The use of antiviral drugs for influenza: Recommended guidelines for practitioners

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The present document outlines current guidelines and supporting literature relating to the use of antiviral drugs for chemoprophylaxis and influenza illness therapy in paediatric and adult settings. The focus is on the management of influenza in interpandemic periods. Where appropriate, the areas in need of additional research are identified. It will be necessary to update aspects of these guidelines as new information emerges. The recommendations that follow represent the results of a joint effort supported by the Canadian Paediatric Society and the Association of Medical Microbiology and Infectious Disease Canada.

Key Words: *Antiviral therapy; Influenza; M2 inhibitors; Neuraminidase inhibitors*

Le recours aux antiviraux contre l'influenza : Les lignes directrices recommandées pour les praticiens

Le présent article expose les lignes directrices actuelles et les publications justificatives reliées au recours aux antiviraux pour la chimioprophylaxie et le traitement de l'influenza en milieu pédiatrique et chez les adultes. On s'intéresse à la prise en charge de l'influenza entre les pandémies. Les domaines qui nécessitent des recherches plus approfondies sont indiqués. Il faudra mettre à jour les divers aspects des présentes lignes directrices à mesure qu'on obtiendra de nouvelles données. Les recommandations qui suivent représentent les résultats d'un effort conjoint soutenu par la Société canadienne de pédiatrie et l'Association pour la microbiologie médicale et l'infectiologie Canada.

INTRODUCTION AND BACKGROUND

Influenza A viruses, and occasionally influenza B strains, cause recurrent, almost annual epidemics in Canada, with significant morbidity, mortality and economic loss (1). The principle of immunization to minimize the impact of influenza illness in individuals and populations is widely accepted, as is the notion that antiviral drugs have a role in the management and control of influenza. However, our knowledge of best practices in immunization, such as the question of immunizing healthy children, adults and pregnant women, continues to evolve, as do our recommendations on the optimal use of antiviral drugs. While acknowledging that the latter area of practice continues to evolve, it was thought appropriate, nonetheless, to develop contemporary guidelines on the use of antiviral drugs for chemoprophylaxis and therapy, which are appropriate for the management of influenza in interpandemic periods. The recommendations that follow represent the results of a joint effort supported by the Canadian Paediatric Society (CPS) and the Association of Medical Microbiology and Infectious Disease Canada (AMMI Canada). The guidelines reflect the current state of knowledge regarding the use of influenza antiviral drugs, and may be modified by additional, forthcoming research data. Additional information on strategies to prevent influenza illness in the interpandemic period may be obtained from the annual statement by the National Advisory Committee on Immunization (2).

INFLUENZA ANTIVIRAL DRUGS

In Canada, currently licensed influenza antiviral agents are composed of two classes of drugs: the influenza A virus M2 ion channel blocker amantadine (Symmetrel, Endo Pharmaceuticals, USA), and the influenza A and B virus neuraminidase inhibitors (NAIs) zanamivir (Relenza, GlaxoSmithKline, USA) and oseltamivir (Tamiflu, Roche Laboratories Inc, USA).

Rimantadine, an M2 ion channel blocker similar to amantadine but with fewer side effects, is licensed in the United States but not in Canada. Although a rationale for marketing rimantadine in Canada has recently been published (3), it is

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not currently approved for use; therefore, influenza chemoprophylaxis and therapy with this drug will not be discussed further. Cross-resistance occurs between amantadine and rimantadine. These agents have no effect on influenza B due to differing conformation of the proton channel protein BM2.

Similarly, ribavirin administered to children ill with influenza as aerosol or oral tablets has been demonstrated to ameliorate symptoms and to be acceptably safe. However, because ribavirin is not licensed for influenza treatment or prophylaxis in Canada, it will also not be discussed further.

The NAIs are effective against recently emerging avian strains of influenza A H5N1 (4-6), but virtually all of these highly virulent strains are resistant to amantadine (7).

Antiviral drugs can be useful in the following settings:

1. As prophylaxis in a pandemic where an antigenic shift in the influenza A virus has resulted in widespread influenza for which a vaccine is not yet available.
2. As prophylaxis where a major antigenic drift or mutation has resulted in circulation of an influenza strain not well matched to the currently available vaccine (eg, drift from A/Sydney [H3N2]-like virus to A/Fujian [H3N2]).
3. As interim prophylaxis of high-risk patients who have received vaccine during an outbreak but need time to develop a protective antibody response (two to three weeks postvaccination).
4. As postexposure prophylaxis for high-risk patients who cannot be vaccinated or who are not expected to respond to the vaccine (eg, immunocompromised patients).
5. For prophylaxis of individuals who will be exposed to avian influenza, in consultation with the local medical office of health.
6. As treatment of influenza-like illness in patients not expected to have developed a protective antibody response to vaccination (eg, frail and elderly persons or immunosuppressed persons).
7. As treatment for persons with a high risk of morbidity and mortality who have not received the influenza vaccine for that influenza season.
8. For unvaccinated persons who provide care for people at high risk during an outbreak, until two weeks postvaccination of the caregiver.
9. As treatment for influenza-like illness during a pandemic until the population can be immunized with an effective vaccine.
10. For the control of influenza outbreaks (treatment and/or prophylaxis) among high-risk residents of institutions.

PROPHYLACTIC EFFICACY

Children

The prophylactic efficacy of amantadine has been evaluated in four placebo-controlled trials in children eight years of age and older (Table 1) (8). Amantadine reduced the incidence of laboratory-confirmed influenza illness by 80% (median; range 69% to 92%).

Zanamivir prophylactic efficacy has not been evaluated in controlled trials in children. However, children five to 17 years of age were included in a placebo-controlled trial of zanamivir for postexposure prophylaxis of influenza in families (9). All families had two to five members, including at least one child five to 17 years of age. Zanamivir reduced the incidence of laboratory-confirmed illness from 18% (30 of 168 families) to 4% (six of 169 families), a statistically significant difference. Tolerance was comparable between zanamivir and placebo therapy. Among asthmatics requiring regular use of medication, exacerbation occurred in 11% in the placebo group and 6% in the zanamivir groups (10).

In a similar study of oseltamivir (11), postexposure prophylaxis (75 mg daily for seven days) reduced the incidence of laboratory-confirmed influenza in families from 23% (18 of 79 households treated with placebo) to 3.6% (three of 84 households treated with oseltamivir), a protective efficacy of 84% ($P<0.001$). Each household consisted of two to eight contacts at least 12 years of age. Amantadine and oseltamivir are approved for influenza prophylaxis in children aged one year or older and children aged 13 years and older, respectively.

Adults

Double-blind, placebo-controlled trials of influenza antiviral drugs for the prophylaxis of influenza have demonstrated prophylactic efficacy ranging from 3% – when rimantadine was used to prophylax the household contacts of index cases treated with rimantadine, whereupon resistant virus was transmitted (12) – to 100% – when the index case was not treated with amantadine (Table 1) (13-20). Both zanamivir and oseltamivir prevent influenza A and B, with an efficacy relative to placebo of 56% (14) to 90% (15).

WHICH PROPHYLACTIC REGIMENS ARE BEST?

There are no head to head trials comparing amantadine with the NAIs, but the prophylactic efficacy of the two classes of agents is comparable. One should consider the potential side effects, cost, laboratory monitoring, and particularly the chance of virus resistance, when choosing a regimen. The doses for prophylaxis are listed in Table 2. The problem of the emergence of influenza viruses that are resistant to amantadine in nursing homes (21) and in households where an index case has been treated with amantadine (and the family contacts therefore ineffectively prophylaxed with rimantadine [12,14]) has been demonstrated. However, as noted in the 2004 recommendations of the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (22), the effect of amantadine and rimantadine resistance on the control of influenza has not been well studied. Swedish recommendations (23) published in a 2003 report state that amantadine was withdrawn in Sweden in part because of the rapid emergence of resistance, as well as the "high frequency of central nervous system [CNS] side effects". With regard to the latter reason, rimantadine would likely be more tolerable, but neither of the ion channel blockers have any effect on influenza B. Furthermore, amantadine/rimantadine resistance has been steadily increasing worldwide (24), and H3N2 isolates from the 2005/2006 season were 91% and 89% amantadine-resistant in the United States (25) and Canada (Y Li, Public Health Agency of Canada, personal communication), respectively. Zanamivir is the recommended drug for the treatment of influenza B in the Swedish recommendations, but this distinction

TABLE 1
Results of selected randomized, double-blind, controlled trials of antiviral drug prophylaxis of influenza

Author, reference	Drug	Study population and setting	Influenza virus type	PE	Comments
Oker-Blom et al, 1970 (16)	Amantadine 100 mg twice daily × 5 weeks	Healthy medical students during a community influenza outbreak. Amantadine (n=192), placebo (n=199)	A (H3N2)	66%	PE with pre-outbreak HI titre ≤1:10 = 72% PE with pre-outbreak HI titre ≥1:20 = 58%
Dolin et al, 1982 (17)	Amantadine 100 mg twice daily × 4 weeks Rimantadine 100 mg twice daily × 4 weeks	Healthy volunteers 18 to 45 years of age during a community influenza outbreak. Amantadine (n=145), rimantadine (n=147), placebo (n=148)	A (H3N2)	91% 85%	CNS side effects (insomnia, jitteriness, poor concentration); 13% amantadine, 6% rimantadine, 4% placebo
Payler and Purdham, 1984 (18)*	Amantadine 100 mg once daily	Prophylaxis of 13- to 19-year-old male students during a boarding school influenza outbreak. Amantadine (n=21), control (n=30)	A (H3N2)	90%	No reported side effects at the 100 mg per day dose
Galbraith et al, 1969 (13)	Amantadine 100 mg twice daily	Postexposure prophylaxis of family contacts of a nonamantadine-treated index case. Amantadine (n=102), placebo (n=100)	A (H3N2)	100%	No significant differences in reported side effects compared with placebo
Hayden et al, 1989 (12)	Rimantadine 100 mg twice daily × 10 days	Postexposure prophylaxis of family contacts of a rimantadine-treated index case. Amantadine (n=61), placebo (n=54)	A (H1N1 and H3N2)	3%	Rimantadine-resistant H3N2 virus shed by treated case-infected contacts
Monto et al, 1999 (19)	Zanamivir 10 mg inhaled daily × 28 days	Pre-exposure prophylaxis of healthy volunteers during a community influenza outbreak. Zanamivir (n=554), placebo (n=553)	A (H3N2)	67%; febrile influenza 81%	No bronchospasm reported in the zanamivir group, versus two of 655 persons in the placebo group
Hayden et al, 1989 (12)	Zanamivir 10 mg inhaled once daily for 10 days	Postexposure prophylaxis of family contacts of a zanamivir-treated index case. Zanamivir (n=414), placebo (n=423)	A B	77% 68%	Side effects 3% to 5%; not statistically different than placebo
Hayden et al, 1999 (20)	Oseltamivir 75 mg orally once or twice daily × 6 weeks	Pre-exposure prophylaxis of healthy volunteers during a community influenza outbreak. Oseltamivir 75 mg daily (n=520), oseltamivir 75 mg twice daily (n=520), placebo (n=519)	A	74% (twice daily dose); 90% (once daily dose)	Side effects: Nausea 10% to 12% more than placebo; vomiting 1.7% more than placebo. No differences in discontinuation of drug over 6 weeks
Welliver et al, 2001 (11)	Oseltamivir 75 mg orally once daily × 7 days	Postexposure prophylaxis of family contacts of a nonoseltamivir-treated index case. Oseltamivir (n=497), placebo (n=465)	A (H3N2) B	84% 78.5%	
Peters et al, 2001 (15)	Oseltamivir 75 mg orally once daily × 6 weeks	Persons ≥65 years of age living in residential homes or sheltered accommodation for seniors, 80% of whom had received influenza vaccine. Oseltamivir (n=276), placebo (n=272)	A	90%	78% reduction in complications. Side effects: Headache 3% more than placebo; nausea 1% more than placebo; vomiting less than 2% of all subjects
Hayden et al, 2004 (14)†	Oseltamivir postexposure prophylaxis with and without treatment of the index case	Family contacts of an index case of influenza during a naturally occurring influenza outbreak. Oseltamivir (n=410), controls (n=402)	A	56% (index cases treated)	

**This study was randomized but not blinded and had no placebo; †Controls received oseltamivir treatment if illness developed. CNS Central nervous system; HI Hemagglutination inhibition; PE Protective efficacy*

is not made in the CDC recommendations. Despite comparable efficacy in the trials listed in Table 1, Sweden has decided to recommend oseltamivir for prophylaxis over zanamivir, possibly because of rare reports of bronchospasm and 'throat tightness' with zanamivir.

TREATMENT WITH ANTIVIRAL DRUGS

Clinical characteristics and diagnosis of influenza

Proper diagnosis of influenza is important because the current influenza antivirals have no effect on other respiratory virus infections. Influenza illness in older children and adolescents is

TABLE 2
Recommended doses of antiviral agents for the prevention of influenza in children and adults

Drug	Viruses prevented	Age or weight	Dose	Evidence grade*
Amantadine	Influenza A	<1 year of age	No data available	–
		1–9 years of age	5 mg/kg/day to maximum	Evidence grade for tolerance only IA
		or <40 kg	150 mg/day in 2 doses	–
		10–64 years of age	200 mg once daily, or divided twice daily†	Evidence grade for tolerance only IA
		≥65 years of age	100 mg once daily	–
Zanamivir‡	Influenza A and B	<5 years of age	No data available	–
		5 to 17 years of age	10 mg once daily	Evidence grade IA
		18 to 69 years of age	10 mg once daily	Evidence grade IA
		≥70 years of age	10 mg once daily	Evidence grade IB
Oseltamivir‡§	Influenza A and B	<1 year of age	No data available	–
		>1 year of age and ≤15 kg	30 mg once daily	Evidence grade IA
		>15 kg to 23 kg	45 mg once daily	Evidence grade IA
		>23 kg to 40 kg	60 mg once daily	Evidence grade IA
		>40 kg	75 mg once daily	Evidence grade IA
		18 to 65 years of age	75 mg once daily	Evidence grade IA
		>65 years of age	75 mg once daily	Evidence grade IA

**Data from reference 59; †100 mg once daily for those with seizure disorder; ‡Oseltamivir is not licensed for prophylaxis in individuals younger than 13 years of age. Zanamivir is not licensed for prophylaxis; §Oseltamivir dose for renal failure: A dose reduction is required if the creatinine clearance is less than 30 mL/min. For adults, give 75 mg every other day for prophylaxis (52). A corresponding adjustment is recommended for children. NOTE: Duration of exposure: Seasonal prophylaxis – usually six to eight weeks; Postexposure household prophylaxis – 10 days; Institutional exposure – until eight days after onset of last case; After influenza vaccine – until two weeks after appropriate vaccination (one or two doses)*

classically characterized by the sudden onset of fever and chills and is accompanied by headache, malaise, myalgia and nonproductive cough (26). As the illness evolves, respiratory tract signs become prominent, with throat soreness, nasal congestion, rhinitis and a worsening cough. Influenza in younger children may be manifested as upper respiratory tract infection with a few additional symptoms or as a febrile illness with few respiratory symptoms. In infants, influenza may result in a clinical picture that mimics sepsis, and can also present as croup, bronchiolitis and pneumonia. A well-recognized feature in some patients is acute myositis with calf tenderness and refusal to walk. This feature is particularly seen in children with influenza B infection. Other manifestations of influenza illness include Reye's syndrome and CNS infection. Otitis media is a complication in 10% of children (27).

In adults, the typical influenza syndrome is an acute onset of fever with subsequent tracheobronchitis, although any upper respiratory infection syndrome can occur. Serious infection complications include bacterial pneumonia and, rarely, primary influenza virus pneumonia.

Treatment of influenza reduces the duration and severity of acute symptoms. Amantadine or rimantadine treatment has been associated, in a period as short as three days, with excretion of amantadine-resistant virus (despite a clinical response by the patient), which may infect close contacts (12).

Emergence of resistance to the NAI oseltamivir has been reported in 18% of children being treated with this agent, (28). Development of zanamivir-resistant strains has been described in immunocompromised patients (29,30). It has been suggested that neuraminidase resistance mutations result in a virus that is less fit (31). Person-to-person transmission of oseltamivir-resistant strains is suggested in one report (32), but otherwise appears to be quite rare.

Influenza antivirals should only be used for treatment when a patient demonstrates acute clinical symptoms compatible with influenza at a time when public health agencies report that influenza is prevalent in the community, or when influenza is specifically diagnosed by rapid tests at any time. Zanamivir and oseltamivir should not be used if the duration of symptoms has been longer than 48 h because effectiveness is negligible after this time, unless the patient has significant immunodeficiency and has progressive respiratory disease

Antiviral agents could potentially reduce the incidence of major, life-threatening secondary complications of influenza illness, including bacterial pneumonia. In one study (33), antiviral compounds were tested in a mouse model of secondary pneumococcal pneumonia after influenza. Oseltamivir therapy improved survival in mice from 0% to 75%, even when therapy was delayed for up to five days after infection with influenza virus. Interestingly, treatment with rimantadine had no effect on survival. In addition, treatment with ampicillin cleared infection but did not improve survival unless oseltamivir treatment was also administered. The mechanism of the effect is that oseltamivir prevents neuraminidase-induced exposure of epithelial cell ligands for *Streptococcus pneumoniae*.

Diagnosing influenza illness by clinical criteria in adults is difficult and even more problematic in children. Among nonimmunized young healthy adults, the combination of a fever of 37.8°C or higher plus at least one respiratory symptom (sore throat, cough or nasal symptoms) and one constitutional symptom (myalgia, headache, sweats, chills or fatigue) are predictive of influenza by laboratory testing in 60% to 71% of cases (34,35). The presence of cough and a fever of 37.8°C or higher has a positive predictive value of 86.8% for a laboratory-confirmed diagnosis of influenza, although the negative predictive value is poor at 39.3% (36).

TABLE 3
Randomized treatment trials of neuraminidase inhibitors involving children with influenza virus infections

Authors and reference	Study design and study arms	Target population and sample size	Influenza virus type	Outcomes
Hayden et al, 1997 (43)	Randomized double-blind study design	Age ≥13 years	A and B	Active drug arms reduced median duration of symptoms by 1 day (P=0.05 for inhaled and P=0.02 for inhaled + intranasal)
	• Zanamivir 10 mg by oral inhalation BID for 5 days	n=85 inhaled		
	• Zanamivir 10 mg by oral inhalation BID for 5 days + intranasal zanamivir	n=88 inhaled + intranasal		Adverse events: 18% inhaled, 23% inhaled + intranasal and 25% placebo (P=NS)
	• Placebo	n=89		
MIST Study Group, 1998 (44)	Randomized double-blind study design	Age ≥12 years	A and B	Active drug reduced median duration of symptoms by 1.5 days (P=0.004)
	• Zanamivir 10 mg by oral inhalation BID for 5 days	n=161		Adverse events profile similar to placebo
	• Placebo	n=160		
Makela et al, 2000 (57)	Randomized double-blind study design	Age 12 to 81 years	A (H3N2) and B	Active drug reduced median duration of symptoms by 2.5 days (P=0.001)
	• Zanamivir 10 mg by oral inhalation BID for 5 days	n=136		Adverse events profile similar to placebo
	• Placebo	n=141		
Hedrick et al, 2000 (58)	Randomized double-blind study design	Age 4 to 12 years	A and B	Active drug reduced median duration of symptoms by 1.25 days (P=0.001). Similar rates of adverse events
	• Zanamivir 10 mg by oral inhalation BID for 5 days	n=164		No drug resistance
	• Placebo	n=182		
Whitley et al, 2001 (40)	Randomized double-blind study design	Age 1 to 12 years	A and B	Active drug reduced median duration of illness by 36 h (P=0.0001). Reduced otitis media by 44%
	• Oseltamivir 2 mg/kg po BID (maximum 100 mg po BID)	n=217		Emesis: 14.3% oseltamivir versus 8.5% placebo; 5.5% of isolates resistant to oseltamivir
	• Placebo	n=235		
Whitley et al, 2000 (49)*	• Oseltamivir 2 mg/kg po BID (maximum 100 mg po BID)	Age 6 to 12 years with asthma (n=334; n=179 with laboratory-confirmed influenza)	A and B	Active drug reduced median duration of illness by 10.3 h (P=0.54). Active drug reduced asthma exacerbations by 36% (P=0.0143)
	• Placebo			

**Abstract; limited details available. BID Twice daily; NS Not significant; po Orally*

Among immunized patients 60 years of age and older, the combination of fever, coughing and acute onset have a predictive value of 44% for a laboratory-confirmed diagnosis of influenza (37).

The sensitivity and specificity of the clinical diagnosis of influenza in individuals at high risk of premature death and the development of complications of influenza due to older age or the presence of significant comorbid medical conditions or prior immunization are not known.

In children, the clinical picture may be even less specific than in adults because children cannot articulate their symptoms as readily. Exclusive pediatric studies evaluating the sensitivity and specificity of a clinical diagnosis of influenza compared with a laboratory gold standard are limited (38). In one study (39), fever, cough and rhinorrhea were the most common clinical manifestations, but these are all nonspecific. Almost one-third of pediatric patients seen in an emergency department during an epidemic had laboratory-confirmed influenza. Coexisting outbreaks of respiratory syncytial virus and influenza are not uncommon.

Point of care or rapid laboratory tests to confirm the clinical diagnosis of influenza are sensitive (69% to 89%) and specific (83% to 99%) in children, but much less so in adults. Children shed viruses in higher titre and for longer duration than adults. Rapid tests could be used to confirm the clinical diagnosis in children seen during an epidemic, and to add to the evidence supporting a decision to prescribe anti-influenza drugs and to not prescribe antibiotics. Alternatively, they could be used simply to affirm that influenza is circulating in the community. The exact role for such tests remains unclear and will depend on the peculiar economics of pediatric care in a region, as well as the operating characteristics of the test.

Treatment efficacy

Children: Clinical trials of the NAIs in children have shown that the duration of acute symptoms are reduced by 36 h compared with placebo, incidence of otitis media is reduced by 44% and the use of antibiotic therapy is reduced by 25% (Table 3) (40).

TABLE 4
Results of selected randomized, double-blind, placebo-controlled clinical trials of antiviral drug therapy of influenza in adults

Drug	Study setting	Population	Influenza virus type	Duration of symptoms	Resumption of normal activity	Complication rate
Amantadine 100 mg bid for 10 days (41)	Naturally-occurring influenza	Prison volunteers. Amantadine (n=54), placebo (n=48)	A	(reduction of fever) D = 96 h P = 120 h	NR	NR
Amantadine 100 mg bid or rimantadine 100 mg bid for 10 days (42)	Wild-type influenza	Selected families. Amantadine (n=23), Rimantadine (n=24), placebo (n=47)	A	1.6 to 2.5 days less than placebo	1.5 days less than placebo	NR
Zanamivir 10 mg by inhaler bid or qid for 5 days (34)	Wild type outbreak treated <48 h after symptoms started. Influenza attack rate = 57%. Setting: North America and Europe	Previously healthy adults and young adults. Zanamivir bid (n=419), Zanamivir qid (n=415), placebo (n=422)	56% A 44% B	ITT: D = 5.3 days P = 6.0 days Confirmed influenza: D = 5.1 days P = 7 days	After 5.5 days: D = 54% P = 45% Confirmed influenza: D = 4 days P = 5 days	Confirmed influenza: D = 8% P = 12%
Zanamivir 10 mg by inhaler bid for 5 days (44)	Wild type outbreak treated ≤48 h after start of symptoms. Influenza attack rate = 71%. Setting: Southern hemisphere	General adult and young adult community of low- and high-risk (17%) patients. Zanamivir (n=227), placebo (n=228)	67% A 33% B	D = 4.5 days P = 6 days	D = 7 days P = 9 days	High risk patients: D = 14% P = 46%
Zanamivir 10 mg by inhaler bid for 5 days (57)	Wild type outbreak treated ≤48 h after symptom onset. Influenza attack rate = 78%. Setting: Europe	Previously healthy adults and young adults plus high-risk patients (9%). Zanamivir (n=174), placebo (n=182)	96% A 4% B	D = 5 days P = 7.5 days	D = 7 days P = 8.5 days	D = 34% P = 23%
Zanamivir 10 mg by inhaler bid for 5 days (43)	Wild type outbreak treated ≤48 h after symptom onset. Influenza attack rate = 63%. Setting: North America and Europe	Healthy plus high-risk adult and young adult patients. Zanamivir (n=132), placebo (n=145)	91% A 9% B	Overall ITT: D = 4 days P = 7 days Significant difference only for treatment <30 h after illness onset	After 5.5 days: D = 54% P = 45%	NR
Oseltamivir 75 mg bid or 150 mg bid orally for 5 days (35)	Wild type outbreak treated ≤36 h after symptom onset. Influenza attack rate = 66%. Setting: Worldwide	Previously healthy adults and young adults. Oseltamivir 75 mg (n=243), oseltamivir 150 mg (n=245), placebo (n=238)	97% A 3% B	ITT: D = 4 days P = 4.8 days Confirmed influenza: D = 3.6 days P = 4.9 days	(resumption normal sleep): ITT: D = 8.3 days P = 10.4 days Confirmed influenza: D = 7.1 days P = 8.5 days	Less antibiotic use in drug-treated group compared with placebo
Oseltamivir 75 mg bid orally for 5 days (45)	Wild type outbreak treated ≤36 h after symptom onset. Influenza attack rate = 60%. Setting: USA	Previously healthy adults and young adults	98% A 2% B	ITT: D = 3.2 days P = 4 days Confirmed influenza: D = 3 days P = 4.3 days	ITT: D = 7.2 days P = 9.6 days Confirmed influenza: D = 6.5 days P = 9.4 days	NR D = 6% P = 15%

BID Twice daily; D Drug; ITT Intent to treat; NR Not recorded; P Placebo; QID Four times daily

Adults

In adults, randomized controlled trials of amantadine for the early treatment of influenza (within 24 h of the onset of fever) show a reduction in the severity of symptoms (41,42). The more recent trials with zanamivir or oseltamivir started within 48 h of the onset of symptoms demonstrate a reduction in symptoms of fever and cough from 1.5 days to three days. Significant differences versus placebo were found only in those treated within 36 h of onset for oseltamivir and within 30 h of onset for zanamivir (Table 4) (34,35,43-45). The earlier the drugs are given after the onset of symptoms, the greater the reduction in duration of symptoms compared with placebo (46).

THE USE OF INFLUENZA ANTIVIRALS IN PREGNANCY

There are no published trials of the use of either M2 ion channel blockers or NAIs in pregnancy. The M2 blockers have both been shown to be teratogenic in animals in very high doses. If

clinical circumstances warrant treatment or prophylaxis with an influenza antiviral agent in pregnant women, then zanamivir is likely the best choice because it is administered by inhalation and the systemic blood levels are comparatively lower than oseltamivir. The use of oseltamivir in lactating women should be decided on a case by case basis because it is not known whether the drug is excreted in human milk.

SAFETY, TOLERANCE, AND DRUG INTERACTIONS AND FORMULATIONS

Amantadine

Because amantadine has some CNS stimulatory properties, adults may complain of jitteriness, insomnia and, rarely, nightmares. These symptoms may be more common (up to 15%) when the drug is used for several weeks for prophylaxis. Generally, however, and especially for the short time it is used for treatment (five days), it is as well tolerated as placebo. Toxicity may be greater if there is accumulation in patients with impaired renal excretory mechanisms, and this applies particularly to the elderly. To avoid this, it is recommended that elderly patients have serum creatinine levels measured at the beginning of treatment. Effective levels of amantadine are achieved in elderly patients given a reduced daily dose of 100 mg, rather than the usual dose of 200 mg (47) (Tables 5 and 6).

In children, due to concerns regarding CNS toxicity caused by amantadine, plus the fact that it is only active against influenza A, attention has been directed at developing the role of the NAIs.

Drug interactions: Concomitant administration of triamterene, hydrochlorothiazide and trimethoprim-sulfamethoxazole causes CNS toxicity in adults, presumably due to interference with renal elimination of amantadine, resulting in accumulation and toxicity.

Available formulations: Amantadine is available in 100 mg capsules and as a 100 mg/10 mL syrup.

NAIs

Zanamivir: Zanamivir is administered as a powder by inhalation via a diskhaler. Because only 10% to 20% of the 10 mg inhaled dose is absorbed in adults, systemic exposure is minimal. The drug is safe and well tolerated, as evidenced by studies revealing no adverse effects after intravenous injection of 1200 mg/day to adult volunteers for five days. However, when administered as an oral inhaled powder, practitioners are advised nevertheless to be aware of bronchospasm in zanamivir-treated patients. One study (9) of once-daily inhaled zanamivir as prophylaxis of family members of index cases was unable to find an increased rate of asthma exacerbations in asthmatic contacts receiving zanamivir (6%) versus placebo (11%). Another double-blind, placebo-controlled trial of zanamivir treatment of influenza in patients 12 to 88 years of age (median 38 years of age) with asthma or chronic obstructive pulmonary disease did not find an increased incidence of bronchospasm in the zanamivir group (48). In fact, the morning and evening peak expiratory flow rates were significantly increased in the zanamivir group (10). Despite this evidence, there have been reports of acute bronchospasm in patients taking zanamivir; as a result, the Advisory Committee on Immunization Practices of the CDC advised caution in using zanamivir for asthmatic and chronic obstructive pulmonary disease patients and advised that the patient should have a short-acting bronchodilator available during treatment (22).

Drug interactions: Interactions between zanamivir and other drugs coadministered systemically are neither likely nor expected due to the trivial absorption of zanamivir after oral inhalation.

TABLE 5
National Advisory Committee on Immunization recommended dosage adjustments of amantadine according to creatinine clearance

Creatinine clearance (mL/min/1.73 m^2)	Dosage	
	10 to 64 years of age	≥65 years of age
≥80	100 mg twice daily	100 mg twice daily
60–79	Alternating daily doses of 200 mg and 100 mg	Alternating daily doses of 100 mg and 50 mg or 75 mg daily
40–59	100 mg once daily	100 mg every 2 days or 50 mg daily
30–39	200 mg twice weekly	100 mg twice weekly or 25 mg daily
20–29	100 mg three times weekly	50 mg three times weekly or 25 mg daily
10–19	Alternating weekly doses of 200 mg and 100 mg	Alternating weekly doses of 100 mg and 50 mg

Data from reference 2

TABLE 6
Recommended doses of antiviral agents for the treatment of influenza in children and adults

	Children		Adults	
	Age and/or weight	Dose	Age	Dose
Amantadine*	1 to 9 years of age	5 mg/kg/day, max 150 mg/day in two doses	13 to 64 years of age	100 mg twice daily
	≥10 years of age and <40 kg	5 mg/kg/day in 2 doses	≥65 years of age	100 mg/day
	≥10 years of age and ≥40 kg	200 mg/day in 2 doses		
Oseltamivir†	1 to 12 years of age and ≤15 kg	30 mg twice daily	13 to 64 years of age	75 mg twice daily
	1 to 12 years of age and >15 kg to 23 kg	45 mg twice daily	≥65 years of age	75 mg twice daily
	1 to 12 years of age and >23 kg to 40 kg	60 mg twice daily		
	1 to 12 years of age and >40 kg	75 mg twice daily		
Zanamivir	1 to 6 years of age	N/A	13 to 64 years of age	10 mg twice daily
	7 to 12 years of age	10 mg twice daily	≥65 years of age	10 mg twice daily

*The usual duration of treatment is five days. A longer duration of therapy may be required in immunocompromised patients. *Amantadine dose adjustment required in renal failure (see Table 5); †Oseltamivir dose for renal failure: A reduction in oseltamivir dose is required if the creatinine clearance is less than 30 mL/min. In adults with a creatinine clearance 10 mL/min to 30 mL/min, give 75 mg once daily for treatment (56). A corresponding adjustment is recommended for children*

Available formulations: Zanamivir is supplied in 'Rotadisks' (GlaxoSmithKline, USA) with four blisters containing 5 mg of powder each. Five Rotadisks are packaged with a Diskhaler inhalation device (GlaxoSmithKline, USA). Generally, children younger than seven years of age and incompetent adults are unlikely to reliably exhibit the proper coordination required to use this product. Children should use zanamivir only under adult supervision.

Oseltamivir: The incidence of nausea or vomiting was increased by 3% over placebo in the therapeutic trials of oseltamivir, and by 3% to 12% in the prophylaxis trials, but rates of discontinuation were low and not different between the two groups, which consisted mostly of adults. Nausea or vomiting occurred early during therapy, and then usually subsided despite continuation of the drug. No other side effects occurred significantly more frequently in oseltamivir recipients than in placebo recipients.

Published pediatric data on the safety and efficacy of oseltamivir exist for children one year of age and older (49,50). Pharmacokinetic data (50) show that 2 mg/kg twice daily resulted in drug exposures within the range associated with tolerability and efficacy in adults who were administered approximately 1 mg/kg twice daily. A liquid formulation was shown in a randomized, placebo-controlled trial (49) to be safe and well accepted by healthy children one to 12 years of age and in children with asthma aged six to 12 years. In the placebo-controlled trial evaluating the therapeutic efficacy of oseltamivir in children one to 12 years of age, emesis occurred in 14.3% of children receiving oseltamivir 2 mg/kg/dose twice daily for 10 doses (maximum 100 mg/dose) and in 8.5% of children receiving placebo. Discontinuation rates for oseltamivir (1.8%) and placebo (1.1%) due to adverse events were not significantly different (50).

The safety and efficacy of oseltamivir in infants younger than one year of age have not been established. This is clearly an area where additional research is needed. A caution was issued due to deaths observed in seven day-old mice receiving extremely high doses of the drug (51). The mice were fed a dose that was approximately 250 times the dose recommended for children. The concentrations of the prodrug in the brain were 1500 times those of the adult animals exposed to the same dose. Thus, it was thought than an immature blood-brain barrier may have caused the toxicity in these animals. Based on the ages of the animals and the stage of development of their blood-brain barrier, the human equivalent was thought to be infants younger than one year of age. However, recent reports from Japan did not show CNS toxicity in infants younger than one year of age who were treated with oseltamivir (52,53).

In November 2005, there were reports of neuropsychiatric events and deaths in Japanese children receiving oseltamivir. The United States Food and Drug Administration has reviewed the available information and has concluded that the increased reports of neuropsychiatric events in Japanese children are most likely related to an increased awareness of influenza-associated encephalopathy, increased access to oseltamivir in that population, and a coincident period of intensive monitoring of adverse events (54). They were not able to establish a causal relationship between oseltamivir and the reports of pediatric deaths. Of note, deaths occurred in children two years of age and older, but the ages of those with neuropsychiatric manifestations were not reported (55).

Drug interactions: Interactions during the coadministration of oseltamivir with other drugs are unlikely because it is eliminated largely unchanged into urine by glomerular filtration and renal tubular secretion by an anionic transporter and does not cause dose-related adverse effects, even at high doses.

Available formulations: Oseltamivir is available as 75 mg capsules or as an oral suspension containing 12 mg/mL.

SUMMARY OF RECOMMENDATIONS

With respect to the role of antiviral drugs for the treatment or prevention of influenza infection, the CPS and AMMI Canada recommend the following:

I. Drugs for the prevention and treatment of influenza

A. Amantadine is approved and recommended for the prevention (evidence grade IB) and treatment (evidence grade IB) of influenza A virus infection in individuals one year of age or older only if the strain in circulation is susceptible to amantadine.

B. Zanamivir is approved and recommended for the treatment of influenza A and B virus infection in individuals older than seven years of age (evidence grade IA). It may be used off-label for the prevention of influenza A and B virus infection in individuals aged five years or older (evidence grade IA).

C. Oseltamivir is approved for the prevention of influenza A and B virus infection in individuals 13 years of age or older (evidence grade IA). The drug is also approved for the treatment of influenza A and B virus infection in individuals one year of age or older (evidence grade IA). It may be used off-label for the prevention of influenza A and B virus infection in individuals aged one year and older (evidence grade IA). Based on current evidence, it should not be used in infants younger than one year of age (evidence grade IIID).

D. Given that there are no antivirals currently approved for use in infants younger than one year of age, the CPS and AMMI Canada strongly encourage research on this issue.

II. Prevention of influenza

Antiviral drugs are recommended as a substitute for immunization to prevent influenza in the situations outlined below. These strategies should be accompanied by the appropriate education and awareness to enable early access to antivirals.

A. When a vaccine that is effective against strain(s) of influenza circulating in the community is not available, and exposure and the risk of illness is considered to persist through the outbreak, amantadine, zanamivir or oseltamivir may be administered until a vaccine becomes available or the outbreak has subsided (so called 'seasonal prophylaxis') (evidence grade IB). The data shown in Table 1 illustrate that the experience with these three drugs for seasonal prophylaxis is not uniform across all age groups.

   Because no comparative trials have been conducted to support the selection of one agent from among the

group, the choice of which drug to administered will depend on other factors, such as virus susceptibility (eg, influenza A H5N1 is susceptible to NAIs but not M2 inhibitors), ease of dosing (zanamivir = oseltamivir >> amantadine), tolerance (zanamivir > oseltamivir >> amantadine) and cost (amantadine << zanamivir = oseltamivir). Zanamivir is not easy to administer in young children or adults incapable of operating the inhalation device.

Prophylaxis may be continued until the outbreak has subsided (usually six to eight weeks). Alternatively, it may be discontinued if a vaccine has become available or if it is suspected that the individual has experienced (mild) influenza attenuated by chemoprophylaxis or has been shown to have been infected, based on laboratory testing demonstrating that subclinical influenza has occurred as demonstrated by culture, rapid antigen testing or polymerase chain reaction of respiratory secretions.

B. When vaccine is contraindicated, seasonal chemoprophylaxis (as discussed in recommendation IIA) may be considered (evidence grade IIIC). For example, when a high-risk individual has immediate-type hypersensitivity to egg protein, traces of which may be present in vaccines prepared in embryonated chicken eggs, or to some other substance in the vaccine formulation, chemoprophylaxis is recommended. The choice of drug will require consideration, at least, of the factors listed above (recommendation IIA). The duration of prophylaxis may be as described above (recommendation IIA).

C. When an immediate protective effect is required, chemoprophylaxis has been shown to be effective and well tolerated. Such a need may exist when:

- an outbreak is diagnosed in a closed institutional setting;
- an outbreak is diagnosed in the family setting; or
- when influenza is causing illness in the community, even as vaccine is being administered.

i) Prophylaxis in a closed institutional setting may be initiated when an outbreak is diagnosed (evidence grade IIB). An outbreak may be diagnosed if at least two residents develop acute influenza-like illness within 72 h of each other and have laboratory-proven influenza illness that confirms that influenza is being transmitted. All three drugs have been used for outbreak control in nursing homes. Zanamivir and oseltamivir may be preferable to amantadine (evidence grade IB).

Usually, chemoprophylaxis for outbreak control in an institution is administered for at least 10 days. Prophylaxis may be discontinued if at least eight days have elapsed since the onset of the last case of influenza in the unit. If new cases continue to appear, then prophylaxis will, by corollary, need to be continued so that this strategy could become, in effect, seasonal prophylaxis.

ii) When influenza occurs in the family setting, postexposure chemoprophylaxis in unaffected members should be considered to reduce illness in the family (evidence grade IA).

Unaffected family members should be started on chemoprophylaxis as soon as possible after recognition of influenza-like illness in the index case. All three drugs are recommended for postexposure prophylaxis when the virus is susceptible. The duration of prophylaxis is usually seven to 10 days.

The index case may be treated with the recommended five-day course of zanamivir or oseltamivir, but not amantadine. Treatment of the index case with amantadine has resulted in failure of amantadine prophylaxis in other family members due to the rapid development of amantadine-resistant mutants in the treated index case. If amantadine is the only option available for the index case in a household, then it should not be used for prophylaxis for other family members.

iii) Chemoprophylaxis may be utilized to protect individuals until vaccine-induced immunity develops (evidence grade IIIB). Chemoprophylaxis should be continued for two weeks after appropriate vaccination (one or two doses). When vaccine that is expected to protect against a circulating strain causing illness in the community is coadministered, chemoprophylaxis should be continued until vaccine-induced immunity is likely to have developed. The time for vaccine-induced immunity to develop may be seven to 10 days if the virus strains in the vaccine are drift variants of strains that have been causing illness in one or more previous years, such that some heterologous immunity is likely to exist that can be boosted by the current vaccine.

Where the vaccine contains a virus arising as a result of antigenic shift (eg, a pandemic strain), vaccine-induced immunity may require two or more doses of vaccine. Chemoprophylaxis will need to be continued until it is probable that immunity has developed (most likely a duration of two to three weeks), as demonstrated by clinical trials.

D. When high-risk individuals have been immunized but the vaccine strain(s) poorly match one or both of the hemagglutinin and/or neuraminidase antigens of the circulating strain, seasonal chemoprophylaxis is recommended (evidence grade IIIB). The duration of prophylaxis will be as stated above.

E. When individuals are not likely to respond to vaccine because of an immunocompromised state due to drugs or disease, seasonal chemoprophylaxis is recommended (evidence grade IIIB). The duration of prophylaxis will be as stated in recommendation IIA.

III. Treatment of influenza illness

In general, antiviral chemotherapy is recommended for individuals with severe illness and those most likely to develop complications or die prematurely as a result of influenza.

The duration of therapy is five days (longer therapy may be indicated in patients with severe immunodeficiency who remain symptomatic and virus positive).

A. When antiviral drugs are administered for the treatment of influenza A or B infection, it is recommended that amantadine not be prescribed because of the high probability of the emergence of resistance (evidence grade IA), with possible treatment failure (evidence IB) and spread to others receiving amantadine for prophylaxis (evidence grade IA).

   Because there have been no studies directly comparing the relative efficacies and safety of zanamivir and oseltamivir, selecting one drug from among these agents will need to be based on such considerations as the ability to orally inhale zanamivir or the ability to tolerate its uncommon irritant effect on the tracheobronchial tree with resulting bronchospasm.

B. When zanamivir or oseltamivir are administered for the treatment of influenza, they should be started as soon as possible after the onset of symptoms (evidence grade IA) and within 48 h of symptoms.

C. When the patient has been symptomatic for more than 48 h, it is recommended that antiviral therapy not be prescribed unless the patient is immunocompromised and has progressive respiratory infection (evidence grade IIIC).

D. For seriously ill patients, combination therapy with amantadine and an NAI may be considered (evidence grade IIIC).

E. For treatment of pregnant women ill with influenza, it is noted that none of the drugs listed above can be recommended because they have not been evaluated for efficacy or safety in pregnant women or approved for administration in these individuals (evidence grade IIIC). However, zanamivir is minimally bioavailable after oral administration. Thus, zanamivir administered by inhalation to pregnant women is unlikely to cause much fetal exposure. Hence, from the point of view of safety, it may be the drug of choice for administration to pregnant women (evidence grade IIIC).

APPENDIX
Levels of evidence and strength of recommendations*

Level of evidence	Description
I	Evidence obtained from at least one properly randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trial without randomization.
II-2	Evidence obtained from well-designed cohort or case-controlled analytical studies, preferably from more than one centre or research group.
II-3	Evidence obtained from comparisons between times and places, with or without the intervention. Dramatic results in uncontrolled experiments could also be included in this category.
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
Grade	**Description**
A	There is good evidence to recommend the clinical preventive action.
B	There is fair evidence to recommend the clinical preventive action.
C	The existing evidence is conflicting and does not allow a recommendation to be made for or against use of the clinical preventive action; however, other factors may influence decision-making.
D	There is fair evidence to recommend against the clinical preventive action.
E	There is good evidence to recommend against the clinical preventive action.
I	There is insufficient evidence to make a recommendation; however, other factors may influence decision-making.

**Data from reference 59*

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