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REVIEW

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Risk profile and mode of transmission of Mpox: A rapid review and individual patient data meta-analysis of case studies

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Abstract

Since May 2022, an outbreak of Mpox in non-endemic countries has become a potential public health threat. The objective of this rapid review was to examine the risk profile and modes of transmission of Mpox. PubMed, Web of Science, and Scopus were searched from inception through July 30 to collect case reports/series on patients with Mpox infection. For meta-analysis, data on the total number of participants and deaths by binary categories of exposure (age, sex, country, other co-infections or existing conditions, and mode of contagion) were used. A total of 62 studies (4659 cases) were included. Most cases came from Africa (84.3%), followed by Europe (13.9%). In 63.6% of the cases, the mode of contagion was human contact, while 22.8% of the cases were by animal contact, and 13.5% were unknown or not reported. The mortality rate was 6.5% throughout these studies. The risk of mortality was higher in the younger age group (risk difference: 0.19; 95% CI: 0.02–0.36), in cases with other co-infections or current chronic conditions (risk difference: 0.03; 95% CI: 0.01–0.05) and in the category of low- and middle-income countries (risk difference: 0.06; 95% CI: 0.05–0.08). There were no significant differences with respect to sex or mode of contagion. These results help to understand the major infection pathways and mortality risk profiles of Mpox and underscores the importance of preventing outbreaks in specific settings, especially in settings densely populated by children, such as day care centres and schools.

KEYWORDS
infections, mortality, orthopoxvirus, public health, viral Zoonoses

Abbreviations: CDC, Centers for Disease Control and Prevention; CIs, confidence intervals; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.

1 | INTRODUCTION

Mpox is a viral zoonosis endemic to West and Central Africa. It was first identified in the Democratic Republic of Congo in 1970.[1,2] Since then, several outbreaks of Mpox in humans have been regularly reported in African countries.[3] The first outbreak of Mpox outside Africa occurred in the United States of America in 2003 and was linked to the importation of infected Gambian giant rats that infected the prairie dogs' pets.[4] Between 2018 and 2022, sporadic cases have also been reported in travellers from Africa to Israel,[5] Singapore,[6] and the United Kingdom.[7] In May 2022, multiple cases of Mpox were identified in several non-endemic countries, On July 25th, the World Health Organization declared the spread of Mpox infection as a 'public health emergency of international concern'. Since the beginning of the current Mpox outbreak, until 27 September 2022, 20,083 confirmed cases have been reported in 29 EU/EEA countries, mainly in Spain, Germany, France and the Netherlands.[8] Thus, in recent months, there has been a major resurgence of Mpox outbreaks.

Mpox virus is a DNA virus belonging to the genus Orthopoxvirus that is transmitted to humans through close contact with a person (lesions, body fluids, respiratory droplets), by contact with an infected animal or by material contaminated with the virus (e.g. bedding).[9,10] This infection is characterised as self-limiting (symptoms last 2–4 weeks) and usually presents clinically with fever, rash and swollen lymph nodes.[11] Complications are frequent (e.g. secondary bacterial infections), severe cases are more common in children and the mortality rate is approximately 3%–6%.[12] Polymerase chain reaction (PCR) is the laboratory test of choice for diagnosis, given its very high accuracy and sensitivity.[12,13]

More confirmed cases of Mpox have been reported since 2016 than in the previous 40 years.[1] Most of the current cases are those with a previous or concomitant sexually transmitted infection.[14] Indeed, the first case of Mpox virus, SARS-CoV-2 and human immunodeficiency virus (HIV) co-infection was recently reported, and health systems should be alert to this eventuality.[14] Thus, Mpox has become the most important orthopoxvirus of concern for public health. Since there is no specific treatment, objective data on modes of transmission and groups with increased vulnerability are needed. Thus, the objective of this rapid review was to analyse the risk profile and modes of transmission of Mpox in cases reported in the literature in any clinical setting.

2 | METHODS

This study follows the recommended guidelines for conducting rapid reviews,[15] and in accordance with the PRISMA 2020 guidance.[16] As this was a rapid review, patients and the public were not involved in the design, conduct, or reporting of this study.

2.1 | Search strategy

Two of the authors (RL-B and RN-C) conducted a systematic search in PubMed, Web of Science and Scopus from inception to 30 July 2022 (Table S1). Only articles in the English language were considered. The aforementioned authors independently screened records, abstracts, and full text articles using the free web version of Rayyan (http://rayyan.qcri.org).[17] Thereupon, they independently extracted data, and when there was no consensus, a third reviewer was consulted (JC). The reference lists of all retrieved studies were screened to identify additional studies that met inclusion criteria.

2.2 | Inclusion criteria

We included any study that described any patients with Mpox infection either confirmed or highly suspected, from any clinical setting. Study designs eligible for inclusion were both case reports and case series. We excluded reviews, editorials, other qualitative, cross sectional, case-control, cohort studies as well as grey literature.

2.3 | Data extraction

Two authors (RL-B and RN-C) independently extracted data using a standardised form. Retrieved data encompassed author, year of publication, country, number of cases, sex, age, ascertainment of the infection, mode of transmission, other current co-infections or chronic conditions, and number of deaths. For quantitative analyses, we used data on total number of participants and deaths per exposure categories. This included sex, categorised age (i.e., 18 years old as cut-off point), country (developed or low- and middle-income countries according to United Nations identification criteria and indicators),[18] modes of infection, and co-infection or other current chronic conditions.

2.4 | Quality assessment

Quality was assessed using the tool provided by Murad et al.[19] for methodological quality assessment and synthesis of case series and case reports. This comprises eight items clustered in four domains: selection, ascertainment, causality, and reporting. Because items 4, 5, and 6 are only relevant to studies of adverse drug events, we did not consider them for the present study. Thus, a score of 5 was considered as the highest quality. Two reviewers (RL-B and RN-C) conducted this assessment independently. Discrepancies or disagreements between the reviewers' judgements were resolved by consensus with a third reviewer (JC).

2.5 | Statistical analyses

When data were available for two or more studies, we used Stata version 16.1 software (StataCorp). We combined individual data extracted from eligible studies to calculate mortality risk in relation to binary categories of age, sex, country, other existing infections or chronic conditions, and mode of infection. Because not all studies reported information on all the examined variables, the number of included studies for each risk difference estimate varies. Results are displayed as risk differences with 95% confidence intervals.

3 | RESULTS

3.1 | Study selection

The initial database search identified 1790 records. A total of 577 studies were eliminated as duplicates, and 1097 were excluded in the title and abstract screening. Subsequently, in the full-text screening, 15 records were eliminated for 'other' study design, 18 for 'other' outcome, and one for 'other' language. Finally, a total of 62 studies were included in this rapid review (Figure 1).[5–7,20–78]

3.2 | Study characteristics and participants

The articles included were published between 1972 and 2022, of which 18 correspond to case reports and 44 to case series. Sample size ranged from 1 to 1057 participants. Most cases originated in Africa (3928 cases, 84.3%), followed by Europe (646 cases, 13.9%). The remaining cases came from North America (79 cases, 1.7%), Asia (5 cases, 0.1%) and Oceania (one case, 0.02%) (Table 1).

In total, 4659 cases with Mpox were enroled in the included studies. The age range varied from <1 to 71 years. Fifty-three studies reported the variable sex; 68% of the cases enroled in these studies were male and 32% were female. Fifty-five studies reported the method of diagnosis; 91% of the cases included in these studies were diagnosed by PCR and 9% by other laboratory tests. Only one case was diagnosed by autopsy. Forty-one studies did not report information on the presence of other co-infections or current chronic conditions in the included patients. In the remaining 21 studies (n = 1794), 252 cases had a history of HIV infection, 170 cases had a history of Varicella Zoster virus infection, seven cases had a history of syphilis, and one case of measles.

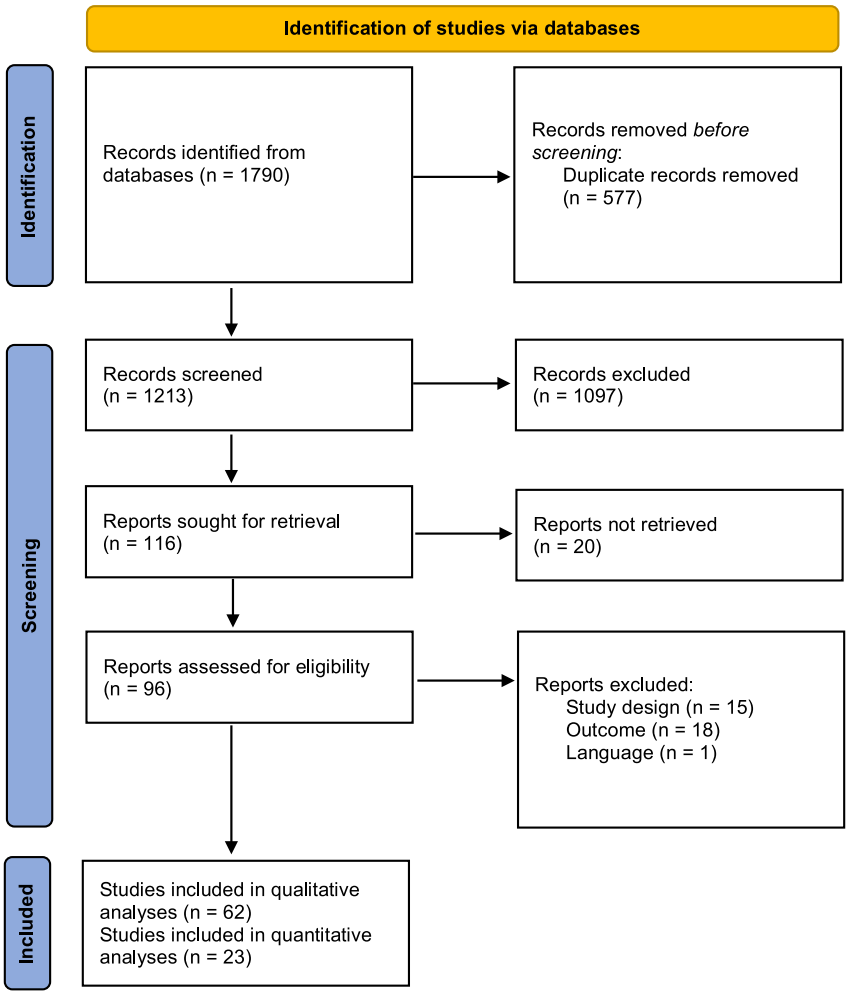

FIGURE 1 Prisma flow diagram.

TABLE 1 Description of the included studies

Report	Year	Country	Number of cases	Sex	Age, y	Confirmed test	Transmission	Other current infections or conditions	Deaths
Adler	2022	UK	7	Male (*n* = 4) Female (*n* = 3)	<2–40	PCR	Travel contact (*n* = 3) Household contact (*n* = 2) Medical centre (*n* = 2)	Negative (HIV, Hepatitis B, C)	0
Anderson	2004	USA	1	Female	<16	PCR	Animal contact	No medical history of diseases	0
Angelo	2019	UK (*n* = 2) Israel (*n* = 1)	3	Unknown	Unknown	Unknown	Household (*n* = 2) Animal contact (*n* = 1)	Not reported	Not reported
Antinori	2022	Italy	4	Male	≥30 to ≤39	PCR	Sexual contact	HIV (*n* = 2)	Not reported
Arita	1985	Cameroon (*n* = 2) Ivory Coast (*n* = 2) Liberia (*n* = 4) Nigeria (*n* = 3) Sierra Leone (*n* = 1) Zaire (Democratic Republic of the Congo) (*n* = 143)	155	Not reported	<10 (*n* = 122) ≥10 (*n* = 21) Not reported (*n* = 12)	Laboratory tests (*n* = 155)	Animal contact (*n* = 121) Human transmission (*n* = 34)	Not reported	Not reported
Atkinson	2022	UK	1	Not reported	≥40 to ≤49	PCR	Unknown	Not reported	Not reported
Berthet	2011	Central African Republic	2	Male (*n* = 2)	14–15	PCR	Animal contact (*n* = 2)	Not reported	0
Besombes	2019	Central African Republic	5	Female (*n* = 5)	<1–33	PCR	Household contact (*n* = 4) Animal contact (*n* = 1)	Not reported	Not reported
Bízová	2022	Czech Republic	1	Male	34	PCR	Sexual contact	HIV Syphilis	Not reported
Breman	1980	Zaire (Democratic Republic of the Congo)	47	Male (*n* = 24) Female (*n* = 23)	1–40	Laboratory test	Human transmission (*n* = 8) Animal contact (*n* = 39)	Not reported	8
Bruno	2022	Italy	1	Female	71	PCR	Sexual contact	No	0
Costello	2022	USA	1	Male	28	PCR	Unknown	Not reported	Not reported
Damon	2006	Sudan	2	Female	Not reported	PCR	Not reported	Not reported	Not reported
Erez	2019	Israel	1	Male	38	PCR	Animal contact	Not reported	0
Fan Yong	2020	Singapore	1	Male	38	PCR	Unknown	Not reported	Not reported

TABLE 1 (Continued)

Report	Year	Country	Number of cases	Sex	Age, y	Confirmed test	Transmission	Other current infections or conditions	Deaths
Fine	1988	Zaire (Democratic Republic of the Congo)	209	Not reported	Not reported	Not reported	Animal contact (*n* = 162) Household contact (*n* = 36) Neighbourhood contact (*n* = 11)	Not reported	Not reported
Formently	2010	Sudan	19	Male (*n* = 9) Female (*n* = 10)	<1–32	PCR (*n* = 10)	Human contact (*n* = 14) Medical centre (*n* = 1) Unknown (*n* = 4)	Not reported	Not reported
Foster	1972	Liberia (*n* = 4) Sierra Leone (*n* = 1) Nigeria (*n* = 1)	6	Male (*n* = 3) Female (*n* = 3)	4–24	Laboratory test	Animal contact (*n* = 5) Unknown (*n* = 1)	Not reported	Not reported
Hammerschlag	2022	Australia	1	Male	≥30 to ≤39	PCR	Sexual contact	HIV Syphilis	Not reported
Hobson	2022	UK	3	Unknown	Unknown	PCR	Household contact (*n* = 3)	Not reported	Not reported
Hutin	1997	Democratic Republic of the Congo	92	Male (*n* = 51) Female (*n* = 41)	3 to <15 (*n* = 67) ≥15 (*n* = 25)	Not reported	Household contact (*n* = 65) Unknown (*n* = 27)	Not reported	3 (aged <3 years in 3 weeks)
Hutin	2001	Democratic Republic of the Congo	88	Male (*n* = 50) Female (*n* = 38)	<1–62	PCR (*n* = 7)	Unknown (*n* = 88)	Not reported	Not reported
Iñigo Martínez	2022	Spain (Madrid)	508	Male (*n* = 503) Female (*n* = 5)	18–67	PCR	Sexual contact (*n* = 206)	HIV (*n* = 225)	Not reported
Jang	2022	South Korea	1	Male	34	PCR	Sexual contact	Not reported	Not reported
Janseghers	1984	Zaire (Democratic Republic of the Congo)	1	Male	<3	Laboratory test	Not reported	Measles (1 month before)	1
Jezek A	1986	Zaire (Democratic Republic of the Congo)	214	Not reported	Not reported	Laboratory tests (*n* = 56)	Animal contact (*n* = 130) Human transmission (*n* = 40) Unknown (*n* = 44)	Not reported	Not reported
Jezek B	1986	Zaire (Democratic Republic of the Congo)	5	Male (*n* = 4) Female (*n* = 1)	<8	Laboratory tests (*n* = 5)	Animal contact (*n* = 1) Household contact (*n* = 4)	Not reported	1
Jezek	1987	Zaire (Democratic Republic of the Congo)	282	Male (*n* = 143) Female (*n* = 139)	<10 (*n* > 233) ≥10 (*n* > 17)	Not reported	Not reported	Not reported	27

(Continues)

TABLE 1 (Continued)

Report	Year	Country	Number of cases	Sex	Age, y	Confirmed test	Transmission	Other current infections or conditions	Deaths
Jezek	1988	Zaire (Democratic Republic of the Congo)	388	Male (*n* = 182) Female (*n* = 156)	<10 (*n* = 189) ≥10 (*n* = 149)	Not reported	Animal contact (*n* = 203) Household contact (*n* = 40) Neighbourhood contact (*n* = 9) Other human contact (*n* = 136)	Not reported	Not reported
Kabuga	2018	Nigeria	121	Not reported	11–39	PCR	Household contact (*n* = 5) Unknown (*n* = 116)	Not reported	7 (4 immunocompromised)
Kalthan	2016	Central African Republic	12	Male (*n* = 6) Female (*n* = 6)	<1–50	PCR (*n* = 4)	Unknown (*n* = 12)	Not reported	3
Kalthan	2018	Central African Republic	26	Male (*n* = 14) Female (*n* = 12)	1–58	PCR	Animal contact (*n* = 1) Human transmission (*n* = 23) Not reported (*n* = 2)	Not reported	2
Kile	2005	USA	9	Not reported	1–49	PCR (*n* = 3)	Animal contact (*n* = 8) Medical centre (*n* = 1)	Not reported	Not reported
Learned	2005	Republic of the Congo	12	Male (*n* = 8) Female (*n* = 4)	<1 >30	PCR (*n* = 3)	Household (*n* = 10) Medical centre (*n* = 1) Unknown (*n* = 1)	Not reported	2
Mauldin	2022	Nigeria (*n* = 4) UK (*n* = 1) Israel (*n* = 1)	6	Male (*n* = 5) Female (*n* = 1)	30–40	PCR	Medical centre (*n* = 2) Meat consumption (*n* = 2) Animal contact (*n* = 1) Unknown (*n* = 1)	Not reported	Not reported
McCollum	2015	Democratic Republic of the Congo	3	Male (*n* = 2) Female (*n* = 1)	23–28	PCR	Animal contact (*n* = 2) Unknown (*n* = 1)	Not reported	Not reported
Melsky	2003	USA	53	Male (*n* = 29) Female (*n* = 22) Unknown (*n* = 2)	4–53	PCR (*n* = 10)	Animal contact (*n* = 53)	Not reported	Not reported
Meyer	2002	Democratic Republic of the Congo	14	Male (*n* = 8) Female (*n* = 2) Unknown (*n* = 4)	<2–30	PCR (*n* = 7)	Animal contact (*n* = 14)	Varicella Zoster (*n* = 1)	5
Mileto	2022	Italy	1	Male	33	PCR	Sexual contact	HIV	0
Müller	1988	Gabon	1	Female	<1	Autopsy	Not reported	Not reported	1

TABLE 1 (Continued)

Report	Year	Country	Number of cases	Sex	Age, y	Confirmed test	Transmission	Other current infections or conditions	Deaths
Nakoune	2016	Central African Republic	10	Male (*n* = 3) Female (*n* = 2) Not reported (*n* = 5)	<2	PCR (*n* = 3)	Animal contact (*n* = 1) Household contact (*n* = 4) Medical centre contact (*n* = 3) Transport contact (*n* = 2)	No (*n* = 2)	2
Noe	2022	GerMaley	2	Male (*n* = 2)	26–32	PCR	Sexual contact (*n* = 2)	HIV	Not reported
Nolen	2016	Democratic Republic of the Congo	63	Male (*n* = 36) Female (*n* = 27)	<1–68	PCR (*n* = 20)	Household contact (*n* = 32) Unknown (*n* = 31)	Not reported	Not reported
Ogoina	2019	Nigeria	21	Male (*n* = 17) Female (*n* = 4)	6–45	PCR (*n* = 18)	Not reported	HIV (*n* = 2) Syphilis (*n* = 2)	0
Oprea	2022	RoMaleia	1	Male	26	PCR	Unknown	HIV	Not reported
Peiró-Mestres	2022	Spain (Barcelona)	12	Male	32–52	PCR	Sexual contact (*n* = 12)	HIV (*n* = 4) Syphilis (*n* = 2)	Not reported
Pembi	2022	Nigeria	1	Male	30	PCR	Unknown	Syphilis	Not reported
Perez Duque	2022	Portugal	27	Male (*n* = 27)	22–51	PCR	Sexual contact (*n* = 14)	HIV (*n* = 14)	Not reported
Rao	2022	USA	1	Male	Unknown	PCR	Unknown	Not reported	Not reported
Reed	2004	USA	11	Male (*n* = 5) Female (*n* = 6)	3–43	PCR (*n* = 11)	Animal contact (*n* = 11)	Not reported	Not reported
Reynolds	2013	Republic of the Congo	2	Female (*n* = 2)	7–16	PCR	Household (*n* = 1) Unknown (*n* = 1)	Not reported	0
Reynolds	2019	Sierra Leone	2	Male	<1–35	PCR	Animal contact (*n* = 1)	Not reported	Not reported
Sejvar	2004	USA	3	Male (*n* = 1) Female (*n* = 2)	6–33	PCR (*n* = 3)	Animal contact (*n* = 3)	Not reported	0
Selb	2022	GerMaley	521	Male	20–67	PCR	Sexual contact (*n* = 349)	Not reported	Not reported
Tutu van Furth	2022	Netherlands	1	Male	<10	PCR	Unknown	Negative (HIV, Syphilis, Varicella Zoster, Hepatitis B-C, Gonorrhoea, Chlamydia)	Not reported

(Continues)

TABLE 1 (Continued)

Report	Year	Country	Number of cases	Sex	Age, y	Confirmed test	Transmission	Other current infections or conditions	Deaths
Vallée	2022	France	1	Male	20–63	PCR	Sexual contact	HIV	Not reported
Vaughan	2018	UK	2	Male	Not reported	PCR	Household contact (n = 1)	Not reported	0
Vaughan	2020	UK	1	Unknown	Unknown	PCR	Medical centre	Not reported	Not reported
Vivancos	2022	United Kingdom	72	Male (n = 69)	32–43	PCR	Travel contact (n = 1) Household contact (n = 2) Sexual contact (n = 69)	Not reported	Not reported
Whitehouse	2021	Democratic Republic of the Congo	1057	Male (n = 568) Female (n = 486)	<20 (n = 707) ≥20 (n = 350)	PCR	Animal contact (n = 309) Human transmission (n = 279) Household (n = 247)	Varicella Zoster virus (n = 169)	Not reported
World Health Organization	1997	Democratic Republic of the Congo	419	Male (≥189) Female (≥155)	<16 (85%)	Not reported	Household contact (n = 137) Neighbourhood (n = 190) Unknown (n = 92)	Not reported	5
Yinka-Ogunleye	2019	Nigeria	122	Male (n = 84) Female (n = 38)	<1–50	PCR (n = 118)	Household contact (n = 7) Prison contact (n = 4) Medical centre (n = 1) Unknown (n = 106)	HIV (n = 4)	7 Three had stopped antiretroviral therapy more than 3 months before Mpox virus infection and one had never been on antiretroviral therapy

3.3 | Transmission

In 63.6% of the cases (2964/4659), the mode of contagion was human contact, while 22.8% (1063/4659) of the cases were by animal contact, and 13.5% (630/4659) were unknown or not reported. Two cases (0.2%) reported contagion due to meat consumption. Among the identified cases of human contact infection, a total of 1480 cases had more detailed information on the mode of transmission, of which 662 (44.7%) were by sexual contact, 592 (40%) by household contact, 210 (14.2%) by neighbourhood contact, seven cases (0.5%) by contact in medical centres, 5 (0.3%) by travel contact and 4 (0.2%) by prison contact.

3.4 | Mortality

A total of 24 studies (n = 1205) reported information regarding mortality. The mortality rate was 6.5% (78/1205 cases) throughout these studies. Regarding the meta-analysis of individual patient data (Figure 2), the risk of mortality was higher in the younger age group (risk difference: 0.19; 95% CI: 0.02–0.36), in cases with other co-infections or current chronic conditions (risk difference: 0.03; 95% CI: 0.01–0.05) and in the category of low- and middle-income countries (risk difference: 0.06; 95% CI: 0.05–0.08). There were no significant differences with respect to sex or mode of contagion (Figure 2).

3.5 | Quality assessment

Finally, the quality of all included articles was formally evaluated. The percentage of compliance in each of the four domains assessed was: selection: 100%, ascertainment: 75%, causality: 100%, and reporting: 9.7%. The results of the assessment of the methodological quality of the individual studies are presented in Table S2.

4 | DISCUSSION

The aim of this rapid review was to analyse the risk profile and modes of transmission of Mpox in cases reported throughout the literature in any clinical setting. Mpox is a resurgent disease that is now spreading rapidly outside endemic countries, to multiple countries in all continents. Our results indicate that in approximately two out of three cases of Mpox the mode of infection was human contact. In addition, the risk of mortality was higher in younger cases, with other co-infections or current chronic conditions and from low- and middle-income countries. The current outbreak of Mpox could be explained in part by the increasing mobility of the world's population (e.g., commercial air travel),[79] but also by the cessation of vaccination against smallpox, a disease declared eradicated in 1980.[80,81] Smallpox vaccination is considered to provide some cross-protection against Mpox, which is now almost nil in people over 40 years of age.[80] For example, Nguyen et al.[81] estimated that 1 year before the 2016 outbreak in Nigeria, only 10.1% of the population was vaccinated. Therefore, the importance of this resurgent disease should not be underestimated, and health authorities should allocate resources to strengthen prevention measures. To date, the new Mpox vaccines are approved in some regions for adults, but are not yet available for public use worldwide.

The Centers for Disease Control and Prevention (CDC) has proposed interim clinical considerations for the use of ACAM2000 and JYNNEOS vaccines during the 2022 Mpox outbreak in the United States.[82] The ACAM2000 vaccine is not recommended for

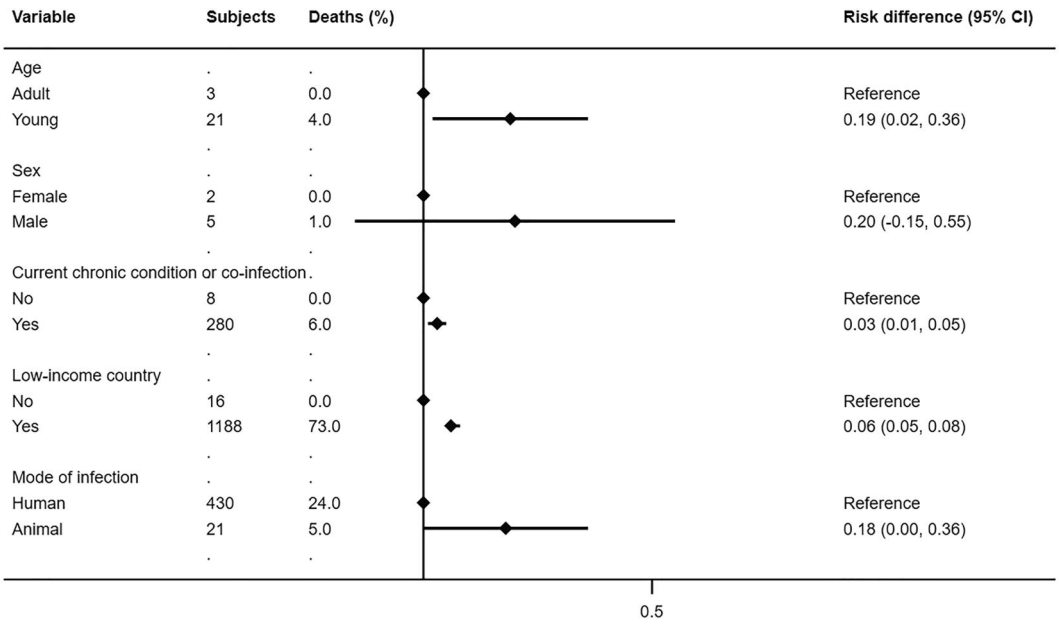

FIGURE 2 Risk difference for mortality of different patient profiles.

pregnant women, children younger than 12 months, and people with certain medical conditions, such as a weakened immune system. For example, the CDC does not recommend the ACAM2000 vaccine for people with HIV because of the increased risk of serious side effects such as pain and swelling at the inoculation site, lymphadenitis, and constitutional symptoms, such as malaise, fatigue, fever, myalgia, headache.[82] In contrast, JYNNEOS is considered safe for people with HIV.[82] Thus, individuals with the highest potential for exposure to Mpox virus may be offered vaccination to help prevent disease.

The clinical presentation of current Mpox cases differs from the results of African patients prior to 2022. For example, the frequency of fever was higher and the current outbreak is more associated with rash in the pelvic area and groin, given possible transmission during sexual intercourse, particular in men having sex with men.[83] Although half of the current cases have severe skin lesions, the disease in the current outbreak is milder, with a hospitalisation rate of approximately 1:6 among European versus African cases.[83]

The case fatality rate identified across all studies included in our rapid review was 6.5%, close to that reported in previous reviews.[83,84] Bunge et al.[84] in a systematic review conducted before the May 2022 Mpox outbreak, reported the overall case fatality rate of Mpox to be 8.7%, with a significant difference between the Central and West African cases of 10.6% versus 3.6%, respectively. In our rapid review, most of the fatal cases identified occurred in the Democratic Republic of Congo and Nigeria. Both countries are on the list of least developed countries according to United Nations criteria.[18] Thus, our results confirm that Mpox affects mostly the poorest communities (i.e. low- and middle-income countries).[85] Historically, public health threatening diseases such as the 1918–1919 influenza pandemic and COVID-19 have resulted in higher mortality rates in the most vulnerable populations.[86,87] Therefore, our results reinforce the message that policy efforts should focus on reducing health inequalities for future generations.

Another important finding of this review is the evidence of a higher mortality risk in younger cases and in those with other co-infections or current conditions. A recent systematic review of global guidelines for the clinical management of Mpox identified that the available evidence specifically discourages the use of the vaccine in immunocompromised persons (e.g., persons with HIV) and infants (<1 year),[88] which may partly explain why both groups have a higher mortality risk. However, most of the guidelines identified were of low methodologic quality.[88] Therefore, further research is needed on optimal prophylaxis and treatment strategies for at-risk groups. In general, very young children are at increased risk of disease complications and have higher mortality rates.[7,8,89] Thus, paediatric treatment requires careful interdisciplinary coordination and communication at all times.[7] Also, younger people may also be more susceptible to Mpox due to the cessation of smallpox vaccination campaigns worldwide in previous decades.[80,81,84] For these reasons, prevention of Mpox outcomes in paediatric populations in densely populated settings such as nurseries and schools seem of the utmost importance. On the other hand, cases with other co-infections or current choronic conditions (especially persons living with HIV or varicella-zoster virus) also had an increased risk of Mpox-associated mortality. This finding is relevant, as current cases of Mpox have commonly occurred in subjects with previous or concomitant sexually transmitted infection.[14] Furthermore, in our rapid review, we identified that the main mode of transmission was human contact (63.6%), with sexual contact transmission being one of the most frequent. Recent studies have identified that the current spread has disproportionately affected homosexual or bisexual men.[90] However, these results could be associated with a detection bias, as many of the initial May 2022 cases were diagnosed in this community and sexual health providers and linked populations increased surveillance.[91] Therefore, it is critical that the scientific community spread the word that this virus can affect anyone regardless of gender identity or sexual orientation. Thus, the entire population should take preventive measures, avoiding stigmas similar to those that occurred with HIV.[92] However, as a Public Health warning, it makes sense that, for the time being, all Mpox patients, whatever their sex or sexual orientation, use condoms and reduce the number of sexual partners, especially when pustules continue to appear on the skin.

4.1 | Strength and weakness

This systematic review retrieved data from 62 studies with more than 4000 cases of Mpox. In addition, to our knowledge, this is the first review with meta-analysis of individual patient data that analyzes the risk profile and modes of transmission of Mpox. On the other hand, this rapid review has a number of limitations: (1) It is difficult to determine the mode of infection in many cases, and lack of reporting on the final outcome of a substantial number of cases; (2) comparing modern cases with old cases introduces a bias since modern treatments might reduce severity and mortality risk of the disease. Also, different Mpox strains might influence the severity of the disease; and (3) the low number of fatal cases for each examined category suggest that the risk estimates obtained should be interpreted with uncertainty.

4.2 | Practice and research implications

Therapeutic options such as cidofovir and brincidofovir have demonstrated efficacy in in vitro and animal studies, but data on the treatment of Mpox in humans are limited.[93,94]

Recently, the real-life use of cidofovir for the treatment of severe cases of Mpox has shown success in a small series of cases, with no adverse events reported.[95] In frail subjects, such as AIDS patients requiring hospitalisation for a severe course of Mpox, Cidofovir may also be considered as a valuable component of treatment.[96] In addition, another antiviral, tecovirimat, could be used for the treatment of Mpox. In fact, a preliminary study identified that oral tecovirimat was well tolerated by 25 males (age range: 26–76) with Mpox

infection, with minimal adverse effects.[97] However, to date, there are few data to support the use of cidofovir or tecovirimat for the treatment of Mpox and clinical trials with control groups are needed to establish the role of this antiviral therapy in severe cases. Therefore, recognition of the major modes of infections and the higher-risk cases will enable clinicians to develop more effective strategies to protect the population from the consequences of Mpox, including prevention through implementation of infection control measures, appropriate follow-up, and supportive interventions.[98,99] For example, to help control infection, estimated data from Miura et al.[100] on the Mpox incubation period of 8.5 days for May 2022 cases in the Netherlands, with a 97.5 percentile of 19.9 days, support the recommendation to monitor and isolate/quarantine contacts of cases for at least 21 days. Also, following the management example of the UK health authorities, vaccination should be offered to higher-risk contacts.[101] In addition, reinforce other intensive public health measures, such as active surveillance, standard contact and droplet infection control precautions for healthcare workers and other caregivers of patients with suspected or confirmed Mpox, hand hygiene with soap and water or an alcohol-based disinfectant, and avoidance of contact with animals that may harbour the virus (rodents, marsupials, primates) in endemic countries.[101] Given that the paediatric population is particularly vulnerable, specific prevention strategies need to be designed, especially in environments densely populated by children, such as day care centres and schools. Last but not least, again those with acute Mpox infection should use condom and reduce the number of sexual partners, whatever their gender or sexual orientation.

5 | CONCLUSIONS

In the studies included in this review, two out of three cases of Mpox showed human contact as the mode of transmission. The risk of mortality was particularly high in younger cases, so prevention in settings such as day care centres and schools appear to be of utmost importance. Additionally, higher risk was also observed in subjects with other co-infections or current chronic conditions and in those individuals from undeveloped countries. These results help to understand the major infection pathways and mortality risk profiles of this resurgent disease.

AUTHOR CONTRIBUTIONS

Conceptualization: Rubén López-Bueno. Data curation: Rodrigo Núñez-Cortés and Rubén López-Bueno. Investigation: Rodrigo Núñez-Cortés, Joaquín Calatayud, José Francisco López-Gil, Ai Koyanagi, José Casaña, and Rubén López-Bueno. Method: Rubén López-Bueno. Writing original draft: Rodrigo Núñez-Cortés and Rubén López-Bueno. Writing review and editing: Rodrigo Núñez-Cortés, Joaquín Calatayud, José Francisco López-Gil, Ai Koyanagi, José Casaña, and Rubén López-Bueno. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

No conflict of interest declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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