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Awareness of monkeypox outbreaks, mechanisms of transmission, diagnostics, and countermeasures-A mini review

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Monkeypox virus (MPXV) a member of the *Poxviridae* family is a double-stranded DNA, and in humans, causes a zoonotic disease similar to smallpox known as monkeypox, which is endemic to Africa. Now it's a public health issue worldwide and in May 2022 outbreak of monkeypox occurred in Europe. Monkeypox (MPX) is a contagious disease that can be transmitted by infected animals, direct skin-to-skin contact, and respiratory droplets. As countermeasures different antiviral drugs are available like tecovirimat, brincidofovir, and cidofovir. Globally to support public health prevention and control measures for such outbreaks public should be aware of pathogenetic epidemiological and diagnostic aspects. The purpose of this review is to discuss the different aspects of this disease including outbreaks, diagnosis, pathogenesis, and treatment measures. Globally it is an issue for health security and to tackle this problem it's necessary to develop a multidisciplinary approach involving veterinarians, physicians, virologists, and public health experts.

Keywords: Monkeypox, smallpox, orthopoxviruses, zoonotic diseases, epidemic.

INTRODUCTION: Worldwide the outbreaks of zoonotic infections such as dengue, ebola, chikungunya, salmonellosis, rabies, bird flu, anthrax, Rift Valley fever, etc. remained major threats to humans and always affected the health security systems at local, national, international, and worldwide levels (WHO, 2018). Whereas from each outbreak some lessons are being learned for future perspectives but now one concept is gaining attention known as one human-environmental-animal health approach (Zumla *et al.*, 2017; Eteng, 2018). In recent times pathogens have emerged in humans from domestic and wild animal reservoirs such as coronavirus, influenza virus, and HIV (Human immunodeficiency virus) (Plowright *et al.*, 2017). Any pathogen becomes a risk to the human population from the event of first-time contact between humans and animal reservoirs which is the source of pathogen transmission known as pathogen spillover. After this contact pathogens become able to transmit from human to human and this transmission allows the pathogens to expand in geographical boundaries outside the spillover zone. The risk of viral spillover is expected to increase significantly due to land expansion and changing climate (Lloyd-Smith *et al.*, 2009; Zhou and Shi, 2021). Different infectious diseases caused extensive morbidity and mortality in humans before the development of vaccines such as diphtheria, polio, smallpox, and tuberculosis (Roeder *et al.*, 2013). But now access to health care, improved sanitation, and medical advances have decreased the rate of morbidity and mortality due to these pathogenic diseases. As in the case of SARS-CoV-2, the swift development of the vaccine is proof of modern sciences' efficacy in rapidly countering pathogenic threats (Baker *et al.*, 2022). However, in low and middle-income countries the burden of infectious diseases is very significant. In these areas, morbidity and mortality rates linked to malaria, tuberculosis, and HIV infection remain high.

Additionally, deaths from emerging and re-emerging infections have continued throughout the twenty-first century as compared to seasonal and endemic infections. This indicates a new era of infectious pathogenic diseases which are defined as outbreaks that spread quickly in a population (Nova *et al.*, 2022). Furthermore, changes are also occurring in the human population having exposure to pathogenic spillover. For example, smallpox vaccination was ceased due to the elimination of smallpox which may have allowed the expansion of monkeypox (Rimoin *et al.*, 2010). Since the discovery of monkeypox about 70 years ago, it is considered a self-limiting and rare disease thus much attention is not given to this disease. In recent years the geographic distribution and frequency of monkeypox have increased among humans, especially in regions of Africa, where it is known as a major public health hazard. Areas with increased infection rates indicated a close interaction between human and wild animal reservoirs (Cook and Zumla, 2009; Petersen *et al.*, 2019). The severity of monkeypox is less than smallpox in terms of complication, case fatality, and scarification level. The clinical signs and symptoms of monkeypox are similar to those of smallpox such as symptom onset, rash occurrence, and rash distribution (Cook and Zumla, 2009; WHO, 2019b). Even 40 years ago smallpox was eliminated worldwide through vaccination, but due to the resemblance of monkeypox with smallpox recently its re-emergence has increased the severe concerns. It's also a challenge to differentiate monkeypox from chickenpox during disease outbreaks. However, sporadic zoonotic infections need attention along with other orthopoxviruses (OPV). As in Brazil vaccinia virus infection in cattle affected a large number of the human population, similarly, in India outbreaks of buffalopox have caused infections in humans (Oliveira *et al.*, 2017). The objective of this paper is to provide a concise and comprehensive overview of the monkeypox virus, including its epidemiology, transmission dynamics, and recent outbreak patterns, which are critical for understanding the current public health implications. Secondly, it delves into the pathogenesis of the virus, elucidating the biological mechanisms and progression of the disease, thereby contributing to a deeper scientific understanding necessary for developing effective treatments and preventive strategies.

Monkeypox: An emerging zoonotic disease: Poxviruses are a member of the *Poxviridae* family, which is a huge and assorted family. Viruses from this family are oval-shaped with double-stranded DNA and multiply in the cytoplasm of infected cells (figure 1) (Hughes *et al.*, 2010).

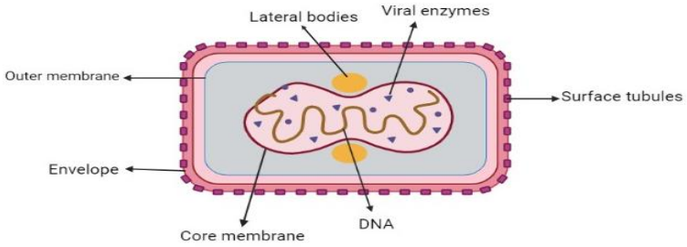

Figure 1: Schematic representation of a Monkeypox virus.

These are also known as ancient viruses because they have been identified in birds, insects, reptiles, and mammals. These viruses evolved due to their ability to manipulate and modulate the immune response of the host and they form visible pox in infected persons (Lefkowitz *et al.*, 2006; Essbauer *et al.*, 2010). The human MPXV belongs to the genus Orthopoxvirus and *Poxviridae* family and contains double-stranded DNA. Monkeypox is an emerging zoonotic infective disease caused by the monkeypox virus. Monkeypox virus has been categorized into three strains, Central African, West African, and Congo Basin strain. The latter has been known to cause more morbidity and mortality rates along with rapid transmission. Orthopoxvirus species are pathogenic for humans and include four different types of viruses such as cowpox virus, monkeypox virus, variola virus, and vaccinia virus (Rimoin *et al.*, 2010; Durski, 2018). It can affect a large range of mammalian hosts. Rabbits, primates (non-human), and rodents are the hosts for the poxviruses. They can also be transferred to humans and there are chances for the human-to-human transfer of the virus. The virus is transferred through

respiratory disease, saliva, lesion extrusion, and feces (Hutson *et al.*, 2009; Haller *et al.*, 2014). Clinically monkeypox has a resemblance to smallpox but the major factor that differentiates monkeypox is the early lymph node enlargement with fever. Thus in monkeypox, lymphadenopathy may develop before or during the rash. After 1-3 days of infection, rashes appear on the body along with headache, fatigue, and lesions that spread on the body at an increasing rate. Lesions are distributed on the whole body or spread in a peripheral pattern. The infection lasts up to four weeks until the lesions peel off in the form of scales (Wang and Lun, 2023). Patients also suffer several other complications like bacterial infections, broncho-pneumonia, corneal infection, dehydration, encephalitis, gastro-intestinal issues, respiratory problems, and sepsis. The spectrum of disease ranges from mild to severe and fatal (Reynolds *et al.*, 2017). In pregnant women, the causes of miscarriage have also been reported as the result of this disease (Mbala *et al.*, 2017). The incubation period for the monkeypox virus is from 7 to 14 days but patients are still considered infectious from the phase of rashes to the time lesions peel off in the form of scales, this desquamation stage lasts up to 4 weeks (Adnan *et al.*, 2022). This is a contagious disease and thus can spread through direct contact with lesions, placenta, and droplets of sneezing and cough (Parker *et al.*, 2007). In the current situation, there is no specific treatment to treat the monkeypox infection so patients depend on symptomatic treatment along with supportive care. It has been assessed that the smallpox vaccine showed 85% efficiency against monkeypox. Due to past vaccination, residual immunity decreases the intensity of this disease and its signs and symptoms (Rizk *et al.*, 2022).

Most of the viruses of the orthopoxviruses have the same genetic as well as antigenic features, so in case of any infection caused by any other virus can be protected by the infection of these viruses (García-Casal *et al.*, 2016). Thus, the chances of the illness by any other virus of the orthopoxvirus lessened due to the cross-immunity responses. It can be seen by history that the vaccination that was in use for the cure of smallpox had shown protection against the viruses that caused monkeypox (Mahmoud and Nchasi, 2023). The vaccination for smallpox was discontinued as the smallpox was completely eradicated in the 1970s. As a result, the cross-immunity started to fade against other Orth poxviruses (Petersen *et al.*, 2019). People below the age of 50 years were less vaccinated for smallpox and as a result, the chance for infection by the orthopoxviruses increases for example monkeypox infection. In the later generations after the least vaccinations emerged the chances of re-infection by the virus (Shchelkunova and Shchelkunov, 2022).

Monkeypox outbreaks: Worldwide monkeypox disease has gained attention as an important health problem for the public. Since the discovery of this disease, it has been endemic to Central and West Africa, now it is not only confined to these regions but is spreading globally. The populations involved in hunting, killing, handling, and consuming bushmeat mainly suffer the monkeypox outbreaks (Antunes *et al.*, 2022). In 1958 orthopoxvirus was isolated from skin lesions in macaques in a Danish laboratory, which later caused the disease outbreaks in captive primates (Mitjà *et al.*, 2023). Primarily monkeypox infection was introduced into humans through the respiratory droplets and lesion secretions entered percutaneously and mucocutaneously. In 1959, the first time monkeypox virus was reported to cause pox-like disease in monkeys kept at a research institute in Copenhagen, Denmark (Mitjà *et al.*, 2023). In 1970, the first occurrence of monkeypox in the human population was reported in an infant having eruptions like smallpox (Kabuga and El Zowalaty, 2019). Over the last 20 years cases of the human population infected by the monkeypox virus are increasing rapidly (Durski, 2018; Sklenovská and Van Ranst, 2018).

From 1970 to 1986 WHO conducted a surveillance program in DRC (the Democratic Republic of the Congo) and reported 404 human cases, while from 2004 to 2005 another surveillance study showed a rapid increase in infected cases as compared to the previous program. Disease cases were higher in lower age groups who did not get a vaccination in the smallpox eradication program, the incidence was also high in forested regions having wild animals (Rimoin *et al.*, 2010). Until now from ten different African countries human monkeypox cases have been discovered including the Central African Republic, Cameroon, DRC, Gabon, Ivory Coast, Liberia, Nigeria, Republic of the Congo, Sierra Leone, and South Sudan (Formenty *et al.*, 2010; WHO, 2019a). The increasing number of human monkeypox cases in these areas is considered due to the decreasing cross-protective immunity developed among the population after the cessation of smallpox vaccination. This vaccination was discontinued in the early 1980s as the smallpox disease was eradicated (Durski, 2018). Since 2017, Nigeria has experienced a large outbreak, with over 500 suspected cases over 200 confirmed cases, and a case fatality ratio of approximately 3%. Cases continue to be reported until today. In 2003, the first monkeypox outbreak outside of Africa was in the United States of America this outbreak led to over 70 cases of monkeypox in the US, and it gained international attention. During this outbreak disease rapidly spread in six US states including Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin (CDC, 2022). Monkeypox has also been reported in travelers from Nigeria to Israel in September 2018, to the United Kingdom in September 2018, December 2019, May 2021, and May 2022, to Singapore in May 2019, and to the United States of America in July and November 2021 (WHO, 2021). In May 2022, multiple cases of monkeypox were identified in several non-endemic countries. Studies are currently underway to further understand the epidemiology, sources of infection, and transmission patterns.

Pathogenesis: Based on taxonomy, these viruses have two categories, one is *Entomopoxvirinae* and the other *Chorodopox-virinae*. The subfamily classification is done based on the infection caused by the virus. If the virus is infecting the insects, these are *Entemopovirinae*, and if the virus is infecting vertebras then *Chorodopoxvirinae*. This family has 18 genera. All viruses of these genera have a zoonotic origin (Rubins *et al.*, 2011). The patho-physiology and pathogenesis of monkeypox start from the transmission of the virus, whether it be animal-to-human trans-mission or human-to-human transmission (Okyay *et al.*, 2022). Respiratory droplets are the most prevalent factor of human-to-human transmission, as rare as it is thought to be. The infection course of the monkeypox virus is similar to that of smallpox, commencing with exposure to the host's oropharyngeal or respiratory mucosa. Following virus entrance, the monkeypox multiplies at the site of the injection which is respiratory and oropharyngeal mucosa in human transmission. The viral burden spreads in local lymph nodes after viral replications the viral burden circulates to distant lymph nodes and organs in secondary viremia. The entire process reflects the incubation phase which normally lasts seven to fourteen days with a maximum of twenty-one days (Hraib *et al.*, 2022). Monkeypox clinical manifestations are not observable during the stage of incubation, hence the incubation phase is not communicable. Monkeypox symptoms are linked to the pre-monitory stage. It also spreads from lymphoid organs to the skin and tertiary organs such as the lungs, eyes, and gastrointestinal system during the prodromal stage. An individual is considered most infectious during the prodromal stage (Bunge *et al.*, 2022).

Symptoms: The most common symptoms of monkeypox begin to appear after two weeks of the infection with the virus of monkeypox. The non-specific symptoms include lymphadenopathy, myalgias, fever, etc. As these symptoms are similar to the symptoms of the seasonal flu as well as the common cold the infected human confuses the situation with these issues (Okyay *et al.*, 2022). After the occurrence of the fever and lymphadenopathy, it is observed that the skin rashes develop after one to three days. The intensity of the symptoms can be mild or sometimes even go unnoticed before the appearance of the rashes (Hraib *et al.*, 2022). There is a different presentation of the rash in the infected patients. After the rashes have begun to develop there is a decline in the fever on that day or after three days (Petersen *et al.*, 2019). Firstly, the rashes appear on the face. Afterward, they begin to appear across the body in a distribution known as centrifugal which is more on the extremities than on the abdomen. The oral cavity lesions make it difficult to eat and drink (Petersen *et al.*, 2019; Afshar *et al.*, 2022). The rash enters the desquamation phase in which the peeling off of the scabs has been noticed. The lesions will eventually become crusted in two to three weeks (Reynolds *et al.*, 2017). When crusted lesions are peeled off and new skin is revealed, it means that the patient is no longer infected. In enanthem, the rash is present on the tongue in the mouth. In all stages, these lesions are very painful (Azkur *et al.*, 2022). At the margins of the infected areas, edema can be developed that results in the development of crevices between the calls which can accumulate fluids as well as debris (Okyay *et al.*, 2022). Moreover, infected areas are thick wounds and if there is an injury to these swollen lesions there are chances of severe bacterial

infections which can even cause cellulitis. The infection also includes gastrointestinal symptoms. These symptoms can arise after two weeks of the infection. It results in vomiting and diarrhea that results in dehydration in the infected patient. One of the most serious complications can be a corneal infection (Petersen *et al.*, 2019). The chances of complications are higher in patients who are not vaccinated (Likos *et al.*, 2005; Petersen *et al.*, 2019).

Transmission: It was seen that the virus had the capability of transferring from one to another animal and there are also chances for transferring the virus to humans (Simpson *et al.*, 2020). The dogs were supposed to get the virus from the rodents that were infected and they were shipped from Ghana to the US. In the year 2003 US, there arose a Midwest outbreak, the cause was the transmission of monkeypox to humans by an intermediate host. The rodents were shipped to Ghana, while the pet dogs had taken the virus as an intermediate host from the rodents (Simpson *et al.*, 2020). There are numerous transmission modes for the virus (figure 2).

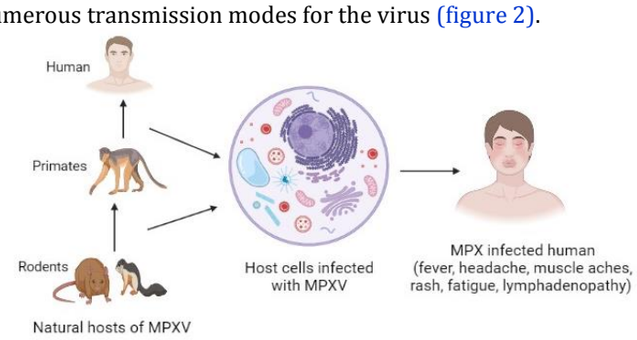

Figure 2: Schematic representation of the transmission of infection of MPXV.

It includes direct contact of the human with the animals that are infected, or it can be due to the contact of a healthy human with an infected human. Human diseases are interlinked with animals, although recognizing the particular contact of human cases could be problematic in regions where animal interaction with household mouse invasions is prevalent. Transfer of the virus to the human body through direct contact of any individual with infected animals and typically transferred through body fluids like respiratory extraction, saliva, or secretions from cutaneous or mucosal lesions. Another route of exposure might be viral shedding through feces (Bunge *et al.*, 2022). An important risk factor is exposure to infected animals' feces, where it is unusual, to have resources and infrastructure causing people to sleep on the ground, live nearby, or visit the jungle in which diseased animals are more prevalent. In regions where resources are insufficient, particularly in homes, residents have no option but to be forced to hunt animals, increasing the chance of monkeypox manifestation. However, the transmission of monkeypox is less prevalent in comparison to animals to humans, it frequently comprises respirational droplets with continued interaction or contact with cuts of infected individuals. Contaminated substances, such as living in the same household, and sleeping on the same bedding are thought to be a hazardous factor for virus-related transmission between individuals of the same homes (Simpson *et al.*, 2020).

The transmission of monkeypox also involves several molecular mechanisms that facilitate the virus's entry, replication, and spread within a host. The monkeypox virus primarily enters host cells through interactions between viral surface proteins and host cell receptors. Once the virus attaches to the host cell membrane, it is internalized via endocytosis, a process mediated by clathrin-coated vesicles or macropinocytosis (Kataria *et al.,* 2023). After entry, the viral envelope fuses with the endosomal membrane, releasing the viral core into the cytoplasm. The viral genome, a double-stranded DNA, is then uncoated and translocated to the cytoplasm, where it undergoes replication and transcription. The viral DNA-dependent RNA polymerase transcribes early genes, which are crucial for viral replication and host immune evasion. The synthesis of viral proteins follows, and these proteins assemble into new viral particles. The newly formed virions are transported to the host cell membrane, where they are released either through cell lysis or budding, leading to cell death and inflammation (Kieser *et al.,* 2020). This release of virions into the extracellular environment facilitates the spread of the virus to adjacent cells and, ultimately, to other individuals through direct contact with infectious lesions, body fluids, respiratory droplets, or contaminated objects (Bunge *et al.*, 2022).

Diagnosis methods: Genetic: It implies using real-time PCR or PCR (polymerase chain reaction), and this is preferable to PCR tests taken in level-three facilities of Biosafety (Ferdous *et al.*, 2023). MPXV DNA schedule detection from veterinary specimens and clinical, in addition to cell cultures that are MPXV-infected, is proficient alongside real-time PCR in selecting the conserved domain of protein genes of extracellular-envelop (Yinka-Ogunleye *et al.*, 2019), DNA polymerase gene, E9L (Cohen-Gihon *et al.*, 2020). Entire genome sequencing, utilizing technologies next generation sequencing, residue the benchmark for the depiction of other OPVs and MPXVs, but the machinery is high-cost, and seawards refining of data sequencing needs vast power of computation. Therefore, for characterization, the next-generation sequencing method might not be applicable, mainly in African poor resource countries (Beer and Rao, 2019).

Phenotypic: Established on clinical diagnoses, the maturation duration of MPXV is surrounded by 4 to 21 days, and it acts by prodromal illness with various symptoms including fever, headache, myalgia, severe headache, pharyngitis, malaise, enlargement of lymph node, headache, and sweats (Beer and Rao, 2019). MPX Tentative recognition based on clinical signs is important for recognition of doubtful instances during observation but clinical instances MPX definition in absenteeism of laboratory verification have been manifest in a group of 645 particulars to have low sensitivity and top sensitivity (MacNeil *et al.*, 2011).

Immunological: It involves utilizing an enzyme-linked immune-sorbent assay for immunohistochemistry and IgM and IgG (Immunoglobulin M and G) antibody observation for escalating antigen detection. Immunochemistry examination can be utilized to differentiate between the herpes virus and poxvirus infection, utilizing monoclonal or polyclonal antibodies as opposed to all OPVs. It set up that antiviral antibody, in addition to T-cell responses, grows around the onset of disease. However, IgG and IgM are observed in serum for about 5 days and additionally 8 days after rash onset, sequentially. Morphologically, OPV species might not be differentiated, but it grants a hint that the virus is in the hands of the *Poxviridae* family (MacNeil *et al.*, 2011).

Electron microscopy: Due to morphological similarities in orthopoxvirus species, diagnosis by electron microscope is not a perfect approach. It cannot differentiate them but only indicates that the virus is a member of the *Poxviridae* family. Under an electron microscope, monkeypox viruses appear to have a central core of 200–300 nm along with an intracytoplasmic brick-type shape with lateral bodies (Jenewari, 2019; Cieslak *et al.*, 2020).

Treatment: To cure monkeypox, no specific antiviral drug treatment is presently available and is mostly handled symptommatically or by giving supportive care (CDC, 2022; UK Health Security Agency, 2022). However, these treatment options and control regulations have discrepancies as viral DNA shedding incessantly happens in the upper respiratory tract even after the resolution of skin lesions in monkeypox patients (Adler *et al.*, 2022). As the disease is spreading continuously around the globe with no signs of abating, there is a robust need to develop a suitable drug to minimize and control serious morbidities incurred during disease progression and mortalities. The need to use antiviral drugs becomes more pronounced in immunocompromised individuals, severely infected patients, pediatric patients, and pregnant women (Singhal *et al.*, 2022). Despite the unavailability of specific pharmaceutical products to treat monkeypox, some drugs previously used against other viruses showed promising results and may be used for treating monkeypox (table 1).

Drug Name	Category	Characteristics	Reference
ACAM 2000	Vaccines	Second-generation vaccine	(Brown and Leggat, 2016)
IMVAMUNE		Third-generation vaccine	(Petersen *et al.*, 2019b)
Tecovirimat	Antiviral drugs	Small molecule virus inhibitor	(Thakur *et al.*, 2022)
Cidofovir		Viral DNA polymerase inhibitors	
Brincidofovir (CMX001)			(Delaune and Iseni, 2020)
Nioch-14		Nucleoside analogs inhibitor	
Ribavirin, Tiazofurin		Inosine monophosphate dehydrogenase inhibitors	(Baker *et al.*, 2003)
Adenosine N1 oxide (ANO)		DNA polymerase inhibitors	

Table 1: Antiviral drugs and vaccines used for the treatment of poxvirus.

Tecovirimat: Tecovirimat (also known as Arestvyr, ST-246, TPOXX) is a small molecule with inhibitory activity against many

orthopoxviruses, including vaccinia, cowpox, ectromelia, rabbitpox, variola, and monkeypox. Tecovitimat has been authorized to be used in exceptional cases in Europe (Okyay *et al.*, 2022). It is also being used in America to treat monkeypox infection in immune-compromised individuals (e.g., those with autoimmune disease, cancer, HIV/AIDS, biological immunosuppressant, receipt gluco-corticoids in high dose, solid organ and bone marrow transplant), severely infected patients (e.g., hemorrhagic disease, encephalitis, sepsis, and confluent lesions), pediatric patients (especially those aged less than eight years), breastfeeding/pregnant women, patients with a secondary bacterial infection in monkeypox lesions, atopic dermatitis, or severe localized disease in areas such as genitals, anus, mouth or eyes following consultation with Centers for Disease Control and Prevention (CDC) under an Expanded Access Investigational New Drug (EA-IND) protocol (CDC, 2022). Tecovirimat is the first drug used clinically against the monkeypox virus as an intracellular viral release inhibitor due to its potential therapeutic effects during monkeypox disease progression (Afshar *et al.*, 2022). Tecovirimat inhibits monkeypox virus envelope protein VP37, and in this way prevents final phases related to the maturation of viral particles and blocks the egress of new viroid from infected cells, thus stopping the spread of viruses within the host even after the onset of infection (Russo *et al.*, 2021). In recent human trials, tecovirimat was studied to find a suitable dose to prompt recovery from monkeypox but the efficacy results are still under further consideration (Adler *et al.*, 2022). In the United States of America (USA), tecovirimat was used for the treatment of a patient infected with monkeypox during his travel to an African country (Rao, 2022). Earlier, in the Central African Republic, 500 courses of tecovirimat were specified to treat monkeypox under an expanded access protocol. In a recent report, out of initially confirmed 17 monkeypox cases in the USA, one patient with high severity of illness was treated with tecovirimat (Minhaj *et al.*, 2022). In another reported case series, 2 weeks of oral treatment of tecovirimat was given to a patient and resultantly, a remarkable reduction in the duration of viral shedding and infection was observed with no side effects (Adler *et al.*, 2022). Recently, a monkeypox clade 3 patient (West African clade) was given 600 mg of tecovirimat twice a day which has resulted in the cessation of development of new lesions, reduction in pain, and pruritus. The tecovirimat treatment has also exhibited other beneficial results including a reduction in the size of more recent lesions, lessening their expansion and settlement of vesicles without forming pustules. The majority of lesions were resolved after providing consistent therapy with tecovirimat for a period of 14 days. Interestingly, no side effects were observed during the treatment therapy except for a mild nonfocal headache just after intake of the first dose (Matias *et al.*, 2022). In other confirmed monkeypox clade 3 patients, tecovirimat treatment had resulted in the resolution of skin lesions with no biochemical abnormalities. Moreover, tecovirimat can be considered for severely ill monkeypox pregnant women (Dashraath *et al.*, 2022). Within monkeypox clade 3, divergent phylogenetic lineage was revealed in genomic analysis, and tecovirimat was found highly efficient against these new strains (Frenois-Veyrat *et al.*, 2022). The tecovirimat can be used as oral capsular formulations or intravenous (IV) vials and both forms are easily accessible from the US Strategic National Stockpile (SNS) (TPOXX, 2018). The side effects of tecovirimat taken orally include vomiting (2%) abdominal pain (2%), nausea (5%), headache (12%), and neutropenia in one studied subject. Contrary to this, more pronounced adverse effects were associated with IV tecovirimat which include headache (15%), infusion site extravasation (19%), infusion site pain (19%), infusion site erythema (23%), and infusion site swelling (39%) (NYSDOH, 2022). Tecovirimat therapy and resultant outcomes are given in table 2.

Cidofovir: Cidofovir (also known as Vistide, Empovir) is an IV-injected antiviral that is excreted by renal tubules. This small molecule actively targets the DNA polymerase of cytomegalovirus (CMV). Cidofovir is approved by the FDA for treating CMV retinitis in Human Immunodeficiency Virus (HIV) infected patients. Cidofovir possesses wide-ranging antiviral activities against different viral families such as orthopoxviruses, adenoviruses, and herpes viruses (Titanji *et al.*, 2022). For cidofovir to become active, phosphorylation is necessary at different set points during cell entry. Firstly, it phosphorylated as enters the cell. Two more rounds of phosphorylation are needed to prevent viral DNA replications and induce termination (Parker *et al.*, 2008). However, inhibition of trans-lesion DNA synthesis was shown by the incorporation of cidofovir into the template strand (Magee *et al.*, 2008). In an outbreak situation, The CDC allowed the use of cidofovir under EA protocol as a treatment option against orthopoxviruses (including monkeypox) (CDC, 2022). The clinical trials exhibiting cidofovir potency against the human monkeypox virus are lacking. However, in vitro and in vivo studies using animals reported antiviral activity and effectiveness against the lethal monkeypox virus (Baker *et al.*, 2003). The benefits associated with cidofovir treatment during severe monkeypox infection are still unknown but its use is authorized in severe outbreak situations and is available in US SNS (CDC, 2022). During cidofovir treatment, probenecid therapy must be concomitantly used along with a normal saline solution for better clinical outcomes (Rizk *et al.*, 2022). The adverse effects of cidofovir are significantly higher predominantly myelosuppression and nephrotoxicity that may outweigh the advantages (Aus-Govt Guidelines, 2022).

Brincidofovir: Brincidofovir (CMX001 or Tembexa) is a prodrug of an acyclic nucleotide analog of IV cidofovir. It is orally given and hepatically excreted antiviral with potent inhibitory activity against smallpox DNA polymerase. This drug is better in efficacy than cidofovir due to improved safety profile and less renal toxicity (Chittick *et al.*, 2017). Since June 2021, brincidofovir has been listed as a promising drug for treating smallpox in USA (FDA, 2021). Currently, an EA-IND is being developed by CDC to allow the use of brincidofovir in patients infected with monkeypox due to its role in the inhibition of viral DNA polymerase (Lanier *et al.*, 2010). However, brincidofovir is presently missing in US SNS (CDC, 2022). The use of brincidofovir to treat monkeypox infection is in its initial stages. Very little information is available in animal models and human studies although its effectiveness was well established against other orthopoxvirus infections (Rice *et al.*, 2011; Parker *et al.*, 2012). Interestingly, brincidofovir treatment during CMV infections has resulted in a reduction in kidney toxicity and other serious adverse outcomes so it is a better drug than cidofovir in safety profile. Before brincidofovir treatment, liver function tests must be done and should be continuously monitored as brincidofovir may elevate liver enzymes, particularly serum transaminase and bilirubin. Despite favorable outcomes in case of other viral diseases, no substantial benefits were observed in recent monkeypox patients treated with brincidofovir (table 3) (Adler *et al.*, 2022).

Vaccinia immune globulin: Vaccinia Immune Globulin Intravenous (VIGIV) is a plasma product of individuals that possess high titers of antibodies against the vaccinia virus after immunization with smallpox (vaccinia vaccine) and contains hyperimmune globulin (IgG). FDA has designated it as an orphan drug to be used for the treatment of some complexities that arise after smallpox vaccination including severe generalized vaccinia, progressive vaccinia, eczema vaccinatum, vaccinia infection in patients with certain skin disorders such as extensive eczematous skin lesions, varicella-zoster virus infection, burns, poison ivy and impetigo and aberrant vaccinia infection caused by accidental autoinoculation to the mouth, eyes, and any other parts where such infection might be hazardous (Sheean *et al.*, 2020). Due to contradiction of the vaccinia virus in individuals with severe immuno-deficiency in functional aspects of T-cells, VIGIV may be given as alternate therapy (Shchelkunova and Shchelkunov, 2022). Although VIGIV is a potential treatment option human efficacy trials are lacking against smallpox and monkeypox. VIGIV might be a suitable strategy in severely infected monkeypox patients but conduction of VIGIV as treatment therapy should follow an IND protocol (CDC, 2022). Moreover, VIGIV can also be considered for treating severely ill monkeypox pregnant women (Dashraath *et al.*, 2022).

Other potential drugs: Recently, 5 poxvirus targets namely F13L, D13L protein trimer complex, I7L, A50R, and A48R were investigated (Lam *et al.*, 2022) and previously suggested as probable targets in intervention strategies both in vitro and in vivo evidence (Prichard and Kern, 2012). In silico studies revealed strong binding affinities of many FDA-approved drugs including NMCT, rutaecarpine, nilotinib, simeprevir, hypericin, naldemedine, fosdagrocorat, and lixivaptan with these viral protein targets. These drugs should be further investigated to obtain novel repurposing drugs to reduce morbidities and mortalities due to monkeypox (Lam *et al.*, 2022).

A brief case history	Dosage	Duration of treatment	Hospitalization period	Site of infection	Other symptoms	Positive effects of treatment	Adverse effects of treatment	Reference
An early middle-aged man returning from Nigeria to Dallas- Texas	Not reported	Not reported	32 days	The onset of a diffuse and purulent skin rash on a covered part of the body and then on the face	Fever, cough, fatigue, diarrhea, vomiting	All lesions fully healed	Not reported	(Rao, 2022)
30–40 year female developed monkeypox from her infected daughter	600 mg twice daily	14 days	10 days	Rash on face, trunk, arms, and hands	Headache fever, pharyngitis	After one day of tecovirimat therapy, no new lesions formed	No side effects	(Adler *et al.*, 2022)
1 among 17 patients recently reported monkeypox infection in the USA	Not reported	Not reported	Not reported	Rash on arms, trunk, legs, and face	Fatigue, fever, or headache before the onset of rash	All lesions were completely resolved	Not reported	(Minhaj *et al.*, 2022)
A male in his 20s having unprotected sex with men during his tour to a country affected by the present monkeypox outbreak	600 mg twice daily	14 days	10 days	Vesiculopustu-lar lesions on hands oropharynx, face, and feet which are painful and pruritus	Malaise, subjective chills, and mild ulcer	No new lesions formed after the 4th day of treatment, decrease in pain and pruritus, and lesions regressed and ultimately resolved.	The mild nonfocal headache just after the first dose, increases in ALT during treatment which spontaneously normalizes.	(Matias *et al.*, 2022)
HIV-infected male aged in the 20s affected after anal-receptive intercourse with subsequently confirmed monkeypox partner	600 mg twice daily	14 days	7 days	Erythematous pustules on hands, forearms, gingiva, upper and lower extremities	Fever and odynophagia	All skin lesions had crusted on day 9 of therapy	No biochemical abnormalities, 1-2 loose stools after a few hours of treatment	(Matias *et al.*, 2022)
A man in his 40s having sexual activity with many males during his tour to a non-endemic country	600 mg twice daily	14 days	4 days	Erythematous rashes on the perineum and many umbilicated pustules on the arms, chest,	malaise, subjective fevers	Less erythematous perineal rashes and several pustular lesions resolved after day 2 of therapy.	No biochemical abnormalities or side effects	(Matias *et al.*, 2022)

Table 2: Clinical use of Tecovirimat for the treatment of monkeypox

A brief case history	Dosage	Duration of treatment	Hospitalization period	Site of infection	Other symptoms	Positive effects of treatment	Adverse effects of treatment	Reference
30-40-years old male tested positive for monkeypox after his return from Nigeria to the UK	A single dose of 200 mg	7 days	26	Face, limbs, palms, trunk, scalp, scrotum	emotional disturbances, low mood and ulcerated inguinal lesions	Not reported	The rise in ALT level with a peak value of 331 U/L	(Adler *et al.*, 2022)
30-40 years old male tested positive for monkeypox after his return from Nigeria to the UK	Two doses of 200 mg at a weekly interval	14 days	27	Face, limbs, palms, trunk, scrotum, and soles	Low mood, painful lesions, and deep tissue abscesses	Not reported	A rise in ALT level with a peak value of 550 U/L	(Adler *et al.*, 2022)
30-40 years old female Healthcare worker infected by post-exposure to monkeypox patient	Two doses of 200 mg at a weekly interval	14 days	35	Hands, nail bed, face, trunk, and labia majora	A sensation of pain due to subungual lesions and the appearance of conjunctivitis	Not reported	A rise in ALT level with a peak value of 127 U/L, abdominal discomfort, and nausea	(Adler *et al.*, 2022)

Table 3: Clinical use of Brincidofovir for the treatment of monkeypox.

Combination therapy: Certain viruses develop resistance to drugs that are used as viral DNA polymerase inhibitors. Some resistant viral strains were isolated in a culture medium to various compounds including tecovirimat (Wang *et al.*, 2023) and cidofovir (Farlow *et al.*, 2010). In such situations, combination therapy is a preferred treatment option to reduce the chances of development of drug resistance in viral strains, and reduction in drug dosage and duration which are ultimately beneficial in reducing toxic adverse effects. Moreover, survival rates increase by operating combination therapy due to a decrease in intervention time (Angst *et al.*, 2021).

Hence, the use of antivirals along with VIGIV or other treatment options might play a pivotal role in reducing the severe outcomes of monkeypox infection. Previously, the disease was restricted to some African countries but recently the disease has spread all over the world and was declared a global public health emergency of international concern by the World Health Organization. The monkeypox disease has now spread in 75 countries with more than sixteen thousand cases in the current 2022 outbreak. About 70% of cases were reported from America and 15% from European countries (Taylor, 2022). As the cases are continuously rising, the need to use antiviral drugs and other treatments also increasing. Recently, 5% of patients received different treatments (2% of patients were treated with topical or intravenous cidofovir, 2% with tecovirimat, and about 1% with vaccinia immunoglobulin) urging to develop a specific drug to treat monkeypox patients (Thornhill *et al.*, 2022).

Natural remedies: The continuous surge in Orthopox viral infections in the recent past emphasizes the quick discovery of more efficacious therapeutic poxvirus countermeasures. Natural remedies based on plants and plant products offer mankind new insight into valuable components for the treatment of emerging and re-emerging viral strains. The utilization of these components is critically important to provide consistent and long-lasting impacts by increasing immunity in the eradication of viral diseases (Mahwish *et al.*, 2022). To cure monkeypox, certain plants and plant products might play a role in the current global health emergency. Resveratrol is a stilbenoid polyphenol naturally present in grapes

(particularly red grapes), berries, peanuts, cocoa beans, and several other plants. The resveratrol possesses diverse antiviral activities including retardation in the synthesis of viral DNA, assembly of viral protein particles, and boosting functional aspect of host responses necessary to fight viral infections (Abba *et al.*, 2015). The ability of resveratrol to suppress the very initial phase of the transcription process and subsequent monkeypox viral replications is worth consideration in new drug development strategies (Cao *et al.*, 2017). At the end of the nineteenth century, plant-based infusion obtained from a carnivorous plant, *Sarracenia purpurea* was revealed to help treat smallpox by Micmac Indians of Nova Scotia. Meanwhile, in vitro characterization of an extract derived from *S. purpurea* revealed promising results in the prevention of symptoms related to smallpox infection (Arndt *et al.*, 2012). Recently, it was reported that *S. purpurea* extracts possessed inhibitory activity during viral replications without any cytopathic effects or cellular toxicity against different Orthopoxviruses including the monkeypox virus. Since *S. purpurea* specifically targets early viral transcription, this plant might help isolate such compounds that block poxviruses at a very early phase of the replication cycle (Arndt *et al.*, 2012). Some medicinal plants used in herbal practices to treat monkeypox are *Acacia nilotica* (L.) Delile, *Adansonia digitata* L., *Allium sativum* L., *Azadirachta indica* A. Juss., *Anogeissus leiocarpus* (DC.) Guill. & Perr., *Alstonia boonei* De Wild, *Balanites aegyptiaca* (L.) Delile, *Cassia occidentals* L., *Cissus populnea* Guill. & Perr., *Citrullus lanatus* (Thunb.) Matsum. & Nakai, *Combretum micranthum* G. Don., *Detarium senegalense*, *Diospyros mespiliformis*, *Eleusine coracana* (L.) Gaertn., Euphorbia hirta L., *Ficus polita* Vahl, *Ficus platyphylla* Delile, *Guiera senegalensis* J. F. Gmel., *Lagenaria breviflora* (Benth.) Roberty, *Lawsonia inermis* L., *Mangifera indica*, *Maytenus senegalensis* (Lam.) Exell, *Momordica charantia* L., *Moringa oleifera* Lam., *Nigella sativa* L., *Olea europea* L., *Parinari macrophylla* Sabine, *Piper guineense* Schumach. & Thonn., *Tamarindus indica*, *Terminalia avicenoides* Guill. & Perr., *Vernonia amygdalina*, *Vitellaria paradoxa, Viscum album* L., and *Ziziphus mauritiana* Lam (Abubakar *et al.*, 2022). To validate the claims associated with these plants and their components, further in vitro and in vivo investigations are needed to ascertain their potency against the monkeypox virus. In the future, these and other medicinally valuable plants could be a source of discovering novel potential antiviral drugs against monkeypox. Hence, more research is needed at this particular time to isolate potent chemicals particularly bioactive molecules from these plants and divulge the individual and combined bioactivity of these compounds.

CONCLUSION: Monkeypox virus is an important orthopoxvirus and over the past years, the spread of zoonotic monkeypox disease in various regions across the African region indicates that this disease is no longer considered a rare viral disease. In recent years the spread and frequency of monkeypox in humans have increased. Since May 2022, in the above twenty countries, the outbreak of monkeypox has become endemic. Still, it is considered a major health issue due to its possibility of spreading worldwide. Concerning public health, the monkeypox virus is considered a threat pathogen to humans so for the prevention of viral transmission, it's required to adopt effective intervention strategies. Further, it's necessary to understand the gaps between ecology, epidemiology, and the emergence of disease. Due to the worldwide spread of this disease, it is important to adopt and implement global approaches. Policymakers should implement comprehensive public awareness campaigns to educate the public on monkeypox symptoms, transmission, and prevention while strengthening surveillance systems for early detection and reporting. They should support research and development for vaccines and treatments, ensure equitable vaccine distribution, and enforce regulations on wildlife trade to prevent zoonotic transmission. Collaboration with international health organizations is essential for resource sharing and coordinated response. Healthcare professionals need to remain vigilant for symptoms, apply strict infection control measures, and educate patients on prevention.

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REFERENCES:

Abba, Y., H. Hassim, H. Hamzah and M. M. Noordin, 2015. Antiviral activity of resveratrol against human and animal viruses. Advances in virology, 2015.

Abubakar, I. B., S. S. Kankara, I. Malami, J. B. Danjuma, Y. Z. Muhammad, H. Yahaya, D. Singh, U. J. Usman, A. N. Ukwuani-Kwaja and A. Muhammad, 2022. Traditional medicinal plants used for treating emerging and re-emerging viral diseases in northern nigeria. European journal of integrative medicine, 49: 102094.

Adler, H., S. Gould, P. Hine, L. B. Snell, W. Wong, C. F. Houlihan, J. C. Osborne, T. Rampling, M. B. Beadsworth and C. J. Duncan, 2022. Clinical features and management of human monkeypox: A retrospective observational study in the uk. The lancet infectious diseases, 22(8): 1153-1162.

Adnan, N., Z. ul Haq, A. Malik, A. Mehmood, U. Ishaq, M. Faraz, J. M. MSf and M. Amin Mehmoodi, 2022. Human monkeypox virus.

Afshar, Z. M., H. N. Rostami, R. Hosseinzadeh, A. Janbakhsh, A. T. Pirzaman, A. Babazadeh, Z. Aryanian, T. T. Sio, M. Barary and S. Ebrahimpour, 2022. The reemergence of monkeypox as a new potential health challenge: A critical review. Authorea preprints.

Angst, D. C., B. Tepekule, L. Sun, B. Bogos and S. Bonhoeffer, 2021. Comparing treatment strategies to reduce antibiotic resistance in an in vitro epidemiological setting. Proceedings of the national academy of sciences, 118(13): e2023467118.

Antunes, F., R. Cordeiro and A. Virgolino, 2022. Monkeypox: From a neglected tropical disease to a public health threat. Infectious disease reports, 14(5): 772-783.

Arndt, W., C. Mitnik, K. L. Denzler, S. White, R. Waters, B. L. Jacobs, Y. Rochon, V. A. Olson, I. K. Damon and J. O. Langland, 2012. In vitro characterization of a nineteenth-century therapy for smallpox. PLoS one, 7(3): e32610.

Azkur, A. K., E. Aksoy and C. Akdiş, 2022. Monkeypox and other zoonotic poxviruses. Ankara Üniversitesi Veteriner Fakültesi dergisi, 69(4): 445-459.

Baker, R. E., A. S. Mahmud, I. F. Miller, M. Rajeev, F. Rasambainarivo, B. L. Rice, S. Takahashi, A. J. Tatem, C. E. Wagner and L.-F. Wang, 2022. Infectious disease in an era of global change. Nature reviews microbiology, 20(4): 193-205.

Baker, R. O., M. Bray and J. W. Huggins, 2003. Potential antiviral therapeutics for smallpox, monkeypox and other orthopoxvirus infections. Antiviral research, 57(1-2): 13-23.

Beer, E. M. and V. B. Rao, 2019. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. PLoS neglected tropical diseases, 13(10): e0007791.

Brown, K. and P. A. Leggat, 2016. Human monkeypox: current state of knowledge and implications for the future. Tropical Medicine and Infectious Disease, 1(1): 8.

Bunge, E. M., B. Hoet, L. Chen, F. Lienert, H. Weidenthaler, L. R. Baer and R. Steffen, 2022. The changing epidemiology of human monkeypox—a potential threat? A systematic review. PLoS neglected tropical diseases, 16(2): e0010141.

Cao, S., S. Realegeno, A. Pant, P. S. Satheshkumar and Z. Yang, 2017. Suppression of poxvirus replication by resveratrol. Frontiers in microbiology, 8: 307678.

Centers for Disease Control and Prevention (CDC), 2022. Monkeypox - Treatment Information for Healthcare Professionals. Available at: https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html. Accessed 15 August 2022.

Chittick, G., M. Morrison, T. Brundage and W. G. Nichols, 2017. Short-term clinical safety profile of brincidofovir: A favorable benefit–risk proposition in the treatment of smallpox. Antiviral research, 143: 269-277.

Cieslak, T. J., M. G. Kortepeter, C. J. Kratochvil and J. V. Lawler, 2020. Nebraska isolation and quarantine manual. U of Nebraska Press.

Cohen-Gihon, I., O. Israeli, O. Shifman, N. Erez, S. Melamed, N. Paran, A. Beth-Din and A. Zvi, 2020. Identification and whole-genome sequencing of a monkeypox virus strain isolated in israel. Microbiology resource announcements, 9(10): 10.1128/mra.

01524-01519.
Cook, G. and A. Zumla, 2009. Chapter 47. Cutaneous viral diseases. Monkeypox. Manson's tropical diseases 22nd edition London: Harcourt Brace Saunders, Publishing Group: 839-840.
Dashraath, P., K. Nielsen-Saines, C. Mattar, D. Musso, P. Tambyah and D. Baud, 2022. Guidelines for pregnant individuals with monkeypox virus exposure. The lancet, 400(10345): 21-22.
Delaune, D. and F. Iseni, 2020. Drug development against smallpox: present and future. Antimicrobial Agents and Chemotherapy, 64(4): 10-1128.
Durski, K. N., 2018. Emergence of monkeypox—West and Central Africa, 1970–2017. MMWR Morbidity and mortality weekly report, 67.
Essbauer, S., M. Pfeffer and H. Meyer, 2010. Zoonotic poxviruses. Veterinary microbiology, 140(3-4): 229-236.
Eteng, W.-E., 2018. Notes from the field: Responding to an outbreak of monkeypox using the one health approach Nigeria, 2017–2018. MMWR Morbidity and mortality weekly report, 67.
Farlow, J., M. A. Ichou, J. Huggins and S. Ibrahim, 2010. Comparative whole genome sequence analysis of wild-type and cidofovir-resistant monkeypoxvirus. Virology journal, 7: 1-15.
Ferdous, J., M. A. Barek, M. S. Hossen, K. K. Bhowmik and M. S. Islam, 2023. A review on monkeypox virus outbreak: New challenge for world. Health science reports, 6(1): e1007.
Food and Drug Administration (FDA), 2021. US Food and Drug Administration: FDA approves drug to treat smallpox. Available at: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-treat-smallpox. Accessed 18 August 2022.
Formenty, P., M. O. Muntasir, I. Damon, V. Chowdhary, M. L. Opoka, C. Monimart, E. M. Mutasim, J.-C. Manuguerra, W. B. Davidson and K. L. Karem, 2010. Human monkeypox outbreak caused by novel virus belonging to congo basin clade, sudan, 2005. Emerging infectious diseases, 16(10): 1539.
Frenois-Veyrat, G., F. Gallardo, O. Gorgé, E. Marcheteau, O. Ferraris, A. Baidaliuk, A.-L. Favier, C. Enfroy, X. Holy and J. Lourenco, 2022. Tecovirimat is highly efficient on the monkeypox virus lineage responsible for the international 2022 outbreak. bioRxiv: 2022.2007. 2019.500484.
García-Casal, M. N., J. P. Peña-Rosas and H. G. Malavé, 2016. Sauces, spices, and condiments: Definitions, potential benefits, consumption patterns, and global markets. Annals of the new york academy of sciences, 1379(1): 3-16.
Haller, S. L., C. Peng, G. McFadden and S. Rothenburg, 2014. Poxviruses and the evolution of host range and virulence. Infection, genetics and evolution, 21: 15-40.
Hraib, M., S. Jouni, M. M. Albitar, S. Alaidi and Z. Alshehabi, 2022. The outbreak of monkeypox 2022: An overview. Annals of medicine and surgery, 79: 104069.
Hughes, A. L., S. Irausquin and R. Friedman, 2010. The evolutionary biology of poxviruses. Infection, Genetics and evolution, 10(1): 50-59.
Hutson, C. L., V. A. Olson, D. S. Carroll, J. A. Abel, C. M. Hughes, Z. H. Braden, S. Weiss, J. Self, J. E. Osorio and P. N. Hudson, 2009. A prairie dog animal model of systemic orthopoxvirus disease using west african and congo basin strains of monkeypox virus. Journal of general virology, 90(2): 323-333.
Jenewari, F., 2019. Monkey pox in nigeria: Epidemiology and prevention. Proceedings of the Problems and Prospects for the Development of Modern Medicine, GomSMU, Kharkiv, Ukrainian: 2-3.
Kabuga, A. I. and M. E. El Zowalaty, 2019. A review of the monkeypox virus and a recent outbreak of skin rash disease in nigeria. Journal of medical virology, 91(4): 533-540.
Kataria, R., S. Kaur and R. Kaundal, 2023. Deciphering the complete human-monkeypox virus interactome: Identifying immune responses and potential drug targets. Frontiers in Immunology, 14, 1116988.
Kieser, Q., R. S. Noyce, M. Shenouda, Y. C. J. Lin and D. H. Evans, 2020. Cytoplasmic factories, virus assembly, and DNA replication kinetics collectively constrain the formation of poxvirus recombinants. PLoS One, 15(1): e0228028.
Lam, H. Y. I., J. S. Guan and Y. Mu, 2022. In silico repurposed drugs against monkeypox virus. Molecules, 27(16): 5277.
Lanier, R., L. Trost, T. Tippin, B. Lampert, A. Robertson, S. Foster, M. Rose, W. Painter, R. O'Mahony and M. Almond, 2010. Development of cmx001 for the treatment of poxvirus infections. Viruses, 2(12): 2740.
Lefkowitz, E., C. Wang and C. Upton, 2006. Poxviruses: Past, present and future. Virus research, 117(1): 105-118.
Likos, A. M., S. A. Sammons, V. A. Olson, A. M. Frace, Y. Li, M. Olsen-Rasmussen, W. Davidson, R. Galloway, M. L. Khristova and M. G. Reynolds, 2005. A tale of two clades: Monkeypox viruses. Journal of general virology, 86(10): 2661-2672.
Lloyd-Smith, J. O., D. George, K. M. Pepin, V. E. Pitzer, J. R. Pulliam, A. P. Dobson, P. J. Hudson and B. T. Grenfell, 2009. Epidemic dynamics at the human-animal interface. Science, 326(5958): 1362-1367.
MacNeil, A., J. Abel, M. G. Reynolds, R. Lash, R. Fonnie, L. D. Kanneh, W. Robert, V. K. Lungay, A. Goba and L. M. Moses, 2011. Serologic evidence of human orthopoxvirus infections in sierra leone. BMC research notes, 4: 1-5.
Magee, W. C., K. A. Aldern, K. Y. Hostetler and D. H. Evans, 2008. Cidofovir and (s)-9-[3-hydroxy-(2-phosphonomethoxy) propyl] adenine are highly effective inhibitors of vaccinia virus DNA polymerase when incorporated into the template strand. Antimicrobial agents and chemotherapy, 52(2): 586-597.
Mahmoud, A. and G. Nchasi, 2023. Monkeypox virus: A zoonosis of concern. Journal of medical virology, 95(1): e27968.
Mahwish, F. Saeed, M. Afzaal, M. Hussain, M. Imran, T. Nawaz and A. Siddeeg, 2022. Dietary guidelines to boost immunity during pre and post covid-19 conditions. International journal of food properties, 25(1): 1246-1265.
Matias, W. R., J. M. Koshy, E. H. Nagami, V. Kovac, L. R. Moeng, E. S. Shenoy, D. C. Hooper, L. C. Madoff, M. B. Barshak and J. A. Johnson, 2022. Tecovirimat for the treatment of human monkeypox: An initial series from massachusetts, united states. In: Open forum infectious diseases. Oxford University Press: pp: ofac377.
Mbala, P. K., J. W. Huggins, T. Riu-Rovira, S. M. Ahuka, P. Mulembakani, A. W. Rimoin, J. W. Martin and J.-J. T. Muyembe, 2017. Maternal and fetal outcomes among pregnant women with human monkeypox infection in the democratic republic of congo. The Journal of infectious diseases, 216(7): 824-828.
Minhaj, F. S., Y. P. Ogale, F. Whitehill, J. Schultz, M. Foote, W. Davidson, C. M. Hughes, K. Wilkins, L. Bachmann and R. Chatelain, 2022. Monkeypox outbreak nine states, may 2022: Weekly/june 10, 2022/71 (23); 764–769. Wiley Online Library.
Mitjà, O., D. Ogoina, B. K. Titanji, C. Galvan, J.J. Muyembe, M. Marks and C. M. Orkin, 2023. Monkeypox. The lancet, 401(10370): 60-74.
New York State Department of Health (NYSDOH), 2022. Bureaus of communicable disease control (BCDC) and healthcare associated infections (BHAI). Health advisory: monkeypox cases not associated with travel to areas where monkeypox is enzootic. July 8, 2022. Available at: https://www.health.ny.gov/diseases/communicable/zoonoses/monkeypox/docs/2022-07-08_han.pdf. Accessed 17 August 2022.
Nova, N., T. S. Athni, M. L. Childs, L. Mandle and E. A. Mordecai, 2022. Global change and emerging infectious diseases. Annual review of resource economics, 14: 333-354.
Okyay, R. A., E. Bayrak, E. Kaya, A. R. Şahin, B. F. Koçyiğit, A. M. Taşdoğan, A. Avcı and H. E. Sümbül, 2022. Another epidemic in the shadow of covid 19 pandemic: A review of monkeypox. proteins, 7(10): 10.14744.
Oliveira, J. S. O. Figueiredo, G. B. Costa, F. L. d. Assis, B. P. Drumond, F. G. Da Fonseca, M. L. Nogueira, E. G. Kroon and G. d. S. Trindade, 2017. Vaccinia virus natural infections in brazil: The good, the bad, and the ugly. Viruses, 9(11): 340.
Parker, S., N. G. Chen, S. Foster, H. Hartzler, E. Hembrador, D. Hruby, R. Jordan, R. Lanier, G. Painter and W. Painter, 2012. Evaluation of disease and viral biomarkers as triggers for therapeutic intervention in respiratory mousepox–an animal model of smallpox. Antiviral research, 94(1): 44-53.
Parker, S., L. Handley and R. M. Buller, 2008. Therapeutic and prophylactic drugs to treat orthopoxvirus infections.
Parker, S., A. Nuara, R. M. L. Buller and D. A. Schultz, 2007. Human monkeypox: An emerging zoonotic disease.
Petersen, E., I. Abubakar, C. Ihekweazu, D. Heymann, F. Ntoumi, L. Blumberg, D. Asogun, V. Mukonka, S. A. Lule and M. Bates, 2019. Monkeypox—enhancing public health preparedness for an emerging lethal human zoonotic epidemic threat in the wake of

the smallpox post-eradication era. International journal of infectious diseases, 78: 78-84.

Petersen, E., A. Kantele, M. Koopmans, D. Asogun, A. Yinka-Ogunleye, C. Ihekweazu and A. Zumla, 2019. Human monkeypox: Epidemiologic and clinical characteristics, diagnosis, and prevention. Infectious Disease Clinics, 33(4): 1027-1043.

Plowright, R. K., C. R. Parrish, H. McCallum, P. J. Hudson, A. I. Ko, A. L. Graham and J. O. Lloyd-Smith, 2017. Pathways to zoonotic spillover. Nature Reviews Microbiology, 15(8): 502-510.

Prichard, M. N. and E. R. Kern, 2012. Orthopoxvirus targets for the development of new antiviral agents. Antiviral research, 94(2): 111-125.

Rao, A. K., 2022. Monkeypox in a traveler returning from nigeria—dallas, texas, july 2021. MMWR Morbidity and mortality weekly report, 71.

Reynolds, M. G., A. M. McCollum, B. Nguete, R. Shongo Lushima and B. W. Petersen, 2017. Improving the care and treatment of monkeypox patients in low-resource settings: Applying evidence from contemporary biomedical and smallpox biodefense research. Viruses, 9(12): 380.

Rice, A. D., M. M. Adams, G. Wallace, A. M. Burrage, S. F. Lindsey, A. J. Smith, D. Swetnam, B. R. Manning, S. A. Gray and B. Lampert, 2011. Efficacy of cmx001 as a post exposure antiviral in new zealand white rabbits infected with rabbitpox virus, a model for orthopoxvirus infections of humans. Viruses, 3(1): 47-62.

Rimoin, A. W., P. M. Mulembakani, S. C. Johnston, J. O. Lloyd Smith, N. K. Kisalu, T. L. Kinkela, S. Blumberg, H. A. Thomassen, B. L. Pike and J. N. Fair, 2010. Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the democratic republic of congo. Proceedings of the National Academy of Sciences, 107(37): 16262-16267.

Rizk, J. G., G. Lippi, B. M. Henry, D. N. Forthal and Y. Rizk, 2022. Prevention and treatment of monkeypox. Drugs, 82(9): 957-963.

Roeder, P., J. Mariner and R. Kock, 2013. Rinderpest: The veterinary perspective on eradication. Philosophical Transactions of the Royal Society B: Biological sciences, 368(1623): 20120139.

Rubins, K. H., L. E. Hensley, D. A. Relman and P. O. Brown, 2011. Stunned silence: Gene expression programs in human cells infected with monkeypox or vaccinia virus. PLoS one, 6(1): e15615.

Russo, A. T., D. W. Grosenbach, J. Chinsangaram, K. M. Honeychurch, P. G. Long, C. Lovejoy, B. Maiti, I. Meara and D. E. Hruby, 2021. An overview of tecovirimat for smallpox treatment and expanded anti-orthopoxvirus applications. Expert review of anti-infective therapy, 19(3): 331-344.

Shchelkunova, G. A. and S. N. Shchelkunov, 2022. Smallpox, monkeypox and other human orthopoxvirus infections. Viruses, 15(1): 103.

Sheean, M. E., E. Malikova, D. Duarte, G. Capovilla, L. Fregonese, M. P. Hofer, A. Magrelli, S. Mariz, F. Mendez-Hermida and R. Nistico, 2020. Nonclinical data supporting orphan medicinal product designations in the area of rare infectious diseases. Drug discovery today, 25(2): 274-291.

Simpson, K., D. Heymann, C. S. Brown, W. J. Edmunds, J. Elsgaard, P. Fine, H. Hochrein, N. A. Hoff, A. Green and C. Ihekweazu, 2020. Human monkeypox–after 40 years, an unintended consequence of smallpox eradication. Vaccine, 38(33): 5077-5081.

Singhal, T., S. Kabra and R. Lodha, 2022. Monkeypox: A review. Indian journal of pediatrics, 89(10): 955-960.

Sklenovská, N. and M. Van Ranst, 2018. Emergence of monkeypox as the most important orthopoxvirus infection in humans. Frontiers in public health, 6: 383729.

Taylor, L., 2022. Monkeypox: Who declares a public health emergency of international concern. BMJ: British medical journal (Online), 378: o1874.

Thakur, V., P. Thakur, S. Srivastava and P. Kumar, 2022. Monkeypox virus (MPX) in humans a concern: Trespassing the global boundaries–Correspondence. International journal of surgery, 104: 106703.

Thornhill, J. P., S. Barkati, S. Walmsley, J. Rockstroh, A. Antinori, L. B. Harrison, R. Palich, A. Nori, I. Reeves and M. S. Habibi, 2022. Monkeypox virus infection in humans across 16 countries—april–june 2022. New england journal of medicine, 387(8): 679-691.

Titanji, B. K., B. Tegomoh, S. Nematollahi, M. Konomos and P. A. Kulkarni, 2022. Monkeypox: A contemporary review for healthcare professionals. In: Open forum infectious diseases. Oxford University Press: pp: ofac310.

TPOXX (tecovirimat) [Package Insert]. Corvallis, OR: SIGA Technologies, Inc, 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208627s000lbl.pdf. Accessed 17 August 2022.

UK Health Security Agency. (2022). Monkeypox: background information. Available at: Monkeypox: background information - GOV.UK (www.gov.uk). Accessed 15 August 2022.

Wang, J., M. Shahed-AI-Mahmud, A. Chen, K. Li, H. Tan and R. Joyce, 2023. An overview of antivirals against monkeypox virus and other orthopoxviruses. Journal of medicinal chemistry, 66(7): 4468-4490.

Wang, X. and W. Lun, 2023. Skin manifestation of human monkeypox. Journal of clinical medicine, 12(3): 914.

World Health Organization (WHO), 2018. Human monkeypox (MPX). http://www.who.int/emergencies/diseases/ monkeypox/en/. [Accessed 1st November 2018].

World Health Organization (WHO), 2019a. Human monkeypox. Available at: https://www.who.int/emergencies/ diseases /monkeypox/en/. Accessed February 22, 2019.

World Health Organization (WHO), 2019b. Smallpox. Available at: https://www.who.int/biologicals/vaccines/ smallpox/en/. Accessed February 20, 2019.

World Health Organization (WHO), 2021. Monkeypox fact sheet. Available at: https://www.who.int/en/news-room/fact-sheets/detail/monkeypox. Accessed May 22, 2022.

Yinka-Ogunleye, A., O. Aruna, M. Dalhat, D. Ogoina, A. McCollum, Y. Disu, I. Mamadu, A. Akinpelu, A. Ahmad and J. Burga, 2019. Outbreak of human monkeypox in nigeria in 2017–18: A clinical and epidemiological report. The Lancet Infectious diseases, 19(8): 872-879.

Zhou, P. and Z.-L. Shi, 2021. Sars-cov-2 spillover events. Science, 371(6525): 120-122.

Zumla, A., G. Ippolito, B. McCloskey, M. Bates, R. Ansumana, D. Heymann, R. Kock and F. Ntoumi, 2017. Enhancing preparedness for tackling new epidemic threats. The lancet respiratory medicine, 5(8): 606-608.