

The time scale of asymptomatic transmission affects estimates of epidemic potential in the COVID-19 outbreak

Sang Woo Park,¹ Daniel M. Cornforth,² Jonathan Dushoff,^{3,4,5,*} and Joshua S. Weitz^{2,6,†}

¹ *Department of Ecology and Evolutionary Biology,
Princeton University, Princeton, NJ, USA*

² *School of Biological Sciences, Georgia Institute of Technology, Atlanta, GA, USA*

³ *Department of Biology, McMaster University, Hamilton, Ontario, Canada*

⁴ *Department of Mathematics and Statistics,
McMaster University, Hamilton, Ontario, Canada*

⁵ *M. G. DeGroote Institute for Infectious Disease Research,
McMaster University, Hamilton, Ontario, Canada*

⁶ *School of Physics, Georgia Institute of Technology, Atlanta, GA, USA*

(Dated: March 8, 2020)

We assess the impact of asymptomatic cases on epidemic potential of COVID-19 (and COVID-19 like pathogens) – as measured both by the basic reproduction number (i.e., the expected number of secondary cases generated by an average primary case in a fully susceptible population) and the fraction of new secondary cases attributable to asymptomatic individuals. As we show, the impact of asymptomatic cases depends on their generation intervals (i.e., time between when an individual is infected and when that individual infects another person). If the generation intervals of asymptomatic cases differs from that of symptomatic cases, then estimates of the basic reproduction number which do not explicitly account for asymptomatic cases may be systematically biased. Specifically, if asymptomatic cases have a shorter generation interval, \mathcal{R}_0 will be over-estimated, and if they have a longer generation interval, \mathcal{R}_0 will be under-estimated. The analysis provides a rationale for assessing the duration of asymptomatic cases of COVID-19 in addition to their prevalence in the population.

*Electronic address: dushoff@mcmaster.ca; URL: <https://mac-theobio.github.io/dushoff.html>

†Electronic address: jswertz@gatech.edu; URL: <http://ecothery.biology.gatech.edu>

I. INTRODUCTION

In an epidemic, symptomatic cases are the predominant focus of treatment and usually represent the bulk of reported cases. However, infected individuals who are asymptomatic yet infectious can be a critical factor in the spread of some pathogens [1]. Asymptomatic individuals are hard to trace, unlikely to self-isolate, and are likely to retain normal social and travel patterns.

There is significant ongoing interest in asymptomatic infections in COVID-19 for two major reasons. First, the proportion of infections that are asymptomatic (see [2]) is critical to attempts to estimate the likely burden of severe outcomes (including mortality [3]) when the virus spreads through a population. Second, understanding the possible role of *transmission* by asymptomatic individuals is crucial to planning surveillance and control efforts [1].

Here, we focus on a third effect. If asymptomatic cases are important for transmission, they also have the potential to affect estimates of key parameters of disease spread such as the basic reproduction number \mathcal{R}_0 (i.e., the expected number of secondary cases generated by an average primary case in a fully susceptible population [4]). Thus, we investigate the relationship between individual-level features of asymptomatic cases (e.g., the probability that an infection is asymptomatic, asymptomatic case duration, transmission by asymptomatic individuals) to dynamics at the population scale.

II. METHODS

We model viral spread using a renewal-equation framework [5], which allows us to model the current incidence of infected individuals (i.e., the the rate at which new infections occur in the population) as a function of previous incidence and how infectiousness of an infected individual varies over the course of their infection. We divide incidence i into two categories – i_a and i_s – corresponding to incidence of asymptomatic and symptomatic cases, respectively. Newly infected individuals that are either asymptotically or symptomatically infected can transmit the disease to others, but they differ in their intrinsic reproduction numbers, \mathcal{R}_a and \mathcal{R}_s , respectively, as well as intrinsic generation-interval distributions [6], $g_a(\tau)$ and $g_s(\tau)$. Generation intervals, which are defined as the time between when an individual is infected and when that individual infects another person [7], depend on the natural history

of infection: individuals with subclinical infections may have fast clearance and short generation intervals, or slow viral reproduction and long generation intervals (cf. [8]). The shape of the generation-interval distribution characterizes the relationship between the epidemic growth rate r and the reproduction number [9].

Neglecting births and loss of immunity on the time scale of the outbreak, the dynamics of susceptibles and incidence are:

$$\dot{S} = -i(t) \quad (1)$$

$$i(t) = \mathcal{R}_a S(t) \int_0^\infty i_a(t-\tau) g_a(\tau) d\tau + \mathcal{R}_s S(t) \int_0^\infty i_s(t-\tau) g_s(\tau) d\tau. \quad (2)$$

The basic reproduction number of this system is:

$$\mathcal{R}_0 = p\mathcal{R}_a + (1-p)\mathcal{R}_s, \quad (3)$$

where p is the proportion of *incident cases* that are asymptomatic: $i_a(t) = pi(t)$. The corresponding intrinsic generation-interval distribution of an average infected individual is given by:

$$g(\tau) = zg_a(\tau) + (1-z)g_s(\tau), \quad (4)$$

where we define the “intrinsic” proportion of asymptomatic transmission z as the relative contribution of asymptomatic cases to the basic reproduction number:

$$z = p\mathcal{R}_a/\mathcal{R}_0. \quad (5)$$

Note that the intrinsic proportion of symptomatic transmission satisfies

$$1 - z = (1 - p)\mathcal{R}_s/\mathcal{R}_0. \quad (6)$$

Yet, this information is not sufficient to disentangle the role of asymptomatic cases, i.e., what fraction of secondary cases can be ascribed to *realized* transmission from asymptomatic cases vs. symptomatic cases?

The intrinsic proportion of asymptomatic transmission z is a useful benchmark, but does not necessarily reflect the realized proportion of asymptomatic transmission, unless both types of infection have the same generation-interval distribution. The *realized* proportion of asymptomatic transmission, q at time t is given by:

$$\frac{q}{1-q} = \frac{\mathcal{R}_a S(t) \int_0^\infty i_a(t-\tau) g_a(\tau) d\tau}{\mathcal{R}_s S(t) \int_0^\infty i_s(t-\tau) g_s(\tau) d\tau}, \quad (7)$$

During the period of exponential growth, we assume S remains nearly constant, and $i(t)$ is proportional to $\exp(rt)$, and simplify:

$$\frac{q}{1-q} = \left(\frac{z}{1-z} \right) \frac{\delta_a}{\delta_s}. \quad (8)$$

Here, δ_c for each of the two classes is the average “discount” of a new infection – the average relative contribution of a secondary infection to the epidemic, taking exponential growth into account:

$$\delta_c = \int_0^\infty \exp(-r\tau) g_c(\tau) d\tau. \quad (9)$$

$\delta_c < 1$ and grows smaller as the generation interval grows longer. Thus, the realized proportion of asymptomatic infections will be increased (resp., decreased) if transmission is relatively faster (slower) along the asymptomatic route. The discount δ also depends on the relative variation in the generation-interval distribution, the “dispersion”: more variation in generation intervals leads to more opportunities for fast spread and thus to higher values of δ (similar to shorter average generation intervals).

To estimate the effects of assumptions about asymptomatic transmission on the importance of asymptomatic transmission and estimates of the basic reproduction number \mathcal{R}_0 , we parameterize the generation interval distributions of asymptomatic and symptomatic cases based on their means, \bar{G}_a and \bar{G}_s , and dispersions, κ_a and κ_s . We assume that generation intervals are gamma distributed, and we set the dispersion to be equal to the squared coefficient of variation (the reciprocal of the gamma shape parameter, see Appendix). We assume that epidemic growth rate r and the generation-interval distribution of symptomatic case are known, using parameter values that are consistent with earlier COVID-19 models [10]: $1/r = 7$ days, $\bar{G}_s = 8$ days, and $\kappa_s = 0.5$. We infer values of q using Eq. (8) and \mathcal{R}_0 using the Euler-Lotka equation [11]:

$$\frac{1}{\mathcal{R}_0} = \int \exp(-r\tau) g(\tau) d\tau. \quad (10)$$

In the supplementary material, we also use ODEs to give a concrete example of how differences in generation intervals affect both q and estimates of \mathcal{R}_0 .

III. RESULTS

We explore the effects of different assumptions about speed and effectiveness of asymptomatic transmission on the importance of asymptomatic transmission and estimates of the

basic reproduction number \mathcal{R}_0 , using a gamma assumption (see Methods). Across the range of parameters we explore, the intrinsic proportion of asymptomatic transmission z is similar to the realized proportion q (Figure 1A). As the relative mean generation interval of asymptomatic transmission, \bar{G}_a/\bar{G}_s , increases, q decreases because symptomatic cases are more likely to have short generation intervals (i.e., fast transmission events), which drive the spread during the growth phase (Figure 1A).

Figure 1B shows the effect of different assumptions about the generation interval of asymptomatic cases, \bar{G}_a , on the basic reproduction number \mathcal{R}_0 . When \bar{G}_a is long compared to \bar{G}_s , then we are effectively assuming a longer mean for the overall generation interval. This assumption leads to a larger estimate of \mathcal{R}_0 for a fixed value of r . (see [12]). Conversely, when $\bar{G}_a < \bar{G}_s$, generation intervals are shorter, leading to lower estimates of the epidemic strength \mathcal{R}_0 . Both of these effects are stronger when the intrinsic proportion of asymptomatic transmission z increases (and disappear as $z \rightarrow 0$). Therefore, when \mathcal{R}_0 is

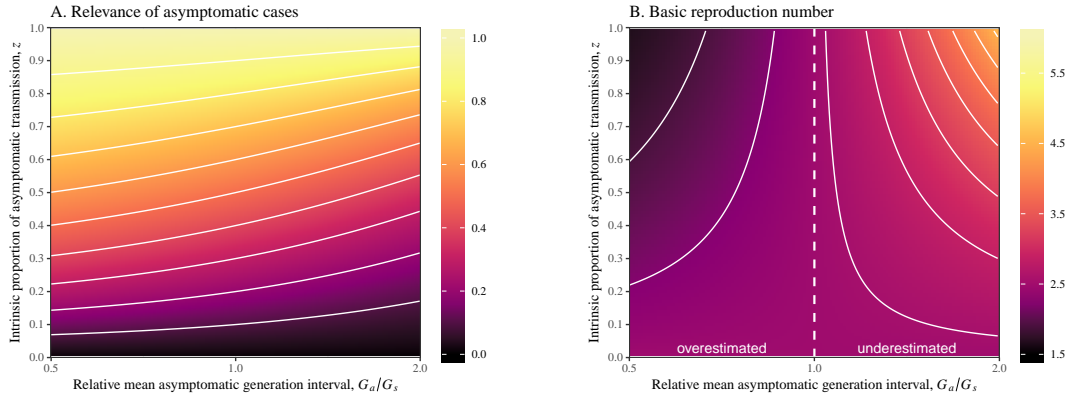


FIG. 1: Effects of intrinsic proportion of asymptomatic transmission on the realized proportion of asymptomatic transmission and basic reproduction number, given variation in the mean generation interval of asymptomatic cases. (A) Increasing the speed of asymptomatic transmission (shorter generation intervals) increases the importance of asymptomatic cases in transmission, q . (B) Increasing generation intervals of asymptomatic cases increases the basic reproduction number \mathcal{R}_0 ; When \bar{G}_a is smaller (larger) than \bar{G}_s , estimates based on the observed generation distribution for symptomatic cases (dashed line) are expected to over- (under-) estimate the true \mathcal{R}_0 . Solid lines show contours for \mathcal{R}_0 values. Here, we assume $1/r = 7$ days, $\bar{G}_s = 8$ days, and $\kappa_s = \kappa_a = 0.5$.

estimated without explicitly accounting for asymptomatic spread (white, dashed line in Figure 1B), it can be over- or under- estimated depending on the relative duration of infection between symptomatic and asymptomatic individuals. The qualitative effects of z and \bar{G}_a/\bar{G}_s on q and \mathcal{R}_0 remain robust when we assume narrower ($\kappa_s = \kappa_a = 0.3$; Figure S1) or wider ($\kappa_s = \kappa_a = 0.8$; Figure S2) generation intervals.

Relative generation-interval dispersion of asymptomatic cases κ_a/κ_s have similar, but smaller, effects on q and \mathcal{R}_0 (Figure S3). Since a wider generation-interval distribution has a higher proportion of early transmission than a narrow one, increasing the generation-interval dispersion has qualitatively similar effects on q and \mathcal{R}_0 as decreasing the mean generation interval.

IV. DISCUSSION

Much is still unknown about course of asymptomatic infection compared to symptomatic infection in COVID-19. Our current work highlights the need to characterize the duration of asymptomatic infections, relative to that of symptomatic ones, and their consequences not only for contact tracing but for precise estimation of the basic reproduction number of the ongoing COVID-19 outbreak [10]. The present findings are also consistent with a recent generalization linking speed, strength, and generation intervals, such that for a given observed speed increases in the mean generation interval imply larger reproduction number [12].

If mild, asymptomatic infections are more persistent than severe, symptomatic ones, the mean generation interval for COVID-19 could be longer than estimated from symptomatic cases alone - possibly increasing \mathcal{R}_0 (Figure 1B). However, if asymptomatic cases tend to have shorter infection, then current estimates of \mathcal{R}_0 may be over-estimates of the underlying strength (Figure 1B), although asymptomatic cases may be driving a larger fraction of secondary cases than we would expect without accounting for their differences (Figure 1A). Therefore, current estimates of \mathcal{R}_0 that do not account for asymptomatic cases may be systematically biased.

Finally, it is important to note we focused here on the exponential phase, but that the realized proportion of asymptomatic transmission q is time-dependent, and will vary given the population state structure of infected individuals. Such variation in the ratio of

asymptomatic to symptomatic cases will also impact estimates of case fatality rates insofar as many asymptomatic cases are not counted, particularly early in an outbreak. Future work might also consider the ways in which asymptomatic individuals modulate resurgent epidemics in a networked metapopulation [13]. Characterizing the role of asymptomatic individuals in driving the persistence of the epidemic will be critical for assessing the post-pandemic outcome [14].

Acknowledgments: The authors thank John Glasser for comments and discussion on the manuscript, particularly on short notice. This work was supported, in part, by support from the Army Research Office to JSW (W911NF1910384).

Data Availability: All code is available at https://github.com/mac-theobio/coronavirus_asymptomatic.

Supplementary Materials

A gamma approximation to generation-interval distributions

Assuming that the intrinsic generation-interval distribution for each class (asymptomatic and symptomatic) follows a gamma distribution with mean \bar{G}_c and dispersion κ_c , the average discount of a new infection can be written as:

$$\delta_c = (1 + \kappa_c r \bar{G}_c)^{-1/\kappa_c}, \quad (\text{S1})$$

which shows that the average discount increases with smaller \bar{G}_c and with larger κ_c . Then, the odds of the realized proportion of asymptomatic transmission can be written as:

$$\frac{q}{1-q} = \left(\frac{z}{1-z} \right) \left[\frac{(1 + \kappa_s r \bar{G}_s)^{1/\kappa_s}}{(1 + \kappa_a r \bar{G}_a)^{1/\kappa_a}} \right], \quad (\text{S2})$$

where \bar{G}_a and \bar{G}_s are the mean generation intervals for asymptomatic and symptomatic cases, and κ_a and κ_s are the generation-interval dispersions for asymptomatic and symptomatic cases. Finally, the basic reproduction number is calculated by

$$\mathcal{R}_0 = (z(1 + \kappa_a r \bar{G}_a)^{-1/\kappa_a} + (1-z)(1 + \kappa_s r \bar{G}_s)^{-1/\kappa_s})^{-1}. \quad (\text{S3})$$

A compartmental model for asymptomatic/symptomatic cases

Consider an SEIR model variant in which an infected individual can be either asymptomatic, I_a , or symptomatic, I_s . We note that I_a and I_s represent prevalence (i.e., the total number of currently infectious individuals) of asymptomatic and symptomatic individuals; these quantities are different from i_s and i_a that we present in the main text, which represent incidence (i.e., the rate at which new cases are generated) of asymptomatic and symptomatic individuals. While both cases can recover, we assume that only symptomatic cases can lead to fatalities, denoted by the D category. In total, the dynamics of susceptibles, exposed, infectious, recovered, and dead are:

$$\dot{S} = -\beta_a S I_a - \beta_s S I_s \quad (\text{S4})$$

$$\dot{E} = \beta_a S I_a + \beta_s S I_s - \gamma_e E \quad (\text{S5})$$

$$\dot{I}_a = p\gamma_e E - \gamma_a I_a \quad (\text{S6})$$

$$\dot{I}_s = (1-p)\gamma_e E - \gamma_s I_s \quad (\text{S7})$$

$$\dot{R} = \gamma_a I_a + (1-f)\gamma_s I_s \quad (\text{S8})$$

$$\dot{D} = f\gamma_s I_s. \quad (\text{S9})$$

Here, β_a and β_s denote transmission rates, γ_e denotes the transition from exposed to infectious, p is the fraction of asymptomatic cases that are generated for each exposed individual, $1-p$ is the fraction of symptomatic cases that are generated for each exposed individual, γ_a and γ_s denote recovery rates, and f denotes the case fatality ratio for symptomatic cases.

Given that the number of infected individuals increase exponentially at rate r initially, the equations for the infectious cases can be rewritten given the ansatz $E(t) = c_e e^{rt}$, $I_a(t) = c_a e^{rt}$, $I_s(t) = c_s e^{rt}$. Then, it follows that

$$rc_a = p\gamma_e c_e - \gamma_a c_a, \quad (\text{S10})$$

$$rc_s = (1-p)\gamma_e c_e - \gamma_s c_s, \quad (\text{S11})$$

which implies that

$$\frac{c_a}{c_s} = \frac{p}{1-p} \left[\frac{r + \gamma_s}{r + \gamma_a} \right]. \quad (\text{S12})$$

This shows that the prevalence of asymptomatic and symptomatic individuals is different from p and $1-p$ because prevalence measures the individuals that are currently infectious

and does not account for individuals that have already recovered. Finally, the ratio of secondary case production caused by asymptomatic vs. symptomatic individuals during the exponential phase should be

$$\frac{q}{1-q} = \left(\frac{\beta_a}{\beta_s} \right) \frac{p}{1-p} \left[\frac{r + \gamma_s}{r + \gamma_a} \right], \quad (\text{S13})$$

where q is the fraction of new secondary cases caused by asymptomatic individuals.

The basic reproduction number of this system is:

$$\mathcal{R}_0 = p\mathcal{R}_a + (1-p)\mathcal{R}_s, \quad (\text{S14})$$

where

$$\mathcal{R}_a = \frac{\beta_a}{\gamma_a}, \quad (\text{S15})$$

$$\mathcal{R}_s = \frac{\beta_s}{\gamma_s}. \quad (\text{S16})$$

The generation-interval distributions for asymptomatic and symptomatic individuals follow the same functional form as the corresponding generation-interval distribution for a single-type SEIR model since both asymptomatic and symptomatic individuals have exponentially distributed latent and infectious periods [15]:

$$g_a(\tau) = \frac{\gamma_e \gamma_a}{\gamma_e - \gamma_a} (\exp(-\gamma_a \tau) - \exp(-\gamma_e \tau)), \quad (\text{S17})$$

$$g_s(\tau) = \frac{\gamma_e \gamma_s}{\gamma_e - \gamma_s} (\exp(-\gamma_s \tau) - \exp(-\gamma_e \tau)). \quad (\text{S18})$$

It immediately follows that

$$\left(\frac{z}{1-z} \right) \left[\frac{\int_0^\infty \exp(-r\tau) g_a(\tau) d\tau}{\int_0^\infty \exp(-r\tau) g_s(\tau) d\tau} \right] = \left(\frac{\beta_a}{\beta_s} \right) \frac{p}{1-p} \left[\frac{r + \gamma_s}{r + \gamma_a} \right], \quad (\text{S19})$$

where $z = p\mathcal{R}_a/\mathcal{R}_0$ and $1-z = (1-p)\mathcal{R}_s/\mathcal{R}_0$.

Supplementary figures

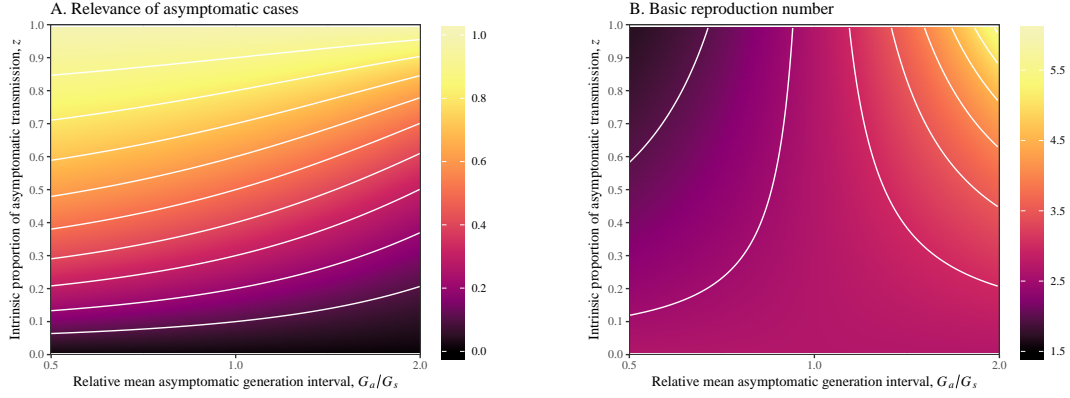


FIG. S1: Effects of intrinsic proportion of asymptomatic transmission on the relevance of asymptomatic transmission and basic reproduction number, given variation in the mean generation interval of asymptomatic cases when generation-interval distributions are narrow. Here, we assume $1/r = 7$ days, $\bar{G}_s = 8$ days, and $\kappa_s = \kappa_a = 0.3$. See Figure 1 in the main text for figure caption.

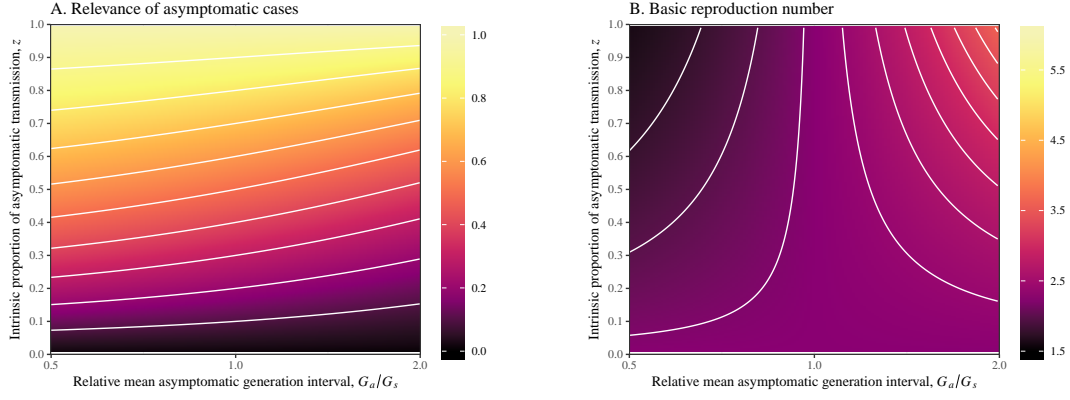


FIG. S2: Effects of intrinsic proportion of asymptomatic transmission on the relevance of asymptomatic transmission and basic reproduction number, given variation in the mean generation interval of asymptomatic cases when generation-interval distributions are wide. Here, we assume $1/r = 7$ days, $\bar{G}_s = 8$ days, and $\kappa_s = \kappa_a = 0.8$. See Figure 1 in the main text for figure caption.

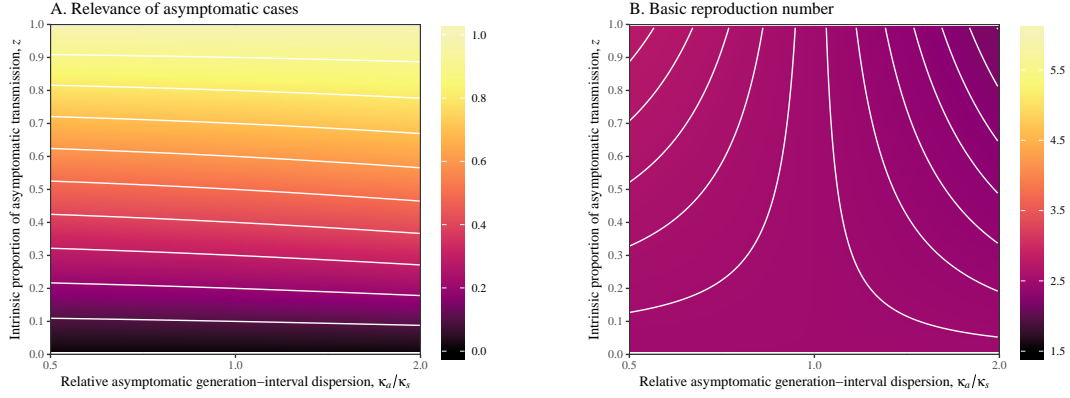


FIG. S3: Effects of intrinsic proportion of asymptomatic transmission on the relevance of asymptomatic transmission and basic reproduction number, given variation in the generation-interval dispersion of asymptomatic cases. (A) Wide/narrow generation intervals of asymptomatic cases increase/decrease the relevance of asymptomatic cases, q . (B) Wide/narrow generation intervals of asymptomatic cases decrease/increase the basic reproduction number \mathcal{R}_0 . The white, solid lines represent the contour lines. Here, we assume $1/r = 7$ days, $\bar{G}_s = \bar{G}_a = 8$ days, and $\kappa_s = 0.5$.

-
- [1] Fraser, C., Riley, S., Anderson, R. M. & Ferguson, N. M. Factors that make an infectious disease outbreak controllable. *Proceedings of the National Academy of Sciences* **101**, 6146–6151 (2004).
 - [2] Mizumoto, K., Kagaya, K., Zarebski, A. & Chowell, G. Estimating the asymptomatic ratio of 2019 novel coronavirus onboard the Princess Cruises Ship, 2020. *medRxiv* (2020). URL <https://www.medrxiv.org/content/10.1101/2020.02.20.20025866v2.full>.
 - [3] Fauci, A. S., Lane, H. C. & Redfield, R. R. Covid-19 – navigating the uncharted. *New England Journal of Medicine* (2020). URL <https://doi.org/10.1056/NEJMe2002387>.
 - [4] Anderson, R. M. & May, R. M. *Infectious diseases of humans: dynamics and control* (Oxford university press, 1992).
 - [5] Heesterbeek, J. & Dietz, K. The concept of \mathcal{R}_0 in epidemic theory. *Statistica Neerlandica* **50**, 89–110 (1996).
 - [6] Champredon, D. & Dushoff, J. Intrinsic and realized generation intervals in infectious-disease transmission. *Proceedings of the Royal Society B: Biological Sciences* **282**, 20152026 (2015).
 - [7] Svensson, Å. A note on generation times in epidemic models. *Mathematical biosciences* **208**, 300–311 (2007).
 - [8] Roberts, M. & Heesterbeek, J. Model-consistent estimation of the basic reproduction number from the incidence of an emerging infection. *Journal of mathematical biology* **55**, 803 (2007).
 - [9] Wallinga, J. & Lipsitch, M. How generation intervals shape the relationship between growth rates and reproductive numbers. *Proceedings of the Royal Society B: Biological Sciences* **274**, 599–604 (2007).
 - [10] Park, S. W. *et al.* Reconciling early-outbreak estimates of the basic reproductive number and its uncertainty: framework and applications to the novel coronavirus (SARS-CoV-2) outbreak. *medRxiv* (2020). URL <https://www.medrxiv.org/content/10.1101/2020.01.30.20019877v4.full.pdf>.
 - [11] Lotka, A. J. Relation between birth rates and death rates. *Science* **26**, 21–22 (1907).
 - [12] Park, S. W., Champredon, D., Weitz, J. S. & Dushoff, J. A practical generation-interval-based approach to inferring the strength of epidemics from their speed. *Epidemics* **27**, 12–18 (2019).
 - [13] Watts, D. J., Muhamad, R., Medina, D. C. & Dodds, P. S. Multiscale, resurgent epidemics in

- a hierarchical metapopulation model. *Proceedings of the National Academy of Sciences* **102**, 11157–11162 (2005).
- [14] Kissler, S. M., Tedijanto, C., Goldstein, E., Grad, Y. H. & Lipsitch, M. Projecting the transmission dynamics of SARS-CoV-2 through the post-pandemic period. *medRxiv* (2020). URL <https://www.medrxiv.org/content/10.1101/2020.03.04.20031112v1>.
- [15] Svensson, Å. The influence of assumptions on generation time distributions in epidemic models. *Mathematical biosciences* **270**, 81–89 (2015).