Use of neuraminidase inhibitors to combat pandemic influenza

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Since the last influenza pandemic in 1968, neuraminidase (NA) inhibitors have been licensed for the treatment and prophylaxis of seasonal influenza. Continuing outbreaks of highly pathogenic avian influenza H5N1 since 2004 have focused attention on the timing of the next pandemic and preparedness plans. Although immunization is the principal means of influenza prophylaxis, a well-matched efficacious vaccine is unlikely to be widely available for several months following the emergence of the pandemic strain. NA inhibitors could be used to contain and eliminate an emerging pandemic virus at source. If unsuccessful, they could still play a crucial role in reducing the medical impact of pandemic influenza as it spreads through countries. Accordingly, many authorities are creating stockpiles of NA inhibitors. However, the use of stockpiled drugs for treatment or prophylaxis, the rapid delivery to newly diagnosed cases and unknown characteristics of an emergent pandemic strain pose significant challenges to determining optimal use of stockpiles.

Keywords: resistance, treatment, prophylaxis

Antiviral treatment of influenza

There are two classes of specific antiviral agents against influenza: M2 channel inhibitors (rimantadine and amantadine) and neuraminidase (NA) inhibitors (zanamivir and oseltamivir). M2 inhibitors are limited in clinical practice by their toxicity, lack of activity against influenza B and rapid emergence of drug resistance. Drug-resistant variants appear following 48–72 h of treatment, and transmission of drug-resistant virus from treated index cases to close contacts is responsible for failure of chemoprophylaxis during outbreaks. Rates of M2 inhibitor resistance among community isolates of A/H3N2 viruses have increased recently and exceeded 70% in China and Asia during 2004, and over 90% in the US during 2005–06. In addition, most of the recent H5N1 virus isolates from humans and birds exhibit genotypic resistance to M2 inhibitors. Thus, they are likely to be of limited use in an evolving H5 pandemic.

Neuraminidase inhibitors

Mechanism of action

The NA is a good target for drug action, as it is essential for virus infectivity and has a highly conserved active site across influenza A and B viruses. Several highly selective competitive NA inhibitors have been developed that bind tightly to the active site. They inhibit release of new virion progeny from an infected cell, prevent digestion of neuraminic acid in mucus and reduce the ability of the virus to spread through the respiratory epithelium. Zanamivir, a dehydrated sialic acid derivative, and oseltamivir, the oral produg of the active oseltamivir carboxylate containing a cyclohexane ring structure, both entered clinical practice in 1999.
Peramivir, a cyclpentane NA inhibitor, is currently in clinical development.

**Spectrum of activity**

NA inhibitors are effective against human and non-human subtypes of influenza A and B, including the 1918 pandemic virus, amantadine-resistant strains and circulating highly pathogenic H5N1 isolates. In mouse studies, oseltamivir has a dose-dependent antiviral effect against H5N1 infection. However, higher doses and longer duration of treatment with oseltamivir are needed to treat mice infected with more recent human H5N1 isolates from 2004 compared with 1997 human H5N1 isolates. In vitro and animal studies using peramivir show its potential in inhibiting some zanamivir- and oseltamivir-resistant strains.

**Drug formulation and adverse effects**

Zanamivir has poor bioavailability and must be administered directly into the respiratory tract via an inhalation device, posing concern in those who have poor inhaler technique, and in H5N1-infected patients where extrapulmonary virus replication has been detected. Side effects are rare, although it has been associated with bronchospasm. As oseltamivir is available as an oral formulation, it is a more attractive agent in pandemic planning, although uncertainties exist regarding absorption in critically ill patients. It is generally well tolerated, with its principal adverse reaction being minor gastrointestinal disturbance in <10% recipients.

**Clinical use in seasonal influenza**

Systematic review of randomized controlled trials, primarily recruiting healthy adults and children, supports the use of NA inhibitors in the treatment and prophylaxis of influenza A and B infections. In acute influenza, treatment within 36–48 h of symptom onset with NA inhibitors is associated with significant reductions in median times to alleviation of symptoms and return to normal activities. Treatment of confirmed influenza among community-living patients significantly reduces the risk of lower respiratory complications, hospitalizations and related antibiotic use by 55%, 59% and 27%, respectively, when compared with placebo. In addition, treatment of community-dwelling and hospitalized patients with influenza with oseltamivir significantly reduces risk of death by 68–91%. The use of NA inhibitors in treatment does not impair induction of influenza-specific antibody responses. Seasonal prophylaxis of 6–8 weeks duration with once daily oseltamivir or inhaled zanamivir is highly effective in preventing against influenza infection and illness in healthy adults, nursing home residents and immunocompromised children. When used for post-exposure prophylaxis for contacts in households with index cases of influenza, NA inhibitors reduce influenza infection by up to 90%, although the protective efficacy may be lower in younger children than adults.

**Resistance to NA inhibitors**

NA inhibitors are less prone to selecting for drug resistance than M2 inhibitors, as the NA active site is highly conserved and essential for viral replication. Resistance has been studied in vitro by multiple passages of virus in tissue culture in the presence of drug. Two mechanisms of resistance have been identified: one involving NA mutations and the other involving mutations around the binding site of the viral haemagglutinin (HA). HA mutations decrease the binding of virus to host-cell sialic acid receptors, reducing dependency on NA activity necessary for release of new viruses from the cell. HA mutations are infrequent, and their clinical significance is unclear. NA resistance generally results from single amino acid changes in the active site. In order to accommodate the oseltamivir molecule, the active site undergoes rearrangement to create a pocket into which the drug will fit. Any of several mutations in the active site, typically R292K, N294S or H274Y, limit the formation of this pocket and prevents binding of oseltamivir. In contrast, zanamivir binds to the active site without the need for the formation of a pocket, so some oseltamivir-resistant strains remain susceptible to zanamivir. In animal models, viruses with NA mutations are associated with reduced infectivity and transmissibility compared with wild-type virus. To date, there is only one report of zanamivir resistance emerging with clinical use when an influenza B isolate with both HA and NA mutations was recovered from a paediatric bone marrow transplant recipient during 14 days of intravenous treatment. For oseltamivir, the frequency of drug resistance is higher. In treatment studies, the frequency of post-treatment viruses exhibiting resistance was greatest in children compared with adults, ~4% versus 0.4% of samples, respectively. However, worrying rates of resistance have been detected in Japanese children with A/H3N2 infection treated with oseltamivir. Of 50 children studied, nine (18%) had resistant viral clones mixed with wild-type virus detected after 4–6 days of oseltamivir. This may be related to suboptimal dosing as children in Japan receive 2 mg/kg of oseltamivir, in contrast to weight-tailored dosing (generally leading to higher doses) used elsewhere. During the 2003–04 influenza season in Japan, the country with the highest per capita use of oseltamivir, only 4 (0.4%) of 1180 A/H3N2 community isolates were shown to exhibit oseltamivir resistance, suggesting very low frequency of person-to-person transmission of drug-resistant viruses.

**Clinical use in avian influenza**

Although the clinical benefits of treating seasonal influenza are established, care must be taken in extrapolating findings to those with primary H5N1 infection. With case-fatality rates exceeding 50%, H5N1 infection is clearly more aggressive than seasonal influenza. Clinical infection with H5N1 promotes excessive cytokine release and is associated with severe systemic disease including gastrointestinal symptoms, and there is evidence of extrapulmonary virus replication in mammals and humans. Intervention with standard doses of oseltamivir, if initiated late into the course of the illness, does not improve outcomes in patients with H5N1 infection. When administered within 48 h of symptom onset, six of eight Vietnamese patients with H5N1 infection achieved complete suppression of viral replication and survived. However, persistent viral replication was detected and drug-resistant H274Y variants were recovered from two patients, both of whom died, despite prompt oseltamivir treatment. The bioavailability and tissue penetration of oseltamivir administered to severely ill H5N1-infected patients is unknown. This has led to suggestions that increased doses and prolonged duration of oseltamivir for H5N1 infection should be considered.
Emerging pandemic in the United Kingdom

Combating pandemic influenza

Faced with the H5N1 pandemic threat, strategies designed to contain an emerging pandemic should be considered a public health priority. The basic reproduction number $R_0$ is the average number of secondary cases generated by an index case in a susceptible population. Disease spreads through a population if $R_0 > 1$; the aim of intervention is to reduce $R_0 < 1$ by disrupting transmission.

The effectiveness of interventions, including estimates of number of courses of drug required to contain pandemic influenza, can be assessed by modelling.28–32 Pandemic models are reliant on estimates of clinical parameters and assumptions (Table 1). Although the characteristics of a future pandemic virus are unknown, variables can be estimated by experience of previous pandemics and epidemics. Studies use a range of parameters to ensure that a spectrum of scenarios is considered.

Transmission may be broken by non-pharmaceutical measures, or reducing infectivity of infected persons and decreasing susceptibility of non-infected people with antivirals and vaccines. Non-pharmaceutical intervention includes restrictions on travel and mass gatherings including schools, and personal hygiene measures (e.g. masks).33 The benefits of such measures are unclear, but they are likely to be ineffective if used in isolation. Vaccination is the mainstay of prevention of seasonal influenza. However, global vaccine manufacturing capacity is unlikely to meet the demands of a pandemic threat. In addition, clinical trials of H5N1 candidate vaccines have proved disappointing, and the antigenic diversity of circulating H5N1 viruses means that stockpiled vaccines may be mismatched to an emergent strain.5 As efficacious vaccines are unlikely to be widely available during at least the first wave of pandemic influenza,32 NA inhibitors form critical components of preparedness plans.

Table 1. Variables required for modelling spread of pandemic influenza at source or in the United Kingdom28–31

<table>
<thead>
<tr>
<th>Emerging pandemic at source</th>
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<tbody>
<tr>
<td>population density and movements</td>
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<tr>
<td>rapid and sensitive case detection</td>
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<tr>
<td>reproduction number $R_0$ of pandemic virus</td>
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<td>background population immunity to pandemic virus</td>
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<tr>
<td>household transmission rates</td>
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<tr>
<td>age-specific attack rates</td>
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<tr>
<td>clinical attack rates</td>
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<tr>
<td>duration of virus shedding</td>
</tr>
<tr>
<td>time to deliver antiviral therapy to target population</td>
</tr>
<tr>
<td>high cooperation among population with containment strategy</td>
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<tr>
<td>high compliance with antiviral therapy</td>
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<tr>
<td>limited development of transmissible drug-resistant strains</td>
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<table>
<thead>
<tr>
<th>Emerging pandemic in United Kingdom (additional to above)</th>
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<tbody>
<tr>
<td>high-resolution population density data</td>
</tr>
<tr>
<td>travel patterns within United Kingdom</td>
</tr>
<tr>
<td>multiple seeding at ports of entry</td>
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<tr>
<td>absenteeism work rates</td>
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</table>

Antiviral use in pandemic influenza

NA inhibitors offer advantages over vaccination including activity against antigenically diverse viral strains and subtypes, rapid onset of chemoprophylactic efficacy and therapeutic benefit in established infection. Potential roles for antivirals include post-exposure prophylaxis of those exposed to cases, long-term prophylaxis and early treatment. Although blanket prophylaxis of a population during a pandemic would afford best protection, this approach is impossible to achieve with limited drug availability and resources. Clearly, targeted antiviral strategies are needed to optimize use of available supplies. Limited chemoprophylaxis could protect key workers and minimize disruption to healthcare services. Early antiviral treatment of newly identified cases may reduce infectivity, interrupt transmission and lower morbidity and mortality.31,32

Owing to lengthy lead times in drug manufacture, it will not be feasible to respond to an emerging threat with surge capacity. Therefore, pre-pandemic stockpiling of drugs is necessary. Current 2006 global production capacity for oseltamivir is ~190 million doses per year, and this will rise to 400 million doses in 2007. In addition, licences and technology transfer have been granted by Roche to a number of manufacturers for generic production in India, China and South Africa.

Containing an emerging pandemic at source

Models indicate that elimination of an emergent pandemic virus in south-east Asia is feasible using a combination of antiviral drugs and quarantining measures.26,30 Simply offering antiviral chemoprophylaxis to contacts exposed to influenza cases might not be successful in containment, as this strategy would require identification of cases, contact tracing and delivery of drugs more rapidly than logistically feasible. Therefore, ‘ring prophylaxis’ strategies that require less intense contact tracing, but increased numbers of drug doses particularly in urban settings, have been evaluated. Administration of antiviral prophylaxis to >90% of the population in a 5 km zone within 48 h of detecting illness in 20 people should contain a virus with $R_0 < 1.5$.30 However, when combined with quarantining and area-based school/workplace closures, ring prophylaxis carries a high probability of pandemic containment even if $R_0$ approaches 2.

The WHO is creating stockpiles of at least 5 million oseltamivir treatment courses that can be rapidly delivered to the locality of an emergent virus. Although formidable obstacles to successful containment exist (rapid case identification, drug delivery, good compliance with treatment and quarantining) this approach offers the potential to prevent huge mortality and morbidity worldwide.

Impact of pandemic influenza in the United Kingdom

Models can estimate patterns of spread of novel influenza within a country. However, because the characteristics of a future pandemic virus are unknown, detailed epidemiological information must be collected early to allow interventions to be assessed in real time and policies reformulated for maximal impact on control of the actual strain. In particular, age-specific clinical attack rates and transmissibility within specific populations will be key factors.

Historical evidence suggests that, without interventions, $R_0$ of pandemic influenza will average ~1.4–1.8.31,32 It has been
suggested that although most people will be susceptible, ~50% of those infected may be symptomatic, resulting in a cumulative attack rate of 25% of the population over one or more waves of infection. By using these assumptions, specific models have suggested that an excess of 1.5 million primary care consultations, 750,000 emergency department attendances, and 56,000 deaths could occur during the first wave.\textsuperscript{31,32} Many national authorities including the United Kingdom have planned or established stockpiles to treat 25% of the population.

### Strategies for containing pandemic influenza in the United Kingdom

Once a novel virus arrives in the United Kingdom, repeat seeding will occur at ports of entry, so interventions aimed at elimination will be unfeasible.\textsuperscript{30–32} Long-term prophylaxis would require a prohibitively large drug stockpile, rapidly deplete stocks and postpone the outbreak by the period for which prophylaxis is provided. As influenza-infected patients display greatest infectivity shortly after onset of symptoms, the most efficient use of antivirals would be early treatment to reduce disease severity, and possibly overall attack rates. One model, for a virus of high transmissibility, suggests that treatment of 90% cases within 24 h of symptoms would reduce the cumulative population clinical attack rate from 34% to 29%, and peak daily attack rates from 1.9% to 1.6%.\textsuperscript{31} A stockpile sufficient to treat 25% of the population is needed to implement this policy. If access to treatment is delayed by 1 day, its impact is reduced and greater stockpiles are needed. In practice, combinations of control measures will be applied, and models can predict their impact (Table 2).\textsuperscript{31} While non-pharmaceutical measures have value if compliance is high, targeted post-exposure prophylaxis could provide significant benefits, but this strategy requires much greater stockpiles than currently provisioned.

Significant threats to the effectiveness of antiviral treatment policies exist. If there are higher clinical attack rates (>50% of infections causing clinical illness), treatment may need to be prioritized.\textsuperscript{31,32} Antiviral prophylaxis of essential workers and/or their contacts would have a high cost on stockpiles but could be considered if absence rates rise unexpectedly.

Additionally, the emergence of transmissible drug-resistant variants would have a serious impact. Although transmissible strains have not been detected, emergence of resistant clones following oseltamivir treatment of seasonal influenza in children\textsuperscript{20} and H5N1 infection\textsuperscript{26} are concerning. Virological monitoring during the pandemic would be essential. If resistance emerges, temporary cessation of antiviral therapy might allow wild-type virus to re-establish itself before further use of treatment.

Regardless of the level of stockpile, the provision of safe storage and rapid access to drugs form key elements of planning, and could be challenging issues.\textsuperscript{34} In the United Kingdom, primary care trusts must develop arrangements to ensure rapid access to drugs whilst allowing hospitals and general practitioners to focus on clinical needs. This may include telephone diagnosis and remote prescribing, pharmacist-led prescribing, use of walk-in centres, home-visiting teams and designated influenza centres.

### Concluding remarks

WHO has declared that the world is as close as ever to the next pandemic.\textsuperscript{7} For the first time during an inter-pandemic period, effective treatment and prophylaxis with NA inhibitors is available. Antiviral stockpiling to allow ring prophylaxis around infected cases emerging at source could eliminate a pandemic virus. If this fails, antivirals will play a crucial role in reducing its impact as it spreads through countries. Accordingly, many authorities including the United Kingdom have stockpiled sufficient antiviral therapy to treat 25% of the population. Although models show that this strategy could successfully reduce disease severity and transmission, it remains possible that this will not be enough. Identification and rapid delivery to newly diagnosed cases remains a formidable logistic challenge and it remains unclear how this is to be implemented in practice.

### Table 2. Impact of antiviral and non-pharmaceutical measures on high transmissibility scenarios of pandemic influenza\textsuperscript{31,32}

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Cumulative attack rate (%)</th>
<th>Peak daily attack rate (%)</th>
<th>Proportion of population requiring drug (%)</th>
<th>Treatment courses required (million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High transmissible pandemic virus with no intervention</td>
<td>34</td>
<td>1.9</td>
<td></td>
<td></td>
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<tr>
<td>School closures</td>
<td>32</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quarantine of cases (50% compliance)</td>
<td>30</td>
<td>1.6</td>
<td>25</td>
<td>14.5</td>
</tr>
<tr>
<td>Treatment of 90% cases within 24 h\textsuperscript{a}</td>
<td>29</td>
<td>1.6</td>
<td>25</td>
<td>14.5</td>
</tr>
<tr>
<td>Treatment of 90% cases within 48 h</td>
<td>32</td>
<td>1.9</td>
<td>29</td>
<td>17.1</td>
</tr>
<tr>
<td>Treatment of 90% cases within 24 h and household prophylaxis</td>
<td>22</td>
<td>1.0</td>
<td>57</td>
<td>33.6</td>
</tr>
<tr>
<td>Treatment of 90% cases within 24 h and household prophylaxis plus quarantine of cases (50% compliance)</td>
<td>20</td>
<td>0.9</td>
<td>57</td>
<td>33.6</td>
</tr>
<tr>
<td>School closures with 90% contact prophylaxis plus treatment of 90% cases within 24 h and household prophylaxis</td>
<td>13</td>
<td>0.3</td>
<td>102</td>
<td>60.2</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Indicates assumption in UK pandemic contingency plan.
pandemic virus of high transmissibility or the emergence of oseltamivir resistance would significantly reduce the impact of any stockpile; the current planned number of doses allow for little flexibility. The French authorities have increased investment in their antiviral stockpile of both oseltamivir and zanamivir to levels in excess of 50% population treatment doses so as to allow greater flexibility in responding. The characteristics of the next pandemic cannot be predicted. Enormous effort and resources have gone into preparedness plans. The millions who died during the 1918 Spanish influenza pandemic, the greatest outbreak of infectious disease in history, would consider this effort worthwhile, whilst hoping that the plans in place are not tested.

Transparency declarations
I. S. has received grants for scientific research, speaker honoraria and travel to international meetings from pharmaceutical industry including Roche and GSK who manufacture NA inhibitors. J. D. and M. P. have no conflicts of interest.

References