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Mpox and related poxviruses: A literature review of evolution, pathophysiology, and clinical manifestations

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ABSTRACT

The recently re-emerged mpox (monkeypox) virus that causes mpox disease is a member of genus *Orthopoxvirus* and has unprecedentedly spread worldwide. Numerous studies have contributed to our understanding of its evolution, pathophysiology, and clinical manifestations. The current outbreak of the mpox virus depicts its novel route of transmission as a new variant. However, the exact reason for its transition from an epidemic to a pandemic remains unclear. Furthermore, other poxviruses such as vaccinia virus, variola virus, and cowpox virus, also belong to the same genus, *Orthopoxvirus*. In the present review, our objective was to summarize the evidence on evolution, pathophysiology, and clinical manifestations of mpox virus and its related poxviruses. The present review would aid in a better understanding of the current circulating mpox virus and its differences from other poxviruses. In addition, the shared genetic factors contributing to virulence in these *Orthopoxvirus* highlight their evolutionary connections and genetic similarities. While they exhibit differences in virulence, studying these genetic relationships is crucial for understanding their biology, pathogenicity, and the development of effective vaccines and antiviral therapeutics to curb mpox disease.

KEYWORDS: Evolution; Mpox; *Orthopoxviruses*; Pathophysiology; Poxviruses; Transmission

1. Introduction

The mpox (monkeypox) virus, a zoonotic virus, re-emerged in 2022 and subsequently, sparked the concern regarding the commencement of a new pandemic. On 26th May 2022, WHO reported a total of 257 confirmed mpox cases and 120 suspected cases[1]. The name mpox has been derived from the virus discovery in monkeys

in a Danish laboratory in 1958[2]. It is a member of the genus *Orthopoxvirus* that belongs to the family Poxviridae and subfamily Chordopoxvirinae[3,4]. The mpox virus-caused mpox disease in humans was first detected in 1970 in the Democratic Republic of the Congo. Mpox was marked by sporadic infections, limited to a few countries in Western Africa and Central Africa (Congo basin)[5,6]. Due to the sudden rise of mpox outside Africa, the WHO announced it as a public health emergency in July 2022[7]. On 29th August 2023, more than 89000 confirmed mpox cases and 157 deaths, have been reported from 114 countries[8]. The most worrisome about recent emerging mpox is that some of the contracted individuals had no history of travel or in contact with any infected person of mpox virus, highlighting its unidentified novel route of transmission[1]. However, based on its wide range of manifestations, the disease varies from mild to severe and can also lead to death[9]. Surprisingly, it has been observed that the frequency and degree of clinical manifestations of mpox were reduced in the patients who had been vaccinated with smallpox, conferring the 85% effectiveness of the small-pox vaccination against mpox, while fatality rates varied from 1% to 11% in mpox patients who were unvaccinated[9,10]. Intriguingly, the recently emerged mpox showed distinguished symptoms in comparison to its classic symptoms making the

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diagnosis difficult. Also, numerous clinical studies have reported its novel epidemiology and clinical manifestations due to genetic mutations affecting the pathology of the virus[11,12]. A study reported that the median age of patients affected by the mpox virus has also increased from the age of 4 years (1970) to 21 years in 2019 along with a fatality rate of 8.7%[13]. The genomic mutations in the mpox virus might be transforming it to become more virulent and fatal. The genomic mutations in the mpox virus and its unprecedented evolution might be occurring due to global changes such as climate change, increasing rate of trade and travel, and population growth[14].

The mpox virus genome is large and consists of 200-kilo base pairs and has a highly conserved central region and a variable terminal region that codes for replication, host determination, and pathogenesis, respectively[15]. The other viruses belonging to the genus *Orthopoxvirus*, are variola virus (VARV), cowpox virus (CPXV), and vaccinia virus (VACV), and also known to be genetically similar to mpox virus[16]. Studies reported that different poxviruses have undergone a gradual process involving nonsense mutations and high-frequency recombination leading to gene gain or loss[17,18]. Although, the mpox virus has a low mutation rate due to its stabilized double-strand DNA genome; however, genomic analysis of the mpox virus-2022 strains revealed 46 single nucleotide polymorphisms in comparison to the NCBI mpox reference sequence NC_063383[19]. The high-frequency recombination within the mpox virus and VARV might cause gene gain and gene loss, respectively, resulting in divergent severity of these viruses[19,20]. Similarly, poxviruses differ in their transmission; only two genera *Molluscipoxvirus* and *Orthopoxvirus* infect humans as the primary host, remaining are zoonotic transmission from animals to humans[21,22]. Most of the characteristics of the mpox virus are identical to VARV, the virus causes smallpox disease including their clinical symptoms and incubation period. However, the host range and degree of virulence varied for mpox virus and pox-related viruses. Therefore, our objective is to review the evidence on the evolution, pathophysiology, and clinical manifestations of mpox virus and its related poxviruses.

2. Evolution of mpox virus and related poxviruses

The evolution of zoonotic pathogens over some time has always been a matter of major concern resulting in more virulent variants. This not only poses a threat to higher infection rates but also to possible situations of widespread infection due to the pattern of transmission, which may or may not be limited to specific geographical boundaries. Over the past few decades, the incidence of infections due to mpox virus across several parts of the world has gained considerable attention from the scientific community. From the year 1958 to 1964, the mpox virus was found in monkeys in the United States and European countries[23–25]. Based on the region of origin in Africa and potency of virulence, whole genome sequencing

analysis categorized the mpox virus broadly into two clades *i.e.* the Central African clade (Congo Basin) and the West African clade[26,27]. The Central African clade of the mpox virus (CA MPXVs/Clade I) is reported to be more virulent in comparison to the West African clade (WA MPXVs/Clade II a)[28–31]. The WA MPXVs lineage differs by 900 bp from CA MPXVs[32]. Interestingly, WA MPXVs/Clade II a was responsible for causing an outbreak in 2017–2018 due to human-to-human transmission in Nigeria[31,33], subsequently leading to the spread of infection to other countries such as Singapore, the United Kingdom, and Israel. Based on the new nomenclature, the mpox virus further was divided into 3 clades *viz.* (i) Clade 1: CA MPXVs/ Congo Basin/Clade I , (ii) Clade 2: WA MPXVs/Clade II a detected before 2017, and (iii) Clade 3: WA MPXVs/Clade II b detected after 2017 outside Africa using core single nucleotide polymorphisms, inverted terminal repeats (ITRs)[34,35]. Furthermore, WA MPXVs/Clade II b were divided into, A.1 and A.2 subgroups diverged from hMPXV-1A circulating in the year 2018–2021, while, A.1 is later subdivided into two lineages, A.1.1 and B.1, where B.1 lineage diverged during the year 2018–2019 (Figure 1)[34]. Further, several B.1.1, B.1.2, B.1.3, B.1.4, B.1.5, B.1.6, B.1.7, and B.1.8 have been diverged from B.1 due to microevolution. A total of 46 B.1 specific single nucleotide polymorphisms have been found that separate these lineages from the original sequence.

Furthermore, the mpox virus encodes ~190 genes while the *Orthopoxvirus* encodes around 200 genes involving three regions, a core region, a left arm, and a right arm. The genome in the core region is relatively conserved and codes for viral replication. While the genome in the left arm, and the right arm is responsible for host range and virus's pathogenicity[35]. Also, these regions harbor identical and opposite sequences known as inverted terminal repeat (ITR), which is susceptible to forming hairpin loops out[36]. The ITR regions at the end of the genome confer genome plasticity to *Orthopoxviruses*. Modifications in ITRs are the primary mechanism behind the rapid adaptability of *Orthopoxviruses* in changing different hosts[37]. Thus, significant deletions and insertions in the ITRs made it possible for Western and Central mpox virus clades to differ from each other[36,37].

The genomic analysis of the Central and West African strains has displayed a nucleotide difference of 0.56% approximately, with 170 shared orthologs. Though the two classes of strains have 99.4% similarity at the protein level, there are differences in the virulence between them. Out of 56 virulent genes, the two classes of strains share 53 such virulent genes. The latter comprises 276 silent substitutions encompassing 61 conservative, 93 non-conservative, and 121 silent amino acid changes. The marked difference between the two strains occurs in the orthologs of BR-203, BR-209, and COP-C3L which confer differential virulence to the strains[26,27]. The functional implications of such orthologs at the protein level involve evasion of infected lymphocytes from apoptosis, prevention of interleukin -1 β (IL-1 β) and IL-1R binding, and inhibition of initial steps of complement cascade in host cells, respectively, thereby imparting immunomodulatory roles in virulence[38–44].

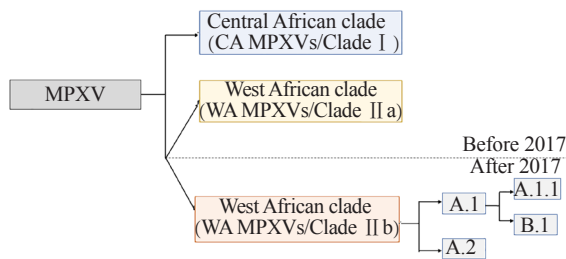


Figure 1. Schematic flow diagram of classification of mpox virus (MPXV). MPXVs are classified into 3 clades, viz. (i) Clade 1: CA MPXVs/Clade I, (ii) Clade 2: WA MPXVs/Clade II a detected before 2017, and (iii) Clade 3: WA MPXVs/Clade II b detected after 2017. WA MPXVs/Clade II b are divided into A.1 and A.2 subgroups, while, A.1 is further subdivided into two lineages, A.1.1 and B.1.

The sequence analysis of the mpox virus which re-emerged in the United States in 2022 demonstrated several GA-to-AA mutations in the apolipoprotein B mRNA editing catalytic polypeptide-like 3 (APOBEC3) motif. It works on single-stranded DNA and plays a significant role in the vertebrate immune system by blocking the replication of foreign viruses through C-to-U deaminase activity[45,46]. Such G-to-A mutations were prominent in WA MPXV sequences sampled between 2017-2022 in comparison to the same clade before 2017 or CA MPXV clades[47]. In addition, 41 out of 46 SNPs found in the mpox virus-2022, might be APOBEC3-like driving mutations[19]. However, further investigations are warranted to determine the APOBEC3 activity among different mpox virus lineages and to decipher the mechanisms responsible for these mutations.

The mutations found in the mpox virus-2022 strains affect 20 proteins; however, whether these proteins aid in pathogenesis or transmission of the virus remains ambiguous. The recent study also revealed that OPG105 and OPG210 have nucleotide substitutions in the mpox virus-2022 strain. Previous studies demonstrated that the homologous protein L6R of OPG105 has been conserved among VARV and VACV[48]. However, the effect of these mutations on virus activity or virulence is still unexplored.

Factors determining host range and degree of virulence among different clades of mpox virus and other pox-related viruses such as VARV, VACV, and CPXV are associated with genes causing virulence, which can further be attributed to their evolutionary history and shared genetic components. These viruses share a common ancestor; however, over time, they have evolved and diverged, leading to variations in their virulence and host specificity. While mpox virus and VARV (responsible for smallpox) are reported to cause severe diseases in humans, VACV and CPXV are known to be less virulent. Despite these differences in virulence, studies have shown that there are genetic similarities and overlaps in the genes responsible for various aspects of viral replication, host immune evasion, and virulence factors among these viruses. Understanding these genetic relationships can facilitate deciphering

the evolution of these viruses and assist in development of antiviral therapeutics and vaccines[49]. Upon delving deeper into evolutionary dynamics among mpox virus and other pox-related viruses, the study suggested that the shared genes and genetic relatedness allow for the exchange of genetic material between these viruses. This can lead to the acquisition of virulence factors from one virus by another through genetic recombination events. For instance, the lower virulence in VARV might be due to gene loss[50]. The discovery of MPXgp090 and MPXVgp182 which are responsible for forming surface glycoprotein suggests only a single recombination event and possibly highlights the evolution of the mpox virus[51]. However, a mutational study by Yadav *et al.* demonstrated the function of host APOBEC3 during the evolution of the virus, indicating its spread in the ongoing microevolution, thus highlighting host-virus interrelation in the evolutionary mechanism[52]. Phylogenomic studies revealed that the general appearance of illness by smallpox and mpox virus is identical, even then three clades of the mpox virus, indicating a distinct evolutionary divergence[53]. Furthermore, understanding the genetic relatedness between these viruses has been instrumental in vaccine development. VACV, which is less virulent to humans, has been employed as a vaccine vector against mpox and smallpox. The shared genetic elements between these viruses pave the way for vaccine development that protects multiple *Orthopoxviruses* and aids in the management of pathophysiology of mpox virus and poxviruses.

3. Transmission and pathophysiology of mpox virus and related poxviruses

3.1. Transmission of mpox virus and related poxviruses

In general terms, there are two types of pox infections: those brought on by an infection with the variola major virus and those brought on by an infection with the variola minor virus, sometimes referred to as the alastrim virus. The infections with the variola minor virus produced a mild illness and had a low mortality rate of about 1%, while infections with the variola major virus were characterized by a severe illness with a high fatality outcome (20%-50%).

The human smallpox virus is typically spread by aerosol or droplet contact[30]. Mpox is the most common *Orthopoxvirus* infection in people after smallpox was eradicated in humans. In 1958, the first cases of mpox in Copenhagen's experimental monkey population were found, and in 1970 Copenhagen[2] saw the first report of illnesses in people. Until now, mpox has only seldom affected humans. Since African gophers and rodents are thought to be the *Orthopoxvirus* species' reservoirs, mpox is a zoonosis. Mpox in humans has an incubation period of 10-14 days, which is similar to human pox (smallpox). Additionally, the clinical pathology is similar to that of human pox. Those who have the infection are contagious for the first week after the erythema appears[54,55].

The mpox virus has the potential to induce severe zoonotic pathology, and its transmission can occur through several pathways as shown in Figure 2: from animals to animals, animals to humans, and even human-to-human transmission[56].

3.2. Transmission from animals to human beings

The ability of the mpox virus to infect both animals and humans stems from their broad host range specificity, which enhances their adaptability and efficiency in spreading to human populations. The virus finds its natural reservoirs in various species, including Gambian pouched rats, squirrels, non-human primates, and dormice[57,58]. An illustrative instance of zoonotic transmission took place in the United States in 2003, where exposure to infected pet prairie dogs' excretions and secretions triggered an outbreak resulting in 47 human cases. Remarkably, epidemiologic investigations uncovered that these dogs had come into close contact with rodents imported from Ghana[4]. Moreover, there have been multiple reports of human-to-pet transmission of the mpox virus, emphasizing the complexity of the disease transmission routes[59]. Although pet owners face a potential risk of contracting mpox virus from their pets, the overall likelihood of such transmission remains relatively low[60]. Infection can also occur directly from animals through bites, scratches, or the consumption of meat or animal products from infected animals. Dead animals and contaminated objects (fomites) are of concern as well, given that the mpox virus remains stable, with evidence of infectious virions being isolated from smallpox

scabs even after 13 years of storage at room temperature.

3.3. Transmission from human to human

Human-to-human transfers of the poxvirus fundamentally sustain its infection cycle. Droplets and aerosols, which people expect just before the symptomatic phase, are the primary transmission media. The spread of the infectious agent has been partially attributed to contaminated bedding and clothes. In most cases, cowpox infections of humans occur either by direct contact with body fluid or tissue or through skin lesions of infected rats or cats. There are a few different ways by which the mpox virus is thought to spread, but they are all linked to coming into close contact with sick people or animals. Broadly, the transmission mode of mpox virus has been classified into two categories: non-sexual and sexual transmission[61,62].

3.3.1. Non-sexual transmission

In the non-sexual mode of transmission, the mpox virus is capable of transmission through close, direct contact with mpox rash, scabs, or body fluids from a previously infected individual. Additionally, transmission can occur through contact with fabrics (such as bedding or clothing), objects, and contaminated surfaces by an infected mpox person. Direct contact with infectious lesions, eschars, or exudates, as well as the exchange of bedding or garments, can facilitate viral transmission. Respiratory secretions can also serve as a means of contact transmission. Furthermore, pregnant women have the potential to pass the virus to their fetuses through the placenta[63–65].

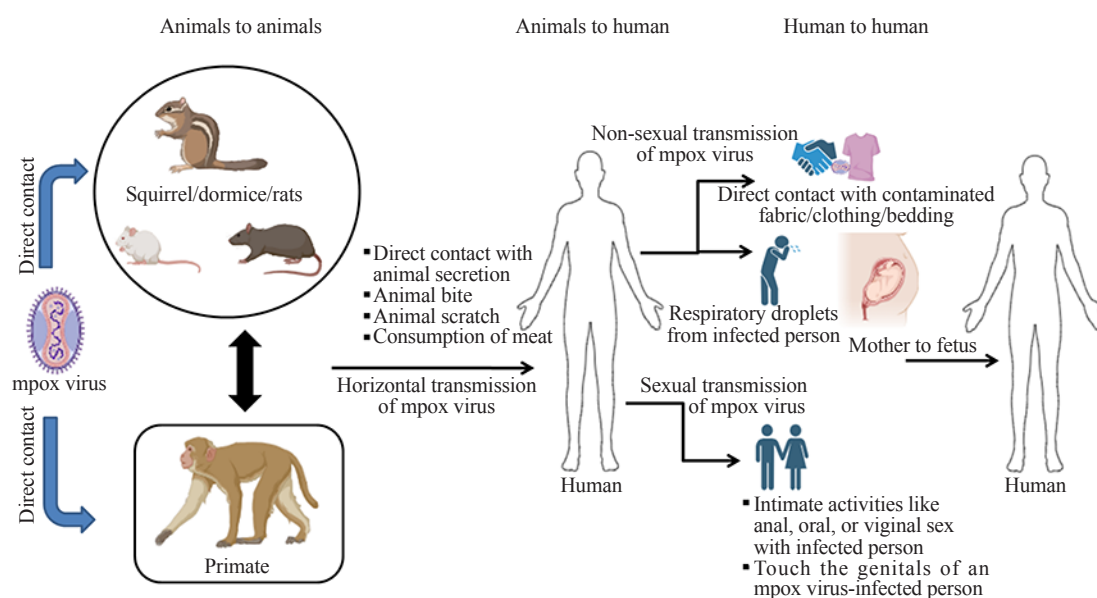


Figure 2. Transmission of mpox virus. Mpox virus transmission can occur through several pathways such as animals to animals, animals to human, and human-to-human.

3.3.2. Sexual transmission

Intimate activities like anal, oral, and vaginal sex, or touching the genitals of a person infected with mpox virus, can facilitate direct transmission of the virus. The infectious period starts when symptoms appear and lasts until the rash has completely healed, with a typical illness duration of about 2-4 weeks. A significant number of cases in the present mpox outbreak have been associated with sexual transmission, particularly among bisexuals and gays[66,67]. Further, in regard to contagion susceptibility, males exhibit a higher vulnerability compared to females. This susceptibility can be attributed not only to the immunosuppressive effects of androgens but also influenced by sex steroid hormones on infection-resistance genes[68].

The majority of human CPXV infections result from skin lesions, direct contact with body fluids or secretion, and tissue, as well as from sick rats or cats. There have also been reports of infections in the ocular area, most likely stemming from smear infections[69–73].

Importantly, the transmission of mpox virus infection within humans or reverse transmission to pets or wild animals is growing nowadays, therefore, surveillance of humans or animals in close contact with affected individuals is needed to diagnose them and to inhibit formation of infection reservoirs. However, active surveillance cannot diagnose those cases which are asymptomatic or with mild symptoms. A serology-based survey study by the Centers for Disease Control and Prevention (CDC) in the United States found anti-*Orthopoxvirus* immunoglobulin (Ig) G or IgM in the blood of 3 individuals substantiating the previous undiagnosed mpox virus infection[74]. Therefore, proper case tracking is required to identify the professional, community, and household contacts of a person infected with mpox virus, that can aid in post-exposure prophylaxis.

For the early detection of mpox virus infection, a validated diagnostic assay needs to be developed and the early identification of infection will further facilitate the disruption of the transmission chain. An effective diagnostic test is required because mpox virus lesions are often considered secondary herpesvirus infection, syphilis, and molluscum infection[75,76]. The mitigation strategies to develop rapid diagnostic tests should be similar to the home COVID-19 detection kit which is portable, sensitive, and easy, however, development of such a diagnostic assay requires in-depth knowledge of mpox virus infection and its growth kinetics in an infected individual. Several studies have shown sensitive assays to detect mpox virus traces in sewer water[77–80]. In fact, in the United States, a wastewater scan dashboard has been placed that can scan mpox virus, SARS-CoV-2, human metapneumovirus, norovirus, and influenza virus[81].

Importantly, genomic surveillance is another essential approach to identifying circulating strains of mpox virus and it aids in identification of the spread of virus[34,82]. Moreover, genomic surveillance is also a vital way to monitor and track the evolution of pathogens. It also helps identify distinct mutations of the mpox virus and subsequent host alternation along with different clades

having distinct transmission patterns[83]. A report by Luna *et al.* showed the evolution and diversity of the mpox virus by employing phylogenomic. The study reported that the mpox virus genome can be categorized into three monophyletic clades where two clades have been characterized previously and one newly derived clade comprising a genome from the 2022 mpox outbreak[84]. Mpx Radar is a developed tool using several keys for the genomic surveillance of the mpox virus worldwide. It assists public health authorities in rapidly following up on the mpox virus variants and facilitates the comparison of new sequences of the mpox virus with the different identified genomes of mpox virus as a reference[85].

3.4. Pathophysiology of mpox virus and related poxviruses

A small number of infectious particles of human poxvirus are reported to be sufficient for infection in the nasopharynx or respiratory tract mucosa. The virus then multiplies further in the regional lymph nodes and goes on to infect all lymphatic organs, including the lymph nodes, bone marrow, and spleen, before entering the first viremia phase, which largely manifested as asymptomatic, on the third or fourth day after infection[57]. Around the eighth day following infection, the second phase of viremia begins, during which infected leukocytes spread the virus to the body's peripheral tissues. There were specifically infected cells in the mucosae and tiny blood vessels of the skin. The afflicted patients showed symptoms including high fever, malaise, acute tiredness, headache, and backache for approximately 12 to 14 days after infection. A maculopapular exanthema, also known as a macula, begins on the oral and throat mucosae and extends to the face, lower arms, torso, and legs[50].

After the rash appears, on days 8 and 9, the exanthema turns into papula (vesicles) and pustulas. The round pustules have a profound skin embedment. Afterward, crusts (crusta) form and heal, leaving scars during the healing phase[64]. The ulcerating lesions in the mouth and throat discharge a large number of virus particles into the saliva. These patients were especially contagious during the first week of the clinical illness as this phenomenon happened then. Around the second week of the illness, circulating immune complexes and viral proteins trigger toxic reactions (cytokine storms), which cause some patients to pass away[86].

An uncommon adverse reaction to the VACV vaccination, encephalitis can also arise as a consequence, similar to perivascular demyelination in severe cases of measles or chickenpox. Malignant smallpox and hemorrhagic smallpox are two types of poxvirus infections that typically result in death. It is unclear if this is caused by variations in the virulence of VARV strains[87].

Mpox, an *Orthopoxvirus*-driven zoonotic malady, engenders human symptoms akin to smallpox[88]. This infrequent viral ailment commonly manifests as fever, cephalalgia, myalgia, and a rash that commences on the face before disseminating to other body regions. The rash typically advances into pustules and scabs

before eventual resolution. The current outbreak of mpox has presented atypical cases, wherein the distinctive rash initiates in the perianal and vaginal regions and may subsequently extend to other body areas either with or without concurrent involvement in the initial sites[89]. Additional poxviruses, such as smallpox and cowpox, may induce analogous symptoms; however, disparities in severity and clinical presentation exist. For instance, smallpox was typified by hyperpyrexia, a rash encompassing the entire body, and pronounced scarring, whereas cowpox typically induced localized skin lesions with fewer systemic manifestations. These distinctive clinical features facilitate the discrimination of various poxviruses, thereby contributing to accurate diagnosis and treatment. Mpox displays clinical characteristics reminiscent of smallpox, with a prodromal phase marked by prompt lymphadenopathy and fever. Following this phase, rash symptoms, comprising the appearance of lesions, manifest within a brief period of 1-3 days after the onset of lymphadenopathy and fever[87]. Additionally, there exists a potential for secondary bacterial infections, including bronchopneumonia, gastrointestinal complications, respiratory distress, corneal infection, sepsis, encephalitis, and dehydration, which may carry the potential risk of leading to visual impairment[90,91]. Moreover, mpox can induce swollen lymph nodes, chills, and fatigue. The rash undergoes distinct stages, beginning as elevated papules that evolve into vesicular blisters before forming scabs, which eventually separate from the skin. The rash may elicit discomfort and itching, with the illness persisting for several weeks[67]. Smallpox was an extremely infectious and lethal ailment that triggered fever, cephalalgia, lumbago, and a widespread rash. The rash advanced through various stages, commencing as erythematous spots that transformed into vesicular papules, then pustules, and ultimately forming scabs. Smallpox caused profound scarring and frequently resulted in vision impairment or mortality. Cowpox typically resulted in a solitary skin lesion, characterized by redness, elevation, and fluid-filled content. This lesion typically emerges on the hands or face and might be accompanied by fever and swollen lymph nodes. Historically, the illness was considered mild and usually resolved spontaneously within a few weeks. Nonetheless, its significance lies in its historical use as a vaccine against smallpox. These instances represent just a few of the diverse clinical presentations of various poxviruses. It is essential to recognize that although these viruses may provoke similar symptoms, they are distinct diseases requiring different treatment approaches. If there is suspicion of exposure to any of these viruses, seeking immediate medical attention is crucial[92].

For CPXV, after seven to twelve days, the infection site becomes covered with papules that eventually turn into vesicles, painful hemorrhagic pustules, and black crusts that are usually on the shoulders, hands, or face. Patients with the infection exhibit nausea, sore muscles, and influenza-like symptoms. Lesions are usually restricted to the infection site, although severe cases have been documented where the patient needs to be hospitalized[71,93].

Only lymphadenopathy in the local lymph nodes is seen in numerous infections. The pustules or crusts dry up after 6 to 8 weeks, sometimes leaving scars behind. Even though only local

symptoms were seen in certain CPXV-infected patients, quantitative PCR was able to identify viremia in the blood. This was surprising because following a VACV vaccine, no viraemic phase was seen in those who experienced local reactions[94]. However, those who are immunosuppressed or have a compromised cellular immune response may experience generalized exanthema and a deadly systemic illness. These signs and symptoms resemble those of a virus called VARV[95].

VACV has been used as an immunization virus for human smallpox prophylaxis but it has some side effects, such as widespread vaccinia, bacterial contamination that leads to further bacterial infections, vaccinated eczema, and gangrenous vaccinia can, however, rarely happen. In addition, there may also be fatalities (1 in 1 million) or vaccination-induced encephalitis (1 in 100000)[96].

The contentious topic of viremia is brought up in relation to immunization. While some research groups assert that only vaccines experiencing significant side effects have detectable virus genomes in their blood, others report that using extremely sensitive detection techniques (PCR), viral genomes could be found in some vaccines up to three weeks post-vaccination, however, no infectious virus could be isolated.

4. Trends in mpox treatment and vaccination

At present, there are no specific antiviral therapeutics available for mpox. However, supportive care, such as adequate hydration, wound care, and pain management, has a significant role in alleviating the symptoms and preventing long-term sequelae. The smallpox vaccination was reported to be protective in case of mpox. In addition, IMVANEX in Europe, JYNNEOS in the United States, and IMVAMUNE in Canada are the only available licensed vaccines for mpox and Tecovirimat SIGA (Tpxx) is available approved medicine for treating mpox patients[97]. Ongoing research is exploring experimental treatments, including antiviral drugs and monoclonal antibodies, but these interventions are still in the early stages of testing.

Usually, mpox is a self-limiting disease and, therefore does not demand therapy except in immunocompromised patients and in the case of children who are prone to develop severe complications. The disease prognosis relies on several factors such as the severity of patients, previous vaccination status, and comorbidities in mpox patients. The different categories of mpox patients might require potential antiviral therapeutics as given by CDC[98].

- a. Patients with severe illness who require hospitalization;
- b. Young patients (Children with mpox illness);
- c. Immunocompromised patients such as those having autoimmune disease, or HIV-AIDS, and any malignancies;
- d. Patients with any comorbidity;
- e. Pregnant and breastfeeding mothers;
- f. Patients developing any long-term sequelae.

As the given patient categories might develop disease complications, it is recommended to give specific therapy to these

patients. There are three categories of medications available for management of mpox patients. The first category is immunoglobulin such as Vaccinia Immune Globulin (VIG) followed by vaccination such as ACAM2000, JYNNEOS, and other vaccines (IMVANEX, Aventis Pasteur Smallpox Vaccine, LC16m8, Imvamune) and antiviral drugs such as Tecovirimat, Brincidofovir, and Cidofovir. Among these medications, antiviral drugs and immunoglobulin are used for the management while vaccines are used for prevention of the disease. When it comes to treating *Orthopoxvirus* species, three of the most promising medicines are ACAM2000, LC16m8, modified vaccinia Ankara, IMVANEX (Europe), and IMVAMUNE (US)[67].

4.1. VIG

VIG is FDA-approved immunoglobulin for the management of adverse effects following smallpox vaccination such as eczema vaccinatum, generalized vaccinia, and progressive vaccinia, in patients with skin disorders[99]. VIG consists of purified human gamma globulin (IgG) containing antibodies against the VACV. Thus, it aids in providing passive immunity to individuals experiencing adverse effects following vaccinia vaccination. According to the CDC, VIG could be used as prophylaxis treatment for mpox patients who are immunocompromised, and mpox vaccination is contraindicated; however, data on the safety and efficacy of VIG in mpox patients is not available presently[100]. According to guidelines, VIG is either not used or used with caution in individuals having renal complications or having a history of diabetes mellitus, and sepsis. A study reported that the administration of VIG might impact the efficacy of live attenuated vaccines such as mumps, rubella, varicella, and measles. Therefore, live attenuated vaccine administration should be avoided till 3 months following VIG vaccination[101].

4.2. JYNNEOS vaccine

It is a live attenuated modified vaccinia Ankara vaccine approved by the FDA for emergency use in mpox virus-infected individuals involving two doses with an interval of 4 weeks. It works against *Orthopoxvirus* infection by eliciting humoral and cellular immune responses[102]. Although the JYNNEOS vaccine was found to be safe in immunodeficient patients, there is no preclinical study available for its efficacy in mpox pediatric patients[103]. A retrospective cohort study revealed cardiac events and increased levels of troponin- I were attributed to JYNNEOS vaccination for prevention of mpox, the exact reason for these adverse events is not known[104]. Also, preclinical studies found JYNNEOS vaccine is safe during pregnancy and lactation[105].

4.3. ACAM2000

It is an approved vaccine for smallpox and also approved for mpox under the Expanded Access Investigational New Drug. It is a live vaccinia vaccine that needs to be administered in single

doses, accessible in lyophilized form for extended preservation. It is necessary to weigh the danger of adverse events from replicative vaccinations, like ACAM2000, against the risk of pathogenic mpox.

VACV causes a localized skin infection and its surrounding tissue at the site of administration. The presence of a virus in the blood for a transient period leads to infection in the reticuloendothelial system including other organs. During the early stage, the virus multiplies in specific Langerhans cells present in the epidermis. The development of protective immunity is indicated by pustule formation at the administration site. Following replication, the viral antigens are exposed to the immune system. The neutralized antibodies and T and B cells aid in long-term memory. Furthermore, the safety and efficacy of ACAM2000 have not been explored in the pediatric population, pregnant women, and lactating mothers. However, live VACV vaccination, if administered to pregnant women, can lead to complications such as preterm delivery, congenital malformations, stillbirth, or perinatal deaths. Also, live VACV can be transmitted from breast milk to the baby and can lead to severe adverse effects. Moreover, it is available in a market with a warning note of pericarditis, and myocarditis. Rare adverse effects such as Stevens-Jonson Syndrome and encephalitis can occur. The second is the attenuated VACV, also known as modified vaccinia Ankara (IMMVAMUNE; US); IMVANEX (Europe); it replicates very slowly in mammalian cells. There should be no wound formed at the immunization site, and two injection doses are needed. The primate (macaques with AIDS) exposed to lethal levels of the mpox virus, administration of modified vaccinia Ankara has not shown protection against mpox due to decreased T-cell function[106]. LC16m8, a third vaccine, is an attenuated form of the VACV that is capable of replicating in mammalian cells. This needs to be administered in a single dosage. When it comes to human and animal immunizations, LC16m8 shows a safer profile and fewer side effects than ACAM2000. This vaccine has been modified to cease the circulation of the virus and has protected nonhuman primates against serious mpox[107]. In Japan, almost 50 000 school children were immunized with LC16m8, however, fewer adverse side effects were reported[108].

Notably, attenuated poxvirus vaccines have been utilized to combat the most lethal member of their family. The horsepox virus and CPXV were broadly employed for this purpose, undergoing passages in cattle and humans. Eventually, VACV emerged as the primary vaccine employed in the final campaigns to get rid of smallpox, an attempt successfully achieved by the WHO in the year 1980[49].

Subsequently, naturally occurring strains employed in vaccination were introduced to research laboratories, leading to the generation of VACV and other poxviruses including enhanced safety profiles. The recombinant DNA technology and the unique DNA genome characteristics of this virus family were employed for creating vaccines targeting different diseases. Moreover, the specific deletion and insertion of poxvirus genes resulted in an expanded array of alternated viruses exhibiting novel attributes, consisting of enhanced immunogenicity and effective safety as vaccine vectors[49]. In the 1970s, a vaccine for mpox was developed, derived from live

VACV, akin to the virus responsible for smallpox. While the vaccine exhibits high effectiveness in preventing mpox, it is not routinely administered to the general public due to the infrequency of mpox cases, which are typically confined to specific geographic regions. The vaccine is primarily reserved for people who have high chances of exposure, such as healthcare personnel or laboratory workers engaged in treating mpox patients.

In recent times, there has been an increasing emphasis on creating novel mpox vaccines with improved safety and efficacy compared to the existing vaccine. Experimental vaccines are currently undergoing testing in animal models, though further research is essential before human trials can be conducted. The overall direction of mpox treatment and vaccination revolves around developing innovative approaches to prevent and manage this uncommon ailment more effectively. Although mpox is not a significant public health concern, it remains crucial to persist in research and development endeavors to safeguard individuals vulnerable to potential exposure.

Several antiviral drugs have shown potential for treating *Orthopoxvirus*. For instance, by preventing viral DNA polymerase from functioning, cidofovir exhibits antiviral efficacy against several viruses. Unlike cidofovir, a modified cidofovir called CMX-001 does not have nephrotoxicity. CMX-001 was reported to have antiviral action against several *Orthopoxvirus* species. Further, the medication ST-246 inhibits the intracellular release of virus from the cell and has shown encouraging outcomes against several *Orthopoxvirus* species, such as VARV[109]. These modified medications or molecules were further explored and utilized in many combinations, involving VIG, for the treatment of adverse effects associated with vaccines[110,111].

In the current scenario, it is crucial to think about developing methods for treating sickness in endemic areas using these medications. Vaccines against smallpox, which include the fully replicating VACV, are not currently administered in regions where mpox is endemic due to worries about serious side effects in a population with a variable HIV status. A vaccination that does not include any risk factor and is easily given to children would be the best option for areas where mpox is endemic[90]. While there is no available vaccine that comprises all requirements, certain vaccines

from the following generation come closer to achieving that objective.

5. Clinical trials on mpox

Numerous clinical trials have been done and are in progress in various countries for investigating the efficacy and safety of available antiviral drugs and vaccines based on different measuring parameters such as reduction in the severity of disease, mortality rate, and viral load and providing antibodies against mpox virus. Table 1 summarizes the vaccines that are under clinical trials registered in the International Clinical Trials Registry. The recent re-emerged mpox outbreak provided real-world pieces of evidence related to the correlation between duration of immunity and protection against mpox virus infection. Moreover, potential predictive biomarkers could be identified by analyzing the immune response after vaccination in mpox patients.

6. Conclusions and future directions

In summary, viral diseases like mpox can pose significant threats to individuals and communities if not effectively managed and controlled. Understanding the mode of transmission is crucial, and appropriate precautions must be taken to prevent the spread of these diseases. Advancements in medical science have brought significant progress in the prevention and therapeutics of various viral infections. Vaccination, in particular, has proven highly successful in preventing viral diseases and even eradicating certain illnesses, such as smallpox. The currently undergoing clinical trial will facilitate the screening of effective vaccines for mpox virus. Nevertheless, managing viral diseases will continue to pose a challenge, including the emergence of new strains and the potential for outbreaks in vulnerable populations. Continuous research and surveillance are essential for early detection and swift responses to new outbreaks, as well as for the development of novel treatments and prevention

Table 1. Vaccines under clinical trials for the management of mpox virus.

Vaccine name	Vaccine platform	Study design	Age of participants	Phase	Clinical trial registry number	References
IMVAMUNE	Live attenuated, non-replicating vaccine	Prospective cohort of HCWs in DRC	18 years and older	Phase 3	NCT02977715	[112]
MVA vaccine	Live attenuated vaccines	Prospective cohort study	18 years and older	-	NCT05438953	[113]
MVA-BN	Live attenuated vaccines	Randomized, double-blind, multicentric study	18 to 45 years	Phase 3	NCT03699124	[114]
Imvanex®	Live attenuated vaccines	Non-randomized study	18 to 55 years	Early phase 1	NCT03953196	[115]
Biological: monkeypox vaccine	Smallpox and mpox vaccine (Live MVA)	Observational cohort study	18 years and older	-	NCT05522296	[116]
LC16m8	Live attenuated smallpox vaccines	A single-arm study	-	Phase 2	JPRN-jRCTs031220171	[98]

DRC: Democratic Republic of the Congo; HCWs: healthcare workers; MVA: modified vaccinia Ankara; MVA-BN: modified vaccinia Ankara-Bavarian Nordic; -: not available.

approaches. Overall, it is vital to remain well-informed about viral diseases and adopt appropriate measures to safeguard both ourselves and our communities. Also, pre and post-exposure prophylaxis with either vaccine or drug should be implemented to combat the circulation of mpox. With the right tools and strategies in place, we can persist in the fight against viral diseases and enhance public health outcomes for everyone.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

PB and RM conceived the idea of the manuscript and wrote and edited the manuscript. SS wrote a part and edited the manuscript. All authors have read and approved the manuscript submitted to the journal.

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