centres for Disease Control and Prevention

was also reported in Nigeria in October 2017, with approximately 146 clinically suspected and 42 confirmed cases (29). Fig. 4 depicts the spread of confirmed human monkeypox virus cases in the world. After the first documented MPX case in 1970 in the DRC, modest and massive outbreaks, especially in Central and West Africa, were recorded (Fig. 3). Most laboratory-confirmed MPX cases have been recorded in the WHO European area (n = 11865), followed by the Americas (n = 3772), African region (n = 301), Western Pacific regions, Eastern Mediterranean, and South-East Asia Region. With the exception of countries in the African Region, the ongoing outbreak of monkeypox continues to primarily affect men who identify as gay, bisexual, and other men who have sex with men, and who have reported recent sex with one or multiple partners (30). As of August 1st, 2022, four deaths have been documented in non-endemic nations (2 in Spain, 1 in Brazil, and 1 in India) contributing to 10 deaths globally during this COVID-19 pandemic (4 from non-endemic countries and 6 from endemic countries) (31). The West African clade causes all instances outside Africa. It is still unknown regarding natural history, so our following discussion will focus on the animal origin and reservoir host for viral circulation. Monitoring the monkeypox virus in endemic locations can help us understand its zoonotic origin.

Clinical presentation of monkeypox

The MPXV transmission to humans is still a mystery. A zoonotic animal-to-human transfer may result from direct contact with infected animals (e.g., bites, scratches) or indirect contact with contaminated animal fluids or wound material (32-34). Direct contact with an infected person is the primary mode of transmission by respiratory droplets and exposure to infectious wounds or body fluids (35). For the past five years, the Democratic Republic of the Congo has been the most affected by monkeypox outbreaks, while Nigeria and the Republic of the Congo have been the second and third most affected (36). Fig. 2 shows a timeline of human monkeypox outbreaks since 1970 when the first case was found in a 9-month-old baby in a remote village in the Democratic Republic of the Congo (DRC) (35, 36). Human-to-human transmission occurs via direct skin-to-skin contact with gaping sores and indirect contact with infected fomites such as bedding or clothes (37). Additionally, it is important to consider a vertical transfer from the mother to the foetus (38, 39). To date, there is no evidence that only human-to-human transmission in the general population can spread monkeypox infection. On aspects of animal-to-human transmission, only wild animals (rodents and primates) have been found to carry the monkeypox virus in endemic countries (40). However, the monkeypox virus transmission in prairie dogs has been documented in the United States (41). In 2003, human monkeypox outbreak occurred in America due to the import of wild rodents from Africa, which resulted in 47 human cases across six states in the United States (42). Instances of animal-to-animal and animal-to-human transmission in the 2003 outbreak highlight the need to isolate infected people and expose infected animals to reduce the risk of secondary infections to and from animals. Similarly, the transmission factors must still be thoroughly investigated for other domesticated animals, such as dogs and cats (43). Monkeypox transmission in both endemic and nonendemic environments is summarised in Fig. 5. The scientists estimated the R0 value of monkeypox to be between 1.10 and 2.40 in areas where exposure to orthopoxvirus species is negligible, implying that a monkeypox epidemic is imminent in these settings on the occasion of imported human or animal cases (44-46).

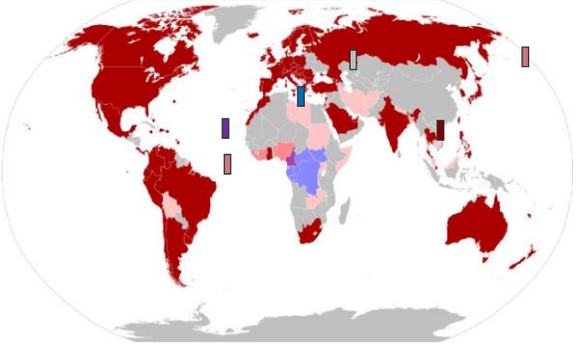

Fig. 4. Using national borders, a world map depicts the spread of monkeypox by virus clade No known cases Endemic the West African clade Endemic the Congo Basin (Central African) clade Both clades recorded West African clade outbreak in 2022 Suspected cases

Clinical features and diagnosis

The zoonotic viral disease monkeypox is caused by a double-stranded DNA virus belonging to the Poxviridae family. Monkeypox infections typically persist between two and four weeks (47). Compared

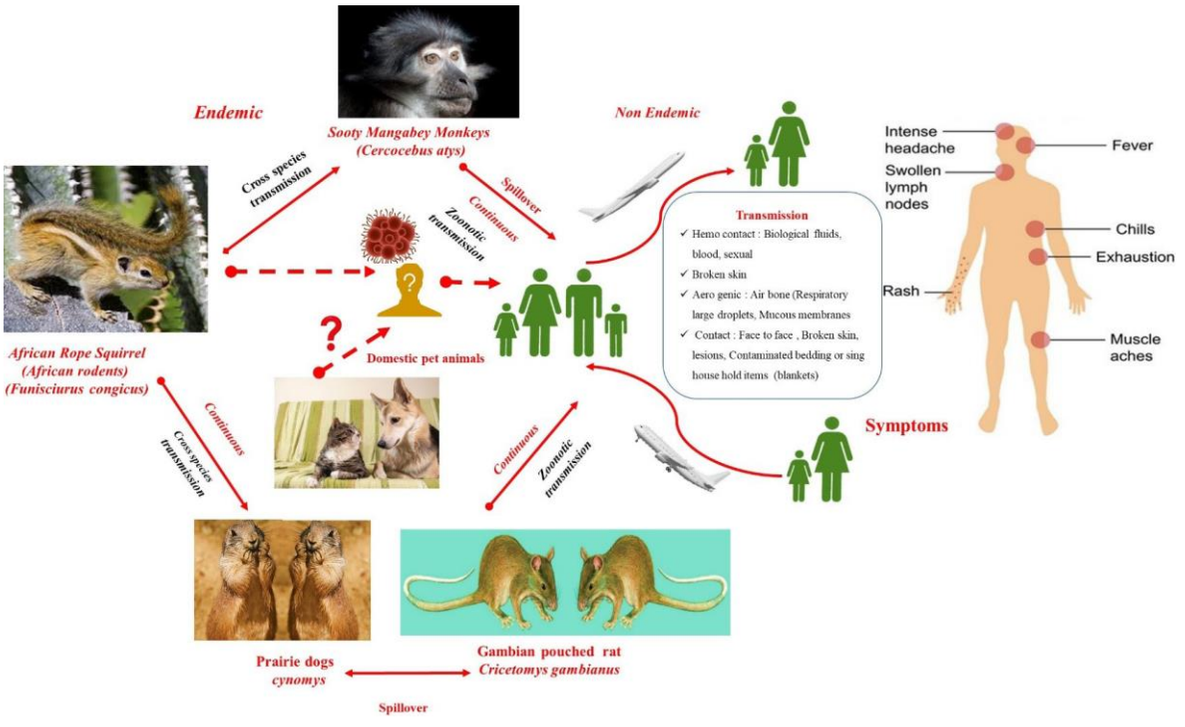

Fig. 5. Summarises the monkeypox transmission in both endemic and non-endemic environments

to the Central African clade of the monkeypox virus, the West African clade often produces less severe disease (48). However, monkeypox infections may be dangerous to children, pregnant mothers, and elderly people with impaired immune systems (49). The typical clinical presentation of monkeypox is characterized by fever, enlarged lymph nodes, and rashes. Furthermore, prodromal symptoms such as chills, myalgia, fatigue, headache, back pain, and, in rare cases, sore throat and cough may appear (50). After 1-5 days of fever, a maculopapular rash develops on the face, hands, soles, and other body areas. Each lesion develops as a macule and then becomes papules, vesicles, pustules, and scabs. Fig. 6 shows the appearance of different enanthem stages of the vesiculo-pustular skin lesions. Table 1 shows the different enanthem stages of the vesiculo-pustular rash and its common features in monkeypox patients. Rashes on the palms of the hands and soles of the feet, the anogenital areas, and the oral or ocular mucosa (enanthem) are common in many cases (70 percent) (47). Table 2 lists the clinical features of human monkeypox infection that are similar to smallpox (simple discrete type or modified type) (51-53). Lesions often progress from macules to papules, vesicles, pustules, crusts, and scabs within 12 days (54). The lesions can be very distressing and centrally depressive (55).

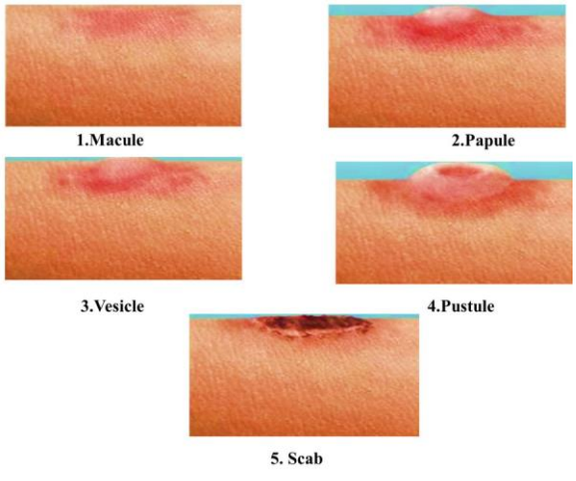

Fig. 6. Various enanthem stages of the vesiculo-pustular skin rash in monkeypox

Many symptoms of monkeypox are similar to those of smallpox (56). However, monkeypox is mild and manifests with lymphadenopathy, which was absent in chickenpox. Itching in the mouth might lead to rashes, impairing dietary intake. Secondary bacterial infections of the skin lesions are common in patients. Lesions in the cornea may result in scarring and subsequent visual loss. Another issue that might arise is bronchopneumonia, especially in those who already have the flu. Sepsis and septic shock may develop

Table 1. Shows the general characteristics of Monkeypox in patients

Different Stages	Duration of Stages	General Characteristics
Enanthem		Lesions appear on the tongue and mouth.
Macules	Two days	After the enanthem, a macular rash forms over the face, arms, legs, feet, palms, and soles.
Papules	Two days Two	The rash spreads to the face, arms, and legs within 24 hours (centrifugal distribution). The lesions evolved from macular (flat) to vesicular (round) on the third day of the rash.
Vesicles	days Usually	Towards the fourth or fifth day, lesions have developed into vesicles (raised and filled with clear fluid).
Pustules	five to seven days	By the sixth to the seventh day, lesions grow pustular (filled with opaque fluid) - sharply elevated, spherical, and stiff to the touch (deep-seated). Lesions will create a depression in the middle (umbilication). The pustules last 5 to 7 days before crusting.
Scabs	Seven to fourteen days	On the end of second week, the pustules had become hard and scaly. The scabs persist for approximately a week and then fall off.

from excessive immune reactions (57-59). The cutaneous signs of monkeypox may be misinterpreted as chickenpox, molluscum contagiosum, herpes simplex virus, syphilis, impetigo, early measles, or rickettsial infections. Several individuals have presented unusual symptoms in the monkeypox epidemic of 2022. The distinctive rash might be restricted to the vaginal, perigenital, and perianal regions; individuals may also present with /absent or minor prodromal symptoms after a localized rash appears (60). Clinicians must examine various illness manifestations to appropriately identify patients and restrict the epidemic. Diagnostic tests are critical components in determining an orthopoxvirus infection. These tests are most effective when combined with clinical and epidemiological information, such as a patient's vaccination history. Without laboratory confirmation, a diagnosis can be established using immunological techniques such as ELISA, polymerase chain reaction, electron microscopy, and phenotypic and clinical disease presentation (59, 60).

Antiviral drugs for Monkeypox virus

There is no particular therapy for Monkeypox at the moment. The major suggestions for treating MPXV infection are supportive care, symptomatic management, and treatment of subsequent bacterial infections (61). Based on smallpox treatment results, antiviral drugs such as cidofovir, brincidofovir, and tecovirimat are effective against MPXV (62, 63). Tecovirimat inhibits viral envelope protein p37, stopping viral egress from infected cells. Brincidofovir, a lipid compound of the nucleotide analog cidofovir, inhibits viral DNA polymerase, inhibiting viral DNA synthesis and replication (64). The FDA has previously recognized vaccinia immune globulin intravenous (VIGIV) for treating vaccination-related side effects, such as progressive vaccinia and severe generalized vaccinia (65). Under Expanded Access Investigational New Drug (EA-IND) protocols held by the Centers for Disease Control and Prevention (CDC), tecovirimat, cidofovir, and VIGIV are currently accessible from the Strategic National Stockpile for use in treating OPXV infections in an outbreak scenario (66). Table 3 summarises three of the most promising antiviral treatment agents against Orthopoxvirus species. Various State and territory health authorities in the United States may seek access to these pharmaceuticals via the CDC. Currently, the CDC is establishing EA-IND for Brincidofovir therapy in treating OPXV infections (66). The specific therapy for human MPXV infection is unknown.

Antivirals vaccines for monkeypox virus

There are now two approved vaccinations in the United States to prevent monkeypox and smallpox. One vaccine (JYNNEOSTM) is based on a live, attenuated vaccinia virus that cannot replicate in the body but may trigger robust immune responses (67-69). In contrast, this vaccination does not protect primates with substantially impaired T-cell function (70). The second vaccine, ACAM2000®, is a replication-competent live vaccinia virus vaccine, meaning that the vaccine virus may be transmitted from vaccinated to unvaccinated people (71). Another vaccine developed to stop viral replication is

Table 2. Clinical characteristics of human monkeypox infection that most closely resemble those of smallpox (ordinary discrete type or modified type)

Characteristics	Smallpox	Monkeypox	Chickenpox or Varicella-Zoster virus (VZV)
Biological characteristics (50)			
Virus	Double standard DNA	Double standard DNA	Double standard DNA
Hosts	Humans	Rope squirrels, tree squirrels, Gambian pouched rats, dormice, non-human primates and humans	Humans
Mode of transmission	It spreads directly from person to person through the accumulation of infected droplets in the nose, mouth, pharynx, or pulmonary alveoli. It is also spread through face-to-face contact with an infectious person. Indirect transmission via small particle aerosols or virus-containing fomites is rare.	Direct contact with blood, body fluids or cutaneous or mucosal lesions of infected animals and the consumption of raw meat and animal byproducts from diseased animals result in animal-to-human (zoonotic) spread. Similarly, respiratory secretions, skin sores from an infected person, or contact with recently contaminated materials may all lead to human-to-human transmission. The virus is also transmissible through respiratory droplet particles.	Varicella and herpes zoster are spread from person to person, mainly through the lungs, by inhaling aerosols from the fluid inside the blisters on the skin caused by varicella or herpes zoster. VZV can also be spread through direct contact with fluid inside, blisters on the skin, and possibly infected secretions from the respiratory tract.
Dominance	Both the sexes	Occurs only in males	Both the sexes
Age of infected individuals	(Male and female) 0 – >50 years	0 – 65 years	(Male and female) 0 – >70 vears
Clinical characteristics (51, 52)			
Incubation	Days (7-14)	Days (7-14)	Days (10-22)
Prodromal stage	Days (1-4)	Days (1-4)	2 - Days Days
Rash duration	Days (14-28)	Days (14-28)	(10-22) Up to
Fever	Above 40°C	In the range of 38.5°C to 40.5°C	38.8°C
Malaise	Present	Present	Present
Headache	Present	Present	Present
Body pain	Present	Present	Present
Lymphadenopathy	Absent	Present	Absent
Lesions on the palm or sole of your feet	Present	Present	Very little
Lesions near genitals or anus	Absent	Present	Absent
Lesion distribution	Centrifugal	Centrifugal	Centrifugal
Lesion appearance	Rough and dense, well-rounded and umbilical	Rough and dense, well-rounded and umbilical	Irregular boundaries superficial
Lesion progression	Lesions generally develop slowly, with each phase lasting 1-2 days.	Lesions generally develop slowly, with each phase lasting 1-2 days	Body lesions typically have multiple development phases; fast development

LC16m8, which protects against severe monkeypox disease in nonhuman primate animals (72). Over 50 000 Japanese schoolchildren received the LC16m8 vaccine, with very few reported side effects (73). Antivirals have not been the subject of large-scale, randomized controlled studies to treat OPXV infections. (63, 65). Drug approvals and therapeutic approaches are based on in vitro data, animal research, human pharmacokinetic and pharmacodynamic data, case reports, and case series (73-75).

Preventative steps and procedures

Prior research suggested that as MPXV and smallpox belong to the same genus, the vaccinia vaccine may offer approximately 85% protection and decrease disease severity (80). Preventing infectious disease outbreaks is a major concern for global public health. Reusing Vaccinia Vaccination on a Large Scale should be implemented on affected countries. According to reports, the vaccinia vaccine used to eradicate smallpox successfully does the same for monkeypox (81). We may need to reuse it immediately in large quantities to prevent the spread of the monkeypox epidemic, given its rapid spread. Furthermore, it is crucial to take preventative actions to minimize zoonotic and human-to-human infections (64, 67). About 75% of today's emerging infectious diseases is zoonotic, spread by wildlife or exotic pets, such as SARS, Ebola, Salmonella, and Monkeypox. Hence, we feel that as most of zoonotic diseases have the high chance by spreading through imported exotic pets, strict guidelines to prevent illegal animal traffic and stern animal quarantine procedures for the import of pets from disease - endemic areas should be implemented worldwide. The CDC says there are several ways to avoid getting infected with MPXV as follows (82).

1. Staying away from animals that can carry the virus or anything that has come into contact with a sick animal.
2. Avoiding contact with sick or dead animals in locations where the disease is prominent.
3. Isolation procedures to be carried out on infected patients.
4. Washing the hands or using an alcohol-based hand sanitizer after contacting contaminated people or animals.
5. Wearing safety harnesses like masks and gloves when caring for someone sick.
6. Educating the public and making people more aware

Table 3. Promising antiviral treatment agents against Orthopoxvirus species

Drug	Route of administration	Stage of Development	Mechanism of Action	Side-Effects	References
Cidofovir (Vistide)	Intra-venous	AIDS patients with CMV retinitis are treated with molluscum contagiosum and ORF virus.	Inhibits viral DNA synthesis by inhibiting DNA polymerase competitively.	Nausea and vomiting are common side effects, in addition to a decrease in intraocular pressure.	(76)
Brincidofovir, (CMX-001) Tembexa	Oral	In developmental stages against Ebola virus, CM virus. Used to treat Small Pox	Lipid conjugate Prodrug of Cidofovir; inhibits DNA Polymerase.25 times more efficacy than Cidofovir	High liver transaminases and bilirubin levels accompanied abdominal discomfort, nausea, vomiting, and diarrhea.	(77)
Tecovirimat (ST-246)	IV and oral	For the treatment of both adults and children with smallpox, the Canadian Department of Health has authorized Tecovirimat, which is maintained in the Strategic National Reserve of the United States. For use with further orthopoxvirus infections.	The protein inhibits the activity of VP37, which prevents the formation of viruses that can be released from an infected host cell, thereby preventing replication and dissemination within the host.	IV: Pain, redness, and swelling at the site of the infection; contamination in the infected area and headache. Oral symptoms include headache, stomach pain, feeling sick, coughing, and vomiting.	(78)
VIGIV	IV	Problems with vaccinating against infectious diseases (progressive vaccinia, severe generalized vaccinia, etc.)	OPXV-specific antibodies derived from pooled human plasma of smallpox vaccination recipients, providing passive immunity.	Hypersensitivity; Local injection-site sensitivity (contraceptive in people with IgA deficiency or suspected IgA deficiency)	(79)

of the virus could also help stop it from spreading.
7. During shipping of exotic pets or other animals, those which are found to be infected and other exposed animals should be quarantined or euthanized as per CDC issued guidelines (83).

CONCLUSION

The human monkeypox virus is spreading, and its incidence is increasing nationally and worldwide, especially in central and western Africa. Because of globalization, Monkeypox outbreaks will occur with different mutant strains in upcoming years. It seems more contagious, with a higher mortality rate than other viruses or disorders. In our review, we provide information on human monkeypox outbreaks worldwide, especially outbreaks in India, and we also summarized the currently available repurposing agents effective against the virus. The COVID-19 pandemic sadly taught us that awareness and preparedness are two keywords to tackle these dire situations. Now, due to the high pandemic situation of nCOVID-19, India must follow tactics and strategies to develop many therapeutic drugs and vaccines. The country should also increase its vaccination units in primary health care centers and hospitals in all districts and create many advertisements on public health awareness programmes and preventive measures. Collaborating with medical doctors and the scientific committee will help to overcome this situation. Also, the public health authorities, clinicians, and the community must coordinate to distribute information, get diagnostic tests, execute contact tracing, and ensure affected people and their contacts have access to medical treatment. Frequent surveillance of animal reservoirs is also required to prevent future outbreaks. Until now, no promising treatment or prevention strategies have been developed against the human monkeypox virus. From the current outbreak perspective, developing an effective vaccine and therapeutic agent against the re-emerging monkeypox virus is another great challenge for virologists and scientists. Although existing smallpox virus repurposing antiviral agents inhibited orthopoxvirus replication in vitro, developing a new vaccine against all MPX viruses will be the ultimate treatment strategy locally and globally. As a result, strict guidelines and policies are required to stop monkeypox from evolving into another COVID or smallpox pandemic.

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