Liu *et al. Zoonoses* (2022) 2:20
DOI 10.15212/ZOONOSES-2022-0022

COMMENTARY

The Novel Monkeypox Outbreak: What Should We Know and Reflect On?

Xiaoning Liu[1,2,#], Xiao Jiang[1,#], Zheng Zhu[3,4], Liqin Sun[1] and Hongzhou Lu[1,*]

Abstract

While the COVID-19 pandemic continues, the world is on high alert regarding the second public health threat of a global monkeypox outbreak. Monkeypox, a relative of smallpox, is a zoonotic disease that was initially restricted to Africa. However, a novel outbreak has occurred in Europe, a non-endemic region, starting in May 2022. In the face of this unprecedented event, people should be aware of several crucial facts regarding monkeypox to support global public health prevention and control of the outbreak, including pathogenetic epidemiological and diagnostic aspects. As the cases outside Africa rapidly increase, including in a large proportion of men who have sex with men, thinking about the potential effects on global public health, as well as the shifting epidemiological trends of monkeypox and the insights from this novel outbreak, will be crucial.

Keywords: Monkeypox, non-endemic region, global public health

Edited by:
Wanbo Tai, Shenzhen Bay Laboratory, The Institute of Infectious Diseases, China

Reviewed by:
Reviewer1: Zhendong Guo, Changchun Veterinary Research Institute, Chinese Academy of Agricultural Sciences, Changchun, China.
The other reviewer chose to be anonymous.

[#]These authors contributed equally to this work.
*__Corresponding author:__
E-mail: luhongzhou@fudan.edu.cn (HL)

[1]Department of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Shenzhen Third People's Hospital, Shenzhen 518112, Guangdong Province, China
[2]National Heart & Lung Institute, Faculty of Medicine, Imperial College London, London, UK
[3]School of Nursing, Fudan University, Shanghai, China
[4]Fudan University Centre for Evidence-based Nursing, Shanghai, China

Received: June 04 2022
Revised: June 21 2022
Accepted: June 22 2022
Published Online: June 28 2022

INTRODUCTION

As the COVID-19 pandemic continues, the world is on high alert regarding the second public health threat of a global monkeypox outbreak. Monkeypox is a zoonotic disease caused by monkeypox virus (MPXV), which causes symptoms similar to those of smallpox, but with less severe clinical signs. After the eradication of smallpox in 1980 and the subsequent discontinuation of smallpox vaccination, monkeypox has become one of the most important pox viruses affecting public health [1].

Eleven African countries have reported human monkeypox cases since the first case was confirmed in the Democratic Republic of Congo in 1970. The first human monkeypox case outside Africa was discovered in the United States in 2003 [2]. Subsequently, sporadic cases of infections in non-African countries were detected in people with a history of travel to African countries. In May 2022, multiple cases of monkeypox were detected in several non-endemic countries (including the UK, US, Portugal and Spain), in people without direct travel to endemic areas. The number of cases is rising rapidly. Consequently, numerous countries and scientists have expressed deep concern about this potential changing epidemiological trend and its possible influence on global health. This article aims to highlight key facts regarding MPXV and provide reflections on the 2022 epidemic outbreak.

PATHOGENETIC CHARACTERISTICS

MPXV is a double-stranded DNA virus of the genus orthopoxvirus, a close relative of smallpox. The total case fatality rate has been 8.7%, with substantial variation among clades (10.6% in Central Africa vs 3.6% in West Africa) [3].

EPIDEMIOLOGICAL CHARACTERISTICS

Monkeypox is predominantly endemic to central and western Africa. Tree squirrels, Gambian kangaroos, mice, rats, nonhuman primates and other species have been recognized as vulnerable to MPXV, and infections have been observed in these species [4,5]. Monkeypox can be transmitted from animal-to -human, or from human to human. Humans are infected primarily through direct contact with infected animals' blood, bodily fluids, damaged skin or mucous membranes, or contaminated skin or objects within 21 days after contact with an infected person, and through intimate contact with respiratory secretions. Vertical transmission from mother to child, or close perinatal contact can lead to congenital monkeypox. Recent research has indicated that MPXV may be present in droplets such as saliva or respiratory secretions that fall quickly from the air [6]. In contrast to viral particles that become suspended in the air, remain there for extended periods of time and can cause airborne transmission, droplets are much larger, can travel only short distances and have a much shorter lifespan. Therefore, infection from exposure to an infected person's respiratory droplets is possible. Wearing masks would be an effective method to prevent the transmission of respiratory droplets in monkeypox.

Since 1970, human monkeypox cases have been documented in 11 African countries, and the number of cases has been increasing, particularly in the Democratic Republic of Congo [2,7]. Cases outside Africa have also emerged in recent years. The median age at presentation has risen from 4 years in the 1970s to 21 years at present (2010–2019) [3]. These findings may be associated with the cessation of smallpox vaccination, which provided some cross-protection against monkeypox, including human-to-human transmission. Of note, most monkeypox cases in May 2022 in non-endemic areas were in men who have sex with men, most of whom had no history of travel to monkeypox endemic areas. No previous evidence has suggested monkeypox transmission via sexual routes; therefore, further study is necessary to determine whether the epidemiological features of this outbreak are due to transmission triggered by mucosal exposure from close man-to-man contact, anal intercourse or other sexual transmission.

CONSIDERATIONS REGARDING DIAGNOSIS

Monkeypox is usually a self-limited disease, with symptoms that may last 2–4 weeks. Severe cases are more common in children and are associated with the degree of virus exposure, patient health status and the nature of the complications [8,9]. An underlying immune deficiency may lead to poorer outcomes. The clinical stages can be divided into incubation, invasion and skin eruption phases. Different clinical phases of monkeypox have different features and pathological alterations as clinical symptoms progress (Fig 1). Notably, lymphadenopathy during the invasion period is a specific feature of monkeypox and a clinical feature that distinguishes it from other diseases that may initially appear similar, such as chickenpox, measles and smallpox. Unlike chickenpox, monkeypox evokes a rash that is more concentrated on the face and extremities than on the trunk: the face, palms and soles of the feet, and oral mucosa are involved in more than 70% of cases, whereas genital, conjunctival or corneal lesions are present in approximately one-third of patients with monkeypox [1]. Complications of monkeypox include

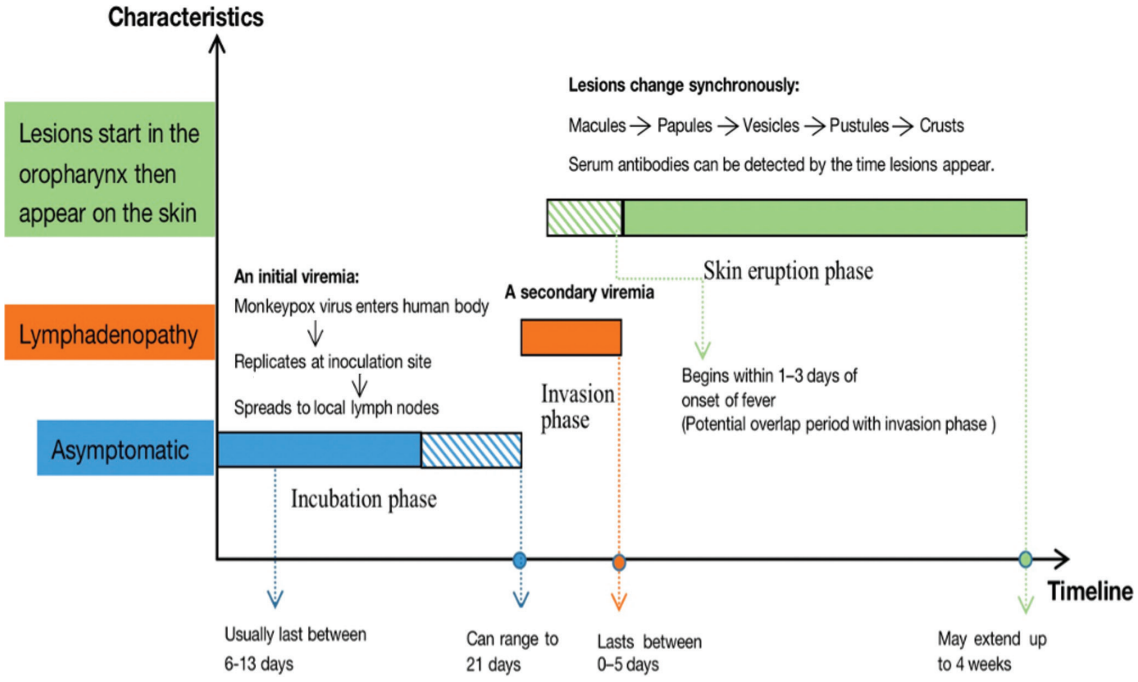

FIGURE 1 | Symptomatic progression of monkeypox, including characteristics and pathological alterations at each stage.

secondary infections, bronchopneumonia, sepsis, encephalitis and corneal infections with resultant loss of vision.

The diagnosis of monkeypox is based on a combination of clinical manifestations and epidemiological history, and confirmation by laboratory pathogenic diagnosis is required. However, owing to the lack of epidemiologic association in most monkeypox outbreaks in European countries since May, the WHO has also suggested that non-endemic countries or regions must be considered for inclusion of suspected cases of monkeypox after patients present with an unexplained rash with fever and other symptoms.

Herpes exudate swabs or scabs are optimal specimens for pathogenic testing [10], and polymerase chain reaction (PCR) is the preferred detection method, owing to its accuracy and sensitivity. The obtained specimens must be preserved in a dry, sterile tube, and must be kept cool, refrigerated (2–8°C) or frozen (-20°C or lower) to ensure the purity and safe handling of the samples. MPXV samples are categorized as dangerous goods of class 6 and must be transported in triple packing in compliance with WHO guidelines for infectious substance transportation [11].

Collection of serum samples for PCR or monkeypox antigen/antibody testing is not recommended as a diagnostic test for the pathogen. The results of PCR blood tests are usually ambiguous, because the general length of viremia is relatively short after symptom onset. Hence, blood should not be routinely collected from patients for PCR testing. Furthermore orthopoxvirus is serologically cross-reactive, recent or previous vaccination with cowpox-based vaccines might result in false-positive results.

TREATMENT AND PREVENTION OF MONKEYPOX

Currently, drug treatment options for monkeypox are limited. Europe, the United States and other nations have approved the VP37 protein inhibitor of the positive pox virus genus tecovirimat [12] for the treatment of monkeypox; however, data regarding its efficacy and safety are scant. Moreover, various DNA polymerase inhibitors and nucleoside analogues have demonstrated in vitro inhibition of the pox virus [13,14]. Adler et al. have acknowledged the use of brincidofovir in a retrospective analysis [15] of seven UK patients with monkeypox, but the patients who used the drug discontinued treatment because of elevated liver enzymes.

Previous research has demonstrated that smallpox vaccination provides approximately 85% protection against monkeypox [16]. However, smallpox vaccination has not been promoted for monkeypox prevention in areas where the disease is endemic, because of the high incidence of adverse events after vaccination with the first- and second-generation vaccines. In 2019, the U.S. Food and Drug Administration (FDA) approved Jynneos, a highly attenuated third-generation smallpox vaccine, for the prevention of smallpox and monkeypox in adults [17]. However, post-exposure prophylaxis is currently recommended only for high-risk groups and close contacts, and the vaccine's efficacy of blocking and preventing outbreaks has yet to be determined.

MONKEYPOX AND GLOBAL PUBLIC HEALTH

Simultaneous immunization against MPXV was previously achieved through cowpox vaccination; however, smallpox eradication and a subsequent lack of vaccination efforts paved the way for monkeypox to gain clinical ascendancy [18]. In addition, because most monkeypox cases occur in rural Africa, suspected underreporting may lead to an underestimation of the potential threat of this pathogen [5]. In May 2022, atypical clusters of monkeypox cases were discovered in many nonendemic nations in patients with no direct travel to endemic areas. To ensure global public health security, investigating and determining the source and likely mode of transmission of this outbreak are critical.

However, unlike SARS-CoV-2, which is transmitted through tiny droplets called aerosols, monkeypox is transmitted through close contact with body fluids (e.g., saliva from coughing). Thus, people with monkeypox are likely to infect far fewer close contacts than people infected with SARS-CoV-2. In addition, monkeypox is caused by a relatively large DNA virus. DNA viruses are better at detecting and repairing mutations than RNA viruses; therefore, MPXV is less likely to suddenly mutate into a strain that can be easily transmitted from person to person and thus cause a global pandemic [19].

REFLECTIONS AND RECOMMENDATIONS REGARDING THE 2022 MONKEYPOX OUTBREAK

First, because of the cessation of smallpox vaccination, most of the world's population currently has low immunity to orthopoxvirus. Second, scientists should be aware that this outbreak particularly affects the population of men who have sex with men; the likelihood of HIV co-infection should be considered, because it would enhance the risk and severity of monkeypox infection. Furthermore, the monkeypox outbreak in 2022 has occurred mainly in non-endemic Europe. No cases of monkeypox have been reported in populous countries such as China, India and Indonesia. However, as global travel and trade resume, the prospect of more cross-continental transmission of MPXV cannot be discounted. The risk of endemic infectious disease spillover has been highlighted by the monkeypox outbreak, which serves as a warning that, in an increasingly interconnected world, infectious disease risks are also shared globally.

To date, sequencing of viral genomes collected from patients with monkeypox in Belgium, France, Germany, Portugal and the United States has revealed that each sequence is highly similar to the monkeypox strain found in West Africa. The current sequences are most similar to those of the few cases of monkeypox that emerged outside

of Africa in 2018 and 2019, which were associated with travel in West Africa. However, MPXV genetic variation as the cause of the current monkeypox outbreak has not yet been determined. Moreover, with the previous restriction of monkeypox to poorer parts of Africa, few resources have been dedicated to genomic surveillance efforts in Africa. Scientists also have yet to identify a natural animal host for monkeypox in affected areas of Africa. Therefore, more resources and research are needed to understand the evolution of the virus regarding the changes in monkeypox genes [20], which might have positive implications in global public health prevention and control of monkeypox.

ACKNOWLEDGEMENTS

The authors wish to acknowledge and thank all participants and the authors for their contributions. Shenzhen Science and Technology Innovation committee project ([2022] No. 48): Research on the characteristics and laws of human-to-human transmission of SARS-CoV-2.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

REFERENCES

1. Monkeypox. Available from: https://www.who.int/news-room/fact-sheets/detail/monkeypox. Accessed on May 28, 2022.
2. Moore M, Zahra F. Monkeypox. 2021. Cited in Ovid MEDLINE(R) Epub Ahead of Print at Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medp&NEWS=N&AN=34662033. Accessed on May 31, 2022.
3. Bunge EM, Hoet B, Chen L, Lienert F, Weidenthaler H, Baer LR, et al. The changing epidemiology of human monkeypox-A potential threat? A systematic review. PLoS Negl Trop Dis. 2022;16(2):e0010141.
4. Monkeypox. Wkly Epidemiol Rec. 2011;86(41):448-51.
5. Sklenovská N, Van Ranst M. Emergence of monkeypox as the most important orthopoxvirus infection in humans. Front Public Health. 2018;6:241.
6. CDC Monkeypox Response: Transmission. Available from: https://www.cdc.gov/media/releases/2022/0509-monkeypox-transmission.html. Accessed on Jun 20, 2022.
7. Rimoin AW, Mulembakani PM, Johnston SC, Lloyd Smith JO, Kisalu NK, Kinkela TL, et al. Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo. Proc Natl Acad Sci U S A. 2010;107(37):16262-16267.
8. Harris E. What to know about monkeypox? JAMA. 2022;327:2278-2279.
9. Monkeypox multi-country outbreak, RR ASSESSMENT - 2022 - ecdc.europa.eu. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Monkeypox-multi-country-outbreak.pdf. Accessed on May 31, 2022.
10. Laboratory testing for the monkeypox virus, Interim guidance. Available from: https://www.who.int/publications/i/item/WHO-MPX-laboratory-2022.1. Accessed on May 31, 2022.
11. WHO Guidance on regulations for the transport of infectious substances 2021-2022 [Internet]. Available from: https://www.who.int/publications/i/item/9789240019720. Accessed on May 28, 2022.
12. Parrino J, McCurdy LH, Larkin BD, Gordon IJ, Rucker SE, Enama ME, et al. Safety, immunogenicity and efficacy of modified vaccinia Ankara (MVA) against Dryvax challenge in vaccinia-naïve and vaccinia-immune individuals. Vaccine. 2007;25(8):1513-1525.
13. Yakimovich A, Huttunen M, Zehnder B, Coulter LJ, Gould V, Schneider C, et al. Inhibition of poxvirus gene expression and genome replication by bisbenzimide derivatives. J Virol. 2017;91(18):e00838.
14. Myskiw C, Piper J, Huzarewich R, Booth TF, Cao J, He R. Nigericin is a potent inhibitor of the early stage of vaccinia virus replication. Antiviral Res. 2010;88(3):304-310.
15. Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis. 2022;5:24.
16. Fine PE, Jezek Z, Grab B, Dixon H. The transmission potential of monkeypox virus in human populations. Int J Epidemiol. 1988;17(3):643-650.
17. McCollum AM, Damon IK. Human monkeypox. Clin Infect Dis. 2014;58(2):260-267.
18. Monkeypox - United Kingdom of Great Britain and Northern Ireland. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON383. Accessed on May 28, 2022.
19. Kozlov M. Monkeypox goes global: why scientists are on alert. Nature. 2022;606:15-16.
20. Zumla A, Valdoleiros SR, Haider N, Asogun D, Ntoumi F, Petersen E, et al. Monkeypox outbreaks outside endemic regions: scientific and social priorities. Lancet Infect Dis. 2022. doi: 10.1016/S1473-3099(22)00354-1.