ISBN 978-1-960740-53-3

EPIDEMIOLOGY – FUNDAMENTAL CONCEPTS AND MANAGEMENT

Review Based Book Chapter

EXPLORING THE INTRICACIES OF MONKEYPOX: FROM EMERGENCE TO EPIDEMIOLOGY, DIAGNOSTICS AND TREATMENT

June 18, 2024
doi: 10.5281/zenodo.11524206

Scientific Knowledge Publisher (SciKnowPub), USA
info@sciknowpub.com

REVIEW BASED BOOK CHAPTER

EXPLORING THE INTRICACIES OF MONKEYPOX: FROM EMERGENCE TO EPIDEMIOLOGY, DIAGNOSTICS AND TREATMENT

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Abstract

First documented in 1958, monkeypox is a serious zoonotic disease that affects human beings and its symptoms include rash, fever, sore throat, headache, back discomfort, muscular aches, low energy, and enlarged lymph nodes, and it is spread by human-to-animal contact, person-to-person contact, and infected items. It is prevalent in Africa and was verified to be causing an epidemic in May 2022. There are currently no proven cures and vaccinations available for monkeypox infection. The antivirals and vaccinations used to eradicate smallpox can also be used to control monkeypox because the various orthopoxviruses are closely linked and immune responses toward a single orthopoxvirus can recognize other orthopoxviruses and protect against it. The objective of this manuscript was to assess the effectiveness of smallpox antivirals and vaccinations against monkey infection. To find pertinent articles on smallpox vaccines and antivirals used to treat monkeypox, a systematic review was conducted. According to the data collected, vaccinia immune globulin, replication-deficient smallpox vaccines, replication-competent vaccinations, and smallpox antivirals (tecovirimat, cidofovir, and brincidofovir) have shown to be quite successful against monkeypox infections, in both animal models and human clinical trials. To ascertain the specific role that orthopoxvirus inhibitors and smallpox immunizations play in human monkeypox infections, it is recommended to repurpose these vaccines and antiviral drugs and to carry out more research in human models.

Keywords
Smallpox, Monkeypox, Vaccinations, Tecovirimat, Cidofovir

1. Introduction

Monkeypox (Mpox) is a zoonotic orthopoxvirus closely mimicking smallpox and presenting a major public health challenge. The disease, which has its roots in the same viral family as smallpox, has symptoms that are similar to those of its more well-known cousin in humans. Clinicians have difficulties in distinguishing between smallpox and

monkeypox because of their clinical resemblances [1]. In recent years, monkeypox has attracted attention as a re-emerging zoonotic danger, with cases recorded across 16 countries, underlining the need for a full study of its epidemiology and clinical manifestations [2]. The aim of this review is to inform clinicians about the current state of knowledge on monkeypox, covering its etiology, clinical presentation, and changing epidemiology.

Monkeypox, caused by the monkeypox virus (MPXV), first emerged in 1958 among laboratory monkeys in Copenhagen, Denmark. The virus was found during an epidemic of smallpox-like diseases among cynomolgus monkeys [3]. In 1970, the initial case of monkeypox in humans was reported in a nine-month-old kid in the Democratic Republic of the Congo (DRC). In May of 2022, an epidemic of Mpox arose abruptly and spread over Europe, the Americas and eventually all six WHO regions, with 110 nations reporting roughly 87000 cases and 112 fatalities [4]. A recent epidemic of monkeypox has been observed, specifically in the DRC. In August 2023, cases were verified in Kinshasa, the capital of the DRC, marking the first incident of monkeypox in this area. The epidemic has resulted to a considerable number of suspected cases and fatalities, with 12,569 suspected cases and 581 deaths recorded in the DRC since January 1, 2023 [5].

A clade IIb MPXV outbreak that began in 2022 spreads to numerous nations outside of Africa, mostly as a result of male-to-male sexual interactions. Only MPXV clade I have been found in the DRC; no cases of Mpox connected to clade IIb MPXV during the worldwide epidemic have been reported from the nation. When a Belgian man tested positive for clade I in Kenge, Kwango province, while visiting the DRC, it was claimed to be the first known case. This is the first time that a clade I MPXV infection has been connected to intra-cluster sexual transmission. Since the 1970s, there have been reports of human-to-human spread of Mpox infection by intimate contact; these cases have mostly involved small-scale household or community epidemics. Due to inadequate epidemiological and contact tracing studies, delayed diagnostics availability, and challenges in connecting cases to contact with infected animals, the dynamics of

MPXV clade I transmission in the DRC remain poorly known [5]. Figure 1 shows geographic distribution of DRC's confirmed Mpox cases by province in 2023.

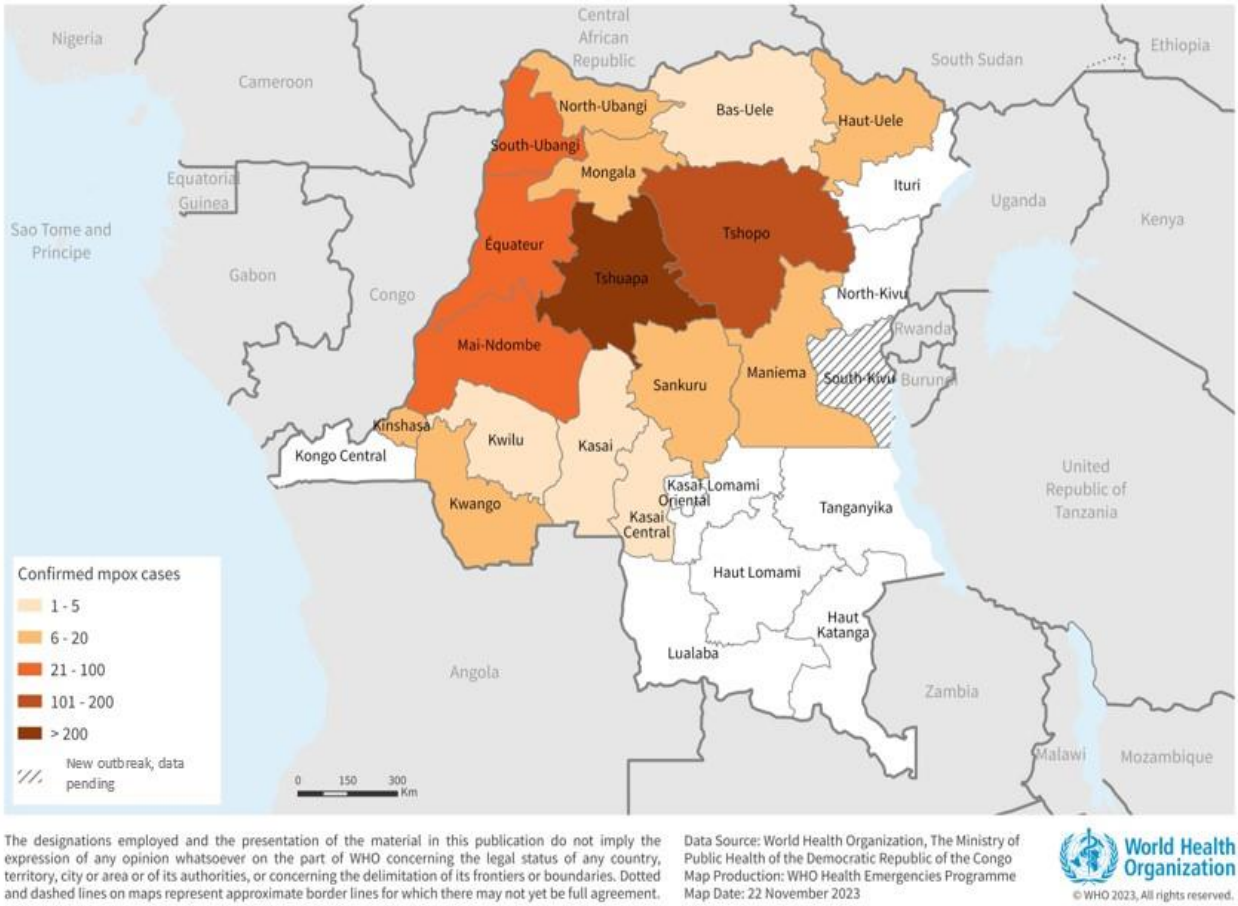

Figure 1 Geographic distribution of DRC's confirmed Mpox cases by province, from January 1, 2023, to October 7, 2023 (epi weeks 1 through 40) with courtesy of World Health Organization (WHO)

Treating Mpox aims to control the rash, minimize discomfort, and avoid consequences. In order to effectively manage symptoms and prevent further issues, early and supportive treatment is crucial. Having the Mpox vaccination may aid in infection prevention. If you come into touch with someone who has the Mpox, you should get the vaccination within 4 days (or up to 14 days if no symptoms are present). It is best to care for Mpox patients apart from other individuals. Studies are being conducted on the use of many antivirals, including tecovirimat, which was first created to treat smallpox, to treat Mpox [6].

2. Monkeypox Epidemiology, Including its Global Distribution

A major public health issue that affects the whole modern world as well as central and western Africa is monkeypox (MPOX). In the 1970s, the DRC reported the first case of human monkeypox (HMPX), and occasional cases were later documented in 11 additional African republics. A significant MPX outbreak happened in the DRC between 1996 and 1997; 511 infected patients were examined. Information on the number of cases and fatal Mpox cases by country and year was provided via a systematic review and meta-analysis [7]. The current global health crisis highlights the need for action to combat this devastating disease. Table 1 shows the incidence of MPOX between 1970 and 2021.

Table 1 MPOX incidence and number of deaths between 1970 and 2021

Region/Country	Duration	No. of cases	No. of deaths
DRC	1970-2020	11619	632
Central African Republic	2001-2018	116	9
Republic of the Congo	2003-2017	111	8
Sudan Cameroon	2005	37	0
Gabon	1987	10	1
Nigeria	1971-1978, 2017-2018	232	6
Sierra Leone	1970-1971	1	0
	2014-2017	2	1
Liberia	1970-1971	4	0
Céte d'Ivoire	1971	1	0
USA	2003	47	0
	2021	2	0

The monkeypox virus (MPXV) is the infectious agent that causes Mpox. MPXV is known to exist in two clades: clade II, also known as the West Africa clade, and clade I, previously known as the Congo Basin clade. Clade II also contains two subclades, clade IIa and clade IIb (WHO). The mortality rate from the Mpox virus, Clade I, is 10%. The infections from Clade IIb are the cause of the 2022–2023 outbreak. Infections with Clade IIb are seldom fatal [8].

Between the years 2022 and 2023, there was a worldwide epidemic of monkeypox that affected more than 113 nations outside of Africa. Sexual contact is the main source of the virus, especially for guys who have sex with other men (MSM). The worldwide epidemic is caused by the clade IIb MPXV strain, and evidence of sexual transmission has been found. During the current worldwide epidemic, clade I MPXV has been found but no cases connected to clade IIb MPXV have been reported from the DRC. Since the 1970s, there have been reports of human-to-human transmission of monkeypox in the area, often in the form of minor household or community outbreaks that are thought to be zoonotic. An insufficient knowledge of the dynamics of transmission in the area is a result of difficulties with diagnosis, the inability to connect cases to infected animals, and the shortcomings of epidemiological studies. At the moment, most WHO areas are still experiencing clade IIb MPXV transmission, while certain nations often experience clade I MPXV community breakouts [5, 8].

3. Clinical Features of Monkeypox and Correlation with Smallpox

Human Mpox was first identified as a distinct human infection in 1970, after being isolated from a suspected smallpox patient in the Democratic Republic of the Congo. Clinical characteristics of human monkeypox largely resemble those of smallpox [1].

Mpox illness has distinct stages including an incubation period, prodrome, and subsequent rash. The incubation period lasts one to two weeks and is not transmissible. Prodrome symptoms include sore throat, fever, headache, and swollen lymph nodes. Lymphadenopathy is an important feature of Mpox, and patients may be contagious during this period. Patients should be instructed to isolate if symptoms develop. In some cases, a rash without a recognized prodrome has been present, with localized lesions progressing from macules, papules, pustules, vesicles, and scabs. A person is infectious until all scabs have fallen off and a fresh layer of intact skin forms underneath. Regional or state health authorities should be consulted before deciding to stop using isolation precautions. Regional or state health authorities should be consulted before deciding to stop using isolation precautions [9, 10]. Table 2 summarizes the features of Monkeypox and Smallpox.

Table 2 Characteristics features of Monkeypox and Smallpox

Characteristics		Monkeypox	Smallpox
Time period	Incubation period	7 to 17 d	7 to 17 d
	Prodromal period	1 to 4 d	1 to 4 d
	Rash period	14 to 28 d	14 to 28 d
Symptoms	Fever	often between 38°C-41°C	often >40°C
	Malaise	Noted	Noted
	Headache	Noted	Noted
	Lymphadenopathy	Manifested	No
	Lesions on palms or soles	Present	Present
	Lesion distribution	Centrifugal	Centrifugal[a]
	Lesion appearance	Hard and deep, raised and filled with clear fluid	Hard and deep, raised and filled with clear fluid, umbilicated
	Lesion progression	Lesions often progress slowly, with every stage of growth for 1 to 3 d on the body	Lesions are often progress slowly, with every stage of growth for 1 to 3 d on the body[a]

d: Days, [a]Vaccinated individual show fewer, smaller, and better regional monomorphism and centrifugal distribution of rash compared to unvaccinated individuals, who were less than 20 years prior to illness

3.1 Dermatological Lesions

The Mpox virus outbreak in the DRC has been linked to contact during sexual intercourse as the main transmission mechanism. The clinical presentation of the virus began with a prodromal phase characterized by fever, malaise, and lymphadenopathy, followed by a skin rash. The majority of patients had no systemic symptoms or developed them after or at the same time as skin lesions. Mucocutaneous lesions were preferred to be in the genital or Genito-anal area. The majority of patients reported a median of five lesions. Numerous individuals exhibited cutaneous lesions at various stages. Lesions in the locations most likely to have been inoculated were described as white papules with a necrotic core that resembled pustules (pseudo pustules) as shown in Figure 2. Eosinophilic cytoplasmic inclusions, full-thickness epidermal necrosis, keratinocyte ballooning, and a mostly lymphocytic inflammatory

infiltration were the histological features that defined these lesions as shown in Figure 3. Compared to previously reported mortality rates of 3.3%–10.6%, the WHO's figure of 81 fatalities was much lower [11].

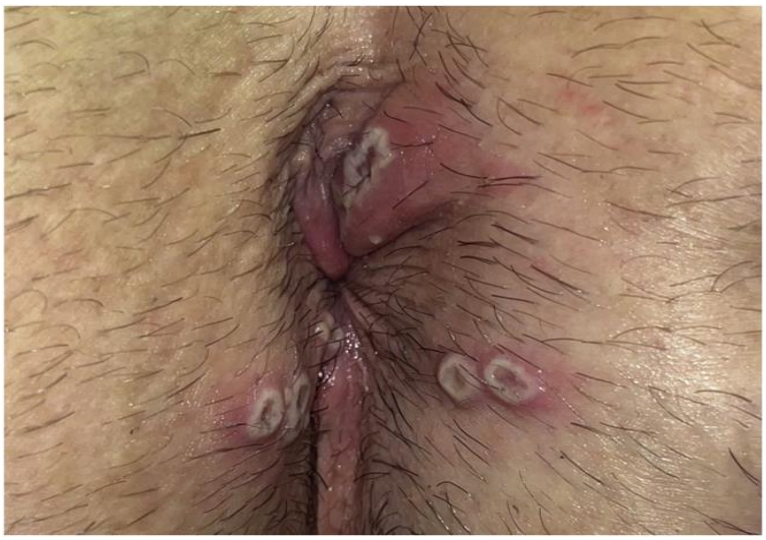

Figure 2 White, necrotic papules on the perianal surface (pseudo-pustules)

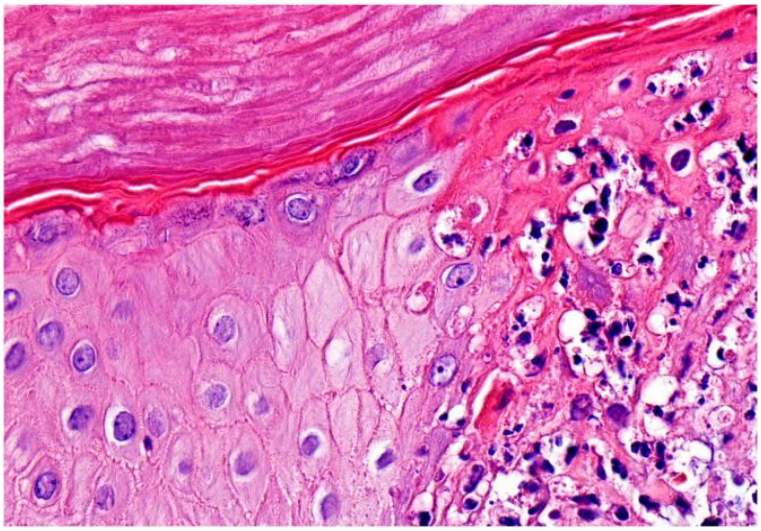

Figure 3 Histologic characteristics (Eosin and Hematoxylin, ×400). Epidermal keratinocytes with balloon cell degeneration and an inflammatory infiltration around the borders of the lesion that is mostly lymphocytic

3.2 Signs and Symptoms

Mpox symptoms can appear one to twenty-one days after exposure, however they usually occur within a week. When an individual's immune system is compromised, symptoms can linger longer than the usual duration of 2-4 weeks. Generally speaking, Mpox symptoms include rash, fever, sore throat, headache, back discomfort, muscular aches, low energy, and enlarged lymph nodes [6].

Usually, the Mpox symptoms include sore throat, fever, and muscle aches. The Mpox virus rash starts on the face, moves to the body, and eventually appears as macules, papules, vesicles, and pustules over a period of two to four weeks. Lesions begin to dip in the middle and then crust over. After that, scabs come off. One of the hallmarks of Mpox is lymphadenopathy, or enlarged lymph nodes. Some individuals may carry the infection yet show no symptoms [12].

In the context of the global Mpox epidemic of 2022, which was mostly caused by the Clade IIb virus, some people got the disease at a different time than others. A rash, which often does not extend over the body and may appear in conjunction with other symptoms, is present in less than 50% of cases. The mouth, anus, or groin region might be the site of the first lesion [6].

4. Transmission: Crucial for Controlling its Outbreak

Human-to-animal contact, infected items, and person-to-person contact are the three ways Mpox may spread. Skin-to-skin, mouth-to-mouth, respiratory droplets, and oral sex are the considered forms of person-to-person contact. The respiratory tract, mucosal surfaces, or damaged skin are the entry points for the virus into the body. People who have several sexual partners are more likely to have Mpox, which can also spread to other family members and sexual partners. Afflicted animals can spread the disease to people by bites, scratches, hunting, trapping, skinning, cooking, or eating other animals. Mpox can be acquired from contaminated materials, sharps injuries received in medical facilities, or public places like tattoo shops [6].

Men made up 96.6% of cases in 2022, according to WHO statistics, with 84.2% of those cases being Men having Sex with Men (MSM). The most often reported mode of transfer

was sexual intercourse, and the most likely exposure category was parties involving sexual interactions. In large case series, the prevalence of MSM infection was substantially greater, ranging from 35.5% to 42% HIV positive [11, 13].

5. Monkeypox Diagnosis: Techniques and Innovations

Diagnostic assays can classify monkeypox or Orthopoxvirus from clinical specimens, particularly when combined with clinical and epidemiological information. Due to limited cold chain and resources, lesion exudate on swabs or crust specimens remains the best and least invasive acute patient specimens. Conventional tests like viral culture isolation, electron microscopy, Anti-Orthopoxvirus IgG or IgM (Tests for the presence of Orthopoxvirus antibodies) and immunohistochemistry require advanced technical skills and a sophisticated laboratory. While real-time polymerase chain reaction (PCR) is a useful tool for effectively detecting viral DNA in samples, its application in remote areas is now limited to large facilities. Technological developments could make real-time PCR diagnosis more practical outside of large facilities [8].

6. Treatment Strategies of Monkeypox

The treatment of Mpox focuses on managing the rash, pain, and preventing complications. Early and supportive care is crucial for managing symptoms and avoiding further issues. Vaccination is recommended for high-risk individuals, such as health workers, men with multiple sex partners, and sex workers. Vaccination should be given within 4 days of contact with someone with Mpox, and individuals should be cared for away from others. Antivirals like tecovirimat, originally developed for smallpox, have been used to treat Mpox, with further studies underway (WHO).

6.1 Smallpox Antiviral Drugs for Treatment of Monkeypox

There are currently no reliable treatments or sufficient evidence-based guidelines available for the management of MPX. Monkeypox virus (MPXV) exposure results in a very mild to moderate illness that is usually self-limiting. Tecovirimat, cidofovir, brincidofovir, and vaccinia immune globulin intravenous (VIGIV), are effective antiviral treatments approved for smallpox and can be used for severe cases of MPX illness that necessitate hospitalization. These treatments are particularly useful when lesions

develop complications or occur in sensitive areas such as the genitals, eyes, and mouth. Additionally, they are recommended for immunodeficient patients, infants, and children under the age of 8, as well as breastfeeding or pregnant women [14].

6.1.1 Tecovirimat

Human monkeypox virus (HMPXV), vaccinia virus, and variola virus (VARV) are classified as orthopoxviruses. With broad efficacy against orthopoxviruses both in vitro and in vivo, the FDA has approved tecovirimat (TPOXX/ST-246), a 4-trifluoromethylphenol derivative, in July 2018, that can be used to combat newly emergent MPX cases. There are two available forms of tecovirimat (TCV): IV and oral [15].

6.1.1.1 Mechanism of Action

A gene identical to the F13L gene of the vaccinia virus, the V061 gene in cowpox, is the target of tecovirimat. It is responsible for the production of extracellular enveloped virus (EV) and encodes for membrane protein p37, a well-conserved protein in orthopoxviruses. It is believed that EV is the primary cause of transfer from cell to cell as well as from the bloodstream to other locations. TCV does not affect viral DNA replication or protein synthesis but it inhibits virus activity by inhibiting the VP37 protein required for assembly and release of enveloped virus particle from cell [16]. Figure 4 summarizes the mode of action of Tecovirimat.

6.1.1.2 Contradictions

When administered intravenously, the sole contraindication for tecovirimat is a severe renal damage characterized by a creatinine clearance <30 mL/min. But there is no side effect for oral administration. Tecovirimat has not been examined in females who are breastfeeding or pregnant. The presence of tecovirimat in breast milk is unknown. Tecovirimat should be the primary line of treatment for pregnant or breastfeeding females affected with the Mpox virus [17].

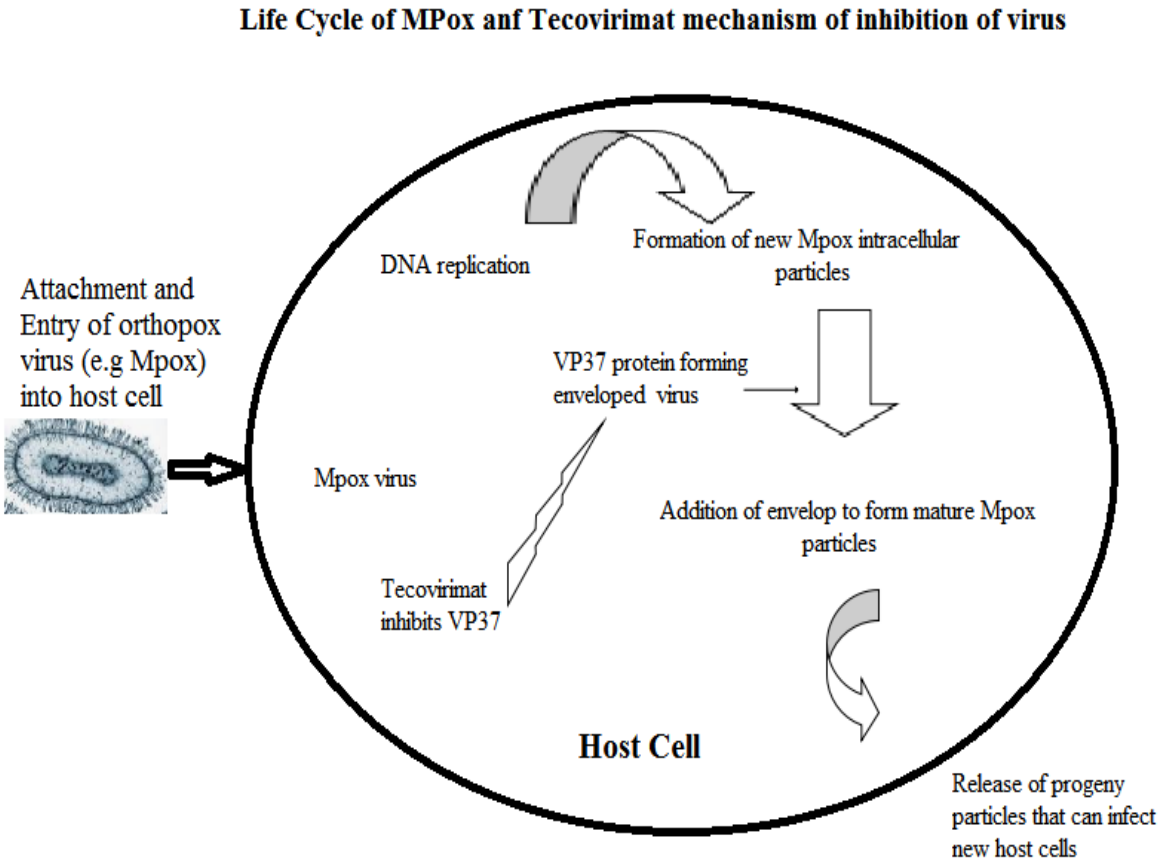

Figure 4 Mechanism of viral DNA replication inhibition by Tecovirimat

6.1.1.3 Dosage

The molecular weight of tecovirimat is 376.33 g/mol. Its dosage is recommended according to the weight of the infected person [18] as outlined in Table 3.

Table 3 Weight-based recommendations for oral TCV capsules

Weight	Oral Dose of TCV
13 to less than 25Kg	200mg/12hours
25 to less than41 Kg	400mg/12hours
41 to less than 120Kg	600mg/12hours
120 Kg and more	600mg/8hours

6.1.1.4 Tecovirimat Efficacy Data from Human Studies

Treatment was administered to individuals affected with monkeypox with lesions in the face or genital area, or those with disseminated disease. Adult patients received weight-based oral tecovirimat therapy every 8 or 12 hours. There was a complete resolution of lesions in 40% patients by day 7 while 92% patients had lesions resolved by day 21. No deaths and adverse events were reported [19]. A forty-year-old man receiving preexposure prophylaxis for HIV arrived for an outpatient visit with a maculopapular rash associated with the perineum, subjective fevers, and malaise. His first outpatient appointment confirmed that he had previously tested positive for Orthopoxvirus by PCR and was subsequently identified as MPXV clade 3. Antibacterials did not help his rash, so tecovirimat 600 mg was started on an oral twice-daily regimen. On the second day of tecovirimat, many of his pustular lesions had started to heal and the perineal rash became less erythematous. On the seventh day of tecovirimat, the lesion on his right eyelid showed a noticeable improvement and his rash had almost completely resolved. No biochemical imbalances and tecovirimat adverse effects were noticed [20].

6.1.1.5 Tecovirimat Efficacy Data from Animal Studies

To assess TPOXX's antiviral effectiveness in an animal model of MPXV illness, Clade 1 and Clade 2 viruses were administered intranasally to mice. They received oral treatments of TPOXX every day. According to the research, the treatment with TPOXX significantly lowered viral replication in the lungs, resulting in a quicker clearance of the virus [21]. A deadly dose of the monkeypox virus (MPXV) was given to cynomolgus macaques via aerosol. The macaques were then treated orally with 10 mg/kg tecovirimat once a day for up to eight days. The the lifespan, lesions, and clinical indications of illness of the monkeys were observed. In animals starting treatment up to five days after the challenge, 100% of them survived. Animals treated six, seven, or eight days after the challenge had survival rates of 67%, 100%, and 50%, correspondingly. Starting treatment up to four days after the challenge lessened the severity of the infection's clinical symptoms [22].

6.1.2 Cidofovir

An acyclic nucleoside analog exhibiting antiviral activity, cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine] was first investigated for the treatment of AIDS patients' cytomegalovirus retinitis in 1986. When other antivirals are ineffective against orthopoxviruses, parapox, molluscum, or Herpesviridae family viruses, cidofovir is a useful therapeutic and preventive measure [23]. There are not a lot of clinical studies regarding its effectiveness in treating human monkeypox. However, research on animals has shown that this drug is effective against monkeypox.

After a lethal MPXV infection in cytomegalic monkeys, the effects of administering antiviral medications, such as cidofovir and an acyclic phosphonate nucleoside analog (related to cidofovir), and immunizing (post-exposure) with smallpox vaccination, were assessed. According to the study, antiviral therapy dramatically reduced mortality 24 hours after a deadly MPXV challenge more effectively than smallpox vaccination (Elstree-RIVM) [24].

6.1.2.1 Mechanism of Action

Cidofovir blocks the activity of DNA polymerase of pox viruses. When it gets into host cells, it is phosphorylated into CDV diphosphate (CDV-pp), the active form, by intracellular enzymes. CDV-pp has an extended intracellular half-life now. As DNA replication proceeds, CDV-pp is integrated into the developing DNA strand, hindering DNA synthesis. Cidofovir diphosphate can also prevent the 3′–5′ exonuclease activity of DNA polymerase [25]. Figure 5 summarizes the mode of action of cidofovir.

6.1.2.2 Contradictions

A US-boxed warning for cidofovir mentions the risk of severe nephrotoxicity. It is not recommended to patients with a serum creatinine (SCr) level more than 1.5 mg/dL Every time cidofovir is administered, renal function needs to be observed [26]. Oral probenecid and intravenous saline for rehydration should be administered to patients who require this treatment in addition. By preventing the tubular secretions of kidney, probenecid lowers the kidney's elimination of cidofovir and lowers the risk of renal toxicity. Additionally, individuals on this medicine can develop neutropenia; so, it is

important to monitor the patient's neutrophil levels. Based on studies conducted on animals, this drug may be teratogenic and carcinogenic. Pregnant women should not use cidofovir but if systemic medication is necessary, it is best to avoid using it in the first trimester. Hepatic impairment, pancreatitis, and metabolic acidosis are other possible outcomes [27].

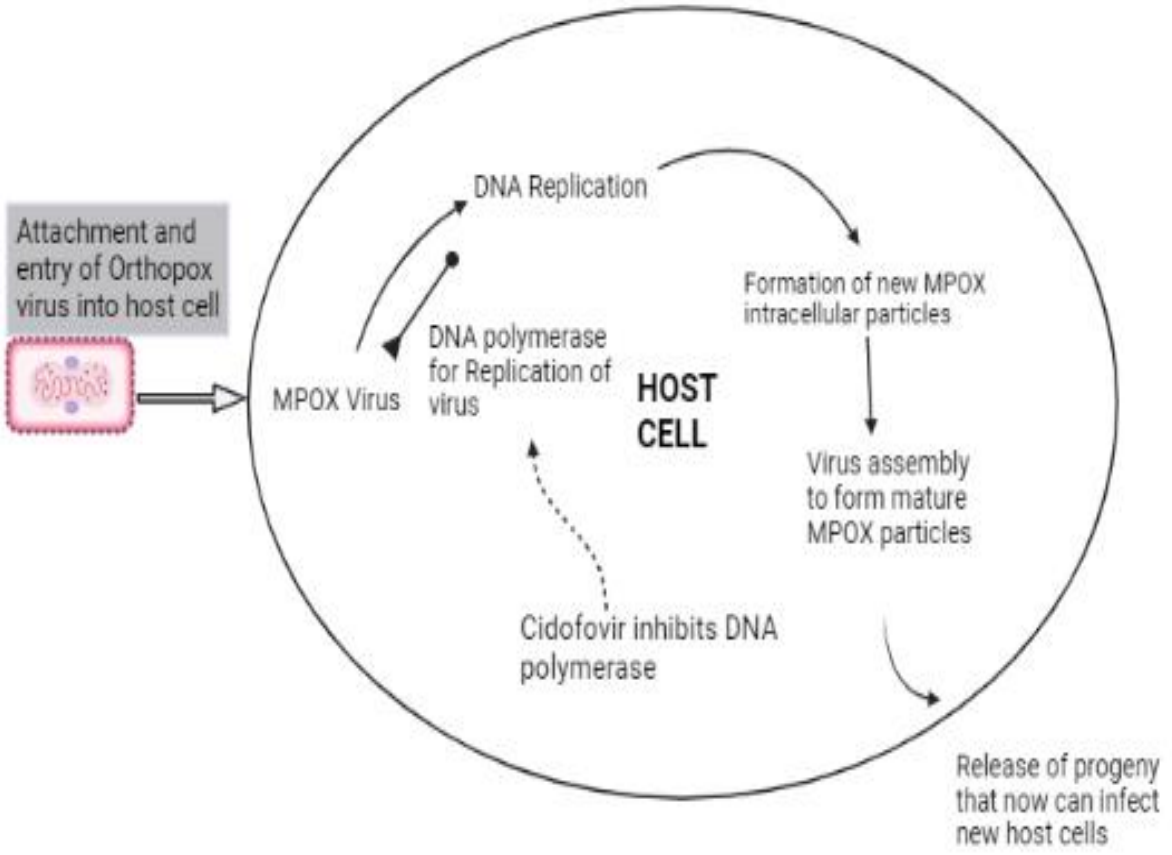

Figure 5 Mechanism of Viral DNA Replication inhibition by cidofovir

6.1.2.3 Dosage

Cidofovir is available in intravenous (IV) as well as topical formulations. However, IV administration is the standard method for cidofovir. cidofovir has a long half-life of 48 h. Its dosage is recommended according to the weight of the infected person [28] as outlined in Table 4. 70–85% of unaltered cidofovir is eliminated in urine in 24 hours.

Table 4 Weight-based recommendations of IV Cidofovir administration

Route	Dosing
IV	5mg per kg body weight administered once weekly for 2 weeks followed by 5mg per kg once every other week

If there is 0.3–0.4 mg/dL increase in SCr from baseline, reduce the dose to 3 mg/kg, and stop if the SCr rises by 0.5 mg/dL or if ≥3+ proteinuria develops. Cidofovir is sold under the brand name "Vistide" and comes in a flint glass vial containing 375 mg of the drug at a 75 mg/ml concentration in 5 milliliters of water.

6.1.2.4 Cidofovir Efficacy Data from Human Studies

A prospective study was carried out to gather information on the clinical and virologic history of individuals who had skin lesions from monkeypox. Topical cidofovir 1% was used to treat twelve patients, with the remaining patients receiving merely symptomatic care. In the group treated with cidofovir, lesions resolved in 12 to 18 days more quickly. Although systemic adverse effects were not documented, local adverse effects were common. Although, there was no placebo-controlled group in this study, and it was not a clinical trial [23]. In 2023, a case report presented the treatment of a hospitalized HIV-positive patient infected with complicated monkeypox with cidofovir. Cidofovir was given to this patient twice, with a week's gap between each dosage, and the patient responded well to treatment [29]. However, to evaluate the effectiveness and safety of cidofovir as a therapy for those suffering from human monkeypox, more research is required with addition of control group in the experiments.

6.1.2.5 Cidofovir Efficacy Data from Animal Studies

The mousepox virus, ectromelia virus (ECTV), was administered intranasally to the animals. The animals were treated with several doses of cidofovir on different days, and their humoral response, morbidity, and mortality were observed. Depending on the treatment period and dosage (2.5–100 mg/kg), a single CDV treatment is adequate to provide protection. Even though a low dose (5 mg/kg) of CDV was administered on day 6 post-exposure, or around 4 days before the control group of infected, untreated

mice died, solid protection was still obtained [30]. When administered up to 48 hours after infection, CDV has been demonstrated to stop lesion formation in nonhuman primates who were exposed to Mpox. Still, monkeys given a placebo developed multiple lesions and viremia [15]. In another experiment, both mortality and the number of cutaneous monkeypox lesions in monkeys were considerably reduced when antiviral treatment was started 24 hours after deadly intratracheal MPXV infection. On the other hand, no appreciable decrease in mortality was seen when monkeys received a typical human dosage of the smallpox vaccination that is now advised (Elstree-RIVM) 24 hours after MPXV infection [31].

6.1.3 Brincidofovir

Lipid-conjugated CDV analog, brincidofovir (BCV), is sold under the Tembexa (Chimerix) brand. The FDA authorized brincidofovir in 2021 to treat smallpox. Similar to CDV, BCV exhibits broad action against dsDNA viruses; but, in comparison to CDV, it has a decreased half-maximal effective concentration (EC50) against a greater number of dsDNA viruses, such as orthopoxviruses, herpesviruses, and adenoviruses [32].

6.1.3.1 Mechanism of Action

BCV is lipophilic, which allows it to enter host cells more easily than CDV and this overcomes two of CDV's key drawbacks, nephrotoxicity and the lack of oral bioavailability [33]. Cellular phospholipases then hydrolyze brincidofovir into CDV, which is further phosphorylated into CDV-pp. Because of its improved capacity to penetrate cellular membranes, cidofovir diphosphate can reach larger intracellular concentrations following BCV treatment. Similar to CDV, BCV prevents the DNA replication of poxviruses and has an extended intrinsic half-life [32]. Figure 6 summarizes the mode of action of Brincidofovir.

6.1.3.2 Contradictions

One of the major negative effects is hepatotoxicity. The liver enzymatic profile should be regularly monitored and if a patient's alanine transaminase (ALT) level is persistently elevated or more than ten times the upper limit of normal, it may be necessary to stop

the treatment. This drug should not be taken by pregnant and breastfeeding women, newborns, and immunocompromised individuals [34].

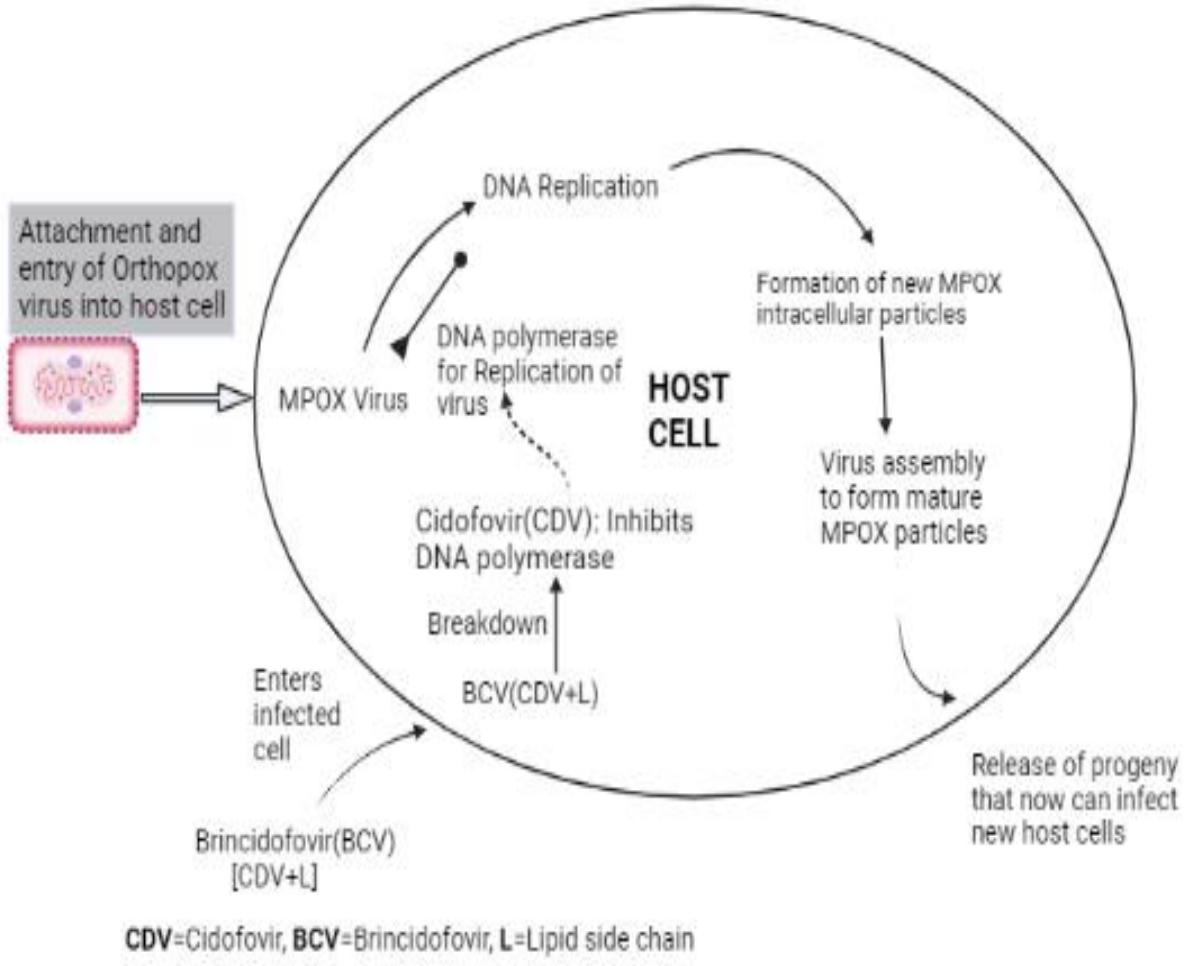

Figure 6 Mechanism of viral DNA replication inhibition by Brincidofovir

6.1.3.3 Dosage

Brincidofovir is 1-O-hexadecyloxypropyl Cidofovir compound of molecular weight of 561.7g/mol and is available in oral dosage forms (tablets and suspensions). It is orally available as 100mg tablet and 10 mg/mL Oral Suspension. Its dosage is recommended according to weight of infected person [32] as outlined in Table 5.

Table 5 Weight-based recommendations of oral BCV

Weight	Oral Dose of BCV
Below 10 Kg	oral suspension; 6mg/kg once a week (2 doses)
10 Kg to <48 Kg	oral suspension; 4mg/kg once a week (2 doses)
48Kg or more	200mg once a week (2 doses)

6.1.3.4 Brincidofovir Efficacy Data from Human and Animal Studies

Three monkeypox patients were administered 200mg of BCV orally. Although all of them survived monkeypox, one of them experienced nausea and abdominal pain, and all three had elevated alanine transaminase levels [35]. Furthermore, additional clinical research on human Mpox cases is needed. Prairie dog Mpox is marked by an incubation period of 10 to 13 days, followed by 2 days of fever, and formation of widespread lesions. This infection course is remarkably similar to the human Mpox infection course. When administered soon after Mpox exposure, BCV was found to increase survival in prairie dogs [36].

6.2 Smallpox Vaccines gainst Monkeypox Viral Infection in Humans

According to how closely linked the various orthopoxviruses are, immune responses to a single orthopoxvirus can recognize other orthopoxviruses and produce differing degrees of protection because orthopoxviruses share a huge number of immunologically important proteins, which leads to a high degree of sequence similarity between them; also, the response is broad, with antibodies attacking a minimum of 24 structural and membrane proteins [37]. The immunization against smallpox (vaccinia) is cross-protective against both smallpox as well as monkeypox, preventing around 85% of Monkeypox Virus Infection in Humans; however, the availability and manufacturing of these vaccines are currently restricted [38]. Results from research conducted in the 1960s provide some of the early proof that immunity specific to the vaccinia can protect against monkeypox. The use of first-generation smallpox vaccinations such as Dryvax or others produced full protection against disease in nearly all inoculated animals in three different investigations including cynomolgus

macaques, chimpanzees, and rhesus macaques.Vaccinations against smallpox and monkeypox can be applied either pre-exposure or post-exposure. Vaccination for pre-exposure is recommended to safeguard the most vulnerable individuals. The post-exposure vaccine can be used up to 14 days following exposure to lessen the severity of the disease, although it is best taken within 4 days after exposure to avoid infection. Second- or third-generation vaccines are the most effective for pre-exposure and post-exposure vaccination [39]. A brief review and discussion of the therapeutic benefits and risks of each smallpox vaccine in smallpox and monkeypox infection are presented next.

6.2.1 Replication-competent Smallpox Vaccines against Monkeypox

Vaccinations against smallpox that use live, replicating viruses are known as replication-competent vaccinations. Due to their comparable antigens, these vaccinations have been used previously to prevent smallpox and have demonstrated cross-protective benefits against monkeypox. Replication competent smallpox vaccines against monkeypox include ACAM2000, LC16m18, and APSV.

6.2.1.1 ACAM2000

Based on a single clonal viral strain from Dryvax that showed decreased neurovirulence in animal models, ACAM2000 is a second-generation vaccination that was prepared by cell culture. Clinical trials revealed an identical safety profile to Dryvax, while immunogenicity testing demonstrated non-inferiority to Dryvax. It is administered using a split needle in a multiple-puncture procedure. Only one dose is required with booster doses every 3 years for individuals with a high-risk exposure [38]. It can be administered both as pre-exposure vaccination for cinical laboratory personanel or healthcare personnel working with orthopoxviruses or as post-exposure prophylaxis for those with unprotected direct touch with an infectious orthopoxvirus lesion, fluid, or contaminated object or being within two meters of someone who has an active orthopoxvirus case for three hours or longer. Lymphadenopathy, pruritus, headache, fever, rash, exhaustion, discomfort, and bacterial infection at the administration site are among the usual adverse effects while serious adverse effects consist of encephalitis, myopericarditis and pericarditis, erythema multiforme major, eczema, encephalitis, autoinoculation-

related blindness, and fetal mortality in expecting mothers. The use of ACAM2000 is contraindicated in pregnant and breastfeeding women, infants, immunosuppressed individuals and in those with underlying heart disease, and are being allergic to any vaccine component [39]. Some other characteristics of ACAM2000 are presented in Table 6.

Table 6 Characteristics of ACAM2000 vaccine [40]

Type of vaccine	Second generation live vaccinia virus vaccine
Status of approval	FDA approved in 2007
Cells used in development	Vero cells or kidney cells of African green monkey
Purpose	Active immunity against smallpox and monkeypox
Dosage	Single dose required; 0.0025 ml of live vaccinia virus, having 2.5–12.5 x10^5 plaque-forming units (PFU)/dose,
Administration	Percutaneous route
Supplied as	Lyophilized powder
Advantages	• Safe • Effective • Cannot cause smallpox
Disadvantages	• Ability to replicate in human cell • Adverse symptoms can occur in susceptible individuals • Virus can transmit from vaccinated individuals to non-vaccinated individuals in close contact with them

6.2.1.2 Aventis Pasteur Smallpox Vaccine or APSV

APSV is another vaccine against the replication-competent vaccinia virus. It seems likely that APSV will have a comparable safety and efficacy profile to ACAM2000. A vaccinia virus seed taken from the New York City Board of Health (NYCBOH) strain is used to create the APSV. To make the vaccine, 50% glycerol, 0.00017% Brilliant Green, and 0.4% phenol are added to the live vaccinia virus. In those who have never had a poxvirus, the APSV vaccination has an efficacy rate of higher than 95%. Although there is a decreased likelihood of serious side effects from the smallpox vaccination derived from the NYCBOH strain of the virus, young people who received the first dose of the vaccine are still susceptible to them. The three most frequent major side effects of

vaccination are encephalitis, progressive vaccine-induced vaccinia, and vaccinatum eczema. Myopericarditis caused by APSV was predicted to have a risk comparable to that of ACAM2000. When ACAM2000 is unavailable or not recommended, the FDA approves APSV as an emergency use authorization (EUA) or investigational new drug (IND) for usage based on individual circumstances [41]. The Basic characteristics of the APSV vaccine are outlined in Table 7 [40].

Table 7 The basic characteristics of the APSV vaccine

Type of vaccine	Second generation live vaccine
Status of approval	FDA authorized as IND and EUA
Strain used for development	Created from a seed of NYCBOH strain of the vaccinia virus
Purpose	To be used on an individual basis when ACAM2000 is not accessible or recommended
Dosage	Single dose required containing 2.5–1.25 x10^5 PFU
Administration	Percutaneous route
Advantages	• Safe • Effective • Cannot cause smallpox • Can be used as pre-exposure prophylaxis
Disadvantages	• Ability to replicate in human cell • Virus can transmit from vaccinated individuals to non-vaccinated individuals in close contact with them • Adverse effects can occur in young children and in those people vaccinated for the first time

6.2.1.3 LC16m18

A frameshift mutation in the B5R gene causes an extremely attenuated replication-competent vaccinia virus strain known as LC16m8 (m8). The m8 was initially approved in Japan as a smallpox vaccination. A genetically stable variation known as m8Δ was created to enhance m8, eliminating the complete B5R gene and offering enhanced immunogenicity. In a recent outbreak, vaccination against monkeypox with a vaccinia virus lacking in B5R was found to be protective [42]. It is a third-generation vaccination that uses a virus that is originated from the first-generation vaccines' Lister strain. Rabbit kidney cells are used in cell culture to create the vaccine. It is recommended for those with atopic dermatitis, immunological deficiencies, immunosuppression, or

contraindications to vaccine propagation. As of June 2022, it is not advised for the general public. Only one dose is administered using a split needle in a multiple-puncture procedure. Administration site discomfort, fever, pruritus, headache, lymphadenopathy, rash, and fatigue are the common side effects. Its use is contraindicated in individuals having adverse vaccine-component allergies [39].

6.2.2 Replication-deficient Smallpox Vaccines against Monkeypox

Replication-deficient vaccines are those that cannot rapidly replicate inside the host organism, hence lowering the chance of illness and unfavorable side effects. Modified vaccinia Ankara Bavarian Nordic is an example of a replication-deficient vaccinia vaccine against monkeypox and smallpox transmission and infection.

6.2.2.1 Modified vaccinia Ankara Bavarian Nordic (MVA-BN)

MVA-BN is a third-generation, live, highly attenuated vaccination against the vaccinia virus. MVA-BN can be administered to immune-competent people as well as those with allergic rhinitis, atopic dermatitis, HIV infections, or immunological deficiencies. In comparison to ACAM2000, 0.5 ml of MVA-BN is given in two doses at 0 and 4 weeks apart for the main vaccination. Those already immunized against smallpox are given a single 0.5 ml dose. The booster dose is given every 2 years. It can be given pre-exposure as well as post exposure vaccination. Except for mild to moderate local side effects such as discomfort at the injection site, headache, nausea, fatigue, myalgia, and chills, MVA-BN is an easily tolerated vaccination. Its use is contraindicated in individuals having adverse vaccine-component allergies [40]. The basic characteristics of the MVA-BN vaccine are outlined in Table 8 [40].

Table 8 The basic characteristics of the MVA-BN vaccine

Type of vaccine	Third generation highly attenuated live vaccinia vaccine
Other names	Imvanex in EU JYNNEOS in US Imvamune in Canada
Status of approval	FDA approved
Purpose	Prevention against monkeypox and smallpox
Dosage	A single dose of 0.5 mL for those who have been vaccinated previously Two doses of 0.5ml each for those never vaccinated
Administration	Subcutaneous
Advantages	• Less side effects • No adverse effects • Can be used in immunocompromised individuals
Disadvantages	• Effectiveness and safety have not studied in people below 18 years of age • Risk in pregnant women is not known • Its secretion in milk is not studied • Sufficient studies are not available for use in people above 65 years of age

6.2.3 Vaccinia immune globulin (VIG)

The FDA has approved the use of vaccinia immune globulin (VIG), a hyperimmune globulin, to treat the adverse effects associated with the vaccinia vaccination. However, because of a shortage of human data, the efficacy of VIG against monkeypox and smallpox is still unclear. Patients with a history of severe immunodeficiency in T-cell function may not benefit from the vaccinia virus vaccination; yet, VIG has been demonstrated to be safe in these patients. When a patient develops smallpox vaccination problems, tecovirimat has been administered in conjunction with VIG. Recombinant VIG (rVIG) is effective against a variety of orthopoxviruses both in vivo and in vitro. After receiving rVIG treatment, mice showed a substantial decrease in the amount of viral DNA in their bloodstream, and no obvious side effects were reported [14]. For this agent to be provided for the patient in case of need, the CDC must be notified. The basic characteristics of VIG are outlined in Table 9 [40].

Table 9 The basic characteristics of VIG

Other names	VIGI VIGIV
Purpose	For treatment of complications arose from active immunization
Dosage	Sterile solution is provided in 15 ml vials with a dose of 50,000 or less units per vial
Administration	Intravenous
Mechanism of action	Antibodies extracted from previously vaccinated immune-competent donors suppress viral infection
Advantages	• Can be used in people having ocular complications • Appropriate for use in people with severe immunodeficiency
Disadvantages	• Encephalomyelitis, erythema multiforme, myocarditis, encephalitis, vaccinia keratitis are among the conditions for which it is not advised • Not to be used in people with kidney dysfunctions • The safety and effectiveness of treating adolescent and elderly patients has not been investigated

7. Conclusion

The global monkeypox outbreak, caused by clade IIb strain, provoked concerned and prompted global cooperation. The impact of this extends beyond the borders of health, exerting influence on public health policies and measures for preparedness. Informed decision-making is vital to curb the virus's spread. There are no evidence-based treatments or prevention measures for monkeypox infections. The current findings lead us to believe that antiviral medications and smallpox vaccinations can reduce outbreaks of monkeypox. It is advised to repurpose these smallpox vaccinations and antiviral medications and to conduct more research in human models to determine the precise function that Orthopoxvirus inhibitors and smallpox immunizations play in human Mpox infections. The World Health Organization (WHO) can authorize specialists to evaluate smallpox and monkeypox vaccinations and antivirals to advise states on how to use them to prevent monkeypox infection. Monkeypox outbreaks may be prevented by public education, suitable preventative measures, quick case detection and isolation, tracking contacts, and appropriate treatment.

Author Contributions

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Acknowledgement

The authors would like to acknowledge the Centre for Applied Molecular Biology for providing them with the platform to write and publish this manuscript.

Conflicts of Interest

There are no conflicts of interest among authors.

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