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Editorial

The 2023 – 2024 multi-source mpox outbreaks of Clade I MPXV in sub-Saharan Africa: Alarm bell for Africa and the World ☆

Human mpox (formerly monkeypox) has historically received little attention until 2022, when we saw a reemergence beyond endemic countries [1,2]. In this global outbreak, mpox caused by Clade IIb monkeypox virus (MPXV) was introduced to countries that had never experienced mpox or had collectively reported fewer than ten imported cases, with few secondary cases. This global outbreak was characterised by unique patterns of person-to-person transmission [3] sustained within sexual networks among men who have sex with men (MSM) [4]. Few clinical cases in women were reported [5]. This outbreak of Clade IIb MPXV decelerated at the beginning of 2023; [6] however, in April 2024, 27 countries still reported new cases to the World Health Organization, including the growing Clade IIb outbreak in South Africa mainly affecting MSM. Meanwhile, the increasing frequency of outbreaks with Clade I MPXV in endemic regions, especially in the Democratic Republic of Congo (DRC), has become a major source of concern.

MPXV is subdivided into two distinct clades: Clade I (formerly known as the Congo Basin or Central African clade) and Clade II (formerly known as the West African clade) [7]. Clade II is subdivided into two subclades, IIa and IIb, the latter being responsible for the 2022 – 2024 ongoing multi-country outbreak having originated in Nigeria.

The number of reported cases of mpox linked to Clade I MPXV has been progressively rising in Central Africa in all age groups, especially in infants and young children, characterised by different epidemiological patterns, with more severe clinical symptoms and higher mortality than Clade II. Notably, in 2023, the DRC reported a record number of suspected (clinically-compatible) cases, especially in provinces which have never reported mpox cases before [1], suggesting a growing outbreak and a shift towards increased human-to-human transmission. As of May 2024, 23 out of 26 provinces reported at least 1 suspected case. In 2024 alone, over 7000 suspected cases were reported with case fatality ratio of 5.3%. Children $\leq$ 15 years represent 67% of suspected cases and 84% of the deaths. According to the surveillance data, children under the age of 1 are reported to be four times more likely to die than those over the age of 15.

Based on epidemiological and genomic sequencing data, there appear to be at least two independent Clade I MPXV outbreaks ongoing in the DRC: (i) among adults, with affected women identifying as sex workers and (ii) in new provinces mostly affecting children. The transmission of Clade I through sexual contact was reported for the first time in April 2023 [8]. The first documented case of Clade I MPXV transmitted through sexual contact was confirmed in a man who had travelled between Belgium and the DRC and had sexual encounters in Kwango province (southwest) [8]. Subsequent epidemiological reports from South Kivu (east) in Kamituga health zone suggested a shift towards transmission through sexual contact between adults, with many of the women identifying as sex workers [9-12]. Phylogenetic analyses of the outbreak in Kamituga have identified a new sublineage of Clade I MPXV distinct from the strains found in established endemic areas to date [11,13]. Comparing these sequences to earlier zoonotic infections in neighbouring provinces suggests that this lineage likely pre-existed in a local, non-human animal reservoir [6,11]. While DRC has identified local transmission in urban settings related to travel and trade from endemic provinces, health areas continuously reporting mpox cases in South Kivu tend to be in poor, densely populated, mining areas with a high number of bars that are sustaining the local sex industry [10,11]. However, genomic evidence from limited sequences represents multiple independent spillover events from reservoir hosts followed by secondary transmission, suggesting that most cases elsewhere in the country are not linked to a single human outbreak or increased transmissibility [11,13]. Cases being reported in several previously unaffected areas of DRC confirms these observations. Overall, in the DRC outbreaks, children are the most affected population with high mortality rates. This suggests that direct transmission through family and community contact remains a major route of infection. However, further genomic analysis is needed to ascertain these observations.

Without intervention, given the proximity of DRC to neighbouring countries, these outbreaks have the potential to lead to a multi-country outbreak. There are limited investigations available from the current DRC outbreaks, and published reports from Kamituga represent a minority of mpox cases reported during this surge. Nevertheless, these investigations suggest a shift in the transmission dynamics of Clade I MPXV and at-risk populations. Current outbreaks highlight the vulnerability of the global health efforts and need for rapid response in the region. Similarly important, transmission of other sexually transmitted infections particularly HIV remains a major concern. A previously

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undescribed severe disseminated and necrotising form of Clade II infection with multi-organ involvement including lung, and secondary bacterial infections, and death, was associated with people living with HIV who fell below CD4 threshold that defines an opportunistic illness (CD4<200 cells/mm^3) [14]. Therefore, it is imperative to understand whether the new lineage of Clade I can also present similarly. As observed during the 2022 mpox outbreaks, the sexually associated secondary attack rate of mpox may be higher than previous estimates in non-sexually-associated contexts highlighting an immediate need for control efforts to inform and protect affected communities [15].

There are important actions to consider, including enhanced surveillance to track the growth of mpox epidemics as well as control and prevention strategies, which include vaccination. Leveraging diagnostic capacities in the region is urgently needed, to understand transmission dynamics that could inform prevention strategies and particularly for diagnosis of people with symptoms to get medical care, and know for whom isolation at home or in hospital is needed. The armed conflicts in the region have adverse effects on community surveillance and reporting of cases further limiting efforts to determine the true burden of mpox. Risk management and communication is also crucial to enhance equitable access to vaccines and reduce mpox stigma.

Vaccination remains the most effective strategy, particularly given the high mortality rates seen in children. Since the beginning of the millennium, experts have warned about the effects of waning immunity, after cessation of smallpox vaccination [16]. During the global outbreak, third-generation vaccines proved to be safe and greatly effective. However, access to vaccines and especially the distribution efforts in a conflict zone remains challenging. While there are active discussions between vaccine suppliers and the DRC, there is no active immunisation campaign yet. We are aware that CEPI and Bavarian Nordic are planning vaccine trials of the MVA-BN® non-replicating vaccine among children in Africa [17]. Bavarian Nordic also announced that they have submitted an application to the US FDA for approval of a freeze-dried formulation, which will ease logistics and hopefully be stable at room temperature [18]. Therefore, an immediate plan is urgently needed for development and deployment of a vaccination strategy, that makes sure sex workers and other vulnerable or marginalised populations at risk will be prioritised.

A high-level emergency meeting on mpox took place in Kinshasa from 11-13 April 2024. Participants acknowledged the alarming, protracted and ongoing mpox epidemics in several countries in Central and West Africa. Amidst calls to implement an urgent and coordinated response, the main outcome of the meeting was an agreement to draft a regional roadmap for addressing mpox in Africa, after more than 50 years of mpox epidemics in the region. The outcome of this high-level meeting falls far short of expectations. There are serious concerns about the changing dynamics of transmission and high mortality particularly among children, as well as the disease's effects on morbidity and the social and economic spheres. Given the possible risk of transmission to neighbouring countries and beyond, there is an urgency for action, led by African countries, governments, and scientists to address these unmet needs. Ongoing mpox outbreaks in Africa, especially affecting the vulnerable in inaccessible areas, represent an alarm bell for not only the African region but also the world especially given the newly recognised route of transmission through sexual contact amid repressive government policies and limited social acceptance of diversity of sexual orientation in some countries. In addition, given that animal-to-human transmission accounts for at least some of the Clade I infections, there is need to move from a crisis response model to a risk-based One Health approach that would improve disease control and management capacities in endemic countries and enhance prevention strategies in disease-free countries [19]. "No one is safe until everyone is safe" is a slogan we heard often during the COVID-19 pandemic, which is now also required for the growing global and regional mpox outbreaks.

Declaration of competing interest

We declare that we have no conflicts of interest. The opinions expressed in this article are those of the authors and do not reflect the official position of any of their affiliating organisations.

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Authors' contributions

LC and SH conceptualised this editorial, MC wrote the first and subsequent drafts and all authors contributed to the final version of the manuscript and approved it for publication.

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