Analysing the Effect of Pre-Distributing Antivirals during an Epidemic

Master of Philosophy Research Proposal

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1 Project Summary

Infectious diseases, and particuarly epidemics, are an area of high interest both in terms of what makes the disease and how it spreads. While vaccines are useful to prevent infection they are often of little use once the infection has taken hold. The development of antiviral drugs has been shown to reduce the period of time that an individual is infectious [9], and also reduce the infectiveness and transmissibility of each individual [4]. It is clear then, that intervention by antivirals would be desired in the event of an influenza epidemic.

It is sensible to think that the earlier a person who is infected begins taking antivirals, the better the effect will be. This has been shown by [1], where it was demonstrated that the 'doubling time' of an epidemic (that is, the expected amount of time for the number of infected people to double) is quite sensitive to the delay before an infected person receives antivirals.

This project aims to investigate what effect pre-distributing antivirals to households before they become infected would have during an epidemic, and also to attempt to derive conditions for which pre-distributing is considered better than the current system of only receiving antivirals after an infection.

Further to this, the project will look to investigate partial pre-distribution and attempt to derive optimality in terms of the proportion of households to pre-distribute antivirals to.

2 Project Details

2.1 Main Model

The disease we will be focussing on will follow the Susceptible-Exposed-Infected-Recovered (S-E-I-R) model, formulated as a Continuous Time Markov Chain. Individuals begin as susceptible (except for the initial infected person who starts the epidemic) and then are exposed to the virus at some constant rate per infected person. Once they have been exposed, they progress into infection and then recovery at a constant rate.

Note that an individual in the exposed class can be thought of as a carrier of the disease, but is unable to infect anyone until they progress into the infectious class.

The model of interest is a compartmentalised (household) model. Our population is divided up into a number of 'households' of variable size. This gives us two methods of infection: internal and external infection. We will make the assumption that the internal infection rate (denoted β) is higher than the external infection rate (denoted α). This makes physical sense as people generally have a much higher contact rate with people inside their household than with other people in the population. We also make the assumption that each person in a household is equally likely to contract the disease.

We will also assume that when a household has antivirals present, the infection rate will be reduced by some constant factor and the infectious period could also be reduced.

Our parameters of interest are R^* which is defined as the expected number of secondary households infected by a single infected household, and r (sometimes called the 'Malthusian' parameter) which is an approximation to the early growth rate of the epidemic. Other statistics of interest could potentially be the final epidemic size (proportion of people who become infected over the course of an epidemic), epidemic duration and cost to authorities.

[8] showed that the parameter R^* is the solution of

$$\Gamma = \mathbb{E}\left[\int_0^\infty \alpha I(X(t))dt\right] \tag{1}$$

conditioned on starting in state i, where $I(X(t))$ is the number of infected people in a single household at time t. This expectation of a path integral can be efficiently evaluated as a system of linear equations [7].

This was then extended in [1] to a model with variable household size, and it has been shown that conditioned on starting in state i,

$$R^* = \sum_k \pi_k \mathbb{E}\left[\int_0^\infty \alpha I(X_k(t))dt\right]$$

where π_k is the proportion of households of size k and $I(X_k(t))$ is the number of infected people in a household of size k and time t. This can again efficiently be evaluated as a system of linear equations, just as in eqn 1

[8] also showed that the growth parameter r is the solution to

$$\pi_k \mathbb{E}\left[\int_0^\infty \alpha I(X(t))e^{-rt}dt\right] = 1 \tag{2}$$

[1] then extended these equations further to incorporate use of antivirals that are delivered post-infection. They found that the delay of receiving antivirals has a large impact on the doubling time of the epidemic. Their assumption for the antivirals was that the infectivity of others in the household and the susceptibility were reduced while the antivirals were present. They also assumed that the external force of infection from the household with antivirals was reduced.

2.2 Other models

There has been work in this area that has focussed on other types of model. For example, in [6], a model that includes travel in and out of cities was studied. Their model had people being vaccinated as soon as an epidemic had begun, with more vaccine being available at the beginning of each day. It was their conclusion that up to a threshold, it is better to focus vaccination of a particular city rather than spread the dosage equally over a larger area. Our model does not include travel, but rather assumes a fixed population size over the epidemic.

[5] has looked at intervention during an epidemic, but only on deterministic system. They have formulated the structure as a 'gas' model and then produce numeric results on the influence of antiviral measures. Our system does not have the 'gas' structure, and also has stochasisity.

[3] uses a model to analyse the idea of pre-dispensing antivirals. Using this, they are able to break down the possible situations into three categories and provide conditions on when pre-distribution is optimal in each of them. Our model has a more robust setting, and also allows for more flexibility in terms of the effect that antivirals have, but we hope to attempt to derive similar conditions.

2.3 Work

Our aim is to extend the work that has been done on these types of models previously to include the delay to delivery of antivirals, as well as the antivirals also being active for a finite time. This will help to add to the realism of the model. The average duration for Zanamivir and Oseltamivir (two of the recommended treatments in [9]) is five days, but the expected duration of an epidemic is far longer ([2] suggests around ten weeks). We consider four cases of delays and durations:

1. Exponential delay and exponential duration
2. Exponential delay and constant duration
3. Constant delay and exponential duration
4. Constant delay and constant duration

Case two is of particular interest, as it seems to make the most realistic sense.

Case one is a simple extension of the work in [1], where we add another section to the generator matrix of the CTMC which captures the dynamics in a single household after the antivirals have finished.

$$Q = \begin{bmatrix} Q_1 & Z & 0 \\ 0 & Q_2 & K \\ 0 & 0 & Q_1 \end{bmatrix}$$

where Q_1 and Q_2 represent the dynamics of the system without and with antivirals respectively, and Z, K represent the rates at which antivirals are introduced and removed from the household respectively. We can use this Q in the equations in 1 to get the early growth rate and R^*. We also confirm these results (and all future results) via a simulation of the epidemic over the whole system.

Incorporating the constant delay into the system is more difficult. Focussing on R^*, we can break the integral into three sections: The period before antivirals, the period with antivirals and the period after antivirals. For case 2, these integrals are the following:

$$R^* = \int_0^{T_1} \alpha I(X(t))dt + p(T_1)\int_0^{T_2} (1-\tau)\alpha I(X(t))dt + p(T_2)\int_0^{\infty} \alpha I(X(t))dt \tag{3}$$

where T_1 is the time at which antivirals become available and T_2 is the time at which antivirals are no longer available. To solve the first term, we consider an alternative chain where the process

is absorbed after some exponential time T_1. If we use this chain, then the first integral can be evaluated from 0 to ∞. The second term can be solved as a system of differential equations [1]:

$$\frac{d\psi_i}{dt} = f(i) + \sum_j q(i,j)\psi_j(t), \quad i,j \in C$$

where C is the states that form an irreducible transient class of the Markov chain.

References

[1] AJ Black, T House, MJ Keeling, and JV Ross. Epidemiological consequences of household-based antiviral prophylaxis for pandemic influenza. *J R Soc Interface*, 2013.

[2] D M Fleming, M Zambon, A I M Bartelds, and J C de Jong. The duration and magnitude of influenza epidemics: A study of surveillance data from sentinel general practices in england, wales and the netherlands. *European Journal of Epidemiology*, 1999.

[3] Edward Goldstein, Joel C Miller, Justin O'Hagan, and Marc Lipsitch. Predispensing of antivirals to high-risk individuals in an influenza pandemic. *NIH*, 2010.

[4] Frederick G. Hayden, Robert Belshe, Catalina Villanueva, Riin Lanno, Claire Hughes, Ian Small, Regina Dutkowski, Penelope Ward, and Jackie Carr. Manage of influenza in households: A prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. *Journal of Infectious Diseases*, 189(3):440–449, 2004.

[5] Thomas House and Matt J Keeling. Deterministic epidemic models with explicit household structure. *ScienceDirect*, 2008.

[6] L Matrajt, Halloran ME, and Longini IM. Optimal vaccine allocation for the early mitigation of pandemic influenza. *PLoS Comput Biol*, 2013.

[7] PK Pollett and VT Stefanov. Path integrals for continuous-time markov chains. *Applied Probability*, 2002.

[8] JV Ross, T House, and MJ Keeling. Calculation of disease dynamics in a population of households. *PLoS ONE*, 2010.

[9] Grant Stiver. The treament of influenza with antiviral drugs. *Canadian Medical Assocation Journal*, 168(1):49–57, 2003.