Antivirals and the Control of Influenza Outbreaks

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During annual influenza epidemics, outbreaks of influenza in closed institutions are common. Among healthy children or young adults, such outbreaks are uncommonly associated with serious morbidity or mortality; however, in hospitals and nursing homes, attack rates as high as 60% and case-fatality rates as high as 50% have been reported. Annual influenza vaccination of both patients or residents and hospital and nursing home staff has had a substantial impact on mortality and has reduced the number of outbreaks. Nonpharmacologic interventions (e.g., handwashing and contact isolation of case patients) may reduce the spread of influenza, although evidence for their efficacy is lacking. Nonetheless, long-term care facilities for the elderly population with high vaccination rates and better-than-average infection-control programs have a 25%–50% chance of experiencing an influenza outbreak each year, with an expected resident attack rate of 35%–40%. Thus, antiviral drugs have been increasingly used to mitigate the impact of influenza outbreaks. There are 2 classes of antiviral drugs that are active against influenza: adamantanes and neuraminidase inhibitors. Drugs of the 2 classes appear to be equally effective for the treatment and prophylaxis of susceptible influenza A virus strains. However, adamantanes are not active against influenza B virus, and an increasing proportion of influenza A isolates are resistant to adamantanes. Admantanes are associated with higher rates of adverse events than are neuraminidase inhibitors. There is substantial evidence that antiviral prophylaxis is effective in terminating outbreaks of seasonal influenza in closed institutions. If stockpiles are adequate, antiviral drugs are likely to be even more important in mitigating the impact of influenza transmission in health care institutions during the next influenza pandemic.

Influenza has received much recognition recently as a looming threat that is poised to cause the next pandemic. The devastation created by the 1918 Spanish influenza pandemic, which was responsible for at least 40 million deaths, is a recent reminder of the damage that this virus is capable of producing. What is consistently underappreciated, however, is the burden associated with interpandemic, or seasonal, influenza. In North America, seasonal influenza remains the most common infectious cause of death, responsible for ∼40,000 deaths and at least 150,000 hospitalizations annually [1, 2].

Every year, 12%–20% of the population becomes infected with the influenza virus [3]. Elderly individuals and the very young comprise the most vulnerable population groups; just under 1% of persons >65 years of age and 2 per 1000 children <1 year of age can be expected to be hospitalized because of influenza each year [4, 5].

Outbreaks of influenza are common and have been reported in a wide range of environments, including aircraft, youth hostels, boarding schools, acute-care hospitals, and nursing homes. Outbreaks can be explosive, with attack rates >60% over periods as short as 10 days [6, 7]. In settings other than hospitals and nursing homes, mortality and serious morbidity associated with seasonal influenza outbreaks are low, and no systematic attempts have been made to prevent or control outbreaks. In contrast, in long-term care facilities for elderly individuals, where case-fatality rates have been reported to be as high as 55%, prevention and control of outbreaks is an important priority [8, 9]. For this reason, most of our knowledge about outbreak control is derived from outbreaks in nursing homes.

OPTIONS FOR OUTBREAK CONTROL OTHER THAN ANTIVIRAL DRUGS

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suggest that, in the absence of antiviral use, influenza outbreaks main common and difficult to control. Recent publications by facilities to institute such measures, influenza outbreaks intervention against influenza. It is clear that, despite attempts no prospective studies have tested any nonpharmacologic in-

of at least 1 of these studies have been withdrawn [20], and respiratory tract infection [18, 19]. However, the conclusions may have an impact on the incidence or size of outbreaks of facilities have been interpreted to suggest that such measures large groups of residents, and restriction of staff to individual units. A few publications describing the experience in individual facilities have been interpreted to suggest that such measures may have an impact on the incidence or size of outbreaks of respiratory tract infection [18, 19]. However, the conclusions of at least 1 of these studies have been withdrawn [20], and no prospective studies have tested any nonpharmacologic intervention against influenza. It is clear that, despite attempts by facilities to institute such measures, influenza outbreaks remain common and difficult to control. Recent publications suggest that, in the absence of antiviral use, influenza outbreaks occur in 25%–50% of long-term care facilities for elderly individuals each year, with resident attack rates of 35%–40% [15–17, 21–23]. This risk has led to the consideration of antiviral drugs for treatment and prophylaxis of influenza and for outbreak control.

ANTIVIRAL DRUGS FOR INDIVIDUAL THERAPY AND PROPHYLAXIS

There are 2 classes of drugs licensed for the treatment and prophylaxis of influenza: M2 ion channel inhibitors (the adamantanes amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir). Both drug classes are effective for both treatment (table 1) [24–31] and prophylaxis (table 2) [25–27] of influenza A virus infection. No comparative trials have been performed; however, on the basis of currently available information, these medications appear to be of equal

Table 1. Impact of therapy with antiviral agents on the outcome of influenza A virus infection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Amantadine&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Zanamivir&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Oseltamivir&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms</td>
<td>Reduced by ~30%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Reduced by ~30%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Reduced by ~30%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Transmission</td>
<td>…&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Reduced by 19%&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Reduced by 80%&lt;sup&gt;c,e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Complications&lt;sup&gt;f&lt;/sup&gt;</td>
<td>…&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Reduced by 20%–50%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Reduced by 30%–60%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hospitalization&lt;sup&gt;f&lt;/sup&gt;</td>
<td>…&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Reduced by 45%&lt;sup&gt;c,g&lt;/sup&gt;</td>
<td>Reduced by 55%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mortality&lt;sup&gt;f&lt;/sup&gt;</td>
<td>…&lt;sup&gt;d&lt;/sup&gt;</td>
<td>…&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Reduced by 60%&lt;sup&gt;e,h&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Amantadine and rimantadine therapy appear to be of approximately equal efficacy, although there are fewer data for rimantadine therapy [23].

<sup>b</sup> Neuraminidase inhibitors (e.g., zanamivir and oseltamivir) are also effective against influenza B virus.

<sup>c</sup> These data are drawn from an analysis of 4 randomized, controlled trials that were conducted in households; the estimate of zanamivir efficacy is not significantly different from that of placebo. The estimate of oseltamivir efficacy is significantly different from that of placebo, but not significantly different from that of zanamivir [28].

<sup>d</sup> No data or too few data to estimate outcome.

<sup>e</sup> Too few data to have confidence in the size of the estimated effect.

<sup>f</sup> Data on reduction in complications and mortality are taken from the Cochrane meta-analysis [25, 26].

<sup>g</sup> Not statistically significant.

<sup>h</sup> In pooled, randomized controlled trials, the power was not adequate to assess the impact of therapy on mortality [29]. However, in 2 cohort studies, oseltamivir therapy has been associated with a reduction in mortality among influenza-infected adults [30, 31].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prophylaxis efficacy, median % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug class</td>
<td>Seasonal influenza community&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>adamantanes</td>
<td>62 (41–78)</td>
</tr>
<tr>
<td>Neuraminidase inhibitors</td>
<td>85 (36–99)</td>
</tr>
</tbody>
</table>

<sup>a</sup> In studies of seasonal influenza prophylaxis, prophylactic antiviral drugs were administered daily for 6 weeks during the peak of the influenza season.

<sup>b</sup> For household contacts of an ill index patient, prophylaxis was given daily for 10 days.

<sup>c</sup> When adamantanes are used for treating the index case patient as well as for prophylaxis, drug-resistant infection commonly emerges in the index case patient. The transmission of these adamantine-resistant variant strains to household contacts reduces the efficacy of adamantanes in the prevention of illness to close to 0%.
efficacy for prophylaxis against influenza A virus infection, preventing ∼65% of cases of symptomatic disease. M2 inhibitors are not active against influenza B virus. Although data regarding influenza B virus are relatively limited, neuraminidase inhibitors appear to be as active against influenza B virus as they are against influenza A virus for prophylaxis and nearly as active against influenza B virus as they are against influenza A virus for treatment [24].

Adamantanes and neuraminidase inhibitors differ, not only in their activity against influenza B, but also in their propensity to select for drug resistance and in their adverse effects (tables 3 and 4). In the past 3 years, significant adamantane resistance has emerged among influenza A viruses. In Canada, resistance to M2 inhibitors among influenza A (H3N2) viruses has increased rapidly, to >90% of isolates in the 2005–2006 influenza season, followed by a decrease to 37% during the 2006–2007 influenza season [33, 34]. In Australia, the rate of resistance to M2 inhibitors has increased more slowly, peaking at 59% of A (H3N2) isolates obtained in 2006 [35]. Drug resistance was first detected among influenza A (H1N1) strains in Australia in 2005 and in Canada in 2006, and it appears to be increasing [34, 35]. Adamantanes should no longer be used for the treatment or prophylaxis of influenza unless the isolate is known to be susceptible to those drugs. Although the prevalence of resistance to neuraminidase inhibitors remains <2%, neuraminidase-resistance rates may change over time, and ongoing surveillance is needed.

**ANTIVIRAL PROPHYLAXIS AND INFLUENZA OUTBREAK CONTROL**

Expert bodies have recommended mass antiviral prophylaxis as a control measure for nursing home outbreaks for >1 decade. These recommendations have, until recently, been based on data establishing the effect of prophylaxis in individuals and on observations (largely unpublished) of the course of influenza outbreaks with and without antiviral prophylaxis. Two recent cohort studies have provided additional support for the practice. Bowles et al. [30] reported the use of mass antiviral prophylaxis with neuraminidase inhibitors to control outbreaks in nursing homes in Ontario, Canada, during the 1999–2000 influenza season. Use of mass prophylaxis with neuraminidase inhibitors was associated with prompt termination of all 8 evaluable outbreaks [30]. Monto et al. [23] observed influenza outbreaks in Michigan nursing homes during the 2000–2001 and 2001–2002 seasons. Among 8 outbreaks in which mass prophylaxis was started, no further cases were seen in units using prophylaxis in 5 outbreaks, and the outbreak was terminated after a small number of additional cases in the other 3 outbreaks. In contrast, cases continued to occur for as long as 1 month prior to the initiation of prophylaxis, and in 1 facility in which prophylaxis was not initiated, cases continued to occur until 40% of residents were affected [23].

Antiviral prophylaxis must be initiated quickly and efficiently if illness is to be minimized. However, mass prophylaxis during outbreaks is expensive and may create selective pressure for antiviral resistance. Therefore, it is useful for long-term care facilities to have clearly defined policies and procedures that define when and how such prophylaxis is to be used. Such policies are likely to also be applicable to units in chronic-care hospitals and other long-stay institutions for adults and chronically ill children. To write these policies, a series of practical questions must be answered.

**What evidence is required to declare an outbreak?** There are no controlled studies defining the minimum number of cases that constitute an influenza outbreak or the conditions that amplify the spread of influenza from a single case. Sporadic respiratory tract infections occur at a rate of ∼1 case every 7 days in a 40-resident unit [36, 37]. Thus, 2 unrelated infections with onset within 72 h would be expected to occur with a frequency of 7%; 3 unrelated infections would be expected to

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**Table 3. Comparison of adverse effects associated with antiviral drugs that are active against influenza A virus.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common adverse effects</th>
<th>Serious adverse effects</th>
<th>Other issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Nausea, vomiting, lightheadedness, insomnia, anxiety, impaired coordination, nervousness</td>
<td>Hallucinations, suicidal ideation, neurological malignant syndrome, increased risk of seizures</td>
<td>Low toxic to therapeutic ratio; deaths have occurred as a result of overdoses; dosage adjustment based on estimated creatinine clearance necessary for older adults with normal serum creatinine levels</td>
</tr>
<tr>
<td>Rimantadine</td>
<td>Nausea, anxiety</td>
<td>None proven</td>
<td>...</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Nausea, vomiting</td>
<td>None proven; surveillance data suggest possible neurobehavioural abnormalities (~1 case per 100,000 population)</td>
<td>...</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>None</td>
<td>None proven; case reports of airway hyperreactivity after inhalations</td>
<td>Disabled and/or confused persons will have difficulty using inhaler</td>
</tr>
</tbody>
</table>

* For additional information, see the US Food and Drug Administration Web site [32].
Table 4. Characteristics of strains with resistance to antivirals that are active against influenza A.

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Rate of resistance in North America, 2006–2007 influenza season</th>
<th>Selection for resistance during therapy</th>
<th>Infectivity in animals</th>
<th>Virulence in animals</th>
<th>Human transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine and rimantadine</td>
<td>All H1N1 isolates, 2%; H3N2 isolates, 30%; B isolates, 100% (intrinsic resistance)</td>
<td>High (~30% of isolates)</td>
<td>Wild-type</td>
<td>Wild-type</td>
<td>Yes (households and nursing homes)</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Very low</td>
<td>Low</td>
<td>Reduced</td>
<td>Reduced</td>
<td>None to date</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Very low</td>
<td>Low (&lt;1% of isolates in adults; 4%–5% of isolates in children)</td>
<td>Reduced</td>
<td>Reduced</td>
<td>None to date</td>
</tr>
</tbody>
</table>

When should dosage adjustment for reduced creatinine clearance levels be considered? Many elderly residents of long-term care facilities have impaired renal function, often with normal serum creatinine levels [42]. Oseltamivir is excreted renally, and residents with documented impaired renal function should have their dosage adjusted (for suggested adjustment, see the Ontario Ministry of Health and Long Term Care Web site [38]). However, it is important to recall that the toxic-to-therapeutic ratio of oseltamivir is high. Thus, residents whose renal function is not known or who have impaired renal function with normal serum creatinine levels may safely be given usual doses of this medication.

Which residents should receive prophylaxis? Experience with outbreaks in long-term care facilities has demonstrated that influenza outbreaks often spread from one unit to another, and expert committees have recommended that, in general, when outbreaks are declared, prophylactic measures should include the entire facility. Data from recent observations in Michigan support this recommendation [23]. Exceptions may be considered when the number of cases is small (<5) or when there is little mixing of staff and residents between units. In this circumstance, prophylaxis should be given to all residents in the outbreak unit. Enhanced surveillance for respiratory tract infections in units where prophylaxis is not being recommended is critical.

Which staff should receive prophylaxis? Outbreaks of influenza involve staff as well as residents of long-term care facilities. One option to protect residents is restriction of ill health care workers. This has 4 drawbacks: health care workers themselves are unprotected from illness, health care workers may be noncompliant with restrictions, staffing may become critically short if many health care workers are ill, and staff may transmit disease in the hours before they become ill or at the onset of illness, if illness onset occurs during a work period. It is clearly of benefit that health care workers be protected from influenza.

Vaccination of health care workers prevents at least 80% of influenza cases due to strains that match the vaccine and re-
duces the severity of disease when it does occur [10]. Thus, the benefit of antiviral drugs for vaccinated health care workers is usually very limited. There are 2 exceptions to this. Health care workers who are immunocompromised (e.g., those with HIV infection), for whom protection resulting from vaccination is reduced, may benefit from prophylaxis. In addition, if the outbreak is known to be caused by a strain that is not matched well to the vaccine that has been administered, prophylaxis should be considered. Although information is improving, real-time assessments of the degree of mismatch and of the likely protective efficacy of vaccination remain difficult. Decisions need to be made on the basis of the best available data about the mismatch and the amount and severity of illness that has already occurred among vaccinated staff.

Unvaccinated staff, if they are to continue working in the facility during the outbreak, should be offered prophylaxis. Staff should be educated and offered their choice of neuraminidase inhibitor. Because influenza is a serious disease among nursing home residents, and because unprotected staff pose some risk of infection, an increasing number of long-term care facilities in Canada have policies that require that workers receive vaccination, take antiviral drugs, or not work during an outbreak [38].

When can prophylaxis be discontinued? Outbreaks can be declared over when it is clear that transmission has been interrupted. This can be assumed when no new case of disease has onset during 1 complete incubation period after the last day that an ill individual capable of transmitting influenza was in the facility, with the last infectious case was present in the facility. Usually, this individual will have been a resident. Because persons with influenza shed appreciable concentrations of influenza virus and are presumed to be infectious for 3–5 days after the onset of symptoms, and because the maximal incubation period of influenza is 4–5 days, an outbreak can be declared over 7–10 days after the onset of the last case. When antiviral prophylaxis is started, some residents and staff will be incubating influenza and can be expected to develop symptoms in the 48-h period after prophylaxis is started. Thus, most authorities recommend that antiviral prophylaxis be prescribed for 14 days. It is important to remember that sporadic cases of viral respiratory tract illness will continue to occur at a rate of just over 2 cases of infection per 100 residents per week; cases of infection that occur at or below this rate should not be interpreted as an ongoing outbreak [36, 37].

What response is appropriate if cases continue to occur despite prophylaxis? If new cases continue to develop >48 h after the start of prophylaxis, further investigation is warranted. In most circumstances, these new cases will be caused by a virus other than influenza virus, because outbreaks associated with cocirculation of 2 viruses are not uncommon [36, 37]. This can be detected by ongoing testing of nasopharyngeal swab samples or aspirate specimens obtained from newly ill residents. Multiplex PCR testing for respiratory viruses is optimal, if available, because of its increased sensitivity and ability to detect multiple viruses. Failure of amantadine and/or rimantadine therapy to control outbreaks of influenza occurs at a low but detectable rate [30]. To date, there have been no published reports of failure of outbreak control when neuraminidase inhibitors have been used.

WHAT IMPLICATIONS DOES THIS HAVE FOR THE NEXT PANDEMIC?

The new strains of influenza virus that arise each year and cause seasonal influenza outbreaks are closely related to previous strains. Most people have some degree of immunity as the result of previous exposure to these related strains, making seasonal influenza a disease of the semi-immune. In contrast, influenza strains that cause pandemics are unrelated to previous strains, and as a result, there is no degree of population immunity. Certainly, during a pandemic, the attack rate in all populations will be higher and the risk of outbreaks in closed institutions will be greater than during a usual influenza season. In addition, because of the rate of illness in the population, acute health care services will be stressed, transfers from residential to acute health care institutions may be restricted, and shortages of health care personnel, anti-infective drugs, and other health care supplies are likely to occur.

Closed institutions of all types need to consider how cases of influenza infection can be prevented in their facility and how cases that do develop can be optimally managed. In previous pandemics, particularly during the 1918–1919 pandemic, some small communities and closed institutions attempted to “cloister” themselves from the outside world and prevent the introduction of the pandemic strain. This was effective or partially effective in only a limited number of circumstances, even in extremely isolated areas, and this strategy will not be effective as long as employees or other persons move back and forth into the community [43]. Although cloistering should be considered, it will not be a viable option for most institutions. Nonpharmacologic interventions (e.g., good hand hygiene, a reduction in mixing during activities, and visitor restrictions) are likely to reduce the risk and impact of outbreaks to some degree, but their efficacy will be limited.

For these reasons, all closed institutions that house or care for populations at risk for complications of influenza should also be considering policies for the use of antiviral drugs for both patients or residents and staff during the pandemic. There are a number of challenges to this planning. Production of antiviral drugs cannot be increased rapidly; therefore, the usual stocks of antiviral drugs will be depleted very early in the pandemic. Institutions that wish to use these drugs must create stockpiles before the pandemic. Physicians may need experience

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with their use for treatment and prophylaxis to be comfortable prescribing them when the pandemic arrives. Antivirals are not a panacea. Although drug resistance is not currently an issue, it may evolve either before or during the pandemic. Antiviral treatment of pandemic influenza may be less effective than treatment of seasonal influenza because of higher viral loads and more-severe infections. Higher dosages, prolonging the duration of therapy, and using combinations of antiviral drugs have all been proposed as potential solutions [42, 44]; each of these potential strategies will have an impact on the selection of antiviral drugs and the volume of stockpiles. In the absence of drug resistance, prophylaxis is likely to be as effective against pandemic influenza as it is against current seasonal influenza; however, stockpiles for prophylaxis will need to be much larger than stockpiles for treatment.

In sum, antiviral therapy has been a very useful adjunct therapy for the protection of residents of closed institutions from outbreak-associated influenza. It is likely that, if access to antiviral drugs during a pandemic can be assured, they will also be of significant benefit during the next influenza pandemic.

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33. Centers for Disease Control and Prevention. Health alert. CDC recommends against the use of amantadine and rimantadine for the treat-


