Intermediate levels of asymptomatic transmission can lead to the highest epidemic fatalities

Sang Woo Park[1], Jonathan Dushoff[2,3,4], Bryan T. Grenfell[1,5], Joshua S. Weitz[6,7,8,*]

1 Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ, USA
2 Department of Biology, McMaster University, Hamilton, ON, Canada
3 Department of Mathematics and Statistics, McMaster University, Hamilton, ON, Canada
4 M. G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton, ON, Canada
5 Princeton School of Public and International Affairs, Princeton University, Princeton, NJ, USA
6 School of Biological Sciences, Georgia Institute of Technology, Atlanta, GA, USA
7 School of Physics, Georgia Institute of Technology, Atlanta, GA, USA
8 Institut de Biologie, École Normale Supérieure, Paris, France

*Corresponding author: jsweitz@gatech.edu

Abstract

Asymptomatic infections have hampered the ability to characterize and prevent the transmission of SARS-CoV-2 throughout the pandemic. Although asymptomatic infections reduce severity at the individual level, they can make population-level outcomes worse if asymptomatic individuals—unaware they are infected—transmit more than symptomatic individuals. Using an epidemic model, we show that intermediate levels of asymptomatic infection lead to the highest levels of epidemic fatalities when the decrease in symptomatic transmission, due either to individual behavior or mitigation efforts, is strong. We generalize this result to include presymptomatic transmission, showing ~~how~~ that intermediate levels of non-symptomatic transmission lead to the highest levels of fatalities. Finally, we extend our framework to illustrate how the intersection of asymptomatic spread and immunity profiles determine epidemic trajectories, including population-level severity, of future variants. In particular, when immunity provides protection against symptoms, but not against infections or deaths, epidemic trajectories can have faster ~~infection~~ growth rates and higher ~~peak, which in turn can lead to more deaths. Nonetheless, even a modest~~ peaks, leading to more total deaths. Conversely, even modest levels of protection against infection can mitigate the population-level effects of asymptomatic spread.

Significance

During an epidemic, asymptomatically infected individuals may avoid severe outcomes but can still transmit to others, potentially leading to severe outcomes~~and~~ , including fatalities. This manuscript ~~proposes and~~ analyzes the population-level effects of asymptomatic spread in the presence of strong transmission reduction among symptomatic individuals due to behavioral change and interventions. Theory and simulations reveal that ~~although~~ when reduction is strong the number of infections increases with asymptomatic ~~prevalence, epidemic~~ proportion, while fatalities peak at intermediate levels~~of asymptomatic prevalence~~. The same framework also shows how milder variants at the individual level can potentially lead to worse outcomes for the population—of relevance to ongoing efforts to explore the interplay between behaviour, immunity, and viral variants.

Introduction

SARS-CoV-2 has had devastating effects at the population level. However, many individuals experienced mild cases, making it harder to estimate the magnitude of spread and fatality rate [1]. The ratio of fatalities to documented ~~cases~~ *cases* (the case-fatality rate, CFR) is typically between 1%–4%, varying across population because of testing patterns, treatment practice, case definitions, and other factors [2, 3, 4]. But many infections are never documented; the ratio of fatalities to total ~~infections~~ *infections* (the infection fatality rate, IFR) has been estimated to be closer to 0.5%–1% for pre-vaccinated populations whose demographics are similar to those of the United States [5]. This means that more than 99% of individuals infected with COVID-19 will survive. Moreover, at least half of the infections are sufficiently mild that they could be classified as subclinical or even asymptomatic.

Early in the pandemic, a COVID-19 outbreak on the Diamond Princess cruise ship played a critical role in understanding the role of asymptomatic infections in the spread of SARS-CoV-2; the outbreak occurred among 3711 passengers and crew, of whom 634 individuals tested positive by 20 February 2020 [9]. It has been estimated that 75% (95% ~~C~~CI: 70%-78%) of all infections on the cruise ship were asymptomatic (Fig. 1A) with about half of total infections undetected [6]. The relative transmission rate of asymptomatic individuals aboard the Diamond Princess was not well constrained by the analysis, but low relative transmission rate (below 25%) by asymptomatic individuals was ruled out because it required unrealistically high transmissibility for symptomatic individuals (Fig. 1B).

Modeling studies have typically assumed that transmissibility is lower for asymptomatic than for symptomatic individuals; assumptions have ranged from 10%–100% [10, 11]. Similarities in viral load trajectories of asymptomatic and symptomatic individuals provide indirect support for the transmissibility of asymptomatic individuals (Fig. 1C, [7]); however, differences between inferred ~~total~~ *total* viral load from Ct values and ~~infectious~~ *infectious* viral load add ~~uncertainties to how well asymptomatic individuals can transmit relative to that of symptomatic individuals~~ uncertainty [12]. We note also that asymptomaticity ~~is expected to be more heterogeneous in a diversity of~~ can change across outbreak settings [13]. For example, during the early pandemic, Davies *et al.*'s analyses of surveillance data across six countries revealed that older individuals were less likely to have subclinical infections (Fig. 1D), providing indirect evidence for heterogeneity in asymptomaticity [8]. Differences in contact rates between age classes further contribute to the heterogeneity in asymptomatic transmissibility. For now, we primarily focus on a homogeneous population and return to the age effect in discussing our model-based findings.

Despite quantitative uncertainties in asymptomatic transmissibility, individuals infected asymptomatically with SARS-CoV-2 can still transmit to others. This means that the presence of asymptomatic infections may have countervailing effects at the population level. On one hand, an asymptomatic infection means that the individual infected avoids hospitalization and death. On the other hand, asymptomatic infec-

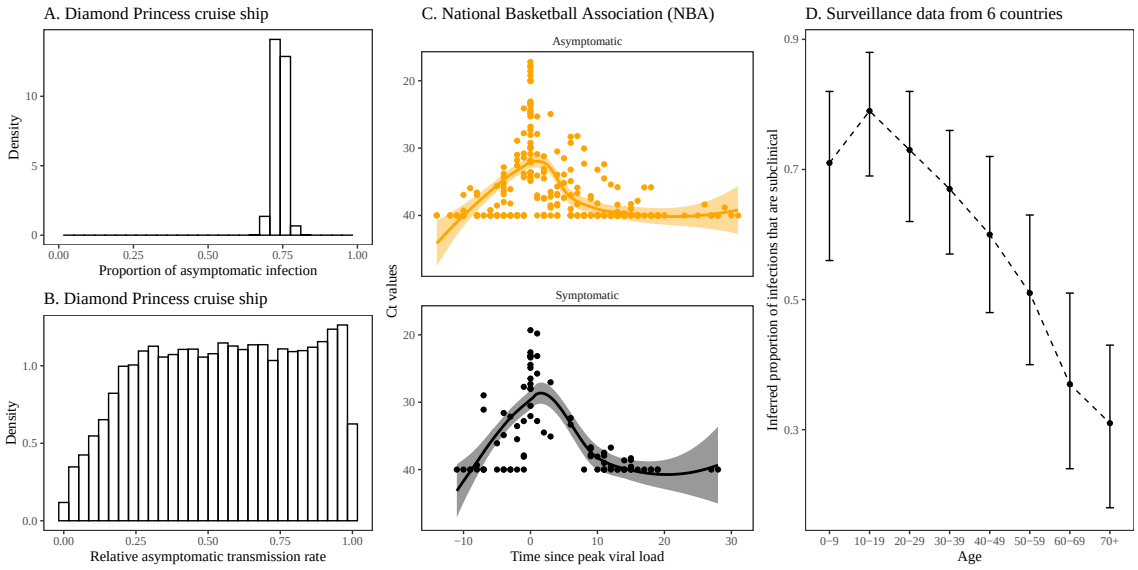

Figure 1: **Asymptomatic transmissibility of SARS-CoV-2.** (A) Posterior estimates of the proportion of asymptomatic infections from the Diamond Princess cruise ship [6]. (B) Posterior estimates of the ratio θ_a of the transmission rates between asymptomatic and symptomatic individuals from the Diamond Princess Cruise Ship [6]. ~~Bar charts represent the posterior distributions.~~ Symptomatic individuals were assumed to transmit at rate $\beta(t)$ for an average of 2.9 days, followed by a pre-symptomatic stage with an average of 2.1 days. Asymptomatic individuals were assumed to transmit at rate $\theta_a\beta(t)$ for an average of 5 days. Both estimates are publicly available with further details in [6]. (C) Viral load trajectory data from players, staff, and vendors of the National Basketball Association (NBA). Points represent each Ct measurement. Lines and shaded areas ~~represent the smooth trajectories estimated via~~ show LOESS ~~and the associated 95% confidence intervals~~fits. [JD: *I don't really like calling them CIs. Maybe say default loess fits from R or something.*] Data are publicly available in [7]. (D) Inferred proportion of infections that are subclinical for each age group using surveillance data from six countries (China, Italy, Japan, Singapore, South Korea, and Canada) [8].

tions are less likely to be detected [14, 15], meaning that asymptomatic individuals are less likely to take precautions and relatively more likely to infect others; asymptomatic SARS-CoV-2 infections present additional challenges to managing overall disease burden due to the possibility of long COVID [16].

In this manuscript, we explore the effects of asymptomatic infection and transmission on disease severity at the population level. In doing so, we assume that symptomatic individuals reduce their transmission, reflecting changes in behavior (e.g., self-isolation after symptom onset) and/or nonpharmaceutical intervention measures. Under this assumption, we show that ~~the prevalence~~ a high proportion of asymptomatic infections could paradoxically make population-level outcomes worse than

if SARS-CoV-2 was more dangerous at the individual level. We further extend our framework to understand the interaction between immunity against symptomatic infections on the dynamics of emerging variants and explore mechanisms by which milder variants at the ~~individual-level~~ individual level can nonetheless lead to similar or worse population-level outcomes.

Results and Discussion

We propose an epidemic model ~~,~~in which infected individuals can be asymptomatic or symptomatic, with probabilities p and $1-p$, respectively (Fig. 2A). Asymptomatic individuals always recover, whereas a fraction f of symptomatic individuals die. Asymptomatic and symptomatic individuals can also have different infection characteristics, including their transmission rates (β_a and β_s) and removal rates (γ_a and γ_s). Our key assumption is that symptomatic individuals take greater precautions than do asymptomatic individuals (e.g., ~~via~~ reducing contacts or ~~increased~~ increasing mask-wearing) and therefore reduce their transmission rate by a fraction δ; the parameter δ may also capture intervention measures that target symptomatic individuals, such as symptom-based isolation. We note that intervention measures that target asymptomatic infections would reduce the effective value of δ—for example, frequent testing and isolation may effectively increase the removal rate γ_a of asymptomatic individuals. For our main simulations, we assume that asymptomatic individuals have a lower reproduction number—this is ~~modeled by assuming~~ implemented via lower transmission rates for asymptomatic individuals ($\beta_a = 0.75\beta_s$) and equal removal rates ($\gamma_a = \gamma_s$). We then evaluate the effects on population-level mortality of changing the asymptomatic proportion p while holding the fatality rate ~~for~~ *for symptomatic cases*, f, constant (the population-level IFR $(1-p)f$ thus decreases as p increases).

Fig. 2B–C shows simulated epidemic outcomes using parameters similar to those of the originating strain of SARS-CoV-2 (Table S1), without any mitigation other than that individuals who are symptomatic reduce their transmission rate by δ. For this model, the basic reproduction number is given by:

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

where $\mathcal{R}_s = \beta_s/\gamma_s$ and $\mathcal{R}_a = \beta_a/\gamma_a$ represent the reproduction numbers of asymptomatic and symptomatic individuals (i.e., the average number of secondary infections caused by asymptomatic and symptomatic individuals); therefore, in the absence of the behavioral effect ($\delta = 0$), the final size decreases with the asymptomatic proportion p because more symptomatic infections leads to a higher basic reproduction number.

This relationship changes as δ increases. In particular, when $\delta > 1 - \mathcal{R}_a/\mathcal{R}_s$ (in this case, $\delta > 0.25$), the basic reproduction number (and thus epidemic size) increases with p because the effective symptomatic reproductive number (including behavioral

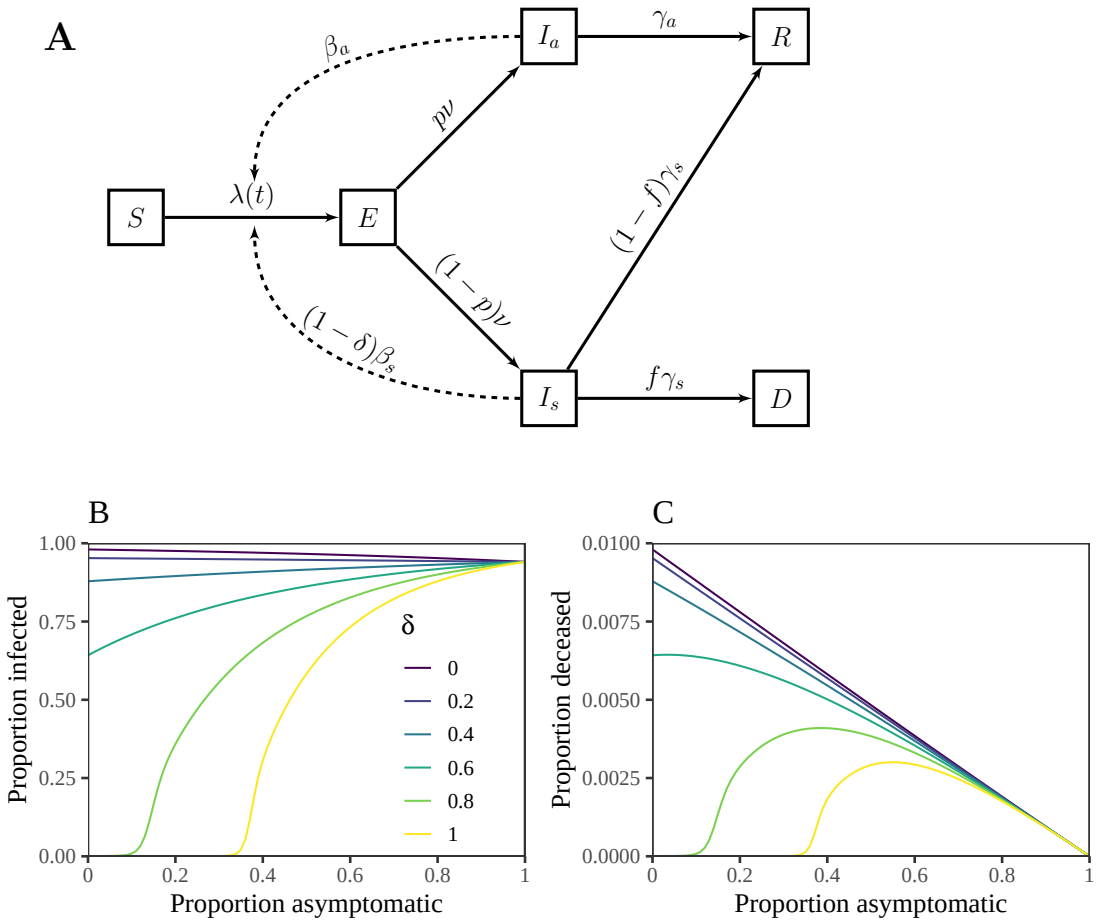

Figure 2: **Schematic diagram and simulations of a model with asymptomatic transmission and symptom-responsive transmission reduction.** (A) S represents susceptible individuals; E represents exposed individuals; I_a represents asymptomatic individuals; I_s represents symptomatic individuals; R represents recovered individuals; and D represents deceased individuals. See Methods for model details. (B) Total infections as a function of the proportion of asymptomatic infections p across a wide range scenarios for δ. (C) Total deaths as a function of the proportion of asymptomatic infections p across a wide range scenarios for δ. We simulate the model for 365 days, assuming $\beta_s = 0.8$/day, $\beta_a = 0.75\beta_s$, $\nu = 0.5$/day, $\gamma_s = \gamma_a = 0.2$/day, and $f = 0.01$, and an initial exposed proportion of 10^{-4}. See Materials and Methods for model details and Supplementary Table S1 for parameter descriptions and values.

response) is less than that the asymptomatic reproductive number. ~~For high values of δ~~When $\delta > 1 - 1/\mathcal{R}_s$(and $\mathcal{R}_a > 1$), we can find a critical ~~level of~~ asymptomatic

proportion, p_c:

$$p_c = \frac{1 - (1-\delta)\mathcal{R}_s}{\mathcal{R}_a - (1-\delta)\mathcal{R}_s} \tag{2}$$

such that an outbreak will occur exactly when $p > p_c$ ~~is required for an outbreak~~ (see threshold effects for large values of δ in Fig. 2B).

When behavioral protection is high, the effect of asymptomatic proportion on fatalities shows countervailing effects of individual-level protection and population-level risk (Fig. 2C). For high values of δ, the peak fatality occurs at intermediate levels of asymptomatic spread: although fewer individuals die per infection for higher values of p, the increase in total infections ~~also~~ still leads to an increase in total fatalities. In contrast, when δ is small enough ~~such~~ that $(1-\delta)\mathcal{R}_s \geq \mathcal{R}_a$ (in this case, $\delta < 0.25$), ~~then total fatalities decrease with p because because~~ both the number of infections and the IFR ($(1-p)f$) decrease with increasing p. [JD: *Got rid of a few words that might imply that this is necessary as well as sufficient for a decreas*

~~High~~ We can ask whether the high values of δ required for the nonlinear effects of asymptomaticity on deaths ~~may seem unrealistic~~are realistic. For this particular model, it does not make biological sense for δ to be greater than the amount of post-symptomatic transmission, because pre-symptomatic transmission is implicitly included in the I_s compartment. While several studies have estimated the proportion of pre-symptomatic transmission to be around 30%–60% for the SARS-CoV-2 wildtype strain, many of these were likely affected by intervention and behavioral effects, as they were conducted after SARS-CoV-2 awareness became widespread [17]. Instead, [18] recently estimated that the proportion of pre-symptomatic transmission could have been as low as 20% (95%CI: 6%–32%) during the first few weeks of the pandemic when the pandemic-awareness and intervention measures were minimal. There are two implications of this updated estimate—first, a low proportion of pre-symptomatic transmission ~~suggests that~~ makes high δ values ~~are feasible (although not necessarily likely)~~ at least somewhat more likely during the initial pandemic phase; and second, intermediate levels of behavioral effects ($\delta > 0$) would have been already present early in the pandemic to reduce the proportion of pre-symptomatic transmission from 80% to as low as 40%.

We therefore extend our model to consider the effects of generalized *non-symptomatic* transmission, which includes both pre-symptomatic and asymptomatic transmission~~, to ask the following question: does an intermediate amount of non-symptomatic transmission lead to a peak in fatalities?~~ . For this model, we assume that δ decreases transmission only after symptom onset. We then fix the reproduction number of symptomatic individuals and calculate fatalities at the population level as a function of the proportion of total non-symptomatic transmission and the proportion of non-symptomatic transmission that is caused by pre-symptomatic transmission (see Materials and Methods for model details and Supplementary Table S2 for parameter descriptions and values).

Using the generalized non-symptomatic transmission model, we find a wide vari-

ety of scenarios for which peak fatalities occur at intermediate levels of non-symptomatic transmission in the presence of moderate to strong behavioral effects, $\delta > 0.6$ (Supplementary Figure S1; Table S2). One exception is the extreme (and unrealistic) case, in which all non-symptomatic transmission is caused by pre-symptomatic transmission (i.e., there are no asymptomatic cases); in this case, total infections and fatalities are maximized when all transmission is caused by pre-symptomatic transmission. Hereafter, we focus on asymptomatic infections for simplicity, but our conclusions have implications for the more general case of non-symptomatic transmission.

We now apply our framework to understand the impact of immunity on total fatalities at the population scale by dividing the population into two groups: immunologically naive and protected. For simplicity, we do not distinguish whether the immunity is derived from natural infections or vaccines. The dynamics of immunologically naive individuals are equivalent to our original model (Fig. 2). The dynamics of protected individuals include three additional parameters, which characterize the amount of protection against infection ϵ_i, symptoms (given infection) ϵ_s, and deaths (given symptoms) ϵ_d (Fig. 3). For simplicity, we assume that the population is split in half (50% naive and 50% protected) and mixes homogeneously. We also do not consider the separate effect of immunity on transmission (beyond the effect on infection). In other words, we assume that asymptomatic infections in protected and unprotected people have the same reproduction numbers (and likewise for the symptomatic infections). In practice, both asymptomatic and symptomatic infections in protected people are less likely to transmit than their unprotected counterparts [19]: asymptomatic infections in protected people may indicate limited viral replication or even immune boosting, in which case an exposed individual may successfully fight off the pathogen early in infection before it can be transmitted; and symptomatic infections in protected people may reflect a strong immune response (rather than high viral load), in which case symptomaticity can be a poor proxy for transmission. We assume a relatively strong behavioral effect $\delta = 0.8$ for illustration (Table S3).

We consider each protection effect—ϵ_i, ϵ_s, and ϵ_d—separately and consider joint effects later on. The impact of protection against infection ϵ_i is analogous to changing $\mathcal{R}_0$ in the original model: as immunity provides stronger protection against infection (higher ϵ_i), the number of deaths decreases and a higher asymptomatic fraction p is required for the infection to spread (Fig. 3B). We note that protection against infection scales the fatality curve nonlinearly, reflecting the nonlinear relationship between $\mathcal{R}_0$ and the final size of the outbreak. The impact of protection against symptoms ϵ_s is equivalent to changing the asymptomatic fraction p for the protected population because protected individuals are less likely to develop symptoms: the peaks of the fatality curves move to lower values of p as we increase the degree of protection ϵ_s (Fig. 3C). Therefore, for low values of p, protection against symptoms can increase the total number of fatalities at the population level by increasing the proportion (and number) of asymptomatic individuals, who can readily transmit infections to other individuals. This also means that the critical ~~level of~~ asymptomatic

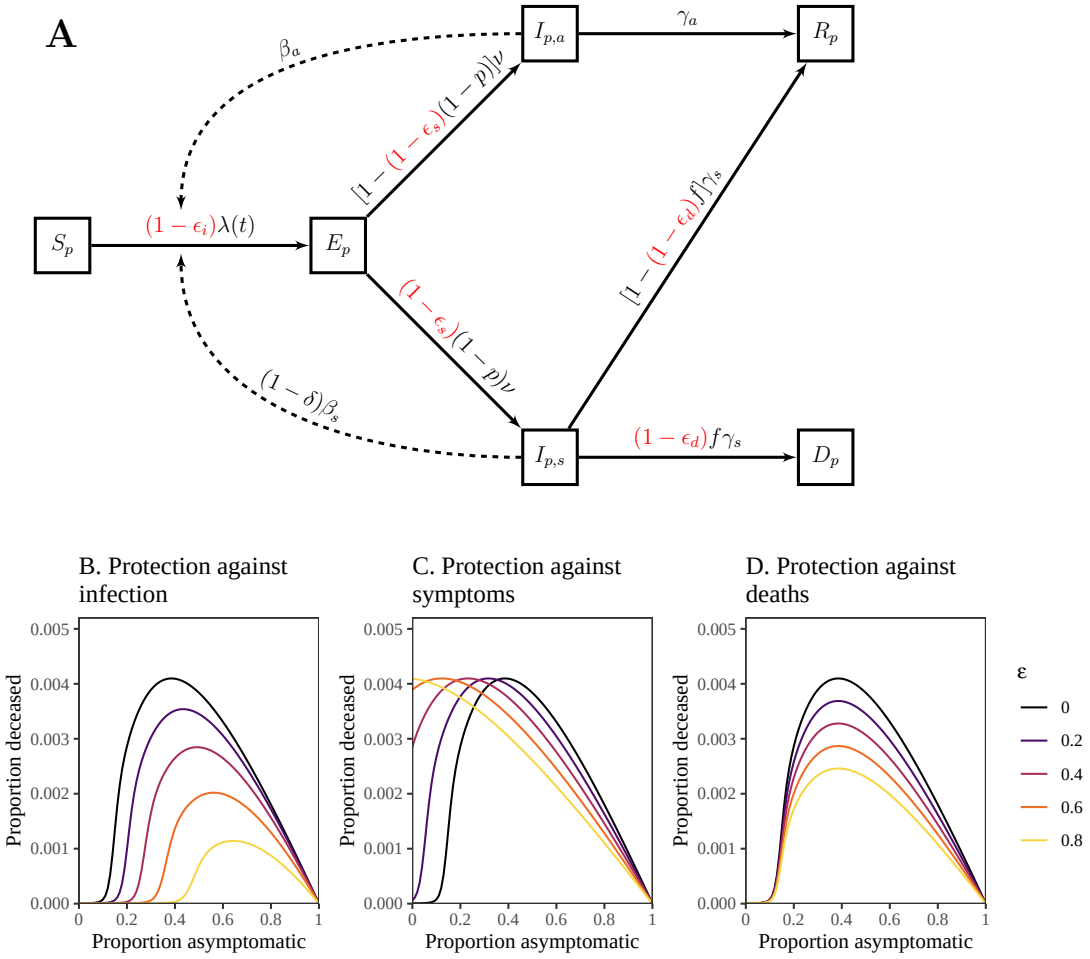

Figure 3: **Schematic diagram and simulations of a model with symptom-responsive transmission reduction and immunity.** (A) The subscript p represents protected individuals. Immunity may provide protection against infection, symptoms, or deaths. The dynamics of immunologically naive individuals are described in Fig. 2. (B–D) Total deaths as a function of the proportion of asymptomatic infections p across a wide range scenarios for protection against infection ϵ_i (B), symptoms ϵ_s (C), and deaths ϵ_d (D). We simulate the model for 365 days, assuming $\beta_s = 4/5/\text{day}$, $\beta_a = 0.75\beta_s$, $\nu = 1/2/\text{day}$, $\gamma_s = \gamma_a = 1/5/\text{day}$, $f = 0.01$, and $\delta = 0.8$. ~~We assume that 10^{-4}~~ [JD: *Please change all fractions to decimals in above s.*] The initial exposed proportion ~~of individuals are initially infected~~is 10^{-4}. See Materials and Methods for model details and Supplementary Table S3 for parameter descriptions and values.

proportion decreases, allowing more dangerous infections (with lower p) to invade, which would not have been able to spread in an otherwise immunologically naive population. We note that the equivalence between protection against symptoms ϵ_s and

fraction asymptomatic p relies on our assumption that immunity does not provide protection against transmission. Protection against deaths ϵ_d directly modulates the fatality rate for symptomatic cases and therefore linearly scales the fatality curves (Fig. 3D).

Finally, we use our framework to understand the impact of behavioral effects on invading variants (Fig. 4). ~~In doing so, we~~ We first simulate the dynamics of a wildtype variant for 1 year using our base model ~~using identical~~ with parameters as in Fig. 2. We then simulate a new variant invading a partially immune population using our extended model (Fig. 3A), where the immunity is solely derived from natural infections caused by the wildtype variant in the first year. We consider two types of variants (which are simulated separately): one with the same severity p (variant 1, orange) and a milder one with higher p (variant 2, purple). [JD: *The more severe variant has the same severity. There is no conceptual problem, but I'm worried*

First, we consider a scenario in which immunity only provides protection against symptoms, $\epsilon_s = 0.4$ (Fig. 4A–C). In this case, protection against symptoms allows new variants to spread faster by increasing the amount of asymptomatic infections, resulting in larger outbreaks (Fig. 4B). Although the milder (purple) variant exhibits a faster epidemic growth rate and reaches a higher peak (Fig. 4B), it reaches similar peak fatality as the more severe (orange) variant (Fig. 4C). The asymptomaticity–fatality curve provides additional insight (Fig. 4A): even though a milder, invading variant (purple square) gives higher peak fatality than the original, wildtype variant (black circle), it leads to lower fatalities overall because deaths are concentrated over a shorter period of time in the epidemic; the relatively severe second-wave variant causes more deaths than the wildtype first wave, despite causing many fewer cases. In general, when δ is large, invading variants with similar asymptomaticity p will spread more effectively and result in worse population-level outcomes if immunity (either from vaccination or natural infection) provides protection against symptoms but not against infection or transmission.

Next, we consider a more realistic scenario in which immunity provides protection against both symptoms, $\epsilon_s = 0.4$, and infection, $\epsilon_i = 0.4$ (Fig. 4D–F). In this case, cross-protection against infection has a large effect on the more severe (orange) variant, causing its peak infection prevalence (Fig. 4E) and fatality (Fig. 4F) to be lower than that of the original, wildtype variant. Across a wide range of asymptomatic proportion p, we find that this immunity profile is sufficient to prevent worse outcomes at the population level; we note that the second wave of deaths is still high (and having higher peaks in some cases) even if the overall deaths are lower.

The outcomes in our simulations of invading variants resemble the dynamics of the SARS-CoV-2 Omicron variant. Despite moderate levels of vaccine effectiveness against symptomatic and reduced levels of severe cases caused by the Omicron variant, especially after booster shots [20], both vaccine- and infection-derived immunity provided limited protection against infections [21]. This immune evasion helped the Omicron variant to cause more infections in South Africa than previous variants [22].

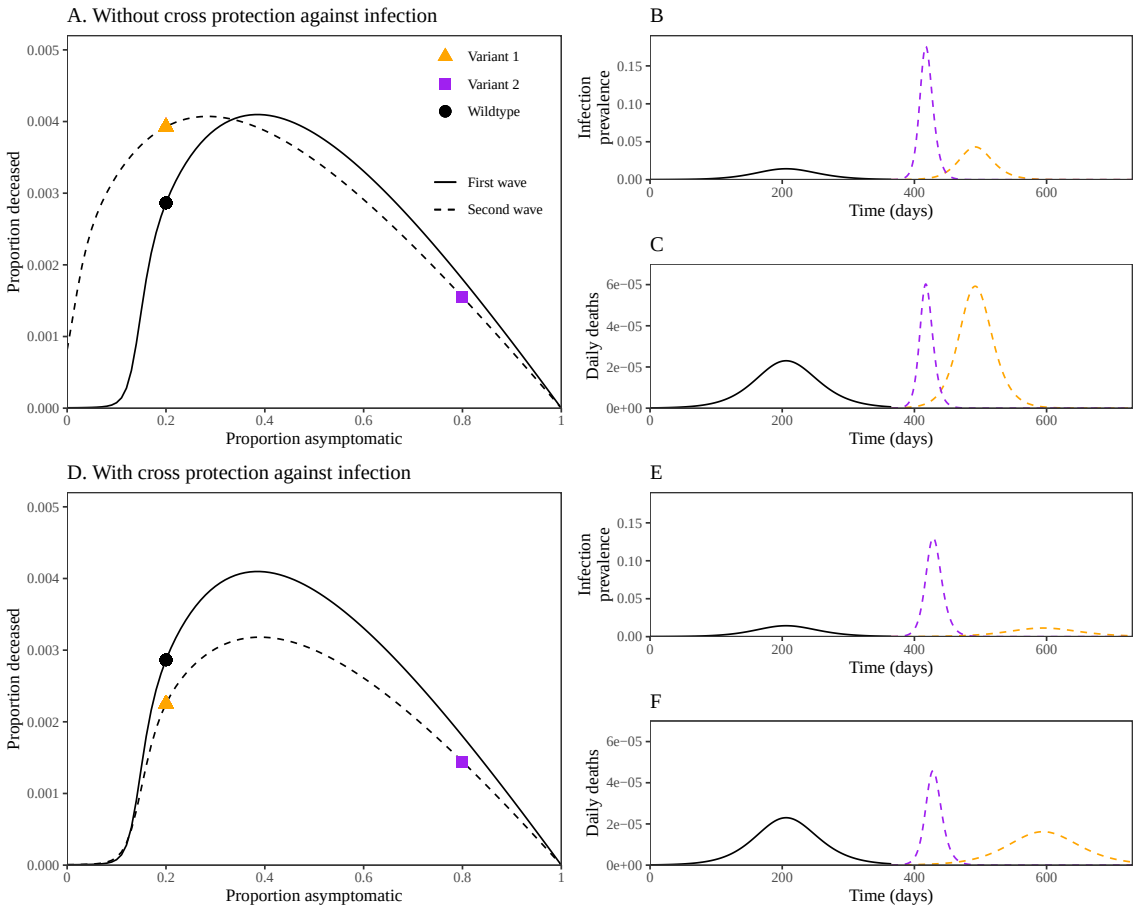

Figure 4: **Dynamics of invading variants under symptom-responsive transmission reduction and immunity.** (A, D) Asymptomaticity–fatality curves for the first (solid lines) and second waves (dashed lines). Points represent specific scenarios we assume for the first and second waves. Fatality curves for the first wave are calculated by simulating an epidemic for 1 year using parameters from Fig. 2 with $\delta = 0.8$. Fatality curves for the second wave are calculated by first simulating the first wave assuming $p = 0.2$ for 1 year to calculate the proportion immune and then simulating the extended model presented in Fig. 3 for ~~two different values of p as shown~~*either* a milder ($p = 0.8$) or a not-milder ($p = 0.2$) variant. [JD: *not-milder is not an actual sugggestion. . .*] (B, E) Dynamics of infection prevalence for the wildtype variant (black, solid line) and ~~two possible~~ milder (purple) and similar (orange) invading variants (~~colored,~~ dashed ~~line~~lines). (C, F) Dynamics of daily deaths for the wildtype variant (black, solid line) and two possible invading variants (colored, dashed line).

Moreover, even though the Omicron variant is probably milder than the Delta variant [23, 24], the number of hospitalizations and deaths caused by the Omicron variant was higher than those caused by the Delta variant in many locations [25, 26, 27].

There are several limitations to our analysis. First, while we are able to generalize the model to include both pre-symptomatic and asymptomatic transmission, behavioral and intervention effects must be relatively large in order for the fatality to peak at intermediate levels of asymptomaticity (typically requiring a reduction in transmission rate of 60% or more for most of our chosen parameter sets). Second, the model framework is able to incorporate the impacts of immunity of infection, symptoms, and severity, but we neglected ~~the~~ additional specific effects of immunity on transmission, which ~~also has~~ can also have important effects on disease dynamics [28, 29]. In particular, if immunity provides stronger protection against transmission among immune individuals, population-level outcomes will be better than what our model predicts. Estimating protection against different endpoints (e.g., infection, symptom, death, and transmission) can help narrow this uncertainty. Finally, we assumed that asymptomatic and symptomatic individuals are infected for the same amount of time. Analysis of viral load trajectories suggests that asymptomatic individuals may clear infections faster [7]; however, asymptomatic individuals may still transmit for a longer period of time if symptomatic individuals self-isolate quickly after symptom onset. The individual-level differences in the asymptomatic and symptomatic transmission time scale can have important implications for the inferences and predictions of pathogen dynamics [30, 31]; nonetheless, we expect that predictions on the final size of the epidemic and total fatalities will be robust to small differences in the transmission time scale between asymptomatic and symptomatic individuals.

Even though we assumed a homogeneous population ~~throughout~~here, our analysis also has important implications for age-dependent heterogeneity in asymptomaticity (as shown in Fig. 1D). For example, vaccinations and intervention measures primarily targeting older individuals can prevent severe infections and improve individual-level outcomes. However, asymptomatic individuals, especially younger individuals with high contact rates, can still transmit to other, older individuals, potentially making population-level outcomes worse than they would be if intervention measures were distributed differently. We note that other factors, such as the efficacy of a vaccine and types of immunity provided by the vaccine, also play critical roles in making these decisions—in many cases, protecting the most vulnerable will be the optimal decision to minimize deaths [32].

Via theory and simulation analysis of a series of simplified models, we have shown that asymptomatic infections (or, more generally, non-symptomatic transmission) can ~~represent a double-edged sword leading~~ under some conditions lead to a better outcome for many individuals while facilitating onward transmission that leads to a worse outcome for the population as a whole. Extending our framework further shows that immunity profile (i.e., reduction of infection, symptoms, and/or severity due to immunity) plays a critical role in determining the dynamics of future variants; these results extend previous work on post-pandemic trajectories that focus primarily on cross-immunity [33, 34]. For example, while protection against symptoms ~~unaccompanied by protection against transmission~~ protects health at the individual

level, it can lead to more infections, and potentially more deaths, at the population level. A similar concern was raised in prioritizing vaccine choices that could reduce severe outcomes vs. others that could reduce transmission [35].

As is increasingly evident, SARS-CoV-2 has proven hard to control in large part because transmission is often decoupled from symptoms. Our model reinforces the need for dual approaches—prioritizing the reduction of asymptomatic spread (e.g., via risk awareness campaigns [36, 37, 38], asymptomatic testing programs [39, 40, 41], mask-wearing indoors and in crowded environments [42, 43, 44], and through improvements in ventilation [45, 46]) while also improving the treatment of symptomatic cases, particularly amongst older individuals at highest risk for severe outcomes. Given the link between age and asymptomatic infections [8], interventions may consider different approaches in strongly age-structured populations (e.g., schools or long-term care facilities). Mass vaccination is also expected to be important especially if future vaccines induce more transmission blocking. As more variants continue to emerge, monitoring the impacts of preexisting immunity (whether through vaccination and/or infections [47]) on preventing infections, and not just disease, will be critical to controlling the course of the pandemic.

Materials and Methods

Epidemic models with asymptomatic infection and transmission in the absence of immunity

We consider a compartmental model with asymptomatic and symptomatic infections in a homogeneously mixing population. The basic model dynamics are as follows:

$$\dot{S} = -\beta_a S I_a - (1-\delta)\beta_s S I_s \tag{3}$$

$$\dot{E} = \beta_a S I_a + (1-\delta)\beta_s S I_s - \nu E \tag{4}$$

$$\dot{I}_a = p\nu E - \gamma_a I_a \tag{5}$$

$$\dot{I}_s = (1-p)\nu E - \gamma_s I_s \tag{6}$$

$$\dot{R} = \gamma_a I_a + (1-f)\gamma_s I_s \tag{7}$$

$$\dot{D} = f\gamma_s I_s \tag{8}$$

where the transmission rate β and removal rate γ can be potentially differ between asymptomatic and symptomatic individuals. Here, δ denotes the reduction in transmissibility due to responsive measures taken by symptomatic individuals. Throughout the paper, we use parameters that are broadly consistent with the dynamics of the originating strain of SARS-CoV-2: $\beta_s = 0.8$/day, $\beta_a = 0.75\beta_s$, $1/\nu = 2$ days, $1/\gamma_s = 1/\gamma_a = 5$ days, and $f = 0.01$ [48]. Under this parameterization, we have symptomatic and asymptomatic reproduction numbers of $\mathcal{R}_s = 4$ and $\mathcal{R}_a = 3$.

We then extend this model to include both pre-symptomatic and asymptomatic transmission:

$$\dot{S} = -\beta_p I_p - \beta_a S I_a - (1-\delta)\beta_s S I_s \tag{9}$$

$$\dot{E} = \beta_a S I_a + (1-\delta)\beta_s S I_s - \nu E \tag{10}$$

$$\dot{I}_p = \nu E - \sigma I_p \tag{11}$$

$$\dot{I}_a = p\sigma I_p - \gamma_a I_a \tag{12}$$

$$\dot{I}_s = (1-p)\sigma I_p - \gamma_s I_s \tag{13}$$

$$\dot{R} = \gamma_a I_a + (1-f)\gamma_s I_s \tag{14}$$

$$\dot{D} = f\gamma_s I_s \tag{15}$$

For this generalized model, the pre-symptomatic $\mathcal{R}_p$, symptomatic $\mathcal{R}_s$, and asymptomatic $\mathcal{R}_a$ reproduction numbers are given by $\mathcal{R}_p = \beta_p/\sigma$, $\mathcal{R}_s = \beta_s/\gamma_s$, and $\mathcal{R}_a = \beta_a/\gamma_a$ in the absence of the behavioral effect; these reproduction numbers represent the average number of secondary cases caused by an infected individual in each compartment. Then, the reproduction number of individuals who will eventually develop symptoms is equal to: $\mathcal{R}_p + \mathcal{R}_s$; similarly, the reproduction number of individuals who remain asymptomatic is equal to: $\mathcal{R}_p + \mathcal{R}_a$. Since the proportion p of all infections is asymptomatic, the basic reproduction number is given by the weighted average of these two reproduction numbers:

$$\mathcal{R}_0 = p(\mathcal{R}_p + \mathcal{R}_a) + (1-p)(\mathcal{R}_p + \mathcal{R}_s) = \mathcal{R}_p + p\mathcal{R}_a + (1-p)\mathcal{R}_s. \tag{16}$$

Then, the proportion of non-symptomatic transmission ϕ is given by:

$$\phi = \frac{\mathcal{R}_p + p\mathcal{R}_a}{\mathcal{R}_0}. \tag{17}$$

For simulations of the combined model, we start by fixing the reproduction number of individuals who will eventually develop symptoms: $\mathcal{R}_{\text{symp}} = \mathcal{R}_p + \mathcal{R}_s = 4$. Consistent with previous assumptions, we also assume that asymptomatic reproduction number is lower than that of the symptomatic reproduction number: $\mathcal{R}_a = \rho\mathcal{R}_s$ where $\rho = 0.75$. Then, for a given value of the proportion of non-symptomatic transmission ϕ and proportion of non-symptomatic transmission caused by the pre-symptomatic transmission, $\eta = \mathcal{R}_p/(\mathcal{R}_p + p\mathcal{R}_a)$, we can solve for the transmission rate for each compartment β and the proportion asymptomatic p. More specifically:

$$\mathcal{R}_p = \frac{\mathcal{R}_{\text{symp}}}{1+y} \tag{18}$$

$$\mathcal{R}_s = \mathcal{R}_{\text{symp}} - \mathcal{R}_p \tag{19}$$

$$\mathcal{R}_a = \rho\mathcal{R}_s \tag{20}$$

$$p = \left(\frac{1}{\eta} - 1\right)\frac{\mathcal{R}_p}{\mathcal{R}_a}, \tag{21}$$

where $y = (1/\phi - 1)/\eta + (1/\eta - 1)/\rho$. In order to keep the mean infectious period fixed, we assume $1/\sigma = 2$ days and $1/\gamma_s = 1/\gamma_a = 3$ days. All other parameters are same as before.

Epidemic models with asymptomatic infection and transmission in the presence of immunity

We model the spread of infection in a partially immune population as follows:

$$\dot{S} = -\lambda(t)S \tag{22}$$
$$\dot{E} = \lambda(t)S - \nu E \tag{23}$$
$$\dot{I}_a = p\nu E - \gamma_a I_a \tag{24}$$
$$\dot{I}_s = (1-p)\nu E - \gamma_s I_s \tag{25}$$
$$\dot{R} = \gamma_a I_a + (1-f)\gamma_s I_s \tag{26}$$
$$\dot{D} = f\gamma_s I_s \tag{27}$$
$$\dot{S}_p = -(1-\epsilon_i)\lambda(t)S_p \tag{28}$$
$$\dot{E}_p = (1-\epsilon_i)\lambda(t)S_p - \nu E_p \tag{29}$$
$$\dot{I}_{p,a} = (1-(1-\epsilon_s)(1-p))\nu E_p - \gamma_a I_{p,a} \tag{30}$$
$$\dot{I}_{p,s} = (1-\epsilon_s)(1-p)\nu E_p - \gamma_s I_{p,s} \tag{31}$$
$$\dot{R}_p = \gamma_a I_{p,a} + (1-(1-\epsilon_d)f)\gamma_s I_{p,s} \tag{32}$$
$$\dot{D}_p = (1-\epsilon_d)f\gamma_s I_{p,s} \tag{33}$$

where $0 \leq \epsilon_i, \epsilon_s, \epsilon_d \leq 1$ represents the degree of protection against infection, symptoms and death, respectively. The force of infection $\lambda(t)$ is given by:

$$\lambda(t) = \beta_a(I_a + I_{p,a}) + (1-\delta)\beta_s(I_s + I_{p,s}). \tag{34}$$

Here, subscripts p denote individuals who are immune and therefore are protected, and as before the subscripts a and s denote asymptomatic and symptomatic infections.

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Data availability

All data and code are stored in a publicly available GitHub repository (`https://github.com/parksw3/asymptomaticvariant`).

Supplementary Tables

Parameter	Description	Assumed values
β_s	Symptomatic transmission rate	0.8/days
β_a	Asymptomatic transmission rate	$0.75\beta_s$
$1/\nu$	Mean latent period	2 days
$1/\gamma_s$	Mean symptomatic infectious period	5 days
$1/\gamma_a$	Mean asymptomatic infectious period	5 days
p	Proportion asymptomatic	0–1
f	Fatality rate for symptomatic case	0.01
δ	Reduction in symptomatic transmission rate	0–1

Table S1: ~~Paramter~~ Parameter descriptions and values for the basic asymptomatic model.

Parameter	Description	Assumed values
β_s	Symptomatic transmission rate	See Materials and Methods
β_a	Asymptomatic transmission rate	See Materials and Methods
β_p	Presymptomatic transmission rate	See Materials and Methods
$1/\nu$	Mean latent period	2 days
$1/\sigma$	Mean presymptomatic infectious period	2 days
$1/\gamma_s$	Mean symptomatic infectious period	3 days
$1/\gamma_a$	Mean asymptomatic infectious period	3 days
p	Proportion asymptomatic	0–1
f	Fatality rate for symptomatic case	0.01
δ	Reduction in symptomatic transmission rate	0–1

Table S2: ~~Paramter~~ Parameter descriptions and values for the generalized asymptomatic model.

Parameter	Description	Assumed values
β_s	Symptomatic transmission rate	0.8/days
β_a	Asymptomatic transmission rate	$0.75\beta_s$
$1/\nu$	Mean latent period	2 days
$1/\gamma_s$	Mean symptomatic infectious period	5 days
$1/\gamma_a$	Mean asymptomatic infectious period	5 days
p	Proportion asymptomatic	0–1
f	Fatality rate for symptomatic case	0.01
δ	Reduction in symptomatic transmission rate	0–1
ϵ_i	Protection against infection	0–0.8
ϵ_s	Protection against symptoms	0–0.8
ϵ_d	Protection against deaths	0–0.8

Table S3: ~~Paramter~~ Parameter descriptions and values for the asymptomatic model with immunity.

Supplementary Figures

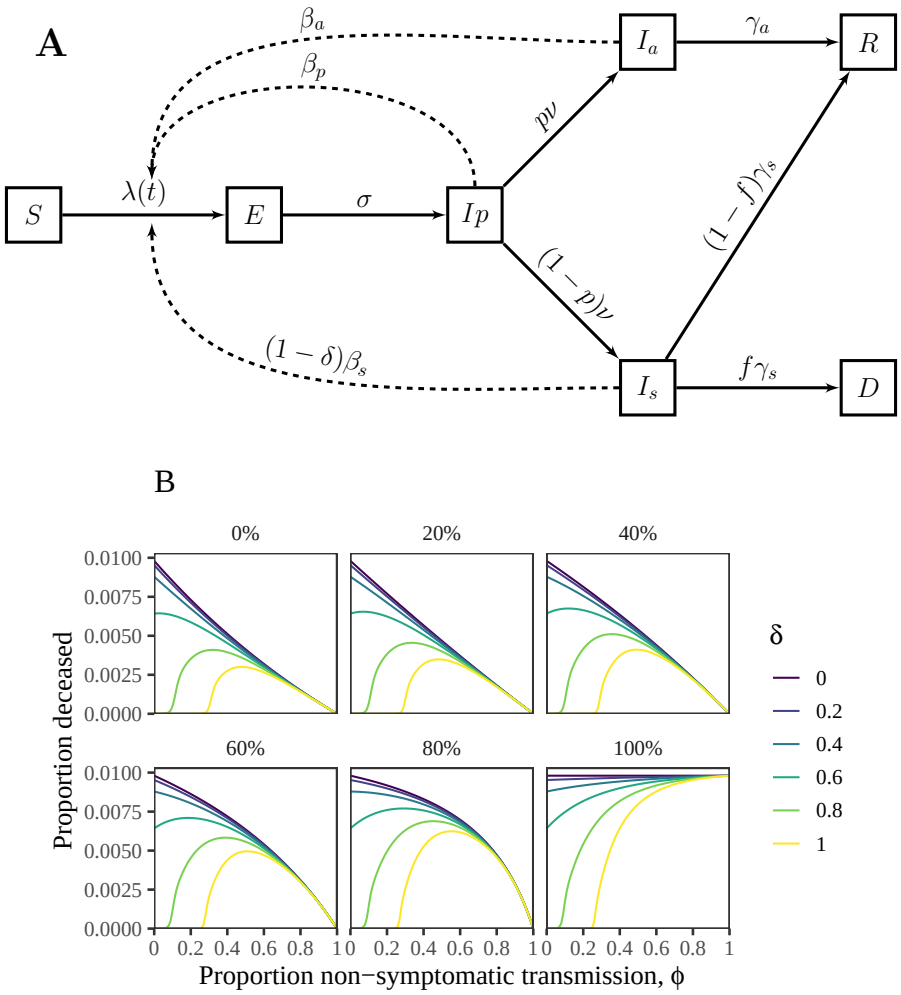

Figure S1: **Schematic diagram and simulations of a model with pre-symptomatic and asymptomatic transmission and symptom-responsive transmission reduction.** (A) S represents susceptible individuals; E represents exposed individuals; I_p represents pre-symptomatic individuals; I_a represents symptomatic individuals; I_s represents symptomatic individuals; R represents recovered individuals; and D represents deceased individuals. See Methods for model details. (B) Total deaths as a function of the proportion of non-symptomatic transmission ϕ across a wide range scenarios for δ and proportion of non-symptomatic transmission caused by the pre-symptomatic transmission, η (between 0% and 100%). See Materials and Methods for model details and Supplementary Table S2 for parameter descriptions and values.

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