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Commentary

The Novel Monkeypox Outbreak: What should we know and reflect on?

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Summary： While the COVID-19 pandemic rages on, the world is on high alert for a second public health threat: a global monkeypox outbreak. As a relative of smallpox, monkeypox, a zoonotic disease, used to restrict in Africa. However, a novel outbreak has been seen in Europe, a non-endemic region, since May 2022. In the face of this unprecedented event, there are specific vital facts concerning monkeypox that people should be aware of for global public health prevention and control, including pathogenetic and epidemiological aspects, as well as diagnostic issues. As the cases outside Africa are soaring and the large proportion of men have sex with man (MSM) population among them, it is imperative to think about the potential impacts on global public health, as well as the shifting epidemiological trend of monkeypox and the insight of this novel outbreak.

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

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1. Introduction

While the COVID-19 pandemic rages on, the world is on high alert for a second public health threat: a global monkeypox outbreak. Monkeypox is a zoonotic disease caused by monkeypox virus with symptoms similar to smallpox, but with less severe clinical signs. Due to 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 (DRC) in 1970. The first human monkeypox outside Africa was discovered in the United States in 2003 [(2)]. Following that, sporadic cases of infected people in non-African countries were detected and found to have a history of travelling in African countries. In May 2022, multiple cases of monkeypox were detected in several non-endemic countries (the UK, US, Portugal, Spain, etc.) without direct travel linkages to endemic areas, and the cases are rising rapidly. As a result, numerous countries and scientists have expressed deep concern about the potential changing epidemiological trend and its possible influence on global health. This paper aims to highlight some key facts regarding the virus and provide reflections on the 2022 epidemic outbreak.

2. Pathogenetic characteristics

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

3. Epidemiological characteristics

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

Since 1970, human monkeypox cases have been documented in eleven African countries, and the number of cases has been increasing, with the most substantial increase appearing in the DRC [(2,7)].

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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 today (2010-2019) [3]. These findings could be related to the abolition of smallpox vaccination, which provided some cross-protection against monkeypox and increased human-to-human transmission. Of note, most monkeypox cases in May 2022 in non-endemic areas were in men who have sex with men (MSM), and most of them had no history of travel associated with monkeypox endemic areas. There has been no previous evidence of monkeypox transmission via sexual routes, so it's worth looking into whether the epidemiological features of this outbreak are due to transmission triggered by mucosal exposure from close contact or anal intercourse during man-to-man activity or due to sexual transmission.

4. Consideration in treatment Diagnosis

Monkeypox is usually a self-limited disease, with symptoms that may last 2 to 4 weeks. Severe cases are more common in children and are related to the degree of virus exposure, the patient's health status, and the nature of the complications [8,9]. An underlying immune deficiency may lead to a worse outcome. 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 (Figure 1). It's worth mentioning that lymphadenopathy during the invasion period is a specific feature of monkeypox and a clinical feature that distinguishes it from other diseases that may appear similar initially, such as chickenpox, measles, and smallpox. Unlike chickenpox, the rash of monkeypox is more concentrated on the face and extremities than on the trunk, with the face, palms and soles of the feet and oral mucosa involved in more than 70% of cases, and genital, conjunctival, or corneal lesions in about 1/3 of patients [1]. Complications of monkeypox include secondary infections, bronchopneumonia, sepsis, encephalitis, and corneal infections with resultant loss of vision.

The diagnosis of monkeypox requires a combination of clinical manifestations and epidemiological history, and a laboratory pathogenic diagnosis is required to confirm the diagnosis. However, due to the lack of epidemiologic association in most of the monkeypox outbreaks in European countries since May, WHO also suggested that non-endemic countries or regions need to be considered for inclusion of suspected cases of monkeypox once an unexplained rash with fever and other symptoms appears.

Herpes exudate swabs or scabs are optimal specimens for pathogenic testing [10], and polymerase chain reaction (PCR) is the preferred detection method due to its accuracy and sensitivity. The obtained specimen must be preserved in a dry, sterile tube and kept cool, refrigerated (2 to 8° C) or frozen (-20° C or lower) to ensure the purity of the sample and the safety of the sacred substance. Monkeypox virus samples are categorized as dangerous goods 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 since the general length of viremia is relatively short after symptom onset. Hence blood should not be

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routinely collected from patients for PCR testing. Whereas orthopoxvirus are serologically cross-reactive, recent or previous vaccination with cowpox-based vaccines might result in false-positive results.

5. Treatment and Prevention of Monkeypox

Currently, drug 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 rare. Moreover, various DNA polymerase inhibitors and nucleoside analogues have demonstrated in vitro inhibition of the pox virus [13, 14]. Hugh Adler et al. acknowledged the use of brincidofovir in a retrospective analysis [15] of seven UK monkeypox patients, but patients who used the drug discontinued treatment due to elevated liver enzymes.

Previous research has demonstrated that the smallpox vaccination provides around 85% protection against monkeypox [16]. However, smallpox vaccination has not been promoted for monkeypox prevention in areas where the disease is endemic due to the high incidence of adverse events following the first and second generations of vaccination. 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 efficacy of blocking and preventing outbreaks has yet to be determined.

6. Monkeypox and global public health

Simultaneous immunization against monkeypox virus was previously achieved through cowpox vaccination; however, smallpox eradication and 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, atypically, clusters of monkeypox cases were discovered in many nonendemic nations with no direct travel linkages to endemic areas. To guarantee global public health security, it is critical to investigate and determine the source and likely mode of transmission of this outbreak.

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). This indicates that people with monkeypox are likely to infect far fewer close contacts than those infected with SARS-CoV-2. Also, monkeypox is caused by a relatively large DNA virus. DNA viruses are better at detecting and repairing mutations than RNA viruses, which means that monkeypox viruses are less likely to suddenly mutate into a strain that can be easily transmitted from person to person and thus cause a global pandemic [19].

7. Reflections and recommendations on the 2022 monkeypox outbreak.

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To begin with, due to the cessation of smallpox vaccination, most of the world's population currently has low immunity to the orthopoxvirus. Second, scientists should be aware that this outbreak affects the MSM population; while no instances of HIV co-infection have been reported, the likelihood of HIV co-infection should be considered since it can enhance the risk and severity of monkeypox infection. Furthermore, the monkeypox outbreak in 2022 occurs mainly in non-endemic Europe. No case of monkeypox has 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 the monkeypox virus cannot be discounted. The risk of endemic infectious diseases spilling over 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 monkeypox patients in Belgium, France, Germany, Portugal, and the United States has revealed that each sequence is very similar to the monkeypox strain found in West Africa. The current sequences are most similar to those of the few cases of monkeypox that have emerged outside of Africa in 2018 and 2019 that have been associated with travel in West Africa. However, monkeypox virus genetic variation as the cause of the current monkeypox outbreak has not yet been determined; what’s more, with the previous restriction of monkeypox to poorer parts of Africa, few resources have been dedicated to genomic surveillance efforts in Africa. Scientists have also yet to find 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 concerning the changes in monkeypox genes [20], which could have positive implications for the global public health prevention and control of monkeypox.

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