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Novel clinical and genomic signatures of the 2022 monkeypox virus

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The monkeypox outbreaks started in 2022 have constituted Public Health Emergency of International Concern (PHEIC) unexpectedly. What factors drove this neglected zoonosis in Africa into global focus remains largely unknown. Combined clinical, epidemiology, and phylogenomic analysis have indicated substantial genome mutation, deletion and rearrangement might contribute to the sudden outbreak and unusual features in transmission and clinical outcome. As no vaccine or antiviral drug is available in China, we call for immediate action and collaboration in response to the new MPX crisis.

Keywords: monkeypox, outbreak, evolution, treatment and prevention

Introduction

Monkeypox (MPX) is a typical zoonosis that is caused by the monkeypox virus (MPXV) from the *Orthopoxvirus* genus, which includes the well-known smallpox, vaccinia, and cowpox viruses. Similar to smallpox virus, MPXV infection begins clinically with fever, myalgia, fatigue, headache, and frequently followed by skin lesions with pustular papules and ulcerations [1]. Generally, lymphadenopathy differentiated MPXV infection from smallpox. MPXV was initially identified and endemic in the Central and West Africa countries, where its natural hosts are rodents and non-human primates[2-3]. For decades, human MPX cases were mostly restricted to zoonotic infections with limited human-to-human spread. However, since the first confirmed case on 7 May 2022 in the United Kingdom[4], more than 78,000 confirmed cases have been reported in more than 110 countries including China, as of 8 November 2022 (WHO). FDA has approved two vaccines and three antiviral drugs to prevent and treat MPX, while none of them is available in China.

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The sudden expansion of MPX cases and geography came along with some unusual clinical outcomes and transmission routes. The number of MPX infections rapidly increased, suggesting a more effective human-to-human transmission than previously recorded. However, the case-fatality rate (0.025%) of the current outbreak is much lower than that of classic MPX (1% to 15%) prior to 2022[1]. Notably, the majority of the reported cases are identified in men who have sex with men (MSM), and the rapid spread of MPX in MSM has been attributed to sexual promiscuity of affected individuals[5]. Contact with infectious viral material from skin lesions occurring during sexual intercourse has been identified as the main risk factor[6-7]. Additionally, during the present outbreak, some MPX patients showed asymptomatic infections or milder symptoms with fewer skin lesions, implying that the current monkeypox might have been cryptically transmitted in populations for a long time[8]. Besides, other changes might be responsible for the novel features of this epidemic.

Monkeypox virus mutations

Viral adaptive mutation has been evidenced to contribute to the initiation of the pandemic as well as enhanced phenotypes in pathogenicity and transmissibility[9-10]. Direct genome comparison of historical and contemporary MPXV strains are supposed to provide clues to these open questions. MPXV genome consists of a large double-stranded DNA, encoding about 190 genes. Before the 2022 outbreak, monkeypox virus was classified into two clades: the Congo Basin Clade (clade 1), which is predominant in Central Africa with severe symptoms and higher mortality rates (>10%), and clade 2, which circulates in West Africa with milder cases, has a lower case fatality rate (1% to 3%). The rapid transmission of MPXV might be related to the genomic divergence from these two clades. Recently, Gomes and colleagues analyzed the phylogenomic characterization of the first viral genome sequences of the 2022 MPXV outbreak[11]. They found that the current outbreak virus clustered with 2018–2019 cases (clade 2) linked to an endemic country, indicating that the current global outbreak might originate from a single epidemic region. However, the current lineage is segregated to a different phylogenetic branch (B.1), since about 50 genetic differences in the recent epidemic MPXV genomes. What should be concern is that the substitution rate of current MPXV was far more than that previously estimated of Orthopoxviruses, and most of the nucleotide substitutions involved in conserved features with GA>AA and TC>TT nucleotide replacements[12]. Another study also finds similar mutation features in the cases of 2022 MPX in the United States[13]. This mutational bias might associate with Apolipoprotein B mRNA-editing catalytic polypeptide-like 3 (APOBEC3) enzymes, one of the DNA cytidine deaminase, which could inhibit virus replication by editing the viral genome mutations. The excess of mutations in the 2022 MPXV indicates an accelerated adaptive evolution derived by host APOBEC3. This highlights the need of further functional studies to determine whether

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these mutations contribute to the enhanced transmissibility of virus or help the virus evade host immunity.

Genomic rearrangements of monkeypox virus

Additionally, besides the single nucleotide polymorphisms (SNPs), insertions, deletions and genome rearrangements are commonly detected in the terminal of poxvirus genome, which may be associated with altered infectivity and pathogenicity. It has been reported that genome end-region rearrangements play an important role in the virulence and evolution of smallpox virus[14-15]. The genomic rearrangements had also been detected in the current outbreak MPXV. A recent study by Li and colleagues identified large genomic deletion and rearrangement in MPXV sequences from MSM cases in the United States[16], where the largest number of cases have been reported. They found the large-scale genomic changes, range from 2.3 to 15kb, involved in several protein coding sequences (CDS) and inverted terminal repeat (ITR) region of the terminal regions. Especially the deletion of gene encode surface glycoprotein (*B21L*) and zinc finger-like protein (*D5R*), as well as truncated ITR were considered to be involved in the immunomodulation, virulence and the host range of poxvirus[14, 17]. However, it is early to tell whether these large genomic changes are beneficial, neutral, or harmful to MPXV transmission and pathogenicity. Additionally, the authors also found that a genomic deletion of one sample involved in the target gene of Clade Ⅱ MPXV-specific PCR assays. The large-scale genomic deletion might eventually render it ineffective, and PCR assays targeting the terminal regions may be most at risk. Consequently, PCR assays targeting the conserved region or targeting multiple different regions may be necessary to ensure the identification of viruses harboring large deletions. Overall, the emergence of genomic rearrangements highlights the continued need for genomic surveillance of MPXV to study viral evolution during the current epidemic.

In the last decades, the refinement of genetic engineering methods based on vaccinia virus have contributed to facilitate the reverse genetic manipulation of the genomes of poxviruses[18]. Using standard recombination technology, researchers have found that the loss of D14L is not the sole virulence factor responsible for the different pathogenicity between MPXV clade1 and clade 2 [19]. The observed rapid mutations and large-scale genomic rearrangements in MPXV genome raise concern that the contemporary circulating strains might be undergoing accelerated evolution with unusual clinical outcomes. Ongoing investigation with reverse genetics will help clarify this issue. More importantly, extensive molecular surveillance and epidemiology investigation should be warranted to identify any novel mutations that are potentially related to viral transmission, pathogenicity, and escape from available countermeasures.

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Treatment and prevention

Two treatments are currently authorized for monkeypox, Tecovirimat and Brincidofovir, which inhibit the viral envelop protein p37 and block viral DNA polymerase, respectively[20]. Several compounds, such as adamantane derivatives, NIOCH-14, PAV-886, Mitoxantrone and Ribavirin, have been reported to be effective against Orthopoxviruses in vitro by blocking viral protein p37 formation, viral DNA and protein synthesis, viral release and entry[21-23]. These compounds would enhance the availability and spectrum of the effective antiviral drug against poxviruses. However, their efficacy and safety against the current emerging monkeypox are largely unknown and require further preliminary and clinical research. As all approved vaccines and antivirals are originally designed to prevent smallpox, whether the vaccines could efficiently prevent the current MPX remains unknown. According to a recent study, people vaccinated with 2-shot MVA-BN, a third-generation attenuated smallpox vaccine approved for use as a vaccine against MPX, yield relatively low levels of neutralizing antibodies to the epidemic MPXV strain, indicating the need to develop vaccines tailored to prevent current MPXV[24]. Innovative vaccine platforms like mRNA vaccines have exhibited excellent protection efficacy and great application prospect during COVID-19 pandemic, which will facilitate the development of MPX vaccines. To thwart the continuation of the current monkeypox epidemic, it is important to raise awareness and build diagnostic capacity for populations, especially at-risk groups. Additionally, eliminate stigma and discrimination within the MSM community and to provide equal access to diagnosis, treatment and vaccines. Finally, we should initiate global collaborations to evaluate the effectiveness of current treatments, vaccines and vaccination strategies.

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Author contribution
M.X.S. and X.Y.H. collected references and drafted the manuscript. X.Y.H. revised the paper. M.X.S. drew the figures. C.F.Q. reviewed the article and provided professional guidance. All authors have read and approved the manuscript

Conflict of interest statement
The authors declare no competing interests.

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Figure legend.

Viral adaptive evolution may be responsible for the new clinical and epidemiologic features of the monkeypox outbreak in 2022. Prior to 2022, MPX was a rare zoonosis with limited human-to-human transmission in Central and West Africa. The current MPX outbreak has spread to 110 countries with more than 78,000 confirmed cases. Epidemiology and phylogenomic analysis indicate that the current MPX outbreak might originate from epidemic regions. Additionally, APOBEC3-derived mutations as well as viral genomic rearrangement may lead to viral adaptive evolution which could account for the new clinical-epidemiologic features of current MPX.