Human-to-human transmission with a novel Mpox virus identified in the eastern Democratic Republic of Congo

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This week an international group of researchers from Africa, Europe and North America, the Mpox Research Consortium, published in preprint form a study describing an epidemiologic investigation into a recent epidemic of new Mpox (previously known as Monkeypox) infections with the clade I lineage, a more dangerous form of the disease.

The Mpox virus is an enveloped double-stranded DNA virus from the poxviridae family that includes smallpox and cowpox. There are two known clades of the Mpox virus known to be endemic in Africa. The more common infections used to occur with clade I, previously known as the Congo Basin clade. It is characterized by severe clinical symptoms and a mortality rate of up to 10 percent. Only 5 percent of all Mpox infections in humans used to be with clade II, previously known as the West African clade. These infections, which came to worldwide notice in last year's global monkeypox outbreak, portend a milder course and a much lower fatality rate.

The new clade I virus was detected in the mining town of Kamituga, estimated population 242,000, located in South Kivu Province of the Democratic Republic of the Congo (DRC). The outbreak that erupted in October 2023 was the first time that Mpox cases were detected in the Kamituga Health Zone.

This report comes amid a rising tide of Mpox infections across the DRC. From the beginning of 2023 until March 29, 2024, there have been a total of 18,922 suspected Mpox cases and 1,007 fatalities. In the first three months of 2024, there were a total of 4,488 cases with 279 deaths, for a somewhat higher case fatality ratio of 6.7 percent, indicating rising lethality. Twenty-three of DRC's 26 provinces have reported cases. However, the cases described in the investigation are qualitatively new, in that the evidence supports, for the first time, human-to-human transmission with the clade I lineage of the Mpox virus.

The study notes there had been 241 suspected cases recorded by South Kivu's provincial surveillance between September 29, 2023, and February 29, 2024. Ninety-one percent were hospitalized. Samples from 119 individuals were obtained for genomic analysis. Among these 108 (91 percent) were confirmed positive for Mpox infection. Professional sex workers accounted for 30 percent of all confirmed and suspected cases.

All confirmed cases had the characteristic rash. Most had fevers and approximately 40 percent had swollen lymph nodes. One hundred and fourteen presented with genital lesions. Two patients died accounting for 1.4 percent of confirmed cases.

Genomic sequencing from 22 patients were obtained confirming the clade I infections, suggesting the event started as a zoonotic spillover. However, five sequences showed a mutation mechanism known as Apolipoprotein B Editing Complex (APOBEC3) mediated cytosine deanimation, which is indicative of human-to-human transmission. According to a recent report published in the journal *Virus Evolution*, reviewing the APOBEC3-induced mutations in the evolution of Mpox viruses, these human enzymes of the innate immune system have the ability to inhibit certain types of viruses. However, they also confer a signature for their evolution within humans.

The impact of APOBEC3 modifications to the sequenced clade IIB Mpox viruses were also seen during the 2022-2023 global Mpox outbreak. As the report in *Virus Evolution* notes in their conclusions, "When we applied our analysis to monkeypox virus (MPXV), we find that there are two distinct groups of MPXV genomes, those collected before 2016 and those after … We conclude that the most likely scenario is that pre-2016, MPXV

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genomes evolved in the animal host. The post-2016 group of MPXV genomes has undergone persistent and continuous human APOBEC3 editing after zoonotic transmission circa late 2016/early 2017."

Applying similar genomic techniques learned from the human clade IIB outbreak, the authors of the Kamituga investigation estimated that the recent Mpox clade emerged in mid-September, consistent with the earliest reported case. The authors of the epidemiological investigation wrote, "This report describes a novel clade I Mpox lineage associated with sustained human-to-human transmission in an ongoing outbreak in eastern DRC. Identification of APOBEC3-related mutations—the hallmark of efficient Mpox spread via human-to-human transmission—bolsters this assertion."

Historically, Mpox infections had been characterized as an endemic zoonotic disease, meaning the virus living in rodent reservoirs [rope and sun squirrels, giant-pouched rats, and African dormice] spills over into humans that inhabit the same locale. Although the infected individual can infect others through close contact, these remained limited, and the outbreak would soon extinguish itself. The few cases identified outside of Africa usually were imported by travelers from endemic regions. Between 1970 and 2022, there have been approximately 38,000 Mpox cases recorded in West and Central Africa.

Then, in May 2022, with the lifting of the COVID restrictions, the global Mpox outbreak saw a sustained human-to-human transmission of the virus that rapidly spread across 113 countries infecting over 94,000 people between January 2022 and March 5, 2024. Thus far, 174 deaths have been tallied for a case fatality rate of almost 0.2 percent. The World Health Organization (WHO) designated this lineage as clade IIb, distinguishing it from clade IIA and I which, until now were still considered zoonotic.

Prior to 2018, very few cases of Mpox were reported outside of Africa. However, the large epidemic in Nigeria in 2017 that was driven by a sustained human-to-human transmission meant the epidemiological landscape for Mpox had undergone a radical shift and should have alerted public health agencies across the globe to take notice. These were, for the most part, dismissed by health authorities until a related lineage of the same clade from Nigeria spawned the global outbreak in 2022 amid the ongoing COVID pandemic garnered the world's attention.

Now, in light of the recent failure by the World Health Organization to reach an agreement on how to move forward on a global approach to preparing and preventing future pandemics, the developments in the eastern DRC with the clade IB of the Mpox virus in the context of the Mpox global outbreak just two years ago should raise alarms and call to action. Public health agencies worldwide seem to have learned nothing from the deaths of nearly 30 million people from COVID-19.

Complacency and reaction have been the hallmark to such epidemics, and with the COVID pandemics, public health has been enchained to the demands of the state and corporate entities. In this regard, the European CDC's threat assessment from April 5, 2024, is quite revealing. Despite having access to the latest information on monkeypox, they crassly concluded, "[The] increase in cases, the overall risk from this outbreak in the DRC for the general population in the EU/EEA and for MSM with multiple sexual partners in the EU/EEA remains low."

As the authors of the eastern DRC outbreak study warned, "The sustained spread of clade I MPXV in Kamituga, a densely populated, poor mining region, raises significant concerns. Local healthcare infrastructure is ill-equipped to handle a large-scale epidemic, compounded by limited access to external aid. The 241 reported cases are likely an underestimate of the true prevalence of Mpox cases occurring in the area."

They added, "Frequent travel occurs between Kamituga and the nearby city of Bukavu, with subsequent movement to neighboring countries such as Rwanda and Burundi. Moreover, a considerable number of sex workers operating in Kamituga are foreigners and frequently return to their countries of origin, although at present, there is no evidence of wider dissemination of the outbreak. The highly mobile nature of this mining population poses a substantial risk of outbreak escalation beyond the current area and across borders."

This only further raises the specter of yet another public health threat among the various other pathogens that are simultaneously and rapidly evolving to adapt themselves among human populations.

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