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# Monkeypox: In Quest of Effective Vaccines

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**ABSTRACT:** Purpose: The main objective of the study includes various aspects of monkeypox, its biology and transmutability that are relevant for risk assessment and preparedness for a monkeypox epidemic, with an emphasis on recent progress in the understanding the virus host range, evolutionary potential, neutralization targets, and promising treatment options.

Methods: Published research including the origin, epidemiology, pathophysiology, signs & symptoms, transmission route, therapy, and vaccinations of monkeypox were carefully reviewed from various servers like Google Scholar, ScienceDirect, ResearchGate and others. Primary searches included the keywords 'monkeypox', 'Orthopox virus', 'etiology of monkeypox', 'symptoms', 'transmission', 'possibility', and 'antiviral medications' Secondary searches used 'vaccine for monkeypox', 'possible drug candidate', 'antimicrobial', 'therapeutic impact', 'pathogenesis', 'prevention', We examined relevant search results.

Results: Human monkeypox is a rare viral zoonosis indigenous to central and western Africa that has re-emerged in several nations, threatening public health. The significant number of human monkeypox cases and lack of direct ties to endemic nations after May 2022 raises worries about a probable shift in transmission pattern that might represent a wider global danger. Due to monkeypox's similarity to smallpox, smallpox vaccinations are a potential therapy for this epidemic. Antiviral medicines, vaccinia immune globulin, DNA polymerase inhibitors, anti-poxvirus monoclonal antibodies, nucleoside analogue compounds, and reverse transcriptase inhibitors are being researched to treat monkeypox. Before discussing treatment alternatives, monkeypox and smallpox differential diagnostic processes must be addressed.

Conclusion: A comprehensive understanding of the virulence and transmissibility of human monkeypox is crucial, yet epidemiological limits have rendered it infrequent and self-limiting. Further extensive research is highly recommended to find efficient vaccines against monkeypox before it's too late. 

## INTRODUCTION

The recurrence of viral pandemics has aroused extreme apprehension. We may expect COVID-19 to become endemic very soon. Unfortunately, we will likely be facing a second new viral pandemic after COVID-19 has had a significant impact on the world economy and healthcare for more than two years because of the monkeypox virus (MPV). The first instance of MPV was uncovered in 1958 in Copenhagen, Denmark [1]. The first isolate was given the humorous label monkeypox. It was in the Democratic Republic of the Congo (DRC) in 1970 that the first instance of zoonotic MPV transmission from animals to humans was documented [2]. The MPV is classified as an Orthopoxvirus, part of the family Poxviridae.

The Orthopoxvirus genus includes the pathogens responsible for the common smallpox disease, variola, and vaccinia, a research vector tool used to create a vaccine against smallpox [3]. Aside from the pronounced lymphadenopathy, the clinical presentation is remarkably similar to smallpox (pustular rash, fever, respiratory symptoms) [4]. In individuals previously immunized against smallpox with the vaccinia vaccine, the disease is less severe when Monkeypox strikes [5]. Seven incidences of human Monkeypox were recorded in the United

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Kingdom between September 2018 and November 2021 [6], and one case each in Israel and Singapore. Between May 7 and June 9, 2022, 1,273 confirmed cases were recorded in 31 countries outside the Monkeypox endemic areas. The majority of reported instances include guys who have had intercourse only with other men [7,8] and have nothing to do with having visited an endemic country. All viruses recovered from patients up to this point are shown to be members of the West African clade [7, 8]. More research is needed to determine whether a new transmission pattern has arisen. However, the present outbreak does have some uncommon traits, such as continuous human-to-human transmission among males who have sex with men. Regardless, human Monkeypox is becoming a common zoonotic disease and deserves more attention from the public health community [9]. Although smallpox was declared eradicated in the 1970s, the United States has spent the last 20 years developing and stockpiling smallpox vaccines and antivirals in case of a bioterrorist attack in which smallpox would be used. These vaccines and antivirals are also expected to be effective against Monkeypox. However, in this review, we aimed to discuss the nature of Monkeypox along with potential treatment options, including vaccines that can be used to prevent Monkeypox.

# METHODOLOGY

A comprehensive overview of Monkeypox was gathered from published articles, including its etiology, epidemiology, pathogenesis, signs and symptoms, transmission process, treatment, and vaccines for this disease. In addition, possible vaccine candidates and the management of this disease were described. The articles were excluded if the experimental design was inadequate in accomplishing the goal, for example, due to a lack of adequate control or incorrect dosages. Each piece of information was accompanied by experimental data demonstrating biological activities. Primary searches were conducted in electronic databases, such as PubMed, Google Scholar, ScienceDirect, Web of Science, SpringerLink, Semantic Scholar, Scopus, BanglaJOL, and others, using the keywords' monkeypox', 'Orthopox virus,' 'etiology of monkeypox,' 'symptoms,' 'transmission,' 'possibility' and 'antiviral drugs,' and secondary searches were conducted using the following keywords, either alone or in combination: 'vaccine for monkeypox,' 'potential drug candidate,' 'antimicrobial,' 'therapeutic effect,' 'pathogenesis,' 'prevention,' and others. Significant information from the search results related to the topic was carefully reviewed.

# ETIOLOGY

Monkeypox is from-
Family: *Poxviridae*
Subfamily: *Chordopoxvirinae*
Genus: *Orthopoxvirus*
Species: *Monkeypox virus*

The monkeypox virus has a linear double-stranded DNA genome encased in a lipoprotein envelope with a 200-250 nm diameter. The genomes of these viruses include everything needed for replication, transcription, and assembly, but mRNA translation requires the host cell's ribosomes [10].

# EPIDEMIOLOGY

In 1958, the Statens Serum Institute in Copenhagen, Denmark, isolated the monkeypox virus for the first time from monkeys. Monkeypox virus also infects other mammals, such as rope squirrels, tree squirrels, Gambian pouched rats, and dormice. Like many zoonoses, this pox virus is spread to humans by accidental contact with sick animals. The Democratic Republic of the Congo documented the first incidence of Monkeypox in humans in 1970 [11]. There have been very few reports of human cases outside of Africa before 2022. The United States recorded its first instances of Monkeypox in 2003, when a shipment of infected Gambian pouched rats infected prairie dogs stored in the same facility and, ultimately, sickened 71 people who had adopted these animals as pets. Two British citizens contracted Monkeypox in Nigeria in 2018, and one healthcare professional contracted the virus as a result of treating these patients. Hundreds of instances of Monkeypox have been documented in Nigeria during the previous 5 years, with the majority of cases being reported in males, some of whom had genital lesions, suggesting the disease was spread from person to person through sexual contact [12]. This recent epidemic demonstrates how easily the virus may spread from person to person through casual, close contact with infected areas. The first cases of Monkeypox in non-endemic regions were recorded in early May of 2022. More than 1,350 laboratory-confirmed cases of Monkeypox have been recorded from 31 non-endemic countries throughout the world as of June 9, 2022, with over 60% of these cases reported from just three countries: Portugal, Spain, and the United Kingdom [13]. Across 15 US states and DC, the CDC has confirmed 45 cases [14]. Most of the reported cases have no connection to an endemic nation, and the majority of cases have been among males who have sex with men, suggesting a sexual transmission risk. The virus that causes Monkeypox is not often spread through sexual contact, but it is nonetheless quite contagious and can be passed on to a partner. Direct contact, whether sexual or skin-to-skin, and maybe also transmission via fomites such as towels, bedding, and sex toys, is the primary route of inoculation of the virus into the skin and mucosal surfaces [11].

# PATHOGENESIS

MPV may invade its host through the oropharynx, nasopharynx, and skin. The replication occurs at the incision site and subsequently progresses to lymph nodes in the surrounding area. Following an early phase of viremia, the virus spreads to other organs. MPV shares a morphology similar to that of other known Orthopox viruses. MPVs are oval or brick-shaped and have an outer membrane composed of lipoproteins [15]. The MPV genome is a double-stranded DNA molecule (197 kb). **[Figure 1]**

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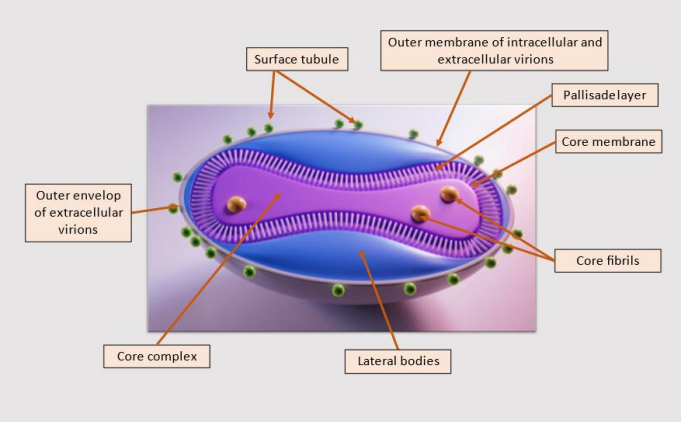


**Figure 1: Cellular structure of Monkeypox**

Despite being a DNA virus, the MPV's life cycle occurs in the cytoplasm. Multiple proteins are necessary for viral transcription, DNA replication, and virion formation [16]. Through macropinocytosis and fusion, poxviruses infect host c ells [17]. **[Figure 2]**

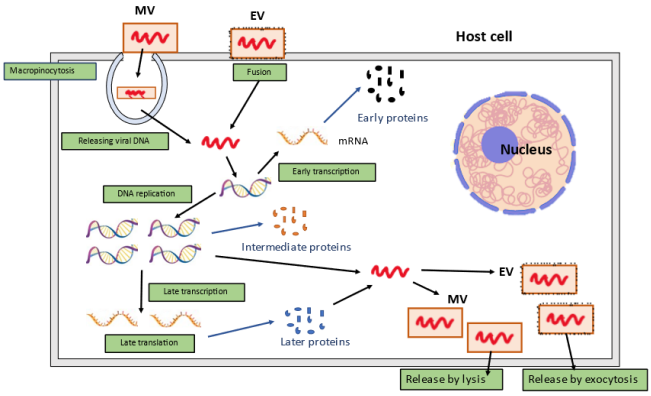


**Figure 2: Pathogenesis of Monkeypox**

As MPV is a DNA virus, it typically exhibits fewer mutations than RNA viruses such as HIV and SARS-CoV-2 [18]. During the 2022 MPV pandemic, the virus appeared to have undergone more mutations. It indicates that the virus is adapting to propagate more effectively. Surprisingly, the 2022 outbreak's isolates shared 40 mutations that distinguished them from their nearest variant. Researchers need to do further study to fully understand the mechanism of action of these recently generated mutations because of the alarming number of alterations in the MPV gene sequences from the current epidemic [19, 20].

**How does Monkeypox relate to smallpox?**

Clinical manifestations of Monkeypox mimic those of smallpox, an Orthopoxvirus outbreak linked to Monkeypox that has been eradicated. Smallpox was more transmissible and lethal since around 30% of patients perished. The final instance of spontaneously acquired smallpox occurred in 1977, and the disease was proclaimed eliminated globally in 1980 following a global vaccination and containment effort. All nations have discontinued routine smallpox immunization using vaccinia-based vaccinations for at least 40 years. Since immunization also protected people from Monkeypox in West and Central Africa, non-vaccinated populations are now more susceptible to infection with the monkeypox virus [21].

# CLINICAL FEATURES

**1. Transmission**

There is still a lack of information on the reservoir host of MPV. Nevertheless, African rodents are believed to have a role in the spread of disease. Transmission of MPV occurs by contact with skin lesions, bodily fluids, or respiratory droplets from infected animals [22]. **[Figure 3]** The virus can enter the body through a cut, scratch, or mucosal membrane (eyes, nose, or mouth). Scratches, bites, bush meat preparation, and direct or indirect contact with animal bodily fluids or lesion material are potential transmission routes [23].

Large respiratory droplets, such as those produced by sneezing and coughing, along with others, are responsible for transmitting diseases from person to person. Due to the limited range of respiratory droplets (just a few feet), sustained face-to-face contact is required for transmission. Exposure to viral lesions or bodily fluids and indirect contact with contaminated objects like clothes or infected linens are additional routes of human-to-human transmission [20].

Placental transmission (congenital Monkeypox) is another potential route of MTCT. It occurs when a mother comes into intimate contact with her newborn child. Although direct contact is required to spread Monkeypox, it is unclear if the virus may also be spread sexually. More research investigations using carefully monitored animal models are required to confirm or refute the sexual transmission of the virus. In 2020, researchers used mathematical modeling and comparisons with smallpox viruses to establish that MPV has an epidemic potential due to its reproduction number (R) being more than 1 [23]. Keeping sick and potentially infected people in isolation can help stop the spread of the virus [24]. Therefore, it is crucial to detect sick persons and quarantine the possibly infected person for a prolonged period, including up to 3 weeks, to restrict viral transmission.

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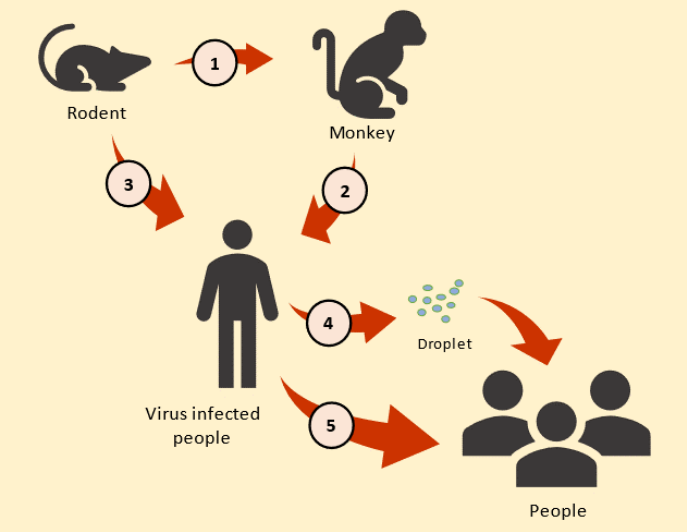


**Figure 3: Transmission of monkey virus from animal to human**

**2. Symptoms**

Similar to but less severe than extinct smallpox, human Monkeypox has three phases: incubation, prodrome, and rash [4]. Usually, the incubation period is 13 days in Monkeypox, followed by fever and lymphadenopathy, which marks the initiation of the prodromal phase [4, 25]. Lymphadenopathy mainly distinguishes Monkeypox from chickenpox and smallpox. The rash begins as macular and goes through the papular, vesicular, and pustular stages before scabbing and dropping off. The rash frequently affects the face and limbs but can also affect the genitalia [25]. Rash lesions along the whole body are at the same development stage, separating Monkeypox and smallpox from less common rashes such as chickenpox [4]. The lesions host a virus that is transmitted by direct contact. Secondary consequences of infection include bacterial skin infections, sepsis, gastroenteritis, encephalitis, bronchopneumonia, and keratitis [26]. Following the closure of ulcerated face lesions, clinical sequelae may include hypo- and hyper-pigmented atrophic scars, hypertrophic skin scarring, patchy baldness, and facial muscle deformity. Compared to the West African clade, the Congo Basin clade is linked to more severe illness and a higher fatality rate. Secondary bacterial skin infections are more common in HIV patients and are a leading cause of mortality. With only a 0.5% difference in genomic sequence, MPV variants may be broken down into two clades found in different African regions. The Congo Basin clade is projected to have a 10.6% higher case fatality rate in humans than the West African clade. Cynomolgus monkeys have a 3.5% higher incidence of fatality [27]. **Table 1** summarises the distinguishing features of Monkeypox, smallpox, and chickenpox infections.

**3. Diagnosis**

Diagnostic tests can be coupled with clinical and epidemiological data, including a patient's vaccination history, to detect Monkeypox precisely and efficiently. Conventional diagnostic procedures include virus isolation from a clinical specimen, electron microscopy, and immunohistochemistry. Lesion samples may be tested for Orthopox or Monkeypox using real-time PCR [28-31]. These assays detect viral DNA accurately. RT-PCR is highly successful in big labs, limiting usage in rural, resource-poor areas. Antibody-based diagnostics are also popular. Anti-Orthopox virus immunological tests cross-react to a spectrum of Orthopox viruses and might be helpful in regions where the causative virus is identified. Anti-Orthopox virus immunoglobulin G (IgG) alone cannot diagnose patients exposed to the virus, notably through vaccination. Serological assays that assess anti-Orthovirus IgM (IgM) are more important for identifying recent retrospective infections, especially in previously vaccinated people [32].

**Viral culture:** A patient sample cultivates a live virus and analyzes its genetic makeup. It provides a pure, living virus culture, allowing for accurate species identification. Chorioallantoic membranes will develop characteristic "pocks" when infected with an orthopoxvirus. Several days are required to finish the test. The identification of viruses requires further characterization [33].

**Electron microscopy:** When a poxvirus other than Parapox virus is stained negatively, a distinct picture of a brick-shaped particle is shown. Viral particles in a biopsy specimen, scab material, vesicular fluid, or viral culture can be identified using this method. Although Orthopox viruses and other members of the Herpesviridae family seem similar under the microscope, electron microscopy can tell them apart [34].

**Immunohistochemistry:** The test detects the presence of Orthopox virus-specific antigen that can be used to detect antigens in biopsies. This method can also eliminate or identify other suspicious chemicals [35].

**PCR, including real-time PCR:** These assays are extremely sensitive to the presence of DNA markers specific to Monkeypox. It can diagnose an active case utilizing lesion tissue from a patient. The test utilizes viral DNA, which is stable under dark, cold storage conditions. It is meant to target only the virus that causes Monkeypox [30].

**Anti-Orthopox virus IgG:** These tests evaluate the presence of anti-Orthopox virus antibodies. It is beneficial for evaluating a previous exposure to an Orthopoxvirus, such as vaccination against smallpox. This test does not detect the monkeypox virus specifically. Vaccination against smallpox in the past will influence the outcomes. The duration of response may vary [36].

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**Anti-Orthopox virus IgM:** Likewise, this is an antibody test. This test might be used to diagnose Orthopox virus in people previously vaccinated against smallpox. This test does not explicitly detect monkeypox virus [32].

**Tetracore Orthopox BioThreat Alert:** This point-of-care diagnostic test promptly detects an active case utilizing lesion material from the patient. Therefore, this test is not specific for the monkeypox virus and must be evaluated in endemic areas. It is less precise than PCR [37].

# TREATMENT AND MANAGEMENT

There are currently no clinically helpful particular treatments for monkeypox infection. The therapy includes supportive care, symptomatic management, and treating subsequent bacterial infections, as with most viral diseases. However, there are preventative steps that can aid in preventing an epidemic. For instance, the infected individual should remain isolated, wear a surgical mask, and keep lesions protected until all crusts fall off and a new layer of skin has formed [38]. The lesions should also be covered as much as possible during this time. For severe circumstances, medicines having established efficacy against orthopox viruses in animal trials and severe vaccinia vaccination sequelae may be evaluated for exploratory usage. The effectiveness of the oral DNA polymerase inhibitor brincidofovir, intracellular viral release inhibitor tecovirimat, and vaccinia immune globulin against the monkeypox virus is uncertain [4].

Several antivirals and vaccines of the next generation have been developed against smallpox and have demonstrated potential efficacy against the monkeypox virus [39 - 44]. Developing two antivirals with distinct modes of action and two vaccinations required roughly two decades. As a result, there are currently two FDA-approved vaccines and two FDA-approved antivirals that can be used against monkeypox [45].

# POSSIBLE VACCINE CANDIDATES

The U.S. govt. has considered three different smallpox vaccines for use in case of monkeypox outbreak: ACAM2000, Imvamune (JYNNEOS in the United States, Imvamune in Canada, and Imvanex in the European Union), and Aventis Pasteur Smallpox Vaccine (APSV). FDA licenses ACAM2000, whereas Imvamune and APSV are expected to be used under Investigational New Drug (IND) or Emergency Use Authorization (EUA) regulatory mechanisms. Although an EUA cannot be issued until an emergency determination and declaration are in place, the FDA can review submitted product data as a pre-EUA before a formal EUA request [46].

ACAM2000 and APSV are considered replication-competent vaccinia virus vaccines because of their ability to replicate in mammalian cells.

**Table 1:** Differentiating characteristics of Monkeypox, Smallpox, and chickenpox.

| Characteristics | Monkeypox | Smallpox | Chickenpox |
|---|---|---|---|
| Incubation period | 7-17 days | 7-17 days | 10-21 days |
| Prodromal period | 1-4 days | 1-4 days | 0-2 days |
| Appearance of rash | 14-28 days | 14-28 days | 10-21 days |
| Prodromal fever | Appears | Appears | It does not usually appear; if it appears, then it is mild |
| Fever | Present, the range is about 38.5°C to 40.5°C | Present, often goes beyond 40°C | Present, goes up to 38.8°C |
| Lymphadenopathy | Present | Absent | Absent |
| Lesions seen on palms or soles | Appears | Appears | Rare |
| Lesion distribution type | If infected, vaccinated individuals show fewer and smaller lesions, regional monomorphism type, and centrifugal distribution of rash. | Centrifugal | Centripetal |

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Replication-competent vaccines are associated with severe adverse events and produce infectious lesions that can cause vaccinia virus infections attributed to autoinoculation and inadvertent transmission.

In contrast, Imvamune is derived from a replication-deficient vaccinia virus strain that has been attenuated through multiple passages in tissue culture and has lost the ability to replicate in mammalian cells [47-50]. Replication-deficient vaccines were developed for use in persons at high risk for vaccination complications involving systemic viral spread (i.e., progressive vaccinia and eczema vaccinatum) [51, 52]. **[Figure 4].**

In this part, we shall discuss some of the vaccines that can potentially combat Monkeypox.

**1. ACAM2000**

First-generation smallpox vaccines, such as Dryvax, which were produced by replicating live vaccinia virus on the skin of living animals, are known to produce long-lasting protection, with particular antibodies and memory B cells being discovered more than 60 years after inoculation [53]. According to historical statistics, the vaccine offers 85% protection against human Monkeypox. However, the Dryvax vaccine is known to be associated with some serious adverse events [54]. Serious adverse events following vaccination with Dryvax occurred in the United States (2002–2005) were: myopericarditis, postvaccinal encephalitis, autoinoculation (nonocular), and ocular vaccinia [55, 56]. ACAM2000 is a live vaccinia virus vaccine derived from a plaque-purified clone of the same New York City Board of Health (NYCBOH) strain used to manufacture the Dryvax vaccine (discontinued). ACAM2000 is grown in African green monkey kidney (Vero) cells, made free of known adventitious agents [57], and further cultured in a chorioallantoic membrane or cell culture.

ACAM2000 is a second-generation smallpox vaccine created by Acambis that includes a replication-competent vaccine virus against smallpox (VACV) [58]. ACAM2000 is marketed as a lyophilized preparation of purified live virus containing the following nonactive excipients: 6–8 mM HEPES (pH 6.5–7.5), 2% human serum albumin USP, 0.5%–0.7% sodium chloride USP, 5% mannitol USP, and trace amounts of neomycin and polymyxin B.

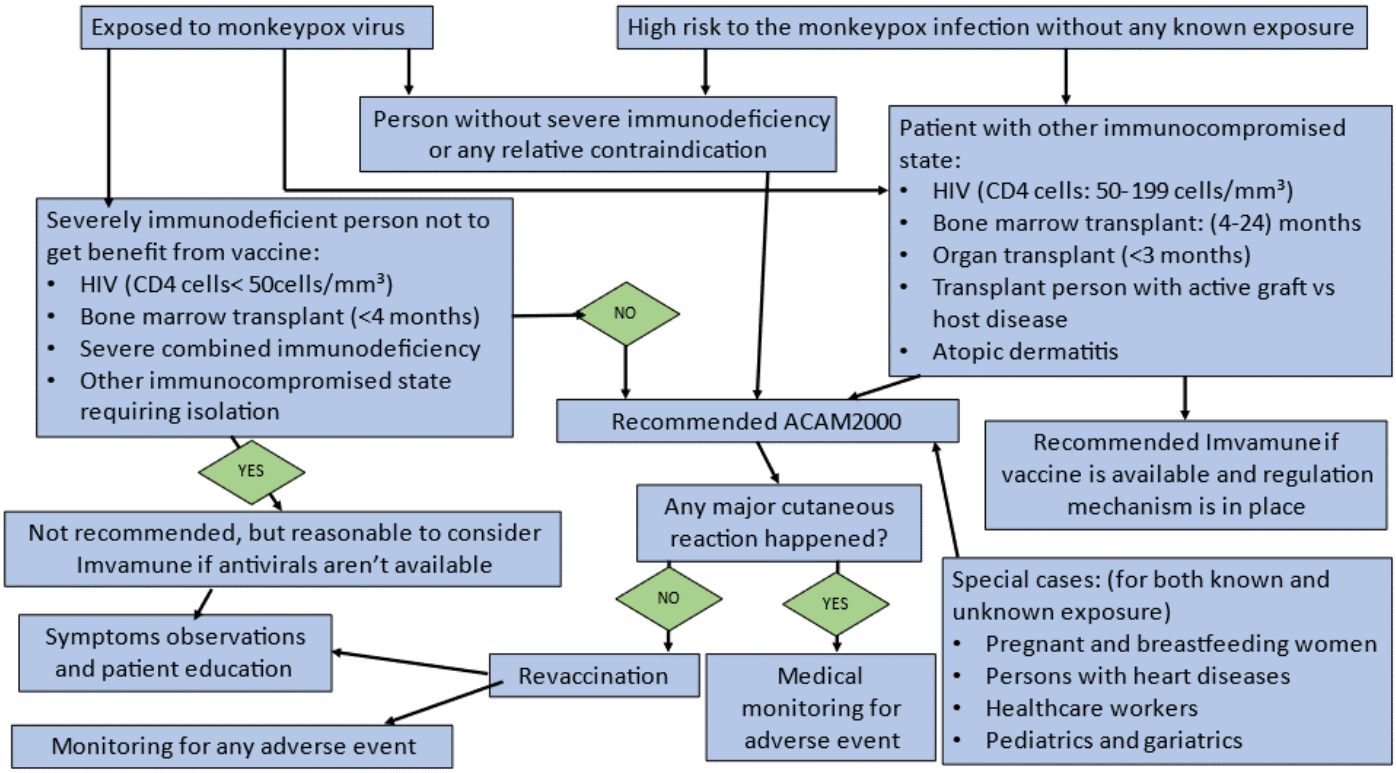


**Figure 4: Algorithm for the management of vaccination program against Monkeypox.**

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ACAM2000 is administered in a single dose (~2.5 uL) by the percutaneous route (scarification) using 15 jabs of a stainless-steel bifurcated needle in the upper arm. ACAM2000 has been licensed by the FDA since August 2007 for active immunization against smallpox disease for high-risk persons regardless of age. When individuals were vaccinated with ACAM2000 in the phase III clinical trial, the most common serious adverse event was myocarditis/pericarditis. An effective vaccination procedure results in a take at the vaccination site that contains a virus that can spread by autoinoculation and unintentional inoculation of close contacts. The vaccination is not recommended for those who are pregnant, have atopic dermatitis, or have immune system deficits, among other conditions [59].

### 2. JYNNEOS or MVA-BN

JYNNEOS is an attenuated, live, non-replicating smallpox and monkeypox vaccine that elicits humoral and cellular immune responses to Orthopox viruses. Vaccinia-neutralizing antibody responses in humans were evaluated to establish the effectiveness of JYNNEOS for preventing smallpox and Monkeypox [60]. This third-generation smallpox vaccine is developed using the modified vaccinia Ankara (MVA) strain, also known as MVA-BN [61]. An attenuated (weakened) variant of the vaccinia virus (MVA) is given as a pre-vaccine just before a replicating vaccination. It is done to lower the side effects in people at high risk with this vaccination program [62]. MVA-BN is considered safe for pregnant and nursing mothers [63]. This vaccine is indicated for Monkeypox and smallpox in adults 18 years and older [64]. The CDC states that immunization within four days of exposure might stop the start of the disease, and immunization within 14 days may lessen its severity.

In comparison to first- and second-generation smallpox vaccinations, the replication-defective (owing to the lack of two genes) modified vaccinia Ankara vaccine is a two-shot regimen, each dose containing 0.5mL given in subcutaneous route into the upper arm following four weeks interval. Persons at continued risk for occupational exposure to more virulent Orthopox viruses like variola or Monkeypox should receive a booster dose of JYNNEOS every 2 years after the primary JYNNEOS series. This vaccine is stored and handled within the -25°C to -15°C temperature range. Giving modified vaccinia, Ankara does not cause a skin lesion or increase the danger of local or widespread transmission, unlike live vaccinia viral preparations. Additionally, clinical studies have demonstrated that modified vaccinia Ankara is safe and promotes the generation of antibodies in patients with atrophy and weakened immune systems—conditions that are known contraindications to the injection of live vaccinia [65]. However, precautions must be taken while vaccinating immunocompromised patients, pregnancy or breastfeeding mothers, persons with cardiac risk factors, children, and adolescents below 18 years. Based on findings from animal challenge experiments and clinical research on the vaccine's immunogenicity, both smallpox and Monkeypox are now considered preventable diseases in the US [39].

The exact mechanism of the high efficacy of the MVA-BN vaccine against the Orthopox virus is still being unfolded in the therapeutic setting. However, the clinical effectiveness of this vaccine in generating an immune response has been evaluated through some clinical studies. This vaccine can elicit a humoral immune response, which has been evaluated through total IgG antibody enzyme-linked immunosorbent assay (ELISA), plaque reduction neutralization (PRNT) assays, and vaccinia virus-specific total IgG ELISA [32]. As a non-replicating vaccine, the viral vectors used are replication non-competent, which makes them sufficient to induce host immune responses but cannot replicate inside host cells. Thus, non-replicating vaccines are very safe as there is a very low risk of vaccine antigen-induced disease onset [66]. Also, there is evidence of improved protection conferred by MVA due to the significantly higher standard dose of MVA. Intriguingly, the improved protection conferred by MVA may depend on its loss of genes encoding immunomodulatory proteins, permitting enhanced innate immune responses and/or the more rapid development of an adaptive immune response [67].

### 3. The live attenuated LC16m8

Kaketsuken in Japan produces the replicating attenuated strain of vaccinia known as LC16m8. Hashizume, a researcher at the Chiba Serum Institute in Japan, passed the Lister strain through 45 iterations in primary rabbit kidney cells; the resultant variety was given the name LC16m8 (Lister clone 16, medium pocks, clone 8). Animal models have demonstrated that antibodies against the other membrane proteins are suitable for protection despite the shortened protein reducing the formation of an extracellular enveloped virus. In Japan, LC16m8 was authorized in 1975 following testing on more than 50,000 kids. LC16m8 vaccination causes a vaccine "take," although safety is comparable to MVA. LC16m8 produces neutralizing antibody titers against many poxviruses, such as Monkeypox and vaccinia [68].

The attenuated vaccinia virus vaccine strain LC16m8, having a mutation in the immunogenic membrane protein B5R, was compared to the original Lister strain. Monkeys were inoculated with LC16m8 or Lister and subsequently infected with Liberia or Zr-599. Immunized monkeys displayed no signs of Monkeypox after intranasal injection, but controls did. In the subcutaneous-inoculation paradigm, monkeys vaccinated with LC16m8 showed no signs of Monkeypox except for a small ulcer at the inoculation site, while nonimmunized controls displayed fatal and typical symptoms. These data imply that LC16m8 may generate monkeypox immunity in humans [69].

### 4. Aventis Pasteur Smallpox Vaccine

Aventis Pasteur Smallpox Vaccine (APSV), also known as "WetVax," is a liquid formulation of calf-lymph-origin vaccinia virus vaccine that has been maintained at -4°F (-

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20°C) since it was manufactured from the NYCBOH strain in 1956 and 1957. It was manufactured under the license of Aventis Pasteur. The formulation contains live vaccinia virus in 50% glycerol, 0.4% phenol, and 0.00017% Brilliant Green. No antibiotics or other additives are present. APSV is administered in a single dose (~2.5 uL) by the percutaneous route (scarification) using 15 jabs of a stainless-steel bifurcated needle that has been dipped into the vaccine. The site of vaccination is the upper arm over the deltoid muscle. Live replication-competent vaccines derived from viruses used during the smallpox eradication campaign, like Dryvax and APSV, are estimated to be >95% effective when used as pre-exposure prophylaxis. The most frequent severe vaccination complications are encephalitis, progressive vaccinia, and eczema vaccinatum [70].

**5. Protein-based sub-unit vaccines**

Recombinant protein antigen-based subunit vaccines may be risk-free for everyone and a valuable option, especially if live virus vaccines are no longer considered safe. If newly acquired Orthopox viruses produce major human diseases, such a subunit vaccine would be helpful in the pre-event environment to establish baseline protection. Additionally, if a completely replication-competent vaccine is required to manage a sizable smallpox epidemic, a protein vaccine may increase the safety of a live vaccination for vaccinia. As an alternative, it would be beneficial to increase immunity among the elderly with smallpox vaccinations as children, saving any remaining live vaccine for the most vulnerable. A trivalent (A33, B5, and L1 (ABL)) or tetravalent (ABL+A27 (ABLA)) protein-based adjuvanted vaccine has been shown by Buchman et al. (2010) to protect monkeys against deadly MPV exposure by inducing humoral immune responses. This study found that NHPs were protected from a fatal MPV challenge by as low as 2 doses of an adjuvanted protein-based subunit vaccination. In a situation where screening large groups to identify people with a higher risk of problems from live VACV inoculation is challenging, such a vaccine might be beneficial. Additionally, it might be utilized to immunize those refusing VACV and safely establish baseline protection against the poxvirus [71]. **[Table 2]**

# OTHER PROMISING OPTIONS

**1. Antiviral drugs**

Antiviral drugs that show promising efficacy against the monkeypox virus are DNA polymerase inhibitor brincidofovir (taken orally), vaccinia immune globulin (VIG) (taken intravenously), and intracellular viral release inhibitor tecovirimat (taken orally). Smallpox can be treated with two antiviral drugs, ST-246 (tecovirimat) and brincidofovir, both of which have received FDA approval in the United States [72]. Brincidofovir is an orally bioavailable lipid conjugate and an acyclic nucleoside analog. The antiviral mechanism of brincidofovir is the inhibition of poxvirus DNA replication. Brincidofovir is also a prodrug of cidofovir, which has been proven to be effective in treating cytomegalovirus (CMV) retinitis in HIV-positive individuals. In 2018, the FDA authorized tecovirimat (4-triflfluoromethylphenol derivative) for treating smallpox, and the CDC has an Expanded Access-Investigational New Drug (EA-IND) protocol allowing for its usage in non-variola orthopox viruses such as monkeypox virus [73]. Based on a few human monkeypox cases treated with the medications, tecovirimat appears to be efficacious, whereas brincidofovir is less effective. In addition to the aforementioned medications, other medicines are available that have potential antiviral potential to act against Monkeypox. Among them, inhibitors of nucleoside analogs are N-methanocarbathymidine, a 40-thio derivative of idoxuridine, and KAY-2-41. N-methanocarbathymidine (N-MCT) mediates its antiviral effect by the N-methyl-cytidine triphosphate metabolite, the synthesis of which requires viral thymidine kinase. 40-thio derivative of idoxuridine (40-thioIDU) exhibited activity against cowpox virus, chickenpox virus, and those resistant viral strains to cidofovir or tecovirimat. KAY-2-41 effectively prevented the spread of orthopox viruses when tested in a laboratory setting. Similar to Tecovirimat, the effectiveness of the tricyclic dicarboxylic acid derivative, NIOCH-14, against poxviruses was investigated. Despite similar *in vitro* performance to Tecovirimat against monkeypox virus, NIOCH-14 is still a promising antiviral alternative for the future due to its potent antiviral activity against several orthopox viruses and its relative ease of production compared to Tecovirimat [74].

Baker et al. examined prospective medications against the orthopox virus and grouped them by their antiviral capabilities into IMP dehydrogenase, S-adenosylmethione, reverse transcriptase inhibitors, DNA polymerase inhibitors, and protease inhibitors [75]. Among all orthopox viruses, Monkeypox was more susceptible to IMP dehydrogenase inhibitors named ribavirin and tiazofurin. Protease inhibitors (saquinavir, ritonavir, and nelfinavir) and reverse transcriptase inhibitors (zidovudine, efavirenz, and stavudine) were inert against orthopox viruses. However, two adenosine analogs (C-ca3-Ado and C3-Npc A) had a protective effect against the tested orthopox viruses, through viral replication. SAH hydrolase inhibitors have broad antiviral action, but none against cowpox virus *in vitro* [76, 77].

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**Table 2**: Currently available vaccines for Monkeypox

| Vaccine | Country | Dosing frequency | Vaccine type | Company | Date of approval | Indications |
|---|---|---|---|---|---|---|
| ACAM2000 (2nd generation) | USA | One dose, booster dose every three years | Live, replicating vaccinia virus, derived from NYCBOH strain | Emergent Biosolution | August, 2007 | Active immunization against smallpox for persons at high risk for infection |
| JYNNEOS (3rd generation) | USA | Two doses, booster in previously vaccinated | Live, non-replicating vaccine produced from Modified Vaccinia Ankara, attenuated (MVA) | Bavarian Nordic | September, 2019 | Smallpox and monkeypox disease prevention in adults above 18 years and older are at high risk. |
| APSV (3rd generation) | USA | Single dose | Live, replicating vaccinia virus, derived from NYCBOH strain | Sanofi Pasteur Biologics Co. | Investigational vaccine IND/EUA held by CDC | Strategic National Stockpile to be used in smallpox emergency |
| IMVANEX (3rd generation) | Europe | Two doses, booster in previously vaccinated | Live, non-replicating vaccine produced from Modified Vaccinia Ankara, attenuated (MVA) | Bavarian Nordic | July, 2013 | Active immunization against smallpox for persons 18 years & older |
| IMVAMUNE (3rd generation) | Canada | Two doses, booster in previously vaccinated | Live, non-replicating vaccine produced from Modified Vaccinia Ankara, attenuated (MVA) | Bavarian Nordic | 2013, extended to include Monkeypox in 2020 | Active immunization against smallpox, Monkeypox, and related orthopoxvirus infection in adults ≥ 18 years to be at high risk |
| Smallpox Vaccine (1st generation) | Canada | Single dose | Live vaccinia virus, derived from NYCBOH | Sanofi Pasteur Biologics Co. | Investigational strategic reserve | To be released in emergencies for active immunization against smallpox |
| LC16m8 (3rd generation) | Japan | Single dose | Live, replicating attenuated vaccine (derived from Lister (Elstree) strain) | Chemo-Sero-Therapeutic Institute (Kaketsuken) | 1975: Chiba Serum Institute, since 2013 Kaketsuken | Active immunization against smallpox |

**2. Targets of neutralizing antibodies**

Antibody responses against the vaccinia (smallpox vaccination) virus (VACV) protect against smallpox [78]. Vaccinia immune globulin (VIG) is a therapy for smallpox and vaccination complications [79]. Intravenous vaccinia immune globulin (VIG) may be explored for patients with severe monkeypox infection or as prophylactic in exposed persons with T-cell immunodeficiency. Orthopox virus generates two virions with different surface antigens; antibodies against both are needed for protection [80, 81]. The mature virion (MV) has a single membrane with 20 proteins, whereas the encapsulated virion (EV) has a second outer membrane with eight proteins [82]. Seven MV (A13, A17, A27, A28, D8, H3, L1) and two EV (A33, B5) proteins are neutralization targets [83]. Anti-B5 antibodies are the dominant EV neutralizing antibodies, however, none of the MV neutralizing antibodies are essential for MV neutralization or dominant in all vaccinated people. Instead, the smallpox vaccine's extremely repetitive neutralizing antibody responses may protect diverse human populations. Human monoclonal antibodies (mAbs) against D8, L1, B5, A33, A27, and H3 neutralized various Orthopox virus species. In a mouse model

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of deadly VACV infection, MV and EV-targeting mAbs combinations were more protective than VIG [84].

# PREVENTION

Primarily, Monkeypox is prevented by increasing public knowledge of risk factors and teaching individuals about the actions they may take to decrease their exposure to the virus. Currently, scientists are evaluating the viability and suitability of vaccination for the prevention and control of Monkeypox. Some nations have or are establishing programs to vaccinate those at risk, including laboratory technicians, fast response teams, and health care professionals [85, 86].

Reducing human-to-human transmission: Containing an outbreak requires surveillance and timely case identification. Close contact with infected people is the biggest danger during monkeypox epidemics. Health workers and family members are at risk of infection. Health personnel caring for patients with suspected or confirmed monkeypox virus infection or handling specimens should use infection control procedures. If feasible, use smallpox-vaccinated caregivers.

Qualified workers in well-equipped labs should handle human and animal samples suspected of having Monkeypox. Patient specimens must be triple-packaged per WHO guidelines for transporting infectious substances. Atypical monkeypox clusters in non-endemic nations without direct travel to an endemic location were identified in May 2022. Investigations are ongoing to discover the infection's source and restrict its spread. As the outbreak's origins are examined, all possible transmission mechanisms must be considered to protect public health.

Reducing the risk of zoonotic transmission: Most human illnesses have originated via animal-to-human transmission over time. Unprotected contact with wild animals, especially ill or dead ones, and their flesh, blood, and other components should be avoided. Additionally, all foods containing meat or animal parts must be adequately cooked before consumption.

Preventing Monkeypox through restrictions on animal trade: Some nations have enacted restrictions on the importing of rodents as well as non-human primates. Potentially infected captive animals with Monkeypox should be immediately quarantined and segregated from other animals. All animals that may have had contact with an infected animal must be isolated, handled with conventional procedures, and monitored for 30 days for monkeypox signs [87].

# DISCUSSION AND FUTURE PERSPECTIVES

Monkeypox is a misnomer because rodents, not monkeys, are its main natural reservoir in absolute numbers and percentages. Human Monkeypox behaves like a classic zoonosis in that most cases are original infections from animals, and the causative agent cannot survive secondary transmission in humans. Human infections can be clinically indistinguishable from smallpox, chickenpox, and other vesiculopustular rashes. Human Monkeypox is characterized by significant lymphadenopathy, although laboratory testing is required for diagnosis [88, 89].

In the post-smallpox period, human Monkeypox is the most critical Orthopox virus infection. Monkeypox incidence increased as 1980s surveillance programs strengthened. Although the documented rates of monkeypox transmission and mortality increased considerably from the 1970s to the 1990s, detailed examination reveals that these fluctuations are an artifact induced by changing case definitions in different epidemiological contexts [90]. Active surveillance data from 1981–86 seem the most accurate [91]. Prevention rates for human monkeypox vaccinations hover around 85%, but there is presently no treatment that is shown to be successful [92]. However, early detection of patients is crucial to controlling possible outbreaks. Thus, speedy diagnosis is still important. Molecular biology has advanced so that MPV may no longer have such a low potential as an agent of biological warfare [89].

The WHO has warned that the world may face another significant challenge following the COVID-19 epidemic and the Ukraine-Russian war [92]. Globally, 1,475 monkeypox cases have been confirmed through June 10, 2022. The UK has 366 monkeypox cases. Spain (n = 275), Portugal (n = 209), Canada (n = 112), and the USA (n = 49) have seen a rise in cases. MPV epidemic is a global problem. Scientists, epidemiologists, doctors, and policymakers are concerned about Monkeypox. UK health officials advise monkeypox patients to self-isolate. Belgium announced a three-week quarantine for monkeypox patients. Vaccinations, adequate cleanliness, self-isolation, and quarantine can control this disease. Men having sex with men (MSM) are at a higher risk of additional STDs, including HIV/AIDS. It is unique to the present outbreak and was not documented previously [94].

Clinical virologists do not know if MPV is sexually transmitted. MPV has expanded among PLWH on cART in Spain with completely suppressed viremia [48]. MPV and HIV coinfection pathogenesis must be monitored. How HIV-positive people's immune systems will react to MPV is unknown. Other comorbidities, such as coinfection with MPV and hepatitis B or C, will need constant monitoring. The COVID-19 epidemic is causing economic problems. The rise of monkeypox infections in the US and globally threatens economic growth. If Monkeypox is not contained promptly, the economy will suffer. Even among the wealthy and educated, illness dynamics are poorly understood. People have ignored illness screenings and quarantines. Better public health initiatives, including animal model research, are needed to prevent the virus's spread. Children, seniors, and pregnant women are susceptible to transmission [94].

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Overall, two takeaways can be drawn from this human monkeypox outbreak. To begin, we can no longer afford to discount the threat posed by rare, regional, or ostensibly vanquished infectious pathogens. Second, scientific knowledge and the rising worldwide mobility of people, animals, and other possible disease vectors necessitate revisions to government legislation, especially those governing trade in wild animals. The greatest method to ensure this does not happen is to improve public health resources worldwide.

## CONCLUSION

Monkeypox cannot be eradicated since its unknown animal reservoir and virulent forms may exist. Non-synonymous mutations in new viral isolates garner much attention, but OPXV evolution history tells us that MPXV gene loss events should also be carefully explored. Current epidemic MPXV genomes are still being examined. MPXV evolution requires a deeper understanding of poxvirus evolving mechanisms and gene functions. In endemic locations, a safe, noninfectious vaccine could prevent illness suffering. Research on novel and existing vaccines that are effective against Monkeypox should be carried out with greater intensity.

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## AUTHOR'S CONTRIBUTION

Conceptualization: MSA, Methodology: MSA, AS (Abida Sultana), and AS (Arifa Sultana), Software: AS (Abida Sultana), AS (Arifa Sultana), NJS, Validation: MSA, AAC, and SK, Formal analysis: MSA, AAC, and SK, Investigation: AS (Abida Sultana), AS (Arifa Sultana), NJS, and MSA, Resources: MSA, AAC, and SK, Data curation: MSA, AS (Abida Sultana), AS (Arifa Sultana) and NJS, Draft preparation: AS (Abida Sultana), and AS (Arifa Sultana), Review and editing: MSA, AS (Abida Sultana), AS (Arifa Sultana), and NJS, Visualization: AS (Arifa Sultana), and NJS, Supervision: MSA, AAC, and SK. All authors have read and agreed to the published version of the manuscript.

## ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. The Journal and Publisher will not be responsible for any copyright infringement or plagiarism issues.

## CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

## DATA AVAILABILITY

The data used for this study are available from the corresponding author upon reasonable request.

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