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# The current emergence of monkeypox: The recurrence of another smallpox?

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ABSTRACT

Since its first confirmation in London on 12 May 2022, many monkeypox cases have been reported worldwide. Noticeably, the epidemiology, pathology, and clinical features of the current emergence have been compared to those of smallpox, a severe contagious disease historically epidemic worldwide for nearly 3,000 years. However, some characteristics of the present outbreak differed from those of previous monkeypox outbreaks. Herein, we ask if this emergence of monkeypox could cause another global pandemic similar to smallpox or influenza or if it is only the re-emergence of a new strain. To address these questions, we reviewed its virology, transmission, clinical characteristics, experimental diagnosis, and prevention and intervention, giving our commentary along the way.

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## 1. Introduction

Currently, cases of monkeypox have broken out in several non-endemic countries, causing global attention and alarm. Although its causative pathogen, epidemiology, clinical characteristics, interventions, and preventions were studied decades ago, many features of this outbreak differed from its historical versions and remained puzzling. Herein, we summarize some of these novel features and provide commentary from virological and biosafety perspectives.

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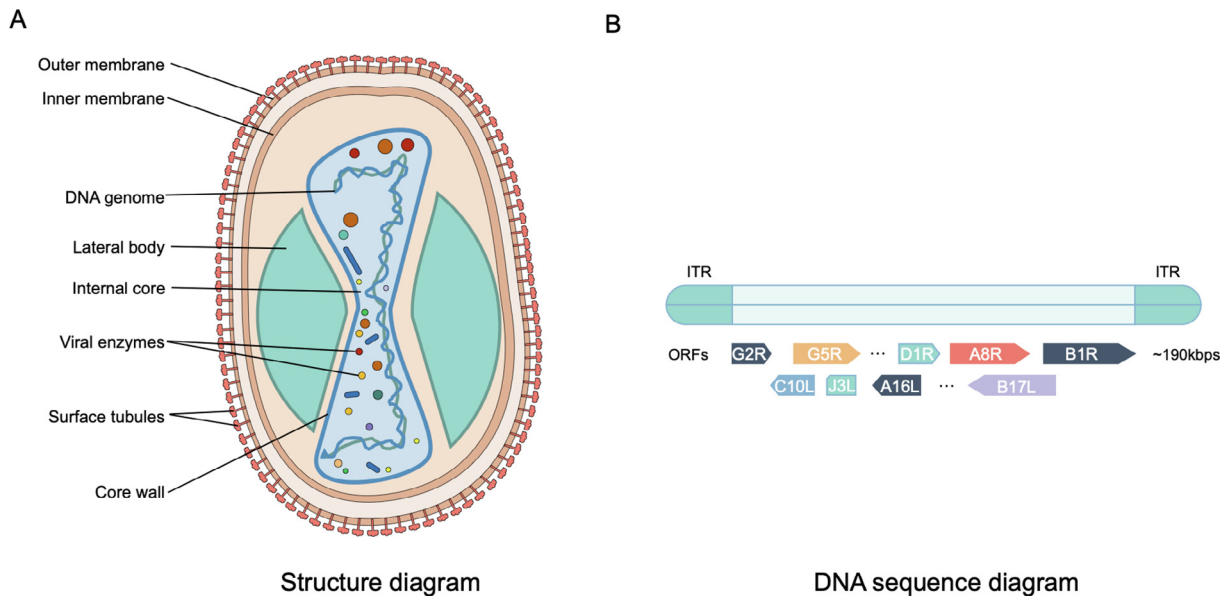


**Fig. 1. Virological characteristics of monkeypox virus (MPXV).** A) Structure of two MPXV formations, the mature virion (MV) and the extracellular enveloped virion (EV). Outside of a MV was a lipid membrane, and a MV enclosed by another lipid membrane was the EV formation. Inside the membrane were lateral bodies and the dumbbell-like internal core, which contained MPXV double-stranded DNA and some other proteins. B) A diagram displaying MPXV genomic structure and compositions. It was linear double-stranded DNA with nearly 190 kilobase pairs and contained more than 190 ORFs. 5′- and 3′- ends of the genome were inverted terminal repetitions, which formed hairpin-like structures.

## 2. Monkeypox virology

Monkeypox was a contagious and rash-developing disease caused by zoonotic monkeypox virus (MPXV), a biosafety-level 3 pathogenic microorganism, belonging to the genus Orthopoxvirus, subfamily Chordopoxvirinae, family Poxviridae [1,2]. MPXV, along with other members of Poxviridae (POXV), had a barrel-like shape with a diameter of approximately 250 nm, larger than most other known viruses [3]. Outside of the mature virion (MV) was a lipid membrane with complicated internal structures, including a dumbbell-like internal core and lateral bodies around it, and MV enclosed by an extra lipid membrane was another form of MPXV, called the extracellular enveloped virion (EV) (Fig. 1A) [3,4]. The genome of MPXV was linear double-stranded DNA and had nearly 190 kilobase pairs. Both 5′- and 3′- ends of the genome were identical but oppositely oriented sequences for the maintenance of double-stranded structure as hairpins, termed inverted terminal repetitions (ITRs) (Fig. 1B) [3,5]. More than 190 open reading frames were detected in its genome with greater than 90 % nucleotide similarity to other Orthopoxviruses. Some genes common to Orthopoxvirus were located in the central region of the MPXV genome, while MPXV-specific genes existed in 5′- and 3′- terminals [5]. Although the functions of many proteins encoded by these ORFs remained unknown, some ORFs had been studied with identified functions like cell entry, intracellular pathway regulation, or interference with host immune molecules. For example, the entry fusion complex (EFC), containing proteins like A16L, A21L, G3L, and O3L, was essential for membrane fusion and entry of MPXV and other Orthopoxviruses. In particular, virulence protein (BR-203 ortholog encoded) could inhibit the host cell's apoptosis to facilitate viral replication, and interleukin-1β (IL-1β) binding protein (BR-209 ortholog encoded) could prevent IL-1β binding with its receptor to suppress the proliferation of lymphocytes and its immune effects. Moreover, complement control protein (COP-C3L ortholog encoded) could inhibit complement cascade reactions to defend innate immunity, and another protein, secreted natural killer (NK) cell inhibitor, acted as an NKG2D competitive antagonist to inhibit the killing of NK cells [3,6].

Traditionally, MPXV was sketchily classified into two phylogenetic clades, the West Africa clade, and the Central Africa clade, and these two clades had distinct epidemiological, genetic, pathogenic, and clinical features [7]. However, based on the technologies of next-generation sequencing and metagenomics, phylogeny, evolution, and molecular epidemiology of MPXV have been clearly illustrated. Generally, MPXV is divided into three clades. Clade 1 (formally designated Central Africa clade), which is the most ancestral strain endemic in the Democratic Republic of Congo, caused more severe symptoms and higher fatality (greater than10 %) [8,9]. Meanwhile, Clade 2 (formally designated West Africa clade) exhibits less virulence, limited transmissibility, milder symptoms, and lower fatality (<1%), and it was responsible for several outbreaks in West Africa and other countries worldwide [8,9]. Finally, Clade 3, also previously classified as the West Africa clade, is the causative clade for outbreaks from 2017 to 2019 in countries like the UK, Israel, Nigeria, the United States, and Singapore, as well as the current outbreak in 2022 [8]. Additionally, these strains of clade 3 exhibits person-to-person transmission and are distinct from former strains; therefore, they were designated as a new subclade, hMPXV1, for better communication and specifical reference [10]. Among this hMPXV1 sub-clade, different lineages are designated as A, A.1, A.1.1, A.2, and B.1, according to their genealogical and descendent relationships, while MPXV causes the current outbreak belongs to lineage B.1 [9–11].

## 3. Monkeypox epidemiology

The first discovery of MPXV traced back to 1958 when a non-fatal rash disease burst in cynomolgus monkeys of an animal institute in Copenhagen, and the causative pathogen was subsequently identified and named monkeypox virus [12]. Since the initial report of monkeypox in a 9-year-old child in 1970 in the Democratic Republic of the Congo (DRC), it has become a substantial public health issue globally [13]. In its first decade (1970–1981), monkeypox sporadically spread among tropical rainforest areas in finite countries of central and western Africa. However, since it had limited transmission and low

**Table 1**
Differences between smallpox and monkeypox outbreaks.

| | Smallpox in history | Monkeypox in endemic regions | Monkeypox in non-endemic regions (2022)[†] |
|---|---|---|---|
| Causative agents | Variola virus | Monkeypox virus | |
| Taxonomy | Genus Orthopoxvirus, subfamily Chordopoxvirinae, family Poxviridae | | |
| Times | Greater than 3,000 years up to 1980 | 1970 ~ now | April 2022 ~ now |
| Regions | Globally | Central and Western Africa | Globally |
| Sources of infections | Droplets or body fluids of infected humans | Major: droplets, body fluids, tissues, and feces of animal reservoirs (rodents, nonhuman primates)<br>Minor: droplets or body fluids of infected humans | Droplets or body fluids of infected humans |
| Spreading ways | Person-to-person | Mainly animals-to-person or environment-to-person | Person-to-person |
| Susceptible populations | All the vaccinia unvaccinated humans | Mainly children | Mainly homosexual males |
| Clinical manifestations | Prodrome: fever, headache, fatigue<br>No lymphadenopathy<br>Rash: centrifugal (primary) or centripetal<br>(minor)<br>Sequelae: blindness, pneumonia, encephalitis, osteomyelitis | Prodrome: fever, headache, fatigue<br>Classic lymphadenopathy<br>Rash: centrifugal<br>Sequelae: encephalitis, pneumonia, septicemia, and dehydration | |
| Mortality | Nearly 30% | Nearly 10%* | None |
| Preventions | Vaccinations<br>Avoid contact with patients and their items<br>Use personal protective equipment<br>Practice good hygiene | Vaccinations<br>Avoid contact with animal reservoirs<br>Avoid contact with patients and their items<br>Use personal protective equipment<br>Practice good hygiene | Vaccinations<br>Avoid homosexual or any other dangerous sexual behaviors<br>Avoid contact with patients and their items<br>Use personal protective equipment<br>Practice good hygiene |
| Interventions | Antiviral drugs<br>Nutritional support<br>Nursing of cutaneous lesionsVaccinia Immune Globulin Intravenous (VIGIV)<br>Prevention of sequelae | | |

* Data varied among different surveys by about $<20\%$.
[†] Based on data collected up to July 29, 2022.

frequency, only 59 cases were reported in the DRC, Zaire, Liberia, Nigeria, Ivory Coast, and Sierra Leone [14,15]. Then, its prevalence changed dramatically, with a total of 404 cases accompanied by an 8-fold increase in incidence between 1981 and 1986 because of intensive surveillance, reset of diagnostic criteria, and uncontrollable outdoor activities [1,15,16]. Although this increase was silenced from 1987 to 1995, several large-scale outbreaks have occurred, along with geographical expansion worldwide since 1996. Countries involved included the DRC (1996–1997), the United States (2003), the Republic of the Congo (2017), Nigeria (2017–2018), the DRC (2017–2018), and Singapore (2019) [7,17–22]. In May 2022, a new round of monkeypox broke out unexpectedly and rapidly in many non-endemic countries outside Africa, with entirely different transmission features and prevailing patterns. The first case of the 2022 outbreak, a man with a travelling history to Nigeria, was confirmed on 07 May in the United Kingdom; however, it could not be referred to as the index case (the first documented case of an infectious disease), because monkeypox symptoms of some patients in Portugal and the United Kingdom dated back to late April of 2022 [9,23]. Afterward, confirmed cases were reported continuously in several countries, especially in Europe and North America. In Spain, seven suspected cases were first discovered on 17 May, and 508 patients were subsequently confirmed from 17 May to 22 June. In Portugal, the first three cases were reported on 17 May, and 96 cases were reported up to 27 May 2022; in Germany, the first case was notified on 20 May, with 521 confirmed cases till 22 June 2022. In the United States, its first case was identified on 18 May, and monkeypox transmitted quickly and broadly, with 34 confirmed cases in 12 states as of 07 June 2022 [24–28]. According to the global outbreak map, till 29 July 2022, the top five prevailing countries were the United States, Spain, Germany, the United Kingdom, and France [29].

We noticed some unique transmission characteristics when comparing this outbreak round with serial outbreaks in history (Table 1). First, in previous epidemics, the major infection sources were abundant zoonotic reservoirs like rodents and nonhuman primates, and secondary transmission (person-to-person transmission) was rare, accounting for only 28 % in the DRC (1981–1986) [15]. In contrast, except for initial patients in the United Kingdom and Italy, none of the patients had any travel history from monkeypox-prevalent areas or contact with zoonotic reservoirs, and MPXV had not been detected in suspicious host animals or imported items in these countries, indicating that person-to-person transmission was the major mode [23,30,31]. Differences also existed in the manner of viral spread. In Africa, MPXV was usually obtained from bodily fluids, tissues, and feces of reservoirs through damaged skin, mucous, or respiratory tract; however, during this outbreak, the transmission was mainly through close contact with respiratory droplets and bodily fluids [7,30]. Viral DNA was identified in seminal specimens of three homosexual patients in Italy, two of them were AIDS patients with hepatitis concomitantly, and the third one was a syphilitic patient, which indicated that in the current outbreak, MPXV might also be obtained from infectious semen [32]. Additionally, susceptible populations were also distinct. Studies proved that age less than ten years (80 %) and male (58 %) were two significant susceptibility factors for African patients; however, the most notable characteristics of patients in Europe and America during this outbreak were those associated with homosexual men (men who have sex with men, MSM) aged 20–50 [15,30,33]. Unlike cases in villages of Central and Western Africa, where clusters of patients had complicated associations in time and zone, clusters of this outbreak were independent [23,34]. Moreover, although the subclinical proportion was small in the previous prevalence ($<30$ % in the DRC between 1980 and 1986), such a relatively independent mode of transmittal of the current outbreak indicated a larger subclinical component [15]. Taken together, it is likely that the virus was silently transmitted and became widespread in these countries without notice, highlighting the necessity of morbidity surveillance in both epidemic and non-epidemic regions. These differences prove that mutation or evolution might have occurred with the concomitant likelihood of new variants

appearing. Hence, genomic mutation or evolution of monkeypox also needs to be monitored for a better understanding of its pathogenicity and clinical features. Recent studies have proven such mutations and evolutions happening during the 2022 outbreak. Based on genomic sequencing, MPXV causing the 2022 outbreak displays nearly 50 single nucleotide polymorphisms (SNPs) descending from the 2018–2019 outbreak, which indicates an accelerated evolution faster than normal evolutions of the genus Orthopoxvirus, and the mutating bias of these SNPs are GA > AA and TC > TT base substitutions [9]. Some of these mutations have been classified into low, medium, and high priority; one middle-priority mutation is E353K on F13L, which is the target of anti-MPXV drug tecovirimat, three high-priority mutations (D209N, P722S, M1741I) were also found on B21/22, which are responsible for the virulence and mortality of Orthopoxvirus [35]. Additionally, 10 MPXV proteins were found with the highest number of mutations, like D2L-like, OPG071, OPG023 (viral multiplication needed), OPG210 (with MPXV antibody epitopes), etc., and mutations of OPG023, OPG105, OPG153, and OPG210 exist among different groups [36]. Besides nucleotide mutations, loss of accessory genes is another evolving appearance of orthopoxvirus, possibly restricting its host range and elevating its mortality. Such gene-losing phenomena were also monitored in 17 % of samples during surveillance in South Africa, which partially explains its increased human-to-human transmission [37]. Current epidemiological features also revealed a non-negligible possibility of sexual transmission, especially homosexuality, via bodily fluids, seminal fluids, or other fluids through a damaged mucous membrane. This hypothesis was supported by a case series study containing 528 confirmed cases from 16 countries between 27 April and 24 June. 98 % of these patients were homosexual or bisexual males, and 95 % of these transmissions possibly happened through sex [38]. Among another 152 patients surveyed in the United Kingdom, 151 were MSM, 44 % had more than ten sexual mates, and 44 % had group sex, strongly suggesting the possibility of sexual transmission [39]. Considering that MSM were also susceptible to AIDS, hepatitis, and tuberculosis, they would constitute an important population of monkeypox surveillance for better disease control and public health. Actually, the case series study above have reported that 41 % of the confirmed cases were also infected with human immunodeficiency virus (HIV) [38].

## 4. Monkeypox clinical manifestations

Symptoms in monkeypox prodrome appeared as fever, headache, fatigue, malaise, and unilateral or bilateral lymphadenopathy in submandibular, cervical, postauricular, axillary, and inguinal places. Lymphadenopathy was classic to monkeypox rather than smallpox [1,7]. After prodrome, a classic rash appeared on the face and then spread centrifugally and quickly to the whole body, including palms and soles, with lesions varying (papular, vesicular, pustular, and crust) [1,7]. Furthermore, several complications, like encephalitis, pneumonia, pulmonary distress, septicemia, and dehydration, might also occur [7]. Several studies indicated that the mortality of monkeypox in Africa was nearly 10 %, significantly lower than that of smallpox (30%) [14,15,17]. The fatality was extremely low in outbreaks outside Africa, and no deaths have been reported in the current outbreak [1,19,40].

However, even though the present prevalence had higher subclinical components, milder symptoms, and lower fatality, we could not underestimate the pathogenicity of monkeypox, potential risks of underlying severe symptoms, and the necessity of proper intervention or prevention. As noted above, biased nucleotide mutations occurred with an accelerated evolution associated with the alerting transmissibility, pathogenicity, and drug resistance. Additionally, such mutations might be selected under the pressure of host factors like apolipoprotein B mRNA-editing catalytic polypeptide-like 3 (APOBEC3) enzyme and may facilitate immune evasion [9]. Therefore, it was uncertain if it would evolve into some unknown or fierce variants in the future. Previously, the vaccinia vaccine was shown to cross-protect monkeypox and minimized its susceptibility, severity of symptoms, incidence of sequelae, and secondary attack rates [1,15,17]. However, the global smallpox vaccination programs were stopped after the eradication of the variola virus, currently unvaccinated populations might be more susceptible than the previously vaccinated populations.

Meanwhile, no specific drugs were developed for MPXV, except routine treatments like classic antiviral agents, antibiotics against secondary infections, nutritional support, and nursing of cutaneous lesions. Therefore, heavy public health and medicine burdens might result from large-scale global outbreaks. Additionally, children, pregnant women, the elderly, and MSM with AIDS, tuberculosis, or hepatitis had weak immunity to the defense against monkeypox. Thus, monkeypox might strike them severely and cause fatal symptoms, exacerbating the public health burden.

## 5. Monkeypox experimental diagnosis and detection

Generally, virological diagnosis and detection had three approaches: MPXV culture, MPXV genetic polymerase chain reaction (PCR), and MPXV immunoglobulin enzyme-linked immunosorbent assay (ELISA). MPXV genetic PCR was highly recommended by the World Health Organization (WHO) owing to its accuracy and sensitivity for MPXV detection. It was further recommended that specimens be derived from biopsy or cutaneous lesions like vesicles, pustules, and dry crusts rather than blood samples, owing to the short duration of viremia from the onset of monkeypox symptoms [41]. The Centers for Disease Control and Prevention (CDC) of the United States have issued the standard generic Real-Time PCR procedure for non-variola Orthopoxvirus detection. However, MPXV was still hard to distinguish from other Orthopoxviruses like camelpox, ectromelia, or taterapox [42]. To specifically detect MPXV among various Orthopoxviruses, a double-PCR combined assay was designed, verified, and noted for its reliability and sensitivity. A TaqMan-based assay may specifically detect the DNA polymerase gene of Orthopoxvirus and exclude other Variola. Then, a hybridization assay targeting the MPXV B6R gene can distinguish MPXV from all other Orthopoxviruses [43]. According to the latest diagnosing procedure released by the Poxvirus & Rabies Branch (PRB) of CDC on 6 June 2022, MPXV DNA can be generically detected via real-time PCR using a pair of primers amplifying MPXV generic gene and a pair of primers amplifying human DNA as a quality control [44]. Besides PCR, ELISA was also an essential method for MPXV detection. An IgM and IgG ELISA assay was constructed for monkeypox diagnosis, and IgG and IgM response rates were 29/36 and 34/36, respectively, among 36 confirmed cases in the United States in 2003, suggesting that it would be an efficient method for MPXV detection [45]. However, it did not eliminate the serological cross-reactivity between MPXV and other Orthopoxviruses. Immunoglobulin induced by vaccinia-based vaccines could also produce false positive results [41]. Nevertheless, ELISA was still an optimal measure for epidemiological surveys after a large-scale outbreak or investigations aimed at determining the protective efficiency of vaccinia-based vaccines [46]. However, the virological culture was rarely used for MPXV detection, although it could be cultured in several mammalian cells and chorioallantoic membrane of chicken embryos, albeit at the cost of tedious procedures and long durations [47]. Therefore, WHO did not recommend it as a routine diagnostic method [48].

Although real-time quantitative PCR was the optimal method for experimental diagnosis, it still had some disadvantages. Strict diagnostic and biosafety requirements were imposed on every procedure of MPXV detection. First, specimens must be sampled from the correct

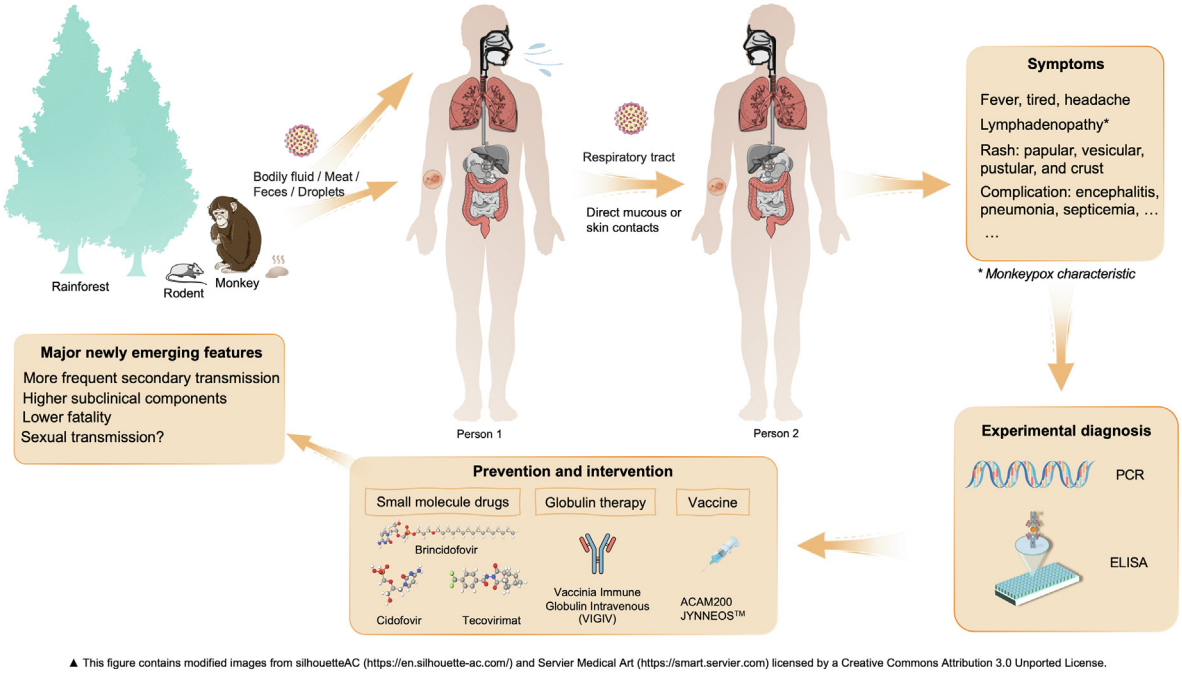


**Fig. 2. Summary of epidemiological and clinical characteristics of monkeypox.** A flow chat displayed monkeypox zoonotic transmission, person-to-person transmission, clinical manifestations, experimental diagnostic methods, and current prevention and intervention methods. Some important newly emerging features of the current outbreak were also listed in the figure.

roof or fluid of vesicles, pustules, and dry crusts because sampling from incorrect tissues or sites could influence the quality of specimens, leading to inaccurate results [41]. In addition, samples need to be stored in a sterile, dry, frozen environment immediately after they were obtained to ensure the best quality [41]. When sampling specimens, exact personal protection equipment (PPE) was needed to reduce the risk of exposure. Then, as proposed by CDC of the United States, for laboratory staff getting vaccinated in the past three years, further diagnostic experiments should be performed in biosafety level 2 (BSL-2) facilities with BSL-2 practices; however, for staff without vaccination in the past three years, such experiments should be performed with BSL-3 practices in BSL-2 facilities [49]. Such rigorous biosafety requirements restricted the widespread and immediate performance of MPXV detection, leading to more considerable detection expense and longer diagnostic time. For better surveillance in combating monkeypox globally, surrogate and convenient detection methods need to be developed with lower biosafety risks. For instance, an instantly diagnostic method detecting the antigen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from nasal swabs, the colloidal gold method, could be applied to monkeypox using specimens from lesions [50]. Therefore, a cheap, feasible, and quick MPXV-specific antigen detecting method could be established. The rapid diagnostic method could act as the primary screening to help healthcare providers discover susceptible patients quickly. As the diagnostic kits were portable, tests could be completed on sight without the shipment of infectious specimens of the patients. Additionally, such a diagnostic method is suitable for large-scale screening, especially considering the increasing monkeypox incidence in some areas. Moreover, although the WHO recommended that specimens be obtained from biopsy or cutaneous lesions, the newest study found that viral DNA could constantly be detected in the upper respiratory tract even several days after lesions healed [51]. As the healing of cutaneous lesions was considered the main criterion judging the infectivity of monkeypox patients, this result prompted us to revisit this criterion critically, and it might need further evolutions with longer quarantining days and stricter discharging standards.

## 6. Monkeypox prevention and intervention

Although the traditional vaccinia vaccine conferred 85% cross-protection against monkeypox, large-scale vaccinations were stopped in the 1980s, and protective efficacy may well have waned several years post-immunization [1,15]. Moreover, vaccinia immunization might cause some adverse effects like sores in vaccination sites or lymph nodes, fever, rash, allergy, or even severe reactions like encephalitis and myocarditis [52]. Two licensed vaccines in the United States, ACAM200 and JYNNEOS$^{TM}$, are available. ACAM200 is a live-virus preparation that could cause lesions at the injection site and spread to other sites or people; in contrast, JYNNEOS$^{TM}$, a non-replicating virus vaccine, does not have such side effects [53]. However, the effectiveness of these two vaccines needs further observations through more extensive population studies. Besides live-virus vaccines, other kinds of vaccines are also under research. A subunit DNA vaccine encoding genes of L1R, A27L, A33R, and B5R was designed and protected rhesus macaques potently from severe diseases after a lethal dose MPXV challenge [54]. A DNA-protein combined vaccine (primarily vaccinated with DNA and boosted with protein) contained the same antigens and protected rhesus macaques successfully with milder symptoms and lesions [55]. The protective efficacy of these subunit vaccines also needs further validation in human clinical trials. Considering the features and genomic similarities among different MPXV variants and Orthopoxviruses, it is feasible and promising to design highly efficient, long-acting, and broad-spectrum vaccines to combat monkeypox or some unknown pox that might appear in the future.

Although vaccines effectively eliminate monkeypox, some specialists claimed that antiviral drugs would be a better option. When lethal intratracheal MPXV infection was induced, it was found that Macaca fascicularis displayed reduced mortality and lesions after administration of cidofovir and HPMPO–DAPy, while Macaca fascicularis previously administered with vaccinia vaccines had worse outcomes [56]. However, available antiviral agents in clinical like tecovirimat, cido-

fovir, and brincidofovir were limited [57]. Therefore, more specific drugs with higher efficiency and lower toxicity must be generated to combat MPXV infection. For exploring MPXV-specific drugs, more targets could be identified from the whole-life cycle activities of MPXV and its different components. At the same time, drugs can be developed based on these targets' physiological, pharmacological, and structural features. Since MPXV is an enveloped virus that enters cells through membrane fusion and endocytosis, effective drugs can also be screened from universal and broad-spectrum fusion or endocytosis inhibitors [58].

## 7. Conclusion

Since May 2022, an outbreak of monkeypox quickly spread, and more than 20,000 confirmed cases have been reported in several countries in Europe, America, Oceania, Asia, and Africa. Would it be another global pandemic similar to smallpox or influenza? Further observation is needed; although notable features like accelerated evolutions, new-emerging variants, transmission through close contact, the rapid expansion of confirmed cases in several countries, and limited anti-MPXV specific agents in clinics, the susceptible population are mainly limited to homosexuals. Nevertheless, on 23 July 2022, WHO declared the 2022 outbreak of monkeypox a public health emergency of international concern (PHEIC), a critical alarm worldwide [59]. Therefore, international cooperation needs to be intensified in public health policy, populational prevention, clinical treatment, and the development of drugs and vaccines to effectively control this outbreak [60,61].

Increased attention was concentrated on its pathogenicity, transmission, and clinical characteristics by clinicians and researchers worldwide. This article reviewed virology, epidemiology, clinical features, experimental diagnosis, prevention, and disease intervention (Fig. 2) and compared the current and historic outbreaks between monkeypox and smallpox. Additionally, we proposed the importance of intensive surveillance, development of surrogate and convenient detection methods, design of highly efficient, long-acting, and broad-spectrum vaccines, and the discovery of highly efficient MPXV-specific drugs with low toxicity to better combat monkeypox and benefit public health endeavour worldwide.

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## Conflict of interest statement

The authors declare that there are no conflicts of interest.

## Author contributions

**Tianyu Lu:** Conceptualization, Investigation, Writing – review & editing. **Zongzhen Wu:** Conceptualization, Writing – review & editing. **Shibo Jiang:** Conceptualization, Writing – review & editing, Supervision. **Lu Lu:** Conceptualization, Investigation, Writing – review & editing, Supervision. **Huan Liu:** Conceptualization, Writing – review & editing, Supervision.

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