**Epidemiological parameters related to the transmission and severity of the 2022-23 mpox outbreak: a systematic review.**

**Authors**

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**Abstract: Objective:** We aim to 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 reproductive number, and case fatality rate). **Methods:** Systematic review and meta-analysis of nonrandomized studies in MEDLINE, EMBASE, CENTRAL, and other sources, up to September 2023. For the quality assessment, we used the Joanna Briggs Institute Critical Appraisal for case series, cross sectional, and cohort studies, and designed a checklist for mathematical models. The meta-analysis was performed using a random effect model. **Results:** We found an incubation period of 7.56 (95% confidence interval [CI] 7.13-8.02) days, serial interval of 8.25 (95% CI 6.45-10.55) days, generation time of 10.83 (95% CI 8.11-14.46) days and CFR of 0.0003 (95% CI 0.0000-0.0024). The infectious period was reported in one study (3.7 days, 95% CI 1.5-11.7). Eleven studies estimated the basic reproduction number, varying between 0.19 to 3.02. Eight studies reported the effective reproduction number, showing a peak between late August and early September 2022. **Conclusions:** Our study providesrelevant information about epidemiological parameters of the mpox outbreak that will help improve mathematical models for evaluating the impact of interventions for future outbreaks (Words: 200)

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

**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). The is divided into two clades, clade I and clade II. Clade I has historically been found in the Congo Basin, while clade II has historically been found in West Africa (3). Traditionally, transmission of mpox was thought to be primary acquired from infected animals to humans via scratches or bites while hunting and preparing wild game or contact with infectious fomites (4). The animal reservoir(s) is still unknown, but small mammals including rodents could play a role in the maintenance and spread of the virus (2). Nowadays, 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 October 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). The majority of 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 as 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, among others, 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 learnt 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 protocol of 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 semi-structured 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"). Search strategies are available in Supplementary table 1.

*Studies 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

types of studies included were descriptive or analytical observational studies, experimental or quasi experimental 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 the following:

* 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, 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) Information related to the estimation of the parameters. 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); 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 subgroup 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 lack of data. Results from the only study found in the review are presented (22).

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 tables.

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

A subgroup analysis was performed for incubation period and CFR according to the geographical distribution of the estimates and type of study (parameters obtained by mathematical models vs other study designs). Although we planned to perform a subgroup analysis of estimates according to sex assigned at birth, mechanism of transmission, HIV status and type of vaccine strategy used (pre- and post-exposure 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 6110 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 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, 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 Supplementary Table 2.

*Included studies.*

Forty-seven references were included in the analysis. The predominant study designs were mathematical models n=24 (51%), followed by case series n=13 (28%), cross sectional studies/surveillance reports n=8 (17%) 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=24), generation time (n=2) and infectious period (n=1). The proportion of each study design and epidemiological parameters evaluated in the included references is visualized in Figure 2.

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, United States of America, and United Kingdom, respectively. A map of the number of articles selected per country is represented in Figure 2.

*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’s 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).

Lastly, 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%, = 0.0047, p = 0.24. (Figure 4a). It is important to note that some of the patients included across the studies have 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 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) for both common and random effect models, = 0%, = 0, p = 0.51 (Supplementary Figure 1a). As 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%, = 0.0079, 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, 29) 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 1d). 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), 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-five studies (see Table 1) reported the proportion of deaths related to mpox in its study populations, for a total of 67395 suspected or confirmed mpox cases. Pooling these estimates, we obtained a CFR of 0.0003 (95% CI: 0.0000-0.0024) using a random effect model, = 94%, = 6.9665, p <0.01 (Figure 4d).

*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 (See table 2).

*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 (See table 3).

**Discussion**

The objective of this systematic review and meta-analysis was to synthesize key epidemiological parameters related to the transmission and severity of the 2022-23 mpox outbreak. We found an incubation period of 7.56 days (26 studies; 95% CI 7.13 to 8.02; I2 =15%, p=0.24), a serial interval of 8.25 (five studies; 95% CI 6.45 to 10.55; I2 =90%, p<0.01), a generation time of 10.83 (two studies; 95% CI 8.11 to 14.46; I2 =0%; p=0.6) and a CFR of 0.0003 (25 studies; 95% CI 0.0000-0.0024; I2 =94%; p<0.01). 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 multi-county 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 (30) reported an analysis of active surveillance data collected in the Democratic Republic of Congo (DRC) between 1980 and 1984, demonstrating a R0 of 0.8 (31). 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 (31). In 2020, Grant et al., (32) performed estimations of 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 an 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 non-endemic regions, showing a different pathogenicity and less severity (33).

As for the effective reproduction number (Rt), our results are in line with recent reports, demonstrating a steadily increase in Rt (estimated of 0.82; 95% CI: 0.79 – 0.85) between 2013 and 2017 in DRC (34). This finding could be attributed to the reduction of population-level immunity conferred by smallpox vaccination, behavior change, ecological and environmental changes, among other factors (34, 35).

In terms of the CFR, a systematic review (7) reported a pooled estimate of 8.7% from confirmed or suspected mpox cases between 1970 to 2019 (78/892; 95% CI 7.0 to 10.8), with variations according to the 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 (I2=94%; p<0.01) when pooling the estimates from all over the world, so we decided to perform a sensitivity analysis comparing references from and outside Africa, demonstrating a reduction in heterogeneity, with greater CFR reported for African countries. Possible explanations for this finding could include a diminished access to medical care, and a greater rate of comorbidities such as HIV, malaria, or malnutrition states. We also acknowledge that the results from individual studies may be biased due to delayed reporting, which may decrease the estimate for the CFR. Care should be taken to limit bias in 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 outcome (36).

Concerning the infectious period, only one study (17) estimated this parameter, which was around 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) (37). Unfortunately, a precise definition of this parameter was not clearly provided in the mentioned study which could have improved the interpretation of this finding.

As for the generation time, this parameter was reported in only two studies (22, 29). 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.

Finally, 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. On the contrary, if pre-symptomatic transmission occurs, the mean serial interval is shorter than the mean incubation period (38). It is still debated whether pre-symptomatic transmission occurs for mpox, and if so, to what extent (25, 28, 29). Pre-symptomatic transmission has implications for how easily an outbreak can be controlled by isolating infectious individuals and contact tracing and quarantining their contacts (39). Our results suggest that the role of pre-symptomatic transmission of mpox in the 2022-23 outbreak may be limited, as mean serial interval (and generation time) are greater than the pooled estimation of incubation period.

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 (36) and Rt (40) 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 characterization of key parameters in special populations such as HIV patients and others who are immunocompromised. Forth, some of the cases across the studies are shared for incubation period estimations, so it is possible that we double counted some cases. In order to overcome this, we would need to access to the raw data and re-estimate the parameters, which was not feasible.

Had more data been available, it would have been interesting to perform a sub-analysis by outbreak phase (prior to 2022 vs 2022 onwards). We would expect a difference in the presented findings if the early studies did not appropriately adjust for epidemic phase bias and right truncation.

**Conclusion**

In conclusion, synthesized information about key epidemiological parameters from the 2022-23 mpox multi-county outbreak. The identification of these parameters may serve to address the pressing need for real-time information to track the spread of mpox in endemic and non-endemic countries, evaluate the impact of public health interventions, and assess their effectiveness.

**Author contributions**

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

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

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author (year)** | | **Study design** | **Region** | **Parameters evaluated** | **Study period** | **Sex (n, %)** | **Age** | **Sexual orientation and gender identity** | **People living with HIV (n, %)** |
| UKHSA (2022) Technical briefing 1 | Surveillance report | | UK | Incubation period, serial interval, 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 (2022) Technical briefing 2 | Surveillance report | | UK | Incubation period, 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) | 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) | Cross-sectional study | | North America, Europe, Argentina, South Africa | Incubation period, CFR | May 1 to July 1, 2022 | Male (226/226,100) | Median 37 (IQR 32-43) |  | 92/209 (44) |
| Betti (2022) | Mathematical model | | Canada and global | Basic reproduction number | May to Aug, 2022 | NA | NA | NA | NA |
| Bragazzi (2023) | Mathematical model | | Canada | Basic reproduction number | May 19 to July 25, 2022 | NA | NA | NA | NA |
| Branda (2022) | Mathematical model | | Europe | Basic reproduction number | May to Aug, 2022 | NA | NA | NA | NA |
| Català (2022) | Prospective cross-sectional study | | Spain | Incubation period | 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) | Mathematical model | | USA | Incubation period | May 17 to June 6, 2022 | Male 22/22 (100) | Range 28 to 61 | 22/22 (100) men identified as GBMSM | NA |
| Chitwood (2023) | Mathematical model | | USA | Effective reproduction number | May to Nov, 2022 | NA | NA | NA | NA |
| Choudhury (2022) | Case series | | Germany | Incubation period | 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) | Case series | | Spain | Incubation period | 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) | Mathematical model | | Argentina, Chile, Colombia, Mexico, Peru, Brazil | Effective reproduction number | June to November, 2022 | NA | NA | NA | NA |
| Du (2022) | Mathematical model | | USA, France, Germany, Spain, England, Portugal | Effective reproduction number | May to July, 2022 | NA | NA | NA | NA |
| Endo (2022) | Mathematical model | | Global | Basic reproduction number | Up to May 31, 2022 | NA | NA | NA | NA |
| Eustaquio (2023) | Surveillance report | | USA | Case fatality rate | 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) | Mathematical model | | Global | Basic reproduction number | January to August,2022 | NA | NA | NA | NA |
| Garcia-Garcia (2023) | Mathematical model | | Spain | Effective reproduction  number | April to August 2022 | NA | NA | NA | NA |
| Gaspari (2022) | Case series | | Italy | Incubation period | 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) | Case series | | Spain | Incubation period | 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) | Mathematical model | | Global | Serial interval, basic reproduction number | January to August, 2022 | NA | NA | NA | NA |
| Guzzetta (2022) | Mathematical model | | Italy | Incubation period, generation time, and basic reproduction number | 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) | Case series | | Germany | Incubation period | 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) | Mathematical model | | England, Portugal, and Spain | Basic reproduction number | May 18 to June 18, 2022 | NA | NA | NA | NA |
| Liao (2023) | Mathematical model | | USA, Brazil, UK,DRC | Effective reproduction number | May to September, 2022 | NA | NA | NA | NA |
| Madewell (2023) | Mathematical model | | USA | Incubation period, serial interval | May to August, 2022 | Female (5/112,5)  Male (106/112,  95) | Median 35 (Range 1-76) | NA | NA |
| McFarland (2023) | Mathematical model | | Germany | Incubation period | May to June 2022 | NA | NA | NA | NA |
| Mailhe (2023) | Case series | | France | Incubation period | 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) | Case series | | Peru | Incubation period | 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) | Mathematical model | | Netherlands | Incubation period | Up to May, 2022 | Male 18 pairs (100) | NA | NA | NA |
| Miura (2023) | Mathematical model | | Netherlands | Incubation period, serial interval, basic reproduction number | May to September, 2022 | Male 109 pairs (100) | NA | 109 pairs (100) men identified as GBMSM. | NA |
| Mitjà (2023) | Case series | | Global | Case fatality rate | 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) | Case series | | Italy | Incubation period | May to June, 2022 | Male (32/32, 100) | Median 38 (Range 34-42) | 32 (100) men identified as GBMSM | 16/32 (50) |
| Núñez (2023) | Surveillance-based study | | Mexico | Incubation period | 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) | Mathematical model | | Nigeria | Effective reproduction number | January to September, 2022 | NA | NA | NA | NA |
| Ogoina (2023) | Cohort study | | Nigeria | Case fatality rate | 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) |
| Okyere (2023) | Mathematical model | | Ghana | Basic reproduction number | May to October, 2022 | NA | NA | NA | NA |
| O’Laughlin (2022) | Case series | | USA | Incubation period | 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) | Surveillance report | | USA | Case fatality rate | 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) | Mathematical model | | Spain, France, Germany, UK, the Netherlands, Portugal, and Italy | Effective reproduction number | May to September, 2022 | NA | NA | NA | NA |
| Schrarstzhaupt (2022) | Mathematical model | | Brazil | Effective reproduction number | June to August 22, 2022 | NA | NA | NA | NA |
| Suárez Rodríguez (2022) | Case series | | Spain | Incubation period | 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) | Multicentre, prospective, observational cohort study | | Spain | Incubation period | 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) | Case series | | 16 countries from  Europe, Americas, Western Pacific, and Eastern Mediterranean | Incubation period | 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) | Case series | | 15 countries from North and South America, Europe, and Africa | Incubation period | 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) | Mathematical model | | UK | Incubation period, serial interval | May 6 to August 1, 2022. | NA | Mean 37.8 (SE 9.1) | 1160/1213 (95) men identified as GBMSM | NA |
| Wei (2022) | Mathematical model | | USA, Europe, Global | Infectious period, generation time, basic reproduction number, incubation period | 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, USA: United States of America, UK: The United Kingdom, DRC: Democratic Republic of Congo.

**Table 2: Basic reproduction number from the included studies.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author (year)** | **Study period** | **Location** | **Mean or median** | **Lower uncertainty measure** | **Upper uncertainty measure** |
| Betti (2022) | May to Aug, 2022 | Canada | 2.3 | - | - |
| Bragazzi (2023) | May to July 25, 2022 | Canada | 1.46 | - | - |
| Branda (2023) | May to Aug, 2022 | Europe | 2.44 | 1.35 | 4.9 |
| Endo (2022) | Up to May, 2022 | Global | - | 1.63 | 1.73 |
| Gao (2023) | January to August, 2022 | Global | - | 0.7 | 4.13 |
| Guo (2022) | January to August, 2022 | Global | 1.33 |  |  |
| Guzzetta (2022) | May to June, 2022 | Italy | 2.43 | 1.82 | 3.26 |
| Kwok (2022) | May to June, 2022 | England | - | 1.5 | 1.7 |
| Portugal | - | 1.2 | 1.6 |
| Spain | - | 1.7 | 2 |
| Miura (2022) | Up to May, 2022 | Netherlands | - | 1.3 | 1.6 |
| Okyere (2023) | May to October, 2022 | Ghana | 0.194 | - | - |
| Wei (2023) | May to October, 2022 | Global | 3.012 | - | - |

(-): Not available

**Table 3: Effective reproduction number from the included studies.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author (year)** | **Study period** | **Location** | **Mean or median** | **Lower uncertainty measure** | **Upper uncertainty measure** |
| Chitwood (2023) | May to Nov, 2022 | USA | - | 1.2 | 2 |
| Diaz-Brochero (2023) | June to November, 2022 | Argentina | 2.63 | 0.85 | 5.39 |
| Brazil | 3.13 | 2.61 | 3.69 |
| Chile | 2.91 | 1.55 | 4.7 |
| Colombia | 3.15 | 2.07 | 4.44 |
| Mexico | 2.28 | 1.18 | 3.75 |
| Peru | 2.84 | 2.33 | 3.4 |
| Du (2022) | May to July, 2022 | Global | 1.29 | 1.26 | 1.33 |
| Garcia-Garcia (2023) | April to August 2022 | Spain | - | 0.8 | 8 |
| Liao (2023) | May to September, 2022 | USA | 1.16 | 1.15 | 1.17 |
| Spain | 1.2 | 1.2 | 1.2 |
| Brazil | 1.34 | 1.34 | 1.35 |
| UK | 1.33 | 1.33 | 1.33 |
| Musa (2022) | January to September, 2022 | Nigeria | 1.92 | 1.45 | 2.48 |
| Saldaña (2022) | May to September, 2022 | Spain | 2.32 | 1.81 | 3.05 |
| France | 2.91 | 2.33 | 3.52 |
| UK | 1.84 | 1.55 | 2.31 |
| Germany | 3.16 | 2.55 | 3.64 |
| Netherlands | 2.97 | 2.01 | 4.32 |
| Portugal | 1.18 | 0.98 | 1.33 |
| Italy | 3.74 | 2.91 | 4.49 |
| Schrarstzhaupt (2022) | June to August 22, 2022 | State of Goias plus Federal District (Brazil) | 2.07 | 1.98 | 2.16 |
| Sao Paulo (Brazil) | 1.7 | 1.68 | 1.72 |
| Rio de Janeiro (Brazil) | 1.65 | 1.61 | 1.7 |
| Minas Gerais (Brazil) | 1.64 | 1.57 | 1.72 |

(-): Not available. UK: United Kingdom, USA: United States of America.

**Figure 1: PRISMA flow diagram**

**Identification of studies via databases and registers**

**Identification of studies via other methods**

Records identified from preliminary references repositories, websites, organizations, and citation searching (n = 148)

Records removed *before screening*:

Duplicate records removed (n =2808)

Records identified from electronic databases: n = 5962

Medline: n= 1714

Embase: n= 1351

Scopus and Web of Science: n= 2897

**Identification**

Records screened.

(n =3154)

Records excluded.

(n =3000)

Reports not retrieved.

(n = 0)

Reports sought for retrieval.

(n =3)

Reports sought for retrieval.

(n =154)

Reports not retrieved.

(n = 1)

**Screening**

Reports excluded: (n = 109)

Failing to evaluate epidemiological parameters of interest (n =77)

Wrong study design (n = 2)

Not study period of interest (n=2)

Theoretical model only (n=24)

Poster abstract (no full text) (n=4)

Reports excluded: (n = 0)

Reports assessed for eligibility.

(n = 3)

Reports assessed for eligibility.

(n =153)

Studies included in review (n =47)

Case fatality rate: n= 24

Incubation period: n = 26

Basic reproduction number: n = 11

Effective reproduction number: n = 8

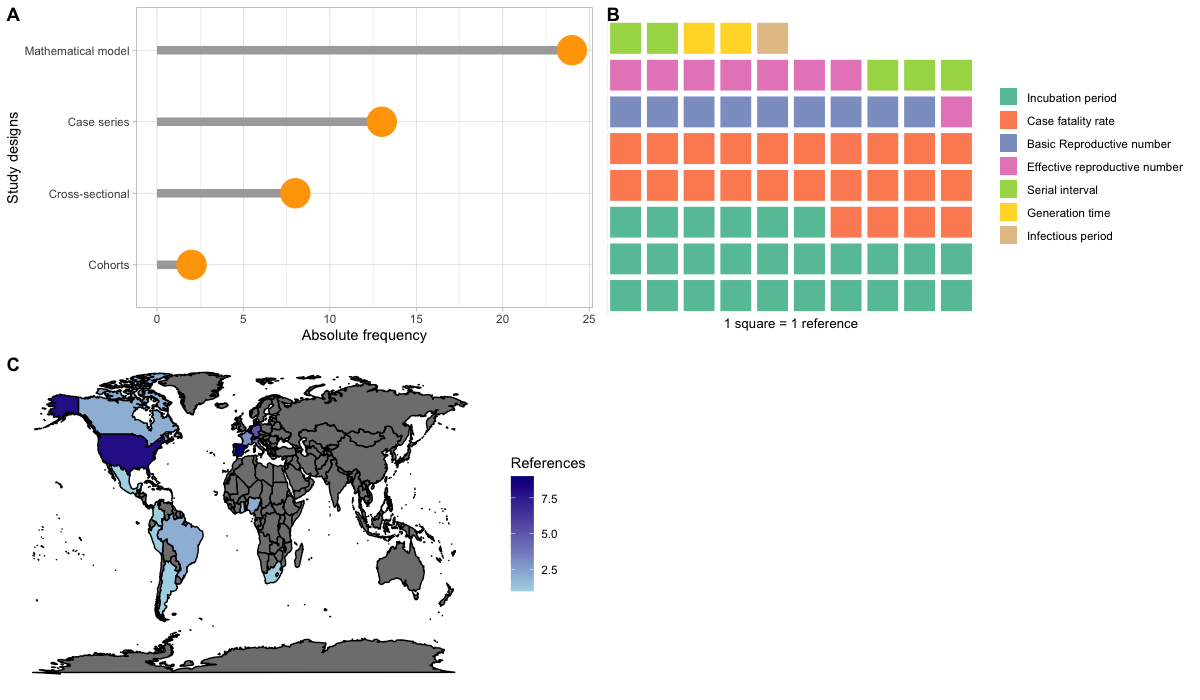
Serial interval: n = 5

Generation time: n = 2

Infectious period: n = 1

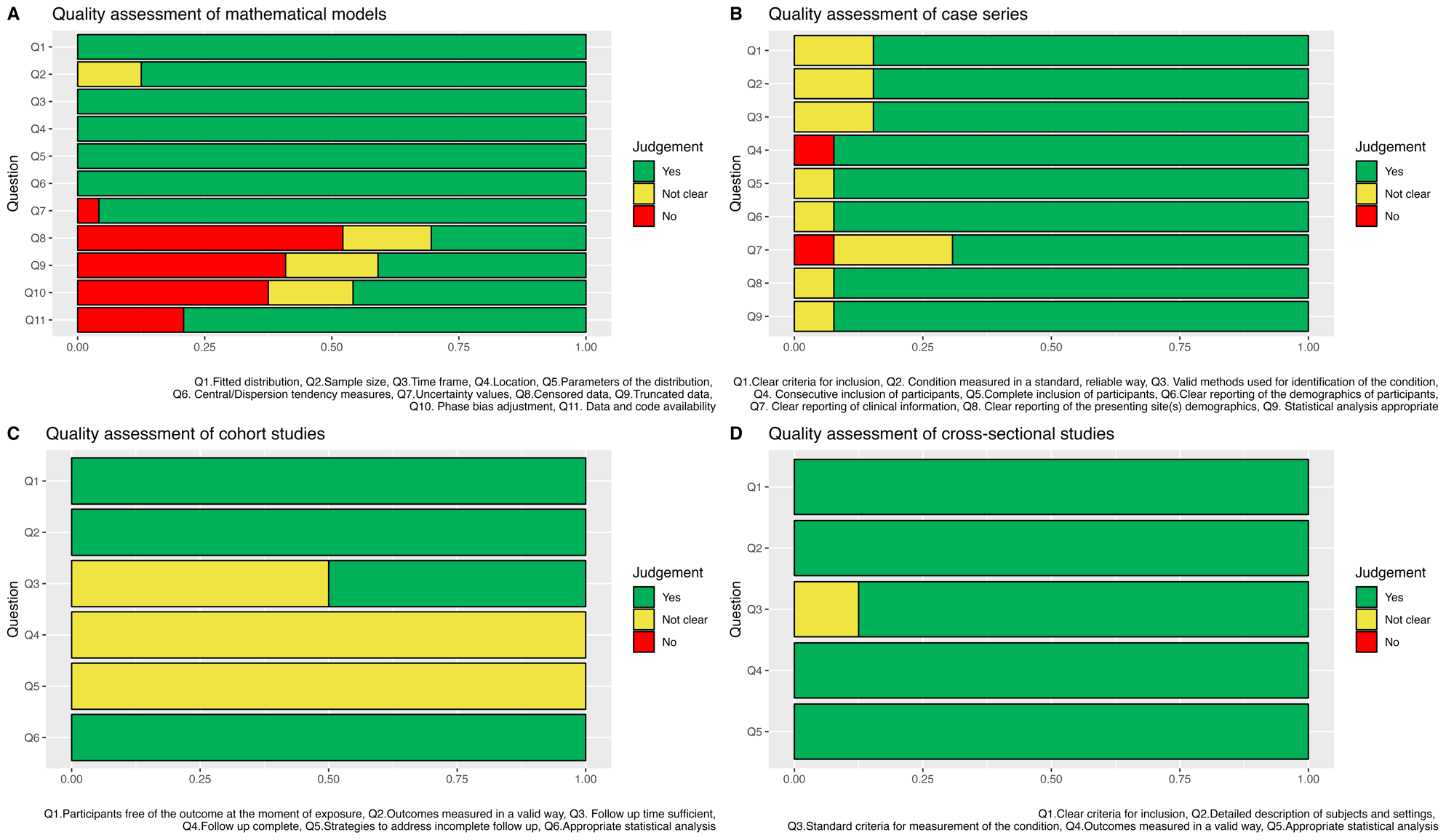
**Included**

**Figure 2: Visual representation of study characteristics included in the systematic review.**



**A:** Lollipop plot of the distribution of the included study designs by reference number; **B**: Waffle plot of the distribution of the number of references by epidemiological parameter evaluated in the analysis (one reference may report more than one parameter); **C:** Map of the number of references included per country

**Figure 3: Quality assessment of included studies**



**Figure 4: Pooled analysis of epidemiological parameters for mpox during the 2022-2023 global outbreak**

Note: The blue diamonds correspond to the pooled estimates, and the gray shaded boxes to the 95% uncertainty around the mean.

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