A population-dynamic model for evaluating the potential spread of drug-resistant influenza virus infections during community-based use of antivirals

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A mathematical model of influenza transmission dynamics is used to simulate the impact of neuraminidase inhibitor therapy on infection rates and transmission of drug-resistant viral strains. The model incorporates population age structure, seasonal transmission, immunity and inclusion of elderly nursing home residents or non-residents. Key parameter values are estimated from epidemiological, clinical and experimental data. The analysis examines the factors determining the population spread of antiviral resistance, and predicts no significant transmission of neuraminidase inhibitor resistant virus. This conclusion is robust even at high therapy levels and under conservative assumptions regarding the likely frequency of transmission of resistant virus. The predicted incidence of resistance following protracted usage reflects primary drug resistance, currently estimated as ∼2% for neuraminidase inhibitor therapy. It is also shown that until high levels of therapy are attained, early treatment of symptomatic cases is more efficient (per unit of drug) at preventing infections than prophylactic therapy.

Introduction

Influenza A and B virus (and associated co-infections) are estimated to be responsible for 18–20 million excess respiratory illnesses and 20000 deaths per annum in the USA alone.1–3 Influenza A pandemics have induced even greater levels of mortality in the past, 40 million in the 1918 pandemic4 and a total of 6 million in 1957 and 1968 pandemics,5 and remain one of the major global public health threats posed by emerging infections in the coming century. Vaccination remains the primary public health intervention and has been demonstrated to reduce influenza-related morbidity. However, the antigenic variability of influenza virus necessitates continuous surveillance to identify new vaccine candidate strains, and vaccine efficacy is reduced in key target groups such as the elderly and immunocompromised.6

Antiviral agents therefore represent a useful additional tool for the control and treatment of influenza infection. The amantadines were the first such agents identified, but have the drawbacks of being effective only against influenza A, significant contraindications and a high frequency of development of drug resistance. Recently, a new class of antivirals with a different biological action, the neuraminidase inhibitors (NAIs), have been developed. Two NAI drugs have been approved for clinical use, oseltamivir (Roche) and zanamivir (GlaxoSmithKline). These drugs are active against both influenza A and B infections and have greater potency and tolerability compared with the amantadines. The current heightened concern over influenza morbidity and mortality is likely to result in the use of these drugs expanding rapidly in the future.

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In such a context, past experience with antimicrobial treatments for a variety of infectious diseases has highlighted the importance of understanding the potential for emergence of drug resistance at a community level. This paper uses experimental and clinical trial data in a mathematical model of influenza transmission to predict potential trends in evolution of resistance to the NAIs. The early development of this model provides information concerning the critical factors predicted to drive development of resistance, and offers the ability to highlight areas where collection of additional data could be used to monitor the spread of resistance in future surveillance studies.

The use of mathematical models to explain observed patterns of drug-resistant microorganisms and predict future trends is well established\textsuperscript{7}–\textsuperscript{11} and has proved a powerful tool for understanding the processes determining the evolution and frequency of resistance of drug-resistant pathogens in hospital and community settings. The only previous analysis of the spread of drug resistance to influenza treatment focused on amantadine use in a small closed population (a boarding school) during a single outbreak.\textsuperscript{12} Resistance to NAIs has been documented both in \textit{vivo} and in \textit{vivo}.\textsuperscript{13,14} In contrast to amantadine-resistant mutants, which exhibit fitnesses close to that of wild-type infectivity and appear to be transmissible, NAI-resistant viruses appear to be 100- to 1000-fold less infectious than wild-type and do not appear to transmit readily in animal models.\textsuperscript{13,14}

The model developed in this paper describes the dynamics of influenza transmission and treatment and uses these characteristics to predict the potential emergence of drug resistance over many years in a large population with demographic characteristics typical of most developed countries. The model captures heterogeneity of transmission within an age-structured population, and allows the effect of a wide range of targeted treatment scenarios for NAI usage on incidence of drug-susceptible and -resistant influenza to be simulated. The relatively complex framework used enables exploration of a range of realistic future treatment and prophylaxis scenarios. Predictions of the frequency of resistant virus are placed in the context of the effect of treatment on influenza transmission, and susceptibility analyses are carried out to test the robustness of model predictions to varying assumptions about the value of key parameters.

**Materials and methods**

**Model structure**

A deterministic modelling framework was used, since the intention was to capture influenza transmission dynamics in a large population with characteristics representative of the USA or other developed countries. This framework is appropriate to represent average seasonal epidemic behaviour, since for large populations the relative magnitude of random fluctuations around the mean (demographic stochasticity) is small.

The model (see Figure 1 for overall structure and the Appendix for details and parameter values) divides the population into five compartments as a function of disease status: susceptible, exposed but not infected, asymptomatic infected, symptomatic infected and immune. An ‘exposed’ state (corresponding to people who have recently been in contact with an infected individual but not infected) is used to allow realistic modelling of treatment involving post-contact (but perhaps pre-infection) prophylactic drug use. Symptomatic infected and immune. An ‘exposed’ state (corresponding to people who have recently been in contact with an infected individual but not infected) is used to allow realistic modelling of treatment involving post-contact (but perhaps pre-infection) prophylactic drug use. Symptomatic infected and immune. An ‘exposed’ state (corresponding to people who have recently been in contact with an infected individual but not infected) is used to allow realistic modelling of treatment involving post-contact (but perhaps pre-infection) prophylactic drug use. Symptomatic infected and immune. An ‘exposed’ state (corresponding to people who have recently been in contact with an infected individual but not infected) is used to allow realistic modelling of treatment involving post-contact (but perhaps pre-infection) prophylactic drug use. Symptomatic infected and immune. An ‘exposed’ state (corresponding to people who have recently been in contact with an infected individual but not infected) is used to allow realistic modelling of treatment involving post-contact (but perhaps pre-infection) prophylactic drug use. Symptomatic infected and immune. An ‘exposed’ state (corresponding to people who have recently been in contact with an infected individual but not infected) is used to allow realistic modelling of treatment involving post-contact (but perhaps pre-infection) prophylactic drug use. Symptomatic infected and immune. An ‘exposed’ state (corresponding to people who have recently been in contact with an infected individual but not infected) is used to allow realistic modelling of treatment involving post-contact (but perhaps pre-infection) prophylactic drug use.
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Individuals never develop significant symptoms. This stratification is also necessary if both prophylactic and symptomatic treatment regimens are to be modelled.

Age structure

The model adopted here, unlike earlier models, explicitly stratifies the population by age, since we wished to explore how treatment in an age-restricted patient group (e.g. elderly persons) might impact on potential development of virus resistance in the population. This allows age-targeted treatment strategies to be modelled, more realistic heterogeneous contact patterns between age groups to be captured and enables other key parameters (viral shedding, infectivity, mortality, immunity, vaccination) to vary with age. The model further subdivides the population aged >65 years into two subgroups corresponding to those in residential nursing homes and those remaining in the general community. This allows different mixing, treatment, vaccination efficacy and mortality parameters to be assigned to these groups of elderly persons.

Symptomatic/asymptomatic states

We assumed that 50% of individuals in the age range 18–65 years who are infected with influenza develop severe symptoms (including a fever) and hence enter the symptomatic model state. The other 50% move straight from the asymptomatic to the immune state on clearing infection. To reflect higher morbidity and longer durations of viral shedding in the young and old compared with the general population, we assumed that 75% of infected individuals in the age range 0–18 and 65+ years develop severe symptoms and enter the symptomatic model state. Consistent with reported data, the duration of the asymptomatic phase of infection was assigned to be 2 days, and the symptomatic phase 4 days, although model results are not highly sensitive to small changes in these values.

Given that viral shedding before development of severe symptoms accounts for ~25% of total virus shedding, the net infectiousness of asymptomatic individuals was calculated as approximately twice that of symptomatic individuals. This estimate was based on the additional assumption that the contact rate of symptomatic individuals is one-third that of asymptomatics (since most symptomatic patients will not attend work/school), and also allows for the different durations of the asymptomatic and symptomatic periods.

Epidemic characteristics

Cohort studies and population surveillance have generated data showing variation in influenza attack rates across different age groups, measuring either infection incidence using serology (change in antiviral antibody titres), viral isolation or disease incidence. Model transmission parameters were conservatively selected to reproduce the higher attack rates seen when viral antigenicity changes significantly, rather than the lower rates seen (as in the last few years) when antigenic change is limited.

The seasonal characteristics of epidemic influenza are evident in collated incidence data from many different countries and communities. In the UK influenza incidence figures, the peak of cases is seen from December to March. A variety of mechanisms may be responsible for this pattern, including seasonal fluctuations in contact patterns in children caused by school terms and holidays, and temperature dependence in influenza transmissibility. We represented this variability through a sinusoidal oscillation of the transmission coefficients with a period of 1 year. This follows the example of much previous modelling of childhood diseases. However, while the model captures average seasonal epidemic behaviour well, we do not attempt to reproduce inter-season variability in epidemic size. To do so would require incorporation of antigenic drift and demographic stochasticity.

Immunity

Recovery from influenza infection results in the acquisition of immunity, resulting in partial protection from re-infection with similar strains of the virus (we assume that NAI treatment of an infected individual has no effect on this process). However, circulating strains of influenza strains are continuously changing, with a typical strain being extinct in three to four seasons due to competitive exclusion by new, antigenically distinct strains. As multi-strain models are computationally complex, we have modelled a single strain and captured the effect of drift generating antigenically novel strains by assuming acquired immunity to the circulating strain wanes over time. Average duration of immunity was set to 5 years (for 18–60 year olds) to reproduce an age-related attack profile typical of influenza A, although influenza B differs relatively little. The parameter values used to represent decreased immunocompetence and immune experience in older and younger age groups are given in the Appendix.

As the effects of antigenic drift are not included in this model, the competitive pressures imposed on both wild-type and resistant virus by new, antigenically novel strains are not reproduced. Thus the model is likely to over-estimate the probability that resistant virus generated in one season will survive to the next.

Wild-type and resistant virus

Two classes of virus are modelled, wild-type and drug resistant. Modelling a single wild-type influenza strain limits model complexity and thus enhances tractability. A single
drug-resistant strain is modelled, based on the characteristics of resistant mutants identified during studies with oseltamivir. All resistant viruses isolated in NAI treatment and in vitro studies share very similar properties. Genotyping shows all involve single point mutations in the neuraminidase gene sequence, and most have similar viral pathogenicity and transmission characteristics in animal studies in mice and ferrets.14,42,43

Resistance can arise in a treated population in two ways. The first is through fixation of mutants that arise de novo in a treated patient. Oseltamivir trial data indicate this to occur with an average frequency of 1.8% across all ages.44 There are insufficient published data available from zanamivir studies to estimate the frequency of emergence of drug-resistant viruses during treatment. One influenza B-resistant mutant was identified during zanamivir treatment of an immuno-compromised child.42 We therefore conservatively assume a fixed 1.8% frequency across all treated patients for both agents.

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The second way for resistance to develop is for an individual infected with resistant virus to transmit that virus to another person. The rate of such transmission is critically dependent on the absolute transmissibility of resistant virus, and its transmissibility relative to wild-type. Transmissibility must be correlated with viral shedding and infectivity measures estimated in experimental infection studies in animals, but the precise quantitative relationships between these covariates has not been established. The relationship is unlikely to be linear, one possibility being that viral shedding needs to exceed some threshold (dependent on the nature of the contact process involved) before transmission becomes likely. In view of this uncertainty, we made the assumption that the relative fitness of resistant virus is ∼10% that of wild-type. This is a deliberately pessimistic value, given that all oseltamivir-resistant isolates show a >100-fold drop in infectivity in animal studies, and all zanamivir-resistant isolates (except one, which has only been identified in vitro) show a 60-fold or more drop.14,42 The sensitivity of results to this assumption is discussed later.

**Treatment model**

We concentrate on two forms of therapy in this paper, post-contact prophylaxis (equal treatment of the exposed and asymptomatic infected model compartments) and symptomatic disease treatment (affecting only the symptomatic infected compartment). NAI treatment is assumed to have the following biological effects:

(i) treatment of symptomatically infected individuals reduces the duration of the symptomatic period and their infectiousness.

(ii) treatment of asymptomatic infected individuals reduces the probability that symptoms will develop, hastens infection clearance and lowers infectiousness. If symptoms do develop they are reduced as above.

(iii) treatment of susceptible or exposed individuals results in a lower probability of infection. If infection does occur, its severity is reduced as above.

Vaccination is also modelled, and when effective is assumed to have the same immune protective effect as infection in the model. Vaccination is characterized by age-specific level of effective immunization, the product of vaccine uptake and efficacy (the latter of which declines markedly in older age classes). Different levels of vaccine uptake and protection afforded are modelled for elderly people in residential care and in the community, based on available published data.6

**Results**

**Pre-treatment dynamics**

The epidemic transmission model reproduces typical patterns of seasonal influenza epidemics, with realistic age-related attack rates and realistic changes in disease incidence due to vaccination. Figure 2(a) illustrates the seasonal epidemic dynamics generated by the model, showing an ∼12 week epidemic ‘season’ each year, consistent with national influenza reporting data in the USA and Europe.38,39 Average annual age-stratified attack rates produced by the model are shown in Figure 2(b), reproducing, as observed,35,37 the much higher attack rates in young children (who have never previously been exposed to influenza), and in the elderly. The average annual infection attack rate across the whole population in this model is 17%, or 10% if only severely symptomatic infections are considered.

The effect of vaccination targeted at elderly persons in reducing overall incidence through time is shown in Figure 2(c), and the much more significant effect on attack rates in the vaccinated age groups in Figure 2(d). Overall, therefore, the model provides a good ‘average’ description of seasonal influenza epidemics in a population with characteristics similar to the USA.
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We initially consider trends in the incidence of resistance under estimated current patterns of usage of oseltamivir in the USA based on a treatment of 6% of symptomatic influenza infections in individuals aged 18–65 years (licensed treatment population for oseltamivir in 1999/2000 season). Figure 3 shows incidence of resistance per 100000 per annum for the first 3 years after treatment is introduced in the population. This indicates that current treatment patterns will generate ∼4.65 cases of resistance per 100000 of the population per year. This corresponds to 1.8% of the treated patients, or 0.049% of all symptomatic influenza infections.

**NAI usage: current treatment patterns**

We subsequently model levels of resistance based on anticipated future oseltamivir usage in a wider age range (>1 year) of population with characteristics of the USA, resulting in treatment of a larger number of persons. Table 1 shows predicted results for four different treatment scenarios: (a) treatment of 6% of symptomatic infections; (b) treatment of 6% of symptomatic infections and post-contact prophylaxis following 1% of exposure events; (c) treatment of 40% of symptomatic infections; (d) treatment of 40% of symptomatic infections and post-contact prophylaxis following 5% of exposure events. The maximum possible NAI usage level

**Figure 2.** (a) Simulated time series of monthly influenza infection incidence per 100000 population over a 3 year period, in the absence of treatment and vaccination. (b) Simulated average annual percentage attack rate stratified by age of population. (c) Simulated time series of monthly influenza infection incidence per 100000 population over a 5 year period, but introducing 25% effective vaccination of adults over 60 years of age at the end of year 2 of the simulation; (d) as (b), but 3 years after the introduction of 25% effective vaccination in adults over 60 years. It should be noted that whereas 95% of cases are modelled to occur within a 12 week “influenza season” window, a small number of cases occur throughout the year.

**Figure 3.** Predicted monthly incidence of resistance for the first 3 years where 6% of symptomatic influenza patients (age group 18–65 years) are treated with oseltamivir at start of symptoms per 100000 of the total population. These figures represent a constant 0.049% of all influenza cases following the introduction of treatment, with no evidence of an increasing trend over time; 25% effective vaccination in adults over 60 years is assumed.
was chosen as 40%, given current proportions of influenza-infected patients estimated to show healthcare seeking behaviour. Whereas we have assumed that the majority of future treatment will be symptomatic, scenarios (b) and (d) examine the effect of a small proportion of post-contact prophylaxis. Detailed population structure (e.g. schools, workplaces) necessary for a full evaluation of the community benefit of prophylaxis is not included in the model, but realism in capturing the individual benefit of prophylaxis is achieved (see Appendix) by explicitly tracking contacts (which may or may not cause infection) as well as infections (a subset of contacts). Under scenarios (a) and (c), 10.4 and 65.1 cases of resistance per 100 000 of the population are predicted to arise, respectively. These levels are only marginally different under low levels of post-contact prophylaxis usage, such that 12.1 and 63.5 cases of resistance per 100 000 are generated, respectively, for scenarios (b) and (d).

Allowing for heterogeneous rates of generation of resistance changes model results little; e.g. assuming rates of 4% in children under 18 and 0.7% in adults for scenario (a) of Table 1, the number of cases of resistance per 100 000 of the population increases to 10.4. These levels are only marginally different under low levels of post-contact prophylaxis usage, such that 12.1 and 63.5 cases of resistance per 100 000 are generated, respectively, for scenarios (b) and (d).

The low levels of resistance for all the scenarios examined above are due to the predicted lack of significant transmission of resistant virus, due its low relative transmissibility (10%) compared with wild-type virus. At this level, transmissibility is below the critical level required for self-sustaining transmission of an infectious agent (see Discussion).

It should be noted that the predicted incidence of resistance is always substantially lower than the estimated numbers of influenza infections predicted to be prevented by these levels of treatment (also given in Table 1). The latter quantities are also likely to be underestimates of the true effect of treatment, as the model does not capture the spatially clustered nature of influenza transmission within small populations.

### NAI usage in the elderly

The elderly population represents a high risk group for influenza, with high levels of morbidity and mortality. This group of patients is targeted for intensive preventative treatment through influenza vaccination; however, the outcomes have differed according to setting and there is clearly room for additional preventative measures. We therefore explore the effect of highly intensive (90%) post-contact prophylactic treatment of elderly persons in residential homes, and the levels of resistance expected to arise as a result of such treatment programmes.

Table 2 shows the effect of this NAI treatment regimen on overall influenza incidence to be dramatic within the residential population. This reflects patterns seen in clinical trials, where it has been shown that prophylaxis in residential homes can reduce the probability of infection by 90%, and prophylactic treatment of experimental infections can reduce viral shedding by 70%. Table 2 also demonstrates that the predicted level of resistance generated is low, namely 24.4 cases per 100 000 (half of which arise from the background level of 6% symptomatic treatment assumed) or 0.5% of the treated population (assuming treatment is given regardless of vaccination or immune status). This resistance arises nearly entirely through de novo generation of resistance within a treated individual. There is no predicted significant spread of resistant virus to the general population (where 6% of symptomatic infections are assumed treated), again due to its low transmissibility.
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Sensitivity of predictions to key parameter values

We explored the robustness of resistance incidence predictions to varying key parameter values, in particular treatment intensity and modality, the relative transmissibility of resistant virus, and the timescale over which the effect of treatment is observed. Predicted levels of resistance were calculated for a grid of values of treatment intensity and relative transmissibility of resistant virus and the results presented as a surface.

Figure 4 shows predicted incidence of resistance for two treatment scenarios: (a) symptomatic treatment of the general population (>1 year old), with treatment levels varying between 0% and 40%; (b) post-contact prophylactic treatment of the general population, with treatment levels varying between 0% and 40%. Prophylactic treatment at the 40% level could represent an emergency mass treatment programme given a particularly virulent new strain of influenza. The relative transmissibility of resistant virus compared with wild-type varies between 0% and 100%, in order to examine the circumstances required for substantial transmission of resistant virus and the results presented as a surface.

Figure 4 illustrates that the level of resistance is a non-linear function of viral fitness and treatment usage. Treatment exerts a selective pressure on the virus by disadvantageing drug-susceptible strains relative to drug-resistant strains. However, for substantial transmission of resistant virus to occur, resistant virus firstly needs to out-compete wild-type in the population as a whole, requiring the net fitness (i.e. a weighted average of transmissibility in the treated and untreated population) of resistant virus to exceed that of wild-type. Secondly, the absolute transmissibility of resistant virus needs to be sufficient to permit sustained transmission: i.e. the average number of individuals infected by a single infected individual in a susceptible population (the basic reproduction number) needs to exceed 1. Figure 4 demonstrates that as soon as both of these criteria are met, resistant virus rapidly dominates wild-type, leading to a very sharp increase in the incidence of resistance.

For symptomatic treatment, such a negative outcome can only occur if the relative transmissibility of resistant virus is very close to that of wild-type (in excess of 90%). This is because symptomatic treatment, even at high levels, exerts a limited selective pressure, partly because 50% of transmission is estimated to occur before an infectious individual develops severe symptoms (and so before treatment), and because only 50% of individuals develop severe symptoms.

Table 2. Predicted annual incidence of resistance and of severely symptomatic influenza in care home residents per 100000 of the total population averaged over the 3rd and 4th years after treatment introduction

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Predicted incidence of resistance in total population</th>
<th>Predicted incidence of symptomatic infection in care home residents</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>0</td>
<td>1112</td>
</tr>
<tr>
<td>a</td>
<td>10.4</td>
<td>1105</td>
</tr>
<tr>
<td>b</td>
<td>24.4</td>
<td>293</td>
</tr>
</tbody>
</table>

(a) 6% of symptomatic patients >1 year of age treated, (b) 6% symptomatic treatment of patients >1 year of age plus 90% use of post-contact prophylaxis in elderly patients in care homes. Results in the absence of treatment are also shown.

Figure 4. Predicted annual number of cases of resistance (per 100000 of the total population averaged over 3rd and 4th years post-treatment introduction) for: (a) symptomatic treatment of general population (>1 year old), with treatment levels varying between 0% and 40%; (b) post-contact prophylactic treatment of general population, with treatment levels varying between 0% and 40%. In both cases, the relative transmissibility of resistant virus varies in the range 0–100%. Case numbers are shown on a log scale to permit system dynamics to be seen across the full range of parameters explored; 25% effective vaccination in adults over 60 years is assumed.
warranting treatment. Post-contact prophylaxis imposes a much greater selective pressure, as its effect can be either to protect people from being infected with wild-type (if they were not infected when they started treatment), or potentially to allow generation of resistance much earlier in disease pathogenesis and viral shedding (for people who have been infected before start of treatment). Hence the threshold transmissibility of resistant virus for widespread transmission is lower for prophylaxis, so the inverse correlation between treatment usage and the position of this threshold can be seen more easily.

**Duration of usage**

Table 3 shows the effect of changing the duration of use of treatment, by reproducing the same scenarios as in Table 1, but showing average incidence of resistance per 100000 for the 15th year after treatment starts (as compared with the 3rd and 4th year used earlier). The minimal differences between Tables 1 and 3 are due to short-term dynamic transient effects caused by sudden perturbation of the epidemic dynamics due to introduction of high treatment levels. Long-term clinical use of NAIs is therefore predicted to be unlikely to generate significant increases in the incidence of resistance per treated individual.

**Relative benefits of prophylactic and symptomatic treatment**

Figure 5 examines the long-term community benefits of treatment as a function of drug usage and the relative transmissibility of resistant virus. The numbers of infections prevented per individual treated is used as the outcome measure. It is interesting to note that at lower treatment levels, symptomatic treatment outperforms prophylactic treatment, as a significant proportion of those given post-exposure prophylaxis would not be expected to develop influenza infection even without treatment. However, the relationship between benefit and treatment level is more non-linear for prophylaxis than for symptomatic treatment, since the former reduces transmission more significantly, lowering exposure event incidence and consequently net treatment usage. Hence prophylaxis begins to outperform symptomatic treatment once usage exceeds ~30%. If resistant virus transmissibility is 10% that of wild-type virus, Figure 5 also shows that at (improbably) high levels (80%+) of prophylaxis, influenza transmission could be dramatically lowered or even pushed below self-sustaining levels. For increased resistant virus transmissibility, the community benefits of treatment are reduced by increasing the spread of resistant virus at higher usage levels.

**Discussion**

The analysis demonstrates that while the evolution of virus mutants exhibiting resistance to any antiviral agent is nearly inevitable, the threat such mutants pose to successful treat-
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The occurrence of resistance is predicted both to optimize clinical outcome and minimize the occurrence of resistance.

In this context, it is interesting to compare the estimate of 1.8% or less (based on Phase III trial results to date) measured incidence of NAI resistance in treated patients with the 30% incidence of resistance measured following treatment with amantadines. This difference suggests that amantadine-resistant mutants have much higher replicative fitness than NAI-resistant mutants. This inference is supported by data indicating that amantadine resistance mutations in the M2 virus protein are not associated with a detectable loss in viral function, and that transmissibility, experimental infectivity and pathogenesis of resistant mutants are comparable to wild-type. For such parameter values, our analysis predicts that widespread use of amantadines for the treatment of symptomatic influenza could result in substantial transmission of resistant virus.

Influenza strains are continuously changing such that when followed longitudinally particular antigenic variants typically circulate for three to four seasons before extinction due to competitive exclusion by new, more antigenically novel strains. As this model does not include antigenic diversity explicitly, the predictions of the incidence of oseltamivir-resistant infections must be regarded as pessimistic, as even relatively transmissible drug-resistant strains would be subject to the same competitive pressures from antigenically fitter new strains generated in populations without significant drug use.

Our analysis indicates that higher transmissibility mutants would be required for NAI resistance to reach high frequencies. The greater potential for generation of viral diversity in immunocompromised patients, for whom influenza infection can become a chronic infection, is reflected in reports of resistance to zanamivir and isolation of multiple sequential amantadine-resistant mutations within such individuals. Surveying for potentially higher fitness NAI multipoint resistant mutants (and care in prescribing treatment) should therefore be directed towards this patient group.

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References


Appendix: model definition and parameterization

We adopt a deterministic, age-structured compartmental epidemic model of a similar form to that used for many past studies of childhood disease, but modified to take account of waning immunity against the pathogen and co-circulation of both wild-type and drug-resistant viral strains:

\[ f(m_i) = \frac{m_i}{\omega_i} \]

where \( m \) represents any age-specific state variable, \( \omega \) is the width (in years) of age class \( i \), and \( I \) is the proportion of individuals who enter residential care homes when entering age class \( i \).

Much of the apparent complexity of the above equations lies in the detailed representation of the impact of antiviral treatment. Treatment and vaccination are modelled via the three age-specific and time-varying functions \( E(t) \), \( D(t) \) and \( V(t) \). The first represents the proportion of exposure events that are treated via post-contact prophylaxis, the second the proportion of severely symptomatic influenza cases treated and the third the per capita vaccination rate of susceptibles. For instance, 6% prophylactic treatment from time \( t = 20 \) across all ages corresponds to \( E(t) = 0 \) for \( t < 20 \) and \( 0 \leq i \leq 20 \), and \( E(t) = 0.06 \) for \( t \geq 20 \) and \( 0 \leq i \leq 20 \).

The forces of infection for susceptible and resistant strains of virus are given by:

\[ \lambda^S = \frac{1}{N} \sum\beta_j \left[ 1 + \chi \cos\left(\frac{\pi t}{2}\right) \right] \left( \psi H_j S^U + \psi H_j S^F + \eta S^U + \psi F S^U \right) \]

\[ \lambda^R = \frac{1}{N} \sum\beta_j \left[ 1 + \chi \cos\left(\frac{\pi t}{2}\right) \right] \left( \psi H_j R^U + \psi H_j R^F + \eta R^U + \psi F R^U \right) \]

where \( \psi, \psi^F, \psi^U \), respectively, represent differences in infectiousness (relative to a symptomatic, untreated wild-type infection) in latent (non-severely symptomatic) infection, treated infection and infections with resistant virus. The sinusoidally varying term in the force of infection is employed (as in previous work\(^{25,26}\)) to reproduce the seasonal pattern of infection incidence observed. Heterogeneity of mix-
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Patterns between different age classes is represented in the force of infection equations via the mixing matrix $\beta_{ij}$:

$$\beta_{ij} = \tau$$

where the numerical values shown are largely derived from prior modelling studies of childhood diseases, and $\tau$ is the baseline transmission coefficient (estimated by matching to incidence data).

Values of model parameters used in this study are listed in Table A1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Assigned value and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>total population size</td>
<td>$3 \times 10^8$ (USA population)</td>
</tr>
<tr>
<td>$b$</td>
<td>births (per annum)</td>
<td>$N/75$ (assuming static demography)</td>
</tr>
<tr>
<td>$\mu_i$</td>
<td>age-dependent natural death rate</td>
<td>0 for 0–60, 0.05 for 60–65, 0.07 for 65–70, 0.1 for 70–75, 0.2 for 75+ (simplified survivorship profile used, though inclusion of population-specific values has little effect on results)</td>
</tr>
<tr>
<td>$\psi^H$</td>
<td>relative infectiousness of latent compared with symptomatic stage</td>
<td>2 (see text)</td>
</tr>
<tr>
<td>$\rho_i^{SU}/\rho_i^R$</td>
<td>proportion of untreated wild-type/resistant infections that become severely symptomatic</td>
<td>0.5 for 18–65, 0.75 for 18–19 otherwise (resistant virus conservatively assumed same as wild-type)</td>
</tr>
<tr>
<td>$\sigma_i^{SU}/\sigma_i^R$</td>
<td>rate of progression from asymptomatic to symptomatic or immune phase for untreated infections with susceptible/resistant virus</td>
<td>182.5 (2 day incubation period, see text; resistant virus conservatively assumed same as wild-type)</td>
</tr>
<tr>
<td>$\nu_i^{SU}/\nu_i^R$</td>
<td>rate of recovery (to immune state) from symptomatic infection for untreated wild-type/resistant infections</td>
<td>91.25 (4 day infectious symptomatic period, see text; resistant virus conservatively assumed same as wild-type)</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>mutation rate per unit time of treated infection</td>
<td>0.018 $\nu_i^{ST}$ (to give 1.8% probability of resistance per symptomatically treated case, see text)</td>
</tr>
<tr>
<td>$\psi^R$</td>
<td>relative transmissibility of resistant virus</td>
<td>0.1 (see text for sensitivity analysis)</td>
</tr>
<tr>
<td>$\gamma_i^{SU}$</td>
<td>age-dependent influenza-related probability of death for untreated infections with wild-type virus</td>
<td>0.001 for age &lt;1, 0.0005 for 1–3, 0 for ages 3–60, 0.0005 for 60–70, 0.001 for 70–75, 0.005 for 75+</td>
</tr>
<tr>
<td>$\gamma_i^R$</td>
<td>age-dependent influenza related probability of death for infections with resistant virus</td>
<td>0.2$\gamma_i^{SU}$ (assumed less pathogenic from animal study data)</td>
</tr>
<tr>
<td>$\tau$</td>
<td>baseline transmission coefficient</td>
<td>100 (estimated from attack rate data)</td>
</tr>
<tr>
<td>$\chi$</td>
<td>magnitude of seasonal oscillation of transmission coefficients</td>
<td>0.12 (estimated by matching to case incidence data to give 12 week influenza season)</td>
</tr>
<tr>
<td>$c$</td>
<td>ratio of incidence of all exposure events (leading to infection or not) to those causing infection</td>
<td>2 (no data: assumption represents infection following half of all recognized exposure events, i.e. those events that might be judged grounds for prophylactic treatment. Estimates of $c$ and $\xi$ only significantly affect Figure 5)</td>
</tr>
<tr>
<td>$\xi$</td>
<td>rate of moving from recognized exposure (but uninfected class) to unexposed susceptible class</td>
<td>121.7 (3 days spent in exposed but uninfected class—chosen as 1 day more than typical asymptomatic incubation period)</td>
</tr>
</tbody>
</table>
### Table A1. (Continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Assigned value and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_i$</td>
<td>proportion of population effectively vaccinated</td>
<td>0 for 0–60 year olds, 0.25 for 61+ year olds. Extending vaccination to &gt;50 year olds has little impact on predicted levels of NAI resistance</td>
</tr>
<tr>
<td>$\phi_i$</td>
<td>immunity waning rate</td>
<td>0.2 for 3–60 year olds (5 year duration of immunity). Duration of immunity assumed to decrease linearly with age in those over 60 (to an average of 3 years in the oldest age category or in residential care), and to fall off to 4 years in 1–2 year olds and to 3 years in 0–1 year olds</td>
</tr>
<tr>
<td>$s_{proph}$</td>
<td>relative susceptibility of prophylactically treated individuals to infection with susceptible virus</td>
<td>0.5 (estimated from prophylaxis clinical trial data)</td>
</tr>
<tr>
<td>$\psi^T$</td>
<td>relative infectiousness of treated wild-type infection relative to untreated</td>
<td>0.5 (estimated from clinical trial data and data on reduced shedding. Combined with $\nu^ST$ estimate, gives overall 2/3 reduction in infectiousness)</td>
</tr>
<tr>
<td>$\rho_i^{ST}$</td>
<td>proportion of pre-symptomatic infections with susceptible virus developing severe symptoms if treated on exposure (post-contact prophylaxis)</td>
<td>0.2$\rho_i^{SU}$ (prophylaxis reduces likelihood of clinically severe infection)</td>
</tr>
<tr>
<td>$\sigma^{ST}$</td>
<td>progression rate from latent to symptomatic infection for drug-susceptible virus if treated on exposure (post-contact prophylaxis)</td>
<td>1.5$\nu^{SU}$ (treatment assumed to speed up overall course of infection by 33%$^{19}$)</td>
</tr>
<tr>
<td>$\nu^{ST}$</td>
<td>rate of progression from symptomatic infection to immune (no virus shedding) state for treated susceptible infections</td>
<td>1.5$\nu^{SU}$ (treatment results in 33% shorter symptomatic infection)</td>
</tr>
<tr>
<td>$\gamma_i^{ST}$</td>
<td>age-dependent influenza-related probability of death for treated infections with wild-type virus</td>
<td>0.1$\gamma_i^{SU}$ (assumed substantially reduced compared with untreated infection).$^{19}$ Data showing reductions in secondary complications from influenza, are used to guide this parameter$^a$</td>
</tr>
<tr>
<td>$\nu^{ST}$</td>
<td>rate of recovery from symptomatic infection to immune (no virus shedding) state for treated susceptible infections</td>
<td>1.5$\nu^{SU}$ (treatment results in 33% shorter symptomatic infection)</td>
</tr>
</tbody>
</table>

*Time units are in years.

$^a$Precise parameter value not critical to predictions of resistance.