LEARNING OBJECTIVES

1. Diagnose and promptly treat influenza in accordance with national guidelines and emerging evidence.

2. Appropriately utilize approved antiviral medications to better treat influenza based on efficacy and safety data, so as to reduce the symptoms, prevent associated complications, and reduce the burden of disease.

INFLUENZA VIRUS

► Orthomyxoviridae family
  - Segmented - s RNA
  - Enveloped virus
  - Helical nucleocapsid

► 3 subgroups
  - Influenza A
    - multiple subtypes
  - Influenza B
  - Influenza C

INFLUENZA SUBTYPE SURVEILLANCE (2017-18 SEASON)

PROGRAM OVERVIEW

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**BACTERIAL CO-INFECTION**

**CLINICAL CONSIDERATIONS**

**CLINICAL TIPS**
- Symptoms and clinical findings should guide blood tests, cultures, and imaging studies.
- Infectious disease consult
  - Especially if the patient is severely ill or immunosuppressed.
- Expand differential diagnosis to include bacterial infection in patients whose condition deteriorates rapidly.

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**UNCOMPROMISED**

- Adults typically have fever and symptoms for about 3 days
  - Most show signs of improvement by this point.
- Complete recovery may take 10–14 days
  - Longer in older adults.

**CO-INFECTION**

- Febrile for more than 3–5 days.
- Fever that reoccurs.
- Develop fever, worsening symptoms, or progressive disease.

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**WHICH INDIVIDUALS ARE CANDIDATES FOR ANTIVIRAL TREATMENT FOR INFLUENZA?**

*Antiviral therapy is considered an important adjunct to vaccination in order to reduce the risk for severe illness from influenza among both adults and children, particularly those with underlying health conditions.*
PERSONS AT HIGHER RISK FOR INFLUENZA COMPLICATIONS
RECOMMENDED FOR ANTIVIRAL TREATMENT

- Children < 5 years old (especially those < 2 years old)
- Individuals < 19 years old receiving long-term aspirin therapy
- Adults ≥ 65 years old
- Morbidly obese persons (BMI ≥ 40 kg/m²)
- Women who are pregnant or ≤ 2 weeks postpartum
- Persons of American Indian/Alaska Native heritage
- Residents of nursing homes or other chronic care facilities
- Those who are immunosuppressed or have certain chronic medical conditions (including pulmonary, cardiovascular, renal, hematological, metabolic, neurologic, or neurodevelopmental disorders)

DO I HAVE TO TEST FOR INFLUENZA TO CONFIRM THE CLINICAL DIAGNOSIS OR TO DECIDE WHETHER TO PRESCRIBE ANTIVIRAL MEDICATIONS TO AN INDIVIDUAL WITH INFLUENZA?

A 69-year-old male with a history of CAD and hypertension presents with a 30-hour history of influenza-like illness to your office. He has an active lifestyle and lives at home with his wife.

GUIDE FOR CONSIDERING INFLUENZA TESTING
WHEN VIRUSES ARE CIRCULATING IN THE COMMUNITY (REGARDLESS OF INFLUENZA VACCINATION HISTORY)

https://www.cdc.gov/flu/professionals/diagnosis/consider-influenza-testing.htm

- Does the patient have signs/symptoms suggestive of influenza, including atypical clinical presentation or findings suggestive of complications associated with influenza?
  - Yes
  - Is the patient being admitted to the hospital?
    - Yes
      - Test for influenza
      - Start empiric antiviral treatment for hospitalized patients while results are pending
      - Will influenza testing results influence clinical management?
        - Yes
          - Influenza clinically diagnosed
          - Advise close follow-up if worsening
        - No
          - Influenza testing probably NOT indicated
          - Consider other etiologies
    - No
      - Influenza testing probably NOT indicated
      - Consider other etiologies
INFLUENZA DIAGNOSTIC TESTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Time to Results</th>
<th>Performance</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid diagnostic test</td>
<td>Antigen detection</td>
<td>&lt; 15 min</td>
<td>Low to moderate sensitivity; High specificity</td>
<td>ALL TESTS: Negative results may not rule out influenza; most assays are approved for point-of-care use</td>
</tr>
<tr>
<td>Rapid molecular assay</td>
<td>Viral RNA detection</td>
<td>15-30 min</td>
<td>Moderate to high sensitivity; High specificity</td>
<td>Immunofluorescence assay requires trained laboratory personnel with fluorescent microscope in a moderately sophisticated clinical laboratory</td>
</tr>
<tr>
<td>Immunofluorescence assay</td>
<td>Antigen detection</td>
<td>1-4 hours</td>
<td>Moderate sensitivity; High specificity</td>
<td></td>
</tr>
<tr>
<td>Molecular assay</td>
<td>Viral RNA detection</td>
<td>60-80 min for some assays; up to 4-6 h for others</td>
<td>High sensitivity; High specificity</td>
<td></td>
</tr>
<tr>
<td>Tissue cell viral culture</td>
<td>Virus isolation</td>
<td>3-10 days</td>
<td>High sensitivity; High specificity</td>
<td></td>
</tr>
</tbody>
</table>

Molecular assays are the most accurate influenza tests

INFLUENZA TESTING CONSIDERATIONS IN HOSPITALIZED PATIENTS

- All hospitalized patients with suspected influenza should be tested with molecular assays.

- Molecular assays can detect influenza viral nucleic acids in respiratory specimens for longer periods and with much higher accuracy than antigen detection assays.

- If testing of upper respiratory tract yields a negative result:
  - Collect specimens from lower respiratory tract.
  - Viral shedding in the lower respiratory tract may be detectable for longer periods than in the upper respiratory tract.

- If the patient is critically ill on invasive mechanical ventilation and has tested negative for influenza viruses on an upper respiratory tract specimen:
  - Collect a lower respiratory tract specimen (endotracheal aspirate or bronchoalveolar lavage fluid).

Influenza testing is NOT needed to confirm the clinical diagnosis or to decide whether to prescribe antiviral medications to a patient when influenza viruses are circulating in the community.

WHEN SHOULD I START ANTIVIRALS TO TREAT INFLUENZA?
WHEN TO START ANTIVIRALS

OUTPATIENTS WITH UNCOMPLICATED INFLUENZA

- Established efficacy of early (≤ 48 hours after illness onset) NAI treatment
- Reduce the duration of illness by approximately 0.6–1 day

OUTPATIENTS WITH SUSPECTED OR CONFIRMED INFLUENZA IN A GROUP AT HIGH RISK FOR COMPLICATIONS AND FOR THOSE WITH PROGRESSIVE DISEASE WHO DO NOT REQUIRE HOSPITALIZATION

- Antiviral treatment is recommended even if > 48 hours have passed since illness onset

WHEN TO START ANTIVIRALS

OTHERWISE HEALTHY PERSONS WITH SUSPECTED OR CONFIRMED UNCOMPLICATED INFLUENZA WHO ARE NOT AT HIGH RISK FOR COMPLICATIONS AND WHO PRESENT WITHIN 48 HOURS OF ILLNESS ONSET

- Clinical judgment can be used to decide whether to prescribe antiviral treatment

MORTALITY IS REDUCED WHEN TREATMENT IS INITIATED EARLY

Reduced mortality in adult patients admitted to hospital with influenza A H1N1pdm09 virus infection

- Early NAI treatment (within 2 days)
- Treated day 3
- Treated day 4
- Treated day 5
- Treated after day 5

CDC recommends to start antiviral treatment as soon as possible (ideally within 48 hours) after illness onset without waiting for the results of influenza testing

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However... Clinicians infrequently prescribe antiviral treatment in the outpatient settings (2011-2016 influenza seasons)

<table>
<thead>
<tr>
<th>Year</th>
<th>All High-Risk Patients Prescribed Neuraminidase Inhibitor (NAI)</th>
<th>High-Risk Patients Presenting Early</th>
<th>High-Risk Patients Presenting Early With Laboratory Confirmed Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-2012</td>
<td>9%</td>
<td>9%</td>
<td>36%</td>
</tr>
<tr>
<td>2012-2013</td>
<td>3%</td>
<td>9%</td>
<td>43%</td>
</tr>
<tr>
<td>2013-2014</td>
<td>7%</td>
<td>15%</td>
<td>43%</td>
</tr>
<tr>
<td>2014-2015</td>
<td>8%</td>
<td>10%</td>
<td>39%</td>
</tr>
<tr>
<td>2015-2016</td>
<td>5%</td>
<td>12%</td>
<td>35%</td>
</tr>
</tbody>
</table>

37% of high-risk patients with rRT-PCR-confirmed influenza received a prescription for an antiviral medication.

Which antivirals should I use to treat influenza?

**Antivirals for Influenza**

- Neuraminidase inhibitors
- Adamantanes
- Cap-dependent endonuclease inhibitor

**Mechanism of Action of Neuraminidase Inhibitors**

HIGH-RISK PATIENTS = < 2 years of age; ≥ 65 years; pregnant women; those with extreme obesity (BMI ≥ 40 kg/m²); those with documentation of chronic underlying health condition(s) that increase the risk of influenza-associated complications; and Native Americans, Alaska Natives, and Native Hawaiians.


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NEURAMINIDASE INHIBITORS (NAIs)

Have activity against both influenza A and B viruses

<table>
<thead>
<tr>
<th>Neuraminidase Inhibitors</th>
<th>Dosage</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir (Tamiflu)</td>
<td>30, 45, 75 mg caps</td>
<td>5 mg/blist for inhalation</td>
</tr>
<tr>
<td></td>
<td>6 mg/mL oral suspension</td>
<td>200 mg/20 mL single-use vials</td>
</tr>
<tr>
<td>Zanamivir (Relenza)</td>
<td>10-45 mg caps</td>
<td>5 mg/blist for inhalation</td>
</tr>
<tr>
<td></td>
<td>Inhale</td>
<td>2 inhalations BID x 5 days</td>
</tr>
<tr>
<td>Peramivir (Rapivab)</td>
<td>200 mg/20 mL single-use vials</td>
<td>Intravenously</td>
</tr>
</tbody>
</table>

*Generic: $98.60, Tamiflu: $151.90, Zanamivir: $59.00, Peramivir: $950.00*

NEURAMINIDASE INHIBITORS (NAIs)
UNCOMPLICATED INFLUENZA

**Oseltamivir (Tamiflu)**
- Adult dosage: 75 mg PO BID x 5 days
- Pediatric dosage: 30-75 mg PO BID x 5 days
- Dosage of renal impairment: Adults: CrCl 30-60 mL/min: 30 mg BID
- **Zanamivir (Relenza)**
- Adult dosage: 2 inhalations BID x 5 days
- Pediatric dosage: 30-75 mg PO BID x 5 days
- Dosage of renal impairment: Adults: CrCl 30-60 mL/min: 30 mg QD
- **Peramivir (Rapivab)**
- Adult dosage: 600 mg IV once
- Pediatric dosage: 60 mg/kg (max 600 mg) IV once
- Dosage of renal impairment: Adults: CrCl 30-60 mL/min: 200 mg once

**Dosage of renal impairment**
- Adults: CrCl 30-60 mL/min: 30 mg BID
- Pediatric: CrCl 30-49 mL/min: 4 mg/kg once
- Pediatric: CrCl 10-29 mL/min: 2 mg/kg once
- **≥ 13 yrs**
- Adults: CrCl 30-60 mL/min: 200 mg once
- Pediatric: CrCl 10-29 mL/min: 100 mg once
- No dosage adjustment required

NAI EFFICACY

**DECREASE THE TIME TO FIRST ALLEVIATION OF SYMPTOMS OF INFLUENZA-LIKE ILLNESS BY…**

- **Oseltamivir**
  - Adults: 16.8 - 17.8 hours
  - Children: 29 hours
- **Zanamivir**
  - Adults: 14.4 hours
  - Children: Not significant

ARE THERE ANY CONTRAINDICATIONS OR ADVERSE EFFECTS THAT I SHOULD CONSIDER WITH NAIS?


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A pregnant 34-year-old female with a history of asthma (on daily inhaler use) presents with about 24 hours of influenza-like illness. You decide to treat her with an antiviral.

**PREGNANCY**
- Pregnancy category C drugs
- Oseltamivir is recommended over inhaled zanamivir
  - Lower lung volumes in pregnancy → reduced zanamivir distribution and potential bronchospasm
- Oseltamivir treatment is safe and not associated with any adverse pregnancy or birth outcomes.

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CDC advises that pregnancy should NOT be considered a contraindication to influenza antivirals.

**ADAMANTANES**

- Amantadine (Symmetrel) & rimantadine (Flumadine)
- Active against influenza A viruses but NOT influenza B viruses
- High levels of resistance (> 99%) to adamantanes among circulating influenza A(H3N2) and influenza A(H1N1)pdm09 (“2009 H1N1”) viruses in past seasons

NOT RECOMMENDED
for antiviral treatment or chemoprophylaxis of currently circulating influenza A viruses

**BALOXAVIR MARBOXIL (XOFLUZA)**

- Effective against influenza A and B & avian-origin H5N1 and H7N9 influenza viruses
- Oral single dose
- Adults and children > 12 years old
- Symptomatic for ≤ 48 hours
- More effective if given as soon possible (within 24 hours of symptom onset)


**CAP-DEPENDENT ENDONUCLEASE INHIBITOR MECHANISM OF ACTION**

CAP-dependent endonuclease inhibitor (Baloxavir Marboxil)

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**Baloxavir Marboxil (Xofluza) Was Associated With Significantly More Rapid Declines in Viral Load Than Placebo or Oseltamivir**

![Graph showing more rapid declines in viral load](image)

**Baloxavir Marboxil (Xofluza) Decreased Duration of Flu Symptoms and Duration of Fever**

![Graph showing decreased duration of symptoms and fever](image)

**Baloxavir Marboxil (Xofluza) Safety**

<table>
<thead>
<tr>
<th>Any Adverse Event</th>
<th>Baloxavir Marboxil (%)</th>
<th>Placebo (%)</th>
<th>Oseltamivir (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.6%</td>
<td>24.8%</td>
<td>20.7%</td>
<td></td>
</tr>
</tbody>
</table>

**Antiviral Resistance**

- Resistance to oseltamivir, zanamivir, and peramivir among circulating influenza viruses is currently low (can change anytime)
- Resistance can emerge during or after treatment in some patients (e.g., immunocompromised)
  - Weekly surveillance data on antiviral resistance this season
  - FluView U.S. Influenza Surveillance Report
    [https://www.cdc.gov/flu/weekly/index.htm](https://www.cdc.gov/flu/weekly/index.htm)

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A 71-year-old male with chronic lymphocytic leukemia (on chemotherapy) calls your office to inform you that his friend came down with influenza today, the day after they spent an entire day together (two days ago). He asks whether he should be tested or treated for influenza.

**CHEMOPROPHYLAXIS WITH NAIs**

NAIs are approximately 70% to 90% effective in preventing influenza, however...

**CDC does NOT recommend routine seasonal or pre- and post-exposure antiviral chemoprophylaxis**

Except in the following situations...

- Prevention of influenza in persons at high risk of influenza complications
  - During the first two weeks following vaccination after exposure to a person with influenza
  - Who cannot receive influenza vaccine due to a contraindication after exposure to a person with influenza.
- Prevention for people with severe immune deficiencies or others who might not respond to influenza vaccination, such as persons receiving immunosuppressive medications, after exposure to a person with influenza
- Control outbreaks among high risk persons in institutional settings

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
**CHEMOPROPHYLAXIS WITH NAIS**

### Timing of Treatment

- Generally not recommended if more than 48 hours have elapsed since the first exposure to a person with influenza.
- Antiviral medication must be taken each day for the duration of potential exposure to a person with influenza.
- Continued for 7 days after the last known exposure.

### Alternative to Chemoprophylaxis

- Close monitoring and early initiation of antiviral treatment if fever and/or respiratory symptoms develop.

### Chemoprophylaxis with NAIs

- **Oseltamivir** (Tamiflu)
  - 75 mg PO once/day x 7 days
  - Not FDA-approved for prophylaxis

- **Zanamivir** (Relenza)
  - 2 inhalations once/day x 7 days
  - ≥ 5 yrs: 2 inhalations once/day x 7 days

- **Peramivir** (Rapivab)
  - Not FDA-approved for prophylaxis

### Pediatric Dosage

- Adults: CrCl 30-60 mL/min: 30 mg QD
- CrCl > 10-30 mL/min: 30 mg every other day

### Dosage for Renal Impairment

- No dosage adjustment required

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WHEN SHOULD I CONSULT AN INFECTIOUS DISEASE EXPERT?

CONSULT AN INFECTIOUS DISEASE EXPERT WHEN...

DIAGNOSIS

- Seriously ill patients in whom influenza is suspected but unproven
- Atypical presentations
- Severe complications are suspected
- Broad differential diagnosis
  - e.g., immunosuppressed patients with pneumonia

TREATMENT

- Guide the use of antiviral agents
- Help determine the need for antimicrobial agents
- If antiviral resistance is suspected
- Help manage severely immunosuppressed patients
- Guide use of investigational antivirals either through a clinical trial or for compassionate use

Let's review...

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.
► Influenza testing is not needed to confirm the clinical diagnosis or to decide whether to prescribe antiviral medications to a patient when influenza viruses are circulating in the community.

► CDC recommends to start antiviral treatment as soon as possible (ideally within 48 hours) after illness onset without waiting for the results of influenza testing.

► These agents are most effective if started within the first 24 hours of symptoms and less effective if begun 24-48 hours after symptoms appear.

► Antiviral treatment is recommended for all individuals with suspected or confirmed influenza who have severe, complicated, or progressive illness, require hospitalization, or are at higher risk for complications (i.e., immunosuppression, adults ≥ 65 years old, children < 5 years old, etc.).

► Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment if treatment can be initiated within 48 hours of illness onset.

► Chemoprophylaxis is not routinely recommended except in individuals in whom vaccination is contraindicated or who are not expected to benefit.

► In the U.S., only NAlIs and adamantanes are approved for treatment of influenza.

► Adamantanes are NOT recommended for treatment of influenza A virus infection.

► Pregnancy is NOT a contraindication to using NAlIs.

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