Activity presentations are considered intellectual property

These slides may not be published or posted online without permission from Vindico Medical Education (cme@vindicocme.com).

Please be respectful of this request so we may continue to provide you with presentation materials.

FLU FORUM

Are You Ready for the 2020-2021 Influenza Season?

This continuing education activity is provided by

VINDICO medical education

This activity is supported by an educational grant from Genentech, Inc.

This continuing education activity is provided by

This activity is supported by an educational grant from Genentech, Inc.

Activity Co-Chairs

Paul G. Auwaerter, MD, MBA, FIDSA
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Director, Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases
Johns Hopkins University School of Medicine
Baltimore, MD

John J. Russell, MD, FAAFP
Clinical Professor of Family and Community Medicine
Sidney Kimmel Medical College
Thomas Jefferson University
Philadelphia, PA
Chair, Department of Family Medicine
Program Director, Family Medicine Residency
Abington – Jefferson Health
Abington, PA

Agenda

Improving Early Treatment Through Prompt Diagnosis

John J. Russell, MD, FAAFP

Flu Treatment: Are You Ready for the 2021 Season?

Paul G. Auwaerter, MD, MBA, FIDSA

Case Challenges in Flu

Improving Early Treatment Through Prompt Diagnosis

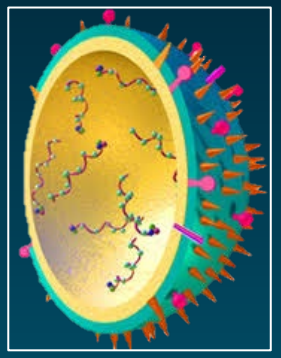
John J. Russell, MD, FAAFP

Clinical Professor of Family and Community Medicine
Sidney Kimmel Medical College
Thomas Jefferson University
Philadelphia, PA
Chair, Department of Family Medicine
Program Director, Family Medicine Residency
Abington – Jefferson Health
Abington, PA

Disclosures

- *Consulting Fee:* GlaxoSmithKline, Sanofi Pasteur
- *Speakers Bureau:* Sanofi Pasteur

History of Influenza



- **Felt to be due to the "influence of the stars"**
- **Epidemics every 1 to 3 years for the past 400 years**
- **Pandemics ("worldwide epidemics")**
  - Occur less often
  - First was in 1590, 31 since then; last major pandemic occurred in 1977 (H1N1 in 2009)
  - 1918-1919: 21 million deaths worldwide; >500,000 deaths in the United States alone

The College of Physicians of Philadelphia. Accessed September 24, 2020. https://www.historyofvaccines.org/content/articles/influenza-pandemics

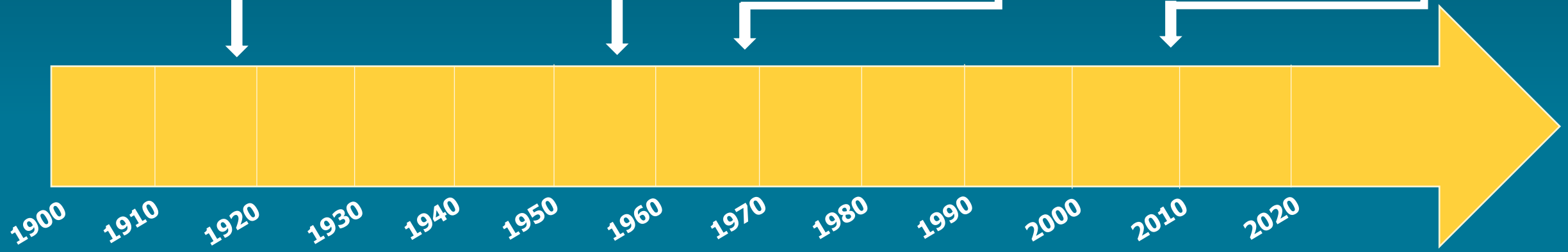
Flu Pandemics in the 20th and 21st Centuries

1918 – H1N1
~50-100 million deaths

1957 – H2N2
~1-2 million deaths

1968 – H3N2
~1 million deaths

2009 – H1N1
>12,700 deaths



Centers for Disease Control and Prevention (CDC). Accessed September 24, 2020. https://www.cdc.gov/flu/pandemic-resources/basics/past-pandemics.html

Flattening the Curve

Effects of social distancing on 1918 flu deaths

As the first cases of the 1918 flu were reported in Philadelphia in September 1918, authorities played down the significance and allowed public gatherings to continue. Closures in Philadelphia were only enacted once the virus had spread. The first cases in St. Louis were reported in early October, with measures to contain the spread enacted two days later. This resulted in a slower spread and lower mortality rate.

Sources: "Public health interventions and epidemic intensity during the 1918 influenza pandemic" by Richard J. Hatchett, Carter E. Mecher, Marc Lipsitch, Proceedings of the National Academy of Sciences May, 2007. Data derived from "Public health interventions and epidemic intensity during the 1918 influenza pandemic" by Richard J. Hatchett, Carter E. Mecher, Marc Lipsitch, Proceedings of the National Academy of Sciences May, 2007.

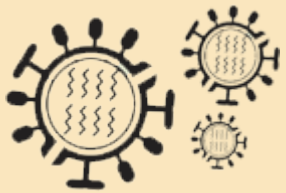
2019-2020 US Influenza Season*: Preliminary Burden Estimates

39 to 56 million
flu illnesses

18 to 26 million
flu medical visits

410,000 to 740,000
flu hospitalizations

24,000 to 62,000
flu deaths



*Data from October 1, 2019 to April 4, 2020.

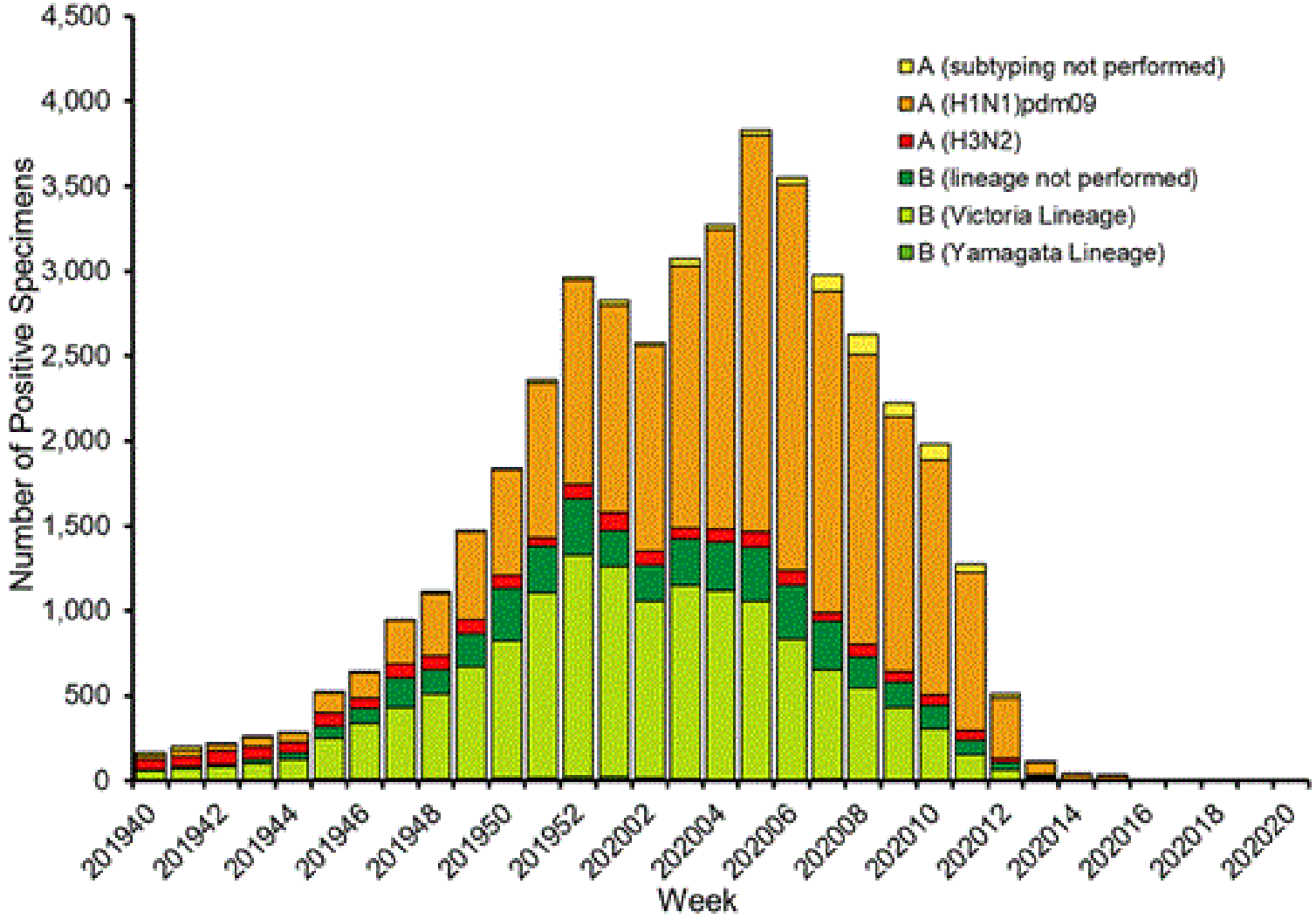
Centers for Disease Control and Prevention. Accessed August 19, 2020. https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm
Images courtesy of Gan Khoon Lay and Nubala Karim Barsha from the Noun Project.

Factors Affecting the Burden of Influenza

- Burden of disease varies widely and determined by:
  - Characteristics of circulating viruses
  - Timing of the season
  - Vaccine efficacy
    (may be poor match for circulating strains in some years)
  - How many people were vaccinated

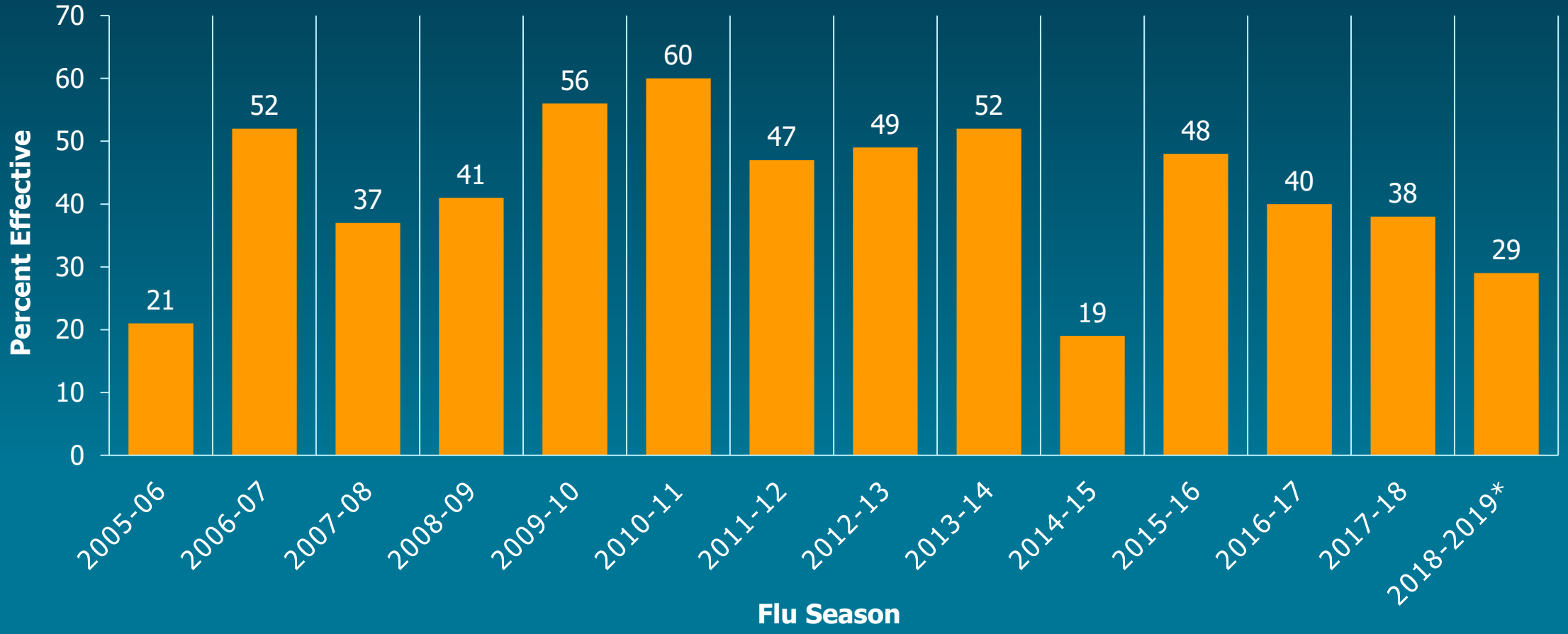
Centers for Disease Control and Prevention. Accessed August 16, 2020. https://www.cdc.gov/flu/about/burden/index.html

Influenza Positive Tests Reported to the CDC by U.S. Public Health Laboratories, National Summary, 2019 – 2020 Season



Centers for Disease Control and Prevention. Accessed September 14, 2020. https://www.cdc.gov/flu/weekly/weeklyarchives2019-2020/Week15.htm

Effectiveness of Seasonal Flu Vaccines: 2008-2019 Flu Seasons



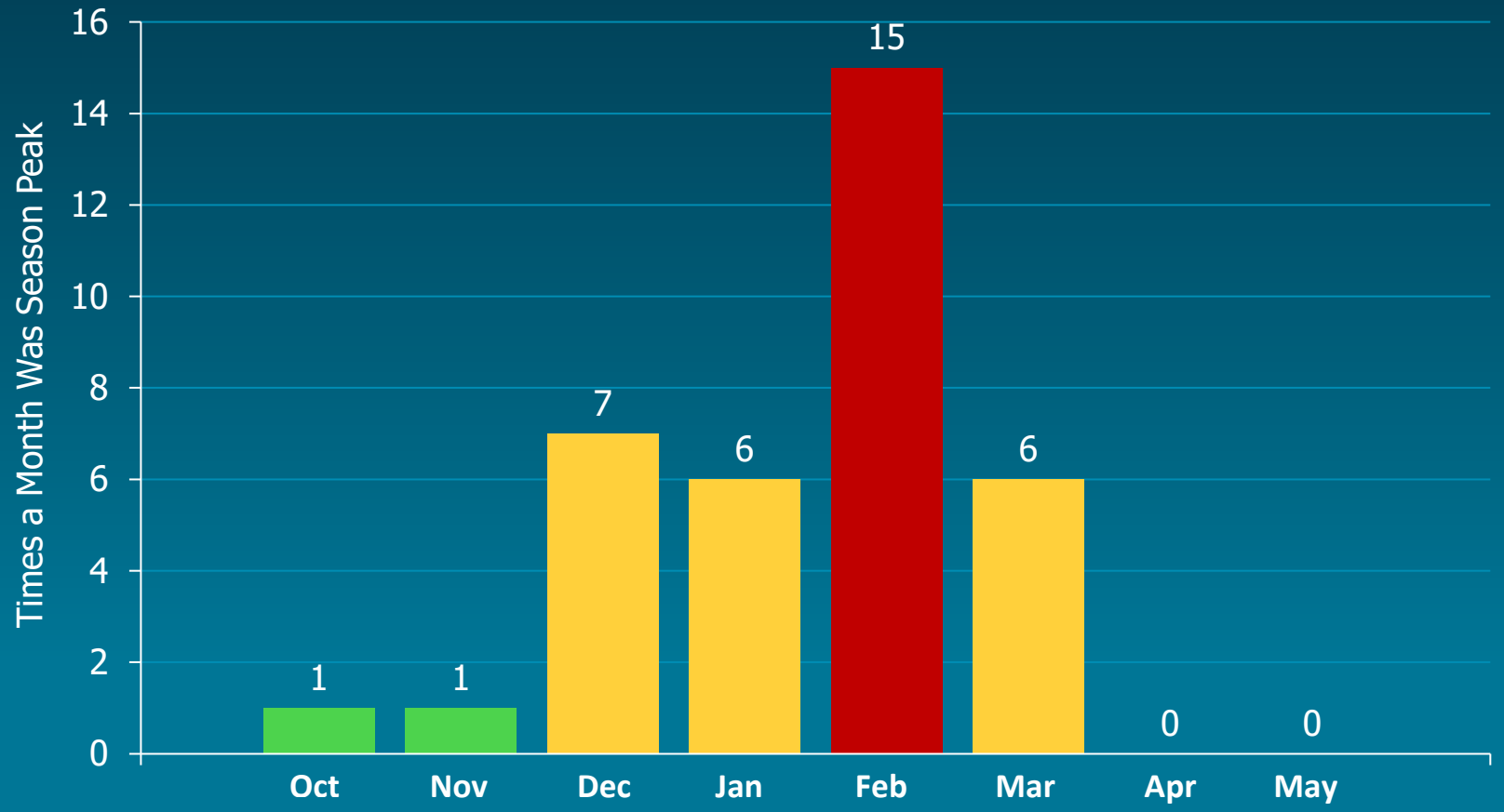
*Vaccine effectiveness estimates for 2018-2019 are preliminary estimates and will be updated with final estimates at the end of the 2018-2019 US influenza season.
Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm

Vaccine Coverage – How Are We Doing?

	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018
6 months-4 years	70.4%	70.4%	70.0%	70.4%	**67.8%**
5-12 years	61.0%	61.8%	61.8%	59.9%	**59.5%**
13-17 years	46.4%	46.4%	46.8%	48.8%	**47.4%**
18-49 years with high-risk condition	38.7%	39.3%	39.5%	39.3%	**31.3%**
18-49 years without high-risk condition	31.1%	32.6%	31.5%	32.6%	**26.1%**
50-64 years	45.3%	47.0%	43.6%	45.4%	**39.7%**
65+ years	65.0%	66.7%	63.4%	65.3%	**59.6%**

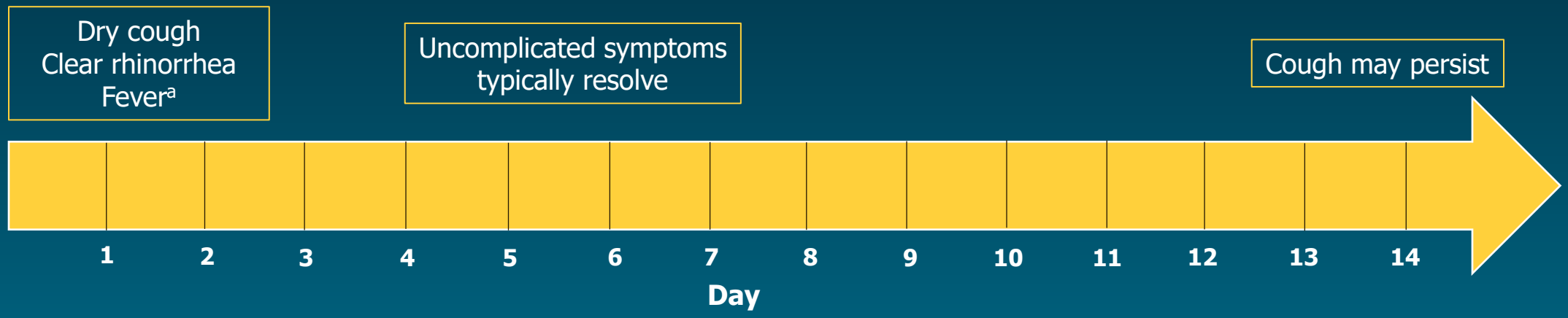
Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/fluvaxview/coverage-1718estimates.htm
Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/fluvaxview/coverage-1718estimates-children.htm

Peak Month of Flu Activity 1982-1983 Through 2017-2018



"Peak month of flu activity" is the month with the highest percentage of respiratory specimens testing positive for influenza virus infection during that influenza season. Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/about/season/flu-season.htm

Influenza Clinical Course



- Abrupt onset of constitutional and upper respiratory tract symptoms:

Fever[b]/chills	Nonproductive cough
Myalgia	Sore throat
Headache	Rhinitis
Malaise	Vomiting and diarrhea (more common in children)

- Nausea, vomiting, diarrhea may occur with respiratory symptoms in children
- Atypical signs/symptoms can occur in frail and institutionalized elderly patients

[a]Increases to 104°F within 12 hours, then decreases 0.5 to 1.0°F/day.
[b]Elderly and immunosuppressed patients may not have fever.

Centers for Disease Control and Prevention. Accessed August 19, 2020. https://www.cdc.gov/flu/professionals/acip/clinical.htm

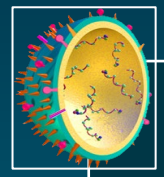
Influenza Complications

- Although most patients recover quickly from influenza, some develop complications that may be life-threatening:
  - Pneumonia (viral, bacterial, mixed viral and bacterial, fungal)
  - Asthma/COPD exacerbation
  - Myocarditis, worsening of congestive heart failure
  - Myocardial infarctions
  - Stroke, encephalitis
  - Sepsis, multi-organ failure

COPD = chronic obstructive pulmonary disease.

Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/symptoms/symptoms.htm

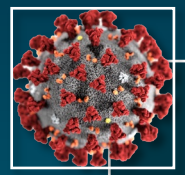
Differentiating Influenza From COVID-19



Influenza[1]

- Transmission: respiratory droplets, contaminated surfaces
- Incubation period: mean 2 days, range 1 to 4 days
- Overall hospitalization rate: 2%
- Overall fatality rate: ~0.1%

VS



COVID-19*

- Transmission: respiratory droplets, contaminated surfaces
- Incubation period: mean 6.4 days, range 2 to 12 days[2]
- Hospitalization rate: 1.1% (aged 20–29 years) to 18.4% (aged ≥80 years)[3]
- Estimated fatality rate[3,4]:
  - Approximately 6 to 12× greater than seasonal influenza, but it has an extremely steep age gradient
  - Current data suggest a range (0.66% to >4%)
- Children are less symptomatic with infection and much less prone to severe illness[2]

To be determined…

- How common is asymptomatic infection and transmission?
- Rates of symptomatic infection/complications in the pediatric population?

*Information is rapidly evolving and subject to change.

COVID-19 = 2019 corona virus disease.

1. Centers for Disease Control and Prevention. Accessed August 19, 2020. https://www.cdc.gov/flu/about/disease/spread.htm
2. Auwaerter PG. Accessed August 19, 2020. https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2_
3. Verity R, et al. *Lancet Infect Dis*. 2020;20(6):669-677.
4. Johns Hopkins Coronavirus Resource Center. Accessed April 3, 2020. https://coronavirus.jhu.edu/map.html

Commonly Used Influenza Virus Testing Methods: Overview

Type of Test	Acceptable Specimens	Time to Results	Sensitivity/ Specificity
Rapid influenza diagnostic test (RIDT)	NP swab, nasal swab, throat swab, aspirate or wash	10-15 minutes	*Low to moderate* sensitivity High specificity
Rapid molecular assay (influenza viral RNA or nucleic acid detection)	NP swab, nasal swab	15-30 minutes	High sensitivity High specificity
Direct and indirect immunofluorescence assays	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours	*Moderate* sensitivity High specificity
Molecular assays (including RT-PCR)	NP or throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	1-8 hours	High sensitivity High specificity
Multiplex molecular assays	NP or throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	1-2 hours	High sensitivity High specificity

NP = nasopharyngeal probe; RNA = ribonucleic acid; RT-PCR = reverse transcription-polymerase chain reaction.

Centers for Disease Control and Prevention. Accessed August 19, 2020. https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm;
Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.

Influenza Testing – RIDT

Rapid Influenza Diagnostic Tests (RIDTs):

- Office-based, point-of-care tests
- Immunochromatographic assays detect specific influenza viral antigens in a respiratory specimen
- Have inconsistent accuracy; historically, sensitivity has ranged from 10% to 80%, with specificity above 90%
- Meta-analysis[1] had pooled sensitivity of 62.3%; specificity was 98.2%
- Sensitivity was 13% higher in children
- In 2017, the FDA reclassified RIDTs to meet minimum specific criteria for sensitivity/specificity[2]

FDA = US Food and Drug Administration.

1. Chartrand C, et al. *Ann Intern Med*. 2012;156(7):500-511.
2. Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

Influenza Rapid Molecular Assays

- Tests for nucleic acid
- Tests for influenza A or B
- Does not distinguish strain of influenza
- Results in 15 to 30 minutes
- High sensitivity
- High specificity

Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.
Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

Influenza RT-PCR Testing

- RT-PCR is a highly sensitive and highly specific testing modality for detection of influenza A and B viral RNA in respiratory specimens
- Results may take 4 to 6 hours or more once testing is started
- Some of the newer cartridge-based RT-PCR assays can yield results in 60 to 80 minutes
- RT-PCR can be useful as a confirmatory test and identify influenza virus types and influenza A virus subtypes
- *Recommended* test by IDSA for hospitalized patients
- Three multiplex RT-PCR assays target a panel of microorganisms using multiplex RT-PCR. Multiplex respiratory pathogen panels range from narrow (targeting influenza A and B viral and RSV RNA) to broad (targeting more than a dozen respiratory viruses and other pathogens in respiratory specimens)
- Turnaround times to results range from 1 to 8 hours. These assays are preferred for immunocompromised patients and may be useful for other hospitalized patients

IDSA = Infectious Disease Society of America; RSV = respiratory syncytial virus.

Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.
Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

Office-Based PCR

- Real-time PCR testing
- Closed system
- CLIA-waived
- Less than 5 minutes of hands-on time; 20 minutes total
- Compared with routine PCR, sensitivity is 99.2% and specificity is 100%
- Other CLIA-waived, point-of-care FDA-cleared nucleic acid amplification

ID NOW:	sensitivity 96.3%; specificity 97.4% (influenza A)
	sensitivity 100%; specificity 97.15% (influenza B)
cobas Liat:	sensitivity 100%; specificity 100%

CLIA = Clinical Laboratory Improvement Amendments; PCR = polymerase chain reaction.

Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm
Binnicker MJ, et al. *J Clin Microbiol*. 2015;53(7):2353-2354.
Nolte FS, et al. *J Clin Microbiol*. 2016;54(11):2753-2766.
ID NOW INFLUENZA A & B 2. Accessed September 24, 2020. https://www.alere.com/en/home/product-details/id-now-influenza-ab-2.html

Which Tests Should Be Used to Diagnose Influenza?

Guidelines from the Infectious Diseases Society of America

In ***outpatients***, clinicians should use rapid molecular assays (ie, NAATs) over RIDTs to improve detection of influenza virus infection.

In ***hospitalized patients***, clinicians should use RT-PCR or other molecular assays over other influenza tests to improve detection of influenza virus infection.

For initial or primary diagnosis of influenza, clinicians should ***not*** use viral cultures, because results will not be available in a timely manner to inform clinical management.

For diagnosis of influenza, clinicians should ***not*** use serologic testing, because results from a single serum specimen cannot be reliably interpreted.

NAAT = nucleic acid amplification test.

Infectious Diseases Society of America. Accessed August 19, 2020. https://www.idsociety.org/practice-guideline/influenza/; Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.

Influenza Testing – Negative Predictive Values (NPV)

Influenza Prevalence	Sensitivity	Negative Predictive Value	False-Negative Rate
Moderate 20%	Low 50%	Moderate 86%-89%	Moderate 11%-14%
Moderate 20%	High 90%	High 97%-99%	Low 2%-3%
High 40%	**Low 50%**	**Moderate 70%-75%**	**Moderate 25%-30%**
High 40%	High 90%	High 93%-94%	Low 6%-7%

When influenza prevalence is relatively high, the NPV is low, and false-negative test results are more likely.

Centers for Disease Control and Prevention. Rapid Diagnostic Testing for Influenza: Information for Clinical Laboratory Directors. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm

Influenza Testing – Positive Predictive Values (PPV)

Influenza Prevalence	Specificity	Positive Predictive Value	False-Positive Rate
Very low 2.5%	**Moderate 80%**	**Very low 6%-12%**	**Very high 88%-94%**
Very low 2.5%	High 98%	Low 39%-56%	High 44%-61%
Moderate 20%	Moderate 80%	Low 38%-56%	High 44%-62%
Moderate 20%	High 98%	High 86%-93%	Low 7%-14%

When influenza prevalence is relatively low, PPV is low and false-positive test results are more likely.

Centers for Disease Control and Prevention. Rapid Diagnostic Testing for Influenza: Information for Clinical Laboratory Directors. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm

Populations at Higher Risk for Medical Complications Attributable to Severe Influenza

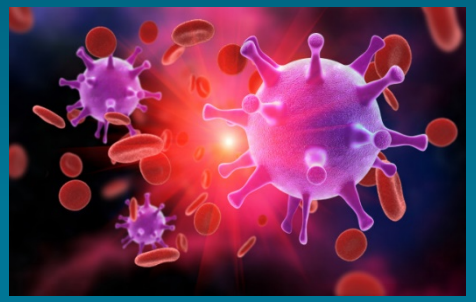
Children <5 years, especially <2 years

Children/adolescents on aspirin or salicylate-containing medications

Chronic disorders/disease (eg, diabetes, heart, liver, renal disease, COPD)

Neurologic conditions or disorders

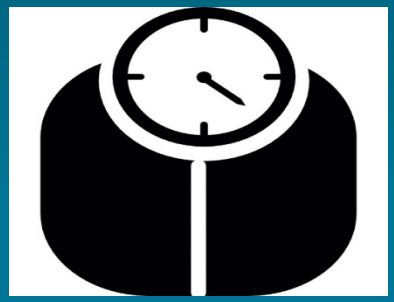
Adults ≥65 years



Immunosuppressed, HIV+

Pregnant or postpartum (2 weeks after delivery)

American Indians/ Alaska Natives



Extreme obesity (BMI ≥40 kg/m^2)

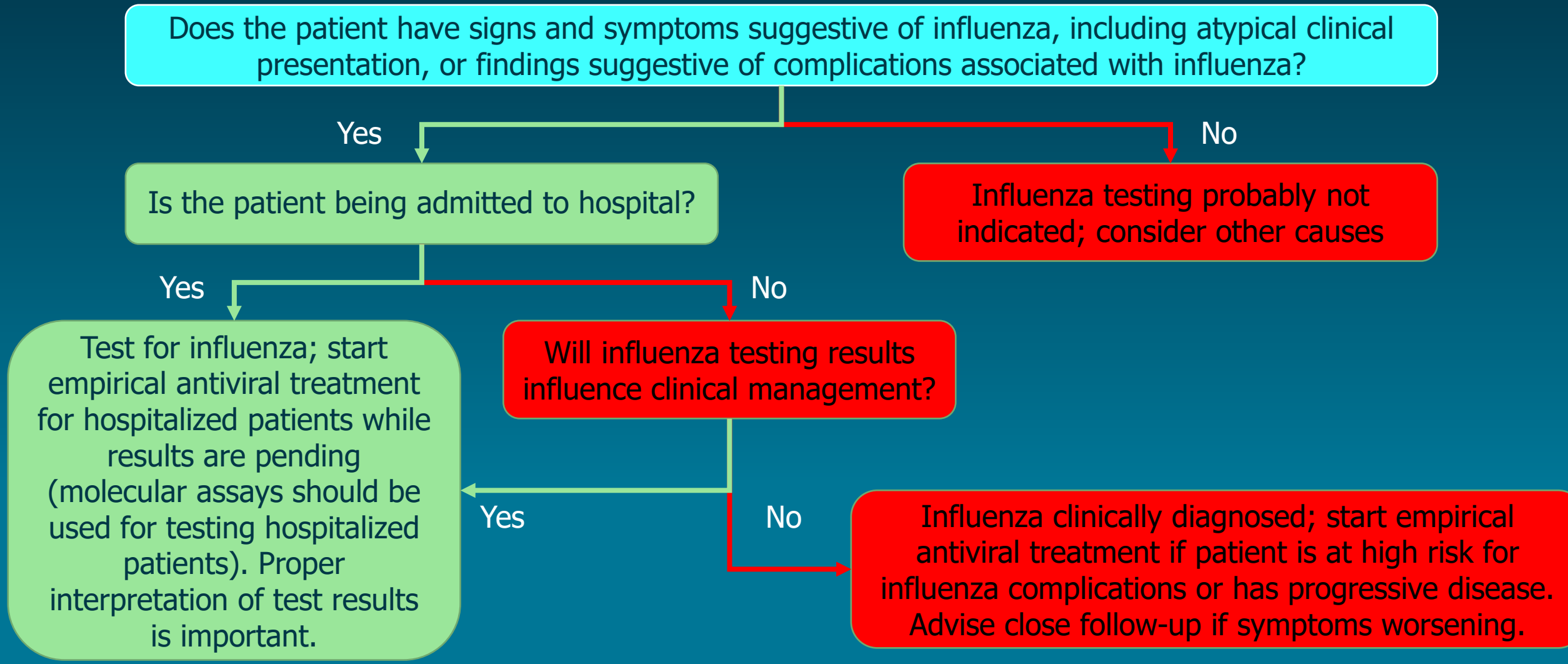
Nursing home residents

BMI = body mass index; HIV = human immunodeficiency virus.

Grohskopf LA, et al. *MMWR Recomm Rep*. 2017;66(2):1-20; Centers for Disease Control and Prevention. Accessed Sep 24, 2020. https://www.cdc.gov/flu/highrisk/index.htm

Images courtesy of John J. Russell, MD, FAAFP

Influenza Antiviral Treatment Guideline



Centers for Disease Control and Prevention. Accessed August 19, 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm#summary

Flu Treatment: Are You Ready for the 2021 Season?

Paul G. Auwaerter, MD, MBA, FIDSA

Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Director, Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases
Johns Hopkins University School of Medicine
Baltimore, MD

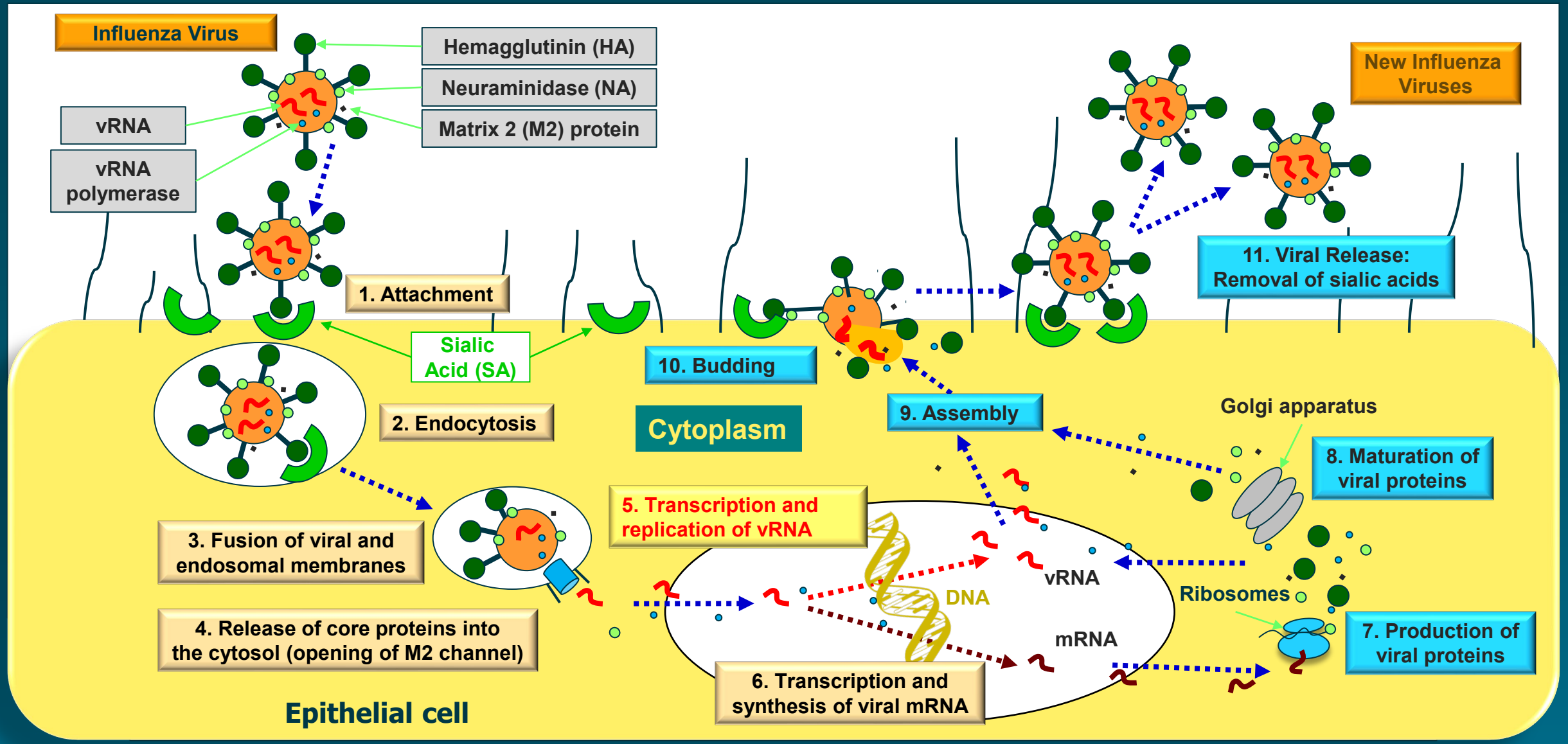
Disclosures

- *Consulting Fee:* Advanced Biotherapeutics, DiaSorin
- *Ownership Interest:* Johnson & Johnson

Influenza Treatment and Prophylaxis

- Influenza replication and mechanisms of antiviral action
- Agents for treatment of flu:
  - Adamantanes (amantadine, rimantadine)
  - Neuraminidase inhibitors (oseltamivir, peramivir, zanamivir)
  - Endonuclease inhibitors (baloxavir marboxil)
- Guidelines for treatment of influenza

Influenza Lifecycle



mAb = monoclonal antibody; mRNA = messenger RNA; RNA = ribonucleic acid; vRNA = viral RNA.

Ramirez J. *The University of Louisville Journal of Respiratory Infections*. 2019;3(1):Article 9. https://ir.library.louisville.edu/jri/vol3/iss1/. Open Access.

6 FDA-approved Drugs for Influenza

- **4 recommended for influenza A + B:**
  - Neuraminidase inhibitors:
    1. Oseltamivir phosphate (oral)
    2. Zanamivir (inhaled)
    3. Peramivir (IV)
  - Cap-dependent endonuclease inhibitor:
    4. Baloxavir marboxil (oral)

Not recommended:

- Adamantanes (M2 ion channel):
  - Amantadine
  - Rimantadine
    - High levels of drug resistance to circulating influenza A, ineffective for influenza B

Current FDA indications for recommended oral agents:

Oseltamivir: for treating influenza in patients ≥1 year who have been symptomatic for no more than 2 days, and for prophylaxis of influenza in patients ≥1 year

Baloxavir: for treating acute uncomplicated influenza within 2 days of illness onset in people ≥12 years who are otherwise healthy or at high risk of developing flu-related complications

FDA = US Food and Drug Administration; IV = intravenous; M2 = Matrix-2.

Centers for Disease Control and Prevention (CDC). Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Key Treatment Points:
When Should Treatment Be Considered?

IDSA Guidelines

Criteria for considering antiviral treatment*:
Outpatients with illness onset ≤2 days before presentation
Symptomatic outpatients who are household contacts of persons who are at high risk for developing complications from influenza, particularly those who are severely immunocompromised
Symptomatic health care providers who care for patients who are at high risk for developing complications from influenza, particularly those who are severely immunocompromised

*Regardless of influenza vaccination history

Guideline are paraphrased from cited article.

IDSA = Infectious Diseases Society of America.

Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.

Key Treatment Points:
Who Should Be Treated for a Positive Influenza Test?

IDSA Guidelines

Criteria for initiating antiviral treatment as soon as possible*:
Persons (any age) who are hospitalized with influenza, regardless of illness duration prior to hospitalization
Outpatients (any age) with severe or progressive illness, regardless of illness duration
Outpatients who are deemed at high risk for developing complications from influenza (ie, those with chronic medical conditions and immunocompromised patients)
Children <2 years of age and adults ≥65 years of age
Pregnant women and those within 2 weeks postpartum

*Regardless of influenza vaccination history

Guidelines are paraphrased from cited article. For items indicated in parentheses, see Table 1 of the cited article for category, grade, and definition for ranking recommendations.

Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.

Populations at Higher Risk for Medical Complications Attributable to Severe Influenza

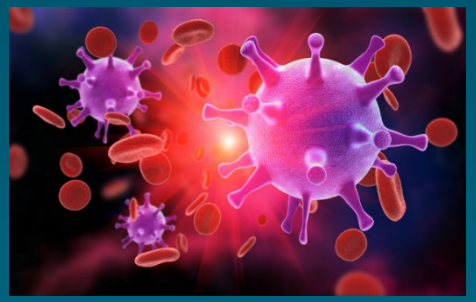
Children <5 years, especially <2 years

Children/adolescents on aspirin or salicylate-containing medications

Chronic disorders/disease (eg, diabetes, heart, liver, renal disease, COPD)

Neurologic conditions or disorders

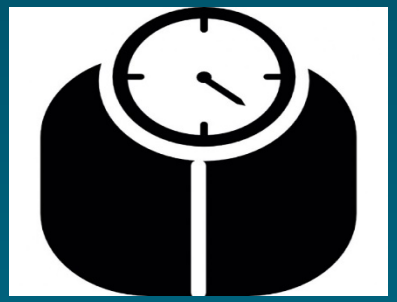
Adults ≥65 years



Immunosuppressed, HIV+

Pregnant or postpartum (2 weeks after delivery)

American Indians/ Alaska Natives



Extreme obesity (BMI ≥40 kg/m^2)

Nursing home residents

BMI = body mass index; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.

Grohskopf LA, et al. *MMWR Recomm Rep*. 2017;66(2):1-20; Centers for Disease Control and Prevention. Accessed Sep 24, 2020. https://www.cdc.gov/flu/highrisk/index.htm

Images courtesy of John J. Russell, MD, FAAFP

FDA-approved Drugs for Influenza Treatment

Antivirals	Mechanism of Action	Route of Administration	Dosing (Adults)
Neuraminidase inhibitors			
Oseltamivir phosphate	Block viral neuraminidase enzyme; active against influenza A and B	Oral (capsules, suspension)	**75 mg BID x 5 days**
Zanamivir		Inhaled	**10 mg BID x 5 days**
Peramivir		Intravenous	**600 mg IV (1 dose)**
Cap-dependent endonuclease inhibitor			
Baloxavir marboxil	Interferes with viral RNA transcription and blocks virus replication; active against influenza A and B	Oral (tablets) 20 mg and 40 mg (blister card contains two tablets)	40 to <80 kg (88 lb to <176 lb): **One 40 mg dose** (Two 20-mg tablets taken at same time) ≥80 kg (≥176 lb): **One 80 mg dose** (Two 40-mg tablets taken at same time)
Adamantanes			
Amantadine	Target M2 ion channel protein of influenza A viruses; active against influenza A, not B	**As in past seasons, high levels of resistance (>99%) to adamantanes**	
Rimantadine		**Not recommended for treatment or prophylaxis of influenza A**	

BID = twice daily.

Baloxavir marboxil [prescribing information]. Accessed September 24, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210854s001lbl.pdf
Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm#overview

Side Effects of Available Antivirals

Drug	Side Effects
Oseltamivir	• **AEs:** nausea, vomiting, headache • **Post-marketing reports:** serious skin reactions, sporadic neuropsychiatric events*
Peramivir	• **AEs:** diarrhea • **Post-marketing reports:** serious skin reactions; sporadic, transient neuropsychiatric events*
Zanamivir	• **Allergic reactions:** oropharyngeal or facial edema, skin rash • **AEs:** risk of bronchospasm, especially in those with underlying airways disease; dizziness; ear, nose, and throat infections • **Post-marketing reports:** sporadic, transient neuropsychiatric events*
Baloxavir	• **AEs:** diarrhea, bronchitis, nasopharyngitis, headache, nausea

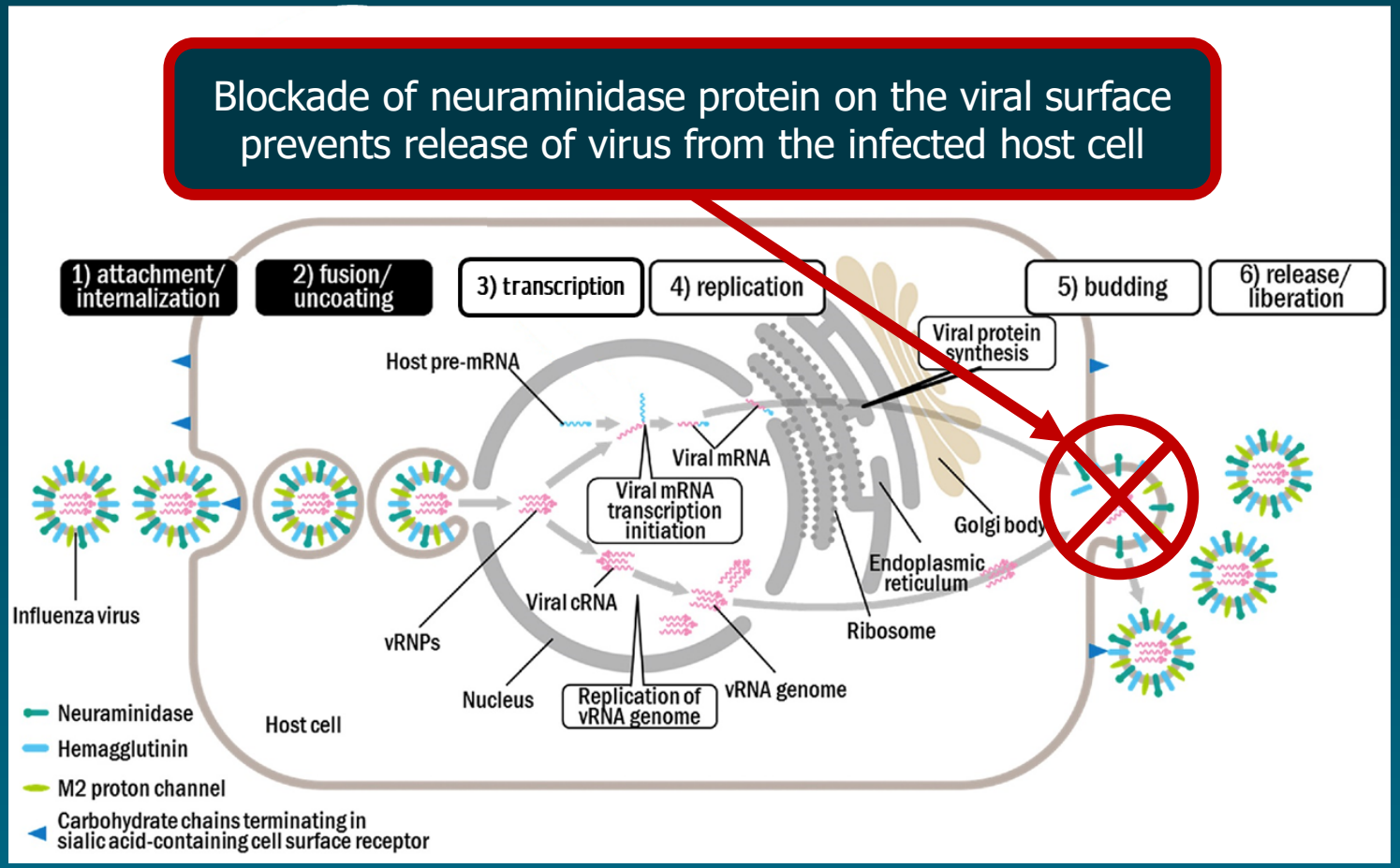
*Self-injury or delirium, mainly reported among Japanese adolescent and adults, may be due to the viral infection itself

AEs = adverse events.

Centers for Disease Control and Prevention. Accessed September 24, 2020. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Treatment of Influenza: Neuraminidase Inhibitors (NAIs)

Neuraminidase Inhibitors



- Influenza virus peak release occurs 24 to 72 hours after symptom onset:
  - Informs when antivirals are most beneficial
  - Important that the drug acts as soon as possible
  - No viral "killing"; different than an antibacterial

cRNA = complementary RNA; vRNP = viral ribonucloprotein particles.
Adapted from Noshi T, et al. *Antiviral Res*. 2018;160:109-117. Open Access.

Meta-analysis of Oral Oseltamivir vs No Antiviral Therapy

Outcome	Number of Patients (Studies)	Pooled Odds Ratio (95% CI)
Mortality	681 (3)	0.23 (0.13-0.43)
Hospitalization	150,710 (4)	0.75 (0.66-0.89)
Otitis media	78,407 (2)	0.75 (0.64-0.87)
Pneumonia	150,466 (3)	0.83 (0.59-1.16)
Cardiovascular events	100,830 (2)	0.58 (0.31-1.10)
		<1.0: favors oseltamivir; >1.0 favors no antiviral

- Observational studies of hospitalized patients, no RCTs
- Studies of both seasonal influenza and pandemic influenza

- **Findings suggest that neuraminidase inhibitors decrease mortality**
  - **Odds ratio 0.23 for oral oseltamivir (95% CI 0.13-0.43)**
  - **Mortality effect mostly derived from use in patients with <3 days of symptoms**
- Low-quality evidence and many unmeasured confounders

RCTs = randomized controlled trials.
Adapted from: Hsu J, et al. *Ann Intern Med*. 2012;156(7):512-524.

Oseltamivir vs Placebo: Meta-analysis Findings

- Oseltamivir was associated with about a 1-day improvement in clinical symptoms

Key On-treatment AEs

Adverse Event	Oseltamivir (n=2401)	Placebo (n=1917)	*P*-value	Risk Difference (95% CI)
Gastrointestinal disorders	574	370	.0019	**4.0%** (1.4 to 6.9)
Nausea	247	118	<.0001	**3.7%** (1.8 to 6.1)
Vomiting	201	63	<.0001	**4.7%** (2.7 to 7.3)
Diarrhea	147	147	.016	−1.9% (−3.1 to −0.4)
Neurological disorders	124	93	.97	−0.3% (−1.7 to 1.6)
Psychiatric disorders	11	13	.27	−0.1% (−0.5 to 0.7)

Adapted from: Dobson J, et al. *Lancet*. 2015;385(9979):1729-1737.

Efficacy and Safety of Oseltamivir in Children

- Systematic review identified RCTs of oseltamivir in children
  - Examined protocol-defined outcomes based on individual patient data
  - 2-stage, random-effects meta-analysis conducted to determine efficacy of treatment in reducing duration of illness (differences in RMST by treatment group)
- Data from 5 trials included
  - ITT: N=2561; ITT infected (ITTI): N=1598

Findings:

- **Oseltamivir significantly reduced duration of illness in the ITTI population**
  - RMST difference −17.6 hrs; CI −34.7 to −0.62 hrs
  - Reduction larger in trials that enrolled patients **without asthma** −29.9 hours; 95% CI, −53.9 to −5.8 hours
- Risk of otitis media 34% lower in ITT population
- Vomiting was the only AE with significantly higher risk in treatment group

ITT = intent-to-treat; RMST = restricted mean survival time.

Malosh RE, et al. *Clin Infect Dis*. 2018;66(10):1492-1500.

Other NAIs: Peramivir

- Parenteral agent
  - Single dose
- FDA approved for uncomplicated influenza, <48 hours from symptom onset
- Mostly used off-label:
  - ICU
  - Lack of GI absorption

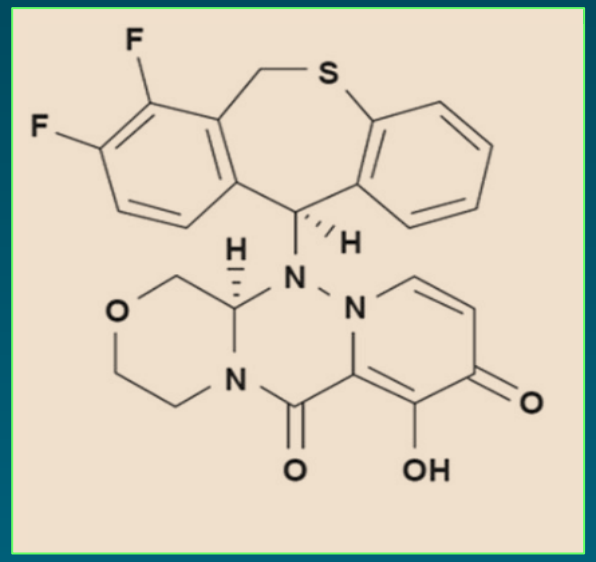
RCT of Peramivir
N=398 **hospitalized patients**
Over half were >48 hours from symptom onset
Peramivir + SOC vs placebo + SOC • The primary efficacy analysis included 121 patients who did not receive a concurrent NAI as part of the SOC
Endpoints: median time to clinical resolution and change in viral shedding
No significant clinical benefit demonstrated for peramivir + SOC compared with placebo + SOC

GI = gastrointestinal; ICU = intensive care unit; SOC = standard of care.

deJong MD, et al. *Clin Infect Dis*. 2014;59(12):e172-185.

Treatment of Influenza: Baloxavir Cap-dependent Endonuclease Inhibitor

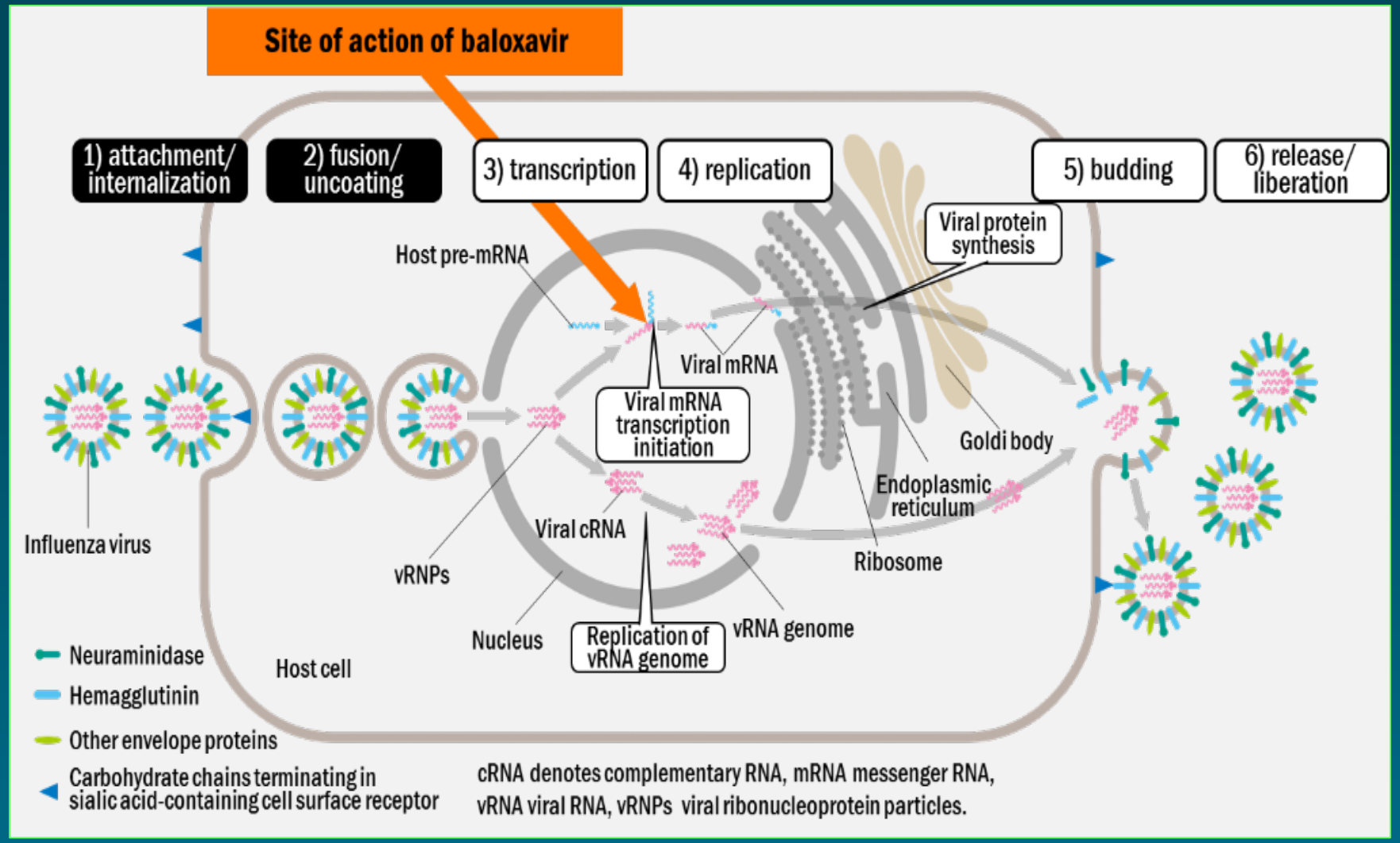
Baloxavir: Cap-dependent Endonuclease Inhibitor



- Baloxavir marboxil is a prodrug of baloxavir acid
- FDA approved (2018) for acute uncomplicated influenza A and B:
  - ≥12 years symptomatic <48 hours
- Additional approval (October 2019) for patients at high risk of developing influenza-related complications
  - ≥12 years of age, <48 hours of symptoms
- Inhibits cap-dependent endonuclease
- Given as a **single dose** (2 tablets):
  - Avoid co-administration with polyvalent cation-containing laxatives, antacids, or oral supplements (eg, calcium, iron, magnesium, selenium, or zinc)
- Adverse event profile comparable to oseltamivir

Abraham GM, et al. *Clin Infect Dis*. Published online February 5, 2020. doi:10.1093/cid/ciaa107; Noshi T, et al. *Antiviral Res*. 2018;160:109-117. Open Access. Baloxavir marboxil [prescribing information]. Accessed September 24, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210854s001lbl.pdf

Baloxavir: Mechanism of Action



Noshi T, et al. *Antiviral Res*. 2018;160:109-117. Open Access.

Baloxavir: CAPSTONE-1 Study

Phase 3, randomized, double-blind, placebo- and oseltamivir-controlled study:

- Outpatients 12-54 years old
- Patients 12-19 years randomly assigned to baloxavir or placebo (Day 1 only)
- 1436 randomized; 1064 intention-to-treat population

RANDOMIZED

2:1

Baloxavir single dose
(40 mg for BW <80 kg;
80 mg for BW ≥80 kg)

Oseltamivir 75 mg BID
Days 1-5

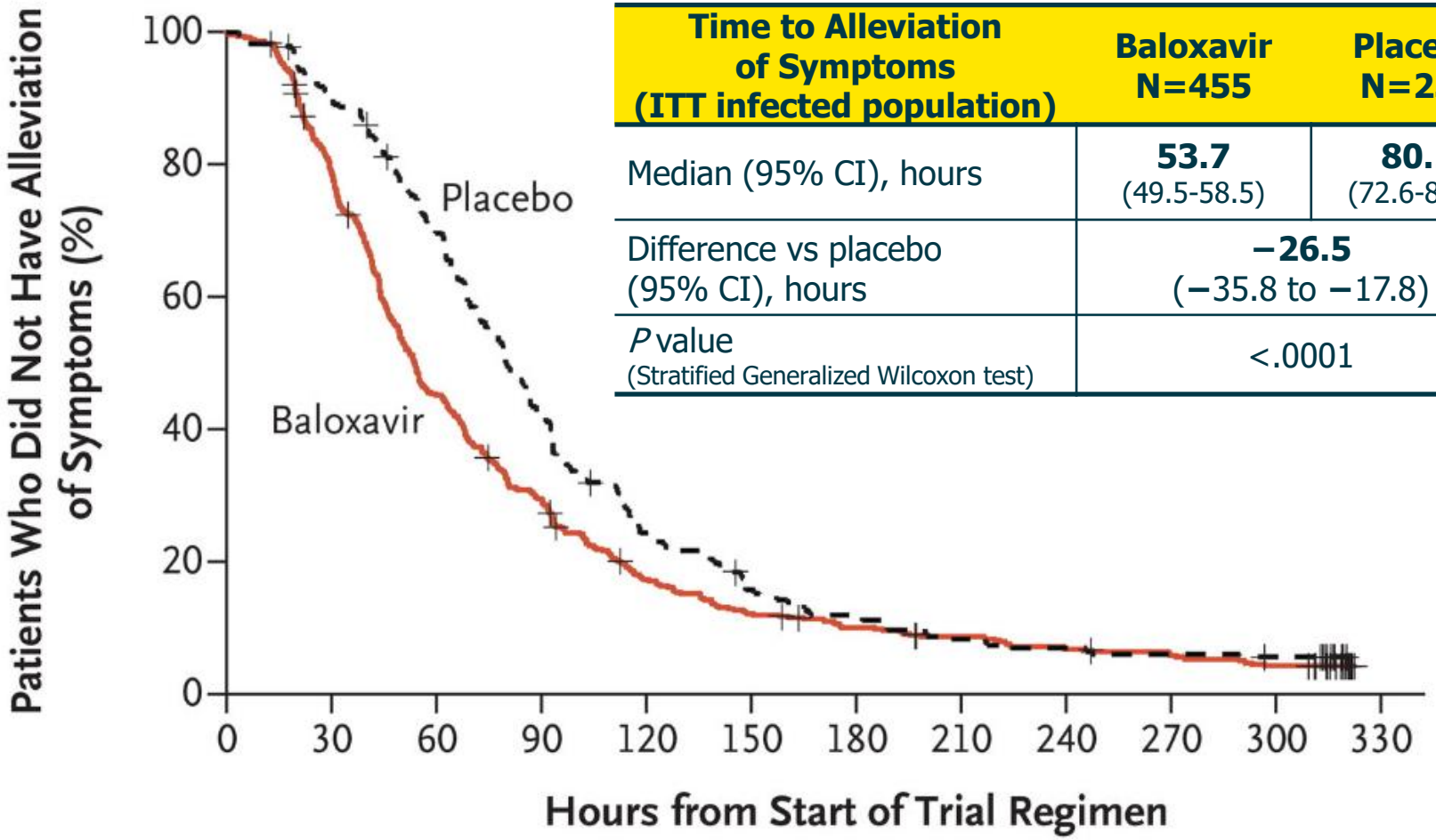
Matching placebos

Primary endpoint
Time to alleviation of influenza symptoms

BW = body weight.

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

CAPSTONE-1: Baloxavir for Uncomplicated Influenza



Time to Alleviation of Symptoms (ITT infected population)	Baloxavir N=455	Placebo N=230
Median (95% CI), hours	**53.7** (49.5-58.5)	**80.2** (72.6-87.1)
Difference vs placebo (95% CI), hours	**−26.5** (−35.8 to −17.8)	
P value (Stratified Generalized Wilcoxon test)	<.0001	

- Baloxavir significantly reduced duration of fever by ~1 day versus placebo (median time: 24.5 hours versus 42 hours; *P*<.0001)
- Median time to alleviation of symptoms was similar for baloxavir and oseltamivir (~54 hours)

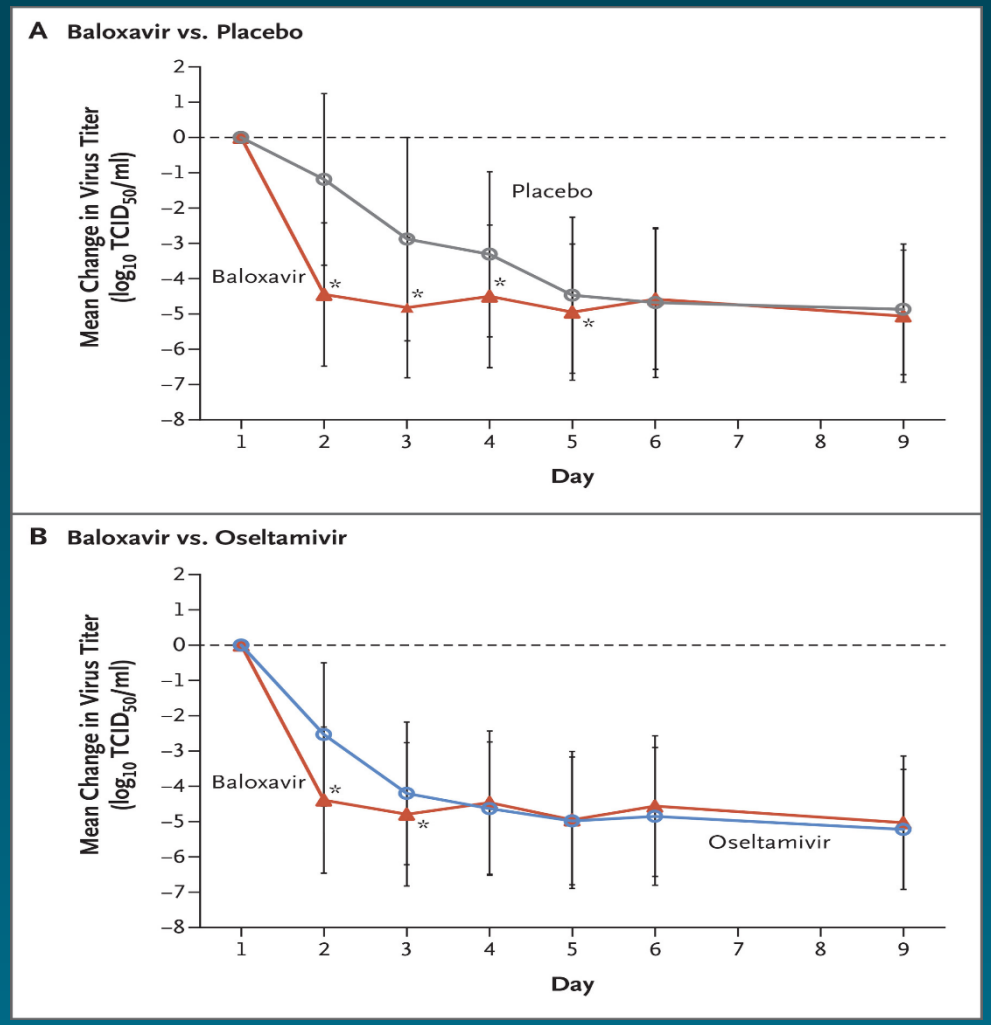
Overall incidence of AEs:

- **Baloxavir:** 20.7%
- **Oseltamivir:** 24.8%
- **Placebo:** 24.6%

Baloxavir has a similar overall AE incidence, with a potentially lower rate of nausea and vomiting than oseltamivir

From Hayden FG, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. *N Engl J Med*. 2018;379(10):913-923.

Baloxavir CAPSTONE-1 Study: Change From Baseline in Viral Load Over Time



Panel A:

- Change from baseline in influenza infectious viral load over time
- Mean viral loads on day 1:
  - 5.79 ± 1.87 baloxavir
  - 5.56 ± 1.89 placebo

Panel B:

- Change from baseline in influenza infectious viral load in adults 20 to 64 years
- Mean viral loads on day 1:
  - 5.76 ± 1.90 baloxavir
  - 5.94 ± 1.69 placebo

Median duration of infectious virus detection was significantly shorter in the baloxavir group (24 hrs) vs placebo (96 hrs, *P*<.001) and oseltamivir (72 hrs, *P*<.001)

$TCID_{50}$ = tissue culture infective dose.

From Hayden FG, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. *N Engl J Med*. 2018;379(10):913-923.

Baloxavir CAPSTONE-2 Design

Phase 3, multicenter, randomized, double-blind, placebo- and oseltamivir-controlled study:

- Patients with influenza at **higher risk of influenza complications**
- Inclusion criteria:
  - Age ≥12 yrs
  - Fever + influenza symptoms of ≤48 hrs duration
  - **Presence of at least 1 higher risk factor (from CDC criteria)**
- 38%-44% of patients had influenza B; 56%-62% had influenza A

RANDOMIZED

1:1:1

Baloxavir single dose
(40 mg for BW <80 kg;
80 mg for BW ≥80 kg)
+ placebo[a] BID days 1-5
(N=388)

Oseltamivir 75 mg BID
Days 1-5 and placebo[b] on day 1
(N=389)

Placebo BID days 1-5
(placebo to baloxavir on day 1
(N=386)

Primary endpoint
Time to improvement of influenza symptoms (TTIIS)

Secondary endpoints
- Infectious virus detection in serial nasopharyngeal swabs
- Prescription of antibiotics
- Influenza-related complications

High-risk factors: asthma or chronic lung disease (39.2%), age ≥65 years (27.4%), endocrine disorders (32.8%), metabolic disorders (13.5%), heart disease (12.7%), morbid obesity (10.6%)

[a]Placebo to oseltamivir; [b]Placebo to baloxavir

Ison MG, et al. Presented at: Infectious Disease Week (IDWeek) 2018; October 3-7, 2018; San Francisco, CA. Abstract #LB16; ClinicalTrials.gov Identifier: NCT02949011.
Ison MG, et al. *Lancet Infect Dis.* 2020;20(10):1204-1214.
Baloxavir marboxil [prescribing information]. Accessed September 24, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210854s001lbl.pdf

CAPSTONE-2: Baloxavir Marboxil in High-risk Adults

CAPSTONE-2 Outcomes (1163 patients)	
Time to Clinical Recovery	**Reduced time to clinical recovery for:** • Baloxavir vs placebo (73.2 vs 102.3 hrs; *P*<.0001); Difference of 29.1 hrs • Baloxavir for influenza A vs placebo (75.4 vs 100.4 hrs; *P*=.014) • Baloxavir for influenza B vs placebo (74.6 vs 100.6 hrs; *P*=.0138) • Baloxavir for influenza B vs oseltamivir (74.6 vs 101.6 hrs; *P*=.0251) **Similar time to clinical recovery:** • Baloxavir for influenza A vs oseltamivir (75.4 vs 68.2 hrs; *P*=NS)
Viral Shedding	Reduced in patients who received baloxavir vs oseltamivir or placebo (48 vs 96 and 96, respectively; *P*<.0001)
Influenza-related complications	Treatment with either baloxavir or oseltamivir was associated with reduced risk of complications compared with placebo
Safety	Similar incidence of AEs for baloxavir (25.1%) versus placebo (29.7%) or oseltamivir (28.0%)

FDA approved supplemental New Drug Application for people 12 years of age and older who have been symptomatic for no more than 48 hours and **who are at high risk for developing flu-related complications**. (October 2019)

Ison MG, et al. *Lancet Infect Dis.* 2020;20(10):1204-1214.
Baloxavir marboxil [Approval letter]. October 16, 2019. Accessed September 24, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/210854Orig1s001.pdf

CAPSTONE-2 Study: Clinical Response by Virus Type

- Median TTIIS in oseltamivir group was similar to that in the baloxavir group in in those infected with influenza A H3N2 virus (–7.2 hours [–31.5 to 14.5), but was significantly shorter in baloxavir group than in the oseltamivir group in those with influenza B virus (27.1 hours [6.9 to 42.3]; *P*=.025)

Type A /H3N2	Baloxavir	Placebo	Oseltamivir
n	180	185	190
Median	75.4	100.4	68.2

Type B	Baloxavir	Placebo	Oseltamivir
n	166	167	148
Median	74.6	100.6	101.6

Ison MG, et al. *Lancet Infect Dis.* 2020;20(10):1204-1214.

CAPSTONE-2 Study: Fewer Antibiotics Needed With Treatment

Proportion of patients requiring systemic antibiotics for secondary bacterial infections

3.4%
Baloxavir
13/388 patients
***P*=.01 vs placebo**
P=NS vs oseltamivir
95% CI: 1.8 to 5.7

7.5%
Placebo
29/386 patients
95% CI: 5.1 to 10.6

3.9%
Oseltamivir
15/389 patients
95% CI: 2.2 to 6.3

NS = not significant.

Ison MG, et al. *Lancet Infect Dis.* 2020;20(10):1204-1214.

Pediatric Baloxavir Studies Conducted in Japan, 2016-2017

Pediatric patients aged 1 to 11 years (N=107)

- Laboratory-confirmed, febrile influenza virus infection of ≤48 hours duration

Body weight	Dose	Tablets
5 to <10 kg	5 mg	Half a 10-mg tablet
10 to <20 kg	10 mg	One 10-mg tablet
20 to <40 kg	20 mg	Two 10-mg tablets or one 20-mg tablet
≥40 kg	40 mg	Two 20-mg tablets

Results

- *Median time to alleviation of influenza illness:* **44.6 hours** (95% CI, 38.9-62.5 hours)
- *Time to sustained cessation of infectious viral shedding:* **24.0 hours**
- Amino acid substitutions in viral polymerase acidic protein at position I38 (PA/I38T/M) emerged in 18 of 77 (**23.4%**) patients
  - Longer infectious virus detectability (median time, 180.0 hours)
  - Longer time to illness alleviation (median, 79.6 vs 42.8 hours)

Hirotsu N, et al. *Clin Infect Dis.* 2020;71(4):971-981.

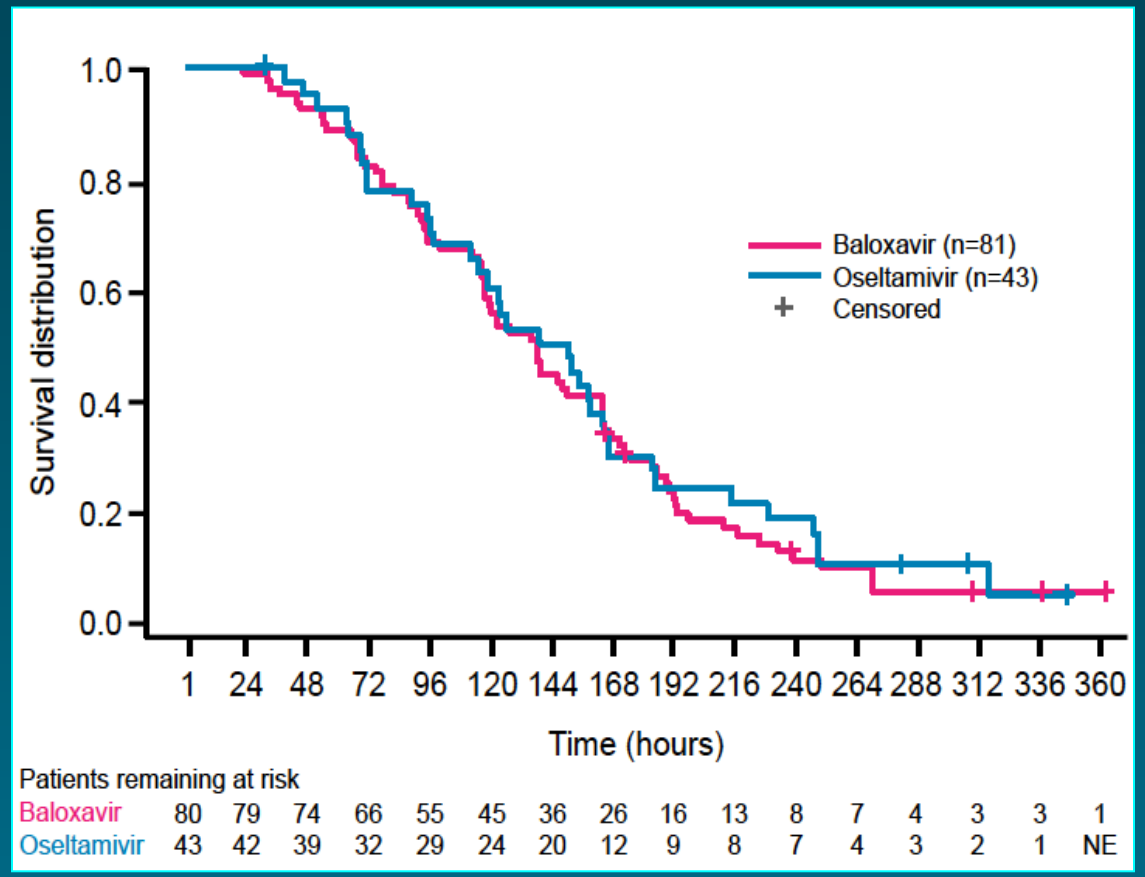
MINISTONE-2: Time to Alleviation of Influenza Symptoms in Children—Baloxavir vs Oseltamivir

- Phase 3 RCT among healthy children ill <48 hours; aged 1 to 12 years
- Baloxavir single dose: 2 mg/kg if <20 kg, 40 mg if ≥20 kg vs oseltamivir BID X 5 days; weight-based dosing
- Randomized 2:1, N=112/57; 81/54 with confirmed flu
- Primary endpoint was met: similar safety between baloxavir and oseltamivir

	Baloxavir (hours, 95% CI)	Oseltamivir (hours, 95% CI)
Time to alleviation of symptoms	138 (117-163)	150 (115-165)
Time to culture negativity	24.2 (23.5-24.6)	75.8 (68.9-97.8)

- sNDA submitted for baloxavir for treating acute uncomplicated influenza in children between 1 and 12 years of age within 48 hours of symptom onset
- NDA submitted for new oral suspension formulation of baloxavir (2 mg/mL)

Time to Alleviation of Signs and Symptoms: Similar Between Study Arms



NDA = new drug application; PDUFA = Prescription Drug User Fee Act; sNDA supplemental NDA.

Baker J, et al. *Pediatr Infect Dis J.* 2020;39(8):700-705. Open Access.

MINISTONE-2: Single-dose Baloxavir in Children Aged 1 to 12 Years

A. Adverse Events

GI AEs were the most common (vomiting/diarrhea)

122 AEs were reported in 84 (48.6%) children

- Incidence of AEs was similar between baloxavir and oseltamivir groups (46.1% vs 53.4%, respectively)
- Gastrointestinal AEs (vomiting/diarrhea)
  - *Baloxavir:* 12 children (10.4%)
  - *Oseltamivir:* 10 children (17.2%)

B. Viral Shedding

Viral shedding was shorter in the baloxavir arm

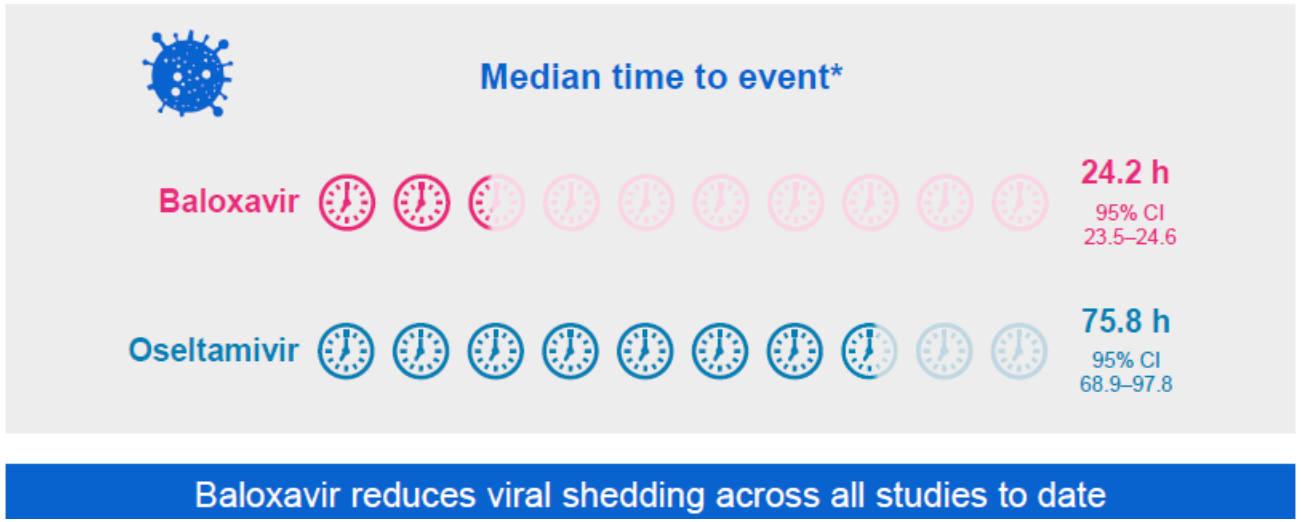


Image from Baker J. Presented at: OPTIONS X 2019; August 28-September 1, 2019; Singapore. Abstract #11756.
Baker J, et al. *Pediatr Infect Dis J*. 2020;39(8):700-705. Open Access.

Resistance to Baloxavir: Proportion of PA-I38X Emergence

Proportions of PA-I38X Variant Emergence	Total % n/N	Viral Type/Subtype		
		A/H1N1	A/H3N2	B
Ph2 OwH (T0821) in Japan	**2.2%** 4/182	3.6% 4/112	0% 0/14	0% 0/56
CAPSTONE-1 (T0831)	**9.7%** 36/370	0% 0/4	10.9% 35/330	2.7% 1/37
Pediatric Study in Japan (T0822)	**23.4%** 18/77	0% 0/2	25.7% 18/70	0% 0/6
CAPSTONE-2 (T0832)	**5.2%** 15/290	5.6% 1/18	9.2% 13/141	0.8% 1/131

Hayden FG, et al. *N Engl J Med*. 2018;379(10):913-923; Hirotsu N, et al. *Clin Infect Dis.* 2020;71(4):971-981; Uehara T, et al. *J Infect Dis.* 2020;221(3):346-355.

Baloxavir: Key Take-home Points

Approved as a single-dose therapy for acute, uncomplicated influenza in patients aged 12 years and older who have been symptomatic for no more than 48 hrs or who are at high risk for influenza complications

- *Limited data* on safety in patients with renal dysfunction (CrCl <50 mL/min) and advanced liver failure of developing flu-related complications
- Associated with significantly *more rapid declines* in infectious viral titers (viral shedding), starting from 1 day after treatment initiation, compared with either placebo or oseltamivir
- More rapid clinical improvement for patients with *influenza B* compared with placebo and oseltamivir
- No prospective data on hospitalized patients, length of stay

CrCl = creatinine clearance.

Baloxavir marboxil [prescribing information]. Accessed September 24, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210854s001lbl.pdf
Hayden FG, et al. *N Engl J Med*. 2018;379(10):913-923; Ison MG, et al. *Lancet Infect Dis*. 2020;20(10):1204-1214.

Chemoprophylaxis

- The CDC does *not* recommend routine use
  - **Prevention exceptions include:**
    - High-risk people in the first 2 weeks postimmunization
    - High-risk people with no vaccine or expected poor response (immunosuppressed)
- Not recommended if ≥48 hours after exposure
- The CDC and the American Academy of Pediatrics recommend the use of oseltamivir for prophylaxis in infants aged 3 months and older
- Has efficacy of 69% to 92% in preventing influenza

Centers for Disease Control and Prevention. Updated August 10, 2020. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm; Carey WA, et al. *Pediatrics*. 2018;141(3):e20173108; Moscona A. *N Engl J Med*. 2005;353(13):1363-1373.

Prophylaxis: Oseltamivir and Zanamivir

Systematic Review of Data on NAIs for Prophylaxis of Influenza	
Studies examining secondary transmission of **symptomatic** influenza:	• Jackson et al, 2011 • Jefferson et al, 2014 • Khazeni et al, 2009 • Okoli et al, 2014
Studies examining secondary transmission of **asymptomatic** influenza:	• Jefferson et al, 2014 • Khazeni et al, 2009
Data were classified by **pre-exposure prophylaxis**, **post-exposure prophylaxis**	

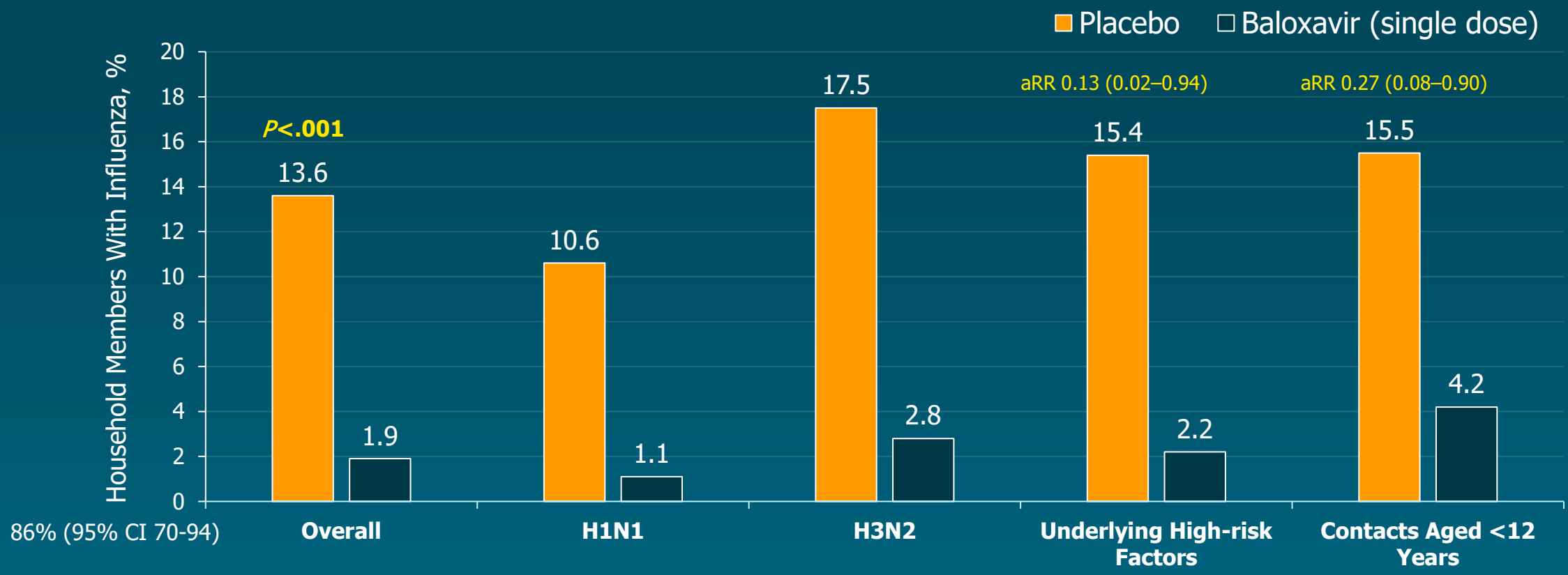
Findings

In situations of pre-exposure and post-exposure prophylaxis, oseltamivir or zanamivir consistently and significantly lowered the odds or risk of symptomatic influenza

For asymptomatic influenza: Prophylaxis with either oseltamivir or zanamivir did not reduce the odds or risk of secondary transmission

Doll MK, et al. *J Antimicrob Chemother*. 2017;72(11):2990-3007.

BLOCKSTONE: Preventative Treatment With Baloxavir After Exposure to an Infected Household Member



- Baloxavir had a comparable safety profile to placebo (adverse events: 22.2% with baloxavir, 20.5% with placebo)
- At this time, baloxavir is not approved by the FDA nor recommended by the CDC for prophylaxis
- March 2020: The FDA accepted the sNDA for baloxavir for post-exposure prophylaxis of influenza in people ≥1 year of age. PDUFA date: November 23, 2020.

aRR = Adjusted Risk Ratio; PDUFA = Prescription Drug User Fee Act.

Ikematsu H, et al. *N Engl J Med.* 2020;383(4):309-320.

Treatment: Key Take-home Points

- Start therapy early for best outcomes
- Antiviral treatment for influenza recommended within 48 hours of symptom onset
  - Shorter duration of clinical illness
  - Fewer complications and need for antibiotics
  - Reduced mortality and length of stay for hospitalized patients
- Newer therapies and new indications are on the horizon

FLU FORUM

Are You Ready for the 2020-2021 Influenza Season?

Case Presentation

Case Challenges in Flu:
13-Year-Old Asthmatic Patient With Symptoms of Flu

John J. Russell, MD, FAAFP

Clinical Professor of Family and Community Medicine
Sidney Kimmel Medical College
Thomas Jefferson University
Philadelphia, PA
Chair, Department of Family Medicine
Program Director, Family Medicine Residency
Abington – Jefferson Health
Abington, PA

Case: Details

Patient is a 13-year-old male with history of asthma who presents with 12 hours of fever, chills, and muscle aches

A large percentage of his class is "out sick with flu"
He is attending school in person

COVID is still present in your community, but the overall positivity rate is 1.8%

He did *not* get a flu shot this year

He has needed his PRN albuterol 3 times in the last day

COVID = corona virus disease; PRN = as needed.

Case: Physical Exam

Vitals – HR: 98/minute; BP: 102/58 mm Hg bilaterally; RR: 14/minute; pulse oximetry: 96%; temperature: 102.8°F; weight 40 kg

Nontoxic but sick appearing, no respiratory distress

TMs clear, pharynx clear, nose non-congested

Heart regular, without murmur

Lungs – few wheezes, no accessory muscle use

Abdomen: positive BS, nontender, no masses

No edema

BP = blood pressure; BS = bowel sounds; HR = heart rate; RR = respiration rate; TMs = tympanic membranes.

Case: Medical History

Past medical history: asthma, seasonal allergies, atopic dermatitis

Immunizations: up to date, except flu shot this season

Medications: albuterol PRN, hydrocortisone cream 2.5% PRN, fluticasone 44 mcg BID

Drug allergies: amoxicillin (rash)

No smokers in the home
7th grader; lives with parents and 3 siblings who are 9, 5, and 2 years of age

BID = twice daily.

What Should You Do?

Influenza testing?

Empiric treatment?

- Impact of COVID-19?

Case: Testing

- **Testing:** he has office-based testing via PCR that is **positive for influenza B**
  - Test has sensitivity/specificity about 99% each
- You also send off a COVID swab for testing that will be back in 2-3 days

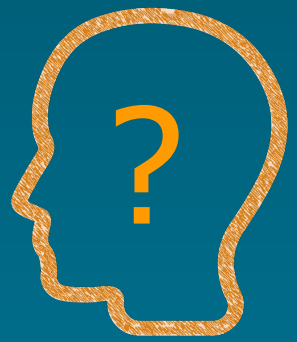
Uyeki TM, et al. *Clin Infect Dis.* 2019;68(6):e1-e47.
Centers for Disease Control and Prevention. Accessed August 19, 2020. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

What Should You Do?

What would you recommend to treat the patient?

How would you counsel the patient?

Does anyone in the household need prophylaxis?



Case: Treatment

Agent	Route of Administration	Age (Years)	Treatment Duration	Dosing
Baloxavir	Oral; tablet (twin pack)	≥12	1 day	**40 to <80 kg: 40 mg orally, single dose (two 20 mg tablets)** >80 kg: 80 mg orally, single dose (two 40 mg tablets) *Note: FDA approved for the treatment of influenza, or flu, in people 12 years of age and older who have been symptomatic for no more than 48 hours and who are at high risk for developing flu-related complications.*
Oseltamivir	Oral; capsule or oral suspension	≥1 (FDA) Any age (CDC)	5 days	Adults: 75 mg twice daily Children <1 year: 3 mg/kg/dose twice daily Children >1 year: • 15 kg or less: 30 mg twice daily • >15 to 23 kg: 45 mg twice daily • **>23 to 40 kg: 60 mg twice daily** • >40 kg: 75 mg twice daily

Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Conclusion: Case Challenge

Children are at high risk for influenza!

- They have a high risk of infection and pneumonia, and they spread disease

Prevention of influenza is best

Treatment of influenza should be considered, especially in young children OR a high-risk host

- Oseltamivir is currently the only licensed agent for children aged <12 years
- Both oseltamivir and baloxavir are licensed for aged ≥12 years
- Baloxavir is safe, effective, and well tolerated in adolescents
- Concern over high rates of resistance in children requires further study

New drugs like baloxavir are under study in children aged <12 years

- FDA review pending for pediatric indication for children aged 1 to 12 years
  (Baker J, et al. *Pediatr Infect Dis J*. 2020;39(8):700-705.)

Case Challenges in Flu:
The Nursing Home Patient With COPD

Paul G. Auwaerter, MD, MBA, FIDSA

Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Director, Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases
Johns Hopkins University School of Medicine
Baltimore, MD

Case: Details

- Patient is a 78-year-old female resident of a nursing home (NH)
- February, widespread influenza in area; no COVID-19 cases recently in NH
- Patient received an influenza vaccine in October
- Patient has 1 day of fever, body aches, and coughing
- No shortness of breath
- No problems with eating, drinking, or thinking

COVID = corona virus disease.

Case: Medical History

- Past history: COPD / DM / HTN
- Immunizations: up to date
- Medications: tiotropium daily / fluticasone and salmeterol combo daily / lisinopril 40 mg/ metformin 1000 mg twice daily / atorvastatin 20 mg once daily / amlodipine 5 mg once daily
- No known drug allergies
- Former smoker – quit 10 years ago (after smoking 1 pack per week)

COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HTN = hypertension.

Case: Physical Exam

Vitals – HR: 78/minute; BP: 132/78 mm Hg bilaterally; RR: 12/minute; RA pulse ox: 96%; temperature: 100.8 °F; weight: 52 kg; BMI 19.9 kg/m^2

Patient not toxic, but appears unwell

TMs clear, pharynx clear an uninjected, nose non-congested

Heart rate regular, without murmur

Lungs clear

Abdomen – positive BS, nontender, no masses

No edema

BMI = body mass index; BP = blood pressure; BS = bowel sounds; HR = heart rate; RA= room air; RR = respiration rate; TMs = tympanic membranes.

What Should You Do?

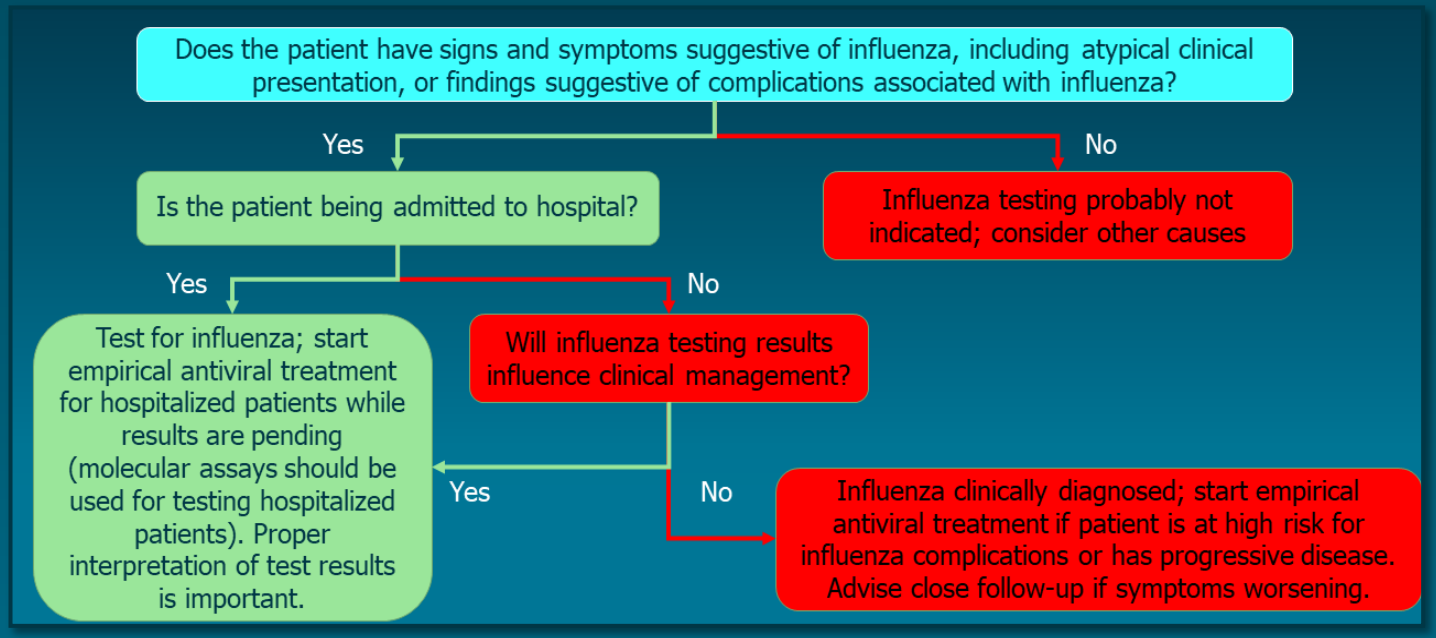
Influenza testing?

Empiric treatment?

- Impact of COVID-19?
  - Similar symptoms—unable to distinguish clinically

Empiric Treatment of Influenza: Impact of COVID-19

- Historically, the CDC and IDSA have provided algorithms and guidelines for influenza testing and treatment
- Recommendations were tailored to the presence or absence of influenza circulating in the community



Influenza-like Illness Considerations:

- What is the appropriate protocol for managing a patient who tests negative for influenza?
- Do we need to re-evaluate the safety of empiric influenza treatment based on clinical suspicion of influenza?

CDC = Centers for Disease Control and Prevention; IDSA = Infectious Diseases Society of America.

Centers for Disease Control and Prevention. Accessed Sept 22, 2020. https://www.cdc.gov/flu/professionals/diagnosis/consider-influenza-testing.htm
Centers for Disease Control and Prevention. Accessed Sept 22, 2020. https://www.cdc.gov/flu/professionals/diagnosis/algorithm-results-circulating.htm
IDSA. Accessed Sept 22, 2020. https://www.idsociety.org/practice-guideline/influenza/; Uyeki TM, et al. *Clin Infect Dis.* 2019;68(6):e1-e47.

Influenza Prevalence and Predictive Value of Testing

Positive predictive value (PPV) = probability that patients with a positive screening test truly have the disease

Negative predictive value (NPV) = probability that patients with a negative screening test truly do not have the disease

When influenza prevalence is relatively low, the PPV is low and **false-positive test results more likely**

When influenza prevalence is low, the NPV is high and **negative results more likely to be true**

When influenza prevalence is relatively high, the NPV is low and **false-negative test results more likely**

When influenza prevalence is high, the PPV is high and **positive results more likely to be true**

Centers for Disease Control and Prevention. Rapid Diagnostic Testing for Influenza: Information for Clinical Laboratory Directors. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm

For This Patient, What Test(s) Should Be Used to Diagnose Influenza?

What Do the IDSA Guidelines Tell Us?

- ✓ Use rapid molecular assays, ie, nucleic acid amplification tests (NAATs), favored over rapid influenza diagnostic tests (RIDTs) in outpatients
- ✓ Use reverse-transcription polymerase chain reaction (RT-PCR) or other molecular assays over other influenza tests in hospitalized patients

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

Case: Testing

- Rapid molecular assay (NAAT) performed during outpatient visit.

Test Attributes
Tests for nucleic acid
Tests for influenza A or B (does not distinguish influenza strain)
Provides results in 15 to 30 minutes
High sensitivity, high specificity

- Result: Positive for influenza A

Uyeki TM, et al. *Clin Infect Dis.* 2019;68(6):e1-e47.
Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

Impact of Office-based Testing

- Why do office-based testing?
- Do patients do better with a confirmed diagnosis?
- Is an intention to test an intention to treat?

Who Should Be Treated for a Positive Influenza Test?

Criteria for initiating antiviral treatment as soon as possible*:
Persons (any age) who are hospitalized with influenza, regardless of illness duration prior to hospitalization
Outpatients (any age) with severe or progressive illness, regardless of illness duration
Outpatients who are deemed at high risk for developing complications from influenza (ie, those with chronic medical conditions and immunocompromised patients)
Children <2 years of age and adults ≥65 years of age
Pregnant women and those within 2 weeks postpartum

*regardless of influenza vaccination history

Guidelines paraphrased from cited article. For items indicated in parentheses, see Table 1 of the cited article for category, grade, and definition for ranking recommendations.
Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.

When Should Treatment Be Considered?

Criteria for considering antiviral treatment*:
Outpatients with illness onset ≤2 days before presentation
Symptomatic outpatients who are household contacts of persons who are at high risk for developing complications from influenza, particularly those who are severely immunocompromised
Symptomatic health care providers who care for patients who are at high risk for developing complications from influenza, particularly those who are severely immunocompromised
*regardless of influenza vaccination history

Guideline paraphrased from cited article.
Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.

Six FDA-approved Drugs for Influenza

- **4 recommended for influenza A + B**
  - Neuraminidase inhibitors
    - Oseltamivir phosphate (oral)
    - Zanamivir (inhaled)
    - Peramivir (IV)
  - Cap-dependent endonuclease inhibitor
    - Baloxavir marboxil (oral)
- Not recommended:
  - Adamantanes (M2 ion channel)
    - Amantadine
    - Rimantadine
  - High levels of drug resistance to circulating influenza A, ineffective for influenza B

Current FDA indications for recommended oral agents:

Oseltamivir: for treating influenza in patients ≥1 year who have been symptomatic for no more than 2 days, and for prophylaxis of influenza in patients ≥1 year

Baloxavir: for treating acute uncomplicated influenza within 2 days of illness onset in people ≥12 years who are otherwise healthy, or at high risk of developing flu-related complications

FDA = US Food and Drug Administration; IV = intravenous; M2 = Matrix-2.

Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Case: Treatment

Agent	Route of Administration	Age (Years)	Treatment Duration	Dosing
Baloxavir	Oral; tablet (twin pack)	≥12	1 day	**40 to <80 kg: 40 mg orally, single dose (two 20 mg tablets)** >80 kg: 80 mg orally, single dose (two 40 mg tablets)
Oseltamivir	Oral; capsule or oral suspension	≥1 (FDA) Any age (CDC)	5 days	**Adults: 75 mg twice daily** Children <1 year: 3 mg/kg/dose twice daily Children >1 year: • 15 kg or less: 30 mg twice daily • >15 to 23 kg: 45 mg twice daily • >23 to 40 kg: 60 mg twice daily • >40 kg: 75 mg twice daily
Peramivir	IV	≥2	1 day	≥13 years: One 600-mg dose via IV infusion for a minimum of 15 minutes 2-12 years: One 12-mg/kg dose, up to 600 mg maximum, via IV infusion for at least 15 minutes
Zanamivir	Inhaled	≥7	5 days	Adults: 10 mg (two 5-mg inhalations daily) Children ≥7 years: 10 mg (two 5-mg inhalations daily)

Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

When Would You Utilize Prophylaxis for Others in the Facility?

- If 2 cases of health care-associated, laboratory-confirmed influenza are identified within 72 hours of each other in residents or patients of the same ward or unit
- If 1 or more residents or patients has suspected health care-associated influenza and results of influenza molecular testing are not available on the day of specimen collection

Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.

Chemoprophylaxis

- Remember to immunize
- The CDC does not recommend routine chemoprophylaxis
  - Exceptions to this recommendation include:
    - High-risk people in the first 2 weeks postimmunization
    - High-risk people with no vaccine or expected poor response (immunosuppressed)
- Not recommended 48 hours or more after exposure
- The CDC and the American Academy of Pediatrics recommend the use of oseltamivir for prophylaxis in infants aged >3 months
- Institutional prophylaxis duration up to 2 weeks after last known case identified

Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/highrisk/children-antiviral.htm
Committee on Infectious Diseases. *Pediatrics*. 2019;144(4):e20192478.

Neuraminidase Inhibitors Reduce Influenza by 69% to 92%

- Several large, controlled studies of prophylaxis demonstrated that zanamivir and oseltamivir are effective in preventing clinical influenza in healthy adults:
  - Prophylaxis after exposure for close contacts, such as household members
  - Seasonal prophylaxis in the community
- Both oseltamivir and zanamivir were ~70% to 90% effective in reducing incidence of influenza when used for prophylaxis before or after exposure to influenza A or influenza B
- Currently, oseltamivir is the only oral medication approved for prophylaxis in the United States

Moscona A. *N Engl J Med*. 2005;353(13):1363-1373.

CDC Antiviral Chemoprophylaxis[1]

Antiviral	Indication	Age	Routine Duration[2]	Dosing
Baloxavir	Chemoprophylaxis not currently recommended, under investigation[3]			
Oseltamivir	Yes	≥3 months	7 days	**Adults: 75 mg orally once daily** Children 3 months to <1 year old: • 3 mg/kg/dose once daily Children >1 year old: • 15 kg or less: 30 mg once daily • >15 to 23 kg: 45 mg once daily • >23 to 40 kg: 60 mg once daily • >40 kg: 75 mg once daily
Peramivir	Chemoprophylaxis not recommended			
Zanamivir	Yes	≥5 years	7 days	**Adults and children: 10 mg** (two 5-mg inhalations daily)

1. Centers for Disease Control and Prevention. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
2. See CDC guidance for special institutionalized settings with an outbreak. Accessed September 24, 2020. https://www.cdc.gov/flu/professionals/infectioncontrol/ltc-facility-guidance.htm
3. Ikematsu H, et al. *N Engl J Med.* 2020;383(4):309-320.

BLOCKSTONE: Baloxavir Prophylaxis in Households

Study of baloxavir prophylactic efficacy among HHCs with influenza

Multicenter, double-blind, placebo-controlled study of HHCs in Japan during the 2018-2019 season

- All index patients were treated
- Asymptomatic HHCs randomized to baloxavir or placebo

Endpoint: Proportion of HHCs who developed clinical influenza over a 10-day observation period

HHCs = household contacts.

Ikematsu H, et al. *N Engl J Med.* 2020;383(4):309-320.