

CAN ANIMALS OUTSIDE AFRICA BE AFFECTED BY THE ONGOING MONKEYPOX OUTBREAK, OR EVEN BECOME KEY PLAYERS?

LES ANIMAUX HORS D'AFRIQUE PEUVENT-ILS ÊTRE CONCERNÉS PAR LA FLAMBÉE DE MONKEYPOX EN COURS, VOIRE EN DEVENIR DES ACTEURS IMPORTANTS ?

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ABSTRACT

The unprecedented outbreak of monkeypox outside Africa raises questions about the risk of the monkeypox virus (MPXV) being transmitted to animals from newly-infected countries, and their ability to serve as spillover hosts, or even constitute autochthonous reservoirs for this zoonotic virus. This is all the more legitimate since the role of reservoir played by small mammals, rodents and squirrels in particular, is strongly suspected in traditionally-infected central and west African countries. In addition, several species from other continents have proven to be receptive or even susceptible, and capable of retransmitting the virus to other animals and/or humans. Because of the reality of human-to-human transmission of MPXV, it should be recommended, as a precautionary principle, to avoid all contact and proximity between humans likely to shed the virus and pets, including exotic pets or synanthropic rodents and squirrels, in order to anticipate any risk of even theoretical infection.

Keywords: monkeypox, MPXV, Orthopoxvirus, zoonosis, wildlife, domestic animals

RÉSUMÉ

La flambée extra-africaine inédite de monkeypox questionne sur le risque de transmission du virus Monkeypox (MPXV) à des animaux des pays nouvellement infectés et sur leur capacité à servir d'hôtes de liaison, voire à constituer des réservoirs autochtones pour ce virus zoonotique. Cette question est d'autant plus légitime que le rôle de réservoir de petits mammifères, rongeurs et écureuils en particulier, est fortement suspecté dans les pays d'Afrique centrale et de l'Ouest traditionnellement infectés. De plus, plusieurs espèces d'autres continents se sont montrées réceptives voire sensibles et capables de retransmettre le virus à d'autres animaux et/ou des humains. Du fait de la réalité de la transmission interhumaine, il devrait être recommandé, par principe de précaution, d'éviter tout contact et toute proximité entre les humains susceptibles d'excréter le virus et les animaux de compagnie, dont les NAC, les rongeurs synanthropes et les écureuils, afin d'anticiper tout risque même théorique d'infection.

Mots clés : Variole du singe (monkeypox), MPXV, Orthopoxvirus, zoonose, faune sauvage, animaux domestiques.

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Since the beginning of May 2022, outbreaks of monkeypox have been multiplying almost simultaneously on several continents outside Africa, in a context of apparently exclusive human-to-human transmission. As of 4 July, 6027 laboratory confirmed cases of monkeypox and three deaths had been notified by WHO out of the African continent (WHO, 2022), but the case count by Global Health (Mathieu *et al.* 2022) showed 11595 confirmed cases worldwide as of 14 July. In France, 908 cases have been notified as of this date.

As monkeypox is a zoonotic disease, the question arises as to whether animals could be contaminated by humans (reverse zoonosis) in these countries, and thus be likely to recontaminate humans. If so, could at least some species constitute perennial reservoirs of the virus, capable of contaminating humans in the long term, which is already the case in the traditionally-infected areas of Africa. This article aims to review these risks, after a necessary reminder of the state of knowledge.

Since the advent of the modern history of anti-infectious control, poxviruses have been part of the One Health concept, which advocates both a holistic vision of health that integrates human and animal health, and the preservation of balance in ecosystems. Indeed, the development of the first effective vaccine against a human disease – the smallpox vaccine, which led to the official declaration of the worldwide eradication of this disease in 1980 (the first human infectious disease ever eradicated) – owes much to the interactions between animals and humans and the links between their respective pathogens. While known to have a strictly human reservoir, the smallpox virus (VARV) belongs to the *Poxviridae* family and the *Orthopoxvirus* genus, which also includes the cowpox (CPXV) and vaccinia (VACV) viruses, both zoonotic. The observation that cowpox infected farmers were protected from smallpox led Jenner to develop 'vaccination' (from "vacca", which means "cow" in latin). Monkeypox virus (MPXV), also a member of the *Orthopoxvirus* genus, is an integral part of this historical development concerning smallpox, since it was during the process of smallpox eradication that human infection was discovered and that monkeypox was recognised as zoonotic. Like the other *Orthopoxviruses*, MPXV is characterised by a cutaneous tropism and in susceptible hosts causes a cutaneous rash punctuated by pustules accompanied in most cases by lymphadenopathy; it can however be associated with serious or even fatal diseases. Let us first put MPXV into perspective with respect to the characteristics of other members of its family, and provide some clinical elements relating to monkeypox.

MAIN FEATURES OF MPXV AND MONKEYPOX

Positioning of MPXV within the *Poxviridae* and variations in host spectra

Poxviridae are a family of large, pleomorphic, enveloped viruses with double-stranded DNA. They are 220-450 nm long, 140-260 nm wide and 140-260 nm thick. The genome has the capacity to encode a large number of proteins (150 to 300 depending on the species). One of the major characteristics of these viruses is their marked resistance in the external environment. This

family contains many members. All the viruses that are pathogenic to animals and humans belong to the subfamily *Chordopoxirinae* and are currently divided into nine genera (*Avipoxvirus*, *Capripoxvirus*, *Cervidpoxvirus*, *Leporipoxvirus*, *Orthopoxvirus*, *Parapoxvirus*, *Suipoxvirus*, *Yatapoxvirus*), but a significant number of viruses are awaiting assignment.

The majority of genera and species express a restricted host tropism. Consequently, the designation of genera by host species category (*Avipoxvirus*, *Capripoxvirus*, *Cervidpoxvirus*, *Leporipoxvirus*, *Suipoxvirus*) and the designation of species by host species (e.g. Canarypox virus - CNPV, or Sheeppox virus - SPPV) appears to be appropriate and most virus species that are pathogenic to animals are not zoonotic.

Only four genera are exceptions in this respect:

- either because they harbour viruses that are strictly pathogenic for humans: one genus falls into this category, the *Molluscipoxvirus* genus (responsible for molluscum contagiosum),
- or because they are home to zoonotic species: *Orthopoxvirus*, *Parapoxvirus* and *Yatapoxvirus*.

The *Parapoxvirus* genus includes viruses that are pathogenic to some domestic ruminants and cause mild skin disease in humans, with the exception of the BPSV species, which causes bovine papular stomatitis. The genus *Yatapoxvirus* includes two zoonotic species affecting non-human primates (NHPs), including the monkey Yaba tumour virus (YMTV), which causes histiocytomas, and the Tanapox virus (TANV).

Finally, the *Orthopoxvirus* genus, to which the MPXV species belongs, currently comprises nine species, all of which are responsible for animal or human "pox" ("variole" in French). Only some of them are recognised as zoonotic: Buffalopox virus (BPXV), Camelpox virus (CMLV), Cowpox virus (CPXV), Monkeypox virus (MPXV) and Vaccinia virus (VACV) (Diaz, 2021). Smallpox virus (VARV), the human pox virus, was officially declared by the WHO to have been eradicated from the face of the earth in 1980 thanks to a combination of two elements: the fact that the reservoir was strictly human and the fact that a highly effective heterologous vaccine (anti-CPXV) was available. This monotropism of VARV to humans is not absolute, however, since while the virus was still circulating in humans, smallpox was reported on several occasions in free-ranging and captive non-human primates (NHPs) (Arita and Henderson, 1968). This situation indicates the apparently limited but real ability of this virus to be transmitted naturally from humans to some monkeys, though only one case was confirmed by virus isolation.

Thus, CPXV and MPXV appear to be the most ubiquitous of the *Poxviridae* in terms of its natural host range, along with VACV. This aspect will be developed below for MPXV. It is interesting to note in this context that according to recent data, VARV and MPXV are now believed to derive from two different branches of a CPXV ancestor (Babkin *et al.* 2022).

MPXV, a virus with some variability

Although DNA viruses are thought to be less variable than RNA viruses, this does not mean that they do not evolve. Indeed, the

analysis of viral strains has shown the existence of two distinct clades (or lineages) that differ genomically, geographically and in their degree of virulence both in humans and in experimentally-inoculated animal species (non-human primates and rodents) (Parker and Buller, 2013; Nakazawa *et al.* 2015; Bunge *et al.* 2022):

- A clade found in Central Africa and more precisely in the Congo Basin (CB), first identified in the Democratic Republic of Congo (DRC) (formerly Zaire), was later found in Gabon, the Central African Republic (CAR), southern Sudan and Cameroon. It is the most virulent clade, with a case-fatality rate of 10.6% [8.4-13.3%] in the areas concerned.

- A clade present in West Africa (WA) has been identified in Liberia, Nigeria, Sierra Leone, Côte d'Ivoire and Cameroon, the only country known to host both clades. The case-fatality rate of reported cases is 3.6% [1.7-6.8%]. This clade is the only one to date to have caused cases outside Africa, none of which have been lethal to date.

Furthermore, evolution is possible within clades, which may be of great epidemiological interest. Thus, a recent study has shown the cohabitation in the CB clade of three sub-lineages among ten strains from human cases originating from the same area of CAR and genetically very close to the strains circulating in DRC. Whole genome sequencing also revealed that all of these strains had originally emerged in the primary forest of the Congo Basin (Berthet *et al.* 2021).

Key clinical features of MPXV

As already mentioned, the *Poxviridae* family is characterised by a marked skin tissue tropism. All members of the *Orthopoxvirus* genus are agents of human and/or animal pox (although other non-zoonotic genera may also be considered agents of pox, based on the lesions they cause).

Monkeypox in humans

Monkeypox in humans is therefore characterised by symptoms and lesions that are very similar to, or even indistinguishable from, those of human smallpox. After an average incubation period of one to two weeks with a range of five to 21 days (Nolen *et al.* 2016, World Health Organization, 2022), two successive phases are described (Centers for Disease Control and Prevention, 2021):

- A prodromal phase, corresponding to a non-specific febrile syndrome with hyperthermia above 38.5°C, chills, asthenia, myalgia and voluminous polyadenopathies, more frequently cervical and cephalic, but possibly inguinal (Diaz, 2021).

- An eruptive phase, which begins one to three days after the onset of hyperthermia, characterised by skin lesions that develop uniformly over time in the following sequence: macules, papules and vesicles maturing into crusts. Due to the inflammation, these lesions are painful and pruritic. These lesions first affect the face before appearing on other areas, including the palms and soles of the feet. Lesions may affect genital areas, and it is noteworthy that the preponderance of genital lesions is particularly common in patients in the current extra-African episode (Kozlov, 2022) as well as in the current

outbreak in Nigeria (Ogoina *et al.* 2019). The time from the onset of the first symptoms to the fall of the crusts is 2-3 weeks, and the disease can leave indelible scars.

This clinical picture corresponds to the mild form of the disease. More severe, and even lethal, forms can also be encountered. These are notably linked to superinfections and/or to significant dehydration in the case of extensive lesions. Cases of encephalitis have even been observed (Sejvar *et al.* 2004) as well as haemorrhagic lesions, particularly of the liver and spleen (Meyer *et al.* 1991). Various elements may be associated with an unfavourable evolution, including the viral clade, as mentioned above, and co-infection with other pathogens such as HIV (Ogoina *et al.* 2020) or *Plasmodium falciparum* (Müller *et al.* 1987). MPXV also causes severe forms more frequently in children than in adults (Huhn *et al.* 2005; Nakoune *et al.* 2017). For the less recent observations, this could be partly related to lower vaccination coverage. Finally, an association is suspected between monkeypox, abortion and in utero death (Kisalu *et al.* 2017) but very few studies have yet documented this relationship. It is also very likely that the case fatality rate associated with each clade would be lower outside Africa. In any case, no deaths have been reported to date either in the current extra-African episode or in previous sporadic cases.

It should be noted that in humans some features are more suggestive of monkeypox than smallpox, notably the presence of polyadenomegalia.

Monkeypox in other susceptible species

To date, only wild species have been described as affected. Only the natural disease in free-living wild animals, captive animals or exotic pets will be discussed here, in the context of outbreaks in which a number of animals have been observed. This description will be brief, not only because observations are limited, but also because the clinical signs and lesions are very similar to those described in humans.

Thus, the two phases of the disease can be observed in NHPs (non-human primates) just as in humans. The severity of the disease and its evolution seem to depend very much on the species, if we refer to the episode of monkeypox that occurred in the Rotterdam Zoological Park in 1964. Eleven NHPs out of 23 affected animals died. Of those affected, ten were orangutans, of which six succumbed to the disease. One out of the two gorillas affected died. Among other species, the proportion of animals that died was lower (e.g. marmosets), or even zero with a mild disease (chimpanzees). On the other hand, a recent long-term follow-up of chimpanzees under natural conditions in the Taï forest, Côte d'Ivoire, has shown that, like in humans, the disease can be very severe – and even fatal – in young or adolescent chimpanzees (Patrono *et al.* 2020). It is interesting to note that in this outbreak, while some animals showed the classical forms described in humans, others developed severe respiratory signs with dyspnoea and no skin lesions or extremely discrete or diffuse lesions. In addition to NHPs, there are clinical descriptions in prairie dogs (*Cynomys ludovicianus*), the first indigenous victims of the importation of Gambian pouched rats (*Cricetomys gambianus*) into the USA. They report skin disorders along with eye and nose discharge and some deaths. This ability to spread to hosts on continents other than the continent where MPXV

naturally circulates in wildlife clearly raises the issue of the spectrum of hosts receptive and susceptible to the virus.

A VERSATILE VIRUS WITH A VERY ADAPTABLE HOST TROPISM

It should be remembered that MPXV appears to have diverged from a close common ancestor of cowpox virus (CPXV) (Babkin *et al.* 2022), itself zoonotic and multi-host.

Searching for the reservoirs

While MPXV is an African virus, it should be noted that the NHPs that were the source of its discovery in Denmark came from Singapore, and were not African monkeys. On the one hand, the identity of the natural animal hosts of this virus and their role in its epidemiological cycle remains a gray area, and, on the other hand, this virus has proved to be particularly versatile in its ability to naturally and experimentally infect a wide variety of animal species, with a twofold consequence: firstly, this does not facilitate the identification of the species that contribute to the natural cycle of infection and secondly, this lends credibility to the hypothesis that animal species can become infected in regions where the virus does not usually circulate.

However, investigations to find traces of infection in potential natural hosts were carried out very soon after the first case was notified.

Animals in the wild

The first studies mainly attempted to confirm or refute the hypothesis that monkeys were the most likely source of contamination for humans. This hypothesis was quickly challenged and studies, initially serological studies, were carried out on other animal species, including a large serological study in the DRC that included at least 43 animal species (Khodakevich *et al.* 1986). This survey helped identify squirrels as a significant source of MPXV for humans due to the frequency of their seroconversion, which is consistent with the results of another study which had shown a year earlier that in 12% of human infections resulting from presumed animal contact, squirrels were mentioned (Arita *et al.* 1985). The hypothesis that squirrels were involved in the epidemiological cycle was consolidated by the isolation of MPXV from a ground and tree squirrel known as Thomas's rope squirrel (*Funisciurus anerythrus*) (Khodakevich *et al.* 1986). While the fact that it was symptomatic – and that some squirrel species proved susceptible after experimental inoculation – may raise questions about their actual role as a reservoir, most studies have confirmed the frequency of seropositivity in asymptomatic squirrels tested (particularly in areas where squirrels were exported to the USA prior to 2003). A large retrospective study of museum specimens of *Funisciurus* squirrels supports this hypothesis and potentially even broadens the spectrum of species within this genus thought to act as reservoirs (Tiee *et al.* 2017). Asymptomatic infection of mammals belonging to other species – detected by PCR, viral

isolation or serology (antibodies) – has been demonstrated either during field surveys or during importation into the USA (Doty *et al.* 2017; Parker and Buller, 2013). Examples include the Gambian pouched rat (*Cricetomys gambianus*), the African hedgehog (*Atelerix sp.*), the jerboa (*Jaculus sp.*), the brush-tailed porcupine (*Atherurus africanus*), Lorraine's African dormouse (*Graphiurus lorraineus*) and the common rufous-nosed rat (*Oenomys hypoxanthus*). In addition, positive PCR results have been obtained in American animal species, probably due to their cohabitation with imported species: the common opossum (*Didelphis marsupialis*), the grey short-tailed opossum (*Monodelphis domestica*) and the woodchuck (*Marmota monax*) (Parker and Buller, 2013). The virus (clade WA) was also isolated a second time in 2012 in Côte d'Ivoire, from a young sooty mangabey monkey (*Cercocebus atys*) found dead with disseminated skin lesions (Radonic *et al.* 2012). It is currently accepted that NHPs are accidental hosts in the same way as humans. This assumption has recently been further supported by the observation of repeated episodes of clinical monkeypox in chimpanzees (*Pan troglodytes verus*) in Côte d'Ivoire, near the Taï forest, which led to the molecular detection of MPXV followed by sequencing (Patrono *et al.* 2020).

Captive animals and exotic pets

Additional information has been gathered following episodes in captive animals. For example, an outbreak at Rotterdam Zoo in 1964 affected 23 NHPs of seven different species, some Asian (orangutans) and some African (chimpanzees, cercopithecines, gibbons, gorillas, marmosets, saimiris). Eleven of them died, thus confirming their susceptibility (probably exacerbated in captivity) (Arita and Henderson, 1968; Gispén *et al.* 1967). The index cases were positively identified as two anteaters (*Myrmecophaga tridactyla*) imported from Central America and bearing lesions. They were not considered natural hosts of the virus, as the epidemiological investigation showed that they had been previously infected by monkeys before their sale to the zoo. It was concluded that accidental hosts could be 'effective' hosts, as confirmed by the current strictly human-to-human emergence. The same was true in 2003 in the USA, where the importation of Gambian pouched rats from Africa resulted in the infection of native prairie dogs, which were the source of many human infections (see below). It should be noted that prairie dogs belong to the *Sciuridae* family, like squirrels.

Laboratory animals

The susceptibility of many NHPs – especially Asian NHPs – has been confirmed experimentally. The susceptibility of rodents under experimental conditions has been shown to be very variable depending on the species. Thus, African dormice, Natal multimammate rats (*Mastomys natalensis*), cotton rats (*Sigmodon sp.*), and Gambian pouched rats are very susceptible. Squirrels are susceptible under certain conditions, and adult rabbits are susceptible subcutaneously, while recovering; however, in one study with albino rabbits, swelling appeared at the point of inoculation, followed 7 days later by a cutaneous eruption that

led to death. In contrast, when adults were inoculated by routes consistent with natural infection, mice, white rats, guinea pigs, hamsters and chickens showed no susceptibility to MPXV (Parker and Buller, 2013).

Non-exotic pets

Negative results were found in limited serological surveys carried out among domestic animals (120 small ruminants and 67 cats) in an agro-forestry setting where the virus and/or anti-MPXV antibodies had been detected in humans and squirrels (Khodakevich *et al.* 1987).

The bottom line is that there is currently no certainty about the nature of MPXV reservoirs. The very patchy data collected suggest that the natural maintenance of MPXV in the depths of African forests may involve multiple wild hosts, including rodents and squirrels (as suggested by seroconversion rates), with possible incursions into particularly susceptible accidental hosts such as humans and non-human primates.

An additional benefit of field and experimental studies has been to show that MPXV can be transmitted in different ways and by different routes. This knowledge is essential for understanding the risks of zoonotic transmission, human-to-human transmission and potential reverse transmission from humans to animals.

A virus capable of infecting its hosts in multiple modes

Direct transmission

Limiting ourselves to what could be natural routes of infection, it appears that MPXV can be transmitted directly through skin or mucous membrane contact with an infected individual. This route has already been demonstrated for many other poxviruses, whether strictly animal, zoonotic (cf. CPXV with transmission by skin contact from rats) or strictly human such as VARV. Transmission by bites can also be envisaged. The respiratory route is another hypothetical means of direct MPXV transmission, a mode already proven for VARV and other poxviruses (Aubry, 2022). According to some authors, the virus is projected into the air as infected droplets from the oral cavity. However, Hobson *et al.* (2021) recently detected MPXV DNA in respiratory secretions 20 days after clinical recovery, and Adler *et al.* (2022) found it up to 40 days after recovery. Unfortunately, there was no investigation into whether infectious particles persisted. Patrono *et al.* (2020) have recently shown that delousing activity promotes the spread of infection within chimpanzee communities, which in this case could be due to both dermal and respiratory routes. The same could be true for the episodes of human-to-human transmission in Nigeria, CAR, and outside Africa since May 2022. In these cases, transmission during intimate and sexual contact is a prime suspect due to the frequency of lesions in the genital area and the frequency of male patients who reported having had recent homosexual relations (though this is not a rule). Such close contact facilitates transmission of MPXV: while the R0 of monkeypox is naturally

low, it can under such circumstances significantly exceed 1, making epidemics in unvaccinated populations possible (Grant *et al.* 2020).

Indirect transmission

It is also possible for MPXV to be transmitted indirectly in an experimental context, when animals are housed in rooms or cages that have contained sick animals (Parker and Buller, 2013). It has long been established that the environment contaminated by secretions and scabs can be the source of VARV transmission. The poxviruses present in the scabs are particularly resistant. Lumpy skin disease virus (LSDV), a *Capripoxvirus*, can remain infectious for up to 35 days in dry scabs, for example. Scabs are therefore a major source of environmental contamination for a fairly long period of time. In addition, it has been shown that the virus can persist for several months on farm premises, protected from light (Anses, 2017). Nosocomial transmission of MPXV to a nurse via patient bedding occurred in the UK in 2018 (Vaughan *et al.* 2020). Furthermore, the study by Patrono *et al.* (2020) under natural conditions suggests that the virus could also be inoculated by flying insects, as MPXV RNA was detected in flies collected in the vicinity of the outbreak of sick monkeys. This is reminiscent of LSDV, which can be transmitted by the bites of flying insects. The finding by Patrono *et al.* (2020) of infectious MPXV in the faeces and urine of chimpanzees in a population known to be infected is consistent with this hypothesis. Infectious virus was even detected close to a monkey corpse, on leaves on which flies belonging to the family *Calliphoridae* had regurgitated and defecated (Patrono *et al.* 2020).

All of these transmission modalities can be considered in the context of the current emergence of human-to-human transmission of MPXV: skin-to-skin transmission, including but not limited to sexual or intimate contact; respiratory transmission and indirect transmission via secretions.

All these elements show that MPXV is a versatile virus in terms of its hosts and modes of transmission. But are these elements sufficient to explain the changes that have occurred after a long period of real or apparent epidemiological silence, particularly in West Africa?

Now that we have set the scene, it is time to discuss the circumstances of the discovery of MPXV in 1958 and the highly evolving nature of its epidemiology in humans from 1970 to the present.

A RECENT DISCOVERY AND A SHIFTING AND CONFUSING EPIDEMIOLOGY

The discovery

The virus responsible for monkeypox (MPXV) was first identified in animals in 1958 (Reynolds *et al.* 2019). It was found in two batches of cynomolgus macaques (*Macaca fascicularis*) imported from Singapore to Denmark for a research laboratory. The skin rash from which they suffered was tested, and a virus similar to the smallpox virus (VARV) was isolated. As the

virus was first isolated from monkeys, it was named monkeypox virus (MPXV). It was not until 1970 that it was unexpectedly discovered that MPXV was also a zoonotic virus, with the first description of a human case in the DRC (Ladnyj *et al.* 1972) in the context of global smallpox eradication efforts. Until then, the ubiquity of smallpox and the lack of routine laboratory diagnosis of suspected smallpox had clearly masked the existence of monkeypox in humans. This is not surprising, given the similarity of smallpox and monkeypox in humans. But that year, a suspected case of smallpox was further investigated, as the area had been free of smallpox for two years. The case was a nine-month-old hospitalised child with a severe form of smallpox (children were known to be more severely affected than adults in cases of smallpox). These investigations revealed that the infection was due to a virus that was very similar to but different from VARV, and which was none other than the MPXV virus isolated twelve years earlier from cynomolgus macaques in Denmark (Ladnyj *et al.* 1972).

Relatively reassuring answers after the shock of the discovery

This discovery was a shock to health authorities: would this zoonotic virus replace the smallpox virus and undermine all their efforts to eradicate it?

The responses over time have been quite reassuring for the following reasons:

- Although clinically affecting primates (human and non-human), MPXV is less pathogenic to humans than VARV (although it is more pathogenic – but not necessarily lethal – to NHPs), with the exception of children in whom it tends to cause more severe forms. However, this statement must be qualified according to the MPXV clades, as indicated above.

- Early on, the probability of humans being infected by MPXV was considered much lower than for VARV. The reasoning behind this was firstly the need for initial zoonotic contamination, and thus interaction with an animal source (in this case a wild animal), and secondly the lower efficiency of human-to-human dissemination of MPXV, which can be explained by (i) the lower capacity for transmission of MPXV by humans compared to VARV (estimated to be 10 times lower within domestic households) (Jezek *et al.* 1983), (ii) the contamination of index cases in the sparsely populated rainforest areas of central and west Africa, making significant human-to-human viral spread within these areas highly unlikely, and even less likely beyond these areas.

- Smallpox vaccination has been estimated to be 85% effective against MPXV and has recently been re-evaluated at 65% (Karem *et al.* 2007), limiting the consequences of infection both clinically and in terms of shedding, and thus the risk of secondary human-to-human transmission.

Unlike VARVs, MPXV appeared to be confined to two well-defined areas in Africa corresponding to the two clades CB and WA, i.e. the forest areas of the Congo Basin and West Africa respectively, where reservoirs of unknown identity were thought to live. Surveillance activities under the aegis of the WHO led to the rapid detection (between 1971 and 1972) of MPXV in three west African countries: Liberia (four cases), Nigeria (one case)

and Sierra Leone (one case) (Foster *et al.* 1972). The virus spread to other countries, but with very limited incidence and little or no linkage between cases, suggesting sporadic zoonotic infections. Thus, by the end of the 1970s, 48 confirmed or probable cases had been recorded in six countries; those already listed as well as Cameroon and Côte d'Ivoire, suggesting that the virus was spreading geographically more in West Africa than in Central Africa, even though the DRC accounted for 79% of the total number of reported cases (38 cases).

This situation was amplified during the following decade (1980s), with 14 cases reported in West Africa and 343 cases in Central Africa, all of which were still reported in the DRC (i.e. 96% of cases), reflecting an endemic situation for clade CB. At the same time in West Africa, the trend was towards sporadicity, probably with a certain level of under-reporting linked to the milder cases associated with clade WA. During the following decade (1990s), only two countries reported cases, all of which were *a priori* attributable to the CB clade: the DRC with 511 confirmed, probable or suspected cases and Gabon, which – after being reported as infected for the first time in 1987 – suffered another episode in 1991 including a family cluster of four children, two of whom died (Meyer *et al.* 1991). Nine cases in all were confirmed in this country.

The WA clade thus seemed to have disappeared, and this hope increased in West Africa during the 2000s, when no cases were reported there.

The 'awakening' of the monkeypox virus

Thus, after the apparent epidemiological silence that had fallen over West Africa, and a relative stability of cases in Central Africa, three very probably related trends have been observed: the re-emergence of cases in countries already recognised as affected; the emergence of cases in neighbouring countries; and the "export" of cases outside Africa, which has taken a spectacular turn since the beginning of May 2022.

Firstly, countries in which MPXV had previously been described have seen a resurgence of human cases. The CB clade not only caused an explosion of confirmed, probable or suspected cases in the DRC (10,027) between 2000 and 2009 (Rimoin *et al.* 2010; Bunge *et al.* 2022), but also appeared to be expanding, with 73 cases reported in the Republic of Congo and 19 in southern Sudan. Meanwhile, the WA clade appeared to have disappeared for good. However, a discordant note resounded that could have been a warning signal as to the reality of the circulation of the WA clade. Indeed, the outbreaks of monkeypox in humans and prairie dogs in the USA were not only caused by this clade but involved Gambian pouched rats imported from Ghana, where MPXV had never been reported. This unexpected occurrence, which will be detailed below, strongly suggested that the WA clade was still actively circulating, in all likelihood in a multi-species wildlife reservoir that could include these rats, and that it had a much wider area of distribution than previously thought. The spread of the CB clade into new countries suggested that this clade also had a much wider area of circulation than the primary forests of DRC. The 2010-2020 decade saw the 'official' reappearance of the WA clade in four of the countries where it had been detected in the

1970s, but in an apparently sporadic form in three of them: Cameroon (three notified cases), Liberia (six notified cases) and Sierra Leone (one notified case). A new country was added to this list during this time: the Central African Republic (CAR). But the most striking event was the number of cases in Nigeria where monkeypox re-emerged in September 2017 (Yinka-Ogunleye *et al.* 2018), reaching 181 notified cases by the end of 2019. This episode is still ongoing at the time of writing, with a total of 813 suspected cases of which 327 were confirmed as of 10 July 2022, and eleven that proved fatal (Nigerian Centre for Diseases Control and Prevention, 2022). One striking feature is the wide dispersion of cases, which have been reported in 35 of the country's 36 states, including a significant proportion in urban areas. The number of CB clade cases in the DRC rose to even more impressive levels between 2010 and 2019 (18,788 confirmed, probable or suspected cases), with 24 cases reported in the Republic of Congo. The CAR has not been spared, with a long-term epidemic starting in 2011 (Berthet *et al.* 2021).

This explosion of cases, particularly in the DRC and Nigeria (though to a much more limited extent in the latter), is not the only epidemiological feature to be noted compared with episodes between 1970 and the late 1980s (Bunge *et al.* 2022):

- Firstly, the median age of patients has increased markedly, from 4-5 years in the 1970s to the late 1980s, to 10 years in the 2000s and 21 years in the following decade. The numerical increase in cases as well as the increase in patient age is highly suggestive of a detrimental effect of the cessation of smallpox vaccination on the incidence of monkeypox (in the same way that cross-protection was efficient against VARV).

- Secondly, the frequency of secondary human-to-human transmission versus zoonotic (primary) transmission has also changed considerably according to the available data. The percentage of zoonotic transmission has been reported to have declined from over 70% in 1980 to less than 25% in recent years (Bunge *et al.* 2022). This evolution is attributed to a growing increase in cases in enzootic areas (fostered by the cessation of vaccination), which subsequently led to an increase in rural and then urban cases associated with increased secondary human-to-human transmission. The strong demographic growth in urban areas may have done the rest, as it is a condition for intra-family contamination or contamination between close neighbours. This is particularly true in the slums, by direct or indirect contamination. In addition, certain intimate or sexual practices (particularly homosexual ones), could increase the risk of contamination.

Logically, the increase in rural and urban cases has been accompanied by the emergence of monkeypox cases in other countries. The incubation period of up to 21 days (Nolen *et al.* 2016, World Health Organization, 2022) increases the risk that an infected person who is not yet symptomatic will travel undetected. This evolution can be roughly divided into three phases:

Phase 1: exportation of infected animals and zoonotic infections in the country of destination

This modality corresponds very precisely to the outbreaks resulting from the introduction of wild rodents from Ghana into the USA. These animals, commonly referred to as the

Gambian pouched rat, are being domesticated in West Africa for food and can be adopted as exotic pets, for which purpose a number of individuals were imported into the USA in 2003. They were mixed with autochthonous prairie dogs that were themselves sold as pets and that acted as liaison hosts and host amplifiers of MPXV, resulting in 72 confirmed or suspected human cases of monkeypox (Reed *et al.* 2004). Outbreaks were reported in six states and led to an aggressive federal and state government response to isolate and treat affected individuals, identify and vaccinate contacts, and prevent the development of an indigenous animal reservoir, a fear that was not borne out as the virus was eliminated from the USA with the extinction of human cases (Reynolds *et al.* 2009). This first stage corresponds to the period when the infection appeared to have died out in West Africa, with the virus circulating silently in the animal reservoirs. It is also important to remember that the pouched rats came from Ghana, a country that has never been recognized as infected until June 2022 (ProMED mail, 2022), and that the animals themselves had never been identified as being infected. This leads to consider that on the one hand that the African territories where MPXV circulates is more extensive than suggested by epidemiological surveys and reported African human cases, and on the other hand that various rodent species (wild, synanthropic and/or domestic) could be unknown reservoirs of MPXV. Regarding Ghana, a survey carried out in 2004, in the area supposed to have been the source of the Gambian pouched rats exported to the USA, tends to confirm that MPXV was already circulating there not only in several wildlife species (including Gambian pouched rats, *Sciuridae* and *Graphiurus*), but also within humans (presence of antibodies) (Reynolds *et al.* 2010).

2nd phase: entry of infected individuals into non-African free countries, without secondary infection in the destination country or with infrequent secondary infection of a limited extent

A clear relationship was established in 2018 between the epidemic active in Nigeria since 2017 and human cases outside Africa, which were always linked with travellers from Nigeria (Mauldin *et al.* 2022). Human cases have been sporadically reported in Israel, the UK, Singapore and the USA. Although they have occurred repeatedly, they have never challenged the idea that animal sources of infection are essential to prevent the eventual drying up of human outbreaks and/or to generate new ones. This assessment was based on the one hand on the sporadic nature of these cases and their independent nature, except for one case of nosocomial transmission in England in 2018 (Kunasekaran, 2018) and one case of intra-family transmission in the same country in 2021 (Hobson *et al.* 2021). On the other hand, it also took into account the epidemiological pattern of African human outbreaks, with a gradual extinction of human-to-human transmission after a maximum of four to nine generations of human-to-human transmission (Fine *et al.* 1988; Nolen *et al.* 2016; World Health Organization, 2022). Although some authors have raised the alarm about the risk of increased sporadic introduction of monkeypox into non-African countries, epidemic-like human-to-human transmission has

never been considered and the situation has therefore never been of real concern until the cases in May 2022.

3rd phase: entry of infected individuals into non-African free countries, with emergence of secondary outbreaks in the destination country

This occurrence, considered highly unlikely, became a tangible reality from the beginning of May 2022. On 7 May, a case was notified to the WHO by the United Kingdom concerning a person from Nigeria. Since then, confirmed cases have been notified in another 61 non-African countries on all other continents (Mathieu *et al.* 2022): Europe: 9045 cases (i.e. 78% of notified cases), America: 2380 cases, Middle East: 104 cases, Asia: 10 cases, Oceania: 30 cases, with an epidemic aspect in some (Spain: 2,447 cases; Germany: 1790 cases; UK: 1736 cases; USA: 1464 cases). For the great majority of them there is no history of travel to infected African countries and no chain of transmission could be established for many of them. At most, for some patients in Spain and Italy, a link with a festive event that brought together 80,000 people in the Canary Islands is evoked, but has not (yet) been confirmed by the scientific authorities (Warren, 2022). The same applies to the incrimination of a gay sauna in Spain (AFP, 2022). The clade in question is still WA and the first genomic comparisons of MPXV genomes from Monkeypox cases that emerged since May 2022 showed that they derive phylogenetically from the WA clade and more precisely from 2017 to 2019 strains obtained from Monkeypox cases identified in Nigeria and from sporadic cases in travelers coming from Nigeria and diagnosed in the UK, Singapore and Israel (Isidro *et al.* 2022; Selhorst *et al.* 2022). The current strains from the 2022 outbreak, however, share 47 nucleotide mutations as compared to those strains from 2017-2019, which is a much higher number of non-random mutations than expected (anticipation of only 2 nucleotide mutations per year for the *Poxviridae* based on a VARV model). The whole question is therefore whether these mutations are associated with a greater capacity for human-to-human transmission or whether circumstances have caused greater human-to-human circulation at the origin of these accumulations of mutations. The first hypothesis is consistent with that of Kugelman *et al.* (2014), who observed deletions in different variants of the CB clade that were statistically correlated with human-to-human transmission. However, 45 of these 47 mutations could be explained by enzymatic processes which are only present in the human species and lead to such nucleotide changes. Thus, repeated passages within the human species could explain these mutations, without adaptive significance. The last two mutations are largely compatible with the supposed mutation rate of the virus, independently of a change in host species and/or its speed of circulation within the human species (Rambaut *et al.* 2022). If at the present time, the genomic data do not seem particularly worrying, it will be important to wait for the results of other genomic analyses to search for the presence or absence of mutations, calculate their frequency of accumulation and deepen their significance.

In addition to ongoing genomic analyses, it might be possible to shed some more light on the current situation by trying to explain all the successive epidemiological changes since 1970.

HYPOTHESES TO EXPLAIN THE EMERGENCE OF HUMAN CASES IN AND OUTSIDE AFRICA

Many authors have attempted to explain the epidemiological developments described above, the main hypothesis being that these are most certainly complex multifactorial phenomena and that the processes at work have at least partially evolved over time. Some of the hypotheses put forward will be briefly summarised here, as the main aim of this article is to try to estimate the risk of humans infecting animals, but not the reverse. However, the current epidemic in Europe is the result of the increase in human cases in Nigeria and some of the knowledge gained in Africa could shed light on the factors involved in the current emergence.

Initial emergence of MPXV in its traditional territories

One of the most common explanations given is the cessation of smallpox vaccination. There are several arguments in favour of this hypothesis: the cross-protection of the VACV vaccine against MPXV due to their genetic proximity; the fact that the eradication of smallpox thanks to this vaccination may have revealed previously masked cases of monkeypox that were no longer attributed to smallpox; greater vigilance against possible residual cases of smallpox at the end of eradication, leading to the discovery of genuine cases of monkeypox (including the first human case); and technological improvements allowing for faster diagnosis and better discrimination between MPXV and VARV when the latter was still present. According to these hypotheses, the initial emergence of MPXV was more of a 'false' emergence than a real one, and the cessation of smallpox vaccination only helped to reveal it. Tiew *et al.* (2017) lent strong plausibility to this hypothesis. They searched for MPXV DNA in 1,000 animals from five species of African squirrels of the genus *Funisciurus* that were kept in museums over a period of 120 years. They managed to find MPXV DNA in 9% of them, including one animal dating back to 1899, more than 50 years before the virus was discovered. They showed that all five species of *Funisciurus* are concerned and even went so far as to consider that the poxvirus that occurred in humans in Africa and against which vaccination was carried out was MPXV from the outset and not VARV.

It would be interesting to carry out similar studies on human remains to test this hypothesis.

Sharp increase in monkeypox cases in the DRC and at least an apparent re-emergence in Nigeria

Increase in zoonotic transmission

Initially, this increase appears to be linked to zoonotic transmission, which is still predominant. Several hypotheses, which are not necessarily mutually exclusive and could even work in synergy, could be envisaged. Of these, we shall consider the following:

- An increase in infection among reservoirs and/or linkage hosts living in primary forests. This would logically lead to an increase

in viral circulation and an increased risk of transmission to humans. An indirect argument in favour of this hypothesis could be the introduction of monkeypox into the USA. Numerous animals, including Gambian pouched rats, had been imported into the USA on several occasions without leading to the emergence of MPXV in the USA. It cannot be ruled out that viral circulation may have increased in wildlife, although this does not explain why no animal or, more importantly, human cases have been reported in Ghana until June 2022 (still without any confirmation of an autochthonous circulation of MPXV). Basing their conclusions on longitudinal studies in the Tai forest, Patrono *et al.* (2021) consider the hypothesis of the reality of a virtual disappearance of MPXV followed by a sharp increase in its circulation and monkeypox cases as plausible. They base their argument on the fact that an analysis of monkey carcasses covering the 25 years during which the virus appeared to have disappeared did not find any evidence of the virus (although their sample size was small). They suggest that this increase could have been driven by ecological changes, in particular by the significant reduction by humans in the size of primary forests and subsequent destruction of the habitat of NHPs and changes in their environment. This could have led the NHPs to a change in their behaviour, and in particular to aggressive and predatory behaviour, generating more skin or mucous contacts with both conspecifics and prey, especially small mammals that are reservoirs of the virus or spillover hosts eaten more frequently by chimpanzees. However, this hypothesis does not mention the impact that deforestation could have on these small mammal populations, either in terms of numbers or in terms of changes in their interactions with humans or their environment.

- An increase in the human/animal interface. It seems plausible that the reduction of primary forests accompanied by the intrusion of humans into areas previously occupied by animals could foster the zoonotic transmission of MPXV: humans destroy the forest to extend their villages and/or farm the land (which potentially generates sources of food for small mammals, likely to facilitate their proliferation and thus the circulation of the virus), and many may continue to hunt and consume bushmeat. Nakazawa *et al.* (2013) point out that various species of sciurids receptive and/or susceptible to MPXV infection, such as squirrels of the genera *Funisciurus* and *Heliosciurus*, in addition to *Cricetomys*, live at the forest edge. Their demography and contact with humans could therefore be affected by human actions affecting their environment. Approaching areas likely to be inhabited by these African squirrels is significantly associated with an increase in monkeypox, albeit with a low odds ratio (OR = 1.32; 95% CI 1.08–1.63) (Fuller *et al.* 2011). The same authors point out that the 1970s and 1980s were not the only period of human intervention, but rather a period of large-scale replacement of forests by urban areas, fields and pastures. Their modelling work lead to the conclusions that changed land use is more conducive to MPXV transmission than are forested areas. Nguyen *et al.* (2021) showed that between 1975 and 2013, a sharp increase in cases occurred in Nigeria in areas of very dry savannah, traditionally unfavourable to the transmission of the virus to humans, and that this was due to the fact that much of

this savannah had been converted to agricultural land, which is more conducive to the creation of interfaces between wildlife and humans.

- Cessation of immunisation coverage in a context of high population growth. It is clear that the cessation of vaccination has strongly contributed to the increase in susceptibility to MPXV. Nguyen *et al.* (21) have shown using a statistical model that in 2016, one year before the sudden re-emergence of monkeypox in Nigeria, only 10.1% of the Nigerian population was still vaccinated against smallpox, resulting in a drastic reduction in population immunity (2.2% in 2018 versus 65.6% in 1970). This is evidenced in particular by the progressive increase in the age of patients, as already mentioned, even though a zoonotic source was still most frequently identified (if this had not been the case, this increase could have been attributable to certain sexual practices in a more urbanised context than in the past). In addition, Nguyen *et al.* (2021) found that the four most affected states had a higher annual population growth than the average state and that in these four states, the frequency of monkeypox cases was more than twice as high as in the other states.

Increased human-to-human transmission in and outside Africa

Increase in the proportion of infected individuals

From a certain level of incidence of human cases, it seems logical that transmission accelerates in an urban environment and within a family setting (the example of four Gabonese children from the same family could be an illustration) given that this virus can be transmitted by the cutaneous, mucous and respiratory routes either directly or indirectly (i.e. via contamination by patients' secretions and excretions of the environment). The same applies to the nosocomial risk, especially when cases are hospitalised (with reported examples).

Individual and collective human behaviour

It is likely that in low-income families (but not only), sleeping in the same bed, eating from the same plate or drinking from the same glass is a type of behaviour that fosters viral transmission (Bunge *et al.* 2022). Dietary behaviours can also have an impact on the level of risk, including taste for bushmeat (even in urban areas) (Diaz, 2021). This can lead to skin infection (during food preparation) or even mucosal infection (contact of the oral cavity with the virus in undercooked food). Sexual behaviour has probably played and continues to play a significant role in recent outbreaks, as shown by the frequency of genital lesions observed during recent episodes of monkeypox in Nigeria, the CAR, the DRC and in the ongoing epidemic outside Africa. In this context, participation in collective festive events can greatly amplify the spread of MPXV.

Level of immunity and health

Here again, the cessation of vaccination has no doubt greatly contributed to the virus becoming endemic to urban areas. In addition, the level of individual and collective immunity – strongly affected by the advent of AIDS from the 1980s onwards – must have intervened in Africa both at the animal/human interface and as a facilitator of inter-human transmission

(Ogoina *et al.* 2020). Other comorbidities may also have been involved, notably malaria or other conditions reported in clinical cases, though this is certainly not exhaustive. It should be added that the increased movements of people, whether within infected countries or to other countries (especially non-African countries), facilitates secondary spread (Mauldin *et al.* 2020; Hobson *et al.* 2021; Adler *et al.* 2022; Costello *et al.* 2022).

Indirect transmission of the virus

In the light of the results of Patrono and colleagues (Patrono *et al.* 2020), and in addition to the virus's strong resistance in the environment, which facilitates indirect transmission, the role of flying insects should also be explored as they are abundant in countries where the temperature favours their activity.

Evolution of the virus

An increase in mutations or deletions has been observed in both the CB and WA lineages and appears to go hand in hand with an increase in the frequency of human-to-human transmission (Kugelman *et al.* 2014; Rambaut *et al.* 2022). It is entirely consistent that mutations increase as the frequency of host-to-host transmission increases. It is also consistent that maintenance within a single species – in this case the human species – is likely to result in the selection of variants more adapted to that species, though this remains to be demonstrated at this time, as mentioned above.

All in all, various mechanisms (probably associated) are likely to have contributed to the emergence of monkeypox and the successive changes in its epidemiology up to its current emergence outside Africa. Can we rule out the possibility that animals in non-African countries affected by this emergence may in turn be involved?

WHAT ROLE(S) IS/ARE ANIMALS LIKELY TO PLAY OUTSIDE AFRICA IN THE CURRENT HUMAN MONKEYPOX EPIDEMIC?

As monkeypox is a zoonotic disease, it is logical to ask whether animals can become infected and play a role in the infection cycle in Africa. In particular, it is legitimate to ask the following two questions:

- What do we know about the intrinsic ability of animals from infected countries outside Africa to become infected?
- What is the risk of these species becoming infected and then serving as spillover hosts or even as an indigenous animal reservoir?

Intrinsic ability to infect animal species from countries outside Africa

As we have seen above, the current state of knowledge does not allow us to inventory receptive and/or susceptible species in the countries where the virus is circulating. It is therefore a fortiori only possible to make speculations for species in non-African countries where the virus is currently actively circulating in humans, based on available field and experimental data and

knowledge of Orthopoxviruses. It should be noted that if MPXV is tending to adapt to humans, resulting in more efficient human-to-human transmission, this could lead to decreased adaptation to animals, but this hypothesis needs to be tested.

Rodents and other small mammals

In the case of rodents, the risk of infection is to be considered non-negligible a priori. This is because on the one hand they are considered more than likely reservoirs in African countries, and on the other, surveys and/or laboratory inoculations have demonstrated that various rodents living outside the African continent are receptive (and some susceptible) to MPXV. For the most common synanthropic and domestic species (exotic pets), laboratory studies have shown the lack of susceptibility and even receptivity of highly ubiquitous rodents (at least when adult) such as rats, mice, hamsters and guinea pigs. For adult rats, given that the dominant synanthropic species in Europe and France is the brown rat (*Rattus norvegicus*), which is also the source of laboratory lines and pet rats, laboratory data (Parker and Buller, 2013) could lead to the exclusion of its ability to play a role in MPXV transmission. However, in addition to the fact that laboratory strains correspond to particular lineages compared to wild rats, only one inoculation trial has been described in white rats, which indicates a 100% lethality rate in newborn pups (Marennikova *et al.* 1976). Furthermore, as for cats, brown rats kept as pets are considered a major source of zoonotic CPXV contamination for humans. The same reasoning can be applied to the other rodents mentioned above (mice, hamsters and guinea pigs), which have also been implicated in the carriage and/or transmission of CPXV to humans but are considered experimentally non-susceptible to MPXV as adults (Parker and Buller, 2013), with the exception of the Thai house mouse (*Mus musculus castaneus*), as opposed to the common grey mouse (*Mus musculus domesticus*) (Reynolds *et al.* 2019). In addition, many other wild and some synanthropic and even exotic pet rodent species are present in the countries where recent human cases have been reported. Indeed, some of them (such as the bank vole (*Myodes glareolus*) or the wood mouse (*Apodemus sylvaticus*) are considered to be CPXV reservoirs (Chantrey *et al.* 2013). Although it would be inaccurate to infer their ability to serve as reservoirs or spillover hosts for MPXV from this observation, their diversity and the role played by prairie dogs in the USA in 2003 encourage us not to rule out any hypothesis. In this respect, the case of squirrels is even more critical since they are directly involved as reservoirs of MPXV in Africa; they are also abundant in the non-African countries currently concerned by the monkeypox outbreak, and belong to the *Sciuridae* family, like the American prairie dogs that are very susceptible to MPXV. It is however important to remember that European and American squirrel species are very different from African squirrel species, as the term 'squirrel' includes very disparate species of climbing rodents. The risk of squirrels becoming infected should therefore not be considered negligible. No data are available on them, but the risk is potentially even greater for Siberian chipmunks (*Eutamias sibiricus*). Although they are now banned from being kept as pets in France, this is not necessarily the case in all countries.

Domestic carnivores

There have been no reports of infection among dogs and cats in areas where MPXV is enzootically present. One survey of 67 cats showed no seroconversion, but this was an ad hoc survey conducted in an area of MPXV circulation (Khodakevich *et al.* 1987). The fact that the literature is almost silent on the subject does not mean that they could not amplify the virus, at least transiently. It should be remembered that felines are highly susceptible to CPXV, which is thought to be an ancestor of MPXV, and that the hypothesis of their contamination from excreting humans or their infected environment remains plausible. Dogs are apparently much less susceptible to CPXV, with far fewer case descriptions and very limited lesions when present (von Bomhard *et al.* 2011). In the context of the emergence of vaccinia among humans in Latin America, which seems concomitant with the cessation of smallpox vaccination, certain studies have shown that the strain of VACV which circulates in Brazil within a reservoir supposed to be associated with wild rodents, can also infect dogs asymptotically (Abs and/or viral DNA) (Costa *et al.* 2018; Peres *et al.* 2016). VACV DNA was also found in a minor study in asymptomatic cats (Costa *et al.* 2017).

Non-human primates

Given the susceptibility of both African and Asian species both in the wild or in captivity (Gispén *et al.* 1967), confirmed for some of them by experimental inoculations, any NHP species should be considered a priori as susceptible.

Food-production animals

The risk to food-production animals is largely unknown. The study by Khodakevich and colleagues (Khodakevich *et al.* 1987) showed no seroconversion among sheep and goats in an area of MPXV circulation, but this study involved only 200 animals and remains the only one of its kind to date. It may be noted that ruminants are susceptible to various Orthopoxviruses, whether non-zoonotic (CMLV, BPXV) or zoonotic for cows (CPXV, VACV). Indeed, CPXV is thought to be an ancestor of MPXV. Finally, the risk of infection of production rabbits should not be overlooked. Not only can rabbits be infected by an *Orthopoxvirus* which is specific to them (Rabbitpox virus or RPXV) but newborn laboratory rabbits are very susceptible to MPXV and certain studies have shown a real susceptibility of adult rabbits, as already mentioned (Parker and Buller, 2013).

Probability of animals being infected by humans and consequences in terms of the development of reservoirs or link hosts, including their probability of exposure

What then is the degree of risk of contamination by humans for animals in our countries? The first obstacle to transmission is linked to the fact that MPXV seems to be a virus that is not easily transmitted as it appears necessary to be in close proximity to infected individuals (direct contact with monkeypox skin lesions or scabs; respiratory droplets from an individual with monkeypox) or to an environment soiled by their secretions. With this in mind, let us now consider exotic pets, which are in

close proximity to humans (risk of contact, transmission by aerosols and the contaminated environment). If they were to prove receptive, they would at most amplify the virus in their owners' homes. Housed in isolation or in very small numbers within a household, it is therefore highly unlikely that they will lead to the formation of a reservoir whose adaptation to a new virus can only be conceived on a population scale allowing the infection to persist or even amplify over time. At most, if the infecting person works in a rodent pet shop, this could lead to multiple outbreaks among different pet owners, as was observed in the cowpox outbreak brought about by the sale of exotic pet rats by a 'wholesaler' from Czechoslovakia to pet shops in France, Belgium and Germany (Campe *et al.* 2009; Ninove *et al.* 2009), and in the 2003 US monkeypox outbreak.

With regard to wild synanthropic rodents, the current assumption is that they are unlikely to be susceptible to MPXV, so the likelihood of them becoming infected from the contaminated environment of an infected person is low.

With regard to non-synanthropic wild rodents, some of which could be receptive or even susceptible, the probability of contamination by humans (and by any potential spillover host) is to be considered very low in the absence of contact with humans or with their contaminating secretions. As a result, the risk of a reservoir being formed is currently considered unlikely. The only potential exception is grey squirrels, which infected humans could approach in order to feed them, a common behaviour in North America and the UK. This could theoretically be possible in the case of excretory humans (Hobson *et al.* 2021) and could then pose a significant risk if these grey squirrel species were found to be receptive or susceptible to MPXV.

As far as NHPs are concerned, there are very strict laws governing their detention. The risk of an NHP becoming infected by an infected human, except in the case of illegal detention, is therefore minimal. There is a potential risk of infection by zoo keepers, especially among very young and thus highly susceptible animals that may be in close contact during feeding and play times in particular. Veterinarians called upon to handle these animals or their corpses during autopsy may also be a source of infection.

Finally, with regard to domestic animals, the hypothesis of cats being infected by excreting humans or their contaminated environment remains plausible, provided that the cat is receptive to MPXV. On the other hand, it seems reasonable to assert that cats are at most only occasional amplifiers and spillover hosts, with or without lesions, as in the case of CPXV. Dogs are supposed to be less susceptible but can also be clinically infected by SPXV and are receptive to VACV. Thus, the role of dogs as occasional amplifiers of MPXV cannot be excluded neither. Nothing is known about ferrets apart from the fact that they are able, like dogs and cats, to replicate recombinant vaccines including a vaccinia vector. As for cattle, it appears from the above elements that they could also potentially be infected by a human with MPXV. According to this hypothesis, they could play the same role as cats if we refer to their receptivity and sensitivity to CPXV. However, the likelihood of them becoming infected would be extremely low (as it would require a human caring for cows to be infected and excreting) and cattle would need to be susceptible. Even if cattle were to be infected, there

would be a numerically very small risk of infecting humans, even considering that cows could excrete the virus.

In fine:

- The risk of building up wild or domestic reservoirs is to be considered very low.
- The risk of commensal wildlife becoming infected is low for some species, and the risk of them serving as spillover hosts and being the source of zoonotic transmission is almost nil.
- The risk of exotic pets becoming infected is low for some species, as their susceptibility is considered low (except for young animals). Furthermore, the risk of them serving as spillover hosts and becoming a source of zoonotic transmission is very limited, while the risk that they could currently act as a reservoir can be considered zero.
- The risk of infection of domestic cats and dogs cannot be totally ruled out and their ability to reinfect humans in turn will depend on their susceptibility.

In conclusion, the risk of human-to-human transmission in non-African countries is to be considered much higher than the risk of zoonotic transmission, and the risk of establishing an animal reservoir is currently low, although particular vigilance is required for squirrels. The study of the receptivity and susceptibility of indigenous wild animal species as well as domestic species (food production animals and pets, including exotic pets) should however be encouraged, even in such a context, if only to refine the risk analysis and therefore control measures.

WHAT ACTIONS SHOULD BE TAKEN TO INTERRUPT CURRENT HUMAN-TO-HUMAN TRANSMISSION?

Even if such deliberations and actions go far beyond the scope of this article and the competencies of the veterinarian writing these lines, there are a few major principles that should be recalled, as this is (still!) a zoonotic disease and stopping the current human epidemic would be the best way to prevent the occurrence of any risk of reverse zoonosis, i.e. transmission of MPXV by humans to animals. The main principles of the actions, in terms of those aimed at preventing strict human-to-human transmission, can be summarised as follows:

Identify and manage suspected cases

In France, internal procedures for health personnel have already been drafted and disseminated so that medical staff are armed to establish a suspicion of monkeypox and act appropriately if the suspicion is raised, in particular to determine whether or not hospitalisation is necessary. This is accompanied by a mandatory declaration to the regional health agency, ARS. The stakes are very high: it is crucial not to miss potential cases, to prescribe immediate isolation at home (unless hospitalisation is required, in which case suspects are placed in isolation in the hospital) so as to prevent secondary cases and to trace possible contacts. Indeed, a patient is considered to excrete the virus as soon as clinical signs appear. Biosafety recommendations are

prescribed to health workers who deal with such suspects (wearing gloves and masks). The question arises as to whether health workers will consider asking suspects to isolate themselves from their animals insofar as possible, as no instructions have been given in this regard, apart those published by the COREB website (Coordination opérationnelle - Risque épidémique et biologique / Operational Coordination - Epidemic and Biological Risk - National Mission).

Actions in the event of confirmed infection

If the suspected case is confirmed, the following actions are implemented:

- Isolation of patients for 21 days after the onset of the clinical phase. After this period patients are no longer considered to excrete the virus (based on published data, it would be appropriate to test their secretions for DNA, especially if there are still infectious particles in these secretions after this time).
- Treatment of patients during their period of isolation.
- Recommendations for cleaning and disinfection of the patient's environment are also important.
- Management of contacts with post-contamination vaccination to prevent the occurrence of monkeypox. A highly effective vaccine is available specifically for this purpose.

To control the epidemic, it is of key importance to trace and manage contacts. According to the available data, despite the efforts of health authorities in the countries concerned, for the time being many cases cannot be linked epidemiologically, suggesting that the epidemic will continue to spread.

What about preventive vaccination, which is also available? It seems unlikely that the disease will spread to the point where collective vaccination is required, which is fortunate because this could be a very unpopular measure. Targeted vaccination (of certain professionals or at-risk groups) may be appropriate, but such a measure could not only be seen as ostracizing, but would also represent a failure of the control strategy to manage cases and their contact(s).

ARE THERE ANY ACTIONS TARGETING ANIMALS THAT SHOULD BE RECOMMENDED?

In the case of monkeypox, actions under the "One Health" approach should aim not only to avoid human contamination from animals in Africa, but also to avoid animal contamination from humans in non-African countries affected by the current epidemic.

Actions upstream of human infection in African countries where infection is enzootic and endemic

Formally identifying reservoir species remains a priority. While it will not be possible to eliminate the perennial sources of infection (as it can be assumed that this is a multi-species wild reservoir), it will be possible to issue recommendations to limit or even eliminate contact with animals of the species concerned and their carcasses, particularly in the context of hunting.

Identifying the level of infection of NHPs will allow the populations that hunt them and consume bushmeat to be informed of the risk of infection, particularly in the areas where the CB lineage circulates. Regardless of lineage, these measures would not only protect local and national populations but also reduce the risk of MPXV being exported out of Africa.

The creation in 2019 of a project called Afripox (Institut Pasteur, 2020) in the framework of a partnership between the CAR and France (Institut Pasteur) is to be welcomed in this context. It should be noted that the CB lineage has never been reported outside Africa to date, and it is particularly desirable to prevent its emergence elsewhere, even though a lower case-fatality rate than in Africa could be expected. In this context, it is worth considering why non-African countries have been spared by this virus, but such a debate is beyond the scope of this article.

Actions downstream of human infection in non-African countries currently affected by the monkeypox outbreak

Prevention of animals being infected by humans

As mentioned above, it is clear that controlling the current outbreak would be the best way to limit or even eliminate any risk of animal infection. This control of human-to-human transmission is mediated through medical (vaccination of contacts, treatment of cases) and health measures (identification and notification of cases, isolation of cases, cleaning and disinfection, tracing of contacts, etc.).

Downstream of the human infection, and taking into account the above considerations regarding the at least theoretically greater risk of contamination of certain species rather than others, the following recommendations can be made in order to limit any risk of retro-transmission (reverse zoonosis) from infected humans to animals likely to amplify or even retransmit MPXV, if only as a precautionary principle:

- Humans who have contracted monkeypox should be isolated for three weeks and should not approach squirrels during this period, for example to feed them.

- In addition, it is desirable that humans with monkeypox are not put in a situation where they are approached by synanthropic rodents or their secretions. It is currently recommended to eliminate these pests from human environments, but this recommendation could become a rule to be strictly enforced in the environment of monkeypox patients, including in hospitals, for at least three weeks after the onset of symptoms. The risk of transmission of MPXV by people in extreme precariousness (e.g. homeless, prisoners...) must be considered here in particular.

- Finally, it is advisable to keep pets away from anyone with monkeypox for at least three weeks after the onset of symptoms. In addition, professionals working with animals – and in particular veterinarians and veterinary surgeons (VSAs) (Croft *et al.* 2007) – should as a precautionary measure routinely wear gloves and masks when handling animals, since the owner of an animal will not necessarily inform them that he/she or a family member has monkeypox. It is advisable for such professionals to systematically ask, before any action is taken, about the possibility of monkeypox in the environment of any animal they

receive in an animal clinic or for consultation, especially if it is an exotic pet rodent. They should also ask for the date of onset if there are cases. Particular care should then be taken to clean and disinfect the consultation table and all instruments used for these animals, using gloves. The question could also arise, at least theoretically, of vaccinating animals in contact with a human infected with monkeypox to prevent the occurrence of the disease as in humans. Apart from the fact that no vaccine currently has a marketing authorisation for animals, it cannot be ruled out that the vaccinated animal is protected against clinical disease but continues to excrete the virus asymptomatically, thus silently exposing other animals (potentially including wild animals likely to relay the infection) and humans.

Measures in the event of suspected monkeypox in a domestic animal

Although hypothetical, this risk should be anticipated. If an animal shows clinical signs and lesions suggestive of monkeypox and is brought to the clinic, it would be advisable (if there is still time) for the animal to be isolated on arrival. The owner and family, as well as the veterinarian and VSA, should take extra precautions when handling the animal (gloves and mask). The animal should be isolated during the clinical phase, either at the owner's home or during hospitalisation in appropriate facilities adapted to ensure this isolation. In the latter case, the area where the animal is kept should be considered as 'contagious', with careful cleaning and disinfection of the environment during the disease and especially after the end of the disease or the death of the animal (Croft *et al.* 2007). This would clearly raise the issue of how to manage a suspected or actual case, as animal monkeypox is not a regulated disease in France or neither in Europe. It might be advisable to inform the DDPP (Direction Départementale de la Protection des Populations / Departmental Directorate of the Protection of the Populations) of the occurrence of a suspected or actual animal case.

Notifying the DDPP would allow the ARS to be made aware of the existence of such cases and to trace any human contact with the animal, within or outside the family that is hosting it. It may, however, be difficult to confirm a suspicion of animal monkeypox in the absence of regulations.

Finally, there is the question of how to manage the carcasses of animals that may have monkeypox. It should be recommended that corpses be treated as infectious material, and therefore sent to a rendering company, but as this is an unregulated disease, it seems difficult to impose such a measure on owners who have already been affected by the death of their animal. At the very least, the corpse should be handed over to the owner in a sealed bag that cannot be opened and with strict recommendations for the company responsible for the animal's funeral.

CONCLUSION

In conclusion, the current unexpected episode of monkeypox owes no part to animal transmission, at least considering only the 'post-African' part, which involves only human-to-human transmission. In the African cradle of MPXV, the share of zoonotic transmission has also dropped while human-to-human

transmission has increased considerably, making it inevitable that the virus will be exported outside Africa by people leaving endemic countries. While the risk of an animal reservoir outside Africa is highly unlikely (but not entirely impossible given the current state of knowledge), this episode highlights the importance of a control effort based on the "One Health" concept upstream of human contamination in countries where the virus is traditionally present. Monkeypox emergence, both in Africa and outside Africa illustrates how a combination of events (here in particular the end of smallpox vaccination, demographic explosions, societal changes and rapid human movements over

long distances) may eventually lead to near-global emergences. Limiting ecological disturbances and animal-human interfaces could help avoid the risk of zoonotic transmission, thereby reducing the risk of further amplification between humans. In non-African countries affected by monkeypox, controlling this human episode is an important contribution to the effort needed to prevent the risk of even theoretical contamination of indigenous animals/species in the affected countries. The same applies to common sense measures at the interface between humans and animals in these countries.

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Table II : Highly hypothetical estimates of the level of risk of MPXV infection in animal species present in France, based on their assumed receptivity and/or susceptibility and their possible interactions with infected humans and/or other potentially infected animals, and measures to prevent animal infection that might be recommended in the event of confirmed human infection

Animals		Data relating to their receptivity and/or susceptibility		Interpretative hypothesis as to their role as host and/or their host potential
		Terrain	Laboratory (routes consistent with natural infection)	
Non-Human Primates	African and Asian NHP	Susceptible to very susceptible: Primary forests, zoos, experimental units	Susceptible to very susceptible	Accidental hosts
	African squirrels	1 clinical case MPXV+ A least highly receptive (High prevalence of Abs in infected areas)	-	Potential reservoir hosts
Sciuridae	Prairie dogs (USA)	Susceptible to very susceptible (US outbreak episode 2003)	Susceptible to very susceptible	Non-African hosts with reservoir potential?
	Red squirrel	-	Very susceptible at high dose	
Other small or medium sized mammals, including rodents	Other small wild African mammals	Receptive to susceptible: Gambian pouched rat, jerboa, common rufous-nosed rat, African hedgehog, brush-tailed porcupine, Lorraine's African dormouse: MPXV+ or DNA or Abs	Very susceptible: Gambian pouched rat, African dormouse, Natal multimammate rat, cotton rat	Potential reservoir hosts
	Other American mammals	Common opossum, grey short-tailed opossum, American woodchuck: MPXV+ or DNA or Abs	Thirteen-lined Ground Squirrel (<i>Ictidomys tridecemlineatus</i>)	Non-African hosts with reservoir potential?
	Brown rat and house mouse		Newborns: very susceptible Adults: not susceptible (apart the Thai house mouse)	No role? Accidental hosts if newborn? Potential spillover hosts?
	Hamster, Guinea pig	-	Not tested by routes compatible with natural infection, only adults have been tested	
Lagomorphs	Rabbit		Newborns: very susceptible Adults: not susceptible to very susceptible	Potential accidental host
Felids	Cat	Non receptive (no Abs in infected areas)?, but limited study	-	No role? Accidental hosts? Potential spillover hosts?
Small ruminants	Sheep and goat	Non receptive (no Abs in infected areas)? but limited study	-	No role? Accidental hosts?

Abs = antibodies. - : No data



Table II : Highly hypothetical estimates of the level of risk of MPXV infection in animal species present in France, based on their assumed receptivity and/or susceptibility and their possible interactions with infected humans and/or other potentially infected animals, and measures to prevent animal infection that might be recommended in the event of confirmed human infection

Category of species	Species	Data relating to their receptivity and/or susceptibility		Direct (D) or indirect (I) interactions with humans	Interactions with possibly infected animals (primary or secondary hosts)*	Very hypothetical level of risk of infection	Measures to prevent potential infection of animals in the event of confirmed human infection, in the context of the current outbreak of monkeypox
		Direct	Indirect				
Production animals (PA)	Cattle	-	Susceptibility to CPXV	+++ (D)	NSW, SW, P	None to minimal	Isolation of the farmer if infected, rodent control (deratting, reduction of food resources, etc.)
	Small ruminants	No Abs in an infected area	-				
Pets (P)	Cat	No Abs in an infected area	Susceptibility to CPXV	++++ (D et I)	NSW, SW, P	None to extremely low	Isolation of the owner if infected, disinfection of the environment, rodent control, collar with bell)
	Dog, Ferret	-	-	++++ (D et I)	SW, P	None to minimal	
	Rabbit	NB experimentally highly susceptible, adults potentially susceptible	-	+++ (D et I)	P	Low to fairly high (NB)	Isolation of the owner if infected, disinfection of the environment, rodent control
	Rat, mouse	NB experimentally very susceptible	-	++++ (D et I)	P, SW?	Extremely low to fairly high (NB)	
	Hamster, guinea pig	Mild adult infection (intracardiac route), NB not tested	-	+++ (D et I)	P	Almost nil to low (NB?)	
Synanthropic wildlife (SW)	Siberian chipmunk	-	African sciurids: presumed reservoirs	+++ (D et I)	P?	High in absolute terms but currently almost zero in France	Holding currently prohibited in France (residual risk with "old" chipmunks born before 2017)
	Rat, mouse	NB experimentally very susceptible		++ (I)	NSW	Minimal to extremely low (NB)	Rodent control
	Dormouse	-	Abs in African dormice	+ (I)	NSW, SW	None	Rodent control
	Hedgehog	-	Abs in African hedgehogs	+ (I)	NSW, SW(?)	Almost none	None (predators ?)
Non-synanthropic wildlife (NSW)	Rodents	-	Abs in African rodents	-	NSW, SW, P	Almost none to minimal	Rodent control
	Red squirrel	Experimentally very susceptible	African sciurids: presumed reservoirs	-	NSW, SW?	None to almost none	None (predators ?)
	Gray squirrel	-		+ (D) (feeding)	NSW	None to almost none (France)	Do not approach them to feed them, absolute prohibition if human beings are sick (isolation)

Abs = antibodies, - : No data
NB = Newborn

