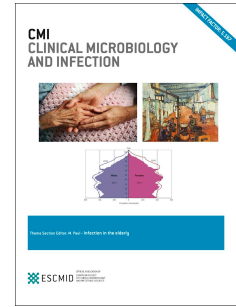


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Emergence of mpox in the post-smallpox era - a narrative review on mpox epidemiology

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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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19

**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.

**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 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 MPXV was more common, and caused outbreaks of increasing size and frequency, mainly in the Democratic Republic of the Congo. Clade II MPXV was rarely observed, until its reemergence and ongoing transmission in Nigeria, since 2017. Both clades showed a shift from zoonotic to human-to-human transmission, with potential transmission through sexual contact being observed in Nigeria. In 2022, clade II MPXV caused a large human outbreak which to-date has caused over 86,000 cases in 110 countries, with strong evidence of transmission during sexual contact. By February 2023, the global epidemic has waned in most countries, but endemic regions continue to suffer from mpox.

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

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

45

## 46 **Introduction**

47 Mpox (formerly monkeypox) is caused by the mpox virus (MPXV), which is a zoonotic  
48 orthopoxvirus in the poxvirus family.[1] MPXV was first discovered in 1958 following an  
49 outbreak among captive primates in Copenhagen. [2] The zoonotic reservoir for MPXV probably  
50 includes small rodents such as squirrels, and it is likely that many other mammalian species are  
51 involved.[3] There are two known clades of human MPXV, which originated from  
52 geographically distinct areas in Africa. Both clades cause a smallpox-like disease, but clade I  
53 MPXV, which is endemic in Central Africa, appears to cause a more severe disease than clade II  
54 MPXV, which is endemic in West Africa.[4,5] Based on genetic differences, clade II MPXV is  
55 further subdivided into two subclades that are each endemic in specific regions in West Africa:  
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  
58 centuries.[6] Before 2022, clade I MPXV infections predominated, with most mpox cases being  
59 detected in Central Africa. While countries such as the Central African Republic (CAR),  
60 Cameroon, the Republic of the Congo (ROC) and Gabon regularly report cases, the Democratic  
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.

65 This review will discuss the epidemiological aspects of mpox. We will describe the history and  
66 rise of clade I MPXV in Central Africa, followed by the emergence of clade II MPXV in West  
67 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  
77 available. Second, the spread of MPXV was likely kept in check by smallpox vaccination  
78 campaigns. As there is a substantial antigenic similarity among orthopoxviruses, 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]

83 However, the gradual eradication of smallpox – the last smallpox case in the DRC was reported in  
84 1971 and the last case worldwide in 1977 [8] – marked the beginning of the mpox era.[9].  
85 Smallpox was declared eradicated in 1980, which resulted in the subsequent end of most smallpox  
86 vaccination campaigns, including in the DRC.[8] As a result, the population of individuals

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  
96 smallpox vaccination was not warranted to prevent mpox infection.[1,12] In 1986, the mpox  
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]

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

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

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

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

127 Parallel to the rise in cases in the DRC, an increase in human-to-human transmission was observed,  
128 especially within households and between neighboring houses. Epidemiological assessment during  
129 the WHO surveillance efforts in DRC from 1980-1984 found that most cases (130/214 or 61%)  
130 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].

139 Despite observed increases in human-to-human transmission of mpox, the exact mechanisms of  
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  
145 mpox within households include sharing of a bed/bedroom or plates or cups with the index  
146 cases.[26]

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

148 Similar to clade I MPXV, outbreaks of clade II MPXV were first reported in the 1970s. Between  
149 1970-1979, a small number of cases were detected in rainforest areas of Liberia, Sierra Leone and  
150 Nigeria.[27] One epidemiological study reported on 47 mpox cases from West (n=9) and Central  
151 Africa (n=38) during 1970-1979.[27] Patients were primarily young (mean age 8 years) and male  
152 (55.3%). Household transmission was reported infrequently with similar or milder disease in



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  
159 with zoonotic transmission from direct contact with, or proximity to, infected prairie dogs. [28]  
160 No secondary transmission of MPXV was noted. [28]

161 The absence of reported clade II cases changed abruptly in 2017, when Nigeria faced its first  
162 reported large nationwide outbreak.[29] The detection of MPXV in an 11-year old boy triggered a  
163 national outbreak response, which eventually identified 122 cases over 17 states within the  
164 subsequent year.[29] Since then, sporadic cases have been reported throughout the country, often  
165 without reported wildlife contact.[29] Studies estimate that the true number of cases in Nigeria  
166 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**

177 To date, despite the incidence of several thousands of yearly cases in some regions in Central  
178 Africa, no infections with clade I MPXV have been reported outside the continent. In contrast,  
179 following the resurgence of clade I Ib MPXV in Nigeria, several travel-related clade I Ib MPXV  
180 infections have been reported internationally, including in the United Kingdom (UK, n=4 in 2018,  
181 2019, 2021), Israel (n=1 in 2018), Singapore (n=1 in 2019) and the USA (n=2 in 2021).[3] These  
182 cases caused no more than a handful of secondary infections, possibly thanks to their rapid  
183 recognition and isolation of cases.

184 On May 7 2022, a report of a travel related MPXV infection from Nigeria was quickly followed  
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]

198 Phylogenetic studies indicate that almost all isolates from the 2022 global outbreak were caused  
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]

216 Unlike previous epidemics in Central and West Africa, the 2022 global outbreak was uniquely  
217 driven by human-to-human transmission and patients were linked through sexual contact rather  
218 than household or wildlife contacts. More than 95% of patients were men with a median age of 34  
219 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  
233 had already begun declining.[46] Thus, the reasons for the decline in cases are not fully clear.[46]  
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  
247 prioritize collaborative research and clinical partnerships with endemic countries.[47] We also  
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**

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

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261

262 **Figure legend**

263 **Figure: Overview of transmission, clinical presentation and geographical distribution of**  
264 **mpox in endemic countries and during the 2022 global outbreak. The map of cumulative**  
265 **confirmed cases for the 2022 global outbreak is adapted from <https://ourworldindata.org>**  
266 **(Mathieu Edouard, Spooner Fiona, Dattani Saloni, Ritchie Hannah, Roser Max. “Mpox**  
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