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

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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-influenzal influenza-like illness (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 reminding individuals about their previous influenza infections, as well as communicating facts about vaccine efficacy and the difference between influenza and niILI, may be an effective way to increase vaccine coverage and prevent unexpected drops in coverage.

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Introduction

Influenza continues to significantly impact morbidity, mortality, and economic outcomes in many populations (Lee et al., 2002; Nichol, 2001; Schoenbaum, 1987; Szucs, 1999). The primary intervention for influenza infection is vaccination (CDC, 2012a). However, influenza vaccine coverage remains below optimal levels in many populations (Nichol, 2001; Kwong et al., 2007). 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 (Chapman and Coups, 2006; Kwong et al., 2007). 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 (Fiore et al., 2010)—can shape the individual’s assessment of vaccine risk and ultimately their future vaccinating decisions (Chapman and Coups, 1999, 2006; Bordon, 2010). Concerns about vaccine safety and efficacy were also a cause of low uptake of pandemic H1N1 vaccines in 2009 (Bordon, 2010). 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 (Chapman and Coups, 2006). Personal infection history also matters: an individual having had a recent influenza infection is positively correlated with their seeking influenza vaccination (Chapman and Coups, 1999).

Influenza-like-illnesses (ILI) impose a considerable health burden on populations (Akazawa et al., 2003; CDC, 2012b). A large portion of ILI is actually caused by pathogens other than influenza...
virus, and influenza vaccine does not offer protection against such non-influenzal IILI (niILII) (Akazawa et al., 2003; Rothberg et al., 2008). However, the presence of niILII in a population can potentially influence vaccinating behaviour for influenza. Symptoms of niILII are very similar to influenza, therefore, many cases of niILII may be mistaken for influenza. As a result, individuals who become vacci-
nated for influenza but experience niILII anyway may think that the influenza vaccine is not efficacious. Alternatively, experiencing niILII 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 unnec-
essary vaccine surpluses, and it also creates uncertainty regarding where to allocate potentially limited vaccine supplies (Fedson, 2003). In Canada for instance, vaccine coverage has been gradually increasing over the past decade and manufacturers have been expanding capacity accordingly (Kwong et al., 2007). However, in other instances, demand for influenza vaccine has surged beyond what was expected (Treanor, 2004).

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 (Merrill et al., 1958). Similarly, it has been found that vaccine sentiments are clustered on social media networks (Salathe and Kandelwal, 2011).

An increasing number of mathematical models analyse how vaccine coverage emerges from the interplay between infection dynamics and individual vaccinating decisions (Bauch and Earn, 2004; Bauch, 2005; Reluga et al., 2006; Galvani et al., 2007; Funk et al., 2009; Perisic and Bauch, 2009; Vardavas et al., 2010; Xia, 2009; Fu et al., 2011; Cornforth et al., 2011; Wells et al., 2011; Bauch and Bhattacharyya, 2012). These models typically couple a model of transmission dynamics (Weycker et al., 2005; Dushoff et al., 2007; Qiu and Feng, 2010) 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 (Funk et al., 2009; Perisic and Bauch, 2009; Xia, 2009; Fu et al., 2011; Cornforth et al., 2011), and among these, several furthermore assume that history of infection can directly influence future vaccine decisions (Xia, 2009; Fu et al., 2011; Cornforth et al., 2011). 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) (Cornforth et al., 2011), while in others it is the individual’s own history of infection that matters (Xia, 2009; Fu et al., 2011), although in some cases the individual’s memory of their past infec-
tions is retained only over the past flu season (Fu et al., 2011). The impact of infection history has also been explored in homogeneous mixing (non-network) models (Vardavas et al., 2010). 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 (Bauch, 2005; Cornforth et al., 2011). 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 coverage is relevant to determining how they can be used in design-
ing optimal non-mandatory vaccine policies, by suggesting suitable model structure and parameterisation.

Influenza transmission models must often contend with the confounding effects of niILII (Orenstein et al., 2007; Chowell et al., 2011; van Noort et al., 2012). However, the impact of niILII on behaviour–incidence dynamics has not been explored to a signifi-
cant extent, despite the fact that niILII 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 (Salathe and Bonhoeffer, 2008; Fu et al., 2011), including whether this clustering has implications for disease control (Salathe and Bonhoeffer, 2008). 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 popu-
lation vaccine coverage is sufficient to eliminate the infection (Salathe and Bonhoeffer, 2008). The structure of non-vaccinator clusters can also be influenced by how likely individuals are to copy successful strategies (Fu et al., 2011). Under conditions where individuals on a network imitate their neighbours, it is easy to see how clusters of vaccinators and non-vaccinators can arise. How-
ever, 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 transmis-
sion 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 niILII 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.

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 $\delta$ 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 $\rho$ per season, representing the effects of antibody loss and antigenic drift. Similarly, each vaccinated individual loses vaccine immunity $(V \rightarrow S)$ with prob-
ability $\omega$ per season. Individuals do not know whether or not
they have lost their vaccine immunity. Lastly, a proportion \( l(0) \) 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 \( \alpha \) of nILI in a given season from a log-normal distribution with mean \( \langle \alpha \rangle \) and variance \( \langle \alpha^2 \rangle \).

\[
\alpha \sim \ln N(\mu, \sigma^2) \tag{1}
\]

\[
\mu = \ln \langle \alpha \rangle - \frac{1}{2} \ln \left( 1 + \frac{\langle \alpha^2 \rangle}{\langle \alpha \rangle^2} \right) \tag{2}
\]

\[
\sigma^2 = \ln \left( 1 + \frac{\langle \alpha^2 \rangle}{\langle \alpha \rangle^2} \right) \tag{3}
\]

where the probability of an individual experiencing nILI is \( \alpha \). We assumed that individuals experience influenza and nILI independently from one another. We also assumed that an individual will mistake nILI for influenza with probability \( \beta \), hence the average number of nILI cases relevant to vaccine decision making is simply \( \langle \alpha \rangle \beta \). (We note that one could instead sample the percentage of individuals experiencing nILI 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 according 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

\[
P_V = L - c_{vacc} - c_{inf} (1 - \varepsilon(t)) \tag{4}
\]

where \( c_{inf} \) is the cost of infection, \( c_{vacc} \) 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

\[
P_N = L - c_{inf}. \tag{5}
\]

Each season, the individual will vaccinate if \( P_V > P_N \), otherwise non-vaccination is the more appealing choice.

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

\[
c_{vacc} = c_{vacc} + c_{vacc} e^{-mT_c} \tag{6}
\]

where \( c_{vacc} \) 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 \( c_{vacc} \) 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 \( \gamma \), hence \( T_c = T_c(\gamma) \) is a function of \( \gamma \).

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

\[
c_{inf} = c_{inf} e^{-mT_i} \tag{7}
\]

where \( T_i \) is the time since the individual's most recent infection (either with true influenza, or with a case of nILI that has been mistaken for influenza) and \( m_{inf} \) 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

\[
\varepsilon(t) = \left\{ \begin{array}{ll} 
\xi & \text{if 'unsuccessful'} \\
1 - \varepsilon & \text{if 'successful'} \\
1 - e^{-m/\xi} & \text{if did not vaccinate} \end{array} \right. \tag{8}
\]

where \( \xi \) 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 \( \varepsilon \). 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 \( (m/\xi) \) 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 \( \varepsilon \). This quantity influences transmission dynamics explicitly, but also perceived vaccine efficacy implicitly through the 'successful' outcome of Eq. (8).

We can substitute Eqs. (6) and (7) into the payoff functions, Eqs. (4) and (5), to obtain the history dependent payoff functions

\[
P_V = L - c_{vacc} e^{-mT_c} - c_{inf} e^{-mT_i} (1 - \varepsilon(t)) \tag{9}
\]

\[
P_N = L - c_{inf} e^{-mT_i}. \tag{10}
\]

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 \( T_c \). 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.
Table 1
Parameter definitions and baseline parameter values used in the simulations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>Number of individuals in network</td>
<td>10,000</td>
<td>Assumption</td>
</tr>
<tr>
<td>$k$</td>
<td>Average node degree</td>
<td>10</td>
<td>Assumption</td>
</tr>
<tr>
<td>$R_0$</td>
<td>Initial number of infected individuals per season</td>
<td>10</td>
<td>Assumption</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Average incidence for nilI</td>
<td>0.12</td>
<td>Fleming and Ayres (1988)</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>Variance of incidence for nilI</td>
<td>0.000064</td>
<td>calibrated $^1$</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Probability of an individual mistaking nilI for influenza</td>
<td>0.50</td>
<td>Assumption</td>
</tr>
<tr>
<td>$L$</td>
<td>Baseline payoff</td>
<td>1</td>
<td>Assumption</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Probability of moving from state $I$ to state $R$, per day</td>
<td>0.20</td>
<td>Lee et al. (2002), Earn et al. (2002)</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Probability of moving from state $R$ to state $S$, per season</td>
<td>0.25</td>
<td>Earn et al. (2002), Longini et al. (2000), and Cox et al. (2004)</td>
</tr>
<tr>
<td>$\omega$</td>
<td>Probability of moving from state $V$ to state $S$, per season</td>
<td>0.50</td>
<td>Ambrose et al. (2008)</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Actual vaccine efficacy</td>
<td>0.70</td>
<td>Bridges et al. (2000) and Demicheli et al. (2007)</td>
</tr>
<tr>
<td>$\epsilon^p$</td>
<td>Minimum perceived vaccine efficacy</td>
<td>0.25</td>
<td>Assumption</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Probability of experiencing vaccine complications, per vaccination</td>
<td>0.01</td>
<td>Nichol (2001)</td>
</tr>
<tr>
<td>$c_{vac}$</td>
<td>Minimum cost of vaccination</td>
<td>0.0015</td>
<td>Calibrated; Lee et al. (2002), Nichol (2001), Bridges et al. (2000), and Meltzer et al. (1999)</td>
</tr>
<tr>
<td>$c_{comp}$</td>
<td>Additional cost of vaccination due to a complication</td>
<td>0.0035</td>
<td>Calibrated $^1$; Lee et al. (2002), Nichol (2001), Bridges et al. (2000), and Meltzer et al. (1999)</td>
</tr>
<tr>
<td>$\rho_t$</td>
<td>Probability of transmitting infection along edge per day</td>
<td>0.055</td>
<td>Calibrated $^1$; Bridges et al. (2000) and Couch (1993)</td>
</tr>
<tr>
<td>$c_{max}$</td>
<td>Maximum cost of infection</td>
<td>0.0055</td>
<td>Lee et al. (2002), UBLS (2011) and Keech et al. (1998)</td>
</tr>
<tr>
<td>$m$</td>
<td>Memory decay rate, per season</td>
<td>0.25</td>
<td>Assumption</td>
</tr>
<tr>
<td>$\xi$</td>
<td>Vaccine efficacy memory decay rate factor</td>
<td>4</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

$^1$ The values for $c_{comp}$ and $c_{max}$ were calibrated within plausible ranges from empirical data on vaccine complication risks from Refs. Lee et al. (2002) and Bridges et al. (2000), to obtain a vaccine coverage of approximately 40% for the baseline scenario.

$^2$ $p$ was calibrated to obtain a 15% infection rate on average in each season, in the absence of vaccination Bridges et al. (2000), Couch (1993), Keitel et al. (1997), and Molinari et al. (2007); this corresponds to basic reproduction number $R_0 = 2.2$ Meyers (2006), Miller (2007), and Anderson (1997).

$^3$ The value of $\alpha$ was calculated by determining the ratio of nilI cases to influenza cases in Fleming and Ayres (1988) then multiplying that ratio by 15% to obtain $\alpha$.

$^4$ 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 $\sigma^2$.

Results

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 (Fig. 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 $V(t+1)$ (Fig. 1(a)). The dynamics also exhibit occasional periods where vaccine coverage is relatively constantly 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 (Fig. 1(b)).

(c) Constant vaccine coverage

When payoffs are such that vaccination is more appealing, vaccine coverage is higher than the baseline case, and relatively constant (Fig. 1(c)). 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 (Fig. 1(d)). 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 is 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 nilI on vaccinating decisions, especially for parameter values $\omega = 1$ and $\epsilon = 0.90$ (Fig. 1(e)). 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 (Fig. 1(f)). 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.)

Determinants of vaccinating behaviour–incidence dynamics

In this section we explore how model parameter values drive behaviour–incidence dynamics. We will consider two cases for the remainder of the paper: (1) nillI can be mistaken for influenza (0 < β ≤ 1, containing our baseline assumption) and (2) nillI is never mistaken for influenza (β = 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 Fig. 2.

Case 0 < β ≤ 1

As the proportion β of nillI 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 (ω) produces a similar result. This surprising result occurs because when β is higher and thus nillI is more often mistaken for influenza, vaccination is spread more evenly through the population over time: individuals who vaccinated and experienced nillI 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 nillI, 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.
Fig. 2. 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).

As a result of the possibility of mistaking nilILI for true influenza, increasing β (⟨σ⟩) also decreases the perceived vaccine efficacy ε(t) (Supplementary Figure 1a)). ε(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, ε(t) is also higher when the minimum perceived vaccine efficacy ε is higher or when the actual vaccine efficacy ε is higher; other parameters have little impact on ε(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 resistance with respect to vaccine coverage: an increase in vaccine efficacy makes vaccine more attractive (Eq. (4)), 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.
Table 1
The statistics for the vaccination coverage ($\langle \psi(t) \rangle$) and influenza incidence ($\langle i(t) \rangle$), where $\langle \cdot \rangle$ denotes the average and $\sigma^2(\cdot)$ denotes the variance, over time. All other parameter values for each case are the same as the baseline case.

<table>
<thead>
<tr>
<th>Case</th>
<th>$\langle \psi(t) \rangle$</th>
<th>$\sigma^2(\langle \psi(t) \rangle)$</th>
<th>$\langle i(t) \rangle$</th>
<th>$\sigma^2(\langle i(t) \rangle)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.4147</td>
<td>0.0022</td>
<td>0.0799</td>
<td>0.0057</td>
</tr>
<tr>
<td>$m = 0.01$</td>
<td>0.2039</td>
<td>5 x $10^{-5}$</td>
<td>0.1089</td>
<td>0.0079</td>
</tr>
<tr>
<td>$m = 0.10$</td>
<td>0.4085</td>
<td>0.0007</td>
<td>0.055</td>
<td>0.0031</td>
</tr>
<tr>
<td>$m = 0.01$ and $z = 0.65$</td>
<td>0.6304</td>
<td>3 x $10^{-5}$</td>
<td>0.0116</td>
<td>0.0001</td>
</tr>
<tr>
<td>$m = 0.10$ and $z = 0.65$</td>
<td>0.5997</td>
<td>0.0004</td>
<td>0.0213</td>
<td>0.0005</td>
</tr>
<tr>
<td>$\omega = 0.05$</td>
<td>0.2171</td>
<td>5 x $10^{-5}$</td>
<td>0.0043</td>
<td>6 x $10^{-6}$</td>
</tr>
<tr>
<td>$\omega = 0.05$ and $\beta = 0$</td>
<td>0.1419</td>
<td>0.0018</td>
<td>0.02954</td>
<td>0.0011</td>
</tr>
<tr>
<td>$\omega = 1$</td>
<td>0.4529</td>
<td>0.0026</td>
<td>0.1013</td>
<td>0.0084</td>
</tr>
<tr>
<td>$\omega = 1$ and $\beta = 0$</td>
<td>0.4664</td>
<td>0.0089</td>
<td>0.1114</td>
<td>0.01442</td>
</tr>
<tr>
<td>$\varepsilon = 0.5$</td>
<td>0.2565</td>
<td>0.0014</td>
<td>0.1059</td>
<td>0.0077</td>
</tr>
<tr>
<td>$\varepsilon = 0.95$</td>
<td>0.3989</td>
<td>0.0027</td>
<td>0.0644</td>
<td>0.0045</td>
</tr>
<tr>
<td>$m = 1.5$</td>
<td>0.1684</td>
<td>0.0111</td>
<td>0.1291</td>
<td>0.0117</td>
</tr>
<tr>
<td>$m = 1.5$ and $\beta = 0$</td>
<td>0.1391</td>
<td>0.0135</td>
<td>0.14</td>
<td>0.0135</td>
</tr>
<tr>
<td>$\beta = 0$</td>
<td>0.414</td>
<td>0.0046</td>
<td>0.0945</td>
<td>0.0077</td>
</tr>
<tr>
<td>$\beta = 1$</td>
<td>0.4217</td>
<td>0.0012</td>
<td>0.0664</td>
<td>0.0041</td>
</tr>
<tr>
<td>$\varepsilon = 0.27$</td>
<td>0.4164</td>
<td>0.0022</td>
<td>0.0797</td>
<td>0.0057</td>
</tr>
<tr>
<td>$\varepsilon = 0.28$</td>
<td>0.4756</td>
<td>0.0024</td>
<td>0.0657</td>
<td>0.0045</td>
</tr>
<tr>
<td>$\varepsilon = 0.60$</td>
<td>0.4906</td>
<td>0.0022</td>
<td>0.0612</td>
<td>0.0038</td>
</tr>
</tbody>
</table>

Increasing the minimum perceived vaccine efficacy ($\varepsilon$) increases the vaccination coverage, but only up to a threshold $\varepsilon \approx \text{cost/Inf}$ (i.e., $P_V < P_{RV}$ when $\varepsilon(t) = \varepsilon$ and there has been no recent vaccine complication), after which vaccine coverage no longer changes with further increases in $\varepsilon$ (Table 2).

When the probability of vaccine complications ($\gamma$) increases significantly from the baseline values, vaccine coverage declines (as expected) but both vaccine coverage and infection dynamics also become more variable and a ‘coast-tail’ pattern emerges (Fig. 2(b)). 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% (Fig. 2(b)).

Changes in the memory decay rate ($m$) can strongly impact model dynamics. Longer-term memory (lower $m$) strongly stabilizes vaccine coverage (Fig. 2(c) and (d)) whereas shorter-term memory (higher $m$) results in a ‘coast tail’ pattern of extreme variability (results not shown). Decreasing $m$ stabilizes 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 (Fig. 2(d)) 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 ($\varepsilon$) is increased then it is possible to obtain vaccine coverage that is both high and stable, even when $m = 0.01$ (Fig. 2(e); Table 2).

The value of $\omega$ (waning vaccine immunity) does not directly impact the payoff functions in Eqs. (4–5) but does have an impact on the vaccine coverage. As $\omega$ decreases (immunity wanes slower) the vaccine coverage decreases and stabilizes (Fig. 2(f)). 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 $\omega$ 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 to 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 $\psi$ 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 $\psi$ 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 nilILI 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 section (case $0 < \beta \leq 1$).

The effects of changing $\omega$ (probability of vaccine waning immunity) are dramatically different when $\beta = 0$. There is still a decrease in vaccine coverage as $\omega$ decreases. However, compared to the $\beta > 0$ case, vaccine coverage is more variable and sporadic outbreaks can occur (Fig. 2(g) vs. Fig. 2(f)). This occurs because the additional vaccination from the mistaken nilILI 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 $\omega$ increases, vaccine coverage becomes even more variable than the case where $\beta > 0$ (Fig. 2(h) vs. Table 2).

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 $R(1) (-1 \leq R(1) \leq 1)$. To calculate the auto-correlation for the time series of vaccinating individuals from time $t = 1$ to time $t = T$ we use

$$
R(1) = \frac{\sum_{i=1}^{T-1} (V(i) - \langle V(i) \rangle)(V(i+1) - \langle V(i) \rangle)}{(T-1)(\langle V(i) \rangle)^2},
$$

where $\langle V(i) \rangle$ is average vaccine coverage from $t = 1$ to $t = T$, $\langle V(i) \rangle$ is the variance of the vaccine coverage from $t = 1$ to $t = T$ and $V(i)$ corresponds to the vaccine coverage is season i. Positive values of $R(1)$ 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 $R(1)$ 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.

Case $0 < \beta \leq 1$

Vaccine coverage tends to be more stable (higher $R(1)$) when vaccine immunity lasts longer ($\omega$ is smaller), the cost of infection is
The plot of the auto-correlation ($R(1)$) for a variety of parameters. (a) $m$ vs. $c_{\text{inf}}$ with $\beta = 0$; (b) $m$ vs. $\omega$; (c) $\omega$ vs. $\epsilon$ with $\beta = 0$; (d) $\omega$ vs. $\epsilon$; (e) $c_{\text{vac}}$ vs. $\epsilon$ with $\beta = 0$ and (f) $c_{\text{inf}}$ vs. $\epsilon$.

higher ($c_{\text{inf}}$ is larger), or when memory lasts longer ($m$ is smaller) (Fig. 3(b), (d), and (f)). The impact of $m$ is particularly strong (Fig. 3(b)). 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 ($\gamma$) or the cost of vaccine complications ($c_{\text{vac}}$) 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 $c_{\text{inf}}$, changes in $\gamma$ or $c_{\text{vac}}$ have little effect because vaccine complications are rare. Hence, a greater contribution to vaccine decision making is the minimum cost of vaccination, $c_{\text{vac}}$, which is always applied upon vaccination (unlike $c_{\text{inf}}$).

An increase in $\epsilon$ can either increase or decrease the autocorrelation (Supplementary Figure 3). The dual effect of changes in $\epsilon$ 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 $m$, $\omega$, or $c_{\text{inf}}$ do not impact the strength of herd immunity, and hence changes in those parameters result in unequivocal changes in stability (Fig. 3).

For some parameter combinations, vaccination can become sufficiently unattractive that vaccine coverage stabilizes by virtue of dropping to low values and staying there. This occurs when both cost of infection $c_{\text{inf}}$ and vaccine efficacy $\epsilon$ are very low, or when the probability of complications $\gamma$ is high and the vaccine efficacy $\epsilon$ is low (results not shown).

Case $\beta = 0$

Vaccine coverage stability in the case where individuals cannot mistake nILI for influenza ($\beta = 0$; Fig. 3(a), (c), and (e)) is broadly similar to stability in the case where they can ($\beta > 0$; Fig. 3(b), (d), and (f)). However, vaccine coverage is generally less stable (lower $R(1)$ values) when $\beta = 0$. This mirrors results seen in previous sections (e.g., Fig. 2(g) vs. (f)). This effect is attributable to the random nature of nILI 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 Fig. 3(c) ($\beta = 0$) for $\omega = 1$, $\epsilon = 0.9$, that does not appear in Fig. 3(d) ($\beta > 0$). 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 (Fig. 1(e)). When nILI 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 $c_{\text{inf}}$ and large $m$ for both $\beta = 0$ and $\beta > 0$ cases (Fig. 3(a) and (b)) corresponds to a 2-cycle (Fig. 1(d)).

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

$$C_{AB} = \frac{N}{n} \frac{[AB]}{[A][B]},$$

(12)

where $N$ 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, $N$) (Keeling et al., 1997; Keeling, 1999).

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

We measured $C_{VV}$, $C_{VN}$ and $C_{NN}$ from the model simulations. We also measured $C_{VW}$, $C_{VN}$ and $C_{NN}$ 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 (Fig. 4(a)–(c), (e), and (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 $e_{mI}$). 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 $e_{mI}$ can increase assortativeness simply by making vaccinators rare, however, the decline in $e_{mI}$ is very steep, requiring $e_{mI} < e_{wI}$. As the probability of symptomatic infection decreases ($\psi \rightarrow 0$) the pair correlations become randomly distributed because vaccination becomes increasingly dependent on nilLI mistaken for influenza (Supplementary Figure 4a).

Case $\beta = 0$

When nilLI cases are not mistaken for influenza, assortativeness is stronger (Fig. 4(d), (f), and (b)). This occurs because the random influence of nilLI on vaccinating decisions is removed. The difference are particularly pronounced for $m$ and $\omega$. When $\beta = 0$, $C_{VV}$ can be large for small $\omega$ 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 Fig. 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 $\psi$ causes correlations to disappear even in the absence of nilLI because there is less perceived influenza infection, and hence infection history becomes a less important driver of vaccine uptake.

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 (Cornforth et al., 2011) 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 frequent outbreaks are possible with a vaccine that confers long-term protective immunity (Vardavas et al., 2010), which also occurs in our model, but only if the effects of nilLI 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 (Bauch, 2005; Reluga et al., 2006). 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 (Trenor, 2004). 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 vaccine 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 nilLI effects did not significantly impact these trends.
Table 3
The pair correlation values for randomly distributed vaccinations and our model where $C_{NN}$ is the non-vaccinator–non-vaccinator pair correlation, $C_{VN}$ is the vaccinator–non-vaccinator pair correlation and $C_{VV}$ 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.

<table>
<thead>
<tr>
<th>Method</th>
<th>$\langle C_{NN} \rangle$</th>
<th>$\langle\langle C_{NN} \rangle\rangle$</th>
<th>$\langle C_{VN} \rangle$</th>
<th>$\langle\langle C_{VN} \rangle\rangle$</th>
<th>$\langle C_{VV} \rangle$</th>
<th>$\langle\langle C_{VV} \rangle\rangle$</th>
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</thead>
<tbody>
<tr>
<td>Randomly distributed</td>
<td>0.4999</td>
<td>2.45 $\times$ 10^{-6}</td>
<td>1.0004</td>
<td>1.97 $\times$ 10^{-3}</td>
<td>0.4997</td>
<td>1.16 $\times$ 10^{-5}</td>
</tr>
<tr>
<td>Model ($\beta=0.50$)</td>
<td>0.5228</td>
<td>3.05 $\times$ 10^{-5}</td>
<td>0.9366</td>
<td>8.90 $\times$ 10^{-3}</td>
<td>0.5458</td>
<td>1.42 $\times$ 10^{-4}</td>
</tr>
<tr>
<td>Model ($\beta=0$)</td>
<td>0.5451</td>
<td>8.01 $\times$ 10^{-5}</td>
<td>0.8728</td>
<td>1.84 $\times$ 10^{-4}</td>
<td>0.5983</td>
<td>1.83 $\times$ 10^{-3}</td>
</tr>
</tbody>
</table>

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 (Salathe and Bonhoeffer, 2008; Fu et al., 2011). 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.

Fig. 4. The pair correlation values across a range of parameter values: (a) probability of niILI being mistaken for influenza ($\beta$), (b) the average incidence of niILI ($\alpha$), (c) memory decay rate ($m$), (d) memory decay rate ($m$) with $\beta=0$, (e) vaccine waning immunity ($\omega$), (f) vaccine waning immunity ($\omega$) with $\beta=0$, (g) maximum cost of infection ($c_{inf}$) and (h) maximum cost of infection ($c_{inf}$) with $\beta=0$. The pair correlation $C_{NN}$ is the black line, $C_{VN}$ is the red line and $C_{VV}$ is the green line. The vertical line in (g) and (h) represents where $c_{inf} = c_{vac}$, i.e. $c_{inf} = c_{vac} + c_{vac}$. 
although the presence of nullI considerably weakens the correlations.

Unlike many previous behaviour–incidence models for influenza, we attempted to account for the effects of nullI being mistaken for true influenza. By virtue of weakening the feedback between influenza vaccinating behaviour and influenza transmission dynamics, the presence of nullI generally served to stabilise vaccine coverage and reduce strategy correlations on the network. nullI could often boost vaccine coverage if individuals mistook nullI for influenza and were thus motivated to seek influenza vaccine in the next season. However, nullI could also reduce vaccine coverage in other scenarios, if individuals acquired an influenza vaccine, subsequently experienced nullI, 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 (Fu et al., 2011); the individual's vaccinating decisions depends on the individual's personal history of infection, rather than on the entire population's history (Cornforth et al., 2011); we assume that individuals do not use social learning or imitation in their decision-making (Bauch, 2005; Fu et al., 2011; Cornforth et al., 2011); we assume individuals do not know their immune status, as opposed to knowing whether vaccine immunity has wanted (Vardavas et al., 2010); and we consider transmission as occurring on a network rather than using traditional compartmental approaches (Vardavas et al., 2010).

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 (Chapman and Coups, 1999). 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 (Salathe and Bonhoeffer, 2008; Fu et al., 2011), 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 (Salathe and Bonhoeffer, 2008).

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 (Bauch and Earn, 2004; Vardavas et al., 2010; Wells et al., 2011; Salathe and Bonhoeffer, 2008; Poletti et al., 2009; Perisic and Bauch, 2009). We neglected age structure for the sake of simplicity, but also because we were not addressing issues of targeted, age-specific vaccine strategies (Dushoff et al., 2007; Miller et al., 2008; Mylius et al., 2008).

We made assumptions about the psychology of vaccine decision-making that are consistent with the existing literature regarding determinants of vaccine uptake (Chapman and Coups, 1999). 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 parameterised. 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 (Szilagyi et al., 2000).

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 (Kaiser, 2006, 2004; Fiers et al., 2004). In the absence of nullI effects, occasional sporadic outbreaks were still possible with long-term vaccine immunity (Vardavas et al., 2010), but these outbreaks disappeared when the influence of nullI 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 informing influenza immunisation policies in many countries.

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 $T_j = -1$
6. Repeat Step 3 to Step 5 until the infection dies out
7. Sample the percentage of nilLI cases in the population, denote as $\alpha$
8. Determine whether the individual experiences nilLI (probability $\alpha$)
   (a) Determine whether the individual mistakes nilLI for influenza (probability $\beta$)
      i. If nilLI mistaken for influenza set $T_j = -1$

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

1. Increase $T_j$ 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 $\rho$)
4. Determine who loses vaccine immunity and becomes susceptible (probability $\omega$)
5. Calculate $P_\lambda$ and $P_\lambda'$ to determine who vaccinates (i.e., $P_\lambda > P_\lambda'$)
   (a) If vaccination occurs
      i. Determine whether the vaccine was effective (probability $\epsilon$); if vaccine successful then the individual is no longer susceptible for this season
      ii. Determine whether the individual experienced a vaccine complication (probability $\gamma$); if experienced a vaccine complication then set $T_j = -1$
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 $T_j = -1$
(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 nilLI cases in the population, denote as $\alpha$
12. Determine whether the individual experiences nilLI (probability $\alpha$)
    (a) Determine whether the individual mistakes nilLI for influenza (probability $\beta$)
       i. If nilLI mistaken for influenza set $T_j = -1$
       ii. If the individual vaccinated set their perceived vaccine efficacy to the minimum
13. Start back at Step 1

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2012.06.002.

References


