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Monkeypox: a potential global threat?

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Monkeypox, a largely neglected disease endemic in Western and Central Africa, has recently attracted global attention due to over 100 confirmed and suspected cases (by May 21, 2022) in more than ten countries in Europe, North America, and Australia. The number is expected to continue to increase. There have been some monkeypox cases outside of Western and Central Africa in the past years, e.g., an outbreak with 71 confirmed and suspected cases in the United States of America caused by imported animals from Ghana [1], and multiple sporadic cases associated with travels in the United Kingdom, the United States of America, Singapore, and Israel [2–6]. While it is not a surprise to see increasing monkeypox cases over time to those who have been closely watching the situation, the current outbreak is still very unusual based on the current information from health authorities and news outlets, mainly for two reasons. First, most of the patients did not travel to the endemic area in Africa., suggesting under-detected community transmission. Second, it occurs in multiple countries during the same time period, suggesting multiple possible sources of introduction. While some hypotheses have been raised to explain the usual current outbreak of monkeypox, more thorough investigations are needed to answer many outstanding questions associated with this outbreak. This outbreak reinforces that monkeypox has the potential to grow as a global threat. However, monkeypox has not been paid enough attention in the past, although it has emerged to be a smallpox-like (but milder) disease in humans since the 1970s.

The causative pathogen of monkeypox is monkeypox virus (MPXV), a member of the family *Poxviridae* that includes dozens of different viruses infecting humans and animals, causing a wide range of diseases. MPXV is a close relative of variola virus, the causative agent of smallpox that had killed 300 million people in the 20th century alone [7]. MPXV has a large double-stranded DNA genome of ~200kb [8]. Primates are not the natural hosts of MPXV and the virus was named because it was first isolated from laboratory monkeys in 1958 [9]. Monkeypox is a zoonotic disease, with the first human case reported in 1970 [10]. There are two known MPXV genetic clades– the Central African (Congo Basin, CB) clade and the West African (WA) clade [11]. The MPXV(CB) clade is more virulent than the MPXV(WA). The range of case fatality rates of monkeypox had been from 1 to 11% [12]. The disease is usually more severe in young children [13]. MPXV transmission

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AUTHOR CONTRIBUTIONS

Zhilong Yang conceived, wrote, and revised the manuscript.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

mainly through contacting infected people and animals, as well as materials contaminated with the virus. Poxviruses are quite stable in environment. The avoidance of contacting infected people and animals, and potentially contaminated materials can help prevent MPXV infection. More details about the symptoms, transmission, and other monkeypox disease information can be found on the World Health Organization Website (https://www.who.int/news-room/fact-sheets/detail/monkeypox). This commentary aims to discuss monkeypox as a potential and growing global health threat in the foreseeable future, which requires significant efforts to minimize the damage it may cause.

Rising cases in Africa and other regions of the world.

Since the first human infection of monkeypox was reported in 1970, growing numbers of monkeypox cases have been reported over the past five decades. Bunge et al. systematically reviewed the trend during the past 50 years based on peer-reviewed articles and grey literature sources [14]. The confirmed and suspected case numbers have risen over time: 1970–1979 with 47 cases, 1980–1989 with 356 cases, 1990–1999 with 520 cases, 2000–2009 with 10,166 cases, and 2010–2019 with 19,068 cases [14]. The WHO Bulletin reported over 6200 and 9400 confirmed and suspected cases in 2020 and 2021, respectively [15, 16]. These numbers are likely under-reported due to a lack of robust surveillance systems in the endemic regions. The geographic areas of monkeypox cases have also expanded [14]. More travel and non-travel related cases have been reported outside of Western and Central Africa, including Europe, North America, Australia, and Asia, in the past few years. One main reason for the increasing numbers of monkeypox cases is believed to be the termination of smallpox vaccination in the general population, resulting from the greatest achievement of model medicine: the eradication of smallpox in 1980 through a global vaccination campaign [17]. Smallpox vaccine cross-protects against MPXV infection. In an analysis of individuals born before 1980, when the smallpox vaccine was routinely offered in the general population, vaccinated individuals had a 5.21-fold lower risk of monkeypox than unvaccinated individuals (vaccine efficacy ~81%) [18]. With the smallpox immunity waning in the general population, the world population is more susceptible to monkeypox. In addition, increased human-animal contacts and human-human contacts due to expanded human activities likely contribute to this trend. With the continuous decrease of people with smallpox immunity, as well as more human-animal and human-human contacts, it is conceivable that monkeypox will continue to expand its geographic areas and susceptible population. More frequent outbreaks in and outside of its endemic regions will be expected in the future.

Lack of robust surveillance and awareness.

The countries in Western and Central Africa with monkeypox endemic areas are developing countries. The capability of health systems to monitor and report monkeypox cases is limited. Many cases are likely not detected and recorded. Doctors may also miss monkeypox cases as it is rare, and the clinical symptoms have similarities with some other diseases, such as syphilis and chickenpox (shingles). The lack of robust surveillance and awareness likely increases the spread of monkeypox.

Underinvestment in understanding many unknowns of MPXV (and other poxviruses).

Our understanding of MPXV biology, epidemiology, transmission, and pathogenesis remains limited. While the natural reservoir of MPXV is believed to be rodents, the ecology and natural history of MPXV are largely unknown, which prevents the identification of potential sources of zoonotic transmission. One major reason smallpox could be eradicated is that humans are the only hosts of the variola virus that causes smallpox. With the existence of natural animal reservoirs for MPXV, the eradication of monkeypox is less likely. Like other poxviruses, MPXV encodes hundreds of genes. The molecular functions of these genes and their contributions to pathogenesis need more intensive investigations. Many outstanding questions remain to be answered, for example, the cellular receptor of MPXV (and other poxviruses) is unknown. However, the investment in poxvirus research has been limited in the past decade, evidenced by the decreasing numbers of publications since 2009 when searching in PubMed with the term “poxvirus”. This contrasts with the trend of increasing scientific publications over the past decade [19].

Needs for the development of specific vaccines and drugs.

It is fortunate that the smallpox vaccines also provide robust protection against monkeypox, and the smallpox drug, TPOXX, is promising and likely effective for treating monkeypox. ACAM2000 (a live-attenuated replicating vaccine) and JYNNEOS (a live-attenuated, non-replicating vaccine) are two US FDA-approved vaccines that can prevent monkeypox. Other smallpox vaccines used in the smallpox era should also be able to provide protection. However, there is still a need to develop effective and safe new generation of vaccines specific for monkeypox. While MPXV has a DNA genome that generally has a lower mutation rate than RNA viruses, poxviruses have their unique ways to rapidly adapt to environmental changes through events like gene deletion or addition of gene copies during their DNA replication processes, in addition to point mutations. Resistance to antiviral drugs is not uncommon, and additional drugs with different viral targets need to be developed to treat monkeypox and other poxviruses. MPXV transmissibility among humans has been suggested to be inefficient (R_0<1) [20]. While it is unclear if the MPXV associated with the current outbreak gains higher transmissibility among humans, it is possible that MPXV may increase its transmissibility among humans during evolution.

In summary, it is conceivable that monkeypox outbreaks will likely be more frequent in the future. More intensive surveillance and research on MPXV biology (and other closely related poxviruses), natural history, transmission, pathogenesis, host interactions, evolution, as well as drug and vaccine development are urgently needed to prevent uncontrollable spread and situations. This asks for concerted efforts among the governments, academics, industries, and healthcare systems. Without such proactive actions, the chance for monkeypox to become a global threat will grow.

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