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Monkeypox-Associated Manifestations and Complications Involving the Eye: A Systematic Review and Meta-Analysis of Previous and Current Outbreaks

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Purpose: The purpose of this study was to pool the prevalence rate of monkeypox-associated eye manifestations and/or complications during the current and previous outbreaks.

Design: A systematic review and meta-analysis.

Materials and Methods: On August 7, 2022, PubMed, Scopus, Web of Science, EMBASE, and Google Scholar were searched for relevant articles. We included all studies that reported the involvement of the eye (either as a manifestation or a complication) among patients with monkeypox. The primary outcome included pooling the effect size (ES) of reported manifestations and complications, and the secondary outcome included the conduct of a subgroup analysis based on the timing of the monkeypox outbreak (before vs. during 2022).

Results: Eleven studies reporting 3179 monkeypox-confirmed cases were included. Eye manifestations included conjunctivitis, corneal, conjunctival, and eyelid lesions, photophobia, and eye pain. Compared with previous monkeypox outbreaks, the current outbreak revealed much lower rates of ocular involvement in terms of conjunctivitis (ES = 1%; 95% CI: 0%–1% vs. ES = 17%; 95% CI: 11%–22%), corneal and conjunctival lesions (ES = 1%; 95% CI: 0%–2% vs. ES = 13%; 95% CI: 4%–22%), and eyelid lesions (ES = 1%; 95% CI: 0%–4% vs. ES = 13%; 95% CI: 5%–28%). Monkeypox-associated eye complications were reported only in the previous outbreaks which included keratitis (ES = 4%; 95% CI: 3%–6%), corneal ulceration (ES = 4%; 95% CI: 2%–5%), unilateral (ES = 3%; 95% CI: 1%–4%) and bilateral blindness (ES = 0%; 95% CI: 0%–2%), and impaired vision (ES = 4%; 95% CI: 1%–8%).

Conclusions: Ophthalmic manifestations and complications are common among monkeypox-confirmed cases. Although these data are mainly related to previous outbreaks, health care workers should familiarize themselves with these signs to provide better care for monkeypox patients.

Key Words: blindness, conjunctiva, cornea, eye, keratitis, monkeypox, photophobia

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INTRODUCTION

Monkeypox (MPX) was first reported in Danish laboratory monkeys in 1958. It was first detected in humans in the 1970s in Central and West African countries. Multiple outbreaks of the disease have been reported since then, with most cases confined to Africa.[1–3] In May 2022, a recent multicountry outbreak was declared, and the number of cases dramatically increased, urging the World Health Organization to announce a Public Health Emergency of International Concern.[4] Monkeypox virus (MPXV) belongs to the Orthopox family, which includes the smallpox virus. The smallpox epidemic was successfully eliminated by the 1980s after the effective application of mass vaccination campaigns.[5] Despite the similarities between the 2 diseases, the current MPX outbreak indicates a significant shortage of knowledge about the disease.

Reporting and studying the clinical features of the disease is essential in identifying it and implementing approaches aiming at establishing better interventions. Since the current outbreak occurred, different reports have been published reporting the clinical spectrum of the disease. For instance, a recent systematic review showed that the most common presentations of MPX cases include rash with pruritis, fever, and lymphadenopathy. Other manifestations included fatigue, sore throat, headache, cough, myalgias, photophobia, arthralgia,

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difficulty breathing, conjunctivitis, nausea/vomiting, and diarrhea. Moreover, it has been reported that the severity of the current disease is milder than in previous outbreaks.[6] However, this review did not adequately represent some manifestations, such as ophthalmic ones.

A recently published review highlighted that ocular complications following MPX infection occur in 4%–5% of cases, with immunocompromised individuals, pregnant women, and children (less than 8 y of age) being the most vulnerable.[7] Controversially, in our previous research, we highlighted the involvement of the eye in MPX-confirmed cases (ie, conjunctivitis, photophobia, keratitis, and lesions affecting the eyelids and conjunctiva, and even vision loss), which surpassed the rare event assumption.[8] In 2023, several reviews have been published on the ocular manifestations and/or complications of MPX[9,10]; however, these reviews lack a thorough systematic search across a wide variety of databases and registries, where gray literature is being published. In addition, these reviews have not performed an authentic meta-analysis to reflect the overall prevalence of such events. Therefore, by conducting this meta-analysis, we aim to:

- Summarize all of the reported ocular manifestations and complications among MPX-confirmed cases.
- Estimate the pooled prevalence of each of the reported ocular manifestations and complications to determine if they surpass the rare event assumption (5%) and warrant careful consideration in clinical practice.
- Determine whether or not the prevalence of such symptoms could differ based on the timing of the outbreak (before vs. during 2022) to reach hypothesis-generating findings that would direct future research.

MATERIALS AND METHODS

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the review protocol was preregistered on PROSPERO (registration number: CRD42022354476). On August 7, 2022, a thorough electronic search was conducted (B.A.) through PubMed, Scopus, Web of Science, EMBASE, and Google Scholar. Of note, only the first 200 records from Google Scholar were retrieved and screened according to recent guidelines.[11] A detailed search strategy is provided in Supplementary Digital Content Table 1, http://links.lww.com/APJO/A234. Noteworthy, all of the available references, regardless of the year of publication or language of the original manuscript, were retrieved.

Records identified through the database search were then imported into EndNote for duplicate removal, and then the remaining records were exported into an Excel sheet for screening. In addition, following the full-text screening phase, a manual search was carried out to identify any potentially missing, relevant articles. This method was carried out by screening the reference lists of included articles, screening "similar articles" to included ones through PubMed, and randomly searching Google for relevant articles with the use of keywords "eye" and "monkeypox." Noteworthy, the database search was updated on October 5, 2022, to find any newly published, relevant articles before the conduct of the analysis.

Eligibility Criteria

In accordance with the PICO framework, we included studies that reported eye manifestations and/or complications (outcome) among MPX-confirmed cases (population). No exposure or comparison were required for inclusion. Articles were included if they were consistent with all of the following criteria: (1) original research, (2) the inclusion of MPX-confirmed cases, and (3) the availability of data on eye involvement either in the form of presenting symptoms or subsequent complications. In contrast, research articles were excluded if they complied with one of the following criteria: (1) nonoriginal research (ie, review articles, commentaries, guidelines, editorials, correspondence, letters to editors), (2) nonhuman studies (ie, in vivo, in vitro, animal studies), (3) no report of MPX, (4) lack of outcome data (no eye involvement), (5) duplicated records or records with overlapping datasets, and (6) unavailable full texts.

Two reviewers (A.H. and A.M.) screened articles against our predefined eligibility criteria in 3 steps: title, abstract, and full-text screening. Any differences between reviewers were discussed with the senior author (A.A.). Retrieval of full texts was conducted by B.A., A.H., and A.M., and studies with unavailable full texts were excluded.

Outcomes of Interest

The primary outcome of this research was to determine the prevalence rate of each eye manifestation and/or complication associated with MPXV infection. The secondary outcome included a subgroup analysis of the primary outcome based on the year of the MPX outbreak (before vs. during 2022) to determine whether or not there is a change in the presentation pattern of the disease, as suggested in recent research.[12] In addition, we aimed to determine if the frequency of these outcomes would differ based on age, smallpox vaccination status, or disease severity. However, we could not find data to support a meta-analysis, and therefore, this observation, based on a single study, was qualitatively analyzed in the discussion.

Data Extraction

The senior author (A.A.) formatted a data extraction sheet following the review of data reported in finally included studies (Supplementary Digital Content Table 2, http://links.lww.com/APJO/A235). The sheet consisted of 2 sections. The first section included studies' information (ie, author name, year of publication, recruitment period, study design, and sample size) and patients' characteristics [age, sex, diagnostic method for MPX, previous smallpox vaccination, duration from initial exposure to symptom or complication onset, and transmission method (animal or human transmission)]. The second part included the study outcomes in the form of eye manifestations [conjunctivitis, eye lesions involving the cornea/conjunctiva, eyelid involvement (in the form of vesicles, pustules, or pseudo-pustules), photophobia, and eye pain] and complications (keratitis, corneal ulceration, unilateral and bilateral blindness, and impaired vision). Data were extracted

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by A.M. and A.H. and revised by A.A. before the analysis stage.

Quality Assessment

To assess the quality of included studies, we used the National Health Institute (NIH) quality assessment tool for cohort/cross-sectional studies[13] and case series.[14,15] The first tool is composed of 14 questions, assessing the quality of included studies at 14 different domains, while the second tool consists of 9 questions. Each question was given a score of 0, 1, or 2 for not reported, no, or yes. The overall quality was determined as good, fair, or poor based on the overall score. Two reviewers assessed the quality of included studies (A.M. and A.H.), and any differences between reviewers were solved by consulting the senior author (A.A.).

Data Synthesis and Analysis

All quantitative analyses were carried out through STATA Software—Version 17 (StataCorp LLC). A meta-analysis of prevalence, using the metaprop command,[16] was done to estimate the pooled effect size (ES)—prevalence rate—of reported eye manifestations and complications among MPX-confirmed cases. The random-effects and fixed-effects models were selected according to the presence or absence of significant heterogeneity, respectively.[17] Between-study heterogeneity was deemed significant by observing the I^2 statistic and P-value, where an I^2 of $> 50\%$ and a P-value <0.05 indicates significant heterogeneity. The assessment of publication bias, through funnel plots, was not feasible due to the unavailability of enough studies (< 10 studies).[18]

The certainty level of evidence was assessed using the GRADE framework for prognostic studies since the original GRADE framework was designed to assess the certainty of evidence regarding studies of intervention.[15]

RESULTS

Search Results

The search and screening processes are illustrated in Figure 1. The database search yielded 352 articles eligible for title and abstracted screening, following which, the full texts of 22 articles were screened for final inclusion into our review. Eleven articles were excluded because they did not have a full text (in 3 articles),[19–21] did not report any eye manifestations or complications in MPX-confirmed cases (in 7 articles),[4,12,22–26] or did not have original data-review (in 1 article).[27] No additional articles were found through the updated database search or manual search, resulting in a total of 11 articles[15,27–36] included in the final qualitative and quantitative analysis of this study.

Baseline Characteristics

The baseline characteristics of included studies are presented in Table 1. Eleven studies reporting 3179 MPX-confirmed cases were included with a mean sample size of 289 patients. The study design of included studies differed widely as follows: case series (N = 2), surveillance-based (N = 2), cross-sectional (N = 1), prospective observational (N = 1), chart reviews (N = 2), and retrospective observational studies (N = 3). Based on the timing of MPX outbreaks, 3 studies reported data related to the current multicountry outbreak,[29,34,35] while 8 studies reported cases owing to previous sporadic outbreaks before 2022.[15,28,30–32,36–38] The percentage of male patients ranged from 28.57%[28] to as high as 100%.[29,34] History of previous smallpox vaccination was reported in 6 studies,[28–32,36] and among MPX-confirmed cases, only a minority was vaccinated ranging from 0%[28] to 20.5%.[30] In addition, only 2 studies reported the rate of men who have sex with other men. One study[29] reported that 184 out of 185 (99.45%) participants were men who have sex with other men and the other study[34] reported a very similar rate of 170 out of 177 (96.04%).

Noteworthy, none of the included studies reported the age nor the sex of MPX cases with ocular involvement; thus, it was not feasible to detect any age-related or sex-related differences in such cases. This needs to be investigated and reported in future research.

Quality Assessment

The quality of included case series and cross-sectional/cohort studies are provided in Tables 2 and 3. The 2 case series had good overall quality (Table 2), while 5 cohort/cross-sectional studies[15,29,32,33,36] had fair quality and 4 had poor quality[28,30,31,38] (Table 3).

MPX-associated Manifestations Involving the Eye

Eye manifestations among MPX-confirmed cases during the time of presentation included conjunctivitis, photophobia, eye pain, eye lesions involving the cornea and conjunctiva (in the form of vesicles), and lesions involving the eyelids (ie, vesicles, pustules, or pseudo-pustules) (Table 4). Conjunctivitis was reported in 8 studies (2374 eyes) with a pooled prevalence rate of 12% (95% CI: 5%–18%, $I^2 = 97.89\%$). The subgroup analysis based on the timing of the outbreak showed a remarkable difference in the prevalence of conjunctivitis between outbreaks before 2022 and the current multicountry outbreak, with pooled prevalence rates of 17% (95% CI: 11%–22%) and 1% (95% CI: 0%–1%), respectively (Fig. 2).

Eye lesions involving the cornea and/or conjunctiva were reported in 5 studies (773 eyes), with an overall prevalence rate of 7% (95% CI: 2%–13%, $I^2 = 93.68\%$). This rate differed greatly between previous MPX outbreaks (3 studies, ES = 13%; 95% CI: 4%–22%) and the current outbreak (2 studies, ES = 1%; 95% CI: 0%–2%] (Fig. 3). Meanwhile, the involvement of the eyelids was reported in 2 studies (217 eyes) with a pooled rate of 1% (95% CI: 0%–3%; $I^2 = 0.0\%$), which was higher in the previous outbreak (1 study, ES = 13%; 95% CI: 5%–28%) than the current one (1 study, ES = 1%; 95% CI: 0%–4%). However, it should be noted that the interpretation value of this finding is limited because of the low number of included studies (Supplementary Digital Content Fig. 1, http://links.lww.com/APJO/A236).

Photophobia is a sign that was reported only in the previous MPX outbreaks (2 studies, 1039 eyes) with no reports in the current multicountry outbreak, with a pooled prevalence of 33% (95% CI: 30%–36%; $I^2 = 0.0\%$) (Supplementary Digital Content Fig. 2, http://links.lww.com/APJO/A237). In addition, eye pain was reported in only 1 study during the previous MPX outbreaks (216 eyes) with a rate of

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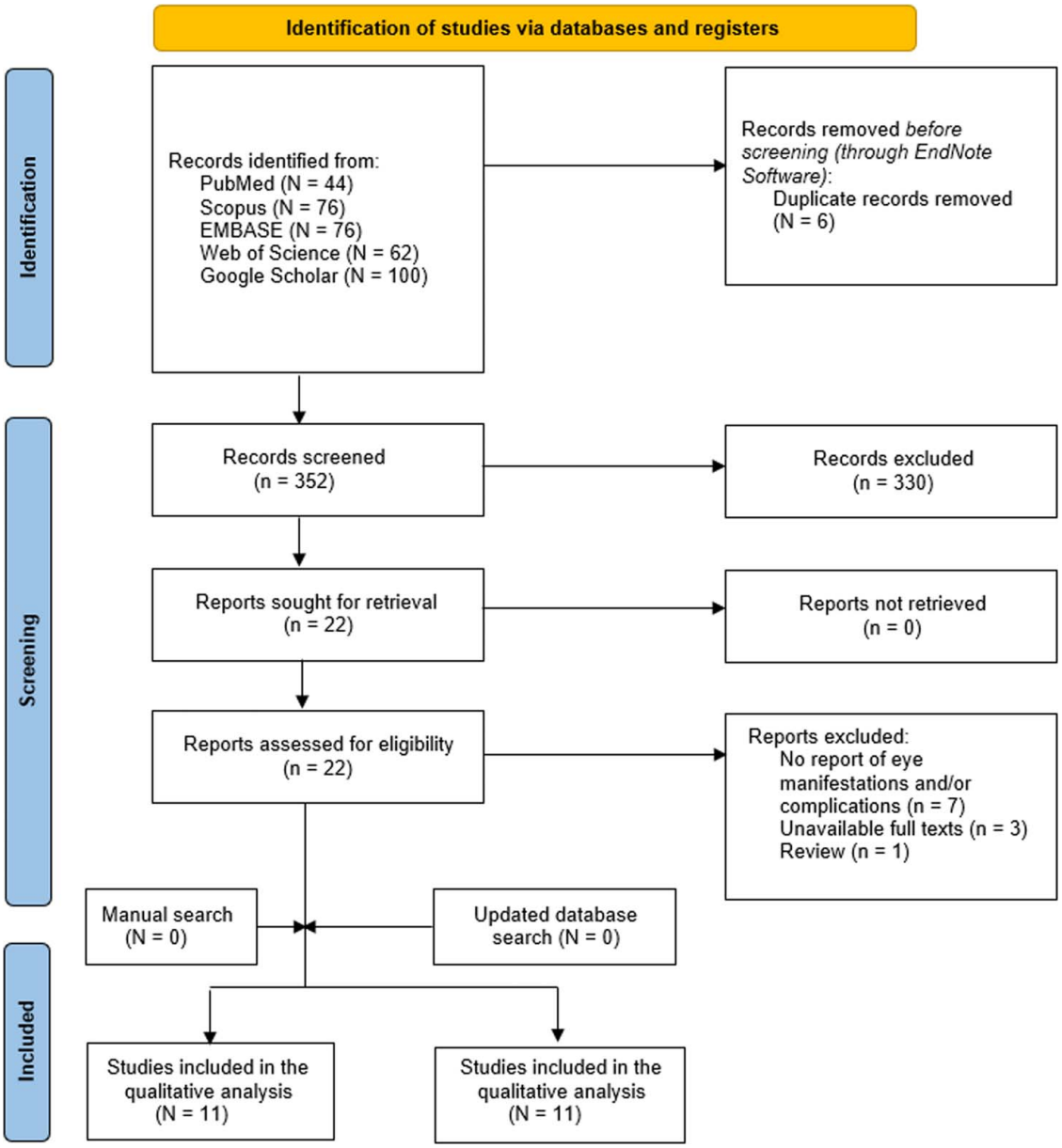


FIGURE 1. PRISMA flow diagram of the database search and screening processes.

9% (95% CI: 6%–14%). There are no reports on the occurrence of eye pain in the current outbreak.

MPX-associated Complications Involving the Eye

MPX-associated eye complications included keratitis, corneal ulceration, unilateral and bilateral blindness, and impaired vision; all of which were reported in the previous outbreaks with no reports regarding these complications during the current multicountry outbreak (Table 5). Keratitis was reported in 4 studies (833 eyes) with a pooled rate of 4% (95% CI: 3%–6%; $I^2 = 0.0\%$) (Fig. 4). Similarly, corneal ulceration was reported in 3 studies (611 eyes), showing an overall prevalence rate of 4% (95% CI: 2%–5%; $I^2 = 0.0\%$) (Fig. 5). Unilateral and bilateral blindness were documented among MPX-infected cases with an occurrence rate of 3% (2 studies, 95% CI: 3%–4%; $I^2 = 0.0\%$) (Supplementary Digital Content Fig. 3, http://links.lww.com/APJO/A238) and 0% (1 study, 95% CI: 0%–2%; $I^2 = 0.0\%$), respectively. Meanwhile, impaired vision was reported 3 studies (836 eyes) with a pooled prevalence rate of 4% (95% CI: 1%–8%; $I^2 = 86.32\%$) (Fig. 6).

Certainty of Evidence Using the GRADE Framework

The certainty of evidence regarding each of the analyzed outcomes (manifestations and complications) was rated as very low (Tables 4 and 5) due to the study design, study limitations, and poor quality.

DISCUSSION

The present systematic review and meta-analysis aims to determine whether presentation with eye manifestations and/or complications during the current multicountry outbreak is different from that of previous years. Various ophthalmic manifestations of MPX-confirmed cases were reported, including conjunctivitis, photophobia, eye pain, eye lesions involving the cornea, conjunctiva, and eyelids. Our pooled analysis shows that conjunctivitis

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TABLE 1. Baseline Characteristics of Studies Reporting Monkeypox-associated Eye Manifestations and Complications (N = 11)

						Age		Sex (male)		Smallpox vaccination (yes)		Time from exposure to symptom onset (d)		Transmission method				Ocular pathology (yes)	
														Human-to-human		Animal Exposure			
References	Country	Study design	Timing	Sample	Diagnostic method	Mean	SD	N	T	N	T	Mean	SD	N	T	N	T	N	T
Adler et al[28]	UK	Retrospective observational study	Before 2022	7	PCR	—	—	4	7	0	7	—	—	—	—	—	—	—	—
Català et al[29]	Spain	Prospective cross-sectional study	During 2022	185	PCR	38.7	8.2	185	185	20	185	6.25	0.833	125	185	—	—	—	—
Hughes et al[37]	DRC	Retrospective observational study	Before 2022	295	PCR	—	—	182	295	—	—	—	—	—	—	—	—	—	—
Huhn et al[30]	United States	Retrospective observational study	Before 2022	34	PCR	26	10.5	18	34	7	34	10	5.5	—	—	29	34	—	—
Ježek et al[32]	Zaire	Observational surveillance-based study	Before 2022	282	Clinicoepidemiological diagnosis carried out by the WHO	1 mo-69 y	143	282	32	282	—	—	—	—	—	—	—	—	
Ogoina et al[33]	Nigeria	Retrospective chart review	Before 2022	40	PCR	32*	—	31	40	—	—	—	—	—	—	—	—	—	—
Patel et al[34]	England	Case series	During 2022	197	PCR	38*	—	197	197	—	—	—	—	41	155	—	—	—	—
Pittman et al[38]	DRC	Prospective observational study	Before 2022	216	PCR	14	—	138	216	—	—	—	—	—	—	—	—	—	—
Whitehouse et al[36]	DRC	Retrospective chart review	Before 2022	1057	PCR	14*	—	568	1054	97	1057	—	—	279	837	309	837	—	—
Thornhill et al[35]	16 countries	Case series	During 2022	528	PCR	38*	—	527	528	—	—	—	—	—	—	—	—	—	—
Ježek et al[31]	Switzerland	Observational surveillance-based study	Before 2022	338	Clinicoepidemiological diagnosis carried out by the WHO	4.4*	—	182	338	43	338	—	—	73	338	222	338	—	—

DRC indicates Democratic Republic of the Congo; N, number; PCR, polymerase chain reaction; T, total; WHO, World Health Organization.

*Data reported as median.

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TABLE 2. Quality Assessment of Included Case Series With the Use of National Institutes of Health (NIH) Quality Assessment Tool

References	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall quality
Patel et al[34]	Y	Y	N	Y	NA	Y	NI	Y	Y	Good
Thornhill et al[35]	Y	Y	N	Y	NA	Y	NI	Y	Y	Good

N indicates no; NA, not applicable; NI, no information; Y, yes.

Q1: Was the study question or objective clearly stated?

Q2: Was the study population clearly and fully described, including a case definition?

Q3: Were the cases consecutive?

Q4: Were the subjects comparable?

Q5: Was the intervention clearly described?

Q6: Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?

Q7: Was the length of follow-up adequate?

Q8: Were the statistical methods well-described?

Q9: Were the results well-described?

and photophobia were the most common manifestations reported during all-time MPX cases. Lower rates were reported for eye pain, lesions involving the cornea and/or conjunctiva, and others involving the eyelids. Moreover, different complications were also retrieved, including keratitis, corneal ulceration, unilateral and bilateral blindness, and impaired vision. Of note, none of these complications surpasses the rare event assumption (ranging from 0% to 4%).

The current findings indicate the high prevalence of ophthalmic manifestations among all-time MPX cases. However, it should be noted that our subgroup analysis demonstrates that these high prevalence rates are attributed to previous outbreaks. For instance, conjunctivitis was prevalent in 1% of MPX cases in the current outbreak compared with 17% of earlier outbreaks. Similarly, the prevalence of lesions involving the cornea and/or conjunctiva and others involving the eyelids varied remarkably between the current and previous outbreaks. Moreover, evidence regarding some manifestations (photophobia and eye pain) was obtained from previous outbreaks, with no investigations reporting these manifestations among their MPX in the current outbreak.

Noteworthy, MPX outbreaks have been categorized into clades according to the timing of the outbreak. For instance, the outbreak that occurred in Central Africa is named Clade I, while the one that occurred in West Africa is named Clade II which is further subcategorized into 2 subclades. Each of these clades has been associated with varying severity, with the West African clade having less severe disease presentation which could reflect the lower rate of complications and mortality.[39] We assume that the current outbreak is associated with even a milder disease form as compared with all of the previous clades, particularly when it comes to eye involvement. However, this still warrants further confirmation.

TABLE 3. Quality Assessment of Included Cross-Sectional and Cohort Studies With the Use of National Institutes of Health (NIH) Quality Assessment Tool

References	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality rating
Ježek et al[32]	Y	Y	NR	Y	NI	N	NI	NA	Y	Y	Y	NI	NI	NA	Fair
Ježek et al[31]	Y	Y	NR	Y	NI	NI	NI	NA	Y	NI	NI	NI	NI	NA	Poor
Pittman et al[38]	Y	Y	NR	NR	NI	N	NI	NA	Y	Y	NI	NI	NI	NA	Poor
Ogoina et al[33]	Y	Y	NR	Y	NI	NI	NI	NA	Y	NI	Y	NI	NI	NA	Fair
Whitehouse et al[36]	Y	Y	NR	NR	NI	N	NI	NA	Y	Y	Y	NI	NI	NA	Fair
Adler et al[28]	Y	Y	NR	Y	NI	NI	NI	NA	Y	NI	NI	NI	NI	NA	Poor
Hughes et al[37]	Y	Y	NR	Y	NI	N	NI	NA	Y	NI	Y	NI	NI	NA	Fair
Huhn et al[30]	Y	Y	NR	NR	NI	NI	NI	NA	Y	NI	Y	NI	NI	NA	Poor
Català et al[29]	Y	Y	NR	Y	NI	NI	NI	NA	Y	Y	N	NI	NI	NA	Fair

N indicates no; NA, not applicable; NI, no information; NR, not reported; Y, yes.

Q1: Was the research question or objective in this paper clearly stated?

Q2: Was the study population clearly specified and defined?

Q3: Was the participation rate of eligible persons at least 50%?

Q4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?

Q5: Was a sample size justification, power description, or variance and effect estimates provided?

Q6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?

Q7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?

Q8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)?

Q9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

Q10: Was the exposure(s) assessed more than once over time?

Q11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

Q12: Were the outcome assessors blinded to the exposure status of participants?

Q13: Was loss to follow-up after baseline 20% or less?

Q14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome (s)?

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TABLE 4. The Pooled Prevalence Rate of MPXV-associated Eye Manifestations

Manifestations	Subgroup	Studies (N)	Eyes (N)	Pooled ES (95% CI)	I^2 (%)	Model	Grade
Conjunctivitis							
	Overall	8	2374	012 (0.05–0.18)	97.89	Random-effects	⊕⊖⊖⊖ Very low
	Before 2022	6	1649	0.17 (011–0.22)	83.39		
	During 2022	2	725	0.01 (0.00–0.01)	65.17		
Eye lesions (ie, vesicles) involving the cornea or conjunctiva							
	Overall	5	773	0.07 (0.02–0.13)	93.68	Random-effects	⊕⊖⊖⊖ Very low
	Before 2022	3	359	0.13 (0.04–0.22)	93.13		
	During 2022	2	414	0.01 (0.00–0.02)	89.96		
Eyelid involvement (vesicle, pustules, pseudo-pustules)							
	Overall	2	217	0.01 (0.00–0.03)	0.00	Fixed-effects	⊕⊖⊖⊖ Very low
	Before 2022	1	32	0.13 (0.05–0.28)	NA		
	During 2022	1	185	0.01 (0.00–0.04)	NA		
Photophobia							
	Overall	2	1039	0.33 (0.30–0.36)	0.00	Fixed-effects	⊕⊖⊖⊖ Very low
	Before 2022	2	1039	0.33 (0.30–0.36)	0.00		
	During 2022	NA	NA	NA	NA		
Eye pain							
	Overall	1	216	0.09 (0.06–0.14)	NA	NA	⊕⊖⊖⊖ Very low
	Before 2022	1	216	0.09 (0.06–0.14)	NA		
	During 2022	NA	NA	NA	NA		

ES indicates effect size (prevalence rate); I^2, heterogeneity measure (> 50% indicates significant heterogeneity); MPXV, monkeypox virus; N, number; NA, not applicable (2 studies are required to allow for a meta-analysis of the assessed outcome).

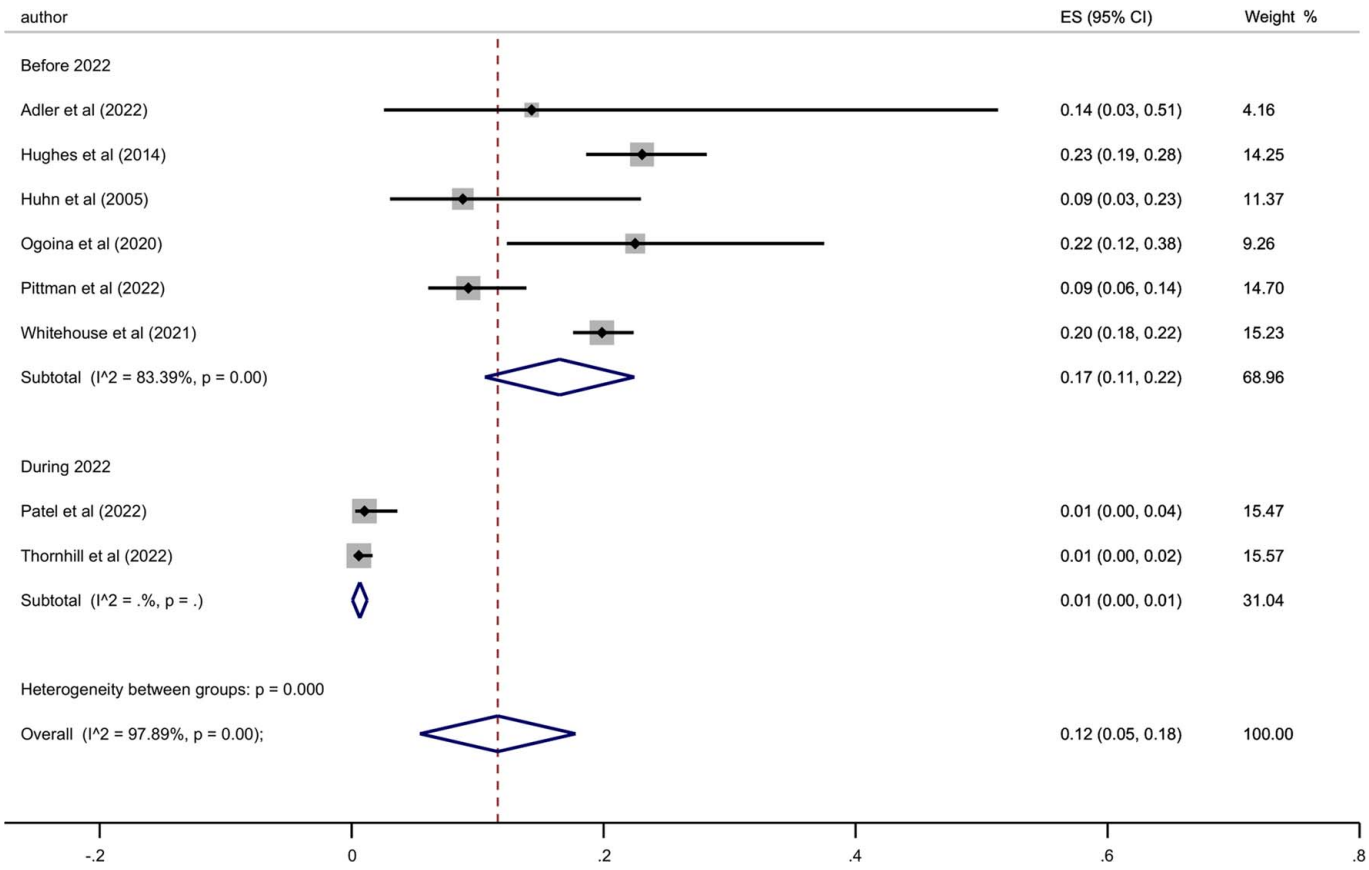


FIGURE 2. A forest plot showing the prevalence of conjunctivitis among monkeypox-confirmed patients categorized by the period of the outbreak. ES indicates effect size.

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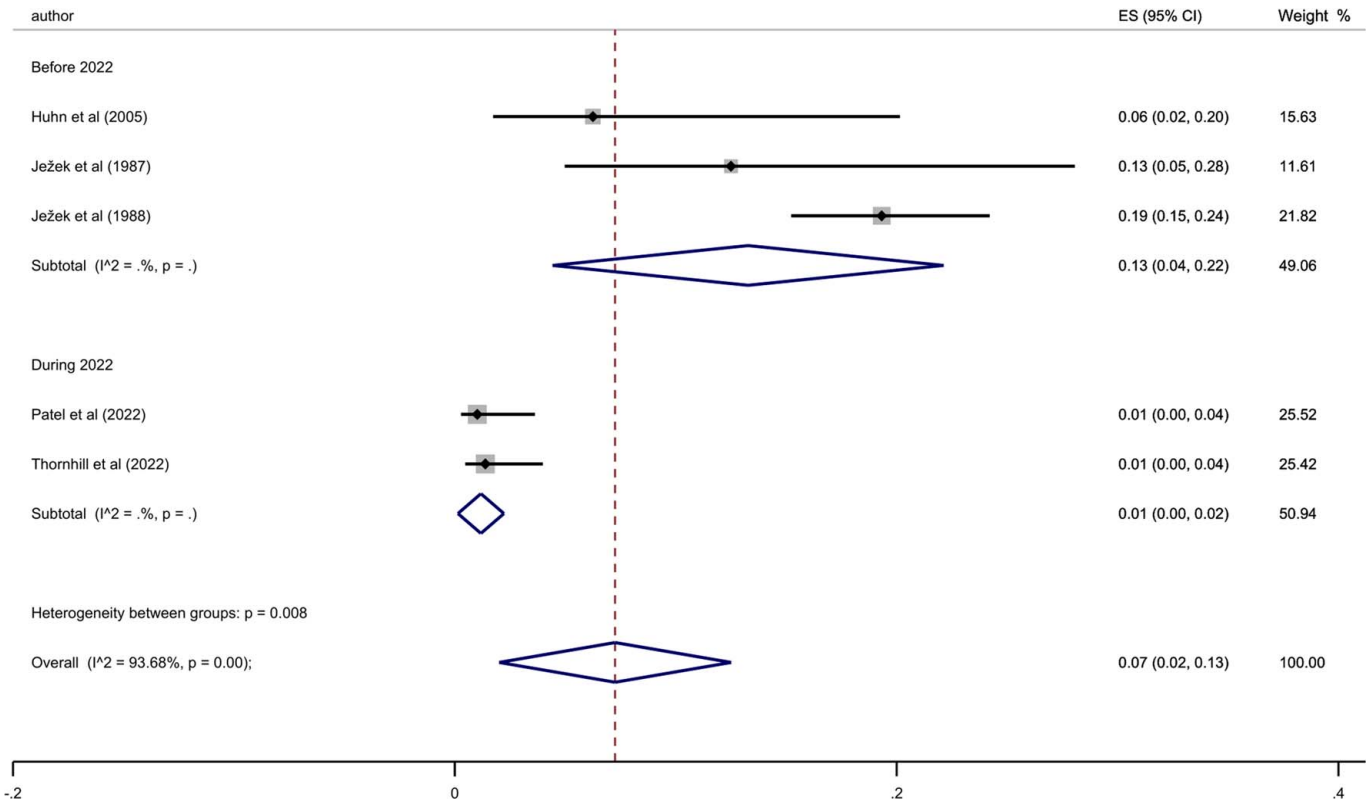


FIGURE 3. A forest plot showing the prevalence of eye lesions of the cornea or conjunctiva among monkeypox-confirmed patients categorized by the period of the outbreak. ES indicates effect size.

Although rare, our study highlights a prevalence rate of 4% of keratitis among MPX-confirmed cases. That being said, it should be mentioned that none of the included studies confirmed whether or not keratitis was viral in origin. Instead, it could have occurred as a complication secondary to bacterial superinfection. Therefore, this finding should be cautiously interpreted.

TABLE 5. The Pooled Prevalence Rate of MPXV-associated Eye Complications

Complication	Subgroup	Studies (N)	Eyes (N)	Pooled ES (95% CI)	I^2 (%)	Model	Grade
Corneal ulceration							
	Overall	3	611	0.04 (0.02–0.5)	0.00	Fixed-effects	⊕⊖⊖⊖ Very low
	Before 2022	3	611	0.04 (0.02–0.5)	0.00		
	During 2022	NA	NA	NA	NA		
Keratitis							
	Overall	4	833	0.04 (0.03–0.06)	0.00	Fixed-effects	⊕⊖⊖⊖ Very low
	Before 2022	4	833	0.04 (0.03–0.06)	0.00		
	During 2022	NA	NA	NA	NA		
Unilateral blindness							
	Overall	2	620	0.03 (0.01–0.04)	0.00	Fixed-effects	⊕⊖⊖⊖ Very low
	Before 2022	2	620	0.03 (0.01–0.04)	NA		
	During 2022	NA	NA	NA	NA		
Bilateral blindness							
	Overall	1	282	0.00 (0.00–0.02)	NA	NA	⊕⊖⊖⊖ Very low
	Before 2022	1	282	0.00 (0.00–0.02)	NA		
	During 2022	NA	NA	NA	NA		
Impaired vision							
	Overall	3	836	0.04 (0.01–0.08)	86.32	Random-effects	⊕⊖⊖⊖ Very low
	Before 2022	3	836	0.04 (0.01–0.08)	86.32		
	During 2022	NA	NA	NA	NA		

ES indicates effect size (prevalence rate); I^2, heterogeneity measure (> 50% indicates significant heterogeneity); MPXV, monkeypox virus; NA, not applicable (2 studies are required to allow for a meta-analysis of the assessed outcome).

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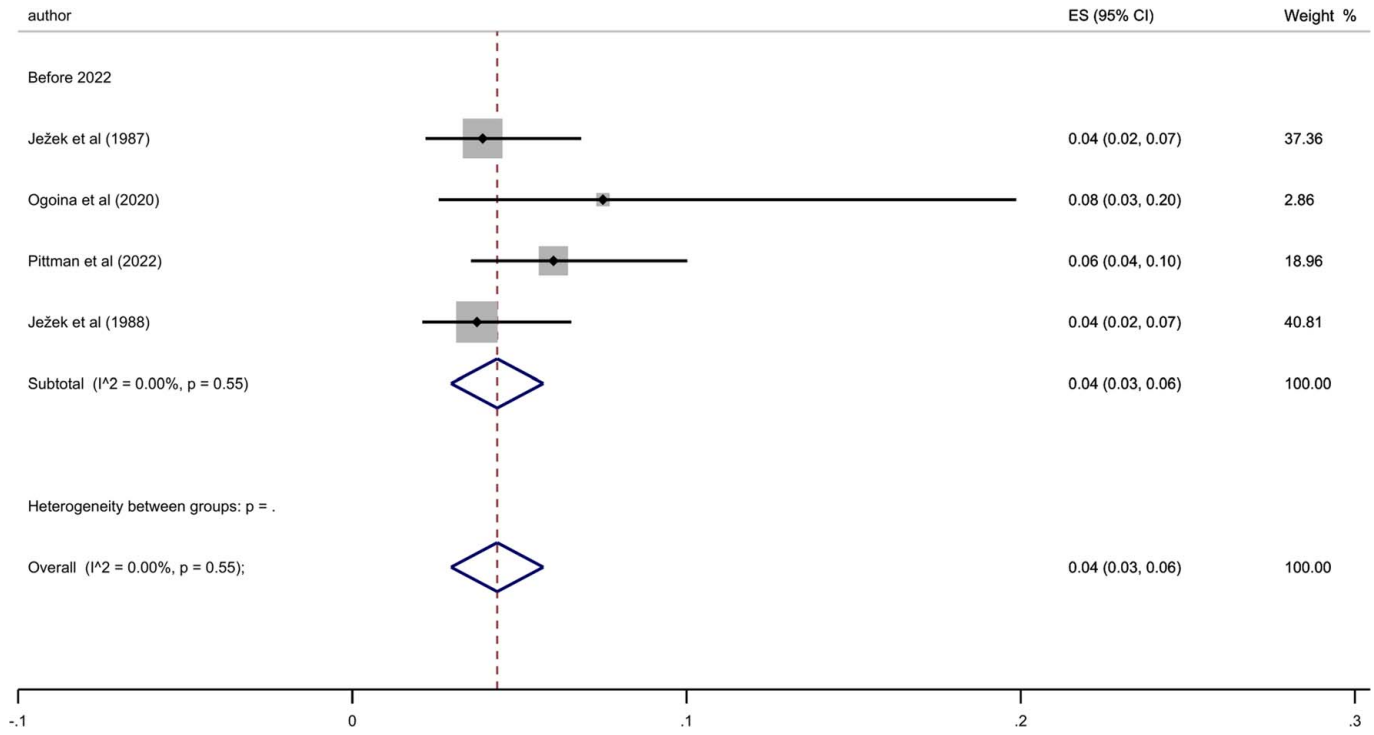


FIGURE 4. A forest plot showing the prevalence of keratitis among monkeypox-confirmed patients categorized by the period of the outbreak. ES indicates effect size.

The current findings might indicate that ophthalmic manifestations of the current outbreak are mild and not as concerning as those reported in previous outbreaks, which led to serious complications, including impaired vision and blindness. A self-limited course of ophthalmic manifestations has been established in the current outbreak. For instance, Benatti et al[40] indicated healing of conjunctivitis in their MPX patient after applying relevant treatment modalities for 3 weeks since the onset of symptoms, although a single whitish ulcer priorly developed from the reported blepharoconjunctivitis. Observational investigations reporting the clinical course of MPX are scarce. Accordingly, the current estimates might be underreported, indicating the need for relevant investigations. This does not exclude the need to establish a differential diagnosis for patients presenting with MPX ophthalmic manifestations to exclude the infection, al-

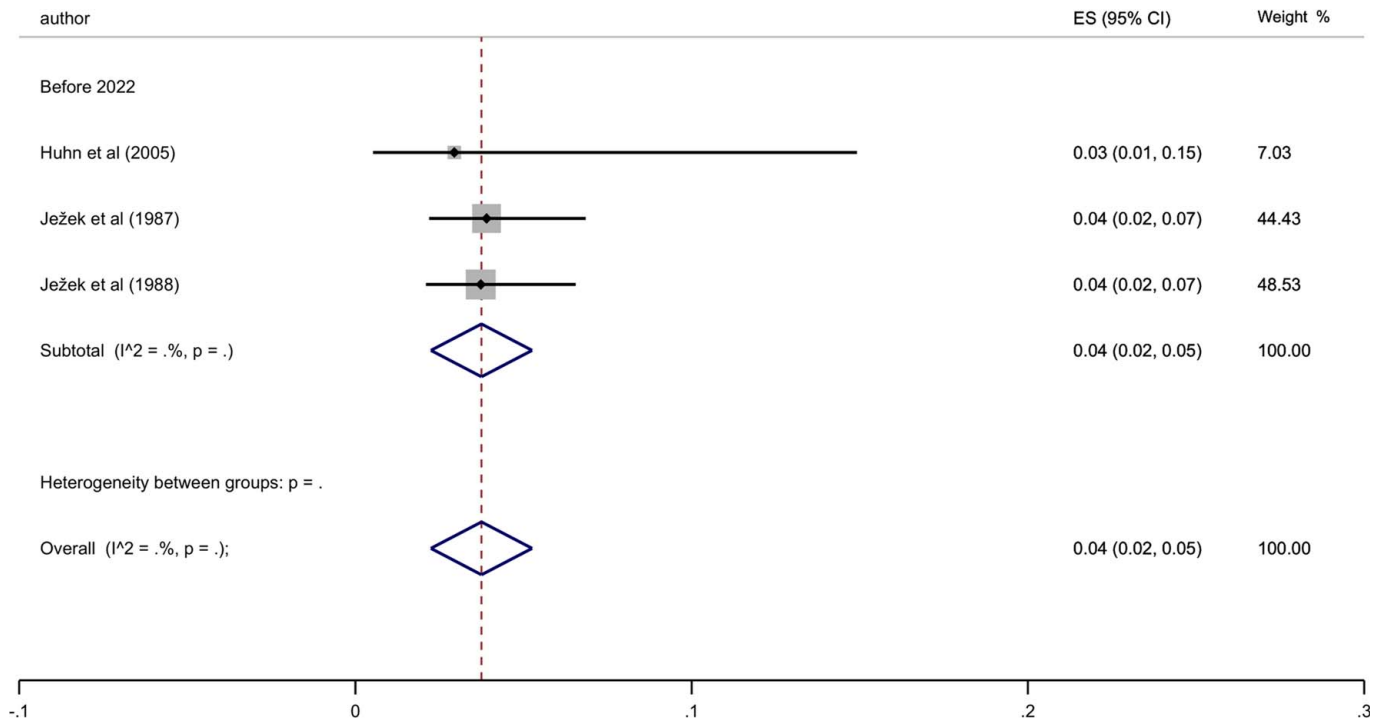


FIGURE 5. A forest plot showing the prevalence of corneal ulceration among monkeypox-confirmed patients categorized by the period of the outbreak. ES indicates effect size.

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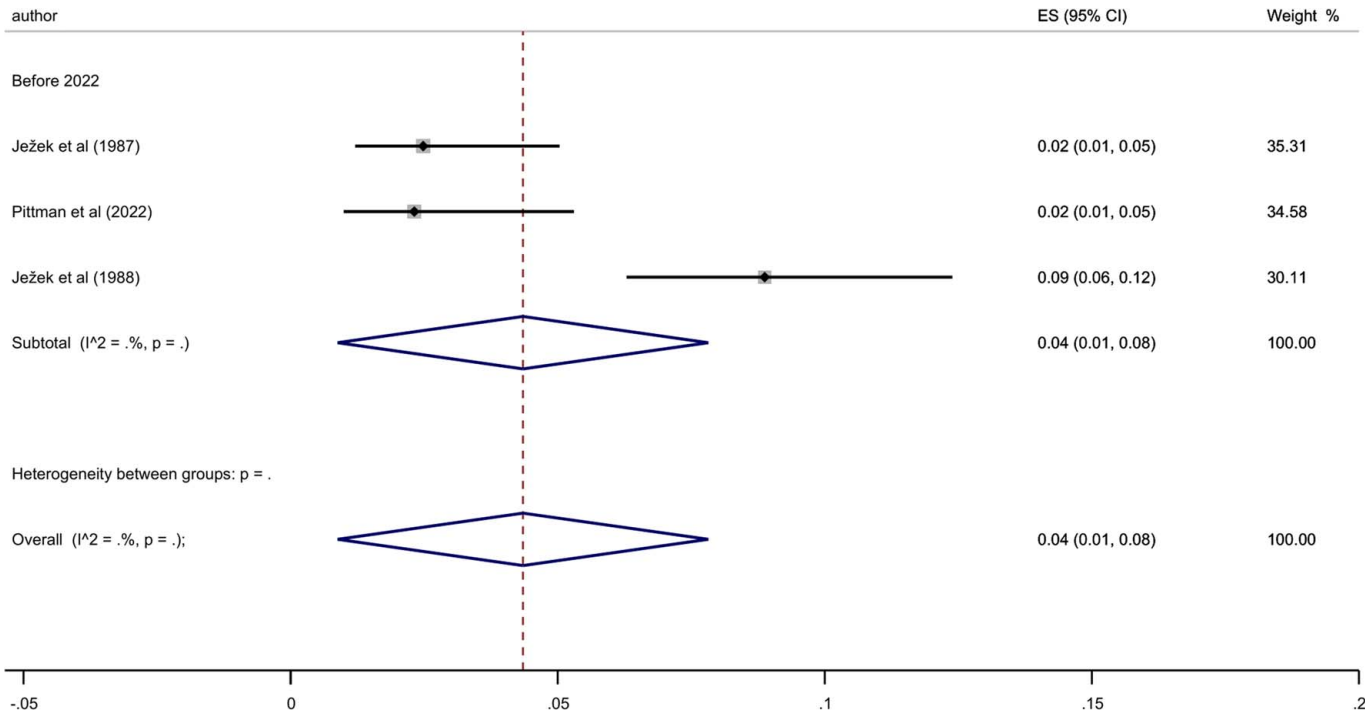


FIGURE 6. A forest plot showing the prevalence of impaired vision among monkeypox-confirmed patients categorized by the period of the outbreak. ES indicates effect size.

though the estimated rates of the current outbreak are too low to be clinically concerning. However, the estimated high rates of the same manifestations from previous outbreaks and the reported ophthalmic complications of smallpox might indicate the underdiagnosis of these ophthalmic manifestations. Therefore, health care workers should adopt the differential diagnosis for excluding MPX, at least as a preventive measurement, particularly since viral transmission through contacting MPX lesions has been previously established in the literature.[41,42]

Furthermore, it has been widely known that MPXV has a lower tendency toward genomic mutations because of the double-stranded structure along with the 3′–5′ exonuclease activity of its DNA.[43] In contrast, during the recent MPX outbreak, genomic studies highlighted that the current MPXV diverges from such speculation by a mean of 50 single-nucleotide polymorphisms, and this substitution rate is much higher than the expected rate nor the observed rate in orthopoxviruses in general.[44,45] This divergence could have fastened the evolution of MPXV, which, in turn, resulted in higher transmission, quicker course of the disease, and lower mortality. Although pathogenicity in the current outbreak explains such observations, its role in changing presentation patterns, particularly those involving the eye, still warrants further research.

It is worth mentioning that Pittman et al[38] estimated the prevalence of eye manifestations (conjunctiva redness, eye pain, eye discharge, etc.) by age group. For instance, the prevalence of ophthalmic symptoms was similar among patients in the <5-year (12.9%, 4/31), 5- to 11-year (9%, 6/67), and ≥12-year (8.5%, 10/113) groups. Similarly, the prevalence of signs was similar among these groups (6.5%, 9%, and 5.1%, respectively). The authors further stratified their MPX cases into 4 levels based on MPX disease severity, as level 1 referred to a mild disease while level 4 indicated death. Regarding ophthalmic symptoms, the rate was significantly higher in patients with level 3 disease severity (27.5%, 11/40) than in others with level 1 (3%, 3/99) and 2 (8.1%, 6/74) ($P = 0.002$). However, the difference was insignificant between the 3 groups regarding eye signs (17.5%, 5.4%, and 3%, respectively; $P = 0.066$). The clinical relevance of these findings should be further investigated in the current outbreak to establish proper evidence highlighting the most vulnerable groups to help health care authorities adopt proper interventions and management approaches.

Strengths and Limitations

The present study provides evidence regarding the prevalence of ophthalmic manifestations and complications of MPX cases. A systematic review was conducted based on the PRISMA guidelines to retrieve all the relevant articles that reported ophthalmic manifestations and complications of MPX cases with no restrictions regarding year or country of publication. Thus, our analysis represents the largest sample size found in the literature. Besides, we conducted a subgroup analysis to compare the rates of the current outbreak to the rates of previous ones.

However, the current findings are inconclusive and need further investigation due to several limitations. First, significant heterogeneity was reported among the findings of some studies regarding some outcomes. In addition, the prevalence rates of some manifestations and complications among individual studies are remarkably variable. For instance, the pooled prevalence of conjunctivitis was 12%, with a 95% CI of 5%–18%. Similarly, the pooled prevalence of lesions involving the cornea and/or conjunctiva was 7%, with a 95% CI of 2%–13%. This wide CI reflects the increased likelihood of imprecision in reported findings. A very important point to consider is that none of the included studies

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reported whether or not the eye was systematically and thoroughly examined in any presenting patient, given the fact that such cases are usually managed by infectious disease specialists with very limited experience in identifying eye pathologies. Based on that, we assume that such reported cases of ocular involvement of MPX in the literature could represent only those who had very apparent symptoms and/or signs warranting ophthalmology consultation. This should be put into account when interpreting our results since this could explain the low rate of ocular manifestations and complications secondary to underdiagnosis and/or underreporting.

Therefore, further investigations are needed to better estimate the prevalence rates. Second, prevalence of such events was estimated from case series, which might contribute to overestimating the prevalence rates of some manifestations. Third, the prevalence of some manifestations and all complications of MPX cases in the current outbreak was not feasible due to lacking relevant data. Although it might be suggested that the prevalence of these events is low in the current outbreak, we encourage further relevant investigations to exclude the potential of misdiagnosis and underreporting of cases.

CONCLUSIONS

Ophthalmic manifestations are common among MPX patients. Conjunctivitis and photophobia are the all-time commonest manifestations. However, data regarding the current outbreak is still meager, and further investigations are encouraged. Severe ophthalmic complications (including keratitis up to vision loss) were also commonly reported. Although these complications are limited to previous MPX outbreaks, health care workers should familiarize themselves with applying the best management approaches to enhance the quality of care for MPX patients.

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