**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:** The 2022-2023 mpox outbreak has been the largest in history. We aim to synthesize the key epidemiological parameters related to the dynamics, 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 of observational studies in MEDLINE, EMBASE and other sources up to September 2023 (PROSPERO: CRD42023404503). Quality assessment using 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: 7.13-8.02) days, a pooled serial interval of 8.25 (95% CI: 6.45-10.55) days, a pooled generation time of 10.83 days (95% CI: 6.45-10.55). Three studies reported pre-symptomatic transmission in 27–50% of paired cases investigated. For severity parameters, we estimated a pooled global CFR of 0.02% (95% CI 0-0.03%). Sub-analysis by geography revealed a greater lethality for the African continent 10.80% (95% CI: 4.60-23.2%). R0 varied between 1.33 and 3.02, highest R(t) varied between 1.22 to 3.78. The epidemic peaked between August and September 2022 worldwide. **Conclusion:** The 2022-23 mpox outbreak exhibited lower severity and higher transmissibility compared to previous outbreaks. Pooled mpox serial interval was slightly larger than pooled incubation period, suggesting transmission occurs mostly post-symptom onset, although pre-symptomatic transmission can occur in an important proportion of cases. The pooled CFR was 2-3 orders of magnitude lower than in previous mpox outbreaks, except in Africa. Our results contribute to a better understanding of mpox dynamics, and the development of mathematical models to assess the impact of current and future interventions.

**Key words:** public health; global health; epidemiology; systematic review.

**What is already known on this topic –** Prior to 2022, the incubation period varied between 5 to 22 days, and the serial interval was expected to be large. However, it is known those estimates were mostly based on data for variola virus. R0 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 0.02% (95% CI 0-0.03%). R0 varied between 1.33 and 3.02. R(t) highest values varied between 1.22 to 3.78, and the epidemic peaked between August and September 2022 worldwide.

**How this study might affect research, practice, or policy –** Our review provides a comprehensive summary of 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 of epidemiological delay distributions and areas of uncertainty for further research in this field crucial to outbreak response in real time.

**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, the 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 crucial 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. 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.

*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, 3) aspects related to viral transmission dynamics, such as sexual or intimate contact in the 21 days prior to symptom onset, suspected source of transmission, 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, 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. A random effects model was 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, 157 references were eligible for full-text evaluation. Of these, a total of 110 studies were excluded: 77 for failing to evaluate epidemiological parameters of interest, 25 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, 47 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 Table S2.

*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-seven references were included in the analysis. The predominant study designs were mathematical or statistical models n=23 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, the incubation period was the main parameter reported (n=26 references), followed by basic reproduction number (n=10), 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 S1, and a detailed description of the decision of each study is available in table S3.

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 S1A).

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 S1B).

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 S1C).

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 S1D).

*Epidemiological parameters*

*Incubation period:* Twenty-six studies [16, 22, 24-47] 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 3A). 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. [27]) 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 subgroup 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) using a random effect model, = 0%, = 0, p = 0.51. For non-mathematical 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.

*Serial interval:* five mathematical or statistical models [27, 28, 30, 32, 48] 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 3B). Four of the studies fitted a gamma distribution to the data, and one study fitted a normal distribution.

*Generation time:* Two mathematical models [22, 25] 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 3C). 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).

*Basic reproduction number:* Ten studies [18, 22, 25, 28, 48-53] reported estimates of the basic reproduction number. The mean or median values ranged from 1.33 to 3.02 across the included references (Figure 3D).

*Effective reproduction number:* Eight studies [54-61] reported estimates of the effective reproduction number. R(t) highest values varied between 1.22 to 3.78 and showed a peak between late August and early September 2022, when R(t) values went below the threshold of 1 (Figure 3E).

*Case fatality rate:* Twenty-five studies [16, 25, 31-47, 62-67] reported the proportion of deaths related to mpox in their study populations, for a total of 68,662 suspected or confirmed mpox cases. Pooling these estimates, we obtained a CFR of 0.02% (95% CI 0-0.03%) using a random effect model, = 97%, = 11.1, p <0.01. Given the high heterogenicity found in our pooled estimates, we also performed a subgroup analysis separating the studies by geographic location (Americas, Europe, Americas and Europe and Africa). For the African continent, we analyzed estimates from two studies and obtained a pooled CFR of 10.8 (95% CI: 4.6-23.2), = 93%, = 0.37, p <0.01 (Figure 4A). For the Americas, we analyzed estimates from six studies and obtained a pooled CFR of 0.13% (95% CI: 0.09-0.17%), = 0%, = 0, p = 0.78 (Figure 4B). For Europe, we analyzed estimates from four studies and obtained a pooled CFR of 0% (95% CI: 0-0%), = 0%, = 0, p = 1.0. Figure 4C). For studies including countries from the Americas and Europe, we analyzed estimates from four studies and obtained a pooled CFR of 0.02% (95% CI: 0-27.8%), = 0%, = 0, p = 1.0. Figure 4D). A subgroup analysis by HIV status, age, biological sex, and sexual orientation was not feasible given the limited data for each category.

**Discussion**

To our knowledge, this is the first systematic review of epidemiological parameters involved in the transmission and severity of the 2022-2023 multicountry mpox outbreak. Concerning transmissibility, we estimated pooled estimates as follows: an incubation period of 7.56 days (95% CI 7.13 to 8.02), a serial interval of 8.25 days (95% CI 6.45 to 10.55), a generation time of 10.83 days (95% CI 8.11 to 14.46), and the infectious period was reported in only one study [22] (3.7 days, 95% CI 1.5-11.7). Additionally, the basic reproduction number varied from 1.33 to 3.02. The effective reproduction number showed a peak between late August and early September 2022, when R(t) values varied between from 1.22 to 3.78. Regarding the severity of the 2022 mpox outbreak, we found a pooled CFR of 0.02% (95% CI 0.0-0.03%) with substantial variation by geographical region.

To reach a better understanding of these results, it is important to compare the estimates from our review with those from mpox outbreaks that occurred prior to 2022.

As the serial interval and incubation periods are correlated, and prior to 2022 it had been suggested that the incubation period varied between 5 to 21 days, serial intervals were expected to be large [68]. However, it is known those estimates were mostly based on data for variola virus. Our results indicate a much shorter pooled incubation period in the 2022 mpox outbreak in 7.56 days (26 studies; 95% CI 7.13 to 8.02, with an upper range of up to 20 days) and a pooled serial interval of 8.25 days (5 studies; 95% CI 6.45-10.55). When the difference between the serial interval and the incubation period is a positive number, it suggests that transmission primarily occurs after symptom onset [69]. Nevertheless, we also found sparse and small studies suggesting between 27-50% of infections may have occurred in the pre-symptomatic period [27, 28, 30]. It is still debated to what extent pre-symptomatic infections play a substantial role in the overall transmission. Presymptomatic transmission has implications for how easily an outbreak can be controlled by isolating infectious individuals and contact tracing and quarantining their contacts [70]. Our results suggest that the role of presymptomatic transmission of mpox in the 2022-23 outbreak may be limited, as the mean serial interval is greater than the pooled estimation of the incubation period.

The generation time was reported in only two studies [22, 25]. The lack of studies 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. We did not find data prior to 2022 concerning the estimation of this parameter in previous outbreaks, to compare our findings.

Concerning the infectious period, only one study [22] estimated this parameter in 3.7 days. This estimate was surprisingly low, considering that the US CDC considers 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) [71]. Unfortunately, a precise definition of this parameter was not clearly provided in the mentioned study, which could have improved the interpretation of this finding.

Based on eight studies, we found an R0 varying between 1.33 to 3.02 and based on 11 studies R(t) values varying between 1.22 and 3.78. Prior estimates of the mpox R0 found an R0 of 0.8, based on a systematic review in 2019 [72], using active surveillance data collected in the Democratic Republic of Congo (DRC) between 1980 and 1984 [73]. 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 [73]. Subsequent reports from DRC prior to 2022, demonstrated a steady increase in R(t) (estimated of 0.82; 95% CI: 0.79 – 0.85) between 2013 and 2017 in the DRC [74]. In 2020, Grant et al. [75] estimated R0 of 2.13 (95% CI 1.46 to 2.67), using data collected in the DRC during 1966–1984. This increase could be attributed to the reduction in population-level immunity conferred by smallpox vaccination, behavioral changes, and ecological and environmental changes, among other factors [74, 76].

In terms of the CFR, we found a pooled estimate of 0.02% with high heterogeneity (=93%; p<0.01). In the subgroup analysis by geography, we found a CFR of 0.13% (95% CI: 0.09-0.17%) for the Americas, 0% (95% CI: 0-0%) for Europe and 10.8 (95% CI: 4.6-23.2), for Africa (Figure 4). 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 [63, 77]. As for the results of the subgroup analysis, we found a greater CFR in the African Region compared to the Americas and Europe. 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. Contrastingly, estimates of CFR for mpox prior to 2022 were much higher. 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. Importantly, there were no deaths reported outside of Africa before the 2022-23 outbreak.

Given our estimates from this systematic review compared to prior mpox estimates, it is evident that the 2022-23 mpox outbreak showed a higher transmissibility but lower severity parameters. Also, the 2022-23 mpox outbreak has spread primarily in closed global networks that disproportionately affected men who have sex with men (MSM) [16]. It has been suggested that R>1 and sustained growth of monkeypox among MSM is due to a heavy-tailed sexual partnership distribution, in which few individuals have disproportionately many partners [18]. Interestingly, the genomes for this outbreak have been classified as clade IIb, formerly ‘West African’ clade, characterized by lower severity than clade I (formerly ‘Congo Basin’ clade) [78]. Contrastingly, historically, mpox outbreaks in DRC were almost always associated with clade I and IIa and primarily linked to zoonotic transmission until 2022 when spread throughout the world [7].

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 a comprehensive eligibility criteria method, included multiple primary study designs and sources, and considered mathematical models fitted to data. We also developed a thorough data extraction form, including aspects such as measures of central tendency and/or variability, fitted probability distribution, and truncation or censoring of data, among others. Second, although recommendations for estimating specific parameters such as CFR [79] and R(t) [80] 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 biases; 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 the estimated parameters. Future studies should focus on improving the characterization of key parameters in special populations, such as HIV patients. Fourth, for the estimation of the incubation period, serial interval, and CFR, we could have double-counted events and total cases for various studies of reports, especially those with overlapped study frame periods. To overcome this, we would need to access the raw data and re-estimate the parameters, which was not feasible. 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 [79].

Had more data been available, it would have been interesting to perform a subanalysis by epidemic phase (growth, peak, decline, and after the end of the outbreak). 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 changes in mpox parameters and their impact over time.

**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 is mostly driven after symptom onset. Although there is sparse evidence of a potentially important proportion of pre-symptomatic transmission. The pooled CFR (0.02%) 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 1.33 to 3.02, while the highest mean R(t) values ranged from 1.22 to 3.78. 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 are publicity available at: https://github.com/zmcucunuba/mpox-SR.

**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.

**Table 1: Main characteristics of the studies included in the analysis.**

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| **First author or institution (year)** | **Study design** | **Region or country** | **Parameters evaluated** | **Study period** | **Sex (n, %)** | **Age, median or mean (IQR or SE)** | **Sexual orientation and gender identity, n (%)** | **People living with HIV (n, %)** |
| Africa CDC (2022) [66] | Surveillance report | Africa | CFR | Up to Jan, 2023 | NA | NA | NA | NA |
| UKHSA (2022a) [31] | Surveillance report | UK | IP, SI, CFR | May 6 to June 8, 2022 | Female (3/314,0.9)  Male (311/314,  99.1) | Median 38 (IQR 32-44) | 151/152 men identified as GBMSM | NA |
| UKHSA (2022b) [32] | Surveillance report | UK | IP, CFR | May 6 to June 22, 2022 | Female (5/810,0.6)  Male (805/810,  99.4) | Median 37 (IQR 31-43) | 308/321 (96%) men identified as GBMSM | 90/321 (28) |
| Alvarez-Moreno (2023) [63] | Cross-sectional study | Colombia | CFR | June 29 to  November 16, 2022. | Female (25/521, 4,8)  Male (496/521, 95.2) | Median 32.6 (IQR 28-38.3) | NA | 367/521 (70.4) |
| Angelo (2023) [33] | Cross-sectional study | Global | IP, CFR | May 1 to July 1, 2022 | Male (226/226,100) | Median 37 (IQR 32-43) |  | 92/209 (44) |
| Betti (2022) [49] | Mathematical model | Global | R0 | May to Aug, 2022 | NA | NA | NA | NA |
| Bragazzi (2023) [50] | Mathematical model | Canada | R0 | May 19 to July 25, 2022 | NA | NA | NA | NA |
| Branda (2022) [51] | Mathematical model | Europe | R0 | May to Aug, 2022 | NA | NA | NA | NA |
| Català (2022) [34] | Prospective cross-sectional study | Spain | IP, CFR | May 28 to July 14, 2022 | Male (185/185,  100) | Mean 38.7 (SE 8.2) | 184/185 (99%) men identified as GBMS | 78/185(42) |
| Charniga (2022) [24] | Mathematical model | USA | IP | May 17 to June 6, 2022 | Male 22/22 (100) | Range 28 to 61 | 22/22 (100) men identified as GBMSM | NA |
| Chitwood (2023) [54] | Mathematical model | USA | R(t) | May to Nov, 2022 | NA | NA | NA | NA |
| Choudhury (2022) [35] | Case series | Germany | IP, CFR | May to September, 2022 | Male 179/179 (100) | Mean 38 (Range 20-67) | 164/169 (97) men identified as GBMSM | 55/131 (42) |
| Cobos (2023) [36] | Case series | Spain | IP, CFR | May 19 to June 7, 2022 | Male 30/30 (100) | Mean 33 | 30/30 (100) men identified as GBMSM | 14/30 (47) |
| Diaz-Brochero (2023) [55] | Mathematical model | Latin America | R(t) | June to November, 2022 | NA | NA | NA | NA |
| Du (2022) [56] | Mathematical model | USA, Europe | R(t) | May to July, 2022 | NA | NA | NA | NA |
| Endo (2022) [18] | Mathematical model | Global | R0 | Up to May 31, 2022 | NA | NA | NA | NA |
| Eustaquio (2023) [64] | Surveillance report | USA | CFR | May 10, 2022, to May 17, 2023 | NA | 2,909/29,984 (9.7%) were aged >50 | -Cisgender men 28,475/29,984 (94.9)  -Cisgender women 897/29,984 (2.9)  -Transgender men 55/29,984 (0.2)  -Transgender women 229/29,984 (0.8)  -Other gender identity 236/29,984 (0.8) | 4,798 (55.4) among 18–50 yrs  552 (66.2) among >50 yrs |
| Gao (2023) [52] | Mathematical model | Global | R0 | January to August,2022 | NA | NA | NA | NA |
| Garcia-Garcia (2023) [57] | Mathematical model | Spain | R(t) | April to August 2022 | NA | NA | NA | NA |
| Gaspari (2022) [37] | Case series | Italy | IP, CFR | June 20 to August 10, 2022 | Male 30/30 (100) | Mean 37.5 (Range 21-65) | 30/30 (100) men identified as GBMSM\* | 12/30 (40) |
| Gomez-Garberi (2022) [38] | Case series | Spain | IP, CFR | May to August 2022 | Male 14/14 (100) | Median 42 (Range 20-56) | 10/14 (71) men identified as GBMSM\* | 8/14 (57) |
| Guo (2022) [48] | Mathematical model | Global | SI, R0 | January to August, 2022 | NA | NA | NA | NA |
| Guzzetta (2022) [25] | Mathematical model | Italy | IP, GT, R0, CFR | May to June, 2022 | Female (2/255,0.8)  Male (253/255,  99.2) | Median 37 (range 20–71) | 190/200 (95) men identified as GBMSM | NA |
| Kroger (2023) [39] | Case series | Germany | IP, CFR | May 22 to October 30, 2022 | Female (1/368,0.3)  Male (367/368,  99.7) | Median 41 (range 12-80) | 247(67) men identified as GBMSM\* | 143/368 (39) |
| Kwok (2022) [53] | Mathematical model | Europe | R0 | May 18 to June 18, 2022 | NA | NA | NA | NA |
| Liao (2023) [58] | Mathematical model | USA, Brazil, UK,DRC | R(t) | May to September, 2022 | NA | NA | NA | NA |
| Madewell (2023) [27] | Mathematical model | USA | IP, SI | May to August, 2022 | Female (5/112,5)  Male (106/112,  95) | Median 35 (Range 1-76) | NA | NA |
| McFarland (2023) [26] | Mathematical model | Germany | IP | May to June 2022 | NA | NA | NA | NA |
| Mailhe (2023) [40] | Case series | France | IP, CFR | May to July, 2022 | Female (1/263, 0.3)  Male (262/263, 99.7) | Median 35 (Range 30-41) | 245/262 (93.5) men identified as GBMSM | 73/256 (29) |
| Maldonado (2023) [41] | Case series | Peru | IP, CFR | July 1 to September 3, 2022. | Female (3/205, 1.5)  Male (202/205, 98.5) | Median 32 (Range 28-38) | 192/205 (94) men identified as GBMSM | 136/205 (66) |
| Miura (2022) [29] | Mathematical model | Netherlands | IP | Up to May, 2022 | Male 18 pairs (100) | NA | NA | NA |
| Miura (2023) [28] | Mathematical model | Netherlands | IP, SI, R0 | May to September, 2022 | Male 109 pairs (100) | NA | 109 pairs (100) men identified as GBMSM. | NA |
| Mitjà (2023) [62] | Case series | Global | CFR | May 11, 2022, and  January 18, 2023, | NA | Median 35 (Range 30–43) | -Cisgender women 4 (1)  -Transgender women 10 (3)  -Cisgender men 367 (96)  -Non-binary  Individual 1 (0) | 382/382 (100) |
| Moschese (2023) [42] | Case series | Italy | IP, CFR | May to June, 2022 | Male (32/32, 100) | Median 38 (Range 34-42) | 32 (100) men identified as GBMSM | 16/32 (50) |
| Núñez (2023) [43] | Surveillance-based study | Mexico | IP, CFR | May 1 to September 10, 2022 | Female (16/565, 2.8)  Male 549/565 (97.2) | Median 34 (Range (30–41) | 327/565 (59.6) men identified as GBMSM | 299/565 (52.9) |
| Musa (2022) [59] | Mathematical model | Nigeria | R(t) | January to September, 2022 | NA | NA | NA | NA |
| Ogoina (2023) [67] | Cohort study | Nigeria | CFR | February 1, 2022, to January 30, 2023 | Female 46/160 (29)  Male 114/160 (71) | <18 years 26/160 (16%)  18–35 years 82/160 (51%)  >35 years 52/160 (33%) | NA | Advanced HIV disease 11/160 (7)  Stable HIV 14/160 (9)  No HIV 69/160 (43)  Unknown HIV status 66/160 (41) |
| O’Laughlin (2022) [44] | Case series | USA | IP, CFR | May to August, 2022 | Female 12/549 (2.3)  Male 515/549 (97.7) | Median 36.5 (IQR 31.4–43.9) | NA | 254/549 (46.3) |
| Riser (2023) [65] | Surveillance report | USA | CFR | May 10, 2022, to March 7, 2023 | NA | Median 34 (Range 0–89) | Survivors (n = 30,183)  Cisgender man 24,759 (94.9)  Cisgender woman 806 (3.1)  Transgender man 55 (0.2)  Transgender woman 227 (0.9)  Another gender identity 235 (0.9)  Decedents (n = 38)  Cisgender man 36 (94.7)  Cisgender woman 1 (2.6)  Transgender man 0 (—)  Transgender woman 1 (2.6) | Survivors: HIV positive 5,186 (38.3)  Decedents: HIV positive 31 (93.9) |
| Saldaña (2022) [60] | Mathematical model | Europe | R(t) | May to September, 2022 | NA | NA | NA | NA |
| Schrarstzhaupt (2022) [61] | Mathematical model | Brazil | R(t) | June to August 22, 2022 | NA | NA | NA | NA |
| Suárez Rodríguez (2022) [45] | Case series | Spain | IP, CFR | May to June, 2022 | Female 14/1256 (1.1) Male 1242/1256 (98.9) | Median 37 | 290/332 (87.3) men identified as GBMSM | NA |
| Tarín-Vicente (2022) [47] | Multicentre, prospective, observational cohort study | Spain | IP, CFR | May 11 to June 29, 2022 | Female 6/181 (3)  Male 175/181 (97) | Median 37, (IQR 31-42) | 166/175 (95) men identified as GBMSM, 9/175 (5) men identified as heterosexual, 6/6 (100) women identified as heterosexual | 72/181 (40) |
| Thornhill (2022) [16] | Case series | Global | IP, CFR | April to June, 2022 | Female 0  Male 527/528 (99.8)  Trans or nonbinary 1/528 (<1) | Median 38 (Range 18–68) | Heterosexual 9/528 (2), Homosexual 509/528 (96), Bisexual 10 (2) | HIV positive 218 (41)  HIV negative or status unknown 310 (59) |
| Thornhill (2022) [46] | Case series | Global | IP, CFR | September 10 to October 4, 2022. | All female sex at birth | Median 34 (IQR 28–40; range 19–84) | 62 trans women, 69 cis women, and five non-binary individuals. 121/136 (89) reported sex with men. | 37/136 (27) |
| Ward (2022) [30] | Mathematical model | UK | IP, SI | May 6 to August 1, 2022. | NA | Mean 37.8 (SE 9.1) | 1160/1213 (95) men identified as GBMSM | NA |
| Wei (2022) [22] | Mathematical model | Global | Infectious period, GT, R0, IP | May to October, 2022 | NA | NA | NA | NA |

GBMSM: gay, bisexual, and other men who have sex with men, NA: not available or applicable, IQR: interquartile range, SE: Standard deviation, USA: United States of America, UK: The United Kingdom, DRC: Democratic Republic of Congo; CFR: Case fatality rate; IP: Incubation period; SI: Serial interval; GT: Generation time; R0: Basic reproduction number; R(t): Effective reproduction number.

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