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 interval over which asymptomatic cases are infectious. If the infectious duration 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 duration, $\mathcal{R}_0$ will be over-estimated, and if they have a longer duration, $\mathcal{R}_0$ 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.

Epidemic outbreaks include a spectrum of illness, including asymptomatic cases that can be mild and/or subclinical. As such, 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, albeit poorly characterized factor in the spread of pathogens, as well as present challenges for control. Asymptomatic individuals are hard to trace, unlikely to self-isolate, may move outside of quarantine, retain normal social and travel patterns, and potentially spark new outbreaks. The COVID-19 outbreak has raised significant questions regarding the role of asymptomatic cases [1]. A key focus has

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been on estimating asymptomatic prevalence (see [2]), e.g., what fraction of individuals have asymptomatic infections relative to those with symptomatic infections? Here, we attempt to address the impact of asymptomatic cases differently, by relating individual-level features of asymptomatic cases (e.g., the probability of initiating an asymptomatic case, asymptomatic case duration, and the tranmission 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.

To begin, consider a SEIR model variant in which there are two infectious categories – I_a and I_s – corresponding to asymptomatic and symptomatic cases, respectively. Both types of individuals can infect others, but, only symptomatic cases can lead to fatalities, denoted by the D category. In total, the dynamics of susceptibles, exposed, infectious, recovered, and dead are:

$$\dot{S} = -\beta_a S I_a - \beta_s S I_s \tag{1}$$

$$\dot{E} = \beta_a S I_a + \beta_s S I_s - \gamma_e E \tag{2}$$

$$\dot{I}_a = p\gamma_e E - \gamma_a I_a \tag{3}$$

$$\dot{I}_s = (1-p)\gamma_e E - \gamma_s I_s \tag{4}$$

$$\dot{R} = \gamma_a I_a + (1-f)\gamma_s I_s \tag{5}$$

$$\dot{D} = f\gamma_s I_s. \tag{6}$$

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.

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 I_a/I_s during the outbreak phase the same or different than $p/(1-p)$? In other words, is the ratio of asymptomatic to symptomatic cases population-wide approximately equal to the ratio of asymptomatic to symptomatic cases generated by newly exposed individuals? To answer this question, note that the equations for the infectious cases can be rewritten given the ansatz $E(t) = c_e e^{rt}$, $I_a(t) = c_a e^{rt}$, $I_s(t) = c_s e^{rt}$,

given the prefactors c_e, c_a, and c_s such that

$$rc_a = p\gamma_e c_e - \gamma_a c_a, \tag{7}$$

$$rc_s = (1-p)\gamma_e c_e - \gamma_s c_s, \tag{8}$$

which implies that

$$\frac{c_a}{c_s} = \frac{p}{1-p}\left[\frac{r+\gamma_s}{r+\gamma_a}\right]. \tag{9}$$

Hence, we conclude that, during the exponential growth phase, the intrinsic ratio of asymptomatic to symptomatic cases ($p/(1-p)$) may differ from the realized ratio at the population level (c_a/c_s). Indeed, the ratio of secondary case production caused by asymptomatic vs. symptomatic individuals during the exponential phase should be

$$\frac{q}{1-q} = \left(\frac{\beta_a}{\beta_s}\right)\frac{p}{1-p}\left[\frac{r+\gamma_s}{r+\gamma_a}\right], \tag{10}$$

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. As is apparent from Eq. (10), relevance increases with both p and β_a/β_s. However, the consequences for outbreak potential depends on the relative duration of infectiousness.

Here, given $1/r = 7$ days, $1/\gamma_e = 4$ days, and $1/\gamma_s = 10$ days, we evaluate the impacts of p and β_a/β_s on the relevance of asymptomatic infections, given variation in p, β_a/β_s, and γ_a. We consider two scenarios, one in which asymptomatic infectiousness is short, i.e., with average duration of $1/\gamma_a = 5$ days, and one in which asymptomatic infectiousness is long,i.e., $1/\gamma_a = 20$ days. We use the renewal equation formalism to explicitly link duration of infectiousness to the basic reproductive number (for technical details and example applications see [3–5]). In brief, we infer $\mathcal{R}_0$ compatible with an estimated value of r from case data given the generation interval distribution (set by q and the duration in the exposed and infectious states). By solving for q, we can then relate the basic reproduction number to the relative transmission rates (β_a/β_s) and the probability, p, of asymptomatic cases at the individual scale. Figure 1C shows that when $\gamma_a < \gamma_s$, then the strength $\mathcal{R}_0$ increases with q. This increase arises because asymptomatic infections that resolve slower increase the duration of overall generation intervals (see [6]). In contrast, Figure 1D show that when $\gamma_a > \gamma_s$ then the strength $\mathcal{R}_0$ decreases with q. This decrease arises because asymptomatic infections that resolve faster decrease the duration of overall generation intervals (again,

see [6]). In both cases, the dependence of $\mathcal{R}_0$ on q is compared to a baseline of $\mathcal{R}_0 \approx 3.1$ in a model with no secondary case production from asymptomatic infections (see filled circle at bottom left of Figure 1C-D. In other words, when $\mathcal{R}_0$ is estimated without explicitly accounting for asymptomatic spread, it can be over- or under- estimated depending on the relative duration of infection between symptomatic and asymptomatic individuals.

The present findings highlight the need to characterize the duration of asymptomatic cases and their consequences not only for contact tracing but for constraining uncertainty in the strength of the ongoing COVID-19 outbreak [7]. 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 [6]. 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 $\mathcal{R}_0$ and driving a larger fraction of secondary cases (see Figure 1 top row). However, if asymptomatic cases tend to be shorter, then current estimates of $\mathcal{R}_0$ may be over-estimates of the underlying strength (see Figure 1 bottom row). 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 [8].

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Data Availabililty: All code is available at weitzgroup.github.io.

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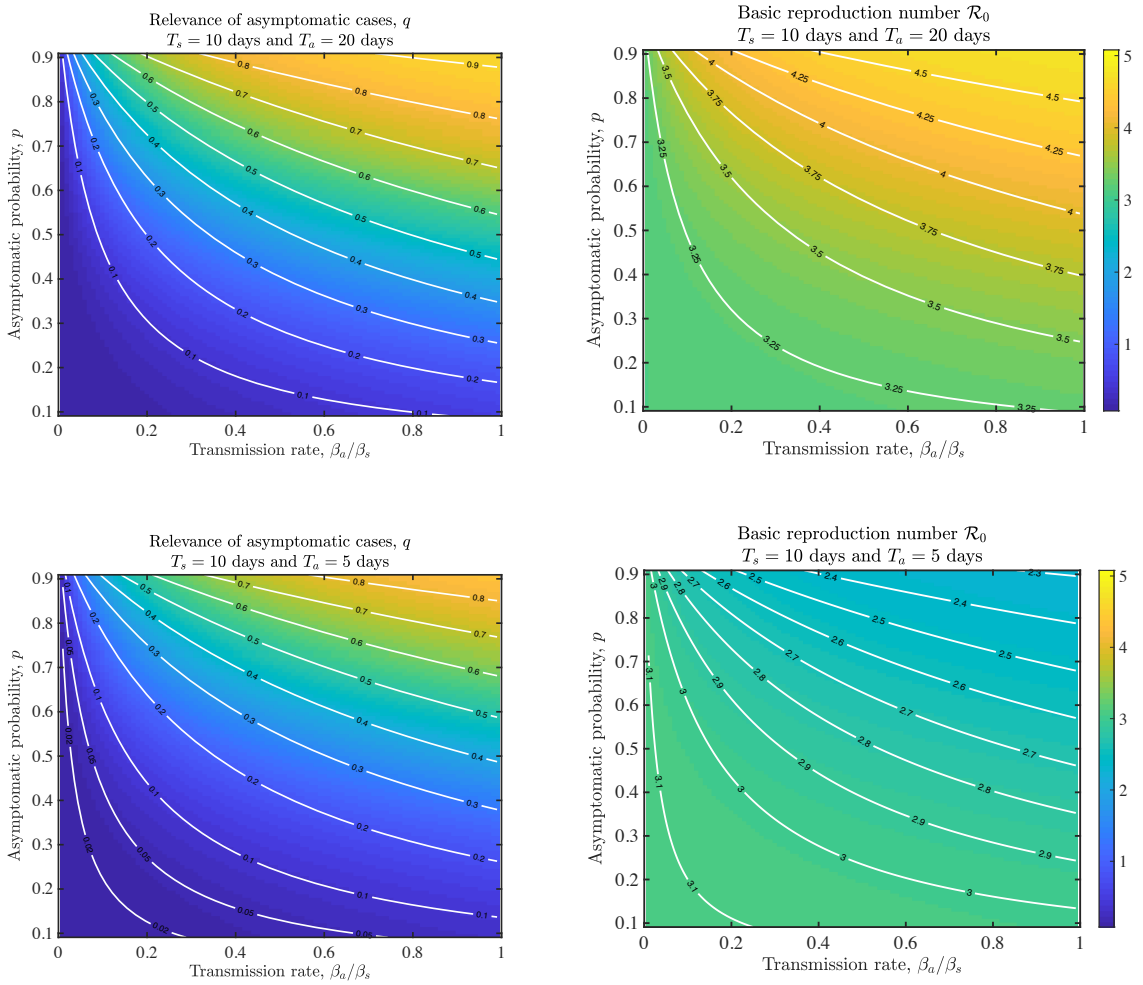

FIG. 1: Relevance of asymptomatic transmission given variation in relative transmission and probability that a given, newly infected individual is asymptomatic. (Top) Long duration asymptomatic cases increase $\mathcal{R}_0$ with increasing relevance. (Bottom) Short duration asymptomatic cases decrease $\mathcal{R}_0$ with increasing relevance. Technically, renewal equations provide a route to connect observed increases in case counts, i.e., $\mathcal{R}_0 = \frac{1}{M(-r)}$ where $M(-r) = \int_0^\infty \mathrm{d}a e^{-ra} g(a)$. For the present model, $M(r) = qM_E(-r)M_{I_a}(-r) + (1-q)M_E(-r)M_{I_s}(-r)$ where each of the component functions are $M_E(-r) = \frac{\gamma_e}{\gamma_e + r}$, $M_{I_a}(-r) = \frac{\gamma_a}{\gamma_a + r}$, $M_{I_s}(-r) = \frac{\gamma_s}{\gamma_s + r}$, and q is the fraction of realized new secondary cases caused by asymptomatic individuals. In all of these heatmaps, $\gamma_e = 1/4$, $\gamma_s = 1/10$, and $r = 1/7$. Here, the average duration in symptomatic and asymptomatic states are $T_s = 1/\gamma_s$ and $T_a = 1/\gamma_a$, respectively. Here the filled circle denotes $\mathcal{R}_0 \approx 3.12$ in the event of $p = 0$ and $\beta_a = 0$, and the open symbols are for $\beta_a/\beta_s = 0.5$ and $p = 0.5$ and $p = 0.9$ for reference.

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