

The potential risks posed by inter- and intraspecies transmissions of monkeypox virus

Since the 1970s, human cases of monkeypox (MPX) have been reported in 11 African countries (Benin, Cameroon, Central African Republic, the Democratic Republic of the Congo, Gabon, Cote d'Ivoire, Liberia, Nigeria, Republic of the Congo, Sierra Leone, and South Sudan), where the monkeypox virus (MPXV) is endemic [1,2]. However, in 2022, human cases of MPX have been reported in Europe (11,212 confirmed cases as of late August 2022), Canada (1,206), and the United States (16,925) from travelers, who have not traveled to any of the regions, where MPXV is endemic [1,3,4]. As the number of human cases of MPX steadily increased outside of these endemic countries, the World Health Organization (WHO) declared it as a Public Health Emergency of International Concern (PHEIC) on 23 July 2022 [5].

While it is not entirely clear how MPXV is transmitted from human-to-human (i.e. intraspecies transmission event) in the current MPX outbreak, multiple routes are possible that include but are not necessarily limited to close contact with lesions, body fluids, and respiratory droplets of the infected individual, or during intimate or sexual contact [6–8]. Transmission can also occur vertically via the placenta to cause congenital MPX [2]. Animal-to-human transmission (i.e. interspecies, zoonotic transmission, or spillover event) of MPXV can occur via a human's direct contact with blood, bodily fluids, or cutaneous and/or mucosal lesions of MPXV-infected animals [2].

A suspected case of human-to-dog MPXV transmission in Paris, France, in June 2022⁷ highlighted a potential for human-to-animal viral transmission. In this case, two homosexual men went to the Pitié-Salpêtrière Hospital in Paris after presenting with perianal ulcerations, vesiculopustular rashes, lethargy, headaches, and fever [7]. MPXV DNA was confirmed in the two samples taken from the men by real-time PCR [7]. Interestingly, their male Italian greyhound (dog) also presented with mucocutaneous lesions 12 d after its primary owner's symptom onset [7]. The dog tested positive for MPXV, and DNA sequences of both the dog and its primary owner were compared by using the state-of-the-art next-generation sequencing method, which showed 100% viral sequence homology of the 19.5 kilobase pairs sequence between the two

samples [7]. The 100% sequence homology and the kinetics of symptom onset in the patients and subsequently in their dog strongly implicates a human-to-animal transmission event of MPXV [7].

MPXV is an orthopoxvirus of the family *poxviridae*. Orthopoxviruses are known to infect humans and animals and then back again [9–11]. The first known outbreak of MPXV outside of Africa was dated back in 2003 in the United States where pet prairie dogs were infected when they were co-housed with Gambian pouched rats and dormice (i.e. inter-species transmissions) imported from Ghana and subsequently led to over 70 human cases of MPXV [2] (i.e. zoonotic transmissions). It has been shown that several different species of rodents (wild and domestic rodents, such as prairie dogs, squirrels, marmots, groundhogs, chinchillas, giant-pouched rats, and possibly guinea pigs, mice, and rats), hedgehogs, and possibly adult rabbits can be infected (experimentally and naturally) with MPXV, and that the majority of the rodent species can also be infected with other orthopoxviruses (e.g. smallpox, cowpox, horsepox, camelpox, etc.) [10,11]. Similarly, other farmed and companion animals (e.g. cows, camels, rabbits, cats, and dogs) can also be infected by MPXV or other orthopoxviruses [10,11]. With so many animals susceptible to MPXV infection, there is clearly an increased probability for zoonotic and reverse zoonotic transmission events.

An important and unaddressed question is whether MPXV has the potential to spread into wildlife species or can become endemic in places where it has been historically absent. There are currently no known animal reservoirs for MPXV outside of Africa; however, during the 2003 outbreak of MPXV in pet prairie dogs in America, there was certainly an opportunity for a new animal reservoir to be established in a separate continent. In this event, about 300 of the 500 animals that were potentially infected with MPXV had never been found after they were distributed to various places in the United States [12]. This event had been described as a “near miss” for MPXV to establish itself in new animal species in North America [13]. The current outbreak might present another (perhaps greater) opportunity for MPXV to establish itself in new animal populations and thus could provide entirely new

animal reservoir(s) for potentially more dangerous virus variants to evolve and emerge. As about half of the poxvirus' genes in its genome encode for factors that can undermine (suppress) host immune responses to the virus infection [14,15], these factors might help explain the potential of poxviruses, including MPXV, to persist in the infected hosts and to potentially establish a productive reservoir [13], as well as their relatively large host range (i.e. the many susceptible animal species to poxviruses as described above [7–11]). Recently, a relatively small study has shown that MPXV DNA can be found in infected human fecal samples ($n = 12$) [16], which might present yet another potential mode/route for virus transmission, as some animals (e.g. rodents) could pick up the virus in the virus-laden human waste matters and thus could establish newly infected wild animal populations in traditionally non-endemic regions [11].

If the current COVID-19 pandemic has taught us anything, it is that we should develop an active surveillance effort to assess and track the prevalence and potential spread of other emerging and re-emerging viruses (and/or other human pathogens) in companion, captive (zoo), farmed, and wild animals. We and other researchers have recently provided original data showing reverse zoonoses (inter-species, human-to-animal transmissions) of SARS-CoV-2, which is the causative agent of COVID-19, in pet dogs and cats in Minnesota [17,18] and elsewhere [19,20], especially during the winter months [18] when humans were living in even closer quarters with their (infected) pets. For example, it has been shown that pets that were sleeping in the same bed with the infected human owner(s) were more likely to be associated with SARS-CoV-2 transmission [19]. It is noteworthy that the Italian greyhound reported to be infected with MPXV was also sleeping in the same bed with its infected human owner before symptom onset [7]. The parallel of MPXV and the SARS-CoV-2 virus being transmitted from human to animals via reverse zoonotic events prompts a similar need for surveillance of MPXV seropositivity in pets, as what had been done in the SARS-CoV-2 (COVID-19) pandemic in companion animals (for a review, see Murphy and Ly [20]) and wild animal species, such as white-tailed deer [20,21].

This type of an approach requires a “One Health” method that would allow for an accurate assessment of the impact that animals and the environment have had (and will continue to have) as probable means for transmission dynamics of potentially deadly pathogens into naïve human populations. This surveillance would ideally include collaboration between human and veterinary public health officials to manage

domesticated, and wherever feasible, wild animals to prevent unintentional exposures of MPXV. Along with active surveillance, reverse zoonotic transmission events of pathogens also call for a plan to prevent and/or control pathogen's spread and evolution. Toward this end, vaccine development against MPXV for vulnerable animals (as the scientific community identifies them) needs to also be considered as there are currently no orthopoxvirus vaccines approved for use in any of the known susceptible animal species [22]. By establishing a “One Health” approach for the containment of MPXV that would include surveillance and vaccination strategies, it is possible that we could effectively control the adaptive evolutionary nature of the virus to a new host species and to decrease the risk of vaccine-resistant virus strains to emerge [23], which would help decrease the risk of MPXV being established in new animal reservoir(s) and outside of the previously known endemic regions.

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