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Mpox poses an ever-increasing epidemic and pandemic risk

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The human interaction with mpox has changed across its entire endemic range, revealing the endemic and pandemic risk of monkeypox virus and the current knowledge gaps on its biology that hamper virus control.

Humans are an ecological niche for orthopoxviruses (OPXV) such as mpox, a niche originally filled by smallpox (variola virus; VARV). Since VARV was eradicated by vaccination with vaccinia virus (VACV)[1], the human niche for OPXV has been vacant, with sporadic OPXV zoonoses from mpox (MPXV) (in Africa), cowpox virus (North Europe), Abatino poxvirus (South Europe), Akhmeta virus (West Asia) and Alaskapox virus (North America) (reviewed in ref. 2). There are also numerous VACV zoonoses in South America attributed to VACV established in rodent populations during the smallpox eradication campaign. The common feature of OPXV zoonoses is the absence of human-to-human (H2H) transmission, except for MPXV, which made limited H2H chains that would generally end after two or three transmissions[3].

Although all OPXV zoonoses cause a local lesion at the infection site, a major clinical difference between mpox and other OPXVs is a disseminated infection with centrifugally distributed secondary lesions (Fig. 1), as seen with smallpox[3]. The mechanisms that underlie disseminated infection in humans are a major gap in our understanding OPXV disease. The high incidence of MPXV zoonoses relative to other OPXVs is likely due to factors that influence human interactions with rodent reservoirs, and both the greater severity and propensity for secondary transmission relative to other OPXVs may arise from the ability of mpox to initiate disseminated infection in primates. Mpox causes severe disease in several primate species, including humans, and is named for epizootic transfer to non-human primates, which are dead-end hosts (Fig. 1). Experimentally, rodents are resistant to infection and disease, with the exception of North American ground squirrels (*Cynomys* spp.) and a limited number of immunodeficient mouse strains[2], hampering laboratory studies on pathogenesis and immunity.

MPXV clades

From a public health perspective, the risk of emergent mpox was limited by an assumed biological barrier that prevented H2H transmission[4]. Mpox zoonoses are traditionally found in very rural areas with limited physical connectivity to urban areas, and primarily occur in adolescent boys, with H2H transmission largely limited to younger siblings[3]. Clade II viruses were known from the 1970s, but zoonoses are rare compared with clade I. Nevertheless, the rapid global spread of mpox in 2022 was a clade IIb outbreak that originated in Nigeria (Fig. 2) and was declared a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO).

The PHIEC did not seem be associated with an identifiable biological change in the virus relative to historic early zoonotic isolates[5] and occurred mainly in adults and largely in gay men and other men who have sex with men. Hence, the introduction to a new human demographic that facilitated more efficient transmission by extended skin-to-skin and mucosal contact is likely to have mediated the rapid spread of clade IIb MPXV globally after 2022 (ref. 6). However, case reports on exported cases as early as 2018 are compatible with this novel clinical manifestation, perhaps indicating that MPXV was exploiting sexual contact transmission earlier.

A new feature of the disease was a multiple lesion primary rash at an anogenital infection site, not always followed by a secondary disseminated rash, rather than the expected single primary lesion followed by a disseminated secondary rash (Fig. 1). This facilitated rapid H2H transmission via the primary lesion or rash at the infection site. It is unclear whether the primary rash in mpox was an adaptation of the virus or due to the anatomical site and/or greater or abrasive skin-to-skin contact after initial infection. Transmission via a primary rash is expected to decrease the interval between transmissions, as it obviates the incubation interval before eruption of a secondary rash[6], and hence favors transmissibility and establishment of longer, compressed H2H chains. Importantly, it also indicates that the historical inefficiency of the classical transmission mode is real, as the global outbreak and continued cases descending from it show no signs of establishing beyond the narrow demographic of high-contact sexual networks.

With recent outbreaks of clade Ia (DRC), clade Ib (DRC) and clade IIa (Cote d'Ivoire)[7], all four mpox clades have independently achieved sustained H2H transmission. The co-circulation of clades Ia and Ib in adult demographics in Kinshasa[8] places the viruses in direct competition and is a potential driver of evolution and adaptation. The recent emergence of H2H-transmitted clade IIa mpox in Cote d'Ivoire is an indication of a widespread change in the interaction of humans with MPXV over its entire endemic range. The underlying mechanisms are likely pleiotropic, but probably include declining anti-OPXV herd immunity, years after smallpox vaccination ceased. The exact suite of enablers may differ across the geographic range. However, the risk of another MPXV, especially clade I, recapitulating the trajectory of the 2022–2023 clade IIb global outbreak but across wider demographics is real. With emerging H2H transmission of all four clades, and the extraordinary number of clade Ia zoonoses, many MPXVs are competing for human niches. Such competition is a further evolutionary driver for these viruses to biologically adapt and refine their H2H transmission.

Mutational drift and emergence of variants

Most MPXV isolates have been obtained from zoonotic or epizootic species jumps rather than from the animal reservoir(s), with only a single isolation from a candidate reservoir. It is therefore difficult to determine whether MPXVs with sustained H2H transmission are better adapted to humans than the isolates circulating in animal reservoirs or have simply

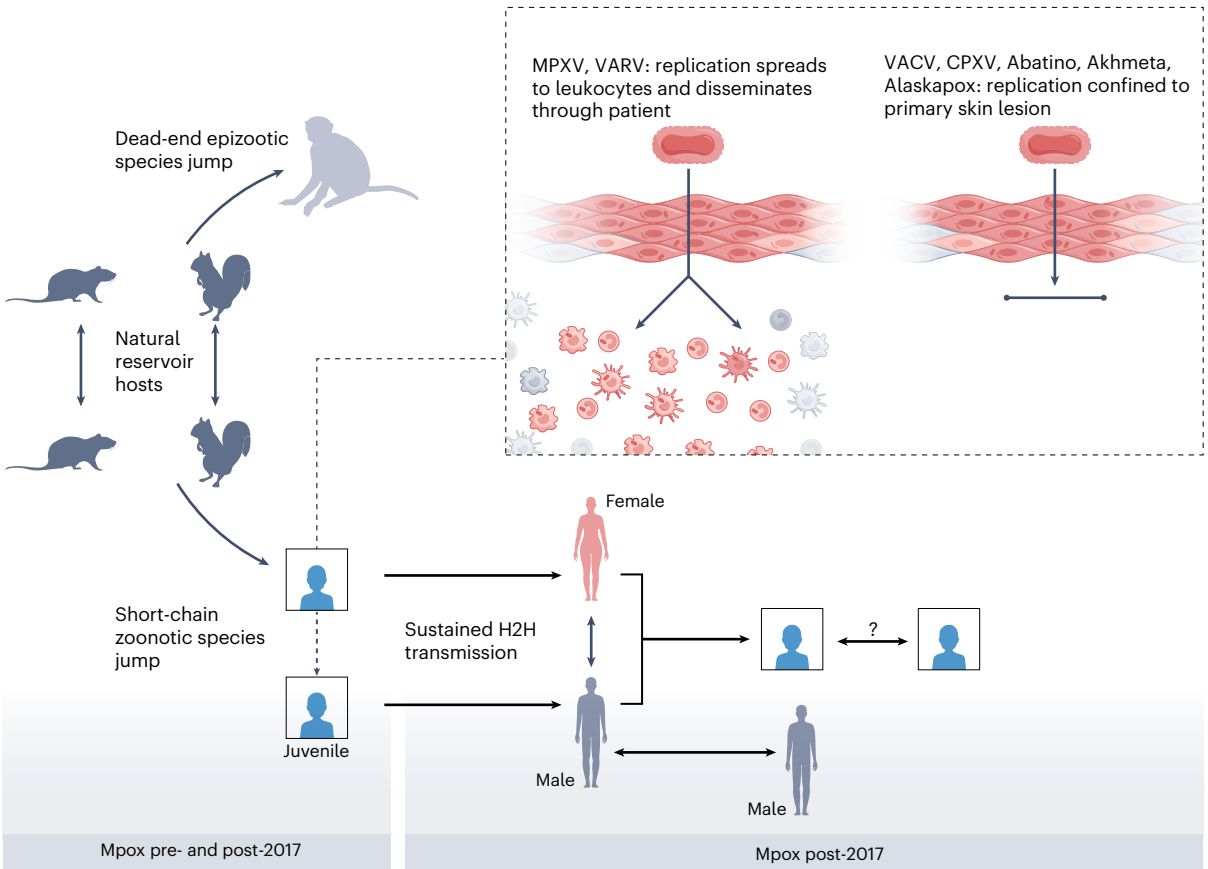

Fig. 1 | Transmission and dissemination of MPXV in animals and humans. MPXV circulates in a poorly defined animal reservoir in the wild, with evidence of infection in mice (*Mastomys natalensis* and *Steatomys parvus*), dormice (*Graphiurus kelleni*), rats (*Cricetomys gambianus*) and squirrels (*Funisciurus* spp., *Heliosciurus* spp. and *Xerus* spp.). From this reservoir, epizootic infections in primates can occur. Human contact with the reservoir results in zoonotic infection and limited H2H transmission (2–3 generations). From 2017, sustained H2H transmission of different MPXV clades is observed and this correlates with a novel transmission mode mediated by intimate sexual contact. The virus has established continuous transmission in gay men and other men who have sex with men as well as heterosexual networks, raising concerns about transmission to and between children. Once primary infection is established, MPXV spreads through the body via inflammatory leukocytes causing disseminated secondary infection. This ability is shared with VARV, the other human-adapted OPXV, but absent in other OPXV capable of causing primary infection in humans.

had the opportunity to move into novel demographics that favor virus spread. Although there has been speculation that clade IIb-lineage B is better adapted for rapid widespread H2H transmission, its predominance in case numbers in 2022–2023 may be due to higher rates of sexual contact among the demographic of men who have sex with men. Thus, it seems likely that the H2H predominance of clade Ib to clade Ia, clade IIb to clade IIa, and clade IIb-lineage B to clade IIb-lineage A is due to founder effects rather than biological differences between viral clades. However, biological differences cannot be discounted, especially as clade IIb-lineage B was already divergent from clade IIb-lineage A when it was first recognized in men who have sex with men. Comparative virology studies are therefore needed, particularly given the existing clinical differences between the clades, and lineages within them.

Notwithstanding their origins, having emerged into humans, mpox viruses are likely to accumulate mutations that distinguish them from their reservoir counterparts and potentially adapt them to humans. OPXVs have been seen as stable viruses not prone to mutation. However, the 2022–2023 global outbreak demonstrated unanticipated mutations via the deamination of cytosine residues, likely by the human APOBEC3A and APOBEC3G deaminase enzymes. Although these enzymes are known to restrict retrovirus replication via error catastrophe, their activity on the much larger MPXV genome seems to avoid error catastrophe and instead provides an unexpected source of variation, causing mutations but seemingly without costs to virus fitness.

The 2022–2023 global outbreak strain has been steadily accumulating APOBEC3-driven mutations, which have been used as a molecular clock to estimate that the initial zoonosis was in 2016, months before it was recognized in 2017 (ref. 9). Whether these genotypic changes confer new phenotypes or have adaptive value for the virus in humans is unclear. However, there are several instances of disruption to immune modulation genes, which is analogous to the observed evolution of smallpox from OPXV ancestors[10]. In this context, the constant acquisition of APOBEC3-driven mutations drives natural selection and could refine mpox H2H transmission routes.

Future trajectory

The increasing incidence of zoonotic mpox over the past 30 years and the ease with which the virus now establishes in adult humans

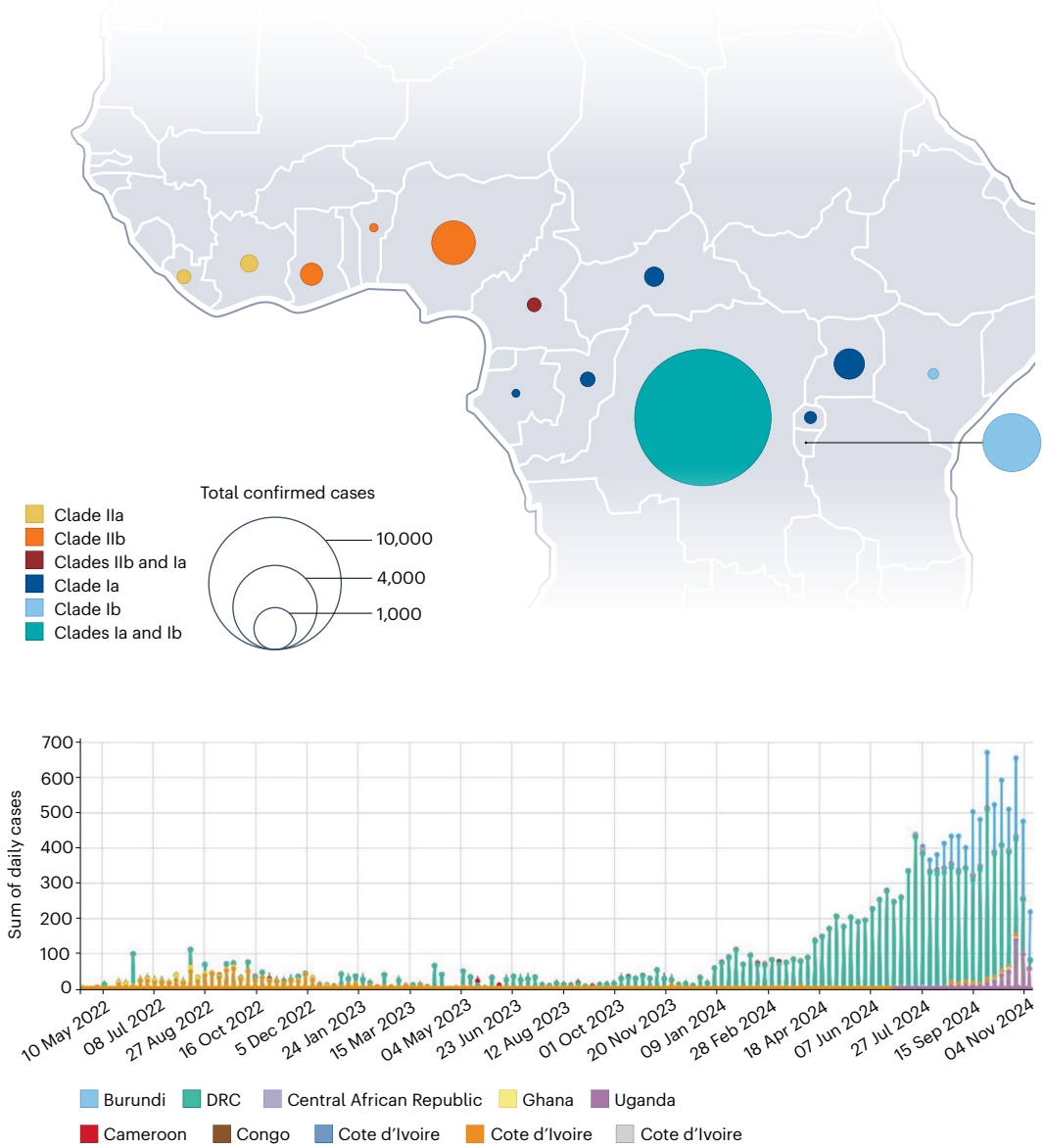

Fig. 2 | Emergence of MPXV clades in Sub-Saharan Africa since 2022. Distribution and timeline of MPXV outbreaks declared in the indicated countries since 2022. Data were sourced from the WHO covering the period between 1 May 2022 and 10 November 2024. Note that Burundi, Uganda and South Africa are outside the MPXV endemic range, and cases in these countries are likely to have arisen from importations. Timeline was produced with microreact.

shows that epidemics of mpox are likely to recur. A major concern is the possibility of MPXV spreading beyond its current narrow demographics, which would require either an alternative to transmission via primary rash, or establishment in an alternative demographic with high tactile contact. To this end, the possibility of mpox establishing in childhood networks is concerning. The continuing increase in clade Ia zoonotic events in DRC is largely in children, but with no evidence of sustained H2H transmission through childhood networks. However, affected rural areas have low population density, which is a barrier to sustained H2H transmission. The clade Ib outbreak has seen H2H transmission to children in more urban settings[11], but whether the transmission is from adults or other children is not clear. Epidemiological analysis may in time provide insights into the risks of extended spread between children, although these risks may not extrapolate well between countries.

The history of smallpox brings the expectation that mpox will induce robust immunity after the infection resolves, but some cases of reinfection will occur. The number of cases outside endemic (zoonotic) regions declined markedly from its peak in 2022–2023, perhaps because the transmission mode confines spread to high-contact sexual networks. However, the 2022–2023 global outbreak strain continues to circulate at low levels via sexual networks across the world[12]. Continued circulation among men who have sex with men is likely facilitated by individuals who avoided exposure in the initial phase, re-infections, waning immunity after vaccination, and young adults becoming sexually active for the first time.

The current demographic restriction of non-endemic mpox cannot, however, be taken for granted and the constant acquisition of APOBEC3-driven mutations provides opportunities for phenotypic variation and different properties. The prospect of clade I mpox spreading globally brings two additional risks relative to clade IIb. Clade Ia MPXVs are historically more virulent in humans than clade II viruses[13], potentially leading to greater morbidity and mortality; and the clade Ia and Ib H2H outbreaks, although apparently transmitting through sexual networks, are not predominantly in men who have sex with men. In particular, mpox cases in women could be transmitted to infants and young children, who are at far greater risk of serious illness and death.

In 2022, the WHO had the laudable goal of ending H2H transmission of mpox. This has not been possible so far, with several barriers including lack of point-of-care (POC) rapid diagnostics, limited supplies of vaccines, and limited supply and lack of diversity of antivirals. A further concern is several independent tecovirimat-resistant variants of mpox that have arisen through natural infections[14], including at least one known to be H2H transmissible[15].

It is not possible to make a definitive prediction of how mpox will evolve, or its impact if it is not controlled. But the ability of mpox to maintain H2H transmission with two independent PHEICs in two years covering four independently sustained H2H outbreaks originating from different clades, and the exceedingly high rate of clade Ia zoonotic events in endemic regions, are clear indications of high pandemic and epidemic risks. From the perspective of disease control, a major difference between smallpox and mpox is the presence of a zoonotic reservoir(s) for mpox. The absence of a reservoir for smallpox was a primary enabler for eradication, as once the human transmission chain was broken there was no natural route back for smallpox. For mpox, once H2H transmission is interrupted, the rodent reservoir(s) will remain a source for new outbreaks.

The primary goal must be to first break H2H transmission of this emergent disease; but to safeguard the investment this will require, a plan to control recurrent zoonoses must be made and implemented. As the WHO has already indicated, this will require POC diagnostics for outbreak identification, vaccines to prevent spread in appropriate demographics and cohorts, and antivirals for cohorts such as the immune compromised and the very young. These are the required tools to enable surveillance and control.

One of the lessons from smallpox eradication was that sustainable control was enabled by the local or regional manufacture of vaccines[1]. This lesson still stands, and international efforts for sustainable, global control of mpox must focus on enabling local and/or regional manufacture of POC diagnostics, vaccines and antivirals. Failure to address this across the international community leaves the future of mpox to nature and chance. We cannot comment on chance, but our understanding of nature suggests that mpox will not stand still, and left alone it will not disappear.

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References

1. Fenner, F., Henderson, D. A., Arita, I., Zdenek, J. & Ladnyi, I. D. *Smallpox and its Eradication* (WHO, 1988).
2. MacNeill, A. L. *Pathogens* **11**, 892 (2022).
3. Ježek, Z., Grab, B., Szczeniowski, M., Paluku, K. & Mutombo, M. *Bull. World Health Organ.* **66**, 459 (1988).
4. Ježek, Z., Grab, B., Szczeniowski, M., Paluku, K. & Mutombo, M. *Bull. World Health Organ.* **66**, 465 (1988).
5. Ndodo, N. et al. *Nat. Med.* **29**, 2317–2324 (2023).
6. Ulaeto, D. O., Dunning, J. & Carroll, M. W. *Lancet Microbe* **3**, e639–e640 (2022).
7. World Health Organization. Multi-country outbreak of mpox, external situation report #42 (9 November 2024).
8. Wawina-Bokalanga, T. et al. *Euro. Surveill.* **29**, 2400592 (2024).
9. O'Toole, Á. et al. *Science* **382**, 595–600 (2023).
10. Aguado, B., Selmes, I. P. & Smith, G. L. *J. Gen. Virol.* **73**, 2887–2902 (1992).
11. Vakaniaki, E. H. et al. *Nat. Med.* **30**, 2791–2795 (2024).
12. Wannigama, D. L. et al. *Lancet Infect. Dis.* **24**, e348–e350 (2024).
13. Likos, A. M. et al. *J. Gen. Virol.* **86**, 2661–2672 (2005).
14. Smith, T. G. et al. *Emerg. Infect. Dis.* **29**, 2426 (2023).
15. Garrigues, J. M. et al. *Antimicrob. Agents Chemother.* **67**, e00972–00923 (2023).

Competing interests

The authors declare no competing interests.