

# Antiviral Strategies for Pandemic Influenza 2009

Gerald A. Evans, MD FRCPC  
Associate Professor of Medicine  
Queen's University  
Kingston, ON

# Antiviral Strategies

- Prophylaxis
  - Pre-exposure vs. post-exposure
    - Health care setting vs. household setting
- Pre-emptive therapy
  - High-risk vs. low-risk individuals
    - Post-exposure vs. early disease
- Active treatment
  - Mono vs. combination therapy
  - Confirmed vs. suspected infection

# Relevant Outcomes for Chemoprophylaxis of Influenza

- Mortality
- Hospitalization
- Influenza cases prevented
- Serious adverse events (not drug-related)
- Drug related adverse events
- Drug resistance
- Cost-effectiveness\*

# Relevant Outcomes for Active Treatment of Influenza

- Mortality
- Hospitalization
- Complications
- Serious adverse events (not drug-related)
- Drug resistance
- Cost-effectiveness\*

**Table 1 - Antiviral (Anti-Influenza) drugs currently approved for use in Canada**

Drug	Trade Name & Manufacturer	Class	Authorized Indications (as per product monograph)	Formulation(s)	Shelf Life/Stability	Proposed Use(s) During Pandemic
Oseltamivir	Tamiflu®, Hoffmann-La Roche Inc.	Neuraminidase Inhibitor	Treatment of influenza A and B in persons 1 year of age and older who have been symptomatic for no more than 2 days  Prevention of influenza A and B in persons 1 year of age and older after close contact with an infected individual for post-exposure prophylaxis (10 days)	Capsules (30 mg, 45 mg and 75 mg): 10 capsules per blister pack  Powder for oral suspension (12 mg/mL when reconstituted): 900 mg per bottle (volume of 75 mL in a 100-mL glass bottle)	Shelf life of capsules: 7 years for new government stockpile orders (previously 5 years)  Shelf life of powder for suspension: 2 years Stability: Once reconstituted, 10 days in refrigerator (at 2°-8° C)	Capsules (adult and paediatric) for early treatment of ill persons and for outbreak control (treatment and post-exposure prophylaxis) in health care and other closed facilities where high-risk persons reside  Oral suspension not included in the national stockpile
Zanamivir	Relenza®, GlaxoSmithKline	Neuraminidase Inhibitor	Treatment of influenza A and B in persons 7 years of age and older who have been symptomatic for no more than 2 days  Prevention of influenza A and B in persons 7 years of age and older (post-exposure prophylaxis and up to 28 days' pre-exposure prophylaxis)	ROTADISK® consisting of a circular foil disk with four blisters each containing 5 mg of zanamivir. A DISKHALER® inhalation device is provided to administer the medication (through inhalation). One box contains 5 disks, which is equivalent to one treatment course	Shelf life: 5 years	Early treatment of ill persons and outbreak control (treatment and prophylaxis) in health care and other closed facilities where high-risk persons reside  Preferred treatment for pregnant and nursing women
Amantadine	Symmetrel® syrup, Bristol-Myers Squibb  <i>Generic amantadine manufacturers:</i> Dominion Pharmacal, GenPharm, Medican Pharma, Pharmed, Pharmascience	M2 ion Channel blocker (cyclic amines or adamantanes)	Treatment of influenza A in persons 1 year of age and older  Prevention of influenza A in persons 1 year of age and older	Capsules (100 mg/capsule): bottles of 100 capsules  Syrup (10 mg/mL): bottles of 500 mL	Shelf life of capsules: 3.5 to 4 years depending on manufacturer*  Shelf Life of syrup: 2 years	For use as combination therapy (with a neuraminidase inhibitor) for the treatment of severe disease  Prophylaxis if strain is known to be susceptible to amantadine

Source: Annex E Canadian Pandemic Influenza Plan for the Health Sector: The Use of Antiviral Drugs During a Pandemic May 12, 2009

# Antivirals for Influenza 2009

As of June 2009, the antiviral susceptibilities of circulating viruses are:

	Oseltamivir	Zanamivir	M2 inhibitors
Pandemic A(H1N1) 2009	Susceptible <sup>a</sup>	Susceptible	Resistant
Seasonal A (H1N1)	Mostly resistant	Susceptible	Mostly susceptible
Seasonal A (H3N2)	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	Resistant
Avian influenza (H5N1)	Susceptible	Susceptible	Variable resistant

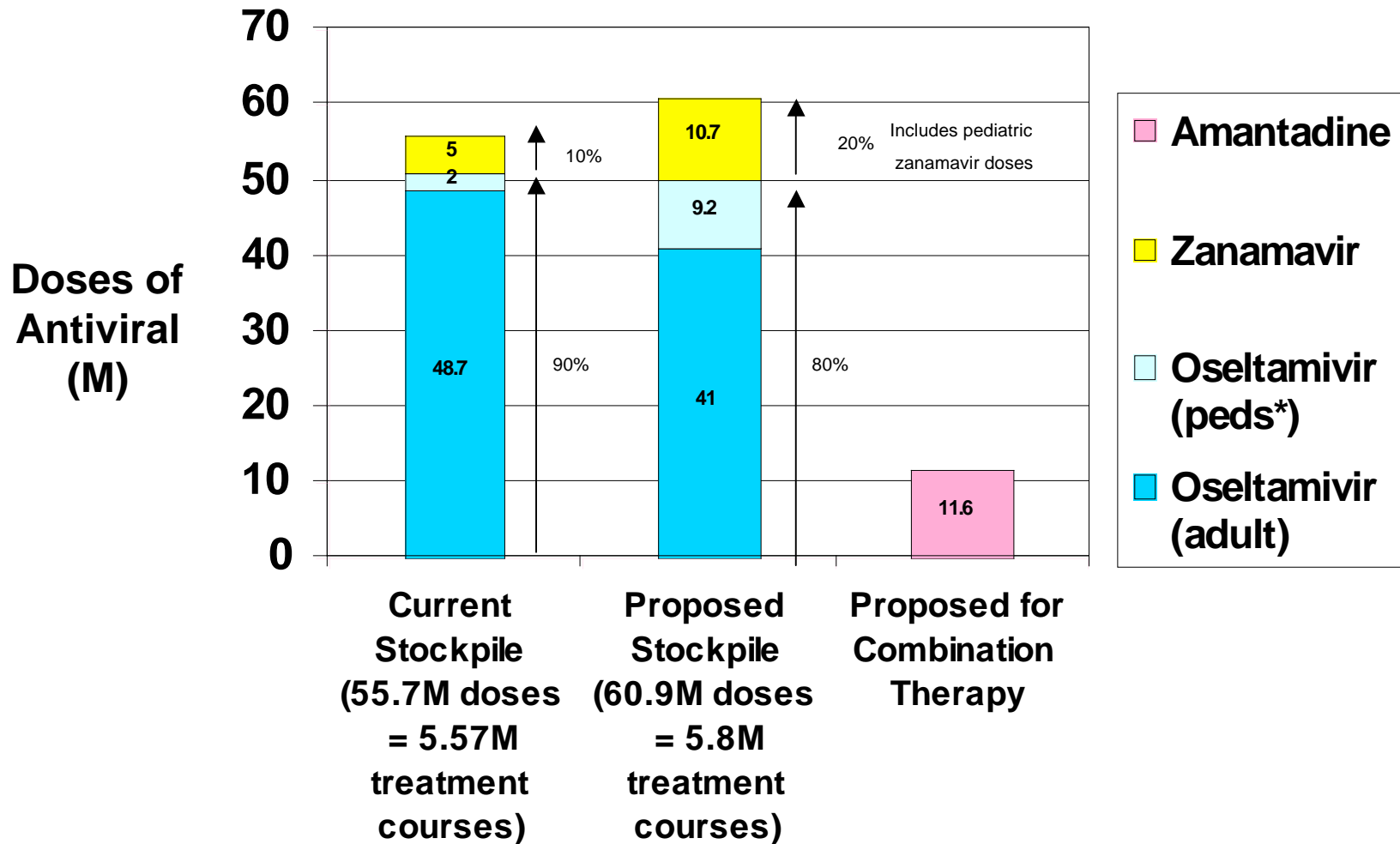
a A small number of isolated cases of resistance to oseltamivir have been reported

Source: WHO Guidance on Antivirals Aug. 20, 2009

# Current Canadian Recommendations for Use of Influenza Antivirals

- Pandemic Period (Phase 6)
  - Early treatment of people with influenza and no post-exposure prophylaxis of close contacts of cases
  - Provide rapid access to antivirals and early treatment to critical infrastructure workers to minimize societal disruption
  - Use antivirals for outbreak control
    - Including treatment of cases and prophylaxis of close contacts of cases in closed health care facilities and other closed facilities where high-risk people reside
  - No use of antivirals from government stockpile for pre-exposure prophylaxis

# National Antiviral Stockpile Composition



\*=peds include both 30 and 45 mg caps

**Table. Settings and strategies for antiviral drug use during an influenza pandemic and rationales.**

Setting and target population	Antiviral strategy	Rationale	Pandemic response goals addressed by antiviral strategy	Estimated number of regimens (million)
<i>Recommendations for antiviral drugs from public sector stockpiles</i>				
Initial pandemic outbreaks overseas and in the U.S.	Treatment; PEP, targeted prophylaxis	-- Effective containment of the initial outbreak of a novel influenza virus strain may prevent the pandemic -- Quenching efforts overseas and in the U.S will slow pandemic spread and provide more time for preparedness	Slow pandemic spread	6
Exposed travelers entering the U.S. early in a pandemic	PEP	-- Contributes to a risk-based policy to reduce the entry of infected persons and delay U.S. outbreaks	Slow pandemic spread	
Persons with pandemic influenza illness	Treatment	-- Reduces influenza complications, hospitalization, and death -- Reduces duration of illness and transmission of infection -- Meets patient and provider expectations for medical care	Reduce health impacts	79*
Outbreak control in closed settings (e.g., nursing homes, prisons)	PEP	-- High risk of illness and death when outbreaks occur in closed settings -- Documented success of PEP for seasonal outbreaks -- Consistent with accepted public health practice -- Protects those in whom vaccination may be less effective	Reduce health impacts	5
<i>Recommendations for antiviral drugs primarily from private sector stockpiles</i>				
Healthcare and emergency service workers	Outbreak (pre-exposure) prophylaxis for workers with high-risk exposure	-- Reduces infection and absenteeism in a critical workforce -- Protects those at highest occupational risk -- Reduces chance of transmitting infection to high-risk patients with illnesses other than influenza	Reduce health impacts Minimize societal disruption	103
	PEP given exposure of other workers			
Persons who are severely immunocompromised	PEP	-- High risk for severe complications and mortality from pandemic influenza, if infected -- Antiviral drugs are the only option for disease prevention	Reduce health impacts	2
<b>TOTAL NUMBER OF ANTIVIRAL DRUG REGIMENS FOR FULL IMPLEMENTATION</b>				<b>195</b>

Source: CDC Guidance on Antiviral Drug Use during an Influenza Pandemic Dec. 2008

**Table. Health impacts, antiviral drug requirements, and cost-effectiveness of antiviral treatment and household post exposure prophylaxis strategies.**

<b>Parameter</b>	<b>Treatment alone</b>	<b>Household PEP alone</b>	<b>Treatment and Household PEP</b>
Number of deaths prevented	144,000	155,000	288,000
Number of hospitalizations prevented	1.845 million	838,000	2.427 million
Number of antiviral regimens	79.4 million	106.4 million	167.1 million
Cost per death prevented*	\$11,200	\$14,000	\$11,800
Cost per hospitalization prevented*	\$900	\$2,600	\$1,400

\*Average cost per regimen based on Federal contract price for oseltamivir and zanamivir, the relative proportions of each agent targeted for acquisition for the national stockpile, rounded to the nearest \$100

Source: CDC Guidance on Antiviral Drug Use during an Influenza Pandemic Dec. 2008

**Table R1: Use of antivirals for treatment of influenza**

Population	Pandemic (H1N1) influenza virus 2009	Multiple co-circulating influenza A sub-types or viruses with different antiviral susceptibilities	Sporadic zoonotic influenza A viruses including H5N1
<b>Mild to moderate uncomplicated clinical presentation</b>			
At-risk <sup>a</sup> population	oseltamivir or zanamivir (04)	Zanamivir, or oseltamivir plus M2 inhibitor <sup>b</sup> (10)	oseltamivir or zanamivir
Otherwise healthy <sup>c</sup>	Need not treat (03)	Need not treat (09)	oseltamivir
<p>a Infants and children aged less than 5, the elderly (&gt;65 years), nursing home residents, pregnant women, patients with chronic co-morbid conditions such as cardiovascular, respiratory or liver disease, diabetes, and those with immunosuppression related to malignancy, HIV infection or other diseases.</p> <p>b Amantadine should not be used in pregnant women (recommendation 12).</p> <p>c All those not covered by the at-risk definition above.</p>			
<b>Severe or progressive clinical presentation<sup>d</sup></b>			
At-risk <sup>a</sup> population	Oseltamivir (01) (zanamivir should be used where virus is known to be resistant to oseltamivir, or if oseltamivir unavailable) (02)	oseltamivir plus M2 inhibitor <sup>b</sup> , or zanamivir (05,06, 07)	oseltamivir plus M2 inhibitor
Otherwise healthy <sup>c</sup>			
d See section 2 Case Description. Would include all patients requiring hospitalization.			

Source: WHO Guidance on Antivirals Aug. 20, 2009

# Complicated or Severe Influenza

- Clinical (shortness of breath, tachypnea, hypoxia)
- Radiological signs of lower respiratory tract disease
- Other direct complications
  - Rhabdomyolysis, myocarditis, encephalopathy, severe dehydration
- Secondary complications
  - Renal failure, multi-organ failure, and septic shock
- Exacerbations of underlying chronic diseases
  - Asthma, COPD, chronic hepatic or renal failure, diabetes or other cardiovascular conditions
- Hospital admission for clinical management
- Any signs of disease progression

# Antivirals as Chemoprophylaxis

- Assumes
  - Other control measures (i.e. infection control) are in place
  - Mechanisms for delivery of drugs and costs are acceptable
  - Vaccination is planned
- Context
  - High risk setting
  - High gain group
  - Higher risk individuals

# Summary Table for Antiviral Chemoprophylaxis Recommendations

Risk		Recommendation	Population	Strength of recommendation
Transmission	Complications			
High	High	If drug available and virus susceptible, use either neuraminidase inhibitor or M2 inhibitor	Defined target population Individual patients Healthcare workers	weak weak weak
High	Low	chemoprophylaxis not recommended	Individual patients Healthcare workers	weak weak
Low	High	If drug available and virus susceptible, use either neuraminidase inhibitor or M2 inhibitor	Individual patients Healthcare workers	weak weak
Low	Low	chemoprophylaxis not recommended	Individual patients Healthcare workers	strong strong

Source: WHO Guidance on Antivirals Aug. 20, 2009

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