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MONKEYPOX: A SYSTEMATIC REVIEW OF EPIDEMIOLOGY, PATHOGENESIS, MANIFESTATIONS, AND OUTCOMES

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Abstract. *Introduction*. Since May 2022, an unusually large number of new monkeypox infections-a previously rare viral zoonotic disease, mainly reported from central and western Africa has been reported globally, and the World Health Organization (WHO) declared a global health emergency in July 2022. We aimed to systematically review the monkeypox virus epidemiology, pathogenesis, transmission, presentations, and outcomes. *Materials and methods*. Our aim is to systematically review the epidemiology, pathogenesis, manifestations, and outcomes of Monkeypox disease. We searched the keywords in the online databases of PubMed, Embase, Scopus, and Web of Science and investigated all English articles until December 2022. In order to ascertain the findings, this study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. In order to optimize the quality, this review study benefits from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. To minimize any probable bias risk, we utilized the Newcastle-Ottawa Scale (NOS) risk assessment tool. *Results*. The most prevalent symptoms were rash and fever. The infection was accompanied by different complications such as, but not limited to, encephalitis (mainly in children), septicemia, bacterial cellulitis, retropharyngeal and parapharyngeal abscesses, etc. A wide range of hospitalization from 3.7% to 100% has been reported. The mortality rate ranged from 0% to 23%, which mainly occurred in infants and children. High mortality of the monkeypox rate was reported among pregnant women. The mortality rate of monkeypox is lower among women and those who received the smallpox vaccine compared to men and those

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who did not receive the vaccine. A wide range of the overall second-rate attack was reported, which is more pronounced in unvaccinated patients. *Conclusion*. In our systematic review of 35 studies on monkeypox, we cast light on the existing evidence on its epidemiology, pathogenesis, manifestation, and outcomes. Further studies are needed to elucidate the natural history of the disease in various patients' population, as well as detailing the monkeypox attack rate.

Key words: *monkeypox, monkeypox virus, monkeypox infections, epidemiology, pathogenesis, manifestations.*

ОСПА ОБЕЗЬЯН: СИСТЕМАТИЧЕСКИЙ ОБЗОР ЭПИДЕМИОЛОГИИ, ПАТОГЕНЕЗА, ПРОЯВЛЕНИЙ И ИСХОДОВ

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Резюме. *Введение.* С мая 2022 г. во всем мире было зарегистрировано необычно большое количество новых случаев заражения оспой обезьян — ранее редкой вирусной зоонозной болезнью, в основном зарегистрированной в Центральной и Западной Африке, а в июле 2022 г. Всемирная организация здравоохранения (ВОЗ) объявила глобальную чрезвычайную ситуацию. Целью настоящей работы было проведение систематическое анализа эпидемиологии, патогенеза, передачи, проявлений и исходов оспы обезьян. *Материалы и методы.* Был проведен поиск по ключевым словам в онлайн-базах данных PubMed, Embase, Scopus и Web of Science и изучены все статьи на английском языке, опубликованные до декабря 2022 г. В целях оптимизации качества использовался контрольный список «Предпочтительные элементы отчетности для систематических обзоров и метаанализов» (PRISMA). Для минимизации потенциального риска систематических ошибок мы использовали оценку риска по шкале Ньюкасла–Оттавы (NOS). *Результаты.* Наиболее распространенными симптомами были сыпь и лихорадка. Инфекция сопровождалась различными осложнениями, среди прочего представленными энцефалитом (преимущественно у детей), септицемией, бактериальным целлюлитом, заглоточными и парафарингеальными абсцессами и др. Были госпитализированы от 3,7 до 100% больных. Уровень смертности колебался от 0 до 23%, преимущественно среди младенцев и детей. Отмечена высокая смертность от оспы обезьян среди беременных женщин. Уровень смертности среди женщин и тех, кто получил вакцину от оспы, был ниже по сравнению с мужчинами и невакцинированными лицами. Зафиксирован широкий диапазон вторичных случаев инфекции, которая более выражена у непривитых пациентов. *Заключение.* В настоящем систематическом обзоре проанализированы 35 исследований оспы обезьян, позволивших пролить свет на имеющиеся данные о ее эпидемиологии, патогенезе, проявлениях и исходах. Необходимы дальнейшие исследования для выяснения естественного течения заболевания у различных групп пациентов, а также детализации частоты заражения оспой обезьян.

Ключевые слова: *оспа обезьян, вирус оспы обезьян, инфекции, вызванные оспой обезьян, эпидемиология, патогенез, проявления.*

Introduction

Monkeypox virus — an enveloped double-stranded DNA virus with linear genome, from the *Orthopoxvirus* genus of the *Poxviridae* family — was first discovered in 1958 in Denmark after two outbreaks of rash disease occurred among monkeys that were kept for research purposes [52]. The first known human infection was diagnosed in the Democratic Republic of the Congo (DRC) in 1970 amid the latest phase of intense smallpox eradication programs in Africa [32]. Despite its nomenclature as "monkeypox", the primary source is unknown and rodents or non-human primates-including monkeys-are mainly considered the possible source for the spread of the disease [8, 54]. Monkeypox was primarily known as a rare zoonotic disease specifically reported from forested regions of central and western Africa, with almost all cases spreading from animals to humans. Since its acknowledgment as a human pathogen, in the twentieth century confirmed cases of the disease have been reported in 11 African countries, and later, some self-restrictive human outbreaks occurred inside and outside Africa as follows; The Republic

of Congo in 2003 (6 cases), the US in 2003 (70 cases), South Sudan in 2005 (9 cases), Nigeria in 2017 (200 cases) [16, 30, 41, 55] but approximately all diagnosed cases outside Africa reported a travel history or a close link to this continent.

Additionally, according to the World Health Organization (WHO) reports in the first two decades of the 21st century the quantity of monkeypox suspected patients was estimated to be approximately 18 000 cases in DRC, and between 2020 to May 2022 around 10 545 possible cases and 362 associated mortalities have occurred in DRC [57]. The most common transmission mode was via physical contact with an infected animal's body fluids, cutaneous or mucosal lesions, respiratory aerosol droplets, and even their meat or corpse [56]. In addition, human-human infection can also occur via respiratory secretions, cutaneous lesions, or contaminated objects [33, 55].

Since May 2022 — in the absence of travel histories or direct links to the endemic countries — an unusual large quantity of monkeypox new cases has been reported, and unfortunately, due to the ascending numbers of new cases WHO declared a global health emergency on July 23 2022. According to the WHO report on August 10 2022, 27 814 laboratory-confirmed cases of monkeypox and 11 deaths have been reported in 89 countries/territories/areas [56]. Confirmed cases were from all six WHO regions as follows; 375 cases and 7 deaths in Africa, 10 815 cases and 1 death in region of the Americas, 31 cases and no deaths in Eastern Mediterranean Region, 16 495 new cases and 2 deaths in European region, 13 cases and 1 death in South-East Asia Region, and 85 cases and no deaths in Western Pacific Region [56]. Of the aforementioned cases that had available data (73%), interestingly, 99% (16 839/17 052) are males, with a median age of 36 years. Monkeypox, affects males between the age of 18 to 44 cases disproportionately, as they account of 77% of cases, and less than 1% (98/17 426) of cases were between 0–17 years [56]. With known sexual orientation, 60% (1214/2025) identified themselves as gay, bisexual and other men who have sex with men. In addition, in cases with known HIV status, 39% (3204/8234) were HIV positive. Also, among the reported cases, 33% (7741/23 290) had available information on sexual orientation, and of these, 97% (7541/7741) identified themselves as gay, bisexual, and other men who have sex with men. In addition, among cases with available information, 91% (4856/5315) of patients reported transmission through sexual contacts [56]. This has risen, worldwide concerns about possible alterations in the disease's mode of transmission and virulence [55].

Monkeypox can cause a spectrum of pox-like signs and symptoms with a milder fashion, a better prognosis, and rare mortalities. The most common signs and symptoms were described as generalized myalgia, headache, fatigue, back pain, and lymphadenopathy followed by a generalized centrifugal rash, which could occur on the face (in 95% of cases), palms, and soles (in 75% of cases), eyes (in 20% of cases), mouth and throat mucous membranes (in 70% of cases), groin, and genitals (in 30% of cases) — that takes 2–4 weeks to resolve without any critical intervention [9]. In this outbreak, widespread rash, fever, and genital rash have been reported in 81%, 50%, and 41% of cases respectively [55].

In regards to the prognosis of the current outbreak as of the beginning of 2022, 73 mortalities have been reported in Africa (endemic region), while 11 deaths have occurred among 27 814 cases reported by WHO on August 10, 2022 [56]. Due to its unusually rapid spread, which could be due to the waning efficacy of smallpox vaccinations worldwide, and the declared global health emergency, this virus has provoked global concerns amid the catastrophic ongoing COVID-19 pandemic, and people are afraid to fall into another disastrous high-burden pandemic. Therefore, we aimed to systematically review the currently available literature on the monkeypox virus, and shed light on changes in its epidemiology, pathogenesis, transmission, presentations, and outcomes.

Materials and methods

The mission of this comprehensive study is to systematically review current literature pertaining to monkeypox disease in terms of epidemiology, pathogenesis, manifestations, and outcomes. In order to ascertain the findings, this study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Data sources. Online databases of PubMed, Embase, Scopus, and Web of Science were considered as sources of data. We browsed the keywords in these databases and inquired all English literature up to December, 2022. The following is a prototype of search strategy we applied in PubMed by using Medical Subject Headings (MeSH). Search strategy of other resources is included in Supplemental material 1. The acronyms "ti" and "ab" stand for "title" and "abstract" respectively.

Study selection. We selected the literature in two steps. First, a group of five researchers screened and initially selected the studies based on pertinence of titles and abstracts. At the next step, seven researchers got through the full texts of these primarily selected studies. The fitting publications fulfilling the eligibility criteria of the study were opted in to advance to the next steps.

Being original, written in English language, peer reviewed prior to acceptance for publication were considered items of inclusion criteria for this study.

Studies in progress but without published data, non-human studies, duplicated publications, review papers, abstracts without available full texts, conference abstracts, editorial letters, case reports, and case series were excluded from our study.

Data extraction. Once the second step of selection process finalized and appropriate publications were included seven researchers explored the full texts and extracted the requisites for our study. These requisites consisted of first author's ID (reference), year and country of publication, type of studies, study population, gender and mean age of population, prevalence of disease, type and route of diagnostic testing, observed signs and symptoms, mortality rate, and summary of findings. Table 1 shows this data. To avoid any remaining duplications and overlaps the finally selected publications and extraction were checked out by other team members.

Quality and risk of bias assessment. In order to optimize the quality, this review study benefits from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. To minimize any probable bias risk, we utilized the Newcastle–Ottawa Scale (NOS) risk assessment tool (Table 2). Worthy to mention that a total score of nine in three categories is calculated in this numerical bias assessment tool. These three categories include selection, comparability, and exposure/outcome. Numerical values of four, two, and three are attributed to these categories respectively.

Results

In the present review, the initial search identified a total of 5010 potential papers; after duplicates were removed, 2133 articles remained, and the titles and abstracts were reviewed for inclusion, leading to retrieval of 593 papers for assessment. An additional of 514 papers was excluded in the full-text screening stage, leaving a final pool of 79 papers that met inclusion criteria for the final review. Ultimately, after full-text papers were evaluated for selection criteria, 31 studies were included in our systematic review (Fig.).

The included studies were performed mostly in Democratic Republic of the Congo (DRC) (n = 11), followed by the USA (n = 5), Zaire (n = 4), Nigeria (n = 3), Liberia (n = 1), Sierra Leone (n = 1), UK (n = 2), Central African Republic (n =1), Portugal (n = 1), Sudan (n = 1), and Spain (n = 1). Review of these studies revealed that rash, fever, chills, nausea, lymphadenopathy, mouth ulcer, sore throat, headache, pruritis, fatigue, sensitivity to light, and malaise are the most common symptoms of human monkeypox. The most prevalent symptoms are rash (ranging from 31% to 100%) and fever (ranging from 43% to 100%). The diagnosis was made using different assays, including PCR (mostly used), IHC, ELISA, culture, electron microscopy, western blot, hemagglutination-inhibition assay, radioimmunoassay (RIA), and the RIA adsorption.

The rate of hospitalization varied between 3.7% and 100%. A number of complications following the infection were reported including, but not limited to, encephalitis (mostly in children), septicaemia, bacterial cellulitis, retropharyngeal and parapharyngeal abscess, mouth ulcers, corneal scar, keratitis, unilateral conjunctivitis, bronchopneumonia, and pulmonary distress.

The mortality rate was between 0% and 23%. Jezek et al. observed no deaths in vaccinated group and 27 (11%) deaths among 250 unvaccinated patients. All deaths happened in patients aged between three months and eight years. The case-fatality rate was twice in patients aged 0–4 years compared to patients aged 5–9 years. The majority of deaths (55%) was occurred during the second week of the disease [27]. Pittman et al. reported the mortality rate of 80% (4 out of 5) among pregnant women [40].

The incidence rate of the infection was lower among women compared to men. Moreover, the incidence rate of the infection was lower among those who received the smallpox vaccine compared to those who did not receive the vaccine [53]. Several studies have investigated the attack rate of the virus. Jezek et al. evaluated second attack rate among 245 patients infected from an animal source. The overall second attack rate was 3%, which was more prominent in unvaccinated household contants and those aged 0–4 years [25]. In another study, Jezek et al., found the attack rate of 7.2% and 0.9% for unvaccinated and vaccinated patients, respectively [26]. However, later, a study showed a much higher household attack rate (50%) [34].

Discussion

The rapid increase of monkeypox cases around the globe forced the World Health Organization (WHO) to declare it an outbreak to Immerse prompt attention toward this matter [19]. This rapid spreading demands preparation and collaboration at different levels, such as diagnosis, therapeutic, and preventive care to avoid another potential pandemic's emergence [31]. Herein, we tracked the course monkeypox since its discovery to deliver a picture of its pattern over time.

Epidemiology. Since the first discovery of monkeypox infection in humans in 1970, concerns have never been more profound, as it was particularly recognized to be endemic to West and central African countries [42]. and contrary to the current outbreak, monkeypox was rarely observed outside the African continent [50]. As of December 7, 110 countries have confirmed monkeypox infection, accounting for more than 82 000 diagnosed cases. Almost 99% of incidents occurred in locations with no history of reported monkeypox [13].

The incidence of monkeypox infection was significantly higher among men than women in our review. This is aligned with other studies: Bunge et al. evaluated that the presentation of monkeypox is 50 folds higher in males than females in most outbreaks in Africa and outside [6]. A systematic review by Beer et al. has also represented that 18 of 26 stud-

Table 1. Description of the findings reported in eligible studies

ID	Author (reference)	Year and country	Population	Gender	Mean age	Prevalence	Type and route of the test (for diagnosis)	Signs and symptoms n (%)												Complications	Mortality rate (%)	Other findings
								Rash	Fever	Nausea	Lymphadenopathy	Chills	Mouth ulcers	Sore throat	Headache	Pruritis	Fatigue	Sensitivity to light	Malaise	Other signs and symptoms			
1	CDC [9]	1997 DRC	419 total cases That 344 cases had available data	55% male	Cases younger than 16 years of age composed 85% of the total cases	*	Fever, and a vesicular-pustular rash similar to a WHO reference photograph	31	98	–	69	–	50	63	–	–	–	–	–	11 diarrhea 41 cough	54% of the cases were incapacitated for more than 3 days	1.5	20 of the 344 cases (6%) had scar evidence of vaccinia vaccination and 19 reported a past history of chickenpox. 5 cases died (case-fatality rate 1.5%) within 3 weeks of rash onset and they ranged in age from 4 to 8 years. Two cases were found with corneal opacities and 6 with alopecia
2	CDC [11]	2003 USA	53 cases	49% male	Median = 26 (4–56) Data not available for 14 cases	*	PCR, IHC	83	73	20	47	37	–	33	33	–	–	–	–	Respiratory symptoms 64	26% of total have been hospitalized, including a child aged < 10 years with encephalitis		Primary route of transmission is from close contact with infected mammalian pets, but the possibility of human-to-human transmission cannot be excluded
3	CDC [12]	July 8 2003 USA	71 cases	45% male	Median = 28 (1–51)	*	32 of 35 (91%) tested positive for monkeypox PCR, culture, IHC, and/or electron microscopy	–	–	–	–	–	–	–	–	–	–	–	–		26% were hospitalized; two patients, both children, had serious clinical illness (1–4); both have recovered	–	The median incubation period was 12 days (range: 1–31 days). 30 persons got vaccinated by smallpox vaccine(7 pre-exposure and 23 post-exposure) three (10%) reported rash within 2 weeks of vaccination. Only one was confirmed having monkeypox. All patients reported having contact with sick pet prairie dogs
4	Reed K.D. [41]	2004 USA	11 cases	45% male	range 3–43	*	3 suspected; 8 Laboratory-Confirmed; The culture was + in 7 patient; Pcr in 6 patient; EM in 3 patients and 1 patient only was diagnose by IHC	100	82	9	55	82	100	55	100	–	–	–	18	Sweat (82), persistent cough (73), pharyngitis (27), tonsillar hypertrophy (18), mild chest tightness	Four patients were hospitalized	0	6 (54%) had got the smallpox vaccine. In all cases, transmission was by direct contact with an infected prairie dog, however, possibility of person to person transmission can not be excluded. Incubation period have ranged from 4 to 24 days (median 15; mean 14.5)

Table 1. Description of the findings reported in eligible studies (continued)

ID	Author (reference)	Year and country	Population	Gender	Mean age	Prevalence	Type and route of the test (for diagnosis)	Signs and symptoms n (%)												Complications	Mortality rate (%)	Other findings
								Rash	Fever	Nausea	Lymphadenopathy	Chills	Mouth ulcers	Sore throat	Headache	Pruritis	Fatigue	Sensitivity to light	Malaise	Other signs and symptoms			
5	Nolen L.D. [35]	2016 DRC	104 cases, 63 during the focused investigation period (July–December 2013)	57.1% male	15.5 (4m–68y) Median = 10	*	50 (48.1%) laboratory-confirmed PCR	57.7	–	–	–	–	–	–	–	–	–	–	–	–	9.6	The median of household attack rate was 50%; mean was 52.1% (range 50–100%). The incubation period was 5–13 day for the central 75% of cases
6	Adler H. [1]	2022 UK	11 cases	57% male	6 cases 30–40 and one under 2 yrs	*	PCR	100	43	0	45.5	–	0	18	–	–	–	–	–	–	All got hospitalized but full recovered. Mood disturbance, acute alcohol withdrawal, severe neuralgia, abscese, unilateral conjunctivitis	0	4 patients acquired virus outside of the UK, in Nigeria. None of the patients got smallpox vaccine
7	Breman J.G. [5]	1980	47	55% male	Mean = 8 Median = 4 83% < 10 55% < 5	*	Virus isolation, electron microscopic (EM) serologic test culture	100	100	–	38	–	–	–	–	–	–	–	–	–	Six (13%) of cases had a mild illness. 23 (49%) had severe disease	23	4 of the 47 patients (9%) had a vaccination scar 4 cases represented the person-to-person spread of monkeypox
8	Doshi R.H. [15]	2020 DRC	223	69.5% male	11.64	*	PCR	100	100	–	–	–	–	–	–	–	–	–	–	–		–	8 subjects reported smallpox vaccination, and there was no significant difference in rash severity according to the presence of vaccination scar [0.66 (95% CI: 0.13, 3.36] Self-reported exposure to both rodents and non-human primates three weeks before the onset of rash was commonplace (91% and 77% for rodents and NHP, respectively)

ID	Author (reference)	Year and country	Population	Gender	Mean age	Prevalence	Type and route of the test (for diagnosis)	Signs and symptoms n (%)												Complications	Mortality rate (%)	Other findings
								Rash	Fever	Nausea	Lymphadenopathy	Chills	Mouth ulcers	Sore throat	Headache	Pruritis	Fatigue	Sensitivity to light	Malaise	Other signs and symptoms			
9	Duque M.P. [38]	2022 Portugal	27	100% male	35.5 Median = 33	96	PCR	52	48	–	74	–	–	–	26	–	26	–	26	Myalgia (18.5), anal ulcers (18.5), genital ulcers and vesicles (22)	Three patients were hospitalized	0	Very few cases (1/10) reported contact with people presenting similar symptoms or a history of travel abroad (4/27) Almost all cases identified themselves as men who have sex with men (MSM) (18/19), whereas one case reported having sex with only women, 3 had contact with animals 14 (52%) had HIV infection
10	Formenty P. [16]	2005 Sudan	19	48% male	79% < 20 yrs All were < 32	49, confirmed = 10, probable = 9 suspected = 30	ELISA/PCR	100	84.2	–	79	–	–	–	55	–	65	–	–	–	Eight patients were hospitalized	0	14 patients reported contact with a suspected monkeypox case-patient before the onset of symptoms
11	Foster S.O. [17]	1972, Liberia, Nigeria, Sierra Leone	6	50% male	8.5	*	4 cases of virus isolation, 2 cases based on epidemiological and serological investigations	100	83	–	–	–	–	16.7	33.3	–	–	–	33.3	Neck stiffness	Bacterial abscess, corneal scar	0	All cases were unvaccinated. No human-to-human transmission of infection could be demonstrated. Mean Prodrome indays = 3.2
12	Girometti N. [18]	2022 UK	54	100% male	39.93	*	RT-PCR assay	100	57	–	56	–	7	20	–	–	67	–	67	Rash [6 (11)]	5 (9%) required admission to the hospital. Localized bacterial cellulitis	0	All have sex with men (MSM). 13 (24%) were living with HIV. 51 (94%) of skin lesions were anogenital

Table 1. Description of the findings reported in eligible studies (continued)

ID	Author (reference)	Year and country	Population	Gender	Mean age	Prevalence	Type and route of the test (for diagnosis)	Signs and symptoms n (%)												Complications	Mortality rate (%)	Other findings
								Rash	Fever	Nausea	Lymphadenopathy	Chills	Mouth ulcers	Sore throat	Headache	Pruritis	Fatigue	Sensitivity to light	Malaise	Other signs and symptoms			
13	Huhn G.D. [21]	2003 USA	34	52.9% male	26 71% > 18 yrs	*	PCR	97	85	–	71	71	–	–	65	–	–	–	–	Myalgias (56)	9 (26%) were hospitalized. Encephalopathy and retropharyngeal abscess in 2 young school-aged children	0	Previous smallpox vaccination was not associated with disease severity or hospitalization. 15% were defined as severely ill. Patients with ages < 18 yrs were more likely to be hospitalized in an intensive care unit. 19 cases (56%) have contact or been bitten by monkeypox-infected animal. The incubation period was 12 days. 7 patients (21%) had previous smallpox vaccination
14	Hutin Y.J. [22]	1997 DRC	88	56% male	Median = 10	2.16%	PCR, hemagglutination-inhibition assay, Western blot, and neutralization assay	100	–	–	54	–	–	–	–	–	–	–	–	Alopecia	–	3.7	13 of 84 (15.5%) patients had vaccination scars. 73% of the case patients reported exposure to another patient or eating wild animals (incubation period 7–21 days)
15	Inigo Martinez J. [23]	Spain 2022	595 508 cases investigated	99% male	Median = 35		PCR	98	63.8	–	61.2	–	–	–	31.9	–	46.9	–	46.9	Myalgia (36.4), odynophagia (28.1), proctitis (15.9), rash was located predominantly in the anogenital and/or perineal area	MPX complications (para pharyngeal abscess, mouth ulcers, and bacterial superinfection) in 7 hospitalized patients. Hospitalized patients: 19 (3.7%)	0	225 (44.3%) patients had HIV infection. 56 (11%) patients were on pre-exposure prophylaxis treatment. 427 cases (84.1%) reported condomless sex or sex with multiple partners within 21 days before the onset of symptoms

ID	Author (reference)	Year and country	Population	Gender	Mean age	Prevalence	Type and route of the test (for diagnosis)	Signs and symptoms n (%)												Complications	Mortality rate (%)	Other findings
								Rash	Fever	Nausea	Lymphadenopathy	Chills	Mouth ulcers	Sore throat	Headache	Pruritis	Fatigue	Sensitivity to light	Malaise	Other signs and symptoms			
16	Jezek Z. [24]	Zaire 1988	338	58% male	Mean = 6.9 Median = 4.4	*	haemagglutination inhibition, fluorescent antibody, ELISA, radioimmunoassay (RIA), and the RIA adsorption	100	–	–	–	–	62.1	–	–	–	–	–	–	Tonsillitis (43.8)	Secondary bacterial infection of skin: 48 (14.2%) Broncho-pneumonia, pulmonary distress: 34 (10%) Vomiting, diarrhoea, dehydration: 22 (6.5%) Keratitis, corneal ulceration: (3.25%) Septicaemia: (0.29%) Encephalitis: (0.29%)	9.8	43 patients (13%) had vaccination scar. 245 (72.5%) patients with animal source of infection and 93 (27.5%) patiens with human source. Unilateral or bilateral blindness, weak vision and deforming scars
17	Jezek Z. [25]	Zaire 1988	2278	52.1% female 47.9% male	–	93 (4.0%)	haemagglutination inhibition, the fluorescent antibody, ELISA, radioimmuno-assay (RIA), and the RIA adsorption	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Vaccination scar present: 1555. Vaccination scar present: 723. Attack rate in vaccinated people: 15 (0.96%). The rate of attack in non-vaccinated people: 54 (7.47%)
18	Jezek Z. [26]	Zaire 1986	2510	–	–	62 (2.5%)	HAI, fluorescent antibody, ELISA, RIA, radioimmunoassay adsorption ELISA and ELISA-adsorption	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Vaccination scar present: 1869. Vaccination scar present: 641. Attack rate in vaccinated people: 16 (0.9%). The rate of attack in non-vaccinated people: 46 (7.2%)

Table 1. Description of the findings reported in eligible studies (continued)

ID	Author (reference)	Year and country	Population	Gender	Mean age	Prevalence	Type and route of the test (for diagnosis)	Signs and symptoms n (%)												Complications	Mortality rate (%)	Other findings
								Rash	Fever	Nausea	Lymphadenopathy	Chills	Mouth ulcers	Sore throat	Headache	Pruritis	Fatigue	Sensitivity to light	Malaise	Other signs and symptoms			
19	Jezek B.Z. [27]	Zaire, 1987	282	50.7% male	90% < 15 yrs	–	HAI test, fluorescent-antibody test, ELISA, RIA and RIA adsorption test	100	100	–	80.3	–	–	–	–	–	–	–	–	–	Secondary bacterial infection of the skin: 49 (17.37%) Bronchopneumonia, pulmonary distress: 30 (10.63%) Vomiting, diarrhea, dehydration marasmus: 17 (6.02%) Keratitis, corneal ulceration: 12 (4.25%) Septicemia: 1 (0.35%) Encephalitis: 1 (0.35%)	9.57	11% had visible smallpox vaccination scars. All deaths were from unvaccinated patients. All death occurred in those aged between 3 months and 8 years
20	Kalthan E. [28]	Central African Republic, 2018	26	53.8% male	Median = 24 (12 months–58 yrs)	0.49%	PCR	100	100	–	34.6	–	–	–	26.9	46.2	–	–	–	Pruritus (46.2), dysphagia (19.2), myalgia (26.9), cough (11.5)	(61.5%) had been hospitalized	7.7	(19.2%) had the smallpox vaccination scar
21	Ogoina D. [36]	2017 Nigeria	21	80.9% male	Median = 29 (6–45 yrs)	35%	PCR-tested	100	90.5	14.2	62	62	52.4	42.8	57	67	62	14.3	62	Genital ulcer (47.6), myalgia, cough, conjuntivitis, hepatomegaly	61.9% were hospitalized	0	There was concomitant chicken pox, syphilis and HIV-1 infections Majority of suspected cases were adults (80.9%)
24	Reynolds M.G. [45]	2005 USA	30	43.3% male	25 yrs	*	combination of clinical symptoms, exposure information, and laboratory criteria of CDC	100	93	–	67	–	27	–	–	–	–	–	–	Cough (56.7)	–	–	Got smallpox vaccine: 20%. 100% had exposure to prairie dog

ID	Author (reference)	Year and country	Population	Gender	Mean age	Prevalence	Type and route of the test (for diagnosis)	Signs and symptoms n (%)												Complications	Mortality rate (%)	Other findings
								Rash	Fever	Nausea	Lymphadenopathy	Chills	Mouth ulcers	Sore throat	Headache	Pruritis	Fatigue	Sensitivity to light	Malaise	Other signs and symptoms			
25	Rimoin A.W. [47]	2010 DRC	Sankuru District	62.1% male	11.9	760	scab or vesicular fluid by PCR	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Vaccine: 3%
26	White-house E.R. [53]	2021 DRC	1057	53.7% male	Median = 14 range (1 months–79 yrs)	average annual incidence was 14.1 per 100 000	real-time PCR assay	100	99.4	24.8	84.7	89.0	56	–	78.4	59.3	86.3	33.2	75.3	Cough (54.8), dyspnagia (71), conjunctivitis (21)	–	9.2% cases received smallpox vaccine. The incidence was higher in men vs women. Animal and human contact as an only source of exposure was found in 36.9% and 33.3%, respectively
27	Osadebe L. [37]	2017 DRC	Total = 752 Confirmed = 333	53% male	5.77 yrs	44.3%	real-time PCR	95.2	100	23	85	80	58.3	76	75.2	53	85	32.5	71.5	Cough (58), conjunctivitis (24), and bedridden (18.4)	–	
28	Pittman R.R. [40]	2022 DRC	214	63.9% male	14 Median = 13 (0–61)		PCR	96.8	–	–	57.4	97	24.5	78.2	23.6	–	85	–	85.2	Anorexia (50), cough, dysphagia, abdominal pain, sweats conjunctiitis, shortness of breat, hepatomegaly/ splenomegaly, lethargy/ stupor, dehydration and confusion	1.38	Fetal death happened in 4 of 5 (80%) patients who were pregnant at admission. 4 cases had vaccination history. Most signs an symtoms lasted 3–5 days

Table 1. Description of the findings reported in eligible studies (continued)

ID	Author (reference)	Year and country	Population	Gender	Mean age	Prevalence	Type and route of the test (for diagnosis)	Signs and symptoms n (%)												Complications	Mortality rate (%)	Other findings
								Rash	Fever	Nausea	Lymphadenopathy	Chills	Mouth ulcers	Sore throat	Headache	Pruritis	Fatigue	Sensitivity to light	Malaise	Other signs and symptoms			
29	Reynolds M.G. [43]	2006 USA	Total = 47 Confirmed = 37	46.8% male				85	93	30	70	70		70	66	–	*	–	*	Myalgia (76), dyspnea, diarrhea, wheeze, abdominal pain, runny nose, back pain, muscle pain, sweats	31% were hospitalized	–	57% reported having exposure to MPXV in a home environment,contact with an ill pet. The remaining (43%) were all exposed in settings of occupational animal care. 17 individuals (36%) received a bite or scratch from an ill prairie dog in addition to other potential noninvasive exposures. Mean incubation period was 11.5 days approximately. 13 was in non-invasive exposure group
30	Rimoin A.W. [46]	2007 DRC	51	48.52% male	mean = 10 Median = 7		PCR	*	*	–	–	–	–	–	–	–	–	–	–	–	–	0.73	recognized the causative agent for a rash-causing infection in 83% of all patients
31	Yinka-Ogunleye A. [58]	2019 Nigeria	122	69% male	27 Median = 29 (0–50 yrs)		real-time PCR	100	88	24	69	65	38	58	79	73	55	24	63	Cough (30), conjunctivitis (25)	secondary bacterial infection of the monkeypox skin lesions	6	30% had contact with people who had similar lesions 10 patients reported contact with animals. 4 of the people who died had HIV with features of AIDS. The greatest affected parts were the face (in 68 [96%])

Table 2. Newcastle–Ottawa Scale (NOS) bias risk assessment of the study

ID	First author	Selection (out of 4)	Comparability (out of 2)	Exposure/Outcome (out of 3)	Total (out of 9)
1	CDC [9]	4	2	3	9
2	CDC [11]	4	2	3	9
3	CDC [12]	2	1	2	5
4	Reed K.D. [41]	4	1	3	8
5	Nolen L.D. [35]	3	2	2	7
6	Adler H. [1]	3	2	3	8
7	Breman J.G. [5]	3	2	3	8
8	Doshi R.H. [15]	2	1	2	5
9	Duque M.P. [38]	3	2	3	8
10	Formenty P. [16]	4	1	3	8
11	Foster S.O. [17]	3	2	2	7
12	Girometti N. [18]	4	2	3	9
13	Huhn G.D. [21]	4	2	3	9
14	Hutin Y.J. [22]	2	1	2	5
15	Inigo Martinez J. [23]	3	2	3	8
16	Jezek Z. [24]	3	2	3	8
17	Jezek Z. [25]	3	2	3	8
18	Jezek Z. [26]	2	1	2	5
19	Jezek B.Z. [27]	2	0	3	5
20	Kalthan E. [28]	2	1	1	4
21	Ogoina D. [36]	2	1	2	5
24	Reynolds M.G. [45]	2	0	3	5
25	Rimoin A.W. [47]	2	1	2	5
26	Whitehouse E.R. [53]	4	2	3	9
27	Osadebe L. [37]	2	1	2	5
28	Pittman R.R. [40]	4	2	2	8
29	Reynolds M.G. [43]	2	1	2	5
30	Rimoin A.W. [46]	2	1	3	6
31	Yinka-Ogunleye A. [58]	3	1	3	7

ies reported more frequency of male cases than female [3]. On the other hand, the transmission of disease through sexual contact in this outbreak has been relatively higher than in previous ones, mainly in men with homosexual behaviors [55]. Tarin-Vicente E.J. et al. recorded that 92% of patients were gay, bisexual, or men who had sex with other men, and most of them had no contact or recent travel to the endemic regions [48].

Smallpox vaccination status. The resurgence of monkeypox provoked controversies about the reasons behind it. One contributing factor in the post-smallpox era is the cessation of vaccination and declining efficacy of the vaccine (Vaccina virus) in the older generation, which was held accountable for having a cross-protection against monkeypox [33]. An increase in the average age of cases in DRC (Democratic Republic of Congo) can support this hypothesis [20]. Bragazzi et al. reported that in endemic African and non-endemic regions, the incidence rate of monkeypox infection in smallpox-vaccinated subjects was significantly lower than in unvaccinated ones [4]. This is in line with the result of this article. Worth mentioning that one Italian case in his 30s was affected by monkeypox despite being vaccinated for smallpox [2].

Presentation. The characteristic features of monkeypox resemble smallpox. However, smallpox symptoms are often more severe, and lymphadenopathy is generally absent [39]. The most prevalent symptoms described in reviewed articles are rash and fever, ranging from 31–100% and 43–100%, respectively. However, other symptoms were reported, such as lymphadenopathy, chills, nausea, mouth ulcer, headache, sore throat, pruritus, fatigue, and light sensitivity. Different studies claimed the atypical manifestation of monkeypox in the current outbreak (2022). Although the rash is still present, the involved areas are more localized and limited, with mild or absent prodromal symptoms, including lymphadenopathy, fever, and often other non-specific symptoms such as headache, malaise, and muscle pains [10, 51].

Complications. The rate and time frame of developing complications in monkeypox-infected individuals have not been scientifically determined [44]. Yet, a rare portion of this community can be affected by complications such as conjunctivitis/keratitis, bacterial superinfection, encephalitis, and pneumonitis [14, 46]. As anticipated, the reported complications in reviewed articles are in line with previous works. Moreover, septicemia, pharyngeal abscesses, and corneal scars have also been reported.

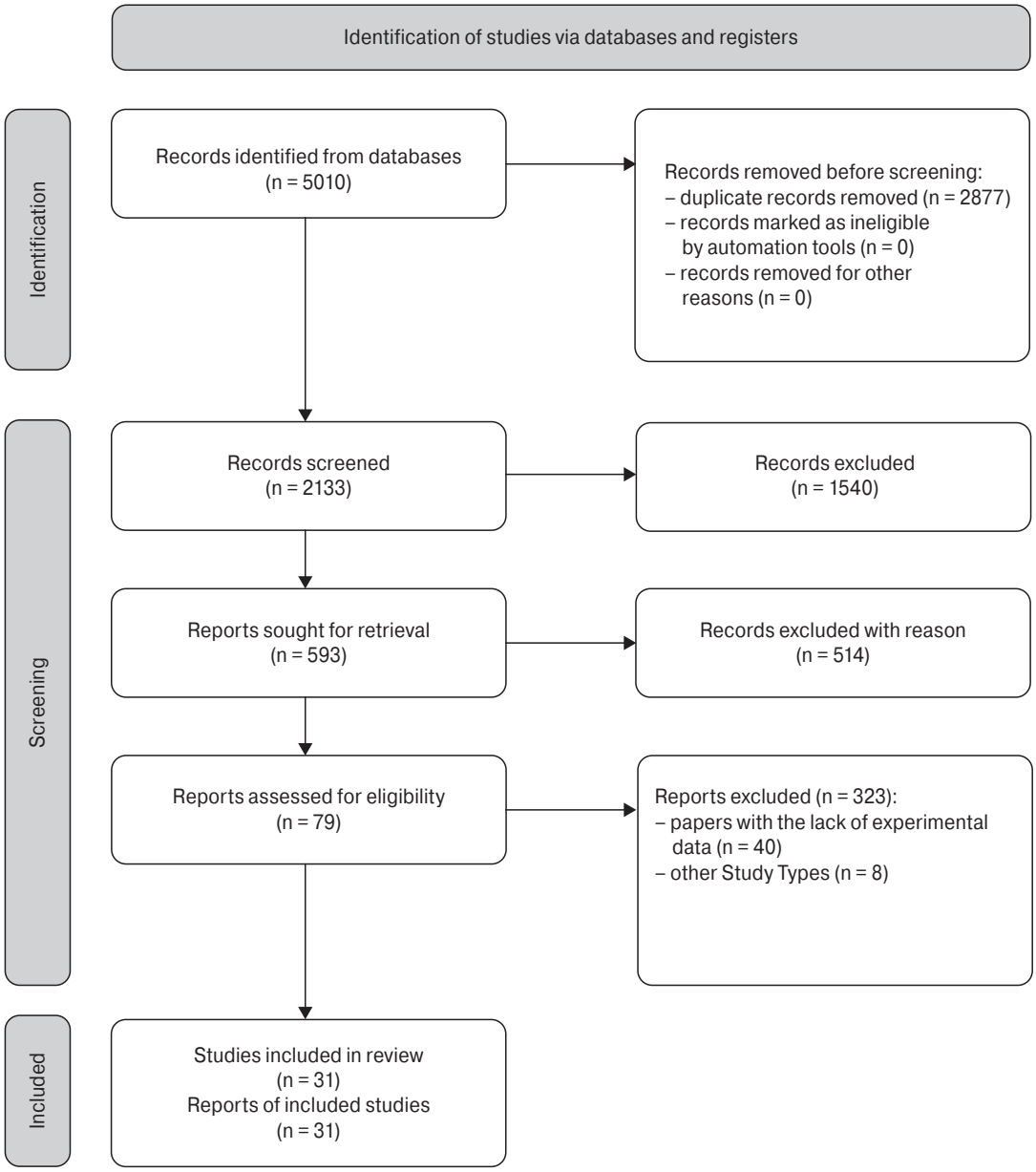

Figure. PRISMA 2020 flow diagram of study retrieval process

Case Hospitalization Rate (CHR), Case Fatality Rate (CFR), and attack rate. Dewitt et al. systematically reviewed monkeypox-related studies from 1950 to 2022. As they declared, Combined CHR was estimated to be 14.1%. Additional analysis during the pre-2017, 2017–2021, and 2022 outbreaks indicates CHRs of 49.8%, 21.7%, and 5.8%, respectively. CFR was estimated to be 0.03%. However, studies have high levels of heterogeneity [13]. The CHR ranged from 3.7% to 100% within our research articles. Also, the CFR was between 0% and 23%. However, in one report, all the demises were under eight years old, with a majority rate in the second week of the disease [27].

The attack rate of the monkeypox virus was significantly higher in unvaccinated individuals. Previous studies achieved different attack rates in the period of each outbreak. For instance, it estimated 9–12% of unvaccinated contacts within households in the Africa outbreak; thus, in the US outbreak, it was 0% [49, 58]. Although some epidemiological links between cases are reported, no transmission with non-sexual contacts has been yet documented in this outbreak.

The contagiousness and severity of any infectious disease can alter by genetic evolution. Only 2 known clades of monkeypox are responsible for all cases [19] Although it is a gray area and needs further investigation, some studies have shown that genetic variations might intensify the disease's transmissibility [29].

Strengths and limitations. Our work faces the inherent limitations of all systematic reviews, which include the risk of selection bias, attrition bias, and selective outcome reporting as well as clinical or statistical heterogeneity. In order to mitigate such

risks, we diligently followed the PRISMA guidelines for systematic reviews, and we quantified the risk of bias using the Newcastle–Ottawa Scale (NOS) risk assessment tool. In this way, we were able to provide an updated, comprehensive, systematic as well as methodologically solid overview of the current literature on our chosen topic.

Suggestions/future implications. It is of outmost importance — especially in high-risk countries — to early detect and promptly diagnose individuals infected by the monkeypox virus. Future implications of our work will hopefully pave the way for large population studies aimed at defining the incidence, prevalence, and attack rate of the infection on a more granular as well as extensive level. Further investigations are also required to elucidate symptoms onset and pathophysiology of the infection in different age, sex, and socioeconomic strata of the population, as well as in patients with pre-existing comorbidities and specific viral infections (e.g., HIV, HBV, HCV, etc).

Conclusion

In conclusion, we performed a systematic review of 31 published studies on the epidemiology, pathogenesis, manifestations, and outcomes of monkeypox. We elucidated the most common symptoms as well as complications, amongst which death usually occurs during the second week of the disease manifestation. Further studies are needed to elucidate the natural history of the disease in various patients' populations, as well as detailing the monkeypox attack rate.

Additional information

Ethics approval and consent to participate: Not applicable.

Consent for publication. Not applicable.

Availability of data and materials. The authors stated that all information provided in this article could be shared.

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