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Breaking Free From the Grasp of Seasonal Influenza: Key Diagnostic and Management Considerations on the Front Lines of Care

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Faculty Disclosures

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No real or apparent conflicts of interest to disclose.

Learning Objectives

- Articulate the role of vaccination in reducing the spread of influenza and improving patient outcomes while emphasizing the importance of vaccination during the COVID-19 pandemic
- Describe how to implement updated guidelines to differentially diagnose influenza in order to initiate early and appropriate therapy
- Discuss how to utilize antiviral chemoprophylaxis in appropriate individuals at high risk of developing influenza and associated complications
- Interpret existing and new evidence with traditional and new influenza treatments, including differences in efficacy and safety, dosage and administration, and reduction in disease burden and complications
- Outline how to individualize flu treatment with antiviral medications among diverse patients

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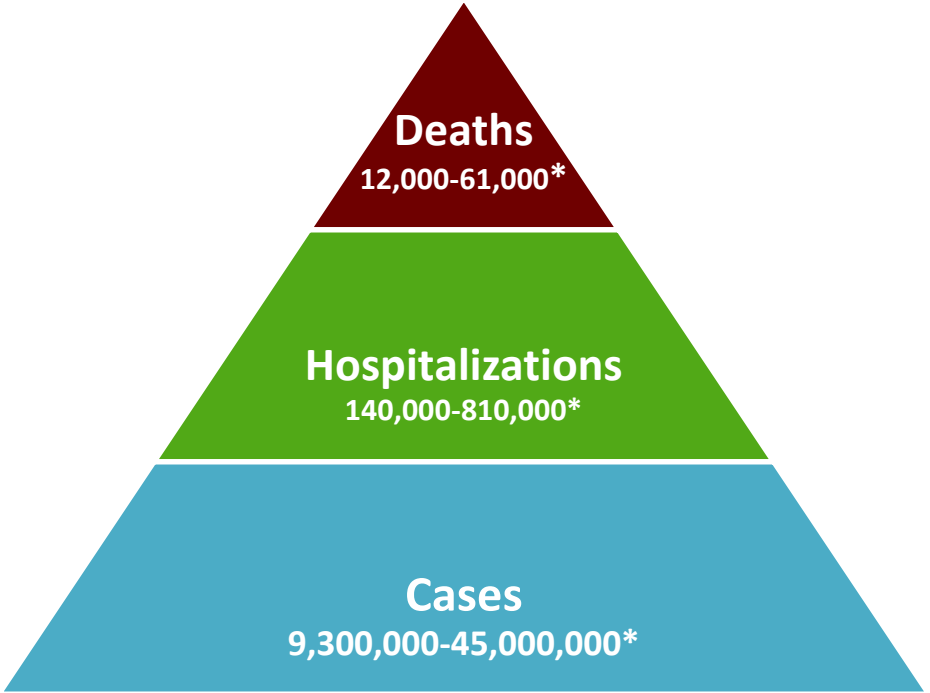
The Burden of Influenza in the US

Influenza—A Recurring and Significant Threat

- Burden of seasonal influenza
  - Substantial
  - Widely variable
- Multiple determining factors
  - Circulating virus characteristics
  - Seasonal timing
  - Vaccine efficacy
  - Number of vaccinated individuals

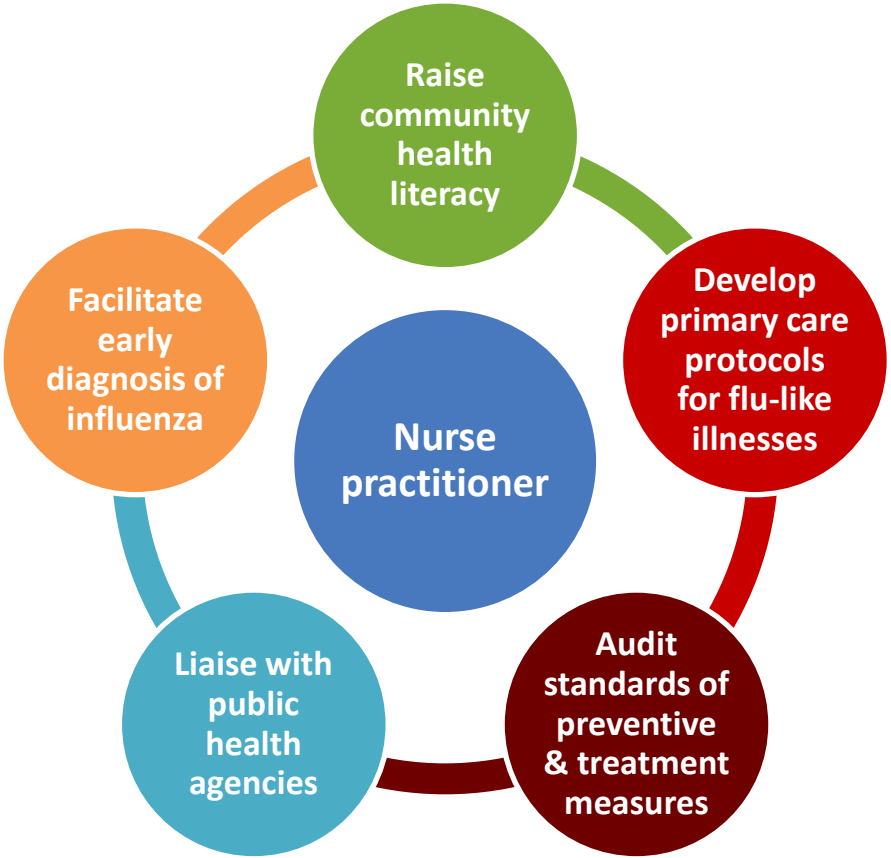


2010-11 Through 2019-20* Influenza Seasons in the US

*The top range of these estimates are from the 2017-2018 flu season.

Centers for Disease Control and Prevention. The burden of influenza. https://www.cdc.gov/flu/about/burden/index.html

The Crucial Role of Nurse Practitioners in Improving Influenza Management



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An Ounce of Prevention

The Benefits of Influenza Vaccination

Illnesses, Hospitalizations, and Deaths *Prevented* by Vaccination During the 2019-2020 Season

Nearly 52% of the US population ≥6 months of age were vaccinated during the 2019–2020 flu season, resulting in prevention of the following:

7.5 million

Symptomatic illnesses

3.7 million

Medical visits

105,000

Hospitalizations

6,300

Deaths

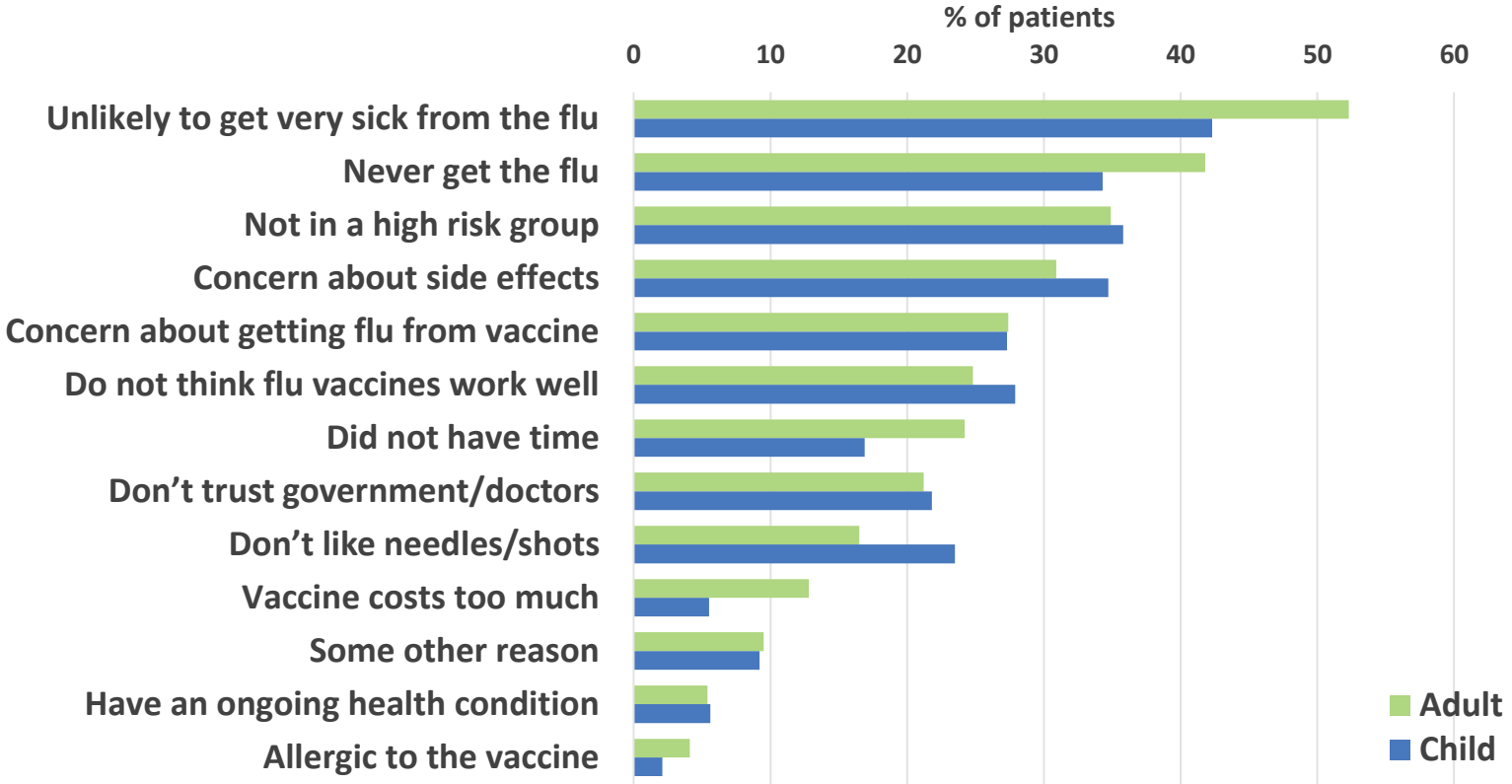
Centers for Disease Control and Prevention. What are the benefits of flu vaccination? https://www.cdc.gov/flu/prevent/vaccine-benefits.htm

Influenza Prevention: Broader Implications for Healthcare in the Era of COVID-19

Influenza vaccines can reduce the burden of flu illnesses during the time of a pandemic.

Centers for Disease Control and Prevention. Key facts about seasonal flu vaccine. https://www.cdc.gov/flu/prevent/keyfacts.htm

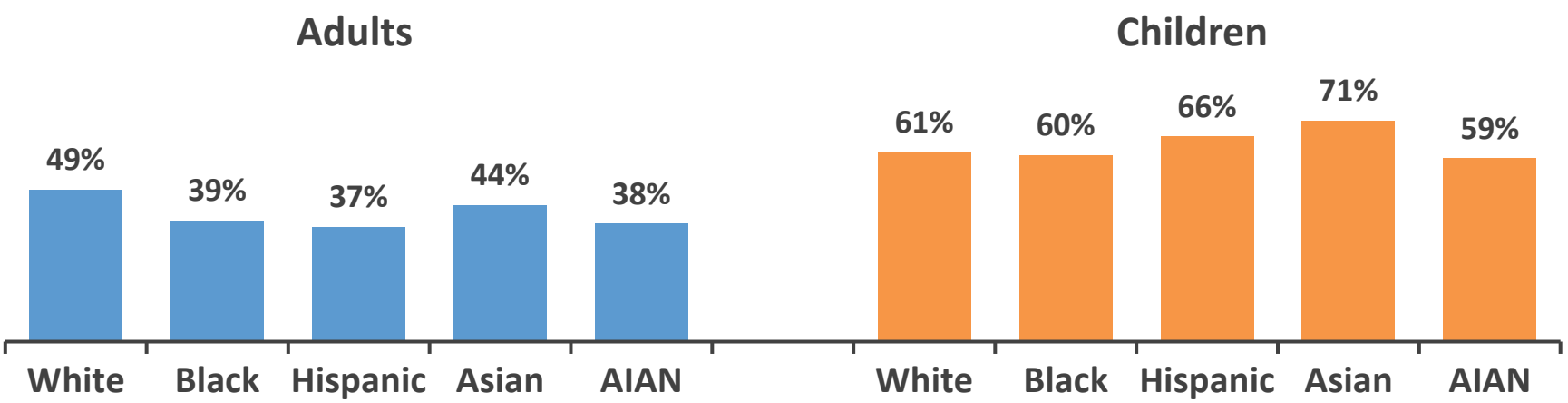
Identifying Barriers to Influenza Vaccination



Santibanez TA, Kennedy ED. *Vaccine*. 2016;34:2671-2678.

Gaps and Racial Disparities in Influenza Vaccination Rates

Influenza Vaccination Rates Among Adults and Children by Race and Ethnicity, 2018–2019 Season



Research indicates that lower rates of insurance coverage, distrust, safety concerns, and experiences with discrimination and other factors contribute to disparities in vaccination rates.

AIAN, American Indian and Alaska Native.

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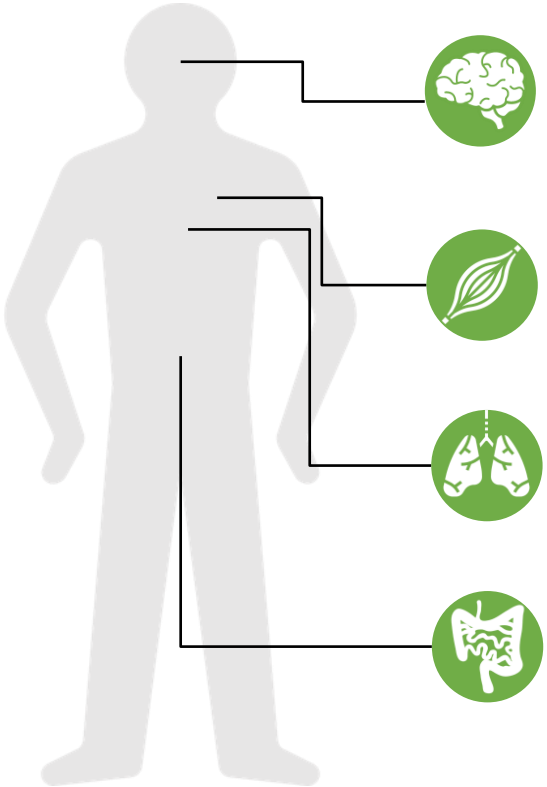
Recognition and Diagnosis of Influenza

Signs and Symptoms of Influenza[1]



Neurological

- Fever
- Headache
- Confusion

Neuromuscular

- Myalgia
- Fatigue

Respiratory

- Dry cough
- Pharyngitis
- Nasal congestion

GI tract

- Nausea
- Vomiting
- Diarrhea

Up to 75% have no symptoms.[2]

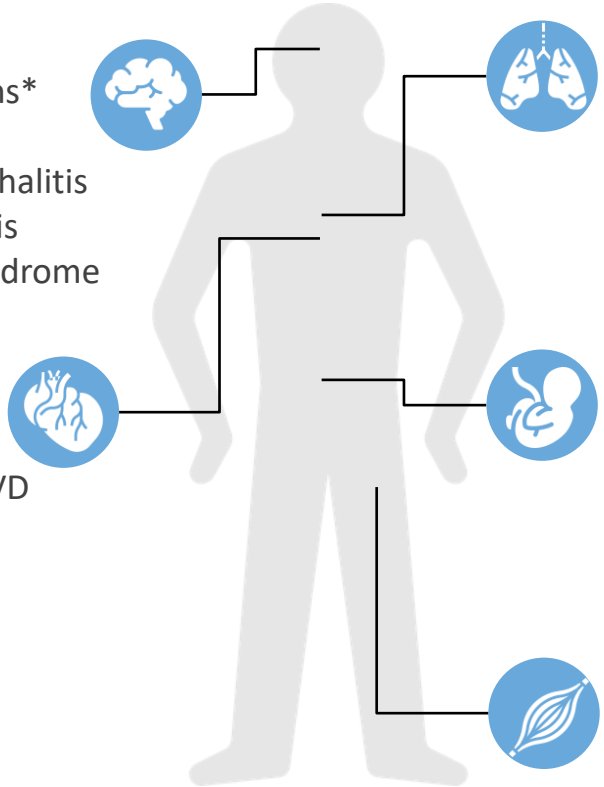
GI, gastrointestinal.

1. Ghebrehewet S, et al. *BMJ*. 2016;355:i6258. **2**. Hayward AC, et al. *Lancet Respir Med*. 2014;2(6):445-454.

Potential Complications of Influenza

Neurologic
- Febrile convulsions*
- Reyes syndrome*
- Meningitis/encephalitis
- Transverse myelitis
- Guillain-Barré syndrome

Cardiac
- Pericarditis
- Myocarditis
- Exacerbation of CVD



Respiratory
- Otitis media*
- Croup*
- Sinusitis/bronchitis/pharyngitis
- Pneumonia (viral or secondary bacterial)
- Exacerbation of chronic lung disease

Pregnancy
- Maternal complications
- Greater perinatal mortality
- Greater risk of prematurity
- Smaller neonatal size
- Lower birth weight

Musculo-skeletal
- Myositis
- Rhabdomyolysis

*More common in children.
CVD, cardiovascular disease.
Ghebrehewet S, et al. *BMJ*. 2016;355:i6258.

Differential Diagnosis

Condition	Clinical Presentation	Fever
Influenza[1]	Fever or chills, cough, pharyngitis, rhinorrhea or nasal congestion, myalgia, headache, fatigue	✓
Common Cold[2]	Nasal congestion, rhinorrhea, sneezing, cough	Rare
Infectious Mononucleosis[3]	Extreme fatigue, fever, pharyngitis, headache and myalgia, cervical and axillary lymphadenopathy, hepatomegaly and/or splenomegaly, rash	✓
COVID-19[4]	Fever or chills, cough, dyspnea, fatigue, myalgia, headache, new loss of taste or smell, pharyngitis, nasal congestion or rhinorrhea, nausea or vomiting, diarrhea	✓

1. Centers for Disease Control and Prevention. Flu symptoms & complications. https://www.cdc.gov/flu/symptoms/symptoms.htm **2**. Centers for Disease Control and Prevention. Cold versus flu. https://www.cdc.gov/flu/symptoms/coldflu.htm **3**. Centers for Disease Control and Prevention. About infectious mononucleosis. https://www.cdc.gov/epstein-barr/about-mono.html **4**. Centers for Disease Control and Prevention. Symptoms of coronavirus. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

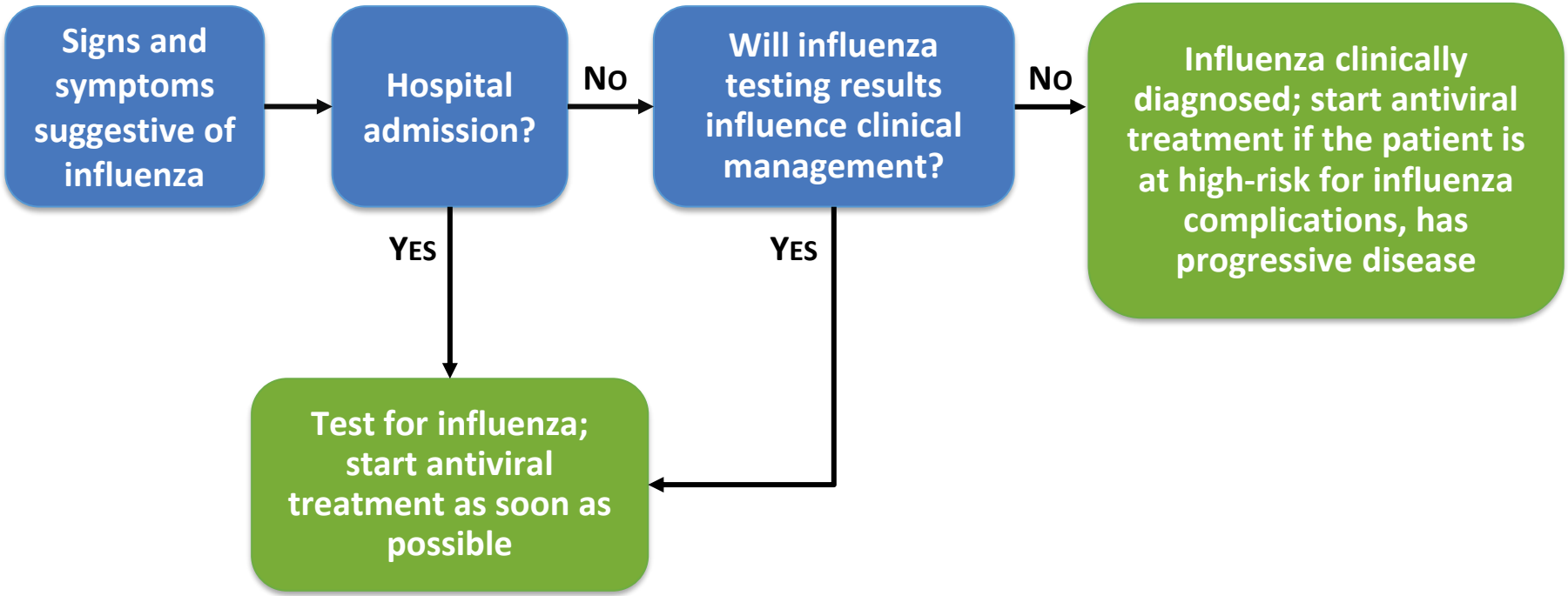
Differential Diagnosis (cont'd)

Condition	Diagnostic Test	Onset	Duration
Influenza	Rapid molecular assays, RT-PCR, nucleic acid amplification tests[1]	Sudden[2]	Few days to <2 weeks[3]
Common Cold	None[2]	Gradual[2]	~ 2-3 weeks[4]
Infectious Mononucleosis	Heterophile antibody testing (Monospot test) and EBV-specific serologies[5]	Gradual[6]	~ 2-4 weeks[6]
COVID-19	RT-PCR, antigen tests[7]	Gradual[3]	~ 1-2 weeks; can be >6 weeks[8,9]

EBV, Epstein-Barr virus; RT-PCR, reverse transcription-polymerase chain reaction.

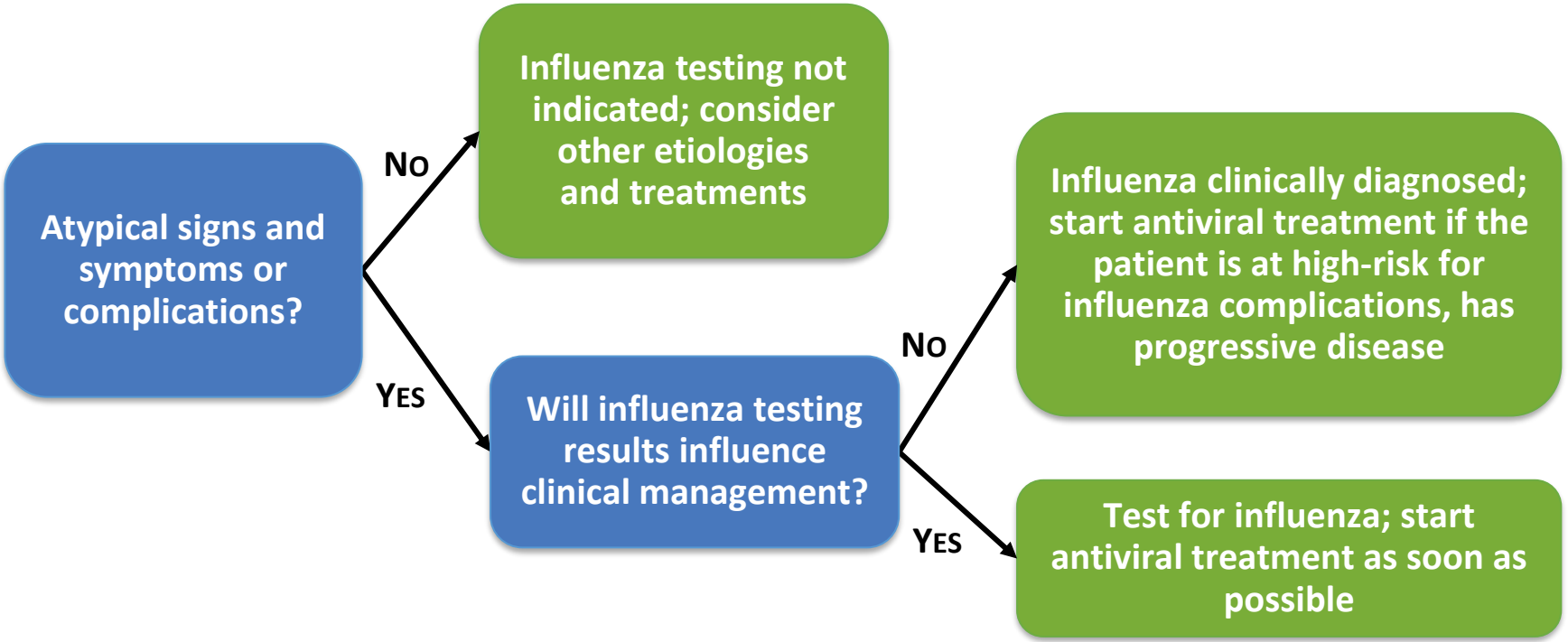
1. Centers for Disease Control and Prevention. Information on rapid molecular assays, RT-PCR, and other molecular assays for diagnosis of influenza virus infection. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm **2**. Centers for Disease Control and Prevention. Cold versus flu. https://www.cdc.gov/flu/symptoms/coldflu.htm **3**. Centers for Disease Control and Prevention. Similarities and differences between flu and COVID-19. https://www.cdc.gov/flu/symptoms/flu-vs-covid19.htm **4**. Centers for Disease Control and Prevention. Common colds: protect yourself and others. https://www.cdc.gov/features/rhinoviruses/index.html **5**. Centers for Disease Control and Prevention. Epstein-Barr virus and infectious mononucleosis: laboratory testing. https://www.cdc.gov/epstein-barr/laboratory-testing.html **6**. Centers for Disease Control and Prevention. About infectious mononucleosis. https://www.cdc.gov/epstein-barr/about-mono.html **7**. United States Food and Drug Administration. Coronavirus disease 2019 testing basics. https://www.fda.gov/consumers/consumer-updates/coronavirus-disease-2019-testing-basics **8**. Centers for Disease Control and Prevention. *MMWR*. 69(30);993-998. https://www.cdc.gov/mmwr/volumes/69/wr/mm6930e1.htm **9**. Nehme M, et al. *Ann Intern Med*. 2020; M20-5926. doi: 10.7326/M20-5926. Online ahead of print.

IDSA Guidelines for Influenza Diagnosis: Presentation Suggestive of Influenza



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

IDSA Guidelines for Influenza Diagnosis: Atypical Presentation or Complications



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

Identifying Patients at Risk for Complications

Age	Pregnancy	Ethnicity	Residential setting
• Adults ≥65 years • All children ≤5 years – Highest risk for those <2 years – Highest hospitalization and death rates among infants <6 months	• Pregnant patients • Patients up to 2 weeks after pregnancy	• Black • Hispanic or Latino • American Indian • Alaska Native	• People living in nursing homes • People living in other LTC facilities

LTC, long-term care.

Centers for Disease Control and Prevention. People at high risk for flu complications. https://www.cdc.gov/flu/highrisk/index.htm

Additional Risk Factors for Complications

- Asthma
- Chronic lung disease (eg, COPD, CF)
- Neurological and neurodevelopmental conditions
- Blood disorders (eg, sickle cell disease)
- Endocrine disorders (eg, DM)
- Heart disease (eg, CHD, CHF, CAD)
- Kidney disorders

- Liver disorders
- Metabolic disorders (eg, inherited metabolic disorders and mitochondrial disorders)
- Obesity (ie, BMI ≥40)
- Patients <19 YO on long-term aspirin- or salicylate-containing medications
- Weakened immune system due to disease or medications

BMI, body mass index; CAD, coronary artery disease; CF, cystic fibrosis; CHD, congenital heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.

Centers for Disease Control and Prevention. People at high risk for flu complications. https://www.cdc.gov/flu/highrisk/index.htm

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Treatment of Influenza

Identification of Candidates for Therapy and Antiviral Selection

IDSA Guidelines for Influenza Treatment

For confirmed or suspected influenza in the following:

- Patients hospitalized with influenza
- Outpatients
  - With severe or progressive illness
  - At high risk of complications
- Children <2 years
- Adults ≥65 years
- Pregnant patients and those ≤2 weeks postpartum

→ **Treat promptly**

- Select patients not at high risk of influenza complications
  - Illness onset ≤2 days
  - Symptomatic with high-risk home contact(s)
  - Symptomatic HCP

→ **Consider treatment**

HCP, healthcare provider.

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

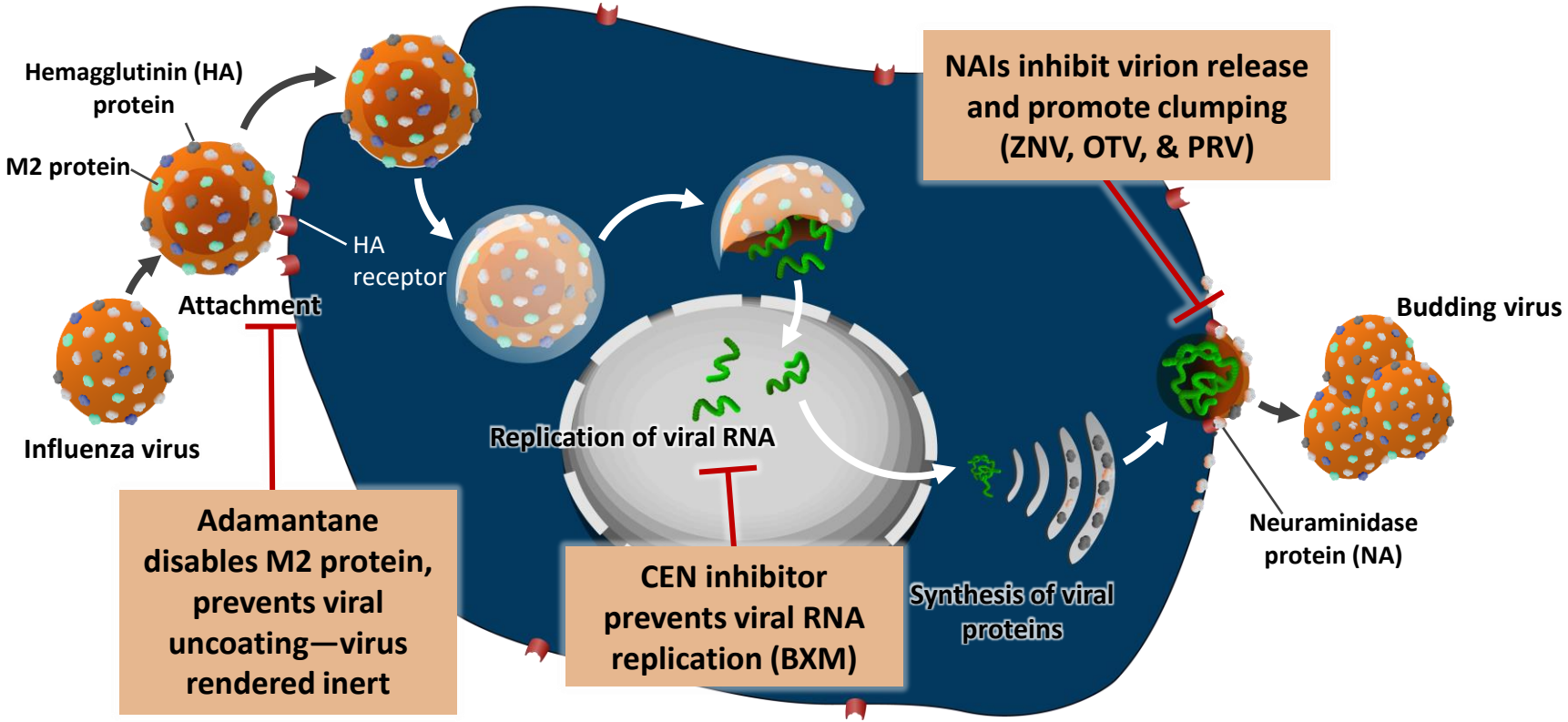
Recommended Antiviral Therapies: Indications and Administration

Agent	Route	Treatment Dosing	Prophylaxis Dosing (Community Outbreak)	Eligibility for Treatment of Acute Uncomplicated Influenza With Symptoms ≤48 hours	Eligibility for Prophylaxis
Oseltamivir[1]	PO	• BID × 5 days (except if renally impaired)	• QD × ≥10 days (≤6 weeks)	• ≥2 weeks old	• ≥1 year old
Peramivir[2]	IV	• Single infusion over ≥15 minutes	• N/A	• ≥2 years old	• N/A
Zanamivir[3]	INH	• 2 inhalations BID × 5 days	• 2 inhalations QD × 10 days (28 days)	• ≥7 years old	• ≥5 years old
Baloxavir marboxil[4]	PO	• Single dose of 2 tablets	• Single dose of 2 tablets	• ≥12 years old	• ≥12 years old

BID, twice a day; INH, inhaled; IV, intravenous; PO, by mouth; QD, once a day.

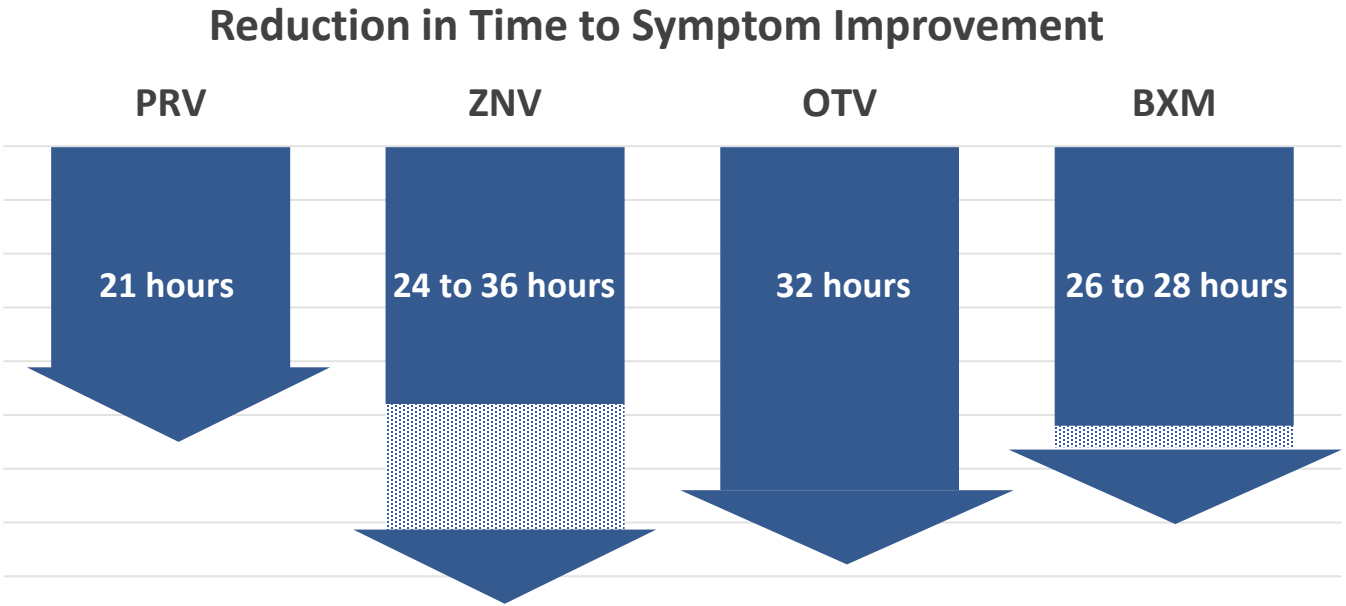
1. Tamiflu (oseltamivir phosphate). Prescribing Information. Genentech, Inc; 2019. **2**. Rapivab (peramivir). Prescribing Information. BioCryst Pharmaceuticals; 2020. **3**. Relenza (zanamivir). Prescribing Information. GlaxoSmithKline; 2018. **4**. Xofluza (baloxavir marboxil). Prescribing Information. Genentech USA, Inc; 2020.

Mechanism of Action of Available Antivirals for Influenza



BXM, baloxavir marboxil; CEN, cap-dependent endonuclease; NAI, neuraminidase inhibitor; OTV, oseltamivir; ZNV, zanamivir; PRV, peramivir.

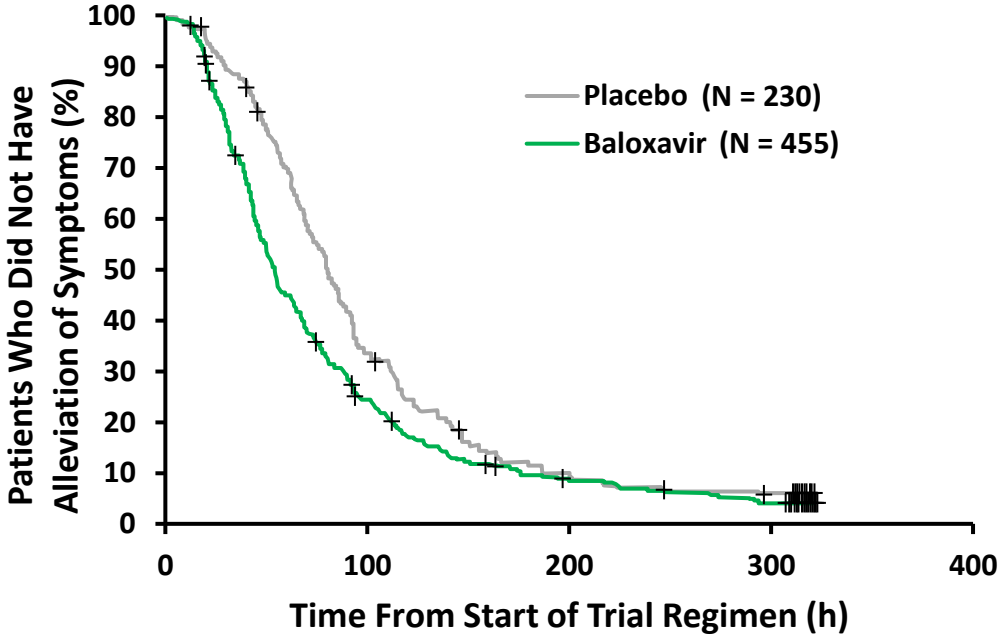
Overview of Antiviral Efficacy



Rapivab. Prescribing Information. BioCryst Pharmaceuticals; 2014; Relenza. Prescribing Information. GlaxoSmithKline; 2018; Tamiflu. Prescribing Information. Genentech; 2016; Xofluza. Prescribing Information. Genentech; 2018.

Efficacy of Baloxavir Marboxil for Patients With Acute Uncomplicated Influenza

CAPSTONE-1 Trial



Patients:

- Otherwise healthy outpatients 12-64Y with acute uncomplicated influenza

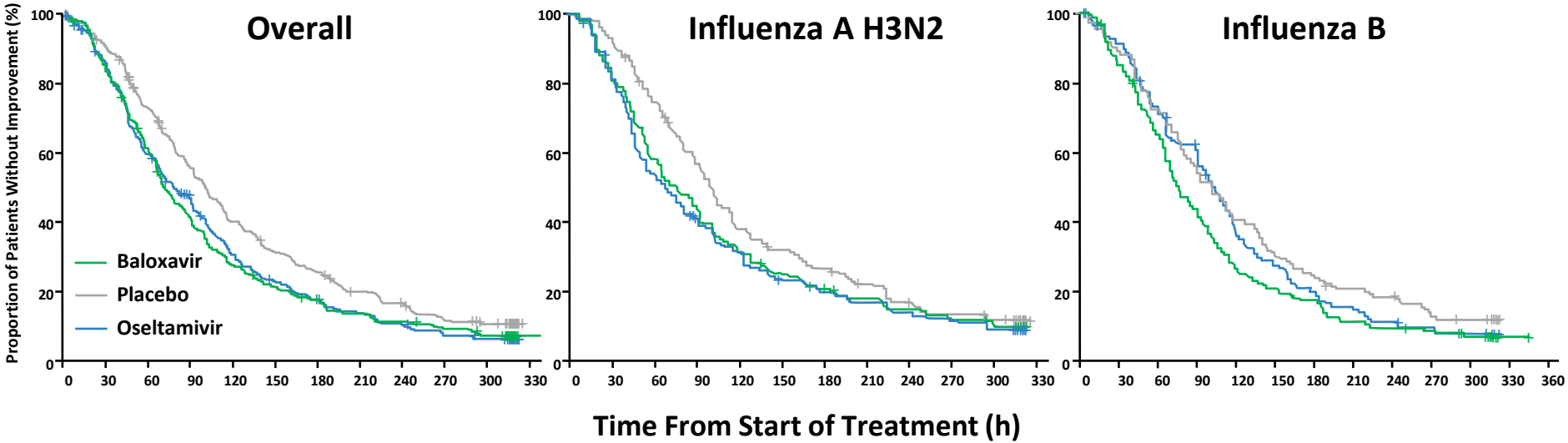
Treatment with baloxavir:

- **Reduced time to symptom alleviation** vs placebo
- Was associated with a **faster decline in viral load** vs placebo or oseltamivir

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

Baloxavir for the Treatment of Influenza in High-risk Patients

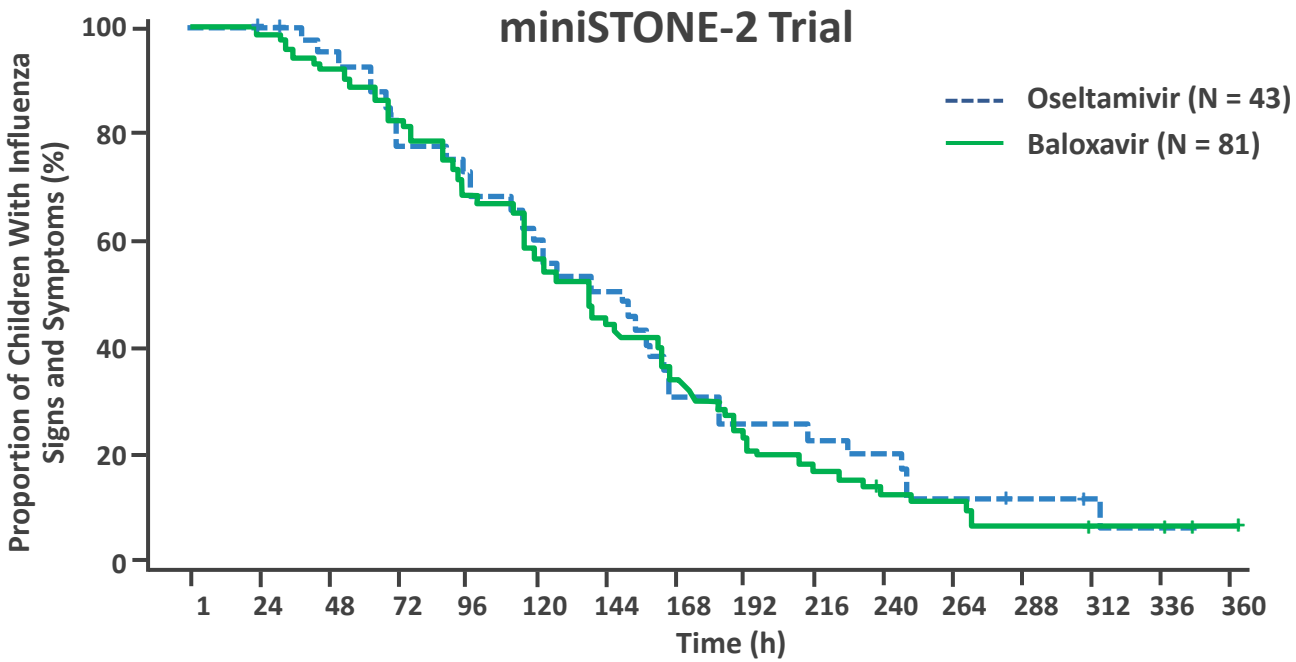
CAPSTONE-2 Trial



- Safety profile was similar across all groups.
- Patients ≥12Y with ≥ 1 CDC-defined factor placing them at increased risk of complications, eg, asthma or chronic lung disease, endocrine disorders, heart disease, age ≥ 65Y, and metabolic disorders.

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

Efficacy of Baloxavir Marboxil in Children with Influenza



Patients:

- 1 to <12Y (otherwise healthy)
- Clinical diagnosis
  - Fever (tympanic temp ≥38°C) at screening and
  - ≥ 1 respiratory symptom (cough or nasal congestion).
- Symptoms ≤48h

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

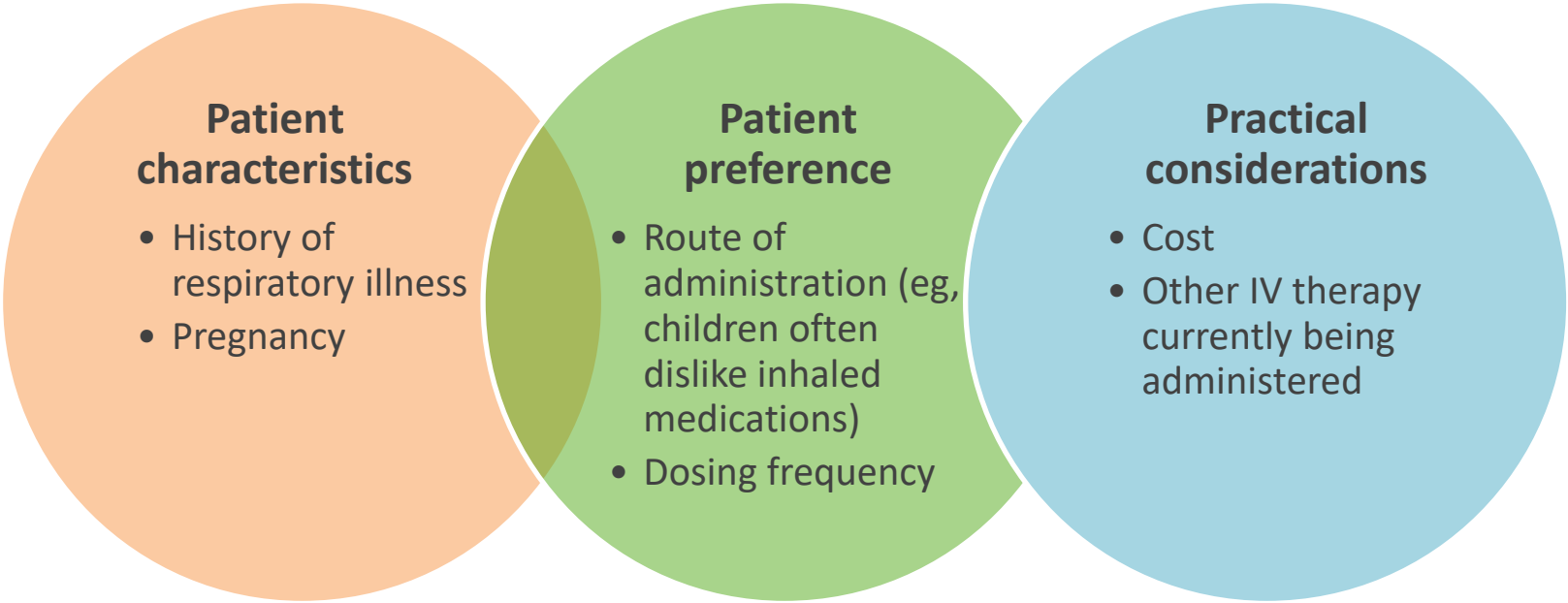
Overview of Antiviral Safety Profiles

	PRV	ZNV	OTV	BXM
Nonserious AEs	• Nausea • Vomiting • Headache	• Potential bronchospasm • Diarrhea • Neutropenia	• Sinusitis • Diarrhea • Nausea • Fever • Arthralgia	None more common vs PBO
Serious skin infection	Yes	Yes	Yes	
Sporadic, transient neuropsychiatric event	Yes	Yes	Yes	

AEs, adverse events; PBO, placebo.

Rapivab. Prescribing Information. BioCryst Pharmaceuticals; 2014; Relenza. Prescribing Information. GlaxoSmithKline; 2018; Tamiflu. Prescribing Information. Genentech; 2016; Xofluza. Prescribing Information. Genentech; 2018.

Considerations for Selecting an Antiviral Therapy

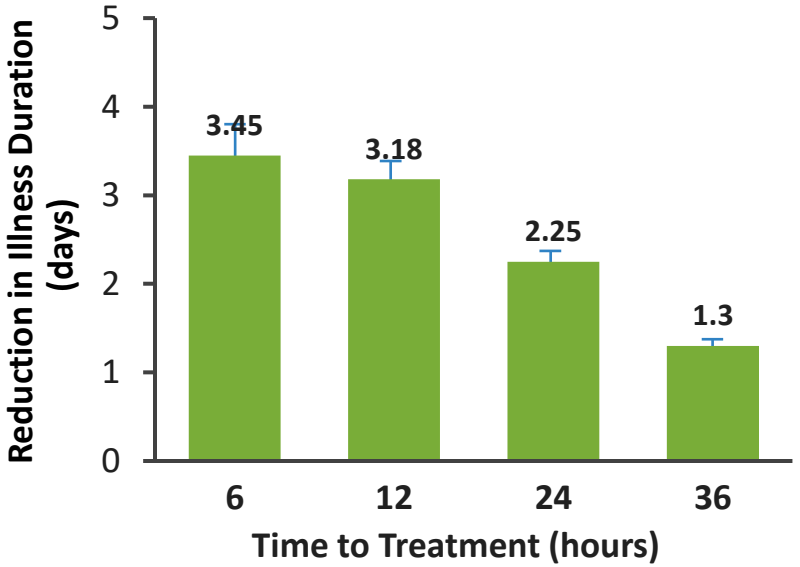


The Importance of Timing: Impact of Earlier vs Delayed Oseltamivir Treatment*

Earlier vs later antiviral treatment:

- ✓ Shorter duration of illness *(graph)*
- ✓ Faster return to normal health
- ✓ Faster return to baseline activity
- ✓ Shorter fever duration

Duration of illness



*Delayed treatment defined at 48 h.

Aoki FY, et al. *J Antimicrobial Chemotherapy*. 2003;51:123–129.

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Influenza Prophylaxis

Prophylaxis with Oseltamivir and Zanamivir Lowers Risk of Symptomatic Influenza

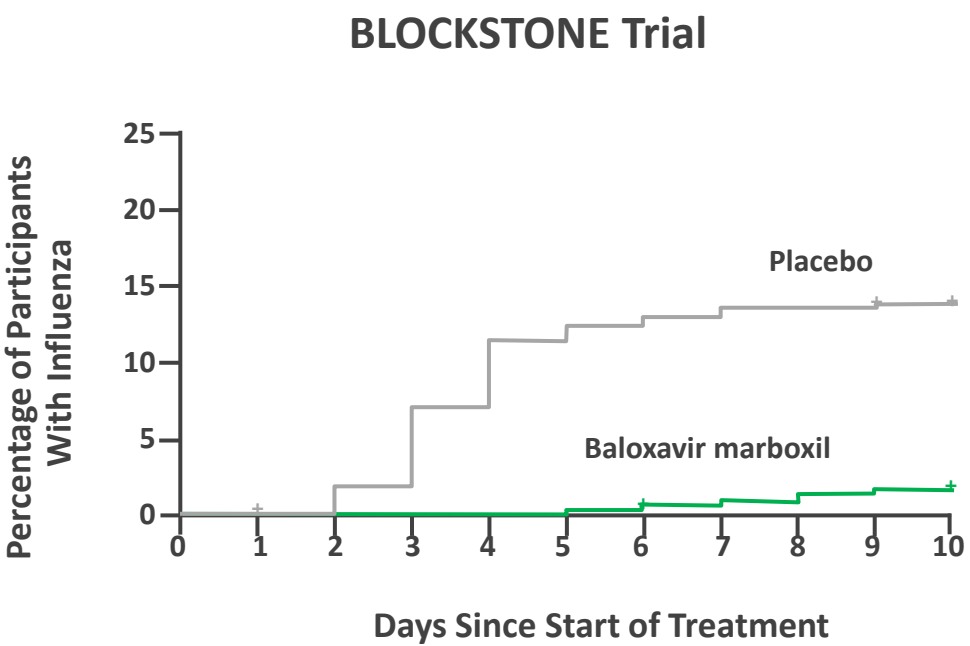
2017 systematic review of literature to date on **effectiveness & safety of NAI antivirals for influenza treatment or prophylaxis**

Study included systematic reviews and meta-analyses of RCTs and/or observational studies

- ✔ Oseltamivir or zanamivir ***consistently and significantly lowered 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.

Efficacy of Baloxavir Marboxil for Postexposure Prophylaxis



Postexposure prophylaxis with baloxavir was associated with a lower percentage of patients developing clinical influenza vs PBO (1.9% vs. 13.6%; aRR, 0.14; 95% CI, 0.06 to 0.30; P < .001).

aRR, adjusted risk ratio; CI, confidence interval.

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

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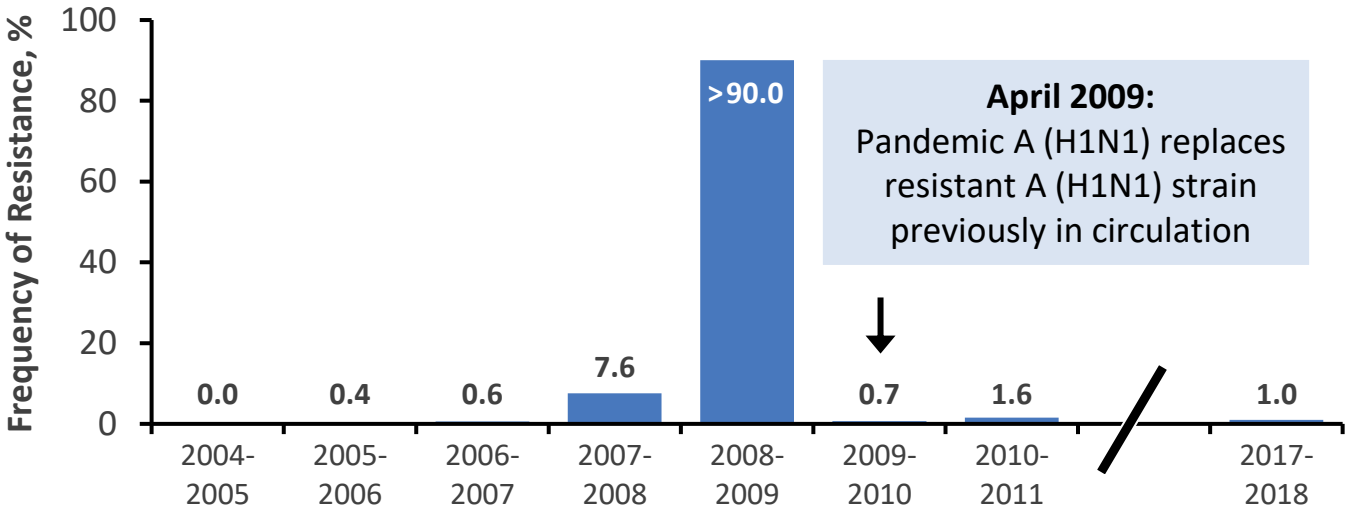
Antiviral Resistance

NAI-Resistant Strains May Emerge Again, Increasing Need for New Antiviral Treatments

Common Mutations Associated With Oseltamivir Resistance:

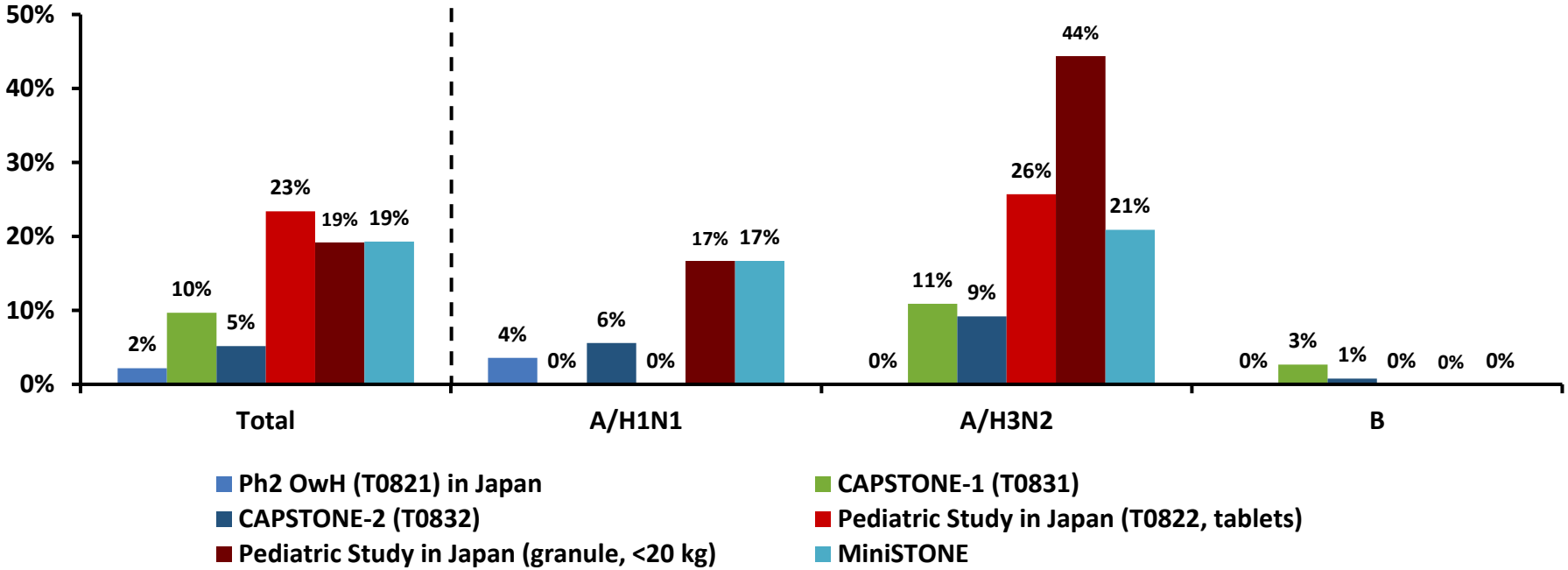
- H274Y A (H1N1) and A (H5N1) subtypes
- E119V A (H3N2) and A (H7N9) subtypes
- R292K A (H3N2) and A (H7N9) subtypes

Global Frequency of Oseltamivir-Resistant Influenza A (H1N1)



Hussain M, et al. *Infect Drug Resist*. 2017;10:121-134.

The Potential Challenge to Baloxavir: Resistance



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Case Evaluations

Case: Patient Description

David is a 12-year-old boy who is brought in by his grandfather for fever, cough, headache, and fatigue over the past 24 hours. His grandfather reports that he is in generally good health although he has a history of mild asthma that is well-controlled. Due to the current pandemic, David is attending school remotely and has limited contact with other individuals. He lives with his parents, but is cared for during the week by his grandfather.

Case: Discussion Question

How would you characterize David's risk for complications of influenza?

A. Low
B. Moderate
C. High
D. Not sure

Case: Discussion Question

Based on the information presented, which of the following actions are most consistent with your approach to David's care?

A. Order a test for influenza and treat with an antiviral if the test is positive
B. Treat empirically with an antiviral
C. Discuss preferences with David's grandfather and consider treatment with an antiviral
D. Do not treat with an antiviral

Case: Discussion Question

Which antiviral agent would you prescribe for David?

A. Baloxavir marboxil
B. Oseltamivir
C. Peramivir
D. Zanamivir

Case: Discussion Question

David's grandfather is 62-years-old and has a history of obesity and T2DM. Do you recommend that David's grandfather be treated prophylactically?

A. Yes

B. No

Program Summary

- Seasonal influenza epidemics are associated with significant morbidity and mortality, especially among high-risk individuals
- Vaccination is essential for reducing the likelihood of illness and poor outcomes in the event of infection
- Nurse practitioners play an important role in managing community influenza infections, in part by educating patients about the need for vaccination and appropriate antiviral therapy
- Several antiviral influenza therapies have been shown to be safe and effective for disease prevention, shortening illness duration, minimizing complications, and reducing hospitalizations
- While effective influenza prophylaxis and treatment are perennially important goals, their impact has taken on an even greater significance in the wake of the current COVID-19 epidemic

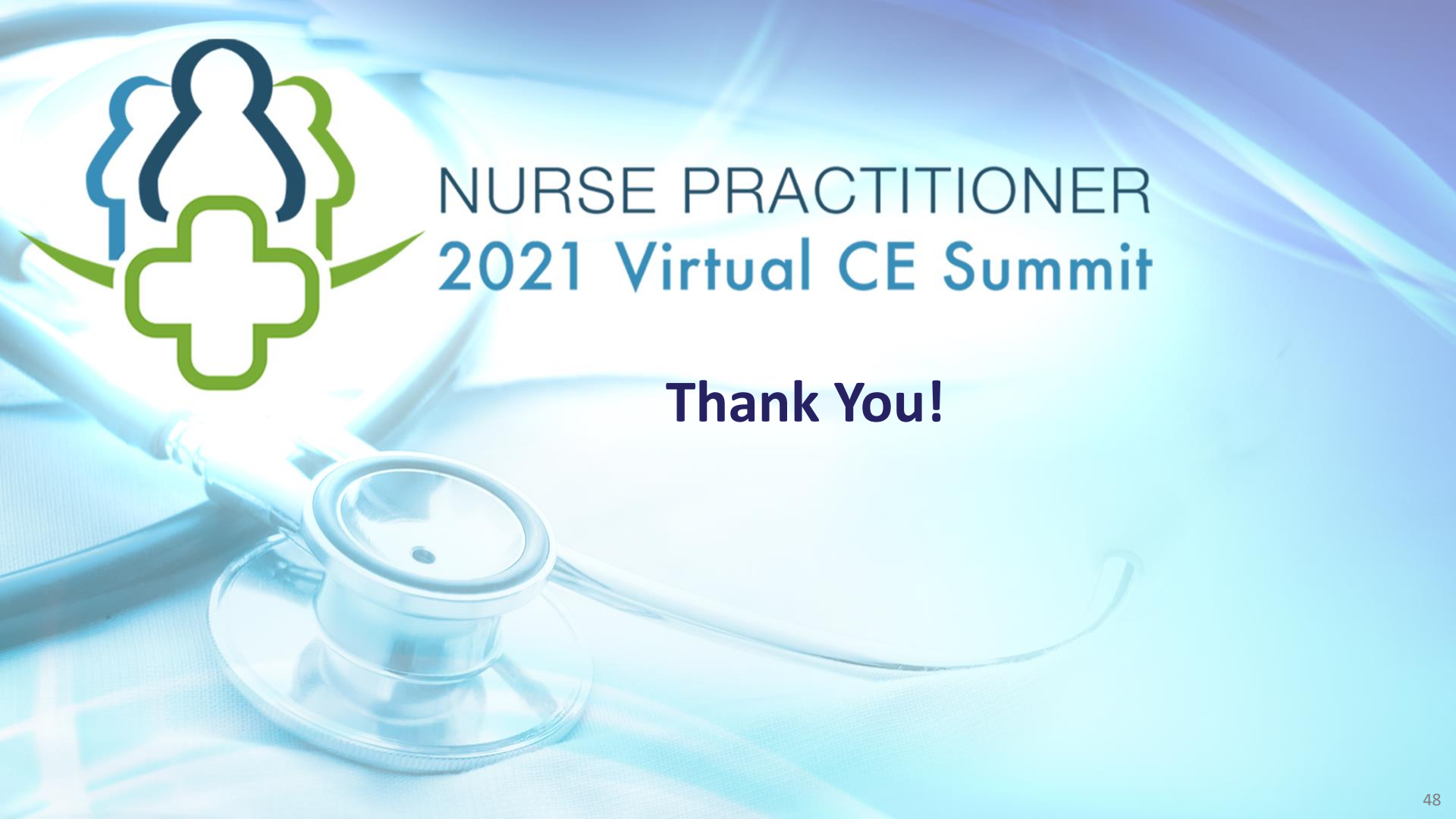
Clinical Pearls

Initiate antiviral therapy as soon as possible for patients with influenza

Do <u>not</u> wait for diagnostic test results to begin antiviral therapy for hospitalized patients with suspected influenza

Vaccinate all patients against influenza

Individualize antiviral selection based on patient characteristics, circumstances, and preferences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Thank You!