Emergence of mpox in the post-smallpox era - a narrative review on mpox epidemiology

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1 Title

2 Emergence of mpox in the post-smallpox era - a narrative review on mpox epidemiology

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20 Abstract

Background: The 2022 mpox outbreak drew global attention to this neglected pathogen. While
most of the world was taken by surprise, some countries have seen this pathogen emerge and
become endemic several decades prior to this epidemic.

Objectives: This narrative review provides an overview of mpox epidemiology since its discovery
through the 2022 global outbreak.

Sources: We searched PubMed for relevant literature about mpox epidemiology and transmission
through 28 February 2023.

28 Content: The emergence of human mpox is intertwined with the eradication of smallpox and cessation of the global smallpox vaccination campaign. The first human clade I and II MPXV 29 30 infections were reported as zoonoses in Central and West Africa, respectively, around 1970 with sporadic infections reported throughout the rest of the decade. Over the next five decades, Clade I 31 32 MPXV was more common, and caused outbreaks of increasing size and frequency, mainly in the 33 Democratic Republic of the Congo. Clade II MPXV was rarely observed, until its reemergence 34 and ongoing transmission in Nigeria, since 2017. Both clades showed a shift from zoonotic to 35 human-to-human transmission, with potential transmission through sexual contact being observed 36 in Nigeria. In 2022, clade II MPXV caused a large human outbreak which to-date has caused over 37 86,000 cases in 110 countries, with strong evidence of transmission during sexual contact. By 38 February 2023, the global epidemic has waned in most countries, but endemic regions continue to 39 suffer from mpox.

40 Implications: The changing epidemiology of mpox demonstrates how a neglected zoonosis turned
41 into a global health threat within a few decades. Thus, mpox pathophysiology and transmission
42 dynamics need to be further investigated, and preventive and therapeutic interventions need to be

evaluated. Outbreak response systems need to be strengthened and sustained in endemic regionsto reduce the global threat of mpox.

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46 Introduction

47 Mpox (formerly monkeypox) is caused by the mpox virus (MPXV), which is a zoonotic orthopoxvirus in the poxvirus family.[1] MPXV was first discovered in 1958 following an 48 49 outbreak among captive primates in Copenhagen. [2] The zoonotic reservoir for MPXV probably includes small rodents such as squirrels, and it is likely that many other mammalian species are 50 51 involved.[3] There are two known clades of human MPXV, which originated from geographically distinct areas in Africa. Both clades cause a smallpox-like disease, but clade I 52 MPXV, which is endemic in Central Africa, appears to cause a more severe disease than clade II 53 54 MPXV, which is endemic in West Africa.[4,5] Based on genetic differences, clade II MPXV is further subdivided into two subclades that are each endemic in specific regions in West Africa: 55 56 clade IIa located to the west and clade IIb to the east of a savanna region called the Dahomey 57 Gap. Clade IIa and IIb MPXV have evolved separately from a common ancestor dating back centuries.[6] Before 2022, clade I MPXV infections predominated, with most mpox cases being 58 59 detected in Central Africa. While countries such as the Central African Republic (CAR), Cameroon, the Republic of the Congo (ROC) and Gabon regularly report cases, the Democratic 60 61 Republic of the Congo (DRC) has historically reported most cases of clade I mpox, accounting 62 for the overwhelming majority of cases worldwide. In contrast, clade II MPXV infections were 63 considered rare, until an outbreak of clade IIb mpox occurred in Nigeria in 2017, which was 64 eventually followed by a global outbreak in 2022.

This review will discuss the epidemiological aspects of mpox. We will describe the history and
rise of clade I MPXV in Central Africa, followed by the emergence of clade II MPXV in West
Africa, and finally, its spread to the rest of the world.

68 The Democratic Republic of the Congo: at the heart of the clade I

69 mpox epidemic

70 Although the virus was discovered in the fifties, [2] human mpox infections were not recognized 71 until 1970 when a 9-year-old boy was diagnosed with mpox in the DRC.[7] This long interval 72 between the initial discovery of mpox and the first confirmed human case might be explained by 73 the intertwined histories of mpox and smallpox. First, before the World Health Organization 74 (WHO) started its intensified global smallpox eradication program in the late 1960s, smallpox was 75 endemic in many countries in Central and West Africa. MPXV infections that occurred during this 76 time may have been misdiagnosed as smallpox, especially as molecular diagnosis was not yet available. Second, the spread of MPXV was likely kept in check by smallpox vaccination 77 78 campaigns. As there is a substantial antigenic similarity among orthopoxyiruses, first-generation 79 smallpox vaccines were believed to induce considerable cross-protection against MPXV.[1] As a 80 result, MPXV did not cause large outbreaks and mathematical models based on pre-1980s 81 epidemiological data estimated that the reproductive number of mpox in the population at the time 82 was <1, indicating a tendency to go extinct.[3]

However, the gradual eradication of smallpox – the last smallpox case in the DRC was reported in
1971 and the last case worldwide in 1977 [8] – marked the beginning of the mpox era.[9].
Smallpox was declared eradicated in 1980, which resulted in the subsequent end of most smallpox
vaccination campaigns, including in the DRC.[8] As a result, the population of individuals
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87 susceptible to mpox grew year after year.[10] After the eradication of smallpox, the Global 88 Commission for the Certification of Smallpox Eradication designated MPXV the most important 89 orthopoxvirus and a WHO-led surveillance program was started in the DRC. This program 90 detected 338 mpox cases between 1981-1986, contrasting with the 59 cases identified throughout 91 the previous decade.[10] Most infected individuals were unvaccinated children and there was very 92 little evidence of onward secondary transmission except in unvaccinated family members.[1,11] 93 These initial surveillance efforts also indicated that mortality from mpox was lower (13%) than 94 from variola major (around 30%), the most common form of smallpox. As a result, WHO 95 determined that mpox did not pose a public health threat and that continued mass vaccination with smallpox vaccination was not warranted to prevent mpox infection.[1,12] In 1986, the mpox 96 97 surveillance program was abandoned and interest in the disease waned.[10]

98 Increasing clade I MPXV transmission in the post-smallpox era

99 Between 1986 and 1996, relatively few MPXV infections were detected until the first large 100 documented mpox outbreak occurred in the Sankuru province of central DRC, in 1996. Over a 101 two-year time period, the 1996 outbreak affected more than 400 patients.[13] Observations during 102 this and subsequent outbreaks included a trend towards a higher age of affected individuals, which 103 could be explained by the aging of the vaccine-naive population.[10,14]

In 2000, the DRC initiated the Integrated Disease and Surveillance Response (IDSR) system, based on guidance from WHO. This system focused on detection of diseases with epidemic potential identified by WHO. Countries were allowed to include additional diseases if they were of concern in their particular setting. In the DRC as well as in the CAR, mpox was included in the passive surveillance efforts, since 2001.[9] In the next 13 years, mpox incidence increased steadily in the

DRC, and an incidence of 2.84 mpox cases per 100,000 population was reported in 2013.[9] In the early 2000s, a number of projects focused on improving surveillance efforts for mpox. From 2002 to 2010, an active surveillance program in Sankuru province of DRC found a 20-fold increase in incidence between 2005-2007 compared to the 1980's WHO active surveillance program.[14] Additionally, from 2007 to 2011, a clinical study in the same sites as the active surveillance program in Sankuru province contributed data on the natural history of disease and also observed potential mother-to-fetal transmission of mpox – which had not been described previously.[15]

Since restarting surveillance in 2001, the number of suspected cases in the DRC has continued to increase, leading to 6,216 reported suspected cases in 2020.[16] In addition, whereas mpox had previously been reported predominantly in highly forested regions, country-wide surveillance data indicate that the virus is spreading to new geographical areas.[9] The most recent example was a large outbreak with over 500 reported cases that started in 2021 in Maniema province, a region that is savannah rather than rainforest (unpublished observations).

Unfortunately, due to gaps in the surveillance system and diagnostic capacity, estimating the true burden of mpox in the DRC is challenging. In many regions, clinically suspected cases may remain unreported. In other regions, overreporting of mpox cases may occur due to a lack of confirmatory testing.[17,18]. Overall, most researchers estimate that the real disease burden is underestimated, and some models indicate that true caseloads may be 5 to 15 times higher than those reported.[19]

Parallel to the rise in cases in the DRC, an increase in human-to-human transmission was observed,
especially within households and between neighboring houses. Epidemiological assessment during
the WHO surveillance efforts in DRC from 1980-1984 found that most cases (130/214 or 61%)
were linked to zoonotic spillover,[20] and that secondary attack rates were overall low (<10%),

131 but significantly higher for household contacts than other contacts. [20] An investigation in 1996 132 noted an increase in the proportion of cases who reported exposure to another case (73% compared 133 to 28% in the 1980s), indicating a steady increase in human-to-human transmission from earlier 134 studies.[21] Moreover, for the first time, prolonged community transmission was suggested.[22] 135 Almost 20 years later, an outbreak investigation from 2013 in the DRC reported a secondary attack 136 rate of 50% and prolonged transmission chains of up to 6 events.[23] Of note, variola major had a 137 similar secondary attack rate in unvaccinated household members (37% - 88%, with an average of 138 58%)[11].

Despite observed increases in human-to-human transmission of mpox, the exact mechanisms of 139 140 transmission remain poorly understood. Smallpox was thought to be transmitted predominantly by 141 inhalation of virus-containing aerosols, but occasionally also by contact with pustules or crusted 142 scabs.[24] There is less evidence for aerosol transmission of mpox and its transmission is thought 143 to occur predominantly through direct contact with infectious saliva and/or respiratory secretions, 144 skin lesions or scabs, and contaminated materials.[25] Factors associated with an increased risk of mpox within households include sharing of a bed/bedroom or plates or cups with the index 145 146 cases.[26]

147 Meanwhile, in West Africa: the emergence of clade II MPXV

Similar to clade I MPXV, outbreaks of clade II MPXV were first reported in the 1970s. Between
1970-1979, a small number of cases were detected in rainforest areas of Liberia, Sierra Leone and
Nigeria.[27] One epidemiological study reported on 47 mpox cases from West (n=9) and Central
Africa (n=38) during 1970-1979.[27] Patients were primarily young (mean age 8 years) and male
(55.3%). Household transmission was reported infrequently with similar or milder disease in
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153 secondary cases. In contrast to clade I MPXV endemicity in the DRC, these initial clade II MPXV 154 outbreaks were followed by several decades of apparent absence of reported infections. However, 155 despite the lack of reported cases in West Africa, an outbreak of clade IIa MPXV occurred in the 156 US in 2002 following importation of clade IIa-MPXV-infected rodents imported to the US from 157 Ghana which resulted in an outbreak of 71 reported cases. [28] Of those, 25.4% were hospitalized 158 including two children with severe illness. [28] All infections during this outbreak were associated with zoonotic transmission from direct contact with, or proximity to, infected prairie dogs. [28] 159 160 No secondary transmission of MPXV was noted. [28]

The absence of reported clade II cases changed abruptly in 2017, when Nigeria faced its first reported large nationwide outbreak.[29] The detection of MPXV in an 11-year old boy triggered a national outbreak response, which eventually identified 122 cases over 17 states within the subsequent year.[29] Since then, sporadic cases have been reported throughout the country, often without reported wildlife contact.[29] Studies estimate that the true number of cases in Nigeria may be much higher than what was reported.[30]

167 The 2017 outbreak in Nigeria was different from large outbreaks of clade I MPXV in Central 168 Africa for several reasons. First, this outbreak occurred in a densely populated area, a minority (< 169 10%) of patients reported contact with wildlife, and patients clustered within households. These 170 aspects suggest that most infections were attributable to human-to-human transmission rather than 171 zoonotic spillover. Second, 69% of cases were men (mostly in their twenties or thirties) and 68% 172 of investigated cases had genital ulcers. [29] Even though these findings did not receive much 173 attention at the time, transmission during sexual contact had been suggested.[31] Last, Nigeria's 174 higher connectivity through international air travel compared to remote forest areas in Central 175 Africa may have contributed to the increased the potential for MPXV to spread across the globe.

176 From West Africa to the rest of the world: the 2022 global epidemic

To date, despite the incidence of several thousands of yearly cases in some regions in Central Africa, no infections with clade I MPXV have been reported outside the continent. In contrast, following the resurgence of clade IIb MPXV in Nigeria, several travel-related clade IIb MPXV infections have been reported internationally, including in the United Kingdom (UK, n=4 in 2018, 2019, 2021), Israel (n=1 in 2018), Singapore (n=1 in 2019) and the USA (n=2 in 2021).[3] These cases caused no more than a handful of secondary infections, possibly thanks to their rapid recognition and isolation of cases.

On May 7 2022, a report of a travel related MPXV infection from Nigeria was quickly followed 184 185 by a report of two additional infections and one probably infected but already recovered case in 186 the UK on May 12. The May 12 patients were not linked to the May 7 case and had no history of 187 recent travel or contact with travelers.[32,33] On May 16, four new confirmed mpox patients were 188 reported in the UK, all of whom were adult men and two were linked as sexual partners.[33] In the 189 months that followed, this would appear to be a massive global outbreak of mpox, mainly 190 transmitted through sexual contact among men who have sex with men, which to date, has caused 191 more than 87,000 confirmed cases in 112 different countries.[34] Europe and the Americas have 192 accounted for the majority of cases and the 10 most affected countries worldwide accounted for 193 almost 85% of reported cases.[34] The epidemic reached a peak in Europe and the Americas in 194 August 2022, and since the beginning of 2023, only sporadic cases or case clusters have been 195 reported from these regions.[34] Some countries in Asia observed almost no cases in 2022, but 196 have reported a surge in cases since the February-March 2023, including China, the Republic of 197 Korea, Japan, and Thailand.[34]

Phylogenetic studies indicate that almost all isolates from the 2022 global outbreak were caused 198 199 by a monophyletic group of viruses designated as a new lineage B1 of clade IIb MPXV.[35–37] 200 This lineage is genetically related to sequences from the outbreak in Nigeria in 2017-2018, travel-201 related cases in the UK, Israel and Singapore in 2018-2019, and a travel-related case in the USA 202 in 2021, but diverged from them by a range of single nucleotide polymorphisms (SNPs).[36,37] 203 The exact course of events between 2017 and 2022 is elusive, but these findings are indicative for 204 host adaptation during prolonged cryptic human-to-human transmission of clade IIb MPXV prior 205 to its detection in the 2022 global outbreak.[35–37]

206 A new side of mpox: sustained human-to-human transmission

207 During the 2022 global outbreak, mpox patients presented clinically with symptoms that were 208 previously not considered common for mpox. Most patients lacked the typically reported 209 generalized rash observed with mpox in endemic regions, but presented with one or more 210 mucocutaneous lesions and relatively limited subsequent dissemination throughout the body.[38] 211 The most common complications requiring medical treatment, and not commonly reported with 212 clade I mpox, were severe rectal pain, anorectal abscesses, penile oedema, and odynophagia.[38] 213 A minority of cases required hospitalization for treatment or isolation, the case-fatality rate was 214 very low (<0.1%), and lethality was primarily observed in severely immunocompromised 215 patients.[38,39]

Unlike previous epidemics in Central and West Africa, the 2022 global outbreak was uniquely driven by human-to-human transmission and patients were linked through sexual contact rather than household or wildlife contacts. More than 95% of patients were men with a median age of 34 years and, where recorded, over 80% identified as gay, bisexual, or other men who have sex with

220 men.[34] Most patients reported having had multiple sexual partners in the previous weeks or 221 months and about one in four presented with a concomitant sexually transmitted infection.[40] 222 The exact mechanism of transmission during sexual contact remains incompletely understood. 223 Possible routes include transmission through respiratory droplets, shared fomites, and contact with 224 infectious skin lesions, semen or mucosa. Indeed, MPXV has been cultured from saliva, other 225 upper respiratory tract samples, anorectal swabs and semen of mpox patients.[41] Viable MPXV 226 was also found in the anorectum of asymptomatic and presymptomatic patients.[42–44] These 227 observations combined with the findings of a contact tracing study linking data on case-contact 228 pairs in the United Kingdom indicate that asymptomatic and presymptomatic transmission may 229 have contributed considerably to the rapid spread of mpox through sexual networks around the 230 world.[45] In response, several countries approved the use of smallpox vaccines and initiated 231 vaccination campaigns among the populations at highest risk of infection. Yet in most of these 232 countries, vaccination campaigns have started after the peak of the epidemic, when reported cases had already begun declining.[46] Thus, the reasons for the decline in cases are not fully clear.[46] 233 234 Infection-induced immunity among individuals at the center of the network, heightened awareness 235 and early symptom recognition, diagnosis and self-isolation, scattering of sexual networks due to 236 a change in behaviour, and a swift response of a healthcare system experienced with contagious 237 diseases since the COVID-19 pandemic may all have played a role. However, the relative 238 contributions of each of these factors are uncertain.[46] Whether new waves of mpox are to be 239 expected in the near or further away future remains unknown.

240 Conclusions and future prospects

241 The recent global mpox outbreak has highlighted the threat of a neglected emerging virus to global 242 health. Although interest in mpox may fade due to the waning of the global epidemic, outbreaks 243 of increasing size and frequency continue to occur in endemic countries in Central and West 244 Africa. There is a need for concerted efforts to control mpox outbreaks, which include increasing 245 our understanding of mpox pathophysiology and transmission dynamics, vaccinating populations 246 at risk, and conducting clinical trials for preventive and therapeutic interventions. We need to prioritize collaborative research and clinical partnerships with endemic countries.[47] We also 247 248 need to enhance surveillance and response capacities in vulnerable regions. It is important to note 249 that concerns regarding MPXV have been raised for many years, but that there has been limited 250 international investment in sustainable preparedness and response efforts despite the well-251 documented health and economic impacts of human mpox in endemic regions of West and Central 252 Africa. Therefore, it is essential to prioritize concerted efforts for control in endemic regions to 253 reduce the threat of MPXV outbreaks worldwide.

254 Author contributions

LL, CVD, and JK conceptualized the scope of the review. All authors contributed to the finalversion of the manuscript and approved it for publication.

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262 Figure legend

Figure: Overview of transmission, clinical presentation and geopgraphical distribution of mpox in endemic countries and during the 2022 global outbreak. The map of cumulative confirmed cases for the 2022 global outbreak is adapted from https://ourworldindata.org (Mathieu Edouard, Spooner Fiona, Dattani Saloni, Ritchie Hannah, Roser Max. "Mpox (monkeypox)". Available at https://ourworldindata.org/monkeypox. Accessed March 10, 2023.).

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