NOTHING TO SNEEZE AT:
INFLUENZA UPDATES

A presentation for HealthTrust Members

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Speaker Disclosure

• The presenter has no real or perceived conflicts of interest related to this presentation.

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Learning Objectives for Pharmacists

- Apply current influenza vaccine recommendations to a variety of patient situations
- Recommend influenza treatment for a patient based on specific factors, including patient age and duration of illness
- Differentiate between currently available antiviral medications, their adverse effects and contraindications
Learning Objectives for Pharmacy Technicians

- Describe methods that can be taken to prevent the spread of influenza
- Identify patients who are eligible to receive an influenza vaccine
A Brief History

1580: First documented influenza pandemic

1919: Spanish influenza pandemic

1933: Influenza A virus isolated

1938: First vaccine developed

1940s: Influenza B virus isolated

1940s: Influenza B virus isolated

1976: Amantadine licensed for influenza treatment

1999: First neuraminidase inhibitors available

Influenza Virus

2 types that cause seasonal epidemics: A and B

Influenza A

- Causes flu pandemics
- Divided into subtypes based on surface proteins hemagglutinin and neuraminidase
  - 18 hemagglutinin subtypes, 11 neuraminidase subtypes
  - "H1N1," "H3N2," etc.
- Can be further classified into groups and subgroups

Influenza B

- Two lineages – Victoria and Yamagata

Vaccines contain H1N1, H3N2, and 1-2 influenza B viruses

1. Influenza virus becomes attached to a target epithelial cell.

2. The cell engulfs the virus by endocytosis.

3. Viral contents are released. Viral RNA enters the nucleus where it is replicated by the viral RNA polymerase.

4. Viral mRNA is used to make viral proteins.

5. New viral particles are made and released into the extracellular fluid. The cell, which is not killed in the process, continues to make new virus.

Signs and Symptoms

- Fever/chills
- Cough
- Sore throat
- Muscle aches
- Headache
- Fatigue

Complications

- Secondary pneumonia
- Myocarditis
- Sinus infection
- Encephalitis
- Sepsis
- Multi-organ failure
- Death

Patients at Highest Risk for Complications

- Children <2 years old
- Adults >65 years old
- Chronic conditions
  - Pulmonary, cardiovascular, renal, hepatic, hematologic, or metabolic disorders
  - Neurologic or neurodevelopment conditions including stroke and epilepsy
- Immunosuppression
  - May be caused by medications or HIV infection
- Pregnant women or women ≤ 2 weeks postpartum
- Children and adolescents up to 18 years old receiving aspirin- or salicylate-containing medications
- American Indian/Alaska Native people
- Extreme obesity (BMI >40 kg/m²)
- Nursing home or other chronic care facility residents

Current Influenza Activity

2019-20 Influenza Season Week 52 ending Dec 28, 2019

ILI Activity Level
- High
- Moderate
- Low
- Minimal
- Insufficient Data

Influenza Burden

2017-2018

- 45 million illnesses
- 21 million medical visits
- 810,000 hospitalizations
- 61,000 deaths

Vaccination prevented...

- 6.2 million illnesses
- 3.2 million medical illnesses
- 91,000 hospitalizations
- 5,700 deaths

Best Treatment: Prevention

- Vaccination
- Good hygiene
- Pre-exposure prophylaxis
- Post-exposure prophylaxis

ACIP* Recommendations for 2019-2020

Basically everybody older than 6 months

- Any age-appropriate flu vaccine
- Two doses, four weeks apart for those 6 months to 8 years who have never been vaccinated

Contraindications

- History of severe allergic reaction to any component of vaccine or a previous dose of influenza vaccine

Precautions

- Moderate or severe acute illness with or without fever
- History of Guillain-Barre Syndrome (GBS) within 6 weeks after receipt of influenza vaccine


*ACIP: Advisory Committee on Immunization Practices
Updates to ACIP* Recommendations for 2019-2020

Afluria®
- Indication age range updated
  - Formerly indicated for ages 5 years and older
  - Now approved for ages 6 months and up
- 0.25 mL dose for ages 6-35 months, 0.5 mL dose for ages 36 months and older
- Quadrivalent vaccine

Fluzone®
- Dosing information updated
  - Formerly 0.25 mL dose recommended for ages 6-35 months
  - Now 0.5 mL dose recommended for all children, including those younger than 35 months
- Quadrivalent vaccine

*ACIP: Advisory Committee on Immunization Practices

Vaccines Available

- Trivalent
- Quadrivalent
- Live
- High-dose
- Adjuvanted
- Cell culture-based
- Egg-based
- Recombinant

Source: Centers for Disease Control and Prevention.
<table>
<thead>
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<th>Vaccine Product</th>
<th>Virus</th>
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Live Influenza Vaccine

Contraindications slightly different

- Concomitant aspirin or salicylate-containing therapy in children and adolescents
- Children ages 2-4 years with asthma or a wheezing episode in the last 12 months
- Immunocompromised patients of all ages
- Close contacts of a severely immunosuppressed person who requires a protected environment
- Pregnancy
- Receipt of influenza antivirals within the last 48 hours

Additional precautions

- Those with asthma
- Those with other chronic medical conditions (pulmonary, cardiovascular, renal, hepatic, neurologic, hematologic, or metabolic disorders)

Egg Allergy?

Not a contraindication!

- Patients with an egg allergy should receive any licensed, recommended influenza vaccine appropriate for their age and health status

Severe reaction (anaphylaxis)

- Supervise administration in inpatient or outpatient setting
- No set duration, but ACIP recommends observing all patients for 15 minutes after vaccination in the event of syncope

Vaccines that don't contain eggs

- Flucelvax®
- Flublok®

RM is a 17-year-old healthy female who has not had her flu vaccine this season. Her current medications include budesonide-formoterol for asthma. She has no allergies and has never had a reaction to an influenza vaccine. Which of the following would be an appropriate choice for her this season?

- a. Afluria® - inactivated quadrivalent influenza vaccine
- b. FluMist® - live attenuated quadrivalent influenza vaccine
- c. Fluzone High-Dose® - inactivated trivalent influenza vaccine
- d. RM does not need an influenza vaccine this season
RM is a 17-year-old healthy female who has not had her flu vaccine yet. Her current medications include budesonide-formoterol for asthma. She has no allergies and has never had a reaction to an influenza vaccine. Which of the following would be an appropriate choice for her this season?

- a. Afluria® - inactivated quadrivalent influenza vaccine
- b. FluMist® - live attenuated quadrivalent influenza vaccine
- c. Fluzone High-Dose® - inactivated trivalent influenza vaccine
- d. RM does not need an influenza vaccine this season
Pre-Exposure Prophylaxis Candidates

For the duration of flu season:

- ≥3 months old at highest risk of complications
  - Stem cell transplant recipients
  - Lung transplant recipient
- ≥3 months with very high risk of complications
  - Vaccine contraindicated or unavailable
  - Vaccine not expected to be effective

For short-term prophylaxis:

- ≥3 months old at high risk of developing complications
  - Vaccine has not yet been administered, but there is influenza activity in community
- Unvaccinated patients ≥3 months
  - If in close contact with people at high risk of developing complications
  - If those in close contact cannot take chemoprophylaxis

Pre-Exposure Prophylaxis Drug Options

Oral oseltamivir

Inhaled zanamivir

Post-Exposure Prophylaxis Candidates

≥3 months with very high risk of complications

- Vaccine contraindicated or unavailable
- Vaccine not expected to be effective

Unvaccinated patients ≥3 months

- If household contacts include people at high risk of developing complications

Vaccinate when not contraindicated

Post-Exposure Prophylaxis Drug Options

- **Inhaled zanamivir**
  - Begin within 48 hours of exposure

- **Oral oseltamivir**
  - Continue for 7 days after most recent exposure

Knowledge Checkpoint 2:

Which of the following patients are eligible for influenza prophylaxis and why?

• a. A 45-year-old male with a history of a lung transplant on immunosuppression
• b. A 22-year-old male with no pertinent medical history who received a flu vaccine six weeks ago and has a roommate with influenza but no other close contacts
• c. A 67-year-old fully vaccinated female whose grandchild, who currently has the flu, visited three days ago
Knowledge Checkpoint 2 Response:

Which of the following patients are eligible for influenza prophylaxis and why?

- a. A 45-year-old male with a history of a lung transplant on immunosuppression
- b. A 22-year-old male with no pertinent medical history who received a flu vaccine six weeks ago and has a roommate with influenza but no other close contacts
- c. A 67-year-old fully vaccinated female whose grandchild, who currently has the flu, visited three days ago
When to Test for Influenza

Signs and symptoms consistent with influenza

Yes

Is the patient being admitted to the hospital?

Yes

Test and start empiric antiviral therapy

No

Will testing results influence clinical management?

Yes

No

Not indicated, consider other etiologies

Diagnose clinically and start empiric antiviral therapy as indicated

Who to Treat?

- All patients hospitalized with influenza
  • Regardless of symptom duration
- Outpatients with severe or progressive illness
  • Regardless of symptom duration
- Outpatients at high risk of complications
  • Regardless of symptom duration

Consider Treating...

Symptomatic outpatients with household contacts at high risk of developing complications

Symptomatic healthcare providers who care for patients at high risk of developing complications

Outpatients not at high risk of complications with symptom onset within 48 hours of presentation

Influenza Treatment

- Oseltamivir
- Peramivir
- Zanamivir
- Baloxavir
- Amantadine

Influenza Treatment

- Oseltamivir
- Peramivir
- Zanamivir

## Neuraminidase Inhibitors

### Indications
- Oseltamivir, zanamivir: influenza treatment and prophylaxis
- Peramivir: influenza treatment only

### Adverse effects
- Headache
- Sore throat
- Decreased appetite
- Vomiting
- Diarrhea

### Warnings and precautions
- Allergic and skin reactions including Stevens-Johnson syndrome
- Neuropsychiatric events: abnormal behavior, delirium, hallucinations, self-harm

Sources: Oseltamivir [package insert]. South San Francisco, CA.
Peramivir [package insert]. Summit, NJ.
Zanamivir [package insert]. Research Triangle Park, NC.
Mechanism of Action

1. Influenza virus becomes attached to a target epithelial cell.
2. The cell engulfs the virus by endocytosis.
3. Viral contents are released. Viral RNA enters the nucleus where it is replicated by the viral RNA polymerase.
4. Viral mRNA is used to make viral proteins.
5. New viral particles are made and released into the extracellular fluid. The cell, which is not killed in the process, continues to make new virus.

Oseltamivir

Administered orally

Indicated for treatment in patients 2 weeks and older, prophylaxis in 1 year and older

Renally adjusted (CrCl <60 mL/min)

Prophylaxis: 75 mg once daily

Treatment: 75 mg twice daily

Treatment duration: 5 days

Preferred agent for pregnant patients, <2 weeks postpartum

Source: Oseltamivir [package insert]. South San Francisco, CA.
Zanamivir

Administered via inhalation

Indicated for patients 5 years and older

Prophylaxis: 10 mg (two inhalations) once daily

Treatment: 10 mg (two inhalations) twice daily

Treatment duration: 5 days

Source: Zanamivir [package insert]. Research Triangle Park, NC.
Peramivir

Administered intravenously

Indicated for patients 2 years and older

Renally adjusted (CrCl <60 mL/min)

Uncomplicated influenza: 600 mg once (12 mg/kg for ages 2-12)

Hospitalized patients: 600 mg once daily for 5-10 days*

CM is a 67-year-old female with a BMI of 42 kg/m² and CrCl ~65 mL/min who has not received a vaccine yet this season. You determine that she requires post-exposure prophylaxis. Her most recent exposure was today. Which of the following regimens should CM receive?

- a. Peramivir 600 mg IV x 1 dose
- b. Oseltamivir 75 mg po daily for 7 days
- c. Oseltamivir 75 mg po BID for 5 days
- d. Zanamivir 10 mg inhalation BID for 7 days
CM is a 67-year-old female with a BMI of 42 kg/m² and CrCl ~65 mL/min who has not received a vaccine yet this season. You determine that she requires post-exposure prophylaxis. Her most recent exposure was today. Which of the following regimens should CM receive?

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- d. Zanamivir 10 mg inhalation BID for 7 days
Baloxavir

**Indication**
- Influenza treatment only

**Adverse effects**
- Diarrhea
- Nasopharyngitis

**Warnings and precautions**
- Hypersensitivity
- Anaphylaxis
- Angioedema

No official recommendation from IDSA 2018 guidelines on influenza treatment for baloxavir, since it was approved after the guidelines were finalized.

Baloxavir

Prodrug (baloxavir marboxil)

Cap-dependent endonuclease inhibitor

- Inhibits polymerase acidic protein activity to inhibit virus replication

Has activity against influenza A and B viruses

- Even those resistant to other antivirals

Mechanism of Action

1. Influenza virus becomes attached to a target epithelial cell.
2. The cell engulfs the virus by endocytosis.
3. Viral contents are released. Viral RNA enters the nucleus where it is replicated by the viral RNA polymerase.
4. Viral mRNA is used to make viral proteins.
5. New viral particles are made and released into the extracellular fluid. The cell, which is not killed in the process, continues to make new virus.

Baloxavir

Administered orally

For patients 40 to <80 kg: 40 mg x 1 dose

For patients 80 kg or more: 80 mg x 1 dose

Indicated for patients 12 years and older

No renal or hepatic adjustments

Source: Baloxavir [package insert]. South San Francisco, CA.
CAPSTONE-1 Trial

Double-blind, placebo- and oseltamivir-controlled, randomized trial

Inclusion criteria

• Outpatients with influenza-like illness in the US and Japan from December 2016 - March 2017
• Fever plus at least one systemic symptom and one respiratory symptom of influenza
• Symptom duration no longer than 48 hours

Exclusion criteria

• Patients receiving any other influenza treatment except acetaminophen (symptomatic management, antivirals, or antibiotics)

CAPSTONE-1 Trial

Adults 20-64 years old received:

- Baloxavir x 1 dose
- Oseltamivir 75 mg BID x 5 days
- Matching placebos

Patients 12-19 years old received:

- Baloxavir x 1 dose
- Matching placebo

CAPSTONE-1 Trial

Primary outcome: time to alleviation of symptoms

- Significantly shorter in baloxavir group compared to placebo
- No significant difference between baloxavir- and oseltamivir-treated patients
- Effect consistent among adolescents and adults
- Greater difference in patients who initiated therapy within 24 hours

Secondary outcomes

- Time to resolution of fever
- Time to return to usual health
- Newly occurring complications leading to antibiotic use

## CAPSTONE-1 Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baloxavir</th>
<th>Placebo</th>
<th>Oseltamivir</th>
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<tbody>
<tr>
<td>Time to alleviation of symptoms</td>
<td>53.5 hours*</td>
<td>80.2 hours</td>
<td>53.8 hours*</td>
</tr>
<tr>
<td>Time to resolution of fever</td>
<td>24.5 hours*</td>
<td>42 hours</td>
<td></td>
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<tr>
<td>Time to return to usual health</td>
<td>129.2 hours</td>
<td>168.8 hours</td>
<td></td>
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<tr>
<td>Frequency of complications resulting in antibiotic treatment</td>
<td>3.5%</td>
<td>4.3%</td>
<td>2.4%</td>
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<tr>
<td>Duration of infectious virus detection</td>
<td>24 hours*</td>
<td>96 hours</td>
<td>72 hours</td>
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<tr>
<td>Rate of adverse events related to trial regimen</td>
<td>4.4%*</td>
<td>3.9%</td>
<td>8.4%</td>
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*statistically significantly different

CAPSTONE-1 Trial

- Single doses of baloxavir superior to placebo in reducing influenza symptoms
- Fewer clinically significant adverse effects
- Initiating therapy early resulted in faster symptom improvement compared to placebo
- Antiviral activity of baloxavir superior to oseltamivir

CAPSTONE-2 Trial

Randomized, double-blind, placebo- and oseltamivir-controlled study

- Included patients at high risk of influenza complications
- 2184 patients included
- Faster relief of symptoms with baloxavir over placebo, no difference compared to oseltamivir
- No difference in influenza complications among three groups

Full study has not yet been published

- Suggests baloxavir may be useful for patients at risk of influenza complications

Source: Ison MG et al. Presented at ID Week 2018; San Francisco, CA.
Baloxavir resistance

"Cause for concern"

- Decreased viral RNA levels at 24 hours
- Shorter duration of infectious virus detection
- Emergence of viral escape mutants with reduced susceptibility to the drug

Viral mutants appeared in up to 10% of patients studied

- Typically appeared at least 5 days after baloxavir treatment
- Duration of symptoms significantly longer when viral escape mutants were present

Role of the Pharmacist

- Appropriate vaccine selection
- Identification of patients at high risk of complications
- Appropriate prophylaxis and treatment selection
Summary

Vaccinate almost everybody

- Very few contraindications to the influenza vaccine
- Select an age-appropriate, ACIP-recommended vaccine

Prophylaxis should be initiated in patients at high risk of complications

- Depending on vaccine history, household contacts

Treat regardless of symptom duration for any patients that are hospitalized, have severe illness, or are at high risk of complications

- For outpatients not at high risk of complications, initiate within 48 hours of symptom onset

Baloxavir not included in 2018 IDSA guidelines, but is an option for influenza treatment for some patients

- Demonstrated superiority over placebo with fewer clinically significant adverse effects than oseltamivir
References


THANK YOU!

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