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Perspectives on antiviral use during pandemic influenza

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Antiviral agents could potentially play a major role in the initial response to pandemic influenza, particularly with the likelihood that an effective vaccine is unavailable, by reducing morbidity and mortality. The M2 inhibitors are partially effective for chemoprophylaxis of pandemic influenza and evidence from studies of interpandemic influenza indicate that the neuraminidase inhibitors would be effective in prevention. In addition to the symptom benefit observed with M2 inhibitor treatment, early therapeutic use of neuraminidase inhibitors has been shown to reduce the risk of lower respiratory complications. Clinical pharmacology and adverse drug effect profiles indicate that the neuraminidase inhibitors and rimantadine are preferable to amantadine with regard to the need for individual prescribing and tolerance monitoring. Transmission of drug-resistant virus could substantially limit the effectiveness of M2 inhibitors and the possibility exists for primary M2 inhibitor resistance in a pandemic strain. The frequency of resistance emergence is lower with neuraminidase inhibitors and mathematical modelling studies indicate that the reduced transmissibility of drug-resistant virus observed with neuraminidase inhibitor-resistant variants would lead to negligible community spread of such variants. Thus, there are antiviral drugs currently available that hold considerable promise for response to pandemic influenza before a vaccine is available, although considerable work remains in realizing this potential. Markedly increasing the quantity of available antiviral agents through mechanisms such as stockpiling, educating health care providers and the public and developing effective means of rapid distribution to those in need are essential in developing an effective response, but remain currently unresolved problems.

Keywords: amantadine; rimantadine; oseltamivir; zanamivir; antivirals; resistance

1. INTRODUCTION

This article provides personal perspectives on selected issues that are relevant to the use of antiviral drugs during the next influenza pandemic. It expands on previously published comments (Hayden 1997) that were made before the availability of the novel class of anti-influenza agents, the neuraminidase inhibitors, and focuses on three areas: antiviral agent selection, antiviral resistance and the application of mathematical models. This discussion does not consider other important public health issues such as costs and their reimbursement, the stability of raw materials or formulated drug and their potential for stockpiling and rationing or distribution of limited drug supplies. However, it is obvious that adequate supplies and rapid access to antiviral drugs are essential if they are to be useful. In this regard, increasing appropriate use and fostering both health care provider and public familiarity with the available agents during the interpandemic period are essential for their effective use during the next pandemic.

Improvements in medical care since the last pandemic, including the introduction of new antiviral drugs that are specific for influenza A and B viruses, offer potential for reducing the impact of the next one. However, the health care systems of the USA and many other countries are sometimes unable to cope with the relatively modest increases in demand that occur with interpandemic disease. Mathematical models based on assumptions derived largely from the 1957 and 1968 pandemic experiences and the recent interpandemic period have estimated that 89 000–207 000 deaths, 314 000–734 000 hospitalizations, 18–42 million out-patient visits and 20–47 million additional illnesses will occur during the next pandemic (Meltzer *et al.* 1999). A pandemic like that occurring in 1918 would probably increase the impact by another order of magnitude. Most of these illnesses and deaths will occur over a short period of weeks to several months in a given region and overwhelm health care services. The mass casualties, which will include health care workers and providers of the essential community services, will not only rapidly fill hospital beds and exhaust available supplies of antivirals, antibiotics and other essential medications, but could also lead to substantial disruption of societal services, industrial production and infrastructure such as transportation, food supply and communications (Schoch-Spana 2000). The 1918 pandemic incapacitated the health care system as well as other basic functions of many cities.

Antiviral agents could potentially play a major role in the initial response to pandemic influenza, particularly with the likelihood that an effective vaccine is unavailable,

Table 1. Currently available antiviral agents for influenza.

(CC, creatinine clearance (ml min^{-1}). Probenicid inhibits renal excretion as potential drug interaction in the case of oseltamivir.)

class and agent	brand name	route	dose adjustments	adverse drug interactions	paediatric/ liquid formula
M2 inhibitors					
amantadine	Symmetrel	oral	CC $\leqslant$ 50–70 age $\geqslant$ 65 years	CNS stimulants, anticholinergics, antihistamines and certain diuretics	yes
rimantadine	Flumadine	oral	CC $\leqslant$ 10 age $\geqslant$ 65 years hepatic disease	not reported	yes
NA inhibitors					
oseltamivir (GS4104)	Tamiflu	oral	CC $\leqslant$ 30	not reported	yes
zanamivir (GG167)	Relenza	inhalation	no	not reported	not applicable

and might substantially reduce morbidity, hospitalizations, other demands on the health care system and mortality. However, a number of limitations regarding antiviral use during a pandemic warrant consideration. The major current impediment to effective use in a pandemic would be limited availability coupled with high demand during a short period. In particular, restricted availability, drug costs, the risks of adverse effects and the potential for the emergence of drug resistance are constraints on prolonged prophylactic administration during the initial wave or waves of a pandemic. Fair allocation of available resources would be extremely difficult in the context of an ongoing pandemic or even major epidemic. As summarized below, antivirals have proven efficacy in treatment and prevention, but an inadequate supply and limited surge capacity in production would result in lack of use. Markedly increasing the quantity of available antiviral agents through mechanisms such as stockpiling and developing effective means of rapid distribution to those in need are essential in developing an effective response, but remain currently unresolved problems.

2. SELECTION OF ANTIVIRALS

A fundamental question is which agent or agents should be selected for potential stockpiling and widespread use in the population. Most countries currently have one M2 inhibitor (amantadine) and one or two neuraminidase inhibitors (zanamivir and oseltamivir) approved for use in influenza treatment and/or prophylaxis and in the USA four agents including rimantadine are currently available (table 1). Although other neuraminidase inhibitors are in various stages of development, these four agents are the ones that require scrutiny at present with regard to their use in response to a pandemic. Efficacy, tolerability, ease of administration and the potential for clinically important drug resistance are all factors that warrant consideration in selecting among the available agents. Data regarding use in pandemic influenza are only available with the M2 inhibitors, but extensive clinical testing of the neuraminidase inhibitors in interpandemic influenza permits reasonable conclusions regarding their efficacy.

Table 2. Amantadine prophylaxis during pandemic influenza.

(The values are the percentage ranges of reported efficacies in studies of oral amantadine. The data are taken from Nafta *et al*. (1970), Oker-Blom *et al*. (1970), Smorodintsev *et al*. (1970), Monto *et al*. (1979), Pettersson *et al*. (1980) and Quarles *et al*. (1981).)

	protective efficacy	
pandemic/subtype	influenza A illness	seroconversion
1968 H3N2	59–100	28–52
1977 H1N1	31–71	18–39

(a) *Efficacy for prophylaxis*

The comparative efficacies of these agents have received limited study. In general, amantadine and rimantadine have comparable antiviral and clinical activities when used in chemoprophylaxis or in the treatment of influenza A virus illness (reviewed in Hayden & Aoki 1999). The evidence from placebo-controlled, blinded studies of amantadine and rimantadine during the 1968 H3N2 pandemic and 1977 H1N1 reappearance establish that these agents are effective for chemoprophylaxis in immunologically naive adult populations (table 2), although the observed levels of protection against influenza illness varied considerably across studies and were generally lower than the 80–90% protective efficacies against illness observed in studies of interpandemic influenza. Lower protection rates are observed for laboratory-documented infection (table 2), an observation that, in part, reflects the occurrence of subclinical and likely immunizing infections during chemoprophylaxis. The neuraminidase inhibitors are highly effective in chemoprophylaxis against epidemic influenza in studies assessing both seasonal prophylaxis in non-immunized adults (Hayden *et al*. 1989; Monto *et al*. 1999*a*) or immunized nursing home residents (Peters *et al*. 2001) and post-exposure prophylaxis in families (Hayden *et al*. 2000; Welliver *et al*. 2001). The single study comparing the

prophylactic efficacy of an M2 with a neuraminidase inhibitor found that inhaled zanamivir was superior to oral rimantadine in short-term influenza prophylaxis in nursing home outbreaks, largely because of frequent rimantadine prophylaxis failures secondary to resistant virus (Gravenstein *et al*. 2000). Such results would predict that the neuraminidase inhibitors would also be effective for prophylaxis of pandemic influenza.

(b) *Efficacy for treatment*

One clinical feature of previous pandemic influenza, particularly the 1918 disease, was that convalescence was protracted, with fatigue and functional impairment lasting for weeks. Early antiviral treatment has been shown to reduce the time to functional recovery by up to several days in adults and children with acute influenza. Placebo-controlled, blinded studies during the 1968 H3N2 pandemic and 1977 H1N1 reappearance showed that amantadine and rimantadine provided therapeutic benefit in uncomplicated illness in previously healthy adults, with reductions in fever, symptom severity and the time to resuming normal activities (Knight *et al*. 1970; Galbraith *et al*. 1971; VanVoris *et al*. 1981). However, most controlled treatment studies of the M2 inhibitors have enrolled relatively few patients and none to date have documented reductions in complications or antibiotic use.

The antiviral and clinical benefits of early antiviral treatment have not been directly compared between an M2 and a neuraminidase inhibitor. Several large placebo-controlled, blinded studies have shown that treatment with either inhaled zanamivir or oral oseltamivir reduces illness duration, the time to resuming normal activities and the likelihood of physician-diagnosed lower respiratory complications leading to antibiotic use in adults (Monto *et al*. 1999*b*; Kaiser *et al*. 2000; Treanor *et al*. 2000). Such benefits have also been observed in zanamivir treatment studies involving patients with asthma or chronic obstructive airways disease (Murphy *et al*. 2000) and in oseltamivir treatment studies involving children aged 1–12 years, in whom new otitis media diagnoses were reduced by over 40% (Whitley *et al*. 2001). In contrast, one earlier paediatric study of rimantadine found no beneficial effects on earache or presumed otitis media risk following influenza (Hall *et al*. 1987). Both intranasal zanamivir and oral oseltamivir reduce otologic abnormalities in experimental human influenza (Hayden *et al*. 1999; Walker *et al*. 1997), whereas oral rimantadine does not (Doyle *et al*. 1998). Furthermore, preliminary analysis of the aggregated clinical trials experience with oseltamivir indicates that early treatment is also associated with reductions in hospitalizations. Until a direct comparison of the relative therapeutic effects of an M2 and a neuraminidase inhibitor is performed, the available data indicate that a neuraminidase inhibitor would be the preferred antiviral agent for treatment during pandemic influenza from the perspective of therapeutic benefit.

(c) *Ease of administration*

The selection of an antiviral agent for wide-scale use also depends heavily on its pharmacological properties, which in turn influence the complexity of its dose regimens, the route and frequency of administration, the need for therapeutic monitoring and dose adjustments and the potential for clinically important drug–drug or drug–disease interactions. Clinically important differences exist among the M2 inhibitors (reviewed in Hayden & Aoki 1999) and the neuraminidase inhibitors (reviewed in Gubareva *et al*. 2000) with regard to their human pharmacology. Each of the available agents can be dosed infrequently, with once daily for prevention and once (rimantadine and amantadine) or twice daily for treatment. Dose adjustments are rarely needed for rimantadine and the neuraminidase inhibitors (table 1). No age-related adjustments are required for the neuraminidase inhibitors.

In contrast, amantadine depends directly on renal excretion for elimination and has a narrow therapeutic index (*ca*. 2:1 ratio of the one associated with frequent adverse effects to the therapeutic dose), such that amantadine dose adjustments are required for relatively modest decrements in renal function, including those usually observed with ageing. Furthermore, amantadine has several recognized drug interactions that increase the likelihood of side-effects (table 1) and the need for close clinical monitoring in certain patient groups. The need for individual prescribing of amantadine based on knowledge of renal function is a significant limitation to its wide-scale use. The inhaler device used for zanamivir dosing is also an obstacle with respect to the ease of administration. The current delivery system requires a cooperative, informed patient who is able to make an adequate inspiratory effort. Elderly hospitalized patients often have problems using the delivery system effectively (Diggory *et al*. 2001) and the current device is not appropriate for use in young children (below 5 years of age) or those with cognitive impairment or marked frailty. While the need for device training is an important concern in treating acutely ill patients, most studies to date have shown good compliance and the inhaled route may offer certain advantages in the chemoprophylaxis of influenza.

(d) *Tolerability and safety*

Similarly, the type, frequency, severity and management of adverse drug effects and their relationships to drug dose are all considerations in agent selection (table 3). The duration of drug exposure, short-term treatment versus longer periods for prophylaxis and the timing of onset with regard to initiation of dosing are, again, all considerations in this regard.

Amantadine has the narrowest toxic:therapeutic ratio among the available agents and is commonly associated with dose-related minor central nervous system (CNS) side-effects, that are probably related to its amphetamine-like CNS stimulatory properties and, less often, severe CNS toxicities (table 3). The latter occur most often in those with high plasma concentrations due to impaired renal excretion. Rimantadine has a significantly lower potential for causing CNS adverse effects, in part related to differences in its pharmacokinetics (Hayden & Aoki 1999), although dose reductions are recommended in the elderly. For example, one recent cross-over study in an elderly nursing home resident population compared prolonged amantadine chemoprophylaxis, at the currently recommended reduced dose of 100 mg day^{-1} further

Table 3. Adverse drug reaction profiles of currently available anti-influenza agents.

agent	adverse reaction	severity	frequency during treatment	dose related	reversible
amantadine	CNS	mild–moderate	10–30%	yes	yes
		severe	uncommon	yes	yes
	gastrointestinal	mild	common	yes	yes
rimantadine	CNS	mild–moderate	< 10%	yes	yes
	gastrointestinal	mild	common	yes	yes
zanamivir	bronchospasm	mild–severe	very uncommon	no	yes
oseltamivir	gastrointestinal	mild	common (5–15%)	yes	yes

adjusted for renal function, with rimantadine chemoprophylaxis at the same dose and found *ca*. 10-fold higher frequencies of overall adverse events, including confusion and hallucinosis and drop-out during amantadine administration (Keyser *et al*. 2000).

Inhaled zanamivir treatment has been very infrequently described as causing bronchospasm, sometimes severe or associated with fatal outcome, in acute influenza sufferers with pre-existing airways disease. Influenza itself often causes severe exacerbations in such patients so that the possible causal relationship to zanamivir administration is uncertain, as is the actual frequency of such events. One large placebo-controlled study of influenza-infected patients with underlying mild–moderate asthma or, less often, chronic obstructive airways disease found no excess of serious respiratory adverse events and more rapid clinical recovery including peak expiratory flow rates in zanamivir recipients (Murphy *et al*. 2000). However, until further data are available, zanamivir use in patients with underlying airways disease requires close clinical monitoring. Like the M2 inhibitors, oseltamivir is associated with mild–moderate gastrointestinal (GI) upset in a minority of patients, but no other serious end-organ toxicity has been recognized to date.

In most instances, the adverse effects associated with these drugs are readily reversible after the cessation of administration. Severe CNS adverse reactions related to excess amantadine accumulation in the blood can be an exception, because such toxicity is usually due to a failure to reduce the dose in the setting of renal impairment with its attendant prolonged elimination half-life. Another concern with regard to extensive community use of antivirals during pandemic influenza is their potential for adverse effects during pregnancy. Amantadine and rimantadine are recognized teratogens in animals and, consequently, are relatively contraindicated in pregnancy. The clinical pharmacology and adverse drug effect profiles of the antivirals for influenza indicate that the neuraminidase inhibitors and rimantadine are preferable to amantadine with regard to the need for individual prescribing, tolerance monitoring and the seriousness of side-effects. When these findings are considered in the context of the available information about efficacy and antiviral resistance (discussed below), it is clear that the neuraminidase inhibitors would be the preferred agent for treatment and, in some instances, prophylaxis during pandemic influenza.

3. ANTIVIRAL RESISTANCE

An important issue in pandemic influenza is the potential for the emergence and spread of drug-resistant influenza A viruses that cause the loss of the clinical effectiveness of antiviral drugs. The M2 and neuraminidase inhibitors have important differences with respect to the frequency and biological properties of resistant variants (table 4). In addition to the selection of drug-resistant variants during antiviral use, the possibility of primary or *de novo* drug resistance in a pandemic strain warrants consideration. Primary resistance to the neuraminidase inhibitors has not been described at the enzyme level and these agents are active against all of the nine neuraminidase subtypes recognized in avian influenza viruses (reviewed in Gubareva *et al*. 2000; Tisdale 2000). In contrast, primary resistance to the M2 inhibitors has been described in swine influenza viruses of the H1N1 subtype in the 1930s in the absence of selective drug pressure. More recently, swine viruses in Europe and North America and isolates from several zoonotically infected humans of H1N1 and H3N2 subtypes have shown primary resistance (A. Hay, personal communication). Amantadine resistance has also been described in a small portion (< 1%) of field isolates (Ziegler *et al*. 1999) and in those receiving the drug for the treatment of Parkinsonian symptoms (Iwahashi *et al*. 2001). Such observations raise the concern that amantadine-resistant isolates circulate naturally under certain conditions. In addition, the use of amantadine for influenza management in China also increases the potential that a pandemic strain might show primary resistance to amantadine and rimantadine.

Another generic issue regarding resistance emergence is the proposed tactic for extending the availability of limited antiviral drug supplies during pandemic influenza by reductions in either the dose level or, in the case of treatment, the duration of therapy. Theoretically, a short course therapy of 1–3 days might reduce viral loads sufficiently to provide clinical benefit. Obvious concerns related to this approach would include the potential loss of therapeutic or prophylactic efficacy, rebound in viral replication and symptoms after the cessation of administration and fostering emergence of drug resistance, in part due to continued viral replication in the setting of subinhibitory drug concentrations. The risks of these events would probably be higher in pandemic influenza

Table 4. Epidemiological and biological features of drug-resistant influenza viruses recovered during clinical use.

(The reported frequency of recovering M2 inhibitor-resistant variants ranges from *ca*. 10% in elderly adults to over 75% of immunocompromised patients shedding virus 3 days or longer (Hayden 1996; Englund *et al*. 1998). Based on ferret studies by Carr *et al*. (2001), the person to person transmissibility of one oseltamivir-resistant variant is reduced in animals.)

	locus of resistance	frequency during therapy	infectivity in animals	virulence in animals	person to person transmissibility
amantadine/rimantadine	M2	high (*ca*. 30%)	wild-type	wild-type	yes
zanamivir	NA	low (?)	reduced	reduced	unstudied
oseltamivir	NA	low (*ca*. 0.4% in adults and 4% in children)	reduced	reduced	unstudied

than in interpandemic disease because of the lack of specific immunity to an antigenically novel strain and the potential for higher or more protracted levels of viral replication in affected persons. Indeed, higher drug doses might be required for exerting comparable antiviral effects and clinical benefits in pandemic as compared with interpandemic infections. Consequently, the minimally effective doses and durations of therapy need careful study in epidemic influenza before recommendations might be considered for the pandemic situation. Conducting such studies in unprimed populations such as young children or in immunocompromised hosts might provide useful insights.

(a) *Amantadine and rimantadine*

The M2 inhibitors have been associated with the rapid emergence of high-level resistant variants during therapeutic use and failures of chemoprophylaxis due to the transmission of such strains under close contact conditions, as in households and nursing homes (reviewed in Hayden 1996). These variants are due to point mutations in the M gene and corresponding single amino acid substitutions in the target M2 protein (reviewed in Hay 1996). They show no obvious loss of virulence or transmissibility in animal models or humans (table 4) and have been shown to compete effectively with wild-type, susceptible virus for multiple-cycle transmission in the absence of selective drug pressure in an avian model (Bean *et al*. 1989). The frequency of observing such resistant variants has averaged *ca*. 30% in treated adults and children, but ranges to over 50% of immunocompromised hosts (Englund *et al*. 1998).

A key aspect of the clinical and public health implications of resistance emergence is the transmissibility of resistant variants. For example, one older study employing rimantadine for index case treatment and post-exposure prophylaxis in families observed negligible prophylactic efficacy due to high rates of resistance emergence and probable transmission leading to failures of drug prophylaxis (Hayden *et al*. 1989). A similar study with amantadine during the 1968 pandemic also found low prophylactic efficacy, although the reasons were not elucidated (Galbraith *et al*. 1969). In contrast, inhaled zanamivir used for both treatment and post-exposure prophylaxis in families was highly effective and not associated with resistance emergence (Hayden *et al*. 2000). A recent nursing home-based study comparing 2 weeks' prophylaxis with oral rimantadine or inhaled zanamivir after recognized outbreaks found over 60% higher protection in zanamivir recipients as compared with rimantadine, in part due to high frequencies of prophylaxis failures due to rimantadine-resistant viruses (Gravenstein *et al*. 2000). The extensive use of rimantadine for prophylaxis and treatment of non-study participants on the same wards may have contributed to the observed prophylaxis failures. Such experiences highlight the potential for the emergence of amantadine-resistant influenza A viruses and spread under close contact conditions.

(b) *Oseltamivir and zanamivir*

The neuraminidase inhibitors appear to be associated with a lower frequency of resistance emergence due to neuraminidase mutations (reviewed in McKimm-Breschkin 2000; Tisdale 2000) and a lower risk of transmission (table 4). To date, only one instance of zanamivir resistance in an immunocompromised host has been documented (Gubareva *et al*. 1998) and no resistance has been found in immunocompetent persons receiving treatment (Barnett *et al*. 2000; Boivin *et al*. 2000; Hayden *et al*. 2000). The frequency of recovering resistant variants may be higher with oseltamivir therapy in that variants exhibiting neuraminidase resistance have been recovered from *ca*. 0.4% of treated adults and 4% of treated children (N. Roberts, personal communication; Treanor *et al*. 2000; Whitley *et al*. 2001). However, the oseltamivir-resistant variants show reduced infectivity and virulence in animal models and the commonest variant with amino acid substitution at position 292 shows reduced transmissibility in a ferret model (Carr *et al*. 2001). These observations indicate that antiviral resistance due to neuraminidase resistance appears to alter the fitness of influenza viruses and suggests that resistance will be much less likely to be a threat during drug use in epidemic or pandemic influenza.

(c) *Modelling studies*

Mathematical models can be used for assessing the potential for the spread of drug-resistant influenza viruses under both epidemic and pandemic circumstances (Stilianakis *et al*. 1998). Such models can be used for assessing the effectiveness and potential impact of antiviral resistance transmission during different strategies of antiviral intervention, such as chemoprophylaxis alone, the treatment of ill persons alone or combined treatment and

Table 5. Effect of the transmissibility of drug-resistant virus on outcomes in a theoretical closed population pandemic influenza outbreak.

(The values for the percentage of residents affected were adapted from Stilianakis *et al*. (1998). They are based on the assumption of a fully susceptible population ($n = 578$), an overall infection frequency of 100% and an illness frequency of 56% in the absence of drug intervention. The third and fourth columns are the transmission probabilities of resistant virus relative to wild-type, susceptible virus. The assumption regarding drug efficacy and the likelihood of resistance emergence are based on studies with amantadine and rimantadine and are detailed in Stilianakis *et al*. (1998).)

		percentage of residents affected	
strategy for drug intervention	outcome	resistant virus fully transmissible	resistant virus 20% transmissible
treatment only	infected	100	100
	ill	56	55
	ill, resistant virus	8	7
prophylaxis only	infected	98	90
	ill	30	23
	ill, resistant virus	11	3
combined treatment and prophylaxis	infected	99	87
	ill	34	23
	ill, resistant virus	17	5

prophylaxis. For example, one such study examined the effect of these different approaches using amantadine or rimantadine in a closed population during a theoretical pandemic outbreak in which all residents were assumed to be susceptible and become infected (Stilianakis *et al*. 1998). The model, which is based on studies with amantadine and rimantadine, predicted that treatment alone would affect the epidemic curve minimally, whereas chemoprophylaxis alone or a combination of treatment and chemoprophylaxis both reduce the number of symptomatic cases (table 5). However, the observed outcomes depended heavily on the transmissibility of drug-resistant virus relative to wild-type, susceptible virus (table 5). When transmissibility of the resistant variant was comparable to the wild-type, prophylaxis failures due to resistant virus were common, particularly with the combined approach for which one-half of illnesses were due to resistant virus. A relatively modest fivefold reduction in transmissibility was associated with substantial reductions in the impact of resistant virus and improved effectiveness for both the prophylaxis alone or combined intervention approaches (table 5). Another recently described model examining the effects of resistance emergence also predicts that decreases in biological fitness and associated transmissibility of drug-resistant virus, as observed with neuraminidase inhibitor-resistant variants, will lead to negligible community spread of such variants (Ferguson & Mallett 2001).

4. THE ECONOMIC IMPACT

In the absence of a mass immunization programme, the costs, excluding disruptions to commerce and society, of the next pandemic are projected to range from US$71.3 billion to US$166.5 billion for hospitalizations, outpatient care, self-treatment and lost work days and wages in the USA alone (Meltzer *et al*. 1999). Formal pharmacoeconomic analyses of antiviral interventions have not been reported to date for pandemic influenza, but could be helpful in selecting the appropriate strategies and target populations for antiviral use. Through use of the economic model developed by Meltzer *et al*. (1999) and assumptions regarding drug effectiveness derived from recent therapeutic trials with oseltamivir, preliminary assessment of the economic impact of using antivirals for treatment during an influenza pandemic are possible (table 6). Extensive therapeutic use would be projected to save many days off work, out-patients visits for presumed complications and, particularly in older adults, hospitalizations (M. I. Meltzer and F. G. Hayden, unpublished observations). These preliminary analyses suggest that treatment in high-risk older adults would reduce hospitalizations, whereas treatment in non-high-risk younger adults and children would reduce out-patient visits and work/school days lost. By assigning direct and indirect dollar valuations to the health outcomes averted, it was estimated that the treatment of high-risk persons aged 65 years and older and non-high-risk persons aged 20–64 years would generate the largest and comparable savings per 1000 ill.

If it were possible to extend early treatment to those who would not seek medical care, considerable savings in indirect costs due to days off work/school could be achieved across all age groups. However, the actual implementation of that strategy would require the development and validation of new treatment paradigms, such as telephone triage by non-physician health care providers or self-diagnosis through symptom checklists and then rapid access to antiviral drugs for patient-initiated therapy. Such assessments need to be undertaken during the interpandemic influenza period so that they might be acceptable for use during the next pandemic. In general, the results of such economic analyses depend on the nature of the pandemic and its associated age-related morbidity and mortality rates, the projected costs of outcomes and the assumed effectiveness of the intervention. Future research will need to include estimates of the cost of delivering treatments to various age and risk

Table 6. Projected economic impact of neuraminidase inhibitor treatment on selected outcomes during pandemic influenza (M. I. Meltzer and F. G. Hayden, unpublished observations).

(The days off work saved only refer to out-patient illnesses and do not consider the effect of hospitalization. Paediatric illnesses were assumed to cause days off work for care givers (Meltzer *et al*. 1999). These outcomes are derived from the use of a previously described mathematical model (Meltzer *et al*. 1999) and the following assumptions regarding the effects of early antiviral treatment derived from studies with oseltamivir: neuraminidase inhibitor treatment reduces the days of illness by 1.5 days, the number of out-patient visits by 20% (0–19 years), 50% (20–64 years) and 30% (> 65 years) and hospitalizations by 50% compared with no treatment. CI, confidence interval.)

	out-patient visits saved per 1000 ill		hospitalizations saved per 1000 ill		out-patient-related days off work saved per 1000 ill	
	mean	95% CI	mean	95% CI	mean	95% CI
0–19 years	162	152–171	2.2	0.8–3.5	800	754–847
20–64 years	296	284–307	4.0	1.8–6.0	585	320–844
65+ years	227	223–229	14.4	11.3–17.6	745	735–755

groups and examine other drug treatments and strategies including prophylaxis. However, such economic models can help guide decisions about the potential benefits of antiviral treatment or prophylaxis in different populations groups.

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