 doi:10.20944/preprints202208.0218.v1

# A Review Of Monkeypox: The New Global Health Emergency

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## Abstract

Monkeypox, once a rare zoonotic disease, was endemic to some African countries since its original identification among humans in 1970. Since then, cases in non endemic regions were linked to returning travelers or those who had contact with transported animals. The causative agent, *Monkeypox virus*, belongs to Orthopoxviruses, the same family as *Variola*; the causative organism for smallpox. Although most Monkeypox outbreaks until recently were linked to zoonotic transmission, secondary human-human transmission in smallpox unvaccinated individuals was observed in a small proportion of overall cases. Smallpox was declared eradicated in 1980 and since its eradication, *monkeypox virus* is the most significant poxvirus to cause human disease. The 2022 monkeypox outbreak marks a significant paradigm shift in the human and poxvirus association, with new modes of transmission, concerns of viral evolution and entrenchment as a sexually transmitted disease. Monkeypox clinically resembles smallpox but is far milder. At this time there are no approved therapies for monkeypox and antiviral agents effective against smallpox are being utilized. Additionally, preventive strategies being utilized include smallpox vaccination like JYNNEOS and ACAM2000. In this narrative review, we discuss the virology, epidemiology, transmission, clinical manifestations, diagnosis, management and prevention strategies associated with monkeypox.

**Key words**: **Public Health Emergency, Sexual Health, Monkeypox, Smallpox, JYNNEOS, ACAM2000, Tecovirimat, Brincidofovir.**

## 1. History & Introduction

Monkeypox, once an uncommon largely ‘zoonotic’ illness with a short chain of human to human transmission [1,2], is caused by the monkeypox virus (MPV) of the Poxviridae family and *Orthopoxvirus* genus. MPV was first isolated from cynomolgus monkeys exhibiting smallpox like lesions. The disease name was coined in 1958; at the Statens Serum Institut research facility in Copenhagen, Denmark, housing monkeys for poliomyelitis vaccine research and production [3].

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Subsequently, the earliest animal-human zoonotic transmission was described in 1970 in a 9 month old male infant, in the Democratic republic of Congo (DRC) [4]. In 1970, 5 more human cases of monkeypox were reported in Liberia and Sierra Leone (4 in children aged 4 - 9 years and a fifth in a 24 year old adult) [5]. A total of 59 cases in other sporadic outbreaks of monkeypox had been reported between 1970-1980s in central and west African countries; mostly associated with wildlife contact [6–8].

Early human monkeypox outbreaks coincided with the last stages of the global smallpox eradication vaccination program. It was observed that vaccination and infection from one member of the *orthopoxvirus* conferred cross-protection against another [5]. Since humans were not seen as a reservoir for MPV the 'global commission for eradication of smallpox' was prompted to consider monkeypox a non-threat to smallpox eradication, thus deciding to cease the vaccination program [8]. Epidemiological surveys of infections during this period indicated an increasing concern for rising human-human transmission of MPV in secondary cases; in otherwise unvaccinated individuals, causing the commision to promote a continuous monkeypox disease surveillance [8]. Subsequently, serological surveys (utilizing the vaccinia haemagglutination-inhibiting (HI) antibody testing) of over 10,000 unvaccinated children in Cote d'Ivoire, Sierra Leone and DRC indicated antibody positivity rates of 12.5-19.2%. Furthermore at least 30% of sera-positive individuals did not recollect any clinical manifestations, indicating a subclinical presentation [8]. As the screening and surveys were intensified, a few hundred cases of monkeypox were reported in DRC between 1981 - 1986, largely in children (86%) and a significant number of remaining cases in smallpox - unvaccinated adults; the overall fatality rate was reportedly 9.8% [6,8]. In DRC, during a significant prolonged outbreak between 1996 - 1997, the fatality rate was 3.7%, with similar epidemiology as earlier, but increasing human-human transmission was observed [8–10]. In all these outbreaks, monkeys, squirrels and other mammalian species were seen as the key participants in MPV lifecycle and transmission to humans [6,10,11]. Significantly, the genomic sequence analysis of MPV was observed to be mostly unchanged and human-human transmission was considered to be low [10]. Another outbreak in DRC, in 2001, reported a total of 31 human cases and pointed to monkeys as one of the sources of primary infection, while secondary human-human transmitted infection was seen in smallpox unvaccinated individuals [6]. From 1970 to 2017, MPV had led to multiple monkeypox cases in sporadic outbreaks across the central and west-African belts, considered endemic regions - including Cameroon, Central African Republic, Congo Brazzaville, Côte d'Ivoire, DRC, Gabon, Liberia, Nigeria, Sierra Leone, and South Sudan [12].

Interestingly, pet prairie dogs, transported with other infected exotic small mammals from Ghana, were associated with the 'first non-endemic outbreak' of human monkeypox, occurring in the United States (US) with 47 confirmed and probable cases but did not feature community transmission [13,14]. Subsequently, a few cases of travel-associated monkeypox; outside of the endemic African regions, were encountered in in Israel in September 2018, in the United Kingdom (UK) in September 2018, December 2019, May 2021 and May 2022, in Singapore during May 2019 and in the US in July and November 2021; all cases were associated with limited secondary spread [15–18]. These cases, in travelers returning from Nigeria, coincided with the Nigerian outbreak of human monkeypox in 2017 - 18, infecting 122 individuals with a fatality rate of 6% [12].

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In May 2022, beginning with a cluster of cases detected in the UK and subsequently through the European union, several countries in historically non-endemic regions reported multiple cases of monkeypox associated with significant human-human transmission, now spread across 81 non-endemic and 7 historically endemic countries [19]. Monkeypox has recently been declared a 'public health emergency of international concern' by the World Health Organization (WHO), a critical designation concurrently shared with COVID-19 and Poliomyelitis. Globally, significant concerns are being raised due to presentation of newer modes of transmission, potential entrenchment as a sexually transmitted disease, evolution of the virus, among others [20].
With an aim to decipher current circumstances, virology of MPV becomes a key first step towards understanding monkeypox.

## 2. **Virology & Pathogenesis**

MPV, a double stranded DNA (dsDNA) virus, is similar in structure to other orthopoxviruses; namely, *Variola, Vaccinia and Cowpox virus*. MPV, like other poxviruses, has a brick-like, oval structure, measuring 200 - 250 nm. The viruses are characterized by a dumbbell-shaped nucleus housing the linear double stranded deoxyribonucleic acid (dsDNA) ~197 kb, surrounded by lateral bodies [21]. The virions are enclosed by a lipoprotein outer membrane with surface tubules. Palindromic hairpins combine the ends of the DNA strands covalently, while inverted terminal repeats, which hold the origins of replication for DNA viruses, are made up of hairpin loop, tandem repeats, and some open reading frames (ORF). DNA synthesis is initiated at one end of the inverted terminal repeats and continues to the other end [22]. Similar to other orthopoxviruses, the MPV genome consists of 190 largely non-overlapping ORF of ≥60 amino acid residues as well as structural features [21]. Additionally, the central part of the MPV genome consists of highly conserved genes, seen across orthopoxviruses. Uniquely though to MPV, significant lengths of its right side genome contain duplication of the four left terminal ORFs; as a part of terminal inverted repeat. These terminal regions exhibit considerable variation as a result of ORF truncation and deletions. There is approximately 84.5-84.6% overlap of genome nucleotide sequences between the MPV and *Variola* virus [21].
The lifecycle of MPV in the host cell cytoplasm is largely similar to other orthopoxviruses [22–25]. Entry of the virus into the host cell is mediated by fusion of viral proteins to host cell membrane glycosaminoglycans. This triggers the virion to release its contents into host cell cytoplasm. In an immediate next phase; as early as 30 minutes post-infection, viral RNA-polymerase transcribes early expression of viral proteins and causes uncoating of its entire genome [23,26]. The next intermediate phase, taking place approximately 100 minutes post-infection involves expressions of a series of genes orchestrating recruitment of viral DNA-polymerase for replication. In the next subsequent - late phase; 2 - 48 hours post infection, structural proteins are produced through transcription of late genes and recruiting host cell endoplasmic reticulum and golgi-apparatus and assembling spherical proto-virions in host cytoplasmic viral factories [23,26,27]. Mature virions can be released from the host cell via lysis as a non-enveloped intracellular mature virion (IMV) or bud out as an external enveloped virion (EEV) having acquired a double membrane from the golgi apparatus. EEV further sets up a cellular microtubule transport that fuses to the host-cell membrane lipoprotein before releasing outside [22,23,26]. Interestingly, these 2 forms of mature virions are believed to exhibit variable antigenic properties and host cell attachment sites. These variations modulate the host immune response and infectivity of progeny virions [26]. Additionally, one study showed that EEV plays a key role in viral dissemination while IMV plays a predominant role in host-host transmission [28]. These factors of virion replication and egress need to be looked at carefully and may hold insights into the new transmission modes associated with the 2022 global monkeypox outbreak.

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The infected cell hosts most of the viral DNA replication, transcription, assembly, and release and all housekeeping genes, present on the conserved central region of the genome [22]. Significantly, there is 83.5% - 93.6% commonality between the *Variola* and MPV putative virulence and immunomodulatory amino acid sequences. Furthermore, previous studies have shown that certain mutations in genes for two interferon (IFN) resistance encoding intracellular proteins, causing IFN sensitivity, could have been key in making human-human transmission of MPV less efficient in earlier outbreaks, while these genes were intact in other orthopoxviruses such as *Variola* [21]. Other differences in complement-binding proteins compared to *Variola* and presence of a L-1β-binding protein in MPV may contribute to a less pronounced clinical disease, while the absence of the latter in *Variola* has been associated with significant pathogenicity and fever [21]. The phylogenetic analysis of orthopoxviruses have shown that MPV is slightly distant from *Variola* and *Vaccinia* viruses while the *Cowpox virus* may be a progenitor [21,29]. These and other discrete differences in MPV genome, compared to other orthopoxviruses, require attention and may hold answers towards its unique virulence, pathogenesis and transmission, particularly as the 2022 monkeypox global outbreak exhibits differences in these aspects from previous outbreaks.

Phylogenetically, MPV has been grouped into two genetic clades based on geography, disease severity and sequence homology - the Central African/Congo Basin (CB) and West African (WA) clades and reports suggest that the latter has been associated with a milder form of disease [30,31]. The human-human transmissibility, disease-associated morbidity, mortality and viraemia are more severe with the CB clade [30]. The most significant difference between the two clades is associated with the DNA sequence diversity at the terminal region, for genes that encode the host-response modulation proteins [30–32]. Prior epidemiological surveys assessing monkeypox showed that infection with either clade has a similar serological response in smallpox unvaccinated individuals, but associated with higher mortality rates in the CB clade infected patients [32,33].

The origins of the 2022 global monkeypox outbreak remain to be determined and most cases lack an obvious epidemiological link to Africa. Viral genomic analysis has recently been performed to understand possible links between global cases, origins of infection, and transmission dynamics. MPV sequence comparison with a 2021 US case, associated with travel from Nigeria, shows high similarity to the 2022 outbreak sequences, suggesting they belong to the WA clade [34,35].

## 3. **Epidemiology** - **Current Status**

Between January 1, 2022 and August 8, 2022, a total of 30,189 cases of Monkeypox have been reported among 88 countries, of which 81 countries have not reported cases hitherto [19,36]. Vast majority of the cases have been reported out of the European region with the most affected countries being the US, Spain, UK, Germany, France, Brazil, Netherlands, Canada, Portugal and Italy. Per recent WHO data, these countries contain 88.9% of all the cases reported globally [37]. On May 17, 2022, the first confirmed case of monkeypox in the US was reported out of the state of Massachusetts [38]. US case counts at the time of this writing are 8,934 with New York being the most affected state (1,960 cases as of August 8, 2022). Coastal states with higher population density have reported more cases than others, namely New York and California [39].

The 2022 Monkeypox outbreak has remarkably affected men who have sex with men (MSM) (97.5%) and bisexual men. Bulk of the global cases have been reported among young males (98.8%) with a median age of 37 years (interquartile range: 31-43 years). Notably, 96 cases reported to date have occurred among those <18 years of age. Human immunodeficiency virus (HIV) infection has been reported among 37.6% of those with Monkeypox and known HIV status. 339 cases occurred among health workers and community versus occupational exposure remains an ongoing investigation. While direct contact seems to be the most likely mode of transmission, a novel finding amid this outbreak is the report of a sexual encounter as a transmission event, specifically large events with sexual contacts [37]. Demographic findings from US data are concordant with global reports published by the WHO and indicate that young MSM make up the majority of cases (median age: 35 years). Of the available data on race and ethnicity, about 38% have been reported to be Caucasian/non hispanic, 26% African American and 32% Hispanic [38]. The US CDC has provided case definitions for suspected, probable and confirmed cases of Monkeypox [40]. Additionally, guidance on epidemiological and exclusion criteria have also been provided as a part of the 2022 Monkeypox response. Suspected cases include those with a new characteristic rash or cases that meet epidemiologic criteria and have a high clinical suspicion. Probable cases have been defined as those without suspicion of other recent Orthopoxvirus exposure and demonstration of Orthopoxvirus DNA by PCR; or demonstration of Orthopoxvirus by immunohistochemistry or electron microscopy of a clinical specimen. Suspected cases could also be established by demonstration of anti-Orthopoxvirus IgM antibodies 4 to 56 days after rash onset. Confirmed cases include those with MPV DNA presence established from clinical specimens by PCR or next generation sequencing (NGS); or those where MPV has been isolated in culture.

Epidemiologic criteria are:

Within 21 days of onset of symptoms:

· Contact with one or more individuals with a similar rash who received a probable or confirmed Monkeypox diagnosis OR

· Close or intimate personal contact with individuals in a social network where Monkeypox is present, including MSM who meet partners on the web or on mobile applications or at social events including parties

· Travel outside the US to a country with confirmed Monkeypox cases or to a Monkeypox endemic country

· Contact with a live or dead wild animal or exotic pet which is an African endemic species or use of a product derived from such animals, including lotions, cream, powder and game meat.

Exclusion criteria are an alternate diagnosis; or lack of rash within 5 days of onset of illness in an individual with symptoms consistent with Monkeypox; or inability to demonstrate Orthopoxvirus or Monkeypox virus or antibodies to Orthopoxvirus despite high quality clinical specimens. More recent Monkeypox case fatality rates are 3-6% per the WHO with historic rates ranging from 0 to 11% among the general population [18].

## 4. **Transmission**

MPV transmission has been observed through two routes - animal-human and human-human. While humans are the sole reservoir for *Variola*, the causative virus of smallpox, rodents are considered to be reservoirs of MPV, though yet to be confirmed. Trapping studies to understand

monkeypox seroprevalence in small African mammals and non-human primates suggested an abundance of seropositivity, isolation of MPV and presence of sparse rash lesions in one small mammalian species - rope squirrels (*Funisciuris),* suggesting that it might be a likely reservoir of MPV [33,41]. Animal-human transmission may occur through direct contact with infected animal skin lesions, bodily fluids, animal bite and scratches, handling infected animal meat and consumption. Human-human transmission may occur through direct, personal contact with lesions and bodily fluids, prolonged face to face contact or indirect contact with fomites such as clothing and bedding. Contact with respiratory secretions may also contribute to transmission, though airborne transmission transmission has not been reported as of this writing [1,2,33,42]. Nosocomial transmission has been observed in previous outbreaks, associated with both clades of MPV [1,12,43].

The incubation period of Monkeypox is usually 6-13 days (range: 5-21 days) [44] but amid the 2022 cases, shorter incubation periods have been reported with a median incubation period of 7 days (range: 3-20 days) [45]. In the current global Monkeypox outbreak, human to human transmission seems to be predominant. While initial US cases reported international travel within 21 days of symptom onset, to countries experiencing Monkeypox outbreaks, more recent cases seem to show signals of community transmission [38]. Close sexual contact has also been observed as a key factor in disease transmission. Replication competent MPV isolation from seminal fluid of a male patient with Monkeypox has been reported and speculated to be a result of passive viral diffusion from blood or exfoliated genital epithelium. However, it remains unclear if MPV can replicate in the seminiferous tubules or the remainder of the genital tract. Interestingly, this patient had received smallpox vaccination during childhood [46]. Although the precise transmission patterns of the 2022 global Monkeypox outbreak are yet to be fully understood, evidence supporting transmission as a result of sexual activity continues to accumulate [45]. Lack of or waning herd immunity from cessation of smallpox vaccination prevents cross protection offered against Monkeypox by smallpox vaccination [47].

Vertical transmission of MPV has been observed in a still-born fetus birthed through a second-trimester loss to a monkeypox infected mother. The case demonstrated generalized skin rashes with detection of viral agents in the fetal tissue, umbilical cord and placenta [48]. Previous outbreaks have shown that monkeypox, like smallpox, can have a high risk for pregnancy loss, severe congenital infection and severe maternal morbidity and mortality; but the impact of MPV on maternal and fetal health during the current outbreak remains unknown as yet. Recent guidelines strongly recommend close observation, reporting, management and prevention mechanisms to aid maternal and fetal health [49].

## 5. **Clinical manifestations & Diagnosis**

Early diagnosis and robust management are key to curtailing the extent of the ongoing Monkeypox outbreak as transmission continues. The diagnosis of Monkeypox is based on patient history, clinical presentation and diagnostic testing. Gathering a detailed travel and sexual history are of the utmost importance given evolving transmission patterns and disease spread beyond its endemic distribution. Clinical features of Monkeypox traditionally include prodromal symptoms such as fever, malaise, chills, lymphadenopathy, myalgia or headache along with a pleomorphic, often umbilicated skin rash. The lesions have been described as firm, deep seated, well circumscribed and may affect palms and soles [50]. Macules, papules, vesicles and pustules

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progress to scab and eventually desquamate. An individual is considered infectious until all skin lesions have completely re epithelialized. Pitted scars or skin with variable pigmentation may result at the sites of prior skin lesions. Monkeypox is generally a self-limited disease that resolves over 2-4 weeks. Severe cases can occasionally occur, are more common among children and worse outcomes remain a possibility among immunocompromised hosts. Features of severe disease include encephalitis, sepsis, hemorrhage, confluent skin lesions or other complications resulting in hospitalization.

Potential complications of Monkeypox include encephalitis, corneal ulceration and scarring resulting in loss of vision, secondary bacterial infection of skin lesions, respiratory tract infection such as bronchopneumonia and sepsis [18]. Disease prognosis depends on several factors including age, prior smallpox vaccination status, medical comorbidities, use of immunosuppressive drugs and the severity of illness.

Although the true extent of asymptomatic Monkeypox remains unknown, fresh reports of this phenomenon have emerged this year. Three Belgian male attendees of a sexual health clinic were identified to be MPV PCR positive on samples collected from the anorectal region, with eventual spontaneous viral clearance [51].

Salient clinical features of the 2022 Monkeypox cases include dermal lesions over the external genitalia, anal region and oral mucosal lesions which are most likely portals of exposure and viral entry. Thornhill et al describe similar clinical presentations among those with and without HIV [45]. Sore throat, penile edema, rectal pain have also been observed among patients from London, UK with PCR confirmed Monkeypox [52]. Patel et al also reported a variable timeline of systemic and mucocutaneous symptoms among cases and described several cases where patients presented solely with dermatological symptoms without systemic features of disease. Novel clinical findings from the 2022 cases also include mucocutaneous ulcers and fewer skin lesions, less disseminated disease and proctitis causing anorectal pain [45].

Confirmatory laboratory tests - immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), viral culture and polymerized chain reaction (PCR) are performed using scab material, lesion fluid, vesicular fluid or biopsy specimens from an individual suspected with monkeypox to confirm diagnosis and rule out other diseases [18,53]. MPV proteins assessment using gel-electrophoresis can also confirm diagnosis, but may not be appropriate as a first-line diagnostic in the clinical setting [54]. Real-time PCR, based on nucleic acid amplification, is considered the gold standard, first-line diagnostic test due to its accuracy and high sensitivity. Other tests are recommended when a suspected case tests negative with PCR [55]. RT-PCR testing targets regions of the DNA polymerase gene, *E9L, F3L* gene, extracellular-envelope protein gene (*B6R*), DNA dependent RNA polymerase subunit 18, among others [12,56]. On the other hand, whole-genome sequencing using NGS is a comprehensive and insightful testing methodology but is seldom used and reserved for use downstream due its laborious, expensive and time-consuming nature. RT-PCR test results can take 24-72 hours and are currently conducted only by public health laboratories and 5 commercial labs - Aegis Science, Labcorp, Mayo Clinic Laboratories, Quest Diagnostics and Sonic Healthcare, in the US [57]. The US CDC has laid down the

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diagnostic process for MPV testing [58]. Testing for non *Variola* orthopoxvirus PCR can be set up after initial patient assessment. Healthcare providers are responsible for establishing contact with public health authorities at the local or state level. If Orthopoxvirus testing (PCR) results positive, MPV characterization is forwarded to the CDC.
Importantly, when possible, vaccinated individuals (smallpox vaccinated within the last 3 years) should handle monkeypox suspected specimens in BSL-2 containment using BSL-3 practices [58]. Laboratory testing of MPV in the US has suggested that cases in the current outbreak are associated with the West African clade [59].

## 6. **Management**

Majority of Monkeypox cases tend to have a mild clinical course with self-resolution even without treatment. There is no current US Food and Drug Administration (FDA) approved antiviral labeled for use specifically against MPV. The antivirals available for use include repurposed agents effective against smallpox; namely,Tecovirimat (TPOXX/ST-246) and brincidofovir. Cidofovir, an antiviral approved for use against cytomegalovirus (CMV) , has also shown efficacy against orthopoxviruses in vitro.

### 6a. Tecovirimat

Tecovirimat (TPOXX) was approved by the FDA in 2018 for the treatment of smallpox in adults and children. It inhibits VP37, a viral envelope wrapping protein and disrupts viral replication and release. It is currently available for use in the US under an expanded access investigational new drug protocol at no cost (EA-IND) [60]. Tecovirimat is available as oral and intravenous formulations. While efficacy data on the use of TPOXX against Monkeypox are lacking, a favorable safety profile with common adverse effects such as headache, nausea, vomiting and abdominal pain has been reported. Neutropenia has also been reported among one trial participant [61]. Intravenous formulation use may result in infusion site erythema, pain and swelling [60]. Thornhill et reported on the treatment of recent Monkeypox cases with TPOXX [45]. Adler et al describe management of a human Monkeypox case with TPOXX with a favorable outcome [62]. Monkeypox in a returning traveler from Nigeria to the US, treated with TPOXX has also been recently described [63].

### 6b. Brincidofovir

Brincidofovir was approved by the FDA for use against smallpox in adults and pediatric patients, in June 2021. It is a prodrug of Cidofovir and contains a lipid conjugate. Intracellularly, it is converted to Cidofovir and eventually its active metabolite, Cidofovir diphosphate (CDP), which incorporates into viral DNA and inhibits viral DNA polymerase, thereby inhibiting viral replication. Large scale human data on the use of Brincidofovir against MPV are lacking but an animal model showed trends of protection against lethal Monkeypox with 29-57% survival rates among infected prairie dogs, depending on the time of treatment initiation [64].
Adler et al also described 3 human cases of Monkeypox treated with Brincidofovir. Treatment cessation occurred due to elevation of liver enzymes [62]. Brincidofovir is available as an oral formulation (tablet and oral suspension) and has a better renal safety profile compared to Cidofovir [62].

 doi:10.20944/preprints202208.0218.v1

6c. Cidofovir

Cidofovir has the same mechanism of action as its prodrug, Brincidofovir. Large scale human data on efficacy of Cidofovir against Monkeypox are lacking. However, animal data on its use against orthopox viruses including Cowpox, Vaccinia, Ectromelia and Rabbitpox exist [65].
Thornhill et al reported cases amid the 2022 Monkeypox outbreak that were treated with Cidofovir. It is only available as an intravenous formulation and can have significant renal toxicity [45].

6d. Vaccinia Immune globulin Intravenous (VIGIV)

VIGIV is FDA licensed for treatment of complications after *Vaccinia* vaccination, including Vaccinia (progressive or severe generalized), eczema vaccinatum and aberrant infections due to *Vaccinia* virus. It can also be used for Vaccinia infections in those with certain skin conditions [66]. Data for its use against Monkeypox are lacking; but, in the US, it is available as a response measure in the event of Orthopoxvirus outbreaks under an EA-IND.

Figure 1 is an illustration of mechanisms of action of available therapies against Monkeypox along with its clinical symptoms.

Interim guidance for the treatment of Monkeypox has been provided by the US CDC [66]. Antiviral use for those with clinical features of aberrant disease in atypical locations, severe disease, complications, and those at high risk for severe disease has been suggested. Risk factors for severe disease includes age < 8 years, atopic or other exfoliative dermatitis, pregnancy, lactation and immunocompromise. Immunocompromising conditions include uncontrolled HIV, acquired immunodeficiency syndrome, leukemia, lymphoma, other malignancy, radiation, solid organ transplantation, hematopoietic stem cell transplantation <24 months post-transplant or >24 months post-transplant with graft-versus-host disease or disease relapse, autoimmune disease with immunodeficiency; and lastly iatrogenic immunosuppression as a result of the use of alkylating agents, antimetabolites, tumor necrosis factor inhibitors or high dose corticosteroids.
Additionally, symptomatic, and supportive care along with effective pain management are paramount [66].

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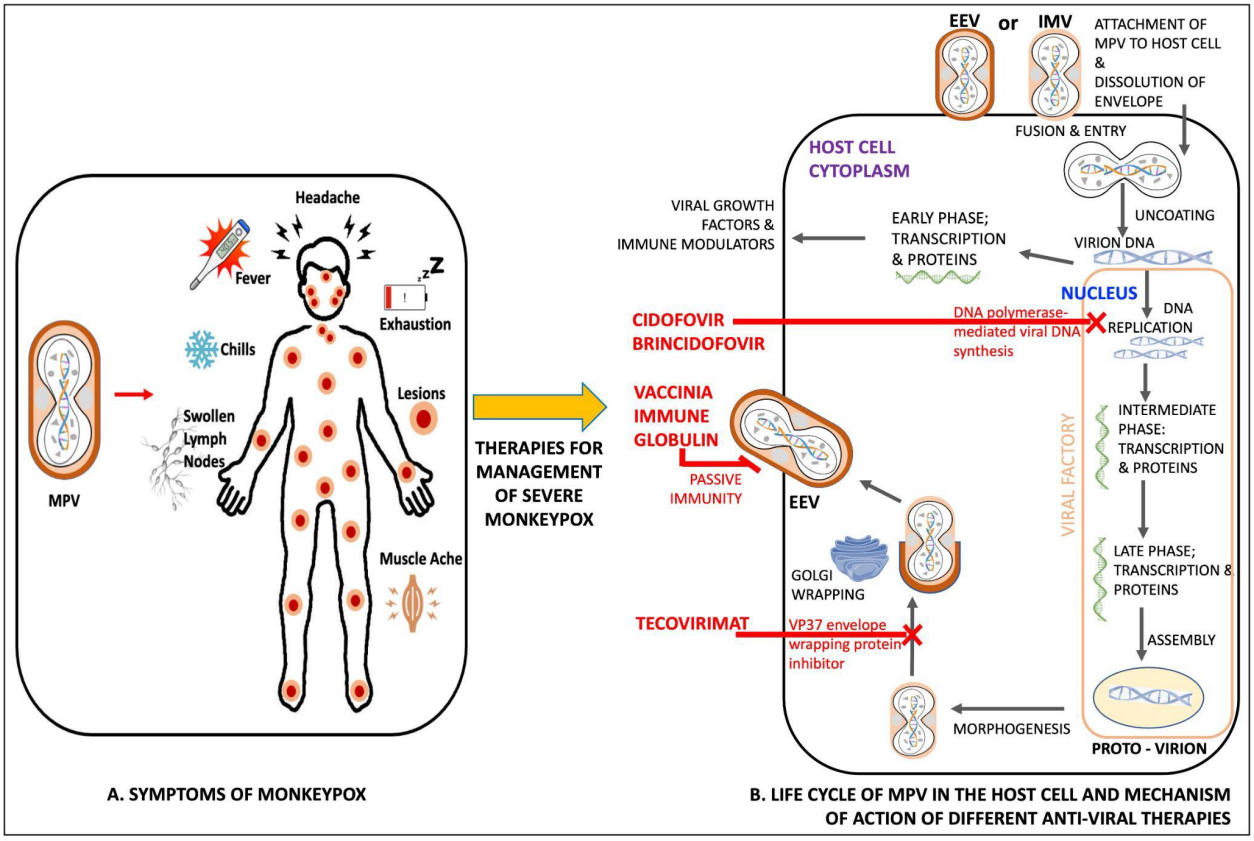


*Figure 1. An illustration of the symptoms of monkeypox (A) and the life cycle of MPV inside the host cell cytoplasm to elicit the mechanism of action of four different antiviral therapies; Cidofovir, Brincidofovir, Vaccinia immune globulin and Tecovirimat (B).*

## 7. **Prevention**

Some measures can help prevent spread of MPV**.** Direct contact based prevention strategies include - avoiding close, direct contact with people who have skin lesions resembling monkeypox, avoid touching the rash and scabs, avoiding close contact including hugging, kissing; avoiding sexual contact with infected individuals and avoiding contact with animals that exhibit monkeypox like symptoms [67]. Other prevention measures include - avoid sharing utensils with a person who has monkeypox, avoid touching items that have been in contact with a person infected with monkeypox, such as bedding and clothes [67]. Washing hands frequently with soap and water or use of an alcohol-based hand sanitizer can be very effective. Healthcare professionals caring for patients should wear proper personal protective equipment, cover their entire body with a water-resistant gown, be double-gloved and use N-95 masks. Patients should be placed under contact isolation in a single patient room until all lesions have crusted and fully re epithelialized [67].

Studies have shown that the smallpox vaccine provides significant protection against monkeypox and may improve disease outcomes [8,68]. The two US FDA approved vaccines - JYNNEOS and ACAM2000 can be useful in prevention strategies for monkeypox. JYNNEOS contains live *Vaccinia* virus that is not replication competent in human cells and is administered as two subcutaneous doses, 28 days apart, with full protection being afforded 14 days after completion of the vaccine series. JYNNEOS is licensed by the FDA for adults 18 years and older against

smallpox and Monkeypox. Unike ACAM2000, JYNNEOS can be given to those with HIV, atopic or other exfoliative dermatitis. ACAM2000 on the other hand, contains live replication-competent *Vaccinia* virus, and is given a single percutaneous dose by multiple puncture technique. After inoculation, a lesion (also called “take”) develops at the injection site and may take upto 6 weeks to heal. Protective immunity is achieved at least 4 weeks after vaccination. ACAM2000 is licensed for use against smallpox and can be used against Monkeypox with an EA-IND. Since this is a live viral vaccine, it should not be given to certain individuals. ACAM2000 has been linked to cases of vaccination induced myocarditis and pericarditis [69].

The US CDC’s recommendation on ‘post-exposure prophylaxis’ (PEP), coupled with isolation and utilizing other preventive methods, is vaccinating individuals 4 days after monkeypox exposure to prevent disease and administration between 4-14 days can improve disease outcome [69]. PEP plus plus (PEP++) is an expanded approach aimed to reach people with certain risk factors even if they have not had documented exposure to confirmed Monkeypox cases, with the objective of flattening the epidemiological curve and slowing disease spread in areas with high levels of transmission [69]. These strategies can help prevent transmission and control disease outbreak further. Additionally, the pre-exposure prophylaxis (PrEP) guidelines by CDC suggests vaccinating individuals at high-risk for monkeypox [69]. While these vaccines have been tested for efficacy against monkeypox in animal studies (JYNNEOS) or allowed for clinical use under FDA’s EA-IND, there is no data hitherto on their efficacy for PEP, PEP++ or PrEP for the current global outbreak [69–72]. Additionally, the administration of ACAM2000 is contraindicated in individuals with immunosuppression or immunocompromise, atopic dermatitis, eczema, pregnancy or breastfeeding, infants, underlying heart disease and among those with major cardiac risk-factors [69,71].

## Supplementary materials:

None

## Funding

None

## Conflicts of interest

The authors declare no conflicts of interest.

## Institutional Review Board Statement:

Not applicable

## Informed Consent Statement:

Not applicable

## Acknowledgements

None

## References

1. Learned, L.A.; Reynolds, M.G.; Wassa, D.W.; Li, Y.; Olson, V.A.; Karem, K.; Stempora, L.L.; Braden, Z.H.; Kline, R.; Likos, A.; et al. Extended Interhuman Transmission of Monkeypox in a Hospital Community in the Republic of the Congo, 2003. *Am. J. Trop. Med. Hyg.* **2005**, *73*, 428–434.
2. Nolen, L.D.; Osadebe, L.; Katomba, J.; Likofata, J.; Mukadi, D.; Monroe, B.; Doty, J.; Hughes, C.M.; Kabamba, J.; Malekani, J.; et al. Extended Human-to-Human Transmission during a Monkeypox Outbreak in the Democratic Republic of the Congo. *Emerg. Infect. Dis.* **2016**, *22*, 1014–1021, doi:10.3201/eid2206.150579.
3. Magnus, P. von; Andersen, E.K.; Petersen, K.B.; Birch-Andersen, A. A POX-LIKE DISEASE IN CYNOMOLGUS MONKEYS. *Acta Pathol. Microbiol. Scand.* **1959**, *46*, 156–176, doi:10.1111/j.1699-0463.1959.tb00328.x.
4. Ladnyj, I.D.; Ziegler, P.; Kima, E. A Human Infection Caused by Monkeypox Virus in Basankusu Territory, Democratic Republic of the Congo. *Bull. World Health Organ.* **1972**, *46*, 593–597.
5. Cho, C.T.; Wenner, H.A. Monkeypox Virus. *Bacteriol. Rev.* **1973**, *37*, 1–18, doi:10.1128/br.37.1.1-18.1973.
6. Meyer, H.; Perrichot, M.; Stemmler, M.; Emmerich, P.; Schmitz, H.; Varaine, F.; Shungu, R.; Tshioko, F.; Formenty, P. Outbreaks of Disease Suspected of Being Due to Human Monkeypox Virus Infection in the Democratic Republic of Congo in 2001. *J. Clin. Microbiol.* **2002**, *40*, 2919–2921, doi:10.1128/JCM.40.8.2919-2921.2002.
7. R Pebody Human Monkeypox in Kasai Oriental, Democratic Republic of Congo, February 1996 – October 1997: Preliminary Report. *Wkly. Releases 1997–2007* **1997**, *1*, doi:10.2807/esw.01.32.01015-en.
8. Heymann, D.L.; Szczeniowski, M.; Esteves, K. Re-Emergence of Monkeypox in Africa: A Review of the Past Six Years. *Br. Med. Bull.* **1998**, *54*, 693–702, doi:10.1093/oxfordjournals.bmb.a011720.
9. Mukinda, V.; Mwema, G.; Kilundu, M.; Heymann, D.; Khan, A.; Esposito, J. Re-Emergence of Human Monkeypox in Zaire in 1996. *The Lancet* **1997**, *349*, 1449–1450, doi:10.1016/S0140-6736(05)63725-7.
10. Hutin, Y.J.F.; Williams, R.J.; Malfait, P.; Pebody, R.; Loparev, V.N.; Ropp, S.L.; Rodriguez, M.; Knight, J.C.; Tshioko, F.K.; Khan, A.S.; et al. Outbreak of Human Monkeypox, Democratic Republic of Congo, 1996 to 1997. *Emerg. Infect. Dis.* **2001**, *7*, 434–438, doi:10.3201/eid0703.017311.
11. Doty, J.; Malekani, J.; Kalemba, L.; Stanley, W.; Monroe, B.; Nakazawa, Y.; Mauldin, M.; Bakambana, T.; Liyandja Dja Liyandja, T.; Braden, Z.; et al. Assessing Monkeypox Virus

Prevalence in Small Mammals at the Human–Animal Interface in the Democratic Republic of the Congo. *Viruses* **2017**, *9*, 283, doi:10.3390/v9100283.
12. Yinka-Ogunleye, A.; Aruna, O.; Dalhat, M.; Ogoina, D.; McCollum, A.; Disu, Y.; Mamadu, I.; Akinpelu, A.; Ahmad, A.; Burga, J.; et al. Outbreak of Human Monkeypox in Nigeria in 2017–18: A Clinical and Epidemiological Report. *Lancet Infect. Dis.* **2019**, *19*, 872–879, doi:10.1016/S1473-3099(19)30294-4.
13. Reed, K.D.; Melski, J.W.; Graham, M.B.; Regnery, R.L.; Sotir, M.J.; Wegner, M.V.; Kazmierczak, J.J.; Stratman, E.J.; Li, Y.; Fairley, J.A.; et al. The Detection of Monkeypox in Humans in the Western Hemisphere. *N. Engl. J. Med.* **2004**, *350*, 342–350, doi:10.1056/NEJMoa032299.
14. Past U.S. Cases and Outbreaks | Monkeypox | Poxvirus | CDC Available online: https://www.cdc.gov/poxvirus/monkeypox/outbreak/us-outbreaks.html (accessed on 25 July 2022).
15. Vaughan, A.; Aarons, E.; Astbury, J.; Brooks, T.; Chand, M.; Flegg, P.; Hardman, A.; Harper, N.; Jarvis, R.; Mawdsley, S.; et al. Human-to-Human Transmission of Monkeypox Virus, United Kingdom, October 2018. *Emerg. Infect. Dis.* **2020**, *26*, 782–785, doi:10.3201/eid2604.191164.
16. Erez, N.; Achdout, H.; Milrot, E.; Schwartz, Y.; Wiener-Well, Y.; Paran, N.; Politi, B.; Tamir, H.; Israely, T.; Weiss, S.; et al. Diagnosis of Imported Monkeypox, Israel, 2018. *Emerg. Infect. Dis.* **2019**, *25*, 980–983, doi:10.3201/eid2505.190076.
17. Yong, S.E.F.; Ng, O.T.; Ho, Z.J.M.; Mak, T.M.; Marimuthu, K.; Vasoo, S.; Yeo, T.W.; Ng, Y.K.; Cui, L.; Ferdous, Z.; et al. Imported Monkeypox, Singapore. *Emerg. Infect. Dis.* **2020**, *26*, 1826–1830, doi:10.3201/eid2608.191387.
18. Monkeypox Key Facts Available online: https://www.who.int/news-room/fact-sheets/detail/monkeypox (accessed on 25 July 2022).
19. 2022 Monkeypox Outbreak Global Map | Monkeypox | Poxvirus | CDC Available online: https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html (accessed on 21 July 2022).
20. WHO Director-General Declares the Ongoing Monkeypox Outbreak a Public Health Emergency of International Concern Available online: https://www.who.int/europe/news/item/23-07-2022-who-director-general-declares-the-ongoing-monkeypox-outbreak-a-public-health-event-of-international-concern (accessed on 25 July 2022).
21. Shchelkunov, S.N.; Totmenin, A.V.; Babkin, I.V.; Safronov, P.F.; Ryazankina, O.I.; Petrov, N.A.; Gutorov, V.V.; Uvarova, E.A.; Mikheev, M.V.; Sisler, J.R.; et al. Human Monkeypox and Smallpox Viruses: Genomic Comparison. *FEBS Lett.* **2001**, *509*, 66–70, doi:10.1016/S0014-5793(01)03144-1.
22. Alakunle, E.; Moens, U.; Nchinda, G.; Okeke, M.I. Monkeypox Virus in Nigeria: Infection Biology, Epidemiology, and Evolution. *Viruses* **2020**, *12*, 1257, doi:10.3390/v12111257.
23. Orthopoxvirus ~ ViralZone Available online: https://viralzone.expasy.org/149?outline=all_by_species (accessed on 26 July 2022).
24. Henderson, D.A.; Borio, L.L. Chapter 58 - Smallpox and Monkeypox. In *Tropical Infectious Diseases (Second Edition)*; Guerrant, R.L., Walker, D.H., Weller, P.F., Eds.; Churchill Livingstone: Philadelphia, 2006; pp. 621–636 ISBN 978-0-443-06668-9.
25. Srinivasan, K.; Rao, M. *Poxvirus Driven Human Diseases and Emerging Therapeutics*; MEDICINE & PHARMACOLOGY, 2022;
26. ClinicalKey Available online: https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323482554001326 (accessed on 27 July 2022).
27. Moyer, R.W.; Graves, R.L. The Mechanism of Cytoplasmic Orthopoxvirus DNA Replication. *Cell* **1981**, *27*, 391–401, doi:10.1016/0092-8674(81)90422-0.
28. Vanderplasschen, A.; Hollinshead, M.; Smith, G.L. Intracellular and Extracellular Vaccinia

Virions Enter Cells by Different Mechanisms. *J. Gen. Virol.* **1998**, *79*, 877–887, doi:10.1099/0022-1317-79-4-877.
29. Douglass, N.J.; Dumbell, K.R. DNA Sequence Variation as a Clue to the Phylogenesis of Orthopoxviruses. *J. Gen. Virol.* **1996**, *77*, 947–951, doi:10.1099/0022-1317-77-5-947.
30. Likos, A.M.; Sammons, S.A.; Olson, V.A.; Frace, A.M.; Li, Y.; Olsen-Rasmussen, M.; Davidson, W.; Galloway, R.; Khristova, M.L.; Reynolds, M.G.; et al. A Tale of Two Clades: Monkeypox Viruses. *J. Gen. Virol.* **2005**, *86*, 2661–2672, doi:10.1099/vir.0.81215-0.
31. Chen, N.; Li, G.; Liszewski, M.K.; Atkinson, J.P.; Jahrling, P.B.; Feng, Z.; Schriewer, J.; Buck, C.; Wang, C.; Lefkowitz, E.J.; et al. Virulence Differences between Monkeypox Virus Isolates from West Africa and the Congo Basin. *Virology* **2005**, *340*, 46–63, doi:10.1016/j.virol.2005.05.030.
32. Parker, S.; Buller, R.M. A Review of Experimental and Natural Infections of Animals with Monkeypox Virus between 1958 and 2012. *Future Virol.* **2013**, *8*, 129–157, doi:10.2217/fvl.12.130.
33. Jezek, Zdenek, and Frank Fenner. *Human MonkeyPox*; Karger, 1988;
34. Gigante, C.M.; Korber, B.; Seabolt, M.H.; Wilkins, K.; Davidson, W.; Rao, A.K.; Zhao, H.; Hughes, C.M.; Minhaj, F.; Waltenburg, M.A.; et al. *Multiple Lineages of* Monkeypox Virus *Detected in the United States, 2021- 2022*; Genomics, 2022;
35. Isidro, J.; Borges, V.; Pinto, M.; Sobral, D.; Santos, J.D.; Nunes, A.; Mixão, V.; Ferreira, R.; Santos, D.; Duarte, S.; et al. Phylogenomic Characterization and Signs of Microevolution in the 2022 Multi-Country Outbreak of Monkeypox Virus. *Nat. Med.* **2022**, 1–1, doi:10.1038/s41591-022-01907-y.
36. Kraemer, M.U.G.; Tegally, H.; Pigott, D.M.; Dasgupta, A.; Sheldon, J.; Wilkinson, E.; Schultheiss, M.; Han, A.; Oglia, M.; Marks, S.; et al. Tracking the 2022 Monkeypox Outbreak with Epidemiological Data in Real-Time. *Lancet Infect. Dis.* **2022**, *22*, 941–942, doi:10.1016/S1473-3099(22)00359-0.
37. 2022 Monkeypox Outbreak: Global Trends Available online: https://worldhealthorg.shinyapps.io/mpx_global/#3_Detailed_case_data (accessed on 6 August 2022).
38. Technical Report: Multi-National Monkeypox Outbreak, United States, 2022 | Monkeypox | Poxvirus | CDC Available online: https://www.cdc.gov/poxvirus/monkeypox/clinicians/technical-report.html (accessed on 6 August 2022).
39. CDC Monkeypox in the U.S. Available online: https://www.cdc.gov/poxvirus/monkeypox/index.html (accessed on 20 July 2022).
40. CDC Monkeypox in the U.S - Case Definitions for Use in the 2022 Monkeypox Response Available online: https://www.cdc.gov/poxvirus/monkeypox/clinicians/case-definition.html (accessed on 9 August 2022).
41. Khodakevich, L.; Ježek, Z.; Messinger, D. Monkeypox Virus: Ecology and Public Health Significance. *Bull. World Health Organ.* **1988**, *66*, 747–752.
42. Formenty, P.; Muntasir, M.O.; Damon, I.; Chowdhary, V.; Opoka, M.L.; Monimart, C.; Mutasim, E.M.; Manuguerra, J.-C.; Davidson, W.B.; Karem, K.L.; et al. Human Monkeypox Outbreak Caused by Novel Virus Belonging to Congo Basin Clade, Sudan, 2005. *Emerg. Infect. Dis.* **2010**, *16*, 1539–1545, doi:10.3201/eid1610.100713.
43. Vaughan, A.; Aarons, E.; Astbury, J.; Balasegaram, S.; Beadsworth, M.; Beck, C.R.; Chand, M.; O'Connor, C.; Dunning, J.; Ghebrehewet, S.; et al. Two Cases of Monkeypox Imported to the United Kingdom, September 2018. *Eurosurveillance* **2018**, *23*, doi:10.2807/1560-7917.ES.2018.23.38.1800509.
44. Monkeypox Fact Sheet Available online: https://www.who.int/news-room/fact-sheets/detail/monkeypox (accessed on 28 July 2022).
45. Thornhill, J.P.; Barkati, S.; Walmsley, S.; Rockstroh, J.; Antinori, A.; Harrison, L.B.; Palich,

R.; Nori, A.; Reeves, I.; Habibi, M.S.; et al. Monkeypox Virus Infection in Humans across 16 Countries — April–June 2022. *N. Engl. J. Med.* **2022**, *0*, null, doi:10.1056/NEJMoa2207323.
46. Lapa, D.; Carletti, F.; Mazzotta, V.; Matusali, G.; Pinnetti, C.; Meschi, S.; Gagliardini, R.; Colavita, F.; Mondi, A.; Minosse, C.; et al. Monkeypox Virus Isolation from a Semen Sample Collected in the Early Phase of Infection in a Patient with Prolonged Seminal Viral Shedding. *Lancet Infect. Dis.* **2022**, *0*, doi:10.1016/S1473-3099(22)00513-8.
47. Alakunle, E.F.; Okeke, M.I. Monkeypox Virus: A Neglected Zoonotic Pathogen Spreads Globally. *Nat. Rev. Microbiol.* **2022**, 1–2, doi:10.1038/s41579-022-00776-z.
48. Mbala, P.K.; Huggins, J.W.; Riu-Rovira, T.; Ahuka, S.M.; Mulembakani, P.; Rimoin, A.W.; Martin, J.W.; Muyembe, J.-J.T. Maternal and Fetal Outcomes Among Pregnant Women With Human Monkeypox Infection in the Democratic Republic of Congo. *J. Infect. Dis.* **2017**, *216*, 824–828, doi:10.1093/infdis/jix260.
49. Dashraath, P.; Nielsen-Saines, K.; Mattar, C.; Musso, D.; Tambyah, P.; Baud, D. Guidelines for Pregnant Individuals with Monkeypox Virus Exposure. *The Lancet* **2022**, *400*, 21–22, doi:10.1016/S0140-6736(22)01063-7.
50. CDC Monkeypox in the U.S - Clinical Recognition Available online: https://www.cdc.gov/poxvirus/monkeypox/clinicians/clinical-recognition.html (accessed on 6 August 2022).
51. Baetselier, I.D.; Dijck, C.V.; Kenyon, C.; Coppens, J.; Bossche, D.V. den; Smet, H.; Liesenborghs, L.; Vanroye, F.; Block, T. de; Rezende, A.; et al. Asymptomatic Monkeypox Virus Infections among Male Sexual Health Clinic Attendees in Belgium 2022.
52. Patel, A.; Bilinska, J.; Tam, J.C.H.; Fontoura, D.D.S.; Mason, C.Y.; Daunt, A.; Snell, L.B.; Murphy, J.; Potter, J.; Tuudah, C.; et al. Clinical Features and Novel Presentations of Human Monkeypox in a Central London Centre during the 2022 Outbreak: Descriptive Case Series. *BMJ* **2022**, *378*, e072410, doi:10.1136/bmj-2022-072410.
53. McCollum, A.M.; Damon, I.K. Human Monkeypox. *Clin. Infect. Dis.* **2014**, *58*, 260–267, doi:10.1093/cid/cit703.
54. Adalja, A.; Inglesby, T. A Novel International Monkeypox Outbreak. *Ann. Intern. Med.* **2022**, M22-1581, doi:10.7326/M22-1581.
55. Girometti, N.; Byrne, R.; Bracchi, M.; Heskin, J.; McOwan, A.; Tittle, V.; Gedela, K.; Scott, C.; Patel, S.; Gohil, J.; et al. Demographic and Clinical Characteristics of Confirmed Human Monkeypox Virus Cases in Individuals Attending a Sexual Health Centre in London, UK: An Observational Analysis. *Lancet Infect. Dis.* **2022**, doi:10.1016/S1473-3099(22)00411-X.
56. Li, Y.; Olson, V.A.; Laue, T.; Laker, M.T.; Damon, I.K. Detection of Monkeypox Virus with Real-Time PCR Assays. *J. Clin. Virol.* **2006**, *36*, 194–203, doi:10.1016/j.jcv.2006.03.012.
57. Affairs (ASPA), A.S. for P. HHS Expanding Monkeypox Testing Capacity to Five Commercial Laboratory Companies Available online: https://www.hhs.gov/about/news/2022/06/22/hhs-expanding-monkeypox-testing-capacity-five-commercial-laboratory-companies.html (accessed on 28 July 2022).
58. CDC Laboratory Procedures and Biosafety Guidelines - Monkeypox in the U.S. Available online: https://www.cdc.gov/poxvirus/monkeypox/lab-personnel/lab-procedures.html (accessed on 28 July 2022).
59. CDC Monkeypox in the U.S. - Preparation and Collection of Specimens Available online: https://www.cdc.gov/poxvirus/monkeypox/clinicians/prep-collection-specimens.html (accessed on 9 August 2022).
60. CDC Monkeypox in the U.S - Guidance for Tecovirimat Use Under Expanded Access Investigational New Drug Protocol during 2022 U.S. Monkeypox Cases Available online: https://www.cdc.gov/poxvirus/monkeypox/clinicians/Tecovirimat.html (accessed on 9 August 2022).
61. SIGA Technologies *A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety, Tolerability, and Pharmacokinetics of TPOXX When Administered Orally*

*for 28 Days in Adult Subjects*; clinicaltrials.gov, 2022;
62. Adler, H.; Gould, S.; Hine, P.; Snell, L.B.; Wong, W.; Houlihan, C.F.; Osborne, J.C.; Rampling, T.; Beadsworth, M.B.; Duncan, C.J.; et al. Clinical Features and Management of Human Monkeypox: A Retrospective Observational Study in the UK. *Lancet Infect. Dis.* **2022**, *22*, 1153–1162, doi:10.1016/S1473-3099(22)00228-6.
63. Rao, A.K.; Schulte, J.; Chen, T.-H.; Hughes, C.M.; Davidson, W.; Neff, J.M.; Markarian, M.; Delea, K.C.; Wada, S.; Liddell, A.; et al. Monkeypox in a Traveler Returning from Nigeria — Dallas, Texas, July 2021. *Morb. Mortal. Wkly. Rep.* **2022**, *71*, 509–516, doi:10.15585/mmwr.mm7114a1.
64. Hutson, C.L.; Kondas, A.V.; Mauldin, M.R.; Doty, J.B.; Grossi, I.M.; Morgan, C.N.; Ostergaard, S.D.; Hughes, C.M.; Nakazawa, Y.; Kling, C.; et al. Pharmacokinetics and Efficacy of a Potential Smallpox Therapeutic, Brincidofovir, in a Lethal Monkeypox Virus Animal Model. *mSphere* **2021**, *6*, e00927-20, doi:10.1128/mSphere.00927-20.
65. Smee, D.F. Progress in the Discovery of Compounds Inhibiting Orthopoxviruses in Animal Models. *Antivir. Chem. Chemother.* **2008**, *19*, 115–124, doi:10.1177/095632020801900302.
66. CDC Monkeypox in the U.S - Treatment Information for Healthcare Professionals Available online: https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html (accessed on 9 August 2022).
67. CDC Prevention - Monkeypox in the U.S. Available online: https://www.cdc.gov/poxvirus/monkeypox/prevention.html (accessed on 28 July 2022).
68. Hammarlund, E.; Lewis, M.W.; Carter, S.V.; Amanna, I.; Hansen, S.G.; Strelow, L.I.; Wong, S.W.; Yoshihara, P.; Hanifin, J.M.; Slifka, M.K. Multiple Diagnostic Techniques Identify Previously Vaccinated Individuals with Protective Immunity against Monkeypox. *Nat. Med.* **2005**, *11*, 1005–1011, doi:10.1038/nm1273.
69. Considerations for Monkeypox Vaccination | Monkeypox | Poxvirus | CDC Available online: https://www.cdc.gov/poxvirus/monkeypox/considerations-for-monkeypox-vaccination.html (accessed on 28 July 2022).
70. Rao, A.K. Use of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Nonreplicating) for Preexposure Vaccination of Persons at Risk for Occupational Exposure to Orthopoxviruses: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022. *MMWR Morb. Mortal. Wkly. Rep.* **2022**, *71*, doi:10.15585/mmwr.mm7122e1.
71. Research, C. for B.E. and ACAM2000. *FDA* **2019**.
72. Research, C. for B.E. and JYNNEOS. *FDA* **2021**.