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Assessing Infection Control Measures for Pandemic Influenza

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We construct a mathematical model of aerosol (i.e., droplet-nuclei) transmission of influenza within a household containing one infected and embed it into an epidemic households model in which infecteds occasionally infect someone from another household; in a companion paper, we argue that the contribution from contact transmission is trivial for influenza and the contribution from droplet transmission is likely to be small. Our model predicts that the key infection control measure is the use of N95 respirators, and that the combination of respirators, humidifiers, and ventilation reduces the threshold parameter (which dictates whether or not an epidemic breaks out) by ≈20% if 70% of households comply, and by ≈40% if 70% of households and workplaces comply (≈28% reduction would have been required to control the 1918 pandemic). However, only ≈30% of the benefits in the household are achieved if these interventions are used only after the infected develops symptoms. It is also important for people to sleep in separate bedrooms throughout the pandemic, space permitting. Surgical masks with a device (e.g., nylon hosiery) to reduce face-seal leakage are a reasonable alternative to N95 respirators if the latter are in short supply.

KEY WORDS: Infection control measures; influenza; pandemic

1. INTRODUCTION

Pandemic influenza (influenza A subtype H5N1) is widely perceived to be one of the world's most serious near-term public health threats.[1] If a strain similar in effect to the 1918 pandemic influenza emerges within the next several years, it is highly likely that an effective vaccine will not be available during the pandemic's first wave,[1] antiviral drug supply will be insufficient for large-scale prophylactic use,[2] and hospitals will be too overwhelmed to treat most cases. Consequently, as in 1918, we will need to rely on voluntary and forced social distancing measures to mitigate the spread of disease, including the closing of schools and churches, the elimination of public gatherings, high worker absenteeism, and the wearing of masks in public.[3]

In this pandemic scenario, we assess infection control measures in the home using a hierarchical mathematical model: a detailed model of the viral shedding and transmission within a four-member household containing one infected is embedded within an epidemic households model[4] in which global contacts occur between households in addition to the within-household local contacts. A prerequisite for assessing infection control measures is the quantification of how much influenza transmission is due to droplet transmission (an infected sneezing or coughing directly into a susceptible's mouth, nose, or eyes), contact transmission (an infected gets virus on his hands and transfers this virus either directly, for example, via a handshake, or indirectly

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via fomites, to the hands of a susceptible, who then places his hand into his mouth, nose, or eyes), and aerosol transmission, in which a susceptible inhales droplet nuclei (i.e., evaporated virus-containing particles in the air). The relative importance of these transmission routes is unknown[1,5] and the subject of some debate.[6–8] In a companion paper,[9] we quantify the routes of transmission using data from interpandemic influenza and rhinovirus (which causes the common cold) and using a mathematical model that incorporates all three modes of transmission; see Reference 10 for another recent model that incorporates all three modes of transmission, although not specifically in an influenza setting.

The analysis in Reference 9 suggests that aerosol transmission is the dominant mode of transmission for influenza and, consequently, the model presented here omits contact and droplet transmission. We will now briefly describe the analysis in Reference 9, which allows us to focus on aerosol transmission in this article. The analysis in Reference 9 incorporates both aerosol and contact transmission within a household model and performs a separate analysis of inspirable, respirable, and droplet transmission from a close expiratory event (such as a cough or sneeze). There is a large empirical component in Reference 9 to estimate the parameters of the model. Data for interpandemic influenza is collected and a comparative analysis of data and experiments for rhinovirus is performed. Based upon the estimates of several key parameters (e.g., the death rate of the virus in the air, on surfaces, and on an individual's hands; see Table 2 in Reference 9 for these parameter values and Section 3.3 in Reference 9 for the analysis), there appears to be several orders-of-magnitude leeway in showing that contact transmission is trivial for influenza. Therefore, several parameters are estimated conservatively to increase the impact of contact transmission. Running the model for the interpandemic and pandemic setting yields that contact transmission is negligible. The analysis is based on data from interpandemic influenza strains, and the characteristics of a future pandemic influenza strain cannot be accurately predicted. However, several of the parameter estimates would have to be highly inaccurate—and biased toward aerosol transmission—to negate the finding that aerosol transmission dominates contact transmission.

The justification for omitting droplet transmission is less convincing. For the analysis of close expiratory events in Reference 9, there is a high probability of infection through droplet transmission from a close, unprotected, horizontally directed sneeze at the peak shedding time. There are insufficient data on the frequency of close expiratory events, and several behavioral and physical factors suggest that actual transmission during close expiratory events may be considerably less than predicted in the analysis of Section 4 of Reference 9. Sneezes are typically directed at a downward angle and are usually protected when two people are close to each other. Furthermore, nasal openings are also oriented downward (in contrast, the analysis in Reference 9 assumes nostrils are more like a pig's snout), making it difficult for droplets to land inside a susceptible's nose. However, if droplet transmission does occur, the intervention most effective in this study (N95 respirators) will also be effective at reducing droplet transmission.

The model is described in Section 2 and the computational results are reported in Section 3 and discussed in Section 4.

2. THE MODEL

The within-household model is taken from Reference 9 and describes how influenza is spread among members of one household. A brief description of the within-household model appears in Section 2.1, and the mathematical formulation of this model is given in Section 1 of Appendix S1. In Section 2.2, we embed the within-household model into an epidemic households model[4] that defines how global infectious contacts occur between households.

2.1. Within-Household Model

The within-household model considers three compartments of the house (Fig. 1a) in which the four household members reside during the infected's 5-day infectious period:[11,12] the living quarters, the infected's bedroom, and a susceptible's bedroom. The infected develops symptoms 24 h after viral shedding begins,[1,13] at which point he retreats full-time to his bedroom (in the base case, bedroom doors are closed when the bedroom is occupied and open when unoccupied) and receives 1 h per day of care from one of the susceptibles, referred to as the caregiver; hence, we are implicitly restricting attention to symptomatic cases of influenza. A set of differential equations (defined in Equations (A.9)–(A.11) of Appendix S1 and illustrated in Fig. 1b) tracks the amount of virus in droplet nuclei of each size that

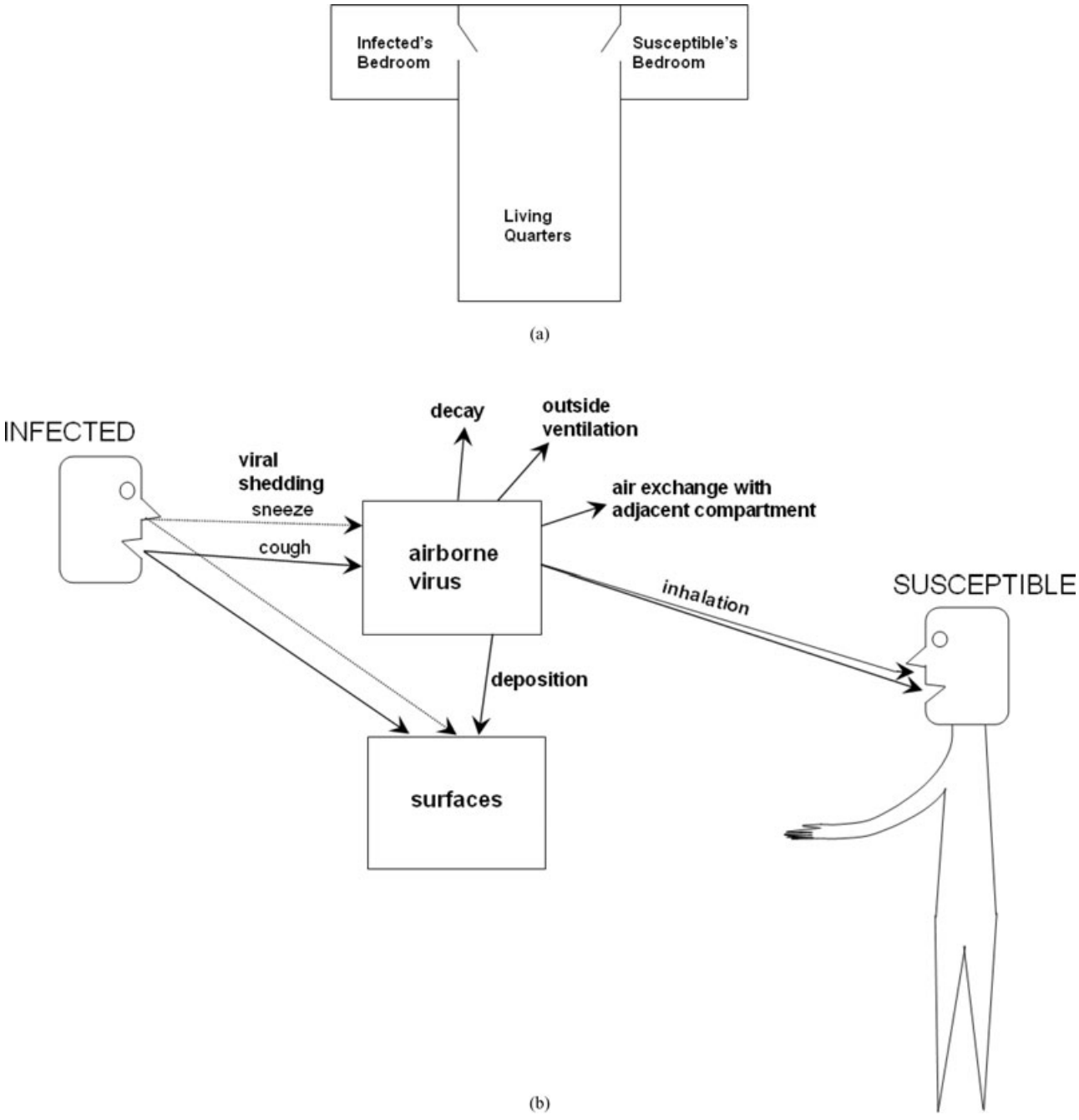

Fig. 1. A graphical depiction of the model. (a) The three-compartment household. (b) The dynamics of viral shedding and transmission. Fig 1(a) is a simplified version of Fig. 1(b) in Reference 9, and Fig. 1(b) is identical to Fig. 1(a) in Reference 9.

is airborne in each of the three compartments. The model includes a viral shedding rate from coughing and sneezing that is a piecewise-exponential function of time during the infectious period with a maximum at the time the infected's symptoms start[11] (this maximum shedding rate follows a log-normal distribution to capture the large interperson heterogeneity in shedding),[14,15] deposition onto surfaces (e.g., hands, tissues) due to the infected's efforts to protect the sneeze or cough,[16] instantaneous deposition for particles >20 μm in diameter,[17] decay in the air, settling from the air to the surfaces, and air

exchange with the outside and adjacent compartments. Susceptibles inhale droplet nuclei of various sizes and human influenza virus preferentially binds to α2-6-linked sialic acids on receptors of ciliated columnar epithelial cells, leading to viral replication in the respiratory epithelium.[18,19] Hence, we calculate the total inhaled dose by computing how much virus (of each particle size) deposits in the respiratory epithelium; in the discussion, we address how our results change if the alveolar region is also a target of infection. Using the Poisson dose-response model, which is reasonably accurate for influenza and other airborne infectious diseases,[20,21] we compute the outputs of the within-household model, which are the infection probabilities for a noncaregiving susceptible and the caregiver. We denote these probabilities as P_{I2} and P_{I3}, respectively, define them in Equation (A.14) of Appendix S1, and determine their values in both the interpandemic and pandemic settings in Section 3 of Appendix S1. Parameters for the within-household model were estimated in Reference 9 and appear in Table A1 of Appendix S1.

2.2. Between-Households Model

In this section, we adapt the results from Ball and Neal[4] to our setting in a heuristic manner. The model and the fundamental threshold result from Reference 4 are described in Section 2.2.1. The threshold parameter is derived in Section 2.2.2 in terms of the infection probabilities P_{I2} and P_{I3} from Section 2.1. The proportion of susceptibles that are infected during the epidemic is derived in Section 2.2.3.

2.2.1. The Model and Threshold Parameter

One of the models considered in Reference 4, referred to as the households model in the literature,[22,23] is a SIR model with two levels of mixing: local mixing within a household and (at a much lower per capita rate) global mixing between households. Although their model does not explicitly include a latent period, all of their results carry over if there is a latent period.

We follow Reference 4 by assuming that there are m households, each of size n ($n = 4$ in our model), so that the total population is $N = mn$, and assume that an infected person makes global infectious contacts according to a homogeneous Poisson process at rate λ_G, and hence infects a random individual not in his household at rate λ_G/N. Whereas Ball and Neal's model[4] assumes that an infected person makes local infectious contacts within his household according to a homogeneous Poisson process with rate λ_L, our model assumes that household infections occur according to the within-household model described in Section 2.1. Their results do not carry over to our model because the within-household infections do not occur according to a homogeneous Poisson process (e.g., the viral shedding rate varies during the infectious period, and the caregiver has a different infection probability than the noncaregiving susceptibles). Nonetheless, we adapt their results to our model in the natural way, which allows us to maintain analytical tractability.

Ball and Neal derive three main results in Reference 4, all of which hold regardless of the pdf of the incubation period: a threshold parameter R_* dictating whether or not a global epidemic occurs, the probability that a global epidemic occurs given that the threshold is exceeded, and the proportion of initial susceptibles that are infected during a global epidemic given that one occurs. We now describe the first of these results and then adapt them to our setting in Section 2.2.2; the third result is adapted to our problem in Section 2.2.3. We can adapt the second result (the probability that a global epidemic occurs) to our model. However, the probability that a global epidemic occurs depends on the configuration of the initial infecteds and the derivation is very tedious. Because the focus of the article is not on the probability of a global epidemic occurring, we do not pursue this here.

Although random infectious periods are allowed in Reference 4, we describe their results in the special case of a deterministic infectious period, as in Section 2.1. We define $T_I = 5$ days to be the length of the infectious period. A study with a general infectious period concluded, based on serological data from two influenza outbreaks in Tecumseh, Michigan, that a deterministic infectious period is adequate for modeling influenza (and is more accurate than an exponential infectious period, which is implicitly assumed in most differential equation models of epidemics).[24]

Ball and Neal show in Theorem 2.1 of Reference 4 that a global epidemic occurs with nonzero probability if and only if $R_* > 1$, where:

$$R_* = \lambda_G T_I E[C] \tag{1}$$

and C is the total (random) number of household infections (including the initial infected) emanating

from a single infected in an isolated household. The threshold parameter R_* plays the role that the basic reproduction number R_0 plays in simpler epidemic models (i.e., it is the household-to-household reproduction number). The λ_G parameter in Reference 4 is an individual's contact rate with the entire population and, therefore, the infectious contact rate with individuals in other households is $\frac{m-1}{m}\lambda_G$ and the definition of the threshold parameter R_* should also include this $\frac{m-1}{m}$ factor. However, we assume a large number of households and to compute R_* we only require an estimate of the value $\frac{m-1}{m}\lambda_G T_I$, and thus we can absorb the $\frac{m-1}{m}$ factor into the λ_G parameter and define $R_* = \lambda_G T_I E[C]$ for simplicity of notation. Furthermore, Equation (1) implies that the infected can infect people outside of the household throughout his infectious period, which is at odds with the behavior described in Section 2.1 where the infected remains in the bedroom after developing symptoms. This inconsistency is of no consequence: the product $\lambda_G T_I$ determines the fraction of the population that is infected during a pandemic (see Equation (4)), and we choose the value of λ_G in Section 3 of Appendix S1 to give the desired fraction.

We emphasize that the embedding of our within-household model into the epidemic households model is inexact (the household model in Reference 4 assumes equal risks to all co-habitants of a household, assumes within-house infections occur according to a homogeneous Poisson process, and that the global infections occur according to a homogeneous Poisson process throughout the infected's entire infectious period, all of which are violated in our household model), although we believe it is sufficiently accurate for policy-making purposes.

2.2.2. *Derivation of the Total Number of Household Infections*

In this subsection, we describe how we approximate $E[C]$, which appears in Equation (1), in terms of the infection probabilities P_{I2} and P_{I3}. These infection probabilities are outputs of the within-household model in Section 2.1 and are the probabilities of being directly infected by the initial infected. However, the quantity C counts all infections within the household that originate both directly and indirectly from the initial infected (e.g., a noncaregiver infected by the caregiver, who is originally infected by the initial infected). While it is possible to extend our within-household model to include multiple infecteds, this would be very tedious. Instead, we use P_{I2} and P_{I3} as building blocks to approximate the probability of these indirect infections, thereby computing $E[C]$.

The household model in Reference 4 assumes infectious contact between infected and susceptibles. In our model, the majority of the exposure happens within 36 h of infection (around the peak shedding time), and thus to mimic the household model in Reference 4, we assume in our model infectious contacts occur 24 h into the infectious period, and that further indirect infections happen in waves every 24 h. The initial infection occurs at time 0 with one sick individual. The first wave occurs 24 h later, when we assume the infected can have infectious contacts with the susceptibles. The second wave occurs 24 h after the first wave (48 h into the initial infectious period), and any person infected in the first wave can now infect any remaining susceptibles (however, the original infected cannot). We can extend this to an arbitrary number of waves, where at any given wave only those people who were infected in the previous wave can infect susceptibles in the current wave. In other words, we make the reasonable assumption that the most recently infected individuals should dominate future transmissions as they will be closest to the peak shedding rate during the next wave.

By framing our household model in terms of these waves of infections, we can use P_{I2} and P_{I3} to determine the indirect infection probabilities. Computing these infection probabilities is now straightforward, though tedious, and the calculations are performed in Section 2 of Appendix S1.

2.2.3. *Proportion of Susceptibles Infected*

In this section, we derive the proportion of initial susceptibles that become infected if a global epidemic occurs. Ball and Neal[25] also have a simpler Poisson approximation for the global epidemic size than the one presented here, but it is only accurate for severe (e.g., $R_* \geq 6$) epidemics, which is not likely to be the case for influenza.[26]

Given that a global epidemic occurs, to find the fraction of initial susceptibles that become infected, Ball and Neal[4] define the random variable S, called the size of the individual susceptibility set, which takes on an integer value between 1 and n. The probability mass function of S is derived by solving the triangular system of n linear equations (see Equation (3.5) in Reference 4):

$$\sum_{l=1}^{k} \frac{\binom{n-l}{k-l} P(S=l)}{e^{-l(n-k)\lambda_L T_I}} = \binom{n-1}{k-1} \quad \text{for} \quad k = 1, \ldots, n, \tag{2}$$

which has solution (fixing $n = 4$):

$$\begin{pmatrix} P(S=1) \\ P(S=2) \\ P(S=3) \\ P(S=4) \end{pmatrix} = \begin{pmatrix} e^{-3\lambda_L T_I} \\ 3(e^{-4\lambda_L T_I} - e^{-5\lambda_L T_I}) \\ 3(e^{-3\lambda_L T_I} - (3e^{-5\lambda_L T_I} - 2e^{-6\lambda_L T_I})) \\ 1 - (4e^{-3\lambda_L T_I} + 3e^{-4\lambda_L T_I} - 12e^{-5\lambda_L T_I} + 6e^{-6\lambda_L T_I}) \end{pmatrix}. \tag{3}$$

In terms of the solution to Equation (3), the proportion of initial susceptibles that become infected if a global epidemic occurs is the unique root $z \in (0, 1]$ of:

$$1 - z = \sum_{l=1}^{n} e^{-l\lambda_G T_I z} P(S=l). \tag{4}$$

This formula corresponds to Equation (2.2) in Reference 4. Note that the parameter λ_L is a parameter in Ball and Neal's model[4] but not in our model. To adapt Ball and Neal's result to our model, we use the fact that $E[S] = E[C]$[4] and set the value of λ_L in Equation (3) so that $\sum_{l=1}^{n} l P(S=l)$ equals the quantity $E[C]$ given in Equation (A.18) in Appendix S1. Hence, for given values of λ_G and T_I, there is a one-to-one correspondence between R_* and z for any interventions, including weighted averages of interventions so as to allow partial compliance, which allows us to create Fig. 2.

We derive the global infection rate λ_G in Section 3 of Appendix S1 by assuming that $z = 0.4$, as in previous pandemics (Figure S17 in Reference 13). The threshold parameter R_* in the base case (i.e., no infection control measures) is 1.38, which is also consistent with observed two-week gradients of excess mortality during the 1918 pandemic[13,26] (Section 3 in Appendix S1).

3. RESULTS

The analysis in Reference 9 predicts that infection control measures (e.g., handwashing) aimed solely at contact transmission will have no impact on influenza transmission. We assess three household interventions: N95 filtering-facepiece respirators, humidifiers, and increased ventilation. We also analyze the impact of opening doors, sharing bedrooms, social distancing, and workplace interventions. We consider several different scenarios regarding when and where these measures occur. Several of these scenarios implement the infection control measures in the presymptomatic period. In these scenarios no one in the household is aware during the presymptomatic

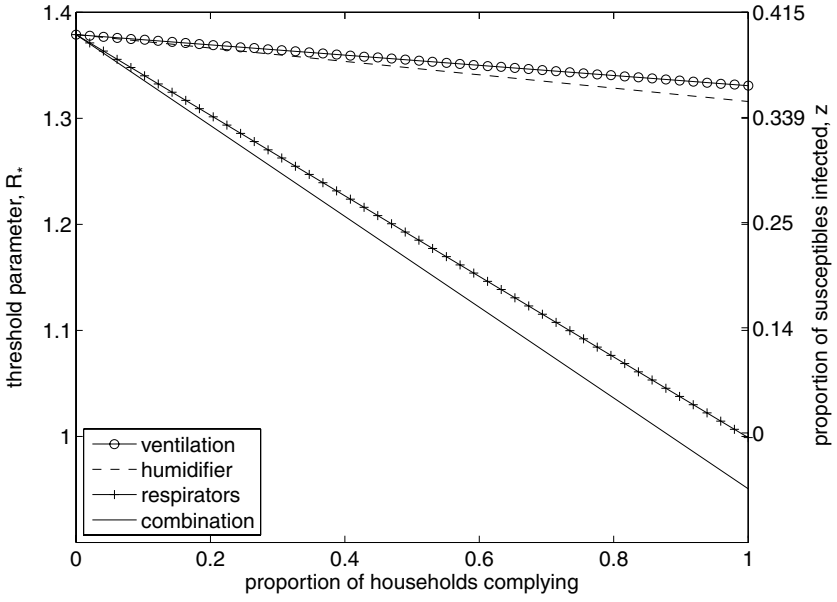

Fig. 2. The threshold parameter R_* (left vertical axis) and the proportion of susceptibles that get infected if an epidemic occurs (right vertical axis) versus the fraction of households that comply with the various interventions. The combination intervention is N95 respirators, humidifiers, and ventilation. In all cases, interventions are used only in the infected's bedroom during the symptomatic period and in the living quarters while people congregate there during the presymptomatic period.

Table I. Efficacy of N95 Respirators with Penetration Factor 0.3

Respirators					
Who	When	P_{I2}	P_{I3}	R_*	z
No one	Never	0.176	0.296	1.38	0.400
Caregiver	Symptomatic period	0.176	0.229	1.28	0.324
All susceptibles	Symptomatic period	0.175	0.229	1.28	0.323
Caregiver	When providing care				
Everyone	In presymptomatic living quarters	0.064	0.189	1.00	—
All but symptomatic infected	Infectious period	0.062	0.188	1.00	—
Everyone	Infectious period	0.062	0.149	0.95	—

Note: P_{I2}, P_{I3}, R_*, and z are the infection probability for a noncaregiving susceptible, the infection probability for the caregiver, the threshold parameter for an epidemic, and the proportion of susceptibles who get infected if there is an epidemic (which can only occur if $R_* > 1$).

period that one of the family members is sick; however, they implement these measures as a precaution to reduce their exposure to the virus in case one of the family members is an asymptomatic infected. The details of most of these scenarios, as well as the results, appear in Section 4.1 and Tables A2–A7 of Appendix S1. The results from the base case scenario for N95 respirators appear in Table I.

Before presenting our results, we discuss the parameter values used for the infection control measures. N95 respirators can be worn by the susceptibles and the infected. We assume that the penetration factor, i.e., the fraction of virus that passes through the mask, is 0.1, where nearly all of the inefficiency is due to face-seal leakage. The penetration factor varies across individuals, and for simplicity we use a single average value, which is a reasonable approximation.[27] The average penetration factor from a 1987 workplace study involving fit-tested respirators is ≈0.1.[28] However, it may not be practical to fit-test everyone in the event of an influenza pandemic. Two more recent studies that test a variety of respirators find large variations across respirator models in their face-seal leakage in the absence of fit-testing.[29,30] However, both studies find that the best respirator models are very effective without fit-testing: Respirator A in Reference 29 has an average penetration factor of 0.053 (0.04 for the 95% of people who would pass the fit test, and 0.3 for the 5% who would fail) and the best three respirator models in Reference 30 had at least a 95% likelihood of achieving a penetration factor less than or equal to 0.1 (Table III in Reference 30). While these two studies appear to suggest a mean penetration value significantly less than our specified value of 0.1, laboratory measurements (such as those presented in Reference 30) tend to overestimate the respiratory efficacy achieved during real-world use.[31,32] Taken together, we view a penetration factor of 0.1 as a reasonable value as long as the best-performing respirators (e.g., the best ones in References 29 and 30) are used without fit-testing.

The penetration factor data in References 28–30 all pertain to inward penetration (i.e., from inhalation), which is applicable to respirators worn by susceptibles. We are aware of only one study that assesses the outward penetration factor, which is applicable for respirators worn by infecteds. This study shows that—like inward penetration—the outward penetration factor is very small during breathing (see Figure 5 and Tables E2 and E3 in Reference 33). However, the study does not assess the penetration factor during a cough or sneeze (although it has been shown that a cough or sneeze causes very little reaerosolization of particles from the respirator[34]). Due to the high velocity, the face-seal leakage may be higher during a cough or sneeze than during breathing. Nonetheless, we assume a 0.1 penetration factor for both inward and outward penetration.

To account for intermittent use, we assume individuals wear their respirators approximately 75% of the time they are supposed to, which yields a penetration factor of 0.3. In Section 4.1 of Appendix S1 we also analyze the scenario where individuals wear their respirators at all times and the inefficency is due only to face-seal leakage (penetration factor of 0.1) and the scenario where individuals wear their respirators approximately 25% of the time (penetration factor of 0.8).

The humidifiers increase the relative humidity from 30% (a typical value in much of the Northern Hemisphere in the winter) to 65%, thereby

increasing the death rate of virus in the air from 0.36/h to 6.0/h.[35] Ventilation increases the outside air exchange rate from 1.0/h to 5.0/h.[36,37]

Because the virus concentration in the air is much higher in the compartment where the infected is (Fig. 3), nearly all of the potential improvements from respirators, humidifiers, and ventilation can be achieved by deploying them only in the infected's bedroom during the symptomatic period and when people congregate in the living quarters during the presymptomatic period (Table I and Tables A2–A5 in Appendix S1). Relative to this type of deployment, interventions used only in the symptomatic period achieve ≈45% of the possible R_* reduction for ventilation and humidifiers and ≈25% for respirators (e.g., compare Rows 3 and 4 of Table I or Rows 4 and 5 of Table A5 in Appendix S1). If 70% of households comply with this near-optimal deployment (mask-use compliance in San Francisco during the 1918 pandemic was 90% and 10% in the first two implementations[3]), then the threshold parameter R_* drops from 1.38 to 1.11, 1.33, and 1.35 with the use of respirators, humidifiers, and ventilation, respectively, and a combination of all three reduces R_* to 1.08 (Fig. 2). Fig. 2 illustrates the relationship between household compliance and R_* (left vertical axis) as well as z, the fraction of susceptibles that will become infected if a global epidemic occurs (right vertical axis). The quantity R_* is a linear function of $E[C]$, and $E[C]$ is a linear function of the household compliance rate; hence, the R_* versus compliance rate curves are linear in Fig. 2. There is also a unique value of z corresponding to $E[C]$. However, this value is a nonlinear function of $E[C]$ (see Equation (4)), which is why the right vertical scale is nonlinear. A pandemic can occur only if $R_* > 1$, and thus the right vertical scale is only valid for values greater than 0. Our analysis does not provide confidence intervals for the results in Fig. 2.

We also measure the impact of whether the bedroom doors are open or closed (air flow rate between two rooms is 60 m^3/h if the door is open and 1.0 m^3/h if the door is closed[38]) when they are occupied (Table A6 in Appendix S1). Keeping the bedroom doors open throughout the infectious period increases R_* from 1.38 to 1.43, with the noncaregiving susceptibles incurring nearly all of the additional risk, although if the infected's bedroom door is closed during the symptomatic period there is little harm in leaving the susceptible bedroom doors open. Leaving bedroom doors open during the presymptomatic period has little effect.

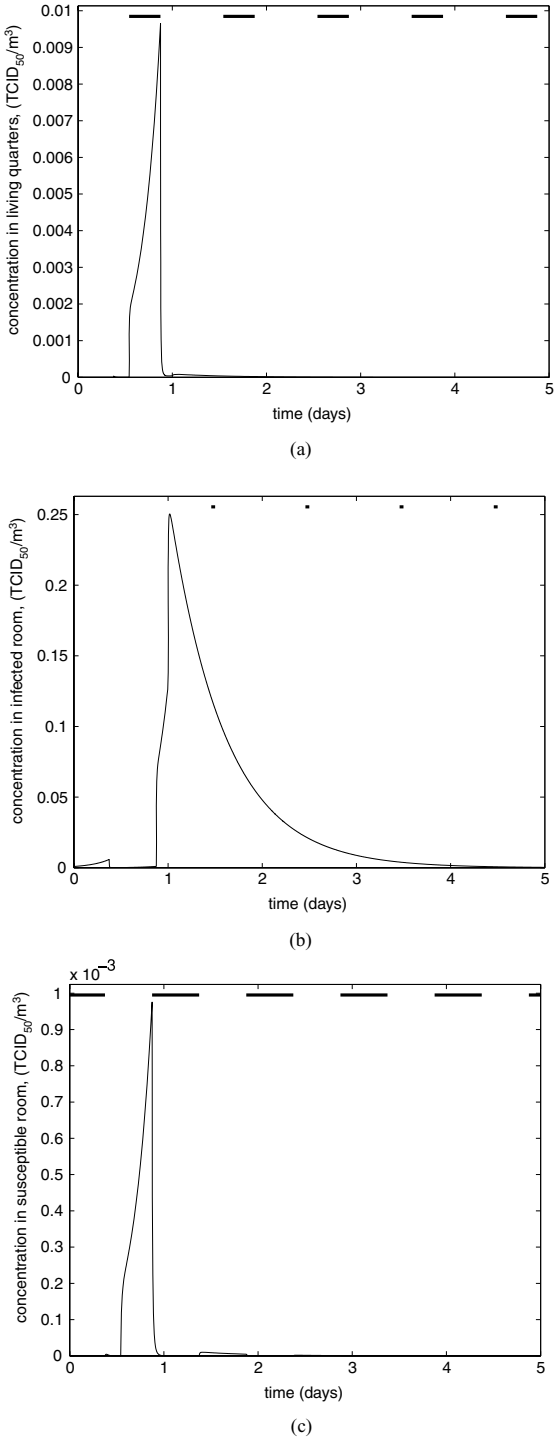

Fig. 3. Virus concentration in the air using the median initial shedding rate. In the pandemic influenza base case, the virus concentration in the air throughout the infectious period in the (a) living quarters, (b) infected's bedroom, (c) susceptible's bedroom. The thick solid lines across the top represent the times when the susceptible(s) are in the compartment. This figure is identical to Fig. 6 in Reference 9.

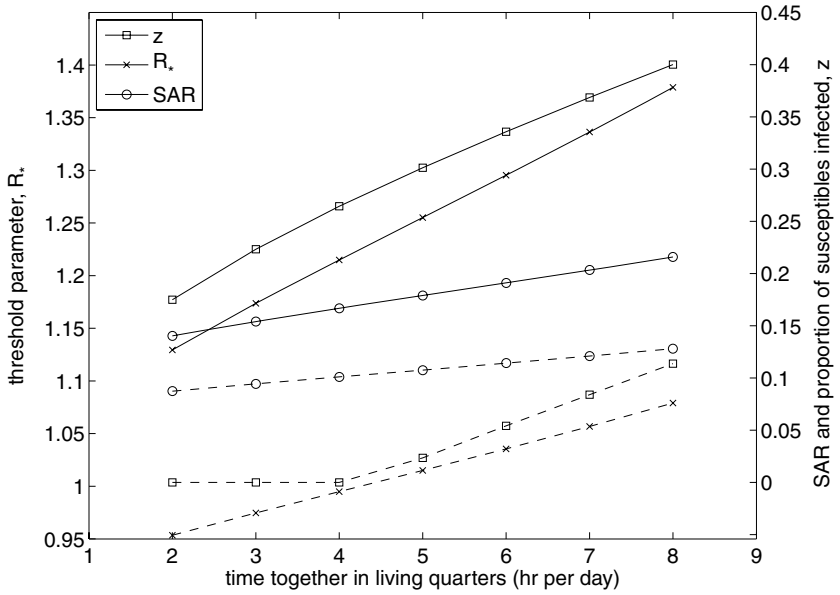

Fig. 4. Social distancing within the house, in which household members spend less time together in the living quarters and more time alone in their bedrooms behind closed doors. We consider no interventions in the home (—) and 70% compliance of the respirators-humidifiers-ventilation intervention in the home (- - -).

If the infected and a noncaregiving susceptible share the same bedroom throughout the entire infectious period (see Section 2 in Appendix S1 to see how $E[C]$ changes in this scenario), then R_* increases from 1.38 to 1.73 if the shared bedroom door is closed and 1.74 if the shared bedroom door is open (Table A7 in Appendix S1). Sharing a bedroom only during the presymptomatic period is also deleterious, increasing R_* from 1.38 to 1.54 when the shared bedroom door is either closed or open.

Social distancing within the house is achieved in our model by simultaneously reducing the amount of time household members spend together in the living quarters and increasing the time they spend alone in their bedrooms with the door closed (Fig. 4). Reducing the time together from 8 to 2 h/day reduces R_* from 1.08 to 0.95 with 70% compliance of the respirators-humidifers-ventilation combination. With no interventions, this fourfold reduction in time together reduces R_* from 1.38 to 1.13, which is not as effective as the 70% respirators-humidifiers-ventilation combination with 8 h/day together.

Our base case value of the global infection rate λ_G already includes significant social distancing (e.g., some schools and workplaces are closed). If we make the strong assumption that the governing dynamics regarding the modes of transmission between the households will be the same as those within households, then a reduction in λ_G in our model can be achieved by deploying the same measures in the workplace that are deployed within the household (see Section 4.1 in Appendix S1 for details). If 70% of workplaces comply with the respirators-humidifiers-ventilation combination, we roughly estimate (Section 4.1 and Fig. A1 in Appendix S1) that R_* is reduced from 1.38 to 1.04 with no interventions in the home, and to 0.81 if there is also 70% compliance among households.

4. DISCUSSION

The following picture emerges from our study. There is great interperson heterogeneity in viral shedding,[14] and the majority of transmissions are caused by the superspreaders, consistent with other transmissible diseases;[39] hence, the high correlation between viral shedding and symptoms[40] suggests that our omission of asymptomatics is inconsequential. Most of the transmissions occur in a small time window near the time that symptoms appear, with slightly more than half occuring during the presymptomatic period (somewhat larger than the 0.3–0.5 estimate in Reference 41). The caregiver is approximately twice as likely to get infected as the noncaregiving susceptibles, although the discrepancy decreases if bedroom doors are kept open. A very small portion ($\approx 10^{-6}$) of the shed virus resides in particles that are small enough ($<20\ \mu$m) to be airborne (i.e., to not undergo instantaneous deposition); it is the larger ($>3\ \mu$m) droplet nuclei that cause most of the infections because they make up most of the

deposition in the respiratory epithelium, which is the location of infection in our model. Moreover, nearly all of the aerosol transmission is within-room because of the high deposition rate of the $>3\,\mu$m droplet nuclei.

In terms of mitigation, separating oneself from the infected by a closed door reduces the virus concentration in the air by ≈40-fold, respirators reduce the inhaled virus by 3.3-fold in the symptomatic period and 11.1-fold in the presymptomatic period (because in this scenario everyone, including the infected, wears a respirator during the presymptomatic period as a precautionary measure even though no one is aware yet that the infected is sick), and humidifiers and ventilation each reduce the virus concentration in the air by ≈20%. The average virus concentration in the absence of control measures during the infectious period in the infected's room ($3.33 \times 10^{-2}\,\mathrm{TCID}_{50}/\mathrm{m}^3$) is 100 times greater than the average concentration in the living quarters ($3.31 \times 10^{-4}\,\mathrm{TCID}_{50}/\mathrm{m}^3$) and 1,000 times greater than the average concentration in the susceptible's room ($3.37 \times 10^{-5}\,\mathrm{TCID}_{50}/\mathrm{m}^3$). See Fig. 3 for the virus concentration in each room over time. The high virus concentration in the infected's bedroom explains why the caregiver is at a greater risk for infection.

A crucial observation is that interventions used solely during the symptomatic period reduce R_* by only ≈30% of what could be achieved by also using them in the presymptomatic period; while it may seem implausible that individuals within a household would wear a respirator when no one in the household is symptomatic, this result suggests the benefit from doing so. This observation is due partly to the nonlinear nature of the dose-response curve: N95 respirators reduce the infection probability of the noncaregiving susceptibles from 0.18 to 0.06 (Table I) if used presymptomatically because these susceptibles are on the steep part of the dose-response curve, while the infection probability of the caregiver decreases from 0.30 to 0.23 (Table I) if used postsymptomatically because the caregiver receives a higher dose and is on the flatter part of the dose-response curve.

The main caveat of our investigation is that many of the influenza characteristics are based on interpandemic influenza strains, which may differ from the characteristics of a future pandemic influenza strain. In particular, the 1918 influenza,[42] the 1957 pandemic strain,[43] and the current H5N1 virus[44] all appear to target the alveolar region in addition to the interpandemic target of the respiratory epithelium. Hence, we reran our entire model under the assumption that the alveolar region, which is attacked by smaller droplet nuclei (Figure 3 in Reference 9), is also a target of infection, and found that the beneficial impact of humidifiers, ventilation, and closing the infected's bedroom door during the symptomatic period all increase slightly, although still remain less important than respirator use (data not shown).

To the extent that respirators (and goggles) and not handwashing or gloves would best protect against droplet transmission, if a small amount of droplet transmission occurs (our analysis in Reference 9 suggests that this could be the case), then our main recommendation about the importance of respirators over gloves, handwashing, and surface cleaning is unaffected. That is, if respirators filter out 70% of inhaled virus, then it does not really matter (in our model) whether the ingested virus comes from the inhalation of droplet nuclei or from a close expiratory event: the reduction in transmission will be very similar in either case. However, our omission of droplet transmission does suggest that we may be slightly overestimating the impact of ventilation, humidifiers, and bedroom doors because these do not protect against droplet transmission. Furthermore, if particles $>20\,\mu$m contribute to aerosol transmission (see Section 4.2 and Table A8 in Appendix S1), increased ventilation and humidifiers will not be as effective because the removal rate of the virus on the larger particles will be dominated by settling. Although not included in our model, fecal aerosol transmission may be possible,[45] as in the case of SARS,[46] in which case the respirators-humidifiers-ventilation combination would be beneficial, as would a separate bathroom for the infected.[47]

Taken together, while it is prudent to recommend frequent handwashing, the use of gloves and goggles, and the cleaning of surfaces, we believe the focus of education and action for pandemic influenza infection control measures should be on the reduction of aerosol transmission. Even assuming that N95 respirators have a penetration factor as high as 0.8, this intervention is more effective than humidifiers and ventilation, and also mitigates contact (by reducing the self-inoculation rate) and droplet transmission. It is important to perform human experiments, which would be possible and ethical, to further assess the efficacy of masks and respirators for seasonal influenza; data are particularly needed to assess the outward penetration factor during a cough or sneeze. But given the lead time necessary for such

experiments and the uncertainty regarding the timing and likelihood of an influenza pandemic, education and action regarding face protection should be undertaken in parallel with human experiments. The public should be strongly encouraged to wear respirators when mixing with other people, both inside and outside of the home, throughout the entire pandemic. While even intermittent use of masks can be effective, it is important for susceptibles to wear them as much as possible when around other people: R_* drops by ≈25% (see Row 4 of Table I and Row 4 of Table A3 in Appendix S1) when the respirator penetration factor drops from 0.8 to 0.3 (which corresponds to increasing respirator compliance within the household from ≈25% to ≈75%). The U.S. government is beginning to move in this direction: its interim guidelines state that facemasks should be considered by individuals who enter crowded settings.[48] Because breathing is more difficult with N95 respirators, we do not believe it is appropriate or practical to expect symptomatic infecteds to wear respirators, nor is it necessary for susceptibles to wear respirators while they are alone in a room. It may be impractical to have young children wear respirators; although they are the biggest spreaders of interpandemic influenza because of their high shedding rate (due to lack of immunity) and their crowded conditions, this may not be so during a pandemic because no one will have immunity and many schools and day care centers will be closed.

Although stockpiling of respirators needs to begin as soon as possible, several important issues need to be addressed. The biggest challenge may be respirator production capacity: if people used a new respirator every day (health-care workers discard theirs after each shift), a family of four would spend ≈ $1,000[5] on N95 respirators throughout the pandemic wave and U.S. demand could be 10 billion. The only practical solution may be to reuse respirators for an extended period of time. Several respirator manufacturers claim that N95 respirators could in theory be worn until moist, damaged, soiled, or difficult to breathe through,[5] and wearing a surgical mask over a N95 respirator may lengthen its usable life.[5] It would certainly appear that respirators could be used during the presymptomatic period for as long as they last. Although it would be prudent for the caregiver to discard his or her respirator after each use during the symptomatic period, even these could probably be reused in light of the high death rate of influenza on porous surfaces. Another important issue is fit, since face-seal leakage is much more problematic than filter efficiency. Face-seal leakage varies widely among different respirator models, but a handful of models have very little face-seal leakage even without fit-testing (Table I in Reference 29, Table I in Reference 30). The government needs to educate the public about these studies and to ensure that these models (or others with similar performance) are the focus of surge capacity efforts; toward this end, the Food and Drug Administration recently cleared for marketing two respirators for use during a health emergency such as an influenza pandemic.[49] The surge capacity challenge for N95 respirators begs the question of whether we can use surgical masks (which are primarily used to mitigate droplet transmission), which are 10 times less expensive[5] and may generate higher compliance because of being less uncomfortable, as a substitute for N95 respirators. Using data from the best surgical masks tested in Reference 50, we estimate (Section 4.1 in Appendix S1) that surgical mask filters worn by susceptibles allow penetration of only 1.0–1.7% of virus during the infectious period (droplet nuclei are typically larger than the particles often used to test masks and respirators). The penetration factor increases to 1.1–1.8% if the next pandemic influenza, as with the 1918 and 1957 pandemics[42,43] and the current H5N1 strain,[44] targets the alveoli in addition to the respiratory epithelium. Although surgical masks have a fit factor of 2.7 (i.e., 37% of virus leaks in),[51] nylon hosiery worn over a respirator has been shown to decrease the penetration factor from 0.19 to 0.006 by reducing face-seal leakage,[52] suggesting that nylon hosiery worn over a good surgical mask may be a feasible alternative to a N95 respirator for a susceptible; however, the surgical mask would be significantly less effective on an infected because the filter penetration factor degrades noticeably with higher velocities.[53] Finally, mask and respirator manufacturers need to be relieved of liability issues.

Although ventilation and humidifiers offer only modest benefits in our model, they should be used because of the possibility that a pandemic influenza could target the alveolar region with small droplet nuclei, which do not settle from the air as quickly as those that target the respiratory epithelium. Leaving windows open and using fans are inexpensive. A recent study showed that influenza transmission in guinea pigs was reduced by high humidity and high temperatures[54] and, hence, it may be important to simultaneously use heating and ventilation, which could lead to substantial additional heating costs. However, the hypothesis in Reference 54 is that

breathing cold air slows mucus clearance in the respiratory tract, and masks or respirators would likely increase the temperature of the inhaled air. Recirculation of air, particularly from the infected's bedroom to the rest of the house, should be kept to a minimum in the home and the workplace. Ideally, each person should sleep in a separate bedroom during the entire pandemic, even if no one in the house has symptoms. For people living in crowded conditions, it is particularly important to physically separate the infected's bed from other parts of the home during the symptomatic period, via makeshift walls or doors, or having some susceptibles sleep in the living quarters. Social distancing of the caregiver within the home may help, not because the caregiver is an effective vector by transmitting the infected's virus to the other susceptibles in the house (he or she is not in our model), but because the caregiver is roughly twice as likely to be an asymptomatic infected in the days following the start of the original infected's infectious period. Although not covered directly in our model, the caregiver should also keep his or her time outside of the house to a minimum,[47] and conversely social distancing within the home of household members that spend considerable time outside of the house would likely be effective.

People who do not have windows that open should use humidifiers, although our result on humidifiers may be less robust than our findings on respirators and ventilation: it is dependent upon the characteristics of the particular influenza strain and humidity can deplete the electrostatic charge in the respirators, which is used to capture small particles[5] (although our analysis of the data on surgical masks suggests that this is not an important issue). Maintaining 65% relative humidity for the entire pandemic could cause damage to the interior of a house or increase mold growth. Also, we are uncertain how the high humidity and ventilation rate affects the infected's health and comfort, although extreme temperature and humidity did not affect the degree of illness in experimentally-infected swine and turkeys.[55]

While it is impossible to accurately predict the R_* of the next influenza pandemic and, hence, the likelihood that these interventions could control an outbreak (in our base case, $R_* = 1.38$ and so a 28% reduction is needed to control an outbreak), our results suggest a nontrivial $\approx$20% reduction in R_* if the respirators-humidifiers-ventilation combination was adopted by 70% of houses, and $\approx$40% reduction in R_* if this combination was also adopted by 70% of the workplaces. Even a 10% reduction in R_* in the base case would avert over 30M cases in the United States. Although these numerical estimates are very rough and likely not predictive of an actual pandemic, due partly to the inexact application of, and the simplicity of, the households epidemic model (e.g., there is no age-dependence in contact rates, susceptibility, or infectiousness), but mostly to the fact that we are very uncertain about the characteristics—including human behavior—of the next pandemic, they do suggest that these interventions should be aggressively pursued since they may be our main line of defense (along with other nonpharmaceutical measures whose benefits have been quantified elsewhere, such as social distancing and school closures[56,57]) during the pandemic's first wave. The government, the health-care supply industry, and the private sector (for use in the workplace) should work together to coordinate production and, if necessary, subsidize the purchases of the necessary equipment, particularly N95 respirators and/or surgical masks. For all of the mask- and respirator-related issues, it is important for the government to switch mindsets, from the perspective of a regulatory agency protecting workers who are paid to do a dangerous job on a daily basis, to that of providing citizens with the tools to best protect themselves during a pandemic.

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Appendix S1.

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Appendix

This Appendix provides a detailed formulation of the model that generated the results reported in the main text. The within-household model is described in §1, and a key component to embed this household model into the the broader epidemiological model of disease spread described in §2.2 of the main text is formulated in §2. The global infection rate is estimated in §3 and infection control measures are assessed in §4.

1 The Within-Household Model

This section describes the mathematical model of disease spread within a household that contains a single infected person and $n-1$ susceptibles. The viral dynamics are modeled in §1.1, the dose is calculated in §1.2 and the dose-response model is formulated in §1.3. For more information about this model see [1].

1.1 The Viral Dynamics

The infected person becomes infectious at time 0, develops symptoms at time T_p, and stops being infectious at time T_I. This subsection develops an ordinary differential equation model for the time period $[0, T_I]$. We assume the house consists of three compartments: the living quarters (indexed by $j = 1$), the infected's bedroom ($j = 2$), and a susceptible's bedroom ($j = 3$). We do not explicitly model multiple susceptible bedrooms, and hence ignore the small amount of virus that could leak out of the living quarters and into these other bedrooms. There are three state variables: the concentration of virus of diameter x in the air at time t in each of the three compartments ($C_j(x,t)$ for $j = 1, 2, 3$).

There are several differences in the model between the pre-symptomatic phase $[0, T_p]$ and the symptomatic phase $(T_p, T_I]$. The infected person stays in his bedroom throughout the symptomatic period and one of the susceptibles, referred to as the caregiver, spends some time in the infected's

bedroom to provide care; during the symptomatic period, the other $n-2$ non-caregiving susceptibles never go into the infected's bedroom. In addition, as described in §3 of [1], some of the parameters take on different values in the pre-symptomatic and symptomatic periods to reflect increased social distancing.

We use the indicator functions $I_{ij}(t)$ to describe the presence or absence of person i ($i = 1$ for infected, $i = 2$ for non-caregiving susceptible, $i = 3$ for caregiver) in compartment j. During the pre-symptomatic period, each person spends Δ_1 hours each day in the living quarters followed by Δ_2 hours in his bedroom, and is out of the house for $24 - \Delta_1 - \Delta_2$ hours. We assume that these times are perfectly synchronized, so that each family member is in his bedroom, in the living quarters, or out of the house during the same hours. The non-caregiving symptomatics follow this same schedule throughout the symptomatic period, and the caregiver does also, except for spending Δ_3 hours providing care in the infected's bedroom in lieu of being out of the house. The indicator functions (where time is in hours and τ_1 and τ_2 specify the beginning of the living quarters time and the caregiving time, respectively - note also that $T_p = 24$ hr and that $x^+ = \max\{x, 0\}$) are

$$I_{11}(t) = \begin{cases} 1 & \text{for } t \in [(24i+\tau_1)^+, \min\{(24i+\tau_1+\Delta_1)^+, T_p\}) \text{ for } i = -1, \ldots, \frac{T_p}{24} - 1; \\ 0 & \text{otherwise,} \end{cases} \tag{1}$$

$$I_{12}(t) = \begin{cases} 1 & \text{for } t \in [\min\{(24i+\tau_1+\Delta_1)^+, T_p\}, \min\{(24i+\tau_1+\Delta_1+\Delta_2)^+, T_p\}) \cup t \in [T_P, T_I] \text{ for } i = -1, \ldots, \frac{T_p}{24} - 1; \\ 0 & \text{otherwise,} \end{cases} \tag{2}$$

$$I_{21}(t) = \begin{cases} 1 & \text{for } t \in [(24i+\tau_1)^+, \min\{(24i+\tau_1+\Delta_1)^+, T_I\}) \text{ for } i = -1, \ldots, \frac{T_I}{24} - 1; \\ 0 & \text{otherwise,} \end{cases} \tag{3}$$

$$I_{31}(t) = \begin{cases} 1 & \text{for } t \in [(24i+\tau_1)^+, \min\{(24i+\tau_1+\Delta_1)^+, T_I\}) \text{ for } i = -1, \ldots, \frac{T_I}{24} - 1; \\ 0 & \text{if } I_{32}(t) = 1 \\ 0 & \text{otherwise,} \end{cases} \tag{4}$$

$$I_{23}(t) = \begin{cases} 1 & \text{for } t \in [\min\{(24i+\tau_1+\Delta_1)^+, T_I\}, \min\{(24i+\tau_1+\Delta_1+\Delta_2)^+, T_I\}) \text{ for } i = -1, \ldots, \frac{T_I}{24} - 1; \\ 0 & \text{otherwise,} \end{cases} \tag{5}$$

$$I_{33}(t) = \begin{cases} 1 & \text{for } t \in [\min\{(24i+\tau_1+\Delta_1)^+, T_I\}, \min\{(24i+\tau_1+\Delta_1+\Delta_2)^+, T_I\}) \text{ for } i = -1, \ldots, \frac{T_I}{24} - 1; \\ 0 & \text{if } I_{32}(t) = 1 \\ 0 & \text{otherwise,} \end{cases} \tag{6}$$

$$I_{32}(t) = \begin{cases} 1 & \text{for } t \in [24i+\tau_3, 24i+\tau_3+\Delta_3) \text{ for } i = 1, \ldots, \frac{T_I}{24} - 1; \\ 0 & \text{otherwise,} \end{cases} \tag{7}$$

and $I_{13}(t) = I_{22}(t) = 0$ for $t \in [0, T_I]$. In the base case, we assume that bedroom doors are closed when the bedroom is occupied and open when the bedroom is unoccupied.

Let $\lambda(t)$ be the rate of viral shedding at time $t \in [0, T_I]$. We assume that the viral shedding rate grows exponentially at rate ν starting from the level Λ_0 during the pre-symptomatic phase and then drops exponentially at rate ω during the symptomatic phase, so that

$$\lambda(t) = \begin{cases} \Lambda_0 e^{\nu t} & \text{for} \quad t \in [0, T_p]; \\ \Lambda_0 e^{\nu T_p - \omega(t-T_p)} & \text{for} \quad t \in [T_p, T_I]. \end{cases} \tag{8}$$

Equation (8) is consistent with the observation that viral shedding is maximal at the time when symptoms appear, and decreases exponentially thereafter [2, 3]. To capture the interperson heterogeneity in viral shedding, we let Λ_0 be a log-normal random variable with probability density function $h(\lambda)$, where the natural logarithm of the iniital shedding rate has mean m_λ (i.e., the median initial shedding

rate is e^{m_λ}) and standard deviation σ_λ (i.e., the dispersion is e^{σ_λ}).

Compartment j has air volume V_j and ventilation (i.e., outdoor air supply) rate Q_j. In addition, Q_{ij} is the air flow rate from compartment i to compartment j, where $Q_{23} = Q_{32} = 0$. We assume that particles smaller than d_c in diameter immediately evaporate in the air and become droplet nuclei with diameter half their original size, and all particles with diameter larger than d_c instantaneously settle on a surface; the actual times until evaporation for sub$-d_c$ particles and settling times for super$-d_c$ particles are orders-of-magnitude smaller than T_p [4, 5]. The diameter of a particle is the aerodynamic diameter and when we refer to a particle of diameter x it is the pre-evaporation size (and thus its size in the air as a droplet nuclei would be of diameter $\frac{x}{2}$). Let $p(x)$ be the probability density function (pdf) of particle sizes (i.e., diameters) emitted by the infected (before evaporation), which represents a weighted average of particle sizes emitted during coughing and sneezing. Because the amount of virus in a particle is roughly proportional to the particle's volume [6], we define $f(x) = \frac{x^3 p(x)}{\int_0^\infty x^3 p(x)\ dx}$, which is the pdf for the proportion of shed virus that is in particles of each size. Let p_r be the penetration factor of the infected's respirator (i.e., the fraction of expelled virus that escapes the respirator and gets into the air), where $p_r = 1$ if the infected person does not wear a respirator. The death rate of virus in the air is μ_a. By Stokes Law, we assume that airborne virus of diameter x deposits on the surfaces at rate proportional to the diameter squared [7], which we denote by κx^2. We also assume that at each point in time and independent of particle size, a fraction p_s of the shed virus ends up on surfaces due to protective measures on the part of the infected (e.g., the virus lands on tissues for a sneeze, or hands for a cough).

The above description implies that for $x \in [0, d_c]$, the state equations are

$$\begin{aligned}\dot{C}_1(x,t) = &\frac{p_r f(x)(1-p_s)\lambda(t) I_{11}(t)}{V_1} + \frac{Q_{21}C_2(x,t) + Q_{31}C_3(x,t)}{V_1} \\ &- \Big[\frac{Q_1 + Q_{12} + Q_{13}}{V_1} + \mu_a + \kappa x^2\Big] C_1(x,t), \end{aligned} \tag{9}$$

$$\dot{C}_2(x,t) = \frac{p_r f(x)(1-p_s)\lambda(t) I_{12}(t)}{V_2} + \frac{Q_{12}C_1(x,t)}{V_2} - \Big[\frac{Q_2 + Q_{21}}{V_2} + \mu_a + \kappa x^2\Big] C_2(x,t), \tag{10}$$

$$\dot{C}_3(x,t) = \frac{Q_{13}C_1(x,t)}{V_3} - \Big[\frac{Q_3 + Q_{31}}{V_3} + \mu_a + \kappa x^2\Big]C_3(x,t). \tag{11}$$

Equations (9)-(11) can be solved numerically for $\{C_j(x,t), t \geq 0\}$ for $j = 1, 2, 3$ and $x \in [0, d_c]$.

1.2 The Dose

Aerosol transmission occurs because a susceptible inhales droplet nuclei that contain virus. In this subsection, we compute the dose received by a susceptible in terms of the solution $C_j(x,t)$ to (9)-(11). The relationship between this dose and the likelihood of infection is described in §1.3.

Let b be the breathing rate and p_{aj} be the penetration factor (the virus concentration in the air outside of the respirator divided by the virus concentraton of the air inside of the respirator) for a susceptible in compartment j, where $p_{aj} = 1$ if no respirator is being worn. Then the total dose inhaled of size x by a non-caregiving susceptible $(i = 2)$ and the caregiver $(i = 3)$ is

$$D_i(x) = b\int_0^{T_I} \sum_{j=1}^{3} p_{aj}C_j(x,t)I_{ij}(t)\, dt. \tag{12}$$

1.3 The Dose-Response Relationship

In this subsection, we derive the probability that a susceptible gets infected in terms of the dose $D_i(x)$ in equation (12). Human influenza virus preferentially binds to $\alpha 2$-6-linked sialic acids on receptors of ciliated columnar epithelial cells, leading to viral replication in the respiratory epithelium [8, 9]. Let $g(x)$ be the fraction of inhaled virus of size x that is deposited on the respiratory epithelium (Figure 3 of [1] illustrates $g(x)$). Then the total dose deposited on the respiratory epithelium for non-caregiving susceptibles ($i = 2$) and the caregiver ($i = 3$) is

$$\bar{D}_i = \int_0^{d_c} D_i(x)g(x)\, dx. \tag{13}$$

We use the Poisson model to compute the likelihood of infection, which is standard in the literature and which has been shown to model influenza infection and other airborne infections reasonably

well [4, 10]. Let ID_{50} denote the median infectious dose for inhaled virus deposited in the respiratory epithelium and define the constant $\alpha = \frac{\ln 2}{\text{ID}_{50}}$. We denote the infection probability as P_{Ii}, where capital I stands for infection and lowercase i distinguishes between the non-caregiving susceptible $(i = 2)$ and the caregiver ($i = 3$). If we write the dose in (13) as a function of the initial viral shedding rate Λ_0, which has pdf $h(\lambda)$, then the probability that a non-caregiving susceptible $(i = 2)$ and the caregiver ($i = 3$) become infected, assuming probabilistic independence between the various modes of infection, is

$$P_{Ii} = 1 - \int_0^\infty e^{-\alpha \bar{D}_i(\lambda)} h(\lambda)\, d\lambda. \tag{14}$$

2 Calculation of the Total Number of Household Infections

In this section we will derive the expression for $E[C]$, introduced in §2.2.1 of the main text, for $n = 4$ because that is the value used in this study. We can no longer describe susceptibles as either caregiver or noncaregiver, for we need to take into account situations where the caregiver becomes ill and a noncaregiver must take over the role as caregiver and care for all sick individuals in the house. We assume that the original caregiver remains caregiver as long as he remains healthy, regardless of how many other susceptibles become sick. However, the noncaregivers are no longer indistinguishable; each is given a rank based on when they will become the caregiver. A noncaregiver becomes the caregiver only if the original caregiver, as well as all other noncaregivers with higher rank, become sick. In this section, to avoid confusion, we will refer to the members of the house as person 1 (initial infected), person 2 (initial caregiver), person 3 (initial noncaregiver, first alternate caregiver), and person 4 (initial noncaregiver, second alternate caregiver). In order to compute $E[C]$ we need to compute the infection probabilities for person 2, person 3, and person 4.

We first analyze person 2, who is infected in the first wave with probability P_{I3}. With probability $(1 - P_{I3})$, person 2 is not directly infected in the first wave, and there are 3 remaining scenarios where person 2 can be infected indirectly. If both person 3 and person 4 get sick in the first wave

(with probability P_{I2}^2), then person 2 now cares for all three sick people, however he can only be infected in the second wave by person 3 or person 4. Assuming transmission from each infected is independent, the total probability of person 2 getting sick in the second wave in this scenario is $(1-P_{I3})P_{I2}^2(1-(1-P_{I3})^2)$. In the next scenario, person 3 gets sick in the first wave but person 4 does not (with probability $(1-P_{I2})P_{I2}$). There are two subcases where person 2 can now get sick. Person 3 can infect person 2 in the second wave (with probability P_{I3}), or person 4 can infect him in the third wave after person 3 infects person 4 in the second wave (which implies person 3 does not infect person 2 in the second wave). The total probability that person 2 gets sick in the second wave in this scenario is $(1-P_{I3})(1-P_{I2})P_{I2}P_{I3}$, whereas the total probability that person 2 gets sick in the third wave in this scenario is $(1-P_{I3})(1-P_{I2})P_{I2}(1-P_{I3})P_{I2}P_{I3}$. The final scenario is person 4 gets sick in the first wave but person 3 does not, however this is equivalent to the last scenario. Thus the total probability person 2 (the original caregiver) gets sick is

$$\begin{aligned} P_c =& P_{I3} + \underbrace{(1-P_{I3})P_{I2}^2}_{\text{1st wave}}\underbrace{(1-(1-P_{I3})^2)}_{\text{2nd wave}} + \underbrace{2(1-P_{I3})(1-P_{I2})P_{I2}}_{\text{1st wave}}\underbrace{P_{I3}}_{\text{2nd wave}} \\ &+ \underbrace{2(1-P_{I3})(1-P_{I2})P_{I2}}_{\text{1st wave}}\underbrace{(1-P_{I3})P_{I2}}_{\text{2nd wave}}\underbrace{P_{I3}}_{\text{3rd wave}} \quad . \end{aligned} \tag{15}$$

The derivation for person 3 is similar. If both person 2 and person 4 get sick in the first wave, then person 3 becomes the caregiver. If person 4 gets sick in the first wave but person 2 does not, then person 3 remains a noncaregiver in the second wave (but may become a caregiver in the third wave). Finally if person 2 gets sick in the first wave and person 4 does not, then person 3 becomes the caregiver. Thus the total probability person 3 (original noncaregiver, first alternate caregiver) gets

sick is

$$P_{nc,1} = P_{I2} + \underbrace{(1-P_{I2})P_{I2}P_{I3}}_{\text{1st wave}}\underbrace{(1-(1-P_{I3})^2)}_{\text{2nd wave}} + \underbrace{(1-P_{I2})(1-P_{I3})P_{I2}}_{\text{1st wave}}\underbrace{P_{I2}}_{\text{2nd wave}}$$
$$+ \underbrace{(1-P_{I2})(1-P_{I3})P_{I2}}_{\text{1st wave}}\underbrace{(1-P_{I2})P_{I3}}_{\text{2nd wave}}\underbrace{P_{I3}}_{\text{3rd wave}} + \underbrace{(1-P_{I2})(1-P_{I2})P_{I3}}_{\text{1st wave}}\underbrace{P_{I3}}_{\text{2nd wave}}$$
$$+ \underbrace{(1-P_{I2})(1-P_{I2})P_{I3}}_{\text{1st wave}}\underbrace{(1-P_{I3})P_{I2}}_{\text{2nd wave}}\underbrace{P_{I3}}_{\text{3rd wave}} . \tag{16}$$

Finally, person 4 becomes the caregiver only when both person 2 and person 3 are sick. Using similar calculations, the total probability that person 4 (original noncaregiver, second alternate caregiver) gets sick is

$$P_{nc,2} = P_{I2} + \underbrace{(1-P_{I2})P_{I2}P_{I3}}_{\text{1st wave}}\underbrace{(1-(1-P_{I3})^2)}_{\text{2nd wave}} + \underbrace{(1-P_{I2})(1-P_{I3})P_{I2}}_{\text{1st wave}}\underbrace{P_{I2}}_{\text{2nd wave}}$$
$$+ \underbrace{(1-P_{I2})(1-P_{I3})P_{I2}}_{\text{1st wave}}\underbrace{(1-P_{I2})P_{I3}}_{\text{2nd wave}}\underbrace{P_{I3}}_{\text{3rd wave}} + \underbrace{(1-P_{I2})(1-P_{I2})P_{I3}}_{\text{1st wave}}\underbrace{P_{I2}}_{\text{2nd wave}}$$
$$+ \underbrace{(1-P_{I2})(1-P_{I2})P_{I3}}_{\text{1st wave}}\underbrace{(1-P_{I2})P_{I3}}_{\text{2nd wave}}\underbrace{P_{I3}}_{\text{3rd wave}} . \tag{17}$$

Putting these values together, we have

$$E[C] = 1 + P_c + P_{nc,1} + P_{nc,2}, \tag{18}$$

which allows us to compute the threshold parameter in equation (1) of the main text. While it is certainly possible to extend these computations for a general n, the number of possible scenarios grows exponentially and there is no obvious way to write the general probabilities in a compact form.

We also look at a situation where a susceptible shares a room with the infected (§4.1). To embed this in the global model we assume that person 3 (original noncaregiver, first alternate caregiver) shares the room. We also assume that the room is shared only during the first wave (e.g., if person

4 gets sick in the first wave, then person 3 does not then share a room with person 4). Making these slight adjustments, and defining P_{Ish} to be the probability the susceptible sharing the room is directly infected by the initial infected (P_{I2} and P_{I3} are the same as in the other situations), we have the following probabilities for the roomsharing scenario:

$$\begin{aligned} P_c =& P_{I3} + \underbrace{(1-P_{I3})P_{I2}P_{Ish}}_{\text{1st wave}}\underbrace{(1-(1-P_{I3})^2)}_{\text{2nd wave}} + \underbrace{(1-P_{I3})(1-P_{I2})P_{Ish}}_{\text{1st wave}}\underbrace{P_{I3}}_{\text{2nd wave}} \\ &+ \underbrace{(1-P_{I3})(1-P_{I2})P_{Ish}}_{\text{1st wave}}\underbrace{(1-P_{I3})P_{I2}}_{\text{2nd wave}}\underbrace{P_{I3}}_{\text{3rd wave}} + \underbrace{(1-P_{I3})(1-P_{Ish})P_{I2}}_{\text{1st wave}}\underbrace{P_{I3}}_{\text{2nd wave}} \\ &+ \underbrace{(1-P_{I3})(1-P_{Ish})P_{I2}}_{\text{1st wave}}\underbrace{(1-P_{I3})P_{I2}}_{\text{2nd wave}}\underbrace{P_{I3}}_{\text{3rd wave}} . \end{aligned} \tag{19}$$

$$\begin{aligned} P_{nc,1} =& P_{Ish} + \underbrace{(1-P_{Ish})P_{I2}P_{I3}}_{\text{1st wave}}\underbrace{(1-(1-P_{I3})^2)}_{\text{2nd wave}} + \underbrace{(1-P_{Ish})(1-P_{I3})P_{I2}}_{\text{1st wave}}\underbrace{P_{I2}}_{\text{2nd wave}} \\ &+ \underbrace{(1-P_{Ish})(1-P_{I3})P_{I2}}_{\text{1st wave}}\underbrace{(1-P_{I2})P_{I3}}_{\text{2nd wave}}\underbrace{P_{I3}}_{\text{3rd wave}} + \underbrace{(1-P_{Ish})(1-P_{I2})P_{I3}}_{\text{1st wave}}\underbrace{P_{I3}}_{\text{2nd wave}} \\ &+ \underbrace{(1-P_{Ish})(1-P_{I2})P_{I3}}_{\text{1st wave}}\underbrace{(1-P_{I3})P_{I2}}_{\text{2nd wave}}\underbrace{P_{I3}}_{\text{3rd wave}} . \end{aligned} \tag{20}$$

$$\begin{aligned} P_{nc,2} =& P_{I2} + \underbrace{(1-P_{I2})P_{Ish}P_{I3}}_{\text{first wave}}\underbrace{(1-(1-P_{I3})^2)}_{\text{2nd wave}} + \underbrace{(1-P_{I2})(1-P_{I3})P_{Ish}}_{\text{1st wave}}\underbrace{P_{I2}}_{\text{2nd wave}} \\ &+ \underbrace{(1-P_{I2})(1-P_{I3})P_{Ish}}_{\text{1st wave}}\underbrace{(1-P_{I2})P_{I3}}_{\text{2nd wave}}\underbrace{P_{I3}}_{\text{3rd wave}} + \underbrace{(1-P_{I2})(1-P_{Ish})P_{I3}}_{\text{1st wave}}\underbrace{P_{I2}}_{\text{2nd wave}} \\ &+ \underbrace{(1-P_{I2})(1-P_{Ish})P_{I3}}_{\text{1st wave}}\underbrace{(1-P_{I2})P_{I3}}_{\text{2nd wave}}\underbrace{P_{I3}}_{\text{3rd wave}} . \end{aligned} \tag{21}$$

3 Estimating the Global Infection Rate λ_G

The values of all of the parameters except for the global infection rate λ_G were estimated in [1], and for convenience are listed in Table 1. In this section, we estimate λ_G. The basic reproductive number R_0 for the 1918 influenza has been estimated to be $\approx 2-3$, which incorporates both social distancing (e.g., limited school and public gatherings, and crude masks often worn in public, sometimes by decree [28, 29]) and partial immunity from the first wave of disease in the spring of 1918 [30]; if the pandemic hit during the first wave and there was no population immunity, then the reproductive number would be $\approx 2.9-3.9$. More recently, the generation time was estimated to be 2.6 days rather than ≈ 4 days, which revises the pandemic influenza value downward to $R_0 \approx 1.8$ [14]. Because R_* and R_0 have different interpretations – R_* is the basic reproductive ratio of within-house infectious clumps, i.e., infected people within a house arising from a single infected household member [31] – we estimate the global infection rate, λ_G, so that equation (4) in the main text is satisfied with z replaced by the fraction of the population that gets infected.

Although our main goal is to estimate λ_G for pandemic influenza, we also estimate it for interpandemic influenza. Typical z values are 0.15-0.25 for interpandemic influenza [32] and 0.4 for pandemic influenza (Fig. S17 in [14]). For interpandemic influenza, we let the residence times in the bedroom and living quarters be $\Delta_1 = 4$ hr and $\Delta_2 = 8$ hr, respectively. The probability of infection in our model varies with the time of day that the household members gather in the living quarters (τ_1) and the time of day that the caregiver initiates care (τ_3), and we choose the base-case values $\tau_1 = 13$ hr and $\tau_3 = 11$ hr (Fig. 5a in [1]), which achieve typical infection probabilities; e.g., we can think of the infection beginning at 5 am, people mixing in the living quarters during 6-10 pm, and the caregiver providing care during 4-5 pm. In [1], we constrain the secondary attack rate (SAR) within the household, which is the weighted average infection probability of susceptible household members, $\frac{2P_{I2}+P_{I3}}{3}$, to be $\frac{1}{6}$ for interpandemic influenza (which agrees with [33]). This yields the infection probabilities for the non-caregiving susceptibles and the caregiver to be $P_{I2} = .109$ and $P_{I3} = .282$.

Inserting these values for P_{I2} and P_{I3} into the analysis in §2 gives $E[C]$ (and hence $E[S]$). Solving equation (4) in the main text with $z = 0.2$ yields $\lambda_G = 5.63 \times 10^{-3}$/hr and, by equation (1) in the main text, $R_* = 1.15$. These values are very similar to those ($R_* = 1.13$, $z = 0.18$) derived in [34], which uses the households epidemic model and interpandemic influenza data from [31].

We assume less time outside the home in the pandemic setting [28, 29, 35] and let $\Delta_1 = 8$ hr and $\Delta_2 = 12$ hr. We again let $\tau_1 = 13$ hr and $\tau_3 = 11$ hr, which also achieve typical infection probabilities for the pandemic case. Running our model in §1 with the pandemic parameters yields $P_{I2} = 0.176$ and $P_{I3} = 0.296$. Solving Solving equation (4) in the main text with $z = 0.4$ yields $\lambda_G = 5.93 \times 10^{-3}$/hr and $R_* = 1.38$ for pandemic influenza. Because R_0 and R_* have different interpretations, we expect the R_* derived here to be less than the $R_0 = 1.8$ value derived in [30]. Indeed, $R_0 - 1 \approx rT_g \approx 0.8$, where $r \approx 0.3$ is the two-week average gradient in the excess mortality curves and $T_g \approx 2.6$ days is the mean generation time [14]. In our model, the role of the net growth rate $R_0 - 1$ is played by $(R_* - 1)E[C] = 0.73$, and so our parameter values are not inconsistent with the gradients of the excess mortality curves in [30, 14].

We conclude this section by comparing the interpandemic and pandemic values of two other measures. First is the secondary attack rate, which is $\frac{1}{6}$ for interpandemic influenza and 0.216 in the pandemic case. The second measure is the fraction of transmissions that occur outside of the home, or $\frac{1}{E[C]}$, which is 0.586 for interpandemic influenza and 0.516 for pandemic influenza, both of which are lower than the $\frac{2}{3}$ estimate in the interpandemic literature [14].

4 Results

In §4.1 we use the model to assess various infection control measures and in §4.2 we include larger particles in the analysis and determine how the effectiveness of several of the control measures will change under this scenario.

4.1 Infection Control Measures

We analyze six control measures in this section: respirators, humidifiers, ventilation, social distancing, workplace interventions, and surgical masks. We also assess the impact of opening doors and sharing a bedroom.

Respirators. An estimate of the average penetration factor (i.e., the fraction of virus that passes through the respirator) for a N95 filtering-facepiece respirator is 0.1 [36, 37], where nearly all of the inefficiency occurs due to face-seal leakage. We consider penetration values of 0.1, 0.3, and 0.8, the latter two values incorporate suboptimal fit and intermittent use [28, 29]. The penetration values of 0.3 and 0.8 correspond to a 0.1 penetration factor when the respirator is worn due to face-seal leakage as well as accounting for individuals only wearing the respirators approximately 75% (penetration value of 0.3) or 25% (penetration value of 0.8) of the time they are suppose to wear the respirators. If an individual only wears the respirator 75% of the time, the average penetration factor will be $0.1 \times 0.75 + 1 \times 0.25 = .325$, and rounding down yields a penetration factor of 0.3. A similar calculation yields a 0.8 penetration factor when the respirator is worn only 25% of the time. We look at five possiblities: (i) respirators are only worn by the caregiver in the infected's bedroom during the symptomatic period; (ii) respirators are worn by all susceptibles during the symptomatic period; (iii) respirators are worn by the caregiver when he is providing care during the symptomatic period and by everyone (including the infected) when they congregate in the living quarters during the pre-symptomatic period; (iv) respirators are worn by everyone during the pre-symptomatic period and by all susceptibles during the symptomatic period; and (v) same as (iv) except the infected also wears a respirator with penetration factor 0.5 during the symptomatic period (in the 0.8 penetration factor scenario, the penetration factor of the infected's respirator is also 0.8). We do not change the protection factor p_s because the infected may still attempt to protect his coughs and sneezes with his hand or a tissue. The results appear in Table 1 of the main text and Tables 2 and 3 for penetration factors 0.3, 0.1, and 0.8, respectively.

Humidifiers. We assume that a humidifier increases μ_a from 0.36/hr to 6.0/hr, which is the loss rate when the relative humidity is 65% [21]. We consider five possibilities for humidifier use: (i) in the infected's bedroom during the symptomatic period; (ii) in the living quarters during the symptomatic period; (iii) in the entire house during the symptomatic period; (iv) in the infected's bedroom during the symptomatic period and in the living quarters when people congregate there during the pre-symptomatic period; and (v) in the entire house during the entire infectious period. The results appear in Table 4.

Ventilation. A portable indoor air cleaner with a fan operated at a flow rate of 404 m^3/hr, which is representative of commercial air cleaners, can achieve an air exchange rate of 3.0/hr in a closed room the size of our infected's bedroom [38]. The outdoor air supply rates range from 0.3 to 2.9 air exchanges per hour in various office buildings, with higher values associated with schools [39]. One wide open window in a house can increase the air exchange rate by approximately 1/hr even without fans [40]. We change the ventilation rates in our model to be five times the room volume in locations where additional ventilation is attempted, e.g., by using fans and wide open windows. We consider the same five possibilities as for the humidifiers. The results appear in Table 5.

Bedroom doors. The air flow rate between two rooms has been measured to be 60 m^3/hr if the door is open and 1.0 m^3/hr if the door is closed [18]. In the base case, bedroom doors are closed when occupied and open when unoccupied. We continue to keep bedroom doors open when unoccupied and explore four other possibilities for opening bedroom doors when occupied: (i) all bedroom doors are open during the pre-symptomatic period; (ii) all bedroom doors are open during the pre-symptomatic period and susceptible bedroom doors are also open during the symptomatic period; (iii) and all bedroom doors are open during the pre-symptomatic period and the infected's bedroom door is also open during the symptomatic period; and (iv) all bedroom doors are open throughout the infectious period. The results appear in Table 6.

Shared bedroom. Here, we consider the possibility that the infected and a non-caregiving suscep-

tible share the same bedroom. We consider four different scenarios: (i) they share during the pre-symptomatic period with their bedroom door open when occupied; (ii) they share during the pre-symptomatic period with their bedroom door closed when occupied; (iii) they share during the entire period with their bedroom door open when occupied; and (iv) they share during the entire period with their bedroom door closed when occupied. The other susceptibles' bedroom doors are as in the base case: closed when occupied and open when unoccupied. Similarly, in scenarios (i) and (ii) above, the infected's bedroom door is closed throughout the symptomatic period, as in the base case. The results appear in Table 7. See section §2 for how the value of $E[C]$ changes in this scenario.

Social distancing. Social distancing within the house is achieved in our model by simultaneously reducing the amount of time household members spend together in the living quarters and increasing the time they spend alone in their bedrooms with the door closed. Fig. 4 in the main text presents the values of R^*, SAR, and the proportion of susceptibles that get infected as a function of the number of hours per day spent together in the living quarters.

Interventions in the workplace. A careful analysis of interventions in the workplace would require a generalization of the households model to the overlapping groups model [41], in which the population is partitioned into households and workplaces. Because it is far more difficult to obtain explicit results for the latter model [41], we obtain a rough assessment of workplace interventions by reducing the global infection rate λ_G in the households model (Fig. 1). We assume that out-of-house transmissions are evenly divided between the community and the workplace [14]. Recall that each household member spends 4 hr out of the house during the 24-hr pre-symptomatic period. Let us redistribute these 16 hr so that 1 of the 4 household members is the worker who spends 8 hr at work and the other 3 members each spend $2\frac{2}{3}$ hr in the community. We conservatively assume that no interventions are used in the community. We further assume that the percentage reduction in the workplace infection rate from the respirators-humidifiers-ventilation combination is equal to the percentage reduction from the combination intervention in the pre-symptomatic SAR in the home, the rationale being that

people spend 8 hr/day in the living quarters during the 24-hr pre-symptomatic period and this is also how long the infected worker spends with his fellow workers during the pre-symptomatic period. To aid in the construction of Fig. 1, we compute the pre-symptomatic SAR in the home (assuming all household members spend 8 hr together in the living quarters) versus the proportion of households complying to the respirators-humidifiers-ventilation combination (Fig. 2).

To review how Fig. 1 is constructed, we derive the global infection rate λ_G that corresponds to 70% of the workplaces complying to the respirators-humidifiers-ventilation combination. By Fig. 2, the pre-symptomatic SAR in the home is reduced from 0.176 to 0.089 if there is 70% compliance in the home. The base-case global infection rate is $\lambda_G = 5.93 \times 10^{-3}$/hr (Table 1). Hence, because the reduction only impacts half of the global infections (the half transmitted in the workplace), the global infection rate that corresponds to 70% workplace compliance is $0.5(5.93 \times 10^{-3}) + 0.5\left(\frac{0.089}{0.176}\right)(5.93 \times 10^{-3}) = 4.46 \times 10^{-3}$/hr, which agrees with the two horizontal axes in Fig. 1.

Surgical masks. Fig. 2 of [42] shows the penetration factor of the filter media of 8 surgical masks, as a function of particle diameter. These eight curves naturally group into three types: Three of these curves (the top 3 in the figure) are very similar and are clearly dominated by the other five, in that they have higher penetration factors at all diameters. Three other curves are very similar and have higher penetration factors than the other two curves (which are similar to each other) at diameters < 2 μm and lower penetration factors at diameters > 2 μm. We compute how much protection these latter two sets of curves offer assuming there is no face-seal leakage and the masks are worn throughout the infectious period. We refer to the two curves with lowest penetration factors at diameters < 2 μm as the "lower" curves and refer to the three non-dominated curves as the "middle" curves. We now view the penetration factor as a function of particle diameter x, and refer to it as $p_a(x)$. We fit the lower curves to the function

$$p_a(x) = \begin{cases} 0.061x^{-0.602} & \text{for} \quad x < 3.0\ \mu\text{m}; \\ 0.939x^{-3.09} & \text{for} \quad x \in [3.0, 4.0)\ \mu\text{m}; \\ 0.013 & \text{for} \quad x \geq 4.0\ \mu\text{m}. \end{cases} \tag{22}$$

and the middle curves to the function

$$p_a(x) = \begin{cases} 0.4 & \text{for} \quad x < 0.4\ \mu\text{m}; \\ 0.158x^{-1.01} & \text{for} \quad x \in [0.4, 1.1)\ \mu\text{m}; \\ 0.182x^{-2.46} & \text{for} \quad x \in [1.1, 4.0)\ \mu\text{m}; \\ 0.006 & \text{for} \quad x \geq 4.0\ \mu\text{m}, \end{cases} \tag{23}$$

The appropriate measure of protection is the ratio of the amount of virus (over the course of the infectious period) that is deposited in the respiratory epithelium with the mask on divided by the amount of virus that is deposited in the respiratory epithelium with the mask off. This quantity differs for the caregiver ($i = 3$) and the non-caregiving susceptibles ($i = 2$) because they are exposed to different doses. By equations (12) and (13) and noting that the particles shrink to half their size while airborne, these ratios are given by

$$\frac{\int_0^{d_c} b[\int_0^{T_I} \sum_{j=1}^{3} p_a(\frac{x}{2}) C_j(x,t) I_{ij}(t) dt] g(x)\ dx}{\int_0^{d_c} b[\int_0^{T_I} \sum_{j=1}^{3} C_j(x,t) I_{ij}(t) dt] g(x)\ dx}. \tag{24}$$

For the lower curves defined by equation (22), the ratio in equation (24) is 0.0167 for the caregiver and 0.0166 for the non-caregivers, and for the middle curves in equation (23), we get 0.0095 for the caregiver and 0.0093 for the non-caregivers.

Because the 1918 and 1957 influenza strains and the current H5N1 strain all bind to receptors on the respiratory epithelium and the alveoli, we re-assess the penetration factor for the surgical mask filters by adding the alveoli deposition function to $g(x)$ (Fig. 3 of [1]). For the lower curves, the penetration factor is now 0.0179 and 0.0177 for the caregiver and non-caregivers; for the middle curves, the factor is 0.0111 for the caregiver and 0.0108 for the non-caregivers.

4.2 Large Particle Transmission

In our analysis we assume that aerosol transmission occurs only with particles that are smaller than $d_c = 20\ \mu$m in diameter. We assume that particles $< 20\ \mu$m immediately shrink to half of the original diameter [5] and become droplet nuclei, and that particles $> 20\ \mu$m immediately settle on surfaces.

In a companion paper [1] we analyze aerosol transmission of larger particles only during an expiatory event (such as a cough or sneeze) directly in front of a susceptible's face. Because particles > 20 μm can stay airborne for several minutes, in this subsection we repeat some of the analysis assuming that larger particles can also contribute to aerosol transmission. If larger particles are a part of aerosol transmission than that would strengthen the finding in [1] that aerosol transmission is the dominant route of transmission.

The removal rate (per minute) of a particle of diameter d from gravitational settling is $\frac{0.0018d^2(1+\frac{0.166}{d})}{H}$ [5], where H is the height of room; we set $H = 2.44$m (8 ft). For particles of size 10 μm (the maximum diameter in the air in our model after they have shrunk to half the original diameter) this removal rate is 0.075/min, and for particles of size 50 μm the rate is 1.85/min. Thus after 5 minutes nearly 70% of the particles of size 10 μm will still be airborne, but essentially all of the particles of size 50 μm will have settled on surfaces. Thus we set $d_c = 100$ μm (which corresponds to 50 μm in the air after evaporation and shrinking to half the original diameter) as the upper bound for the diameter of airborne particles in this analysis.

To perform this analysis we first have to recompute several values. The initial median viral shedding rate, 2.88×10^7 TCID_{50}/day (Table 1), was estimated under the assumption that $d_c = 20$ μm [1]. Assuming that d_c is now 100 μm yields an estimate of the initial median viral shedding rate of 5.79×10^6 TCID_{50}/day (see §3.5 in [1] for details on this estimation procedure). In the interpandemic case the infection probability is 0.281 for the caregiver and 0.110 for a non-caregiving susceptible. For the pandemic case the values increase to 0.177 and 0.295 respectively. As in §3 we solve equation (4) in the main text with $z = 0.4$ to determine $\lambda_G = 5.93 \times 10^{-3}$/hr. The value of $R_* = \lambda_G T_I E[C]$ in this scenario is the same as it was in the case where $d_c = 20$ μm ($R_* = 1.38$).

Table 8 illustrates how effective the three primary interventions (N95 respirators, humidifiers, and ventilation) are when we include these larger particles in the analysis. We only look at the situation where humidifiers and ventilation are implemented in the living quarters when people congregate

there during the pre-symptomatic period and in the infected's bedroom during the symptomatic period. Everyone wears a respirator in the living quarters during the pre-symptomatic period, and during the symptomatic period only the caregiver wears a respirator while tending to the infected. We only analyze these scenarios because as Table 1 of the main text and Tables 2-5 illustrate, most of the potential benefits from the interventions are realized for these implementations.

The relevant comparisons between rows 2, 3, and 4 of Table 8 are row 4 of Table 1 in the main text, row 5 of Table 4, and row 5 of Table 5, respectively. The respirators are as effective in this scenario as they are for $d_c = 20$ μm because the penetration factor is independent of the particle size. The humidifiers and ventilation are less effective when we include particles with diameter greater than 20 μm. The reason for this is that the larger particles play an important role in the the spreading of influenza because there is a much greater quantity of virus on larger particles. The removal rate of the virus on the larger particles is dominated by settling (the κx^2 term in equations (9)-(11)) and thus the ventilation and humidity terms in the removal rate do not have as much of an impact.

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Figure Legends

Fig. 1. The impact of a reduction in the global infection rate λ_G. We assume that out-of-house transmissions are evenly divided between the community (where no interventions are used) and the workplace [14], and that the percentage reduction in the workplace infection rate from the combination intervention is equal to the percentage reduction from the combination intervention in the pre-symptomatic SAR (Fig. 2) in the home (people spend 8 hr/day in the living quarters in the 24-hr pre-symptomatic period, which corresponds to the pre-symptomatic period falling on a typical work day). We consider no interventions in the home (—) and 70% compliance of the respirators-humidifiers-ventilation intervention in the home (- - -). The right vertical axis is color-coded with the two curves.

Fig. 2. Pre-symptomatic secondary attack rate (SAR) vs. the proportion of households complying to the respirators-humidifiers-ventilation combination.

Parameter	Description	Value	References
T_I	Total infectious period	120 hr	[11, 12]
T_p	Pre-symptomatic infectious period	24 hr	[13, 14]
$\Delta_1, \Delta_2, \Delta_3$	Time Durations	8, 12, 1 hr	§3.1 in [1]
τ_1, τ_3	Time Schedules	13, 11 hr	§3.4, §3.5 in [1]
ν	Pre-symptomatic viral shedding parameter	4.94/day	[12]
ω	Symptomatic viral shedding parameter	1.70/day	[12]
e^{m_λ}	Median initial viral shedding rate	2.88×10^7 TCID_{50}/day	[5, 12, 15, 16]
e^{σ_λ}	Dispersal of initial viral shedding rate	40	[3, 10, 17]
V_1, V_2, V_3	Volume	228.3, 32.6, 32.6 m^3	§3.1 in [1]
Q_1, Q_2, Q_3	Ventilation rate	228.3, 32.6, 32.6 m^3/hr	[7]
Q_{13}, Q_{31}	Internal air flow rate (door open)	60, 60 m^3/hr	[18]
Q_{12}, Q_{21}	Pre-symptomatic internal air flow rate (door open)	60, 60 m^3/hr	[18]
$\tilde{Q}_{12}, \tilde{Q}_{21}$	Symptomatic internal air flow rate (door closed)	1, 1 m^3/hr	[18]
d_c	Critical diameter for droplet nuclei	20 μm	[5]
$p(x)$	pdf of pre-evaporation particle diameter	equation (22) in [1]	[5, 19, 20]
p_r	Respirator penetration factor for infected	1.0	§3.1 in [1]
μ_a	Death rate of virus in air	0.36/hr	[21]
κ	Deposition parameter	0.18/hr·μm^2	[22, 23]
p_s	Pre-symptomatic fraction of virus to protective surfaces	0.75	§3.1 in [1]
$\tilde{p}_s$	Symptomatic fraction of virus to protective surfaces	0.5	§3.1 in [1]
b	Breathing rate	20 m^3/day	[24]
p_{a1}, p_{a2}, p_{a3}	Respirator penetration factor for susceptibles	1.0, 1.0, 1.0	§3.1 in [1]
$g(x)$	Deposition fraction to respiratory epithelium	Fig. 3 of [1]	[25, 26]
ID_{50}	ID_{50} in respiratory epithelium	0.671 TCID_{50}	[27]
α	$\ln 2/\text{ID}_{50}$	1.033 TCID_{50}^{-1}	
n	Household size	4	§3.1 in [1]
λ_G	Global infection rate	5.93×10^{-3}/hr	§3

Table 1 Base-case parameters values From [1]. The subscripts 1, 2 and 3 represent the three compartments in our model. Tildes represent values during the symptomatic period.

Respirators					
Who	When	P_{I2}	P_{I3}	R_*	z
no one	never	0.176	0.296	1.38	0.400
caregiver	symptomatic period	0.176	0.197	1.24	0.285
all susceptibles	symptomatic period	0.175	0.197	1.24	0.284
caregiver everyone	when providing care in pre-symptomatic living quarters	0.024	0.121	0.85	—
all but symptomatic infected	infectious period	0.019	0.120	0.84	—
everyone	infectious period	0.019	0.090	0.81	—

Table 2 Efficacy of N95 respirators with penetration factor 0.1. In Tables 2-8 P_{I2}, P_{I3}, R^* and z are the infection probability for a non-caregiving susceptible, the infection probability for the caregiver, the threshold parameter for an epidemic, and the proportion of susceptibles who get infected if there is an epidemic (which can only occur if $R_* > 1$).

Respirators					
Who	When	P_{I2}	P_{I3}	R_*	z
no one	never	0.176	0.296	1.38	0.400
caregiver	symptomatic period	0.176	0.281	1.36	0.384
all susceptibles	symptomatic period	0.176	0.281	1.36	0.384
caregiver everyone	when providing care in pre-symptomatic living quarters	0.149	0.273	1.29	0.328
all but symptomatic infected	infectious period	0.148	0.273	1.29	0.328
everyone	infectious period	0.148	0.258	1.26	0.309

Table 3 Efficacy of N95 respirators with penetration factor 0.8.

Humidifiers					
Where	When	P_{I2}	P_{I3}	R_*	z
nowhere	never	0.176	0.296	1.38	0.400
infected bedroom	symptomatic period	0.176	0.279	1.35	0.382
living quarters	symptomatic period	0.176	0.296	1.38	0.400
entire house	symptomatic period	0.176	0.279	1.35	0.382
infected bedroom living quarters	symptomatic period in pre-symptomatic living quarters	0.161	0.275	1.32	0.352
entire house	infectious period	0.161	0.275	1.32	0.352

Table 4 Efficacy of humidifiers (65% humidity).

Ventilation					
Where	When	P_{I2}	P_{I3}	R_*	z
nowhere	never	0.176	0.296	1.38	0.400
infected bedroom	symptomatic period	0.176	0.283	1.36	0.386
living quarters	symptomatic period	0.176	0.296	1.38	0.400
entire house	symptomatic period	0.176	0.283	1.36	0.386
infected bedroom living quarters	symptomatic period in pre-symptomatic living quarters	0.165	0.280	1.33	0.364
entire house	infectious period	0.165	0.279	1.33	0.364

Table 5 Efficacy of ventilation (5 outside air exchanges per hr).

Open Bedroom Doors When Occupied					
Which	When	P_{I2}	P_{I3}	R_*	z
none	never	0.176	0.296	1.38	0.400
all	pre-symptomatic period	0.177	0.296	1.38	0.402
all susceptibles	pre-symptomatic period symptomatic period	0.177	0.296	1.38	0.403
all infected	pre-symptomatic period symptomatic period	0.192	0.294	1.41	0.424
all	infectious period	0.198	0.297	1.43	0.435

Table 6 Impact of status of bedroom doors when occupied (air flow rate = 1 m^3/hr if closed and 60 m^3/hr if open). Bedroom doors are open when unoccupied.

Status of Shared Bedroom Door When Occupied	When Shared	P_{Ish}	P_{I2}	P_{I3}	R_*	z
—	never	—	0.176	0.296	1.38	0.400
open	pre-symptomatic period	0.348	0.176	0.296	1.54	0.501
closed	pre-symptomatic period	0.356	0.176	0.296	1.54	0.505
open	infectious period	0.552	0.191	0.294	1.74	0.604
closed	infectious period	0.561	0.176	0.296	1.73	0.601

Table 7 Impact of the infected and a non-caregiving susceptible sharing a bedroom. P_{Ish} is the probability of infection for the susceptible who shares the infected's bedroom.

Interventions	P_{I2}	P_{I3}	R_*	z
base case (no interventions)	0.177	0.295	1.38	0.400
N95 respirators (0.3 penetration factor)	0.063	0.188	1.00	—
humidifiers	0.173	0.290	1.36	0.389
ventilation	0.174	0.291	1.37	0.391
N95 respirators, humidifiers, and ventilation	0.060	0.182	0.98	—

Table 8 Results assuming that particles < 100 μm in diameter contribute to aerosol transmission. All interventions are implemented in the living quarters while people congregate there during the pre-symptomatic period and in the infected's bedroom during the symptomatic period

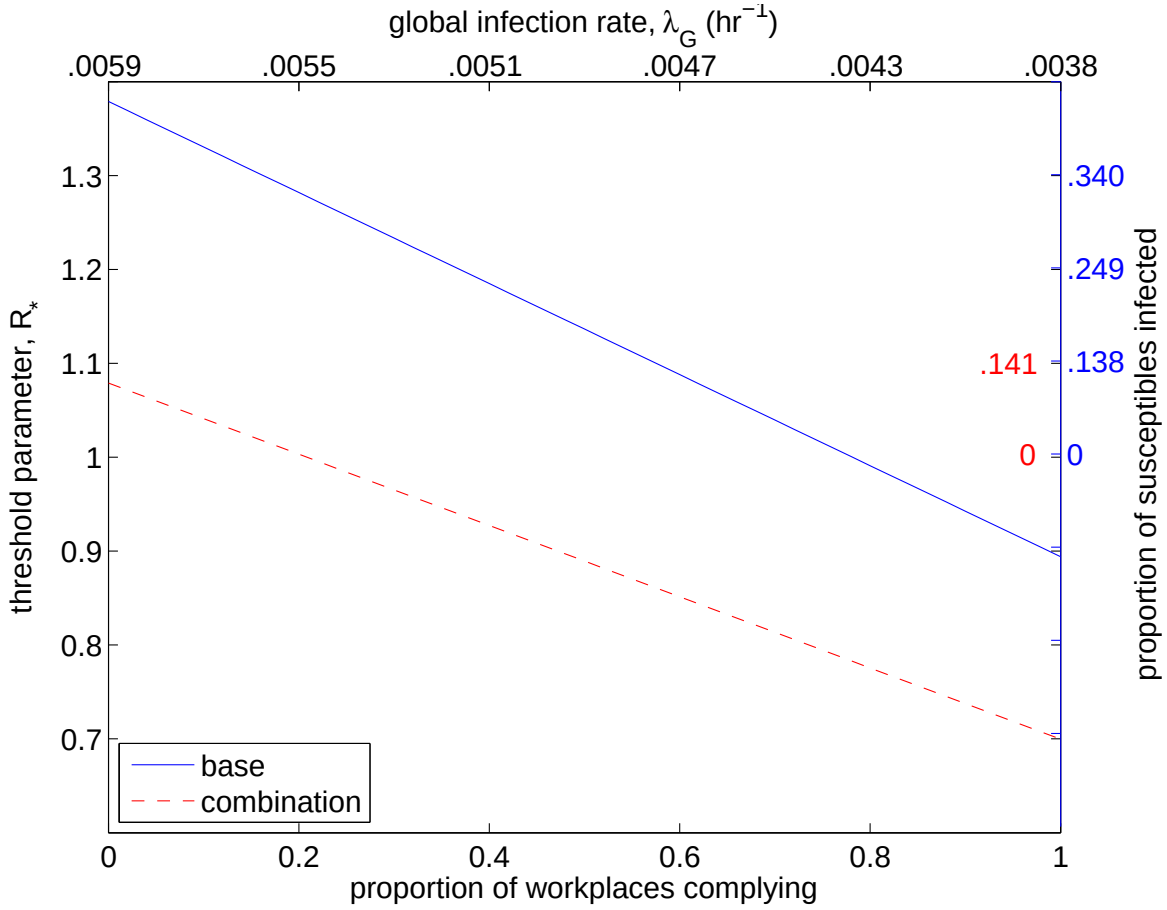
global infection rate, λ_G (hr^{-1})
.0059
.0055
.0051
.0047
.0043
.0038
1.3
1.2
1.1
1
0.9
0.8
0.7
threshold parameter, R_*
.340
.249
.141
.138
0
0
proportion of susceptibles infected
base
combination
0
0.2
0.4
0.6
0.8
1
proportion of workplaces complying

Figure 1

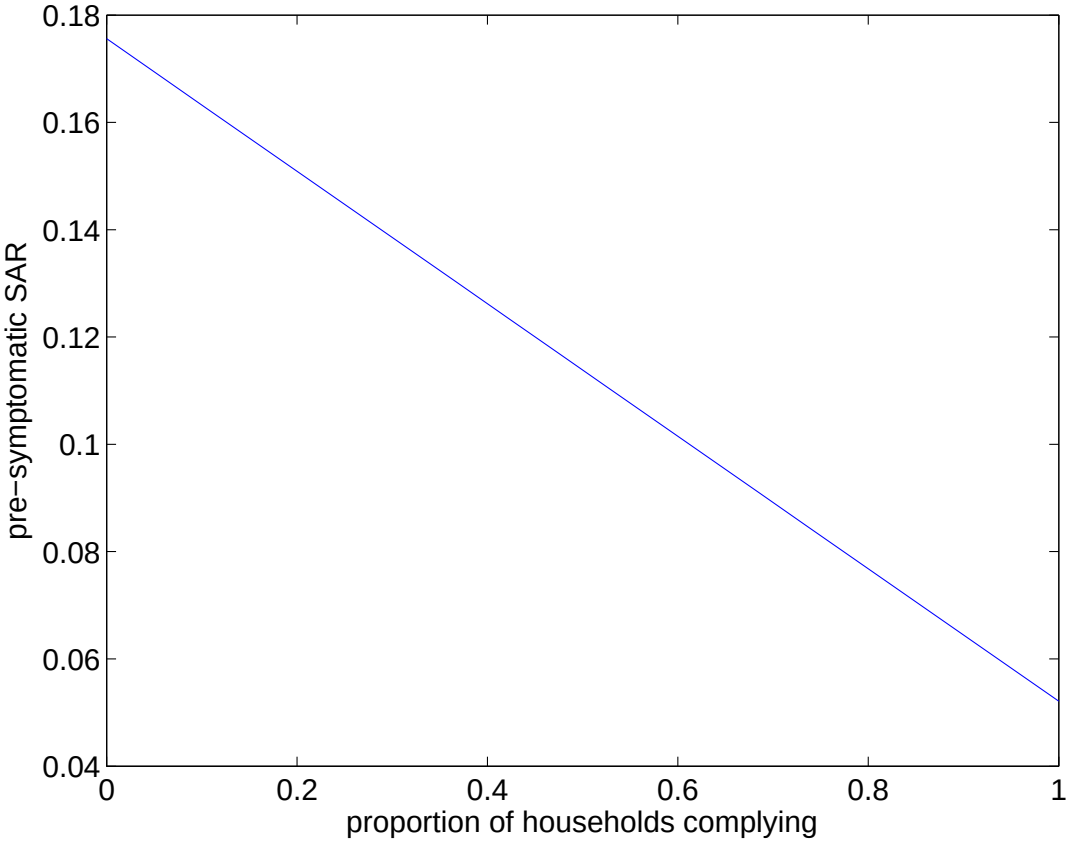
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
pre−symptomatic SAR
0
0.2
0.4
0.6
0.8
1
proportion of households complying

Figure 2