Incubation Period and Serial Interval of Mpox in 2022 Global Outbreak Compared with Historical Estimates

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Understanding changes in the transmission dynamics of mpox requires comparing recent estimates of key epidemiologic parameters with historical data. We derived historical estimates for the incubation period and serial interval for mpox and contrasted them with pooled estimates from the 2022 outbreak. Our findings show the pooled mean infection-to-onset incubation period was 8.1 days for the 2022 outbreak and 8.2 days historically, indicating the incubation periods remained relatively consistent over time, despite a shift in the major mode of transmission. However, we estimated the onset-to-onset serial interval at 8.7 days using 2022 data, compared with 14.2 days using historical data. Although the reason for this shortening of the serial interval is unclear, it may be because of increased public health interventions or a shift in the mode of transmission. Recognizing such temporal shifts is essential for informed response strategies, and public health measures remain crucial for controlling mpox and similar future outbreaks.

Mpox, caused by monkeypox virus (MPXV), is a viral illness characterized by rash, influenza-like symptoms, and fever. A global outbreak of mpox attracted increased public attention in 2022 and became recognized as a public health event of international concern (PHEIC). Historical estimates of the case-fatality ratio (CFR) associated with mpox infection vary by clade; clade I exhibits a CFR of ≈10%, whereas clade II the CFR is ≤1% (*1*). Although mpox historically experienced limited transmission (*2*,*3*), the 2022 outbreak, originating in nonendemic countries in Europe and North America, resulted in ≈90,000 cases by mid-April 2023 and demonstrated enhanced transmissibility (*4*). The outbreak was driven primarily by sexually associated transmission, which altered the clinical manifestations and epidemiology of the infections when compared with historical reports (*5*). Clade II was dominant; its case-fatality ratio was ≈0.1% (*6*). Although certain epidemiologic parameters, such as the incubation period and serial interval, have been estimated using case records from 2022 (*7*–*13*), comprehensive analysis of historical estimates and assessment of their relationship to the recent outbreak is limited (*14*).

After MPXV was identified in imported monkeys in Denmark in 1958, reported mpox infections were frequently associated with contact with monkeys (*15*–*17*). However, subsequent findings revealed that primates are not the only reservoir hosts (*18*). Before the eradication of smallpox in 1980, mpox was rarely observed in humans, in part because mpox is unlikely to have been widespread but also because of cross-immunity between the 2 viruses. The mpox outbreaks in the 1970s–1990s were relatively small in scale, typically involving ≤5 cases, and predominantly affected children because most adults possessed some level of immunity from smallpox infection or vaccination (*18*). However, as herd immunity waned, outbreaks in the 2000s caused dozens of cases (*19*,*20*); mpox became endemic in some regions of Africa, and Nigeria reporting the largest outbreaks (*21*,*22*).

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The first major outbreak reported beyond the borders of Africa occurred in the United States in 2003; there were 81 confirmed cases linked to imported wild animals (*23*). The global outbreak in 2022 caught many by surprise as mpox spread rapidly in countries across Western Europe and North America in which it was not endemic, before expanding worldwide. The World Health Organization (WHO) declared the 2022 mpox outbreak a PHEIC on July 23, 2022 (*24*). By early 2023, case numbers had begun to decline, likely because there were fewer highly connected susceptible persons within sexual networks (*25*). In addition to the depletion of susceptible persons, general behavioral changes in high-risk populations resulting from increased awareness of risk and vaccination of at-risk persons played an important role in the decline in mpox cases (*26*). Modeling of infections caused by sexual interactions among men who have sex with men (MSM) has shown that having fewer 1-time partnerships can significantly reduce mpox transmission (*27*). Furthermore, members of higher-risk populations proactively altered their behaviors in response to the outbreak; many were vaccinated. In August 2022, a survey of MSM in the United States revealed that ≈50% had reduced their use of dating apps, number of sexual partners, and number of 1-time partnerships (*28*).

The clinical manifestation of mpox has historically been similar to that of smallpox or chickenpox, characterized by fever, rash, and lymphadenopathy (*1*). Its distinctive rash initiates as macules and progresses through papules, vesicles, pustules, and crusts before resolving. Lymphadenopathy, reported in 85% of mpox cases (*29*), distinguishes mpox from smallpox and chickenpox. Some mpox patients also exhibit respiratory symptoms such as sore throat, nasal congestion, or cough.

Since 2022, some changes in the clinical manifestations of mpox have been observed (*5*), including a tendency for skin lesions to localize to specific body regions associated with sexual transmission, such as the genital, anorectal, or oral areas. Rectal symptoms such as purulent or bloody stools, rectal pain, or bleeding were frequently reported (*30*). Some patients exhibited only a few cutaneous formations near affected areas, whereas others experienced disseminated body rashes complicating their infection. Although the localized rash may appear almost concurrently with other initial symptoms, the disseminated rash usually appeared several days after symptom onset.

Some estimates of the incubation period and serial interval for the global mpox outbreak in 2022 have been affected by right-truncation bias. This bias arises when only persons who have experienced the event (e.g., symptom onset or rash appearance) and were confirmed by testing at the time of data collection are included in the sample. By accounting for right truncation, we can estimate the length of the incubation period and serial interval more accurately and include cases with symptoms who have not yet been reported. Ignoring right truncation leads to underestimation of such epidemiologic parameters, because cases with longer incubation periods or serial intervals are overlooked in the analysis. Earlier studies reported short mean incubation period estimates of 9.0 days (*7*) and 7.6 days (95% credible interval [CrI] 6.5–9.9 days) (*10*), extended to 9.5 days (95% CrI 7.4–12.3 days) when accounting for right truncation (*10*).

Estimation of the incubation period of mpox presents several difficulties. One challenge arises from the absence of definitive information on times of exposure. The exposure time window for much recorded data was often >1 day, complicating estimation. Excluding records with longer windows may yield biased estimates, as we saw in lower estimates from the exclusion-based approach (*31*) compared with other studies (*32*,*33*). Furthermore, some studies calculated the incubation period from the last known time of contact (*5*) instead of considering the entire exposure period, which also led to underestimation of the true incubation period.

Estimating generation time or serial intervals (time intervals from an event in an infector to the same event in an infectee) for the historical period before 2022 presents even greater uncertainty. As of April 2024, we are aware of no published formal estimates of such intervals from historical data, although estimates for the global 2022 outbreak exist; 34 transmission (infector–infectee) pairs studied in the Netherlands yielded a mean onset-to-onset serial interval estimate of 10.1 days (95% CrI 6.6–14.7 days) (*9*), and another estimate of 9.5 days (95% CrI 7.4–12.3 days) was based on 79 transmission pairs notified in the United Kingdom (*10*). In contrast, limited information on transmission pairs is available for the pre-2022 period; researchers observed onset-to-onset intervals of 8–11 days (*34*,*35*). We analyzed additional published data from before 2022 for rash-to-rash (*2*) and onset-to-onset serial intervals (*19*,*20*,*35*). The aim of our research is to provide historical estimates of the epidemiologic parameters associated with mpox by aggregating available historical data and to compare those estimates with pooled estimates for the global 2022 outbreak. In our analysis, we corrected previous

estimates as appropriate to account for right truncation, enabling systematic comparison of incubation periods and serial intervals across the 2 time periods. Our work did not require the approval of an ethics committee because it was based on a literature search and the analysis of publicly available data.

Despite successful containment of mpox in 2022–2023, monkeypox virus has continued to spread via human-to-human transmission worldwide. Investment in mpox surveillance and prevention methods, including vaccination, are critical to prevent the virus from causing future outbreaks and reaching PHEIC status again. As emphasized by WHO (*24*), it is necessary to remain vigilant and implement preventive measures to stop mpox from becoming endemic worldwide. Improving available knowledge of the epidemiologic parameters characterizing transmission, such as the incubation period and serial interval, represents a fundamental aspect of this global effort.

Methods

Epidemiologic Data

We conducted a comprehensive literature search without language restriction using the electronic databases PubMed, Embase, and Web of Science through January 4, 2024. We searched for the terms monkeypox, mpox, or mpx, and ≥1 occurrence of the terms incubation, serial, symptoms, onset, or rash. We extracted individual case records of infections from the studies published before 2022 and extracted estimates of the incubation period and serial interval from the studies published after 2022. The search yielded a total of 2,384 references after deduplication (Figure 1).

We deemed a total of 101 references published before 2022 relevant for collection of historical data after manual examination. We found specific information on dates of exposure and symptom onset in 21 references. We excluded 6 studies containing duplicate data. Ultimately, we selected 15 studies with a total of 42 case records. Of those, 16 records were associated with clade I MPXV, and all contained information on rash and symptom onset date; 26 records were associated with clade II, and 12 had information on rash and symptom onset date.

Among manuscripts published after 2022, we deemed 42 relevant after manual inspection. We retrieved 12 estimates of the incubation period and 5 estimates of the serial interval from studies providing data from Colombia (*36*), Italy (*8*), the Netherlands (*7*,*9*), Nigeria (*37*), Spain (*5*,*38*), the United Kingdom (*10*,*39*), and the United States (*11*), as well as studies providing data from multiple countries (*12*,*13*,*40*). Three of those publications included estimates that adjusted for right truncation of the data. To account for right truncation in estimates from the other studies, we extracted individual case data from published materials or obtained the data from the authors. We also compared the extracted list of publications with the literature search conducted by WHO as of December 29, 2022 (*41*). Some references listed by WHO were not identified in our search because they were posted on a preprint server and not peer reviewed by the time of our assessment. (Appendix Table 1, https://wwwnc.cdc.gov/EID/article/30/6/23-1095-App1.pdf).

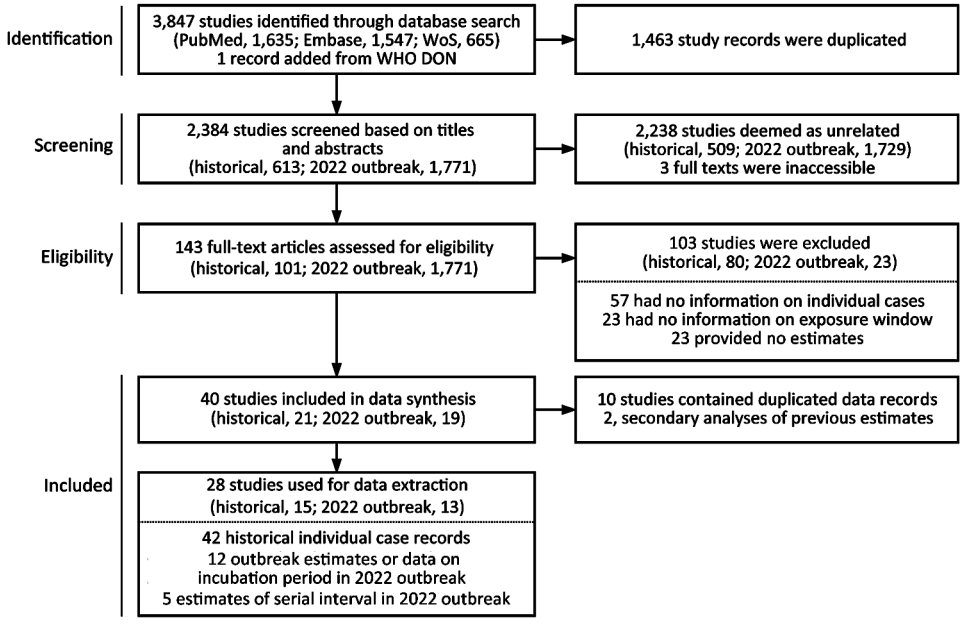

Figure 1. Flow diagram describing identification of historical case records from before the 2022 mpox outbreak eligible for estimation of the incubation period and studies reporting estimates of the incubation period and serial interval during the 2022 outbreak. WoS, Web of Science.

Statistical Analysis

We estimated the incubation period and serial interval distributions using a Bayesian model with Markov chain Monte Carlo implemented in Stan version 2.34.0 (https://mc-stan.org). We used the generalized gamma distribution to determine the incubation period and serial interval because it encompasses 3 commonly used distributions (gamma, Weibull, and log-normal) (*42*). We considered alternative formulations using standalone gamma, Weibull, or log-normal distributions or their mixture and saw no clear differences in the results (Appendix Figure 2).

For identified studies from the 2022 outbreak that did not account for right truncation (*7*,*8*,*11*), we extracted case data. In 2 of those studies (*7*,*8*), the authors provided the truncation date (the final day that case data were available)—day 38 (*7*) and 68 (*8*). With those dates, we could re-estimate the incubation period and serial interval accounting for right truncation. However, in 2 studies (*11*,*39*), no information about truncation date was available, so we were unable to conduct a re-analysis to account for right truncation. The authors of those studies stated that they observed no significant difference between nontruncated and right-truncated likelihoods. We obtained a pooled estimate of the mean incubation period from the meta-analysis using a random-effects model (*43*).

To estimate historical serial intervals, we used data from published studies (*2*,*19*,*20*,*35*). We extracted rash-to-rash time intervals from the dataset provided by Ježěk et al. (*2*) and onset-to-onset intervals (based on generalized symptoms) from other sources (*19*,*20*,*35*); the result was available data from 28 transmission pairs. Consistent with the discussion in Jezek et al., we omitted rash-to-rash intervals of <8 days, which likely resulted from co-primary infections.

To ensure the robustness of our estimates, we conducted a sensitivity analysis (Appendix). First, we considered different cutoff values (2, 4, 6, or 10 days), below which the rash-to-rash intervals were omitted. Second, we fitted the observed distribution to a composition of 2 distributions to allow for the possibility that cases with serial intervals longer than the cutoff value could still be co-primary infections. The first component was modeled either by an exponential distribution or by a scaled standard normal distribution, normal(0, σ), in line with previous studies. The second component was the rash-to-rash serial interval of interest, which was modeled by the generalized gamma distribution.

Results

We report estimates of the mean and SD of the incubation period for mpox based on recent literature (Figure 2, panel A; Appendix Table 2). We obtained those estimates in various ways. For 2 previous studies, we re-derived the estimates in the original articles to account for right truncation (*7*,*8*). We obtained other estimates by either fitting our model to data from the original publications (*5*,*36*,*38*) or reporting the findings from the original studies directly (*10*,*11*). The pooled mean incubation period was estimated to be 8.1 days (95% CrI 7.0–9.2 days); here, we reported all estimates as the posterior median and 95% CrI. The mean between-study variance was 1.8 days^2. Analysis of historical data (before the 2022 outbreak) suggested a mean incubation period of 8.2 days (95% CrI 6.7–10.0 days). Considering only cases associated with clade I resulted in a slightly lower mean of 7.3 days (95% CrI 5.0–10.2 days), whereas clade II infections were characterized by longer mean of 8.9 days (95% CrI 6.6–11.7 days). The 95th percentile of the incubation period distribution, commonly used to determine the quarantine period, was 16–20 days across all studies of the global 2022 outbreak and was 17 days for the historical data.

We also assessed the infection-to-rash incubation period, which tracks the time from infection to the manifestation of a cutaneous rash (Figure 2, panel B; Appendix Table 3). We estimated the pooled mean as 8.7 days (95% CrI 6.5–11.0 days), whereas the between-study variance was 6.4 days^2. Historical data gave a larger estimate of 10.3 days (95% CrI 8.5–12.3 days). We reviewed 3 studies for the 2022 outbreak; Madewell et al. (*11*) estimated a mean incubation period substantially lower than 2 other studies that looked at infection-to-rash time intervals (*5*,*38*), which resulted in a larger discrepancy between the pooled mean and historical estimate compared with the infection-to-onset incubation period estimates. Rash emergence was delayed by a mean of 0.6 days, compared with the infection-to-onset incubation period. Analyzing the data from Viedma-Martinez et al. (*38*), we first calculated the time from infection to the appearance of any cutaneous formations to have a mean value of 9.8 days (95% CrI 8.5–11.2 days). We then calculated the time from infection to the appearance of a disseminated rash, excluding the rash around or at the site of infection. We estimated a mean time period of 11.5 days (95% CrI 10.0–12.8 days). The difference between initial onset of symptoms and rash onset was 1.7 days (95% CrI 0.2–3.7 days) when considering a localized rash and 3.4 days (95% CrI 1.4–5.3 days) when considering a disseminated rash.

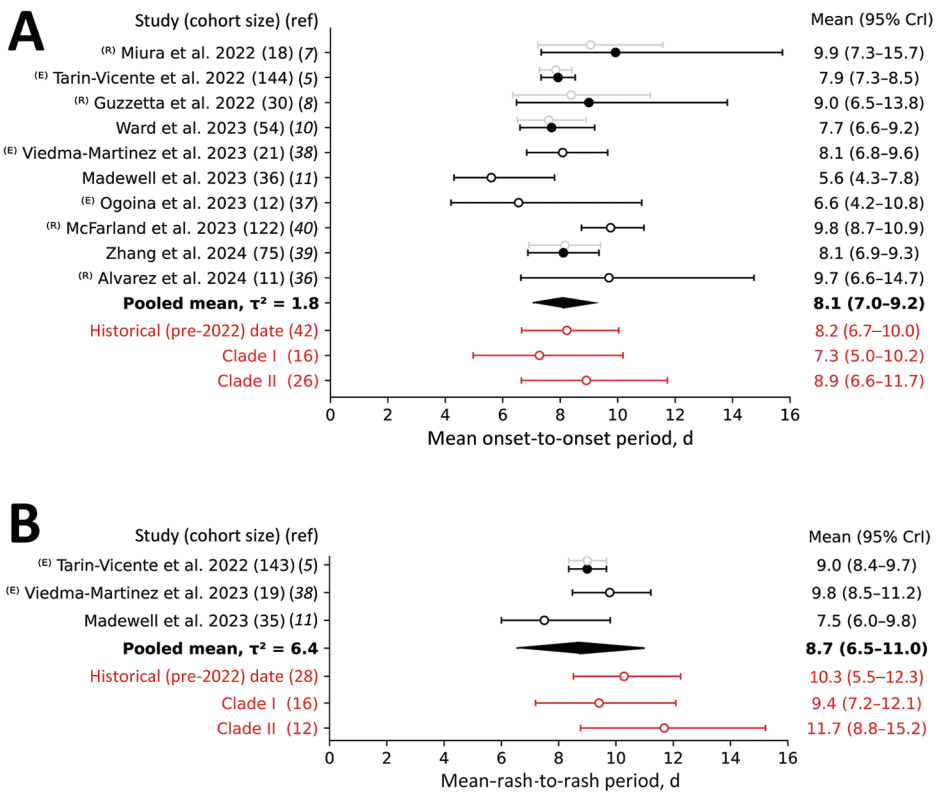

Figure 2. Forest plot of the mean infection-to-onset (A) and infection-to-rash (B) incubation periods for studies conducted during the 2022–2023 global mpox outbreak and analyses of the historical case records. Open circles indicate analyses performed without adjusting for right truncation (ICC); solid circles indicate analysis when an adjustment was made (ICRTC). Whiskers indicate 95% CrIs. Studies are denoted by the leading author and year of publication and ordered by their date of publication; the numbers in parentheses indicate the number of case records used for estimation. (E) indicates that we evaluated the estimates using the data provided in our study; (R) indicates that we re-evaluated estimates for consistency of the methods used. Gray indicates estimates not used for deriving the pooled mean, which is in bold text. Red indicates estimates for historical (pre–2022 outbreak) data, indicating that they were not used for deriving the pooled mean. CrI, credible interval; ICC, interval censoring corrected model; ICRTC, interval censoring and right truncation corrected model; τ^2 = -squared statistics indicating the between-study variance measured in days^2; ref, reference.

As for incubation period estimates, serial interval estimates varied substantially across studies. We estimated the pooled mean for onset-to-onset serial intervals as 8.7 days (95% CrI 6.5–11.0 days) and between-study variance as 6.4 days^2. We estimated the historical mean onset-to-onset serial interval at a much longer 14.2 days (95% CrI 12.5–16.2 days) (Figure 3, panel A; Appendix Table 4, Figure 1, panel A). Madewell et al. (*11*) reported rash-to-rash serial intervals for the 2022 outbreak; they reported a mean of 7.0 days (95% CrI 5.8–8.4 days). That value is much shorter than the historical estimate of the mean rash-to-rash serial interval, which was 14.3 days (95% CrI 13.2–15.3 days) (Figure 3, panel B; Appendix Table 5, Figure 1, panel B). Although Madewell et al. suggested that serial intervals might be shorter than incubation periods for the 2022 outbreak, we found that serial intervals were substantially longer for historical data. Specifically, our analyses suggested that onset-to-onset serial intervals were on average 6.0 days longer than for infection-to-onset incubation periods, and rash-to-rash serial intervals were on average 4.0 days longer than for infection-to-rash incubation periods.

Discussion

In this study, we undertook a systematic literature search and meta-analysis to provide estimates of the incubation period and serial interval of mpox. We compared estimates from the 2022 outbreak with pre-2022 estimates. We found a strong similarity in estimates of infection-to-onset and infection-to-rash incubation periods between studies for the 2022 outbreak and historical case records. However, the serial interval estimates based on historical data were longer than the incubation period estimates based on historical data, which suggests a lower risk of presymptomatic transmission during the pre-2022 period. The shorter serial interval observed in the 2022 outbreak might also be partially attributable to nonpharmaceutical interventions such as contact tracing, active case finding, and behavioral changes, as noted during the COVID-19 pandemic (*44*). A shift toward a sexually associated mode of transmission as the dominant route may also have influenced the serial interval, perhaps by increasing transmission efficiency. All of those theories merit further investigation.

The estimated incubation period in this study remains similar to historical estimates (*45*), suggesting

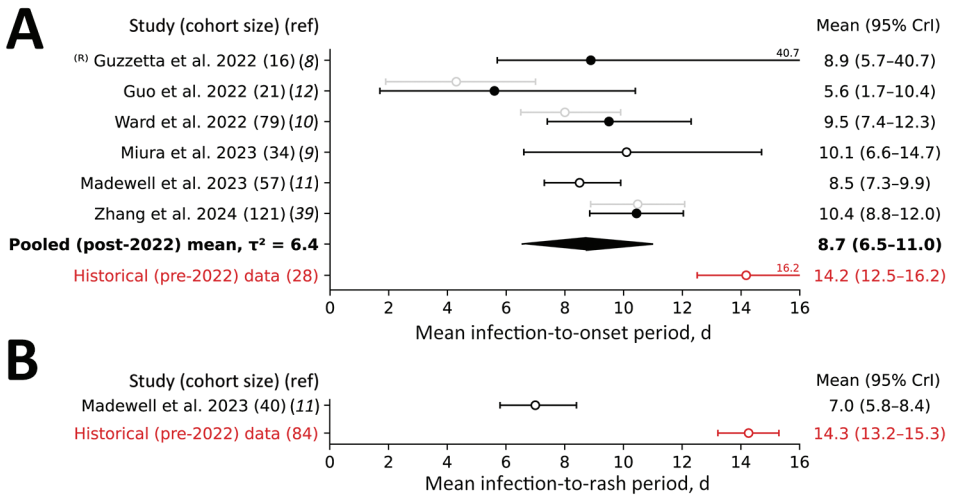

Figure 3. Forest plot of the estimated mean serial interval based on the date of symptom onset (A) and the date of rash onset (B) for studies conducted during the 2022–2023 global mpox outbreak and analyses of the historical case records. Open circles indicate analyses performed without adjusting for right truncation (ICC); solid circles indicate analyses when an adjustment was made (ICRTC). Whiskers indicate 95% CrI. Studies are denoted by the leading author and year of publication and ordered by their date of publication; the numbers in parentheses indicate the number of case records used for estimation. [R] indicates that we re-evaluated estimates for consistency of the methods used. Gray indicates estimates not used for deriving the pooled mean, which is in bold text. Red indicates estimates for historical (pre–2022 outbreak) data, indicating that they were not used for deriving the pooled mean. CrI, credible interval; ICC, interval censoring corrected model; ICRTC, interval censoring and right truncation corrected model; ref, reference; τ^2, -squared statistics indicating the between-study variance measured in days^2.

that the recommended quarantine period of 21 days after contact with a potential infector is still appropriate. However, the possible increase in presymptomatic transmission, as suggested by a shortened serial interval, presents challenges for successful containment of future outbreaks (*9*,*11*). Moreover, underascertainment of cases further reduces the chances of efficient case finding and contact tracing. Vaccination is regarded as the most reliable measure to prevent future waves of infections, but vaccine availability and uptake have been limited. Some countries that observed a spike in cases in 2022 saw their outbreaks fade in 2023, but other countries in the Western Pacific region, such as Japan, South Korea, and Taiwan, observed a rise in cases at the beginning of 2023 (*46*).

The 2022 global mpox outbreak shares some similarities with a previous outbreak in Taiwan involving a sexually transmitted pathogen that also affected a vulnerable group. In 2015–2016, hepatitis A virus (HAV) infections spread progressively among the MSM population. The Taiwan Centers for Disease Control (CDC) reported an increase in HAV cases in 2015. A free HAV vaccination campaign was initiated in October 2016, several months after the peak of disease incidence, targeting at-risk populations. Because it was difficult to quantify the direct impact of vaccination after the peak on the course of the outbreak, many attributed the decline in cases to the promotion of both HAV screening and vaccination by physicians earlier in the outbreak (*47*). In the 2022 global mpox outbreak, there has been much debate about the key factors behind the decline in incidence observed in all hard-hit countries in mid-to-late 2022. Some suggested depletion of susceptible persons within sexual networks of MSM was the key factor (*25*); others argued that a synergetic effect of behavioral change and vaccination was crucial (*48*). Going forward, proactive vaccination campaigns are advised to reduce transmission; such a campaign was implemented in Taiwan at the beginning of 2023 after reports of locally acquired mpox infections.

The first limitation of this study is that we derived the pooled estimates of the mean incubation period and serial interval from various sources, each with their own potential biases and limitations. For example, the study by Ward et al. (*10*) did not consider the possibility of co-primary cases; however, it used personally identifiable information to establish linked pairs. Second, the aggregated historical data could also be prone to selection and recall biases; many studies were conducted retrospectively, and mild cases may have been missed. Third, most cases in the historical datasets involved children and teenagers, whereas in the 2022 outbreak the group that was infected the most was adult males. Such a shift in the age distribution of mpox cases (before and after 2022) may have affected the time delays and introduced bias into our comparison of their estimates. Fourth, the differences in epidemiology of mpox infections respective to their clades remain uncertain. Although our estimated mean incubation period for clade I was shorter than the mean for clade II, the difference was not statistically clear and could simply caused by sampling variability (the samples were

also relatively small). Overall, the studies aggregated in our meta-analysis were conducted during different time periods and in different geographic locations involving diverse social groups. This variation could introduce variability in public health interventions, diagnostic methods, and reporting practices, potentially affecting estimates of epidemiologic parameters such as the incubation period and serial interval. A cohort-based comparison taking account of observed severity, social status, and other factors could help to address potential biases.

Despite those limitations, our study provides evidence that the incubation period for mpox was similar in 2022 to that of historical outbreaks, whereas the serial interval was shorter. This finding likely reflects both the result of interventions and a shift toward a sexually associated mode of transmission in the 2022 outbreak. Because estimated values of epidemiologic parameters are often used to inform interventions against a range of pathogens, our study highlights the importance of monitoring temporal changes in transmission and disease progression. Effective public health interventions that are tailored to the characteristics of future mpox outbreaks could be crucial for mitigating transmission in the future. Overall, our findings provide useful information to inform evidence-based control strategies to curtail the spread of mpox and other directly transmitted infectious diseases.

Study data are available at https://github.com/aakhmetz/Mpox-IncubationPeriodSerialInterval-Meta2023/blob/main/SupplementaryFile1.xlsx.

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Incubation Period and Serial Interval of Mpox in 2022 Global Outbreak Compared with Historical Estimates

Appendix

A. Data Aggregation

a. Inclusion and Exclusion Criteria

Inclusion criteria for selected historical studies required that information on individual pre-2022 mpox cases before were detailed in the text, and that at least one individual case had dates of mpox virus exposure and symptom onset listed, or the period between these two dates listed. Exclusion criteria were: no information on mpox transmission, inaccessible publications, no information on individual mpox cases, and no information on definitive exposure. Inaccessible studies were those that lacked full electronic versions. Studies with overlapping data (i.e., the same individual cases) were included only if they provided additional information about the desired data.

Second, for 2022 and 2023 study inclusion in the meta-analysis, since a standard error value is necessary in addition to the mean incubation period, only peer-reviewed studies with both mean incubation period estimates and their 95% credible interval (CrI) were selected. In addition to the pre-2022 mpox data, we were able to find and use four more datasets. One of these datasets was collected by Viedma-Martinez et al. (*29*), who collected detailed data on mpox cases' dates of exposure and symptom onset that occurred in a tattoo parlor in Cadiz, Spain. However, the authors did not calculate any incubation period estimates, so the estimates were performed in this study. Next was the data used by Miura et al. (*7*). Although Miura et al. had their own incubation period estimates, the statistical methods were re-evaluated and the data were re-analyzed in the present study. Then, the largest available dataset came from Spanish cases collected by Tarin-Vicente et al. (*5*), who did not offer their own Bayesian estimates of the

mean incubation period. Finally, a dataset consisting mostly of U.S. mpox cases, collected by Madewell et al. (*11*), was included in the meta-analysis conducted in this study.

b. Outcome Measures and Study Selection

The outcome variable within each dataset was the mean estimate of the incubation period. It was measured for all cases within each dataset with information on what day they were exposed to mpox and what day their symptoms began.

For the pre-2022 mpox publications, search results were screened first through titles and abstracts. In this screening stage, publications without full electronic texts available and irrelevant studies were removed. The full texts of the remaining studies were examined and, in the next screening stage, those without the required data—definitive exposure and individual case information—were removed during the screening process. For the global 2022 mpox outbreak studies, new studies were included in the meta-analysis as their data became available. Then, data extraction was conducted for the remaining articles that made it through the screening process. When available, we aimed to collect data about studies' author names, publication date, and for each individual case ID, sex, age, country of origin, disease exposure and symptom onset date, rash onset date, list of symptoms, testing date, disease confirmation date, source of infection, transmission method, and disease status (i.e., confirmed, probable, or suspected).

c. Data Descriptions and Preparation for Analysis

To meet the inclusion criteria, each case i found in the literature was required to have, at least, partial information on the time window of exposure $(E_{L,i}, E_{R,i})$ and the time window of symptom onset $(O_{L,i}, O_{R,i})$. The following adjustments could be made:

- When only the lower boundary of the exposure interval $(E_{L,i})$ was definitive, but the upper boundary $(E_{R,i})$ was unknown or it was later than the upper boundary of the symptom onset interval, we set E_R to the upper boundary of the symptom onset interval $O_{R,i}$, i.e., $E_{R,i} \coloneqq O_{R,i}$ IF $E_{L,i}$ is known AND ($E_{R,i}$ is unknown OR $E_{R,i} > O_{R,i}$);
- All symptom onset dates were definitive, implying the respective time interval is of 1-day long ($O_{R,i} \coloneqq O_{L,i}$).

In total, **42 case records** were aggregated, including **38 records** with completely observed exposure time interval, and **4 records** which were censored.

Similar data preparation techniques were applied to estimate the mean exposure-to-rash incubation period, resulting in **20 case records**, including **4 censored records**.

d. Assessing the Retrieved Datasets

Among all of the currently available mpox incubation period estimates, the present study focused on studies reporting the distribution of incubation periods along with the mean and 95% CrI of that distribution for the hierarchical meta-analyses. Then, the present study created incubation period distributions for datasets where they had not yet been estimated or where estimates could be further improved (e.g., by adjusting for right truncation).

Tarin-Vicente et al. (*5*) Data

Tarin-Vicente et al. (*5*) study aimed to investigate the clinical and virological characteristics of human mpox cases in Spain reported in May–June 2022. They conducted a multicenter, prospective, observational cohort study in three sexual health clinics in Madrid and Barcelona, Spain, and enrolled all consecutive patients with laboratory-confirmed mpox from 11 May through 29 June 2022. The authors collected participant data by conducting interviews using a standard case report form and offered lesion, anal, and oropharynx swabs for RT-PCR testing. In addition to collecting data on date of infection and symptom onset, they also collected data on rash onset dates.

Viedma-Martinez et al. (*38*) Data

Identification of case transmission data of mpox from an outbreak rooted in a tattoo parlor in Cadiz, Spain resulted in 21 confirmed reported cases of mpox, all of whom had visited the tattoo parlor around the same couple of weeks. Most of the cases visited the parlor to get a piercing except for one, who got a tattoo only. To extract and synthesize data for the dates of exposure and dates of symptom onset, we retrieved all available information from the relevant sources.

Miura et al. (7) Data

These data were collected from an outbreak of mpox in the Netherlands and had exact dates of exposure for 13 out of 18 cases, and the exact dates of symptom onset for all cases. Where exposure date was uncertain, a range of dates was available, with a left margin and a right margin.

Guzzetta et al. (8) *Data*

An outbreak of confirmed mpox cases in Italy through 8 July 2022 contained complete information (i.e., a known date of exposure and symptom onset) for 15 individual cases. When exposure date was uncertain, a range of earliest exposure and latest exposure was available, for a total of 18 cases included in this study.

B. Statistical Analysis

a. Bayesian Framework

Time interval distributions were estimated using Markov chain Monte Carlo (MCMC) sampling techniques for each available dataset. Subsequently, a meta-analysis was conducted by pooling the time interval estimates reported in the literature, along with the estimated values obtained from the present study's analysis, and employing a Bayesian hierarchical/partial pooling model. Bayesian estimation was implemented using Stan software (https://mc-stan.org). Each run of simulations was consistent of 4 parallel chains with 15,000 posterior draws including 2,500 draws used for tuning-in and disregarded for the final output. Code scripts and all supporting information are publicly available and can be accessed on designated repository: https://github.com/aakhmetz/Mpox-IncubationPeriodSerialInterval-Meta2023

b. Time Interval Estimation

This study involved multiple datasets, each containing information on exposure dates, symptom onset dates, and rash onset dates. Censored data was handled by assigning a weakly informative prior distribution. Then, data lists were constructed for each dataset and descriptively named, including the number of observations (N), exposure dates' lower boundaries, E_L, symptom or rash onset dates' lower boundaries, O_L, and corresponding upper boundaries of these dates, E_R and O_R, when available. The same framework was adapted for transmission (infector-infectee) pairs data set, with the only difference being that the exposure dates, E_L and E_R, would

stand for the onset dates of the infector, and onset dates, O_L and O_R, would stand for the onset dates of the infectee.

For situations where data were missing, the data lists included censored and observed counterparts, such as censored case observations, N_{cens}, complete case observations, N_{obs} ($N = N_{obs} + N_{cens}$), censored lower boundary of the exposure, $E_{L,i} = E_{Lcens,i}$, and observed ones, $E_{L,i} = E_{Lobs,i}$, with the defined prior:

$$E_{R,i} - E_{Lcens,i} \sim \text{Exponential}(\text{rate} = 0.1)$$

The time of exposure, e_i, and the time of symptom onset, o_i, were then assumed to be uniformly distributed within their respective intervals:

$$e_i \sim \text{Uniform}(\text{lower} = E_{L,i}, \text{upper} = E_{R,i} + 1)$$
$$o_i \sim \text{Uniform}(\text{lower} = O_{L,i}, \text{upper} = O_{R,i} + 1)$$

where $i = 1, \dots, N$.

Each time interval (infection-to-onset and infection-to-rash incubation periods, as well as onset-to-onset and rash-to-rash serial intervals) were fitted to the data using five different models—one of three (gamma, Weibull, or lognormal) distributions, their mixture within a Bayesian mixture model, and the generalized gamma distribution (GGD).

In case of using individual distributions l (gamma, Weibull, lognormal, or GGD; $l = 1, 2, 3, 4$, respectively), the likelihood was a product of probability density functions, $f_l(o - e; \theta)$, at each interval $o_i - e_i$, given by:

$$L_l\left(\theta; D \coloneqq \{E_{\circ,i}, O_{\circ,i}\}\right) = \prod_i \iint_{\Phi_i} \frac{f_l(o_i - e_i; \theta)}{F_l(T + 1 - e_i; \theta)} do_i de_i$$

if the data were right truncated at cut-off date T,

$$L_l\left(\theta; D \coloneqq \{E_{\circ,i}, O_{\circ,i}\}\right) = \prod_i \iint_{\Phi_i} f_l(o_i - e_i; \theta) do_i de_i \quad \textbf{(1)}$$

otherwise. Here, $\circ = \{L, R\}$ and the imposed domain Φ_i was defined as follows:

$$\Phi_i \coloneqq \left[\{e_i, o_i\}: O_{L,i} \le o_i \le O_{R,i}, E_{L,i} \le e_i \le \left(\{o_i, E_{R,i}\}\right)\right]$$

The f_l was defined by a set of parameters θ, including the mean, m, and SD, s. All parameters were positive and generic informative priors were assigned to their log-transformed values:

$$\log(m) \sim \text{Normal}(\text{mean} = 2, \text{SD} = 2)$$

$$\log(s) \sim \text{Normal}(\text{mean} = 0, \text{SD} = 2)$$

for all distributions excluding the GGD, and:

$$\log(m) \sim \text{Normal}(\text{mean} = 2, \text{SD} = 2)$$

$$\log(\sigma) \sim \text{Normal}(\text{mean} = 0, \text{SD} = 2)$$

$$\log(a) \sim \text{Normal}(\text{mean} = 0, \text{SD} = 1)$$

otherwise.

In case of the Bayesian mixture model, the overall likelihood, L, was given by a mixture of three component likelihoods with respective weights w_l:

$$L(\theta; D \coloneqq \{E_{\circ,i}, O_{\circ,i}\}) = \sum_{l=1,2,3} w_l L_l(\theta; D)$$

These weights were then estimated as part of the fitting process. To facilitate algorithm convergence, two parameters, the mean and standard deviation (SD), were assigned to be common to all three distributions (*49*).

The posterior probability for selecting the distribution l is defined by the expression:

$$\text{Prob}(l) = \frac{w_l L_l(\theta; D)}{L(\theta; D)}$$

In case of analyzing the rash-to-rash serial interval, the cut-off value, τ, was imposed, when all data points with intervals below τ were truncated. This led to a left-truncated likelihood modified from the form (**1**):

$$L_l(\theta; D \coloneqq \{E_{\circ,i}, O_{\circ,i}\}) = \prod_i \iint_{\Phi_i} \frac{f_l(o_i - e_i; \theta)}{\tilde{F}_l(\tau - 1; \theta)} do_i de_i$$

where $\tilde{F}(\circ; \theta) = 1 - F(\circ; \theta)$ is a complimentary cumulative distribution function.

C. Sensitivity Analysis for Rash-To-Rash Serial Interval

In addition to the eight-day cut-off value considered for **Appendix Figure 1B**, we also calculated the rash-to-rash serial interval under alternative conditions. First, varying the cut-off value between 2 and 10 days yielded a mean rash-to-rash serial interval ranging from 11.9 days to 15.0 days (95% CrI 10.7-16.0 days). Second, we modeled the rash-to-rash interval data using a composition of two distributions: the exponential or scaled standard normal distribution and the serial interval distribution. Both the exponential distribution and the scaled normal distribution as the first component yielded a mean serial interval of 15.1 days (95% CrI 14.2-16.0 days).

Appendix Table 1. Consistency in case definition of symptom onset across different studies

Study	Publication date	Symptom onset definition
Miura et al.	2022-06-16	*Not stated*
Tarin-Vicente et al.	2022-08-08	Fever, lymphadenopathy, influenza-like symptoms, rash
Guzetta et al.	2022-10-01	*Not stated,* but mentioning: fever, rash
Ward et al.	2022-10-10	High temperature, headache, muscle aches, rash
Viedma-Martinez et al.	2023-01-05	Painful regional inflammatory lymphadenopathy
Madewell et al.	2023-04-23	Fever, headache, chills, swollen lymph nodes, exhaustion

Appendix Table 2. Infection-to-onset incubation period in studies of mpox before the 2022 outbreak and in the 2022 outbreak*

Study	# Cases	Publication date	ICC				ICRTC			
			Median, d	Range, d	Mean, d	SD, d	Median, d	Range, d	Mean, d	SD, d
Miura et al.	18	2022-06-16	8.2	2.9–20.3	9.1 (7.2–11.6)	4.6 (3.1–6.4)	8.4	2.8-25.3	9.9 (7.3-15.7)	8.2 (3.2-11.7)
Tarin-Vicente et al.	144	2022-08-08	7.5	2.3–15.6	7.8 (7.3–8.4)	3.5 (3.0–3.9)	7.6	2.2-15.7	7.9 (7.3-8.5)	3.5 (3.1-4.0)
Guzetta et al.	30	2022-10-01	7.0	1.0–23.7	8.4 (6.4–11.1)	6.4 (3.7–9.1)	7.1	0.9-27.8	9.0 (6.5-13.8)	9.4 (3.7-14.4)
Ward et al.	54	2022-10-10	6.5	0.7–20.5	7.6 (6.5–8.9)	5.4 (4.4–6.7)	6.6	0.7-21.0	7.7 (6.6-9.2)	5.6 (4.4-7.1)
Viedma-Martinez et al.	21	2023-01-05	7.6	3.4–16.0	8.1 (6.8–9.6)	3.3 (2.7–4.5)	Not required			
Madewell et al.	36	2023-04-23	n/a	n/a	5.6 (4.3–7.8)	4.4 (2.8–8.7)	Insufficient information			
Ogoina et al.	12	2023-05-17	5.1	0.8–20.8	6.6 (4.2–10.8)	6.7 (2.3–12.0)	Not required			
McFarland et al.	122	2023-07-06	8.7	1.7–23.9	9.8 (8.7–10.9)	5.9 (4.8–6.9)	Not required			
Zhang et al.	75	2023-09-11	6.9	4.1–20.5	8.2 (6.9–9.4)	5.5 (n/a–n/a)	6.9	4.1-20.2	8.1 (6.9-9.3)	5.5 (n/a-n/a)
Alvarez et al.	11	2023-12-07	8.6	1.5–24.2	9.7 (6.6–14.7)	7.0 (2.9–11.8)	Insufficient information			
Historical data	42	Pre-2022	7.4	1.3–19.8	8.2 (6.7–10.0)	4.6 (3.4–6.5)	Not required			
Clade I	16	Pre-2022	6.5	0.8–17.9	7.3 (5.0–10.2)	5.6 (2.6–8.3)	Not required			
Clade II	22	Pre-2022	7.7	1.4–23.5	8.9 (6.6–11.7)	5.1 (3.5–8.4)	Not required			

*The studies are ordered by their publication dates. Mean and SD are represented by their posterior means and 95% CrI; median and range are represented only by their posterior means. ICC, interval censoring corrected model; ICRTC, interval censoring and right truncation corrected model; Range, 95% CrI as the interval between 2.5th and 97.5th percentiles of the posterior distribution; n/a, not available as it was not stated in the original study.

Appendix Table 3. Infection-to-rash incubation period in studies of mpox before the 2022 outbreak and in the 2022 outbreak*

Study	# Cases	Publication date	ICC				ICRTC			
			Median, d	Range, d	Mean, d	SD, d	Median, d	Range, d	Mean, d	SD, d
Tarin-Vicente et al.	143	2022-08-08	8.7	2.3–17.7	9.0 (8.4–9.7)	4.0 (3.5–4.5)	8.8	2.3–18.1	9.2 (8.5–9.9)	4.1 (3.6–4.8)
Viedma-Martinez et al.	19	2023-01-05	9.8	3.7–16.0	9.8 (8.5–11.2)	3.1 (2.2–4.6)	Not required			
Madewell et al.	35	2023-04-23	n/a	n/a	7.5 (6.0–9.8)	4.9 (3.2–8.8)	Insufficient information			
Historical data	28	Pre-2022	9.7	3.4–20.5	10.3 (8.5–12.3)	4.3 (3.1–5.9)	Not required			
Clade I	16	Pre-2022	8.9	2.5–19.4	9.4 (7.2–12.1)	4.1 (2.6–6.6)	Not required			
Clade II	12	Pre-2022	11.1	3.8–23.6	11.7 (8.8–15.2)	5.0 (3.1–8.1)				

*The studies are ordered by their publication dates. Mean and SD are represented by their posterior means and 95% CrI; median and range are represented only by their posterior means. ICC, interval censoring corrected model; ICRTC, interval censoring and right truncation corrected model; Range, 95% CrI as the interval between 2.5th and 97.5th percentiles of the posterior distribution; n/a, not available as it was not stated in the original study.

Appendix Table 4. Serial interval inferred from onset-to-onset case interval data in studies of mpox before the 2022 outbreak and in the 2022 outbreak*

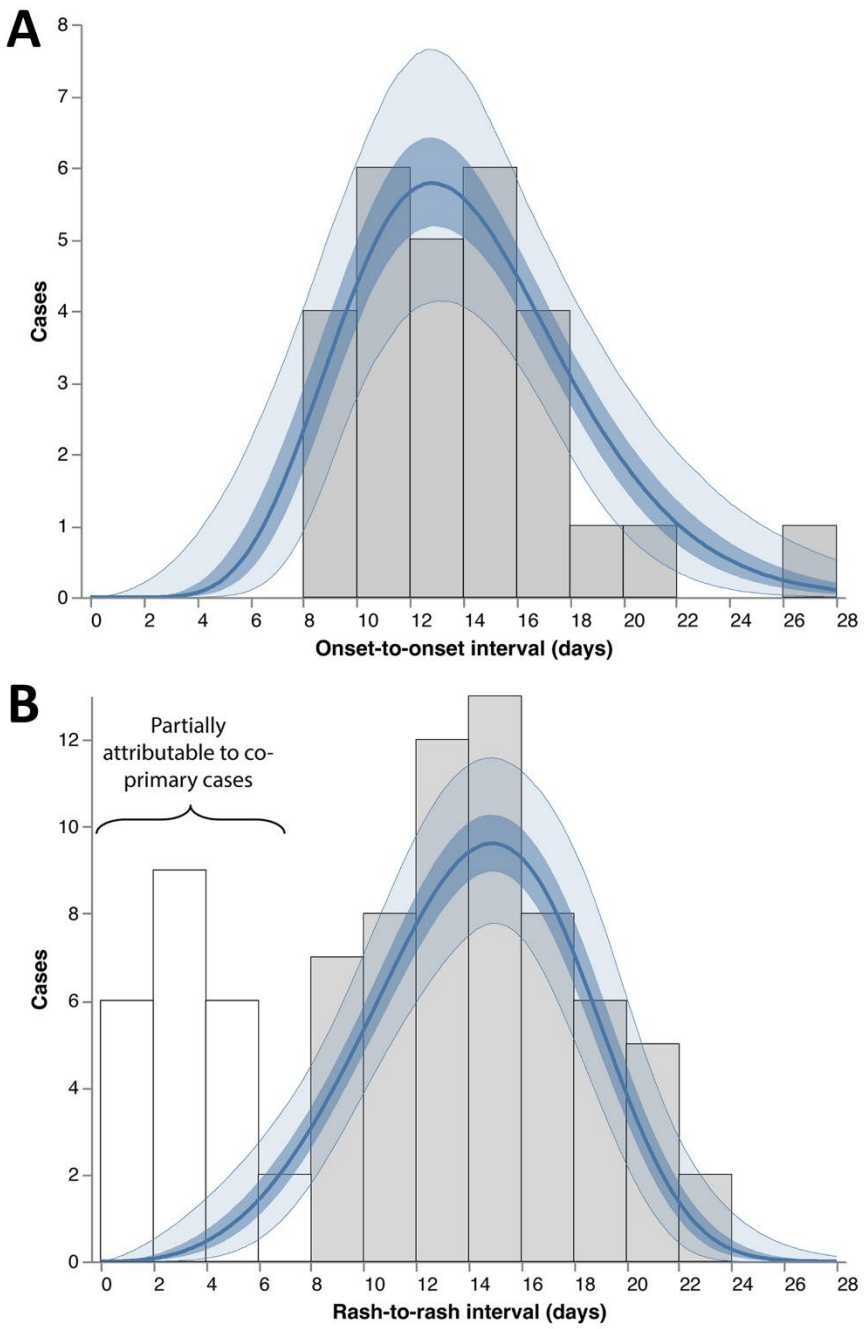
	# of		ICC				ICRTC			
Study	pairs	Publication date	Median, d	Range, d	Mean, d	SD, d	Median, d	Range, d	Mean, d	SD, d
Guzetta et al.	18	2022-10-01	6.5	0.3-29.3	8.2 (5.5-13.8)	6.3 (4.2-18.0)	6.8	0.3-47.8	8.9 (5.7-40.7)	7.2 (4.3-138.5)
Guo et al.	30	2022-10-22	n/a	n/a	4.3 (1.9-7.0)	2.6 (1.1-3.2)	5.5	n/a	5.6 (1.7-10.4)	1.5 (0.4-2.4)
Ward et al.	54	2022-10-10	5.0	0.1-32.2	8.0 (6.5-9.9)	9.0 (7.0-11.7)	5.7	0.1-38.2	9.5 (7.4-12.3)	10.9 (8.0-15.0)
Miura et al.	21	2023-01-05	n/a	n/a	10.1 (6.6-14.7)	6.1 (4.6-8.0)		not required		
Madewell et al.	36	2023-04-23	n/a	n/a	8.5 (7.3-9.9)	5.0 (4.0-6.4)		no difference		
Zhang et al.	121	2023-09-11	8.8	5.2-26.9	10.5 (8.9-12.1)	9.0 (nan-nan)	8.8	5.2-25.8	10.4 (8.8-12.0)	8.9 (nan-nan)
Historical data	42	Pre-2022	13.5	6.9-25.5	14.2 (12.5-16.2)	5.7 (4.1-6.9)		not required		

*The studies are ordered by their publication dates. Mean and SD are represented by their posterior means and 95% CrI; median and range are represented only by their posterior means. ICC, interval censoring corrected model; ICRTC, interval censoring and right truncation corrected model; Range, 95% CrI as the interval between 2.5th and 97.5th percentiles of the posterior distribution; n/a, not available as it was not stated in the original study.

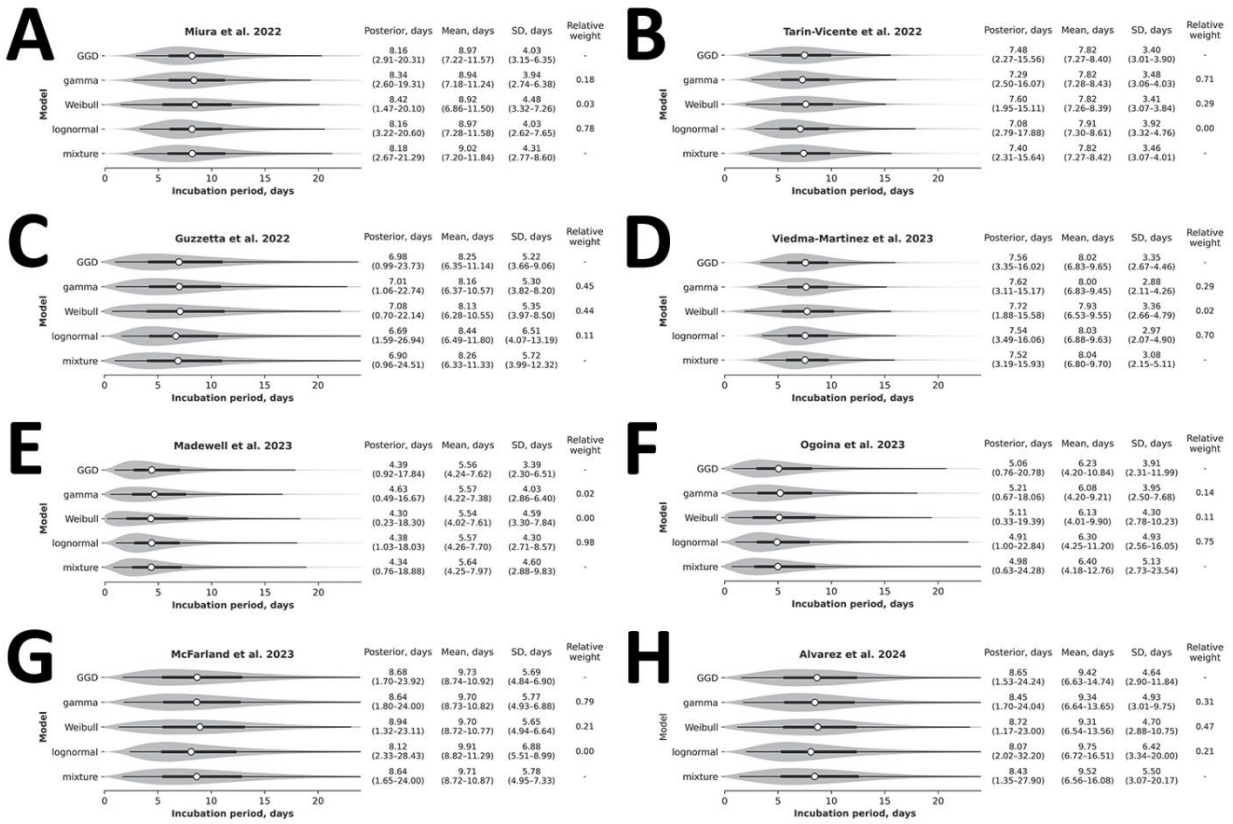
Appendix Table 5. Serial interval inferred from rash-to-rash case interval data in studies of mpox before the 2022 outbreak and in the 2022 outbreak*

	# of		ICC				ICRTC			
Study	pairs	Publication date	Median, d	Range, d	Mean, d	SD, d	Median, d	Range, d	Mean, d	SD, d
Madewell et al.	40	2023-04-23	n/a	n/a	7.0 (5.8-8.4)	4.2 (3.2-5.6)		no difference		
Historical data	28	Pre-2022	14.5	6.1-21.7	14.3 (13.2-15.3)	4.0 (3.4-4.8)		*not required*		

*The studies are ordered by their publication dates. Mean and SD are represented by their posterior means and 95% CrI; median and range are represented only by their posterior means. ICC, interval censoring corrected model; ICRTC, interval censoring and right truncation corrected model; Range, 95% CrI as the interval between 2.5th and 97.5th percentiles of the posterior distribution; n/a, not available as it was not stated in the original study.



Appendix Figure 1. Fitting the serial interval distribution based on symptom onset (A) and rash onset (B) for historical (pre-2022) data. The serial interval is depicted in blue (the solid line represents the median and darker shaded area represents the interquartile range, while the lighter shaded area represents the 95% credible interval). In (A), the bins indicate the onset-to-onset intervals attributable to linked transmission (infector-infectee) pairs. In (B), the filled bins indicate the rash-to-rash intervals likely attributable to transmission pairs, while unfilled bins indicate the rash-to-rash intervals attributable either to co-primary cases or, more likely, to two independent sources of infection. In this situation, a left truncated likelihood was employed for the analysis.



Appendix Figure 2. Estimated infection-to-onset incubation periods fitted using the generalized gamma distribution (GGD), gamma distribution, Weibull distribution, lognormal distribution, or the mixture of the last three distributions (gamma, Weibull, and lognormal) without correcting for right truncation and for various studies. The derived posterior predictive incubation period, mean incubation period and its standard deviation are shown in three columns by their posterior medians and 95% CrI. The last column shows the relative weight of each distribution among three, determined within the Bayesian mixture model. The sum of posterior medians was normalized to one.