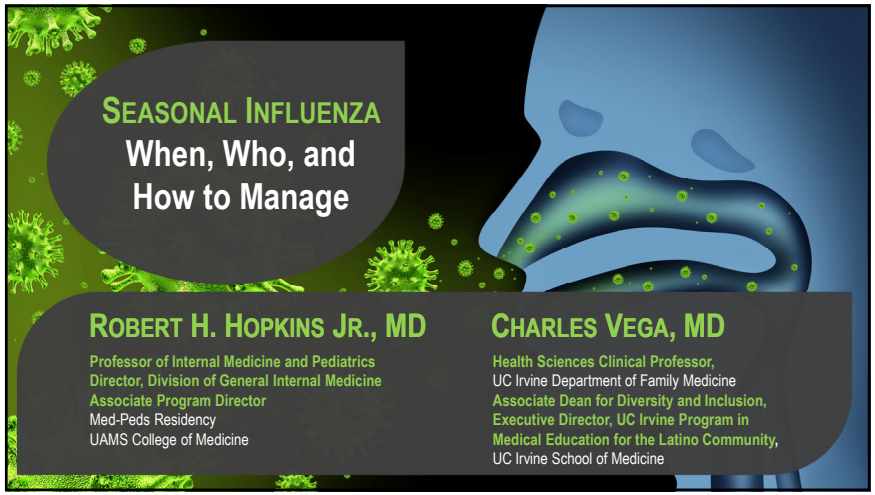

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Presenter Disclosure Information

This session is supported by an independent educational grant from **Genentech.**

The following relationships exist related to this presentation:

- Robert H. Hopkins Jr., MD: No financial relationships to disclose.
- Charles Vega, MD: No financial relationships to disclose.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

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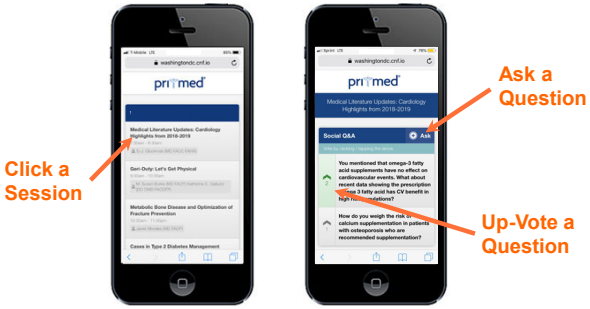

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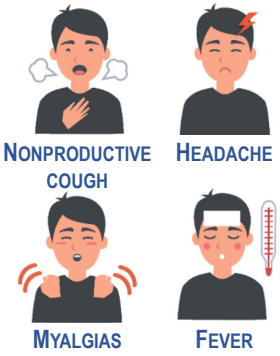
LEARNING OBJECTIVES

1. Diagnose and promptly treat influenza in accordance with national guidelines and emerging evidence
2. Use approved antiviral medications to better treat influenza based on efficacy and safety data in order to reduce symptoms, prevent associated complications, and reduce the burden of disease

Syllabi/slides for this program are a supplement to the live CME session and are not intended for other purposes.

Diagnosis of Influenza
Common Signs/Symptoms



*Not always present in **infants**, **elderly** and **immunocompromised** patients*

Atypical presentations

Infants (e.g. sepsis-like syndrome)

Elderly (e.g. confusion)

47% efficacy

2018-19 influenza vaccine[1]

1) Cdc.gov. (2019). *Seasonal Influenza Vaccine Effectiveness, 2004-2018 | CDC*.

Persons at Higher Risk For Influenza Complications

- **Children < 5 years old**
- Individuals < 19 years on long-term aspirin therapy
- **Adults ≥ 65 years old**
- **Morbidly obese persons (BMI ≥ 40 kg/m^2)**
- **Pregnant women or ≤ 2 weeks postpartum**
- American Indian/Alaska Native heritage
- Residents of nursing homes/chronic care facilities
- **Immunosuppressed** patients
- Patients with **chronic medical conditions**, including pulmonary, cardiovascular, renal, hepatic, hematological, metabolic, neurologic, or neurodevelopmental disorders

Bacterial Co-Infection
Clinical Considerations

Uncomplicated flu

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

Possible Co-Infection

- **Fevers for more than 3–5 days**
- Worsening symptoms or rapid clinical deterioration
- Most common pathogens[1]:
  - ***Streptococcus Pneumoniae***
  - Staphylococcus (MRSA/MSSA)
  - Group A Streptococcus
- Consider ID consult

(1) Shieh WJ, et al. J, et al. . Am J Pathol. 2010;177:166-75

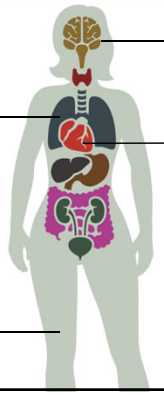
Complications of Influenza

Pulmonary

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

Musculoskeletal

Myositis
Rhabdomyolysis



Neurologic

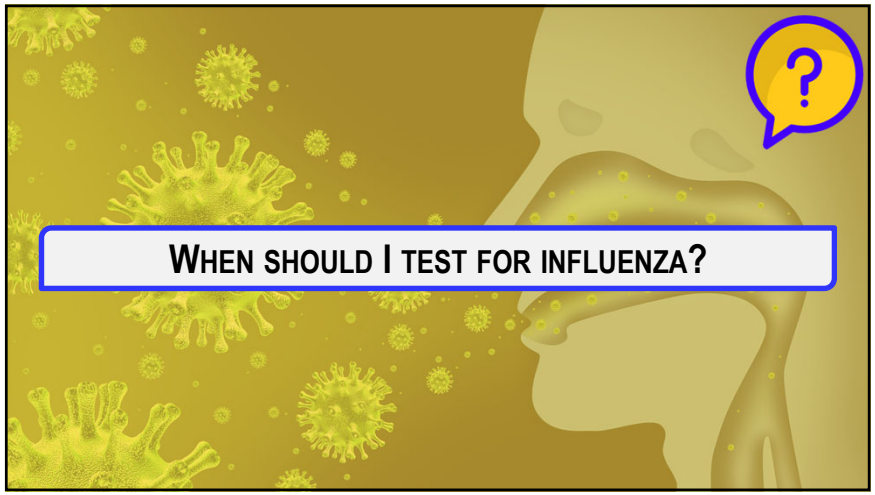
Encephalitis
Seizures
Stroke

Cardiac

Congestive heart failure
Acute myocardial infarction
Myocarditis
Pericarditis

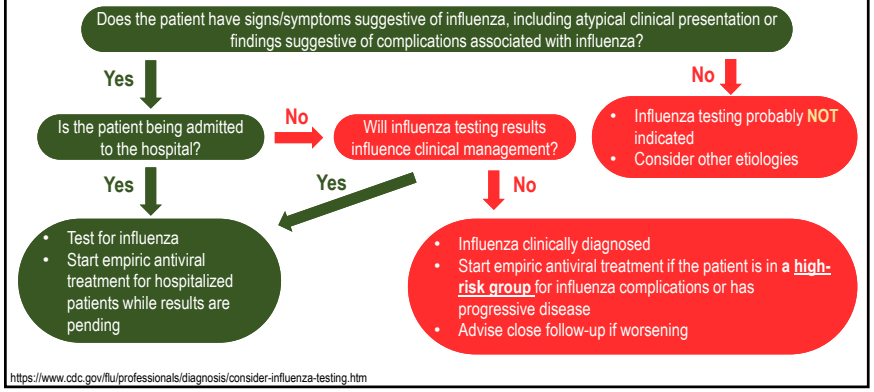
Multi-organ failure

Septic shock
Renal failure
Respiratory failure



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

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 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

INFLUENZA TESTING

…when influenza viruses are circulating in the community…

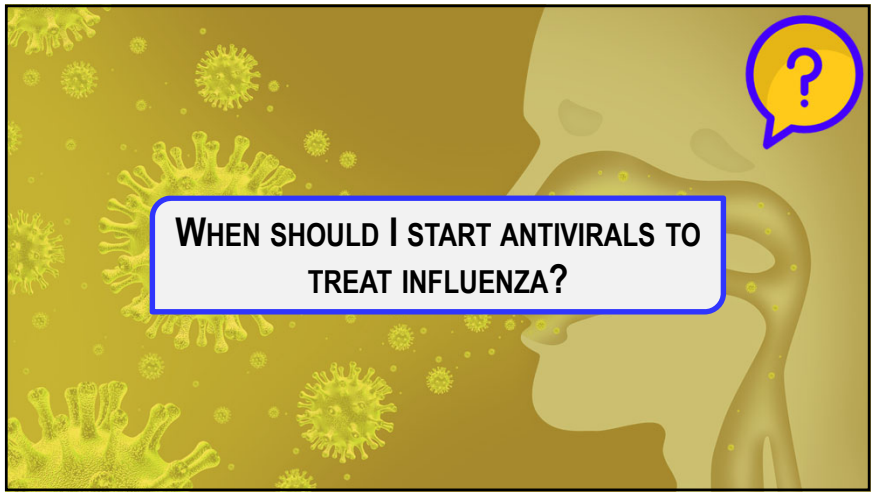
INFLUENZA TESTING IS NOT NEEDED

to confirm the clinical diagnosis
or to decide whether to prescribe antiviral medications

TESTING RECOMMENDED IF WILL CHANGE TREATMENT OR PATIENT REQUIRES HOSPITALIZATION

Molecular assay = Best

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



AUDIENCE RESPONSE QUESTION

Based on the timing of her illness (*60hrs since illness onset*)**, is she a candidate for antiviral therapy for influenza?**

1. NO: Antivirals should be initiated only if influenza testing is positive
2. NO: Treatment should only be started within 24 hours of illness onset
3. NO: Treatment is only effective if started within 48 hours of illness onset
4. YES: Benefits of antivirals are the same in all populations, no matter when treatment is started after illness onset
5. YES: Antiviral therapy is recommended even after 48 hours after illness onset in high-risk patients

RATIONALE

☒ **NO: Antivirals should be initiated only if influenza testing is positive**	▪ **Flu testing is not needed** to initiate treatment ▪ Even with negative testing, antivirals should still be considered if clinical suspicion for flu is high
☒ **NO: Treatment should only be started within 24 hours of illness onset**	Antivirals can be prescribed at anytime during the course of illness based on clinical judgment but are **most effective if started within *48 hours***
☒ **NO: Treatment is only effective if started within 48 hours of illness onset**	
☒ **YES: Benefits of antivirals are the same in all populations, no matter when treatment is started after illness onset**	Mild benefit with later start of antivirals (after 48hrs after illness onset)
☑ **YES: Antiviral therapy is recommended even after 48 hours after illness onset in high-risk patients**	Although benefit of antiviral therapy declines after 48hrs, the CDC strongly recommends initiating treatment in high-risk populations (after 48hrs) to decrease the risk of complications

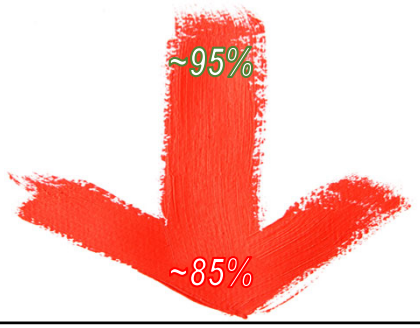
Mortality Is Reduced When Treatment Is Initiated Early

Treatment Initiation after illness onset

≤ 2 days
≤ 48 hrs

≥ 5 days
≤ 120 hrs

Survival Rates



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

When To Start Antivirals in Outpatients

≤ 48 hours after illness onset	> 48 hours after illness onset
Uncomplicated influenza	Use clinical judgment
Suspected/confirmed influenza in a group at high risk for complications	
Progressive disease who do not require hospitalization	

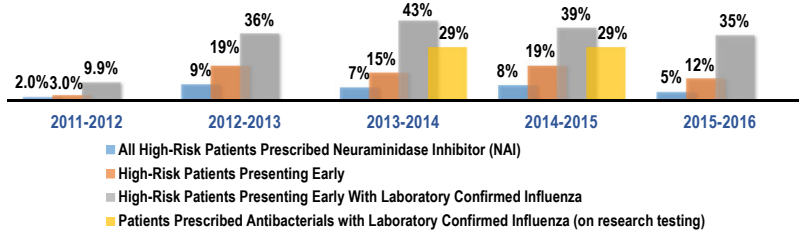
(1) Dobson J, et al. Lancet. 2015;385:1729-37. (2) Jefferson T, et al. Cochrane Database Syst Rev. 2014

Audience Response Question

What portion of high-risk patients with rRT-PCR-confirmed influenza received a prescription for an antiviral medication during 2011-2016 influenza seasons?

1. ~20%
2. ~40%
3. ~60%
4. ~80%
5. > 80%

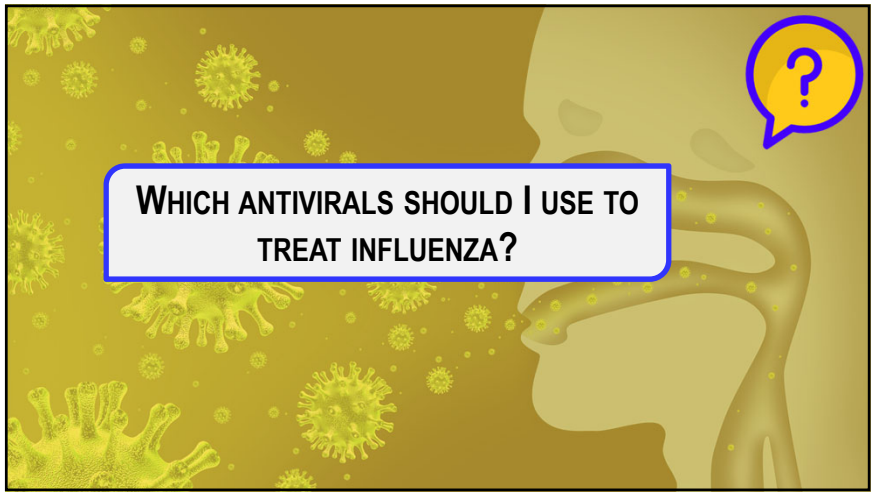
Clinicians Infrequently Prescribe Antiviral Treatment in The Outpatient Settings (2011-2016 Influenza Seasons)



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

29% of patients in outpatient setting with influenza were prescribed antibacterials

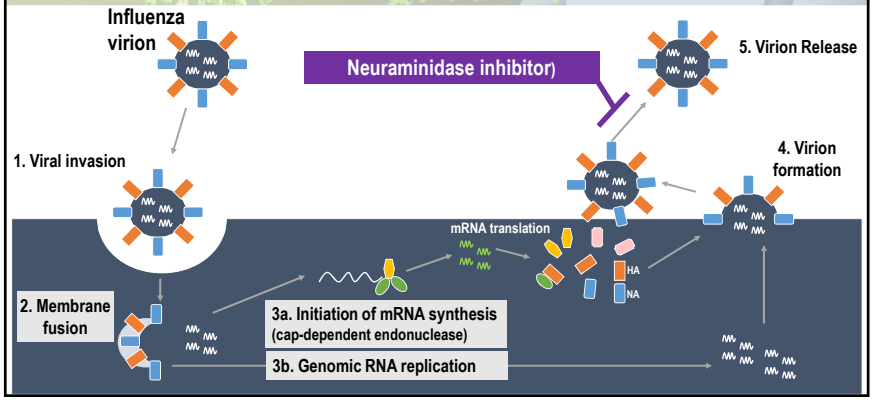
(1) Stewart RJ, Flannery B, Chung JR, Gaglani M, et al. Clin Infect Dis. 2018 Mar 19;66(7):1035-1041. (2) Havers FP, *JAMA Open Network*. 2018;1(2):e180243.



ANTIVIRALS FOR INFLUENZA

- Neuraminidase inhibitors (NAIs)
- Cap-dependent endonuclease inhibitor
- **Adamantanes** *(Not recommended)*

NEURAMINIDASE INHIBITORS
MECHANISM OF ACTION



NEURAMINIDASE INHIBITORS
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
Cost	**Generic**: $98.60 ***Tamiflu***: $151.90	$59.00	$950.00

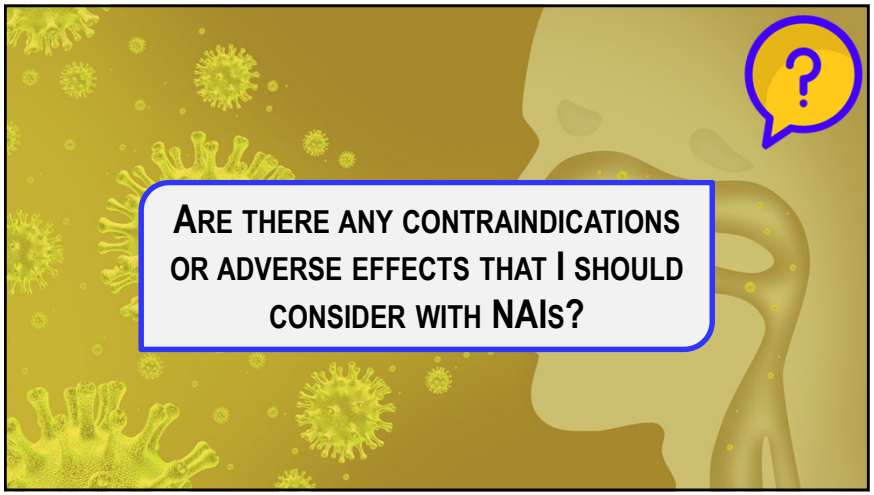
Neuraminidase Inhibitors
Efficacy

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

Oseltamivir (*Tamiflu*)
- ❑ **Adults:** 16.8 - 17.8 hours[1,2]
- ❑ **Children:** 29 hours[2]

Zanamivir (*Relenza*)
- ❑ **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



Neuraminidase Inhibitors
Safety Considerations

Oseltamivir (*Tamiflu*)→ **Nausea and vomiting**
- Does not generally result in discontinuation of therapy
- Taking the drug with food may minimize GI adverse effects

Zanamivir (*Relenza*) → **Bronchospasm and a decline in respiratory function** in patients with chronic respiratory disorders (i.e. asthma, COPD)
- Should **NOT** be used in patients with underlying airway disease (manufacturer warning)

Neuropsychiatric events are **rare** and not proven to be associated with NAIs

(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.

34-year-old
Female

Presents with ~ 24 hours of influenza-like illness
- 20-weeks **pregnant**
- History of **asthma** (daily inhaler use)
- You decide to treat her with an antiviral

Audience Response Question

According to the CDC, which of the following antivirals are recommended for this patient?

1. Zanamivir (*Relenza*)
2. Peramivir (*Rapivab*)
3. Oseltamivir (*Tamiflu*)
4. Amantadine (*Symmetrel*)
5. Baloxavir marboxil (*Xofluza*)
6. Any of the above could be used

Rationale

☒ **Zanamivir** (*Relenza*)	▪ Not 1st choice agent in pregnancy ▪ Contraindicated in this patient with **underlying respiratory disease** given risk of bronchospasm
☒ **Peramivir** (*Rapivab*)	**Not recommended** in pregnant patients by CDC
☑ **Oseltamivir** (*Tamiflu*)	▪ Oseltamivir is **recommended over inhaled zanamivir** ▪ Not associated with any adverse pregnancy or birth outcomes
☒ **Amantadine** (*Symmetrel*)	**No longer recommended** for treatment of influenza due to high resistance rates
☒ **Baloxavir marboxil** (*Xofluza*)	No data on use in pregnancy but no adverse maternal or embryo-fetal effects in animal studies
☒ **Any of the above could be used**	

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

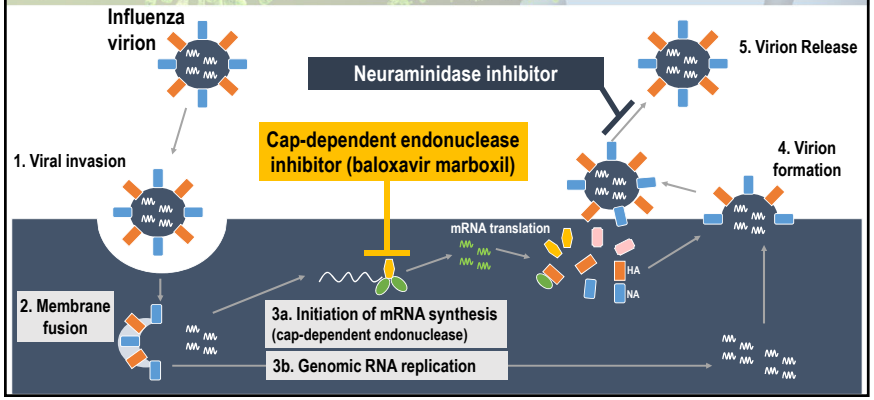
Antivirals
Pregnancy

Antivirals for influenza in pregnancy

(NOT a contraindication)

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

Cap-dependent Endonuclease Inhibitors
Mechanism of Action



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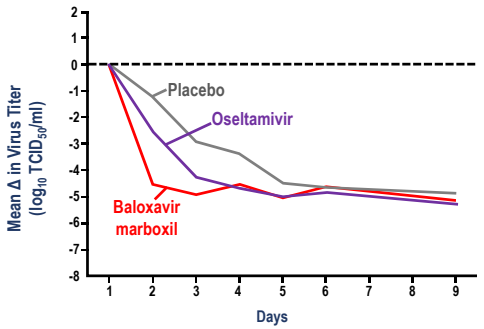
Baloxavir Marboxil (*Xofluza*)

- ***Treatment*** of influenza A and B, including avian-origin H5N1 and H7N9
  (Not approved for chemoprophylaxis)
- Single oral dose
- Adults and children ***> 12 years old***
- Symptomatic for ***≤ 48 hours***
  More effective if given as soon possible (≤ 24 hrs of symptom onset)

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

Baloxavir Marboxil (*Xofluza*) Associated with a More Rapid Decline in Viral Load Than Placebo and Oseltamivir (*Tamiflu*)

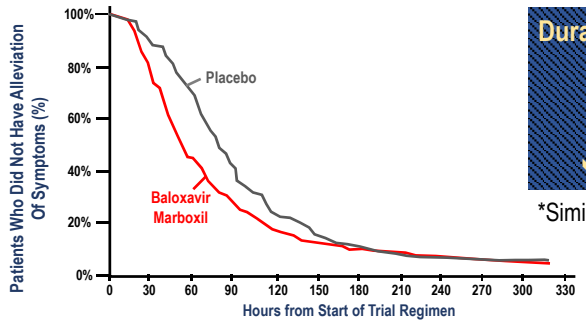


Faster decline in viral load

Faster time to cessation of viral shedding[2]

(1) Hayden FG, Sugaya N, Hirotsu N, et al,. N Engl J Med. 2018 Sep 6;379(10):913-923. (2) Taieb V, Ikeoka H, Ma F-F, et al., *Curr Med Res Opin.* 2019:1-1

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

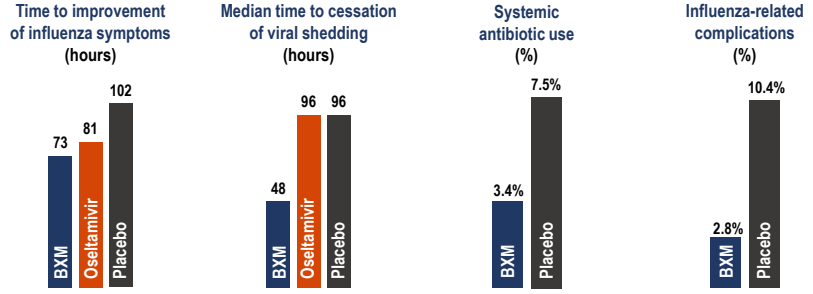


Duration of flu symptoms
↓ by > 1 day*
Duration of fever
↓ by nearly 1 day*

*Similar to oseltamivir (*Tamiflu*)

(1) Hayden FG, Sugaya N, Hirotsu N, et al,. N Engl J Med. 2018 Sep 6;379(10):913-923.; (2) Taieb V, Ikeoka H, Ma F-F, et al., *Curr Med Res Opin.* 2019:1-1.

Baloxavir Marboxil (*Xofluza*)* High Risk Populations



The incidence of **any** or **serious adverse events** did not differ significantly across the groups

BXM: Baloxavir marboxil

Ison MG, et al. Open Forum Infect Dis. 2018 Nov; 5(Suppl 1): S764–S765.

*Under FDA review for additional indication for treatment of influenza in individuals at high-risk for influenza-related complications in individuals ≥ 12yrs

Baloxavir Marboxil (*Xofluza*)
Safety

Compared to oseltamivir…

Baloxavir marboxil is equally safe and potentially associated with ***fewer AEs***

Adverse Event	Baloxavir marboxil (%)	Placebo (%)	Oseltamivir (*Tamiflu*) (%)
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
ANY ADVERSE EVENT	20.7	24.6	24.8

(1) Hayden FG, Sugaya N, Hirotsu N, et al,. N Engl J Med. 2018 Sep 6;379(10):913-923. (2) Taieb V, Ikeoka H, Ma F-F, et al., *Curr Med Res Opin*. 2019:1-1.

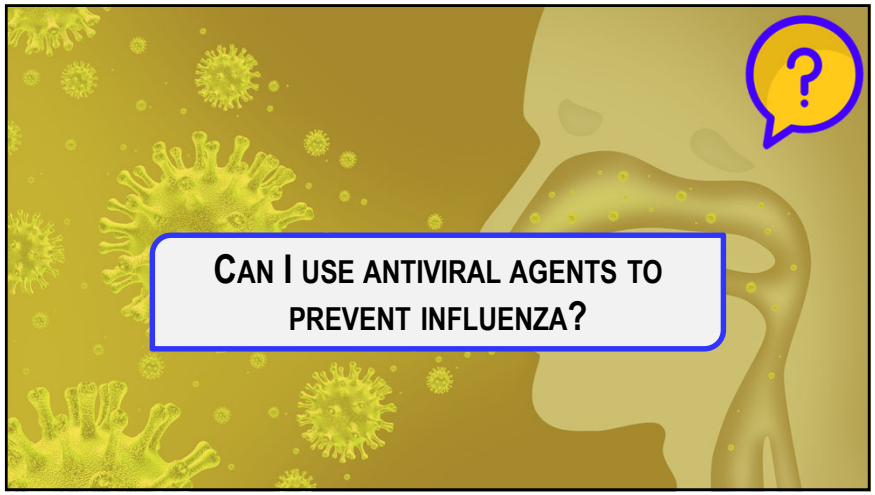
Antiviral Resistance

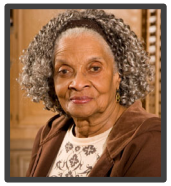
- Currently **low resistance** to…
  - **Oseltamivir** (*Tamiflu*), **zanamivir** (*Relenza*), **peramivir** (*Rapivab*), and **baloxavir marboxil** (*Xofluza*)
- Resistance can emerge at any time, as well as during or after treatment in some patients
  - Flu virus mutations have been shown 3 days following treatment with baloxavir marboxil, associated with initial delay in symptom alleviation but no change in overall prognosis[1]

FluView U.S. Influenza Surveillance Report
(*https://www.cdc.gov/flu/weekly/index.htm*)

Weekly surveillance data on antiviral resistance

(1) Uehara T, et. Al. *J Infect Dis*. 2019. (2) https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm





73-year-old
Female

Calls your office to inform you that her boyfriend came down with influenza today, the day after they spent an entire day together (2 days ago)

- She **refused the flu vaccine**
- History of **COPD**
- Asks whether she should be tested or treated for influenza

Audience Response Question

Which of the following would you recommend to/for her now?

1. Order a molecular assay to test for influenza
2. Prescribe oseltamivir (*Tamiflu*) to prevent influenza
3. Prescribe zanamivir (*Relenza*) to prevent influenza
4. Prescribe baloxavir marboxil (*Xofluza*) to prevent influenza
5. No treatment is necessary unless she develops symptoms

Rationale

☒ **Order a molecular assay to test for influenza**	As she is at high risk for influenza complications, testing is not necessary prior to treatment initiation
☑ **Prescribe oseltamivir (*Tamiflu*) to prevent influenza**	Given her age, lack of immunity and underlying lung disease, oseltamivir is appropriate
☒ **Prescribe zanamivir (*Relenza*) to prevent influenza**	Although zanamivir is approved for prophylaxis, it is **contraindicated in this patient with history of lung disease**. Peramivir is the only NAI not recommended for prophylaxis.
☒ **Prescribe baloxavir marboxil (*Xofluza*) to prevent influenza**	Baloxavir marboxil is **not currently approved for prophylactic treatment,** however a recent study showed promising results for prophylactic use.
☑ **No treatment necessary unless she develops symptoms**	Prophylaxis is recommended as she is high risk based on age and comorbidity; an equal alternative would be to wait and start immediate treatment if she develops illness

Chemoprophylaxis With NAIs

NAIs are

~ 70% to 90%

effective in preventing influenza,

however…

NO routine seasonal or pre-/post-exposure antiviral chemoprophylaxis is recommended, *except in…*

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

Chemoprophylaxis With NAIs
Candidates

Persons at **high risk of influenza complications**
- ≤ 2 weeks following vaccination after exposure to a person with influenza
- Cannot receive influenza vaccine due to a contraindication after exposure to a person with influenza

- Persons with **severe immune deficiencies**
- Persons who **might not respond to influenza vaccination**
  - i.e. those 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

Prophylactic Treatment of Influenza

	Oseltamivir (*Tamiflu*)	Zanamivir (*Relenza*)
	75 mg PO once/day x 7 days	2 inhalations once/day x 7 days
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 48hrs	No dosage adjustment required

Baloxavir Marboxil (*Xofluza*) & peramivir (*Rapivab*)
NOT FDA-approved for prophylaxis

A recent phase III study demonstrated that compared to placebo, baloxavir marboxil significantly reduced the likelihood of people developing the flu after exposure to infected household member (1.9% vs. 13.6%)[1]

(1) Roche.com. (2019). *Phase III study showed Xofluza (baloxavir marboxil) is effective at preventing influenza infection.* https://www.roche.com/investors/updates/inv-update-2019-06-04b.htm [Accessed 11 Jun. 2019].

Chemoprophylaxis With NAIs
Timing of Treatment

Prophylaxis generally **NOT recommended if >48 hours** have elapsed since the first exposure to a person with influenza

Close monitoring and early antiviral treatment *if symptoms develop*

Medication taken **each day** for the duration of potential exposure to a person with influenza

Continued for ***7 days*** *after the last known exposure*

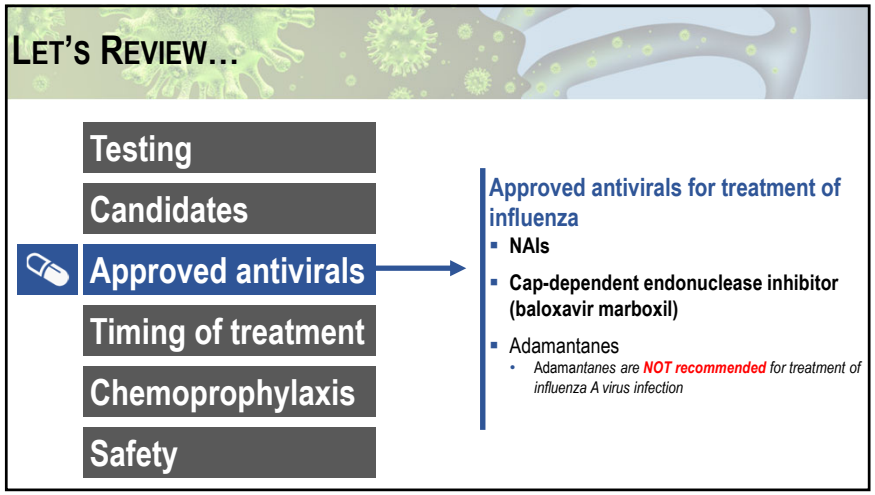
(1) Dobson J, et al. Lancet. 2015;385:1729-37. (2) Jefferson T, et al. Cochrane Database Syst Rev. 2014

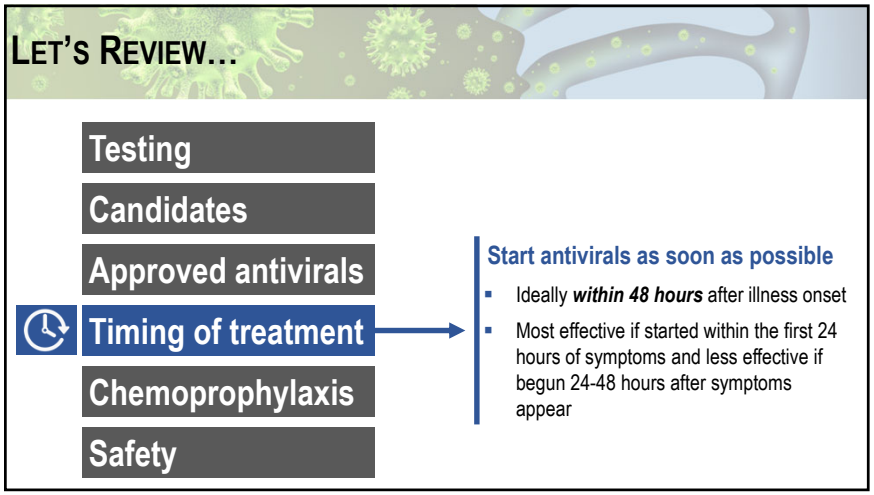
Let's Review…

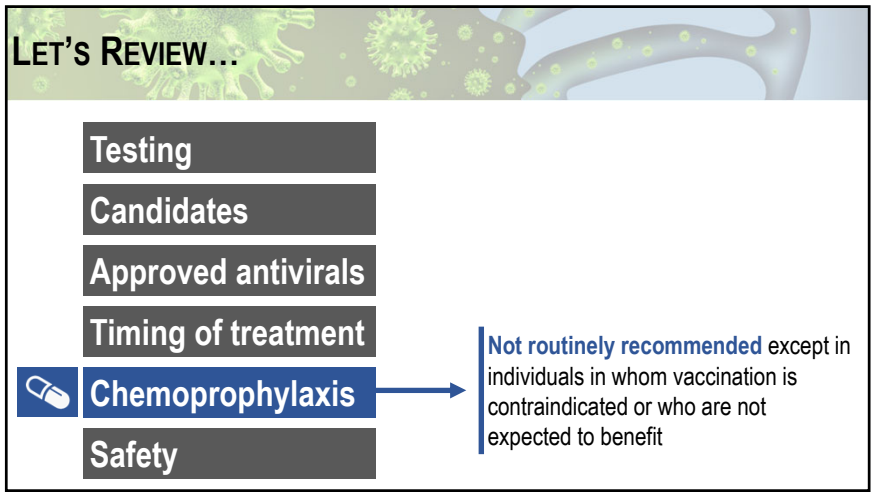
- **Testing** → **Not needed** to confirm the clinical diagnosis or to decide whether to prescribe antiviral medications
- Candidates
- Approved antivirals
- Timing of treatment
- Chemoprophylaxis
- Safety

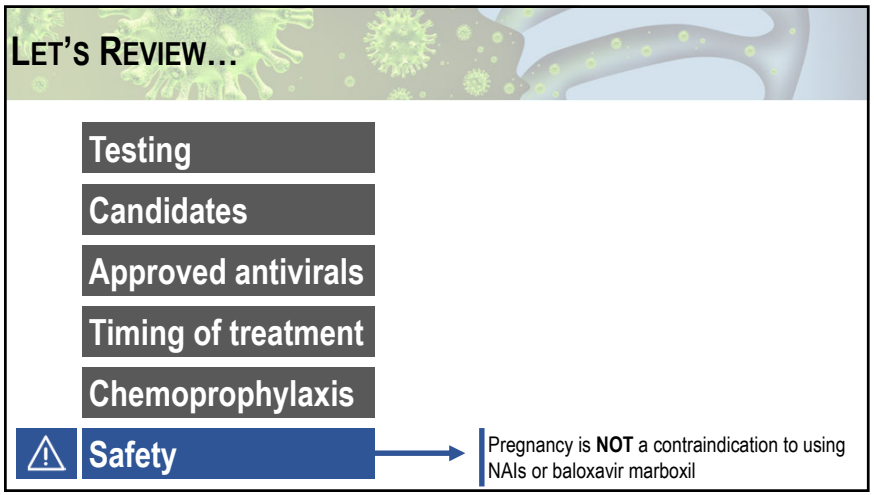
Let's Review…

- Testing
- **Candidates**
  - **Recommended for all individuals with suspected or confirmed influenza who have…**
    - Severe, complicated, or progressive illness
    - Require hospitalization
    - At higher risk for complications (i.e., immunosuppression, adults ≥ 65 years old, children < 5 years old, etc.)
    - Cannot receive influenza vaccine
    - In institutional settings (*if influenza is circulating*)
  - **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
- Approved antivirals
- Timing of treatment
- Chemoprophylaxis
- Safety









Syllabi/slides for this program are a supplement to the live CME session and are not intended for other purposes.