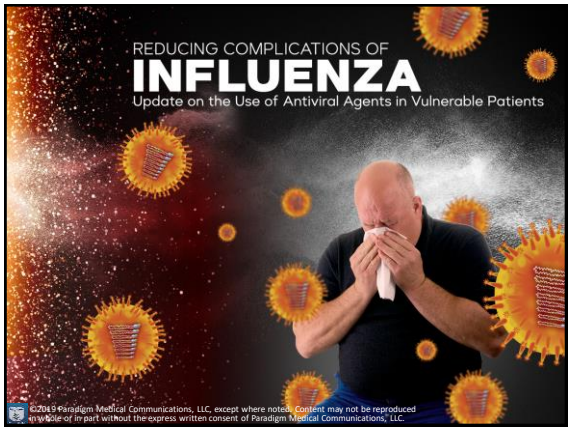

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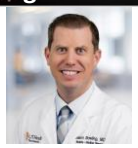
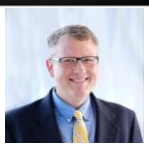
Steering Committee





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2

2

Disclosures

Jason E. Bowling, MD
Retained Consultant: BioGaia Pharma

James S. Lewis II, PharmD, FIDSA
Retained Consultant: Merck & Co, Inc; Tetraphase Pharmaceuticals

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5

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Notes

- There will be a Q&A session at the end of the program
  - If you would like to pose a question to the faculty, please write it on the question card in your folder
- Please silence your cell phones
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CPE Information (continued)

Learning Objectives

- Identify appropriate candidates for antiviral therapy based on risk for influenza-related complications, in accordance with current guideline recommendations
- Determine the need for influenza treatment based on patient signs, symptoms, and accurate interpretation of appropriate diagnostic tests when necessary
- Evaluate the latest safety and efficacy data for novel antiviral treatment to determine its role in the influenza treatment paradigm

Disclosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA.

8

8

Agenda

- Introduction
- Case Studies: Identifying Candidates for Antiviral Therapy
- Antiviral Therapy for Influenza Treatment
- Q&A

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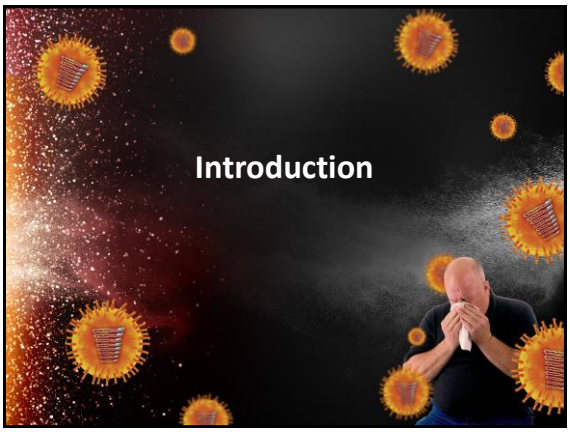
Introduction



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Influenza Is More Than a Nuisance

Burden of Influenza in the United States, 2017-2018

The estimated number of flu **illnesses** during the 2017-2018 season:	The estimated number of flu **hospitalizations** during the 2017-2018 season:	The estimated number of flu **deaths** during the 2017-2018 season:
49 million	**960,000**	**79,000**
More than the combined populations of Texas and Florida	More than the number of staffed hospital beds in the U.S.	More than the average number of people who attend the Super Bowl each year

CDC. 12/18/18. www.cdc.gov/flu/about/burden/2017-2018.htm. Accessed 3/27/19.

11

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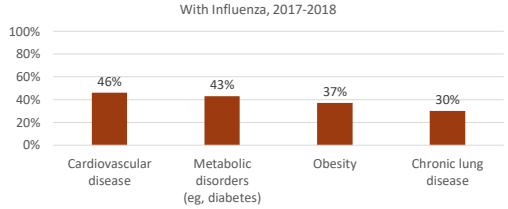
Of Those Hospitalized With Influenza, *Most* Were High-Risk Patients

Of those hospitalized for influenza during the 2017-2018 season, **92% had ≥1 underlying medical condition**

Most Common Underlying Conditions Among Those Hospitalized With Influenza, 2017-2018



PR Newswire. 11/28/18. www.prnewswire.com/news-releases/new-call-to-action-issued-on-the-dangers-of-influenza-among-adults-with-chronic-health-conditions-300756618.html. Accessed 3/27/19.

12

12

The CDC Considers Many Patients High Risk

- Children <2 y old[a]
- Adults ≥65 y old
- Chronic conditions
  - Pulmonary (eg, asthma, COPD)
  - Cardiovascular (except hypertension alone)
  - Renal
  - Hepatic
  - Hematologic (eg, sick cell disease)
  - Metabolic (eg, diabetes)
  - Neurologic (eg, seizures, stroke, developmental delays)
- Immunosuppressed
- Obese (BMI ≥40 kg/m^2)
- Pregnant or postpartum (within 2 wk of delivery)
- <19 y old, receiving long-term aspirin therapy
- American Indians
- Alaska Natives
- Long-term care residents

[a]Although all children <5 y old are considered at higher risk for complications from influenza, the highest risk is for those <2 y

BMI, body mass index; CDC, Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease

CDC. 12/27/18. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed 3/27/19.

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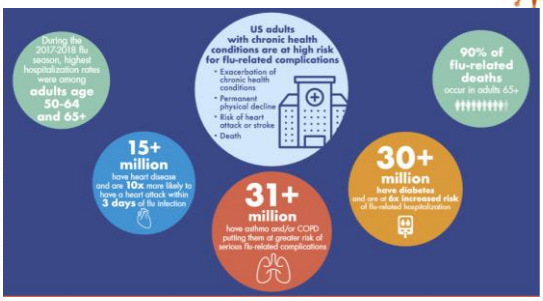
Influenza Is Especially Dangerous in Patients Who Are at High Risk for Complications



National Foundation for Infectious Diseases. www.nfid.org/idinfo/influenza/flu-chc-download-hcp-infographic. Accessed 3/27/19.

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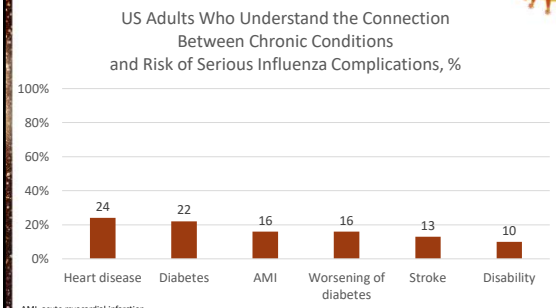
Few Adults Recognize That Chronic Conditions Confer a Higher Risk of Influenza Complications



AMI, acute myocardial infarction

PR Newswire. 11/28/18. www.prnewswire.com/news-releases/new-call-to-action-issued-on-the-dangers-of-influenza-among-adults-with-chronic-health-conditions-300756618.html. Accessed 3/27/19.

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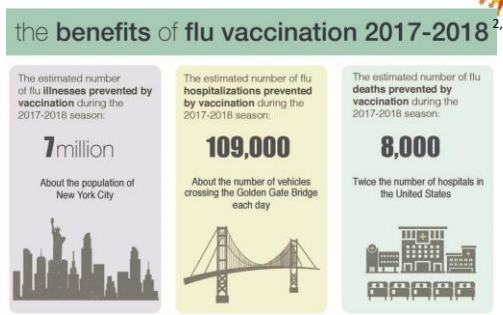
Vaccination, the First Line of Defense: Vaccine Effectiveness ≈36%, 2017-2018[1]



1. Flannery B et al. *MMWR Morb Mortal Wkly Rep.* 2018;67(6):180-185. 2. CDC. www.cdc.gov/flu/about/burden-averted/averted-estimates.htm. Accessed 3/27/19. 3. Rolfes MA et al. *Clin Infect Dis.* 2019 Feb 2. [Epub ahead of print]

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The Role of Antiviral Therapy: CDC and IDSA Recommendations

Recommended ***as soon as possible*** for any patient with confirmed or suspected influenza who:[1,2]

- Is hospitalized
- Has severe, complicated, or progressive illness, or
- **Is at higher risk for influenza complications**

Also consider in:[2]

- Any previously healthy, symptomatic outpatient with symptom onset ≤2 d before presentation
- Symptomatic patients who are household contacts of high-risk patients
- Symptomatic HCPs who care for high-risk patients

HCP, healthcare provider; IDSA, Infectious Diseases Society of America

1. CDC. 12/27/18. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed 3/27/19.
2. Uyeki TM et al. *Clin Infect Dis.* 2019;68(6):895-902.

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Benefits of Early Antiviral Treatment
(Within 2 Days of Symptom Onset)

- ✓Shortens duration of fever and symptoms
- ✓Reduces risk of complications
  - Bronchitis
  - Otitis media
  - Pneumonia
  - Respiratory failure
- ✓Reduces hospital admissions
- ✓May decrease mortality among high-risk populations

Uyeki TM et al. *Clin Infect Dis.* 2019;68(6):895-902.

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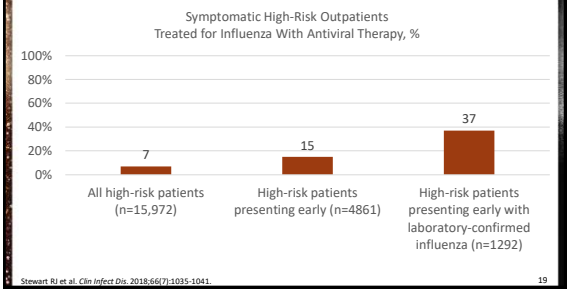
Antivirals Are Prescribed Infrequently for High-Risk Outpatients Who Would Benefit Most

Data Collected Across 5 Influenza Seasons, US Influenza Vaccine Effectiveness Network (2011-2016)



Stewart RJ et al. *Clin Infect Dis*. 2018;66(7):1035-1041. 19

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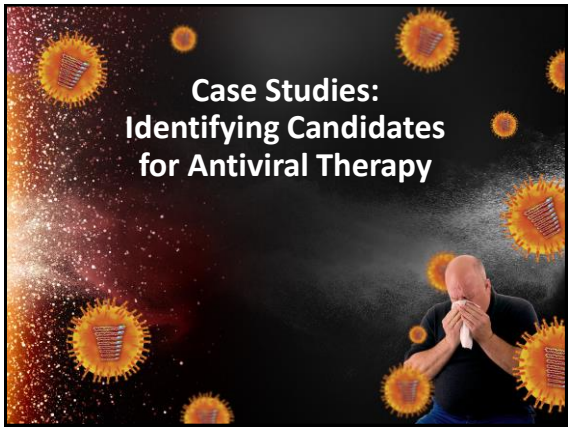
Case Studies: Identifying Candidates for Antiviral Therapy



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Case Study 1

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Patient Presentation

- 52-y-old man presents to ED in January with fever and chills
  - Started suddenly (≈72 h ago)
- Other signs/symptoms:
  - Runny nose, sore throat, cough, muscle aches
- Several coworkers had similar symptoms, missed work
- Visited urgent care clinic first day of symptom onset
  - Reports his "quick flu test was negative"; received levofloxacin
- Symptoms are worsening
- PMH/PSH
  - Obesity (BMI 42 kg/m^2)
  - HTN
  - Dyslipidemia
- No prior surgeries
- Accountant, sedentary lifestyle
- Lives with wife
- No tobacco use, occasional glass of wine, no illicit drugs
- Medications
  - Atorvastatin
  - HCTZ
  - Multivitamin

ED, emergency department; HCTZ, hydrochlorothiazide; HTN, hypertension; PMH, past medical history; PSH, past surgical history 22

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Examination

- Vitals – Temp **101.7° F**, **pulse 122 bpm**, **BP 88/58 mm Hg**, **RR 24**, **O_2 saturation 82% RA**
- Constitutional – **Appears short of breath**, obese, oriented x3
- Eyes – PERRL, EOMI, anicteric sclera
- Ears, nose, mouth, throat – Normal appearing pinnae, **clear nasal discharge**, dentition intact, **oropharynx erythematous** – no purulence, moist mucous membranes
- Dermatologic – No rashes
- Respiratory – **Scattered rhonchi bilaterally**
- Cardiovascular – **Tachycardic**, regular rhythm, nl s1/s2, no s3 or s4
- Abdomen/GI – Soft, NT/ND, normal active bowel sounds, no hepatosplenomegaly
- Extremities – No clubbing, cyanosis, edema, pulses 2+ bilaterally
- Neurologic – Grossly nonfocal, no tremor, no asterixis

BP, blood pressure; bpm, beats per minute; EOMI, extraocular movements intact; GI, gastrointestinal; NT/ND; non tender/non distended; PERRL, pupils equal, round, reactive to light; RA, room air; RR, respiratory rate

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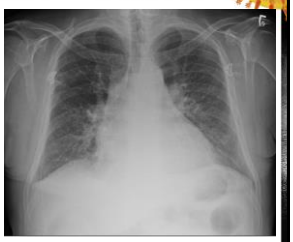
Laboratory and Imaging Results

- **WBC 19k**, normal Hgb and platelets
- Chem – 7 normal except for **increased BUN 24 mg/dL and Cr 1.4 mg/dL** (baseline 0.7 mg/dL)
- Chest radiograph
  - Cardiomegaly with vascular congestion and pulmonary edema
- **DISPOSITION**
  - **ADMIT TO HOSPITAL**



BUN, blood urea nitrogen; Cr, creatinine; Hgb, hemoglobin; WBC, white blood count
Image courtesy of Jason E. Bowling, MD

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Is this patient a candidate for antiviral therapy?

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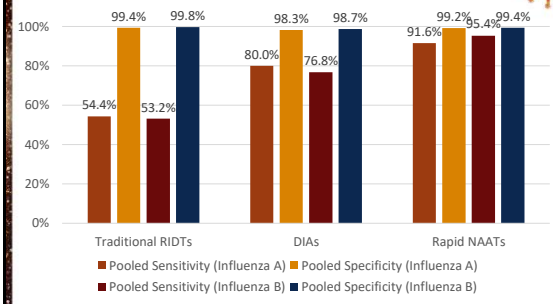
Traditional RIDTs Yield Many False-Negatives



DIA, digital immunoassay; NAAT, rapid nucleic acid amplification test; RIDT, rapid influenza diagnostic test

Merckx J et al. *Ann Intern Med*. 2017;167:394-409.

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Do Not Await Confirmatory Laboratory Results to Start Antivirals in Patients With Influenza Signs/Symptoms[a]

[a]Abrupt onset of respiratory and systemic signs and symptoms, with or without fever

General
Fever[b,c]
Chills
Malaise
Fatigue

Pulmonary
Nonproductive cough
Pleuritic chest pain

Head, Eyes, Ears, Nose, Throat
Headache
Nasal congestion[c]
Runny nose[c]
Sore throat/hoarseness

Gastrointestinal[d]
Abdominal pain
Vomiting
Diarrhea[c]

Neuromuscular
Myalgia, arthralgia
Weakness
Chest pain

[b]Fever can be age-specific: High fever or fever alone may be the only sign in infants and young children; fever may be absent or low grade in infants and the elderly
[c]Fever, nasal congestion, rhinorrhea, and diarrhea may be present among infants and young children
[d]Gastrointestinal symptoms vary with age: Diarrhea is more common among infants, young children, and school-aged children; abdominal pain may be present among school-aged children; vomiting may be present among adults.

Uyeki TM et al. *Clin Infect Dis*. 2019;68(6):895-902.

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Is Influenza Testing Needed?

Outpatients with signs and symptoms consistent with influenza (including atypical presentation) ***should NOT*** be tested if testing will not influence clinical management

NO

Start empiric antiviral treatment if patient is high risk or has progressive disease

Patients with signs and symptoms consistent with influenza (including atypical presentation) ***should*** be tested for influenza if they are being admitted to the hospital

YES

Start empiric antiviral treatment while results are pending

CDC. 2/20/18. www.cdc.gov/flu/professionals/diagnosis/consider-influenza-testing.htm. Accessed 3/27/19.

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The Role of Antiviral Therapy: CDC and IDSA Recommendations

Recommended ***as soon as possible*** for any patient with confirmed or suspected influenza who:[1,2]

- Is hospitalized
- Has severe, complicated, or progressive illness, or
- **Is at higher risk for influenza complications**

Also consider in:[2]

- Any previously healthy, symptomatic outpatient with symptom onset ≤2 d before presentation
- Symptomatic patients who are household contacts of high-risk patients
- Symptomatic HCPs who care for high-risk patients

1. CDC. 12/27/18. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed 3/27/19.
2. Uyeki TM et al. *Clin Infect Dis*. 2019;68(6):895-902.

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According to the CDC, This Patient Is at High Risk for Influenza Complications

- Children <2 y old[a]
- Adults ≥65 y old
- Chronic conditions
  - Pulmonary (eg, asthma, COPD)
  - **Cardiovascular (except hypertension alone)**
  - Renal
  - Hepatic
  - Hematologic (eg, sick cell disease)
  - Metabolic (eg, diabetes)
  - Neurologic (eg, seizures, stroke, developmental delays)
- Immunosuppressed
- **Obese (BMI ≥40 kg/m²)**
- Pregnant or postpartum (within 2 wk of delivery)
- <19 y old, receiving long-term aspirin therapy
- American Indians
- Alaska Natives
- Long-term care residents

[a]Although all children <5 y old are considered at higher risk for complications from influenza, the highest risk is for those <2 y

CDC. 12/27/18. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed 3/27/19.

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Obesity Is Prevalent and Dangerous in the Context of Influenza

- Worldwide obesity has nearly tripled since 1975
  - 650 million (13%) of adults are considered obese[1]
- During the 2009 influenza pandemic, obesity was a high risk factor for developing severe complications and dying from influenza virus infection[2]
  - Death due to hospitalization was nearly triple for obese patients in an international study[3]
    - Pooled OR=2.9 (95% CI 1.3-6.6)

CI, confidence interval; OR, odds ratio
1. World Health Organization. www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 3/27/19.
2. CDC. *MMWR Morb Mortal Wkly Rep*. 2009; 58:749-752. 3. Van Kerkhove MD et al. *PLoS Med*. 2011;8:e1001053.

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Why Is Obesity a Risk Factor for Influenza-Related Complications and Death?

- Obesity leads to:[1]
  - Altered immune function
  - Chronic inflammation
  - Mechanical difficulties in breathing
  - Increased oxygen requirements
- Poor vaccine response in this population[2]
- Associated with longer duration of viral shedding[1]
- Associated with higher prevalence of comorbidities that confer higher risk for influenza complications[3]

1. Maier HE et al. *J Infect Dis*. 2018;218(9):1378-1382. 2. Neidich SD et al. *Int J Obes (Lond)*. 2017;41:1324-1330.
3. CDC. *MMWR Morb Mortal Wkly Rep*. 2009;58:749-752.

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Case Study 2

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Patient Presentation

- 27-y-old pregnant woman presents in January with 2 days of muscle aches, runny nose, and cough
- Noted a fever today, so came to ob/gyn for evaluation due to concern about her baby
- Her husband has been sick, but she doubts she has the same thing because she received the influenza vaccine in November and he didn't
- PMH/PSH:
  - 20 weeks gestation (first pregnancy)
  - Childhood asthma (not currently on meds)
  - Seasonal allergies
  - Tonsillectomy age 9
- 4th grade teacher
- Lives with husband, 1 cat
- No tobacco, alcohol, or drugs
- No drug allergies
- Medications
  - Prenatal vitamins

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Examination

- Vitals – **Temp 102.3°F**, **pulse 112 bpm**, BP 108/58 mm Hg, RR 16, **O_2 saturation 93% RA**
- General: Awake, alert woman; **mild diaphoresis**
- Eyes – PERRL, EOMI, anicteric sclera
- Ears, nose, mouth, throat – Normal appearing pinnae, **boggy turbinates and copious**, **clear nasal discharge**, dentition intact, **oropharynx erythematous**; no purulence, moist mucous membranes
- Dermatologic – No rashes
- Respiratory – **Few scattered bibasilar crackles**, **occasional wheeze**
- Cardiovascular – **Tachycardic**, regular rate and rhythm, nl s1/s2, +s4
- Abdomen/GI – **Gravid abdomen appropriate size for gestational age**, soft, NT/ND, normal active bowel sounds, no hepatosplenomegaly
- Extremities – No clubbing, cyanosis, edema, pulses 2+ bilaterally
- Neurologic – Oriented x 3, grossly nonfocal, no tremor

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Laboratory and Imaging Results

- WBC 18, Hgb 10, and platelets 180
- Chem – 7 normal
- Chest radiograph
  - No evidence of acute cardiopulmonary disease

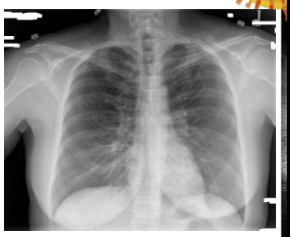

Image courtesy of Jason E. Bowling, MD

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Is this patient a candidate for antiviral therapy?

37

37

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- Immunosuppressed
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[a]Although all children <5 y old are considered at higher risk for complications from influenza, the highest risk is for those <2 y
CDC. 12/27/18. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed 3/27/19.

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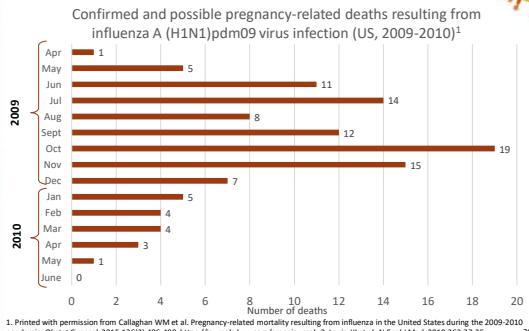
Pregnant Women Have Increased Risk of Severe Influenza and Related Mortality[1,2]



1. Printed with permission from Callaghan WM et al. Pregnancy-related mortality resulting from influenza in the United States during the 2009-2010 pandemic. *Obstet Gynecol*. 2015;126(3):486-490. https://journals.lww.com/greenjournal. 2. Louie JK et al. *N Engl J Med*. 2010;362:27-35.

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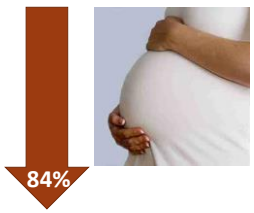
Early Antiviral Treatment Improves Outcomes in Hospitalized Pregnant Women

- 241 women admitted to hospital with laboratory-confirmed AH1N1 virus
  - 83% were treated with antiviral on admission
  - Only 6% had received an antiviral prior to admission
- **Early treatment[a] leads to 84% reduction in odds of ICU admission** (OR 0.16)



[a]Antiviral therapy within 2 days of symptom onset
ICU, intensive care unit
Yates L et al. *Health Tech Assess*. 2010;14(34):109-182.

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Early Antiviral Therapy Reduces Hospital Length of Stay (LOS) in Pregnant Women

N=865 pregnant women hospitalized with laboratory-confirmed influenza; 85% received antiviral therapy[1]

	Treated ≤2 d Onset	Treated >2 d Onset	*P* Value
Median LOS (severe influenza) n=63	2.2 d	7.8 d	.03
Median LOS (nonsevere influenza) n=802	2.4 d	3.1 d	<.01

Safety of Antiviral Therapy in Pregnant Women

- **Oseltamivir:** Not associated with teratogenicity in any trimester; unlikely to lead to toxicity in breastfed infant; preferred for pregnant and breastfeeding women (CDC)[2,3]
- **Baloxavir and peramivir:** No available data in pregnant or breastfeeding women; no teratogenicity reported in animal studies[4,5]
- **Zanamivir:** Pregnancy category C[6]

1. Oboho IK et al. *J Infect Dis*. 2016;214(4):507-515. 2. Tamiflu (oseltamivir) [package insert]. South San Francisco, CA: Genentech, Inc; 12/2018. 3. CDC. 12/27/18. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed 3/27/19. 4. Xofluza (baloxavir marboxil) [prescribing information]. South San Francisco, CA: Genentech, Inc; 10/2018. 5. Rapivab (peramivir) [prescribing information]. Summit, NJ: Seqirus USA Inc; 9/2018. 6. Relenza (zanamivir) [prescribing information]. Research Triangle Park: GlaxoSmithKline; 3/2010.

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Summary

- Many patients are at high risk for influenza-related complications
- Encourage high-risk patients to seek care for influenza symptoms ASAP
  - Many are unaware of their high-risk status
- History of influenza vaccination does NOT rule out the possibility of influenza virus infection
- Use diagnostic tests with high sensitivity and specificity when warranted
- Do not wait for confirmatory laboratory results before starting antiviral therapy in high-risk patients with suspected influenza

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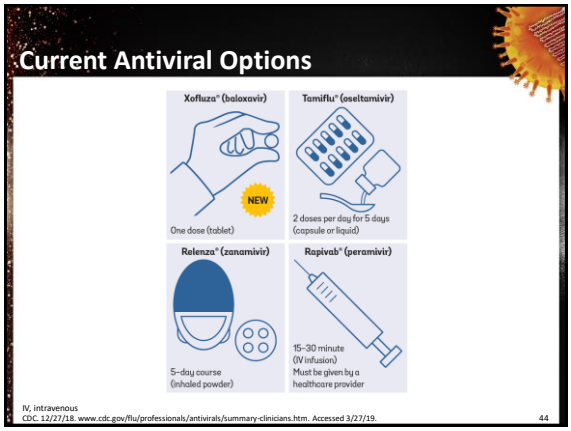

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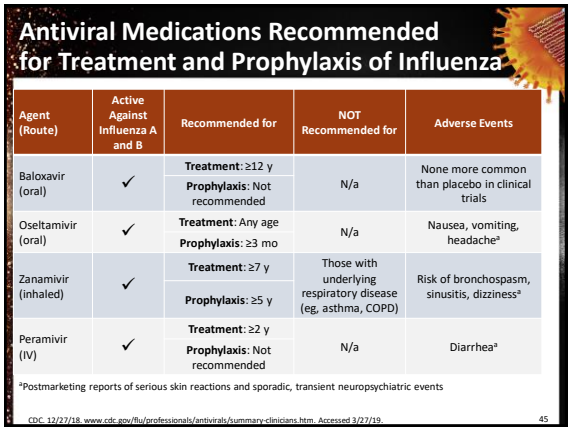

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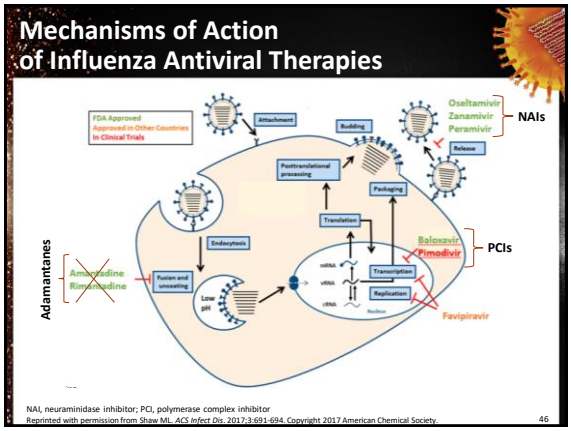

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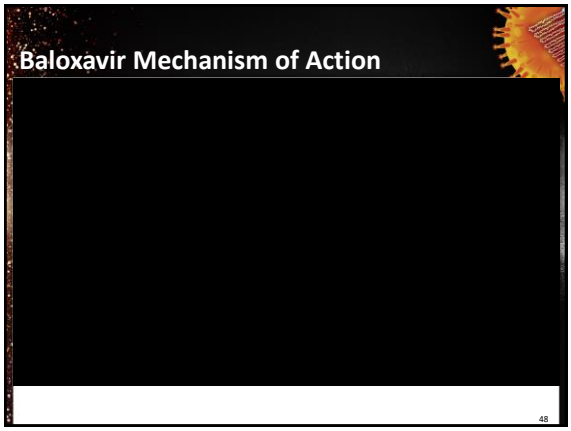

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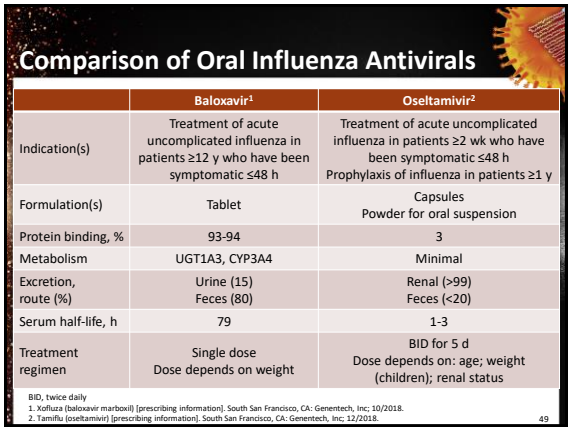

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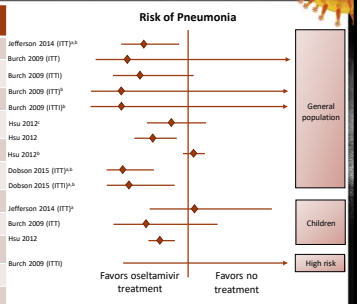
Meta-Analyses: Safety and Efficacy of Oseltamivir

Outcome	Favors Oseltamivir	Favors No Treatment
Mortality Risk in Hospitalized Patients		
General population	✓	
Children	✓	
Pregnant women	✓	
Hospitalization Risk in Nonhospitalized Patients		
General population	✓	
Children	✓	
Time to Alleviation of Symptoms		
General population	✓	
Children	✓	
Elderly	✓	
High risk	✓	



[a]Relative risk [b]Stratified estimates people ≥12 y [c]Adjusted estimates
ITT, intention to treat; ITTI, intention to treat infected (laboratory-confirmed influenza)

Doll MK et al. *J Antimicrob Ther*. 2017;72:2990-3007. 50

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Baloxavir Dosage and Administration

- Single dose
- With or without food
- Available in 20-mg and 40-mg tablets
  - Dose according to weight
  - No renal adjustments noted

Body Weight, kg	Recommended Dose
40 to <80	Single dose 40 mg po
≥80	Single dose 80 mg po

Avoid coadministration with dairy products, calcium-fortified drinks, polyvalent cation-containing laxatives, antacids, or oral supplements
(eg, calcium, iron, magnesium, selenium, or zinc)

Po, by mouth
Xofluza (baloxavir marboxil) [prescribing information]. South San Francisco, CA: Genentech, Inc; 10/2018.

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Baloxavir Marboxil: CAPSTONE-1 Study Design

- Randomized, double-blind, placebo- and oseltamivir-controlled, phase 3 trial conducted during the 2016-2017 influenza season

- Otherwise healthy patients with influenza, 12-64 y of age
- ≤2 d from symptom onset
- Japan and US
- N=1064 (ITT)

Randomized 2:2:1[a]

- Baloxavir marboxil 40 mg or 80 mg, **single dose** (80 mg, body weight ≥80 kg)
- Oseltamivir 75 mg BID, 5 d
- Placebo

- Patients 12-19 y of age were randomized 2:1 to receive either baloxavir or placebo (on day 1 only)
- Primary endpoint: Time to alleviation of symptoms (TTAS)

[a]Patients in all 3 groups received 5-d regimen (baloxavir and a placebo matching oseltamivir, oseltamivir and a placebo matching baloxavir, or placebos only)

Hayden FG et al. *N Engl J Med*. 2018;379:913-923. 52

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Baloxavir Demonstrates Superior TTAS vs Placebo in the CAPSTONE-1 Trial

- Superior TTAS vs placebo in both adolescents and adults
  - Adolescents (median difference, 38.6 h; *P*=.006)
  - Adults (median difference, 25.6 h; *P*<.001)
- More rapid TTAS with baloxavir was evident by day 2

TTAS	Baloxavir, h	Placebo, h	*P* Value	Median Difference, h
ITTI infected	53.7	80.2	<.001	26.5
ITT	65.4	88.6	<.001	23.2
Therapy started within 24 h of symptom onset	—	—	.001	32.8
Therapy started after 24 h of symptom onset	—	—	.008	13.2

Hayden FG et al. *N Engl J Med*. 2018;379:913-923. 53

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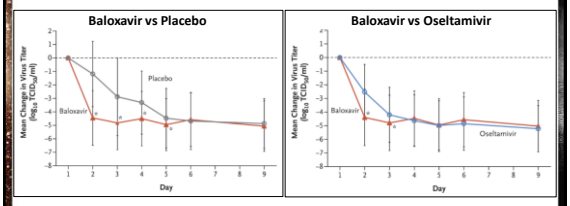
Baloxavir Reduces Viral Load Significantly More Rapidly Than Placebo and Oseltamivir

Change From Baseline in Influenza Infectious Virus Titers Over Time in the CAPSTONE-1 Trial



From *N Engl J Med*, Hayden FG et al, Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents, Volume 379, Pages 913-923.
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Viral Shedding in High-Risk Patients With Influenza vs Otherwise Healthy Patients

- Longer duration of viral shedding
  - Hospitalized patients with underlying medical conditions[1]
    - Shed influenza A virus beyond traditional 5- to 7-d period
  - Obese patients[2]
  - Younger and older patients[3,4]
- Associations with prolonged viral shedding[5]
  - Increased mortality[6]
  - Increased need for mechanical ventilation
  - ECMO dependence
- Reduction in viral load can improve outcomes in H7N9[5]

ECMO, extracorporeal membrane oxygenation
1. Leekha S et al. *Infect Control Hosp Epidemiol*. 2007;28:1071-1076. 2. Maier HE et al. *J Infect Dis*. 2018;218(9):1378-1382. 3. Meschi S et al. *BMC Infect Dis*. 2011;11:140. 4. Ng S et al. *Pediatr Infect Dis J*. 2016;35(5):583-586. 5. Hu Y et al. *Lancet*. 2013;381:2273-2279. 6. de Jong MD et al. *Nat Med*. 2006;12:1203-1207. 55

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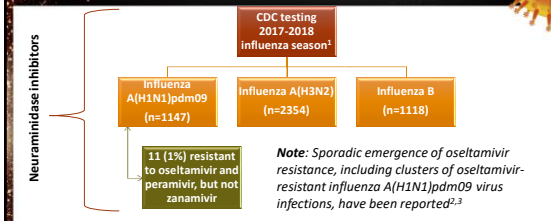
Influenza Antiviral Resistance



***Note**: Sporadic emergence of oseltamivir resistance, including clusters of oseltamivir-resistant influenza A(H1N1)pdm09 virus infections, have been reported[2,3]*

Baloxavir

- In CAPSTONE-1, influenza A(H3N2) virus predominated; 10% of baloxavir recipients with paired sequenced samples had escape mutants detected[4]
- I38T substitution in the polymerase acidic subunit associated with reduced susceptibility of influenza A(H1N1), A(H3N2), and B viruses to baloxavir[5-7]

1. CDC. Updated 11/2/18. www.cdc.gov/flu/about/season/flu-season-2017-2018.htm. Accessed 3/27/19. 2. Hurt AC et al. *Antiviral Res*. 2009;83:90-93. 3. Meijer A et al. *Emerging Infect Dis*. 2009;15:552-560. 4. Hayden FG et al. *N Engl J Med*. 2018;379:913-923. 5. Omoto S et al. *Sci Rep*. 2018;8:9633-9633. 6. Takashita E et al. *Front Microbiol*. Dec 2018. https://doi.org/10.3389/fmicb.2018.03026. Accessed 3/27/19. 7. Noshi T et al. *Antiviral Res*. 2018;160:109-117.

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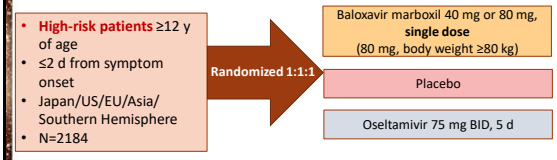
Baloxavir Marboxil: CAPSTONE-2 Study Design

- Randomized, double-blind, placebo-controlled, phase 3 trial



- Primary endpoint: Time to improvement of influenza symptoms (TTIIS)
- Secondary endpoints:
  - Antiviral effects (viral titers, duration of viral shedding)
  - Incidence of influenza-related complications
  - Prescription of antibiotics

Ison M et al. Presented at: IDWeek 2018. Oct 6, 2018; San Francisco, CA. Abstract LB16.

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TTIIS Outcomes in CAPSTONE-2 Trial (High-Risk Patients)

Superior TTIIS in high-risk patients (n=1163) vs placebo, h

Baloxavir	Placebo	*P* Value
73.2	102.3	.0001

Baloxavir	Oseltamivir	*P* Value
73.2	81.0	.8347

Superior TTIIS in high-risk patients with influenza B (n=483) vs both placebo *and* oseltamivir in patients with influenza B, h

Baloxavir	Placebo	*P* Value
74.6	100.6	.0138

Baloxavir	Oseltamivir	*P* Value
74.6	101.6	.0251

Ison M et al. Presented at: IDWeek 2018. Oct 6, 2018; San Francisco, CA. Abstract LB16.

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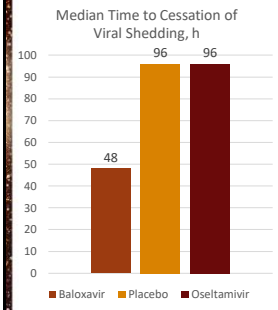
Secondary Outcomes in CAPSTONE-2 Trial (High-Risk Patients)



- Superior viral load reduction vs *both* placebo and oseltamivir
- Reduced incidence of influenza-related complications vs placebo
  - 2.8% vs 10.4% (*P*<.0001)
- Reduced antibiotic use vs placebo
  - 3.4% vs 7.5% (*P*=.0112)

Ison M et al. Presented at: IDWeek 2018. Oct 6, 2018; San Francisco, CA. Abstract LB16.

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CDC Guidance on Selecting an Antiviral[1]

- Any antiviral may be considered for outpatients with acute, uncomplicated influenza in patients with onset within 2 days of presentation
  - *See indications for age restrictions*
- Oseltamivir preferred for:
  - Hospitalized patients
  - Outpatients with severe, complicated, or progressive illness
  - Pregnant or breastfeeding patients
- Zanamivir contraindicated in patients with underlying respiratory conditions; pregnancy category C[2]
- No data *yet* on baloxavir in patients who are hospitalized, pregnant, or have severe renal impairment, or pediatric patients

1. CDC. 12/27/18. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed 3/27/19.
2. Relenza (zanamivir) [prescribing information]. Research Triangle Park: GlaxoSmithKline; 3/2010.

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Baloxavir Is Being Studied in Pediatric Populations: Phase 3 Trials

Study Type (Estimated Enrollment)	Study Population/ Intervention	Primary Outcome Measures	Estimated Primary Completion
Multicenter, single-arm, open-label[1] (n=30)	Cohort 1: ≥3 mo to <12 mo (baloxavir 2 mg/kg) Cohort 2: ≥4 wk to <3 mo (baloxavir 1 mg/kg) Cohort 3: birth to <4 wk (baloxavir 1 mg/kg)	% patients with AEs and SAEs up to day 29	May 2020
Multicenter, randomized, double-blind, active (oseltamivir)-controlled[2] (n=120)	Otherwise healthy patients 1 to <12 y with influenza-like symptoms	% patients with AEs and SAEs up to day 29	June 2020

AE, adverse event; SAE, serious adverse event
1. ClinicalTrials.gov. 11/30/18. www.clinicaltrials.gov/ct2/show/NCT03653364. Accessed 3/27/19.
2. ClinicalTrials.gov. 2/4/19. www.clinicaltrials.gov/ct2/show/NCT03629184. Accessed 3/27/19.
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Baloxavir + NAI Under Investigation in Hospitalized Patients With Severe Influenza

- Randomized, double-blind, placebo-controlled, phase 3 trial

Patients ≥12 y who require hospitalization for severe influenza or acquire influenza during hospitalization (N=240) → **Randomized 2:1**
- Baloxavir marboxil + SOC NAI (oseltamivir, zanamivir, or peramivir)
- Placebo + SOC NAI (oseltamivir, zanamivir, or peramivir)

- Primary endpoint: Time to clinical improvement
  - Time to hospital discharge or time to NEWS2 of ≤2 maintained for 24 h
- Estimated study completion: July 2021

NEWS2, National Early Warning Score 2; SOC, standard of care
ClinicalTrials.gov. 2/4/19. https://clinicaltrials.gov/ct2/show/NCT03684044. Accessed 3/27/19.
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Summary

- Antiviral therapy is recommended as soon as possible in high-risk patients with influenza signs and symptoms—*regardless of whether the patient has been vaccinated*
  - Also consider use in any previously healthy, symptomatic outpatient with symptom onset ≤2 d before presentation AND
  - Symptomatic patients who are household contacts of high-risk patients AND
  - Symptomatic HCPs who care for high-risk patients
- Start antiviral therapy without awaiting laboratory test results in patients with signs and symptoms of influenza
- Choose an antiviral based on efficacy, safety, indications, resistance patterns, and patient characteristics
- Recommendations will likely evolve as new data emerge

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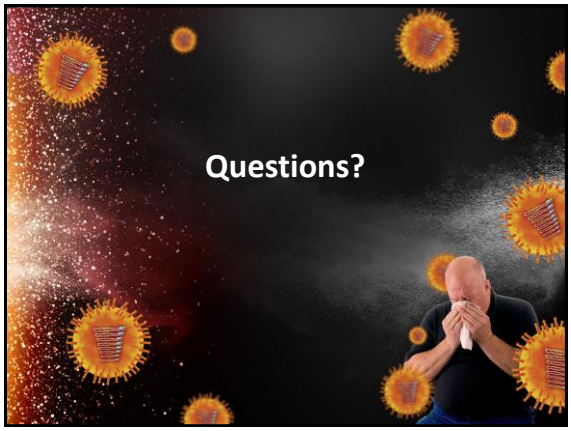

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