

Early Estimates of Monkeypox Incubation Period, Generation Time, and Reproduction Number, Italy, May–June 2022

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We analyzed the first 255 PCR-confirmed cases of monkeypox in Italy in 2022. Preliminary estimates indicate mean incubation period of 9.1 (95% CI 6.5–10.9) days, mean generation time of 12.5 (95% CI 7.5–17.3) days, and reproduction number among men who have sex with men of 2.43 (95% CI 1.82–3.26).

After the first reports of autochthonous cases of monkeypox (MPX) in Europe at the beginning of May, the World Health Organization (WHO) and the European Centre for Disease Prevention and Control alerted member states to report suspected and confirmed cases. Apart from early cases reported in the United Kingdom, most cases were identified in men who have sex with men (MSM) (1–4). We analyzed characteristics of the first 255 PCR-confirmed cases of monkeypox in Italy in 2022.

The Study

In Italy, suspected MPX cases fitting the criteria of the World Health Organization case-definition (5) are reported to the surveillance system of the Ministry of Health. Only those cases testing positive by MPX-specific PCR were considered confirmed. Information on main patient characteristics (age, sex, earliest date of

symptom onset, presence of rash and other signs, exposure modality, and travel abroad) were collected.

As of July 8, 2022, a total of 255 PCR-confirmed cases had been reported in Italy (Figure). All except 2 were men, and 190/200 (95%) men who disclosed information reported having sex with men; median age was 37 (range 20–71) years.

For 139/184 cases for which information was available, rash was localized at the genital or perianal area. Fever was reported in 151/222 cases for which information was available.

Information about travel was available for 228 case-patients; 86 (37.7%) had traveled abroad, and 25 (29.1%) of those had vacationed in the Canary Islands, suggesting a major amplifying event had occurred (Table). Only 1 case-patient had traveled to West Africa and was symptomatic upon arrival in Italy.

We estimated the incubation period for 30 cases with known date of symptom onset and for which epidemiologic investigations enabled the identification of the likely period of exposure (exact date for 15 cases and dates of visit to Canary Islands for 15 cases). We estimated the generation time (time elapsed between date of exposure of a confirmed case and those of secondary cases) by considering 16 infector-infectee pairs identified during contact tracing operations. We assumed the 2 periods were distributed as gamma functions and estimated them using a Bayesian approach similar to that adopted by F. Miura et al. (6). We considered likely dates of exposure for each confirmed case within a Markov chain Monte Carlo procedure. For estimating generation time, we assumed no presymptomatic transmission. Therefore, sampling of candidate dates of exposure was repeated

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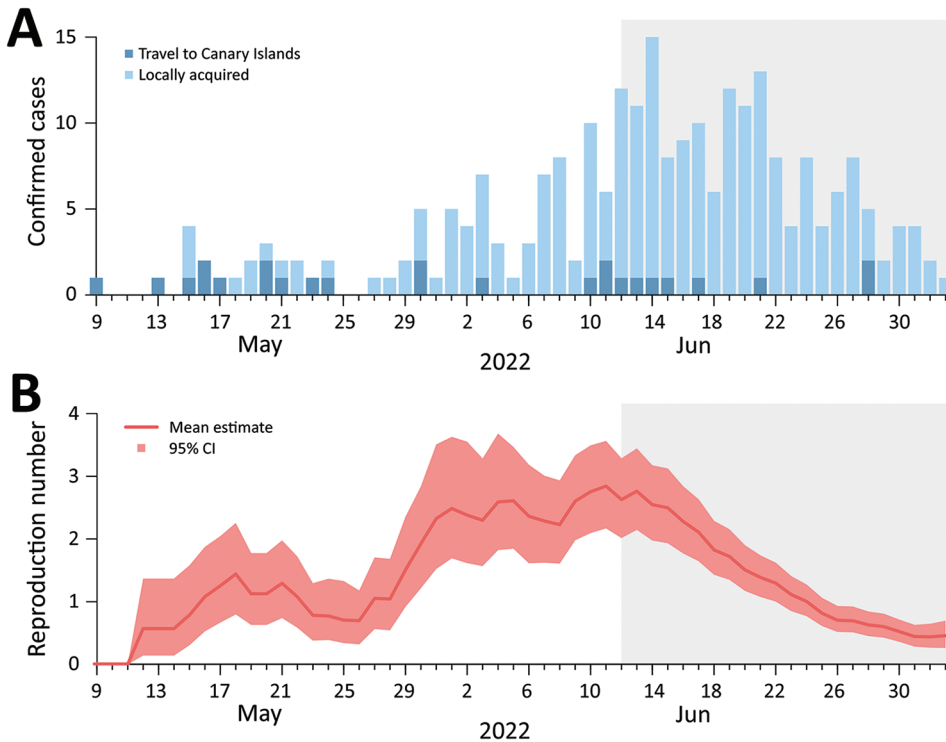


Figure. Epidemic curve and reproduction number of monkeypox cases in Italy through July 8, 2022. A) Number of cases by date of symptom onset and history of travel in Canary Islands. For 4 persons, the date of symptom onset was unknown. B) Estimate of the net reproduction number over time from the epidemic curve by date of symptom onset. We assumed that all cases with a history of travel to Canary Islands were imported and that all the others were locally transmitted, and we used a generation time distribution with mean 12.5 days. Gray shading indicates the part of the epidemic curve that is possibly incomplete because of delays in diagnostic and reporting delays.

if the date of exposure for the infectee was earlier than the date of symptom onset for the infector. We used estimates of the generation time to compute the net reproduction number and used individual anonymized data to estimate the incubation period and generation time (Appendix, <https://wwwnc.cdc.gov/EID/article/28/10/22-1126-App1.pdf>).

The mean incubation period was estimated to be 9.1 days (95% CI 6.5–10.9 days; 5th and 95th percentiles of the distribution 2–20 days). The mean generation time was estimated to be 12.5 days (95% CI 7.5–17.3 days; 5th and 95th percentiles of the distribution, 5–23 days). By assuming a mean generation time of 12.5 days and importation from Canary Islands, we estimate the mean net reproduction number (mean

number of cases generated by a single index case) at 2.43 (95% CI 1.82–3.26) during the first week of June (i.e., when the net reproduction number had stabilized so that the growth of the epidemic curve could be approximated as exponential). A similar estimate was obtained under the assumption of exponential growth in the first week of June (Appendix). After June 12, 2022, we estimated a progressive decrease of the reproduction number.

Conclusions

The first large outbreak of MPX outside Africa is to some extent unique. The analysis of virus genome strongly suggests that the epidemic is caused by the West African clade of the MPX virus (7); however, with the exception of 1 case-patient who reported travels to West Africa (8), ≥60% of cases diagnosed in Italy were autochthonous. Retrospective investigations in Portugal and United Kingdom indicated that the first case-patients had symptoms in April 2022. The presence of skin lesions at the point of sexual contact is suggestive of sexual transmission (9).

After early reports of this multicountry outbreak, the Ministry of Health of Italy issued recommendations consisting of case notification, protective measures to reduce contacts and possible exposure for healthcare workers, tracing of close contacts with monitoring of symptom onset, and the possibility of implementing quarantine measures at the discretion of

Table. Characteristics of 255 confirmed monkeypox cases reported in Italy through July 8, 2022

Characteristic	Value
Sex	
M	253 (99.2)
F	2 (0.8)
Median age, y (range)	37 (20–71)
Clinical symptoms†	
Fever	151/222 (68.0)
Rash	248/251 (98.8)
Genital/perianal rash	139/184 (75.5)
Travel‡	
Travel abroad in previous 21 d	86/228 (37.7)
Travel to Canary Islands in previous 21 d	25/142 (17.6)

*Values are no. (%) patients except as indicated.

†Denominators indicate the total number of available answers.

local health authorities in particular epidemiologic or environmental contexts (10). After the first 4 cases in MSM in Italy who had traveled abroad (4), cases were increasingly notified (8), mostly in the Lombardy and Lazio regions, where Milan and Rome are located; 11 of 21 regional health authorities reported cases. Almost all cases were among MSM. Travel abroad occurred in a substantial fraction of cases (38.9%) identified in Italy, and direct or sexual contact is still likely to be the main transmission mode. Whether the infection was transmitted through direct contact with skin lesions or body fluids remains undefined. The link to different geographic areas (Europe and West Africa) underlines the possibility of multiple independent introductions of the virus, suggesting widespread infection in West Africa before the COVID-19 pandemic (3,11).

Using a limited number of MPX cases, we provided estimates of the mean incubation period (≈ 9 days; $n = 15$ persons with known date of exposure and 15 persons with known travel dates in Canary Islands) and of the mean generation time (≈ 12 days; $n = 16$ infector-infectee pairs). Based on the estimated mean generation time, we found that the reproduction number for this outbreak is ≈ 2.4 , although with a broad uncertainty (95% CI 1.82–3.26) because of the limited number of locally acquired confirmed cases. We found small variations in the estimated reproduction number (mean values ranging from 2.08 to 2.70) when considering different distributions of the generation time (mean 7.5 or 17.3 days) and when exploring alternative assumptions on the importation of cases (Appendix). Our estimates of the reproduction number refer to the community of MSM in which MPX is spreading and not to the general population. The extent to which the decrease of the reproduction number estimated after June 12, 2022, is a result of reduced transmission (e.g., led by increasing awareness about the risk of infection) or from the analysis of incomplete data because of diagnostic and reporting delays is unclear. However, considering that most cases seem to have been transmitted by sexual contact, the reproduction number is likely below threshold in the general population. Besides the limited number of cases, our estimates might be biased by several factors: the assumption that case-patients returning from Canary Islands acquired the infection there, possible recall bias for the dates of exposure, and selection bias in the reconstructed infector-infectee pairs (e.g., a recent sexual partner might be more likely to be identified). Finally, the observed reproduction number might have been inflated by the potential occurrence of superspreading events.

Maintaining a high level of public attention and

providing nonstigmatizing information to at-risk population groups are key to contain the spread of MPX virus, in addition to considering the seasonal intensity of aggregation events and recreational activities. Our estimates provide useful indications to assist with outbreak surveillance and containment. The distribution of the incubation period identifies the period over which symptoms should be monitored among identified contacts, and the generation time provides insight on the recommended duration of isolation for confirmed cases and the time-frame for contact tracing. The generation time is also necessary for computing the net reproduction number, which is critical to monitoring the spread of disease over time.

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Dr. Guzzetta is a researcher at the Bruno Kessler Foundation in Trento, Italy. His primary research interests are epidemiology and mathematical models of infectious disease transmission dynamics with a focus on public health applications, assessments of potential risks, and evaluation of effectiveness of interventions.

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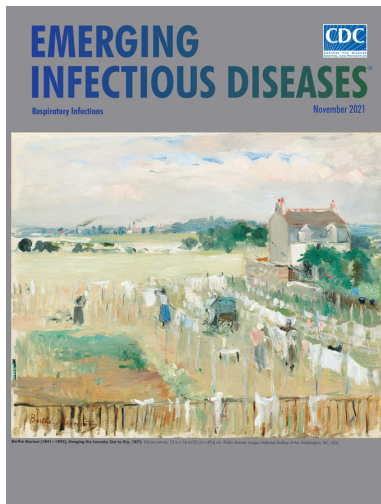
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Appendix

Incubation Period

To compute the incubation period, we considered all monkeypox cases confirmed through July 8, 2022, with a known date of symptom onset and for which ≥ 1 of the following information was reported:

- the latest day of exposure, as ascertained by contact tracing investigation (this information is available for 15 cases);
- a history of travel to Canary Islands, together with the dates of sojourn (this information is available for 15 cases).

As a baseline, we thus considered a total of 30 confirmed cases with prior information on the possible date of exposure (Appendix Table 1).

We assumed that the incubation period is distributed as a gamma function and we estimated the shape (k) and scale parameters (θ) following a Bayesian approach similar to the one adopted in Miura et al. (*1*), based on a Monte Carlo Markov Chain (MCMC) procedure and Metropolis-Hastings sampling. At each MCMC iteration:

- we sampled 1 date of infection for each confirmed case, considering the information available for each subject. For cases with a known latest day of exposure, the date of infection was fixed to this value; for cases with a travel history to Canary Islands, the sampled date of infection was constrained to be between the date of departure to and return from Canary Islands.
- for each confirmed case, we computed the incubation periods as the difference between the date of symptom onset and the sampled date of infections.

- we sampled 1 value for the shape (k) and 1 value for the scale parameter (θ) of the gamma function.
- we compute the gamma likelihood of observing the computed incubation periods given parameters $\{k, \theta\}$

The resulting estimates of the parameters are reported in Appendix Table 2. The cumulative density function estimated for the incubation period is shown in Appendix Figure 1 along with the cumulative distribution of incubation periods associated to the parameter set with the maximum likelihood.

As sensitivity analyses, we estimated the incubation period by considering separately the 15 cases with a known latest date of exposure (sensitivity A) and the 15 cases with a history of travel to Canary Islands (sensitivity B).

Generation Time

The generation time is defined as the difference between the date of infection of a confirmed case and those of secondary cases. To estimate the generation time, we followed a MCMC procedure similar to the one used for the incubation period, by assuming a gamma distributed generation time. In the data, there were 16 identified infector-infectee pairs with known dates of symptom onset (Appendix Table 3). For 2 cases, an exact date of last exposure was identified during epidemiologic investigations and therefore assumed as infection date. For 1 case-patient who reported traveling to Canary Islands but had no other known exposure, we constrained the sampled infection date to be within the dates of departure to and return from Canary Islands. For other cases, the dates of infection were randomly sampled assuming that presymptomatic transmission is not possible (i.e., the date of infection for the secondary cases should always be greater or equal to the date of symptom onset of the infector). Dates of infection were sampled using as a uniform prior between values lying within the 95% CI of the incubation period estimated in the baseline analysis.

The obtained distribution of the generation time is reported in Appendix Figure 2, and the values are summarized in Appendix Table 4.

Reproduction number R_t

We computed the net reproduction number R_t for the monkeypox outbreak using the epidemic curve of cases by date of symptom onset and the estimated distribution of the generation time, by applying a standard statistical method based on the renewal equation. The posterior distribution of R_t can be computed by applying a MCMC algorithm to the following likelihood function:

$$\mathcal{L} = \prod_{t=1}^T P\left(C(t) - I(t); R_t \sum_{s=1}^T \varphi(s)C(t-s)\right)$$

Where:

- $P(k; \lambda)$ is the probability mass function of a Poisson distribution (i.e., the probability of observing k events if these events occur with rate λ).
- $C(t)$ is the total daily number of new cases having symptom onset at time t ;
- $I(t)$ is the total daily number of new cases that are not locally transmitted;
- R_t is the net reproduction number at time t to be estimated;
- $\varphi(s)$ is the probability distribution density of the generation time discretized by day, evaluated at days s .

We considered 3 different assumptions for imported cases:

- 1) we considered only the case with earliest symptom onset as an imported case. This is a rather unrealistic hypothesis that can give an upper bound to the transmissibility of monkeypox;
- 2) we considered as imported cases all cases with a history of travel to Canary Islands; this assumption was considered as a baseline for the results in the main text;
- 3) we considered as imported cases all cases with a history of travel abroad; this is also an unrealistic hypothesis that can be considered as a lower bound to the transmissibility of monkeypox.

Cases for which there are no information for travel abroad are always assumed to be locally transmitted.

In Appendix Figure 3, we report estimates of the reproduction numbers for the 3 hypotheses (rows) as obtained by considering the mean and the lower and upper limits of the 95% CI of the generation time, namely 12.5 days, 7.5 days, and 17.3 days (columns). Appendix Table 5 reports the values of the average reproduction number during the first week of June (i.e., the last week for which the epidemic curve can be reasonably assumed to not suffer from diagnostic and reporting delays).

As a sensitivity analysis, we estimated the reproduction number under the assumption of exponential growth in the first week of June, computed from the formula above by forcing R_t to be constant over the first week of June. Appendix Table 6 shows the estimated value (mean and 95% CI) for all combinations of assumptions on imported cases and mean generation time. The values are in line with those of the main analysis, reported in Appendix Table 5.

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Appendix Table 1. Information on possible dates of monkeypox exposure for 30 cases*

ID	Type of information	Date of symptom onset	Date of earliest exposure	Date of latest exposure
i1	Travel to Canary Islands	8	6	8
i2	Travel to Canary Islands	12	9	12
i3	Travel to Canary Islands	14	2	14
i4	Travel to Canary Islands	15	8	15
i5	Travel to Canary Islands	15	11	14
i6	Travel to Canary Islands	19	11	16
i7	Travel to Canary Islands	20	7	14
i8	Travel to Canary Islands	22	9	14
i9	Known exposure date	23	18	18
i10	Travel to Canary Islands	23	11	17
i11	Known exposure date	28	25	25
i12	Known exposure date	29	27	27
i13	Travel to Canary Islands	29	7	17
i14	Travel to Canary Islands	29	7	14
i15	Travel to Canary Islands	33	9	14
i16	Known exposure date	37	31	31
i17	Known exposure date	38	31	31
i18	Known exposure date	40	21	21
i19	Known exposure date	42	35	35
i20	Travel to Canary Islands	47	32	46
i21	Known exposure date	48	42	42
i22	Known exposure date	49	40	40
i23	Known exposure date	49	40	40
i24	Known exposure date	50	46	46
i25	Known exposure date	51	40	40
i26	Known exposure date	51	40	40
i27	Known exposure date	52	41	41
i28	Known exposure date	54	44	44
i29	Travel to Canary Islands	58	49	56
i30	Travel to Canary Islands	58	44	51

*Dates are expressed in days from a reference date that is not made explicit to preserve anonymity.

Appendix Table 2. Parameters of the incubation period distributions estimated using different methods

Method	Baseline (n = 30)	Sensitivity A (n = 15)	Sensitivity B (n = 15)
Shape (95% CI)	2.42 (1.26–3.62)	3.55 (1.57–6.38)	1.43 (0.62–2.96)
Scale (95% CI)	3.75 (2.17–7.13)	2.67 (1.21–5.73)	7.47 (2.97–16.84)
Mean, d (95% CI)	9.1 (6.5–10.9)	9.5 (6.3–11.2)	10.7 (5.5–14.5)
5th and 95th percentiles of the distribution, d	2–20	3–19	1–28

Appendix Table 3. Information on infector-infectee pairs*

Infector				Infected			
ID	Symptom onset	Earliest exposure	Latest exposure	ID	Symptom onset	Earliest exposure	Latest exposure
g1	9	1	6	g17	18	11	11
g2	9	NA	NA	g18	30	15	15
g3	23	NA	NA	g19	25	NA	NA
g4	27	NA	NA	g20	41	NA	NA
g5	27	NA	NA	g21	39	NA	NA
g6	29	NA	NA	g22	29	NA	NA
g7	31	NA	NA	g23	34	NA	NA
g8	32	NA	NA	g24	43	NA	NA
g9	33	NA	NA	g25	40	NA	NA
g10	33	NA	NA	g26	40	NA	NA
g11	34	NA	NA	g27	39	NA	NA
g12	34	NA	NA	g28	37	NA	NA
g13	35	NA	NA	g29	51	NA	NA
g14	36	NA	NA	g30	46	NA	NA
g15	37	NA	NA	g31	41	NA	NA
g16	44	NA	NA	g32	51	NA	NA

*Dates are expressed in days from a reference date that is not made explicit to preserve anonymity. NA, not applicable.

Appendix Table 4. Parameters of the generation time distributions.

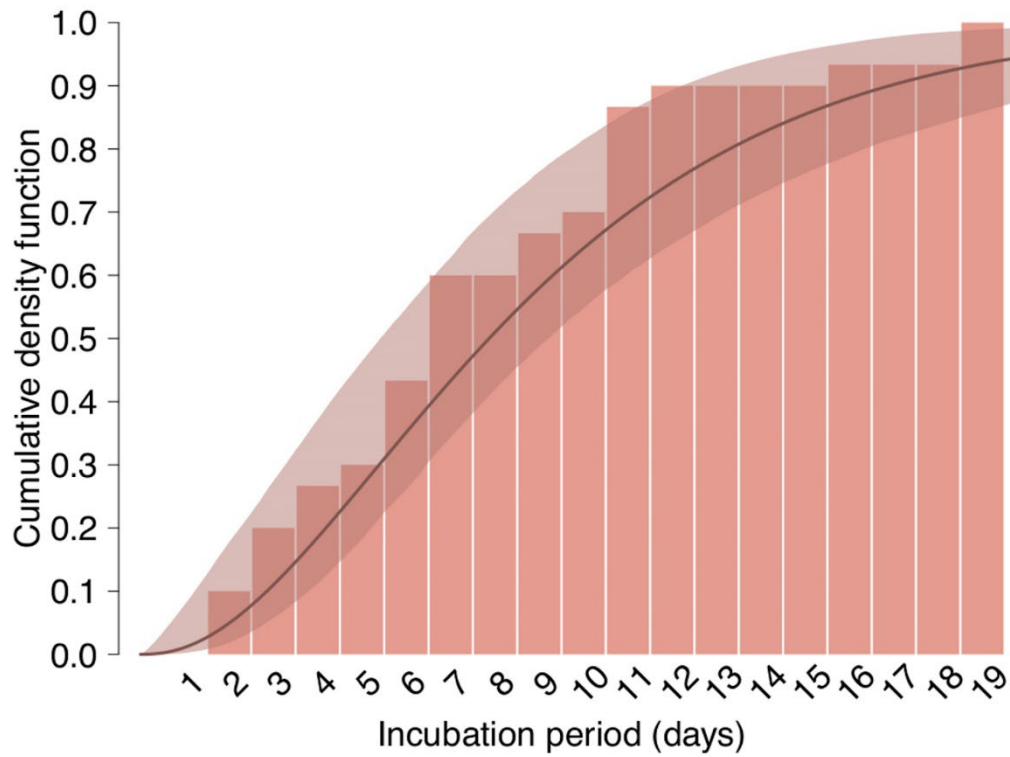
Generation time (n = 16)	Value
Shape (95% CI)	4.85 (3.07–7.20)
Scale (95% CI)	2.57 (1.34–4.07)
Mean (95% CI), d	12.5 (7.5–17.3)
5th and 95th percentiles of the distribution, d	5–23

Appendix Table 5. Estimates of the net reproduction number (mean and 95% CI) in the week of June 1–7 as obtained by considering the mean (first column), lower (central column), and upper (right column) limits of the 95% CI of the generation time

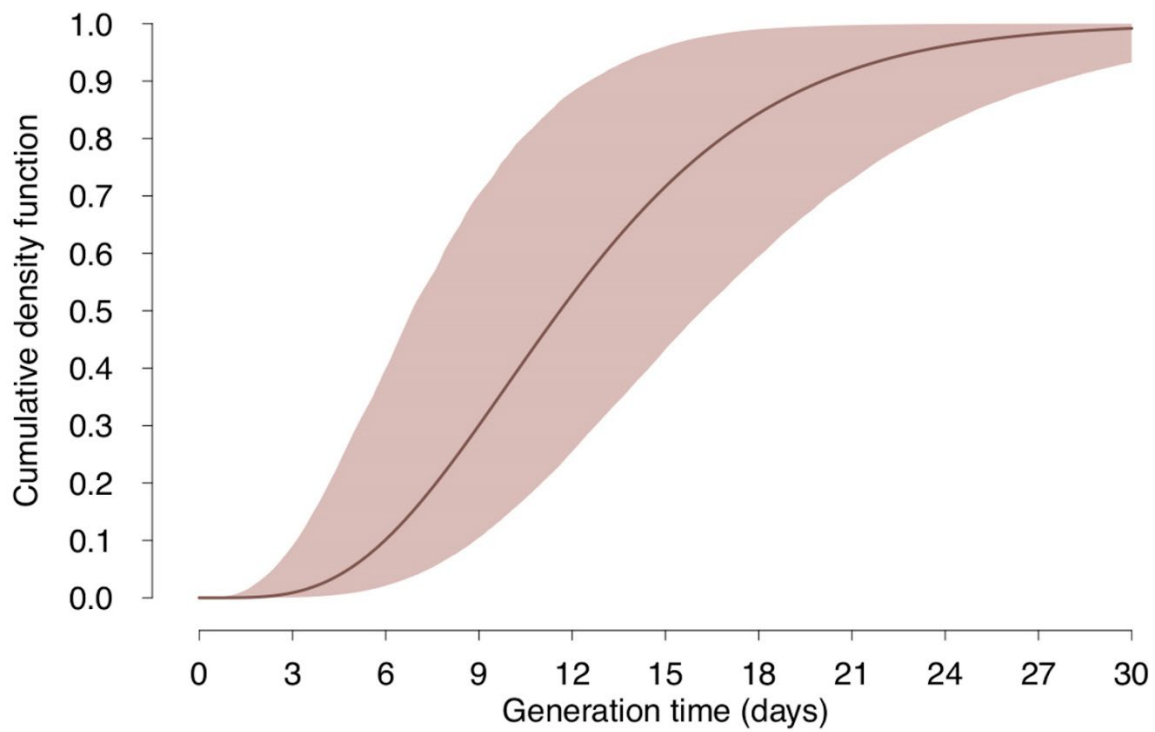
	Mean generation time		
	12.5 d (shape: 4.85, scale: 2.57)	7.5 d (shape: 6.86, scale: 1.10)	17.3 d (shape: 5.67, scale: 3.05)
Assumed imported cases			
Single importation	2.51 (1.90–3.18)	2.34 (1.77–3.00)	2.70 (2.04–3.37)
Importations from Canary Islands, baseline	2.43 (1.82–3.26)	2.24 (1.71–2.99)	2.63 (1.96–3.41)
Importations from abroad	2.23 (1.61–2.92)	2.08 (1.50–2.80)	2.41 (1.77–3.16)

Appendix Table 6. Estimates of the reproduction number (mean and 95%CI) under the assumption of exponential growth in the week of June 1–7, as obtained by considering the mean (first column), lower (central column), and upper (right column) limits of the 95% CI of the generation time

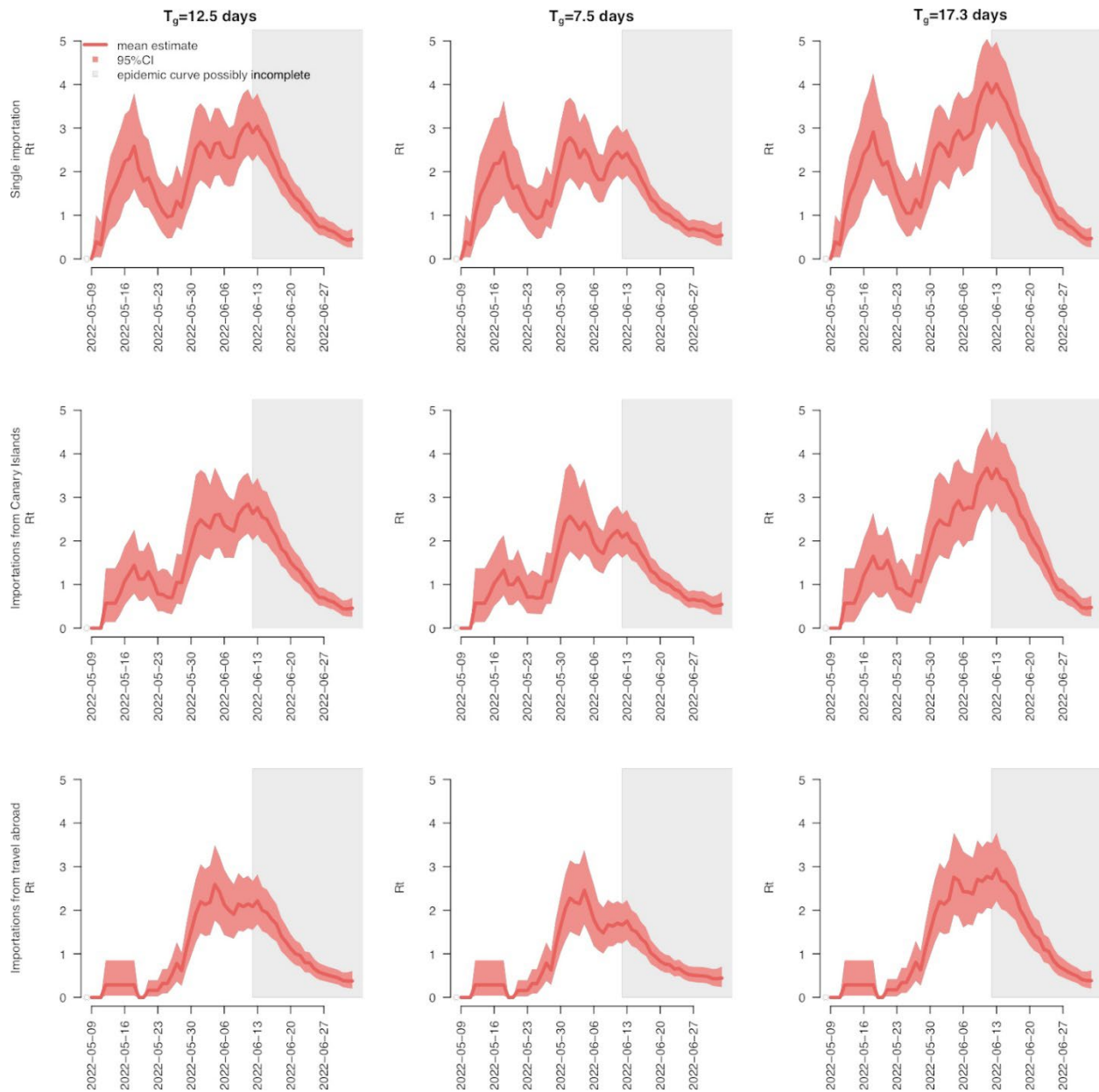
	Mean generation time		
	12.5 d (shape: 4.85, scale: 2.57)	7.5 d (shape: 6.86, scale: 1.10)	17.3 d (shape: 5.67, scale: 3.05)
Assumed imported cases			
Single importation	2.71 (1.67–3.66)	2.31 (1.42–3.15)	3.06 (1.88–4.13)
Importation from Canary Islands, baseline	2.50 (1.71–3.40)	2.14 (1.46–2.95)	2.82 (1.92–3.85)
Importation from travel abroad	2.40 (1.61–3.45)	1.96 (1.33–2.85)	2.75 (1.81–3.86)



Appendix Figure 1. Cumulative density function of the incubation period of monkeypox as estimated from 30 cases confirmed in Italy during May–June 2022 (mean, solid line; 95% CI, shaded areas). Bars represent the cumulative distribution of the incubation periods as obtained for these 30 confirmed cases, according to the maximum likelihood parameter set.



Appendix Figure 2. Cumulative density function of the generation time of monkeypox as estimated from 16 infector-infectee pairs identified during contact tracing operations conducted in Italy during May–June 2022 (mean, solid line; 95% CI, shaded areas).



Appendix Figure 3. Net reproduction number (mean and 95% CI) under the assumption that only the first case was imported (top row), that all cases with a history of travel to Canary Islands were imported (middle row), or that all cases with a history of travel abroad were imported (bottom row). Different distributions of the generation time were used: the first distribution (left column) has mean 12.5 days (corresponding to mean estimates reported in Appendix Table 4); the second distribution (center column) has mean 7.5 days (corresponding to the lower bound of the 95% CI provided in Appendix Table 4); the third distribution (right column) has mean 17.3 days (corresponding to the upper bound of the 95% CI provided in Appendix Table 4). The baseline results for the main text are those assuming importation from Canary Islands and a mean generation time of 12.5 days (middle row, left column).