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Review

Zoonotic orthopoxviruses after smallpox eradication: A shift from crisis response to a One Health approach

Alessandra Mistral De Pascali[a,b], Martina Brandolini[a,b], Ludovica Peli[c], Vittorio Sambri[a,b], Monica Cricca[a,b], Alessandra Scagliarini[b,*]

[a] Unit of Microbiology, The Greater Romagna Area Hub Laboratory, Cesena, Italy
[b] Department Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna, Bologna, Italy
[c] BSc European Public Health, Faculty of Health, Medicine and Life Science, Maastricht University, Maastricht, the Netherlands

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ABSTRACT

A systematic literature review was performed to assess the research trend on zoonotic orthopoxviruses (ZOPXV) as disease agents and as vectors for biomedical during 2000–2023. It has been evidenced that despite the limited number of research groups that have worked on ZOPXV diseases, they largely contributed not to turn off the spotlight. Given the small size of the ZOPXV research network, the epidemiological data remain restricted to a limited number of geographical contexts. Some inconsistencies between the geographic provenance of authors and the study area particularly in Africa were identified. MPX represents an exception, as the scientific interest has grown over the last 20 years, starting with the first outbreak outside endemic areas in 2003 and culminating during and after the 2022 pandemic, that boosted the number of publications from different countries over the last 2 years. Since the beginning of the millennium, authors have warned about the effects of waning immunity, after cessation of smallpox vaccination, and identified many social and ecological factors boosting the emergence and spread of the diseases. ZOPXV diseases remain neglected by the global health agenda, leading to the adoption of reactive measures in the event of an emergency.

Introduction

Zoonotic orthopoxviruses (ZOPXV) are double stranded DNA viruses belonging to the *Poxviridae* family and *Chordopoxvirinae,* subfamily. The latter is now divided into 18 genera, including ZOPXV, Parapoxvirus, and Yatapoxvirus, among others. Poxviruses can be classified into specialized and generalist. Variola virus, the causal agent of smallpox, is an example of a specialized poxvirus having humans as the only susceptible species, whereas the mpox virus (MPXV), cowpox virus (CPXV), vaccinia virus (VACV), and buffalopox (BPX) virus (BPXV) are considered generalist orthopoxviruses capable of infecting diverse mammalian species, including humans. After the eradication of smallpox in 1980, thanks to the cross-protection against the other members of the genus *Orthopoxvirus,* the human population enjoyed an apparently poxvirus-free world. The absence of human cases has polarized researchers' attention, mainly toward their use as vaccine vectors and for anti-cancer gene therapy, overlooking their circulation in endemic areas in several low- and medium-income countries. The first signs of a population decline in ZOPX immunity occurred in the late 1990s when cases of VACV and BPXV infections were reported in humans and animals in South America and Asia [1]. Subsequently, cases of mpox appeared for the first time outside the African endemic areas in 2003 in the United States [2]. More recently (2018–2021), cases of mpox were recorded in Israel, the United Kingdom, and Singapore before the pandemic of 2022 [3]. ZOPXV infections occur in complex and diverse socio-ecological systems; for this reason, a holistic One Health (OH) approach to research would be required to better understand the epidemiology of the diseases and fill the gaps about their determinants to put in place the most effective control measures. This systematic review was primarily aimed at investigating the ZOPXV research trends in 2000–2023. The second objective was to analyze the extent to which the published studies incorporated the core elements of OH to critically synthesize the social and biological determinants of disease occurrence. Finally, the review sought to gather the main scientific evidence on risks, diseases management strategies, and needs for their prioritization.

* Corresponding author.
E-mail address: alessand.scagliarini@unibo.it (A. Scagliarini).

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Methods

A systematic literature search was performed with the aim of collecting, appraising, and analyzing scientific studies published on ZOPXV between 2000 and 2023 to answer the previously mentioned question and sub-questions. Scopus and Web of Science were selected as the main searching databases. Data collection was conducted on June 24, 2023 using the following keywords: “orthopoxvirus,” “human,” “animal,” “environment,” “one health,” “zoonosis.” From the early stages of data collection, the Boolean searching method was applied to the keywords by connecting them through the AND/OR conjunctions and Medical Subject Headings terms. This strategy was deliberately chosen to comprehensively cover the largest number of eligible hits. In addition, research filters were applied to better orientate the data gatherings, including a time frame interval, which limited the search to articles published between 2000 and 2023, and the requirement of English as primary language. Lastly, only final stage open-access articles were considered. These searching criteria lead to the following query: ((TITLE-ABS-KEY(orthopoxvirus) AND TITLE-ABS-KEY (human)) AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (PUBSTAGE,"final")) AND (LIMIT-TO (LANGUAGE,"English")) AND (LIMIT-TO (OA,"Open Access"))). Duplicate articles were removed. Three reviewers collected and analyzed data independently. Titles and abstracts were reviewed, and studies were retained based on the established inclusion and exclusion criteria (Figure 1). Eligible papers were considered only if they focused on ZOPXV species: MPXV, CPXV, and VACV, including bovine vaccinia (BV) and BPX. Specifically, all study types were considered valid if they were focused on ZOPXV as agents of disease or as vectors used for prophylactic or therapeutical purposes. To highlight the research trends, studies were grouped by year, pathogen type, scientific papers or case reports, country of origin of the members of the research team, and study geographic location as follows (i.e. Europe, North America, Latin America, Asia, Africa, and Oceania). During full-text review, studies reporting on ZOPXV as agents of disease in clinical and epidemiological studies were classified to evaluate to what extent the OH elements were integrated. The following were included: studies explicitly mentioning OH in the methodology; involving public health consideration and/or animal, human, and environmental health in a combination or together; and/or socio-ecologic elements including demography, socio-economic status, occupation, livelihood systems, and cultural dynamics that may enhance the exposure to the pathogens.

Results

The comprehensive literature review of studies published from 2000 to June 2023 yielded 669 titles, 318 of which were duplicates (Figure 1). From the review of the abstracts, 22 studies were excluded for not being focused on ZOPXV or not being available in English as full text. After the full-text review of 329 papers, 190 were excluded as mainly considering emerging and re-emerging ZOPXVs other than VACV, CPXV, and MPXV or focusing on virus evolution, diagnostic techniques, or antiviral studies. After all exclusions, in accordance with the aims of the review, 139 studies were retained of which 19 regarded studies on the use of ZOPXV as viral vectors for vaccination and immunotherapy and 120 regarded studies on ZOPXV as disease agents. Publications were sporadic until 2010, with not more than three per year and less than 10 before the end of 2021. A peak of 63 publications was evidenced between 2022 and June 2023, 60 of which regarded MPXV (Figure 2a). Overall, 14% percent of the considered 120 studies were performed in Africa (N = 17), 10% in Asia (N = 12), 32% in Europe (N = 38), and 39% (N = 47) were conducted in America, of which 43% (N = 20) were in North America (United States and Canada) and 57% (N = 27) in Latin America. The United States and Brazil produced the highest numbers of the publications; no studies were collected from Oceania (Figure 2b). The remaining papers (5%; N = 6) could not be related to any specific geographic area. In total, 49 papers were classified as epidemiological studies performed in different parts of the world. The majority of the epidemiological investigations (N = 35; 71%) regarded MPXV and were published in the last 5 years. Throughout the considered period, most of the studies on CPXV were published by European authors (15 of 16 studies) and 18 of 23 studies on VACV were published in Latin America, mostly from Brazilian research groups (Figure 3a, b).

The provenance and number of the MPXV publications produced in 2000–2021 compared with 2022–2023 changed considerably. In the period 2000–2021, 28 of the 30 selected studies were published by North American groups alone or in collaboration with African researchers (Figure 3c). From January 2022 to June 2023, African and North American studies (N = 21; 35%) were complemented by those performed by researchers mainly from Europe, Asia, and Latin America that produced a significant amount of hits (N = 39; 65%) in response to the worldwide spread of the infection (Figure 3d). The origin of the research group was not always consistent with the study area. This observation was particularly evident for research activities focusing on MPXV in Africa, where, from 17 publications, five involved African research institutions only, whereas the remaining were mixed groups including international authors from the United States and Europe. Overall, three publications concerning ZOPXV diseases in Africa had exclusively authors from outside the continent (Europe and United States). As far as Asia is concerned, 100% of the articles had solely Asian authors and only in two cases were contributors from Europe and the USA were included. Publications with a European focus also all involved European authors, with research teams from one or more European countries and, in some cases, in collaboration with North American groups. Regarding Latin America, the 27 selected articles in the considered period (January 2000 to June 2023) were released by Latin American authors, with Brazilians as the most represented. Studies were mainly conducted to understand the epidemiology of VACV infections in humans and domestic and wild animals in Brazil (74%; N = 20). Some research was performed in collaboration with North American authors. All the publications concerning North America were authored locally, with no evidence of international collaborations.

A total of 69 studies focused on zoonosis emergence and transmission as mediated by human-animal interactions, where animals are always depicted as the source of infection. Only one study showed MPXV transmission from human to a dog in August 2022. Regarding the OH paradigm, 33 studies were shown to contain the basic elements. Scientific evidence on the risks related to ZOPXV diseases and possible management strategies are summarized in Table 1.

Discussion

The first aim of the review was to investigate the ZOPXV research trends in 2000–2023 to understand to what extent the representation of these pathogens has been focused on their role as pathogens. Data from published basic and applied studies confirmed the key role of poxviruses in shaping modern medicine and biomedical sciences and their utility in fighting other infectious diseases as vaccines and cancers through oncolytic therapeutics and gene delivery vectors. The trend of publications concerning ZOPXV as disease agents can be considered “constantly sporadic” for VACV and CPXV, with numbers never exceeding five publications per year [4]. The study sites and research groups reflect the epidemiological trend of the diseases, with a greater number of publications on BV coming from Latin America (N = 20), where Brazil is the country where research was mostly carried out. For CPXV, studies were mainly performed in Europe by European groups, with Germany and France as the most represented countries (67%; N = 12). For MPXV, the trend deserves to be analyzed before and after the 2022 pandemic. In 2000–2021, most of the publications were focused on the African Continent, particularly, the Democratic Republic of Congo (DRC) and Nigeria. The studies were carried out by mixed

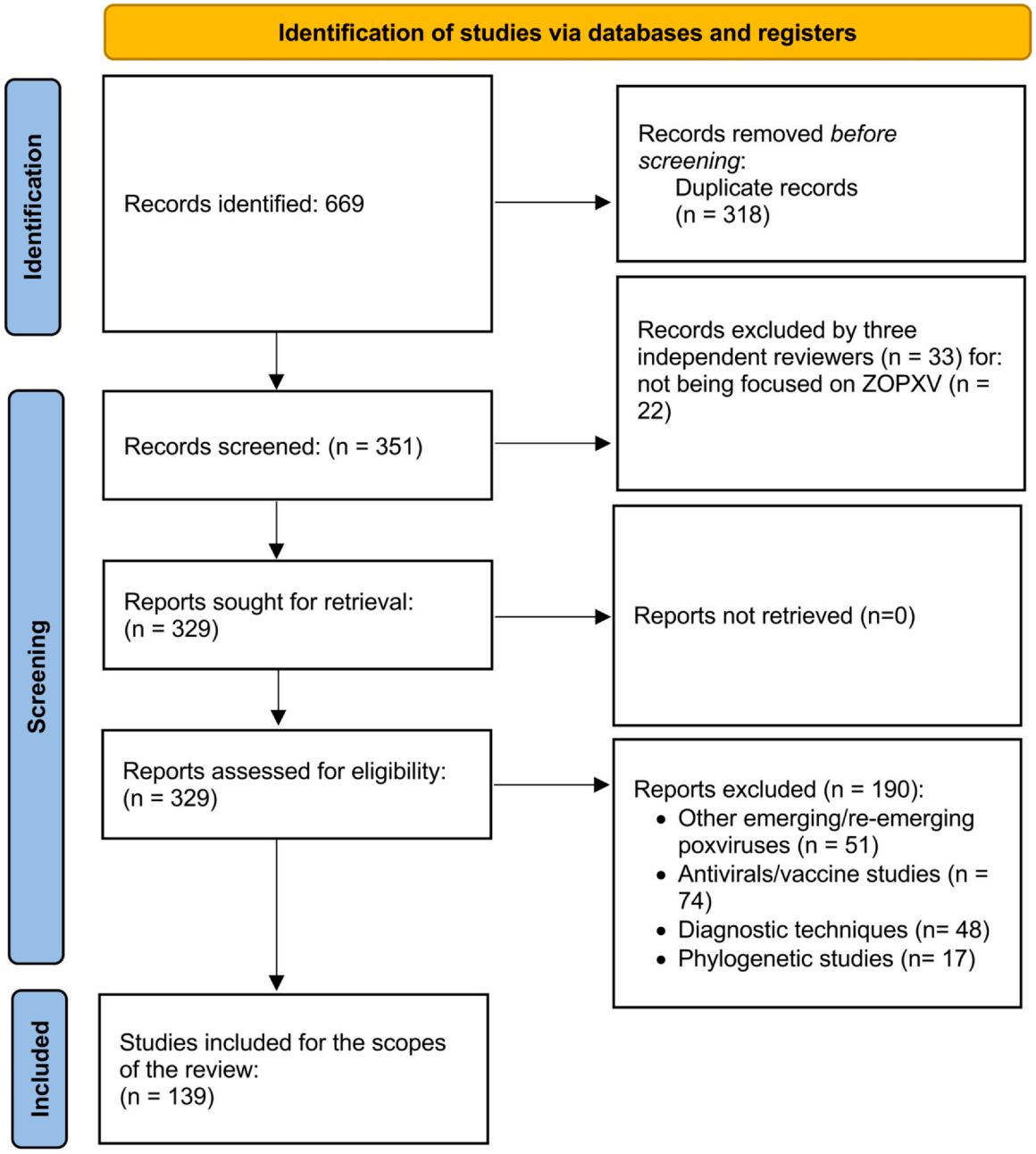

Figure 1. Flowchart showing the identification and selection process for publications included in the review. ZOPXV, zoonotic orthopoxviruses.
Adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. http://dx.doi.org/10.1136/bmj.n71

research groups located in the study areas in collaboration with international groups. A significant number of the studies were conducted in collaboration with researchers from the United States [5]. After the 2022 pandemic, the study sites and provenance of research groups diversified, with publications of numerous case reports from Europe, Africa, the American continent, and Asia, including the Middle East. Regarding study sites and authorship of research teams, the low presence of African researchers despite the acknowledged endemicity of MPXV and other emerging and re-emerging OPXVs in the continent should be emphasized. This inconsistency between authors and study site were not found for papers from other geographical areas and may reflect the limited resources available in terms of funding and infrastructure and possibly access to data. Data collection activities must often take place in remote areas with limited laboratory and analytical infrastructure; thus, it is not surprising that many of the studies are being performed in collaboration with major foreign research groups. Moreover, it should not be ignored that publications on diseases not included in the global health agenda may suffer from poor bibliometric recontraction given the limited research network in the field. This may affect the careers of local researchers who may be more attracted to other diseases that garner greater international attention.

After the recent outbreak of MPXV outside endemic areas, authors advocated for a OH approach to quickly identify the risks associated with human-animal interphases [6]. Thus, the second aim of the review was to analyze the extent to which the published studies incorporated the core elements of OH to disentangle the complexity of the socio-ecological systems in which diseases emerge and spread. Zoonoses emergence and transmission is not only a purely biological process mediated by ecological factors but also includes human-domestic animal and wildlife interactions. Moreover, the human-animal

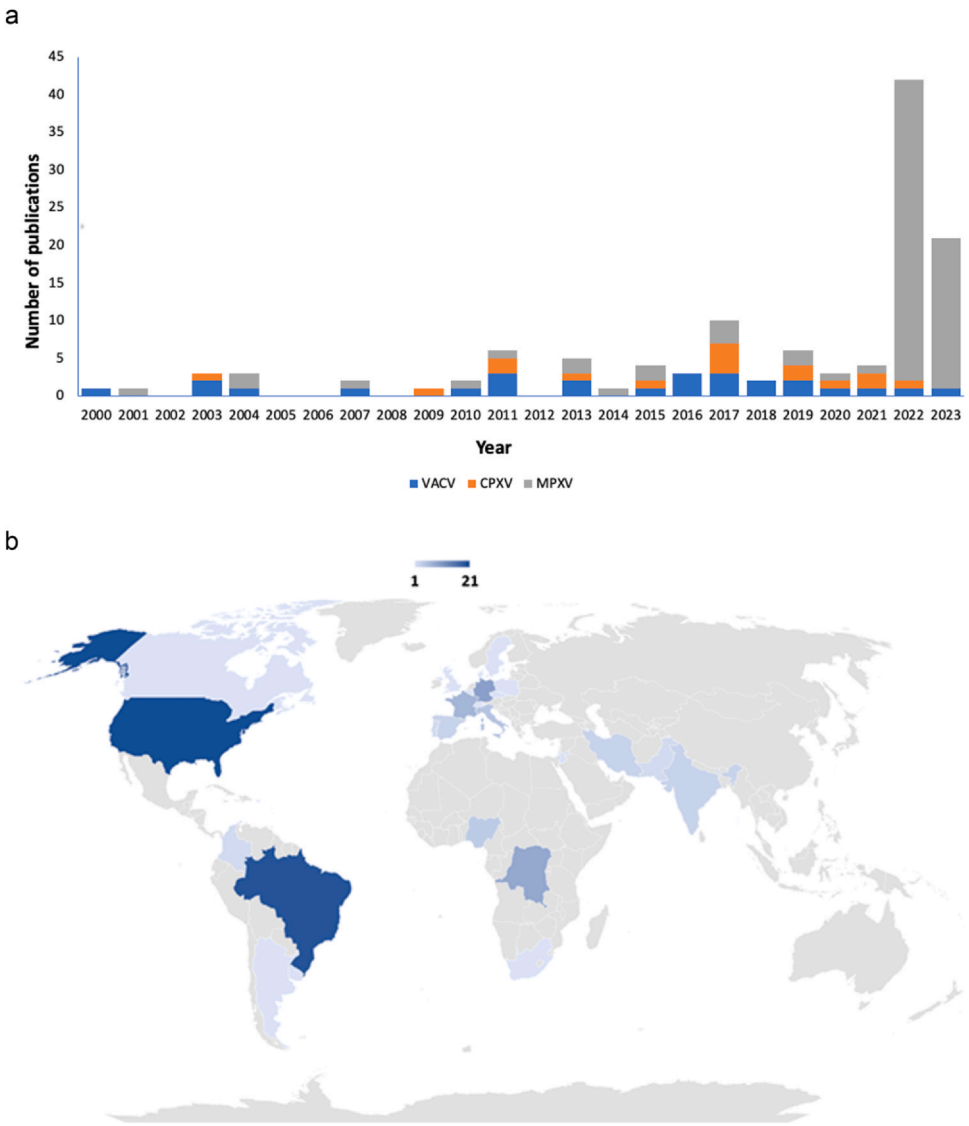

Figure 2. (a) Trend of research publications on zoonotic orthopoxviruses as agents of diseases (b) study sites of the analyzed publications in the considered timeframe 2000–2023. CPXV, cowpox virus; MPXV, mpox virus; VACV, vaccinia virus.

interactions can be affected by social and contextual factors including demography (i.e. gender, age), socio-economic status (i.e. occupation and livelihood systems), culture (i.e. including social norms, family and community dynamics, eating behaviors, religion, sexual orientation), and national and global influences. The socio-ecological systems model [6] can be thus used to answer on the extent to which OH elements are incorporated in the analyzed hits. The interfaces between humans, domestic animals, and wildlife was found to be relevant for all the considered ZOPXVs. BV is widespread in cattle in South America, resulting in economic losses to the dairy industry and it being an important public health issue [1]. The implementation of management and health planning are considered crucial for the prevention of BV in animals and humans. Domestic dogs could be implicated in the transmission cycle acting as a link between the natural wildlife reservoirs and humans in urban areas [7]. The circulation of VACV was demonstrated among equids of southeast Brazil, with possible correlations of outbreaks in bovines and equids [8]. In India and Pakistan and Mongolia, BPX is affecting buffaloes [9]. The virus is highly related to VACV, and the same risk factors were identified. In contrast to VACV infections, which occur mainly in rural areas, CPXV infections have mostly occurred in urban areas of Europe. CPXV can infect a wide range of mammals posing risks for the people as the list of animals known to be susceptible is still growing. The transmission of CPXV to humans is mostly caused by domestic animals such as cats and pet rats and other exotic animals [10,11]. The first MPXV outbreak outside Africa in 2003 was linked to the import of animals, such as Gambian giant rats *(Cricetomys* spp.*)*, squirrels (*Funisciurus* spp. *and Heliosciurus* spp.*)*, striped mice (*Hybomys* spp.), and dormice *Graphiurus* spp., that spread viruses to pet prairie dogs (*Cynomys* spp.) [12]. Behavioral interactions between prairie dogs and pet owners or veterinarians were most likely to have caused MPXV transmission from animals to humans, with no direct parallels with types of animal-human interactions that result in infections in African settings [5]. Wildlife such as small mammals and rodents in the natural cycle of VACV have long been suspected of serving as maintenance reservoirs for vaccinia-like viruses in Brazil [1]. Positive rodent species (*Akodon* sp., *N. squamipes*, *Oligoryzomys* sp., and *M. musculus*) have been found; however, the exact role played by these animals is not yet known. Capuchin (*Cebus spp*.) and black-howling monkeys (*Alouatta spp*.) showed VACV antibodies in the Brazilian Amazon [13]. Monkeys may become infected by mingling with different rodent species [13]. The anthropogenic disturbance of the Amazon ecosystem and increases in agricultural and livestock areas have been associated with a possible surge of contacts between wildlife and domestic animals, leading to possible bovine outbreaks linked to

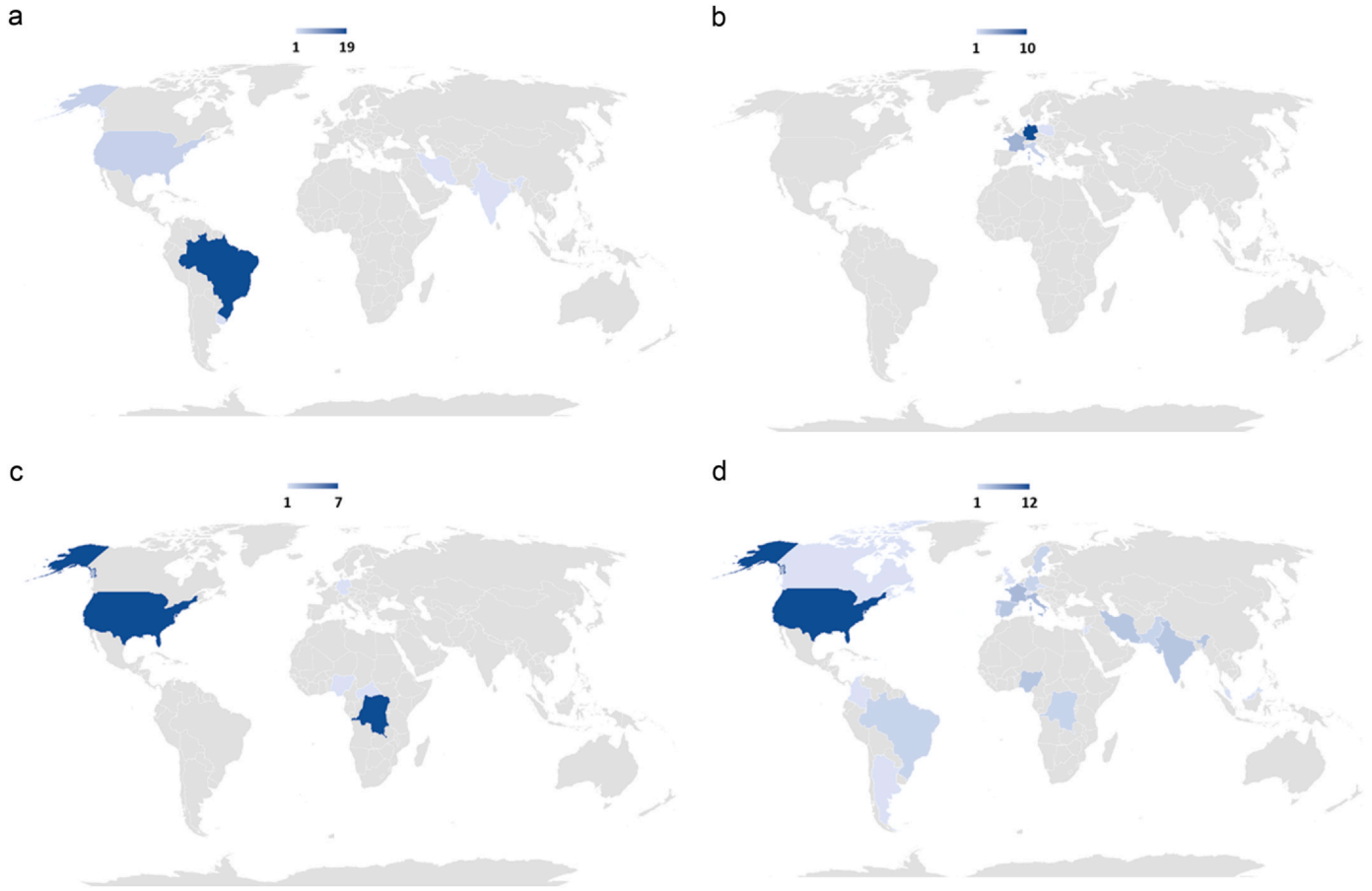

Figure 3. Localization of the study sites for each of the selected ZOPXV in the period 2000–2023 (a) VACV the highest number of the studies had been performed in Latin America by local authors, with or without the contribute of international research groups; (b) CPXV the majority of the studies 2000–2023 have been performed in Europe, particularly, in Germany, France, and Italy; (c) MPXV 2000–2021 the majority of the studies have been performed in the United States and in Africa, mainly in collaboration with international authors, (d) MPXV studies in 2022–2023, a number of study sites have been recorded according to the multi-country outbreak. The United States was the leading study site. CPXV, cowpox virus; MPXV, mpox virus; OPXV, orthopoxviruses; VACV, vaccinia virus; ZOPXV, zoonotic orthopoxviruses.

contact with monkeys and other wild animals. The circulation of OPXV is commonly found in neotropical free-living primates living at the interface between cities and forests (ecotone) and is being commonly found in Brazilian urban areas in close contact with humans. Besides rodents, recent findings reinforced the possible role played by marsupials in VACV maintenance and spread [*110]. Environmental factors such as precipitation of the wettest quarter, annual precipitation, mean temperature of the coldest quarter, and mean diurnal range have been identified as having a potential to influence on VACV transmission. Through the ecological niche models using retrospective data collected from areas where outbreaks occurred, it was possible to identify putative suitable regions for transmission based on bioclimatic factors. Small wild rodents are also the natural reservoir of CPXV. Antibodies were detected in different vole species, such as common voles (*Microtus arvalis*) and bank voles (*Myodes glareolus*), which are considered the main reservoir host [10]. Host-specific differences concerning CPXV-specific virulence have been shown. Antibodies against CPXV and other OPXV have been detected in wild rodents in the Caribbean [*38]. Over 60 cases of elephant CPXV infections have been reported from Germany. These days, most elephants are regularly vaccinated with attenuated modified VACV Ankara; hence, only sporadic cases still occur in unvaccinated elephants [*79]. The second most commonly CPXV infected group are exotic felids such as captive cheetahs (*Acinonyx jubatus*), showing high morbidity and mortality. CPXV outbreaks in cheetahs were detected because of possible contact with voles found seropositive in zoo grounds in Denmark [*129]. CPXV was isolated from llama on a farm in Italy [14] and outbreaks occurred in alpaca herds in Germany causing severe, generalized, and, finally, lethal infection [15]. Direct transmission of CPXV from rodents to humans has also been documented, including pet rats [*39,131]. MPXV is maintained in nature by a group of diverse reservoir taxa rather than single species [16]. The wide host range of MPXV is of concern, especially because the virus has now expanded in novel areas characterized by diverse ecological conditions and by a variety of naive potential hosts. American ground squirrels are susceptible to MPXV infection, and African rope squirrels shed large quantities of virus playing a role as a potential source of MPXV transmission to humans and other animals in endemic regions [16]. Areas where rodents are more abundant owing to higher availability of their major food sources may have consequences for the distribution of MPXV because continued deforestation may result in range expansions [17]. Direct physical contact with MPXV-infected animals and potential exposure to excretions and secretions of a sick animal (urine, feces, saliva) provided insights into how natural infections might occur in Africa during preparation of carcasses, as has traditionally been suggested, and through exposure to animal nests or excreta [5]. Mpox infection in humans is usually associated with direct or indirect contact with infected wild animals; this can be the consequence of preparation and consumption of bushmeat, history of jungle/bush visit(s), and of travels to areas where outbreaks of mpox are ongoing [15]. Moreover, infections in humans have been recorded through direct contact with exotic animals in households [5,18]. The primary routes of transmission of MPXV are through direct contact with

Table 1
Scientific evidence on the main needs and solutions to prevent and control ZOPXV diseases according to the studies performed and published in the last 2 decades.

Scientific evidence	Suggested solution	VACV	CPXV	MPXV
OPXV waning immunity	**Reinvigorate vaccination strategies against OPXV**	da Silva et al., 2018; De Figueiredo et al., 2015; Styczynski et al., 2019	Andreani et al., 2019; Ducournau et al., 2013; Eder et al., 2017; Kurth et al., 2009	Chmel et al., 2022b; Guarner et al., 2004; Karim et al., 2022b; Kukreja et al., 2022; Shah et al., 2023
Risks associated to human/animal interface	**Apply a One Health approach to risk management**	de Assis et al., 2013; De Sant'Ana et al., 2013; Domingos et al., 2023; Miranda et al., 2017	Douglas et al., 2021; Eder et al., 2017; Franke et al., 2017; Pelkonen et al., 2003; Stagegaard et al., 2017	Cassir et al., 2022; Jalilian and Bastani, 2022; Mande et al., 2022; Meseko et al., 2023; Osadebe et al., 2017; Pembi et al., 2022; Whitehouse et al., 2021
Problematic Recognition of ZOPXV infections with consequent unnecessary antibiotic therapy or surgical interventions	**Enhance testing capacities at point of care and promote refresher trainings for medical doctors and veterinarians**	Abrahão et al., 2010a; De Sant'Ana et al., 2013b; Franco-Luiz et al., 2016	Douglas et al., 2021; Eder et al., 2017; Favier et al., 2011; Switaj et al., 2015	Caria et al., 2022; Choudhary et al., 2022; Daneji et al., 2022; Desai et al., 2023; Doshi et al., 2019; Hans et al., 2022; Huggett et al., 2022; Hutin et al., 2001; IV Santaliz-Ruiz et al., 2023; Jang et al., 2023; Kaswa et al., 2022; Kukreja et al., 2022; Lewis et al., 2022; Lopes et al., 2022; Mande et al., 2022; Michel et al., 2022; Nörz et al., 2022; Ortiz-Martínez et al., 2022; Poole et al., 2023; Rodriguez-Nava et al., 2022; Sanromán Guerrero et al., 2023; Vandenbogaert et al., 2022; Vaulhkonen et al., 2023; Vierbaum et al., 2023

CPXV, cowpox virus; MPXV, mpox virus; OPXV, orthopoxviruses; VACV, vaccinia virus; ZOPXV, zoonotic orthopoxviruses.
The references are comprehensively included in the Supplementary material.

the blood, bodily fluids, and lesions of infected animals, as well as via shedding of viral particles in feces and contamination of shared items [19]. Direct engagement with human bodily secretions, ulceration, coughing, or sneezing of infectious animals can result in infection, as can passive exposure to contaminated surfaces. During the 2003 outbreak in the United States, the initial 3-year-old female patient developed cellulitis and fever after being bitten by a prairie dog and her mother later became ill because of the contaminated environment or direct contact in the household [*116]. The risk of infection for contacts living within the same households was also shown also in a surveillance study in Zaire [20]. Clinical and epidemiological findings from a surveillance study performed in DRC showed that MPX incidence was significantly higher in females than in males aged 20–29 years. The authors speculated that women can be at risk of exposure when caring for sick children in households [34]. A case of human-to-animal transmission of MPX in a household has been recently documented in a dog during the 2022 outbreak, showing the possibility of reverse zoonosis [21]. Poxviruses are known to be stable in the environment for long periods; it has been shown that MPXV can be shed in the feces of infected individuals and discharged into the sewerage, leading to environmental contamination. MPXV DNA has been detected in wastewater samples from treatment plants in cities and in the United States, the Netherlands, Italy, France, and Spain. Monitoring of MPXV in the environment (wastewater) would provide information on the level of virus circulating in the population [19,22].

The dynamics of interaction between humans and animals in the shared environment are complex and influenced by social, cultural, professional, and even gender-related factors in different geographic sites. BV impact on animal and human health will continue to be a concern for producers and consumers of dairy products in Brazil [8]. Milkers are also at risk of BPX infection from domestic buffaloes (*Bubalus bubalis*) in India and other parts of the world. Manual milking is a common practice in small and medium herds, which may expose farmers to VACV and BPXV in endemic countries [9]. Cases of VACV infections in patients outside of the categories considered at risk have been reported. In 2008 a cluster of community acquired VACV infections was detected at a martial arts gym in Maryland, United States. The cluster was possibly the result of sequential person-to-person spread of virus through direct physical contact, and the most likely source was a recent vaccine [23]. The increased in use of VACV in research experiments and its use in medical laboratories may expose health personnel, researchers, and patients to the infection. Vaccinia keratoconjunctivitis has been reported as a laboratory-acquired infection, suggesting the need for vaccination for workers handling orthopoxviruses. A further case with severe lesions was reported in a patient previously vaccinated against smallpox [24]. Zookeepers were identified as particularly at risk for CPXV infections [18]. In MPXV endemic areas, men appear to be most often affected owing to the higher risk of exposure to wild animals associated with the occupational practices (hunting, skinning, and trading), whereas women can be exposed while preparing infected bushmeat for food [18]. The speed of international transportation combined with the long incubation of the infection (up to 21 days) increase the risk for MPXV spread from rural regions into urban areas and to countries outside Africa. Human-to-human transmission has been reported as early as the 1996–1997 outbreak in the DRC and it was pointed out that in populations with low herd immunity may lead to more and larger clusters of human MPX cases. The recent outbreaks outside the endemic areas had unique features, with the highest number of cases being associated by human-to-human transmission [25]. Furthermore, a change in age at presentation was observed, with young adults mostly affected and few pediatric cases reported [20]. This was already recorded during the MPXV outbreaks 2017–2018 in Nigeria, affecting mostly young adults and people living in urban or peri-urban areas [*145]. The 2022 MPXV outbreak affected mainly young men who identify as gay or bisexual and other men who have sex with men, with different clinical presentations. Sexual networks and exposure to

multiple condomless sexual contacts [26,27] were identified as relevant risk factors for transmission. Clinical cases in women seemed rare but several were reported [18]. Intrauterine fetal demise was recorded in pregnant women infected with MPXV in DRC [28,*105]. During the 2022 pandemic, substantial attention was focused on sexual risk, particularly, in men who have sex with men; however, other vulnerable populations were identified. Confounding factors, such as nutritional state and poorer health care access, were significantly related to mpox presentation and disease progression [28]. Marginalized people are considered more at risk for sexually transmitted infections, including MPXV, which can frequently occur in association with other diseases, such as syphilis [28]. People experiencing homelessness and those with substance use disorders are considered particularly vulnerable because of the increased risks of exposure social stigma and lack of access to health care [28].

In 2019, Nigerian authors advocated for the inclusion of MPX in the list of the country's priority diseases and in the World Health Organization African region's integrated disease surveillance and response guidelines to improve its surveillance in humans and in animals and to understand of its epidemiology [29]. In July 2022, the World Health Organization labeled MPX infection a global public health emergency and declared the public health emergency of international concern. A year after the pandemic, mpox and the other zoonotic poxvirus diseases remain neglected, and nothing has changed in the global health agenda. This confirms the lack of normative power and the effects that public health emergency of international concern has in outbreak response [5,30]. For a discipline dominated by evidence-based decision-making, scientific data are vital to assess the size of the problem in terms of spread and socio-economic impact. The final objective of the review has been precisely to critically examine the studies published in the selected time frame to evaluate whether they have brought to light risks and management strategies while uncovering scientific evidence in support of ZOPXV diseases prioritization. We showed that, despite the relatively few research groups working in the field, many crucial scientific data have been provided. Building on what has been produced so far, it should be possible to move from a crisis response model to a risk-based OH approach that would improve disease control and management capacities in endemic countries and enhance prevention strategies in disease-free countries.

Limitations

This review aimed to map only reviewed open-access published journal articles according to the search criteria. It is possible that it has left out important studies disseminated in conferences, proceedings, or books. A language bias may exist because only articles in the English language were included. As the title suggests, this is a systematic literature analysis giving an overview of research trends on diseases caused by ZOPXVs. Thus, it is not a meta-analysis attempting to statistically integrate the findings of existing studies.

Ethical approval statement

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Author contributions

AMDP and LP performed the systematic review of the literature, MB analysed data. AMDP, LP, MB wrote the manuscript AS supervised and critically intepreted the results of the systematic review and supported the discussion. MC and VS supervised the writing and critically reviewed the first version of the manuscript. All the Authors contributed to the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijidoh.2024.100018.

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Complete bibliography, including references in the table, is reported as Supplementary Material. The references not included in this list have been indicated in the main text with an asterisk in parentheses referring to the numbering of the supplementary material's list.

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