Individual-level differences in symptomatic and asymptomatic transmission shape population-level dynamics of SARS-CoV-2 outbreaks

Jeremy D. Harris[1,*], Sang Woo Park[2,*], Jonathan Dushoff[3,4,5], Joshua S. Weitz[1,6,7]

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

* These authors contributed equally.

Corresponding Authors:
Joshua S. Weitz: E-mail: jsweitz@gatech.edu
Jonathan Dushoff: E-mail: dushoff@mcmaster.ca

Abstract

The transmission time scale of SARS-CoV-2 may vary across individual disease statuses, potentially biasing population-level estimates of epidemic strength, speed, and controllability. Here, we use a series of nonlinear epidemic models to study the impact of differences in time scales between asymptomatic and symptomatic transmission of SARS-CoV-2 on the relative contribution of asymptomatic infections to epidemic dynamics. We build on prior work and show that differences in time scales of transmission may impact estimates of disease severity throughout the course of the epidemic due to changes in the realized proportion of asymptomatic transmission. We do so in two parts. First, we examine dynamics when transmission outcomes and disease statuses are correlated: that is, transmission from asymptomatic (symptomatic) individuals is more likely to lead to new asymptomatic (symptomatic) infections. Second, we examine dynamics given age-dependent assortative mixing coupled with intrinsic differences in symptomaticity with age. In both cases we find that the realized proportion of asymptomatic transmission and realized proportion of asymptomatic incidence increase over time as total incidence decreases. Moreover, when coupling differences in time scales with age-dependent assortative mixing, we find that the age distribution of infections shifts to younger ages as incidence decreases. These results show the importance of considering differences in time scales of transmission when interpreting mechanisms underlying shifts in the realized proportion of asymptomatic transmission during SARS-CoV-2 outbreaks.

1 Introduction

The role of asymptomatic carriers in driving epidemic dynamics has remained a key question throughout the SARS-CoV-2 pandemic [2, 6, 15, 23]. Asymptomatic carriers have reduced the effectiveness of non-pharmaceutical intervention efforts, such as contact tracing, [4, 7, 12, 15, 16, 34] and have made it more difficult to obtain unbiased estimates of disease severity, including infection fatality ratios [27]. Although several studies have estimated the prevalence of asymptomatic SARS-CoV-2 infections in various settings [18–22], there is still considerable uncertainty in how the transmission dynamics of asymptomatic individuals differ from those of symptomatic individuals. Modeling studies have typically assumed that asymptomatic and symptomatic individuals are infected for an equal amount of time. Some studies have further accounted for the possibility that asymptomatic individuals may be less transmissible than symptomatic individuals, but the range of assumptions vary widely (from 90% less transmissible [11] to equally transmissible [17]).

Prior work has shown that differences in transmission time scales between asymptomatic and symptomatic transmission can have important implications for estimates of epidemic dynamics during the exponential growth phase [25]. For example, if asymptomatic individuals are able to transmit for a longer period of time than symptomatic individuals, the proportion of new infections attributable to asymptomatic transmission will be lower than predicted based on their intrinsic infectiousness because shorter transmission intervals drive the spread during the epidemic growth phase. Under the same scenario, failing to account for differences in time scales of asymptomatic and symptomatic transmission can lead to underestimation of the basic reproduction number (i.e., the average number of secondary infections caused by a primary case [1, 9, 10, 30]) from the epidemic growth rate [25]. These differences in transmission time scales can be driven by both biological (e.g., longer viral shedding period [19]) and behavioral factors (e.g., self-isolation of symptomatic individuals).

The impact of transmission time scale differences on epidemic inference can be better understood using a generation interval-based framework [13]. The generation interval is the time between when an individual is infected and when that individual transmits to another person [5, 29, 31, 32]. The generation interval distribution connects time scale differences in individual-level transmission pairs to population-level dynamics [24]. For example, given an observed epidemic growth rate, a disease with longer generation intervals will be associated with a higher reproduction number [24].

In addition to variation in time intervals of transmission, asymptomatic and symptomatic infections may also correlate with transmission outcomes. That is, new infections caused by asymptomatic transmission may be more likely to remain asymptomatic than new infections caused by symptomatic individuals, leading to correlations between disease statuses of the infector and of the infectee. Such correlations might arise from dose-dependent responses to infection: recent animal model studies of COVID-19 have shown dose-dependent responses [JD: what is "with respect to"? Do we have direct evidence for shedding response to inoculum (as implied here)? Or do we not have that (as implied by "Hence..." just below?] with respect to viral shedding and clinical severity, with a higher initial viral inoculum resulting in more severe outcomes [14, 28]; data from animal model studies of other human coronaviruses, including SARS-CoV, have shown similar trends [33]. Hence, if symptomatic infections typically shed more infectious virus than asymptomatic infections, then the initial viral dose from symptomatic transmission would be higher than from asymptomatic transmission. Higher

initial viral loads might make symptomatic infections more likely, in which case correlations between disease statuses of the infector and the infectee.

Correlations might also arise from age-dependent assortativity in mixing patterns and variation in symptomaticity. Higher contact rates among individuals of similar ages (e.g., in schools) causes more transmission within similar age groups (as opposed to between different age groups). As disease symptomaticity of SARS-CoV-2 varies with age [8, 34], disease statuses of infectees may effectively correlate with disease statuses of their infectors. Irrespective of the mechanism, we predict that such correlations can have important dynamical consequences when they are coupled with the effects of differences in time scales of transmission: if the proportion of new infections attributable to asymptomatic transmission changes over the course of an epidemic, these correlations can further drive changes in the realized proportion of asymptomatic incidence.

In this manuscript, we examine the impacts of individual-level differences between asymptomatic and symptomatic transmission on population-level disease dynamics. First, we consider the possibility that asymptomatic individuals may transmit for longer periods than symptomatic individuals. We show that longer generation intervals of asymptomatic transmission can cause the realized proportion of asymptomatic transmission to increase as the incidence of infection declines after reaching its peak—this pattern is robust whether decline is driven by susceptible depletion or by changes in effective contacts. Second, we additionally account for the correlations between transmission outcomes and individual disease statuses. In this case, we find again that the proportion of asymptomatic transmission as well as incidence can increase as epidemic declines. Finally, we study dynamics of an age-dependent model that includes assortative mixing and increasing chances of asymptomatic infections for younger individuals. In this particular example, we find that asymptomatic incidence and transmission increase over time, especially as total cases decline. Notably, when interventions reduce overall transmission rates, we find that the average age of an incident infection decreases (albeit to a lesser extent than with susceptible depletion) as a result of coupling longer time scales of asymptomatic transmission with increased assortative mixing. Together, these analyses demonstrate how time scales of transmission can lead to substantial changes in the realized importance of asymptomatic transmission throughout epidemics.

2 Methods

2.1 SEIR model of asymptomatic transmission with a fixed intrinsic proportion of asymptomatic incidence

We study the impact of transmission time scales on epidemic dynamics using a series of Susceptible-Exposed-Infectious-Recovered (SEIR) models with asymptomatic and symptomatic transmission. Once infected, susceptible individuals enter an exposed but latent stage, during which they cannot transmit. The first model assumes that a fixed proportion p—which we refer to as the intrinsic proportion of asymptomatic infections—of newly infected individuals remains asymptomatic over the course of infection while transmitting at rate β_a. The remaining proportion $1-p$ develops symptoms after the exposed period and transmit at rate β_s. Then, the proportion of individuals in each compartment can be described by the following set of

equations:

$$\begin{aligned}
\dot{S} &= -\left(\lambda_a(t) + \lambda_s(t)\right)\, S \\
\dot{E}_a &= p\,\left(\lambda_a(t) + \lambda_s(t)\right)\, S - E_a/\tau \\
\dot{E}_s &= (1-p)\,\left(\lambda_a(t) + \lambda_s(t)\right)\, S - E_s/\tau \\
\dot{I}_a &= E_a/\tau - I_a/T_a \\
\dot{I}_s &= E_s/\tau - I_s/T_s \\
\dot{R} &= I_a/T_a + I_s/T_s\ , \qquad (1)
\end{aligned}$$

where subscripts denote asymptomatic (a) vs. symptomatic (s) classes. [JD: maybe have a display eqn for λ; it's a more critical level of explication than the T here.] Here, $\lambda_a(t) = \beta_a\, I_a$ ($\lambda_s(t) = \beta_s\, I_s$) is the force of infection caused by asymptomatic (symptomatic) individuals, $1/\tau$ is the mean exposed period, and T_a (T_s) is the mean duration of asymptomatic (symptomatic) infectious periods.

For this model, the subgroup reproduction number of asymptomatic (symptomatic) individuals is given by $\mathcal{R}_{0,a} = \beta_a\, T_a$ ($\mathcal{R}_{0,s} = \beta_s\, T_s$) and defined as the number of secondary infections caused by a single asymptomatically (symptomatically) infected individual in a fully susceptible population. The basic reproduction number of the system is the weighted average of the two subgroup reproduction numbers:

$$\mathcal{R}_0 = p\,\mathcal{R}_{0,a} + (1-p)\,\mathcal{R}_{0,s}. \qquad (2)$$

Then, we can define [useful for explanation to write the long version of the denominator as well – JD] the intrinsic proportion of asymptomatic transmission, which represents the relative contribution of asymptomatic transmission towards the basic reproduction number [25]:

$$z = \frac{p\,\mathcal{R}_{0,a}}{\mathcal{R}_0}. \qquad (3)$$

[JD: the ff. s. reads pretty tautological. skip?] The intrinsic proportion of asymptomatic transmission provides an equilibrium measure for the importance of asymptomatic transmission. [JD: Maybe define q first and say that it *is* z when the T are the same, *then* say haow they can differ.] However, the realized proportion of asymptomatic transmission (i.e., the proportion of new infections caused by asymptomatically infected individuals) can systematically differ from the intrinsic proportion of asymptomatic transmission if the time scales of transmission differ between symptomatic and asymptomatic infections:

$$q(t) = \frac{\lambda_a(t)}{\lambda_a(t) + \lambda_s(t)}\ . \qquad (4)$$

Here, we generalize prior work [25], which focused on the initial exponential growth phase, and explore how the realized proportion of asymptomatic transmission changes over the course of an epidemic when we assume that asymptomatic infections have longer generation intervals. We fix the mean infectious period to $T_s = 5$ days for symptomatic and $T_a = 8$ days for asymptomatic infections; the mean exposed period is set to $\tau = 3$ days for both groups. To compare across simulations, we fix the intrinsic proportion of asymptomatic infections ($p = 0.4$) and [JD: pick what? a multiplier for β to] match the exponential growth rate ($r = 0.14$/day). We show

simulations for both susceptible depletion and intervention scenarios. For intervention, rates of asymptomatic and symptomatic transmission are reduced equally and the effective reproduction number is reduced over a period of 30 days. The mitigation intensities are such that the final effective reproduction numbers match those in the susceptible depletion scenario for each infectious period. See Table 1 for parameter descriptions and Figure S1 for model schematic.

2.2 SEIR model of asymptomatic transmission with correlations between transmission and disease

Next, we introduce correlations between transmission outcomes and disease statuses: that is, transmission from asymptomatic (symptomatic) individuals is more likely to lead to new, asymptomatic (symptomatic) infections. To study the effects of such correlations on epidemic dynamics, we extend the first model in Eq. (1) and write the following set of equations:

$$\begin{aligned}
\dot{S} &= -\left(\lambda_a(t) + \lambda_s(t)\right) S \\
\dot{E}_a &= \left(p_{a|a}\,\lambda_a(t) + p_{a|s}\,\lambda_s(t)\right) S - E_a/\tau \\
\dot{E}_s &= \left((1-p_{a|a})\,\lambda_a(t) + (1-p_{a|s})\,\lambda_s(t)\right) S - E_s/\tau \\
\dot{I}_a &= E_a/\tau - I_a/T_a \\
\dot{I}_s &= E_s/\tau - I_s/T_s \\
\dot{R} &= I_a/T_a + I_s/T_s \ .
\end{aligned} \tag{5}$$

Here, $p_{a|a}$ ($p_{a|s}$) is the proportion of new asymptomatic infections caused by asymptomatic (symptomatic) transmission, whereas $p_{s|a} = 1 - p_{a|a}$ ($p_{s|s} = 1 - p_{a|s}$) is the proportion of new symptomatic infections caused by asymptomatic (symptomatic) transmission. When $p_{a|a} = p_{a|s}$, the model in Eq. (5) reduces to the first model in Eq. (1).

For this model, the realized proportion of asymptomatic transmission is the same as in Eq. (4). On the other hand, the realized proportion of asymptomatic incidence may change over time when time scales of transmission differ:

$$p(t) = \frac{p_{a|a}\,\lambda_a(t) + p_{a|s}\,\lambda_s(t)}{\lambda_a(t) + \lambda_s(t)}. \tag{6}$$

To explore the effect of correlated transmission, we break the symmetry by increasing $p_{a|a}$ and decreasing $p_{a|s}$ such that the initial realized proportion of asymptomatic incidence is equal to the intrinsic proportion of asymptomatic incidence, $p = 0.4$. In doing so, we match the exponential growth rate ($r = 0.14$/day) across simulations. These constraints provide a baseline for studying changes in the proportion of asymptomatic transmission due to differences in time scales of transmission, due to correlations between transmission and disease status, or due to the interplay between them. See Table 1 for parameter descriptions and Figure S1 for model schematic.

2.3 SEIR model of asymptomatic transmission with assortative mixing and variation in susceptibility/symptomaticity by age

Finally, we study an age-stratified model that includes age-dependent mixing patterns coupled with variation in disease factors by age as an example of how correlations can arise between

transmission outcomes and disease statuses. If younger individuals are more likely to remain asymptomatic and assortatively mix with younger individuals, then asymptomatic infections will effectively cause more asymptomatic infections than symptomatic infections. We stratify the population into age groups spanning intervals of 10 years, going from 0-9 ($n = 1$) up to 60-69 ($n = 7$) with the last group being 70+ ($n = 8$). Each age group n consists of 6 compartments (S_n, $E_{n,a}$, $E_{n,s}$, $I_{n,a}$, $I_{n,s}$, and R_n) representing the number of individuals in each disease state such that $S_n + E_{n,a} + E_{n,s} + I_{n,a} + I_{n,s} + R_n = A_n$, where A_n is the population size in age group n. We study the impact of differences in time scales between asymptomatic and symptomatic transmission on both the relative contribution of asymptomatic infections and changes in the age distribution of infections.

We model the contact patterns between the age groups by including an empirically estimated fixed contact matrix, $(C_{n,m})_{n,m=1}^{N}$, where $C_{n,m}$ is the average number of contacts (per day) that individuals in age group n make with individuals in age group m [35]. In our simulations, we use the baseline contact estimates of Shanghai that were empirically estimated prior to the COVID-19 outbreak, which shows a high degree of age-dependent assortative mixing [35] (See Table S1). To be consistent with estimates of contact rates, we let A_n be the age distribution of the population of Shanghai. We allow variation in the proportion of asymptomatic incidence with respect to age, p_n [8]. Early estimates of susceptibility also included variation in susceptibility with respect to age, α_n, with older individuals tending to be more susceptible to infection than younger individuals [8]. However, these data may underestimate asymptomatic infections, which tend to occur in younger individuals and thus underestimate susceptibility to infection in younger individuals. Thus, in Figure 3 we include equal susceptibility across all age groups (setting $\alpha_n = 1$ for all n) and for comparison, allow for variation in susceptibility in Figure S5. See Table 1 for parameter descriptions. **[SWP:** *how did we chose β_s and β_a for this model? It looks like β_a is suddenly much lower....*]

Then, the number of individuals in each age group and disease state can be described by the following set of equations:

$$\begin{aligned}
\dot{S}_n &= -\left(\lambda_{a,n}(t) + \lambda_{s,n}(t)\right) S_n \\
\dot{E}_{a,n} &= p_n \left(\lambda_{a,n}(t) + \lambda_{s,n}(t)\right) S_n - E_{a,n}/\tau \\
\dot{E}_{s,n} &= (1 - p_n) \left(\lambda_{a,n}(t) + \lambda_{s,n}(t)\right) S_n - E_{s,n}/\tau \\
\dot{I}_{a,n} &= E_{a,n}/\tau - I_{a,n}/T_a \\
\dot{I}_{s,n} &= E_{s,n}/\tau - I_{s,n}/T_s \\
\dot{R}_n &= I_{a,n}/T_a + I_{s,n}/T_s \ ,
\end{aligned} \tag{7}$$

where the forces of infection for each age group n due to asymptomatic (a) and symptomatic (s) transmission are given by

$$\begin{aligned}
\lambda_{a,n}(t) &= \beta_a \left(\sum_{m=1}^{N} C_{n,m} \frac{I_{a,m}(t)}{A_m} \right) \alpha_n \\
\lambda_{s,n}(t) &= \beta_s \left(\sum_{m=1}^{N} C_{n,m} \frac{I_{s,m}(t)}{A_m} \right) \alpha_n .
\end{aligned} \tag{8}$$

As before, we compute the realized proportion of asymptomatic transmission over time

$$q(t) = \frac{\sum_{n=1}^{N} \lambda_{a,n}(t)\, S_n(t)}{\sum_{n=1}^{N} \left(\lambda_{a,n}(t) + \lambda_{s,n}(t)\right)\, S_n(t)}\,, \tag{9}$$

as well as the realized proportion of asymptomatic incidence over time,

$$p(t) = \frac{\sum_{n=1}^{N} p_n\, \left(\lambda_{a,n}(t) + \lambda_{s,n}(t)\right)\, S_n}{\sum_{n=1}^{N} \left(\lambda_{a,n}(t) + \lambda_{s,n}(t)\right)\, S_n}\,. \tag{10}$$

We also calculate the average age of an incident infection over time:

$$\bar{a}(t) = \sum_{n=1}^{N} M_n \left(\frac{i_n(t)}{i(t)}\right)\,, \tag{11}$$

where M_n is the midpoint of age group n, $i_n(t) = \left(\lambda_{a,n}(t) + \lambda_{s,n}(t)\right)\, S_n$ is the incidence of age group n, and $i(t) = \sum_{n=1}^{N} i_n(t)$ is the total incidence across all age groups.

Table 1. Parameters, Values, Descriptions. SEIR models with asymptomatic and symptomatic infections. Parameters for age-dependent model are below the double line. In practice we evaluate the age-dependent model including variation in asymptomatic incidence with age, while considering either constant or varying susceptibility to infection with age. **[SWP:** *any way we can make age-dependent model parameters clearer? maybe make a model column? or add an empty row that say "age-dependent model"?*]

Parameter	Value	Description
β_a	0.33-0.48 days^{-1}	Transmission rate of asymptomatic infections (days^{-1})
β_s	0.33-0.48 days^{-1}	Transmission rate of symptomatic infections
T_a	5-8 days	Infectious period of asymptomatic infections, respectively (days)
T_s	5 days	Infectious period of symptomatic infections (days)
τ	3 days	Exposed period or latent stage (days)
r	0.14 days^{-1}	Exponential growth rate
$\mathcal{R}_0$	2.42-2.63	Basic reproduction number
p	0.4	Proportion of new infections that are asymptomatic
$p_{a\|a}$	0.7	Proportion asymptomatic incidence caused by asymptomatic transmission
$p_{a\|s}$	0.20-0.24	Proportion asymptomatic incidence caused by symptomatic transmission
β_a	0.00785-0.0365	Transmission rate of asymptomatic infections
β_s	0.0492-0.100	Transmission rate of symptomatic infections
$\mathcal{R}_0$	2.40-2.65	Basic reproduction number
α_n	[8], Fig. 2b	Susceptibility to infection for age group n
p_n	[8], Fig. 2b	Proportion of asymptomatic incidence for age group n
A_n	[35], Table S3	Population age distribution of Shanghai
$C_{n,m}$	See Table S1	Average number of contacts between individuals in age group n with individuals in age group m

3 Results

3.1 Differences in time scales of transmission lead to changes in the realized proportion of asymptomatic transmission over time

We study the effects of differences in transmission time scales using the SEIR model with asymptomatic and symptomatic transmission and fixed intrinsic proportion of asymptomatic incidence, p. To do so, we simulate the model under two scenarios: (1) when the epidemic spreads without mitigation, 'Susceptible Depletion' and (2) when interventions reduce intrinsic transmission rates of asymptomatic and symptomatic infections equally, 'Intervention.' Since the exponential growth rate is matched across simulations, the incidence curves start off identically across all simulations (Figure 1A,E). Moreover, when time scales of asymptomatic transmission are longer than symptomatic transmission, incidence curves decay more slowly ($T_a = 6$ days, purple and $T_a = 6$ days, light blue) compared to when time scales of transmission

equal ($T_a = T_s = 5$ days). When time scales of asymptomatic transmission are longer than symptomatic transmission, the realized proportion of asymptomatic transmission, $q(t)$ (Eq. (4)), is initially lower than the intrinsic proportion, z and increases over time as total incidence decreases (Figure 1B,F). The realized proportion of asymptomatic incidence remains constant over time and equals the intrinsic proportion of asymptomatic incidence, $p = 0.4$, regardless of differences in time scales (Figure 1C,G). In the intervention scenarios, the mitigation intensities are such that the final effective reproduction numbers match those in the susceptible depletion scenario for each infectious period (Figure 1D,H). As a result, changes in the realized proportion of asymptomatic transmission are comparable between susceptible depletion (Figure 1B) and intervention scenarios (Figure 1F). [**SWP:** *Why do we say they're comparable instead of identical?*] [**SWP:** *Can we change the Y axis and panels D and H so we can tell the values of R?*]

We further investigate how the magnitude and timing of intervention affect the realized proportion of asymptomatic transmission. When we fix the final effective reproduction and vary the mitigation onset time, we find that the resulting realized proportion of asymptomatic transmission $q(t)$ is identical across all scenarios because $q(t)$ is determined by the exponential decay rate (Figure S2A-D). When we fix the mitigation onset time and vary the final effective reproduction number, we find that more intense interventions cause incidence to decay faster, which in turn corresponds to a larger increase in the realized proportion of asymptomatic transmission (Figure S2E–G).

We obtain similar results when we assume transmission rates are equal for asymptomatic and symptomatic infections (Figure S3) (rather than assuming the basic reproduction numbers equal as in Figure 1). The magnitude of changes in the proportion of asymptomatic transmission are identical. [**SWP:** *identical to what? do you mean between suceptible depletion vs intervention? or equal transmission vs equal reproduction?*] The one difference is in the initial realized proportion of asymptomatic transmission. When transmission rates are equal, the initial realized proportion of asymptomatic transmission is higher than the intrinsic proportion of asymptomatic transmission (Figure S3B,F), whereas when reproduction numbers are equal, the initial realized proportion is lower than the intrinsic proportion (Figure 1B,F).

3.2 Correlations between transmission and disease status lead to changes in the realized proportion of asymptomatic incidence

Next, we study the effects of correlations between transmission outcomes and disease statuses of the infectors on epidemic dynamics across two scenarios (with and without intervention). We account for potential differences in the time scales of asymptomatic and symptomatic transmission and introduce correlations by allowing the proportion of new asymptomatic infections caused by asymptomatic transmission to be higher than that caused by symptomatic transmission (i.e., $p_{a|a} > p_{a|s}$).

When the time scales of asymptomatic and symptomatic transmission are equal, correlations between transmission outcomes and disease statuses have no effect on epidemic dynamics, and incidence curves (Figure 2A,E; dashed dark blue) are identical to those in the case without correlations (Figure 1A,E; solid dark blue). As a result, the realized proportions of asymptomatic transmission and incidence remain constant over time; both of these values are equal to their corresponding intrinsic values (Figure 2B,F and C,G; dashed dark blue). Longer asymptomatic generation intervals slow the decay of incident infections with correlations (Figure 2A,E; dashed light blue) and without correlations (Figure 2A,E; solid light blue). The

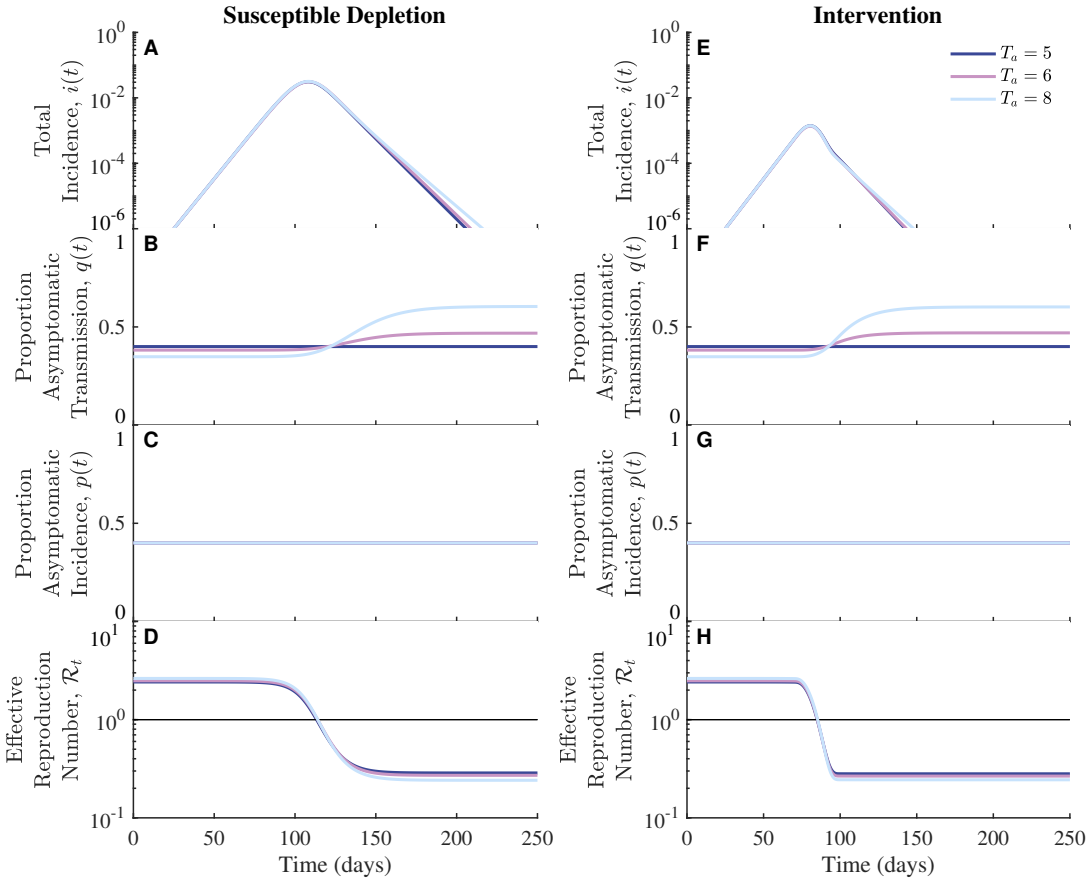

Figure 1. The realized proportion of asymptomatic transmission increases as total incidence decreases over time. We fix the infectious period of symptomatic infections, $T_s = 5$ days and increase the infectious period of asymptomatic infections from $T_a = 5$ days (dark blue), $T_a = 6$ days (purple), $T_a = 8$ days (light blue). (A-D) Without intervention the epidemic spreads through the susceptible population unhindered. As total incidence decreases, the proportion of asymptomatic transmission increases over time when asymptomatic infectious periods are longer than symptomatic infectious periods (purple and light blue). (E-H) With intervention, the reproduction number is reduced over a period of 30 days with mitigation intensities such that the final effective reproduction numbers match those in the susceptible depletion and correspond to each infectious period. Across all simulations, the intrinsic proportion of asymptomatic incidence is $p = 0.4$, and the exponential growth rate is $r = 0.14$/day (Methods). Other parameter values: $\mathcal{R}_0 = 2.42$, $\beta_a = \beta_s = 0.48$ (dark blue); $\mathcal{R}_0 = 2.50$, $\beta_a = 0.42$, $\beta_s = 0.50$ (purple); $\mathcal{R}_0 = 2.63$, $\beta_a = 0.33$, $\beta_s = 0.53$ (light blue).

realized proportion of asymptomatic transmission increases over time in both cases (Figure 2B,F; light blue curves). Correlations between transmission outcomes and disease statuses cause even more asymptomatic transmission later on, thereby further increasing the realized proportion of asymptomatic transmission (Figure 2C,G; dashed light blue) compared to dynamics arising without such correlations (Figure 2C,G; solid light blue). Correlations between transmission outcomes and disease statuses cause the realized proportion of asymptomatic incidence to increase as the realized proportion of asymptomatic transmission

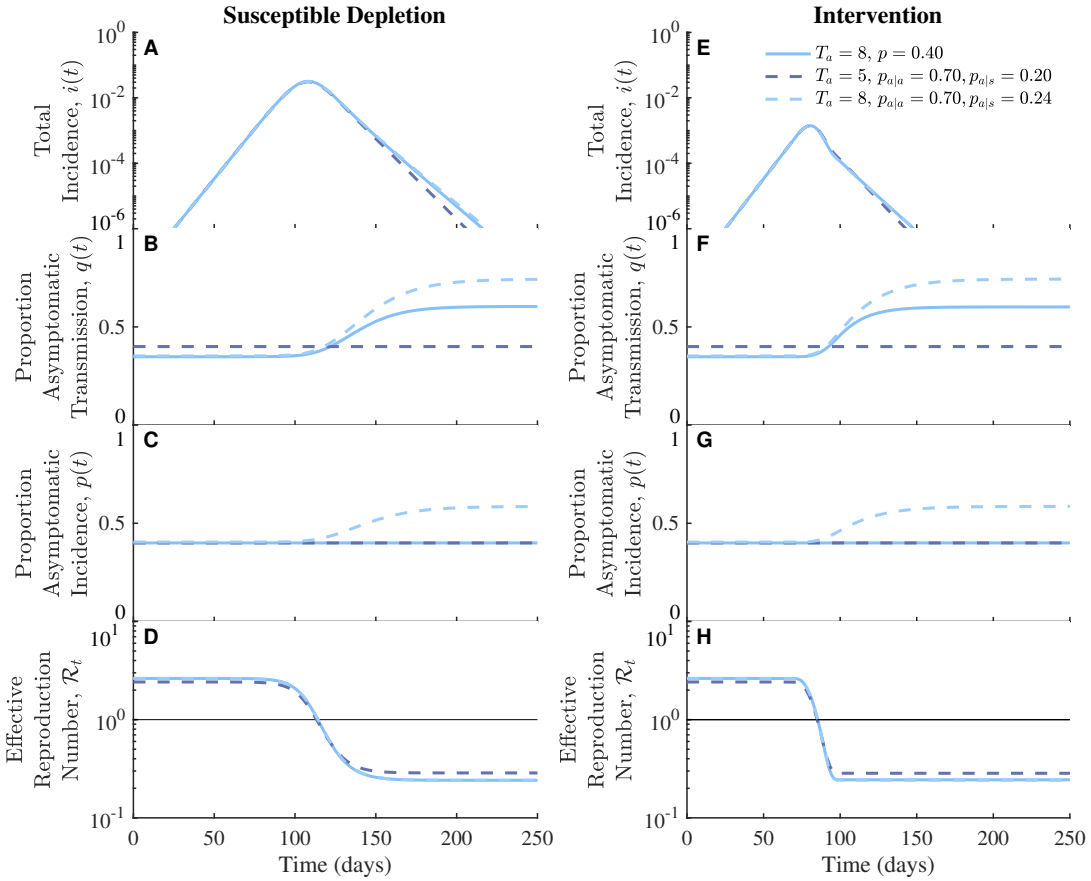

Figure 2. The realized proportions of asymptomatic transmission and incidence increase as total incidence decreases over time. We fix the infectious period of symptomatic infections to $T_s = 5$ days and increase the correlation between transmission and disease status. For comparison, $T_a = 8$ (solid light blue) with fixed intrinsic proportion asymptomatic incidence ($p = 0.40$) is the same as in Figure 1. Increased correlations between transmission and disease status when the infectious period of asymptomatic infections is the same ($T_a = 5$ days, dashed dark blue) and longer ($T_a = 8$ days, dashed light blue). In the susceptible depletion case (A-D), longer time scales of asymptomatic transmission lead to increases in the realized proportion of asymptomatic transmission over time (B, light blue curves) and including correlations between transmission and disease cause the realized proportion of asymptomatic transmission to increases over time (C, dashed light blue). In the intervention case (E-H), the reproduction number is reduced over a period of 30 days with mitigation intensities such that the final effective reproduction numbers match those in the susceptible depletion. As a result, changes in the realized proportions of asymptomatic transmission (F) and incidence (G) over time are comparable with intervention. The intrinsic proportion of asymptomatic incidence, $p = 0.4$, and the exponential growth rate, $r = 0.14$/day, are matched across all simulations (Methods). Other parameter values are the same as in Figure 1 for corresponding colors. Additionally, $p_{a|a} = 0.70$, $p_{a|s} = 0.20$ (dashed, dark blue); $p_{a|a} = 0.70$, $p_{a|s} = 0.24$ (dashed, light blue).

increases over time (Figure 2C,G; dashed light blue).

3.3 Age-dependent assortative mixing and estimates of disease lead to changes in average age of infection

Finally, we consider the effects of coupling age-dependent assortativity and variation in symptomaticity by age as an example of how correlations might arise between transmission outcomes and disease statuses. If younger (older) individuals are more likely to be asymptomatic (symptomatic), then assortative mixing by age may lead to covariation between transmission dynamics by age and disease outcomes such that more asymptomatic (symptomatic) infections result from transmission from asymptomatic (symptomatic) infections. To investigate, we parametrise an age-dependent SEIR model with asymptomatic and symptomatic transmission in which we allow the contact rates and the proportions of asymptomatic (vs. symptomatic) incidence to vary across age groups (Methods). As before, in the susceptible depletion scenario (Figure 3A-E), the disease is allowed to spread unchecked (Figure 3A). If instead transmission rates are reduced during intervention (Figure 3F–I), the peak epidemic is decreased (Figure 3F).

We find that longer time scales of asymptomatic transmission as well as increased assortativity cause the incident infections to decay more slowly (Figure 3A,F). When transmission time scales differ, changes in the proportion of asymptomatic transmission are similar between susceptible depletion and intervention scenarios (Figure 3B,G). When transmission time scales are the same, the realized proportion of asymptomatic transmission increases with depletion of the susceptible population (Figure 3B) but remains constant with mitigation (Figure 3G). In the absence of intervention measures, longer asymptomatic generation intervals have small effects on changes in changes in the proportion of asymptomatic incidence because these changes are dominated by the effects of susceptible depletion (Figure 3C). Even with intervention, longer asymptomatic generation intervals have small effects, except when the assortativity is increased (Figure 3H). Hence, as before, we find that individual-level differences in transmission time scale can lead to population-level differences in the realized asymptomatic incidence and transmission. [**SWP:** *"even in the absence of any behavioural changes" I think it might be better to not say this because intervention is a sort of behavioral change...*]

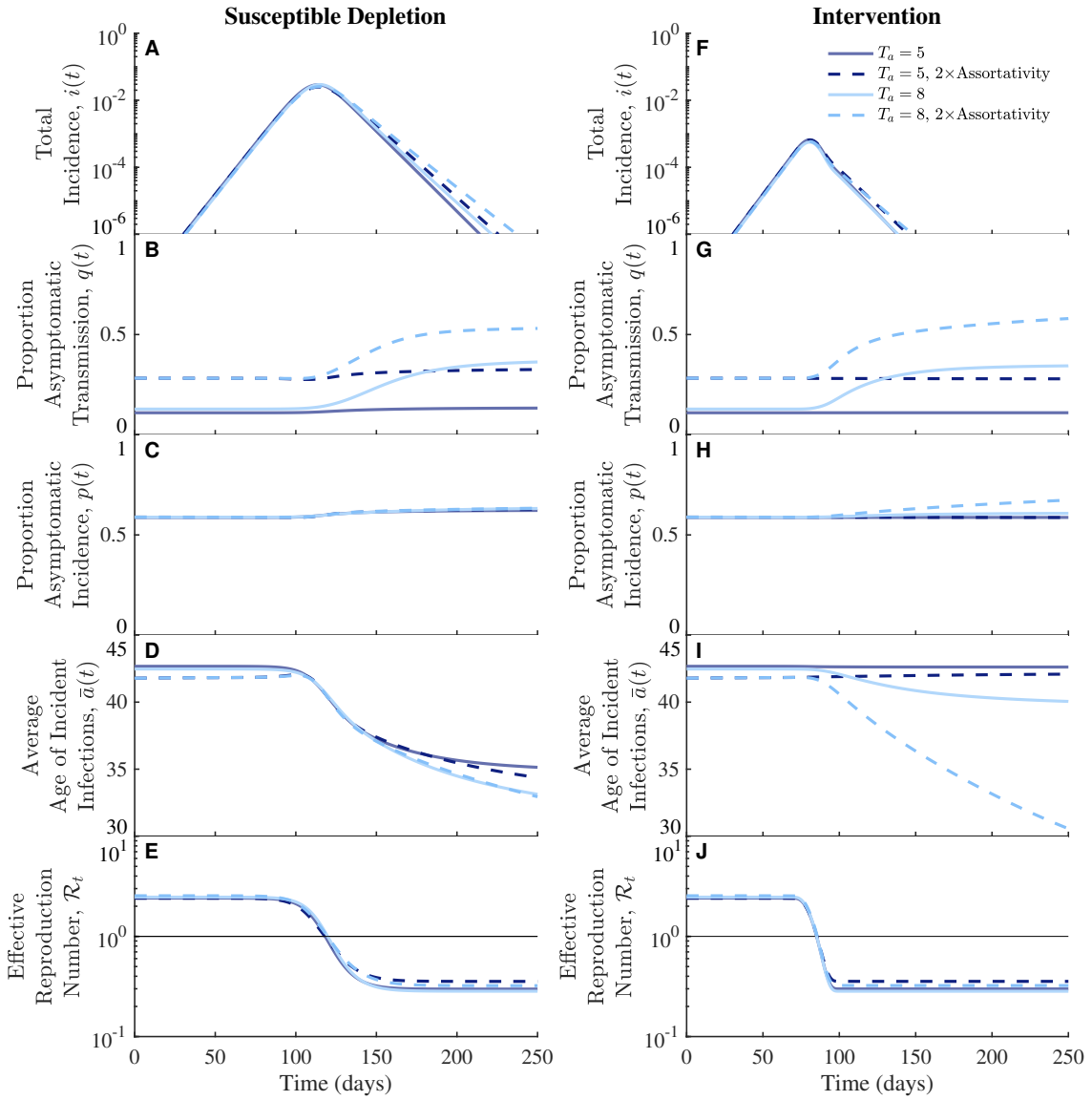

Figure 3. The average age of an incident infection decreases as total incidence decreases over time. We fix the infectious period of symptomatic infections to $T_s = 5$ days and compare when the infectious period of asymptomatic infections is equal to symptomatic infections ($T_a = T_s = 5$ days) and when the infectious period of asymptomatic infections is longer than symptomatic infections ($T_a = 8$). We compare results of baseline assortativity in contact rates (solid) with increased assortativity, specifically, two times the baseline assortativity (2×Assortativity; dashed) in both susceptible depletion (A-E) and intervention scenarios (F-J). As the realized proportion of asymptomatic incidence changes over time (C,H), the average age of an incident infection changes over time (D,I). Across all simulations, the intrinsic proportion of asymptomatic incidence is 0.59, and the exponential growth rate is $r = 0.14$/day (Methods). Other parameter values: $\mathcal{R}_0 = 2.41$, $\beta_a = 0.00864$ $\beta_s = 0.0864$ (solid dark blue); $\mathcal{R}_0 = 2.40$, $\beta_a = 0.0147$, $\beta_s = 0.0492$ (dashed dark blue); $\mathcal{R}_0 = 2.47$, $\beta_a = 0.00785$, $\beta_s = 0.0851$ (solid light blue); $\mathcal{R}_0 = 2.54$, $\beta_a = 0.0115$, $\beta_s = 0.0494$ (dashed light blue).

Changes in the realized proportion of asymptomatic incidence over time further corresponds to changes in the average age of an incident infection (Figure 3D,I). Without intervention, the average age of incident infections decreases even when asymptomatic and symptomatic transmission have the same mean generation interval [**SWP:** *because?*] (Figure 3D); assuming a longer asymptomatic generation interval further exaggerates this effect. With intervention, the average age of an incident infection remains relatively constant over time when asymptomatic and symptomatic transmission have the same mean generation interval. Assuming a longer asymptomatic generation interval causes the average age of an incident infection to decrease by a small amount (Figure 3I); increasing the degree of assortative mixing by two-fold results in a much greater change (> 10 years). When we account for the possibility that younger individuals may be less susceptible to infections [8], we find much larger decreases in the average age of an incident infection over time because older individuals who are more susceptible to infections are infected first (Figure S5H). Intervention diminishes changes in the average age of an incident infection over time for all cases (Figure S5I).

[**SWP:** *Supp figure still has the same issue where we're seeing > 30 years of change but $< 10\%$ change in asymptomatic proportion. What is the assumed proportion symptomatic for 50 year age group vs 10 year age group?*]

4 Discussion

We examined how individual-level differences in transmission dynamics between symptomatic and asymptomatic individuals can shape population-level epidemic dynamics. In particular, when asymptomatic individuals are able to transmit for longer periods of time, the proportion of asymptomatic transmission to increase as the epidemic decays because longer generation intervals of asymptomatic individuals become more important; this result generalizes earlier work, which illustrated the same effect for the growth phase [25]. Further accounting for the possibility that asymptomatic individuals are more likely to generate asymptomatic infections causes the proportion of asymptomatic incidence to increase. Our findings suggest that neglecting differences between symptomatic and asymptomatic individuals can systematically bias estimates of disease severity, not only during the initial growth phase [25] but over the course of the epidemic.

As an example of how correlations between diseases statuses of the infector and the infectee might arise in a population, we extended the model framework to include the effects of age-dependent heterogeneity in disease severity and assortativity in mixing patterns. We examined changes in the relative contribution of asymptomatic transmission over time. As younger individuals are more likely to be asymptomatic (and therefore have longer generation intervals), the proportion of new infections attributable to transmission from younger individuals increases during the decay phase. Assortative mixing can then cause the mean age of infection to decrease even in the absence of susceptible depletion (up to ≈ 2 years under baseline scenario and ≈ 7 years under increased assortativity). These results are qualitatively consistent with the observed shift in age distribution of SARS-CoV-2 infections towards the younger population in the US and UK during summer 2020 [3,26]. For example, the median age of cases decreased from a range of 45–50 years of age to a range of 33–37 years from May to June as the number of cases decreased across all four US census regions ([3], Figure S6). Although these changes were primarily attributed to high contact rates among younger individuals, our analysis shows that dynamical effects could have also contributed to changes in

the mean age of infection.

We emphasize that biological correlations (i.e., asymptomatic transmission is more likely to result in asymptomatic infection) are distinct from demographic correlations (i.e., younger individuals are more likely to infect younger individuals due to assortative mixing). We considered these two correlations separately for simplicity, but both correlations may be present in an actual epidemic: that is, young individuals infected by young asymptomatic infectors may be more likely to remain asymptomatic than those infected by young symptomatic infectors. Coupling of both correlations may further exaggerate changes in the amount of asymptomatic transmission and infections over the course of an epidemic.

Our study comes with a number of caveats. Throughout, we considered an idealized intervention which reduces transmission rate by a fixed amount, but real life interventions can be more complex. Some interventions, such as contact tracing and self-isolation, are more likely to reduce late transmissions of symptomatic individuals and therefore lead to bigger differences between symptomatic and asymptomatic individuals. Other interventions, such as frequent mass testing, will shorten generation intervals of symptomatic and asymptomatic individuals by an equal amount but are also expected to have qualitatively different effects from the intervention we considered (which does not affect generation intervals of either symptomatic or asymptomatic individuals). Nonetheless, major interventions that drove the current pandemic (e.g., social distancing, mask wearing, and vaccination) are expected to be analogous to the idealized intervention we considered. As a result, we expect changes in asymptomatic transmission and incidence to arise generically, provided that asymptomatic individuals are able to transmit for a longer amount of time and are more likely to generate new asymptomatic infections.

The dynamics of asymptomatic transmission remain uncertain, despite SARS-CoV-2 having spread throughout the world for almost 2 years. More work is needed to better characterize the course of asymptomatic infections with respect to both transmission potential and the duration of infection. The former relates to the rate of asymptomatic transmission, and the latter informs the time scale of asymptomatic transmission. Accounting for these sources of individual variation along with the effects of mitigation may aid in understanding how the relative contribution of asymptomatic infections shape epidemic dynamics and in improving the development and deployment of effective control measures.

Acknowledgments

The authors thank Guanlin Li for early model development incorporating correlations and David Demory for code review.

Funding

This work was supported in part by the Simons Foundation (SCOPE Award ID 329108, to JSW), the Charities in Aid Foundation (JSW), and the Marier Cunningham Foundation (JSW).

References

1. R. M. Anderson and R. M. May. *Infectious diseases of humans: dynamics and control*. Oxford university press, 1992.

2. Y. Bai, L. Yao, T. Wei, F. Tian, D.-Y. Jin, L. Chen, and M. Wang. Presumed asymptomatic carrier transmission of COVID-19. *JAMA*, 323(14):1406–1407, 2020.

3. T. K. Boehmer, J. DeVies, E. Caruso, K. L. van Santen, S. Tang, C. L. Black, K. P. Hartnett, A. Kite-Powell, S. Dietz, M. Lozier, et al. Changing age distribution of the COVID-19 pandemic—United States, May–August 2020. *Morbidity and Mortality Weekly Report*, 69(39):1404, 2020.

4. T. S. Brett and P. Rohani. Transmission dynamics reveal the impracticality of COVID-19 herd immunity strategies. *Proceedings of the National Academy of Sciences*, 117(41):25897–25903, 2020.

5. D. Champredon and J. Dushoff. Intrinsic and realized generation intervals in infectious-disease transmission. *Proceedings of the Royal Society B: Biological Sciences*, 282(1821):20152026, 2015.

6. J. F. W. Chan, S. Yuan, K.-H. Kok, K. K.-W. To, H. Chu, J. Yang, F. Xing, J. Liu, C. C.-Y. Yip, R. W.-S. Poon, et al. A familial cluster of pneumonia associated with the 2019 novel Coronavirus indicating person-to-person transmission: a study of a family cluster. *The Lancet*, 395(10223):514–523, 2020.

7. M. Chinazzi, J. T. Davis, M. Ajelli, C. Gioannini, M. Litvinova, S. Merler, A. P. y Piontti, K. Mu, L. Rossi, K. Sun, et al. The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. *Science*, 368(6489):395–400, 2020.

8. N. G. Davies, P. Klepac, Y. Liu, K. Prem, M. Jit, and R. M. Eggo. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nature Medicine*, 26(8):1205–1211, 2020.

9. O. Diekmann and J. A. P. Heesterbeek. *Mathematical epidemiology of infectious diseases: model building, analysis and interpretation*, volume 5. John Wiley & Sons, 2000.

10. O. Diekmann, J. A. P. Heesterbeek, and J. A. Metz. On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations. *Journal of mathematical biology*, 28(4):365–382, 1990.

11. L. Ferretti, C. Wymant, M. Kendall, L. Zhao, A. Nurtay, L. Abeler-Dörner, M. Parker, D. Bonsall, and C. Fraser. Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. *Science*, 368(6491), 2020.

12. C. Fraser, S. Riley, R. M. Anderson, and N. M. Ferguson. Factors that make an infectious disease outbreak controllable. *Proceedings of the National Academy of Sciences*, 101(16):6146–6151, 2004.

13. J. Heesterbeek and K. Dietz. The concept of Ro in epidemic theory. *Statistica neerlandica*, 50(1):89–110, 1996.

14. M. Imai, K. Iwatsuki-Horimoto, M. Hatta, S. Loeber, P. J. Halfmann, N. Nakajima, T. Watanabe, M. Ujie, K. Takahashi, M. Ito, et al. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. *Proceedings of the National Academy of Sciences*, 117(28):16587–16595, 2020.

15. M. A. Johansson, T. M. Quandelacy, S. Kada, P. V. Prasad, M. Steele, J. T. Brooks, R. B. Slayton, M. Biggerstaff, and J. C. Butler. SARS-CoV-2 transmission from people without COVID-19 symptoms. *JAMA network open*, 4(1):e2035057–e2035057, 2021.

16. R. Kinoshita, A. Anzai, S.-m. Jung, N. M. Linton, T. Miyama, T. Kobayashi, K. Hayashi, A. Suzuki, Y. Yang, A. R. Akhmetzhanov, et al. Containment, contact tracing and asymptomatic transmission of novel Coronavirus disease (COVID-19): a modelling study. *Journal of clinical medicine*, 9(10):3125, 2020.

17. E. Lavezzo, E. Franchin, C. Ciavarella, G. Cuomo-Dannenburg, L. Barzon, C. Del Vecchio, L. Rossi, R. Manganelli, A. Loregian, N. Navarin, et al. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. *Nature*, 584(7821):425–429, 2020.

18. S. Lee, T. Kim, E. Lee, C. Lee, H. Kim, H. Rhee, S. Y. Park, H. Son, S. Yu, J. W. Park, et al. Clinical course and molecular viral shedding among asymptomatic and symptomatic patients with SARS-CoV-2 infection in a community treatment center in the Republic of Korea. *JAMA internal medicine*, 180(11):1447–1452, 2020.

19. Q.-X. Long, X.-J. Tang, Q.-L. Shi, Q. Li, H.-J. Deng, J. Yuan, J.-L. Hu, W. Xu, Y. Zhang, F.-J. Lv, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nature medicine*, 26(8):1200–1204, 2020.

20. K. Mizumoto, K. Kagaya, A. Zarebski, and G. Chowell. Estimating the asymptomatic proportion of Coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Eurosurveillance*, 25(10):2000180, 2020.

21. H. Nishiura, T. Kobayashi, T. Miyama, A. Suzuki, S.-m. Jung, K. Hayashi, R. Kinoshita, Y. Yang, B. Yuan, A. R. Akhmetzhanov, et al. Estimation of the asymptomatic ratio of novel Coronavirus infections (COVID-19). *International journal of infectious diseases*, 94:154, 2020.

22. D. P. Oran and E. J. Topol. Prevalence of asymptomatic SARS-CoV-2 infection: a narrative review. *Annals of internal medicine*, 173(5):362–367, 2020.

23. X. Pan, D. Chen, Y. Xia, X. Wu, T. Li, X. Ou, L. Zhou, and J. Liu. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. *The Lancet Infectious Diseases*, 20(4):410–411, 2020.

24. S. W. Park, D. Champredon, J. S. Weitz, and J. Dushoff. A practical generation-interval-based approach to inferring the strength of epidemics from their speed. *Epidemics*, 27:12–18, 2019.

25. S. W. Park, D. M. Cornforth, J. Dushoff, and J. S. Weitz. The time scale of asymptomatic transmission affects estimates of epidemic potential in the COVID-19 outbreak. *Epidemics*, 31:100392, 2020.

26. S. Riley, K. E. Ainslie, O. Eales, C. E. Walters, H. Wang, C. Atchison, C. Fronterre, P. J. Diggle, D. Ashby, C. A. Donnelly, et al. Resurgence of SARS-CoV-2: detection by community viral surveillance. *Science*, 2021.

27. T. W. Russell, J. Hellewell, C. I. Jarvis, K. Van Zandvoort, S. Abbott, R. Ratnayake, S. Flasche, R. M. Eggo, W. J. Edmunds, A. J. Kucharski, et al. Estimating the infection and case fatality ratio for coronavirus disease (COVID-19) using age-adjusted data from the outbreak on the Diamond Princess cruise ship, February 2020. *Eurosurveillance*, 25(12):2000256, 2020.

28. K. A. Ryan, K. R. Bewley, S. A. Fotheringham, G. S. Slack, P. Brown, Y. Hall, N. I. Wand, A. C. Marriott, B. E. Cavell, J. A. Tree, et al. Dose-dependent response to infection with SARS-CoV-2 in the ferret model and evidence of protective immunity. *Nature Communications*, 12(1):1–13, 2021.

29. Å. Svensson. A note on generation times in epidemic models. *Mathematical biosciences*, 208(1):300–311, 2007.

30. P. Van den Driessche and J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences*, 180(1-2):29–48, 2002.

31. J. Wallinga and M. Lipsitch. How generation intervals shape the relationship between growth rates and reproductive numbers. *Proceedings of the Royal Society B: Biological Sciences*, 274(1609):599–604, 2007.

32. J. Wallinga and P. Teunis. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. *American Journal of epidemiology*, 160(6):509–516, 2004.

33. T. Watanabe, T. A. Bartrand, M. H. Weir, T. Omura, and C. N. Haas. Development of a dose-response model for SARS coronavirus. *Risk Analysis: An International Journal*, 30(7):1129–1138, 2010.

34. J. T. Wu, K. Leung, M. Bushman, N. Kishore, R. Niehus, P. M. de Salazar, B. J. Cowling, M. Lipsitch, and G. M. Leung. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. *Nature medicine*, 26(4):506–510, 2020.

35. J. Zhang, M. Litvinova, Y. Liang, Y. Wang, W. Wang, S. Zhao, Q. Wu, S. Merler, C. Viboud, A. Vespignani, et al. Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China. *Science*, 368(6498):1481–1486, 2020.

Supplemental Information

Supplemental Tables

Table S1. Age-dependent Contact Matrix. Contact matrix, $C_{n,m}$, includes baseline contact rates in Shanghai with individuals grouped by age into ten year intervals. The average number of contacts per day recorded by the survey participant (rows) is stratified by the age group of the reported contact (columns).

		Age of Contact							
		0-9	**10-19**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70+**
Age of Participant	**0-9**	4.18	0.47	0.35	1.06	0.18	0.28	0.60	0.74
	10-19	0.30	9.66	0.61	1.43	1.16	0.50	0.22	0.81
	20-29	0.08	0.11	2.18	2.83	2.65	1.65	0.74	1.05
	30-39	0.31	0.22	1.61	3.50	2.67	1.62	0.87	0.90
	40-49	0.06	0.34	1.42	2.72	2.68	1.36	0.48	1.52
	50-59	0.09	0.12	1.17	1.95	1.95	1.90	1.28	2.68
	60-69	0.04	0.08	0.49	1.03	0.88	1.30	1.78	2.46
	70+	0.08	0.06	0.20	0.41	0.72	0.78	1.48	5.56

Supplemental Figures.

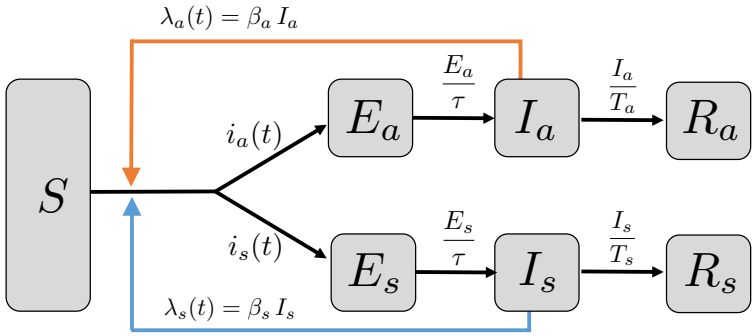

Figure S1. Model structure of SEIR models with asymptomatic and symptomatic transmission. Here, $\lambda_a(t)$ is the force of infection due to asymptomatic transmission (orange arrow), whereas $\lambda_s(t)$ is the force of infection due to symptomatic transmission (blue arrow). Incident infections remain in an exposed period (latent stage) given by τ, which is assumed to be the same for both asymptomatic and symptomatic infections. The asymptomatic (symptomatic) infectious periods, T_a (T_s), may differ (Methods). Asymptomatic (symptomatic) incidence is denoted $i_a(t)$ ($i_s(t)$) and differs based on assumptions on correlations between transmission and disease. With fixed proportion of asymptomatic incidence, p, transmission and disease are uncorrelated. The asymptomatic incidence is $i_a(t) = p\,\left(\lambda_a(t) + \lambda_s(t)\right) S$, and the symptomatic incidence is $i_s(t) = (1-p)\,\left(\lambda_a(t) + \lambda_s(t)\right) S$. With correlations between transmission and disease, the asymptomatic incidence is $i_a(t) = \left(p_{a|a}\,\lambda_a(t) + p_{a|s}\,\lambda_s(t)\right) S$, and the symptomatic incidence is $i_s(t) = \left((1-p_{a|a})\,\lambda_a(t) + (1-p_{a|s})\,\lambda_s(t)\right) S$.For the age-dependent model, asymptomatic incidence is $i_a(t) = \sum_{n=1}^{N} p_n\,\left(\lambda_{a,n}(t) + \lambda_{s,n}(t)\right)\, S_n$ and symptomatic incidence is $i_s(t) = \sum_{n=1}^{N} (1-p_n)\,\left(\lambda_{a,n}(t) + \lambda_{s,n}(t)\right)\, S_n$, where p_n is the proportion of asymptomatic incidence for age group n and the forces of infection are given in Eq. (8).

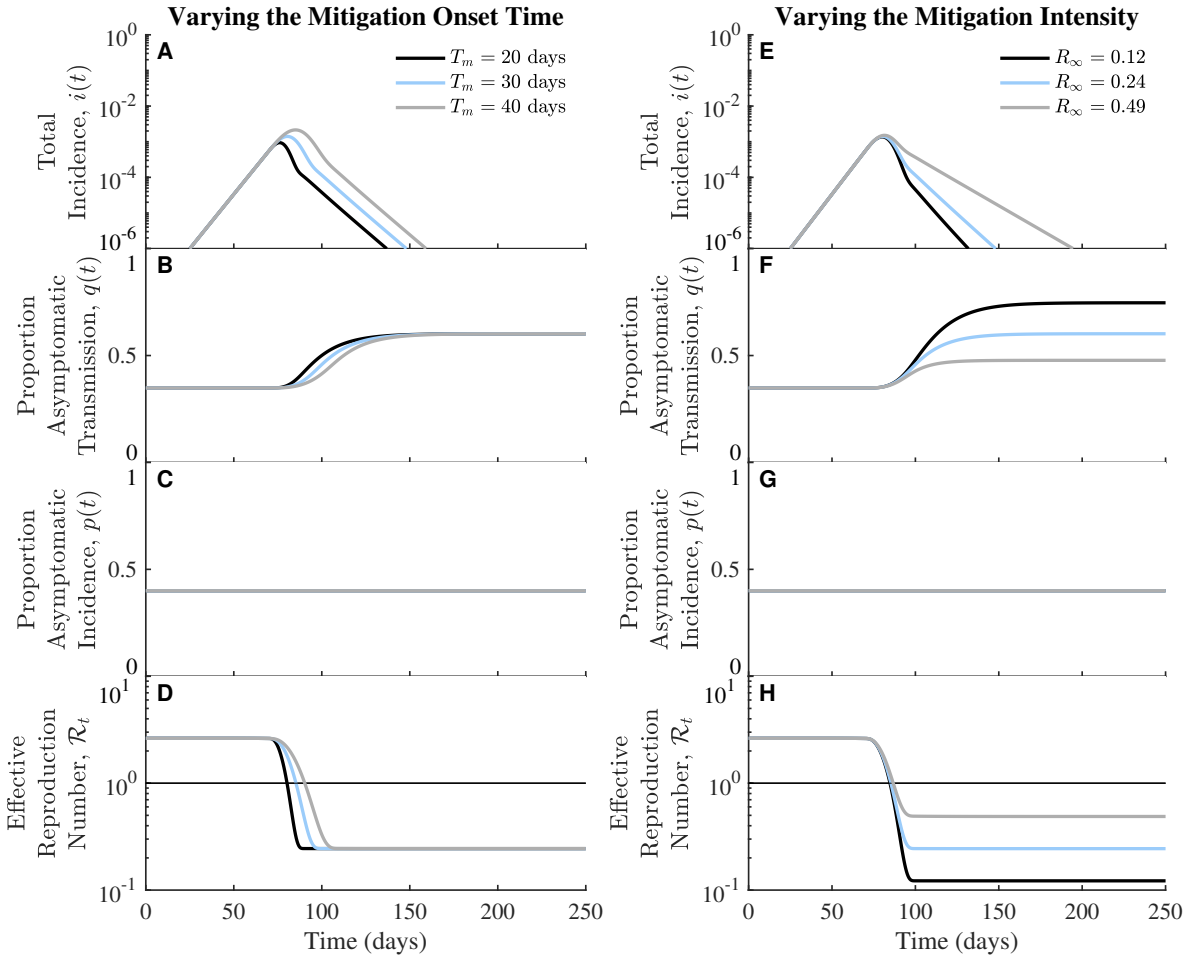

Figure S2. The Mitigation intensity determines the magnitude of change in the realized proportion of asymptomatic transmission over time. For comparison, light blue curves are the same as in Figure 1. (A-D) Fixing the mitigation intensity (i.e., the final effective reproduction number) and varying the mitigation onset time: 20 days (black), 30 days (light blue), and 40 days (gray). (E-H) Fixing the onset time, while varying the mitigation intensity: $\mathcal{R}_\infty = 0.12$ (black), $\mathcal{R}_\infty = 0.24$ (light blue), $\mathcal{R}_\infty = 0.49$ (gray).

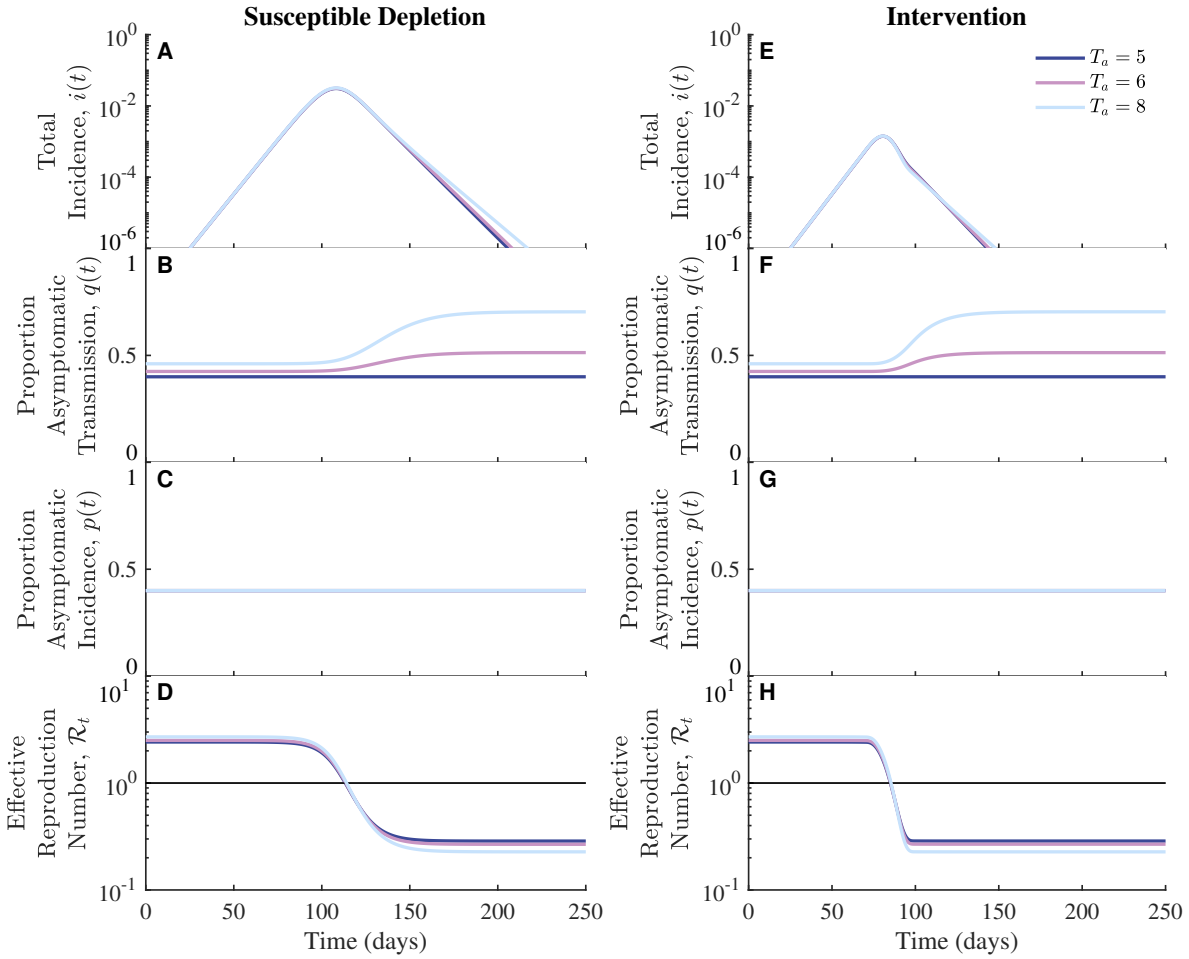

Figure S3. Similar to Figure 1 but assuming asymptomatic and symptomatic infections have the same transmission rates. We fix the symptomatic infectious period, $T_s = 5$ and increase the infectious period of asymptomatic infections: $T_a = 5$ (dark blue), $T_a = 6$ (purple), $T_a = 8$ (light blue). The realized proportion of asymptomatic transmission increases over time with similar magnitude as in Figure 1. However, in contrast to Figure 1, here the initial proportion of asymptomatic transmission is larger than the intrinsic proportion, $p = 0.4$, when time scales of asymptomatic transmission are longer than those of symptomatic transmission.

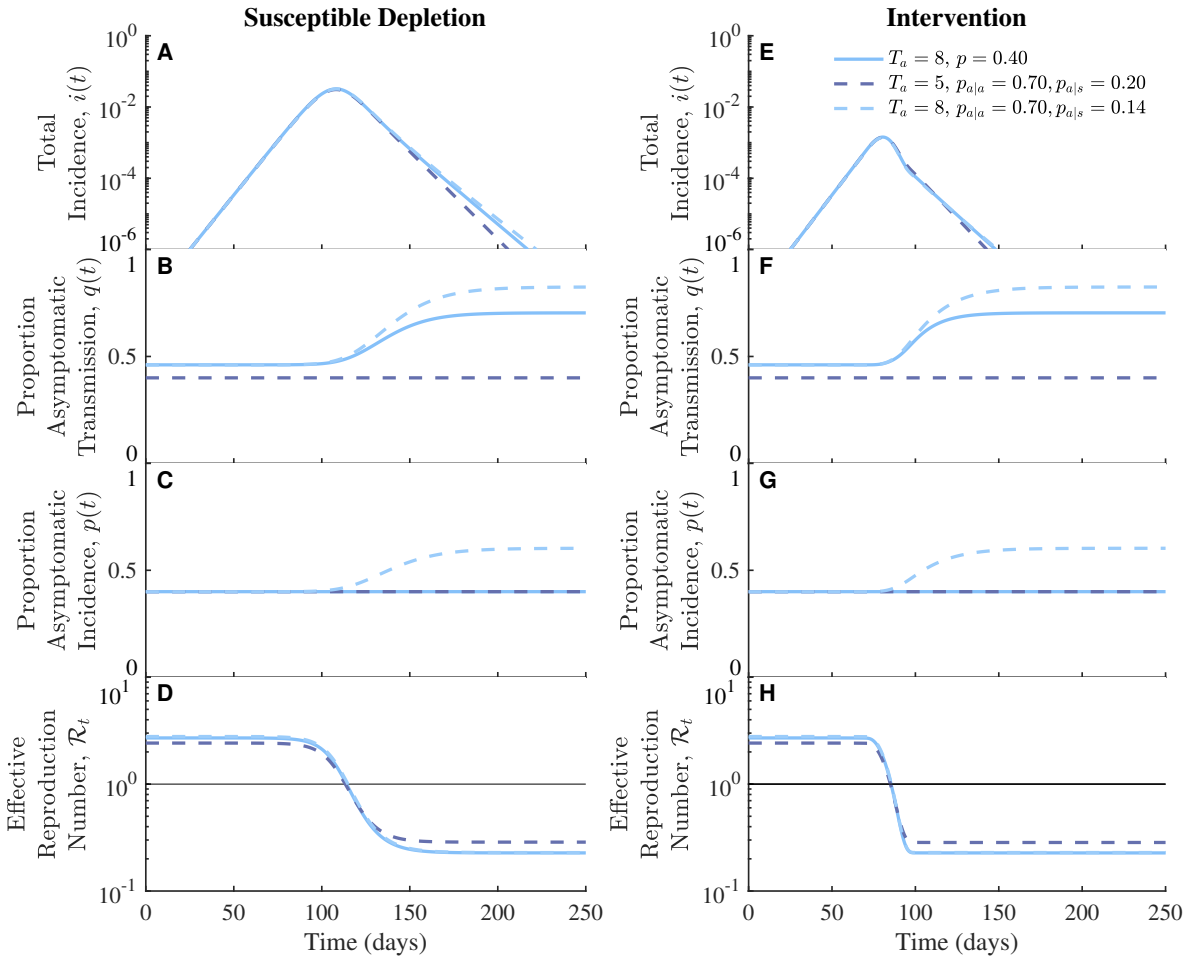

Figure S4. Similar to Figure 2 but assuming asymptomatic and symptomatic infections have the same transmission rates. We fix $T_s = 5$ and increase the infectious period of asymptomatic infections from $T_a = 5$ (dark blue) to $T_a = 8$ (light blue). For comparison, we include simulations with fixed intrinsic proportion of asymptomatic transmission, $p = 0.4$, when $T_a = 8$ (solid light blue, the same as in Figure S3). With correlations between transmission and disease status, the magnitude of changes in the realized proportions of asymptomatic transmission and incidence are similar to those in Figure 2.

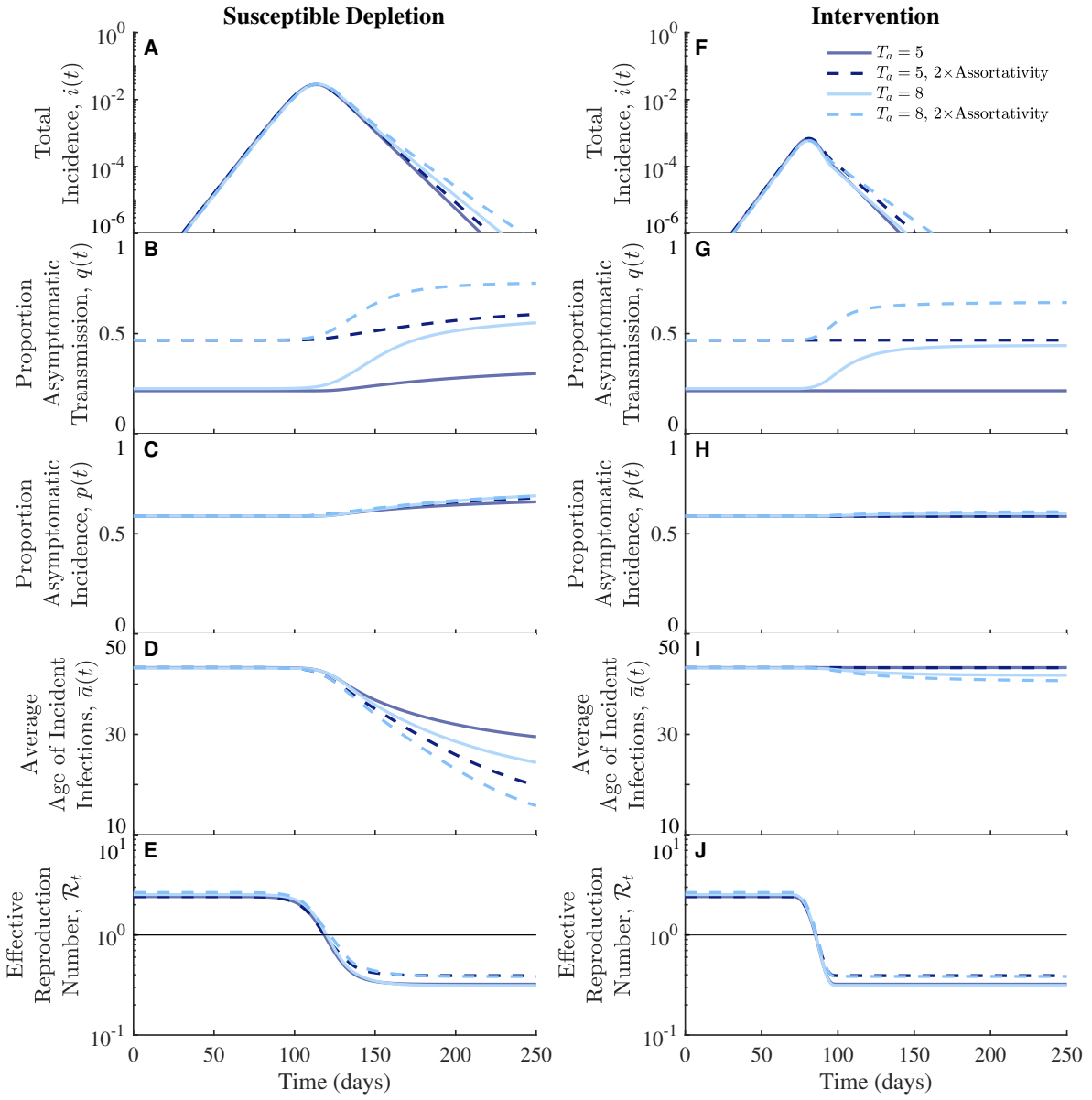

Figure S5. Similar to Figure 3 but including variation in susceptibility by age. (A-E) Susceptible depletion. (F-J) Intervention. Variation in susceptibility causes further decreases in the average age of an incident infection without intervention (D) but diminishes these changes with intervention (I). Across all simulations, the intrinsic proportion of asymptomatic incidence is 0.59, and the exponential growth rate is $r = 0.14$/day (Methods). Other parameter values: $\mathcal{R}_0 = 2.41$, $\beta_a = 0.0220$, $\beta_s = 0.100$ (solid dark blue); $\mathcal{R}_0 = 2.41$, $\beta_a = 0.0365$, $\beta_s = 0.0520$ (dashed dark blue); $\mathcal{R}_0 = 2.53$, $\beta_a = 0.0180$, $\beta_s = 0.0990$ (solid light blue); $\mathcal{R}_0 = 2.65$, $\beta_a = 0.0285$, $\beta_s = 0.0520$ (dashed light blue).

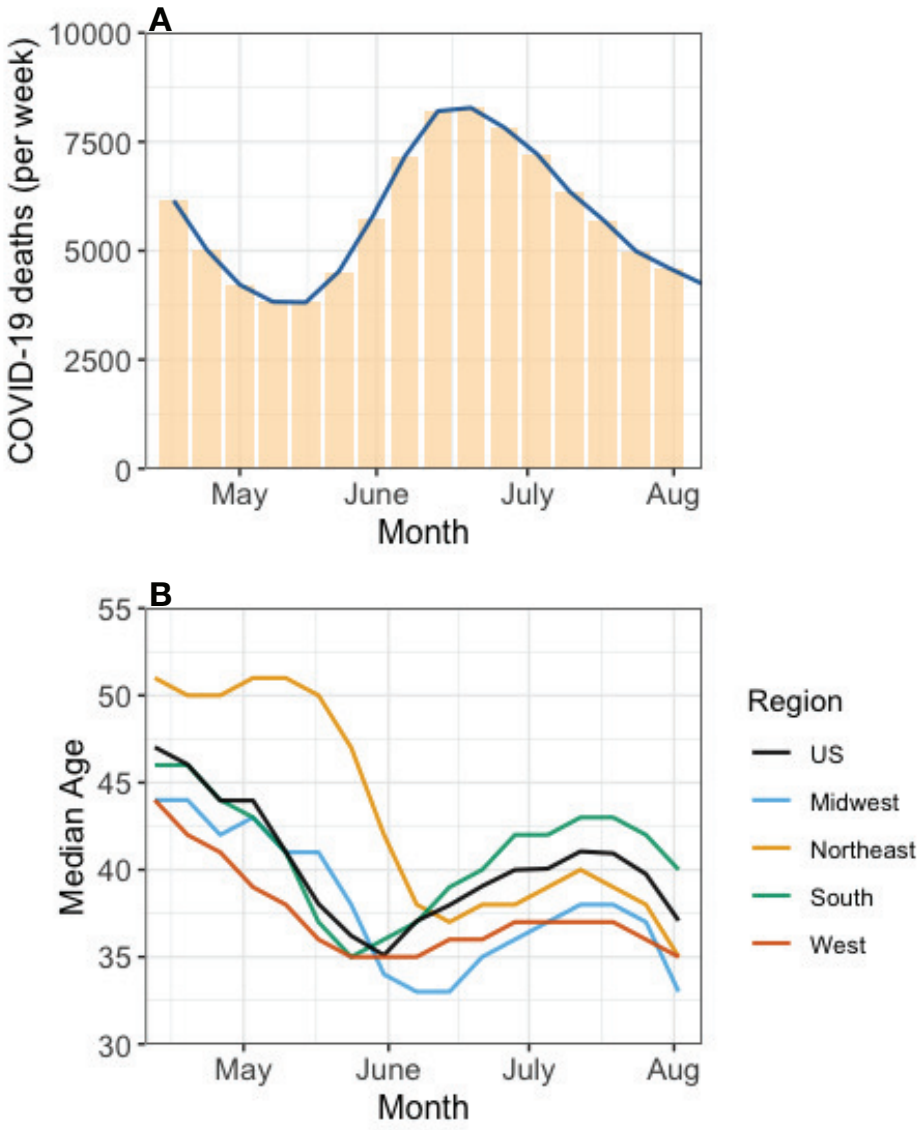

Figure S6. Changes in Median age of COVID-19 infections in US (May-Aug. 2020) as epidemic burden changes over time. (A) End of week deaths due to COVID-19 (bars) from 24 May 2020 to 19 September 2020 (CDC surveillance data). Data are shifted by 21 days to estimate the shape of incident infections from May-August 2020. **(B)** Positive RT-PCR tests reported to the CDC by median age from 3 May 2020 to 23 August 2020 from overall US and four US census regions (Data reproduced from MMWR, October 2020 [3]). Tick marks with monthly labels correspond to the 22^{nd} of each month.