Bull Math Biol (2016) 78:293–321
DOI 10.1007/s11538-016-0144-6

ORIGINAL ARTICLE

Choice of Antiviral Allocation Scheme for Pandemic Influenza Depends on Strain Transmissibility, Delivery Delay and Stockpile Size

Michael Lydeamore[1,3] · Nigel Bean[1,2] · Andrew J. Black[1] · Joshua V. Ross[1]

Received: 28 September 2015 / Accepted: 20 January 2016 / Published online: 3 February 2016

Abstract Recently, pandemic response has involved the use of antivirals. These antivirals are often allocated to households dynamically throughout the pandemic with the aim being to retard the spread of infection. A drawback of this is that there is a delay until infection is confirmed and antivirals are delivered. Here an alternative allocation scheme is considered, where antivirals are instead preallocated to households at the start of a pandemic, thus reducing this delay. To compare these two schemes, a deterministic approximation to a novel stochastic household model is derived, which allows efficient computation of key quantities such as the expected epidemic final size, expected early growth rate, expected peak size and expected peak time of the epidemic. It is found that the theoretical best choice of allocation scheme depends on strain transmissibility, the delay in delivering antivirals under a dynamic allocation scheme and the stockpile size. A broad summary is that for realistic stockpile sizes, a dynamic allocation scheme is superior with the important exception of the epidemic final size under a severe pandemic scenario. Our results, viewed in conjunction with the practical considerations of implementing a preallocation scheme, support a focus on attempting to reduce the delay in delivering antivirals under a dynamic allocation scheme during a future pandemic.

Keywords Antivirals · Epidemic · Household model · Pandemic influenza

✉ Joshua V. Ross
joshua.ross@adelaide.edu.au

1 School of Mathematical Sciences, The University of Adelaide, Adelaide, SA 5005, Australia

2 ARC Centre of Excellence for Mathematical and Statistical Frontiers, Parkville, VIC, Australia

3 Present Address: School of Mathematics and Statistics, The University of Melbourne, Parkville, VIC 3010, Australia

1 Introduction

During the 2009 Swine influenza pandemic, many countries, including Australia, the USA and the UK, utilised antivirals to help combat the spread of pandemic influenza (Commonwealth of Australia 2011; Public Health England 2014; U.S. Department of Health and Human Services 2005). Antivirals, unlike other potential pandemic control measures, such as vaccination, are not strain specific, meaning that they can be used to potentially retard the spread of a number of variants of influenza with little to no development time. Antivirals are believed to achieve two things relevant to infectious disease spread: an infectious individual is less likely to transmit infection when contact occurs with a susceptible individual, and an individual who is not infected has a stronger resistance to infection, even when contact is made with an infectious individual who is not currently taking antivirals (Hayden et al. 2004; Stiver 2003).

Antiviral use is already part of the Australian Health Management Plan for Pandemic Influenza (2009). The way in which these antivirals would be used, similar to in many other countries (Public Health England 2014; U.S. Department of Health and Human Services 2005), is as follows: after the first *confirmed* infectious individual inside a household, a course of antivirals is allocated to each individual inside the household, regardless of their infectious status. We term this antiviral allocation scheme *dynamic allocation*. The reason for the entire household taking antivirals, regardless of whether each individual is infectious or not, is because a noticeable proportion of transmission occurs inside a household—estimated to be approximately 30 % of transmission (Black et al. 2013; Ferguson et al. 2006; Goldstein et al. 2010)—and treatment to susceptible individuals, known as *prophylaxis*, reduces their susceptibility. Furthermore, the household also forms a convenient unit for distributional purposes (Kwok et al. 2013). The potential issue with a dynamic allocation scheme is that there is a delay until antivirals arrive into the household. This delay arises as the individuals in the household must wait until the infection is confirmed (possibly requiring laboratory testing) and then antivirals are delivered, before commencing their course of antivirals. If this delay is large, then the antivirals will have little impact on the pandemic, as all transmission of infection will be complete before the antivirals have started being taken (Ghani et al. 2009; Black et al. 2013).

This paper investigates an alternative allocation scheme, which we call *preallocation*, that effectively removes the delay present in the dynamic allocation scheme, but introduces some potential drawbacks. Under a preallocation scheme, instead of waiting for a doctor's diagnosis, all antivirals are allocated as soon as the pandemic begins, or potentially in the absence of an outbreak in preparation for a pandemic. When an individual begins showing symptoms of influenza, they are diagnosed, potentially in a less precise way (compared to laboratory testing) such as contacting a government help-line and talking to an expert (Public Health England 2014; Pandemic Influenza Preparedness Team 2011). If it is decided that the individual is likely to have influenza, then all members of the household begin taking antivirals just as they would under a dynamic allocation scheme. Goldstein et al. (2010) have previously investigated a similar scheme, but with preallocation to high-risk individuals only, with the aim to minimise the probability of death over the course of the pandemic. In

contrast, this is the first paper to directly compare more general household allocation schemes.

Under a preallocation scheme, then, the delay between becoming infectious and beginning a course of antivirals is reduced as there is no waiting for the delivery of antivirals, and also potentially no waiting for a doctor's diagnosis or laboratory testing. However, it is possible for individuals to take antivirals without being ill, as well as the potential for antivirals to be 'wasted', as they could be preallocated to a household that never becomes infected.

To compare pre- and dynamic allocation, a Markovian household model that can incorporate both types of allocation is created and analysed (Ball 1996; House and Keeling 2008; Ross et al. 2010; Black et al. 2013). The assessment of the different allocations schemes is based upon four key quantities: (expected) epidemic final size, the total number of individuals who become infectious throughout the entire pandemic (Brauer 2001); the (expected) early growth rate, which represents the (exponential) rate of growth early in a pandemic (Ball 1996); the (expected) peak size, which is the maximum number of infectious individuals throughout the pandemic; and the (expected) peak time, which is the time at which the peak size is achieved.

Modelling a pandemic in a structured population via the use of a continuous-time Markov chain is a common technique, allowing for very detailed and intricate models (Colizza et al. 2007; Longini et al. 2004, 2005). Typically these Markov chain models have very large state spaces, so simulation using the so-called Gillespie algorithm (Gillespie 1977) is the only way to study the model. The Gillespie algorithm scales poorly for models with complex dynamics in large populations, and so rigorously examining a variety of pandemic scenarios is time-consuming. More efficient approximations have been developed, at the cost of some detail. The *branching process approximation*, introduced by Ball and Donnelly (1993) and utilised by Ross et al. (2010) and Black et al. (2013) is fast to evaluate, but this only allows calculation of early time quantities. In this paper we take a different approach and derive a deterministic approximation of our stochastic household model, using the results of Kurtz (1970). Deterministic models with household structure have been studied previously (House and Keeling 2008; Black et al. 2014); however, this is the first to offer a detailed investigation into the method of antiviral distribution and is certainly the most detailed model to leverage this technique to date. This allows the efficient computation of all four quantities detailed above as well as a full sensitivity analysis of our results.

The rest of the paper is as follows: In Sect. 2, the stochastic household epidemic model incorporating the two antiviral allocation schemes is presented. In Sect. 3, the deterministic approximation is derived for this model. In Sect. 4, exploration into the effects of the preallocation scheme compared to the dynamic allocation scheme in a mild and a severe pandemic outbreak is performed. It is demonstrated that for a severe outbreak, the preallocation scheme leads to less total infectious individuals over the course of an outbreak. For a mild outbreak, however, it is shown that a dynamic allocation scheme is generally the better scheme. In Sect. 5, the results of this work are summarised, and some of the limitations and potential extensions of the model are discussed.

2 Model

Consider a population that is partitioned into a fixed number, N, of distinct households and assume that each individual belongs to exactly one household. The distribution of household sizes, $\mathbf{h}$, is fixed, where h_k is the proportion of houses of size k in the population. For the disease dynamics, assume a basic SEIR model where *individuals* in each household are categorised as susceptible, exposed (infected but not infectious), infectious, or recovered. While a household is taking antivirals, the susceptibility and the infectivity of all the individuals in the house is reduced (Black et al. 2013). Each *household* can be in one of four states with respect to their antiviral status. A household may not have received antivirals ($a = 0$), be currently taking antivirals ($a = 1$), have completed their course of antivirals ($a = 2$), or have been preallocated antivirals but not begun taking them ($a = 3$). Finally, it is assumed that a household only receives one course of antivirals either from preallocation or dynamically.

The dynamics of the epidemic and antiviral allocation process are modelled as a continuous-time Markov chain. We say a household of size k is in *configuration* (s, e, i, k, a) if the household has s susceptible, e exposed and i infectious individuals, and currently has antiviral status a. Let $H_{(s,e,i,k,a)}(t)$ be the number of households in configuration (s, e, i, k, a) at time t, and $\mathbf{H}(t) = \{H_{(s,e,i,k,a)}(t)\}$. All events correspond to taking a household in a given configuration and replacing it with another; thus, the total number of households remains fixed. For example, an infection event has the transition

$$\left(H_{(s,e,i,k,a)}, H_{(s-1,e+1,i,k,a)}\right) \to \left(H_{(s,e,i,k,a)} - 1, H_{(s-1,e+1,i,k,a)} + 1\right).$$

The set of all configurations for a single household of size k is,

$$C_k = \{(s, e, i, k, a) | s, e, i \in \{0, \ldots, k\},\ s + e + i \leq k,\ a = 0, 1, 2, 3\},$$

and the set of all household configurations

$$C = \bigcup_{k=1,\ldots,k_{\max}} C_k,$$

where $k_{\max}$ is the largest household size in the population. The dynamics of our model are defined by specifying the events and the rates at which they occur. We split these into two parts to simplify our exposition—the disease dynamics and the antiviral allocation dynamics—although these are dependent on each other.

Disease dynamics There are two levels of mixing in this model: within a household and between households (Ball et al. 1997; Ball 1996), so infection is either internal or from an external source. The rate of infection inside a household of size k is governed by the parameter β_k, such that

$$\beta_k = \begin{cases} 0 & k = 1 \\ \frac{\beta}{k-1} & k > 1, \end{cases} \tag{1}$$

as supported by empirical studies (Cauchemez et al. 2004, 2009; House et al. 2012), while the rate of infection between households is governed by the parameter α. If a household is taking antivirals ($a = 1$) then the susceptibility and infectiousness of all those in the house is reduced by ρ and τ respectively. Thus, the overall rate of infection in a house is

$$\begin{array}{ll} \beta_k si + \frac{\alpha}{N\bar{k}} s\Lambda(t), & a = 0, 2, 3 \\ (1-\tau)(1-\rho)\beta_k si + (1-\rho)\frac{\alpha}{N\bar{k}} s\Lambda(t), & a = 1 \end{array}$$

where

$$\Lambda(t) = \sum_{(s,e,i,k,a)\in C} (1 - \tau\delta_{a,1}) i H_{(s,e,i,k,a)}(t) \tag{2}$$

is the total force of infection within the population and $\bar{k}$ is the *mean household size*: $\bar{k} = \sum_k kh_k$. The factor $(1 - \tau\delta_{a,1})$ in Eq. (2) takes into account the reduced infectivity of a house which is currently taking antivirals ($a = 1$). As in the standard SEIR model, the per-individual rate of progression from exposed to infectious is σ, and the per-individual rate of recovery from infectious to recovered is γ.

Antiviral dynamics It is assumed that there is a limited stockpile of M antiviral doses available at the beginning of the epidemic, and this stockpile is not replenished during the outbreak. There is a large amount of flexibility in how these can be potentially distributed, but for this investigation we assume that they can either be all preallocated at the start, or only dynamically allocated during the epidemic. If antivirals are preallocated at the start, only a proportion of households will receive them, so they are allocated randomly to households according to some distribution. In general this distribution is taken to be the household size distribution, $\mathbf{h}$, so that all sized households are equally likely to be allocated antivirals, but in Sect. 5.5 different allocation distributions are investigated.

A household which has been preallocated antivirals ($a = 3$) will start taking them immediately ($a = 1$) upon the appearance of the first infectious individual in that household. This behaviour is encoded by the transition

$$\left(H_{(s,e,0,k,3)}, H_{(s,e-1,1,k,1)}\right) \to \left(H_{(s,e,0,k,3)} - 1, H_{(s,e-1,1,k,1)} + 1\right).$$

There is also the possibility that a household takes its preallocated antivirals incorrectly (i.e. there is no infection within the household, $i = 0$), encoded by the transition

$$\left(H_{(s,e,0,k,3)}, H_{(s,e,0,k,1)}\right) \to \left(H_{(s,e,0,k,3)} - 1, H_{(s,e,0,k,1)} + 1\right),$$

which is assumed to happen at rate ψ.

When considering dynamic allocation the number of antivirals used by the population at time t is required. This can be calculated directly from the state of the system by looking at the number of households not in state $a = 0$ at time t,

$$A(t) = \sum_{(s,e,i,k,a)\in C} (1-\delta_{a,0})kH_{(s,e,i,k,a)}(t). \tag{3}$$

Thus, a household which has not been given antivirals ($a = 0$) is allocated them at a rate ζ *after* the first infection event within the household if they are available (i.e. if $A(t) < M$).

Once a household is taking antivirals ($a = 1$), they last for a mean period of $1/\kappa$ before they are consumed and the household enters state $a = 2$. A household is thus only ever allocated, in either scheme, one course of antivirals, in line with current allocation policies. All the transitions and rates of the stochastic households model are summarised in Table 1.

The state space for the process, $\mathbf{H}(t)$, is,

$$S = \left\{ \{H_{(s,e,i,k,a)}(t)\} \middle| (s,e,i,k,a) \in C,\ H_{(s,e,i,k,a)}(t) \in \{0,\ldots,N_k\}, \right.$$
$$\left. \sum_{(s,e,i,k,a)\in C_k} H_{(s,e,i,k,a)}(t) = N_k \right\},$$

where N_k is the number of households of size k. It can be seen that the size of the state space, $|S|$, will be too large to allow numerical solution of the forward equations when $\{N_k\}$ is anything other than trivial. The process may be simulated using the Gillespie algorithm (Gillespie 1977), but such simulations are computationally intensive for the population sizes of interest for comparing antiviral schemes, in particular when desiring a reasonable level of accuracy on estimates and conclusions. These computational considerations motivate the derivation of a deterministic approximation in the next section.

3 Deterministic Approximation

As we are interested in the average behaviour of a pandemic in a large population, a deterministic approximation to the stochastic household model which is fast to compute is desired (Kurtz 1970; Ross et al. 2010). The first step in this derivation is to write the transitions of our process in terms of stoichiometric matrices and corresponding rate vectors. Each matrix here has dimension $|S| \times |S|$, while the vectors are all of length $|S|$.

The (m,n)th entry of a stoichiometric matrix corresponds to a transition from a household in configuration n to m for each $n = (s,e,i,k,a) \in C$ and $m = (s^*,e^*,i^*,k^*,a^*) \in C$. The stoichiometric matrix, L_1, corresponding to infection has (m,n)th entry,

$$L_1^{(m,n)} = \delta_{a,a*}\delta_{k,k^*}\delta_{i,i^*}(-\delta_{s,s^*}\delta_{e,e^*} + \delta_{s,s^*+1}\delta_{e,e^*-1}).$$

The matrix L_1 can be used to represent infection both with antivirals, and without antivirals. As such, set $L_2 = L_1$. The vectors which encapsulate the rates at which these two transitions occur have nth component,

Table 1 Transition rates for the stochastic household model including antiviral intervention

Event	Transition $(H_X, H_Y)[\rightarrow (H_X - 1, H_Y + 1)]$	Rate	Stoichiometric matrix j (L_j)
Internal infection	$\left(H_{(s,e,i,k,a)}, H_{(s-1,e+1,i,k,a)}\right)$ with $a \in \{0, 2, 3\}$	$\beta_k si$	1
External infection	$\left(H_{(s,e,i,k,a)}, H_{(s-1,e+1,i,k,a)}\right)$ with $a \in \{0, 2, 3\}$	$\frac{\alpha}{Nk} s\Lambda(t)$	1
Internal infection (antivirals)	$\left(H_{(s,e,i,k,1)}, H_{(s-1,e+1,i,k,1)}\right)$	$(1-\tau)(1-\rho)\beta_k si$	2
External Infection (antivirals)	$\left(H_{(s,e,i,k,1)}, H_{(s-1,e+1,i,k,1)}\right)$	$(1-\rho)\frac{\alpha}{Nk} s\Lambda(t)$	2
Progression	$\left(H_{(s,e,i,k,a)}, H_{(s,e-1,i+1,k,a)}\right)$ with $a \in \{0, 1, 2\}$	σe	3
Progression (preallocated)	$\left(H_{(s,e,0,k,3)}, H_{(s,e-1,1,k,1)}\right)$	σe	4
Recovery	$\left(H_{(s,e,i,k,a)}, H_{(s,e,i-1,k,a)}\right)$	γi	5
Antivirals arrival	$\left(H_{(s,e,i,k,0)}, H_{(s,e,i,k,1)}\right)$ with $i > 0$ and $A(t) < M$	ζ	6
Antivirals completion	$\left(H_{(s,e,i,k,1)}, H_{(s,e,i,k,2)}\right)$	κ	7
Incorrect taking	$\left(H_{(s,e,0,k,3)}, H_{(s,e,0,k,1)}\right)$	ψ	8

Each transition is a household of type X becoming a household of type Y

$$\mathbf{y}_1^{(n)} = \left(\beta_k si + \frac{\alpha}{N\bar{k}} s\Lambda(t)\right) H_n,$$
$$\mathbf{y}_2^{(n)} = \left((1-\tau)(1-\rho)\beta_k si + (1-\rho)\frac{\alpha}{N\bar{k}} s\Lambda(t)\right) H_n,$$

representing infection into a household which contains individuals who are not currently taking antivirals, and are taking antivirals, respectively. For the progression of infection in a household, the stoichiometric matrix, L_3, has (m, n)th component,

$$L_3^{(m,n)} = \delta_{a,a^*}\delta_{k,k*}\delta_{s,s^*}(-\delta_{e,e^*}\delta_{i,i^*} + \delta_{e,e^*+1}\delta_{i,i^*-1})(1-\delta_{a,3}),$$

and the corresponding rate vector, $\mathbf{y}_3$, has nth component,

$$\mathbf{y}_3^{(n)} = \sigma e H_n.$$

However, for preallocated households that have not commenced their course of antivirals, the stoichiometric matrix corresponding to progression, L_4, has (m, n)th component,

$$L_4^{(m,n)} = \delta_{k,k^*}\delta_{s,s^*}\delta_{a,3}\delta_{i,0}(-\delta_{a^*,3}\delta_{e,e^*}\delta_{i^*,0} + \delta_{a^*,1}\delta_{e,e^*+1}\delta_{i^*,1}),$$

while the corresponding rate vector, $\mathbf{y}_4$, is identical to $\mathbf{y}_3$. The stoichiometric matrix corresponding to recovery inside a household, L_5, has (m, n)th component,

$$L_5^{(m,n)} = \delta_{a,a^*}\delta_{k,k^*}\delta_{e,e^*}\delta_{s,s^*}(-\delta_{i,i^*} + \delta_{i,i^*+1}),$$

and the corresponding rate vector, $\mathbf{y}_5$, has nth component,

$$\mathbf{y}_5^{(n)} = \gamma i H_n.$$

For the introduction of antivirals into a household after the first infection event, the stoichiometric matrix, L_6, has (m, n)th component,

$$L_6^{(m,n)} = \delta_{k,k^*}\delta_{i,i^*}\delta_{e,e^*}\delta_{s,s^*}\delta_{a,0}(-\delta_{a^*,0} + \delta_{a^*,1})(1-\delta_{i,0}),$$

and the corresponding rate vector, $\mathbf{y}_6$, has nth component,

$$\mathbf{y}_6^{(n)} = \zeta H_n.$$

The stoichiometric matrix, L_7, for the completion of antivirals inside a household has (m, n)th component,

$$L_7^{(m,n)} = \delta_{k,k^*}\delta_{i,i^*}\delta_{e,e^*}\delta_{s,s^*}\delta_{a,1}(-\delta_{a^*,1} + \delta_{a^*,2}),$$

and the corresponding rate vector, $\mathbf{y}_7$, has nth component,

$$\mathbf{y}_7^{(n)} = \kappa H_n.$$

Finally, the stoichiometric matrix for the incorrect taking of antivirals in households preallocated antivirals has (m, n)th element,

$$L_8^{(m,n)} = \delta_{k,k^*}\delta_{i,0}\delta_{i^*,0}\delta_{e,e^*}\delta_{s,s^*}\delta_{a,3}(-\delta_{a^*,3} + \delta_{a^*,1}),$$

and the rate vector for this event, $\mathbf{y}_8$, has nth component,

$$\mathbf{y}_8^{(n)} = \psi H_n.$$

Consider now the proportion of households in each configuration at time t,

$$X_{(s,e,i,k,a)}(t) = N^{-1} H_{(s,e,i,k,a)}(t),$$

and let,

$$\mathbf{X}(t) = \{X_{(s,e,i,k,a)}(t)\} = N^{-1}\mathbf{H}(t).$$

The transition rates $\left\{\mathbf{y}_j^{(n)}\right\}$ of the process $\mathbf{H}(t)$ are *density dependent* in the sense of Kurtz (1970), so they can be written as

$$\mathbf{y}_j^{(n)}(t) = N\mathbf{w}_j^{(n)}(\mathbf{X}(t)), \tag{4}$$

where the functions $\left\{\mathbf{w}_j^{(n)}(\mathbf{X}(t))\right\}$ depend only on the state of the process through the density, $\mathbf{X}(t)$. Writing out the components of these fully gives,

$$\begin{aligned}
\mathbf{w}_1^{(n)} &= \left(\beta_k si + \alpha \hat{I}(t)s\right) X_n(t),\\
\mathbf{w}_2^{(n)} &= \left((1-\tau)(1-\rho)\beta_k si + (1-\rho)\alpha \hat{I}(t)s\right) X_n(t),\\
\mathbf{w}_3^{(n)} &= \sigma e X_n(t),\\
\mathbf{w}_4^{(n)} &= \sigma e X_n(t),\\
\mathbf{w}_5^{(n)} &= \gamma i X_n(t),\\
\mathbf{w}_6^{(n)} &= \zeta X_n(t),\\
\mathbf{w}_7^{(n)} &= \kappa X_n(t),\\
\mathbf{w}_8^{(n)} &= \psi X_n(t),
\end{aligned}$$

with

$$\hat{I}(t) = \frac{1}{\bar{k}} \sum_{(s,e,i,k,a)\in C} (1 - \tau\delta_{a,1}) i X_{(s,e,i,k,a)}(t).$$

It is then possible to apply Theorem 3.1 of Kurtz (1970) to establish convergence, uniformly in probability over finite time intervals, of the scaled stochastic households model $\mathbf{X}(t)$ to the deterministic approximation,

$$\frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} = \sum_{j=1}^{8} L_j \mathbf{w}_j(\mathbf{x}(t)),$$

as the number of households $N \to \infty$; provided the initial density is close to the initial proportion in the deterministic trajectory. This system of differential equations can be solved using Runge–Kutta techniques, such as those implemented in MATLAB's `ode45`, as used herein.

For the dynamic allocation scheme the allocation of antivirals depends on there being sufficient antivirals in the stockpile remaining at time t. Equation (3) can be rewritten in terms of our deterministic variables as,

$$A(t) = N \sum_{(s,e,i,k,a)\in C} (1 - \delta_{a,0}) k x_{(s,e,i,k,a)}(t). \tag{5}$$

Then, the deterministic dynamics can be expressed as,

$$\frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} = \begin{cases} \sum_j L_j \mathbf{w}_j(\mathbf{x}(t)) & \text{if } A(t) < M, \\ \sum_{j\neq 6} L_j \bar{\mathbf{w}}_j(\mathbf{x}(t)) & \text{if } A(t) \geq M, \end{cases} \tag{6}$$

as $\mathbf{w}_6^{(n)} = 0$ for all $n = (s, e, i, k, a) \in C$ when no more antivirals can be introduced into the population.

3.1 Initial Condition

In order to numerically solve the deterministic approximation, a suitable initial condition is required. The initial condition must be such that the proportion of the population in each state is sufficiently large (Kurtz 1970). Further, the initial transient behaviour should be eliminated so that the system starts in the early exponential growth phase of the pandemic. This allows for a fairer comparison of the general behaviour of the pandemic under a dynamic allocation and a preallocation scheme.

The suitable initial condition has the form,

$$\mathbf{x}(0) = \mathbf{x_s} + \frac{i_0}{\mathbf{i} \cdot \mathbf{v}_1} \mathbf{v}_1, \tag{7}$$

where $\mathbf{x_s}$ is the (unstable equilibrium) state in which all individuals are susceptible to the disease, $\mathbf{v}_1$ is the eigenvector corresponding to the dominant eigenvalue of the system and i_0 is the initial proportion of infectious individuals in the population. Full details of this initial condition are contained in "Appendix 1". Note, the dominant eigenvalue is also the early growth rate (Malthusian parameter) of the process.

4 Quantities of Interest

In order to compare antiviral allocation schemes, four key quantities are utilised. The first of these is the expected epidemic final size; this is the total number of individuals who were infected over the course of the pandemic (Brauer 2001). As there is no waning immunity in this model, the total number of infected individuals is equivalent to the total number of recovered individuals once the pandemic is complete. A lower expected epidemic final size means that the pandemic outbreak was less severe. Also calculated are the expected peak size and expected peak time of the pandemic: let $I(t)$ be the number of infectious individuals in the population at time t, then the peak size is,

$$\max\{I(t)|t > 0\},$$

and the peak time is,

$$\arg\max\{I(t)|t > 0\}.$$

Generally, a smaller peak size is desired as this means that there is less peak demand on the health system, and a longer peak time is desired in order to give more time for control measures and management plans to be implemented. The final quantity of interest is the expected early growth rate (Keeling and Rohani 2008). This is given by the dominant eigenvalue of the system, which is calculated when determining the initial condition in Eq. (7) (see "Appendix 1"). A lower early growth rate means that less individuals are being infected per unit time early in the pandemic, and so the pandemic outbreak is not as severe during this time.

4.1 Parameters

Two pandemic scenarios are investigated: a *mild* outbreak which is similar to the 2009 H1N1 Swine influenza pandemic, and also a *severe* outbreak which is similar to the 1918 Spanish pandemic (Mills et al. 2004). The parameters are matched to estimates of the latent and infectious periods, and to previous estimates of R_*, where calculation of the latter for our stochastic households model is effected using the method of Ross et al. (2010) and Black et al. (2013).

Unlike more traditional pandemic analyses, the basic reproductive number, R_0, is not used as a measure of pandemic severity. The basic reproductive number, R_0, is defined to be the expected number of secondary infections caused by one infected individual in an otherwise fully susceptible population (Anderson and May 1991; Pellis

et al. 2012). In a population with household structure, the basic reproductive number cannot reliably be used to predict the severity of an outbreak (Ball et al. 1997; Ross et al. 2010). For example, if the rate of infection between households $\alpha = 0$, then a high R_0 value would not result in a pandemic outbreak; R_0 no longer acts as a *threshold parameter* determining whether invasion is possible in structured models. Instead, we choose to utilise the household reproductive number, R_*, as a measure of pandemic severity (Ball et al. 1997). The household reproductive number, R_*, is the number of infections introduced into susceptible households by a single household, in an otherwise fully susceptible (and infinite) population. It is known that R_* acts as a threshold parameter in a model with this population structure (Ball 1996; Ball et al. 1997).

The 2009 H1N1 Swine influenza pandemic had an estimated R_* of approximately 1.3 (Ghani et al. 2009), while the Spanish influenza pandemic had an estimated R_* of approximately 1.8 (Mills et al. 2004). The rate of recovery is fixed at $\gamma = 1$ for both sets of parameters, scaling time to units of an average infectious period. The purpose of this scaling is to reduce the number of free parameters in the model, and to avoid issues with varying estimates between the different strains of influenza (Ghani et al. 2009; Carrat et al. 2002). For both sets of parameters, we let $\sigma = 1$, so the latent (exposed) period is on average the same duration as the infectious period, as approximately true for influenza, but also assess sensitivity to this parameter. The estimates on the effectiveness of antivirals is varied, with some estimates claiming a 60 % reduction in susceptibility (Ferguson et al. 2006; Longini et al. 2005). However, these figures have been disputed (Jefferson et al. 2012). In this work, a more conservative estimate of antiviral effectiveness is chosen, setting the reduction in susceptibility, ρ, and infectiousness, τ, to 0.3 in line with some experimental estimates (Stiver 2003; Hayden et al. 2004); we also set the mean effective duration of antivirals, $\kappa = 1$, so they last one infectious period on average. However, sensitivity to these parameters is also assessed.

The mean delay until antivirals arrive into a household, ζ, has not been explored previously in detail. One estimate for this delay in the UK during the 2009 Swine influenza pandemic was approximately one infectious period, implying $\zeta = 1$ (Ghani et al. 2009). This is clearly long—half of the index individuals would be recovered before they receive antivirals. Considered here is a smaller mean delay, relative to this UK estimate, effectively representing what would happen if significant effort were made to reduce the delay compared to the 2009 Swine influenza pandemic; we set the rate at which antivirals arrive into a household, $\zeta = 2$, which is a mean antiviral delivery time of approximately half an infectious period. Also investigated is the effect of this delay, ranging from $\zeta = 2$, through to $\zeta = 0.66$, in order to assess the importance of rapid antiviral delivery. This is in addition to a comprehensive sensitivity analysis on all parameters (see Sect. 5.3).

The household size distribution, $\mathbf{h}$, is taken to be that of Australia according to the 2011 national census (Australian Bureau of Statistics 2011). That is,

$$\mathbf{h} = [0.2434, 0.3397, 0.1598, 0.1569, 0.0675, 0.0231, 0.0058, 0.0039],$$

giving a mean household size of approximately $\bar{k} = 2.577$. Note that the household size distributions of the UK and USA are similar to that of Australia. The mild parameter

Table 2 Definition of the *mild* and *severe* parameter sets

	Mild	Severe
β	0.9669	1.1259
α	0.8	1
	Both	
σ	1	
ρ	0.3	
τ	0.3	
ζ	2	
κ	1	
γ	1	
$\mathbf{h}$	Australian Census, 2011	

set is defined to have $\beta = 0.9669$ and $\alpha = 0.8$; this gives (Ross et al. 2010; Black et al. 2013) a household reproductive ratio, R_*, of 1.3. Similarly, the severe parameter set is defined to have $\beta = 1.1259$ and $\alpha = 1$; this gives a household reproductive ratio, R_*, of 1.8. All parameters are presented in Table 2. Finally, the population size is fixed at 10^5 individuals, and so the number of households in the population is,

$$N = \left\lfloor \frac{10^5}{\bar{k}} \right\rfloor = 38804.$$

5 Results

First, a numerical verification of the deterministic approximation is provided. Then, exploration into the key quantities associated with a pandemic for both a mild and severe outbreak under both a dynamic and preallocation scheme is performed. Next, a full sensitivity analysis is undertaken for the eight parameters that govern the dynamics, and finally an assessment is made of the impact of the rate of antiviral intervention, ζ.

5.1 Numerical Verification

In Sect. 3, it was reported that the scaled Markov chain, $N^{-1}\mathbf{H}(t)$, converges uniformly in probability over finite time intervals to the deterministic approximation, $\mathbf{x}(t)$, as the number of households, $N \to \infty$. This result is illustrated numerically in Fig. 1. The figure shows the mean and variance of the difference in the proportion of infectious individuals between one hundred realisations (Gillespie 1977) of the stochastic household model (Table 1), scaled by the number of households, and the deterministic approximation. It can be seen that as the number of households increases, the scaled Markov chain is increasingly well approximated by the deterministic approximation. We adopt the deterministic approximation for the remainder of the results.

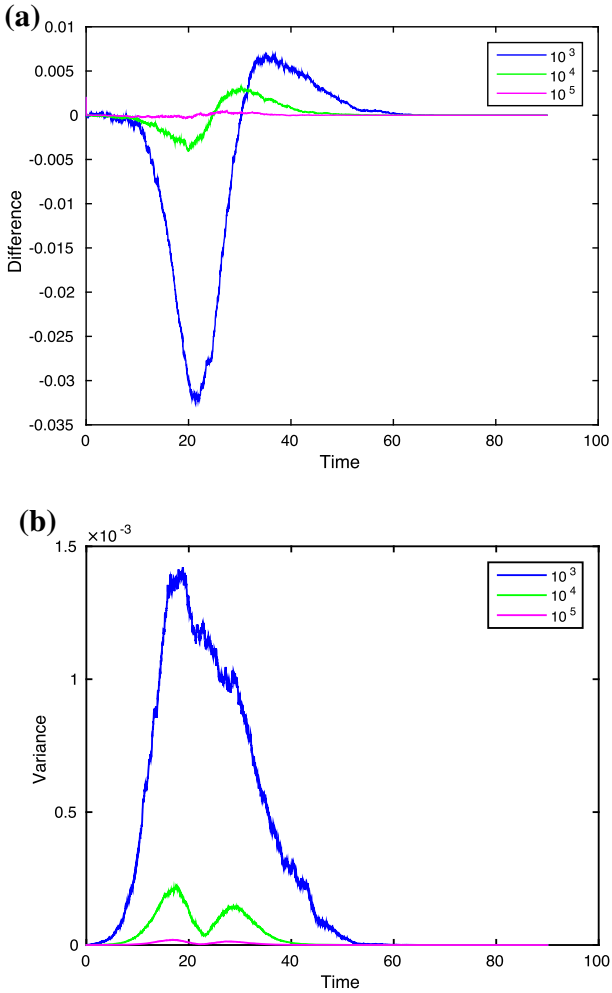

Fig. 1 Difference in the proportion of infectious individuals between 100 realisations of the stochastic household model and its deterministic approximation versus time, using the *severe* parameter set and for varying the numbers of households. **a** Mean difference. **b** Variance of the difference (Color figure online)

5.2 Comparison of Antiviral Allocation Schemes

The Australian Health Management Plan for Pandemic Influenza (2009) currently specifies that antivirals would be utilised according to a dynamic allocation scheme in the event of an influenza outbreak. Investigated here is the differences between the dynamic allocation scheme and the preallocation scheme in terms of expected epidemic final size, expected peak size, expected peak time and expected early growth rate. These are compared as a function of the proportion of the population with antivirals available ($M/N\bar{k}$), at a resolution of 0.02.

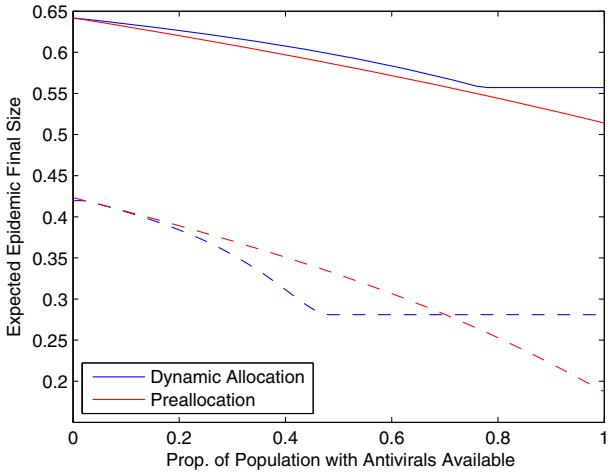

Fig. 2 Comparison of the expected epidemic final size as a function of the proportion of the population with antivirals available ($M/N\bar{k}$) under both a dynamic allocation scheme (*blue*) and a preallocation scheme (*red*). The solid lines are using the *severe* parameter set, and the dashed lines are using the *mild* parameter set (Color figure online)

Figure 2 shows the expected epidemic final size as a function of the number of antivirals available in the population. It can be seen that for a severe pandemic outbreak, the preallocation scheme leads to a smaller expected epidemic final size than the dynamic allocation scheme, regardless of the amount of available antivirals, although the differences are generally small. However, for a mild outbreak the dynamic allocation scheme leads to a smaller expected epidemic final size than the preallocation scheme for antiviral availabilities up to approximately 70 % of the population. The reason that dynamic allocation performs better in a mild outbreak, compared to a severe outbreak, is that there is less infection per unit time, and so the delay until antivirals arrive into a household has less of an impact compared to in a severe outbreak.

Figure 3 compares the (a) expected early growth rate, (b) expected peak time and (c) expected peak size, under both a dynamic and a preallocation scheme. It can seen that the dynamic allocation scheme leads to superior values for all these quantities for antiviral availabilities up to approximately 70 % of the population, regardless of the pandemic severity parameter set. In contrast to the final size of an epidemic, the growth rate, expected peak size and expected peak time are all quantities associated with the earlier stages of the pandemic. Dynamic allocation ensures that all members of a household that have experienced infection receive antivirals (with some delay), at least early in the pandemic. However, preallocation utilises the supply of antivirals more uniformly throughout the pandemic. Therefore it is not unexpected that dynamic allocation yields superior results for these early time quantities compared to preallocation. However, for a severe outbreak, preallocation yields a smaller expected epidemic final size compared to dynamic allocation.

It can also be seen in both Figs. 2 and 3 that for a dynamic allocation scheme, there exists a maximum effective amount of antivirals, indicated by the flattening of

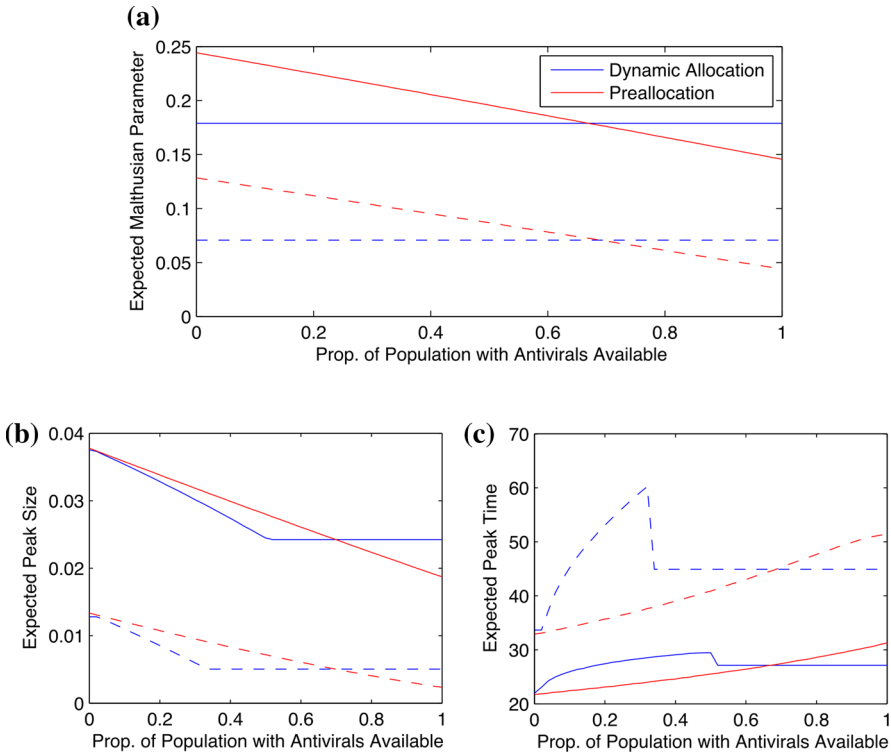

Fig. 3 Comparisons of the **a** expected early growth rate, **b** expected peak size, and **c** expected peak time as a function of the proportion of the population with antivirals available ($M/N\bar{k}$) for an epidemic under a dynamic allocation scheme and a preallocation scheme. The *solid lines* are using the *severe* parameter set, and the *dashed lines* are using the *mild* parameter set (Color figure online)

curves past a particular threshold of proportion of antivirals available. Having more antivirals available than this threshold gives no benefit in terms of the key quantities of a pandemic. This effective amount exists as the pandemic ends before any more antivirals can be given out. It is this maximum effective amount of antivirals that leads to the preallocation scheme having a smaller expected epidemic final size when there is a large amount of antivirals available for the population.

5.2.1 Incorrect Taking of Antivirals

One important consideration in the practical implementation of the *preallocation scheme* is the potential for incorrect taking of antivirals. Unfortunately, there is no data for inferring the value of the parameter ψ, which controls this aspect of the model, as the preallocation scheme is not currently used for antiviral distribution. For this reason, the proportion of households required to use antivirals incorrectly in order for a dynamic allocation scheme to lead to a smaller expected epidemic final size than a preallocation scheme is calculated, and presented in Fig. 4. It can be seen that for a severe pandemic outbreak, if between 30 and 70 % of households have antivirals

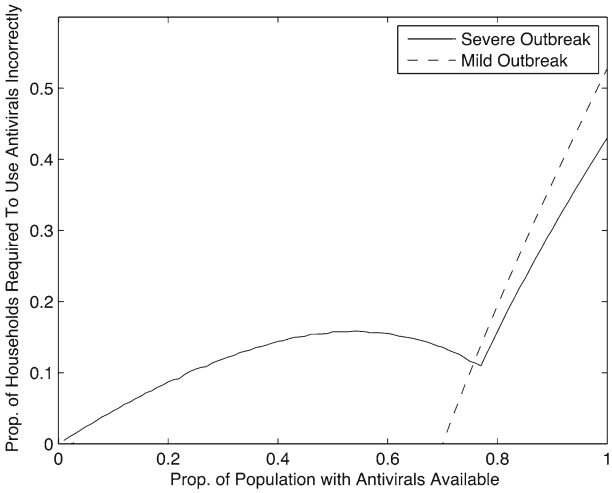

Fig. 4 Required proportion of households who use antivirals incorrectly for a dynamic scheme to be preferable to a preallocation scheme in terms of epidemic final size as a function of the proportion of the population with antivirals available ($M/N\bar{k}$), for a *severe* outbreak (*solid line*) and a *mild* outbreak (*dashed line*)

available, then between 10 and 15 % of households can use their supply of antivirals incorrectly before a dynamic allocation scheme gives the same expected epidemic final size as the preallocation scheme. For a mild outbreak, there is more evidence that a dynamic allocation scheme would be preferable. In particular, until approximately 80 % of households have antivirals available, no more than 10 % of households can use antivirals incorrectly in order for a preallocation scheme to give a lower expected epidemic final size. However, when a large amount of the population have antivirals available, the required proportion of households who can use antivirals incorrectly increases rapidly.

5.3 Sensitivity Analysis

As the deterministic approximation is fast to compute, a full sensitivity analysis of our model can be performed. The sensitivity to the within-household infection rate, β, between-household infection rate, α, recovery rate, γ, progression rate, σ, the reduction in susceptibility, τ, and infectivity, ρ, the rate governing the duration of antivirals, κ, and, for the dynamic allocation scheme, the rate at which antivirals arrive in a household, ζ is assessed. All parameters are varied by 10 %, with the exception of β, which is varied by -5 % in the severe parameter case, and $+4$ % in the mild parameter case, in order to avoid overlapping parameters. The proportion of antivirals available is fixed at 35 %, in line with probable stockpile sizes (Merler et al. 2009; Carrasco et al. 2011). The full sensitivity analysis results in, $\sum_{i=1}^{8} 2^i \binom{8}{i} = 6560$ different combinations of parameters. The results of a one parameter sensitivity analysis are contained in Tables 3, 4, 5 and 6 in the "Appendix".

While some of the parameters cause large increases or decreases in key quantities—in particular the rate of recovery, γ, and also the between-household infection rate, α—the conclusions that are drawn comparing the two allocation schemes are relatively robust. For the mild parameter case, preallocation led to a smaller expected epidemic final size in 35 % of cases, a longer expected peak time in 14 % of cases, but never yielded a smaller expected peak size or a smaller expected early growth rate when compared to the dynamic allocation scheme. For the severe parameter case, preallocation gave a smaller expected epidemic final size in 99 % of cases, a smaller expected peak size in 0.3 % of cases, but never a longer expected peak time or smaller expected early growth rate when compared to the dynamic allocation scheme.

There are a number of interesting features that are observed in the sensitivity analysis, at least in the single parameter case. The effectiveness of antivirals appears to have relatively little impact on the four assessed quantities, regardless of the antiviral allocation scheme or severity of the outbreak. It is important to note here that a 10 % variation in these quantities is not large, but it demonstrates that the effectiveness of antivirals need not be overly precise in this model. It also appears as though the effective antiviral duration, as controlled by κ, has minimal impact on the four key quantities.

Also of interest is the 35 % of times in which preallocation gives a smaller expected epidemic final size in a mild outbreak, when compared to dynamic allocation. In general, this happens when both β and α are increased. The 4 % increase in β and the 10 % increase in α bring the infection parameters very close to the severe parameter set, so it is not surprising that a preallocation scheme gives a better expected epidemic final size.

Finally, the progression rate, σ, has no impact on expected epidemic final size, as expected, but also has only a small impact on the expected peak size, expected peak time and expected growth rate, regardless of the severity of the outbreak.

5.4 Impact of Delay of Antiviral Delivery

Thus far, the rate at which antivirals arrive to a household has been assumed to be fixed at $\zeta = 2$, which corresponds to a mean delay of half an infectious period. One estimate of this delay from the 2009 Swine influenza pandemic is one infectious period, that is, $\zeta = 1$ (Ghani et al. 2009). Hence, we were reasonably optimistic with regards to this aspect of the model. Due to the speed of the deterministic approximation and the importance of this parameter, we explore the impact of the delay on the expected epidemic final size, as shown in Fig. 5. When two thirds of the population has access to antivirals, it can be seen that an average delay higher than 0.6 infectious periods (corresponding to $\zeta < 1.66$) leads to preallocation giving a smaller expected epidemic final size than a dynamic allocation scheme. When one third of the population have access to antivirals, it can seen that an average delay higher than 0.95 infectious periods (corresponding to $\zeta < 1.05$) leads to preallocation giving a smaller expected epidemic final size. This demonstrates that significant effort should be made to ensure that the delay until antivirals arrive into a household is small, or else preallocation is better than dynamic allocation.

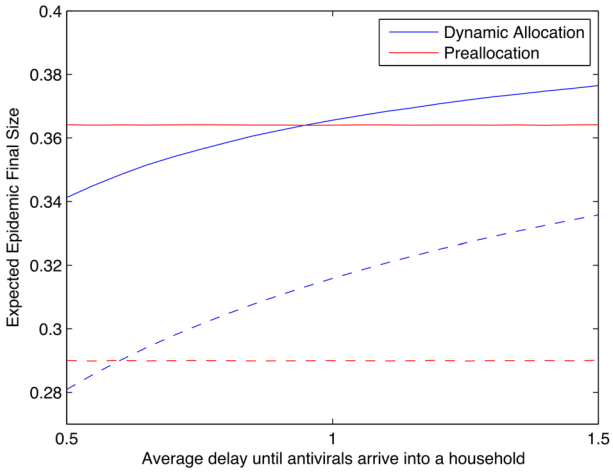

Fig. 5 Comparison of expected epidemic final size for various average delays until antivirals arrive in a household. The number of antivirals is fixed at one third (*solid lines*) or two thirds (*dashed lines*) of the population. All other parameters are taken from the *mild* parameter set (Color figure online)

5.5 Preallocation Schemes

Thus far, all antivirals under a preallocation scheme have been allocated according to the household size distribution, **h**. Implementing such a distribution scheme is relatively straightforward—a household is chosen uniformly at random from the population, and all members of that household are preallocated antivirals. There are other potential methods of preallocation. One alternative preallocation scheme is to utilise the *size-biased* distribution, π. When considering a population with heterogeneous household sizes, the jth component of the size-biased distribution,

$$\pi_j = \frac{jh_j}{\sum_k kh_k},$$

is the probability of contact of an infectious individual with a susceptible individual who belongs to a household of size j (Ball et al. 1997; Black et al. 2013). Other potential preallocation schemes include allocating to the smallest households first, or to the largest households first.

In Fig. 6, comparisons of these different preallocation schemes in terms of the expected epidemic final size are shown, as a function of the maximum proportion of the population who have antivirals available. For the severe parameter set, allocating to the largest household first, smallest household first, or according to the household size distribution or size-biased distribution, produce very similar impacts on epidemic final size. All preallocation schemes are better than dynamic allocation in this case. For the mild parameter set, the differences between the various preallocation schemes are more pronounced. Allocating according to the largest household size first yields the smallest expected epidemic final size, amongst the preallocation schemes. From the

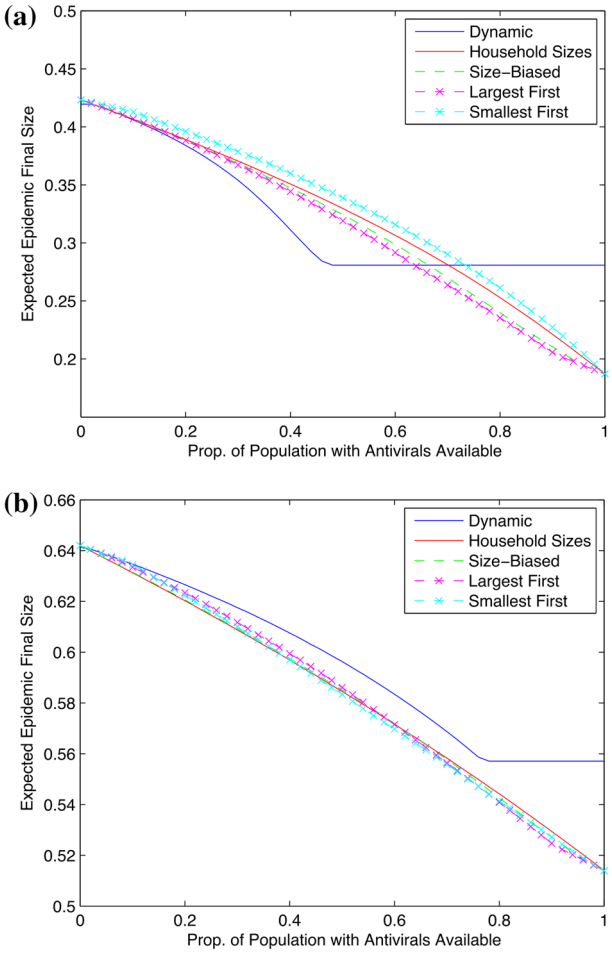

Fig. 6 Comparison of different preallocation methods compared to a dynamic allocation scheme as a function of the proportion of the population with antivirals available ($M/N\bar{k}$) on the expected epidemic final size using the **a** *severe* parameter set and the **b** *mild* parameter set (Color figure online)

results, allocating to the largest household size first appears to be a robust preallocation choice.

6 Discussion

In this paper, an alternative scheme for allocating antivirals during an influenza pandemic, which we have called preallocation, has been investigated. A deterministic approximation, to a new stochastic households model, which is fast to compute has been derived. The deterministic approximation allows exploration of pandemic scenarios efficiently, unlike Monte Carlo simulation methods (Cross et al. 2007; Colizza et al. 2007; Matrajt et al. 2013). However, the deterministic approximation is unable to

assess the effects of stochasticity, unlike some other methods (Ross et al. 2010; Black et al. 2013).

The effectiveness of antivirals during a pandemic has been questioned previously as a consequence of the delays in distributing antivirals to households under the dynamic allocation scheme (Black et al. 2013). This work is one of the first studies which assesses a different antiviral allocation scheme, preallocation, which seeks to remove this delay. A comparison has been performed using the epidemic final size, peak size, peak time and the early growth rate. It has been shown that the theoretical best choice between these allocation scheme depends on the severity of the pandemic outbreak, the antiviral stockpile size, the delay in antiviral delivery under the dynamic allocation scheme, and also on the quantity used to perform the assessment.

For a severe pandemic outbreak, the preallocation scheme generally gave a smaller epidemic final size, but a larger peak size and early growth rate. If only one of these quantities were considered, then the benefits of the allocation schemes may not be seen. Intuitively, the dynamic allocation scheme ensures that all individuals early in the pandemic receive antivirals. However, preallocation has antivirals actively being used more uniformly throughout a pandemic, and so the benefits of preallocation may not be seen when looking at quantities associated with the early stages of the pandemic. It is worth noting that, particularly for a severe outbreak, a preallocation scheme can yield a smaller epidemic final size.

Also considered was households taking antivirals incorrectly under the preallocation scheme. It was shown that, for a severe outbreak, if the proportion of the population which has antivirals available is greater than 20 %, then more than 10 % of those who have been preallocated antivirals would have to use antivirals incorrectly for a dynamic allocation scheme to give a lower epidemic final size than a preallocation scheme. For a mild outbreak though, a dynamic allocation scheme already gives a lower expected epidemic final size until approximately 70 % of the population has antivirals available. After this point, however, the proportion of households that can use antivirals incorrectly increases steeply.

One important consideration for pandemic response is the amount of antivirals that are available for distribution. In this work, all possibilities of stockpile size have been considered. In reality, it is unlikely that a country would stockpile a very large amount of antivirals, due to the cost of maintaining this stockpile. The realistic supply of antivirals is likely to be less than 50 % of the population (Merler et al. 2009; Carrasco et al. 2011). It is worth noting that in the unrealistically high ranges of antivirals, the preallocation scheme consistently yields better results than the dynamic allocation scheme. However, when between 25 and 50 % of the population have antivirals available, the dynamic scheme is superior with the exception of the epidemic final size for a severe outbreak.

Also investigated was different methods of preallocation, based upon how antivirals are distributed to households of different sizes. For a severe outbreak, the tested preallocation methods differed in expected epidemic final size by less than 1 %. From results for both parameter sets, allocating to the largest household size first appears to be a robust preallocation choice. Allocating to the largest household first is similar to the equalisation principle in the optimal vaccination problem (Ball and Lyne 2002; Keeling and Ross 2015). The main difference in this case is that we are allocating to

entire households, not individuals, as is the case in the optimal vaccination problem. Allocating to largest households first may still not be optimal, and a potential extension of this work would be to determine the optimal preallocation method.

A benefit of the deterministic approximation we derived is its computational efficiency, hence allowing us to perform a full sensitivity analysis, consisting of 6560 combinations of parameters. This full set of analyses was completed in approximately five and a half hours on an Intel i5 processor. This type of sensitivity analysis is not practical using Monte Carlo methods. The sensitivity analysis showed that, although key quantities associated with the pandemic can change significantly, the choice of optimal scheme is relatively robust. That is, for a severe outbreak, a preallocation scheme yields a smaller expected epidemic final size, while for a mild outbreak, a dynamic allocation scheme tends to yield a smaller expected epidemic final size.

The model we have described can incorporate much more flexibility in the allocation schemes than we have investigated in this paper. Hybrid schemes can be investigated by preallocating some proportion of antivirals at the beginning and then dynamically distributing the rest. The number of antivirals available, M, could also be made a function of time, representing production during the pandemic.

This work demonstrates the impact of the delay of antiviral distribution under a dynamic allocation scheme. If the delay can be made noticeably smaller than during the 2009 Swine influenza pandemic, then a dynamic allocation scheme often gives a smaller epidemic impact and is more robust than a preallocation scheme. Given the practical considerations of implementing a preallocation scheme in conjunction with our analysis, it motivates a focus on attempting to reduce the delay in delivering antivirals under a dynamic allocation scheme during a future pandemic.

The scenarios we have considered here do have some limitations. One limitation is that we have assumed that there are negligible deaths throughout the pandemic. While death is somewhat similar to recovery as a modelling assumption, the minimisation of death in a population has been a focus of other studies (Glass et al. 2011; Goldstein et al. 2010). We expect that minimisation of epidemic final size would also contribute to a lower number of deaths; however, this concept has not been verified here. Another limitation is that our models do not account explicitly for asymptomatic infections, which are likely to be of significant number, in particular under a mild scenario. However, we anticipate that this feature would impact both allocation schemes in a similar manner, and hence not lead to significant changes when comparing between schemes. Finally, this work does not account for the possibility of vaccine development during the outbreak. Current estimates of the time to produce and commence distribution of such a vaccine is approximately 6 months, but could be potentially longer (Fedson 2003; Webby and Webster 2003; Webby et al. 2004). As such, a vaccine is almost certain to become available post-peak in all scenarios considered here, but potentially at a stage to have some impact upon our assessment with respect to the epidemic final size, in particular under a mild scenario, depending upon the vaccine efficacy and supply levels. The effect would likely be to provide some advantage to dynamic allocation in such a scenario, and hence further supports our overall conclusions.

New strains of influenza have caused pandemics approximately every 30 years. Events of the past would indicate that control of future pandemics is of great importance. With antiviral developments in progress (Bekerman and Einav 2015), research

is needed to fully understand the best use of such antivirals. The extensions and ideas presented throughout this work will hopefully lead to a more efficient use of antivirals, and hence to a smaller impact of future pandemics.

Acknowledgments We gratefully acknowledge the support of the ARC (FT130100254 and ACEMS) and NHMRC (PRISM^2) .

Appendix 1: Derivation of the Initial Condition

Consider the population state $\mathbf{x_s}$, the state in which all individuals are susceptible to the disease. It is ideal to start the system near the point $\mathbf{x_s}$. As such, an initial condition of the form,

$$\mathbf{x}(0) = \mathbf{x_s} + \omega,$$

is sought. To determine ω, a linear stability analysis to the system (Jordan and Smith 1987) is applied. Let $F(\mathbf{x}(t)) = \sum_j L_j \mathbf{w}_j(t)$. The deterministic approximation can then be expressed as,

$$\frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} = F(\mathbf{x}(t)).$$

Let the Jacobian of this system be J. That is,

$$J_{i,j} = \frac{\partial F_i}{\partial x_j}.$$

Let $J_{\mathbf{x}}$ be this Jacobian evaluated at the point $\mathbf{x}$. Linearising this system about the fixed point, $\mathbf{x_s}$, yields,

$$\begin{aligned}\frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} &= F(\mathbf{x_s}) + J_{\mathbf{x_s}}(\mathbf{x}(t) - \mathbf{x_s}) \\ &= J_{\mathbf{x_s}}(\mathbf{x}(t) - \mathbf{x_s}),\end{aligned}$$

as $F(\mathbf{x_s}) = 0$. Let $\mathbf{x}(t) - \mathbf{x_s} = \Delta(t)$. Then, $\frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} = \frac{\mathrm{d}\Delta(t)}{\mathrm{d}t}$ and,

$$\frac{\mathrm{d}\Delta(t)}{\mathrm{d}t} = J_{\mathbf{x_s}}\Delta(t). \tag{8}$$

As Eq. (8) is a system of constant coefficient linear differential equations, the system can be decomposed in terms of its eigenvalues and eigenvectors. Let $J_{\mathbf{x_s}}$ have eigenvalues $\lambda_1, \ldots, \lambda_n$, where $Re(\lambda_1) > \cdots > Re(\lambda_n)$, with corresponding eigenvectors $\mathbf{v_1}, \ldots, \mathbf{v_n}$. It follows that, $\Delta(t) = \sum_{j=1}^{n} \epsilon_j e^{t\lambda_j} \mathbf{v_j}$, where ϵ_j are coefficients that are

yet to be determined. Hence,

$$\mathbf{x}(\mathbf{t}) = \mathbf{x_s} + \sum_{j=1}^{n} \epsilon_j e^{t\lambda_j} \mathbf{v}_j.$$

In the expansion, only the dominant eigenvalue, λ_1, with corresponding eigenvector $\mathbf{v}_1$ is considered. As such,

$$\mathbf{x}(t) = \mathbf{x_s} + \epsilon_1 e^{t\lambda_1} \mathbf{v}_1. \tag{9}$$

Consider now the system at time $t = 0$;

$$\mathbf{x}(0) = \mathbf{x_s} + \epsilon_1 \mathbf{v}_1. \tag{10}$$

Fixing the initial proportion of infection, $i_0 \in (0, 1)$ gives,

$$i_0 = \sum_{(s,e,i,k,a)\in C} x_{(s,e,i,k,a)}(0) i = \mathbf{x}(0) \cdot \mathbf{i},$$

where $\mathbf{i}$ is the vector of infectious individuals, i, in each state $(s, e, i, k, a) \in C$. Using Eq. (10) yields,

$$\mathbf{x}(0) \cdot \mathbf{i} = \mathbf{x_s} \cdot \mathbf{i} + \epsilon_1 (\mathbf{i} \cdot \mathbf{v}_1),$$

but, $\mathbf{x_s} \cdot \mathbf{i} = 0$, as there is no infectious individuals when the population is in state $\mathbf{x_s}$, and so

$$\mathbf{x}(0) \cdot \mathbf{i} = i_0 = \epsilon_1 (\mathbf{i} \cdot \mathbf{v_1}).$$

Rearranging for ϵ_1 gives,

$$\epsilon_1 = \frac{i_0}{\mathbf{i} \cdot \mathbf{v_1}}.$$

Substituting this expression into Eq. (10) gives the equation for the initial condition,

$$\mathbf{x}(0) = \mathbf{x_s} + \frac{i_0}{\mathbf{i} \cdot \mathbf{v}_1} \mathbf{v_1}.$$

Consider the Jacobian of the system. As each stoichiometric matrix, L_i, is constant, the only terms that need to be differentiated are the rate vectors, $\mathbf{w}_i(\mathbf{x}(t))$. The first rate vector, $\mathbf{w}_1$, is nonlinear in $x_n(t)$ as $\hat{I}(t)$ is also a function of $x_n(t)$. To differentiate this vector, consider the nth component,

$$\mathbf{w}_1^{(n)} = \left(\beta_k s_n i_n + \alpha \hat{I}(t) s_n\right) x_n(t),$$

with,

$$\hat{I}(t) = \frac{1}{\bar{k}} \sum_{(s,e,i,k,a)\in C} (1-\tau\delta_{a,1}) i x_{(s,e,i,k,a)}(t)$$
$$= \frac{1}{\bar{k}} \left((1-\tau\delta_{a_n,1}) i_n x_n(t) + \sum_{\substack{j\neq n \\ j\in C}} (1-\tau\delta_{a_j,1}) i_j x_j(t) \right).$$

Then, differentiating term by term gives,

$$\frac{\partial \mathbf{w}_1^{(n)}}{\partial x_m} = \begin{cases} \beta_k s_n i_n + \frac{1}{\bar{k}} s_n \Big(2\alpha(1-\tau\delta_{a_n,1}) i_n x_n(t) \\ \quad + \alpha \sum_{\substack{j\neq n \\ j\in C}} (1-\tau\delta_{a_j,1}) i_j x_j(t) \Big), & \text{if } n = m, \\ \frac{1}{\bar{k}} \alpha s_n (1-\tau\delta_{a_m,1}) i_m x_n(t) & \text{if } n \neq m. \end{cases}$$

Similarly for $\mathbf{w}_2$,

$$\frac{\partial \mathbf{w}_2^{(n)}}{\partial x_m} = \begin{cases} (1-\tau)(1-\rho)\beta_k s_n i_n + (1-\rho)\frac{1}{\bar{k}} s_n \Big(2\alpha(1-\tau\delta_{a_n,1}) i_n x_n(t) \\ \quad + \alpha \sum_{\substack{j\neq n \\ j\in C}} (1-\tau\delta_{a_j,1}) i_j x_j(t) \Big), & \text{if } n = m, \\ (1-\rho)\frac{1}{\bar{k}} \alpha s_n (1-\tau\delta_{a_m,1}) i_m x_n(t), & \text{if } n \neq m. \end{cases}$$

Rate vectors $\mathbf{w}_3$ through to $\mathbf{w}_8$ are linear in $x_n(t)$, and so are straightforward to differentiate, with nth component,

$$\frac{\partial \mathbf{w}_3^{(n)}}{\partial x_m} = \begin{cases} \sigma e_n & \text{if } n = m, \\ 0 & \text{if } n \neq m, \end{cases}$$
$$\frac{\partial \mathbf{w}_4^{(n)}}{\partial x_m} = \begin{cases} \sigma e_n & \text{if } n = m, \\ 0 & \text{if } n \neq m, \end{cases}$$
$$\frac{\partial \mathbf{w}_5^{(n)}}{\partial x_m} = \begin{cases} \gamma i_n & \text{if } n = m, \\ 0 & \text{if } n \neq m, \end{cases}$$
$$\frac{\partial \mathbf{w}_6^{(n)}}{\partial x_m} = \begin{cases} \zeta & \text{if } n = m, \\ 0 & \text{if } n \neq m, \end{cases}$$
$$\frac{\partial \mathbf{w}_7^{(n)}}{\partial x_m} = \begin{cases} \kappa & \text{if } n = m, \\ 0 & \text{if } n \neq m, \end{cases}$$
$$\frac{\partial \mathbf{w}_8^{(n)}}{\partial x_m} = \begin{cases} \psi & \text{if } n = m, \\ 0 & \text{if } n \neq m. \end{cases}$$

The Jacobian of the system is then,

$$J = \sum_{j=1}^{8} L_j \frac{\partial \mathbf{w}_j}{\partial \mathbf{x}}.$$

Appendix 2: Sensitivity Analysis Tables

Tables 3, 4, 5 and 6 contain the results of the sensitivity analysis for varying a single parameter. The number in each cell is the percentage change in the quantity of interest compared to the baseline (no variation). A positive number implies an increase, while a negative number implies a decrease.

Table 3 Sensitivity analysis for *dynamic* allocation scheme using the *severe* parameter set

	+/−	Final size	Peak size	Peak time	Growth
β	+	0.03	0.09	−0.04	0.07
	−	−0.02	−0.05	0.02	−0.04
α	+	0.09	0.30	−0.13	0.23
	−	−0.12	−0.31	0.21	−0.24
γ	+	−0.15	−0.39	0.19	−0.26
	−	0.13	0.52	−0.13	0.27
σ	+	0.0	0.05	−0.04	0.05
	−	0.0	−0.05	0.04	−0.05
τ	+	0.0	0.0	0.02	−0.03
	−	0.0	0.0	−0.02	0.03
ρ	+	0.0	0.0	0.0	0.0
	−	0.0	0.0	0.0	0.0
κ	+	0.0	0.0	0.0	−0.02
	−	0.0	0.0	−0.01	0.02
ζ	+	0.0	0.0	0.0	0.01
	−	0.0	0.0	0.0	−0.01

Table 4 Sensitivity analysis for *dynamic* allocation scheme using the *mild* parameter set

	+/−	Final size	Peak size	Peak time	Growth
β	+	0.04	0.09	−0.04	0.07
	−	−0.11	−0.22	0.11	−0.18
α	+	0.25	0.75	−0.23	0.52
	−	−0.48	−0.65	0.58	−0.55
γ	+	−0.54	−0.75	0.57	−0.66
	−	0.34	1.25	−0.26	0.69
σ	+	0.0	0.05	−0.03	0.04
	−	0.0	−0.05	0.03	−0.05
τ	+	0.0	−0.02	0.04	−0.06
	−	0.0	0.02	−0.04	0.06
ρ	+	0.0	0.0	0.0	−0.01
	−	0.0	0.0	0.0	0.01

Table 4 continued

	+/−	Final size	Peak size	Peak time	Growth
κ	+	0.0	−0.02	0.03	−0.04
	−	0.0	0.02	−0.03	0.05
ζ	+	0.0	0.0	−0.01	0.02
	−	0.0	0.0	0.0	−0.02

Table 5 Sensitivity analysis for *preallocation* scheme using the *severe* parameter set

	+/−	Final size	Peak size	Peak time	Growth
β	+	0.03	0.09	−0.04	0.05
	−	−0.02	−0.04	0.02	−0.03
α	+	0.10	0.29	−0.11	0.19
	−	−0.12	−0.29	−0.16	−0.20
γ	+	−0.15	−0.38	0.13	−0.20
	−	0.14	0.51	−0.10	0.21
σ	+	0.0	0.05	−0.04	0.05
	−	0.0	−0.05	0.05	−0.05
τ	+	0.0	0.0	0.0	0.0
	−	0.0	0.0	0.0	0.0
ρ	+	0.0	0.0	0.0	0.0
	−	0.0	0.0	0.0	0.0
κ	+	0.0	0.0	0.0	0.0
	−	0.0	0.0	0.0	0.0

Table 6 Sensitivity analysis for *preallocation* scheme using the *mild* parameter set

	+/−	Final size	Peak size	Peak time	Growth
β	+	0.03	0.07	−0.02	0.04
	−	−0.09	−0.18	0.06	−0.11
α	+	0.23	0.62	−0.16	0.33
	−	−0.30	−0.53	−0.23	−0.35
γ	+	−0.37	−0.64	0.20	−0.39
	−	0.32	1.06	−0.16	0.41
σ	+	0.0	0.05	−0.04	0.05
	−	0.0	−0.05	0.04	−0.05
τ	+	0.0	−0.01	0.0	0.0
	−	0.0	0.01	0.0	0.0
ρ	+	0.0	0.0	0.0	0.0
	−	0.0	0.0	0.0	0.0
κ	+	0.0	0.0	0.0	0.0
	−	0.0	0.0	0.0	0.0

References

Anderson RM, May RM (1991) Infectious diseases of humans: dynamics and control. Oxford University Press, Oxford

Australian Bureau of Statistics (2011) NPRD number of persons usually resident in dwelling. Census 2011

Ball F (1996) Threshold behaviour in stochastic epidemics among households. In: Heyde C, Prohorov Y, Pyke R, Rachev S (eds) Athens conference on applied probability and time series analysis, Lecture Notes in Statistics, vol 114, pp 253–266. Springer New York. doi:10.1007/978-1-4612-0749-8

Ball F, Donnelly P (1993) Branching process approximation of epidemic models. Theory Probab Appl 37(1):119–121

Ball F, Mollison D, Scalia-Tomba G (1997) Epidemics with two levels of mixing. Ann Appl Probab 7(1):46–89

Ball FG, Lyne OD (2002) Optimal vaccination policies for stochastic epidemics among a population of households. Math Biosci 177:333–354

Bekerman E, Einav S (2015) Combating emerging viral threats. Science 348(6232):282–283

Black AJ, House T, Keeling MJ, Ross JV (2013) Epidemiological consequences of household-based antiviral prophylaxis for pandemic influenza. J R Soc Interface. doi:10.1098/rsif.2012.1019

Black AJ, House T, Keeling MJ, Ross JV (2014) The effect of clumped population structure on the variability of spreading dynamics. J Theor Biol 359:45–53

Brauer F (2001) Mathematical models in population biology and epidemiology, vol 1. Springer, Berlin

Carrasco LR, Lee VJ, Chen MI, Matchar DB, Thompson JP, Cook AR (2011) Strategies for antiviral stockpiling for future influenza pandemics: a global epidemic-economic perspective. J R Soc Interface 8(62):1307–1313. doi:10.1098/rsif.2010.0715

Carrat F, Sahler C, Rogez S, Leruez-Ville M, Freymuth F, Le Gales C, Bungener M, Housset B, Nicolas M, Rouzioux C (2002) Influenza burden of illness: estimates from a national prospective survey of household contacts in France. Arch Intern Med 162(16):1842–1848

Cauchemez S, Carrat F, Viboud C, Valleron A, Boelle P (2004) A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. Stat Med 23:3469–3487

Cauchemez S, Donnelly C, Reed C, Ghani A, Fraser C, Kent C, Finelli L, Ferguson N (2009) Household transmission of 2009 pandemic influenza A(H1N1) virus in the United States. N Engl J Med 361:2619–2627

Colizza V, Barrat A, Barthelemy M (2007) Modeling the worldwide spread of pandemic influenza: baseline case and containment interventions. PLoS Med 4(1):e13. doi:10.1371/journal.pmed.0040013

Commonwealth of Australia (2009) Australian Health Management Plan for Pandemic Influenza

Commonwealth of Australia (2011) Review of Australia's health sector response to pandemic (H1N1) 2009: lessons identified

Cross PC, Johnson PL, Lloyd-Smith JO, Getz WM (2007) Utility of R0 as a predictor of disease invasion in structured populations. J R Soc Interface 4(13):315–324

Fedson D (2003) Pandemic influenza and the global vaccine supply. Clin Infect Dis 36(12):1552–1561

Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS (2006) Strategies for mitigating an influenza pandemic. Nature 442(7101):448–452

Ghani A, Baguelin M, Griffin J, Flasche S, van Hoek AJ, Cauchemez S, Donnelly C, Robertson C, White M, Truscott J et al (2009) The early transmission dynamics of H1N1pdm influenza in the United Kingdom. PLoS Curr 1:RRN1130

Gillespie DT (1977) Exact stochastic simulation of coupled chemical reactions. J Phys Chem 81(25):2340–2361

Glass K, McCaw J, McVernon J (2011) Incorporating population dynamics into household models of infectious disease transmission. Epidemics 3(3):152–158

Goldstein E, Cowling BJ, O'Hagan JJ, Danon L, Fang VJ, Hagy A, Miller JC, Reshef D, Robins J, Biedrzycki P et al (2010) Oseltamivir for treatment and prevention of pandemic influenza A/H1N1 virus infection in households, Milwaukee, 2009. BMC Infect Dis 10:211

Goldstein E, Miller JC, O'Hagan J, Lipsitch M (2010) Predispensing of antivirals to high-risk individuals in an influenza pandemic. Influenza Other Respir Viruses 4(2):101–112. doi:10.1111/j.1750-2659.2009.00128.x.Predispensing

Hayden FG, Belshe R, Villanueva C, Lanno R, Hughes C, Small I, Dutkowski R, Ward P, Carr J (2004) Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J Infect Dis 189(3):440–449

House T, Inglis N, Ross J, Wilson F, Suleman S, Edeghere O, Smith G, Olowokure B, Keeling M (2012) Estimation of outbreak severity and transmissibility: influenza A(H1N1)pdm09 in households. BMC Med 10(1):117

House T, Keeling MJ (2008) Deterministic epidemic models with explicit household structure. Math Biosci 213:29–39. doi:10.1016/j.mbs.2008.01.011

Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ (2012) Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev 1(1):18–35

Jordan DW, Smith P (1987) Nonlinear ordinary differential equations. Clarendon Press, Oxford

Keeling MJ, Rohani P (2008) Modeling infectious diseases in humans and animals. Princeton University Press, Princeton

Keeling MJ, Ross JV (2015) Optimal prophylactic vaccination in segregated populations: when can we improve on the equalising strategy? Epidemics 11:7–13

Kurtz TG (1970) Solutions of ordinary differential equations as limits of pure jump Markov processes. J Appl Prob 7:49–58

Kwok KO, Leung GM, Mak P, Riley S (2013) Antiviral stockpiles for influenza pandemics from the household perspective: treatment alone versus treatment with prophylaxis. Epidemics 5(2):92–97

Longini IM, Halloran ME, Nizam A, Yang Y (2004) Containing pandemic influenza with antiviral agents. Am J Epidemiol 159(7):623–633

Longini IM, Nizam A, Xu S, Ungchusak K, Hanshaoworakul W, Cummings DA, Halloran ME (2005) Containing pandemic influenza at the source. Science 309(5737):1083–1087

Matrajt L, Halloran M, Longini IM Jr (2013) Optimal vaccine allocation for the early mitigation of pandemic influenza. PLoS Comput Biol 9(3):e1002964. doi:10.1371/journal.pcbi.1002964

Merler S, Ajelli M, Rizzo C (2009) Age-prioritized use of antivirals during an influenza pandemic. BMC Infect Dis 9:117

Mills CE, Robins JM, Lipsitch M (2004) Transmissibility of 1918 pandemic influenza. Nature 432(7019):904–906

Pandemic Influenza Preparedness Team (2011) Department of Health: National Pandemic Flu Service: an evaluation

Pellis L, Ball F, Trapman P (2012) Reproduction numbers for epidemic models with households and other social structures. I. Definition and calculation of R_0. Math Biosci 235(1):85–97. doi:10.1016/j.mbs.2011.10.009

Public Health England (2014) Pandemic influenza strategic framework

Ross J, House T, Keeling M (2010) Calculation of disease dynamics in a population of households. PLoS One 5(3):e9666. doi:10.1371/journal.pone.0009666

Stiver G (2003) The treatment of influenza with antiviral drugs. Can Med Assoc J 168(1):49–57

U.S. Department of Health and Human Services (2005) HHS pandemic influenza plan

Webby R, Perez D, Coleman J, Guan Y, Knight J, Govorkova E, McClain-Moss L, Peiris J, Rehg J, Tuomanen E, Webster R (2004) Responsiveness to a pandemic alert: use of reverse genetics for rapid development of influenza vaccines. Lancet 363:1099–1103

Webby R, Webster R (2003) Are we ready for pandemic influenza? Science 302(5650):1519–1522