Global Re-emergence of Monkeypox: A Synoptic Review

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Ibnosina J Med Biomed Sci 2024;16:49–56.

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Abstract

As the coronavirus disease 2019 pandemic continues to rage, the unprecedented manifold increase in monkeypox (mpox) cases throughout the world is raising qualms about a possible pandemic. As of January 2024, the disease has been reported in around 116 countries, with nearly 92,500 confirmed cases and 170 deaths. In this mini-review, we have endeavored to cover multiple aspects of the mpox disease. Mpox virus is an enveloped double-stranded DNA virus that belongs to the *Orthopoxvirus* genus. The disease is endemic in certain African countries. Until recently, however, the disease was rarely reported in Europe and the United States. In contrast to the previous outbreaks outside Africa, reported cases in the 2022 outbreak did not travel to the endemic areas. Superspreading events at mass gatherings, multiple-partner sexual encounters, and international travel were major drivers of the recent global outbreak of mpox. The 2022 mpox virus may have undergone accelerated evolution. It diverges from the related 2018 to 2019 viruses by around 50 single-nucleotide polymorphisms, some of which brought about amino acid changes in immunogenic surface glycoprotein B21. Differential diagnosis for mpox could be quite challenging since it can masquerade as a wide variety of illnesses. Worse still, some patients may be asymptomatic or show subtle symptoms. The infection is confirmed by conventional or real-time polymerase chain reaction on lesion material. Although there is no specific therapy approved for mpox infections, two antivirals (tecovirimat and brincidofovir) and vaccinia immune globulin may be used. Vaccines also provide protection against mpox when properly administered prior to exposure. Finally, the implementation of preventive measures is of paramount importance, especially in regions where mpox transmission is widespread and among high-risk populations.

Keywords
- mpox
- outbreak
- symptoms
- diagnosis
- vaccine

Introduction

While the world continues to struggle with the aftermath of the coronavirus disease 2019 (COVID-19) pandemic, the peril of another outbreak is unsettling.[1] Zoonotic viral diseases such as COVID-19, the Middle East respiratory syndrome (MERS), Crimean-Congo hemorrhagic fever, avian flu, and Zika represent the greatest threat impacting global health.[2,3] For the first time in history, we are witnessing a widespread outbreak of mpox (formerly known as monkeypox) affecting multiple regions of the world. Mpox is a viral zoonotic disease found primarily in tropical rainforests of

article published online
May 8, 2024

DOI https://doi.org/10.1055/s-0044-1786684.
ISSN 1947-489X.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Central and Western Africa. Although the disease has seldom spread beyond Africa, new cases in nonendemic countries have been on the rise since early May, 2022.[4]

The first case of mpox was confirmed in the United Kingdom on May 6, 2022. Since then, events have moved at an alarming pace.[5] As of January 2024, the disease has been reported in around 116 countries, with nearly 92,500 confirmed cases and 170 deaths.[6] Unlike the previous outbreaks of mpox outside of Africa, reported cases in the 2022 mpox outbreak did not travel to the endemic areas. Researchers, public health officials, and physicians are now endeavoring to figure out how the virus spreads and how to stop it. More cases of the disease are expected as surveillance is expanded in nonendemic countries.[7] Indeed, the number of cases detected outside Africa has already surpassed that from 1970 to the present outbreak, raising qualms about a possible pandemic.[7]

Methods

In this narrative mini-review, we aim to provide an overview of the key findings pertaining to human mpox by analyzing English literature sourced from PubMed and Google Scholar since the year 2000. A nonsystematic search strategy was employed using the designated keywords "human monkeypox" or "human mpox." This allowed for the identification of the 8,500 articles. Upon removing the overlapping references and studies that were not pertinent, a total of 150 articles were selected. From the 150 studies read in total, 103 were excluded, and 47 studies were included for the current review article. To ensure a comprehensive overview, the results incorporated a diverse range of research studies, including experimental studies, narrative reviews, systematic reviews, and meta-analyses. The literature was sorted into different sections, which included viral morphology and genome of mpox virus as well as history, epidemiology, transmission, clinical symptoms, laboratory diagnosis, treatment, and prevention of mpox disease.

Viral Morphology and Genome

The morphology of poxviruses shows that virions are ovoid or brick-shaped particles encased by a geometrically corrugated lipoprotein outer membrane. These viruses are 200 to 400 nm in size with large double-stranded DNA (dsDNA) genomes (ranging from 130 to 300 kbp) that multiply in the cytoplasm of infected cells.[8] They are large enough to be visible by the light microscopy, with its ultrastructure resolvable through electron microscopy. The genus *Orthopoxvirus* encompasses several species that can infect humans, including variola virus, mpox virus, vaccinia virus, and cowpox virus.[8] A virion of *Orthopoxvirus* consists of four major elements: a core, two lateral bodies, outer membrane, and the outer lipoprotein envelope. Viral dsDNA and core fibrils reside in the central core, surrounded by a palisade layer. The outer membrane, which is made up of numerous surface tubules, encloses the central core, palisade layer, and lateral bodies (►**Fig. 1A**). Viral particles that are released spontaneously possess the outer lipoprotein envelope, whereas those released by cellular disruption do not.[9]

Smallpox, caused by the variola virus, is restricted to humans, while the other members are zoonotic. In contrast to variola virus and mpox virus, which are potentially life-threatening, vaccinia virus and cowpox virus tend to cause localized lesions.[10] Mpox viruses have been detected in a variety of mammalian species, including squirrels, mice, monkeys, and dogs, with African rodents serving as the reservoir, though it has occasionally infected humans as well.[11]

The mpox virus harbors a dsDNA genome of approximately 197 kb, with 190 open reading frames (ORFs). The ends of *Orthopoxvirus* genomes, such as mpox genome, contain an identical but oppositely oriented sequence called an inverted terminal repetition, which includes a set of short tandem repeats and terminal hairpins.[12] All proteins crucial for viral DNA replication, transcription, virion assembly, and egress are encoded within the genome of mpox virus. Genes involved in housekeeping functions (essential viral functions such as replication and virion assembly) are highly conserved among members of *Orthopoxvirus*, and are located in the central region of the genome. The central core region of mpox virus shares over 90% sequence homology with other orthopoxviruses, especially within the ORF located between C10L and A25R.[13] By contrast, those genes contributing to virus-host interactions are less conserved, and are found near the terminus.[8] Despite being a DNA virus, mpox virus spends its entire life cycle in the cytoplasm of infected cells. Intracellular mature virus (IMV) and extracellular-enveloped virus (EEV) are the two kinds of infective virions formed by these viruses. IMV is liberated upon cell lysis, whereas EEV is produced when cells come into contact with actin tails, enabling the virus to quickly disseminate over long distances within the host body.[14]

According to genomic analysis, two mpox clades exist, namely Clade I (previously called the Congo Basin clade) and Clade II (previously called the West Africa clade). For subsequent variants, Roman numerals will be used for the clade and lowercase letters for the subclade.[15] The Clade I infections are linked with higher rates of morbidity, lethality, and transmissibility.[9] The Clade II also consists of two subclades: IIa and IIb. Subclade IIb encompasses most of the circulating strains from 2017 to 2019, the B.1 lineage that caused the 2022 global mpox outbreak, and the A.2 lineage that caused a minor endemic in 2022.[15] The cryptic transmission and ongoing microevolution of the mpox virus still persist, potentially leading to an unpredictable pathogenicity of the virus.

History, Epidemiology, and Transmission of Mpox

The mpox virus was first discovered in the Statens Serum Institut (Copenhagen, Denmark) in the late 1950s when two outbreaks of an unknown vesicular disease among captive monkeys occurred, hence the name mpox.[16] Nevertheless, the term is misleading because rodents such as squirrels and rats are largest animal reservoirs of the virus.[17] It has been

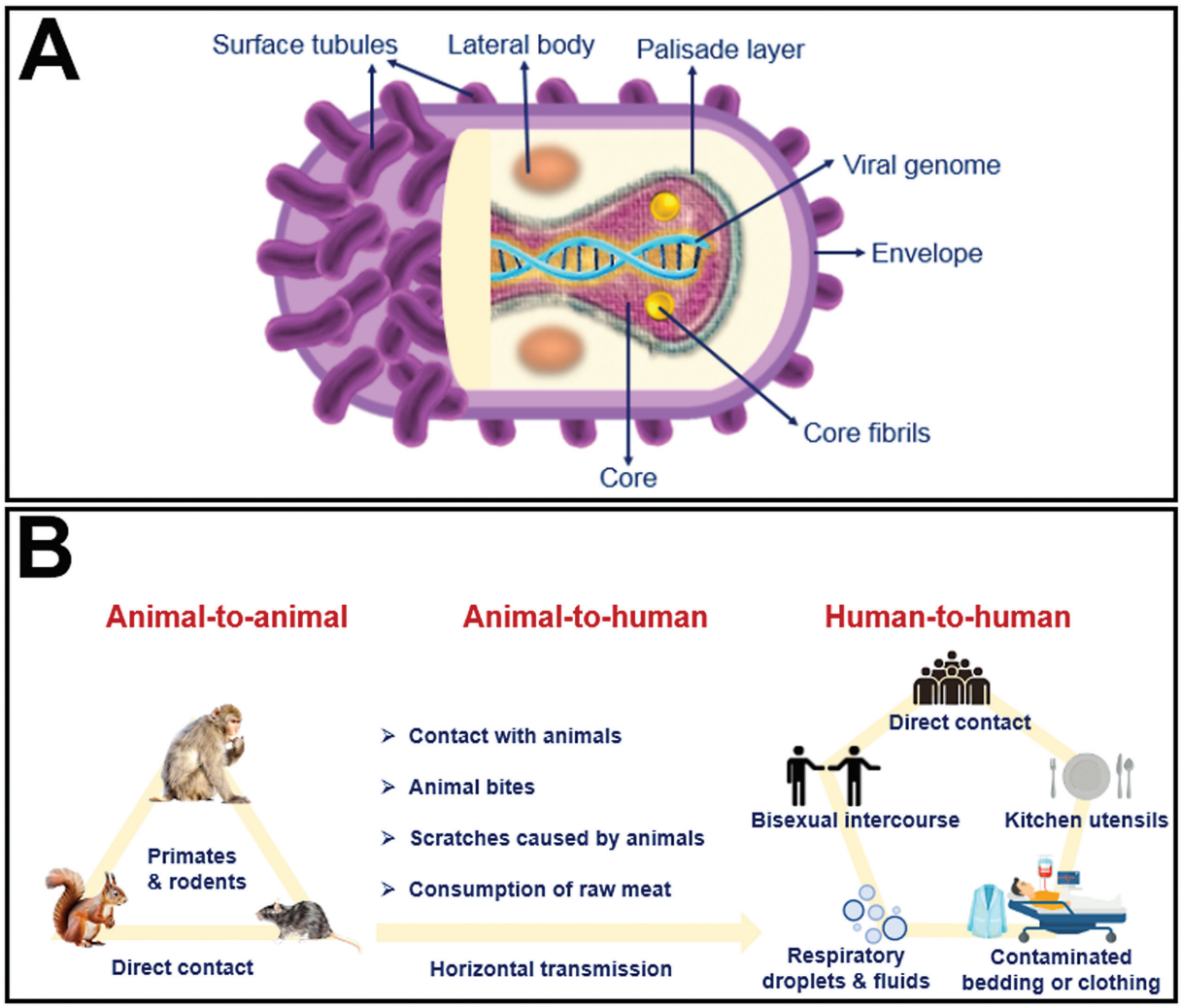

Fig. 1 The structure (**A**) and the transmission (**B**) of monkeypox (mpox) virus.[9] The mpox virus can be transmitted through animal-to-animal, animal-to-human, and human-to-human routes.

observed that individuals in Sub-Saharan Africa have contracted mpox as a result of close contact with infected animals, indicating the presence of this disease for several decades. In 1970, the Democratic Republic of the Congo announced the first human case of mpox. Since its discovery, the disease has been endemic throughout Central and West Africa, with sporadic cases transmitted from local wildlife reported among people.[18]

The potential factors that elevate the risk of exposure to animals and subsequent animal-to-human transmission include the contact between humans and the animal reservoir of mpox due to deforestation for new lodging lands, population migration into the depths of the forest, sleeping outdoors or on the ground, and residing near or visiting the forest. The mpox disease spreads by close contact with body fluids, wounds, tissues, respiratory droplets of patients or wild animals, as well as by contaminated inanimate objects.[19] Overall, the known transmission modes of mpox virus include animal-to-human and human-to-human transmission (►**Fig. 1B**).

In spite of the fact that mpox occurs mainly in Africa, there have been sporadic reports of the disease in other parts of the world in the last couple of decades. Mpox remained an unnoticed global public health menace until 2003, when the first cases (47 confirmed and probable cases) outside of Africa were discovered in the United States.[20] This was linked to an infected pet prairie dog that housed alongside rats imported from Ghana.[21] Since 2003, many cases of mpox have been reported in a number of countries, with Nigeria experiencing the worst epidemic in 2017.[7] When three individuals in the United Kingdom were diagnosed with mpox in September 2018, the disease drew media attention once again. The first two patients had recently returned from Nigeria. The third case was diagnosed in a healthcare worker who was caring for one of the first two patients. Soiled bedsheets most likely contributed to the infection of the mentioned healthcare worker, the first confirmed case of human-to-human transmission outside of Africa. Israel also reported an imported mpox case from Nigeria in the same year. There was no evidence of secondary transmission. A year later, a Nigerian attending a training course in Singapore developed skin lesions shortly after arriving and was diagnosed with the disease.[22] Lastly, there were two confirmed cases of mpox in the United States in 2021. Both of these

patients have returned to the United States after traveling to Nigeria.[23] Many epidemiologists argue that the surge in mpox cases over the past decades corresponds with the diminishing immunity resulting from the cessation of smallpox vaccinations, which previously offered cross-protection against mpox.[24]

The United Kingdom reported a case of mpox in a traveler upon returning from Nigeria on 6th May 2022. Since then, cases have been increasing exponentially in many nonendemic countries. As opposed to previous outbreaks in Europe, the majority of cases in the 2022 outbreak did not have a history of travelling to African countries where mpox is endemic.[25] According to the data, the widespread transmission of mpox has had a higher incidence among gay, bisexual, and other men who engage in sexual activities with men, as well as among racial and ethnic minority groups.[26] The disease was further disseminated due to the increased rates of international travel.[27] In July 2022, the World Health Organization (WHO) declared the global mpox outbreak a public health emergency of international concern.[28] While the latest report from the WHO showed a decrease in the number of cases, it is important to remain cautious. Despite debates about whether mpox is a sexually transmitted disease or not, some recent studies found that the virus persists in semen for weeks after symptoms onset.[29,30] Individuals who are unaware they are infected may be more likely to disseminate the disease due to the way symptoms are appearing. They may be asymptomatic or show subtle symptoms even without fever or swollen lymph nodes.[31]

Evolution of the 2022 Mpox Virus

Recent phylogenomic analyses revealed that mpox viruses related to the 2022 outbreak have a specific monophyletic lineage in comparison to the strains from previous outbreaks, with mutational signatures that may facilitate transmission and dispersion.[27,32] Most of viral genomes from the nonendemic areas belong to the B.1 lineage (proposed Clade III). The lineage B.1 is a divergent branch descendant from a branch with lineage A.1 linked to the exportation of mpox in 2018 and 2019 from Nigeria to the United Kingdom, Israel, and Singapore.[32] A stochastic evolutionary process and genomic divergence may explain the increase in transmission throughout different countries. For instance, the 2022 mpox virus differs from the related 2018-2019 viruses by a mean of 50 single-nucleotide polymorphisms, far greater than expected (about 6–12 times) based on previous estimates of the substitution rates for orthopoxviruses.[33] The apolipoprotein B mRNA-editing catalytic polypeptide-like 3 (APOBEC3) enzyme may account for the global mpox outbreak in 2022. These biased mutations (from GA to AA or TC to TT) in the genomes of the 2022 mpox viruses indicate an accelerated evolution driven by APOBEC3.[34] The APOBEC3-derived mutations may further diminish the pathogenicity and symptoms caused by the mpox virus, leading to the cryptic transmission of the disease in populations and the global mpox outbreak.[35] By conducting further studies on genomes of mpox virus, researchers may be able to observe future adaptations linked to changes in viral properties.

Clinical Symptoms

The incubation period, on average, lasts 7 to 14 days. Symptoms typically encompass a fever, headache, myalgia, and exhaustion, followed by a rash beginning on the face and spreading to other parts of the body.[36] The development of rash is often preceded by or accompanying maxillary, cervical, or inguinal lymphadenopathy in the majority of patients. This development of swollen lymph nodes is a feature that distinguishes mpox from smallpox.[37] In contrast to other diseases that may bear resemblance initially, such as chickenpox, measles, and smallpox, mpox demonstrates the presence of lymphadenopathy during the prodromal stage.[38] Mpox also presents synchronous lesions, while chickenpox usually manifests with skin lesions in different stages (macules, papules, vesicles, and scabs) all at once. The mpox rashes progress through stages from macules to papules to vesicles and then to pustules.[39] These skin lesions can lead to secondary bacterial infections, especially in patients who have not been vaccinated.

Mpox is considered a self-limiting disease; however, its severity can be influenced by various factors, including the specific viral strain, an individual's immune status, and the potential complications that may arise.[13] Severe cases of mpox infection can cause complications such as hemorrhagic disease, necrotic disease, obstructive disease, inflammation of vital organs (e.g., myocarditis and encephalitis), and septicemia. These severe manifestations are more likely to occur in immunocompromised individuals, including children, older adults, and those with immunodeficiencies such as human immunodeficiency virus (HIV) patients and individuals using immunosuppressive drugs.[13]

Laboratory Diagnosis

The sensitivity and accuracy of polymerase chain reaction make it the preferred method for diagnosing mpox. The sample consists of skin lesions collected from various sites, such as fluid samples from pustules, vesicles, exudates, and crusts. If an individual is suspected to be in the prodromal stage of illness and does not exhibit any visible skin lesions, testing can still be conducted using oropharyngeal or nasopharyngeal swabs.[9] To ensure the appropriate transfer of exudate or lesion base specimens to testing media, it is imperative to employ swabs made of dacron, nylon, or polyester instead of cotton.[40] Both the individual collecting the specimen and the laboratory personnel should exercise caution and adhere to a risk-based approach in handling the specimen.[40]

The detection of antibodies in plasma or serum alone does not provide a definitive diagnosis for mpox. When test results yield inconclusive results, the identification of immunoglobulin M in patients or the presence of immunoglobulin G in paired serum samples taken at least 3 weeks apart, with the first sample obtained within the initial week

of the illness, may provide valuable assistance in establishing a diagnosis.[41] The impact of recent vaccinations on serological testing should not be overlooked. The utilization of electron microscopy allows for the visualization of mpox viruses in a clinical sample as well.[9] However, due to availability of molecular techniques as well as facilities and technical expertise required for utilization of electron microscopy, this method is not usually used for diagnosis. In the absence of sufficient experience and containment facilities, virus isolation in cell culture is not recommended as a routine diagnostic procedure.[41]

Treatment and Prevention

At this time, there is no specific treatment approved for mpox infections. Patients are best managed through symptomatic and supportive therapies. Tecovirimat, brincidofovir, and cidofovir are the candidate therapies for the management of mpox.[7] The first Food and Drug Administration (FDA)-approved treatment for smallpox is tecovirimat (TPOXX, ST-246), a low-molecular-weight antiviral drug. Tecovirimat effectively hampers the replication of *Orthopoxvirus* by targeting and inhibiting the p37 envelope protein.[36] In animal studies, tecovirimat exhibited inhibitory effects on a wide range of viruses, including vaccinia, ectromelia, cowpox, variola, and rabbitpox.[42] Brincidofovir (CMX001, Tembexa) is an analogue of cidofovir that undergoes conversion to cidofovir and effectively hinders the viral DNA synthesis mediated by *Orthopoxvirus* DNA polymerase.[36] The drug was granted fast-track designation and Orphan Drug Status for the treatment of smallpox in 2018.[42] Brincidofovir exhibits antiviral properties against various DNA viruses, including adenovirus, BK virus, and cytomegalovirus.[42] Cidofovir, an analogue of cytosine in the form of a cytidine nucleotide, undergoes conversion by the enzymes present in the host cells to produce an active metabolite known as cidofovir diphosphate. This metabolite effectively hinders the activity of the viral DNA polymerase (►**Fig. 2**).[42] As for vaccinia immune globulin intravenous (VIGIV), there is currently no clinical data available to support the use of it for managing complications associated with mpox. Nevertheless, it can be considered as a supplementary treatment option alongside antiviral drugs for severe infections. Additionally, this therapy is safe and may be beneficial for vulnerable patients.[7] The FDA has approved its usage against mpox in the United States. Therefore, Centers for Disease Control and Prevention (CDC) advises administering VIGIV prophylactically to immunocompromised individuals who have been exposed to *Orthopoxvirus*, including mpox, in order to minimize the severity of the infection.[43]

The CDC has implemented several general precautionary measures. One of these measures includes practicing hand hygiene after each patient contact. Additionally, health workers are advised to wear suitable personal protective equipment like gloves, gowns, masks, and face shields to minimize their risk of exposure.[43] To maintain proper hygiene and prevent the spread of infection, it is recommended to cover a patient's skin lesions with a bandage or gauze. Given the stability of poxviruses and their potential for remaining contagious in the environment, it is essential to utilize disinfectants when cleaning high-touch surfaces. Furthermore, it is advisable to refrain from activities like

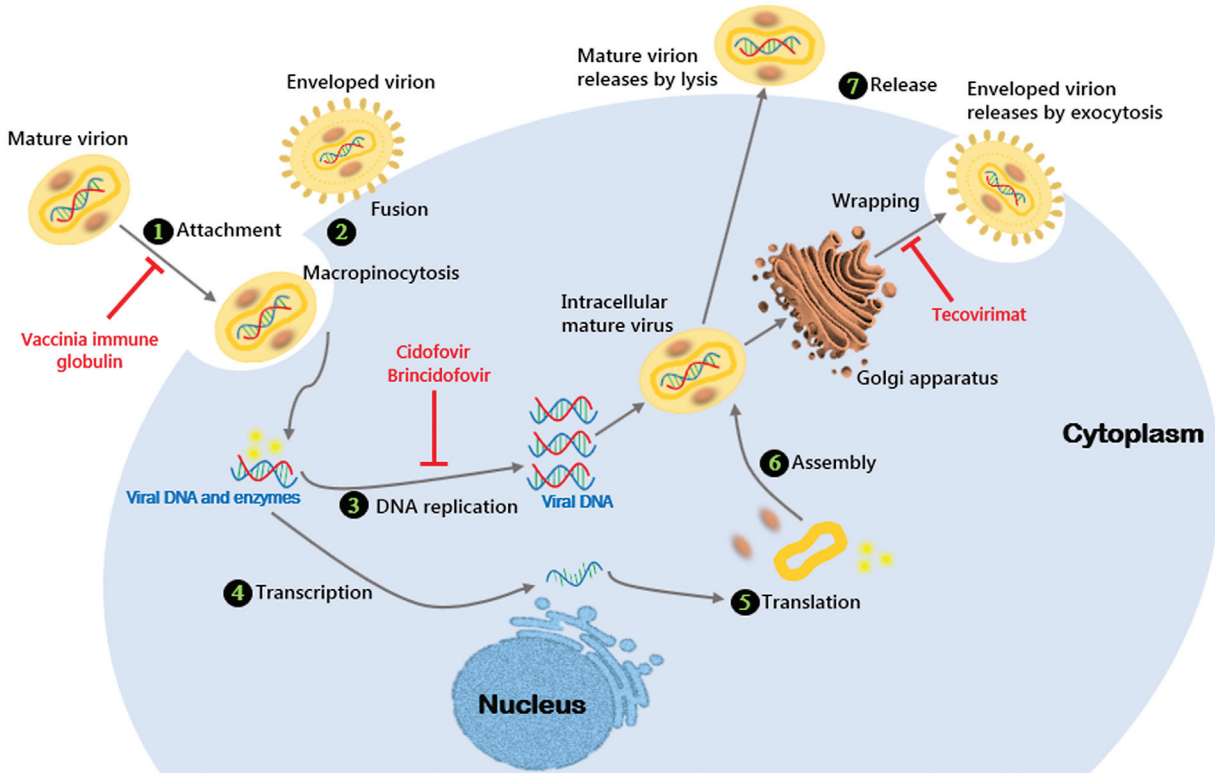

Fig. 2 Schematic overview of the monkeypox virus life cycle within the host cytoplasm and the mechanisms of action of antiviral drugs.[36]

Table 1 Potential options for the prevention and treatment of monkeypox[10,36]

Category	Name	Mechanism of action	FDA approval status
Blood product	VIGIV	Passive immunity by neutralizing antibody	Complications of vaccinia vaccination (progressive vaccinia, severe generalized vaccinia, etc.), 2005
A second-generation vaccine containing live vaccinia virus	ACAM2000	Triggering the immune system to produce antibodies and cells against viruses	Smallpox, 2007
A third-generation vaccine containing live attenuated, nonreplicating virus	JYNNEOS	Eliciting humoral and cellular immune responses against viruses	Smallpox and monkeypox, 2019
A third-generation, live attenuated vaccine containing vaccinia virus (LC16m8 strain)	LC16 KMB (LC16m8)	Triggering the immune system to produce neutralizing antibodies against viruses	Smallpox, 1975
Antiviral drug	Tecovirimat	An inhibitor of VP37 (inhibition of the viral dissemination to other cells)	Smallpox, 2018
Antiviral drug	Cidofovir	An inhibitor of DNA polymerase	CMV retinitis in patients with HIV, 1996
Antiviral drug	Brincidofovir	An inhibitor of DNA polymerase	Smallpox, 2021

Abbreviations: CMV, cytomegalovirus; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; VIGIV, vaccinia immune globulin intravenous.

sweeping, dry dusting, or shaking bed linens, as these actions can potentially aerosolize viral particles.[44] To prevent contact with lesion exudates, it is important to handle towels, clothing, and bedding appropriately. Furthermore, specific guidelines should be followed for the containment and disposal of contaminated wastes.[44]

The immune system's response to a particular *Orthopoxvirus* can also detect other orthopoxviruses and provide varying levels of protection, depending on the degree of relatedness between the different orthopoxviruses. Cross-reactivity is primarily influenced by two factors: First, the high degree of sequence similarity among orthopoxviruses, especially in proteins that are relevant to the immune system, leading to the presence of numerous shared immune epitopes; second, the extensive breadth of the immune response, with antibodies targeting a minimum of two dozen membrane and structural proteins.[45] Postexposure vaccination is ideally provided within 4 days of exposure to prevent infection; however, vaccination within 4 to 14 days of exposure can reduce disease severity.[46] ACAM2000 and JYNNEOS are two licensed vaccines that can inhibit mpox infection (►**Table 1**). JYNNEOS (IMVANEX) is a live viral vaccine produced from the modified vaccinia Ankara-Bavarian Nordic (MVA-BN strain) and is an attenuated, nonreplicating strain. The vaccine is currently recommended for the prevention of smallpox and mpox diseases in adults aged 18 years or older who are identified as being at a high risk of contracting these infections.[10] ACAM2000 also consists of live vaccinia virus. The vaccine is recommended for the active immunization against smallpox disease in individuals identified as being at a high risk of contracting smallpox infection.[7,10] The CDC allows the use of ACAM2000 for nonvariola *Orthopoxvirus* infections.[47] Unlike JYNNEOS, the ACAM2000 vaccine triggers a notable cutaneous reaction at the inoculation site. Furthermore, there exists a risk of accidental inoculation and self-inoculation with ACAM2000, whereas JYNNEOS does not pose such risk.[48]

Closing Remarks

The rapid global spread of mpox, an emerging zoonotic disease, has sparked widespread concern. In order to

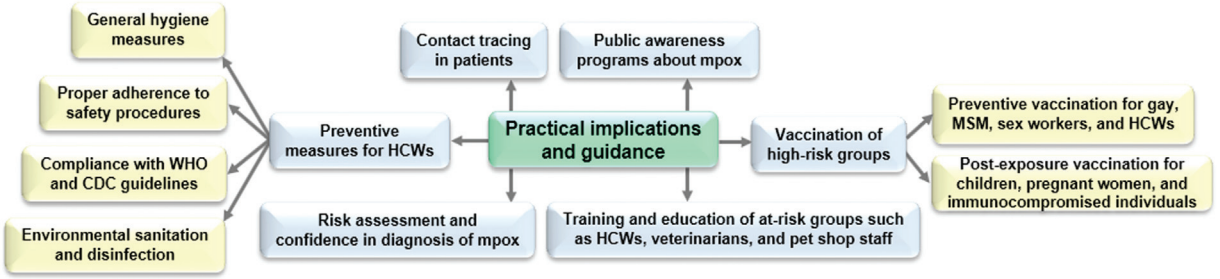

Fig. 3 Important practical implications and guidance for at-risk groups in relation to mpox disease.[17,49] CDC, Centers for Disease Control and Prevention; HCWs, healthcare workers; MSM, men who have sex with men; WHO, World Health Organization.

effectively control the outbreak, it is imperative that the public, healthcare professionals, and government authorities remain vigilant and actively advocate for the implementation of preventive measures and appropriate diagnostic testing (►**Fig. 3**). The implementation of preventive measures is of utmost importance, especially in areas where mpox transmission is prevalent and among high-risk populations like HIV-infected individuals.[44] For instance, vaccination has the potential to be a highly efficacious approach in preventing the disease among individuals with certain risk factors and recent experiences that may heighten their vulnerability to mpox exposure.[49] It is necessary to prioritize public health investments at both national and regional levels, focusing on areas such as environmental sanitation and disinfection. Additionally, the establishment of effective case identification and contact tracing mechanisms is crucial.[44] Educating about mpox, practicing good personal hygiene, implementing personal protective measures, and avoiding contact with sources of infection are all imperative for individuals. Ensuring that frontline medical personnel are educated and trained on the proper adherence to safety procedures when dealing with confirmed or suspected cases is also essential.[49]

Authors' Contributions
M.M. wrote the manuscript. H.M. contributed to the conception of the study and performed the literature searches. M.M. reviewed the manuscript. All authors approved its final version.

Funding
None.

Conflict of Interest
None declared.

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