Monkeypox virus: a neglected zoonotic pathogen spreads globally

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The ongoing monkeypox outbreak in non-endemic countries is likely to be a consequence of the failure to curtail the spread of the disease in endemic regions of Africa despite decades of constant outbreaks. A globally driven one health approach to prevention and treatment of the disease is essential to control present and future outbreaks.

Monkeypox virus (MPXV), a DNA virus, is the aetiological agent of a zoonotic disease known as monkeypox (MPX) and is grouped into two genetic clades, namely West Africa (WA) clade and Congo Basin (CB) clade. MPX has an incubation period of 4–21 days and the symptoms range from fever to respiratory distress, which are similar to symptoms of smallpox except for lymphadenopathy[1,2].

MPX is endemic in west and central Africa[2], but the recent emergence of MPX in several non-endemic regions outside of Africa has generated a great concern. Although the virus causes generally mild symptoms in immunocompetent individuals and inter-human transmission may be inefficient, severe disease or mortality may result if the virus spreads to immunocompromised individuals, children, elderly individuals, pregnant women and individuals living with co-morbidities such as HIV/AIDS and diabetes.

In Nigeria, all regions have now reported MPX cases compared with 2019 when the reported cases came from only the southern parts of the country[3]. The possible explanations for the expansion of the viral ecological niche include the following: diversion of public health resources and surveillance to Lassa fever outbreaks and the COVID-19 pandemic; proximity of residences to forests, which could drive zoonotic infections; and migration from rural to urban areas, which could drive inter-human transmissions.

Although the primary source or sources of MPXV in non-endemic countries is unknown, the detected cases do not seem to be associated with travel history to endemic regions. So far, no animal reservoir for MPXV has been identified in non-endemic regions. We thus hypothesize that it is unlikely a zoonotic spillover from animals to humans, and instead due to a single or multiple importations of the virus from endemic regions, and subsequent cryptic inter-human transmissions that were undetected. By the time the cases in non-endemic regions showed up on the public health radar, several inter-human transmission chains might have already occurred, and thus it became impossible to trace the primary source or sources of infection. Possible reasons why community transmission occurred multiple times without detection may include non-reporting of cases, misdiagnosis of MPX as sexually transmitted diseases especially as it presented with atypical genital and peri-anal lesions, mild or asymptomatic cases and a dearth of active surveillance for MPX.

So far, no new variant of MPXV has been discovered, and draft genomes showed no reduction in genome size and content, which is a predictor of increased virulence in variola virus. Additionally, all the MPXVs recovered from the 2022 MPX cases belong to the WA clade[4,5], which is less virulent than the CB clade and contributed less to the inter-human transmission[2]. A phylogenomics study conducted by Isidro et al.[4] with MPXVs isolated from the 2022 multi-country MPX outbreak suggests continuous accelerated evolution of the virus in humans as indicated by segregation in the divergent phylogenetic branch. However, this finding needs to be corroborated by rigorous time-scaled phylodynamic analysis, and substitution rates per year should be directly inferred from the MPXV genomes isolated from the 2022 MPX outbreak. The accelerated evolution and adaptation of the CB clade of MPXV to humans was previously hypothesized by Kugelman et al.[6].

Although the exact cause for re-emergence of MPX has yet to be identified, the probable drivers for the present MPX global spread could include the cessation of smallpox vaccination in 1980, which has led to lack or wane of population immunity. In agreement with this, demography data revealed that the infected individuals are 50 years or below and vaccination with non-replicating MVA-BN (JYNNEOS or Imvanex) has been shown to provide protection against MPX; of note, the data are derived from animal and not human cohorts[2]. Other possible drivers that led to the re-emergence include a high surge of MPX cases in endemic regions and greater likelihood of exportation of the virus to other countries owing to the global increase in economic, political and cultural relations[7], climate

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https://doi.org/10.1038/s41579-022-00776-z

change (MPX historical data suggest that MPX outbreaks usually occur during fall as a result of increased rainfall resulting in flooding as well as deforestation, both factors driving animals, potential reservoir hosts, into human population and residences), and the absence of active surveillance for MPX. Currently, there is no treatment or specific vaccination against MPX available, but, as mentioned above, animal studies suggest that some smallpox vaccines had shown to be effective against MPX[2] and may also attenuate disease outcome as post-exposure prophylaxis. However, replicating smallpox vaccines should not be used to vaccinate against MPX owing to the documented adverse effects, particularly in immunocompromised individuals, and it may also raise the risk of recombination between MPXV and the vaccine strain in a coinfected or superinfected individual. Recombination among orthopoxviruses is a major driver of their evolution[8] and the characteristics of recombinants are difficult to predict. Clinical trials have documented that the antiviral drugs tecovirimat (NCT00728689), cidofovir and brincidofovir (NCT01143181) are effective against MPX. Tecovirimat and cidofovir have been approved by the United States Food and Drug Administration (FDA) for the treatment of MPX under expanded access protocol.

Swift actions need to be taken to prevent the establishment of MPXV in domesticated and wildlife animal populations, particularly rodents and small mammals, in presently non-endemic regions. Currently, there seems to be no evidence of human-to-animal transmission according to the World Health Organization (WHO)[9], but this observation could be due to luck rather than the dynamics of virus transmission. MPXV, unlike variola virus, which only has humans as a host, is promiscuous and can infect various animals.

The following steps need to be taken globally in an attempt to curtail MPXV spread: administering smallpox vaccination (non-replicating vaccines), to provide cross-protection against MPX to individuals at high risk of exposure; post-exposure vaccination to already infected individuals and their contacts; active MPX surveillance in human populations especially in endemic regions; periodic epidemiological surveillance of MPX in rodents and small mammals; public health regulatory oversight over trade and ownership of pet rodents, small mammals and other wildlife animals; thorough human contact tracing; and the specific MPXV reservoir needs to be identified. Determining the reservoir will also fill our knowledge gaps in regard to virus ecology, evolution and transmission dynamics[2]. Finally, capacity and competences must be built especially in endemic regions to predict disease outbreaks and prevent them rather than just responding to and containing the outbreak.

The current outbreak of MPX in non-endemic regions should be a wake-up call and highlights how little-to-no attention has been paid to the spread of the virus within endemic areas. It should also serve as a reminder that in an inter-connected and globalized world, no region or country is safe from zoonotic pathogens like MPXV unless the virus is contained in endemic regions. The global health response strategies must prioritize MPX outbreaks in endemic regions of sub-Saharan Africa.

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Competing interests
The authors declare no competing interests.