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Monkeypox lineages amid the ongoing COVID-19 pandemic: a global public health concern

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Dear Editor,

The illness caused by the Monkeypox virus (MPXV) is similar to smallpox, but less transmissible and usually less severe. It spreads from infected animals, humans, and contaminated surfaces [1,2]. MPXV was first detected in laboratory monkeys in 1958. Its first human case, a child from the Congo basin country Zaire now known as the Democratic Republic of Congo (DRC), occurred in 1970 [3,4]. Since then, hMPX cases have been continuously reported, with short outbreaks within different countries of Central and Western Africa, particularly in regions where immunity to smallpox was no longer prevalent. Previous smallpox vaccination has been reported to provide 85% protection against MPX infection as well as reduce the severity of MPX symptoms in infected individuals [1]. As reported, the secondary MPX infection rate in unvaccinated individuals has been estimated as 9.3% (compared to 37-88% for smallpox). The case-fatality rate (CFR) has observed to be higher in unvaccinated individuals with severe disease manifestations occurring in children younger than five. In the last few years, MPX cases have started to appear in other countries beyond Africa. Although the MPXV was first discovered in monkeys, it is believed that rodents may be the natural reservoir of the virus. The virus has so far been found in African rainforest squirrels and rats, mice, domestic pigs, hedgehogs, and opossums. In the US, it has been identified in prairie dogs and has infected elephants in zoos. The current number of MPX cases in non-endemic countries, particularly in the U.S, Canada, Brazil and European countries, is rising dramatically and threatens global public health. As of September 8, 2022, the total number of confirmed MPX cases reached 56,609 in 103 countries (including 96 non-endemic countries), with the highest number of cases in the U.S (n = 21,504), Spain (n = 6,749), Brazil (n = 5,525), France (n = 3,646), Germany (n = 3,518), and the UK (n = 3,484) [5].

Although the number of MPX cases is alarming in non-endemic countries amid the ongoing COVID-19 pandemic, MPXV does not spread in the same way as SARS-CoV-2 or its variants. All viruses change and evolve over time, but the MPXV mutates slower than SARS-CoV-2. The majority of MPX cases occurring in the past have been transmitted from infected animals (mainly rodents or monkeys) to humans - either via biting or direct contact with infected blood or other body fluids – with human-to-human transmission uncommon (only 28% of all cases). In the 2022 MPX outbreak, however, most cases are thought to have involved human-to-human transmission. Luckily, MPX is not as contagious as other

infectious diseases (e.g. COVID-19) and the current risk of getting MPX in the general public is low. Transmission usually occurs following close contact (i.e. face-to-face, skin-to-skin, mouth-to-skin or mouth-to-mouth) with an MPX infected person. It may also be transmitted following direct contact with contaminated surfaces. The MPXV has been reported to remain on many common household objects even after regular disinfection. However, the risk of spreading MPX this way is rather low and cleaning practices may limit contamination. It should also be noted that the severity of MPX varies depending on the viral strain and the host involved (e.g. it is relatively severe in orangutans but mild in cynomolgus monkeys). In order to help stop MPX transmission, the WHO recently launched a global awareness program to inform individuals on MPXV transmission routes [6].

There are two known clades of MPXV as per the identification of variants depending on the geographical regions where they were known to circulate. The genetic analysis suggests that MPXV has two genetically discrete virus clades (the Congo Basin or Central African clade and the West African clade), each with distinct clinical and epidemiologic parameters. At a meeting convened by the WHO on 8 August 2022, an open consultation with virologists and public health experts reached consensus on a new terminology for MPX variants/clades to avoid causing offense to any national, regional, cultural, or ethnic groups, and minimize any negative impact on trade, travel, and tourism [7]. It was agreed to rename the MPX clades using Roman numerals. Experts in pox virology and evolutionary biologists reviewed the known and new MPXV variants/clades and renamed the Congo Basin (Central African) clade as Clade I and the West African clade as Clade II. Additionally, they divided the Clade II into the two sub-clades IIa and IIb [7]. The latter (West African clade) is largely circulating in the current global outbreak and has been identified in the U.S, Canada, and several European countries. It tends to cause less severe disease than the Central African, or Congo Basin clade (Clade I). The MPXV responsible to the current 2022 MPX outbreak may be identified as a separate, third clade, however many poxvirus specialists suggested that this may not be the case [7].

It is interesting to note that the ongoing 2022 MPX outbreak in non-endemic countries has no epidemiological link to Africa. As per a recent study (preprint not reviewed yet), among the nine MPXV viral strains isolated from the U.S, Gigante et al. 2022 revealed the occurrence of two lineages of MPXV identified between 2021 and 2022 [8]. This study has shown increased similarity of the 2022 strain with the 2021 MPX viral strain. This finding points to

the fact that the current non-endemic and the previous endemic strains could potentially have a common ancestor. Mutational studies of the two lineages demonstrated the presence of GA-to-AA mutations that are linked to APOBEC3 (Apolipoprotein B mRNA Editing Catalytic Polypeptide-like3) cytosine deaminase activity. This has been a major characteristic noted among MPXV isolated since 2017 from the West African region but absent from Congo Basin lineages. Interestingly, APOBEC3 activity has been recurrent and dominant in the evolution of recent the West African virus, a characteristic not unique among other poxviruses. Based on this mutation, the current human MPXV has been classified into three clusters with Nigerian MPXV isolated in 2017, non-Nigerian MPXV isolated between 2017-2019, and recently isolated MPXV strains from the U.S. and Europe defined as Cluster I, II, and III, respectively. These studies have noted that among the mutations observed across different MPXV clusters, the GA-to-AA mutation in APOBEC3 may contribute to the virulence of the virus [8]. The origin of the 2022 MPX outbreak is still a mystery and its seemingly rapid transmission is currently under investigation. One study reported that some of the 2022 MPXV sequences were similar to those of a 2021 MPXV isolated from a traveller from Nigeria, but showed some nucleotide differences, suggesting the cases could not be directly linked [8]. Genomic sequencing is highly recommended to determine the similarity between viruses, origin of infection, and establish possible links between cases, and transmission dynamics and any probable coinfections [1,4]. Increased surveillance with sequencing will reveal a different predominant future strain and help to mitigate the outbreak [8].

Information on the exact geographical range and diversity of the MPXV is still lacking and it is important to improve disease surveillance. Kugelman et al. (2014) assessed the genome diversity of MPXV in 60 human samples with primary and secondary cases of infection collected from 2005 to 2007 [9]. They detected four distinct lineages and a deletion that resulted in gene loss in 16.7% samples. The results of the study also showed a high frequency of spill over events from the pool of viruses infecting animals, which increased disease transmissibility and severity. Recently, Luna et al. 2022 characterized the genomes of 337 MPXV strains isolated during the current outbreak [10]. The strains were grouped into three monophyletic clades. The analyses revealed the occurrences of two pre-existing clades (clade I and clade II) and a novel clade (clade III) that may potentially be emerging into an ongoing pandemic. Moreover, 2022 has seen the spread of MPXV lineages that include hMPXV-1A, A.1, A.1.1, A.2 and B.1 lineages. Interestingly, the current MPXV has been identified in non-

endemic countries like Germany (n = 110, 32.6%) and Portugal (n = 45, 13.4%). Most MPXV isolates from non-endemic regions belonged to the B.1 lineage of clade III (n = 261, 77.4%), in contrast to the circulation of clades I (n = 35, 10.4%) and clade II (n = 10, 2.5%) within endemic countries like Nigeria, the DRC, and Cameroon. It was only after the 2003 outbreak that these MPXV genomes were identified in non-endemic countries like Europe and the U.S. From the results of the genomic analyses, it was presumed that the current 2022 MPXV may have emerged from Europe [10].

Another study on the 2022 MPXV genome sequences revealed that this strain belonged to clade III (lineage B.1) and this current outbreak most likely had a single origin linked to an endemic country and was continuous rapidly evolving [11]. The mutational analysis showed the role of APOBEC3 in viral evolution and signs of potential MPXV human adaptation. Recent work (not reviewed yet) has categorized the sequenced MPX genomes into B.1, A.1.1 and A.2 clades [12]. Genomic sequencing analysis revealed that a group of 9 proteins including A9L, A36R, B16L, C3L, A50L, B9R, C7L, C12L (SPI-1 and H5R) were essential for virulence and pathogenesis. This study also identified 4 additional proteins (A27L, B5R, A33R, and L1R) that significantly influenced the host's immune response. Studies on MPXV nucleic acid sequencing have also noted the presence of four similar mutations and six amino acid alterations in the conserved regions that results in functional changes in the proteins. The MPXV genome isolated from the 2022 infections lacked C3L protein, which is a strong virulence marker and confers pathogenicity. Although the newer MPXV strain had undergone some genetic variations, these may not significantly affect disease transmission, and signs/symptoms at the clinical presentation [12].

Unlike previous outbreaks, which have been restricted to Africa, we are currently noticing the spread of MPXV to other previously non-endemic geographical regions. Genomic studies have identified that the first case of MPXV outside Africa, a strain isolated from a French person presenting atypical clinical symptoms, belonged to a divergent phylogenetic lineage within clade 3. Further in vitro testing revealed that the FDA approved drug tecovirimat (ST-246) had good anti-MPXV activity (in the nanomolar range) on this strain and was more effective than cidofovir [13]. Vaccination also has a role to play along with measures to minimize the spread of MPX. The 2022 MPX outbreak has primarily affected the MSM (men who have sex with men) group [14]. The pre-approved smallpox vaccine has been recommended to this group of individuals as a part of a clinical trial to study the vaccine efficacy. Such trials could be used to analyse the potential of vaccines to be used as pre-

exposure prophylaxis (PrEP) during sexual intercourse and their efficacy in limiting transmission [15]. However, as MPX infection also targets other populations and with the possibility of viral spill over into animals that could act as new reservoirs in non-endemic regions, further studies are warranted to better understand MPXV pathogenicity and control the spread of MPX.

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