

The impact of psychology on the effectiveness of voluntary vaccination against infectious diseases in networks

by

Chad R. Wells

A Thesis
presented to
The University of Guelph

In partial fulfilment of requirements
for the degree of
Ph.D.
in
Mathematics and Statistics

Guelph, Ontario, Canada

© Chad R. Wells, September, 2012

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Behaviour is often neglected when modelling vaccination policies. This thesis shows the importance of incorporating behaviour in vaccination models of the impact of vaccines on disease dynamics. This thesis consists of three projects pertaining to voluntary vaccination in a network setting. The first project focuses on the effectiveness of voluntary ring vaccination under the presence of imitation. The contacts of a single index case vaccinate when symptoms first appear. We assume the contacts are unable to transmit infection to one another; however, we assume they are able to share their vaccination strategies. Under the presence of strong imitation, the effectiveness of voluntary ring vaccination becomes unpredictable. The second project focuses on the impact of personal experiences on voluntary influenza vaccination in a uniform network. Vaccination behaviour is based upon past infection and vaccination experiences, which creates a feedback loop between incidence and behaviour. Long-term memory acts as a stabilizing factor; however, long-term memory also decreases perceived vaccine efficacy. Vaccines conferring slowly waning immunity decrease vaccination coverage, leading to sporadic outbreaks in the absence of non-influenza-like-illness (niILI). Our results show evidence of vaccination strategy correlations being formed in the absence of imitation through past experiences. Allowing niILI to be mistaken for true influenza breaks up the strategy correlations, while stabilizing dynamics. The final model focuses on vaccination strategies targeting superspreaders, with the option of distributing economic incentives. We take a more psychological approach to influenza vaccination behaviour, where transmission of influenza occurs on an empirically based network. On average, superspreaders view the vaccine to be less effective; however,

superspreaders still find vaccination more appealing because they are at a greater risk of becoming infected. The incorporation of behaviour leads to superspreaders strategies to become less effective due to policy resistance; neglecting behaviour can lead to an overestimation of reduction of incidence. Public health officials should be concerned about the policy resistance and decreased perceived vaccine efficacy among superspreaders. The effectiveness of the vaccination or control policies could be diminished by the presence of behaviour, even when pro-active preventative measures are implemented by public health.

Acknowledgements

I would like to thank all of my collaborators and committee members for all of their input and guidance in the projects contained in this thesis. Special thanks to my advisor and mentor Chris Bauch for all of his support and guidance in reaching my goals.

I would also like to thank my wife, family and friends for all of their support over these past three years.

Dedication

To my loving and supporting wife Amanda

Table of Contents

List of Tables	x
List of Figures	xiii
1 Introduction	1
1.1 Disease Burden: Historical and Current	2
1.2 Infectious Disease Modelling	4
1.3 Network Modelling	12
1.3.1 Network Characteristics	12
1.3.2 Types of Networks	14
1.3.3 Modelling Infectious Disease Transmission on a Network	18
1.4 Vaccination	24
1.5 Modelling Behaviour	29
1.6 Objectives	32
2 Impact of imitation processes on the effectiveness of ring vaccination	57
2.1 Introduction	59
2.2 Model	62
2.2.1 Simple Stochastic Model	62
2.2.2 Distributed Stochastic Model	68
2.2.3 Distributed Stochastic Model with Imitation	68

2.2.4	Simulation Design	69
2.3	Results	69
2.3.1	Simple Stochastic Model	70
2.3.2	Distributed Stochastic Model	71
2.3.3	Distributed Stochastic Model with Imitation	72
2.4	Discussion	80
2.A	Derivation of the Payoff Functions	87
2.B	Simulation Algorithm	93
2.C	Correction	94
2.C.1	Results	95
3	The impact of personal experiences with infection and vaccination on behaviour-incidence dynamics of seasonal influenza	108
3.1	Introduction	110
3.2	Model	114
3.3	Results	121
3.3.1	Description of Dynamical Regimes	121
3.3.2	Determinants of vaccinating behaviour-incidence dynamics	125
3.3.3	Stability of Vaccine Coverage	131
3.3.4	Strategy Correlations	135
3.4	Discussion	139
3.A	Algorithm Outline	145
3.B	Supplimentary Material	148
4	Policy resistance undermines superspreadervaccination strategies for influenza	162
4.1	Introduction	164
4.2	Model	165
4.2.1	Population structure	165

4.2.2	Disease dynamics	166
4.2.3	Vaccinating behavior	167
4.2.4	Vaccination strategies	169
4.2.5	Incentives	171
4.2.6	Model calibration and simulation design	171
4.3	Simulation Results	172
4.4	Discussion	177
4.A	Supplementary Text	180
4.A.1	Disease Dynamics	180
4.A.2	Classifying Super-Spreaders	182
4.A.3	Probability of Vaccination	187
4.A.4	Social Influence	188
4.A.5	Pro-Active Vaccination Policies	189
4.A.6	Quality Adjusted Life Years	191
4.A.7	Cost of Policy	193
4.B	Algorithm Summary	194
4.C	Supplementary Tables	196
4.D	Supplementary Figures	206
5	Discussion	217
5.1	Discussion	218
5.2	Future Research	220

List of Tables

1.1	A list of diseases and their basic reproductive ratio (\mathcal{R}_0)	7
2.1	Parameter definitions and baseline value.	63
2.2	Parameter definitions and baseline values for the corrected version	96
3.1	Parameter definitions and baseline parameter values used in the simulations	120
3.2	The statistics for the vaccination coverage ($V(t)$) and influenza incidence ($I(t)$), where $\langle \cdot \rangle$ denotes the average and $\langle\langle \cdot \rangle\rangle$ denotes the variance, over time. All other parameter values for each case are the same as the baseline case.	125
3.3	The pair correlation values for randomly distributed vaccinations and our model.	135
3.4	The statistics for the vaccination coverage ($V(t)$) and influenza incidence ($I(t)$), * $\psi = 0.7$ was used for all simulations in the table except where otherwise noted.	148
4.1	Average influenza incidence $\langle I(t) \rangle$ and vaccine coverage $\langle V(t) \rangle$ in the entire population, and just in superspreaders ($\langle I(t)^{SS} \rangle$, $\langle V(t)^{SS} \rangle$). Numbers represent mean of 400 simulations (standard deviations were very small). NB indicates that vaccinating behavior is ignored, \$20 (respectively \$50) indicates that \$20 (respectively \$50) incentives are used.	174
4.2	The values and descriptions of the parameters used in the simulations of the model.	199

4.3 Percentage of recruitments where recruitment did not matter, whether due to infection, already vaccinated or will be vaccinating in the future (Useless) and the percentage of incentives actually used (% Υ Used). NB indicates the scenario where vaccination behavior is entirely ignored, (\$20) indicates where \$20 incentives were used and (\$50) for \$50 incentives. The vaccination programs are the passive (PV), along with the pro-active programs: random vaccination (RV), nearest neighbor (NN), page rank (PR) and improved nearest neighbor (INN). 200

4.4 The global clustering coefficient among susceptible individuals (C_S) and the pair correlations between susceptible and infected individuals ($\mathcal{PC}_{[SI]}$) and susceptible and vaccinated individuals ($\mathcal{PC}_{[SV]}$) for the various vaccination strategies. 201

4.5 The statistics regarding the number of superspreaders that were willing to vaccinate prior to being recruited ($V_{S\bar{S}}^{SS}(t)$), that were randomly contacted and then were willing to vaccinate ($V_R^{SS}(t)$) and those contacted through a nearest neighbor and then were willing to vaccinate ($V_{NN}^{SS}(t)$) for the various vaccination strategies (with and without incentives) (empirically-based network). $\Sigma(\cdot) = \langle \cdot \rangle \pm \sqrt{\langle \langle \cdot \rangle \rangle}$, where $\langle \cdot \rangle$ denotes the average and $\sqrt{\langle \langle \cdot \rangle \rangle}$ denotes the standard deviation. NB indicates the scenario where vaccination behavior is entirely ignored, (\$20) indicates where \$20 incentives were used and (\$50) for \$50 incentives. The vaccination programs are the passive (PV), along with the pro-active programs: random vaccination (RV), nearest neighbor (NN), page rank (PR) and improved nearest neighbor (INN). 202

4.6 The estimated costs of the various vaccination strategies for the Realistic networks. The vaccination programs are the passive, along with the pro-active programs: random vaccination (RV), nearest neighbor (NN), page rank (PR) and improved nearest neighbor (INN). Υ indicates an incentive value of \$20.00, where $\hat{\Upsilon}$ indicates an incentive value of \$50.00. I_{cost} refers to the cost of infection, V_{cost} refers to the cost of vaccination and Υ_{cost} refers to the cost associated with incentives. * the strategy was slightly altered to only allow the incentives to be distributed to the acquaintance. 203

- 4.7 Influenza incidence and vaccine coverage for the various vaccination strategies (with and without incentives) where there is heterogeneity in the infectious period and transmission rate (exponential network). $\Sigma(\cdot) = \langle \cdot \rangle \pm \sqrt{\langle \langle \cdot \rangle \rangle}$, where $\langle \cdot \rangle$ denotes the average and $\sqrt{\langle \langle \cdot \rangle \rangle}$ denotes the standard deviation. The annual incidence is denoted by $I(t)$, where $I^{SS}(t)$ denotes the annual incidence of the superspreading population. The annual vaccine uptake is denoted as $V(t)$, where the vaccine uptake in the superspreading population is denoted as $V^{SS}(t)$. NB indicates the scenario where vaccination behavior is entirely ignored, (\$20) indicates where \$20 incentives were used and (\$50) for \$50 incentives. The vaccination programs are the passive (PV), along with the pro-active programs: random vaccination (RV), nearest neighbor (NN), page rank (PR) and improved nearest neighbor (INN). 204

4.8 Influenza incidence and vaccine coverage for the various vaccination strategies (with and without incentives) where there is heterogeneity in the infectious period and transmission rate (Poisson network). $\Sigma(\cdot) = \langle \cdot \rangle \pm \sqrt{\langle \langle \cdot \rangle \rangle}$, where $\langle \cdot \rangle$ denotes the average and $\sqrt{\langle \langle \cdot \rangle \rangle}$ denotes the standard deviation. The annual incidence is denoted by $I(t)$, where $I^{SS}(t)$ denotes the annual incidence of the superspreading population. The annual vaccine uptake is denoted as $V(t)$, where the vaccine uptake in the superspreading population is denoted as $V^{SS}(t)$. NB indicates the scenario where vaccination behavior is entirely ignored, (\$20) indicates where \$20 incentives were used and (\$50) for \$50 incentives. The vaccination programs are the passive (PV), along with the pro-active programs: random vaccination (RV), nearest neighbor (NN), page rank (PR) and improved nearest neighbor (INN). 205

List of Figures

1.1	Comparing a basic compartmental model to a meta-population model	9
1.2	Feedback loop occurring between behaviour and disease	29
2.1	Timeline when $\lambda + \omega < \delta + \sigma$	64
2.2	Mean and \pm the standard deviation of values of \mathcal{R} versus $r_{inf}, r_{vac}, \varepsilon, \omega$. .	70
2.3	Mean and \pm the standard deviation of values of \mathcal{R} versus imitation strength κ for three different functional forms for $g(V)$	74
2.4	The distribution of the number of secondary infections and number of vaccinators for the case of $Q = 10$ neighbours for different values of imitation strength.	74
2.5	The distribution of the number of secondary infections and number of vaccinators for the case of $Q = 100$ neighbours for different values of imitation strength.	77
2.6	The distribution of the number of secondary infections and number of vaccinators for the case of $Q = 100$ neighbours, who are imitating n neighbours to the right and n neighbours to the left, for different values of imitation strength.	79
2.7	The distribution of the infected individuals under full imitation for the case of $Q = 100$ for the parameters $\lambda, \varepsilon, \omega, r_{vac}, r_{inf}, p, \sigma, \delta$	81
2.8	The distribution of the vaccinated individuals under full imitation for the case of $Q = 100$ for the parameters $\lambda, \varepsilon, \omega, r_{vac}, r_{inf}, p, \sigma, \delta$	82
2.9	Mean and \pm the standard deviation of values of \mathcal{R} versus $r_{inf}, r_{vac}, \varepsilon, \omega$. .	97
2.10	Mean and \pm the standard deviation of values of \mathcal{R} versus imitation strength κ for three different functional forms for $g(V)$	98

2.11	The distribution of the number of secondary infections and number of vaccinators for the case of $Q = 10$ neighbours for different values of imitation strength.	99
2.12	The distribution of the number of secondary infections and number of vaccinators for the case of $Q = 100$ neighbours for different values of imitation strength.	100
2.13	The distribution of the number of secondary infections and number of vaccinators for the case of $Q = 100$ neighbours, who are imitating n neighbours to the right and n neighbours to the left, for different values of imitation strength.	101
2.14	The distribution of the infected individuals under full imitation for the case of $Q = 100$ for the parameters $\lambda, \varepsilon, \omega, r_{vac}, r_{inf}, p, \sigma, \delta$	102
2.15	The distribution of the vaccinated individuals under full imitation for the case of $Q = 100$ for the parameters $\lambda, \varepsilon, \omega, r_{vac}, r_{inf}, p, \sigma, \delta$	103
3.1	Dynamical regimes exhibited by the model	124
3.2	See page 128 for the caption.	127
3.2	The impact of vaccine complications, memory decay rate and waning vaccine immunity on dynamics	128
3.3	The plot of the auto-correlation ($\mathcal{R}(1)$) for a variety of parameters.	132
3.4	The pair correlation values across a range of parameter values	137
3.5	The average perceived vaccine efficacy for a range of parameter values.	150
3.6	The impact of introducing symptomatic influenza into the model, where $\psi = 0.70$ is the probability of experiencing symptomatic influenza	152
3.7	The plot of the auto-correlation ($\mathcal{R}(1)$) for a range of values for the vaccine efficacy ε	152
3.8	The pair correlation values versus the probability of symptomatic influenza (ψ)	152

4.1	Model outcomes as a function of neighborhood size k . Average probability of being infected (a-d), probability of being vaccinated (e-h), and perceived vaccine efficacy (i-l) for the scenarios of no incentives (a, e, i); \$20 incentives (b, f, j), \$50 incentives (c, g, k), and no behavior (d, h, l). Strategies include no vaccination (black), passive vaccination (blue), random vaccination (red), nearest neighbor vaccination (green), page rank vaccination (light blue) and improved nearest neighbor vaccination (purple).	173
4.2	The top row shows the degree distribution for each network (black) compared to the original empirical network (gray) of Portland, Oregon [1,2,3]. The second row clearly shows that prevalence peaks between the beginning of January and the end of February. The third row shows the prevalence over many years under no vaccination and the fourth row shows the average vaccine coverage over the years under passive vaccination. The average time for peak of prevalence: Empirically-based $t = 136$, Exponential $t = 123$ and Poisson $t = 147$. The approximate average duration of the season: Empirically-based 181 days, Exponential 124 days and Poisson 217 days. . .	207
4.3	A semi-log plot of the probability of number of incentives received and used by superspreaders (solid line) and non-superspreaders (dashed line) for the four different vaccine strategies a) random vaccination b) nearest neighbor vaccination c) page rank vaccination and d) improved nearest neighbor vaccination.	208

Chapter 1

Introduction

1.1 Disease Burden: Historical and Current

Infectious diseases impose a negative impact on society; the impact ranges from individual level [1, 2, 3, 4, 5] to the population level [4, 6, 7, 8, 9]. The personal impact of infectious disease is more obvious than the public, i.e. influenza results in fever, sore throat and could lead to pneumonia [4, 10]. A good example of how infectious disease affects the public is if an outbreak were to occur in a third world country; the epidemic would be more devastating in the third world because the outbreak could lead to an increase in poverty, which then would lead to further disease, causing a vicious cycle to arise [6].

There have been many key epidemiological events in the past.

1655 Bubonic Plague, London - There was a long series of epidemics from 1499 to 1655, killing between 75,000 to 100,000 people [11, 12]

1721 Smallpox, Boston - In a span of 9 months there were 5,889 infections and 844 deaths. The event was best known for the controversy that arose in the population over vaccination. [11, 13]

1793 Yellow Fever, Philadelphia - Was the first major yellow fever epidemic to hit the United States[11, 14]

1852 Cholera, India - This cholera pandemic that had reached North America, Europe, Asia and Africa is considered to be the deadliest cholera pandemic out of the current seven[15]

1916 Polio, New York - The United States had 27,000 polio infections, New York City alone had 9,000 people infected with polio. There was a 25% mortality rate in the 1916 polio epidemic. [16, 17]

1976 Ebola virus identified, Democratic Republic of the Congo - The Ebola virus has an extremely high fatality rate of 25 – 90%. To date there have been 1850 Ebola cases with over 1200 deaths[18, 19]

1981 Identification of AIDS - AIDS has become the worlds deadliest disease, with over 25 million deaths since its discovery [20, 21]

2003 SARS - 26 countries experienced SARS epidemics that accumulated more than 8000 cases[18, 22]

Influenza is an interesting disease, in that it is vaccine preventable and occurs in all populations [1, 6, 23, 24, 25]. Influenza can be put into two separate categories 1) seasonal influenza and 2) pandemic influenza. Seasonal influenza, as the name indicates, occurs annually with most of the infection occurring between the beginning of January and the end of February [26]. Seasonal influenza undergoes a slight change in its genome each year, known as *antigenic drift*. Due to slight changes in the virus genetics, individuals are typically immune to seasonal influenza for approximately four years [27]. Pandemic influenza is a result of a drastic change in genetics, referred to as *antigenic shift*, resulting in an increase in the susceptible population. Historical influenza events to date include:

1918 Spanish Flu - There was an estimated 40 million deaths in this pandemic, which believed to have originated in a US military camp in the midwestern United States[28,

29, 30]

1957 Asian Flu - Originating in southern China, the pandemic resulted in approximately 69,800 deaths [28, 29, 30]

1968 Hong Kong Flu - The Hong Kong flu pandemic resulted in limited mortalities, 33,800, compared to the Spanish and Asian Flu pandemics [28, 29, 30]

1977 Russian Flu - Originating in China this epidemic spread globally and mainly infected people under the age of 25 [29, 30]

2009 H1N1 - Originating in Mexico and the United States, the pandemic resulted in an estimated 18,500 mortalities [31, 32, 33]

Symptoms of influenza often include fever, sore throat, muscle aches, fatigue and headache; which often come on suddenly [34]. The most common complication of seasonal influenza is pneumonia [3, 34]; other common complications that arise from influenza include bronchitis, sinus infections and ear infections [34]. Public health would like to know when the next pandemic is going to occur and how to mitigate it [35]. However, this requires not only understanding how the infectious disease spreads, but how a population will react to the event of a pandemic and prevention policies.

1.2 Infectious Disease Modelling

To better understand the spread of infectious disease, mathematical models were developed. The most recognizable model is the Susceptible-Infected-Recovered (*SIR*) model and its

variations [36]. The majority of this thesis consists of Susceptible-Infected-Recovered-Susceptible (*SIRS*) approaches, which allow recovered individuals become susceptible. In equations (1.1)-(1.3) the *SIRS* model is described using ordinary differential equations (ODE). When susceptible individuals encounter an infected individual a portion become infected ($\beta I/N$ is known as the force of infection); an infectious individual is only infectious for a given amount of time, $1/\delta$ is the average number of days a person is infectious for, after which they move to the recovered state. Therefore, the rate of recovery (number of infectious individuals moving from the infectious state to the recovered state per unit time) is δI . Once in the recovered state the individual will become susceptible after a given period: $1/\rho$ is the average number of days until the recovered individual becomes susceptible; however, in the case of the *SIR* model the individual remains in the recovered state. Therefore, the rate at which the recovered population moves to the susceptible state is ρR individuals per unit time[36]. The deterministic representation of the *SIRS* model is

$$\frac{dS}{dt} = \mu N - \beta \frac{S}{N} I + \rho R - \mu S \quad (1.1)$$

$$\frac{dI}{dt} = \beta \frac{S}{N} I - \delta I - \mu I \quad (1.2)$$

$$\frac{dR}{dt} = \delta I - \rho R - \mu R, \quad (1.3)$$

where N is the population size, (i.e. $N = S + I + R$), μ is the per capita birth and death rate, δ is the per capita recovery rate ($1/\delta$ is the average infectious period), β is the transmission rate and ρ is the per capita rate at which immunity is lost [36].

Frequency-dependent transmission has the form $\beta S \frac{I}{N}$ and assumes that the infection

rate depends on the frequency $\frac{I}{N}$ of infected individuals in the population (where S , and I are number of susceptible and infected persons respectively)[36, 37, 38]. Mass-action transmission has the form βSI and assumes that the infection rate depends on the number I of infected individuals [36, 37, 38]. Hence, under mass-action transmission, if the number of infected persons doubles, then so does the infection rate of susceptible individuals. However, under frequency-dependent transmission, if the number of infected persons doubles but the population size also doubles, then the infection rate of susceptible individuals does not change [36, 37, 38]. The true distinction between frequency-dependent transmission and mass action transmission is when the size population ($N = S + I + R$) varies; otherwise, if N is constant then β can absorb $1/N$ [36, 37, 38]. However, the meaning of β changes under each assumption, under frequency-dependent transmission β is the “rate at which a susceptible makes contact with other hosts” [37], while under mass action transmission β is the “contact rate per susceptible, which is taken to increase in proportion to the total number of individuals in a population occupying a constant area” [37].

To determine the transmissibility of an infection in a population one can determine the *basic reproductive ratio* (\mathcal{R}_0), which represents the average number of secondary infections that a single infectious individual can produce in a fully susceptible population [36, 39]. The value of \mathcal{R}_0 in a deterministic compartmental setting can often be expressed as

$$\mathcal{R}_0 = \frac{N}{\bar{S}}, \quad (1.4)$$

where N is the population size and \bar{S} is the steady state of the susceptible population. To determine the value of \mathcal{R}_0 for the *SIRS* model the non-zero steady state of the susceptible

Disease	\mathcal{R}_0	Reference
Influenza	1.3-4	[36, 40, 41, 42]
Smallpox	3.5-6	[36, 39, 43, 44]
Rubella	6-7.62	[36, 39, 45, 46]
Chickenpox	8.5-12	[36, 39, 46]
Measles	12.3-18	[36, 39, 46]
Whooping Cough	14.3-18	[36, 46]

Table 1.1: A list of diseases and their basic reproductive ratio (\mathcal{R}_0)

population, S , must be determined. The non-zero steady state of the susceptible population is $\bar{S} = N(\delta + \mu)/\beta$; therefore, the basic reproductive ratio for the *SIRS* model is

$$\mathcal{R}_0 = \frac{\beta}{\delta + \mu}. \quad (1.5)$$

The value of \mathcal{R}_0 can determine whether an outbreak of a disease will result in an epidemic or die out. If $\mathcal{R}_0 > 1$, then an outbreak will result in an epidemic; otherwise, if $\mathcal{R}_0 < 1$, then the outbreak will not proceed to grow but will die out. In Table 1.1, there is a list of infectious diseases with their corresponding basic reproductive ratio.

An aspect often incorporated into models is *heterogeneity*: differences among behaviour, susceptibility, number of contacts, population density or environment. A model with no heterogeneity is a *homogeneous* model. At times, models will assume a population is homogeneous [47, 48]. Good examples include *SIR* type models expressed in equations (1.1)-(1.3)[36]; in reality, there is diversity among individuals and communities [49, 50]. Often, heterogeneity is incorporated into the transmission among different groups of individuals [49, 50, 51]; for influenza, for example, one could assume younger people are more

capable of transmitting influenza than elderly individuals [51]; but heterogeneity can be incorporated into other aspects of the model as well (i.e. behaviour, environment, · · ·).

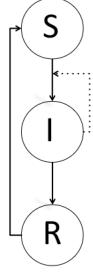
The benefits to using deterministic compartmental models are the analytical properties and tools associated with them; this allows for quick analysis that typically cannot be used in other approaches.

A drawback of using deterministic compartmental models (equations (1.1) -(1.3)) is the lack of information pertaining to the spatial spread of disease. Meta-population models (an ODE approach for the spatial spread of disease) provides information regarding the spatial spread of disease, which is a result of two sub-populations interacting, also known as *coupling*. In a meta-population model, the population is broken up into groups (communities) for determining spatial spread (Figure 1.1), and the dynamics of each group can be represented by equations similar to equations (1.1) - (1.3). Besides the number of equations, the main difference occurs in the force of infection; previously the force of infection was represented as $\beta I/N$, whereas the force infection for the meta-population model is

$$\beta_i \sum_{j=0}^n \rho_{i,j} \frac{I_j}{N_i}, \quad (1.6)$$

β_j would represent the transmission rate in population j , I_j is the prevalence in subpopulation j , $\rho_{i,j}$ is the *coupling factor*, the strength of interaction, between population i and j and N_i is the population size of population i . The assumption of the infection event occurring in population i is the reason N_i is used in equation (1.7) [36]. Alternatively, if the infection event was assumed to occur in population j then the force of infection would

(a) Basic compartmental model



(b) Meta-population model

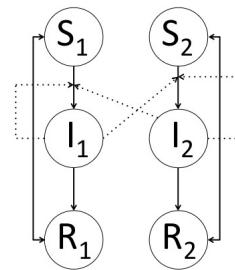


Figure 1.1: Comparing a basic compartmental model to a meta-population model (a) The basic compartmental model where the population is viewed as one single group (b) An example of a meta-population model where the population is broken up into two groups that interact with one another.

be expressed as

$$\sum_{j=0}^n \rho_{i,j} \beta_j \frac{I_j}{N_j}, \quad (1.7)$$

for population i [36]. With the new term for the force of infection, a meta-population model can be expressed as

$$\frac{dS_i}{dt} = \mu N_i - \beta_i \frac{S_i}{N_i} \sum_{j=0}^n \rho_{i,j} I_j + \rho R_i - \mu S_i \quad (1.8)$$

$$\frac{dI_i}{dt} = \beta_i \frac{S_i}{N_i} \sum_{j=0}^n \rho_{i,j} I_j - \delta I_i - \mu I_i \quad (1.9)$$

$$\frac{dR_i}{dt} = \delta I_i - \rho R_i - \mu R_i, \quad (1.10)$$

Coupling allows infection to reach other sections of the population; allowing infection to be introduced (reintroduced) into a susceptible population can feed (restart) an epidemic.

The strength of coupling between two sub-populations is important; if coupling is too strong, the two populations act as one well mixed population and if coupling is too weak then the disease dynamics of the two populations become independent of each other [36].

In meta-population models, the coupling strength is determined by where an individual resides, not the distance between the individuals which can be an issue. A *coupled lattice meta-population model*, where individuals are restricted to a site on the lattice, is a prime example of this problem; assume that individual A and B are contained in the same subpopulation, with C in the neighbouring subpopulation where the distance between A and C is less than the distance between A and B . Since A and B are in the same subpopulation their interaction with one another is stronger than the interaction between A and C .

However, one of the biggest drawbacks of using deterministic compartmental models is their simplifying assumption about the population being homogeneously mixed, that is to say each individual has equal opportunity to interact with every other individual in the population. For many diseases and many research questions, the simplifying assumption of homogeneous mixing may be inadequate, and one should consider a different approach that focuses more open the spatial structure of the population [52].

Unlike ODE models, partial differential equation (PDE) models focus on the spatial spread of the disease, accounting for densities of susceptible, infectious and recovered individuals in the different areas of the population. Here, an *SIRS* model is described in PDE form

$$\frac{\partial S}{\partial t} = \mu N - \beta \frac{S}{N} I + \rho R - \mu S + D_S \nabla^2 S \quad (1.11)$$

$$\frac{\partial I}{\partial t} = \beta \frac{S}{N} I - \delta I - \mu I + D_I \nabla^2 I \quad (1.12)$$

$$\frac{\partial R}{\partial t} = \delta I - \rho R - \mu R + D_R \nabla^2 R, \quad (1.13)$$

where D_Z is the diffusion coefficient for state Z and where

$$\nabla^2 Z = \frac{\partial^2 Z}{\partial x^2} + \frac{\partial^2 Z}{\partial y^2}, \quad (1.14)$$

is the Laplace operator (for two-dimensions). If $D_Z > 0$, the population diffuses outwards from the space; otherwise if $D_Z < 0$ then the population is attracted to the space. It is possible that the diffusive coefficient D_Z depends on the location in the environment ($D_Z = D_Z(x, y)$); in that case $D_Z \nabla^2 Z$ becomes $\nabla \cdot (D_Z(x, y) \nabla Z)$, where

$$\nabla Z = \frac{\partial Z}{\partial x} + \frac{\partial Z}{\partial y}, \quad (1.15)$$

is the gradient (for two-dimensions). Under some assumptions, the susceptible population may want to avoid high density areas of infected individuals, which is known as cross diffusion. The cross diffusion coefficient D_{ZW} corresponds to how Z reacts to W . If $D_{ZW} > 0$ then the Z population will avoid (diffuse) from the larger densities of W ; otherwise, if $D_{ZW} < 0$ then the Z population will tend to the larger W population. Equations (1.16)-(1.18) show how cross-diffusion is implemented into the original diffusion model (equations

(1.11)-(1.13)).

$$\frac{\partial S}{\partial t} = \mu N - \beta \frac{S}{N} I + \rho R - \mu S + D_S \nabla^2 S + \nabla \cdot D_{SI}(S) \nabla I \quad (1.16)$$

$$\frac{\partial I}{\partial t} = \beta \frac{S}{N} I - \delta I - \mu I + D_I \nabla^2 I \quad (1.17)$$

$$\frac{\partial R}{\partial t} = \delta I - \rho R - \mu R + D_R \nabla^2 R, \quad (1.18)$$

where $D_{SI}(S)$ is the cross-diffusion term which is dependent on the density of susceptible individuals [53]. However, PDE models have no concept of an individual or an individual's neighbourhood, which is a drawback when one wants to model at the individual level. Another approach that is often used to describe the spatial spread of disease is network modelling, which also allows for analysis at the individual level. For the rest of this section we will be strictly focusing on network modelling, as it is one of the key components of this thesis. We also note that spatial structure in this Introduction is construed in the broadest possible sense to include network structure, not just geographic structure as captured by PDE models.

1.3 Network Modelling

1.3.1 Network Characteristics

Before introducing the topic of network disease transmission modelling, we first introduce the terminology used when describing networks. A network is made up of nodes and

edges. In infectious disease modelling, a node typically represents an individual, but can also represent a community. Edges in the network connect nodes to one another; therefore representing the connections between individuals that allow for transmission of disease. The number of edges a node has is referred to as the node's *degree*; the *average degree* of the network is the average of all the nodes degrees in the network. A *directed* network only allows infection in one direction (i.e. A can infect B but B cannot infect A), where an *undirected* network allows for transmission in both directions. Most infectious disease models are undirected networks; an example of a directed network would be transmission of a disease through donated blood products [52]. A *semi-directed* network there is a combination of directed and undirected edges throughout the network [54].

A *complete network* refers to a network where each node is connected to every node in the network; that is, if the network has N nodes each node has a degree of $N - 1$ [52]. A *connected network* refers to a network where given any two nodes there exists a path in the network that will connect the two [52]. The *mean path* is the average number of steps between a given node and any other node in the network [55]; averaging the path (of shortest distance) of the furthest node, over all nodes, is referred to as the network's *diameter* [55].

Clustering is a measure of how many triangle connections appear in the network [52]. A cluster is classified to be a connection where A is connected to B , B to C and C to A .

Clustering is often measured through the clustering coefficient

$$\mathcal{C}_i = \frac{2m_i}{k_i(k_i - 1)}, \quad (1.19)$$

$$\mathcal{C} = \frac{\sum_{i=1}^N \mathcal{C}_i}{N}, \quad (1.20)$$

where \mathcal{C}_i is the clustering coefficient of the individual i , k_i is the degree of i and m_i is the number of links that connect i 's contacts with each other (i.e. i is connected to j and k where j and k are connected), where N is the population size. \mathcal{C} is the clustering coefficient for the entire network[56].

Ref [57] found certain network characteristics impact one another: 1) as clustering increases there is a decrease in the mean path and 2) increasing the average node degree increases the level of clustering.

Disease dynamics depend strongly on the characteristics of the network [52, 57, 58, 59]. The shorter the mean path length the sooner the epidemic peak [57]; the mean path and diameter of a network can give indication as to how fast infection can reach another region of the network. If the mean path and diameter are small then infection can reach other regions of the network faster, since there are fewer connections for infection to travel through.

1.3.2 Types of Networks

Here are some of the more familiar networks that are used in infectious disease modelling.

(a) **Lattice Network:** Lattice networks are best described as grids, where the nodes have

a fixed degree; they are most often constructed using squares or triangles. Due to the localization of the nodes and a longer mean path, the spread of infection is initially slow since neighbours are likely to share contacts and infection is unable to reach distant subregions of the network [36, 52, 57].

- (b) ***Random Network:*** Random networks are often used to represent a “well mixed” population. A random network consists of making random connections of nodes, with there being little heterogeneity in the degree. One approach that can be taken to create a random network is to assign a probability that a connection is made between two nodes. If the desired average degree is $\langle k \rangle$, then the probability a node makes a connection with another node is

$$p(k) = \frac{\langle k \rangle}{N - 1}, \quad (1.21)$$

where N is the population size. If each node in the network has the same degree then the network is referred to as a uniform network, where there is no heterogeneity in the node degree [36, 52, 57]. The Poisson network is a random network where the degree distribution is a Poisson distribution. The approach to creating a Poisson network is to sample a node’s degree from a Poisson distribution and connections are made randomly; therefore the probability of a node having degree k is

$$p(k) = \frac{\langle k \rangle^k e^{-\langle k \rangle}}{k!}. \quad (1.22)$$

Another common random network is the exponential network where the degree distri-

bution is the exponential distribution, with the probability of a node having degree k being

$$p(k) = (1 - e^{-1/\langle k \rangle})e^{-(k-1)/\langle k \rangle}. \quad (1.23)$$

- (c) ***Small World Network:*** In a network is classified as being small world if there is a large amount of clustering and short path length [52]. Most small world networks are built on a lattice structure with the insertion of a few long connections. With the addition of long connections into a lattice model infection can reach another region of the network much quicker. In terms of the spreading of disease, infection in a small world network occurs locally but infection spreads quickly because of the short mean path associated with a small world network[52].
- (d) ***Power-Law (Scale-Free) Network:*** In a power-law network, the probability of a node having degree k is

$$p(k) = k^{-\alpha}, \quad (1.24)$$

where α is the power-law exponent. The power-law network is an unrealistic approximation for most epidemiological networks[59, 60]; however, sexual contact networks have been found to have a power-law distribution [61]. The assumption of a power-law network does however provide a “worst case scenario” when used because there is no epidemic threshold [62]; suggesting that if the intervention is effective for a power-law network it should be effective in realistic networks. The power-law network evolves over time, adding new nodes to the network. The new nodes introduced are more likely to be connected to the nodes with larger degrees [52, 62]. This provides the

power-law network with a great deal of heterogeneity among node degree [52]. The power-law distribution is often truncated to better resemble the distributions found in society [60],

$$p(k) = k^{-\alpha} e^{-k/\kappa}. \quad (1.25)$$

- (e) ***Spatial Network:*** Connections between nodes in a spatial network depend on the distance between two nodes. To determine if there is a connection between two nodes a kernel is often used. A kernel describes the probability of two nodes connecting; often the closer (further) a node is from a given node the more (less) likely a connection is made between the two [36, 52]. Since nodes located closer to one another are more likely to be connected, spatial networks tend to have large clustering coefficients [63]. One benefit of using a spatial network is the flexibility it allows in the creation of the network; with the proper choice of kernel a spatial network could represent anything from a lattice to fully connected random networks [52].

A *social network* describes the interaction of individuals in everyday life and is considered to be a small world network [52] because of the amount of clustering and short mean path. The power-law network is the most common network used to capture a social network [59, 64, 65, 66, 67, 68], with evidence of power-law distributions in sexual contacts [61]; however, it is an unrealistic approximation for most epidemiological models[59] because of the possibility of an extreme number of contacts in the tail of the power-law distribution[60]. Social networks often contain *community structure*, groups of highly connected individuals with few connections to other groups [69]. Other complexities of social networks include the number of communities, connections between these communities and

the location of the communities. With all the aspects contained in social networks, they are often difficult to reproduce using the networks listed above. The variability contained in social networks often lie in between the homogeneity of a uniform random network and heterogeneity that is found in power-law networks [59].

1.3.3 Modelling Infectious Disease Transmission on a Network

The choice of what network to use is dependent on the disease and what aspects are included or excluded from the model [52]. For example, modelling the spread of disease in an orchard differs from modelling influenza in a city. A lattice model would better represent the event in the orchard, whereas an exponential network could be used in the case of influenza. Even if one was to model two different types of airborne viruses, different networks may need to be implemented.

Random networks (uniform random network, Poisson random network, etc.) are used to provide a further understanding of the spread of disease on more complex social networks [52]. The benefit of using a random network is the number of analytical tools available that can be used to understand the disease dynamics [36, 59]. However, random networks are often associated with low levels of clustering and are typically not capable of capturing the structure that is observed in social networks [52, 69, 70, 71].

Small world networks are often used to incorporate social structure because both are characterized by their large amount of clustering and short path length [52]. The power-law network is the typical small world network used to try and capture the structure of realistic social networks [59, 64, 65, 66, 67, 68], however, the fat-tailed power-law distribution is

considered to be unrealistic [59]. To better approximate the degree distributions observed in social networks, the power-law degree distribution is often truncated by an exponential to eliminate the fat-tail [60]. Due to the increased level of clustering associated with these more complex networks, traditional network analysis breaks down[72]. Therefore, when choosing a network we must decide whether we want to take a more realistic approach and have fewer analytical tools or a more simple approach with many analytical tools.

In a network, infection is passed along the edges connecting a susceptible individual and infectious individual with probability p . Infection of a susceptible individual can occur in two ways: 1) go through each of the susceptible individual's infectious contacts one by one to see if the susceptible node is infected or 2) determine the probability of the susceptible individual becoming infected, $1 - (1 - p)^n$, where n is the number of infectious contacts and $(1 - p)^n$ is the probability of not being infected by any of the n infectious contacts.

An infectious individual can move to the recovered class in several ways. One approach is that the infected node becomes recovered with a fixed probability per day (stochastic). Alternatively, the infected individual can leave after a fixed number of days (deterministic). A similar process can move a recovered individual to the susceptible state. For the birth (death) process, it is as simple as adding (removing) a node along with adding (removing) connections in the network.

Taking a deterministic compartmental approach, equations (1.1) -(1.3), to modelling has its benefits and its downfalls. The benefits of compartmental modelling is analysis is much more straightforward than using a network model. Also, compartmental models are capable of producing results quickly, which can be needed in the time of a pandemic crisis.

The downfall with compartmental modelling is the assumption that every individual has equal chance of interacting, which can be unrealistic. For example, the compartmental approach would be a poor approximation for modelling the spread of a disease in a large city. On a yearly basis, an individual is unlikely interact with everyone in the population; even if one was able to, the interaction may not even be long enough to be capable of transmitting the disease. Deterministic compartmental models often overlook the underlying individual properties that can influence the spread of disease [59].

Using a network for infectious disease modelling allows a better representation of social networks and a more natural spread of infection with a better understanding of what is occurring at the individual level. Network models also allow for individual heterogeneity to be incorporated into models much more easily[59]. There are network models that consider the spatial spread of a disease, i.e. ability to infect individuals who are not contacts. This could be associated with a highly contagious airborne disease, where individuals surrounding an individual are more likely to be infected, along with any of their contacts. A *transmission kernel* would be used in such a scenario, where susceptible individuals closer to an infectious person are more likely to be infected than susceptible individuals at a further distance.

One of the main differences between network and compartmental modelling is the initial spread of disease. The growth rate is generally slower in a network than the deterministic compartmental model; networks that assume random mixing often show faster growth rates [36]. However, a compartmental model can capture the network dynamics depending on the characteristics of the network [58].

The basic reproductive ratio in a deterministic compartmental *SIRS* model is expressed in equation (1.5); however, if there is heterogeneity among the degree of nodes the homogeneous mixing assumption may be an inappropriate model choice [54, 73]. The basic reproductive ratio in a network can be approximated using

$$\mathcal{R}_0 = T \left(\langle k \rangle - 1 + \frac{\langle\langle k \rangle\rangle}{\langle k \rangle} \right), \quad (1.26)$$

[54, 74, 75, 76, 77] where $\langle k \rangle$ denotes the average degree of the network, $\langle\langle k \rangle\rangle$ denotes the degree variance of the network and T represents the average transmissibility of a disease, where

$$T = 1 - (1 - p)^\delta, \quad (1.27)$$

for a discrete time approximation and

$$T = 1 - e^{-p\delta}, \quad (1.28)$$

for a continuous time approximation; where p is the probability of transmission along an edge per day and δ is the infectious period in days [54, 74]. Assuming heterogeneity among the individuals' susceptibility or transmissibility, the average transmissibility is then

$$T = \langle T_{ij} \rangle = \langle 1 - (1 - p_{ij})^\delta \rangle = 1 - \int_0^\infty P(p)(1 - p)^\delta dp, \quad (1.29)$$

for a discrete time approximation and

$$T = \langle T_{ij} \rangle = \langle 1 - e^{-p_{ij}\delta} \rangle = 1 - \int_0^\infty P(p) e^{-p\delta} dp, \quad (1.30)$$

for a continuous time approximation; where T_{ij} is the probability of transmission from infectious individual i to susceptible j and p_{ij} is the probability of transmission from infectious i to susceptible j per day [54, 74, 78]. In Ref [76], they assumed the infectious periods was distributed exponentially in a continuous time model. The average transmissibility on a random network was found to be

$$T = \frac{\tilde{\beta}}{\tilde{\beta} + \delta + \mu}, \quad (1.31)$$

for an equivalent random network to a compartmental *SIRS*, where $\tilde{\beta}$ is the probability of transmission (per day) along the edge connecting an infectious and susceptible individual. As $\langle k \rangle \rightarrow \infty$, while keeping $\langle k \rangle \tilde{\beta} = \beta$ (where β is held constant) then the basic reproductive ratio for the network is

$$\begin{aligned} \mathcal{R}_0 &= \lim_{\langle k \rangle \rightarrow \infty} T \left(\langle k \rangle - 1 + \frac{\langle \langle k \rangle \rangle}{\langle k \rangle} \right) \\ &= \lim_{\langle k \rangle \rightarrow \infty} \frac{\tilde{\beta}}{\tilde{\beta} + \delta + \mu} \left(\frac{\langle k^2 \rangle - \langle k \rangle}{\langle k \rangle} \right) \\ &= \lim_{\langle k \rangle \rightarrow \infty} \frac{\langle k^2 \rangle}{\langle k \rangle} \frac{\tilde{\beta}}{\tilde{\beta} + \delta + \mu} - \frac{\tilde{\beta}}{\tilde{\beta} + \delta + \mu} \\ &= \lim_{\langle k \rangle \rightarrow \infty} \frac{\tilde{\beta} \langle k \rangle}{\tilde{\beta} + \delta + \mu} - \frac{\tilde{\beta}}{\tilde{\beta} + \delta + \mu}, \text{ assuming } \langle k^2 \rangle \approx \langle k \rangle^2 \\ &= \frac{\beta}{\delta + \mu} \end{aligned}$$

since $\tilde{\beta} \rightarrow 0$ as $\langle k \rangle \rightarrow \infty$ where $\langle k \rangle \tilde{\beta} = \beta$ (where β is held constant).

Network structure is very influential on the value of \mathcal{R}_0 [58]. \mathcal{R}_0 is reduced with a small average degree and a high degree of clustering [58]. Equation (1.26) is only an approximation to the basic reproductive ratio on a network, which accounts for the average degree but not clustering in the network. Networks with high amounts of clustering experience a reduction in \mathcal{R}_0 due to there being many shared contacts among individuals, resulting in limited susceptible individuals among infectious contacts [58].

There has been much work done in the past for understanding the spread of disease in networks [54, 58, 69, 77, 78, 79, 80, 81, 82], as networks provide an understanding of the epidemiological processes that occur in society [52]. There is a strong link between the formation of social connections in society and networks; however, to capture the characteristics of real social networks using the idealized networks discussed in this Introduction is difficult. Work is being done on the formation and characteristics of social networks, such that there is a better understanding of how social networks are formed and how they impact the spread of disease. Currently researchers are focusing on the impact of dynamic social networks on the spread of disease [52, 79]. Past and current models assume connections are static in the network [52, 59, 79]; however, as long as the change in connections is slower than transmission the network will change little during the epidemic [52]. Currently, network models are being used to understand and determine an optimal vaccination strategy that targets individuals with a large number of contacts.

1.4 Vaccination

Vaccination is the main preventative strategy to reduce morbidity and mortality caused by an infectious disease. The effectiveness of a vaccine is referred to as the *vaccine efficacy*, which compares the frequency of disease in the vaccinated and unvaccinated individuals [83]. The amount of vaccination occurring in a population, *vaccine coverage* (or uptake), is often measured as a percentage. Vaccination offers an individual *direct protection* because they are taking action to prevent themselves from being infected. Vaccination offers others in the population *indirect protection* because non-vaccinating individuals are protected by those who are vaccinating, since it reduces transmission and thus the chance of becoming infected. *Herd immunity* occurs when enough people in the population vaccinate to eliminate the disease; therefore, herd immunity is a form of indirect protection[84].

We list and describe a few vaccination strategies that are often adopted by public health

- (a) ***Mass Vaccination:*** Mass vaccination consists of vaccinating as many individuals as possible over a widespread area. Mass vaccination is often applied in situations when there is a limited amount of time to administer a vaccine[85]. A second use for mass vaccination is to quickly increase the vaccine coverage to obtain the level of protection required to reach herd immunity [85]. The benefit mass vaccination is its ability to effectively reduce widespread transmission; however, mass vaccination is often expensive because of the large number of vaccinations that must be administered and also may lead to asynchrony in epidemics between populations, which reduces the chances of extinction of a disease [36].

- (b) ***Ring Vaccination:*** Ring vaccination consists of vaccinating the contacts of an infectious individual, rather than vaccinating the entire population. Ring vaccination is best used in situations where outbreaks are small and localized [86]. If infectious cases can be quickly diagnosed, ring vaccination can be a highly effective strategy [87]. Compared to mass vaccination, ring vaccination only requires a minimal number of vaccinations, therefore reducing the number of complications due to a risky vaccine. The success of ring vaccination requires contact tracing to be efficient, which leads to an increase in costs [36]. Ring vaccination was the driving force behind the eradication of smallpox [88].
- (c) ***Pulse Vaccination:*** Pulse vaccination consists of vaccinating certain groups periodically over the years. The main goal of pulse vaccination is to periodically reduce the susceptible population enough such that in the years of non-vaccination the susceptible population does not grow large enough to sustain an epidemic [36]. An obvious downfall of pulse vaccination is the opportunity for a large outbreak to occur between the periods of vaccination. In regions where health care is limited, pulse vaccination has its benefits; rather than putting a constant effort towards vaccination, public health would only need to send out vaccination teams periodically. Another benefit of pulse vaccination is its ability to synchronize epidemics of connecting populations, which increases the chances of the disease extinction [36]. The main issue with pulse vaccination is determining the frequency with which the vaccine should be administered; 1) too often and the susceptible population dramatically decrease but there is unlikely extinction of the disease 2) infrequent vaccination leads to greater chances for extinction but also a greater chance for large outbreaks to occur between pulses [36].

- (d) ***Targeted Vaccination:*** As the name suggest, targeted vaccination is a policy where a certain group of individuals or a community is targeted for vaccination. Compared to ring vaccination, targeting individuals does not require contact tracing [36]. At times there is conflict as to who should actually be vaccinated, a subpopulation capable of highly efficient at spreading the disease or a subpopulation more vulnerable to the disease [51].

To date, only smallpox has been eradicated, due to the success of surveillance and vaccination. The last known case of naturally acquired smallpox was in 1977 in Somalia; three years later smallpox was declared eradicated [89]. With the eradication of smallpox, eradication of other diseases such as polio and measles have been considered. A target was set by the World Health Organization (WHO) that polio would be eradicated by the year 2000 [90]; however, to date polio still persists in the areas of Nigeria, Afghanistan and Pakistan [91]. Measles is another disease currently being considered for eradication. The WHO set a target to reduce the death due to measles by 90% by 2010 [92] and 95% by 2015 [93]. By the end of 2020 WHO hopes that measles will be eliminated from at least five WHO regions [93].

Some of the factors that lead to eradication of a disease through vaccination include: a safe and effective vaccine, vaccination and recovery from infection providing life-long immunity and easily recognize disease [94]. Eradication of a disease requires an abundance of effort which is expensive; however, there is no future cost due to the disease. Eradication can be difficult for countries where there are political issues or weak health systems [90].

On occasion, problems can arise when introducing a new vaccine. Vaccines, although

effective in decreasing and eliminating disease, can have real or perceived adverse side-effects which impact the overall vaccine coverage in the population. Issues regarding vaccine safety have risen in the past: the pertussis vaccine controversy in Great Britain during the 1970's and 1980's [95], and the Measles-Mumps-Rubella (MMR) vaccine controversy in the United Kingdom [96, 97].

In regards to the pertussis vaccine, it was believed that the vaccine would lead to death or neurologic disease [98], but studies indicate that is not the case [98, 99, 100, 101, 102]. Understanding how a population reacts to such a scare is important for understanding the impact of future vaccination.

Another issue associated with vaccination is *vaccine resistance*, which occurs when the current vaccine no longer provides sufficient protection from the disease. Vaccine (and drug) resistance has been observed in tuberculosis [103, 104, 105], pneumonia [106, 107, 108], HIV [109, 110, 111] and malaria[112, 113, 114]. Vaccinating to eliminate a disease is difficult already, and the addition of vaccine resistant viruses adds another factor of complexity. “The survival of viruses depends on the survival of susceptible hosts” [115]; introducing a vaccine into the population depletes the number of susceptible hosts causing some viruses to adapt to survive [116]. There are many factors that influence the emergence of resistant viruses; some of the key factors involved in the increased frequency of resistant viruses include microbial characteristics, and the changes in society and technology that can lead to an increase in transmission [116].

One of the strategies mentioned earlier in this section referred to targeted vaccination. A current issue being studied is how to target *superspreaders*: individuals who are highly

infectious and capable of producing the majority of secondary infectious cases [117, 118]. A variety of diseases, even influenza, have been influenced by super-spreading events [119, 120, 121, 122, 123]. The problem that super-spreading imposes on society is their efficiency at spreading a disease; super spreaders can be classified as the 20% of the population responsible for 80% of the infection each year, better known as the 20/80 rule [122, 124, 125].

The superspreaders vaccination strategies currently being developed target individuals who have a large number of contacts [126, 127, 128, 129, 130]. Vaccination of superspreaders would drastically reduce the infection incidence in a population; however, identification of superspreaders is not the easiest task. One approach that has been developed is the nearest neighbour (or acquaintance) approach where an individual is selected at random and asked to name a contact for vaccination, because superspreaders are highly connected individuals and are likely to have many contacts[130]; therefore, there is little chance of randomly selecting a superspreaders from the population, but vaccinating through contacts instead allows for a greater chance of selecting a superspreaders, since they are highly connected [120, 130].

As mentioned in the beginning of this chapter, influenza is a vaccine preventable disease [6, 27, 131]; however, it has yet to be eradicated from the population [132]. One reason for this is the drift that occurs in the influenza virus: this results in having to produce new vaccines for the slightly different strands of influenza each year [27, 131]. Vaccination against influenza commences in the early fall (or late summer), slightly prior to when influenza becomes active in the population [132, 133, 134]. There have been many proposed methods on how to allocate influenza vaccination. Some suggest vaccinating young children because they are more likely to spread influenza, others suggest to vaccinate the elderly

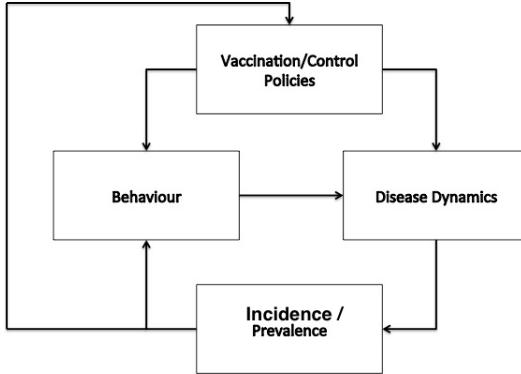


Figure 1.2: A visualization of how each aspect of disease modelling influences other aspects in the model [6]. Neglecting behaviour of an individual or a population impacts the disease dynamics which allows for poor approximation of the efficacy of the vaccination (or control) policy.

because of their vulnerability to influenza [51, 135, 136, 137, 138]. Ref [51] suggests that we must be careful how we allocate vaccines, as allocation of vaccine is sensitive to the characteristics of influenza and the community structuring.

Current vaccine coverage levels have long been below public health's targeted value [24, 139]; however, increasing trends have been observed in Canada [24]. Understanding the factors that influence people's choices is important in predicting vaccine coverage in future years.

1.5 Modelling Behaviour

Incorporating behaviour into a model enhances the results and is an important aspect to be included [140, 141]. In the event of a vaccine scare the vaccine uptake would be expected

to drop because the remaining population’s fear of suffering adverse side-effects[95]. A model incorporating behaviour would predict a drop in vaccine uptake and show that a long period of time must pass before vaccine uptake resumes pre-scare levels [142, 143]; otherwise, neglecting behaviour (a reaction to the scare) would predict that the vaccine uptake would remain fixed throughout the vaccine scare.

The basis of human behaviour consists of not only of the individual attitudes, beliefs, opinions and disease awareness but how the population views these aspects as well. These factors change over time, and with the transmission of the disease influencing behaviour and behaviour influencing disease dynamics a feedback loop is formed between these two aspects (Figure 1.2). Understanding the feedback occurring between behaviour and incidence is important in the understanding vaccine coverage. A change in behaviour, even during an epidemic, can drastically alter the final size of the epidemic [77, 140]. Ref. [144] found perceived vaccine efficacy, experience with bad flu last season, recent vaccine complications and social influences were predictors for future influenza vaccination. If behavioural influences are neglected, the model’s credibility could be hurt in predicting the effectiveness of the vaccine policy [6].

As mentioned in Section 1.4, vaccine complications can have a drastic impact on vaccine coverage due to the negative impact of social influence. However, a decrease in vaccination is often accompanied by an increase in incidence, which leads to an increase in future vaccine coverage. Past models suggest that the oscillatory dynamics between vaccination and infection arise due to the behaviour of the population [143, 145, 146, 147]; as well, oscillations have been observed in data for pertussis incidence and vaccination [143, 148]. A simplified explanation behind the oscillatory effect would be when incidence is low there is

little “fear” (risk) of infection which causes vaccination to decrease; as incidence increases the risk of infection also increases resulting in more individuals vaccinating. Understanding the “why” behind these dynamics and the reasoning for certain behaviour can be a complex matter when dealing with human behaviour in a social setting[71]: that is where behaviour modelling comes into play, as it provides insight into these questions. However, behavioural responses are often neglected in modelling infectious disease [51, 129, 149, 150, 151, 152, 153], even though there is substantial proof of its importance [141].

An excellent example of the importance of incorporating behaviour would be the introduction of a vaccine which prevents HIV [6, 154]. Past models have found the barrier to eliminating HIV is the level of risky behaviour among the individuals; increases in risky behaviour could lead to an increase in the prevalence of HIV due to the vaccine providing a lower risk of HIV [6, 154]; therefore, individuals may be more likely to increase their risky behaviour [6].

Social influence is often incorporated in behaviour modelling. Empirical studies have shown that social influence occurs in populations [144, 155, 156, 157, 158, 159]. Social influence is often introduced as an *imitation process*, a process where an individual imitates another individual’s behaviour or strategy that looks to be better than their current choice. Examples of how social influence has been modelled previously include the number of neighbours with opposite opinions [160]; the opinion of the population at large[143], and media coverage [161]. However, the effect of social influence can entirely depend on how the social and contact network overlap one another [77, 162].

Behavioural responses to local infection can result in a dramatic reduction in incidence

in a structured network [77, 163]. In Ref [163] ring vaccination was found ineffective in eradicating a disease under a homogeneous mixing assumption; when network structure was introduced, outbreaks could be detained under voluntary ring vaccination. Therefore, when behavioural response is included in a well-mixed population the epidemic threshold is not affected [77]. However, under certain circumstances local behavioural responses in a network can stop the disease from spreading [77].

Incorporating behaviour into disease modelling can allow for *opinion clusters*, groups of individuals sharing the same opinion, to form. The formation of susceptible clusters can have a dramatic impact on the final size and duration of the epidemic [160]. Susceptible (non-vaccinating) clusters allow infection to survive for a longer period by jumping from one susceptible cluster to another and therefore, increasing the final size of the epidemic. Vaccinating clusters could allow for an increased chance of the disease to become vaccine resistant, which could allow for a large epidemic to occur. Opinion clusters have the greatest impact when vaccine coverage is close to the required level to reach herd immunity [160]; below the level of herd immunity, infection spreads easily; well above the level of herd immunity susceptible clusters have trouble forming, as well they are protected by the higher levels of vaccination.

1.6 Objectives

Using networks in infectious disease modelling can account for the social structure that appears in society; as well, network models allow for a more realistic setting in the sense that it avoids homogeneous mixing (each individual has equal probability of interacting

with everyone in the population) as assumed in deterministic compartmental models.

A main concern of public health is the effectiveness of a vaccine policy. With the use of mathematical models, theoretical tests can be done on vaccine policies before implementation. Similarly, mathematical models can be used to understand the factors that drive the level of vaccine coverage in a population. Understanding these factors can be key in determining whether or not a policy will be effective. Essentially, mathematical models can save time and money for public health by determining these factors before the policy is even implemented; however, it is important that these models consider human behaviour.

Human behaviour influences the spread of infectious disease, and incorporating behaviour into disease modelling is crucial for determining the true effectiveness of a policy. Past models have incorporated human behaviour [143, 160, 163, 164, 165, 166]; however, they tend to lack psychological realism. Studies have shown that future behaviour is dependent on past experiences and events [144, 156, 167, 168], which past models seem to neglect or simplify when modelling behaviour.

Under voluntary vaccine policies, such as for influenza, models should not assume that vaccination is automatic. There are many factors that go into the decision process of vaccination, and not every individual will vaccinate; these factors may include past experiences, social influence or even perceived vaccine efficacy [144, 156]. Understanding how these factors influence behaviour is key to increasing the vaccine coverage.

Past models have incorporated behavioural changes as a result of disease prevalence; however, these models disregard the experience of the individual. Individual experiences have been found to be important in the distribution of vaccine opinions [169]. Neglecting

the distribution of opinions can have a strong influence on the results of a model, as susceptible clusters can prolong and intensify an epidemic [160].

One aspect that has not been included in past models is how an individual's or population's perceived vaccine efficacy evolves over time. Most models assume the perceived vaccine efficacy is fixed and the event of infection after vaccination is neglected [163, 166, 170]. Perceived vaccine efficacy has been found to be an indicator of future vaccination [144, 156], and neglecting the events that influence perceived vaccination efficacy could mask significant results.

Infectious disease modelling is important for the understanding of the spread and control of disease; including a more psychological approach to human behaviour will enhance the model's integrity and will improve the insight of the control measures.

The objective of this thesis is to analyze the impact of behaviour and vaccination on the spread of disease in a network setting. The thesis is broken down into three separate papers; each with their own separate objective. The three topics that we will be focusing on are 1) a ring vaccination model 2) a network model where behaviour is dependent on personal experiences regarding infection, vaccination and vaccine efficacy and 3) a network model to determine whether incentives should be introduced into the vaccination process to entice superspreaders to vaccinate.

1. Impact of imitation processes on the effectiveness of ring vaccination

The objective of the ring vaccination model is to analyze the efficacy of the ring vaccination strategy under voluntary vaccination where decision making can be determined by imitation processes under individual heterogeneity.

2. The impact of personal experiences with infection and vaccination on behaviour-incidence dynamics of seasonal influenza

The objective of the model regarding personal experiences with infection and vaccination is:

- (i) to understand the impact of personal experiences regarding infection, vaccination and vaccine efficacy on the level of vaccine coverage
- (ii) to understand the impact of non-influenza-like-illness on behaviour-incidence dynamics
- (iii) to understand what parameters drive extreme oscillation in vaccine coverage
- (iv) to determine if strategy correlations on the network appear in the absence of imitation

3. Policy resistance undermines superspreadervaccination strategies for influenza

The objective of the model is to

- (i) understand whether super-spreading strategies are still effective when behaviour is accounted for
- (ii) understand whether economic incentives increase the chances of superspreaders vaccinating
- (iii) understand how individual vaccinating behaviour and perceived vaccine efficacy emerge from interactions in network structure, node degree and vaccine-disease dynamics.

In the next chapter we describe the voluntary ring vaccination model, followed by the model using personal experiences in the vaccination decision process, followed by the analysis of targeted vaccination of superspreaders where behaviour is accounted for. We conclude the thesis in Chapter 5.

Bibliography

- [1] S.C. Schoenbaum. Economic impact of influenza: The individual's perspective. The American Journal of Medicine, 82(6A):26–30, 1987.
- [2] D.B. Martin, L.B. Weiner, P.I. Nieburg, and D.C. Blair. Atypical measles in adolescents and young adults. Annals of Internal Medicine, 90(6):877–881, 1979.
- [3] A.S. Monto. The risk of seasonal and pandemic influenza: Prospects for control. Clin Infect Dis., 48(S1):S20–S25, 2009.
- [4] K. Nichol, A Lind, K Margolis, M Murdoch, R McFadden, S Magnan M Hauge, and M Drake. The effectiveness of vaccination influenza in healthy working adults. The New England Journal of Medicine, 333(14):889–893, 1995.
- [5] M.K. Degenova, D.M. Patton, J.A. Jurich, and S.M. MacDermid. Ways of coping among hiv-infected individuals. The American Journal of Medicine, 134(5):655–663, 1994.
- [6] E Klein, R Laxminarayan, D.L. Smith, and C.A. Gilligan. Economic incentives

- and mathematical models of disease. Environment and development economics, 12(5):707–732, 2007.
- [7] M.I. Meltzer, N.J. Cox, and K. Fukuda. The economic impact of pandemic influenza in the united states: priorities for intervention. Emerging Infectious Diseases, 5(5):659–671, 1999.
- [8] D.E. Bloom and G. Carliner. The economic impact of aids in the united states. Science, 239(4840):604–610, 1988.
- [9] G.H. Dayan, I.R. Oretega-Sanchez, C.W. LeBaron, and M.P. Quinlisk. The cost of containing one case of measles: The economic impact on the public health infrastructureiowa, 2004. Pediatrics, 116(1):e1–e4, 2005.
- [10] A. Monto. The risk of seasonal and pandemic influenza: Prospects for control. Clinical Infectious Diseases, 48(1):S20–S25, 2009.
- [11] The President and Fellows of Harvard College. Contagion: Historical views of diseases and epidemics-timeline. <http://ocp.hul.harvard.edu/contagion/timeline.html>, April 2012.
- [12] The President and Fellows of Harvard College. Contagion: Historical views of diseases and epidemics-the great plague of london, 1665. <http://ocp.hul.harvard.edu/contagion/plague.html>, June 2012.
- [13] The President and Fellows of Harvard College. Contagion: Historical views of diseases and epidemics-the boston smallpox epidemic, 1721. <http://ocp.hul.harvard.edu/contagion/smallpox.html>, June 2012.

- [14] The President and Fellows of Harvard College. Contagion: Historical views of diseases and epidemics-the yellow fever epidemic in philadelphia, 1793. <http://ocp.hul.harvard.edu/contagion/yellowfever.html>, June 2012.
- [15] CBC News. Cholera's seven pandemics: Disease has killed millions since 19th century. <http://www.cbc.ca/news/health/story/2008/05/09/f-cholera-outbreaks.html>, June 2012.
- [16] Alexandra Silver. Top 10 terrible epidemics-the 1916 polio epidemic. http://www.time.com/time/specials/packages/article/0,28804,2027479_2027486_2027527,00.html, May 2012.
- [17] National Museum of American History. What ever happened to polio: Communities. <http://americanhistory.si.edu/polio/americanepi/communities.htm>, June 2012.
- [18] World Health Organization. Who in 60 years: a chronology of public health milestones. pages 1–5, 2008.
- [19] World Health Organization. Ebola haemorrhagic fever. <http://www.who.int/mediacentre/factsheets/fs103/en/>, June 2012.
- [20] E. Fee and T.M. Brown. Michael s. gottlieb and the identification of aids. American Journal of Public Health, 96(6):982983, 2006.
- [21] World Health Organization. Hiv/aids. <http://www.who.int/mediacentre/factsheets/fs360/en/index.html>, June 2012.

- [22] World Health Organization. Sars (severe acute respiratory syndrome). <http://www.who.int/ith/diseases/sars/en/>, June 2012.
- [23] P. Y. Lee, D. B. Matchar, D. A. Clements, J. Huber, J. D. Hamilton, and E. D. Peterson. Economic analysis of influenza vaccination and antiviral treatment for healthy working adults. *Annals of Internal Medicine*, 137(4):225–231, 2002.
- [24] J. C. Kwong, L.C. Rosella, and H. Johansen. Trends in influenza vaccination in canada, 1996/1997 to 2005. *Health Reports*, 18(4):1–11, 2007.
- [25] T. Szucs. The socio-economic burden of influenza. *Journal of Antimicrobial Chemotherapy*, 44:11–15, 1999.
- [26] Centers for Disease Control and Prevention. 2011-2012 influenza season: Disease activity. <http://www.cdc.gov/flu/about/season/flu-season-2011-2012.htm>, April 2012.
- [27] D.J.D. Earn, J. Dushoff, and S.A. Levin. Ecology and evolution of the flu. *TRENDS in Ecology and Evolution*, 17(7):334–340, 2002.
- [28] F.A. Sarubbi. Influenza: A historical perspective. *Southern Medical Journal*, 96(8):735–736, 2003.
- [29] N.J. Cox and K. Subbarao. Global epidemiology of influenza: Past and present. *Annual Review of Medicine*, 51:407–421, 2000.
- [30] E.D. Kilbourne. Influenza pandemics of the 20th century. *Emerg. Infect. Dis.*, 12(1):9–14, 2006.

- [31] A. Flahault and P. Zylberman. Influenza pandemics: past, present and future challenges. Public Health Reviews, 32(1):319–340, 2010.
- [32] CBC News. H1n1 pandemic officially over: Who. <http://www.cbc.ca/news/health/story/2010/08/10/who-h1n1-swine-flu-pandemic.html>, June 2012.
- [33] C. Kingsford, N. Nagarajan, and S.L. Salzberg. 2009 swine-origin influenza a (h1n1) resembles previous influenza isolates. PLoS ONE, 4(7):e6402, 2009.
- [34] Centers for Disease Control and Prevention. Flu symptoms and severity. <http://www.cdc.gov/flu/about/disease/symptoms.htm>, May 2012.
- [35] P.A. Gross. Preparing for the next influenza pandemic: A reemerging infection. Annals of Internal Medicine, 124(7):682–685, 1996.
- [36] M.J. Keeling and P. Rohani. Modeling Infectious Diseases in Humans and Animals. Princeton Press, 2008.
- [37] M. Begon, M. Bennett, R.G. Bowers, N.P. French, S.M. Hazel, and J. Turner. A clarification of transmission terms in host-microparasite models: numbers, densities and areas. Epidemiol Infect, 129(1):147–153, 2002.
- [38] H. McCallum, N. Barlow, and J. Hone. How should pathogen transmission be modelled? TRENDS in Ecology and Evolution, 16(6):295–300, 2001.
- [39] H.W. Hethcote. Mathematical understanding of infectious disease dynamics. Lecture Notes Series, Institute for Mathematical Sciences, National University of Singapore, 16:1–61, 2008.

- [40] L. Mao. Agent-based simulation for weekend-extension strategies to mitigate influenza outbreaks. *BMC Public Health*, 11(522), 2011.
- [41] J. Truscott, C. Fraser, W. Hinsley, S. Cauchemez, C. Donnelly, A. Ghani, N. Ferguson, and A. Meeyai. Quantifying the transmissibility of human influenza and its seasonal variation in temperate regions. *PLoS Currents*, 1:RRN1125, 2009.
- [42] J. Truscott, C. Fraser, S. Cauchemez, A. Meeyai, W. Hinsley, C.A. Donnelly, A. Ghani, and N. Ferguson. Essential epidemiological mechanisms underpinning the transmission dynamics of seasonal influenza. *J. R. Soc. Interface*, pages 304–312, 2012.
- [43] K. Dietz. The evaluation of rubella vaccination strategies. In R. W. Hiorns and K. Cooke (Eds.), *The Mathematical Theory of the Dynamics of Biological Populations*, 2:81–98, 1981.
- [44] R. Gani and S. Leach. Transmission potential of smallpox in contemporary populations. *Letters to Nature*, 414:748–751, 2001.
- [45] N. Sfinkas, D. Greenhalgh, and F. Lewis. The basic reproduction number and the vaccination coverage required to eliminate rubella from england and wales. *Mathematical Population Studies: An International Journal of Mathematical Demography*, 14(1):3–29, 2007.
- [46] R.M. Anderson and R.M. May. Directly transmitted infectious diseases: Control by vaccination. *Science*, 215:1053–1060, 1982.

- [47] J. Dushoff, J.B. Plotkin, S.A. Levin, and D.J.D. Earn. Dynamical resonance can account for seasonality of influenza epidemics. *PNAS*, 101(48):16915–16916, 2004.
- [48] O. Diekmann and M. Kretzschmar. Patterns in the effects of infectious diseases on population growth. *Journal of Mathematical Biology*, 29:539–570, 1991.
- [49] H.W. Hethcote and J.W. VanArk. Epidemiological models for heterogeneous populations:proportionate mixing, parameter estimation, and immunization programs. *Mathematical Biosciences*, 84:85–118, 1987.
- [50] R.M. May and R.M. Anderson. Spatial heterogeneity and the design of immunization programs. *Mathematical Biosciences*, 72:83–111, 1984.
- [51] J. Dushoff, J.B. Plotkin, C. Viboud, L. Simonsen, M. Miller, M. Loeb, and D.J. D. Earn. Vaccinating to protect a vulnerable subpopulation. *PLoS Medicine*, 4(5):0921–0927, 2007.
- [52] M.J. Keeling and K.T.D. Eames. Networks and epidemic models. *J. R. Soc. Interface*, 2:295–307, 2005.
- [53] M.A. Efendiev and H.J. Eberl. On positivity of solutions of semi-linear convection-diffusion-reaction systems, with applications in ecology and environmental engineering. *RIMS Kyoto Kokyuroko*, 1542:92–101, 2007.
- [54] L.A. Meyers. Contact network epidemiology: Bond percolation applied to infectious disease prediction and control. *Bull. Amer. Math. Soc.*, 44:63–86, 2006.

- [55] G. Witten and G. Poulter. Simulations of infectious diseases on networks. *Computers in Biology and Medicine*, 37:195–205, 2007.
- [56] A.L. Barabasi, H. Jeong, Z. Neda, E. Ravasz, A. Schubert, and T. Vicsek. Evolution of the social network of scientific collaborations. *PhysicaA*, 311:590–614, 2002.
- [57] M.D.F. Shirley and S.P. Rushton. The impacts of network topology on disease spread. *Ecological Complexity*, 2:287–299, 2005.
- [58] M. Keeling. The implications of network structure for epidemic dynamics. *Theoretical Population Biology*, 67:1–8, 2005.
- [59] S. Bansal, B.T. Grenfell, and L.A. Meyers. When individual behaviour matters: homogeneous and network models in epidemiology. *J. R. Soc. Interface*, 4:879–891, 2007.
- [60] X. Fu, M. Small, D.M. Walker, and H. Zhang. Epidemic dynamics on scale-free networks with piecewise linear infectivity and immunization. *Physical Review E*, 77:036113, 2008.
- [61] F. Liljeros, C.R. Edling, L.A. Nunes Amaral, H. E. Stanley, and Y. Aberg. The web of human sexual contacts: Promiscuous individuals are the vulnerable nodes to target in safe sex campaigns. *Nature*, 411:907–908, 2001.
- [62] O. Hein, M. Schwind, and W. Konig. Scale-free networks: The impact of fat tailed degree distribution on diffusion and communication processes. *WIRTSCHAFTSINFORMATIK*, 48(4):267–275, 2007.

- [63] M. Barthelemy. Spatial networks. *Physics Reports*, 99(1-3):1–101, 2011.
- [64] E. Volz and L.A. Meyers. Epidemic thresholds in dynamic contact networks. *J. R. Soc. Interface*, 6(32):233–241, 2009.
- [65] Y. Hayashi, M. Minoura, and J. Matsukubo. Oscillatory epidemic prevalence in growing scale-free networks. *Physical Review E*, 69:016112, 2004.
- [66] L.A. Meyers, B. Pourbohloul, M.E.J. Newman, D.M. Skowronski, and R.C. Brunham. Network theory and sars: predicting outbreak diversity. *Journal of Theoretical Biology*, 232(1):71–81, 2005.
- [67] D. M. Cornforth, T. C. Reluga, E. Shim, C. T. Bauch, A. P. Galvani, and L. A. Meyers. Erratic flu vaccination emerges from short-sighted behaviour in contact networks. *PLoS Comp Biol*, 7(1):e1001062, 2011.
- [68] R.M. May and A.L. Lloyd. Infection dynamics on scale-free networks. *Physical Review E*, 64(6):066112, 2001.
- [69] M.E.J. Newman. The structure and function of complex networks. *SIAM Review*, 45:167–256, 2003.
- [70] M.E.J. Newman. Models of the small world. *JOURNAL OF STATISTICAL PHYSICS*, 101(3-4):819–841, 2000.
- [71] R.M. May. Network structure and the biology of populations. *TRENDS in Ecology and Evolution*, 21(7):394–399, 2006.

- [72] M.E.J. Newman. Properties of highly clustered networks. *Physical Review E*, 68:026121, 2003.
- [73] J.O. Lloyd-Smith, S.J. Schreiber, P.E. Kopp, and W.M. Getz. Superspreading and the effect of individual variation on disease emergence. *Nature*, 438:355–359, 2005.
- [74] J.C. Miller. Epidemic size and probability with heterogeneous infectivity and susceptibility. *Physical Review E*, 76(1):010101(4), 2007.
- [75] H. Andersson. Epidemics in a population with social structure. *Mathematical Biosciences*, 140:79–84, 1997.
- [76] M. Keeling and B.T. Grenfell. Individual-based perspectives on r_0 . *Journal of Theoretical Biology*, 203:51–61, 2000.
- [77] S. Funk, E. Gilad, C. Watkins, and V.A.A. Jansen. The spread of awareness and its impact on epidemic outbreaks. *PNAS*, 106(16):6872–6877, 2009.
- [78] M.E.J. Newman. Spread of epidemic disease on networks. *Physical Review E*, 66:016128, 2002.
- [79] S. Bansal, J. Read, B Pourbohloul, and L.A. Meyers. The dynamic nature of contact networks in infectious disease epidemiology. *Journal of Biological Dynamics*, 4(5):478–489, 2010.
- [80] M.E.J. Newman, D.J. Watts, and S.H. Strogatz. Random graph models of social networks. *PNAS*, 99(Suppl1):2566–2572, 2002.

- [81] M. Kretzschmar and M. Morris. Measures of concurrency in networks and the spread of infectious disease. *Mathematical Biosciences*, 133(2):165–195, 1996.
- [82] A.S. Klov Dahl. Social networks and the spread of infectious diseases: The aids example. *Social Science and Medicine*, 121(11):1203–1216, 1985.
- [83] Centers for Disease Control and Prevention. Flu vaccine effectiveness: Questions and answers for health professionals. <http://www.cdc.gov/flu/professionals/vaccination/effectivenessqa.htm#studies-differ>, July 2012.
- [84] C.T. Bauch and S. Bhattacharyya. Evolutionary game theory and social learning can determine how vaccine scares unfold. *PLoS Comput Biol*, 8(4):e1002452, 2012.
- [85] D.L. Heymann and R.B. Aylward. Mass vaccination: When and why. *CTMI*, 304:1–16, 2006.
- [86] W.J. Bicknell. The case for voluntary smallpox vaccination. *The New England Journal of Medicine*, 346:1323–1325, 2002.
- [87] M. Kretzschmar, S. van den Hof, J. Wallinga, and J. van Wijngaarden. Ring vaccination and smallpox control. *Emerging Infectious Diseases*, 10(5):832–841, 2004.
- [88] J.W. Hopkins. The eradication of smallpox: organizational learning and innovation in international health administration. *J Dev Areas*, 22(3):321–332, 1988.
- [89] CMAJ. Who marks 25th anniversary of last naturally acquired smallpox case. *CMAJ*, 167(11):1278, 2002.

- [90] The Economist. Eradicating polio:late? or never?a plan to wipe out polio by the end of next year is in trouble. http://www.economist.com/node/18985991?story_id=18985991&fsrc=rss, May 2012.
- [91] Polio Global Eradication Initiative. Polio this week. <http://www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx>, May 2012.
- [92] M. Cheng. Global measles deaths tumble, but no eradication in sight, 2012.
- [93] World Health Organization. Measles-fact sheet. <http://www.who.int/mediacentre/factsheets/fs286/en/>, May 2012.
- [94] A. Hinman. Eradication of vaccine-preventable diseases. Annu. Rev. Public Health, 20:211–229, 1999.
- [95] J.C. Baker. The pertussis vaccine controversy in great britain, 1974-1986. Vaccine, 21:25–26, 2003.
- [96] V.A.A. Jansen, N. Stollenwerk, H.J. Jensen, M.E. Ramsay, W.J. Edmunds, and C.J. Rhodes. Measles outbreaks in a population with declining vaccine uptake. Science, 301(5634):804, 2003.
- [97] A. Nicoll, D. Elliman, and E. Ross. Mmr vaccination and autism 1998. BMJ, 316(7133):715–716, 1998.
- [98] J.D. Cherry. Historical review of pertussis and the classical vaccine. The Journal of Infectious Diseases, 174(3):S259–263, 1996.

- [99] J.D. Cherry, P.A. Brunell, G.S. Golden, and D.T. Darzon. Report of the task force on pertussis and pertussis immunization. Pediatrics, 81:939–984, 1988.
- [100] S.L. Hodder and E.A. Mortimer. Epidemiology of pertussis and reactions to pertussis vaccine. Epidemiological Review, 14:243–267, 1992.
- [101] W.D. Sheilds, C. Nielson, V. Jacobsen, P. Christenson, B. Zachau-Christiansen, and J.D. Cherry. Relationship of pertussis immunization to the onset of neurologic disorders: a retrospective epidemiologic study. The Journal of Pediatrics, 113(5):801–805, 1988.
- [102] M.R. Griffin, W.A. Ray, E.A. Mortimer, G.M. Fenichel, and W. Schaffner. Risk of seizures and encephalopathy after immunization with the diphtheria-tetanus-pertussis vaccine. JAMA, 263(12):1641–1645, 1990.
- [103] S.E. Weis, P.C. Slocum, F.X. Blais, B. King, M. Nunn, G.B. Matney, E. Gomez, and B.H. Foresman. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. The New England Journal of Medicine, 330:1179–1184, 1994.
- [104] World Health Organization. Multidrug-resistant tuberculosis (mdr-tb). <http://www.who.int/tb/challenges/mdr/en/>, May 2012.
- [105] D.E. Snider, G.M. Cauthen, L.S. Farer, .D. Kelly G, J.O. Kilburn, R.C. Good, and S.W. Dooley. Drug-resistant tuberculosis. The American Review of Respiratory Disease, 144(3):732, 1991.

- [106] J.L. Trouillet, J. Chastre, A. Vuagnat, M.L. Joly-Guillou, D. Combaux, M.C. Dom-bret, and C. Gibert. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am. J. Respir. Crit. Care Med., 157(2):531–539, 1998.
- [107] S. Ewig, M. Ruiz, A. Torres, F. Marco, J.A. Martinez, M. Sanchez, and J. Mensa. Pneumonia acquired in the community through drug-resistant streptococcus pneumoniae. Am. J. Respir. Crit. Care Med., 159(6):1835–1842, 1999.
- [108] J. Garau. Treatment of drug-resistant pneumococcal pneumonia. The Lancet Infectious Disease, 2(7):404–415, 2002.
- [109] D.D. Richmann. Hiv drug resistance. AIDS Research and Human Retroviruses, 8(6):1065–1071, 1992.
- [110] World Health Organization. Hiv drug resistance. <http://www.who.int/hiv/topics/drugresistance/en/index.html>, May 2012.
- [111] D. Boden, A. Hurley, L. Zhang, Y. Cao, Y. Guo, E. Jones, J. Tsay, J. Ip, C. Farthing, K. Limoli, N. Parkin, and M. Markowitz. Hiv-1 drug resistance in newly infected individuals. JAMA, 282(12):1135–1141, 1999.
- [112] M.B. Reed. Malaria drug resistance. Bulletin of the World Health Organization, 78(3):407, 2000.
- [113] W.H. Wernsdorfer. Epidemiology of drug resistance in malaria. Acta Tropica, 56(2-3):143 – 156, 1994.

- [114] N.J. White. Drug resistance in malaria. British Medical Bulletin, 54(3):703 – 715, 1998.
- [115] R.M. Zinkernagel. Immunology taught by viruses. Science, 271:173–178, 1996.
- [116] M.L. Cohen. Epidemiology of drug resistance: Implications for a post-antimicrobial era. Science, 257:1050–1055, 1992.
- [117] M. Small and C.K. Tse. Clustering model for transmission of the sars virus: application to epidemic control and risk assessment. PHYSICA A, 351:499–511, 2005.
- [118] J. Wang, Z. Liu, and J. Xu. Epidemic spreading on uncorrelated heterogeneous networks with non-uniform transmission. PHYSICA A: Statistical Mechanics and its Applications, 382:715–721, 2007.
- [119] J.T. Kemper. On the identification of superspreaders for infectious disease. Mathematical Biosciences, 48:111–127, 1980.
- [120] A.P. Galvani and R.M. May. Dimensions of superspreading. Nature, 438:293–295, 2005.
- [121] T. Mkhatchwati A. Mummert. Modeling super-spreading events for infectious diseases: Case study sars. IAENG International Journal of Applied Mathematics, 41(2), 2011.
- [122] R.A. Stein. Super-spreaders in infectious diseases. International Journal of Infectious Disease, 15:510–513, 2011.

- [123] S.H. Paull, S. Song, K.M. McClure, L.C. Sackett, A.M Kilpatrick, and P.T.J. Johnson. From superspreaders to disease hotspots: linking transmission across hosts and space. *Frontiers in Ecology and the Environment*, 48:111–127, 2011.
- [124] M.E. Woolhouse, C. Dye, J.F. Etard, T. Smith, L.D. Charlwood, G.P. Garnett, P. Hagan, J.L. Hii, P.D. Ndhlovu, R.J. Quinnell, C.H. Watts, S.K. Chandiwana, and R.M. Anderson. Heterogeneities in the transmission of infectious agents: implications for the design of control programs. *Proc Natl Acad Sci U S A.*, 94(1):338–342, 1997.
- [125] R.A. Stein. Lessons from outbreaks of h1n1 influenza. *Annals of Internal Medicine*, 151:59–62, 2009.
- [126] W.J. Bai, T. Zhou, and B.H. Wang. Immunization of susceptibleinfected model on scale-free networks. *PHYSICA A*, 384:656–662, 2007.
- [127] G. Hartvigsen, J.M. Dresch, A.L. Zielinski, A.J. Macula, and C.C. Leary. Network structure, and vaccination strategy and effort interact to affect the dynamics of influenza epidemics. *Journal of Theoretical Biology*, 246:205–213, 2007.
- [128] J.C. Miller and J.M. Hyman. Effective vaccination strategies for realistic social networks. *Physica A*, 386:780–785, 207.
- [129] P. Holme. Efficient local strategies for vaccination and network attack. *Europhysics Letters*, 68(6):908–914, 2004.
- [130] R. Cohen, S. Havlin, and D. ben Avraham. Efficient immunization strategies for computer networks and populations. *Physical Review Letters*, 91(24):247901, 2003.

- [131] J. Treanor. Influenza vaccine- outmaneuvering antigenic shift and drift. New England Journal of Medicine, 350:218–220, 2004.
- [132] Centers for Disease Control and Prevention. Ithe flu season. <http://www.cdc.gov/flu/about/season/flu-season.htm>, May 2012.
- [133] Centers for Disease Control and Prevention. Final state-level influenza vaccination coverage estimates for the 2010-11 season: United states, national immunization survey and behavioral risk factor surveillance system, august 2010 through may 2011. http://www.cdc.gov/flu/professionals/vaccination/coverage_1011estimates.htm, April 2012.
- [134] Centers for Disease Control and Prevention. Influenza vaccination coverage: Fluvaxview:2010-11 influenza season. <http://www.cdc.gov/flu/professionals/vaccination/vaccinecoverage.htm>, May 2012.
- [135] A.R. Tuite, D.N. Kwong, and A.L. Greer. Optimal pandemic influenza vaccine allocation strategies for the canadian population. PLoS ONE, 5(5):e10520, 2010.
- [136] S.D. Mylius, T.J. Hagenaars, A.K. Lunger, and J. Wallinga. Optimal allocation of pandemic influenza vaccine depends on age, risk and timing. Vaccine, 26:3742–3749, 2008.
- [137] L. Matrajt and I.M. Longini. Optimizing vaccine allocation at different points in time during an epidemic. PLoS ONE, 5(11):e13767, 2010.
- [138] J. Medlock and A. Galvani. Optimizing influenza vaccine distribution. Science, 325(5948):1705–1708, 2009.

- [139] K. L. Nichol. Cost-benefit analysis of a strategy to vaccinate healthy working adults against influenza. *Arch Intern Med.*, 161(5):749–759, 2001.
- [140] S. Funk, M. Salathe, and V.A.A. Jansen. Modelling the influence of human behaviour on the spread of infectious diseases: a review. *The Journal of the Royal Society Interface*, 7(50):1247–1256, 2010.
- [141] N. Ferguson. Capturing human behaviour. *Nature*, 446:733, 2007.
- [142] C.T. Bauch and D.J.D. Earn. Vaccination and theory of games. *PNAS*, 101(36):13391–13394, 2004.
- [143] C.T. Bauch. Imitation dynamics predict vaccinating behaviour. *Proceedings of the Royal Society B*, 272(1573):1669–1675, 2005.
- [144] G. Chapman and E. Coups. Predictors of influenza vaccine acceptance among healthy adults. *Preventive Medicine*, 29(4):249–262, 1999.
- [145] T.C. Reluga, C.T. Bauch, and A.P. Galvani. Evolving public perceptions and stability in vaccine uptake. *Mathematical Biosciences*, 204(2):185–198, 2006.
- [146] R. Vardavas, R. Breban, and S. Blower. Can influenza epidemics be prevented by voluntary vaccination? *PLoS Computational Biology*, 3(5):e85, 2007.
- [147] A. d’Onofrio, P. Manfredi, and E. Salinelli. Fatal sir diseases and rational exemption to vaccination. *Mathematical Medicine and Biology*, 25(4):337–357, 2008.
- [148] E. Miller and N.J. Gay. Epidemiological determinants of pertussis. *Dev. Biol. Stand*, 89:15–23, 1997.

- [149] A. d'Onofrio. Stability properties of pulse vaccination strategy in seir epidemic model. *Mathematical Biosciences*, 179(1A):57–72, 2002.
- [150] R. Patel, I.M. Logini, and M.E. Halloran. Finding optimal vaccination strategies for pandemic influenza using genetic algorithms. *Journal of Theoretical Biology*, 234(2):201–212, 2005.
- [151] A. Grabowski and R. Kosinski. The sirs model of epidemic spreading in a virtual society. *ACTA PHYSICA POLONICA A*, 14(3):589–596, 2008.
- [152] F. Takeuchi and K. Yamamoto. Effectiveness of vaccination strategies for infectious diseases according to human contact networks. In Vaidy Sunderam, Geert van Albada, Peter Sloot, and Jack Dongarra, editors, *Computational Science ICCS 2005*, volume 3514 of *Lecture Notes in Computer Science*, pages 956–962. Springer Berlin / Heidelberg, 2005.
- [153] S. Bansal, J. Read, B Pourbohloul, and L.A. Meyers. A comparative analysis of influenza vaccination programs. *PLoS Medicine*, 3(10):e387, 2006.
- [154] S.M. Blower and A.R. McLean. Prophylactic vaccines, risk behavior change, and the probability of eradicating hiv in san francisco. *Science*, 256:1451–1454, 1994.
- [155] M.H. Merrill, A.C. Hollister, S.F. Gibbens, and A.W. Haynes. Attitudes and reactions of the public to health programs ii. attitudes of californians toward poliomyelitis vaccination. *Am J Public Health Nations Health*, 48(2):146–152, 1958.
- [156] K.M. Cummings, A.M. Jette, B.M. Brock, and D.P. Haefner. Psychosocial deter-

- minants of immunization behavior in a swine influenza campaign. Medical Care, 17(6):639–649, 1979.
- [157] P. Streefland, A.M.R. Chowdhury, and P. Ramos-Jimenez. Patterns of vaccination acceptance. Social Science and Medicine, 49(12):1705–1716, 1999.
- [158] L.A. Sturn, R.M. Mays, and G.D. Zimet. Parental beliefs and decision making about child and adolescent immunization: from polio to sexually transmitted infections. J. Dev. Behav. Pediatr, 26(6):441–452, 2005.
- [159] A.L. Johnson, C.D. Jenkins, R. Patrick, and T.J. North Cutt. Epidemiology of Polio Vaccine Acceptance. A Social and Psychological Analysis. Florida State Board of Health, monograph 3 edition, 1962.
- [160] M. Salathe and S. Bonhoeffer. The effect of opinion clustering on disease outbreaks. J. R. Soc. Interface, 5(29):1505–1508, 2005.
- [161] J.M. Tchuenche, N. Dube, C.P. Bhunu, R.J. Smith?, and C.T. Bauch. The impact of media coverage on the transmission dynamics of human influenza. BMC Public Health, 11(Suppl 1):S5, 2011.
- [162] K.T.D. Eames. Networks of influence and infection: parental choices and childhood disease. Journal of the Royal Society Interface, 6(38):811–814, 2009.
- [163] A. Perisic and C.T. Bauch. Social contact networks and disease eradicability under voluntary vaccination. PLoS Computational Biology, 5(2):e1000280, 2009.

- [164] H. Zhang, J. Zhang, C. Zhou, M. Small, and B. Wang. Hub nodes inhibit the outbreak of epidemic under voluntary vaccination. *New Journal of Physics*, 12(2):023015, 2010.
- [165] F. Fu, D. I. Rosenbloom, L. Wang, and M. A. Nowak. Imitation dynamics of vaccination behaviour on social networks. *Proc. Biol Sci*, 278(1702):42–49, 2011.
- [166] P.E.M. Fine and J.A. Clarkson. Individual versus public priorities in the determination of optimal vaccination policies. *American Journal of Epidemiology*, 124(6):1012–1020, 1986.
- [167] I. Ajzen. The theory of planned behaviour. *Organizational Behavior and Human Decision Processes*, 50:179–211, 1991.
- [168] G.B. Chapman and E.J. Coups. Emotions and preventive health behavior: Worry, regret, and influenza vaccination. *Health Psychology*, 25(1):82–90, 2006.
- [169] C.R. Wells and C.T. Bauch. The impact of personal experiences with infection and vaccination on behaviour-incidence dynamics of seasonal influenza. *EPIDEMICS*, 4(3):139–151, 2012.
- [170] B. Wu and L. Wang. Imperfect vaccine aggravates the long-standing dilemma of voluntary vaccination. *PLoS ONE*, 6(6):e20577, 2011.

Chapter 2

Impact of imitation processes on the effectiveness of ring vaccination

C.R. Wells, J.M. Tchuenche, L.A. Meyers, A.P. Galvani and C.T. Bauch (2011), Bulletin of Mathematical Biology, Volume 73, Number 11, pages 2748-2772

Abstract

Ring vaccination can be a highly effective control strategy for an emerging disease or in the final phase of disease eradication, as witnessed in the eradication of smallpox. However, the impact of behavioural dynamics on the effectiveness of ring vaccination has not been explored in mathematical models. Here we analyze a series of stochastic models of voluntary ring vaccination. Contacts of an index case base vaccinating decisions on their own individual payoffs to vaccinate or not vaccinate, and they can also imitate the behaviour of other contacts of the index case. We find that including imitation changes the probability of containment through ring vaccination considerably. Imitation can cause a strong majority of contacts to choose vaccination in some cases, or to choose non-vaccination in other cases—even when the equivalent solution under perfectly rational (non-imitative) behaviour yields mixed choices. Moreover, imitation processes can result in very different outcomes in different stochastic realizations sampled from the same parameter distributions, by magnifying moderate tendencies toward one behaviour or the other: in some realizations, imitation causes a strong majority of contacts not to vaccinate, while in others, imitation promotes vaccination and reduces the number of secondary infections. Hence, the effectiveness of ring vaccination can depend significantly and unpredictably on imitation processes. Therefore our results suggest that risk communication efforts should be initiated early in an outbreak when ring vaccination is to be applied, especially among subpopulations that are heavily influenced by peer opinions.

2.1 Introduction

Mass vaccination has historically been the dominant means of reducing morbidity and mortality due to vaccine-preventable infectious diseases [1]. However, in some contexts, other strategies such as ring vaccination are preferable. Ring vaccination involves identifying infectious index cases and vaccinating their close contacts to prevent them from being infected [2, 3]. Ring vaccination tends to be more efficient and more effective than UMV for preventing outbreaks when (1) outbreaks are localized, (2) infected individuals and their exposed contacts can be rapidly identified, and (3) the vaccine induces an immune response rapidly enough for contacts to be protected before they can become infected.

Ring vaccination has been applied to outbreak control for hepatitis A [4], foot-and-mouth disease in cattle [5, 6] and smallpox [7]. Ring vaccination was credited as the strategy that culminated the eradication of smallpox [8]. One of the earliest applications of ring vaccination was in Nigeria, when a smallpox outbreak developed among a religious sect. Faced with limited resources and vaccine supplies, staff learned to isolate infected individuals and identify and vaccinate their contacts, leading to successful containment of the outbreak [8, 9]. In the case of smallpox, the vaccine can prevent both infection and disease in persons who have already been infected, meaning that ring vaccination could be particularly effective despite delays in identifying index cases. For pandemics of novel emerging pathogens, ring vaccination may likewise be an optimal strategy if there are not sufficient vaccine supplies to mount mass vaccination campaigns.

Because ring vaccination involves reaching a relatively small number of individuals, the success or failure of ring vaccination can depend strongly on stochastic effects. The

debate about whether to include stochastic effects in infection transmission models is long-running [10]. Often, the average of many realizations of a stochastic model is identical to what would be predicted from a deterministic model, in which case the primary advantage of the stochastic model is to provide an estimate of variability. However, in other situations the average of many stochastic realizations may differ from the prediction of the equivalent deterministic model or there may be other important qualitative differences. For instance, if the number of secondary infections per index case is modelled as a negative binomial distribution, a stochastic modelling approach can predict more frequent extinctions, and rarer but more severe outbreaks, than a deterministic modelling approach [10]. Similarly, network models have been used to demonstrate that a wide range of outbreak sizes and outbreak probabilities caused by severe acute respiratory syndrome (SARS) are possible even for the same R_0 , highlighting the role of underlying contact networks [11].

In a separate but related vein, models have been used to explore the interaction between disease transmission and individual vaccinating behaviour [12, 13, 14, 15, 16, 17, 18] and how model dynamics change if transmission is modelled as occurring on a network instead of through homogeneous mixing [19, 20, 21, 22]. Conversely, there have been a number of mathematical models of ring vaccination that do not explicitly incorporate behaviour considerations [2, 3, 23, 24]. However, relatively little work has focussed on behavioural effects and ring vaccination per se [20, 21].

Some of these previous models have assumed that individuals adopt new strategies through an imitation process, where individuals base their vaccinating decisions partly on the experiences or opinions of other individuals in the population. Empirical studies confirm the common knowledge that the opinion of the healthcare provider is important

determinant of vaccine uptake [25]. However, empirical studies also find that peer opinion has a very large influence on individual vaccinating decisions [26, 27, 28, 29]. For example, Merrill et al (1958) [26] found that vaccinating decisions of mothers in California were influenced by their peer groups. Sturm et al (2005)[28] review Merrill et al (1958) [26] and other more recent publications documenting the strong roles of peer group opinion and social norms in vaccinating decisions. An empirical study analyzing perceptions of vaccination on real-world social networks likewise found that peer opinion is an important determinant of perceive value of vaccination and vaccinating behaviour, to the point that " students coordinate their vaccinating decisions with their friends" [29]. Hence, imitation processes appear to be an important mechanism in individual vaccination decisions.

Here, we evaluate the impact of imitation dynamics on the success of voluntary ring vaccination. We develop a series of simple stochastic models in which individuals can choose whether or not to vaccinate based on the benefits (to themselves) of vaccinating versus the benefits of not vaccinating. Moreover, in some versions of the model the individual decision whether or not to vaccinate is influenced by the decisions of other contacts of the index case. We incorporate stochasticity since stochastic effects can be important determinants the success or failure of ring vaccination. The vaccinating choices of the index case.s contacts therefore determine whether or not ring vaccination will be successful. The particular question of interest is whether models that include stochastic effects and imitation processes have qualitatively different predictions from a model that is deterministic, and/or does not include imitation processes.

2.2 Model

We describe three models in this subsection (see Appendix 2.C for corrected version). In the “simple stochastic model”, we employ a stochastic model of vaccine decision-making among the contacts of an index case, where the payoffs of vaccinating versus not vaccinating are the same for all contacts of the index case. We analyze this model to generate expressions for the probability of outbreak control and the expected number of secondary infections created by the index case. In the “distributed stochastic model”, this stochastic model is further extended by drawing parameters for vaccine and disease risks for each individual from probability distributions, meaning that contacts of the index case can have different payoff functions, leading to different decisions. Finally, for “the distributed stochastic model with imitation”, the distributed stochastic model is extended by including an imitation process between contacts of the index case. All three models are also simulated for a range of parameter values to gain insights into impact of imitation behaviour in the context of voluntary ring vaccination.

2.2.1 Simple Stochastic Model

We suppose the index case has Q contacts, each contact is initially susceptible, and there is a daily probability p of transmitting infection to a given contact. We assume that the infection has an incubation period of ω days, an infectious period of δ days, and a latent period of σ days. Likewise, we assume that the time between the decision to vaccinate and attainment of protective immunity (where individuals do not develop disease and do not transmit further) is λ days, as a result of either logistic delays and/or the time required

Parameter	Definition	Baseline Value
Q	Number of contacts of index case	10 or 100
p	Transmission probability per edge per day	0.05
ω	Incubation period	5 days
δ	Infectious Period	5 days
σ	Latent Period	4 days
λ	Time between decision to vaccinate and attainment of protective immunity	1 day
ε	Vaccine Efficacy	0.95
r_{vac}	Penalty due to being vaccinated (e.g. adverse events, potential monetary cost)	0.001
r_{inf}	Penalty due to being infected (e.g. disease complications)	0.3
L	Baseline payoff	1
\mathcal{P}_V	Payoff to vaccinate as soon as index case exhibits symptoms	
\mathcal{P}_N	Payoff not to vaccinate	

Table 2.1: Parameter definitions and baseline values. Note: Number of contacts of index case (Q) has been corrected from the original paper

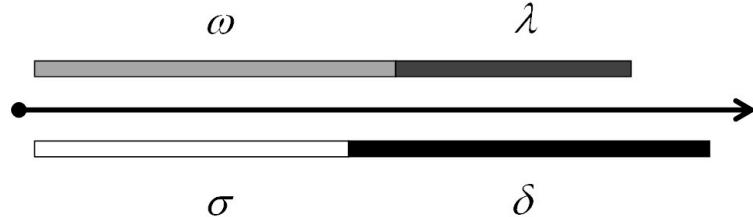


Figure 2.1: Timeline when $\lambda + \omega < \delta + \sigma$

for the immune system to mount a fully protective response. The vaccine efficacy is ε . Parameter values and definitions appear in Table 2.1.

We will derive \mathcal{P}_{cont} , defined as the probability that there is no secondary transmission, as well as \mathcal{R}_{cont} , the expected number of secondary infections produced by the index case if some of the contacts have the option to vaccinate and thereby reduce secondary transmission. We assume that the payoff of vaccinating as soon as the index case exhibits symptoms is \mathcal{P}_V , the payoff of not vaccinating is \mathcal{P}_N , the baseline payoff is L , the cost of vaccinating is r_{vac} , and the cost of infection is r_{inf} . We assume that, if individuals decide to vaccinate at all, they decide to do so as soon as the index case exhibits symptoms. If they wait to vaccinate, then they incur the same cost of vaccinating as if they decided to vaccinate right away, but incur additional costs due to the possibility of exposure because of their delay. Therefore, rational individuals either vaccinate as soon as the index case exhibits symptoms, or not at all, depending on conditions. We restrict attention to the case $\omega \geq \sigma$ since $\omega < \sigma$ is not biologically plausible. This is further broken down into two cases:

Case 1: Vaccine does not work in time $\lambda + \omega \geq \sigma + \delta$

In this case, the vaccine does not provide protective immunity in contacts until after the index case has recovered, and therefore does not provide any benefit in the current outbreak. Hence, we assume that no one will vaccinate and from basic probability theory we have that

$$\mathcal{P}_{cont} = (1 - \zeta)^Q \quad (2.1)$$

$$\mathcal{R}_{cont} = \sum_{k=0}^Q k \binom{Q}{k} \zeta^k (1 - \zeta)^{Q-k} \quad (2.2)$$

where

$$\zeta = 1 - (1 - p)^\delta \quad (2.3)$$

is the probability that a given neighbour who remains susceptible is infected by the index case before the index case recovers.

Case 2: Vaccine may work in time to prevent infection $\lambda + \omega < \sigma + \delta$

In this case (Figure 2.1) we derive the payoff to vaccinate immediately and the payoff not to vaccinate, and we assume that a contact vaccinates if

$$\mathcal{P}_V > \mathcal{P}_N. \quad (2.4)$$

The payoff not to vaccinate is given by

$$\mathcal{P}_N = (L - r_{inf})\zeta + L(1 - \zeta), \quad (2.5)$$

where the first term of the equation represents the outcome in which the unvaccinated contact is infected by the index case, and the second terms represent the outcome in which the unvaccinated contact is not infected by the index case. The payoff to vaccinate is given by

$$\begin{aligned} \mathcal{P}_V &= (L - r_{vac} - r_{inf})\{[1 - (1 - p)^{\lambda+\omega-\delta}] + [(1 - \varepsilon)(1 - p)^{\lambda+\omega-\delta}(1 - (1 - p)^{\delta-(\lambda+\omega-\sigma)})]\} \\ &\quad + (L - r_{vac})\{[\varepsilon(1 - p)^{\lambda+\omega-\sigma}(1 - (1 - p)^{\delta-(\lambda+\omega-\sigma)})] + (1 - p)^\delta\} \end{aligned} \quad (2.6)$$

Details of the derivation are given in Appendix 2.A. The expression in the first square brackets of the top line of Equation (2.6) represents the outcome where an individual chooses to vaccinate but makes an effective contact before vaccine-derived protective immunity is developed (and is thus infected). The expression in the second square bracket of the top line represents the outcome where the individual chooses to vaccinate, makes an effective contact after the time required for protective immunity to develop but is still infected because of ineffective vaccination. The expression in the first square bracket of the bottom line represents the outcome where the individual choose to vaccinate, makes an effective contact after the time required for protective immunity to develop but is not infected because the vaccine was efficacious. The expression in the second square bracket of the bottom line represents the outcome where the individual vaccinates but is never

challenged because an effective contact is never made.

When $\mathcal{P}_N \geq \mathcal{P}_V$, there is no incentive for any of the contacts of the index case to vaccinate and so \mathcal{P}_{cont} and \mathcal{R}_{cont} are given by Equations (2.1) and (2.2). However, when $\mathcal{P}_N < \mathcal{P}_V$, every contact of the index case vaccinates as soon as the index case exhibits symptoms, and we have

$$\mathcal{P}_{cont} = (1 - \varsigma)^Q \quad (2.7)$$

$$\mathcal{R}_{cont} = \sum_{k=0}^Q k \binom{Q}{k} \varsigma^k (1 - \varsigma)^{Q-k} \quad (2.8)$$

where

$$\varsigma = 1 - \{(1 - p)^{\lambda + \omega - \sigma} (1 - p[1 - \varepsilon])^{\delta - (\lambda + \omega - \sigma)}\} \quad (2.9)$$

is the probability that a given neighbour who decides to vaccinate as soon as the index case exhibits symptoms is infected by the index case. Together, Equations (2.1)-(2.9) under the various cases for parameter values determine the probability \mathcal{P}_{cont} that an outbreak is controlled through ring vaccination as well as the average number of secondary infections \mathcal{R}_{cont} produced by the index case.

The simple stochastic model was simulated in Matlab version 7.6.0. The algorithm used for the simulation appears in Appendix 2.B.

2.2.2 Distributed Stochastic Model

In the distributed stochastic model, the parameters values for the infectious period δ , latent period σ , vaccine efficacy ε , cost of infection r_{inf} , cost of vaccination r_{vac} , time to protective immunity λ , incubation period ω , and transmission probability p are sampled from a lognormal distribution for each individual. The resulting variation between individuals can be conceived of either as real or perceived differences. This model was likewise simulated in Matlab version 7.6.0.

2.2.3 Distributed Stochastic Model with Imitation

The distributed stochastic model with imitation is identical to the distributed stochastic model except for the imitation-based decision making process used by contacts of the index case. On the first day that the index case is symptomatic, we determine \mathcal{P}_V and \mathcal{P}_N as before from Equations (2.5) and (2.6). We let V denote the number of individuals for whom $\mathcal{P}_V > \mathcal{P}_N$ (hence $Q - V$ is the number for whom $\mathcal{P}_V \leq \mathcal{P}_N$). Each individual chooses to vaccinate with probability ν , where

$$\nu = (1 - \kappa)H(\mathcal{P}_V - \mathcal{P}_N) + \kappa g(V) \quad (2.10)$$

and where $H(\cdot)$ is the Heaviside function, $g(V)$ is a function of V describing how individuals tend to imitate the most prevalent strategy among the contacts, and κ is a parameter governing the relative importance to an individual's decision making process of imitation processes versus weighing the individual's own values of \mathcal{P}_V and \mathcal{P}_N . The function $g(V)$ is

an increasing function of V , indicating a higher probability that the individual vaccinates if vaccinating is also favourable for the majority of other contacts. We explore cases where $g(V)$ is a hyperbolic tangent function or a step function. With ν thus calculated for each individual, we determine whether individuals vaccinate by sampling a random number between 0 and 1.

2.2.4 Simulation Design

For each parameter set analyzed we ran 2,500 realizations, computing the mean and standard deviation of the average number of secondary infections \mathcal{R} across all realizations. We explored \mathcal{R} as it depended on parameters governing natural disease history and imitation behaviours. We also plotted the frequency distribution of the number of secondary infections and the number of vaccinators for certain scenarios of the distributed stochastic model in the presence of imitation.

2.3 Results

The mean and standard deviation of \mathcal{R} across all 2,500 realizations were calculated as a function of cost of infection r_{inf} , cost of vaccination r_{vac} , vaccine efficacy ε and incubation period ω for all three models. The standard deviation for these realizations is large since the neighbourhood size Q is approximately 10. However, the mean value of \mathcal{R} varies within certain parameter regimes, as described below.

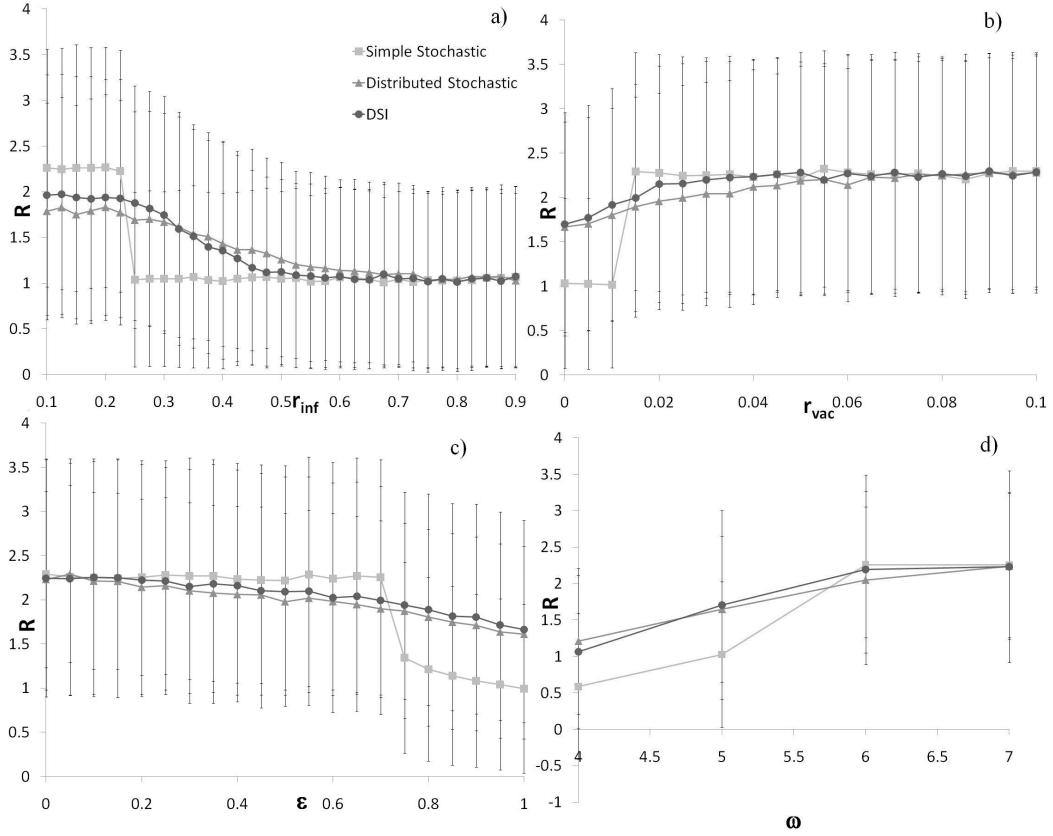


Figure 2.2: Mean and \pm the standard deviation of values of \mathcal{R} versus r_{inf} , r_{vac} , ϵ , ω with all other parameter values fixed at values in Table 2.1. “DSI” indicates the distributed stochastic model with imitation.

2.3.1 Simple Stochastic Model

In the simple stochastic model, all individuals make the same decision: all individuals either vaccinate or do not vaccinate at a given set of parameter values, because the payoff function and its constituent parameter values are the same for all contacts of the index case. Hence, the value of \mathcal{R} can change suddenly as certain threshold parameter values are surpassed (Figure 2.2). For instance, for low infection risk, none of the contacts of

the index case vaccinate since $\mathcal{P}_V < \mathcal{P}_N$ and thus the average value of \mathcal{R} is 2.3. However, for the cost of infection $r_{inf} > 0.25$, $\mathcal{P}_V > \mathcal{P}_N$, all of the contacts vaccinate and the mean value of \mathcal{R} becomes approximately 1 (Figure 2.2a)). A similar effect appears in the plot of \mathcal{R} versus r_{vac} , cost of vaccination, (Figure 2.2b)) and ε , vaccine efficacy, (Figure 2.2c)). The mean value of \mathcal{R} is constant on either side of these thresholds for the plots of mean \mathcal{R} versus r_{inf} and r_{vac} because these parameters influence vaccinating behaviour but not the probability that a susceptible or vaccinated person becomes infected. However, the mean value of \mathcal{R} declines with increasing ε beyond the threshold in ε because beyond this threshold, all contacts vaccinate, and ring vaccination is more successful at higher vaccine efficacy.

Although a threshold is not observed in the plot of mean \mathcal{R} versus the incubation period ω at the parameter values tested, the mean value of \mathcal{R} increases as ω increases because contacts are exposed to infection for a longer period before symptoms appear in the index case, giving contacts the first opportunity to vaccinate (Figure 2.2d)).

The deterministic predictions from equation (2.2) in the case of no vaccination and equation (2.8) in the case of vaccination agree with the mean values of the realizations of the simple stochastic case (results not shown).

2.3.2 Distributed Stochastic Model

In the distributed stochastic model, each individual is assigned a parameter value for: time to protective immunity λ , latent period σ , infectious period δ , incubation period ω , vaccine efficacy ε , cost of vaccination r_{vac} , cost of infection r_{inf} and transmission probability p . The

values are drawn from a log-normal distribution with the same mean value as in the simple stochastic model (see values in Table 2.1). The distributed stochastic model is otherwise identical to the simple stochastic model. The resulting mean value of \mathcal{R} is plotted against the mean parameter values for r_{inf} , r_{vac} , ε and ω from the log-normal distribution (Figure 2.2). The model predictions are qualitatively different from the simple stochastic model. Primarily, the thresholds in r_{vac} , r_{inf} , and ε appear to be “smeared out” relative to the simple stochastic model, because heterogeneity in the sampled parameter values means that the payoff functions for individuals are also variable. Therefore, in general there is no parameter value for which either $\mathcal{P}_V > \mathcal{P}_N$ or $\mathcal{P}_V < \mathcal{P}_N$ is true for all individuals. In general, for any given mean parameter value, $\mathcal{P}_V > \mathcal{P}_N$ will hold for some individuals and $\mathcal{P}_V < \mathcal{P}_N$ will hold for others. However, as the mean parameter values change, so does the mean behaviour: the mean value of \mathcal{R} increases for increasing r_{vac} and ω , because vaccination becomes less favourable as the perceived vaccine risk and the incubation period increase (Figure 2.2b),d)). In contrast, the mean value of \mathcal{R} decreases for increasing r_{inf} and ε , because vaccination becomes more favourable as the disease risk and vaccine efficacy increase.

2.3.3 Distributed Stochastic Model with Imitation

In the imitation model, individuals consider both their own values of \mathcal{P}_V and \mathcal{P}_N as well as the inclination of other contacts (as measured by whether $\mathcal{P}_V > \mathcal{P}_N$ or $\mathcal{P}_V < \mathcal{P}_N$) in making their decision about whether or not to vaccinate, as specified in Equation (2.10). We use the stepwise functional form for $g(V)$ for our analyses, except where noted otherwise,

because the impact of imitation is most clear with this functional form. In the presence of imitation, the mean value of \mathcal{R} (the average number of secondary infections) appears to be roughly the same as the mean value of \mathcal{R} in the distributed stochastic model without imitation, for a broad range of parameters, including the lack of a threshold (Figure 2.2). Moreover, the mean value of \mathcal{R} does not change across a wide range of values of the imitation strength κ , under three different functional forms for the function $g(V)$ (Figure 2.3). We attribute this to the fact that imitation does not have a bias: individuals tend to imitate whichever strategy appears to be favoured. However, if we examine how the values of \mathcal{R} are distributed across the stochastic realizations, some interesting differences emerge. The distribution of \mathcal{R} , and also of the number of individuals who are vaccinated, changes as the imitation strength κ increases (Figure 2.4). For low values of κ , both distributions are unimodal and clustered around the same mean value as for the distributed stochastic model without imitation. However as κ increases, the distribution of the number of vaccinated individuals becomes bimodal: for some parameter sets, vaccination is the favoured strategy in terms of what the payoff functions indicate for most individuals, and thus a strong majority of contacts opt for vaccination; for other parameter sets, non-vaccination is the favoured strategy and most contacts refuse vaccination (even those for whom the payoff to vaccinate exceeds the payoff not to vaccinate). This bimodal effect occurs at parameter values such that, on average, neither vaccination nor non-vaccination are favoured by a strong majority of contacts. (We note that the special case $\kappa=0$ recovers the case of the distributed stochastic model without imitation, and simulations of the distributed stochastic model without imitation at the same parameter values fail to show bimodality (results not shown)). Interestingly, at the same parameter values where the number of

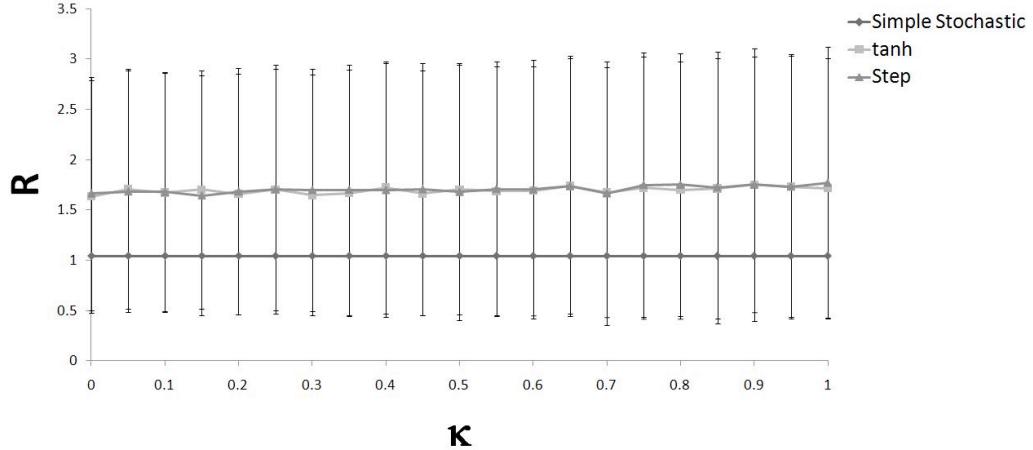


Figure 2.3: Mean and \pm the standard deviation of values of \mathcal{R} versus imitation strength κ for three different functional forms for $g(V)$, with all of the other parameter values fixed at values in Table 2.1

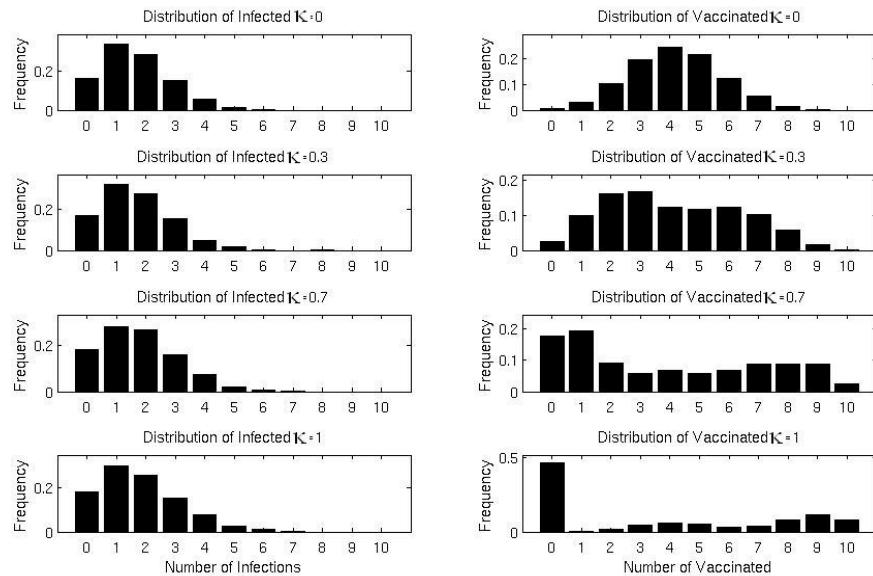


Figure 2.4: The distribution of the number of secondary infections (left) and number of vaccinators (right) for the case of $Q = 10$ neighbours for different values of imitation strength κ and other parameter values as in Table 2.1

contacts who vaccinate is bimodal, the distribution of secondary infections appears to remain relatively unimodal (Figure 2.4). This is partly because imitation has larger impact on the first order effect of distribution of vaccinators than on the second order effect of the distribution of secondary infections. However, this is also because a relatively low number of contacts ($Q = 10$) does not provide sufficient resolution to distinguish two close peaks. Indeed, when the number of neighbours is increased to $Q = 100$ and parameter values are otherwise unchanged, clear bimodality in the distribution of secondary infections emerges as κ increases (Figure 2.5, $p = 0.05$ results). Bimodality in the number of vaccinators remains dominant (in fact, with some appearance of trimodality) (Figure 2.5, $p = 0.05$ results). The stronger unimodality in the distribution of the number of secondary infections compared to the distribution of the number of vaccinators also explains why the variance in the average number of secondary infections \mathcal{R} is so similar for the distributed stochastic models with and without imitation (Figure 2.2), despite the fact that the parameter ranges covered in Figure 2.2 include baseline parameter values where the number of vaccinators is known to be bimodal for the model with imitation. For all values of the imitation strength κ , the peaks in the distribution of secondary infections shift to higher values (i.e., more simulations with a large number of secondary infections) when the transmission p is increased from the baseline value $p = 0.05$ to a higher rate $p = 0.2$ (Figure 2.5). This effect is not surprising because a higher transmission rate implies a greater number of secondary transmissions, even when vaccination is taken up and provides some reduction in secondary cases. However, what is more interesting is that the relative magnitude of the two peaks in the distribution of number vaccinated changes as p is increased: when $p = 0.05$ most individuals do not vaccinate, whereas when $p = 0.2$, most of them do (i.e. the relative

size of the two peaks in the distribution of vaccinators is switched in the case for $p = 0.05$ compared to $p = 0.2$). An increase in p increases the probability of eventually becoming infected and thus experiencing disease penalties, hence vaccination becomes attractive for higher p , at least at these parameter values. This switch is again observed in the distribution of the number of secondary infections: when $p = 0.05$, the peak corresponding to more secondary infections (i.e. less vaccination) is larger, indicating that in most realizations, the majority of contacts do not vaccinate and the number of secondary infections increases. By comparison when $p = 0.2$, the peak corresponding to fewer secondary infections (i.e. more vaccination) is larger, indicating that in most realizations, the majority of contacts vaccinate. As noted above, we used a step function to represent our imitation function $g(V)$ in the case of distributed stochasticity with imitation (Figures 2.4-2.5). However we also explored these results for a hyperbolic tangent function (results not shown) and found that instead of obtaining a bimodal distribution, we obtained a distribution that resembled a skewed normal distribution. This effect occurs because for most parameter values, the switch between favouring vaccination versus favouring non-vaccination is much sharper at the origin for the step function than for tanh under most parameter choices. These results imply a fully-connected network where each contact of the index case is connected to - and exchanges information with - every other contact of the index case. To understand the impact of this assumption, we also explored the semi-connected case where individuals can only imitate the nearest plus or minus n neighbours in the ring. The introduction of semi-connectedness can change the results significantly for certain values of connectedness. For the special case of no connectedness ($n = 0$), the case of the distribution stochastic model without imitation is recovered and distributions are unimodal (results not shown).

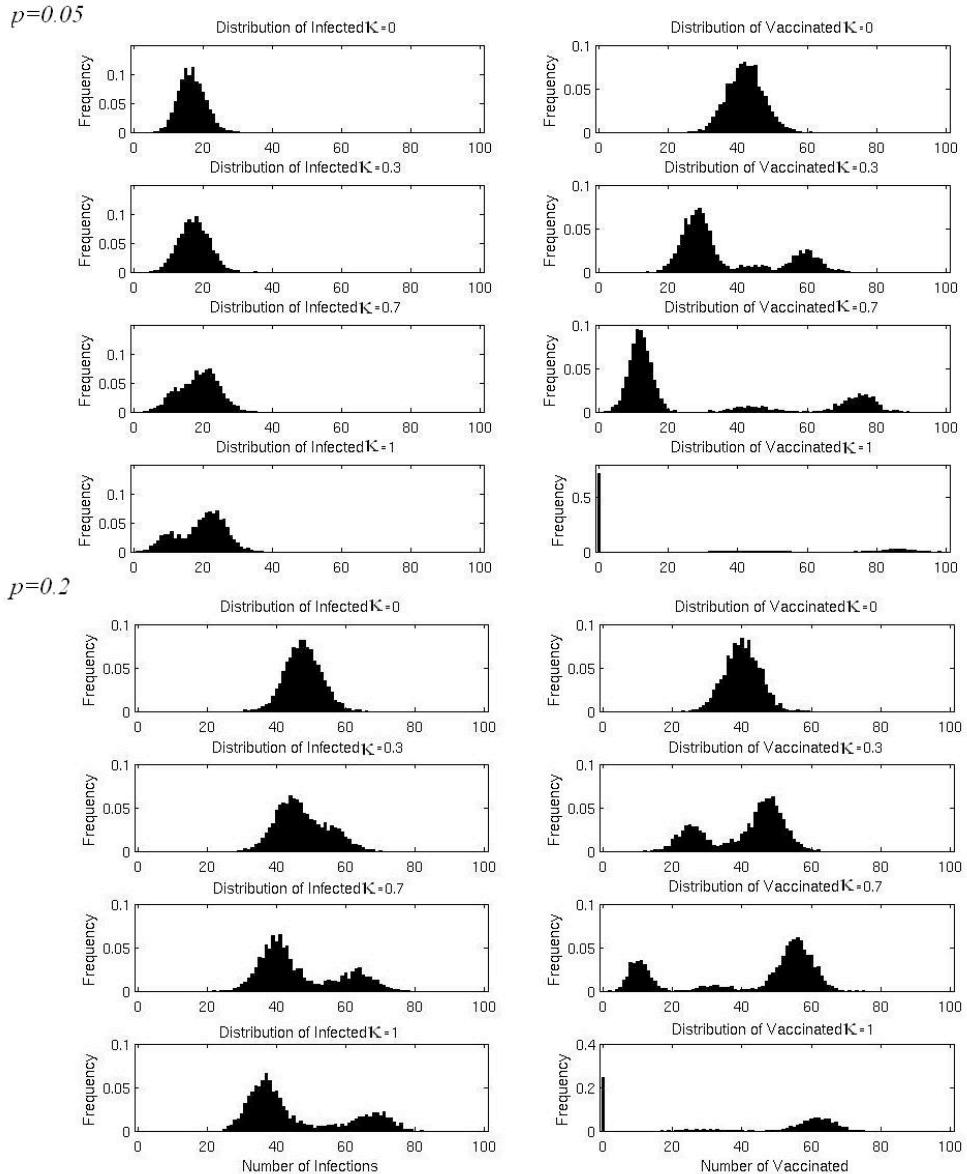
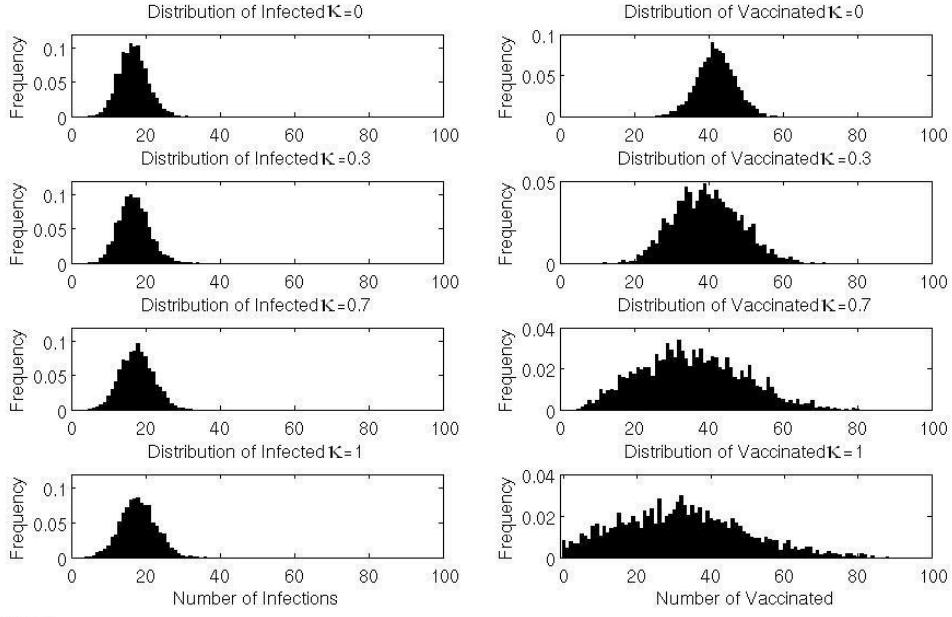


Figure 2.5: The distribution of the number of secondary infections (left) and number of vaccinators (right) for the case of $Q = 100$ neighbours for different values of imitation strength κ and other parameter values as in Table 2.1

For $n = 3$ there was likewise little impact and the distributions remained unimodal (results not shown). For cases of intermediate connectedness ($n = 12$ and $n = 25$), the results change significantly (Figure 2.6). The distribution of the number of vaccinators is no longer bimodal but becomes a highly skewed unimodal distribution with a high variance. The variance increases as the strength of imitation κ increases. This spreading effect occurs because in the semi-connected case, individuals are sampling a small proportion of the total number of contacts of the index case and therefore the average attractiveness of vaccinating versus not vaccinating is more highly variable than in the fully connected case, giving rise to greater variation in the level of vaccine adherence overall. Although the bimodality disappears, the greater variance still supports the conclusion that adding imitation can increase the variability in the predicted vaccine adherence, relative to the case of the distribution stochastic model without imitation. For the case $n = 50$, the fully-connected case is recovered, including bimodality (results not shown). The emergence of bimodality occurs for parameter sets such that the payoff to vaccinate is close to the payoff not to vaccinate. In such situations, individual variability in model parameters means that for some stochastic realizations, the payoff to vaccinate will be higher for the majority of contacts and hence vaccination tends to dominate. For other stochastic realizations, however, the payoff not to vaccinate will be higher and hence non-vaccination will dominate for the same mean parameter values. Moving away from this parameter regime sufficiently far means that either vaccination or non-vaccination will be favoured for all stochastic realizations, and imitation will only strengthen this tendency. This should cause a unimodal distribution of the number of secondary infections and the number of vaccinators. This effect is seen in the distribution of secondary infections (Figure 2.7) and

24 Node Case



50 Node Case

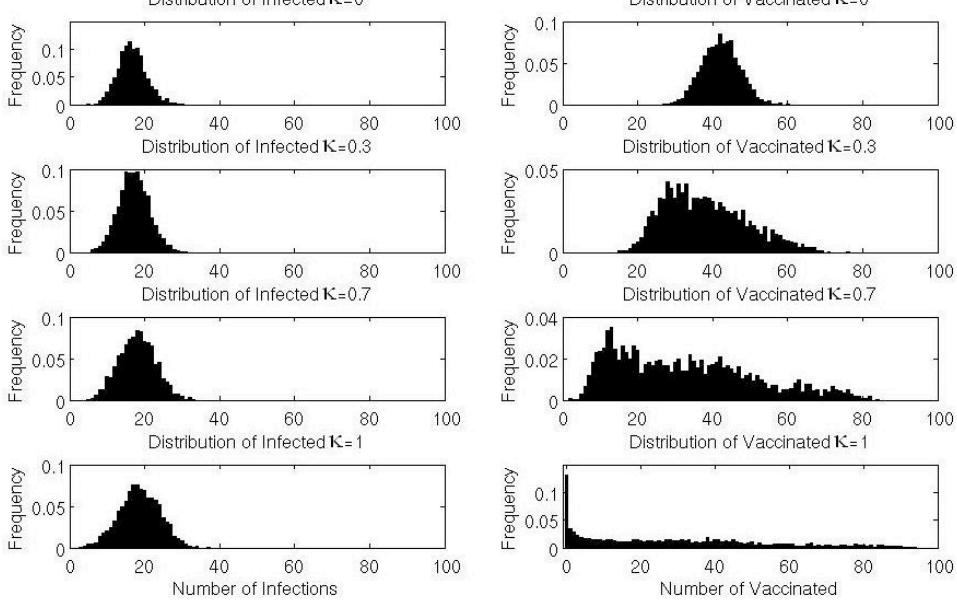


Figure 2.6: The distribution of the number of secondary infections (left) and number of vaccinators (right) for the case of $Q = 100$ neighbours, who are imitating n neighbours to the right and n neighbours to the left, for different values of imitation strength κ and other parameter values as in Table 2.1. The values of n are $n = 24$ (top half of panels) and $n = 50$ (bottom half of panels)

vaccinators (Figure 2.8) for a range of possible values for eight of the model parameters: λ , ε , ω , r_{vac} , δ , σ , p , r_{inf} . For most parameters, moving away from the baseline values collapses the bimodal distribution function into a unimodal function that represents either dominant vaccination or dominant non-vaccination, depending on whether there has been an increase or a decrease relative to the baseline parameter value (Figures 2.7 and 2.8). For instance, increasing the cost of vaccination r_{vac} above the baseline value makes vaccination unattractive, collapsing the bimodal distribution to a unimodal distribution that represents dominant non-vaccination behaviour. In contrast, decreasing r_{vac} below the baseline value creates a unimodal distribution representing dominant vaccinating behaviour. However, for the transmission probability p , the distribution remains bimodal across a broad range of parameter values before collapsing to a unimodal distribution. This is because p appears in both the payoff to vaccinate and the payoff not to vaccinate (Equations (2.5) and (2.6)). Increasing p decreases both payoffs because the individual is more likely to get infected for higher values of p , thus the relative size of \mathcal{P}_V versus \mathcal{P}_N does not change as much. Therefore, the distribution of secondary infections and vaccinators remains bimodal for a range of values of p .

2.4 Discussion

In this paper we developed three models of ring vaccination where individual contacts of the index case choose whether or not to vaccinate according to payoffs for vaccinating versus not vaccinating. These payoffs depend on disease and vaccine risks. We considered a simple stochastic model that permitted us to derive expressions for the probability of

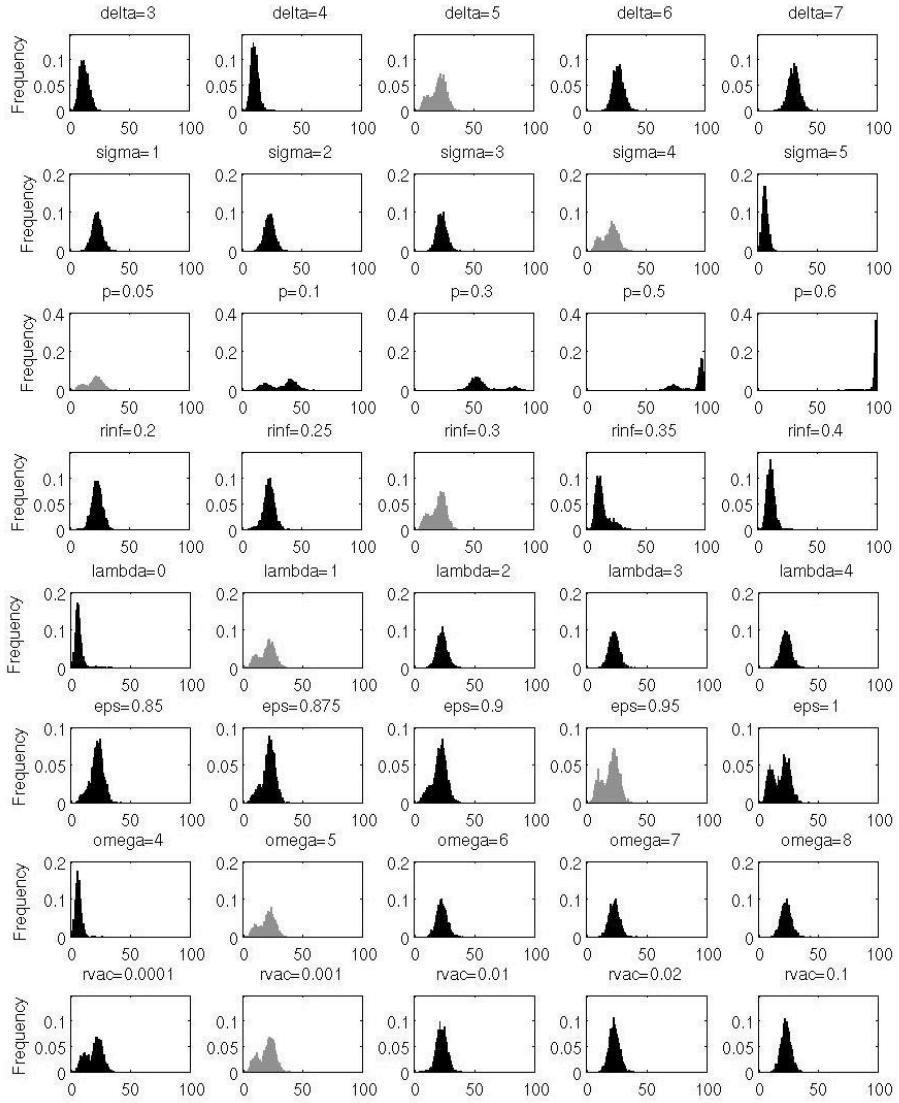


Figure 2.7: The distribution of the infected individuals under full imitation for the case of $Q = 100$ for the parameters $\lambda, \varepsilon, \omega, r_{vac}, r_{inf}, p, \sigma, \delta$. The baseline parameter values are used to generate the gray distributions and black distributions represent variations from baseline

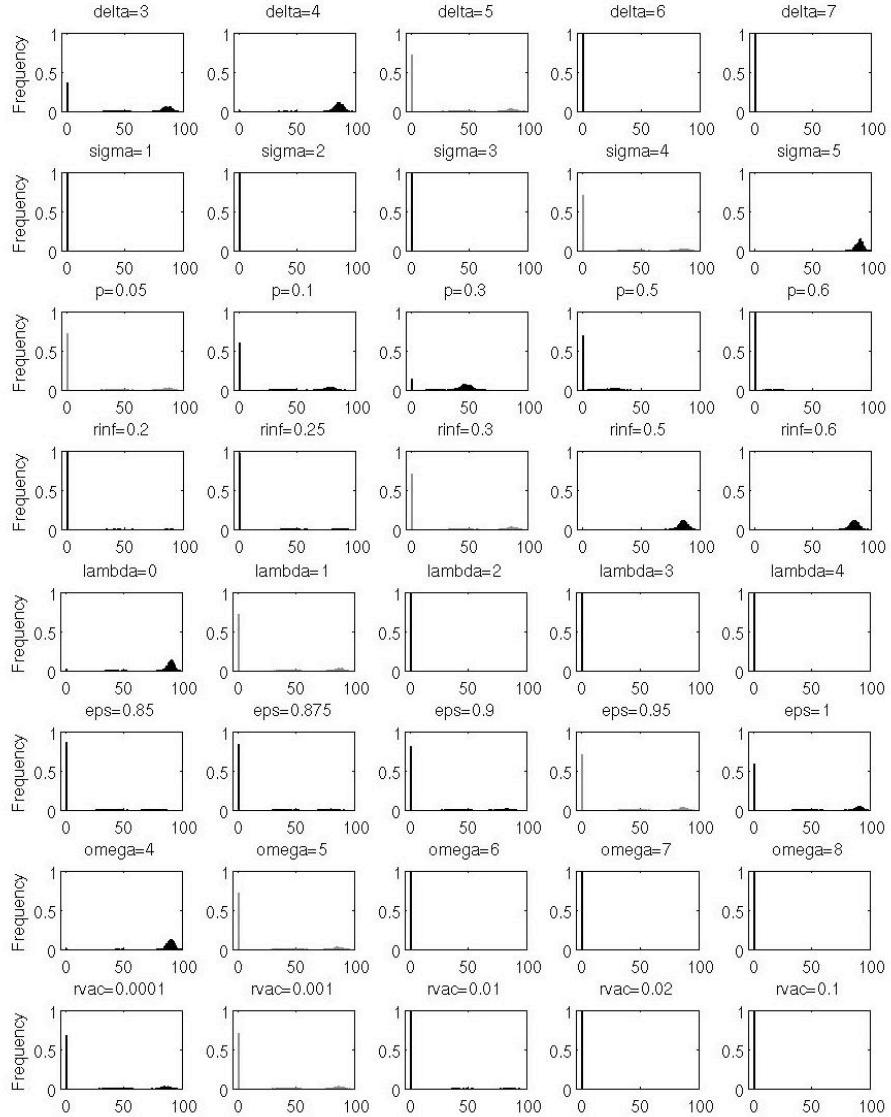


Figure 2.8: The distribution of the vaccinated individuals under full imitation for the case of $Q = 100$ for the parameters $\lambda, \varepsilon, \omega, r_{vac}, r_{inf}, p, \sigma, \delta$. The baseline parameter values are used to generate the gray distributions and black distributions represent variations from baseline

no secondary cases \mathcal{P}_{cont} and the expected number of secondary infections \mathcal{R} . In the distributed stochastic model, we also developed an extension where the parameter values constituting the payoff functions were sampled from a log-normal distribution for each individual, resulting in heterogeneous payoff functions. This was further extended in the distributed stochastic model with imitation, where the individual vaccine decision-making process was partly determined by imitating the vaccinating decisions to which the majority of contacts are inclined.

In the simple stochastic model, all contacts are assigned the same parameter values and hence all contacts either vaccinate or do not vaccinate depending on the parameter values that influence the payoff functions. As a result, there are threshold parameter values at which all contacts of the index case switch from vaccinator to non-vaccinator or vice versa. The effect of sampling parameter values from log-normal distributions for each individual (i.e., the distributed stochastic model) is to moderate this effect and remove the thresholds, since each individual can have a different payoff. Consequently, mixed outcomes are possible where some contacts vaccinate and some do not. Adding imitation to the model has little effect on the mean and variability of the number of secondary infections at the parameter values tested. However, even when the mean and variability do not change very much, the distribution of the number of secondary infections and number of vaccinators can become bimodal at certain parameter values when imitation is strong (for the assumption of fully connected contacts of the index case). This occurs because individuals adopt whichever strategy appears to be favourable to the majority. For some stochastic realizations the apparently favourable strategy is vaccinating, whereas for others it is not vaccinating. The consequence is that ring vaccination can be highly

successful under some realizations (when imitation causes most contacts to vaccinate), but can completely fail under other realizations of the same parameter values (when imitation causes most contacts not to vaccinate), resulting in failure to contain the outbreak. This occurs despite the average outcome being the same as for the model without imitation. If the contacts are semi-connected instead of fully connected, the distribution of the number of vaccinators is no longer bimodal but it remains very broad, with many possible outcomes for the same mean parameter values.

Previous work has analyzed how the predictions of models that include stochastic effects or contact structure differ qualitatively from the predictions of models that do not include such effects [10, 11]. Similarly, it has been shown how opinion formation in social networks can lead to pockets of susceptibility, ensuring the persistence of infection despite high vaccine coverage even when homogeneous mixing models predict that the infection should already be eliminated [19]. Here we have shown how imitation behaviours can exacerbate such differences in situations where ring vaccination is employed, by making the contacts of an index tend to behave in similar ways. As a result, there is a parameter regime where, for approximately the same input parameter values, vaccinating is a dominant strategy in some realizations and non-vaccinating is a dominant strategy in others. Even for parameter regimes where either vaccinating or non-vaccinating is always favoured, imitation has the role of ensuring greater homogeneity in vaccination decisions than would occur under purely rational behaviour.

Given that social contact networks tend to be highly clustered, especially for close contact infections, the contacts of an index case are likely to know one another. Moreover, imitating the decisions of others in one's peer group is often an important factor in vac-

cine decision-making [26, 30]. Therefore the results of our model suggest that imitation effects may have an important additional role in determining the success or failure of ring vaccination strategies for many infectious diseases where vaccination is voluntary or where a mandatory policy is not enforceable.

Network models are a natural way to describe infection transmission through a social contact network and the effects of ring vaccination, although they tend to be difficult to analyze [20, 21]. Here we opted for a simpler approach that did not model the full network but rather just the contacts of the index case. This model has the advantage of being much easier to analyze than network models; it has the disadvantage of not capturing the full network-this is relevant to imitation processes in ring vaccination since contacts of the index case may imitate individuals who are not contacts of the index case. One rationale for only modelling the contacts of the immediate case is that if ring vaccination fails for the contacts of a single index case, it will likely fail in more complex situations where the infection has already started to spread through the social contact network. However, this may not be the case in clustered networks where the possibility of containment is determined not only by edge-wise transmissibility but also by the structure of the emerging cluster of infections [14, 31]. Thus, an important limitation of our model is that it does not describe the links between contacts of the index case. We also did not capture changes in the contact structure in response to the appearance of symptoms in the index case [32] or other interventions such as antiviral drugs.

Mathematical models have often suggested that early intervention is valuable for controlling an outbreak, because the effectiveness of early intervention is disproportionately higher than the impact of later intervention [33, 34, 35]. Typically, these models have

considered interventions such as vaccination, contact precautions, and antiviral drugs and have implicitly assumed that the uptake of these interventions can be set at any level desired. Our model shows that the success of containment through ring vaccination can be highly variable in cases where the uptake cannot be guaranteed by the public health authorities, such as when the contacts of the index case are free to choose whether or not to vaccinate and in cases where contacts also tend to be influenced by the vaccination decisions of other contacts. Under some circumstances, these imitation processes can lead to a failure of ring vaccination. Therefore, early action to counter the possible emergence of vaccine exemption in epidemiologically important peer groups during an outbreak may be warranted. Our findings suggests that risk communication should also be thought of as an important public health intervention during a disease outbreak and that it should be likewise be applied in a timely fashion at the start of an outbreak.

2.A Derivation of the Payoff Functions

(Note: Corrections have been made in this section from the original published document)

Let Q be the number of neighbours and ε the vaccine efficacy. We want to derive a conservative estimate for outbreak control.

Let q_i be the probability of not infecting neighbour i during the infectious period, q_{tot} the probability of not infecting any neighbour. Thus, the probability of not infecting anyone is

$$q_{tot} = \prod_{i=1}^Q q_i$$

For identical neighbours $q_{tot} = q^Q$. Let $q_{i,j}$ be the probability of no transmission to neighbour i on day j . Thus,

$$q_i = \prod_{k=1}^{\delta} q_{i,k},$$

where δ is the duration of infection in days (integer). So, what is $q_{i,j}$?

Let τ be the time required for vaccine to mount a protective immune response, and δ the duration of infection. If $\tau > \delta$, then, assume that no one will vaccinate. On the contrary, if $\tau < \delta$ then some or all would vaccinate.

Case where $\tau > \delta$

Under assumption of identical neighbours, $q_{i,j} = 1 - p$, where p is the per day transmission probability. So

$$q_i = (1 - p)^{\delta} \Rightarrow q_{tot} = q^Q = (1 - p)^{\delta Q}$$

Case where $\tau < \delta$

In this case, some may vaccinate since the vaccine may protect before the individual is infected by the index case. Let

$\mathcal{P}_V(t)$ be the payoff to vaccinate on day t where $t = 1$ is the day that the index case is infectious and starts showing symptoms.

\mathcal{P}_N is the payoff not to vaccinate at all

r_{vac} the penalty to vaccinate (i.e. the risk of adverse advents)

r_{inf} the penalty due to being infected (i.e. the disease complication risk)

L is the payoff before penalties (i.e. the number of life years if never vaccinated and never infected)

Assume $\mathcal{P}_V(1) < \mathcal{P}_N$, this implies that $\mathcal{P}_V(t) < \mathcal{P}_V(1)$ and $\mathcal{P}_V(t) < \mathcal{P}_N(t) \forall t$.

Since a person who waits several days to vaccinate accepts the same vaccine penalty as the individual who immediately vaccinates, $\mathcal{P}_V(1)$, say, but also accepts a greater risk of infection since the individual may be infected during the time the individual waited (waiting time), the two possible outcomes are:

$\mathcal{P}_V(1) < \mathcal{P}_N \Rightarrow$ never vaccinate (same q_{tot} as in the case $\tau > \delta$ above)

$\mathcal{P}_V(1) > \mathcal{P}_N \Rightarrow$ vaccinate as soon as a neighbour exhibits symptoms. But what are the explicit expressions for $\mathcal{P}_V(1)$ and \mathcal{P}_N . Now let $\rho(t)$ be the probability of infection on day

t (and not before), p the transmission probability per day. Thus

$$\begin{aligned}
\mathcal{P}_{\mathcal{N}} &= \rho(1)(L - r_{inf}) + \rho(2)(L - r_{inf}) + \cdots + \rho(\delta)(L - r_{inf}) \\
&\quad + (1 - \rho(1) - \rho(2) - \cdots - \rho(\delta))L \\
&= p(L - r_{inf})\{1 + (1 - p) + (1 - p)^2 + \cdots + (1 - p)^{\delta-1}\} \\
&\quad + L\{1 - p[1 + (1 - p) + \cdots + (1 - p)^{\delta-1}]\}
\end{aligned}$$

Using Taylor series expansion of the function $\frac{1}{1-x}$, we have $\frac{1-x^n}{1-x} = 1 + x + x^2 + \cdots + x^{n-1}$.

Therefore, the above expression for $\mathcal{P}_{\mathcal{N}}$ simplifies to

$$\mathcal{P}_{\mathcal{N}} = (L - r_{inf})[1 - (1 - p)^{\delta}] + L(1 - p)^{\delta} \quad (2.11)$$

Payoff to Vaccinate Immediately

This involves the following scenarios: $t < \tau$, $t > \tau$ but the vaccine failed ($t < \delta$), $t > \tau$

and the vaccine worked and $t > \delta$ (not infected)

$$\begin{aligned}
\mathcal{P}_V(1) &= [\rho(1) + \rho(2) + \cdots + \rho(\tau)](L - r_{vac} - r_{inf}) \quad t < \tau \\
&+ (L - r_{vac} - r_{inf})(1 - \varepsilon)[\rho(\tau + 1) + \rho(\tau + 2) + \cdots + \rho(\delta)] \quad t > \tau \\
&\quad \text{but the vaccine failed}(t < \delta) \\
&+ \varepsilon(L - r_{vac})[\rho(\tau + 1) + \rho(\tau + 2) + \cdots + \rho(\delta)] \quad t > \tau \text{ and vaccine worked} \\
&+ (L - r_{vac})[1 - \rho(1) - \rho(2) - \cdots - \rho(\delta)] \quad t > \delta \text{ (not infected)} \\
&= (L - r_{vac} - r_{inf})[p + p(1 - p) + p(1 - p)^2 + \cdots + p(1 - p)^{\tau-1}] \\
&+ (L - r_{vac} - r_{inf})(1 - \varepsilon)[p(1 - p)^{\tau} + p(1 - p)^{\tau+1} + \cdots + p(1 - p)^{\delta-1}] \\
&+ (L - r_{vac})\varepsilon[p(1 - p)^{\tau} + p(1 - p)^{\tau+1} + \cdots + p(1 - p)^{\delta-1}] \\
&+ (L - r_{vac})[1 - p - p(1 - p) - \cdots - p(1 - p)^{\delta-1}]
\end{aligned}$$

The terms in brackets are geometric series and can simply be written as

$$\begin{aligned}
\mathcal{P}_V(1) &= (L - r_{vac} - r_{inf})\{[1 - (1 - p)^{\tau}] + (1 - \varepsilon)(1 - p)^{\tau}[1 - (1 - p)^{\delta-\tau}]\} \\
&+ (L - r_{vac})\{\varepsilon(1 - p)^{\tau}[1 - (1 - p)^{\delta-\tau}] + [1 - (1 - (1 - p)^{\delta})]\}.
\end{aligned}$$

After some rearrangements we have

$$\begin{aligned}
\mathcal{P}_V(1) &= (L - r_{vac} - r_{inf})\{[1 - (1 - p)^{\tau}] + (1 - \varepsilon)(1 - p)^{\tau}[1 - (1 - p)^{\delta-\tau}]\} \\
&+ (L - r_{vac})\{\varepsilon(1 - p)^{\tau}[1 - (1 - p)^{\delta-\tau}] + (1 - p)^{\delta}\}. \tag{2.12}
\end{aligned}$$

There are two subclass under this scenario Case where $\mathcal{P}_V(1) < \mathcal{P}_N$ with payoff $\mathcal{P}_V(1)$ and

$\mathcal{P}_{\mathcal{N}}$ given by (2.11) and (2.12).

$$q_{tot} = (1 - p)^{\delta Q}$$

Case where $\mathcal{P}_{\mathcal{V}}(1) < \mathcal{P}_{\mathcal{N}}$. Hence, the individuals vaccinate immediately. Thus, $q_{i,j} \equiv \tilde{q}_j$ under the assumption of identical neighbours, where \tilde{q}_1 is the probability of no transmission on day 1, that is, $\tilde{q}_1 = 1 - p$. Similarly,

$$\tilde{q}_2 = 1 - p,$$

⋮

$$\tilde{q}_\tau = 1 - p \text{ (the probability of no transmission on day } \tau),$$

$$\tilde{q}_{\tau+1} = 1 - p(1 - \varepsilon),$$

⋮

$$\tilde{q}_{\delta-1} = 1 - p(1 - \varepsilon),$$

$$\tilde{q}_\delta = 1 - p(1 - \varepsilon).$$

Therefore, $\tilde{q}_{tot} = \tilde{q}^Q$ where \tilde{q} is the probability that the neighbour never gets infected. Thus,

$$\tilde{q} = \tilde{q}_1 \tilde{q}_2 \cdots \tilde{q}_\delta = (1 - p)^\tau [(1 - p(1 - \varepsilon))^{\delta - \tau}].$$

Thus,

$$\tilde{q}_{tot} = \{(1 - p)^\tau [(1 - p(1 - \varepsilon))^{\delta - \tau}]\}^Q.$$

Summary or Results

$\tau > \delta$, no one vaccinates, $q_{tot} = (1 - p)^{\delta Q}$ (probability of no secondary transmission)

$\tau < \delta$ some may vaccinate Case $\mathcal{P}_V(1) \leq \mathcal{P}_N$ no one vaccinates and $q_{tot} = (1-p)^{\delta Q}$ Case $\mathcal{P}_V(1) > \mathcal{P}_N$ all neighbours vaccinate and $\tilde{q}_{tot} = \{(1-p)^{\tau-1}[(1-p(1-\varepsilon))^{\delta-\tau+1}\}^Q$. $\varepsilon = 1$, then

$$\begin{aligned}\mathcal{P}_V(1) &= (L - r_{vac} - r_{inf})[1 - (1-p)^{\tau-1}] + (L - r_{vac})(1-p)^\tau, \\ \mathcal{P}_N &= (L - r_{inf})[1 - (1-p)^\delta] + L(1-p)^\delta.\end{aligned}$$

$r_{vac} \ll r_{inf} \Rightarrow L - r_{vac} - r_{inf} \cong L - r_{inf}$ and $L - r_{vac} \cong L$. Thus,

$$\begin{aligned}\mathcal{P}_V(1) &= (L - r_{inf})[1 - (1-p)^{\tau-1}] + L(1-p)^\tau, \\ \mathcal{P}_N &= (L - r_{inf})[1 - (1-p)^\delta] + L(1-p)^\delta.\end{aligned}$$

Generalization

Let ω be the incubation period, τ the time required for the vaccine to provide protection, σ the latent period and δ the infectious period. *Case 1:* $\omega < \sigma$ this is not biologically relevant. *Case 2:* $\omega \geq \sigma$ *Scenario 1:* $\tau + \omega > \delta + \sigma \Rightarrow$ no one vaccinates and

$$q_{tot} = (1-p)^{\delta Q}$$

Scenario 2: $\tau + \omega < \delta + \sigma$ $\mathcal{P}_V(1) \leq \mathcal{P}_N$, no one vaccinates, thus $q_{tot} = (1-p)^{\delta Q}$ $\mathcal{P}_V(1) > \mathcal{P}_N$

all neighbours vaccinate

$$\begin{aligned}
\tilde{q}_{tot} &= \left\{ \underbrace{(1-p)^\tau}_{\text{No infection before vaccine}} \underbrace{[(1-p(1-\varepsilon)]^{\delta-\tau}}_{\text{No infection after vaccine should}} \right\}^Q \\
\mathcal{P}_N &= \underbrace{(L - r_{inf})[l - (1-p)^\delta]}_{\text{Infected}} + \underbrace{L(1-p)^\delta}_{\text{Not Infected}} \\
\mathcal{P}_V(1) &\quad \text{is the payoff to vaccinate as soon as index case symptoms show,} \\
\mathcal{P}_V(1) &= (L - r_{vac} - r_{inf}) \left\{ \underbrace{1 - (1-p)^{\tau+\omega-\sigma}}_a \right. \\
&+ \underbrace{(1-\varepsilon)(1-p)^{\tau+\omega-\sigma}[1 - (1-p)^{\delta+\sigma-\omega-\tau}]}_b \} \\
&+ (L - r_{vac}) \left\{ \underbrace{\varepsilon(1-p)^{\tau+\omega-\sigma}[1 - (1-p)^{\delta+\sigma-\omega-\tau}]}_c + \underbrace{(1-p)^\delta}_d \right\}
\end{aligned}$$

- a) Those infected before the vaccine could start working
- b) Those infected after vaccine started working plus infected due to ineffective dose
- c) Those infected after vaccine started working plus not infected due to effective dose
- d) Those never infected

2.B Simulation Algorithm

In the simulation, the following algorithm was used for each day

1. Determine if it is the first day that symptoms show in the index case. If it is the first

day that symptoms show and $\mathcal{P}_V > \mathcal{P}_N$ (where \mathcal{P}_V and \mathcal{P}_N comes from Equation (2.5) and (2.6)), then all contacts of the index case will vaccinate.

2. To determine which contacts are successfully vaccinated one samples Q random numbers between 0 and 1. The individuals for whom the random sample is less than or equal to ε are considered to have been successfully vaccinated (although it will still require a time λ before they are protected).
3. Determine if the index case is still infectious. If so, then determine which susceptible individuals are infected. Sampling random numbers from 0 to 1 for each susceptible individual, the individuals whose sample is less than or equal to p become infected.

Steps 1 and 2 are repeated until either the maximum simulation time is exceeded or the infectious period of the index case ends. After each day, individual states are updated as well as the counter for days remaining in each state. The natural history assumptions are as given in the first part of this subsection: individuals who have been vaccinated but are not yet immune remain fully susceptible to infection because the vaccine has yet to take full effect; when a susceptible contact becomes infected they enter the latent stage. Recall that payoffs are such that vaccination can only occur once for each individual, on the first day that symptoms appear in the index case.

2.C Correction

In Section 2.2, under the scenario of case 2: vaccine may work in time to prevent infection ($\lambda + \omega < \sigma + \delta$), there was a mistake in the payoff to vaccinate (equation (2.6)). The

probability that the individual was not infected prior to the vaccine becoming effective was incorrect; the given probability was $(1 - p)^{\lambda + \omega - \delta}$ when it should have been $(1 - p)^{\lambda + \omega - \sigma}$. The correct payoff to vaccinate function is

$$\begin{aligned}\mathcal{P}_V &= (L - r_{vac} - r_{inf})\{[1 - (1 - p)^{\lambda + \omega - \sigma}] + [(1 - \varepsilon)(1 - p)^{\lambda + \omega - \sigma}(1 - (1 - p)^{\delta - (\lambda + \omega - \sigma)})]\} \\ &\quad + (L - r_{vac})\{[\varepsilon(1 - p)^{\lambda + \omega - \sigma}(1 - (1 - p)^{\delta - (\lambda + \omega - \sigma)})] + (1 - p)^\delta\}\end{aligned}\quad (2.13)$$

Due to the correction in the payoff to vaccinate, a new set of parameter values were used and are listed in Table 2.2.

2.C.1 Results

The overall conclusion of the model does not change under the corrected version. The new results under the correct payoff to vaccinate can be seen in Figure 2.9 - Figure 2.15. The only significant change to the results is the distribution of secondary infections and vaccinators no longer remain bimodal for a range of values of p ; however, the distribution of secondary infections and vaccinators remain bimodal for a small range of values for ε (Figure A6-A7).

Parameter	Definition	Baseline Value
Q	Number of contacts of index case	10 or 100
p	Transmission probability per edge per day	0.05
ω	Incubation period	5 days
δ	Infectious Period	5 days
σ	Latent Period	4 days
λ	Time between decision to vaccinate and attainment of protective immunity	1 day
ε	Vaccine Efficacy	0.95
r_{vac}	Penalty due to being vaccinated (e.g. adverse events, potential monetary cost)	0.024
r_{inf}	Penalty due to being infected (e.g. disease complications)	0.3
L	Baseline payoff	1
\mathcal{P}_V	Payoff to vaccinate as soon as index case exhibits symptoms	
\mathcal{P}_N	Payoff not to vaccinate	

Table 2.2: Parameter definitions and baseline values for the corrected version

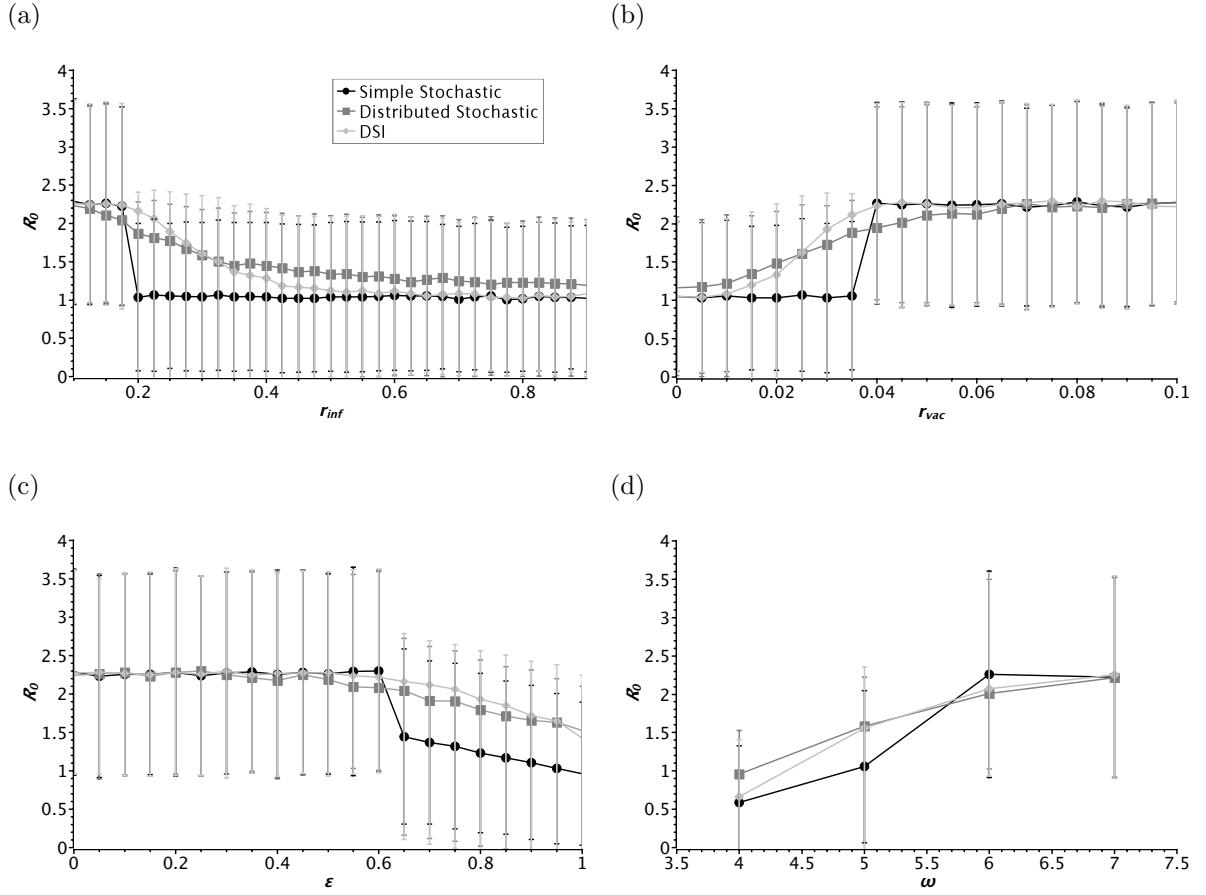


Figure 2.9: Mean and \pm the standard deviation of values of \mathcal{R} versus r_{inf} , r_{vac} , ϵ , ω with all other parameter values fixed at values in Table 2.2. “DSI” indicates the distributed stochastic model with imitation.

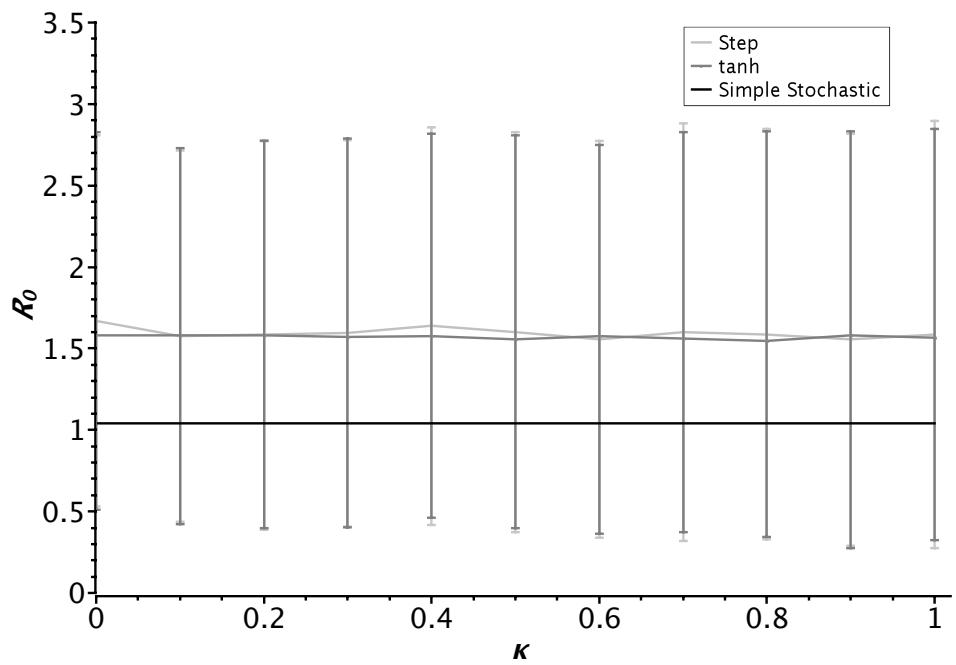


Figure 2.10: Mean and \pm the standard deviation of values of \mathcal{R} versus imitation strength κ for three different functional forms for $g(V)$, with all of the other parameter values fixed at values in Table 2.2

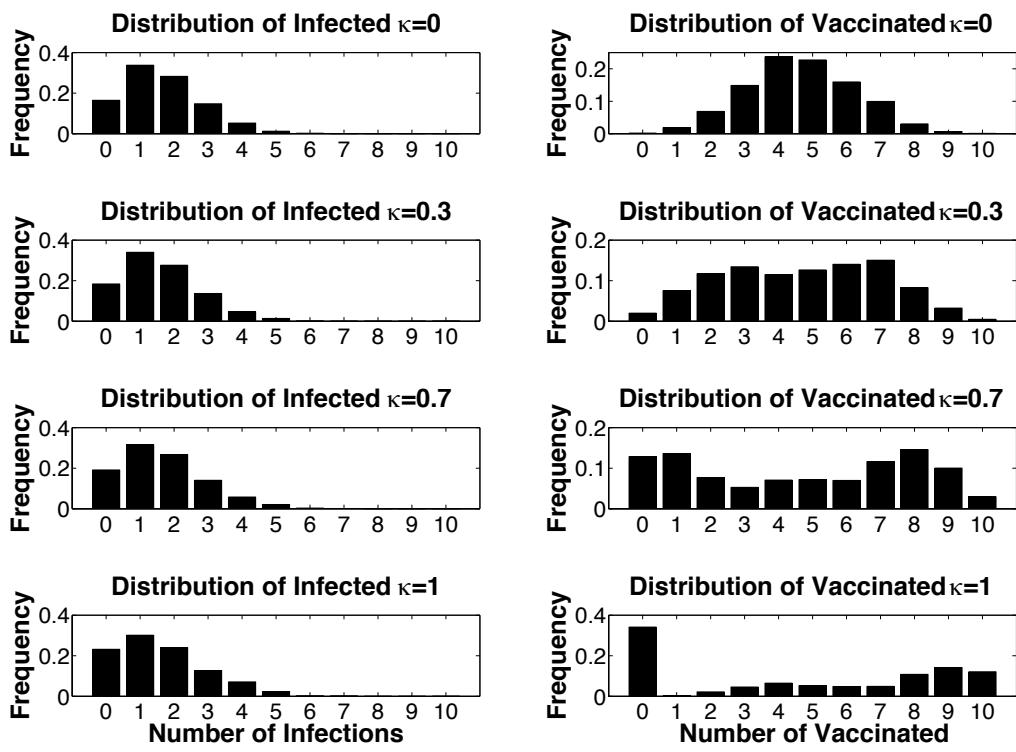
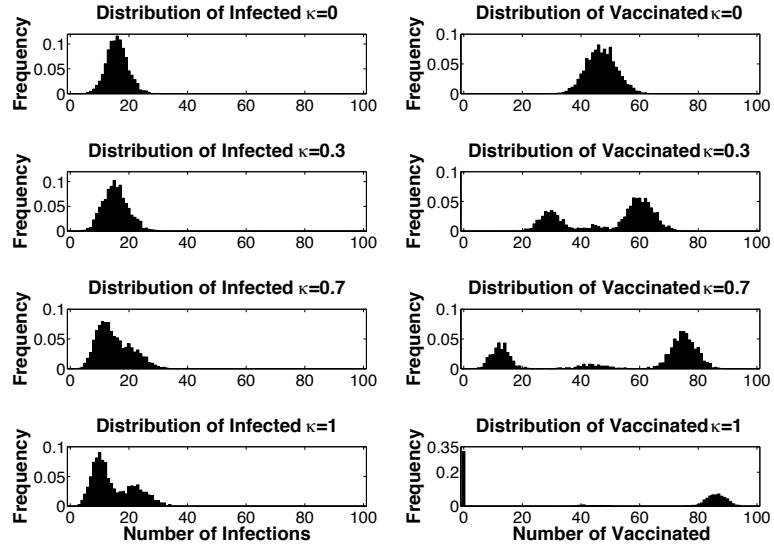


Figure 2.11: The distribution of the number of secondary infections (left) and number of vaccinators (right) for the case of $Q = 10$ neighbours for different values of imitation strength κ and other parameter values as in Table 2.2

(a) $\varepsilon = 0.95$



(b) $\varepsilon = 0.875$

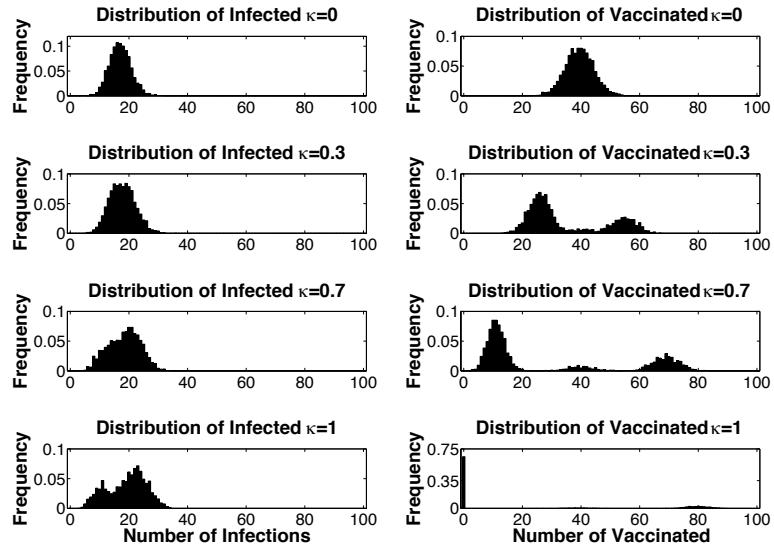
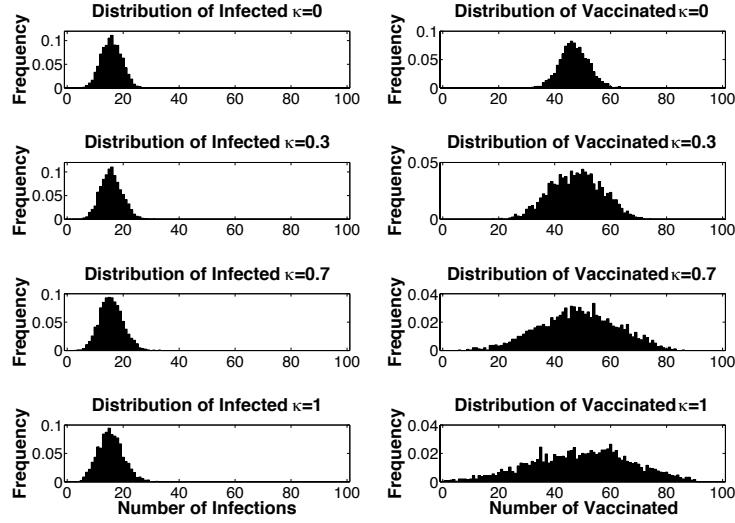


Figure 2.12: The distribution of the number of secondary infections (left) and number of vaccinators (right) for the case of $Q = 100$ neighbours for different values of imitation strength κ and other parameter values as in Table 2.2

(a) 24 nodes ($n = 12$)



(b) 50 nodes ($n = 25$)

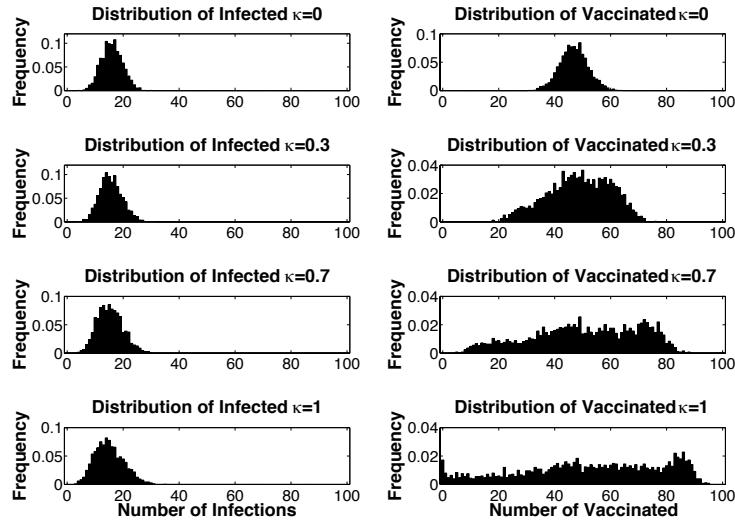


Figure 2.13: The distribution of the number of secondary infections (left) and number of vaccinators (right) for the case of $Q = 100$ neighbours, who are imitating n neighbours to the right and n neighbours to the left, for different values of imitation strength κ and other parameter values as in Table 2.2. The values of n are $n = 12$ (top half of panels) and $n = 25$ (bottom half of panels)

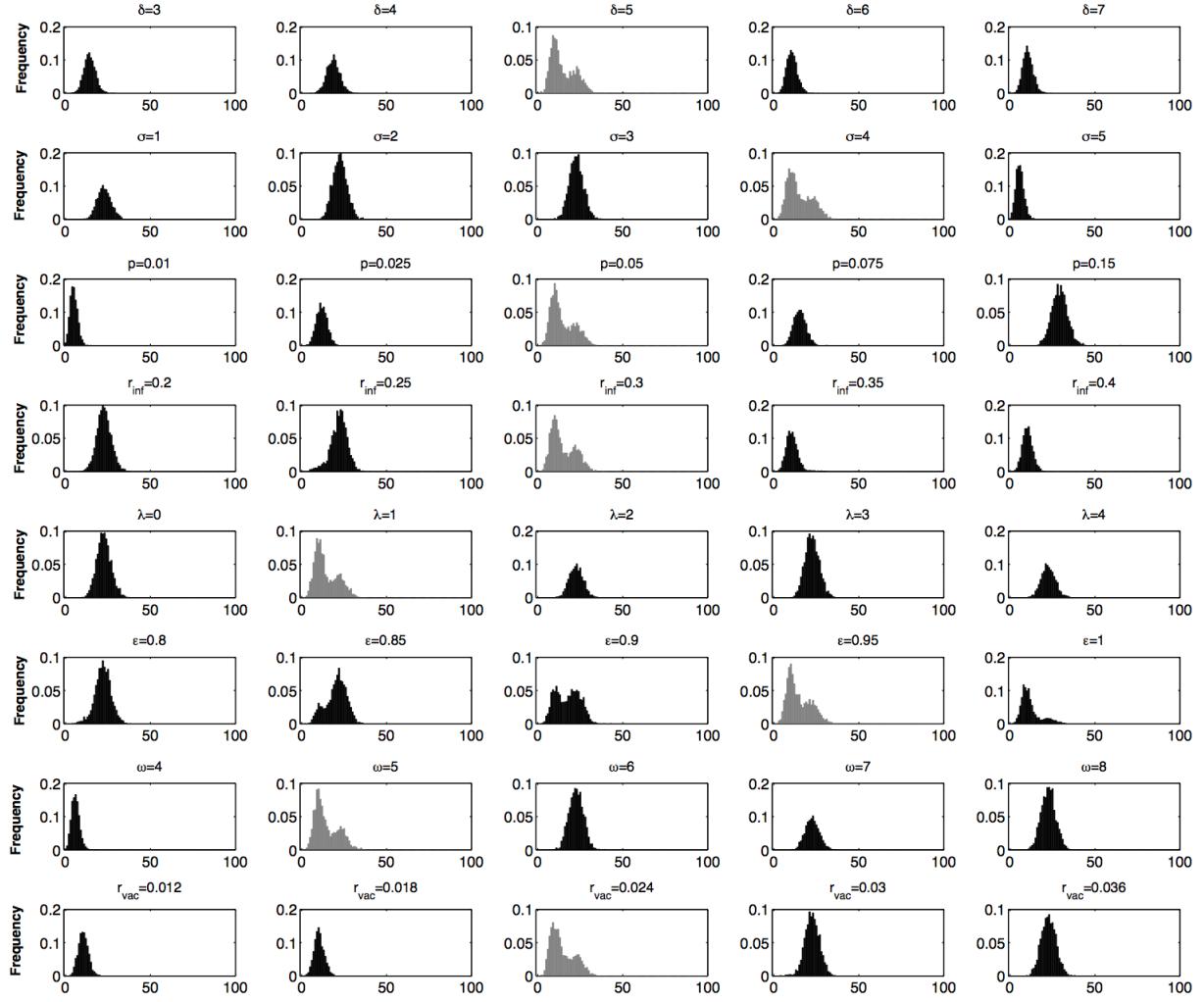


Figure 2.14: The distribution of the infected individuals under full imitation for the case of $Q = 100$ for the parameters $\lambda, \varepsilon, \omega, r_{vac}, r_{inf}, p, \sigma, \delta$. The baseline parameter values are used to generate the gray distributions and black distributions represent variations from baseline

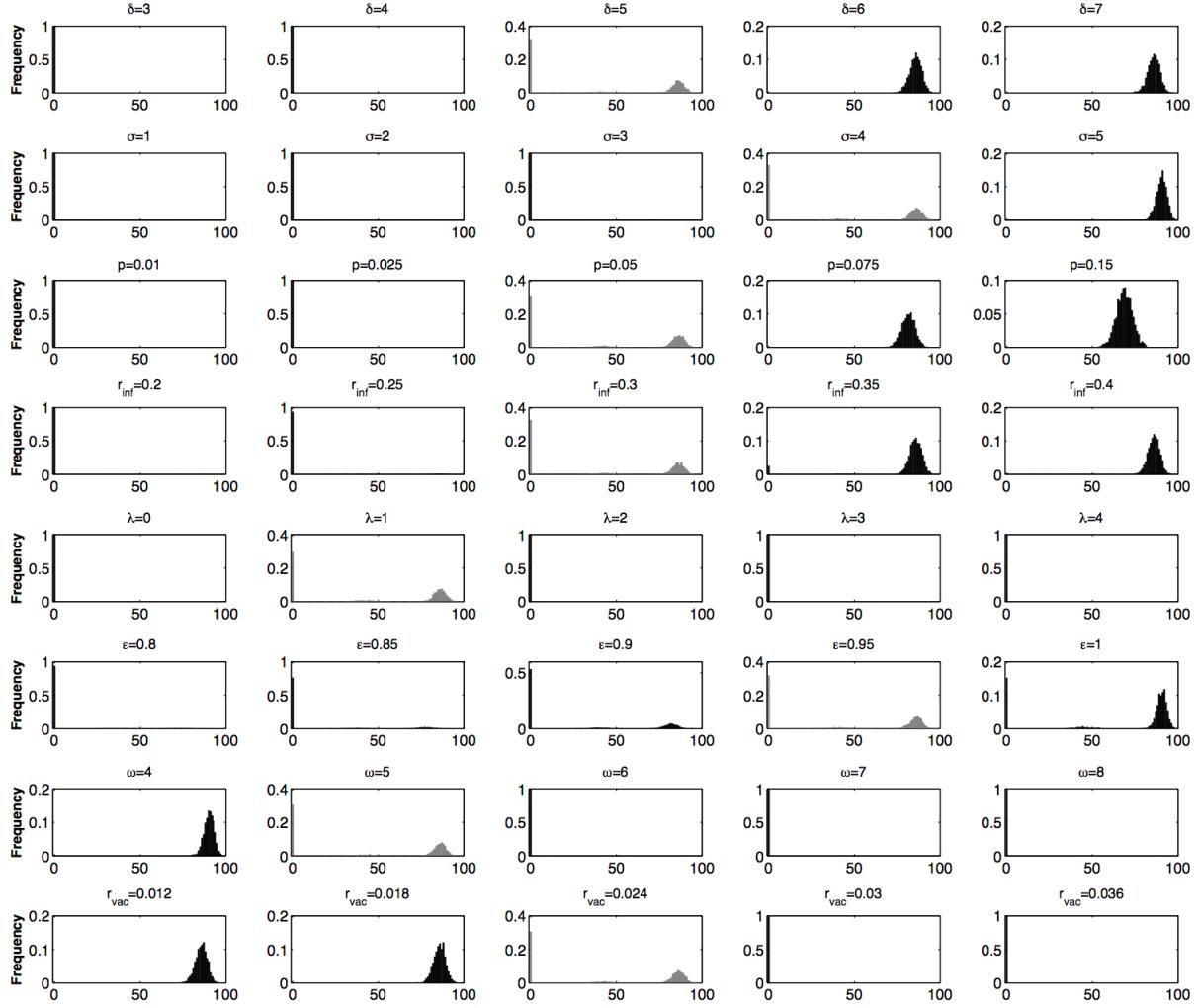


Figure 2.15: The distribution of the vaccinated individuals under full imitation for the case of $Q = 100$ for the parameters $\lambda, \varepsilon, \omega, r_{vac}, r_{inf}, p, \sigma, \delta$. The baseline parameter values are used to generate the gray distributions and black distributions represent variations from baseline

Bibliography

- [1] P. Bonanni. Demographic impact of vaccination: a review. *Vaccine*, 17:S120–S125, 1998.
- [2] D. Greenhalgh. Optimal control of an epidemic by ring vaccination. *Comm. Stat. Stoch. Models*, 2:339–363, 1986.
- [3] J. Muller, B. Schonfisch, and M. Kirkilionis. Ring vaccination. *J. Math. Biol.*, 41:143171, 2000.
- [4] R. Diel, B. Rappenhoener, and S. Schneider. Cost-effectiveness of hepatitis a immunization of children and adolescents in germany. *The European Journal of Health Economics*, 2(3):96–103, 2000.
- [5] B. Toma, F. Moutou, B. Dufourc, and B. Durand. Ring vaccination against foot-and-mouth disease. *Compar. Immun. Microbiol. Infec. Dis.*, 25:365372, 2002.
- [6] M.J. Keeling, M.E.J. Woolhouse, R.M. May, G. Davies, and B.T. Grenfell. Modelling vaccination strategies against foot-and-mouth disease. *Nature*, 421:136–142, 2003.
- [7] F.D.A. Fenner, D.A. Henderson, I. Arita, Z. Jezek, and I.D. Ladnyi. Smallpox and its eradication. *Geneva: World Health Organization*, 1988.
- [8] J.W. Hopkins. The eradication of smallpox: organizational learning and innovation in international health administration. *J. Dev. Areas*, 22(3):321–332, 1988.
- [9] M.A Strassburg. The global eradication of smallpox. *Am. J. Infect. Control*, 10(2):53–59, 1982.

- [10] J. O. Lloyd-Smith, S. J. Schreiber, P. E. Kopp, and W. M. Getz. Superspreading and the effect of individual variation on disease emergence. *Nature*, 438:355–359, 2005.
- [11] L. A. Meyers, B. Pourbohloul, M.E.J. Newman, D. M. Skowronski, and R. C. Brunham. Network theory and sars: predicting outbreak diversity. *Journal of Theoretical Biology*, 232:71–81, 2005.
- [12] D.L. Brito, E. Sheshinski, and M.D.Intriligator. Externalities and compulsory vaccinations. *J. Public Econ*, 45:6990, 1991.
- [13] C.T. Bauch and D.J.D. Earn. Vaccination and theory of games. *Proc. Natl. Acad. Sci. USA*, 101:1339113394, 2004.
- [14] C.T. Bauch. The spread of infectious diseases in a spatially structured population: an invasory pair approximation. *Mathematical Biosciences*, 198:217–237, 2005.
- [15] E. Klein, R. Laxminarayan, D. Smith, and C. Gilligan. Economic incentive and mathematical models of disease. *Environ. Dev. Econ.*, 12:707732, 2007.
- [16] C.T. Reluga, C.T. Bauch, and A.P. Galvani. Evolving public perceptions and stability in vaccine uptake. *Math. Biosci.*, pages 185–198, 2006.
- [17] A. Galvani, T. Reluga, and G. Chapman. Longstanding influenza vaccination policy is in accord with individual self interest but not with the utilitarian optimum. *Proc. Natl. Acad. Sci. USA*, 104:56925697, 2007.
- [18] F.H. Chane and A. Cottrell. Dynamic equilibria in an epidemic model with voluntary vaccination. *J. Biol. Dyn*, 2009.

- [19] M. Salathe and S. Bonhoeffer. The effect of opinion clustering on disease outbreaks. *Journal of the Royal Society*, pages 1505–1508, 2008.
- [20] A. Perisic and C.T. Bauch. Social contact networks and disease eradicability under voluntary vaccination. *PLoS Comput. Biol.*, 5(2):e1000280, 2009.
- [21] A. Perisic and C. T Bauch. A simulation analysis to characterize the dynamics of vaccinating behaviour on contact networks. *BMC Infectious Diseases*, 9:77, 2009.
- [22] S. Funk, E. Gilad, C. Watkins, and V.A.A. Jasen. The spread of awareness and its impact on epidemic outbreaks. *Proc. Natl. Acad. Sci. USA*, 106:68726887, 2009.
- [23] M. Kretzschmar, S. van den Hof, J. Wallinga, and J. van Wijngaarden. Ring vaccination and smallpox control. *Emerging infectious diseases*, 10(5):832–841, 2004.
- [24] E. Kaplan. Preventing second-generation infections in a smallpox bioterrorist attack. *Epidemiology*, 15(3):264–270, 2004.
- [25] P.J. Smith, A.M. Kennedy, K. Wooten, D.A. Gust, and L.K. Pickering. Association between health care providers influence on parents who have concerns about vaccine safety and vaccination coverage. *Pediatrics*, 118(5):1287–1292, 2006.
- [26] M. Merrill, A. Hollister, and S.Gibbens et al. Attitudes of californians toward poliomyelitis vaccination. *Am J Public Health*, 48:146–152, 1958.
- [27] P. Streefland, A.M.R. Chowdhury, and P. Ramos-Jimenez. Patterns of vaccination acceptance. *Social Science and Medicine*, 49:1705–1716, 1999.

- [28] L.A. Sturm, R.M. Mays, and G.D. Zimet. Parental beliefs and decision making about child and adolescent immunization: From polio to sexually transmitted infections. *Journal of Developmental and Behavioral Pediatrics*, 26(6):441–452, 2005.
- [29] N. Rao, M. Mobius, and T. Rosenbalt. Social networks and vaccination decisions. *FRB of Boston Working Paper*, 07(12):1–50, 2007.
- [30] A. F. Dempsey, G. D. Zimet, R. L. Davis, and L. Koutsky. Factors that are associated with parental acceptance of human papillomavirus vaccines: a randomized intervention study of written information about hpv. *Pediatrics*, 117:1486–1493, 2006.
- [31] M.J. Keeling. The effects of local spatial structure on epidemiology invasions. *Proc. Roy. Soc. Lond. B*, 266:859–867, 1999.
- [32] D.H. Zanette and S.R. Gusman. Infection spreading in a population with evolving contacts. *Journal of Biological Physics*, 34:135–148, 2008.
- [33] S. Moghadas, C. Bowman, G. Rost, and et al. Population-wide emergence of antiviral resistance during pandemic influenza. *PLoS ONE*, 3:e1839, 2008.
- [34] M. Zivkovic Gojovic, B. Sander, D. Fisman, M. Krahn, and C.T. Bauch. Modelling mitigation strategies for pandemic (h1n1) 2009. *CMAJ*, 181:673–680, 2009.
- [35] N.M. Ferguson, D.A.T. Cummings, S. Cauchemez, C. Fraser, and S. Riley et al. Strategies for containing an emerging influenza pandemic in southeast asia. *Nature*, 437:209–214, 2005.

Chapter 3

The impact of personal experiences with infection and vaccination on behaviour-incidence dynamics of seasonal influenza

C.R. Wells and C.T. Bauch (2012), EPIDEMICS, Volume 4, Number 3, pages 139-151

Abstract

Personal experiences with past infection events, or perceived vaccine failures and complications, are known to drive vaccine uptake. We coupled a model of individual vaccinating decisions, influenced by these drivers, with a contact network model of influenza transmission dynamics. The impact of non-influenza-like influenza (niILI) on decision-making was also incorporated: it was possible for individuals to mistake niILI for true influenza. Our objectives were to (1) evaluate the impact of personal experiences on vaccine coverage; (2) understand the impact of niILI on behaviour-incidence dynamics; (3) determine which factors influence vaccine coverage stability; and (4) determine whether vaccination strategies can become correlated on the network in the absence of social influence. We found that certain aspects of personal experience can significantly impact behaviour-incidence dynamics. For instance, longer-term memory for past events had a strong stabilising effect on vaccine coverage dynamics, although it could either increase or decrease average vaccine coverage depending on whether memory of past infections or past vaccine failures dominated. When vaccine immunity wanes slowly, vaccine coverage is low and stable, and infection incidence is also very low, unless the effects of niILI are ignored. Strategy correlations can occur in the absence of imitation, on account of the neighbour-neighbour transmission of infection and history-dependent decision making. Finally, niILI weakens the behaviour-incidence coupling and therefore tends to stabilise dynamics, as well as breaking up strategy correlations. Behavioural feedbacks, and the quality of self-diagnosis of niILI, may need to be considered in future programs adopting “universal” flu vaccines conferring long-term immunity. Public health interventions that focus on remind-

ing individuals about their previous influenza infections, as well as communicating facts about vaccine efficacy and the difference between influenza and nILI, may be an effective way to increase vaccine coverage and prevent unexpected drops in coverage.

3.1 Introduction

Influenza continues to significantly impact morbidity, mortality, and economic outcomes in many populations [1, 2, 3, 4]. The primary intervention for influenza infection is vaccination [5]. However, influenza vaccine coverage remains below optimal levels in many populations [2, 6]. Influenza immunisation is voluntary in the general population, and, as for many vaccine programs, reaching high coverage levels in adults can be difficult.

Because influenza vaccination is voluntary, understanding the determinants of vaccine uptake is key for understanding vaccine coverage levels. Factors that influence individual influenza vaccine uptake include fear/history of complications, peer vaccine uptake, medical professional opinion, and having a history of infection [6, 7]. Complications from influenza vaccine—ranging from minor symptoms such as red eyes, a hoarse voice or a mild case of hives to a major reaction such as anaphylaxis [8])—can shape the individual’s assessment of vaccine risk and ultimately their future vaccinating decisions [7, 9, 10]. Concerns about vaccine safety and efficacy were also a cause of low uptake of pandemic H1N1 vaccines in 2009 [10]. In a similar vein, it has been found that individuals may regret being vaccinated if they subsequently contract influenza infection anyway, and this will again influence future vaccinating decisions [7]. Personal infection history also matters: an individual having had a recent influenza infection is positively correlated with their seeking influenza vaccination

[9].

Influenza-like-illnesses (ILI) impose a considerable health burden on populations [11, 12]. A large portion of ILI is actually caused by pathogens other than influenza virus, and influenza vaccine does not offer protection against such non-influenza ILI (niILI) [11, 13]. However, the presence of niILI in a population can potentially influence vaccinating behaviour for influenza. Symptoms of niILI are very similar to influenza, therefore, many cases of niILI may be mistaken for influenza. As a result, individuals who become vaccinated for influenza but experience niILI anyway may think that the influenza vaccine is not efficacious. Alternatively, experiencing niILI may convince individuals to become vaccinated for influenza in the next season.

From a public health perspective, understanding year-to-year variability in vaccine coverage is also important, since highly variable vaccine coverage could lead to vaccine shortages or unnecessary vaccine surpluses, and it also creates uncertainty regarding where to allocate potentially limited vaccine supplies [14]. In Canada for instance, vaccine coverage has been gradually increasing over the past decade and manufacturers have been expanding capacity accordingly [6]. However, in other instances, demand for influenza vaccine has surged beyond what was expected [15].

Variability can occur not only in the form of season-to-season heterogeneity but also in the form of spatial or social heterogeneity. For instance, opinions of vaccination have been found to spread within a community from parent to parent, suggesting that vaccine opinions might vary between different social groups [16]. Similarly, it has been found that vaccine sentiments are clustered on social media networks [17].

An increasing number of mathematical models analyse how vaccine coverage emerges from the interplay between infection dynamics and individual vaccinating decisions [18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29]. These models typically couple a model of transmission dynamics [30, 31, 32] with a model of vaccinating behaviour, either game theoretical or otherwise. The coupling arises from the fact that individual vaccinating decisions collectively determine vaccine coverage and therefore influence the incidence of new infections or cases of disease, which in turn influences the likelihood that individuals will choose to vaccinate.

Several of these models describe transmission as occurring on a network [22, 23, 25, 26, 27], and among these, several furthermore assume that history of infection can directly influence future vaccine decisions [25, 26, 27]. In some of these models, it is the global (population-wide) risk of infection observed in past seasons that partly determines individual decisions (along with information about their own node degree) [27], while in others it is the individual's own history of infection that matters [25, 26], although in some cases the individual's memory of their past infections is retained only over the past flu season [26]. The impact of infection history has also been explored in homogeneous mixing (non-network) models [24]. Because infection and vaccination history influence vaccinating decisions, they should thereby influence the size of future outbreaks and hence form an important part of the behaviour-incidence feedback loop.

Some behaviour-incidence models also display a tendency for vaccine coverage to oscillate over time [19, 27]. However, in real populations, vaccine coverage appears not to oscillate with the extreme amplitude sometimes observed in models. Understanding the conditions under which behaviour-incidence models exhibit oscillations in vaccine cover-

age is relevant to determining how they can be used in designing optimal non-mandatory vaccine policies, by suggesting suitable model structure and parameterisation.

Influenza transmission models must often contend with the confounding effects of niILI [33, 34, 35]. However, the impact of niILI on behaviour-incidence dynamics has not been explored to a significant extent, despite the fact that niILI should play a major role in determining influenza vaccinating behaviour. In particular, it may weaken the behaviour-incidence coupling.

Other models have explored geographic or social clustering of vaccine opinions [26, 36], including whether this clustering has implications for disease control [36]. These models assume that individuals imitate vaccine strategies adopted by their neighbours on the contact network. The models have suggested that non-vaccinating clusters can allow the disease to persist even when theory based on homogeneous mixing suggests the overall population vaccine coverage is sufficient to eliminate the infection [36]. The structure of non-vaccinator clusters can also be influenced by how likely individuals are to copy successful strategies [26]. Under conditions where individuals on a network imitate their neighbours, it is easy to see how clusters of vaccinators and non-vaccinators can arise. However, it is not clear to what extent such clusters might develop without imitation, although it does seem possible: if individuals base vaccine decisions partly on past experience with infection, and if infection spreads through a contact network, then clustering may also emerge on the network even in the absence of imitating neighbours.

Here, our objective is to explore the parameter space of a network-based behaviour-incidence model of influenza transmission and vaccinating behaviour, in order to address

some of the issues described in the preceding paragraphs. In particular, we wish to (1) understand the impact of individual histories of infection and vaccination on individual vaccinating decisions, vaccine coverage, and disease dynamics, (2) understand the impact of niILI on influenza behaviour-incidence dynamics, (3) determine which parameters drive extreme (and generally unrealistic) oscillations in vaccine coverage, and (4) determine whether vaccine opinions can become correlated on a contact network even in the absence of neighbour imitation processes.

3.2 Model

The contact network through which influenza is transmitted was built according to the following procedure: two nodes that are not already connected are picked at random; a network edge is formed between the two nodes; this process is repeated until k connections have been made for each node. The resulting network structure remains fixed throughout the rest of the simulation. We assumed that the contact structure was a uniform network (each node has exactly k contacts).

We used a Susceptible-Infectious-Recovered-Vaccinated-Susceptible (*SIRVS*) natural history: a susceptible node can become infected by infectious neighbour ($S \rightarrow I$) with a probability p per day. An infectious individual recovers to a state of temporary natural immunity ($I \rightarrow R$) with probability δ per day. A season was defined as lasting from the time the infection is first introduced to the time the last infection disappears from the population. At the end of every season, each recovered individual loses natural immunity ($R \rightarrow S$) with probability ρ per season, representing the effects of antibody loss and

antigenic drift. Similarly, each vaccinated individual loses vaccine immunity ($V \rightarrow S$) with probability ω per season. Individuals do not know whether or not they have lost their vaccine immunity. Lastly, a proportion $I(0)$ of randomly chosen individuals are inoculated with infection, and a new season begins. We also assumed that natural immunity supersedes vaccine immunity, i.e. the individual does not obtain vaccine immunity if they have not lost natural immunity at the time of vaccination.

We also accounted for the possibility of individuals experiencing ILI not caused by true influenza infection. We sampled the incidence α of niILI in a given season from a log-normal distribution with mean $\langle\alpha\rangle$ and variance $\langle\langle\alpha\rangle\rangle$.

$$\alpha \sim \ln \mathcal{N}(\mu, \sigma^2) \quad (3.1)$$

$$\mu = \ln(\langle\alpha\rangle) - \frac{1}{2} \ln(1 + \frac{\langle\langle\alpha\rangle\rangle}{\langle\alpha\rangle^2}) \quad (3.2)$$

$$\sigma^2 = \ln(1 + \frac{\langle\langle\alpha\rangle\rangle}{\langle\alpha\rangle^2}) \quad (3.3)$$

where the probability of an individual experiencing niILI is α . We assumed that individuals experience influenza and niILI independently from one another. We also assumed that an individual will mistake niILI for influenza with probability β , hence the average number of niILI cases relevant to vaccine decision making is simply $\langle\alpha\rangle\beta$. (We note that one could instead sample the percentage of individuals experiencing niILI mistaken for influenza, thus introducing only one parameter, but we represent the steps separately for conceptual clarity.)

Individuals choose whether to become vaccinated prior to each season and decide ac-

cording to payoff functions. An individuals' payoff functions are determined partly by the individual's past experiences regarding infection and vaccination. The payoff for an individual to vaccinate is

$$\mathcal{P}_V = L - c_{vac} - c_{inf}(1 - \varepsilon(t)) \quad (3.4)$$

where c_{inf} is the cost of infection, c_{vac} is the cost of vaccination, $\varepsilon(t)$ is the perceived vaccine efficacy at time t , and L is a baseline payoff representing a state of full health. The payoff not to vaccinate is

$$\mathcal{P}_N = L - c_{inf}. \quad (3.5)$$

Each season, the individual will vaccinate if $\mathcal{P}_V > \mathcal{P}_N$, otherwise non-vaccination is the more appealing choice.

The quantities c_{vac} , c_{inf} and $\varepsilon(t)$ are themselves functions of more fundamental quantities that reflect the individual's history of infection and vaccination. c_{vac} depends upon a constant, baseline vaccine cost plus a cost due to the individual's most recent experience of a vaccine complication, if any. c_{vac} is given by

$$c_{vac} = \underline{c}_{vac} + \overline{c}_{vac} e^{-mT_C} \quad (3.6)$$

where \underline{c}_{vac} represents the baseline cost (including cost of material or administration, time costs, and discomfort of a needle injection), T_C is the time since the most recent perceived vaccine complication, m is the memory decay rate, i.e., the rate at which the memory of the most recent complication fades, and \overline{c}_{vac} is the maximal cost of experiencing the complication. Note that as the memory of the vaccine complication fades, the cost of

vaccinating fades. If an individual experiences a vaccine complication in a given season, then $T_C = 0$ in the next season, $T_C = 1$ in the following season, etc. Each time an individual is vaccinated, complications occur with probability γ , hence $T_C \equiv T_C(\gamma)$ is a function of γ .

The quantity c_{inf} depends on the individual's most recent experience of an infection, and is expressed by

$$c_{inf} = \bar{c}_{inf} e^{-mT_I} \quad (3.7)$$

where T_I is the time since the individual's most recent infection (either with true influenza, or with a case of nILLI that has been mistaken for influenza) and \bar{c}_{inf} is the maximal cost of experiencing an infection.

In order to capture the variability in perceived vaccine efficacy between individuals, and how it may depend upon their experiences with the vaccine, we allow an individual's perceived vaccine efficacy $\varepsilon(t)$ to depend on their most recent (un)successful vaccination. A vaccination is perceived as ‘successful’ if the individual vaccinates and did not get infected that season. A vaccination is perceived as ‘unsuccessful’ if the individual vaccinates but perceives being infected with influenza nonetheless. $\varepsilon(t)$ is expressed as

$$\varepsilon(t) = \begin{cases} \underline{\varepsilon} & \text{if ‘unsuccessful’} \\ \varepsilon(t-1)e^{-m} + [1 - e^{-m}]\bar{\varepsilon} & \text{if ‘successful’} \\ \varepsilon(t-1)e^{-m/\xi} + [1 - e^{-m/\xi}]\bar{\varepsilon} & \text{if did not vaccinate} \end{cases} \quad (3.8)$$

where $\underline{\varepsilon}$ is the minimum perceived vaccine efficacy and $\bar{\varepsilon}$ is the maximum perceived vaccine efficacy. An individual experiencing an unsuccessful vaccination decreases their perceived

vaccine efficacy to $\underline{\varepsilon}$. However, perceived vaccine efficacy will climb over time at a rate dictated by the memory parameter m to $\bar{\varepsilon}$ if individuals vaccinate and do not perceive an infection. If an individual did not vaccinate in a season, we assumed that their memory of a (previously ineffective) vaccination fades at a slower rate (m/ξ) than if they had experienced a successful vaccination, since they have less information with which to update their impression. (We note that preventing $\varepsilon(t)$ from recovering in individuals who do not vaccinate would cause some individuals to remain permanently as non-vaccinators.)

The actual vaccine efficacy for preventing influenza infection is a constant ε . This quantity influences transmission dynamics explicitly, but also perceived vaccine efficacy implicitly through the ‘successful’ outcome of equation (3.8).

We can substitute equations (3.6) and equation (3.7) into the payoff functions, equations (4.1) and (4.2), to obtain the history dependent payoff functions

$$\mathcal{P}_V = L - (\underline{c}_{vac} + \overline{c}_{vac} e^{-mT_C}) - \overline{c}_{inf} e^{-mT_I} (1 - \varepsilon(t)) \quad (3.9)$$

$$\mathcal{P}_N = L - \overline{c}_{inf} e^{-mT_I}. \quad (3.10)$$

Payoff functions normally represent the anticipated payoff to an individual for adopting a given strategy. Here, we have made payoffs explicitly dependent only on past events. However, there is an implicit dependence on future events in the sense that individuals use the frequency of their own past infections and vaccine complications as a “rule of thumb” for predicting how many future infections and vaccine complications they can anticipate. These payoff functions have not been used in previous publications, to our knowledge.

The impact of herd immunity on decision-making can be expressed explicitly in many behaviour-incidence models. In the present model, herd immunity is implicit in the payoff functions. An individual with more vaccinated contacts is less likely to be infected and is therefore more likely to have a large value of T_I . As a result, they may be less willing to vaccinate, which can be thought of as free-riding since in future they may contract, and further transmit, the infection.

In summary, individuals are infected and recover during each influenza season, and are vaccinated and/or lose vaccine/natural immunity between influenza seasons. Each simulation consisted of 10,000 seasons, and the transient dynamics of the first 100 seasons were discarded before analysing the results. The parameter descriptions and baseline values that were used in simulations appear in Table 1. Except where otherwise noted, all simulations used these baseline values.

Parameter	Description	Value	Reference
N	Number of individuals in network	10000	assumption
k	Average Node Degree	10	assumption
$I(0)$	Initial number of infected individuals per season	10	assumption
$\langle \alpha \rangle$	Average incidence for niILI	0.12 †	[37]
$\langle\langle \alpha \rangle\rangle$	Variance of incidence for niILI	0.000064	calibrated ††
β	Probability of an individual mistaking niILI for influenza	0.50	assumption
L	Baseline payoff	1	assumption
δ	Probability of moving from state I to state R , per day	0.20	[1, 38]
ρ	Probability of moving from state R to state S , per season	0.25	[38, 39, 40]

Parameter	Description	Value	Reference
ω	Probability of moving from state V to state S , per season	0.50	[41]
ε	Actual vaccine efficacy	0.70	[42, 43]
$\underline{\varepsilon}$	Minimum perceived vaccine efficacy	0.25	assumption
$\bar{\varepsilon}$	Maximum perceived vaccine efficacy	0.90	assumption
γ	Probability of experiencing vaccine complications, per vaccination	0.01	[2]
c_{vac}	Minimum cost of vaccination	0.0015	calibrated*; [1, 2, 42, 44]
$\overline{c_{vac}}$	Additional cost of vaccination due to a complication	0.0035	calibrated*; [1, 2, 42, 44]
p	Probability of transmitting infection along edge per day	0.055	calibrated**; [42, 45]
$\overline{c_{inf}}$	Maximum cost of infection	0.0055	[1, 46, 47]
m	Memory decay rate, per season	0.25	assumption
ξ	Vaccine efficacy memory decay rate factor	4	assumption

Table 3.1: Parameter definitions and baseline parameter values used in the simulations. * The values for c_{vac} and $\overline{c_{vac}}$ were calibrated within plausible ranges from empirical data on vaccine complication risks from Refs.[1, 42], to obtain a vaccine coverage of approximately 40% for the baseline scenario. ** p was calibrated to obtain a 15% infection rate on average in each season, in the absence of vaccination [42, 45, 48, 49]; this corresponds to basic reproduction number $\mathcal{R}_0=2.2$ [50, 51, 52]. † The value of $\langle \alpha \rangle$ was calculated by determining the ratio of nILI cases to influenza cases in [37] then multiplying that ratio by 15% to obtain $\langle \alpha \rangle$. ‡ The variance for the baseline case was calibrated such that the distribution resembled a normal distribution. The same variance was used for all values of $\langle \alpha \rangle$.

3.3 Results

3.3.1 Description of Dynamical Regimes

The model can exhibit a wide range of possible behaviour-incidence dynamics. Time series of incidence and vaccine coverage per season, and corresponding return maps, show at least six types of dynamics (Figure 1). These categories are:

(a) Baseline Behaviour

At baseline parameter values (Table 1) intended to capture patterns similar to those observed in influenza vaccine programs in many countries, vaccination coverage varies slightly around an average value of about 40%, and the incidence likewise varies from season to season stochastically. However, a significant increase in incidence in season t is followed by a significant increase in vaccine coverage in season $t+1$ from one season to the next. This pattern can also be seen in the return map plotting $I(t)$ versus $V(t+1)$ (Figure 1a). The dynamics also exhibit occasional periods where vaccine coverage is relatively constant from one season to the next, which is exhibited by the clustering of points along the diagonal in the return map plotting $V(t)$ versus $V(t+1)$. Finally, dynamical phases where lower vaccine coverage is followed by high vaccine coverage in the following season, due to boom-bust cycles arising from the coupling between vaccinating behaviour and disease dynamics, are also apparent as off-diagonal clusters in the return map plotting $V(t)$ versus $V(t+1)$.

(b) No Vaccination

When vaccine costs are sufficiently high or infection costs are sufficiently low, no individuals find vaccination appealing. Hence, vaccine coverage is zero in every season and infection spreads freely throughout the population leading to high overall incidence in each season, but with significant variability from one season to the next (Figure 1b).

(c) Constant Vaccine Coverage

When payoffs are such that vaccination is more appealing, vaccine coverage is higher than the baseline case, and relatively constant (Figure 1c). In the simulation, those who are not vaccinating have experienced a recent vaccine complication (low T_C value) or have been protected by herd immunity. If the vaccine was free ($c_{vac} = 0$) then those who are not vaccinating only have experienced a recent vaccine complication. Points are clustered along the diagonal in the return map plotting $V(t)$ versus $V(t + 1)$, and the return map plotting $I(t)$ versus $V(t + 1)$ shows that incidence in season t has little predictive value for vaccine coverage in season $t + 1$.

(d) Two-Cycle

Transient two cycle behaviour-incidence dynamics emerge at points in the time series under certain parameter values (Figure 1d). Incidence peaks are always followed by incidence troughs, and seasonal vaccine coverage is out of phase with seasonal incidence. In the return map plotting $V(t)$ versus $V(t+1)$, this is apparent in two large off-diagonal clusters corresponding to alternating low and high vaccine coverage. It is also apparent in the return map plotting $I(t)$ versus $I(t + 1)$, where low incidence in season t is more likely to be followed by high incidence in season $t + 1$ and vice versa. Under better resolution, the third return map would clearly indicate that higher incidence is season

t is usually followed by higher vaccine coverage in season $t + 1$ (i.e. there are two separate clusters appearing in the infection vs vaccination return map).

(e) **Episodic**

Episodic dynamics occur when $\beta = 0$, corresponding to no influence of niILI on vaccinating decisions, especially for parameter values $\omega = 1$ and $\varepsilon = 0.90$ (Figure 1e). A large incidence peak in season t is followed by high coverage not only in season $t + 1$ but also $t + 2, t + 3$ and subsequent years. Vaccine coverage in subsequent years is high enough to prevent outbreaks. However, vaccine coverage gradually wanes as memory of the most recent incidence peak fades, and eventually it falls dramatically, precipitating another large peak in incidence. Trajectories in the return maps are highly clustered around certain points in the phase portrait.

(f) **Coat-tails**

When memory is very short (the memory decay rate m is large), individuals only use information from the most recent season in their vaccinating decisions. Hence, vaccine coverage rides on the ‘coat tails’ of last season’s incidence: changes in incidence from one season to the next are very closely shadowed by changes in vaccine coverage from one season to the next, such that vaccine coverage depends strictly on the incidence from the last season (Figure 1f). The return map plotting $V(t)$ versus $V(t + 1)$ closely matches the return map plotting $I(t)$ versus $I(t + 1)$ and incidence in season t strongly predicts vaccine coverage in season $t + 1$. (However, because vaccine coverage also influences incidence, it could equally well be said that incidence is riding on the ‘coat tails’ of last season’s vaccine coverage.)

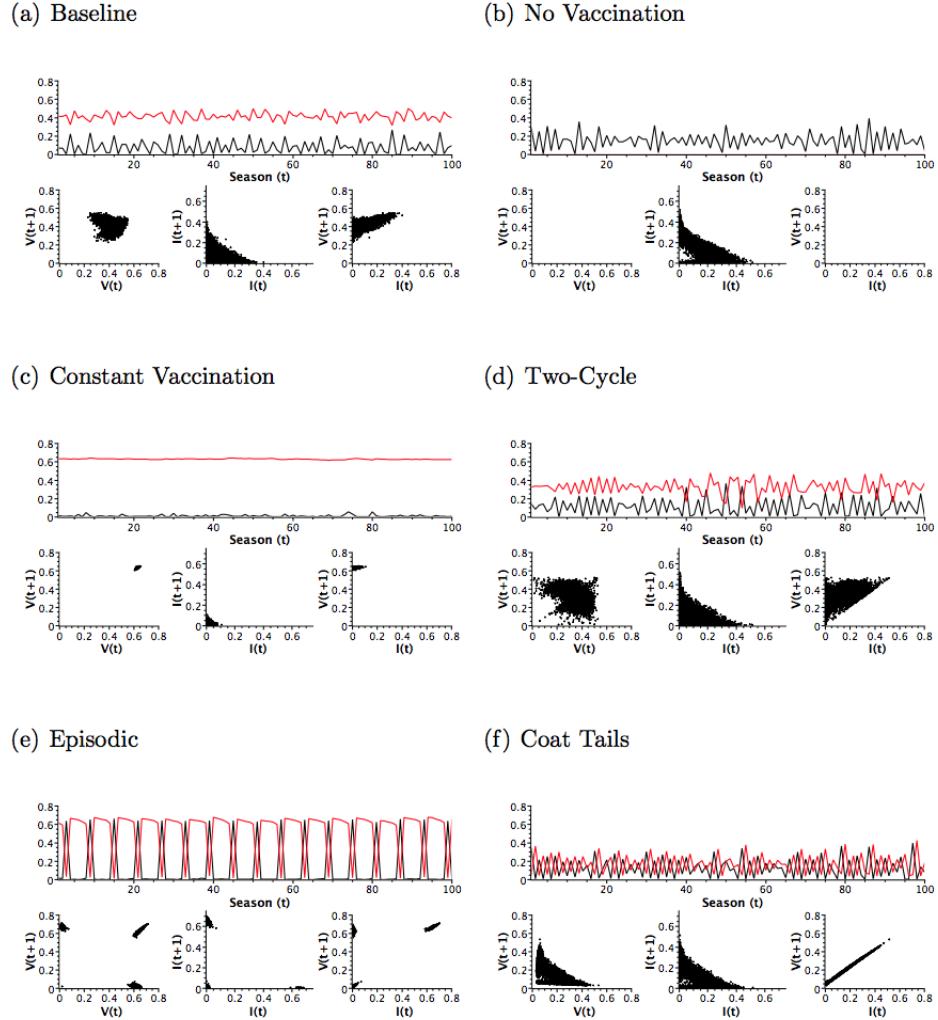


Figure 3.1: Dynamical regimes exhibited by the model: a) Baseline dynamics; b) $\bar{c}_{inf} = 0$; c) $m = 0.01$ and $\underline{\varepsilon} = 0.65$, d) $m = 0.45$, $\bar{c}_{inf} = 0.009$, $\underline{\varepsilon} = 0.65$, $\bar{\varepsilon} = 0.75$, and $\beta = 0$; e) $\omega = 1$, $\varepsilon = 0.90$ and $\beta = 0$; f) $m = 1.50$; other parameter values as in Table 1. Top sub-panels show a portion of the time series of the percentage of individuals infected by influenza per season, $I(t)$ (black), and the percent vaccine coverage per season, $V(t)$ (red). The bottom left sub-panel shows the vaccination return map, $V(t)$ vs. $V(t + 1)$, where t represents the current season and $t + 1$ the next. The bottom middle sub-panel shows the infection return map, $I(t)$ vs. $I(t + 1)$. The bottom right sub-panel shows the infection/vaccination return map, $I(t)$ vs. $V(t + 1)$.

Case	$\langle V(t) \rangle$	$\langle\langle V(t) \rangle\rangle$	$\langle I(t) \rangle$	$\langle\langle I(t) \rangle\rangle$
Baseline	0.4147	0.0022	0.0799	0.0057
$m = 0.01$	0.2039	5×10^{-5}	0.1089	0.0079
$m = 0.10$	0.4805	0.0007	0.055	0.0031
$m = 0.01 \ \& \ \underline{\varepsilon} = 0.65$	0.6304	3×10^{-5}	0.0116	0.0001
$m = 0.10 \ \& \ \underline{\varepsilon} = 0.65$	0.5997	0.0004	0.0213	0.0005
$\omega = 0.05$	0.2171	5×10^{-5}	0.0043	6×10^{-6}
$\omega = 0.05 \ \& \ \beta = 0$	0.1419	0.0018	0.02954	0.0011
$\omega = 1$	0.4529	0.0026	0.1013	0.0084
$\omega = 1 \ \& \ \beta = 0$	0.4664	0.0089	0.1114	0.01442
$\underline{\varepsilon} = 0.40$	0.4265	0.0014	0.1059	0.0077
$\underline{\varepsilon} = 0.95$	0.3989	0.0027	0.0644	0.0045
$m = 1.5$	0.1684	0.011	0.1291	0.0117
$m = 1.5 \ \& \ \beta = 0$	0.1391	0.0135	0.14	0.0135
$\beta = 0$	0.414	0.0046	0.0945	0.0077
$\beta = 1$	0.4217	0.0012	0.0664	0.0041
$\underline{\varepsilon} = 0.27$	0.4146	0.0022	0.0797	0.0057
$\underline{\varepsilon} = 0.28$	0.4756	0.0024	0.0657	0.0045
$\underline{\varepsilon} = 0.60$	0.4906	0.0022	0.0612	0.0038

Table 3.2: The statistics for the vaccination coverage ($V(t)$) and influenza incidence ($I(t)$), where $\langle \cdot \rangle$ denotes the average and $\langle\langle \cdot \rangle\rangle$ denotes the variance, over time. All other parameter values for each case are the same as the baseline case.

3.3.2 Determinants of vaccinating behaviour-incidence dynamics

In this subsection we explore how model parameter values drive behaviour-incidence dynamics. We will consider two cases for the remainder of the paper: (1) niILI can be mistaken for influenza ($0 < \beta \leq 1$, containing our baseline assumption) and (2) niILI is never mistaken for influenza ($\beta = 0$, as in many previous models). Results are summarised in Table 2, which provides mean and variance of vaccination coverage and influenza incidence for various scenarios, as well as Figure 2.

Case $0 < \beta \leq 1$

As the proportion β of niILI cases mistaken for influenza increases from baseline to 1 there is a very little increase in the vaccination coverage. However, there is a significant decrease in influenza incidence, which is surprising in light of the fact that vaccine coverage is not changing very much as β increases. Increasing $\langle\alpha\rangle$ produces a similar result. This surprising result occurs because when β is higher and thus niILI is more often mistaken for influenza, vaccination is spread more evenly through the population over time: individuals who vaccinated and experienced niILI in the same season will tend not to vaccinate the following season due to lower perceived vaccine efficacy, whereas there will be more individuals who did not vaccinate this season but experienced niILI, and hence will vaccinate in the next season. In contrast, when β is lower, individual behaviour is more consistent between seasons, with some individuals never vaccinating and other individuals repeatedly vaccinating each season, thus nullifying the benefits of residual vaccine immunity from last season.

As a result of the possibility of mistaking niILI for true influenza, increasing β ($\langle\alpha\rangle$) also decreases the perceived vaccine efficacy $\varepsilon(t)$ (Supplementary Figure 1a)). $\varepsilon(t)$ depends sensitively on the memory parameter m and in particular is much lower for long-term memory (small m ; Supplementary Figure 1d)). As expected, $\varepsilon(t)$ is also higher when the minimum perceived vaccine efficacy $\underline{\varepsilon}$ is higher or when the actual vaccine efficacy ε is higher; other parameters have little impact on $\varepsilon(t)$ (Supplementary Figure 1). Increasing the actual vaccine efficacy (ε) from 40 % to 95% has almost no impact on the vaccine coverage but leads to significantly reduced incidence (Table 2). This represents policy

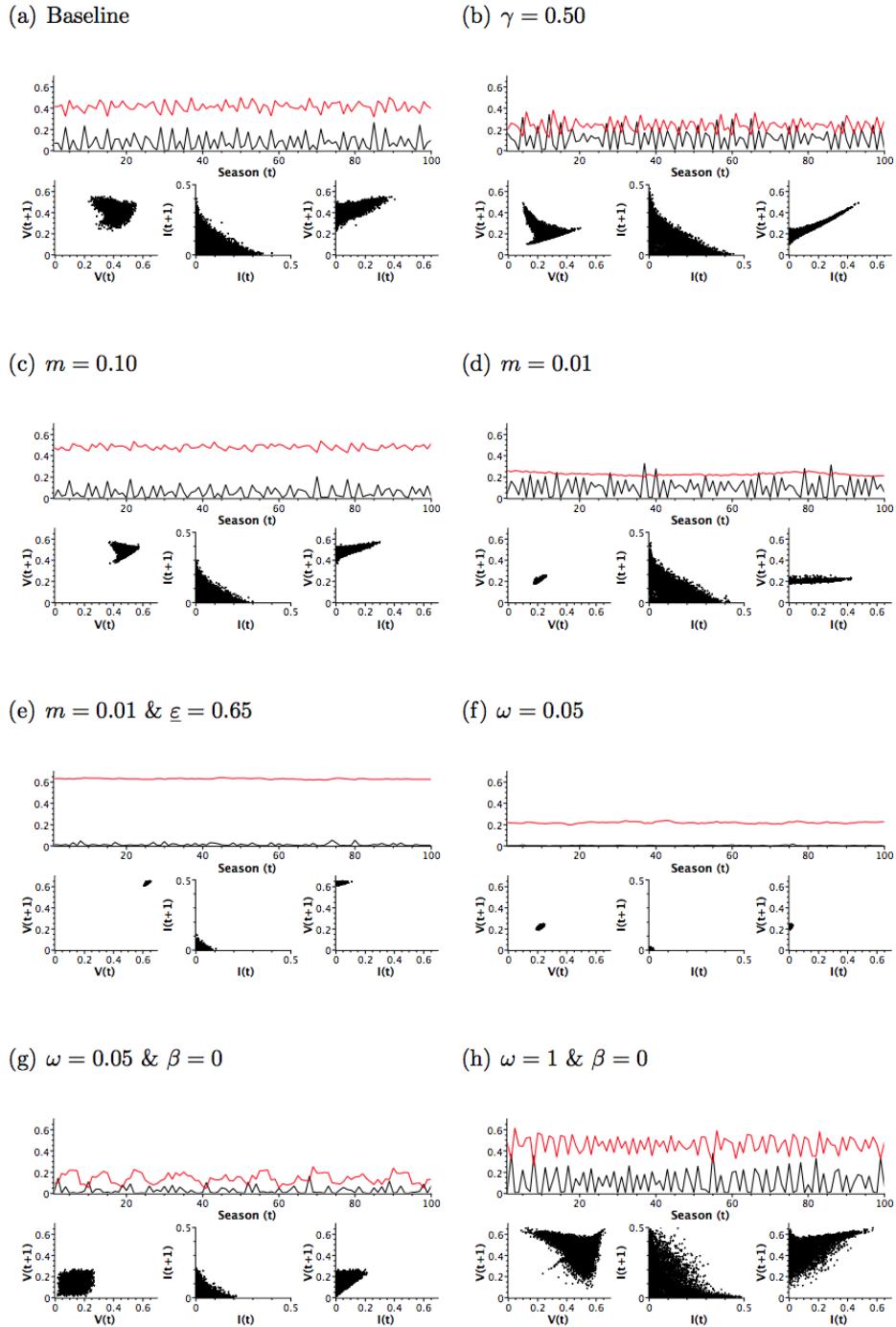


Figure 3.2: See page 128 for the caption.

Figure 3.2: (Figure on page 127) The impact of a) baseline dynamics b) vaccine complications (γ), c)-e) memory decay rate (m) and f)-h) waning vaccine immunity (ω). Top sub-panels show a portion of the time series of the percentage of individuals infected by influenza per season, $I(t)$ (black), and the percent vaccine coverage per season, $V(t)$ (red). The bottom left sub-panel shows the vaccination return map, $V(t)$ vs. $V(t + 1)$, where t represents the current season and $t + 1$ the next. The bottom middle sub-panel shows the infection return map, $I(t)$ vs. $I(t + 1)$. The bottom right sub-panel shows the infection/vaccination return map, $I(t)$ vs. $V(t + 1)$.

resistance with respect to vaccine coverage: an increase in vaccine efficacy makes vaccine more attractive (equation (4.1)), but this effect is cancelled by a decreased incentive to vaccinate, since a higher vaccine efficacy generates more herd immunity to protect non-vaccinated individuals.

Increasing the minimum perceived vaccine efficacy ($\underline{\varepsilon}$) increases the vaccination coverage, but only up to a threshold $\underline{\varepsilon} \approx \underline{c}_{vac}/\overline{c}_{inf}$ (i.e. $\mathcal{P}_V < \mathcal{P}_N$ when $\varepsilon(t) = \underline{\varepsilon}$ and there has been no recent vaccine complication), after which vaccine coverage no longer changes with further increases in $\underline{\varepsilon}$ (Table 2).

When the probability of vaccine complications (γ) increases significantly from the baseline values, vaccine coverage declines (as expected) but both vaccine coverage and infection dynamics also become more variable and a ‘coat-tail’ pattern emerges (Figure 2b)). Compared to the baseline scenario, we observe that incidence peaks are generally larger due to the lower average vaccine coverage, but at the same time (and despite lower average coverage), there are occasional seasons with very low incidence, since vaccine coverage can occasionally go above 40% (Figure 2b)).

Changes in the memory decay rate (m) can strongly impact model dynamics. Longer-

term memory (lower m) strongly stabilises vaccine coverage (Figure 2c,d)) whereas shorter-term memory (higher m) results in a ‘coat tail’ pattern of extreme variability (results not shown). Decreasing m stabilises dynamics because the impact of past incidence fluctuations are averaged out by taking more of the past influenza seasons into account. Changing m can either decrease or increase average vaccine coverage, depending on whether the net effect of decreasing m is to increase memory of past infections or memory of past vaccine failures (or, to a lesser extent, past vaccine complications). For very small $m = 0.01$, vaccine coverage is greatly reduced (Figure 2d)) because the population views the vaccine efficacy to be much lower than its actual value of 70 % (Supplementary Figure 1d)). However, if the minimum perceived vaccine efficacy ($\underline{\varepsilon}$) is increased then it is possible to obtain vaccine coverage that is both high and stable, even when $m = 0.01$ (Figure 2e); Table 2).

The value of ω (waning vaccine immunity) does not directly impact the payoff functions in equations (4.1-4.2) but does have an impact on the vaccine coverage. As ω decreases (immunity wanes slower) the vaccine coverage decreases and stabilises (Figure 2f)). This occurs because individuals are protected for much longer after their most recent vaccination, which leads to fewer infections in the future and therefore a decrease in long-term vaccine coverage. As ω increases from baseline, vaccine coverage increases slightly, as does the average seasonal incidence. Incidence is also somewhat more variable (Table 2).

In all our simulations we assumed that the initial number of infectious individuals I_0 at the start of each season was always the same. Assuming instead that it varies from season has relatively little impact on the dynamics (results not shown). We also assumed the same population size N for all simulations. Increasing N causes a slight decrease in incidence and vaccine coverage (results not shown). This difference may occur because

clustering (triangles in the network) is more likely for smaller N , and clustering could impact infection incidence.

Our baseline assumption is that all cases of influenza are recognised by the individual as influenza infection; however, in reality this is not likely since some influenza infections are asymptomatic. In sensitivity analysis we explored the impact of the alternative assumption that an infected individual recognises it as influenza only with a probability $\psi = 0.70$. The main effect of decreasing ψ is to decrease and stabilise vaccine coverage since there are fewer individuals experiencing influenza symptoms, and as a result it also increases infection incidence (Supplementary Table 1, Supplementary Figure 2). Decreasing ψ also increases the average perceived vaccine efficacy $\varepsilon(t)$, since individuals are less likely to perceive a vaccine failure due to asymptomatic infections (Supplementary Figure 1).

Case $\beta = 0$

In this case we assume that niILI is never mistaken for influenza ($\beta = 0$). As expected, perceived vaccine efficacy $\varepsilon(t)$ increases when $\beta = 0$ (Supplementary Figure 1). However, influenza incidence also increases despite overall vaccine coverage being similar, for reasons discussed at the start of the previous subsection (case $0 < \beta \leq 1$).

The effects of changing ω (probability of vaccine waning immunity) are dramatically different when $\beta = 0$. There still is a decrease in vaccine coverage as ω decreases. However, compared to the $\beta > 0$ case, vaccine coverage is more variable and sporadic outbreaks can occur (Figure 2g) versus Figure 2f)). This occurs because the additional vaccination from the mistaken niILI cases is no longer present, which both decreases vaccine coverage and

makes it more variable across the network, which is thus more prone to sporadic outbreaks in pockets of susceptible individuals. For similar reasons, as ω increases, vaccine coverage becomes even more variable than the case where $\beta > 0$ (Figure 2h) versus Table 2).

3.3.3 Stability of Vaccine Coverage

To investigate what factors most influence the stability of the vaccine coverage, we used auto-correlation. The auto-correlation (with a lag of one) is denoted as $\mathcal{R}(1)$ ($-1 \leq \mathcal{R}(1) \leq 1$). To calculate the auto-correlation for the time series of vaccinating individuals from time $t = 1$ to time $t = T$ we use

$$\mathcal{R}(1) = \frac{\sum_{i=1}^{T-1} (V(i) - \langle V(t) \rangle)(V(i+1) - \langle V(t) \rangle)}{(T-1)\langle\langle V(t) \rangle\rangle}, \quad (3.11)$$

where $\langle V(t) \rangle$ is average vaccine coverage from $t = 1$ to $t = T$, $\langle\langle V(t) \rangle\rangle$ is the variance of the vaccine coverage from $t = 1$ to $t = T$ and $V(i)$ corresponds to the vaccine coverage in season i . Positive values of $\mathcal{R}(1)$ implies that the dynamics are more stable, since the points remain relatively in the same location above or below the mean. More negative values of $\mathcal{R}(1)$ correspond to more extreme oscillations in the dynamics (e.g. a two-cycle).

To calculate $R(1)$ we ran 1600 seasons, discarding the first 100 seasons due to transient dynamics. We present surface plots of $R(1)$ on the vertical axis versus pairs of model parameters on the two horizontal axes. The pairs were chosen in order to highlight parameter combinations that had a significant impact on $R(1)$. Many pairings involved the memory parameter m , since that was found to be a major determinant of dynamics.

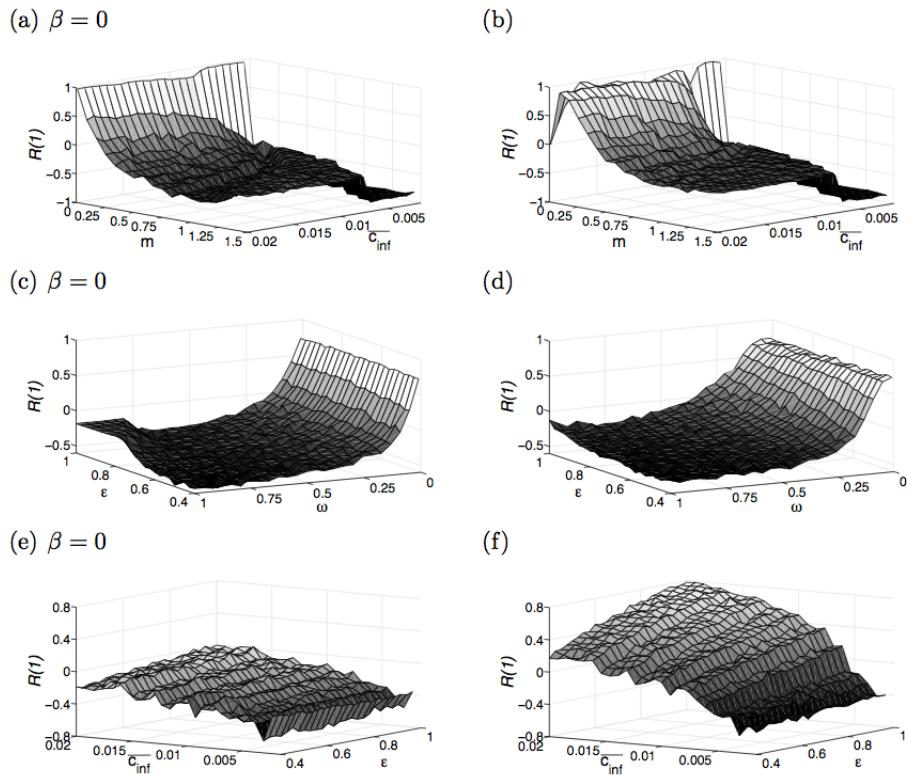


Figure 3.3: The plot of the auto-correlation ($\mathcal{R}(1)$) for a variety of parameters. a) m versus \bar{c}_{inf} with $\beta = 0$; b) m versus \bar{c}_{inf} ; c) ω versus ε with $\beta = 0$; d) ω versus ε ; e) \bar{c}_{inf} versus ε with $\beta = 0$ and f) \bar{c}_{inf} versus ε .

Case $0 < \beta \leq 1$

Vaccine coverage tends to be more stable (higher $R(1)$) when vaccine immunity lasts longer (ω is smaller), the cost of infection is higher ($\overline{c_{inf}}$ is larger), or when memory lasts longer (m is smaller) (Figure 3b),d),f)). The impact of m is particularly strong (Figure 3b)). These three changes all make vaccination look more attractive, preventing temporary declines in vaccine coverage that generate instability and thus a lower $R(1)$ score.

Changes in the probability of vaccine complications (γ) or the cost of vaccine complications ($\overline{c_{vac}}$) seem to have a weaker effect and can either increase or decrease stability although, interestingly, a higher probability of vaccine complications will often increase the autocorrelation, presumably because it forces vaccine coverage to remain permanently depressed (results not shown). Compared to changes in $\overline{c_{inf}}$, changes in γ or $\overline{c_{vac}}$ have little effect because vaccine complications are rare, hence, a greater contribution to vaccine decision making is the minimum cost of vaccination, $\underline{c_{vac}}$, which is always applied upon vaccination (unlike $\overline{c_{vac}}$).

An increase in ε can either increase or decrease the auto-correlation (Supplementary Figure 3). The dual effect of changes in ε likely relate to the fact that increases in vaccine efficacy generate more herd immunity and thus more potential for free-riding, which can counteract the benefits of a more efficacious vaccine. We also expect instability to be greater when free-riding is more likely. In contrast, changes in m , ω , or $\overline{c_{inf}}$ do not impact the strength of herd immunity, and hence changes in those parameters result in unequivocal changes in stability (Figure 3).

For some parameter combinations, vaccination can become sufficiently unattractive

that vaccine coverage stabilises by virtue of dropping to low values and staying there. This occurs when both cost of infection $\overline{c_{inf}}$ and vaccine efficacy ε are very low, or when the probability of complications γ is high and the vaccine efficacy ε is low (results not shown).

Case $\beta = 0$

Vaccine coverage stability in the case where individuals cannot mistake niILI for influenza ($\beta = 0$; Figure 3a), c), e)) is broadly similar to stability in the case where they can ($\beta > 0$; Figure 3b), d), f)). However, vaccine coverage is generally less stable (lower $R(1)$ values) when $\beta = 0$. This mirrors results seen in previous subsections (e.g., Figure 2g versus 2f)). This effect is attributable to the random nature of niILI infection, which occurs independently of influenza infection and vaccination and thus serves to weaken the nonlinear coupling between influenza vaccinating behaviour and transmission dynamics that produces oscillations.

For the same reasons, when $\beta = 0$, sudden, qualitative shifts in stability as parameter values are varied are more common. For example, a plateau in $R(1)$ occurs in Figure 3c) ($\beta = 0$) for $\omega = 1$, $\varepsilon = 0.9$, that does not appear in Figure 3d) ($\beta > 0$). The plateau corresponds to episodic behaviour, wherein deep troughs in incidence caused by high vaccine uptake suddenly give way to a very large incidence spike brought on by a season where no one got vaccinated (Figure 1e)). When niILI occurs randomly and consistently in each influenza season, these episodic dynamics are not possible because perceived influenza incidence is never zero.

The plateau observed for small $\overline{c_{inf}}$ and large m for both $\beta = 0$ and $\beta > 0$ cases (Figure

Method	$\langle \mathcal{C}_{NN} \rangle$	$\langle\langle \mathcal{C}_{NN} \rangle\rangle$	$\langle \mathcal{C}_{VN} \rangle$	$\langle\langle \mathcal{C}_{VN} \rangle\rangle$	$\langle \mathcal{C}_{VV} \rangle$	$\langle\langle \mathcal{C}_{VV} \rangle\rangle$
Randomly Distributed	0.4999	2.45×10^{-6}	1.0004	1.97×10^{-5}	0.4997	1.16×10^{-5}
Model ($\beta = 0.50$)	0.5228	3.05×10^{-5}	0.9366	8.90×10^{-5}	0.5458	1.42×10^{-4}
Model ($\beta = 0$)	0.5451	8.01×10^{-5}	0.8728	1.84×10^{-4}	0.5983	1.83×10^{-3}

Table 3.3: The pair correlation values for randomly distributed vaccinations and our model where \mathcal{C}_{NN} is the non-vaccinator-non-vaccinator pair correlation, \mathcal{C}_{VN} is the vaccinator-non-vaccinator pair correlation and \mathcal{C}_{VV} is the vaccinator-vaccinator pair correlation. $\langle \cdot \rangle$ denotes the average and $\langle\langle \cdot \rangle\rangle$ denotes the variance of the pair correlations over time.

3a), b)) corresponds to a 2-cycle (Figure 1d)).

3.3.4 Strategy Correlations

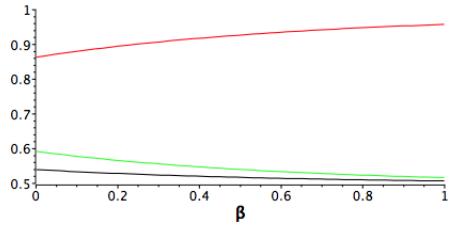
To determine whether vaccinators were more likely to be found next to other vaccinators on the network (and non-vaccinators next to non-vaccinators), we used a measure of pair correlations given by

$$\mathcal{C}_{AB} = \frac{\mathcal{N}}{n} \frac{[AB]}{[A][B]}, \quad (3.12)$$

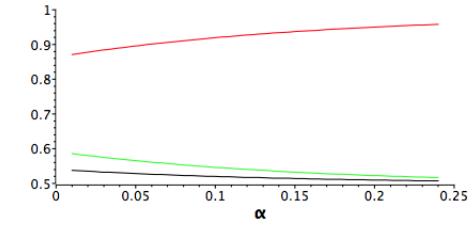
where \mathcal{N} is the number of individuals in the network, n the average node degree, $[AB]$ number of pairs where one individual is playing strategy A and the other is playing B , $[A]$ is the number of individuals playing strategy A and $[B]$ is the number of individuals playing strategy B (here, the strategies are vaccinate, V , or do not vaccinate, N) [53, 54].

For a purely random distribution, it is easy to show that we should obtain $\mathcal{C}_{VV} = 0.50$, $\mathcal{C}_{VN} = 1$ and $\mathcal{C}_{NN} = 0.50$, unless using the counting convention where $[AA]$ is twice the number of $A - A$ pairs. Thus, for clustering of vaccinators with vaccinators and non-vaccinators with non-vaccinators, we expect $\mathcal{C}_{VV} > 0.5$, $\mathcal{C}_{VN} < 1$ and $\mathcal{C}_{NN} > 0.50$.

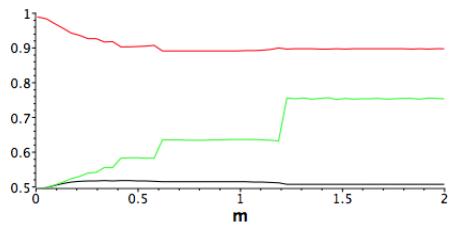
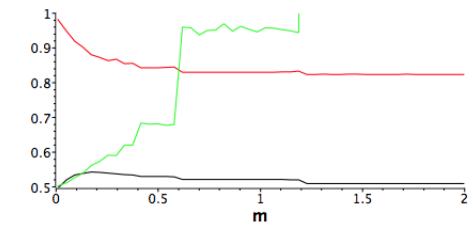
(a)



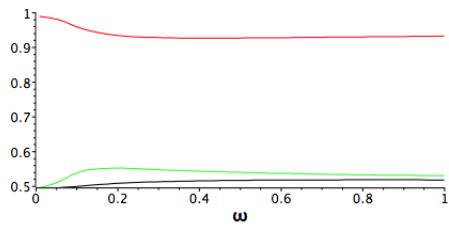
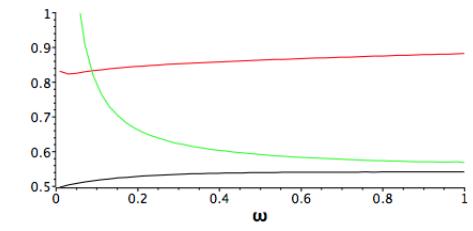
(b)



(c)

(d) $\beta = 0$ 

(e)

(f) $\beta = 0$ 

(g)

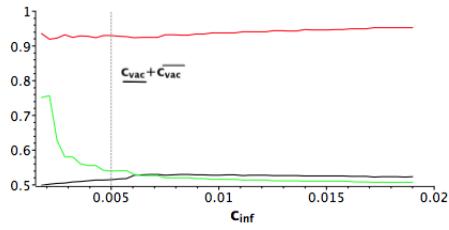
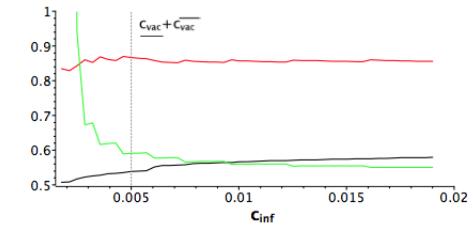
(h) $\beta = 0$ 

Figure 3.4: See page 137 for the caption.

Figure 3.4: (Figure on page 136) The pair correlation values across a range of parameter values: a) probability of nIILI being mistaken for influenza (β), b) the average incidence of nIILI ($\langle \alpha \rangle$), c) memory decay rate (m), d) memory decay rate (m) with $\beta = 0$, e) vaccine waning immunity (ω), f) vaccine waning immunity (ω) with $\beta = 0$, g) maximum cost of infection ($\overline{c_{inf}}$) and h) maximum cost of infection ($\overline{c_{inf}}$) with $\beta = 0$. The pair correlation \mathcal{C}_{NN} is the black line, \mathcal{C}_{VN} is the red line and \mathcal{C}_{VV} is the green line. The vertical line in g) and h) represents where $c_{inf} = c_{vac}$, i.e. $\overline{c_{inf}} = \overline{c_{vac}} + \underline{c_{vac}}$.

We measured \mathcal{C}_{VV} , \mathcal{C}_{VN} and \mathcal{C}_{NN} from the model simulations. We also measured \mathcal{C}_{VV} , \mathcal{C}_{VN} and \mathcal{C}_{NN} from the same simulations after randomly re-distributing the strategies on the network after each season, to provide a random contrast to the potentially correlated results of the original simulation.

Case $0 < \beta \leq 1$

At baseline parameter values, the average pair correlation values of the model over multiple seasons show a clear divergence from the pair correlations of the randomly redistributed network, indicating a tendency for assortativeness based on strategy (Table 3). The correlation occurs because individuals tend to vaccinate based on their past history of infection, and infection is transmitted through network edges, therefore vaccinators are more likely to be found in parts of the network where influenza has been recently active.

Assortative strategy correlations persists under a large range of parameter values (Figure 4a-c,e,g). For most parameter regimes, the degree of clustering is relatively unchanged. However, particularly strong correlations are possible when memory is short-term (large m) or when the cost of infection is small (small $\overline{c_{inf}}$). Short-term memory makes vaccine

status highly contingent upon recent infection activity in the network, and thus vaccinators are more likely to be found adjacent to one another, whereas long-term memory makes individuals average infection events over many seasons and thus erases transient fluctuations in prevalence in different parts of the network. A small $\overline{c_{inf}}$ can increase assortativeness simply by making vaccinators rare, however, the decline in $\overline{c_{inf}}$ is very steep, requiring $c_{inf} < c_{vac}$. As the probability of symptomatic infection decreases ($\psi \rightarrow 0$) the pair correlations become randomly distributed because vaccination becomes increasingly dependent on niILI mistaken for influenza (Supplementary Figure 4a).

Case $\beta = 0$

When niILI cases are not mistaken for influenza, assortativeness is stronger (Figure 4d,f,h). This occurs because the random influence of niILI on vaccinating decisions is removed. The difference are particularly pronounced for m and ω . When $\beta = 0$, C_{VV} can be large for small ω because when vaccine immunity wanes very slowly, individuals only need to be vaccinated only occasionally to be protected; an outbreak, when it occurs, is limited to a small part of the network consisting of connected individuals who have recently lost immunity (compare Figure 2); as a result of infection, those individuals become vaccinated in the next season, resulting in a small but highly correlated group of newly vaccinated individuals. As the probability of symptomatic infection decreases ($\psi \rightarrow 0$) vaccine strategy correlations again disappear, but less quickly than for $\beta > 0$ (Supplementary Figure 4). Decreasing ψ causes correlations to disappear even in the absence of niILI because there is less perceived influenza infection, and hence infection history becomes a less important driver of vaccine uptake.

3.4 Discussion

Here we analysed a model of influenza transmission on a contact network. Individuals choose whether or not to vaccinate each season based on their history of infections and vaccine complications. The role of influenza-like infection on vaccine decision making was also accounted for. The model was found to exhibit a wide range of behaviour-incidence dynamics, ranging from constant vaccine coverage to highly variable vaccine coverage and including dynamical features such as two-cycles or highly intermittent outbreaks.

We found that the duration of individual memory for past infections or vaccine complications can be a major driver of different types of dynamics, ranging from relatively constant coverage for long-term memory to highly variable coverage for shorter-term memory, and ranging from very high to very low coverage. When memory duration is long, decisions are based on a history of many past flu seasons, which tends to stabilise dynamics. This has been observed in a model where past epidemics can be remembered [27] but not in a model where past vaccine complications are also remembered and factored into decisions. Longer-term memory can either increase or decrease average vaccine coverage depending on whether the longer-term memory favours remembering vaccine failures or infection events.

A higher probability of vaccine complications can make dynamics very irregular, and generally depresses vaccine coverage. The effect of changing vaccine efficacy can be blunted by policy resistance, because the first order effect of higher vaccine efficacy is to make the vaccine more attractive, but higher efficacy simultaneously strengthens herd immunity and therefore allows for free-riding non-vaccinators to emerge. In comparison, the effect of

changing the duration of vaccine immune protection is not mitigated by nonlinear feedbacks because changing this parameter does not alter the strength of herd immunity; for very long vaccine protection, vaccine coverage is low (since individuals do not need to re-vaccinate every season) and infection incidence is close to zero; a different but related behaviour-incidence model has also predicted that infrequent outbreaks are possible with a vaccine that confers long-term protective immunity [24], which also occurs in our model, but only if the effects of niILI are ignored. For very short vaccine protection, vaccine coverage is high and disease incidence is irregular but generally high.

As for many behaviour-incidence models, our model was capable of exhibiting sustained oscillations in both vaccine coverage and disease incidence [19, 20]. Vaccine coverage in real populations does not generally exhibit the extreme variability exhibited by these models in some parameter regimes. However, when they do emerge, a severe mismatch between vaccine supply and demand may occur [15]. We found that behaviour-incidence dynamics are more stable when vaccine immunity lasts longer, the cost of infection is higher, or when memory lasts longer. Memory has a particularly strong influence on stability. In comparison, stability had weaker dependence on the probability of vaccine complications, the cost of vaccine complications, and vaccine efficacy. Stability was less dependent on parameters relating to vaccine complications because the total cost of vaccination was the sum of a term due to complications experienced plus a baseline cost, and when vaccine complications are rare, the payoff to vaccinate can be dominated by the baseline cost. Stability was less dependent on vaccine efficacy because changes in efficacy also changed the strength of herd immunity and thus the strength of policy resistant feedback loops. The presence or absence of niILI effects did not significantly impact these trends.

We also explored the issue of assortativeness in strategy choices on the network. Previous models have explored how clusters of vaccinators or non-vaccinators can emerge when individuals are prone to adopt the strategies of those around them [26, 36]. However, to our knowledge, models have not explored whether such correlations can occur in the absence of direct influence of the opinions of neighbours. Here, we found that strategy correlations can emerge only due to individuals basing vaccinating decisions on their personal history of infection, combined with the fact that the infection is constrained to pass through the network. This effect was also robust, occurring for a broad range of parameter values, although the presence of niILI considerably weakens the correlations.

Unlike many previous behaviour-incidence models for influenza, we attempted to account for the effects of niILI being mistaken for true influenza. By virtue of weakening the feedback between influenza vaccinating behaviour and influenza transmission dynamics, the presence of niILI generally served to stabilise vaccine coverage and reduce strategy correlations on the network. niILI could often boost vaccine coverage if individuals mistook niILI for influenza and were thus motivated to seek influenza vaccine in the next season. However, niILI could also reduce vaccine coverage in other scenarios, if individuals acquired an influenza vaccine, subsequently experienced niILI, and therefore concluded that the vaccine did not work for them.

The model we analysed shares elements with previously published models, although we combine these elements in a different way. For example, we allowed memory to span multiple seasons, instead of just one season [26]; the individual's vaccinating decisions depends on the individual's personal history of infection, rather than on the entire population's history [27]; we assume that individuals do not use social learning or imitation in their

decision-making [19, 26, 27]; we assume individuals do not know their immune status, as opposed to knowing whether vaccine immunity has wanted [24]; and we consider transmission as occurring on a network rather than using traditional compartmental approaches [24].

We used a uniform network for the sake of simplicity. However, a network where the node degree varies among individuals might give significantly different predictions. For instance, in a network with a power-law, Poisson or exponential node degree distribution, nodes of higher degree would be at greater risk of infection, and therefore would be more likely to seek vaccination. In turn, incidence would be more strongly reduced since these individuals are responsible for more infection than nodes with low degree. For a given level of vaccine coverage, we should observe a greater reduction in incidence than for a vaccine strategy that distributes vaccination randomly in the network. This represents opportunity for further research. We also used a static network that does not change within or between seasons. If we were to consider a dynamic network it is likely there would be a decrease in strategy correlations, simply due to network turnover. Other types of network structures, for instance to represent contact patterns specific to certain at-risk groups or targeted vaccination of health care workers, could result in very different predictions. We also neglected births and deaths, but given that new susceptible individuals arise primarily due to antigenic drift, we suspect that birth per se would not have a qualitative impact on dynamics.

We neglected imitation processes in our model, which is not entirely realistic since social influences are important determinants of vaccine uptake [9]. Adding imitation processes would allow us to capture certain aspects of real-world vaccinating behaviour, such as

preventive vaccination by individuals without any history of infection, due to social learning or social norms. However, neglecting imitation allowed us to explore whether strategy correlations can occur even in the absence of imitation. Clustering has been shown to arise in previous models that allow individuals to imitate neighbours on the network [26, 36], but individual decisions were not based on their own infection history and thus these models could not exhibit the type of clustering we observed in our model. We speculate that a model combining both sources of clustering could exhibit significantly stronger clustering than a model with only one of the two sources of clustering. The presence of strategy clustering can influence the effectiveness of vaccination policies [36].

We also made other simplifying assumptions that could influence model predictions. For instance, we assumed that individuals only recalled the most recent infection or vaccine complication, whereas in reality they might be influenced by multiple past events. We assumed that individuals' assessment of their personal infection risk was not influenced by the population's infection history, whereas in reality some individuals might perceive a heightened risk even if they have not been infected recently, if the disease incidence in the rest of the population was very high in recent years. Finally, we neglected heterogeneity relating to age or health status, as per previous models [18, 24, 28, 36, 55, 56]. We neglected age structure for the sake of simplicity, but also because we were not addressing issues of targeted, age-specific vaccine strategies [31, 57, 58].

We made assumptions about the psychology of vaccine decision-making that are consistent with the existing literature regarding determinants of vaccine uptake [9]. However, more detailed quantitative data need to be collected on the psychology of vaccinating behaviour, if behaviour-incidence models are to be accurately structured and param-

terised. This represents an opportunity for future collaboration between modellers and public health researchers.

We found that memory has a strong stabilising influence on dynamics. However, it could either bring vaccine coverage up or down depending on whether the influence of past perceived vaccine failures, or past infections events, were a more important driving factor. Hence, a possible strategy to increase influenza vaccine coverage is for public health messages to emphasise individuals' memory of their past encounters with influenza. This messaging could be incorporated into existing systems for reminding patients to get immunised [59].

We also found that the duration of vaccine immunity was an important parameter, which longer-lasting vaccine immunity being associated with greater stability in vaccine coverage and less incidence. Existing influenza vaccines are only thought to protect individuals for a short period of time, due to continual antigenic drift of influenza viruses. However, scenarios of long-lasting influenza vaccine immunity will become more relevant as universal influenza vaccines enter production [60, 61, 62]. In the absence of niILI effects, occasional sporadic outbreaks were still possible with long-term vaccine immunity [24], but these outbreaks disappeared when the influence of niILI was included.

This paper shows how behaviour-incidence models that include realistic details of human behaviour, such as memory for past infections or perceived vaccine failures, or the confounding effects of influenza-like illness, can generate predictions that are significantly different from those of simple, classical models. Behaviour-incidence models with greater psychological realism, validated against empirical data, could therefore be useful for in-

forming influenza immunisation policies in many countries.

3.A Algorithm Outline

Here we provide a brief outline of the algorithms we implemented in C for our model. For the creation of our uniform random network we used the following algorithm

1. If i requires more contacts then randomly choose a contact, j for node i
2. Determine whether or not j is already a contact and if j has reached the desired degree already
3. If j is suitable to be a contact make the connection and add one to the degree of i and j
4. If i has reached the desired level of contacts move on to the next node that requires more contacts

For the spread of infection we used the following algorithms. For the first season no vaccination occurs and the following steps are implemented

1. Ensure all individuals are susceptible
2. Randomly infect I_0 individuals
3. Compute each individual's probability of becoming infected
4. Determine whether the infectious individual moves to the recovered state

5. Determine whether the susceptible individuals become infected
 - (a) If infected set $T_I = -1$
6. Repeat Step 3 to Step 5 until the infection dies out
7. Sample the percentage of ILI cases in the population, denote as α
8. Determine whether the individual experiences ILI (probability α)
 - (a) Determine whether the individual mistakes ILI for influenza (probability β)
 - i. If ILI mistaken for influenza set $T_I = -1$

After the first season has completed the following steps are implemented for the rest of the simulation

1. Increase T_I and T_C by one
2. Determine the individual's perceived vaccine efficacy
3. Determine who moves from the recovered state to the susceptible state (probability ρ)
4. Determine who loses vaccine immunity and becomes susceptible (probability ω)
5. Calculate \mathcal{P}_V and \mathcal{P}_N to determine who vaccinates (i.e. $\mathcal{P}_V > \mathcal{P}_N$)
 - (a) If vaccination occurs
 - i. Determine whether the vaccine was effective (probability ε); if vaccine successful then the individual is no longer susceptible for this season

- ii. Determine whether the individual experienced a vaccine complication (probability γ); if experienced a vaccine complication then set $T_C = -1$
- 6. Randomly infect I_0 susceptible individuals
 - (a) If the individual vaccinated set their perceived vaccine efficacy to the minimum
- 7. Compute each individual's probability of becoming infected
- 8. Determine whether the infectious individual moves to the recovered state
- 9. Determine whether the susceptible individuals become infected
 - (a) If infected set $T_I = -1$
 - (b) If the individual vaccinated set their perceived vaccine efficacy to the minimum
- 10. Repeat Step 7 to Step 9 until the infection dies out
- 11. Sample the percentage of ILI cases in the population, denote as α
- 12. Determine whether the individual experiences ILI (probability α)
 - (a) Determine whether the individual mistakes ILI for influenza (probability β)
 - i. If ILI mistaken for influenza set $T_I = -1$
 - ii. If the individual vaccinated set their perceived vaccine efficacy to the minimum
- 13. Start back at Step 1

3.B Supplimentary Material

Case	$\langle V(t) \rangle$	$\langle\langle V(t) \rangle\rangle$	$\langle I(t) \rangle$	$\langle\langle I(t) \rangle\rangle$
$\psi = 0.70 *$	0.3652	0.0012	0.0857	0.0061
$\psi = 0.40$	0.3062	0.0004	0.0928	0.0067
$m = 0.01$	0.2081	5×10^{-5}	0.1075	0.0079
$m = 0.10$	0.4451	0.0004	0.0602	0.0035
$m = 0.01 \& \underline{\varepsilon} = 0.65$	0.6257	3×10^{-5}	0.012	0.0001
$m = 0.10 \& \underline{\varepsilon} = 0.65$	0.5742	0.0003	0.0243	0.0007
$\omega = 0.05$	0.2133	4×10^{-5}	0.0045	7×10^{-6}
$\omega = 0.05 \& \beta = 0$	0.1285	0.0011	0.0381	0.0018
$\omega = 1$	0.3908	0.0013	0.1054	0.0082
$\omega = 1 \& \beta = 0$	0.3581	0.0035	0.1187	0.0119
$\varepsilon = 0.40$	0.3743	0.0008	0.1100	0.0079
$\varepsilon = 0.95$	0.3532	0.0013	0.0700	0.0048
$m = 1.5$	0.1363	0.0053	0.1311	0.0112
$m = 1.5 \& \beta = 0$	0.0994	0.0065	0.1427	0.0132
$\beta = 0$	0.3295	0.0024	0.1049	0.0084
$\beta = 1$	0.3920	0.0006	0.0696	0.0044

Table 3.4: The statistics for the vaccination coverage ($V(t)$) and influenza incidence ($I(t)$), where $\langle \cdot \rangle$ denotes the average and $\langle\langle \cdot \rangle\rangle$ denotes the variance, over time. * $\psi = 0.7$ was used for all simulations in the table except where otherwise noted.

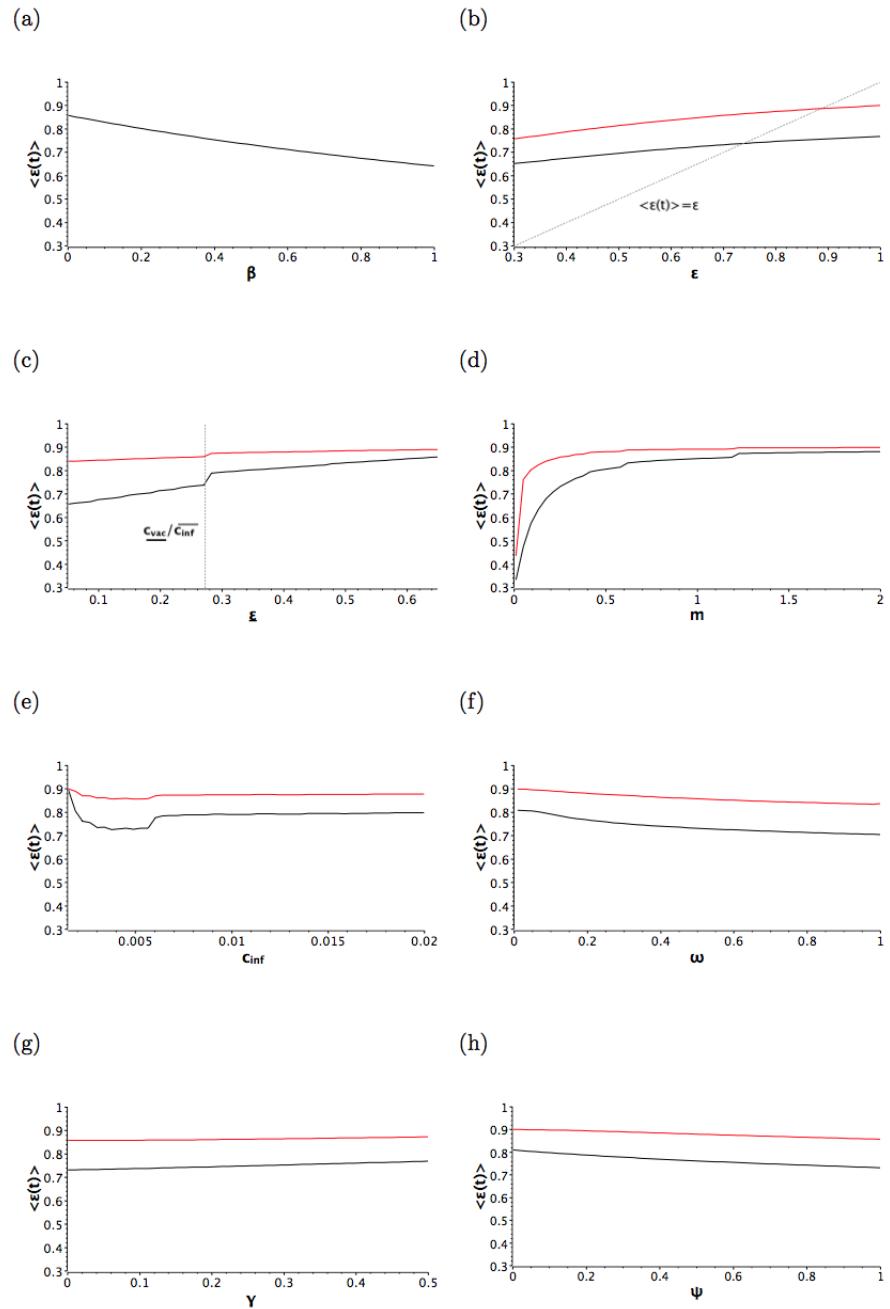


Figure 3.5: See page 150 for the caption.

Figure 3.5: (Figure on page 149) The average perceived vaccine efficacy for a range of parameter values: a) probability of ILI being mistaken for influenza (β) b) vaccine efficacy (ε) c) minimum perceived vaccine efficacy ($\underline{\varepsilon}$) d) memory decay rate (m) e) maximum cost of infection ($\overline{c_{inf}}$) and f) vaccine waning immunity (ω). In b)-f) the black (red) line corresponds to the average perceived vaccine efficacy with $\beta = 0.5$ ($\beta = 0$). In b) the grey dashed line corresponds to $\langle \varepsilon(t) \rangle = \varepsilon$. In c) the grey dashed line corresponds to $\underline{\varepsilon} = \underline{c_{vac}}/\overline{c_{inf}}$

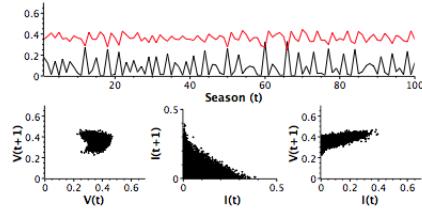
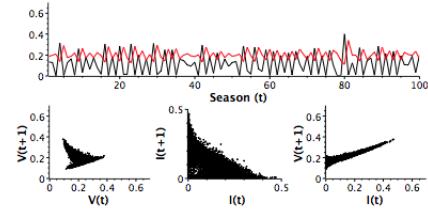
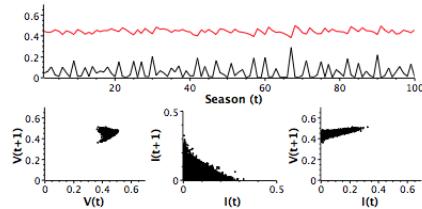
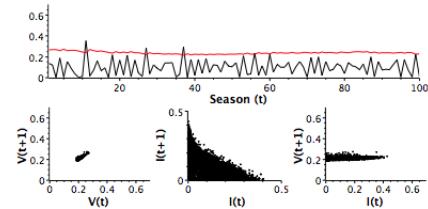
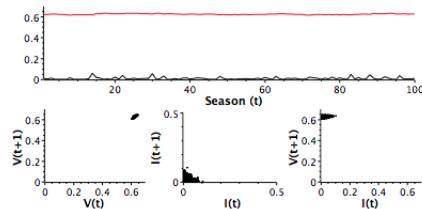
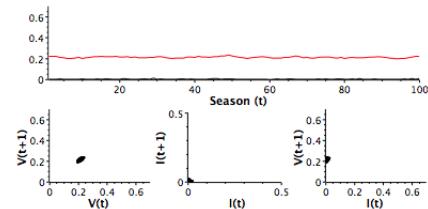
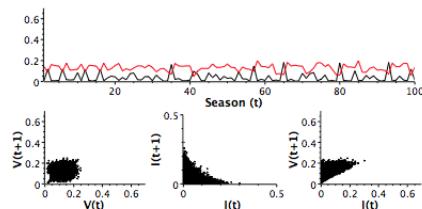
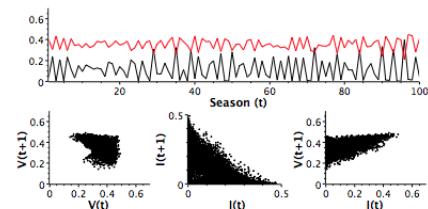
(a) Baseline ($\psi = 0.7$)(b) $\psi = 0.7 \& \gamma = 0.50$ (c) $\psi = 0.7 \& m = 0.10$ (d) $\psi = 0.7 \& m = 0.01$ (e) $\psi = 0.7, m = 0.01 \& \varepsilon = 0.65$ (f) $\psi = 0.7 \& \omega = 0.05$ (g) $\psi = 0.7, \omega = 0.05 \& \beta = 0$ (h) $\psi = 0.7, \omega = 1 \& \beta = 0$ 

Figure 3.6: See page 152 for the caption.

Figure 3.6: (Figure on page 151) The impact of introducing symptomatic influenza into the model, where $\psi = 0.70$ is the probability of experiencing symptomatic influenza a) Baseline dynamics b) vaccine complications (γ), c)-e) memory decay rate (m) and f)-h) waning vaccine immunity (ω). Top sub-panels show a portion of the time series of the percentage of individuals infected by influenza per season, $I(t)$ (black), and the percent vaccine coverage per season, $V(t)$ (red). The bottom left sub-panel shows the vaccination return map, $V(t)$ vs. $V(t+1)$, where t represents the current season and $t+1$ the next. The bottom middle sub-panel shows the infection return map, $I(t)$ vs. $I(t+1)$. The bottom right sub-panel shows the infection/vaccination return map, $I(t)$ vs. $V(t+1)$.

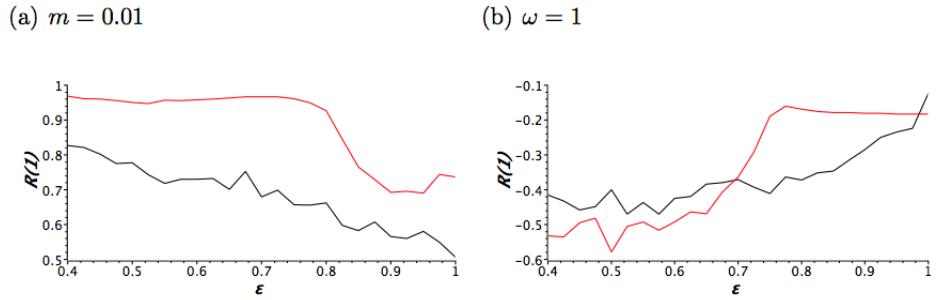


Figure 3.7: The plot of the auto-correlation ($\mathcal{R}(1)$) for a range of values for the vaccine efficacy ε when: a) $m = 0.01$ and b) $\omega = 1$. The black line denotes when $\beta = 0.5$ and the red line denotes when $\beta = 0$.

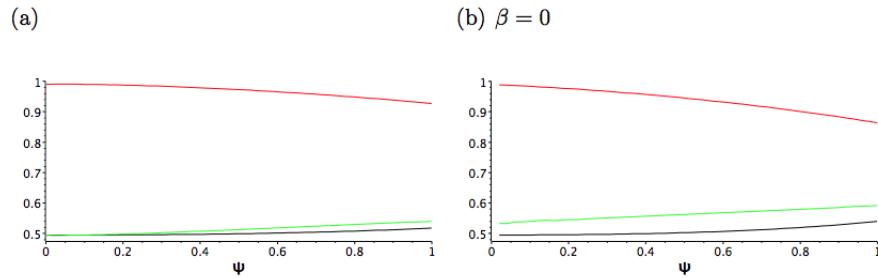


Figure 3.8: The pair correlation values versus the probability of symptomatic influenza (ψ). The pair correlation \mathcal{C}_{NN} is the black line, \mathcal{C}_{VN} is the red line and \mathcal{C}_{VV} is the green line.

Bibliography

- [1] P. Y. Lee, D. B. Matchar, D. A. Clements, J. Huber, J. D. Hamilton, and E. D. Peterson. Economic analysis of influenza vaccination and antiviral treatment for healthy working adults. *Annals of Internal Medicine*, 137(4):225–231, 2002.
- [2] K. L. Nichol. Cost-benefit analysis of a strategy to vaccinate healthy working adults against influenza. *Arch Intern Med.*, 161(5):749–759, 2001.
- [3] S.C. Schoenbaum. Economic impact of influenza: The individual's perspective. *The American Journal of Medicine*, 82(6A):26–30, 1987.
- [4] T. Szucs. The socio-economic burden of influenza. *Journal of Antimicrobial Chemotherapy*, 44:11–15, 1999.
- [5] Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the advisory committee on immunization practices (acip). <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5208a1.htm>, February 2012.
- [6] J. C. Kwong, L.C. Rosella, and H. Johansen. Trends in influenza vaccination in canada, 1996/1997 to 2005. *Health Reports*, 18(4):1–11, 2007.
- [7] G.B. Chapman and E.J. Coups. Emotions and preventive health behavior: Worry, regret, and influenza vaccination. *Health Psychology*, 25(1):82–90, 2006.
- [8] A.E. Fiore, T.M. Uyeki, K. Broder, L. Finelli, G.L. Euler, J.A. Singleton, J.K. Iskander, P.M. Wortley, D.K. Shay, J.S. Bresee, and N.J. Cox. Prevention and control of

influenza with vaccines: Recommendations of the advisory committee on immunization practices. MMWR, 59(RR-8):1–61, 2010.

- [9] G. B. Chapman and E. J. Coups. Predictors of influenza vaccine acceptance among healthy adults. Preventive Medicine, 29(4):249–262, 1999.
- [10] Y. Bordon. Flu vaccine surplus. Nature Reviews Immunology, 10(88), 2010.
- [11] M. Akazawa, J.L. Sindelar, and A.D. Paltiel. Economic costs of influenza-related work absenteeism. Value in Health, 6(2):107–115, 2003.
- [12] Centers for Disease Control and Prevention. United states surveillance data:1997-1998 through 2009-2010 seasons. <http://www.cdc.gov/flu/weekly/ussurvdata.htm>, April 2012.
- [13] M.B. Rothberg, S.D. Haessler, and R.B. Brown. Complications of viral influenza. The American Journal of Medicine, 121(4):258–264, 2008.
- [14] D. S. Fedson. Pandemic influenza and the global vaccine supply. Clin Infect Dis, 36(12):1552–61, 2003.
- [15] J. Treanor. Influenza vaccine—outmaneuvering antigenic shift and drift. N Engl J Med, 350:218–220, 2004.
- [16] M.H. Merrill, A.C. Hollister, S.F. Gibbens, A.W. Haynes, and V.H. Leslau. Attitudes of californians toward poliomyelitis vaccination. American Journal of Public Health, 48(2):146–152, 1958.

- [17] M. Salathe and S. Khandelwal. Assessing vaccination sentiments with online social media: implications for infectious disease dynamics and control. *PLoS Comp Biol*, 7(10):e1002199, 2011.
- [18] C. T. Bauch and D. J. D. Earn. Vaccination and the theory of games. *PNAS*, 101(36):13391–13394, 2004.
- [19] C. T. Bauch. Imitation dynamics predict vaccinating behaviour. *Proc Biol Sci*, 272(1573):1669–1675, 2005.
- [20] T. C. Reluga, C. T. Bauch, and A. P. Galvani. Evolving public perceptions and stability in vaccine uptake. *Mathematical Biosciences*, 204(2):185–198, 2006.
- [21] A.P. Galvani, T.C. Reluga, and G.B. Chapman. Long-standing influenza vaccination policy is in accord with individual self-interest but not with the utilitarian optimum. *PNAS*, 104(13):5692–5697, 2007.
- [22] S. Funk, E. Gilad, C. Watkins, and V.A.A. Jansen. The spread of awareness and its impact on epidemic outbreaks. *PNAS*, 106(16):6872–6877, 2009.
- [23] A. Perisic and C. T. Bauch. Social contact networks and disease eradicability under voluntary vaccination. *PLoS Comp Biol*, 5(2):e1000280, 2009.
- [24] R. Vardavas, R. Breban, and S. Blower. A universal long-term flu vaccine may not prevent severe epidemics. *BMC Research Notes*, 3(92), 2010.
- [25] S. Xia. Modeling and simulating human vaccinating behaviors on a disease diffusion

network. In Post Graduate Research Symposium, pages 1–12. The HKBU Computer Science Department, 2009.

- [26] F. Fu, D. I. Rosenbloom, L. Wang, and M. A. Nowak. Imitation dynamics of vaccination behaviour on social networks. Proc. Biol Sci, 278(1702):42–49, 2011.
- [27] D. M. Cornforth, T. C. Reluga, E. Shim, C. T. Bauch, A. P. Galvani, and L. A. Meyers. Erratic flu vaccination emerges from short-sighted behaviour in contact networks. PLoS Comp Biol, 7(1):e1001062, 2011.
- [28] C. R. Wells, J.M. Tchuenche, L.A. Meyers, A. P. Galvani, and C. T. Bauch. Impact of imitation processes on the effectiveness of ring vaccination. Bulletin of Mathematical Biology, 73(11):2748–2772, 2011.
- [29] C. T. Bauch and S. Bhattacharyya. Evolutionary game theory and social learning can determine how vaccine scares unfold. PLoS Comp Biol, 8(4):e1002452, 2012.
- [30] D. Weycker, J. Edelsberg, M. E. Halloran, I.M. Longini Jr, A. Nizam, V. Ciuryla, and G. Oster. Population-wide benefits of routine vaccination against children against influenza. Vaccine, 23(10):1284–1293, 2005.
- [31] J. Dushoff, J.B. Plotkin, C. Viboud, L. Simonsen, M. Miller, M. Loeb, and D.J. D. Earn. Vaccinating to protect a vulnerable subpopulation. PLoS Medicine, 4(5):0921–0927, 2007.
- [32] Z. Qiu and Z. Feng. Transmission dynamics of an influenza model with vaccination and antiviral treatment. Bulletin of Mathematical Biology, 72(1):1–33, 2010.

- [33] E.W. Orenstein, G. De Serres, M.J. Haber, D.K. Shay, C.B. Bridges, P. Gargiullo, and W.A. Orenstein. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. *International Journal of Epidemiology*, 36(3):623–631, 2007.
- [34] G. Chowell, C. Viboud, C.V. Munayco, J. Gomez, L. Simonsen, M.A. Miller, J. Tamerius, V. Fiestas, E.S. Halsey, and V.A. Laguna-Torres. Spatial and temporal characteristics of the 2009 a/h1n1 influenza pandemic in peru. *PLoS One*, 6(6):e21287, 2011.
- [35] S.P. van Noort, R. Aguas, S. Ballesteros, and M.G.M. Gomes. The role of weather on the relation between influenza and influenza-like illness. *Journal of Theoretical Biology*, 298(7):131–137, 2012.
- [36] M. Salathe and S. Bonhoeffer. The effect of opinion clustering on disease outbreak. *Journal of the Royal Society Interface*, 5:1505–1508, 2008.
- [37] D.M. Fleming and J.G. Ayres. Diagnosis and patterns of incidence of influenza, influenza-like illness and the common cold in general practice. *Journal of the Royal College of General Practitioners*, 38(309):159–162, 1988.
- [38] D.J.D. Earn, J. Dushoff, and S.A. Levin. Ecology and evolution of the flu. *TRENDS in Ecology and Evolution*, 17(7):334–340, 2002.
- [39] I.M. Longini Jr., M. E. Halloran, A. Nizam, M. Wolff, P. M. Mendelman, P. E. Fast, and R. B. Belshe. Estimation of the efficacy of live, attenuated influenza vaccine from

a two-year, multi-center vaccine trial: implications for influenza epidemic control. Vaccine, 18:1902–1909, 2000.

- [40] R. J. Cox, K. A. Brokstad, and P. Ogra. Influenza virus: Immunity and vaccination strategies. comparison of the immune response to inactivated and live, attenuated influenza vaccines. Scandinavian Journal of Immunology, 59:1–15, 2004.
- [41] C.S. Ambrose, T. Yi, R.E. Walker, and E.M. Connor. Duration of protection provided by live attenuated influenza vaccine in children. Pediatric Infectious Disease Journal, 27(8):744–748, 2008.
- [42] C.B. Bridges, W.W. Thompson, M.I. Meltzer, G.R. Reeve, W.J. Talamonti, N.J. Cox, H.A. Lilac, H. Hall, A. Klimov, and K. Fukuda.. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomized controlled trial. JAMA, 284(13), 2000.
- [43] V. Demicheli, C. Di Pietrantonj, T. Jefferson, A. Rivetti, and D. Rivetti. Vaccines for preventing influenza in healthy adults. Database of Systematic Reviews 2007, 2, 2007.
- [44] M. I. Meltzer, N. J. Cox, and K. Fukuda. The economic impact of pandemic influenza in the united states: Priorities for intervention. Emerging Infectious Diseases, 5(5):659–671, 1999.
- [45] R.B. Couch. Advances in influenza virus vaccine research. Annals of the New York Academy of Sciences, 685:803–812, 1993.

- [46] U.S. Bureau of Labor Statistics. Average annual pay by state and industry. <http://www.bls.gov/news.release/anppay.nr0.htm>, November 2011.
- [47] M. Keech, A. J. Scott, and P. J. J. Ryan. The impact of influenza and influenza-like illness on productivity and healthcare resource utilization in a working population. *Occupational Medicine*, 48(2):85–90, 1998.
- [48] W. A. Keitel, T. R. Cate, R. B. Couch, L. L. Huggins, and K. R. Hess. Efficacy of repeated annual immunization with inactivated influenza virus vaccines over a five year period. *Vaccine*, 15:1114–1122, 1997.
- [49] N. M. Molinari, I. R. Ortega-Sanchez, M. L. Messonnier, W. W. Thompson, P. M. Wortley, E. Weintraub, and C. B. Bridges. The annual impact of seasonal influenza in the us: Measuring disease burden and costs. *Vaccine*, 25:50865096, 2007.
- [50] L.A. Meyers. Contact network epidemiology: Bond percolation applied to infectious disease prediction and control. *Bull. Amer. Math. Soc.*, 44:63–86, 2006.
- [51] J.C. Miller. Epidemic size and probability with heterogeneous infectivity and susceptibility. *Physical Review E*, 76(1):010101(4), 2007.
- [52] H. Andersson. Epidemics in a population with social structure. *Mathematical Biosciences*, 140:79–84, 1997.
- [53] M. J. Keeling, D. A. Rand, and A. J. Morris. Correlation models for childhood epidemics. *Proc Biol Sci.*, 264(1385):1149–1156, 1997.

- [54] M.J. Keeling. The effects of local spatial structure on epidemiological invasions. *Proc Biol Sci.*, 266(1421):859–867, 1999.
- [55] P. Poletti, B. Caprile, M. Ajelli, A. Pugliese, and S. Merler. Spontaneous behavioural changes in response to epidemics. *Journal of Theoretical Biology*, 260(1):31–40, 2009.
- [56] A. Perisic and C. T. Bauch. A simulation analysis to characterize the dynamics of vaccinating behaviour on contact networks. *BMC Infectious Diseases*, 9(77):1–15, 2009.
- [57] M.A. Miller, C. Viboud, D.R. Olson, R.F. Grais, M.A. Rabaa, and L. Simonsen. Prioritization of influenza pandemic vaccination to minimize years of life lost. *Journal of Infectious Diseases*, 198(3):305–311, 2008.
- [58] S.D. Mylius, T.J. Hagenaars, A.K. Lugner, and J. Walling. Optimal allocation of pandemic influenza vaccine depends on age, risk and timing. *Vaccine*, 26(29-30):3742–3749, 2008.
- [59] P. Szilagyi, C. Bordley, J.C. Vann, A. Chelminski, R.M. Kraus, P.A. Margolis, and L.E. Rodewald. Effect of patient reminder/recall interventions on immunization rates. *JAMA*, 284(14):1820–1827, 2000.
- [60] J. Kaiser. A one-size-fits-all flu vaccine? *Science*, 312(5772):380–382, 2006.
- [61] W. Fiers, M. De Filette, A. Birkett, S. Neirynck, and W. Min Jou. A universal human influenza a vaccine. *Virus Research*, 103:173–176, 2004.

- [62] J. Kaiser. Facing down pandemic flu, the world's defenses are weak. Science, 306:394–397, 2004.

Chapter 4

Policy resistance undermines superspreadер vaccination strategies for influenza

C.R. Wells, E. Klein and C.T. Bauch (2012), in preparation for submission to PNAS

Abstract

Theoretical models of infection spread on networks predict that targeting vaccine at individuals with a very large number of contacts (superspreaders) can reduce infection incidence by a significant margin. These models generally assume that superspreaders will always agree to be vaccinated. Hence, they cannot capture phenomena such as policy resistance, where the behavioral response induced by a new vaccine policy tend to defeat the policy. Here, we couple a model of influenza transmission on an empirically-based contact network with a psychologically detailed model of influenza vaccinating behavior, where individual vaccinating decisions depend on social learning and past experiences of perceived infections, vaccine complications and vaccine failures. We find that policy resistance almost completely undermines the effectiveness of superspreader strategies: the most commonly explored approaches that target a randomly chosen neighbor of an individual, or that preferentially choose neighbors with many contacts, provide at best a 2% relative improvement over their non-targeted counterpart (compared to 12% when behavioral feedbacks are ignored). Increased vaccine coverage in super spreaders is offset by decreased coverage in non-superspreaders, and superspreaders also had a higher rate of perceived vaccine failures on account of being infected more often. Including vaccinating incentives provides modest improvements in outcomes. We conclude that the design of influenza vaccine strategies involving widespread incentive use and/or targeting superspreaders should account for policy resistance, and mitigate it whenever possible.

4.1 Introduction

Seasonal influenza imposes significant health burdens: in the United States alone there are an estimated 25-50 million cases per year, with 30,000 deaths and numerous hospitalizations, especially among the elderly and individuals with severe medical conditions [1, 2]. Vaccination generally commences in September prior to the influenza season and is non-mandatory for the general public [1, 2, 3, 4]. Like many infectious diseases, influenza exhibits a highly heterogeneous form of transmission known as “superspreadering”, wherein a minority of individuals are responsible for the majority of secondary infections [5, 6, 7, 8, 9, 10]. In a contact network framework, a superspreader can be represented as an individual with a very large number of contacts. Network-based infectious disease transmission models show how targeting superspreaders can be a highly effective (and efficient) form of infection control [11, 12, 13, 14, 15, 16, 17].

Transmission models generally treat vaccine coverage as a fixed control parameter [18], requiring the implicit assumption that desired vaccine coverage can always be achieved. However, public health authorities do not decide influenza vaccine coverage because they do not control individual vaccinating decisions. Instead, they control decisions such as where to set up immunization clinics, how to disseminate information, and whether to offer incentives to get vaccinated. Using a theoretical model to address factors that public health actually controls requires incorporating individual vaccinating behavior into the model. However, models of superspreader vaccination strategies usually assume that targeted individuals will always agree to be vaccinated.

Incorporating behavior into transmission models is increasingly important in an age of

vaccine exemption, especially for influenza where vaccine coverage is typically suboptimal [19, 20]. Combining incentive use with targeting superspreaders could potentially be very effective, but behavioral feedbacks need to be considered in program design.

Here, we analyze an agent-based simulation model that couples seasonal influenza transmission on an empirically-based contact network with a psychologically realistic model of individual vaccinating decisions. We explore the effectiveness of incentive programs and targeted superspreaders vaccination strategies. Our objectives are to understand 1) whether superspreaders vaccination strategies remain effective when behavior is accounted for, 2) whether economic incentives improve the effectiveness of such strategies, and 3) how perceived vaccine efficacy and the resulting vaccinating decisions are determined by interactions between network structure, transmission heterogeneity, and vaccine-disease dynamics.

4.2 Model

4.2.1 Population structure

For our baseline analysis we generated ten contact networks of 10,000 nodes each, by sampling subnetworks from a large contact network derived from empirical contact patterns in Portland, Oregon [21, 22, 23]. We ensured that the resulting node degree distribution and clustering coefficient matched that of the full empirical network (see Text S1). For influenza, susceptible individuals are recruited primarily through immunity waning, hence we assumed that the networks remained static, with no immigration or emigration. In our

sensitivity analysis we explored hypothetical networks with exponential and Poisson node degree distributions.

The contact network contains individuals representing the full spectrum of neighborhood sizes and does not impose a dichotomy between superspreaders and others. However, to assist with interpreting the output of our simulations, we defined a superspreaders as an individual who infected more than the 95th percentile from a Poisson distribution with mean \mathcal{R}_0 , where \mathcal{R}_0 is the basic reproduction number for the “null” deterministic model’s approximation (see Text S1) [8].

4.2.2 Disease dynamics

We assumed a Susceptible - Infected - Recovered - Vaccinated - Susceptible (*SIRVS*) natural history. An infectious individual transmits influenza to a susceptible contact ($S \rightarrow I$) with probability $p(t)$ per day, where $p(t)$ varies seasonally. An infectious individual moves to the recovered state ($I \rightarrow R$) after a number of days sampled from a Poisson distribution with mean δ days. A recovered individual becomes susceptible ($R \rightarrow S$) with probability ρ per season (natural waning immunity). A vaccinated individual becomes susceptible ($V \rightarrow S$) with probability ω per season (vaccine waning immunity). Vaccination has no impact on individuals who are in the naturally immune R state and the vaccine efficacy is ϵ . Symptomatic infection occurs with probability ψ . In our sensitivity analysis, we also allowed for heterogeneity with respect to the infectious period δ and the infectivity $p(t)$. This creates additional sources of heterogeneity that may cause some individuals to become superspreaders. More details appear in Table S1 and Text S1.

4.2.3 Vaccinating behavior

We structured the decision-making submodel according to known determinants of influenza vaccine acceptance among individuals: perceived vaccine effectiveness, previous acceptance of vaccine, past experiences with infection and vaccine complications, social influence and perceived susceptibility [24, 25]. The payoffs for strategy choices are given by

$$\mathcal{P}_V(t) = L - c_{vac}(t) - [1 - \varepsilon(t)]c_{inf}(t) \quad (4.1)$$

$$\mathcal{P}_N(t) = L - c_{inf}(t), \quad (4.2)$$

where $\mathcal{P}_V(t)$ is the payoff to vaccinate for season t , $\mathcal{P}_N(t)$ is the payoff not to vaccinate, L is the baseline payoff (a state of perfect health), $\varepsilon(t)$ is the perceived vaccine efficacy, c_{vac} is the cost of vaccinating and $c_{inf}(t)$ is the infection cost [26].

The infection cost $c_{inf}(t)$ incorporates perceived susceptibility and past infection experiences. Perceived susceptibility is expressed through past influenza incidence in the population. Past infection experience is expressed through the time since the individual's last perceived infection, T_I . Hence

$$c_{inf}(t) = \lambda \overline{c_{inf}} e^{-mT_I} + (1 - \lambda) \overline{c_{inf}} \sum_{j=0}^{t-1} e^{-mj} I(t-1-j), \quad (4.3)$$

where $I(t)$ is the influenza incidence in season t , $\overline{c_{inf}}$ is the penalty for being infected, λ controls the relative importance of personal history versus population history, and m is the memory decay rate. Severe outcomes are implicitly accounted for in $\overline{c_{inf}}$, which represents the combined foreseen risk of infection and any resulting complications. Thus,

this equation captures how individuals use past experiences to guide future vaccinating decisions.

The perceived vaccine efficacy $\varepsilon(t)$ for an individual in season t generally differs from actual efficacy ϵ and is given by

$$\varepsilon(t) = \begin{cases} (1 - \underline{\varepsilon})\varepsilon(t-1) & \text{vaccinated \& infected} \\ \varepsilon(t-1)e^{-m} + [1 - e^{-m}]\bar{\varepsilon} & \text{vaccinated \& not infected} \\ \varepsilon(t-1)e^{-\frac{m}{\xi}} + [1 - e^{-\frac{m}{\xi}}]\bar{\varepsilon} & \text{did not vaccinate} \end{cases} \quad (4.4)$$

where $\underline{\varepsilon}$ controls how quickly perceived vaccine efficacy drops upon a perceived vaccine failure, $\bar{\varepsilon}$ is the maximum perceived vaccine efficacy, and $\xi > 1$ is a decay factor which causes memory of a previously ineffective vaccination to fade at a slower rate (m/ξ) than a successful vaccination, since they have less information with which to update their impression [26]. The asymmetry between an event where individuals vaccinate and become infected versus an event where they did not vaccinate arises because of the distinction between “evidence of absence” and “absence of evidence”. Only symptomatically infected individuals update their values of T_I and $\varepsilon(t)$.

The cost of vaccination also incorporates past experience:

$$c_{vac}(t) = \underline{c}_{vac} + \overline{c}_{vac}e^{-mT_C}, \quad (4.5)$$

where \underline{c}_{vac} represents time and economic costs, T_C is the time since the last perceived vaccine complication, and \overline{c}_{vac} is the perceived cost of a vaccine complication. The probability an individual perceived a complication upon vaccinating is γ .

We incorporate social influence through a learning process. Before each vaccination season, an individual engages in a social learning process with probability σ , sampling another individual at random and replacing their T_I , T_C and $\varepsilon(t)$ with the average of their pre-existing value and that of the sampled individual, weighted by σ and $1 - \sigma$ respectively. This captures both the tendency to personalize the experiences of others as well as habit, since strategies change slowly as $\sigma \rightarrow 0$.

We also account for the impact of non-influenza-like-illness (niILI) on decision making, since niILI can be mistaken for true influenza and thus alter T_I and $\varepsilon(t)$. The probability an individual experiences niILI each day is α , where α is sampled from a log-normal distribution parameterized from empirical data on niILI incidence. An individual mistakes niILI for true influenza with probability β , in which case T_I and $\varepsilon(t)$ are updated accordingly (see Text S1 for details).

4.2.4 Vaccination strategies

Passive Vaccination (PV) is the baseline strategy corresponding to how most influenza vaccination programs are structured: vaccines are made available (e.g. at drug stores, public health clinics), opening times are widely disseminated, and individuals seek out vaccination on their own, without being individually recruited by public health.

To capture this, we assume an individual decides to get vaccinated for the current season with probability $\Phi(\mathcal{P}_V - \mathcal{P}_N)$, which is a sigmoidal function of $\mathcal{P}_V - \mathcal{P}_N$ such that $\Phi(0) = 0.5$, $\Phi(\infty) = 1$, and $\Phi(-\infty) = 0$ (see Text S1). We assume individuals can be vaccinated only between September 1st ($t = 0$) and December 31 [4]. Those who choose to

vaccinate have their times of vaccination distributed throughout this period according to a process described in Text S1. If an individual perceives having been infected by influenza before it is their time to become vaccinated, they do not seek vaccination.

In addition to making PV available, public health may also implement one of four proactive strategies: 1) random vaccination (RV) which targets a randomly chosen individual; 2) nearest neighbor vaccination (NN), which targets a randomly chosen individual and one of their neighbors (i.e. contacts) 3) page rank vaccination (PR), which either targets a randomly chosen individual or a neighbor of an individual targeted the previous day and 4) improved nearest neighbor vaccination (INN) which targets a randomly chosen individual and one of their most popular neighbors. Under INN, “popular” means having the highest degree, and we assume imperfect knowledge of a neighbor’s neighborhood size. NN, PR, and INN are superspreadер strategies [12, 13, 15, 27].

The number of individuals targeted by public health each day is held constant at \bar{V} for all strategies. In each case, if the targeted individual did not already decide to vaccinate under PV, they reconsider: they undergo the social learning process again and agree to be recruited for vaccination with probability $\Phi(\mathcal{P}_V - \mathcal{P}_N)$. In our sensitivity analysis we also ran simulations where each targeted person was automatically recruited, corresponding to a situation where behavior is neglected (NB). More details on the pro-active strategies appear in Text S1.

4.2.5 Incentives

We allowed for the use of economic vaccination incentives under the pro-active strategies. Each time an individual is targeted they receive an incentive of value Υ if they get vaccinated during the current season. An individual can receive multiple incentives. Hence superspreaders should receive more incentives, since they are likely to be targeted multiple times under NN, PR and INN. We considered $\Upsilon = \$0$ (baseline), $\$20$, and $\$50$. Under incentives, the probability of vaccinating becomes a function of $\mathcal{P}_V - \mathcal{P}_N + n\Upsilon$ (where n is the number of times they have been targeted) instead of $\mathcal{P}_V - \mathcal{P}_N$. In order to express \mathcal{P}_V , \mathcal{P}_N and Υ in the same payoff currency, $\overline{c_{inf}}$, $\overline{c_{vac}}$, and $\underline{c_{vac}}$ were expressed in quality-adjusted life years (QALYs) (see Text S1).

4.2.6 Model calibration and simulation design

For each of the ten networks, the transmission probability and amplitude of seasonality were calibrated so that the average seasonal incidence of influenza in the absence of vaccination was 15% [28, 29, 30], and prevalence peaked between January and February. $\overline{c_{inf}}$ was based upon utility scores derived from patient surveys [31]. $\underline{c_{vac}}$ was based on published vaccine costs [29, 32, 33, 34]. m and ε were calibrated such that the average annual vaccine coverage was 35%. Examples of calibrated time series of annual coverage and weekly incidence appear in Fig. S1. For each network we generated 400 realizations of 150 years each, discarding the first 125 years to avoid transient effects.

4.3 Simulation Results

In the absence of incentives, the improved nearest neighbor strategy (INN) is the most effective in reducing influenza incidence, followed by page rank (PR), nearest neighbor (NN), random vaccination (RV), and the baseline strategy of passive vaccination alone (PV) (Table 1).

This relative ordering is to be expected, since previous research shows the advantages of targeting individuals with many contacts [11, 13, 14, 15, 16, 17]. However, feedbacks due to the dependence of vaccinating decisions on infection history generates some surprises [35, 36, 37, 38]. In this system, the feedbacks manifest as policy resistance [36], where the response of the population to an intervention (in this case, pro-active strategies and incentives) tends to defeat the intervention. Policy resistance arises because increased vaccine coverage in one season reduces incidence due to both direct and indirect (herd) protection, which in turn disincentives vaccination in future seasons, since decisions are based partly on infection history and perceived vaccine failure/complications. An additional source of policy resistance in this system is the tendency for pro-active strategies to waste recruitments on individuals who already decided to get vaccinated under passive vaccination, or who have already been infected (this is a problem especially among superspreaders, who are both targeted more often and tend to get infected earlier in the season) (Table S2).

Policy resistance almost completely undermines the benefits of using pro-active strategies: compared to passive vaccination (PV), the improved nearest neighbor strategy (INN) provides a 5% additional reduction in incidence, and the other pro-active strategies (NN, PR, RV) do even worse (Table 1). Moreover, among pro-active strategies, superspreaders

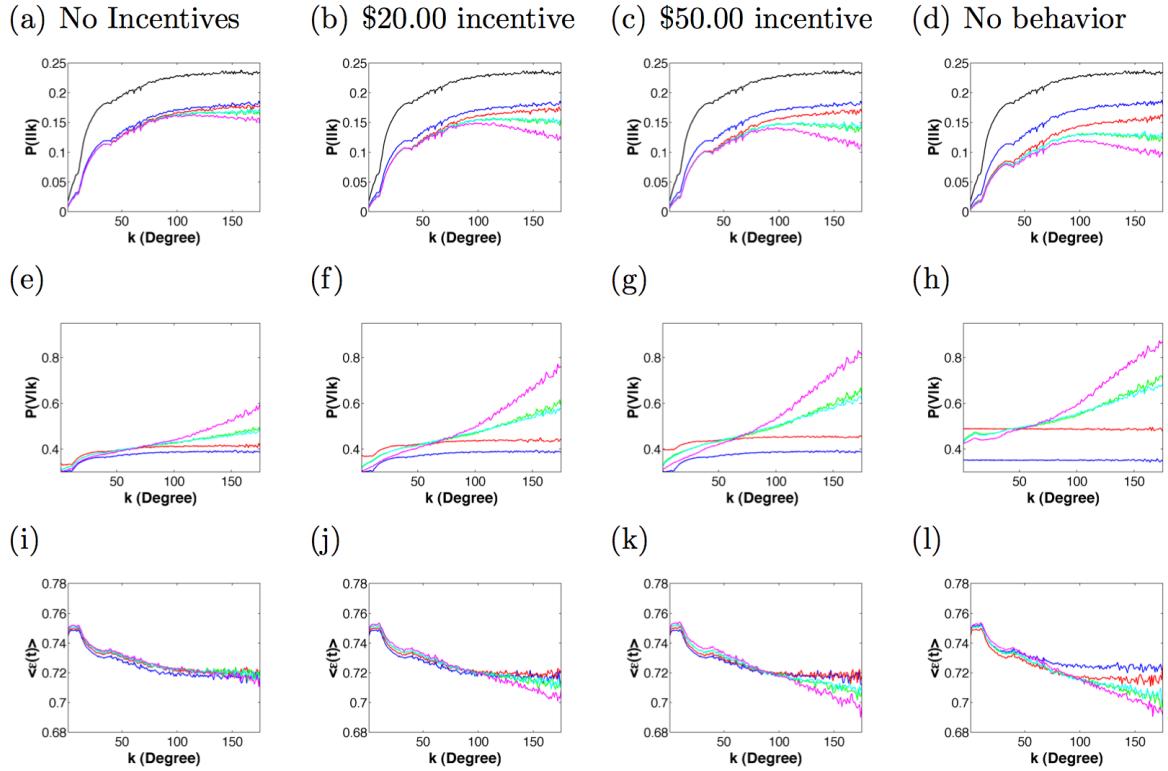


Figure 4.1: Model outcomes as a function of neighborhood size k . Average probability of being infected (a-d), probability of being vaccinated (e-h), and perceived vaccine efficacy (i-l) for the scenarios of no incentives (a, e, i); \$20 incentives (b, f, j), \$50 incentives (c, g, k), and no behavior (d, h, l). Strategies include no vaccination (black), passive vaccination (blue), random vaccination (red), nearest neighbor vaccination (green), page rank vaccination (light blue) and improved nearest neighbor vaccination (purple).

Strategy	$\langle I(t) \rangle$	$\langle V(t) \rangle$	$\langle I^{SS}(t) \rangle$	$\langle V^{SS}(t) \rangle$
No Vaccination	0.150	0	0.23	0
PV	0.100	0.35	0.17	0.39
PV + RV	0.097	0.38	0.17	0.41
PV + NN	0.096	0.37	0.16	0.43
PV + PR	0.096	0.37	0.16	0.43
PV + INN	0.095	0.37	0.16	0.46
PV (NB)	0.098	0.35	0.17	0.35
PV + RV (NB)	0.075	0.49	0.15	0.49
PV + NN (NB)	0.070	0.49	0.13	0.57
PV + PR (NB)	0.070	0.48	0.13	0.57
PV + INN (NB)	0.066	0.48	0.12	0.63
PV + RV (\$20)	0.092	0.41	0.16	0.44
PV + NN (\$20)	0.090	0.40	0.15	0.49
PV + PR (\$20)	0.090	0.40	0.15	0.49
PV + INN (\$20)	0.088	0.38	0.14	0.53
PV + RV (\$50)	0.088	0.43	0.16	0.45
PV + NN (\$50)	0.085	0.41	0.15	0.52
PV + PR (\$50)	0.085	0.41	0.15	0.52
PV + INN (\$50)	0.083	0.40	0.14	0.57

Table 4.1: Average influenza incidence $\langle I(t) \rangle$ and vaccine coverage $\langle V(t) \rangle$ in the entire population, and just in superspreaders ($\langle I(t)^{SS} \rangle$, $\langle V(t)^{SS} \rangle$). Numbers represent mean of 400 simulations (standard deviations were very small). NB indicates that vaccinating behavior is ignored, \$20 (respectively \$50) indicates that \$20 (respectively \$50) incentives are used.

strategies are only marginally more effective than random vaccination (Table 1). As expected, the superspreadер strategies improve vaccine coverage among superspreaders. However, this is offset by lower coverage among non-superspreaders. As a result, the average vaccine coverage under superspreadер strategies is the same as under random vaccination (Fig. 1, Table 1).

The impact of policy resistance is made clear by considering the case where vaccinating behavior is neglected (by assuming that targeted individuals are automatically recruited for vaccination). Neglecting behavior (NB) significantly overestimates both effectiveness and vaccine coverage for the pro-active strategies, both in superspreaders and non-superspreaders (Table 1). Hence, without accounting for behavior, we might have concluded that superspreadер vaccination strategies can be significantly more effective than their non-targeted counterpart, but if we take behavior into account, their impact is almost negligible.

We note that the slightly higher effectiveness of the improved nearest neighbor strategy also arises because by preferentially immunizing those individuals with a large number of contacts, susceptible individuals tend to be clustered together on the network, reducing the opportunities for the susceptible-infected contacts necessary for transmission (Table S3).

Individuals with more neighbors were more likely to be infected (Fig. 1a)-d)). This resulted in a higher probability of them getting vaccinated (Fig. 1e)-h)), but it also caused them perceive the vaccine to be less effective (Fig. 1i)-l)), on account of higher infection rates causing higher rates of perceived vaccine failure.

The effect of adding vaccinating incentives is likewise blunted by policy resistance (Table 1). Any increase in vaccine coverage due to use of incentives reduces incidence, which in turn disincentivizes future vaccine uptake (especially among superspreaders under passive vaccination, Table S4). Also, incentives often reach individuals who are already prone to get vaccinated (Table S1). However, modest improvements in program effectiveness due to the use of incentives are still possible. For example, adding a \$50 incentive to the improved nearest neighbor strategy reduces influenza incidence from 9.5% to 8.3% (Table 1).

We estimated the total costs (vaccine costs plus treatment costs) for each strategy. The least expensive strategy was the improved nearest neighbor strategy (INN) without incentives, at a total cost of \$16.88 per individual. In contrast, passive vaccination on its own (PV) costs \$17.11 per individual because infection costs are higher under PV than INN. Using vaccinating incentives increased the total cost of all strategies, but not always significantly. Further details appear in Text S1 and Table S5.

On average, most individuals received few incentives and only a few individuals received many incentives (Fig. S2). Superspreaders tended to receive more incentives by virtue of having more contacts, but the benefit of this was partly mitigated by the fact that they are likely to be infected and/or seek vaccination earlier in the season than individuals with few contacts, and hence have less time to accumulate incentives.

Our baseline assumption was that superspreading is driven only by heterogeneity in neighborhood size. Incorporating heterogeneity into the infectious period, transmission rate, or both did not significantly impact the results (the superspreader strategies become slightly less effective in the absence of incentives). For simulations on the hypothetical

Poisson or exponential networks instead of the empirically-based network, we found that the pro-active strategies continued to provide very small reductions in incidence compared to passive vaccination alone (Table S6 and Table S7). Results were also qualitatively unchanged when incentives were distributed only to the recruited neighbor of individuals targeted under NN and INN (Tables S2, S5); however, the cost of the policies was reduced due to fewer incentives being distributed (Table S5).

4.4 Discussion

Previous models of superspreadер vaccination strategies have shown how targeting individuals with a very large number of contacts can be a very effective way to control infection [11, 12, 13, 14, 15, 16, 17, 27]. These models have generally assumed that targeted individuals will always agree to be vaccinated. For voluntary influenza vaccination, this assumption may introduce inaccuracies, since individual choice is a major determinant of influenza vaccine uptake [19, 24, 25].

Here, we developed a psychologically detailed model of influenza vaccinating behavior and coupled it to a model of seasonal influenza transmission through an empirically-based contact network. Our assumptions about vaccinating behavior were based on empirical studies exploring determinants of vaccine uptake [24, 25]. We found that three of the most commonly investigated superspreadер vaccination strategies (nearest neighbor, page rank, improved nearest neighbor) provided little or no improvements over their non-targeted counterpart (random vaccination).

This surprisingly strong policy resistance is driven by multiple mechanisms: individuals are less likely to get vaccinated if their most recent influenza infection was a long time ago, if they perceive low susceptibility to infection (which can emerge from herd immunity generated by vaccination), or if they perceive recent vaccine complications or low vaccine efficacy. The presence of non-influenzal influenza-like illness (nILI) reinforces this because it can create the perception of vaccine failure. Moreover, superspreadер strategies tend to reach individuals who are already more prone to get vaccinated without the need for active recruitment, on account of their history of more frequent infections. Contact-based recruiting was also stymied by the fact that neighbors tended to share similar experiences and information, which led to neighbors more often than not sharing the same opinion regarding vaccination [26, 39].

Providing vaccinating incentives boosted effectiveness somewhat, including for superspreadер strategies, although these gains were again partly mitigated by policy resistance. The most effective overall strategy was the improved nearest neighbor strategy (INN) with \$50 incentive: this strategy reduced the average annual influenza incidence to 8.3% (compared to 10% under passive vaccination). The improved nearest neighbor strategy may also be cost-saving compared to passive vaccination. A few empirical studies have found that incentives can increase vaccine uptake [40, 41]. However, these studies focused on incentivization for small groups of elderly individuals over the course of a single season, not widespread incentivization for individuals with a large number of contacts.

Individuals with more contacts were more likely to be infected, which agrees with results from past models [42, 43]. This resulted in an individual's perceived vaccine efficacy declining with their number of contacts. This is a potential barrier in superspreadер vacci-

nation compliance. More generally, how perceived vaccine efficacy evolves over time and in response to disease dynamics and the collective effects of individual vaccinating decisions merits further study.

As for any model, our model made simplifying assumptions. For example, we assumed a targeted individual who is asked to recommend a contact for vaccination would always comply. We could address this limitation by introducing a parameter for compliance failure. This would result in a similar strategy to the page rank strategy, where occasionally the recruitment process jumps to another individual rather than continuing along the chain of contacts. We also neglected age structure in the model, which did not allow us to address issues such as age-related heterogeneity in infection severity, and correlations between infection severity and neighborhood size.

These areas suggest potential for further work at the interface of theoretical modeling and empirical surveys. In particular, surveys of determinants of vaccinating behavior can be designed to better meet the needs of models that couple disease dynamic models to vaccinating behavior models. Thoroughly validated “behavior-incidence” models of influenza vaccinating behavior will help public health authorities to optimize influenza vaccine programs. However, as we have found here, vaccination strategies that target superspreaders and/or provide vaccinating incentives must be carefully designed to mitigate the potentially strong effects of behavioral feedbacks and policy resistance.

4.A Supplementary Text

The values and description of the parameters used are listed in Table S1.

4.A.1 Disease Dynamics

We assumed a Susceptible-Infected-Recovered-Vaccinated-Susceptible (*SIRVS*) natural history and voluntary vaccination. A susceptible individual becomes infected ($S \rightarrow I$) by a single infectious contact with probability $p(t)$ per day, which varies seasonally. The seasonality probability of transmission is represented as

$$p(t) = \langle p \rangle \left(1 + p_s \sin \left(\frac{2\pi(t - \bar{t})}{365} \right) \right) \quad (4.6)$$

where $p(t)$ is the probability (per day) of infection passing along the edge connecting an infected individual and a susceptible individual, $\langle p \rangle$ is the average transmission rate from an infected individual to a single susceptible individual per day and the constant $p_s \in (0, 1)$ represents the impact of seasonality on the rate of transmission (i.e the change in the seasonal transmission amplitude). An infectious individual moves to the recovered state ($I \rightarrow R$) after δ days. A recovered individual becomes susceptible ($R \rightarrow S$) with probability ρ per year (natural immunity). A vaccinated individual becomes susceptible ($V \rightarrow S$) with probability ω per year (vaccine immunity). We assume that vaccination has no impact on individuals who are infectious or recovered. We assume an individual does not attain vaccine immunity if they have already obtained natural immunity.

We assume non-influenza-like-illness (niILI) is also present, where niILI is

randomly distributed throughout the network daily for the entire year. The probability of an individual experiencing niILI daily is denoted by α , where α is sampled from a log-normal distribution with mean $\langle \alpha \rangle$ and variance $\langle\langle \alpha \rangle \rangle$,

$$\alpha \sim \ln \mathcal{N}(\mu, \sigma^2) \quad (4.7)$$

$$\mu = \ln(\langle \alpha \rangle) - \frac{1}{2} \ln \left(1 + \frac{\langle\langle \alpha \rangle \rangle}{\langle \alpha \rangle^2} \right) \quad (4.8)$$

$$\sigma^2 = \ln \left(1 + \frac{\langle\langle \alpha \rangle \rangle}{\langle \alpha \rangle^2} \right), \quad (4.9)$$

where μ and σ^2 represent the mean and variance of the Normal distribution (i.e. $\ln(\alpha) \sim \mu + \sigma \mathcal{Z}$, where $\mathcal{Z} \sim \mathcal{N}(0, 1)$). We assume an individual mistakes niILI for true influenza with probability β .

We assume infection is introduced slowly into the population starting in mid-November, where a randomly chosen individual will be infected every few weeks. The main reason for the exogenous introduction of infection each year is to compensate for stochastic extinction that may occur in the network in the summer months. Infection is introduced in mid-November such that the peak of infection corresponds to a time between the start of January and end of February [44]. A typical influenza season generally starts approximately at the end of October/mid part of November and lasts until the end of April/middle of May [3]. The infection parameter values for equation (4.6) were calibrated to obtain incidence of approximately 15% [28, 29, 30] for each network (Poisson, exponential and empirically-based), under the condition of no vaccination (Table S1).

The average transmission rate among individuals is $\langle p \rangle = q/\langle k \rangle$, where q is the average

number of people infected per day and $\langle k \rangle$ is the average degree of the network. For the empirically-based network, the value of $\langle k \rangle$ was taken to be the minimum average node degree of the 10 empirically-based networks, such that, $\langle p \rangle$ would be sufficiently large enough to produce an epidemic in all of the empirically-based networks. The simulation started at $t = 0$. The days that the exogenous infections were introduced for the Poisson and exponential networks were: $t = 68, 89, 96, 99, 117, 119$ and 121 ; for the empirically-based network this was: $t = 75, 89, 97, 103, 110, 117, 118, 119, 120, 121$ and 122 . We increased the frequency of infection near the end of the sequence to increase the force of infection such that the average peak would occur at a realistic time of year. In the exponential network, the first four exogenous infections only infected nodes of degree one or two; this allowed the infection to spread at a slower rate and not peak as quickly. See Figure S1 for the results of the calibration regarding prevalence in each of the networks.

4.A.2 Classifying Super-Spreaders

A super-spreader is classified as an individual who infects more people than the 95^{th} percentile from a Poisson distribution with mean \mathcal{R}_0 ; \mathcal{R}_0 is the basic reproduction value from the “null” deterministic model[7, 8]. The “null” deterministic model is

$$\frac{dS}{dt} = \bar{\rho}R - \frac{qSI}{N} \quad (4.10)$$

$$\frac{dI}{dt} = \frac{qSI}{N} - \bar{\delta}I \quad (4.11)$$

$$\frac{dR}{dt} = \bar{\delta}I - \bar{\rho}R \quad (4.12)$$

where $\bar{\delta} = 1/\delta$ (δ is the average infectious period) is the rate (per day) at which a single infectious individual moves to the recovered state ($I \rightarrow R$) and $\bar{\rho} = 1/(365\rho)$ (ρ is the natural waning immunity in years) is the rate (per day) at which a recovered individual becomes susceptible ($R \rightarrow S$). The basic reproductive value for the “null” deterministic model is

$$\mathcal{R}_0 = \frac{q}{\bar{\delta}} = q\delta. \quad (4.13)$$

The value q/N represents the probability that a single infectious individual infects a susceptible individual, i.e. $\langle p \rangle = q/N$. However, in our network model an individual only has a given number of contacts and the transmission rate can vary between individuals. We assume the number of daily infections, q , can be approximated by the average transmission rate $\langle p \rangle$ and the average degree $\langle k \rangle$, where

$$q = \langle p \rangle \langle k \rangle. \quad (4.14)$$

Our assumption comes from the fact that a network’s \mathcal{R}_0 approaches the null deterministic model’s \mathcal{R}_0 as $\langle k \rangle$ increases, where $\langle p \rangle \langle k \rangle \rightarrow q$, while keeping q constant [45].

We assume the basic reproduction value for an individual is

$$\begin{aligned} \mathcal{R}_0 &= \sum_{i=1}^k \binom{k}{i} i(1 - (1 - \langle p \rangle)^\delta)^i (1 - \langle p \rangle)^{\delta(k-i)} \\ &= k(1 - (1 - \langle p \rangle)^\delta), \end{aligned} \quad (4.15)$$

where $(1 - \langle p \rangle)^\delta$ is the probability that an individual is not infected for δ days; therefore,

$(1 - (1 - \langle p \rangle)^\delta)$ is the probability that an individual is infected during the δ days, k is the number of contacts of the infected individual and δ is the infectious period.

There are three possible sources of super-spreading that we focus on:

1. a large number of contacts
2. increased infectious period
3. increased transmission of the disease

We consider four separate cases of super-spreading 1) heterogeneity in node degree 2) heterogeneity in node degree and infectious period 3) heterogeneity in node degree and transmission rate and 4) heterogeneity in node degree, infectious period and transmission rate.

Super-spreader: Number of Contacts

In the case of the super spreader having a large number of contacts, social contact networks will be used. For simple network analysis our first choice is a network with a Poisson degree distribution, where the cumulative distribution function is

$$d(k) = \sum_{n=0}^k \frac{\langle k \rangle^n e^{-\langle k \rangle}}{n!} \quad (4.16)$$

Social contact networks have been shown to be well represented by an exponential degree distribution [46], where the cumulative distribution function for the exponential distribu-

tion is

$$d(k) = 1 - e^{-k/\langle k \rangle} \quad (k > 0) \quad (4.17)$$

For influenza, the exponential network falls in between the unrealistic power-law and unrealistic Poisson. The average degree ($\langle k \rangle$) for both the Poisson and exponential networks was obtained from the empirical data from Ref [21, 22, 23], describing Portland, Oregon.

We also created scaled down empirically-based networks using data from Portland, Oregon[21, 22, 23]. To scale down the Portland network, we randomly selected an individual, recorded their contacts, then recorded their contact's contacts and so on, until the desired population size was reached. We then rewired the network such that the degree distribution of the sampled network resembled the original empirical degree distribution. We produced 10 Portland-like networks for our sample.

We assumed an individual's infectious period (δ), transmission ($\langle p \rangle$), natural waning immunity (ρ), vaccine waning immunity (ω) come from a delta-distribution (i.e. there is no heterogeneity). The reason for this approach is it allows for the impact of the different networks to be analyzed without having to understand the impact of extra parameter sampled from distributions. The average transmission will be calculated by

$$\langle p \rangle = \frac{q}{\langle k \rangle}, \quad (4.18)$$

where $\langle k \rangle$ is the average degree in the network. The degree distributions for each network can be seen in Figure S1.

Super-spreader: Increased Infectious Period & Number of Contacts

In the case of an increased infectious period, we assumed an individual's infectious period is described by a Poisson distribution with mean δ , and remains that value throughout the simulation. We resampled any infectious period that was zero or too large; i.e. for the case where $\delta = 5$, we resampled any infectious period larger than 14 days. We ran this scenario on the three networks (Poisson, exponential and empirically-based) and assumed all other parameters come from a delta distribution.

Super-spreader: Increased Transmission & Number of Contacts

In the case of an increased transmission probability, we assume an individual's average transmission is provided by a log-normal distribution with mean $\langle p \rangle$, which remains static through a simulation. We assumed a skewed log-normal distribution to allow for extreme cases of super-spreading in some individuals. We ran this scenario on the three networks (Poisson, exponential and empirically-based) and assumed all other parameters come from a delta distribution.

Super-spreader: Heterogeneous Population

We assumed heterogeneity in the number of contacts, infection period and transmission. We assumed the infectious period is sampled from a Poisson distribution with mean δ , the transmission rate is sampled from a log-normal distribution with mean $\langle p \rangle$ and the network is created from the three networks discussed earlier, where all other parameters come from a delta distribution.

4.A.3 Probability of Vaccination

An individual first determines whether or not they will seek vaccination for this upcoming season or not, based upon their payoffs. The probability that an individual seeks vaccination for this upcoming season is

$$\Phi(\mathcal{P}_V - \mathcal{P}_N) = \frac{\arctan(b(\mathcal{P}_V - \mathcal{P}_N)/(\$QALY)) + \frac{\pi}{2}}{\pi}, \quad (4.19)$$

The value of b in equation (4.19) was used to calibrate the vaccine coverage of the model, along with the dollar per Quality Adjusted Life Year (QALY) ($\$/QALY$). Each value of b for the corresponding network is given in Table S1. As the difference in payoffs, $\mathcal{P}_V - \mathcal{P}_N$, increases (decreases) the more (less) likely the individual will seek vaccination this season, since vaccination becomes more (less) appealing. If incentives are included, we use $\Phi(\mathcal{P}_V - \mathcal{P}_N + \Upsilon n)$ in determining whether or not the individual seeks vaccination this season, where Υ is the value of the monetary incentive and n is the number of incentives received.

Once it is determined that an individual is going to vaccinate, the following process is used to determine when the individual vaccinates. Prior to the new vaccination season we determine the vaccine uptake for each month, ϕ_{month} , by sampling from a log-normal

distribution with a mean of $\langle \phi \rangle$ and a variance of $\langle\langle \phi \rangle\rangle$ (Table S1), that is

$$\phi_{month} \sim \ln \mathcal{N}(\mu, \sigma^2) \quad (4.20)$$

$$\mu = \ln(\langle \phi_{month} \rangle) - \frac{1}{2} \ln \left(1 + \frac{\langle\langle \phi_{month} \rangle\rangle}{\langle \phi_{month} \rangle^2} \right) \quad (4.21)$$

$$\sigma^2 = \ln \left(1 + \frac{\langle\langle \phi_{month} \rangle\rangle}{\langle \phi_{month} \rangle^2} \right). \quad (4.22)$$

With these values we can determine when the individual vaccinates. We start off by selecting a uniform random number $0 < r < 1$, then find the first month such that

$$r \left(\sum_{\forall j} \phi_j \right) < \sum_{j \leq month} \phi_j, \quad (4.23)$$

Once a month is determined for the individual, a day is then chosen at random from that month for the individual to vaccinate on.

If the individual is seeking vaccination, they will only vaccinate if they have not experienced influenza in the current season; experiencing influenza includes cases of nILLI being mistaken for influenza and excludes non-symptomatic cases of influenza. The average annual vaccine coverage can be seen in Figure S1.

4.A.4 Social Influence

We incorporate social influence by using an imitation process or learning process; the learning process consists of individuals exchanging information regarding time since last infection, time since last complication and perceived vaccine efficacy. The learning process

occurs with a probability σ , which we call the imitation strength; the process consists of individual i randomly selecting one of their contacts, individual j , as well as randomly selecting an individual from the network, individual k . Individual i then updates their informations as follows

$$T_I^{i_{new}} = (1 - \sigma)T_I^i + \sigma(\nu T_I^j + (1 - \nu)T_I^k) \quad (4.24)$$

$$T_C^{i_{new}} = (1 - \sigma)T_C^i + \sigma(\nu T_C^j + (1 - \nu)T_C^k) \quad (4.25)$$

$$\varepsilon^{i_{new}}(t) = (1 - \sigma)\varepsilon^i(t) + \sigma(\nu\varepsilon^j(t) + (1 - \nu)\varepsilon^k(t)), \quad (4.26)$$

where the super-script denotes the individual and ν denotes the preference of using a contacts information to the randomly selected individual (i.e. $\nu = 1$ the individual prefers to imitate their contact). This corresponds to the sampler internalizing the experience of the sampled individual.

4.A.5 Pro-Active Vaccination Policies

We focus on four pro-active approaches public health could implement in society; we are assuming public health will contact $\bar{\mathcal{V}}$ individuals per day and recommend vaccination.

In each pro-active policy, if the selected individual decided not to vaccinate at the beginning of the season they proceed through the learning (imitation) process again and determine whether or not they will seek vaccination, using equation (4.19), with their new updated payoffs. The individual will decide when to vaccinate using an approach similar to that in equation (4.23); however, if the month has passed, it is no longer used in

determining when the individual will vaccinate. That is, if September has passed then ϕ_{Sept} will be removed from equation (4.23) i.e. $(\sum_{\forall j} \phi_j = \phi_{Oct} + \phi_{Nov} + \phi_{Dec})$. The following pro-active approaches will be combined with the baseline passive vaccination.

(a) Random Vaccination

For the random vaccination policy (RV), each day a number of individuals are selected at random and told about the upcoming or current flu clinics.

(b) Nearest Neighbor

The nearest neighbor approach (NN) (or acquaintance approach) is similar to the RV, in the way that each day a number of individuals are selected at random. However, the randomly selected individuals now recommends a “friend” for vaccination as well. [12]

(c) Page Rank

The Page Rank approach (PR) is similar to the NN; however, the policy consists of moving from one node to another with probability Δ and jumping to a random node with probability $1 - \Delta$. The PR approach would be considered a chain vaccination strategy, since recruitment runs along a chain of contacts until the chain is broken. That is, the following day public health would inform a contact of the individual about the vaccination program with probability Δ ; where another random individual would be contacted the following day with probability $1 - \Delta$. Δ could represent the probability of complying to recommending a friend. [13, 15]. We assumed a value of 0.50 for Δ .

(d) Improved Nearest Neighbor

The improved nearest neighbor (INN) approach is the same process as NN; however, now the random individual is asked to recommend a contact for vaccination who they view as “popular”. This will allow for the higher degree individuals to more likely be recommended for vaccination. An approach similar to this was taken in Refs [13, 27]; the assumption allows for the individual to have some knowledge, but not complete knowledge, about the degree of their contacts. To implement such a process we use a cumulative distribution function approach, where each contact is assigned a weight corresponding to their degree size. The process consists of choosing a random number $0 < r < 1$ and finding contact j such that

$$r \sum_{n=1}^{k_i} k_n < \sum_{n=1}^j k_n \text{ where } j \leq k_i, \quad (4.27)$$

such that j is the smallest possible number to satisfy equation (4.27), k_n is the degree for i 's n^{th} contact and k_i is the degree of i . This will allow for some error in the individual's incomplete knowledge of their contacts degree.

4.A.6 Quality Adjusted Life Years

To monetize the risk of infection and the risk associated with vaccination we used Quality Adjusted Life Years (QALYs). The cost of infection ($\overline{c_{inf}}$) is based upon the QALY penalties due to flu symptoms, plus the QALY penalty due to death, and can be expressed

as

$$\begin{aligned}\overline{c_{inf}} &= (\text{prob. infection this year}) \times (\text{cost of} \\ &\quad \text{infection in QALY's}) \times (\$/\text{QALY}).\end{aligned}\tag{4.28}$$

The probability of infection this year corresponds to the incidence of the population, the cost of infection expressed in QALY's equals (QALY penalty from symptoms) + (probability of death)x(QALY penalty from death). The value for the QALY penalty from influenza symptoms is 4.3/365, where 4.3 is the Quality Adjusted Life Days penalty from influenza symptoms [31], and the QALY penalty from death is 15, where the probability of death is 0.00075 [31].

For the cost of experiencing a vaccine complication, we calibrated the value of $\gamma \times$ (cost of vaccination in QALY's) such that it was the same magnitude as (prob. infection this year) \times (cost of infection in QALY's). We express the cost of vaccination as

$$\begin{aligned}\overline{c_{vac}} &= \gamma \times (\text{cost of vaccination in QALY's}) \\ &\quad \times (\$/\text{QALY}),\end{aligned}\tag{4.29}$$

where γ is the probability of a vaccine complication occurring.

The value of $\overline{c_{inf}}$ was based upon utility penalties constructed from patient surveys [31]. The value of $\overline{c_{vac}}$ was based on published vaccine costs and held fixed for the calibration of the vaccine coverage. Since vaccine complications are rare, the value of $\overline{c_{vac}}$ was obtained by determining the cost of vaccine complications in QALYs such that the probability of

complications (γ) times the cost of vaccine complications in QALYs was similar magnitude as incidence times the cost of influenza infection in QALYs.

4.A.7 Cost of Policy

We had to determine an estimated cost for the policies to determine whether the cost of incentives outweigh the cost saved from infection. The average cost of a single influenza infection is \$100.00, where the cost of a single vaccine is \$20.00 [47]. To determine the cost of incentives we used the percentage of incentives used and multiplied by the total number distributed and the monetary value of the incentive. Therefore, the total cost of a policy can be expressed as

$$\begin{aligned} \text{Cost} &= N \times (\$100.00\langle I(t) \rangle + \$20.00\langle V(t) \rangle) \\ &\quad + 122\bar{V}\Upsilon(\%_{\text{used}}), \end{aligned} \tag{4.30}$$

where N is the population size, $\langle I(t) \rangle$ is the average annual incidence, $\langle V(t) \rangle$ is the average annual vaccine uptake, \bar{V} is the number of individuals recruited each day and given an incentive, Υ is the monetary value of the incentive and $\%_{\text{used}}$ is the percentage of incentives used each year.

4.B Algorithm Summary

For each network we generated 400 simulations of 125 years each, discarding the transient dynamics of the first 100 years, with no vaccination occurring in the first year of each simulation. The following steps were taken to implement the behavior and vaccination process after the initial non-vaccination year. Prior to the vaccination season

1. Update the individual's perceived vaccine efficacy
2. Individual's proceed through the learning (imitation) process
 - i) Determine whether the individual imitates or not
 - ii) If they imitate randomly select a contact and individual from the network
 - iii) Assign the individual their new information using equations (4.24)-(4.26)
3. Individual determines both \mathcal{P}_V and \mathcal{P}_N
4. Individual determines whether or not they are going to vaccinate this season
5. Then we determine when the Individual vaccines

Afterwards, during the time period of the vaccination program, the following steps are implemented daily for the vaccination program

1. We randomly choose \bar{V} individuals and recommend vaccination
2. If the selected individual decided not to vaccinate this season they repeat Step 2 to Step 5 above

- i) If the selected individual had originally decided to vaccinate this season then do not repeat Step 2 to Step 5 above
3. If the individual vaccines today
- i) Determine whether or not the vaccine was effective
 - ii) Determine whether or not the individual experienced a complication
 - iii) If the individual experienced a complication set the individuals time since last vaccine complication to -1 day ($T_C = -1/365$)

The overall model with vaccination and infection follows the process below

1. Determine whether the individual looses vaccine immunity
2. Determine whether the individual looses natural immunity
3. Apply the process of determining whether the individual vaccinates this year and when
4. Start the year and vaccination program
5. Add one day to both T_I and T_C (i.e. $T_I = T_I + 1/365$)
6. If time corresponds to period of vaccination program
 - i) Randomly select individuals to inform about vaccination
 - ii) Apply the process of determining whether the randomly selected individuals vaccinate this year

- iii) Follow the process for an individual vaccinating today
7. If time corresponds to introducing an infected individual
- i) Randomly select a susceptible individual to be infected with influenza
8. Compute the individuals probability of becoming infected today
9. Determine if the individual becomes infected and determine if symptomatic
10. If the individual is infected and the flu is symptomatic
- i) Set the individuals time since last infection to -1 day ($T_I = -1/365$)
 - ii) If the individual vaccinated set the perceived vaccine efficacy to ε
11. Determine whether the individual leaves the infectious state or not
12. Infect the population with niILI
13. If individual is infected with ILI determine whether niILI is mistaken for influenza
14. If niILI is mistaken for influenza
- i) Set the individuals time since last infection to -1 day ($T_I = -1/365$)
 - ii) If the individual vaccinated set the perceived vaccine efficacy to ε
15. If end of year go to Step 1, otherwise go to Step 5 until the desired time is reached

4.C Supplementary Tables

Parameter	Description	Value	Reference
\mathcal{N}	Number of individuals in network	10000	assumption
$\langle k \rangle$	Average node degree for networks	39	[21, 22, 23]
\mathcal{R}_0^P	Null Deterministic Basic Reproductive Value (Poisson)	2.2	calibrated **; [28, 48, 49, 50]
\mathcal{R}_0^E	Null Deterministic Basic Reproductive Value (exponential)	2.875	calibrated **; [28, 48, 49, 50]
\mathcal{R}_0^{ED}	Null Deterministic Basic Reproductive Value (empirically-based)	3.45	calibrated **; [28, 48, 49, 50]
p_s	Change in Seasonality Amplitude (Poisson)	0.03	[48, 51]
p_s	Change in Seasonality Amplitude (exponential)	0.0525	[48, 51]
p_s	Change in Seasonality Amplitude (empirically-based)	0.03	[48, 51]
\bar{t}	Shift in Seasonality function (Poisson)	76	calibrated**
\bar{t}	Shift in Seasonality function (exponential)	122	calibrated **
\bar{t}	Shift in Seasonality function (empirically-based)	120	calibrated**
\bar{I}	Number of Exogenous Infections (Poisson)	7	calibrated **
\bar{I}	Number of Exogenous Infections (exponential)	7	calibrated **
\bar{I}	Number of Exogenous Infections (empirically-based)	11	calibrated **
ψ	Probability of influenza being symptomatic	0.70	[52]
δ	Average number of days to move from state I to state R (recovery rate)	5	[32, 52, 53, 54]
ρ	Probability of moving from state R to state S , per season	0.25	[53, 55, 56]
$\langle \alpha \rangle$	Average incidence for niILI, per day	0.00035 †	[57]

Parameter	Description	Value	Reference
$\langle\langle\alpha\rangle\rangle$	Variance of incidence for niILI	12.25×10^{-10}	calibrated ††
β	Probability of an individual mistaking niILI for influenza	0.50	assumption
V	Number of individual's contacted for vaccination, per day	20	assumption
ω	Probability of moving from state V to state S , per season	0.50	[58]
ε	Vaccine efficacy	0.70	[29, 59]
γ	Probability of experiencing vaccine complications, per vaccination	0.01	[33]
$$/QALY$	Dollar per Quality Adjusted Life Years	\$50,000	[31]
L	Baseline payoff	\$50,000	assumed
Υ	Monetary value of the incentive	\$20, \$50	[29, 32, 33, 34, 40, 41, 60]
m	Memory decay rate, per season	0.30	calibrated
$\underline{\varepsilon}$	Minimum perceived vaccine efficacy	0.65	calibrated
$\bar{\varepsilon}$	Maximum perceived vaccine efficacy	0.90	assumption
ξ	Vaccine efficacy memory decay rate factor	15	assumption
c_{vac}	Minimum cost of vaccination	\$45	◊[29, 32, 33, 34]
\bar{c}_{vac}	Additional cost of vaccination due to a complication	\$115	assumption [29, 32, 33, 34]
\bar{c}_{inf}	Maximum cost of infection	\$172.5	[31]
λ	Weight assigned to personal experiences	0.50	assumption
σ	Probability that the individual imitates	0.50	assumption
ν	Strength of preference to imitate contacts	0.50	assumption
b	Parameter for equation (4.19) (Poisson)	1360	calibrated

Parameter	Description	Value	Reference
b	Parameter for equation (4.19) (exponential)	4000	calibrated
b	Parameter for equation (4.19) (empirically-based)	3950	calibrated
$\langle \phi \rangle_{SEPT}$	Average vaccine uptake for September	0.0593	[61]
$\langle\langle \phi \rangle \rangle_{SEPT}$	Variance in vaccine uptake for September	0.00015	[61]
$\langle \phi \rangle_{OCT}$	Average vaccine uptake for October	0.1842	[61]
$\langle\langle \phi \rangle \rangle_{OCT}$	Variance in vaccine uptake for October	0.00072	[61]
$\langle \phi \rangle_{NOV}$	Average vaccine uptake for November	0.1012	[61]
$\langle\langle \phi \rangle \rangle_{NOV}$	Variance in vaccine uptake for November	0.00038	[61]
$\langle \phi \rangle_{DEC}$	Average vaccine uptake for December	0.0238	[61]
$\langle\langle \phi \rangle \rangle_{DEC}$	Variance in vaccine uptake for December	0.00004	[61]

Table 4.2: The values and descriptions of the parameters used in the simulations. The values were calibrated for each network using the passive vaccination approach. * The values m , b and $\underline{\varepsilon}$ were calibrated such that the average annual vaccine coverage on each network was approximately 35% using appropriate values. ** \mathcal{R}_0 was used in calibrating influenza incidence (15%) using values similar to influenza's \mathcal{R}_0 [28, 29, 30] on each network such that the average peak of prevalence occurred between January 1st and February 28th [44]. † The value for $\langle \alpha \rangle$ was calculated such that the annual incidence of non-influenza-like-illness (niILI) was 12%, corresponding to the ratio of niILI incidence to influenza incidence estimated in [57] and multiplied by the average annual influenza incidence (15%)[26, 28, 29, 30]. ‡ The variance for α was calibrated such that the log-normal distribution best resembled the shape of a normal distribution. ◊ c_{vac} was computed as the cost of the actual vaccination \$20 and plus the time required to receive the vaccination \$25.

Strategy	% Useless	% Υ Used
PV + RV	36.82%	<i>N/A</i>
PV + NN	37.43%	<i>N/A</i>
PV + PR	37.63%	<i>N/A</i>
PV + INN	38.58%	<i>N/A</i>
<hr/>		
PV + RV (NB)	43.49%	<i>N/A</i>
PV + NN (NB)	44.63%	<i>N/A</i>
PV + PR (NB)	45.08%	<i>N/A</i>
PV + INN (NB)	47.38%	<i>N/A</i>
<hr/>		
PV + RV (\$20)	37.11%	57.02%
PV + NN (\$20)	37.57%	56.61%
PV + NN (\$20)*	37.34%	57.12%
PV + PR (\$20)	38.01%	57.01%
PV + INN (\$20)	39.31%	56.29%
PV + INN (\$20)*	39.18%	57.10%
<hr/>		
PV + RV (\$50)	37.39%	71.11%
PV + NN (\$50)	37.73%	70.77%
PV + NN (\$50)*	37.33%	70.62%
PV + PR (\$50)	38.34%	70.86%
PV + INN (\$50)	39.85%	69.58%
PV + INN (\$50) <i>t</i>	39.49%	67.89%

Table 4.3: Percentage of recruitments where recruitment did not matter, whether due to infection, already vaccinated or will be vaccinating in the future (Useless) and the percentage of incentives actually used (% Υ Used). NB indicates the scenario where vaccination behavior is entirely ignored, (\$20) indicates where \$20 incentives were used and (\$50) for \$50 incentives. The vaccination programs are the passive (PV), along with the pro-active programs: random vaccination (RV), nearest neighbor (NN), page rank (PR) and improved nearest neighbor (INN).

Strategy	\mathcal{C}_S	$\mathcal{PC}_{[SI]}$	$\mathcal{PC}_{[SV]}$
PV	0.606	0.78	0.69
PV + RV	0.607	0.79	0.69
PV + NN	0.609	0.78	0.70
PV + PR	0.608	0.77	0.71
PV + INN	0.613	0.77	0.72
PV (NB)	0.600	0.82	0.68
PV + RV (NB)	0.594	0.88	0.74
PV + NN (NB)	0.603	0.84	0.77
PV + PR (NB)	0.603	0.83	0.77
PV + INN (NB)	0.612	0.80	0.79
PV + RV (\$20)	0.604	0.81	0.70
PV + NN (\$20)	0.611	0.78	0.73
PV + PR (\$20)	0.610	0.77	0.73
PV + INN (\$20)	0.619	0.75	0.75
PV + RV (\$50)	0.602	0.83	0.71
PV + NN (\$50)	0.611	0.78	0.74
PV + PR (\$50)	0.610	0.78	0.74
PV + INN (\$50)	0.620	0.75	0.77

Table 4.4: The global clustering coefficient among susceptible individuals (\mathcal{C}_S) and the pair correlations between susceptible and infected individuals ($\mathcal{PC}_{[SI]}$) and susceptible and vaccinated individuals ($\mathcal{PC}_{[SV]}$) for the various vaccination strategies.

Strategy	$\Sigma(V_S^{SS}(t))$	$\Sigma(V_R^{SS}(t))$	$\Sigma(V_{NN}^{SS}(t))$
PV	0.39 ± 0.062	0 ± 0	0 ± 0
PV + RV	0.37 ± 0.059	0.041 ± 0.0063	0 ± 0
PV + NN	0.37 ± 0.059	0.02 ± 0.0044	0.051 ± 0.007
PV + PR	0.37 ± 0.059	0.02 ± 0.0043	0.051 ± 0.0071
PV + INN	0.36 ± 0.058	0.019 ± 0.0042	0.081 ± 0.0087
PV (NB)	0.35 ± 0.015	0 ± 0	0 ± 0
PV + RV (NB)	0.35 ± 0.014	0.14 ± 0.01	0 ± 0
PV + NN (NB)	0.35 ± 0.015	0.063 ± 0.0071	0.16 ± 0.011
PV + PR (NB)	0.35 ± 0.015	0.063 ± 0.0073	0.16 ± 0.011
PV + INN (NB)	0.36 ± 0.014	0.058 ± 0.0068	0.22 ± 0.012
PV + RV (\$20)	0.35 ± 0.054	0.094 ± 0.0088	0 ± 0
PV + NN (\$20)	0.33 ± 0.052	0.045 ± 0.0061	0.11 ± 0.0094
PV + PR (\$20)	0.33 ± 0.051	0.045 ± 0.0063	0.11 ± 0.01
PV + INN (\$20)	0.32 ± 0.049	0.043 ± 0.0061	0.18 ± 0.011
PV + RV (\$50)	0.33 ± 0.048	0.13 ± 0.012	0 ± 0
PV + NN (\$50)	0.31 ± 0.044	0.061 ± 0.0077	0.15 ± 0.013
PV + PR (\$50)	0.31 ± 0.045	0.061 ± 0.0079	0.15 ± 0.014
PV + INN (\$50)	0.29 ± 0.042	0.058 ± 0.0075	0.23 ± 0.016

Table 4.5: The statistics regarding the number of superspreaders that were willing to vaccinate prior to being recruited ($V_S^{SS}(t)$), that were randomly contacted and then were willing to vaccinate ($V_R^{SS}(t)$) and those contacted through a nearest neighbor and then were willing to vaccinate ($V_{NN}^{SS}(t)$) for the various vaccination strategies (with and without incentives) (empirically-based network). $\Sigma(\cdot) = \langle \cdot \rangle \pm \sqrt{\langle \langle \cdot \rangle \rangle}$, where $\langle \cdot \rangle$ denotes the average and $\sqrt{\langle \langle \cdot \rangle \rangle}$ denotes the standard deviation. NB indicates the scenario where vaccination behavior is entirely ignored, (\$20) indicates where \$20 incentives were used and (\$50) for \$50 incentives. The vaccination programs are the passive (PV), along with the pro-active programs: random vaccination (RV), nearest neighbor (NN), page rank (PR) and improved nearest neighbor (INN).

Strategy	I_{cost}	V_{cost}	Υ_{cost}	Total
PV	\$101,123.45	\$69,968.98	\$0.00	\$171,092.43
PV + RV	\$96,814.46	\$75,163.34	\$0.00	\$171,977.80
PV + NN	\$95,974.89	\$74,307.91	\$0.00	\$170,282.80
PV + PR	\$95,994.61	\$74,293.25	\$0.00	\$170,287.86
PV + INN	\$95,351.87	\$73,443.82	\$0.00	\$168,795.69
PV (NB)	\$97,708.81	\$70,239.57	\$0.00	\$167,948.38
PV + RV (NB)	\$75,403.22	\$97,665.35	\$0.00	\$173,068.57
PV + NN (NB)	\$70,053.29	\$97,116.51	\$0.00	\$167,169.80
PV + PR (NB)	\$70,399.56	\$96,870.48	\$0.00	\$167,270.04
PV + INN (NB)	\$66,465.58	\$95,767.50	\$0.00	\$162,233.08
PV + RV \$20	\$91,776.33	\$81,049.27	\$27,827.02	\$200,652.62
PV + NN \$20	\$89,939.64	\$79,087.34	\$27,626.24	\$196,653.22
PV + NN \$20*	\$92,470.28	\$75,945.11	\$13,937.53	\$182,352.91
PV + PR \$20	\$90,135.70	\$79,035.00	\$27,822.40	\$196,993.10
PV + INN \$20	\$88,335.36	\$76,943.90	\$27,467.32	\$192,746.58
PV + INN \$20*	\$90,924.69	\$73,885.44	\$13,932.77	\$178,742.90
PV + RV \$50	\$87,977.25	\$85,177.45	\$86,753.29	\$259,907.99
PV + NN \$50	\$85,070.74	\$82,608.28	\$86,342.32	\$254,021.34
PV + NN \$50*	\$89,966.28	\$77,068.94	\$43,078.52	\$210,113.74
PV + PR \$50	\$85,482.37	\$82,491.13	\$86,451.52	\$254,425.02
PV + INN \$50	\$83,209.41	\$79,930.13	\$84,885.34	\$248,024.88
PV + INN \$50*	\$88,015.02	\$74,140.18	\$41,410.88	\$203,566.08

Table 4.6: The estimated costs of the various vaccination strategies for the Realistic networks. The vaccination programs are the passive, along with the pro-active programs: random vaccination (RV), nearest neighbor (NN), page rank (PR) and improved nearest neighbor (INN). Υ indicates an incentive value of \$20.00, where $\hat{\Upsilon}$ indicates an incentive value of \$50.00. I_{cost} refers to the cost of infection, V_{cost} refers to the cost of vaccination and Υ_{cost} refers to the cost associated with incentives. * the strategy was slightly altered to only allow the incentives to be distributed to the acquaintance.

Strategy	$\Sigma(I(t))$	$\Sigma(V(t))$	$\Sigma(I^{SS}(t))$	$\Sigma(V^{SS}(t))$
No Vaccination	0.15 ± 0.087	0 ± 0	0.22 ± 0.13	0 ± 0
PV	0.1 ± 0.077	0.35 ± 0.059	0.16 ± 0.12	0.38 ± 0.07
PV + RV	0.096 ± 0.074	0.37 ± 0.059	0.16 ± 0.12	0.4 ± 0.07
PV + NN	0.095 ± 0.075	0.37 ± 0.059	0.16 ± 0.12	0.42 ± 0.072
PV + PR	0.095 ± 0.075	0.37 ± 0.059	0.16 ± 0.12	0.42 ± 0.071
PV + INN	0.095 ± 0.075	0.36 ± 0.058	0.15 ± 0.12	0.44 ± 0.072
PV (NB)	0.097 ± 0.06	0.35 ± 0.0049	0.16 ± 0.1	0.35 ± 0.014
PV + RV (NB)	0.077 ± 0.051	0.49 ± 0.0053	0.14 ± 0.092	0.49 ± 0.015
PV + NN (NB)	0.071 ± 0.05	0.48 ± 0.0055	0.13 ± 0.09	0.56 ± 0.016
PV + PR (NB)	0.071 ± 0.051	0.48 ± 0.0055	0.13 ± 0.09	0.56 ± 0.016
PV + INN (NB)	0.069 ± 0.05	0.47 ± 0.0054	0.12 ± 0.086	0.59 ± 0.016
PV + RV (\$20)	0.092 ± 0.071	0.41 ± 0.054	0.15 ± 0.12	0.43 ± 0.064
PV + NN (\$20)	0.089 ± 0.071	0.39 ± 0.052	0.15 ± 0.11	0.47 ± 0.062
PV + PR (\$20)	0.089 ± 0.07	0.39 ± 0.051	0.15 ± 0.11	0.47 ± 0.061
PV + INN (\$20)	0.088 ± 0.07	0.38 ± 0.05	0.14 ± 0.11	0.5 ± 0.059
PV + RV (\$50)	0.088 ± 0.065	0.43 ± 0.038	0.15 ± 0.11	0.45 ± 0.049
PV + NN (\$50)	0.084 ± 0.064	0.41 ± 0.037	0.14 ± 0.11	0.51 ± 0.043
PV + PR (\$50)	0.085 ± 0.065	0.41 ± 0.037	0.14 ± 0.11	0.5 ± 0.044
PV + INN (\$50)	0.083 ± 0.064	0.4 ± 0.036	0.14 ± 0.1	0.53 ± 0.041

Table 4.7: Influenza incidence and vaccine coverage for the various vaccination strategies (with and without incentives) where there is heterogeneity in the infectious period and transmission rate (exponential network). $\Sigma(\cdot) = \langle \cdot \rangle \pm \sqrt{\langle \langle \cdot \rangle \rangle}$, where $\langle \cdot \rangle$ denotes the average and $\sqrt{\langle \langle \cdot \rangle \rangle}$ denotes the standard deviation. The annual incidence is denoted by $I(t)$, where $I^{SS}(t)$ denotes the annual incidence of the superspreading population. The annual vaccine uptake is denoted as $V(t)$, where the vaccine uptake in the superspreading population is denoted as $V^{SS}(t)$. NB indicates the scenario where vaccination behavior is entirely ignored, (\$20) indicates where \$20 incentives were used and (\$50) for \$50 incentives. The vaccination programs are the passive (PV), along with the pro-active programs: random vaccination (RV), nearest neighbor (NN), page rank (PR) and improved nearest neighbor (INN).

Strategy	$\Sigma(I(t))$	$\Sigma(V(t))$	$\Sigma(I^{SS}(t))$	$\Sigma(V^{SS}(t))$
No Vaccination	0.15 ± 0.12	0 ± 0	0.15 ± 0.13	0 ± 0
PV	0.065 ± 0.07	0.35 ± 0.03	0.069 ± 0.078	0.35 ± 0.04
PV + RV	0.056 ± 0.062	0.38 ± 0.028	0.06 ± 0.069	0.38 ± 0.038
PV + NN	0.056 ± 0.062	0.38 ± 0.028	0.06 ± 0.069	0.38 ± 0.038
PV + PR	0.056 ± 0.062	0.38 ± 0.028	0.06 ± 0.069	0.38 ± 0.038
PV + INN	0.056 ± 0.061	0.38 ± 0.028	0.059 ± 0.068	0.38 ± 0.038
PV (NB)	0.059 ± 0.059	0.35 ± 0.005	0.063 ± 0.066	0.35 ± 0.025
PV + RV (NB)	0.022 ± 0.025	0.49 ± 0.0046	0.024 ± 0.03	0.49 ± 0.026
PV + NN (NB)	0.022 ± 0.024	0.49 ± 0.0045	0.023 ± 0.029	0.49 ± 0.026
PV + PR (NB)	0.022 ± 0.025	0.49 ± 0.0046	0.023 ± 0.029	0.49 ± 0.026
PV + INN (NB)	0.021 ± 0.024	0.49 ± 0.0046	0.022 ± 0.028	0.5 ± 0.026
PV + RV (\$20)	0.052 ± 0.058	0.39 ± 0.026	0.056 ± 0.065	0.39 ± 0.036
PV + NN (\$20)	0.054 ± 0.06	0.38 ± 0.027	0.058 ± 0.067	0.39 ± 0.037
PV + PR (\$20)	0.052 ± 0.058	0.39 ± 0.026	0.056 ± 0.065	0.39 ± 0.037
PV + INN (\$20)	0.051 ± 0.058	0.39 ± 0.026	0.055 ± 0.064	0.4 ± 0.036
PV + RV (\$50)	0.046 ± 0.051	0.41 ± 0.021	0.049 ± 0.057	0.41 ± 0.033
PV + NN (\$50)	0.05 ± 0.056	0.39 ± 0.025	0.054 ± 0.063	0.4 ± 0.035
PV + PR (\$50)	0.046 ± 0.051	0.41 ± 0.021	0.049 ± 0.057	0.42 ± 0.033
PV + INN (\$50)	0.045 ± 0.05	0.41 ± 0.021	0.048 ± 0.056	0.42 ± 0.033

Table 4.8: Influenza incidence and vaccine coverage for the various vaccination strategies (with and without incentives) where there is heterogeneity in the infectious period and transmission rate (Poisson network). $\Sigma(\cdot) = \langle \cdot \rangle \pm \sqrt{\langle \langle \cdot \rangle \rangle}$, where $\langle \cdot \rangle$ denotes the average and $\sqrt{\langle \langle \cdot \rangle \rangle}$ denotes the standard deviation. The annual incidence is denoted by $I(t)$, where $I^{SS}(t)$ denotes the annual incidence of the superspreading population. The annual vaccine uptake is denoted as $V(t)$, where the vaccine uptake in the superspreading population is denoted as $V^{SS}(t)$. NB indicates the scenario where vaccination behavior is entirely ignored, (\$20) indicates where \$20 incentives were used and (\$50) for \$50 incentives. The vaccination programs are the passive (PV), along with the pro-active programs: random vaccination (RV), nearest neighbor (NN), page rank (PR) and improved nearest neighbor (INN).

4.D Supplementary Figures

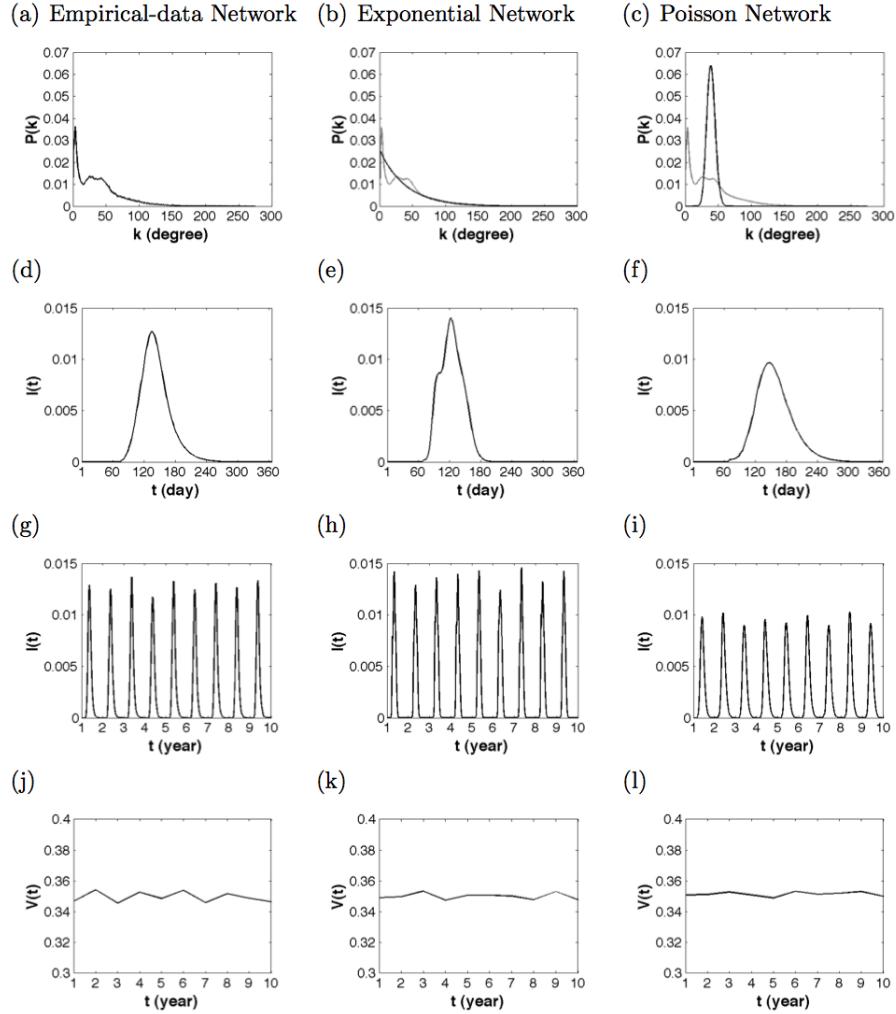


Figure 4.2: The top row shows the degree distribution for each network (black) compared to the original empirical network (gray) of Portland, Oregon [1,2,3]. The second row clearly shows that prevalence peaks between the beginning of January and the end of February. The third row shows the prevalence over many years under no vaccination and the fourth row shows the average vaccine coverage over the years under passive vaccination. The average time for peak of prevalence: Empirically-based $t = 136$, Exponential $t = 123$ and Poisson $t = 147$. The approximate average duration of the season: Empirically-based 181 days, Exponential 124 days and Poisson 217 days.

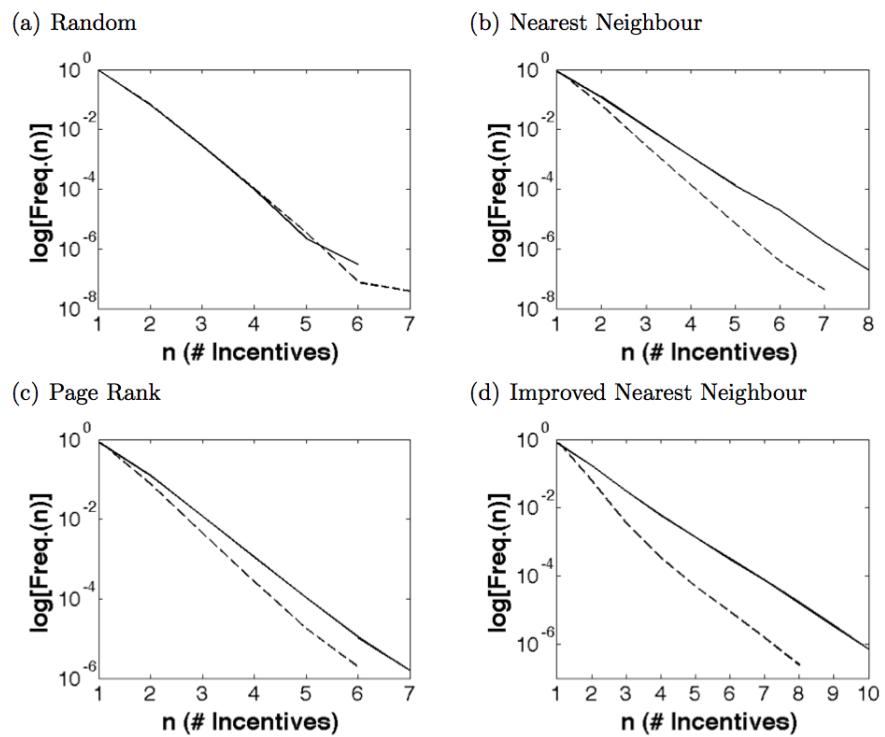


Figure 4.3: A semi-log plot of the probability of number of incentives received and used by superspreaders (solid line) and non-superspreaders (dashed line) for the four different vaccine strategies a) random vaccination b) nearest neighbor vaccination c) page rank vaccination and d) improved nearest neighbor vaccination.

Bibliography

- [1] World Health Organization. Immunization, vaccines and biologicals: Influenza. <http://www.who.int/immunization/topics/influenza/en/index.html>, June 2012.
- [2] T. Szucs. The socio-economic burden of influenza. J. Antimicrob. Chemother., 44(Suppl. 2):11–15, 1999.
- [3] Centers for Disease Control and Prevention. The flu season. <http://www.cdc.gov/flu/about/season/flu-season.htm>, May 2012.
- [4] Centers for Disease Control and Prevention. Final state-level influenza vaccination coverage estimates for the 2010-11 season: United states, national immunization survey and behavioral risk factor surveillance system, august 2010 through may 2011. http://www.cdc.gov/flu/professionals/vaccination/coverage_1011estimates.htm, April 2012.
- [5] J.T. Kemper. On the identification of superspreaders for infectious disease. Mathematical Biosciences, 48:111–127, 1980.
- [6] M.E.J. Woolhouse, C. Dye, J.F. Etard, T. Smith, J.D. Charlwood, G.P. Garnett, P. Hagan, J.L.K. Hii, P.D. Ndhlovu, R.J. Quinnell, C.H. Watts, S.K. Chandiwana, and R.M. Anderson. Heterogeneities in the transmission of infectious agents: Implications for the design of control programs. PNAS, 94(1):338–342, 1997.
- [7] A.P. Galvani and R.M. May. Dimensions of superspreading. Nature, 438:293–295, 2005.

- [8] J.O. Lloyd-Smith, S.J. Schreiber, P.E. Kopp, and W.M. Getz. Superspreading and the effect of individual variation on disease emergence. *Nature*, 438:355–359, 2005.
- [9] R.A. Stein. Lessons from outbreaks of h1n1 influenza. *Annals of Internal Medicine*, 151:59–62, 2009.
- [10] V. Pestre, B. Morel, N. Encrenaz, A. Brunon, F. Lucht, B. Pozzetto, and P. Berthelot. Transmission by super-spreading event of pandemic a/h1n1 2009 influenza during road and train travel. *Scandinavian Journal of Infectious Diseases*, 44(3):225–227, 2012.
- [11] R. Pastor-Satorras and A. Vespignani. Immunization of complex networks. *Physical Review E*, 65:036104, 2002.
- [12] R. Cohen, S. Havlin, and D. ben Avraham. Efficient immunization strategies for computer networks and populations. *Physical Review Letters*, 91(24):247901, 2003.
- [13] P. Holme. Efficient local strategies for vaccination and network attack. *Europhysics Letters*, 68(6):908–914, 2004.
- [14] F. Takeuchi and K. Yamamoto. Effectiveness of vaccination strategies for infectious diseases according to human contact networks. *Japanese Journal of Infectious Disease*, 58(6):956–962, 2005.
- [15] J.C. Miller and J.M. Hyman. Effective vaccination strategies for realistic social networks. *Physica A*, 386:780–785, 2007.
- [16] W.J. Bai, T. Zhou, and B.H. Wang. Immunization of susceptible-infected model on scale-free networks. *PHYSICA A*, 384:656–662, 2007.

- [17] G. Hartvigsen, J.M. Dresch, A.L. Zielinski, A.J. Macula, and C.C. Leary. Network structure, and vaccination strategy and effort interact to affect the dynamics of influenza epidemics. *Journal of Theoretical Biology*, 246:205–213, 2007.
- [18] H. Hethcote. The mathematics of infectious diseases. *SIAM Review*, 42(4):599–653, 2000.
- [19] A.P. Galvani, T.C. Reluga, and G.B. Chapman. Long-standing influenza vaccination policy is in accord with individual self-interest but not the utilitarian optimum. *Proc. Natl. Acad. Sci. USA*, 104(13):5692–5697, 2007.
- [20] P.P. Lam, L.W. Chambers, D.M. Pierrynowski MacDougall, and A.E. McCarthy. Seasonal influenza vaccination campaigns for health care personnel: systematic review. *Can Med Assoc J*, 182(12):E542–E548, 2010.
- [21] Network Dynamics and Simulation Science Laboratory. Synthetic data products for societal infrastructures and proto-populations: Data set 1.0.
- [22] Network Dynamics and Simulation Science Laboratory. Synthetic data products for societal infrastructures and proto-populations: Data set 2.0.
- [23] Network Dynamics and Simulation Science Laboratory. Synthetic data products for societal infrastructures and proto-populations: Data set 3.0.
- [24] G. Chapman and E. Coups. Predictors of influenza vaccine acceptance among healthy adults. *Preventive Medicine*, 29(4):249–262, 1999.

- [25] K.M. Cummings, A.M. Jette, B.M. Brock, and D.P. Haefner. Psychosocial determinants of immunization behavior in a swine influenza campaign. *Medical Care*, 17(6):639–649, 1979.
- [26] C.R. Wells and C.T. Bauch. The impact of personal experiences with infection and vaccination on behaviour-incidence dynamics of seasonal influenza. *Epidemics*, 4(3):139–151, 2012.
- [27] B.J. Kim, C.N. Yoon, S.K. Han, and H. Jeong. Path finding strategies in scale-free networks. *Physical Review E*, 65:027103, 2002.
- [28] L. Mao. Agent-based simulation for weekend-extension strategies to mitigate influenza outbreaks. *BMC Public Health*, 11(522), 2011.
- [29] C.B. Bridges, W.W. Thompson, M.I. Meltzer, G.R. Reeve, W.J. Talamonti, N.J. Cox, H.A. Lilac, H. Hall, A. Klimov, and K. Fukuda. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomized controlled trial. *JAMA*, 284(13), 2000.
- [30] R.B. Couch. Advances in influenza virus vaccine research. *Annals of the New York Academy of Sciences*, 685:803–812, 1993.
- [31] D.A. Turner, A.J. Wailoo, N.J. Cooper, A.J. Sutton, K.R. Abrams, and K.G. Nicholson. The cost-effectiveness of influenza vaccination of healthy adults 5064 years of age. *Vaccine*, 24:1035–1043, 2006.
- [32] P. Y. Lee, D. B. Matchar, D. A. Clements, J. Huber, J. D. Hamilton, and E. D. Pe-

tersson. Economic analysis of influenza vaccination and antiviral treatment for healthy working adults. *Annals of Internal Medicine*, 137(4):225–231, 2002.

- [33] K. L. Nichol. Cost-benefit analysis of a strategy to vaccinate healthy working adults against influenza. *Arch Intern Med.*, 161(5):749–759, 2001.
- [34] M.I. Meltzer, N.J. Cox, and K. Fukuda. The economic impact of pandemic influenza in the united states: Priorities for intervention. *Emerging Infectious Diseases*, 5(5):659–671, 1999.
- [35] C. T. Bauch and D. J. D Earn. Vaccination and the theory of games. *Proc. Natl. Acad. Sci.*, 101:13391–13394, 2004.
- [36] J. D. Sterman. Learning from evidence in a complex world. *Am J Pub Health*, 96(3):505–514, 2006.
- [37] C. T. Bauch and S. Bhattacharyya. Evolutionary game theory and social learning can determine how vaccine scares unfold. *PLoS Comput Biol*, 8(4):e1002452, 2012.
- [38] S. Bhattacharyya and C. T. Bauch. Mathematical models of the interplay between individual vaccinating decisions and disease dynamics: a need for closer integration of models and data. *Human vaccines and immunotherapeutics*, 8(6):842–844, 2012.
- [39] M. Salathe and S. Bonhoeffer. The effect of opinion clustering on disease outbreak. *Journal of the Royal Society Interface*, 5:1505–1508, 2008.
- [40] J. Nexoe, J. Kragstrup, and T. Ronne. Impact of postal invitations and user fee on

influenza vaccination rates among the elderly: A randomized controlled trial in general practice. Scandinavian Journal of Primary Health Care, 15(2):109–122, 1997.

- [41] P. Satterthwaite. A randomised intervention study to examine the effect on immunisation coverage of making influenza vaccine available at no cost. The New Zealand Medical Journal, 110(1038):58–60, 1997.
- [42] N.A. Christakis and J.H. Fowler. Social network sensors for early detection of contagious outbreaks. PLoS ONE, 5(9):e12948, 2010.
- [43] R.M. Christley, G.L. Pinchbeck, R.G. Bowers, D. Clancy, N.P. French, R. Bennett, and J. Turner. Infection in social networks: Using network analysis to identify high-risk individuals. American Journal of Epidemiology, 162(10):1024–1031, 2005.
- [44] Centers for Disease Control and Prevention. 2011-2012 influenza season: Disease activity. <http://www.cdc.gov/flu/about/season/flu-season-2011-2012.htm>, April 2012.
- [45] S. Funk, E. Gilad, C. Watkins, and V.A.A. Jansen. The spread of awareness and its impact on epidemic outbreaks. PNAS, 106(16):6872–6877, 2009.
- [46] S. Bansal, B.T. Grenfell, and L.A. Meyers. When individual behaviour matters: homogeneous and network models in epidemiology. J. R. Soc. Interface, 4:879–891, 2007.
- [47] S.C. Wood, V.H. Nguyen, and C. Schmidt. Economic evaluations of influenza vaccination in healthy working-age adults employer and society perspective. Pharmacoconomics, 18(2):173–183, 2000.

- [48] J. Truscott, C. Fraser, W. Hinsley, S. Cauchemez, C. Donnelly, A. Ghani, N. Ferguson, and A. Meeyai. Quantifying the transmissibility of human influenza and its seasonal variation in temperate regions. *PLoS Currents*, 1:RRN1125, 2009.
- [49] M.J. Keeling and P. Rohani. *Modeling Infectious Diseases in Humans and Animals*, page 21. Princeton Press, 2008.
- [50] J. Truscott, C. Fraser, S. Cauchemez, A. Meeyai, W. Hinsley, C.A. Donnelly, A. Ghani, and N. Ferguson. Essential epidemiological mechanisms underpinning the transmission dynamics of seasonal influenza. *J. R. Soc. Interface*, pages 304–312, 2012.
- [51] J. Dushoff, J.B. Plotkin, S.A. Levin, and D.J.D. Earn. Dynamical resonance can account for seasonality of influenza epidemics. *PNAS*, 101(48):16915–16916, 2004.
- [52] F. Carrat, E. Vergu, N.M. Ferguson, M. Lemaitre, S. Cauchemez, S. Leach, and A. Valleron. Time lines of infection and disease in human influenza: A review of volunteer challenge studies. *American Journal of Epidemiology*, 167(7):775–785, 2008.
- [53] D.J.D. Earn, J. Dushoff, and S.A. Levin. Ecology and evolution of the flu. *TRENDS in Ecology and Evolution*, 17(7):334–340, 2002.
- [54] K.L. Nichol, K. Tummers, A. Hoyer-Leitzel, J. Marsh, and M. Moynihan et al. Modeling seasonal influenza outbreak in a closed college campus: Impact of pre-season vaccination, in-season vaccination and holidays/breaks. *PLoS ONE*, 5(3):e9548, 2010.
- [55] I.M. Longini Jr., M. E. Halloran, A. Nizam, M. Wolff, P. M. Mendelman, P. E. Fast, and R. B. Belshe. Estimation of the efficacy of live, attenuated influenza vaccine from

a two-year, multi-center vaccine trial: implications for influenza epidemic control. Vaccine, 18:1902–1909, 2000.

- [56] R. J. Cox, K. A. Brokstad, and P. Ogra. Influenza virus: Immunity and vaccination strategies. comparison of the immune response to inactivated and live, attenuated influenza vaccines. Scandinavian Journal of Immunology, 59:1–15, 2004.
- [57] D.M. Fleming and J.G. Ayres. Diagnosis and patterns of incidence of influenza, influenza-like illness and the common cold in general practice. Journal of the Royal College of General Practitioners, 38(309):159–162, 1988.
- [58] C.S. Ambrose, T. Yi, R.E. Walker, and E.M. Connor. Duration of protection provided by live attenuated influenza vaccine in children. Pediatric Infectious Disease Journal, 27(8):744–748, 2008.
- [59] V. Demicheli, C. Di Pietrantonj, T. Jefferson, A. Rivetti, and D. Rivetti. Vaccines for preventing influenza in healthy adults. Database of Systematic Reviews 2007, 2, 2007.
- [60] R.L. Kane, P.E. Johnson, R.J. Town, and M. Butler. A structured review of the effect of economic incentives on consumers and preventive behavior. American Journal of Preventive Medicine, 27(4):327–352, 2004.
- [61] Centers for Disease Control and Prevention. Influenza vaccination coverage: Fluview:2010-11 influenza season. <http://www.cdc.gov/flu/professionals/vaccination/vaccinecoverage.htm>, May 2012.

Chapter 5

Discussion

5.1 Discussion

The focus of this thesis was to analyze the impact of vaccination behaviour on the spread of disease in a network setting. The thesis consisted of three different projects

1. Impact of imitation processes on the effectiveness of ring vaccination (Chapter 2)
2. The impact of personal experiences with infection and vaccination on behaviour-incidence dynamics of seasonal influenza (Chapter 3)
3. Policy resistance undermines superspreadер vaccination strategies for influenza (Chapter 4)

Neglecting behaviour overestimates a policy's effectiveness in reducing incidence, which was one of the main results of Chapter 4; evidence of overestimation even occurred in ring vaccination under the simple stochastic assumption (Chapter 2), where individuals still had choice between vaccinating and not vaccinating but everyone made the same decision by disregarding any social influence. The presence of behaviour lead to the presence of policy resistance, whether due to low incidence or social influence.

All three projects showed some form of policy resistance. In Chapter 2, policy resistance was in the form of social influence. Policy resistance due to social influence has been witnessed in history, mainly associated with vaccine scares and negative beliefs associated with vaccines [1, 2, 3, 4]. However, policy resistance can also be associated with diseases that are viewed to be less of a threat, or less lethal [5, 6, 7, 8]. In Chapter 3, a “universal” influenza vaccine lead to policy resistance because of low incidence. The model also associated policy resistance with the duration of memory as individuals tended to view the

vaccine to be less effective. In Chapter 4, policy resistance benefited some of the targeted vaccination strategies making them more efficient by reducing both incidence and vaccine uptake; however, the policy resistance among the super-spreading population remained a problem.

Policy resistance is important in determining the effectiveness of a vaccine policy. Assuming a certain level of vaccine uptake is fine for determining the critical level of vaccination to eliminate infection; however, without accounting for policy resistance (behaviour), one cannot be sure whether or not this critical level can actually be obtained. Past models indicate that critical levels of vaccination cannot be obtained through voluntary vaccination [9, 10] because as the population reaches levels of herd immunity, vaccination becomes less appealing due to the reduction of incidence.

Ref [11] accounted for behaviour through voluntary vaccination in a uniform random network and found policy resistance not to be an issue. There are a few reasons as to why policy resistance was not an issue for Ref [11]: 1) local vaccination during the epidemic focused on the regions where infection is residing can be successful, 2) opinions were based upon the current epidemic and 3) the model does not allow past events to influence future behaviour. Vaccination occurring locally around infection can reduce future incidence, neglecting vaccination elsewhere where infection is not present produces the policy resistance in Ref [11], making policy resistance less of an issue. Allowing opinions to form based on the events of current epidemics does not allow susceptible clusters to form, because once infection is present in the local area individuals will seek vaccination. By not allowing infection to survive due to the absence of susceptible (non-vaccinating) clusters this suppresses the true incidence in the population, making policy resistance less of an issue.

Neglecting the impact of past events and social influence does not allow negative opinions to be formed about vaccination, since vaccination is mainly based upon the presence of current infection. Results from this thesis show that if past incidence is low vaccination becomes less appealing.

One of the main results that comes from this thesis is the impact of super-spreaders on the effectiveness of vaccine policies. Policy resistance is present among super-spreaders and these individuals tend to view the vaccine to be less effective. However, public health officials should be careful when reminding the population about past influenza experiences to increase vaccine uptake, as public health should also reassure the public about the effectiveness of the vaccine. If the public views the vaccine to be less effective, the effect could be much more dramatic among the super-spreading population. This could result in vaccination strategies to become ineffective, even with public health taking the extra measures to reduce incidence. Even in the worst case scenario of super-spreaders not vaccinating, there are still issues surrounding the effectiveness of ring vaccination in communities where social influence is strong.

5.2 Future Research

The current ring vaccination model (Chapter 2) consists of a simple network where there is no connection or clustering among the contacts. It has been found that clustering appears in social networks [12, 13, 14, 15], and past models have shown that clustering can have a profound impact on \mathcal{R}_0 [16]. To determine the effectiveness of voluntary ring vaccination, clustering should be considered; this would provide a better assessment of the effectiveness

of ring vaccination when implemented in reality.

As brought to attention by Ref [17] and Ref [18], most network models currently assume a static network. Dynamic networks would not only have an impact on the spread of a disease, but also on the distribution of behaviour. The issues with modelling dynamic networks are the assumptions made about making and breaking connections in the network. There is insufficient data about how individuals change contacts over time. However, understanding the effect of an evolving network is important in determining the effectiveness of control measures implemented by public health. One could assume a social network slowly evolves over time, whereas a contact network could change daily.

This issue of dynamic networks also leads to a separate network modelling issue: the overlap of social and contact networks. Ref [19] indicates network overlap has a significant effect on the spread of disease and size of an epidemic. This as well would have a strong impact on how behaviour is distributed throughout the network. No longer would individuals share similar infection experiences due to the fact they may not be in the same contact network. In today's society with better technology and social media, it is becoming more apparent that models should consider a separate social and contact network.

There were many assumptions made regarding behaviour in this thesis due to the lack of information pertaining to behaviour and how it evolves over time. To be able to parameterize these behaviour models properly, data pertaining to how perceived vaccine efficacy evolves over time and specific events and how an individual's risk perceptions evolve over time pertaining to personal and social infection/vaccination events would be very beneficial. With this information one could make more accurate predictions pertaining

to how long it will take to recover from a vaccine scare or how long a population is influenced by a pandemic to vaccinate.

Pair approximation models are useful in spatial networks or clustered networks [20]; however, there has been little work where vaccination behaviour and incidence is coupled in a pair approximation model. Using pair approximations we can apply better analysis techniques to provide greater and further understanding of the feedback occurring between behaviour and incidence.

Understanding the formation social networks, as well as vaccination opinions is a pressing issue for public health in determining optimal control strategies. With the complexities associated with social networks and human behaviour the optimal strategy is not always apparent. The use of behaviour-incidence network models provides public health with some intuition as to what the best strategy may be. However, in reality, networks and behaviour are always evolving and future models should take this into consideration.

Bibliography

- [1] J.C. Baker. The pertussis vaccine controversy in great britain, 1974-1986. Vaccine, 21:25–26, 2003.
- [2] M.H. Merrill, A.C. Hollister, S.F. Gibbens, and A.W. Haynes. Attitudes and reactions of the public to health programs ii. attitudes of californians toward poliomyelitis vaccination. Am J Public Health Nations Health, 48(2):146–152, 1958.
- [3] V.A.A. Jansen, N. Stollenwerk, H.J. Jensen, M.E. Ramsay, W.J. Edmunds, and C.J.

Rhodes. Measles outbreaks in a population with declining vaccine uptake. Science, 301(5634):804, 2003.

- [4] A. Nicoll, D. Elliman, and E. Ross. Mmr vaccination and autism 1998. BMJ, 316(7133):715–716, 1998.
- [5] G.A. VanEssen, M.M. Kuyvenhoven, and R.A. DeMelker. Why do healthy elderly people fail to comply with influenza vaccination? Age Ageing, 26(4):275–279, 1997.
- [6] T.F. Jones, I.L. Amanda, A.S. Craig, and W. Schaffner. Determinants of influenza vaccination, 20032004: Shortages, fallacies and disparities. Clin Infect Dis., 39(12):1824–1828, 2004.
- [7] G. Chapman and E. Coups. Predictors of influenza vaccine acceptance among healthy adults. Preventive Medicine, 29(4):249–262, 1999.
- [8] H.S. Canning, J. Phillips, and S. Allsup. Health care worker beliefs about influenza vaccine and reasons for non-vaccination a cross-sectional survey. Journal of Clinical Nursing, 14(8):922–925, 2005.
- [9] C.T. Bauch and D.J.D. Earn. Vaccination and the theory of games. PNAS, 101(36):13391–13394, 2004.
- [10] R. Vardavas, R. Breban, and S. Blower. Can influenza epidemics be prevented by voluntary vaccination? PLoS Comput Biol, 3(5):e85, 2007.
- [11] A. Perisic and C.T. Bauch. Social contact networks and disease eradicability under voluntary vaccination. PLoS Comput Biol, 5(2):e1000280, 2009.

- [12] F. Liljeros, C.R. Edling, L.A. Nunes Amaral, H. E. Stanley, and Y. Aberg. The web of human sexual contacts: Promiscuous individuals are the vulnerable nodes to target in safe sex campaigns. *Nature*, 411:907–908, 2001.
- [13] M.E.J. Newman and J. Park. Why social networks are different from other types of networks. *Physical Review E*, 68:036122, 2003.
- [14] M.E.J. Newman. The structure of scientific collaboration networks. *PNAS*, 98(2):404–409, 2001.
- [15] R.M. May. Network structure and the biology of populations. *TRENDS in Ecology and Evolution*, 21(7):394–399, 2006.
- [16] M. Keeling. The implications of network structure for epidemic dynamics. *Theoretical Population Biology*, 67:1–8, 2005.
- [17] M.J. Keeling and K.T.D. Eames. Networks and epidemic models. *J. R. Soc. Interface*, 2:295–307, 2005.
- [18] S. Bansal, J. Read, B Pourbohloul, and L.A. Meyers. The dynamic nature of contact networks in infectious disease epidemiology. *Journal of Biological Dynamics*, 4(5):478–489, 2010.
- [19] S. Funk, E. Gilad, C. Watkins, and V.A.A. Jansen. The spread of awareness and its impact on epidemic outbreaks. *PNAS*, 106(16):6872–6877, 2009.
- [20] S. Bansal, B.T. Grenfell, and L.A. Meyers. When individual behaviour matters: homogeneous and network models in epidemiology. *J. R. Soc. Interface*, 4:879–891, 2007.