Prevention and Treatment of Influenza in High-Risk Groups: Children, Pregnant Women, Immunocompromised Hosts, and Nursing Home Residents

Richard J. Whitley and Arnold S. Monto[a]

The pediatric population experiences preventable hospitalizations and serves as a reservoir for influenza and its transmission to other children as well as adults. As a consequence, the Advisory Committee on Immunization Practices has recommended initiating influenza immunization of children as young as 6 months of age through 23 months of age and, recently, up to 5 years of age. However, immunization of older children has not yet become a priority of the US Public Health Service. As a consequence, the importance of antiviral agents, particularly neuraminidase (NA) inhibitors, cannot be overemphasized. From an epidemiological perspective, influenza resulted in higher childhood mortality than did *Bordetella pertussis* infection in 2003–2004. During that season, 153 children died of influenza, and two-thirds were <5 years of age. Importantly, nearly 50% of these children were previously healthy, with no underlying illness. Currently, 2 NA inhibitors are approved for the treatment of influenza in children. Zanamivir is approved for children >7 years of age, and oseltamivir is approved for children >1 year of age. Arguably, the younger children are at particular risk for influenza complications and hospitalization. In placebo-controlled studies in children >1 year of age, oseltamivir therapy accelerated resolution of clinical illness and defervescence and decreased both the incidence of otitis media and the concomitant use of antibiotics. However, oseltamivir is not currently approved for children <1 year of age. Three clinical toxicology studies identified neurotoxicity in newborn rats administered this medication. In these preclinical toxicology studies, the dose of oseltamivir exceeded that which would be used in humans. In addition, the metabolism of oseltamivir is different in rats than in humans. A key component of influenza therapy is the possibility for development of resistance. Although in studies performed in North America, resistance was not a frequent event, it has been documented in Japanese children treated with this medication; the adequacy of the dose used has been questioned. Children represent only one unique study population among others. Individuals who are at increased risk for influenza infection include the elderly, the immunocompromised, and pregnant women. Collectively, antiviral medications must be evaluated in populations in which they have not yet been assessed. The development of additional antiviral drugs is an important recommendation for the future, so that antiviral resistance can be circumvented. Similarly, availability of drugs for children <1 year of age is mandatory.

Children are a unique population with respect to influenza. They shed larger quantities of virus and for a longer time than other patient groups and are very effective at transmitting influenza virus to other family members and to others within the community [1]. Young children have high rates of influenza-associated complications that require hospitalization. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC)

recommends routine vaccination of children 6–23 months of age and has recently extended the recommendation to children up to 5 years of age [2]. Older children are not included in the groups targeted for annual vaccination unless they have chronic medical conditions that put them at increased risk for complications. Consequently, vaccination uptake in healthy children is low; for example, in 2004–2005, only 12% of healthy children were vaccinated against influenza [3]. The role of children in the transmission of influenza has generated interest in the potential benefits of routine vaccination of children. However, the current low vaccination uptake rates in children and in other populations mean that there is a need for effective treatments.

Other special populations include pregnant women, immunocompromised hosts, and the elderly, particularly those housed in communal facilities. These patient groups are at increased risk for serious complications of influenza. Here, we consider the epidemiological profile and management of influenza in children and in patient groups who are at increased risk from influenza infection.

CHILDREN

Children at high risk for serious complications of influenza include those who are immunocompromised, those with asthma, and those born prematurely who have chronic lung disease (also known as "bronchopulmonary dysplasia") and are consequently more susceptible to lung infection as they age. Analysis of hospitalization rates by age and risk group shows that, in children <4 years of age, hospitalization rates in high-risk children are significantly greater than in low-risk children and approach those seen in high-risk patients 65–74 years of age (table 1).

The clinical presentation of influenza in school-age children and adolescents is similar to that in adults and includes fever, cough, myalgia, headaches, sore throat, chills, tiredness, and general malaise. In preschool children and infants, influenza can be more difficult to identify, because the symptoms are similar to infections caused by other respiratory viruses, although clearly the epidemiological profile of infection in the local community and the use of rapid diagnostics are of value when treatment options are being considered. Compared with older populations, children experience a higher frequency of central nervous system complications, including encephalitis, myelitis, Guillain-Barré–type polyradiculopathy, and postinfectious encephalitis, often associated with very poor outcomes [4, 5]. Children are also at increased risk for primary viral pneumonia and secondary bacterial lung infections [4].

The 2003–2004 influenza season in the United States was particularly severe, compared with other recent seasons, especially among young children. Because of early reports of death among children, the CDC implemented surveillance of childhood deaths associated with influenza and subsequently

Table 1. Hospitalization rates for patients, by age and risk group (interpandemic years).

	Hospitalization rate per 100,000 persons	
Age, years	With high-risk medical conditions	Without high-risk medical conditions
≤4	3562	509
5–14	274	39
15–64	873	125
65–74	4235	605
≥75	8797	1257

NOTE. Data are from the Centers for Disease Control and Prevention (available at: http://www.cdc.gov). High-risk medical conditions are as defined by the Advisory Committee on Immunization Practices [2]—that is, chronic disorders of the pulmonary or cardiovascular systems, including asthma; immunosuppression; metabolic or endocrine disorder; long-term aspirin therapy; renal disease; pregnancy; and hemoglobinopathy.

conducted a review of case reports, medical records, and autopsy reports of children who had tested positive for influenza and then died [6]. There were 153 deaths among children (<18 years of age): 96 of those deaths occurred in children <5 years of age, but 57 occurred in children 5–17 years of age. Although 33% of the children had an underlying condition recognized to increase the risk of complications and 20% had other chronic conditions, 47% of the children had previously been healthy. Furthermore, among children ≥6 months of age, 59% were otherwise healthy and had no increased risk for mortality secondary to influenza. This highlights the significant impact that seasonal influenza can have on both high-risk and otherwise healthy children during a severe influenza season and emphasizes the need to address influenza management in children. Goals for pediatric patients include educational programs in schools regarding the benefits of childhood immunization and the role of children in the transmission of influenza infection, increasing influenza vaccine uptake particularly among healthy school children, and early diagnosis and treatment (see the Appendix).

Live attenuated vaccines for young children. The article by Nichol and Treanor in this supplement [7] reviews the efficacy and effectiveness of influenza vaccines in older children. A global, pivotal phase 3 study comparing a cold-adapted live attenuated influenza vaccine (LAIV) with trivalent inactivated vaccine (TIV) was conducted in almost 8500 children 6–59 months of age, during the 2004–2005 influenza season. Overall, for matched and mismatched strains, rates of culture-confirmed influenza were reduced by 55% in those vaccinated with LAIV compared with those vaccinated with TIV (3.9% vs. 8.6%, respectively) [8]. Rates of adverse and serious adverse events were comparable. The data for the live vaccine are very encouraging and, if approved, would permit vaccination of young children with an effective LAIV that is currently licensed only for healthy subjects 5–49 years of age.

Table 2. Oseltamivir treatment of influenza in children.

Variable	Oseltamivir (n = 217)	Placebo (n = 235)
Time to resolution of all illness	101.3 h (4.2 d)[a]	137 h (5.7 d)
Time to return to normal health and activity	67.1 h (2.8 d)[b]	111.7 h (4.7 d)
Subjects with otitis media (after initiation), no./total (%)	29/183 (16)[c]	53/200 (27)

NOTE. Data are from [10].

[a] A 36-h (26%) reduction ($P < .0001$), compared with placebo.
[b] A 45-h (40%) reduction ($P < .001$), compared with placebo.
[c] A 40% risk reduction, compared with placebo.

Influenza treatment in children. The neuraminidase (NA) inhibitors zanamivir and oseltamivir are both approved for the treatment of influenza in children. Zanamivir is approved for children starting from 7 years of age. Oseltamivir is the only drug available for treatment of influenza in young children, from 1 year of age, which is particularly important because of the role that young children play in the transmission of influenza. However, it is not approved for use in children <1 year of age, because preclinical animal toxicology indicated significant neurologic toxicity in the rat model [9]. In these studies, the dose of oseltamivir exceeded that which would be used in humans, and the metabolism of oseltamivir in rats is different from that in humans. The unmet need for influenza treatment in children <1 year of age warrants repetition of the animal toxicology studies followed by evaluation of oseltamivir in pharmacokinetic and pharmacodynamic studies, to clarify whether oseltamivir can be used in this group.

A randomized, double blind, placebo-controlled study evaluated oseltamivir in 452 children with influenza, 1–12 years of age [10]. The median duration of illness (primary end point) was reduced by 36 h (26%) in oseltamivir recipients (to 4.2 days) compared with placebo recipients (5.7 days), when the
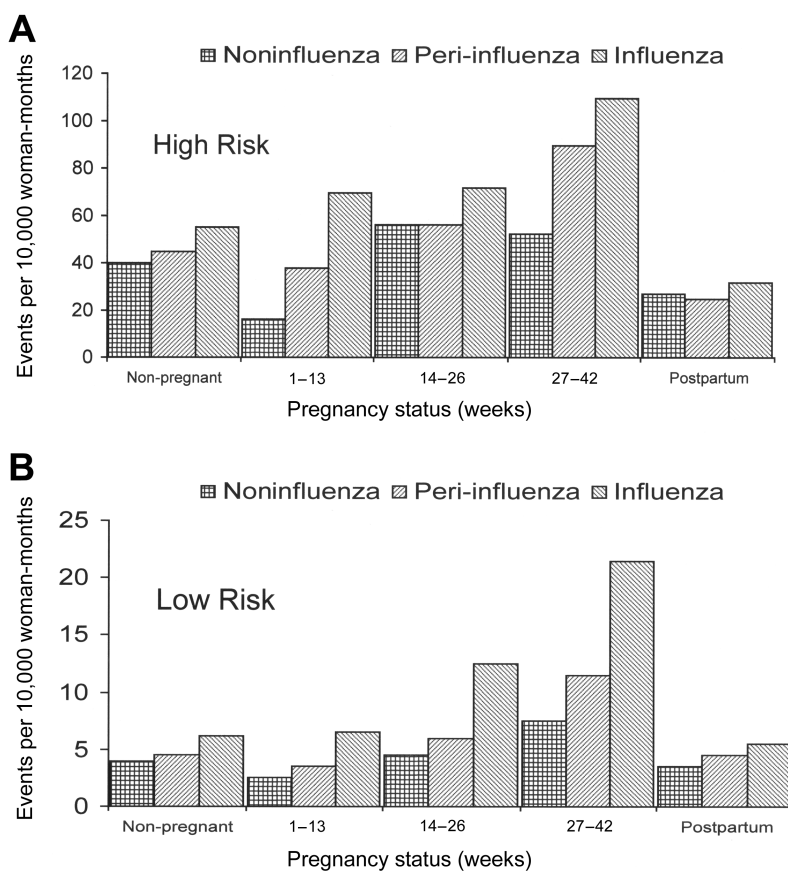
Figure 1. Adjusted rates of acute cardiopulmonary events per 10,000 woman-months of observation, by medical risk and pregnancy status, among women 15–44 years of age. Incidence rates are shown for high-risk (at least 1 risk factor for influenza-related serious morbidity) and low-risk (no identifiable risk factors for influenza morbidity) women. Reprinted with permission from [13].

Table 3. Treatment of influenza in immunocompromised patients.

Population [reference], drug	Episodes, no.	Progression to pneumonia, %		Outcome(s)
		Treatment	No treatment	
BMT, leukemia [17]				
M2 inhibitor	15	NE	NE	Resistant virus in 33%; influenza deaths in 2 patients (13%)
HSCT, leukemia [15]				
M2 inhibitor	55	35	76	Progression to pneumonia in 35% of treated patients vs. 76% of untreated patients
HSCT, leukemia [16]				
Rimantadine	8	13	18[a]	Progression to pneumonia in 1 treated patient (13%) and in 6 (18%) of 34 untreated patients
Oseltamivir	9	0		Progression to pneumonia in 0 treated patients and in 6 (18%) of 34 untreated patients
BMT [18]				
Oseltamivir	41[b]	5	NE	No mortality

NOTE. BMT, bone marrow transplant; HSCT, hematopoietic stem cell transplant; NE, not evaluated.

[a] $n = 34$.

[b] 18 influenza A, 23 influenza B.

drug was given within 48 h of the onset of illness (table 2). Similarly, the median time to return to normal health and activity was reduced by 45 h (40%). There was also a 40% reduction in the number of subjects with otitis media, resulting in a concomitant 40% reduction in antibiotic use.

During treatment, 5.5% of oseltamivir-treated patients had evidence of influenza virus resistant to oseltamivir [10]. However, a Japanese study showed development of resistant virus in 18% of children [11]. Renal clearance of the active carboxylate metabolite of oseltamivir is significantly higher in younger children than in older children and adults [12] and necessitates adjusting drug dosage according to weight for those 1–12 years of age. This was not taken into consideration in the Japanese study and may have resulted in suboptimal dosing, which contributed to a higher frequency of resistant viruses. Furthermore, the majority of the children with resistant virus (8/9) were <3 years of age, the group with the highest level of virus and the longest duration of viral shedding, which would allow more opportunity for selection of resistant virus.

PREGNANT WOMEN

The impact of influenza on pregnant women was evaluated by comparing the rates of acute cardiopulmonary events in women at different stages of pregnancy with those in nonpregnant and postpartum women [13]. The groups were further categorized into low and high risk, according to the presence of risk factors for influenza-related serious morbidity. The incidence of acute cardiopulmonary hospitalizations during the influenza season increased with increasing length of pregnancy and was highest in those in their third trimester of pregnancy who also had high-risk medical conditions (figure 1A). The event rates attributable to influenza were >10 per 10,000 woman-months at all stages of pregnancy in women with identified medical risk

factors (31, 16, and 21 attributable events per 10,000 woman-months among high-risk women in their first, second, and third trimesters, respectively). However, women in their third trimester without other identified risk factors for influenza morbidity also had an increased event rate compared with nonpregnant and postpartum women, with 10.5 excess events per 10,000 woman-months attributable to influenza (figure 1B) [13]. In the United States, the ACIP includes pregnant women in the high-priority group recommended for influenza vaccination [2]. In terms of therapeutic intervention with NA inhibitors, this population has not received significant attention, because of concerns regarding the potential effects of these drugs on the fetus.

THE IMMUNOCOMPROMISED HOST

Influenza causes significant morbidity and mortality in patients with compromised immune systems. Immunocompromised patients are at very high risk for serious complications of influenza that result in high rates of hospitalization, intensive care unit admission, and mortality. Transplant recipients who acquire influenza experience high rates of pulmonary complications, particularly viral pneumonia [14]. A study of hematopoietic stem cell–transplant recipients showed progression to pneumonia in 63% of patients, with 43% of cases associated with mortality [15]. Transplant recipients with influenza also have a high rate of extrapulmonary complications and, subsequent to influenza, may experience high rates of graft dysfunction and rejection [14].

Influenza treatment. One of the key issues in the management of influenza in the immunocompromised host is the higher levels of influenza virus and prolonged viral shedding [16] not dissimilar to that seen in children. There have been several small treatment studies using the currently available

drugs but no large-scale clinical trials adequately powered with well-defined primary end points (table 3). The M2 inhibitors appeared to be effective in reducing progression to pneumonia, but the rapid emergence of drug-resistant virus limits their use in immunocompromised patients [15, 17]. Oseltamivir has also been shown to prevent progression to pneumonia (table 3) [16, 18] and warrants further investigation in well-controlled studies. However, the persistent viral shedding observed in immunocompromised patients, despite antiviral therapy, may promote the emergence of antiviral resistance. Oseltamivir resistance was reported recently in 3 severely immunocompromised patients [19], and it is likely that the degree of immunosuppression contributed to the lack of viral clearance and subsequent emergence of resistant virus. Combination therapy with 2 NA inhibitors should be investigated in this population, to reduce viral levels further. In addition, 2 of the 3 patients had not been vaccinated against influenza, indicating the need for further work to increase vaccination in this patient population.

NURSING HOME RESIDENTS

Elderly persons are among those at greatest risk of developing influenza-related complications. However, compared with elderly persons living in the community, nursing home residents are at even higher risk of serious influenza-related complications [20, 21]. Annual vaccination is an essential component of influenza prevention in the elderly population. The risk of influenza outbreaks is increased in nursing homes where vaccination rates are <80% (outbreaks in 54.5% of nursing homes) compared with those where they are >80% (outbreaks in 21.7% of nursing homes), as well as in large nursing homes (>100 beds; outbreaks in 58.8% of nursing homes) compared with smaller facilities (<100 beds; outbreaks in 25% of nursing homes), suggesting a role of herd immunity [22]. Vaccination also appears to be more effective in younger residents (46% effective in those 65–84 years of age) compared with older residents (34% effective in those >84 years of age) [23]. This reduced effectiveness of influenza vaccination in the very old may be due to suboptimal antibody response resulting from immune senescence [24]. The serious complications associated with influenza in these patients emphasizes the need for new approaches for influenza vaccines, using improved adjuvants or strategies to enhance the immune response. Vaccination of nursing home staff is another important strategy to prevent influenza outbreaks in nursing homes, to help prevent introduction of influenza into the nursing home [22].

Prophylactic use of oseltamivir can provide protection to nursing home residents in addition to that provided by vaccination. In frail, older nursing home residents, the majority of whom had been vaccinated against influenza, oseltamivir (once daily for 6 weeks) was 92% effective in preventing laboratory-confirmed clinical influenza (placebo, 4.4% [12/272]; oseltamivir,

0.4% [1/276]) [25]. Use of oseltamivir to treat influenza outbreaks in nursing homes suggested a reduction in serious complications, use of antibiotics, hospitalization, and death in those given oseltamivir within 48 h after the onset of symptoms, compared with no therapy or with late oseltamivir therapy, although the patient numbers were relatively small [26].

RESEARCH NEEDS

Further research is required on the natural history of influenza in immunocompromised patients and pregnant women, to determine the potential benefits that could be achieved by treatment and to enable consideration of these benefits versus the possible risks of therapy—for example, the development of resistance in the immunocompromised host and the risks to the fetus in pregnant women. Clinical trials of antiviral agents are needed in at-risk populations to address whether monotherapy will be adequate or whether its use in these patients will lead to the rapid emergence of resistance. Combination therapy should be investigated as an option in immunocompromised patients.

For children, initiatives are needed to extend the current vaccine recommendations to older children, because of the role that children play in the transmission of influenza to others in the family, at school, and in the wider community. Consideration should be given to the use of cold-adapted LAIV in young children. With respect to influenza treatment, there is an unmet need in children <1 year of age that warrants reevaluation of oseltamivir in animal models to assess the neurotoxicity issues, followed by pharmacokinetic and pharmacodynamic studies in infants to understand whether oseltamivir can be used in this group.

AUTHOR AFFILIATIONS

Departments of Pediatrics, Microbiology, Medicine, and Neurosurgery and Center for Biodefense and Emerging Infections, University of Alabama at Birmingham, Birmingham (R.J.W.); Department of Epidemiology, University of Michigan School of Public Health, and University of Michigan Bioterrorism Preparedness Initiative, Ann Arbor (A.S.M.).

ica, the Society for Healthcare Epidemiology of America, the National Institute of Allergy and Infectious Diseases, and the Centers for Disease Control and Prevention.

APPENDIX

GOALS FOR PEDIATRIC PATIENTS

Educational programs in the school system
1. Encourage children to be immunized
2. Educate parents and teachers about person-to-person transmission, so that
   - Parents keep sick children at home, thereby preventing person-to-person transmission in the classroom
   - Teachers are not biased against children who miss school because of influenza

Prevent influenza, by use of vaccination
1. Increase vaccine uptake in older healthy children (currently only 12%)
   - To prevent influenza in these children
   - To reduce transmission to others in the community

Diagnose and treat influenza early
1. Increase availability of rapid diagnostics
2. Educate parents about signs and symptoms of influenza, to encourage early diagnosis and treatment.

References

1. Munoz FM. The impact of influenza in children. Semin Pediatr Infect Dis 2002; 13:72–7.
2. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2005; 54(RR08):1–40.
3. Centers for Disease Control and Prevention. Estimated influenza vaccination coverage among adults and children—United States, September 1, 2004–January 31, 2005. MMWR Morb Mortal Wkly Rep 2005; 54: 304–7.
4. Peltola V, Ziegler T, Ruuskanen O. Influenza A and B virus infections in children. Clin Infect Dis 2003; 36:299–305.
5. Morishima T, Togashi T, Yokota S, et al. Encephalitis and encephalopathy associated with an influenza epidemic in Japan. Clin Infect Dis 2002; 35:512–7.
6. Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 200–2004. N Engl J Med 2005; 353:2559–67.
7. Nichol KL, Treanor JJ. Vaccines for seasonal and pandemic influenza. J Infect Dis 2006; 194:S111–8 (in this supplement).
8. MedImmune. Preliminary data from CAIV-T pivotal phase 3 trial demonstrate clinical efficacy over flu shot in head-to-head influenza study.

Press release, 12 December 2005. Available at: http://phx.corporate-ir.net/phoenix.zhtml?c=83037&p=irol-newsArticle&ID=794727&highlight=. Accessed 12 April 2006.
9. Roche Laboratories. Tamiflu (oseltamivir phosphate) capsules [product infomation]. Nutley, NJ: Roche Laboratories, 2000.
10. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 2001; 20:127–33 [erratum: Pediatr Infect Dis J 2001; 20:421].
11. Kiso M, Mitamura K, Sakai-Tagawa Y, et al. Resistant influenza viruses in children treated with oseltamivir: descriptive study. Lancet 2004; 364:759–65.
12. Oo C, Barrett J, Hill G, et al. Pharmacokinetics and dosage recommendations for oseltamivir oral suspension for the treatment of influenza in children. Paediatr Drugs 2001; 3:229–36.
13. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998; 148:1094–102.
14. Ison MG, Hayden FG. Viral infections in immunocompromised patients: what's new with respiratory viruses? Curr Opin Infect Dis 2002; 15:355–67.
15. La Rosa AM, Malik S, Englund JA, et al. Influenza A in hospitalized adults with leukemia and hematopoietic stem cell transplant (HSCT) recipients: risk factors for progression to pneumonia [abstract 418]. In: Program and abstracts of the 38th Annual Meeting of the Infectious Diseases Society of America (San Francisco). Alexandria, VA: Infectious Diseases Society of America, 2001.
16. Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis 2004; 39:1300–6.
17. 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; 26:1418–24.
18. Machado CM, Boas LSV, Mendes AVA. Use of oseltamivir to control influenza complications after bone marrow transplantation. Bone Marrow Transplant 2004; 34:111–4.
19. Ison MG, Gubareva LV, Atmar RL, Treanor J, Hayden FG. Recovery of drug-resistant influenza virus from immunocompromised patients: a case series. J Infect Dis 2006; 193:760–4.
20. Goodman RA, Orenstein WA, Munrow F, Smith SC, Sikes RK. Impact of influenza A in a nursing home. JAMA 1982; 247:1451–2.
21. Budnick LD, Stricof RL, Ellis F. An outbreak of influenza in a nursing home, 1982. N Y State J Med 1984; 84:235–8.
22. Arden N, Monto AS, Ohmit SE. Vaccine use and the risk of outbreaks in a sample of nursing homes during an influenza epidemic. Am J Pub Health 1995; 85:399–401.
23. Ohmit SE, Arden NH, Monto AS. Effectiveness of inactivated influenza vaccine among nursing home residents during an influenza type A (H3N2) epidemic. J Am Geriatr Soc 1999; 47:165–71.
24. Phair J, Kauffman CA, Bjornson A, et al. Failure to respond to influenza vaccine in the aged: correlation with B-cell number and function. J Lab Clin Med 1978; 92:822–8.
25. 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; 49:1025–31.
26. 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; 50:608–16.