

1 Epidemic dynamics shape inferences of the differences in  
2 incubation-period and generation-interval distributions of the  
3 Delta and Omicron variants  
4

## 5 **Abstract**

6 Estimating the differences in the incubation-period and serial-interval distributions  
7 of SARS-CoV-2 variants is critical to understanding changes in their transmission  
8 dynamics and therefore controlling their outbreaks. However, these comparisons  
9 are inherently difficult due to their dependence on epidemic growth rates—for  
10 example, when an epidemic is growing exponentially, we are more likely to observe  
11 individuals who have been infected recently, decreasing the mean observed  
12 incubation period and thereby increasing the mean observed serial interval. Here,  
13 we analyze serial-interval data describing transmissions of the Delta and Omicron  
14 variants from Netherlands at the end of December 2021, during which the number  
15 of infections caused by the Delta variant decreased as the number of Omicron  
16 infections increased. Accounting for growth-rate differences of two variants, we  
17 estimate similar mean incubation periods (3.8–4.5 days) for both variants but a  
18 shorter mean generation interval for the Omicron variant (3.3 days; 95% CI: 2.8–3.7  
19 days) than for the Delta variant (4.2 days; 95% CI: 4.0–4.4 days). These differences  
20 may reflect higher reproduction numbers of the Omicron variant, which can drive  
21 faster susceptible depletion among close contacts. Neglecting differences in the  
22 generation-interval distributions can further bias in estimates of transmission  
23 advantages of the Omicron variant.

# 1 Introduction

Estimating transmission advantages of new SARS-CoV-2 variants is critical to predicting and controlling the course of the ongoing COVID-19 pandemic. Transmission advantages of invading variants are typically characterized by the ratios of reproduction numbers,  $\mathcal{R}_{\text{inv}}/\mathcal{R}_{\text{res}}$ , and the differences in growth rates,  $r_{\text{inv}} - r_{\text{res}}$ . These two quantities are linked by the generation-interval distributions of the resident and invading variants. For example, an invading variant with shorter generation intervals—defined as the time between infection of the infector and the infectee—will exhibit faster epidemic growth ( $r_{\text{inv}} > r_{\text{res}} > 0$ ) even if their reproduction numbers are identical ( $\mathcal{R}_{\text{inv}} = \mathcal{R}_{\text{res}} > 1$ ).

Estimating generation-interval is hard, largely due to difficulties in observing actual infection events. Many researchers primarily focus on comparisons of other transmission intervals, such as time between symptom onsets (also referred to as serial intervals) or between testing events [1] of the infector and the infectee. However, transmission-interval distributions are subject to dynamical effects which can bias estimation. For example, when the epidemic is growing, a cohort of infectors who developed symptoms at the same time are more likely to have been infected recently, shortening their incubation periods—in other words, their incubation periods will be shorter, on average, than those of their infectees, causing the mean serial interval to be longer than the mean generation interval [2]. Therefore, observed differences in transmission-interval distributions between variants can give a biased picture of true differences in their generation-interval distributions, especially if their growth rates differ.

Here, we re-analyze serial-interval data collected by [3], representing within- and between-household transmissions of the Delta and Omicron variants from the Netherlands between 13 and 26 December 2021. The authors of the original article reported shorter serial intervals (3.5 vs 4.1 days) and incubation periods (3.2 vs 4.4 days) for transmission pairs with S-gene target failure (mostly omicron during the study period) and without (mostly delta), but did not consider growth-rate differences in their inference. Here, we discuss the epidemiological context in the Netherlands during the study period and take dynamics into account to provide corrected estimates for the incubation periods and generation-interval distributions of the Delta and Omicron variants.

## 2 Methods

### 2.1 Data

We analyze time series of reported COVID-19 cases (<https://data.rivm.nl/covid-19/>) and proportions of SARS-CoV-2 variants detected (<https://www.rivm.nl/coronavirus-covid-19/virus/varianten>) from the Netherlands between 29 November 2021 and 30 January 2022. Both data are publicly available on the National Institute for Public Health

63 and the Environment (RIVM) website.

64 Serial interval data are taken from the supplementary material of [3]. The data are  
65 aggregated by the length of the serial interval in days and do not include additional  
66 individual-level information, such as exposure dates or symptom onset dates. The  
67 data consists of 2529 transmission pairs and are further stratified by the presence of  
68 S gene target failure, week of infectors' symptom onset date (week 50 and 51), and  
69 the type of transmission (within or between households). For simplicity, we refer  
70 to transmission pairs with and without S gene target failure as Omicron and Delta  
71 transmission pairs, respectively. See original article for details of data collection.

## 72 **2.2 Estimating epidemic growth rates**

73 To estimate the differences in growth rates of the Delta and Omicron variants, we  
74 first estimate the number of COVID-19 cases caused by each variant by multiplying  
75 reported weekly numbers of cases by the proportion of Delta and Omicron variants  
76 detected—we use weekly time series to smooth over patterns of testing and reporting  
77 within each week. We then fit a generalized additive model [4] to the logged weekly  
78 case estimates to obtain smooth trajectories for case time series. Finally, we take the  
79 derivative of the predicted logged numbers of cases caused by each variant to obtain  
80 time-varying growth rate estimates.

81 To obtain confidence intervals on the estimated time-varying growth rates, we  
82 generate 1000 parameter sets by resampling spline coefficients from a multivariate  
83 normal distribution using the estimated variance-covariance matrices. We calculate  
84 time-varying growth rates from each parameter set and use equi-tailed quantiles to  
85 generate 95% confidence limits.

## 86 **2.3 Estimating forward incubation-period distributions from 87 backward incubation-period distributions**

88 [3] estimated the incubation periods from 513 individuals (258 Omicron and 255 Delta  
89 cases), with symptom onsets between 1 December 2021 and 2 January 2022. They  
90 used the methods of [5], which estimates incubation period by inferring distributions  
91 of time of infection for each individual from their known exposure dates, using a  
92 uniform distribution, and compares this to a known symptom-onset time.

93 In practice, incubation periods (and other epidemiological delays) can be mea-  
94 sured in two ways. The forward incubation periods are measured from a cohort of  
95 individuals who were infected at the same time. We expect this forward incubation-  
96 period distribution  $f_I(\tau)$  to remain constant over the course of an epidemic and  
97 provide reliable estimates of the distribution across individuals. Backward incuba-  
98 tion periods are measured from a cohort of individuals who developed symptoms at  
99 the same time. We expect the backward incubation-period distribution to be sensi-  
100 tive to epidemic dynamics. The difference arises because forward incubation periods  
101 look forward from the reference point towards symptom development, which is an

individual-level process, while backward incubation periods look backwards towards an infection event, which requires an interaction with an infectious individual.

In particular, when incidence of infection is growing exponentially, we are more likely to observe shorter backward incubation periods because there will be relatively more individuals who were infected recently. Specifically, the backward incubation-period distribution  $b_I(\tau)$  corresponds to:

$$b_I(\tau) = \frac{\exp(-r\tau)f_I(\tau)}{\int_0^\infty \exp(-rx)f_I(x) dx}, \quad (1)$$

where  $r$  represents the epidemic growth rate. The method of [5] starts from observed symptom onsets, and estimates the backward incubation-period distribution without taking growth rates into account.

We adjust for observed growth rate of each variant by taking the backward incubation-period distributions estimated by [3] and calculating the corresponding forward incubation-period distributions by inverting Eq. (1):

$$f_I(\tau) = \frac{\exp(r\tau)b_I(\tau)}{\int_0^\infty \exp(rx)b_I(x) dx}. \quad (2)$$

We model the backward incubation-period distribution  $b_I(\tau)$  using a Weibull distribution based on the assumptions of [3]. To account for uncertainties in the original parameter estimates, we rely on a sampling scheme, similar to the one we used for the growth rate analysis (in Section 2.2). First, we approximate the previously inferred posterior distributions of the shape and scale parameters of the Weibull distribution using a lognormal distribution—we parameterize the lognormal distribution such that (i) its median matches the median of the posterior distributions and (ii) the probability that a random variable following the specified Gamma distribution falls between the lower and upper credible limits matches 95% [6]. We draw 1000 samples of the shape and scale parameters (for the backward distribution  $b_I(\tau)$ ) from the specified lognormal distributions and estimate the corresponding forward distribution using Eq. (2). We take 95% equi-tailed quantiles to obtain 95% confidence intervals.

## 2.4 Estimating forward generation-interval distributions from forward serial-interval distributions

Dynamical biases in the serial-interval distributions are more complex because the serial interval depends on the incubation periods of the infector and the infectee as well as the generation interval between them. For example, [3] measured the forward serial-interval distributions from cohorts of infectors who developed symptoms during the same week. In this case, the forward serial interval  $\tau_s$  can be expressed in the form [2]:

$$\tau_s = -\tau_{i,1} + \tau_{g,\text{symp}} + \tau_{i,2}, \quad (3)$$

135 where  $\tau_{i,1}$  represents the backward incubation period of the infector (because all  
 136 infectors developed symptoms at the same time), and  $\tau_{i,2}$ , represents the forward  
 137 incubation period of the infectee. Here,  $\tau_{g,\text{symp}}$  represents the generation interval  
 138 between the infector and the infectee; we use the subscript symp to indicate that  
 139 these generation intervals are measured from infectors who developed symptoms at  
 140 the same time.

The symptom-based generation-interval distribution describing Eq. (3) gives a bi-  
 ased picture because infectors who developed symptoms at the same time will have  
 shorter incubation periods (when epidemic is growing) and therefore transmit ear-  
 lier. This symptom-based generation-interval distribution depends on the backward  
 incubation-period distribution:

$$f_{G,\text{symp}}(\tau) = \int_0^\infty f_{G|I}(\tau|x)b_I(x) dx, \quad (4)$$

where  $f_{G|I}(\tau|x)$  represents the forward generation-interval distribution conditional on  
 a known value of the incubation period,  $x$ . Instead, the forward generation-interval  
 distribution measured from a cohort of individuals who were infected at the time is  
 expected to provide reliable estimates of the distribution across individuals (because  
 their incubation-period distribution is expected to remain constant over time):

$$f_{G,\text{inf}}(\tau) = \int_0^\infty f_{G|I}(\tau|x)f_I(x) dx. \quad (5)$$

141 When epidemic is growing is exponentially, we have two opposing effects affecting  
 142 the relationship between the mean serial and generation interval. First, infectors in  
 143 a given cohort are more likely to have shorter incubation periods than their infectees  
 144 on average,  $\mathbb{E}[\tau_{i,1}] < \mathbb{E}[\tau_{i,2}]$ , causing the mean forward serial interval to be longer  
 145 than the mean symptom-based generation interval ( $\mathbb{E}[\tau_s] > \mathbb{E}[\tau_{g,\text{symp}}]$ ). Second, the  
 146 mean symptom-based generation interval will be shorter than the mean infection-  
 147 based generation interval:  $\mathbb{E}[\tau_{g,\text{inf}}] > \mathbb{E}[\tau_{g,\text{symp}}]$ . Therefore, the difference between the  
 148 mean serial interval and the mean infection-based generation interval is difficult to  
 149 predict in general; in most cases, however, we expect the former effect to dominate,  
 150 causing the mean serial interval to be longer than the mean infection-based generation  
 151 interval:  $\mathbb{E}[\tau_s] > \mathbb{E}[\tau_{g,\text{inf}}]$  [2]. For simplicity, we will use the term “forward generation-  
 152 interval” to refer to the infection-based generation-interval distribution (measured  
 153 from a cohort of infectors who were infected at the same infection time), and drop  
 154 the subscript inf.

155 We model the forward incubation-period  $f_I(\tau)$  and generation-interval  $f_G(\tau)$  dis-  
 156 tributions using a bivariate lognormal distribution. The joint distribution is param-  
 157 eterized by log means,  $\mu_I$  and  $\mu_G$ , log variances,  $\sigma_I^2$  and  $\sigma_G^2$ , and the correlation  
 158 coefficient  $\rho$ . Thus, the forward generation-interval distribution conditional on the  
 159 incubation period  $f_{G|I}(\tau|\tau_{i,1})$  has a mean of  $\mu_G + \sigma_G\rho(\log(\tau_{i,1}) - \mu_I)/\sigma_I$  and a log  
 160 variance of  $\sigma_G^2(1 - \rho^2)$ . *[JD: There is some scale mixing going on here and I can't  
 161 figure it all out. Did you mean to write “log mean” just above? That might fix most*

162 *of it, but then you would need to also say that  $\rho$  is the log-scale correlation, or some-*  
 163 *thing like that.]* Assuming that the incidence of infection is changing exponentially  
 164 at rate  $r$ , the forward serial-interval distribution  $f_S(\tau)$  for a cohort of infectors who  
 165 developed symptoms at time  $t = 0$  can be calculated by integrating across infection  
 166 time of the infector  $\alpha_1 < 0$  and of the infectee  $\alpha_2 > \alpha_1$  [2]:

$$f_S(\tau) = \frac{1}{\phi} \int_{-\infty}^0 \int_{\alpha_1}^{\tau} \exp(r\alpha_1) f_{G|I}(\alpha_2 - \alpha_1 | -\alpha_1) f_I(-\alpha_1) f_I(\tau - \alpha_2) d\alpha_2 d\alpha_1, \quad (6)$$

167 where  $\phi$  is a normalization constant chosen so that  $\int f_S(x) dx = 1$ ;  $-\alpha_1$  corresponds  
 168 to the incubation period of the infector;  $\alpha_2 - \alpha_1$  corresponds to the generation interval;  
 169 and  $\tau - \alpha_2$  corresponds to the incubation period of the infectee.

170 For a given value of  $r$ , we first estimate the forward incubation-period distri-  
 171 bution from the backward distribution, previously estimated by [3], using Eq. (2).  
 172 We then approximate the forward incubation-period distribution with a lognormal  
 173 distribution by matching the mean and standard deviation. Using this incubation-  
 174 period distribution, we fit Eq. (6) to the observed serial-interval data by minimizing  
 175 the negative log-likelihood. We then calculate the mean forward generation interval  
 176 using Eq. (??) and approximate the 95% confidence interval using the Delta method.  
 177 *[JD: Fixed one eref, but failed to fix the other.]* We assume  $\rho = 0.75$  throughout  
 178 based on [7]—since we do not have individual-level data on infection and symptom  
 179 onset times, we expect this parameter to be unidentifiable in practice. *[JD: Consider*  
 180 *more discussion and/or sensitivity explorations.]*

## 181 2.5 Estimating instantaneous reproduction number

182 We use our estimates of the generation-interval distributions to infer instantaneous  
 183 reproduction numbers  $\mathcal{R}(t)$  of the Delta and Omicron variant, as well as the ra-  
 184 tio between two reproduction numbers. Estimating the instantaneous reproduction  
 185 number—defined as the average number of secondary infections that a primary case  
 186 will generate if epidemiological conditions remain constant [8]—requires the intrinsic  
 187 generation-interval distribution  $g(\tau)$ : *[JD: We should think about this, too – is it*  
 188 *really just the forward if it's  $\mathcal{R}(t)$ ?)*

$$\mathcal{R}(t) = \frac{i(t)}{\int_0^{\infty} i(t-x)g(x) dx}, \quad (7)$$

189 where  $i(t)$  represents incidence of infection. Here, we approximate the intrinsic  
 190 generation-interval distribution with the forward generation-interval that we esti-  
 191 mate for week 50—when epidemic is growing or decaying exponentially, we expect the  
 192 forward generation-interval to be a good proxy for the intrinsic generation-interval  
 193 distribution [9, 10]. *[JD: Another point that may need a bit more discussion:]* Inci-  
 194 dence of infection is approximated by shifting the smoothed case trajectories by one  
 195 week to account for reporting delays. Confidence intervals are calculated by sam-  
 196 pling parameters of the smoothed case trajectories as well as the generation-interval

distributions from multivariate normal distributions and repeating the analysis 1000 times.

### 3 Results

Fig. 1 summarizes the epidemiological context in the Netherlands during the study period. The first known Omicron case in the Netherlands was sampled on 19 November 2021 [3], during a period when COVID-19 incidence was decreasing (Fig. 1A). As the Omicron variant continued to spread and increase in proportion (Fig. 1B), the number of COVID-19 cases started to increase (Fig. 1A). Multiplying the proportion of each variant with the number of reported COVID-19 cases further allows us to estimate the epidemiological dynamics of each (Fig. 1C). *[JD: Can we simplify following s. by eliminating CIs? Maybe add  $\approx$  to indicate that these are just estimates.]* The number of COVID-19 cases caused by the Delta variant continued to decrease throughout the study period with time-varying growth rates decreasing from  $r = -0.01/\text{day}$  (95% CI:  $-0.04/\text{day}$ – $-0.02/\text{day}$ ) to  $r = -0.09/\text{day}$  (95% CI:  $-0.11/\text{day}$ – $-0.07/\text{day}$ ) by the week of January 16, 2022, and increasing back up to  $r = -0.04/\text{day}$  (95% CI:  $-0.07/\text{day}$ – $-0.01/\text{day}$ ). The number of COVID-19 cases caused by the Omicron variant increased rapidly but decelerated over time with time-varying growth rates decreasing from  $r = 0.18/\text{day}$  (95% CI:  $0.15/\text{day}$ – $0.21/\text{day}$ ) on the week of December 19, 2021, to  $r = 0.04/\text{day}$  (95% CI:  $0.00/\text{day}$ – $0.09/\text{day}$ ). Finally, we find that the growth-rate difference between the Delta and Omicron variants decreased over time—*[JD: The following comes across too strong; the roles work doesn't explain all of the decrease. Something like: this effect is partly due to changes in the overall growth rate and partly due to changes in differential immunity... I'm kind of thinking simplify or omit and come back in Discussion, now.]* this finding echoes our previous work, which showed that growth-rate differences change over the course of an epidemic even when the ratio of the reproduction numbers remain constant [11].

For a cohort of individuals who developed symptoms between 1 December 2021 and 2 January 2022, [3] found longer mean (backward) incubation period for the Delta variant than for the Omicron variant (Fig. 2A). However, these measurements were done during a period when the incidence of Omicron was increasing while the increasing of Delta was decreasing (Fig. 1). Thus, dynamical bias would be expected to lead to shorter observed (backward) incubation periods in Omicron, and longer observed incubation periods in Delta. When we account for these growth-rate differences and re-estimate the forward incubation periods, we find that both variants have similar incubation-period distributions (Fig. 2B)—for illustrative purposes, we assume  $r = -0.05/\text{day}$  and  $r = 0.15/\text{day}$  for the Delta and Omicron variants, respectively. Although the exact estimate of the mean forward incubation periods of both variants are sensitive to the assumed growth/decay rates, we find similar means across a plausible ranges of growth rates with unclear differences between two vari-

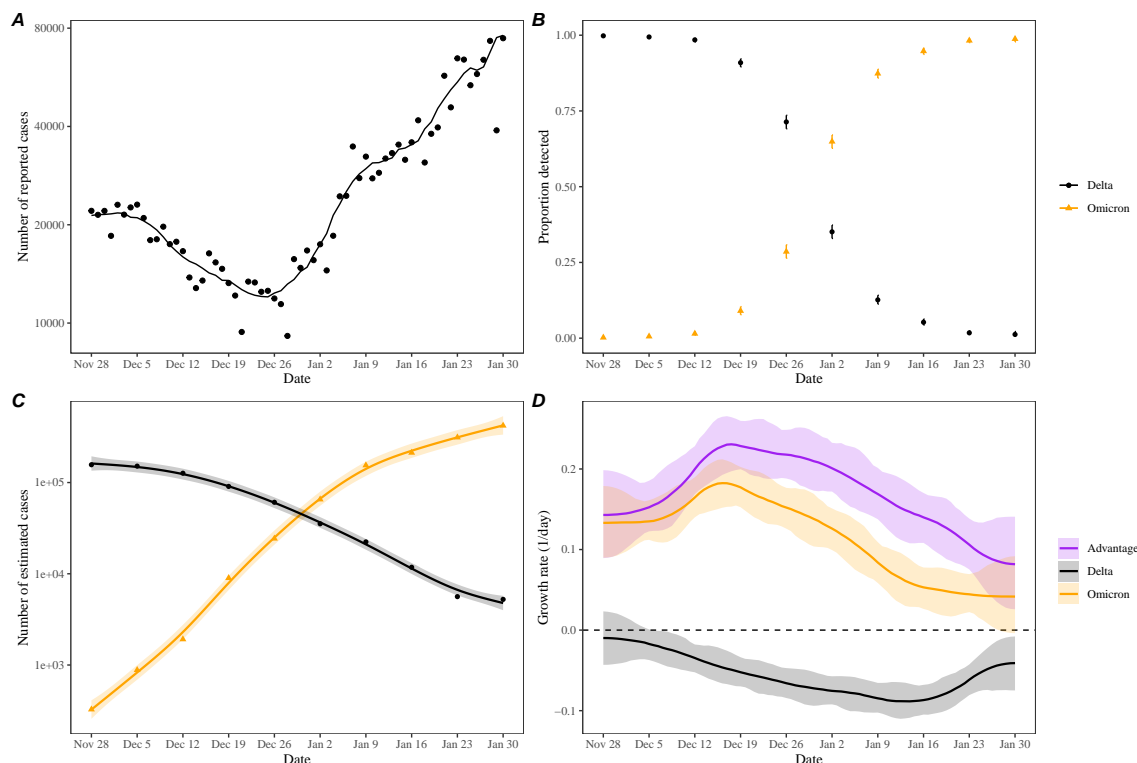
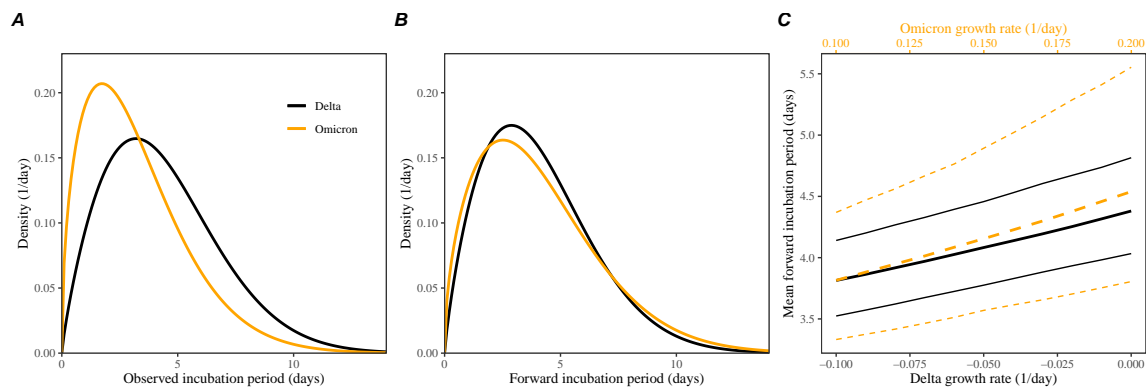


Figure 1: **Epidemic dynamics on the Delta and Omicron variants in the Netherlands.** (A) Daily numbers of reported COVID-19 cases in the Netherlands (points). The solid line represents the 7-day moving average. Data are publicly available on <https://data.rivm.nl/covid-19/>. (B) Proportion of SARS-CoV-2 variants detected from the Netherlands. Data are publicly available on <https://www.rivm.nl/coronavirus-covid-19/virus/varianten>. (C) Weekly numbers of COVID-19 cases caused by the Delta (black points) and Omicron (orange triangles) variants are estimated by multiplying the weekly numbers of cases (A) with the proportion of each variant (B). Solid lines and shaded areas represent fitted lines and corresponding 95% confidence intervals using generalized additive model. (D) Estimated growth rates of the Delta (black) and Omicron variants (orange) and their growth-rate differences (purple). Lines and shaded areas represent medians and corresponding 95% confidence intervals. Growth rates are estimated by taking the derivative of the generalized additive model estimates.

ants (Fig. 2C). *[JD: Do we need the ff. s.? What does it add to the Fig?]* For example, the mean forward incubation period of the Delta variant changes from 3.8 days (95% CI: 3.5–4.1 days) to 4.4 days (95% CI: 4.0–4.8 days) as we change the assumed values of  $r$  from  $-0.1/\text{days}$  to  $0/\text{days}$ , while the mean forward incubation period of the Omicron variant changes from 3.8 days (95% CI: 3.4–4.4 days) to 4.5 days (95% CI: 3.9–5.5 days) as we change the assumed values of  $r$  from  $0.1/\text{days}$  to  $0.2/\text{days}$ .



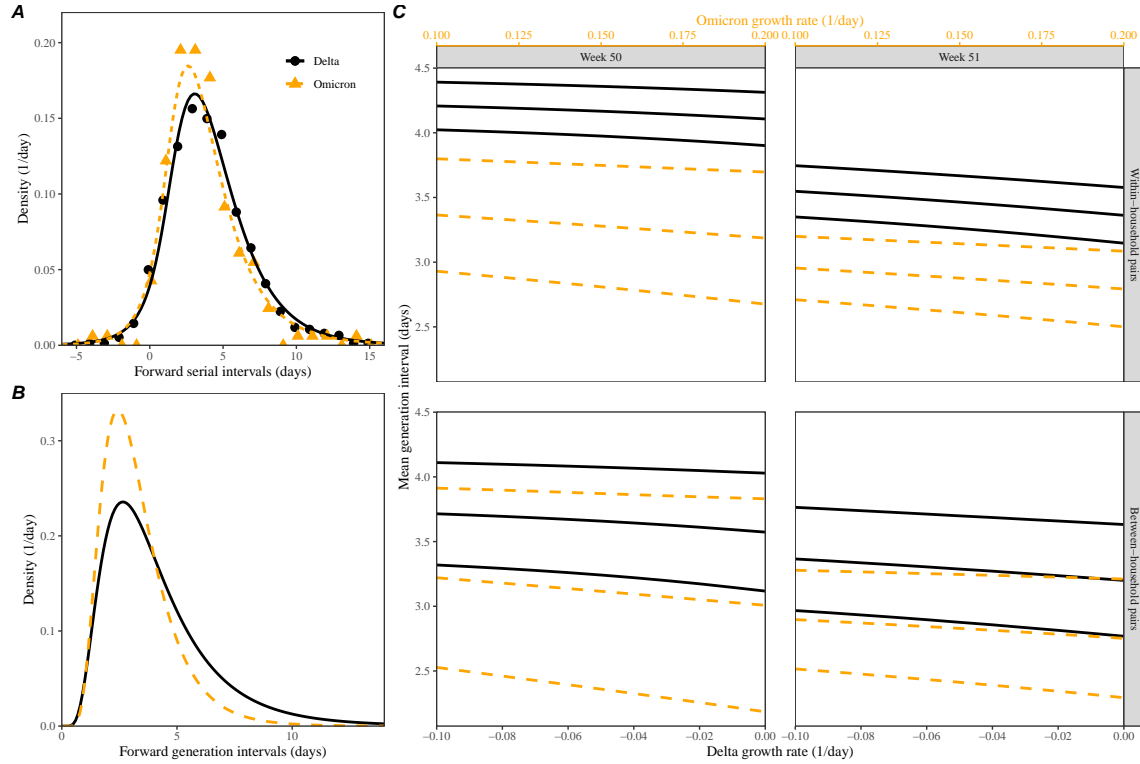


**Figure 2: Observed and corrected differences in incubation-period distributions of Delta and Omicron variants.** (A) Posterior median estimates of the observed (backward) incubation periods of the Delta (black) and Omicron (orange) variants by [3]. (B) Forward incubation-period distributions assuming  $r = -0.05/\text{day}$  and  $r = 0.15/\text{day}$  for the Delta (black) and Omicron (orange) variants, respectively. (C) Corrected estimates of the forward incubation-period distributions for different assumptions about the growth rates of the Delta (black, solid lines) and Omicron variants (orange, dashed lines). Middle lines represent median estimates, and lower and upper lines represent corresponding 95% confidence intervals.

Our corrected estimates of the forward incubation-period distributions further allow us to infer the forward generation-interval distributions. For illustrative purposes, we first focus on within-household serial intervals from infectors who developed symptoms during week 50 (13–19 December, 2021). [3] reported shorter mean serial interval of the Omicron variant (3.5 days) than that of the Delta variant (4.1 days) for this cohort, [JD: *I'm not clear what the last part of this s. means.*] but the overall shapes of the distributions are similar (Fig. 3A). However, when we account for growth-rate differences (assuming  $r = -0.05/\text{day}$  and  $r = 0.15/\text{day}$  for the Delta and Omicron variants, respectively), the estimated mean forward generation interval exhibits a larger difference (Fig. 3B): 3.3 days (95% CI: 2.8–3.7 days) for the Omicron variant and 4.2 days (95% CI: 4.0–4.4 days). Notably, both variants have similar mode, but the transmissibility of the omicron variant is estimated to decay much faster (Fig. 3B). Note that the mean forward generation interval of the Omicron (resp., Delta) variant is shorter (longer) than its mean serial interval due to the effect of a growing (declining) epidemic. [JD: *What is the relevance of the ff. s.? Do we want it?*] Instead, if we neglect growth-rate differences and assume  $r = 0/\text{day}$  for both variants, the estimated shape of the generation-interval distributions become more similar and the differences in their means become smaller (Supplementary Figure S1): 3.5 days (95% CI: 3.1–3.9 days) for the Omicron variant and 4.1 days (95% CI: 3.9–4.3 days).

[JD: *What is up with stratification here? I'm starting to get lost. Is panel C showing CIs again? If so can you say so again, and also use the same style as*

the previous figure?] We estimate shorter mean forward generation intervals for the Omicron variant across all stratification (Fig. 3C), but the differences in the mean generation intervals are unclear for between-household pairs. Consistent with the original study, which also reported shorter mean forward serial intervals for between-household pairs [3], we estimate shorter mean forward generation intervals for between-household pairs. We also estimate a reduction in the mean forward generation intervals from week 50 to week 51.



**Figure 3: Estimated forward generation-interval distributions of Delta and Omicron variants.** (A) Observed and fitted forward serial-interval distributions for within-household transmission pairs in the Netherlands for the Delta (black) and Omicron (orange) variants [3]. Serial intervals are calculated for infectors who developed symptoms on week 50 (13 and 19 December, 2021). Points represent the observed data. Lines represent the fitted lines assuming  $r = -0.05/\text{day}$  for the Delta variant and  $r = 0.15/\text{day}$  for the Omicron variant. Bivariate lognormal distributions with correlation coefficient of 0.75 are used to model relationships between incubation and generation intervals. (B) Estimated forward generation-interval distributions for within-household transmission pairs in the Netherlands. (C) Sensitivity of the mean generation-interval estimates to assumed growth rates of the Delta (black, solid lines) and Omicron variants (orange, dashed lines) stratified by the week of infectors' symptom onset and the type of transmission pairs.

Accounting for differences in the generation-interval distributions, we estimate

that the reproduction number of the Omicron variant decreased from 1.83 (95% CI: 1.65–2.05) to 1.17 (95% CI: 1.00–1.36) between December 12, 2021, and January 23, 2022 (Fig. 4A). On the other hand, the reproduction number of the Delta variant decreased from 0.89 (95% CI: 0.82–0.97) to 0.68 (95% CI: 0.62–0.74) between December 5, 2021, and January 9, 2022, and increased back up to 0.82 (95% CI: 0.72–0.93) by January 23, 2022 (Fig. 4A). We estimate the reproduction number ratios stayed roughly constant at around 2.2 (95% CI: 2.0–2.5) between December 12–26, 2021, and slowly decreased to 1.4 (95% CI: 1.2–1.7). However, if we neglect differences in the generation-interval distributions and solely rely on the generation-interval-distribution estimate for the Delta variant, we over-estimate the reproduction number of the Omicron variant and therefore is transmission advantage (Fig. 4B). In this case, the reproduction ratio decreases from 2.5 (95% CI: 2.2–2.8) to 1.5 (95% CI: 1.2–1.8), corresponding to roughly 7–13% bias.

In both cases, the decrease in the reproduction number ratio coincides with the decrease in the reproduction number of the Omicron variant, implying that epidemiological changes driving the dynamic had larger effects on the transmission of the Omicron variant than on the transmission of Delta variant; a larger reduction in the reproduction number of the Omicron variant also caused its growth rate to decrease faster, causing changes in the growth-rate difference (Fig. 1D).

## 4 Discussion

We compare estimates of the forward incubation-period and generation-interval distributions of the Delta and Omicron variants from the Netherlands. The original analysis detailing the data set previously reported shorter mean incubation period and serial interval for the Omicron variant [3]. Accounting for differences in epidemic growth rates, we find similar incubation-period distributions for both variants but a considerably shorter (0.5–0.9 days) mean generation interval for the Omicron variant. The mean forward generation interval of both variants further decreased between week 50 (13–19 December, 2021) and week 51 (20–26 December, 2021). Finally, we estimate that the transmission advantage of the Omicron variant decreased from 2.2-fold to 1.4-fold between early December and late January. Neglecting differences in the generation-interval distributions can result in  $\approx 10\%$  bias in estimates of the transmission advantage.

The generation-interval distribution describes changes in the individual-level transmission dynamics over the course of infection and therefore provides crucial information for epidemic control. A few studies have estimated the generation-interval distributions of SARS-CoV-2 infections from serial-interval data, but most of them neglect the effects of epidemic growth rates [12, 13, 14, 15]—these practices can be largely attributed to historical work that concluded that serial and generation intervals have the same means based on the assumption that infectors and infectees have identical incubation-period distributions [16, 17, 18]. Here, we build on our

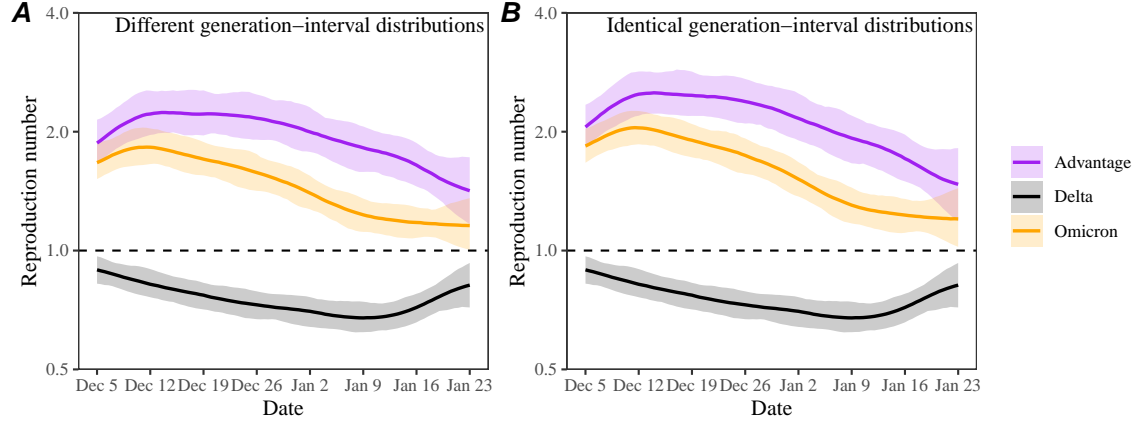


Figure 4: **Estimated time-varying reproduction number advantages of the Omicron variant.** (A) Estimated instantaneous reproduction numbers and their ratios over time while accounting for differences in the generation-interval distributions. (B) Estimated instantaneous reproduction numbers and their ratios over time while assuming identical generation-interval distributions. The instantaneous reproduction number of each variant is estimated using the renewal equation by shifting the smoothed case curves by one week (Fig. 1C). The intrinsic generation-interval distribution is approximated by the maximum likelihood estimates of the generation-interval distributions for within-household transmission pairs based on  $r = -0.05$  for the Delta variant (black) and  $r = 0.15$  for the Omicron variant (orange). Purple lines represent the ratio between the effective reproduction numbers of the Delta and Omicron variants. Lines and shaded regions represent medians and corresponding 95% confidence intervals.

previous work [2], which demonstrated theoretically that forward serial-interval distributions depends on epidemic growth rates, and further confirm that estimates of the forward generation-interval distributions are indeed sensitive to epidemic growth rates. Accounting for the growth-rate effects is especially important when comparing serial and generation intervals of different variants or from different time periods. These effects are also pertinent to all epidemiological inferences of past events from a cohort of infected individuals who experienced the succeeding event at the same time—this includes inferences of other delay distributions, such as incubation-period distributions, as well as viral load trajectories [19].

To our knowledge, our study is the first to estimate the generation-interval distribution of the Omicron variant. Although we estimate a shorter mean generation interval for the Omicron variant, we find the generation-interval distribution of the Omicron and Delta variants have similar modes (around 2.5 days), implying that the realized transmissibility of the Omicron variant decays faster. We tentatively hypothesize that these differences may be primarily driven by the network effect: a higher reproduction numbers of the Omicron variant leads to faster susceptible depletion among close contacts, which in turn prevents long generation intervals from

331 generating infections [10, 15]. While the network effect is expected to be strongest  
 332 among household contacts, it is also applicable to other forms of contact structures  
 333 that involve repeated contacts between the same group of individuals (because only  
 334 the first infectious contact results in infection). The network effect may also explain a  
 335 decrease in the mean generation interval between week 50 and 51, especially among  
 336 household transmission pairs, as a higher proportion of individuals within house-  
 337 holds would have been infected with either the Delta or Omicron variants. Other  
 338 factors, such as more stringent intervention measures against the Omicron variant  
 339 [3] and shorter clearance phase of the Omicron variant [20], also likely contributed  
 340 to shortening of the generation intervals.

341 While our study indicate that the Omicron variant has a shorter mean realized  
 342 generation interval than that of the Delta variant, it is still uncertain how much their  
 343 infectiousness profiles differ intrinsically. In particular, similarities in the incubation-  
 344 period distributions of the Delta and Omicron variants suggest that the differences  
 345 in their intrinsic infectiousness profile may be smaller than the estimated differences  
 346 in their realized generation-interval distributions. Nonetheless, our estimates of the  
 347 realized generation-interval distributions better describe the epidemic dynamics, im-  
 348 plicitly accounting for intervention and behavioral effects, and are therefore should  
 349 be used to estimate current reproduction numbers (rather than a counterfactual  
 350 intrinsic generation-interval distribution, which may have a longer mean).

351 Our study also has important implications for estimating transmission advantages  
 352 of new SARS-CoV-2 variants. In the example we consider, neglecting differences in  
 353 the generation-interval distributions leads to  $\approx 10\%$  bias in the estimates of the re-  
 354 production number ratios; however, the degree of ratio is expected to be sensitive  
 355 to the assumed generation-interval distribution of the resident variant. For example,  
 356 [21] estimated a much higher reproduction ratios ( $> 4$  fold) in South Africa but also  
 357 assumed a longer mean generation interval for the Delta and Omicron variants (6.4 vs  
 358 5.2 days, respectively). With our generation-interval estimates, we estimate that the  
 359 reproduction number ratio of 2.8 assuming  $r = -0.06$  and  $r = 0.26$  for the Delta and  
 360 Omicron variants, respectively—these growth rates were chosen to match the 4-fold  
 361 reproduction number ratios with the estimated growth-rate differences of 0.32/day  
 362 for the Gauteng province, South Africa [21]. We also show that both growth-rate dif-  
 363 ferences and the reproduction number ratios decreased over time—this result further  
 364 corroborates are earlier theoretical framework, which showed that growth-rate dif-  
 365 ferences changes over the course of an epidemic even when the reproduction number  
 366 ratios remain constant [11].

367 We primarily rely on case data to understand epidemic patterns of the Delta and  
 368 Omicron variants. In doing so, we implicitly assume that the delay between infection  
 369 and reports is fixed. However, changes in case trajectories are sensitive to testing  
 370 patterns and therefore may not accurately reflect patterns of infections. While this  
 371 limitation does not affect our generation-interval estimates, our inferences of the  
 372 transmission advantages of the Omicron variant should be interpreted with care.

373 Monitoring changes in key epidemiological parameters is critical to understanding

374 the evolution of SARS-CoV-2 and predicting its future dynamics [22]. Our study syn-  
375 thesises previously developed theoretical framework on serial- and generation-interval  
376 distributions and presents methodological advances in monitoring epidemiological  
377 parameters; however, uncertainty remains in the intrinsic infectiousness profiles of  
378 SARS-CoV-2 variants, especially among asymptotically infected individuals [23].  
379 Future studies extending our framework and combining more detailed epidemiologi-  
380 cal data will be critical to narrowing down these uncertainties.

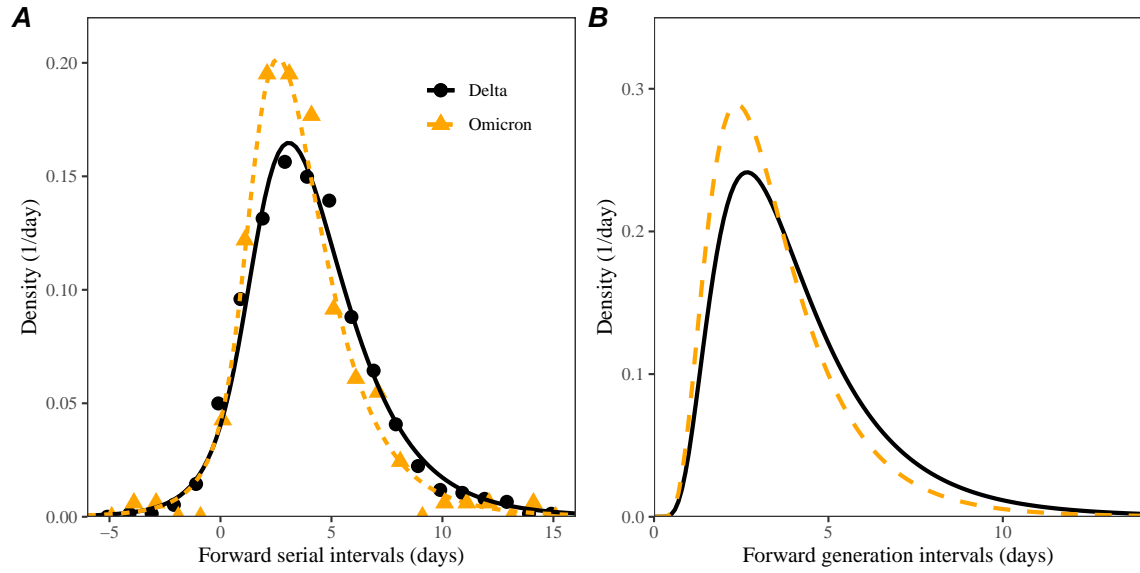


Figure S1: **Estimated forward generation-interval distributions of Delta and Omicron variants while neglecting growth-rate differences.** See Figure 3 in the main text for figure caption.

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