Influenza
A General Practice Perspective

Dr. Michael Cheng
Family Physician

Mortality in US From Influenza Epidemics

10,000 deaths per epidemic are common
20,000 to 40,000 deaths during recent epidemics

### Secondary Complications of Influenza


<table>
<thead>
<tr>
<th>Condition</th>
<th>Complications/1,000 Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusitis</td>
<td>30</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>27</td>
</tr>
<tr>
<td>Otitis Media</td>
<td>22</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>18</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>9</td>
</tr>
</tbody>
</table>

Synergy Health Care, Inc. data, data on file, Outcomes Management, Roche Laboratories. Slide 5.

### Influenza-Related Hospitalization Rates (per 10,000), 1999 (QMH)

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 yr</td>
<td>288.2</td>
</tr>
<tr>
<td>1 to less than 2 yrs</td>
<td>209.3</td>
</tr>
<tr>
<td>2 to less than 5 yrs</td>
<td>77.3</td>
</tr>
<tr>
<td>5 to less than 10 yrs</td>
<td>20.9</td>
</tr>
<tr>
<td>10 to less than 15 yrs</td>
<td>8.1</td>
</tr>
</tbody>
</table>

- Hospitalization: 6-fold > in U.S.
- Significant contributor to mortality in the elderly

Influenza Epidemic in the Community

- Community
- Family/Household
- School-age children infected
- School absenteeism
- Increased visits for medical care
- Employee absenteeism
- Hospitalization (esp. elderly)
- Hospitalization (esp. elderly)

Proportionate distribution of laboratory-confirmed influenza cases, by age groups, Canada, 2001-2002.
### Clinically Relevant Influenza Viruses

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>Potentially severe illness</td>
</tr>
<tr>
<td></td>
<td>Epidemics and pandemics</td>
</tr>
<tr>
<td></td>
<td>Rapidly changing</td>
</tr>
<tr>
<td>Type B</td>
<td>Usually less severe illness</td>
</tr>
<tr>
<td></td>
<td>Epidemics</td>
</tr>
<tr>
<td></td>
<td>More uniform</td>
</tr>
<tr>
<td>Type C</td>
<td>Usually mild or asymptomatic illness</td>
</tr>
<tr>
<td></td>
<td>Minimal public health impact</td>
</tr>
</tbody>
</table>

### Influenza Surface Proteins

- Neuraminidase
- Hemagglutinin
- RNA
- M₂ protein (only on type A)
Occurrence of Influenza Pandemics and Epidemics

<table>
<thead>
<tr>
<th>Time in Years</th>
<th>Disease Incidence</th>
<th>Mean Population Antibody Level</th>
<th>Pandemic</th>
<th>Epidemic</th>
<th>Interpandemic Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>Incidence of clinically manifest influenza</td>
<td>Mean level of population antibody vs A HxNx</td>
<td>Epidemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>Significant minor variation A HxNx may occur at any of these points. Epidemics may or may not be associated with such variations</td>
<td>Mean level of population antibody vs A HyNy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-6</td>
<td>Introduction of hypothetical A HxNx virus</td>
<td></td>
<td></td>
<td>Introduction of hypothetical A HyNy major (new subtype) variant A HxNx disappears</td>
<td></td>
</tr>
</tbody>
</table>

Influenza Pandemics in the 20th Century

<table>
<thead>
<tr>
<th>Years</th>
<th>Flu</th>
<th>Virus</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918-1919</td>
<td>“Spanish”</td>
<td>Type A (H1N1)</td>
<td>20 million worldwide 550,000 US</td>
</tr>
<tr>
<td>1957-1958</td>
<td>“Asian”</td>
<td>Type A (H2N2)</td>
<td>70,000 US</td>
</tr>
<tr>
<td>1968-1969</td>
<td>“Hong Kong”</td>
<td>Type A (H3N2)</td>
<td>34,000 US</td>
</tr>
</tbody>
</table>


Influenza Type A (H5N1)

First appeared in humans in Hong Kong, 1997
Primarily associated with avian species
Fatal epidemic among Hong Kong poultry in 1997
18 total confirmed cases, with 6 deaths


'Slaughter of the innocents'

In December 1997, Hong Kong officials gassed more than a million chickens suspected of harboring the deadly virus

TIME February 1998; Vol. 151, No.7
**Implications of H5N1 Infection**

Potential for pandemic infection by little-known pathogen

Morbidity and mortality in both young and old

No previous human exposure; no vaccine

Signals need for
- Pandemic readiness plan
- Rapid detection and diagnosis of new viral strains
- Veterinary surveillance
- Continuing research for new antiviral agents


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**Pathology of Influenza Infection**

A. Binding to Sialic Acid

B. Entering Cell

C. Replication

D. Release From Cell
Transmission

Transmitted through the air by droplets and particles excreted by infected individuals when they cough or sneeze

Enters the body via nose or throat

Person is infectious 1 - 2 days before they develop symptoms to seven days afterwards

The Value of Surveillance

“…when influenza virus is confirmed in a region or community by the local or state health department or by the CDC, persons with fever, muscle aches, and cough most likely have influenza.”

Treanor JJ. In: Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases. 5th ed. 2000:1837.
2003 Influenza-like-illness in H.K.

Onset of Influenza A in Volunteer

Adapted from Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's Principles and Practice of Infectious Disease. 5th ed. 2000:1831.
Classic Signs and Symptoms of Influenza

- Rapid onset of symptoms
- Fever, usually over 100°F
- Nonproductive cough
- Headache
- Myalgia
- Chills and/or sweats
- Sore throat
- Potentially severe, persistent malaise
- Substernal soreness, photophobia and ocular problems

### Signs and Symptoms of Influenza

<table>
<thead>
<tr>
<th>Type of Symptoms</th>
<th>Children &lt;5 yrs</th>
<th>Adults</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td></td>
<td>Nonproductive cough</td>
<td>Nasal obstruction</td>
</tr>
<tr>
<td>Sore throat</td>
<td></td>
<td>Sore throat</td>
<td></td>
</tr>
<tr>
<td>Nonproductive cough</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Constitutional or systemic</strong></td>
<td></td>
<td>Rapid onset of symptoms</td>
<td>Fever &gt;99.0°F</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td>Fever, usually &gt;100°F</td>
<td>Lassitude</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>Chills/sweats</td>
<td>Confusion</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td>Myalgia</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td>Potentially severe, persistent malaise</td>
<td></td>
</tr>
<tr>
<td>Lassitude</td>
<td></td>
<td>Substernal soreness, photophobia and ocular problems</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>Substernal soreness, photophobia and ocular problems</td>
<td></td>
</tr>
<tr>
<td><strong>Influenza vs Cold Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Sudden</td>
<td>Gradual</td>
<td></td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>Characteristic, high (over 101°F); lasting 3 to 4 days</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td>Nonproductive; can become severe</td>
<td>Hacking</td>
<td></td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>Prominent</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td><strong>Myalgia (aches and pains)</strong></td>
<td>Usual; often severe</td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td><strong>Fatigue, weakness</strong></td>
<td>Can last up to 2 to 3 weeks</td>
<td>Very mild</td>
<td>Never</td>
</tr>
<tr>
<td><strong>Extreme exhaustion</strong></td>
<td>Early and prominent</td>
<td>Never</td>
<td></td>
</tr>
<tr>
<td><strong>Chest discomfort</strong></td>
<td>Common</td>
<td>Mild to moderate</td>
<td></td>
</tr>
<tr>
<td><strong>Stuffy nose</strong></td>
<td>Sometimes</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td><strong>Sneezing</strong></td>
<td>Sometimes</td>
<td>Usual</td>
<td></td>
</tr>
<tr>
<td><strong>Sore throat</strong></td>
<td>Sometimes</td>
<td>Common</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from the National Institute of Allergy and Infectious Diseases.
Rapid Diagnostic Tests

Nasal swab or Nasopharyngeal aspirate

Infection control measures during procedure

Detection of antigen

Detect A only, A+B or A & B separately

Immunochromatographic assay (Qualitative)

Commercially available kits

- Sensitivity: swab (58-78%)  NPA (71-82%)
- Specificity: swab (92-97%)  NPA (94-97%)
**Therapeutic Goals**

- Relieve symptoms
- Improve function
- Prevent complications
- Reduce transmission

**Management Options**

- Vaccinate at start of flu season
- Treat with antiviral agents
- Give antiviral agents prophylactically?
**Inactivated Influenza Virus Vaccine**

**Content**
Updated yearly to protect against anticipated strains, consists of type A (2) and type B (1)

**Process**
Grown in embryonated chicken eggs and formalin inactivated

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**Vaccination**

**Influenza 2003-2004**

- A/Moscow/10/99(H3N2)
- A/New Caledonia/20/99 (H1N1)
- B/ Hong Kong /330/ 2001
Influenza Vaccination recommended

- 50 years of age or older
- Residents of long-term care facilities
- Pregnant woman ≥ 2\textsuperscript{nd} trimester
- 6 months – 18 years on long-term aspirin
- Chronic illness & immunocompromised (>6 months old)
- Health care workers
- Anyone with close contact with people at risk

Influenza Vaccination encouraged

Children 6 – 23 months

Household contacts and caregivers of children and infants

People who provide essential community services

Anyone who wants to reduce their chance of getting influenza
### Influenza Vaccination

<table>
<thead>
<tr>
<th>Age</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5 yrs</td>
<td>44-49%</td>
</tr>
<tr>
<td>6-10 yrs</td>
<td>74-76%</td>
</tr>
<tr>
<td>11-15 yrs</td>
<td>70-81%</td>
</tr>
<tr>
<td>&lt; 65 yrs</td>
<td>75-90%</td>
</tr>
<tr>
<td>&gt; 65 yrs</td>
<td>58%</td>
</tr>
</tbody>
</table>

### Efficacy of the Influenza Vaccine

- Most effective (70%-90%) in preventing illness in persons aged <65 yrs
- 30%-70% in preventing pneumonia & influenza hospitalization in elderly not in chronic care facility
- 30%-40% in preventing illness in frail elderly
- 50%-60% in preventing pneumonia & influenza hospitalization in nursing home elderly
- 80% in preventing death in nursing home elderly

**Efficacy of the Influenza Vaccine**

- A vaccinated person can still get influenza if the strain is not covered by the vaccine.
- Will not protect against non-influenza agents.
- Protection peaks 2 weeks after vaccination.
- Effectiveness of the vaccine depends on the age and immunocompetence of the recipient and the similarity between the viruses in the vaccine and those in circulation.
- Vaccine should not be used by individuals with egg protein allergy.
- Vaccination is highly effective in healthy adults and has been shown to have substantial economic and health-related benefits.

**WHO Recommendations on Influenza Vaccination**

- Most cases of severe illness and deaths associated with influenza occur in certain groups at high risk for developing secondary complications, including pneumonia.
- Such groups include the elderly, the immunocompromised, and persons with underlying chronic cardiopulmonary, renal, or metabolic disease.
- Annual administration of influenza vaccine is the most effective means for preventing influenza.
- Influenza vaccination in high-risk groups and health workers caring for them will reduce the number of pneumonia cases which could be confused with SARS.

Influenza Surface Proteins

- Neuraminidase
- Hemagglutinin
- RNA
- M₂ protein (only on type A)

The Role of Viral Hemagglutinin

A. Binding to Sialic Acid
B. Engulfing Virus
C. Uncoating and Virus Replication
**Viral Resistance**

Caused by point mutations in viral $M_2$ protein gene

Associated with therapeutic use of amantadine and rimantadine (10%-30%)

Causes disease comparable to “wild” virus

Can be transmitted within households

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**Recommended daily dosage of influenza antiviral medications for treatment and prophylaxis**

<table>
<thead>
<tr>
<th>Antiviral agent</th>
<th>1–6</th>
<th>7–9</th>
<th>10–12</th>
<th>13–64</th>
<th>≥65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine* Treatment, influenza A</td>
<td>5 mg/kg/day up to 150 mg in two divided doses†</td>
<td>5 mg/kg/day up to 150 mg in two divided doses†</td>
<td>100 mg twice daily‡</td>
<td>100 mg twice daily‡</td>
<td>≤100 mg/day</td>
</tr>
<tr>
<td>Prophylaxis, influenza A</td>
<td>5 mg/kg/day up to 150 mg in two divided doses†</td>
<td>5 mg/kg/day up to 150 mg in two divided doses†</td>
<td>100 mg twice daily‡</td>
<td>100 mg twice daily‡</td>
<td>≤100 mg/day</td>
</tr>
<tr>
<td>Rimantadine† Treatment, ‡ influenza A</td>
<td>NA‖</td>
<td>NA</td>
<td>NA</td>
<td>100 mg twice daily§</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>Prophylaxis, influenza A</td>
<td>5 mg/kg/day up to 150 mg in two divided doses†</td>
<td>5 mg/kg/day up to 150 mg in two divided doses†</td>
<td>100 mg twice daily‡</td>
<td>100 mg twice daily‡</td>
<td>100 mg/day¶</td>
</tr>
<tr>
<td>Zanamivir*** Treatment, influenza A and B</td>
<td>NA</td>
<td>10 mg twice daily</td>
<td>10 mg twice daily</td>
<td>10 mg twice daily</td>
<td>10 mg twice daily</td>
</tr>
<tr>
<td>Oseltamivir Treatment, influenza A and B</td>
<td>Dose varies by child’s weight</td>
<td>Dose varies by child’s weight</td>
<td>Dose varies by child’s weight</td>
<td>75 mg twice daily</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>Prophylaxis, influenza A and B</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>75 mg/day</td>
<td>75 mg/day</td>
</tr>
</tbody>
</table>

Older Antiviral Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Amantadine</th>
<th>Rimantadine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Interferes with replication of type A</td>
<td>Interferes with replication of type A</td>
</tr>
<tr>
<td></td>
<td>No activity against type B</td>
<td>No activity against type B</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Administer within 48 hrs to reduce severity and</td>
<td>Administer within 48 hrs to reduce severity and</td>
</tr>
<tr>
<td></td>
<td>shorten duration of illness</td>
<td>shorten duration of illness</td>
</tr>
<tr>
<td>Indications</td>
<td>Children and adults</td>
<td>Adults</td>
</tr>
</tbody>
</table>


Without Neuraminidase Inhibition

[Diagram showing influenza virus, neuraminidase, hemagglutinin, and human cells.]
Neuraminidase: A Conserved Site of Action

Type B

The Role of Viral Neuraminidase

With neuraminidase inhibition, virus is unable to cleave sialic acid and escape from the cell resulting in clumping, thereby preventing further spread.
### Selective Neuraminidase Inhibitors

<table>
<thead>
<tr>
<th>Tamiflu™ (oseltamivir phosphate)</th>
<th>Relenza® (zanamivir)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment in adults</td>
<td>Adults &amp; children &gt;5 yr</td>
</tr>
<tr>
<td>and children ≥1 yr</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis in adults</td>
<td></td>
</tr>
<tr>
<td>and adolescents ≥13 yrs</td>
<td></td>
</tr>
<tr>
<td><strong>Spectrum</strong></td>
<td></td>
</tr>
<tr>
<td>Type A, type B</td>
<td>Type A, type B</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>Inhaled</td>
</tr>
<tr>
<td><strong>Precaution</strong></td>
<td></td>
</tr>
<tr>
<td>Transient, mild GI effects</td>
<td>Bronchospasm precaution</td>
</tr>
</tbody>
</table>

### Naturally Occurring Influenza – Tamiflu™ (oseltamivir phosphate) Treatment Studies

- US and European clinical trials
- Fever ≥100°F
- At least 1 respiratory symptom
- At least 1 systemic symptom
- Influenza virus was present in community
- Tamiflu 75 or 150 mg twice daily × 5 days
- Treatment started within 40 hours of symptom onset*
- Complete access to antipyretic medication

*Efficacy of Tamiflu™ (oseltamivir phosphate) in patients who begin treatment after 40 hours of symptoms has not been established.

Naturally Occurring Influenza – Symptom Assessment

Subjects assessed symptoms
None, mild, moderate, severe
Time to improvement: Period from when treatment was started until symptoms were rated as none or mild

Naturally Occurring Influenza – Results – Population

849 influenza-infected subjects
Median age 34 years (18 to 65 years)
Influenza A: 95%
Influenza B: 3%
Influenza type unknown: 2%

TAMIFLU TREATMENT OF INFLUENZA: Adults

50% ↓ complications + antibiotic use

Treanor et al. JAMA 283:1016, 2000

TAMIFLU TREATMENT OF INFLUENZA: Adults

total duration of influenza illness is reduced with early intervention of Tamiflu

resume normal activities: 2-3 days earlier

Treanor et al. JAMA 283:1016, 2000
TAMIFLU TREATMENT OF INFLUENZA: Adults

30 - 40% ↓ severity of illness

- Placebo
- Tamiflu (40%)

Treanor et al. JAMA 283:1016, 2000

TAMIFLU TREATMENT OF INFLUENZA: Adults

59% ↓ overall hospitalizations

- Placebo
- Tamiflu (59%)

**TAMIFLU TREATMENT OF INFLUENZA: Adults**

55% ↓ in antibiotic therapy due to the incidence of influenza-related Lower Respiratory Tract Complications (LRTCs)

[Graph showing comparison between Placebo and Tamiflu treatments with 55% decrease in LRTCs leading to antibiotic use]


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**Oseltamivir Treatment in Children: Study Population**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 351)</th>
<th>Oseltamivir (n = 344)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>5.3</td>
<td>5.4</td>
</tr>
<tr>
<td>Percent male</td>
<td>51%</td>
<td>50%</td>
</tr>
<tr>
<td>Median hours to Rx</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Infected (%)</td>
<td>235 (67%)</td>
<td>217 (63%)</td>
</tr>
<tr>
<td>Influenza A</td>
<td>153</td>
<td>150</td>
</tr>
<tr>
<td>Influenza B</td>
<td>82</td>
<td>67</td>
</tr>
</tbody>
</table>

Oseltamivir Treatment in Children: Rate of Secondary Illnesses


Naturally Occurring Influenza – Tamiflu™ (oseltamivir phosphate) Adverse Events*

Population (N=1440) included 945 healthy young adults and 495 "at-risk" patients (elderly patients and patients with chronic cardiac or respiratory disease).

*Includes only adverse events reported in the treatment studies with frequency ≥1% in the Tamiflu 75 mg bid group compared with the placebo group.
Tamiflu™ (oseltamivir phosphate) – Types of Influenza Prophylaxis

- Postexposure – prophylaxis after exposure to influenza-infected individual(s) in household, workplace, social setting or community
- Seasonal (during community outbreak) – prophylaxis for entire influenza season
- Postvaccination – prophylaxis for 2-4 weeks after receiving influenza vaccine
- Outbreak control – prophylaxis in institutional settings after influenza confirmed as present

Tamiflu™ (oseltamivir phosphate) – Prophylaxis Clinical Overview

- Prevention of influenza in adults and adolescents ≥13 yrs
- Supported by 4 clinical trials
  - Postexposure prophylaxis (PEP trial)
  - Seasonal prophylaxis (3 adult trials)
  - Not studied in postvaccination or outbreak control
- Recommended dosage
  - 75 mg qd × ≥ 7 days (PEP)
  - 75 mg qd × 42 days (seasonal)
    • Safety and efficacy have been demonstrated for up to 6 weeks
- Tamiflu must be taken within 2 days of onset of symptoms in index case (PEP trial)
Tamiflu™ (oseltamivir phosphate) for Prophylaxis – Summary – Efficacy & Safety

Reduced incidence of laboratory-confirmed clinical influenza
- From 4.4% in placebo group to 0.4% in Tamiflu group in elderly nursing home residents study (92% difference)
- From 12% in placebo group to 1% in Tamiflu group in postexposure prophylaxis in household contacts study (92% difference)
- From 4.8% in placebo group to 1.2% in Tamiflu group in healthy unvaccinated adult studies (76% difference)

Adverse events most frequently reported were nausea, vomiting, and headache

No clinically relevant differences in safety observed between elderly and younger adults given Tamiflu; Safety and efficacy demonstrated in elderly nursing home residents who took Tamiflu for up to 42 days
**Tamiflu™ (oseltamivir phosphate) for Prophylaxis Summary – Indications & Dosage**

**Indication:** adults and adolescent ≥13 year of age

**Recommended dosage:**
- Following close contact with infected individual: 75 mg once daily for at least 7 days
- Seasonal (during community outbreak): 75 mg once daily
- Protection lasts as long as dosing is continued

No dosage adjustment required for adults or elderly

Tamiflu is no substitute for early annual flu vaccination per CDC’s ACIP guidelines

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**Antivirals in the Treatment and Prophylaxis of Pediatric Influenza (Cont’d)**

**Tamiflu™ (oseltamivir phosphate)**
- Inhibits viral neuraminidase
- Efficacious against influenza A and B
- Approved for treatment in patients ≥1 year of age
- Approved for prophylaxis in adult patients and adolescents 13 years and older
- Orally administered by liquid or capsule
Thank You