An Outline On Monkeypox Virus And Currently Available Vaccines

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ABSTRACT

Monkeypox is a viral disease caused by the monkeypox virus, first identified in colonies of monkeys, and is closely related to the smallpox virus. Therapeutic agents and vaccines developed for smallpox may also offer efficacy against monkeypox. As a zoonotic orthopoxvirus, monkeypox has the potential for transmission between humans and other mammals. According to recent reports, 136 cases of monkeypox virus infection were documented across 15 countries between May 11 and October 4, 2022. Currently, monkeypox is not entirely curable. This review briefly outlines the monkeypox virus, its epidemiology, and the vaccines available for the prevention and treatment of the disease.

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INTRODUCTION

Monkeypox virus is a double-stranded DNA virus that spreads unintentionally among humans and causes disease with relatively low mortality. It is an encapsulated DNA pathogen, and preliminary genetic evidence identifies the West African clade as the origin of the virus [1]. The monkeypox virus belongs to the Chordopoxvirinae subfamily within the Poxviridae family, which includes the Orthopoxvirus genus [2]. The virus can also infect wild animals, with two different strains reported: one from sooty mangabeys in Côte d'Ivoire, West Africa, and another from rope squirrels in the Democratic Republic of the Congo. The 2022 outbreak is attributed to the West African strain of monkeypox, which has a case fatality rate of 3.6%, compared to 10.6% for the more virulent Congo Basin strain. The West African strain is associated with milder illness than the Congo Basin strain [3]. The monkeypox outbreak that began in early 2022 has emerged as a new threat to global health. A worldwide outbreak beginning in May, 2022, and affecting over 26 000 people to date, was declared a public health emergency of international concern by WHO on July 23, 2022.As of July 8, 2022, a total of 9,069 laboratory-confirmed cases has been reported, the majority of which are from countries where the disease is not endemic. Additionally, cases of human monkeypox infection have been reported in regions previously considered smallpox post-eradication zones. In the current outbreak, human-to-human transmission has been identified as the primary mode of infection. The monkeypox virus has an incubation period of approximately 12 days when transmitted between individuals [4]. Although transmission through contaminated body fluids has been confirmed, it remains unclear whether monkeypox can be spread through sexual contact [1]. As these viruses require direct physical contact with an infected carrier, monkeypox is generally not highly contagious. Consequently, its transmission rate is expected to be slower than that observed in COVID-19 outbreaks and appears to have a significantly lower basic reproduction number compared to COVID-19 [1]. The reported cases in the 2022 outbreak did not appear to be linked to recent travel from endemic regions or prior contact with infected animals [3]. In this review, the epidemiology, transmission, clinical signs and symptoms, and the vaccines available for monkeypox are briefly discussed.

Brief on Monkeypox Virus

The first cases of monkeypox were identified in monkey colonies in 1958. Prior to the current outbreak, the disease was typically reported in Central and West Africa, where it was primarily transmitted by rodents inhabiting tropical rainforests. In 1970, monkeypox was first detected in a 9-month-old infant in the Democratic Republic of the Congo [5]. Monkeypox virus is a brick-shaped, encapsulated virus with a 190 kb double-stranded DNA genome. Its ends are tightly wound, forming a dumbbell-shaped pleomorphic core, and the virus typically ranges in size from 140 to 260 nm. A comparative analysis of the genomic similarities between the variola virus and monkeypox was conducted and described in 2001. The central portion of the monkeypox genome shares 96.3% sequence homology with variola virus and encodes essential enzymes and structural proteins. However, the terminal regions of the monkeypox genome, which are responsible for

virulence and host-range factors, exhibit significant differences. Based on genomic comparisons between monkeypox and smallpox viruses, it is concluded that monkeypox is a distinct species that evolved independently from an orthopoxvirus progenitor, separate from variola virus [6]. Unlike many DNA viruses, monkeypox virus is capable of producing the proteins necessary for transcription and subsequent replication [7-8]. Genome comparisons of strains from West and Central Africa have revealed a set of putative genes that may contribute to the variable virulence observed among clades. Predictions suggest that these open reading frames could influence the pathogenicity of the virus, its host range, immune evasion, and other factors [9]. Viral entry is dependent on the type of cell and viral clade, occurring after an initial attachment to the cell surface. This attachment involves interactions between viral ligands and cellular receptors, such as chondroitin sulfate or heparan sulfate. Both viral fusion with the cell membrane and endosomal uptake—similar to macropinocytosis and facilitated by actin—promote subsequent transit through the cell [10].

Human cells derived from individuals previously infected with monkeypox are unable to produce inflammatory cytokines due to the impairment of T-cell receptor-mediated T-cell activation by the Central African monkeypox strain. These findings suggest that monkeypox may produce a modulator that suppresses host T-cell activation [9]. In contrast, the genome of the monkeypox virus Congo strain consists of 196,858 bp of DNA, exhibiting structural similarities to other orthopoxviruses. It contains 190 largely non-overlapping open reading frames with 60 amino acid residues [11]. This strain is reported to be more virulent than the Liberia strain, a West African variant, as it can replicate in multiple organs, including the skin, reticuloendothelial system, gastrointestinal organs, lymphoid system, genitourinary tract, and respiratory organs. In comparison, the Liberia strain replicates only in the skin, reticuloendothelial system, and lymphoid system, which may account for the differences in virulence and subsequent organ dysfunction [12].

Epidemiology

Human monkeypox cases have increased since the 1970s, particularly in the Democratic Republic of the Congo. The average age at presentation rose from 4 years in 1970 to 21 years in 2019. Although there is a notable difference between clades, the overall case fatality rate stands at 8.7%, with West African cases having a rate of 3.6% and Central African cases showing a rate of 10.6% [13]. The first monkeypox outbreak outside of Africa occurred in the United States in 2003, following interactions with infected pet prairie dogs. These animals had been housed alongside dormice from Ghana, which had travelled from the Gambia, and imported pouched rats. More than 70 cases of monkeypox were reported as a result of this outbreak in the U.S. Additionally, monkeypox was reported among Nigerian travellers to Israel in September 2018, the United Kingdom in September 2018, December 2019, May 2021, and May 2022, Singapore in May 2019, and the United States in July and November 2021. The WHO reported cases of monkeypox in several non-endemic countries in May 2022 [14].

A thorough review of the literature reveals a recent increase in both suspected and confirmed monkeypox cases. According to the WHO, over 19,000 cases were reported between 2000 and 2019, and 15,600 cases occurred in 2021–2022. However, beginning on May 7, 2022, cases of human monkeypox—largely contemporaneous and reportedly unrelated to travel to Africa—were reported in 13 European countries: the United Kingdom, Slovenia, Spain, Italy, Austria, the Czech Republic, Portugal, Germany, Belgium, Denmark, France, and Sweden, as well as in Australia, Canada, Israel, and the United States [15-19].

Human illnesses have been associated with animal contact, although it can be difficult to pinpoint the exact animal exposure that led to a case, particularly in regions where bushmeat from various species is commonly hunted or prepared. For example, mouse infestations in homes are frequent. Although monkeypox appears to be less contagious than smallpox, it was reported in approximately 11.7% of patients' household contacts who had not received the smallpox vaccination [20] (Figure 1). The primary routes of transmission are thought to include respiratory excretions, saliva, or direct contact with lesion exudate or crusted material [21-22]. Additionally, the 2022 outbreak was recently linked to the identification of the virus in seminal fluid, vaginal and rectal lesions, and feces from four men who have sex with men (MSM) in Italy. Monkeypox virus was isolated from the seminal fluids of three individuals, with quantification cycles ranging from 27 to 30, which is relatively low for viral isolation [23]. While further research is necessary to confirm this, current findings support the hypothesis that monkeypox may be sexually transmitted. These results suggest viral shedding, raising the possibility of transmission, although they do not provide conclusive evidence of infectivity [23-24].

Historically, the virus has been endemic primarily in regions of the African continent and typically spreads through intimate contact with infected animals or humans. However, with the increase in tourism, travel, and trade, the virus has spread outside of Africa [25]. Evolutionary changes in these viruses are generally attributed to gradual gene loss at the ends of their genomes, a process that may be accelerated by selective pressure from host species. Additionally, variations in gene copy number provide further evidence for the increasing viral fitness for human infection and transmission [25].

Region	Number of Cases	Case Fatality Rate	Age Distribution	Clade Variation	References
Democratic Republic of the Congo (DRC)	19,000 suspected/confirmed (2000-2019)	10.6% (Central Africa)	Initially more common in children	Central African clade (more virulent)	[13]
West Africa	15,600 cases (2021-2022)	3.6%	Increasing average age (from 4 to 21)	West African clade (less virulent)	[13]
Global (2022 Outbreak)	19,000+ cases (multiple countries)	~8.7%	Higher proportion of adult cases	Increased cases in non-endemic regions (travel-related)	[14, 15-19]

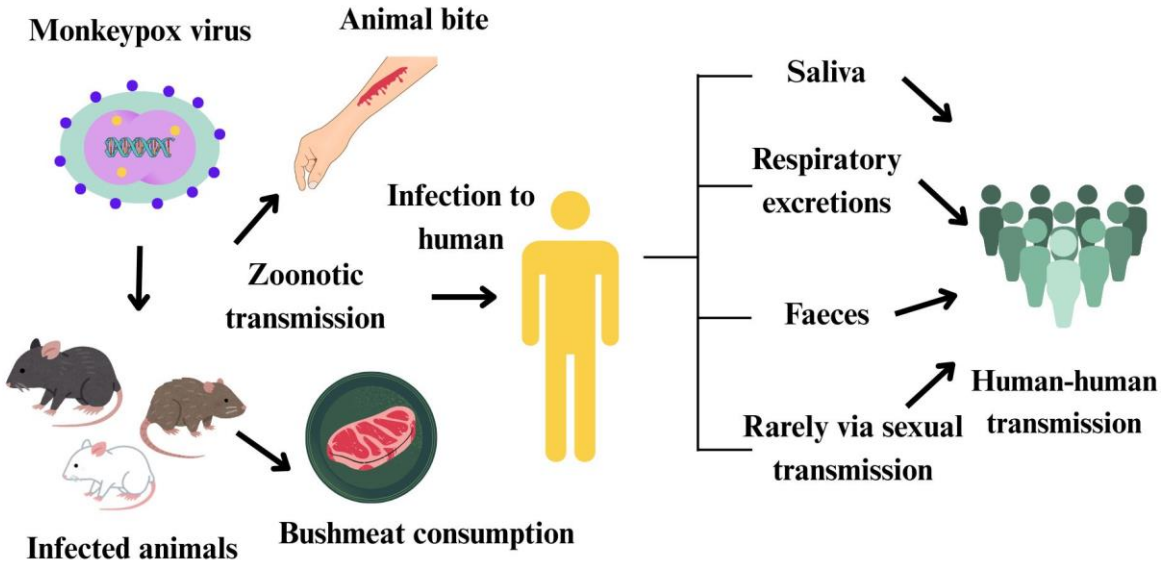

Figure 1. Transmission of monkey pox virus from animals to humans

Signs and Symptoms

The typical monkeypox rash in humans consists of maculopapular lesions with a diameter of 2–5 mm. According to reports from epidemics in Africa, the rash typically spreads in a centrifugal pattern and becomes generalized in distribution [26]. In some cases, a centripetal rash resembling chickenpox may develop. Over a period of 14 to 21 days, the skin lesions usually progress through the papular, vesicular, pustular, and crust phases before sloughing off and leaving dyspigmented scars [6, 27]. The rash typically begins as macules on the lips, with each lesion evolving into papules, vesicles, pustules, and scabs. It then spreads to the face, hands, and feet, including the soles and palms. While the rash may not always be present, the pain associated with it can be severe, and pruritus may occur during the healing phase. Unlike chickenpox, monkeypox skin lesions are often of a similar size and appear simultaneously. The number of lesions can range from 10 to 150 and may persist for up to 4 weeks [28]. Patients are contagious from the onset of symptoms, which includes the prodromal phase preceding the rash, and remain infectious until the lesions scab over and fall off, resulting in the formation of a new layer of skin [6]. The potential complication of monkeypox can occasionally affect patients and may include encephalitis, bacterial superinfection, conjunctivitis or keratitis, pneumonitis, among others [2, 29]. In addition to the characteristic skin rashes and blisters, some individuals may also experience symptoms such as headache, fever, swollen lymph nodes, muscle and body aches, back pain, and fatigue [3]. Asthenia and myalgias are also common prodromal symptoms. Neuralgia and mood disturbances can also manifest. In some people, conjunctivitis can occur, and corneal lesions can cause scarring with vision loss. A study depicted an 11-year-old boy who experienced a wide range of symptoms over the course of 11 days, including a generalized rash, headache, sore throat, malaise, and fever. The patient also exhibited widespread lymphadenopathy, as well as oral and nasal mucosal lesions and ulcers. Five additional family members living in the same household displayed similar signs and symptoms, though with varying degrees of severity. The physical examination revealed umbilication, ulcerations, crusting, and scab formation, along with extensive, well-circumscribed papulopustular rashes on the trunk, palms, soles of the feet, and face [30].

Transmission Mode	Description	Incubation Period	Risk Factors	Prevention Measures	Effectiveness of Interventions	Citations
Direct Contact	Contact with fluids, lesions, or crust material.	12-14 days	Close contact, sexual contact, exposure to lesions.	Avoid contact, PPE, hygiene.	Vaccination, distancing.	[20], [21-22]
Respiratory Droplets	Droplets via prolonged face-to-face contact.	7-14 days	Prolonged contact, confined spaces.	Masks, avoid crowded areas.	Masking, ventilation, isolation.	[21-22]
Sexual Contact	Transmission through sexual fluids and lesions.	Unknown	Unprotected sexual activity, active lesions.	Safe sexual practices, isolation.	Vaccination, safe sexual practices.	[23-24]
Animal-to-Human Transmission	From infected animals (rodents, primates).	7-21 days	Handling or consuming bushmeat.	Avoid bushmeat, PPE, handling animals.	Wildlife monitoring, vaccination.	[25]
Fomites	Spread via contaminated objects or surfaces.	5-14 days	Contact with contaminated surfaces.	Surface disinfection, PPE.	Regular disinfection, PPE use.	[21-22]

Vaccines for Monkeypox

Monkeypox and smallpox are clinically and immunologically comparable. Previous studies indicate that the smallpox vaccine provides 85% protection against monkeypox. As a result, it is recommended to reintroduce smallpox vaccination for the general population, particularly for those considered "at-risk" [31]. Some smallpox vaccines, based on the surface proteins from the two main virion forms—intracellular mature virions and extracellular enveloped virions—have been studied as protective antigens for orthopoxvirus infections. These include the mature virion proteins A13, A17, A27, A28, D8, H3, and L1, as well as the enveloped virion proteins A33 and B5, which are also targets for immune responses [32]. When antibodies target both mature virion proteins and enveloped virion proteins, evidence suggests that this combination may provide an immune response. Although many viral proteins can effectively stimulate the host immune system, humoral immunity is known to have protein targets that vary between individuals, and many viral proteins have not been conclusively linked to protective responses [32-33]. Smallpox vaccines, such as Dryvax and Imvamune, have demonstrated significant reactivity against membrane proteins like A13, H3, D8, and A17 in both monkeypox-infected prairie dogs and humans. These four mature virion proteins have been shown to be effective targets for virus neutralization, making them critical immune system targets for inactivation and halting viral propagation [34]. Antibody responses to core proteins were notably consistent across viral strains and species. These core proteins would only become accessible after the lysis of infected cells, at which point their relative abundance and the availability of immunogenic epitopes would be influenced.

Humans who received the Imvamune vaccine did not show a response to the A17 protein, and their responses to A56, A27, and A33 were also significantly reduced. Furthermore, prairie dogs vaccinated with Imvamune showed no response to any of these antigenic targets [35-36]. A recent study has shown that the monkeypox virus-2022 sequences exhibit low genetic variability when compared to known targets of vaccinia virus-elicited neutralizing antibodies or T cells, either at the epitope level (where available) or the protein level. Furthermore, the majority of the genetic variants associated with monkeypox virus-2022 were frequently observed in the Congo Basin clade of the virus. Based on this and the understanding that vaccinia virus-based vaccines elicit comparable immune responses, it can be inferred that currently available vaccinia virus-based vaccines, such as Bavarian Nordic's modified vaccinia virus Ankara and ACAM2000, will likely induce similar humoral and cellular immunity against monkeypox virus-2022 as first-generation vaccinia virus-based vaccines did for the Congo Basin clade of monkeypox virus B [37-38].

A monkeypox-specific vaccine, "JYNNEOS," also sold under the names Imvamune and Imvanex, has been developed and is the only FDA-licensed vaccine in the United States approved for prevention. However, at the onset of the outbreak, only 2,400 doses were available in the Strategic National Stockpile. As efforts to increase vaccine availability align with the tested and authorized dosing schedule, it is believed that intradermal dosing of JYNNEOS will provide rapid access to this limited resource for populations disproportionately affected by monkeypox, without compromising the immune response. Although clinical data is sparse, intradermal delivery of JYNNEOS is expected to be as immunogenic as subcutaneous administration in preventing monkeypox infection and disease [39-40]. The Lister (Elstree) strain of vaccinia was used to develop the live, replicating third-generation vaccine known as LC16 m8, which has been authorized for active immunization against smallpox in Japan since 1975. In August 2022, Japan expanded the vaccine's indication to include immunity against monkeypox. These vaccines are considered safe for immunocompromised individuals due to their attenuated phenotype and better safety profile against monkeypox [Gruber, 2022].

Bavarian Nordic's modified vaccinia virus Ankara (MVA) is regarded as safe for breastfeeding mothers. As a non-replicating vaccine, there is no theoretical concern about its use during pregnancy, and animal studies have shown no adverse fetal effects. While it is unclear whether MVA enters breast milk, this is unlikely since the vaccine virus cannot replicate in humans. After assessing the risks of monkeypox exposure for both the mother and the child, any breastfeeding woman with significant exposure to the virus should be offered the vaccine. Currently, no vaccine has been authorized for use during pregnancy to prevent monkeypox [42].

Vaccine	Type	Primary Target Population	Administration	Special Considerations	Citations
JYNNEOS (Imvamune, Imvanex)	Non-replicating	At-risk populations (e.g., healthcare workers, exposed individuals)	Subcutaneous or intradermal	Limited initial doses, increased access through intradermal dosing	[39, 40]
LC16 m8	Live, Replicating	Immunocompromised individuals and high-risk groups	Subcutaneous	Safer for immunocompromised individuals, approved in Japan	[42]
Modified Vaccinia Virus Ankara (MVA)	Non-replicating	Pregnant and breastfeeding women, at-risk groups	Intradermal or subcutaneous	Safe for breastfeeding women, not recommended for pregnant women	[42]
ACAM2000	Live, Replicating	Emergency use for those at high risk	Subcutaneous	Riskier for immunocompromised individuals due to live virus replication	[31]

CONCLUSION

As far as public health is concerned, monkeypox has garnered significant attention, especially considering the successful eradication of smallpox in 1980, which led to the cessation of smallpox vaccinations. In comparison, monkeypox remains a threat, especially in regions where it is endemic. The disease typically manifests with symptoms that last between two and four weeks and, in most cases, is self-limiting. However, in extreme instances, complications can arise, leading to severe health outcomes, such as encephalitis, secondary bacterial infections, or organ dysfunction. This highlights the importance of raising public awareness regarding risk factors and educating communities on self-care and preventions. Public health strategies, including proper hygiene, avoiding direct contact with infected individuals or animals, and ensuring timely medical intervention, are vital in controlling its spread. Moreover, as the virus continues to spread beyond endemic areas, the need for preventative measures has become more apparent. The feasibility and effectiveness of monkeypox vaccination programs are actively under review by scientists and health organizations. Given the potential for the disease to spread globally, the development of vaccines tailored specifically to monkeypox or improved versions of existing smallpox vaccines could play a crucial role in curbing future outbreaks. Continued research into the long-term immunity provided by such vaccines, as well as the broader epidemiological patterns of the virus, will be essential in managing public health responses and minimizing the impact of future outbreaks.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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