INFECTIOUS DISEASES

Monkeypox: The consequences of neglecting a disease, anywhere

A disease anywhere can spread everywhere, if neglected

By **Oyewale Tomori**[1] *and* **Dimie Ogoina**[2]

Monkeypox (MPX) is a zoonotic disease caused by the monkeypox virus (MPV), which is a double-stranded DNA virus belonging to the genus Orthopoxvirus, which includes variola virus, the cause of smallpox (*1*). The first human case of MPX was reported in a 9-month-old boy in the Democratic Republic of Congo (DRC) in 1970 (*2*), and MPX cases remained infrequent, until recently. Currently, MPX is endemic in the rainforest areas of West and Central Africa, where human MPX outbreaks often occur, especially in rural settings, owing to spillover events from animal reservoirs and occasionally from human-to-human transmission within households (*3*). On 6 May 2022, a new phase of MPX began when the first case of the disease, not associated with travel from Africa, was reported in the UK (*4*). There is now substantial human-to-human spread of MPX in nonendemic countries. What is the history of MPX and can this help inform control measures now?

Laboratory monkeys imported in 1958 from Singapore to Denmark contracted the disease now known as MPX, after exposure to other laboratory animals already housed in the Copenhagen facility (*5*). The source of infection of the monkeys remains a mystery. The poxvirus family is ubiquitously distributed, parasitizing a host of invertebrates and vertebrates (*1*). MPV is now endemic in sub-Saharan Africa, in unconfirmed animal reservoirs (*6*), which are likely to be rodents. With the successful eradication of smallpox, and the cessation of smallpox vaccination in 1980, over 70% of the global population is unprotected against smallpox, and through cross-immunity, to the closely related orthopoxviruses, such as MPV (*6*). The little-known MPX disease has since begun a slow replacement of smallpox among largely unvaccinated populations (*6*).

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There are two distinct genetic clades of MPV (*1*): the Congo Basin clade (now renamed as Clade I) and the West African clade (now renamed as Clade II) (*7*). Additionally, Clade II consists of two subclades, IIa and IIb, with the latter primarily being the group of variants circulating in the 2022 global outbreak (*7*). Clade II MPV causes less severe disease in West Africa, with a less than 1% case fatality rate (CFR), whereas the Clade I MPV causes more severe disease in Central Africa, with up to a 10% CFR (*1*). Since the first human case was reported in 1970 in DRC, suspected or confirmed human MPX cases have been reported in other African countries (*8*), including Liberia and Sierra Leone (1970–1971), Cote d'Ivoire (1971), Nigeria (1971), Gabon (1987), Cameroon (1989), Central African Republic (2001), and Republic of the Congo (2003).

Outside of Africa, the US was the first country to report human MPX cases in 2003 when individuals were infected by pet prairie dogs that had contact with infected rodents imported from Ghana (*6*). Importations of MPV into other countries by travelers from endemic regions have also occurred between 2018 and 2022, but these did not lead to large outbreaks (*6*). Of the seven cases of MPX in the UK between 2018 and 2021, four were imported, two were household contacts, and one was a health care worker involved in the treatment of an imported case. There was no documented community transmission in these outbreaks (*9*). Importations into Israel and Singapore in 2018 and 2019, respectively, were similarly self-limiting (*6*).

Since 6 May 2022, human MPX has been rapidly spreading in nonendemic countries, including in Europe, the Americas, Asia, and Australia. Three African countries (Benin, Ghana, and South Africa) are also reporting cases for the first time (*4, 10*). MPX-associated deaths, previously limited to outbreaks in endemic countries, have now been reported since 29 July 2022 in nonendemic countries (*4*). Notably, all recent cases outside of the known endemic zones are due to Clade II MPV (*4*). This Clade II strain of MPV has diverged by 50 single-nucleotide polymorphisms (SNPs) from the MPV that caused an outbreak in Nigeria in 2018–2019; these changes rendered the virus more transmissible (*11*).

Has MPX been spreading undetected, and is now established outside the known endemic zones? If so, is there a link between the 2018–2019 importations (*6*), from endemic countries into Europe? Detailed epidemiological studies are required in endemic countries and the emerging zones of the disease to better understand and control MPX. For example, despite more than 50 years since the first human case of MPX was reported, the animal reservoirs of the virus, mistakenly linked to monkeys, are still unknown. However, studies suggest that Gambian pouched rats, which are hunted for food, may play an important role in the transmission of the virus to humans (*12*). Identifying other reservoirs of MPV in different ecosystems will contribute substantially to prevention and control efforts.

Evidence suggests various aspects of the epidemiology of human MPX on the African continent have changed in the past 30 years (*6, 8*). Despite the poor quality of disease surveillance in the two hotspots of MPX in Africa, the number and magnitude of MPX outbreaks have been increasing in DRC and Nigeria (*8, 13*) (see the figure). After the initial report of two cases in 1971, and a single case in 1978, Nigeria did not report any MPX until 2017 with 88 confirmed cases (*13*). Since the first report of MPX in 1970, the DRC has continued to report thousands of suspected MPX cases annually from the 1980s (*8, 10*).

Outbreaks of MPX in DRC caused by Clade I MPV have been increasing in frequency and magnitude, with a surge in 2020, when 6257 suspected cases and 229 deaths were reported (*8, 10*). In 2021, 9155 suspected cases and 310 deaths were reported (*10*). For the first 6 months of 2022, DRC reported 1439 suspected cases with 67 deaths in endemic and new provinces (*10*). However, with only ~10% of suspected cases being laboratory confirmed, it is difficult to estimate the full burden of the disease. In Nigeria, where Clade II MPV circulates, an analogous situation has been reported since the resurgence of cases in 2017. Between 2017 and the end of 2021, Nigeria reported 766 suspected cases, and confirmed 288 with 9 deaths (*13*). Of the 357 suspected cases reported from January to 24 July 2022 in Nigeria, 133 were laboratory confirmed with three deaths (*13*).

There have also been recent changes in the demographics, ecological risk factors, and clinical presentation of the disease. In Nigeria and the DRC, the average age of those most affected has evolved from less than 10 years between 1970 and 2010

to above 15 years after 2010 (*6, 14*). Most confirmed cases during the 2017 Nigeria outbreak lived in urban or peri-urban settings, and only ~8% of the 122 confirmed or probable cases reported contact with animals (*14*). There has been an expansion of human MPX beyond rainforest areas in Nigeria, with confirmed cases reported in the northern dry savannah areas (*14*). Although most patients infected in the 2017 Nigeria outbreak had typical features of MPX, such as fever accompanied by a skin rash, there were also various atypical clinical presentations with 12% of cases having skin rash without fever, and in two cases, genital ulcer was the first symptom (*14*). A few HIV-1–coinfected cases had large nodular ulcerating skin lesions (up to 10 cm in diameter) and more severe systemic illness and complications, which resulted in deaths of three people who had substantial immunosuppression (*14*). The detection of cases among a few married sexual partners, and the high rates of genital ulcers, suggest a role of sexual contact in the transmission of MPX during the 2017 outbreak in Nigeria (*14*).

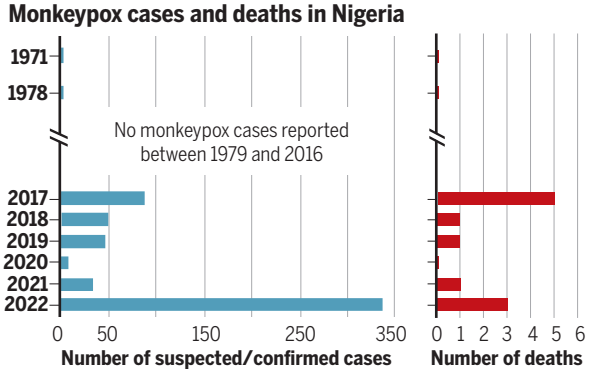
The simultaneous multicountry emergence of MPX cases in various locations outside endemic regions early in May 2022 took the world by surprise. As more cases were reported outside Africa, "global" attention ensured that action plans were rapidly put in place (primarily the release of smallpox vaccines from the global stockpile) to control the outbreak, protect cases and their contacts, and stop MPV from becoming endemic in Europe and other nonendemic countries. However, no such emergency plan has been put in place for the MPX endemic zones, where the first human MPX case was reported in DRC in 1970. Between January and July 2022, African countries have reported 2031 MPX cases and 75 deaths (CFR 3.7%). The number of MPX cases in the nonendemic countries as of 7 August 2022 is 27,439 cases, with four deaths (CFR 0.01%) (*10*).

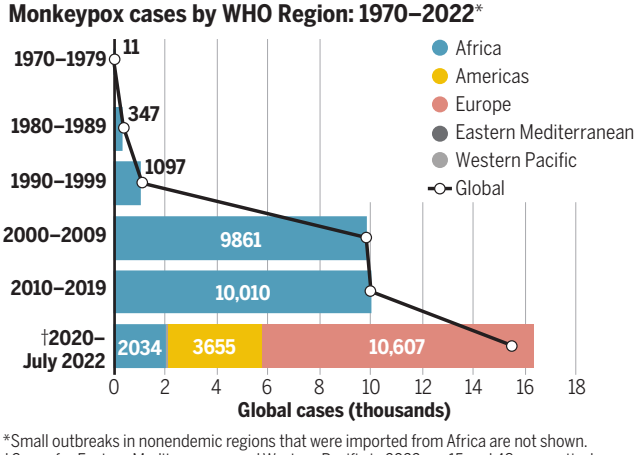
This selective attention, despite the long years of inaction and absence of response to the continuous transmission of MPV in Africa over the past 30 years, highlights the glaring inequity in global health, which is also demonstrated by the inequitable availability of, and access to, COVID-19 vaccines. As MPX ravaged different communities in Africa, the world was silent. Calls for investments in field investigations during and after outbreaks, and research to generate data for a better understanding of MPX epidemiology, went unheeded, both at the national and international levels.

What should be done to control MPX in endemic countries and prevent it from becoming endemic in other parts of the world (if it is not already)? There is an urgent need for a collaborative effort to develop a sustainable and equitable global plan. This plan should address the identification of the natural animal hosts and reservoirs of MPV to improve understanding of the

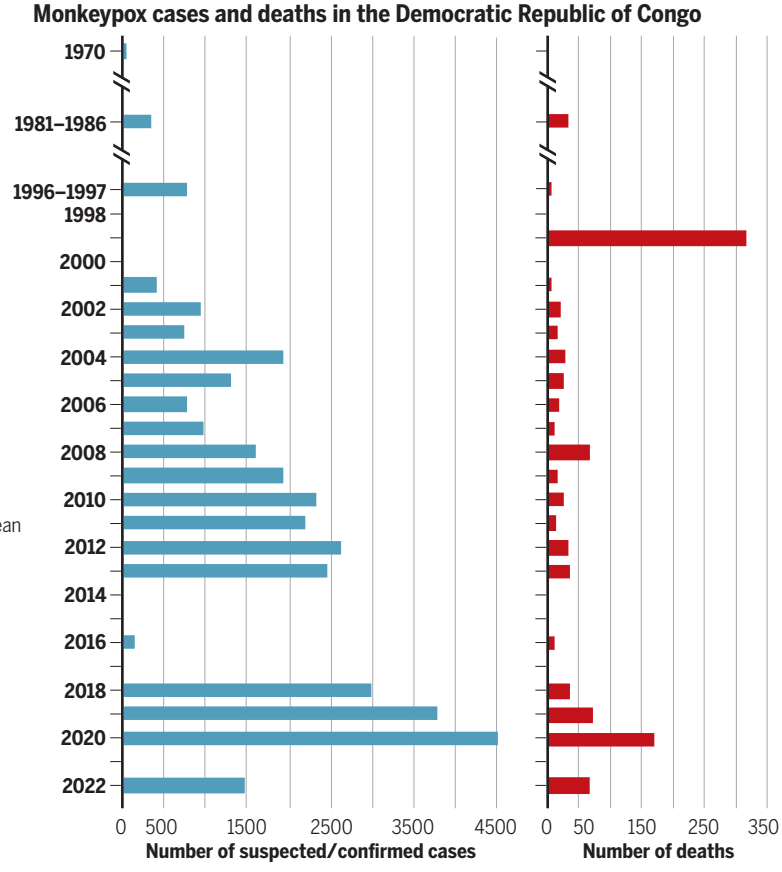
The changing patterns of monkeypox infections

Although human monkeypox was first reported in the 1970s in Nigeria and the Democratic Republic of Congo, there were very few cases until outbreaks began in these endemic regions from around 1980. Recently, there have been larger monkeypox outbreaks—affecting more people and causing more deaths—as well as changes in the demographics of cases and clinical presentation in endemic regions. These changes preceded the emergence of monkeypox outside of endemic countries in May 2022, and within 2 months, the World Health Organization (WHO) declared monkeypox a Public Health Emergency of International Concern. Graphs are based on data to 24 July 2022 from *(4, 8, 10, 13, 15)*.





*Small outbreaks in nonendemic regions that were imported from Africa are not shown.
†Cases for Eastern Mediterranean and Western Pacific in 2022 are 15 and 48, respectively.



transmission and epidemiology of the disease. It should also apply the One Health approach in designing field research and laboratory support that will build the requisite capacity, especially of scientists, in MPX endemic countries. The plan should include drug development and improved vaccines that are readily available and affordable, for the care of the infected and protection of the exposed. Public awareness should also be a focus of the plan, ensuring targeted education and risk communication that clarifies individual roles in preventing infection and spreading the disease.

The current global spread of MPX reminds us once again that infectious diseases know no borders and responses should protect everyone, leaving no country behind. This also requires an equitable contribution from each country and taking ownership of finding solutions to the ravages of such diseases at the national level. By applying resources responsibly, countries where these diseases are endemic can gradually move away from depending on the crumbs of equity for their disease control and response activities and contribute appropriately and effectively to national and global action that is needed to mitigate the effects of emerging infectious diseases. ■

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Maternal transmission of gut bacteria has promoted the maintenance of microbial strains that evolve with specific human populations.

MICROBIOLOGY

Loyal gut microbes

Bacterial strains in the gut microbiota diversified as humans spread across the globe

By **Andrew H. Moeller**

The human gut harbors hundreds of species of bacteria. The most prominent species are found in people worldwide but display substantial genetic differences between human populations (*1*, *2*). Piecing together how this strain-level diversity evolved has been a critical gap in understanding symbiosis between humans and gut bacteria. Because robust archeological and fossil records of human microbiota are lacking, lineage histories must be inferred primarily from genomic data, which have been difficult to produce in sufficient quality and quantity. On page 1328 of this issue, Suzuki *et al.* (*3*) report that strains within dozens of gut bacterial species diversified in parallel (codiversified) with human populations as they spread throughout Africa, Europe, and Asia, showing that these symbionts have kept fidelity to human lineages for thousands of human generations. In addition to revealing the evolution of the human microbiota, this discovery has implications for the generalizability of microbiota-based therapeutics.

When lineages engage in intimate symbioses over evolutionary time, they can codiversify, generating parallelism between the lineages' evolutionary trees. Earlier work found that codiversification between gut bacteria and humans has occurred in at least a few species. For example, the relationships among strains within *Bifidobacterium* spp. (*4*) and *Helicobacter pylori* (*5*) have been shown to align with the dispersal of humans from Africa to other continents. However, the extent of codiversification in the gut microbiota has remained contentious (*6*, *7*). Diet, hygiene practices, and other environmental factors are known to markedly affect the composition of the microbiota, so long-term relationships between bacteria and humans that are needed for codiversification may be rare. Generating the strain-level information required to test for codiversification has been laborious and expensive, so scaling-up such studies has not been readily achievable.

With high-throughput data and recently developed computational tools, it is now possible to assemble hundreds of bacterial genome sequences directly from the complex mixture of DNA (metagenome) present in a single sample of human stool. This new paradigm—termed "genome-resolved metagenomics"—affords new opportunities to study bacterial evolution within and between host individuals, populations, and species (*8*). To test for codiversification between gut bacteria and human populations, Suzuki *et al.* sequenced and assembled thousands of bacterial genomes from hundreds of women and their children living in Gabon, Cameroon, Vietnam, Germany, and the United Kingdom. Using these data, the authors compare the evolutionary trees of strains within gut bacterial species with the evolutionary tree of the humans inferred from genetic analyses of saliva samples. The results are notable: 36 of the 59 bacterial species tested displayed sig-

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