Workshop on the Mathematical Modelling of Variant Replacement of Infectious Diseases Pathogens

Instantaneous Reproduction Number

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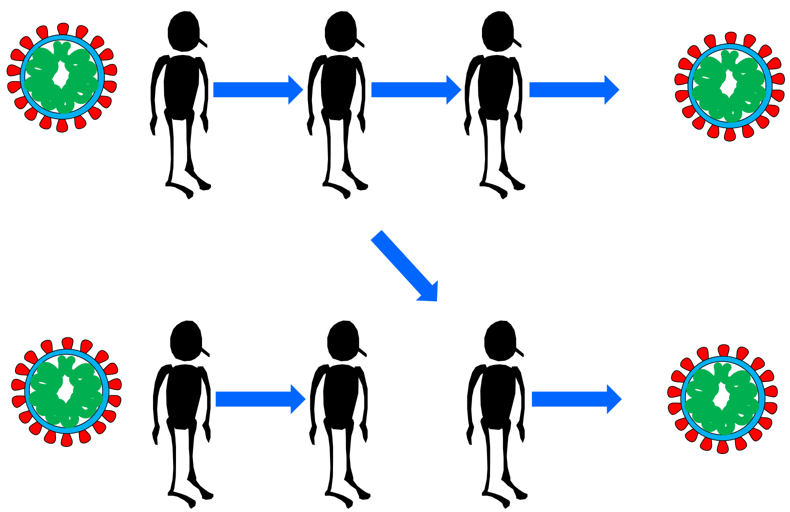
Effective Reproduction Number R_t
The average number of secondary infections

When $R(t) = 1$

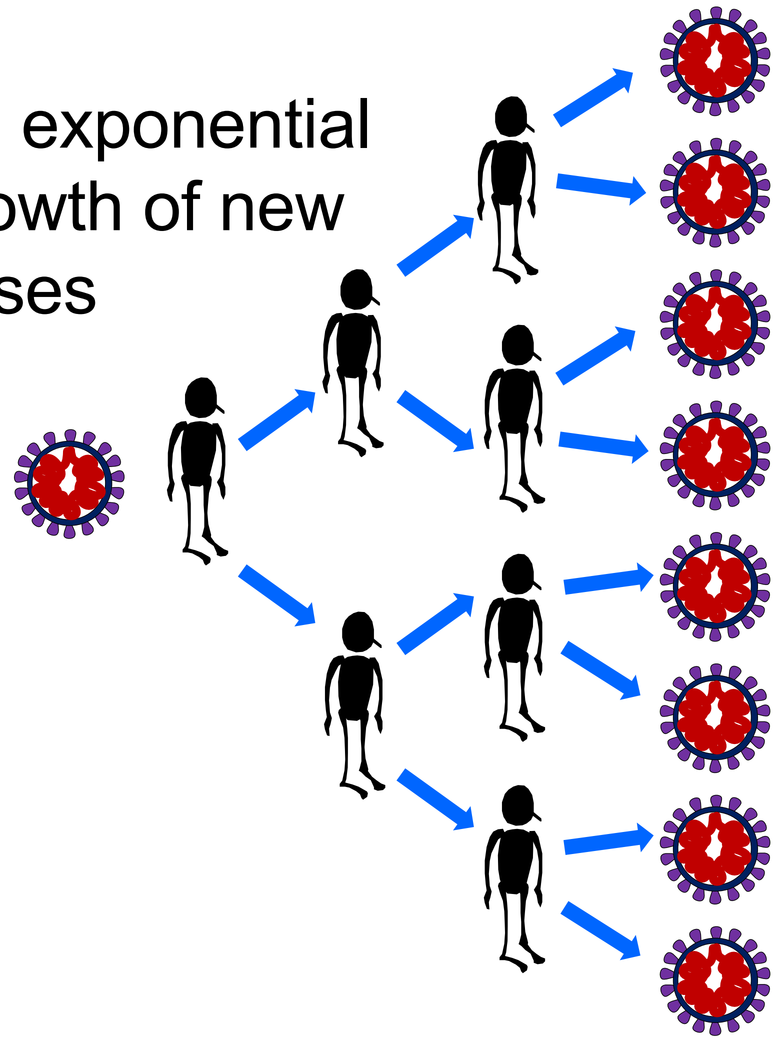
A constant number of new cases



The number of new cases declines when $R(t) < 1$

When $R(t) > 1$

An exponential growth of new cases



Estimation of Effective Reproduction Numbers

The average number of people an infected individual at time *t* could infect

Instantaneous Reproduction Number

$$R(t) = \frac{I(t)}{\sum_{j=1}^{l} g(j) I(t-j)}$$

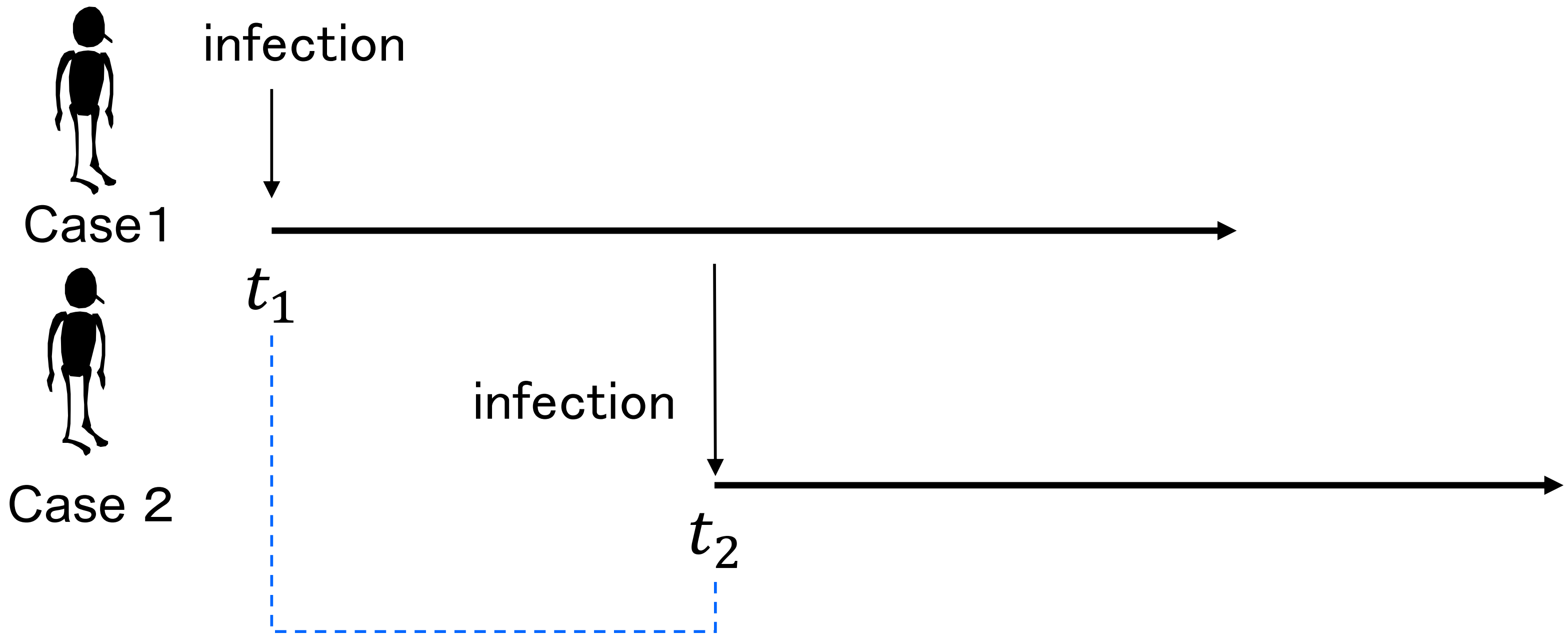
(Fraser 2007)

$I(t)$: The number of new cases at time t
$g(j)$: The probability that generation time is j days

$$R(t) = \frac{\text{(the number of new cases of the current generation)}}{\text{(the number of new cases of the previous generation)}}$$

Generation time

- The time between infection of a primary case and infection of secondary cases caused by the primary case



Generation time : $t_2 - t_1$

Example

Suppose that the observed numbers of new cases were as follows.

t	$I(t)$
⋮	⋮
2021-06-01	1
2021-06-02	2
2021-06-03	4
2021-06-04	5
2021-06-05	8
⋮	⋮

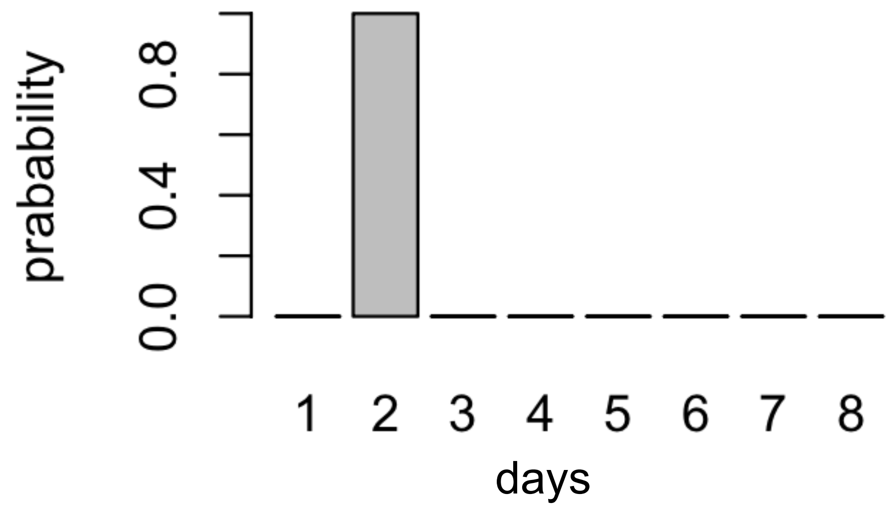
What is $R(t)$ at June 5?

Example

Suppose that the observed numbers of new cases were as follows.

t	$I(t)$
⋮	⋮
2021-06-01	1
2021-06-02	2
2021-06-03	4
2021-06-04	5
2021-06-05	8
⋮	⋮

Let’s sssume the generation time is exactly two days.



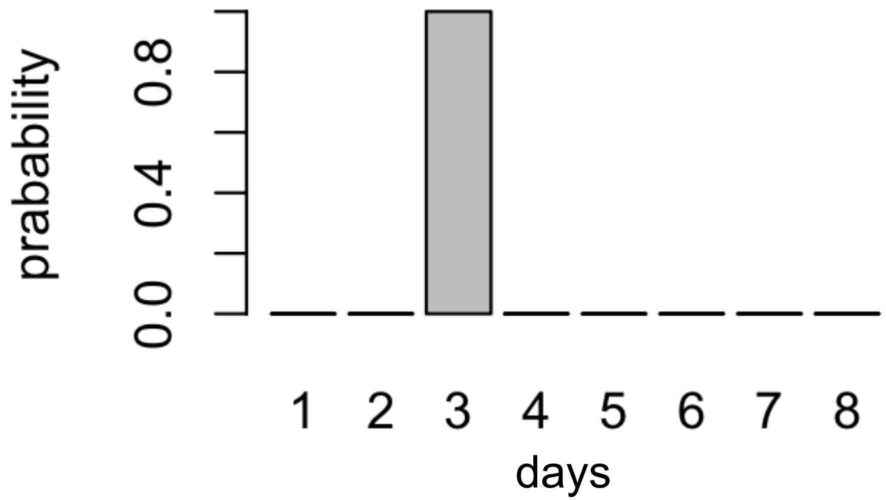
$$R(t) = 8/4 = 2.0$$

Example

Suppose that the observed numbers of new cases were as follows.

t	$I(t)$
⋮	⋮
2021-06-01	1
2021-06-02	2
2021-06-03	4
2021-06-04	5
2021-06-05	8
⋮	⋮

Let's assume the generation time is exactly three days.



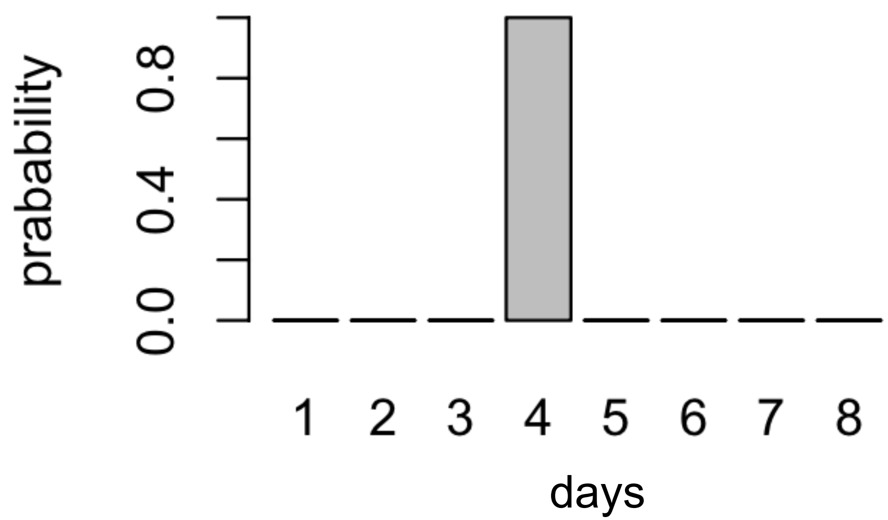
$$R(t) = 8/2 = 4.0$$

Example

Suppose that the observed numbers of new cases were as follows.

t	$I(t)$
⋮	⋮
2021-06-01	1
2021-06-02	2
2021-06-03	4
2021-06-04	5
2021-06-05	8
⋮	⋮

Let's assume the generation time is exactly four days.



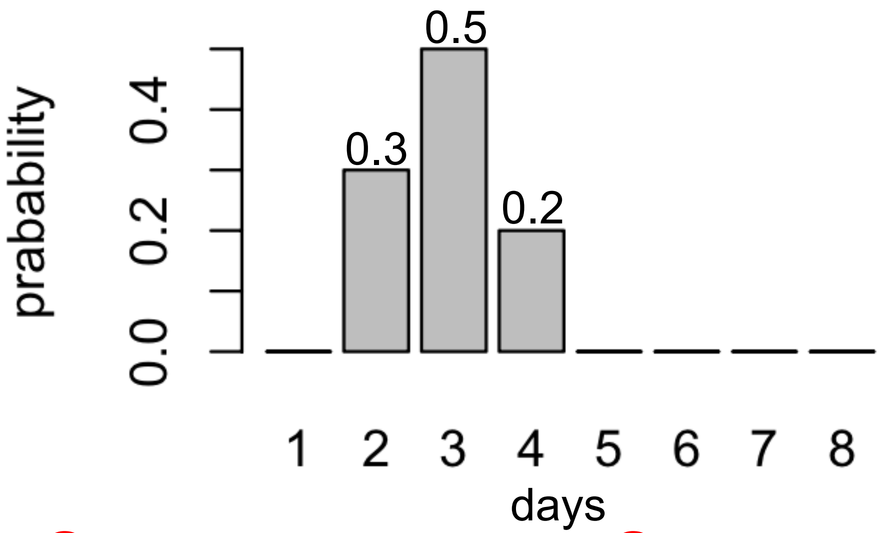
$$R(t) = 8/1 = 8.0$$

Example

Suppose that the observed numbers of new cases were as follows.

t	$I(t)$
⋮	⋮
2021-06-01	1
2021-06-02	2
2021-06-03	4
2021-06-04	5
2021-06-05	8
⋮	⋮

Let's assume the generation time has the following distribution



$$R(t) = \frac{8}{0.3\times 4 + 0.5\times 2 + 0.2\times 1} = \frac{8}{2.4} = 3.33$$

Estimation of
Effective Reproduction Numbers

The average number of people an infected individual at time *t* could infect

Instantaneous Reproduction Number

$$R(t) = \frac{I(t)}{\sum_{j=1}^{l} g(j) I(t-j)}$$

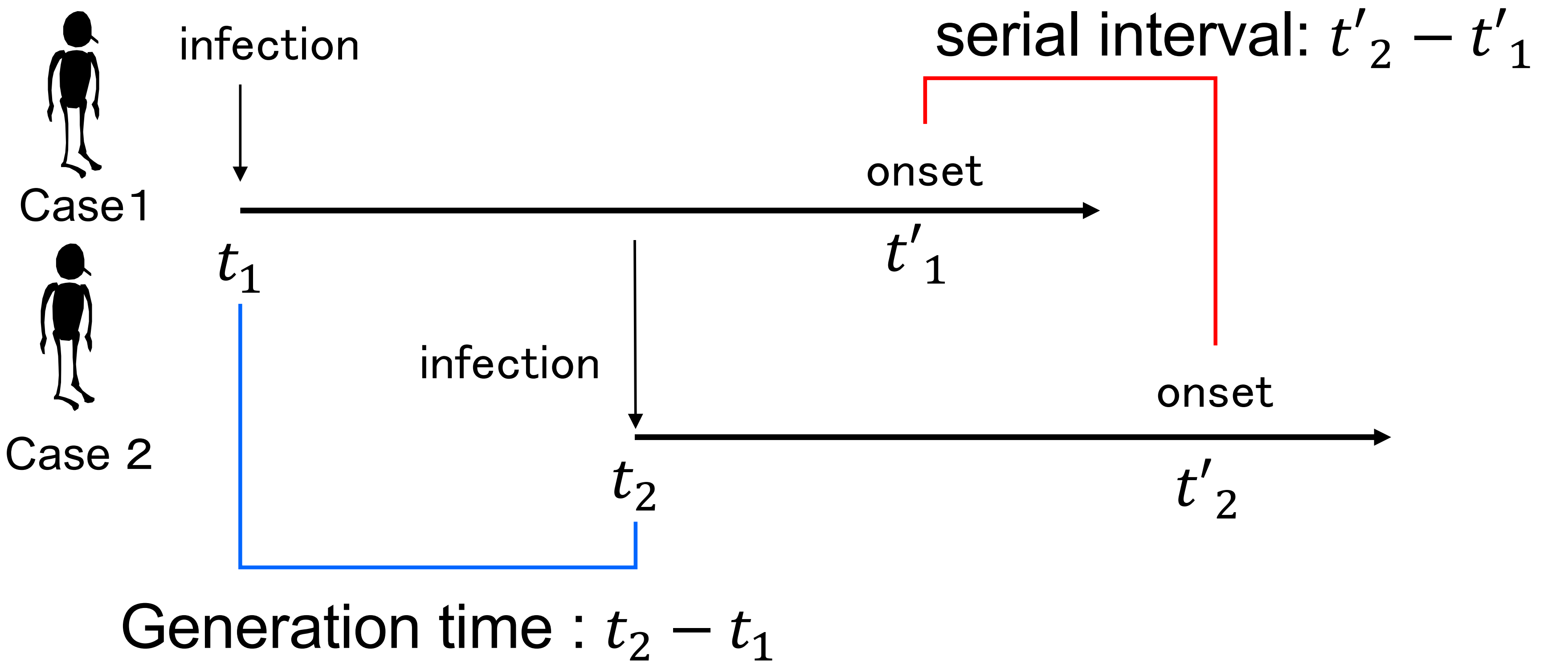
(Fraser 2007)

$I(t)$: The number of new cases at time t
$g(j)$: The probability that generation time is j days

R(t) depends on the generation time distribution.

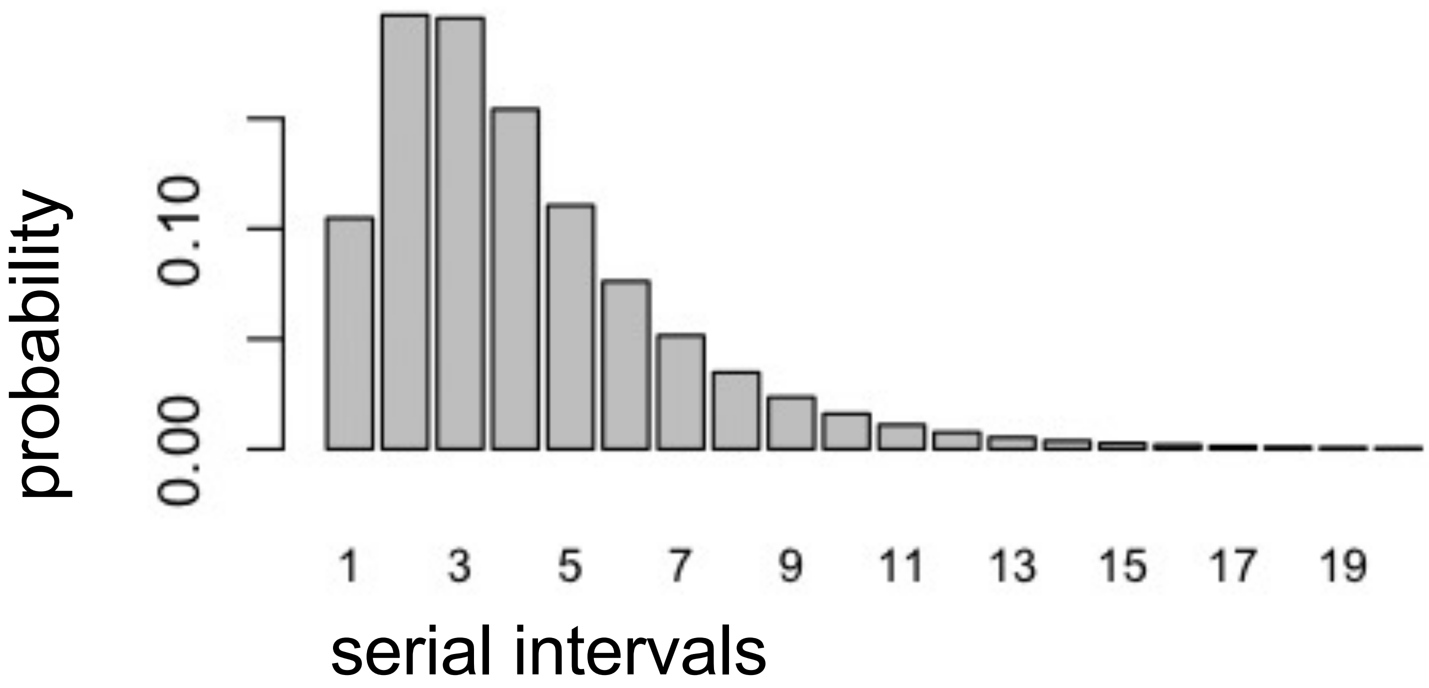
Serial Interval

- The time from symptom onset in a primary case to symptom onset in secondary cases



Serial Intervals of the Wuhan strain

Probability distribution of serial intervals



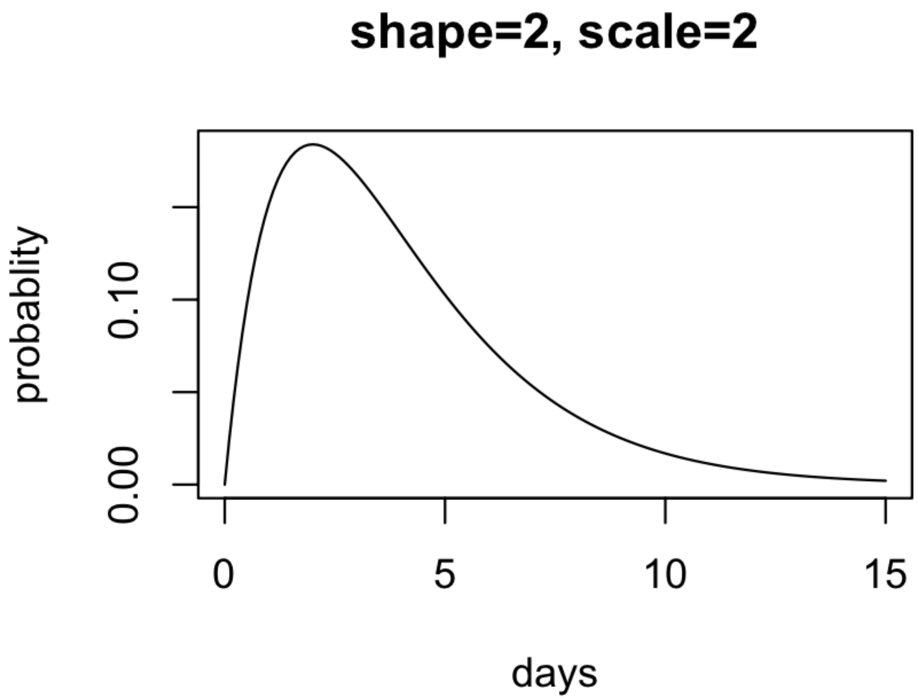
Log-normal distribution with a mean of 4.7 days and a standard deviation of 2.9 days
(Nishiura H et al. Int J Infect Dis. 2020)

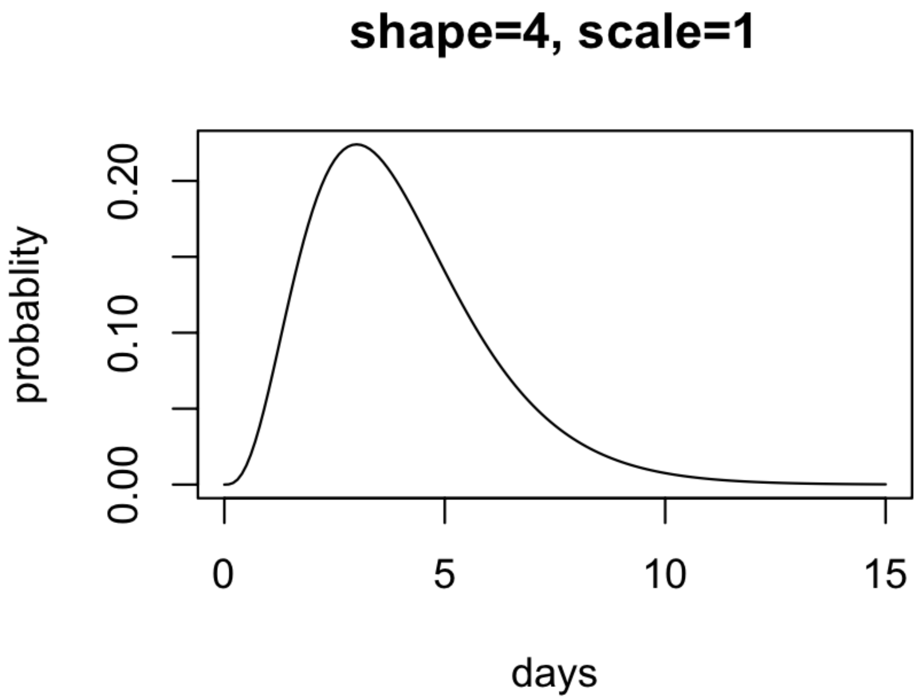
The Generation Times Differ
Depending on Viruses

Virus	**Mean**	**S.D.**	**Remarks**
SARS-CoV-2 (Delta)	4.7	3.3	Hart et al. Lancet Infect Dis. 2022
SARS-CoV-2 (Omicron)	2.97	1.48	Park et al. PNAS, 2023
Influenza Virus (H1N1)	2.95	1.43	Roll et al. BMC Infect Dis . 2011
Measles Virus	11.7	3.0	Akhmetzhanov, et al. PLoS Currents, 2018

Modeling generation time with
Gamma Distribution

A gamma distribution has two parameters of shape (α) and scale (θ).





Mean and variance of Gamma Distribution

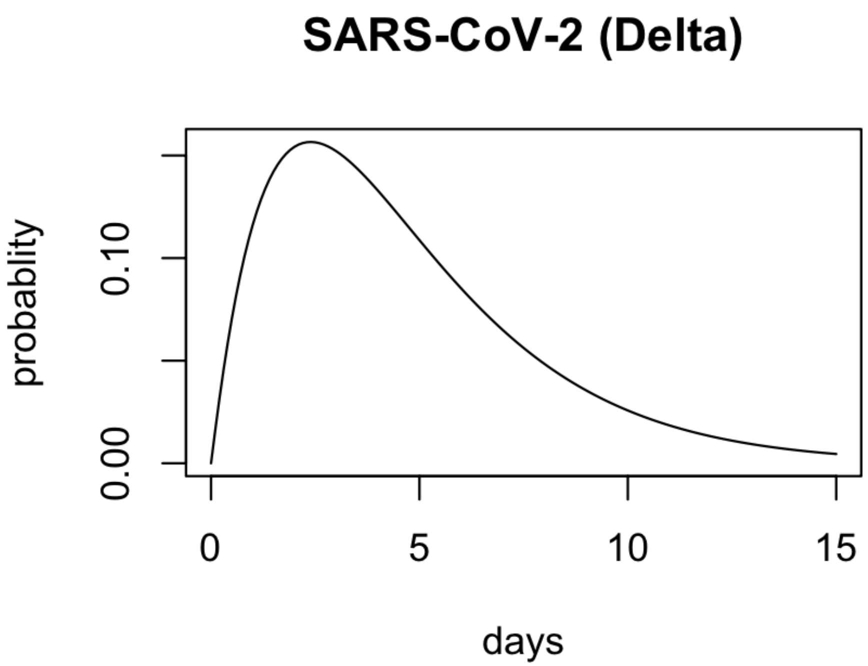
A gamma distribution with shape α and scale θ has a mean $\mu = \alpha\theta$ and variance $\sigma^2 = \alpha\theta^2$.

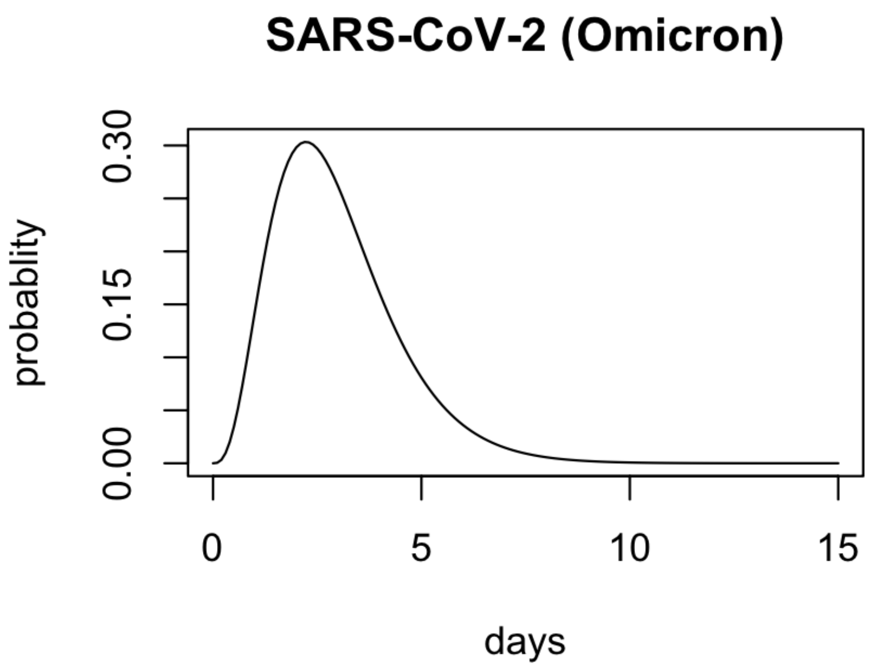
From mean μ and s.d. σ of generation time, we can obtain the shape parameter α and scale parameter θ of the gamma distribution

$$\alpha = \mu^2/\sigma^2$$
$$\theta = \sigma^2/\mu$$

Parameters for Gamma-distributed Generation Times

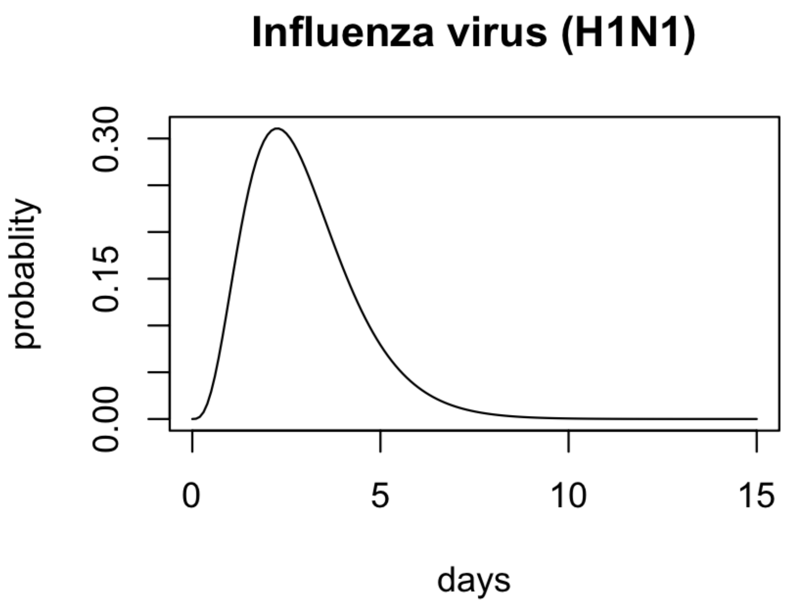
Virus	Mean	S.D.	α	θ	Remarks
SARS-CoV-2 (Delta)	4.7	3.3	2.03	2.32	Hart et al. Lancet Infect Dis. 2022
SARS-CoV-2 (Omicron)	2.97	1.48	4.03	0.735	Park et al. PNAS, 2023

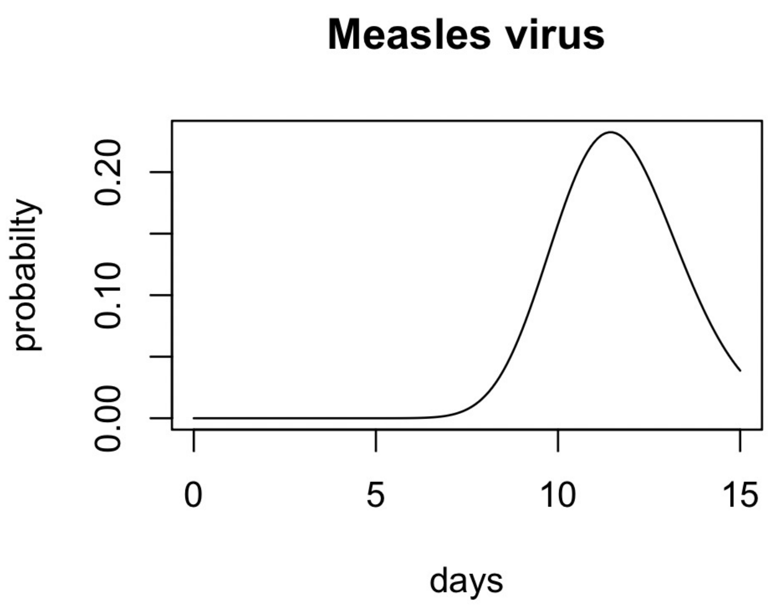




Parameters for Gamma-distributed Generation Times

Virus	Mean	S.D.	α	θ	Remarks
Influenza Virus (H1N1)	2.95	1.43	4.25	0.694	Roll et al. BMC Infect Dis . 2011
Measles Virus	11.7	3.0	45.6	0.26	Akhmetzhanov, et al. PLoS Currents, 2018



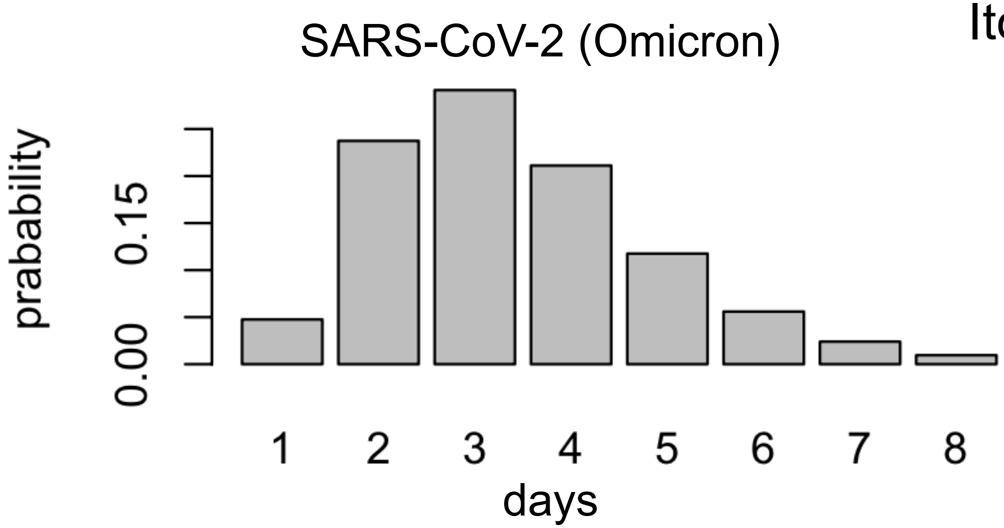


Discretization of Gamma-distributed Generation Time

The continuous generation time distribution of each variant $f_\chi(\tau)$ can be discretized using bins with a width of 1 day and truncated at $\tau = 1$ and $\tau = l$.

$$g_\chi(j) = \begin{cases} 0, & \text{if } j = 0 \\ \int_{(j-1)}^{j} f_\chi(\tau)d\tau \Big/ \int_0^l f_\chi(\tau)d\tau, & \text{if } 1 \le j \le l \\ 0, & \text{if } j > l \end{cases}$$

Ito, K., et al. MBE (2022).



Exercise

- Find the mean and s.d. (or variance) of the generation time (or serial intervals) of other viruses.
- Calculate shape and scale scale parameters from the mean and s.d. (or variance).

Summary

- R(t) is defined as the average number of people an infected individual at time t could be expected to infect given that conditions remain unchanged.
- R(t) depends on the generation time distribution.
- Generation times differ depending on viruses.
- Serial intervals are easier to estimate compared to generation times