Pandemic Influenza

Is an Antiviral Response Realistic?

Frederick G. Hayden, MD

Background: Antiviral agents could play a significant role in the response to a future influenza pandemic, especially if an effective vaccine is unavailable. There is, however, a limited availability of antiviral drugs, as was the case during the A/Fujian(H3N2) epidemic in the 2003–2004 season.

There are major differences among the available antiviral agents in terms of clinical pharmacology, adverse effects and resistance profiles, all of which must be considered when selecting agents for pandemic use and stockpiling. The logistic issues involved in delivering the drug to large populations must also be considered.

The M2 ion channel inhibitors amantadine and rimantadine are partially effective for chemoprophylaxis of pandemic influenza, and when used for early treatment they provide some symptom relief. Interpandemic studies demonstrate that the neuraminidase inhibitors would be effective for both prevention and treatment of influenza.
Conclusion: Given the limited supply and the previously demonstrated inability of the manufacturing sector to meet surging needs, an effective antiviral response could not currently be launched in the United States. Antiviral agents could be important in managing and treating pandemic influenza and reduce lower respiratory complications and hospitalizations.

(*Pediatr Infect Dis J* 2004;23: S262–S269)

The disturbing reality is that despite the certainty of a pandemic, even the developed countries of the world are quite unprepared for such an event. The public health infrastructure is inadequate. Hospitals lack the capacity to accommodate a surge of patients. Vaccine manufacturers had severe problems in meeting the demand. . ., and the repertoire of antiviral drugs is completely inadequate.—Microbial Threats To Health: Emergence, Detection, and Response. Institute of Medicine of the National Academies, p 146, 2003.

From the University of Virginia School of Medicine, Charlottesville, VA
This commentary is based on a presentation at the Third International Congress on Respiratory Viruses, Chicago, IL, April 24-25, 2004.
Address for reprints: Frederick G. Hayden, MD, Department of Internal Medicine, P.O. Box 800473, University of Virginia School of Medicine, Charlottesville, VA 22908. Fax 434-924-9065; E-mail FGH@virginia.edu.

Antiviral agents could be an important part of the response to a future influenza pandemic,[1–4] but the answer to the question of whether such a response is realistic today is a resounding "No." We have limited amounts of antiviral drugs available for response, even to epidemic disease, as was learned during the A/Fujian(H3N2) epidemic during the 2003–2004 season, when shortages of the neuraminidase inhibitor (NA) oseltamivir were experienced in the United States.

In this regard, increased use of antiinfluenza agents during the interpandemic period would help ensure a more effective response to pandemic disease with respect to both increased drug availability and increased familiarity among health care providers and patients with the use of available agents. Furthermore the means to increase drug production rapidly do not exist, because there currently is only 1 manufacturing plant in the world for several of the key antiviral drugs for influenza. Given these limitations on availability and surge capacity, it is clear that we do not have an effective antiviral response today. Only those countries with stockpiles of antiviral drugs will have them in the event of a pandemic or a major epidemic event.

This matter becomes more urgent with the assumption that a vaccine will likely not be available for the first wave of the next major influenza event. This article will expand on previously published articles on this topic[1,3] and will highlight recent observations relevant to assessing the potential usefulness of antivirals in pandemic influenza. These observations relate to differences among the available agents, antiviral resistance and its implications, and the logistic considerations of drug delivery to large populations.

PANDEMIC IMPACT

In gauging the potential for an effective antiviral response, what can we expect of the next pandemic with respect to its impact? One can consider the differing experiences during the 3 pandemics of the 20th century and the reappearance of H1N1 subtype influenza in 1977. Of course, the 1918 pandemic was the most catastrophic, with 20–40 million individuals dying worldwide and >500,000 deaths in the United States, whereas the subsequent 1957 Asian and 1968

Hong Kong pandemics were associated with mortality that was about 10-fold lower, despite the fact the U.S. population had approximately doubled and the world population had more than tripled during that period of time. In contrast to 1918, when H1N1 subtype influenza reappeared in 1977 after a 2-decade hiatus, mortality was negligible, in part because illness was limited to those younger than 25 years of age.

Meltzer et al[5] at the Centers for Disease Control and Prevention have done impact modeling, largely on the basis of epidemiologic observations from 1957 to 1968 in the United States as well as interpandemic periods. They have estimated that illness attack rates during the next pandemic may range up to 35% of the population and may be associated with 24 million outpatient visits, approximately twice as many additional illnesses in individuals who do not seek medical care, nearly 750,000 hospitalizations and >200,000 deaths in the United States.[5] Based on 1995 dollars, the direct and indirect economic costs are projected to range up to $167 billion in the absence of intervention. However, this modeling was based on less severe disease than was observed in 1918. The reasons for the uniquely high mortality in the young and middle-aged population in 1918 still remain to be elucidated, but the case-fatality rates in the general population in young and middle-aged adults were in excess of 1% and at least as high in those younger than 3 years of age.

A worst case scenario, such as the 1918 pandemic, would overwhelm the U.S. health care system. For example, efforts to control health care costs have led to reductions in hospital bed capacity. According to a recent survey in the *Economist*,[56] the United States was ranked 55th in the world in acute care beds per 1000 population and had about one-fourth of the population-adjusted beds available in Japan or Switzerland and about one-half of those in most European countries. We lack the capacity to handle the anticipated massive influx of patients, although effective outpatient use of antiviral agents could mitigate this shortage. One projection based on parameters in the Netherlands indicated that wide scale use of oseltamivir treatment could substantially reduce demands for hospital beds during pandemic influenza.[6]

ANTIVIRAL DRUG EFFICACY

What about the antiviral drugs? With the older M2 ion channel inhibitors (amantadine, rimantadine) and the recent addition of the neuraminidase inhibitors (NA; zanamivir, oseltamivir) in 1999, 4 antiviral drugs for influenza, 3 given orally and 1 by inhalation, are approved in the United States. These drugs have important differences with regard to their pharmacokinetics, their tolerance profiles and antiviral resistance patterns.[3,7–9] The M2 inhibitors were studied in both the 1968 Hong Kong pandemic and again when H1N1 influenza appeared in pandemic form in 1977.

In seasonal prophylaxis studies in which these drugs were given for 4- to 8-week periods to community-dwelling populations, their protective efficacy against influenza illness varied considerably across studies but averaged ~70% overall compared with controls.[3] Compared with the 80–90% efficacy observed with these same agents in studies during the interpandemic period, it is clear that the protective efficacy is somewhat diminished in immunologically naive populations, but is still at a level that could be clinically useful in a pandemic.

Oseltamivir and zanamivir have not been studied in pandemic disease because of their recent availability. However, the results of studies of interpandemic influenza in ambulatory persons give encouragement that their prophylactic efficacy[10–12] would be at least comparable with that of M2 inhibitors and that they would exert substantial therapeutic effects when used for treatment of pandemic disease. These therapeutic effects extend beyond reductions in the durations of illness and functional disability[13] and include decreases in health care utilization.

An aggregated summary of physician-diagnosed complications leading to the use of antibiotics during the month after enrollment into the controlled clinical trials of oseltamivir treatment, found a 24% reduction in such events in children 1–12 years of age, primarily because of a >40% reduction in new otitis media diagnoses.[14] In otherwise healthy adults with acute influenza, the frequency of such events, although lower than in children or in the elderly population, was reduced by ~40%, primarily because of reductions in acute bronchitis diagnoses.[15,16] In the elderly, there was a 35% reduction, primarily because of acute bronchitis and to a lesser extent pneumonia.[17,18] Reductions in lower respiratory tract events have also been confirmed with inhaled zanamivir.[19,20] In the aggregated database comparing oseltamivir with placebo, hospitalization for any cause during the 1 month after influenza diagnosis was reduced by 60% in the healthy adult population and by 50% in the high risk and elderly populations.[18] Similarly one retrospective analysis of early, although not delayed, oseltamivir treatment in elderly nursing home residents also found reductions in influenza-related complications and hospitalizations.[21] Recent studies indicate that oseltamivir, but not rimantadine, was effective at reducing pneumococcal titers and mortality in a murine model of sequential influenza followed by pneumococcal infection, perhaps related to inhibition by oseltamivir of the effects of viral NA on cellular receptors for pneumococci.[22] Such effects on lower respiratory tract complications and hospitalizations would be expected to translate into further reductions in mortality, although that has not been substantiated by large database-type studies.

ANTIVIRAL DRUG RESISTANCE

The M2 protein, a tetrameric transmembrane protein with ion channel function, plays a key role in the release of viral gene segments during the early uncoating phase of the

virus. Single nucleotide changes leading to amino acid substitutions at any 1 of 4–5 sites within the transmembrane region of M2 can lead to high level antiviral resistance. Such variants are fully cross-resistant to all M2 inhibitors but retain susceptibility to NA inhibitors.[22a]

Past surveys indicate that a low frequency of naturally circulating resistant variants occurs in the absence of selective drug.[23,24] M2 inhibitor-resistant variants emerge rapidly when these drugs are used for treatment, and roughly 30% of treated children or adults will shed resistant variants starting 2–5 days after initiation of treatment.[25] This frequency can exceed 50% in immunocompromised hosts, and an immunocompromised host who remains virus-positive on an M2 inhibitor past 3 days is likely to have a resistant variant.[26] Resistant clones have been detected in up to 80% of amantadine-treated children.[27] When M2 inhibitor-resistant viruses are studied in animal models, they retain full virulence, infectivity and ability to transmit.[28,29]

Human-to-human transmission has been seen, not only in the household setting but also in nursing home populations where resistant variants have caused failures of chemoprophylaxis and severe illness.[25] During the 1968 pandemic, Galbraith et al[30] in the United Kingdom tested the strategy of postexposure prophylaxis for healthy household contacts in combination with treatment of the ill index cases. Only a nonsignificant 6% reduction in secondary illnesses in contacts was observed. During the interpandemic period, a similar study of rimantadine found negligible protection against secondary illness events in household contacts,[31] in part because treated index cases rapidly shed resistant variants that then spread to contacts, causing failures of prophylaxis. In contrast, more recent controlled trials of postexposure prophylaxis with the NA inhibitors, either inhaled zanamivir to age 5 years[32] or oseltamivir to age 1 year,[33] documented significant protection against secondary household transmission without evidence for emergence of resistant variants.

The frequency of resistance emergence is low during treatment with the NA inhibitors. Resistance to zanamivir has been observed only in an immunocompromised host to date.[34,35] With oseltamivir <1% of immunocompetent adults and up to ~8–18% of H3N2-infected children have shed resistant variants during or immediately after treatment.[36,36a] When studied in animal models, the viruses that have neuraminidase mutations generally have reduced infectiousness and virulence,[37,38] and there has not been recognized human-to-human transmission to date. Although NA inhibitors are all sialic acid analogs with potent, selective inhibitory effect for influenza A and B virus neuraminidases, they have differing chemical structures that result in differing interactions with the active enzyme site and variable cross-resistance patterns. Consequently some oseltamivir-resistant variants retain full susceptibility to zanamivir.[39]

The issue of potential drug resistance in a future pandemic strain comes up in the context of avian influenza. Human infections caused by avian H7 subtype avian influenza viruses have occurred in 2003 in Europe and more recently in North America. The outbreak of H7N7 disease in the Netherlands and Belgium led to the death of 1 veterinarian and likely caused illness, principally conjunctivitis, in ~350 individuals.[40] However, the immediate threat at present is the ongoing epizootic H5N1 disease in Southeast Asia. This highly pathogenic avian influenza, or fowl plague, virus is notable for its extensive spread, rapid mutability and evolution and high mortality when it causes illness in humans.[41,42] In fact, the particular virus that caused the Hong Kong cluster of cases in 1997 is not the same as the one that is currently circulating with respect to its antigenicity, internal gene segments or antiviral susceptibility.[43]

If one looks back to 1997, when the first interspecies transmission of H5N1 influenza from birds to humans occurred, there were 6 deaths among the 18 recognized cases (33% mortality). In 2003, when a Hong Kong family developed illness, with 2 infections and 1 death caused by H5N1, the virus had not only changed antigenically but had also, importantly from the perspective of antivirals, become resistant to M2 inhibitors.[44] The reasons for this are not clear, but the subsequent H5N1 isolates recovered from children and adults in Vietnam and Thailand have also been resistant to M2 inhibitors.[41,42] In essence, this finding means that a whole class of antiviral drugs has been lost as treatment for this virus.

For an H5N1 pandemic threat, the relevant NA mutation detected in N1-containing viruses during laboratory passage and in clinical trials is a histidine-to-tyrosine substitution at position 274. This N1 mutation results in >600-fold increases in inhibitory concentrations for oseltamivir in enzyme inhibition assays.[39] In contrast, zanamivir retains essentially full inhibitory activity against this variant, so that it remains a potential fallback intervention, if available. This potential problem became evident during studies of experimentally induced influenza A/H1N1 infection in otherwise healthy adults.[45] Although these studies established the efficacy of oseltamivir in humans, 2 participants receiving oseltamivir had the emergence of viruses harboring the 274 mutation ~2 and 3 days after initiation of treatment. In both instances, the emergence of the resistant variant was associated with a resurgence in upper respiratory viral loads, although it was not associated with worsening of symptoms.

The major public health concern about antiviral resistance is potential person-to-person transmissibility of such variants. Although NA inhibitor resistant variants show decreased virulence and infectivity,[46,47] the effects on potential transmissibility depend on the specific mutation conferring resistance. In contrast to the M2 inhibitors, there have been no proven instances of transmission of oseltamivir- or zana-

mivir-resistant variants in clinical trials.[32,33] In a ferret model of influenza, Herlocher et al[48,49] have examined the transmission potential of different oseltamivir-resistant variants. Wild-type viruses are highly infectious and readily transmitted from infected donor animals to close contacts. The H3N2 virus containing the arginine-to-lysine substitution at position 292 was significantly less infectious for donor animals and not transmitted to recipient ferrets.[48] The H1N1 variant with the His274Tyr mutation was also less infectious, and donor animals required a 100-fold higher inoculum to become infected. However, once infected, they were able to efficiently transmit this particular variant to contacts.[49] Such results give concern about the potential for resistance emergence and transmission of some oseltamivir-resistant variants and highlight the need for continued surveillance of susceptibility and the search for other antiviral agents.

We and others have conducted limited modeling studies to understand the impact of changes in viral fitness with regard to transmission and the likelihood of these viruses spreading within a defined community.[50,51] One projection based on a nursing home outbreak in a pandemic setting and the use of an M2 inhibitor (ie, amantadine or rimantadine) found that the incidence of cumulative illnesses at 30 days without intervention would be 56%.[50] If it is assumed that the transmissibility of the wild-type virus was the same as a resistant variant and the drug was used only for prophylaxis, there was a significant dampening of the outbreak (30% of residents ill), although a moderate number of breakthrough cases occurred, including some caused by a resistant variant. If the transmissibility of the resistant variant is reduced by a factor of just 5-fold relative to the wild type, the number of resistant failures is further diminished (23% ill). Similarly, in the setting in which both prophylaxis and treatment were used, a marked reduction in resistant variants causing prophylaxis failures was found in comparison with a situation in which the resistant virus was fully transmissible. Unlike viruses resistant to M2 inhibitors, those resistant to NA inhibitors appear diminished in their transmission potential, at least for some of the mutations, although that still remains to be fully confirmed.

In summary, de novo M2 inhibitor resistance may be present in a future pandemic influenza virus. This prospect would be likely if it were an H5N1 virus, such as the one currently circulating in birds in Southeast Asia. The frequency and consequences of resistance emergence are lower with NA inhibitor than M2 inhibitor treatment in influenza A, and consequently the NA inhibitors would be the preferred agents for management in pandemic disease. Continued susceptibility surveillance for both M2 and NA inhibitors is needed during the interpandemic period, particularly in immunocompromised hosts and other high risk populations, including young children, who are more likely to shed resistant variants. Consideration also must be given to the poten-tial for using combinations of antivirals for treatment to reduce resistance emergence.[52]

PANDEMIC ANTIVIRAL USE

How might antiviral drugs be used, and who would be the targets for intervention? Most of the countries that have examined these questions have concluded that treatment of ill persons would be the most efficient strategy of drug use, because it would directly target those affected, both hospitalized and potentially ambulatory patients. A number of countries are also considering prophylaxis of health care and other essential community workers in efforts to avoid disruption of medical and other key services.

One preemptive strategy that is under discussion is utilizing chemoprophylaxis around a localized outbreak to abort or dampen a pandemic at its outset. Antiviral ring prophylaxis,[53] or "ring Tamifluation," as some of my Japanese colleagues have dubbed it, is based on the concept of providing multiple protective rings of chemoprophylaxis to the contacts of individuals involved in and surrounding an outbreak by a novel virus. This is predicated on the assumption that a pandemic may start with limited clusters of human cases caused by an avian virus that is not well-adapted to humans and does not spread efficiently from person to person. However, if this assumption is incorrect, the short incubation period of influenza, its efficient airborne and droplet transmissibility, its potential for spread from subclinically infected persons and the confounding issue of compliance means that this strategy would have to be combined with other traditional public health measures (ie, isolation, contact tracing, quarantine, travel restrictions) for potential effectiveness.[53]

Although short term prophylaxis (7–10 days) is effective in reducing household transmission, the duration needed for a ring prophylaxis strategy is uncertain. This approach is also predicated on the rapid availability of a sufficient stockpile of antiviral drugs that could be transported to and distributed in the affected area. For a novel pandemic threat virus such as H5N1, a rapid response stockpile could allow both treatment of ill persons and prophylaxis of exposed persons (eg, cullers of poultry, investigative teams, health care providers). One tactic under discussion is the development of an emergency stockpile available to an international agency, such as the World Health Organization.[54]

There are a number of other strategies for prophylaxis (eg, seasonal, postexposure, institutional outbreak control) and target groups (eg, individuals at high risk for complications, health care workers, essential services providers) to be considered. The characteristics of the pandemic with respect to age-related morbidity and mortality, as well as the availability of antivirals, would heavily influence such decisions regarding chemoprophylaxis.

Dr Benjamin Schwartz and his colleagues at the National Vaccine Program Office have developed some projections for size of the target groups in the United States population (Table 1). For example, there are ~9.8 million health care workers, although it is unclear how many are actually front line workers, and ~2.4 million public safety workers (police, firefighters and prison guards). Those at high risk for influenza complications number roughly 80 million, although the degree of risk varies across this large group. If there were sufficient drug available, prophylaxis would more likely be directed to health care workers and the essential community service providers to maintain their capabilities.

If one assumes that ~1 million patients will be hospitalized in a pandemic scenario, a priority ranking for treatment would encompass these hospitalized individuals, despite the uncertainty of drug efficacy in seriously ill persons. The next priority would be treatment of ambulatory persons in efforts to reduce their health care utilization, hospitalizations and risk of complications and possibly to maintain their productivity. Working with Meltzer's model, we explored what might be achieved if antiviral drugs were available for treatment on an outpatient basis for individuals who have acute influenza in a pandemic setting.[3] Not surprisingly, the absolute number of hospitalizations that might be prevented per 1000 ill individuals increases with increasing age, and the number of outpatient visits for complications that could be avoided is highest in the young and middle-aged adult population.

If one has a limited amount of drug available, how should it be used for treatment? The answer depends on what one wants to save. If it is hospital days and mortality, a limited drug supply should be directed to those who are older and at high risk. If it is outpatient visits, the supply should be directed to young and middle-aged adults in the non-high risk group; and if it is outpatient days off from work or school, it should be directed to the pediatric and young adult populations. For dollar savings, based on a series of assumptions in Meltzer's model, treating high risk adults has economic benefits comparable with those that result from treating lower risk young and middle-aged adults. The reason for this is that direct hospital costs and other health care outcomes are reduced in the first instance, whereas productivity losses are reduced in the second.

Where do we stand now with regard to antiviral stockpiling? Several countries have small antiviral stockpiles, the Australian government recently signed a contract to purchase a large stockpile of oseltamivir, and other countries are actively exploring various possibilities. The United States currently has a modest stockpile that was initially established in late 2003. This national stockpile includes ~1 million courses of oseltamivir (primarily capsules and some pediatric suspension) and is maintained partly in the national drug stockpile and partly in a vendor-managed inventory. This is a very small amount compared with what we need.

If one assumed a stockpile of 2 million courses and used it only for therapy for ill persons, that drug supply would treat only ~2% of the projected illnesses in the next pandemic. If the stockpile were increased 10-fold to 20 million courses, coverage could be increased to 20% of projected illnesses. With chemoprophylaxis for a 6-week period, the actual number and percentage of overall infections prevented during the period of use would be quite small, although protection could be important for health care workers and essential community service providers. However, despite the lower daily dose, this approach uses >4 times as much drug per prophylaxis course as treatment. If one assumes a wholesale price of roughly $40 per 5-day treatment course, 20 million courses would cost ~$800 million. Lower purchase costs should be able to be negotiated with the manufacturer.

Although this may seem like a large sum, it is in reality modest and represents only a small fraction of our annual health care expenditures (~14% of gross domestic product) or the projected costs of the next pandemic. Commitment to a much larger antiviral stockpile would be a wise investment. Given the modest national stockpile currently in place and the potential for exhausting available drug supplies, even with epidemic disease, health care institutions need to consider creating their own drug reserves for management of hospitalized patients and for treatment and possible prophylaxis of medical care providers. Given the current 5-year outdate period for oseltamivir, an institution-managed rotation of drug supplies could allow for a stockpile of at least 5 times the average annual use with minimal wastage.

Novel approaches to the practical aspects of antiviral stockpiling and access need exploration. One solution proposed by Roche, the manufacturer of oseltamivir, is the purchase of nonformulated active drug substance in bulk storage containers. Individual drums contain 7 kg of powder, each of which would provide >7000 treatment courses, so that 1 kiloton of drug substance requires 143 drums. The advantages of this approach include ease of storage; lower cost, which is reduced by a factor of roughly 5-fold compared

TABLE 1. Target Populations and Prioritizations for a U.S. Influenza Pandemic

Target Group	Population Size (Millions)	Priority for Prophylaxis	Priority for Treatment
Health care providers	9.8	1	3
Public safety workers	2.4	2	4
High risk persons	~80	3	2
Hospitalized influenza patients	~1	NA	1
Ambulatory, otherwise healthy	~200	4	5 (see text)

Adapted from Benjamin Schwartz, National Vaccine Program Office.
NA indicates not applicable; 1, highest priority; 5, lowest priority.

with current costs of encapsulated drug in blister packages; and projected drug stability of at least 8 years.

The disadvantages include both practical and regulatory hurdles. This unformulated, nongranular material is a fluffy powder that would have to be measured out, dissolved in water with a preservative and then taken orally. Oseltamivir in solution is moderately unpalatable, and the formulated drug in capsules already has an associated 10–15% frequency of nausea and vomiting. This raises concerns regarding compliance. Stability of solubilized bulk drug substance has been shown for 10 days at room temperature, and there is more work in progress. However, this drug substance is not the currently approved form, and regulatory authorities would need additional data to approve its use. This strategy represents one potential way forward for long term stockpiling, but others need consideration.

How do we deliver antiinfluenza drugs to people in a timely manner? This is a critical issue, especially when one considers that early treatment, preferably within 1 day of symptom onset, is essential and that an enormous number of people will be incapacitated within a period of a few months. The current paradigm is that an ill patient usually sees a physician or health care provider for evaluation, obtains a prescription that is filled at the pharmacy and then starts medicating (Fig. 1).

Delays related to obtaining appointments, evaluation and rapid access to prescription medications would mean that the large numbers of afflicted patients would go untreated or receive late, and possibly ineffective, treatment. Slow access to care that is focused on individual patient management is not going to work in a pandemic. Other countries such as the United Kingdom already have used medical care directives involving other health care providers, such as nurses and pharmacists, for making tentative diagnoses and dispensing antiinfluenza drugs. This must be critically studied in this country along with other strategies, including management algorithms that validate the feasibility of diagnosis by non-physician providers, by family members or by the patients themselves, and that allow people to obtain drugs directly from pharmacies or central dispensing locations to initiate treatment.

The most efficient strategy would be to make treatment courses available over the counter in conjunction with management guidelines in a pandemic. However, this would work only if there were an enormous amount of drug available. These are some of the possibilities that must be addressed in the interpandemic period to allow us to have an effective pandemic response.

The World Health Organization has considered these issues as part of their Global Agenda for Influenza and has put forward guidance on the use of antiviral drugs and points for consideration in securing better supplies.[9,54,55] Indeed the WHO Global Agenda for Influenza has increasing pandemic preparedness as one of its key elements. Part of the effort is to increase the utilization of both vaccines and antiviral drugs during the interpandemic period to foster a more effective pandemic response. Obviously an important part of this is additional research on these pandemic viruses and the development of other interventions. In this regard, it is essential that we move from a circumstance where we are heavily dependent on 1 drug, oseltamivir, and 1 manufacturing source in this response. As indicated by the Institute of Medicine, we need other agents.

SUMMARY

Antiviral drugs could potentially play a major role in the initial response to pandemic influenza, particularly given the likelihood that an effective vaccine is unavailable. Prior studies of the M2 ion channel inhibitors amantadine and rimantadine have shown that they are partially effective for chemoprophylaxis of pandemic influenza and can provide some degree of symptom relief when used for early treatment. Studies in interpandemic influenza indicate that the NA inhibitors would be effective for both prevention and treatment.

Major differences exist in the clinical pharmacology, adverse drug effects and resistance profiles of the available antivirals, and these factors must be considered in selecting agents for pandemic use and stockpiling. As illustrated by the appearance of M2 inhibitor-resistant influenza A (H5N1) infections in Southeast Asia, a future pandemic could be caused by an M2 inhibitor-resistant virus. Furthermore transmission of drug-resistant virus could substantially limit the effectiveness of M2 inhibitors if used widely for treatment. Because the frequency of resistance emergence is lower with the NA inhibitors and no transmission of resistant variants has been detected to date, and because of their proven therapeutic effects in reducing influenza lower respiratory
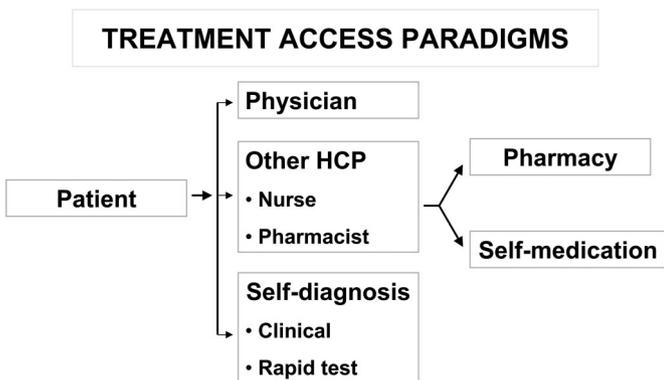

FIGURE 1. Treatment access paradigms. Schematic of different potential pathways to anti-influenza treatment. HCP indicates health care provider.

complications, these agents are the preferred ones for treatment and would be the logical choice for stockpiling.

The extent of antiviral use during the interpandemic period has been limited in the United States and most countries, with one consequence being that there are inadequate amounts available to mount a pandemic response. Currently the surge production capacity for antivirals is negligible. Hence stockpiling is essential for an effective response, and decisions will have to be made with regard to rationing of available agents. Several countries have prioritized treatment of ill persons followed by prophylaxis of health care workers and essential community service workers as their target groups for antiviral use in the event of a pandemic. Practical considerations include education of both health care providers and the public, developing more effective means for rapid distribution of antivirals to those in need, and cost. Although current antiviral drugs hold real promise for mitigating the impact of pandemic influenza, additional agents are needed, and considerable work must be done to secure adequate supplies and validate distribution mechanisms before realizing this potential.

ACKNOWLEDGMENTS

DISCUSSION

Question: Do all of your predictive models of efficacy of treatment assume an unimmunized population, and has anyone thought about how those might change with effective immunization of at-risk individuals before a pandemic year?

Frederick Hayden, MD: There is a substantial amount of evidence to suggest that the effect of the drugs for the use for prophylaxis or treatment is really additive in the background immunity of these individuals. I am sure that there would be better efficacy in that situation. I have not seen good modeling done with that. It may be out there, but I'm not aware of it.

REFERENCES

1. Hayden FG. Antivirals for pandemic influenza. *J Infect Dis*. 1997; 176(suppl 1):S56–S61.
2. Gust ID, Hampson AW, Lavanchy D. Planning for the next pandemic of influenza. *Rev Med Virol*. 2001;11:59–70.
3. Hayden FG. Perspectives on antiviral use during pandemic influenza. *Philos Trans R Soc Lond B Biol Sci*. 2001;356:1877–1884.
4. Webby RJ, Webster RG. Are we ready for pandemic influenza? *Science*. 2003;302:1519–1522.
5. Meltzer MI, Cox NJ, Fukuda K. The economic impact of pandemic influenza in the United States: priorities for intervention. *Emerg Infect Dis*. 1999;5:659–671.
6. van Genugten MLL, Heijnen MLA, Jager JC. Pandemic influenza and healthcare demand in the Netherlands: scenario analysis. *Emerg Infect Dis*. 2003;9:531–537.
7. Hayden FG, Aoki FY. Influenza neuraminidase inhibitors. In: Yu VL, ed. *Antimicrobial Therapy and Vaccines*. 2nd ed. In press.
8. Hayden FG, Aoki FY. Amantadine, rimantadine, and related agents. In: Yu VL, Merigan TC, White NJ, Barriere S, eds. *Antimicrobial Therapy and Vaccines*. Baltimore, MD: Williams & Wilkins; 1999:1344–1365.
9. WHO. WHO Guidelines on the use of vaccines and antivirals during influenza pandemics. Available at: http://www.who.int/emc/diseases/flu/whoguidelines.htm. Accessed October 12, 2004.
10. Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med*. 1999;341:1336–1343.
11. Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial [see comments]. *JAMA*. 2001;285:748–754.
12. Peters PH, Gravenstein S, Norwood P, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. *J Am Geriatr Soc*. 2001;49:1–7.
13. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Chemother*. 2003;51:123–129.
14. Whitley RJ, Hayden FG, Reisinger K, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J*. 2001;20:127–133.
15. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza. *JAMA*. 2000;283:1016–1024.
16. Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner D, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2003;326:1235–1239.
17. Martin C, Mahoney P, Ward P. Oral oseltamivir reduces febrile illness in patients considered at high risk of influenza complications: International Congress Series 1219. London, U.K.: Excerpta Medica; 2001: 807–811.
18. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med*. 2003;163:1667–1672.
19. Kaiser L, Keene ON, Hammond J, Elliott M, Hayden FG. Impact of zanamivir on antibiotics use for respiratory events following acute influenza in adolescents and adults. *Arch Intern Med*. 2000;160:3234–3240.
20. Lalezari J, Campion K, Keene O, Silagy C. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. *Arch Intern Med*. 2001;161:212–217.
21. Bowles SK, Lee W, Simor AE, et al. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999–2000. *J Am Geriatr Soc*. 2002;50:608–616.
22. McCullers JA. Effect of antiviral treatment on the outcome of secondary bacterial pneumonia after influenza. *J Infect Dis*. 2004;190:519–526.
22a. Hayden FG, et al. NISN statement on antiviral resistance in influenza viruses. *Wkly Epidemiol Rec*. 2004;79:306–308.
23. Ziegler T, Hemphill ML, Ziegler ML, et al. Low incidence of rimantadine resistance in field isolates of influenza A viruses. *J Infect Dis*. 1999;180:935–939.
24. Dawson J. Neuraminidase inhibitor and amantadine. *Lancet*. 2000;355: 2254.
25. Hayden FG. Amantadine and rimantadine: clinical aspects. In: Richman DD, ed. *Antiviral Drug Resistance*. Chichester, U.K.: John Wiley & Sons, Ltd., 1996:59–77.
26. Englund JA, Champlin RE, Wyde PR, et al. Common emergence of amantadine and rimantadine resistant influenza A viruses in symptomatic immunocompromised adults. *Clin Infect Dis*. 1998;26:1418–1424.
27. Shiraishi K, Mitamura K, Sakai-Tagawa Y, Goto H, Sugaya N, Kawaoka Y. High frequency of resistant viruses harboring different mutations in amantadine-treated children with influenza. *J Infect Dis*. 2003;188:57–61.
28. Bean WJ, Threlkeld SC, Webster RG. Biologic potential of amantadine-resistant influenza A virus in an avian model. *J Infect Dis*. 1989;159: 1050–1056.
29. Sweet C, Hayden FG, Jakeman KJ, Grambas S, Hay AJ. Virulence of rimantadine-resistant human influenza A (H3N2) viruses in ferrets. *J Infect Dis*. 1991;164:969–972.
30. Galbraith AW, Oxford JS, Schild GC, Watson GI. Study of 1-adaman-

tanamine hydrochloride used prophylactically during the Hong Kong influenza epidemic in the family environment. *Bull World Health Organ*. 1969;41:677–682.

31. Hayden FG, Belshe RB, Clover RD, Hay AJ, Oakes MG, Soo W. Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. *N Engl J Med*. 1989;321:1696–1702.

32. Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for preventing influenza in families. *N Engl J Med*. 2000;343:1282–1289.

33. Hayden FG, Belshe R, Villanueva C, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without post-exposure prophylaxis. *J Infect Dis*. 2004;189:440–449.

34. Gubareva LV. Molecular mechanisms of influenza virus resistance to neuraminidase inhibitors. *Virus Res*. 2004;103:199–203.

35. Gubareva LV. Characterization of influenza A and B viruses recovered from immunocompromised patients treated with antivirals. In: Kawaoka Y, ed. *Options for the Control of Influenza*. International Congress Series 1263. Amsterdam, The Netherlands: Elsevier; 2004:126–129.

36. Roberts N. Treatment of influenza with neuraminidase inhibitors: virological implications. *Philos Trans R Soc Lond B Biol Sci*. 2001;356:1895–1897.

36a. Kiso M, Mitamura K, Sakai-Tagawa Y, et al. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet*. 2004;364:759–765.

37. McKimm-Breschkin JL. Neuraminidase inhibitors for the treatment and prevention of influenza. *Expert Opin Pharmacother*. 2002;3:103–112.

38. Zambon M, Hayden FG. Position statement: global neuraminidase inhibitor susceptibility network. *Antiviral Res*. 2001;49:147–156.

39. Wetherall NT, Trivedi T, Zeller J, et al. Evaluation of neuraminidase enzyme assays using different substrates to measure susceptibility of influenza virus clinical isolates to neuraminidase inhibitors: report of the neuraminidase inhibitor susceptibility network. *J Clin Microbiol*. 2003;41:742–750.

40. Koopmans M, Wilbrink B, Conyn M, et al. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. *Lancet*. 2004;363:587–593.

41. WHO International Avian Influenza Investigative Team. Avian influenza A (H5N1) in 10 patients in Vietnam. *N Engl J Med*. 2004;350:1179–1188.

42. WHO. Avian influenza frequently asked questions. Available at: http://www.who.int/csr/disease/avian_influenza/avian_faqs/en/.2004:January 29.

43. Li KS, Guan Y, Wang J, et al. Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. *Nature*. 2004;430:209–213.

44. Peiris JS, Yu WC, Leung CW, et al. Re-emergence of fatal human influenza A subtype H5N1 disease. *Lancet*. 2004;363:617–619.

45. Gubareva LV, Kaiser L, Matrosovich MN, Soo-Hoo Y, Hayden FG. Selection of influenza virus mutants in experimentally infected volunteers treated with oseltamivir. *J Infect Dis*. 2001;183:523–531.

46. Carr J, Ives J, Kelly L, et al. Influenza virus carrying neuraminidase with reduced sensitivity to oseltamivir carboxylate has altered properties in vitro and is compromised for infectivity and replicative ability in vivo. *Antiviral Res*. 2002;54:79–88.

47. Ives JAL, Carr JA, Mendel DB, et al. The H274Y mutation in the influenza A/H1N1 neuraminidase active site following oseltamivir phosphate treatment leave virus severely compromised both in vitro and in vivo. *Antiviral Res*. 2002;55:307–317.

48. Herlocher ML, Carr J, Ives J, et al. Influenza virus carrying an R292K mutation in the neuraminidase gene is not transmitted in ferrets. *Antiviral Res*. 2002;54:99–111.

49. Herlocher ML, Elias S, Truscon R, Beggs J, Roberts N, Monto AS. Transmission studies in ferrets of influenza viruses resistant to oseltamivir carboxylate carrying three separate neuraminidase mutations. In: Options for the Control of Influenza Conference Program and Abstracts. October 2003:47.

50. Stilianakis NI, Perelson AS, Hayden FG. Emergence of drug resistance during an influenza epidemic: insights from a mathematical model. *J Infect Dis*. 1998;177:863–873.

51. Ferguson NM, Mallett S, Jackson H, Roberts N, Ward P. A population-dynamic model for evaluating the potential spread of drug-resistant influenza virus infections during community-based use of antivirals. *J Antimicrob Chemother*. 2003;51:977–990.

52. Ison MG, Gnann JW Jr, Nagy-Agren S, et al. Safety and efficacy of nebulized zanamivir in hospitalized patients with serious influenza. *Antivir Ther*. 2003;8:183–190.

53. Balicer RD, Huerta M, Grotto I. Tackling the next influenza pandemic. *BMJ*. 2004;328:1391–1392.

54. WHO. WHO consultation on priority public health interventions before and during an influenza pandemic. Available at: http://www.who.int/csr/disease/avian_influenza/guidelines/pandemicconsultation/en/print.html. 2004.

55. Stohr K. The Global Agenda on Influenza Surveillance and Control. *Vaccine*. 2003;21:1744–1748.

56. *The Economist World in Figures*. 2003:83.