MONKEYPOX VIRUS – ZOONOTIC CHARACTERISTICS
LIVING EVIDENCE PROFILE
December 8, 2022

Living Evidence Profile: What is the available evidence related to the zoonotic characteristics of monkeypox virus?

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OVERARCHING QUESTIONS.

What is the available evidence related to the zoonotic characteristics of the Monkeypox virus (MPXV)?

- What evidence is relevant to the Canadian context?
- What are the research gaps?

WHAT WE FOUND.

This living evidence profile (LEP) presents evidence from a total of 148 articles (including 59 articles selected from 2000-2017) that met eligibility criteria (see Box 1 for a description of our approach). We have structured our findings using the revised organizing framework below.

REVISED ORGANIZING FRAMEWORK.

- Reservoirs of MPXV
- Transmissibility of MPXV
    - Animal-animal
    - Animal-human
    - Human-animal
    - Any of the above risk associated with animal waste, wastewater
- Clinical infection in animals (incubation period, shedding)
- Clinical presentation in animals
- Susceptible animals
- Handling of infected susceptible animals

In this evidence synthesis we had initially collected evidence from January 1, 2017 - October 28, 2022. The evidence from a total of 89 articles were presented in 7 successive iterations of the LEP. In this version we have added evidence from 2000 -2017 to the previous iterations of the LEP. In the 2000-2017 evidence synthesis a total of 589 articles were screened. **NEW in this version is the inclusion of 59 additional eligible articles:**

- 2 guideline documents
- 1 full systematic review

BOX 1. OUR APPROACH

We conducted a lookback search, identifying evidence documents published from January 1, 2000 to October 28, 2022 addressing the LEP questions by searching Medline and EMBASE (over the Ovid platform).

We searched for clinical and public health policy guidelines, full systematic reviews, narrative reviews, rapid reviews, primary studies and non-empirical evidence document (editorial, commentaries)

We assess the quality of reporting and methodology, as well as risk of bias, using AMSTAR 2 for systematic and rapid reviews, AGREE II for guidelines, and Newcastle-Ottawa Scale for cohort and case-control studies.

We have included preprints - however, due to an executive decision made by the stakeholders, published editorials, letters to the editor, and commentaries were not included in this iteration. In-depth assessment will be conducted should pre-prints be published in future.

This LEP iteration aims to provide a summary of key findings and details of included eligible evidence documents available on the zoonotic nature of monkeypox globally.

This living evidence profile was prepared in the equivalent of 30 days of a 'full-court

- 25 non-systematic reviews
- 22 single studies
- 6 published reports
- 3 editorials and commentaries

We outline in narrative summary below our key findings related to the question. **Within each domain, we first present the summary of new evidence found in the most recent search followed by existing evidence from previous iterations. Evidence from domains that were later excluded from the organizing framework are also presented in this section (description of the virus, treatment of animals infected with MPXV and additional perspectives).**

Table 1: Provides details of potential animal reservoirs of MPXV, based on evidence identified to date
Table 2: Provides details of potential susceptibility of various animal species to MPXV infection, based on evidence identified thus far
Table 3: Provides a summary of number of evidence documents, by type, for each domain of the organizing framework
Table (4a – 4j): Provides details about key findings and quality assessments of the evidence documents relating to each domain. Domains for which we no longer collect evidence are also included as separate tables. See ***Appendix A*** for a history of the modifications to the LEP throughout the course of the project.

For this evidence synthesis (including evidence from 2000-2017 lookback synthesis) a total of 15/148 articles were found to be eligible for quality assessment. We used specific quality assessment tools based on the study design to assess the quality of these articles (see ***Appendix A*** for details). The quality of evidence presented in this LEP ranges from critically low to moderate category, with 11 of the 15 articles found to have critically low evidence. Hence, we recommend that any decision made based on evidence presented in this LEP needs to account for any methodological shortcomings in the included articles. However, one thing that needs to be noted is that the articles included in this evidence synthesis mostly state facts as opposed to assessing the effectiveness of an intervention or program for which the quality assessment tools were targeted.

A detailed summary of our methods is provided in ***Appendix A***. ***Appendix B*** lists the titles and characteristics of our included studies (original and those included in the current iteration). ***Appendix C*** lists our excluded studies and the reasons for exclusion (original and those excluded in the current iteration).

NARRATIVE SUMMARY.

Below are our findings (results) related to each domain of the organizing framework.

DESCRIPTION OF THE VIRUS:

This domain was included in the original organizing framework and sought data published between January 1, 2017 and September 2, 2022, at which time the domain was no longer prioritized for updating and the search for both new and lookback evidence was discontinued. The searches yielded 25 articles that provide a description of the virus: 1 systematic review, 1 scoping review, 2 single studies, 19 non-systematic reviews, 1 published report, and 1 editorial.

Existing Evidence:

A systematic review, (1) documenting the findings from 10 peer-reviewed studies and 1 published report has described the MPXV to have two distinct genetic clades, the Central African and West African clade.

One scoping review (2) described MPXV's two primary clades based on case-fatality ratios (CFR) and prevalence, with the West African variant having an estimated 4% CFR and the Congo Basin variant have a 10% CFR. The authors also specify a reclassification based on genetic lineages, with the aforementioned clades named as A.1 and A.2, with the newly emerging clade in the 2022 outbreak as B.1.

Two primary studies have reported on the morphologic and evolutionary features of the MPXV. One (3) has described the Monkeypox to be a member of the Orthopoxvirus (DNA virus) genus. This virus is endemic to central and western African countries. It was first identified in 1958 as a pathogen of *Macaca cynomolgus* (then in use as laboratory animals) and then in 1970 was described as a human pathogen in Democratic Republic of Congo. Another *primary study of cross-sectional design* (4) examined the evolutionary history of 337 documented MPXV genomic sequences from GISAID and Viral NCBI databases as of June 29, 2022. The authors noting significant evolutionary divergence of the strain associated with the 2022 outbreak in non-endemic countries from the previously identified West African and Congo Basin clades endemic to West and Central Africa. This is indicative of the most recent MPXV strain (codenamed the B.1 lineage) resulting from a stochastic evolutionary event at some point during the endemic stages of monkeypox disease, leading to its further diversification and potentially expanding its host range.

Ten non-systematic reviews (5–14) has described the MPXV as an enveloped double-stranded DNA virus (200 to 250 nm). MPXV replicates within the cytoplasm of infected cells rather than in the nucleus, in contrast to many DNA viruses, as they can produce the required proteins for both transcription and replication. These reviews have also recognized the two Monkeypox virus clades: West African and Congo, Basin. *Four non-systematic reviews* (15–18) described monkeypox (MPXV) as one of 10 species in the Orthopoxvirus genus, including variola (smallpox) most notably. *Four non-systematic reviews* (19–22) describe MPXV as a double-stranded DNA virus, with a recent genomic analysis stating that the current outbreak is closely related to the 2018 strain exported from Nigeria. These reviews have reported that the MPXV was first discovered during an outbreak among Cynomolgus monkeys in Denmark in 1958. It was first recognized in 1970 when a nine-month-old boy became infected in Democratic Republic of Congo (DRC). MPXV is a double-stranded DNA virus, with differing characteristics between clades (translating to greater case fatality in the endemic Congo Basin clade, unlike the more widespread West African clade). *Box 2 and Table 2* provide descriptions of the virus. Recent evidence has also indicated that cohabitation of multiple subclades, at least one of which is suspected to have propagated the current 2022 outbreak of monkeypox (14).

A mortality and morbidity report by Durski et al. (23) has also described the morphology of the MPXV.

One editorial (24) highlights the entry of poxviruses (of which MPXV is a part) into cells is independent of host-specific receptors, elevating its potential to infect many species. While MPXV's genome size is not restricted like other poxviruses, it is unclear what role this plays in its increased transmissibility in humans.

Box 2. Description of MPXV.

- MPXV is described as an enveloped double-stranded DNA virus (200 to 250 nm). MPXV replicates within the cytoplasm of infected cells rather than in the nucleus, in contrast to many DNA viruses, as they can produce the required proteins for both transcription and replication.
- Recent evidence has suggested that at least one of the clades associated the MPXV virus to have propagated the current 2022 outbreak. Evidence has also noted significant evolutionary divergence of the strain associated with the 2022 outbreak in non-endemic countries from the previously identified clades. Leading to its further diversification and potentially expanding its host range.

RESERVOIR OF THE VIRUS:

To date, there are 87 articles which present and discuss potential reservoirs of the virus: 1 guideline document, 4 full systematic reviews, 1 rapid review, 53 non-systematic reviews, 15 single studies, 9 published reports, 1 preprint, and 3 editorials. **Table 1 is an updated** list of all animal species that have been identified as natural host or possible reservoir of the MPXV.

New Evidence

For this update, based upon our searches from 2000-2017, we have added:

One guideline by CDC was published on the rules and regulation to manage the MPXV outbreak in the US in 2003 (25). The guideline stated that African rodents are considered to be the most likely natural host of the monkeypox virus. Serologic evidence of monkeypox infection has been found in many other species, including some species of primates, rodents, and lagomorphs (which includes such animals as rabbits).

One systematic review (26) stated Gambian pouched rat and rope squirrel to be most likely candidates for the 2003 US outbreak. Additionally the review mentioned that the MPXV to have been isolated in rope squirrels and sooty mangabey monkeys in the Ivory Coast in 2012.

Six single studies (27–32) reported on MPXV animal reservoirs. Most of these studies were animal related experiments and did not follow the classic epidemiological design. Hutin et al. reported on identification of orthopoxvirus antibodies not specifically those of the MPXV (27). Nakazawa et al. reported that the only MPXV isolate from a wild animal was obtained from a squirrel of the genus Funisciurus. Additionally, some species of rodents were also found to be susceptible to MPXV infection (e.g., species of the genera *Funisciurus, Heliosciurus* and *Cricetomys)* (28). Reynolds et al. (2010) stated the only MPX virus isolated was from a wild-caught mammal obtained from a single moribund rope squirrel *(Funisciurus anerythrus)* collected during an outbreak investigation in Zaire. This study mentioned three genera of African rodent identified to be the source of the 2003 outbreak the United States: *Cricetomys , Graphiurus ,* and *Funisciurus* (commonly known as giant pouched rat, African dormouse and rope squirrel, respectively) (29). Fuller et al. aimed to identify ecological risk factors for contracting human monkeypox. Modelling showed that forest vegetation and presence of the rope squirrel (*Funisciurus species, family Scuridae*) were the most important ecological determinants of the MPXV ecological niche in Sankuru, DRC. The study stated more than one species may act as a MPXV reservoir, given that serosurveys have found various species contain MPXV antibodies. Potential reservoir species that were found to be less important in this study's modelling included: African dormice (*Graphiurus crassicaudatus* and *G. lorraineus*, family *Gliridae*) and giant pouched rats (*Cricetomys species, family Nesomyidae*) (32).

A total *of 20 non-systematic reviews* (33–52) reported on the animal reservoirs of the MPXV virus. The specific role of any particular species as a reservoir has not been established (34). MPXV possesses one of the broadest host ranges among poxviruses (37). It is unclear whether MPXV is transmitted from one host species or multiple host species (49). MPXV may be supported in nature through several animal species, including two genera and six species of squirrels, and nine species of non-human primates (51). African arboreal squirrels of the *Funisciurus* (rope squirrels) and *Heliosciurus* species (sun squirrels) living in secondary forest surrounding human settlements and fields have been implicated previously as probable reservoir hosts for monkeypox virus in Zaire on the basis of antibody data and a single viral isolate from a *Funisciurus anerythrus* squirrel (35,47). The seropositivity rate of *Funisciurus* spp. squirrels have arranged from 24-50% (50). Gambian giant rats (*Cricetomys* sp.) have also been indicated as probable natural reservoirs of MPXV as indicated by the isolation of virus from these species and the high seroprevalence (37). Other possible hosts of

monkeypox virus as demonstrated by positive serological evidence (PCR and/or virus isolation) include: Orangutan (*Pongo sp.*); Cynomolgus monkey *(Macaca cynomolgus*), Rope squirrel (*Funisciurus sp.*), Thomas's rope squirrel (*Funisciurus anerythrus*), Prairie dogs (Cynomys sp.), Dormouse (*Graphiurus spp.*), Gambian giant rat (*Cricetomys sp*.) (36). Large mammals, gazelles, and primates have been singled out as potentially important sources of human infection in Central Africa (45). Studies that trapped animals in areas of MPXV human cases found MPXV-specific antibodies in rope squirrels (*Funisciurus genus*), sun squirrels (*Heliosciurus genus*), rodents in the genera *Lemniscomys, Lophuromys, Thamnomys, Oenomys, Praomys*; and in non-human primates in the genera *Cercocebus, Cercopithecus, Colobus, and Allenopithecus* (48).

One non-systematic review by Parker and Buller, 2013 compiled and discussed all published articles that described experimental or natural infections with MPXV, dating from 1958 to 2012 (51). This review identified the following species to be seropositive for the MPXV via serosurveys performed in different countries and year: crowned monkeys *(Cercopithecus ascanius)*, red-tailed monkeys *(Cercopithecus pogonias)*, lesser white-nosed monkeys *(Cercopithecus petaurista)*, western colobus monkey *(Colobus badius)*, *Chlorocebus aethiops*, Thomas's rope squirrel *(Funisciurus anerythrus)*, porcupines *(Atherurus africanus)*, red-legged sun squirrels *(Heliosciurus rufobrachium)*, ribboned rope squirrels *(Funisciurus lemniscatus)*, Gambian sun squirrels *(Heliosciurus gambianus)*, rope squirrels *(Funisciurus sp.)*, African dormice *(Graphiurus sp.)*, Gambian pouched rats *(Cricetomys sp.)*, African hedgehogs *(Atelerix sp.)*, jerboas *(Jaculus sp.)*, short-tailed opposums *(Monodelphis domestica)*, and woodchucks *(Marmota monax)*.

Eleven non-systematic reviews reported on the 2003 outbreak of MPXV in the United States (33,34,38–44,51,52). These reviews stated the source of the outbreak to be an international shipment of African rodents from Ghana to Texas including rope squirrels (*Funisciurus* spp.), tree squirrels (*Heliosciurus* spp.), Gambian giant rats (*Cricetomys* spp.), brush-tailed porcupines (*Atherurus* spp.), dormice (Graphiurus spp.) and striped mice (*Hybomys* spp.). Another review mentioned three more species in the above list including cusimanses, genets, and palm civets (44). Not all the animals were confirmed to be a reservoir of monkeypox virus, but laboratory test reveal that the Gambian giant rat *(Cricetomys spp)*, rope squirrels *(Funisciurus spp)*, and dormice *(Graphiurus spp)* were infected with monkeypox virus. Native pet prairie dogs (*Cynomys* species) and a pet rabbit were infected from African rodents they had been in close contact with.

Five published reports (53–57) have discussed MPVX animal reservoirs. Two reported specifically on the 2003 US outbreak of the MPXV (53,54) and reported the source of the virus to be a shipment of Gambian giant rats (*Cricetomys* sp.) from Ghana that was sold to an Illinois distributor. The Gambian giant rats were traced back to a shipment of animals from Ghana, which contained six rodent African genera (Rope squirrels (*Funiscuirus* sp), tree squirrels (*Heliosciurus* sp.), Gambian giant rats, brushtail porcupines (*Atherurus* sp.), dormice (*Graphiurus* sp.), and striped mice (*Hybomys* sp.)) that may have been the source of MPXV. Additionally, CDC reported that MPXV has been isolated in rope squirrels (*Funisciurus anerythrus*) with skin lesions. Orthopoxvirus antibodies were found in serosurveys of wild-caught rodents (and non-human primates), including *Cricetomys emini* in Africa (53). Other published reports identified the following as probable reservoir of the MPXV: rope squirrels (*Funisciurus anerythrus*), sun squirrels (*Heliosciurus* sp.), tree squirrels, Gambian rats (*Cricetomys* sp.), African dormice (*Graphiurus* spp.), striped mice and a wild primate (*Cercocebus atys*)(55–57).

Two editorials (58,59) discussed reservoirs of the MPXV. One cited the likely sources of human MPXV to be squirrels of the *Funisciurus* and *Heliociurus* genera (58). The other reported that field studies in central and west Africa found squirrels and other rodents to be potential reservoirs (59).

Existing Evidence

A systematic review (60) identified various wild and domestic animals that could be potential reservoirs of MPXV, including non-human primates, dormice, wild squirrels, African pouched rodents and mongoose. However, as reported in previous iterations of the LEP, the natural reservoir is yet to be confirmed. Outside of Africa, the source of infection in the 2003 US outbreak was prairie dogs housed alongside Gambian rodents imported from Ghana into the USA. *Another systematic review* (61) aimed to identify relevant monkeypox literature to inform operational guidance in low-resource settings has indicated that reservoirs are still unknown for MPXV, but implicated species lists in local areas can be useful in informing risk reduction strategies for animal-to-human transmission. *Two full systematic reviews* (62,63) list a wide range of potential animal hosts for MPXV in West and Central Africa, including mice, West African squirrels, and red-legged squirrels, which were found positive for MPXV-specific antibodies in serum. They also cite prairie dogs and imported rodents from Ghana, which harbored the virus leading to the 2003 outbreak in the United States.

A rapid review by Diaz et al. (64) reported the elusive nature of MPXV reservoirs and that monkeys, small mammals, including elephant shrews and rodents are thought to be involved in the natural history of the virus.

Seven single (primary) studies (3,13,65–69) have reported that while it is unconfirmed but native African rodents seem to play a role in harboring MPXV infection, as well as rope squirrels (highest seroprevalence) ubiquitous in surveyed population in Nigeria. MPXV reservoirs have been found in host species as early as 1899 [in Carruther's mountain squirrels (*F. carruthersi*) and in fire-footed rope-squirrels (*F. pyrropus*)]. In Democratic Republic of Congo (DRC), archival animal samples have indicated Congo rope-squirrel (*F. congicus)* to have higher odds of being MPXV-positive. In the DRC in 1985, and Cote d'Ivoire in 2012, respectively, this virus has been isolated from other species, such as Funisciurus squirrel, and mangabey monkey. Meite et al. investigated emerging pathogens in their rodent vectors. Molecular testing of organs of potential reservoir animals showed only one species of mammal [African giant shrew (*Crocidura olivieri*)] positive for Orthopoxvirus but negative for Monkeypox virus. Hence, for pathogens like Monkeypox virus, doubts still exist for the true reservoir. The most suspected reservoir vector was reported to be *Funisciurus anerythrus*.

One preprint of a modelling study (70)*,* provides some preliminary evidence to suggest that animal-to-human transmission from wild rodents may undermine isolation and case management efforts in a simulated urban population. However, the extent of this contribution in the susceptibility of other animals to MPXV is unknown.

Eighteen non-systematic reviews (6,7,9–11,13,14,71–81) have reported that the natural source of MPXV currently unknown but have been isolated naturally in two occasions (sooty mangabey monkey in 2012, rope squirrel in 1986). MPXV infection and positive serology has been detected in many non-human primates (orangutans, chimpanzees, sooty mangabeys, cynomolgus monkeys) and in a variety of rodents (mice, rabbits, squirrels, hamsters, groundhogs, and porcupines). Since MPXV of the West African clade was discovered in a young sootey mangabey monkey (*Cercocebus atys*) in 2012 in Côte d'Ivoire, it is currently accepted that non-human primates are accidental hosts, much like humans, further supported by similar clinical presentation (14). Doty et al. reported that of 353 animal specimens, 6 types of rodents had positive samples for anti-OPXV IgG antibodies: rope squirrels *(Funisciurus spp.)*; an African dormouse *(Graphiurus lorraineus)*; a giant-pouched rat *(Cricetomys emini)*; a sun squirrel *(Heliosciurus sp.)*; a rusty-nosed rat *(Oenomys hypoxanthus)*; one positive sample was collected from an elephant shrew *(order: Macroscelidea, Petrodromus tetradactylus)*. Reynolds et al. has reported evidence generated from outbreak investigations, ecologic analysis, anthropologic information and laboratory studies of reservoir competence that have found peridomestic rodents, newborns of white rabbits, and white rats *(genus Rattus)*, castaneous (CAST) subspecies of the house mouse, New World giant anteaters (*Myrmecophaga tridactyla)*, and three genera of African rodent, *Graphiurus, Cricetomys and Funisciurus* (African dormice, giant pouched rat, rope squirrel, respectively) to be likely reservoir candidates. The review by Hadadd

and Cordevant (14) has added to the evidence same species mentioned above to be likely reservoirs of the MPXV and in addition have stated rodents which have been exported from Africa, including the Gambian pouched rat (Cricetomys gambianus) and the jerboa (Jaculus sp.), have shown asymptomatic infection as detected by PCR or serology during the 2003 US MPXV outbreak. *Seven non-systematic reviews* (15–17,20–22,82) describe potential reservoirs for MPXV, including monkeys, squirrels, Gambian pouched rats (implicated in the 2003 MPXV outbreak in the US), dormice, non-human primates, and other species. While first detected in monkeys in the 1950's, the largest mammal reservoirs of MPXV seem to be rodents, particularly rope and tree squirrels native to the equatorial rainforest in the West African region. However, there are calls for ascertaining the extent of animal reservoirs and pathogenesis of MPXV within these animals via case-control studies. *Focosi et al* (21) has provided a year and location based portray of when various animals have been identified as possible hosts *(see Table 3 in the article)*. *McNeill* (22) has provided a list of species naturally affected by MPXV. However, whether these species are reservoir of the virus remains to be confirmed. *Two non-systematic reviews* (83,84) also report similar sets of species previously implicated in harboring MPXV. *Seven non-systematic reviews* (85–91) reiterate non-human primates and various other small rodent mammals as potential accidental reservoirs of MPXV in Africa, but do not note any known or suspected reservoirs in non-endemic regions. *Ilic et al, 2022* (78) has stated that MPXV can infect multiple animal hosts before spreading to humans.

Two published reports (23,92) have discussed reservoirs of the MPXV and have also reported on the uncertainty surrounding the primary reservoir of the Monkeypox virus (MPXV) and that this virus has been isolated only from two other species, such as *Funisciurus* squirrel, and mangabey monkey. Another *published report* (93) *of an outbreak investigation* described MPXV cases in nine US states describing MPXV as a zoonotic disease with an unknown reservoir, alluding to the last MPXV outbreak being secondary to imported small mammals from Ghana in 2003. However, since MPXV's re-emergence in Nigeria in 2017, isolated cases outside Africa have been mainly linked with person-to-person transmission, with little information on animal contact. *One published surveillance report* (94) reiterate the notion of lack of confirmed reservoirs for MXPV but implicate small rodents as potential reservoirs promoting transmission to humans.

Editorials, letter to editor and commentary: One editorial (95) *echoes the concerns of past iterations that while monkeys and humans are considered accidental MPXV hosts, the true host of MPXV is unknown.*

Box 3. Reservoir of the MPXV.

- Table 1 is an updated list of all animal species that are probable natural host or possible reservoir of the MPXV (see below).
- The primary reservoirs of the MPXV are currently unknown. To date it has been isolated naturally in two occasions (sooty mangabey monkey in 2012, and rope squirrel in 1986).
- Developing species lists in local areas have been recommended to be useful in informing risk reduction strategies for animal-to-human transmission.

Table 1. Reservoir of the MPXV

Natural reservoir of MPXV	Rodents	NHP	Others
Natural host	Rope squirrel *(Funisciurus anerythrus)*	Sooty mangabey monkey *(Cercocebus atys)*	None
Probable	- Gambian pouched rats *(Cricetomys gambianus)* - Jerboa *(Jaculus sp.)* - Tree squirrels - Carruther's mountain squirrels *(F. carruthersi)* - Fire-footed rope-squirrels (F. pyrropus) - Congo rope-squirrel *(F. congicus)* - Mice - peri-domestic rodents - White rats (genus *Rattus*) - Castaneous (CAST) subspecies of the house mouse - Hamsters - Groundhogs - Porcupines - West African squirrels - Red-legged squirrels - Prairie dogs *(Cynomys sp.)* - Sun squirrels *(Heliosciurus species)* - African dormice *(Graphiurus spp.)* - *Gambian giant rat (Cricetomys spp)* - *Rope squirrels (Funisciurus spp)* - Striped mice (*Hybomys* sp.) - Rope squirrel *(Funisciurus species, family Scuridae)* - African dormice *(Graphiurus crassicaudatus and G. lorraineus, family Gliridae)*	- Orangutans *(Pongo sp.)* - Chimpanzees - Cynomolgus monkeys *(Macaca cynomolgus)* - Genera *Cercocebus, Cercopithecus, Colobus, and Allenopithecus* - crowned monkeys *(Cercopithecus ascanius)* - red-tailed monkeys *(Cercopithecus pogonias)* - lesser white-nosed monkeys *(Cercopithecus petaurista)* - western colobus monkey *(Colobus badius)* - *Chlorocebus aethiops*	- New World giant anteaters *(Myrmecophaga tridactyla)* - Elephant shrews *(Macroscelididae sp.)* - Newborns of white rabbits and rabbits - Mongoose* - Gazelles - African hedgehogs *(Atelerix sp.)* - short-tailed opposums *(Monodelphis domestica)* - Woodchucks *(Marmota monax)*

	- Giant pouched rats *(Cricetomys species, family Nesomyidae)* *- Rope squirrels (Funisciurus genus) and sun squirrels (Heliosciurus genus), rodents in the genera Lemniscomys, Lophuromys, Thamnomys, Oenomys, Praomys* - porcupines *(Atherurus africanus)* - red-legged sun squirrels *(Heliosciurus rufobrachium)* - ribboned rope squirrels *(Funisciurus lemniscatus)* - Gambian sun squirrels *(Heliosciurus gambianus)*		

* One of the collaborators identified a contradiction between what was stated in the systematic review *(Eur Rev Med Pharmacol Sci. 2022 Aug 1;26(16):5983–90)* and what was published in the primary paper *(Infect Dis Clin North Am 2019; 33: 1027-1043)* in relation to mongoose being a possible reservoir of the MPXV. Hence, we recommend that mongoose not be considered as a possible reservoir unless further evidence is found.

TRANSMISSIBILITY OF THE VIRUS:

To date, there were 117 records identified which provided data on transmissibility of the virus among animals and between humans and animals: 2 guideline documents, 6 full systematic reviews, 5 rapid/scoping reviews, 62 non-systematic reviews, 23 single studies, 8 published reports, 1 preprint, and 10 non-empirical documents (editorials, letters to the editor, and commentaries). Box 4 shows updated pertinent information related to transmissibility of the virus.

Animal-to-human transmission

New Evidence

For this update, based upon our searches from 2000-2017, we have added:

Two guidelines (25,96) presented the risk of contracting MPXV from infected animals. A CDC guideline on restrictions on exotic animal imports into the US presenting early evidence of humans contracting MPXV from prairie dogs, which had been infected by diseased African rodents. The other guideline document, developed by the Advisory Committee on Immunization Practices (ACIP) in 2015, states that humans (such as laboratory personnel in direct contact with live orthopoxvirus or clinical samples from infected animals) are at risk of occupational exposure of MPXV from infected animal secretions.

One systematic review (26) reiterated the role prairie dogs played in the 2003 outbreak of MPXV in the US, when they became amplifying hosts which infected humans. Indeed, the discovery of MPXV isolates from infected lungs of prairie dogs were the first suggestion of transmission via respiratory droplets, while most other cases have occurred via bites and scratches from infected prairie dogs. Other risk factors in both endemic and non-endemic regions include: living in forested or recently deforested areas and lack of smallpox vaccination (waning immunity). Moreover, it is unknown whether animals indigenous to the US can maintain a zoonotic cycle of MPXV, but this runs the risk of sustaining MPXV circulation in the population.

Fourteen primary studies (27–31,97–105) explored various aspects of animal-to-human transmission of MPXV. Hutin and colleagues' outbreak investigation in DRC from 1996 to 1997 (27) as well as serosurvey by Salzer et al in 2013 (98), implicate exposure to wild animals (either through trapping and hunting, or preparation and consumption of bushmeat) as a major risk factor of MPXV zoonotic transmission among villagers in DRC where MPXV has originated. Similarly, Reynolds et al (29) found a greater risk of MPXV (and general orthopoxvirus) exposure among individuals living in rural communities near the original animal trapping sites in Africa, more so than among persons involved in exotic animal trade in the US. Another investigation led by Reynolds in 2006 (30) stated that MPXV can be transmitted to humans directly (most often through traumatic injury to the skin via bites or scratches) or indirectly through percutaneous, inhalational, or mucotaneous exposures. Guarner and others (104) have found viral antigens and mature poxvirus particles in the tongues of prairie dogs, suggesting direct contact between saliva or lesions on infected prairie dogs and skin/mucous membranes of another animal/human. A case report by Berthet and others (99) resents an example of direct contact leading to MPXV infection presenting as maculopapular lesions in two young boys who hunted and consumed a bemba (wild rodent species native to DRC and Central African Republic) in June 2010. Direct contact with

infected animals, combined with external climate and geopolitical factors, have been implicated in outbreak investigations in the 2003 US outbreak (100,102), the 2005 outbreak in Sudan (103) and more recently the DRC in 2015 (101), Occupationally, during the 2003 outbreak in Wisconsin, USA, 44% of MPXV cases were among veterinary staff where sick prairie dogs had been treated, including 12 veterinarians and 2 pet store employees, emphasizing the occupational risk of MPXV zoonotic transmission (105). A case-control study conducted by Reynolds and colleagues in 2007 (106) have implicated direct and indirect exposures, as well as cleaning the cage of infected animals, touching used bedding were associated with MPXV infection even after accounting for smallpox vaccination.

Twenty non-systematic reviews (33–38,41–44,46–52,107–109) reiterated much of what has been determined about the zoonotic transmission of MPXV in Africa and in the US from past single studies. Di Giulio and Eckburg (50), Moussatché et al (33), Gibbs (34), Lashley (52), and Regnery (49) trace the source of the 2003 outbreak of the US to importation of African rodents and other small mammals from Ghana (in West Africa) to Texas. Several reviews (35–38,41,42,44,46,47,107) suggested that MPXV can be transmitted to humans from infected rodents (such as rope and tree squirrels) and non-human primates to humans via contact with infected bodily fluids or bites. Indeed, all cases during the US outbreak in 2003 resulted from close contact with infected prairie dogs, via bites most commonly, as noted in a three year old girl being hospitalized for MPXV after being bitten by a prairie dog (43). Another notable example involved non-human primates comes from an instance in 1982 of a chimpanzee in the DRC seizing and biting a 6-month old infant in the femur, resulting in MPXV infection later on (108). Four reviews have also stated that preparation and consumption of bushmeat has been implicated in MPXV transmission, due to extensive contact with infected blood and bodily fluids of animals, or handling of infected tissues (40,41,48,52).

Four published reports (53–55,110) examined aspects of animal-to-human transmission of MPXV. The first report by the CDC (110) in the wake of the MPXV outbreak in the US (Illinois, Indiana, Wisconsin) in 2003 traced all identified cases at the time to direct contact with infected rodents during an exotic animal sale. Subsequent CDC reports (53,54) further confirmed this transmission route. Moreover, a 2011 report by the WHO (55) stated direct contact with blood, bodily fluids, and rashes of infected animals were responsible for most index cases of MPXV outbreaks among humans living in the US and in African countries.

Editorials, letters to the editor, and commentaries: One news article published in 2003 (111) further reiterates the close contact mechanism of zoonotic transmission that had been found among the majority of cases during the 2003 outbreak in the US. *Two editorials* (58,59) identified external factors such as deforestation, inappropriate land use, and civil wars, in addition to practices related to hunting and consuming bushmeat, as responsible for growing human MPXV cases in Africa.

Existing Evidence

Three systematic reviews (1,61,112) noted hunting, handling, and preparing bushmeat as consistently implicated exposures in developing clinical MPXV infection, due to direct contact with infected animal (usually non-human primate and rodent) carcasses or bodily fluids (such as blood and saliva). This set of primary exposures have been routinely associated with outbreaks since the 1970s in West and Central Africa. Increasing frequency of MPXV cases have been linked with increasing dependence on bushmeat for subsistence hunting the region from the 1970s until the most recent outbreaks in Nigeria and the Democratic Republic of the Congo (DRC) in 2010-2018. Less frequently reported transmission routes obtained in these systematic reviews included sleeping outside and living near a forest, as well as cleaning cages and bedding of infected animals. *Two systematic reviews* (62,63) also state that MPXV can be transmitted

from animals (particularly prairie canine species and rodents) to humans via direct contact with bodily fluids, lesions, and mucosa of infected animals. Moreover, the authors of the reviews cite preparation and consumption of bushmeat obtained from infected animals.

One rapid review (64) noted rodent-to-human transmission of MPXV to occur most commonly via rodent bites, most notably those of infected, imported Gambian pouched rats (Cricetomys spp.) which were implicated in the US outbreak of MPXV in 2003.

Three scoping reviews (2,113,114) have reported on the animal-to-human transmission of the MPXV. *One scoping review* (2) points out the risk factor of consuming undercooked meat and other animal products from infected animals in MPXV infection. Moreover, MPXV can be transmitted via contaminated bodily fluids and contact with lesions, as well as contact with fomites, respiratory secretions, and skin-to-skin contact with animals. *The other scoping review* (113) stated that animal-to-human transmission occurred through close contact with wild animals, but the exact mechanism is unknown. The relationship was typically found where contact with animals may have occurred through household rodent infestations or preparation of bushmeat, via saliva and respiratory excretions or contact with lesions or feces of infected animals. *Another scoping review* (114) reiterated the known routes of zoonotic transmission, which can occur from consumption of an infected animal host (primates or rodents) or direct contact with infected animal or its blood, other bodily fluids and/or its mucocutaneous lesions, or via animal bites.

A total of five primary studies has discussed animal to human transmission. Four cross-sectional primary studies (3,13,115,116) found MPXV to propagate primarily from infected animals to humans through the aforementioned modalities (i.e. via contact/consumption with infected carcasses or contact with bodily fluids commonly encountered in hunting, bushmeat preparation) or through secondary, inter-human transmission (usually via close contact). Another cross-sectional study (4) has postulated that a series of mutations has occurred within a short period of time within the MPXV strains, which is not often noted in Orthopoxviruses. This has led to rapid adaptive evolution to human hosts and increased advantage in sustained human-to-human transmission in non-endemic countries. Thus, spillover to new animal reservoirs in such countries can be anticipated, leading to persistence in non-endemic regions – however, this has not yet been systematically examined.

From a preprint of a longitudinal modelling study (70) *,* urban populations were found to be at higher risk of outbreaks when suspected animal hosts (particularly wild rodents) were included and allowed to contribute to case counts in the model. As such, rash-motivated isolation may not sufficiently curb MPXV cases due to reinforcement of animal-to-human transmission and is likely to be noted as earlier peaks and multiple waves.

Nineteen non-systematic reviews (5,6,8,9,13,68,74–81,117–121) describe transmission from animals to humans via direct contact with blood and body fluids and inoculation via mucocutaneous lesions of an infected animal, as well as through direct contact with or consumption of one of the natural viral hosts (especially with improper/incomplete cooking practices). In 2003 the outbreak of MPXV in the USA was linked to direct contact with MPXV-infected pets. Due to direct contact with the infected pets, over 70 cases of MPXV were reported in the USA (74). *Five non-systematic reviews* (15–18,82) cite animal-to-human transmission via direct bite/scratch from infected animals, contact with body fluids or mucosal lesions, or consumption of infected animals (usually a rodent or non-human primate). Other risk factors include living in forested or recently deforested areas, not being vaccinated against smallpox, and handling or consuming bushmeat. *One non-systematic review* (122) also postulates potential for aerosol transmission from animals to humans, as noted in community and nosocomial outbreaks in the Democratic Republic of Congo (DRC). *One report*

(82) *of an outbreak investigation* describes an MPXV outbreak in Kpetema town in Sierra Leone in 2014, with an 11-month-old boy serving as the index case. While the family did not report direct contact with animals, the family did prepare and consume meat from wild animals on a regular basis. This is suggestive, according to the authors, of exposure to sylvatic animals (particularly wild rodents) as well as ceased smallpox vaccination contributing to MPXV cases in the region. Moreover, in Nigeria from 2017 to 2018 it has been reported that the MPXV epidemic was caused by the transmission of animals, potentially rodents, to humans (81). In Singapore in May 2019, one case was identified, associated with ingestion of potentially contaminated barbecued bushmeat (119). This is similar to an incident reported in *a non-systematic review* (117), when in 1970 a child from the Bokenda Village in DRC, was found to be positive for MPXV, making this the first recognized human infection. Contact with dead monkeys and consumption of bushmeat were implicated as enablers of this animal-to-human transmission. Evidence from these reviews indicated that contact with animal reservoirs, including live or dead animals, through hunting, butchering, using products derived from infected animals, consumption and preparation of bushmeat is a presumed driver of MPXV infection in humans.

Three non-systematic reviews (19,20,22) reiterate the common transmission paths for MPXV infection between animals and humans (as stated above), with additional evidence of possible transmission of MPXV from dead animals to humans. Moreover, increased land use and deforestation have been implicated in increased consumption of bushmeat. For example, the Nigerian outbreak was preceded by heavy rainfall and flooding, bringing humans and wild animals closer together as both sought higher, drier land. *Two non-systematic reviews* (83,84) suggest that earlier epidemiological studies show transmission of MPXV to be inefficient between humans, and mostly as a result of multiple spillovers from animals, due to various reasons such as deforestation, violence in the region, and lack of conventional food sources. Much of the animal-to-human transmission was suspected to be driven by contact with an increasing synanthropic rodent population in recent years in Africa. However, recent outbreaks have been restricted to human-to-human transmission, with little history of animal contact or travel to endemic countries. *Eight non-systematic reviews* (85–91,123) also cite this method of transmission from animals to humans, while also citing evidence from ecological studies that MPXV outbreaks occur at the “human-animal interface”, such as rural regions and settlements close to forests. Direct and indirect contact (such as via respiratory droplets) have been implicated in both wild animals, as well as domestic rodents (particularly prairie dogs in the US outbreak in 2003).

Three published reports (23,66,72) found MPXV to propagate primarily from infected animals to humans through the aforementioned modalities (i.e. via contact/consumption with infected carcasses or contact with bodily fluids commonly encountered in hunting, bushmeat preparation) or through secondary, inter-human transmission (usually via close contact)

Editorials, letter to editor and commentary: One editorial (95) reports on three international travelers who were infected with MPXV in 2018 after exposure to dead rodents in Nigeria, with one traveler from Israel likely to be infected with MPXV after interaction with another traveler who was exposed to rodents in Nigeria. It is likely that with increasing civil unrest in the West African region, humans and wild animals are being brought closer together, raising the likelihood of environmental disruption and the need to consume wildlife. *A letter to the editor* (124) hypothesizes the potential for aerosol transmission among humans as well as from animals to humans, with different routes of exposure leading to different presentations in humans and animals. This is supported by findings of MPXV DNA shedding from cells of the upper respiratory tract after lesion resolution in monkeys. *One editorial* (24), *one letter to the editor* (125)*, and two commentaries* (126,127) reiterate the common transmission paths, citing the prior experience of the 2003 outbreak in the US, initiated through the import of MPXV-infected rodents from Africa and subsequent spread to captive prairie

dogs and humans, primarily through direct contact with bedding of MPXV-infected exotic rodents (rope squirrels, dormice, Gambian giant pouched rats) imported from Africa.

Human-to-animal transmission

New Evidence

No evidence published between 2000 and 2017 was identified for this domain.

Existing Evidence

One scoping review (128) *cites the paucity of evidence of transmission from humans back to animals (reverse zoonosis), with most reports dating back to the smallpox elimination campaign.*

Five non-systematic reviews (6,14,71,76,81) *have discussed human-animal transmission. Three non-systematic reviews* (6,14,71) posit direct and indirect contagion through skin/mucosal contact, emission of droplets, secretions, or scabs in humans can raise the possibility of risk of animals being infected by humans (i.e., reverse zoonosis). While this has been a concern in pets (such as cats and dogs being amplifiers of MPXV), production animals, and certain wild animals (such as rodents both synanthropic and non-synanthropic), the infection could really only occur indirectly, rendering even lower likelihoods of infection in non-endemic regions. However, it is conceivable that transmission may be silent as infected animals do not necessarily show the same outward signs as humans. Reverse zoonosis is worthy of active monitoring, since this can allow MPXV to be established in wildlife, like in Africa. The non-systematic review by *Haddad and Cordevant* (14) recommends that particular vigilance is required for squirrels, which commonly interact with human settlements. In terms of production animals, such as cows and goats, the possibility of transmission is dependent on the human owners/farmhands to be actively infected and excreting. While these infective paths are plausible, there is a paucity of evidence systematically examining human-to-animal transmission in such a variety of species, especially in a non-endemic region. *One non-systematic review* (83) expresses a prevalent concern among veterinarians and physicians that human patients infected with MPXV can transmit the virus back to their pets, which can in turn transmit to indigenous wild animals to establish a reservoir in non-endemic countries. Evidence to support the hypothesis was presented in the article. Li et al. (81) indicated that similar to SARS-CoV-2, humans infected with MPXV can spread the virus to domesticated animals by close contact. Hasan and Saeed (76) mentioned the first confirmed case of MPXV virus infection in a dog documented in Paris, which may have been acquired through human transmission. These incidences raise the concerns about the role of pets in MPXV transmission.

Two non-systematic reviews (89,91) reiterate the lack of evidence for human-to-animal transmission, with surveys of wild and domestic animals following the 2003 US outbreak showing no evidence of transmission from infected humans.

One published report (93) *of an outbreak of MPXV cases in nine US states in 2022* suggests that patients with an active MPXV infection refrain from directly contacting pets and other animals, as some mammals (particularly cats and dogs) might be susceptible to monkeypox. *A published surveillance report* (94) describes a risk assessment in the UK of MPXV transmission from infected owners to pet and domestic animals (including dogs and cats). The authors of the report did not find any cases of animals (in the public or in veterinary practice in the UK) with clinical signs suggestive of MPXV

infection associated with confirmed human cases. This document however did report two instances of human to animal transmission in France and Brazil.

Editorials, letter to editor and commentary: One editorial (129) illustrates the lack of evidence regarding the potential for human-to-animal transmission for domestic animals, including dogs and cats, as well as rodents – calling for further research to understand the consequences clinically and zoonotically of these transmission patterns. One letter to the editor (130) describes an instance of human-to-dog transmission, The authors suggest this is an example of human-to-animal transmission, as samples from both the men and the dog corresponded to the same clade (B.1) affecting France at the time. *One editorial* (131) highlights the possibility of reverse zoonosis during the 2022 outbreak, with domestic animals living near infected owners most likely to be infected. It is entirely possible that asymptomatic individuals and children infected with MPXV will transmit the disease to domestic animals (such as cats and dogs) due to their increased engagement with them.

Animal-to-animal transmission

New Evidence

For this update, based upon our searches from 2000-2017, we have added:

Two *single studies* reported on animal-to-animal transmission (29,132). A laboratory investigation described naturally infected animals collected during the 2003 USA outbreak that had been co-habiting with known-positive animals or were exhibiting signs of orthopoxvirus infection (132). An animal infection experiment suggested that prairie dogs may have acted as an amplification host for MPXV during the 2003 USA outbreak; each human case had been in contact with infected prairie dogs, while no humans that were exposed to infected African rodents became infected (29).

Eight *non-systematic reviews* reported on animal-to-animal transmission of MPXV (33–36,44,49–51). Most of these reviews discussed how infected rodents spread MPXV to prairie dogs in the 2003 USA outbreak (33–36,44), two reviews reported that a rabbit became infected after exposure to an infected prairie dog at a veterinary clinic during this outbreak (50,51). One review described MPXV outbreaks among captive monkeys (*Macaca fascicularis*) in 1958, 1959 and 1962; in the latter outbreak, almost 90% of animals kept in the same room as two clinically affected monkeys tested seropositive while only 11% of animals in other rooms were seropositive (51). In a 1964 zoo outbreak, giant anteaters (*Myrmecophaga tridactyla*) infected Asian orangutans (*Pongo pygmaeus*) that were kept in a nearby enclosure, either through aerosol or fomite transmission (51). Aerosols were reported as a possible route of MPXV animal-to-animal transmission by Gibbs (34) and Regnery (49), along with skin abrasions, ingestions of infected animal tissues (34), arthropods, and fomites (49).

A *news correspondence* reported that MPXV had spread from an imported Gambian rat to prairie dogs in the 2003 USA outbreak, when both species were kept in the same warehouse (111). The article also reported that a rabbit became infected after being exposed to a sick prairie dog at a veterinary clinic.

An *editorial* described how rodents imported from Ghana transmitted MPXV to American prairie dogs and ground squirrels when they were housed together in the 2003 USA outbreak (59).

Existing Evidence

One prospective cohort study (73) noted additional transmission opportunities through viral DNA shedding in fecal, urine, and fruit wedge bite samples from both symptomatic and asymptomatic chimpanzees in the Ivory Coast. Patrono et al. (133), represented the only investigated instance of MPXV transmission between suspected host animals (chimpanzees). The authors studied interactions with infected rodents as well as maggots and flesh flies (which primarily feed on urine, fecal matter and potentially carry infection) and through mutual grooming behaviors within social (14) networks.

One scoping review (128) *cites reports of MPXV being widely transmitted in animal communities, including chimpanzees in DRC (see Patrono et al, 2020) as well as from imported African rodents to black-tailed prairie dogs during the US MPXV outbreak in 2003. Animal-to-animal transmission (from giant Gambian rat imported from Africa to local pets) was indeed responsible for the initial events triggering the outbreak. Fortunately, in that case the MPXV transmission to the North American native animal species, i.e. the black tailed prairie dogs (Cynomys ludovicianus), did not initiate the virus spread among the wild fauna, so that local endemization did not follow that episode, or at least there is no evidence of it.*

Five non-systematic reviews (5,14,75,92,119) described intermediate hosts in the transmission of MPXV from one animal to another, including rodents, with potential for transmission to humans. For instance, black-tailed prairie dogs *(Cynomys ludovicanus)*, kept as pets, implicated in 2003 MPXV outbreak in the US (Texas) harbored MPXV after being infected by imported rodents (Gambian pouched rats) from Central Africa (specifically in the DRC and Zaire). *One non-systematic review* (88) cites direct transmission between animals occurring through respiratory droplets, skin or eye abrasions, and ingestion of infected animal tissue. *Two non-systematic reviews* (75,119) reviews reported on the 2003 MPXV outbreak in the USA where imported Gambian pouched rats transmitted the virus to prairie dogs housed in the same exotic-animal facility. In particular, Sah et al, 2022 (119) also reported rabbits in close contact with ill prairie dogs caught the infection and then transmitted to humans.

Editorials, letter to editor and commentary: One commentary (126) notes that the 2003 outbreak of MPXV in the US was propagated by exposure to bedding of MPXV-infected exotic rodents (rope squirrels, Gambian rats, dormice) imported from Africa. This has led to concerns that animals infected with MPXV can escape or be let out into the wild and subsequently infect rodents or small mammals indigenous to the US, further increasing the likelihood of reverse zoonoses in turn.

Transmission related to animal waste, wastewater

New Evidence – Lookback to 2000-2017

No evidence published between 2000 and 2017 was identified for this domain.

Existing Evidence

One primary study (134) examined (as a proof of principle) MPXV DNA detection in (bio)solids from wastewater. They presented qualitative detections of MPXV DNA in various samples from five city districts, and two WWTPs in Amsterdam. However, the process through which MPXV ends up in wastewater is unknown. It has been suggested in this study that animal excreta can play a role is accumulating MPXV DNA in wastewater samples, especially different

rodents and small mammals living in the sewerage and can become a reservoir and transmitter of the MPXV. Though the study does justify why the detected DNA could possibly be due to human shedding. Recommendation is that future research is needed to assess the potential of wastewater-based surveillance and the possibility of an early-warning system for transmission of viruses such as MPXV, be it from an animal reservoir or from human shedding.

Box 4. Transmissibility of MPXV.

Animal-to-Human:

- Most cited transition routes include hunting, handling (contact with bodily fluids), preparing, and consumption (incomplete cooking practices) with infected animal or being bitten by infected animal. Less commonly cited transition routes included lying on ground, living near forested areas, handling bedding used by infected animals, and direct contact with live MPXV by laboratory personnel.
- External factors have also been implicated in enhanced zoonotic transmission, including civil wars and deforestation in Central Africa, as well as inappropriate land use in both endemic and non-endemic settings.
- To date, confirmed evidence has shown that wild squirrels *(Funisciurus anerythrus and Heliosciurus rufobrachium*) and prairie dogs (*Cynomys ludovicanus*) have transmitted the virus to humans. Early outbreaks in West and Central Africa have also indicated transmission from infected non-human primates (such as chimpanzees) to humans.

Animal-to-Animal:

- Animal contact with animal urine and fecal matter is the primarily reported MPXV transmission route between animals. Maggots and flesh flies which feed on urine, fecal matter can carry the virus. Respiratory droplets, skin or eye abrasions, and ingestion of infected animal tissue have been reported as potential transmission routes.
- Intermediate hosts (including rodents) can transmit the virus from one animal to another, with potential for transmission to human.
- There have been reports of animal-to-animal transmission during the 2003 US epidemic suggesting potential for endemicity in non-endemic countries. Species such as prairie dogs during the 2003 outbreak have acted as amplification hosts.

Human-to-Animal:

- Reverse zoonosis is conceivable, particularly between infected humans and domestic animals such as dogs and cats.
- There is a paucity of evidence systematically examining human-to-animal transmission, especially in a non-endemic region. A surveillance report of human to animal transmission in the UK concluded that the risk of transmission to pets from owners with a confirmed MPXV infection to be low.
- Two instances of transmission of the virus from human to animal (dog) has been reported in France and Brazil in a review.

Transmission related to animal waste and wastewater:

- MPXV has been isolated from wastewater with possible source of the DNA being human shedding or feces of animals living in sewers. This highlights greater surveillance potential for MPXV in both human and animal waste and a way of viral transmissibility. However, more evidence needs to be collected.

CLINICAL INFECTION in Animals:

To date, 5 studies have been identified discussing the clinical infectivity of MPXV in animals: 3 non-systematic reviews, 1 single study, and 1 published report.

New Evidence based

For this update, upon our searches from 2000-2017, we have added:

One single study (135) reported that MPXV DNA and/or infectious virus was found in the tissues of two pouched rats (*Cricetomys* sp.). Of the two animals, one animal showed relatively high concentrations of both viral DNA and infectious virus throughout all tissues (e.g., spleen), while the other animal showed MPXV DNA presence only in the gonadal tissue. Additionally, evidence of prolonged presence of MPXV DNA was found in two of nine MPXV-positive African dormice (*Graphiurus* sp.).

One non-systematic review (44) report that there is limited data on the duration of MPXV infection, although the virus may be present months after infection in some animals, regardless of clinical illness. In captive primates, the severity of clinical and asymptomatic infection depends on the species of route of inoculation. Elevated tissue MPXV loads were reported in two necropsied prairie dogs by the CDC.

Existing Evidence

One non-systematic review (14) notes non-human primates have been observed to have two phases of MPXV disease, similar to humans: a prodromal phase consisting of a non-specific febrile syndrome, and an eruptive phase characterized by skin lesions. Another *non-systematic review* (22) presents the infection characteristics of MPXV in prairie dogs, having an incubation period of 13-24 days with the duration of infection being 4 weeks long. Thomas' rope squirrel's incubation period was reported to be 6-8 days, with virus shedding lasting up to 25 days afterward.

One published surveillance report (94) expresses uncertainty about whether animals without outward disease presentation are capable of transmission, or whether they still harbor the MPXV virus despite showing no disease signs.

CLINICAL PRESENTATION IN ANIMALS:

To date, 24 studies have been identified discussing the clinical presentation of MPXV infection in animals: 2 full systematic reviews, 13 non-systematic reviews, 6 single studies, 1 published report, 1 editorial, and 1 letter to the editor.

New Evidence

For this update, upon our searches from 2000-2017, we have added:

Three single studies (102,104,105) looked at the clinical presentation of MPXV in infected prairie dogs during the 2003 US outbreak. Guarner et al. (2004) describes two infected prairie dogs, who both presented with yellow mucoid discharge in their eyelids, while one had an ulcer on their tongue. Reed et al. (2004) report signs of ocular discharge, lymphadenopathy, and papular skin lesions in one infected prairie dog. Other infected prairie dogs presented with watery eyes, skin lesions, congestion, and nasal discharge. Croft et al. (2007) report conjunctivitis and skin lesions in two infected prairie dogs, with one presenting with lymphadenopathy while the other had respiratory disease.

Nine non-systematic reviews (34,36,37,43,51,136–139) reported on the clinical presentation of MPXV in animals. The clinical presentation and severity of disease varies between species and strain of virus. One systematic review (37) noted that the MPXV clade I strain results in higher lethality (approximately 10%) in humans and experimentally infected animals, while clade II strains result in milder disease. Radonic et al. (2014) describes MPXV infection in an infant sooty mangabey (*Cercocebus atys*) found dead in Tai National Park in the Ivory Coast. Multiple skin lesions were disseminated over the body as dark red crusts 5 to 7 mm in diameter and partly confluent, mainly affecting the extremities. A high MPXV DNA load was found in most tissues by qPCR, except in the muscle, indicating systemic infection. There were particularly high loads in a sample from a skin lesion and throat swab. Three non-systematic reviews describe the clinical presentation of MPXV in monkeys across various outbreaks (36,51,139). In monkeys, MPXV infection is characterized by generalized skin eruptions that develop into papules on the trunk, face, palm, and soles. The papules then develop into vesicles and scabs that typically fall off approximately 10 days following the onset of the rash. The severity of disease varies with the host species. For example, the disease is mild in Cynomolgus monkeys (*Macaca cynomolgus*), but more severe in orangutans (*Pongo* sp.). During the 1958 outbreak in Denmark among Asian monkeys (*Macaca fasciularis*), clinical signs included vesiculopustular skin eruptions across the body (face, trunk, limbs, tail, palms, and feet soles) which crusted over and healed on their own, resulting in scars. In 1959, the first reported MPXV cases involved cynomolgus macaques (*Macaca fasciularis*) who presented with poxviral exanthema. Another outbreak occurred in 1959 in the US among cynomolgus and rhesus macaques (*Macaca mulatta*), where two manifestations of disease occurred. The first type of disease occurred in *Macaca fasciularis*, presenting with facial and cervical edema, severe breathing difficulties that led to death by asphyxiation, papular eruptions across the body, ulcerative lesions in the oral mucosa, cutaneous lesions and generalized lymphadenopathy. The second type of disease was more common and occurred in both *Macaca fasciularis* and *Macaca mulatta*, resulting in cutaneous lesions that became pustular and crusted, leaving scars behind all over the body (face, hands, feet, hind limbs, and buttocks) and hemorrhagic lesions linked with fatality. During the 1962 US outbreak among two *Macaca fasciularis* monkeys, clinical presentation included pox-like eruptions, bloody diarrhea, dyspnea, hemorrhagic ulcerations, and facial and cervical edema. During the 1964 outbreak at Rotterdam Zoo, animals presented with varying signs of MPXV. A South American squirrel monkey presented with pox lesions, while owl-faced monkeys presented with lesions on the lips. Other animals affected during this outbreak include giant anteaters who presented with skin lesions; Asian orangutans with erythema and nasal discharge with lesions on the body, legs, face; African gorillas and chimpanzees with pox lesions; Asian gibbon with vesicles on the limbs, trunk, face; and a South American common marmoset with red and swollen areas around the nose and eyes, and face and belly lesions. A total of 5 non-systematic reviews (34,43,51,136,138) discussed the clinical presentation of MPXV-infected prairie dogs during the 2003 US outbreak. Signs of infection among prairie dogs included nasal and ocular discharge, lymphadenopathy, papular skin lesions, conjunctivitis, blepharitis, fever, cough, lethargy, anorexia, upper respiratory signs, pneumonia, sudden death, and pathological changes to the lungs and liver. While some prairie dogs died, other prairie dogs recovered from infection. One non-systematic review (136) looked at the extensive lesions in a MPXV-infected prairie dog during this outbreak. Gross lesions included oral ulcers, pulmonary consolidation, enlarged cervical and thoracic lymph nodes, and plaques in the gastrointestinal wall. Extensive signs in the pulmonary system included microscopic lesions in the lung consisting of fibrinonecrotic bronchopneumonia with vasculitis.

One report (53) stated that skin lesions were found on a rope squirrel (*Funisciurus anerythrus*) from which MPXV was isolated in the DRC.

Existing Evidence

Two single studies (67,68) have discussed the clinical presentation of the MPX disease in animals. One study (67) has reported death of most rope squirrels infected with the virus, with high mortality (up to 75% in some populations) and

high degree of respiratory compromise. These findings have been replicated in other comparison studies with another suspected reservoir (Gambian pouched rat). *Patrono et al.* (133) has also reported development of cutaneous rash, with varying levels of exanthema and respiratory syndrome ranging from mild coughing to severe respiratory distress during outbreaks among 36 chimpanzees in Tai National Park, in Ivory Coast.

Two systematic reviews (63) present various signs among prairie dogs and infected rodents with MPXV, including lethargy, inappetence, nasal discharge, respiratory distress, diarrhea, and skin lesions.

Two non-systematic reviews have discussed clinical presentation in animals. *Devaux et al.* (120) has stated that MPXV infection can present as fever, facial edema, Pox-like lesions in monkeys and apes. According to the other non-systematic review (14), only wild species with natural MPXV disease have been described as affected. While some non-human primates have shown human-like disease presentations, others developed severe respiratory signs with dyspnea and no skin lesions, or discrete and diffuse lesions. Skin disorders and discharge has been noted in prairie dogs (*Cynomys ludovicanus*) during the 2003 US outbreak of MPXV. *One non-systematic review* (22) describe the first MPXV outbreak in cynomolgus monkeys in Denmark, with 20-30% of monkeys housed together affected by rash progressed to papules, covering much of the body and limbs. Lesions were ulcerated, and then formed crusts which later left behind scars after 2-4 months. MPXV DNA and secondary bacterial infections were also noted in several organs in a fatal MPXV infection in an infant sooty mangabey monkey. Cutaneous rash, coughing, and severe respiratory distress were also noted in three infant chimpanzees in Tai National Park in the Ivory Coast, with similar presentations in prairie dogs and Thomas' rope squirrels. *Another non-systematic review* (83) presents the clinical characteristics of MPXV in various species, including non-human primates and dogs. Non-human primates (such as chimpanzees and cynomolgus monkeys) exhibit the most similar MPXV infection presentations to humans, with vesiculopustular skin eruptions in the trunk, tail, and limbs within a week of onset. Among rodents, prairie dogs show evidence of MPXV on the nose, lymph nodes, liver, and other internal organs even before the appearance of skin lesions. *The most recently identified non-systematic review in the regular iteration* (117) reported on the clinical impact of the virus in animals. In the 1958 outbreak of MPXV (Denmark), infected crab-eating macaques showed vesiculopustular eruptions in the trunk, tail, face, limbs, palms of the hands and soles of the feet.

Editorials, letter to editor and commentary: One editorial (129) describes MPXV as first described in cynomolgus monkeys imported from Singapore, who exhibited vesiculopustular skin eruptions over the entire trunk, tail, face, and limbs. One letter to the editor (130) describes a case of an Italian greyhound who tested positive for MPXV, most likely receiving infection from two men in the same household, presenting with mucocutaneous lesions, abdominal pustules, and thin anal ulceration.

TREATMENT OF ANIMALS INFECTED WITH MPXV (INCLUDING PREVENTIVE MEASURES):

This domain was included in the original organizing framework and sought data published between January 1, 2017 and September 2, 2022 at which time the domain was no longer prioritized for updating and the search for new evidence was discontinued. The search interval yielded 10 articles which described treatment options and preventive measures against monkeypox in animals: 1 rapid review, 1 single study, 6 non-systematic reviews and 2 published reports.

Existing Evidence:

One rapid review (64) found the intravenous antiviral cidofovir to be effective in post-exposure prophylaxis of monkeypox in monkeys. However, there is paucity of data examining whether intravenous vaccinia immunoglobulin or cidofovir could be used prophylaxis or treatment of MPXV infection in either animals or humans.

One animal-based experiment (140) examined the effectiveness of highly attenuated smallpox vaccine (LC16m8) in preventing MPXV infection in cynomolgus monkeys (*Macaca fascicularis*). The experiment's authors inoculated monkeys and found nearly no MPXV-associated signs compared to mortality in majority of naïve monkeys and concluded LC16m8 generated a protective memory immune response to MPXV.

One non-systematic review and two published reports (23,71) calls for routine information sharing to coordinate preventive measures at the intersection of animal and human spheres. National surveillance systems have been proposed and implemented for both humans and animals, emphasizing a One Health approach in prevention of MPXV and similar zoonoses in endemic regions. However, there is little-to-no information provided regarding surveillance and preventive mechanisms against MPXV infection in non-endemic countries (most notably the US and countries in Europe). For instance, MPXV outbreaks of undetermined origin, live animal markets, zoos, commercial holding facilities and household pets should be considered as potential sources of infection, thus necessitating institution of coordinated, inter-sectoral investigation approaches. *Three non-systematic reviews* (15–17) suggest that MPXV transmission to humans can be avoided by avoiding unprotected contact with wild animals, especially those ill or dead (including consuming or working with bushmeat without proper cooking beforehand). Moreover, two of these reviews (Singhal et al, 2022; Zhu et al, 2022) (122,141) describe potential antiviral treatments against MPXV which have been tested for animals, including ST-246 (or tecovirimat) which has demonstrated efficacy in protecting animals from MPXV. Modified vaccinia Ankara has also been tested and shown some effectiveness in animal studies – however, its safety is yet to be confirmed. *One non-systematic review* (20) emphasizes the importance of mandates surrounding intersectoral coordination between human and animal interventions against MPXV, including a more "One Health" approach and targeted surveillance programs for susceptible and suspected animal reservoirs in order to curb future outbreaks.

Box 5. Treatment and Preventive Measures

- Anti-viral ST-246 (or tecovirimat) and modified vaccinia Ankara has demonstrated efficacy in protecting animals from MPXV
- Intravenous antiviral cidofovir: evidence to support post-exposure prophylaxis in monkeys.
- Intravenous vaccinia immunoglobulin or cidofovir: insufficient evidence to support prophylaxis or treatment in animals or humans.
- Highly attenuated smallpox vaccine (LC16m8): evidence demonstrating protective immunity response in cynomolgus monkeys.
- Need for national surveillance systems in humans and animals emphasizing a One Health approach.

SUSCEPTIBLE ANIMALS TO THE VIRUS:

To date, there were 46 records which identified animal species that were susceptible to infection from MPXV: 1 guideline document, 1 full systematic review, 1 rapid/scoping review, 32 non-systematic reviews, 7 single studies, 1 published report, and 3 non-empirical records (editorials, letters to the editor, and commentaries). **Table 2** provides an updated list of animals identified as susceptible to MPXV infection based on evidence from the published literature.

New Evidence

For this update, upon our searches from 2000-2017, we have added:

A guideline (25) on rules and regulation imposed by the CDC after the 2003 US MPXV outbreak identified animals found to be susceptible to MPXV infection including: rope squirrels (*Funiscuirus sp.*), tree squirrels (*Heliosciurus sp.*), Gambian giant pouched rats (*Cricetomys sp.*), brushtail porcupines (*Atherurus sp.*), dormice (*Graphiurus sp.*), and striped mice (*Hybomys sp.*).

A total of *6 single studies* (29,30,98,132,135,142) reported on animals that may be susceptible to MPXV infection. 4\Four studies reported on susceptible animal during the 2003 MPXV outbreak in the US (29,30,132,135). Susceptible animals identified included Gambian rats (Cricetomys *spp.*), rope squirrels (*Funisciurus spp*.), dormice (*Graphiurus* spp.), sun squirrels (*Heliosciurus* spp.), striped mice (*Lemiscomys barbarous*), and brush-tailed porcupines (*Atherurus africanus*), black-tailed prairie dogs (*Cynomys ludovicianus*), southern opossum (*Didelphis marsupialis*), hedgehog (*Atelerix* sp.), gray short-tailed opossum (*Monodelphis domestica*), jerboa (*Jaculus* sp.), chinchillas (*Chinchilla lanigera*), coatimundis (*Nasua nasua*), woodchucks (*Marmota monax*), rat (*Rattus* sp.), hamster (*Cricetus* spp.), dwarf hamster (*Allocricetulus* sp.), gerbil (*Gerbillus* sp.), mole rat (*Heterocephalus* sp.) and chinchilla (*Chinchilla* sp.). The other two studies indicated on animals found to be susceptible to MPXV in endemic regions (98,142). These included: bonobos and roof rat (*R. rattus*).

A total *of 8 non-systematic reviews* reported on animals that may be susceptible to MPXV infection (33,34,40,44,45,48,50,51). Of these, five reported specifically on the 2003 MPXV outbreak in the USA (33,34,40,44,48). Animals reported to be susceptible during this epidemic included rope squirrels *(Funisciurus spp)*, tree squirrels *(Heliosciurus spp)*, Gambian giant rats *(Cricetomys spp)*, brushtail porcupines *(Atherurus spp)*, dormice *(Graphiurus spp)*, striped mice *(Hybomys spp),* hamsters (*Cricetus* spp.), gerbils (*Gerbillus* spp.), and chinchillas (*Chinchilla spp*.). Later Necropsy and histopathologic studies by the CDC found positive signs of infection in various species and in various tissues in 14 prairie dogs, two Gambian giant pouched rats, 9 dormice, 3 rope squirrels, 1 ground hog, 1 hedgehog, 1 jerboa, and 2 opossums (44). A non-systematic review by Reynolds et al. stated MPXV can infect an array of mammalian taxa including Sciurid, Glirid, and Nesomyid rodents (*Cynomys sp., Funisciurus sp., Graphiurus sp., Cricetomys sp.*), marsupials (*Monodelphis domestica, Delphius marsupialis*), and primates (*Callithrix jacchus, Homo sapiens*) (45). Parker and Buller stated in their non-systematic review various species that live in lowland tropical forest in central and west Africa are susceptible to MPXV infection: 40% of these susceptible species are arboreal, 40% semiterrestrial, and 20% terrestrial. They also identified animals that may have been susceptible to the MPXV virus during the 1964 MPXV outbreak in Rotterdam Zoo: giant anteaters (*Myrmecophaga tridactyla*), Asian orangutans (*Pongo pygmaeus*), African gorillas (*Gorilla gorilla*), chimpanzees (*Pan troglodytes*), Asian gibbon (*Hylobates lar*), South American squirrel monkeys (*Saimiri sciureus*), African owl-faced monkeys (*Cercopithecus hamlyni*), and South American common marmoset (*Hapale jacchus*) (51).

Two published reports (55,56) mentioned on susceptible species: Prairie dogs and rodents of the *Funisciurus, Heliosciurus, Cricetomys,* and *Graphiurus* genera and primates.

An editorial (59) reported on animals susceptible to the MPXV during the 2003 US outbreak: Prairie dogs and American ground squirrels.

Existing Evidence

Two single (primary) studies discussed on susceptibility of animals. One animal-based experiment (67) examined duration and characteristics of MPXV infection in African rope squirrels (*Funisciurus sp.*) and one prospective cohort primary study (133) examined transmission and clinical outcomes in communities of wild chimpanzees in the Ivory Coast. Both studies found their respective species as involved in the natural cycle of transmission of MPXV in Africa, with the most outward clinical features (further examined in the Clinical presentation and impact section) present among non-human primates. However, no single studies from 2017 to present have examined MPXV infection and/or clinical characteristics in wild or imported animal populations in non-endemic countries.

One scoping review (128) *classified MPXV to have a broad host range, citing many ecologic and serological studies in suggesting non-human primates and rodents (particularly rope and tree squirrels, Gambian pouched rats, dormice) as susceptible species. Despite the lack of evidence of MPXV infection in livestock or domestic pets in recent years, the authors hypothesize that cats might be able to spread infection back to wildlife (like native rodents) if infected. Another scoping review* (114) reported that MPXV has been found to be contagious in a variety of animal species including rodents such as mice, rats, and squirrels.

One systematic review (63) *reiterates the list of susceptible species as mentioned above, including other non-human primates such as sooty mangabey monkeys, in which MPXV was isolated in 2012 in Ivory Coast.*

Fifteen non-systematic reviews (5,6,10,13,14,17,61–65,71,73,113,115) cite the following species as susceptible to MPXV infection and potential intermediate hosts, based on past outbreak investigations in and out of endemic countries: sooty mangabey monkey (*Cercocebus atys*), Gambian-pouched rat (*Cricetomys gambianus*), rhesus macaques (*Macaca mulatta*), cynomolgus macaque (*Macaca fascicularis*), asian monkeys, southern opossum (*Didelphis marsupialis*), sun squirrel (*Heliosciuris sp.*), rope squirrels (*Funisciurus sp.*), tree squirrels *(Heliosciurus sp.),* African hedgehogs (*Atelerix sp.*), jerboas (*Jaculus sp.*), woodchucks (*Marmota monax*), shot-tailed opossum (*Monodelphis domestica*), porcupines (*Atherurus africanus*), giant anteaters (*Myrmecophaga tridacyla*), prairie dogs (*Cynomys spp.*), elephant shrew (*Petrodromus tetradactylus*), wild pig (*Sus scrofa*), rope squirrel (*Funisciurus sp.*), African dormice (*Graphiurus spp.*). MPXV infections have also been noted in mice (*Mus musculus*), rabbits (*Oryctolagus cuniculus*), other small rodents, and chimpanzees in Africa. In addition to above, *Haddad and Cordevant* (14) has indicated the susceptibility to MPXV infection among captive primates and rodents (such as African dormice, Natal multimammate rats (*Mastomys natalensis*) that has been shown experimentally. Among domestic animals, negative results were found in limited serological surveys (120 small ruminants and 67 cats) in the 1980s, furthering the need for examining burden in these species using more updated methods in 2022 outbreak. Currently, one can only hypothesize infective paths with these animals in non-endemic regions. For production animals (cattle, goats, sheep), the burden is the least known, with only one study in 1987 showing no seroconversion (143). *Three non-systematic review*s (20–22) focused on susceptibility of various animal species to MPXV infection. All three had mainly reported on susceptibility of various rodents and non-human primates to MPXV infection. However, many of these assumptions were based on experimental infections in various species. Specifically, the review by *McNeill* (22) has extensively discussed on experimental infections in various species with their clinical manifestations. *One non-systematic review* (83) *c*ites a 1964 MPXV outbreak in Rotterdam, the

Netherlands, which infected several animal species, including giant anteaters, orangutans, gorillas, chimpanzees, gibbons, and marmosets. Some of these animals have passed away from the infection as well, but little information is available on the extent of the spread or the severity of the disease, which could provide a better picture of these species' MPXV susceptibility. *Five non-systematic reviews* (85,88,90,91,123) cite numerous African species including rodents (rope and tree squirrels, Gambian pouched rats, dormice), various species of monkeys as having shown signs of MPXV infection. Specifically, while non-human primates and other wild animals living in forested habitats are more likely to become infected and fall ill, small mammals (especially rodents) can be asymptomatic carriers of the virus. MPXV-neutralizing antibodies have also been found in domestic pigs, sun squirrels, as well as non-placental mammals such as opossums. *Sah et al, 2022* (119) reported that during the 2003 MPXV outbreak in the US many small rodents imported from Africa were infected, including striped mice *(Hybomys spp.)*, dormice *(Graphiurus spp.)*, brushtail porcupines *(Atherurus spp.)*, Gambian pouched rat *(Cricetomys gambianus)*, sun squirrels *(Heliosciurus spp.)*, and rope squirrels *(Funisciurus spp.)*.

Editorials, letter to editor and commentary: One editorial (144) described cynomolgus monkeys and various non-human primates as susceptible to MPXV infection. Moreover, large outbreaks in Zaire in 1979 implicated rodents such as Thomas' rope squirrel and redless tree squirrel, as well as Gambian pouched rats and dormice. *A letter to the editor* (131) as indicated dogs, ferrets, and cats to be potentially susceptible to orthopoxvirus infection. Experimental infection has been demonstrated in adult albino rabbits as well as neonates of rats and exotic pet mice. *A commentary* (126) has indicated various rodents, non-human primates, anteaters, hedgehogs, and shrews to be susceptible to MPXV infections.

Box 6. Susceptible animals to MPXV infection:

- An updated list of potentially susceptible animals to the MPXV has been presented in table 2 (see below).
- Additional information on susceptibility of the MPXV please refer to *Haddad and Cordevant, 2022* review and the MacNeill 2022 review.

Table 2. Animal species at risk of MPXV infection

Animal groups				
Wild			Domestic	Pets
Non-human primates	**Rodents**	**Other**		
- Sooty mangabey monkey *(Cercocebus atys)* - Rhesus macaques *(Macaca mulatta)* - Cynomolgus macaque *(Macaca fascicularis)* - Asian monkeys - Wild chimpanzees *(Pan troglodytes)* - Red-tailed monkey *(Cercopithecus ascanius)* - Allen's swamp monkey *(Allenopithecus nigroviridis)* - Lesser spot nosed monkey *(Cercopithecus petaurista)* - Western red colobus *(Piliocolobus badius)* - Orangutans - Gorrillas - Chimpanzees - Gibbons - Marmosets - Lesser and greater-white-nosed-monkeys - Grivets - Red colobus monkeys - Bonobos - *Callithrix jacchus*	- Gambian-pouched rat *(Cricetomys gambianus)* - Emin's pouched rat *(Cricetomys emini)* - Prairie dogs *(Cynomys spp.)* - Sun squirrel (*Heliosciuris spp.*) - Jerboas *(Jaculus spp.)* - Woodchucks *(Marmota monax)* - Porcupines *(Atherurus africanus)* - Brushtail porcupines *(Atherurus spp.)* - Rope squirrel *(Funisciurus anerythrus)* - Congo rope squirrel *(Funisciurus congicus)*, - Tree squirrels *(Heliosciurus spp.)* - Mice *(Mus musculus)* - Striped mice *(Lemniscomys spp.)* - African dormice *(Graphiurus spp.)* - Natal multimammate-rats *(Mastomys natalensis)* - Gambian sun squirrel - Marmot - Groundhog - Chinchilla (*Chinchilla* sp.) - Giant pouched rat - Hamsters (*Cricetus* spp.)	- Southern opossum *(Didelphis marsupialis)* - African hedgehogs *(Atelerix sp.)* - Shot-tailed opossum *(Monodelphis domestica)* - Giant anteaters *(Myrmecophaga tridacyla)* - Elephant shrew (*Petrodromus tetradactylus*) - Wild pig (*Sus scrofa*) - Rabbits (*Oryctolagus cuniculus*) - Hedgehog (*Atelerix* sp.) - Shrew - Anteaters - Opossums - Coatimundis (*Nasua nasua*)	The susceptibility of production animals (cattle, goats, sheep) is the least known. However, as most ruminants are susceptible to other poxviruses (such as cowpox), this should not be overlooked	The susceptibility of pets (such as cats) is unknown. May act as accidental hosts and cause viral spillover. Dogs and ferrets are also regarded in this instance.

- Asian orangutans (*Pongo pygmaeus*) - African gorillas (*Gorilla gorilla*) - Chimpanzees (*Pan troglodytes*) - Asian gibbon (*Hylobates lar*) - South American squirrel monkeys (*Saimiri sciureus*) - African owl-faced monkeys (*Cercopithecus hamlyni*) - South American common marmoset (*Hapale jacchus*)	- African brush-tailed-porcupines - Rope squirrels *(Funisciurus spp.)* - Tree squirrels (*Heliosciurus sp.*) - Gambian giant pouched rats (*Cricetomys sp.*) - Brushtail porcupines (*Atherurus sp.*) - Dormice (*Graphiurus sp.*) - Striped mice (*Hybomys sp.*) - Striped mice (*Lemiscomys barbarous*) - Brush-tailed porcupines (*Atherurus africanus*) - Black-tailed prairie dogs (*Cynomys ludovicianus*) - Jerboa (*Jaculus* sp.) - Chinchillas (*Chinchilla lanigera*) - Rat (*Rattus* sp.) - Dwarf hamster (*Allocricetulus* sp.) - Gerbil (*Gerbillus* sp.) - Mole rat (*Heterocephalus* sp.) - Roof rat (*R. rattus*)			

**The following species has been experimentally found to be susceptible to MPXV infection: CAST/EiJ, PERA/EiJ, and MOLF/EiJ mice; cynomolgus monkeys, Kellen's dormouse (Graphiurus kelleni); Black-tailed prairie dogs (Cynomys ludovicianus); Thomas's rope squirrel (Funisciurus anerythrus); ground squirrels (Ictidomys tridecemlineatus); Gambian pouched rats (Cricetomys gambianus); albino rabbits as well as neonates of rats and exotic pet mice.*

HANDLING OF SUSCEPTIBLE ANIMALS:

To date, 11 eligible studies discussed handling procedures for animals susceptible to MPXV infection: 1 guideline document, 6 non-systematic reviews, 2 single studies, 1 published report, and 1 news correspondence.

New Evidence

For this update, upon our searches from 2000-2017, we have added:

A *guideline* from the Advisory Committee on Immunization Practices in the USA recommended routine vaccination with ACAM2000 for laboratory personnel who directly handle animals infected with MPXV, with revaccination every 3 years (96).

Two *non-systematic reviews* reported on the federal ban in the USA that prohibited importing rodents from Africa during the MPXV outbreak in 2003 (43,44). The FDA also issued an order that prohibited transportation of rodents from the African shipment implicated as the source of the outbreak (44). Furthermore, a ban on the distribution, sale, and transportation of prairie dogs and six African rodent species was established (43).

Two *single studies* reported on handling animals susceptible to MPXV (102,145). An animal experiment by Witmer et al. described how Gambian giant pouched rats (*Cricetomys gambianus*) were captured, treated with insecticide, dewormed, and quarantined for two weeks in individual cages (145). Experimental trials found that a mix of feces and urine from the rats was the most effective attractant, so this mixture could be used as bait for capturing (145). An outbreak investigation by Reed et al. reported that during the 2003 USA outbreak, animals exposed to infected prairie dogs had been quarantined, and veterinarians were recommended to use infection control and PPE measures similar for smallpox (102).

A *report* from the World Health Organization stated that MPXV-infected animals need to be immediately quarantined (55). Animals potentially in contact with infected animals should also be quarantined and monitored for MPXV signs for 30 days. Wearing PPE when handling infected animals and tissues was recommended to prevent MPXV transmission from animals to humans.

A *news correspondence* reported that the CDC recommended standard infection control measures for individuals who investigate or treat animals with MPXV (111). The article also advised that sick animals not be released in the wild, to prevent an enzootic MPXV cycle in local wildlife.

Existing Evidence

Four non-systematic reviews (10,14,16,83) has discussed on handling measures to quell or prevent infection of MPXV from infected animals in a veterinary or field setting, including: animal ought to be brought to the veterinary clinic, isolation from other humans and the animal's environment, avoiding feeding them directly, isolation of the breeder or owner of the infected animal(s), and environmental disinfection of contacted surfaces. The review by *Haddad and Cordevant* (14) has advised that veterinary staff should take extra precautions (such as personal protective equipment, careful disinfection of the animal's isolation environment). *One non-systematic review* (16) maintains that positive or suspected patients and animals need to be isolated promptly, with reverse and positive contact tracing where possible. The authors also suggest strict importation limits on wildlife into countries to avoid contact with sick animals (especially African rodents, marsupials, non-human primates) which may carry MPXV. Any collected samples from suspected

infected animals need to be handled with care and with appropriate protection by trained personnel. *One non-systematic review* (83) classifies potential MPXV reservoirs into low- and high-risk "transmissors". Low-risk transmissors include domestic pet animals such as dogs and cats, for whom the authors suggest that it is prudent for their owners to avoid their contact with other animals in the event they suspect MPXV-like symptoms in their pet. For high-risk transmissors, such as rodents, the authors suggest closer monitoring to examine if the animal is infected with MPXV, with treatment administered promptly and euthanasia used as a last resort. Residues from rodents and other pets ought to be sprayed with home disinfectants as well.

ADDITIONAL PERSPECTIVES:

This domain was included in the original organizing framework and sought data published between January 1, 2017, and September 2, 2022, at which time the domain was no longer prioritized for updating and the search for both new and lookback evidence was discontinued. The search interval yielded 8 total records: 1 non-systematic review, 1 scoping review, 3 single studies, 3 letters to the editor.

Environmental aspects

Existing Evidence

A single study (133) and *a non-systematic review* (72) has reported the impact, changing environment can have on MPXV infection. Ongoing changes in demography, natural seasonal/interannual variation, human-induced changes (e.g., encroaching on African rainforests and destructive land use practices) in West Africa and Nigeria in particular have shown to change the hazard of MPXV spillover events into humans from infected hosts. Identifying competent hosts of MPXV is important to examine associations with urbanization, modified human-animal contacts of epidemic risk. *One primary study of ecological design* (146) examined environmental determinants of MPXV transmission in the Democratic Republic of Congo (DRC). The authors found proximity of human settlements to forested areas, daily temperature, and low socioeconomic status of the human settlements were positively associated with increased incidence of MPXV infection. In particular, frequently visiting forested areas for logging, hunting, and other activities of livelihood allows contact between humans and suspected reservoirs of MPXV. This is particularly true for those in low socioeconomic status communities, as rising urban demand for bushmeat, prompting villagers to hunt more often to make a living.

Occupational exposure

Existing Evidence

One scoping review (2) emphasize the importance of protecting healthcare workers and preventing MPXV transmission in healthcare settings, through the use of personal protective equipment (PPE) as well as infection control and prevention measures. These measures can include standard contact and droplet precautions in outpatient and hospital settings, strict hand hygiene, and regular disinfection of high-contact surfaces.

Two single studies have reported information regarding occupational exposure to the MPXV and how it should be managed. *Petersen et al*. (147) conducted a retrospective study between 2010 and 2014 to understand the risk environment for healthcare workers in Tshuapa, Democratic Republic of Congo. This study reported that among the 699 confirmed cases of MPXV during the study period, six confirmed cases of MPX among HCWs represented a proportion of 0.9% (range of 0.3–3.1% by year). On average, 1.5 HCWs were infected per year during the observation period, yielding an estimated annual HCW incidence rate of 17.4/10,000. Six HCWs reported exposure during their official duties as a HCW, including three of the MPX confirmed cases (42.8%). *Yinka-Ogunleye et al.* (148) has reported nosocomial transmission of monkeypox in the Central African Republic (2015-2016) as well as the USA (2003) and UK (2018). The infection of health-care workers suggests a possible breach in infection prevention and control measures while caring for patients with monkeypox. The potential for infection of health-care workers during monkeypox outbreaks calls for concerted efforts by hospitals to strengthen and routinely follow recommended infection prevention and control practices during patient care".

Editorials, letter to editor and commentary: 3 letters to the editor (149–151) emphasize the importance of protecting healthcare workers and preventing MPXV transmission in healthcare settings, through the use of personal protective

equipment (PPE) as well as infection control and prevention measures. These measures can include standard contact and droplet precautions in outpatient and hospital settings, strict hand hygiene, and regular disinfection of high-contact surfaces.

Table 3: Total number (and new) evidence documents by topic

Type of evidence document	Total	Description of the virus	Reservoirs of the virus	Transmissibility of the virus	Clinical infection in animals	Clinical presentation in animals	Treatment of infected animals	Susceptible animals of the virus	Handling of infected susceptible animals	Additional perspectives (environmental aspects, occupational exposure)
Guidelines	2 (2)		1 (1)	2 (2)				1 (1)	1 (1)	
Full systematic reviews	7 (1)	1	4 (1)	6 (1)		2		1		
Rapid/scoping reviews	5	1	1	5			1	1		1
Non-systematic reviews	71 (25)	19	53 (20)	62 (22)	3 (1)	13 (9)	6	32 (8)	6 (2)	1
Protocols for reviews or rapid reviews that are underway										
Titles /questions for reviews that are being planned										
Single study	37 (22)	2	15 (6)	23 (14)	1 (1)	6 (4)	1	7 (5)	2 (2)	3
Published reports	11 (6)	1	9 (5)	8 (4)	1	1 (1)	2	1 (1)	1 (1)	
Dissertation/thesis										
Preprints*	1		1	1						
Editorials, letter to editor and commentary**	14 (3)	1	3 (2)	10 (1)		2		3	1 (1)	3

Preprints have not undergone peer-review and may have methodological or conceptual shortcomings and will be re-examined when published in a peer-reviewed journal in a future iteration.

Table 4a: Key findings from included evidence documents on RESERVOIRS OF THE VIRUS from all iterations thus far (January 1, 2017 to October 28, 2022, and past evidence from January 1, 2000, to January 1, 2017)

Study Design	Study Quality	References	Evidence
Non-systematic review		Moussatché et al.	The source of the 2003 MPXV epidemic in the US was an international shipment of African rodents from Ghana to Texas. Not all the animals were confirmed to be a reservoir of monkeypox virus, but laboratory test reveal that the Gambian giant rat (Cricetomys spp), rope squirrels (Funisciurus spp), and dormice (Graphiurus spp) were infected with monkeypox virus. ' After the 2003 MPXV epidemic in the US, the possibility of reintroduction from an animal reservoir should be considered. If monkeypox virus could adapt to American native rodents such as rats, squirrels or prairie dogs, it will become a major public health concern regarding the potential for its establishment in novel reservoir species and ecosystems
Non-systematic review		Gibbs EPJ	Epidemiological studies of monkeypox have now established that rodents are the reservoir of the virus and that the disease in monkeys and humans is incidental. The specific role of any particular species as a reservoir has not been established. ' During the 2003 outbreak in the US, laboratory testing of some animals from the original shipment of rodents from West Africa confirmed the presence of monkeypox virus in one Gambian rat, three dormice and two rope squirrels. ' The Gambian giant rat, believed to be the index case in the USA (apparently experienced a much milder illness than that observed in prairie dogs, with no respiratory signs and limited skin lesions).
Single study (outbreak investigation)		Hutin et al.	Animal antibody surveys in the Democratic Republic of Congo (DRC; former Zaire) suggested that squirrels play a major role as a reservoir of the virus. ' Fifty-nine captured animals representing 14 species were tested. Sera from 42% of the various squirrel species (Funisciurus anerythrus, Funisciurus congicus, Heliosciurus rufobrachium), from 16% of Gambian rats (Cricetomys emini), and from an elephant shrew (Petrodromus tetradactylus) and a domestic pig (Sus scrofa) showed orthopoxvirus neutralizing antibodies (Table 2).
Guideline		CDC 2003 rules and regulation	African rodents are considered to be the most likely natural host of the monkeypox virus. Serologic evidence of monkeypox infection has been found in many other species, including some species of primates, rodents, and lagomorphs (which includes such animals as rabbits).

Non-systematic review		Lupi & Tyring	African arboreal squirrels of the Funisciurus and Heliosciurus species (sun squirrels) have been implicated previously as probable reservoir hosts for monkeypox virus in Zaire on the basis of antibody data and a single viral isolate from a Funisciurus anerythrus squirrel. ' To assess the potential role of squirrels as a reservoir for monkeypox virus and to estimate the seroprevalence in wild-caught species, animals were hunted by local villagers and trapped by the study team. Over 4 days, 84 animals representing 16 species were captured; all animals were examined for lesions, and serum specimens were collected from 64. Except for 1 squirrel from which skin biopsy specimens were collected, lesions suspected to be associated with monkeypox were not present on any other animal.
Single study (ecological modelling)		Nakazawa et al.	Details of how is MPXV maintained in nature and transmitted from wildlife to humans are currently unknown. Several mammal species (e.g., rodents, marsupials, primates, etc.) have been identified to be susceptible to experimental or natural infection with this virus. Rodents have been identified as potential reservoirs of monkeypox because they have rapid population turnover that could facilitate perpetuation of the virus. ' The only MPXV isolate from a wild animal was obtained from a squirrel of the genus Funisciurus. Additionally, some species of rodents were also found to be susceptible to MPXV infection (e.g., species of the genera Funisciurus, Heliosciurus and Cricetomys).
Single study (animal infection experiments)		Reynolds et al.	The natural cycle of MPX within its native range is poorly understood, *as is the route of transmission to humans in the tropical forest setting.* The only MPX virus isolated from a wild-caught mammal was obtained from a single moribund rope squirrel (Funisciurus anerythrus) collected during an outbreak investigation in Zaire. ' Old World and New World species, were newly recognized as being capable of hosting infections with monkeypox virus (MPXV). Members of three genera of African rodent were implicated as the initial, inadvertent, source of importation of the virus into the United States, these being Cricetomys , Graphiurus , and Funisciurus (commonly known as giant pouched rat, African dormouse and rope squirrel, respectively). ' To determine which species of interest might be capable of harboring MPXV in nature, local (Ghana) trappers collected 204 animals (***see table 1 for the species included***). The MPXV-specific DNA signals were not reproducibly detected in any of the specimens. Somewhat contrary to expectations, the results of this study did not implicate a single species of animal as being the sylvan source of MPXV for the U.S. outbreak.

Non-systematic review		Essbauer et al.	Possible *hosts* of monkeypox virus as demonstrated by positive serological evidence, PCR (*) and/or virus isolation: Orangutan (Pongo sp.); Cynomolgus monkey (Macaca cynomolgus), Rope squirrel (Funisciurus sp.), Thomas's rope squirrel (Funisciurus anerythrus), Prairie dogs (Cynomys sp.), Dormouse (Graphiurus spp.), Gambian giant rat (Cricetomys sp.).
Non-systematic review		Haller et al.	MPXV possesses one of the broadest host ranges among poxviruses. The natural host reservoirs of MPXV are probably rodents including rope squirrels (Funisciurus sp.), sun squirrels (Heliosciurus sp.) and Gambian giant rats (Cricetomys sp.), as indicated by the isolation of virus from these species and the high seroprevalence. Additionally, many other species can be naturally infected by MPXV including many primate species.
Report		WHO, 2011	In Africa, MPXV infection has been found in rope squirrels, tree squirrels, Gambian rats, striped mice, dormice, and primates. In the United States, several susceptible non-African species contracted MPXV from African animals they were co-housed with. The identification of the exact reservoir of MPXV and how it is maintained in nature requires further studies.
Non-systematic review		Ka-Wai Hui, 2006	Squirrels are the natural reservoir in nature for MPXV. The source of the 2003 outbreak in six Midwestern states in the United States were pet prairie dogs (Cynomys species).
Non-systematic review		McFadden, 2006	Rodents and squirrels are the reservoir hosts for MPXV. In Africa, the animal reservoir for MPXV is unknown; however, likely candidates include several Indigenous members of the squirrel species. During the 2003 US MPXV outbreak, a shipment of rodents from West Africa led to the MPXV outbreak in humans.
Non-systematic review		Lashley, 2004	In the United States, the source of the MPXV outbreak was traced back to pet prairie dogs and a pet rabbit who had been infected by a Gambian giant rat they had been co-housed with before distribution in Illinois.
Report		Orba et al., 2015	In the DRC, MPXV has only been isolated in rope squirrels (Funisciurus anerythrus). In Africa, animals that are naturally infected with MPXV include rope squirrels (Funisciurus sp.), sun squirrels (Heliosciurus sp.), Gambian rats (Cricetomys sp.), and African dormice (Graphiurus spp.). A broad range of mammalian species can be naturally infected with MPXV; however, the exact reservoir remains unknown.
Non-systematic review		Parker et al., 2007	MPXV may be supported in nature through several animal species, including two genera and six species of squirrels, and nine species of non-human primates. MPXV has been isolated in nature from a squirrel (Funisciurus aneryhtrus). During the 2003 US outbreak, MPXV was found in rope squirrels (Funisciurus spp.), giant pouched rats (Cricetomys spp.), and African dormice (Graphiurus spp.). Native prairie dogs were the source of the 2003 US outbreak after being infected from African rodents they had been in close contact with. MPXV has been isolated from the vesiculopustular lesions of

			infected cynomolgus macaques. Please refer to Table 1 of this article to see a list of African animals known to have been naturally infected with MPXV.
Report		CDC, 2003	In the DRC, MPXV has been isolated in rope squirrels (Funisciurus anerythrus) with skin lesions. Orthopoxvirus antibodies were found in serosurveys of wild-caught rodents (and non-human primates), including cricetomys emini in Africa. The source of the 2003 US outbreaks came from a shipment of Gambian giant rats (Cricetomys sp.) from Ghana that was sold to an Illinois distributor, where the virus was transmitted to prairie dogs (Cynomys sp.) they were co-housed with. A rabbit (Family Leporidae) contracted MPXV following exposure to an infected prairie dog.
Non-systematic review		Torres-Velez & Brown, 2004	The 2003 US outbreak was traced back to prairie dogs that became infected after being co-housed with infected Gambian giant rats and dormice imported from Accra, Ghana. Serologic and epidemiologic studies demonstrate that MPXV is supported in nature through squirrels and Gambian giant rats.
Report		CDC, 2003a	Prairie dogs were the source of the 2003 US outbreak after being co-housed with Gambian giant rats (Cricetomys sp.) by an animal vendor in Illinois. The Gambian giant rats were traced back to a shipment of animals from Ghana, which contained six rodent African genera (Rope squirrels (Funiscuirus sp), tree squirrels (Heliosciurus sp.), Gambian giant rats, brushtail porcupines (Atherurus sp.), dormice (Graphiurus sp.), and striped mice (Hybomys sp.)) that may have been the source of MPXV.
Single study (cross-sectional study)		Reynolds et al., 2006	In 2003, MPXV was brought into the US through a shipment of animals from West Africa. It is thought that the African animals transmitted MPXV to the susceptible non-African species that they were housed with, such as prairie dogs. However, the exact animal reservoir of MPXV has not been identified.
Editorial		Kantele et al., 2016	MPXV can infect a range of animals within the mammalian taxa, and can range from rodents to primates. The likely sources of human MPXV are squirrels of the Funisciurus and Heliociurus genera.
Report		Monroe et al., 2015	MPXV has been isolated from a wild primate (Cercocebus atys) that was found dead in Cote d'Ivoire.
Non-systematic review		Lashley, 2006	Prairie dogs that had been co-housed with an infected Gambian giant rat and other exotic rodent species were the source of the 2003 MPXV outbreak in the US.
Editorial		Bray, 2009	- MPXV is a zoonosis maintained in local rodents in the Democratic Republic of the Congo, usually occurring as single cases - MPXV was first discovered in 1958 when it caused an outbreak of smallpox-like disease in monkeys in a holding facility in Copenhagen, Denmark - Field studies in subsequent decades in central and west Africa indicated that squirrels and other rodents were potential reservoirs

Systematic review	Critically low (AMSTAR-2)	Brown and Leggat, 2016	- Natural host is unknown, but the Gambian pouched rat and rope squirrel seem to be most likely candidates - both species were amongst infected rodents imported to the USA in 2003 - Moreover, MPXV has been isolated in rope squirrels and sooty mangabey monkeys in the Ivory Coast in 2012
Non-systematic review		Ligon, 2004	- Probable source of introduction involved a shipment of animals that entered Texas on April 9, 2003 included ~800 small mammals, including six genera of African rodents: rope squirrels (Funisciurus spp.), tree squirrels (Heliosciurus spp.), Gambian giant rats (Cricetomys spp.), brush-tailed porcupines (Atherurus spp.), dormice (Graphiurus spp.) and striped mice (Hybomys spp.) - Of these, one Gambian giant rat, three dormice, and two rope squirrels were infected with MPXV
Non-systematic review		Bernard and Anderson, 2006	- Traceback of cases during an outbreak in 2003 in the US implicated rodents from a shipment of African animals imported to Texas, containing around 800 small mammals of 9 different species - This included rope squirrels, tree squirrels, Gambian giant rats, brushtail porcupines, dormice, striped mice, as well as cusimanses, genets, palm civets - The complete host range of MPXV is unknown, but antibody surveys in disease-endemic areas suggest infection is enzootic among squirrels, other rodents, monkeys
Non-systematic review		Reynolds et al, 2012	- Large mammals, gazelles, and primates have been singled out as potentially important sources of human infection in Central Africa, but consistency of associations between rodent hosts and MPXV suggest a rodent reservoir to be more likely - Rodents such as squirrels and Cricetomys sp., known to be susceptible to MPXV infection, and explot food sources and stays close to forest margins and human communities in DRC, are most likley reservoirs and agents of virus transmission to humans
Non-systematic review		Wolfe et al, 2005	- Suspected reservoir species of monkeypox include squirrels "and other animals".
Non-systematic review		Pattyn, 2000	- Search for the virus reservoir of MPXV was conducted in different stages, starting with serum surveys of primates in West and Central Africa - Since all monkeys live in small troops and no evidence exists of either persistent infections or transmission by flying arthropods, unlikely this population could be a sustained reservoir - Reservoir most likely to be found among animals with high population numbers and rapid turnover, which would lead to production of immunologically naive subjects regularly - After much effort, a diseased squirrel (Funisciurus anerythrus) was found showing superficial skin lesions, virus isolated from organs - Understanding (at the time) was arboreal squirrels (Funisciurus spp. and Heliosciurus spp.) living in secondary forest surrounding human settlements and fields were most likely reservoirs, infecting humans directly or via monkeys

Single study (modelling study)		Thomassen et al, 2013	- Modelling showed that temperature seasonality and annual precipitation are important factors in predicting the distributions of MPXV reservoir species in Tropical Africa. - The majority of the predicted MPXV reservoir species distribution was located in African tropical forests. - From 2050 to 2080 in Tropical Africa, climate change is projected to cause the distribution of tree pangolins (Manis tricuspis) to decrease, and the distribution of rope squirrels (Funisciurus pyrropus) to increase, while African brush-tailed porcupines (Atherurus africanus) would have a similar distribution. - See Figure S2 for maps comparing the current distribution of reservoir species, and future projections at 2050 and 2080.
Non-systematic review		Damon, 2011	- Studies that trapped animals in areas of MPXV human cases found MPXV-specific antibodies in rope squirrels (Funisciurus genus), sun squirrels (Heliosciurus genus), rodents in the genera Lemniscomys, Lophuromys, Thamnomys, Oenomys, Praomys; and in non-human primates in the genera Cercocebus, Cercopithecus, Colobus, and Allenopithecus. - It has been hypothesized that Funisciurus is the most likely reservoir host, based on their relatively high seroprevalence of MPXV-specific antibodies and the variety of squirrel genera that live in forests near human settlements in rural DRC.
Non-systematic review		Regnery, 2007	- It is unclear whether MPXV is transmitted from one host species or multiple host species.
Non-systematic review		Di Giulio and Eckburg, 2004	- From the first human MPXV case in 1970 to early 2003 (before the USA outbreak), human sporadic cases had only been identified in rainforest areas in central and western Africa, and large outbreaks had only occured in DRC. *- Epidemiological studies from DRC have suggested that squirrels (including Funisciurus anerythrus) who live in agricultural areas are a primary source of MPXV infection to humans living nearby:* *- An environmental survey found that Funisciurus spp. squirrels had a MPXV seropositivity rate of 24%, which was the highest rate among all other animals tested such as Heliosciurus spp. squirrels at 15% and primates at 8%.* *- Later, a seroprevalence study conducted during the outbreak investigation in 1997 in DRC found that Funisciurus spp. had a seropositivity rate of 39-50%, Heliosciurus spp. had a seropositivity rate of 50%, and 16% of Gambian giant rats had been exposed to MPVX.*
Single study (modelling study)		Fuller et al, 2011	- Modelling showed that forest vegetation and presence of the rope squirrel (Funisciurus species, family Scuridae) were the most important ecological determinants of the MPXV ecological niche in Sankuru, DRC. - Humans near dense forests with rope squirrels had 32% higher odds of becoming infected with MPXV compared to those in non-forested areas in Sankuru (OR 1.32, 95%CI 1.08-1.63).

			- In Sankuru, modelling predicted a higher likelihood of human MPXV in subdistricts with mostly forests (which provide habitat for rope squirrels), compared to substricts with mostly savannah. - Among all subdistricts, Central Sankuru had the highest risk of MPXV outbreaks as it has the highest number of sites predicted to be in the MPXV ecological niche, and the highest human population density. - The modelling results support previous findings that rope squirrels are a natural host that transmit MPXV to humans. - The authors provide further evidence that rope squirrels could act as a MPXV reservoir in rural Sankuru: - In 1985, MPXV was isolated from a wild rope squirrel in a forest area near Sankuru, and the squirrel had visible signs of infection including skin eruptions; - Seroprevalence studies in Zaire from the 1980s found that rope squirrels had the highest seroprevalence; and - Rope squirrels can spread the virus among each other through feces, vomits and respiratory droplets. - Rope squirrels can also have a high population density (allowing virus propagation) and they tend to live near human settlements in rural DRC. - More than one species may act as a MPXV reservoir, given that serosurveys have found various species contain MPXV antibodies. - Therefore, the hypothesis that terrestrial rodents are the main reservoir in west Africa can still hold true even while the modelling results support rope squirrels as the reservoir in DRC. - Results suggest that MPXV surveillance in DRC should focus more on rope squirrels, compared to other potential reservoir species that were found to be less important in this study's modelling: African dormice (Graphiurus crassicaudatus and G. lorraineus, family Gliridae) and giant pouched rats (Cricetomys species, family Nesomyidae). - Surveillance should also focus specifically on semi-deciduous forests in Sankuru, since they have a main food source for rope squirrels (oil-palm, Elaeis guineensis).
Non-systematic review		Parker and Buller, 2013	- A serosurvey in 1986 in north Zaire found that among 39 primates tested for MPXV-specific antibodies, 2/22 crowned monkeys (Cercopithecus ascanius) and 1/3 red-tailed monkeys (Cercopithecus pogonias) were seropositive, while the rest were seronegative. - Serosurveys in West Africa found that two lesser white-nosed monkeys (Cercopithecus petaurista) and one western colobus monkey (Colobus badius) were seropositive for MPXV-specific antibodies. - Another serosurvey in West Africa with 13 wild monkeys found that two Chlorocebus aethiops and one Cercopithecus petaurista were seropositive for MPXV-specific antibodies. - A serosurvey in 1979 in Zaire found that only Thomas's rope

			squirrel (Funisciurus anerythrus) was seropositive for MPXV-specific antibodies, among all the monkeys, rodents, and bats tested. - A serosurvey in 1985 tested animals from areas near human MPXV cases (terrestrial rodents, squirrels, sheep, goats, cats) and found that a squirrel (Funisciurus anerythrus) presenting with lesions was seropositive for MPXV-specific antibodies, and two other squirrels seemed healthy but were seropositive. - A serosurvey in 1986 in Zaire identified 1/4 porcupines (Atherurus africanus) as seropositive for MPXV-specific antibodies. - A serosurvey in 1986 in Zaire tested rodents from areas with human MPXV cases suspected to be caused by infected squirrels, and results showed that 25% (79/320) of Thomas's rope squirrels (Funisciurus anerythrus) and 16% (6/37) of red-legged sun squirrels (Heliosciurus rufobrachium) were seropositive for MPXV-specific antibodies. - Another survey in Zaire (in an area where there had been no reported human cases) found that 49% (58/119) of ribboned rope squirrels (Funisciurus lemniscatus) were seropositive for MPXV-specific antibodies, and 19% (6/31) of Gambian sun squirrels (Heliosciurus gambianus) were seropositive. - Overall, these serosurveys demonstrate that MPXV is widely present in squirrels of the Funisciurus and Heliosciurus genera in Zaire, and support the hypothesis that these squirrels are a main reservoir. - Among the animals imported from Ghana to USA in 2003, CDC testing found that 3/6 rope squirrels (Funisciurus sp.) and 9/10 African dormice (Graphiurus sp.) were positive for MPXV by PCR and virus isolation; 2/21 Gambian pouched rats (Cricetomys sp.) were positive by MPXV-specific PCR, as well as 1/22 African hedgehogs (Atelerix sp.); 1/4 jerboas (Jaculus sp.); 1/4 short-tailed opposums (Monodelphis domestica); and 1/4 woodchucks (Marmota monax). - CDC testing also found that terrestrial rodents in the genera Lophuromys, Lemniscomys, Oenomys, Thamnomys, and Praomys were seronegative for MPXV-specific antibodies.
Non-systematic review		Farasani, 2022	- Reservoir for MPXV is currently unknown, but primates serve as accidental hosts and the reservoir is likely to be one of many species of rodents and squirrels that live in secondary forest of central Africa
Non-systematic review		Gessain et al, 2022	- MPXV is a zoonotic disease, but its animal reservoir remains unknown - Various rodent species from Central, West African tropical rainforests, including tree squirrels and Gambian pouched rats are currently considered strong candidates - African apes and monkeys, on the other hand, can be infected and are thought to be accidental, intermediate hosts

Non-systematic review		Hasan and Saeed, 2022	- Published literature demonstrates that the true reservoir host for MPXV is presently not known, although the virus may be naturally maintained in rodent populations and non-human primates.
Non-systematic review		Hatmal et al, 2022	- MPXV is mainly found in rodents, which are the likely animal reservoir, and this might have contributed to its emergence in humans - However, the natural reservoir of MPXV remains unknown
Non-systematic review		Ilic et al, 2022	- Even though the natural reservoir of MPXV is unknown, some outbreaks indicate rodents as the probable source of infection - MPXV can infect multiple animal hosts before spreading to humans. - Rodents such as rope squirrels, giant pouched rats, and dormice (the three species implicated in the 2003 US outbreak of MPXV) are examples of potential reservoirs.
Non-systematic review		Jeyaraman et al, 2022	- Despite the name, mice and other small animals are far more frequently implicated than monkeys or other primates. - The natural reservoir of the monkeypox virus is unknown.
Non-systematic review		Kim et al, 2022	- Main reservoirs of MPXV and similar orthopoxviruses may be rodents or other species such as African dormice, giant-pouched rats, rope and sun squirrels in West and Central Africa - however, the primary animal reservoir is still unclear.
Non-systematic review		Li et al, 2022	- The natural host for MPXV is largely unknown, but it is found mainly among rodents in Africa - Other known zoonotic hosts include sooty mangabey monkeys, Gambian pouched rats, rope squirrels, tree squirrels, and possibly other species
Published surveillance report		Shepherd et al, 2022	- Mammals – particularly rodents – have previously been documented as reservoirs of poxviruses from animals to humans
Systematic review	Critically low (AMSTAR-2)	Soheili et al, 2022	- Although the exact natural reservoir of the monkeypox virusis uncertain, various potential hosts have been identified. - However, the authors of this record do not mention the names of these potential hosts
Systematic review	Critically low (AMSTAR-2)	Rahimi et al, 2022	- The reservoir and accidental hosts in its natural ecology are yet to be fully elucidated. - In the 1980s, a serological survey conducted by WHO in the DRC showed and MPXV had a wide range of animal hosts. For instance, 39-50% of West African squirrels and 50% of red-legged sun squirrels were positive for MPXV-specific antibodies in serum, and the virus could also be isolated from sick mice. Moreover, in the

			2003 Human Monkeypox (HMPX) outbreak in the United States, the investigation found that MPXV originated from several African rodents imported from Ghana. - Other studies indicated the infected hosts of MPXV within *in vitro* settings included cynomolgus monkeys, prairie dogs, and ground squirrels.
Non-systematic review		Shafaati & Zandi, 2022	- Rodents are the most plausible candidates for the monkeypox natural reservoir, though this has not yet been determined. Viruses may be found in rodents and non-human primates: Gambian pouched rat *(Cricetomys gambianus)*, Dwarf dormouse *(Graphiurus murinus)*, Sun squirrel *(Heliosciurus spp.)*, Rope squirrel *(Funisciurus spp.)*, Colobus monkey *(Colobus spp.)*, Sooty mangabey *(Cercocebus atys)*.
Non-systematic review		Tiecco et al, 2022	- The diversity and extent of the animal reservoir are still unknown.
Non-systematic review		Dou et al, 2022	- The host range of MPXV is unknown, with rodents being likely hosts - Non-human primates are also considered provisional reservoirs of MPXV
Non-systematic review		Ejaz et al, 2022	- There is no definite animal reservoir for MPXV, but small mammals such as African dormice (*Graphiurus* spp.), sun squirrels (*Heliosciurus* spp.), rope squirrels (*Funisciurus* spp.), giant pouched rats (*Cricetomys* spp.) are thought to spread the virus to humans in Central, West Africa
Non-systematic review		El Eid et al, 2022	- Despite the name, monkeys are not the reservoir of MPXV, but are more incidental hosts - Reservoirs are believed to be mainly rodents including squirrels and Gambian rats
Non-systematic review		Forni et al, 2022	- While wild non-human primates were found to be infected with MPXV, they are not thought to contribute significantly to MPXV circulation - Based on field surveys and analysis of museum specimens, rope squirrels are considered potential natural reservoirs of MPXV - Indeed, first isoaltion of MPXV from a wild animals was from an infected rope squirrel in the DRC in 1986 - Additional small mammals have been found to be potential carriers of MPXV in the DRC, with MPXV DNA found in rodents (Lunda rope squirrels, target rats, giant pouched rats, naked-tail shrews - In West Africa, evidence of orthopoxvirus infection was obtained in giant pouched rats, African, sun squirrels, ground squirrels - Table 2 in this record shows a list of mammlas with potential evidence of natural infection with MPXV

Non-systematic review		Riopelle et al, 2022	- Exact reservoir host complex of MPXV remains unknown, but two major candidates have been posited: giant pouched rats (*Cricetomys gambianus*, detection of OPXV antibodies) and rope squirrels (*Funisciurus* spp., detection of antibodies and virus isolation) - Presence of rope squirrels, but not giant pouched rats, were found to be significant predictor of MPXV's geographical range, particularly in forested areas
Systematic review	Critically low (AMSTAR 2)	Kannan et al, 2022	- MPXV can infect various wild and domestic animals, including primates, dormice, wild squirrels, African pouched rodents and mongoose - However, the exact natural reservoir is yet to be confirmed - Outside of Africa, the source of infection in the US was prairie dogs that were housed with Gambian rodents imported from Ghana into the USA
Non-systematic review		Gomez-Lucia, 2022	- First known episode of MPXV detected in 1958 in laboratory cynomolgus and rhesus monkeys imported to Denmark mainly from Singapore - Within Africa, three rope squirrels, one Gambian pouched rat, a shrew, and a sooty mangabey monkey have yielded the virus, most of these animals trapped thus far have been healthy - Several rodents have been infected experimentally and did not show symptoms: rope squirrels, Gambian squirrels, African dormice, Gambian giant pouched rat, and prairie dogs - See Figure 1 of this review for a comprehensive list of discovered potential reservoirs for MPXV to date
Non-systematic review		Varela et al, 2022	- MPXV can infect rats, mice, rabbits, and prairie dogs, but may not cause clinical signs of disease in infected animals
Non-systematic review		Kumbhar and Agarwala, 2022	Natural host for the monkeypox virus remains elusive. The Gambian pouched rat and the rope squirrel are the most probable candidates, based on evidence from field and laboratory investigations.
Non-systematic review		Focosi et al, 2022	MPXV has been **detected in a variety of hosts** including **in 1985** from Thomas's rope squirrel *(Funisciurus anerythrus)* in the Democratic Republic of the Congo (DRC), **in 1992** from a sooty mangabey monkey *(Cercocebus atys)* in Côte d'Ivoire, **in 2010–2016** from rope squirrels *(Funisciurus anerythrus, Funisciurus bayonii)*, other rodents species *(Stochomys longicaudatus, Cricetomys sp.)* and one shrew *(Crocidura littoralis)* in DRC, **in 2019** in chimpanzee *(Pan troglodytes verus)* faeces in Taï National Park, Côte d'Ivoire, from Gambian

			giant pouched rats *(Cricetomys gambianus)*, and from African dormouse *(Graphiurus kelleni)*.
Non-systematic review		MacNeill et al, 2022	Please see **table 1** of this paper for a list of species naturally affected by MPXV.
Published report		Minhaj et al, 2022	- MPXV is a zoonotic disease for which the animal reservoir is unknown, with the last MPXV outbreak being secondary to imported small mammals from Ghana in 2003 - however, since MPXV's re-emergence in Nigeria, isolated cases outside Africa have been linked with travel history to Nigeria, with little information on animal contact
Non-systematic review		Singhal et al, 2022	- Natural reservoirs of MPXV include monkeys, squirrels, Gambian pouched rats, dormice, non-human primates, and other species - While the earliest monkeypox outbreak outside of Africa was in 2003 linked to prairie dogs infected by imported Gambian pouched rats from Ghana, the recent outbreak of 2022 had an increasing number of cases linked to no travel history to MPXV-endemic countries
Non-systematic review		Zhu et al, 2022	- While MPXV was first detected in monkeys, the largest animal reservoirs seem to be rodents, including rope squirrels, tree squirrels, rats, striped mice, dormice
Non-systematic review		Petersen et al, 2019	- The extent of host animal reservoirs, the natural history, and pathogenesis of MPXV in both animals and humans need to be ascertained via case-control studies - Indirect/direct contact with live or dead animals is assumed to drive human monkeypox infections in humans, usually in animals in equatorial rainforests in West Africa and Central Africa - MPXV was isolated from the moribund rope squirrel (Funisciurus anerthyrus) in Zaire in 1985, and have since been isolated in squirrels (rope and tree), rats, striped mice, dormice, monkeys
Non-systematic review		Lai et al, 2022	- While rodents are considered a potential natural reservoir for MPXV, the most important natural reservoir remains to be identified
Editorial		Angelo et al, 2019	- The true host of MPXV is unknown, bu rodents are suspected, while monkeys and humans are considered accidental hosts
Non-systematic review		Haddad and Cordevant, 2022	- Identity of natural animal hosts of this virus and their role in its epidemiological cycle is still uncertain, as MPXV is versatile in infecting a wide variety of species, potentially allowing infection of animal species in regions where MPXV is not endemic - Studies from the 1980's have implicated various squirrel species in the transmission of MPXV to humans through presumed animal contact with fluids and infected fomites, such as the Thomas's rope

			squirrel (*Funisciurus anerythrus*) - however, the fact that squirrels were usually symptomatic, raised questions about their actual reservoir role - Asymptomatic infection of mammals of other species (detected by PCR and/or serology) have been demonstrated in field surveys or during importation into the USA in 2003 - included species such as the Gambian pouched rat (*Cricetomys gambianus*), African hedgehog (*Atelerix* sp.), jerboa (Jaculus sp.), brush-tailed porcupine (*Atherurus africanus*), Lorraine's African dormouse (*Oenomys hypoxanthus*). - 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*). - 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. It is currently accepted that non-human primates are accidental hosts, much like humans, further supported by clinical presentation of clinical MPXV disease in chimpanzees (*Pan troglodytes verus*) in Ivory Coast, 2020 – *see Patrono et al, (2020) in the July 22 iteration of this living evidence profile*.
Preprint (single study, longitudinal)	Low (provisional)	Yuan et al, 2022	- The increasing pattern of human-to-human transmission in non-endemic countries is concerning, especially if reverse zoonosis occurs in animals outside of Africa. As such, ascertaining The MPXV animal reservoir is key to MPXV control - While natural reservoir is unknown, African rodents and non-human primates have been noted to be particularly susceptible - in this modelling study of MPXV transmission in a simulated urban population (derived from metropolitan cities like Toronto), authors included wild rodents As possible animal reservoirs during this MPXV outbreak, accounting for seasonality of The host rodent population
Single study (cross-sectional)		Doshi et al, 2019	- Previous studies implicate rodents as possible MPXV reservoir (including squirrels), ubiquitous in surveyed population in Nigeria
Review (non-systematic)		Silva et al, 2021	- Natural source of MPXV currently unknown, has only been isolated twice in nature - One cannot exclude the possibility of virus infecting susceptible hosts and establishing reservoirs in new geographical areas
Review (non-systematic)		Haider et al, 2022	- MPXV infection and positive serology has been detected in many non-human primates and small mammals, but only been isolated naturally in two ocassions (sooty mangabey monkey in 2014, rope

			squirrel in 1986) - Definitive reservoir still unknown
Review (non-systematic)		Doty et al, 2017	- Single seropositivity study in DRC examining prevalence of MPXV infection/antibodies in trapped squirrels, rodents of genera *Funisciurus and Heliosciurus* - Of 353 serum specimens, 7 (2%) were found to be positive for anti-OPXV IgG antibodies. 6 of the positive samples were collected from rodents (Rodentia): rope squirrels *(Funisciurus spp.)*; an African dormouse *(Graphiurus lorraineus);* a giant-pouched rat *(Cricetomys emini);* a sun squirrel *(Heliosciurus sp.)*; a rusty-nosed rat *(Oenomys hypoxanthus)*; one positive sample was collected from an elephant shrew *(order: Macroscelidea, Petrodromus tetradactylus)*.
Single study (retrospective cohort study)	Moderate (5/9, NOS)	Tiee et al, 2018	- Evidence of MPXV found in host species (*Funisciurus*) as early as 1899, identified two new host species (*F. carruthersi* and *F. pyrropus*) - Overall prevalence level was 9.0% (93/1038 samples), all belonging tom the Congo-Basin strain of MPXV - Between years and museums from which archival samples were sourced, *F. congicus* had higher odds of being MPXV-positive, compared to other species - all positive samples were in DRC, even though half the species' range occurs to south (into Angola in some cases) - Prevalence of MPXV was significantly higher in later years (1956-1960), compared to 1921-1925
Systematic review	Low (AMSTAR 2)	Beer and Rao, 2019	- Reservoir still unknown for MPXV, but implicated species lists in local areas can be useful in informing risk reduction strategies for animal-to-human transmission
Review (non-systematic)		Kumar et al, 2022	- Reservoir host of MPXV is unknown, but rodents have been suspected in propagating transmission, through skin lesions, body fluids, or respiratory droplets
Review (non-systematic)		Suu-Ire et al, 2021	- Review: notes that reservoir hosts of MPXV include non-human primates and wild-rodents - Rodents captured in Ghana following the 2003 outbreak in the USA, detected MPXV in *Cricetomys, Graphiurus, Funisciurus, and Heliosciurus spp.* - Limited to indirect exposure to infected rodents lead to MPXV infection, based on limited evidence of serology in hunting/trapping sites (as of 2021)
Single study (animal experiment)		Falendysz et al, 2017	- While unconfirmed, native African rodents seem to play a role in harboring MPXV infection, as well as rope squirrels (highest seroprevalence) - current single study found rope squirrels to be

			linked with outbreaks of MPX in humans, with infectious shedding over 5-22 days
Single study (prospective cohort study)	High (8/9, NOS)	Whitehouse et al. 2021,	The reservoir host remains elusive, monkeys, small mammals, including elephant shrews and rodents are thought to be involved in the natural history of the virus.
Review (non-systematic)		Haddad, 2022	
Rapid review	Critically low (AMSTAR 2)	Diaz et al. 2021	
Report		Farahat et al. 2022	Although the Monkeypox virus (MPXV) can infect many mammalian species, the primary reservoir causing human infection has not been identified yet. In addition, this virus has been isolated only from other species, such as Funisciurus squirrel, and mangabey monkey in the DRC in 1985, and Cote d'Ivoire in 2012, respectively.
Report		Durski et al. 2018	
Single study (cross-sectional)		Guargliardo et al. 2020	
Review (non-systematic)		Xiang & White, 2022	
Single study (cross-sectional)		Guargliardo et al. 2020	Ecologic investigations from Ghana and DRC showed that animals most likely to have anti-OPXV antibodies included those of the genera Graphiurus (dormice), Cricetomys (giant pouched rats), Funisciurus (rope squirrels), and Heliosciurus (sun squirrels). Lemniscomys (striped mouse) and Tatera (gerbil) have also been implicated, in addition to Oenomys hypoxanthus (rufous-nosed rat) and Petrodromus tetradactylus (elephant shrew). Gambian rats (Cricetomys spp.) in particular have been repeatedly associated with MPXV, either through detection of anti-OPXV antibodies or MPXV DNA.
Review (non-systematic)		Kabuga & Zowalaty, 2019	Serologic studies have shown that monkeys from Africa have orthopoxvirus antibodies, while natural cases of MPXV are yet to be documented in wild-living primates. It was reported that monkeypox virus neutralizing antibodies have been detected in the domestic pig (Sus scrofa), Gambian rat (Cricetomys emini), elephant shrew (Petrodromus tetradactylus), Thomas's tree/rope squirrel (Funisciurus anerythrus), Kuhl's tree squirrel (Funisciurus congicus), and sun squirrel (Heliosciurus rufobrachium), suggesting the role of wildlife in zoonotic transmission.
Review (non-systematic)		Xiang & White, 2022	Under laboratory or captive conditions, a very broad range of mammalian taxa were found to be susceptible to MPXV infection, including rabbits, ant-eaters, opossums, and additional rodent species such as prairie dogs and ground squirrels. It is worth pointing out that ground squirrels that are abundant in grassland of North America are highly susceptible to MPXV, raising concerns about MPXV establishing reservoirs in North America rodents due to human spillbacks to animals. It is postulated that the maintenance

			of MPXV in nature may depend on its ability to utilize multiple host species.
Single study (cross-sectional)		Meite et al. 2022	In this single study investigation of the pathogens in their rodent vectors were carried out. Small mammal trappings were carried out and liver, lung and kidney tissues from trapped small mammals were sampled. Molecular tests were used to detect pathogens including Orthopoxviruses and specifically Monkeypox virus. One (0.39%) Crocidura olivieri liver was positive for Orthopoxvirus but Monkeypox virus negative. Hence, for pathogen like Monkeypox virus, doubts still exist for the true reservoir. The most suspected reservoir vector would be Funisciurus anerythrus.
Review (non-systematic)		Quarleri et al. 2022	The natural source of MPV and its maintenance cycle in nature remain not completely elucidated. The virus has been isolated from diferent wild animals including non-human primates (orangutans, chimpanzees, sooty mangabeys, cynomolgus monkeys) and in a variety of rodents (mice, rabbits, squirrels, hamsters, groundhogs, and porcupines).
Review (non-systematic)		Reynolds et al. 2019	While reservoir studies in the laboratory and in the field have, to date, not led to the definitive identification of a single MPXV maintenance host, several likely, candidates have been identified based on evidence generated from outbreak investigations, ecologic analysis, anthropologic information and laboratory studies of reservoir competence. These include peridomestic rodents, newborns of white rabbits, and white rats (genus Rattus), castaneous (CAST) subspecies of the house mouse, Mus musculus castaneus, New World giant anteaters (Myrmecophaga tridactyla), Three genera of African rodent, Graphiurus, Cricetomys and Funisciurus (African dormice, giant pouched rat, rope squirrel, respectively).

Table 4b: Key findings from included evidence documents on TRANSMISSIBILITY OF THE VIRUS from all iterations thus far (January 1, 2017, to October 28, 2022, and past evidence from January 1, 2000 to January 1, 2017)

Subdomain	Study Design	Study Quality	References	Evidence
Animal-to-human transmission	News correspondence		Stephenson J	During the 2003 MPXV outbreak in the US, most cases had direct or close contact with pet prairie dogs and one had reported contact with a Gambian giant rat imported from Ghana and one case had contact with a infected rabbit.
	Non-systematic review		Moussatché et al.	The probable source for the introduction of monkeypox virus into the USA was an international shipment of African rodents from Ghana to Texas.
	Non-systematic review		Gibbs EPJ	The source of the outbreak was traced to a legal importation of approximately 800 small mammals from Ghana in West Africa to Texas in April 2003. The consignment contained 762 African rodents.
	Single study		Hutin et al.	- Exposure to an animal reservoir might have been the source of infection for at least 27% of patients who reported no exposure to other patients during the incubation period. - Although the possibility of infection of animals with another unknown indigenous orthopoxvirus cannot be ruled out in animals with neutralizing antibodies, the results of our investigation suggest that, in addition to squirrels, Gambian rats may play a role in monkeypox virus circulation. - Exposure to wild animals (trapping, exposure to raw meat and eating) reported by monkeypox case-patients included: squirrels, monkeys, rats, porcupines, and gazelles. Villagers ate a number of different animals, and it was impossible to draw any conclusions as to whether any one species was a greater risk factor than any other. - Eating wild animals was common for all patients. However, patients who had no

				exposure to other case-patients during the incubation period were more likely to eat porcupine at least once a month (Table 1). All queried participants reported trapping animals less frequently.
	Guidelines		CDC 2003 rules and regulation	In the United States, individuals apparently began contracting monkeypox in early May, 2003, primarily as a result of contact with prairie dogs that had contracted monkeypox from diseased African rodents.
	Non-systematic review		Lupi& Tyring	- Monkeypox is usually transmitted to humans from squirrels and primates through contact with the animal's blood or through a bite. - During the 2003 MPXV epidemic in the USA All cases had direct or close contact with ill prairie dogs, which were kept as pets.
	Single study (animal infection experiments)		Reynolds et al.	- Source of the virus introduced into the United States in 2003 was rodents imported from Ghana. - The results of this study did not show enhanced risk of OPXV exposure among persons directly involved in the exotic animal trade. Instead, we observed IgG against OPXV among a large proportion of those persons living in rural communities near the original animal trapping sites, albeit no persons had serologic evidence suggesting recent infection.
	Single study (modeling study)		Blumberg et al	- In study includes the assessment of whether an infected animal in contact with humans has a distinct set of inferred transmission parameters than infected humans. - The authors use Ra-h to represent the average number of primary cases caused by an infected animal that has contact with humans. The results indicate that the Reff for human-to-human transmission is similar to Ra-h. There is also evidence that animal-to-human transmission is relatively homogeneous. If one takes the MLEs of Ra-h and ka-h for the preferred model at face value, then it was estimated that at least one infection occurs 25% of the time

				that a infected animal has contact with humans.
	Non-systematic review		Essbauer et al.	- Southern Sudan, a rural farming area which ecologically differs tremendously from the tropical rainforest. A followup investigation by the WHO found evidence of sporadic cases of monkeypox in this area, supporting the thesis of recurrent carry-over from local, supposed animal reservoirs. - The particular MPXV strain responsiblein during the 2003 US outbreak seems to have originated from MPXV-infected rodents imported from Ghana. The rodents had been transported and kept with native prairie dogs that were afterwards distributed as pets. Human cases mostly occurred in staff of veterinary facilities seeing ill prairie dogs, in households with prairie dogs, in pet store visitors and employees (59% of the cases occurred among occupationally exposed persons). - ' A recent risk factor analysis revealed that bites and exposure to excretions, secretions and respiratory droplets of MPXV-infected animals can result in infection.
	Non-systematic review		Haller et al.	Humans usually get infected with MPXV by direct contact with infected animals.
	Report		WHO, 2011	The direct contact with blood, bodily fluids, or rashes of infected animals led to the index cases of previous MPXV outbreaks in humans. The handling of infected monkeys, Gambian rats, or squirrels have been reported as a source in human infection in Africa.
	Non-systematic review		Ka-Wai Hui, 2006	MPXV is transmitted to humans by direct contact with animal blood or through rodent bites. The expansion of human habitation through deforestation may place people in direct contact with new animal species and their viruses, as seen in individuals infected with MPXV in Central and Western Africa.

	Non-systematic review		Lashley, 2004	In Africa, the preparation and consumption of infected rodents and monkeys is associated with MPXV outbreaks.
	Non-systematic review		Parker et al., 2007	The handling of tissues from MPXV infected animals resulted in human MPXV outbreaks in the Congo Basin and in West-African countries. MPXV may be transmitted to humans indirectly, through fomite or aerosols, as demonstrated in one case during the 2003 US outbreak.
	Report		CDC, 2003	The primary route of animal to human transmission of MPXV is through the close contact with infected mammalian pets.
	Non-systematic review		Torres-Velez & Brown, 2004	Humans were infected with MPXV during the 2003 US outbreak through indirect or direct contact with infected prairie dogs. Cases in African MPXV outbreaks were exposed to rodents through seasonal hunting activities or deeper retreat into the rainforest.
	Report		CDC, 2003a	During the 2003 US outbreak MPXV was transmitted to humans through wild or exotic mammals such as prairie dogs (Cynomys sp.***) that they had direct or close contact with. Some patients developed symptoms of MPXV after reported petting or handling of prairie dogs.***
	Single study (cross-sectional)		Reynolds et al., 2006	MPXV can be transmitted to humans directly or indirectly, through percutaneous, inhalational, or mucotaneous exposures. Direct contact with infected animals often includes traumatic injury to the skin. During the 2003 US outbreak, some individuals reported being bitten, handling of animals, or being in the same room as an infected prairie dog. Out of the 47 confirmed or probable MPXV cases, 27 reported exposure in a home environment through contact with an ill pet, 12 of which reported a specific invasive exposure such as a bite or scratch. The remaining 20 cases reported exposure through an occupational animal care setting including pet stores, animal swap meets, or

				veterinary clinics, where 5 reported a specific invasive exposure. The rest of the cases reported non-invasive exposures including touching or handling, cleaning an infected animals cage, or being in the same room as an infected animal. The route of transmission was found to influence symptoms and disease severity.
	Editorial		Kantele et al., 2016	MPXV is transmitted to humans through direct contact with infected animals. The increased use of rodents as a food source in the DRC and number of people seeking refuge in rainforests may contribute to increased exposure to the virus.
	Non-systematic review		Lloyd-Smith et al., 2009	MPXV can cause spillover transmission from animal reservoirs into human populations. The spillover force of infection is determined by the prevalence in reservoir, reservoir-human contact rate, and probability of infection.
	Non-systematic review		Lashley, 2006	MPXV is usually transmitted to humans from an infected animal through its bite or close contact. In Africa, the preparation or consumption of infected rodents or monkeys is associated with transmission to humans.
	Editorial		Bray, 2009	- MPXV was only discovered in 1970 during smallpox eradication campaign in the DRC, with smallpox-like infection in an infant in a rural village that could not be linked to prior person-to-person transmission - Feared that child contracted smallpox from an animal reservoir, but further testing found the agent isolated from her skin to be MPXV - Incidence of MPXV markedly increased 30 years later, reflecting increased exposure of population to maintenance hosts due to recurrent civil wars in the region, bringing residents closer to animals, and growing traffic of bushmeat
	Non-systematic review		Wrangham et al, 2000	- Hunting, butchery, consumption of primates has been linked to epidemics of monkeypox - However, MPXV can also transmit due to chimpanzee predation on humans - For instance, in Kivu, DRC in May 1982, a

				chimpanzee seized and bit a 6-month old infant in the left foot, fracturing the left femur. The infant later developed MPXV infection as a result of the bite
	Systematic review	Critically low (AMSTAR-2)	Brown and Leggat, 2016	- Prairie dogs infected during the 2003 outbreak became amplifying hosts which infected humans - Discovery of MPXV in prairie dog lungs was the first suggestion of transmission via infective droplets, while other US patients were infected through bites and scratches from infected prairie dogs - Eating infected bushmeat or monkeys appears to be documented, but to a much lower extent in terms of zoonotic transmission - Other risk factors for zoonotic transmission of MPXV include living in forested or recently deforested areas, no smallpox vaccination, handling or eating bushmeat, sleeping on the floor - It is unknown if animal species indigenous to the USA can maintain a zoonotic cycle of MPXV, but it is believed that repeated animal reintroduction of MPXV is required to sustain the disease in the human population
	Non-systematic review		Ligon, 2004	- A three-year-old girl was hospitalized in central Wisconsin after being bitten by a prairie dog - Within two weeks of this index case, another report from Milwaukee came out of a meat inspector who was also a distributor of exotic animals - had sustained bite and scratch from an infected prairie dog in May - contact tracing found that he had sold the prairie dog to the girl's family during a swap-meet - Transmission usually occurs via animal bite or direct contact with animal lesions or body fluids, with both respiratory and direct mucocutaneous exposures as important routes of MPXV transmission between rodents and humans
	Non-systematic review		Bernard and Anderson, 2006	- Most patients during the 2003 US MPXV outbreak were exposed to prairie dogs, primarily from an animal distributor in Illinois, mostly through direct physical

				contact with infected animals via bites, scratches, and open wounds - Repeated animal reintroduction of MPXV is necessary to endemic infections in human populations - human cases in endemic areas tend to be sporadic, directly associated with direct animal-to-human transmission
	Non-systematic review		Reynolds et al, 2007	- Case control study on the determinants of animal-to-human transmission of MPXV, comparing MPXV-infected cases and uninfected controls - Prairie dogs were considered MPXV-infected if tissues obtained postmortem were positive for MPXV DNA by culture or PCR (barring this, animal was defined as infected if it had signs, symptoms of MPXV infection and housed at a facility where other animals had known MPXV infection) - Several types of direct (touching or receiving a bite/scratch) and indrect (nontactile) exposures with infected animlas were associated with risk of being infected with MPXV and developing MPXV-related illness - Among 61 participants, 9 were scratched by an infected prairie dog - of these, 1 had prior smallpox vaccination - Only one case reported a prairie dog bite vs none of the controls - Having cleaned the cage, touched used bedding of an infected animals was signficantly associated with MPXV illness development, even after adjusting for smallpox vaccination
	Published report		CDC, 2003	- First report from the CDC MMWR in the wake of the 2003 US outbreak of MPXV, from prairie dogs and imported African small mammals and rodents - As of June 10, 2003, total of 53 cases were investigated in Illinois, Indiana, Wisconsin, with detailed clinical information available for 30 cases - All patients reported contact with animals, with atleast 2 also reporting contact with another patient's lesions or ocular drainage - Traceback investigations have identified

				a common distributor where prairie dogs and Gambian giant rats were housed together in Illinois
	Non-systematic review		Wolfe et al, 2005	- Transmission from animals to humans have usually resulted in localized epidemics, with limited chains of transmission (usually upto 4 cycles). - Confirmed and possible transmission routes include: direct contact with body fluids, infected organs and tissues, and bites.
	Single study (serosurvey)		Salzer et al, 2013	- MPXV outbreaks have occurred in the Congo basin where handling of infected animal tissue is thought to be the main source of infection - Previous outbreaks of MPXV have consisted primarily of population of people that rely on hunting and bushmeat as a primary food source
	Single study (case report)		Berthet et al, 2011	- In June 2010, two boys aged 14 and 15 were found tom have diffuse maculopapular lesions associated with pustules and crusts - Boys had been living in a settlement in the deep forest area of the southern Central African Republic - Lesions developed after the boys had hunted and eaten a wild rodent (bemba) - MPXV was detected by quantitative PCR based on partial hemagluttinin gene and identified by sequencing - Strain was identical to one associated with an outbreak of MPXV in 2001 in the border between Central African Republic and DRC - after eating a dead monkey, four members of one family showed similar skin lesions
	Non-systematic review		Pattyn, 2000	- MPXV likely to be transmitted through the skin, specifically by handling infected animals
	Single study (modelling study)		Thomassen et al, 2013	- Modelling of MPXV hotspots in Sankuru district, DRC found that forest clearing and climate were important risk factors for MPXV transmission from reservoir species to humans.

	Non-systematic review		Damon, 2011	- From 1980 to 1986, 245/338 (72%) of MPXV human cases were due to animal exposure, and 93/338 (28%) were due to possible human-to-human transmission. - Interviews with confirmed MPXV cases due to animal exposure revealed that 30% had been in contact with non-human primates, 20% with terrestrial rodents, 13% with antelopes and gazelles, and 7% with tree squirrels. - Forms of contact included hunting, cooking, eating, and contact with the carcass (e.g. skinning, trapping). - From 1996 to 1998, 22% of MPXV human cases were due to animal exposure, while the rest were human-to-human transmission. - In the 2003 USA outbreak, among the 37 confirmed human MPXV cases and 10 probable cases, all cases were associated with exposure to a sick prairie dog.
	Non-systematic review		Regnery, 2007	- In the 2003 USA outbreak of MPXV, infected prairie dogs (Cynomys sp.) transmitted the virus to humans. - More than 500 animals of various species had been shipped from Ghana to Texas, and MPXV had been isolated from at least 3 rodent species that had been shipped: giant pouched rats (Cricetomys gambianus), rope squirrels (Funisciurus spp.), and dormice (Graphiurus murinus). - All confirmed human cases had been in contact with infected prairie dogs, which had been kept at the same distributor facility that some of the animals from Ghana were housed. - Authors suggest that prairie dogs may have been vectors due to their viral shedding (high viral titers have been found in prairie dog urine, feces, and skin tissues), and their behaviour with humans such as biting and scratching.
	Non-systematic review		Di Giulio and Eckburg, 2004	- In the 2003 USA outbreak, the first reports of MPXV cases to the CDC described patients who had been in close contact with pet prairie dogs and other mammals, and then presented with a fever and rash.

				- Based on traceback investigations, a shipment of 800 small mammals from Ghana was identified as the likely source of the outbreak. - CDC laboratory testing of these mammals showed that at least three dormice, two rope squirrels, and one Gambian giant rat were infected with MPXV. - The giant rats had been transported from Texas to an Iowa pet distributor where they were kept with prairie dogs (Cynomys spp.), who became infected and then were transported to a vendor in Wisconsin, where the index case came into contact with them. - Passive surveillance from 1970-1979 found that among 47 reported cases in Central and western Africa, 91% were transmitted from animal to human (while 9% were transmitted from human to human). - Active surveillance from 1981-86 found that among 338 reported cases in DRC, 72% were transmitted from animal to human, and the suspected source was forest animals. - Outbreak investigations from 1996-1997 in the DRC found that among 419 cases in the outbreak, 22% were transmitted from animal to human. - A theory as to why there was a large MPXV outbreak in 1996-97 in DRC is because of greater contact between infected animals and a human community displaced by civil war. - An outbreak investigation in 2003 in the USA found that among 81 cases in the outbreak, 100% were transmitted from animal to human, and the suspected sources were prairie dogs and Gambian giant rats.
	Single study (outbreak investigation)		Kile et al, 2005	- In Indiana, two MPXV-infected prairie dogs had been bought and kept in a home child care facility for 11 days; 13% (9/70) of humans exposed to the prairie dogs reported MPXV clinical illness. - The risk of symptomatic infection (clinical illness) was correlated with the extent of

				exposure to the prairie dogs: 100% (4/4) of family members with "extensive direct contact" had clinical illness; 19% (6/26) of vets and child care attendees with moderate exposure had clinical illness; and 0% (0/40) of the students at the school where the prairie dogs had visited (with limited exposure) had clinical illness. - 2/5 children with symptoms reported direct contact with the prairie dogs, while 4/20 children without symptoms reported contact; none were bitten or scratched by the prairie dogs. - The authors suggest that direct contact with the prairie dogs was the most likely transmission route, based on the fact that all confirmed human cases had reported "extensive contact" with the prairie dogs, and historical data.
	Single study (outbreak investigation)		Nolen et al, 2015	- In a community case-control investigation in the DRC during a 2013 outbreak, there was no significant association between risk of MPXV and animals in the house; dead animals around the house; contact with animal feces; being bitten or scratched by an animal; and hunting or cooking wild animals. - Two families with cases described how their children had played with squirrels in the days before the first MPXV case in the household. - Among three rope squirrels (Funisciurus spp.) tested from the affected outbreak area in the DRC, two tested positive for IgG antibodies to Orthopoxviruses. - All other animals that were tested (65 animals, belonging to the orders Rodentia, Insectivora, Macroscelidea) from the same area were seronegative.
	Single study (outbreak investigation)		Reed et al, 2004	- In the 2003 USA outbreak, a three-year-old girl was bitten by a prairie dog and then became hospitalized with cellulitis and fever; the prairie dog had become sick the same day it bit the girl. - A man was bitten and scratched by a prairie dog, then 5 days later he developed a nodular skin lesion where he had been scratched, and then another 3 days later

				he developed fever, chills, sweats and lymphadenopathy. - The prairie dogs had been transported with a sick Gambian giant rat (Cricetomys sp.) from one distributor to another, and had no direct contact with the sick rat (in its own cage) during the trip; five days later the prairie dogs became sick. - In all 11 initial human cases in Wisconsin, MPXV transmission was suggested due to direct contact with an infected prairie dog. - Two of these cases had been scratched or bitten by a prairie dog, and three cases had likely been infected through open wounds (a cat scratch on the hand; a cut on the hand; and brush scratches on the legs).
	Single study (outbreak investigation)		Nakazawa et al, 2013	- For the origins of the 2005 MPXV outbreak in Sudan, authors had two hypotheses: an unknown local MPXV strain was naturally occuring in the outbreak area, or MPXV was imported from another area where it is endemic. - Phylogenetic analysis found that isolates from the 2005 Sudan outbreak were most closely related to isolates from northern DRC, which indicates that the outbreak likely originated from that area. - Ecological niche models identified that the 2005 outbreak occured in areas not suitable for MPXV transmission, so the first hypothesis (a naturally occuring local MPXV strain) is unlikely. - Considering that genetic analysis found the outbreak isolates to fall within the Congo basin clade (i.e. isolates from the outbreak and DRC were genetically similar), the importation hypothesis is more likely. - Civil war had also been going on at the time of the outbreak, in which people fled from Sudan to DRC and then back when the war ended, which supports the importation hypothesis.
	Non-systematic review		Lashley, 2004	- In the 2003 USA outbreak, MPXV in humans was due to close contact with pet prairie dogs, who had been kept in the same warehouse as an infected Gambian

				giant rat before distribution to pet stores. - One MPXV human case in the USA outbreak was due to contact with a pet rabbit. - MPXV outbreaks in Africa are often due to handling and consuming rodents and monkeys infected with the virus.
	Single study (animal report)		Guarner et al, 2004	- Prairie dogs infected with MPXV during the USA 2003 outbreak had many viral antigens and mature poxvirus particles in their tongue and conjunctival lesions, so it is possible that the virus was transmitted through direct contact between the saliva or lesions of the infected prairie dog and the skin or mucous membrane of another animal or human. - Since the prairie dogs' lungs showed many replicating MPVX, it is possible the virus was transmitted to other animals or humans through coughing and respiratory droplets.
	Guidelines		Petersen et al, 2016	- Humans at risk of occupational exposure to orthopoxviruses (such as MPXV) include laboratory personnel who are in contact with or who handle live orthopoxviruses or clinical samples from orthopoxvirus cases; animal care personnel who are in direct contact with infected animals or secretions; and health care personnel in contact with infected patients.
	Single study (outbreak investigation)		Croft et al, 2007	- In an outbreak investigation in 2003 in Wisconsin, USA, 12/27 cases (44%) were staff in veterinary facilities where sick prairie dogs had been treated; the other cases were 6 individuals in households with prairie dogs; 1 who visited a household with prairie dogs; 2 employees at pet stores where the prairie dogs had been kept; 4 visitors to the pet store; and 2 animal distributors that had kept and transported the prairie dogs. - The two infected pet store employees had reported handling the sick prairie dogs; however, four other pet store employees who had handled the sick prairie dogs tested seronegative for orthopox IgM antibodies 2 months after the last exposure to the sick prairie dogs.

				- Two animal distributors who had kept the sick prairie dogs in their home became a confirmed case and suspected case, while an immunocompromised member in their household who did not have direct contact with the prairie dogs became a confirmed case. - Among personnel at four veterinary facilities that had treated 3 prairie dogs linked to the outbreak, 17 MPXV cases occured, and never having handled a sick prairie dog was a significant protective factor against MPXV. - Working in a role that involved direct animal care (e.g. veterinarian) was a significant risk factor for being a MPXV confirmed case. - Exposures that were significant risk factors for being a MPXV confirmed case included: feeding the sick prairie dog; conducting an examination of a sick prairie dog; and treating an animal within 6 feet of a sick prairie dog. - All of the cases at the veterinary facilities reported hand hygiene after contact with the sick prairie dog (examination or feeding), although none had worn surgical masks, goggles, or face shields; some had worn gloves (40% of personnel wore gloves when conducting an initial exam, 60% for the follow-up exam, 75% for feeding). - Among 7 MPXV cases who reported no contact with a prairie dog, they had all experienced indirect exposure: 5/7 were within 3 feet of a prairie dog, 1/7 was in the same room as a prairie dog, 1/7 was not present at the facility when the prairie dog was present, but was there within 48 hours of the prairie dog's death; these 7 cases without direct contact suggest that fomite and/or aerosol transmission may have occured. - Antihistamine use during the prairie dog's visit was a significant risk factor for being a MPXV case, and the authors theorize that this may be because individuals who use antihistamines tend to

				have allergies or rhinorrhea and would therefore often touch their eyes or nose. - Overall, veterinary staff were at higher risk of occupational exposure to MPXV (23% attack rate) compared to pet store employees (7% attack rate), and the authors hypothesize that this is because the infected prairie dogs were likely more sick and shedding higher amounts of virus when they were at the veterinary facility compared to the pet store.
	Scoping review	Critically low (AMSTAR 2)	Kipkorir et al, 2022	- Zoonotic transmission can occur from consumption of an infected animal host (primates or rodents) or direct contact with infected animal or its blood, other bodily fluids and/or its mucocutaneous lesions, or via animal bites - Important risk factors of MPXV disease from a zoonotic transmission standpoint include exposure to animal reservoirs, handling or consumption of uncooked meat products, and living near deforested regions with high rates of animals infected with virus - Human MPXV infection can be acquired through various routes (respiratory tract, skin, mucous membranes) and from various sources (rodents, other humans, and nonhuman primates)
	Non-systematic review		Antunes et al, 2022	- Nearly two years after last smallpox case, on September 1, 1970, a 9-month-old child suspected of having smallpox was admitted - Rash lasted two weeks, specimens from the patient were found to be positive for MPXV, making this the first recognized human infection - Child was from the Bokenda Village, located near tropical rain forest and where monkeys are eaten from time to time - implicating contact with dead monkeys and consumption of bushmeat as enablers of animal-to-human transmission - Contact with animal reservoirs, including live or dead animals, through hunting and preparation of bushmeat is a presumed driver of MPXV infection in humans -

				primarily through direct (bite, scratch) or indirect contact - Closer contact can be enabled with animals through deforestations, demographic changes, climate change, hunting, population movement closer to forests
	Non-systematic review		Chowdhury et al, 2022	- Sleeping outside the home, or near the forest can increase the risk of direct contact with animals. - Acquiring MPXV contact with sick animals every day or cleaning their bedding and cages are also risk factors, sufficient to break in skin by catching or touched by an infected animal
	Non-systematic review		Farasani, 2022	- Outbreak of MPXV in the USA in 2003 was linked to direct contact with MPXV-infected pets - Rats and dormice brought from Ghana to the USA, shared a cage with other pets - due to direct contact with the infected pets, over 70 cases of MPXV were reported in the USA
	Non-systematic review		Gessain et al, 2022	- Zoonotic transmission occurs through contact with the lesions or biologic fluids of an infected animals, often during hunting, butchering, or game consumption.
	Non-systematic review		Hasan and Saeed, 2022	- Many animal species are prone to infection, with zoonotic transmission occurring through handling and consuming infected animals in endemic regions. - MPXV infection primarily spreads through direct physical contact, scratches or bites from an infected animal, or consumption of the host animal - Those responsible for handling and consuming dead animlas are more vulnerable to the zoonotic spread of the infection

	Non-systematic review		Hatmal et al, 2022	- Zoonotic infections occur by direct contact with mucocutaneous lesion content, body fluid, and blood of infected animals, or even by consuming undercooked meat of an infected animal. - Complex exposure that recognizes groups of patients who were scratched and bitten by infected animals, in addition to exposure to non-invasive virus transmission such as touching or standing close (<6 feet) to an infected animal or fomite transmission were significantly associated with serious systemic illness needing hospitalization
	Non-systematic review		Ilic et al, 2022	- MPXV is transmitted to humans via contact with infected animal, or through contact with contaminated material - Zoonotic trasnmission can occur via broken skin, respiratory tract droplets, or mucous membranes - Another possible risk factor is the consumption of inadequately cooked meat and other animal products originating from infected animals - Animal-to-human transmission through contact with animals was considered the main factor for human MPXV infections
	Non-systematic review		Jeyaraman et al, 2022	- MPXV is transferred through contact with an infected person or animal, as well as other materials contaminated with the virus. - Animal bites or scratches, meat processing, direct and indirect contact with contaminated animal debris, and other factors can all contribute to the spread of MPXV from animals.
	Non-systematic review		Kim et al, 2022	- When a person contacts an infected animal, MPXV can be transmitted via bites and scratches by an infected animal, handling wild animals, or using products derived from infected animals - MPXV can also be transmitted via direct contact with infected bodily fluids or lesions from an infected person, or contaminated fomites like bedding.

	Scoping review	Critically low (AMSTAR 2)	Kipkorir et al, 2022	- Zoonotic transmission can occur from consumption of an infected animal host (primates or rodents) or direct contact with infected animal or its blood, other bodily fluids and/or its mucocutaneous lesions, or via animal bites - Important risk factors of MPXV disease from a zoonotic transmission standpoint include exposure to animal reservoirs, handling or consumption of uncooked meat products, and living near deforested regions with high rates of animals infected with virus - Human MPXV infection can be acquired through various routes (respiratory tract, skin, mucous membranes) and from various sources (rodents, other humans, and nonhuman primates)
	Non-systematic review		Li et al, 2022	- MPXV can be transmitted from animals to humans through direct contact, respiratory droplets, or fomites - It has been reported that the MPXV epidemic in Nigeria from 2017 to 2018 was caused by the transmission of animals, potentially rodents, to humans and the limited and unsustainable chains of transmission between humans
	Non-systematic review		Sah et al, 2022	- In addition to the 2003 outbreak of MPXV in the US, one case was identified in Singapore in May 2019, associated with ingestion of potentially contaminated barbecued bushmeat was reported
	Systematic review	Critically low (AMSTAR-2)	Rahimi et al, 2022	- In 1973, DRC, Liberia, and Sierra Leone reported a total of 6 cases of HMPX (including the first case), four of them were classmates, and two others had close contact with monkeys. - In 1981, an intensive active surveillance program in The DRC identified 338 HMPX

				cases, of these, 245 infections (72%) were revealed to be animal-originated. - The outbreaks of HMPX in the United States in 2003 was all animal-to-human A retrospective investigation confirmed that all HMPX cases have been linked to purchasing prairie canine species from an animal dealer. The prairie canine species became infected by contact with rodents imported from Ghana (west of Africa) to Texas. - The MPXV is conventionally transmitted by direct contact with fluids, lesions, and mucosa of the infected animals.
	Non-systematic review		Tiecco et al, 2022	- During the 2003 outbreak in the US, 71 human cases derived from a shipment of infected Gambian pouched rats which subsequently infected prairie dogs. - The MPXV infection affects several different animals, with both monkeys and humans being accidental hosts. One of the routes of transmission is contact with an infected animal's body fluid, through an animal bite or through the consumption of raw or minimally processed meat. The intensity of animal contact correlates to the severity of clinical manifestations
	Non-systematic review		Shafaati & Zandi, 2022	- Direct contact with the blood, body fuids, cutaneous or mucosal lesions of infected animals can result in animal-to-human (zoonotic) transfer. Eating raw meat and other animal products from infected animals is one potential risk factor.
	Non-systematic review		Dou et al, 2022	- Occurrence of MPXV was more due to animal-to-human transmission than human-to-human transmission - Direct contact is the main route of transmission from animals to humans, such as through contact with live and dead animals through hunting and consumption of bushmeat - Outside of Africa, children are infected by exposure to infected pet rodents

	Non-systematic review		Ejaz et al, 2022	- MPXV is transmitted through large respiratory droplets, direct skin-to-skin contact, contaminated fomites, respiratory secretions, and vertical transmission in animals, and between animals and humans - MPXV is transmitted from animals to humans during trapping, hunting, processing infected animals, and dealing with their bodily fluids - Animal-to-human transmission of MPXV Is a risk for people who sleep outside, live near, or work in forests, deal with rodents, or care for animals.
	Non-systematic review		El Eid et al, 2022	- Animal-to-human transmission is well documented, usually through contact with infected animal's bodily fluids or through a bite - For example, during the US outbreak, exposure was often classified as "noninvasive" (touching an infected animal) or "complex" (invasive bite from an ill animal) - Historically, most MPXV outbreaks have occurred in rural populations living in small villages abutting or contained within humid evergreen tropical rainforests ("human-animal interface") - As such, most MPXV cases found in young human males, who have been noted to trap and play with small rodents and their carcasses - Indeed, an outbreak in Nigeria from Sept 2017-April 2018, had an initial cluster of 4 male individuals who became ill after killing and eating a captured, infected monkey from the area
	Non-systematic review		Forni et al, 2022	- In endemic regions, human cases occur in rural areas and derive from independent introductions from animal reservoirs (such as rodents). - Surge in human cases started in 2017 in West Africa alongside an increased incidence in primate communities, after decades of viral inactivity in the Ivory Coast - Rise in cases in 2017 could be associated

				with changes in MPXV disease transmission within animals, as well as increased susceptibility to poxviruses in humans owed to reduced smallpox immunity in the population - Before May 2022, MPXV transmission was characterized by interactions with infected animals, with little human-to-human transmission
	Non-systematic review		Kolte et al, 2022	- Conditions that promote circulation of MPXV in humans and animals include constant MPXV circulation in animals in forest and agricultural areas surrounding human settlements - As well as the use of meat of wild animals as an important source of animal protein, as well as close contact of humans with wild animals - Since 1970, most cases of MPXV have been reported in rural, rainforest regions of the Congo Basin in the DRC - MPXV can spread from animals to humans via direct contact with blood, bodily fluids, or cutaneous/mucosal lesions of infected animals
	Non-systematic review		Riopelle et al, 2022	- Many potential routes of zoonotic (animal-to-human) transmission have been posited. In endemic areas, direct contact with animals, including dead or sick animals, and hunting, butchering, and eating bushmeat have been linked with MPXV infection - Bites and scratches have also been implicated, as has indirect transmission (such as via respiratory droplets) - Most notable importation of MPXV into non-endemic countries due to prairie dogs transmitting disease to human owners via bites and contact with bodily secretions, during the US outbreak in 2003 - Clear information on specific routes of zoonotic transmission are lacking, but there is potential for peri-domestic cycle of MPXV and preventive measures against such cycles need to be developed

	Scoping review	Critically low (AMSTAR 2)	Adnan et al, 2022	- Animal-to-human infection has been linked to contact with wild animals - however, the precise exposure mechanism is unknown - This is particularly true in areas where contact with animals may have occurred through household rodent infestations or hunting/preparation of bushmeat for domestic consumption - Transmission shown to occur via saliva and respiratory excretions, or contact with lesion exudate, crust material, or feces of infected animals
	Non-systematic review		Gomez-Lucia, 2022	- Earlier epidemiological studies (prior to the current outbreak) suggest transmission of virus between humans was not efficient, with most cases occurring from repeated spillovers from animals - Factors include deforestation (increased exposure to animals usually in the jungle), violence in the region, and lack of conventional food (increasing consumption of bushmeat) - Synanthropic rodent population, which has increased in recent years in Africa, has led to more human-rodent interactions and increased transmission of MPXV - During the 2003 outbreak of MPXV in the US, the first 53 cases had been in contact with prairie dogs, traced back to animal distributors in Texas - 22 animals were tested positive for MPXV including Gambian pouched rats, and squirrels
	Non-systematic review		Varela et al, 2022	- 2003 outbreak of MPXV highlights the effect of comingling wildlife and domestic animals on public health through emergence of MPXV - Exposures to infected prairie dogs occurred among several groups including children attending in-home childcare, and healthcare workers

	Scoping review	Critically low (AMSTAR 2)	Di Gennaro et al, 2022	- First outbreak outside of Africa was in the US in 2003, which occurred due to exposure to infected prairie dogs which had contracted MPXV from infected exotic animals imported from Ghana - A possible risk factor for transmission is consumption of undercooked meat and other animla products from infected animals - People living in or near wooded regions may be exposed to infected animals in an indirect/low-level manner - Can be transmitted (with difficulty) via contaminated body fluids/lesion materials, both directly and indirectly - direct exposure includes fomites, respiratory secretions, skin-to-skin contact with MPXV-infected humans or animals
	Non-systematic review		Ranganath et al, 2022	- The first outbreak outside the African continent occurred in the United States of America (USA) in 2003 when native prairie dogs served as vectors and amplifying hosts after they were cohabited with imported small African mammals. - The Nigerian outbreak of 2017-2018 befits a special mention as it was till then the largest West African clade outbreak to occur. Both primary zoonotic and secondary human-to-human transmission was noted. - A number of reasons for the resurgence of monkeypox cases have been proposed, the primary ones being waning immunity after the cessation of smallpox vaccination in 1980, deforestation, climatic change, armed conflict, mass population displacement, increased consumption of bush meat and greater global travel. The Nigerian outbreak was preceded by heavyrainfall and flooding that is hypothesised to have increased animal-human contact as both reached out for dryer, high lands. - The primary zoonotic transmission of the virus can occur via contact with blood, body fluid and lesions of infected animals

				that most commonly happens while hunting. Similar routes have been described for human to human transmission, along with fomites and respiratory transmission which needs prolonged face to face contact. - Earlier studies found the human-to-human transmission reproductive rate (R0) to be 0.8, thus dismissing the self-sustained transmission and epidemic potential of the virus. - Although sexual transmission has not been established for the virus previously, early evidence from the ongoing outbreak has suggested transmission within sexual networks, particularly in men having sex with men.
	Non-systematic review		Kumbhar and Agarwala, 2022	- Outside of Africa human MPX was first reported in 2003, when 43 cases occurred across USA after direct or indirect contact withinfected pet prairie dogs (*Cynomys sp.)*. - The latter had been in turn infected after housing in Illinois close to a shipment of rodents (including rope squirrels *(Funiscuirus sp.)*, tree squirrels *(Heliosciurus sp.)*, Gambian giant rats *(Cricetomys sp.*), brushtail porcupines *(Atherurus sp.)*, dormice *(Graphiurus sp.)*, and striped mice *(Hybomys sp.)*) imported from Ghana (which has never reported a human case) to Texas. No interhuman transmission was detected. - Nearly 300 of the animals imported from Ghana and the exposed prairie dogs were not traced. - MPXV transmission to humans mainly occurs through direct and strict contact with an infected patient or animal, or with contaminated materials. The virus penetrates mucosae or skin wounds. - MPXV transmission through live or dead infected animals has represented the leading route to human MPX infections: the contact can be either direct (body fluids or lesions, bites, bush meat preparation or raw eating) or indirect via

				fomites (e.g. surface contamination in hospital rooms). - Interhuman transmission is driven by large respiratory droplets during strict and prolonged face-to-face contact, because of lesions in oral and respiratory mucosae, or via sexual contact. - Human-to-dog transmission (reverse zoonosis) has been documented in a pet contact of confirmed cases. Whether MPXV can infect rodents in sewages remains to be established.
	Non-systematic review		MacNeill et al, 2022	- Transmission of MPXV occurs via contact with skin lesions and respiratory droplets. The disease can also be spread through scratches and bite wounds from infected animals. Human-to-human transmission has been well documented.
	Editorial		Rothenburg et al, 2022	- MPXV is similar to smallpox, but does not have a restricted host range, employs wild rodents as primary reservoirs with occasional spillover leading to cases of MPXV in humans (until recently, when outbreaks have been more commonly propagated by human-to-human contact) - Establishment of a reservoir of MPXV in the wild rodent population is a possibility in a previously non-endemic region, making control and eradication of MPXV more challenging
	Letter to the editor		Alavi-Moghaddam, 2022	- MPXV is transmitted via direct contact with blood, bodily fluids, spots, blisters, or scabs of infected animals or infected persons, as well as through contact with infected fomites (such as clothing, bedding, or towels of infected persons) and consumption of raw/under-cooked meat from infected animals
	Commentary		Brewer et al, 2022	- Outbreak in 2003 was initiated through import of MPXV-infected exotic rodents from Africa and subsequent spread to captive prairie dogs and humans - Animal-to-animal transmission: Domestic animals in the 2003 outbreak were

				exposed to bedding of MPXV-infected exotic rodents (rope squirrels, Gambian rats, dormice) imported from Africa - This led to concern that animals infected with MPXV may escape and/or be released into the wild and subsequent infect rodent or other small mammal populations in the US - This, among other instances with other orthopoxviruses (such as the feral vaccinia virus outbreak in 2008 in South America), highlights the potential for reverse zoonoses, including transmission of current MPXV strain from humans to indigenous animal populations, establishing endemicity outside Africa
	Commentary		Okonji and Okonji, 2022	- MPXV can be transmitted via direct contact with bodily fluids, lesions, respiratory droplets, and contaminated items such as bedding or other fomites used by either infected animals or infected humans - Consumption of inadequately cooked/prepared meat from infected animals and other animal products is a potential risk factor for acquiring MPXV - Other factors related to waning of MPXV- and other orthopoxvirus-related herd immunity from prior smallpox vaccination and increased human contact with suspected reservoirs include: deforestation, trade, animal husbandry, and climate change - Monitoring of potential animal reservoirs, such as rodents, but also of novel transmission routes needs to be considered
	Non-systematic review		Petersen et al, 2019	- Primary animal-to-human transmission is assumed to occur through direct or indirect contact with monkeypox infected animal body fluids through handling, bites or scratches, or consumption of bushmeat

	Non-systematic review		Singhal et al, 2022	- Humans are infected by bite/scratch, close contact, eating inadequately cooked meat of infected animals
	Non-systematic review		Zhu et al, 2022	- Animal-human transmission is somewhat unclear, with aerosol transmission implicated in animals such as in the nosocomial outbreak in the Central African Republic - However, zoonotic transmission seems to have increased alongisde increasing rates of poverty and persistent civil strife, forcing people to hunt small mammals for bush meat and increasing interactions with wild rodents which may carry MPXV - MPXV is also believed to be transmitted by being bitten or scratched by infected animals, or eating meat from infected animals that are improperly cooked
	Non-systematic review		Lai et al, 2022	- Animal-to-human transmission occurs through direct contact with infected animal's blood, body fluid, skin, or mucosal lesions - Moreover, consuming inappropriately cooked meats/products of infected animals could be another transmission route - Risk factors include close contact with infected animals
	Non-systematic review		Cheema et al, 2022	- Animal-human transmission: direct contact, bite, scratch from infected Animal, or consumption of an Animal host, usually a rodent or a primate - RIsk factors include: living in forested/recently deforested areas, no smallpox vaccination, handling or eating bushmeat or monkeys, sleeping on the floor (mainly in endemic areas) - First MPXV outbreak outside of Africa reported in the USA, with infected African mammals were shipped from Ghana, and transmitted MPXV to native American

				prairie dogs and spreading the disease to humans
	Editorial		Angelo et al, 2019	- In September-October 2018, three international travellers became infected with MPXV after exposure in Nigeria - one traveller from Israel was likely infected with MPXV in Nigeria after exposure to two dead rodents in his home - In recent years, it is possible that increasing civil unrest in West and Central Africa is bringing humans closer to animals harboring MPXV, raising the likelihood of environmental disruption and the need to eat wildlife - MPXV transmission occurs through direct contact with skin lesions, feces of ill animals, as well as exposure to bushmeat
	Letter to the editor		Saied, 2022	- Aerosol route could play an important role in secondary transmission, however this is still unclear - Different routes of human MPXV exposure can lead to variations in disease course in humans and monkeys, with aerosolized MPXV showing similar susceptibility of cynomolgus monkeys to MPXV as humans to smallpox - This has been corroborated by findings of MPXV DNA shedding from upper respiratory tract after skin lesion resolution in monkeys
	Published report		Reynolds et al, 2019	- Outbreak of MPXV investigated in Kpetema town in Sierra Leone, with the first case found in an 11-month-old male in Mano village, evaluated for fever and lesions - Following investigations of residents in the village, found that the boy did not have any contact with animals, but the family reported regularly preparing and consuming meat from wild animals and some exposure to rodents in the family house

				- Similar presentations were noted in a 35-year-old male farmer - Routine encounters with sylvatic animals which may harbor MPXV, in addition to ceased routine vaccination against smallpox (known to also confer some protection against monkeypox)
	Non-systematic review		Haddad and Cordevant, 2022	- Indirect transmission has been noted experimentally, in animals housed in rooms or cages that have contained sick animals - environmental contamination from secretions and scabs can lead to indirect infection of animals, similar to nosocomial infection of healthcare staff from infection blankets
	Preprint (single study, longitudinal)	Low (provisional)	Yuan et al, 2022	- From the modelling study looking at MPXV transmission in a simulated metropolitan city, humans were found to be at greater risk of outbreaks when animal hosts were included and allowed to contribute to cases in the model - Rash motivated isolation of individuals may not be sufficient to curb MPXV cases due to potential reinforcement of animal-to-human transmission - This effect can be seen as earlier peaks and multiple waves driven by animal transmission - isolation alone may not be effective if MPXV spreads to animal populations
	Systematic review	Low (AMSTAR 2)	Beer and Rao, 2019	- Hunting, handling, preparing bushmeat consistently implicated in developing clincial MPXV disease, finding that did not change over time since MPXV was first discovered, reported in 6 of 22 such reports identified in this systematic review - Of 22 reports describing routes of animal-to-human transmission between 1988 and 2018, 5 could not identify an animal source, 27 did not mention an animal source or other related risk factors for the outbreak

	Systematic review	Critically low (AMSTAR 2)	Bunge et al, 2022	- 29 peer-reviewed studies ADD DESIGN, reported mode of transmission for MPXV cases - Study from 1980s with 338 MPXV cases from Democratic Republic of the Congo (DRC) suspected animal sources in 72.5% of cases - 419 cases from the DRC in the 1990s showed only 22% of cases were animal-implicated - Nigerian outbreak in Sept 2017 found transmission was unknown for 62.3% of cases, with 8.2% reporting animal contact - UNCLEAR WHY CERTAIN STUDIES OF THE 29 were reported on and others were note. - Risk factors for transmission only reported in 5 studies from 3 countries (DRC, US, Republic of the Congo) - Risk factors related to animal contact included sleeping outside or on the ground or living near a forest - Adjusting for vaccination status against smallpox, daily exposure to sick animals (aOR: 4.0 (1.2-13.4)) and cleaning cages/bedding (aOR: 5.3 (1.4-20.7)) were idenitified as risk factors in 2003 US outbreak
	Review (non-systematic)		Doty et al, 2017	- Majority of captured animals, according to habitat analysis, were found to frequent areas close to human settlements, increasing likelihood of MPXV animal-to-human transmission
	Single study (cross-sectional)	High (8/9, NOS)	Whitehouse et al. 2021,	Of 837 confirmed cases with completed exposure history, 309 (36.9%) reported having had contact with ≥1 animal as their only exposure in the 3 weeks prior to symptom onset, and 279 (33.3%) reported contact with ≥1 symptomatic human with monkeypox-like symptoms as their only exposure in the 3 weeks before symptom onset. An additional 109 confirmed case patients (13.0%) reported contact with both animals and symptomatic humans, and 140 (16.7%) reported no known

				exposures; both groups were excluded from further analysis of exposure history. There were significant differences in exposure type by age (within males) and sex among cases with mutually exclusive exposures. Overall, males (57.1%; n = 176) were more likely than females (42.9%; n = 132) to report animal exposures ($\chi 2$ = 6.53; P = .01). Among females, those aged 5–19 and ≥40 years had higher frequency of exposures to animals than to symptomatic humans, although there was no significant difference by age groups ($\chi 2$ = 6.60; P = .25). Seventy-five percent of animal exposures among females occurred among those aged 5–29 years. Animal exposures differed significantly by age group among males ($\chi 2$ = 19.68; P = .001). Males aged 0–9 years were reported to have had more exposures to symptomatic humans than animals, a trend that was reversed beyond 10 years of age. Among males, the frequency of animal exposures ranged between 11.4% and 14.2%, except for males aged 10–19 years, who accounted for 37.5% of animal exposures. Monkeypox cases with animal exposures had contact with nonhuman primates (68.4%; n = 199), "rats" (typically refers to pouched rats of genus Cricetomys spp) (17.5%; n = 51), squirrels (10.3%; n = 30), or other domestic or wild animal species (15.2%; n = 44). Males were more likely than females to report contact with rats (72.6% vs 27.5%; $\chi 2$ = 5.43; P = .02), but there were no significant differences by age group . Females (58 of 132; 47.2%) were more likely than males (56 of 176; 34.8%) to report contact with a dead animal purchased for meat ($\chi 2$ = 4.44; P = .04). There were no significant differences by sex with other types of animal-human contact. Of the 279 case patients reporting contact with a symptomatic person, 96.1% (n = 268) reported 1 symptomatic contact, 2.9% (n = 8) reported 2 symptomatic contacts, and 1.1% (n = 3) reported 3 symptomatic contacts. Females (n = 149;

				53.4%) reported more contact than males with symptomatic people (n = 130; 46.6%; χ2 = 6.53; P = .01). Among 264 case patients with complete information on contact with symptomatic humans, family members were the most frequently reported contact (90.5%; n = 239), followed by friends (6.4%; n = 17), and others (3.4%; n = 9).
	Review (non-systematic)		Alakunle et al, 2020	- Animal-human transmission via respiratory droplets, contact with bodily fluids, contaminated items/fomites, skin lesions, consumption of infected animals
	Review (non-systematic)		Silva et al, 2021	- Consumption, hunting, handling of meat from non-human primates, rodents, other small mammals have been associated with human cases of MPXV infection - Close contact with rodents has also been implicated as source of human infection
	Review (non-systematic)		Xiang & White, 2022	Monkeypox in Africa is typically a zoonosis involving contacts with animals or their bodily fluids, respiratory droplets, and lesion materials. The point of contact is almost always speculated, but dead animals and fomites are also of suspicion as OPXV virion is remarkably stable, an extreme example being the isolation of infectious virus from smallpox scabs after 13 years of room temperature storage. Humanto-human transmission occurs also through close contacts.
	Review (non-systematic)		Quarleri et al. 2022	The two possible routes of MPV transmission are animal-human transmission and human–human transmission. Respiratory droplets and contact with body fuids, contaminated patient surroundings or objects, and skin lesions from an infected person have been found to be associated with human-to-human transmission. Zoonotic transmission occurs through direct contact with blood and body fuids and inoculation via mucocutaneous lesions of an infected

				animal, as well as through direct contact with or consumption of one of the natural viral hosts. Nosocomial transmission has also been reported. Currently a potential risk for reverse zoonotic transmission (human-to-animal transmission) is being monitored, as this could allow the virus to become established in wildlife, as is the case in Africa. New reservoirs of viruses would thus increase the likelihood of repeated transmission to humans. Therefore, it is important that rodents belonging to confirmed human disease cases be kept isolated and monitored to avoid possible transmission. In addition, despite the low risk for this phenomenon, such transmission may be silent because infected animals usually do not show the same visible symptoms as humans.
	Published report		Farahat et al. 2022	Human monkeypox transmission occurs through close contact with skin lesions, respiratory secretions, and bodily fluids of infected animals, either with direct or indirect contact through contaminated fomites.
	Systematic review	Critically low (AMSTAR 2)	Chauhan et al, 2020	- Dependence of humans on bushmeat in West Africa is a major driving factor behind the spread of monkeypox in west Africa - Until 1990, two confirmed MPXV cases were linked with monkeys being eaten as a delicacy, significant source of disease transmission, as well as hunting and butchering - Cases of MPXV in 1971 linked to spillover from possible reservoir host within the country, with similar conclusions drawn for September 2017 (61 cases out 172 suspected) - again, suggested that cultural, traditional practice of bushmeat hunting and trade - MPXV was reported in DRC between 2000-2009, 3 cases out of 12 suspected, with increasing frequency until 98 suspected cases in 2010-2018 - linked to

				higher human-wildlife conflict for bushmeat
	Single study (cross-sectional)		Quiner et al, 2017	- Humans acquire MPXV from either contact with an infected animal (primary zoonotic transmission) or from stuttering chains (R0 <1) propagated by inter-human transmission - To date, the virus has only been isolated twice from wild animals, once from a squirrel (Funisciurus sp.) in Congo and once from a sooty mangabey (Cercocebus sp.) - Hunting and butchering of bushmeat are presumed to be risk activities for primary zoonotic transmission.
	Published report		Yinka-Ogunleye et al. 2019	Among all confirmed cases, ten patients reported contact with animals (two with monkeys, two with rodents, two with unspecified wild animal [consumed as meat—ie, bush meat], and four with domestic animals). No one reported contact with sick or dead animals.
	Review (non-systematic)		Devaux et al, 2019	- Can be transmitted to humans via bites, scratches, scraping of lesions, cough, respiratory droplets, insufficiently cooked meat consumption
	Review (non-systematic)		Fenollar & Mediannikov, 2018	The virus is capable of infecting humans, other primates and rodents. Most of the reported cases were related to animal-to-human transmission and were associated with the handling and eating of infected animals (dead or alive) through hunting and preparation of bushmeat as food, but several cases of human-to-human transmission occurred.
	Published report		Durski et al. 2018	

	Single study (cross-sectional)		Guargliardo et al. 2020	
	Review (non-systematic)		Kabuga & Zowalaty, 2019	
	Single study (cross-sectional)		Guargliardo et al. 2020	Monkeypox outbreaks have occurred among captive chimpanzees housed at wildlife sanctuaries in SanagaYong in Sanaga-Yong in 2014 and in Mfou district in 2016.This study aimed to explore the frequency and type of contact with bushmeat, with focus on Gambian rats. Contact with the following animals was reported among participants: porcupines (82, 65.6%), Gambian rats (71, 56.8%), sun squirrels (35, 28%), and rope squirrels (33, 26.4%). Among villagers, we found contact with wildlife to be common, with near ubiquitous contact with porcupines. In addition to reports of hunting porcupines noted in our survey data, which reflects the popularity of this protein source, we also anecdotally observed the abundance of porcupine meat in local restaurants. Research from Nigeria, Gabon and the DRC have similarly identified porcupines as a common food source. As other researchers have noted, serological surveys of porcupines could be used to determine whether they may serve as a potential reservoir of MPXV and other zoonoses. Univariable regression models showed that participants with no formal education were significantly more likely to report any type of contact with Gambian rats, in addition to selling/touching, preparing, and eating. Park staff members were less likely to engage in hunting, selling/touching, or having any type of

				contact with Gambian rats. Multivariable modeling showed participants reporting more than one visit to the forest per week were 3.36 times as likely as those reporting < 1 visit to the forest per week to have recently eaten Gambian rats (95% CI: 1.91–5.92, P < 0.001). In comparison with community members, primate sanctuary staff were 0.23 times as likely (95% CI: 0.19–0.28, P < 0.001) to have recently touched or sold Gambian rats.
	Review (non-systematic)		Kabuga & Zowalaty, 2019	The most recent outbreak in the southern part of Nigeria started in September 2017 in the Yenagoa Local Government Area of Bayelsa State. It was suggested that the index case of this outbreak was not imported, and that the cases were rather a spillover from the reservoir hosts. Reported cases of MPXV infection in humans outside Africa occurred in the United States in 2003, where 37 were laboratory confirmed and 10 probable cases were reported. Most patients were reported to have had close contact with pet prairie dogs that were infected by African rodents imported into Texas and other states within the United States in a shipment of wild animals from Ghana, West Africa.
	Rapid review	Critically low (AMSTAR 2)	Diaz et al. 2021	Monkeypox is transmitted from rodents to humans by rodent bites and close contact with infected live or dead animals or their bodily fluids, often through hunting, skinning, or butchering of bushmeat as food. Human-to-human transmission occurs in approximately 10% of cases by respiratory droplets and by close contact with infected lesions or bodily fluids. Between May and July 2003, 71 cases of monkeypox were reported from 5 Midwestern US states. The outbreak was traced to imported, infected Gambian pouched rats (Cricetomys spp.) that were shipped from Texas to an exotic animal distributor in Illinois, who housed them with prairie dogs destined for retail sale.

Human-to-animal transmission	No additional evidence identified in the lookback for this domain.			
	Non-systematic review		Hasan and Saeed, 2022	- The current MPXV outbreak also saw the potential for human-to-animal transmission. - First confirmed case of MPXV virus infection in a dog was documented in Paris, which may have been acquired through human transmission
	Non-systematic review		Li et al, 2022	- Similar to SARS-CoV-2, humans infected with MPXV have recently been reported to spread the virus to domesticated animals by close contacts, raising concerns about the role of pets in MPXV transmission
	Non-systematic review		Sah et al, 2022	- Some animals imported into the US in 2003 from Ghana were infected with MPXV, and transmitted the virus to prairie dogs before their distribution led to a viral transmission - Moreover, rabbits in close contact with ill prairie dogs caught the infection and were considered the main source of transmitting the illness to one person.
	Published surveillance report		Shepherd et al, 2022	- This report outlined the current UK risk assessment and the surveillance system, and discuss the implications of surveillance findings on the future MPX outbreak response. This reported 3.5 months of surveillance (1 June–16 September 2022) data of pet animals (154 pets) cohabitating with a confirmed human MPX case (n=40). - The surveillance outcome showed that

				there have been no cases of animals with clinical signs suggestive of MPXV infection associated with confirmed human cases. Of these animals, 42 were dogs and 26 were cats. No animals have been presented to a veterinary practice, placed into quarantine, or tested for MPXV in the UK at the time of publication. - Conclusion from this report was the risk of transmission to pets from owners with a confirmed MPXV infection to be low. - This report also mentioned other incidents of human to animal transmission of MPXV - A recent report from France suggested a potential case of reverse zoonotic transmission of MPXV to a dog during the current MPX outbreak; the animal tested positive for MPXV by cutaneous swab but negative by serology. A single case of reverse transmission to a dog has also been reported in Brazil.
	Scoping review	Critically low (AMSTAR-2)	Capobianchi et al, 2022	- Transmission of MPXV (and orthopoxviruses in general) from humans back to animals have not been reported widely, with most reports dating back to the smallpox elimination campaign
	Systematic review	Critically low (AMSTAR-2)	Soheili et al, 2022	- Monkeypox transmission occurs through direct contact with infected humans and animals. Contact with infected animals and consumption of infected meat are possible ways of animal-human transmission.
	Non-systematic review		El Eid et al, 2022	- Concerns were raised during the current outbreak that MPXV could undergo "reverse zoonosis" by infecting wildlife outside of Africa, forming a reservoir leading to future human outbreaks - As of May 24, 2022, the European Food Safety Authority have stated no pets or wild animals had been infected and none have been identified outside of Africa - Moreover, during the 2003 outbreak in the US, surveys of wild animals in Wisconsin and Illinois never found any evidence of MPXV and none of the

				infected humans passed disease to other people
	Non-systematic review		Riopelle et al, 2022	- Prior to current outbreak, there has been no spillover from humans to animals, nor were there any outbreaks among domestic animals
	Non-systematic review		Gomez-Lucia, 2022	- From largely animal-based spillovers in previous outbreaks, recent outbreaks in 2022 have been characterized by human-to-human transmission without history of travel or animal contact - Big concern that patients can transmit MPXV to their pets, which can transmit to wild animals in turn to start a new, indigenous reservoir in non-endemic countries
	Editorial		Afrooghe et al, 2022	- Although MPXV has been transmitted to humans from African rodents (such as rope and tree squirrels), reverse zoonoses may increase with the ongoing 2022 outbreak of MPXV - Domestic animals living near infected owners are more likely to become contaminated - It is entirely possible that asymptomatic individuals and children infected with MPXVV may pose a higher risk of transmitting disease to domestic animals due to their increased engagement with them
	Published report		Minhaj et al, 2022	- Patients ought to avoid contact with pets and other animals while infectious, because some mammals might be susceptible to monkeypox

	Editorial		Bonilla-Aldana et al, 2022	- More studies are needed to understand the risk of human-to-animal transmission during the current outbreak of MPXV, and if other rodents and even closer mammals (e.g. dogs and cats) would be at risk of being infected with potential consequences
	Letter to the editor		Seang et al, 2022	- Two men who have sex with men (MSM) were admitted to a hospital in Paris, France in June 2022 with anal ulceration and vesiculopustular rash on the face, ears, legs, along with rash, asthenia, fever, and headaches - Their male Italian greyhound dog tested positive for MPXV, presenting with mucocutaneous lesions, and abdomen pustules and a thin anal ulceration - men reported co-sleeping with their dog, but avoided dog's contact with other animals - This is likely to be representative of human-to-dog transmission, as the MPXV viral load in the dog's samples, as well as the mens', corresponded with the same clade (B.1) as MPXV spread in France at the time
	Non-systematic review		Haddad and Cordevant, 2022	- Given that MPXV is primarily transmitted through close contact, human-to-animal transmission may occur with frequent close contact with pets if they are proven to be receptive - on a population-level, however, a formation of a reservoir is less likely - however, cats and dogs could still play a role as potential amplifiers - In the absence of contact with secretions, the likelihood of transmission from humans to rodents (both synanthropic and non-synanthropic) would be low, with a new reservoir being formed being unlikely as they are commonly avoided by individuals in the UK and North America - however, particular vigilance will be required for squirrels, which commonly interact with human settlements - While less frequently studied, the possibility of transmission to cows and other production animals would require the human caring for such animals to be

				actively infected and excreting - however, it is imperative that this be studied further, as the above hypotheses are based on limited examination of MPXV and other pox viruses in these species
	Review (non-systematic)		Haddad, 2022	The current large number of potential human shedders, occasioning during the clinical phase (3 weeks maximum) either direct contagiousness through skin and/or mucosal contact and emission in the air of infectious droplets, or indirect contagiousnessthrough contamination of the patient's environment by secretions and scabs, raises the possibility of a risk of contamination not ofhumans by animals (as in Africa, or the USA in 2003), but rather of animals by humans (reverse zoonosis). This transmission could potentially concern pets, production animals and/or wild animal. Any contamination by infected humans could only occur indirectly, rendering even lower the likelihood of infection.
	Single study (cross-sectional)		Luna et al, 2022	- While still yet to be determined, appearance of series of mutations in such a short period of time, not often observed in Orthopoxviruses, suggests rapid adaptive evolution to human hosts and increased advantage in sustained human-to-human transmission in non-endemic countries - Would be worthwhile to anticipate spillover to new animal reservoirs in non-endemic countries and similar environmental niches, contributing to disease persistence in non-endemic regions
Animal-to-animal transmission	News correspondence		Stephenson J	By June 2003, 81 confirmed cases of MPX infection was reported in four states in the US. The MPXV apparently spread from an imported Gambian rat into prairie dogs when both species were warehoused together in an exotic pet distributor. One case had exposure to a rabbit that had

				become sick after exposure to an ill prairie dog at a veterinary clinic.
	Single study (laboratory investigation of naturally infected animals)		Kulesh et al.	All animals used in this study were collected from either an exotic pet dealer or private homes in the Chicago, Illinois metropolitan area. The animals were voluntarily released to public health and veterinary health officials as a result of either *cohabitation* ***of these animals with known positive animals or those that exhibited signs of orthopox infection.***
	Non-systematic review		Moussatché et al.	During the 2003 MPXV epidemic in the US the Gambian giant rat may also have infected prairie dogs (Cynomys spp) in captivity.
	Non-systematic review		Gibbs EPJ	- Native pet prairie dogs (Cynomys species) housed near some of the possibly infected rodents imported from West Africa, in a distributor's premises in Illinois became infected, and it was the subsequent distribution, exhibition and sale of the prairie dogs that spread the virus to people. - The route of transmission in animals is less clear. The virus might have been transmitted by aerosol, through skin abrasions, or through the ingestion of infected animal tissues.
	Non-systematic review		Lupi& Tyring	During the 2003 MPXV epidemic in the USA infected prairie dogs had been purchased from pet stores where they had been caged adjacent to Gambian rats, which had been imported from West Africa and were thought to be the source of the virus.

	Single study (animal infection experiments)		Reynolds et al.	- The presence of substantial clinical illness associated with MPXV infection among persons in the United States might be explained by the virus having passed through an amplification host, namely prairie dogs. Contact with MPXV-infected prairie dogs was identified in each instance of human infection, whereas no persons coming into contact with infected African rodents became infected.
	Non-systematic review		Essbauer et al.	During the 2003 US outbreak the rodents had been transported and kept with native prairie dogs that were afterwards distributed as pets. Human cases mostly occurred in staff of veterinary facilities seeing ill prairie dogs, in households with prairie dogs.
	Editorial		Bray, 2009	- Unexpected outbreak in 2003 in the US also saw MPXV being able to spread to animals outside Africa, when rodents imported from Ghana were co-housed with American prairie dogs and ground squirrels
	Non-systematic review		Bernard and Anderson, 2006	- Rodents from Africa were in the same shipment as, and in close proximity to, prairie dogs from Illinois, some of which died or were sold in unrecorded swap meets
	Non-systematic review		Di Giulio and Eckburg, 2004	- During the 2003 USA outbreak, a rabbit (in the Leporidae family) became infected with MPXV after being exposed to an infected prairie dog at a vet clinic. - The rabbit was suggested to be the source of primary infection in one human MPXV case.
	Non-systematic review		Regnery, 2007	- Fomites, arthopod transmission, and aerosol transmission are possible routes of animal to animal MPXV transmission.

	Non-systematic review		Parker and Buller, 2013	- No MPXV transmission was found between infected squirrels and other uninfected squirrels through ants. - MPXV was first identified in 1958 during an outbreak at a research facility in Denmark, among Asian monkeys (Macaca fascicularis) from Singapore; MPXV had been isolated from the infected animals' pustules. - A MPXV outbreak among captive monkeys in the USA in 1959 mostly affected Macaca fascicularis, while Macaca mulatta were infected less severely (many of them had no clinical signs of infection). - A MPXV outbreak occured in the USA in 1962 in two captive monkeys (Macaca fascicularis) who presented with clinical signs and died: 89% of animals kept in the same room as these two infected monkeys tested seropositive, while only 11% of animals in other rooms were seropositive. - In 1964 a MPXV outbreak among various animal species occured in Rotterdam Zoo, which originated from giant anteaters (Myrmecophaga tridactyla) who had arrived at the zoo. - It is theorized that the anteaters were infected from monkeys they had come into contact with before arrival. - These anteaters were kept at the zoo near the enclosure for Asian orangutans (Pongo pygmaeus), which became infected; it is uncertain whether aerosol or fomite transmission occured. - In the 2003 USA outbreak, a rabbit became sick after exposure to an infected prairie dog at a vet clinic.
	Non-systematic review		Gessain et al, 2022	- During the 2003 outbreak of MPXV in the USA, imported Gambian pouched rats (from Ghana to Texas) transmitted the virus to prairie dogs housed in the same exotic-animal facility, and the prairie dogs in turn infected humans, mostly young adults and children.

	Scoping review	Critically low (AMSTAR-2)	Capobianchi et al, 2022	- Animal to animal transmission of MPXV occurs systematically, with signs of increased circulation in wild chimpanzees recently reported (see Patrono et al, 2020) - Indeed, animal-to-animal transmission remains the main route for maintaining MPXV endemicity in endemic countries - Notable example: US outbreak of MPXV In 2003 originated from infection of local pets by infected giant Gambian pouched rats imported from Africa, including black-tailed prairie dogs (Cynomys ludovicianus) - Moreover, subsequent investigation found cotton rats (native to Mexico) and prairie dogs were susceptible to infection from imported animals (potential role as amplifying hosts).
	Non-systematic review		Ejaz et al, 2022	- Transmission from one animal to another can occur through the animal's respiratory droplets, inhalation of aerosolization of viral particles/organic matter, skin or eye abrasions, ingestion of infected animal tissue
	Commentary		Brewer et al, 2022	- Two possible mechanisms of reverse zoonosis: MPXV spreads to rodents/small mammals kept as pets from their infected owners, which could then be passed to wild animals directly or indirectly - Other possible mechanism: if not properly sterilized before discarding, the virus could spread to rodents infesting the waste management system - Care should be taken to limit the potential spread to indigenous animal populations, local animals need to be closely monitored for infections
	Non-systematic review		Haddad and Cordevant, 2022	- Transmission tends to occur directly through skin or mucous membrane contact with infected individual, something that has been demonstrated for MPXV and other pox viruses, in addition to the respiratory route of aerosolized particles - Under natural conditions, viruses can also be inoculated by flying insects such as

				fruit flies, as MPXV RNA was detected in flies collected in vicinity of outbreak of sick monkeys - While there are no vaccines marketed for animals against MPXV, cannot be ruled out that even vaccinated animals are protected against clinical disease but continues to excrete asymptomatically, silently exposing other animals and humans
	Review in a conference report		Simpson et al. 2020	The animal reservoirs of monkeypox viruses and the human behaviours that facilitate initial animal to human transmission are unconfirmed. It has been shown that in intermediate hosts the virus can be transmitted from one animal to another, and subsequently to humans. This occurred in the US Midwest outbreak (2003), when 47 confirmed and probable cases, including many children, were infected by prairie dogs thought to have contracted monkeypox from rodents shipped to the United States from Ghana. Prior to 1986, population-based surveys in West and Central Africa showed cases of monkeypox were linked to animal sources in 245 of 338 cases. A major outbreak of human monkeypox occurred in Katako-Combe, Zaire in 1996, 89 persons in this outbreak were diagnosed with human monkeypox. 73% of cases reported contact with another human case while 27% had known contact with wild animal. In 2017, outbreaks of human monkeypox in Nigeria were preceded by very heavy rainfall and flooding that is hypothesised to have brought animal hosts and human populations into close proximity, as both sought higher ground and dry environments. The chains of transmission investigated in this outbreak suggest a primary infection contracted from an animal, with subsequent human-to-human transmission.

	Single study (prospective cohort study)	High (7/9, NOS)	Patrono et al, 2020	- Shedding of viral DNA was found to be present in fecal, urine, and fruit wedge bite samples in both symptomatic and asymptomatic chimpanzees - Grooming behaviors within chimpanzee social networks were linked with asymptomatic transmissions between chimpanzees - Moreover, fecal matter fed on by blowflies and flesh flies, maggots feed on infected corpses - both flies and maggots found to harbor MPXV and have the potential to transmit MPXV between chimpanzee individuals
	Single study (cross-sectional)		Doshi et al, 2019	- Zoonotic transmission may occur by direct inoculation via bites and scratches, or direct contact with bodily fluids of infected animals when hunting, preparing carcasses for meals, or playing with animals - Hypothesized that direct contact with blood, saliva from infected animal may deliver larger inoculum, resulting in more severe disease - Single study, cases reported hunting non-human primates prior to rash onset had greater odds (2.78x) of serious/severe rash presentation than those without - no association with rodent exposure - Subsistence farmers and hunters obtain virtually all protein from hunting wildlife (duikers, monkeys, rodents) - provides ample opportunity for transmission of MPXV - overlaps between multiple species in the same region make it difficult to implicate or isolate effects of a single species
	Review (non-systematic)		Deshmukh et al, 2022	- Study conducted in late 1900s showed wild squirrels (Funisciurus anerythrus and Heliosciurus rufobrachium) played significant role in steady transmission - Epidemiological reports from US outbreak in 2003 showed prairie dogs housed with rodents imported from Ghana to be potent animal contact - similar to Gambian pouched rats, dormice,

				many species of monkeys as possible animal contacts for MPXV transmission
Transmission related to animal waste, wastewater	No additional evidence identified in the lookback for this domain.			
	Primary study (wastewater surveillance)		de Jonge et al, 2022	- MPXV from crusts and scabs can be released in wastewater while rinsing, showering, or toilet usage, including animal feces and human anal swabs from diagnostic testing - Indicates that feces either contained excreted MPXV, or can become contaminated when defecating - An important caveat for MPXV surveillance is that MPXV has been isolated from rodents and other small mammals, suggesting that small mammals living in sewerage, such as rats, could serve as a reservoir for MPXV - In high traffic areas (with rapid turnover of human individuals, such as the Schiphol Airport in the Netherlands, which was examined in this study), detection of MPXV from humans would be less consistent than those derived from animal reservoirs

Table 4c: Key findings from included evidence documents on CLINICAL INFECTION OF MONKEYPOX from all iterations thus far (January 1, 2017 to October 28, 2022, and past evidence from January 1, 2000 to January 1, 2017)

Study Design	Study Quality	References	Evidence
Non-systematic review		Bernard and Anderson, 2006	- Data on duration of infection is limited, with MPXV seeming to be present in some animals months after infection, regardless of clinical illness - Clinical and asymptomatic infections have been found in captive primates, but severity varied depending on species and route of inoculation - CDC reported elevated tissue MPXV loads in 2 necropsied prairie dogs
Single study (serosurvey)		Hutson et al, 2007	- Tissues from 2 pouched rats (*Cricetomys* sp.) had MPXV DNA and/or infectious virus, with one animal showing relatively high concentrations of both viral DNA and infectious virus throughout all tissues (e.g. spleen), and the other animal showing MPXV DNA presence only in gonadal tissue - 2 of the 9 MPXV-positive African dormice (*Graphiurus* sp.) showed evidence of prolonged presence of MPXV DNA
Published surveillance report		Shepherd et al, 2022	- The study also reported - "It is unknown at this stage whether non-human species have sub-clinical carriage, or if there is zoonotic transmission from asymptomatic animals".
Non-systematic review		MacNeill, 2022	- In Prairie dog, incubation period was reported to be 13–24 days and the duration of infection was 4 weeks. - In Thomas's rope squirrel incubation period was reported to be 6–8 days and Virus shedding up to 25 days. - MPXV was found in feces, urine, and discarded food of Chimpanzees.
Non-systematic review		Haddad and Cordevant, 2022	- Non-human primates have been observed to have two phases of the disease, similar to humans (a prodromal phase consisting of a non-specific febrile syndrome with hyperthermia, chills, asthenia, myalgia, and voluminous polyadenopathies + an eruptive phase, characterized by skin lesions).

Table 4d: Key findings from included evidence documents on CLINICAL PRESENTATION OF MONKEYPOX from all iterations thus far (January 1, 2017, to October 28, 2022, and past evidence from January 1, 2000 to January 1, 2017)

Study Design	Study Quality	References	Evidence
Report		CDC, 2003	In the DRC, skin lesions were found on a rope squirrel (*Funisciurus anerythrus*) from which MPXV was isolated.
Non-systematic review		Ligon, 2004	- MPXV-infected prairie dog which bit and infected a 3-year old girl in 2003, was found to have ocular discharge, lymphadenopathy, papular skin lesions
Non-systematic review		Langohr et al, 2004	- MPXV infection with extensive lesions was diagnosed in a prairie dog that was involved in the 2003 US outbreak - Gross lesions included oral ulcers, pulmonary consolidation, enlarged cervical and thoracic lymph nodes, plaques in the gastrointestinal wall - Microscopic lesions were extensive in the lungs, consisted of fibrinonecrotic bronchopneumonia with vasculitis, and other extensive signs in the pulmonary system - Multifocal necrotizing lesions, accompanied by myxedema, were also present in most of the other examined organs
Non-systematic review		Radonic et al, 2014	- Infant sooty mangabey monkey was found dead in Tai National Park in the Ivory Coast in March 2012 - Multiple lesions typical of MPXV infection occurred as dark red crusts 5-7mm in diameter, partly confluent, disseminated over the body, mainly in the extremities - High MPXV DNA load was found in most tissues by qPCR, except in the muscle, indicative of systemic infection (particularly high loads in a skin lesion and from a throat swab sample
Non-systematic review		Tack and Reynolds, 2011	- MPXV can present with sudden death, as well as consist of upper respiratory signs, anorexia, lymphadenopathy, blepharitis, and generalized papular rash - These signs were particularly prominent in prairie dogs during the 2003 US outbreak of MPXV, in addition to lethargy, ocular discharge, and nasal discharge which eventually led to pneumonia, and disseminated skin lesions - Photographs of the presentation are presented in Figure 2 of this record
Single study (animal report)		Guarner et al, 2004	- This report describes two prairie dogs infected with MPXV during the USA outbreak in 2003, who both presented with yellow mucoid discharge in their eyelids, while one had an ulcer on their tongue.

Single study (outbreak investigation)		Reed et al, 2004	- In the 2003 USA outbreak, one infected prairie dog presented with ocular discharge, lymphadenopathy, and papular skin lesions. - Other infected prairie dogs presented with watery eyes, skin lesions, congestion, and nasal discharge.
Non-systematic review		Parker and Buller, 2013	- In the 1958 Denmark outbreak among Asian monkeys (Macaca fascicularis), clinical signs included vesiculopustular skin eruptions across the body (face, trunk, limbs, tail, palms, and feet soles), which crusted over and healed on their own, resulting in scars. - In the 1959 USA outbreak that occured among captive monkeys (Macaca fascicularis and Macaca mulatta), there were two manifestations of disease: - The first type of disease occured only in Macaca fascicularis, with facial and cervical edema; severe breathing difficulties that led to death by asphyxiation; papular eruptions across the body; ulcerative lesions in the oral mucosa; and generalized lymphadenopathy. - The second type of disease occured in both Macaca fascicularis and Macaca mulatta, which was more common and caused cutaneous lesions that became pustular and crusted, leaving scars behind all over the body including face, hands, feet, hind limbs, buttocks; and hemorrhagic lesions were linked with fatality. - In a 1962 USA outbreak among two Macaca fascicularis monkeys, clinical signs included pox-like eruptions, bloody diarrhea, dyspnea, hemorrhagic ulcerations, and facial and cervical edema. - In a 1964 Rotterdam Zoo outbreak, giant anteaters presented with skin lesions; Asian orangutans with erythema and nasal discharge with lesions on the body, legs, face; African gorillas and chimpanzees with pox lesions; Asian gibbon with vesicles on the limbs, trunk, face; a South American squirrel monkey with pox lesions; owl-faced monkeys with lesions on the lips; and a South American common marmoset with red and swollen areas around the nose and eyes, and face and belly lesions. - In the 2003 USA outbreak, infected prairie dogs presented with nasal and ocular discharge, tongue ulcers, swollen eyes, anorexia, and pathological changes to the lungs and liver.
Non-systematic review		Cann et al, 2013	- In the first reported MPXV cases in 1959 among cynomolgus macaques (Macaca fascicularis), the infected animals presented with poxviral exanthema. - In another 1959 outbreak among cynomolgus and rhesus macaques (Macaca mulatta), only the cynomolgus showed clinical disease, with two types of disease reported: - The most common type involved cutaneous disease, and hemorrhagic lesions tended to occur in younger monkeys and those whose disease was fatal. - The second type involved facial edema, generalized

			lymphadenopathy, cutaneous lesions and ulcerative mucosal lesions.
Single study (outbreak investigation)		Croft et al, 2007	- In the 2003 USA outbreak, two infected prairie dogs both presented with conjuctivitis and skin lesions; one also experienced lymphadenopathy while the other had respiratory disease.
Non-systematic review		Gibbs EPJ	The illness in prairie dogs was reported to include fever, cough, conjunctivitis and lymphadenopathy, followed by a nodular rash. Some prairie dogs died, whereas others apparently recovered.
Non-systematic review		Essbauer et al.	In monkeys the disease is characterized by generalized skin eruptions, developing to papules on the trunk, face, palms and soles. Papules subsequently develop into vesicles and scabs which usually fall off after about 10 days after the rash developed. The severity of the disease varies with regard to the host species, e.g. it is mild in Cynomolgus monkeys (Macaca cynomolgus), but more severe in orangutans (Pongo sp.)
Non-systematic review		Haller et al.	Infections with MPXV clade I strains cause higher lethality (approximately 10%) in humans and experimentally infected animals, clade II strains cause milder diseases.
Systematic review	Critically low (AMSTAR-2)	Soheili et al, 2022	- Signs including lethargy, inappetence, nasal discharge, respiratory distress, diarrhea, skin lesions have been noted in animals infected with, or susceptible to infection with, MPXV, including rope and tree squirrels as well as prairie dogs
Systematic review	Critically low (AMSTAR-2)	Rahimi et al, 2022	- Studies indicated that infected ground squirrels of MPXV within in-vitro settings showed fulminant disease and died 6 to 9 days later
Non-systematic review		Gomez-Lucia, 2022	- Infection in non-human primates present similarly to humans, such as vesiculopustular skin eruptions in the trunk, tail, face, limbs, and palms in Macaca fascicularis and *Macaca mulatta* species - Most times, lesions formed crusts, falling off and leaving behind a scar - First case of natural infection in a dog was in August 2022 - 4-year-old male Italian greyhound had contracted infection and developed mucocutaneous lesions, pustules in the abdomen, and fine anal ulceration, positive for MPXV as found via real-time PCR - In cynomolgus monkeys (Macaca fascicularis), fever developed 2-6 days after virus inoculation, palpable lymphadenopathy at

			days 3-4, and papovesiculopustular skin lesions on days 4-6 - Skin pocks first became visible on the face, oral mucosa, axillary and inguinal regions, and then became generalized before time of death - In prairie dogs, in vivo imaging showed the presence of MPXV in the nose, lymph nodes, intestines, heart, lung, kidneys, liver even before the appearance of skin lesions - Similar infection patterns were noted in rabbits and white mice
Non-systematic review		MacNeill et al, 2022	- Monkeypox virus (MPXV) was first described as pox-like outbreaks in two groups of cynomolgus monkeys *(Macaca fascicularis)* at the State Serum Institute in Copenhagen, Denmark. - A total of 20 to 30% of monkeys housed together were affected by a rash that progressed to papules, which covered the trunk, tail, face, limbs, hands, and feet. Lesions ulcerated, then formed crusts, which fell off, leaving scars after a period of two to four months. - The animals were healthy otherwise, and no lesions were observed in internal organs at necropsy. - Fatal MPXV infection was described in an infant sooty mangabey *(Cercocebus atys)* from the Ivory Coast. The monkey was found dead with disseminated red crusts on its extremities and abdomen. Eosinophilic cytoplasmic viral inclusion bodies and severe secondary bacterial infection were observed in histologic sections of skin. MPXV DNA was isolated from several organs. - Disease in wild chimpanzees (Pan troglodytes) at the Taï National Park in the Ivory Coast was described in three infant chimpanzees, one of whom died. The chimpanzees had a cutaneous rash, coughing, and respiratory distress. 'Disease symptoms in prairie dogs (including watery eyes, congestion, andgeneratized skin lesions) were noted. - In Thomas's rope squirrel skin lesions were located in ocular, oral area and can become generalized. They showed respiratory distress, hepatic necrosis with fatality rate ~75% .
Editorial		Bonilla-Aldana et al, 2022	- MPXV was first identified in an outbreak among cynomolgus monkeys impored from Singapore - infected monkeys developed vesiculopustular skin eruptions observed over the entire trunk, tail, face, limbs, hands and feet

Letter to the editor		Seang et al, 2022	- Two men who have sex with men (MSM) were admitted to a hospital in Paris, France in June 2022 with anal ulceration and vesiculopustular rash on the face, ears, legs, along with rash, asthenia, fever, and headaches - Their male Italian greyhound dog tested positive for MPXV, presenting with mucocutaneous lesions, and abdomen pustules and a thin anal ulceration - men reported co-sleeping with their dog, but avoided dog's contact with other animals
Non-systematic review		Haddad and Cordevant, 2022	- To date, only wild species with natural MPXV disease have been described as affected - While some chimpanzees and orangutans during the 2022 outbreak have shown "classical" forms as described in humans, others developed severe respiratory signs with dyspnea and no skin lesions, OR extremely discrete and diffuse lesions - Skin disorders and eye, nose discharge has been noted in prairie dogs (*Cynomys ludovicianus*), which were infected by imported Gambian pouched rats (*Cricetomys gambianus*) during the 2003 US outbreak of MPXV
Review (non-systematic)		Devaux et al, 2019	- MPXV infection presents as fever, facial edema, Pox-like lesions in monkeys, apes
Single study (animal experiment)		Falendysz et al, 2017	- MPXV lead to death of most rope squirrels in the single study, with high mortality (upto 75% in some populations) and high degree of respiratory compromise, and has been replicated in other comparison studies with another suspected reservoir (Gambian pouched rat)
Single study (prospective cohort study)	High (7/9, NOS)	Patrono et al, 2020	- Uniquely respiratory syndrome ranging from mild coughing to severe respiratory distress observed in outbreak among 36 chimpanzees in Tai National Park, Ivory Coast - Developed systemic signs, cutaneous rash - however, with varying levels of exanthema

Table 4e: Key findings from included evidence documents on SUSCEPTIBLE ANIMALS TO MONKEYPOX from all iterations thus far (January 1, 2017 to October 28, 2022, and past evidence from January 1, 2000 to January 1, 2017)

Study Design	Study Quality	References	Evidence
Single study (animal experiment study)		Kulesh et al, 2004	Animal species tested during the course of this study included: prairie dog (Cynomys sp.), rat (Rattus sp.), hamster (Cricetus spp.), dwarf hamster (Allocricetulus sp.), gerbil (Gerbillus sp.), Jerboa (Jaculus sp.), mole rat (Heterocephalus sp.), and chinchilla (Chinchilla sp.). These animals had history of cohabitation with known positive animals or those that exhibited signs of orthopox infection.
Non-systematic review		Moussatché et al, 2008	In 2003, the probable source for the introduction of monkeypox virus into the USA was an international shipment of African rodents from Ghana to Texas. These mammals were rope squirrels (Funisciurus spp), *tree squirrels* (Heliosciurus spp), *Gambian giant rats* (Cricetomys spp), *brushtail porcupines* (Atherurus spp), *dormice* (Graphiurus spp), *and striped mice* (Hybomys spp).
Non-systematic review		Gibbs EPJ, 2005	In 2003 the consignment of African rodents, included rope squirrels (Funisciurus species), tree squirrels (Heliosciurus species), Gambian giant rats (Cricetomys species), brushtail porcupines (Atherurus species), dormice (Graphiurus species) and striped mice (Hybomys species).
Guidelines		CDC 2003 rules and regulation	Investigations indicate that a Texas animal distributor imported a shipment of approximately 800 small mammals from Ghana on April 9, 2003, and that shipment contained 762 African rodents, including rope squirrels (Funiscuirus sp.), tree squirrels (Heliosciurus sp.), Gambian giant pouched rats (Cricetomys sp.), brushtail porcupines (Atherurus sp.), dormice (Graphiurus sp.), and striped mice (Hybomys sp.). Some animals were infected with monkeypox, and CDC laboratory testing confirmed the presence of monkeypox in several rodent species, including one Gambian giant pouched rat, three dormice, and two rope squirrels.
Single study (animal experiment study)		Reynolds et al, 2010	Ghanaian mammal species shipped to the United States included several rodent species including Gambian rats (Cricetomys spp.), rope squirrels (Funisciurus spp.), dormice (Graphiurus spp.), sun squirrels (Heliosciurus spp.), striped mice (Lemiscomys barbarus), and brush-tailed porcupines (Atherurus africanus).
Report		WHO, 2011	Prairie dogs are among the susceptible non-African species infected with MPXV during the 2003 US outbreak.

Report		Orba et al., 2015	Susceptible species of MPXV include several rodents of the Funisciurus, Heliosciurus, Cricetomys, and Graphiurus genera and primates.
Non-systematic review		Parker et al., 2007	The tissues of animals that cohabited with MPXV infected animals during the 2003 US outbreak underwent PCR testing, which indicated that potential hosts of MPXV include hamsters (Cricetus spp.), gerbils (Gerbillus spp.), and chinchillas (Chinchilla spp.).
Single study (Cross-sectional)		Reynolds et al.	A number of susceptible non-African species, including prairie dogs, were infected during the 2003 US outbreak.
Editorial		Bray, 2009	- Prairie dogs and American ground squirrels were infected with MPXV in the 2003 US outbreak, raising concerns about the range of New World species that could serve as reservoir hosts could be quite large
Non-systematic review		Bernard and Anderson, 2006	- Number of animals infected or susceptible to infection in the US is unknown, hard to estimate - Although 800 animals were recorded in the African shipment, disposition information was only available for rodents (a Gambian giant pouched rat, 3 dormice, 2 rope squirrels, and unknown number of prairie dogs were found to be MPXV-positive) - Later necropsy and histopathologic studies by the CDC found positive signs of infection in various species and in various tissues, including in 14 prairie dogs, 2 Gambian giant pouched rats, 9 dormice, 3 rope squirrels, 1 ground hog, 1 hedgehog, 1 jerboa, and 2 opossums immediately after the initial outbreak from the Texas shipment
Single study (ecological study)		Inogwabini and Leader-Williams, 2012	- MPXV occurrence in the DRC was very widespread across the known extent of occurrence of bonobos in the region - Strikingly, MPXV seems to be absent from areas within the extent of occurrence of bonobos where bonobos were absent - The above observations are supported by models, showing a positive relationship between presence/absence of MPXV and presence/absence of bonobos - Confirmed MPXV cases in humans overlapped extnesively with known extent of bonobos, possibly for two reasons: bonobos may enjoy natural portection from MPXV even though it is known to infect other non-human primates + bonobos may have adapted to the presence of MPXV, as they can survive without experiencing severe symptoms
Non-systematic review		Reynolds et al, 2012	- MPXV can infect an array of mammalian taxa including Sciurid, Glirid, and Nesomyid rodents (Cynomys sp., Funisciurus sp., Graphiurus sp., Cricetomys sp.), marsupials (Monodelphis domestica, Delphius marsupialis), and primates (Callithrix jacchus, Homo sapiens) - In each example provided, infections ocucrred without experimental induction by humans, but for most, human intervention was responsible for bringing the species in question

			into proximity with MPXV - Host range of naturally-occurring MPXV remains undefined
Single study (serosurvey)		Salzer et al, 2013	- Authors found 18 out of 44 roof rat (R. rattus) samples obtained from the wild to be positive for anti-OPXV antibodies, including antibodies against MPXV - While similar in presentation to those from MPXV- and VACV-exposed individuals, whether MPXV was solely responsible for the observations is unclear.
Single study (serosurvey)		Hutson et al, 2007	- Animal specimens were submitted to the US CDC for MPXV evaluation by state departments of health and agriculture, including animals involved directly with the Ghana shipment of exotic animals into the US (in wake of the 2003 US outbreak of MPXV) - 33 individual animals tested positive for MPXV-specific DNA, with virus isolate successfully obtained from 22 animals - 3 species showed evidence of MPXV infection: 3 rope squirrels (Funisciurus sp.), 2 giant pouched rats (Cricetomys spp.), and 9 dormice (Graphiurus sp.) - Table 1 in this record provides a summary of animals identified from the Ghana shipment and individual animal distributors, as well as their MPXV positivity - In addition to African animals, all human MPXV cases were associated with contact with infected black-tailed prairie dogs (Cynomys ludovicianus) - 14 of 20 were found to be MPXV positive - Other animals, sourced from the same distributors, were found to be MPXV positive with varying tissue viral loads: southern opossum (Didelphis marsupialis), hedgehog (Atelerix sp.), gray short-tailed opossum (Monodelphis domestica), jerboa (Jaculus sp.), chinchillas (Chinchilla lanigera), coatimundis (Nasua nasua), and woodchucks (Marmota monax)
Non-systematic review		Di Giulio and Eckburg, 2004	- Serological surveys have indicated that various animals can become naturally infected with MPXV including non-human primates, squirrels, and rats.
Non-systematic review		Damon, 2011	- In the 2003 USA outbreak, the prairie dogs had been susceptible to MPXV and were infected from rodents that came from Ghana, West Africa.
Non-systematic review		Parker and Buller, 2013	- Various species that live in lowland tropical forest in central and west Africa are susceptible to MPXV infection: 40% of these susceptible species are arboreal, 40% semiterrestrial, and 20% terrestrial. - In the 1964 MPXV outbreak in Rotterdam Zoo, which originated from giant anteaters (Myrmecophaga tridactyla), species that became infected include: Asian orangutans (Pongo pygmaeus), African gorillas (Gorilla gorilla) and chimpanzees (Pan troglodytes), Asian gibbon (Hylobates lar), South American squirrel monkeys (Saimiri sciureus), African owl-faced monkeys

			(Cercopithecus hamlyni), and South American common marmoset (Hapale jacchus). - This zoo outbreak demonstrates the wide range of susceptible animals from various geographic regions.
Scoping review	Critically low (AMSTAR 2)	Kipkorir et al, 2022	- MPXV has been found to be contagious in a variety of animal species including rodents such as mice, rats, and squirrels.
Non-systematic review		Antunes et al, 2022	- MPXV first discovered during a nonfatal outbreak in an animal facility in Copenhagen, Denmark in 1958, occurring in *Macaca fascicularis* (crab-eating macaque) which had arrived from Singapore - Similar outbreaks of MPXV were reported in a colony of captive monkeys in Philadelphia, USA in two monkeys are exposure to whole-body irradiation, as well as among various animals in Rotterdam Zoo, in the Netherlands - Later, in 2003, occurred in prairie dogs in the USA, living in close contact with various rodents imported from Ghana - Some species that can be infected with MPXV include various rodents (prairie dog, squirrel, marmot, groundhog, chinchilla, giant pouched rat), carnivores (dogs), insectivores (hedgehog, shrew), and non-human primates (monkey, ape).
Non-systematic review		Gessain et al, 2022	- Between 1960 and 1968, since MPXV was first isolated in cynomolgus monkeys in Denmark, several other outbreaks were reported in colonies of captive monkeys in the United States and the Netherlands
Non-systematic review		Hassan and Saeed, 2022	- Many animals, such as rabbits, prairie dogs, other rodents and monkeys, are susceptible to infection in captivity, including laboratory animals
Non-systematic review		Hatmal et al, 2022	- MPXV infection was recognized as a zoonotic disease that infects a wide range of animals, including chimpanzees, lesser and greater white-nosed monkeys, grivets, red colobus monkeys, African brush-tailed porcupines, and the Gambian sun squirrel
Non-systematic review		Ilic et al, 2022	- According to serological surveys, different wild animals can be infected under natural conditions, such as non-human primates (orangutans, chimpanzees, sooty mangabeys, cynomolgus monkeys), rodents (mice, rabbits, squirrels, hamsters, groundhogs), anteaters, prairie dogs, southern opossums, marmosets, hedgehogs.
Non-systematic review		Jeyaraman et al, 2022	- Some rodents (dormice, rope squirrels, tree squirrels, Gambian pouched rats) and non-human primates are inherently vulnerable to the monkeypox virus.

Non-systematic review		Sah et al, 2022	- In 2003, importing wild/exotic animals from Africa led to the first appearance of MPXV outside Africa, in the USA. - Many small rodents imported from Africa were infected, including striped mice (*Hybomys* spp.), dormice (*Graphiurus* spp.), brushtail porcupines (*Atherurus* spp.), Gambian pouched rat (*Cricetomys gambianus*), sun squirrels (*Heliosciurus* spp.), and rope squirrels (*Funisciurus* spp.)
Scoping review	Critically low (AMSTAR-2)	Capobianchi et al, 2022	- Based on genetic evolution and number of genes dedicated to host species adaptation in the genome, MPXV has been classified as having a broad host range - The potential sources of MPXV outside Africa remain unknown. - However, many ecologic and serological studies suggest non-human primates, rodents (such as rope and tree squirrels, Gambian pouched rat, dormice) are susceptible to MPXV infection - MPXV has only twice been isolated from wild animals: rope squirrel in Zaire/DRC in 1985, and sooty mangabey in Ivory Coast in 2012 - No evidence has been documented on MPXV infection in livestock or in domestic pets (cats or dogs, for example) - However, cats, especially those only partially domestic, if infected, might be able to spread infection back to wildlife (such as native rodents) - Hypothetical risk of human-to-animal transmission cannot be overlooked and appropriate measures such as distancing from suspected/confirmed infected animals should be instated
Systematic review	Critically low (AMSTAR-2)	Soheili et al, 2022	- Susceptible species to monkeypox virus include rope squirrels, tree squirrels, Gambian pouched rats, dormice, sooty mangabey,and non-human primates.
Non-systematic review		Shafaati & Zandi, 2022	- Numerous animals in Africa, including rope squirrels, tree squirrels, Gambian pouched rats, dormice, various species of monkeys, and others, have shown signs of monkeypox virus infection.
Non-systematic review		Ejaz et al, 2022	- Non-human primates can become infected with MPXV and fall ill, while small mammals can be asymptomatic carriers of the virus - Domesticated prairie dogs in the US also become infected with the virus when they share caging and bedding with infected mammals from West Africa - Rodents (*Cricetomys gambianus, Heliosciurus* spp, *Jaculus* spp), squirrels, non-human primates (Cercocebus atys,, Macaca mulatta, M. fascicularis) have been found with MPXV infection on

			serological examination in Africa - Wild animals from forested habitats are more likely to become infected
Non-systematic review		Forni et al, 2022	- Knowledge about the host range of MPXV in natural settings suggests that the main reservoir is represented by squirrels - The virus has been detected in several small mammal species, Old World non-human primates, as well as non-placental mammals such as opossums - However, although wild non-human primates were found to be infected with MPXV, they are not thought to contribute significantly to MPXV circulation
Non-systematic review		Kolte et al, 2022	- MPXV neutralizing antibodies were detected in domestic pigs (*Sus scrofa*), Gambian rats (*Cricetomys emini*), elephant shrew (*Petrodromus tetradactylus*), Thomas' tree and rope squirrels (*Funisciurus anerythrus*), sun squirrel (*Heliosciurus rufobrachium)*
Non-systematic review		Riopelle et al, 2022	- MPXV is thought to have a range of potentially suitable hosts, based on presence of MPXV and OPXV antibodies, ecnompassing various rodents and primates as dead-end hosts - MPXV has been successfully isolated from a dead sooty mangabey monkey, a symptomatic rope squirrel, and feces of symptomatic chimpanzee - Among domestic animals, the detection of OPXV antibodies was noted in a domestic pig in the DRC, as well as most peri-domestic rats in Uganda
Non-systematic review		Gomez-Lucia, 2022	- A 1964 outbreak in Rotterdam, the Netherlands sickened various animlas, several of which had died: giant anteaters, orangutan, gorilla, chimpanzees, gibbons, and marmosets
Non-systematic review		Kumbhar and Agarwala, 2022	- The susceptibility of a large number of animal species, mainly rodents and non-human primates reflects upon the adaptability of the virus, with the latter believed to be incidental hosts. - Experimental infections have been induced in animals through numerous inoculation routes; however the natural route of transmission is believed to be species-specific. - A serological survey in healthy Rhesus monkeys done in 1974 in outskirts of Delhi did not reveal the presence of antibodies against

			monkeypox, thus negating the possibility of existence of reservoirs for the virus in the country
Non-systematic review		Focosi et al, 2022	- In 2003, infected pet prairie dogs (Cynomys sp.), were infected after housing close to a shipment of rodents (including rope squirrels *(Funiscuirus sp.*), tree squirrels *(Heliosciurus sp.)*, Gambian giant rats *(Cricetomys sp.)*, brushtail porcupines *(Atherurus sp.)*, dormice *(Graphiurus sp.)*, and striped mice) imported from Ghana to Texas.
Non-systematic review		MacNeill et al, 2022	- Experimental infection of 38 strains of mice found CAST/EiJ, PERA/EiJ, and MOLF/EiJ mice susceptible - Aerosolized MPXV infection showed the susceptibility of various species cynomolgus monkeys; Kellen's dormouse *(Graphiurus kelleni);* Black-tailed prairie *dogs (Cynomys ludovicianus);* Thomas's rope squirrel *(Funisciurus anerythrus);* ground squirrels *(Ictidomys tridecemlineatus);* Gambian pouched rats *(Cricetomys gambianus)*; red-legged sun squirrel *(Heliosciurus rufobrachium)*, Congo rope squirrel *(Funisciurus congicus)*, Thomas's rope squirrel *(Funisciurus anerythrus),* Emin's pouched rat *(Cricetomys emini)*, four-toed elephant shrew *(Petrodromus tetradactylus)*, and wild boar *(Sus scrofa)*; birds, and antelope; red-tailed monkey *(Cercopithecus ascanius)*, Allen's swamp monkey *(Allenopithecus nigroviridis)*, lesser spotnosed monkey *(Cercopithecus petaurista)*, and, possibly, western red colobus *(Piliocolobus badius)*.
Letter to the editor		Afrooghe et al, 2022	- While dogs and ferrets seem to be invulnerable for the time being, previous reports have shown infections of cowpox and other zoonotic orthopoxviruses in cats - Moreover, MPXV might infect adult albino rabbits as well as neonates of rats and exotic pet mice (however, this susceptibility has only been demonstrated in vitro) - It is also possible that wild animal populations, due to extensive land use and deforestation in both endemic and non-endemic countries, would be susceptible to reverse zoonoses - however, this is not systematically examined.
Commentary		Brewer et al, 2022	- MPXV is thought to reside primarily in rodent populations of west and central Africa, including multiple squirrel species (rope, sun, tree squirrels), giant pouched rats, and African dormice. - Other species such as non-human primates, anteaters, hedgehogs, shrews, prairie dogs are also susceptible to MPXV infections

Non-systematic review		Lai et al, 2022	- Many Animal species are susceptible to the Monkeypox virus, including rope squirrels, tree squirrels, Gambian pouched rats, dormice, and non-human primates
Editorial		Bonilla-Aldana et al, 2022	- In addition to cynomolgus monkeys, other non-human primates (such as African gorillas, chimpanzees, Asian gibbons, South American squirrel monkeys, African owl-faced monkeys, mangabeys, South American marmosets) have demonstrated susceptibility to MPXV - Moreover, large outbreaks in Zaire in the 1979 implicated rodents such as Thomas' rope squirrel and redless tree squirrel - Viral infections have been discovered in squirrels, Gambian pouched rats, dormice and some monkey species
Non-systematic review		Haddad and Cordevant, 2022	- In addition to rodent and non-human primates in the wild, some of which are "accidental hosts", susceptibility to MPXV infection has been confirmed experimentally in captive non-human primates, as well as laboratory based rodents (such as African dormice, Natal multimammate rats *Mastomys natalensis*), cotton rats (*Sigmodon* sp.), Gambian pouched rats) - Among domestic animals, negative results were found in limited serological surveys (120 small ruminants and 67 cats) in an agro-forestry setting as early as the 1980s - however, there is a lack of recent studies into these animal populations to understand their MPXV susceptibility/burden during the 2022 outbreak - In non-endemic countries, can only hypothesize what may happen based on field and experimental data of MPXV actively circulating between humans, to understand transmission to animals - Risk of infection of rodents and small animals outside of Africa, as demonstrated by prairie dog infection during the 2003 US outbreak, is the most plausible, as surveys and laboratory studies have shown such rodents are most receptive of MPXV - studies of cats and dogs have shown no seroconversion, however - Non-human primates have been shown to be clearly susceptible based on studies in the field and in the laboratory - However, the susceptibility of food production animals (cattle, goats, sheep) is the least known, with only one study of 200 animals in 1987 showing no seroconversion however, as most ruminants are susceptible to other poxviruses (such as cowpox), this should not be overlooked

Table 4f: Key findings from included evidence documents on HANDLING OF SUSCEPTIBLE ANIMALS TO MONKEYPOX from all iterations thus far (January 1, 2017 to October 28, 2022, and past evidence from January 1, 2000 to January 1, 2017)

Study Design	Study Quality	References	Evidence
News correspondence		Stephenson J	Individuals who owned sick prairie dogs were instructed to contact their veterinarian or their state or local health department to have the animal evaluated for MPXV. Animals that were diagnosed with MPXV euthanasia was recommended. Sick animals were asked not to be released into the wild because this action may raise the potential for setting up an enzootic cycle in local wild life. CDC recommended standard infection control for individuals involved in the investigation or treatment of sick animals.
Report		WHO, 2011	Infected animals need to be immediately quarantined, and animals that may have been in contact should also be quarantined and monitored for signs of MPXV for 30 days. Animal-to-human transmission could be prevented in endemic regions by thoroughly cooking animal products before consumption, and the use of personal protective equipment during slaughter and handling of infected animals and tissues.
Non-systematic review		Ligon, 2004	- On June 11, 2003, US Department of Health and Human Services announced an immediate embargo on importing all rodents from Africa, as well as a ban on distribution, sale, transport of prairie dogs and six specific African rodent species
Non-systematic review		Bernard and Anderson, 2006	- FDA issues order that prohibited importation of all rodents from Africa, transportation of the rodents from the implicated African shipment during the 2003 US MPXV outbreak - FDA also imposed import restrictions on all African rodents, as well as other animals with the potential to transmit MPXV - however, neither CDC nor FDA exercised its statutory authority to seize and destroy animals to prevent MPXV spread
Single study (animal experiment)		Witmer et al, 2009	- Gambian giant pouched rats (Cricetomys gambianus), which are susceptible to MPXV, were captured in Grassy Key Island, Florida, dusted with an insecticide (Delta-Dust), and dewormed. - Then they were transported in cages to the National Wildlife Research Center in Colorado, where they were checked for health and given another dusting of insecticide. - The rats were then put in individual cages (rabbit rack cages) for a quarantine of two weeks. - Experimental trials were conducted to evaluate 15 potential attractants and found that a mix of feces and urine from Gambian rats had the highest number of visits by rats compared

			to the other attractants, therefore this attractant can be used to capture Gambian giant pouched rats.
Single study (outbreak investigation)		Reed et al, 2004	- In the 2003 USA outbreak, health care providers and vets were recommended infection control and PPE measures similar for smallpox. - Pet owners and businesses that were affected by the outbreak had their premises inspected and exposed animals were put under quarantine. - Any mammals that had been in contact with sick prairie dogs were quarantined where they were kept.
Guidelines		Petersen et al, 2016	- In the USA, the Advisory Committee on Immunization Practices recommended routine vaccination with ACAM2000 (a live smallpox vaccine) for laboratory personnel who directly handle animals infected with orthopoxviruses that can be transmitted to humans, including MPXV. - Revaccination every 3 years is recommended for personnel at risk of occupational exposure to MPXV.
Non-systematic review		Gomez-Lucia, 2022	- Low-risk transmissors of MPXV include dogs, cats, and birds - while at low of MPXV infection and its clinical consequences, it is prudent for their owners to avoid their contact with other animals - High-risk transmissors include pet rodents such as hamsters, guinea pigs, mice, rats, and rabbits - need to be monitored more closely if found to be infected with MPXV, and euthanized as a last resort - Residues from rodents and other pets need to be sprayed with home disinfectants, such as chlorine bleach, and introduced in hermetically closed bags - Consult Table 2 in this review for recommendations for veterinarians
Non-systematic review		Zhu et al, 2022	- Positive and suspected patients and animals ought to be isolated promptly, with reverse and positive contact tracing as possible - Moreover, the authors suggest strict restrictions on importation of wildlife into countries, to avoid contact with sick animals (especially African rodents, marsupials, primates) that may carry MPXV - Samples collected from suspected infected animals need to be handled safely by trained personnel in an appropriately equipped laboratory

Non-systematic review		Haddad and Cordevant, 2022	- If an animal shows signs and lesions suggestive of monkeypox and is brought to the clinic, it would be advisable for the animal to be isolated on arrival, with veterinary staff taking extra precautions handling the animal (PPE) - Careful cleaning and disinfection of the animal's environment is necessary, especially during the end of disease or death of the animal - While the above guidance is more applicable to confirmed or otherwise outwardly presenting animal cases, guidance is limited for handling suspected or otherwise asymptomatic animal cases - Human-to-animal transmission could be prevented from susceptible animals by isolating humans infected with MPXV, preventing infected humans from situations where they might contact secretions from rodents (such as pets, the homeless or prisoner population)
Non-systematic review		Haddad, 2022	No contact with humans and with the aimal environment for 21 days after symptom onset (left in cage in a dedicated room). Don't approach or feed them. Rat/rodent control program (rat extermination, food resource reduction). Isolation of the ower/breeder and disinfection of the environment.

Table 4g: Key findings from included evidence documents on DESCRIPTION OF THE VIRUS from all iterations thus far (January 1, 2017 to September 2, 2022)

This domain was included in the original organizing framework and sought data published between January 1, 2017 and September 2, 2022, at which time the domain was no longer prioritized for updating and the search for new evidence was discontinued.

Study Design	Study Quality	References	Evidence
Scoping review	Critically low (AMSTAR 2)	Di Gennaro et al, 2022	- MPXV has two clades, with the West African variant having an estimated 4% case fatality ratio and higher prevalence among HIV patients, and the Congo Basin (Central African) variant with the case fatality ratio of 10% - Majority of cases noted in the 2022 MPXV outbreak were not directly related to human and animal travels from endemic areas - Whether or not MPXV has developed more capacity for transmission between humans is unknown, since little is known of its general viral evolution and dynamics - Moreover, the MPXV genomes are classified into 3 monophyletic clades: two previous characterized clades (A.1, A.2) and 1 newly emerging clades containing genomes from ongoing outbreak (B.1)
Non-systematic review		Ranganath et al, 2022	- MPXV possesses a DNA genome, making it less prone to high mutation rates compared to RNA viruses - Increased rate of human-to-human spread during 2022 outbreak, however, has raised questions about whether the currently circulating virus has acquired traits that enhance transmission - Sequencing to date has revealed that the current outbreak is closely related to the 2018 strain exported from Nigeria, leading to cases in the United Kingdom, Israel, Singapore - However, there were no significant genetic differences in the 2022 MPXV to suggest increased transmissibility or disease severity
Non-systematic review		Kumbhar and Agarwala, 2022	- MPXV is a brick-shaped enveloped virus measuring 200–250 nm, which replicates in the cytoplasm, despite being a DNA virus. The double stranded DNA genome is approximately 197 kbp in size, which is among the largest of all viral genomes consisting of about 190 non-overlapping open reading frames. - Genomic sequencing has identified two distinct phylogenetic clades of MPVXes, with a distinct geographical distribution. They are the West African (WA) clade and the Congo Basin (CB) clade (also called Central Africa clade). WA and CB MPXV also differ in virulence and transmissibility.

Non-systematic review		Focosi et al, 2022	MPXV is an enveloped virus with a 196,858 base pairs double-stranded DNA genome encoding 90 open reading frames, originated approximately 600 years ago. Viral entry depends on multiple receptors (mostly glycosaminoglycans), with fusion to the cellular membrane. Replication occurs within the cytoplasm. 'Two clades of MPXV exist: the Central African (Congo Basin) clade (associated with more severe disease, 10.6% mortality and higher transmissibility2,8–10) and the West African clade (associated with a milder presentation and 3.6% mortality).
Non-systematic review		MacNeill et al, 2022	- There are two clades of MPXV that are genetically distinct: one isolated in West Africa and one in the Congo Basin. The Congo Basin MPXV is more virulent than the west African MPXV. The fatality rate associated with the Congo Basin MPXV is estimated to be 10.6%, while the West African MPXV is less than 3.6%.
Editorial		Rothenburg et al, 2022	- Entry of poxviruses into cells is independent of host-species-specific receptors, and MPXV thus has the potential to infect many different species - While poxviruses such as MPXV have less constraints on their genome size, it is unknown to what extent this affected transmissibility, especially with the risk of expanded host range and recombination with other poxviruses
Non-systematic review		Cheema et al, 2022	- Monkeypox is one of 10 species in the Orthopoxvirus genus, including variola (smallpox) - MPXV was first discovered during an outbreak among Cynomolgus monkeys in Denmark in 1958, first recognized as a human disease in 1970, when a nine-month-old became infected in Democratic Republic of Congo (DRC) - Two phylogenetic clades of MPXV have been described - Congo Basin (more virulent) and West African - largely due to ability to inhibit T cell receptor-mediated T cell activation and prevention production of inflammatory cytokines - MPXV is an enveloped double-stranded DNA virus, with differing characteristics between clades (translating to greater case fatality rates in the endemic Congo Basin clade, compared to the more widespread West African clade
Non-systematic review		Lai et al, 2022	
Non-systematic review		Singhal et al, 2022	
Non-systematic review		Zhu et al, 2022	
Non-systematic review		Haddad and Cordevant, 2022	- MPXV exists in two genetically and geographically distinct clades: Congo Basin and West African, with more recent evidence suggesting cohabitation of multiple subclades within each clade, with one suspected to be the most prevalent in the current 2022 outbreak of monkeypox - MPXV belongs to the Orthopoxvirus genus, and is considered one of the most ubiquitous (alongside cowpox) in terms of natural host range - MPXV appears to have diverged from a close

			common ancestor of cowpox virus (CPXV), which is itself zoonotic and multi-host
Single study (cross-sectional)		Luna et al, 2022	- Sudden emergence of monkeypox cases in non-endemic countries has raised questions about the natural evolution of the virus - Study examined 337 MPXV genomes from GISAID and Viral NCBI databases as of June 29, 2022 to examine evolutionary history of MPXV strains associated with the 2022 outbreak in non-endemic countries, compared to traditional West African and Congo Basin clades identified previously - MPXV has undergone stochastic evolutionary event leading to further diversification of MPXV, tracing back to the 1971 Nigerian genome, potentially expanding its range of traditional hosts to ignite the latest outbreak in 2022 - B.1 lineage of MPXV closest to human outbreak in 2022
Systematic review	Critically low (AMSTAR 2)	Bunge et al, 2022	- Two distinct genetic clades of MPXV, the Central African and West African clade, as judged by 10 peer-reviewed studies and 1 report from grey literature
Review (non-systematic)		Alakunle et al, 2020	- MPXV is a ovioid (round-shaped) virion enclosed by geometrically corrugated lipoprotein outer membrane - Membrane-bound, densely-packed core containing enzymes, double-stranded DNA genome, transcription factors, protected by outer membrane
Review (non-systematic)		Silva et al, 2021	- MPXV of the *Poxviridae* family, characterized by large, brick-shaped or ovoid enveloped viruses containing linear, dsDNA genome ~200 kbps
Review (non-systematic)		Kumar et al, 2022	- Phylogenetically, MPXV has two clades: West-African and Congo Basin (more pathogenic), with the current strains in 2022 outbreak in Europe closer to West-African clade - Clades have 0.55-0.56% nucleotide difference between strains
Review (non-systematic)		Fenollar & Mediannikov, 2018	Monkeypox is a zoonotic disease caused by Orthopoxvirus (DNA virus), a virus very close to that causing smallpox in humans. This virus is endemic to central and western African countries. It was first identified in 1958 as a pathogen of Macaca cynomolgus (then in use as laboratory animals) and then in 1970 was described as a human pathogen in Democratic Republic of Congo.
Single study (prospective cohort study)	High (8/9, NOS)	Whitehouse et al. 2021,	
Review (non-systematic)		Kabuga & Zowalaty, 2019	
Review (non-systematic)		Haddad, 2022	
Report		Durski et al. 2018	Monkeypox virus has two recognized clades: West African and Congo Basin. Differences in epidemiologic and clinical features

Review (non-systematic)		Xiang & White, 2022	between viral isolates support the distinction between these two clades. Advances in the use of DNA sequencing to understand viral strains and populations will be valuable for interpreting transmission events and confirming the existence of endemic variants.
Review in a conference report		Simpson et al. 2020	
Review (non-systematic)		Haddad, 2022	
Review (non-systematic)		Kabuga & Zowalaty, 2019	MPXV is an enveloped double-stranded DNA virus with an approximate genome size of 190 kb, and is enclosed in a slightly pleomorphic dumbbell-shaped core of 140 to 260 nm diameter, giving a brick-shaped virion. MPXV replicates within the cytoplasm of infected cells rather than in the nucleus, in contrast to many DNA viruses, as they can produce the required proteins for both transcription and replication.
Review (non-systematic)		Quarleri et al. 2022	The size of MPV virus particles ranges from 200 to 250 nm and appears as egg-shaped or brick-shaped particles enclosed by a geometrically corrugated lipoprotein outer membrane. Membrane junctions as well as the densely packed core containing enzymes, a double stranded DNA genome, and transcription factors are protected by the outer membrane. Based on an electron microscopy fixation artifact, the core is described as biconcave and has a side body on each side.

Table 4h: Key findings from included evidence documents on TREATMENT OF INFECTED ANIMALS from all iterations thus far (January 1, 2017 to September 2, 2022)

This domain was included in the original organizing framework and sought data published between January 1, 2017 and September 2, 2022, at which time the domain was no longer prioritized for updating and the search for new evidence was discontinued.

Study Design	Study Quality	References	Evidence
Non-systematic review		Kumbhar and Agarwala, 2022	- Monkeypox being a viral zoonosis mandates intersectoral coordination between human and animal health interventions. - Being a zoonotic agent maintained in wild animals, the virus is not amenable to eradication measures. - This outbreak should serve as a wakeup call for the scientific community to engage more into One Health approach and targeted surveillance programs to detect evolved viral strains in order to curb future outbreaks of monkeypox and other similar zoonoses.
Non-systematic review		Lai et al, 2022	- MPXV zoonotic transmission to humans can be avoided by avoiding unprotected contact with wild animals, especially those sick or dead (including consuming or working with meat and blood from such animals - In endemic countries, where animals may carry monkeypox, food containing animal meat or parts should be cooked thoroughly before eating
Non-systematic review		Singhal et al, 2022	- ST-246 (or tecovirimat) has been approved for treatment for orthopoxvirus infection (including monkeypox), as it has demonstrated efficacy in protecting animals from MPXV with no serious side effects
Non-systematic review		Zhu et al, 2022	- Tecovirimat (TPOXX), an antiviral drug used to treat smallpox, was approved for MPXV treatment by the FDA in January 2022 - Studies of TPOXX's therapeutic efficacy in various animal species have shown that Tecovirimat is effective in treating orthopoxvirus-induced disease, with clinical signs of disease decreased in Tecovirimat-animals vs placebo - Moreover, modified vaccinia Ankara (MVA, an attenuated vaccinia virus which cannot achieve complete replication in mammalian cells) has shown some effectiveness in animal studies - however, its safety has not been thoroughly evaluated in either animals or humans

Single study (animal experiment)		Iizuka et al, 2017	- Cynomolgus monkeys (Macaca fascicularis) were inoculated with either LC16m8, Lister (parental strain of LC16m8), or a mock-up vaccine, and then challenged with MPXV via a subcutaneous route, at 6 and 12 months after vaccination, which we compared with either Lister or the mock-up vaccination. The LC16m8 monkeys exhibited almost no MPX-associated symptoms, whereas most of the naïve monkeys died. LC16m8 generated the protective memory immune response against MPXV.
Report		Durski et al. 2018 (preventive measures)	Because monkeypox is a viral zoonosis, coordination of interventions between the human and animal (wildlife) health sectors is necessary, including routine sharing of information. Better collaboration between human and animal health personnel is needed to understand the impact of monkeypox among humans and animals and the mechanisms of animal-to-human transmission and to implement adequate prevention and response measures. To improve understanding of mechanisms of virus transmission, both zoonotic and interhuman, national disease surveillance systems need to be strengthened for humans, as well as for wildlife, using community-based event reporting. Improvements in the capacity to detect monkeypox virus have been found to increase zoonotic disease detection and response, as seen during the Ebola virus disease response in Tshuapa Province of DRC. As with all zoonotic diseases, a comprehensive One Health approach is necessary for disease detection and response, including wildlife surveillance and investigations into the animal reservoir/reservoirs, which require dedicated resources. Insights into the animal reservoir and ecological niche will enable monitoring the virus's movements outside the natural ecological setting.
Rapid review	Critically low (AMSTAR 2)	Diaz et al. 2021	Intravenous cidofovir has proven effective in the postexposure prophylaxis of monkeypox in monkeys.
Review (non-systematic)		Reynolds et al. 2019 (preventive measures)	- Multi-sectoral disease prevention strategies have gained visibility and traction through various global health initiatives, such as the Global Health Security Agenda, often falling under the egis of 'One Health'. - Captive animals can serve as sentinels to alert health authorities of the circulation of MPXV in the immediate captive environment or in the environment from which the animals originated. Recent examples of this include outbreaks among captive, roaming chimpanzees at primate sanctuaries in Cameroon (2014, 2016) [8] and the geographically widespread outbreak of MPX that affected

			‘pocket pets’ (and their humans) in the Midwestern United States in 2003. - For MPX outbreaks of undetermined origin, live animal markets, zoos, commercial holding facilities and household pets should be considered as potential sources of infection, thus necessitating the institution of coordinated, inter-sectoral investigation approaches.

Table 4i: Key findings from included evidence documents on ENVIRONMENTAL ASPECTS OF MONKEYPOX INFECTION from all iterations thus far (January 1, 2017 to September 2, 2022)

This domain was included in the original organizing framework and sought data published between January 1, 2017 and September 2, 2022, at which time the domain was no longer prioritized for updating and the search for new evidence was discontinued.

Study Design	Study Quality	References	Evidence
Primary study (ecological study)		Mandja et al, 2022	- Study into the environmental determinants of MPXV transmission in the Democratic Republic of Congo (DRC) - Found that proximity of settlements to a primary forested areas was identified as a key factor for MPXV incidence, similar to past studies where MPXV cases were primarily found in villages situated near rainforests - the geographical space allows close contact between humans and suspected reservoirs during hunting, logging, agriculture - Moreover, temperature during the day was positively associated with annual MPXV incidence, mainly in equatorial and territorial regions of the DRC - however, how forest coverage and temperature influence MPXV transmission is still unknown, especially as reservoirs are unknown - Low socioeconomic status (measured using relative income measures) showed a positive association with annual MPXV incidence, with those most severely affected being low-income families - likely explained by rising urban demand for bushmeat grows as ease of access increases, prompting low-income villagers to hunt for bushmeat more often (for themselves or to turn a profit)
Review (non-systematic)		Haider et al, 2022	- Environmental: ongoing land-use change in West Africa and Nigeria in particular, can change the hazard of MPXV spillover events into humans from infected hosts - Identifying competent hosts of MPXV important to examine associations with urbanization, modified human-animal contacts of epidemic risk
Single study (prospective cohort study)	High (7/9, NOS)	Patrono et al, 2020	- Environmental: contemporary re-emergence in humans and non-human primates throughout West Africa could be due to changes in demography, natural seasonal/interannual variation, human-induced changes (e.g. encroaching on African rainforests and destructive land use practices)

Table 4j: Key findings from included evidence documents on OCCUPATIONAL ASPECTS OF MONKEYPOX INFECTION from all iterations thus far (January 1, 2017 to September 2, 2022)

This domain was included in the original organizing framework and sought data published between January 1, 2017 and September 2, 2022, at which time the domain was no longer prioritized for updating and the search for new evidence was discontinued.

Study Design	Study Quality	References	Evidence
Scoping review	Critically low (AMSTAR 2)	Di Gennaro et al, 2022	- Protecting healthcare workers and preventing transmission in healthcare settings (PPE, infection prevention and control procedures) should be guaranteed as soon as an outbreak occurs - Standard contact and droplet precautions, both in outpatient and hospital settings, with hand hygiene strictly followed
Letter to the editor		Alavi-Moghaddam, 2022	- Healthcare workers occupational exposure: HCWs who examine or practice with a suspected case of MPXV should appropriately use infection prevention and control measures including PPE (medical mask, gloves, gown, eye protection) and hand hygiene
Letter to the editor		Athar et al, 2022	- Poxviruses such as MPXV can be very stable and remain contagious for long periods of time - As such, healthcare providers need to apply PPE while regularly disinfecting frequent contact spots on the body, double gloving, proper hand hygiene - Those providing care to MPXV patients with skin lesions should use proper PPE including disposable gown and hand gloves eye protections, and fit-tested N95 respirators
Letter to the editor		Lo Muzio and Spirito, 2022	- Skin and mucous membrane lesions remain contagious until complete healing, whereby healthcare workers and close contacts of active cases could be at greater risk of infection - Thus, essential that oral care providers wear personal protective equipment (PPE) such as N95 masks, FFP3 respirators, fluid-resistant attire, and eye protection - High touch surfaces need to be decontaminated with appropriate disinfectants, aerosolizing procedures ought to be avoided

Single study (retrospective study)		Petersen et al. 2019	- Healthcare workers risk infection with MPXV when they provide consultation and care for patients with MPX. Between 2010 and 2014, 1266 suspect MPX cases were investigated in Tshuapa, wherein eleven instances the case identified themselves as a 'healthcare worker'. Among the 699 confirmed cases during this time period, six confirmed cases of MPX among HCWs represented a proportion of 0.9% (range of 0.3–3.1% by year). On average, 1.5 HCWs were infected per year during the observation period, yielding an estimated annual HCW incidence rate of 17.4/10,000. - To understand the risk environment for healthcare workers in Tshuapa, we retrospectively investigated 14 instances of suspected HCW infections that occurred between 2009 and 2014. Diagnostic specimens had been collected and tested for 12 of the 14 ill HCWs, 7 were confirmed to have MPX. Five of the 7 confirmed MPX cases (71.4%) had a vaccination scar. - Each HCW reported exposure to a person who had a similar illness; one HCW reported exposure to five suspect cases. Six HCWs (42.9%) reported exposure during their official duties as a HCW, including three of the MPX confirmed cases (42.8%).
Single study mentioned as a report		Yinka-Ogunleye et al. 2019	This study has reported - "Nosocomial transmission of monkeypox was previously reported in the Central African Republic.32,33 Post-outbreak assessment of health workers in the USA in 2003 also suggested possible acquisition of asymptomatic infection in hospital settings.32 Nosocomial infection in a health-care worker who cared for a patient with confirmed monkeypox was also reported in the UK.34 The infection of health-care workers suggests a possible breach in infection prevention and control measures while caring for patients with monkeypox. The potential for infection of health-care workers during monkeypox outbreaks calls for concerted efforts by hospitals to strengthen and routinely follow recommended infection prevention and control practices during patient care".

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APPENDIX A. Research Methods

We used a standardized protocol for preparing this living evidence profile (LEP) to ensure transparency and consistency of methods between iterations, with any changes clearly described and justified in future iterations.

Identifying research evidence

For this LES, we searched Medline and EMBASE (both over the Ovid platform) from January 1, 2000 to October 28, 2022 for the following document types:

- Guidelines (documents providing recommendations derived from explicit evidence synthesis activities)
- Reviews (systematic reviews, rapid reviews, non-systematic reviews, scoping reviews)
- Primary studies (including randomized trials, comparative non-randomized studies, observational studies)
- Grey literature (dissertations and theses)
- Reports (published as journal articles)
- Preprints (non-peer reviewed studies)
- Editorial, letters, and commentaries (included in the 2000-2017 lookback evidence)

The below search strategy (composed of a combination of MeSH terms, subject headings, and keywords) was used in databases (Medline and Embase) to seek eligible documents. We plan on generating updated LES iterations every second week, refining the search strategy throughout to optimize sensitivity and specificity of searches.

Search strategy

Embase Classic+Embase <1947 to 2022 July 08>
Ovid MEDLINE(R) ALL <1946 to July 11, 2022>

1 Monkeypox/
2 Monkeypox virus/
3 (monkeypox or MPXV* or hmpxv* or chimpanzeepox*).ti,ab,kf.*
4 ((monkey or simian*) adj3 (pox* or smallpox* or orthopox*)).ti,ab,kf.*
5 or/1-4
6 5 not (comment or letter or editorial or news or note or erratum).pt.
7 limit 6 to yr="2017 -Current"(for the lookback evidence this criteria was excluded)

Evidence documents resulting from the search was imported into Covidence, with each record screened in two stages (title and abstract, then full text). One team member conducted the searches using pre-specified keywords to identify potentially relevant documents. A final inclusion assessment was performed by two members of the rapid evidence profile team, with conflicts or uncertainties discussed and resolved by consensus or input from a third reviewer (if required). Records were included if they discussed, examined using analytic methods, or pertained to any of the domains in the organizing framework regarding the zoonotic nature of MPXV. Evidence documents published in other languages were excluded if an English version was unavailable. For this iteration, only preprints were included. Reporting quality of preprints will be examined, should they be published in future in a peer-reviewed journal. Team members used a dedicated virtual channel to discuss and refine eligibility criteria throughout the process.

Assessing study quality

One member of the team evaluated the quality of the evidence with a second member as the auditor. Any query by the first member was discussed with the auditor and decision was based on consensus. Following tools were used for assessment of quality of the different type of evidence documents:

- Guidelines: For guidelines, three domains of the AGREE II tools were used (stakeholder involvement, rigour of development and editorial independence) to assess Quality (152). Domain scores are reported, with scores 60% or greater deemed as meeting a threshold of adequate quality.

- Systematic Reviews, Rapid Reviews, and Scoping Reviews: For systematic reviews and rapid reviews, AMSTAR 2.0 was used to assess the quality of the document. Overall confidence in the results of the review was assessed based on the number of weaknesses detected in critical and non-critical items (153):

    - "High" quality: reviews with no or one non-critical weakness provide an accurate and comprehensive summary of results from included studies
    - "Moderate" quality: reviews with more than one non-critical weakness may provide an accurate summary of results. Multiple non-critical weaknesses can reduce confidence in the review and may justify a "Low" quality rating as well.
    - "Low" quality: reviews with one critical flaw may not provide an accurate summary of included studies
    - "Critically low" quality: reviews with more than one critical flaw should not be relied on to provide an accurate, comprehensive summary of included studies
    - *It is important to note that due to compromises in methods when conducting rapid and scoping reviews, AMSTAR 2.0 ratings may be systematically lower for these reviews compared to full systematic reviews.*

- Primary studies: Quality was assessed based on the study design mentioned in the manuscript. For cohort and case-control studies the Newcastle-Ottawa Scale (NOS) for Cohort and Case-Control designs was used respectively (154). Randomized trials were assessed using the Cochrane Risk of Bias tool (155). Some domains were not relevant to some study designs (such as studies of animal populations), and this is reflected in the denominator of NOS scores provided in the review. As such, judging relative quality of studies needs to account for both numerator and denominator of the score.

- Non-systematic reviews, reports, and grey literature: Not appraised as they are considered lower quality sources of evidence.

Quality ratings of selected records for all iterations

LEP VERSION	ARTICLE TYPE	QUALITY RATING (TOOL)	CITATION
1.0	Systematic review	Critically low (AMSTAR 2)	Bunge et al, 2022
	Systematic review	Low (AMSTAR 2)	Beer and Rao, 2019
	Systematic review	Critically low (AMSTAR 2)	Chauhan et al, 2020
	Rapid review	Critically low (AMSTAR 2)	Diaz et al. 2021
	Single study (prospective cohort study)	High (8/9, NOS)	Whitehouse et al. 2021,
	Single study (retrospective cohort study)	Moderate (5/9, NOS)	Tiee et al, 2018
	Single study (prospective cohort study)	High (7/9, NOS)	Patrono et al, 2020
1.4	Scoping review	Critically low (AMSTAR 2)	Di Gennaro et al, 2022
1.5	Systematic review	Critically low (AMSTAR 2)	Kannan et al, 2022
	Scoping review	Critically low (AMSTAR 2)	Adnan et al, 2022
1.6	Systematic review	Critically low (AMSTAR-2)	Soheili et al, 2022
	Systematic review	Critically low (AMSTAR-2)	Rahimi et al, 2022
	Scoping review	Critically low (AMSTAR-2)	Capobianchi et al, 2022
1.7	Scoping review	Critically low (AMSTAR 2)	Kipkorir et al, 2022
1.8	Systematic review	Critically low (AMSTAR-2)	Brown and Leggat, 2016

Preparing the Profile

Each included document is hyperlinked to its original source to facilitate easy retrieval. For all included evidence document, we identify the key messages (based on the organizing framework) and present them in Tables 4a-4j as the key findings. We also assess quality of pre-specified evidence documents (guidelines, systematic reviews, rapid reviews, primary studies of cohort and case-control design), using the relevant quality assessment tools. These findings are then summarized in the narrative summary in the main text. The narrative summary highlights the total number of different types of evidence documents and are organized by the different domains of the organizing framework.

Changes made to the scope of the LEP since its initiation

Dates	**Summary of changes**

Original iteration (Version 1) – 22nd July, 2022	Original types of evidence document screened:
	- Guidelines
	- Full systematic reviews
	- Rapid reviews/scoping reviews
	- Non-systematic reviews
	- Protocols for reviews or rapid reviews that are underway
	- Titles/questions for reviews that are being planned
	- Single studies (any design)
	- Published reports
	- Published dissertations/theses
	
	Original domains in organizing framework
	- Description of the virus
	- Reservoirs of the virus
	- Transmissibility of the virus
	  o Animal-to-human
	  o Human-to-animal
	  o Animal-to-animal
	- Clinical infection in animals
	- Treatment of infected animals
	  o Domestic animals
	  o Cattle
	  o Wildlife
	- Susceptible animals of the virus
	- Handling of susceptible animals
	- Additional perspectives
	  o Environmental factors
	  o Occupational exposure

Version 1.1 – 5th August, 2022	No changes
Version 1.2 – 19th August, 2022	Types of evidence documents added: - Preprints (given provisional low study quality until published in a peer-reviewed publication)
Version 1.3 – 2nd September, 2022	Types of evidence documents added: - Editorials - Letters to the editor

	- Commentaries in academic journals
Version 1.4 – 15th September, 2022	No changes

Version 1.5 – 29th September, 2022	Types of evidence documents removed:
	- Editorials
	- Letters to the editor
	- Commentaries in academic journals
	Domains added to organizing framework:
	- Transmissibility of virus
	  o Risks of transmission associated with animal waste, wastewater
	
	Domains removed from organizing framework:
	- Description of the virus
	- Treatment of infected animals
	  o Domestic animals
	  o Cattle
	  o Wildlife
	- Additional perspectives
	  o Environmental factors
	  o Occupational exposure

Version 1.6 – 27th October 2022	No changes
Version 1.7 – 10th November 2022	Separation of Table 4 by domains included in the organizing framework: Table 4a: description of the virus Table 4b: reservoirs of the virus Table 4c: transmissibility of the virus Table 4d: clinical infection of MPXV in animals Table 4e: clinical presentation of MPXV in animals Table 4f: treatment of infected animals with MPXV Table 4g: susceptible animals to MPXV Table 4h: handling of MPXV-infected animals Table 4i: environmental aspects of MPXV zoonoses Table 4j: occupational aspects of MPXV zoonoses

Version 1.8 – 8th December 2022 (**final iteration)**	Screened and collected data from evidence documents published between January 1, 2000 and January 1, 2017 as part of the lookback iteration. This search also included non-empirical evidence documents (editorials, letters to the editor, and commentaries). Rearranged Table 4: Table 4a: reservoirs of the virus Table 4b: transmissibility of the virus Table 4c: clinical infection of MPXV in animals Table 4d: clinical presentation of MPXV in animals Table 4e: susceptible animals to MPXV Table 4f: handling of MPXV-infected animals Table 4g: description of the virus Table 4h: treatment of infected animals with MPXV Table 4i: environmental aspects of MPXV zoonoses Table 4j: occupational aspects of MPXV zoonoses

APPENDIX B. List and characteristics of our included evidence documents (new evidence documents from this iteration are highlighted)

#	Title	Authors	Published Year	Type of study	Country/Jurisdiction
1	Emerging infectious diseases in Africa in the 21st century	Fenollar & Mediannikov	2018	Review (non-systematic)	France
2	Clinical and Epidemiological Findings from Enhanced Monkeypox Surveillance in Tshuapa Province, Democratic Republic of the Congo during 2011-2015	Whitehouse et al.	2021	Single study (prospective cohort study)	Democratic Republic of Congo
3	Monkeypox and human transmission: Are we on the verge of another pandemic?	Farahat et al.	2022	Report	Egypt
4	Emergence of Monkeypox - West and Central Africa, 1970-2017	Durski et al.	2018	Report	United States
5	Vaccinating against monkeypox in the Democratic Republic of the Congo	Petersen et al.	2019	Single study (retrospective study)	Democratic Republic of Congo
6	Evidence for asymptomatic circulation of orthopoxvirus in Mfou district, Cameroon	Guargliardo et al.	2020	Single study (cross-sectional)	Cameroon
7	A review of the monkeypox virus and a recent outbreak of skin rash disease in Nigeria	Kabuga & Zowalaty	2019	Review (non-systematic)	Nigeria
8	Human monkeypox - After 40 years, an unintended consequence of smallpox eradication	Simpson et al.	2020	Review in a conference report	United Kingdom
9	Outbreak of human monkeypox in Nigeria in 2017-18: a clinical and epidemiological report	Yinka-Ogunleye et al.	2019	Single study mentioned as a report	Nigeria
10	Monkeypox Virus Emerges from The Shadow of Its More Infamous Cousin: Family Biology Matters	Xiang & White	2022	Review (non-systematic)	United States
11	The presumed receptivity and susceptibility to monkeypox of European animal species	Haddad	2022	Review (non-systematic)	France
12	The Disease Ecology, Epidemiology, Clinical Manifestations, Management, Prevention, and Control of Increasing Human Infections with Animal Orthopoxviruses	Diaz et al.	2021	Rapid review	United States
13	Investigation of rodent reservoirs of emerging pathogens in Cote d'Ivoire, West Africa	Meite et al.	2022	Single study (cross-sectional)	Cote d'Ivoire

14	Monkeypox: considerations for the understanding and containment of the current outbreak in non-endemic countries	Quarleri et al.	2022	Review (non-systematic)	Argentina
15	Monkeypox re-emergence in Africa: a call to expand the concept and practice of One Health	Reynolds et al.	2019	Review (non-systematic)	United States
16	Monkeypox Rash Severity and Animal Exposures in the Democratic Republic of the Congo	Doshi et al.	2020	Single study (cross-sectional)	Democratic Republic of Congo
17	Monkeypox virus emergence in wild chimpanzees reveals distinct clinical outcomes and viral diversity	Patrono et al.	2020	Single study	Germany
18	The changing epidemiology of human monkeypox-A potential threat? A systematic review	Bunge et al.	2022	Systematic review	Netherlands
19	Monkeypox virus in nigeria: Infection biology, epidemiology, and evolution	Alakunle et al.	2020	Review (non-systematic)	Nigeria
20	Epidemiologic and ecologic investigations of Monkeypox, Likouala department, Republic of the Congo, 2017	Doshi et al.	2019	Single study (cross-sectional)	Democratic Republic of Congo
21	Here, there, and everywhere: The wide host range and geographic distribution of zoonotic orthopoxviruses	Silva et al.	2021	Review (non-systematic)	Brazil
22	Infectious Disease Risk Across the Growing Human-Non Human Primate Interface: A Review of the Evidence.	Devaux et al.	2019	Review (non-systematic)	France
23	Presumptive risk factors for monkeypox in rural communities in the Democratic Republic of the Congo	Quiner et al.	2017	Single study (cross-sectional)	Democratic Republic of Congo
24	Increased outbreaks of monkeypox highlight gaps in actual disease burden in Sub-Saharan Africa and in animal reservoirs	Haider et al.	2022	Review (non-systematic)	United Kingdom
25	A single vaccination of nonhuman primates with highly attenuated smallpox vaccine, LC16m8, provides long-term protection against monkeypox	Iizuka et al.	2017	Single study (animal experiment)	Japan
26	Assessing monkeypox virus prevalence in small mammals at the human-animal interface in the democratic republic of the congo	Doty et al.	2017	Review (non-systematic)	Democratic Republic of Congo

27	Ghosts of infections past: using archival samples to understand a century of monkeypox virus prevalence among host communities across space and time.	Tiee et al.	2018	Single study (retrospective cohort study)	United States
28	Systematic review of important viral diseases in africa in light of the 'one health' concept	Chauhan et al.	2020	Systematic review	South Africa
29	A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy	Beer & Rao	2019	Systematic review	United Kingdom
30	The 2022 outbreak and the pathobiology of the monkeypox virus	Kumar et al.	2022	Review (non-systematic)	United States
31	Viral Zoonoses of National Importance in Ghana: Advancements and Opportunities for Enhancing Capacities for Early Detection and Response	Suu-Ire et al.	2021	Review (non-systematic)	Ghana
32	Characterization of Monkeypox virus infection in African rope squirrels (Funisciurus sp.)	Falendysz et al.	2017	Single study (animal experiment)	United States
33	Monkeypox: What do we know so far? A short narrative review of literature	Deshmukh et al	2022	Review (non-systematic)	India
34	Phylogenomic analysis of the monkeypox virus (MPXV) 2022 outbreak: Emergence of a novel viral lineage?	Luna et al	2022	Single study (cross-sectional)	Colombia
35	Can animals outside Africa be affected by the ongoing monkeypox outbreak, or even become important players?	Haddad and Cordevant	2022	Review (non-systematic)	France
36	Assessing transmission risks and control strategy for monkeypox as an emerging zoonosis in a metropolitan area	Yuan et al	2022	**Preprint (single study, longitudinal)**	Canada
37	Monkeypox outbreak - Nine states, May 2022	Minhaj et al	2022	Report (outbreak investigation)	USA
38	Human Monkeypox in Sierra Leone after 44-Year Absence of Reported Cases	Reynolds et al	2019	Report (outbreak investigation)	USA and Sierra Leone
39	Monkeypox: A Review of Clinical Features, Diagnosis, and Treatment	Cheema et al	2022	Non-systematic review	Pakistan and Nigeria

40	Monkeypox: An emerging global threat during the COVID-19 pandemic	Lai et al	2022	Non-systematic review	Taiwan
41	Monkeypox: A Review	Singhal et al	2022	Non-systematic review	India
42	Unusual global outbreak of monkeypox: what should we do?	Zhu et al	2022	Non-systematic review	China
43	Monkeypox — Enhancing public health preparedness for an emerging lethal human zoonotic epidemic threat in the wake of the smallpox post-eradication era	Petersen et al	2022	Non-systematic review	Various countries
44	Monkeypox transmission among international travellers - serious monkey business?	Angelo et al	2019	Editorial	USA
45	Is monkeypox another reemerging viral zoonosis with many animal hosts yet to be defined?	Bonilla-Aldana et al	2022	Editorial	Colombia and Peru
46	Should not airborne transmission be ignored in the 2022 monkeypox outbreak?	Saied	2022	Letter to the editor	Egypt
47	Evidence of human-to-dog transmission of monkeypox virus	Seang et al	2022	Letter to the editor	France
48	Human Monkeypox: A Comprehensive Narrative Review and Analysis of the Public Health Implications	Di Gennaro et al	2022	Scoping review	Italy and Turkey
49	Environmental Drivers of Monkeypox Transmission in the Democratic Republic of the Congo	Mandja et al	2022	Primary study (ecological study)	Democratic Republic of Congo
50	Monkeypox: An international epidemic	Focosi et al	2022	Non-systematic review	Italy
51	The lurking threat of monkeypox in current times	Kumbhar and Agarwala	2022	Non-systematic review	India
52	Comparative Pathology of Zoonotic Orthopoxviruses	MacNeill	2022	Non-systematic review	USA
53	Monkeypox 2022: Gearing Up for Another Potential Public Health Crisis	Ranganath et al	2022	Non-systematic review	USA
54	Reverse zoonosis and monkeypox: Time for a more advanced global surveillance system for emerging pathogens	Afrooghe et al	2022	Letter to the editor	Iran
55	Monkeypox Outbreak in Non-Endemic Areas: Will it Cause a New Pandemic? a Letter to Editor	Alavi-Moghaddam	2022	Letter to the editor	Iran

56	Monkeypox infection: risk for oral healthcare provider	Lo Muzio and Spirito	2022	Letter to the editor	Italy
57	Advancing surgical setting: A paradigm for healthcare workers during the monkeypox outbreak	Athar et al	2022	Letter to the editor	Iran
58	Monkeypox emergency: Urgent questions and perspectives	Rothenburg et al	2022	Editorial	USA
59	Monkeypox: Considerations as a New Pandemic Looms	Brewer et al	2022	Commentary	USA
60	Monkeypox during COVID-19 era in Africa: Current challenges and recommendations	Okonji and Okonji	2022	Commentary	South Africa
61	Monkeypox: epidemiology, mode of transmission, clinical features, genetic clades and molecular properties	Kannan et al	2022	Systematic review	Maldives
62	The detection of monkeypox virus DNA in wastewater samples in the Netherlands	de Jonge et al	2022	Primary study (wastewater surveillance)	The Netherlands
63	Human monkeypox virus: An updated review	Adnan et al	2022	Scoping review	Pakistan
64	Monkeypox: Some Keys to Understand This Emerging Disease	Gomez-Lucia	2022	Non-systematic review	Spain
65	A Review of Zoonotic Disease Threats to Pet Owners: A Compendium of Measures to Prevent Zoonotic Diseases Associated with Non-Traditional Pets: Rodents and Other Small Mammals, Reptiles, Amphibians, Backyard Poultry, and Other Selected Animals	Varela et al	2022	Non-systematic review	USA
66	Monkeypox 2022 outbreak in non-endemic countries: Open questions relevant for public health, nonpharmacological intervention and literature review	Capobianchi et al	2022	Scoping review	Italy
67	Monkeypox virus: past and present	Dou et al	2022	Non-systematic review	China
68	Emergence and dissemination of monkeypox, an intimidating global public health problem	Ejaz et al	2022	Non-systematic review	Saudi Arabia, China, Pakistan, Sudan
69	Human monkeypox: A review of the literature	El Eid et al	2022	Non-systematic review	Lebanon
70	Monkeypox virus: The changing facets of a zoonotic pathogen	Forni et al	2022	Non-systematic review	Italy
71	Human Monkeypox - Spillover Event	Kolte et al	2022	Non-systematic review	India

72	Atypical and Unique Transmission of Monkeypox Virus during the 2022 Outbreak: An Overview of the Current State of Knowledge	Riopelle et al	2022	Non-systematic review	USA
73	The Historical Epidemiology of Human Monkeypox: A Review of Evidence from the 1970 Emergence to the 2022 Outbreak	Rahimi et al	2022	Systematic review	Iran
74	State-of-the-art on monkeypox virus: an emerging zoonotic disease	Shafaati and Zandi	2022	Non-systematic review	Iran
75	The risk of reverse zoonotic transmission to pet animals during the current global monkeypox outbreak, United Kingdom, June to mid-September 2022	Shepherd et al	2022	Published report	United Kingdom
76	Monkeypox: Virology, Pathophysiology, Clinical Characteristics, Epidemiology, Vaccines, Diagnosis, and Treatments	Soheili et al	2022	Systematic review	USA and Iran
77	Monkeypox, a Literature Review: What Is New and Where Does This concerning Virus Come From?	Tiecco et al	2022	Non-systematic review	Italy
78	The re-emerging monkeypox disease	Kipkorir et al	2022	Scoping review	Kenya, USA, UK
79	Monkeypox: From A Neglected Tropical Disease to a Public Health Threat.	Antunes et al	2022	Non-systematic review	Portugal
80	A Brief Report on Monkeypox Outbreak 2022: Historical Perspective and Disease Pathogenesis	Chowdhury et al	2022	Non-systematic review	Bangladesh
81	Monkeypox virus: Future role in Human population	Farasani	2022	Non-systematic review	Saudi Arabia
82	Monkeypox	Gessain et al	2022	Non-systematic review	France
83	Monkeypox Disease: An Emerging Public Health Concern in the Shadow of COVID-19 Pandemic: An Update.	Hasan and Saeed	2022	Non-systematic review	India
84	Comprehensive Literature Review of Monkeypox	Hatmal et al	2022	Non-systematic review	Jordan
85	Global Outbreak of Human Monkeypox in 2022: Update of Epidemiology.	Ilic et al	2022	Non-systematic review	Serbia
86	Monkeypox: An Emerging Global Public Health Emergency	Jeyaraman et al	2022	Non-systematic review	India, USA, Italy

87	Monkeypox: the resurgence of forgotten things	Kim et al	2022	Non-systematic review	Korea
88	The evolving epidemiology of monkeypox virus	Li et al	2022	Non-systematic review	China
89	The Emergence of Monkeypox: A Global Health Threat.	Sah et al	2022	Non-systematic review	India, Egypt
90	Keeping an Eye on Poxviruses	Bray	2009	Editorial	USA
91	Chimpanzee predation and the ecology of microbial exchange	Wrangham et al	2000	Non-systematic review	USA, Democratic Republic of the Congo
92	Human Monkeypox: Current State of Knowledge and Implications for the Future	Brown and Leggat	2016	Systematic review	Australia, Switzerland
93	Monkeypox: A review of the history and emergence in the Western hemisphere	Ligon	2004	Non-systematic review	USA
94	Qualitative Assessment of Risk for Monkeypox Associated with Domestic Trade in Certain Animal Species, United States	Bernard and Anderson	2006	Non-systematic review	USA
95	Extensive Lesions of Monkeypox in a Prairie Dog (*Cynomys* sp.)	Langohr et al	2004	Single study (case report)	USA
96	Fatal Monkeypox in Wild-Living Sooty Mangabey, Côte d'Ivoire, 2012	Radonic et al	2014	Single study (case report)	Germany
97	Spectrum of Infection and Risk Factors for Human Monkeypox, United States, 2003	Reynolds et al	2007	Single study (case-control study)	USA
98	Zoonotic Poxviruses Associated with Companion Animals	Tack and Reynolds	2011	Non-systematic review	USA
99	Effects of Epidemic Diseases on the Distribution of Bonobos	Inogwabini and Leader-Williams	2012	Single study (ecological study)	UK, Democratic Republic of the Congo
100	Factors affecting the likelihood of monkeypox's emergence and spread in the post-smallpox era	Reynolds et al	2012	Non-systematic review	USA
101	Multistate Outbreak of Monkeypox - Illinois, Indiana, and Wisconsin, 2003	CDC	2003	Published report	USA
102	Bushmeat hunting, deforestation, and prediction of zoonotic disease emergence	Wolfe et al	2005	Non-systematic review	USA
103	Serologic Evidence For Multiple Genera Of Poxviruses Circulating In The Peridomestic Rodent Population In Western Uganda	Salzer et al	2003	Single study (serosurvey)	Uganda, USA

104	Maculopapular lesions in the Central African Republic	Berthet et al	2011	Single study (case report)	Central African Republic, France
105	Monkeypox zoonotic associations: Insights from laboratory evaluation of animals associated with the multi-state US outbreak	Hutson et al	2007	Single study (serosurvey)	USA
106	Monkeypoxvirus infections	Pattyn	2000	Non-systematic review	Belgium
107	Monkeypox	World Health Organization (WHO)	2011	Report	Switzerland
108	Reasons for the increase in emerging and re-emerging viral infectious diseases	Ka-Wai Hui	2006	Non-systematic review	USA
109	Poxvirus tropism	McFadden	2005	Non-systematic review	Canada
110	Emerging infectious diseases: vulnerabilities, contributing factors and approaches.	Lashley	2004	Non-systematic review	USA
111	Orthopoxvirus infection among wildlife in Zambia	Orba et al.	2015	Report	Zambia
112	Human monkeypox: An emerging zoonotic disease	Parker et al.	2007	Non-systematic review	USA
113	Multistate outbreak of monkeypox--Illinois, Indiana, and Wisconsin, 2003.	Centers for Disease Control and Prevention (CDC)	2003	Report	USA
114	Emerging infections in animals - Potential new zoonoses?	Torres-Velez & Brown	2004	Non-systematic review	USA
115	Update: multistate outbreak of monkeypox--Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003.	Centers for Disease Control and Prevention (CDC)	2003	Report	USA
116	Clinical manifestations of human monkeypox influenced by route of infection	Reynolds et al.	2006	Single study (cross-sectional study)	USA
117	Emerging diseases-the monkeypox epidemic in the Democratic Republic of the Congo	Kantele et al.	2016	Editorial	Finland
118	Collection and Utilization of Animal Carcasses Associated with zoonotic Disease in Tshuapa District, the Democratic Republic of the Congo, 2012	Monroe et al.	2015	Report	

119	Epidemie dynamics at the human-animal interface	Lloyd-Smith et al.	2009	Non-systematic review	USA
120	Emerging infectious diseases at the beginning of the 21st century	Lashley	2006	Non-systematic review	USA
121	Use of Vaccinia Virus Smallpox Vaccine in Laboratory and Health Care Personnel at Risk for Occupational Exposure to Orthopoxviruses — Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2015	Petersen et al.	2016	Guidelines	USA
122	Introduction of Monkeypox into a Community and Household: Risk Factors and Zoonotic Reservoirs in the Democratic Republic of the Congo	Nolen et al.	2015	Single study (outbreak investigation)	Democratic Republic of the Congo
123	Phylogenetic and Ecologic Perspectives of a Monkeypox Outbreak, Southern Sudan, 2005	Nakazawa et al.	2013	Single study (outbreak investigation)	South Sudan
124	Pathogen-Host Associations and Predicted Range Shifts of Human Monkeypox in Response to Climate Change in Central Africa	Thomassen et al.	2013	Single study (modelling study)	Democratic Republic of Congo
125	Comparative Pathology of Smallpox and Monkeypox in Man and Macaques	Cann et al.	2013	Non-systematic review	USA
126	A review of experimental and natural infections of animals with monkeypox virus between 1958 and 2012	Parker and Buller	2013	Non-systematic review	USA
127	Using Remote Sensing to Map the Risk of Human Monkeypox Virus in the Congo Basin	Fuller et al.	2011	Single study (modelling study)	Democratic Republic of the Congo
128	Potential attractants for detecting and removing invading Gambian giant pouched rats (Cricetomys gambianus)	Witmer et al.	2009	Single study (animal experiment)	USA
129	Poxviruses and the Passive Quest for Novel Hosts	Regnery	2007	Non-systematic review	USA
130	Occupational Risks during a Monkeypox Outbreak, Wisconsin, 2003	Croft et al.	2007	Single study (outbreak investigation)	USA
131	Transmission of monkeypox among persons exposed to infected prairie dogs in Indiana in 2003	Kile et al.	2005	Single study (outbreak investigation)	USA

132	Emerging infectious diseases: vulnerabilities, contributing factors and approaches	Lashley	2004	Non-systematic review	USA
133	Monkeypox Transmission and Pathogenesis in Prairie Dogs	Guarner et al.	2004	Single study (animal report)	USA
134	The Detection of Monkeypox in Humans in the Western Hemisphere	Reed et al.	2004	Single study (outbreak investigation)	USA
135	Human monkeypox: an emerging zoonosis	Di Giulio and Eckburg	2004	Non-systematic review	USA
136	Status of human monkeypox: clinical disease, epidemiology and research	Damon	2011	Non-systematic review	USA
137	Detecting Differential Transmissibilities That Affect the Size of Self-Limited Outbreaks	Blumberg et al.	2014	Single study (modelling study)	USA
138	Control of communicable diseases; restrictions on African rodents, prairie dogs, and certain other animals. Interim final rule; opportunity for public comment.	CDC	2003	Guideline	USA
139	Zoonotic poxviruses	Essbauer et al.	2010	Non-systematic review	Germany
140	Emerging zoonotic epidemics in the interconnected global community	Gibbs	2005	Non-systematic review	USA
141	Poxviruses and the evolution of host range and virulence	Haller et al.	2014	Non-systematic review	USA
142	Outbreak of human monkeypox, Democratic Republic of Congo, 1996 to 1997	Hutin et al.	2001	Single study	Democratic Republic of Congo
143	Monkeypox virus detection in rodents using real-time 3'-minor groove binder TaqMan assays on the Roche LightCycler	Kulesh et al.	2004	Single study	USA
144	Tropical dermatology: Viral tropical diseases	Lupi & Tyring	2003	Non-systematic review	USA, Brazil
145	When good vaccines go wild: Feral Orthopoxvirus in developing countries and beyond	Moussatche et al.	2008	Non-systematic review	USA
146	Mapping Monkeypox Transmission Risk through Time and Space in the Congo Basin	Nakazawa et al.	2013	Single study (ecological modelling)	Congo Basin
147	A silent enzootic of an orthopoxvirus in Ghana, West Africa: Evidence for multi-species involvement in the absence of widespread human disease	Reynolds et al.	2010	Single study (animal infection experiments)	Ghana

148	Monkeypox outbreak a reminder of emerging infections vulnerabilities	Stephenson J.	2003	News correspondence	USA

APPENDIX C. List of excluded articles (articles excluded from this iteration are highlighted)

#	Title (with URL)	Authors	Published Year	Notes
1	Monkeypox, wild animals, and potential big problem	Song & Zheng	2022	Letter to the editor/correspondence/news article
2	Characterization of Monkeypox virus dissemination in the black-tailed prairie dog (Cynomys ludvicianus) through in vivo bioluminescent imaging	Weiner et al.	2019	Information related to human population
3	Revised recommendations for health monitoring of non-human primate colonies (2018): FELASA Working Group Report	Balansard et al.	2019	Information related to human population
4	Mapping the environmental suitability of monkeypox in humans across Africa	Hulland et al.	2020	Abstract only
5	Ortopoxviruses: Past, present and future	Borisevich et al.	2020	Not in English
6	The clinical characterization of human monkeypox infections in the Democratic Republic of Congo	Mbala et al.	2017	Abstract only
7	A One Health team to improve Monkeypox virus outbreak response: An example from the Democratic Republic of Congo	Laudisoit et al.	2017	Abstract only
8	Monkeypox: Key Concepts.	Pinto-Pulido et al.	2022	Not in English
9	Participatory-based surveillance and detection of viral zoonotic pathogens in the Democratic Republic of Congo	Mulembakani et al.	2017	Abstract only
10	Panorama des poxvirus : emergence du monkeypox, Review of poxvirus: emergence of monkeypox	Morand et al.	2017	Not in English
11	Studies of nonhuman primates: key sources of data on zoonoses and microbiota	Davoust et al.	2018	Not related to MPV zoonosis
12	Frameworks for preventing, detecting, and controlling zoonotic diseases	Shiferaw et al.	2017	Information related to human population
13	Impact of One Health approach in management of monkeypox outbreaks in Nigeria from September 2017 to August 2021	Mokwugwo et al.	2022	Abstract only
14	Wildlife surveillance for emergent disease	Kuhn	2020	Letter to the editor/correspondence/news article
15	Co-administration of tecovirimat and ACAM2000TM in non-human primates: Effect of tecovirimat treatment on	Russo et al.	2020	Information related to human population

	ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge			
16	Emergence of monkeypox: Another concern amidst COVID-19 crisis	Shanmugaraj et al.	2022	Letter to the editor/correspondence/news article
17	Insufficient Innate Immunity Contributes to the Susceptibility of the Castaneous Mouse to Orthopoxvirus Infection.	Earl et al.	2017	Related to viral immunity
18	Attitudes, practices, and zoonoses awareness of community members involved in the bushmeat trade near Murchison Falls National Park, northern Uganda	Dell et al.	2020	Information related to human population
19	Atypical zoonotic pox: Acute merging illness that can be easily forgotten	Wiwanitkit & Wiwanitkit	2018	Information related to human population
20	Investigation and prevention against Monkeypox in Mefou Primate Sanctuary, Cameroon, 2016	Moundjoa et al.	2017	Abstract only
21	Monkeypox could establish new reservoirs in animals	Cohen	2022	Letter to the editor/correspondence/news article
22	Illegal Wildlife Trade: A Gateway to Zoonotic Infectious Diseases	Bezerra-Santos et al.	2021	Not related to MPV zoonosis
23	What has been researched about monkeypox? a bibliometric analysis of an old zoonotic virus causing global concern.	Rodriguez-Morales et al.	2022	Letter to the editor/correspondence/news article
24	A methodology for determining which diseases warrant care in a high-level containment care unit	Cieslak et al.	2019	Not related to MPV zoonosis
25	Use of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Nonreplicating) for Preexposure Vaccination of Persons at Risk for Occupational Exposure to Orthopoxviruses: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022	Rao et al.	2022	Not related to MPV zoonosis
26	Imvamune and acam2000 provide different protection against disease when administered postexposure in an intranasal monkeypox challenge prairie dog model	Keckler et al.	2020	Information related to human population
27	Monkeypox in Europe and beyond - tackling a neglected disease together	Kluge & Ammon	2022	Letter to the editor/correspondence/news article
28	Geographic structuring and divergence time frame of monkeypox virus in the endemic region	Forni et al	2022	Not related to MPXV zoonosis

29	Rapid Diagnostic Testing for Response to the Monkeypox Outbreak - Laboratory Response Network, United States, May 17-June 30, 2022	Aden et al	2022	Information related to the human population
30	Rapid Response for Notification of Monkeypox Exposure, Exposure Risk Assessment and Stratification, and Symptom Monitoring	Simpson et al	2022	Information related to the human population
31	Monkeypox 2022 Identify-Isolate-Inform: A 3I Tool for frontline clinicians for a zoonosis with escalating human community transmission	Koenig et al	2022	Information related to the human population
32	Monkeypox virus neurological manifestations in comparison to other orthopoxviruses	Shafaati et al	2022	Mainly concerns the human population
33	Monkeypox emerges on a global scale: A historical review and dermatologic primer	Bryer et al	2022	Mainly concerns the human population
34	Human monkeypox outbreak: global prevalence and biological, epidemiological and clinical characteristics - observational analysis between 1970-2022	Meo and Klonoff	2022	Mainly concerns the human population
35	Monkeypox outbreak in Europe, UK, North America, and Australia: A changing trend of a zoonotic disease	Cabanillas et al	2022	Mainly concerns the human population
36	Monkeypox outbreak and response efforts in the Eastern Mediterranean Region	Al-Mandhari et al	2022	Mainly concerns the human population
37	Rising Concern of Monkeypox as a Viral Zoonosis After COVID-19 Era	Mardani and Pourkaveh	2022	Mainly concerns the human population
38	Confronting 21st-century monkeypox	Osterholm and Gellin	2022	Mainly concerns the human population
39	Emergence of monkeypox: Risk assessment and containment measures	Dhawan et al	2022	Mainly concerns the human population
40	Monkeypox: a neglected old foe	The Lancet Infectious Diseases	2022	Mainly concerns the human population
41	Multinational monkeypox outbreak: what do we know and what should we do?	Memariani et al	2022	Mainly concerns the human population
42	Of migration, macaques, mice and men	Tay et al	2022	Mainly concerns the human population
43	The Threat of Emerging and Re-emerging Infections in Indonesia	Nelwan	2019	Not related to monkeypox
44	An overview of monkeypox virus and its neuroinvasive potential	Pastula and Tyler	2022	Mainly concerns the human population
45	Emergence of human monkeypox in west Africa	Rezza	2019	Mainly concerns the human population

46	Monkeypox virus neurological manifestations in comparison to other orthopoxviruses	Shafaati et al	2022	Mainly concerns the human population
47	A Novel International Monkeypox Outbreak	Adalja and Inglesby	2022	Not related to zoonotic factors
48	Global re-emergence of human monkeypox: Population on high alert	Banerjee et al	2022	Not related to zoonotic factors
49	Monkeypox: a new face of outbreak	Chavda et al	2022	Not related to zoonotic factors
50	Investigating the monkeypox outbreak	Dye and Kraemer	2022	Not related to zoonotic factors
51	The Evolving Epidemiology of Human Monkeypox: Questions Still to Be Answered	Heymann and Simpson	2022	Not related to zoonotic factors
52	Monkeypox is an emerging threat to low-middle-income countries amid COVID-19	Jahan	2022	Not related to zoonotic factors
53	The never-ending global emergence of viral zoonoses after COVID-19? The rising concern of monkeypox in Europe, North America and beyond	Leon-Figueroa et al	2022	Not related to zoonotic factors
54	Combating the global spread of poverty-related Monkeypox outbreaks and beyond	Tambo and Al-Nazawi	2022	Not related to zoonotic factors
55	Monkeypox contacts: a puzzling problem	The Lancet	2018	Not related to zoonotic factors
56	Appearance and re-appearance of zoonotic disease during the pandemic period: long-term monitoring and analysis of zoonosis is crucial to confirm the animal origin of SARS-CoV-2 and monkeypox virus	Chakraborty et al	2022	Not related to zoonotic factors
57	Current efforts and challenges facing responses to Monkeypox in United Kingdom	Idris and Adesola	2022	Not related to zoonotic factors
58	The spreading of monkeypox in nonendemic countries has created panic across the world: Could it be another threat?	Islam et al	2022	Not related to zoonotic factors
59	Human monkeypox outbreak in 2022	Kumar et al	2022	Not related to zoonotic factors
60	Unexpected sudden rise of human monkeypox cases in multiple non-endemic countries amid COVID-19 pandemic and salient counteracting strategies: Another potential global threat?	Mohapatra	2022	Not related to zoonotic factors
61	Monkeypox: An extra burden on global health	Saied et al	2022	Mainly concerns the human population
62	Monkeypox outbreak: New zoonotic alert after the COVID-19 pandemic	Sharma	2022	Mainly concerns the human population
63	Multiple lineages of Monkeypox virus detected in the United States, 2021-2022	Gigante et al	2022	Cellular/molecular/in vitro genetic studies
64	Monkeypox: A focused narrative review for emergency medicine clinicians	Long et al	2022	Mainly concerns human disease
65	Monkeypox: Potentially another pandemic or a mere hoax?	Saeed et al	2022	Mainly concerns human disease

66	Monkeypox infection: An update for the practicing physician	Patauner et al	2022	Mainly concerns human disease
67	Is there a need to be worried about the new monkeypox virus outbreak? A brief review on the monkeypox outbreak	Shaheen et al	2022	Mainly concerns human disease
68	The first imported case of monkeypox in Singapore during the 2022 outbreak - Reflections and lessons.	Tan et al	2022	Mainly concerns human disease
69	Global monkeypox outbreak 2022: First case series in Singapore.	Koh et al	2022	Mainly concerns human disease
70	The global emergence of monkeypox	Tan and Hsu	2022	Mainly concerns human disease
71	Monkeypox 22: A Review on the monkeypox disease general approaches, outbreaks, and detection	Hussain et al	2022	Full text not available, original source no longer accessible
72	Relooking the monkeypox virus during this present outbreak: epidemiology to therapeutics and vaccines	Chatterjee et al	2022	Mainly concerns human disease
73	Management of patients with monkeypox virus (MPXV) infection and contacts in the community and in healthcare settings: A French position paper	Lepelletier et al	2022	Mainly concerns human disease
74	Multi-origins and complex transmission paths of monkeypox viruses	Yuan et al	2022	Not related to MPXV zoonosis
75	A commentary on "Unexpected sudden rise of human monkeypox cases in multiple non-endemic countries amid COVID-19 pandemic and salient counteracting strategies: Another potential global threat?" (Int J Surg 2022;103:106705)	Khani and Entezari-Maleki	2022	Insufficient information on zoonotic characteristics of MPXV
76	The 2022 monkeypox outbreak — Special attention to nurses' protection should be a top priority	Ibrahim et al	2022	Letter to the editor
77	Unusual spread of the monkeypox virus: An emerging threat to the public health and the possible containment	Islam et al	2022	Letter to the editor
78	Recent outbreak of monkeypox: Overview of signs, symptoms, preventive measures, and guideline for supportive management	Shuvo et al	2022	Letter to the editor
79	Monkeypox virus: An emerging epidemic	Aljabali et al	2022	Mainly concerns human disease
80	Reemergence of monkeypox: prevention and management	Nadar et al	2022	Mainly concerns human disease
81	What should we do about monkeypox?	Chen et al	2022	Non-empirical record (commentary/editorial/letter to the editor/etc.)

82	A Comprehensive Review on Monkeypox Virus Transmission, Pathogenesis, Treatments and its Preventive Measures	Yadav et al	2022	Full text not available (NQ)
83	Serial intervals and incubation periods of the monkeypox virus clades	Wang et al	2022	Mainly concerns human disease
84	HIV and Mediterranean Zoonoses: A Review of the Literature.	Russotto et al	2022	Not related to monkeypox disease
85	From a Neglected Pathogen to a Public Health Emergency: Connecting the Dots in Monkeypox Emergence.	Fahmy et al	2022	Mainly concerns human disease
86	A Review of the Recent Monkeypox Outbreak in 2022.	Al-Gburi and Namuq	2022	Mainly concerns human disease
87	A Short Review on Monkey Pox Disease	Nasih et al	2022	Mainly concerns human disease (NQ)
88	Zoonoses and Animal Culling: The Need for One Health Policy.	Lederman	2022	Not related to monkeypox disease
89	Monkeypox and children	Cohen and Ladhani	2022	Mainly concerns human disease
90	Monkeypox viral disease outbreak in non-endemic countries in 2022: What clinicians and healthcare professionals need to know	Onchonga	2022	Mainly concerns human disease
91	[Monkeypox, a new pandemic?]	de Stoppelaar et al	2022	Article not in English
92	First case report of human monkeypox in Latin America: The beginning of a new outbreak.	Pérez-Barragán and Pérez-Cavazos	2022	Insufficient information on MPXV zoonosis
93	The current outbreak of Monkeypox virus (MPXV); what strategies can be adopted to control its transmission?	Bukhari and Goodarzian	2022	Non-empirical evidence (commentary)
94	[A grave concern for the prevalence of monkeypox virus].	Feng et al	2022	Record not in English
95	Neglected Zoonotic Monkeypox in Africa but Now Back in the Spotlight Worldwide.	Tan and Gao	2022	Non-empirical evidence (opinion article)
96	Estimation of the serial interval of monkeypox during the early outbreak in 2022	Guo et al	2022	Insufficient information on MPXV zoonosis
97	The current emergence of monkeypox: The recurrence of another smallpox?	Lu et al	2022	Insufficient information on MPXV zoonosis
98	Monkeypox: A Comprehensive Review.	Harapan et al	2022	Mainly concerns human disease
99	Human Monkeypox: Old virus with new Epidemiological and Transmission Trends	Meo	2022	Insufficient information on MPXV zoonosis
100	Serological Evidence of Orthopoxvirus Infection in Neotropical Primates in Brazil.	de Abreu et al	2022	Study based on animal models or experimental infection

101	Epidemiologic features and scientific prevention and control of monkeypox	Wu et al	2022	Record not in English
102	Un cas de variole simienne chez l'humain au Canada	Sukhdeo et al	2022	Record not in English
103	On nonlinear dynamics of a fractional order monkeypox virus model.	El-Mesady et al	2022	Insufficient information on MPXV zoonosis
104	MONKEYPOX VIRUS. A BRIEF REVIEW	Teglia et al	2022	Record not in English
105	Retrospective detection of monkeypox virus in the testes of nonhuman primate survivors	Liu et al	2022	Study based on animal models or experimental infection
106	Ecological Niche and Geographic Distribution of Human Monkeypox in Africa	Levine et al	2006	Mainly concerns human disease/manifestation of MPXV infection
107	Animal Models of Orthopoxvirus Infection	Chapman et al	2010	Information related to human monkeypox; mainly describes disease from animal models
108	Further Assessment of Monkeypox Virus Infection in Gambian Pouched Rats (Cricetomys gambianus) Using In Vivo Bioluminescent Imaging	Falendysz et al	2015	Mainly describes disease in animals via experimental/artifical MPXV infection
109	Monkeypox outbreak among pet owners	Maskalyk	2003	Mainly concerns human disease/manifestation of MPXV infection
110	Laboratory Investigations of African Pouched Rats (Cricetomys gambianus) as a Potential Reservoir Host Species for Monkeypox Virus	Hutson et al	2015	Mainly describes disease in animals via experimental infection
111	Control of communicable diseases; restrictions on African rodents, prairie dogs, and certain other animals. Interim final rule; supplement and partial reopening of comment period	Anonymous	2007	Insufficient evidence specific to monkeypox
112	Monkeypox disease transmission in an experimental setting: Prairie dog animal model	Hutson et al.	2011	Study using animal models
113	Evaluation of human-to-human transmission of monkeypox from infected patients to health care workers	Fleischauer et al.	2005	Mainly concerns human disease
114	Evaluation of monkeypox virus infection of black-tailed prairie dogs (Cynomys ludovicianus) using in vivo bioluminescent imaging	Falendysz et al.	2014	Prairie dogs were experimentally infected with MPXV
115	Orthopoxvirus: Biology, pathology and therapy	Byrd et al.	2008	Full text not available
116	One health: zoonoses in the exotic animal practice.	Souza & Marcy	2011	Full text not available
117	Prevalence of antibodies against orthopoxviruses among residents of Likouala	Lederman et al.	2007	Mainly concerns human disease

	region, Republic of Congo: Evidence for Monkeypox virus exposure			
118	Discovery of monkeypox in Sudan [15]	Damon et al.	2006	Mainly concerns human disease
119	Monkeypox confirmed in the USA	Anonymous	2003	Full text not available
120	Virulence and pathophysiology of the Congo Basin and West African strains of monkeypox virus in non-human primates	Saijo et al.	2009	Challenge study/animal not end-user of therapy
121	Public health implications of emerging zoonoses	Meslin et al.	2000	Mainly concerns human disease
122	Infectious diseases on the world wide web	Hartmann	2004	Not related to MPXV zoonosis
123	A tale of two clades: Monkeypox viruses	Likos et al.	2005	Not related to MPXV zoonosis
124	Treatment with the smallpox antiviral tecovirimat (ST-246) alone or in combination with ACAM2000 vaccination is effective as a postsymptomatic therapy for monkeypox virus infection	Berhanu et al.	2015	Challenge study/animal not end-user of therapy
125	Experimental infection of an African dormouse (Graphiurus kelleni) with monkeypox virus	Schultz et al.	2009	Study using animal models/laboratory-based strains
126	The monkeypox virus outbreak: Reflections from the frontlines	Edminston et al.	2003	Mainly concerns human disease
127	Biodiversity, Bushmeat and Monkeypox in the Democratic Republic of the Congo: Another viral threat upon larger cities?	Laudisoit et al.	2015	Conference abstract
128	A fine-scale geospatial analysis of factors associated with monkeypox transmission, Tshuapa District, Democratic Republic of the Congo, 2013	Monroe et al.	2015	Conference abstract
129	Transmissibility of the Monkeypox Virus Clades via Respiratory Transmission: Investigation Using the Prairie Dog-Monkeypox Virus Challenge System	Hutson et al.	2013	Challenge study/animal not end-user of therapy
130	Fever of Unknown Origin Due to Zoonoses	Cleri et al.	2007	Mainly concerns human disease
131	Attenuated NYCBH vaccinia virus deleted for the E3L gene confers partial protection against lethal monkeypox virus disease in cynomolgus macaques	Denzler et al.	2011	Challenge study/animal not end-user of therapy
132	Identification of wild-derived inbred mouse strains highly susceptible to monkeypox virus infection for use as small animal models	Americo et al.	2010	Study using animal models/laboratory-based strains
133	Reducing the risks of the wildlife trade	Smith et al.	2009	Commercial news article

134	Virulence differences between monkeypox virus isolates from West Africa and the Congo basin	Chen et al.	2005	Mainly concerns human disease
135	LC16m8, a highly attenuated vaccinia virus vaccine lacking expression of the membrane protein B5R, protects monkeys from monkeypox	Saijo et al.	2006	Challenge study/animal not end-user of therapy
136	Smallpox DNA Vaccine Protects Nonhuman Primates against Lethal Monkeypox	Hooper et al.	2004	Challenge study/animal not end-user of therapy
137	Validation of a pan-orthopox real-time PCR assay for the detection and quantification of viral genomes from nonhuman primate blood	Mucker et al.	2017	Not related to MPXV zoonosis
138	An Increasing Danger of Zoonotic Orthopoxvirus Infections	Shchelkunov	2013	Not related to MPXV zoonosis
139	U.S. monkeypox outbreak traced to Wisconsin pet dealer	Enserink	2003	Commercial news article
140	The zoonotic poxviruses	Lewis-Jones	2002	Not related to MPXV zoonosis
141	A prairie dog animal model of systemic orthopoxvirus disease using west African and Congo Basin strains of Monkeypox virus	Hutson et al.	2009	Study using animal models/laboratory-based strains
142	Outbreak of monkeypox in the United States. Description of a case report in the United States. Just an incident, or a prelude to a scary development?	Verkleij	2003	Not in English
143	Poxvirus Zoonoses - Putting Pocks into Context	Frey & Belshe	2004	Insufficient evidence specific to monkeypox
144	Fierce creatures. Zoonoses, diseases that jump from animals to humans, are a growing health around the world. Understanding their causes and their effects on humans have therefore become an important topic for global public health	Breithaupt	2003	Not related to MPXV zoonosis
145	Risk factors associated with human monkeypox in the democratic republic of Congo	Hoff et al.	2014	Conference abstract
146	Lessons from naked apes and their infections	Weiss	2007	Not related to monkeypox
147	Reemergence of monkeypox: Prevalence, diagnostics, and countermeasures	Nalca et al.	2005	Mainly concerns human disease
148	Enhancing health care worker capabilities to detect and care for patients with monkeypox	Bass et al.	2013	Mainly concerns human disease
149	Investigation and prevention against Monkeypox in Mefou Primate Sanctuary, Cameroon, 2016	Moundjoa et al.	2017	Conference abstract

150	Human monkeypox in the Kivus, a conflict region of The Democratic Republic of the Congo	McCollum et al.	2014	Conference abstract
151	Monkeypox in the United States: an occupational health look at the first cases	Cunha	2004	Mainly concerns human disease
152	[Gambian giant pouched rat and prairie dogs: monkeypox outbreak in America].	Schwarz & Hassler	2003	Not in English
153	Monkeypox outbreak diagnostics and implications for vaccine protective effect.	Karem et al.	2006	Mainly concerns human disease
154	The pathology of experimental aerosolized monkeypox virus infection in cynomolgus monkeys (Macaca fascicularis)	Zaucha et al.	2001	Challenge study/animal not end-user of therapy
155	[Mechanisms of viral emergence and interspecies transmission: the exemple of simian foamy viruses in Central Africa].	Gessain	2003	Not in English
156	Historical, new, and reemerging links between human and animal health	Marano & Pappaioanou	2004	Not related to monkeypox
157	Monkeypox - First cases in Western Hemisphere	Fox	2003	Full text not available
158	Monkeypox spreads as US public-health system plays catch-up	Larkin	2003	Commercial news article
159	Monkeypox without exanthem [24]	Lewis et al.	2007	Mainly concerns human disease
160	Monkeypox virus infections in healthcare workers	McCollum et al.	2015	Conference abstract
161	Immunogenicity of a highly attenuated MVA smallpox vaccine and protection against monkeypox	Earl et al.	2004	Challenge study/animal not end-user of therapy
162	Emerging viral infections	Su	2004	Mainly concerns human disease
163	Global threats from emerging viral diseases	Chastel	2007	Not in English
164	Hamster rats and prairie dogs: Monkeypox outbreak in the USA	Schwarz & Hassler	2003	Full text not available
165	Emerging viral diseases	Bricaire & Bossi	2006	Not in English
166	Introduction: Conceptualizing and partitioning the emergence process of zoonotic viruses from wildlife to humans	Childs et al.	2007	Not related to MPXV zoonosis
167	Simian smallpox virus (monkeypox) appears in the American continent [2]	Franco-Paredes et al.	2003	Not in English
168	Crossing the Species Barrier - One Small Step to Man, One Giant Leap to Mankind	Klempner & Shapiro	2004	Editorial/correspondence
169	One Medicine One Science: A framework for exploring challenges at the intersection of animals, humans, and the environment	Travis et al.	2014	Not related to MPXV zoonosis

170	Mouse models for studying orthopoxvirus respiratory infections	Schriewer et al.	2004	Study using animal models/laboratory-based strains
171	Trade in wild animals: A disaster ignored	Anonymous	2003	Editorial/correspondence
172	[The monkeypox virus appears in the American continent].	Franco-Paredes et al.	2003	Not in English
173	Cross-species transfer of viruses: Implications for the use of viral vectors in biomedical research, gene therapy and as live-virus vaccines	Louz et al.	2005	Not related to MPXV zoonosis
174	Subunit recombinant vaccine protects against monkeypox	Herauld et al.	2006	Challenge study/animal not end-user of therapy
175	Characterization of macaque pulmonary fluid proteome during monkeypox infection: Dynamics of host response	Brown et al.	2010	Challenge study/animal not end-user of therapy
176	Immunopathogenesis of poxvirus infections: Forecasting the impending storm	Stanford et al.	2007	Challenge study/animal not end-user of therapy
177	Development of the disease in marmot at the intranasal infection with the monkeypox virus	Kabanov et al.	2015	Not in English
178	Exotic pets and monkeypox	Estrada	2003	Full text not available
179	Efficacy of the antipoxvirus compound ST-246 for treatment of severe orthopoxvirus infection	Sbrana et al.	2007	Study using animal models/laboratory-based strains
180	DNA/MVA HIV-1/AIDS vaccine elicits long-lived vaccinia virus-specific immunity and confers protection against a lethal monkeypox challenge	Nigam et al.	2007	Challenge study/animal not end-user of therapy
181	[Antiviral treatment is more effective than smallpox vaccination upon lethal monkeypox virus infection].	Cuervo	2006	Challenge study/animal not end-user of therapy
182	Comparison of Monkeypox Virus Clade Kinetics and Pathology within the Prairie Dog Animal Model Using a Serial Sacrifice Study Design	Hutson et al.	2015	Challenge study/animal not end-user of therapy
183	Handling infectious disease: how Wisconsin copes with monkeypox and more.	Kennedy	2003	Full text not available
184	Hedgehog zoonoses	Riley & Chomel	2005	Not related to MPXV zoonosis
185	Longitudinal analysis of changes in 18FDG uptake in bone marrow and lymph node and in lymph node volume in the nonhuman primate model of monkeypox infection	Dyall et al.	2012	Conference abstract
186	Susceptibility of marmosets (Callithrix jacchus) to monkeypox virus: A low dose prospective model for monkeypox and smallpox disease	Mucker et al.	2015	Study using animal models/laboratory-based strains

187	Management and care of African dormice (Graphiurus kelleni)	Kastenmayer et al.	2010	Not related to MPXV zoonosis
188	A novel highly reproducible and lethal nonhuman primate model for orthopox virus infection	Kramski et al.	2010	Study using animal models/laboratory-based strains
189	Evaluation of monkeypox disease progression by molecular imaging	Dyall et al.	2011	Study using animal models/laboratory-based strains
190	Zoonoses of dermatologic interest	Wilson et al.	2009	Mainly concerns human disease
191	Orthopoxvirus DNA in Eurasian Lynx, Sweden	Tryland et al.	2011	Not related to MPXV zoonosis
192	Smallpox Vaccines: Looking Beyond the Next Generation	Enserink	2004	Commercial news article
193	Application of the Ibis-T5000 pan-Orthopoxvirus assay to quantitatively detect monkeypox viral loads in clinical specimens from macaques experimentally infected with aerosolized monkeypox virus	Grant et al.	2010	Study using animal models/laboratory-based strains
194	The role of evolution in the emergence of infectious disease	Antia et al.	2003	Not related to MPXV zoonosis
195	Experiment infection of prairie dogs with monkeypox virus	Xiao et al.	2005	Challenge study/animal not end-user of therapy
196	Experimental infection of cynomolgus macaques (Macaca fascicularis) with aerosolized monkeypox virus	Nalca et al.	2010	Challenge study/animal not end-user of therapy
197	A mouse model of lethal infection for evaluating prophylactics and therapeutics against monkeypox virus	Stabenow et al.	2010	Study using animal models/laboratory-based strains
198	Experimental infection of ground squirrels (Spermophilus tridecemlineatus) with monkeypox virus	Tesh et al.	2004	Challenge study/animal not end-user of therapy
199	A history of biological disasters of animal origin in North America	Ackerman & Giroux	2006	Not related to MPXV zoonosis
200	Ecology and geography of human monkeypox case occurrences across Africa	Ellis et al.	2012	Mainly concerns human disease
201	Monkeypox in the United States	Perkins	2003	Full text not available
202	ST-246 antiviral efficacy in a nonhuman primate monkeypox model: Determination of the minimal effective dose and human dose justification	Jordan et al.	2009	Challenge study/animal not end-user of therapy
203	Health concerns prompt US review of exotic-pet trade	Check	2004	Commercial news article
204	Genetic studies of the susceptibility of classical and wild-derived inbred mouse strains to monkeypox virus	Earl et al.	2015	Study using animal models/laboratory-based strains

205	SARS: Here to stay? Monkeypox: Beware of exotic pets	Gordon	2003	Mainly concerns human disease
206	Monkeypox: a first for the United States	West	2003	Full text not available
207	Monkeypox virus infection	Zhao et al.	2003	Not in English
208	Clinical and epidemiological features of monkeypox	Merouze	2002	Not in English
209	Pet related infections	Rabinowitz et al	2007	Not related to monkeypox
210	Prairie-dog model offers hope of tackling monkeypox virus	Knight	2003	Commercial news article
211	Monkeypox Pathogenesis Study Using A Serial Sacrifice Technique	Hutson et al.	2010	Challenge study/animal not end-user of therapy
212	Monkeypox confirmed in rodents	Anonymous	2003	Full text not available
213	Problem pets	Silverberg	2003	Editorial/correspondence
214	A novel respiratory model of infection with monkeypox virus in cynomolgus macaques	Goff et al.	2011	Study using animal models/laboratory-based strains
215	Monkeypox virus infection of rhesus macaques induces massive expansion of NK cells, but suppresses NK cell function (P4369)	Song et al.	2013	Not related to MPXV zoonosis
216	Infectious disease: The human costs of our environmental errors	Weinhold	2004	Not related to monkeypox
217	Bacterial and viral epidemics of zoonotic origin; the role of hunting and cutting up wild animals	Chastel & Charmot	2004	Full text not available
218	Wildlife trade and global disease emergence	Karesh et al.	2005	Not related to monkeypox
219	Update on Emerging Infections: News From the Centers for Disease Control and Prevention	Gross	2003	Not related to MPXV zoonosis
220	Monkeypox in the Western Hemisphere [2] (multiple letters)	Huhn et al.	2004	Editorial/correspondence
221	Sequence of pathogenic events in cynomolgus macaques infected with aerosolized monkeypox virus	Tree et al	2015	Study using animal models/laboratory-based strains
222	Pathogenesis of fulminant monkeypox with bacterial sepsis after experimental infection with West African monkeypox virus in a cynomolgus monkey	Nagata et al.	2014	Challenge study/animal not end-user of therapy
223	Molecular evolution of poxviruses	Babkin & Shelkunov	2008	Not related to MPXV zoonosis
224	Zoonotic viral diseases and the frontier of early diagnosis, control and prevention	Heeney	2006	Not related to MPXV zoonosis
225	Human monkeypox	Chastel	2009	Not in English

226	Monkeypox detection in maculopapular lesions in two young Pygmies in the Central African Republic	Nakoune & Kazanji	2012	Conference abstract
227	The Detection of Monkeypox in Humans in the Western Hemisphere	Anonymous	2004	Mainly concerns human disease
228	On alert for monkeypox	Snow	2005	Mainly concerns human disease
229	Zoonoses associated with petting farms and open zoos	Stirling et al.	2008	Insufficient evidence specific to monkeypox
230	Poxvirus Antigen Staining of Immune Cells as a Biomarker to Predict Disease Outcome in Monkeypox and Cowpox Virus Infection in Non-Human Primates	Song et al.	2013	Study using animal models/laboratory-based strains
231	Susceptibility of marmosets (Callitrix Jacchus) to monkeypox virus	Mucker et al.	2011	Conference abstract
232	Preventing monkeypox	Anonymous	2003	Full text not available
233	Update on monkeypox outbreak	Fox	2003	Full text not available
234	Comparative pathology of North American and Central African strains of monkeypox virus in a ground squirrel model of the disease	Sbrana et al.	2007	Study using animal models/laboratory-based strains
235	Mechanisms of virulence of monkeypox virus: Deletion of genomic regions and their effects in pathogenesis	Lopera et al.	2014	Conference abstract
236	Effective antiviral treatment of systemic orthopoxvirus disease: ST-246 treatment of prairie dogs infected with Monkeypox virus	Smith et al.	2011	Challenge study/animal not end-user of therapy
237	A phylogeographic investigation of African monkeypox	Nakazawa et al.	2015	Not related to MPXV zoonosis
238	Smallpox vaccine-induced antibodies are necessary and sufficient for protection against monkeypox virus	Edghill-Smith et al.	2005	Study using animal models/laboratory-based strains
239	Comparative live bioluminescence imaging of monkeypox virus dissemination in a wild-derived inbred mouse (Mus musculus castaneus) and outbred African dormouse (Graphiurus kelleni)	Earl et al.	2015	Study using animal models/laboratory-based strains
240	Proteomic basis of the antibody response to monkeypox virus infection examined in cynomolgus macaques and a comparison to human smallpox vaccination	Keasey et al.	2010	Challenge study/animal not end-user of therapy
241	Globalization of infectious diseases: The impact of migration	Gushulak & MacPherson	2004	Insufficient evidence specific to monkeypox
242	Risk and risk management for xenotransplantation	Julvez et al.	2000	Not in English
243	No longer an island - The global threat of emerging disease	Anonymous	2005	Editorial/correspondence

244	Assessment of the protective effect of imvamune and Acam2000 vaccines against aerosolized monkeypox virus in cynomolgus macaques	Hatch et al.	2013	Challenge study/animal not end-user of therapy
245	Globalization and infectious diseases	Garavelli & Peduzzi	2006	Not in English
246	Recent animal disease outbreaks and their impact on human populations	Bender	2006	Mainly concerns human disease
247	The 'One Health' paradigm: Time for infectious diseases clinicians to take note?	Fisman & Laupland	2010	Not related to monkeypox
248	Infection of cynomolgus macaques with a recombinant monkeypox virus encoding green fluorescent protein	Goff et al.	2011	Challenge study/animal not end-user of therapy
249	Progress in the discovery of compounds inhibiting orthopoxviruses in animal models	Smee	2008	Study using animal models/laboratory-based strains
250	Monkey-pox, a model of emergent then reemergent disease	Georges et al.	2004	Not in English
251	Monkeypox virus infections in small animal models for evaluation of anti-poxvirus agents	Hutson & Damon	2010	Study using animal models/laboratory-based strains
252	Infectious diseases. U.S. monkeypox outbreak traced to Wisconsin pet dealer.	Enserink	2003	Commercial news article
253	Circulation of virus and interspecies contamination in wild animals	Osterhaus	2000	Not in English
254	Comparison of West African and Congo Basin monkeypox viruses in BALB/c and C57BL/6 mice	Hutson et al.	2010	Challenge study/animal not end-user of therapy
255	The global burden of bacterial and viral zoonotic infections	Christou	2011	Mainly concerns human disease
256	Human monkeypox in a conflict region of the democratic republic of the Congo	McCollum et al.	2013	Conference abstract
257	Correction: Transmissibility of the monkeypox virus clades via respiratory transmission: Investigation using the prairie dog-monkeypox virus challenge system (PLoS ONE)	Hutson et al	2014	Study using animal models/laboratory-based strains
258	Transmission of zoonoses through immigration and tourism.	Mavroidi	2008	Not related to MPXV zoonosis
259	Prairie Dog: Cuddly Pet or Trojan Horse?	Azad	2004	Editorial/correspondence
260	Characterization of monkeypox infection in cynomolgus macaques using 4 routes of exposure	Lanning et al.	2015	Conference abstract
261	[Epidemiology of Ebola virus disease and of other highly contagious, life-threatening diseases with low incidence in Germany].	Ehlkes et al.	2015	Not in English

262	The Possibility of Using the ICR Mouse as an Animal Model to Assess Antimonkeypox Drug Efficacy	Kabanov et al.	2016	Study using animal models/laboratory-based strains
263	Orthopoxvirus variola infection of Cynomys ludovicianus (North American Black tailed prairie dog)	Carroll et al.	2013	Study using animal models/laboratory-based strains
264	Nonhuman primates are protected from smallpox virus or monkeypox virus challenges by the antiviral drug ST-246	Huggins et al.	2009	Challenge study/animal not end-user of therapy
265	Inhalational monkeypox virus infection in cynomolgus macaques	Barnewall	2012	Study using animal models/laboratory-based strains
266	Monkeypox out of Africa	Chastel	2004	Full-text not available
267	Perceived threats and real killers	Glass	2004	Editorial/correspondence
268	Side-by-side comparison of gene-based small pox vaccine with MVA in nonhuman primates	Golden	2012	Study using animal models/laboratory-based strains