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Monkeypox: we cannot afford to ignore yet another warning

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Abstract

An unintended consequence of smallpox eradication and ending the smallpox vaccination campaign has been to render the global human population immunologically naïve to orthopoxvirus infection for the first time in history. This has occurred at a time when the majority of people worldwide live in high population densities in cities and when connectivity across the world has never been higher, both of which facilitate the emergence and spread of infectious diseases. It is not surprising, therefore, that novel zoonotic orthopoxvirus infections have been increasing in recent years, or that an international outbreak of human monkeypox disease has occurred. A One Health approach, including consideration of land-use change and the bushmeat and exotic pet trades, is required to prevent opportunities for the emergence of monkeypox, or diseases cause by other orthopoxviruses, and for a rapid and effective response to any outbreaks in order to limit their spread.

One Health Impact Statement

The current global outbreak of monkeypox is yet another warning for the adoption of a preventative, One Health, approach to minimise the risk of future emergence of known and unknown zoonotic pathogens. This includes the need to consider the roles, and to mitigate the impacts, of land-use change and the bushmeat and exotic pet trades in order to prevent opportunities for the emergence of monkeypox virus, or other orthopoxviruses, and for a rapid and effective response to any outbreaks in order to limit their spread.

As of 9 September 2022, there have been 56,098 confirmed cases of monkeypox in people in 96 countries since an initial case was confirmed in the UK on 7 May (CDC, 2022). However, this does not include infections in Central and West Africa where the infection is endemic and where human cases of the disease have been escalating dramatically in recent years following smallpox eradication (Tasamba, 2022). Monkeypox virus (MPV), the causative agent of monkeypox, is an orthopoxvirus (OPV) closely related to smallpox virus. Following a global vaccination campaign, the World Health Assembly confirmed the eradication of smallpox in 1980, after which vaccination against this disease was ended. During the following 40 years, therefore, and for the first time in history, the global human population has become immunologically naïve to OPVs (Dye and Kraemer, 2022). This has created a gaping ecological niche that is open to exploitation by a new OPV. It is perhaps not surprising, therefore, that zoonotic infections with at least two previously unknown OPVs have emerged in recent years: Akhmeta pox and Alaska pox (Vora *et al*., 2015; Springer *et al*., 2017). Monkeypox virus is also a zoonotic OPV and, although recognized for many years as a public health threat in waiting subsequent to the decline of smallpox vaccination (Heymann *et al*., 1998), monkeypox has remained a neglected disease (Di Giulio and Eckburg, 2004; Parker *et al*., 2007), which is only now receiving attention following its spread to high-income countries.

Monkeypox (re)emergence

On 1 June 2022, the World Health Organization (WHO) stated that the simultaneous appearance of monkeypox in multiple countries outside Africa indicated that 'there may have been undetected transmission for some time' and on 3 June the United States Centers for Disease Control (CDC) announced they had found two strains of MPV in the USA (Promed, 2022a). On 7 June 2022, the UK Health Security Agency declared the virus a notifiable disease (Promed, 2022b) and on the 23 July the WHO Director-General declared monkeypox to be a Public Health Emergency of International Concern (Kozlov, 2022). The current outbreak has been associated with super-spreader events in May: namely festivals in Belgium and Gran Canaria plus a sauna in Spain. Media coverage has focused on human sexual contact, particularly male/male, as a primary mode of transmission in this outbreak but this should not be surprising given close human-to-human contact is a known method of MPV spread. Other modes of spread of this relatively environmentally robust virus should also be considered, including via contaminated fomites and mechanical spread by invertebrate vectors. Although not yet identified as routes of

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transmission for MPV, these are recognized means of transmission for other OPVs and related pox viruses.

The name monkeypox originates from its initial discovery in a group of crab-eating macaque monkeys held in a lab in Denmark in 1958 (Von Magnus *et al*., 1958). However, subsequent evidence points to one or more species of African rodent as the primary reservoir for this OPV rather than non-human primates. During the smallpox eradication campaign, a single case of monkeypox disease was found in a moribund rope squirrel *Funisciurus anerythrus* in the Democratic Republic of Congo (DRC) in 1985 (Khodakevich *et al*., 1985) and the disease was next found in the wild in Côte d'Ivoire in a juvenile sooty mangabey *Cercocebus atys* in 2012 (Radonic *et al*., 2014); clinical disease is therefore very infrequently found in wildlife. Serological surveys for MPV have found evidence of infection in several species of wild African rodent, including the rope squirrel *Funisciurus spp*., the sun squirrel *Heliosciurus spp*., the tiny fat mouse *Steatomys parvus*, the multimammate mouse *Mastomys natalensis*, the African dormouse *Graphiurus kelleni* and the Gambian giant pouched rat *Cricetomys gambianus* (Hutin *et al*., 2001; Reynolds *et al*., 2010; Nolen *et al*., 2015; Orba *et al*., 2015). Epidemiological studies in DRC have highlighted squirrels, particularly rope squirrels occupying agricultural areas close to human settlements, as possible primary candidates for repeated zoonotic transmission (Khodakevich *et al*., 1985). A seroprevalance study found that MPV seropositivity rates were highest in *Funisciurus spp.* squirrels (24%) compared to those in *Heliosciurus* spp squirrels (15%) or primates (8%) (Khodakevich *et al*., 1988). During an outbreak of MPV in people in 1997, seropositivity rates in wildlife were higher at 39–60% in *Funisciurus spp*., 50% in *Heliosciurus* spp. and 16% in Gambian giant pouched rats (Hutin *et al*., 2001). While these squirrels are rare in primary rainforest, they are commonly found in inhabited human-degraded secondary forests, especially where oil palm is grown (Khodakevich *et al*., 1985). This supports reviews reporting increased zoonotic host frequency in human-dominated ecosystems (Gibb *et al*., 2020).

Bushmeat trade

Wild meat, known as bushmeat in Africa, is meat obtained from hunting wild animals for local consumption or income generation through sale as food. In several low-income African countries reporting human MPV outbreaks, there has been a marked decrease in the size of wild animals on sale at markets over time as larger species are hunted out with a subsequent increase in reliance on the consumption of smaller species, particularly rodents (Fa *et al*., 1997, 2015). The Gambian giant pouched rat, for example, is commonly eaten due to its relatively large size and is, therefore, of particular interest as a potential source of zoonotic infection (Malekani *et al*., 1994). Further research into the reservoir hosts for MPV is urgently required and is currently in progress in countries with high numbers of human cases such as the DRC. However, less widely known is that demand also comes from in-country and expatriate urban elite who regard bushmeat as a prestigious delicacy and a way of maintaining cultural ties (Walz *et al*., 2017; Gombeer *et al*., 2021). As a consequence, and despite extensive legislation banning the import of threatened taxa or indeed any wild meat from Africa, significant quantities of bushmeat are smuggled via personal luggage into major European and US cities on passenger flights from West and Central African source countries where MPV is endemic (Chaber *et al*., 2010; Falk *et al*., 2013; Bair-Brake *et al*., 2014; Ecojust, 2020). A 2018 Belgian study, in which passengers' luggage was searched at Brussels airport, estimated an average of 3.7 tonnes of bushmeat was smuggled in each month; the top countries of origin were DRC, Cameroon and Côte d'Ivoire (Musing *et al*., 2018). Highly organized, lucrative, typically clandestine and illegal international bushmeat trade networks now provide an additional potential route for the global transmission of MPV (Ecojust, 2020).

Pet trade

In 2003, an outbreak of human MPV affected six US states. The source was traced to a consignment of 800 live small mammals imported from Ghana to Texas. This comprised six genera of rodents, namely tree squirrels *Heliosciurus* spp., rope squirrels *Funisciurus* spp., dormice *Graphiurus* spp., striped mice *Hybomys* spp., brushtail porcupines *Atherurus* spp., and Gambian giant pouched rats *Cricetomys* spp (CDC, 2003). An Iowa animal vendor transported some of the latter to a Chicago pet dealer where they were housed with, and infected, another rodent species, the North American prairie dog *Cynomus* spp. Prairie dogs from this environment were transferred to a vendor in Wisconsin who sold them to buyers including the index case of the multi-state outbreak. Infected prairie dogs seem to have been the primary source of infection for most of the human cases, having been further distributed in Indiana, Ohio and Illinois. The CDC and the US Food and Drug Administration subsequently banned the importation of all rodent taxa from Africa (CDC, 2020). Considerable effort was invested in tracing and destroying or quarantining the 800 mammals from the infected African shipment. Virological testing of some of these animals found MPV infection in three dormice, two rope squirrels and at least one Gambian giant pouched rat. It is relevant to note that escaped pet Gambian giant pouched rats have established as an invasive species in Florida (Reuters, 2007). Also the olfactory abilities of the species have led them to be trained to sniff out land mines and tuberculosis infections, thus expanding international demand for the species (APOPO, 2022). Animals should, therefore, test seronegative for MPV prior to being trained. In addition to the legal wild animal pet trade, there is large-scale illicit trafficking of exotic animals as pets and this forms a substantial part of the multibillion dollar illegal wildlife trade. This has recently expanded in scale and taxonomic composition, facilitated by e-commerce and social media via which wild animals can be relatively easily traded illegally (Hernandez, 2021). The demand is global with intercontinental smuggling involving South America and Asia, as well as Africa and Europe, fuelling the biodiversity conservation and ecosystem services crises and escalating the threat of human exposure to known and unknown pathogens harboured by wildlife along trade routes and within destination countries (Hall, 2019).

Need for a One Health approach

While the eradication of smallpox was a major achievement for human health globally, we have to be cognisant to the vulnerabilities it, along with the ending of smallpox vaccination, has created through the development of an ecological niche for human OPV infection. This has occurred at a time in human history when the majority of people worldwide live in high population densities in cities and when connectivity across the world has never been higher, both of which facilitate the emergence and spread of infectious diseases. That monkeypox has emerged as a public health threat in the global north is not a surprise as its emergence as a public health threat following smallpox eradication was predicted (Heymann *et al*., 1998; Grant *et al*., 2020). This emergence may have been facilitated by the international demand for African bushmeat and exotic pets. As with other zoonotic diseases, there needs to be a One Health approach to preventing opportunities for the emergence of monkeypox, or other OPVs, and for a rapid and effective response to any emergence to limit spread. The former includes identifying and minimising risky human activities, such as land-use change and the hunting, keeping or eating of wildlife, especially rodents, or doing so in ways that mitigate the likelihood of zoonotic disease emergence, such as promoting alternatives to bushmeat (Khodakevich *et al*., 1988) , routinely vaccinating people at high risk of exposure, such as those who have close contact with wildlife, and educating people in hygienic procedures such as the use of gloves when handling live and dead wild animals while making such measures available. Preparedness and response could include public awareness campaigns and readily accessible, freely available rapid diagnostics in countries where monkeypox is endemic. The absence of such an approach lends the human population vulnerable to epidemic infection with a novel or known extant OPV.

During the current outbreak, monkeypox has been spreading internationally with cases now recognized in 103 countries (96 where the disease is new and seven where it is already known to be endemic) (CDC, 2022). Historically, the rate of human-to-human transmission (R_0) for monkeypox virus has been < 1, which means that infection chains are more likely to be short and to die out than they are to continue to be propagated (Grant *et al*., 2020). This has, however, been the case in populations where immunity from smallpox vaccination has been present to varying degrees, whereas it has been estimated that the R_0 in naïve populations would be 1.46–2.67, meaning epidemic disease outbreaks could occur (Grant *et al*., 2020). This is what is now underway with the current international outbreak and it remains to be seen if repeated transmission amongst people leads to pathogen evolution and a change in pathogenicity or in the transmission rate.

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AUTHORS' CONTRIBUTIONS

The two authors contributed equally to the writing of this manuscript.

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CONFLICTS OF INTERESTS

We have no competing interest to declare.

ETHICS STATEMENT

No people or animals were used for this study. No ethics committee approval was required.

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