



OPEN ACCESS



Check for updates

**FAST TRACK**

# Transmission dynamics of monkeypox in the United Kingdom: contact tracing study

Thomas Ward,<sup>1</sup> Rachel Christie,<sup>1</sup> Robert S Paton,<sup>1</sup> Fergus Cumming,<sup>1</sup> Christopher E Overton<sup>1,2,3</sup><sup>1</sup>Data, Analytics and Surveillance, UK Health Security Agency, London SW1P 3JR, UK<sup>2</sup>Department of Mathematical Sciences, University of Liverpool, Liverpool, UK<sup>3</sup>Department of Mathematics, University of Manchester, Manchester, UKCorrespondence to: T Ward  
Tom.Ward@UKHSA.gov.uk  
(ORCID 0000-0001-8801-747X)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2022;379:e073153  
<http://dx.doi.org/10.1136/bmj-2022-073153>

Accepted: 10 October 2022

**ABSTRACT****OBJECTIVE**

To analyse the transmission dynamics of the monkeypox outbreak in the UK, declared a Public Health Emergency of International Concern in July 2022.

**DESIGN**

Contact tracing study, linking data on case-contact pairs and on probable exposure dates.

**SETTING**

Case questionnaires from the UK Health Security Agency (UKHSA), United Kingdom.

**PARTICIPANTS**

2746 people with polymerase chain reaction confirmed monkeypox virus in the UK between 6 May and 1 August 2022.

**MAIN OUTCOME MEASURES**

The incubation period and serial interval of a monkeypox infection using two bayesian time delay models—one corrected for interval censoring (ICC—interval censoring corrected) and one corrected for interval censoring, right truncation, and epidemic phase bias (ICRTC—interval censoring right truncation corrected). Growth rates of cases by reporting date, when monkeypox virus was confirmed and reported to UKHSA, were estimated using generalised additive models.

**RESULTS**

The mean age of participants was 37.8 years and 95% reported being gay, bisexual, and other men who have sex with men (1160 out of 1213 reporting). The mean incubation period was estimated to be 7.6 days (95% credible interval 6.5 to 9.9) using the ICC model and 7.8 days (6.6 to 9.2) using the ICRTC model. The estimated mean serial interval was 8.0 days (95% credible interval 6.5 to 9.8) using the ICC model and 9.5 days (7.4 to 12.3) using the ICRTC model.

Although the mean serial interval was longer than the incubation period for both models, short serial intervals were more common than short incubation periods, with the 25th centile and the median of the serial interval shorter than the incubation period. For the ICC and ICRTC models, the corresponding estimates ranged from 1.8 days (95% credible interval 1.5 to 1.8) to 1.6 days (1.4 to 1.6) shorter at the 25th centile and 1.6 days (1.5 to 1.7) to 0.8 days (0.3 to 1.2) shorter at the median. 10 out of 13 linked patients had documented pre-symptomatic transmission. Doubling times of cases declined from 9.07 days (95% confidence interval 12.63 to 7.08) on the 6 May, when the first case of monkeypox was reported in the UK, to a halving time of 29 days (95% confidence interval 38.02 to 23.44) on 1 August.

**CONCLUSIONS**

Analysis of the instantaneous growth rate of monkeypox incidence indicates that the epidemic peaked in the UK as of 9 July and then started to decline. Short serial intervals were more common than short incubation periods suggesting considerable pre-symptomatic transmission, which was validated through linked patient level records. For patients who could be linked through personally identifiable data, four days was the maximum time that transmission was detected before symptoms manifested. An isolation period of 16 to 23 days would be required to detect 95% of people with a potential infection. The 95th centile of the serial interval was between 23 and 41 days, suggesting long infectious periods.

**Introduction**

Monkeypox, a zoonotic disease, was identified in 1958 in monkeys showing signs of a poxvirus.<sup>1</sup> The disease is caused by a virus belonging to the orthopoxvirus genus and was first detected in humans in 1970 in the Democratic Republic of the Congo.<sup>2</sup> The disease has since become endemic in that region and spread to other central and west African countries. Such spread has resulted in divergence of the virus, with two distinct clades circulating in different regions of Africa. The two clades, the Congo Basin and Western African, show distinct epidemiological characteristics. Surveillance and laboratory studies have found the Congo Basin clade to be the more severe of the two, with higher transmissibility.<sup>3 4</sup> In May 2022, the World Health Organization reported a monkeypox outbreak in several originally non-endemic countries,<sup>5</sup> since linked to the Western African clade.<sup>6</sup> These cases were of considerable concern as they could not be clearly linked to recent travel from an endemic area. On 6 May 2022, monkeypox was detected in England in a patient who had recently travelled to Nigeria. A week later

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Monkeypox was first detected in 1970 in the Democratic Republic of the Congo. The incubation period and serial interval have been estimated from observational studies.

Since the international outbreak of monkeypox in May 2022 a study estimated a mean incubation period of 8.5 days; however, the sample size was small (n=18).

**WHAT THIS STUDY ADDS**

This study found evidence of pre-symptomatic transmission of monkeypox, using contact tracing data and adjustments for interval censoring, right truncation, and epidemic phase bias.

The maximum time that transmission was detected before symptoms manifested for infected individuals who could be linked through reliable personal identifiable information was four days.

monkeypox was identified in two more people, with no links to the first patient. Between 6 May 2022 and 12 September 2022, 3552 cases of monkeypox have been confirmed in the United Kingdom.<sup>7</sup> The international dispersion of the virus has resulted in the largest outbreak of monkeypox reported outside of Africa. In July 2022 WHO declared the outbreak a Public Health Emergency of International Concern.<sup>8</sup>

To understand the transmission dynamics of the monkeypox outbreak, accurate estimates are needed of the time between subsequent infections (generation time) and time from becoming infected to developing symptoms (incubation period). Infection time is rarely observed directly, so the generation time is generally approximated using the serial interval—the time from symptom onset in a primary case (an individual with the index infection) to symptom onset in a secondary case (an individual who becomes infected by the primary case).<sup>9</sup> Typical monkeypox symptoms are listed on the National Health Service website and include rash (for example, on the mouth, genitals, anus), high temperature, headache, and muscle aches.<sup>10</sup> Serial interval and incubation period estimates are important for informing policy decisions around post-infection quarantine periods and post-contact isolation periods, respectively, as well as for understanding the dynamics of viral transmission, such as potential transmissibility before symptoms manifest.<sup>11 12</sup> Based on observational studies of monkeypox from the Democratic Republic of the Congo, estimates for the incubation period range from 4–14 days and for the serial interval from 8–11 days.<sup>13 14</sup> For the Western Africa clade that is currently circulating in the UK,<sup>15</sup> early research suggests a mean incubation period of between 6.6 and 10.9 days.<sup>16</sup> This estimate is, however, based on limited data and thus far no research pertaining to the serial interval has been released.

To estimate both the serial interval and the incubation period of monkeypox we used a large sample from the UK Health Security Agency (UKHSA) surveillance and contact tracing data. To obtain data on the incubation period we analysed completed case questionnaires and linked infected individuals to probable exposure dates. To obtain the serial interval data we used self-reported symptom onset dates and linked case-contact pairs (linked pairs of primary and secondary cases). We then applied a bayesian model correcting for double interval censoring (ICC)<sup>17</sup> and a bayesian model correcting for double interval censoring, right truncation, and epidemic phase bias (ICRTC) to these data to estimate the serial interval and incubation period distributions of monkeypox.

## Methods

### Epidemiological data

Data were collected on monkeypox from UKHSA health protection teams, targeted testing of infected individuals (with specimens processed by UKHSA affiliated laboratories and NHS laboratories), and questionnaires (collected by UKHSA health protection teams). We defined a confirmed case as an individual

with a positive polymerase chain reaction (PCR) test result for monkeypox virus, and a highly probable case as an individual with a positive PCR test result for orthopoxvirus. As of 25 July 2022, both definitions were recognised in the UK as representing a case of monkeypox.

UKHSA health protection teams identified pairs of linked individuals through contact tracing. If an individual was identified as a contact by a case and became a case or was already a case, we recorded these as a case-contact pair. In the analysis, we assume that the direction of transmission is based on the date order of symptom onset, because the direction of transmission cannot be otherwise ascertained.

### Data preparation

Data were extracted as of 1 August 2022, at which time 2746 people had been identified with monkeypox in the UK. We identified the dates of symptom onset for the case-contact pairs from HPZone (see box 1) by matching pseudo identifier numbers to the line list (see box 1), and we selected only case-contact pairs with a confirmed positive PCR test result for monkeypox for both individuals. From the dataset we removed records with missing data for symptom onset and pseudo identifier number, as well as duplicates. If two records had the same pseudo identifier numbers for both individuals in the case-contact pair we assumed these to represent duplicates. A total of 220 case-contact pairs were reported in HPZone, 79 with a symptom onset date for both individuals in the case-contact pair, forming our serial interval cohort. For each case-contact pair, we refer to the individual with the primary infection as a primary case, and the individual infected by the primary case as the secondary contact.

We identified exposure dates for the incubation period from questionnaire data filled out by cases. Cases had the option of answering “On what date did

#### Box 1: Data source definitions

##### HPZone

UKHSA health protection teams store data collected during an incident in the HPZone

##### Line list

The line list contains a list of confirmed infected individuals in the UK obtained from test data (compiled and deduplicated) from UKHSA affiliated laboratories, National Health Service trust laboratories, and HPZone data, along with supplementary data from the case questionnaires

##### Questionnaires

Data are obtained from three types of questionnaires:

- The rapid sexual health questionnaire
- A questionnaire administered by health practitioners
- An anonymous self-completed questionnaire
- All questionnaires are optional, and individuals are not required to complete all questions

UKHSA=UK Health Security Agency

**Table 1 | Proportion of patients who reported being gay, bisexual, and other men who have sex with men (GBMSM) and mean age of each study sample compared with the total set of patients**

	No of patients	% GBMSM (No with variable/Total No)	Mean (SD) age (years)
Total cases (patient)	2746	95 (1160/1213)	37.8 (9.1)
Serial interval (primary case)	79	96 (67/70)	36.8 (9.7)
Incubation period (patient)	54	93 (50/54)	35.6 (8.2)
Linked serial interval and incubation period (primary case)	13	89 (8/9)	36.6 (7.9)

SD=standard deviation.

your illness begin?," "In the 21 days (3 weeks) before first symptom onset did you have contact with anyone with suspected or confirmed monkeypox infection?," and "Date of last contact with case." An exposure date was therefore defined as the last date an individual reported contact with a known case in the 21 days before symptoms manifested, and symptom onset was defined as the date symptoms manifested. This definition of symptom onset describes the date that an individual first noticed their symptoms; however, the true date of symptom onset could have been earlier but not detected. As of 1 August 2022, 650 people had completed questionnaires, 54 of whom had provided information on symptom onset date and had reported the date of last contact with a primary case, forming our incubation period cohort.

When negative incubation periods were identified, we assumed that the patient was not infected by the named contact, as this is not possible. If we identified

negative serial intervals, we assumed that this record in the dataset had incorrectly identified the direction of transmission in the case-contact pairs, and the order of the primary case and secondary contract were reversed. Negative serial intervals are possible in the presence of pre-symptomatic transmission, although the nature of contact tracing data means that the direction of transmission can be difficult to infer from the data, and positive serial intervals are more likely than negative serial intervals.

To investigate potential exposure dates that occurred before symptom onset in a primary case, which would suggest pre-symptomatic transmission, we linked data on the date of symptom onset in the primary case with exposure dates in their secondary contacts. Firstly, we linked case-contact pairs to questionnaire records for each secondary contact, which enabled the primary case and the exposure date to be identified for the secondary contact. We then used the pseudo identifier number to link the identified primary case to the line list to obtain the date of symptom onset. This relies on the assumption that the primary case identified by the secondary contact in the questionnaire is the same primary case identified in case-contact pair. As of 1 August 2022, 92 records (from 650 questionnaires) showed complete data for exposure date from the questionnaire and the pseudo identifier number needed for linking the datasets. From those, 30 had documented case-contact links in the HPZone data, allowing the primary case to be identified. Of the 30 primary cases, 19 had a symptom onset date recorded in the line list.

Three of the 19 records we identified reported a negative incubation period and were excluded. From the remaining 16 records, seven primary cases had personal identifiable information in both the questionnaire and the line list, allowing us to verify whether the individual identified by the secondary contact was also the primary case from the case-contact pair. For the seven primary cases with available personal identifiable information, four matched and three did not match. After excluding the primary cases who did not match on personal identifiable information, 13 case-contact pairs remained. These 13 form our cohort for investigating pre-symptomatic transmission.

When we compared the subsamples obtained through this data processing with the total set of patients (table 1), the mean age and proportion of patients who reported being gay, bisexual, and other men who have sex with men was consistent across all samples. The subsamples therefore captured the two key personal characteristics of infected individuals in the outbreak.

### Time delay distribution modelling

Incubation periods and serial intervals are examples of time delay distributions, which describe the distribution of times between two coupled events. For the incubation period, this is the time between the date patients were exposed (primary event) and

#### Equation 1

$$P(E \in [e_1, e_2] \mid S \in [s_1, s_2], E < T) = \frac{P(E \in [e_1, e_2], S \in [s_1, s_2])}{P(E < T, S \in [s_1, s_2])}$$

Within the context of this paper, the events  $E$  and  $S$  refer to:

Time period	$E$	$S$
Incubation period	Exposure	Symptom onset
Serial interval	Symptom onset case	Symptom onset contact

#### Equation 2

$$P(E = e^* \mid S = s^*, E < T) = \frac{e^* \sim \text{Uniform}(e_1, e_2), s^* \sim \text{Uniform}(s_1, s_2), P(E = e^*, S = s^*)}{\frac{P(E < T, S = s^*)}{P(E = e^* \mid S = s^*)}} = \frac{P(E = e^* \mid S = s^*) P(S = s^*)}{\frac{P(E < T, S = s^*)}{P(E = e^* \mid S = s^*)}} = \frac{f_\theta(e^* - s^*)}{F_\theta(T - s^*)}$$

where  $f_\theta(\cdot)$  and  $F_\theta(\cdot)$  are the probability density function and cumulative distribution function, respectively, of the parametric delay distribution, parameterised by two parameters,  $\theta_1$  and  $\theta_2$

#### Equation 3

$$\begin{aligned} \theta_1 &\sim \text{prior}(\theta_1), \\ \theta_2 &\sim \text{prior}(\theta_2), \\ e^* &\sim \text{Uniform}(e_1, e_2), \\ s^* &\sim \text{Uniform}(s_1, s_2), \\ \text{loglikelihood} &\sim \log(f_\theta(e^* - s^*)) - \log(F_\theta(T - s^*)) \end{aligned}$$

#### Equation 4

$$\begin{aligned} \theta_1 &\sim \text{prior}(\theta_1), \\ \theta_2 &\sim \text{prior}(\theta_2), \\ e^* &\sim \text{Uniform}(e_1, e_2), \\ s^* &\sim \text{Uniform}(s_1, s_2), \\ \text{loglikelihood} &\sim \log(f_\theta(e^* - s^*)) \end{aligned}$$

**Fig 1 | Equations**

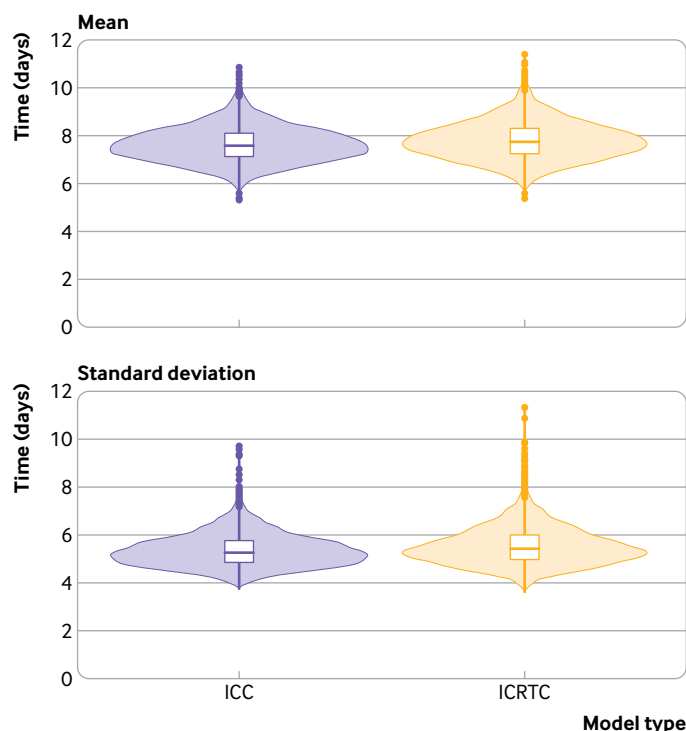


Fig 2 | Posterior distributions for mean and standard deviation of the incubation period for monkeypox. Posteriors are reported for the ICC (interval censoring corrected) model and the ICRTC (interval censoring right truncation corrected) model, fit to data from 54 patients using a Weibull distribution

their symptom onset date (secondary event). For the serial interval, this is the time between the symptom onset date in the primary case (primary event) and the symptom onset date in the secondary contact (secondary event).

During an ongoing epidemic, time delay distribution observations are either right truncated or right censored. Right truncation emerges when data are only observed after the second event occurs, such as infections being identified only after cases emerge. Right censoring occurs when an individual is known to have been exposed to an event, but the event has not occurred yet.

In the context of our study, a right truncation bias exists because individuals only enter our data after they develop symptoms and seek a test. Right truncation leads to the observed distribution of time delays being biased towards shorter observations, since for a delay when the primary event occurs close to the final date of observation, only the secondary event will be observed if the delay is short. To adjust for the right truncation, we fitted a double interval censoring and right

truncation corrected parametric delay distribution. The right truncation primarily affects recent observations and has less of an influence on older observations. We adapted the method from Ward and Johnsen<sup>17</sup> and Vekaria et al.<sup>18</sup> The double interval censoring corrects for the coarseness of the data, whereby only the date each event occurs is known rather than the time, which leads to a 24 hour window during which each event could have occurred.

In this method, we assume that the primary event (symptom onset in the primary case for serial interval or exposure date for incubation period) for each individual sits within an interval  $[e_1, e_2]$ , where  $e_1$  is the reported event date and  $e_2$  is the day after. Similarly, the secondary event time (symptom onset in secondary contact for serial interval or symptom onset for incubation period) sits within an interval  $[s_1, s_2]$ . Equation 1 (fig 1) shows the probability of observing a given second event time (denoted by a random variable  $S$ ), conditional on the observed first event time (denoted by a random variable  $E$ ) given that the final observation date is  $T$ .

Equation 1 could be solved by integrating across the observation intervals. However, this would be computationally expensive. Instead, within our model we included estimated event times for each patient,  $z^* \in [z_1, z_2]$  for  $z \in \{e, s\}$ , as an unobserved variable. Our likelihood function therefore relies on three functions (equation 2, fig 1). We considered three parametric distributions: gamma, Weibull, and lognormal. For the gamma and Weibull distributions, we parameterised the models for mean,  $\theta_1$ , and the shape parameter,  $\theta_2$ , which describes the shape of the distribution, controlling the variance and skewness. For both distributions, it is assumed that the mean follows a normal distribution prior, with mean 5 and standard deviation 1, and that the shape parameters follow a flat prior. For lognormal the model was parameterised in terms of the log mean,  $\theta_1$ , and log standard deviation,  $\theta_2$ , parameters. It is assumed both  $\theta_1$  and  $\theta_2$  follow a standard normal prior distribution. These priors were chosen to be sufficiently informative to penalise unrealistic parameter combinations but specified with low precision to allow the data to maximally inform the estimates. Recentring the priors to alternative means with the same precision yielded consistent results.

To fit the model to the data, we used a Markov chain Monte Carlo (MCMC) implemented in Stan through the Cmdstanr package, with full model formula (equation 3, fig 1).

The data sharing section includes a link to a repository containing the code for the model and the trace results from the MCMC sample. To compare the model fits we calculated the leave-one-out cross validation (LOO) through Pareto smoothed importance sampling, using the LOO package in R.<sup>19</sup> We applied MCMC to each model and evaluated its convergence using potential scale reduction factor, or  $\hat{R}$  (calculated using Cmdstanr<sup>20</sup>), where it is desirable to have a value  $<1.05$ . From the MCMC output, we obtained a posterior distribution of parameters, which describes

Table 2 | Summary statistics of the incubation period for monkeypox, fit to data from 54 patients using a Weibull distribution

Model	Mean (95% CrI)	Standard deviation (95% CrI)	Shape (95% CrI)	Scale (95% CrI)	$\hat{R}$ - mean
ICC	7.6 (6.5 to 8.9)	5.4 (4.4 to 6.7)	1.5 (1.2 to 1.7)	8.4 (7.1 to 9.8)	1.00
ICRTC	7.8 (6.6 to 9.2)	5.6 (4.4 to 7.1)	1.4 (1.2 to 1.7)	8.5 (7.2 to 10.1)	1.00

CrI=credible interval; ICC=interval censoring corrected; ICRTC=interval censoring right truncation corrected.



**Table 3 | Cumulative parametric estimates for the distribution of monkeypox incubation periods, fit to data from 54 patients using a Weibull distribution**

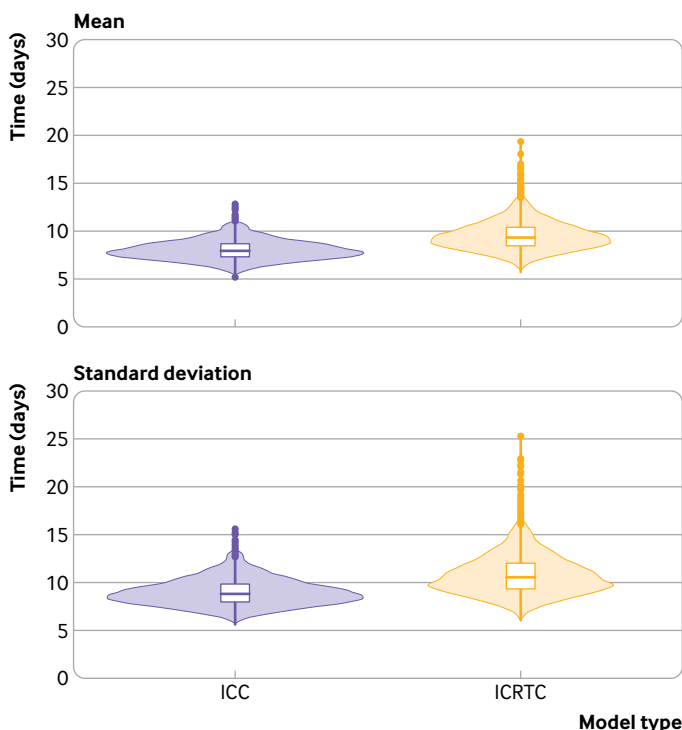
Model	Centile (95% CrI)				
	25th	50th	75th	90th	95th
ICC	3.6 (2.7 to 4.5)	6.6 (5.5 to 7.7)	10.5 (9.1 to 12.4)	14.9 (12.8 to 18.0)	17.8 (15.2 to 21.9)
ICRTC	3.6 (2.7 to 4.5)	6.6 (5.5 to 7.9)	10.7 (9.2 to 12.6)	15.2 (13.0 to 18.5)	18.1 (15.5 to 22.5)

CrI=credible interval; ICC=interval censoring corrected; ICRTC=interval censoring right truncation corrected.

the distribution of parameters considered by the model. The MCMC algorithm preferentially selects parameters that better describe the data. From this posterior distribution, credible intervals are calculated and reported for the mean, standard deviation, and cumulative distribution function. We refer to this model as the double interval censoring and right truncation corrected model (ICRTC).

If an epidemic is stable or declining the right truncation bias has less of an effect on the data. In such cases it may be reasonable to consider a model without the right truncation correction—that is, assuming that  $P(S < T | E = e^*) \approx 1$ . Under this assumption the model becomes simplified (equation 4, fig 1). We refer to this model as the double interval censoring corrected model (ICC).

Other approaches can be applied to handle right truncation bias.<sup>21</sup> We opted for our approach because the epidemic phase related terms,  $P(E = e^*)$ , cancel each other out, so we do not need to explicitly describe the phase of the epidemic within the model. Often, other methods introduce further assumptions to handle this term, which risk introducing bias.



**Fig 3 | Posterior distributions for mean and standard deviation of the serial interval for monkeypox. Posteriors are reported for the ICC (interval censoring corrected) model and the ICRTC (interval censoring right truncation corrected) model, fit to data from 79 patients using a gamma distribution**

### Instantaneous growth rate

We used a previously described method<sup>22</sup> to estimate the growth rate of monkeypox cases since the start of the outbreak in England. To estimate the exponential growth rate, we need to assume an exponential structure to the data. In a period of constant exponential growth, an epidemic can be approximated using  $y(t) = y(0)e^{rt}$ , where  $y(0)$  is the initial number of cases and  $r$  is the exponential growth rate. Following the methods of Ward et al,<sup>22</sup> this can be generalised to an epidemic that is not in an exponential phase, by replacing  $rt$  with a smooth function of time,  $s(t)$ . To estimate this smooth function, we fit a generalised additive model to daily confirmed case counts with a negative binomial error structure and log link. We used the reporting date as it was robust to the (often long) reporting lags associated with specimen date. Cubic regression splines were used with one knot every 14 days. Under this model ( $y(t) = y(0)e^{s(t)}$ ), the number of cases at time  $t$ ,  $y(t)$ , is proportional to the exponential of the smooth function with time,  $\exp(s(t))$ . The time derivative of the smoother  $ds(t)/dt$  is therefore the instantaneous growth rate,  $r_s$  and doubling times can be interpreted as  $t_d = \log(2)/r_s$ . A random effect on the day of week accounts for the average difference in reporting between days.

### Patient and public involvement

We did not directly involve patients and members of the public in the design and conception of the study, primarily because of the pace at which this study was conducted to inform the UK government's response to the monkeypox outbreak in the UK. The paper was, however, read by members of the public upon submission.

### Results

#### Incubation period

The posterior estimate for the mean incubation period of monkeypox from the UK sampling was 7.6 days (95% credible interval 6.5 to 9.9) for the ICC model and 7.8 days (6.6 to 9.2) (fig 2 and table 2) for the ICRTC model. A Weibull distribution gave the best fit to the data for both models (see supplementary material A for results of the lognormal and gamma models).

Table 3 shows the results of the cumulative distribution function of the incubation period distribution. The median incubation period for the ICC model was 6.6 days (95% credible interval 5.5 to 7.7) and for the ICRTC model was 6.6 days (5.5 to 7.9). At the 95th centile, the posterior estimates were 17.8 days (95% credible interval 15.2 to 21.9) for the ICC model and 18.1 days (15.5 to 22.5) for the ICRTC model.

#### Serial interval

The estimated serial interval posterior distributions for the mean serial interval from the UK sampling was 8.0 days (95% credible interval 6.5 to 9.9) for the ICC model and 9.5 days (7.4 to 12.3) (fig 3 and table 4) for the ICRTC model. The data were found to be best

**Table 4 | Summary statistics of the serial interval for monkeypox, fit to data from 79 patients using a gamma distribution**

Model	Mean (95% CrI)	Standard deviation (95% CrI)	Shape (95% CrI)	Rate (95% CrI)	$\hat{R}$ - mean
ICC	8.0 (6.5 to 9.9)	9.0 (7.0 to 11.7)	0.8 (0.6 to 1.1)	0.1 (0.1 to 0.2)	1.00
ICRTC	9.5 (7.4 to 12.3)	10.9 (8.0 to 15.0)	0.8 (0.6 to 1.0)	0.1 (0.1 to 0.1)	1.00

CrI=credible interval; ICC=interval censoring corrected; ICRTC=interval censoring right truncation corrected.

described by a gamma distribution for both models. Greater uncertainty can be observed for the model that adjusts for right truncation. Supplementary material B shows the results of the Weibull and lognormal models.

Using the cumulative distribution function of the serial interval distribution, the median number was 5.0 days (95% credible interval 3.8 to 6.2) for the ICC model and 5.8 days (4.3 to 7.6) for the ICRTC model (table 5). At the 95th centile the posterior estimates were 25.7 days (95% credible interval 20.7 to 33.7) for the ICC model and 30.3 days (23.3 to 41.7) for the ICRTC model.

For the ICC and ICRTC models, we found that the 25th and 50th centiles were shorter for the serial interval distribution than for the incubation period distribution (fig 4), ranging from 1.8 days (95% credible interval 1.5 to 1.8) to 1.6 days (1.4 to 1.6) shorter at the 25th centile and 1.6 days (1.5 to 1.7) to 0.8 days (0.3 to 1.2) shorter at the median, respectively. Under an assumption of statistical independence between the serial interval and incubation period, the probability that the serial interval would be shorter than the incubation period (and therefore the proportion of patients with pre-symptomatic transmission) was 53% (95% credible interval 43% to 62%).

Figure 5 shows the relative times from the symptom onset date in the primary case (primary case onset) to the date of exposure for the secondary contact (secondary contact exposure), serial interval, and the incubation period of the 13 case-contact pairs for whom all events could be linked. Negative times from primary case onset to secondary contact exposure indicate pre-symptomatic transmission. Analysis of these 13 case-contact pairs showed 10 with pre-symptomatic transmission. This sample size is small and relies on the completion of an optional case questionnaire and on the cases being linked by contact tracing. Our finding does, however, provide evidence that there are patients who showed pre-symptomatic transmission in the monkeypox outbreak data. The maximum time that transmission was detected before symptoms manifested was nine days. For the more reliable sample where personal identifiable information was available for linkage, this time decreased to four days, with three out of the four more reliable (ie, personal identifiable

information available) case-contact pairs showing pre-symptomatic transmission.

## Growth rates

Figure 6 shows the instantaneous growth rate of case numbers over time and log scale model fit to case counts. On the day of the first reported case of monkeypox in the UK (6 May), we estimated that case numbers were doubling every 9.07 days (95% confidence interval 12.63 to 7.08). The central estimate for the doubling time declined throughout the outbreak up to 9 July, when it reached a growth rate of about zero (infinite doubling time). At the end of the study period, 1 August, case numbers were halving every 29 days (38.02 to 23.44). By the most recent modelled dates (15 September) case numbers were declining relatively quickly and halving every 16.89 days (27.40 to 12.19).

## Discussion

### Principal findings

The global transmission of monkeypox from May 2022 in non-endemic countries necessitated further understanding of the transmission dynamics of the virus. The mean incubation period and mean serial interval were found to range from 6.6 to 9.2 days and 7.4 to 12.3 days, respectively, when adjusted for right truncation and epidemic phase bias. The median serial interval was estimated to be shorter than the incubation period, which indicates considerably greater pre-symptomatic transmission than previously thought,<sup>23</sup> and was validated by analysis of individual level data. Analysis of the instantaneous growth rate indicates that as of 9 July the epidemic peaked in the UK. Although case numbers are declining, increased international transmission would facilitate infection importation and might drive stochastic outbreaks even if vaccination in local networks limits transmission.

### Context of UK monkeypox outbreak

The monkeypox epidemic in the UK has been largely based in dense social networks with high contact rates.<sup>24</sup> Particularly, transmission has been largely clustered around a subset of gay, bisexual, and other men who have sex with men who engage in behaviours that put them at higher risk of infection and transmission. For example, more than half of respondents to case questionnaires in the UK had a history of a sexually transmitted infection over the past year, and 31% had at least 10 or more sexual partners in the past three months.<sup>25</sup> In the UK outbreak, the median age of infected individuals was 37 years,<sup>25</sup> in contrast with earlier outbreaks in the Democratic Republic of the Congo where in 2016 the median age was 10 years and by 2020 only 42% of cases were older than 5 years.<sup>14 26</sup> This is indicative of changes in the primary routes of transmission for the monkeypox virus in the 2022 epidemic. The current strain of monkeypox in the UK shows 48 single mutations in the genome compared with strain sequencing from 2018.<sup>27</sup> The impact of these mutations is difficult to assess

**Table 5 | Cumulative parametric estimates for the distribution of the serial interval for monkeypox, fit to data from 79 patients using a gamma distribution**

Centile (95% CrI)					
Model	25th	50th	75th	90th	95th
ICC	1.8 (1.1 to 2.5)	5.0 (3.8 to 6.2)	11.0 (8.9 to 13.9)	19.3 (15.7 to 24.8)	25.7 (20.7 to 33.7)
ICRTC	2.0 (1.3 to 3.0)	5.8 (4.3 to 7.6)	12.9 (10.1 to 16.9)	22.5 (17.6 to 30.6)	30.3 (23.3 to 41.7)

CrI=credible interval; ICC=interval censoring corrected; ICRTC=interval censoring right truncation corrected.

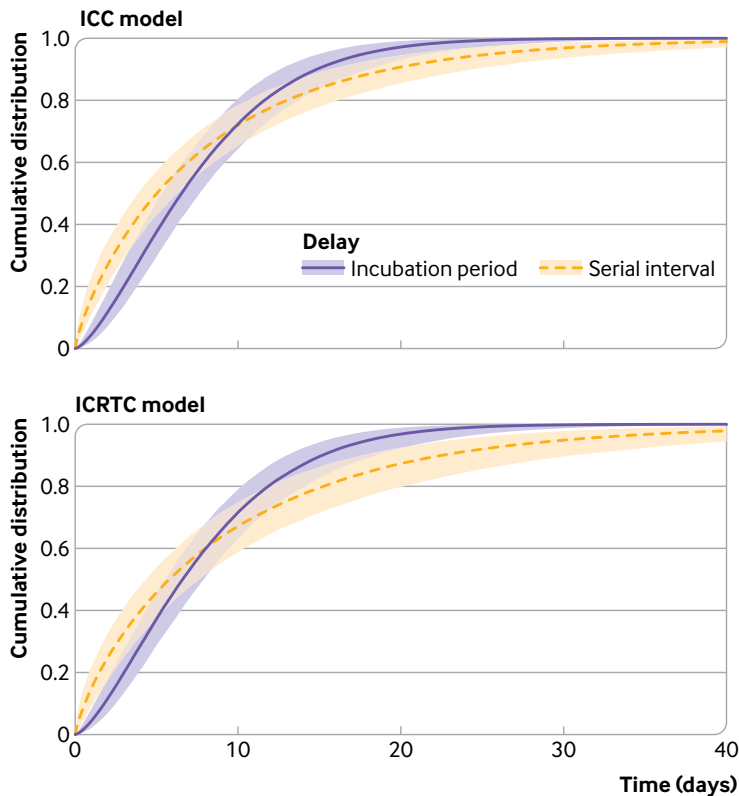


Fig 4 | Cumulative distribution function of the serial interval and incubation period for monkeypox. Using the ICC (interval censoring corrected) model and the ICRTC (interval censoring right truncation corrected) model, fit to data using a gamma distribution for the serial interval and a Weibull distribution for the incubation period, with 95% credible interval

currently, although several have been associated with increased virulence and severity.

#### Comparison with other studies

The international outbreak of monkeypox since May 2022 has produced more contemporary estimates of the incubation period with this mutated clade. In one study involving 18 infected participants, the estimated mean incubation period was 8.5 days (95% credible interval 6.6 to 10.9).<sup>16</sup> A limitation of this study was the small sample size, and therefore the findings were unlikely to be representative of the full distribution. Adjustments for interval censoring, right truncation, and epidemic phase bias are essential for data that are coarsely collected<sup>28</sup> and linked to probable, not deterministic, exposure events. In the absence of adjustment for right truncation, longer incubation periods from recent infections will be underrepresented. These estimates are specific to the demographic distribution of this outbreak (age and sexual orientation) and severity of this clade. In other populations and with different disease severity, the incubation periods are likely to differ.<sup>29–32</sup>

#### Strengths and limitations of this study

The primary strength of this analysis is the large sample size, obtained from the UKHSA surveillance

and contact tracing data, enabling the distributions to be estimated with reasonably narrow credible intervals. Another strength was the application of robust methods to estimate distributions, adjusting for the key biases of interval censoring and right truncation that are present in the data.

The conclusions are robust to the choice of model (with or without correction for right truncation) and choice of parametric distribution. This gives greater confidence in the conclusions because they are not driven by methodological choices. Additionally, the conclusions around the presence of pre-symptomatic transmission are supported by analysis of the relative shapes of both the incubation period and the serial interval distributions as well as individual level patient data. These two sources of evidence provide greater confidence in the conclusions.

The main limitations of this analysis relate to the nature of the data, which often rely on patient reported variables. In particular, symptom onset date is defined as the date patients noticed they had an infection. This corresponds to the date when the patient recognised that they had symptoms of monkeypox. Assuming all individuals behaved similarly, this is unlikely to have materially affected the serial interval distribution. If clinical symptoms occurred before patients recognised they had symptoms, however, then the true incubation period could be shorter than the patients' recognised incubation period. Therefore, some of the identified pre-symptomatic transmission could have occurred after clinical symptom onset, but before patients were aware of their symptoms.

Another challenge arising from the patient reported data is that we relied on contact tracing to identify case-contact pairs. Individuals report other individuals who they have been in contact with or who they think might have infected them, but this does not necessarily mean transmission occurred during that contact. Although the outbreak was large, however, incidence was still low relative to the population size at risk. Named contacts are therefore likely to correspond to genuine transmission events. A side effect of this is that, assuming the linked pair are a genuine transmission event, we cannot directly ascertain the direction of transmission. We have assumed that transmission follows the direction of symptom onset dates. This is likely to be true in most cases but will lead to some overestimation of the serial interval because some negative observations will be replaced with positive values. However, this overestimation of the serial interval will bias the data away from pre-symptomatic transmission, which further supports the evidence of pre-symptomatic transmission we identified.

Our analyses were specific to the dynamics of the outbreak. Incubation periods can vary with severity and personal characteristics of infected individuals,<sup>29–32</sup> and serial intervals are highly dependent on viral transmission dynamics. Therefore, these distributions might not be the same for outbreaks in other settings.

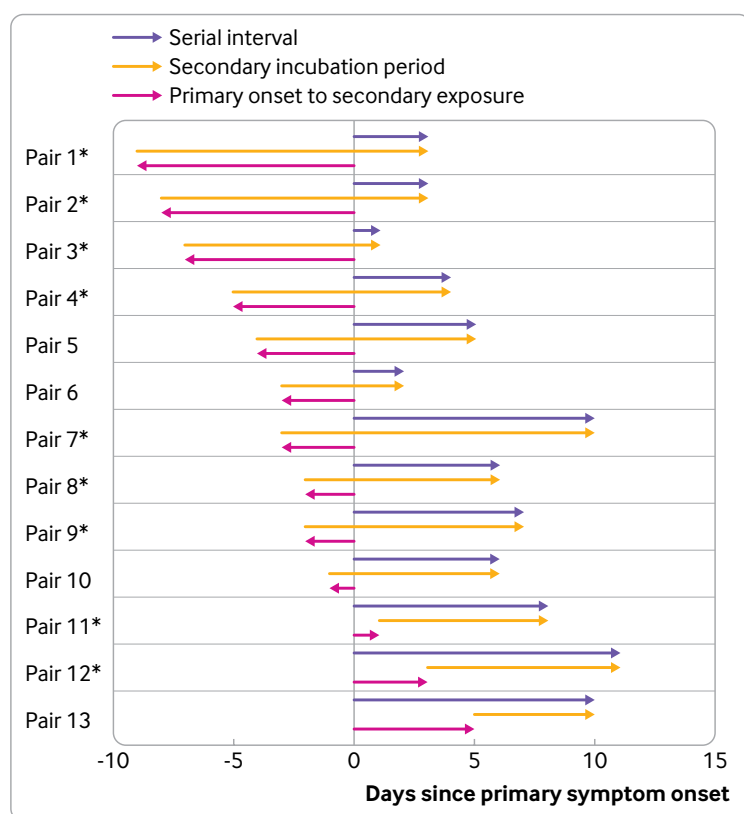


Fig 5 | Onset to exposure, serial interval, and incubation period for 13 primary cases with monkeypox who had matching personal identifiable information or were matched but without such information. The origin is symptom onset date of the primary case, with the x axis showing number of days between subsequent events. Purple arrow indicates number of days between primary onset and secondary exposure. Blue arrow indicates number of days between secondary exposure and secondary onset (incubation period). Red arrow indicates number of days between primary onset and secondary onset (serial interval). \*Personal identifiable information not available and therefore data considered less reliable

### Implications

We found that shorter serial intervals are more common than short incubation periods for monkeypox, which suggests considerable pre-symptomatic transmission. This has also been observed for other viral infections<sup>11 12</sup> and is a consequence of transmission during the pre-symptomatic period. Previous research has not found evidence of transmission and substantial shedding of monkeypox virus before symptom onset, which is reflected in guidance from WHO and the European Centre for Disease Prevention and Control.<sup>23 33</sup> Assuming statistical independence between the serial interval and incubation period, we found that 53% (95% credible interval 43% to 62%) of transmission occurs in the pre-symptomatic phase. However, since serial intervals depend on the incubation period this finding is an approximation of the proportion of infections due to pre-symptomatic transmission. This finding is consistent with the proportion of pre-symptomatic transmission among the subset of case-contact pairs where transmission can be identified relative to the date of symptom onset after exposure. Data for both the serial interval and the

incubation period are similarly distributed across the monkeypox outbreak in the UK, so temporal changes in reporting should affect both distributions comparably (see supplementary material C).

The identification of pre-symptomatic transmission might be indicative of changes to the primary route of transmission. Pre-symptomatic transmission may be facilitated by specific types of high intensity interactions (eg, sexual contacts) where lower pre-symptomatic viral loads are infectious. This pre-symptomatic transmission could also be transmission before symptoms are detected rather than before clinical symptom onset because individuals could have lesions of which they are unaware—this might be more important for internal lesions. From the perspective of public health policy, this transmission before the detection of symptoms is equivalent to pre-symptomatic transmission, as it concerns when individuals might become aware of their infection. If a substantial proportion of secondary transmission occurs before symptom onset, the implications will be that many infections cannot be prevented by isolating individuals with symptoms. Furthermore, the effectiveness of contact tracing will be affected because when contacts are traced, they might already have generated secondary cases. Therefore, backward contact tracing strategies should account for a pre-symptomatic infectious period when trying to find the contacts of confirmed cases. The maximum time before symptoms that transmission was detected for patients who could be linked through personal identifiable infection was four days.

### Conclusions

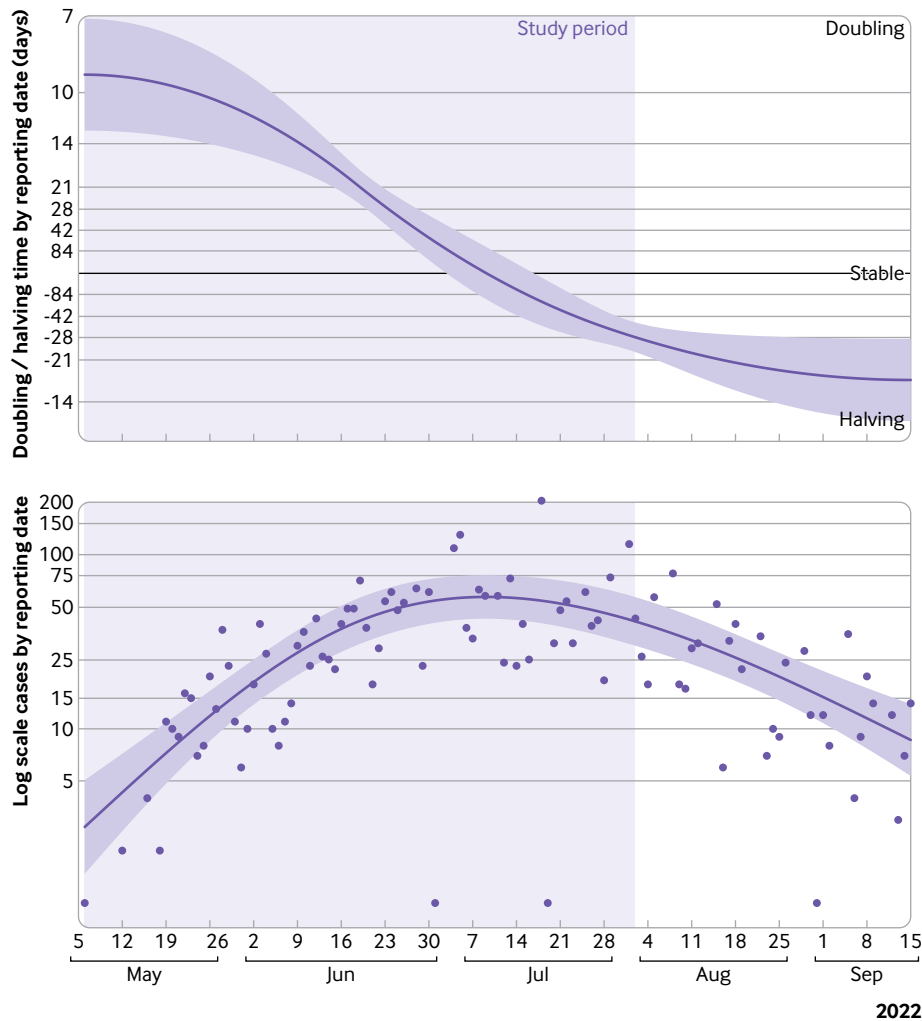
The global transmission of the monkeypox virus has been on a scale not previously seen outside of Central Africa. The shorter median estimate for the serial interval relative to the incubation period suggests that pre-symptomatic transmission might be more substantial than was previously thought, which is further supported by linked patient level data. The 95th centile of the serial interval ranged from 23 to 41 days, which suggests a potential for long infectious periods that are consistent with research of earlier clades. In the present study the incubation period, ranging from 16 to 23 days after exposure, would be adequate to identify 95% of infected individuals, so would be the required length of post-exposure isolation policies.

**Contributors:** TW conceived and led the study. TW and CO developed the methodology. TW, CO, RP, and RC developed the model code and wrote the original manuscript. RC worked on data processing. TW, CO, and FC reviewed the manuscript. TW, CO, RP, and RC wrote the manuscript revisions. TW is the study guarantor. All authors have read and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Funding:** The authors were employed by the UK Health Security Agency but received no specific funding for this study.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/doi\\_disclosure.pdf](http://www.icmje.org/doi_disclosure.pdf) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.





**Fig 6 | Doubling and halving times and log scale model fit of case numbers of monkeypox by reporting date.** Cases were modelled as a smooth function of time using a generalised additive model with a negative binomial error distribution. Shaded area denotes span of time series where the serial intervals and incubation period distributions were estimated (6 May to 1 August 2022)

**Ethical approval:** This study was conducted for the purpose of informing the outbreak response to the monkeypox pandemic. Work was undertaken in line with national data regulations.

**Data sharing:** An application can be made to the UK Health Security Agency. Data requests can be made to the Office for Data Release (<https://www.gov.uk/government/publications/accessing-ukhsa-protected-data/accessing-ukhsa-protected-data>) and by contacting [DataAccess@ukhsa.gov.uk](mailto:DataAccess@ukhsa.gov.uk). All requests to access data are reviewed by the Office for Data Release and are subject to strict confidentiality provisions in line with the requirements of: the common law duty of confidentiality, data protection legislation (including the General Data Protection Regulation), Caldicott principles, the Information Commissioner's statutory data sharing code of practice, and the national data opt-out programme. The trace results for the shape and scale parameter from the Markov chain Monte Carlo sampler and the model code can be found here: <https://github.com/OvertonC/Transmission-Dynamics-of-Monkeypox-in-the-United-Kingdom>.

The lead author (TW) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Dissemination to participants and related patient and public communities:** We will disseminate the results to governmental organisations and agencies through official channels and publications.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

- 1 Magnus PV, Andersen EK, Petersen KB, et al. A Pox-like disease in Cynomolgus monkeys. *Acta Pathol Microbiol Scand* 1959;46:156-76
- 2 WHO. Monkeypox, 2022. <https://www.who.int/news-room/fact-sheets/detail/monkeypox>.
- 3 Beer EM, Rao VB. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. *PLoS Negl Trop Dis* 2019;13:e0007791. doi:10.1371/journal.pntd.0007791
- 4 Hutson CL, Abel JA, Carroll DS, et al. Comparison of West African and Congo Basin monkeypox viruses in BALB/c and C57BL/6 mice. *PLoS One* 2010;5:e8912. doi:10.1371/journal.pone.0008912
- 5 WHO. Multi-country monkeypox outbreak in non-endemic countries, 2022. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON385>.
- 6 Chen N, Li G, Liszewski MK, et al. Virulence differences between monkeypox virus isolates from West Africa and the Congo basin. *Virology* 2005;340:46-63. doi:10.1016/j.virol.2005.05.030

- 7 UK Health Security Agency. Monkeypox outbreak: epidemiological overview. 13 September 2022. <https://www.gov.uk/government/publications/monkeypox-outbreak-epidemiological-overview/monkeypox-outbreak-epidemiological-overview-13-september-2022>. (Accessed 16 September 2022.)
- 8 WHO. WHO Director-General declares the ongoing monkeypox outbreak a Public Health Emergency of International Concern. 2022. <https://www.who.int/europe/news/item/23-07-2022-who-director-general-declares-the-ongoing-monkeypox-outbreak-a-public-health-event-of-international-concern>.
- 9 Lehtinen S, Ashcroft P, Bonhoeffer S. On the relationship between serial interval, infectiousness profile and generation time. *J R Soc Interface* 2021;18:20200756. doi:10.1098/rsif.2020.0756
- 10 NHS. Monkeypox. 2022. <https://www.nhs.uk/conditions/monkeypox/>.
- 11 Casey-Bryars M, Griffin J, McAloon C, et al. Presymptomatic transmission of SARS-CoV-2 infection: a secondary analysis using published data. *BMJ Open* 2021;11:e041240. doi:10.1136/bmjopen-2020-041240
- 12 Nishiura H, Linton NM, Akhmetzhanov AR. Serial interval of novel coronavirus (COVID-19) infections. *Int J Infect Dis* 2020;93:284-6. doi:10.1016/j.ijid.2020.02.060
- 13 Jezek Z, Grab B, Paluku KM, Szczeniowski MV. Human monkeypox: disease pattern, incidence and attack rates in a rural area of northern Zaire. *Trop Geogr Med* 1988;40:73-83.
- 14 Nolen LD, Osadebe L, Katomba J, et al. Extended Human-to-Human Transmission during a Monkeypox Outbreak in the Democratic Republic of the Congo. *Emerg Infect Dis* 2016;22:1014-21. doi:10.3201/eid2206.150579
- 15 UK Public Health Agencies. Principles for monkeypox control in the UK: 4 nations consensus statement. 2022. <https://www.gov.uk/government/publications/principles-for-monkeypox-control-in-the-uk-4-nations-consensus-statement/principles-for-monkeypox-control-in-the-uk-4-nations-consensus-statement#:~:text=In%20the%20UK%2C%20all%20reported,about%20the%20West%20Afr.ES.2022.27.24.2200448>
- 16 Miura F, van Ewijk CE, Backer JA, et al. Estimated incubation period for monkeypox cases confirmed in the Netherlands, May 2022. *Euro Surveill* 2022;27. doi:10.2807/1560-7917.ES.2022.27.24.2200448
- 17 Ward T, Johnsen A. Understanding an evolving pandemic: An analysis of the clinical time delay distributions of COVID-19 in the United Kingdom. *PLoS One* 2021;16:e0257978. doi:10.1371/journal.pone.0257978
- 18 Vekaria B, Overton C, Wiśniowski A, et al. Hospital length of stay for COVID-19 patients: Data-driven methods for forward planning. *BMC Infect Dis* 2021;21:700.
- 19 Goodrich B, Gabry J, Ali I, et al. Information criteria and cross-validation, 2020. <https://mc-stan.org/rstanarm/reference/loo.stanreg.html>.
- 20 Gelman A, Rubin D. Inference from Iterative Simulation Using Multiple Sequences. *Stat Sci* 1992;7:457-72. doi:10.1214/ss/1177011136.
- 21 Seaman SR, Presanis A, Jackson C. Estimating a time-to-event distribution from right-truncated data in an epidemic: A review of methods. *Stat Methods Med Res* 2022;31:1641-55. doi:10.1177/09622802211023955
- 22 Ward T, Glaser A, Johnsen A, Xu F, Hall I, Pellis L. Growth, reproduction numbers and factors affecting the spread of SARS-CoV-2 novel variants of concern in the UK from October 2020 to July 2021: a modelling analysis. *BMJ Open* 2021;11:e056636. doi:10.1136/bmjopen-2021-056636
- 23 ECDC. Considerations for contact tracing during the monkeypox outbreak in Europe, 2022. 2022. [https://www.ecdc.europa.eu/sites/default/files/documents/Considerations-for-Contact-Tracing-MPX\\_June%202022.pdf](https://www.ecdc.europa.eu/sites/default/files/documents/Considerations-for-Contact-Tracing-MPX_June%202022.pdf).
- 24 UK Health Security Agency. Investigation into monkeypox outbreak in England: technical briefing 1. 2022. <https://www.gov.uk/government/publications/monkeypox-outbreak-technical-briefings/investigation-into-monkeypox-outbreak-in-england-technical-briefing-1#part-2-epidemiology-update>.
- 25 UK Health Security Agency. Investigation into monkeypox outbreak in England: technical briefing 3. 2022. <https://www.gov.uk/government/publications/monkeypox-outbreak-technical-briefings/investigation-into-monkeypox-outbreak-in-england-technical-briefing-3>.
- 26 WHO. Monkeypox - Democratic Republic of the Congo. 2020. <https://web.archive.org/web/20220605103903/https://www.who.int/emergencies/disease-outbreak-news/item/monkeypox-democratic-republic-of-the-congo>.
- 27 UK Health Security Agency. Investigation into monkeypox outbreak in England: technical briefing 1. 2022. <https://www.gov.uk/government/publications/monkeypox-outbreak-technical-briefings/investigation-into-monkeypox-outbreak-in-england-technical-briefing-1#part-3-genomics>.
- 28 Reich NG, Lessler J, Cummings DA, Brookmeyer R. Estimating incubation period distributions with coarse data. *Stat Med* 2009;28:2769-84. doi:10.1002/sim.3659.
- 29 Lai C, Yu R, Wang M, et al. Shorter incubation period is associated with severe disease progression in patients with COVID-19. *Virulence* 2020;11:1443-52.
- 30 Virlogeux V, Fang VJ, Wu JT, et al. Brief Report: Incubation Period Duration and Severity of Clinical Disease Following Severe Acute Respiratory Syndrome Coronavirus Infection. *Epidemiology* 2015;26:666-9. doi:10.1097/EDE.0000000000000339
- 31 Virlogeux V, Park M, Wu JT, Cowling BJ. Association between Severity of MERS-CoV Infection and Incubation Period. *Emerg Infect Dis* 2016;22:526-8. doi:10.3201/eid2203.151437
- 32 Glynn JR, Palmer SR. Incubation period, severity of disease, and infecting dose: evidence from a Salmonella outbreak. *Am J Epidemiol* 1992;136:1369-77. doi:10.1093/oxfordjournals.aje.a116449
- 33 WHO. Surveillance, case investigation and contact tracing for monkeypox: interim guidance, 25 August 2022. 2022. <https://www.who.int/publications/i/item/WHO-MPX-Surveillance-2022.3>.

**Supplementary information:** Supplementary material A-C