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Abstract

Background: Human influenza is characterized by seasonal epidemics, caused by rapid viral adaptation to population immunity. Vaccination against influenza must be updated annually, following surveillance of newly

decreasing the number of hosts in which the virus may replicate.

States labelled with I denote symptomatic infection, and those labelled with A denote asymptomatic infection. The P states describe immunity to one strain but not the other: P_j is the state with immunity to strain j ($j = 1, 2$), and R the state with immunity to both strains. In this model, we exclude co-infection: at any given time, an individual may be infected with at most one strain. State I_j denotes infection with strain j; and I_{jk} denotes previous infection with (and subsequent recovery from) strain j and current infection with strain k (where $k \neq j$). A similar notation applies to the A-classes. The efficacy of the vaccine against strain j is denoted by s_j.

Subscript 'V' denotes states of infection (or partial recovery) arising from failure of the vaccine; and as before, labels states with infection due to, or partial recovery from, one of the strains. Following vaccination, infection due to strain j occurs with probability $(1-s_j)$. In general, for seasonal influenza, the vaccine is targeted against the earlier-occurring strain 1 virus; its efficacy against the later-occurring strain 2 (mutated) virus is expected to be less, i.e., $s_2 < s_1$. As in [6], the delay T^* in appearance of strain 2 in the population is a parameter of the model.

In Figure 1, the diverging pairs of directed edges areIn Figue

then using the above expressions for b and R_0 we derive $\tau = 3.5\ d^{-1}$ for the transmission rate to be used in the simulations. The value of R_0 corresponding to this τ in the absence of vaccination is $R_0 = 2.34$.

In keeping with the definition of the two age class model (see Appendix), the estimates of death rates [18,19] arising from symptomatic or asymptomatic infection (d, d_A, respectively) for the two age-class model correspond to the general population above and below the median of the age distribution P_a which, for the city of Vancouver, is about 38 years [20]. We assume that the death rates due to natural causes are negligible, and choose nominal values for the disease-induced rates: $d(a_1) = d(a_2) = 0.002\ d^{-1}$ (Ref.[10]). These rates vary with the particular circulating influenza strains. Furthermore, we set $d = d_A$ in this illustrative study.

In the model described above, the total number of individuals $N_{k,a}$ in each (k,a) class is fixed, and hence the total population N (summed over all (k,a) classes) is constant. Therefore, by dividing the number of individuals in class (k,a) in state X at any given time by N, we may express the model in terms of the probability $X_{k,a}(t)$ that a randomly chosen individual is in state X, and belongs to class (k,a), at time t. The resulting set of ordinary differential equations describing this deterministic model is given in the Appendix.

Results

The initial state was specified as follows. For pre-vaccination, a prescribed fraction $V_0(a)$ of individuals in each age class a receive vaccination. Infection by strain 1 is introduced into fraction ε_1 of the remaining susceptibles residn res382T6-4(u)-1(3500002Td[377(in)-202(a)-285sid)1(ngle

of 5 for the mean field model, and a factor of 10 for the one age class network model. Again, this may be accounted for by the reduced transmissibility between different age classes. Notice also that, as in Figure 2, the two age class model exhibits a single peak of infection for both levels of vaccination.

In Figure 4, the two age class network model is used to explore the effects of vaccination during an epidemic outbreak, with no vaccination prior to the initial appearance of strain 1 infection, where vaccination rates are determined according to the "social response" to total

infection when $T^* = 10$ days and $\delta = 0.4$ (top left in Figure 4), there is only one peak of infection which occurs consistently at very similar times (50 days after

thereafter. Thus, for the parameter values used, it appears that vaccination is most effective around these values, with diminishing returns for higher V_0. Tables 6, 7 show that death rates due to pre-vaccination are lower than predicted for the entire range of vaccination rates during an epidemic; and in both cases the death rates decrease with increasing levels of vaccination. Analogous to the attack rates, there is a small increase in mortality for vaccination coverage around 20%, due to increased numbers of strain 2 infections at the expense of reduced numbers of strain 1 infections; however, the mortality rate drops sharply once

drop off sharply for higher coverage levels. This phenomenon is reminiscent of the development of drug resistance, where there is an optimal level of drug treatment (compare: vaccination coverage) that minimizes the overall infection [10]. This could have significant implications for vaccination strategies in realistic models of populations in which more than one strain is circulating.

It was found that increasing either pre-vaccination or vaccination during an outbreak, reduces the disease-induced mortality. Furthermore, pre-vaccination appears to be more effective than vaccination during an outbreak in reducing overall mortality, though this needs further investigation as it may depend critically on how the latter is implemented. This study considered only a simple model in which at any given time vaccination rates during an outbreak were governed by the total infection in the population at that time, and considers only vaccination of the susceptible class S, neglecting vaccination of other classes (e.g., P_1 and P_2 and asymptomatic cases).

As mentioned earlier, the particular form of the terms included in the model to incorporate local network structure and the effects of age classes was chosen for illustrative purposes. This approach, though, can be used on a specific population if sufficient data are available to determine realistic estimates of the age classes and network structure present and of the parameters of the model. The main difficulty is in determining the form of the two-point correlations between vertices of the contact network for a realistic particular population, and this must be derived indirectly from estimates of network structure extracted from the data [16]. An intermediate approach is to explore the effects of a few network structure parameters – e.g., clustering, associativity, betweenness, and centrality [7,16], obtaining expressions for the two-point probabilities defining the Markov network directly in terms of these parameters. This is currently under investigation.

Appendix: Effects of vaccination and population structure on influenza epidemic spread in the presence of two circulating strains

The various parameters in the model (Figure 1 of main text) are defined below:

τ = baseline transmission rate between a susceptible-infected pair

p = probability of developing symptomatic infection with no prior exposure

p_{V1}, p_{V2} = probabilities of pre-vaccinated individuals developing symptomatic infection from strains 1 and 2, respectively, with no prior exposure

σ_1, σ_2 = effectiveness of vaccine to strains 1 and 2, respectively

δ_{V1}, δ_{V2} = reduction in transmissibility of strains 1 and 2, respectively, for vaccinated individuals

p_{12} = probability of developing symptomatic infection with prior exposure to strain 1

p_{V12} = probability of pre-vaccinated individuals developing symptomatic infection with prior exposu9(w)4(ith1f46Tc9

for $U \in \{A_1, A_{V1}, I_1, I_{V1}, A_{21}, A_{V21}, I_{21}, I_{V21}, A_2, A_{V2}, I_2, I_{V2}, A_{12}, A_{V12}, I_{12}, I_{V12}\}$, denote the force of infection for age-class a and degree-class k. Here, $M(a,a')$ denotes the relative transmission coefficient between age-groups, so that $\tau M(a,a')$ = transmission coefficient between a susceptible individual of age-class a in contact with an infected individual of age-class a'. Also, $P(k',a'|k,a)$ is the probability that an individual (node) of age-class a and degree-class k has a neighbour (adjacent node) of age-class a' and degree-class k'.

In the special case that the contact network is the same for all age-classes, $P(k',a'|k,a) = P_a(a'|a)P(k'|k)$, where $P_a(a'|a)$ denotes the probability that an age-class a individual has an age-class a' neighbour. The two conditional distributions obey the conditions

$$\sum_{a'} P_a(a'|a) = 1;$$

$$\sum_{k'} P(k'|k) = 1.$$

In the general case, $\sum_{k'}\sum_{a'} P(k',a'|k,a) = 1$. If the node-degrees are uncorrelated, then $P(k'|k) = P_e(k')$, where $P_e(k)$ is the edge distribution [22], defined as the probability of randomly drawing an edge connected to a vertex of degree k. It is related to $P(k)$, the vertex distribution, by $P_e(k) = kP(k)/\bar{k}$. Similarly, if the age distributions are uncorrelated, then $P_a(a'|a) = P_a(a')$. Thus, for uncorrelated age-structured networks, which are considered in this paper, $P(k',a'|k,a) = P_a(a')P_e(k')$. In the present study, the degree distribution follows a scale-free form [7] $P(k) \sim k^{-\gamma}$.

$$\frac{\partial A_2}{\partial} = (1 - \quad)\left(\Theta + d_2 \Theta\right) - (m_A + \quad_A) A_2$$

$$\frac{\partial A_2}{\partial} = (1 - \quad_2)(1 - s_2)\left(\Theta + d_2 \Theta\right) - (m_A + \quad_A) A_2$$

$$\frac{\partial I_2}{\partial} = \left(\Theta + d_2 \Theta\right) - (m + \quad) I_2$$

$$\frac{\partial I_2}{\partial} = \quad_2 (1 - s_2)\left(\quad + \quad_2 \quad \right) - (\quad + \quad) I_2$$

$$\frac{\partial P_2}{\partial} = \quad I_2 + \quad A_2 - \quad_{21} P_2 \left(\quad + \quad_1 \quad \right)$$

∂P

Using this approximate relationship enables us to

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