Linking asymptomatic case characteristics with the epidemic potential of coronavirus-like outbreaks

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We analyze a mechanistic model of a coronavirus-like pathogen to assess the impact of asymptomatic cases on epidemic potential – as measured both by the basic reproduction number and the fraction of new secondary cases attributable to asymptomatic individuals. As we show, the impact of asymptomatic cases depends on the generation intervals of asymptomatic cases. If the generation intervals of asymptomatic cases differs than that of symptomatic cases, then estimates of the basic reproductive ratio 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.

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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. The COVID-19 outbreak has raised significant questions regarding the role of asymptomatic cases [2]. A key focus has been on estimating asymptomatic prevalence (see [3]), e.g., what fraction of individuals have asymptomatic infections relative to those with symptomatic infections?

There is currently a lot of interest in the role of asymptomatic infections in SARS-CoV-2 for two major reasons. First, the proportion of infections that are asymptomatic is critical to attempts to estimate the likely burden of severe outcomes (including mortality) 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.

Here, we focus on a third effect. If asymptomatic cases are important for transmission, they also have the potential to affect estimates of key epidemiological parameters. Here, we investigate the relationship between individual-level features of asymptomatic cases (e.g., the probability of initiating an asymptomatic case, asymptomatic case duration, and the transmission rates from asymptomatic individuals) to dynamics at the population scale. That is, rather than focusing on the prevalence of asymptomatic cases, we are interested in understanding the relevance of asymptomatic infections to secondary case production – including to the production of symptomatic cases.

II. METHODS

We model viral spread using a renewal-equation framework [4], which allows us to model the current incidence of infected individuals 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. Both types of individuals can infect others, but they differ in their intrinsic reproduction numbers, $\mathcal{R}_a$ and $\mathcal{R}_s$, as well as intrinsic generation-interval

distributions, $g_a(\tau)$ 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 [5], depend on the natural history of infection: individuals with subclinical cases may have fast clearance and short generation intervals, or slow viral reproduction and long generation intervals.

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

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

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

Here, p is the proportion of *incident cases* that are asymptomatic.

The basic reproduction number – the expected number of secondary cases generated by an average primary case in a fully susceptible population [6] – of this system is:

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

We define the "intrinsic" proportion of asymptomatic transmission as the relative contribution of asymptomatic cases to the basic reproduction number:

$$z = p\mathcal{R}_a/\mathcal{R}_0. \tag{4}$$

Note that the intrinsic proportion of symptomatic transmission satisfies

$$1 - z = (1-p)\mathcal{R}_s/\mathcal{R}_0. \tag{5}$$

The intrinsic generation-interval distribution depends on the intrinsic proportion of asymptomatic vs. symptomatic transmission and their corresponding intrinsic generation-interval distributions:

$$g(\tau) = z g_a(\tau) + (1-z) g_s(\tau), \tag{6}$$

which allows us to express incidence of infection as a renewal process that depends on previous incidence:

$$i(t) = \mathcal{R}_0 \int_0^\infty i(t-\tau) g(\tau) \mathrm{d}\tau. \tag{7}$$

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 number of infected cases is expected to increase exponentially at rate r at the outset of an outbreak. We note that, in practice, counted cases may largely be of the symptomatic type. Hence, we ask: is the expected ratio of incidence caused by asymptomatic cases vs. symptomatic cases during the outbreak phase the same or different than $z/(1-z)$? The ratio of secondary case production caused by asymptomatic vs. symptomatic individuals during the exponential phase should be

$$\frac{q}{1-q} = \left(\frac{z}{1-z}\right)\left[\frac{\int_0^\infty \exp(-r\tau)g_a(\tau)\mathrm{d}\tau}{\int_0^\infty \exp(-r\tau)g_s(\tau)\mathrm{d}\tau}\right], \tag{8}$$

where q is the fraction of new secondary cases caused by asymptomatic individuals or 'relevance' of asymptomatic cases. The value of q is an unknown feature of outbreaks at the population scale, distinct from p the probability of becoming asymptomatic upon infection or z the intrinsic proportion of asymptomatic transmission.

In order to understand how the shape of asymptomatic and symptomatic generation-interval distributions affects q and $\mathcal{R}_0$, we summarize the distributions in terms of their means and dispersions. Assuming that the intrinsic generation-interval distributions for asymptomatic and symptomatic cases follow gamma distributions with different means, $\bar{G}_a$ and $\bar{G}_s$, and dispersions (represented by squared coefficients of variations), κ_a and κ_s. Then, we have

$$\frac{q}{1-q} = \left(\frac{z}{1-z}\right)\left[\frac{(1+\kappa_s r\bar{G}_s)^{1/\kappa_s}}{(1+\kappa_a r\bar{G}_a)^{1/\kappa_a}}\right]. \tag{9}$$

As is apparent from Eq. (8), relevance q increases with z, i.e., with both p and $\mathcal{R}_a/\mathcal{R}_s$. The consequences for outbreak potential further depends on the relative lengths of generation intervals as well as the relative amount of dispersions in them. In Supplementary Materials, we use a compartmental ordinary differential equations model to show that the duration of infectious period of asymptomatic individuals affects both q and $\mathcal{R}_0$, which is a special case of Eq. (8).

III. RESULTS

Here, given $1/r = 7$ days, $\bar{G}_s = 7$ days, and $\kappa_s = \kappa_a = 0.5$, we evaluate the impacts of intrinsic proportion of asymptomatic transmission z on the realized relevance of asymptomatic infection, given variation in relative mean generation interval $\bar{G}_a/\bar{G}_s$ of asymptomatic cases. We vary $\bar{G}_a/\bar{G}_s$ between 0.5 and 2 and infer q and $\mathcal{R}_0$ compatible with an estimated

value of r from case data given the generation interval distributions of asymptomatic and asymptomatic cases. Across the ranges 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 cases, $\bar{G}_a/\bar{G}_s$, 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 compares the effect of relative mean generation interval of asymptomatic cases, $\bar{G}_a/\bar{G}_s$, on $\mathcal{R}_0$. When $\bar{G}_s < \bar{G}_a$, then the strength $\mathcal{R}_0$ increases with z. This increase arises because asymptomatic infections that have long generation intervals increase the duration of overall generation intervals (see [7]) Conversely, when $\bar{G}_s > \bar{G}_a$ then the strength $\mathcal{R}_0$ decreases with z because short generation intervals of asymptomatic cases reduce the overall mean generation interval. The qualitative effects of z and $\bar{G}_a/\bar{G}_s$ on q and $\mathcal{R}_0$ remain robust when we assume narrower ($\kappa_s = \kappa_a = 0.2$; 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 also have qualitatively similar effects on q and $\mathcal{R}_0$. When the asymptomatic cases have a wider/narrower

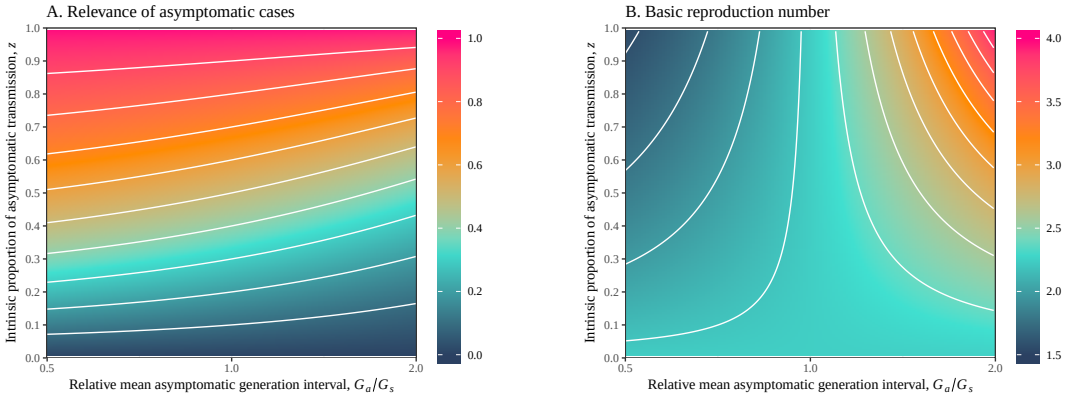

FIG. 1: Effects of intrinsic proportion of asymptomatic transmission on the relevance of asymptomatic transmission and basic reproduction number, given variation in the mean generation interval of asymptomatic cases. (A) Long/short generation intervals of asymptomatic cases decrease/increase the relevance of asymptomatic cases, q. (B) Long/short generation intervals of asymptomatic cases increase/decrease the basic reproduction number $\mathcal{R}_0$. As our baseline parameters, we assume $1/r = 7$ days, $\bar{G}_s = 7$ days, and $\kappa_s = \kappa_a = 0.5$.

generation-interval distribution, higher intrinsic proportion of asymptomatic transmission z increases/decreases the relevance of asymptomatic transmission q but decreases/increases the basic reproduction number (Figure S3). Since a wider generation-interval distribution has a higher proportion of early transmission, it has qualitatively similar effects on q and $\mathcal{R}_0$ as a generation-interval distribution with a small mean.

IV. DISCUSSION

The present findings highlight the need to characterize the course of infection of asymptomatic cases and their consequences not only for contact tracing but for constraining uncertainty in the strength of the ongoing COVID-19 outbreak [8]. 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 [7]. Hence, reports of individuals with mild, persistent cases suggest the possibility that 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 when both asymptomatic and symptomatic cases have identical generation-interval distributions (Figure 1A).

Finally, it is important to note we focused here on the exponential phase, but that the asymptomatic relevance 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 [9]. Characterizing the role of asymptomatic individuals in driving the persistence of the epidemic will be critical for assessing the post-pandemic outcome [10].

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

Supplementary Materials

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. 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:

$$\dot{S} = -\beta_a S I_a - \beta_s S I_s \tag{S1}$$

$$\dot{E} = \beta_a S I_a + \beta_s S I_s - \gamma_e E \tag{S2}$$

$$\dot{I}_a = p\gamma_e E - \gamma_a I_a \tag{S3}$$

$$\dot{I}_s = (1-p)\gamma_e E - \gamma_s I_s \tag{S4}$$

$$\dot{R} = \gamma_a I_a + (1-f)\gamma_s I_s \tag{S5}$$

$$\dot{D} = f\gamma_s I_s. \tag{S6}$$

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

$$r c_a = p\gamma_e c_e - \gamma_a c_a, \tag{S7}$$

$$r c_s = (1-p)\gamma_e c_e - \gamma_s c_s, \tag{S8}$$

which implies that

$$\frac{c_a}{c_s} = \frac{p}{1-p}\left[\frac{r+\gamma_s}{r+\gamma_a}\right]. \tag{S9}$$

Therefore, the ratio of secondary case production caused by asymptomatic vs. symptomatic individuals during the exponential phase should be

$$\frac{q}{1-q} = \left(\frac{\beta_a}{\beta_s}\right) \frac{p}{1-p} \left[\frac{r+\gamma_s}{r+\gamma_a}\right], \tag{S10}$$

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

The basic reproduction number of this system is:

$$\mathcal{R}_0 = p\mathcal{R}_a + (1-p)\mathcal{R}_s, \tag{S11}$$

where

$$\mathcal{R}_a = \frac{\beta_a}{\gamma_a}, \tag{S12}$$

$$\mathcal{R}_s = \frac{\beta_s}{\gamma_s}. \tag{S13}$$

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 exponenitally distributed latent and infectious periods [11]:

$$g_a(\tau) = \frac{\gamma_e\gamma_a}{\gamma_e-\gamma_a}\left(\exp(-\gamma_a\tau) - \exp(-\gamma_e\tau)\right), \tag{S14}$$

$$g_s(\tau) = \frac{\gamma_e\gamma_s}{\gamma_e-\gamma_s}\left(\exp(-\gamma_s\tau) - \exp(-\gamma_e\tau)\right). \tag{S15}$$

It immediately follows that

$$\left(\frac{z}{1-z}\right)\left[\frac{\int_0^\infty \exp(-r\tau)g_a(\tau)\mathrm{d}\tau}{\int_0^\infty \exp(-r\tau)g_s(\tau)\mathrm{d}\tau}\right] = \left(\frac{\beta_a}{\beta_s}\right)\frac{p}{1-p}\left[\frac{r+\gamma_s}{r+\gamma_a}\right], \tag{S16}$$

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

Supplementary figures

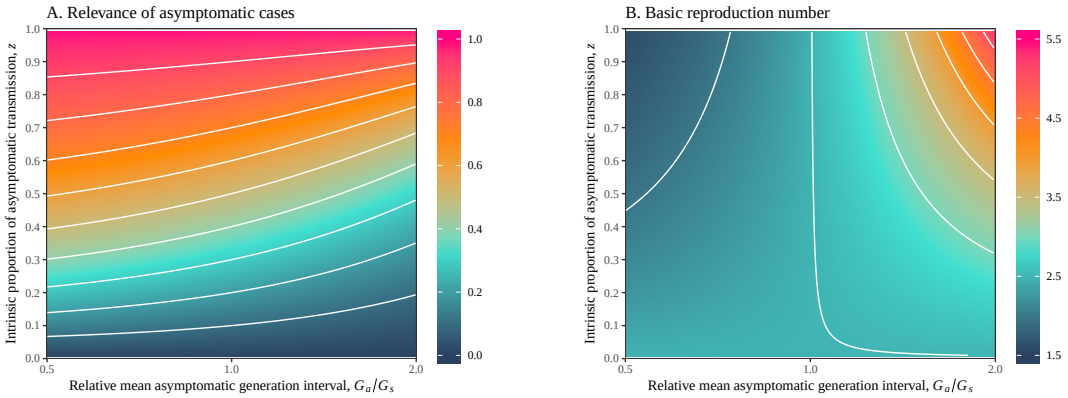

FIG. S1: Effects of intrinsic proportion of asymptomatic transmission on the relevance of asymptomatic transmission and basic reproduction number, given variation in the mean generation interval of asymptomatic cases when generation-interval distributions are narrow. See Figure 1 in the main text for figure caption. Here, we assume $1/r = 7$ days, $\bar{G}_s = 7$ days, and $\kappa_s = \kappa_a = 0.2$.

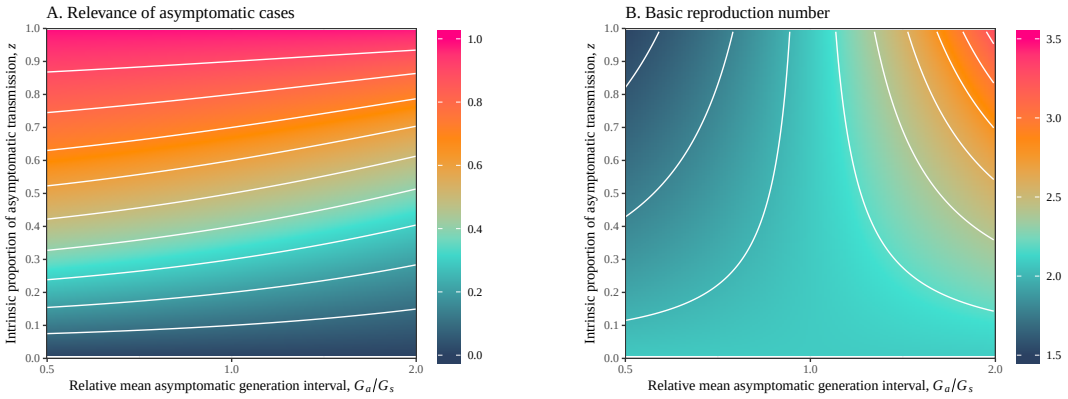

FIG. S2: Effects of intrinsic proportion of asymptomatic transmission on the relevance of asymptomatic transmission and basic reproduction number, given variation in the mean generation interval of asymptomatic cases when generation-interval distributions are wide. See Figure 1 in the main text for figure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

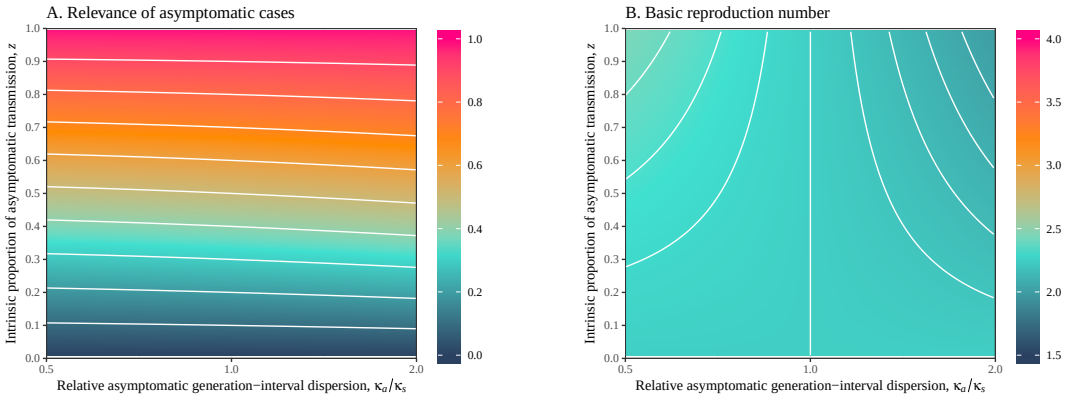

FIG. S3: Effects of intrinsic proportion of asymptomatic transmission on the relevance of asymptomatic transmission and basic reproduction number, given variation in the generation-interval dispersion of asymptomatic cases. (A) Wide/narrow generation intervals of asymptomatic cases increase/decrease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

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