MONKEY POX VIRUS – ZOONOTIC CHARACTERISTICS
LIVING EVIDENCE PROFILE
September 15, 2022

OVERARCHING QUESTIONS.

What is the available evidence related to the zoonotic characteristics?

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

WHAT WE FOUND.

This updated search yielded 13 articles that met eligibility criteria (see Box 1 for a description of our approach). We have structured our findings using the organizing framework below.

ORGANIZING FRAMEWORK.

- Description of the monkeypox virus (MPXV; viral phenotypic description)
- Reservoirs of MPXV
- Transmissibility of MPXV
    - Animal-animal
    - Animal-human
    - Human-animal
- Clinical infection in animals (incubation period, shedding)
- Clinical presentation in animals
- Treatment options (and preventive measures)
    - Domestic animals
    - Cattle
    - Wild animals or animals in captivity
- Susceptible animals
- Handling of infected susceptible animals
- Additional perspectives
    - Environmental risks (animal waste, etc.)
    - Occupational exposure risks

A total of 148 articles were screened in this iteration of the evidence profile. **NEW in this update is the inclusion of 13 additional eligible articles:**

- 1 scoping review
- 4 non-systematic reviews
- 1 single study (of ecological design)

BOX 1. OUR APPROACH

We identified evidence documents published from January 1st, 2017 to September 2, 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, or primary studies.

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 primary studies.

We have included preprints and published editorials, letter to editor and commentary with this iteration. The quality of evidence for these types of articles should be judged as low. In-depth assessment will be conducted should pre-prints be published in a 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 14 days of a 'full-court press' by all involved staff.

- 7 editorials/letter to editor/commentary

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.**

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 4: Provides details about key findings and quality assessments of the evidence documents.

In terms of quality of the evidence, one of the articles identified in the current iteration was eligible to undergo quality assessment. We applied AMSTAR-2 to assess the quality of evidence for one scoping review. Due to compromises in methods when conducting scoping reviews, AMSTAR 2.0 rating was lower in comparison to full systematic reviews. Overall quality if evidence presented in this LEP ranges from critically low to moderate category. Hence, we recommend that any decision made based on evidence presented in this LEP needs to account for any methodological shortcomings in the included evidence.

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:

To date, there are 25 articles that provide a description of the virus: 1 systematic reviews, 1 scoping review, 2 single studies, 19 non-systematic reviews, 1 published report, and 1 editorial.

New Evidence

September 15, 2022 (latest iteration):

One scoping review (1) 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 higher prevalence among HIV patients and the Congo Basin variant have a 10% CFR. Most cases noted in the 2022 outbreak, however, were not directly related to human and animal travels from endemic areas. 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.

Four non-systematic reviews (2–5) 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.

One editorial (6) 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.

September 2, 2022 iteration:

Four non-systematic reviews (7–10) described monkeypox (MPXV) as one of 10 species in the Orthopoxvirus genus, including variola (smallpox) most notably. 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).

Existing Evidence:

A systematic review, (11) documenting the findings from 10 peer-reviewed studies and 1 published report (12) has described the MPXV to have two distinct genetic clades, the Central African and West African clade.

Two primary studies have reported on the morphologic and evolutionary features of the MPXV. One (13) 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* (14) 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 (15–24) have recognized the two Monkeypox virus clades: West African and Congo, Basin. *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 (24). A mortality and morbidity report by Durski et al. (12) has also described the morphology of the MPXV.

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 28 articles which present and discuss potential reservoirs of the virus: 1 systematic review, 1 rapid review, 7 single studies, 1 preprint of a single study, 14 non-systematic reviews, 3 published reports and 1 editorial. **Table 1** lists all animal species that been identified as natural host or possible reservoir of the MPXV.

New Evidence

September 15, 2022 (latest iteration):

A total of 3 non-systematic reviews (3–5) have discussed extensively on the reservoir characteristics of the MPXV. Focosi et al (4) has provided a year and location based portray of when various animals have been identified as possible hosts *(see Table 3)*. McNeill (5) has provided a list of species naturally affected by MPXV. However, whether these species are reservoir of the virus remains to be confirmed.

September 2, 2022 iteration:

One report (25) *of an outbreak investigation* described MPXV cases in nine US states describe 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.

Four non-systematic reviews (7–9,26) 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.

Editorials, letter to editor and commentary: One editorial (27) *echoes the concerns of past iterations that while monkeys and humans are considered accidental MPXV hosts, the true host of MPXV is unknown.*

Existing Evidence:

A systematic review (28) aiming 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. A rapid review by Diaz et al. 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 (13,23,29–33) 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 (34), 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.

Ten non-systematic reviews (16,17,19–21,23,24,35–37) 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 (24). 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 (24) 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.

Two reports (published) (12,38) 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.

Box 3. Reservoir of the MPXV.

- Table 1 lists all animal species that been identified as 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)*	NA
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	Orangutans Chimpanzees Cynomolgus monkeys	New World giant anteaters *(Myrmecophaga tridactyla)* Elephant shrews *(Macroscelididae sp.)* Newborns of white rabbits and rabbits

TRANSMISSIBILITY OF THE VIRUS:

To date, there were 46 records identified which provided data on transmissibility of the virus among animals and between humans and animals: 3 systematic reviews, 1 rapid review, 1 scoping review, 20 non-systematic reviews, 8 single studies, 3 reports, 1 preprint of a primary study, 7 editorials, and 2 letters to the editor.

Animal-to-human transmission

New Evidence

September 15, 2022 (latest iteration):

One scoping review (1) 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.

Three non-systematic reviews (2,3,5) reiterate the common transmission paths for MPXV infection between animals and humans, with contact with live infected or dead animals with MPXV being the leading route to human MPXV infection. 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.

One editorial (6)*, one letter to the editor* (39)*, and two commentaries* (40,41) 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.

September 2, 2022 iteration:

One report (26) *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.

Five non-systematic reviews (7–10,26) 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 (Zhu et al, 2022) also postulates potential for aerosol transmission from animals to humans, as noted in community and nosocomial outbreaks in the Democratic Republic of Congo (DRC).

Editorials, letter to editor and commentary: One editorial (27) 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* (42) 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.

Existing Evidence:

Three systematic reviews (11,28,43) 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. One rapid review (44) 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.

A total of five primary studies has discussed animal to human transmission. Four cross-sectional primary studies (13,23,45,46) 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 (14) 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 (34) , 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.

Eight non-systematic reviews (15,16,18,19,23,32,47) (48) 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). Nosocomial transmission has also been reported in some instances.

Three published reports (12,30,36) 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)

Human-to-animal transmission

New Evidence

September 15, 2022 (latest iteration):

Editorials, letter to editor and commentary: One editorial (49) 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.

September 2, 2022 iteration:

One published report (25) *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.

Editorials, letter to editor and commentary: One editorial (50) 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 (51) 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.

Existing Evidence:

Three non-systematic reviews have discussed human-animal transmission. All three non-systematic reviews (16,24,35) 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. New reservoirs would thus increase likelihood to animal-to-human transmission. Isolation and monitoring of rodents, for instance, can prevent possible transmission. The non-systematic review by *Haddad and Cordevant* (24) 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.

Animal-to-animal transmission

New Evidence

September 15, 2022 (latest iteration):

Editorials, letter to editor and commentary: One commentary (40) 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.

September 2, 2022 iteration:

No additional evidence was identified for this part of the organizing framework.

Existing Evidence:

One prospective cohort study (37) 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. (52), 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 (24) networks.

Three non-systematic reviews (15,24,38) 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).

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 lying on ground, being in forest, or handling animals.
- To date confirmed evidence has shown that wild squirrels *(Funisciurus anerythrus and Heliosciurus rufobrachium*) and prairie dogs (*Cynomys ludovicanus*) to have transmitted the virus to humans.

Animal-to-Animal:

- Animal contact with animal urine and fecal matter.
- Recent evidence has noted that due to series of mutations in a short period may have caused spillover to new animal reservoirs in non-endemic countries. However, this has not yet been systematically examined.

Human-to-Animal:

- Uncertain. 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.
- One instance of transmission of the virus from human to animal (dog) has been reported in France. This was reported in a letter to the editor, but human-to-animal transmission has not been systematically examined.

CLINICAL INFECTION:

To date, 2 studies have been identified discussing the clinical infectivity of MPXV in animals: 2 non-systematic reviews.

New Evidence

September 15, 2022 (latest iteration):

One non-systematic review (5) presents the infection characteristics of MPXV in prairie dogs, one of the infected animals during the 2003 outbreak, 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 upto 25 days afterward.

September 2, 2022 iteration:

No additional evidence was identified for this part of the organizing framework.

Existing Evidence

One non-systematic review (24) 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.

CLINICAL PRESENTATION:

To date, 7 studies have been identified discussing the clinical presentation of MPXV infection in animals: 2 single studies, 3 non-systematic reviews, 1 editorial, and 1 letter to the editor.

New Evidence

September 15, 2022 (latest iteration):

One non-systematic review (5) 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.

September 2, 2022 iteration:

Editorials, letter to editor and commentary: One editorial (50) *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* (51) *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.*

Existing Evidence:

Two single studies (31,32) have discussed the clinical presentation of the MPX disease in animals. One study (31) 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.* 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 non-systematic reviews have discussed on clinical presentation in animals*. Devaux et al.* (47) 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 (24), 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.

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

To date, there were 8 articles which described treatment options and preventive measures against monkeypox in animals: 1 rapid review, 1 single study, 5 non-systematic reviews and 1 published report.

New Evidence

September 15, 2022 (latest iteration):

One non-systematic review (3) 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.

September 2, 2022 iteration:

Three non-systematic reviews (7–9) 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) 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.

Existing Evidence:

One rapid review (44) 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 (53) 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 one published report (12,35) 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.

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 11 records which identified animal species that were susceptible to infection from MPXV: 2 single studies, 8 non-systematic reviews, and 1 editorial. **Table 2** provides an updated list of animals identified as susceptible to MPXV infection based on evidence from the published literature.

New Evidence

September 15, 2022 (latest iteration):

A total of three non-systematic reviews (3) (5) (4) 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 (5) has extensively discussed on experimental infections in various species with their clinical manifestations.

Editorials, letter to editor and commentary: A letter to the editor (49) 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* (40) has indicated various rodents, non-human primates, anteaters, hedgehogs, and shrews to be susceptible to MPXV infections.

September 2, 2022 iteration:

One non-systematic review (9) cites several animal species as vulnerable to MPXV infection, including rope and tree squirrels, Gambian pouched rats, dormice, and non-human primates.

Editorial/subjective evidence: One editorial (54) 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.

Existing Evidence:

Two single (primary) studies discussed on susceptibility of animals. One animal-based experiment (31) examined duration and characteristics of MPXV infection in African rope squirrels (*Funisciurus sp.*) and one prospective cohort primary study (52) 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.

Seven non-systematic reviews (15,16,20,23,24,35,37) 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.*), 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* (24) 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 (55).

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)*	Gambian-pouched rat *(Cricetomys gambianus)* Emin's pouched rat *(Cricetomys emini)* Prairie dogs *(Cynomys spp.)* Sun squirrel (*Heliosciuris sp.*) Jerboas *(Jaculus sp.)* Woodchucks *(Marmota monax)* Porcupines *(Atherurus africanus)* Brushtail porcupines *(Atherurus sp.)* Rope squirrel *(Funisciurus anerythrus)* Congo rope squirrel *(Funisciurus congicus)*, Tree squirrels *(Heliosciurus sp.)* Mice *(Mus musculus)* Striped mice *(Lemniscomys sp.)* African dormice *(Graphiurus sp.)* Natal multimammate rats *(Mastomys natalensis)*	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*)	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.

**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, 2 eligible studies discussed handling procedures for animals susceptible to MPXV infection: 2 non-systematic reviews.

New Evidence

September 15, 2022 (latest iteration):

No additional evidence was identified for this domain.

September 2, 2022 iteration:

One non-systematic review (8) maintains that positive or suspected-positive patients for MPXV 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 need to be handled with care and with appropriate protection by trained personnel.

Existing Evidence:

Two non-systematic reviews (20,24) 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* (24) has advised that veterinary staff should take extra precautions (such as personal protective equipment, careful disinfection of the animal's isolation environment).

ADDITIONAL PERSPECTIVES:

To date, 9 studies have been identified which discuss additional considerations related to MPXV infection in animals, specifically environmental and occupational aspects: 1 scoping review, 4 single studies, 1 non-systematic review, and 3 editorials.

Environmental aspects

New Evidence

September 15, 2022 (latest iteration):

One primary study of ecological design (56) 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.

September 2, 2022 iteration:

No additional evidence was identified for this part of the organizing framework.

Existing Evidence:

A single study (52) and *a non-systematic review* (36) 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.

Occupational exposure

New Evidence

September 15, 2022 (latest iteration):

One scoping review (1) and *3 letters to the editor* (57–59) 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.

September 2, 2022 iteration:

No additional evidence was identified for this part of the organizing framework.

Existing Evidence:

Two single studies have reported information regarding occupational exposure to the MPXV and how it should be managed. *Petersen et al*. (60) 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.* (61) 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".

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										
Full systematic reviews	3	1		3						
Rapid/scoping reviews	2 (1)	1 (1)	1	2 (1)			1			1 (1)
Non-systematic reviews	25 (4)	19 (4)	16 (3)	19 (3)	2 (1)	2 (1)	5 (1)	11 (3)	3	1
Protocols for reviews or rapid reviews that are underway										
Titles /questions for reviews that are being planned										
Single study	14 (1)	2	9	8		2	1	2		4 (1)
Published reports	4	1	3	3			2			
Dissertation/thesis										
Preprints**	1		1	1						
Editorials, letter to editor and commentary	11 (7)	1 (1)	1	9 (5)		2		3 (2)		3 (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 4: Key findings from included evidence documents from all iterations thus far (July 22 to September 15)

Domain	Study Design	Study Quality	References	Evidence
Description of the virus	NEW 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)
	NEW 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
	NEW 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.

	NEW 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).
	NEW 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%.
	NEW 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 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 (non-systematic)		Xiang & White, 2022	
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.

Reservoir of the virus	NEW 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.
	NEW 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)*.
	NEW 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).
Transmissibility of the virus	NEW 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
	NEW 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
	NEW 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
	NEW 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.

	NEW Editorial		Afrooghe et al, 2022	- Human-to-animal: 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
	NEW 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
	NEW 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
	NEW 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 - 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
	NEW 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
	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 inthe 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)
	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

	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
	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/porducts of infected animals could be another transmission route - Risk factors include close contact with infected animals
	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 bittne or scratched by infected animals, or eating meat from infected animals that are improperly cooked
	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

	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
	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		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
	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	- 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 - 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 - 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 - 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 - 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

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
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
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
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)		Alakunle et al, 2020	- Animal-human transmission via respiratory droplets, contact with bodily fluids, contaminated items/fomites, skin lesions, consumption of infected animals
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)		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)		Devaux et al, 2019	- Can be transmitted to humans via bites, scratches, scraping of lesions, cough, respiratory droplots, insufficiently cooked meat consumption

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.
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
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
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

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
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.
Report		Durski et al. 2018	
Single study (cross-sectional)		Guargliardo et al. 2020	
Review (non-systematic)		Kabuga & Zowalaty, 2019	
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%; $\chi 2$ = 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).

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.
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 otherzoonoses. 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.
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.
Single study mentioned as a 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 reportedcontact with sick or dead animals.
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.
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.
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.
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.
Clinical infection	NEW 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)
Clinical presentation/clinical impact	NEW 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
Treatment of Infected Animals	NEW 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.
Susceptible animals to the virus	NEW 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
	NEW 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.

	NEW 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)*.
	NEW 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.
	NEW 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

Handling of susceptible animals	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)
	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.
Additional Perspectives - Environmental	NEW 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 socieconomic 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)
Additional Perspectives - Occupational	NEW 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
	NEW 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

	NEW 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
	NEW 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".

Kawsari Abdullah, Junayd Hussain, Emilie Chan, Valentina Ly, Melissa C. Brouwers.
Living Evidence Profile #1. What is the available evidence related to the zoonotic characteristics of monkeypox?
Content Expert Consultants: J Scott Weese (University of Guelph), Manisha Kulkarni (University of Ottawa)

CoVaRR-Net: Pillar 9 Knowledge Implementation and Training Team. (KITT). 5th August 2022

To help health- and social-system leaders as they respond to pressing challenges, the KITT prepares rapid evidence profiles like this one. This rapid evidence profile was requested by the Public Health Agency of Canada. This rapid evidence profile is funded by CoVARR-Net. The opinions, results, and conclusions are those of the KITT and are independent of the funder. No endorsement by the Public Health Agency of Canada is intended or should be inferred. KITT is part of the Knowledge Synthesis and Application Unit at University of Ottawa's School of Epidemiology and Public Health.
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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 August 06, 2022 to August 19, 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)
- Published editorial, letter to editor or commentary

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 terms used:

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"*

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, preprints and published editorial, letter to editor and commentaries were included. Reporting quality of preprints will be examined, should they be published in future in a peer-reviewed journal.** Team members use 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 (62). 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 (63):

    - "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 (64). Randomized trials were assessed using the Cochrane Risk of Bias tool (65). 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.

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 4 as the key findings. We also assess quality of certain 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.

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	Quarleri et al.	2022	Review (non-systematic)	Argentina

	the current outbreak in non-endemic countries				
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

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 ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge	Russo et al.	2020	Information related to human population

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

APPENDIX D. Potential susceptibility of various animal species to risk of MPXV infection (based on evidence identified from the MPXV zoonosis LEP)

Animal groups				
Wild			**Domestic**	**Pets**
Non-human primates	**Rodents**	**Other**		
Sooty mangabey monkey *(Cercocebus atys)*	Gambian-pouched rat *(Cricetomys gambianus)*	Southern opossum *(Didelphis marsupialis)*	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
Rhesus macaques *(Macaca mulatta)*	Prairie dogs *(Cynomys spp.)*	African hedgehogs *(Atelerix sp.)*		
Cynomolgus macaque *(Macaca fascicularis)*	Sun squirrel (*Heliosciuris sp.*)	Shot-tailed opossum *(Monodelphis domestica)*		
Asian monkeys	Jerboas *(Jaculus sp.)*	Giant anteaters *(Myrmecophaga tridacyla)*		
Wild chimpanzees *(Pan troglodytes)*	Woodchucks *(Marmota monax)*	Elephant shrew (*Petrodromus tetradactylus*)		
	Porcupines *(Atherurus africanus)*	Wild pig (*Sus scrofa*)		
	Rope squirrel *(Funisciurus sp.)*	Rabbits (*Oryctolagus cuniculus*)		
	Mice (Mus musculus)			
	African dormice *(Graphiurus spp.)*			
	Natal multimammate rats (Mastomys natalensis)			