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Practical clinical reviews

Clinical manifestations and outcomes of human mpox infection from 1970 to 2023: A systematic literature review

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ABSTRACT

Mpox is an important emerging infectious disease spreading rapidly with a changing geographical, clinical, epidemiological, virological, and clinical manifestations. The identification of clade I virus, the variant associated with severe disease and higher risk of death outside Africa in August 2024 is alarming. It is vital to document its changing epidemiology, clinical manifestations, and outcome to better understand how to prevent and treat the disease. We aimed to describe the clinical features and disease outcome of patients with mpox from 1970 to 2023. We performed a systematic search of peer-reviewed publications and grey literature using PubMed, MEDLINE, CINAHL, and EMBASE, published between 1973 and 2023. Thirty-seven articles met the inclusion criteria. We pooled data from 19 studies with at least 10 cases to enhance the appreciation of the review findings. A clear distinction was observed regarding the age, gender, sexual orientation, and HIV status distribution of mpox cases before and after May 2022. From May 2022 onwards, a high prevalence of mpox, almost exclusively, was observed among individuals identifying as men who have sex with men (MSM) 20–40 years with high-risk sexual behaviour and/or HIV immunosupression. No change in the common clinical manifestations – mucocutaneous rash, fever, lymphadenopathy, headache, and generalized malaise, typically during prodrome. However, certain symptoms such as myalgia/arthralgia, oropharyngitis, proctitis, and depression/anxiety were typically reported from May 2022 onwards. We could not establish from the review if the observed symptomatology change was real or resulting from an observation bias. Notably, a clear change in symptomatology was observed among individuals with immunosuppression who do not necessarily experience the prodromal stage and present with significantly more and larger mucocutaneous lesions that sometimes coalesced to form ulcers. Our pooled data report a CFR of 8.3 % before May 2022 and 1.2 % from May 2022 onwards. We show that mental health in patients with mpox has not received the attention required. There is a need for a strategic and strong approach to revamp mpox services to improve clinical suspicion and treatment, protect individuals most at risk including healthcare workers in high risk areas.

Background

Mpox (formerly monkeypox) is a zoonotic illness caused by the mpox virus (MPXV), a stable DNA *Orthopoxvirus* from the *Poxviridae* family. Although initially the virus was isolated in monkeys (Di Gennaro et al., 2022); its definitive primary host remains unknown. However, mammals such as non-human primates, certain species of African rodents, and prairie dogs carry the virus as zoonotic vectors. (Mpox (CDC), 2024); MPXV is categorized into two genetically distinct clades: clade I previously known as the Congo Basin (Central African) clade which include sub-clades Ia and Ib, and clade II, formerly referred to as the West African clade comprising sub-clades IIa and IIb. Genetic disparities of the two clades determine variations in viral antigenicity and pathogenicity, with Clade I been linked to higher mortality and a more severe course of illness (Di Gennaro et al., 2022; Mpox (CDC), 2024).

Between 1970 and 2002, mpox cases were exclusively reported in

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central and west Africa, (Jezek et al., 1987). Ten countries which reported mpox cases during this period include Cameroon, Central Africa Republic, Congo Brazzaville, Cote d'Ivoire, DRC (Zaire), Gabon, Liberia, Nigeria, Sierra Leone, and South Sudan, with about 1,500 cumulative cases and about 130 deaths. Consistent case identification and reporting has been ongoing in the DRC and in affected West African nations (Jezek et al., 1987 Aug; Yinka-Ogunleye et al., 2019; Bunge et al., 2022). The USA was the first country outside central and west Africa to report mpox cases in 2003, with 47 cases linked to contact with prairie dogs that acquired mpox from infected rodents imported from Ghana. Subsequently, sporadic cases have been identified mainly in the USA and UK (Bunge et al., 2022).

In May 2022 the mpox outbreak was reported in Europe and was declared a Public Health Emergency of International Concern (PHEIC) by the World Health Organisation (WHO) in July 2022, however, in May 2023, mpox was declared as no longer a PHEIC (WHO, 2023; World Health Organization. Mpox. Who.int. World Health Organization: WHO;, 2024). Sadly, in August 2024 the WHO declared mpox as a PHEIC again due to the emergence of clade Ib epidemic in the DRC and reports of cases from Burundi, Kenya, Rwanda, and Uganda, countries that had never reported a single case of mpox in the past (Kuppalli et al., 2024 Nov; NIH: National Institute of Allergy and Infectious Diseases Mpox (formerly Monkeypox) |, 2024). August 2024 also saw clade Ib cases been detected beyond Africa (World Health Organization. Mpox. Who.int. World Health Organization: WHO;, 2024; NIH: National Institute of Allergy and Infectious Diseases Mpox (formerly Monkeypox) |, 2024).

In March 2023, the DRC documented its initial case of clade I mpox among men who have sex with men (MSM). Between September 2023 and August 2024, persistent human-to-human transmission of mpox were observed within the sexual networks of adult heterosexuals and female sex workers in North and South Kivu. These networks were caused by a recently described variant of the clade Ib strain (Kuppalli et al., 2024).

As of October 2024, the WHO situation report presented 106,310 confirmed cases with 234 deaths from 123 countries of which Africa continent reported 7,535 confirmed cases with 32 deaths from 16 countries. The most affected African countries are the DRC (6,169 confirmed, 25 deaths) followed by Burundi (987 confirmed, 0 death) and Nigeria (94 confirmed, 0 death) (Multi-country outbreak of mpox, External situation report. 13 October, 2024).

Before May 2022, the disease was documented as self-limiting, with a clade-dependent case fatality rate (CFR) ranging from 1 % to 10 % in adults. In children less than 10 years, a higher CFR of 37.5 % to 100 % has been reported. Neonates, pregnant women, and individuals with compromised immunity experience a more severe illness and higher fatality regardless of the viral clade (Mpox (CDC), 2024; Bunge et al., 2022; NIH: National Institute of Allergy and Infectious Diseases Mpox (formerly Monkeypox) |, 2024).

From May 2022 onwards, the disease clinical presentation, susceptibility profile and outcome are different, with higher infection rates among adults and a higher co-infection with STIs (CDC., 2023; Thornhill et al., 2022; Caria et al., 2022). Several epidemiological and clinical studies have established that the 2022 mpox outbreak disproportionately affected men between 20 and 40 years who identify as Men who have Sex with Men (MSM) in 98 % to 99 % of cases (Di Gennaro et al., 2022; World Health Organization. Mpox. Who.int. World Health Organization: WHO;, 2024).

Before May 2022, mpox transmission was almost always linked to a zoonotic source and typically presented with a characteristic two to four days prodromal stage characterized by fever, lymphadenopathy, headache, and malaise before the appearance of the mucocutaneous rash (Thornhill et al., 2022; Caria et al., 2022). From May 2022 onwards, cases have been linked to sexual transmission and altered symptomatology, often complicated by co-infection with HIV/AIDS or other STIs (Mitjà et al., 2023). Newer manifestations, including conjunctivitis, proctitis, urinary tract infection (UTI), penile oedema, and neurological symptoms, have been described (Tarín-Vicente et al., 2022). The observed change in mpox demographic susceptibility and clinical presentation pose an additional challenge to health systems, most of which are still recovering from the effects of the COVID-19 pandemic.

Although studies reveal a change in the pattern and severity of symptoms, higher hospitalization rates, and higher case fatality rates in immunocompromised individuals (Mitjà et al., 2023); some have reported the occurrence of asymptomatic cases (Nörz et al., 2022). Of note is the lack of mental health identification and management during the mpox outbreaks. We could not identify any publications relating to investigation into the mental health aspect of mpox outbreak. However, we recognise that during the outbreak the main focus is to manage physical symptoms of mpox rather than a focus on mental health, especially in resource constrained settings.

We present a systematic literature review of the clinical manifestations and disease outcome of mpox from 1970 to 2023, providing an in-depth description of mpox symptomatology and the disease outcome before and after the May 2022 outbreak. In addition, we describe the change in the epidemiology of the population at risk, the need to update the assessment and reporting tools and discuss considerations for healthcare staff occupational safety.

Methodology

Search strategy

The search strategy followed the Cochrane and PRISMA 2020 guidelines using four electronic databases Excerpta Medical Database (EMBASE), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Medical Literature Analysis and Retrieval System Online (MEDLINE), and PubMed. The review question followed the Population, Interventions, Comparisons, Outcome and Study (PICOS) format.

Inclusion and exclusion criteria

The review included original quantitative studies on mpox infection clinical manifestations and outcomes including case reports, case series, cross sectional, and longitudinal studies published in English language from 1970 to 2023 globally. The last search was performed in November 2023. In addition, a manual search was performed from the identified articles, from key organization websites such as WHO and CDC and from country reports where mpox is endemic such as the Nigerian Centre for Disease Control and Prevention (NCDC). The search excluded systematic reviews.

Literature search process

MESH terms, subject headings and BOOLEAN operators applied included Monkeypox OR monkeypox disease OR monkeypox virus OR monkey pox OR MPV OR Monkey* OR mpox OR mpox virus or MPXV AND Presenting complains OR symptoms OR symptomatology OR clinical presentation AND Outcomes OR results OR treatment outcome.

Table 1
PICOS search tool.

PICOS	Search Term
Population/ Patient/ Problem	Monkeypox OR monkeypox disease OR monkeypox virus OR monkey pox OR mpox OR mpox virus OR mpox disease OR MPXV AND Presenting complains OR symptoms OR symptomatology OR clinical manifestation OR clinical presentation OR signs OR characteristics
Interventions	N/A
Comparisons	N/A
Outcomes	Outcomes OR results OR treatment outcome
Study design	'Case report' OR 'case series', OR 'observational' OR 'descriptive' OR 'analytical' OR 'cross sectional', OR 'longitudinal', OR 'quantitative'

Table 1 below summarizes the BOOLEAN operators for each category of the PICOS.

Articles selection

Following the search, titles and abstracts were reviewed for relevance, and those found to be potentially relevant had their complete titles checked to see if they specifically described the symptoms and/or signs of patients with mpox and the patient's outcome. Two people scrutinized the articles independently and reconciled the findings. The disagreements were resolved amicably through discussion. Table 2 presents a summary of the number of studies retrieved per search engine, studies excluded, and studies included. The Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flowchart (Fig. 1) summarises the number of articles identified at each step of the search process.

Table 2
Studies retrieved per database.

Database yield	Search terms and yield
CINAHL	(S1) Monkeypox (984) Subject heading applied:
Yielded = 5	(S2) Monkeypox OR monkeypox disease OR monkeypox virus OR monkey pox OR mpox OR mpox virus OR mpox disease OR MPXV (1,101).
Excluded = 3	(S3) Presenting complains OR symptoms OR symptomatology OR clinical presentation OR signs OR characteristics (823,731)
Included = 2	(S4) Outcomes OR results OR treatment outcome (2,491,454)
	(S5) 'Case report' OR 'case series' OR 'cross sectional', 'longitudinal', OR 'quantitative studies' OR 'grey literature' (572,482)
	(S2 + S3) = (S6) 210
	(S4 + S6) = (S7) 30
	(S5 + S7) = (S8) 5
MEDLINE	(S1) Monkeypox (3,519) MeSH Term applied:
Yielded = 42	(S2) Monkeypox OR monkeypox disease OR monkeypox virus OR monkey pox OR mpox OR mpox virus OR mpox disease OR MPXV (3,699).
Excluded = 26	(S3) Presenting complains OR symptoms OR symptomatology OR clinical presentation OR signs OR characteristics (3,451,339)
Included = 16	(S4) Outcomes OR results OR treatment outcome (10,018,211)
	(S5) 'Case report' OR 'case series' OR 'cross sectional', 'longitudinal', OR 'quantitative studies' OR 'grey literature' (2,049,019)
	(S2 + S3) = (S6) 683
	(S4 + S6) = (S7) 172
	(S5 + S7) = (S8) 42
PubMed	Monkeypox MeSH applied:
Yielded = 57	(S1) Monkeypox OR monkeypox disease OR monkeypox virus OR monkey pox OR mpox OR mpox virus OR mpox disease OR MPXV (3,721).
Excluded = 48	(S2) Presenting complains OR symptoms OR symptomatology OR clinical presentation OR signs OR characteristics (1,347,782)
Included = 9	(S3) Outcomes OR results OR treatment outcome (13,709,247)
	(S4) 'Case report' OR 'case series' OR 'cross sectional', 'longitudinal', OR 'quantitative studies' OR 'grey literature' (3,874,041)
	(S1 + S2) = (S5) 1463
	(S3 + S5) = (S6) 520
	(S4 + S6) = (S7) 57
EMBASE	(S1) Monkeypox (10,100) MeSH Term applied:
Yielded = 406	(S2) Monkeypox OR monkeypox disease OR monkeypox virus OR monkey pox OR mpox OR mpox virus OR mpox disease OR MPXV (10,905).
Excluded = 399	(S3) Presenting complains OR symptoms OR symptomatology OR clinical presentation OR signs OR characteristics (11013775)
Included = 7	(S4) Outcomes OR results OR treatment outcome (30,284,530)
	(S5) 'Case report' OR 'case series' OR 'cross sectional', 'longitudinal', OR 'quantitative studies' OR 'grey literature' (6,901,730)
	(S2 + S3) = (S6) 2924
	(S4 + S6) = (S7) 1484
	(S5 + S7) = (S8) 406
Manual search:	
Yielded = 8, Excluded = 5, Included = 3	
Total:	
Yielded = 518, Excluded = 483, Duplicate removed = 105, Included = 37	

Data extraction

We used a standardised data extraction form to ensure uniformity and minimize observer's bias. The form which was entered electronically contained the name of author(s), year of publication, title, study design, quality assessment (JBI) score, study country (countries), the number of confirmed cases studied, the demographic, clinical presentations, and outcome.

Quality assessment

We used the Joanna Briggs Institute (JBI) tool, to appraise the quality of studies identified. We used a specific JBI tool type depending on the type of study, case report, case series, cross-sectional study, longitudinal (cohort) study.

Data synthesis and presentation

The author's name, year of publication, study title, study design, JBI appraisal score, total number of cases, patient characteristics, symptoms & signs, and the disease outcome are presented as Supplementary Material (Table SM).

In our systematic review, we observed significant variability in the reporting of clinical manifestations and outcomes of human mpox infection across the included studies. This heterogeneity was primarily qualitative, stemming from differences in study design, study population, and outcome measures. For example, in describing the location of lesions on the perineum, studies used the terminologies genital, anogenital, perianal, penile, scrotal, etc in describing the lesions located in the torso, authors reported the location to be trunk, abdomen, back, or those located in the upper limb as arm, forearm, upper limb, hands, palms, etc. In addition, apart from case reports and case series, there is potential double counting of epidemiological and clinical data reported. For example, Ogoina et al., (2020) provides a deeper analysis of a subset of data reported by Yinka-Ogunleye et al (2019) (Yinka-Ogunleye et al., 2019; Ogoina et al., 2020). Hence, we were not able to perform a *meta*-analysis.

Results

A total of 37 articles were identified for the final analysis. Detailed data extraction from each article is presented as Supplementary material.

Type, number and quality assessment of articles analysed

Of the 37 articles; 16 (43.2 %) were case reports, 13 (35.1 %) case series, 6 (16.2 %) retrospective cohort studies, and 2 (5.4 %) were cross-sectional studies.

The Joanna Briggs Institute (JBI) quality assessment tool showed a score of 8/8 for all 16 case reports. The score for most case series was 8/10 with a range from 5/10 to 10/10, the cohort studies scored between 8/11 and 11/11 while the two cross-sectional study articles scored 7/8. The high scores indicate that the articles included were overall of good quality.

Six (16.2 %) studies reported concerns about the infection prevention and control (IPC) practices in hospitals that mpox patients were admitted or managed. They either emphasized the need to improve the infection prevention and control (IPC) practices to prevent nosocomial infection and reduce health care worker exposures or reported the attitude of health care workers towards mpox patient due to fear of been infected (Yinka-Ogunleye et al., 2019; Anderson et al., 2003; Cunha, 2004).

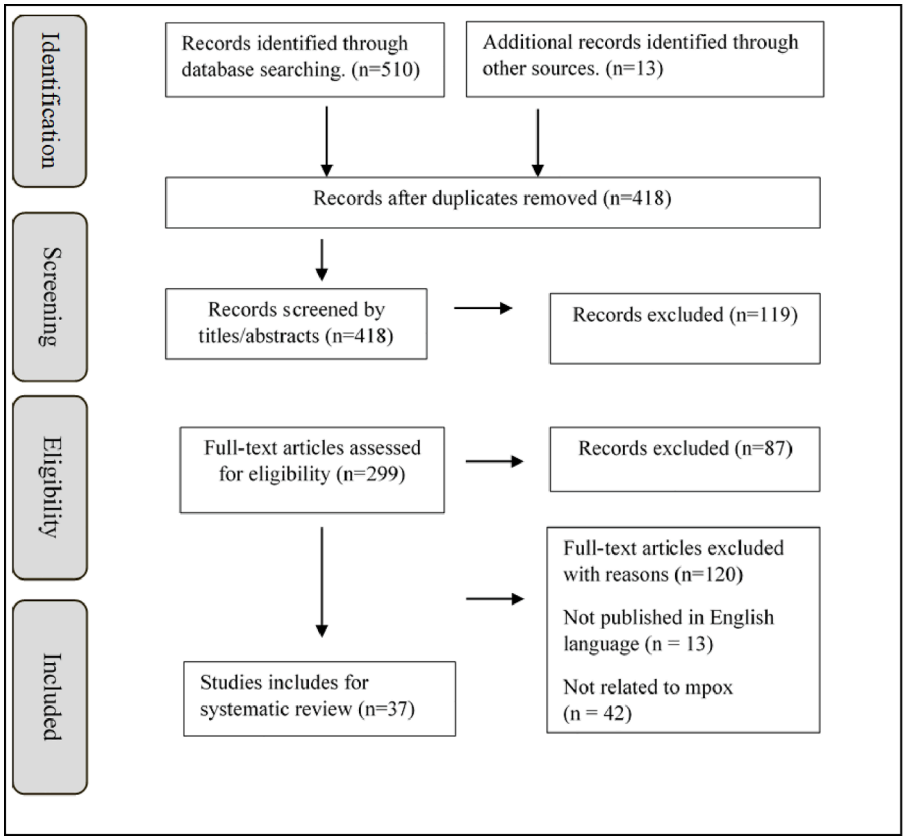


Fig. 1. The PRISMA flow chart.

Mode of transmission

The possible or definite mode of transmission of mpox disease leading to infection was documented in 31 (83.8 %) articles. The transmission was either zoonotic or secondary infection from the primary case resulting from close physical contact, mostly in the family environment. Nine studies from September 1970 to April 2022 reported an initial contact with animals (rodents, prairie dogs, or monkeys) then a secondary human to human transmission (Jezek et al., 1987; Yinka-Ogunleye et al., 2019; Anderson et al., 2003; Cunha, 2004; Ladnyj et al., 1972; Breman and Kalisa-Ruti, 1980; Meyer et al., 2002; Sejvar et al., 2004; Adler et al., 2022). While 18 studies documented the possibility of sexual transmission, or through close intimate contact mainly occurring during unprotected MSM penile/anal, or oral sex (Thornhill et al., 2022; Caria et al., 2022; Mitjà et al., 2023; Tarín-Vicente et al., 2022; Nörz et al., 2022; Minhaj et al., 2022 Jun 10; Pérez-Martín et al., 2022; Patel et al., 2022; Wong et al., 2022; María et al., 2023; Hussein et al., 2023; Núñez et al., 2023; Angelo et al., 2023; Mitchell et al., 2023; Patalon et al., 2023; Pérez et al., 2023; Sharma et al., 2023; Von Schreeb et al., 2023).

One study reported a possible transmission through injecting drug use (Caria et al., 2022).

Clinical manifestation and disease outcome

Prior to May 2022, the incubation period for mpox ranged from 10 to 14 days, with a prodrome of one to four days associated with fever, headache, generalised malaise, fatigue, and lymph node enlargement (Di Gennaro et al., 2022; Multi-country outbreak of mpox, External situation report. 13 October, 2024). The prodromal stage was typically followed by a characteristic maculopapular synchronous rash on the face, trunk, palm, and soles. Clinical features such as anogenital lesions, conjunctivitis, or neurological symptoms including encephalitis were seen exclusively in children under 10 years (Jezek et al., 1987).

From May 2022, studies demonstrated an attenuated incubation period of 7 to 10 days without the prodrome, and associated with non-specific symptoms of the disease notably with a different pattern of mucocutaneous lesions. Severe complications such as bronchopneumonia, encephalitis, epiglottitis, conjunctivitis, and proctitis were more common (Thornhill et al., 2022). Rectal symptoms were more commonly reported, symptoms such as rectal pain, rectal discharge, tenesmus, purulent discharge, and diarrhoea (Tarín-Vicente et al., 2022). In patients presenting with a mucocutaneous asynchronous rash, mostly presenting as multiple lesions, and with a predilection to the anogenital region, the lesions being larger and with a tendency to coalesce and/or ulcerate in patients with CD4 count $< 200/mm^3$ (Mitjà et al., 2023; Jang et al., 2023). A case of disseminated mpox disease was reported in a severely immunocompromised renal transplant patient (Attieh et al., 2023).

The occurrence of solitary lesions is documented in both periods, solitary lesions on the soles, palms or the genitals and differentiating co-infections with STIs, particularly syphilis chancre (Thornhill et al., 2022; Breman and Kalisa-Ruti, 1980; Patel et al., 2022).

Throughout, HIV status without immunosuppression has not been found to alter the clinical presentation nor to influence the outcome of disease particularly in patients with undetectable viral load (Thornhill et al., 2022; Caria et al., 2022).

Analysis of the disease outcomes

Three main outcome variables were chosen: treated as an outpatient, hospital admission, or death.

In most cases patients were treated as outpatients. However, hospitalization was reported in 31 (83.9 %) studies, 11 (29.7 %) studies before May 2022 and 20 (54.1 %) studies from May 2022 onwards. (We recognise that inpatient/outpatient management decisions may reflect

health system factors such as availability of resources, including the health workforce, and the infrastructure, rather than an indication of the severity of illness). Complications necessitating admission included epiglottitis, myocarditis, adrenal insufficiency, deep tissue abscess including perianal, proctitis, and groin abscesses, tonsillar abscess, myopericarditis and penile oedema. Death was reported in nine studies, six studies before May 2022, a total of 53 deaths (N = 638, CFR = 8.3 %) and three studies from May 2022 onwards, a total of 29 patients (N = 2324, CFR = 1.2 %), although one of the reported deaths was considered to be unrelated to mpox (Jezek et al., 1987; Yinka-Ogunleye et al., 2019; Mitjà et al., 2023; Ogoina et al., 2020; Ladnyj et al., 1972; Breman and Kalisa-Ruti, 1980; Meyer et al., 2002; Núñez et al., 2023; Mitchell et al., 2023).

Sadly, from May 2022 onwards, majority of deaths from mpox occurred among severely immunocompromised patients who were HIV+ ve (Mitjà et al., 2023).

Mental health disorders were reported in five studies (Yinka-Ogunleye et al., 2019; Caria et al., 2022; Mitjà et al., 2023; Adler et al., 2022; Sharma et al., 2023). Adler et al. (2022) reported on mood changes among patients with mpox (Adler et al., 2022); while Sharma et al. (2023) reported on altered mental state in patients with mpox following changes in the cerebral spinal fluid (CSF) chemistry (Sharma et al., 2023); and Mitja et al. (2023) reported serious neurological symptoms in 12 seriously immunocompromised patients CD4 < 200/mm^3 (Mitjà et al., 2023). Yinka-Ogunleye et al (2017) reported a case of suicide from the 2017 outbreak in Nigeria (Yinka-Ogunleye et al., 2019). The low reporting of the mental health status of patients with mpox might be due to comprehensiveness of the reporting tool rather than the absence of symptoms.

Two articles reported the occurrence of mpox in pregnancy. One of the studies documented that a spontaneous abortion at 26 weeks' gestation occurred (Yinka-Ogunleye et al., 2019); while the other mentioned it as a concomitant condition (Huhn et al., 2005). No detailed clinical information about the two women was reported.

Pooled data analysis

To enhance the visualization of the differences in the clinical manifestation between the two periods, we pooled data from studies with at least 10 cases. Nineteen (51.4 %) studies met this criteria, eight (21.6 %) studies before May 2022 (Jezek et al., 1987; Yinka-Ogunleye et al., 2019; Ogoina et al., 2020; Cunha, 2004; Jang et al., 2023; Meyer et al., 2002; Reed et al., 2004; Huhn et al., 2005) and 11 (29.7 %) studies from May 2022 onwards (Thornhill et al., 2022; Caria et al., 2022; Mitjà et al., 2023; Tarín-Vicente et al., 2022; Nörz et al., 2022; Minhaj et al., 2022 Jun 10; Patel et al., 2022; Núñez et al., 2023; Angelo et al., 2023; Von Schreeb et al., 2023; Prasad et al., 2023) from which we present a selection of data including the demographic variables, symptomatology and disease outcome using pie and bar charts.

It is important to note that although the studies identified for pooled analysis had a total of 2962 patients; 638 patients before May 2022, and 2324 patients from May 2022 onwards, there was marked heterogeneity in both the way data were captured and reported. Hence the data is reported in absolute numbers rather than proportions to depict the way data was captured and reported. Reporting the data as proportion(s) or ratios would be misleading as not all the numerator values would be part of the denominator for a particular variable.

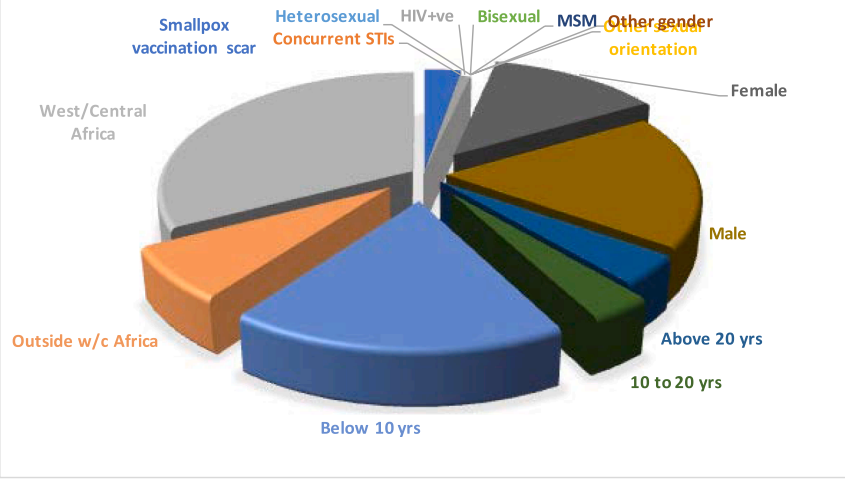
Sociodemographic characteristics (Pooled analysis)

We present a summary of data for selected variables in Fig. 2a and Fig. 2b below. Before May 2022, most mpox cases occurred in endemic countries located in west and central Africa, but from May 2022 onwards majority of cases occurred outside the endemic zone of west and central Africa. Similarly, before May 2022, majority of patients with mpox were below 10 years with males being affected slightly more than females. However, from May 2022 onwards patients who contracted mpox were almost exclusively males above 20 years, characteristically MSM with high-risk sexual behaviour, and majority were immunocompromised with HIV + ve with one or more concurrent STIs. Several studies reported that presence of smallpox vaccination scar was associated with some degree of protection from infection by mpox in both periods (Jezek et al., 1987; Bunge et al., 2022; Breman and Kalisa-Ruti, 1980; Huhn et al., 2005).

A comparison of mpox clinical manifestations before May 2022, and from May 2022 onwards is presented in Fig. 3 while Fig. 4 presents a detailed breakdown of the mucocutaneous lesion location (both from pooled data).

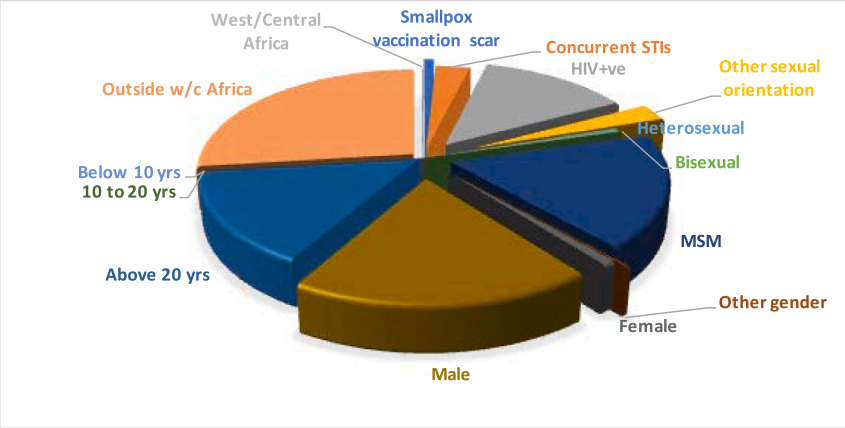
Mucocutaneous rash was the commonest presenting symptom followed by fever and lymphadenopathy in both periods. Notably from May 2022 onwards, some symptoms such as myalgia/arthralgia, oropharyngitis and proctitis were observed more often in patients with mpox.

More patients presented or developed severe disease with complications requiring hospitalization from May 2022 onwards, however the mortality rate (Case Fatality Rate) from the disease was higher before May 2022 (8.2 %) than from May 2022 onwards (7.1 %). We note that this comparison may not be equal for eaqual for several reasons including the difference in health system capacities and the difference in HIV-prevalence/therapy across the two periods.



MSM, men who have sex with men

Fig. 2a. Demographic characteristics of patients, september 1970 to april 2022 (n = 638).



MSM, men who have sex with men

Fig. 2b. Demographic characteristics of patients, May 2022 to December 2023 (N = 2324).

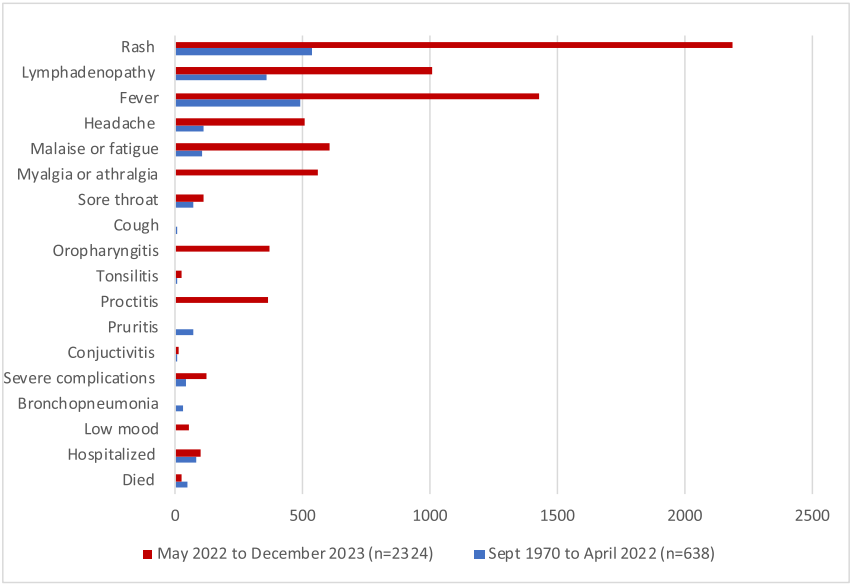


Fig. 3. Clinical manifestations and outcome of mpox before and after April 2022*.

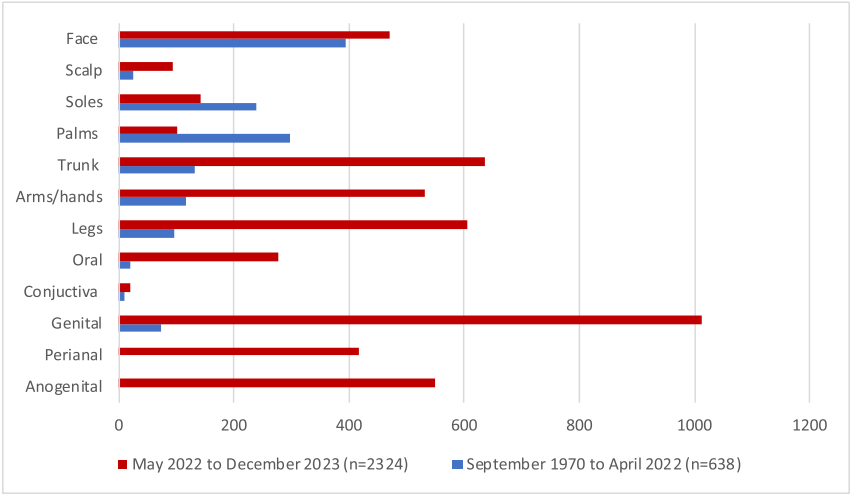


Fig. 4. Characteristics of rash in patients with mpox before and after April 2022* *Clinical manifestations reported in absolute numbers and not proportions due to heterogeneity in reporting.

Before May 2022, the commonest site for the mucocutaneous rash was the face, the soles, and palms. However, from May 2022 onwards the commonest site were the genitals, the trunk, upper and lower limbs, the anogenital and perianal regions.

Discussion

Mpox is a threat to public health globally, with more countries reporting the disease for the first time and the clade I severe form of disease diagnosed outside Africa. Concerted efforts are needed to sustain the gains achieved in controlling the outbreak, to protect frontline health workers and the members of the public at higher risk of the infection.

Sociodemographic characteristics

A clear distinction is seen in the age, gender, sexual orientation, and HIV status distribution in mpox cases before and after May 2022 (Fig. 2a and Fig. 2b). The demographic most affected before April 2022 was children below 10 years (Jezek et al., 1987; Breman and Kalisa-Ruti, 1980; Meyer et al., 2002). A systematic review by Bunge et al. (2022) revealed a change in the median age at presentation from 4 years in 1970s to 21 years in 2010s (Bunge et al., 2022). Our pooled data show a similar trend, with all patients who contracted mpox from May 2022 onwards being above 20 years.

Smallpox vaccination which provides cross protection against mpox has dwindled in many settings around the world including in west and central Africa where the disease is endemic (Liu et al., 2024). The observed lower smallpox vaccination rates and the immunosuppression caused by late-stage HIV disease may have a contribution to the emergence of recent outbreaks. Smallpox vaccination status (where reported) resulted in significantly fewer constitutional symptoms of fever and generalised malaise, fewer mucocutaneous lesions, and less severity and shorter duration of disease (Di Gennaro et al., 2022; Jezek et al., 1987 Aug; Breman and Kalisa-Ruti, 1980; Sejvar et al., 2004; Angelo et al., 2023).

The higher risk of mpox infection in males compared to females shown in both periods could be related to the difference in the exposure risk than inherent biological factors. However, the higher vulnerability among males is an area that warrants further investigation (Thornhill et al., 2022; Huhn et al., 2005; Liu et al., 2024).

HIV status did not show any difference in prevalence which concurs with previous studies (Caria et al., 2022). However, immunosuppression defined as CD4 count lower than 200/mm^3 and concomitant STIs was associated with a marked increase in mpox prevalence, severe complications, and death (Mitjà et al., 2023). A similar severe disease outcome was observed with mpox infection in an immunosuppressed patient after renal transplant who experienced disseminated mpox infection (Attieh et al., 2023).

From May 2022 onwards, the high prevalence of mpox among males is shown by the almost exclusive occurrence of mpox among MSM especially without barrier protection. The finding is corroborated by our pooled data (Fig. 2a and Fig. 2b). The close intimate contact, oral, and anogenital route from condomless sex have been established as possible transmission routes (Caria et al., 2022; Jang et al., 2023). The absence of mpox transmission through sexual contact in central and west Africa before April 2022 may reflect under reporting of cases among the MSM community, the lack of documentation, or possible misdiagnosis by health care staff as suggested by some researchers (Kuppalli et al., 2024 Nov; Liu et al., 2024). For example, case definition during the 2017–18 mpox outbreak in Nigeria specified physical contact as, *"Contact person: any person who has no symptoms but had been in physical contact with a suspected case or with body fluids (ie, skin secretions, oral secretions, urine, faeces, vomitus, or blood) of a case in the past 3 weeks"* The lack of specific instructions to ask about the patients' sexual orientation/behaviour, no mention of exposure to vaginal, or anorectal secretions would clearly translate to underreporting specific symptoms and signs (Yinka-Ogunleye et al., 2019).

Similarly, the lack of the variables in the case assessment form and case report form may have led to this information being missed as majority of cases 84 (69 %) were males. Prasad et al. (2023) notes that establishing MSM history could prove a challenge in settings where same-sex relationships are stigmatised and criminalised like in Nigeria. Stigmatization and discrimination of minority groups in the population hinders the effectiveness of mpox preventative and control measures (Mitchell et al., 2023). A high degree of clinical acumen among healthcare professionals especially those working in STI clinics and using a diagnostic tool with specific mpox screening questions could help improve the diagnosis. Such a practice needs to be embedded in with the existing service in mpox endemic areas, cognizant of the social-cultural barriers to implementation in some countries.

Mode of transmission

Before May 2022, mpox was primarily a zoonotic infection with secondary human to human transmission although the knowledge regarding its mode of transmission keeps evolving (World Health Organization. Mpox. Who.int. World Health Organization: WHO;, 2024; Kuppalli et al., 2024). The earliest documented reports revealed a primary infection from animals (prairie dogs, monkeys, or other rodents) then a secondary human to human infection in a cluster of closed contacts (Jezek et al., 1987; Yinka-Ogunleye et al., 2019; Anderson et al., 2003; Cunha, 2004; Ladnyj et al., 1972; Breman and Kalisa-Ruti, 1980; Meyer et al., 2002; Sejvar et al., 2004). However, to date, no primary host has been identified.

From May 2022 onwards, more cases of human-to-human transmission have been documented (Kuppalli et al., 2024 Nov). The findings corroborate with studies done during this period. Thornhill et al. (2022) point out that even among the MSM, intimate body contact is probably the most important route rather than the sexual transmission route (Thornhill et al., 2022). A higher viral load yield from skin lesions than oral, nasal, or rectal swabs indicates skin-to-skin contact as the predominant route of human-to-human transmission of the virus (Di Gennaro et al., 2022; Thornhill et al., 2022; Caria et al., 2022).

Jang et al. (2023) and Adler et al. (2022) suggest the possibility of sexual transmission via primary genital, anal, and perianal lesions in patients with high-risk sexual contact (Adler et al., 2022; Jang et al., 2023). The isolation of mpox in semen strengthens the argument (Peiró-Mestres et al., 2022). CDC asserts that close intimate or sexual contact with mpox lesions on the skin or mucosal surfaces, such as the throat, anus, or rectum, of an infected person accounted for most of the transmission for the May 2022 outbreak (Mitchell et al., 2023). As discussed above, cases of sexual or intimate contact transmission before May 2022 may have been significantly few and were missed in the examination, testing, and/reporting. However, identifying such cases would have provided further insights in the disease epidemiology, including how sporadic cases were identified in non-endemic countries such as the UK and USA through travel from endemic areas.

Occasional mpox transmission have been documented to healthcare workers through needle prick or other sharp object injuries posing an occupational hazard. Transmission through skin piercing and tattooing have also been reported. In one incident a patient presented with the characteristic mpox lesions at a venepuncture site from intravenous drug needle-sharing (Caria et al., 2022). The public health implication of this finding warrants further investigation.

The shift in the mode of transmission from a zoonotic route to a human–human (Mpox., 2024; Jezek et al., 1987 Aug; Bunge et al., 2022; Kuppalli et al., 2024 Nov; CDC., 2023) transmission needs urgent, targeted, and sustained attention, not only in the developed country settings where most of the May 2022 outbreak occurred, but in west and central Africa as well where the disease is endemic. Such informed attention would help characterise better the mode and pattern of disease

transmission and strengthen its control measures especially in countries that have reported mpox cases for the first time (Kuppalli et al., 2024 Nov). The development should inform the assessment and reporting tools, healthcare safety – particularly those working in high-risk areas such as STI clinics, infection prevention and control (IPC) training and practice and should influence public messaging.

Clinical manifestation and disease outcome

The clinical symptoms before May 2022 were severe in infants with a high CFR, particularly in neonates (Jezek et al., 1987; Cunha, 2004; Sejvar et al., 2004; Huhn et al., 2005). One of the possible reasons for the comparatively low mpox CFR from May 2022 onwards could be that majority of cases occurred among young males living is high income countries with modern and efficient healthcare systems. Also, the heightened advocacy on mpox including major news channel coverage, may have resulted in early health seeking reducing the severity of the disease morbidity at presentation.

In immunocompetent individuals, the mpox constitutional features including mucocutaneous rash, fever, lymphadenopathy, headache, and generalized malaise were common before or after May 2022. However, certain symptoms such as pruritis, bronchopneumonia, and cough were commonly reported symptoms before May 2022, whereas myalgia/arthralgia, oropharyngitis, proctitis, and depression/anxiety were typical mpox symptoms from May 2022 onwards (Fig. 3) (Jezek et al., 1987; Thornhill et al., 2022; Caria et al., 2022; Tarín-Vicente et al., 2022; Nörz et al., 2022; Anderson et al., 2003; Cunha, 2004; Breman and Kalisa-Ruti, 1980; Sejvar et al., 2004; Minhaj et al., 2022; Pérez-Martín et al., 2022; Patel et al., 2022; Huhn et al., 2005).

A notable change in the clinical profile of mpox among immunosuppressed patients was observed. The classical prodrome features such as fever, headache, malaise/myalgia, and lymphadenopathy no longer precede the occurrence of rash. In addition, immunosuppressed patients presented with significantly more and larger mucocutaneous lesions that sometimes coalesced to form ulcers (Mitjà et al., 2023; Ogoina et al., 2020). The observation of asynchronous rash in immunosuppressed individuals could also be an indication of the altered immune response to the rash. In support of the findings from primary studies our pooled data show that severe complications such as respiratory, pericarditis, myocarditis, ophthalmological, adrenal insufficiency, and neurological symptoms were more common among the immunocompromised patients providing evidence of the key role cell-mediated immunity play in the fight against mpox infection (Thornhill et al., 2022; Caria et al., 2022; Nörz et al., 2022; Pérez-Martín et al., 2022; Patel et al., 2022; Liu et al., 2024; Mohammed and Zaki, 2023).

Dermatological presentations in the form of rash on the skin or mucous membrane in various parts of the body is a unanimous feature in mpox disease in both periods (Fig. 4). However, the type of rash (macules, papules or, vesicles), the distribution, the number of lesions, the progression to crusting and healing was distinct before May 2022. During this period, areas with the highest percentage of skin rashes were the face, trunk, arms, legs, palms, soles, lips and rare on the genitalia, scalp, and eyes. The rash was mostly centrifugal and synchronous, and the lesions rarely coalesced to form ulcers (Jezek et al., 1987; Yinka-Ogunleye et al., 2019; Ogoina et al., 2020; Huhn et al., 2005).

From May 2022, apart from the face, trunk and limbs, the rash is characteristically located in the anogenital or anorectal regions (penile, scrotum, anus, rectum), with oral, perioral, oropharyngeal, epiglottis and conjunctiva commonly involved with resultant complications of proctitis, tonsillitis, epiglottitis, pharyngitis, rectal pain, perianal and tonsillar abscesses (Thornhill et al., 2022; Caria et al., 2022; Tarín-Vicente et al., 2022; Nörz et al., 2022; Minhaj et al., 2022 Jun 10; Pérez-Martín et al., 2022; Patel et al., 2022; Wong et al., 2022; María et al., 2023; Hussein et al., 2023; Núñez et al., 2023; Angelo et al., 2023; Mitchell et al., 2023; Patalon et al., 2023; Pérez et al., 2023; Sharma et al., 2023; Von Schreeb et al., 2023; Jang et al., 2023; Attieh et al., 2023; Prasad et al., 2023; Mohammed and Zaki, 2023). It is important to note that the lack of standardised reporting of the location and characteristics of the dermatological lesions is a key impediment to making comparison and makes *meta*-analysis challenging (Prasad et al., 2023).

Ophthalmic presentations reported before May 2022 were mostly conjunctivitis and blepharitis (Reed et al., 2004), while from May 2022 onwards, more ophthalmic complications have been reported including photophobia, keratitis, and periorbital cellulitis/oedema, corneal lesion causing unilateral blindness, eyelash vesicles, and eye discharge (Caria et al., 2022; Ogoina et al., 2020).

Before May 2022, neurological features such as encephalitis were a rare complication of mpox (Jezek et al., 1987). However, from May 2022 onwards, more neurological, and mental health manifestations have been reported including confusion/altered mental state, seizures, facial palsy, anxiety and depression. Some researchers reported myalgia, headache, fatigue, confusion, and encephalitis as neurological findings (Badenoch et al., 2022; Patalon et al., 2023), again highlighting the importance of a standardised reporting for a more meaningful comparison.

Patalon et al. (2023) suggests the reason mental health problems are not reported among patients with mpox, particularly the MSM who constitute the majority in the May 2022 outbreak could be due to the lack of awareness among healthcare staff and the lack of mental health focus in the assessment and reporting forms rather than a low prevalence of the conditions (Patalon et al., 2023). We add that, the same reason could explain why mental health problems associated with endemic mpox was not reported in central/west Africa, and the USA during mpox outbreaks before April 2022 (Jezek et al., 1987; Yinka-Ogunleye et al., 2019; Breman and Kalisa-Ruti, 1980; Reed et al., 2004; Huhn et al., 2005).

Co-infection with HIV and other STIs such as syphilis, gonorrhoea, condylomata acuminata, chanroid and chlamydia was a common finding in the May 2022 outbreak especially among MSM. Numerous studies have shown that patients with immune deficiencies, particularly those with late-stage HIV infection, often present with atypical clinical features of mpox. Our pooled data corroborate this finding. These patients will commonly have another active STI(s) which would cause diagnostic delays, increasing the risk of severe disease, and the risk of mpox exposure to close contacts or healthcare staff (Caria et al., 2022; Tarín-Vicente et al., 2022; Minhaj et al., 2022 Jun 10; Wong et al., 2022; Núñez et al., 2023; Jang et al., 2023).

Since its discovery in 1970, pox infection is frequently a self-limiting disease with a low potential to sustain human-to-human transmission, and supportive care is typically used to treat systemic involvement. This is in keeping with the findings in this review as majority of patients both before May 2022 and from May 2022 onwards were managed on outpatient basis, although outpatient/inpatient management options may have been based on available resources than a marker of disease severity. Our study indicated a CFR of 8.3 % before May 2022, and 1.2 % from May 2022 onwards which is in agreement with a global CFR report of 8.7 % from a cumulative 1970 to 2019 data. (Bunge et al., 2022).

Use of standardized forms for data collection

Use of standardized reporting forms such as Case Reporting Form (CRF) and Case Investigation Form (CIF) is imperative in epidemiological and clinical studies including clinical trials. Of the 37 studies we included in the review, only 11 studies (29.7 %) used the standard WHO assessment and reporting forms (Yinka-Ogunleye et al., 2019; Thornhill et al., 2022; Mitjà et al., 2023; Tarín-Vicente et al., 2022; Ogoina et al., 2020; Sejvar et al., 2004; Patel et al., 2022; Núñez et al., 2023; Von Schreeb et al., 2023; Huhn et al., 2005 Dec 15; Prasad et al., 2023). This is a major weakness in mpox research. A disease which was first identified more than half a century ago should have well-developed structured tools to enable a standardized epidemiological and clinical assessment and reporting. It is also important to highlight that although

the current assessment and reporting forms from various international and national health authorities have undergone several revisions, they still need further development to become comprehensive. The current WHO mpox CRF does not include mental health assessment (WHO, 2023) and in one study using UKHSA case definition missed 27 (13.7 %) of mpox cases (Patel et al., 2022).

Public health implications

The higher prevalence of mpox among MSM with high-risk sexual behaviour, and the observed sexual transmission among both heterosexual and MSM route in central and east Africa has changed the approach to the disease prevention and control strategies (Kuppalli et al., 2024; CDC., 2023; Liu et al., 2024). The close link between the May 2022 mpox outbreak and HIV/STIs co-infection and immunosuppression means that public messaging regarding STIs needs to be reviewed and aspects relating to STIs detection strengthened.

The change in the clinical manifestations requires a review of the screening tools, physical examination, diagnosis (including laboratory findings), and treatment. Newer symptoms and signs including rectal pain, proctitis, penile oedema, epiglottitis, pharyngitis, neurological symptoms, and mental health conditions should be considered when revising mpox management guidelines (Tarín-Vicente et al., 2022; Patel et al., 2022). The clinicians should suspect mpox, when individuals with high-risk sexual behaviours present with lesions around the anogenital and oral regions with history of recent sexual activities with those manifesting or yet to manifest the typical mpox rash.

Suggested considerations for protecting individuals at a higher risk of infection include adding mpox screening as routine in STI clinics, offering mpox Prep in tandem with HIV Prep among MSM with high-risk sexual behaviour and availing antiviral treatment such as tecovirimat. MSM with high-risk sexual behaviour could also be offered vaccines against mpox such as JYNNEOS and ACAM2000. These vaccines could also be offered to healthcare staff working in high-risk areas e.g. STI clinics, emergency departments, or at GPs – an intervention happening in several locations including some clinics in Denmark and the USA (Angelo et al., 2023; Mitchell et al., 2023; Von Schreeb et al., 2023). Occupational safety to healthcare staff e.g. PPEs fit for the purpose, needs to be strengthened. IPC guidelines need to be fit for purpose and regular healthcare staff training is needed (Anderson et al., 2003; Cunha, 2004).

Strengths and limitations

Our study involved a thorough global search on mpox articles for a period of 52 years spanning from the first reported case in September 1970 to December 13th 2023 in more than 40 relevant sources including grey literature from the endemic countries, the WHO and CDC. In addition, we have included information from the ongoing 2024 mpox outbreak. Two researchers scrutinized the eligibility for inclusion, and the use of JBI quality appraisal tools adds to the reliability of our findings. The possibility of double counting or data omissions, especially in endemic areas as the scientific community and international organisations may have given more attention to the outbreak in Europe and other developed nations from May 2022 onwards. The lack of standardize tools for assessment and reporting may have affected the internal validity, however we only pooled together variables with unambiguous similarity.

Conclusion and recommendations

The emergence and rapid spread of mpox presents ongoing public health challenges in already under resourced settings, and an added burden of disease globally. The diagnosis of clade I disease outside Africa in August 2024 is concerning. The May 2022 mpox outbreak showed distinct clinical manifestations and disease outcome compared to before May 2022. The evolving mpox epidemiology, mode of transmission and clinical manifestation, is evident – from a mild, zoonotic, self-limiting disease, with infants most at risk of severe disease and death before May 2022, to a human-to-human transmissible disease in which the immunosuppressed individuals are at higher risk of severe complications and death. There is need to reorganise provision of healthcare, demystify the stigma to allow early health seeking particularly in settings where same-sex relations are criminalised.

It is important to urgently standardise the case definition, the assessment and reporting forms to ensure uniform reporting which will not only lead to effective country and international monitoring but will also help to improve the clinical acumen, identify and treat comobidity including mental health conditions, provide vaccination and/or pre to healthcare staff and individuals most at risk, and inform diagnostic algorithms to allow early diagnosis and effective management, prevention and control.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinpr.2024.100397.

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