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Review

Mpox infection in animals: A systematic review and meta-analysis

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ABSTRACT

Mpox is a zoonotic disease that became epidemic in multiple countries in 2022. There is a lack of published systematic reviews on natural animal infection due to Mpox. We performed a systematic literature review with meta-analysis to assess animal Mpox prevalence. We performed a random-effects model meta-analysis to calculate the pooled prevalence and 95% confidence interval (95%CI) for prevalence studies. After the screening, 15 reports were selected for full-text assessment and included in qualitative and quantitative analyses. Ten reports assessed Mpox infection by molecular or serological tests (n = 2680), yielding a pooled prevalence of 16.0% (95%CI: 3.0–29.0%) for non-human primates; 8.0% (95%CI: 4.0–12.0%) for rodents and 1.0% (95%CI: 0.0–3.0%) for shrews. Further studies in other animals are required to define the extent and importance of natural infection due to Mpox. These findings have implications for public human and animal health. OneHealth approach is critical for prevention and control.

Contents

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Introduction

Mpox (MPX) is initially a zoonotic disease first described in 1958 [1] in non-human primates at the Stantens Serum Institut in Copenhagen, Denmark [2]. The MPX virus belongs to the Poxviridae family, the Chordopoxvirinae subfamily and the Orthopoxvirus genus. Genomically, they had two original lineages, the West African (WA) and the Congo Basin (Central Africa) clades, that differ genetically and in their virulence capacity, the latter being associated with more severe disease with higher mortality [3]. During the 2022 epidemics, evolutionary changes and a new proposed clade have been identified and reported [4,5].

In Europe, the first reported cases occurred in 2018 in Israel and the United Kingdom due to a traveller from Nigeria [6,7]. In May 2022, four positive cases of MPX were identified in the United Kingdom (UK), which had no link of origin or travel to endemic areas of the disease [8]. Other European countries reported positive cases in the coming months. Given the situation and possible additional transmission routes besides close contact, including sex, the World Health Organization declared mpox a public health emergency of international concern [9–12]. As of April 23, 2024, 95,340 cases were reported in 118 countries, with 184 confirmed deaths in 27 countries [13,14].

The transmission of MPX from infected animals to humans occurs mainly through direct contact with skin wounds, scabs, rashes, saliva, respiratory secretions, and body secretions through ingesting contaminated tissues and bites of infected animals [15]. In humans, transmission is associated with close contact with infected people with skin lesions or other areas, such as the mouth or genitals [16], with the virus entering through the injured skin, respiratory tract, and mucous membranes such as the oral, pharyngeal, ocular, genital, and anorectal [17]. The virus has been detected in sexual secretions, including semen [18,19]. In addition, the virus can be transmitted by fomites recently contaminated and vertically through the mother's placenta [13,20]. Then, Mpox has also been defined as a sexually transmitted infection (STI) and also associated with other STIs, including HIV, syphilis, and *Chlamydia* infection, among others [21,22]. Even in humans, a few cases of Mpox without detectable cutaneous/mucosal lesions have been described [23].

In humans, the disease has a prodromal period, which lasts from zero to five days with symptoms such as fever, headache, chills, myalgia, intense fatigue, and lymphadenopathy, mainly in the submandibular, postauricular, cervical, and inguinal areas. It should be noted that lymphadenopathy is a hallmark of MPX infection with other viruses such as measles, smallpox, and varicella [24,25]. Following fever, within one to three days, patients develop skin lesions frequently located on the mouth, face, palms of the hands and feet, genital area, conjunctiva, and perineal or perianal area [26,27]. Initially, rashes evolve from macules to papules, vesicles, pustules, and scabs that dry up and fall off, causing intense itching. Lesions in individuals vary from 10 to 150 and can last from 2 to 4 weeks until a new layer of skin is generated. The sequelae of the disease are evidenced in hypopigmented or hyperpigmented varioliform scars [28].

Although the exact natural reservoir of the virus is not known, MPX has been isolated in multiple animal species so far, such as rodents (*Cricetomys* sp., *Jerbillo* sp. and *Chinchilla* sp.), non-human primates (*Cercocebus atys* and *Pan troglodytes verus*) and mammals (*Cynomys* sp.), among others [29–31]. In humans, the first case reported was in a 9-month-old boy in the Democratic Republic of the Congo in 1970, in which the family reported that they occasionally fed on monkeys [25]. Since then, cases have been confirmed and documented, especially in Africa (Cameroon, Ivory Coast, Liberia, Nigeria and Sierra Leone) in the 1970 s [32]. In 2003, a human outbreak occurred in the United States of America (USA) due to commercialising rodents imported from African countries that infected prairie dogs that were later commercialised [33,34].

Particularly with the 2022–2023 epidemics, multiple studies in humans and animals have been performed because there is concern about the role of animals as reservoirs, sources of infection, and receptors of infection from human sources, as confirmed initially in France in August 2022 [35,36].

According to the study, the observed range of the prevalence of Mpox infection in animals varies from 0% to 100%, according to the generated evidence. A systematic review with meta-analysis may help understand the risk and precisely know the global relative frequency of natural infection due to Mpox in animals. Unfortunately, to our knowledge, no other systemic reviews or meta-analyses have been published on this topic. The study's objective was to estimate the pooled prevalence of Mpox natural infection in animals based on available reports and observational studies.

Methods

To achieve a thorough and accurate review, our work strictly followed the criteria outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) [37].

Information sources and search strategy

On May 18, 2023, we conducted a literature search to find out the prevalence of animals diagnosed with Mpox. Using a controlled vocabulary thesaurus, the following databases were searched: PubMed, Scopus, Web of Science, and Ovid Medline. The search strategy was built using the Peer Review of Electronic Search Strategies (PRESS) Checklist [38]. No language nor geographic restrictions were applied. Please refer to Supplementary Table S1 for the complete search strategy.

Eligibility criteria

This review included cross-sectional/cohort studies that reported the prevalence of Mpox in either domestic or wild animals.

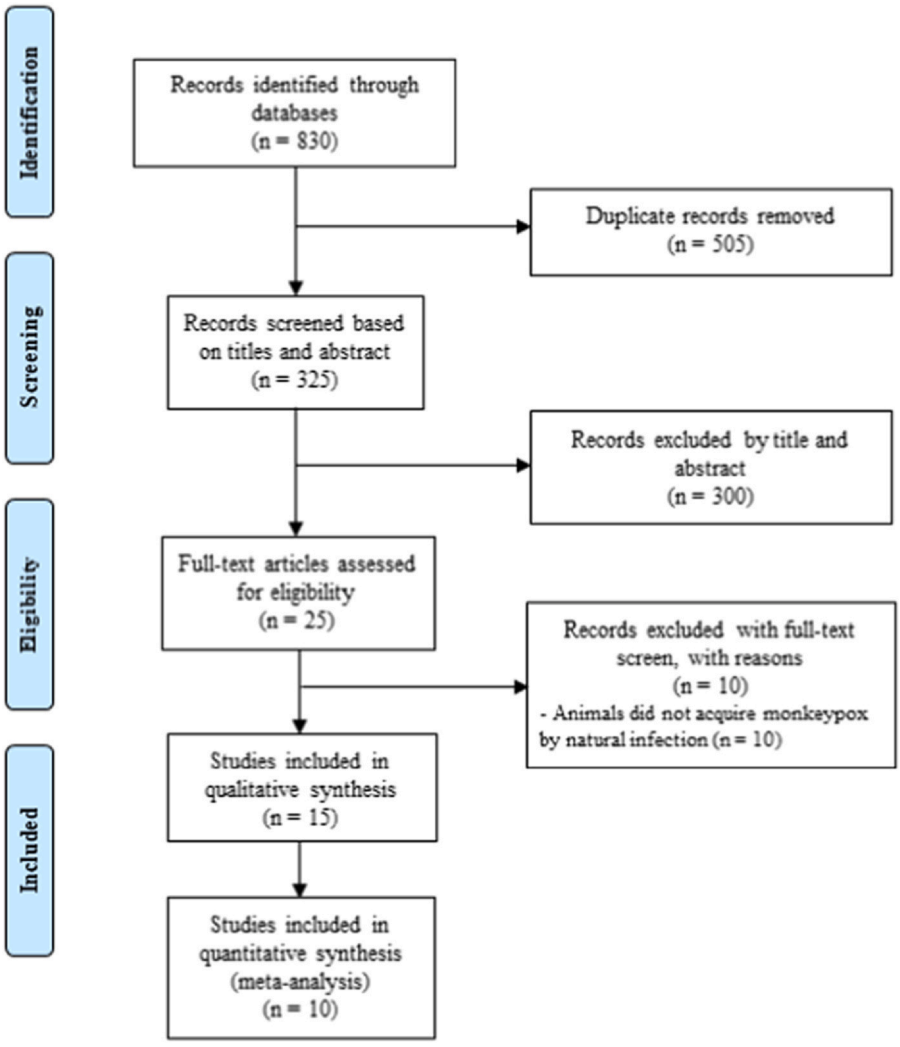

Fig. 1. Study selection and characteristics based on the PRISMA 2020 Standard for Systematic Reviews.

Additionally, we analyzed case reports and case series. All infections must have occurred naturally; owing to this, animals inoculated with the virus or that were part of experimental studies were not included. We also excluded articles that were 1) systematic reviews, 2) narrative reviews, 3) conference abstracts, 4) letters to the editor and 5) scoping reviews.

Study selection and data extraction

The findings from the literature search were transferred to the data management software 'Rayyan QCRI'. Four reviewers independently evaluated the titles and abstracts of the articles. Subsequently, each reviewer individually assessed the full text of the articles based on the predefined selection criteria. Any disagreement regarding the inclusion or exclusion of an article was resolved by reaching a consensus among the authors.

A data extraction sheet made in Google Sheets was used to collect the data from the selected articles. The following information was extracted: title, first author, study location, year, type of animal, and prevalence of Mpox infection.

Evaluation of studies quality and publication bias

For the risk of bias assessment, we used the Newcastle Ottawa scale adapted for Cross-sectional studies (NOS-CS), the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports and the Joanna Briggs Institute Critical Appraisal Checklist for Case series. In all three scales, a score of seven or more stars was considered as having a low risk of bias, whilst a score of fewer than seven stars indicated that the study being evaluated had a high risk of bias. The assessment was done independently by four reviewers. All disagreements were resolved by reaching a consensus among the authors.

The research team decided not to include the evaluation of publication bias. This decision was made in light of the shortcomings of Egger's tests and conventional funnel plots for assessing publication bias when used for proportional meta-analysis. As stated in previously published studies, this is based mainly on the following two factors. First, there needs to be more information to show that proportions fit these tests correctly. Second, it should be noted that the tests created to measure publication bias were initially based on the presumption that studies with favourable results were more likely to be published than those with unfavourable outcomes. There is no consensus on a favourable/unfavourable result in the case of proportions [39,40].

Data synthesis and analysis

The pooled prevalence rates with their corresponding 95% confidence intervals (95%CI) were calculated using STATA 16.0 with the package *metaprop*. For this quantitative analysis, we used a random

Table 1
Characteristics of the included studies.

Author	Year	Country	Animals	Detection Method	Total Study	N	n (+)	%
Tiee M et al.	2018	Central Africa	Rodent	PCR	1038	1038	93	9.0
Orba Y et al.	2015	Zambia	Non-Human Primates	ELISA	978	188	4	2.1
			Rodents	ELISA		259	38	14.7
			Shrews	ELISA		42	14	33.3
			Non-Human Primates	PCR		188	0	0.0
			Rodents	PCR		259	0	0.0
			Shrews	PCR		42	0	0.0
Doty J et al.	2017	Democratic Republic of the Congo	Rodent	ELISA	346	262	6	2.3
			Shrews	ELISA		84	1	1.2
Hutson CL et al.	2007	USA	Rodent	PCR	254	254	33	13.0
Breman JG et al.	1977	Ivory Coast and Mali	Non-Human Primates	PRNT	206	206	44	21.4
Douglas KO et al.	2021	Barbados	Rodent	PCR	160	160	6	3.8
Huntin Y et al.	2001	Democratic Republic of the Congo	Non-Human Primates	PRNT	54	6	0	0.0
			Rodent	PRNT		44	13	29.5
			Pig	PRNT		4	1	25.0
Kulesh D et al.	2004	USA	Rodent	PCR	52	52	7	13.5
Patrono L et al.	2020	Ivory Coast	Non-Human Primates	PCR	36	36	14	38.9
Goldberg TL et al.	2008	Uganda	Non-Human Primates	ELISA	31	31	8	25.8
Marennikova S et al.	1972	Democratic Republic of the Congo	Non-Human Primates	PRNT	9	9	2	22.2
Langohr M et al.	2004	USA	Prairie Dog	PCR	1	1	1	100.0
Guarner J et al.	2004	USA	Prairie Dog	PCR	2	2	2	100.0
Radonić A et al.	2014	Ivory Coast	Non-Human Primates	PCR	1	1	1	100.0
Seang S et al.	2022	USA	Dog	PCR	1	1	1	100.0

effects model (Dersimonian and Laird method) and the 95%CI for each prevalence rate was calculated using the Clopper-Pearson method. The general meta-analysis was performed according to the kind of animal: non-human primates, shrews, and rodents. The Freeman-Tukey Double Arscine Transformation was used as the variance stabiliser. Cochran's Q test and I2 statistics were used to assess the heterogeneity between the studies. A p-value of less than 0.05 in Cochran's Q test revealed the presence of heterogeneity. For the I^2 statistic, values below 40% were deemed to represent mild heterogeneity, while values ranging from 41% to 60% indicated moderate heterogeneity and values exceeding 60% revealed substantial heterogeneity [39–41]. Subgroup analyses were conducted based on the detection method used (serological or molecular). For the sensitivity analysis, we excluded studies at high risk of bias. Case reports and case series were not included in meta-analyses.

Results

Study selection and characteristics

The search strategy returned 830 results. After eliminating duplicates, 325 articles were analysed, contrasting the selection criteria with the titles/abstracts. Then, 300 articles were evaluated in full text, and 15 studies were finally included in the review [29,34,35,42,43–52]. Fig. 1 illustrates the selection process with a PRISMA flowchart found in Fig. 1.

The characteristics of the included studies are summarised in Table 1. Of the 15 included studies, four were case reports, one a case series, and the remaining ten were cross-sectional studies; for a total of 16 datasets. The population of the included studies amounted to 2680 subjects, of which 477 were Non-Human Primates (NHP), 2069 were rodents, and 126 shrews, which were considered for meta-analysis. Additionally, four pigs, three prairie dogs and one domestic dog were analysed. The geographic location of the included studies was as follows: USA (5 studies), Democratic Republic of Congo (3 studies), Ivory Coast (3 studies but 1 of these studies was also conducted in Mali), Uganda (1 study), Zambia (1 study), Barbados (1 study), Central Africa (1 study). Regarding the detection method, six studies used a serological detection method (PRNT or ELISA) and ten studies used a molecular method (PCR).

As mentioned above, the risk of bias was assessed using three scales: the NOS-CS, the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports, and the Joanna Briggs Institute Critical Appraisal Checklist for Case series. The evaluation identified that there were two studies at high risk of bias. The remaining studies were at low risk of bias. The table showing detailed information is found in Supplementary Table S2.

The quantitative synthesis of the prevalence of Mpox in dogs and pigs was not performed. In the case of pigs, the meta-analysis could not be performed because there was only 1 study assessing this population. In addition, quantitative synthesis was not conducted for dogs or prairie dogs in the case of reports due to the small sample size of only four animals, which could have introduced bias in the estimation.

The prevalence of Mpox varied according to the animals, and diagnostic tests were used across the different studies (Table 2).

Prevalence of Mpox in non-human primates

The pooled prevalence of the studies evaluating the prevalence of Mpox in NHP was 16.0% (95%CI: 3.0–29.0%, five studies), showing

Table 2
Summary of each meta-analysis results for the pool prevalence of Mpox among animals.

Animals and Diagnostic Methods*	Number of studies	N	Pool prevalence (%)	95%CI	$I^{2‡}$	p
Non-human primates (NHP)	5	467	**16.0**	3.0–29.0	93.30	< 0.01
NHP, only assessed by serological methods	4	431	10.0	0.0-29.0	93.78	< 0.01
Rodents	7	2069	**8.0**	4.0-12.0	90.66	< 0.01
Rodents, only assessed by serological methods	3	565	14.0	2.0-26.0	95.05	< 0.01
Rodents, only assessed by molecular methods	5	1763	7.0	3.0-12.0	87.66	< 0.01
Shrews	2	126	1.0	0.0-3.0	0.00	p > 0.05

95%CI = 95% confidence interval. ‡ I2 index for the degree of heterogeneity.
* Some studies assessed simultaneous variables. Multiple studies assessed the prevalence by different methods.

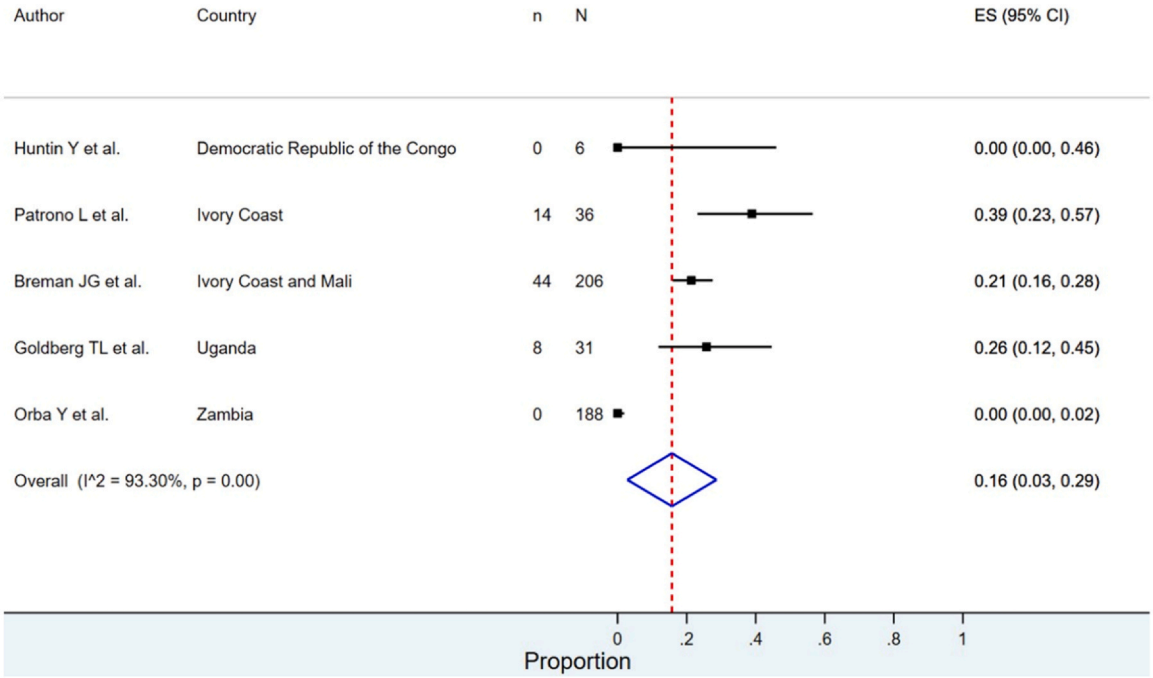

Fig. 2. Prevalence of Mpox in Non-Human Primates.

severe heterogeneity (I^2 =93.30%) (Fig. 2). In the subgroup of studies that evaluated NHP with serological methods (Supplementary Fig. S1), the prevalence was 10.0% (95%CI: 0.0–29.0%). The sensitivity analysis (Supplementary Fig. S2) showed a prevalence of 27.0% (95%CI: 17.0–37.0%) with moderate heterogeneity (I^2 =52.78%).

Prevalence of Mpox in rodents

The overall prevalence of Mpox in rodents was 8.0% (95%CI: 4.0–12.0%, seven studies) with severe heterogeneity (I^2 =90.66%) (Fig. 3). In the subgroup of studies that evaluated rodents with serological methods (Supplementary Fig. S3), the prevalence was 14.0% (95%CI: 2.0–26.0%, three studies), and in the case of the studies that evaluated rodents with molecular methods (Supplementary Fig. S4), there was a prevalence of 7.0% (95%CI: 3.0–12.0%, five studies). The sensitivity analysis (Supplementary Fig. S5) showed a prevalence of 8.0% (95%CI: 3.0 - 12.0%) with severe heterogeneity (I^2 =90.69%).

Prevalence of Mpox in shrews

The overall prevalence of Mpox in shrews was 1.0% (95%CI: 0.0 - 3.0%, I^2 =0.0%, two studies) (Fig. 4). No subgroup or sensitivity analysis was performed due to the few available studies.

Discussion

The Mpox global outbreak has caused more than 95,000 cases in humans, with more than 180 associated deaths up to April 23, 2024, in 118 countries (111 that never reported mpox). Fortunately, the impact of this zoonotic disease has been entirely different compared to SARS-CoV-2/COVID-19 [53,54]. Mpox is not airborne nor transmitted by airdrops. The 2022–2023 outbreak has been associated with close contact, especially during human sexual activity [55,56], and the epidemic decreased after education and the use of vaccines against the disease [57,58].

Given the vast number of countries affected (> 110), in addition to the origins of the Mpox virus, it is critical, considering the extent of human-animal contact, to understand the potential risk derived from the Mpox-infected humans to animals, especially outside Africa [3,35], but also there, where recently Mpox is also reemerging in some countries, as is the case the Democratic Republic of Congo (DRC) (almost 4,000 cases and more than 270 deaths in the last few months of 2023-2024) [59]. The main finding of the current meta-analysis indicated that around one in eight non-human primates (NHP) suspected and assessed by laboratory tests for Mpox infection was positive. That is a remarkable proportion of infection. Serological tests also found a high seroprevalence among NHP when the assessment was performed. Also, in this context, serological cross-reactions may occur, especially with other poxviridae that may infect animals. Some authors suggest that considering the Mpox evolution [4,5], the number of infected people and recent reports of environmental contamination [60–64], the possibility of Mpox transmission to animals can be expected more and more [65].

Indeed, in the current systematic review, the prevalence of Mpox was high in both molecular and serological analyses. However, more studies are needed, especially outside Africa, even after 2003 [52]. No studies about animals were published during 2022–2023, except a case report in France about the human-dog transmission of the virus [35]. Unfortunately, Mpox has been neglected for decades [66], and only recently, interest in the topic has increased with the 2022–2023 epidemics [67]. Even in Africa, where the disease has been endemic since the 1970 s, there needs to be more knowledge regarding the disease burden in animals and humans [66]. It is of the utmost importance that more studies be performed on different groups of animals to approach the actual situation of natural infection in animals from this emerging family of poxviridae and understand its potential role as a reservoir and in transmission.

Since the 2003 epidemic in the USA, rodent animals have been on the radar of research-oriented efforts to describe the presence of Mpox infection, possible transmission and risk for humans [68,69]. However, early in the 2022–2023 epidemics, especially after the domestic dog case in France [35], the risk from humans to domestic animals and humans began to be assessed [70]. The increase in human Mpox cases raised concerns about the possibility of reverse zoonotic virus transmission from humans to animals. Consequently, in the UK, surveillance of pet animals living with individuals

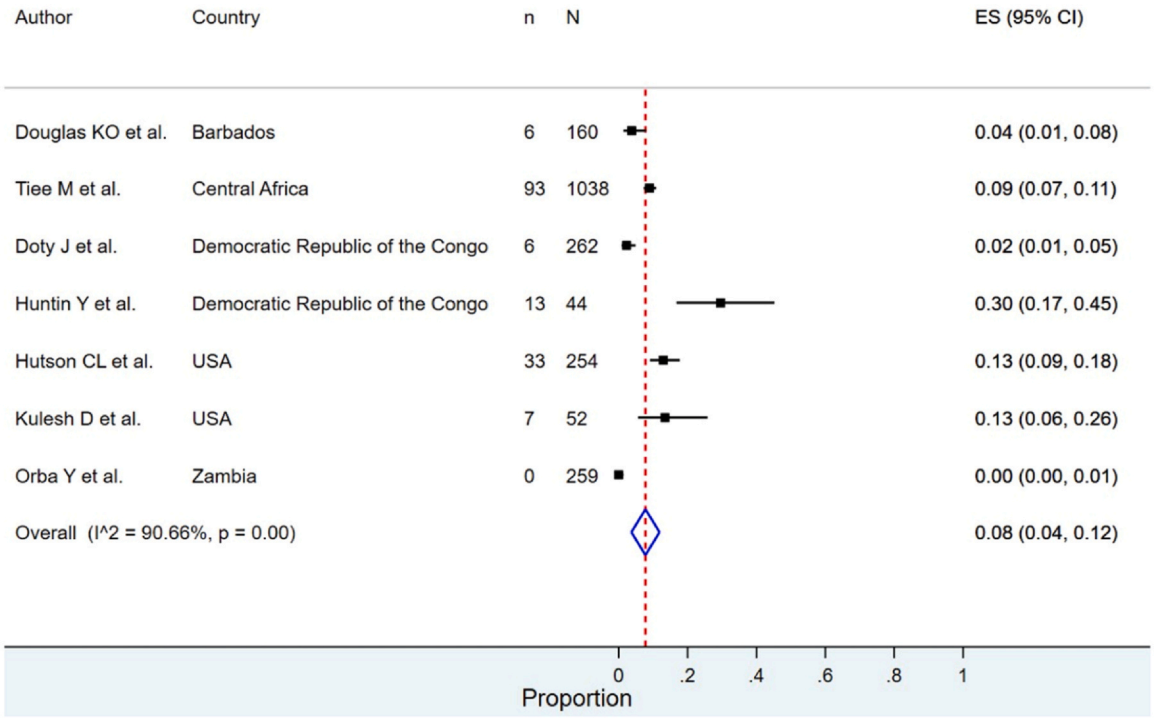

Fig. 3. Prevalence of Mpox in Rodents.

searching for the MPX virus started in May 2022 to assess the risk of this type of transmission. From June 1 to September 16, 2022, researchers collected data and observations during this time, showing that there have been no cases of animals with clinical signs suggestive of MPXV infection associated with confirmed human cases [70].

Understanding reverse zoonotic transmission of Mpox virus (MPXV) through pet animals is crucial for comprehending the potential risks of further transmission to humans and other animals. This information is valuable for informing the development and implementation of effective control measures to limit the spread of the virus through this particular pathway. Surveillance of pets that cohabitate with individuals confirmed to have MPX is essential to this research. By monitoring and studying these pets, researchers can learn whether the virus can be transmitted from humans to animals and vice versa. By surveilling pets, scientists can assess the likelihood of reverse zoonotic transmission and quantify the risk it poses to humans and animals. This information is critical for understanding the potential for the virus to establish a reservoir in animal populations. If reverse zoonotic transmission is a significant risk, public health authorities can develop and refine measures to prevent such transmission. That might involve guidelines for

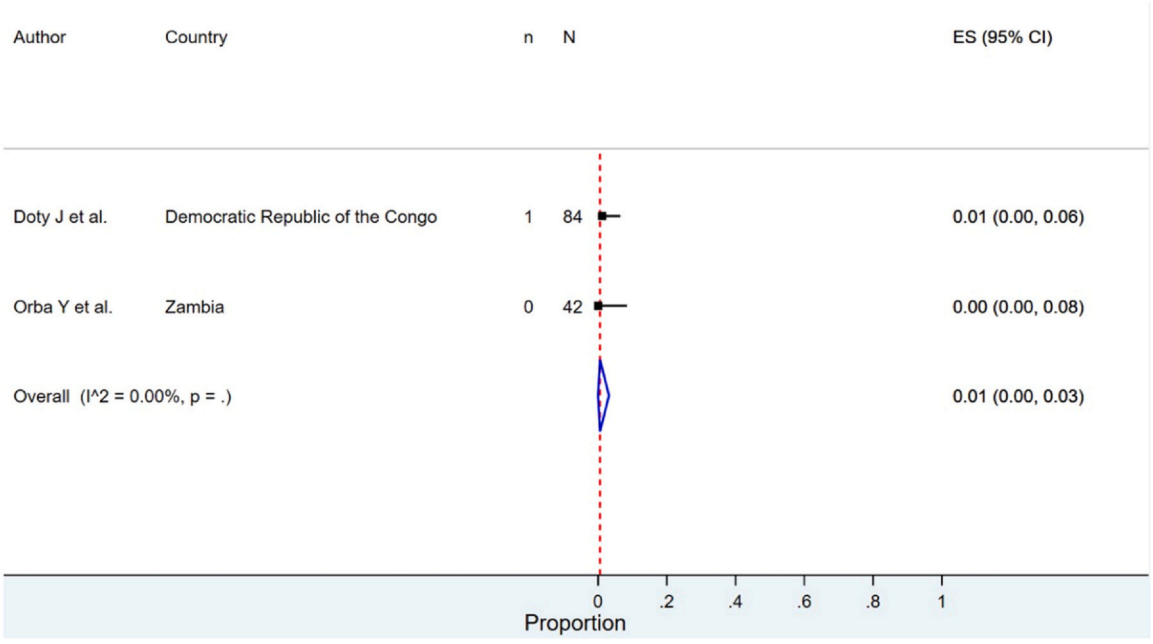

Fig. 4. Prevalence of Mpox in Shrews.

handling pets in households with confirmed cases of MPX or recommendations for reducing close contact between infected individuals and their animals. Also, understanding how MPXV can potentially spread between humans and animals allows for proactive measures to prevent spillover events, where the virus jumps between species, is critical. That can help contain outbreaks and minimise the risk of broader transmission [71].

Addressing the potential for reverse zoonotic transmission requires a holistic approach to disease control. By considering the human-animal interface, control strategies can be more comprehensive and practical [55]. The results of animal surveillance can contribute to a better understanding of the dynamics of MPXV transmission, potential reservoir hosts, and the overall epidemiology of the disease. This knowledge is essential for formulating evidence-based strategies to manage and control human and animal cases, reducing the potential for further spread and cross-species transmission [70].

In the current meta-analysis, NHP, rodents and shrews showed a high prevalence of Mpox by different laboratory methods. However, most studies fail to indicate the clinical implications of MPXV infection in animals. Just a few of them described skin lesions in monkeys [1], as well as some in the Gambian pouched rats, showing lethargy, anorexia, weight loss, numerous skin lesions, vesicles on the tongue, and necrosis of the gingiva [72].

A study on prairie dogs also reported MPXV compromise in multiple organs and systems, including the liver, spleen, lungs, and heart, where the virus was detected [73]. Although more studies are needed on animals, those findings are consistent with those reported in humans during the extensive clinical studies performed during the 2022–2023 epidemics showing compromise of multiple organs and systems [74–77], especially in immunocompromised patients [78,79].

In the case of animals, although more animals would be involved, more studies need to address susceptibility to this virus. Domestic and wild animals must be investigated in different regions to understand better their potential role in disease and how many may act as animal reservoirs. So far, the number of animals assessed is globally limited, probably leading to overestimating the infected proportion in some animals but underestimating in others. Although individual case reports and small case series do not support prevalence figures, they may help as there is still a lack of studies on Mpox in animals.

In addition, many other animals may be included in similar systematic reviews in the future as soon as more studies are available, as is the case for non-human primates, especially rodents, which are susceptible to the infection caused by Mpox [3].

Considering the global epidemiology of Mpox, some countries with a high incidence of the disease have still not even published a single case of Mpox infection in these animals. That is the case of Brazil, Spain, Colombia, Mexico, and Peru, among others, which have reported more than 32% of all Mpox cases during the 2022–2023 epidemics. However, in the case of Brazil, there is an epidemiological report of a symptomatic 5-month-old dog in contact with a human confirmed case that also gets infected and confirmed [80]. Not much information regarding clinical evolution and outcome was available regarding the infected animals, but we could not find deaths associated with animals. These are uncommon in humans [14].

As observed, many of the most affected countries are in Latin America [81,82], a region severely affected by other sexually transmitted infections, such as HIV and syphilis [83–85], which also led to coinfections between Mpox virus and other sexually transmitted pathogens [86,87].

Public health implications

Many questions can be raised from the current cumulated evidence regarding the natural infection of Mpox in animals. However, with the data available, there is an urgent need to consider its potential importance in transmission, interspecies, from human-to-animals, OneHealth perspectives that integrate human and animal health, when assessing cases occurring in domestic or wild environments, integrated surveillance and the need for increase regular testing among animals, beyond just research. There is a need to standardise molecular and serological tests for Mpox among animals [88], allowing these to be offered to the owners and increasing the diagnosis. At the same time, there is space for the discussion of more active surveillance instead of a passive report to OIE from the countries, promoting the search of animal cases among the cluster of human cases, as the UK has done [70]. Mpox deserves a comprehensive approach from the OneHealth approach [89,90]. More integration is still needed to increase our understanding of transmission, risks and consequences of this emerging poxviridae disease. Finally, now that vaccination is being used more widely than in the past in humans [57], there is also the question of its use in animals. So far, there has not been an approved orthopoxvirus vaccine for animals in the USA and other countries. However, developments may have occurred since then. It is now more apparent than ever that we need a better and more proactive approach. One possibility is to eliminate the threat of spillover before it occurs using vaccines capable of autonomously spreading through wild animal reservoirs. We are poised to develop self-disseminating vaccines targeting many human pathogens, including Mpox. However, essential decisions remain about how they can be most effectively designed and used to target pathogens with a high risk of spillover and emergence [91].

Limitations

In this study, we did not differentiate studies assessing the prevalence of screenings and the prevalence of outbreaks in closed groups of animals in detail. Due to an inherent limitation of cross-sectional/survey studies included in this review, the estimates in the primary studies could change from time to time. On the other hand, the merit of observational studies is that they can assess health problems in a natural setting, reflecting real-life situations. Some studies were performed in the context of epidemics but needed to be specified. Nevertheless, then, the data for it is still limited. Subsequently, additional analysis should be performed using more available and specific studies. In future assessments, it would be good to have a clear distinction between studies testing randomly in the wild population where animals are tested or when found dead and animals in commercial situations (tested when there appears to be an outbreak) or companion animals (tested often concerning positive PCR results of their owners) all of which has a high impact on the chances of finding a PCR-positive result. Doubtless, a more in-depth analysis of this would be interesting. Likewise, substantial heterogeneity may exist even with several stratifications of analysis of studies with more homogenous subgroups (e.g., g by species, diagnostic methods, or animal categories). True heterogeneity is expected in prevalence estimates due to variations in the time and place of included studies. Therefore, a high I^2 does not necessarily mean inconsistent data (Barker et al., 2021). Hence, interpretation of the findings should be undertaken with caution.

Finally, a thorough review of Mpox natural infections in animal species is needed, emphasising how to interpret the findings of other authors in future systematic reviews and meta-analyses.

Ethical approval

Approval was not required.

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Declaration of Competing Interest

All authors report no potential conflicts.

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Declaration of competing interest

All authors report no potential conflicts.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2024.04.015.

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