Estimating antiviral effectiveness against pandemic influenza using household data

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Current estimates of antiviral effectiveness for influenza are based on the existing strains of the virus. Should a pandemic strain emerge, strain-specific estimates will be required as early as possible to ensure that antiviral stockpiles are used optimally and to compare the benefits of using antivirals as prophylaxis or to treat cases. We present a method to measure antiviral effectiveness using early pandemic data on household outbreak sizes, including households that are provided with antivirals for prophylaxis and those provided with antivirals for treatment only. We can assess whether antiviral drugs have a significant impact on susceptibility or on infectivity with the data from approximately 200 to 500 households with a primary case. Fewer households will suffice if the data can be collected before case numbers become high, and estimates are more precise if the study includes data from prophylaxed households and households where no antivirals are provided. Rates of asymptomatic infection and the level of transmissibility of the virus do not affect the accuracy of these estimates greatly, but the pattern of infectivity in the individual strongly influences the estimate of the effect of antivirals on infectivity. An accurate characterization of the infectiousness profile—informed by strain-specific data—is essential for measuring antiviral effectiveness.

Keywords: influenza; antiviral drugs; estimation; transmission model; pandemic

1. INTRODUCTION

In the event of an influenza pandemic, antiviral drugs such as oseltamivir and zanamivir will be used to reduce disease transmission. For the currently circulating strains of influenza, these drugs have been found to reduce the risk of infection in susceptible individuals (Hayden *et al.* 2000, 2004; Welliver *et al.* 2001; Monto *et al.* 2002; Jefferson *et al.* 2006), and to reduce the levels of virus shedding in infected individuals who are treated soon after symptom onset (Hayden *et al.* 1996, 1997, 1999; Nicholson *et al.* 2000; Treanor *et al.* 2000; Jefferson *et al.* 2006). Many countries have or will obtain a stockpile of antivirals for use in an influenza pandemic (Cheng 2005; Lett 2005; Esveld 2006; Harrod *et al.* 2006) and mathematical models have been used to investigate the relative benefit of using antivirals for prophylaxis and treatment (Ferguson *et al.* 2005; Longini *et al.* 2005; Barnes & Glass 2007; McCaw & McVernon 2007) using data for the currently circulating influenza. However, the effectiveness of antivirals for a pandemic strain is not known, and strain-specific estimates of antiviral effectiveness will be urgently required to assist policy makers in making the optimal use of the stockpile. During an influenza pandemic,

health care workers will be very busy caring for patients and so will have limited time to collect extensive data. Here, we propose a method for estimating the parameters describing the effectiveness of antivirals using data on household outbreak size that are relatively easy to collect.

Most existing household studies that assess antivirals for prophylaxis observe contacts of the index case only (Hayden *et al.* 2000, 2004; Welliver *et al.* 2001; Monto *et al.* 2002). Under this study design, it is not possible to distinguish the effects of antivirals in reducing the infectivity of cases on antivirals from the effect of antivirals in reducing susceptibility of their prophylaxed contacts. However, to compare a strategy of using antivirals for treatment with one of using them for prophylaxis, the estimates of both effects are needed. One recent approach to providing both estimates (Halloran *et al.* 2006) combines studies, but it is difficult to ensure consistency across studies, and the authors note the need to improve the study design in the future. By incorporating transmission into our model, we are able to include information from all individuals exposed to household cases, and so distinguish the effects of antivirals on infectivity and on susceptibility within a single study.

Data from antiviral trials indicate that the infectivity of influenza cases varies over the course of the infectious period, with a fairly early peak in shedding (Hayden *et al.* 1996, 1999). Thus, the potential benefit

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of antivirals to reduce transmission is strongly influenced by the time that they are administered. These findings are reflected in the recommendations that antivirals will only be provided to individuals who are diagnosed within 2 days of symptom onset (Lett 2005; Harrod *et al.* 2006). In the clinical trials of antiviral drugs, changes in infectivity over the infectious period are controlled by ensuring that study participants are given antivirals at a fixed time following exposure. This study design is likely to pose ethical and practical difficulties during an influenza pandemic. In the methods presented here, we assume that individuals may be provided with antivirals prior to infection or at various times following infection, and explicitly model the effect of timing on the impact of the drugs. We investigate the effect of different assumptions about infectivity on our estimates, and determine the household data that are most useful for obtaining good estimates of antiviral effectiveness.

2. METHODS

2.1. Transmission probabilities

We use the Reed–Frost assumptions (Bailey 1975) to describe transmission within households. In the absence of antivirals, θ is the probability that an individual escapes infection from an infected household member, and s is the probability that an individual escapes infection from outside the household over a period of time equal to the mean generation interval. The escape probability s applies for each generation of transmission, so that if the household outbreak is observed to last g generations, the probability of an individual escaping infection from outside the households throughout that period is s^g .

2.2. Model of infectivity and the effect of antivirals

We model changes in the infectiousness of individuals over the course of the infectious period using a deterministic birth–death process for the growth of the virus population, with birth rate λ and death rate μ .

infectiousness function under this model. Although a smoother peak could be obtained with more parameters, a comparison of this curve with shedding data (Hayden *et al.* 1996, 1999) confirms that this simple model reflects shedding patterns fairly well. The use of fewer parameters is attractive because it tends to produce more precise parameter estimates.

We consider the following five possible times at which the antivirals are administered relative to the infection of the primary case:

- (i) antivirals given prior to infection of the primary case: $T_A = 0$,
- (ii) antivirals given upon onset of symptoms in the primary case: $T_A = T_I$,
- (iii) antivirals given 1 day after the onset of symptoms in the primary case: $T_A = T_I + 1$,
- (iv) antivirals given 2 days after the onset of symptoms in the primary case: $T_A = T_I + 2$, and
- (v) antivirals not provided.

Figure 1 illustrates the effect of antivirals on infectiousness for three of these scenarios.

We model the effect of antivirals on susceptibility by assuming that an individual's probability of escaping infection during a single contact is changed by a factor σ while on antivirals. Antivirals have no effect on susceptibility if $\sigma = 1$ and antivirals prevent the infection with certainty if $\sigma = 0$. The probability that an individual who is continuously on antivirals is not infected by a specific household case is θ^σ . The inclusion of σ in the exponent can be understood if we consider θ to be of the form $\theta = \exp(\beta \int_0^\infty \text{infectivity function})$, where the protective effect of the antivirals acts multiplicatively on β . Similarly, the probability that an individual on antivirals escapes infection from outside the household during one generation time is s^σ . For simplicity, we assume that s does not depend on the calendar time that antivirals are provided to the individual. We discuss alternative assumptions about transmission from outside the household below.

Table 1 shows the probability that there is only one case in a household of size 2 (given a primary household case), for different interventions, where $f(t)$, $g(t)$ and $h(t)$ are given by

$$\begin{aligned} f(0) &= \frac{Y}{(\delta - \lambda)}(1 - Z) & f(T_I) &= 1 - \frac{\delta X}{(\mu + \delta - \lambda)} & f(T_I + k) &= 1 + (f(T_I) - 1)e^{(\lambda - \mu)k} \\ g(0) &= \sigma & g(T_I) &= 1 - (1 - \sigma)X & g(T_I + k) &= 1 + (g(T_I) - 1)e^{(\lambda - \mu)k} \\ h(0) &= \sigma f(0) & h(T_I) &= 1 - X + \frac{\sigma(\mu - \lambda)X}{(\mu + \delta - \lambda)} & h(T_I + k) &= 1 + (h(T_I) - 1)e^{(\lambda - \mu)k} \end{aligned}$$

The death rate applies once the immune system becomes active, T_I days after infection. We assume that T_I is also the time of the onset of symptoms, which is broadly consistent with the data on viral titre and symptom scores in clinical trials (Hayden *et al.* 1996). The effect of antivirals is to introduce an additional death rate δ at the time (T_A) they are administered. The solid curve in figure 1 gives an example of the

with

$$\begin{aligned} X &= \frac{\lambda e^{\lambda T_I}}{(\mu e^{\lambda T_I} - \mu + \lambda)}, & Y &= \frac{\lambda(\mu - \lambda)}{(\mu e^{\lambda T_I} - \mu + \lambda)}, \\ Z &= \frac{\mu e^{(\lambda - \delta) T_I}}{(\mu + \delta - \lambda)}, & k &= 1, 2. \end{aligned}$$

Figure 1. (a–c) Infectiousness over time with (dashed curves: (a) intervention prior to infection, (b) intervention upon symptom onset, (c) intervention at time T_A) and without (solid curves) antivirals. The plots show the effect of providing antivirals at different times in an individual's infectious period on their infectiousness.

Table 1. The probability that there is only one case in a two-person household with a primary case under different intervention scenarios. (Parameters and functions are specified in table 2.)

	antivirals given to primary case only	antivirals given to partner of primary	antivirals given to both indi- viduals
time, t	$\theta^{f(t)} s$	$\theta^{g(t)} s^\sigma$	$\theta^{h(t)} s^\sigma$
no intervention	θs	θs	θs

Note that $f_T = f(T_I)$ is the fraction of infectiousness experienced by an individual given antivirals at symptom onset, relative to an individual not given antivirals. Alternatively, this can be interpreted as the ratio of the area under the infectiousness function of an individual given antivirals at symptom onset to the area under the infectiousness function of an individual not given antivirals. As the parameter f_T reflects the impact of antivirals on transmission more directly than δ , we will use f_T to describe the effect of antivirals on infectiousness. A summary of all parameters in the model is given in table 2, including the values assumed for simulations. We consider two sets of values for the transmission parameters to compare relatively high and low levels of transmission. Under the low transmission rates in the absence of antivirals, there is an average of two secondary cases in a household of size 6, whereas there are 3.5 secondary cases on average under high transmission rates.

2.3. Estimating unknown parameters

We expand the two-person household scenario described above to consider larger households under two possible intervention scenarios.

- Scenario A: prophylaxis and treatment in households. Antivirals are given to the entire household T_A days after infection of the primary case.
- Scenario B: treatment only in households. Antivirals are given to the primary case T_A days after infection, and to each subsequent case in the household upon onset of their symptoms.

Using the above formulae for $f(t)$, $g(t)$ and $h(t)$, we can write down a likelihood function for this model, assuming that the data include household size, household outbreak size, timing of introduction of the antivirals relative to the infection of the primary case and intervention scenario as above (see the appendix in the electronic supplementary material for more details). That is, we use the final outbreak size in the household, but do not require data on the time that secondary cases become infected, nor data on who infected whom within the household. We observe households until there is a generation in which there are no new cases. In practice, there may be some difficulties translating this into calendar time. However, in our study, the aim is to determine how much data are needed for useful inferences, and for this aim the assumed setting is convenient and informative. This is confirmed by calculations for an alternative period of observation of five generation times.

We find maximum-likelihood estimates for the parameters f_T , σ , θ and s , under the case where λ , μ and T_I are known, and also considering the case where all parameters are estimated simultaneously. All confidence intervals for parameters, calculated using profile likelihoods, are 95 per cent confidence intervals. Parameter values are assigned to λ , μ and T_I so that the infectiousness function reflects observed data on virus shedding.

To assess the estimates of the parameters f_T , σ , θ and s , we compute their estimates corresponding to the data generated from the above model. We exclude single-person households and those with more than six members, assuming that the remaining households are distributed in accordance with the 2001 Australian census data. That is, 44 per cent are of size 2, 21 per cent are of size 3, 21 per cent are of size 4, 10 per cent are of size 5 and 4 per cent are of size 6.

2.4. Alternative assumptions and sensitivity analysis

2.4.1. Alternative period of household observation. Under our baseline framework, we observe all households from the primary case until there is a generation in which there are no cases. Thus, a household with only the primary case is observed for one generation only, while a household with many secondary cases may be observed for up to five generations, depending on the chain of infections. We then adjust for these different observation periods in the likelihood function. In order to confirm that this method does not influence our results, we considered an alternative framework, in which all households are observed for five generations, regardless of the household size or the number of cases.

Table 2. Summary of parameters in the model.

parameter	value	description
θ	low: 0.7 high: 0.5	probability that an individual escapes infection from an infected household member if neither is on antivirals
s	low: 0.98 high: 0.96	probability that an individual not on antivirals escapes infection from outside the household over one generation
λ	4	birth rate of the virus within the host
μ	5	death rate of the virus within the host due to the immune response
δ	0.5	death rate of the virus within the host due to antivirals
σ	0.5	factor by which the probability of infection per contact is reduced for an individual on antivirals
T_1	2	days after infection that the immune system becomes active; assumed to be the time of onset of symptoms
T_A	varies	days after infection of the primary case that antivirals are provided to individuals in the household
f_T	$f(T_1)$	relative infectiousness of a case given antivirals at symptom onset, compared with a case not given antivirals

The likelihood function (see the appendix in the electronic supplementary material) is considerably more complicated under this model, as the probability of infection from outside the household must be taken into account for a full five generations, regardless of the chain of infections.

2.4.2. Alternative model of infectiousness. We test the sensitivity of the parameter estimates to our model of infectiousness by generating data from an alternative model in which infectiousness is constant over the infectious period. This ‘constant infectiousness’ model assumes that individuals are not infectious on day 1 or after day 4, and are equally infectious on days 2–4, with symptoms appearing at the end of day 2. We assume that individuals’ susceptibility per contact is reduced by a factor σ_S while on antivirals, as with σ in the original model. The effect on infectivity is to reduce infectiousness by a factor σ_I while on antivirals. That is, if a case is on antivirals throughout the infectious period, their probability of infecting a household member not on antivirals is reduced to $1 - \theta^{\sigma_I}$, and if both the case and the household member are on antivirals, the probability of infection is reduced to $1 - \theta^{\sigma_I \sigma_S}$. We estimate σ_S and f_T from the data generated by this alternative model, where $f_T = ((1/3) + (2/3)\sigma_I)$ is the fraction of infectiousness experienced by an individual put on antivirals upon onset of symptoms.

2.4.3. Sensitivity to asymptomatic cases. We test the sensitivity of our estimates to some level of asymptomatic infection by generating data in which a third of cases are asymptomatic, and thus are not recorded in the household outbreak. Clearly, there are many different scenarios for asymptomatic transmission. Here, we look at two extremes: one in which asymptomatic cases are not infectious at all, and another in which they are as infectious as symptomatic cases.

2.4.4. Alternative models of transmission from outside the household. Our baseline model of transmission assumes that over each generation of infection, a

susceptible individual has a probability s of escaping infection from outside the household. In order for infection rates to be realistic over the course of a population outbreak, s must be approximately constant over time. We consider two alternative models: one in which there is no transmission from outside the household during the household outbreak, and another in which transmission from outside the household increases while data are collected, to reflect a growing epidemic.

Most household outbreaks will include at most two generations after the primary case. If the force of infection from outside the household is small—e.g. in the very early stages of an outbreak—then the chance of a household member becoming infected from outside the household over these generations is negligible. By eliminating the parameter s from the model, we may be able to obtain tighter bounds on the other parameters.

On the other hand, if case numbers increase considerably over the study period, individuals will be more likely to be infected from outside the household as time goes on. To model this, we replace s with $s_0 \exp(-\gamma d)$, where γ is determined by the increase in case numbers, which can be estimated separately, and d is the day of the first household case, relative to the start of the outbreak. This model is likely to be more appropriate if the household data are collected over an extended period of time, as it takes account of the increase in the force of infection acting on the household as the outbreak progresses.

2.4.5. Alternative assumption about mixing within households. The original likelihood function assumes that the within-household transmission rate between individuals does not vary with household size. We compare this model with one in which the escape probability varies according to household size as $\theta^{1/(n-1)}$, where n is the household size. This formulation would arise if we assumed that every household member had a fixed number of contacts and distributed them evenly among the household members.

Figure 2. Estimates of parameters f_T (effect of antivirals on infectivity), σ (effect of antivirals on susceptibility), θ (quantifies within-household transmission) and s (quantifies transmission from outside the household) for three different intervention strategies of a study comprising 500 households. In each case, the circles and lines show the estimates and confidence intervals, while the crosses show the true values. (a) Prophylaxis and treatment in households, (b) treatment only in households and (c) equal combination of the above two strategies. Parameters used to generate the data were: $\lambda=4$, $\mu=5$, $T_1=2$, $f_T=0.73$, $\sigma=0.5$, $\theta=0.7$ and $s=0.98$, which correspond to fairly low transmission rates.

3. RESULTS

3.1. Impact of antiviral distribution strategies

We want to compare the precision of the parameter estimates under two different antiviral distribution strategies: one that includes prophylaxis, and the other that only includes treated cases. The plots in figure 2 show these estimates for a simulated dataset with 500 households under true parameter values that describe relatively low transmission. In each plot, the circles and the lines show the estimates and confidence intervals, while the crosses show the true values. Figure 2a is for the prophylaxis and treatment strategy, figure 2b is for the treatment-only strategy and figure 2c assumes that half of the households were given antivirals according to each strategy. Each part of figure 2 illustrates estimates for a single randomly selected dataset. This allows us to demonstrate the width of the confidence intervals. Repetitions produced similar results. We see that we can get tighter bounds on the estimates of all parameters if the study includes households with both types of intervention. In the case of figure 2b, antivirals are not given to uninfected household members, so it is not possible to estimate their effect on susceptibility. Repeating these calculations using high transmission rate parameters, we find that the estimates of s and θ become a little less precise, while the estimates of σ and f_T become more precise. It is still preferable to have data from both treatment-only and prophylaxis and treatment households.

3.2. Impact of antiviral timing strategies

The example in figure 2 assumes 100 households of each type, where antivirals are equally likely to be provided to the primary case at the five possible times, namely

- (i) prior to infection of any member,
- (ii) upon onset of symptoms of the primary case,
- (iii) 1 day after symptom onset of the primary case,
- (iv) 2 days after symptom onset of the primary case, and
- (v) antivirals not given at all.

Antivirals are also provided to the remainder of the household under the prophylaxis and treatment scenario. In figure 3, we compare the parameter

estimates under different combinations of antiviral distribution times, assuming low transmission rates, as follows:

- figure 3a includes an equal number of households of the above five types,
- figure 3b excludes households of type (i) and has an equal number of the remaining types,
- figure 3c excludes households of type (v) and has an equal number of the remaining types, and
- figure 3d excludes households of types (iii) and (iv) and has an equal number of the remaining types.

Each example has the same total number of households.

We see that the estimates of the effect of antivirals on susceptibility (σ) and infectivity (f_T) are more precise if the data include some households of types (i) and (v)—that is, households in which the primary case was taking antivirals as prophylaxis, and households that do not receive any antivirals. Data from the households where antivirals are provided 1 or 2 days after symptoms contribute less information, and slightly tighter bounds are possible if antivirals are provided early, or not at all. These results remain true if the transmission rates are higher.

3.3. Data requirements

In the early stages of a pandemic, when only minimal data are available, the priority will be to assess whether antivirals have a beneficial impact on susceptibility and infectiousness. That is, we will want to know whether either or both of σ (measuring antiviral impact on susceptibility) and f_T (measuring antiviral impact on infectiousness) are significantly less than 1. For figure 4, we simulated 100 datasets and show the percentage of simulations in which the confidence interval does not include 1 for each parameter, for both low and high transmission rates.

In general, it is slightly easier to distinguish an effect of antivirals if transmission rates are high, as this creates more exposures within households. There is a good chance that an effect on infectiousness and susceptibility such as that assumed here can be demonstrated if data on 200–500 households with a primary case have been collected.

Figure 3. Estimates of parameters f_T (effect of antivirals on infectivity), σ (effect of antivirals on susceptibility), θ (quantifies within-household transmission) and s (quantifies transmission from outside the household) for four different intervention strategies of a study comprising 500 households. In (a), all intervention times are included equally; in (b), none of the primary cases were given antivirals prior to infection; in (c), there were no households included in which antivirals were not provided; and in (d), individuals were either given antivirals at (or before) symptom onset or not at all. In each case, the circles and lines show the estimates and confidence intervals, while the crosses show the true values. Parameters used to generate the data were: $\lambda=4$, $\mu=5$, $T_1=2$, $f_T=0.73$, $\sigma=0.5$, $\theta=0.7$ and $s=0.98$, which correspond to fairly low transmission rates.

3.4. Alternative period of household observation

We have assumed that a household is observed until there are no cases in a generation. This observation period is attractive because it captures most within-household transmissions with a relatively short observation period and computation is relatively shorter because expressions for the chain probabilities are simpler. However, there may be practical difficulties with this stopping rule. To assess this concern, the results were compared with those for the scenario where all households are observed for a fixed time period equal to five generation times. We found no appreciable difference in estimates or confidence intervals for the antiviral parameters. In other words, recommendations on study size would be the same.

3.5. Alternative model of infectiousness

Our analysis assumes an underlying model of infectiousness with a fairly sharp rise and fall in infectivity (figure 1). We investigate the sensitivity of our estimates to this model by generating data using an extreme alternative in which infectiousness is constant over a 3-day infectious period. We generate the data using this flat infectiousness model, and then estimate the parameters f_T , σ , θ and s , where f_T under each model is the fraction of infectiousness experienced by an individual put on antivirals at symptom onset when compared with an individual not given antivirals.

Table 3 shows the percentage of 100 trials in which the confidence intervals for the parameters contained the true value when the data were generated using the varying infectiousness model, compared with the case

Figure 4. The percentage of 100 trials in which the computed 95% confidence interval did not include 1 for each parameter for (a) low and (b) high transmission rates, and for increasing numbers of households (100–1000). Black bars, 100; dark grey bars, 200; light grey bars, 500; white bars, 1000. Parameters f_T and σ measure the effect of antivirals on infectivity and susceptibility (respectively), while θ and s are the escape probabilities for infection from within and outside the household. Parameters used to generate the data were: $\lambda=4$, $\mu=5$, $T_1=2$, $f_T=0.73$, $\sigma=0.5$, with $\theta=0.7$ and $s=0.98$ for low transmission, and $\theta=0.5$ and $s=0.96$ for high transmission.

when the data were generated using a model in which infectiousness was constant over the infectious period. In both cases, the analysis assumes the varying infectious model, which allows us to test the impact of this assumption if the data do not conform to this model. Under the constant infectiousness model, the confidence intervals for σ (the impact of antivirals on

Table 3. The effect of assumptions about infectiousness on parameter estimates. (The table compares the percentage of 100 trials in which the 95% confidence interval contained the true value when the data were generated using the underlying model with varying infectiousness, and when the data were generated using an alternative model where infectiousness is constant over the infectious period. Parameters f_T and σ measure the effect of antivirals on infectivity and susceptibility (respectively), while θ and s are the escape probabilities for infection from within and outside the household. Parameters used to generate the data were: $\lambda=4$, $\mu=5$, $T_1=2$, $f_T=0.73$, $\sigma=0.5$, $\theta=0.7$ and $s=0.98$.)

	100 house- holds	200 house- holds	500 house- holds	1000 households
<i>data simulated assuming varying infectiousness</i>				
f_T	100	98	97	99
σ	96	95	93	97
θ	98	99	99	98
s	100	98	99	96
<i>data simulated assuming constant infectiousness</i>				
f_T	93	85	57	28
σ	98	97	92	88
θ	97	99	88	74
s	95	95	89	82

susceptibility), θ (the within-household transmission parameter) and s (the between-household transmission parameter) contain the true value in approximately 90 per cent of the trials for up to 1000 households, but the estimate of f_T (the impact of antivirals on infectiousness) is much less reliable, owing to the large differences in the infectiousness functions under the two models. In order to get precise and accurate estimates of the effect of antivirals on infectiousness, the model needs to reflect the pattern of infectiousness in the individual fairly accurately.

In light of this result, we investigated the potential to estimate the three parameters defining the infectiousness function in addition to the four parameters of the model using these household data. When we try to estimate all seven parameters in the model simultaneously, more households are needed to obtain precise estimates. For example, once all parameters are included, approximately 1000 households are needed to assess whether antivirals are having an impact on susceptibility, in comparison with approximately 500 when the infectiousness function parameters are fixed. Confidence intervals for the three additional parameters are still wide with 1000 households.

3.6. Impact of asymptomatic cases

A further test of model assumptions was to assess the impact of undetected asymptomatic cases in the household outbreaks. We generated the data under an alternative model in which 33 per cent of cases were asymptomatic, considering both the scenario where asymptomatic cases are as infectious as symptomatic cases, and the scenario where they are not infectious at all. We find inclusion of asymptomatic cases has a large effect on the estimation of θ , which captures the within-household transmission rate, but has no noticeable effect on the accuracy of other parameter

estimates. We find that the precision of the estimate of the effect on susceptibility (σ) is slightly decreased by the presence of asymptomatic cases, but otherwise, the estimates of parameters measuring antiviral effectiveness do not seem to be affected.

3.7. Alternative model of transmission from outside the household

If it is possible to collect data from households in the very early stages of the outbreak, we can adopt a simpler model of transmission that ignores the impact of transmission from outside the household. That is, once there is a primary case in a household, we assume that the force of infection acting on individuals from outside the household is negligible for the duration of the household outbreak. Under this assumption, we fix $s=1$, and so the number of parameters to be estimated is reduced to three. Most of the results presented above continue to hold for this simpler model, except that estimates of f_T and θ are considerably more precise, and the estimates of σ are a little more precise. In particular, 100–200 households are sufficient to detect an effect of antivirals on infectivity, although at least 200 households are still needed to detect an effect of antivirals on susceptibility.

By contrast, if the household data are collected over an extended period of time during which the current case numbers increase considerably, then it may be necessary to take account of the changing force of infection acting on the household. This model requires us to estimate the increase in case numbers separately, but otherwise, the results remain similar under these assumptions, with the estimates of f_T , θ and σ all becoming slightly more precise under this model.

3.8. Alternative assumption about within-household mixing

We tested the effect of an alternative assumption in which the escape probability varies according to the household size as $\theta^{1/(n-1)}$, where n is the household size. Reproducing figure 4 with the corresponding new likelihood function, we find that slightly more data are required to test the impact of antivirals on infectivity f_T , while the other estimates are similar. When the infectivity function is changed to a constant function (as shown in table 3 for the original likelihood function), f_T is still unlikely to be estimated accurately, but the other parameters are slightly more likely to be unaffected by the change to the infectivity function. Overall, the effect of this change in assumptions is fairly minor.

4. DISCUSSION

This paper shows that the data on household outbreak size can be used to estimate the effect of antiviral drugs in the early stages of an influenza outbreak. Even with relatively low levels of transmission within households, it is possible to confirm that antivirals are having a significant effect using the data from 200 to 500 households. If these data can be collected very

early in the outbreak, only 100–200 households are needed to detect whether antivirals are reducing the infectiousness of cases. In the event of an influenza pandemic, there will be limited resources for collecting data, as health workers will have many claims on their time. Our methods do not require extensive data to be collected from households, and so will not place a large burden on health care workers.

We considered a range of timing and distribution strategies to identify those that provide the most informative data for estimating antiviral effects. We find that it is useful to have a range of intervention scenarios in the study, including some households where antivirals are given as prophylaxis, as well as some households in which antivirals are only given as treatment, and some in which no antivirals are provided. It is plausible that prophylaxis may be provided to households in which one family member is at a high risk of exposure to infection—say, a health care worker. Provided they are the only family members at high risk and they are the primary cases, these households would provide valuable data for a study of antiviral effectiveness. There are also likely to be households in which antivirals are not provided because the primary case was not diagnosed sufficiently early. Including such households is also of great benefit.

In addition to the baseline transmission model, we considered the effect of alternative assumptions about transmission from outside the household and the infectiousness of individuals on the accuracy and precision of parameter estimates. If it is possible to collect very early outbreak data, a simpler model applies which increases the precision of the parameter estimates. If the data are collected over an extended period of time, then it may be necessary to adjust for the increasing force of infection acting on households. This requires slightly more data to be collected, but otherwise has little impact on the results presented here. Inclusion of asymptomatic cases has little effect on the accuracy of the estimates of parameters measuring antiviral efficacy, which is reassuring, as it may be difficult to measure the rate of asymptomatic infections in the early stages of the outbreak.

By contrast, incorrect assumptions about the infectiousness of individuals over their infectious period can lead to very inaccurate estimates of the effect of antivirals on infectivity. Shedding data from antiviral trials suggest an early peak in infectiousness and it is crucial that this is taken into account when measuring antiviral effectiveness for reducing infectivity. This is particularly important in the event of an influenza pandemic, when the timing of the administration of antivirals cannot generally be predetermined. A good understanding of the infectiousness profile of influenza cases is also needed for a number of intervention strategies, such as isolation of cases, so it is clearly a high priority to measure this for a new pandemic strain. With proper surge capacity to collect data on household outbreaks as part of the process for distributing antivirals and with the assumption that infectiousness within pandemic flu cases evolves as for seasonal flu, one can apply these methods to obtain

useful estimates of antiviral effectiveness with the data on approximately 200 household outbreaks. For estimates that are robust against variations from the properties of seasonal flu, the data from approximately 1000 household outbreaks are needed. This remains feasible, particularly when the data from different jurisdictions are pooled. These methods use the data on household outbreak size, and do not require the data to be collected on who infected whom, or detailed data on the time that secondary cases develop in the household. This is a deliberate restriction to ensure that the task of data collection is not burdensome. However, if there were sufficient resources to gather data on the timing of secondary cases, it seems likely that both the antiviral impact and the shape of the infectiousness function could be estimated using fewer households. We are currently investigating the potential of this approach in comparison with a method of using linked pairs of cases to build a model of the infectiousness function. Together with the methods presented here, these techniques will allow us to estimate the impact of a number of pandemic influenza control measures from early outbreak data.

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REFERENCES

- Bailey, N. J. T. 1975 *The mathematical theory of infectious diseases and its applications*. London, UK: Griffin.
- Barnes, B. & Glass, K. 2007 The role of health care workers and antiviral drugs in the control of pandemic influenza. *Math. Biosci.* **209**, 403–416. (doi:10.1016/j.mbs.2007.02.008)
- Cheng, M. H. 2005 Flu, what flu. *Lancet Infect. Dis.* **5**, 746. (doi:10.1016/S1473-3099(05)70290-5)
- Esveld, M. 2006 Influenza as an issue on the agenda of policy makers and government representatives. What can we do? What do we need? *Vaccine* **24**, 6793–6795. (doi:10.1016/j.vaccine.2006.06.068)
- Ferguson, N. M., Cummings, D. A. T., Cauchemez, S., Fraser, C., Riley, S., Meeyai, A., Iamsirithaworn, S. & Burke, D. S. 2005 Strategies for containing an emerging influenza pandemic in southeast Asia. *Nature* **437**, 209–214. (doi:10.1038/nature04017)
- Halloran, M. E., Hayden, F. G., Yang, Y., Longini, I. M. & Monto, A. S. 2006 Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials. *Am. J. Epidemiol.* **165**, 212–221. (doi:10.1093/aje/kwj362)
- Harrod, M. E., Emery, S. & Dwyer, D. E. 2006 Antivirals in the management of an influenza pandemic. *Med. J. Aust.* **185**, S58–S61.
- Hayden, F. G., Treanor, J. J., Betts, R. F., Lobo, M., Esinhart, J. D. & Hussey, E. K. 1996 Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. *J. Am. Med. Assoc.* **275**, 295–299. (doi:10.1001/jama.275.4.295)
- Hayden, F. G. *et al.* 1997 Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. *N. Engl. J. Med.* **337**, 874–880. (doi:10.1056/NEJM199709253371302)

- Hayden, F. G. *et al.* 1999 Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza. *J. Am. Med. Assoc.* **282**, 1240–1246. (doi:10.1001/jama.282.13.1240)
- Hayden, F. G., Gubareva, L. V., Monto, A. S., Klein, T. C., Elliott, M. J., Hammond, J. M., Sharp, S. J. & Ossi, M. J. 2000 Inhaled zanamivir for the prevention of influenza in families. *N. Engl. J. Med.* **343**, 1282–1289. (doi:10.1056/NEJM200011023431801)
- Hayden, R. G., 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**, 440–449. (doi:10.1086/381128)
- Jefferson, T., Demicheli, V., Rivetti, D., Jones, M., Pietrantoni, C. D. & Rivetti, A. 2006 Antivirals for influenza in healthy adults: systematic review. *Lancet* **367**, 303–313. (doi:10.1016/S0140-6736(06)67970-1)
- Lett, D. 2005 Feds to stockpile antivirals as pandemic “speed bump”. *Can. Med. Assoc. J.* **172**, 1167. (doi:10.1503/cmaj.050332)
- Longini, I. M., Nizam, A., Xu, S., Ungchusak, K., Hanshaworakul, W., Cummings, D. A. T. & Halloran, M. E. 2005 Containing pandemic influenza at the source. *Science* **309**, 1083–1087. (doi:10.1126/science.1115717)
- McCaw, J. M. & McVernon, J. 2007 Prophylaxis or treatment? Optimal use of an antiviral stockpile during an influenza pandemic. *Math. Biosci.* **208**, 336–360. (doi:10.1016/j.mbs.2007.02.003)
- Monto, A. S., Pichichero, M. E., Blanckenberg, S. J., Ruuskanen, O., Cooper, C., Fleming, D. M. & Kerr, C. 2002 Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J. Infect. Dis.* **186**, 1582–1588. (doi:10.1086/345722)
- Nicholson, K. G., Aoki, F. Y., Osterhaus, A., Trottier, S., Carewicz, O., Mercier, D. H., Rode, A., Kinnersley, N. & Ward, P. 2000 Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. *Lancet* **355**, 1845–1850. (doi:10.1016/S0140-6736(00)02288-1)
- Treanor, J. J. *et al.* 2000 Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza. *J. Am. Med. Assoc.* **283**, 1016–1024. (doi:10.1001/jama.283.8.1016)
- Welliver, R. *et al.* 2001 Effectiveness of oseltamivir in preventing influenza in household contacts. *J. Am. Med. Assoc.* **285**, 748–756. (doi:10.1001/jama.285.6.748)