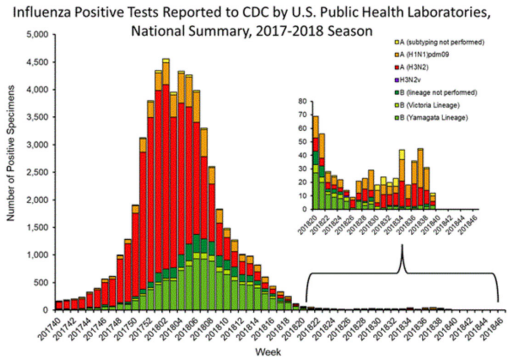
pri med | connectED LEARNING

PROGRAM OVERVIEW

- **Pre-curriculum Assessment**
- **Expert Perspective** — Available **on-demand** now
- **Pri-Med Session (Live & Simulcast)**
- **Case 1** / **Case 2** — Available **on-demand**
- **Live Audio Webcast** — **October 16** 12:00 PM - 1:00 PM ET
- **Post-curriculum Assessment**

INFLUENZA SUBTYPE SURVEILLANCE (2017-18 SEASON)



https://www.cdc.gov/flu/weekly/

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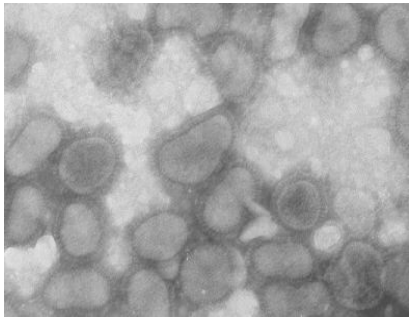
INFLUENZA VIRUS

- **Orthomyxoviridae family**
  - Segmented -s RNA
  - Enveloped virus
  - Helical nucleocapsid
- **3 subgroups**
  - Influenza A
    - multiple subtypes
  - Influenza B
  - Influenza C



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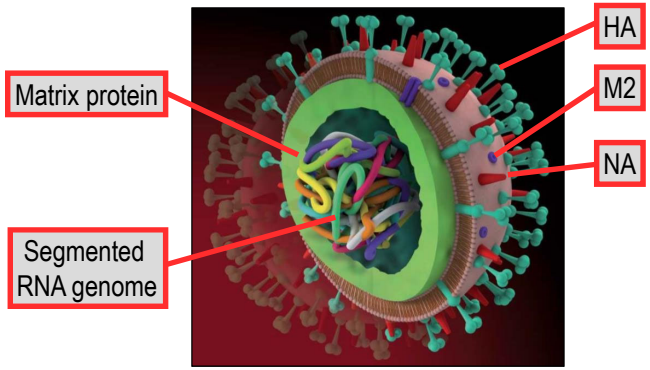
HA & NA DEFINE INFLUENZA A SUBTYPES



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Diagnosis of Influenza
Common Signs/Symptoms

Nonproductive cough

Myalgias

Headache

Fever

Not always present, including in premature and young infants, immunocompromised and immunosuppressed persons, and especially in elderly persons

Atypical presentations

- Especially infants (e.g. sepsis-like syndrome)
- Elderly (e.g. confusion)

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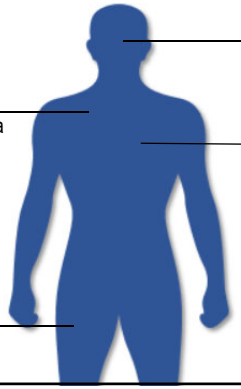
Complications of Influenza



Pulmonary

Worsening of COPD & Asthma
Pneumonia
Bronchiolitis
Croup
Respiratory failure
Invasive bacterial co-infection

Musculoskeletal

Myositis
Rhabdomyolysis

Neurologic

Encephalitis
Seizures

Cardiac

Congestive heart failure
Myocarditis
Pericarditis

Multi-organ failure

Septic shock
Renal failure
Respiratory failure

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Bacterial Co-Infection
Clinical Considerations

Bacteria

- Most commonly implicated in community-acquired pneumonia with influenza
  - *Streptococcus pneumoniae*, ***Staphylococcus aureus*** (methicillin-sensitive and methicillin-resistant)
  - ***Group A Streptococcus***[1]
- An association between bacterial meningitis due to ***Neisseria meningitidis*** and influenza has been reported[2]

(1) Shieh WJ, et al. J, et al. . Am J Pathol. 2010;177:166-75. (2) Jacobs JH, et al. PLoS One. 2014; 9:e107486

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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

(1) Shieh WJ, et al. J, et al. . Am J Pathol. 2010;177:166-75. (2) Jacobs JH, et al. PLoS One. 2014; 9:e107486

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Bacterial Co-Infection
Clinical Considerations

Uncomplicated	Co-Infection
Adults typically have fever and symptoms for about 3 days	**Febrile for more than 3–5 days**
▪ Most show signs of improvement by this point	Fever that reoccurs
Complete recovery may take 10–14 days	Develop fever, worsening symptoms, or progressive disease
▪ Longer in older adults	

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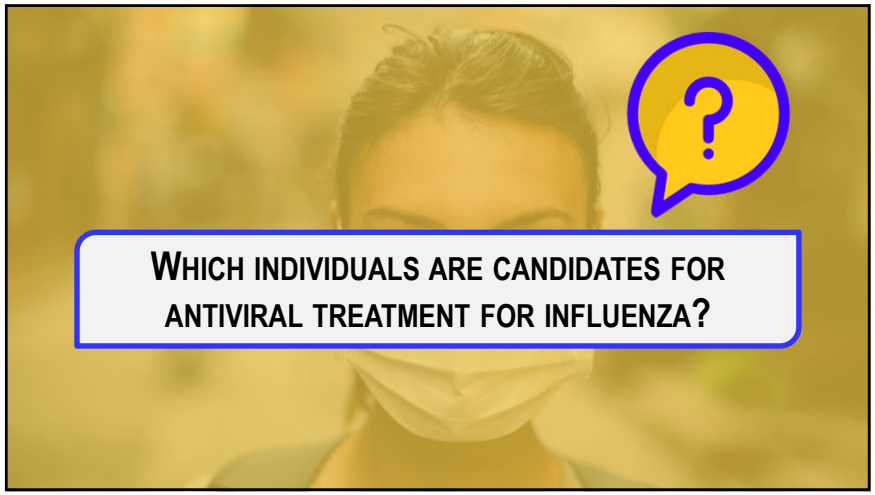
Antiviral therapy
is considered an important
adjunct to vaccination
in order to reduce the risk for severe illness from influenza among both adults and children, particularly those with underlying health conditions



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/m^2)**
- 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, hepatic, hematological, metabolic, neurologic, or neurodevelopmental disorders)

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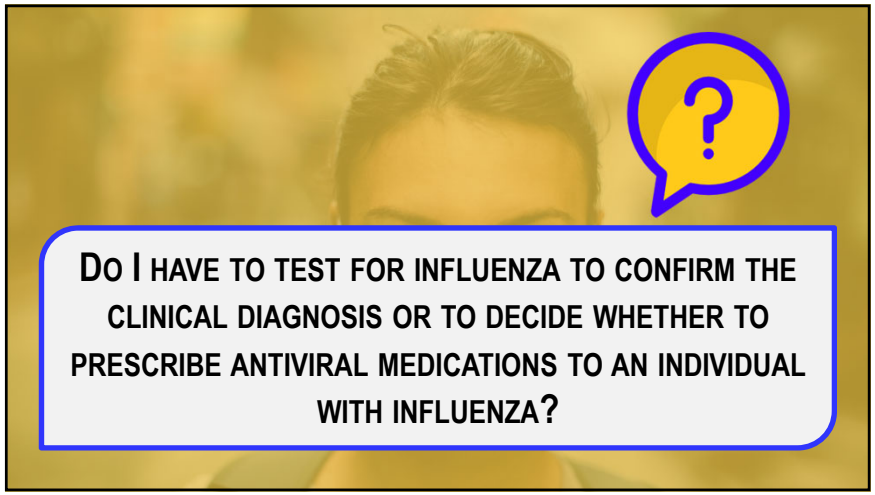
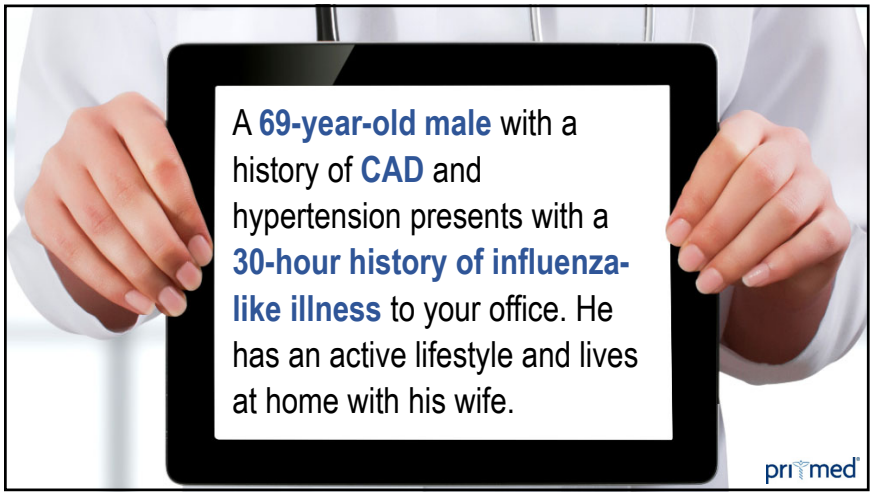
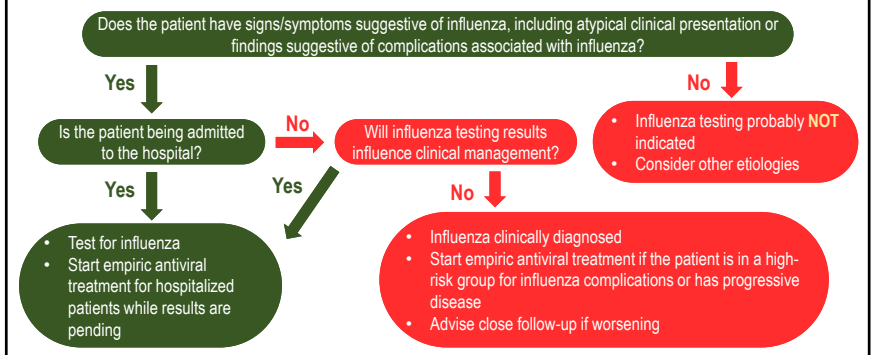




GUIDE FOR CONSIDERING INFLUENZA TESTING

WHEN VIRUSES ARE CIRCULATING IN THE COMMUNITY (REGARDLESS OF INFLUENZA VACCINATION HISTORY)



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

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INFLUENZA DIAGNOSTIC TESTS

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

Molecular assays are the most accurate influenza tests

https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm

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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)

https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm

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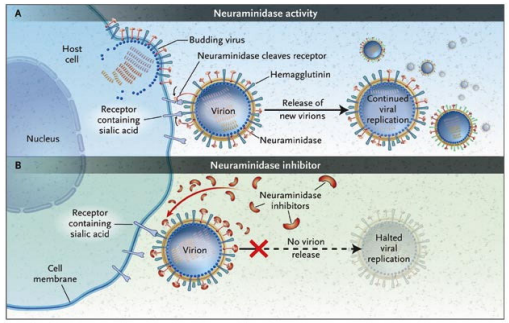
Influenza testing is NOT needed to confirm the clinical diagnosis or to decide whether to prescribe antiviral medications to a patient when influenza viruses are circulating in the community

When should I start antivirals to treat influenza?

Mechanism of Action of Neuraminidase Inhibitors



Moscona A. N Engl J Med 2005;353:1363-1373.

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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[1,2]

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

(1) Dobson J, et al. Lancet. 2015;385:1729-37. (2) Jefferson T, et al. Cochrane Database Syst Rev. 2014

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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

(1) Dobson J, et al. Lancet. 2015;385:1729-37. (2) Jefferson T, et al. Cochrane Database Syst Rev. 2014

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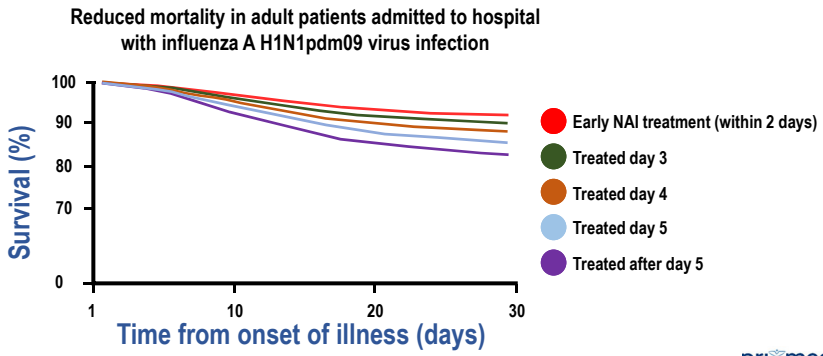
Mortality Is Reduced When Treatment Is Initiated Early



Mathuri SG, et al. Lancet Respir Med. 2014 May;2(5):395-404.

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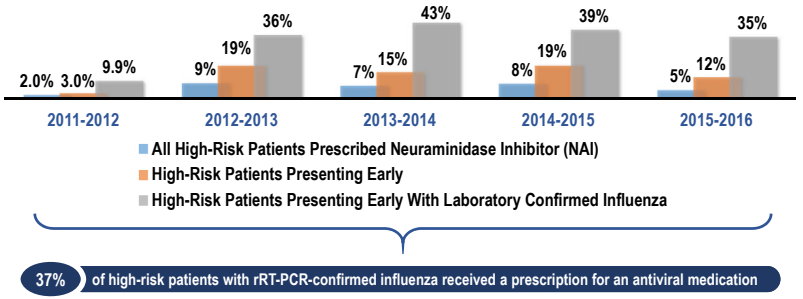
CDC recommends to
start antiviral treatment as soon as possible
(ideally within 48 hours)
after illness onset without waiting for the results of influenza testing

However… Clinicians Infrequently Prescribe Antiviral Treatment in The Outpatient Settings (2011-2016 Influenza Seasons)



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

HIGH-RISK PATIENTS = < 2 years or ≥ 65 years; pregnant women; those with extreme obesity (BMI ≥ 40 kg/m^2); 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.

Stewart RJ, Flannery B, Chung JR, Gaglani M, et al. Clin Infect Dis. 2018 Mar 19;66(7):1035-1041.

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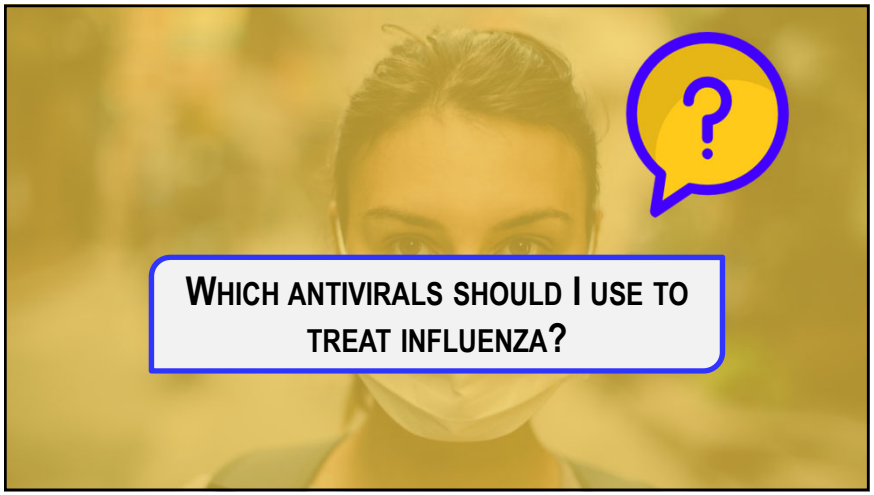

Neuraminidase Inhibitors (NAIs)

Have activity against both influenza A and B viruses

Oseltamivir (*Tamiflu*)	Zanamivir (*Relenza*)	Peramivir (*Rapivab*)
▪ 30, 45, 75 mg **caps** ▪ 6 mg/mL **oral suspension**	5 mg/blister for **inhalation**	200 mg/20 mL single-use vials **Intravenously**
Generic: $98.60 ***Tamiflu***: $151.90	$59.00	$950.00

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Neuraminidase Inhibitors (NAIs) Uncomplicated Influenza

	Oseltamivir (*Tamiflu*)	Zanamivir (*Relenza*)	Peramivir (*Rapivab*)
Adult dosage	75 mg PO BID x 5 days	2 inhalations BID x 5 days	600 mg IV once
Pediatric dosage	30-75 mg PO BID x 5 days	**≥ 7 yrs**: 2 inhalations BID x 5 days	▪ **2-12 yrs**: 12 mg/kg (max 600 mg) IV once ▪ **≥ 13 yrs**: 600 mg IV once
Dosage of renal impairment	Adults: CrCl 30-60 mL/min: 30 mg BID CrCl > 10-30 mL/min: 30 mg QD	No dosage adjustment required	**2-12 yrs** CrCl 30-49 mL/min: 4 mg/kg once CrCl 10-29 mL/min: 2 mg/kg once **≥ 13 yrs** CrCl 30-49 mL/min: 200 mg once CrCl 10-29 mL/min: 100 mg once

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

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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/professionals/antivirals/summary-clinicians.htm

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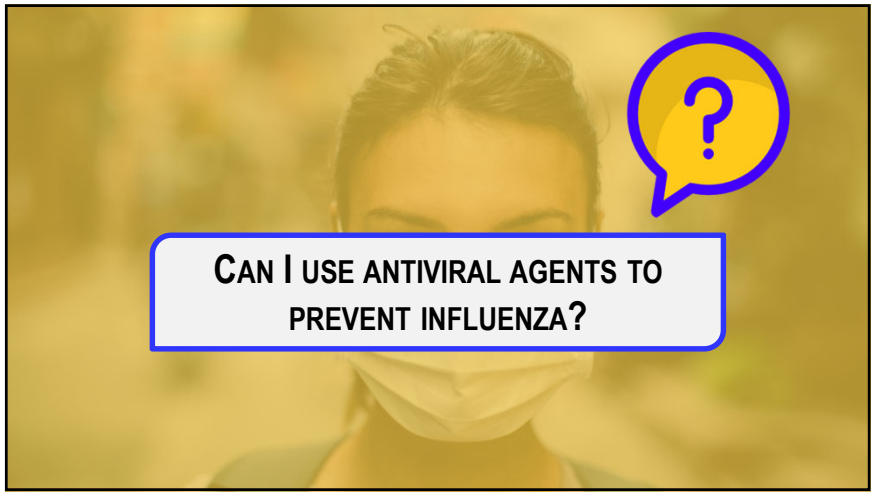

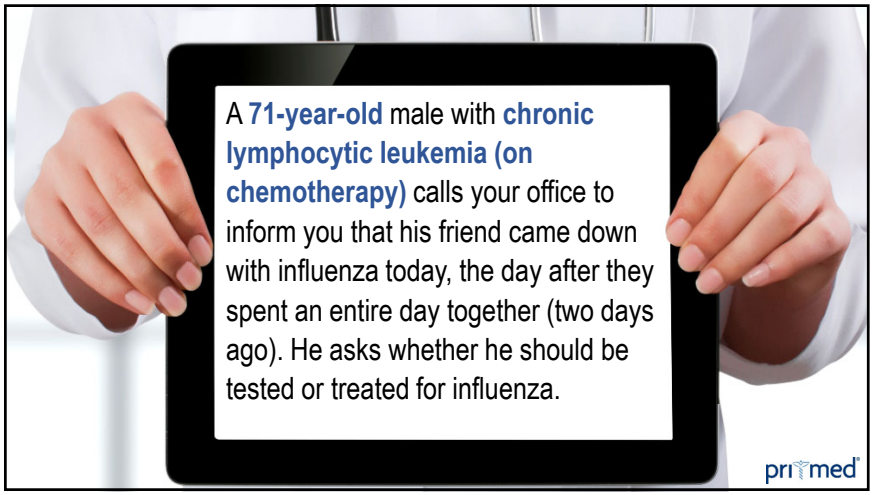

Chemoprophylaxis With NAIs

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…

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

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Chemoprophylaxis With NAIs

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

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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

(1) Dobson J, et al. Lancet. 2015;385:1729-37. (2) Jefferson T, et al. Cochrane Database Syst Rev. 2014

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Chemoprophylaxis With NAIs

Alternative to Chemoprophylaxis

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

(1) Dobson J, et al. Lancet. 2015;385:1729-37. (2) Jefferson T, et al. Cochrane Database Syst Rev. 2014

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CHEMOPROPHYLAXIS WITH NAIS

	Oseltamivir (*Tamiflu*)	Zanamivir (*Relenza*)	Peramivir (*Rapivab*)
	75 mg PO once/day x 7 days	2 inhalations once/day x 7 days	Not FDA-approved for prophylaxis
Pediatric dosage	30-75 mg PO once/day x 7 days	**≥ 5 yrs**: 2 inhalations once/day x 7 days	
Dosage for renal impairment	Adults: CrCl 30-60 mL/min: 30 mg QD CrCl > 10-30 mL/min: 30 mg every other day	No dosage adjustment required	

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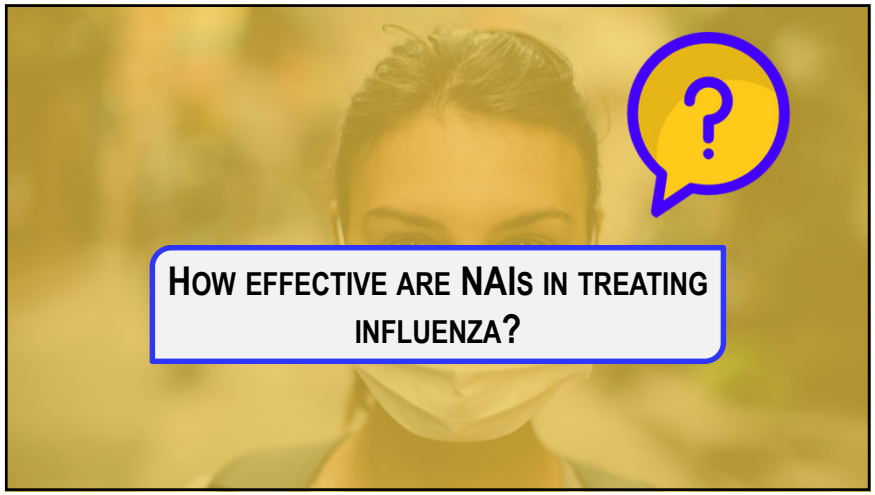
Chemoprophylaxis with NAIs
is recommended for individuals:

- ***At high risk of influenza complications***
- ***Who cannot receive influenza vaccine***
- ***Are immunocompromised***
- ***In institutional settings***



NAI EFFICACY

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

Oseltamivir

- **Adults:** 16.8 - 17.8 hours[1,2]
- **Children:** 29 hours[2]

Zanamivir

- **Adults:** 14.4 hours[2]
- **Children**: Not significant[2]

(1) Dobson J, et al. Lancet. 2015;385:1729-37. (2) Jefferson T, et al. Cochrane Database Syst Rev. 2014

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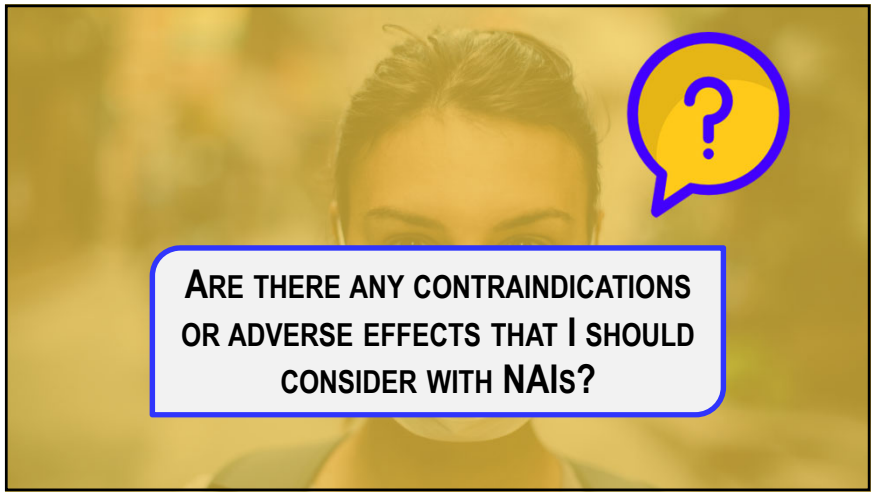

NAIs
SAFETY CONSIDERATIONS

ADVERSE EFFECTS

- **Typically mild**, although more serious side effects have been described
- **Neuropsychiatric events**
  - Self-injury and delirium
    - Cause-and-effect relationship has not been established, and neuropsychiatric dysfunction is a known complication of influenza illness itself

(1) Rasmussen SA, et al. Am J Obstet Gynecol. 2011 Jun;204(6 Suppl 1):S13-20. (2) Graner S, et al. BMJ. 2017; 356: j629. (3) Dunstan HJ, et al. BJOG. 2014 Jun;121(7):901-6.

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NAIs
SAFETY CONSIDERATIONS

ADVERSE EFFECTS

- **Oseltamivir → Nausea and vomiting**
  - Does not generally result in discontinuation of therapy
  - Taking the drug with food may minimize GI adverse effects
- **Zanamivir → Bronchospasm and a decline in respiratory function** in patients with asthma and other chronic respiratory disorders
  - Should **NOT** be used in patients with underlying airway disease (manufacturer warning)

(1) Rasmussen SA, et al. Am J Obstet Gynecol. 2011 Jun;204(6 Suppl 1):S13-20. (2) Graner S, et al. BMJ. 2017; 356: j629. (3) Dunstan HJ, et al. BJOG. 2014 Jun;121(7):901-6.

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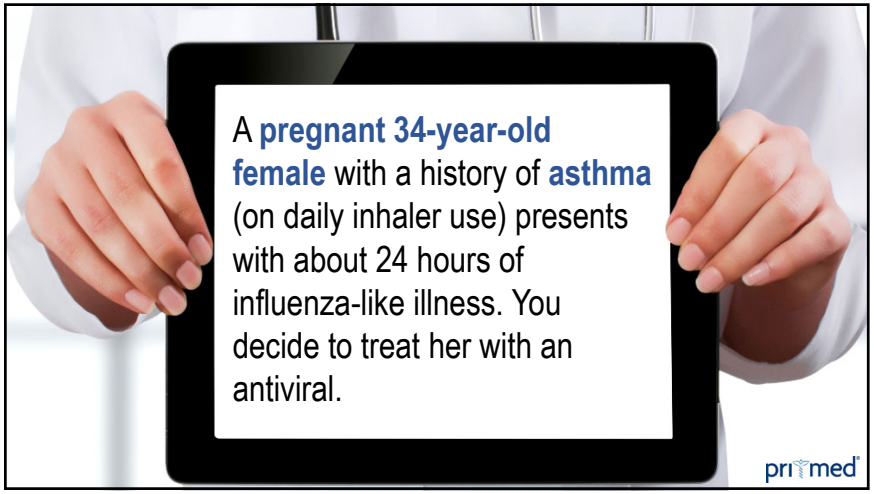

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NAIs
Safety Considerations

PREGNANCY

- Pregnancy category C drugs
- **Oseltamivir is recommended** over inhaled zanamivir[1,4]
  - 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.[2,3]

(1) Rasmussen SA, et al. Am J Obstet Gynecol. 2011 Jun;204(6 Suppl 1):S13-20. (2) Graner S, et al. BMJ. 2017; 356: j629. (3) Dunstan HJ, et al. BJOG. 2014 Jun;121(7):901-6. (4) https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

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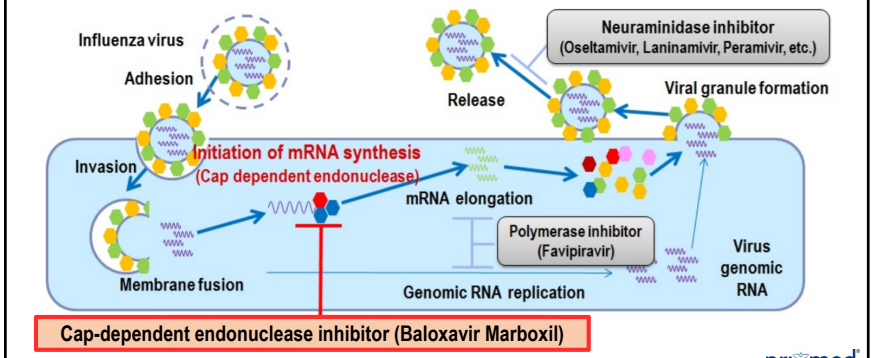
CDC advises that pregnancy should NOT be considered a contraindication to influenza antivirals

ARE THERE ANY NEW ANTIVIRAL AGENTS ON THE HORIZON TO TREAT INFLUENZA?

Baloxavir Marboxil*



*Pending FDA approval for treatment of seasonal influenza A and B viruses

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Baloxavir Marboxil*

- Effective against influenza A and B as well as avian-origin H5N1 and H7N9 influenza viruses
- Oral
- Single dose
- More effective if given as soon possible
  - Within 24 hours of symptom onset
- Adults and children > 12 year old

*Pending FDA approval for treatment of seasonal influenza A and B viruses

Hayden FG, Sugaya N, Hirotsu N, et al,. N Engl J Med. 2018 Sep 6;379(10):913-923.

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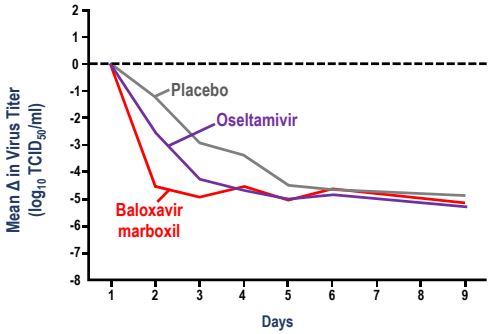
Baloxavir Marboxil* Was Associated With Significantly More Rapid Declines in Viral Load Than Placebo or Oseltamivir



*Pending FDA approval for treatment of seasonal influenza A and B viruses

Hayden FG, Sugaya N, Hirotsu N, et al,. N Engl J Med. 2018 Sep 6;379(10):913-923.

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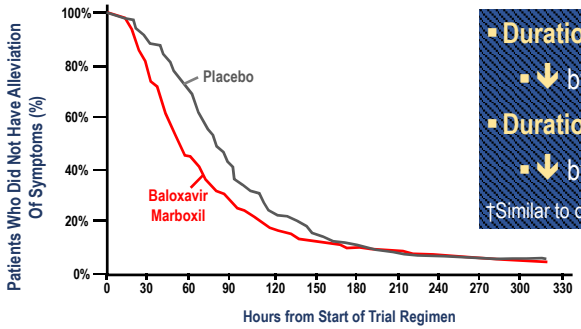
Baloxavir Marboxil* Decreased Duration of Flu Symptoms and Duration of Fever



- Duration of flu symptoms
  - ↓ by > 1 day†
- Duration of fever
  - ↓ by nearly 1 day†

†Similar to oseltamivir

*Pending FDA approval for treatment of seasonal influenza A and B viruses

Hayden FG, Sugaya N, Hirotsu N, et al,. N Engl J Med. 2018 Sep 6;379(10):913-923.

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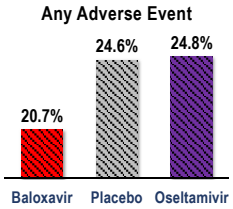
Baloxavir Marboxil* Safety



No evident safety concerns

Adverse Event	Baloxavir Marboxil (%)	Placebo (%)	Oseltamivir (%)
Diarrhea	3	4.5	2.1
Bronchitis	2.6	5.5	3.5
Nasopharyngitis	1.5	0.6	0.8
Nausea	1.3	1.3	3.1
Sinusitis	1.1	2.6	1.0
Increase in ALT	1.0	1.3	1.4
Headache	0.8	1.0	0.8
Vomiting	0.8	0.6	1.2
Dizziness	0.5	1.3	0.2
Leukopenia	0	1.0	0.2
Constipation	0	1.0	0

*Pending FDA approval for treatment of seasonal influenza A and B viruses

Hayden FG, Sugaya N, Hirotsu N, et al,. N Engl J Med. 2018 Sep 6;379(10):913-923.

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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

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CONSULT AN INFECTIOUS DISEASE EXPERT WHEN…

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

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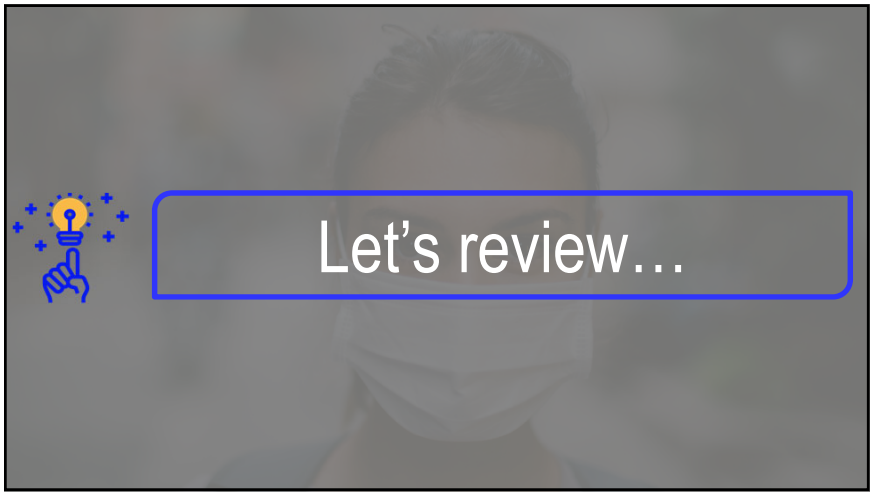

- Influenza testing is not needed to confirm the clinical diagnosis or to decide whether to prescribe antiviral medications to a patient when influenza viruses are circulating in the community
- CDC recommends to start antiviral treatment as soon as possible (ideally within 48 hours) after illness onset 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 NAIs 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 NAIs

ASK QUESTIONS USING OUR NEW SOCIAL Q&A FEATURE!

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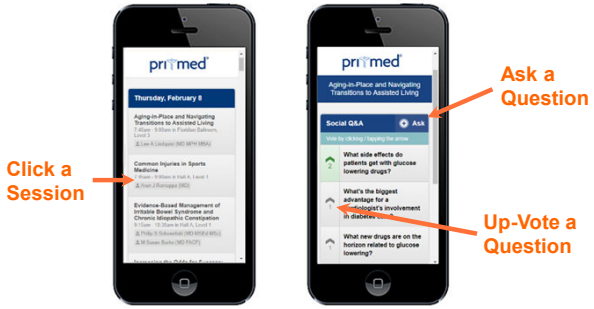

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