






REVIEW

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

Rodrigo Núñez-Cortés^{1,2}  | Joaquín Calatayud^{3,4}  | José Francisco López-Gil⁵  |
Ai Koyanagi⁶  | José Casaña³ | Rubén López-Bueno^{3,4,7} 

¹Department of Physiotherapy, Physiotherapy in Motion Multispeciality Research Group (PTinMOTION), University of Valencia, Valencia, Spain

²Department of Physical Therapy, Faculty of Medicine, University of Chile, Santiago, Chile

³Exercise Intervention for Health Research Group (EXINH-RG), Department of Physiotherapy, University of Valencia, Valencia, Spain

⁴National Research Centre for the Working Environment, Copenhagen, Denmark

⁵Health and Social Research Center, Universidad de Castilla-La Mancha, Cuenca, Spain

⁶Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, ISCIII, ICREA, Barcelona, Spain

⁷Department of Physical Medicine and Nursing, University of Zaragoza, Zaragoza, Spain

Correspondence

Joaquín Calatayud, Department of Physiotherapy, University of Valencia, Valencia 46010, Spain.
Email: joaquin.calatayud@uv.es

Funding information

European Union - NextGeneration - EU; National Research and Development Agency of Chile, Grant/Award Number: ANID/2020-72210026

Abstract

Since May 2022, an outbreak of monkeypox 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 monkeypox. PubMed, Web of Science, and Scopus were searched from inception through July 30 to collect case reports/series on patients with monkeypox 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 monkeypox 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.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2022 The Authors. Reviews in Medical Virology published by John Wiley & Sons Ltd.

1 | INTRODUCTION

Monkeypox 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 monkeypox in humans have been regularly reported in African countries.³ The first outbreak of monkeypox 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 monkeypox were identified in several non-endemic countries. On July 25th, the World Health Organization declared the spread of monkeypox infection as a 'public health emergency of international concern'. Since the beginning of the current monkeypox 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 monkeypox outbreaks.

Monkeypox 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 monkeypox 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 monkeypox 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, monkeypox 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 monkeypox 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 monkeypox 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 monkeypox were enrolled in the included studies. The age range varied from <1 to 71 years. Fifty-three studies reported the variable sex; 68% of the cases enrolled 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.

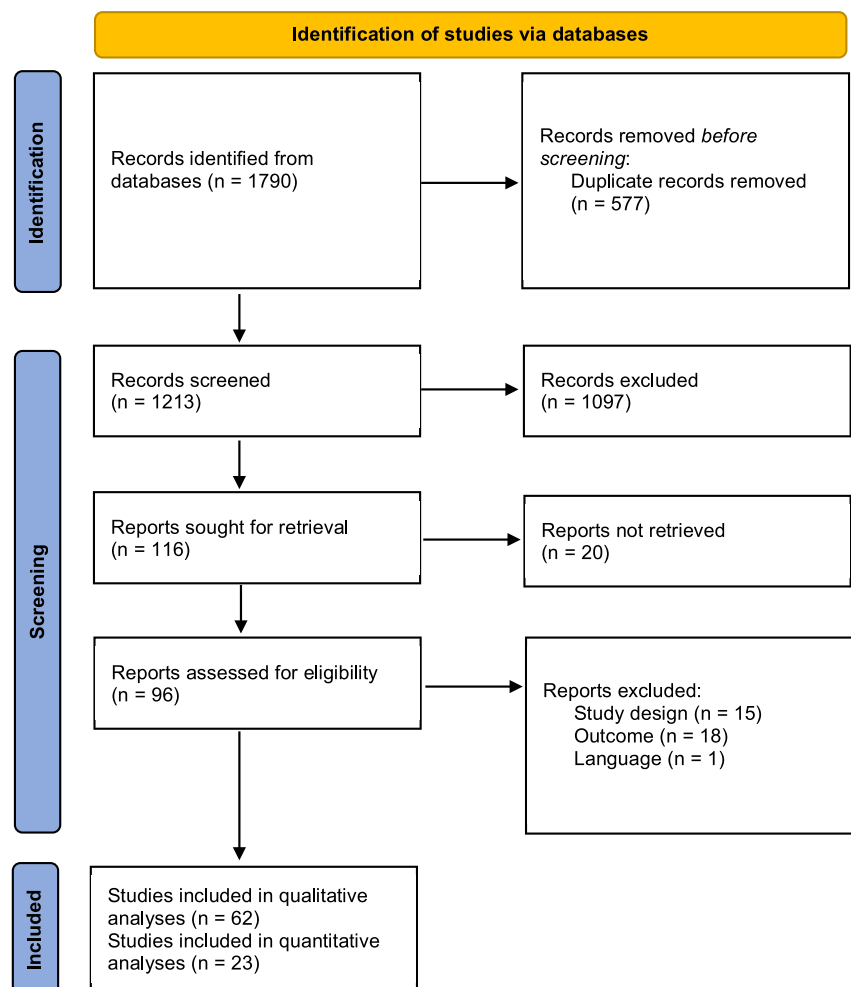


FIGURE 1 Prisma flow diagram.

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
Bizová	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)	<10 (n = 189)	Not reported	Animal contact (n = 203)	Not reported	Not reported
				Female (n = 156)	≥10 (n = 149)		Household contact (n = 40)		
Kabuga	2018	Nigeria	121	Not reported	11–39	PCR	Household contact (n = 5)	Not reported	7 (4 immunocompromised)
							Unknown (n = 116)		
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)	1–58	PCR	Animal contact (n = 1)	Not reported	2
				Female (n = 12)			Human transmission (n = 23)		
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)	<1 >30	PCR (n = 3)	Household (n = 10)	Not reported	2
				Female (n = 4)			Medical centre (n = 1) Unknown (n = 1)		
Mauldin	2022	Nigeria (n = 4) UK (n = 1) Israel (n = 1)	6	Male (n = 5)	30–40	PCR	Medical centre (n = 2)	Not reported	Not reported
				Female (n = 1)			Meat consumption (n = 2)		
							Animal contact (n = 1) Unknown (n = 1)		
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)	4–53	PCR (n = 10)	Animal contact (n = 53)	Not reported	Not reported
				Female (n = 22)					
				Unknown (n = 2)					
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 monkeypox 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 monkeypox in cases reported throughout the literature in any clinical setting. Monkeypox 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 monkeypox 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 monkeypox 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 monkeypox, 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 monkeypox 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 monkeypox outbreak in the United States.⁸² The ACAM2000 vaccine is not recommended for

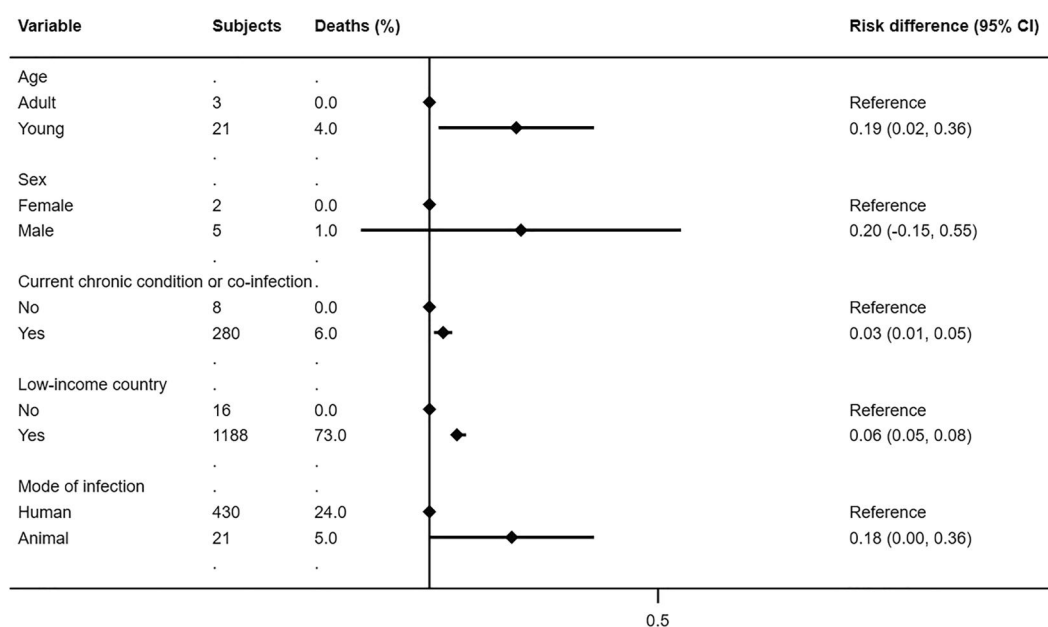


FIGURE 2 Risk difference for mortality of different patient profiles.

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 monkeypox virus may be offered vaccination to help prevent disease.

The clinical presentation of current monkeypox 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 monkeypox outbreak, reported the overall case fatality rate of monkeypox 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 monkeypox 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 monkeypox 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 monkeypox due to the cessation of smallpox vaccination campaigns worldwide in previous decades.^{80,81,84} For these reasons, prevention of monkeypox 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 chronic conditions (especially persons living with HIV or varicella-zoster virus) also had an increased risk of monkeypox-associated mortality. This finding is relevant, as current cases of monkeypox 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 monkeypox 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 monkeypox. 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 monkeypox. 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 monkeypox 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 monkeypox in humans are limited.^{93,94}

Recently, the real-life use of cidofovir for the treatment of severe cases of monkeypox 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 monkeypox, Cidofovir may also be considered as a valuable component of treatment.⁹⁶ In addition, another antiviral, tecovirimat, could be used for the treatment of monkeypox. In fact, a preliminary study identified that oral tecovirimat was well tolerated by 25 males (age range: 26–76) with

monkeypox 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 monkeypox 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 monkeypox, 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 monkeypox 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 monkeypox, 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 monkeypox 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 monkeypox 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.

ACKNOWLEDGEMENTS

Rubén López-Bueno and José Francisco López-Gil are supported by the European Union - NextGeneration - EU. Rodrigo Núñez-Cortés is supported by the National Research and Development Agency of Chile (ANID/2020-72210026). The other authors have nothing to disclose.

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.

ORCID

Rodrigo Núñez-Cortés  <https://orcid.org/0000-0002-4068-9338>

Joaquín Calatayud  <https://orcid.org/0000-0002-8670-8346>

José Francisco López-Gil  <https://orcid.org/0000-0002-7412-7624>

Ai Koyanagi  <https://orcid.org/0000-0002-9565-5004>

Rubén López-Bueno  <https://orcid.org/0000-0002-7865-3429>

REFERENCES

1. Durski KN, McCollum AM, Nakazawa Y, et al. Emergence of monkeypox—West and Central Africa, 1970–2017. *MMWR Morb Mortal Wkly Rep.* 2018;67(10):306–310. <https://doi.org/10.15585/mmwr.mm6710a5>
2. Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. *Bull World Health Organ.* 1972;46(5):593–597.
3. Heymann DL, Szczeniowski M, Esteves K. Re-emergence of monkeypox in Africa: a review of the past six years. *Br Med Bull.* 1998;54(3):693–702. <https://doi.org/10.1093/oxfordjournals.bmb.a011720>
4. Centers for Disease Control and Prevention (CDC). Update: multistate outbreak of monkeypox—Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. *MMWR Morb Mortal Wkly Rep.* 2003;52(27):642–646.
5. Erez N, Achdout H, Milrot E, et al. Diagnosis of imported monkeypox, Israel, 2018. *Emerg Infect Dis.* 2019;25(5):980–983. <https://doi.org/10.3201/eid2505.190076>
6. Yong SEF, Ng OT, Ho ZJM, et al. Imported monkeypox, Singapore. *Emerg Infect Dis.* 2020;26(8):1826–1830. <https://doi.org/10.3201/eid2608.191387>
7. Adler H, Gould S, Hine P, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. *Lancet Infect Dis.* 2022;22(8):1153–1162.
8. Monkeypox multi-country outbreak. European Centre for Disease Prevention and Control. Accessed August 25, 2022. <https://www.ecdc.europa.eu/en/monkeypox-outbreak>
9. McCollum AM, Damon IK. Human monkeypox. *Clin Infect Dis.* 2014;58(2):260–267. <https://doi.org/10.1093/cid/cit703>
10. Ophinni Y, Frediansyah A, Sirinam S, et al. Monkeypox: immune response, vaccination and preventive efforts. *Narra J.* 2022;2(3). <https://doi.org/10.52225/narra.v2i3.90>
11. Damon IK. Status of human monkeypox: clinical disease, epidemiology and research. *Vaccine.* 2011;29 suppl 4:D54–D59. <https://doi.org/10.1016/j.vaccine.2011.04.014>
12. Monkeypox. 2022. Accessed August 25, 2022. <https://www.who.int/news-room/fact-sheets/detail/monkeypox>

13. Allan-Blitz LT, Carragher K, Sukhija-Cohen A, Li H, Klausner JD. Laboratory validation and clinical implementation of human monkeypox saliva-based tests. <https://doi.org/10.1101/2022.08.08.22278498>
14. Nolasco S, Vitale F, Geremia A, et al. First case of monkeypox virus, SARS-CoV-2 and HIV co-infection. *J Infect.* 2022. <https://doi.org/10.1016/j.jinf.2022.08.014>
15. Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. *Syst Rev.* 2012;1:10. <https://doi.org/10.1186/2046-4053-1-10>
16. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Rev Esp Cardiol.* 2021;74(9):790-799.
17. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev.* 2016;5(1):210. <https://doi.org/10.1186/s13643-016-0384-4>
18. LDC Identification Criteria & Indicators. Accessed August 23, 2022. <https://www.un.org/development/desa/dpad/least-developed-country-category/ldc-criteria.html>
19. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med.* 2018;23(2):60-63. <https://doi.org/10.1136/bmjebm-2017-110853>
20. Anderson MG, Frenkel LD, Homann S, Guffey J. A case of severe monkeypox virus disease in an American child: emerging infections and changing professional values. *Pediatr Infect Dis J.* 2003;22(12):1093-1096. <https://doi.org/10.1097/01.inf.0000101821.61387.a5>
21. Angelo KM, Petersen BW, Hamer DH, Schwartz E, Brunette G. Monkeypox transmission among international travellers-serious monkey business? *J Trav Med.* 2019;26(5). <https://doi.org/10.1093/jtm/taz002>
22. Antinori A, Mazzotta V, Vita S, et al. Epidemiological, clinical and virological characteristics of four cases of monkeypox support transmission through sexual contact, Italy, May 2022. *Euro Surveill.* 2022;27(22). <https://doi.org/10.2807/1560-7917.ES.2022.27.22.2200421>
23. Arita I, Jezek Z, Khodakevich L, Ruti K. Human monkeypox: a newly emerged orthopoxvirus zoonosis in the tropical rain forests of Africa. *Am J Trop Med Hyg.* 1985;34(4):781-789. <https://doi.org/10.4269/ajtmh.1985.34.781>
24. Atkinson B, Burton C, Pottage T, et al. Infection-competent monkeypox virus contamination identified in domestic settings following an imported case of monkeypox into the UK. *Environ Microbiol.* 2022;24(10):4561-4569. <https://doi.org/10.1111/1462-2920.16129>
25. Berthet N, Nakouné E, Whist E, et al. Maculopapular lesions in the Central African Republic. *Lancet.* 2011;378(9799):1354. [https://doi.org/10.1016/s0140-6736\(11\)61142-2](https://doi.org/10.1016/s0140-6736(11)61142-2)
26. Besombes C, Gonofio E, Konamna X, et al. Intrafamily transmission of monkeypox virus, Central African Republic, 2018. *Emerg Infect Dis.* 2019;25(8):1602-1604. <https://doi.org/10.3201/eid2508.190112>
27. Bížová B, Veselý D, Trojáněk M, Rob F. Coinfection of syphilis and monkeypox in HIV positive man in Prague, Czech Republic. *Trav Med Infect Dis.* 2022;49:102368. <https://doi.org/10.1016/j.tmaid.2022.102368>
28. Breman JG, Kalisa-Ruti, Steniowski MV, Zanotto E, Gromyko AI, Arita I. Human monkeypox, 1970-79. *Bull World Health Organ.* 1980;58(2):165-182.
29. Bruno G, Fabrizio C, Rodano L, Buccoliero GB. Monkeypox in a 71-year-old woman. *J Med Virol.* 2022. <https://doi.org/10.1002/jmv.27993>
30. Costello V, Sowash M, Gaur A, et al. Imported monkeypox from international traveler, Maryland, USA, 2021 (response). *Emerg Infect Dis.* 2022;28(8):1739. <https://doi.org/10.3201/eid2808.220830>
31. Damon IK, Roth CE, Chowdhary V. Discovery of monkeypox in Sudan. *N Engl J Med.* 2006;355(9):962-963. <https://doi.org/10.1056/nejmc060792>
32. Fine PE, Jezek Z, Grab B, Dixon H. The transmission potential of monkeypox virus in human populations. *Int J Epidemiol.* 1988;17(3):643-650. <https://doi.org/10.1093/ije/17.3.643>
33. Formenty P, Muntasir MO, Damon I, et al. Human monkeypox outbreak caused by novel virus belonging to Congo Basin clade, Sudan, 2005. *Emerg Infect Dis.* 2010;16(10):1539-1545. <https://doi.org/10.3201/eid1610.100713>
34. Foster SO, Brink EW, Hutchins DL, et al. Human monkeypox. *Bull World Health Organ.* 1972;46(5):569-576.
35. Hammerschlag Y, MacLeod G, Papadakis G, et al. Monkeypox infection presenting as genital rash, Australia, May 2022. *Euro Surveill.* 2022;27(22). <https://doi.org/10.2807/1560-7917.ES.2022.27.22.2200411>
36. Hobson G, Adamson J, Adler H, et al. Family cluster of three cases of monkeypox imported from Nigeria to the United Kingdom, May 2021. *Euro Surveill.* 2021;26(32). <https://doi.org/10.2807/1560-7917.es.2021.26.32.2100745>
37. Hutin YJ, Williams RJ, Malfait P, et al. Outbreak of human monkeypox, Democratic Republic of Congo, 1996 to 1997. *Emerg Infect Dis.* 2001;7(3):434-438. <https://doi.org/10.3201/eid0703.017311>
38. Centers for Disease Control and Prevention (CDC). Human monkeypox—Kasai Oriental, Zaire, 1996–1997. *MMWR Morb Mortal Wkly Rep.* 1997;46(14):304-307.
39. Martínez JI, Montalbán EG, Bueno SJ, et al. Monkeypox outbreak predominantly affecting men who have sex with men, Madrid, Spain, 26 April to 16 June 2022. *Euro Surveill.* 2022;27(27). <https://doi.org/10.2807/1560-7917.es.2022.27.27.2200471>
40. Jang YR, Lee M, Shin H, et al. The first case of monkeypox in the Republic of Korea. *J Kor Med Sci.* 2022;37(27):e224. <https://doi.org/10.3346/jkms.2022.37.e224>
41. Janseghers L, Matamba M, Colaert J, Vandepitte J, Desmyter J. Fatal monkeypox in a child in Kikwit, Zaire. *Ann Soc Belg Med Trop.* 1984;64(3):295-298.
42. Jezek Z, Arita I, Mutombo M, Dunn C, Nakano JH, Szczeniowski M. Four generations of probable person-to-person transmission of human monkeypox. *Am J Epidemiol.* 1986;123(6):1004-1012. <https://doi.org/10.1093/oxfordjournals.aje.a114328>
43. Jezek Z, Marennikova SS, Mutombo M, Nakano JH, Paluku KM, Szczeniowski M. Human monkeypox: a study of 2, 510 contacts of 214 patients. *J Infect Dis.* 1986;154(4):551-555. <https://doi.org/10.1093/infdis/154.4.551>
44. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. *J Infect Dis.* 1987;156(2):293-298. <https://doi.org/10.1093/infdis/156.2.293>
45. Jezek Z, Grab B, Szczeniowski MV, Paluku KM, Mutombo M. Human monkeypox: secondary attack rates. *Bull World Health Organ.* 1988;66(4):465-470.
46. Kabuga AI, El Zowalaty ME. A review of the monkeypox virus and a recent outbreak of skin rash disease in Nigeria. *J Med Virol.* 2019;91(4):533-540. <https://doi.org/10.1002/jmv.25348>
47. Kalthan E, Dondo-Fongbia JP, Yambale S, Dieu-Creer LR, Zepio R, Pamatika CM. [Twelve cases of monkeypox virus outbreak in Bangassou District (Central African Republic) in December 2015]. *Bull Soc Pathol Exot.* 2016;109(5):358-363. <https://doi.org/10.1007/s13149-016-0516-z>
48. Kalthan E, Tenguer J, Ndjapou SG, et al. Investigation of an outbreak of monkeypox in an area occupied by armed groups, Central African Republic. *Med Mal Infect.* 2018;48(4):263-268. <https://doi.org/10.1016/j.medmal.2018.02.010>

49. Kile JC, Fleischauer AT, Beard B, et al. Transmission of monkeypox among persons exposed to infected prairie dogs in Indiana in 2003. *Arch Pediatr Adolesc Med.* 2005;159(11):1022-1025. <https://doi.org/10.1001/archpedi.159.11.1022>
50. Learned LA, Bolanda JD, Li YU, et al. Extended interhuman transmission of monkeypox in a hospital community in the Republic of the Congo, 2003. *Am J Trop Med Hyg.* 2005;73(2):428-434. <https://doi.org/10.4269/ajtmh.2005.73.428>
51. Mauldin MR, McCollum AM, Nakazawa YJ, et al. Exportation of monkeypox virus from the African continent. *J Infect Dis.* 2022;225(8):1367-1376. <https://doi.org/10.1093/infdis/jiaa559>
52. McCollum A, Nakazawa Y, Mutombo Ndongala G, et al. Human monkeypox in the Kivus, a conflict region of the Democratic Republic of the Congo. *Int J Infect Dis.* 2014;21:192. <https://doi.org/10.1016/j.ijid.2014.03.820>
53. Centers for Disease Control and Prevention (CDC). Multistate outbreak of monkeypox—Illinois, Indiana, and Wisconsin, 2003. *MMWR Morb Mortal Wkly Rep.* 2003;52(23):537-540.
54. Meyer H, Perrichot M, Stemmler M, et al. Outbreaks of disease suspected of being due to human monkeypox virus infection in the Democratic Republic of Congo in 2001. *J Clin Microbiol.* 2002;40(8):2919-2921. <https://doi.org/10.1128/jcm.40.8.2919-2921.2002>
55. Mileto D, Riva A, Cutrera M, et al. New challenges in human monkeypox outside Africa: a review and case report from Italy. *Trav Med Infect Dis.* 2022;49:102386. <https://doi.org/10.1016/j.tmaid.2022.102386>
56. Müller G, Meyer A, Gras F, Emmerich P, Kolakowski T, Esposito JJ. Monkeypox virus in liver and spleen of child in Gabon. *Lancet.* 1988;1(8588):769-770. [https://doi.org/10.1016/s0140-6736\(88\)91580-2](https://doi.org/10.1016/s0140-6736(88)91580-2)
57. Nakoune E, Lampaert E, Ndjapou SG, et al. A nosocomial outbreak of human monkeypox in the Central African Republic. *Open Forum Infect Dis.* 2017;4(4):ofx168. <https://doi.org/10.1093/ofid/ofx168>
58. Noe S, Zange S, Seilmaier M, et al. Clinical and virological features of first human Monkeypox cases in Germany. <https://doi.org/10.21203/rs.3.rs-1725831/v1>
59. Nolen LD, Osadebe L, Katomba J, et al. Extended human-to-human transmission during a monkeypox outbreak in the Democratic Republic of the Congo. *Emerg Infect Dis.* 2016;22(6):1014-1021. <https://doi.org/10.3201/eid2206.150579>
60. Ogoina D, Izibewule JH, Ogunleye A, et al. The 2017 human monkeypox outbreak in Nigeria—report of outbreak experience and response in the Niger Delta University Teaching Hospital, Bayelsa State, Nigeria. *PLoS One.* 2019;14(4):e0214229. <https://doi.org/10.1371/journal.pone.0214229>
61. Oprea C, Ianache I, Piscu S, et al. First report of monkeypox in a patient living with HIV from Romania. *Trav Med Infect Dis.* 2022;49:102395. <https://doi.org/10.1016/j.tmaid.2022.102395>
62. Peiró-Mestres A, Fuertes I, Camprubí-Ferrer D, et al. Frequent detection of monkeypox virus DNA in saliva, semen, and other clinical samples from 12 patients, Barcelona, Spain, May to June 2022. *Euro Surveill.* 2022;27(28). <https://doi.org/10.2807/1560-7917.ES.2022.27.28.2200503>
63. Pembri E, Awang S, Salaudeen SO, Agaba IA, Omoleke S. First confirmed case of monkeypox in Adamawa State, Nigeria: a clinico-epidemiological case report. *Pan Afr Med J.* 2022;42:38. <https://doi.org/10.11604/pamj.2022.42.38.34715>
64. Perez Duque M, Ribeiro S, Martins JV, et al. Ongoing monkeypox virus outbreak, Portugal, 29 April to 23 May 2022. *Euro Surveill.* 2022;27(22). <https://doi.org/10.2807/1560-7917.ES.2022.27.22.2200424>
65. Rao AK, Schulte J, Chen TH, et al. Monkeypox in a traveler returning from Nigeria—Dallas, Texas, July 2021. *MMWR Morb Mortal Wkly Rep.* 2022;71(14):509-516. <https://doi.org/10.15585/mmwr.mm7114a1>
66. Reed KD, Melski JW, Graham MB, et al. The detection of monkeypox in humans in the Western Hemisphere. *N Engl J Med.* 2004;350(4):342-350. <https://doi.org/10.1056/nejmoa032299>
67. Reynolds MG, Emerson GL, Pukuta E, et al. Detection of human monkeypox in the Republic of the Congo following intensive community education. *Am J Trop Med Hyg.* 2013;88(5):982-985. <https://doi.org/10.4269/ajtmh.12-0758>
68. Reynolds MG, Wauquier N, Li Y, et al. Human monkeypox in Sierra Leone after 44-year absence of reported cases. *Emerg Infect Dis.* 2019;25(5):1023-1025. <https://doi.org/10.3201/eid2505.180832>
69. Sejvar JJ, Chowdhury Y, Schomogyi M, et al. Human monkeypox infection: a family cluster in the midwestern United States. *J Infect Dis.* 2004;190(10):1833-1840. <https://doi.org/10.1086/425039>
70. Selb R, Werber D, Falkenhorst G, et al. A shift from travel-associated cases to autochthonous transmission with Berlin as epicentre of the monkeypox outbreak in Germany, May to June 2022. *Euro Surveill.* 2022;27(27). <https://doi.org/10.2807/1560-7917.es.2022.27.27.2200499>
71. Tutu van Furth AM, van der Kuip M, van Els AL, et al. Paediatric monkeypox patient with unknown source of infection, the Netherlands, June 2022. *Euro Surveill.* 2022;27(29). <https://doi.org/10.2807/1560-7917.ES.2022.27.29.2200552>
72. Vallée A, Farfour E, Zucman D. Monkeypox virus: a novel sexually transmitted disease? A case report from France. *Trav Med Infect Dis.* 2022;49:102394. <https://doi.org/10.1016/j.tmaid.2022.102394>
73. Vaughan A, Aarons E, Astbury J, et al. Two cases of monkeypox imported to the United Kingdom, September 2018. *Euro Surveill.* 2018;23(38). <https://doi.org/10.2807/1560-7917.es.2018.23.38.1800509>
74. Vaughan A, Aarons E, Astbury J, et al. Human-to-human transmission of monkeypox virus, United Kingdom, October 2018. *Emerg Infect Dis.* 2020;26(4):782-785. <https://doi.org/10.3201/eid2604.191164>
75. Vivancos R, Anderson C, Blomquist P, et al. Community transmission of monkeypox in the United Kingdom, April to May 2022. *Euro Surveill.* 2022;27(22). <https://doi.org/10.2807/1560-7917.ES.2022.27.22.2200422>
76. Whitehouse ER, Bonwitt J, Hughes CM, et al. Clinical and epidemiological findings from enhanced monkeypox surveillance in Tshuapa Province, Democratic Republic of the Congo during 2011–2015. *J Infect Dis.* 2021;223(11):1870-1878. <https://doi.org/10.1093/infdis/jiab133>
77. Centers for Disease Control and Prevention (CDC). Human monkeypox – Kasai Oriental, Democratic Republic of Congo, February 1996–October 1997. *MMWR Morb Mortal Wkly Rep.* 1997;46(49):1168-1171.
78. Yinka-Ogunleye A, Aruna O, Dalhat M, et al. Outbreak of human monkeypox in Nigeria in 2017–18: a clinical and epidemiological report. *Lancet Infect Dis.* 2019;19(8):872-879. [https://doi.org/10.1016/s1473-3099\(19\)30294-4](https://doi.org/10.1016/s1473-3099(19)30294-4)
79. Au NH, Portillo MT, Marwah A, et al. Potential for monkeypox exportation from west and Central Africa through global travel networks. *J Trav Med.* 2022;29(6). <https://doi.org/10.1093/jtm/taac072>
80. Jezek Z, Khodakevich LN, Wickett JF. Smallpox and its post-eradication surveillance. *Bull World Health Organ.* 1987;65(4):425-434.
81. Nguyen PY, Ajisegiri WS, Costantino V, Chughtai AA, MacIntyre CR. Reemergence of human monkeypox and declining population immunity in the context of urbanization, Nigeria, 2017–2020. *Emerg Infect Dis.* 2021;27(4). <https://doi.org/10.3201/eid2704.203569>
82. CDC. Interim clinical considerations for use of JYNNEOS and ACAM2000 vaccines during the 2022 U.S. monkeypox outbreak.

- Centers for Disease Control and Prevention. 2022. Accessed November 14, 2022. <https://www.cdc.gov/poxvirus/monkeypox/clinicians/vaccines/vaccine-considerations.html>
83. Benites-Zapata VA, Ulloque-Badaracco JR, Alarcon-Braga EA, et al. Clinical features, hospitalisation and deaths associated with monkeypox: a systematic review and meta-analysis. *Ann Clin Microbiol Antimicrob*. 2022;21(1):36. <https://doi.org/10.1186/s12941-022-00527-1>
 84. Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox—a potential threat? A systematic review. *PLoS Negl Trop Dis*. 2022;16(2):e0010141. <https://doi.org/10.1371/journal.pntd.0010141>
 85. McCollum AM, Reynolds MG, Ndongala GM, et al. Human monkeypox in the Kivus, a conflict region of the Democratic Republic of the Congo. *Am J Trop Med Hyg*. 2015;93(4):718–721. <https://doi.org/10.4269/ajtmh.15-0095>
 86. Summers JA, Stanley J, Baker MG, Wilson N. Risk factors for death from pandemic influenza in 1918–1919: a case-control study. *Influenza Other Respir Viruses*. 2014;8(3):329–338. <https://doi.org/10.1111/irv.12228>
 87. Núñez-Cortés R, Ortega-Palavecinos M, Soto-Carmona C, Torres-Gangas P, Concha-Rivero MP, Torres-Castro R. Social determinants of health associated with severity and mortality in patients with COVID-19. *Gac Med Mex*. 2021;157(3):263–270.
 88. Webb E, Rigby I, Michelen M, et al. Availability, scope and quality of monkeypox clinical management guidelines globally: a systematic review. *BMJ Glob Health*. 2022;7(8):e009838. <https://doi.org/10.1136/bmjgh-2022-009838>
 89. Beer EM, Rao VB. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. *PLoS Negl Trop Dis*. 2019;13(10):e0007791. <https://doi.org/10.1371/journal.pntd.0007791>
 90. Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox virus infection in humans across 16 countries – April–June 2022. *N Engl J Med*. 2022;387(8):679–691. <https://doi.org/10.1056/nejmoa.2207323>
 91. Daskalakis D, Paul McClung R, Mena L, et al. Monkeypox: avoiding the mistakes of past infectious disease epidemics. *Ann Intern Med*. 2022;175(8):1177–1178. <https://doi.org/10.7326/m22-1748>
 92. Bragazzi NL, Khamisy-Farah R, Tsigalou C, Mahroum N, Converti M. Attaching a stigma to the LGBTQI community should be avoided during the monkeypox epidemic. *J Med Virol*. 2022;95(1). <https://doi.org/10.1002/jmv.27913>
 93. Hutson CL, Kondas AV, Mauldin MR, et al. Pharmacokinetics and efficacy of a potential smallpox therapeutic, brincidofovir, in a lethal monkeypox virus animal model. *mSphere*. 2021;6(1). <https://doi.org/10.1128/msphere.00927-20>
 94. Andrei G, Snoeck R. Cidofovir activity against poxvirus infections. *Viruses*. 2010;2(12):2803–2830. <https://doi.org/10.3390/v2122803>
 95. Raccagni AR, Candela C, Bruzzesi E, et al. Real-life use of cidofovir for the treatment of severe monkeypox cases. *J Med Virol*. 2022. <https://doi.org/10.1002/jmv.28218>
 96. Fabrizio C, Bruno G, Cristiano L, Buccoliero GB. Cidofovir for treating complicated monkeypox in a man with acquired immune deficiency syndrome. *Infection*. 2022. <https://doi.org/10.1007/s15010-022-01949-x>
 97. Desai AN, Thompson GR, Neumeister SM, Arutyunova AM, Trigg K, Cohen SH. Compassionate use of tecovirimat for the treatment of monkeypox infection. *JAMA*. 2022;328(13):1348. <https://doi.org/10.1001/jama.2022.15336>
 98. Response E. Clinical management and infection prevention and control for monkeypox: interim rapid response guidance, 10 June 2022. 2022. Accessed August 28, 2022. <https://www.who.int/publications/i/item/WHO-MPX-Clinical-and-IPC-2022.1>
 99. Monkeypox Outbreak Toolbox. Accessed August 28, 2022. <https://www.who.int/emergencies/outbreak-toolkit/disease-outbreak-toolboxes/monkeypox-outbreak-toolbox>
 100. Miura F, van Ewijk CE, Backer JA, et al. Estimated incubation period for monkeypox cases confirmed in the Netherlands, May 2022. *Euro Surveill*. 2022;27(24). <https://doi.org/10.2807/1560-7917.ES.2022.27.24.2200448>
 101. Monkeypox - United Kingdom of Great Britain and Northern Ireland. Accessed August 28, 2022. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON383>

SUPPORTING INFORMATION

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

How to cite this article: Núñez-Cortés R, Calatayud J, López-Gil JF, Koyanagi A, Casaña J, López-Bueno R. Risk profile and mode of transmission of monkeypox: a rapid review and individual patient data meta-analysis of case studies. *Rev Med Virol*. 2022;e2410. <https://doi.org/10.1002/rmv.2410>