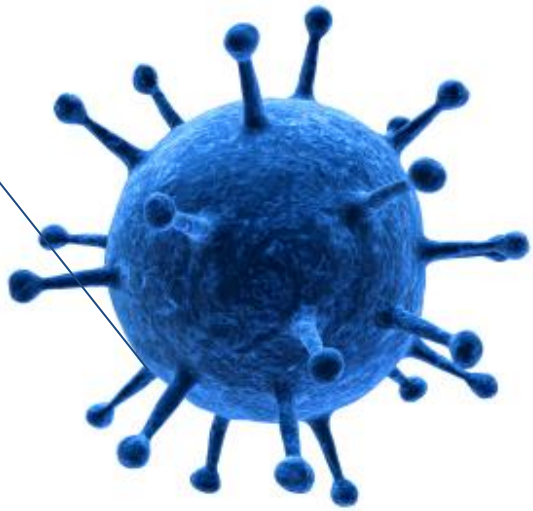

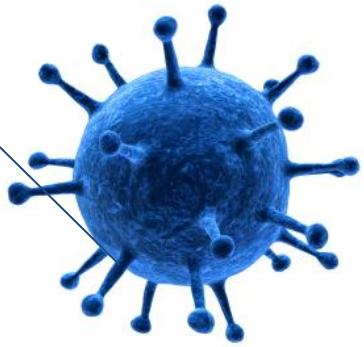

Impact of demographical change on the severity of an epidemic

Master thesis

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24th of January 2013

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In obtaining the Master of Science degree
of
Mathematical Sciences
Specialization: Stochastics and Financial Mathematics
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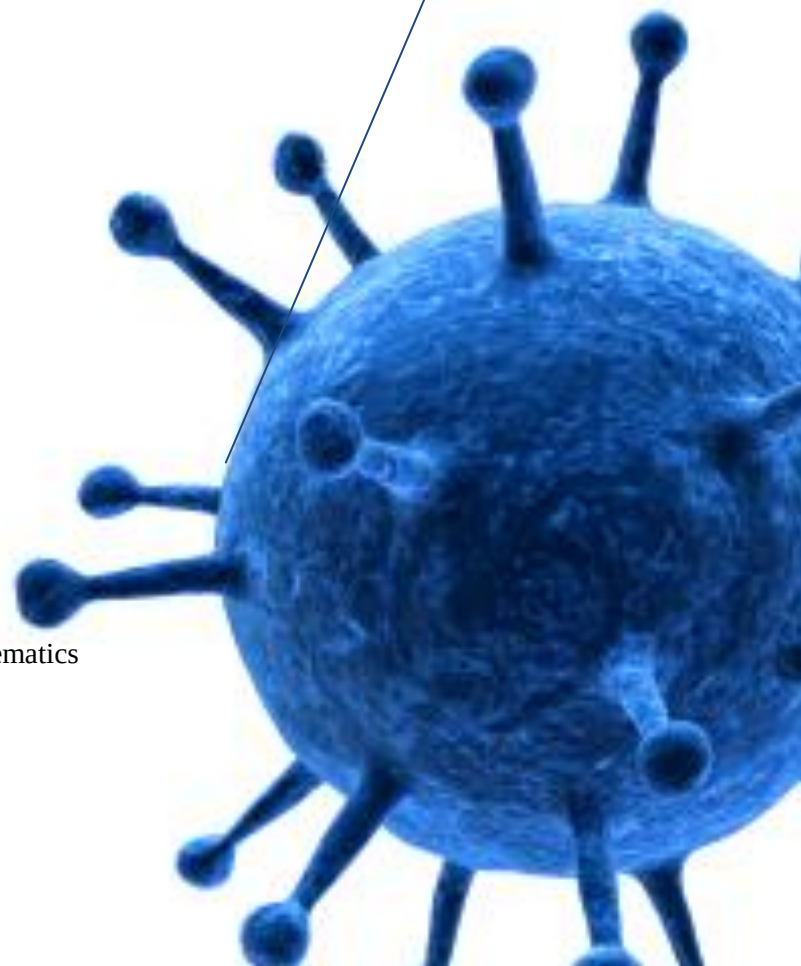

The impact of demographical change such as ageing on the severity of an epidemic: a theoretical and numerical study of the final size and the basic reproduction number

and

Effectiveness of interventions targeted at health care workers and residents in reducing the probability and the size of an infectious disease outbreak in a long-term care facility for the elderly

Master thesis

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Contents

1. Preface

This master thesis is written by Danny Chan in the field of mathematical infectious disease epidemiology. The research has been conducted between December 2011 and January 2013. A part of this study was done at The University of Hong Kong, The School of Public Health. It has been written under the supervision of dr. Martin Bootsma (Utrecht University), dr. Hiroshi Nishiura, dr. Joseph Wu (The University of Hong Kong) and prof. dr. Odo Diekmann (Utrecht University).

Epidemics have caused great disorders in the history of human kind and novel infectious diseases likely will remain a threat for all societies in the world. Examples of recent epidemics are the H1N1-2009 pandemic and the SARS outbreak in 2002. Both epidemics caused great disorders as school closures and excess of health care capacity. To be able to control future outbreaks, it is important to have an understanding of the dynamics of infectious diseases. A lot of work has been done in this area in the 20th century. A part of this work is in mathematical modelling. The aim of mathematical modelling is to create and analyze simplified models of reality that capture the most important determinants of the dynamics. The advantage of a mathematical framework is that it helps to explain and predict events in infectious disease epidemiology.

For this thesis we have conducted two separate studies with two different mathematical models. We have attempted to answer the two questions: 1) What is the relation between the final size [1] and the basic reproduction number [2] with the demography of a population? 2) Under what conditions are interventions which reduce infectiousness and susceptibility of health care workers useful in reducing the

[1] The cumulative number of individuals that became infected over the course of the infectious disease outbreak..

[2] The average number of new infections made by an infectious individual at the most early stage of an epidemic.

probability of a major outbreak in a long-term care facility for the elderly? The questions are explained further in this introduction.

Most of the developed countries are facing the problem of an ageing population. An extreme example is Japan, where only 18% of the population existed of individuals between 0 and 19 years old in 2012. In the Netherlands this age group consists of around 24% of the population and in USA it is around 30% in 2012. In all these countries it is expected that the fraction consisting of individuals between 0 and 19 years old will decrease. A higher fraction of elderly in the population may result in a higher mortality in case of an infectious disease outbreak, as the case fatality of elderly is usually above average. As the fraction of younger individuals decreases, the spread of the infectious disease may decrease as well since young individuals have a key role in the spread of most respiratory pathogens. This is explained by the relative high contact rate of young individuals with their own group (<20 years) in comparison with older individuals. This trade-off suggests that the effect of ageing on the severity of an infectious disease outbreak may be difficult to predict. The results on this topic are presented in chapter 2.

As ageing occurs in many societies, it is expected that the number of long-term care facilities for the elderly will increase as well. Successful protection of long-term care facilities for the elderly against major outbreaks may, therefore, become even more important than it is now due to the high case fatality among elderly. Typically, a novel pathogen is introduced in a long-term care facility for the elderly by health care workers or visitors. We have studied how interventions, which lower the infectiousness and susceptibility of health care workers and visitors, effect the probability of a minor outbreak in a long-term care facility for the elderly. We will show that weak[3] interventions, for example socially acceptable non-pharmaceutical interventions, only reduce the probability of a major outbreak in the facility when the basic reproduction

[3] Interventions which reduce susceptibility and infectiousness by 40% or less.

number of the pathogen is lower than around 1.6. Our work attempts to clarify the results of earlier work on the effectiveness of interventions in long-term care facilities for the elderly. Our results coincide and extend the work of Van den Dool et al., 2008 [I], but are different from the one presented by Nuño et al. in 2008 [II], which showed that the same interventions as in this study can reduce the probability of a major outbreak in a facility greatly even for higher values of the basic reproduction number. We support our simulation results by analytical approximations. The results of our study on this topic are presented in chapter 3.

2. The impact of demographical change such as ageing on the severity of an epidemic: a theoretical and numerical study of the final size and the basic reproduction number

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Abstract

Ageing and the effect of birth restriction change the demography in populations. These changes in demography influence contact patterns in societies, and, since contact patterns are important in disease transmission, influence the severity of infectious disease outbreaks. Here we use a deterministic multi-type SIR model to study theoretically and numerically how demographical changes impact the basic reproduction number R_0 and the final size of an infectious disease outbreak. We study either a density dependent contact pattern or a frequency dependent contact pattern. There is no consensus in literature in which multi-type contact pattern should be called frequency dependency. We have defined several new contact patterns in which the number of contacts per unit of time of an individual with a specific group is constant if we scale all group sizes by the same factor. In a model with reciprocal contacts where individuals have a fixed amount of contacts per unit of time with their own group and each young individual has a fixed amount of contacts per unit of time with older individuals, the basic reproduction number and final size increases when the number of young individuals increases. For other contact patterns, including the density dependent contact pattern, we have found theoretical results of a similar character. Numerical results suggest that if the society would have been more aged in Hong Kong in 2009, the number of cases of H1N1-2009 infection would have been smaller. However, due to the dependence of severity of an infection on the characteristics of the infected individuals, this need not imply a decrease in burden on the health care system. In a case study, we have found that birth restriction in Hong Kong may prolong the time before a similar H1N1 strain to the H1N1-2009 can cause an epidemic in Hong Kong.

1. Introduction

In many developed countries like Hong Kong, the USA and Japan, the national institutes of demography predicts that the fraction elderly will increase in the forthcoming years. Ageing can cause problems varying from an increased public health burden due to the increase of elderly (Yoshikawa, 1997), to a lack of work force due to a decrease of young adults. These problems are currently major issues in countries as Japan (Muramatsu, Akiyama, 2011). So far, the impact of ageing on the severity of infectious disease outbreaks with short duration has not been studied. Changes in demography influence contact patterns in society, and, since contact patterns affect disease transmission, it influences the severity of infectious disease outbreaks. For policy makers it is vital to understand how ageing affects the severity of an outbreak in order to design effective intervention strategies to prevent or mitigate epidemics.

Here we study theoretically and numerically the qualitative relationship between demographic changes, such as ageing, and the severity of an infectious disease outbreak. We only consider outbreaks that have a short duration in comparison with demographic changes, which implies that we can neglect the effect of demographic changes during the outbreak. An important example is the yearly influenza pandemic which lasts for several months, while ageing occurs at a time scale of decades. We focus on the basic reproduction number R_0 and the final size of a deterministic multi-type SIR model. The type of an individual corresponds to its age. The basic reproduction number can be interpreted as the average number of new infections due to an infectious individual at the earliest phase of an outbreak and the final size measures the cumulative number of infected individuals during the course of the outbreak.

We focus on frequency and density dependent contact patterns in the multi-type model. In single type models, these contact patterns have been extensively discussed in previous work (e.g. Begon et al., 2002, McCallum et al., 2001). The two contact patterns have different assumptions on how the contact process changes as a result of a change in population size. In a density dependent contact pattern the number of contacts

per unit of time per individual increases linearly if we scale all group sizes by the same factor. In a frequency dependent contact pattern, the number of contacts per unit of time of an individual is constant if we scale all group sizes by the same factor. There is no consensus in the literature on which multi-type contact pattern should be called frequency dependency. In section 2 we present several contact patterns where the number of contacts per unit of time of an individual is constant if all group sizes are scaled by the same factor. In general, the best contact pattern description of the transmission dynamics in a population, depends on the type of the population under consideration (Smith et al., 2009, Kelly et al., 2011).

In the theoretical part, which is also the main part of this paper, we present situations where the qualitative changes of the final size and the basic reproduction number due to a change in demography is revealed and proven formally. Almost all theoretical results hold for general *m*-type SIR models, $m \in \{1,2,3,...\}$, as formulated in section 2.

Apart from theoretical work, a case study has been performed on the relation between the final size and demography of the Hong Kong population. We have estimated the next generation matrix of the H1N1-2009 virus in Hong Kong in a 2- and 3-type model using similar methods as Nishiura et al., *2*010. We used the demographic predictions of the birth and death rate of the national institute of Hong Kong to calculate the effect of demographic changes on the outbreak size of an epidemic caused by an introduction of a H1N1 strain similar to the H1N1-2009 in Hong Kong in the period 2010-2039. To prepare a society for an outbreak, an accurate prediction of the public health burden during an outbreak is important. As the disease severity may depend on the age of the individual, the burden of an epidemic can, therefore, not be directly derived from the final size. In the numerical study we will use mortality as an additional measure for public health burden.

The article has the following structure. A description of the multi-type deterministic model with different contact patterns is presented in section 2. This is

followed by main results in section 3. The proofs which involve more abstract mathematics are given in section 4. Numerical results of the case study are presented in section 5 and we end with a discussion.

2. Model and properties

2.1. Model

We use a deterministic model with $m \in \{1,2,3,...\}$ disjunct types of individuals. Let group $i \in \{1,...,m\}$ be the set of type *i* individuals and let N_i be the size of group *i* and $\vec{N} = (N_1,...,N_m)^T$ be the vector of all group sizes and $N = \sum_{i=1}^{m} N_i$ the population size. We denote the fraction of the population that belongs to group *i* by $n_i = N_i / N$, we call the vector $\vec{n} = (n_1,...,n_m)^T$ the composition of the population. We have the relation $\vec{N} = N(n_1,...,n_m)^T$. In this paper the term demography is referred to the composition and the size of the population. In order to avoid ambiguity we will speak about these terms separately if not stated otherwise. We think of a group as an age category, but the results are equally valid for other interpretations of disjunct groups.

Individuals can be in one of the three disease stages: susceptible, infectious and removed. The number of *i*-type individuals in each disease stage at time *t* is denoted by $S_i(t)$, $I_i(t)$ and $R_i(t)$ respectively and the vector with the number of susceptible individuals in each group at time $t \in \mathbb{R}$ is denoted by $\vec{S}(t) = (S_1(t),...,S_m(t))^T$. All individuals are assumed susceptible before the first infectious individual arises in the population. When an *i*-type individual becomes infectious, it will remain in the infectious stage for an exponentially distributed period with mean $1/\alpha_i > 0$. The mean $1/\alpha_i$ is independent of the composition and the size of the population. We write

$\vec{\alpha} = (\alpha_1, ..., \alpha_m)^T$. When an *i*-type infectious individual recovers, it changes its disease stage to R_i instantaneously and remains in that stage forever.

We think of the model in a timeframe of $(-\infty, \infty) = \mathbb{R}$. When we look back in time, the population is infection free when $t \downarrow -\infty$. The introduction of a new pathogen cannot be controlled in a deterministic model, since it does not incorporate individual events. We leave therefore open how and when the pathogen is introduced in the population and assume only for all $i \in \{1, ..., m\}$ that $I_i(t_i) > 0$, for some $t_i \in \mathbb{R}$. As stated in the introduction, we neglect change in composition and population size (e.g. disease-induced deaths) during the time scale of the epidemic, so N_i is constant for all $i \in \{1, ..., m\}$. As R_i satisfies the relation $R_i = N_i - S_i - I_i$, the system of disease stages and group types over time is fully described by S_i and I_i only, $i \in \{1, ..., m\}$. Let $p_{ij} \geq 0$, $i, j \in \{1, ..., m\}$, denote the probability of a susceptible *i*-type individual becoming infectious due to contact with an infectious *j*-type individual given contact of the susceptible *i*-type and the infectious *j*-type individual. We assume p_{ij} to be independent of the composition and the size of the population. Let $k_{ij}(\vec{N}) > 0$, $1 \leq i, j \leq m$, denote the number of contacts per unit of time of a *j*-type individual with group *i* individuals which can depend on the composition and the size of the population. We write $K(\vec{N})$ for the $m \times m$ matrix $(k_{ij}(\vec{N}))_{1 \leq i, j \leq m}$.

For notational convenience, we will sometimes suppress the dependency of variables on the composition and size of the population (e.g. $K = K(\vec{N})$). In this paper, unless specified otherwise, vectors are *column* vectors. We say that an expression is positive and negative respectively when the expression is larger and smaller than 0. We say that an expression is non-positive and non-negative respectively when the

expression is equal to 0 or smaller than 0 and equal to 0 or larger than 0. Let $\vec{x}$ and $\vec{y}$ be real vectors of dimension $m \in \{1,...,m\}$. We write $\vec{x} > \vec{y}$ when entry $i \in \{1,...,m\}$ of $\vec{x}$ is larger than entry i of $\vec{y}$ for all $i \in \{1,...,m\}$. We extend this notation naturally to $\vec{x} \geq \vec{y}$, $\vec{x} < \vec{y}$, $\vec{x} \leq \vec{y}$ and $\vec{x} = \vec{y}$. A diagonal line "/" through the symbols $>$, $\geq$, $<$, $\leq$, $=$ means that the statement is false. We denote the *m*-dimensional unit and zero vector by $\vec{1}$ and $\vec{0}$ respectively.

Let β to be the $m \times m$ matrix with elements $\beta_{ij} = p_{ij} k_{ij}$ for $i, j \in \{1,...,m\}$, β_{ij} can be interpreted as the average number of new infections per unit of time in group *i* due to an infectious individual in group *j*, given that all individuals in group *i* are susceptible. At time t, a fraction $S_i(t)/N_i$ of group *i* is susceptible. The deterministic model is therefore fully described by the following set of differential equations:

$$\begin{aligned} \frac{dS_i}{dt} &= -\frac{S_i}{N_i}\sum_{j=1}^{m}\beta_{ij} I_j \\ \frac{dI_i}{dt} &= \frac{S_i}{N_i}\sum_{j=1}^{m}\beta_{ij} I_j - \alpha_i I_i \\ \frac{dR_i}{dt} &= \alpha_i I_i, \end{aligned} \tag{2.1}$$

with the condition $(S_i(-\infty), I_i(-\infty)) := \lim_{t \downarrow -\infty}(S_i(t), I_i(t)) = (N_i, 0)$ for all $i \in \{1,...,m\}$.

Assumption

The $m \times m$ matrix $\beta = (\beta_{ij})_{1 \leq i,j \leq m}$ is irreducible, i.e., for every pair of indices $i, j \in \{1,...,m\}$ there exists an l_{ij} such that $(\beta^{l_{ij}})_{ij}$ is positive.

Note that irreducibility of β implies that any susceptible individual of any group can be infected through a chain of infections starting from an infectious individual of any group.

Define $S_i(\infty) = \lim_{t \uparrow \infty} S_i(t)$ for all $i \in \{1,...,m\}$. Convergence of $S_i(t)$ follows from monotonicity and boundedness. We denote the *absolute* final size of group $i \in \{1,...,m\}$ by $R_i(\infty) = N_i - S_i(\infty)$ and the *fractional* final size by $1-\sigma_i := 1 - S_i(\infty)/N_i$ and the *normalized* total final size by $R(\infty)/N$ with $R(\infty) = \sum_{i=1}^{m} R_i(\infty)$. Note that the 3 types of final size are related by the involvement of $S_i(\infty)$ in all measures. We write $\vec{S}(\infty) = (S_1(\infty),...,S_m(\infty))^T$ and $\vec{\sigma} = (\sigma_1,...,\sigma_m)^T = (S_1(\infty)/N_1,...,S_m(\infty)/N_m)^T$. Note that the following holds,

$$\log(S_i(\infty)) - \log(S_i(-\infty)) = \int_{-\infty}^{\infty} \frac{dS_i(t)}{dt} \frac{1}{S_i(t)} dt = -\frac{1}{N_i} \sum_{j=1}^{m} \beta_{ij} \int_{-\infty}^{\infty} I_j(t) dt, \qquad (2.2)$$

$$S_i(\infty) - S_i(-\infty) = \int_{-\infty}^{\infty} \frac{dS_i(t)}{dt} + \frac{dI_i(t)}{dt} dt = -\alpha_i \int_{-\infty}^{\infty} I_i(t) dt, \qquad (2.3)$$

for all $i \in \{1,...,m\}$. The first and second equality of equation (2.2) and (2.3) follow from the standard integration rules and the differential equations (2.1) respectively. It follows from (2.3) that $(S_i(\infty) - S_i(-\infty))/\alpha_i = -\int_{-\infty}^{\infty} I_i(t) dt$ for all $i \in \{1,...,m\}$. Substituting this expression in (2.2) gives $\log(\sigma_i) = \sum_{j=1}^{m} \frac{\beta_{ij}}{\alpha_j} \frac{N_j}{N_i} (\sigma_j - 1)$ with $N_i = S_i(-\infty)$ and $\sigma_i = S_i(\infty)/N_i$ for all $i \in \{1,...,m\}$. Hence the relation between β, $\vec{\alpha}$, $\vec{N}$ and $\vec{\sigma}$, is give by the so-called final size equations

$$\sigma_i = \exp[\sum_{j=1}^{m} \frac{\beta_{ij}}{\alpha_j} \frac{N_j}{N_i} (\sigma_j - 1)], \qquad (2.4)$$

$i = 1,...,m$. Note that the *m*-dimensional unit vector, $\vec{1}$, is always a solution of (2.4). The final size equations (2.4) can also be derived heuristically as follows (see, e.g., Diekmann, Heesterbeek, Britton, 2013). If irreducibility of β holds, any susceptible individual of any group can be infected through a chain of infections starting from an infectious individual of any group, therefore, the transmission dynamics in the

population depends on the transmission rate from all groups, and, hence, the fractional final size of a specific group should depend on the fractional final size of all groups. Denote $F_i(t)$ to be the probability of an *i*-type individual to be susceptible at time *t*. Note that $F_i(-\infty) := \lim_{t \downarrow -\infty} F_i(t) = 1$. We reason that the probability of being susceptible over the course of the epidemic is equal to the fraction individuals that did not become infected over the course of the epidemic, therefore, $F_i(\infty) := \lim_{t \uparrow \infty} F(t) = \sigma_i$. From the interpretation of the differential equations (2.1) we have the expression

$$\frac{dF_i(t)}{dt} = -F_i(t) \sum_{j=1}^{m} \frac{\beta_{ij}}{N_i} I_j \tag{2.5}$$

for all $i \in \{1, ..., m\}$. Hence, $F_i(t) = \exp[-\int_{-\infty}^{t} \sum_{j=1}^{m} \frac{\beta_{ij}}{N_i} I_j(\tau) d\tau]$ and $\sigma_i = F_i(\infty) = \exp[-\int_{-\infty}^{\infty} \sum_{j=1}^{m} \frac{\beta_{ij}}{N_i} I_j(\tau) d\tau]$. Note that $\int_{-\infty}^{\infty} \sum_{j=1}^{m} \frac{\beta_{ij}}{N_i} I_j(\tau) d\tau$ is the cumulative force of infection (FOI; the rate of a susceptible individual becoming infected) of group $i \in \{1, ..., m\}$ individuals. The total number of infections in group *j* is equal to $(N_j - S_j(\infty))$. A fraction $1/N_i$ of the contacts of each *j*-type individual is with a specific individual in group *i*. Hence, $\int_{-\infty}^{\infty} \sum_{j=1}^{m} \frac{\beta_{ij}}{N_i} I_j(\tau) d\tau = \sum_{j=1}^{m} \frac{\beta_{ij}}{\alpha_j} \frac{N_j}{N_i} (1 - \sigma_j)$ and the final size equations (2.4) follow from the equality $\sigma_i = \exp[-\int_{-\infty}^{\infty} \sum_{j=1}^{m} \frac{\beta_{ij}}{N_i} I_j(\tau) d\tau]$.

The basic reproduction number in a finite discrete multi-type model is defined (Diekmann, Heesterbeek, Metz, 1990) as the dominant eigenvector of the next generation matrix (NGM). The *i*,*j*th entry (*i*th row, *j*th column) of the next generation matrix is the average number of new infections in group *i* due to a single *j*-type infectious individual at the earliest phase of the epidemic.

Choose $i, j \in \{1, ..., m\}$. Each *j*-type individual has $k_{ij}(\bar{N})$ contacts per unit of time with group *i* individuals, hence when all *i*-type individuals are susceptible, which

holds at the earliest phase of the epidemic, an infectious *j*-type individual infects $\beta_{ij}(\vec{N}) = p_{ij}k_{ij}(\vec{N})$ *i*-type individuals per unit of time. Each *j*-type infected individual is infectious for an average duration of $1/\alpha_j$. Therefore, the next generation matrix X for general contact pattern K is

$$X = \begin{pmatrix} \frac{\beta_{11}(\vec{N})}{\alpha_1} & \cdots & \frac{\beta_{1m}(\vec{N})}{\alpha_m} \\ \vdots & \ddots & \vdots \\ \frac{\beta_{m1}(\vec{N})}{\alpha_1} & \cdots & \frac{\beta_{mm}(\vec{N})}{\alpha_m} \end{pmatrix}. \qquad (2.6)$$

Note that, since $\vec{\alpha} > \vec{0}$, irreducibility of β implies irreducibility of X.

2.2 Contact patterns

For this study, we have to make assumptions on how the contact process changes when the composition and the size of the population changes. In this study we distinguish two main types of contact patterns: frequency and density dependency.

In multi-type human contact patterns, contacts are often reciprocal, i.e., if person A has contact with person B, then person B has contact with person A as well. The mathematical formulation of this condition is $k_{ij}/N_i = k_{ji}/N_j$ (or equivalently $k_{ij}N_j = k_{ji}N_i$).

2.3.1 Frequency dependent contact patterns

We introduce frequency dependency by an example to give the reader an intuition. Imagine the situation of a sandbank with a group of seals on it. It is known that seals, when lying on the sandbank, have the tendency to lie at a fixed distance next to other seals. Hence, the distance between neighbouring seals on the sandbank, which is a proxy for the contact rate, is independent of the population size. This typical example of

a population with frequency dependent contact pattern was studied in Diekmann et al., 1995.

There is no consensus in the literature on the exact definition of frequency dependency in a multi-type model. Recall $\vec{N} = (N_1,...,N_m)^T = N(n_1,...,n_m)^T = N\vec{n}$, where N is called the population size and $\vec{n} = (n_1,...,n_m)^T$ the composition. In this article we say that a contact pattern is a *candidate of frequency dependency* if the number of contacts per unit of time of all individuals, 1) only depends on the composition $\vec{n}$ of the population and 2) satisfies the reciprocal condition $k_{ij} / N_i = k_{ji} / N_j$.

2.3.2 Proportionate mixing

Assume that a *j*-type individual, $j \in \{1,...,m\}$, has a fixed amount of contacts $k_j > 0$ which is independent of time, composition and population size. If the fraction of contacts per unit of time of any individual with individuals of any group is proportionate to the number of contacts of that group, then, the contact pattern is called proportionate mixing. For proportionate mixing the elements of K are equal to

$$k_{ij}^{prop} = \frac{k_i N_i}{\sum_{s=1}^{m} k_s N_s} k_j, \qquad (2.7)$$

for $1 \le i, j \le m$. Clearly, k_{ij}^{prop} depends on the composition of the population but not on the population size and satisfies the reciprocal condition, hence, proportionate mixing is a candidate of frequency dependency.

Note that a change in size of any group affects the value of k_{ij}^{prop} for all $i, j \in \{1,...,m\}$. The advantage of proportionate mixing is that it allows us to think intuitively about the contact pattern. A disadvantage is that it does not allow individuals of specific pairs of groups to have a certain number of contacts per unit of time, which

is needed to model, for example, contacts of children with parents and contacts of grandchildren with grandparents.

2.3.3 Semi-domination contact patterns

We show the expression of k_{ij} in a semi-domination contact pattern and present the interpretation in section 2.3.4. The semi-domination contact pattern is given by

$$k_{ij}^s = q_{ij}^s \frac{N_i}{c_{ij}N_i + (1-c_{ij})N_j}, \tag{2.8}$$

$1 \le i, j \le m$, with $q_{ij}^s = q_{ji}^s > 0$ and $c_{ij} = 1 - c_{ji}$ with $c_{ij} \in [0,1]$. Note that, when $i = j$, k_{ij}^s is equal to $q_{ij}^s = q_{ji}^s$. It is clear that the semi-domination contact pattern is independent of the population size and satisfies the reciprocal conditions. Hence, the semi-domination contact pattern is a candidate of frequency dependency.

Note that, for every $i, j \in \{1,...,m\}$, k_{ij}^s depends only on the sizes of group *i* and *j*. In the context of three age groups: young, middle-aged and elderly, this means that a change in number of elderly does not change the number of contacts between young and middle-aged individuals. Note that q_{ij}^s gives the freedom to choose a specific number of contacts per unit of time between groups *i* and *j*. The importance of the group sizes of group *i* and *j* in determining the number of contacts per unit time between group *j* and *i* is determined by the parameter c_{ij}.

By substituting the expression of (2.8) into the differential equations (2.1) we obtain the model with semi-domination contact pattern in differential equations

$$\frac{dS_i}{dt} = -\frac{p_{ii}q_{ii}^s}{N_i} S_i I_i - S_i \sum_{\substack{j=1 \\ j \neq i}}^{m} \frac{p_{ij}q_{ij}^s}{c_{ij}N_i + (1-c_{ij})N_j} I_j, \tag{2.9}$$

$1 \le i \le m$. We write $a_{ij}^s = \frac{p_{ij} q_{ij}^s}{\alpha_j}$, $1 \le i, j \le m$. Each j-type, $j \in \{1,...,m\}$, infected individual is infectious for an average duration of $1/\alpha_j$ units of time and infects $\frac{p_{ij} q_{ij}^s N_i}{c_{ij} N_i + (1-c_{ij}) N_j}$ i-type, $i \in \{1,...,m\}$, individuals per unit of time when all individuals in group i are susceptible. Hence, the next generation matrix in a model with semi-domination contact pattern is

$$X_s = \begin{pmatrix} a_{11}^s & \cdots & a_{1m}^s \frac{N_1}{c_{1m} N_1 + (1-c_{1m}) N_m} \\ \vdots & \ddots & \vdots \\ a_{m1}^s \frac{N_m}{c_{1m} N_1 + (1-c_{1m}) N_m} & \cdots & a_{mm}^s \end{pmatrix}. \qquad (2.10)$$

The derivation of the final size equations (2.4) does not depend on the choice of contact pattern. Hence, the final size equations with a semi-domination contact pattern can be obtained by substituting (2.8) in (2.4). The final size equations are

$$\sigma_i = \exp[a_{ii}^s (\sigma_i - 1) + \sum_{\substack{j=1 \\ j \ne i}}^{m} \frac{a_{ij}^s N_j}{c_{ij} N_i + (1-c_{ij}) N_j} (\sigma_j - 1)], \qquad (2.11)$$

for $1 \le i \le m$.

2.3.4 Domination contact patterns

In general, the semi-domination contact pattern does not allow for a simple intuitive interpretation. We introduce a subset of the semi-domination contact pattern, which we call the *domination contact pattern* and show that it can be interpreted intuitively. Choose two groups, which we denote by group $i, j \in \{1,...,m\}$ and assume that the contacts between the 2 groups are described by the semi-domination contact pattern. If $c_{ij} = 1$, then $k_{ij}^s = q_{ij}^s$ and $k_{ji}^s = q_{ij}^s \frac{N_j}{N_i} = k_{ij}^s \frac{N_j}{N_i}$, hence, the number of contacts of a j-type individual with group i individuals is independent of the composition of the population.

We can think of this contact pattern as that group *j* individuals want to keep the number of contacts per unit of time with group *i* individuals fixed and that group *i* individuals feels comfortable to adjust their number of contacts per unit of time with group *j* as a result of a change in size of group *j* and group *i*. In this case, we say that group *j* *dominates* group *i* and that group *i* is being *dominated* by group *j*. We call a pair of groups $i, j \in \{1,...,m\}$ a *domination pair* when group *i* dominates group *j* or group *j* dominates group *i*.

We define a semi-domination contact pattern to be a domination contact pattern when each pair of groups in the population is a domination pair.

Thus a domination contact pattern is a semi-domination contact pattern with $c_{ij} \in \{0,1\}$, for all $i, j \in \{1,...,m\}$. By allowing c_{ij}, $i, j \in \{1,...,m\}$, to obtain values in between 0 and 1, we introduce contact patterns that are in between contact patterns with the characteristic that group *j* dominates *i* and vice versa. This explains the choice of calling the contact pattern (2.8) a *semi*-domination contact pattern.

Additionally we introduce two terms. We say that group *i* is a *royal group* if group *i* dominates all other groups in the population. We call group *i* a *servant group* if group *i* is being dominated by all other groups in the population. Note that a domination contact pattern does not necessarily have a royal or servant group and that a semi-domination contact pattern with a royal or servant group is not necessarily a domination contact pattern.

We think in this article that children have a fixed number of contacts per unit of time with middle-aged (parents) and aged (grandparents) individuals, independent of the composition and the size of the population. Also, we assume that the aged individuals adjust their number of contacts per unit of time with the younger groups to the need of contacts of the younger individuals (including middle-aged individuals). Therefore, in the context of semi-domination contact patterns, the group of children and aged individuals are respectively a royal and a servant group.

2.3.5 Power contact patterns

We present the set of power contact patterns first and explain the advantages and disadvantages of the contact pattern afterwards. We call the following set of contact patterns the power contact patterns:

$$k_{ij}^{p} = q_{ij}^{p}\left(\frac{N_i}{N_j}\right)^{d}, \tag{2.12}$$

for $1 \le i, j \le m$, with $q_{ij}^{p} = q_{ji}^{p} > 0$ and $d \in \mathbb{R}$. Note that k_{ij}^{p} is independent of the population size and satisfies the reciprocal condition only for $d = 1/2$. Hence, the power contact pattern is a candidate of frequency dependency only for $d = 1/2$. Note that, when $i = j$, we have $k_{ij}^{p} = q_{ij}^{p}$. We emphasize that for $d \neq 1/2$, the power contact pattern does not satisfy the reciprocal condition and is, hence, not a candidate of frequency dependency.

The power contact pattern does not allow for a simple intuitive interpretation for general $d \in \mathbb{R}$. Although the following subset of power contact patterns do not satisfy the reciprocal condition, these contact patterns are easy to be interpreted. When $d = 0$, the number of contacts per unit of time of any individual in the population with individuals of any group is independent of composition. When $d = 1$, the number of contacts per unit of time of a *j*-type individual with individuals of group *i* has an inversely proportional relation with the size of group *j*, hence, the total number of contacts per unit of time of group *j* individuals with group *i* individuals is independent of the size of group *j*.

The power contact pattern is interesting from a mathematical point of view. We will show in section 3 that the basic reproduction number, in a model with the power contact pattern, is independent of the composition for all $d \in \mathbb{R}$. Also, when $d = 1$, the fractional final size is independent of the composition of the population.

The differential equations, next generation matrix and final size equations in the case of a power contact pattern can be obtained by substituting (2.12) in the associated expressions in section 2.1. We write $a_{ij}^{p} = \dfrac{p_{ij} q_{ij}^{p}}{\alpha_j}$ .The differential equations, next generations matrix X_p and final size equations are respectively

$$\frac{dS_i}{dt} = -\frac{p_{ii} q_{ii}^{p}}{N_i} S_i I_i - S_i \sum_{\substack{j=1 \\ j \neq i}}^{m} p_{ij} q_{ij} \frac{N_i^{d-1}}{N_j^{d}} I_j \,, \tag{2.13}$$

$$X_p = \begin{pmatrix} a_{11}^{p} & \cdots & a_{1m}^{p} \left(N_1 / N_m \right)^{d} \\ \vdots & \ddots & \vdots \\ a_{m1}^{p} \left(N_m / N_1 \right)^{d} & \cdots & a_{mm}^{p} \end{pmatrix}, \tag{2.14}$$

$$\sigma_i = \exp[a_{ii}^{p} (\sigma_i - 1) + \sum_{\substack{j=1 \\ j \neq i}}^{m} a_{ij}^{p} N_i^{d-1} N_j^{1-d} (\sigma_j - 1)] \,, \tag{2.15}$$

for $1 \leq i \leq m$.

2.4 Density dependency

We illustrate density dependency by an example. Imagine a swimming pool of fixed size with an increasing number of swimmers. We assume that the number of contacts per unit of time increases when the distance between individuals decreases. As the number of swimmers increases, the average area available per swimmer decreases which results in a smaller distance between swimmers, causing an increase in contacts per unit of time between swimmers.

We say that a contact pattern is a density dependent contact pattern when the number of contacts per unit of time of a *j*-type, $j \in \{1,...,m\}$, individual with group $i \in \{1,...,m\}$ individuals has a linear relation with the size of group *i* and satisfies the reciprocal condition, thus the elements of K are equal to

$$k_{ij}^{d} = q_{ij}^{d} N_i \,, \tag{2.16}$$

for $1 \le i, j \le m$, with $q_{ij}^d = q_{ji}^d > 0$. The reciprocal condition is clearly satisfied. The main difference between the candidates of frequency dependency and the density dependent contact pattern is that K, in the density dependent case, depends on the size of the population. The total number of contacts of a group $j \in \{1,...,m\}$ individual is $\sum_{i=1}^{m} k_{ij}^d = \sum_{i=1}^{m} q_{ij}^d N_i$. Hence, when all group size are increased by the same factor, the total number of contacts of a group *j* individual increase as well.

The differential equations, next generation matrix and final size equations in the case of density dependency is obtained by substituting (2.16) in the associated expressions in section 2.1. Write $a_{ij}^d = \frac{p_{ij} q_{ij}^d}{\alpha_j}$. Then the differential equations, next generations matrix and final size equations are respectively

$$\frac{dS_i}{dt} = -S_i \sum_{j=1}^{m} p_{ij} q_{ij}^d I_j \,, \tag{2.17}$$

$$X_d = \begin{pmatrix} a_{11}^d N_1 & \cdots & a_{1m}^d N_1 \\ \vdots & \ddots & \vdots \\ a_{m1}^d N_m & \cdots & a_{mm}^d N_m \end{pmatrix}, \tag{2.18}$$

$$\sigma_i = \exp[\sum_{j=1}^{m} a_{ij}^d N_j (\sigma_j - 1)] \,, \tag{2.19}$$

for $1 \le i \le m$.

3. Results

3.1. General results

In this section we show results which hold for general contact patterns. These results form the basis of the proofs of the other results in section 3. All proofs of section 3.1 are given in section 4. We define the matrix

$$X(\vec{S}(t)) = \begin{pmatrix} \frac{S_1(t)}{N_1}\frac{\beta_{11}}{\alpha_1} & \cdots & \frac{S_1(t)}{N_1}\frac{\beta_{1m}}{\alpha_m} \\ \vdots & \ddots & \vdots \\ \frac{S_m(t)}{N_m}\frac{\beta_{m1}}{\alpha_1} & \cdots & \frac{S_m(t)}{N_m}\frac{\beta_{mm}}{\alpha_m} \end{pmatrix}. \qquad (2.20)$$

Note that $X(\vec{S}(t))$, $t \in \mathbb{R}$, is the next generation matrix of a population where the number of *i*-type susceptible individuals at the earliest phase is $S_i(t)$, $1 \le i \le m$, hence, $X = X(\vec{S}(-\infty))$. We define $X_s(\vec{S}(t))$, $X_p(\vec{S}(t))$ and $X_d(\vec{S}(t))$ to be $X(\vec{S}(t))$ for a semi-domination, power and density dependent contact pattern respectively. Let *M* be an *m*-dimensional real valued irreducible square matrix, in the forthcoming we write $\rho(M)$ for the dominant eigenvalue of the matrix *M*.

Theorem 1

Assume the model as described by (2.1) with a general contact pattern *K* and $\beta = (\beta_{ij})_{1 \le i,j \le m}$ irreducible. If and only if $R_0 = \rho(X(\vec{S}(-\infty))) > 1$, the final size equations (2.4) has a solution in $(0,1)^m$. If so, this solution is unique.

Theorem 1 shows that $R_0 \le 1$ and $R_0 > 1$ corresponds respectively to no occurrence and occurrence of an outbreak in the population. Also, it states that the final size given an outbreak is unique. In the forthcoming, if $R_0 > 1$, we refer to $\vec{S}(\infty)$ as the unique solution of (2.4) in $(0, N_1) \times ... \times (0, N_m)$.

Theorem 2

Assume the model as described by (2.1) with a general contact pattern *K* and $\beta = (\beta_{ij})_{1 \le i,j \le m}$ irreducible. If $R_0 = \rho(X(\vec{S}(-\infty))) > 1$, then $\rho(X(\vec{S}(\infty)) < 1$.

Theorem 2 is expected intuitively. $X(\vec{S}(\infty))$ is the next generation matrix when the number of susceptible individuals in each group is equal to the number of uninfected individuals at the end of the epidemic. Intuitively, it is expected that the state of the population after an epidemic does not allow for a new outbreak. We expected $\rho(X(\vec{S}(\infty)) < 1$, since outbreaks in the deterministic model occur if and only if the basic reproduction number is larger than 1 as stated in Theorem 1. The above reasoning should be read to obtain an intuition only, since $I(t) \neq 0$ for $t \in \mathbb{R}$ and, hence, the end of an epidemic cannot be trivially be defined as the $t_0 \in \mathbb{R}$ for which $I(t_0)$ is equal to 0 for the first time.

Theorem 3

Assume the model as described by (2.1) with K continuously differentiable to $\vec{N}$ and $\beta = (\beta_{ij})_{1 \leq i,j \leq m}$ irreducible in the domain of $\vec{N}$, $p_{11}, p_{12}, ..., p_{mm}$, $\vec{\alpha}$. If $R_0 = \rho(X(\vec{S}(-\infty))) > 1$, then $S_i(\infty)$ is continuously differentiable to $\vec{N}$, $p_{11}, p_{12}, ..., p_{mm}$, $\vec{\alpha}$ for all $i \in \{1, ..., m\}$.

Lemma 4

Assume the model as described by (2.1) with a general contact pattern K and $\beta = (\beta_{ij})_{1 \leq i,j \leq m}$ irreducible in the domain of $\vec{N}$. Choose $i \in \{1, ..., m\}$. Fix N_j for all $j \in \{1, ..., m\}$ except for $j=i$. Assume K to be element-wise differentiable to N_i. Let $x^{*T} > \vec{0}^T$ and $x > \vec{0}$ be respectively the left and right eigenvector corresponding to the dominant eigenvalue of X and $x^{*T} x = 1$. Then the basic reproduction number, $R_0 = \rho(X(\vec{S}(-\infty)))$, is differentiable to N_i and $\frac{dR_0}{dN_i} = x^{*T} X'(N_i) x$, $i=1,...,m$.

3.2.1 Frequency dependent contact patterns

It has been argued in section 2 that all candidates of frequency dependency do not depend on the population size. Therefore, when the contact pattern is a candidate of frequency dependency, a change in population size, does not change the transmission dynamics and hence, the basic reproduction number and fractional final size. In the case of candidates of frequency dependency, we study the qualitative impact of a change in size of any group on the basic reproduction number and fractional final size. Recall that the vector, $\vec{N}$, with on the *i*th entry the size of group *i*, can be written as $\vec{N} = (N_1,...,N_m)^T = N(n_1,...,n_m)^T = N\vec{n}$. When the size of the group with index 1 increases by $\delta > 0$, N clearly increases by δ too. The vector $\vec{N}$ becomes $(N_1^* + \delta,...,N_m^*)^T = (N^* + \delta)(\frac{N_1^* + \delta}{(N^* + \delta)},...,\frac{N_m^*}{(N^* + \delta)})^T$ with $(N_1^*,...,N_m^*)^T$ the initial vector $\vec{N}$ and N^* the initial population size. Clearly, after the increase, the relative size of group 1 has increased in comparison with the other groups, while the ratio between all other pairs of groups, excluding group 1, has not changed. Therefore, since population size has no effect on transmission dynamics, the effect of increasing the size of one group is equivalent to the effect of increasing the proportion of that group in the population while keeping the ratio between all other pairs of groups and the population size constant.

3.2.2 Semi-domination contact patterns

Theorem 5

Assume the model as described by (2.1) with a semi-domination contact pattern $K = (k_{ij}^s)_{1\le i,j\le m}$ and $\beta = (p_{ij}k_{ij}^s)_{1\le i,j\le m}$ irreducible for $\vec{N} > \vec{0}$ and $R_0 = \rho(X_s) > 1$. Assume the population to have a royal group $z \in \{1,...,m\}$. Then $\frac{dR_0}{dN_z} > 0$ and $\frac{d\sigma_i}{dN_z} < 0$, $1 \le i \le m$.

The proof of Theorem 5 is presented in section 4. Theorem 5 is expected from the definition of a royal group and the intuition behind a semi-domination contact pattern. An individual of the royal group z has a fixed number, k_{iz}^{s}, of contacts with group $i \in \{1,...,m\}$ individuals. For any time $t \in \mathbb{R}$ we can reason as follow. As the size of the royal group z increases, the number of contacts per unit of time of each individual of group $i \neq z$ with the royal group z increases. Hence, the force of infection in group $i \neq z$ increases. Since the contact rates between groups other than the royal group do not change, we expect $\frac{d\sigma_i}{dN_z} < 0$, $i \neq z$, $1 \leq i \leq m$. The number of contacts per unit of time of individuals in the royal group does not change, but as an effect of $\frac{d\sigma_i}{dN_z} < 0$, $i \neq z$, $1 \leq i \leq m$, we expect also $\frac{d\sigma_z}{dN_z} < 0$. By a same reasoning we expect that $\frac{dR_0}{dN_z} > 0$. The same type of reasoning applies for servant groups and the following theorem is expected.

Theorem 6

Assume the model as described by (2.1) with a semi-domination contact pattern $K = (k_{ij}^{s})_{1 \leq i,\, j \leq m}$ and $\beta = (p_{ij} k_{ij}^{s})_{1 \leq i,\, j \leq m}$ irreducible for $\vec{N} > \vec{0}$ and $R_0 = \rho(X_s) > 1$. Assume the population to have a servant group $z \in \{1,...,m\}$. Then $\frac{dR_0}{dN_z} < 0$ and $\frac{d\sigma_i}{dN_z} > 0$, $1 \leq i \leq m$.

The proof is given in section 4. Theorem 5 and 6 are useful in a population where individuals are categorized in for example 3 groups: young, middle-aged and aged individuals. As mentioned in section 2.3.4, young individuals can intuitively be associated with the royal group and aged individuals can be associated with the servant group. By this association, we can interpret that a fractional increase of the number of aged individuals, which can be interpreted as ageing, will decrease the severity of an epidemic, if severity is measured in the basic reproduction number and the fractional

final size. Theorem 5 and 6 show that whether the number of contacts per unit of time of individuals of a group is fixed or depends in a manner such that the number of contacts per unit of time of other groups is fixed, is a major factor in the qualitative impact of a change in size of the group on the basic reproduction number and the fractional final size.

3.2.3 Power contact patterns

As mentioned in section 2.3.5, power contact patterns are independent of the population size for all $d \in \mathbb{R}$, but only satisfy the reciprocal condition for $d = 1/2$, hence, power contact patterns are only a candidate of frequency dependency when $d = 1/2$. An interesting property in a model with the power contact pattern is that the basic reproduction number is independent of the composition of the population.

Theorem 7

Assume the model as described by (2.1) with a power contact pattern $K = (k_{ij}^{p})_{1 \le i, j \le m}$ and $d \in \mathbb{R}$ and β irreducible for $\vec{N} > \vec{0}$. Then the basic reproduction number, $R_0 = \rho(X_p)$, is independent of the size and composition of the population.

Proof

Since β is irreducible for $\vec{N} > \vec{0}$ and $\vec{\alpha} > \vec{0}$ we conclude that also X_p is irreducible. Existence of $R_0 > 0$ follows directly from the Perron-Frobenius Theorem. The power contact pattern is independent of the population size as mentioned in section 2.3.5, hence, also the next generation matrix, which depends on $\vec{N}$ only in $(k_{ij}^{p})_{1 \le i, j \le m}$, is independent of the population size. Let $Diag(\vec{\upsilon})$ denote the diagonal matrix with at the *j*th diagonal the *j*th entry of vector $\vec{\upsilon}$ for $j \in \{1, ..., m\}$ and 0 for all other entries. Call

$\Delta_p(d) = Diag((N_1^d,...,N_m^d)^T)$, $d \in \mathbb{R}$. Note that the next generation matrix (2.14), in a model with a power contact pattern with $d \in \mathbb{R}$, can be written in the form

$$X_p = \Delta_p(d) \begin{pmatrix} a_{11}^p & \dots & a_{1m}^p \\ \vdots & \ddots & \vdots \\ a_{m1}^p & \dots & a_{mm}^p \end{pmatrix} \Delta_p^{-1}(d). \qquad (2.21)$$

Thus X_p is similar to a matrix which is independent of the composition (and the size) of the population. Since similar matrices have the same eigenvalues, we conclude that $R_0 = \rho(X_p)$ is independent of the composition of the population. QED

Theorem 8

Assume the model as described by (2.1) with a power contact pattern $K = (k_{ij}^p)_{1 \le i, j \le m}$ and $\beta = (p_{ij} k_{ij}^p)_{1 \le i, j \le m}$ irreducible for $\vec{N} > \vec{0}$ and $d = 1$. Then the fractional final size is independent of the size and composition of the population.

Proof

The statement is directly proven by substitution of $d = 1$ in the final size equations (2.15). QED

3.3 Density dependency

Theorem 9

Assume the model as described by (2.1) with a density dependent contact pattern $K = (k_{ij}^d)_{1 \le i, j \le m}$ and $\beta = (p_{ij} k_{ij}^d)_{1 \le i, j \le m}$ irreducible for $\vec{N} > \vec{0}$. Then $\frac{dR_0}{dN_z} > 0$, $1 \le z \le m$.

Proof

We are in the situation of Lemma 4 since β is irreducible for $\vec{N} > \vec{0}$ and K continuously differentiable to $\vec{N} > \vec{0}$. Choose $z \in \{1,...,m\}$. $X_d'(N_z)$ is the matrix with

elements $a_{zj}^d \geq 0$ for all $j \in \{1,...,m\}$ in the *z,j*th position and 0 for positions other than the *z*th row. By irreducibility of β, a_{zj}^d is positive for at least one $j \in \{1,...,m\}$. Since $x^{*T} > \vec{0}$ and $x > \vec{0}$ (notation as in Lemma 4), we conclude $\frac{dR_0}{dN_i} > 0$ for all $i \in \{1,...,m\}$.

QED

Theorem 10

Assume the model as described by (2.1) with a density dependent contact pattern $K = (k_{ij}^d)_{1 \leq i,j \leq m}$ and $\beta = (p_{ij} k_{ij}^d)_{1 \leq i,j \leq m}$ irreducible for $\vec{N} > \vec{0}$. Assume $R_0 = \rho(X_d) > 1$, then $\frac{d\sigma_i}{dN_z} < 0$ for $i, z \in \{1,...,m\}$. Additionally, if $a_{zz}^d N_z > 1$, then $\frac{dS_z(\infty)}{dN_z} < 0$ for $z \in \{1,...,m\}$.

The proof of Theorem 10 is presented in section 4. In a density dependent contact pattern, both the size as the composition of the population has influence on the basic reproduction number and the fractional final size. Therefore, the impact of an increase of the group size of any group on the basic reproduction number and the fractional final size is a result of both a change in composition and size of the population. Note the difference with the theorems involving candidates of frequency dependency, where the impact is only due to a change in composition. Clearly, when the population size increases, all group sizes changes and hence, the qualitative results of Theorem 9 and 10 also holds for $\frac{dR_0}{dN}$ and $\frac{d\sigma_i}{dN}$, $1 \leq i \leq m$.

Theorem 9 is intuitively expected by the fixed pool metaphor; an increase of individuals, increases the number of contacts and hence increases the average number of infections due to a single infectious individual at the earliest phase of an epidemic.

The impact on the basic reproduction number as an effect of a change in composition $\vec{n} = (n_1, ..., n_m)$ only (population size N is fixed) is different than stated as in Theorem 9. We write for convenience $\tilde{a}_{ij} = a_{ij}^d N$ for all $i, j \in \{1, ..., m\}$. The next generation matrix with the density dependent contact pattern can then be written in the form

$$X_d = \begin{pmatrix} \tilde{a}_{11} n_1 & \cdots & \tilde{a}_{1m} n_1 \\ \vdots & \ddots & \vdots \\ \tilde{a}_{m1} n_m & \cdots & \tilde{a}_{mm} n_m \end{pmatrix}. \qquad (2.22)$$

When β is irreducible for $\vec{n} \in (0,1)^m$, the expression $\frac{dR_0}{dn_i} = x^{*T} X_d'(n_i) x$ follows directly from Lemma 4, with $x^{*T} > \vec{0}^T$ and $x > \vec{0}$ as in the notation of Lemma 4. In the *m*-type model, with *m* large, it is difficult to determine the sign of the expression $\frac{dR_0}{dn_i} = x^{*T} X_d'(n_i) x$ due to the condition $\sum_{i=1}^{m} n_i = 1$. In the 2-type model we have the following theorem.

Theorem 11

Assume the 2-type (*m=2*) model as described by (2.1) with a density dependent contact pattern $k_{ij}^d > 0$ for $n_1 \in (0,1)$ and $p_{ij} > 0$ for $i, j \in \{1, 2\}$, and a fixed population size N (i.e. $n_1 = 1 - n_2$). Then R_0 is a differentiable function to n_1 on $[0,1]$, with at most 1 extremum. The sign of the slope of R_0 in $n_1 = 0$, $n_1 = 1/2$ and $n_1 = 1$ corresponds respectively to the sign of $\tilde{a}_{12}\tilde{a}_{21} - \tilde{a}_{22}^2$, $\tilde{a}_{11} - \tilde{a}_{22}$ and $\tilde{a}_{11}^2 - \tilde{a}_{12}\tilde{a}_{21}$.

The proof of Theorem 11 is presented in section 4. Theorem 11 implies that the qualitative behaviour of the basic reproduction number as a function of n_1 depends on the values of $n_1 \in [0,1]$ and the terms $(\tilde{a}_{ij})_{1 \le i, j \le 2}$. This is different in the case of a non-

fixed population, where the basic reproduction number has a monotone relation with N_i, $i \in \{1,...,m\}$ as shown in Theorem 9. Note that the signs of $\frac{dR_0}{dn_1}$ at $n_1 = 0$, $n_1 = 1/2$ and $n_1 = 1$, i.e. the signs of $\tilde{a}_{12}\tilde{a}_{21} - \tilde{a}_{22}^2$, $\tilde{a}_{11} - \tilde{a}_{22}$ and $\tilde{a}_{11}^2 - \tilde{a}_{12}\tilde{a}_{21}$, determine the existence of an extremum and whether the extremum is located at a value of n_1 greater, smaller or equal to $1/2$ by Theorem 11.

4. Proofs

In this section we present the skipped proofs in section 3. This section can be skipped if one is not interested in technical details. The proofs use foremost the ideas of Schmidt, 1990.

Proof of Theorem 1

The following proof follows the steps of a more general proof as described in Rass & Radcliffe, 2003. Assume all conditions as stated in Theorem 1. We define $\nu_i := (1-\sigma_i) \in [0,1]$ and $b_{ij} := \frac{\beta_{ij}}{\alpha_j}\frac{N_j}{N_i}$ for all $i, j \in \{1,...,m\}$ and $B := (b_{ij})_{1 \le i,j \le m}$. Note that B is irreducible when β is irreducible, since $\vec{\alpha} > \vec{0}$ and $\vec{N} > \vec{0}$. The final size equations (2.4) are now $1-\nu_i = \exp[-\sum_{j=1}^{m} b_{ij}\nu_j]$, which are equivalent to

$$-\log(1-\nu_i) = \sum_{j=1}^{m} b_{ij}\nu_j \,, \qquad (2.23)$$

$i \in \{1,...,m\}$. Note that $\vec{\nu} = (\nu_1,...,\nu_m)^T = \vec{0}$ is a solution of (2.23) and other solutions of (2.23) cannot have entries equal to 1, since exp(·) has a range of $(0,\infty)$. We are therefore only interested in solutions of (2.23) with $\vec{\nu} \in [0,1)^m$. There is a one to one correspondence between values of $x \in [0,1)$ and $z \in [0,\infty)$ when the equation

$-\log(1-x)=z$ holds, or equivalently, $1-\exp(-z)=x$. Note that $x=0$ if and only if $z=0$. Now, solutions of (2.23) corresponds to solutions of

$$z_i=\sum_{j=1}^{m} b_{ij}(1-\exp[-z_j]), \tag{2.24}$$

$i=1,...,m$, with $\vec{z}=(z_1,...,z_m)^T\geq\vec{0}$ and $\nu_i=1-\exp[-z_i]$ and $z_i=-\log(1-\nu_i)$. In matrix notation (2.24) is equivalent to

$$\vec{z}=B(1-\exp[-\vec{z}]), \tag{2.25}$$

with $(1-\exp[-\vec{z}])$ the *m*-dimensional vector with at the *i*th entry $1-\exp[-z_i]$, $i\in\{1,...,m\}$. Theorem 1 can now be stated as: (2.25) has a unique solution $\vec{z}>\vec{0}$ if and only if $R_0>1$

First we prove that (2.25) only has the trivial $\vec{0}$ solution when $\rho(X)=R_0\leq 1$. Let $Diag(\vec{\upsilon})$ denote the $m\times m$ diagonal matrix with at the *j*th diagonal the *j*th entry of the *m*-dimensional vector $\vec{\upsilon}$ for all $j\in\{1,...,m\}$ and 0 for all other entries. We define $\Delta=Diag(\vec{N})$. Note that $\Delta^{-1}X\Delta=B$, hence B and X are similar matrices and if $\rho(X)\leq 1$ then $\rho(B)\leq 1$. Let $\vec{x}^T=(x_1,...,x_m)^T>\vec{0}$ be the left eigenvector of B corresponding to $\rho(B)$, which exists by irreducibility of B and the Perron-Frobenius Theorem. Assume that $\vec{z}(0)=(z_1(0),...,z_m(0))^T\in[0,\infty)$ is a solution of (2.25). Then, we have $\vec{x}^T\vec{z}(0)=\vec{x}^TB(1-\exp[-\vec{z}(0)])=\rho(B)\vec{x}^T(1-\exp[-\vec{z}(0)])$. Hence, $\sum_{j=1}^{m}x_jz_j(0)=\rho(B)\sum_{j=1}^{m}x_j(1-\exp[-z_j(0)])$, and equivalently,

$$\sum_{j=1}^{m}x_j(z_j(0)-\rho(B)(1-\exp[-z_j(0)]))=0. \tag{2.26}$$

Define the function $f(z) = z - \rho(B)(1 - \exp[-z])$ for $z \in [0, \infty)$, then $f(0) = 0$ and $f'(z) = 1 - \rho(B)\exp(-z) > 0$, since $\rho(B) \leq 1$ and $0 < \exp(-z) < 1$. Hence $f(z) > 0$ for $z > 0$. Since $\vec{x}^T > \vec{0}$, we conclude that only $\vec{z}(0) = \vec{0}$ can be a solution of (2.25).

We prove that (2.25) has a unique solution $\vec{z}(1) > \vec{0}$ if $\rho(X) = R_0 > 1$. Note that $\rho(X) > 1$ implies $\rho(B) > 1$ by similarity of X and B. Let $\vec{w} > \vec{0}$ be the right eigenvector of B corresponding to $\rho(B)$, which exists by irreducibility of B and the Perron-Frobenius Theorem. Choose a $0 < \mu < 1$ such that $\rho(B)\mu > 1$. Since $1 - \exp(-z)$ is continuous and differentiable to $z \in [0, \infty)$, there exists by the Mean Value Theorem for any $z \in [0, \infty)$ a $0 < \zeta_z < z$ such that $(1 - \exp[-z] - (1 - \exp[-0])) / (z - 0) = \exp[-\zeta_z]$, which is equivalent to $1 - \exp[-z] = \exp[-\zeta_z]z$. Clearly $\exp[-\zeta_z] \uparrow 1$ as $z \downarrow 0$. Hence, for z sufficiently small we have $1 - \exp[-z] \geq \mu z$. There exists therefore an $\varepsilon > 0$ such that $1 - \exp[-\varepsilon w_i] \geq \mu \varepsilon w_i$ for all $i \in \{1, ..., m\}$. Now define $\vec{u}^{(0)} = \varepsilon \vec{w}$ and $\vec{u}^{(n)} = B(1 - \exp[-\vec{u}^{(n-1)}])$ for $n \in \{1, 2, 3, ...\}$. Then $\vec{u}^{(1)} = B(1 - \exp[-\varepsilon \vec{w}]) \geq B\vec{w}\mu\varepsilon = \rho(B)\vec{w}\mu\varepsilon > \varepsilon\vec{w} = \vec{u}^{(0)}$. Choose $n \geq 2$ and assume $\vec{u}^{(n-1)} > \vec{u}^{(n-2)}$, then we have $\vec{u}^{(n)} = B(1 - \exp[-\vec{u}^{(n-1)}]) \geq B(1 - \exp[-\vec{u}^{(n-2)}]) = \vec{u}^{(n-1)}$ since $(1 - \exp[-z])$, $z \in [0, \infty)$, is a strictly increasing function. Hence, by induction, we conclude that $\vec{u}^{(n)}$ is a strict increasing sequence of vectors and is bounded from above by $B\vec{1}$. We conclude that $\vec{u}^{(n)}$ converges to a vector $\vec{z}(1) > \vec{0}$ satisfying $\vec{z}(1) = B(1 - \exp[-\vec{z}(1)])$.

We prove uniqueness by contradiction. Note that each solution of (2.25) with at least one zero entry, must be the trivial $\vec{0}$ solution by irreducibility of B. Assume

therefore two solutions of (2.25), $\vec{z}_1 > \vec{0}$ and $\vec{z}_2 > \vec{0}$ and assume without loss of generality $\vec{z}_1 \not\geq \vec{z}_2$, which means that there is a $j \in \{1,...,m\}$ such that the *j*th entry of $\vec{z}_1$ is smaller than the *j*th entry of $\vec{z}_2$. Define $t_0 = \min_{i \in \{1,...,m\}} ((\vec{z}_1)_i / (\vec{z}_2)_i)$ with $(\vec{z}_1)_i$ and $(\vec{z}_1)_i$ the *i*th entry of $\vec{z}_1$ and $\vec{z}_2$ respectively, $j \in \{1,...,m\}$. We have $0 < t_0 < 1$ and $(\vec{z}_1)_i = t_0(\vec{z}_2)_i$ for some $i \in \{1,...,m\}$ and $(\vec{z}_1) \geq t_0(\vec{z}_2)$. Additionally we have by strict concavity of $1 - \exp[-z]$ for $z \in [0,\infty)$ the following inequality,

$$\begin{aligned} 1 - \exp(-(t_0 z + (1-t_0)0)) &> t_0(1-\exp[-z]) + (1-t_0)(1-\exp[-0]) \\ &= t_0(1-\exp[-z]). \end{aligned} \tag{2.27}$$

Hence, $\vec{z}_1 = B(1-\exp[-\vec{z}_1]) \geq B(1-\exp[-t_0\vec{z}_2]) > Bt_0(1-\exp[-t_0\vec{z}_2]) = t_0\vec{z}_2$, which contradicts the previous result that $(\vec{z}_1)_i = t_0(\vec{z}_2)_i$ for some $i \in \{1,...,m\}$. We conclude by contradiction that $\vec{z}(1) > \vec{0}$ must be the unique solution of the equation (2.25) in $(0,\infty)^m$.

QED

Proof of Theorem 2

This proof uses the ideas of Schmidt, 1990. Assume all conditions as stated in Theorem 2. Theorem 1 states that the condition $R_0 > 1$ and irreducibility of β imply the existence and uniqueness of the non-trivial solution of the final size equations: $\vec{S}(\infty) \in (0, N_1) \times ... \times (0, N_m)$. Let $Diag(\cdot)$ be defined as in the proof of Theorem 1. Since $Diag(\vec{\sigma})$ has positive entries in the diagonal and $X = X(\vec{S}(-\infty))$ is a nonnegative irreducible matrix, it follows that $Diag(\vec{\sigma})X(\vec{S}(-\infty)) = X(\vec{S}(\infty))$ is also a non-negative irreducible matrix. The final size equations in terms of $S_1(\infty),...,S_m(\infty)$ are given by

$$\frac{S_i(\infty)}{N_i} = \exp[\sum_{j=1}^{m} \frac{\beta_{ij}}{\alpha_j} \frac{N_j}{N_i} (\frac{S_j(\infty)}{N_j} - 1)], \tag{2.28}$$

i=1,...,m (see (2.4)). Choose $i \in \{1,..,m\}$. We rewrite (2.28) by taking logarithm and multiplying by $S_i(\infty)$ on both sides. We obtain:

$$\log(\frac{S_i(\infty)}{N_i})S_i(\infty) = \sum_{j=1}^{m} \frac{S_i(\infty)}{N_i} \frac{\beta_{ij}}{\alpha_j}(S_j(\infty) - N_j). \tag{2.29}$$

We write this in matrix notation,

$$\log(\frac{S_i(\infty)}{N_i})S_i(\infty) = (X(\vec{S}(\infty))(S_1(\infty) - N_1,..., S_m(\infty) - N_m)^T)_i. \tag{2.30}$$

From the irreducibility of $X(\vec{S}(\infty))$, the Perron-Frobenius Theorem guarantees the existence of a unique, real valued dominant eigenvalue $\rho(X(\vec{S}(\infty)))$ and a corresponding left eigenvector $y^T > \vec{0}$. Summing over the expression (2.30) over all $i \in \{1,...,m\}$ and using the left eigenvector property we obtain

$$\begin{aligned}
\sum_{j=1}^{m} y_j \log(\frac{S_j(\infty)}{N_j})S_j(\infty) &= y^T(\log(\frac{S_j(\infty)}{N_j})S_j(\infty))_{1\le j\le m} \\
&= y^T \left(X(\vec{S}(\infty)) \begin{pmatrix} S_1(\infty) - N_1 \\ \vdots \\ S_m(\infty) - N_m \end{pmatrix} \right) \\
&= \rho(X(\vec{S}(\infty)))y^T \begin{pmatrix} S_1(\infty) - N_1 \\ \vdots \\ S_m(\infty) - N_m \end{pmatrix} \\
&= \rho(X(\vec{S}(\infty)))\sum_{j=1}^{m} y_j(S_j(\infty) - N_j),
\end{aligned} \tag{2.31}$$

the third equality follows from the associative property of vector-matrix multiplication and the definition of the left eigenvector. Now, $\rho(X(\vec{S}(\infty)))$ satisfies

$$\sum_{j=1}^{m} y_j(\log(\frac{S_j(\infty)}{N_j})S_j(\infty) - \rho(X(\vec{S}(\infty)))(S_j(\infty) - N_j)) = 0. \tag{2.32}$$

We prove by contradiction and assume $\rho(X(\vec{S}(\infty))) \geq 1$. Let $i \in \{1,..,m\}$ and define the differentiable function $f_i(x_i) = x_i \log(\frac{x_i}{N_i}) - \rho(X(\vec{S}(\infty)))(x_i - N_i)$ with $x_i \in (0, N_i]$. The derivative of f_i to x_i is equal to $\frac{d}{dx_i} f_i(x) = \log(\frac{x_i}{N_i}) + 1 - \rho(X(\vec{S}(\infty)))$, which is smaller than 0 for $x_i \in (0, N_i)$ by the assumption $\rho(X(\vec{S}(\infty))) \geq 1$. Hence, f_i is a strict decreasing function in $x_i \in (0, N_i)$. It follows that f_i is a positive function in $x \in (0, N_i)$ by $f_i(N_i) = 0$. We conclude that $\sum_{j=1}^{m} y_j f_j(x_j) > 0$, $x_j \in (0, N_j)$, by the positivity of f_j, *j=1,...,m* and $y^T > \vec{0}$. Since $\vec{S}(\infty) \in (0, N_1) \times ... \times (0, N_m)$ by Theorem 1, the above conclusion contradicts condition (2.32) and hence $\rho(X(\vec{S}(\infty))) < 1$. QED

Proof of Theorem 3

Assume all conditions as stated in Theorem 3. Define the function $\vec{F} = (F_1,..., F_m)^T : (\vec{N}, (p_{11}, p_{12},..., p_{mm}), \vec{\alpha}, \vec{x}) \to \mathbb{R}^m$ by

$$F_i = x_i - N_i \exp[\sum_{j=1}^{m} \frac{p_{ij} k_{ij}(\vec{N})}{\alpha_j N_i}(x_j - N_j)], \tag{2.33}$$

for *i=1,...,m* with $\vec{x} = (x_1,..., x_m)^T \in (0, N_1) \times ... \times (0, N_m)$. Note that $\vec{F}$ is continuously differentiable to $\vec{N}$, $(p_{11}, p_{12},..., p_{mm})$, $\vec{\alpha}$ and $\vec{x}$ since $k_{ij}(\vec{N})$ is continuously differentiable to $\vec{N}$. Then $\vec{F} = \vec{0}$ is equivalent to the system of final size equations (2.4). Define the indicator function $I_{condition}$ which is 1 if 'condition' is true and 0 otherwise. Recall that we are in the situation $R_0 > 1$. Fix $i, j \in \{1,..., m\}$, $\vec{N} \in \mathbb{R}^m_{>0}$, $(p_{11}, p_{12},..., p_{mm}) \in \mathbb{R}^{m^2}_{\geq 0}$ and $\vec{\alpha} \in \mathbb{R}^m_{>0}$, then the derivative of F_i to x_j satisfies:

$$\frac{dF_i}{dx_j} = \mathrm{I}_{\{i=j\}} - \frac{p_{ij}k_{ij}(\vec{N})}{\alpha_j N_i} N_i \exp[\sum_{j=1}^{m} \frac{p_{ij}k_{ij}(\vec{N})}{\alpha_j N_i}(x_j - N_j)]. \qquad (2.34)$$

Since β is irreducible in the domain $\vec{N}$, $(p_{11}, p_{12}, ..., p_{mm})$ and $\vec{\alpha}$ and $R_0 > 1$, it follows by Theorem 1 that the equation $\vec{F} = \vec{0}$ has a unique solution $\vec{S}(\infty) \in (0, N_1) \times ... \times (0, N_m)$. Hence in matrix formulation, the equality holds

$$\left(\frac{dF_i}{dx_j} \right)_{1 \le i, j \le m} \Bigg|_{\vec{x} = \vec{S}(\infty)} = (Diag(\vec{1}) - X(\vec{S}(\infty))), \qquad (2.35)$$

with $Diag(\cdot)$ as defined in the proof of Theorem 1 and $X(\vec{S}(\infty))$ as defined in (2.20) and $p_{ij}k_{ij}(\vec{N}) = \beta_{ij}$ and $S_i(\infty) = N_i \exp[\sum_{j=1}^{m} \frac{p_{ij}k_{ij}(\vec{N})}{\alpha_j N_i}(S_j(\infty) - N_j)]$ for all $i, j \in \{1, ..., m\}$. By Theorem 1 we have that $\rho(X(\vec{S}(\infty))) < 1$, therefore, all eigenvalues of $X(\vec{S}(\infty))$ are less than 1 in absolute value and, hence, $\det(I - X(\vec{S}(\infty))) \neq 0$, which implies that $\left(\frac{dF_i}{dx_j} \right)_{1 \le i, j \le m} \Big|_{\vec{x} = \vec{S}(\infty)}$ is an invertible matrix. By the Implicit Function Theorem we conclude that $S_i(\infty)$ is differentiable $\vec{N}$, $(p_{11}, p_{12}, ..., p_{mm})$ and $\vec{\alpha}$ for all $i \in \{1, ..., m\}$. QED

Proof of Lemma 4

Assume the conditions as stated in Lemma 4. Irreducibility of $X(N_i)$ follows from irreducibility of β and $\vec{\alpha} = (\alpha_1, ..., \alpha_m)^T > \vec{0}$. Therefore, by the Perron-Frobenius Theorem, there exist, corresponding to the dominant eigenvalue $\rho(X)$ with multiplicity 1, left and right eigenvectors $x^{*T}(N_i) > \vec{0}^T$ and $x(N_i) > \vec{0}$. By scalar multiplication we choose the eigenvectors such that $x^{*T} x = 1$. Since K is element-wise differentiable to

N_i, also $X(N_i)$ is element-wise differentiable to N_i. It follows from Lax, 1996, that the dominant eigenvalue $R_0 = \rho(X)$ and the left and right eigenvector, x^{*T} and x, of X are differentiable to N_i. The left and right eigenvectors satisfy the equations

$$X(N_i)x = R_0 x \tag{2.36}$$

$$x^{*T} X(N_i) = R_0 x^{*T} \tag{2.37}$$

Differentiation of (2.36) to N_i gives

$$X'(N_i)x + X(N_i)\frac{dx}{dN_i} = R_0 \frac{dx}{dN_i} + \frac{dR_0}{dN_i} x \tag{2.38}$$

by the product rule. Left multiplication of (2.38) by x^{*T} gives

$$x^{*T} X'(N_i)x + R_0 x^{*T} \frac{dx}{dN_i} = R_0 x^{*T} \frac{dx}{dN_i} + \frac{dR_0}{dN_i}. \tag{2.39}$$

Hence, the identity

$$\frac{dR_0}{dN_i} = x^{*T} X'(N_i)x \tag{2.40}$$

holds. QED

Proof of Theorem 5

Assume all conditions as stated in Theorem 5. Since $K = (k_{ij}^s)_{1\le i,j\le m}$ is element-wise differentiable to N_z and β is irreducible for $\vec{N} > \vec{0}$, we are in the situation of Lemma 4, and we have, using the notation in Lemma 4, the expression $\frac{dR_0}{dN_z} = x^{*T} X_s'(N_z)x$. Only the entries in the *z*-th column and row of $X_s(N_z)$ depend on N_z, therefore, $X_s'(N_z)$ is 0 in the entries other than the *z*-th column and row. Since *z* is the royal group, we have $c_{jz} = 1$ for all $j \in \{1,...,m\}$. Hence, the *j,z*th entry of $X_s(N_z)$ is a_{jz}^s, and the *z,j*th entry

of $X_s(N_z)$ is $a^s_{zj}N_z / N_j$, $j \in \{1,...,m\}$. Therefore, the *z*-th column and row of $X_s'(N_z)$ exists respectively of zeros only and $a^s_{zj}(1/N_j) > 0$ for $z \neq j$, $1 \leq j \leq m$. Since $x^{*T} > \vec{0}^T$ and $x > \vec{0}$, we conclude $\frac{dR_0}{dN_z} = x^{*T} X_s'(N_z)x > 0$.

We are working in the conditions of Theorem 3 since β is irreducible for $\vec{N} > \vec{0}$ and K is continuously differentiable to $\vec{N}$ and $R_0 > 1$, hence, σ_i, $i \in \{1,...,m\}$, is continuously differentiable to N_z by Theorem 3. Recall the final size equations (2.11) in a semi-domination contact pattern. Since z is a royal group, we have $c_{iz} = 1$ for all $i \in \{1,...,m\}$. Using this substitution, we obtain, by the standard rules of differentiation for $i \neq z$,

$$\frac{d\sigma_i}{dN_z} = \sigma_i[\sum_{\substack{j=1 \\ j\neq i}}^{m} \frac{a^s_{ij}N_j}{c_{ij}N_i + (1-c_{ij})N_j}\frac{d\sigma_j}{dN_z} + a^s_{ii}\frac{d\sigma_i}{dN_z} + \frac{a^s_{iz}}{N_i}(\sigma_z - 1)], \tag{2.41}$$

and for $i = z$,

$$\frac{d\sigma_i}{dN_z} = \sigma_i[\sum_{\substack{j=1 \\ j\neq i}}^{m} a^s_{ij}\frac{d\sigma_j}{dN_z} + a^s_{ii}\frac{d\sigma_i}{dN_z}]. \tag{2.42}$$

Equations (2.41) and (2.42) are respectively equivalent to

$$\sigma_i \frac{a^s_{iz}}{N_i}(\sigma_z - 1) = (1 - a^s_{ii}\sigma_i)\frac{d\sigma_i}{dN_z} - \sum_{\substack{j=1 \\ j\neq i}}^{m} \frac{a^s_{ij}\sigma_i N_j}{c_{ij}N_i + (1-c_{ij})N_j}\frac{d\sigma_j}{dN_z} \tag{2.43}$$

$$0 = (1 - a^s_{ii}\sigma_i)\frac{d\sigma_i}{dN_z} - \sum_{\substack{j=1 \\ j\neq i}}^{m} a^s_{ij}\sigma_i\frac{d\sigma_j}{dN_z}. \tag{2.44}$$

Let $Diag(\cdot)$ be defined as in the proof of Theorem 1 and recall $\Delta = Diag(\vec{N})$. Define $X^*_s(\vec{S}(\infty)) = \Delta^{-1}X_s(\vec{S}(\infty))\Delta$, hence, $X^*_s(\vec{S}(\infty))$ and $X_s(\vec{S}(\infty))$ are similar matrices. Using the expressions of $X_s(\vec{S}(\infty))$ as defined in (2.20), the *i,j*th entry of $X^*_s(\vec{S}(\infty))$ is

equal to $\frac{a_{ij}^s \sigma_i N_j}{c_{ij} N_i + (1-c_{ij}) N_j}$, $1 \le j \le m$. Therefore, we can write the equations (2.43) and (2.44) in the following matrix notation,

$$\vec{b}_z = (Diag(\vec{1}) - X_s^*(\vec{S}(\infty)))\vec{D}_k, \tag{2.45}$$

with $\vec{b}_z$ the column vector with at the *j*th entry $\sigma_j \frac{a_{jz}^s}{N_j}(\sigma_z - 1)$, for $j \neq z$ and 0 for $j = z$ and $\vec{D}_z$ the column vector with at the *j*th entry $\frac{d\sigma_j}{dN_z}$, $1 \le j \le m$. By similarity it follows that $X_s^*(\vec{S}(\infty))$ and $X_s(\vec{S}(\infty))$ share the same eigenvalues. By Lemma 4 we conclude $\rho(X_s^*(\vec{S}(\infty))) < 1$ and hence, all eigenvalues of $X_s^*(\vec{S}(\infty))$ is smaller than 1 in absolute value. Hence $(Diag(\vec{1}) - X_s^*(\vec{S}(\infty)))$ is an invertible matrix and

$$\begin{aligned} \vec{D}_z &= (Diag(\vec{1}) - X_s^*(\vec{S}(\infty)))^{-1}\vec{b}_z \\ &= \sum_{l=1}^{\infty} (X_s^*(\vec{S}(\infty)))^l \vec{b}_z. \end{aligned} \tag{2.46}$$

The second equality follows from the convergence of the geometric series for matrices with spectral radius less than 1. By irreducibility, each column of β must have at least 1 positive entry. Since $R_0 > 1$ and β is irreducible, it follows from Theorem 1, that $(\sigma_1, ..., \sigma_m) \in (0,1)^m$. Therefore, $\vec{b}_z \le \vec{0}$ and has at least one negative entry. Assume that the $n \in \{1, ..., m\}$ entry is negative. By irreducibility, there exists an $l_0(j)$, such that the *j,n*th entry of $(X_s^*(\vec{S}(\infty)))^{l_0}$ is positive for all *j=1,...,m*. We conclude that $\vec{D}_z = \sum_{l=1}^{\infty} (X_s^*(\vec{S}(\infty)))^l \vec{b}_z < \vec{0}$. QED

Proof of Theorem 6

The proof of Theorem 6 goes analogue to the proof of Theorem 5. We give the proof for completeness of this paper. Assume all conditions as stated in Theorem 6. Since

$K = (k_{ij}^s)_{1\le i,\, j\le m}$ is element-wise differentiable to $N_z > 0$ and β is irreducible for $\vec{N} > \vec{0}$, we are in the situation of Lemma 4, and we have, using the notation in Lemma 4, the expression $\frac{dR_0}{dN_z} = x^{*T}\, X_s'(N_z) x$. Only the entries in the *z*-th column and row of $X_s(N_z)$ depend on N_z, therefore, $X_s'(N_z)$ is 0 in the entries other than the *z*-th column and row. Since *z* is the servant group, we have $c_{jz} = 0$ for all $j \in \{1,...,m\}$. Therefore the *j,z*th entry of $X_s(N_z)$ is $a_{jz}^s \frac{N_j}{N_z}$ and the *z,j*th entry of $X_s(N_z)$ is a_{zj}^s, $1 \le j \le m$. Hence, the *z*-th column and row of $X_s'(N_z)$ is respectively $-a_{jz}^s (N_j / N_z^2) < 0$ for $z \ne j$, $1 \le j \le m$ and zeros only. Since $x^{*T} > \vec{0}^T$ and $x > \vec{0}$, we conclude $\frac{dR_0}{dN_z} = x^{*T}\, X_s'(N_z) x < 0$.

We are working in the conditions of Theorem 3 since β is irreducible for $\vec{N} > \vec{0}$ and $R_0 > 1$ and K is continuously differentiable to $\vec{N}$, hence, σ_i is differentiable to N_z for all $i \in \{1,...,m\}$ by Theorem 3. Recall the final size equations (2.11) in a semi-domination contact pattern. Since *z* is a servant group, we have $c_{zi} = 1$ for all $i \in \{1,...,m\}$. Using this substitution, we obtain by the standard rules of differentiation for $i \ne z$,

$$\frac{d\sigma_i}{dN_z} = \sigma_i [\sum_{\substack{j=1 \\ j\ne i}}^{m} \frac{a_{ij}^s N_j}{c_{ij} N_i + (1 - c_{ij}) N_j} \frac{d\sigma_j}{dN_z} + a_{ii}^s \frac{d\sigma_i}{dN_z}], \tag{2.47}$$

and for $i = z$,

$$\frac{d\sigma_i}{dN_z} = \sigma_i [\sum_{\substack{j=1 \\ j\ne i}}^{m} a_{ij}^s \frac{N_j}{N_z} \frac{d\sigma_j}{dN_z} + a_{ii}^s \frac{d\sigma_i}{dN_z} - \sum_{\substack{j=1 \\ j\ne i}}^{m} a_{ij}^s \frac{N_j}{N_z^2} (\sigma_j - 1)]. \tag{2.48}$$

Equations (2.47) and (2.48) are respectively equivalent to

$$
\begin{aligned}
0 &= (1-a_{ii}^{s}\sigma_i)\frac{d\sigma_i}{dN_z} - \sum_{\substack{j=1\\ j\neq i}}^{m} \frac{a_{ij}^{s}\sigma_i N_j}{c_{ij}N_i + (1-c_{ij})N_j}\frac{d\sigma_j}{dN_z} \\
\sum_{\substack{j=1\\ j\neq i}}^{m} a_{ij}^{s}\frac{N_j}{N_z^2}(1-\sigma_j) &= (1-a_{ii}^{s}\sigma_i)\frac{d\sigma_i}{dN_z} - \sum_{\substack{j=1\\ j\neq i}}^{m} a_{ij}^{s}\sigma_i\frac{N_j}{N_z}\frac{d\sigma_j}{dN_z}.
\end{aligned}
\tag{2.49}
$$

Let $Diag(\cdot)$ be defined as in the proof of Theorem 1 and recall $\Delta = Diag(\vec{N})$ and $X_s^*(\vec{S}(\infty)) = \Delta^{-1}X_s(\vec{S}(\infty))\Delta$. Note that $X_s^*(\vec{S}(\infty))$ and $X_s(\vec{S}(\infty))$ are similar matrices. Using the expressions of $X_s(\vec{S}(\infty))$ as defined in (2.20), the *i,j*th entry of $X_s^*(\vec{S}(\infty))$ is equal to $\frac{a_{ij}^{s}\sigma_i N_j}{c_{ij}N_i + (1-c_{ij})N_j}$ for $i, j \in \{1,...,m\}$. Therefore, we can write (2.49) in the following matrix notation

$$
\tilde{b}_z = (Diag(\vec{1}) - X_s^*(\vec{S}(\infty)))\vec{D}_z, \tag{2.50}
$$

with $\tilde{b}_z$ the column vector with at the *z*th entry $\sum_{\substack{j=1\\ j\neq i}}^{m} a_{ij}^{s}\frac{N_j}{N_z^2}(1-\sigma_j)$ and 0 for $j \neq z$. Recall that $\vec{D}_z$ is the column vector with at the *j*th entry $\frac{d\sigma_j}{dN_z}$, $1 \leq j \leq m$ (see proof of Theorem 5). By similarity, $X_s^*(\vec{S}(\infty))$ and $X_s(\vec{S}(\infty))$ share the same eigenvalues. By Lemma 4 we conclude $\rho(X_s^*(\vec{S}(\infty))) < 1$, and hence, all eigenvalues of $X_s^*(\vec{S}(\infty))$ is smaller than 1 in absolute value. Hence $(Diag(\vec{1}) - X_s^*(\vec{S}(\infty)))$ is an invertible matrix and therefore,

$$
\begin{aligned}
\vec{D}_z &= (Diag(\vec{1}) - X_s^*(\vec{S}(\infty)))^{-1}\tilde{b}_z \\
&= \sum_{l=1}^{\infty}(X_s^*(\vec{S}(\infty)))^{l}\tilde{b}_z.
\end{aligned}
\tag{2.51}
$$

The second equality follows from the convergence of the geometric series for matrices with spectral radius less than 1. By irreducibility, each column of β must have at least 1 positive entry. Since $R_0 > 1$, it follows from Theorem 1, that $(\sigma_1,...,\sigma_m) \in (0,1)^m$.

Therefore, $\tilde{b}_z \geq \vec{0}$ with at the *z*th entry a positive number. By irreducibility, there exists an $l_0(j)$, such that the *j,z*th entry of $(X_s^*(\vec{S}(\infty)))^{l_0}$ is positive for all $j \in \{1,...,m\}$. We conclude $\vec{D}_z = \sum_{l=1}^{\infty} (X_s^*(\vec{S}(\infty)))^l \tilde{b}_z > \vec{0}$. QED

Proof of Theorem 10

Assume all conditions as stated in Theorem 10. We can use Theorem 1 since β is irreducible for $\vec{N} > \vec{0}$, hence, by $R_0 > 1$, $\vec{\sigma}$ is in $(0, N_1) \times ... \times (0, N_m)$ and is unique. Choose $z \in \{1,...,m\}$. Since β is irreducible for $\vec{N} > \vec{0}$ and K continuously differentiable to $\vec{N} > \vec{0}$ and $R_0 > 1$, we have by Theorem 3 that $\vec{\sigma}$ is continuously differentiable to N_z. We prove in the forthcoming $\frac{d\sigma_i}{dN_z} < 0$ for all $i \in \{1,...,m\}$. Write $X_d^*(\infty) = \Delta^{-1} X_d(\infty) \Delta$, with $\Delta = Diag(\vec{N})$ as introduced in the proof of Theorem 1. Note that $X_d^*(\infty)$ is irreducible since $X_d(\infty)$ is irreducible and $\vec{N} > \vec{0}$. $X_d^*(\infty)$ and $X_d(\infty)$ are similar matrices by the identity of $X_d^*(\infty)$ and, hence, share the same eigenvalues. Recall the final size equations (2.19) in the case of a density dependent contact pattern. Using these equations and the standard differentiation rules we have

$$\frac{d\sigma_i}{dN_z} = \sigma_i \left(\sum_{j=1}^{m} a_{ij}^d N_j \frac{d\sigma_j}{dN_z} + a_{iz}^d (\sigma_z - 1) \right), \tag{2.52}$$

for $i \in \{1,...,m\}$. After rewriting equation (2.52) such that all derivatives of σ_i, $i \in \{1,...,m\}$, is in the RHS, we obtain

$$\sigma_i a_{iz}^d (\sigma_z - 1) = \sum_{j=1}^{m} \frac{d\sigma_j}{dN_z} (\mathrm{I}_{\{i=j\}} - S_i(\infty) a_{ij}^d \frac{N_j}{N_i}), \tag{2.53}$$

with $I_{condition}$ as defined in the proof of Theorem 3. Recall $\vec{D}_z$ from the proof of Theorem 5 and define $\hat{b}_z$ to be the *m*-dimensional vector with at the *j*th entry, $j \in \{1,...,m\}$, $\sigma_j a_{jz}^d (\sigma_z - 1)$. Then (2.53) can be written in matrix notation

$$\hat{b}_z = (Diag(\vec{1}) - X_d^*(\infty))\vec{D}_z, \tag{2.54}$$

With $Diag(\cdot)$ as defined in Theorem 1. By Theorem 2, which is applicable since β is irreducible for $\vec{N} > \vec{0}$ and $R_0 > 1$, and similarity of $X_d^*(\infty)$ and $X_d(\infty)$, it follows that all eigenvalues of $X_d^*(\infty)$ is smaller than 1 in absolute value. We conclude that $(Diag(\vec{1}) - X_d^*(\infty))$ is an invertible matrix. Therefore the following expression holds

$$\begin{aligned} \vec{D}_z &= (Diag(\vec{1}) - X_d^*(\infty))^{-1}\hat{b}_z \\ &= \sum_{l=1}^{\infty} (X_d^*(\infty))^l \hat{b}_z. \end{aligned} \tag{2.55}$$

The second equality follows from the convergence of the geometric series for matrices with spectral radius less than 1. By irreducibility, each column of β must have at least one positive entry. Recall that $\vec{\sigma}$ is in $(0,1)^m$ and is unique by Theorem 1. Therefore we have $\hat{b}_z \leq \vec{0}$ with at least one negative entry. Assume that this is entry $n \in \{1,...,m\}$. By irreducibility of $X_d^*(\infty)$, there exists an $l_0(j)$, such that the *j,n*th entry of $(X_d^*(\infty))^{l_0}$ is positive for all *j=1,...,m*. Hence, we conclude $\vec{D}_z = \sum_{l=1}^{\infty} (X_d^*(\infty))^l \hat{b}_z < \vec{0}$.

Differentiability and $\frac{dS_i(\infty)}{dN_z} < 0$ for $i \in \{1,...,m\}$, $i \neq z$ follow from Theorem 3 and the first part of this proof. We are left to show that $\frac{dS_z(\infty)}{dN_z} < 0$ when $a_{zz}N_z > 1$. We proceed as before. The following follows from the final size equations (2.19) and the standard rules of differentiation

$$\begin{aligned}\frac{dS_i(\infty)}{dN_z} &= \mathrm{I}_{\{i=z\}}\frac{S_z(\infty)}{N_z} + S_i(\infty)[\sum_{j=1}^{m} a_{ij}^d \frac{dS_j(\infty)}{dN_z} - a_{iz}^d] \\ &= S_i(\infty)\sum_{j=1}^{m} a_{ij}^d \frac{dS_j(\infty)}{dN_z} + \mathrm{I}_{\{i=z\}}\frac{S_z(\infty)}{N_z} - S_i(\infty)a_{iz}^d,\end{aligned} \tag{2.56}$$

for all $i \in \{1,...,m\}$. After rewriting (2.56) such that all derivatives of $S_j(\infty)$, $j=1,...,m$, is in the RHS, we have

$$\mathrm{I}_{\{i=z\}}\frac{S_z(\infty)}{N_z} - S_i(\infty)a_{iz}^d = \sum_{j=1}^{m}\frac{dS_j(\infty)}{dN_Z}(\mathrm{I}_{\{j=i\}} - a_{ij}^d S_i(\infty)). \tag{2.57}$$

Denote $\vec{D}_z(S(\infty)) = (dS_1(\infty)/dN_z,...,dS_m(\infty)/dN_z)^T$ and $\hat{b}_z(S(\infty)) = (S_1(\infty)(I_{\{z=1\}}\frac{1}{N_z} - a_{1z}^d),...,S_m(\infty)(I_{\{z=m\}}\frac{1}{N_z} - a_{mz}^d))^T$. In matrix notation, equation (2.57) is equivalent to $\hat{b}_z(S(\infty)) = (Diag(\vec{1}) - X_d(\infty))\vec{D}_z(S(\infty))$. By Theorem 2, all eigenvalues of $X_d(\infty)$ is smaller than 1 in absolute value, hence, $(Diag(\vec{1}) - X_d(\infty))$ is invertible and $\vec{D}_z(S(\infty)) = (Diag(\vec{1}) - X_d(\infty))^{-1}\hat{b}_z(S(\infty))$. Now $\hat{b}_z(S(\infty)) \le \vec{0}$ with at least 1 negative entry by the irreducibility of β and the assumption $a_{zz}^d N_z > 1$. By the same reasoning as in the first part of the proof of this theorem, we conclude $\vec{D}_z(S(\infty)) < \vec{0}$ and in particular $\frac{dS_z(\infty)}{dN_z} < 0$. QED

Proof of Theorem 11

Note that $n_1 = 1 - n_2$. Assume all conditions as stated in Theorem 11. Since $k_{ij}^d > 0$ for $n_1 \in (0,1)$ and $p_{ij} > 0$, we conclude that $\beta_{ij} = p_{ij}k_{ij}^d > 0$ for $i, j \in \{1,2\}$, hence, β is an irreducible matrix for $n_1 \in (0,1)$. In addition, K is clearly differentiable to n_1, therefore, differentiability of R_0 to $n_1 \in (0,1)$ follows directly from Lemma 4. We show differentiability of R_0 in 0 and 1. By simple algebra, the expression of the basic reproduction number in the 2-type model is

$$R_0 = \tfrac{1}{2}(\tilde{a}_{22} + n_1(\tilde{a}_{11} - \tilde{a}_{22}) + \sqrt{D(n_1)}), \tag{2.58}$$

with $D(n_1) = ((\tilde{a}_{11} + \tilde{a}_{22})^2 - 4\tilde{a}_{12}\tilde{a}_{21})n_1^2 + n_1(4\tilde{a}_{12}\tilde{a}_{21} - 2\tilde{a}_{22}(\tilde{a}_{11} + \tilde{a}_{22})) + \tilde{a}_{22}^2$. $D(n_1)$ is clearly a differentiable function in n_1, hence, the square root of $D(n_1)$ is differentiable to n_1 in $n_0 \in \mathbb{R}$ if and only if $D(n_0) > 0$. Since $D(0) = \tilde{a}_{22}^2 > 0$ and $D(1) = \tilde{a}_{11}^2 > 0$ by the assumption $k_{ij}^d > 0$ for $i, j \in \{1,2\}$, it follows that R_0 is differentiable to $n_1 \in [0,1]$. By standard rules of differentiation we have for $n_1 \in [0,1]$,

$$\frac{dR_0}{dn_1} = \frac{1}{2}(\tilde{a}_{11} - \tilde{a}_{22} + \frac{\tilde{a}_{12}\tilde{a}_{21}(2-4n_1) + (\tilde{a}_{11} + \tilde{a}_{22})(\tilde{a}_{22}(n_1 - 1) + \tilde{a}_{11}n_1)}{\sqrt{D}}). \tag{2.59}$$

The expression of $\frac{dR_0}{dn_1}$ is in general complex, but it obtains simpler forms in the cases $n_1 = 0$, $n_1 = 1$, $n_1 = 1/2$. The expressions are respectively

$$\begin{aligned} \frac{dR_0}{dn_1}\Big|_{n_1=0} &= \frac{\tilde{a}_{12}\tilde{a}_{21} - \tilde{a}_{22}^2}{\tilde{a}_{22}}, \\ \frac{dR_0}{dn_1}\Big|_{n_1=1/2} &= \frac{(\tilde{a}_{11} - \tilde{a}_{22})(\tilde{a}_{11} + \tilde{a}_{22} + \sqrt{A})}{2\sqrt{A}}, \\ \frac{dR_0}{dn_1}\Big|_{n_1=1} &= \frac{-\tilde{a}_{12}\tilde{a}_{21} + \tilde{a}_{11}^2}{\tilde{a}_{11}}. \end{aligned} \tag{2.60}$$

with $A = 4\tilde{a}_{12}\tilde{a}_{21} + (\tilde{a}_{11} - \tilde{a}_{22})^2$. Hence, the signs of $\frac{dR_0}{dn_1}\Big|_{n_1=0}$, $\frac{dR_0}{dn_1}\Big|_{n_1=1/2}$ and $\frac{dR_0}{dn_1}\Big|_{n_1=1}$ correspond respectively to the signs of $\tilde{a}_{12}\tilde{a}_{21} - \tilde{a}_{22}^2$, $\tilde{a}_{11} - \tilde{a}_{22}$ and $\tilde{a}_{11}^2 - \tilde{a}_{12}\tilde{a}_{21}$.

To prove that R_0 has at most 1 extremum, we show that $\frac{dR_0}{dn_1} = 0$ has at most 1 solution to $n_1 \in [0,1]$. Rewriting $\frac{dR_0}{dn_1} = 0$ gives

$$(\tilde{a}_{11} - \tilde{a}_{22})\sqrt{D} = -[\tilde{a}_{12}\tilde{a}_{21}(2-4n_1) + (\tilde{a}_{11} + \tilde{a}_{22})(\tilde{a}_{22}(n_1 - 1) + \tilde{a}_{11}n_1)]. \tag{2.61}$$

Equation (2.61) is solved analytically by taking the square in the LHS and RHS of the equation. The square operation increases the solution set by 1 since the equation after taking the square satisfies additionally

$$(\tilde{a}_{11}-\tilde{a}_{22})\sqrt{D}=\tilde{a}_{12}\tilde{a}_{21}(2-4n_1)+(\tilde{a}_{11}+\tilde{a}_{22})(\tilde{a}_{22}(n_1-1)+\tilde{a}_{11}n_1). \qquad (2.62)$$

This implies that the solution of (2.61) is one of the two unique solutions of the root of a second order polynomial. The Fundamental Theorem of Algebra states that a second order polynomial has 2 roots (possibly complex and with multiplicity 2), hence, the basic reproduction number as a function of n_1 has at most 1 unique extremum in $n_1 \in [0,1]$. QED

5. Case study: impact of demographical change on the severity of a H1N1 strain outbreak in Hong Kong

5.1 Introduction

In this section we illustrate the impact of demographical change on the severity of an outbreak in the setting of Hong Kong and an H1N1 strain similar to the H1N1-2009. We focus in this numerical study on the qualitative relation only. The fraction of the population that is 20 years or older is projected to increase between the years 2010 and 2039 in Hong Kong, the USA and Japan (see Figure 1A). The projection of the age composition of Hong Kong is shown in figure 1B. The population is categorized in the age groups 0-19, 20-59 and 60+. These projections are made available by the Hong Kong Census and Statistics Department, the United States Census Bureau and The National Institute of Population and Social Security Research of Japan respectively.

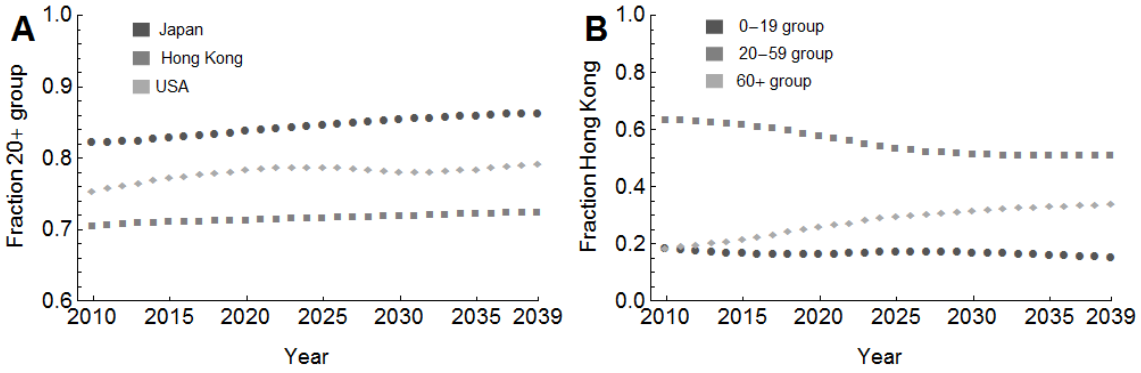

Figure 1. Evidence of ageing in Hong Kong, the USA and Japan.
Projections of the age demography in Hong Kong, the USA and Japan of the period 2010-2039. Figure 1A shows a relative increase of the number of individuals of age 20+ in all three countries. Figure 1B shows the change of age composition in Hong Kong.

5.2 Impact of demographical change on the final size and normalized total mortality of a H1N1 virus outbreak in Hong Kong

In the following we adjust the definition of a contact pattern, K, as defined in section 2 by requiring additionally that a contact pattern must satisfy the reciprocal condition. We define the normalized total mortality of an epidemic by the fraction of individuals of the total population that die killed due to infection. In this case study, we consider a H1N1 strain similar to the H1N1-2009 (in the sense of similar transmission dynamics) in the population of Hong Kong and study the final size and normalized total mortality for different age distributions. We use the estimated case fatality ratios per age group (Dawood et al., 2012), defined as the average number of individuals that die given an infection, to show the relation between age distribution and normalized total mortality.

We use the estimation method as in Nishiura et al., 2010 to estimate the next generation matrix of the H1N1-2009 virus in a model with 2 or 3 age groups. Individuals in the 2-type model are categorized as 0-19 years old or 20+ years old, which we label as group 1 and 2 respectively. Individuals in the 3-type model are categorized in the groups 0-19, 20-59 and 60+ and are labelled by group 1, 2 and 3

respectively. We illustrate the estimation method of the next generation matrix for the 2-type model only, since the method is similar for the 3-type model. First we introduce some concepts to estimate the next generation matrix.

Let the relative susceptibility of group 2 with respect to group 1 be denoted by $\tilde{s}_2 \in \mathbb{R}_{>0}$, i.e., given the same number of contacts with infectious individuals in the population at any time, the rate at which a type 2 susceptible individual gets infected is a factor $\tilde{s}_2$ lower than a type 1 susceptible individual. We define the dummy variables $\tilde{k}_{ij} \geq 0$, $i, j \in \{1,...,m\}$, which is interpreted as the average number of contacts per day of a group *j* individual with group *i* individuals. The interpretation of $\tilde{k}_{ij}$ is the same as k_{ij}, $i, j \in \{1,...,m\}$, but it does not necessarily satisfy the reciprocal condition in general and is, hence, not a contact pattern. In this study we will use $(\tilde{k}_{ij})_{1\leq i,j\leq 2}$ to obtain a relative relation between contact rates of individuals of different groups. Therefore, we are free to multiply all elements of $(\tilde{k}_{ij})_{1\leq i,j\leq 2}$ by the same scalar. Mossong et al., 2008, estimated the average number of contacts of individuals in the age groups 0-4, 5-9,...,65-69, 70+ with individuals of different age groups in 8 European countries. We adjusted the estimated average number of contacts per day of Mossong et al., 2008, of the population of the UK to estimate the average number of contacts per day of different individuals of different age groups in Hong Kong. We have calculated the number of contacts per day of individuals in the groups 0-19 and 20+ with individuals of the groups 0-4, 5-9,..., 70+ by summing over the estimated number of contacts per day of individuals in the groups 0-4, 5-9, ..., 15-19 and 20-24,...,70+ with the groups 0-4, 5-9,..., 70+ respectively. The number of contacts per day of an individual in the age group 0-19 and 20+ with the age groups, 0-4, 5-9,..., 70+ were then summed over the age groups 0-4, 5-9, ..., 15-19 and 20-24,...,70+ with weights based on the fractional size of the age groups of Hong Kong in 2009 to obtain the number of contacts per day of individuals in the groups 0-19 and 20+ with individuals of the groups 0-19 and 20+.

To obtain the estimate for $K=(k_{ij})_{1\le i,j\le 2}$ in Hong Kong in 2009, this 2×2 matrix is adjusted such that the number of contacts per day between the 0-19 and 20+ group satisfies the reciprocal conditions under the condition that the sum of the total number of contacts of individuals of age 0-19 with group 20+ and the total number of contacts of individuals of age 20+ with group 0-19 is constant (see Appendix A). Define $\tilde{s}_1=1$ and choose $\tilde{s}_2=0.185$ which is in agreement with the estimations given in Nishiura et al., 2010. $(\tilde{s}_i k_{ij})_{1\le i,j\le 2}$ is a matrix which indicates the relative infectiousness and does not state the actual infectiousness between the age groups, in contrast to $(p_{ij}k_{ij})_{1\le i,j\le 2}$ (see section 2 for notation). As mentioned earlier, we are free to multiply $(\tilde{s}_i k_{ij})_{1\le i,j\le 2}$ by a constant $\tilde{c}>0$ such that the dominant eigenvalue of $(\tilde{s}_i k_{ij})_{1\le i,j\le 2}$ is exactly 1. Define $s_i=\tilde{c}\tilde{s}_i$ for $i\in\{1,2\}$. We model the next generation matrix as follows

$$X_{ij}=R_0 s_i k_{ij}, \tag{2.63}$$

$1\le i,j\le 2$. Recall that X_{ij}, $i,j\in\{1,2\}$, is the *i,j*th element of the next generation matrix and R_0 is the basic reproduction number. We use $R_0=1.22$ which is in agreement with the estimated basic reproduction number of the H1N1-2009 virus as given in Nishiura et al., 2010 of Japan. A detailed description of the estimation method is given in Appendix A. The estimated next generation matrix is

$$\begin{pmatrix} 1.17 & 0.25 \\ 0.20 & 0.23 \end{pmatrix}. \tag{2.64}$$

The difference between the 0-19 and 20+ group is large. In the earliest phase of the outbreak, an infectious individual between 0 and 19 year old infects on average 1.17 individuals of their own group before recovery. This differs greatly from individuals of age 20 or older, they infect 0.23 individuals of the same age group before recovery. This

difference is explained by the low relative susceptibility among individuals in the 20+ group in comparison with younger individuals.

As shown in section 2 and 3, the next generation matrix depends on the composition and the size of the population, where the qualitative dependency is determined by the choice of contact pattern K. We show numerical results of the relation between final size and normalized total mortality in models with the semi-domination and density dependent contact pattern. Our opinion is that these contact patterns can be well interpreted and represent two extremes of the contact dynamics, frequency and density dependent contact patterns, of a human population (semi-domination contact pattern representing 'frequency dependency'). In order to estimate $(a_{ij}^s)_{1\le i,j\le 2}$, $(c_{ij})_{1\le i,j\le 2}$ and $(a_{ij}^d)_{1\le i,j\le 2}$ from the estimated next generation matrix (2.64), we assumed that 20% of the population in Hong Kong exists of individuals in the 0-19 group in 2009 ($(n_1,n_2)=(0.2,0.8)$), which is in agreement with the data from the Hong Kong Census and Statistics Department. The values $(a_{ij}^s)_{1\le i,j\le 2}$, $(c_{ij})_{1\le i,j\le 2}$ and $(a_{ij}^d)_{1\le i,j\le 2}$ are estimated by equating the analytical expression of the next generation matrix in a model with the semi-domination and density dependent contact pattern, X_s and X_d, with the estimated next generation matrix (2.64). We assume a fixed population size N. The expression of the estimated next generation matrix in the case of a semi-domination contact pattern where group 1 dominates group 2 ($c_{12}=0$), group 2 dominates group 1 ($c_{12}=1$) and exactly in between ($c_{12}=1/2$) is respectively (see section 2 for notation)

$$X_d\big|_{c_{12}=0} = \begin{pmatrix} 1.17 & \dfrac{n_1}{n_2} \\ 0.2 & 0.23 \end{pmatrix}$$

$$X_d\big|_{c_{12}=1} = \begin{pmatrix} 1.17 & 0.625 \\ 0.125\dfrac{n_2}{n_1} & 0.23 \end{pmatrix} \qquad (2.65)$$

$$X_d\big|_{c_{12}=1/2} = \begin{pmatrix} 1.17 & 0.25\dfrac{2n_1}{n_1+n_2} \\ 0.05\dfrac{2n_2}{n_1+n_2} & 0.23 \end{pmatrix}.$$

The expression of the next generation matrix with a density dependent contact pattern is

$$X_d = \begin{pmatrix} 5.85n_1 & 1.25n_1 \\ 0.25n_2 & 0.29n_2 \end{pmatrix}. \qquad (2.66)$$

The final size equations given in (2.4) are solved numerically in *Wolfram Mathematica version 7*, for different age compositions (recall $n_2 = 1 - n_1$).

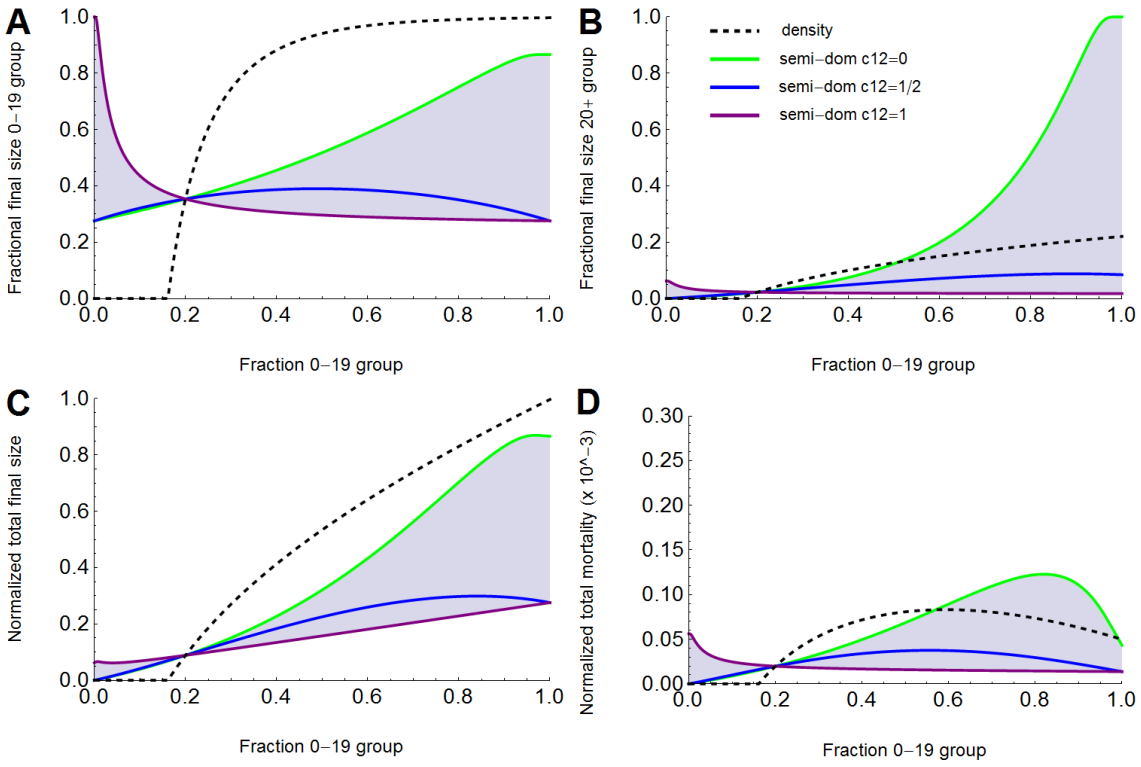

Figure 2. Relation of final size and normalized total mortality with age distribution

A 0.2 fraction existing of individuals in the 0-19 group of the Hong Kong population in 2009 is chosen. The black and dashed line is the curve related to the model with density dependent contact pattern. The green, blue and purple solid line is the curve related to the model with semi-domination contact pattern with $c_{12}=0$ (group 1 dominates group 2), $c_{12}=1/2$ and $c_{12}=1$ (group 2 dominates group 1) respectively and $c_{23}=c_{13}=1/2$ for all three cases. Figure 2A shows the development of the fractional final size of the 0-19 group. Figure 2B shows the fractional final size of the 20+ group. Figure 2C shows the change of the normalized total final size. Figure 2D shows the normalized total mortality. Case fatality ratios of 0.005% and 0.09% for the 0-19 and 20+ group has been used.

Figure 2A and 2B illustrate the relation between the fractional final sizes, $(1-\sigma_1)$ and $(1-\sigma_2)$, and the age composition (fixed population size). Figure 2A and 2B suggest that a change in composition in a model with density dependent contact pattern has a higher impact on the fraction final sizes than in a model with semi-domination contact pattern (for all $c_{12}\in[0,1]$). In the case of the semi-domination we have revealed in section 3 (Theorem 5 and 6) that the fractional final size can either increase or

decrease due to a change in composition depending on whether group 1 dominates group 2 or the other way around. Figure 2A and 2B agree with the theoretical results. Numerical experiments suggest that curves related to a semi-domination contact pattern with $c_{12} \in (0,1)$, as in Figure 2, are in between the curves that relate to $c_{12} = 0$ and $c_{12} = 1$ (between the green and purple lines). The curve corresponding to $c_{12} = 1/2$ supports this suggestion. Figure 2C illustrates the relation between the normalized total final size, $\frac{R(\infty)}{N}$, and composition (fixed population size). We see that, when the fraction of 0-19 individuals decreases, the normalized total final decreases. Hence, if ageing corresponds to a relative decrease of the size of group 1 (and constant population size), then in an aged Hong Kong population the cumulative number of infections due to the H1N1 strain in 2009 would be smaller.

We have estimated the normalized total mortality by using the estimated case fatality ratios per group as given in Dawood et al., 2012. Normalized total mortality per group is hence estimated by multiplying the normalized final size per group by the corresponding case fatality ratio. The normalized total mortality of the total population is the sum of the normalized mortality per group. Recall that the model considered in this study neglects death over the course of the epidemic, hence, this method of calculation is only approximately correct, but, since the case fatality ratio is in general low the difference is expected to be small. Case fatality ratios of 0.005% and 0.09% are used for individuals in the 0-19 and 20+ group respectively (Dawood et al., 2012). In figure 2D, the relation between normalized total mortality and age composition (fixed population size) is shown. If the fraction of the 0-19 group was lower than in 2009, the normalized mortality would be lower if the density dependent or semi-domination with $c_{12} = 0$ and $c_{12} = 1/2$ contact pattern is an appropriate contact pattern for the Hong Kong population. But, if the semi-domination contact pattern with $c_{12} = 1$ is more appropriate for the Hong Kong population, then the normalized total mortality would

increase. We conclude that a lower normalized total final size due to a different composition of the population does not imply immediately a decrease in public health burden measured in normalized total mortality.

In the same manner, as in the 2-type model, an estimation can be made of the next generation matrix for the H1N1 virus in 2009 in Hong Kong in a 3-type model. Again the basic reproduction number is chosen to be 1.22. Relative susceptibility of group 2 and 3 with respect to group 1 is chosen to be $\tilde{s}_2 = 0.30$ and $\tilde{s}_3 = 0.07$ as given in Nishiura et al., 2010. The resulting next generation matrix in the 3-type model is

$$\begin{pmatrix} 1.13 & 0.28 & 0.12 \\ 0.28 & 0.31 & 0.20 \\ 0.01 & 0.01 & 0.02 \end{pmatrix}. \qquad (2.67)$$

The extra subdivision of groups increases the number of free parameters by 1 in the composition of the population. For example, in contrary to the 2-type model, an increase of n_1 does not imply a decrease of n_2 by the constraint $\sum_{i=1}^{3} n_i = 1$. Therefore we assume additionally that the ratio of the size of the 20-59 and the size of the 60+ group is constant: 1:0.28, which agrees with the data of the Hong Kong population in 2009. In the semi-domination contact pattern we choose $c_{12} = c_{13} = c_{23} = 1/2$. By equating the expressions of the next generation matrices in a model with the semi-domination and density dependent contact pattern (see section 2 for expressions) with (2.67) we obtain estimations of $(a_{ij}^s)_{1\le i,j\le 3}$ and $(a_{ij}^d)_{1\le i,j\le 3}$.

Figure 3 shows the normalized total final size in the 2-type and 3-type model. The major heterogeneity in the population in terms of transmission is between the younger (<19) and older individuals (see the estimated next generation matrices). The contact rates of individuals in the 20-59 and 60+ groups are different, but since the transmission rates are relatively low, the additional subdivision does not has a major impact, see figure 3.

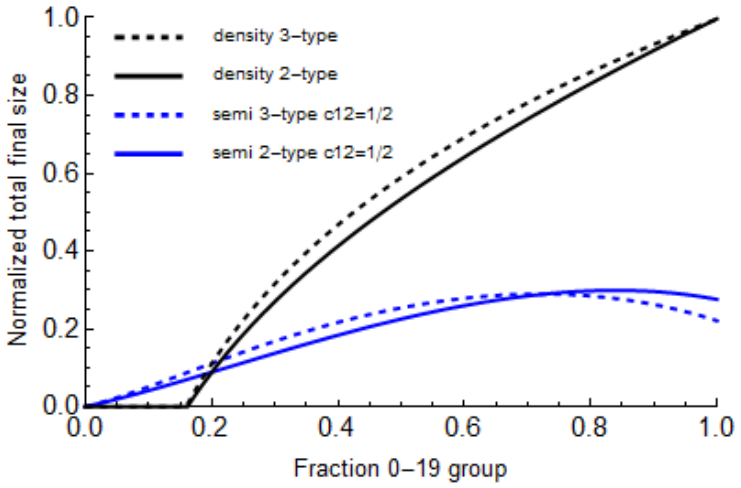

Figure 3. Comparison of 2- and 3-type model

The normalized total final size as a function of the fractional size of group 0-19 is shown for a 2- (solid line) and 3-type (dashed line) model. The blue line is the curve related to the model with semi-domination contact pattern with $c_{12} = 1/2$ and the black line is the curve related to the model with density dependent contact pattern. The difference between the curves related to the 2- and 3-type model are almost negligible.

5.3 Impact of birth restriction on the expected absolute final size of a first new H1N1 strain introduction in Hong Kong after the H1N1-2009 pandemic in the period 2010-2039

For a pathogen to cause an outbreak in a population, it is necessary that the infectiousness of the infectious disease is strong 'enough', i.e., an outbreak can occur if and only if $R_0 > 1$ (Diekmann, Heesterbeek, Metz, 1990). The infectiousness of a pathogen depends not only on the transmission parameters, but also on the number of susceptible individuals in the population. For example, in 2009, the H1N1 virus decreased the size of the susceptible group in Hong Kong so much, that the virus lost the capability to spread further. Therefore, when assuming lifelong immunity after

infection and unchanged contact dynamics of the population, an outbreak due to a H1N1 strain similar to the H1N1-2009 can only occur when the size of the susceptible group has increased sufficiently. Assuming lifelong immunity, we studied the expected absolute final size for a first new introduction of a H1N1 strain after the H1N1-2009 pandemic in Hong Kong.

Based on the composition and the size of the population of Hong Kong in 2009 and the projected birth and death rate in the period 2010-2039 provided by the Hong Kong Census and Statistics Department, we have made a projection of the number of susceptible individuals in the groups 0-19, 20-59 and 60+ in Hong Kong. These projections combined with the estimated transmission values of the H1N1-2009 virus in the first part of section 5, are used as input for the final size equations. Projections of the absolute final size given an introduction of a H1N1 strain similar to the H1N1-2009 in Hong Kong in the period 2010-2039 are then calculated by solving the final size equations numerically.

For this study, we use the 3-type model as described in section 5.2. We assume the following 1) there is no migration in the period 2010-2039 in Hong Kong, 2) natural deaths occur only in the 60+ group and the death rate among individuals in the 60+ group is independent of the H1N1-2009 infection history, 3) all individuals are susceptible before the 2009 outbreak, except for individuals of the 60+ group, 70% of these individuals are susceptible (Hancock et al., 2009), 4) the newly introduced H1N1 strain has exactly the same transmission values as the H1N1-2009 strain in the sense that $(a_{ij}^{s})_{1\le i,j\le 3}$ and $(a_{ij}^{d})_{1\le i,j\le 3}$ are equal to the situation in 2009, and, 5) susceptible individuals are assumed to be distributed uniformly over the age groups 0-4, 5-9, ..., 80-84, 85+ (i.e. 100 susceptible individuals in age group 0-4 implies 20 susceptible individuals of age 2). The 30% immunity of individuals in the 60+ group in assumption 3) is caused by previous exposure to the H1N1 strain in the period 1918-1956.

Data of the composition and the size of the population in 2009 and the projected birth and death rate of the period 2010-2039 in Hong Kong is provided by the Hong Kong Census and Statistics Department. The data of the age distribution of Hong Kong in 2009 is given in the age groups 0-4, 5-9, ..., 80-84, 85+. To obtain a projected number of susceptible individuals in the age groups 0-19, 20-59 and 60+ of all years in the period 2010-2039, we project the number of susceptible individuals per year class, i.e., the age classes of the projection must be 0, 1, 2, ..., 59, 60+. Using assumption 3) and the transmission values as estimated in the first part of section 5 ($(a_{ij}^s)_{1\leq i,j\leq 3}$, $(a_{ij}^d)_{1\leq i,j\leq 3}$), we calculate the number of susceptible individuals in each age group 0-4, 5-9, ..., 80-84, 85+ after the H1N1-2009 pandemic in Hong Kong (using the final size equations). By assumption 5), it is straightforward to obtain the age distribution of susceptible individuals in 2009 after the H1N1-2009 pandemic in the age classes 0, 1, 2, ..., 59, 60+. Each year, susceptible individuals become 1 year older and shifts to the age group that is 1 age class higher. In the years 2010-2039, the number of susceptible individuals in age group 0, is equal to the projected birth rate of that year. By assumption 2), deaths occur only in the 60+ group and the death rate among susceptible individuals is calculated by multiplying the projected death rate by the fraction of susceptible individuals in the 60+ group. With this method, we have obtained a projection of the number of susceptible individuals in the groups 0-19, 20-59 and 60+ in the period 2010-2039. Alternatively, we considered the situation of lowering the birth rate such that it equals the projected death rate in Hong Kong (birth rate is projected to be higher than death rate by the Hong Kong Census and Statistics Department). Note that the population size remains constant in this alternative situation. This fictive situation can occur when the government accepts a birth restrictive law. An example of birth restriction, is the one-child policy in People's Republic of China which was introduced in 1978.

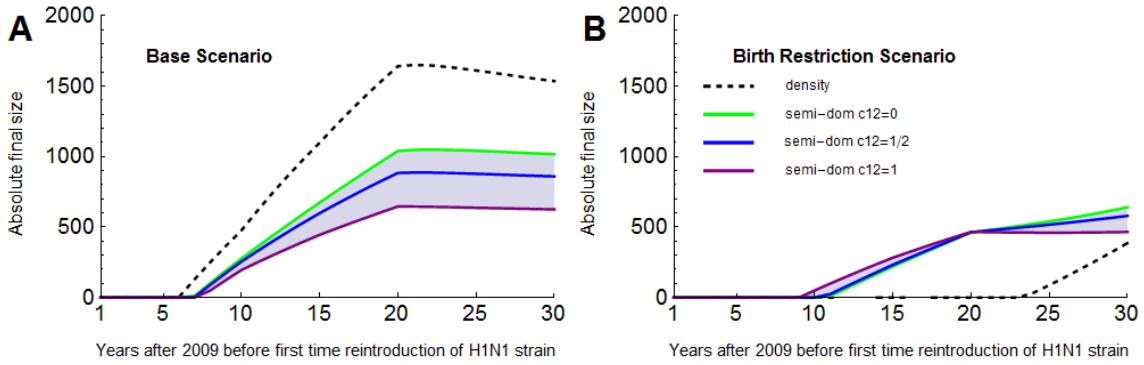

Figure 4. Absolute final size of an outbreak caused by a first new introduction of a H1N1 strain similar to the H1N1-2009 in Hong Kong after the H1N1-2009 pandemic

The black and dashed line is the curve related to the model with density dependent contact pattern. The green, blue and purple solid line is the curve related to the model with semi-domination contact pattern with $c_{12}=0$ (group 1 dominates group 2), $c_{12}=1/2$ and $c_{12}=1$ (group 2 dominates group 1) respectively and $c_{23}=c_{13}=1/2$ for all three cases. Figure 4A illustrates the base case in which birth and death rates are as projected by the Hong Kong Census and Statistics Department. Figure 4B illustrates the alternative case in which birth rate is lowered to equal the death rate. The figure should be read as follows. If in year 2025 (16 years after the H1N1-2009 pandemic) a first new introduction occurs of a H1N1 strain similar to the H1N1-2009 in Hong Kong, given no epidemics or interventions in the past which causes immunity, the average outbreak size is 1200 and 700 in a model with the density dependent and semi-domination (with group 1 a royal group) contact pattern respectively in the base case. Clearly, a reduction of birth rate extends the average time before an introduction of a H1N1 strain similar to the H1N1-2009 can cause an outbreak.

Figure 4 shows the absolute final size in Hong Kong for a first time introduction of a H1N1 strain similar to the H1N1-2009 in the years 2010-2039 given the outbreak in 2009. In both the model with semi-domination and density dependent contact pattern, it is observed that an introduction of a similar H1N1 strain to the H1N1-2009 in Hong Kong will not lead to an outbreak until 2016. Due to the 2009 outbreak, the fraction of susceptible individuals of age 0 to 19 was relatively low in 2009 after the pandemic. Each year after 2009 until 2029, the number of susceptible individuals of age 19 becoming 20 is significant lower than the new born (susceptible) individuals of age 0. The net difference in susceptible individuals has therefore a steady increasing character in the period until 2029. In 2030, all individuals who were in the 0-19 group during the

2009 outbreak are in the 20+ group and, hence, the net difference in susceptible individuals in the 0-19 group between year 2029 and 2030 is lower than before. Therefore, we expect, since the 0-19 group is the major determinant in the spread of the H1N1-2009 virus, a qualitatively different slope of the absolute final size (see Figure 4). After the 19 years, the absolute final size changes, mainly, due to changes in the size of the 0-19 group. The number of susceptible individuals before the first new H1N1 outbreak after 2009 is exactly the same in a model with the semi-domination and density dependent contact pattern. The difference between the curves related to the semi-domination and density dependent contact pattern can therefore be fully contributed to the number of contacts per unit of time, K. Recall that K depends on the group sizes N_1, N_2 and N_3 and not on the number of susceptible individuals in each group.

In the alternative situation, where birth rate is lowered to equal the death rate, a first new introduction of a H1N1 strain similar to the H1N1-2009 after the 2009 pandemic does not lead to a new outbreak until 2019 and 2033 in a model with the semi-domination and density dependent contact pattern as seen in figure 4B. Figure 4 shows that restrictions on birth and migration rate can delay the time before an introduction of a H1N1 strain similar to the H1N1-2009 can cause an outbreak in Hong Kong and if an outbreak occurs then the outbreak size is likely to be smaller. Comparing Figure 4A and 4B we find that the effect of birth restriction on the absolute final sizes in the period 2010-2039 has a higher impact in the model with the density dependent than in the semi-domination contact pattern.

6. Discussion

We have shown in this paper that the effect of demographical changes on the severity of an outbreak depends both on the contact pattern of the population and the measure of severity (final size, basic reproduction number and mortality). In a semi-domination contact pattern where each young individual has a fixed amount of contacts (royal

group), we have shown theoretically that a decrease of the number of young individuals in the population decreases the fractional final size of each age group and the basic reproduction number for any infectious disease with a short infectious period and $R_0 > 1$. The case study suggests that ageing, if defined as a fractional increase of older individuals (with fixed population size), will decrease the absolute final size in both a model with the density dependent and the semi-domination contact pattern. On the other hand, depending on the choice of contact pattern, the normalized total mortality increases or decreases due to ageing. The case study shows that birth restriction or other forms of restrictions that prevents a rapid growth of the number of young individuals (e.g. migration restriction for young individuals) can prolong the expected time needed before a new introduction of a H1N1 strain similar to the H1N1-2009 can cause an outbreak in Hong Kong.

The message for policy makers from this study is that ageing and other types of demographical change can influence the severity of future infectious disease outbreaks. When faced with a comparable outbreak in the past, policy makers should consider the demographical changes that have occurred and change intervention strategies accordingly. Although ageing can imply a lower severity measured in final size, still an increase of public health burden is possible (see section 5).

This study has been conducted in the framework of a deterministic SIR multi-type model. It is unclear whether and how the results change in a stochastic model where the concept of final size has a stochastic definition. The SIR model is a rough simplification of the reality. Although the final size and basic reproduction number (Ma and Earn, 2006) are in most situations (almost) not sensitive to extensions of the SIR model, e.g. multistage of infections, it is unclear whether a model which incorporates high mortality rate infectious diseases, as SARS, will have the same results. This holds especially when disease-induced deaths impact the contact structure.

The numerical study on the expected outbreak size of a first new H1N1 epidemic in Hong Kong is based on many unrealistic assumptions as no migration in the population and no deaths in individuals younger than 60 years. Although many key factors of ageing still holds in the projection, the results must therefore not be used as an actual forecast. Instead it should be used as an example to grasp an idea of the qualitative relation between the size of the susceptible groups, the composition and size of the population, and the final absolute final size.

This study, both the theoretical as the numerical part, has been conducted in the spirit of qualitative impact of demographical change on the severity of an outbreak. To understand the quantitative impact, it is important to conduct empirical studies to find the best contact pattern to the population of interest. In order to study, for example, the validity of a model with the semi-domination contact pattern, one can repeat a study as Mossong et al., 2008, and try to find fitting values for $(c_{ij})_{1\leq i,j\leq m}$.

We revealed that contact patterns and the transmission rates of the pathogen, determine the quality of the effect of demographical change on the final size, the basic reproduction number and mortality. As effects of demographical change can change the severity of an epidemic significantly, policy makers should consider demographical change as ageing in future strategies of outbreak control.

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Appendix

A. Estimation of the next generation matrix in the 2-type model in Hong Kong

The estimated average number of contacts per day of an individual of any group with any group in the UK is extracted from Mossong et al., 2008. See the last page of this section of the appendix. In the following we use the same notation as in the main text.

Step 1: we sum over the number of contacts per day that individuals with age 0-19 and 20+ have with the other groups. The resulting matrix is Table A1.

	Age group of participant	
Age of contact	0-19	20+
0-4	3.22	4.30
5-9	9.41	6.46
10-14	10.16	5.28
15-19	8.41	7.61
20-24	1.90	9.82
25-29	2.63	9.88
30-34	3.16	9.75
35-39	4.35	10.85
40-44	3.63	10.39
45-49	2.17	9.64
50-54	1.52	7.68
55-59	1.10	7.21
60-64	0.94	5.60
65-69	0.52	3.35
70+	0.55	6.15

Table A1. Data from Mossong et al., 2008 of the average number of contacts per day of an individual from the age group 0-19 or 20+ group with individuals of any age group in the UK.

Step 2: we calculate the fractional weights of the age classes with respect to the age groups 0-19 and 20+ in Hong Kong in 2009. The results are given in Table A2.

Group sizes Hong Kong

Age group	Group size (x1000)
0-19	1308.70
20+	5695.00

Age group	Group size (x1000)	Weights relative to age group 0-19	Weights relative to age group 20+
0-4	229.20	0.18	N.A.
5-9	265.30	0.20	N.A.
10-14	378.90	0.29	N.A.
15-19	435.30	0.33	N.A.
20-24	458.50	N.A.	0.08
25-29	536.70	N.A.	0.09
30-34	539.70	N.A.	0.09
35-39	574.80	N.A.	0.10
40-44	599.80	N.A.	0.11
45-49	673.20	N.A.	0.12
50-54	609.20	N.A.	0.11
55-59	476.20	N.A.	0.08
60-64	333.40	N.A.	0.06
65-69	222.10	N.A.	0.04
70+	671.40	N.A.	0.12
Total	7003.70	1.00	1.00

Table A2. Group sizes of Hong Kong in 2009 as given by the Hong Kong Census and Statistics Department and the fractional weights of the age groups within the age group 0-19 and 20+.

Step 3: we sum, weighted by the size of the age classes, over the number of contacts per day that an individual of type 0-19 (20+) has with the groups 0-19 and 20+. In order to be consistent in the interpretation of matrices with the main text, we take the transpose of this matrix and obtain Table A3.

	0-19	20+
0-19	8.21	2.17
20+	6.12	8.58

Table A3. Estimated number of contacts per day of an individual from the age group 0-19 or 20+ with individuals from the age group 0-19 or 20+ before reciprocity adjustment.
The table should be read as follows. An individual of age between 0 and 19 years old has on average 6.12 contacts per day with individuals older than 19.

Table A3 should be read as follows: an individual in the group 0-19 has on average 6.12 contacts with individuals of the 20+ group. Note that this matrix is not equal to $(k_{ij})_{1\le i,j\le 2}$ since it does not satisfy the reciprocity conditions.

Step 4: let N_1 and N_2 denote the group sizes of group 1 (0-19 group) and 2 (20+ group). The reciprocity condition states that the total contacts of group 1 with group 2 should be equal to the total contacts of group 2 with group 1, thus: $k_{21}N_1 = k_{12}N_2$. We assume that the true total number of contacts of group 1 with group 2 is equal to the average number of contacts between group 1 with 2 and 2 with 1 in the resulting matrix of Step 3. It is easy to check that only $k_{ij} = \frac{6.12N_1 + 2.17N_2}{2N_j}$, $1 \le i, j \le 2$, satisfy the above 2 conditions. Note that the group sizes are known from Table A2. Hence, we have the following estimation of $(k_{ij})_{1\le i,j\le 2}$

	0-19	20+
0-19	8.21	1.79
20+	7.79	8.58

Table A4. Estimated number of contacts per day of an individual from the age group 0-19 or 20+ with individuals from the age group 0-19 or 20+ after reciprocity adjustment.
The table should be read as follows. An individual of age between 0 and 19 years old has on average 7.79 contacts per day with individuals older than 19.

Step 5: recall that $s_1' = 1$ and $s_2' = 0.185$. Hence $(s_i' k_{ij})_{1\le i,j\le 2}$ is given by Table A5.

	0-19	20+
0-19	8.21	1.79
20+	1.44	1.59

Table A5. Estimation of $(s_i' k_{ij})_{1\le i,j\le 2}$.

The dominant eigenvalue of $(s_i' k_{ij})_{1\le i,j\le 2}$ is 8.6.

Step 6: the estimate of the next generation matrix is now obtained by dividing the resulting matrix in Step 5 by the dominant eigenvalue 8.6 and multiplying by the basic reproduction number 1.22.

Contact frequency the UK extracted from Mossong et al., 2008

Age of contact	Age group of participant															
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70+
0-4	1.92	0.65	0.41	0.24	0.46	0.73	0.67	0.83	0.24	0.22	0.36	0.20	0.20	0.26	0.13
5-9	0.95	6.64	1.09	0.73	0.61	0.75	0.95	1.39	0.90	0.16	0.30	0.22	0.50	0.48	0.20
10-14	0.48	1.31	6.85	1.52	0.27	0.31	0.48	0.76	1.00	0.69	0.32	0.44	0.27	0.41	0.33
15-19	0.33	0.34	1.03	6.71	1.58	0.73	0.42	0.56	0.85	1.16	0.70	0.30	0.20	0.48	0.63
20-24	0.45	0.30	0.22	0.93	2.59	1.49	0.75	0.63	0.77	0.87	0.88	0.61	0.53	0.37	0.33
25-29	0.79	0.66	0.44	0.74	1.29	1.83	0.97	0.71	0.74	0.85	0.88	0.87	0.67	0.74	0.33
30-34	0.97	1.07	0.62	0.50	0.88	1.19	1.67	0.89	1.02	0.91	0.92	0.61	0.76	0.63	0.27
35-39	1.02	0.98	1.26	1.09	0.76	0.95	1.53	1.50	1.32	1.09	0.83	0.69	1.02	0.96	0.20
40-44	0.55	1.00	1.14	0.94	0.73	0.88	0.82	1.23	1.35	1.27	0.89	0.67	0.94	0.81	0.80
45-49	0.29	0.54	0.57	0.77	0.97	0.93	0.57	0.80	1.32	1.87	0.61	0.80	0.61	0.59	0.57
50-54	0.33	0.38	0.40	0.41	0.44	0.85	0.60	0.61	0.71	0.95	0.74	1.06	0.59	0.56	0.57
55-59	0.31	0.21	0.25	0.33	0.39	0.53	0.68	0.53	0.55	0.51	0.82	1.17	0.85	0.85	0.33
60-64	0.26	0.25	0.19	0.24	0.19	0.34	0.40	0.39	0.47	0.55	0.41	0.78	0.65	0.85	0.57
65-69	0.09	0.11	0.12	0.20	0.19	0.22	0.13	0.30	0.23	0.13	0.21	0.28	0.36	0.70	0.60
70+	0.14	0.15	0.21	0.10	0.24	0.17	0.15	0.41	0.50	0.71	0.53	0.76	0.47	0.74	1.47

Table A6. Data from Mossong et al., 2008 of the average number of contacts per day of an individual from any age group with individuals any age group in the UK.

3. Effectiveness of interventions targeted at health care workers and residents in reducing the probability and the size of an infectious disease outbreak in a long-term care facility for the elderly

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Abstract

Protecting elderly from an infectious disease infection is important due to the high case fatality ratio among elderly. It is predicted that the fraction elderly will increase in most developed countries, which can lead to an increase of the number of required long-term care facilities for the eldery in the future. Hence, in the future, protection of individuals in long-term care facilities for the elderly from infectious diseases infection becomes even more important in order to reduce the severity of an outbreak of an infectious disease outbreak. Previous studies contradict each other on how effective of interventions targeted at residents and health care workers are in reducing the probability of a major outbreak in a long-term care facility for the elderly. We used a stochastic simulation model and an analytical model to clarify this issue. Interventions can target health care workers and/or residents and may reduce the susceptibility and/or infectiousness of the individuals. In this study we define the level of an intervention of any type by the reduction of susceptibility and/or infectiousness of the targeted individual in percent. We call an intervention of any type weak, if the level of the intervention is less than 40% in comparison with the situation with no interventions. This study shows that weak interventions targeted at health care workers or visitors cannot reduce the probability of a major outbreak in the facility when the infectious disease has a basic reproduction number higher than 1.6 in the general population. These interventions hardly influence the average outbreak size given a major outbreak in the facility, in contrast to residents of the facility. Weak interventions aimed at residents can be effective even when the basic reproduction number exceeds 1,6. We showed that intervention level and the effectiveness of interventions in reducing the size and probability of a major outbreak in the long-term care facility for the elderly are in general not linearly related. Our study also reveals that interventions must start early in the epidemic and should not be stopped when the peak of the force of infection has been reached.

1. Introduction

Novel infectious diseases can lead to high morbidity and mortality as experienced in the H1N1-2009 pandemic. An global study showed that the case fatality ratio of the H1N1-2009 virus among elderly was significantly higher compared to other age groups (1). Interventions like frequent hand washing, wearing facemask, pre-pandemic vaccination, prophylactic antiviral therapy and isolation of health care workers and residents may mitigate the epidemic in the long-term care facility for the elderly.

In the beginning of an infectious disease outbreak, both economically developed and developing countries need to rely on non-pharmaceutical interventions (NPIs) to control the speed and the size of the outbreak. Reasons are that pharmaceutical based interventions may not exist, are not properly distributed or it is not yet known whether the epidemic is severe enough to justify pharmaceutical based interventions.

Previous simulation studies did not provide a clear overview of the effectiveness of interventions targeted at health care workers and residents in reducing the probability and the size of a major outbreak in a long-term care facility for the elderly. Interventions targeted at health care workers and residents which reduces susceptibility (2) and infectiousness (3) has been studied for a limited range of basic reproduction number and combination of intervention types. The basic reproduction number is defined as the average number of new infections caused by an infectious individual in its infective period at the earliest phase of the outbreak. Nuño et al., 2008 (3), identified re-entry in the facility of health care workers as the critical factor in causing an outbreak in a long-term care facility. Van den Dool et al., 2008 (2) showed a linear relation between health care worker vaccine uptake and average attack rate, defined as the fraction residents who have experienced the infection at the end of the epidemic. Additionally, Nuño et al., revealed that socially acceptable NPIs for health care workers and visitors can reduce the probability of a major outbreak in a long-term care facility substantially. Also Van den Dool et al., 2008, revealed a positive relation between probability of a major

outbreak and pharmaceutical interventions on health care workers, but, for the same reduction in susceptibility and infectiousness of health care workers, Nuño et al., 2008, predicted a significantly higher effectiveness of the interventions than Van den Dool et al., 2008.

For a moderate value of the basic reproduction number, 1.4, approximately fifty percent of the population will become infected in a standard deterministic SIR model when all individuals are susceptible before the outbreak (see Diekmann, Heesterbeek, Britton 2013 (9), for a detailed discussion of the deterministic SIR model). As health care workers are a substantial part of their days off-duty they also have a substantial chance to acquire the pathogen when off-duty, and, if so, they have a chance to enter the facility when being infectious. Because most long-term care facilities have more than 50 health care workers, it is likely that one of the health care workers will introduce the pathogen into the facility by one of the health care workers during the epidemic if no interventions are applied. Since for high basic reproduction number, a single infectious individual in the facility already has a substantial chance to cause a major outbreak, we expect that the number of infectious health care workers who enter the facility must be greatly reduced before the probability of a major outbreak in the facility reduces substantially. Assuming this reasoning to be true and complete, socially acceptable NPIs should have almost no effect on the probability of a major outbreak in the facility when the basic reproduction number is high.

The primary aim of this paper is to clarify the discrepancy between the results in the paper of Nuño et al., Van den Dool et al., and the given reasoning. We created a stochastic simulation model and provide two analytical approximations for the probability of that no major outbreak occurs in the facility. These approximations have the advantage that they require hardly any computation time.

2. Methods

2.1. Long-term care facility for the elderly and community

Our model consists of one community and a single long-term care facility for the elderly. In the forthcoming, a long-term care facility should be read as a long-term care facility for *the elderly*. Residing individuals in the community are called community members and residing individuals in the long-term care facility are called residents. A third group, which completes the categorization of the population, are the health care workers. Health care workers like nurses and physicians alternate between locations. If a health care worker is in the long-term care facility, we call the health care worker on-shift and otherwise off-shift. Visitors are neglected in this model, but, as explained in the discussion, a visitor has a similar role in the spread of the disease as a health care worker. The community should be interpreted as the group of all citizens of a country or city excluding individuals of a single long-term care facility. The size of the community is assumed to be 7 million which is in agreement with the size of Hong Kong. Our long-term care facility has 150 residential beds which are 100% occupied during the period of the epidemic. It is assumed that 60 health care workers work for the long-term care facility. Health care workers are divided in 2 groups of 30; when one group is on-duty, the other is off-duty. These groups alternate every 12 hours. It is assumed that individuals in the community mix randomly with other individuals of the community and individuals of the long-term care facility mix randomly with other individuals of the long-term care facility. Hence, health care workers mix 12 hours with community members and 12 hours with residents in 1 day.

2.2. Stages of infection and disease properties

We assume that individuals can be in 3 disease stages: susceptible, infectious and removed. An individual is susceptible when he/she has never been infected by the disease. An individual is infectious when he/she has acquired the disease and is infectious towards others. An individual is called removed when the individual has

recovered and is no longer infectious. It is assumed that recovered individuals cannot go to the susceptible disease stage again. In literature, this model is called the SIR model. Note that this model neglects asymptomatic individuals and disease-induced deaths.

In this study, we consider a disease with properties similar to the influenza virus. The duration of the infectious period of an individual is chosen to be exponentially distributed with mean 2.8 (4-5). The basic reproduction number of influenza is assumed to be in the range 1.2 to 2.2 (6-8).

2.3 Deterministic and stochastic simulation model

The disease stage of community members and, hence, the force of infection, FOI, (the average rate at which a susceptible individuals becomes infectious) in the community is modelled by a deterministic SIR model. It is assumed that the FOI of susceptible community members does not change due to the alternating locations of the health care workers. This assumption is valid when the relative number of health care workers is negligible small in comparison to the number of community members.

The transmission parameters $\beta > 0$ and $\alpha > 0$, which reflects the rate of transmission of an infectious individual to all individuals in the population if all individuals are susceptible and the average rate of recovery respectively are assumed to be equal in the community and the long-term care facility. Note that the FOI in a site at any time is calculated by multiplying β by the number of infectious individuals at that time and dividing by the total number of individuals in that site.

The occurrence of infections among residents and on-duty health care workers is modelled stochastically. The Poisson rate of new infections in the facility is equal to the FOI in the long-term care facility multiplied by the number of susceptible individuals in the facility. Note that susceptible on-duty health care workers and susceptible residents are infected at the same rate. We assume that all health care workers and residents are

susceptible at the beginning of the outbreak, and, hence, the FOI in the facility is equal to 0 at the earliest phase of the outbreak. Therefore, an outbreak in the facility can only occur when an off-duty infectious health care worker enters the facility. Due to stochastic extinction, an introduction of the infectious disease by a health care worker need not lead to a major outbreak in the facility, e.g., because the infectious health care worker did not infect any individual in the facility before he/she recovered.

By the random mixing assumption and the negligible number of health care workers with respect to the number community members, we set the FOI of off-duty susceptible health care workers equal to the FOI of community members in a population without health care workers. A scheme of the model is depicted in Figure 1.

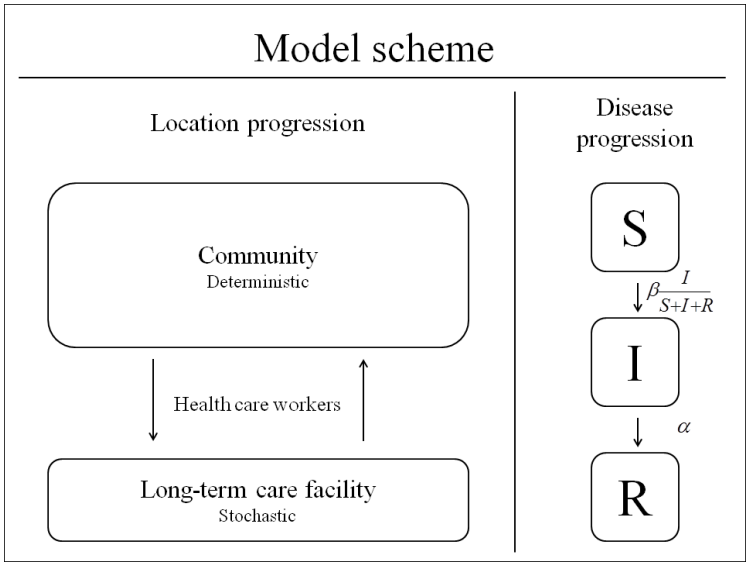

Figure 1. Schematic of the studied model
A scheme of the location (left) and disease (right) progression. Health care workers can switch location between community and long-term care facility. *S*, *I*, *R*, denote respectively the size of the number of susceptible, infectious and removed individuals in the population.

The basic reproduction number, R_0, in the community is defined as the average number of new infections due to 1 infectious individual given that all community

members are susceptible, is given by $R_0 = \frac{\beta}{\alpha}$. It is assumed that at the first occurrence of an infected case (time is 0), 100 community members are infectious and that the outbreak ends after 1 year of the outbreak (time is 360) or when the incidence rate (number of new infections per day among residents and health care workers) is below 10^{-10}. For each parameter combination we performed 300 independent runs of the simulation model. The analytical model is described in section 2.6. A more detailed description of the stochastic simulation model and techniques can be found in Appendix A and B.

2.4 Intervention types

In this study, we distinguish three types of interventions targeted at health care workers and residents. We call interventions, which reduce the risk for a susceptible health care worker to acquire the infection in the community, 'HCs interventions'. H, C and s represents health care workers, community and susceptibility respectively. Examples of HCs interventions are: 1) isolation of health care workers before re-entering the long-term care facility, 2) recommendations for health care workers to avoid large gatherings and public transport, and, 3) voluntary or mandatory prophylactic usage of antivirals by health care workers. The second type of interventions, 'HFi interventions' (F for facility and i for infectiousness), reduces the infectiousness of infectious health care workers within the long-term care facility. Examples are 1) the use of facemask, 2) better hand hygiene, and, 3) a reduction of close contact in the facility. The third prevention strategy considered, an 'RFi intervention' (R for residents), reduces the infectiousness of residents. Examples are 1) isolation of infectious residents, 2) use of facemasks by residents and 3) use of antiviral prophylaxis. All interventions are applied for the whole period of the epidemic unless stated otherwise. Note that interventions can be of more than 1 type, e.g., the usage of facemask by health care workers and residents over the whole epidemic is an intervention of the types HCs, HFi and RFI. The interventions are implemented in the model by reducing the FOI upon health care workers in the

community, the FOI in the facility due to infectious on-duty health care workers and the FOI in the facility due to residents respectively for intervention types HCs, HFi and RFi. We say that an intervention is of level x% if the FOI as described above is reduced by x%. An intervention is called weak if the level is smaller than or equal to 40%, otherwise it is called a 'strong intervention'. In the forthcoming, we write "HCs&HFi intervention" for the intervention where both the HCs and HFi interventions are applied with the same level. We note that socially and ethically acceptable NPIs are mostly weak interventions. This corresponds roughly with the category 1-2 interventions as defined in the paper of Nuño et al., 2008. We have not considered explicitly interventions which reduce the susceptibility of on-duty health care workers, we expect that the effect is small, since the number of on-duty health care workers is relative small in comparison with the total number of individuals in the facility..

2.5 Measures for severity of an infectious disease outbreak in the facility

The probability density function of the attack rate in the facility has typically two peaks, a peak close to zero, which represents the probability of a minor outbreak, and a bell-shaped peak that corresponds to a major outbreak. In this study, we are interested in two quantities, the probability of a major outbreak and the average attack rate *given a major outbreak*. We define an outbreak in the long-term care facility to be major when the attack rate exceeds 10% and minor otherwise. We define the average attack rate to be the mean attack rate of all simulations with a major outbreak. Hence, the average attack rate should be read as the average attack rate *given a major outbreak* in the facility.

2.6 Analytical model

We also use an analytical model to understand which parameters critically influence the probability of a major outbreak in the facility. We present 2 approximations of the probability of a minor outbreak in the facility, including one with an explicit analytical expression.

In the analytical model we denote the level of the inventions HCs, HFi and RFi by $1-c_1$, $1-c_2$ and $1-c_3$ respectively. For example, a HCs intervention which reduces the susceptibility of health care workers by 30% corresponds with $c_1 = 0.7$. Assuming a deterministic SIR model of the community and that we can neglect health care workers in the community, we can define σ_{com} by the fraction of total susceptible individuals in the community at the end of the epidemic. This fraction can be calculated by solving the so-called final size equation: $\sigma_{com} = \exp[-R_0(1-\sigma_{com})]$, with R_0 the basic reproduction number, see, e.g., Diekmann, Heesterbeek, Britton, 2013 (9).

The probability that a health care worker will be infected over the course of the epidemic given that he/she did not get infected in the facility is $1-e^{-\frac{1}{2}c_1R_0(1-\sigma_{com})}$ (see Appendix C for derivation). In this study we use this quantity as an approximation for the probability that a health care worker becomes infected when off-duty given that no major outbreak occurs in the facility. When no major outbreak has occured in the facility and assuming that the number of health care workers is negligible compared with the number of resident, each infectious health care worker infects on average approximately $\frac{1}{2}c_2R_0$ residents in the facility. The basic reproduction number arises in the expression since approximately all individuals in the facility are susceptible when no major outbreak has occurred in the facility. The factor $\frac{1}{2}$ arises because health care workers spend approximately half of their infectious period in the facility as they work in 12 hour shifts. The multiplication by c_2 follows directly from the definition of a HFi intervention. In appendix C3 we show an alternative approximation of the number infections caused by an infectious health care workers among residents given no major outbreak in the facility. Let N_{hcw} denote the total number of health care workers. Then, on average, approximately $c_2\frac{R_0}{2}N_{hcw}(1-e^{-\frac{1}{2}c_1R_0(1-\sigma_{com})})$ residents become infectious in

the facility due to health care workers who became infectious in the community. We approximate the probability of a minor outbreak given an infectious individual in the population by the known formula in a homogeneously mixing population: $\frac{1}{c_3 R_0}$, see e.g., Diekmann, Heesterbeek, Britton, 2013 (9). Hence, we obtain the following expression for the probability of a minor outbreak:

$$P(\text{minor outbreak}) = \min\left(\left(\frac{1}{c_3 R_0}\right)^{c_2 \frac{R_0}{2} N_{hcw}\left(1-e^{-\frac{1}{2}c_1 R_0(1-\sigma_{com})}\right)}, 1\right). \qquad (2.68)$$

We call this approximation, *Approximation 1*. A more detailed description of the derivation can be found in Appendix C.

In a more precise approximation, which we call *Approximation 2*, the number of new infections among residents due to an infectious health care worker is considered from a stochastic point of view. Unfortunately, this model does not provide an explicit expression for the probability of a minor outbreak, but the computer time needed to calculate this probability is negligible in comparison with the stochastic simulation model. The full derivation, the description and the comparison of the results of the two approximations is given in Appendix C.

3. Results

3.1 Probability of a minor outbreak in the facility in a stochastic simulation model and Approximation 1 and 2 compared.

The probability of a minor outbreak in the facility in the stochastic simulation model coincides very well with the results of Approximation 1 and 2. As seen in Figure 2, Approximation 1 and 2 suggest a higher probability of minor outbreak than the simulation model for $R_0 = 1.2$. Since for R_0 small, the average outbreak size in the facility is typically small, major and minor outbreaks in the facility are difficult to distinguish. Hence, for R_0 small, the randomly chosen definition of a minor outbreak

(recall the 10% threshold in section 2) in a stochastic simulation model can explain the difference in results with the analytical approximations.

Approximation 1 underestimates the probability of a minor outbreak in the facility by 10 to 20 percent. This can be the result of the overestimation of new infections among residents caused by an infected health care worker given no major outbreak in the facility, which we approximated by $c_2 R_0 / 2$. Although Approximation 1 is quantitatively not always accurate, it provides similar qualitative results as the simulation results. As Approximation 1 provides an explicit expression it can help in understanding the qualitative dependency of the probability of a minor outbreak in the facility on the size of the community and the facility, the basic reproduction number and the intervention types HCs, HFi and RFi. Approximation 2 gives for $R_0 \geq 1.4$ very similar estimates of the minor outbreak probability as the simulation model, see Figure 2. In the text to follow we focus on the simulation results. We want to emphasize that all results on the probability of a minor outbreak in the facility are supported by Approximation 1 and 2 as well.

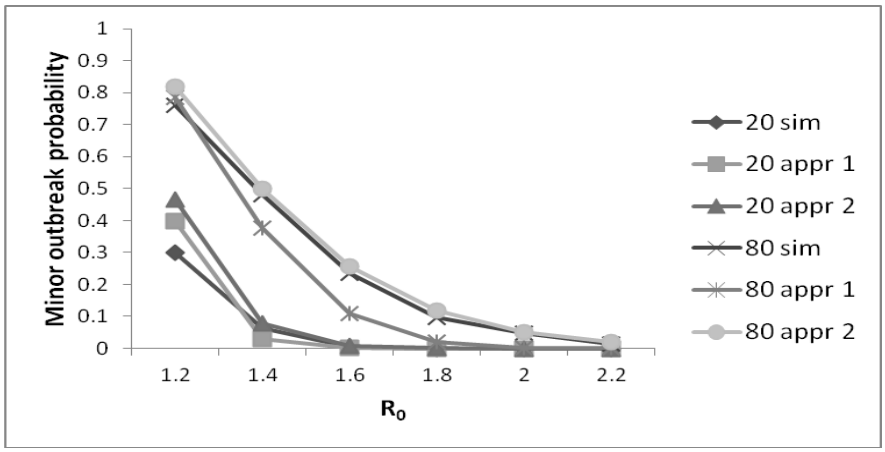

Figure 2. Similarity between the probability of a minor outbreak in the facility in a stochastic simulation model and Approximation 1 and 2 for a HCs intervention.

The probability of a minor outbreak in the facility is plotted against the basic reproduction number. In the legend, 'sim', 'appr 1' and 'appr 2' denote respectively the results of the stochastic simulation model, Approximation 1 and Approximation 2. The numbers before 'sim', 'appr 1' and 'appr 2' denote the level of the HCs intervention in %.

3.2 Probability of a minor outbreak in the facility

A high basic reproduction number implies a high probability of a major outbreak in the facility given an infectious individual in the facility. Therefore, we expect for high R_0, that HCs interventions, which reduce the number of infectious health care workers entering the facility, only have effect in reducing the probability of a major outbreak when the level is near 100%. This reasoning is supported by our simulation results, see Figure 3C-3F: when the basic reproduction number is greater than or equal to 1.6, weak HCs interventions will hardly effect the major outbreak probability in the facility. Our study shows, that the effect of interventions which reduce the susceptibility of off-duty health care workers (HCs) and interventions which reduce the infectiousness of on-duty health care workers (HFi) are nearly the same. When both types the HCs and HFi interventions are executed with the same level (HCs&HFi intervention), the effectiveness in reducing the major outbreak probability in the facility increases significantly for all basic reproduction numbers in the range 1.2 to 2.2. In the case of $R_0 = 1.2$, an intervention of level 40% of type HCs or HFi reduces the probability of a minor outbreak by 40 to 60 percent. The probability of a minor outbreak in the facility is almost a linear function of the level of intervention when $R_0 = 1.2$ (see Figure 3A). However, this linearity breaks down as the basic reproduction number increases, see Figure 3B-3F.

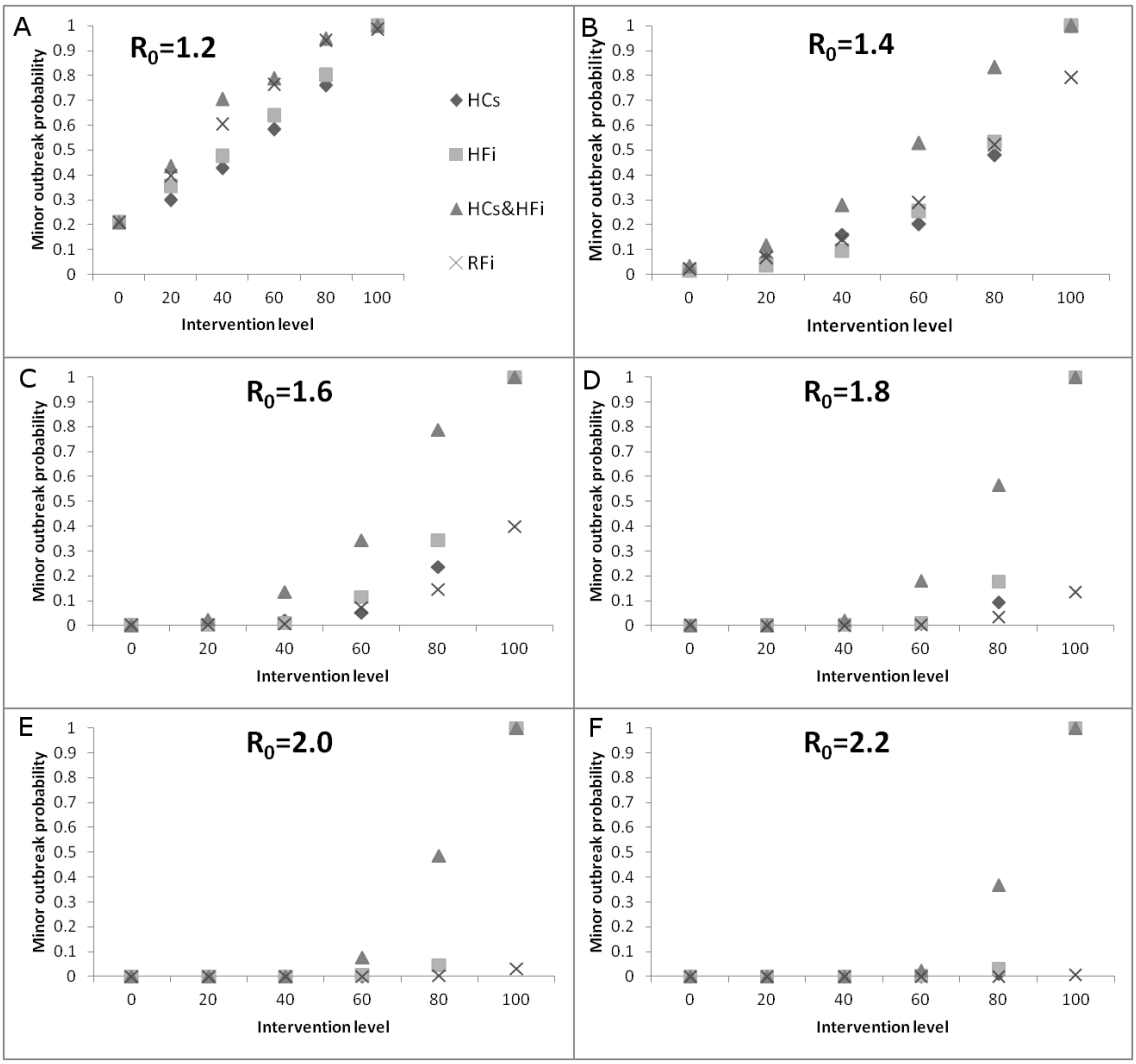

Figure 3. Effectiveness of interventions in increasing the probability of a minor outbreak in the facility

The probability of a minor outbreak in the facility has been plotted for different values of the basic reproduction number and types and levels of interventions. Diamonds and squares denote HCs and HFi interventions respectively. Triangles represent the situation where both the HCs and HFi interventions are applied with the same level (HCs&HFi intervention). Crosses denote RFi interventions.

Interventions which reduce the infectiousness of residents (RFi interventions) have a different character than interventions aimed at health care workers (HCs and HFi interventions). Health care workers are pivotal in triggering a major outbreak in the facility, but have, in contrast to residents, a minor role in disease transmission in the facility when a major outbreak is occuring. Any weak RFi intervention (recall that an intervention is weak if the level is less than 40%) has nearly no effect on the probability

of a minor outbreak in the facility when R_0 is larger than or equal to 1.6 (see Figure 3C-3F). When the level of an RFi intervention is 100%, still a major outbreak can occur due to infectious on-duty health care workers who infect residents (see e.g. Figure 3F). For low R_0 (see Figure 3A) a reduction of infectiousness of residents (RFi intervention) by a chosen level reduces the probability of a major outbreak more than a reduction of infectiousness of on-duty health care workers (HFi). An RFi intervention reduces the basic reproduction number in the facility effectively (see section 3.3), and, hence, the average attack rate. Therefore, since the average attack rate given a major outbreak in the facility for low R_0 is near the range of a minor outbreak, 0 to 10 percent, an RFi intervention shifts the mass of the probability density function of the attack rate to the range of 0 to 10 percent, increasing the probability of a minor outbreak in the facility. This effect is no longer present when $R_0 \geq 1.4$ as the average attack rate is then further away from the range of a minor outbreak.

3.3 The average attack rate given a major outbreak in the facility

Once the facility faces a major outbreak, on-duty health care workers are less important in the spread of the infectious disease among the individuals in the facility than residents, simply because there are far more residents than on-duty health care workers. In Figure 4 we show that HCs and HFi interventions have a small positive effect on the average attack rate given a major outbreak in the facility. For all R_0, a HCs or HFi intervention of level 80% results in approximately a drop of 10% in the average attack rate given a major outbreak in the facility. Let $0 \leq f \leq 1$ denote the fraction of the number of on-duty health care workers in the facility with respect to the total number of individuals in the facility and c_2 and c_3 as defined in section 2.4. The *i,j*th position, $i, j \in \{1, 2\}$, of the next generation matrix (*NGM*) of the population in the facility is

defined as the average number of new *i*-type individual infections due to one *j*-type infectious individual given that all individuals in the facility are susceptible. In this study, index "1" refers to residents and index "2" refers to on-duty health care workers. By the assumption of random mixing the next generation matrix is equal to

$$NGM = R_0 \begin{pmatrix} (1-f)c_3 & (1-f)c_2 \\ fc_3 & fc_2 \end{pmatrix}. \qquad (2.69)$$

The basic reproduction number in the facility, R_0^{fac}, is defined (10) as the dominant eigenvalue of the next generation matrix. Calculation of the dominant eigenvalue shows that $R_0^{fac} = R_0(c_2 f + c_3(1-f))$. In this study f is $1/6$ (150 residents and 30 on-duty health care workers), therefore $R_0^{fac} = R_0(c_2 \frac{1}{6} + c_3 \frac{5}{6})$. This reasoning shows that RFi interventions should decrease R_0^{fac} more than HFi interventions if the level of the interventions are the same. From this, we expect that the average attack rate given a major outbreak in the facility will react stronger to RFi interventions than HFi interventions, due to the monotone relationship between the average attack rate and the basic reproduction number (9). In Figure 4 we find that RFi interventions outperform HCs or HFi interventions in reducing the average attack rate given a major outbreak in the facility. A reduction of 10 to 30 percent can be reached with weak RFi interventions. This holds for all basic reproduction numbers between 1.2 and 2.2. The level of RFi interventions and the average attack rate given a major outbreak in the facility shows no linear relation. The qualitative effect of RFi interventions is similar for all values of the basic reproduction number between 1.2 and 2.2.

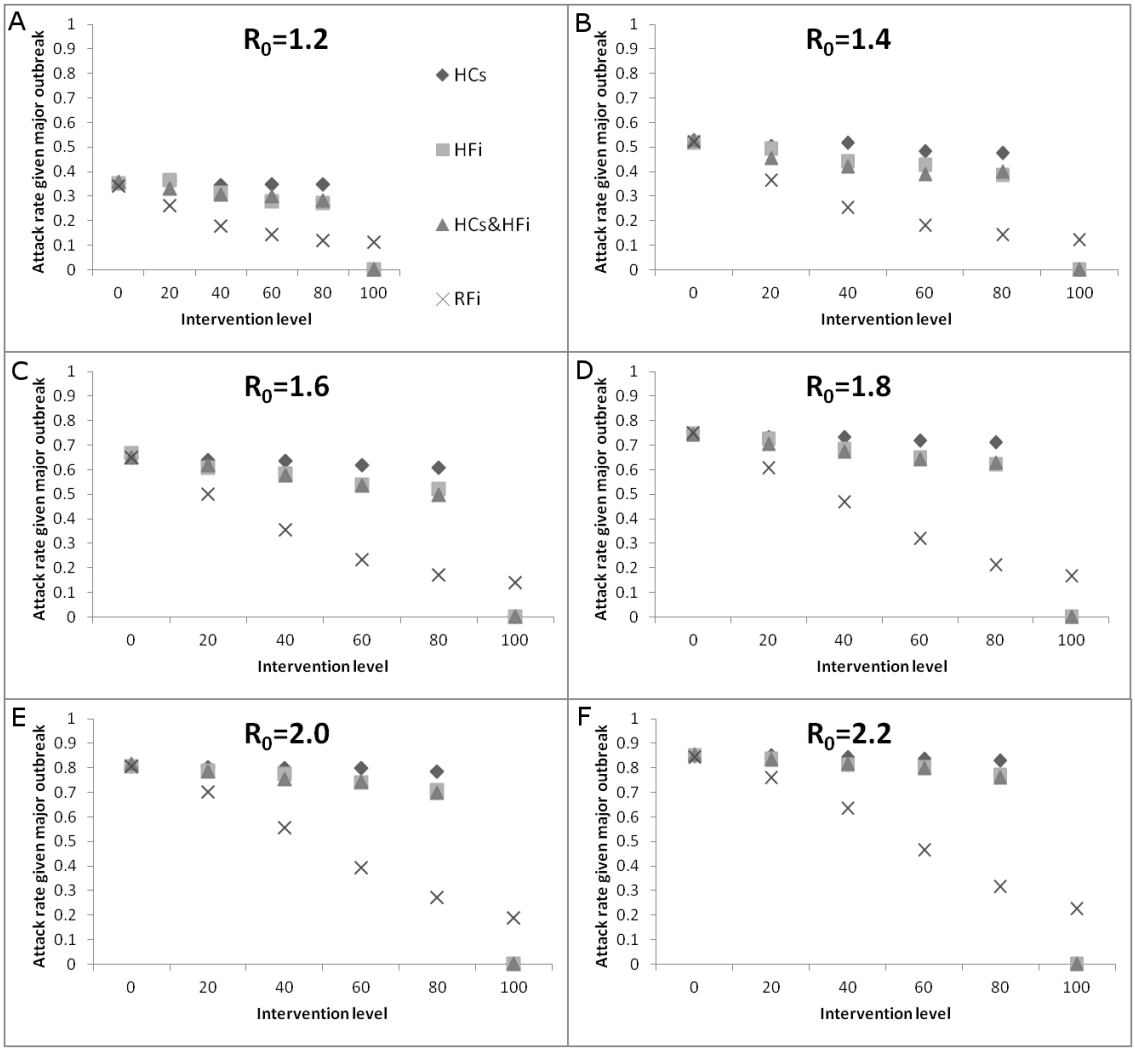

Figure 4. Effectiveness of interventions in reducing the average attack rate given a major outbreak in the facility

The average attack rate given a major outbreak in the facility has been plotted for different values of the basic reproduction number and intervention levels and types. Diamonds and squares denote HCs and HFi interventions respectively. Triangles represents the situation where both the HCs and HFi interventions are applied with the same level (HCs&HFi interventions). Crosses denote RFi interventions.

3.4 Effect of starting late and ending early of interventions on the minor outbreak probability and average attack rate given a major outbreak in the facility

For a basic reproduction number of 1.2 the (deterministic) force of infection in the community peaks at 118 days after the first infection in the community. See Figure 5.

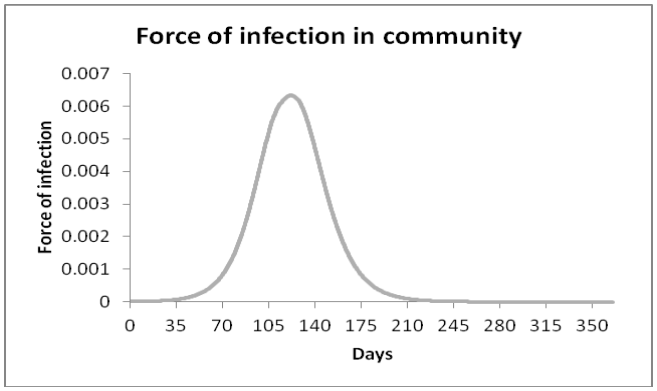

Figure 5. Force of infection in the community

The force of infection is defined as the rate at which a single susceptible individual becomes infected. The horizontal axis denotes the number of days after the first infected case in the community. The vertical axis denotes the force of infection of susceptible individuals in the community for an infectious disease with a basic reproduction number of 1.2 and an average infectious duration of 2.8 days. The top is reached at 118 days after the first infected case in the community.

In the rest of this section we assume that the disease in consideration has a basic reproduction number of 1.2. In real life, interventions cannot be applied directly after the first infected case. After the first infected case, it takes time to 1) detect the infectious disease outbreak in the community, 2) to decide on the intervention strategy, and, 3) to execute the interventions. Our assumption so far, that interventions start directly after the first infection in the community is, by the above reasoning, false. A delay in implementation of interventions will always increase the probability of a major outbreak and the average attack rate given a major outbreak in the facility. It is expected that it is most important to have the interventions implemented when the force of infection is high. Figure 6 shows the effect on the probability of a minor outbreak and the average attack rate given a major outbreak in the facility of HCs&HFi and RFi interventions of level 40%. The horizontal axis of Figure 6 indicates the number of days after the first infected case before implementing the interventions. The drop in effectiveness in reducing the probability of a minor outbreak is around 50% when the start of the interventions of level 40% exceeds the day that the top of the force of infection in the community has been reached (118 days). Simulations with interventions

which stop at day 118 after the first infected case in the community (Figure 6B), suggest that the effectiveness of the interventions in reducing the probability of major outbreak and the average attack rate given a major outbreak in the facility drops with approximately 50% due to the early stop of the intervention. The results suggest that it is wise to apply the interventions early and only lift the interventions when the epidemic is over.

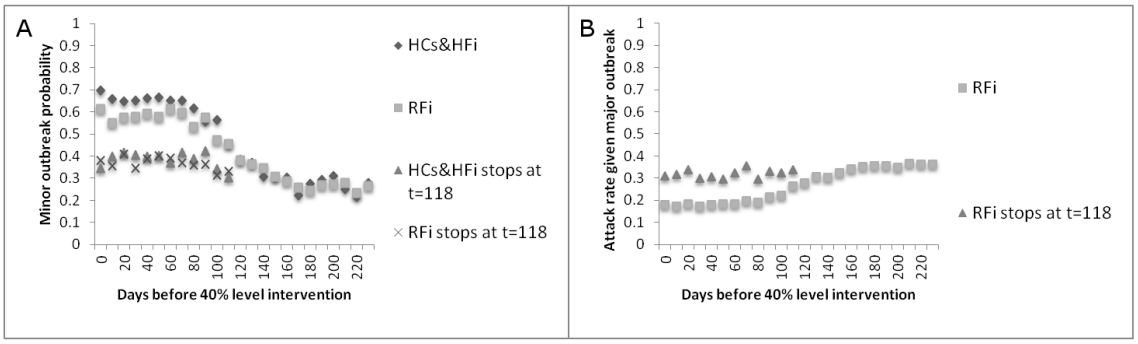

Figure 6. Importance of day of starting and ending of interventions on reducing the major outbreak probability and average attack rate given a major outbreak in the facility.
The basic reproduction number is 1.2. Figure 6A: diamonds represent HCs&HFi interventions and squares represent RFi interventions. The horizontal axis denotes the day of the start of the interventions of level 40%, the interventions are applied until the end of the epidemic. Triangles and crosses represent respectively HFs&HFi and RFi interventions applied until 118 days after the first infected case in the community. A value *c* on the horizontal axis below 118 should be interpreted as that interventions has been applied between day *c* and day 118. Figure 6B: the vertical axis shows the attack rate given a major outbreak in the facility. Squares denote RFi interventions and triangles denote RFi intervention which are applied until day 118.

4. Discussion

We have used a stochastic simulation model and analytical approximations to show that interventions of more than 40% level (strong interventions) are needed to decrease the probability of a major outbreak in the facility effectively when the basic reproduction number is larger than or equal to 1.6. When the reproduction number is below 1.6 a decrease of the probability of a major outbreak in the facility by 10 to 40 percent can be reached by weak HCs or HFi interventions. The results in this article contradicts the

message of Nuño et al., 2008, (3) which states that weak interventions are effective in reducing the probability of a major outbreak in a facility for higher values of R_0. Nuño et al., 2008 distinguish different categories of intervention strategies. The category 1-2 intervention strategy, which reduces the infectiousness of health care workers and visitors by at most 60% (HFi intervention), reduced the probability of a major outbreak in the facility (defined in Nuño et al., 2008 by attack rate < 5%) by at least 50% for $R_0 = 1.6$. Our study shows that NPIs alone are not effective enough to prevent an outbreak in a long-term care facility when R_0 exceeds 1.6. In this case the infectiousness of off-duty and susceptibility of on-duty health care workers must be reduced by more than 80% in order to have a substantial effect. Pharmaceutical based interventions seem to be necessary to achieve these levels of interventions. This study shows that there is almost a linear relation between the intervention level and the minor outbreak probability in the facility when the basic reproduction number is between 1.2 and 1.4. However, the linearity breaks down when the basic reproduction number is higher than 1.4. These findings generalize the results of Van den Dool et al., 2008, (2) who revealed a linear relation in their article for a low R_0. This result coincides with our analytical approximation with explicit expression, which suggests the absence of a linear relationship.

Our study shows that interventions, which reduce the infectiousness of on-duty and susceptibility of off-duty health care workers (HCs and HFi interventions), have little effect on the average attack rate given a major outbreak in the facility, in contrast to RFi interventions. As HCs and HFi interventions can be effective in preventing an outbreak, RFi interventions primarily reduce the size of the outbreak given a major outbreak. It depends on the aims and resources which interventions should be implemented. An RFi intervention requires in general more resources because of the high number of residents in the facility. If resources are scarce, one should analyse the potential of HCs and HFi interventions in preventing a major outbreak in the facility. If the potential is low, one might need to put more weight in RFi interventions. Early

implementation of interventions is also crucial. When the intervention starts after the peak of the force of infection in the community, the effectiveness of interventions dilutes almost completely. Also, an early withdrawal of interventions may dilute the effect of reducing the probability of a major outbreak and the average attack rate given a major outbreak in the facility substantially.

Since the effectiveness of interventions depends on the basic reproduction number, it is of great importance to obtain an estimate of R_0 as soon as possible by public health organizations. Before an estimation is available, decisions of policy makers on intervention strategies cannot be evidence based, but implementation of interventions may be advisable as the starting day of interventions is crucial in long-term care facilities.

We have run extra simulations for a model where the probability of a minor outbreak in the facility is defined as in Nuño et al., 2008. For a basic reproduction number of 1.2 and 1.4 we found that the probability of a minor outbreak in the facility is lower than in the original results. Hence, if using the definition as in Nuño et al., 2008, we expect that the interventions are less effective than the results in this study. For values of the basic reproduction number larger than 1.4 we found almost the same results.

In Nishuira et al., 2010 (11), the importance of heterogeneity with respect to age groups has been stressed. The H1N1-2009 virus features a high transmission rate among young adults and a low transmission rate among elderly. For infectious diseases with this characteristic, it is clear that the basic reproduction number in the long-term care facility for the elderly should be lower than in the community. An important difference between the community and a long-term care facility is that health care workers have relatively many contacts in comparison with residents and the majority of the community members. This leads to a larger role for health care workers in spreading the disease in the facility. The question remains whether we can translate the basic

reproduction number in the community to the long-term care facility. Heterogeneity is an important aspect for future studies to take into account for.

The SIR model is a standard model, which captures many basic properties of an outbreak. It is a rough simplification of the reality. Ma et al., 2006 (12) showed that extensions of a deterministic SIR model, e.g., in the form of more infectious compartments do not change the attack rate significantly. As Nuño et al., 2008, suggest in their study, we believe also that an extra asymptotic compartment will hardly influence the results because of the typically low transmission rate of individuals in the asymptotic disease stage. Anderson and Watson, 1980 (13), showed that the assumption of the infectious period being exponential distributed period can be replaced by the gamma distribution without changing the final size equation. This suggests that the results of this study might also hold for gamma distributed infectious periods.

The staff size in this study is chosen such that the ratio of health care workers and residents is 1:5. When the staff size increases, the probability of an infectious on-duty health care worker entering the facility increases, hence, the probability of a major outbreak in the facility increases. This implies that interventions on health care workers and residents will become less efficient than shown as in this study.

We did not explicitly incorporated visitors in this study. However, visitors of the facility have similar characteristics as health care workers from an epidemiological point of view. The major role of health care workers and visitors is to provide a bridge for the infectious disease to enter the facility. The group of health care workers in this study can therefore be read as a group consisting of visitors and health care workers.

We conclude that interventions which reduce susceptibility of off-duty and infectiousness of on-duty health care workers are not effective in reducing the probability of a major outbreak probability in a long-term care facility when $R_0 \geq 1.6$. This result contradicts the message of Nuño et al., 2008. Intervention strategies for protecting facility outbreaks may need to be reconsidered. Effectiveness of interventions

are highly dependent on R_0 and a linear relation between effectiveness and intervention level should only be assumed for low values of the basic reproduction number.

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Appendix

A. SIR model

In the SIR model it is assumed that individuals can be in 3 disease stages: susceptible, infectious and removed. Let $S(t)$, $I(t)$ and $R(t)$ denote the number of susceptible, infectious and removed individuals in the population after $t \geq 0$ days of the first occurrence of an infectious individual in the population and let N denote the total population size. The rate of change of $S(t)$, $I(t)$ and $R(t)$ is determined by the transmission rate β and the exponential distributed duration of the infectious period with mean $1/\alpha$. The transmission rate can be interpreted as the rate at which an infectious individual infects all individuals in the population given that all individuals are susceptible. Hence, at any time $t \geq 0$ an infectious individual spreads the disease with rate $\beta \frac{S}{N}$. Therefore, the number of individuals in the disease stages, $S(t)$, $I(t)$ and $R(t)$, satisfy the differential equations

$$\begin{aligned} \frac{dS}{dt} &= -\beta \frac{S}{N} I \\ \frac{dI}{dt} &= \beta \frac{S}{N} I - \alpha I \\ \frac{dR}{dt} &= \alpha I, \end{aligned} \tag{2.70}$$

with $(S(0), I(0), R(0)) = (N - 100, 100, 0)$. Note that the SIR model neglects disease-induced deaths. At time 0, an infectious individual infects on average β susceptible individuals per unit of time. Since an infectious individual is on average infectious for $1/\alpha$ units of time, the basic reproduction number, R_0, defined as the expected number

of secondary cases per primary case in the earliest phase of the epidemic is given by the formula $R_0 = \frac{\beta}{\alpha}$. β can therefore be calculated if R_0 and α are given.

B. Stochastic simulation model

B1. Simulation model

In the simulation model we keep track of the location and disease stage of 3 types of individuals: community members, health care workers and residents. Community members and residents are located in the community and the facility respectively and cannot change site. Health care workers alternate their location between the community and the facility every 12 hours. The disease stage progression of community members is modelled by the deterministic SIR model as described in Appendix A. The disease stage and location progression of health care workers and residents are modelled stochastically and individually. Let *t* denote the time in days after the first occurrence of an infectious individual in the population. It is assumed the community exists of 7×10^6 community member of which 100 are infectious and the rest susceptible at $t = 0$. The number of community members in each disease stage, $S(t)$, $I(t)$ and $R(t)$, is updated each 0.05 day by the discretized version of (2.70). This is valid since we assume that health care workers do not impact the transmission dynamics in the community because the number of health care workers in the community is negligible in comparison with the number of community members. We checked in all runs of the simulation model

that $I(t) \geq 0$, which ensures that the simulation runs correctly. We assume that at the beginning of the epidemic, all residents and health care workers are susceptible.

Health care workers mix randomly with community member and residents when off- and on-duty respectively. We model this assumption by setting the FOI of off-duty and on-duty health care workers to equal the FOI of community members and residents at any time $t \geq 0$. Further details on the calculation of the FOI of health care workers and residents is explained in Appendix B2.

The stochastic events: 1) infection of an off-duty health care worker, 2) infection of an on-duty health care worker or resident, and, 3) loss of infectiousness of a health care worker or resident, are updated in discrete time steps of at most 0.05 days, more details about the stochastic simulation are presented in Appendix B2.

Each simulation is either run for 360 days or until the sum of the incidence rate of health care workers (both off- and on-duty) and residents is below 10^{-10}, which are on average 360, 271, 200, 162, 140 and 122 days for a basic reproduction number of 1.2, 1.4, 1.6, 1.8, 2.0 and 2.2 respectively. For each set of parameters we have performed 300 independent runs. These runs are used to calculate the probability of a major outbreak in the facility and the average outbreak size given a major outbreak for the chosen set of parameters. See main article section 2.5 for a detailed description of the chosen measures for describing the outbreak severity in the facility.

B2. Calculation of time and type of next event

We denote the number of susceptible and infectious residents at time $t \geq 0$ by $S_{res}(t)$ and $I_{res}(t)$ respectively. The number of susceptible and infectious health care workers in the community and the facility at time $t \geq 0$ is denoted by $S_{hcw}^{com}(t)$, $I_{hcw}^{com}(t)$, $S_{hcw}^{fac}(t)$ and $I_{hcw}^{fac}(t)$ respectively. The number of susceptible and infectious community members at time $t \geq 0$ is denoted by $S_{com}(t)$ and $I_{com}(t)$ respectively. Let N_{fac} and N_{com} denote the number of individuals in the facility and the community respectively. The force of infection in the community at time $t \geq 0$, $FOI_{com}(t)$, is calculated by the formula $\frac{\beta}{N_{com}} I_{com}(t)$ (as shown in section 2.3). In absence of interventions, the force of infection in the facility at time $t \geq 0$, $FOI_{fac}(t)$, is given by $\frac{\beta}{N_{fac}}(I_{res}(t) + I_{hcw}^{fac}(t))$. The incidence rate, defined as the rate of new infections, among off-duty susceptible health care workers is denoted by $\lambda_{com}(t)$ and calculated by $FOI_{com}(t) S_{hcw}^{com}(t)$. The incidence rate among susceptible on-duty health care workers and residents is denoted by $\lambda_{fac}(t)$ and calculated by $FOI_{fac}(t)(S_{res}(t) + S_{hcw}^{fac}(t))$. The incidence rate among susceptible health care workers and residents is the sum of incidence rates: $\lambda_{com} + \lambda_{fac}$. λ_{com} and λ_{fac} are modelled as step functions and can only change its value at $t \in \{0, 0.05, 0.1, 0.15, ...\}$ days, hence, λ_{com} and λ_{fac} are modelled to be constant in the interval $(t, t + 0.05)$ for all $t \in \{0, 0.05, 0.1, 0.15, ...\}$. λ_{com} and λ_{fac} is updated every time $t \in \{0, 0.05, 0.1, 0.15, ...\}$ by using the value of $I_{com}(t)$, $I_{res}(t)$, $I_{hcw}^{fac}(t)$, $S_{hcw}^{com}(t)$, $S_{res}(t)$ and $S_{hcw}^{fac}(t)$ at that time. Only $I_{com}(t)$ is a deterministic quantity (as explained in

Appendix B1), the other states follow the mechanics of the simulation, which we explain below. The simulation is an iterative run. It can therefore be fully described when we give the mechanics of a single run. Assume that the simulation is currently at time $t \in \{0, 0.05, 0.1, 0.15, ...\}$ days. We simulate the time until a new infection by drawing from an Exp($\lambda_{com} + \lambda_{fac}$) distribution and repeat this drawing until the sum of the outcomes exceed 0.05. The number of draws made subtracted by 1 is the number of new infections in the period $(t, t + 0.05)$ and the sum of the first *i*th, $i \in \mathbb{N}$, draws is the time until the *i*th infection. This sampling method follows directly from the definition of a Poisson process. The duration of the infectious period of the new infectious individuals is simulated by drawing from an exponential distribution with mean 2.8. Given an infection in the period $(t, t + 0.05)$, the infection occurs with probability $\frac{\lambda_{fac}}{\lambda_{fac} + \lambda_{com}}$ in the facility and with probability $\frac{\lambda_{com}}{\lambda_{fac} + \lambda_{com}}$ in the community. When the infection occurs in the facility, a susceptible individual is chosen uniformly and randomly among all on-duty health care workers and residents to become infected. When the infection occurs in the community, a susceptible off-duty health care worker is chosen randomly to become infected. New infections, shift changes and recoveries planned for the period $(t, t + 0.05)$ are processed before the model updates $\lambda_{com} + \lambda_{fac}$ at $t + 0.05$. At time $t = 0$, the value of $I_{com}(t)$, $I_{res}(t)$, $I_{hcw}^{fac}(t)$, $S_{hcw}^{com}(t)$, $S_{res}(t)$ and $S_{hcw}^{fac}(t)$ is known and the list of future events is empty. Therefore, the above description of a single run of the iteration is applicable to all $t \in \{0, 0.05, 0.1, 0.15, ...\}$.

B3. Implementation of interventions in the stochastic simulation model

We distinguish, as described in the main text, three types of interventions. An HCs intervention reduces the susceptibility of off-duty health care workers. An HFi intervention reduces the infectiousness of on-duty health care workers. Finally, RFi interventions reduce the infectiousness of residents. All interventions are applied during the whole period of the epidemic unless stated otherwise. The interventions are implemented in the model by reducing the FOI of health care workers in the community, the FOI in the facility due to infectious on-duty health care workers and the FOI in the facility due to residents respectively for intervention types HCs, HFi and RFi.

C. Analytical model

C1. Derivation of the probability that a health care worker is susceptible at the end of the epidemic given no major outbreak in the facility.

We write $F(t)$, $t \in \mathbb{R}$, for the probability that a chosen health care worker is susceptible at day *t* after the first occurrence of an infected case given that he/she did not become infected in the facility. In this section we show the derivation of $F(\infty)$, defined as $\lim_{t \uparrow \infty} F(t)$. We will use $F(\infty)$ as an approximation for the probability that a health care worker is susceptible at the end of the epidemic given no major outbreak in the facility. Given that the health care worker did not become infected in the facility, we can ignore the force of infection in the facility. Therefore, the following equation holds, $\frac{dF(t)}{dt} = -\frac{1}{2} FOI_{com}(t) F(t)$ with $F(0) = 1$ and $t \geq 0$. The factor $\frac{1}{2}$ follows from the assumption that health care workers alternate location every half day. The explicit expression of $F(t)$ is hence,

$$F(t) = e^{-\frac{1}{2}\int_0^t FOI_{com}(\tau)d\tau}. \quad (2.71)$$

By continuity of the exponential function we conclude $F(\infty) = e^{-\frac{1}{2}\int_0^\infty FOI_{com}(\tau)d\tau}$. Note that $\int_0^\infty FOI_{com}(\tau)d\tau$ is the cumulative force of infection in the community. During the epidemic, $N_{com} - S_{com}(\infty)$ (with $S_{com}(\infty)$ defined as $\lim_{t\uparrow\infty} S_{com}(t)$) individuals become infected. Each infected individual spreads the infectious disease with rate β among all individuals in the population (including infected and removed individuals) for an average duration of $1/\alpha$. A fraction $1/N_{com}$ of the contacts of an infected individual is with one single specific individual. Therefore, the cumulative force of infection is equal to $\frac{\beta}{\alpha}\frac{N_{com} - S_{com}(\infty)}{N_{com}}$, which is equal to $R_0(1-\sigma_{com})$, with $\sigma_{com} = \frac{S_{com}(\infty)}{N_{com}}$. σ_{com} satisfies the so-called final size equation $\sigma_{com} = e^{-R_0(1-\sigma_{com})}$ (see Diekmann, Heesterbeek, Britton, 2013 for a detailed discussion of the derivation of the final size equation). We conclude $F(\infty) = e^{-\frac{1}{2}R_0(1-\sigma_{com})}$. An HCs intervention reduces the susceptibility of off-duty health care workers. We denote c_1 for the fraction of reduction of FOI of off-duty health care workers due to an HCs intervention. For example, when a HCs intervention reduces susceptibility by 40% we have $c_1 = 0.6$. Finally, incorporating HCs interventions in the calculation, we obtain

$$F(\infty) = e^{-\frac{1}{2}c_1R_0(1-\sigma_{com})}. \quad (2.72)$$

Note that if $c_1 = 0$, $F(\infty)$ is 1 and no health care worker can get infected. In this case, the probability of a major outbreak in the long-term care facility is 0.

C2. Approximation 1 of probability of no major (minor) outbreak in the facility

In section C1 we have mentioned that we will approximate the probability of a health care worker becoming infectious in the community given no major outbreak in the facility by $1-F(\infty)=1-e^{-\frac{1}{2}c_1R_0(1-\sigma_{com})}$. Thus on average, $(1-F(\infty))N_{hcw}$ health care workers become infectious during the epidemic given no major outbreak in the facility. In this section we assume that the actual number of health care workers who acquired infection in the community given no major outbreak equals its expectation. In Appendix C3, we incorporate the stochasticity in the number of infected health care workers at the expense of more complicated expressions.

If we assume that no major outbreak has occurred in the facility and on-duty health care workers do not infect other on-duty health care workers (which holds approximately when the number of on-duty health care workers is relative small in comparison with the number of residents), each infectious health care worker will infect on average, $\frac{1}{2}R_0$ residents. The factor $\frac{1}{2}$ follows from the assumption that health care workers spend half of their time in the facility (this factor $\frac{1}{2}$ will be improved as well in section C3). We denote the fraction of reduction of infectiousness among health care workers due to a HFi intervention by $1-c_2\in[0,1]$. The average number of infections among residents due to a single infectious off-health care workers is therefore $\frac{1}{2}c_2R_0$ when incorporating HFi interventions. We denote the fraction of reduction of infectiousness of residents by an RFi intervention by $1-c_3\in[0,1]$. We approximate the

probability of no major outbreak in the facility, given that a resident became infectious and $c_3 R_0 \geq 1$, by $\frac{1}{c_3 R_0}$ (see e.g. Diekmann & Heesterbeek, 2000) which holds exactly in the case of a deterministic model with homogeneous mixing and infinite size. We assume that no major outbreak occurs in the facility when $c_3 R_0 < 1$. The probability of no major (minor) outbreak is therefore

$$P(\text{minor outbreak}) = \min((\frac{1}{c_3 R_0})^{N_{hcw}(1-e^{-\frac{1}{2}c_1 R_0(1-\sigma_{com})})\frac{1}{2}c_2 R_0}, 1). \qquad (2.73)$$

C3. Approximation 2 of probability of no major (minor) outbreak in the facility

Instead of averaging, we can choose to calculate the probability of *k* infections, $k \in \mathbb{N}$, in the facility due to an infected health care worker which got in infected in the community. Fix a $t \geq 0$ and assume that a chosen off-duty susceptible health care workers will get infected at a time in the 12 hours off-duty period. We assume that the probability of the chosen off-duty health care worker to become infected at $x \in [0,1/2]$ days after the beginning of the 12 hours off-duty period is uniformly distributed over the half day. Note that this assumption violates the Poisson assumption made in the stochastic simulation model, but as long as the probability of an off-duty health care worker to get infected is low in each 12 hours off-duty period (which is the case for the moderate values of R_0 we consider), the approximation is very accurate. We assume that the time of becoming infected and the duration of being infectious are independent

quantities. Under this assumption, the probability that the chosen health care worker is still infectious when entering the facility is

$$p_{\text{int}ro} = \int_0^{1/2} 2Exp(-\alpha x)dx = \frac{2-2e^{-\alpha/2}}{\alpha}. \tag{2.74}$$

$Exp(-\alpha x)$ is the probability that the infectious period of an individual exceeds $x \geq 0$ days. The factor 2 is the probability density function of the uniform distribution at $[0, 0.5]$.

In the following we assume that the chosen off-duty health care worker is still infectious when entering the facility. If the chosen health care worker recovers in the community, the length of the infectious period spend in the facility is a multiple of $\frac{1}{2}$. We denote the probability that this duration is $\frac{i}{2}$, with $i \in \mathbb{N}_+$, by $p_{dur}(i)$. An infectious health care worker has spend exactly half a day in the facility before recovery, when the infected health care worker is $\frac{1}{2}$ to 1 day infectious after the first time re-entering the facility. The probability of entering the facility when still infectious is $p_{\text{int}ro}$ and the probability that the health care worker recovers between the first shift and the second shift in the facility is $E\,\text{xp}(-\alpha/2)(1-Exp(-\alpha/2))$ (recall the interpretation of $Exp(-\alpha x)$ as described above) by the memoryless property of the exponential distribution. Expanding this reasoning we obtain

$$p_{dur}(i) = p_{\text{intro}} Exp(-\alpha(2i-1)/2)(1-Exp(\alpha/2)). \tag{2.75}$$

If a health care worker recovers in the facility, the duration of the infectious period spend in the facility will be a continuous distribution. For $t \in (0,1/2)$ and $i \in \mathbb{N}_+$, we

denote by $p_{dur}(i+t)$ the probability that the infectious duration in the facility is exactly $i+t$. By the memoryless property we have the formula

$$p_{dur}(i+t) = p_{\text{int}ro} Exp(-\alpha i)\alpha Exp(-\alpha t), \tag{2.76}$$

Formula (2.76) should be read as that the probability of the infectious duration in the facility of the chosen health care worker is $i+t$, is equal to the probability of being infectious for longer than i days multiplied by the probability of being infectious for exactly t days.

Recall the definition of c_1, c_2, c_3 as denoted in Appendix C2. Given no major outbreak in the facility, new infections due to an on-duty single infectious health care worker among residents arise in the facility with the rate $R_0\alpha c_2$. The probability of no new infections in the facility given an off-duty infectious health care worker is calculated by summing over all possibilities of not infecting any resident in the long-term care facility. For this we need to integrate (and sum) over all possible infectious durations of health care workers in the facility multiplied by the probability of 0 infections in that period. Denote the probability of having $k \in \mathbb{N}_+$ infections, given that the infectious health care worker stays exactly $i/2+t$ days, $i \in \mathbb{N}_+$, $t \in [0,1/2]$, in the facility before recovering by $Poiss(R_0\alpha c_2(i/2+t), k)$. We have the expression

$$Poiss(R_0\alpha c_2(i/2+t), k) = \frac{(R_0\alpha c_2(i/2+t))^k}{k!} e^{-R_0\alpha c_2(i/2+t)}. \tag{2.77}$$

The probability of no new infection in the long-term care facility given infection of an off-duty health care worker in the facility is now equal to

$$P(\text{no infection}) = (1 - p_{\text{int}ro}) + \sum_{i=1}^{\infty} p_{dur}(i) Poiss(R_0 \alpha c_2 (i/2), 0) + \int_0^{1/2} \sum_{i=0}^{\infty} p_{dur}(i+t) Poiss(R_0 \alpha c_2 (i/2+t), 0) dt. \quad (2.78)$$

and for integer $k \geq 1$ we have

$$P(k \text{ infections}) = \sum_{i=1}^{\infty} p_{dur}(i) Poiss(R_0 \alpha c_2 (i/2), k) + \int_0^{1/2} \sum_{i=0}^{\infty} p_{dur}(i+t) Poiss(R_0 \alpha c_2 (i/2+t), k) dt. \quad (2.79)$$

The probability that an infectious resident will not cause a major outbreak in the facility is approximated by $z = \frac{1}{c_3 R_0}$ as introduced in Appendix C2. Therefore, the probability that a health care worker gets infected in the community and does not cause a major outbreak in the facility is $p_{no} := \sum_{k=0}^{\infty} z^k P(k \text{ infections})$. Each health care worker has a probability $(1 - F(\infty))$ to become infectious in the community as discussed in Appendix C2. Hence the probability of no major (minor) outbreak in the facility is

$$P(\text{minor outbreak}) = \sum_{k=0}^{N_{hcw}} \left(\frac{N_{hcw}}{k} \right) (1 - F(\infty))^k (F(\infty))^{N_{hcw}-k} {p_{no}}^k . \quad (2.80)$$

C4. Results of stochastic simulation model and Approximation 1 and 2 compared.

The explicit expressions of *k* infections in the facility due to a health care worker that got infected in the community as in (2.78) and (2.79) are in general long and complex. We have therefore approximated the probability of no outbreak by $p_{no} \approx \sum_{k=0}^{10} z^k P(k \text{ infections})$. The difference of the real value and this approximated value should be small since $P(\text{k infections})$ is in general very small for large *k*, which

we verified numerically. We have plotted the results of the stochastic simulation model, Approximation 1 and Approximation 2 for different intervention levels, types and values of the basic reproduction number. See Figure A1.

The analytical approximations coincide very well with the simulation results, only when $R_0 = 1.2$ there is some discrepancy. We believe that the discrepancy arises because the average attack rate given a major outbreak is in general small for low R_0, and, hence, the randomly chosen definition of a 'major outbreak in the facility' in the simulation model becomes important. Approximation 1 underestimates the probability of no major outbreak for $R_0 \geq 1.2$. We believe that we have overestimated the number of new infections among residents due to an on-duty infectious health care worker by assuming it to be equal to $1/2c_2R_0$.

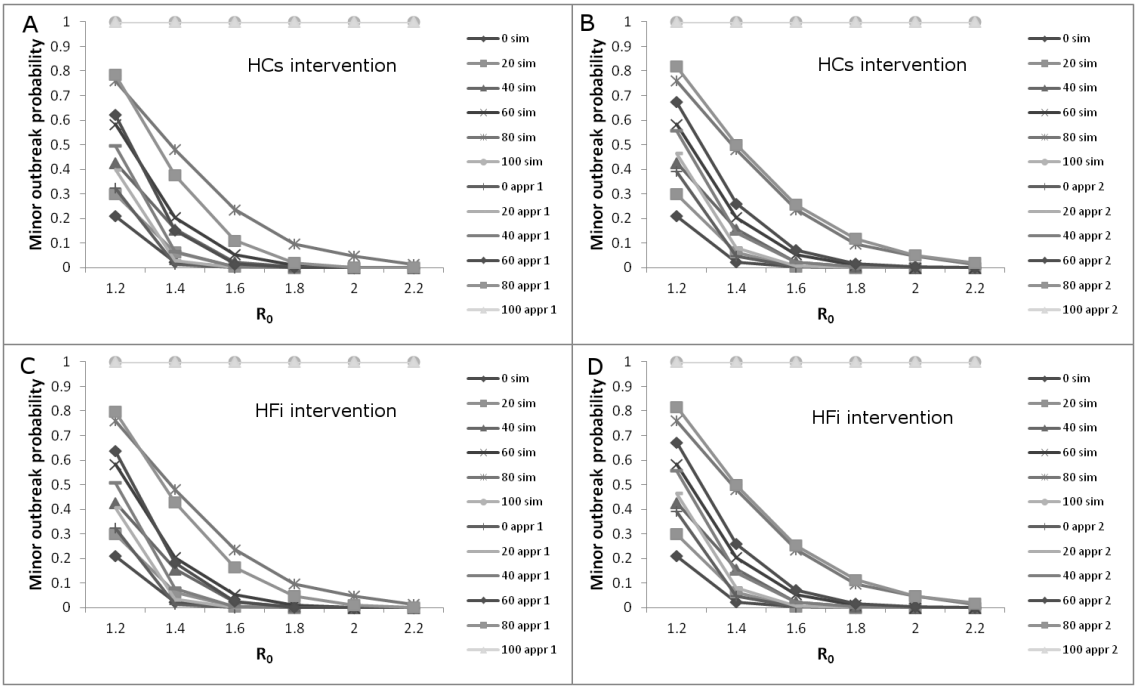

Figure A1. Comparison stochastic simulation model and Approximation 1 and 2

The probability of a minor outbreak is plotted against the basic reproduction number. In the legend, 'sim', 'appr 1' and 'appr 2' denote simulation, Approximation 1 and Approximation 2 results respectively. In the legend, the numbers before ´sim´, 'appr 1' and 'appr 2' denote the level of intervention. Figure A1A and A1B show the effect of HCs interventions and Figure A1C and A1D show the effect of HFi interventions.

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5. References of Preface

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6. C++ code of simulation in Chapter 2

Header file

```
#include <ctime>
#include <iostream>
#include <fstream>
#include <cstdlib>
#include <string>
#include <cassert>
#include <cmath>
#include <iomanip>

using namespace std;

//Constants

//Disease
#define NUM_DISEASE_STAGES 3
#define SUSCEPTIBLE 0
#define INFECTIVE 1
#define REMOVED 2

//Sites
#define NUM_SITES 2
#define ON_SITE 0
#define OFF_SITE 1

//Groups
#define NUM_GROUPS 2
#define RESIDENT 0
#define STAFF 1

//Events
#define NO_EVENTS 2
#define PROGRESSION 0
#define CHANGE_SITE 1

//Constants
#define IS_EQUAL_MARGIN 0.0001
#define SMALLEST_DOUBLE 0.000001
#define LARGE_NUMBER 1e+36
```

```
//Random Number Generator

int idummy;
double numRan=0;

double ranGen2(int &idum)
{
	numRan += 1;
	const int IM1=2147483563,IM2=2147483399;
	const int IA1=40014,IA2=40692,IQ1=53668,IQ2=52774;
	const int IR1=12211,IR2=3791,NTAB=32,IMM1=IM1-1;
	const int NDIV=1+IMM1/NTAB;
	const double EPS=3.0e-16,RNMX=1.0-EPS,AM=1.0/double(IM1);
	static int idum2=123456789,iy=0;
	static vector<int> iv(NTAB);
	int j,k;
	double temp;

	if (idum <= 0) {
		idum=(idum==0 ? 1 : -idum);
		idum2=idum;
		for (j=NTAB+7;j>=0;j--) {
			k=idum/IQ1;
			idum=IA1*(idum-k*IQ1)-k*IR1;
			if (idum < 0) idum += IM1;
			if (j < NTAB) iv[j] = idum;
		}
		iy=iv[0];
	}
	k=idum/IQ1;
	idum=IA1*(idum-k*IQ1)-k*IR1;
	if (idum < 0) idum += IM1;
	k=idum2/IQ2;
	idum2=IA2*(idum2-k*IQ2)-k*IR2;
	if (idum2 < 0) idum2 += IM2;
	j=iy/NDIV;
	iy=iv[j]-idum2;
	iv[j] = idum;
	if (iy < 1) iy += IMM1;
	if ((temp=AM*iy) > RNMX) return RNMX;
	else return temp;
}

//draws a random number between 0 and 1
```

```
inline double Probability() {return ranGen2(idummy);}

//draws according a discrete uniform distribution between a and b
inline int DiscreteUniformDeviate(const int a, const int b){ return
static_cast<int>(0.5+a+ranGen2(idummy)*(b-a));}

//draws from a exponential distribution with input the mean of the next
exponential distribution
inline double ExponentialDeviate(const double a){ return -
log(ranGen2(idummy))*a;}

//Pause function
inline void Pause()
{
	cout << "Press ENTER to continue" << endl;
	getchar();
}

//class for individuals in the local community
class CIndividual
{
private:
    int m_iIndex, m_iDiseaseStatus, m_iType, m_iSiteStatus;

public:
    //function of class
    void SetIndex(int x){m_iIndex =x ;}
    int GetIndex(){return m_iIndex;}

    void SetDiseaseStatus(int x){m_iDiseaseStatus =x;}
    int GetDiseaseStatus(){return m_iDiseaseStatus;}

    void SetType(int x){m_iType =x ;}
    int GetType(){return m_iType;}

    void SetSiteStatus(int x){m_iSiteStatus =x;}
    int GetSiteStatus(){return m_iSiteStatus;}

    //will be defined in .cpp file
    void DiseaseProgression();
    void ChangeSite();

    //for setting objects of this type to be equal
    CIndividual & operator = (CIndividual &y)
```

```
    {
        m_iIndex = y.m_iIndex;
        m_iDiseaseStatus = y.m_iDiseaseStatus;
        m_iType = y.m_iType;
        m_iSiteStatus = y.m_iSiteStatus;
        return *this;
    }
};

//define a function that gives true back when it the numbers are equal
inline bool IsEqual(const double x, const double y)
{
    if(fabs(x) < SMALLEST_DOUBLE && fabs(y) < SMALLEST_DOUBLE)
    {
        return true;
    }
    else if (fabs(x) < SMALLEST_DOUBLE)
    {
        if(fabs(y) > SMALLEST_DOUBLE)

            return false;

        return true;
    }
    else if (fabs(y) <SMALLEST_DOUBLE)
    {
        if (fabs(x) > SMALLEST_DOUBLE)

            return false;

        return true;
    }
    else if (fabs(1-x/y) > IS_EQUAL_MARGIN)
        return false;
    else
        return true;
}

//class for Events
class CEvent
{
private:
    double m_dTime;
    int m_iEvent, m_iType, m_iIndex;
```

```
public:
    CEvent(){};
    CEvent(double dTime, int iEvent, int iType, int iIndex): m_dTime(dTime),
m_iEvent(iEvent), m_iType(iType), m_iIndex(iIndex){}

    //class functions
    double GetTime(){return m_dTime;}
    int GetEvent(){return m_iEvent;}
    int GetType(){return m_iType;}
    int GetIndex(){return m_iIndex;}

    //define when objects are equal
    friend bool operator == (CEvent & x, CEvent y)
    {
        if(IsEqual(x.m_dTime,y.m_dTime)==true  &&  x.m_iType  ==  y.m_iType  &&
x.m_iEvent == y.m_iEvent && x.m_iIndex == y.m_iIndex)
            return true;
        return false;
    }

    //for priority_queue (priority_queue needs this to run correctly)
    friend bool operator < (const CEvent & x, const CEvent & y)
    {
        if(x.m_dTime > y.m_dTime)
            return true;
        return false;
    }
};
```

Main file

```
#include <ctime>
#include <iostream>
#include <fstream>
#include <cstdlib>
#include <string>
#include <cassert>
#include <iterator>
#include <queue>
#include <algorithm>
#include <cmath>
```

```
#include <iomanip>

#include "nursing_home_danny_basic_model_intervention.h"

using namespace std;

//Constants

//Population Constants
int Size[NUM_GROUPS]={150,60};
int N=7000000;
int Seeds=100;

//Disease Constants
double MeanInfectiveDuration[NUM_DISEASE_STAGES]={0,2.8,0};
double R0 = 1.2;
double Beta = (R0)/ MeanInfectiveDuration[INFECTIVE];
double   RestrictionEffect[NUM_GROUPS][NUM_SITES];   //Restriction   parameter,
controls the FOI
double InterventionTime=0;
double AbruptInterventionTime;

//Time Constants
double dt=0.05;
int MaxTime = 360;
double ShiftTime=0.5;
int NumSim=300;

//Variables

//Time Variables
double PotentialTimeNextInfection;
double TimeNextEvent;
double GlobalUpdateTime;
double LocalUpdateTime;

//Disease Variables
double dX[NUM_DISEASE_STAGES], X[NUM_DISEASE_STAGES];
double FOI[NUM_SITES];
int NumSusceptibles[NUM_SITES];

//Queue
priority_queue<CEvent> pEventList;
```

```
//List
CIndividual *IndividualList;

//Counter
int Counter[NUM_GROUPS][NUM_SITES][NUM_DISEASE_STAGES];

//Dummy
CEvent dum;
bool breaked;

//RV for the length of the disease duration which is exponential distributed
double                  DiseaseStageDuration(int                  stage){return
ExponentialDeviate(MeanInfectiveDuration[stage]);}

void ClearMemory()
{
    delete [] IndividualList;

    //clear EventList
    while(pEventList.empty() == false)
    {
        pEventList.pop();
    }
}

//Add new event to EventList, clear memory makes sure that it will be empty
when we run a new simulation
void AddEvent(CEvent x)
{
    pEventList.push(x);
}

//Initialize and reset the system variables and constants
void Initialize()
{
    ClearMemory();
    breaked= false;

    //Initializes the Counter function
    for(int i=0; i <NUM_DISEASE_STAGES; i++)
    {
        for(int j=0; j<NUM_SITES; j++)
        {
            for(int k=0; k<NUM_GROUPS; k++)
```

```
            {
                Counter[k][j][i]=0;
            }
        }
    }

    for(int i=0; i<NUM_GROUPS; i++)
        {
        for(int j=0; j< NUM_SITES; j++)
        {
            RestrictionEffect[i][j]=1;
        }
    }
    //Initializes the IndividualList
    IndividualList = new CIndividual[Size[RESIDENT]+Size[STAFF]];

    //Initiliazes Residents and Staffs
    for(int i=0; i<Size[RESIDENT]; i++)
    {
        IndividualList[i].SetIndex(i);
        IndividualList[i].SetDiseaseStatus(SUSCEPTIBLE);
        IndividualList[i].SetSiteStatus(ON_SITE);
        IndividualList[i].SetType(RESIDENT);
    }

    for(int                          i=Size[RESIDENT];                          i
<(Size[RESIDENT]+static_cast<int>(floor(Size[STAFF]/2)));i++)
    {
        IndividualList[i].SetIndex(i);
        IndividualList[i].SetDiseaseStatus(SUSCEPTIBLE);
        IndividualList[i].SetSiteStatus(ON_SITE);
        IndividualList[i].SetType(STAFF);

AddEvent(CEvent(dt,CHANGE_SITE,IndividualList[i].GetType(),IndividualList[i].G
etIndex()));
    }

    for(int    i=(Size[RESIDENT]+static_cast<int>(floor(Size[STAFF]/2)));    i<
(Size[STAFF]+Size[RESIDENT]); i++)
    {
        IndividualList[i].SetIndex(i);
        IndividualList[i].SetDiseaseStatus(SUSCEPTIBLE);
        IndividualList[i].SetSiteStatus(OFF_SITE);
        IndividualList[i].SetType(STAFF);
```

```
AddEvent(CEvent(dt,CHANGE_SITE,IndividualList[i].GetType(),IndividualList[i].G
etIndex()));
    }

    //Initialize Counter
    for(int i=0; i<(Size[RESIDENT]+Size[STAFF]);i++)
    {

++Counter[IndividualList[i].GetType()][IndividualList[i].GetSiteStatus()][Indi
vidualList[i].GetDiseaseStatus()];
    }

    //Initialize numbers in compartments
    X[SUSCEPTIBLE]= N-Seeds;
    X[INFECTIVE]= Seeds;
    X[REMOVED]=0;

    //Initialize Time variables
    PotentialTimeNextInfection=0;
    GlobalUpdateTime=0;
    LocalUpdateTime=0;
}

//define the function diseaseprogression in the class CIndividual
void CIndividual :: DiseaseProgression()
{
    if(Counter[m_iType][m_iSiteStatus][m_iDiseaseStatus]      ==      0      ||
Counter[m_iType][m_iSiteStatus][m_iDiseaseStatus] < 0 )
    {
        cout << "an error occured in DiseaseProgression, counter error" <<
endl;
        Pause();
    }
    else
    {
        --Counter[m_iType][m_iSiteStatus][m_iDiseaseStatus];
    }

    //remember the diseasestatus
    int stage = m_iDiseaseStatus;

    //choose the correct process
    switch(stage)
```

```
    {
        case SUSCEPTIBLE:
            m_iDiseaseStatus = INFECTIVE;
            break;

        case INFECTIVE:
            m_iDiseaseStatus = REMOVED;
            break;

        case REMOVED:
            cout << "an error has occured in DiseaseProgression, a removed
individual cannot proceed in diseasestatus" << endl;
            break;
    }

    //update the counter due to status change of this individual
    ++Counter[m_iType][m_iSiteStatus][m_iDiseaseStatus];

    //AddEvent of becoming removed when the individual just becomes infectious
    if(m_iDiseaseStatus == INFECTIVE)
    {
        AddEvent(CEvent(TimeNextEvent                                          +
DiseaseStageDuration(m_iDiseaseStatus),PROGRESSION,m_iType,m_iIndex));
    }
}

//define the function ChangeSite in the class CIndividual
void CIndividual :: ChangeSite()
{
    if(Counter[m_iType][m_iSiteStatus][m_iDiseaseStatus]      ==      0      ||
Counter[m_iType][m_iSiteStatus][m_iDiseaseStatus] < 0 )
    {
        cout << "an error occured in ChangeSite, counter error" << endl;
        Pause();
    }
    else
    {
        --Counter[m_iType][m_iSiteStatus][m_iDiseaseStatus];
    }

    //memorize the site
    int site = m_iSiteStatus;

    switch(site)
```

```
    {
        case ON_SITE:
            m_iSiteStatus = OFF_SITE;
            break;

        case OFF_SITE:
            m_iSiteStatus = ON_SITE;
            break;
    }

    //update the counter due to status change of this individual
    ++Counter[m_iType][m_iSiteStatus][m_iDiseaseStatus];

    //AddEvent for new shift change
    AddEvent(CEvent(TimeNextEvent + ShiftTime,CHANGE_SITE,m_iType,m_iIndex));
}

//Defines function that process events of the EventList
void ProcessEventOnList()
{
    if(pEventList.empty() == true)
    {
        cout << "an error occured in ProcessEventOnList, the list is empty" <<
endl;
        Pause();
    }

    //Extract the data of the first event in line
    CEvent indiv= pEventList.top();
    int event = indiv.GetEvent();
    int index = indiv.GetIndex();

    //delete the event first in line
    pEventList.pop();

    //choose the right processing
    switch(event)
    {
        case PROGRESSION:
            IndividualList[index].DiseaseProgression();
            break;

        case CHANGE_SITE:
            IndividualList[index].ChangeSite();
```

```
            break;
    }
}

//This function is used to select an infectee
void SelectInfectee()
{
    if(Counter[RESIDENT][ON_SITE][SUSCEPTIBLE]                                    +
Counter[STAFF][ON_SITE][SUSCEPTIBLE]   +   Counter[STAFF][OFF_SITE][SUSCEPTIBLE]
==         0         ||         Counter[RESIDENT][ON_SITE][SUSCEPTIBLE]         +
Counter[STAFF][ON_SITE][SUSCEPTIBLE] + Counter[STAFF][OFF_SITE][SUSCEPTIBLE] <
0)
    {
        cout << "an error occured in SelectInfectee, no susceptibles are left"
<< endl;
        Pause();
    }

    //initialize variables
    int   ChosenSite=0,   ChosenIndex=0,   ChosenRandomNumber=0,   ChosenType=0,
ithSusceptible=0;
    CIndividual *ChosenIndividual;
    bool bFound = false;

    double p=Probability();

    //Selecting whether the individual will be from on site or off site
    if(                                    p                                      <
(FOI[ON_SITE]*(double(Counter[RESIDENT][ON_SITE][SUSCEPTIBLE])+double(Counter[
STAFF][ON_SITE][SUSCEPTIBLE]))/(FOI[ON_SITE]*(double(Counter[RESIDENT][ON_SITE
][SUSCEPTIBLE])+double(Counter[STAFF][ON_SITE][SUSCEPTIBLE]))+FOI[OFF_SITE]*do
uble(Counter[STAFF][OFF_SITE][SUSCEPTIBLE])*RestrictionEffect[STAFF][OFF_SITE]
)))
    {
        ChosenSite = ON_SITE;
    }
    else
    {
        ChosenSite = OFF_SITE;
    }

    p=Probability();

    //Chooses randomly a resident or a staff
```

```
    if( ChosenSite == ON_SITE)
    {
        if(p                                                                    <
double(Counter[RESIDENT][ON_SITE][SUSCEPTIBLE])/(double(Counter[RESIDENT][ON_S
ITE][SUSCEPTIBLE])+double(Counter[STAFF][ON_SITE][SUSCEPTIBLE])))
        {
            ChosenType= RESIDENT;
        }
        else
        {
            ChosenType = STAFF;
        }
    }
    else
    {
        ChosenType= STAFF;
    }

    //Choose a random individual that is susceptible and satisfies the above
conditions
    if     (     Counter[ChosenType][ChosenSite][SUSCEPTIBLE]     ==     0     ||
Counter[ChosenType][ChosenSite][SUSCEPTIBLE] < 0)
    {
        cout << "an error occured in SelectInfectee, no SUSCEPTIBLES of the
chose  type  are  left"  <<  "\t"  <<  Counter[STAFF][OFF_SITE][INFECTIVE]  +
Counter[STAFF][OFF_SITE][REMOVED] << endl;
        Pause();
    }
    else
    {
        ChosenRandomNumber                                                      =
DiscreteUniformDeviate(0,Counter[ChosenType][ChosenSite][SUSCEPTIBLE]-1);
    }

    //Selecting the ChosenRandomNumberth SUSCEPTIBLE in the chosen type
    if(ChosenType ==RESIDENT)
    {
        for(ChosenIndex=0; ChosenIndex <Size[RESIDENT]; ++ChosenIndex)
        {
            ChosenIndividual = &IndividualList[ChosenIndex];
            if((*ChosenIndividual).GetDiseaseStatus() == SUSCEPTIBLE)
            {
                if(ithSusceptible == ChosenRandomNumber)
                {
```

```
                    bFound = true;
                }
                ++ithSusceptible;
            }
            if(bFound == true)
            {
                break;
            }
        }
        if(bFound == false)
        {
            cout    <<    "an    error    occured    in    SelectInfectee,    no
ChosenRandomNumberth SUSCEPTIBLE is found in the selected type " << endl;
            Pause();
        }
        else
        {
            (*ChosenIndividual).DiseaseProgression();
        }
    }
    else
    {
        for(ChosenIndex=Size[RESIDENT];     ChosenIndex     <     (Size[STAFF]+
Size[RESIDENT]); ++ChosenIndex)
        {
            ChosenIndividual = &IndividualList[ChosenIndex];
            if((*ChosenIndividual).GetDiseaseStatus()    ==    SUSCEPTIBLE    &&
(*ChosenIndividual).GetSiteStatus() == ChosenSite)
            {
                if(ithSusceptible == ChosenRandomNumber)
                {
                    bFound = true;
                }
                ++ithSusceptible;
            }
            if(bFound == true)
            {
                break;
            }
        }
        if(bFound == false)
        {
            cout    <<    "an    error    occured    in    SelectInfectee,    no
ChosenRandomNumberth SUSCEPTIBLE is found in the selected type" << endl;
```

```
            Pause();
        }
        else
        {
            (*ChosenIndividual).DiseaseProgression();
        }
    }
}

int main()
{
    //Create file
    FILE * pFile;
    pFile = fopen ("Output.txt","w");


    for(int k=0; k<24; k++)
    {
    int probnooutbreak=0;
    double sumoutbreak=0;
    InterventionTime=k*10;

    //Loop for Output of results

    //Loop for many simulations
    for (int n=0; n< NumSim; ++n)
    {
        Initialize();


        //Loop until end of epidemic
        while(GlobalUpdateTime < MaxTime)
        {


            //Timing of Restriction
            if(GlobalUpdateTime < InterventionTime)
            {
                RestrictionEffect[RESIDENT][ON_SITE]=1;
                RestrictionEffect[STAFF][ON_SITE]=1;
                RestrictionEffect[STAFF][OFF_SITE]=1;
                R0=1.2;
                Beta = (R0)/ MeanInfectiveDuration[INFECTIVE];
            }
```

```
            if(GlobalUpdateTime >= InterventionTime && GlobalUpdateTime < 118)
            {
                RestrictionEffect[RESIDENT][ON_SITE]=0.6;
                RestrictionEffect[STAFF][ON_SITE]=1;
                RestrictionEffect[STAFF][OFF_SITE]=1;
                R0=1.2;
                Beta = (R0)/ MeanInfectiveDuration[INFECTIVE];
            }

            if(GlobalUpdateTime >= 118)
            {
                RestrictionEffect[RESIDENT][ON_SITE]=1;
                RestrictionEffect[STAFF][ON_SITE]=1;
                RestrictionEffect[STAFF][OFF_SITE]=1;
                R0=1.2;
                Beta = (R0)/ MeanInfectiveDuration[INFECTIVE];
            }

            //Reset the FOI
            FOI[ON_SITE]=0;
            FOI[OFF_SITE]=0;

            //initializing FOI
            FOI[ON_SITE]                =                Beta                *
(double(Counter[RESIDENT][ON_SITE][INFECTIVE])*RestrictionEffect[RESIDENT][ON_
SITE]+double(Counter[STAFF][ON_SITE][INFECTIVE])*RestrictionEffect[STAFF][ON_S
ITE]) / (double(Size[STAFF])/double(NUM_SITES)+double(Size[RESIDENT]));
            FOI[OFF_SITE]= Beta * X[INFECTIVE] /double(N);

            //Draw, if this is smaller than dt, then a new infection occurs,
if not, no new infection occurs

if(FOI[ON_SITE]*(double(Counter[RESIDENT][ON_SITE][SUSCEPTIBLE])+double(Counte
r[STAFF][ON_SITE][SUSCEPTIBLE]))+FOI[OFF_SITE]*double(Counter[STAFF][OFF_SITE]
[SUSCEPTIBLE]) < 1e-10)
            {
                //cout << "everyone got infected" << endl;
                //Pause();
                breaked=true;
                break;
            }

            PotentialTimeNextInfection        =        LocalUpdateTime        +
```

```
ExponentialDeviate(1.0/
(FOI[ON_SITE]*(double(Counter[RESIDENT][ON_SITE][SUSCEPTIBLE])+double(Counter[
STAFF][ON_SITE][SUSCEPTIBLE]))+FOI[OFF_SITE]*double(Counter[STAFF][OFF_SITE][S
USCEPTIBLE])*RestrictionEffect[STAFF][OFF_SITE]));

            //Determining when the next event is
            if(pEventList.empty()== true)
            {
                TimeNextEvent=LARGE_NUMBER;
            }
            else
            {
                dum=(pEventList.top());
                TimeNextEvent=dum.GetTime();
            }

            //Processing Events
            if(PotentialTimeNextInfection < GlobalUpdateTime + dt)
            {
                int checker =1;
                while(PotentialTimeNextInfection > TimeNextEvent)
                {
                    ProcessEventOnList();
                    if(pEventList.empty()== true)
                    {

                        TimeNextEvent=LARGE_NUMBER;
                    }
                    else
                    {
                        dum=(pEventList.top());
                        TimeNextEvent=dum.GetTime();
                    }
                    if(checker >80)
                    {
                        cout << "more than 80 events happened in 1 dt" << endl;
                        Pause();
                    }
                    ++checker;
                }
                SelectInfectee();

                //Update Local time
                LocalUpdateTime= PotentialTimeNextInfection;
```

```
            }
            else
            {
                int checker =1;
                while(TimeNextEvent <= GlobalUpdateTime + dt)
                {
                    ProcessEventOnList();
                    if(pEventList.empty()== true)
                    {

                        TimeNextEvent=LARGE_NUMBER;
                    }
                    else
                    {
                        dum=(pEventList.top());
                        TimeNextEvent=dum.GetTime();
                    }
                    if(checker >80)
                    {
                        cout << "more than 80 events happened in 1 dt, current
size of EventList is " << pEventList.size() << endl;
                        Pause();
                    }
                    checker++;
                }

                //Update the Global Community
                dX[SUSCEPTIBLE] = -FOI[OFF_SITE]*X[SUSCEPTIBLE];
                dX[INFECTIVE]       =       FOI[OFF_SITE]*X[SUSCEPTIBLE]       -
X[INFECTIVE]/MeanInfectiveDuration[INFECTIVE];
                dX[REMOVED] = X[INFECTIVE]/MeanInfectiveDuration[INFECTIVE];

                for(int diseasestage = 0; diseasestage < NUM_DISEASE_STAGES;
++diseasestage)
                {
                    X[diseasestage] += dX[diseasestage]*dt;
                }

                //Update Global and Local time
                GlobalUpdateTime += dt;
                LocalUpdateTime = GlobalUpdateTime;

                //Shows the run
                //cout << GlobalUpdateTime << "\t" << X[SUSCEPTIBLE]/N << "\t"
```

```
<<        Counter[STAFF][OFF_SITE][SUSCEPTIBLE]        <<        "\t"        <<
Counter[RESIDENT][ON_SITE][SUSCEPTIBLE]
                //          << "\t" << FOI[ON_SITE] << "\t" <<FOI[OFF_SITE] <<
endl;
                //cout      <<      GlobalUpdateTime      <<      "\t"      <<
Counter[STAFF][ON_SITE][INFECTIVE]            <<            "\t"            <<
Counter[RESIDENT][ON_SITE][INFECTIVE]
                //        << "\t" << endl;
                //fprintf                                                (pFile,
"%f %f %f\r\n",GlobalUpdateTime,FOI[ON_SITE],FOI[OFF_SITE]);
            }

        }
        //Shows final size
        //cout                                                                <<
double(Counter[RESIDENT][ON_SITE][REMOVED])/double(Size[RESIDENT])  <<  "\t"  <<
(double(Counter[STAFF][OFF_SITE][REMOVED])                                    +
double(Counter[STAFF][ON_SITE][REMOVED]))/(Size[STAFF]) << endl;


if(double(Counter[RESIDENT][ON_SITE][REMOVED])/double(Size[RESIDENT])>0.1)
        {
            probnooutbreak++ ;
            sumoutbreak=                        sumoutbreak                       +
double(Counter[RESIDENT][ON_SITE][REMOVED])/double(Size[RESIDENT]);
        }

        //cout                                                                <<
double(Counter[RESIDENT][ON_SITE][REMOVED])/double(Size[RESIDENT])<< endl;
    }
    fprintf (pFile, "%f \r\n", double(sumoutbreak)/double(probnooutbreak));

    }
    fclose (pFile);
        return 0;
}
```