Estimates of Serial Interval and Reproduction Number of Sudan Virus, Uganda, August–November 2022

Valentina Marziano, Giorgio Guzzetta, Ira Longini, Stefano Merler

We estimated the mean serial interval for Sudan virus in Uganda to be 11.7 days (95 CI% 8.2–15.8 days). Estimates for the 2022 outbreak indicate a mean basic reproduction number of 2.4–2.7 (95% CI 1.7–3.5). Estimated net reproduction numbers across districts suggest a marked spatial heterogeneity.

On September 20, 2022, Uganda's Ministry of Health declared an Ebola disease outbreak after a case caused by Sudan virus (SUDV) was confirmed in a village in Mubende District (*1*). Suspicious deaths in the same district had occurred earlier in the month. Investigations conducted by the National Rapid Response Team allowed the identification of probable SUDV cases dating back to mid-August 2022 (*2*,*3*). As of November 2, 2022, a total of 149 cases (131 PCR-confirmed and 18 probable) were reported in the country; most cases occurred in the districts of Mubende (63 confirmed, 17 probable), Kassanda (42 confirmed, 1 probable), and Kampala (18 confirmed) (*2*) (Figure 1, panels A–C). On January 11, 2023, the outbreak was declared over with a total of 164 cases (142 confirmed, 22 probable) (*4*).

The Study

We provide 2 estimates of the serial interval distribution (the time elapsed between the symptom onset in an index case-patient and in their secondary case-patients) by using observed serial intervals in infector–infectee pairs as identified during contact-tracing operations conducted in 2 SUDV outbreaks in Uganda, during 2000–2001 (24 pairs) (*5*) and the 2022 outbreak (12 pairs) (*6*). We fitted 3 families of distributions (Weibull, Gamma, and log-normal) with a possible offset (*5*,*6*). We obtained the best fit for the serial interval distribution for both datasets with a Weibull distribution. We estimated the mean serial interval to be 12.0 days (95% CI 10.0–14.2 days) by using the 2000–2001 outbreak data and 11.7 days (95% CI 8.2–15.8 days) by using the 2022 outbreak data.

We then used estimates of the serial interval as a proxy of the generation time to compute the basic (R_0) and net (R_t) reproduction numbers. We defined R_0 as the average number of secondary infections generated by an infectious person in a fully susceptible population. If R_0 <1, transmission is expected to fade out, whereas if R_0 >1, the epidemic has the potential to continue; the larger R_0, the more difficult it is to control the epidemic. We defined R_t as the average number of secondary cases per infectious person at time t; R_t is key to monitor the effectiveness of interventions throughout the epidemic. In the main analysis, we computed R_t and R_0 by using a method based on the renewal equation in the formulation by Cori et al. (*7*). In additional analyses, we used the assumption of exponential (*8*) or subexponential (*9*) growth of the cumulative case incidence curve to compute R_0. We also provided an alternative estimate of R_t obtained by applying a recently proposed approach (*10*) that has been suggested to perform better with low case counts (Appendix, https://wwwnc.cdc.gov/EID/article/29/7/22-1718-App1.pdf).

R_0 of the 2022 outbreak, as estimated from the epidemic curve of Mubende District, was 2.7 (95% CI 1.9–3.5) based on the serial interval distribution from the 2000–2001 outbreak. R_0 was 2.4 (95% CI 1.7–3.3) based on the serial interval distribution from the 2022 outbreak.

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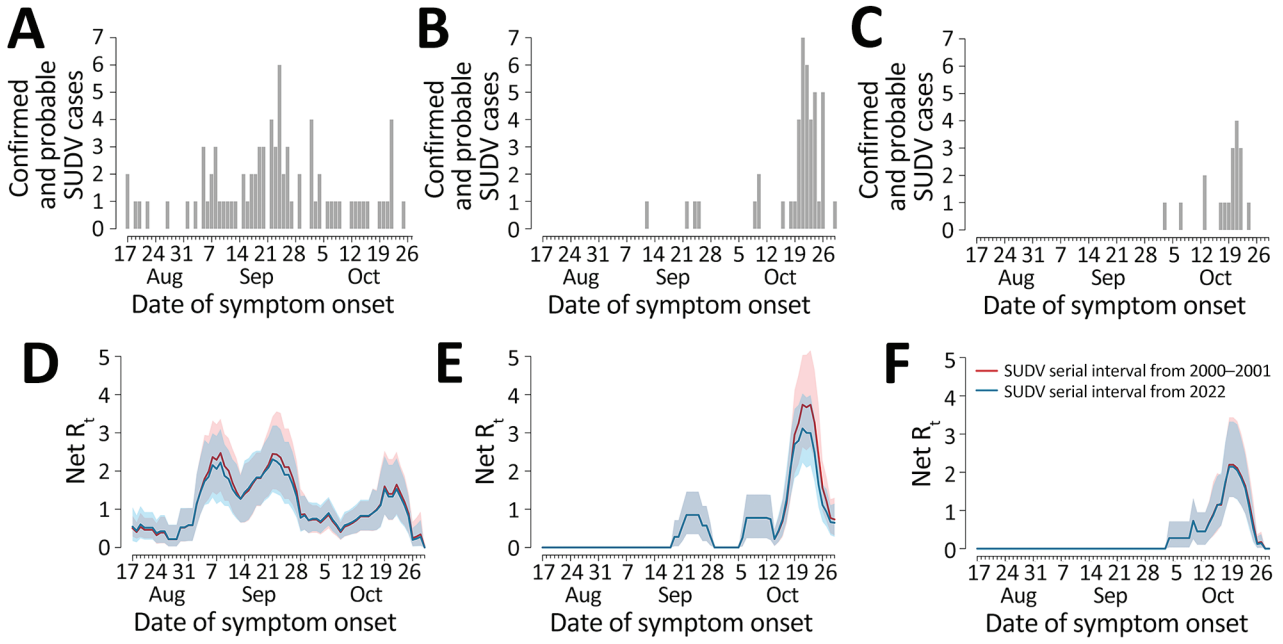

Figure 1. Epidemic curves and reproduction numbers for SUDV outbreaks in Mubende, Kassanda, and Kampala districts, Uganda, August–November 2022. A–C) Number of confirmed and probable cases by date of symptom onset in the 3 considered districts (comprising 95% of cases reported in the whole country, as of November 2, 2022) (*2*): Mubende (A), Kassanda (B), and Kampala (C). D–F). Estimates of the net reproduction number over time in the 3 districts: Mubende (D), Kassanda (E), and Kampala (F). Estimates from the corresponding epidemic curves by date of symptom onset were computed using the serial interval distributions from the 2000–2001 outbreak (*5*) (red) and the 2022 outbreak (*6*) (blue). Shaded areas represent 95% CIs of estimates. We assumed that the first case of the epidemic curve in each district was imported and that all the others were locally transmitted. SUDV, Sudan virus.

We estimated R_t in the 3 districts and according to the 2 estimated serial interval distributions (Figure 1, panels D–F). For convenience and given their similar values, numbers reported hereafter refer to the 2000–2001 serial interval; corresponding numbers for the 2022 serial interval are reported separately (Appendix). In Mubende District, R_t reached a peak during September 21–23, 2022, with an estimated value for R_t that was close to R_0 (mean 2.4 [95% CI 1.5–3.5]). R_t fell rapidly below the epidemic threshold during September 28–October 15 (mean 0.71 [95% CI 0.50–0.91]), possibly because of control interventions and population behavior changes after awareness of the outbreak had increased. In the second half of October, R_t increased again, reaching a peak of 1.34 (95% CI 0.78–2.13) in the week October 18–24. In the districts of Kassanda and Kampala, R_t increased rapidly in the second half of October. In Kassanda, R_t reached a peak of 3.5 (95% CI 2.5–4.9) during October 20–24. In Kampala, the peak R_t value was 2.0 (95% CI 1.3–3.2) during October 18–22.

Estimates of R_t at the national level (Figure 2) are characterized by 2 peaks in September, which were

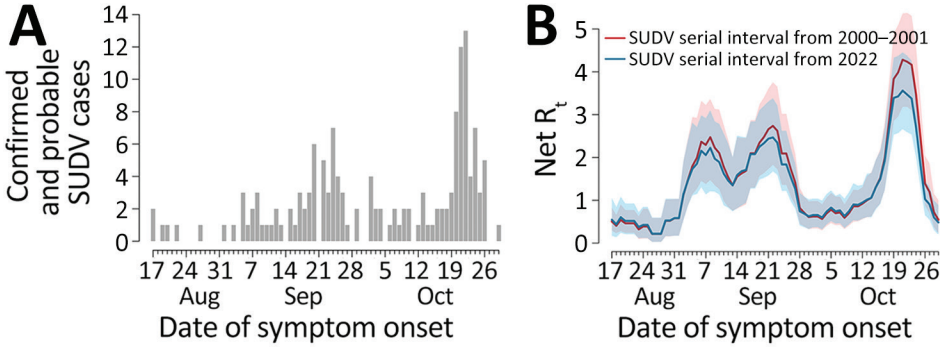

Figure 2. Epidemic curves and reproduction number for SUDV outbreaks, Uganda, August–November 2022. A) Number of confirmed and probable cases, by date of symptom onset, in Uganda as obtained from district-level epidemic curves reported previously (*2*). B) Net reproduction number over time in Uganda, as estimated from the epidemic curve, by date of symptom onset, using the serial interval distributions from the 2000–2001 outbreak (*5*) (red) and from the 2022 outbreak (*6*) (blue). Shaded areas represent 95% CIs of estimates. We assumed that the first case of the epidemic curve was imported and that all the others are locally transmitted. SUDV, Sudan virus.

driven by SUDV transmission in Mubende. A third marked peak that occurred in the second half of October was sustained mainly by increasing transmission in the districts of Kassanda and Kampala, as well as by a resurgence in Mubende.

Conclusions

We estimated the distribution of the serial intervals for SUDV by using 2 different datasets from the 2000–2001 outbreak and from the ongoing outbreak in Uganda, finding similar distributions and an average serial interval of ≈12 days. On the basis of those estimates and publicly available data on the epidemic curve made available by the Ugandan Ministry of Health (*2*), we found the R_0 in Mubende District, the district first and most affected by the current outbreak, was ≈2.4–2.7, although with broad uncertainty (95% CI 1.7–3.5). Those estimates are in line with previous estimates for SUDV, which ranged from 1.3 to 4.1 (*11*), and with estimates obtained using alternative methods (*8*,*9*) (Appendix). After a temporary containment of the outbreak from the end of September until mid-October 2022, with R_t hovering around 0.7, the third week of October marked a resurgence of transmissibility in Mubende (R_t ≈1.3) and the emergence of new outbreaks in the Kassanda (R_t ≈3.5) and Kampala (R_t ≈2.0) districts. The R_0 associated with the national aggregation shows the same temporal features but suggests even higher numbers for the R_0 in the fourth week of October (mean R_0 ≈4), demonstrating the important role played by spatial heterogeneity of transmission in the 2022 outbreak.

Our estimates should be interpreted with caution, considering the following limitations. Estimates of the serial interval distributions are based on small numbers of infector–infectee pairs. Reproduction numbers have a broad uncertainty because of limited case numbers and may be substantially affected by superspreading events, biasing estimate upward with respect to the average transmissibility in the general population. However, the proposed estimates are in line with those obtained using an alternative method that was suggested to be more robust for low case counts (*10*) (Appendix). Moreover, a potential increase in reporting rates of confirmed cases after the discovery of the first cases in each district may inflate the estimate of the reproduction numbers.

Given the geographic expansion of the outbreak, which included urban settings, and the absence of therapeutics and licensed vaccines to treat and prevent SUDV, by the end of October 2022, the World Health Organization assessed the risk for infection at the national level to be very high (*12*). However, the rapid deployment of interventions (including contact tracing, isolation of case-patients, and informational activities to promote community engagement) was sufficient to contain the outbreak, which was declared over on January 11, 2023. Our analysis provides quantitative information on the evolution of SUDV transmissibility in the different districts of Uganda during the 2022 outbreak. Estimates provided for the serial interval may be instrumental in planning control interventions in possible future outbreaks of SUDV.

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About the Author

Dr. Marziano is a researcher at the Bruno Kessler Foundation in Trento, Italy. Her primary research interests are mathematical models to investigate the epidemiology of infectious diseases, support public health decisions, and assess the effectiveness of interventions.

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Appendix

Serial interval

The serial interval is defined as the difference between the date of symptom onset of a case and those of his secondary cases. We estimated the serial interval distribution of Sudan Virus (SUDV) using two different datasets:

- previously published data on SUDV transmission chains from the 2000–2001 outbreak in Uganda (*1*);
- data reported by the Ministry of Health of Uganda on the transmission chains generated by one case in the 2022 SUDV outbreak in Uganda (*2*).

For each dataset, we considered observed serial intervals from infector–infectee pairs for which the symptom onset date was known (24 infector–infectee pairs from (*1*); 12 infector–infectee pairs from (*2*)) and we fitted three families of distributions to the data (Weibull, Gamma, log-normal) allowing for an offset to reproduce the observation that no serial interval was below 4 and 2 days respectively in the considered data (*1*,*2*).

For both datasets, the best fitting distribution according to maximum likelihood, Akaike Information Criterion and Bayesian information Criterion was the Weibull distribution (Appendix Table 1).

The resulting estimates of the parameters of the two Weibull distributions of the serial intervals are reported in Appendix Table 2. The best-fitting cumulative density functions estimated for the serial intervals are shown in Appendix Figure 1 along with the cumulative distribution of observed serial intervals from the two datasets.

For the computation of the net reproduction number R_t and the basic reproduction number R_0, we assume that the distribution of the generation time (i.e., the difference between the date of infection of a case and those of his secondary cases) can be approximated by the distribution of the serial interval.

Basic reproduction number R_0 and net reproduction number R_t

The basic reproduction number R_0 is defined as the average number of secondary infections generated by an infectious individual in a fully susceptible population. R_0 is a key epidemiologic parameter characterizing the transmission potential of an infectious pathogen in the early epidemic phase. If $R_0 < 1$, transmission is expected to fade out even in absence of control, whereas if $R_0 > 1$, the epidemic has the potential to continue; the larger R_0, the more difficult it is to control the epidemic.

During outbreaks, the transmissibility of an infectious pathogen may vary, e.g., because of population immunity, changes in social contacts of the population, or the implementation of control measures. Temporal variations in the transmission potential are monitored through the net reproduction number, R_t, defined as the average number of secondary cases per infectious individual at time t. Both parameters play an essential role in the planning and design of control measures, as well as in the monitoring of their effectiveness.

Different methods have been proposed in the literature to estimate the net reproduction number R_t from case incidence data (*3*–*5*). In this study, we estimate the distribution of the net reproduction number R_t at the national and district level by applying the statistical method of Cori et al. (*3*), based on the knowledge of the distribution of the generation time and on the time series of cases.

The posterior distribution of R_t for any time point t was estimated by applying the Metropolis-Hastings MCMC sampling to a likelihood function defined as follows:

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

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 daily number of new cases having symptom onset at time t;
- R_t is the net reproduction number at time t to be estimated;
- $\varphi(s)$ is the integral of the probability density function of the generation time evaluated between day s-1 and s; we considered the distribution of the serial interval estimated above as an approximation of the distribution of the generation time.

We considered only the case with earliest symptom onset as imported case.

For comparison, we also computed estimates of R_t using the method proposed by Parag (*5*).

To estimate the basic reproduction number, in the main analysis, we use the method for R_t proposed by Cori et al. based on the renewal equation, forcing the value of R_t to be constant and equal to the value of R_0 between September 20 and 24. The time window is chosen in such a way that the impact of population behavior change, control interventions and accumulation of immunity can be considered negligible and that a sufficient number of cases have had symptom onset. The first case in the outbreak was confirmed on September 20, 2022.

We also consider alternative methods to estimate the basic reproduction number R_0. If the cumulative case incidence in the early phase of the epidemic is assumed to grow exponentially, R_0 can be estimated by fitting the exponential growth rate r (*6*,*7*). If the growth of cumulative cases is sub-exponential, a generalized-growth model may be more appropriate where the growth rate r is estimated in combination with an additional parameter p representing the deceleration of growth (*8*,*9*).

We provide estimates of R_0 for the Mubende district from both approaches estimating their parameters through nonlinear least-square fitting to the cumulative case incidence in the first 36 days (about three generations of cases), from August 18 to September 22, 2022.

Additional results

Alternative estimates of the basic reproduction number

The fit of the cumulative case incidence using the exponential growth model and the generalized-growth model is reported in Appendix Figure 2. Using the exponential growth model (*6*,*7*), we estimated an exponential growth rate $r = 0.082$ (95% CI: 0.080- 0.084) and a corresponding basic reproduction number $R_0 = 2.68$ (95% CI: 2.62–2.74). Using the generalized-growth model (*8*,*9*), we estimated a growth rate $r = 0.11$ (95% CI: 0.05–0.19) and a growth deceleration parameter $p = 0.84$ (95% CI: 0.64–1.15), resulting in a reproduction number $R_g = 1.99$ (95% CI: 1.40–2.90). Both results are in line with those of the main analysis (mean 2.4–2.7, range of 95% CIs: 1.7–3.5).

Estimates of R_t considering the 2022 serial interval

We report hereafter estimates of the net reproduction numbers over time as obtained by assuming the 2022 serial interval (*2*) (blue lines in Figure 1 and 2 of the main text).

In Mubende district, the net reproduction number R_t reached a peak between September 21 and September 23, 2022, with an estimated value for R_t that was close to R_0 (mean September 21–23: 2.2; 95% CI: 1.4–3.1). The reproduction number fell rapidly below the epidemic threshold between September 28 and October 15 (mean September 28 - October 15: 0.72, 95% CI: 0.54–0.93), possibly due to implemented control interventions and population behavior change following increased awareness of the outbreak. In the second half of October the net reproduction number increased again reaching a peak of 1.32 (95% CI: 0.75–2.03) in the week October 18–24. In the district of Kassanda and Kampala, the net reproduction number increased rapidly in the second half of October. In Kassanda, it reached a peak of 2.9 (95% CI: 2.1–3.8) between October 20 and October 24. In Kampala, the peak value was 2.0 (95% CI: 1.3–3.1) between October 18 and 22.

Estimates of R_t and R_0 are obtained using the serial interval as a proxy of the generation time. Given the relationship of direct proportionality existing between the reproduction number and the generation time (*6*,*7*), estimates of the reproduction numbers obtained using the 2000–2001 serial interval (mean: 12 days) are slightly higher than those obtained using the 2022 serial interval (mean: 11.7 days).

Estimates of R_t obtained using the *Epifilter* method

Finally, we estimated R_t for the district of Mubende using the method proposed in (*5*) (R implementation of *EpiFilter* available at https://github.com/kpzoo/ EpiFilter). We applied *Epifilter* assuming a uniform prior distribution for R_t over a grid of size m = 1000, defined between $R_{min} = 0.01$ and $R_{max} = 10$, and a state noise parameter $\eta = 0.1$. Except for the first 10 days, when the cumulative number of observed cases was still very low (6), the 95% CI of our estimates always intersect with the 95% CI of estimates obtained through this alternative method (Appendix Figure 3).

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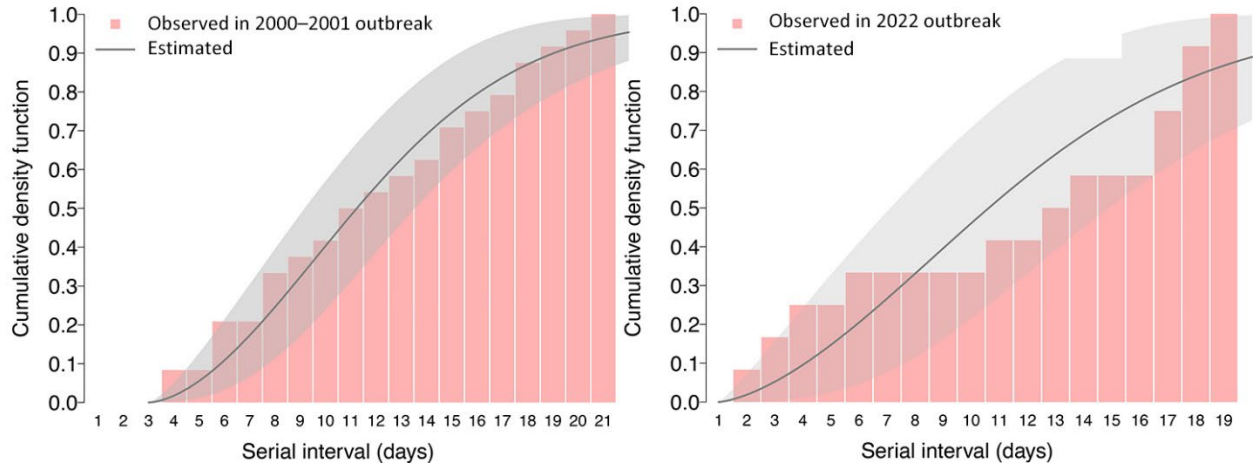
Appendix Table 1. Fit of the SUDV serial interval. Log-likelihood, Akaike Information Criterion (AIC) score and Bayesian information criterion (BIC) score as obtained from the fit of the three families of distributions to the two different datasets (*1*,*2*). The best-fitting value of the three scores is highlighted in bold.

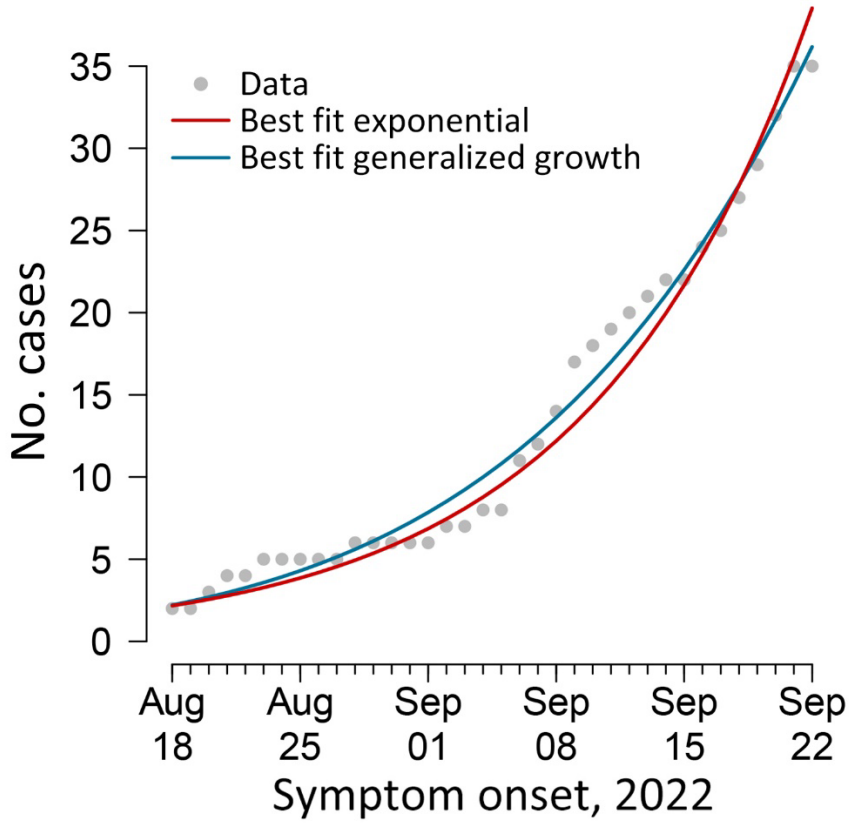
	2000–2001 SUDV outbreak (*1*) (n = 24)			2022 SUDV outbreak (*2*) (n = 12)		
Distribution	Log-likelihood	AIC	BIC	Log-likelihood	AIC	BIC
Gamma	−73.3	150.7	153.1	−39.6	83.3	84.2
Weibull	−72.4	148.9	151.2	−39.0	82.1	83.1
Log-normal	−75.8	155.6	158	−41.2	86.3	87.3

Appendix Table 2. Parameters of the Weibull distribution of the serial interval as estimated from the different datasets.

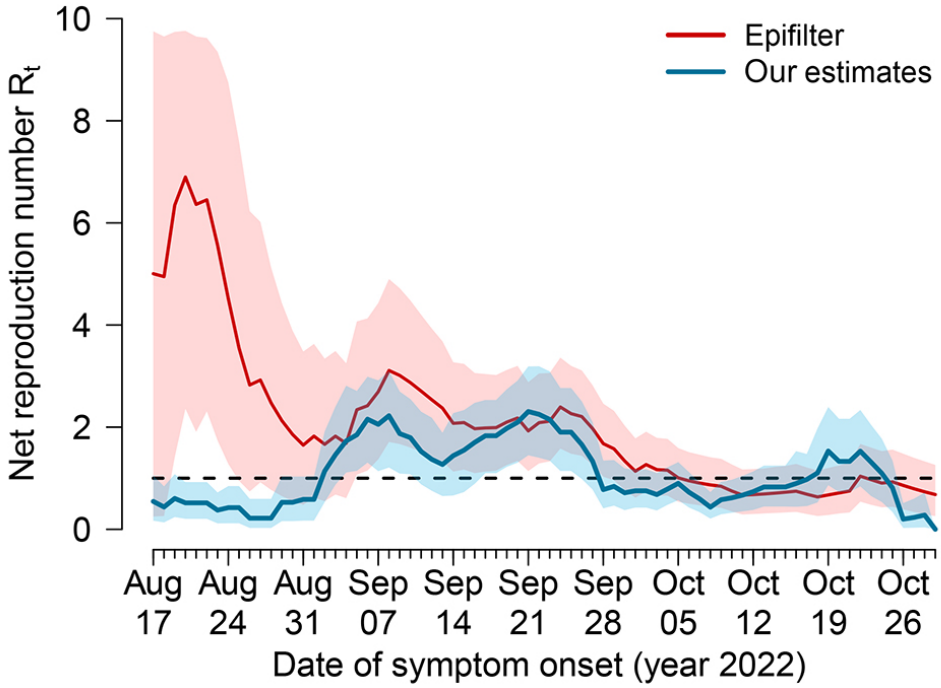
Dataset	2000–2001 SUDV outbreak (*1*) (n = 24)	2022 SUDV outbreak (*2*) (n = 12)
Offset (days)	3	1
Shape (mean)	1.76 (1.35–2.60)	1.63 (1.15–3.04)
Scale (95% CI)	10.14 (7.77–12.58)	11.97 (7.9–16.56)
Mean (95% CI) (days)	12 (10–14.2)	11.7 (8.2–15.8)



Appendix Figure 1. A) Cumulative density function of the serial interval of SUDV as estimated from 24 infector–infectee couples with known symptom onset in the 2000–2001 outbreak in Uganda (*1*) (mean, solid line; 95% CI, shaded areas). Bars represent the cumulative distribution of the serial interval observed for the considered couples. B) As A but as estimated from 12 infector–infectee couples with known symptom onset in the 2022 SUDV outbreak in Uganda (*2*).



Appendix Figure 2. Cumulative case incidence in the first 36 days (about three generations of cases), from August 18 to September 22, 2022, in the district of Mubende: data (gray) (*10*); fit obtained with the exponential growth model (*6*,*7*) (red); fit obtained with the generalized-growth model (*8*,*9*) (blue).



Appendix Figure 3. Net reproduction number over time (R_t) in the district of Mubende, as estimated from the epidemic curve by date of symptom onset and using the serial interval distributions from 2022 outbreak (*2*): method based on Cori et al. (*3*) (blue); *Epifilter* method (*5*) (red). Shaded areas represent 95% CI of estimates.