Title

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

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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

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

Introduction

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 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 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 MPXV, which is endemic in Central Africa, appears to cause a more severe disease than clade II 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: clade IIa located to the west and clade IIb to the east of a savanna region called the Dahomey 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 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 Republic of the Congo (DRC) has historically reported most cases of clade I mpox, accounting for the overwhelming majority of cases worldwide. In contrast, clade II MPXV infections were considered rare, until an outbreak of clade IIb mpox occurred in Nigeria in 2017, which was 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.

The Democratic Republic of the Congo: at the heart of the clade I mpox epidemic

Although the virus was discovered in the fifties, [2] human mpox infections were not recognized until 1970 when a 9-year-old boy was diagnosed with mpox in the DRC.[7] This long interval between the initial discovery of mpox and the first confirmed human case might be explained by the intertwined histories of mpox and smallpox. First, before the World Health Organization (WHO) started its intensified global smallpox eradication program in the late 1960s, smallpox was endemic in many countries in Central and West Africa. MPXV infections that occurred during this 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 campaigns. As there is a substantial antigenic similarity among orthopoxviruses, first-generation smallpox vaccines were believed to induce considerable cross-protection against MPXV.[1] As a result, MPXV did not cause large outbreaks and mathematical models based on pre-1980s epidemiological data estimated that the reproductive number of mpox in the population at the time 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

susceptible to mpox grew year after year.[10] After the eradication of smallpox, the Global Commission for the Certification of Smallpox Eradication designated MPXV the most important orthopoxvirus and a WHO-led surveillance program was started in the DRC. This program detected 338 mpox cases between 1981-1986, contrasting with the 59 cases identified throughout the previous decade.[10] Most infected individuals were unvaccinated children and there was very little evidence of onward secondary transmission except in unvaccinated family members.[1,11] These initial surveillance efforts also indicated that mortality from mpox was lower (13%) than from variola major (around 30%), the most common form of smallpox. As a result, WHO 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 surveillance program was abandoned and interest in the disease waned.[10]

Increasing clade I MPXV transmission in the post-smallpox era

Between 1986 and 1996, relatively few MPXV infections were detected until the first large documented mpox outbreak occurred in the Sankuru province of central DRC, in 1996. Over a two-year time period, the 1996 outbreak affected more than 400 patients.[13] Observations during this and subsequent outbreaks included a trend towards a higher age of affected individuals, which 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%),

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

Despite observed increases in human-to-human transmission of mpox, the exact mechanisms of transmission remain poorly understood. Smallpox was thought to be transmitted predominantly by inhalation of virus-containing aerosols, but occasionally also by contact with pustules or crusted scabs.[24] There is less evidence for aerosol transmission of mpox and its transmission is thought to occur predominantly through direct contact with infectious saliva and/or respiratory secretions, 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 cases.[26]

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

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.

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

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

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

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

men.[34] Most patients reported having had multiple sexual partners in the previous weeks or months and about one in four presented with a concomitant sexually transmitted infection.[40] The exact mechanism of transmission during sexual contact remains incompletely understood. Possible routes include transmission through respiratory droplets, shared fomites, and contact with infectious skin lesions, semen or mucosa. Indeed, MPXV has been cultured from saliva, other upper respiratory tract samples, anorectal swabs and semen of mpox patients.[41] Viable MPXV was also found in the anorectum of asymptomatic and presymptomatic patients.[42–44] These observations combined with the findings of a contact tracing study linking data on case-contact pairs in the United Kingdom indicate that asymptomatic and presymptomatic transmission may have contributed considerably to the rapid spread of mpox through sexual networks around the world.[45] In response, several countries approved the use of smallpox vaccines and initiated vaccination campaigns among the populations at highest risk of infection. Yet in most of these 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] Infection-induced immunity among individuals at the center of the network, heightened awareness and early symptom recognition, diagnosis and self-isolation, scattering of sexual networks due to a change in behaviour, and a swift response of a healthcare system experienced with contagious diseases since the COVID-19 pandemic may all have played a role. However, the relative contributions of each of these factors are uncertain.[46] Whether new waves of mpox are to be expected in the near or further away future remains unknown.

Conclusions and future prospects

The recent global mpox outbreak has highlighted the threat of a neglected emerging virus to global health. Although interest in mpox may fade due to the waning of the global epidemic, outbreaks of increasing size and frequency continue to occur in endemic countries in Central and West Africa. There is a need for concerted efforts to control mpox outbreaks, which include increasing our understanding of mpox pathophysiology and transmission dynamics, vaccinating populations 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 need to enhance surveillance and response capacities in vulnerable regions. It is important to note that concerns regarding MPXV have been raised for many years, but that there has been limited international investment in sustainable preparedness and response efforts despite the well-documented health and economic impacts of human mpox in endemic regions of West and Central Africa. Therefore, it is essential to prioritize concerted efforts for control in endemic regions to reduce the threat of MPXV outbreaks worldwide.

Author contributions

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

Transparency declaration

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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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