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Review Article

Exploring Monkeypox: An In-depth Examination of Its History, Current Status, and Prospects

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Abstract

Introduction: Neglected infectious infections have become more prevalent in recent decades. One example is the monkeypox virus (MPV), genus *Orthopoxvirus*, capable of spreading between animals and humans. Human monkeypox (MPX) outbreaks have occurred in numerous countries, posing an escalating threat to global health.

Methods: Relevant articles were gathered till July 2024 on the MPV using a variety of pertinent information sources, including Elsevier, Science Direct, PubMed, ACS articles, SciFinder, Wiley, and Google Scholar. BioRender was used for creating scientific images on MPV and chemical structures of antivirals were created by using ChemDraw software. Clinical studies information related to MPV was taken from the clinicaltrials.gov website. This review was conducted succeeding PRISMA guidelines to encapsulate the literature accessible on the adopted review topic.

Discussion: It is essential to comprehend the variables influencing the MPV's spread to ensure preparedness for healthcare, and to develop protection against possible threats. The field of MPX emergence has expanded, with a significant increase in infectivity and notable changes in epidemiology in recent years. Collaborative efforts in sharing resources and data globally are essential to facilitate the study of viruses and develop effective countermeasures. To mitigate the serious consequences of new outbreaks and their spread, it is imperative to enhance our understanding of this infection, particularly focusing on prevention strategies, clinical courses, and epidemiology.

Conclusion: This article offers a concise review of literature spanning from historical accounts to the latest advancements in knowledge regarding the epidemiology, etiology, transmission, clinical characteristics, available treatments, and vaccines for human MPV infection. It consolidates data on the most recent developments in the prevention as well as management of human MPX, providing a detailed overview for reference.

Keywords: monkeypox, pathogenesis, *Orthopoxvirus*, epidemiology, antiviral, prevention

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1. Introduction

Monkeypox (MPX), a zoonotic virus, belongs to the family *Poxviridae* and genus *Orthopoxvirus*, distinguishing itself in this category. The *Poxviridae* viruses are big with double-stranded DNA-encased and have been found in various animal species [1]. While primarily hosted by nonhuman primates, rodents, and rabbits, they occasionally transmit to individuals, increasing the danger of transmission from person to person [2]. *Entomopoxvirinae* and *Chorodopoxvirinae* are the two divisions of the *Poxviridae* family, targeting insects or vertebrates, respectively [3]. Though less lethal (4–25%) than smallpox, MPX remains easily transmissible from animals or natural sources and can be manipulated for increased virulence [4]. Even at low viral levels, MPX significantly dampens 80% of T-cell-mediated cytokine response, suggesting the virus possesses immune response suppressors [5]. While there are eight genera in *Chordopoxvirinae* (*Orthopoxvirus*, *Parapoxvirus*, *Avipoxvirus*, *Capripoxvirus*, *Leporipoxvirus*, *Suipoxvirus*, *Molluscipoxvirus*, and *Yatapoxvirus*), there are only three genera in *Entomopoxvirinae* (*Entomopoxvirus* A, B, and C). The most researched of these is the *Orthopoxvirus*, which harbors the vaccinia virus (VACV) and the variola virus (VARV) [6]. Highly conserved viruses, like those belonging to the *Orthopoxvirus* genus, can infect humans and potentially cause fatal outcomes [7].

Poxviruses, characterized by their large, linear, double-stranded DNA, reproduce exclusively within the cytoplasm of cells and are found in the cells of vertebrates and invertebrates. These viruses exhibit genome sizes ranging from 130 to 360 kilo-base pairs (kbp). Unlike typical DNA viruses that heavily rely on cellular proteins for replication and gene expression within the nucleus, poxviruses have evolved alternative mechanisms [8]. Instead, they are reliant on virus-encoded proteins for their cytoplasmic replication processes. Studies by Moss, highlight the significance of these virus-encoded proteins in facilitating poxvirus replication within the cytoplasmic environment [9]. Genes at the termini of the poxvirus genome are primarily involved in virus-host interactions. At the same time, those located in the central region play essential roles in processes including virus assembly and transcription [10]. The large size of poxviruses poses challenges for their penetration through host defenses, such as gap junctions. Consequently, viruses like MPX must employ broad survival strategies within the host environment due to their size, hindering rapid replication. This characteristic prompts an earlier alert from the immune system of the host, facilitating to create robust immunological response [11].

2. Methods

In this review, all the information related to the monkeypox virus (MPV), such as the epidemiology, etiology, transmission, clinical characteristics, available treatments, and vaccines for human MPV infection has been included. An extensive search was conducted using online databases such as Elsevier, PubMed, Science Direct, and Taylor and Francis to locate the pertinent literature. The scientific figures were created by the bioRender software and the chemical structures of antivirals were created using ChemDraw software. The

information from the ongoing and completed clinical trials was gathered from clinicaltrials.gov website. The search strategy and protocol are listed below as steps:

Step 2.1. Search Strategy and Protocol

The search strategy has been organized by choosing the source databases and appropriate search – terms such as, “Monkeypox,” “Orthopoxvirus,” “history of monkeypox,” “etiology,” “transmission,” “pathogenesis,” “treatment of monkeypox,” “vaccines for monkeypox,” “mpox or pox,” “current status of monkeypox,” “clinical trials on monkeypox” and “Prevention and management of monkeypox.” Also, the whole paper has been included based on particular inclusion criteria like articles relevant to the research topic. Meanwhile, the specific papers have been removed with respect to specific exclusion criteria such as papers published before 1965 and papers in other languages except English.

The search strategy has been structured by selecting the source databases and the relevant search terms. The study emphasizes to cover the relevant review papers, and no particular data range was used. In the present study, a specific selection of numerous online databases has been considered such as Elsevier, Science Direct, PubMed, and Taylor and Francis. Similarly, this present study emphasizes reviewing all the relevant papers in literature. The scientific databases were utilized to perform the analysis, and those databases were chosen due to various reasons. Those reasons are that it will deliver excellent coverage of associated literature and are the most famous scientific databases. The selected databases are,

- PubMed (https://pubmed.ncbi.nlm.nih.gov)
- Science Direct(https://www.sciencedirect.com/)
- Elsevier(https://www.elsevier.com/en-in)
- Taylor and Francis (https://www.tandfonline.com/)

Step 2.2. Inclusion Criteria (IC) and Exclusion Criteria (EC)

IC:

The inclusion criteria were utilized to determine which articles must be included in the review for analysis and the criteria utilized in this review are listed below:

- The paper must take account of review papers and literature reviews, which were issued after 1965 and should contain the appropriate content
- The complete research work should be associated with the objective of this study.

EC:

The exclusion criteria must be utilized to determine which articles must be omitted from the review. The exclusion criteria are stated below:

- If the articles or papers were duplicate reports or papers of similar research studies
- The informal literature reviews that have no suitable research question, no defined search process, and no proper data extraction process
- If the paper or review work is written in other languages instead of English language.

Step 2.3. Article Selection Based on PRISMA Guidelines

The below table enumerates the steps involved in evaluating and picking out the relevant papers, articles, or reviews for this study. The filtration levels or stages in refining the entire papers were described in Table **1**.

Table 1: Summary of phases of assessing and choosing relevant papers for this study.

Filtration levels	Technique	Assessment standards
Identification of relevant review papers	Decide all the related researches from the database	Search terms are included
Identification of relevant reviews in a stipulated time period	The removal of studies performed based on a publication date.	Exclude the studies that are published before 1965
Employing 1st filtration	Choosing only related review titles to the keywords	If the review title consists of inputted keywords, like “Monkeypox current status, history, pathogenesis, etiology, clinical trials, vaccines, prevention and management, and future aspects”
Employing 2nd filtration	Removing repeated or duplicated results	If two papers or more than that resemble a single paper, then duplicated publications or papers were abandoned.
Employing 3rd filtration	Selecting only related results based on the abstract	If the abstract of the study seems relevant to the present study, it is included or else excluded.

2.3.1. Procedure of Selecting Studies

When the existing studies fulfill the search strategy and the inclusion criteria, then the next step involves the selection of the studies. This step is usually performed in two stages. Initially, the reviewers examine the studies whether it matches the keywords and contains related content. In the second stage, the reviewers usually read the content of the abstract and check if it matches the requirements. The standard process for choosing studies to be included in the review are as follows,

- Merge search results

- Examine the titles and keywords
- Recovering the full text of the selected articles
- Associate the links of multiple reports of the same research
- Read the abstract carefully and examine whether it satisfies the requirements
- Explore the full-text documents of the selected articles
- Inspecting whether the studies satisfy the inclusion criteria and re-investigate if some content is missing or tampered
- Refinement of studies
- Making a final decision regarding which studies need to be integrated
- The selected studies are documented and reviewed.

In accordance with the process of study selection, which is illustrated in Figure **1**, nearly 300 papers were determined after searching out the publication venues. Among those reviewed papers, few papers were neglected or excluded based on the publication date and other languages, and around 250 review papers were considered. Further, the studies were eliminated because inappropriate keywords and titles were added to 188 papers. The papers are refined based on the title and abstract using the eligibility criteria. Moreover, by applying the fourth filtration, the studies were refined to 105 papers as the finalized ones. In this stage, the research abstracts are read and then assessed to neglect irrelevant research papers. After the evaluation, the count of research papers was minimized and refined for review analysis to 90. Figure **1** illustrates the PRISMA guidelines for search process.

Step 2.4. Quality Evaluation

The topic's relevancy has been appraised in accordance with the exclusion and inclusion criteria. All the selected 90 papers were carefully considered with specific parameters. Each of the eligible papers encompass the analysis of the MPX virus's current status, history, etiology, pathogenesis, clinical management, prevalence, prevention, clinical trials, vaccines, and future prospects.

Step 2.5. Data Analysis

Every single paper selected for this study was analyzed in accordance with scope, area of topic, and summary. Based on this analysis, the chosen papers were classified into various broad areas such as history, etiology, clinical features, prevalence, pathogenesis, antiviral agents in the treatment of MPX, etc.

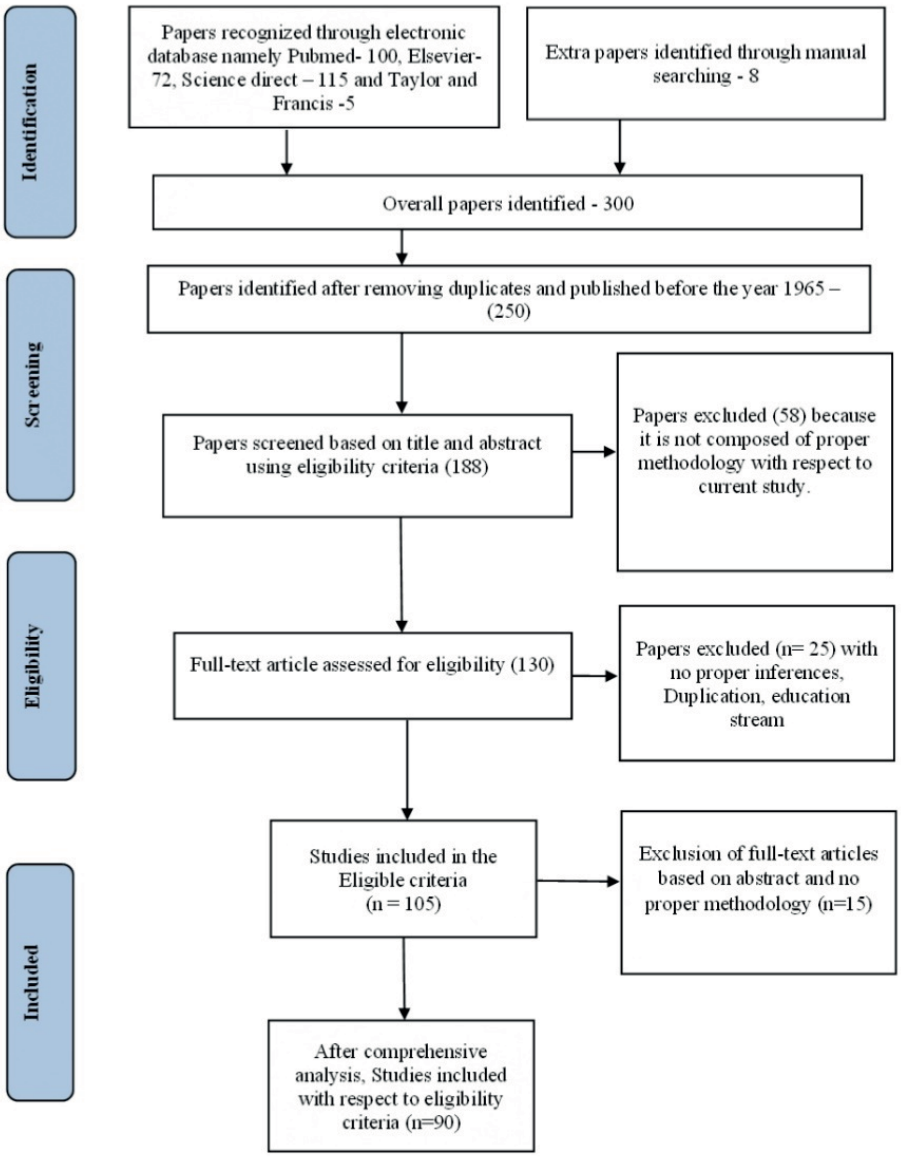

Figure 1: PRISMA guidelines for search process.

3. Mapping History of MPX

Human MPX, a rare and endemic illness, typically manifests in human settlements in Western and Central African tropical rainforests. The origin of MPX is traced back to a smallpox infection outbreak between cynomolgus monkeys in 1958 in Copenhagen, where the MPV was first identified [12]. The inaugural human MPX instance occurred in Africa in 1970 affecting a 9-month-old boy, detected through the national program for smallpox surveillance and eradication [13]. The occurrence of MPX cases in regions traditionally unaffected by the virus has raised concerns due to its association with the deadly VARV, or smallpox, which claimed millions of lives over centuries [14]. Between 1970 and 1979, 47 human MPX cases were reported across various African countries [15]. With 47 cases dispersed throughout six Midwest

states in 2003, the United States experienced its first known epidemic outside of Africa. Contact with sick small mammals from Ghana and infected prairie dogs served as the means of transmission [16]. Notably, MPV can be divided into two distinct clades: the West African and the Congo Basin clades. In comparison to the Congo Basin clade, which has case fatality rates of about 10%, the latter is thought to be less virulent, with rates ranging from 1% to 3%. Recent studies, including those in 2017-2018 MPX outbreak in Nigeria, have employed phylogenetic analysis, constructing a tree encompassing 29 MPV isolates and 23 other *Orthopoxvirus* isolates, shedding light on the virus's evolutionary dynamics [17].

According to Saied et al., the approximate MPV death rate from the West African clade ranges between 3% and 6%, causing the current outbreaks [18]. Two occurrences of secondary MPX infection in patients who had visited Nigeria to the United Kingdom (UK) were notified in 2018 [19]. From January to September 2020, the Democratic Republic of the Congo (DRC) recorded 4594 suspected cases, with Nigeria ranking as the second most affected country [20]. As of May 21, 2022, 13 nonendemic nations around the world—the United Kingdom, the United States of America (USA), Canada, Australia, France, Belgium, Italy, Portugal, Germany, Netherlands, Sweden, and Spain—had confirmed 92 cases of MPX [21]. By September 27, 2022, the World Health Organization (WHO) obtained reports of over 66,000 suspected or confirmed cases, predominantly from Europe and the Americas, spanning 100 countries [22]. On November 28, 2022, the WHO suggested replacing the term "monkeypox" with "mpox," with a 1-year transition period during which both terms will be used interchangeably [23]. As of June 5, 2023, the WHO documented a total of 146 deaths and 87,929 laboratory-confirmed MPX cases. Since May 2022, numerous cases have been documented from countries where MPX transmission was previously undocumented [24].

4. Etiology

MPV is a DNA virus that causes human MPX , and is a member of the *Orthopoxvirus* genus in the *Poxviridae* family [25]. MPV is one of four *Orthopoxviruses* capable of infecting humans, the others being VARV, cowpox virus, and variola minor virus, with smallpox caused by the latter three now eradicated [26]. Transmission happens when a person or object comes into close contact with an infected one, including skin lesions, secretions, or bodily fluids [27]. Direct contact through inhalation or saliva with diseased creatures or their bodily fluids, primarily spreads human MPV. Person-to-person transmission, often observed in hospice or family settings [28], can occur, as can zoonotic transmission through biting or scratching [29].

According to a WHO report, MPX can be transferred through vertical transmission via the placenta between the mother and the fetus, with severe outcomes for newborns reported, including miscarriage and fetal death [30-32]. Numerous studies have revealed that air travel is the primary source of infectious disease transmission. The transmission of infectious diseases originates from air travel [33]. Other modes of transmission are when hunting for wild animals, hunters may also come into direct contact with the bodily

fluids of diseased animals, and the virus can even spread to people when cooking meals with carcasses [34]. Anogenital mucosal membrane contact [35] and indirect transmission through contaminated surroundings (bedding, clothing, crockery, bathroom linens, etc.) are also possible routes of MPV transmission [36]. The Center for Disease Control and Prevention (CDC) notes potential transmission through various activities, including sexual intercourse, hugging, and kissing, possibly facilitated by genetic alterations in MPV [37]. Figure **2** Illustrates the causes of MPX infection.

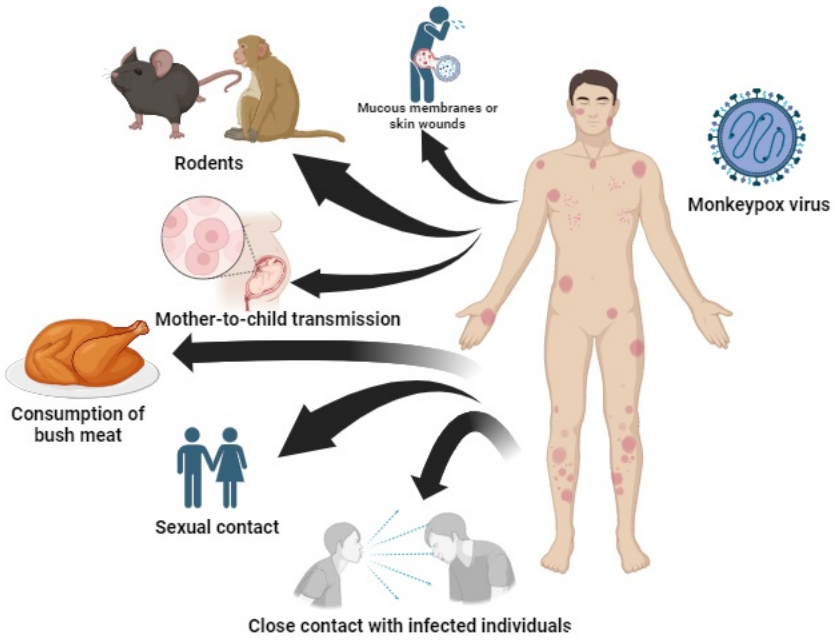

Figure 2: Causes of monkeypox infection.

5. Clinical Features

MPX symptoms resemble those of smallpox, but with a little variation in the VARV. Patients with MPX may present with a rash like varicella, or chickenpox, making diagnosis challenging. The incubation period of MPV is 2 to 3 weeks [26]. Skin eruption and invasion are the two stages. The initial stage, referred to as the invasion stage, starts in the first week and is marked by fever, myalgia, arthralgia, asthenia, and lymphadenopathy. The primary characteristic that sets human MPX apart from other *Orthopoxviruses* is lymphadenopathy, which is not caused by measles, smallpox, or chickenpox. Fever is followed by the skin eruption phase, during which rashes are primarily seen on the trunk, face, and extremities [38]. The face is typically affected first, then the hands, feet, mouth, cornea, and genitalia. Figure **3** depicts the five successive stages of the MPX rash, which are marked by crusts, pustules, vesicles, macules, and papules [38]. Headache, low energy, fever, chills, sore throat, muscle pain, and lymphadenopathy are some of the early signs of MPV infection. Usually, the rash develops a few days following lymphadenopathy and fever (Figure **4**).

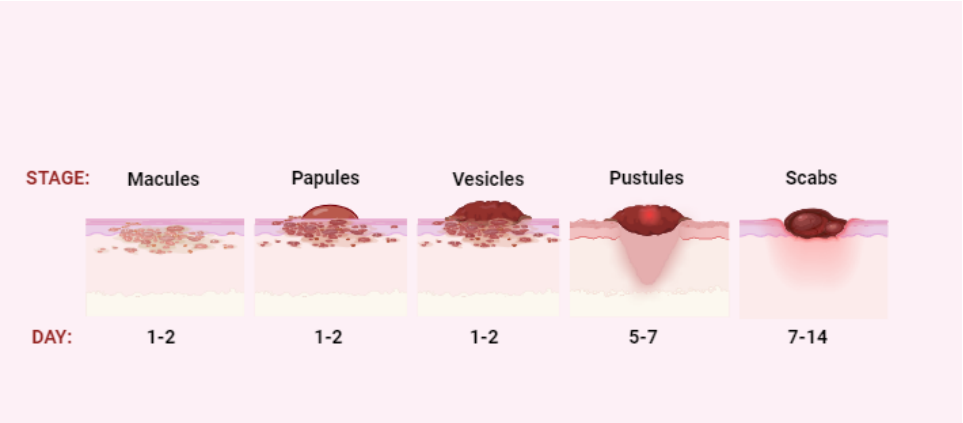

Figure 3: Five consecutive stages of the monkeypox rash-macules, papules, vesicles, pustules, and crusts.

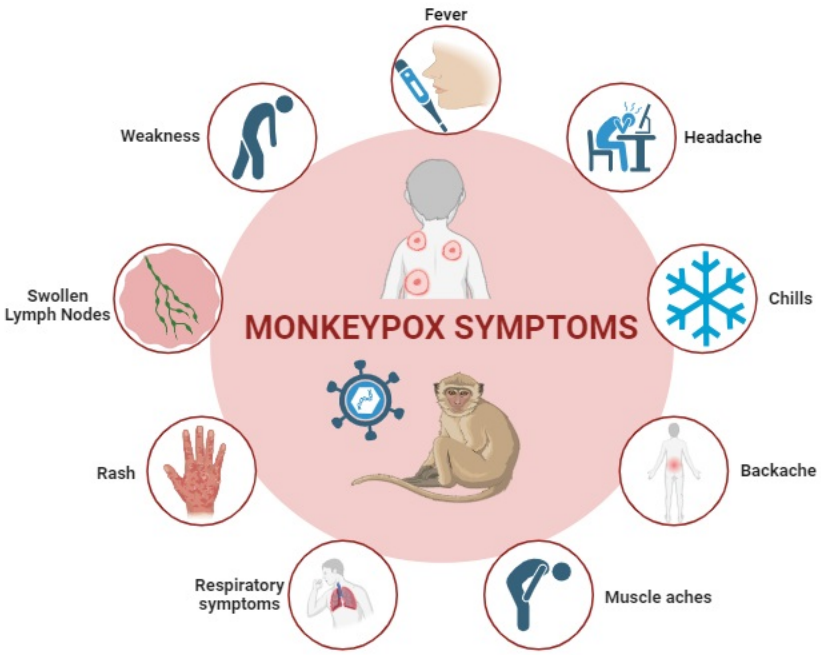

Figure 4: Signs and symptoms of monkeypox infection.

6. Prevalence

In 1970, the first recorded human infection of MPX occurred, marking the beginning of a significant rise in confirmed, possible, and probable cases [39]. MPX typically remains confined to Africa, with occurrences outside the continent often tied to animal trafficking or international travel [40, 41]. In 2022, there was a transformational shift in the disease's epidemiological paradigm. The virus invaded many foreign places in Europe and North America after spreading outside of its endemic areas [42]. The degree and transmissibility of the disease are associated with genomic variants of the MPV seen in samples from the Democratic Republic of the Congo (DRC) [43]. Historically, zoonotic reservoirs like

rodents and nonhuman primates were the primary sources of infection in past epidemics. Person-to-person transmission, or secondary transmission, was relatively uncommon, accounting for only 28% of cases in the DRC between 1981 and 1986 [44].

The two primary clades of MPV, which vary in severity, are indigenous to Africa. The Central African clade exhibits a case fatality rate of 10.6%, whereas the Western African clade displays a lower rate of 3.6% [45]. The infection initially spread to 72 individuals across several states, connected to a consignment of strange creatures originating in Ghana [46]. In 2003, families in the US experienced an outbreak after purchasing prairie dogs that were affected via imported rats from Ghana. Despite claims of "no epidemiological linkages across states," the outbreak likely stemmed from an underlying epizootic [47]. The current outbreak has disproportionately affected men compared to previous epidemics [48].

MPX outbreaks predominantly occur in rural areas, particularly small villages that are close to or within damp tropical forests, known as the human-animal interface [49]. Genetic analysis of samples from the Nigerian outbreak of 2017–2018 revealed a high degree of similarity to a 1971 sample from the state of Abia [50]. Various rodent species were found infected during a significant MPX outbreak linked to animals imported into an animal trading company [51]. Recent research underscores the complexity of MPX epidemiology in contrast to other viruses such as SARS-CoV-2 or human immunodeficiency virus (HIV) [52]. . The virus, previously prevalent in Central and West Africa, saw a sudden increase in worldwide exposure and illness outside of the African continent in 2022, sparking a multicountry epidemic with substantial fatality rates [53]. Between 1970 and 1980, 59 reported and confirmed cases were thoroughly investigated, and their findings were integrated into a comprehensive database for ongoing analysis. After smallpox was declared eradicated in 1980, the DRC implemented rigorous surveillance for MPX over 5 years, during which 338 new infections were identified and scrutinized [54].

The WHO called a meeting on May 20, 2022 of technical advisory groups and specialists to investigate the reasons for the outbreak. They also announced new guidelines on contact tracing, surveillance, and case investigation. The research communities, as well as national and international public health organizations, are looking into the cause behind the outbreak's wider geographic spread [55]. The WHO has received reports of MPX cases from 116 member states across all six regions of WHO. The WHO stated MPX a Public Health Emergency of International Concern on July 23, 2022, prompting swift action from the US Department of Health and Human Services (HHS) on August 4, 2022 [56, 57]. Due to the outbreak of human MPX in Australia, America, and Europe on May 7, 2022, among people who had never visited an endemic area before, international health authorities expressed concerns about MPX potentially evolving into a global pathogen and spreading beyond Africa [58]. As of January 31, 2024, the WHO had received reports from 93,921 laboratory-confirmed illnesses and 662 probable cases, including 179 deaths [30] (Figure **5**).

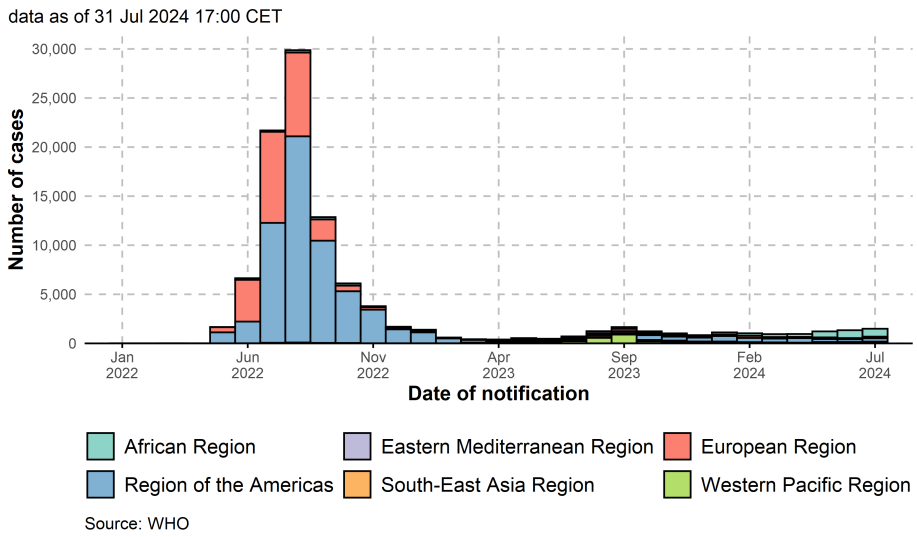

Figure 5: Epidemic curve shown by month for cases reported up to July 31, 2024 (Source: WHO).

7. Pathogenesis

The highly contagious MPV can spread through intimate contact between people and animals, marking the initial stage of the pathogenesis and pathogenicity of the virus. The entry of virus particles into human host cells is the first stage of viral pathogenesis. The association between the host cell's reaction and the virus has been the subject of extensive research, which has revealed a substantial genetic variation in the genes encoding Clade I and II. This discovery helps elucidate previously observed variations in pathogenicity displayed by these strains. Many genes found in the genomes of the MPV encode host-response modifier (HRM) proteins, known as MPX virulence factors. Various routes of MPV introduction into the human body have been proposed, including respiratory (oropharyngeal nasopharyngeal), intradermal, or sexual transmission [59]. Following inoculation, the virus multiplies at the point of entrance, quickly disseminates to the lymph nodes, or likely enters the bloodstream, reaching the bone marrow, tonsils, and spleen, leading to primary viremia [60].

Furthermore, the Congo clade of the MPV exhibits greater virulence and pathogenicity compared to the clade of West African, there may be differences between the two clades [61]. Although MPV has been experimentally infected in nonhuman primates, African dormice, ground squirrels, and prairie dogs, due to the intricate requirements for husbandry and the accessibility of immunoreagents, these models are limited [62]. It is uncertain that the establishment of MPV will become a new illness that replaces smallpox in the human population. Possible paths for the emergence of MPX in humans could be illuminated by studying the smallpox evolution, a virus that is unique to individuals [63]. With the notable exception of the interleukin1 beta gene, the majority of the changes in the Central African clade were discovered to have occurred in the noncoding area of the genome. The mutation causes the immune system to function less effectively and reduces the binding of cytokines. The development of MPV and the severity of the

illness may be significantly influenced by the mode of transmission. The degree of the disease may be affected by mutations in the *CAR15c/18c* sequences [64].

Large viruses with double-stranded DNA are called poxviruses. Cells from vertebrate and invertebrate multiply in the cytoplasm. Using CD8+ cells, the big *Orthopoxviruses* can stimulate immune response early. The infection of virus is self-restraining because the successive generation of gamma interferons, MCP-1, IL-1rs, IL-6, IL-8, and IFN-γ, suppresses the virus's replication. A suspected case in the laboratory diagnosed by using *Orthopoxvirus* DNA was tested using polymerase chain reaction (PCR) on the lesion fluid, brick-shaped poxvirus virions were identified by electron microscopy, and anti-*Orthopoxvirus* IgM and IgG were detected by enzyme-linked immunosorbent assay (ELISA) 5-8 days after the rash appeared, respectively [65].

Additionally, genetic alterations and mutations have changed the virus's pathogenicity. According to meta-analysis studies, children were most affected by MPV in the 1970s. The average age of individuals affected had increased as a result of genetic mutation; in 2010, it was reported that the average age of those infected was 21. The MPV was undergoing fast alterations, which might make it more deadly and hazardous [66]. In cynomolgus monkeys, the pathophysiology and virulence of two strains, the West African strain and the Congo Basin strain of MPV were assessed. The results indicated that compared to Liberia, Zr-599 was more virulent [67].

8. Antiviral Agents in the Treatment of Monkeypox

Several antiviral medications show potential in treating MPX infection, but their efficacy remains uncertain [68]. Treatment is recommended for individuals infected with the MPV who are currently experiencing severe illness or who may be at heightened risk of developing serious complications. This includes immune-compromised individuals, pediatric populations, individuals with a history of dermatitis, those with exfoliating skin symptoms, pregnant women, or individuals with atypical MPV infections affecting sensitive areas such as the eyes, mouth, or genital and anal regions. Most patients receive supportive and symptomatic care, as there is no known treatment for smallpox or MPX. However, antiviral medicines like Cidofovir, Tecovirimat, and Brincidofovir may be effective against MPX due to genetic similarities with related viruses [69]. Figure **6** depicts the chemical structures of various antivirals used in treating MPV infection.

8.1. Tecovirimat

Tecovirimat, formerly known as ST-246, is a small chemical compound that inhibits virus entry and exit and has demonstrated efficacy against various *Orthopoxviruses*, including VARV, camelpox, cowpox, in vitro and in vivo MPX, VACV, and mousepox [70]. It is the most commonly used antiviral medication for

individuals with MPX infection, having been discovered through high throughput screening and approved by the US FDA in 2018 [71]. Tecovirimat functions by blocking the VP37 viral envelope protein, which stops the virus from maturing and escaping from infected cells, as well as impeding virus distribution within the host [72]. While its efficacy against MPX in humans has not been specifically studied, research has shown that treatment of animals with Tecovirimat at different phases of sickness exhibit improved survival rates compared to those treated with a placebo in deadly infections caused by the MPV [73].

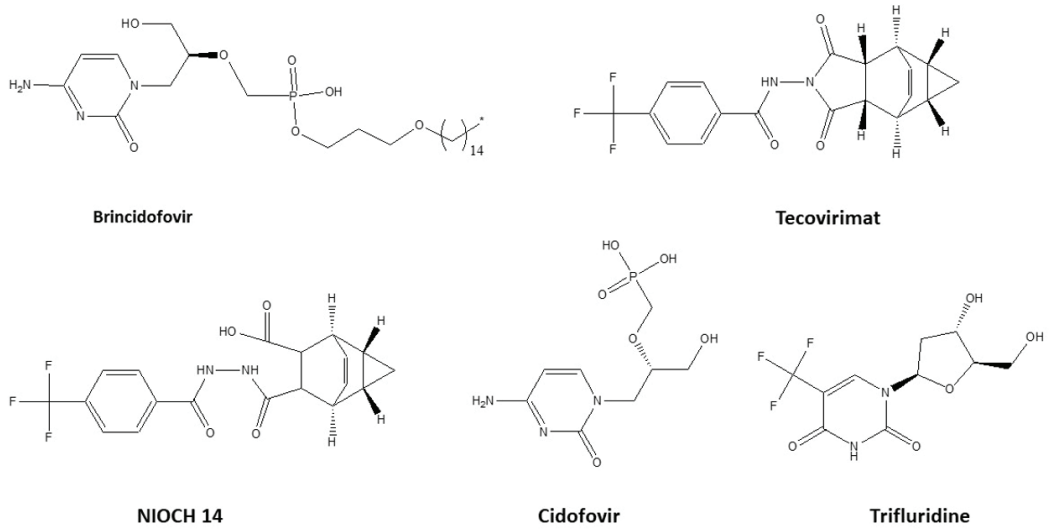

Figure 6: Chemical structure of antivirals used for the treatment of MPV infection.

8.2. Cidofovir

The US FDA approved Cidofovir in 1996 to treat acquired immunodeficiency syndrome (AIDS) patients' retinitis brought on by the *Cytomegalovirus* (CMV). Adenoviruses, poxviruses, and herpesviruses are only a few of the virus families against which it demonstrates broad-spectrum antiviral efficacy [74]. There is little clinical information regarding Cidofovir's efficiency against MPX in people, despite evidence of its in vitro activity and efficacy against lethal animal infections of the MPV [75]. A nucleoside analog called Cidofovir is intracellularly metabolically activated to produce Cidofovir-diphosphate. By competitively limiting viral DNA polymerase and integrating it into the viral genome, this active form prevents further expansion of viral DNA and obstructs viral DNA synthesis [76].

8.3. Brincidofovir

Brincidofovir, also known as Tembexa or CMX001 (Chimerix Inc.), is a prodrug of Cidofovir coupled with lipids that inhibits viral DNA polymerase and is an analog of 2′-deoxycytidine. It has been approved for smallpox treatment and shows promise against MPX with reduced renal toxicity and an improved safety profile. Brincidofovir exhibits improved cellular absorption and a more effective conversion to its

active form, compared to Cidofovir [77, 78]. Despite the lack of efficacy data, patients with MPX are currently treated with Brincidofovir off-label [79]. Studies in mice with fatal MPX infections have shown that Brincidofovir provides protection when administered on the day of infection [80].

8.4. NIOCH-14

In 2009, NIOCH-14, a novel chemical compound was developed. NIOCH-14, also known as ST-246, has received patent certification [81]. Operating through the same mechanism as Tecovirimat, NIOCH-14 is officially registered as an antipox medication in Russia. Administered orally in capsule form, it acts as a prodrug of Tecovirimat, swiftly metabolizing into Tecovirimat upon entering the body. Many *Orthopoxvirus*-related in vitro and in vivo investigations, including the MPV, have indicated comparable or slightly enhanced efficacy and bioavailability of NIOCH-14 when compared to Tecovirimat [82].

8.5. Trifluridine

Trifluridine has been utilized in treating MPV infection, functioning as a structural analog of fluorinated thymidine, a crucial component of DNA. Its mechanism involves blocking DNA production and potentially integrating into DNA to inhibit the responsible enzymes. When applied topically, particularly as eye drops for MPV infections affecting the eyes, trifluridine has been reported to be safe, as it does not penetrate the intact cornea. A study involving five patients treated locally with both Tecovirimat and trifluridine observed that despite differences in their ocular presentations, four individuals shared a common ophthalmological involvement. Following treatment, four patients were discharged after recovery, while one patient continued to experience deteriorating eye conditions and loss of vision clarity. In these instances, there were no known side effects linked to trifluridine [83, 84].

8.6. Vaccinia Immune Globulin (VIG)

In the 1950s, vaccinia immune globulin (VIG) was derived from hyperimmunized plasma obtained from the United States Army recruits, initially for addressing complications arising from smallpox vaccination. VIG, administered intramuscularly, consists of a sterile solution containing high levels of immunoglobulin G (IgG) antibodies targeting the VACV [85]. It is prepared using pooled blood from individuals previously vaccinated with the live VACV. Typically, an intravenous dose of 6000 U/kg is administered after symptom onset, with additional doses possibly required based on the clinical profile and treatment response [86]. While VIG holds promise as a treatment, its efficacy against smallpox and MPX is not well established. Patients with severe T-cell immunodeficiency should avoid the VACV vaccine and opt for VIG if exposed to the virus [87].

9. Prevention and Management

Research suggests that having received the smallpox vaccination before may protect against MPV and might also enhance the infection's clinical manifestations [4]. It is essential to teach medical professionals and patients how to recognize, isolate, and handle MPX cases since prompt treatment and early detection can lessen the effects of the illness and stop its spread. By educating the population and promoting readiness for any outbreaks, the safety and health of individuals as well as communities can be safeguarded against the spread of MPX [88]. Improved laboratory and diagnosis services, along with well-versed staff, are necessary for controlling any diseases. It is advised to work in a Biosafety Level-III (BSL-III) laboratory with this virus due to the possibility of infection. Standard operating procedure (SOP) should be closely followed by exporting laboratories [89]. Full personal protective equipment (PPE) like head covers, face masks, gloves, safety glasses, and foot protective covers, must always be worn in the laboratory. Making plans and sticking to established protocols is necessary for proper waste management. Vaccination is advised for individuals handling infectious materials in laboratories [90].

Currently, the United States has two licensed smallpox vaccines: JYNNEOS and ACAM2000. JYNNEOS was permitted in 2019 for the inhibition of both MPX and smallpox virus, while ACAM2000 was authorized in 2007 and is limited to smallpox prevention. Both have been tested for their ability to prevent animal infections with the MPV. The ACAM2000 vaccine, which was developed from a solitary clonal virus isolated from Dryvax, is the 2nd-generation vaccine in animal models that demonstrated reduced neurovirulence [91]. Some characteristic features of approved vaccines for the treatment of MPV infection are shown in Table **2**.

Table 2: Characteristic features of approved vaccines for the treatment of MPV infection.

Vaccine	**ACAM2000**	**JYNNEOS/ Imvanex**
Generation	2nd generation	3rd generation
Effective for	Adults (18–64)	Adult population
Manufacturer	Gaithersburg Inc.	Bavarian Nordic AS
Molecule type	Live attenuated vaccine	Live virus vaccine
Structure	Live, replication competent virus	Nonreplicating vaccinia virus
Injection materials	Bifurcated needle	Needle and syringe
Inoculation site	Subcutaneous, intradermal	Percutaneous
Dosing interval	2 doses administered 28 days (4 weeks)	Single dose
Injection volume	0.5 ml, 0.1 ml	0.0025 ml droplet of reconstituted vaccine (100 doses)
Presentations	Lyophilized multidose vials	Liquid frozen or lyophilized single-dose and multidose vials
Contraindications	Immunocompromised, history with atopic dermatitis, pregnancy or breastfeeding, heart disease such as coronary artery disease, cardiomyopathy and cardiac risk factors like hypertension, diabetes, smoking, etc.	History of atopic dermatitis, allergy to one of the vaccine components
Side effects	Pain at the injection site, headache, fever, tiredness, nausea, redness, chills, and muscle aches	Headache, nausea, injection site pain, injection site purities, fatigue

Drugs repurposing, particularly herbal preparations, has long been regarded as a workable key in the event of newly developing illnesses for which there are few effective treatment options currently available [92]. Maintenance therapy is the cornerstone of clinical treatment for MPX which involves maintenance of fluid balance, hemodynamic and respiratory support, mucosal and skin infection treatment, and for the prevention of damage to the eye, topical antibiotics and lubricants can be used [93].

People should try to keep away from wild animals with unprotected contact, particularly ill or deceased animals and their blood or flesh, to lower the danger of exposure as well as infection. Before eating, any food containing animal organs or flesh needs to be cooked completely. In MPX epidemic areas, people who are suspected of being infected should not engage in sexual activity such as men having sex with men. Wear a medical mask for protection, disposable clothing, and latex gloves, among other appropriate measures for personal protection, when providing care to MPX patients. If there is a need to contact with MPX patients, then stay away from intimate physical contact and sharing of clothing and bedding with them. Wash your hands frequently under running water with soap and sanitize them regularly to practice good hand hygiene [94].

10. In-process and Completed Clinical Trials for the MPV

Clinical management of individuals with confirmed cases of MPX may be hampered by inadequate laboratory diagnosis, vaccinations, and antivirals. The majority of researchers are working on clinical trials to lower death and morbidity rates, review the safety and effectiveness of already available antivirals, discover viable treatments for mpox, and analyze the pharmacokinetic characteristics of certain medications. The largest clinical trial database currently accessible is ClinicalTrials.gov. To locate and describe mpox interventional clinical trials, we concentrated on the active trials that were registered on ClinicalTrials.gov for this evaluation. This is significant to us because we anticipate a rise in the mpox incidence rate and we need to take the appropriate safety measures, such as efficient contact tracing, isolation, and surveillance. All the interventional clinical trials that are ongoing for MPX were searched up to May 30, 2024. We discussed the characteristics of all the recent and completed clinical trials. Table **3** depicts the characteristics of the current ongoing clinical trials on the MPV. There are a total of 18 clinical trials underway as of May 30, 2024. Ten of the 18 experiments were interventional, and eight were observational. Table **4** depicts the characteristics of the completed clinical trials on the MPV. Of the 10 trials, 5 were observational studies and 5 were interventional studies.

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Table 3: Characteristics of the current ongoing clinical trials on the MPV.

Sr. No.	ClinicalTrials.gov ID	Title of the study	Intervention/ Treatment	Phase	Age	Enrollment	Type of study	Study design	Start date	Completion date (Estimated)
1.	NCT05627713	Clinical and biological aspects of the MPX disease	▷ Other: Blood sample collection ▷ Other: Urine sample collection	Not applicable	18 years and older (adult, older adult)	330	Interventional	Primary Purpose: Basic science; Interventional model: Single group assignment	2022-12-01	2026-12-01
2.	NCT05559099	Tecovirimat for treatment of MPV	▷ Drug: Tecovirimat oral capsule; ▷ Drug: Placebo	Phase 2	Child, adult, older adult	600	Interventional	Randomized; Interventional model: Parallel assignment; Purpose: Treatment	2022-10-10	2024-09
3.	NCT05534165	Tecovirimat in non-hospitalized patients with MPX	▷ Drug: Tecovirimat; ▷ Drug: Placebo	Phase 3	18 years and older (adult, older adult)	120	Interventional	Randomized; Interventional model: Parallel Assignment; Purpose: Treatment	2023-08-14	2025-03
4.	NCT05988203	A clinical study investigating the safety and immune responses after immunization with investigational MPX vaccines	Biological: BNT166a	Phase 1	18 to 65 years (adult, older adult)	64	Interventional	Randomized; Interventional model: Sequential assignment; Purpose: Prevention	2023-09-21	2025-05
5.	NCT05879965	Prospective study for the Follow-up of human MPX cases and smallpox vaccines at risk	_	_	18 years and older (adult, older adult)	345	Observational	Observational Model: Cohort; Time Perspective: Prospective	2022-10-06	2024-10
6.	NCT06223919	Efficacy/Effectiveness, safety, and immunogenicity of LC16m8 MPX vaccine in Colombia	Biological: LC16m8	Phase 3	18 to 50 years (adult)	8686	Interventional	Randomized; Interventional Model: Parallel assignment; Purpose: Prevention	2023-12-16	2024-12-06

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Table 3: Continued.

Sr. No.	ClinicalTrials.gov ID	Title of the study	Intervention/ Treatment	Phase	Age	Enrollment	Type of study	Study design	Start date	Completion date (Estimated)
7.	**NCT06291259**	MPX prospective observational cohort study	_	_	Child, adult, older adult	250	Observational	Observational Model: Cohort; Time Perspective: Prospective	2022-06-21	2024-09
8.	**NCT05734508**	Assessment of safety profile of MVA-BN vaccine in the PALM-007 study in DRC	Biological: MVA-BN vaccine	Phase 4	18 years and older (adult, older adult)	1000	Interventional	Interventional model: Single group assignment; Purpose: Prevention	2023-03-23	2024-08
9.	**NCT05627713**	Clinical and biological aspects of the MPX disease	▷ Other: Blood sample collection; ▷ Other: urine sample collection	Not applicable	18 years and older (adult, older adult)	330	Interventional	Interventional model: Single group assignment; Purpose: Basic science	2022-12-01	2026-12-01
10.	**NCT05534984**	Study of Tecovirimat for human MPV	▷ Drug: Tecovirimat oral capsule; ▷ Drug: Placebo; ▷ Drug: Tecovirimat oral capsule (open label)	Phase 3	Child, adult, older adult	530	Interventional	Randomized interventional Model: Parallel assignment; Purpose: Treatment	2022-09-12	2025-09-30
11.	**NCT05597735**	Assessment of the efficacy and safety of Tecovirimat in patients with MPV disease	▷ Drug: Tecovirimat; ▷ Drug: Placebo	Phase 3	14 years and older (child, adult, older adult)	150	Interventional	Randomized; Interventional model: Parallel Assignment; Purpose: Treatment	2023-03-03	2025-01-01
12.	**NCT05567939**	Clinical, virological, immunological, psychosocial and epidemiological consequences of human MPV (ProMPX)	Other: Natural course of disease	_	16 Years and older (Child, Adult, Older Adult)	300	Observational	Observational Model: Cohort; Time Perspective: Prospective	2022-09-19	2023-12-19

Table 3: Continued.

Sr. No.	ClinicalTrials.gov ID	Title of the study	Intervention/ Treatment	Phase	Age	Enrollment	Type of study	Study design	Start date	Completion date (Estimated)
13.	**NCT06353737**	Looking for asymptomatic MPX in a population at high risk	_	_	Child, Adult, Older Adult	450	Observational	Observational Model: Other; Time perspective: Prospective	2024-04-01	2026-03-31
14.	**NCT05947786**	MPX pediatric and adolescent clinical study	_	_	0 to 18 years (child, adult)	20	Observational	observational Model: Cohort; Time Perspective: Other	2023-03-17	2025-07-31
15.	**NCT05654883**	New York City observational study of MPX immunity	_	_	18 yto 100 years (adult, older adult)	300	Observational	Observational model: Cohort; Time perspective: Prospective	2022-11-11	2028-12-31
16.	**NCT05698082**	FOS Immunohisto-chemical staining of colorectal cancer and its adjacent tissues	Diagnostic Test: Immunohistochemi-cal staining with anti-FOS	Phase 2, Phase 3	18 to 75 years (adult, older adult)	120	Interventional	Interventional model: Single group assignment; Purpose: Diagnostic	2020-12-01	2025-01-01
17.	**NCT06045923**	Virologic and immunologic characteristics of severe MPX in persons with advanced HIV	_	_	18 years and older (adult, older adult)	100	Observational	Observational model: Cohort; Time Perspective: Prospective	2023-03-17	2024-10-01
18.	**NCT06136117**	MPX, biology, outcome, transmission and epidemiology -prospective follow-up of high-risk contacts	_	_	Child, adult, older adult	150	Observational	Observational model: Case-crossover; Time Perspective: Prospective	2023-05-22	2025-05

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Table 4: Characteristics of the completed clinical trials on the MPV.

Sr. No.	ClinicalTrials.gov ID	Title of the study	Intervention/ Treatment	Phase	Age	Enrollment	Type of study	Study design	Start date	Completion date
1.	**NCT05476744**	Viral clearance and epidemiological characteristics in patients with MPX	_	_	18 years and older (adult, older adult)	77	Observational	Observational model: Cohort; Time perspective: Prospective	2022-06-28	2023-03-30
2.	**NCT03745131**	Cohort study of healthcare workers receiving Imvanex®	Other: Blood draw	_	18 years and older (adult, older adult)	120	Observational	Observational model: Cohort; Time perspective: Prospective	2018-10-30	2019-11-30
3.	**NCT05443867**	Monkeypox Asymptomatic Shedding: Evaluation by self-sampling MPX-ASSESS	_	_	18 years and older (adult, older adult)	27	Observational	Observational Model: Cohort; Time Perspective: Prospective	2022-06-22	2022-08-25
4.	**NCT05651581**	Efficacy and acceptability of a MPX curriculum for disproportionately impacted communities	Other: Online module	Not applicable	18 years and older (adult, older adult)	200	Interventional	Interventional Model: Single group assignment; Purpose: Supportive care	2023-05-24	2023-08-24
5.	**NCT05543577**	Assessing the preparedness and knowledge of pharmacists in the current monkeypox outbreak	Other: Questionnaire	_	Child, adult, older adult	500	Observational	Observational Model: Other; Time Perspective: Cross-Sectional	2022-09-14	2022-12-01
6.	**NCT00728689**	Phase I trial of an investigational small pox medication	▷ Drug: ST-246 Days 1 – 3; ▷ Drug: ST-246 Days 11 - 13	Phase 1	18 to 50 years (Adult)	12	Interventional	Randomized; Interventional model: Crossover Assignment; Purpose: Treatment	2008-08	2008-10

Table 4: Continued.

Sr. No.	ClinicalTrials.gov ID	Title of the study	Intervention/ Treatment	Phase	Age	Enrollment	Type of study	Study design	Start date	Completion date
7.	**NCT05976100**	Study of the safety, tolerability, pharmacokinetics of NIOCH-14 in volunteers aged 18-50 years	▷ Drug: NIOCH-14, 200 mg capsule: 1 capsule (200 mg) of NIOCH-14 once orally ▷ Drug: NIOCH-14, 200 mg capsule: 3 capsules (200 mg each) of NIOCH-14 once orally. (Total 600 mg NIOCH-14 per day) ▷ Drug: NIOCH-14, 200 mg capsule: 6 capsules (200 mg each) of NIOCH-14 per day orally. (Total 1200 mg NIOCH-14 per day) ▷ Drug: NIOCH-14, 200 mg capsule: 1 capsule (200 mg) of NIOCH-14 a day orally for 6 days ▷ Drug: NIOCH-14, 200 mg capsule: 3 capsules (200 mg each) of NIOCH-14 a day orally for 6 days. (Total 600 mg NIOCH-14 per day for 6 days) ▷ Drug: NIOCH-14, 200 mg capsule: 3 capsules (200 mg each) of NIOCH-14 twice a day orally for 6 days. (Total 1200 mg NIOCH-14 per day for 6 days)	Phase 1	18 to 50 years (adult)	90	Interventional	Nonrandomized; Interventional model: Parallel assignment; Purpose: Treatment	2020-09-04	2022-03-09

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Table 4: Continued.

Sr. No.	ClinicalTrials.gov ID	Title of the study	Intervention/ Treatment	Phase	Age	Enrollment	Type of study	Study design	Start date	Completion date
8.	**NCT05846243**	Study on immunogenicity, reactogenicity and safety of the VACΔ6 vaccine in volunteers aged 18-60 years	▷ Biological: VACΔ6 vaccine (10^7 PFU) ▷ Biological: VACΔ6 vaccine (10^6 PFU) ▷ Biological: Live smallpox vaccine ▷ Other: Placebo (Sodium chloride bufus, 0.9%)	Phase 2, Phase 3	18 Years to 60 Years (Adult)	334	Interventional	Randomized; Interventional model: Parallel assignment; Purpose: Prevention	2021-10-01	2022-04-01
9.	**NCT05762523**	Safety and tolerability study of the VACΔ6 vaccine in volunteers aged 18-40 years	▷ Biological: VACΔ6 vaccine - once at a dose of 10^6 PFU ▷ Biological: VACΔ6 vaccine - once at a dose of 10^7 PFU ▷ Biological: VACΔ6 vaccine - twice at a dose of 10^6 PFU ▷ Biological: Live smallpox vaccine (smallpox vaccine) + The OspaVir® inactivated smallpox vaccine	Phase 1	18 to 40 years (adult)	60	Interventional	Randomized; Interventional model: Parallel assignment; Purpose: Prevention	2019-05-18	2020-01-27
10.	**NCT05522296**	Break-through infection following MPX vaccination	Drug: Mpox vaccine	_	18 and older (adult, older adult)	3125	Observational	Observational Model: Cohort; Time Perspective: Prospective	2022-09-01	2024-03-30

11. Discussion

Monitoring the progression of MPV, especially in African countries, requires the use of genomic surveillance. Further investigation into the role of MPV proteins in host interaction and immune evasion is needed to understand pathogenesis and transmission factors [95]. The ability to detect and monitor cases is fundamental for outbreak preparedness. Developing and distributing validated diagnostic assays globally is essential for prompt case identification and interrupting transmission cycles, especially as MPV lesions can mimic other conditions [96].

Vaccination plays a vital role in MPX prevention, with the WHO recommending vaccination for individuals exposed to infected persons, including healthcare workers. Ring vaccination strategies, adopted by several countries including the US, Europe, and India, emphasize precision prevention through rapid identification and contact tracing [97].

Nanotechnology-based therapies are another significant advancement that bodes well for the future development of better MPX treatment options. Studies have been conducted on silver nanoparticles because of their demonstrated antimicrobial properties. In various studies, silver nanoparticles (AGNPs) are used to reduce the infectivity of MPX. Therapies based on nanotechnology provide innovative, affordable, and broad-spectrum treatment alternatives for a variety of illnesses. The fundamental idea was to enhance the physiochemical characteristics at the nanoscale by altering the properties of both current and new antivirals and related medicinal qualities. An additional strategy involved combining approved drugs with nanoparticles to enhance drug delivery to the body at the same time improved efficacy and targeted delivery. The dose-dependent inhibitory effect of AGNPs against MPX has been demonstrated in specific studies. Further studies are needed to demonstrate the research implications of the clinical model. Moreover, by combining molecular models and bioinformatics statistics as well as in silico with a theory based on biomarkers, more advanced treatments with less adverse effects, decreased risk of resistance, improved delivery, or better pharmacokinetic qualities could be developed [98].

Training community health representatives, medical professionals, and the public on emerging disease risks is essential. Countries must reassess pandemic readiness, as demonstrated by the pandemic of COVID-19, and prioritize education, treatment, testing, and tracing frameworks to safeguard population health and economies against future threats like MPX.

12. Conclusion

- Understanding the constantly evolving epidemiology of MPX is vital due to its potential for rapid spread. There is a continued resurgence of MPX cases that needs to be addressed. Therefore, an urgency to understand and gain knowledge regarding the current clinical trials, vaccines, and treatments that are ongoing. Several treatments and vaccines are still under evaluation. One of

the primary ongoing clinical trials on MPX that is currently underway are 1) Viral clearance and epidemiological characteristics in patients with MPX. This study aimed to gain a better understanding of the dynamics of viral clearance in patients who have been diagnosed with MPX. The study is still ongoing, but positive results should come soon. 2) Description of immunization-induced reactions examining the humoral and cellular immune responses in individuals with HIV following MPX vaccination is the aim of this study, which is directed against MPX. The trial aims to assess the immunogenicity of the JYNNEOS MPX vaccine's dose reduction strategies. Specifically, it will compare two intradermal treatments containing the modified vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine to the standard subcutaneous regimen. Adults and children with MPX infection are currently being enrolled in a Phase 3 clinical trial in the US, which assesses the antiviral medication Tecovirimat. The National Institute of Allergy and Infectious Diseases (NIAID), a division of the National Institutes of Health, is funding the trial. Although several trials have been carried out, there is not enough data at this time to assess the current level of MPX infection.

- Recent studies have highlighted the effectiveness of newly approved vaccines and novel antivirals in preventing and treating *Orthopoxviruses*, with Tecovirimat showing promise. Currently, smallpox vaccines are used as a preventative measure against MPX. Currently approved and in use as a vaccine against MPX virus are JYNNEOS and ACAM2000. Since JYNNEOS is a nonreplicating virus vaccine, it is crucial in the ongoing MPX outbreak. For high-risk immunocompromised populations, including those with HIV, LC16m8 is a safe and effective vaccine. It is in a phase 3 clinical trial right now. Our study demonstrates the global safety and efficacy of the smallpox vaccine against MPX.

- To prevent MPX virus infection and transmission, government agencies should step up their vaccination campaign. Raising public awareness of the MPX virus could involve educating and counseling people via print and digital media, lectures, and seminars. In order to stop the virus from spreading further, people should increase awareness of the MPX epidemic and develop their ability to diagnose cases. Public awareness and education are essential for addressing this growing health threat. Enhancing comprehension and clinical management, particularly among healthcare providers, is imperative. The CDC suggests several preventive actions, including avoiding close contact with infected individuals and practicing good hygiene.

- We request scientists and decision-makers to come together and devise the appropriate plans to stop the virus's recent spread. Health decision-makers worldwide, clinicians, lab technicians, epidemiologists, and others should give serious consideration to a comprehensive preventive plan. Furthermore, the intricate epidemiological characteristics of the present MPX outbreak in nonendemic nations demand the implementation of successful preventive measures that encompass community and healthcare settings. Accurate and timely diagnosis of active cases is critical in healthcare facilities. To prevent missing confirmed, possible, or probable cases, this task requires

well-trained staff supported by all clinical and laboratory diagnostic tools. Simultaneously, for both inpatient wards and outpatient clinics, the protection of healthcare personnel should be prioritized through stringent adherence to infection control protocols, including standard, contact, and droplet precautions. In a one-health context, community-focused education and awareness campaigns can offer protection against multiple pathogens.

- Despite progress in vaccination and medication, more research is needed for contemporary treatment options tailored to MPX. In order to determine the extent of MPX virus infection, studies like epidemiological metrics need to be evaluated. Mathematical modeling is used at the population level to predict characteristics of outbreaks, including recovery rates, transmission, virulence, and reproduction numbers. Population metrics, such as contact tracing data, cumulative case counts, and wastewater surveillance, are utilized in this process. The results of these studies can help determine when and to whom to target vaccination or education campaigns in order to reduce the spread of infection in the future. Public health policy decisions can be informed by mathematical modeling, which can assist in predicting the percentage of people expected to experience long-term consequences from an MPX infection. Another study, such as a longitudinal study, comprehends the risks associated with vaccination in the population. It will be more crucial to conduct this kind of research to determine the scope of these possible long-term effects for moderate-to-severe MPX cases. More research is required to fully comprehend the effectiveness of vaccinations. A small number of research gaps are noted, including the need for quick studies to gain a deeper understanding of the disease's epidemiology, clinical implications, and the role of different modes of transmission. Additionally, clinical studies of vaccines and treatments are necessary to confirm their efficacy and determine the best ways to employ them in this and future outbreaks.

- Considering the global implications of MPX, in order to support the international response to the MPX outbreak and to ensure that all people have equitable access to vaccines, national and international governments and stakeholders must collaborate. Countries are faced with challenges in combating the rapidly spreading MPX outbreak as there is a significant shortage of MPX vaccines compared to current anticipated needs. Additionally, the manufacturing ramp-up will take time to provide even high-income countries with sufficient doses of MPX vaccines. Gaining international support for enhanced surveillance and case detection of MPX is crucial to comprehend the dynamic epidemiology of this incursion. However, there is still a lot to learn about the research priorities for MPX, which must be supported at the national and worldwide levels. It is crucial to share best practices. Coordination of global research is necessary to advance local competency, equity, generalizability, and timeliness. In conclusion, efforts to understand, prevent, and manage MPX must be intensified to curb its spread and impact.

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Ethical Statement

The research is exclusively based on published literature; Ethical Approval is not required.

Conflict of Interest

The authors declare that there is no conflicts of interest.

Artificial Intelligence (AI) Disclosure Statement

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