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Antiviral stockpiles for influenza pandemics from the household perspective: Treatment alone versus treatment with prophylaxis

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ABSTRACT

Model-based studies of antiviral use to mitigate the impact of moderate and severe influenza pandemics implicitly take the viewpoint of a central public health authority. However, it seems likely that the key decision of when to use antivirals will be made at the household level. We used a stochastic compartmental model of the transmission of influenza within and between households to evaluate the expected mortality under two strategies: households saving available antivirals for treatment only and households implementing prophylaxis as well as treatment. Given that every individual in the population was allocated a single course of antivirals, we investigated the impact of these two strategies for a wide range of AVE_D, the efficacy of antivirals in preventing death in severe cases ($AVE_D = 1$ for complete protection). We found a cross-over point for our baseline parameter values in a regime where antivirals were still highly effective in reducing the chance of death: below $AVE_D = 0.9$ the optimal strategy was for households to use both treatment and prophylaxis. We also considered the possibility that a small number of households might "cheat" by choosing to follow the treatment-only strategy when other households were following treatment with prophylaxis. The cross-over point for cheating households was considerably lower, at $AVE_D = 0.6$, but substantially above 0. These results suggest that unless antivirals are almost completely effective in reducing the chance of death in serious cases, households will likely be better served implementing prophylaxis as well as treatment. More generally, our study illustrates the potential value of considering viewpoints other than a central authority when conducting model-based analysis of interventions against infectious disease.

Introduction

Between the 1997 outbreak of H5N1 influenza in Hong Kong and the 2009 H1N1 influenza pandemic, there was considerable interest in the stockpiling of antivirals in readiness for an influenza pandemic. It was envisaged that antivirals could be used both to attempt containment (Halloran et al., 2008; Ferguson et al., 2005) and, if containment failed, to mitigate the impact of the pandemic at the population level (Ferguson et al., 2006; Germann et al., 2006; Wu et al., 2009). Implicitly, these strategies were designed for moderate or severe pandemic strains. In the event, the 2009 pandemic was caused by a strain with a low overall infection mortality rate (Riley et al., 2011). Therefore, there was no opportunity to attempt containment (because the virus had spread too far before it was discovered; Lipsitch et al., 2009) and antivirals were used for mild cases only in the very early stages of the pandemic in the countries that did hold stockpiles (Ghani et al., 2009). However, recent laboratory studies of ferret-transmissible H5N1 influenza strains (Russell et al., 2012; Imai et al., 2012) highlight the need to prepare for moderate and severe pandemics.

Previous mitigation studies of pandemic influenza took the viewpoint that a central authority would decide the mode of use for stockpiles of antivirals. However, we suggest that the most important allocation decisions may be made at the household level. Our approach is motivated by observations during the 2009 pandemic that reactive distribution systems, where attempted, were slow, unpopular and expensive (Ghani et al., 2009). In the absence of effective and rapid central distribution systems, countries with large stockpiles designed for the general population will be left with little choice, in the event of a moderate or severe pandemic, other than to distribute the stockpile to households immediately prior to the arrival of the novel strain.

Whenever antivirals are available to a household, and the circulating strain is known to carry a substantial risk of death, any rational decision-maker would use the stockpile to treat symptomatic individuals. However, the choice between commencing the

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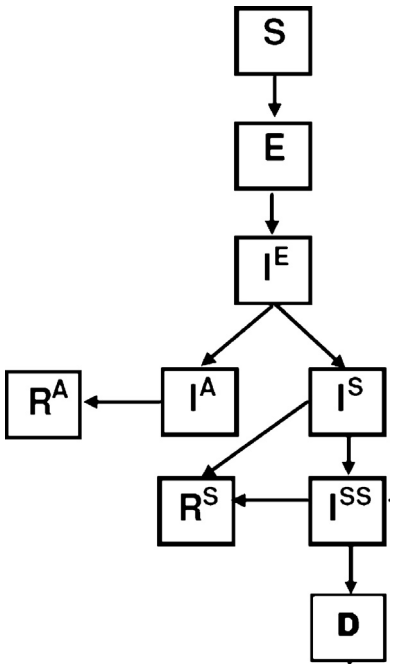

Fig. 1. Schematic of the assumed natural history for influenza. All states shown here (other than R^S) were duplicated in our model with one instance for individuals taking antivirals and one for individuals not taking antivirals.

use of antivirals for prophylaxis of not-yet-symptomatic individuals, or saving them to prolong treatment opportunities for severe cases is less obvious. Each household would have to weigh the potential benefits of averting infections against the future availability of treatment for those severely affected.

Here, we use a parsimonious mathematical model of influenza transmission in a population of households to address exactly this question. For transmission parameters that reflect the 2009 pandemic and a range of assumptions about severity, we attempt to obtain qualitative insight into the optimal strategy for within-household antiviral distribution during a moderate or severe pandemic.

Methods

A schematic of our assumed natural history is displayed in Fig. 1. Given that there are N_H households in the study population and there are n_i household members in ith household. The size of the population is N_p and is defined as the total number of individuals in households (i.e. $N_P = \sum_{i=1}^{N_H} n_i$). For those not receiving antivirals, at any time t, in the ith household there are $S_i(t)$ susceptible individuals, $E_i(t)$ exposed and infected but not yet infectious individuals, $I_i^E(t)$ early infectious individuals, $I_i^A(t)$ infectious asymptomatic individuals, $I_i^S(t)$ mildly symptomatic individuals, $I_i^{SS}(t)$ severely symptomatic individuals, $R_i^A(t)$ recovered individuals who were never symptomatic, $R_i^S(t)$ recovered individuals who were symptomatic, and $D_i(t)$ dead individuals. Similarly, at time t, the following compartments describe those who receive antiviral drugs: $S_i^D(t)$ susceptible individuals, $E_i^D(t)$ exposed and infected but not yet infectious individuals, $I_i^{ED}(t)$ early infectious individuals, $I_i^{AD}(t)$ infectious asymptomatic individuals, $I_i^{SD}(t)$ mildly symptomatic individuals and $I_i^{SSD}(t)$ severely symptomatic individuals. We assumed that individuals either died or recovered and that recovered individuals could not become susceptible again to the pandemic strain. Note that we distinguish between recovered symptomatic individuals $R_i^S(t)$ and recovered asymptomatic individuals $R_i^A(t)$ because the latter class would still receive prophylaxis and thus consume part of the household stockpile.

The overall force of infection $\lambda_i(t)$ experienced by each susceptible individual was made up of two parts: we defined $\lambda_i^C(t)$ to be the between household (or community) contribution to the risk of infection for each susceptible individual in the ith household:

$$\lambda_i^C(t) = \frac{\beta_{\text{base}}}{N_P}\sum_{j=1}^{N_H}[(I_j^A + I_j^S + I_j^{SS} + I_j^E) + AVE_I(I_j^{AD} + I_j^{SD} + I_j^{SSD} + I_j^{ED})]$$

where AVE_I was the efficacy of antivirals in reducing infectivity; N_p was the total number of individuals who were still alive in the community and index j was used to sum over all households. Similarly, $\lambda_i^H(t)$ was defined to be the force of infection from within the household experienced by each susceptible individual in the ith household.

$$\lambda_i^H(t) = \frac{h\beta_{\text{base}}}{n_i}[(I_i^A + I_i^S + I_i^{SS} + I_i^E) + AVE_I(I_i^{AD} + I_i^{SD} + I_i^{SSD} + I_i^{ED})]$$

where h was the infectivity within households relative to that between households, and n_i was the number of individuals in the ith household who were still alive.

For each time step, the community force-of-infection term was calculated prior to the calculation of individual household forces-of-infection. The two were then added together for each household for each time step to generate the overall hazard of infection. For example, the number of infections in the ith (non-singleton) household at time t was drawn from a binomial distribution with probability $1 - e^{[\lambda_i^C(t)+\lambda_i^H(t)]\Delta t}$ for those not taking antivirals and probability $AVE_S(1 - e^{[\lambda_i^C(t)+\lambda_i^H(t)]\Delta t})$ for those taking antivirals. The full probabilistic equations for the time evolution of these state variables are described in Appendix A. Also, we assumed that the action of antivirals in reducing the chance of death occurred only when individuals exited the I_i^{SSD} state. The probability of death from I_i^{SSD} state was $p_D(1 - AVE_D)$, whereas from the I_i^{SS} state it was p_D. The model was coded in C++.

Transmissibility in our model was parameterized using the single wave cumulative attack rate and a simple relationship between attack rate and the basic reproduction number. We used an empirical optimization approach to set β_{base} from a value of the basic reproduction number R_0, while assuming that the single-wave cumulative attack rate a and the basic reproduction number were related by the equation $R_0 = -ln(1-a)/a$ and found (iteratively) values of β_{base} that gave an attack rate consistent with the desired R_0. We did not use the attack rate explicitly as a parameter because most similar models are parameterized using R_0. The total number of infections was independent of the balance of infectivity between households and the community: if scenarios when high between-household infectivity is assumed, the number of within-household infections will be reduced so as to allow the same attack rate.

We assumed that a household-based treatment policy was always in effect. At the start of each day, all individuals with mild symptoms and severe symptoms were given 2 tablets. Priority was given to those with severe symptoms if sufficient tablets were not available. When prophylaxis was also in effect, and there were sufficient tablets, 1 tablet per day was given to all individuals who may have been susceptible. When insufficient tablets were available for all individuals who may have been susceptible, we prioritized the disease states as follows (from highest priority to lowest priority): asymptomatic recovered, exposed but not yet infectious, early infectious, asymptomatic infectious, and susceptible. This prioritization schedule for prophylaxis was conservative in the sense that our intention was to not over estimate the efficacy of prophylaxis in addition to treatment.