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The evolving epidemiology of monkeypox virus

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ABSTRACT

Monkeypox, caused by the monkeypox virus (MPXV), is a zoonotic disease endemic mainly in West and Central Africa. As of 27 September 2022, human monkeypox has occurred in more than 100 countries (mostly in non-endemic regions) and caused over 66,000 confirmed cases, which differs from previous epidemics that mainly affected African countries. Due to the increasing number of confirmed cases worldwide, the World Health Organization (WHO) has declared the monkeypox outbreak as a Public Health Emergency of International Concern on July 23, 2022. The international outbreak of human monkeypox represents a novel route of transmission for MPXV, with genital lesions as the primary infection, and the emergence of monkeypox in the current outbreak is also new, as novel variants emerge. Clinical physicians and scientists should be aware of this emerging situation, which presents a different scenario from previous outbreaks. In this review, we will discuss the molecular virology, evasion of antiviral immunity, epidemiology, evolution, and detection of MPXV, as well as prophylaxis and treatment strategies for monkeypox. This review also emphasizes the integration of relevant epidemiological data with genomic surveillance data to obtain real-time data, which could formulate prevention and control measures to curb this outbreak.

1. Introduction

Human monkeypox is an important zoonotic disease that was previously endemic mainly to central and western Africa and is caused by the monkeypox virus (MPXV), the most virulent Orthopoxvirus threatening human public health since the abolition of the variola virus [1,2]. MPXV is a close relative of the variola virus and can cause severe smallpox-like clinical disease in humans. Whole genome sequencing (WGS) confirmed that there are two distinct MPXV clades, the Central and West African clades, with case fatality rates of 10.6 % and 3.6 %, respectively [3]. There has long been speculation that the MPXV could eventually occupy the ecological niche once occupied by the now-extinct smallpox virus [4,5].

According to the epidemiological characteristics and geographical distribution of monkeypox, cases occurring outside Africa are uncommon and typically related to international travel or animal trafficking.

Abbreviations: AIDS, Acquired immunodeficiency syndrome; APOBEC3, Apolipoprotein B mRNA-editing catalytic polypeptide-like 3; CCL5, C-C Motif Chemokine receptor 5; CDC, Center of Disease Control and Prevention; COG4, Conserved oligomeric Golgi 4; COVID-19, Coronavirus disease 2019; C3L, Complement binding protein; dsDNA, double-stranded DNA; dsRNA, double-stranded RNA; EEV, Extracellular enveloped virus; eIF2α, eukaryotic translation initiation factor 2α; ELISA, enzyme linked immunosorbent assay; EMA, European Medicines Agency; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; HA, Haemagglutinin; IEV, Intracellular enveloped virus; IFN, Interferon; IgG, Immunoglobulin G; IL-2, Interleukin 2; IMV, Intracellular mature virus; LAMP, Loop-mediated isothermal amplification; MOPICE, Monkeypox inhibitor of complement enzyme; MPXV, Monkeypox virus; MVA, modified vaccinia Ankara; NGS, Next-generation sequencing; NK, Natural killer; PHEIC, Public Health Emergency of International Concern; PKR, Protein kinase R; PRRs, Pattern recognition receptors; RFLP, restriction fragment length polymorphism; RNAs, RNA polymerases; RT-qPCR, Reverse transcription quantitative polymerase chain reaction; SNPs, Single-nucleotide polymorphisms; TFN-α, Tumor necrosis factor alpha; UK, United Kingdom; UKHSA, United Kingdom Health Security Agency; USA, United States of America; VIG, Vaccinia immune globulin; VPSS2, Vacular protein sorting 52; WGS, Whole genome sequencing.

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despite it has been proposed that viral entry is associated with infected individuals or endemic travel. Also, most current MPXV-related cases are transmitted specifically by means of sexual contact, particularly, for men who have sex with men [8,9], which is different from previous outbreaks. In addition, genetic variation is essential for the survival of MPXV, promoting adaptation to hosts and ever-changing environments. The two major African clades contain several lineages, and each lineage has multiple mutations. Genomic variation of the MPXV was reported in samples from the Democratic Republic of the Congo, which is related to the disease’s transmissibility and severity [10]. Recent studies have also shown that the current MPXV has undergone evolution and potential human adaptation [11,12]. Hence, in this review, we focus on discussing the latest advances in the changing epidemiology and evolution of the MPXV and highlight the importance of combining epidemiological and genetic surveillance in controlling and preventing this outbreak.

2. History of monkeypox

MPXV was first isolated in captive monkeys imported from Africa to Copenhagen, Denmark in 1958 [13]. In 1970, the Democratic Republic of the Congo reported the first known case of human MPXV infection [14]. Over the past 50 years, imported human MPXV infections outside the African continent have rarely been observed. The first human case of monkeypox outside of Africa was reported in the United States of America (USA) in 2003, and it was transmitted to humans by infected Gambian rats [15]. In 2018, the United Kingdom (UK) reported two patients with secondary monkeypox infection who had traveled to Nigeria [16]. Over the past 5 years, several thousand cases of human monkeypox have been reported in a number of different countries, mostly in Africa [17,18]. Monkeypox was imported to Singapore, Israel, the USA, and the UK [19–21]. On May 7, 2022, a confirmed monkeypox patient who had traveled back from Nigeria was reported by the United Kingdom Health Security Agency (UKHSA) [22]. As of 27 September 2022, more than 66,000 suspected and/or confirmed cases have been reported to WHO from 100 countries, most of them from the Europe and Americas [23]. An outbreak is considered to have occurred as long as a single case of monkeypox is confirmed in a country. Monkeypox has unexpectedly appeared in multiple countries and regions in the absence of an initial epidemiological link to areas that are historically endemic to the MPXV, suggesting that undetected transmission has occurred for some time. Therefore, an open-minded and vigilant attention to the monkeypox epidemic is required.

3. Molecular virology

The MPXV virions are brick or ovoid-shaped particles measuring about 200–250 nm and surrounded by a geometrically corrugated lipoprotein outer membrane, similar to other orthopoxviruses [24]. The mature virus particle is composed of several morphologically distinct structural components, including an outer membrane, surface tubules, two lateral bodies, a large double-stranded linear DNA genome (approximately 197 kb in length), and a double-concave dumbbell-shaped nucleoprotein core [25]. Remarkably, MPXV replication occurs in the cytoplasm of host cells and requires the use of a virally encoded RNA polymerase, which is uncommon among DNA viruses. However, the specific receptors for MPXV entry are still unknown, despite it has been proposed that viral entry is associated with host cell type and viral clades, involving multiple surface receptors, such as heparan sulfate [26–28], glycosaminoglycans [29,30], and chondroitin sulfate [31].

MPXV infects host cells through multiple steps, including viral particle entry (endocytosis), uncoating (fusion), viral genome replication, virion assembly, and virion release from the infected cells (Fig. 1). MPXV produces two morphologically distinct infectious forms: extracellular enveloped virus (EEV), which is thought to be responsible for early dissemination, and intracellular mature virus (IMV), which is released during cell lysis [32,33]. EEV and IMV particles have a different number of surface glycoproteins and enveloping membranes. Viral particles bind to the host cell’s surface via extracellular matrix components or unknown receptors. Following attachment, the virions enter host cells via direct fusion with the plasma membrane at neutral pH or by a low pH endosomal pathway, releasing the viral core into the cytoplasm [34]. MPXV replication is initiated through MPXV-encoded multi-subunit DNA-dependent RNA polymerases (RNAPs), followed by the translation of early, intermediate, and late proteins on host ribosomes [35,36]. The late proteins assemble into infectious virion IMVs. Some IMVs are transported through microtubules and wrapped by a double membrane derived from the endoplasmic reticulum or Golgi to produce an intracellular enveloped virus (IEV). These enveloped virions can further fuse with the cell membrane via triggering actin polymerization and be released to form EEVs [36,37]. Notably, recent studies have shown that several cellular proteins, such as conserved oligomeric Golgi 4 (COG4), COG7, vacuolar protein sorting 52 (VPS52), and VPS54, are required for the viral replication cycle [37,38]. Although how these proteins cooperate to facilitate MPXV-induced host pathogenesis is unclear, identifying these host targets may provide potential intervention strategies for MPXV infection.

4. Evasion of antiviral immunity

Evasion of antiviral immunity has been widely reported in orthopoxvirus infection [39–41]. The orthopoxvirus genome possesses many genes encoding proteins that disrupt host cellular signaling pathways involved in immune regulation and virus recognition [42,43]. Importantly, MPXV can evade targeting and recognition by the host immune system through a variety of mechanisms (Fig. 2).

The induction of immune mediators and type I interferon (IFN) responses are critical for host antiviral immune responses, which are also pivotal targets of viral immune evasion. It has been reported that MPXV shows an IFN-resistant phenotype [44]. MPXV evades type I IFN antiviral response via preventing phosphorylation of Protein kinase R (PKR) and eukaryotic translation initiation factor 2α (eIF2α) [44]. MPXV encodes multiple proteins that facilitate immune evasion. For example, MPXV encodes the F3 protein, which binds to double-stranded RNA (dsRNA) and sequesters it away from pattern recognition receptors (PRRs), blocking cellular antiviral signaling [44,45]. The MPXV B16 protein was also reported to suppress antiviral type I IFN-induced signaling pathway [46]. Besides, MPXV also evades host immune responses via regulating immune mediators, such as cytokines and chemokines. A study of nineteen confirmed cases of MPXV infection showed a significant decrease in Th1 immune response-associated cytokines, such as tumor necrosis factor alpha (TNF-α), IFN-γ, interleukin 2 (IL-2), and IL-12. The in vitro experiments showed that MPXV infection impairs Natural killer (NK)-cell functions and inhibits the secretion of IFN-γ and TNF-α, as well as the expression of C-C Motif Chemokine receptor 5 (CCL5), CXCR3, and CCR6 [47]. MPXV infection-induced alterations in immune mediators are linked to disease severity. Another mechanism of MPXV immune evasion involves regulation of the complement system. The Central African MPXV strain but not the West African strain encodes the monkeypox inhibitor of complement enzyme (MOPICE) from the DI-IL gene, which evades complement activation by preventing the formation of a C3 convertase complex [48,49]. In addition, MPXV also interferes with adaptive immune responses of antiviral CD8+ and CD4+ T cell responses via inhibiting T cell receptor-mediated T cell activation [50]. Collectively, these studies indicate that MPXV promotes immune subversion and evasion mechanisms, allowing it to spread
indefinitely and potentially leading to more serious clinical disease.

5. Changes in the epidemiological characteristics of the current monkeypox outbreak

5.1. New clinical symptoms

The typical clinical manifestations of monkeypox in humans resemble those of smallpox but are generally less severe than smallpox. The typical symptoms of monkeypox include muscle aches, malaise, intense headaches, back pain, fever, fatigue, sore throat, chills, swollen lymph nodes, and skin lesions or rashes [51,52]. Remarkably, rashes in the genital area are the main feature of monkeypox in the current outbreak. The genital rash frequently precedes the generalized pustular rash in non-endemic areas outside of Africa [55,56]. A prospective observational study of 14 patients diagnosed with monkeypox disease showed that genitourinary involvement is common in MPXV infection and is frequently the reason for the consultation appointment [57]. The genital area, according to this presentation, is the site of a primary infection that causes a localized rash and, in some cases, a secondary disseminated infection. In addition, the clinical manifestations of monkeypox are similar to syphilis [58], which could easily lead to misdiagnosis.

In addition to primary genitourinary involvement, other clinical pathological manifestations, such as myopericarditis and neurologic symptoms, have also been reported in the current monkeypox outbreak. Pinho et al. recently reported a 31-year-old male patient with confirmed MPXV infection who developed acute myocarditis days after skin lesions appeared [59], highlighting cardiovascular involvement as a potential complication associated with MPXV infection. Further studies are necessary to investigate the pathological mechanism underlying...
MPXV-related heart injury. Besides, there is also preliminary evidence for a wide range of neurological manifestations of monkeypox, including vomiting, nausea, anorexia, agitation, altered consciousness, fatigue, malaise, myalgia, and headache [60,61]. It has been reported that MPXV enters the central nervous system mainly by infected circulatory monocytes/macrophages and olfactory epithelium [62]. In vitro and in vivo studies investigating the long-term effects of MPXV on the central nervous system may help reveal the exact mechanism of MPXV-induced neurologic symptoms.

5.2. Natural host

The natural animal host of MPXV is still largely uncertain, although it is found among rodents in Africa. Other known zoonotic hosts for the MPXV are sooty mangabey monkeys, Gambian pouched rats, rope squirrels, tree squirrels, and possibly other species [63,64]. The wide host range and geographic distribution of MPXV is a cause for concern because it may contribute to the adaptation of MPXV to new reservoirs or environments. The broad host range of MPXV may facilitate its worldwide spread. Nevertheless, identifying the exact reservoir(s) of MPXV will help determine the mode of transmission of this zoonotic disease and prevent ongoing outbreaks.

5.3. Transmission

The MPXV can be transmitted not only from animals to humans, but also from human to human through direct contact, respiratory droplets, or fomites. Transmission through respiratory droplets typically requires extended face-to-face contact, putting family members, health care workers, and other close contacts of active cases at a higher risk of infection. Similar to SARS-CoV-2, humans infected with MPXV have recently been reported to spread the virus to domesticated animals by close contacts (kissing and hugging) [65,66], raising concerns about the role of pets in MPXV transmission. This virus can also be vertically transmitted from mother to fetus through the placenta, which results in congenital monkeypox [67]. Recent studies have shown that MPXV is mainly spread through sexual contact, despite the fact that it is not primarily a sexually transmitted disease [8,68,69]. Thus, the relative importance of different transmission routes to monkeypox epidemics may have changed. Besides, the main transmission routes of MPXV also require re-examination. It has been reported that the monkeypox epidemic in Nigeria from 2017 to 2018 was caused by the transmission of animals, possibly rodents, to humans, and the limited and unsustainable chains of transmission between humans [54,70]. In recent years, population immunity to smallpox has decreased over time, which may favor monkeypox outbreaks and increase the risk of sustained human-to-human transmission within and beyond Africa [71,72]. The unexpected and sudden appearance of monkeypox in several regions at the same time, with no direct travel links to areas that have long experienced monkeypox, suggests that undetected chains of transmission have been occurring.

5.4. Susceptible population

All age groups of humans are generally susceptible to MPXV. The contemporary susceptible population consists primarily of working adults who usually have broader social networks and contacts and are more likely to engage in activities involving the risk of exposure to animals [72,73]. Besides, the elderly, immunocompromised individuals, children, and people with chronic underlying diseases are at higher risk of severe disease [72,74]. Pregnant patients infected with MPXV carry a high risk of maternal mortality and pregnancy loss [75,76]. Therefore, it is necessary to focus on these vulnerable patients during the prevention and management of monkeypox. In addition, the proportion of MPXV-induced infections that lead to serious or fatal illnesses may have changed. To date, all cases genotyped in Europe as well as in Asia during the current outbreak are closely associated with the West African clade and with viruses exported from Nigeria to the UK, Singapore, and Israel [6,77]. The central African clade causes a high case fatality rate and more severe illness (10.6 %) than the west African clade (3.6 %). Of note, asymptomatic cases may be part of the undetected chains of transmission. Thus, these estimates of the case fatality may be too high, if some infections are asymptomatic.

5.5. Incubation period

The estimated incubation period for human monkeypox is typically 6–13 days (range 5–21 days) [78], suggesting a long transmission period of MPXV. The longest incubation period for monkeypox is 21 days, facilitating public health agencies to recommend active surveillance and isolation of close contacts for at least 21 days after the last exposure. Previous cases of monkeypox outbreaks had a history of contact with infected animals or travel to endemic countries, whereas most cases in the current outbreak occurred in non-endemic countries or regions [79]. In addition, recent studies have demonstrated that monkeypox is mainly transmitted specifically by means of sexual contact, particularly, for men who have sex with men [80,81]. Given these differences in transmission routes and exposure, the incubation period of monkeypox in the current outbreak may also vary from previously reported values. Therefore, as the outbreak grows, further studies and data are required to continue to monitor and assess the incubation period of monkeypox.

5.6. Basic reproduction number (R0)

A very essential threshold parameter related to viral transmissibility is the basic reproduction number, usually expressed as R0 (R zero or R naught). R0 is defined as the average number of new infections transmitted by an infected individual during the entire infectious period. When R0 is above 1, the number of infected people will grow exponentially and cause an epidemic. Previous studies using mathematical modeling to quantitate the R0 showed that MPXV infection could cause self-terminating epidemics as the estimated R0 was 0.83 [82]. Notably, in a recent mathematical modeling study, Grant et al. calculated the R0 for monkeypox ranged from 1.10 to 2.40 in countries where orthopoxvirus has not historically been endemic [71]. The change of R0 may be related to the following reasons. 1) Decreased herd immunity may result in sustained epidemics with an initial R0 greater than 1 [72]. 2) The uncertainty of the ultimate host also affects the R0 value. 3) The reporting system, diagnosis, and contact tracking have been significantly improved, making it easy to detect more cases of MPXV infection and obtain new epidemiological parameters [83,84]. 4) Rodents and other animals adapt to urban environments, increasing their contact with humans and transmitting more zoonotic diseases [85]. Therefore, more epidemiological data in future studies is required to reevaluate the R0 in different populations.

6. The evolutionary landscape of MPXV

According to an evolutionary perspective, MPXV first appeared in the Old World orthopoxvirus clade about 3500 years ago. Since then, it has undergone evolution and further segregated into other genetic variants, such as the MPXV West African subtype, which dates back to about 600 years ago [86]. MPXV has been historically divided into two distinct genetic clades, Central African (Congo Basin) and West African. However, a novel nomenclature has been proposed to classify MPXV into three clades, with clade 1 representing the Congo Basin lineage, clade 2 referring to the West African lineage, and clade 3 indicating the current outbreaks outside Africa. The distinctions among these clades are primarily related to coding regions involved in host recognition of antigenic determinants, such as B21R and H3L [89,90]. At present, multiple lineages (hMPXV-1A, B.1, A.1.1, A.1, and A.2) classified from MPXV Clade 3 have been identified [88] (Fig. 3). This suggests
that secondary evolutionary events appear to have occurred in the current MPXV, resulting in further diversification of MPXV Clade 3, allowing it to disperse into other geographic locations and potentially adapt to new hosts across new regions. The A.1 and A.2 clades are diverged from the hMPXV-1A ancestral clade circulating in 2018–2021. Notably, the lineage B.1, diverged from A.1 (2018–2019 outbreak), is considered to be closely related to the current outbreak of human monkeypox [91]. Although the B.1 lineage was found to be clustered with cases associated with an endemic country in 2018–2019, it segregates in a divergent phylogenetic branch, possibly reflecting accelerated micro-evolutionary events [91]. Indeed, the microevolution of the B.1 lineage have formed several clusters, such as 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 [92], suggesting an ongoing viral evolution. There have been 46 B.1-specific single-nucleotide polymorphisms (SNPs) found, including four intergenic, 18 synonymous, and 24 non-synonymous mutations that separate the clade from the closest ancestor.

Fig. 3. Schematic representation of the major evolutionary events and MPXV variants in sequential order. MPXV has been classified into three clades, clade 1 (the Congo Basin lineage), clade 2 (the West African lineage), and clade 3 (the current MPXV lineage). The MPXV Clade 3 contains multiple lineages, including hMPXV-1A, B.1, A.1.1, A.1, and A.2. The B.1 lineage is considered to be closely related to the current outbreak of human monkeypox. Additionally, several clusters (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) classified from the B.1 lineage have been identified, suggesting a continuous viral evolution.

Fig. 4. Schematic representation of current methods for the detection of MPXV. Human MPXV detection methods currently available include nucleic acid-based detection (RT-qPCR, RCR-RFLP, LAMP, RPA, and NGS), antibody-based detection (ELISA), and antigen-based detection (RAT). Emerging approaches include CRISPR-based assays, surface plasmon resonance, optical biosensors, electrochemical biosensors, nanomaterials-based detection, and aptamer-based detection. RT-qPCR, reverse transcription quantitative polymerase chain reaction; RCR-RFLP, PCR-restriction fragment length polymorphism; LAMP, loop-mediated isothermal amplification; RPA, recombinase polymerase amplification; NGS, next-generation sequencing; RAT, rapid antigen test.
7. Detection of MPXV

Rapid, sensitive, and accurate detection of MPXV can promote timely control of the outbreaks of monkeypox. Current methods for the detection of human MPXV include nucleic acid-based detection (RT-qPCR etc.), antibody-based detection (IgM/IgG serology testing), and specific peptide-based rapid antigen test (RAT) (Fig. 4). Many of these protocols, however, are relatively nonspecific and cannot distinguish MPXV infection from other orthopoxvirus infections. Real-time or conventional PCR is still the main route for confirming MPXV infection by detecting unique sequences of virus DNA. PCR can also be used in combination with restriction fragment length polymorphism (RFLP), sequencing, and species-specific probes/primers. Some methods involve at least a two-step procedure: first, a PCR assay detects MPXV but does not identify a specific subtype; next, PCR-based or using sequencing is used to specifically detect MPXV. Several studies have reported that MPXV DNA is routinely detected in veterinary and clinical specimens and MPXV-infected cells via PCR targeting conserved genes, such as N3R [96], F3L [97], envelope protein gene (B6R) [98], G2R [99], haemaglutinin (HA) [100], complement binding protein (C3L) [101] and E9L [54]. Besides, RFLP assays have been developed for the detection of MPXV DNA [102,103]. However, RFLP requires virus culture, restriction enzyme digestion, and polyacrylamide gel electrophoresis, which is time-consuming and expensive. Recently, a newly developed recombinase polymerase amplification (RPA) assay targeting the G2R gene was reported to rapidly detect the virus within 7 min [104]. A loop-mediated isothermal amplification (LAMP) assay has been developed to be highly specific, sensitive, rapid, and quantifiable for the detection of MPXV [105]. The LAMP assay has the ability to distinguish between West African and Center African strains of MPXV and evaluate MPXV infection [105]. Remarkably, next-generation sequencing (NGS) of the whole genome is recognized as the golden standard for characterization of orthopoxvirus and more specifically MPXV [106,107], however, the technology is costly, time-consuming, and requires extensive data processing. Therefore, NGS may not be an appropriate characterization method in resource-poor countries, especially in sub-Saharan Africa. Despite PCR assays are still the main routine method for the detection of MPXV, they must be combined with field genome sequencing technology, such as the Nanopore MinION [108], to obtain real-time viral genome data that are essential for evidence-based epidemiological interventions.

In addition, biosensors are promising diagnostic tools and have well been established in clinical diagnostics for the detection and/or monitoring of various analytes, in particular viruses. Novel biosensors that have been demonstrated to detect DNA viruses include nucleic acid-based CRISPR-Cas12a-based, nanomaterials-based, aptamer-based, optical biosensors, electrochemical biosensors, and surface plasmon resonance [109,110]. These biosensors provide effective and rapid instruments for the real-time quantitative and qualitative detection of infectious diseases. In addition, numerous studies have demonstrated that biosensors can provide fast and sensitive detection and precise diagnosis for SARS-CoV2 infection [111,112]. Therefore, further studies are required to develop the application of biosensors for the diagnosis and detection of MPXV infection.

Serological assays provide evidence of orthopoxvirus exposure, but this method lacks a practical ability to reliably distinguish between orthopoxvirus species. Although this testing has limitations in diagnosis, the immunoglobulin G (IgG) together with the IgM enzyme linked immunosorbent assay (ELISA), can characterize the acute-phase humoral response following MPXV [113]. The IgG ELISA was used to detect prolonged exposure after the onset of the rash, while the IgM ELISA is helpful for providing evidence of recent infection with and exposure to MPXV and defining the acute-phase humoral response [113]. Compared to PCR, serological assays provide a wider time window to detect evidence of monkeypox infection.

8. Prophylaxis and treatment

The principal way to reduce or prevent MPXV infection is by raising awareness of risk factors and educating people about the measures they can take to decrease exposure to MPXV. Any direct contact with the materials used by patients infected by MPXV or skin rashes should be avoided. Patients with suspected, probable, or confirmed monkeypox should be isolated immediately in a single-person room. If the patient’s condition requires hospitalization, they should be placed in negative pressure and ventilated room if available. Besides, avoiding contact with wild animals (giant Gambian rats, dogs, etc.) that look sick is critical to reducing the risk of infection. Prairie dogs infected with MPXV have skin lesions, respiratory symptoms, and missing fur [114]. Importantly, sick prairie dogs should not be released into the wild as they may infect other wild prairie dogs.

The smallpox vaccine offers cross-protection against other orthopoxvirus species, including MPXV. Among all vaccinated people, smallpox vaccination provides 85 % effective protection against MPXV [115]. During the 2003 USA monkeypox endemic, the Center of Disease Control and Prevention (CDC) recommended the ACAM2000™ vaccine, which reduced symptoms but did not prevent the disease [102]. Due to several issues like unknown side effects of the vaccine in immunosuppressed patients and the safety of the vaccine containing live vaccinia virus, this vaccination is neither widely accessible nor used in MPXV endemic areas. JYNNEOS (IMVAMUNE), a third-generation smallpox vaccine derived from the modified vaccinia Ankara (MVA) strain, has also been licensed by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for use in the prevention of monkeypox and smallpox. Importantly, the FDA recently issued an Emergency Use Authorization (EUA) to allow intradermal rather than subcutaneous injection of JYNNEOS [116]. This allows for smaller doses to be used in adults, effectively increasing the number of patients who can be treated with existing vaccine supplies by up to five-fold [116]. JYNNEOS, unlike ACAM2000™, is not contraindicated for use in people with immunodeficiencies such as atopic dermatitis and acquired immunodeficiency syndrome (AIDS) [117]. LC16m8, another third-generation vaccine, is derived from the Lister strain of vaccinia virus and produced in cell culture using rabbit kidney cells [118]. Japanese regulators fully licensed the vaccine in 1980, and it is currently manufactured by Kaketsuken (Kumamoto, Japan). LC16m8 triggers an immune response similar to the parental Lister vaccine, but with a higher safety profile and no serious adverse events [119,120]. However, it is unclear whether these licensed smallpox vaccines will provide effective protection against monkeypox in the current outbreak. Also, the protective efficiency of these vaccines in individuals and populations should be reevaluated. The smallpox vaccine is approximately 85 % effective in preventing monkeypox before exposure. However, when administered
after exposure, the vaccine offers less protection. Thus, the effectiveness of these smallpox vaccines in practice will depend on how many high-risk groups can be vaccinated before becoming infected when tracing and vaccinating case contacts.

Antiviral therapy should be considered for pregnant individuals, patients with immunodeficiency or severe disease, and young children under the age of eight [121,122]. Brincidofovir and tecovirimat are two FDA-approved antiviral drugs for the treatment of smallpox and also for monkeypox. Tecovirimat (ST-246), a 4-trifluoromethylphenol derivative, was reported to protect against several orthopoxviruses including monkeypox [123,124]. Tecovirimat targets the viral p37 protein, a protein that is highly conserved in all orthopoxviruses, to suppress the viral envelope formation and the egress of the virus [125,126]. Although there is little clinical experience with the medication in human outbreaks, investigations on animals have demonstrated its efficacy in the treatment of patients with MPXV infection in the ongoing monkeypox outbreak. Brincidofovir, also known as CMX001 or hexadecyloxypropyl-cidofovir, is an orally bioavailable lipid conjugate of cidofovir with broad antiviral efficacy against double-stranded DNA (dsDNA) viruses via suppressing DNA polymerase [130]. Both cidofovir and brincidofovir have been shown to have antiviral activity against a number of orthopoxvirus species in both in vivo and in vitro studies [131–133]. Notably, a recent retrospective observational study revealed that three individuals who received brincidofovir treatment failed to demonstrate any significant effect [134]. Patients who received tecovirimat treatment, in contrast, exhibit less viral shedding and shorter illness duration with no side effects [134]. However, the relatively small patient population included in this study makes it challenging to assess the connection between bucindofovir treatment and disease progression. Antiviral therapeutic agents are summarized in Table 1 [121].

Vaccinia immune globulin (VIG), which was isolated from the plasma of vaccinees and previously used to treat smallpox, could also be considered for monkeypox treatment. VIG has been recommended for the treatment of patients with contraindications to smallpox vaccines, exposed individuals with T-cell immunodeficiency, or patients with severe monkeypox infection [135,136]. Thus, VIG therapy may be a safe and effective way to ameliorate the outcomes of patients with severe MPXV infection.

9. Conclusions and future perspectives

Human monkeypox is a re-emerging zoonotic disease that has long been neglected. Nearly three-quarters of emerging pathogens and two-thirds of all pathogens are zoonotic, which is contrary to the geographical distribution of about 5000 mammalian species carrying one or more zoonotic diseases [137]. Monkeypox is a typical example of the potentially volatile combination of anthropogenic activities and zoonotic spillovers that make up most of the global epidemic potential. Almost 50 years after its discovery, multiple aspects of monkeypox need to be clarified and reevaluated, especially its epidemiology. Indeed, the currently increasing number of confirmed cases in non-endemic regions suggests that the epidemiology of monkeypox may have changed and that the MPXV has undergone evolution.

| Antiviral therapeutic agents | Dosages | Administration routes | Use of particular populations | Antiviral mechanisms | Side effects | Drug interactions |
|-----------------------------|---------|-----------------------|-----------------------------|---------------------|-------------|------------------|
| Tecovirimat                 | Pediatrics: 200 mg for 14 days (13–25 kg), 400 mg twice per day for two weeks (25–40 kg), 600 mg twice per day for two weeks (>40 kg); Adults: 600 mg twice per day for two weeks. | IV, PO | IV: Patients with severe renal impairment are not suitable. PO: Renal/ hepatic adjustment not needed. | Inhibits viral envelope formation by targeting the viral p37 protein | Vomiting, abdominal pain, nausea, and headache. With IV form, infusion-site reactions could happen. | Midazolam: reduced its effectiveness. Repaglinide: hypoglycemia |
| Brincidofovir               | Pediatric: 6 mg/kg given once each week for 2 doses (<10 kg), 4 mg/kg given once each week for 2 doses (10–48 kg); Adults: 200 mg given once each week for 2 doses. | PO | Liver function examination should be carried out before and during treatment, because brincidofovir may cause the increase of serum bilirubin and transaminase. | Inhibits viral DNA polymerase | Abdominal pain, vomiting, nausea, and diarrhea | Brincidofovir exposure is increased by 1B3 and OATP1B1 inhibitors, which may promote Brincidofovir-associated adverse reactions. Consider using an alternative drug that is not a 1B3 or OATP1B1 inhibitor. Nephrotoxic agents, probenecid |
| Cidofovir                   | 5 mg/kg per week for 2 weeks, then 5 mg/kg once every other week | IV | Dosage adjustment is required based on renal function: urine protein > 100 mg/dl, CrCl ≤ 55 mL/minute, or serum creatinine > 1.5 mg/dl. | Inhibits viral DNA polymerase | Fever, nephrotoxicity, uveitis, iritis, hypotony of eye, neutropenia, and proteinuria | |
| VIG                         | 6000 U/kg once symptoms appear; repeat doses may be necessary depending on the severity of the symptoms and the treatment’s effectiveness; If the patient doesn’t respond to the initial dose, 9000 U/kg may be considered. | IV | Passive protection is provided by antibodies derived from pooled human plasma of smallpox vaccine recipients | Dizziness, rigors, nausea, and headache | Contains maltose-1, may cause increased glucose levels, which could result in improper insulin dosing or untreated hypoglycemia; could reduce the effectiveness of live attenuated virus vaccinations; may affect certain serological tests; Revaccination might be required. | |
A number of hypotheses have been proposed to explain the recent surge in cases in non-endemic areas (Fig. 5). One hypothesis is that the accelerated evolution and adaptation of MPXV to humans increases viral survival and human susceptibility to the virus. Non-synonymous mutations in the coding region of the host recognition element may be important for viral adaptation [138,139]. For instance, H3L is an important viral envelope protein that has been closely implicated in immune system recognition, poxvirus internalization, and host cell attachment. Compared with the variola virus, the H3L protein of MPXV has 21 amino acid variations, accounting for 6.5% of the total protein sequence [87], indicating differences in the natural history of MPXV and variola virus. In contrast to the variola virus, MPXV has a wider host range, and continued transmission of the virus across interspecies interfaces may cause MPXV to become more adapted to humans, increasing the effectiveness of transmission. In addition, it has also been reported that MPXV evades the host antiviral innate immunity, referring to inhibition of the type I IFN responses as the main mechanism [44,50,140]. Another hypothesis holds that after mass vaccination against smallpox was discontinued in the 1980s, cross-immunity to MPXV was as high as 85%, increasing human susceptibility to the virus. This, in turn, puts MPXV under selective pressure, promoting the development of immune evasion mechanisms and increasing viral transmissibility [44,91].

In the current outbreak, MPXV seems to be transmitted by localized genital lesions (primary lesions). Remarkably, the transmission of MPXV through this primary lesion (primary transmission) eliminates the potential of a widespread infection, which may contribute to the evolution of variants. What is more, the primary transmission bypasses the secondary transmission bottleneck, which can promote the co-transmission of multiple variations. If MPXV is adapting to human transmission through this new route, this adaptation should be most evident in genomes sequenced from primary rashes. Although the mechanism leading to these mutations is largely unknown, recent research demonstrated that the host APOBEC3-like deaminase may be responsible for many of these SNPs [91]. Thus, it is necessary to closely monitor APOBEC’s potential genome-editing activity and its regulatory roles in MPXV infection.

Considering the threat to global health from MPXV, there is an urgent need for the effective prevention and treatment of monkeypox. It is essential to prevent virus spread via effective epidemic prevention and control measures such as controlling the source of infection and isolating infected patients. Moreover, a well-established protocol for clinical diagnosis, treatment, and management of monkeypox is also required. As there are clinically reported cases of asymptomatic carriers of MPXV [141,142], it is important to develop rapid, sensitive, and efficient detection technologies to control and further prevent this disease. In addition, increasing the stock of relevant vaccines and antiviral drugs, vaccinating high-risk groups, and accelerating the research and development of safe and effective monkeypox vaccines and therapeutic drugs are also essential to enhance the immune protection of the general population and curb the current outbreak.

The development of future monkeypox outbreaks should also be mindful of several possible scenarios, such as the emergence of livestock epidemiological events that could lead to the persistence of the disease in non-endemic areas and disease spillover to novel animal hosts in these newly expanded niches. Thus, genomic epidemiology efforts should be bolstered, with special attention to the mysterious transmission routes that result in the establishment and prevalence of MPXV in previously unaffected areas, human-to-human interactions in anticipation of zoonotic or human amplification events, and the wider interface between humans and susceptible animal species. The COVID-19 pandemic has emphasized the importance of translating genomic research into useful tools, which is essential for tracking the transmission dynamics of MPXV and predicting the emergence of its rapidly evolving pathogens. Collectively, given the outbreak’s unique characteristics, genomic surveillance efforts must continue to identify and inform genomic changes in the virus to aid in the development of timely control and prevention measures.

**Conflict of interest**

The authors declare they do not have anything to disclose regarding conflicts of interest with respect to this manuscript.
Data Availability
Not applicable.

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