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Mpox neglect and the smallpox niche: a problem for Africa, a problem for the world

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Mpox (formerly known as monkeypox) is a zoonotic viral disease endemic in parts of Africa. In May, 2022, the world was alerted to circulation of monkeypox virus in many high-income countries outside of Africa. Continued spread resulted in a WHO declaration of a Public Health Emergency of International Concern. Although there has been much attention on the global outbreak, most of the focus has been on high-income countries outside of Africa, despite the fact that monkeypox virus has been causing disease in parts of Africa for at least 50 years. Furthermore, the long-term consequences of this event, especially the risk that mpox fills the niche vacated through smallpox eradication, have not been sufficiently considered. The heart of the problem is the historical neglect of mpox in Africa where the disease is endemic, and the actual and potential consequences if this neglect is left uncorrected.

Mpox (formerly known as monkeypox) is a zoonotic viral disease endemic in parts of Africa. However, from January, 2022, to February, 2023, more than 85 000 cases and 100 deaths were reported in 110 countries, the vast majority high-income countries outside of the African continent, propagated almost exclusively by human-to-human transmission.[1] The outbreak awoke the world to what was previously a largely ignored tropical disease considered of relevance only to remote parts of Africa. But should we be surprised? For those who cared to look, the signs were many.

There are two distinct monkeypox virus clades with differing pathogenicity: Clade I, almost exclusively found in the Congo Basin or central Africa, associated with smallpox-like disease and has an estimated case fatality of 10%, and Clade II, found in west Africa, usually causes a milder disease with scant lesions in patients who are not at high risk and lower viraemia and transmissibility, with a case fatality of 1–3%.[2,3] Two Clade II sublineages, IIa and IIb, are now delineated. Clade IIb, which is derived from IIa and thought to have emerged from west Africa in 2017, is primarily behind the global outbreak, and is believed to have become better adapted to human-to-human transmission than other monkeypox viruses.[4,5] Circulation of other Clade II sublineages has also been reported.[6]

Monkeypox virus is generally transmitted via close physical contact. Transmission through sex or intimate contact has been the driver and focus of the outbreak in high-income countries, although this might not be a new phenomenon, since genital lesions have previously been noted and transmission through intimate contact suspected in people with mpox in Africa.[7]

Variola virus, which causes smallpox in humans, and monkeypox virus are closely related: both belong to the orthopoxvirus genus.[8] After a sustained global vaccination effort, smallpox was declared eradicated in 1980—an event considered one of the greatest public health achievements in history.[9] Eradication was possible in part because variola virus infects only humans, whereas monkeypox virus has a broad spectrum of animal reservoirs, thought to include various types of rodents and squirrels.[8,10,11] Although more specific studies are yet to be done, smallpox vaccination is estimated to be approximately 85% protective against mpox.[12]

Monkeypox virus was discovered (and misnamed, since monkeys turned out to be a dead-end host, not a natural reservoir) from infection in monkeys being used for laboratory research in Denmark in 1958.[13] The first human case was reported in the Democratic Republic of the Congo in 1970, after which sporadic human cases occurred across five central and west African countries throughout the 1970s.[14,15] These cases led to concerns from WHO that mpox might fill smallpox's epidemiological niche now that routine smallpox vaccination programmes were discontinued and population immunity was inevitably starting to wane with almost all people younger than 40 years unvaccinated and susceptible.[14,15]

In the Democratic Republic of the Congo, reported index cases of mpox were primarily young and unvaccinated children, with occasional transmission to again younger unvaccinated family members, although chains of transmission were short.[16] Continued surveillance, some of it actively searching for cases in defined areas of the country, supported this finding, with index cases often happening after close contact with wild animals, including through hunting.[16] Subsequent serological surveys of more than 10 000 children with no smallpox vaccination scar were done in the early 1980s in central and west Africa, with monkeypox-specific antibodies found in less than 1%, indicating that the disease was still rare.[14]

However, reported cases increased during the next few decades,[17] a finding initially attributed to improved surveillance.[14] A large cluster of cases occurred in the Democratic Republic of the Congo in 1996, with extended chains of transmission among people who were unvaccinated.[18] For the first time, human-to-human transmission accounted for the majority of cases.[19] Genetic sequence data did not reveal substantial mutations to account for this event.[19] By the early 2000s, outbreak investigations in the Democratic Republic of the Congo suggested that the risk of mpox was five times higher among people who had not received smallpox vaccination, and that the incidence had increased by

20 times since the 1980s, again with the majority of cases occurring in children and young adults.[20]

Although the severity of disease during the global outbreak has generally been mild,[21] we cannot assume that this will be the case for future outbreaks. All reported cases of mpox outside of Africa to date have been due to the less pathogenic Clade II, probably reflecting the far greater frequency of intercontinental travel from west Africa, especially Nigeria with its large population, than from central Africa. However, the majority of reported cases in recent decades in Africa have been Clade I.[17] With ever increasing travel and trade, it is probably just a matter of time until a traveller or small mammal carries the more dangerous Clade I virus, with its close resemblance to smallpox, to faraway places.

The shock of mpox spreading around the globe has spurred intense interest, but the talk and concern is still primarily oriented towards high-income countries. Meanwhile, mpox continues to cause illness and death in Africa, with 1267 confirmed cases and 226 deaths (case fatality 17·8%) in 2022.[22] The number of reported cases (probably a substantial underestimate due to inadequate surveillance) has continued to steadily rise on the continent in the past few decades. Nevertheless, apart from a few research protocols, there are still no vaccines or antivirals available in Africa as part of the global response to mpox. Vaccine use or mobilisation of the global stockpiles, which might have stemmed transmission in west Africa in 2017 and prevented the eventual emergence of the human-adapted Clade IIb and the global outbreak, was never recommended for use in these settings by global health experts and institutions.[23]

Through time and neglect, from its origins in Africa (an epidemiological fact, not a designation of blame), mpox has now become a global problem, prompting WHO to declare the outbreak a Public Health Emergency of International Concern (PHEIC).[24] Although transmission has decreased in recent months in many high-income countries, probably due to a combination of behaviour change and immunity in groups at high risk through either natural infection or immunisation, in February, 2023, WHO opted to continue the PHEIC designation, in part due to recognition of the continued transmission in Africa.[25] This was a wise decision, since lack of action now risks at least three non-mutually exclusive and potentially grave consequences: (1) monkeypox virus becomes widely disseminated and entrenched in humans, maintaining itself through human-to-human transmission, especially through sex and intimate contact (this could include potential reverse exportation of the more human-adapted Clade IIb from high-income countries back to Africa, including to countries where mpox is not endemic); (2) mpox fills the epidemiological niche left by smallpox eradication, undermining that incredible achievement and resulting in orthopoxvirus outbreaks becoming a common event; and (3) reverse zoonotic transmission (in which the virus is passed from humans to a species of animal not previously infected), resulting in more diversity in reservoirs and geographical expansion of endemicity with increased risk of zoonotic transmission. DNA viruses, such as monkeypox virus, are more stable in the environment compared with RNA viruses, such as SARS-CoV-2 and Ebola virus, which could facilitate passage back to animals. Recent human-to-dog transmission of monkeypox virus in France[26] and Brazil,[27] as well as the capacity for North American prairie dogs (genus *Cynomys*)[28] to be infected and transmit virus to humans, highlight the risk.

All of these events could potentially force widespread re-initiation of vaccination against orthopoxviruses. In contrast with smallpox, monkeypox virus, with its zoonotic reservoirs, would be nearly impossible to eradicate.[8,10,11] This eventuality has relevance not only for mpox, but also begs considerable forethought in approaches and consequences to eradication of other diseases, including poliovirus and measles, as well as for careful contemplation regarding destruction of the last stocks of remaining virus once eradication is achieved.

Confronting mpox rapidly and globally is imperative. Research questions of particular importance include arriving at an improved understanding of transmission patterns and associated risk behaviours; the natural reservoir(s); the natural history of infection, especially in people who are immunosuppressed; the efficacy of existing vaccines and therapeutics; the duration of protection after natural infection and vaccination; and effective infection control strategies, especially with regard to person-to-person transmission. Many of the answers can only come from research in Africa where mpox is endemic.

Public health workers and researchers in Africa have the needed technical skills but, because of competing and often concurrent public health threats and priorities, will continue to require complementary external financial and technical support. Although collaboration is always welcome, research should be African-led, with partners selected by researchers in Africa, rather than so-called parachute research directed by foreign scientists, who have in some instances taken data and specimens back to their own countries to complete their studies.[29] In the USA in July, 2022, President Joe Biden estimated a budget of US$7 billion to control mpox. Although the breakdown of this sum has not yet been released, the prudent move would be to make sure that it includes support for African public health leaders and researchers to address mpox in Africa.[30] Governments in Africa are also called to increasingly contribute to public health research required for their own national health security. We must ensure that African people not only participate substantially, including in leadership roles in the research, but also benefit from the results.

The global mpox outbreak, similar to the Zika virus and Ebola virus epidemics in recent years, is a reminder of just

how small and connected the planet has become. Assisting our fellow humans when they ask for support to decrease illness and death from emerging infections is our collective duty; in addition, from a purely strategic perspective, there is now no place so remote, no virus so exotic, that it can be considered strictly someone else's problem. Keeping everyone safe will require a global outlook and approach and should always start with addressing the problem where it is endemic and causing the most illness and death—a strategy in everyone's best interest.

Contributors
DLH and DGB conceptualised the manuscript, with input from IA and J-JM. A medical writer funded by FIND assisted with writing the first draft, which all authors then reviewed and edited, before agreeing on the final version.

Declaration of interests
DGB is a member of and DLH is an adviser for the WHO Mpox International Health Regulations Emergency Committee. IA and J-JM declare no competing interests.

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