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Social contact patterns and control strategies for influenza in the elderly

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ABSTRACT

Despite dramatic increases in influenza vaccination coverage in the elderly population over the past 30 years, influenza mortality rates have remained static in this age group. Children are believed to be the primary spreaders of diseases such as influenza due to their high degree of inter-contact in school settings, and several studies have examined control of influenza in the entire population, including the elderly, via targeted vaccination of school children. However, such vaccination programs are expensive, and fraught with difficulties of public perception of what may be seen as an unnecessary vaccination against a disease that is normally mild in the children themselves.

In the study presented here, we examine the control of influenza in the elderly using simple social distancing measures during an influenza epidemic. The recent work of Glasser et al. characterizes daily contact interactions within the population in terms of preferential mixing between age group peers, coworkers, and parents and children. We expand upon this to include interactions between grandparents and grandchildren, and fit the parameters of this formulation to the recently published social contact survey data of Mossong et al. Using this formulation, we then model an influenza epidemic with an age-structured deterministic disease model and examine how reduction in contacts between grandchildren and grandparents affects the spread of influenza to the elderly.

We find that over 50% of all influenza infections in the elderly are caused by direct contact with an infected child, and we determine that social distancing between grandparents and grandchildren is remarkably effective, and is capable of reducing influenza attack rates in the elderly by up to 60%.

Introduction

Influenza, a seasonal viral disease, presents a significant morbidity and mortality burden on the population, with a typical seasonal influenza epidemic in the United States killing around 40,000 people per year [1]. Most of the hospitalization and mortality burden is carried by people aged over 65 years (the influenza mortality and hospitalization rates of elderly people are 100 and 20 times higher than those of people aged 5–49, respectively [2,3]), and the direct cost of influenza hospitalizations in the elderly in the U.S. approaches half a billion dollars each year [4].

Because of the high morbidity and mortality burden in this age group, attempts have been made in recent decades to increase the vaccination rates among the elderly, and indeed vaccine coverage is highest in this age group, at a current level of 65%, compared to 20% for children age 5–19 years [5]. Despite a rise in elder vaccination rates from 15% to 65% between 1985 and 2000, however, elderly influenza mortality rates remained largely unaffected [6], likely due to low vaccine efficacy among people aged 65 and older [7,8].

Children are thought to be the primary spreaders of diseases like influenza within a population because of their high contact rate with their peers in school settings [9], and it has been shown that optimal influenza control in the entire population, including the elderly, can thus be achieved if vaccines are preferentially distributed to children [10–13]. However, such vaccination programs are expensive, and also can be fraught with particular difficulties of public acceptance when children are involved. Ref. [14] discusses the issue of individual perspectives often being at odds with those of policy makers when it comes to vaccinations, and notes the 'need for improved, less expensive systems for protecting individuals against influenza.' In this analysis, we thus explore the efficacy of reduction of influenza in the elderly by perhaps the cheapest means possible; simple social distancing.

The types of social contacts people preferentially make each day depend on age, but most can be approximately categorized as peer-to-peer interactions (i.e., interactions with people of approximately one's own age), parent/child interactions, grandparent/grandchild interactions, and co-worker interactions [15]. Since children are the primary spreaders of influenza in a population, the social distancing measures we examine here are reduction of grandparent/grandchild interactions.

The simplest parameterization of the preferential contacts amongst members of a population includes only the dominant

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peer-to-peer interactions, as described in Refs. [16,17]. The recent work of Glasser et al. extends this parameterization to include the additional preference for parents to interact with children (and vice versa), and co-worker interactions [15].

A recent study by Mossong et al. asked respondents in eight European countries to keep daily diaries of their contacts [18]. Because we wish to examine the effect on influenza spread of social distancing (reduced contacts) between grandchildren and grandparents, in this analysis we further extend the parameterization of Glasser et al. to include grandparent/grandchild interactions. We then use the contact survey data of Mossong et al. to fit the parameters of this formulation.

We model the spread of influenza within a population with a Susceptible, Infected, Recovered (SIR) mathematical model with age-heterogeneity, using our formulation of the contact matrix to describe mixing between the age groups. Using this model, we study the impact of reduced interaction between grandparents and grandchildren on the attack rates of influenza in the elderly. We study three scenarios; the first two keep the total number of contacts per day of the elderly person the same, and simply reapportion contacts from grandchildren to peers, or to adult children. In the third scenario, the number of contacts the elderly person makes per day are reduced because of the reduced interaction with grandchildren.

We find with this model that 50% of influenza infections in the elderly are due to direct contact with an infected child, and we subsequently show that even moderate social distancing between grandparents and grandchildren has the potential to significantly reduce the morbidity burden on the elderly during an influenza epidemic. These results underline the role that mathematical models can play in helping to assess disease intervention strategies.

In the following sections we describe the model and our formulation of the contact matrix, including the details of our fit of the parameters of that formulation to the contact survey data of Mossong et al. We then describe the simulation studies whereby we scale the grandparent/grandchild interactions, followed by a summary of results.

Methods

Model

Spread of disease between n age groups is described in these studies using an age-structured Susceptible, Infected, Recovered 'SIR' model, with infectious symptomatic and asymptomatic classes, I^s and I^a [19]:

$$\begin{aligned}
S_i' &= -\beta S_i \sum_{j=1}^{n} (\eta C_{ij}^a I_j^a/N_j + C_{ij}^s I_j^s/N_j),\\
I_i^{a\prime} &= \alpha\beta S_i \sum_{j=1}^{n} (\eta C_{ij}^a I_j^a/N_j + C_{ij}^s I_j^s/N_j) - \gamma I_i^a,\\
I_i^{s\prime} &= (1-\alpha)\beta S_i \sum_{j=1}^{n} (\eta C_{ij}^a I_j^a/N_j + C_{ij}^s I_j^s/N_j) - \gamma I_i^s,\\
R_i' &= \gamma I_i^a + \gamma I_i^s,
\end{aligned} \tag{1}$$

where γ is the recovery rate (assumed to be the same for symptomatics and asymptomatics [20–22]), β is the transmission rate on contact,[1] $0 \leqslant \eta \leqslant 1$ is the discount on transmission for the asymptomatic class, $0 \leqslant \alpha \leqslant 1$ is the fraction of infections that are asymptomatic, and where the population size is

$$N = \sum_i (S_i + I_i^s + I_i^a + R_i) = \sum_i N_i. \tag{2}$$

We ignore vital dynamics in the model, under the assumption that the epidemic occurs on a very short time scale relative to human reproduction and lifespan dynamics. The matrices C_{ij}^a and C_{ij}^s are known as *contact matrices*, and are the average number of contacts made per day by an individual in class i with an individual in class j, where the individual in class j is in the asymptomatic or symptomatic class, respectively. The system of equations has initial conditions at the time of introduction, $t = 0$, of the infection into the population:

$$\begin{aligned}
S_i(0) &= f_i N_i - 1,\\
I_i^a(0) &= \alpha,\\
I_i^s(0) &= 1-\alpha,\\
R_i(0) &= (1-f_i)N_i,
\end{aligned} \tag{3}$$

where $1 - f_i$ is the pre-immune fraction in age group i, due to, for instance, vaccination or prior infection.

Numerical solutions to Eq. (1) are obtained with methods in *odesolve* library of the *R* statistical programming language [23].

The basic reproduction number, $\mathcal{R}_0$, the average number of secondary infections produced by one infected individual during his/her entire period of infection in an entirely susceptible population, is calculated from the next generation matrix of Eq. (1). If we assume that symptomatic sick people on average reduce their contacts by a fraction $1 - f_{\text{reduc}}$, then $C_{ij}^s = f_{\text{reduc}} C_{ij}^a$, and we obtain $\mathcal{R}_0$ to be the largest eigenvalue of the $C_{ij}^a N_i/N_j$ matrix, times $\beta(f_{\text{reduc}} - \alpha f_{\text{reduc}} + \alpha\eta)/\gamma$. The effective reproduction number, taking into account pre-immunity, is the largest eigenvalue of the $C_{ij}^a f_i N_i/N_j$ matrix, times $\beta(f_{\text{reduc}} - \alpha f_{\text{reduc}} + \alpha\eta)/\gamma$.

Parameterization of the contact matrix

In a closed population, a contact matrix C_{ij} must satisfy reciprocity, which at the population level means that the total number of contacts between group i to group j must equal the total number of contacts from group j to group i [24,25]. This implies that $C_{ij}N_i = C_{ji}N_j$, where N_i is the number of people in group i. We define $a_i = \sum_j C_{ij}$, and the matrix $c_{ij} = C_{ij}/a_i$. Note that $\sum_j c_{ij} = 1$.

In the simplest of preferential mixing formulations, a proportion, ϵ_i, of the total i group-contacts is reserved for others ('peers') in group i, and the complement $(1 - \epsilon_i)$ is split among all groups [16]:

$$c_{ij} = \epsilon_i \delta_{ij} + (1-\epsilon_i)\frac{(1-\epsilon_j)a_j N_j}{\sum_k (1-\epsilon_k)a_k N_k}, \tag{4}$$

where $\delta_{ij} = 1$ if $i = j$, and is 0 otherwise.

The recent work of Glasser et al. extends this formulation with a parameterization of the contact matrix that includes the additional preferences of co-workers to interact, and parents to interact with children [15]. In this work we extend the formulation of Glasser et al. to include interactions between grandparents and grandchildren, thus allowing us to study how reduction of contacts between these two groups can influence the spread of influenza within a population.

In order to capture the various preferential mixing patterns, we thus parameterize the c_{ij} matrix as [15]

$$c_{ij} = \phi_{ij} + \left(1 - \sum_{l=1}^{6} \epsilon_{li}\right) f_j, \tag{5}$$

[1] In this analysis we assume the transmission rate is constant, and ignore possible year-to-year fluctuations in transmissibility, since the goal of these studies is not to explore the periodicity or long-term dynamics of influenza outbreaks, but merely to compare theoretical expectations in influenza disease burden under various social distancing scenarios.

where ϵ_{li} is the fraction of contacts group i reserves for peers ($l = 1$), children ($l = 2$), parents ($l = 3$), grandchildren ($l = 4$), grandparents ($l = 5$), and co-workers ($l = 6$), and f_j is the fraction of 'everyone else' in group j,

$$f_j = \frac{\left(1 - \sum_{l=1}^{6} \epsilon_{lj}\right) a_j N_j}{\sum_{k=1}^{n} \left(1 - \sum_{l=1}^{6} \epsilon_{lk}\right) a_k N_k}. \tag{6}$$

We define

$$\phi_{ij} = \epsilon_{1i} \frac{q_{ij}}{\sum_k q_{ik}} + \epsilon_{2i} \frac{r_{ij}}{\sum_k r_{ik}} + \epsilon_{3i} \frac{s_{ij}}{\sum_k s_{ik}} + \epsilon_{4i} \frac{t_{ij}}{\sum_k t_{ik}} + \epsilon_{5i} \frac{u_{ij}}{\sum_k u_{ik}} + \epsilon_{6i} v_{ij}, \tag{7}$$

where v_{ij} parameterizes the workplace interactions (more on that in a moment), and $q_{ij}, r_{ij}, s_{ij}, t_{ij}$, and u_{ij} parameterize the peer-to-peer, parent-to-child, child-to-parent, grandparent-to-child, and child-to-grandparent interactions.

In Fig. 1 we show the contact matrices for various settings, as determined from the Mossong et al. contact survey data. Note that the contact matrix for interactions in the home in particular shows clear evidence of peer-to-peer interactions along the main diagonal, and parent/child and grandparent/grandchild interactions along the first and second off-diagonals, respectively. The parent/child interactions are separated from the main diagonal by the generation length G (the average age at which women bear daughters), and the grandparent/grandchild interactions are $2G$ from the main diagonal. As seen in Fig. 2 we parameterize these interactions using Gaussian 'tubes' that run along the diagonals; for instance, for the peer-to-peer interactions along the main diagonal, the Gaussian tubes take into account the fact that people tend to interact with people of roughly the same age, but not necessarily exactly the same age [15,17]. The spread in ages of contacts (the width of the Gaussian tube) may depend on the age of participant. The Gaussian tube parameterization of the peer-to-peer, parent/child, child/parent, grandparent/grandchild, and grandchild/grandparent interactions is thus

$$\begin{aligned}
q_{ij} &= \int_{ymin}^{ymax} dy \int_{xmin}^{xmax} dx \frac{1}{\sigma_{1i}\sqrt{2\pi}} \exp\left[\frac{-(x-y)^2}{2\sigma_{1i}^2}\right], \\
r_{ij} &= \int_{ymin}^{ymax} dy \int_{xmin}^{xmax} dx \frac{1}{\sigma_{2i}\sqrt{2\pi}} \exp\left[\frac{-(x-y+G)^2}{2\sigma_{2i}^2}\right], \\
s_{ij} &= \int_{ymin}^{ymax} dy \int_{xmin}^{xmax} dx \frac{1}{\sigma_{3i}\sqrt{2\pi}} \exp\left[\frac{-(x-y-G)^2}{2\sigma_{3i}^2}\right], \\
t_{ij} &= \int_{ymin}^{ymax} dy \int_{xmin}^{xmax} dx \frac{1}{\sigma_{4i}\sqrt{2\pi}} \exp\left[\frac{-(x-y+2G)^2}{2\sigma_{4i}^2}\right], \\
u_{ij} &= \int_{ymin}^{ymax} dy \int_{xmin}^{xmax} dx \frac{1}{\sigma_{5i}\sqrt{2\pi}} \exp\left[\frac{-(x-y-2G)^2}{2\sigma_{5i}^2}\right],
\end{aligned} \tag{8}$$

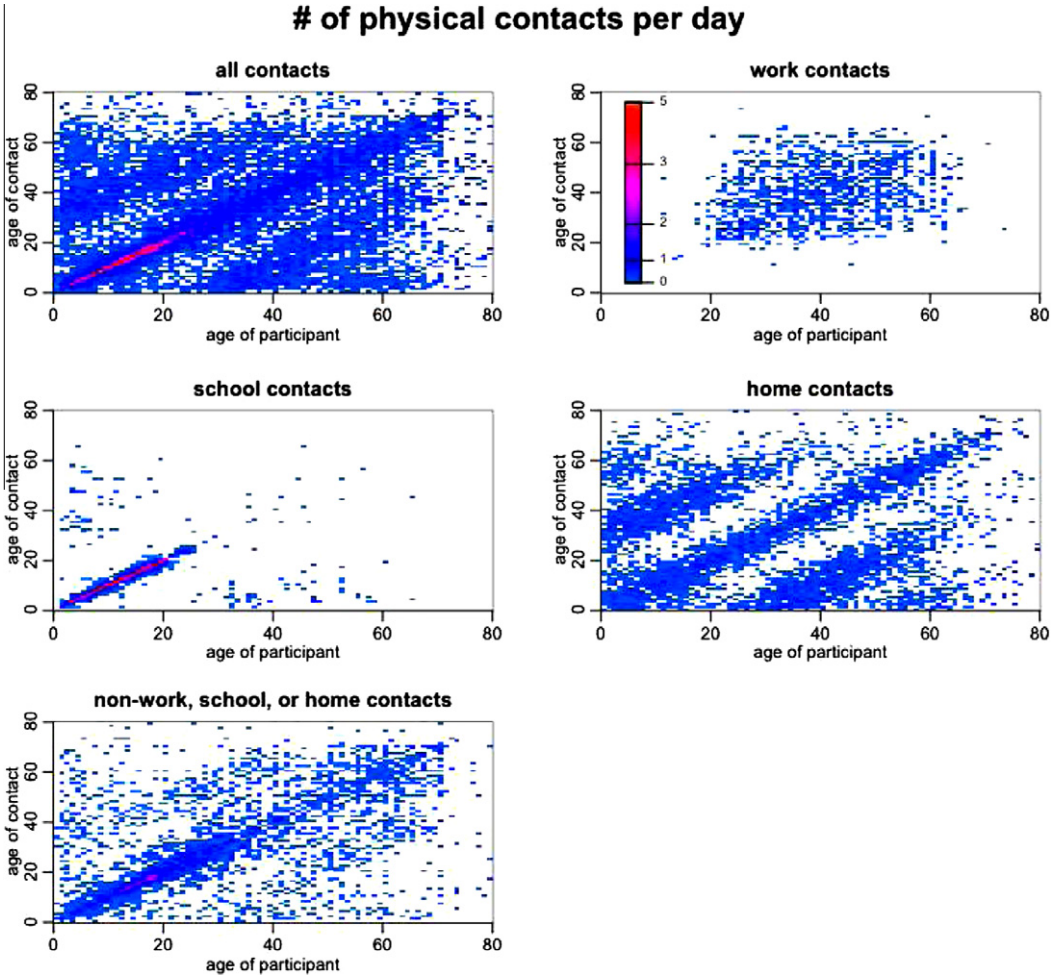

Fig. 1. The average number of daily contacts, weighted by duration, made by participants vs age of contact (binned in age groups of one year) derived from the contact survey data of Mossong et al., and corrected for reciprocity. The Mossong data allows for determination of where contacts occurred (work, school, home, etc.). Note that the home contacts in particular show evidence of peer-to-peer, parent/child, and grandparent/grandchild interactions, indicating that such interactions should be considered in a parameterization of the contact matrix.

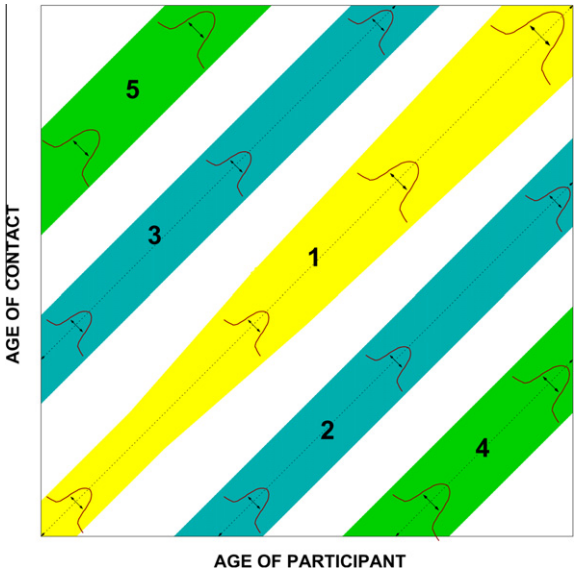

Fig. 2. As demonstrated in this graphic, we parameterize interactions using Gaussian 'tubes' that run along the peer-to-peer (yellow), parent/child (blue), and grandparent/grandchild (green) interaction diagonals. The parent/child and grandparent/grandchild off-diagonals are separated from the main peer-to-peer diagonal by G and $2G$, respectively, where G is the average generation length. As seen in Eq. (8), the Gaussian tubes have widths that may vary with age (the widths are determined from fits to the contact matrices derived from the Mossong et al. contact survey data). Note that the widths and heights of the Gaussian tubes shown along the diagonals are merely for illustrative purposes, and do not reflect the values fitted to the Mossong data. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

respectively, where the age limits on the ith bin in contact matrix are $[xmin, max]$, and the age limits on the jth bin are $[ymin, ymax]$. Note that the contact matrix is not continuous, but rather discretely binned, thus the double integral translates the continuous Gaussian tube formulation into an estimated total number of contacts within a bin of $xmin$ to $xmax$ in the participant age, and $ymin$ to $ymax$ in the contact age.

Because reciprocity must be satisfied, the amount of time parents spend with children must equal the amount of time children spend with parents, and similarly for the grandparent/grandchild interactions. This leads to the constraints

$$\epsilon_{3i} = \epsilon_{2(i+G)} \frac{a_{(i+G)} N_{(i+G)}}{a_i N_i},$$
$$\epsilon_{5i} = \epsilon_{4(i+2G)} \frac{a_{(i+2G)} N_{(i+2G)}}{a_i N_i}, \tag{9}$$

where $\epsilon_{3i} = 0$ if $i < G$ and $\epsilon_{5i} = 0$ if $i < 2G$. Reciprocity also leads to the constraints

$$\sigma_{3i} = \sigma_{2(i+G)},$$
$$\sigma_{5i} = \sigma_{4(i+2G)}. \tag{10}$$

Examination of the patterns in the contact survey data of Mossong et al. indicate that co-worker contacts are approximately described by a rectangular area bounded by minimum and maximum worker ages, $W_{\min}$ and $W_{\max}$, respectively, within which contacts are roughly independent of age, as seen in Fig. 1 [15]. The workplace interaction term in Eq. (7) must also satisfy reciprocity, which implies that $N_i a_i \upsilon_{ij} = N_j a_j \upsilon_{ji}$. We thus define for υ_{ij}:

$$\upsilon_{ij} = \frac{\delta_{W_{\min} \leqslant i,j \leqslant W_{\max}}}{(W_{\max} - W_{\min})} \frac{(a_i N_i + a_j N_j - \sum_k a_k N_k / n)}{a_i N_i}, \tag{11}$$

where $\delta_{W_{\min} \leqslant i,j \leqslant W_{\max}}$ is a two-dimensional rectangular Heaviside step function, which is equal to one when i and j are both between $W_{\min}$ and $W_{\max}$, and zero otherwise.

In this analysis we fit the parameters of ϕ_{ij}

$$\vec{\theta} = (\epsilon_{1i}, \epsilon_{2i}, \epsilon_{4i}, \epsilon_{6i}, \sigma_{1i}, \sigma_{2i}, \sigma_{4i}, G, W_{\min}, W_{\max}) \tag{12}$$

by fitting to the daily contact survey data of Mossong et al. [18].

The data from the Mossong et al. surveys are contained in two databases; one contains the participant demographic information, and the other contains the contact information for each participant derived from their daily diaries. Since close contacts are more likely to spread disease, we select the contact survey data for conversations that that involved physical contact. We cross-reference the data-bases, selecting diary entries that are complete in all information that is relevant to this analysis. We pre-process the data by looping over the diary for each participant and calculating the total number of contacts, and the number of contacts vs contact age.

When the maximum age cut-off in the Mossong data for participants and their contacts is set to 80 years, the output file of preprocessing includes, in essence, a very sparse 80×80 contact matrix for each of the n participants, A_k, $k = 1, \ldots, n$. In order to determine an average 80×80 contact matrix for the population, B, we take the average of the A_k, weighted with the Mossong et al. diary weights, w_k^{diary}:

$$B = \sum_k \hat{w}_k^{\text{diary}} A_k, \tag{13}$$

where $\hat{w}_k^{\text{diary}} = \frac{w_k^{\text{diary}}}{\sum_j w_j^{\text{diary}}}$. The weighted variance of B will be needed for calculation of the Pearson-χ^2 statistic when fitting to the contact matrix. It is:

$$(\Delta B)^2 = \sum_k \hat{w}_k^{\text{diary}} (A_k - B)^2. \tag{14}$$

The matrix B does not necessarily fulfill reciprocity conditions, because the Mossong et al. survey population was not necessarily closed. We thus perform a reciprocity correction by setting [13]

$$C_{ij} = (B_{ij} N_i + B_{ji} N_j)/2N_i. \tag{15}$$

The variance of C, $(\Delta C)^2$, is straightforwardly calculated from Eqs. (15) and (14) by propagation of errors. Population sub-group sizes are estimated from U.S. census data [26].

The resulting 80×80 contact matrix is shown in Fig. 1. Also shown are the contact matrices for contacts that occur in work, school, home, or other places, as keyed in the Mossong et al. database. The average 80×80 contact matrix is too sparse for fitting purposes because many of the bins have estimates of an average contact rate of zero; because there are a finite number of diaries in the Mossong data set, if we use very fine age binning there may be some age groups for which there are no reported contacts with another particular age group (say, for instance 77 year olds contacting a 1 year old), but common sense dictates that while the true average contact rate between those two age groups might be low, it is certainly non-zero because there obviously exists somewhere a 77 year old who routinely contacts a 1 year during the course of their day (however, such 77 year olds did not happen to submit a diary in the Mossong survey). Bins for which the estimated contact rate is zero are problematic in part because ΔC is also estimated to be zero, and, as seen below, the variance appears in the denominator in the calculation of the Pearson-χ^2 fitting statistic. In addition, the calculation of the Pearson-χ^2 statistic carries the underlying assumption that the estimates of the contact rate within a bin in the matrix are drawn from a Normal distribution centered about the true value, with variance estimated by $(\Delta C)^2$

[27]. The Normal approximation to the estimates of the mean and variance is approached when the number of non-zero elements contributing to the average is at least 5 [27]. However, many bins in the 80×80 contact matrix do not have at least 5 non-zero elements contributing to the average within that bin.

Equally problematic is that an $n \times n$ matrix necessitates fitting $\mathcal{O}(7n)$ parameters, but even the most sophisticated non-linear optimization packages have difficulty with simultaneous optimization of more than just a few dozen parameters. The solution to both problems is thus to combine rows and columns of this matrix. We choose a binning in 16 increments of 5 years between 0 and 80 years of age. In order to maintain reciprocity, columns (j) are summed, and rows (i) are averaged with weights $\sum_k N_k/N_i$. The resulting contact matrix, C_{ij}, is shown in Fig. 3. Each bin of this matrix has at least nine non-zero elements of A contributing to the average within that bin (on average over 100 non-zero contributions per bin).

We use the Minuit non-linear optimization fitting package [28] to determine the parameters of Eq. (7) that minimize the Pearson-χ^2 statistic [27]:

$$\chi^2 = \sum_{i=1}^{15}\sum_{j=1}^{15} \frac{[C_{ij} - a_i c_{ij}(\vec{\theta}_i, \vec{\theta}_j)]^2}{[\Delta C_{ij}]^2}, \tag{16}$$

where $a_i = \sum_j C_{ij}$. Based on the patterns observed in the Mossong et al. work-place contact data (Fig. 1), in the fit we set $W_{\min} = 20$ years, $W_{\max} = 65$ years, and we assume that the ϵ_{6i} are independent of age. The results of the σ's from the fit are shown in Fig. 4. The Pearson-χ^2 statistic is 165 for 154 degrees-of-freedom ($p = 0.26$). Note that many of the σ are zero due to age constraints (for instance, only people older than G can be considered old enough to be parents). The σ_{2i} and σ_{4i} are all statistically consistent with being independent of age, and with being equal to each other (and likewise the σ_{3i} and σ_{5i} through the reciprocity constraint). We thus repeat the fit, holding all the off-diagonal σ_{2i} to σ_{5i} equal to a single value, which is allowed to float. The Pearson-χ^2 statistic for the new fit is 175 for 168 degrees-of-freedom ($p = 0.34$). The value of the off-diagonal σ's is found to be 4.50 ± 0.33 years. The resulting parent/child, grandparent/grandchild, and peer-to-peer interaction fractions from the fit are shown in Fig. 5. The value of G from the fit is $G = 29.30 \pm 0.27$ years, and co-worker interaction fraction $\epsilon_6 = 0.095 \pm 0.022$. The results are summarized in Table 1.

We assume in this analysis that the contact matrix to asymptomatic individuals, C^a_{ij} is equal to this parameterization. The contact matrix to symptomatic individuals, C^s_{ij} is derived from this parameterization, multiplied by a factor f_{reduc} to reflect the fact that sick people tend to reduce contacts with others in the population, where $f_{\text{reduc}} = 0$ would reflect complete isolation of the sick individual.

Results

Children are hypothesized to be the primary spreaders of disease within a population, due to their strong peer-to-peer contacts which dominate the C_{ij} matrix, as seen in Fig. 3. We determine their impact on the spread of influenza in the elderly, we simulate an influenza epidemic using ODE disease model in Eq. (1) and the parameterization of C_{ij} described in the previous section, with effective reproduction number $\mathcal{R}_0^{\text{eff}} = 1.4$ [29], and $1/\gamma = 4.8$ days [30]. The transmission rate, β, is calculated from $\mathcal{R}_0^{\text{eff}}\gamma/(f_{\text{reduc}} - \alpha f_{\text{reduc}} + \alpha\eta)$, divided by the largest eigenvalue of the $C_{ij}f_i N_i/N_j$ matrix.

Challenge studies have shown that the asymptomatic fraction of influenza infections is around $\alpha = 33\%$ [30], however this is likely an underestimate since the volunteers knew they had been challenged, and thus were anticipating symptoms to develop. Seroepidemiological studies in conjunction with population surveys of illness recollection indicate that the fraction of asymptomatic infections is likely much higher, up to 60% for seasonal influenza, and even higher for pandemic strains[34–37]. We assume $\alpha = 0.50$ here.

The amount of virus shed by asymptomatics has been poorly studied, however two viral challenge studies have found that nearly all infected and asymptomatic people shed detectable amounts of virus, and find a positive correlation between the

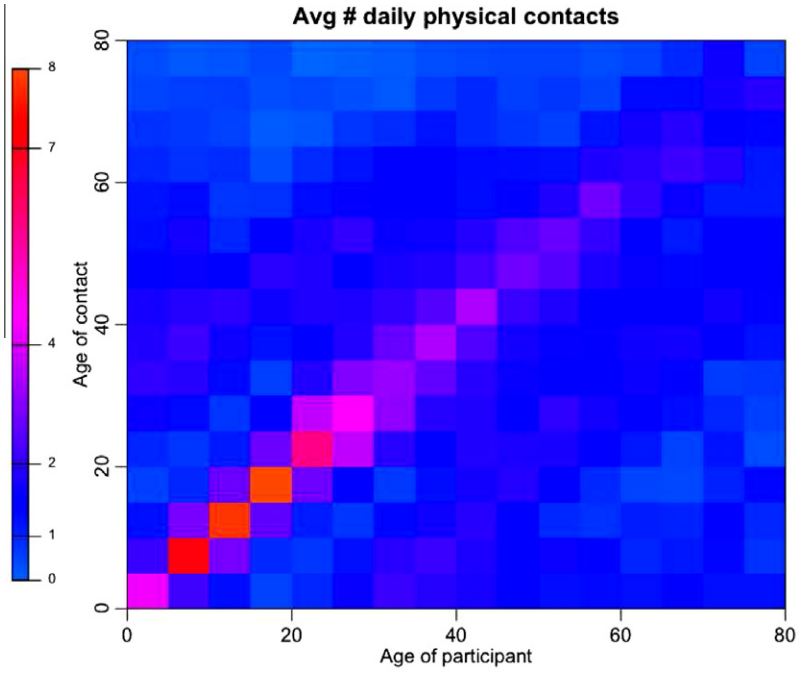

Fig. 3. The average number of daily contacts made by participants vs age of contact derived from the contact survey data of Mossong et al., and corrected for reciprocity. This contact matrix is used in this analysis to fit the parameters of ϕ_{ij}.

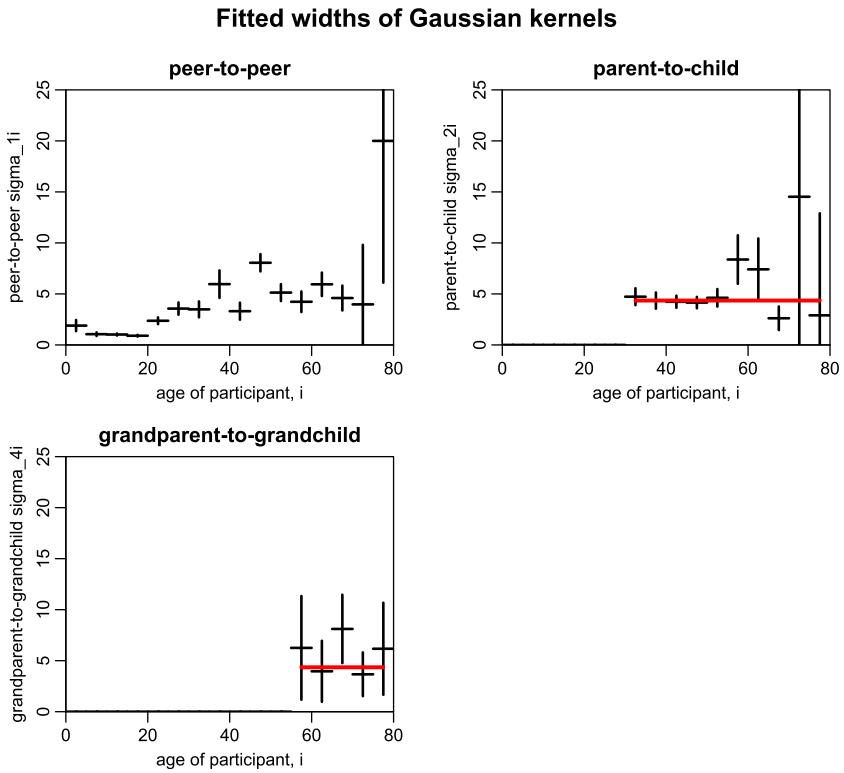

Fig. 4. Widths of the Gaussian kernels, as determined by the first iteration of the fit to the contact matrix, where all parameters freely float. The red lines denote the flat line fit to ϵ_{2i} and ϵ_{4i}. The child-to-parent, σ_{3i}, and grandchild-to-grandparent, σ_{5i}, are not shown because they are directly related to ϵ_{2i} and ϵ_{4i} due to reciprocity constraints on the contact matrix. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

amount of virus shed and the severity of clinical symptoms [30–32]. Ref. [33] fits an SEIR-type model to 1918 pandemic influenza incidence data, examining values of η between 0.4 and 0.6, and finds the best-fit value $\eta \sim 0.5$. We thus assume that asymptomatic infected people have a discount on transmission of $\eta = 0.50$. We also assume that symptomatic infected people reduce their contacts by a factor of $f_{\text{reduc}} = 0.50$.

The vaccination coverage within each of the age groups is assumed to be 34% age 0–4 years, 20% age 5–19 years, 17% age 20–49 years, 35% age 50–64 years, and 63% age 65 years and over [5]. The vaccine efficacy at producing immunity is assumed to be 80% below age 65, and 60% age 65 years and over [38]. Very few (if any) serological studies have assessed seasonal influenza pre-immunity of the population due to prior infection with related seasonal influenza strains. However, a 2009 Finnish study assessed immunity within the population to two AH1N1 and AH3N2 seasonal influenza strains that had circulated in the prior year [39]. The age-specific immune fractions within the population were in most cases less than, or similar to, the vaccination pre-immunities we assume. The age-specific immune fractions to strains that are somewhat mutated from these two strains would be even smaller. We thus assume in this study that the pre-immunity due to vaccination coverage approximates pre-immunity due to vaccination coverage and/or prior infection with related strains.

From the model simulation using Eq. (1) and our parameterized contact matrix, we determine the final fraction of elderly people over age 65 infected by the end of the epidemic, and the fraction of those infections that were due to direct contact with an infected child under the age of 20. The results are shown in Fig. 6. We note that 50% of all influenza infections in the elderly are caused by direct contact with infected children. Note that even though the estimated attack rates in the elderly are relatively low compared to the overall model estimated population attack rate of 14%, the morbidity and mortality burden is disproportionately carried by the elderly in a seasonal flu epidemic, likely because the existence of co-morbidities and weakened immune systems tends to make influenza infection much more serious in this age group than it is for younger people.

We examine whether or not the spread of influenza among elderly people can be significantly influenced by simple reduction of the fraction of their contacts with their grandchildren during the influenza season. Note that due to reciprocity constraints, scaling the fraction of the grandparent-to-grandchild contact fraction similarly scales the grandchild-to-grandparent contact fraction. We repeat the model simulations using Eq. (1), examining three scenarios:

- The total average number of contacts, a_i, remain the same, and the contacts are re-apportioned to their elder peers.
- The total average number of contacts, a_i, remain the same, and the contacts are re-apportioned to their children. Note that the children of the elderly are adults.
- As ϵ_{4i} and ϵ_{5i} are scaled by a factor, f, the contacts are not re-apportioned, and the average number of contacts made between the elderly and their grandchildren, and vice versa, are correspondingly reduced by $\epsilon_{4i}a_i f$ and $\epsilon_{5i}a_i f$, respectively.

The results are shown in Fig. 7. Reduction of elder contacts by reducing contacts with their grandchildren appears to be the most effective control measure, reducing the final size of the epidemic in the elderly by a relative factor of over 60% if grandparents completely avoid their grandchildren, and an approximate 30% reduction in the final size of the epidemic if grandparents reduce contact with grandchildren by half. A 10% reduction is achieved if grandparents reduce contact by 15% (i.e., equivalent to around one day out of every seven, if they normally see their grandchil-

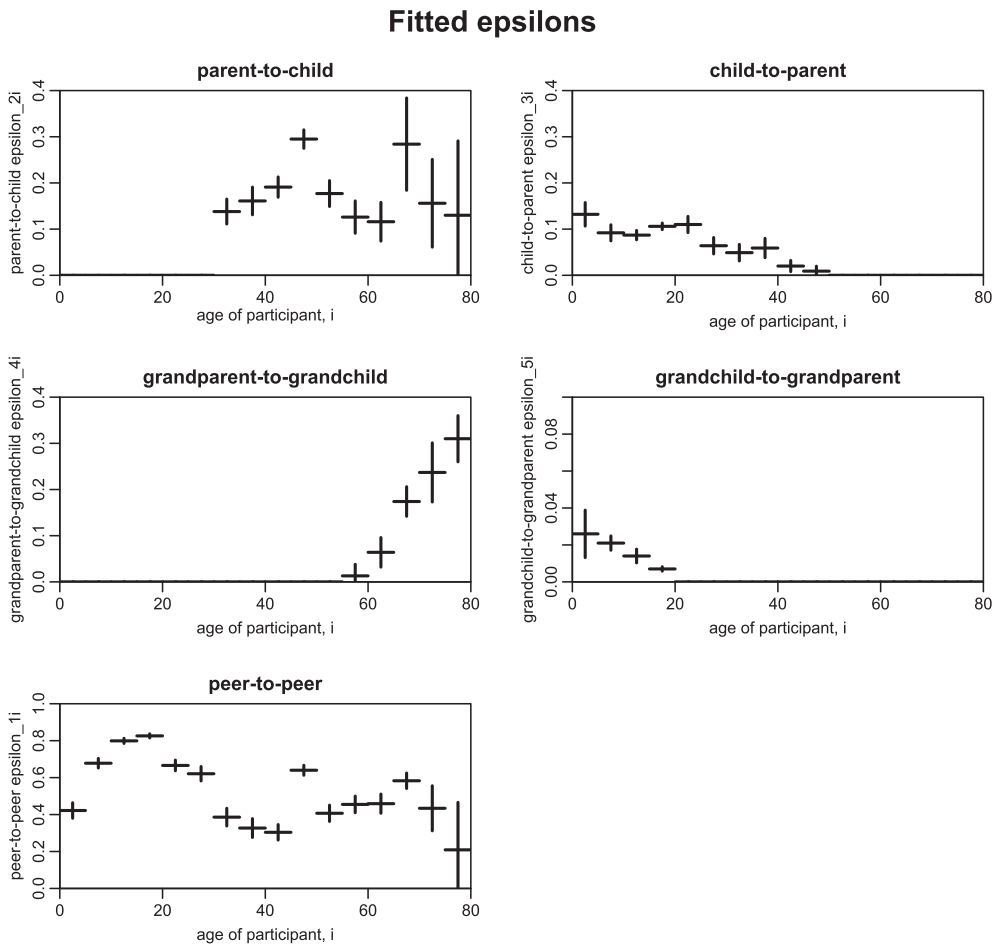

Fig. 5. Contact fractions, as determined by the second iteration of the fit to the contact matrix, wherein the widths of the off-diagonal Gaussian kernels were constrained to be equal.

Table 1
Parameters of our formulation of the contact matrix, as fitted to the data of Mossong et al. Additional parameters are $G = 29.30$ years, $\epsilon_6 = 0.095$, and $\sigma_2 = \sigma_3 = \sigma_4 = \sigma_5 = 4.50$ years. The N_i are taken from Ref. [26], and are expressed in millions of people.

Age group i	N_i	a_i	σ_{1i}	ϵ_{1i}	ϵ_{2i}	ϵ_{3i}	ϵ_{4i}	ϵ_{5i}
0–4	20.66	4.25	1.93 ± 0.54	0.42 ± 0.04	–	0.13 ± 0.03	–	0.03 ± 0.01
5–9	20.00	8.15	1.06 ± 0.18	0.68 ± 0.03	–	0.09 ± 0.02	–	0.02 ± 0.01
10–14	20.25	10.29	1.02 ± 0.11	0.80 ± 0.01	–	0.09 ± 0.01	–	0.01 ± 0.01
15–19	21.59	10.21	0.90 ± 0.09	0.83 ± 0.01	–	0.11 ± 0.01	–	0.01 ± 0.01
20–24	21.17	5.32	2.37 ± 0.34	0.67 ± 0.03	–	0.11 ± 0.02	–	–
25–29	21.38	4.66	3.69 ± 0.56	0.62 ± 0.04	–	0.06 ± 0.02	–	–
30–34	19.70	4.24	3.60 ± 0.79	0.39 ± 0.05	0.14 ± 0.03	0.05 ± 0.02	–	–
35–39	21.25	4.40	5.81 ± 1.29	0.33 ± 0.05	0.16 ± 0.03	0.06 ± 0.02	–	–
40–44	21.88	4.35	3.47 ± 0.86	0.30 ± 0.04	0.19 ± 0.02	0.02 ± 0.01	–	–
45–49	22.90	3.46	7.92 ± 0.84	0.64 ± 0.03	0.30 ± 0.02	0.01 ± 0.01	–	–
50–54	21.21	3.29	5.00 ± 0.85	0.41 ± 0.04	0.18 ± 0.03	–	–	–
55–59	18.38	2.74	4.41 ± 1.05	0.46 ± 0.04	0.13 ± 0.04	–	0.01 ± 0.02	–
60–64	14.73	2.42	5.99 ± 1.17	0.46 ± 0.05	0.12 ± 0.04	–	0.06 ± 0.03	–
65–69	10.95	1.77	4.67 ± 1.2	0.58 ± 0.04	0.28 ± 0.10	–	0.17 ± 0.03	–
70–74	8.64	1.38	9.64 ± 5.70	0.43 ± 0.12	0.16 ± 0.10	–	0.24 ± 0.06	–
75–79	7.30	0.72	17.20 ± 11.03	0.21 ± 0.26	0.13 ± 0.16	–	0.31 ± 0.05	–

dren daily). We note, however, that the final size of the epidemic in the entire population is only reduced by a relative factor of at most 2% by this control measure, indicating it is the elderly who reap nearly all the benefit.

Re-apportionment of grandparent/grandchild contacts by the elderly to their elder peers is a close second as a control measure, reducing the final size of the epidemic by nearly as much as a simple reduction in contacts. Re-apportionment of grandparent/grandchild contacts by the elderly to their adult children is not as effective (although up to a 40% relative reduction is still seen), likely because these adult children pass infections to the elderly from their own young children.

Discussion and summary

In this analysis we used contact survey data and expanded upon the work of Glasser et al. [15] to obtain an age-stratified parame-

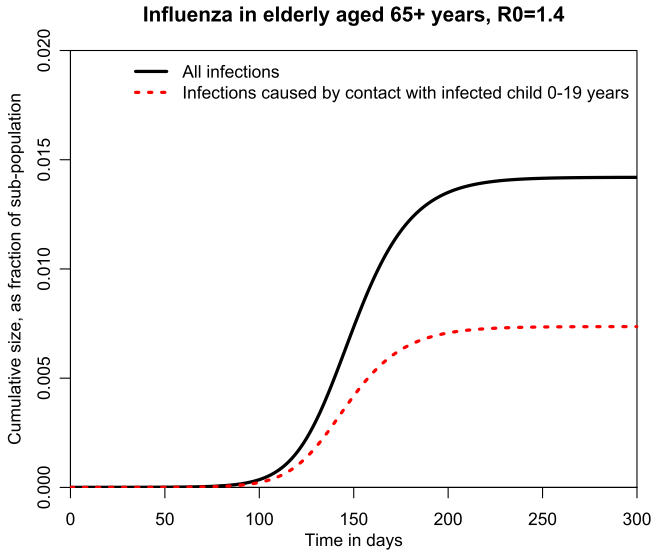

Fig. 6. Cumulative fraction of elderly people (age 65 years and over) infected in an influenza epidemic as simulated using the parameterization of C_{ij} determined by this analysis. Shown in red are the infections that are caused by direct contact with an infected child aged less than 20 years. Over 50% of infections in elderly people are caused by direct contact with an infected child. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

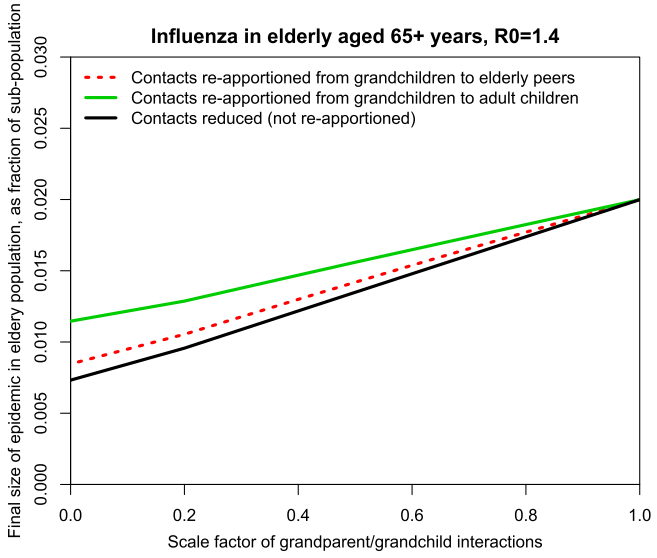

Fig. 7. Final size of influenza epidemic in sub-population of elderly people (as fraction of that sub-population) for three different scenarios of grandparents avoiding contact with grandchildren: the fraction of contacts made between grandparents and grandchildren is scaled, and the contacts are either re-apportioned to elderly peers or adult children such as to maintain the total number of contacts made by the elderly person (red and green, respectively), or the number of total contacts is simply reduced by the reduction in contacts with grandchildren (black). Re-apportionment of contacts to elder peers during the flu season is nearly as effective at reducing the attack rate as reduction in contacts. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

terization of a population contact matrix in terms of peer-to-peer, parent/child, grandparent/grandchild, and co-worker interactions.

Using this parameterized contact matrix, we modeled a hypothetical influenza epidemic using an age-stratified SIR model with preferential mixing between groups. We determined that over 50% of influenza infections in the elderly are caused by direct contact with an infected child.

This result is in notable agreement with analyses of ILI mortality rates in Japan between 1949 and 1998; between 1962 and 1987 most Japanese school children were vaccinated for influenza, but mandatory vaccination laws were relaxed in 1987 and repealed in 1994 [40,41]. The studies found that as mandatory influenza vaccination of school children ceased, excess ILI mortality, dominated by deaths in the elderly, increased. The Japanese studies indicate that children are indeed significant spreaders of influenza to the elderly.

The elderly carry much of the hospitalization and mortality burden of influenza during a typical influenza season, but because vaccines are known to not be very effective in the elderly [7,8], other control measures must be considered, such as vaccination programs of those whom they contact, as noted in the Japanese experience and other studies [10–13,40,41]. Social distancing is an inexpensive disease intervention to implement, and, given the apparent strong influence of children on the spread of influenza to the elderly, the efficacy of social distancing between these two groups during an influenza epidemic is worthy of assessment.

The most likely children an elderly person will contact are his or her grandchildren. Using our parameterized contact matrix, we thus examined the effect of scaling the grandparent/grandchild interactions on the final size of the influenza epidemic in the elderly population. Three scenarios were examined; in the first two, the total number of daily contacts of the elderly individuals was kept the same, but the reduction in their contacts with grandchildren was either re-apportioned to their elderly peers, or to their adult children. In the third scenario, the elderly simply avoided contact with grandchildren to some greater or lesser degree, and their contacts were correspondingly reduced.

We found that re-apportionment of grandchild contacts to elder peers was almost as effective as simply reducing contacts by that amount, reducing the final size of the epidemic in the elderly by a relative fraction of 60% if the elderly were to completely avoid their grandchildren (and a 30% reduction if the elderly reduce their contacts with their grandchildren by half). Re-apportionment of contacts, rather than a reduction in contacts, is perhaps a more ideal result for disease control, given that studies have shown that loneliness and lack of social contact can detrimentally affect peoples' health, making them more prone to fall ill with infectious disease [42,43].

It is quite interesting to note that all three reduction of grandparent/grandchild interaction scenarios had essentially no effect on the final size of the epidemic in the rest of the population. This implies that, on average, an elderly person has much to gain by social distancing, but the rest of the population will not be detrimentally affected if an elderly person chooses not to reduce contacts with his or her grandchildren during an influenza season. This is in sharp contrast with almost any other control measure, for which the choice of an individual to not participate will likely detrimentally affect not only the individual, but the rest of the population as well. For example, in influenza vaccination programs of school children, both a child *and* the rest of the population will, on average, tend to be detrimentally affected if the child is not vaccinated. The spread of influenza to both an individual and the rest of the population may also be affected by the hygiene habits of the individual (for instance, the regularity of hand washing).

Our study has some limitations; in particular we note that since the contact matrix parameterization is fit to European contact survey data, the results of this study are most applicable to European populations, and may or may not apply to U.S. populations where the elderly may have somewhat different contact patterns with children. For instance, the population simulations of Ref. [44] suggest that U.S. elderly spend roughly 10% of their contacts with children (in Europe it is more than 20%).

In summary, our model studies suggest that influenza vaccination strategies need not be the only disease interventions considered for elderly persons, and that simple social distancing can be remarkably effective in reduction of influenza attack rates in this age group. Our studies underline that mathematical models, such as the ones we have implemented here, can be helpful for understanding complex disease transmission dynamics, and can be useful for identifying optimal control strategies.

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