**Decoding mpox: A Systematic Review and Meta-analysis of the Transmission and Severity Parameters of the 2022-23 Global Outbreak**

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**Abstract. Introduction:** In 2022-2023, the largest outbreak of mpox in history occurred. Epidemiologic parameters of mpox can help to elucidate the dynamics of the infection and better understand the behavior of the current outbreak. We aim to synthesize the key epidemiological parameters related to the transmission and severity of mpox (incubation period, serial interval, generation time, infectious period, basic (R0) and effective (Rt) reproductive number, and case fatality rate (CFR)). **Methods:** Systematic review and meta-analysis of observational studies in MEDLINE, EMBASE and other sources up to September 2023 (PROSPERO: CRD42023404503). To assess the standard quality of studies, we used the Joanna Briggs Institute Critical Appraisal for case series, cross-sectional, and cohort studies, and a designed quality assessment questionnaire for mathematical models. Meta-analysis was performed using a random-effects model. **Results:** For transmissibility parameters, we estimated a pooled incubation period of 7.56 (95% CI 7.13-8.0) days, a pooled serial interval of 8.25 (95% CI 6.4-10.5) days, a pooled generation time of 10.83 (95% CI 8.1-14.5) days. 97th percentile of the IP distribution varied between XX and XX. Two studies reported pre-symptomatic transmission in 20 – 50% of paired cases investigated. For severity parameters, we estimated a pooled global CFR of 0.03% (95% CI 0-0.24%). Sub-analysis of CFR by geographic region showed a greater lethality for the African continent 10.80% (95% CI: 4.60%-23.2%). R0 varied between 0.19 and 3.02. R(t) highest values varied between 1-4 and showed a peak between late August and early September 2022. **Conclusion:** our study showsthat pooled mpox serial interval is slightly larger than pooled incubation period, suggesting that transmission occurs after symptom onset in most cases. Although pre-symptomatic transmission can occur in an important proportion of cases. The pooled CFR was two orders of magnitude lower than in previous mpox outbreaks and was higher for the African continent. Mean R0 and Rt estimations were higher than those observed before 2022. Our results could contribute to the development of mathematical models to assess the impact of interventions and help improve epidemic responses for future outbreaks.

**Key words:** mpox, monkeypox, outbreak, epidemiological parameters, systematic review, meta-analysis.

**What is already known on this topic –** Prior to 2022, the R0 of mpox was reported to be approximately 0.8, between 1980 and 1984. The CFR was estimated to be approximately 8.7%, between 1970 and 2019, with variation depending on the clade. No deaths were reported outside the African endemic countries before 2022. From 2022 to the present, several studies on the epidemiology and transmission of mpox have been published. However, no systematic reviews summarizing the available literature on this topic have been published.

**What this study adds –** Here we present pooled estimates of epidemiologic parameters of the 2022-23 mpox global outbreak concerning the infection dynamics and severity, obtained from a systematic review and meta-analysis. We found an incubation period of 7.56 (95% CI 7.13-8.0) days, a serial interval of 8.25 (95% CI 6.4-10.5) days, a generation time of 10.83 (95% CI 8.1-14.5) days, a CFR of 0.03% (95% CI 0-0.24%). The basic reproduction number varied between 0.19 and 3.02, and the effective reproduction number showed a peak between late August and early September 2022.

**How this study might affect research, practice, or policy –** Our review provides a comprehensive summary on key epidemiologic parameters of mpox transmission and severity, that can serve as input to statistical and mathematical models to understand the 2022-23 outbreak, and better prepare for future outbreaks. Our study also identifies gaps in knowledge and areas of uncertainty for further research.

**Introduction**

Mpox (formerly known as monkeypox) is a zoonotic disease that is endemic in Central and West Africa. The first case in humans was reported in 1970 [1]. Since then, intermittent cases of infection have been reported in endemic countries, characterized by a febrile prodrome followed by vesiculopustular skin eruptions [2]. There are two genetic clades. Clade I has historically been found in the Congo Basin, while clade II has been found in West Africa [3]. Traditionally, transmission of mpox was thought to be primarily acquired from infected animals to humans via scratches or bites while hunting or contact with infectious fomites [4]. The animal reservoir is still unknown, but small mammals, including rodents, could play a role in the maintenance and spread of the virus [2]. Currently, it is known that after one or more spillover events from the reservoir, human-to-human transmission can occur through close contact with infectious material from skin lesions, respiratory secretions during prolonged face-to-face contact, and fomites [5].

In 2022–2023, the largest outbreak of mpox in history occurred. As of December 2023, mpox has spread across 115 countries with more than 91,000 confirmed cases and 157 deaths worldwide [6]. Compared to previous mpox outbreaks, the current outbreak has shown some critical differences related to modes of transmission, clinical presentation, and population at risk [7]. Most cases include men who report male-to-male sexual contact, and the most common form of transmission is skin-to-skin contact during sexual encounters [8]. Most cases reported globally are in the Americas and Europe, with more severe cases related to immunosuppressive conditions such as HIV [9], who may benefit from antiviral treatment in some cases [10]. In 2019, the US Food and Drug Administration (FDA) approved the modified vaccinia Ankara vaccine to prevent mpox infection, but for antivirals, their availability in many regions is scarce [11].

Due to the new mode of transmission and speed with which the outbreak spread, the Director-General of World Health Organization (WHO) declared mpox a Public Health Emergency of International Concern between July 2022 and May 2023 [12]. In outbreaks of emerging or re-emerging infectious diseases, one of the main priorities is to establish and intensify epidemiological disease surveillance. It is also important to collect and analyze key epidemiological and clinical parameters related to the dynamics of transmission and severity of the disease [13]. Parameters such as the incubation period, serial interval, generation time, infectious period, basic and effective reproduction numbers, and case fatality rate have been shown to be especially useful for assessing the trajectory of an epidemic and the impact of control strategies [14-16].

Although the number of mpox cases has diminished considerably since the beginning of 2023 [6], some lessons can be learned from this outbreak that could be used in future outbreaks. Several studies of mpox epidemiology and transmission have been published during the current outbreak [16-18]. Epidemiological parameters estimated from these studies can serve as input for statistical and mathematical models to retrospectively understand the 2022-23 outbreak and to be better prepared for future mpox outbreaks. In this way, summarizing the available evidence could help provide a comprehensive overview of parameter estimates from multiple studies, providing modelers with robust and well-informed parameter values.

Here, we aim to identify and synthesize the key epidemiological parameters related to the transmission and severity of the 2022-23 mpox outbreak (incubation period, serial interval, generation time, infectious period, basic and effective reproduction number, and case fatality rate) through a systematic review and meta-analysis.

**Material and methods**

*Protocol*

We conducted this systematic review following the reporting guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), and the protocol was registered at the International Prospective Registry of Systematic Reviews (PROSPERO): CRD42023404503.

*Search strategy*

A search strategy was developed to identify as many studies as possible (sensitive), including controlled vocabulary (Medical Subject Headings (MeSH), Emtree (EMB)) and free text terms (considering variant spellings, synonyms, acronyms and truncators), using field tags, Boolean and proximity operators adapted for each search engine, without language restrictions, from May 1, 2022, to September 10, 2023. The search strategy was adapted for the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid Platform), EMBASE (Elsevier), Web of Science, Scopus, Latin American and Caribbean Literature in Health Sciences (LILACS) and Clinical Trials.

We also performed a semistructured search in repositories of preliminary reports or preprints of scientific articles in the following sources: medRxiv, bioRxiv, arXiv, SSRN, Research Square, Virological. Additionally, we searched websites, institutional repositories, and electronic databases of the following institutions: the London School of Hygiene & Tropical Medicine (LSHTM), Imperial College London, the US Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC), and UK Health Security Agency (UKHSA), given their involvement in outbreak response work for mpox.

Additional references were requested from opinion leaders and clinical experts in infectious diseases via email and ResearchGate. Finally, a manual search was performed by reviewing the list of bibliographic references of the selected studies ("snowball"). The search strategies are available in Supplementary Table 1.

*Study selection*

Two authors (CDB and LNB) independently reviewed the studies identified with the search strategy. Initially, they performed it by title and abstract, later by full text. Disagreements were resolved by consensus or by involving a third review author (ABL).

*Eligibility Criteria*

The types of publications included were published or preprinted original articles, short reports, short communications, and epidemiological surveillance reports. The

The types of studies included were descriptive or analytical observational studies, experimental or quasiexperimental studies, statistical or mathematical modeling studies, and simulation studies. We excluded purely theoretical mathematical models (i.e., not fitted to data). The types of participants were adults, categorized as suspected or confirmed cases of mpox infection, or their contacts in follow-up. The types of outcome measures were as follows:

* Basic reproduction number, 𝑅0: Number of secondary infections caused by a primary case in a fully susceptible population.
* Effective reproduction number, 𝑅(𝑡): Number of secondary infections caused by a primary case in a partially susceptible population.
* Incubation period: Period between the time of exposure to the pathogen and the time of symptom onset.
* Serial interval: Time from the onset of symptoms in the primary case to the onset of symptoms in the secondary case.
* Generation time: Time from infection in the primary case to infection in the secondary case.
* Infectious period: Time during which an infected host, with or without symptoms, can transmit an infectious agent to susceptible persons.
* Case fatality ratio (CFR): proportion of confirmed cases that result in death.
* Infection fatality ratio (IFR): Proportion of all infections (confirmed, symptomatic, asymptomatic) that result in death.

*Data extraction*

Two review authors (CDB and LNB) independently extracted the following data from each of the included studies using a previously tested data extraction form: 1) general information about the study, such as type of publication, type of study, country or region, inclusion and exclusion criteria, and sample size; 2) baseline characteristics of study participants/population/patients, such as age, sex, race, sexual orientation, gender identity, HIV status, other non-HIV immunosuppressive conditions, baseline CD4 count, concomitant antiretroviral treatment, HIV viral load, history of smallpox vaccine, history of smallpox vaccine in the current outbreak (JYNNEOS, ACAM2000); 3) aspects related to viral transmission dynamics (for suspected or confirmed cases), such as sexual or intimate contact in the 21 days prior to symptom onset, suspected source of transmission, type of sexual or intimate contact, close contact with suspected or confirmed case, when available; 4) description of the disease and its severity: signs and symptoms, total duration of symptoms, location of lesions, concomitant diagnosis of another sexually transmitted disease (STD), treatment administered, hospital or intensive care unit (ICU) admission, and final outcome of last contact, when available; and 5) For all parameters, we extracted information about the definition used by the authors, sample size to fit the distribution (when applicable), study period and availability of code and data. For the incubation period, infectious period, serial interval, and generation time, we collected information about measures of central tendency and variability (mean or median, range, interquartile range, coefficient of variation, among others), uncertainty (confidence intervals or credible intervals), probability distribution (e.g., Weibull, beta, gamma), and recorded whether authors adjusted for bias (e.g., censoring or truncation). Investigators of included studies were contacted by e-mail to request missing data when necessary.

*Assessment of quality of included studies*

For mathematical models, we designed a checklist, considering the following aspects: 1) the availability of code and data; 2) the report of central tendency and variability measures (e.g., mean, standard deviation, median, range, IQR) with their respective uncertainty values (95% or 90% confidence or credible intervals, according to the method used: frequentist vs Bayesian analysis, respectively); and 3) the description of the type of distribution fitted (e.g., Weibull, gamma, log-normal, etc.). ), sample size used to fit the distribution and the parameters of the distribution; and 4) if methods to adjust the model for bias were used (e.g., censored or truncated data or the application of other statistical methods for adjustment).

For the remaining study designs, we used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series [19], Cross Sectional Studies and Cohort studies [20] included in our analysis, with minor modifications according to a preliminary analysis of the included studies and their objectives and methods.

*Analysis*

We used descriptive tables and figures to present the collated data. Unless otherwise specified, uncertainty intervals in tables and figures (e.g., 95% confidence intervals (CI) or credible intervals (CrI)) were extracted from the papers or computed from reported central estimates and standard errors.

For the incubation period, serial interval and generation time, meta-analyses were performed using the meta-R package [21] by calculating an overall mean from studies reporting a single mean using the inverse variance method for pooling. Random effects models were used, with the study as the random effect. A sensitivity analysis was performed by dividing the studies into mathematical models or primary studies when applicable.

For the CFR, a meta-analysis was performed by calculating an overall proportion from studies reporting a single proportion using a generalized linear mixed model (GLMM) for pooling, given the expected low frequency of the outcome. Both common effect and random effects models were estimated along with statistics on heterogeneity in CFR across studies.

For the infectious period, we could perform a meta-analysis due to a lack of data. The results from the only study [22] found in the review are presented.

Likewise, for the basic and reproduction numbers, we decided not to perform an aggregated analysis of estimates because of difficulties in the interpretation of the results, given heterogeneity in the times, locations, and methods used to calculate these parameters. Instead, we present the findings summarized in a forest plot.

When analyses of aggregated results were performed, statistical heterogeneity was assessed by visual inspection of forest plots and the , and statistical tests.

A sub-group analysis was performed for the CFR and incubation period, according to the geographical distribution of the estimates and type of study (mathematical models compared to other types of designs), respectively. Although we planned to perform a sub-group analysis of estimates according to sex assigned at birth, mechanism of transmission, HIV status and type of vaccine strategy used (pre- and postexposure prophylaxis), these were not possible due to limited data. Analyses were conducted using R (version 4.2.2) [23].

**Results**

*Search Results*

A total of 6111 references were identified from the electronic search of databases and other mentioned sources. After removing duplicates and performing an initial screening by title and abstract, 158 references were eligible for full-text evaluation. Of these, a total of 109 studies were excluded: 77 for failing to evaluate epidemiological parameters of interest, 24 for being theoretical models only (not fitted to data), two for wrong study design, two for not corresponding to the study period of interest and four for no full-text availability (only poster abstracts). Finally, 48 studies were identified and included in the present systematic review, as shown in the PRISMA flow diagram (Figure 1). Table 1 shows the characteristics of the included studies. The characteristics of the excluded studies are found in Supplementary Table 2.

*Included studies.*

The main characteristics of the studies included in this review are detailed in Table 2. The studies were carried out in different countries and locations worldwide, but most of the evidence comes from Spain, the United States of America, and the United Kingdom. A map of the number of articles selected per country is represented in Figure 2A.

Forty-eight references were included in the analysis. The predominant study designs were mathematical or statistical models n=24 references (50%), followed by descriptive case series n=13 (27%), cross-sectional studies/surveillance reports n=9 (19%) and cohort studies n=2 (4%). Regarding the epidemiological parameters estimated by the studies, incubation period was the main parameter reported (n=26 references), followed by basic reproduction number (n=11), effective reproduction number (n=8), serial interval (n=5), CFR (n=25), generation time (n=2) and infectious period (n=1). The proportion of each study design (Figure 2B) and epidemiological parameters evaluated in the included references (Figure 2C).

*Assessment of quality of included studies*

The results of the quality assessment are summarized in Figure 3, and a detailed description of the decision of each study is available in supplementary table 3.

For mathematical models, most of the studies reported the fitted distribution used and their parameters, the time frame, and central or dispersion tendency measures with their respective uncertainty intervals. Nevertheless, more than 25% of the studies failed to perform model adjustments to overcome critical aspects, such as phase bias when the outbreak was in an ascending or descending phase or did not account for censoring or truncated data when necessary. Additionally, 21% of the studies did not explicitly report the code and data used for their reported parameter estimations (Figure 3a).

For case series, 84% of the studies reported clear eligibility criteria and provided information about the case definition of mpox disease, including a detailed description of demographics of patients and the setting where the patients were identified (i.e., clinic, residence). Seven percent of the studies had limitations in reporting complete clinical information, treatment received and need for hospital admission (Figure 3b).

In the case of cross-sectional and surveillance reports, all included studies had clear criteria for including patients, offered a detailed description of patients and the settings where they were identified, and demonstrated reliability in the measurement of the outcomes evaluated (Figure 3c).

Last, the two cohort studies included in this review demonstrated adequate standardization of the processes and diagnostic tests performed in the cohort; however, they failed to provide detailed information about the follow-up of the patients and the reasons for loss to follow-up (Figure 3d).

*Epidemiological parameters*

*Incubation period:* Twenty-six studies (see Table 1) reported estimates of this parameter, combining data on a total of approximately 2034 confirmed or suspected mpox cases. Pooling these estimates yielded a mean incubation period of 7.56 days (95% CI: 7.13-8.02) using a random effect model, = 15%, = 0.005, p = 0.24. (Figure 4a). It is important to note that some of the patients included across the studies overlapped (e.g., cases were partly shared between Charniga et al. [24] and Madewell et al. [25]) because of the time they were conducted. The most common fitted distributions across the studies that were used by the authors to estimate the parameter were gamma, log-normal, and Weibull, in that order.

We performed a sensitivity analysis according to the type of study design (mathematical model vs other study designs). For mathematical models, we analyzed estimates from 10 studies, obtaining a pooled mean incubation period of 7.67 (95% CI: 7.13-8.25) for both common and random effect models, = 0%, = 0, p = 0.51 (Supplementary Figure 1a). For nonmathematical models, we analyzed estimates of 16 studies, obtaining a pooled mean incubation period of 7.46 (95% CI: 6.87-8.10) using a random effect model, = 30%, = 0.008, p = 0.13 (Supplementary Figure 1b).

*Serial interval:* five mathematical models [25-29] reported estimates of this parameter. We combined the data to obtain a total of 225 confirmed or suspected mpox cases. Pooling these estimates yielded a mean serial interval of 8.25 days (95% CI: 6.45-10.55) using a random effect model, = 90%, = 0.06, p <0.01. (Figure 4b). Four of the studies fitted a gamma distribution to the data, and one study fitted a normal distribution.

*Generation time:* Two mathematical models [22, 30] reported estimates of this parameter, and we obtained a pooled mean generation time of 10.83 days (95% CI: 8.11-14.46) using a random effect model, = 0%, = 0, p = 0.60 (Figure 4c). A gamma distribution was fitted to the data in both studies.

*Infectious period:* Only one study [22] reported estimates of this parameter. It was an analysis and prediction system for epidemics based on a general SEIR model (susceptible (S), exposed (E), infectious (I), and recovered (R)) fitted to data of confirmed mpox cases from the US CDC and the WHO. For the USA, the mean infectious period was 4.01 days (95% CI 1.6-11.6); for Europe, it was estimated as 3.89 days (95% CI 1.6-12.1); and globally, the mean infectious period was 3.7 (95% CI 1.5-11.7).

*Case fatality rate:* Twenty-six studies (see Table 1) reported the proportion of deaths related to mpox in their study populations, for a total of 68662 suspected or confirmed mpox cases. Pooling these estimates, we obtained a CFR of 0.0003 (95% CI: 0- 0.0028) using a random effect model, = 98.1%, = 9.5, p <0.01 (Figure 4d). Given the high heterogenicity found in our pooled estimates, we also performed a sensitivity analysis separating the studies by geographic location (Global, Americas, Europe, and Africa). For the global stratum, we analyzed estimates from four studies and obtained a pooled CFR of 0.0002 (95% CI: 0-0.278), I2 = 0%, Tau2 = 15.8, p = 1.0 (Supplementary Figure 2a). For the Americas, we analyzed estimates from six studies and obtained a pooled CFR of 0.001 (95% CI: 0.0009-0.0017), I2 = 0%, Tau2 = 0, p = 0.78 (Supplementary Figure 2b). For Europe, we analyzed estimates from four studies and obtained a pooled CFR of 0.0 (95% CI: 0-1), I2 = 0%, Tau2 = 0, p = 1.0 (Supplementary Figure 2c). For the African continent, we analyzed estimates from two studies and obtained a pooled CFR of 0.108 (95% CI: 0.046-0.232), I2 = 92%, Tau2 = 0.37, p <0.01 (Supplementary Figure 2d). The intention was to perform a sensitivity analysis according to HIV status, age, biological sex and sexual orientation, but this was not feasible given the limited separate data for each category.

*Basic reproduction number:* Eleven studies reported estimates of the basic reproduction number. The mean or median values ranged from 0.19 to 3.01 across the included references (Figure 4e).

*Effective reproduction number:* Eight studies reported estimates of the effective reproduction number. The peak of the epidemic was reached for all countries between late August and early September 2022, when R(t) values went below the threshold of 1 (Figure 4f).

**Discussion**

Our systematic review and meta-analysis was able to synthesize key epidemiological parameters related to the transmission and severity of the 2022-23 mpox outbreak that can support mathematical modeling. We found an incubation period of 7.56 days (95% CI 7.13 to 8.02), a serial interval of 8.25 (95% CI 6.45 to 10.55), a generation time of 10.83 (95% CI 8.11 to 14.46) and a CFR of 0.0003 (25 studies; 95% CI 0.0000-0.0024). The infectious period was reported in only one study [22] (3.7 days, 95% CI 1.5-11.7). Additionally, we identified 11 studies that estimated the basic reproduction number of mpox, varying from 0.19 to 3.02. Eight studies reported the effective reproduction number for different periods of the epidemic, showing a peak between late August and early September 2022, when R(t) values went below 1 for most of the affected countries. To our knowledge, this is the first systematic review of epidemiological parameters involved in the transmission and severity of the 2022-2023 multicounty mpox outbreak. To reach a better understanding of these results, it is important to compare parameter estimates from our review with those from outbreaks that occurred prior to 2022.

Regarding the basic reproduction number (R0), a systematic review in 2019 [31] reported an analysis of active surveillance data collected in the Democratic Republic of Congo (DRC) between 1980 and 1984, demonstrating an R0 of 0.8 [32]. Interestingly, when the upper confidence interval limit for the crude secondary attack rate was taken, the R0 was 1.0, which may indicate the possibility of persistence in human populations [32]. In 2020, Grant et al. [33] estimated R0 using data collected in the DRC during 1966–1984. Smallpox vaccination in this country ended in 1980, with vaccination coverage of nearly 100%. Assuming 85% efficacy against mpox, they calculated an R0 of 2.13 (95% CI 1.46 to 2.67). It is important to note that historically, DRC outbreaks are almost always associated with Clade I until 2022, when Clade IIb outbreaks begin to be observed in endemic and nonendemic regions, showing a different pathogenicity and less severity [34].

For the effective reproduction number (Rt), our results are in line with recent reports, demonstrating a steady increase in Rt (estimated of 0.82; 95% CI: 0.79 – 0.85) between 2013 and 2017 in the DRC [35]. This finding could be attributed to the reduction in population-level immunity conferred by smallpox vaccination, behavioral changes, and ecological and environmental changes, among other factors [35, 36]

In terms of the CFR, a systematic review [7] reported a pooled estimate of 8.7% from confirmed or suspected mpox cases between 1970 and 2019 (78/892; 95% CI 7.0 to 10.8), with variations according to clade. For Clade I, CFR was 10.6% (68/640; 95% CI 8.4 to 13.3), compared to 3.6% (9/247; 95% CI 1.7 to 6.8) for Clade II. There were no deaths reported outside of Africa before the 2022-23 outbreak. In contrast, in our review, we estimated much lower values for this parameter, with a global CFR of less than 0.05%. It is important to note that we found high heterogeneity in our results (=94%; p<0.01) when pooling the estimates from all over the world, so we decided to perform a sensitivity analysis separating the studies by geographic location (global, Americas, Europe and Africa), demonstrating a significant reduction in statistical heterogeneity for each stratum, except for the African continent (=92.6%; p<0.01).  The observed decline in heterogeneity in the subsequent analysis could be explained by differences in the number of events among the studies and comorbidities of the included patients, such as HIV, malaria, and malnutrition states. In fact, clinical data from case series and cohorts have shown that complications occur more frequently among patients living with HIV, especially those from the Americas [37, 38]. As for the results of the sensitivity analysis, we found a greater CFR in the African Region compared to the Americas and Europe (11% vs less than 0.001%). Our review was able to identify such aspects that affect the results and due to different scenarios in different areas of the world.  We also acknowledge that the results from individual studies may be biased due to delayed reporting, which may decrease the estimate for the CFR. Also, one important limitation of the estimation of CFR is the fact that we could have double counted events and total cases for various studies of reports, especially those with overlapped study frame periods.  For future studies, care should be taken to limit bias in the estimation of the CFR, such as by limiting the analysis to those cases with sufficiently long follow-up for a death to occur and/or excluding those with unknown outcomes [39].

Concerning the infectious period, only one study [22] estimated this parameter, which was approximately 3.7 days. This estimate was surprisingly low, considering that the US CDC accounts someone to be infectious from the time lesions start until the time all scabs have fallen off and new skin has formed (approximately 3 to 4 weeks) [40]. Unfortunately, a precise definition of this parameter was not clearly provided in the mentioned study, which could have improved the interpretation of this finding.

For the generation time, this parameter was reported in only two studies [22, 30]. The lack of studies reporting generation time may be due to the difficulties in its estimation due to limited contact tracing data and the fact that this delay is generally not observable.

Our pooled estimate for the serial interval of mpox was slightly longer than our pooled estimate of the incubation period (8.25 days vs 7.56 days, respectively). If transmission occurs after symptom onset, the mean serial interval is longer than the mean incubation period. In contrast, if presymptomatic transmission occurs, the mean serial interval is shorter than the mean incubation period (38). It is still debated whether presymptomatic transmission occurs for mpox and, if so, to what extent [25, 28, 29]. Presymptomatic transmission has implications for how easily an outbreak can be controlled by isolating infectious individuals and contact tracing and quarantining their contacts [41]. Our results suggest that the role of presymptomatic transmission of mpox in the 2022-23 outbreak may be limited, as the mean serial interval (and generation time) are greater than the pooled estimation of the incubation period. Had more data been available, it would have been interesting to perform a subanalysis by epidemic phase (before 2022 compared to after 2022). We would expect a difference in the results presented if the early studies did not adequately adjust for epidemic phase bias and right truncation. Further high-quality research is needed to better understand the impact of the epidemic in the past and now.

Our systematic review has several limitations. First, there is currently no international consensus on the appropriate structuring of systematic reviews of epidemiological parameters of infectious diseases. To overcome this challenge, we proposed clear and comprehensive eligibility criteria, included multiple primary study designs and sources, and considered mathematical models based on real data. We also developed a thorough data extraction form, including aspects such as measures of central tendency and/or variability, fitted probability distribution, truncation or censoring of data, among others. Second, although guidelines for estimating the CFR [39] and Rt [42] have been published, clear best practices for estimating and reporting epidemiological delay distributions are lacking in the literature. Therefore, we opted to design a simple checklist for the appropriateness and comprehensiveness related to the reporting of the parameters and checked if the authors reported performing statistical methods to adjust for potential bias; we did not review the code or equations to ensure that when authors reported adjustment for bias, they did it correctly. Third, we were also unable to assess the impact of different phases of the current mpox outbreak on patient prognosis due to limited data. Future studies should focus on improving the characterization of key parameters in special populations, such as HIV patients and others who are immunocompromised. Fourth, some of the cases across the studies are shared for incubation period estimations, so it is possible that we double counted some cases. To overcome this, we would need to access the raw data and re-estimate the parameters, which was not feasible.

**Conclusion**

Here, we synthesize information on key epidemiologic parameters from the 2022-23 multicounty outbreak of mpox. In summary, pooled estimates show that the mpox serial interval is slightly larger than the incubation period, suggesting that transmission occurs after symptom onset in most cases. The pooled CFR (0.03%) was found to be two orders of magnitude lower than in previous mpox outbreaks, being higher for the African continent (around 11%). Mean R0 values ranged from 0.12 to 3.14, while highest mean R(t) values ranged from 1.2 to 3.7. We believe that the identification of these parameters may serve to address the urgent need for real-time information to track the spread of mpox in endemic and non-endemic countries, assess the impact of public health interventions, and evaluate their effectiveness.

**Declarations**

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**Availability of data and materials**

Data and R code used for the statistical analysis relies on the online public GitHub repository: xxx

**Author contributions**

CDB contributed to conceptualization, literature search, figures, study design, data collection, analysis, and interpretation and led manuscript writing. LCN contributed to data collection, analysis, and interpretation. JAC contributed to writing, review and editing. KC contributed to interpretation, review and editing. ABL contributed to the analysis, interpretation, review and editing. ZMC contributed to conceptualization, supervision, figures, administration, and writing – review & editing.

**Competing interests**

The authors have no competing interests to declare in this publication.

**Ethical Approval statement**

The protocol was approved by the ethics committee of the Faculty of Medicine of the Pontificia Universidad Javeriana, carried out on 26/01/2023, act number 1/2023.

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