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ORIGINAL ARTICLE

A Vaccination Model for a Multi-City System

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Abstract A modelling approach is used for studying the effects of population vaccination on the epidemic dynamics of a set of n cities interconnected by a complex transportation network. The model is based on a sophisticated mover-stayer formulation of inter-city population migration, upon which is included the classical SIS dynamics of disease transmission which operates within each city. Our analysis studies the stability properties of the Disease-Free Equilibrium (DFE) of the full n-city system in terms of the reproductive number R_0. Should vaccination reduce R_0 below unity, the disease will be eradicated in all n-cities. We determine the precise conditions for which this occurs, and show that disease eradication by vaccination depend on the transportation structure of the migration network in a very direct manner. Several concrete examples are presented and discussed, and some counter-intuitive results found.

Keywords Vaccination · Network model · Epidemic model · Reproduction number

1 Introduction

Understanding how to control epidemics as they spread through populations is an issue of great concern in the present era of emerging and reemerging diseases (Riley 2007; Eames and Keeling 2002; Keeling and Eames 2005). Mathematical modelling approaches have much to contribute toward this important research challenge.

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In the past, mathematical modelling studies have been the inspiration behind a number of major epidemiological principles and they are being called upon more and more to assess and provide guidelines for public health and policy decision makers. The mathematical formulation of a disease's basic reproduction number R_0, for example, is now considered one of the foundation principles in epidemiology. Whether R_0 is less or more than unity determines whether a disease can, on average, reproduce itself in a susceptible population. Under conditions for which $R_0 > 1$, and thus above threshold, a disease can be expected to invade. The threshold has in fact become the basis of the now well-known herd immunity concept (Fine 1993), which states that it is only necessary to vaccinate a certain proportion of the population (as opposed to the entire population) to keep R_0 below threshold, and thereby prevent a disease from spreading. The herd immunity concept should be viewed as one of the major achievements of disease modelling, and constitutes the theoretical justification for mass immunization schemes that have been implemented across the world, saving uncountable lives.

Over the last decade, interest has turned to understanding the dynamics of a disease spreading through a meta-population network of cities. Such modelling studies attempt to take into account the network topology of the interconnected cities, including the structure and intensity of the travel links between them (Ruan et al. 2006; Riley 2007; Eames and Keeling 2002; Keeling and Eames 2005; Eubank et al. 2004; Lloyd and May 2001; Pastor-Satorras and Vespignani 2001; Fine 1993; Pastor-Satorras and Vespignani 2001, 2002; Brockmann et al. 2006). Here, we focus on modelling vaccination as a method of disease control using a multi-city model that treats the travel of individuals between cities in a very general way. There are three layers to the model. The first is a "mover-stayer" mobility model which describes how individuals travel through a network of cities. This incorporates detailed travel patterns and allows a subset individuals to always stay in their cities of residence while others are free to travel around the network eventually to return to their city of origin. The second layer is a set of epidemic models that characterise the disease dynamics providing equations that describe the numbers of susceptible and infected individuals present in each city at any given time. Finally, the third layer adds a vaccination scheme, and keeps track of the number of vaccinated individuals to be found in any city. Although some previous studies have analysed mobility-epidemic models, this is the first attempt that we are aware of with a vaccination scheme that retains the full details of the city-network. We would suppose the same model may have applications for studying antivirus dynamics in computer networks. The epidemic model is of the SIS type, where the susceptible individual (S) becomes infected after contact with infected individuals (I). Upon recovery from the disease, infected individuals return again to the susceptible pool, thus closing the SIS loop. The SIS framework has been widely used for studying disease dynamics both for meta-population networks based on mobility models (Sattenspiel and Dietz 1995; Arino and van den Driessche 2003, 2004; Ruan et al. 2006), and also for simple vaccination models (Hadeler and Castillo-Chavez 1995, 1997; Brauer 2008; Kribs-Zaleta and Velasco-Hernandez 2000; Kribs-Zaleta and Martcheva 2002). The SIS with vaccination model has in the past been considered a useful tool for studying pertussis, tuberculosis (Pastor-Satorras and Vespignani 2001), hepatitis B (Kribs-Zaleta and Martcheva 2002), and gonorrhea (Hethcote and Yorke 1984). The paper is

structured as follows. We first describe earlier models that deal with intercity travel, including both the mobility model (Sect. 1), and the epidemic model (Sect. 2) (Sattenspiel and Dietz 1995; Arino and van den Driessche 2003, 2004; van den Driessche and Watmough 2002). In Sect. 3, we formulate the vaccination model for the case of multiple cities connected in an arbitrary network. In the fourth section, we analyse the model, determine its disease free equilibrium (DFE), find the system's "next generation matrix", and derive an expression for the reproductive number R_0. In the fifth section, three examples are given with the aim of demonstrating the interplay between the transmission coefficients in the vaccination model and the stability of the DFE via determination of R_0. The examples show different applications of the theoretical ideas developed, sometimes with non-intuitive outcomes.

2 Model Development

2.1 The Mobility Model

The first layer of the multi-city epidemic model analysed here is based on the mobility model of Sattenspiel and Dietz (1995). The latter considers the transportation of individuals between n-cities, whereby each city has a component of its population that remains stationary, while the remainder is free to move to other cities across the city network. As such, it is referred to as a mover-stayer model. We follow Arino and van den Driessche (2003) who extended the basic mobility model of Sattenspiel and Dietz (1995). Consider a network of n-cities. The number of *residents* of city-i, $N_i^r(t)$ at time t, are all those individuals who were born and who normally live in city-i. Of these, $N_{ii}(t)$ are the number of residents that are actually present in city-i at time t, while $N_{ij}(t)$ is the number of travellers from city-i who are visiting city-j at time t. We can thus write the resident population of city-i as

$$N_i^r = \sum_{j=1}^{n} N_{ij}. \tag{1}$$

Similarly, the number of individuals (residents and travelers) who are physically present in city i at time t, is given by

$$N_i^p = \sum_{j=1}^{n} N_{ji}. \tag{2}$$

Following Sattenspiel and Dietz (1995), suppose that the per capita rate per unit time of residents of city i that leave the city is given by the outward bound transportation coefficient $g_i \geq 0$, and the fraction $m_{ji} \geq 0$ of outgoing individuals travel to city j. Note that $m_{ii} = 0$ and $\sum_{j=1}^{n} m_{ji} = 1$. The outgoing mobility matrix $M = [g_i m_{ji}]$ specifies the rate of outgoing travellers from city-i to city-j. It also necessary to take into account $r_{ij} \geq 0$, the per capita rate of residents of city-i that are in city-j who return back to city i. In this scheme, an individual from city-i who travels to city-j must return to city-i before he can move on to city-k.

The Arino and van den Driessche (2003) model also takes into account the birth and death process. The per capita rate of births in each home city is given by $d > 0$, while it is assumed that individuals travelling outside their home city do not give birth. The per capita death rate for all individuals anywhere is also d. Putting all this together, yields the ordinary differential equations that describe the dynamics of the population, first in terms of residents of city-i who are present in city-i only (Arino and van den Driessche 2003):

$$\frac{dN_{ii}}{dt} = d\big(N_i^r - N_{ii}\big) + \sum_{j=1}^{n} r_{ij}N_{ij} - g_i N_{ii} \tag{3}$$

Similarly, the dynamics of residents from city-i who travelled to city-j $(i \neq j)$ is given by

$$\frac{dN_{ij}}{dt} = g_i m_{ji} N_{ii} - r_{ij}N_{ij} - dN_{ij} \tag{4}$$

It is possible to show from manipulating the above equations that the resident population $N_i^r = \sum_{j=1}^{n} N_{ij} = c$, a constant, which is a property that is used shortly. In contrast N_i^p is a variable quantity.

For $d > 0$, subject to the initial values $N_{ij} \geq 0$ at $t = 0$ with fixed $N_i^r > 0$, it is not hard to show that the above model has the following unique equilibrium:

$$\hat{N_{ii}} = \left(\frac{1}{1 + g_i C_i}\right) N_i^r \tag{5}$$

and for $j \neq i$

$$\hat{N_{ij}} = g_i \frac{m_{ji}}{d + r_{ij}} \left(\frac{1}{1 + g_i C_i}\right) N_i^r \tag{6}$$

where $C_i = \sum_{k=1}^{n} \frac{m_{ki}}{d + r_{ik}}$ for $i = 1, \ldots, n$. Arino and van den Driessche (2003) proved that the equilibrium is globally stable.

2.2 The Epidemic Model

We now describe the standard SIS epidemic framework for the network of n-cities with an underlying mobility model. Define S_{ij} and I_{ij} as the number of susceptible and infective residents from city i, who are now present in city-j at time-t, respectively.

We restrict our attention to susceptibles originating from city-i and travelling to city-j. These susceptibles increase the new infectives in city-j by a rate:

$$\sum_{k=1}^{n} \kappa_j \beta_{ikj} \frac{S_{ij} I_{kj}}{N_j^p}. \tag{7}$$

Here, the disease transmission rate $\beta_{ikj} > 0$ is the proportion of contacts that meet in city-j, between susceptibles originating from city-i and infectives that originate from

city-k that actually result in transmission of the disease. The total number of contacts in city j per day is set as $\kappa_j > 0$. The disease recovery rate is the same for all cities and is set as $\gamma > 0$, which means that the average infection time is $1/\gamma$ days.

We can now write down the various equations. The dynamics of the susceptibles and infectives originating from and residing in city-i (with $i = 1, \ldots, n$), can be modelled by:

$$\frac{dS_{ii}}{dt} = \sum_{k=1}^{n} r_{ik} S_{ik} - g_i S_{ii} - \sum_{k=1}^{n} \kappa_i \beta_{iki} \frac{S_{ii} I_{ki}}{N_i^p} + d\left(N_i^r - S_{ii}\right) + \gamma I_{ii} \tag{8}$$

$$\frac{dI_{ii}}{dt} = \sum_{k=1}^{n} r_{ik} I_{ik} - g_i I_{ii} + \sum_{k=1}^{n} \kappa_i \beta_{iki} \frac{S_{ii} I_{ki}}{N_i^p} - (\gamma + d) I_{ii} \tag{9}$$

Similar equations can be constructed that describe the dynamics of the variables S_{ij} and I_{ij}. For $j \neq i$,

$$\frac{dS_{ij}}{dt} = g_i m_{ji} S_{ii} - r_{ij} S_{ij} - \sum_{k=1}^{n} \kappa_j \beta_{ikj} \frac{S_{ij} I_{kj}}{N_j^p} - d S_{ij} + \gamma I_{ij} \tag{10}$$

$$\frac{dI_{ij}}{dt} = g_i m_{ji} I_{ii} - r_{ij} I_{ij} + \sum_{k=1}^{n} \kappa_j \beta_{ikj} \frac{S_{ij} I_{kj}}{N_j^p} - (\gamma + d) I_{ij} \tag{11}$$

Note that referring back to Eqs. (3) and (4) of the mobility model corroborates that

$$\dot{N}_{ij} = \dot{S}_{ij} + \dot{I}_{ij},$$

and thus the epidemic model is fully consistent with the mobility model. The epidemic model just described always has a Disease Free Equilibrium (DFE) whereby $I_{ij}^* = 0$ and $S_{ij}^* = \hat{N}_{ij}$ and the disease is eradicated in each city. We seek to find conditions for which the DFE is locally stable. Various properties of the equilibria of the above model may be described in terms of the connected components of the transportation network (i.e., the outgoing mobility matrix M). A connected component is a set of cities connected in a fashion such that it is possible to reach any city from any other city. If the entire outgoing mobility matrix M is irreducible then all cities in the network can reach every city. Arino and van den Driessche (2003) showed rigorously that for any connected component, it is not possible to have an equilibrium in which one city is maintained without any disease while other connected cities remain with endemic disease. Thus, a disease that persists in a single city will continuously infect every other city in the connected component.

3 The Epidemic Model with Vaccination

We extend the above SIS network model to include vaccination of individuals in manner similar to Kribs-Zaleta and Velasco-Hernandez (2000). This requires dividing the population of each city now into three classes—S_{ij}—susceptibles, I_{ij}—infectives, V_{ij}—vaccinated, respectively. Residents from city i who are now in city j at time t are thus

$$N_{ij} = S_{ij} + I_{ij} + V_{ij}$$

for $i, j = 1, \ldots, n$.

It is assumed that vaccinated individuals are still capable of being infected if the vaccine is not completely effective. We thus let σ represent the effectivity of the vaccine; $\sigma = 0$ implies the vaccine is completely effective in preventing infection,while $\sigma = 1$ means that the vaccine is completely ineffective. To include this new source of infections arising from inefficient vaccination, the rate of new infections in Eq. (9) and Eq. (11) needs to be modified to

$$\sum_{k=1}^{n} \kappa_j \beta_{ikj} \frac{(S_{ij} + \sigma V_{ij}) I_{kj}}{N_j^p} \tag{12}$$

Two other parameters are required to characterize this vaccination scheme: ϕ—defines the rate at which the newborn or infant population is vaccinated. $\phi = 1$ implies all newborn susceptibles are vaccinated, while $\phi = 0$ implies the absence of vaccination altogether. The parameter θ models the rate at which the vaccination wears off or wanes, and controls the number of individuals reentering the susceptible class.

The dynamics of the vaccinated people originating from and residing in city-i are thus given by

$$\frac{dV_{ii}}{dt} = \sum_{k=1}^{n} r_{ik} V_{ik} - g_i V_{ii} + \phi_i S_{ii} - \sum_{k=1}^{n} \kappa_i \beta_{iki} \frac{\sigma V_{ii} I_{ki}}{N_i^p} - (\theta_i + d) V_{ii}$$

Taking this further, it is possible to write the full equations for the epidemic-mobility model with vaccination. We take advantage of the fact that the number of equations can be reduced by rewriting

$$S_{ij} = N_{ij} - I_{ij} - V_{ij}.$$

Since N_{ij} is known from the mobility model, the equations describing the susceptible dynamics are redundant and may be eliminated. Now the full model becomes

$$\begin{aligned} \frac{dI_{ii}}{dt} &= \sum_{k=1}^{n} r_{ik} I_{ik} - g_i I_{ii} + \sum_{k=1}^{n} \kappa_i \beta_{iki} \frac{N_{ii} - I_{ii} + V_{ii}(\sigma - 1)}{N_i^p} I_{ki} \\ &\quad - (\gamma + d) I_{ii} \end{aligned} \tag{13}$$

$$\begin{aligned} \frac{dV_{ii}}{dt} &= \sum_{k=1}^{n} r_{ik} V_{ik} - g_i V_{ii} + \phi_i (N_{ii} - I_{ii} - V_{ii}) - \sum_{k=1}^{n} \kappa_i \beta_{iki} \frac{\sigma V_{ii} I_{ki}}{N_i^p} \\ &\quad - (\theta_i + d) V_{ii} \end{aligned} \tag{14}$$

for $j \neq i$,

$$\begin{aligned} \frac{dI_{ij}}{dt} &= g_i m_{ji} I_{ii} - r_{ij} I_{ij} + \sum_{k=1}^{n} \kappa_j \beta_{ikj} \frac{N_{ij} - I_{ij} + V_{ij}(\sigma - 1)}{N_j^p} I_{kj} \\ &\quad - (\gamma + d) I_{ij} \end{aligned} \tag{15}$$

$$\frac{dV_{ij}}{dt} = g_i m_{ji} V_{ii} - r_{ij} V_{ij} - \sum_{k=1}^{n} \kappa_j \beta_{ikj} \frac{\sigma V_{ij} I_{kj}}{N_j^p} - (\theta_i + d) V_{ij} + \phi_i (N_{ij} - I_{ij} - V_{ij}). \tag{16}$$

The analysis that follows relates to the reduced equations (13)–(16).

4 Analysis

We first show that system (13)–(16) has a disease-free equilibrium. Setting $I^* = 0$ in Eqs. (14) and (16) gives

$$\sum_{k=1}^{n} r_{ik} V_{ik}^* - V_{ii}^* (g_i + \phi_i + \theta_i + d) + \phi_i N_{ii} = 0 \tag{17}$$

$$g_i m_{ji} V_{ii}^* - V_{ij}^* (r_{ij} + \theta_i + d + \phi_i) + \phi_i N_{ij} = 0, \quad j = 1, \ldots, n, \, j \neq i. \tag{18}$$

Since the coefficients of V_{ij} form an M matrix (Berman and Plemmons 1979), then Eqs. (17)–(18) must admit a unique positive solution $V_i^* = (V_{i1}^*, \ldots, V_{in}^*)$. Thus, in the same notation

$$P_0 = \left(V_1^*, I_1^*, \ldots, V_n^*, I_n^*\right),$$

where $I_i^* = 0$, and we have arrived at the disease-free equilibrium.

It is now possible to use the methods of van den Driessche and Watmough (2002) to calculate the reproductive number R_0. Set $w_{ii}^I = (\gamma + d + g_i)$ and $w_{ij}^I = (\gamma + d + r_{ij})$ for $i \neq j$ and also ordering the infective variables as

$$I_{11}, \ldots, I_{1n}, I_{21}, I_{22}, \ldots, I_{1n}, \ldots I_{nn}.$$

This gives the diagonal block matrix $V = diag(V_{ii})$, where for $i = 1, \ldots, n$, V_{ii} is the $n \times n$ matrix:

$$V^{ii} = \begin{pmatrix} w_{i1}^I & 0 & \ldots & -g_i m_{1i} & 0 & \ldots & 0 \\ 0 & -w_{i2}^I & \ldots & -g_i m_{2i} & 0 & \ldots & 0 \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ -r_{i1} & -r_{i2} & \ldots & w_{ii}^I & -r_{i,i+1} & \ldots & -r_{in} \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & \ldots & -g_i m_{ni} & \ldots & 0 & w_{in}^I \end{pmatrix}$$

The matrix V^{ii} characterizes the loss of infected individuals from city-i in the n cities and the travel by infected individuals of city-i among the n-cities.

Let F be the block matrix with n^2 blocks, where each block F_{ij} is $n \times n$ diagonal and has the form $F_{ij} = diag(f_{ijq})$ where

$$f_{ijq} = \kappa_q \beta_{ijq} \frac{\hat{N_{iq}} + \hat{V_{iq}}(\sigma - 1)}{\hat{N_q^p}} \tag{19}$$

for $q = 1, \ldots, n$.

Recall that for $\sigma = 1$, the vaccination has no effect, and would represent the multi-city epidemic model without vaccination, as studied in Arino and van den Driessche (2003). Since V^{-1} is block diagonal, FV^{-1} can be written in block form, where the i, j block is $F_{ij}V_{jj}^{-1}$. FV^{-1} is the "next generation" matrix of the full model (Diekmann et al. 1990; Diekmann and Heesterbeek 2000; van den Driessche and Watmough 2002) and its spectral radius gives the basic reproduction number for the system (13)–(16), namely

$$R_0 = \rho\left(FV^{-1}\right). \tag{20}$$

The above formula allows evaluation of R_0, and thus is the key to determining local stability of the DFE for the full system under vaccination.

5 Applications

We now discuss three examples that make use of the vaccination model and Eq. (20) for evaluating R_0 to demonstrate potential applications.

5.1 The Effect of Travel

Before examining the effects of incorporating transportation between two cities, we first consider a single isolated city as a reference. Rewriting Eqs. (13) and (14) (taking $i = 1$, $j = 1$, and $r_{ij} = 0$, $g_i = 0$, $I_{i\neq j} = 0$ and zeroing inter-city transmission terms), we obtain

$$\frac{dI_{11}}{dt} = \kappa_1\beta_{111}\frac{N_{11} - I_{11} + V_{11}(\sigma - 1)}{N_1^p}I_{11} - (\gamma + d)I_{11}$$

$$\frac{dV_{11}}{dt} = \phi_i(N_{11} - I_{11} - V_{11}) - (\theta_1 + d)V_{11}.$$

Setting $I_{11} = 0$, $\dot{V} = 0$, $\phi = \phi_1$, $\theta = \theta_1$, $\beta = \beta_{111}$, $N_{11} = N_1^p$, then at the infection free equilibrium, and after some rearrangement, the reproduction number of a single city is found to be

$$R_0 = \frac{\kappa\beta}{\gamma + d}\frac{\theta + d + \sigma\phi}{\phi + \theta + d} \tag{21}$$

The same result is also found in Kribs-Zaleta and Velasco-Hernandez (2000).

Consider now transportation between two such cities. Using the notation of the previous section, we proceed to calculate the reproduction number of the full system by determining V and F from Eq. (19) and Eq. (20), namely

$$V = \begin{pmatrix} g_1 + \gamma + d & -r_{12} & 0 & 0 \\ -g_1 & r_{12} + \gamma + d & 0 & 0 \\ 0 & 0 & r_{21} + \gamma + d & -g_2 \\ 0 & 0 & -r_{21} & g_2 + \gamma + d \end{pmatrix}$$

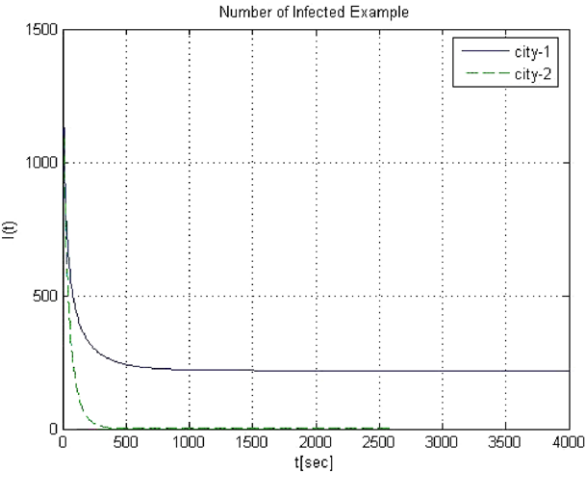

Fig. 1 Two isolated cities with absence of transportation ($g_1 = g_2 = 0, r_{12} = r_{21} = 0$. City-2 is given a higher rate of vaccination than city-1 and also has a lower transmission rate with $\phi_1 = 0.01$, $\phi_2 = 0.1$, $\beta_1 = 0.059$, $\beta_2 = 0.048$. For these parameters, $R_0^1 = 1.1059$, $R_0^2 = 0.6541$ so that the DFE is unstable

and,

$$F = \begin{pmatrix} \frac{\kappa_1\beta_1(N_{11}+V11(\sigma-1))}{N_{1p}} & 0 & \frac{\kappa_1\beta_1(N_{11}+V11(\sigma-1))}{N_{1p}} & 0 \\ 0 & \frac{\kappa_2\beta_2(N_{12}+V12(\sigma-1))}{N_{2p}} & 0 & \frac{\kappa_2\beta_2(N_{12}+V12(\sigma-1))}{N_{2p}} \\ \frac{\kappa_1\beta_1(N_{21}+V21(\sigma-1))}{N_{1p}} & 0 & \frac{\kappa_1\beta_1(N_{21}+V21(\sigma-1))}{N_{1p}} & 0 \\ 0 & \frac{\kappa_2\beta_2(N_{22}+V22(\sigma-1))}{N_{2p}} & 0 & \frac{\kappa_2\beta_2(N_{22}+V22(\sigma-1))}{N_{2p}} \end{pmatrix}$$

Hence,

$$R_0 = \rho\left(FV^{-1}\right).$$

We follow both Arino and van den Driessche (2003), McCluskey et al. (2003) and Hethcote and Yorke (1984) (the latter in a study of gonorrhea vaccination) who used the following parameter values: $\sigma = 0.5$ (vaccine is 50 % effective), $\kappa_1 = \kappa_2 = 1$, $\theta_1 = \theta_2 = 0.01$ (average vaccine waning time 10 years), $\gamma = 1/25$ (average infectious period 25 days), $d = 1/(75 * 365)$ (average lifespan 75 years), $N_{1r} = N_{2r} = 1500$, $m_{12} = m_{21} = 1$, $r_{12} = r_{21} = 0.05$. City 2 is given a higher rate of vaccination than city 1 and also has a lower transmission rate with $\phi_1 = 0.01$, $\phi_2 = 0.1$ (daily vaccination rates), $\beta_1 = 0.059$, $\beta_2 = 0.048$ (transmission rates) (Arino and van den Driessche 2003; McCluskey et al. 2003).

For these parameters, in the absence of transportation, $g_1 = g_2 = 0$, the two cities have reproduction numbers $R_0^1 = 1.1059$, $R_0^2 = 0.6541$ as obtained from Eq. (21). Thus, the disease persists in the first city, which has the lower vaccination rate, but goes extinct in the second city, as shown in the model simulations of Fig. 1. The full system thus fails to converge to the DFE.

In making these claims, we have assumed that the second city converges to the disease-free equilibrium (DFE) and it is in fact the unique attractor. This may not be the case if the model has a backward bifurcation as discussed in Kribs-Zaleta and Velasco-Hernandez (2000). According to their work, the incorporation of vaccination can lead to two possibilities depending on parameters: either the DFE is globally

stable, or it competes with another locally stable endemic equilibrium. Their analysis led to the following theorem:

(i) If $(d+\theta+\sigma\phi)^2 < (d+\gamma)\sigma(1-\sigma)\phi$ and $\beta_b < \beta < \beta_0$, then two endemic equilibria exist, one of which is locally stable and competes with the locally stable disease-free equilibrium;
(ii) otherwise, the disease-free equilibrium is the unique attractor when $R_0 < 1$.

For our parameters values:

$$(d+\theta+\sigma\phi)^2 = 0.0036$$

and

$$(d+\gamma)\sigma(1-\sigma)\phi = 0.001$$

so, the inequality is clearly violated in (i) and we therefore accept the conclusion in (ii). Thus, for our parameters, the DFE of this model of vaccination is the unique attractor.

We now suppose the cities are connected together via transportation, $g_1 = g_2 = 0.1$, which implies that about 10 % of the population leaves each city per day(we note that g_i is only an approximation of the actual fraction leaving since technically it is a per capita rate coefficient). As calculated above from V and F, the reproduction number for the full system is $R_0 = 0.8599$. Since $R_0 < 1$, the DFE is stable leading to extinction of the disease in both cities as shown in the model simulations of Fig. 2. Thus, the transportation of vaccinated individuals from city-2 to city-1 led to eradication of the disease that otherwise would have been present were there no inter-city travel. It is interesting to calculate the value of the critical outward bound transportation coefficient—g_c ($g_c = g_1 = g_2$), the point where the two cities switch so that they both sit at the DFE. Numerical calculations plotted in Fig. 3 show that the critical transmission rate is $g_c \approx 0.0075$. A simple calculation shows that this corresponds to a reproduction number—$R_0 = 1$, as would be expected. So one can conclude that even a small movement of the order of 1 % of the population leaving the city per day, bring the change in the state of system of two cities from non-DFE state to DFE state.

5.2 Two-Group Versus a Two-City Vaccination Model

Kribs-Zaleta and Velasco-Hernandez (2000) describe an SIS model with vaccination for two interacting groups of individuals. They assume that the two groups are fully mixing with one another and every individual from one group can equally come into contact with members of the other group. This is quite different from the multi-city model outlined here, since for the mover-stayer model, some residents may never leave their city of origin, and thus will never mix with individuals from other cities. It is interesting to compare conclusions from the two-group mixing model as opposed to the more realistic two-city mover-stayer model.

Kribs-Zaleta and Velasco-Hernandez (2000) determine the reproduction number for an isolated city or single group with vaccination, and this turns out to be exactly

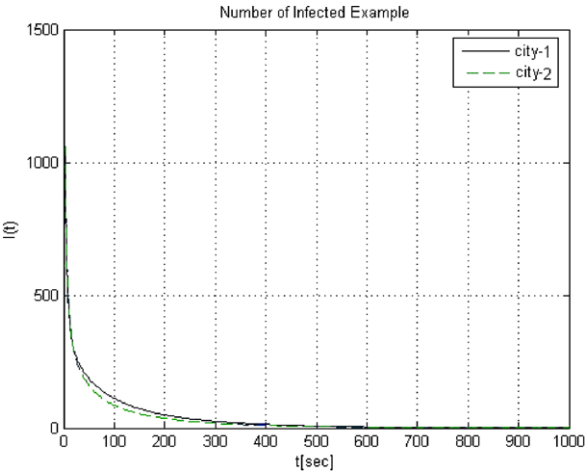

Fig. 2 Active transportation between the two cities ($g_1 = g_2 = 0.1$, $r_{12} = r_{21} = 0.05$). Otherwise, parameters are the same as in previous figure. The reproduction number for the system is $R_0 = 0.8599$, thus the two city system has a stable DFE

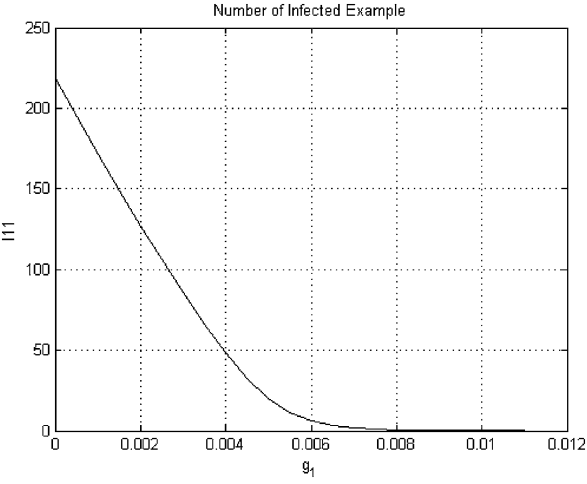

Fig. 3 Plot of I_{11} with increasing values of g_1. The critical value of g is $g_c \approx 0.0075$ that gives a reproduction number—$R_0 = 1$. When $g_1 > g_c c$, the whole system is in the DFE state

the same as that predicted by our single-city model, as would be expected (see previously paragraph Eq. (21)). Consider again the two isolated cities example given above with the same parameters. There the reproduction number for the first city is $R_0^1 = 1.106$ and for the second city is $R_0^2 = 0.654$.

Kribs-Zaleta and Velasco-Hernandez (2000) analysis finds that the reproduction number for the system of two cities, treated as mixing groups, is given by

$$R(\phi) = R_1(\phi_1)\frac{N_1}{N} + R_2(\phi_2)\frac{N_2}{N}$$

where N_1 and N_2 are the sizes of the two groups, assumed constant, and $N = N_1 + N_2$. Based on the parameters we are using here, the above expression corresponds to a reproduction number of $R_0 = 0.88$, which would imply the system of two mixing groups will reach the stable DFE. However, according to our two-city mover-stayer model in Eq. (20), using a transportation coefficient $g_1 = g_2 = 0.1$, we

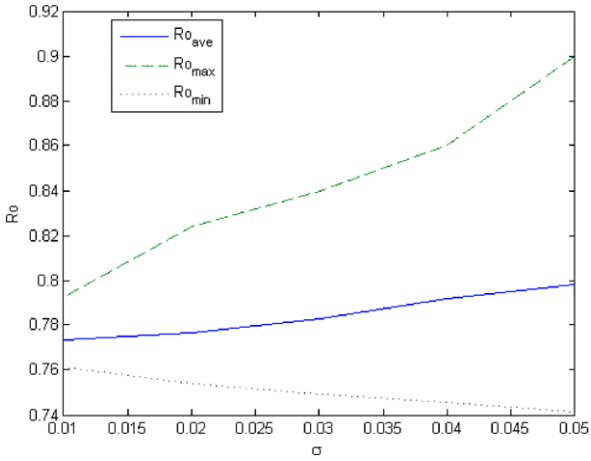

Fig. 4 The proportions ϕ_i are normally distributed random variables with mean $\phi_i = \phi$ and standard deviation—σ. For each σ three values calculated—$\bar{R}_0$, 95 % of $R_{0\max}$, $R_{0\min}$

obtain $R_0 = 1.1047$ (based on $r_{12} = 0.07$, $r_{21} = 0.05$). This would imply the two city mover-stayer system lacks a stable DFE. Thus, we reach the important finding that the manner in which transportation routes are modelled greatly affects our conclusions regarding vaccination effectiveness.

5.3 Comparison Between Constant Vaccination and Heterogeneous Vaccination

Examine now how heterogeneous vaccination of a set of cities might affect the epidemic threshold. We consider five cities and vaccinate a fraction ϕ_i of each population ($i = 1, 2, \ldots, 5$). The proportions ϕ_i are normally distributed random variables with mean $\phi_i = \phi$ and standard deviation σ. Thus, σ controls the heterogeneity of the vaccination, with $\sigma = 0$ implying that all cities are vaccinated equally. For the case of homogeneous vaccination, when $\phi = 0.1$ and $\sigma = 0$, the system has the reproduction number—$R_0 = 0.7728$. For heterogeneous vaccination, for each value of $\sigma > 0$, we study 100,000 different random systems and calculate the average $\bar{R}_0$. As Fig. 4 shows, in all cases the average $\bar{R}_0$ is always greater than the R_0 obtained for homogeneous vaccination. In this sense, the heterogeneity has a tendency to boost R_0, and thus enhances the possibility of escaping from the DFE. In Fig. 4, for each value of ϕ, we show the envelope of values for the reproductive number bounded below by $R_{0\min}$ and above by $R_{0\max}$. The latter designates the point where all but 5 % of the highest values fall below. Note that constant vaccination is always better than the mean value, always having a smaller reproductive number R_0. In practice results, such as those shown in Fig. 4 may help health authorities as they are not able to provide the precise vaccination coverage as they might want. The figure shows the repercussions of uncertainties in coverage on the epidemic threshold.

6 Discussion

We have outlined a method for analysing the effects of vaccination in a mobility-SIS-epidemic model for multiple cities connected in a network. After formulating

the model, we derive expressions for the "next generation matrix" and R_0. This allowed us to investigate a number of scenarios as to precisely how different vaccination strategies and different network structures affect disease eradication. The role of human mobility patterns is understood to be one of the major factors responsible spatial disease propagation, and the last decade has witnessed a dearth of studies that attempt to increase our understanding of these patterns (Brockmann et al. 2006). It has become clear that the mobility model of the type proposed by Sattenspiel and Dietz (1995) has more realistic features than simple spatial diffusion, especially in the manner in which they capture the limitations imposed by "stayers" who never leave their city of origin, and thus slow down disease spread. In addition, it has become clear that network topology plays a crucial role. Thus, scale-free type networks in which there are a few cities that act as hubs, will tend to enhance disease persistence as compared to random Erdos Renyi networks which have more defined threshold dynamics. The reader is also referred to the work of Arino and van den Driessche (2006) and Arino (2009), Arino et al. (2012) for recent applications and advances of this methodology. The framework we have proposed should facilitate a deeper investigation into these more complex phenomena. We are currently in the process of exploring these interesting research directions.

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References

Arino, J. (2009). Diseases in metapopulations. In: *Modeling and dynamics of infectious diseases. Series in contemporary applied mathematics* (Vol. 11, 65–123).

Arino, J., & van den Driessche, P. (2003). A multi-city epidemic model. *Math. Popul. Stud.*, *10*, 175–193.

Arino, J., & van den Driessche, P. (2004). The basic reproduction number in a multi-city compartmental epidemic model. *Lect. Notes Control Inf. Sci.*, *294*, 100.

Arino, J., & van den Driessche, P. (2006). Metapopulations epidemic models. A survey. *Fields Inst. Commun.*, *48*, 1–12.

Arino, J., Ducrot, A., & Zongo, P. (2012). A metapopulation model for malaria with transmission-blocking partial immunity in hosts. *J. Math. Biol.*, *64*, 423–448.

Berman, A., & Plemmons, R. J. (1979). *Nonnegative matrices in the mathematical sciences*. San Diego: Academic Press.

Brauer, F. (2008). Epidemic models with heterogeneous mixing and treatment. *Bull. Math. Biol.*, *70*, 1869–1885.

Brockmann, D., et al. (2006). The scaling laws of human travel. *Nature*, *439*, 462–465.

Diekmann, O., & Heesterbeek, J. A. P. (2000). *Mathematical epidemiology of infectious diseases: model building, analysis and interpretation*. New York: Wiley.

Diekmann, O., et al. (1990). On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations. *J. Math. Biol.*, *28*, 365.

Eames, K. T., & Keeling, M. J. (2002). Modeling dynamic and network heterogeneities in the spread of sexually transmitted diseases. *Proc. Natl. Acad. Sci. USA*, *99*(20), 13330–13335.

Eubank, S., et al. (2004). Modelling disease outbreaks in realistic urban social networks. *Nature*, *429*, 180–184.

Fine, P. E. (1993). Herd immunity: history, theory, practice. *Epidemiol. Rev.*, *15*, 265–302.

Hadeler, K. P., & Castillo-Chavez, C. (1995). A core group model for disease transmission. *Math. Biosci.*, *128*, 41–55.

Hadeler, K. P., & van den Driessche, P. (1997). Backward bifurcation in epidemic control. *Math. Biosci.*, *146*, 15–35.

Hethcote, H. W., & Yorke, J. A. (1984). *Lecture notes in biomathematics: Vol. 56*. *Gonorrhea transmission dynamics and control*. Berlin: Springer.

Keeling, M. J., & Eames, K. T. (2005). Networks and epidemic model. *J. R. Soc. Interface*, *2*, 295–307.

Kribs-Zaleta, C., & Martcheva, M. (2002). Vaccination strategies and backward bifurcation in an age-since-infection structured model. *Math. Biosci.*, *177*, 317–332.

Kribs-Zaleta, C. M., & Velasco-Hernandez, J. X. (2000). A simple vaccination model with multiple endemic states. *Math. Biosci.*, *164*, 183–201.

Lloyd, A. L., & May, R. M. (2001). How viruses spread among computers and people. *Science*, *292*, 1316–1317.

McCluskey, C.C., et al. (2003). Global results for an epidemic model with vaccination that exhibits backward bifurcation. *SIAM J. Appl. Math.*, *64*(1), 260–276.

Pastor-Satorras, R., & Vespignani, A. (2001). Epidemic spreading in scale-free networks. *Phys. Rev. Lett.*, *86*, 3200–3203.

Pastor-Satorras, R., & Vespignani, A. (2001). Epidemic dynamics and endemic states in complex networks. *Phys. Rev. E, Stat. Phys. Plasmas Fluids Relat. Interdiscip. Topics*, *63*, 066117.

Pastor-Satorras, R., & Vespignani, A. (2002). Immunization of complex networks. *Phys. Rev. E, Stat. Phys. Plasmas Fluids Relat. Interdiscip. Topics*, *65*, 036104.

Riley, S. (2007). Large-scale spatial-transmission models of infectious diseases. *Science*, *316*, 1298–1301.

Ruan, S., et al. (2006). The effect of global travel on the spread of Sars. *Math. Biosci. Eng.*, *3*, 205–218.

Sattenspiel, L., & Dietz, K. (1995). A structured epidemic model incorporating geographic mobility among regions. *Math. Biosci.*, *128*, 71–91.

van den Driessche, P., & Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math. Biosci.*, *180*, 29–48.