Monkeypox virus: an ongoing global outbreak hitting the non-endemic countries - a comprehensive review.

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Abstract

Monkeypox is a rare zoonotic DNA virus with lineage from the Poxviridae family, Chordopoxvirinae subfamily, and Orthopoxvirus genus. (1) With a previous history of controlled and contained occasional outbreaks of the virus, currently a widely erupted outbreak of monkeypox with progressively rising numbers has been reported since May 2022 in multiple countries of the western hemisphere that are not historically endemic for this infection, particularly the UK and EU countries. The global cessation of smallpox vaccination has been hypothesized to cause the rise in monkeypox infections in recent years. (5) (7) Monkeypox like any other viral infection commences with prodromal symptoms; a maculopapular rash with centrifugal distribution usually follows. (16) (9) Polymerase Chain Reaction (PCR) confirms the diagnosis. (16) Transmission in humans is possible through infected animals or humans. (5) (27) In the ongoing 2022 outbreak, monkeypox virus has been undergoing novel mutations at an alarming rate. (56) Treatment options for monkeypox is an area that still requires extensive research, the utility of certain antiviral medications in treating monkeypox infection is currently being explored but is still controversial and debatable.

Introduction

Monkeypox is a rare zoonotic DNA virus belonging to the same family as smallpox, the Poxviridae family, Chordopoxvirinae subfamily, and Orthopoxvirus genus. (1) The virus was first isolated from monkeys at a laboratory in Copenhagen, Denmark in 1958; hence the name but some rodents and non-human primates can also act as natural reservoirs of this virus. (2) (3) The first ever case of monkeypox in humans was reported in an infant in the Democratic Republic of Congo in 1970. (4) Since then, small outbreaks have frequently occurred in Central and West Africa which are historically endemic areas while regions outside Africa are categorized as non-endemic areas for monkeypox infection. (5) (6) Two main genetic clades of Monkeypox have been distinguished till date; namely, the Central African clade and the West African clade, the former manifesting more severe disease progression and a relatively higher mortality rate (10.6% and 3.6% respectively). Monkeypox infections have been on the rise in the last few years. Between the years 2010 and 2019, the average age at the time of presentation has progressively increased from 4 years to 21 years (5) (7) Only about 10 cases of monkeypox had been reported from 1978 till 2017 in West Africa, with no case being reported from Nigeria during this time until the reemergence of the West African clade was observed as a major outbreak in 2017 in Nigeria with a total of 188 cases (146 suspected, 42 confirmed). (5) The first monkeypox outbreak outside the historically endemic areas of Africa, occurred in 2003 in the United States with a total of around 71 cases, both confirmed and suspected ones, caused by some infected animals that were imported from Ghana to Texas. These infected animals included African rodents that got domesticated with prairie dogs after arrival in USA, and this contact chain erupted a monkeypox outbreak in the US, infecting a total of 81 humans according to the Centers for Disease Control and Prevention (CDC) (8) (9) (10) (11) The second incidence of monkeypox cases outside Africa occurred when a person with recent travel history tested positive for the infection in Israel in September 2018 and this was the first ever case taken outside Africa by a human reservoir; followed by cases reported in the United Kingdom in September 2018, December 2019, May 2021 and May 2022; Singapore in May 2019, and United States of America in July and November 2021. Since May 2022, several cases of monkeypox have been observed in the historically non-endemic countries, particularly in Europe and the UK and still continue to be on the rise. The viral strains isolated during the ongoing outbreak show the West African Clade, with most cases having a recent travel history to non-endemic areas while two cases from the UK surprisingly had no travel history or outside contact. No single case among these had any traveling history in Africa. (9) (16) (18) (21) The infected individuals were mostly men who had sex with men (MSM). (12)

We went through the available literature on monkeypox virus and found articles that discussed different aspects of this viral outbreak with the majority of the articles highlighting the recent epidemiological trends. However, we decided to write a comprehensive review inclusive of other aspects as well, like clinical manifestations, mode of transmission, prevention and potential treatment options.

Epidemiology

A total of 79,231 confirmed cases of monkeypox with 49 deaths have been reported around the globe till 10 Nov 2022 5:00 PM EDT, among which the United States was leading with 28,881 cases. In the current outbreak, 98.8% of cases (78,278 out of 79,231) are in the non-endemic locations for monkeypox meanwhile only 953 cases are in the previously endemic areas. (See graph 01) A death toll of 49 out of 79,231 cases makes the global case fatality ratio for monkeypox of about 0.0618%

For a more detailed breakdown of locations, please see the table below. (13)

Table 1

Note: The locations with asterisk sign * are historically endemic for Monkeypox outbreaks.
Signs And Symptoms

Monkeypox like any other viral infection commences with prodromal symptoms. It manifests in a way similar to smallpox but with a less severe course, starting with a prodromal phase which includes fever, flu-like symptoms, headache, myalgia with addition of lymphadenopathy which is absent in the latter. (6) (12) (14) According to a case series of recent monkeypox outbreak from Portugal, inguinal lymphadenopathy was found to be more common than cervical and axillary lymphadenopathy. (15) The mean latency period for symptoms to appear is 5 to 13 days or as some literature sources quote it as 5 to 21 days. (16) A maculopapular rash with centrifugal distribution usually follows 3–4 days after the prodrome. (17) The rash may start around the genitals or anus and spread out to reach hands, feet, chest or face. The rash appears on the face in 95% of the cases, on palms and soles in 75%, mucous membranes in 70%, genitalia in 30% meanwhile cornea and conjunctiva in 20% of cases. (11) The infected lesions are embedded in deeper skin layers, well-circumscribed, with central depression, may be painful or itchy; they progress through various stages as macules (non-elevated discolored skin patch), papules (slightly raised skin lesions), vesicles (fluid-filled blisters), pustules (pus-filled blisters) and then eventually scabs or crusts that desiccate and later fall off. Other patients may get a rash first followed by flu-like symptoms or vice versa, or just the rash with no prodromal symptoms. (16) (18) The infectious state starts with the symptomatic phase and ends after desiccation of lesions and skin healing, which may take up to 4 weeks. The current outbreak of monkeypox shows several atypical features as compared to the past. Previously reported cases report appearance of rash after 1 to 3 days of prodrome, however, in the 2022 outbreak, the prodrome has milder symptoms which may even go unnoticed in some cases until the appearance of rash later on; in MSM or people with peri-genital rash, even the skin lesions manifest a limited distribution. (15) (19) (20) (21) Enanthem on oropharyngeal mucosa can impose pain and difficulty in oral intake. The disease severity is directly correlated to the count of skin lesions, higher counts of muco-cutaneous lesions pose an increased risk of complications. Skin lesions in individuals who are unvaccinated against smallpox are also susceptible to superimposed bacterial infections of skin. (22) Complications include secondary bacterial infections that can involve eyes, CNS, GI and respiratory system to cause bronchopneumonia, encephalitis, corneal infection, diarrhea, and even sepsis. (5) (11)

Diagnosis

Samples are collected from skin lesions and tested on Polymerase Chain Reaction (PCR), identification of monkeypox DNA confirms the diagnosis. CDC guidelines recommend collection of multiple samples by vigorous swabbing or brushing of the lesion. Two aseptic swabs made of polyester or Dacron are used for sample collection; next, the applicator of each swab is broken and placed into a capped tube with O-ring or they are placed in two separate sterile containers and no media should be added to these. In case of a positive confirmatory diagnosis, all contacts within the symptomatic period should be tracked and observed for any signs and symptoms for at least 21 days from the last exposure to the infected individual. (5) (16) Scabs, swabs and aspirated fluids from lesions is preferred over blood samples for PCR testing due to shortened lifespan of virus in blood. These samples require room temperature but no media for transportation except for tissue biopsies which require transportation in frozen state on dry ice. Immunohistochemistry can also identify antigens on biopsies while the modality of PCR can even differentiate between the two monkeypox clades. Serology has a limited diagnostic utility due to cross-immunological reactivity with other human orthopoxviruses but antibody titers can be measured to check vaccine responses. In addition, these contacts also cannot donate blood, organ or bone marrow within this 21 days time window. (12) One would typically expect a rising pattern in the Total Leucocyte Count (TLC) in case of bacterial sepsis. However, a decline in the differential count of neutrophils or neutropenia, can occur in fulminant monkeypox infections with bacterial sepsis and is related to higher morbidity and mortality. (23) Therefore, it is important to rule out any coexisting bacterial sepsis and treat it accordingly.

Transmission

In the endemic parts of Africa, monkeypox virus has survived through some rodents and mammals acting as natural reservoirs such as squirrels, African giant pouched rats, striped mice, non-human primates, and dormice with sporadic animal to human transmission, possibly consequential to mutations in the viral strains. (3) (5) (13) (24) (25) (26) Reservoir animals can transmit the virus to humans through direct or indirect exposure of humans with their saliva, blood or other body secretions, inadequately cooked meat or mucocutaneous lesions. (5) Transmission among humans is also possible by inhalation of infected respiratory droplets during extended periods of physical proximity, infected sores, body secretions and common bedding or clothing. (27) In this light, healthcare professionals...
dealing with suspected or confirmed infected patients or handling contaminated materials have higher chances of acquiring the infection and therefore require personal protective equipment including gowns, gloves, face mask, face shield and goggles. Among the re-emergence of monkeypox virus, data trends also show a probable sexual transmission hypothesised to be via direct skin to skin contact or through exchange of genital secretions because of presence of genital lesions in infected patients, since the majority of cases have been reported in individuals who identify as gay, bisexual or more precisely, men who copulate with other men. Some patients may additionally have proctitis, in which case the clinical picture might get mistaken for a sexually transmitting infection (STI) specially if no preceding prodromal symptoms are present. (16). The recent monkeypox outbreak reports some cases with no symptoms other than genital lesions. Semen specimens collected from three males infected with monkeypox in Italy tested positive for the presence of virus, strengthening the implication of sexual transmission of monkeypox in males. (28) (21) Misdiagnosis or delayed diagnosis results in increased dissemination of monkeypox infection as the infected individual is not correctly diagnosed and hence not isolated, and sent home on antibiotics.

Although sufficient evidence exists in literature that reports transmission of monkeypox infection from animals to humans and also among humans themselves, Seang et al. reported a unique case of human-to-animal transmission of the virus. Two men in Paris who were inhabiting the same household under polyandrous partnership, presented with anal ulceration and vesiculo-pustular body rash 6 days after having sex with other men. Real-time PCR confirmed the diagnosis of monkeypox West African Clade. 12 days following their infectious manifestation, their domesticated dog, a male Italian and otherwise healthy greyhound, started to develop abdominal pustules with anal ulceration. A PCR test performed on the dog's sample revealed monkeypox virus. The report described this case as the first ever known event of transmission of monkeypox infection from a human to an animal. (29) Additionally, pregnant ladies infected with monkeypox can also communicate the infection to their fetus(es) through placenta during pregnancy or via physical contact around birth that can result in monkeypox infection in the neonates. (11) (30)

A provisional diagnosis of monkeypox infection should be considered in patients with peri-genital rash, have a recent travel history to affected areas, categorize as men who copulate with men, contact history with people having identical rash or those who are suspected or diagnosed cases of monkeypox infection. (16) However, it is still unknown if an asymptomatic infected person can pose transmission risk to the general public. (30) It is hypothesized that immunity status and route of infection determine the level of disease severity. In the 2017 monkeypox epidemic in Nigeria, HIV positive individuals exhibited greater morbidity with higher numbers of skin lesions along with genital lesions than the HIV negative population. In addition to this, invasive routes of infection that cause breach of mucocutaneous membranes, such as an animal bite, are likely to cause disease with shorter incubation period but with a more severe disease course (49.1% vs. 16.7%) and higher chances of hospitalization (68.8% vs. 10.3%) as compared to non-invasive modes of exposure, for instance, fomites. (31) (32)

Key Definitions
Following provisional definitions have been proposed by European Centre for Disease Prevention and Control:

1. "A confirmed case of monkeypox is that which is confirmed by laboratory tests, that is, either a monkeypox specific positive PCR or an orthopox virus specific positive PCR which further detects monkeypox virus on nucleotide sequence determination.

2. A probable or suspected case of monkeypox has an unexplained generalized or centrifugally spreading localized maculopapular or vesiculopustular rash with central depression or scabbing, lymphadenopathy and one or more other monkeypox symptoms (including but not limited to fever usually >38.5°C, headache, back ache, fatigue, lymphadenopathy) OR an unexplained rash on any body part in addition to one or more monkeypox symptoms with an onset from or after 01 March 2022 and one of the following:

   a. An orthopox specific positive PCR without further testing for nucleotide sequencing, electron microscopy, serology etc.
   b. An exposure to suspected or confirmed monkeypox case(s) within 21 days prior to the onset of symptoms
   c. A travel history to monkeypox endemic countries within 21 days prior to the onset of symptoms
   d. A history of multiple or anonymous sexual partners within 21 days prior to the onset of symptoms, irrespective of the sexual orientation.
   e. Men who have sex with men (MSM)"

Patients who fit the aforementioned definition of probable or suspected case, should undergo a monkeypox specific PCR, or an orthopox specific PCR followed by confirmation by nucleotide sequencing. If these tests come out to be negative, these patients should be excluded. (12)
**Molecular Pathogenesis**

Monkeypox is oblong or brick shaped, enveloped DNA virus which is slightly pleomorphic, with a biconcave shaped nucleic acid core and two lateral bodies, and an overall size of 200 to 400 nm. Its genome, despite being a double stranded DNA, measures 197 kilo–base-pair linearly, with around 200 genes; the viral life cycle occurs in cytoplasm of host cells. (33) (34) Like all orthopoxviruses, its genome comprises two terminal ends, called Telomeres. These contain identical but oppositely oriented adjacent repetitive nucleotide sequences, called Inverted Terminal Repeats (ITRs); they make up about 3% of monkeypox viral genome and are responsible for genetic variation and mutations. (35) The monkeypox genome encodes several essential viral proteins that are categorized into three groups:

i) Viral proteins that assist the virus to invade host cells by attaching to their glycoprotein receptors and enter via macropinocytosis; ii) viral proteins that liberate intracellularly proliferated viral replicas into the extracellular environment; iii) proteins that serve as immune modulators to host cell defenses. (36)

Poxviruses including monkeypox are proportionately larger than other viruses, hence they cannot breach mechanical barriers in the target cell by passage through host cell gap junctions The relatively large size of monkeypox alerts the host immune system easily and early on, hence monkeypox virus needs an extensive strategy to invade and survive within the host cells. In order to evade the host immune system, the virulence genes in monkeypox virus encode proteins that modulate host immune responses to facilitate viral survival inside the host. These immunomodulating proteins are further divided into three categories: Virotransducer proteins, Virostealth proteins, and Viromimic proteins. The former two work intracellularly while the latter works extracellularly. The virotransducer proteins interfere with host immune responses to monkeypox infection by inhibiting innate antiviral signaling pathways that involve oxidative burst and apoptosis. (37) (38) The virostealth proteins impede viral detection by the infected host's immune system through inhibition of its antigen recognition receptors and cells, such as the major histocompatibility complex class 1 (MHC 1) and CD4+. (39) This reduces cell-mediated immunity and impairs the cytotoxic T-cell mediated annihilation of the virus-infected cells. The viromimic proteins are of two types, viro-receptors and virokines. The viro-receptors are encoded by the viral genome, express as glycoprotein receptors on the host cells and attach host cytokines and chemokines to themselves, thus preventing their bonding to the original target receptors and subsequent functioning; meanwhile, the virokines imitate reservoir’s cytokines and chemokines, dysregulating their physiological operations. All these immunomodulatory factors in monkeypox work synergistically to elude host immune responses and facilitate viral replication. (40) (41) (36)

Following its entry into the reservoir cell by macropinocytosis and fusion, the virus starts to uncoat and release viral genome in the host cell's cytoplasm where this viral DNA replicates to generate more viral entities, along with viral genomic transcription and translation to produce viral proteins which modulate the host immune system. (42) From the entrance site, the infection then extends to regional lymph nodes. Next, it reaches the bloodstream through lymphatic drainage and Primary viremia occurs, which coincides with the incubation period, conventionally ranging from 7 to 17 days. The primary viremia results in dissemination to other organs by the circulation, this is called Secondary viremia which coincides with the prodromal period and usually lasts 1 to 4 days. The secondary viremia coincides with the prodromal phase which lasts 1-4 days, followed by skin rash and other symptoms typical of the monkeypox infection. (43) (44) The virus invades cutaneous blood vessels preceding the development of skin rash. The mechanism through which the virus ascends to the superficial avascular planes of skin, is not exactly known but it is hypothesized that dermal macrophages such as Langerhans cells are involved in it, as this is the known mechanism for vaccinia virus infection. This explanation sounds convincing because monkeypox-infected skin pustules show an influx of resident antigen presenting cells and CD3+ T cells. Eventually, enanthem erupts on mucous membranes including oropharynx as well, which then transform into ulcers and shed virus in the saliva. (33) (45)

Genomic analysis of the two monkeypox clades, Central African clade (alternatively called Congo Basin clade) and West African clade reveal genes that determine virulence in the respective clades. Open reading frames of the West African clade contain deletions and fragmentations which result in relative decrement in its pathogenicity as opposed to the other clade. (46) (47) A study done in Wisconsin, USA during the 2003 monkeypox outbreak by Hammarlund et al. revealed that antiviral cytotoxic and helper T-cells could perceive monocytes infected with Vaccinia virus and in response, produced inflammatory cytokines like Interferon gamma (IFN-γ) and Tumor Necrosis Factor alpha (TNFa) but could not generate the same immune response to monkeypox-infected monocytes. The inhibition of cytotoxic T-cell response against monkeypox-infected monocytes was found to be mediated by the impaired receptor-mediated T cell activation; unlike the other Orthopox virus, Cowpox, no interference in the MHC expression was observed. The study inferred that monkeypox virus produces immunomodulating proteins which suppress immune responses by the host's T-cells. (48) A gene that encodes a protein called Complement Control Protein (CCP) is unique to the Central African clade and deficient in the West African clade due to deletions in open reading frames. This protein impairs both classical and alternative pathways of complement system, and is reportedly one of the multiple immunomodulating factors that are responsible for higher virulence in the Central African clade. (46) (49) (50)
Kindrachuk et al. (2012) proposed that the Congo Basin clade modulates host cell responses differently than the West African clade, since the former manifests increased disease severity with higher case fatality rate. Their experiment demonstrated that the Central African clade downregulates apoptosis in infected cells. Moreover, different patterns of phosphorylation were also observed in the two clades which were proven as potential targets for pharmacological intervention, including excessive Akt S473 phosphorylation and deficient p53-Ser15 phosphorylation. Impedance of Akt S473 phosphorylation by pharmacologic intervention led to a 261-fold decline in the Central African clade yield, however, the West African monkeypox clade remained unaffected. (51)

Genetic analysis of the Central African strain (ZAI-96) and three West African strains (SL-V70, COP-58, and WRAIR-61) disclosed a difference of 0.55–0.56% in the nucleotides between the Central and West African strains, with 173 and 171 unique functional genes respectively. (52)

**Novel Mutations**

Monkeypox is a DNA virus, so it does not exhibit multiple novel mutations like RNA viruses, for instance, HIV or SARS-CoV-2. (53) Nevertheless, monkeypox viral strains procured during the 2022 outbreak are reported to have undergone multiple, about 40 mutations so far. In typical evolutionary timelines, a microbe would be expected to undergo these many mutations in about 50 years. Rampant transmission among humans has been hypothesized as a reason for monkeypox mutations. In evolution, pathogens usually undergo such mutations to adapt better against emerging sustainability threats but sometimes, harmless mutations occur as well. The exact mechanism behind the development of such mutations is unknown but literature suggests that certain enzymes in the host's immune system induce mutations in them if they encounter viruses. (54) A systemic analysis by Wang et al. (July 2022) of the ongoing, widespread monkeypox epidemic in historically non-endemic countries for this infection, revealed that 2022-strains phylogenetically belong to the same lineage as 2018-strains. However, the strains from 2022 contain 46 new consensus mutations, inclusive of 24 nonsynonymous mutations. If enough of such mutations are triggered in this virus, this can get more detrimental, since nonsynonymous mutations change protein sequences and favor evolutionary progression via natural selection. 187 proteins were found to be encoded by the mutations, of which 10 proteins are more susceptible to mutations; they include D2L-like, OPG023, OPG047, OPG071, OPG105, OPG109, A27L-like, OPG153, OPG188, and OPG210 proteins. The exact effect of these mutations on viral functionality is still unknown. (55) Based on the literature, the first ever case of transmission of monkeypox among humans was known in 2018. Since then, monkeypox virus has exhibited a mutation rate that is ten-fold of its standard mutation rate. Currently, sufficient knowledge does not exist about the consequences of these mutations but the rate is alarming to scientists and warrants more research into the area. (56)

**Prevention**

Variola, Cowpox, Vaccinia, and monkeypox virus all belong to the Orthopox genus. Immunological cross-reactivity and cross-protection exists among the Orthopox species and hence, infection with any one of these species provides some extent of protection against the others. (57) It has been found that vaccination against smallpox offers immunological protection against all orthopox viruses including monkeypox. The termination of smallpox vaccination due to global elimination of smallpox after 1980 is hypothesized to instigate rampant re-eruption of the monkeypox infection with a twenty-fold increase in the incidence reported in 2010 than that in the 1980s. (58) A live attenuated vaccine of vaccinia virus with genetic modification (Ankara-Bavarian Nordic / MVA-BN strain) has been developed under brand names JYNNEOS and ACAM2000® in the USA, IMVANEX in the EU and IMVAMUNE in Canada against smallpox and monkeypox. (59) The Food and Drug Administration (FDA) approved JYNNEOS in 2019 for prophylaxis of Smallpox and monkeypox in high risk groups, aged 18 years and above. (60) The recommended dosing for JYNNEOS is two subcutaneous doses of 0.5 ml, with an interval of 4 weeks for first smallpox vaccination. Individuals previously vaccinated receive only one dose. (61) ACAM2000® is administered intradermally as a single dose through multiple punctures. (62) Historical data shows vaccinia virus vaccination to be 85% effective against monkeypox. (63) Vaccinated individuals have significantly lower chances of being infected and even if they do get infected, the disease morbidity is markedly reduced.

The percentage of various symptoms in vaccinated versus unvaccinated groups is depicted in the chart below (31)

Smallpox vaccination can be given prophylactically to prevent monkeypox infection before or after a suspected or confirmed viral exposure. Pre-exposure prophylaxis (Pre-EP) is indicated only in high risk groups, such as immunocompromised persons or medical personnel who are frequently exposed to orthopoxviruses. It is indicated when prolonged high exposure contact has taken place. Exposures that warrant a Pre-EP include unprotected direct mucocutaneous exposure to infected patient’s skin, body fluids, contaminated fomites or standing with no personal protective equipment within 6 feet radius of an infected patient during any procedure that may produce aerosol from patient’s secretions, body fluids and dry exudates or presence within 6 feet of an unmasked patient for at least 3 hours. (64) Centers
for Disease Control and Prevention (CDC) recommends post-exposure prophylaxis (Post-EP) to be given within 4 days of exposure. A Post-EP given between 4–14 days after the exposure, reduces the disease severity but does not protect from the infection incidence in the first place. (65)

Sexual transmission has been implicated in vaccinia virus following its administration as the smallpox vaccine and multiple cases have been reported so far. In one such case, a military man who was recently vaccinated with smallpox vaccine, removed his bandages covering the vaccination site and had unprotected sexual intercourse following a digital vaginal contact. His female partner had atopic dermatitis and developed a vulvar lesion four days after this event which tested positive for vaccinia virus on PCR assay. (66) In another case, a painful perianal rash and an upper lip lesion was reported in a man who had unprotected sexual intercourse with another man who had been recently vaccinated with smallpox and had his vaccination site uncovered. This second contact while experiencing perianal rash, had a sexual contact with a third man who developed papular lesions on his penis along with prodromal symptoms 2 days following this sexual contact. In both patients, testing of the lesions confirmed presence of non-variola Orthopoxvirus (67)

No doubt there is sufficient literary evidence for utility of smallpox vaccine for pre and post-exposure prophylaxis but care must be taken for not leaving the vaccination site uncovered and covering it with a bandage until the scab that forms after vaccination falls off on its own which may take 2 to 3 weeks due to risk of viral shedding from the vaccine site and possible transmission to immunocompromised or atopic individuals. Other precautions for this include, changing the bandage every 1–2 days, proper disposal of the removed bandages and proper hand sanitization while handling the wound and bandages. (68) Another study demonstrated the role of topical application of povidone iodine ointment in reducing the risk of contact spread from the vaccine site, from 7 days post-vaccine administration to complete skin healing. (69)

**Treatment**

Monkeypox infection conventionally exhibits mild clinical manifestations and the majority of patients can recuperate without any treatment. As per the CDC guidelines, no definitive treatment is currently known for monkeypox infection, symptomatic management and prevention of complications are the key therapeutic goals. Treatment options should only be considered for high-risk groups; these include immunocompromised or people having comorbidities, elderly, pregnant or breastfeeding individuals, children younger than 8 years of age, people having skin conditions that cause breach in mucocutaneous barriers, and patients experiencing severe symptoms for monkeypox infection that may or may not require hospitalization. Treatment options for monkeypox is an area that still requires extensive research, the utility of certain antiviral medications in treating monkeypox infection is still controversial and debatable. The evidence available in the literature is preclinical with an insignificant amount of data available on human disease models. (70) Literature proves effectiveness of smallpox vaccination for pre and post-exposure prophylaxis; antiviral drugs (Tecovirimat and Brincidofovir), and Vaccinia Immune Globulin (VIG) have shown promising results in active infections. Tecovirimat and Brincidofovir, are licensed by the United States Food and Drug Administration (FDA) for treatment of smallpox, meanwhile cidofovir is FDA approved for the treatment of CMV retinitis in patients with AIDS. These antivirals are now being explored as possible treatment options for monkeypox infection.(37) (45) (56)

Tecovirimat, a 4-trifuoromethyl phenol derivative antiviral (also known as ST-246 or TPOXX®®), has now been approved by the European Medicines Agency (EMA) for treatment of monkeypox. Although a variety of animal species models have demonstrated therapeutic effectiveness of Tecovirimat against all orthopox virus infections, no significant data is available in the literature to establish its efficacy in humans; however, a clinical trial called STOMP is currently under progress to assess it. (70) (71) The drug by targeting the orthopox virus F13L gene that encodes VP37 membrane protein, prevents enveloping of intracellular mature viral particles that would otherwise disseminate outside the infected cell into the host’s body. (72) (73) Tecovirimat shows an established safety profile in humans at an oral dosage of 600 mg twice daily, headache and nausea are the two most commonly reported adverse effects. (71) Non-human primate models show that Tecovirimat reduces morbidity and mortality in monkeypox infection, and its maximum effect is seen when administered within 5 days of the infection. In real scenarios, the symptoms appear much later following the onset of infection, and this suggests a decrease in the effectiveness of tecovirimat in treating symptomatically active monkeypox infection than when given as post-exposure prophylaxis. Smallpox vaccine alone was not found to be much effective for post-exposure prophylaxis, as it only reduces the disease severity but does not prevent it, but its combination with oral tecovirimat or oral administration of tecovirimat alone was found to be 100% protective against the infection. (74) (75) (76) (77) Apart from NPH models, certain studies provide the evidence of effectiveness of tecovirimat in human models too. A case series of monkeypox infected humans from Massachusetts, USA, reported markedly reduced disease severity and resolution of symptoms around day 5, 9, or 14 when they were administered tecovirimat 600 mg, orally, every 12 hours for 2 weeks during active symptomatic phase of the infection. (78)
Tecovirimat can be administered either orally or intravenously. Fecal elimination is the major clearance route, and no fetal risks have been reported with gestational usage in animal models. Some major adverse reactions reportedly include headache, gastrointestinal upset, xerostomia, and hypersensitivity reactions. The recommended dosage regimen for monkeypox treatment is 14 days in animal models, 21 days in safety data, while further clinical trials are still ongoing to explore 28 days regimens.

Daily oral dosage for tecovirimat is as follows:

- 13 kg–24 kg: 200 mg 12 hourly;
- 25 kg–39 kg: 400 mg 12 hourly;
- 40 kg–119 kg: 600 mg 12 hourly;
- 120 kg or above: 600 mg 8 hourly."

In contrast, the IV dosage of tecovirimat is recommended as follows:

- 3 kg–34 kg: 6 mg/kg 12 hourly, over 6 hours;
- 35 kg–119 kg: 200 mg 12 hourly, over 6 hours;
- 120 kg and above: 300 mg 12 hourly." (79)

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The table is the authors' own creation, based on the data available in literature (79)

An acyclic nucleoside phosphate, Cidofovir, and its lipid conjugated prodrug, Brincidofovir (also known as CMX001) are antivirals that block viral DNA synthesis of orthopoxviruses, including monkeypox virus, by inhibiting the viral DNA polymerase. Cidofovir is a monophosphate nucleotide and needs to be phosphorylated by intracellular kinases to get activated. In contrast, Brincidofovir is cleaved following its intracellular uptake to release the phosphorylated cidofovir molecule already present in the drug. This explains brincidofovir’s higher cellular toxicity and stronger antiviral activity, greater selective index, and 25-fold efficacy than cidofovir against monkeypox, vaccinia, variola and cowpox virus. (72) Brincidofovir has exhibited antiviral activity against monkeypox in animal models. (80) (81)

Brincidofovir is available in oral formulation only. 51% of the drug undergoes urinary clearance while 50% of it is excreted in feces. Risk of teratogenicity has been reported in animal models, partners should use contraception during and after the treatment till at least 4 months after the last dose. Nausea, vomiting, diarrhea, abdominal pain, and elevation of liver enzymes are the major known adverse effects.

Brincidofovir is recommended to be taken as 2 doses, 1 week apart (day 1 and 8), with following weight-adjusted dosage:

- “<10 kg: 6 mg/kg (suspension);
- 10 kg to <48 kg: 4 mg/kg (suspension);
- 48 kg and above: 200 mg (20 mL or 1 tablet).” (79)
Cidofovir is available in IV formulation only. It is known to be teratogenic, hence not recommended in pregnant patients. Up to 75–80% of the drug undergoes renal clearance. Adverse effects include neutropenia, decreased ocular pressure, and nephrotoxicity. Limited data is available on its dosage regimen but the available literature recommends a single dose of 5 mg/kg. About 2 gm Probenecid is given 3 hours prior to cidofovir to prevent potential nephrotoxicity, followed by 1 L 0.9% NS prior to administration of 5 mg/kg cidofovir, diluted in 100 ml NS, infused IV over 1 hour. If further volume can be tolerated, an additional 1 L NS can be given over 1–3 hours, started with cidofovir infusion. Finally, 1 g probenecid should be repeated 2 and 8 hours post cidofovir infusion. The goal is to reduce the nephrotoxic potential of cidofovir by administration of probenecid to reduce tubular secretion of the antiviral along with good IV hydration to reduce the renal contact time. (79) (82)

Among the aforementioned three antiviral drugs, tecovirimat is considered as the first-line and the best treatment option for monkeypox infection because of an established safety profile in humans, great antiviral response in both prophylactic and therapeutic terms, broad antiviral spectrum, and a more tolerable adverse effects profile. (74) (83) Vaccinia Immune Globulin (VIG) can treat complications of vaccinia/smallpox vaccination such as eczema vacciniam, severe generalized vaccinia etc. when given intravenously. However, it is neither approved by CDC or EMA. No significant literary evidence exists to demonstrate efficacy of VIG in monkeypox infection. However, a healthcare provider may decide to administer it to severely immunocompromised individuals with impaired T cell responses, conditions which contraindicate the usage of smallpox vaccination for post-exposure prophylaxis to monkeypox. (70)

**Conclusion**

Monkeypox has now become a globally emerging public health challenge, with static statistics in historically endemic areas and rampant growth throughout the non-endemic areas. Global cessation of smallpox vaccine after 1970 has been hypothesized to be the cause for recurrent monkeypox outbreaks across various parts on the globe, from time to time. (58) Previous outbreaks outside the endemic areas were usually limited to single countries but the ongoing 2022 outbreak has hit multiple countries in the western hemisphere simultaneously. (13) Many atypical features have been observed in this outbreak, including sexual transmission among men who copulate with men, along with peri-genital lesions and rectal symptoms. (12) (15) (18) (19) (20) Two clades with several mutated strains have been identified so far. The current outbreak is of the West African clade, which is less virulent than the Central African clade. (5) (7) The infection is usually self-limiting, with low death tolls. Smallpox vaccine has proven to be effective for pre and post-exposure prophylaxis of the infection and is also known to reduce the severity of illness in previously vaccinated individuals. (31) (60) Like any other viral illness, the treatment is mainly symptomatic; however, severely immunocompromised groups or those developing severe complications can be given certain antiviral drugs that have shown promising results but further research is still needed in this area to establish solid treatment guidelines in order to abolish the viral outbreak. (33) (45) (56)

**Declarations**

*Conflicts of interest: The authors declare no conflicts of interest.*

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Table 1 is available in the Supplementary Files section

Figures

Figure 1
DISTRIBUTION OF MONKEYPOX CASES. (Graph 1)

Figure 2
Legend not included with this version.
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx