NURSE PRACTITIONER
2021 Virtual CE Summit

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

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Supported by an educational grant from Genentech, a member of the Roche Group

Supporter Acknowledgement

- This activity is supported by an educational grant from Genentech, a member of the Roche Group.

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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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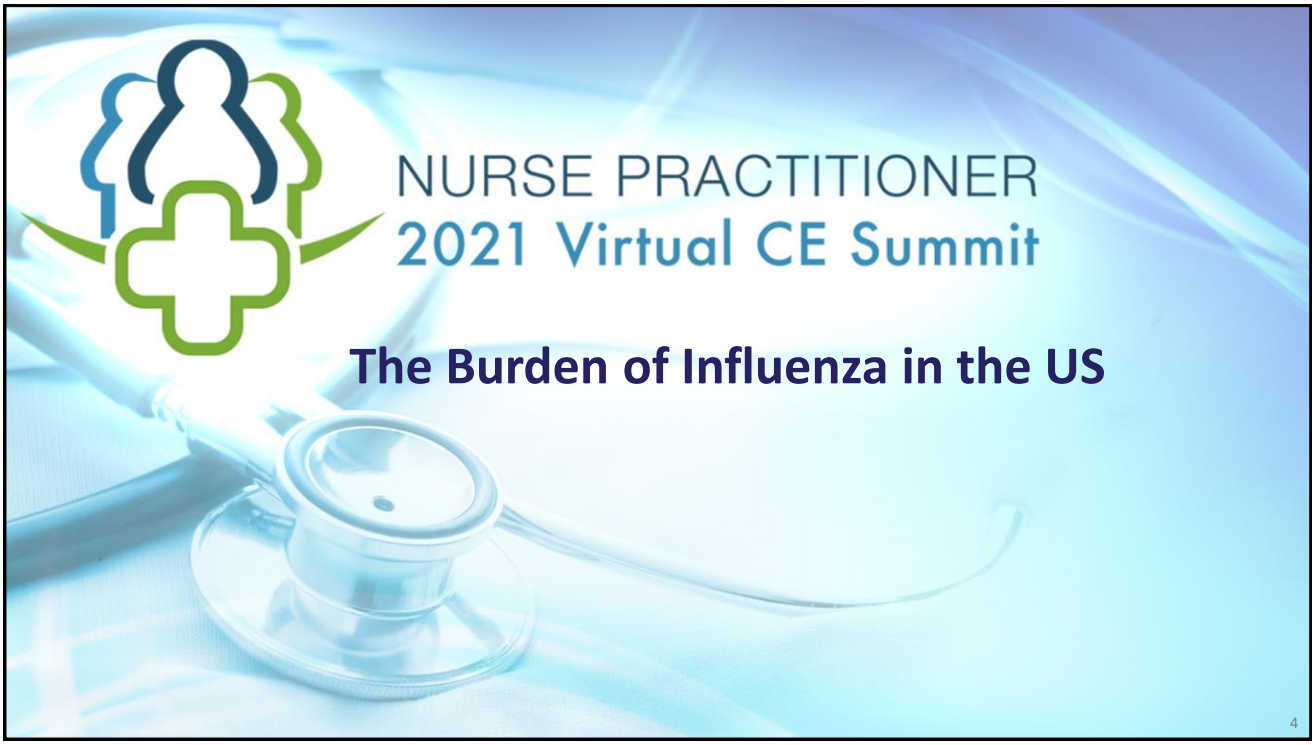

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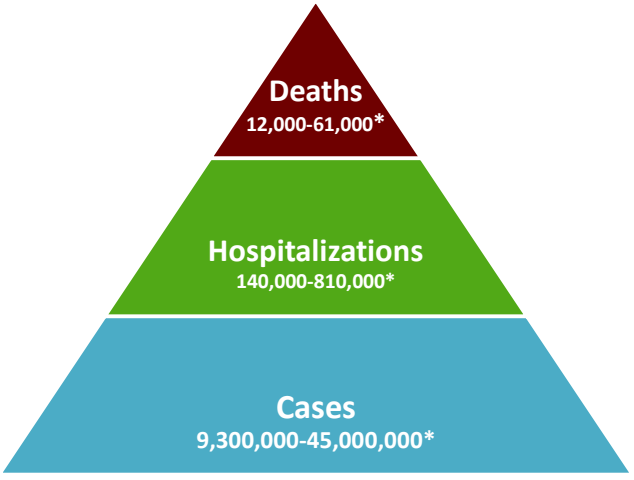
Influenza—A Recurring and Significant Threat

- 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

5

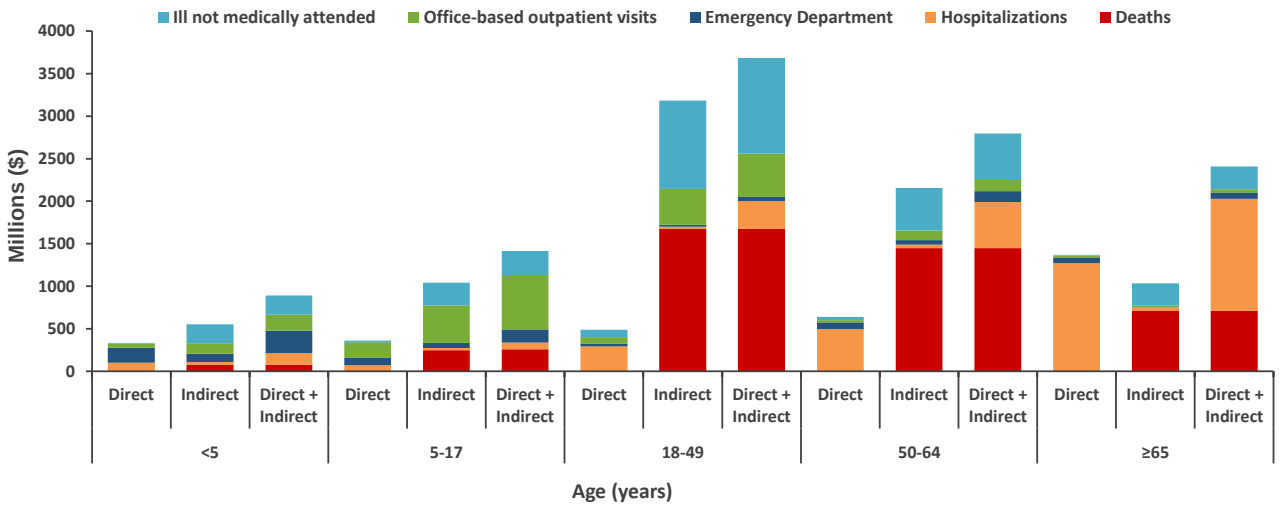
Estimates of Influenza Disease Burden by Season

United States, 2010-11 Through 2019-20 Influenza Seasons

Centers for Disease Control and Prevention. Estimated influenza illnesses, medical visits, hospitalizations, and deaths in the United States. https://www.cdc.gov/flu/about/burden/2019-2020.html

6

The Substantial Economic Costs of Influenza



Putri WCWS, et al. *Vaccine*. 2018;36(27):3960-3966.

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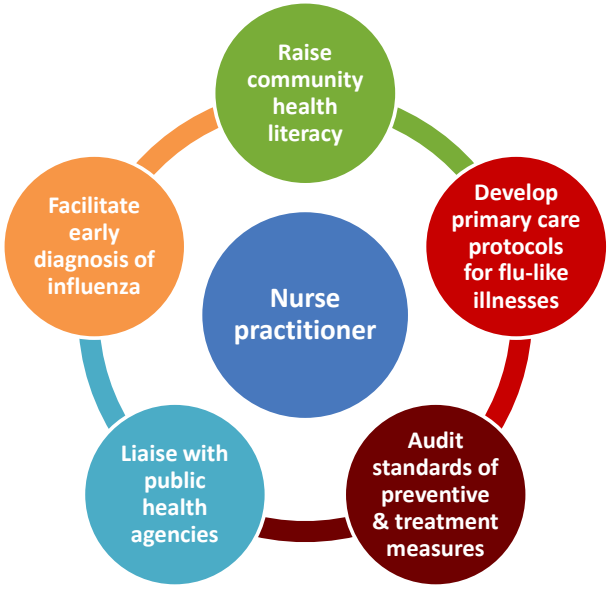
The Crucial Role of Nurse Practitioners in Improving Influenza Management



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An Ounce of Prevention

The Benefits of Influenza Vaccination

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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	3.7 million	105,000	6,300
Symptomatic illnesses	Medical visits	Hospitalizations	Deaths

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

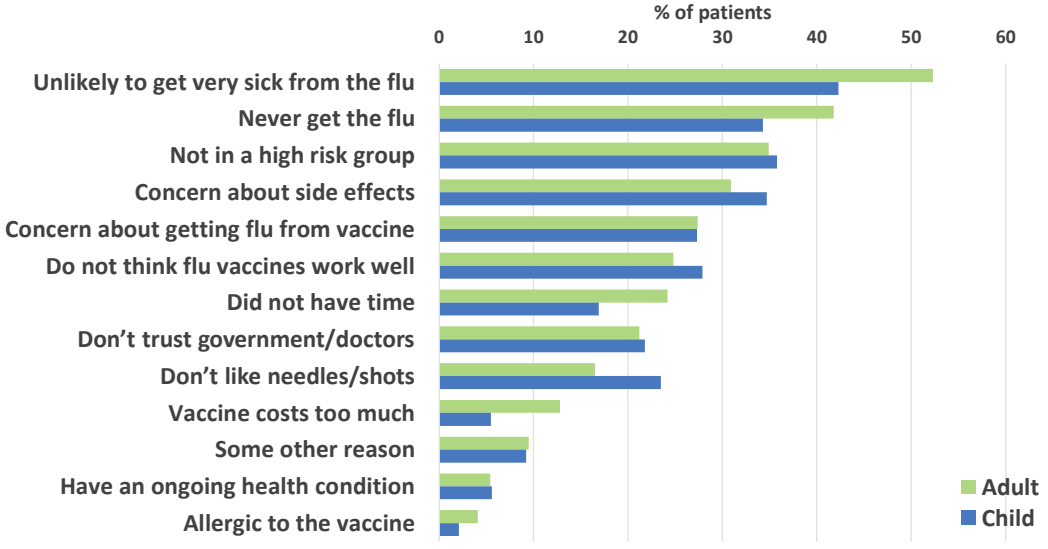
10

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

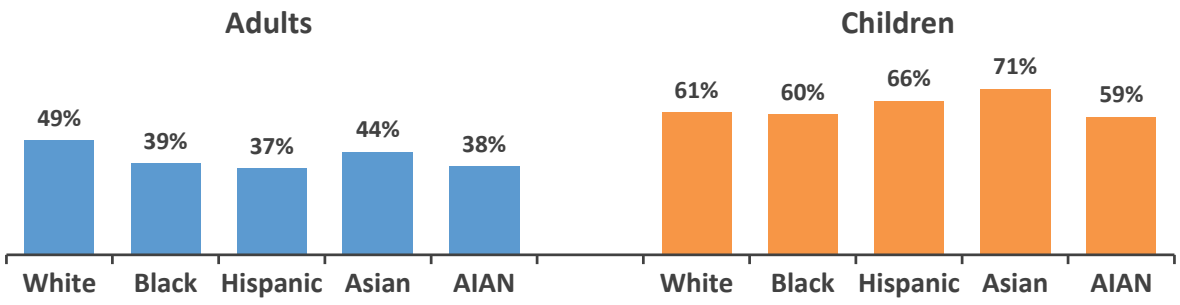
Identifying Barriers to Influenza Vaccination



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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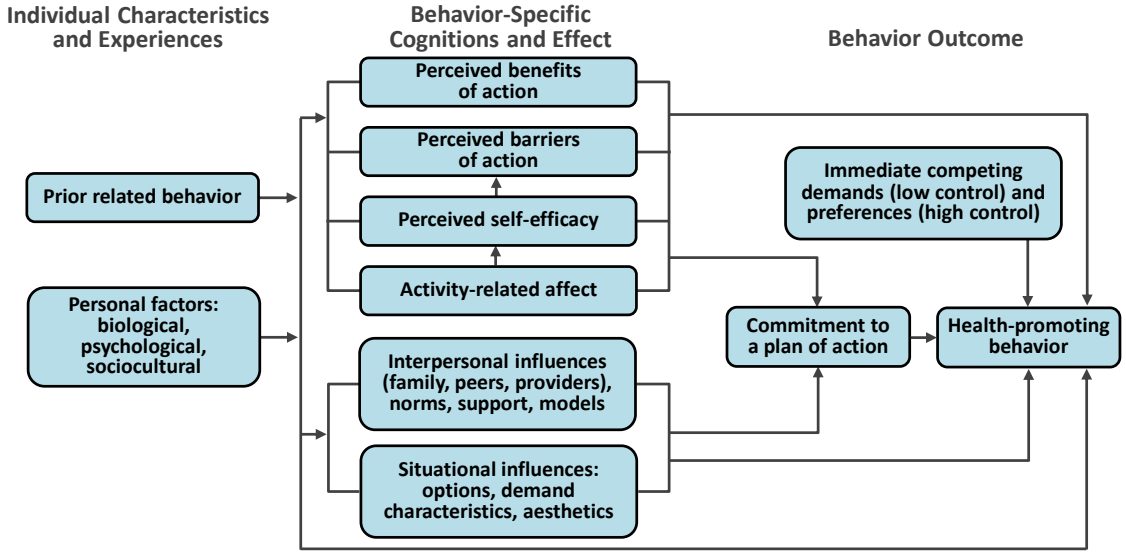
Overcoming Vaccination Barriers: Pender's Health Promotion Model



Murdaugh CL, Parsons MA, Pender NJ. *Health Promotion in Nursing Practice*, New York: Pearson Education; 2019.

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Recognition and Diagnosis of Influenza

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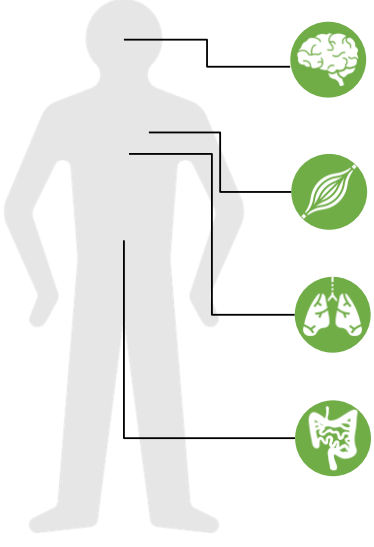
Signs and Symptoms of Influenza[1]



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.

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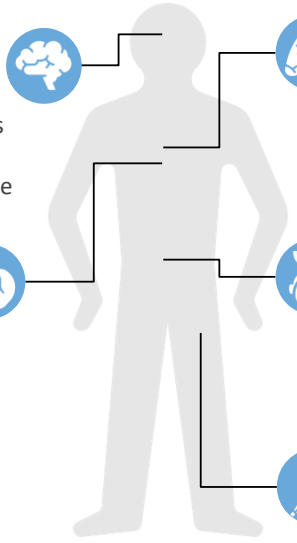
Potential Complications of Influenza



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.

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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

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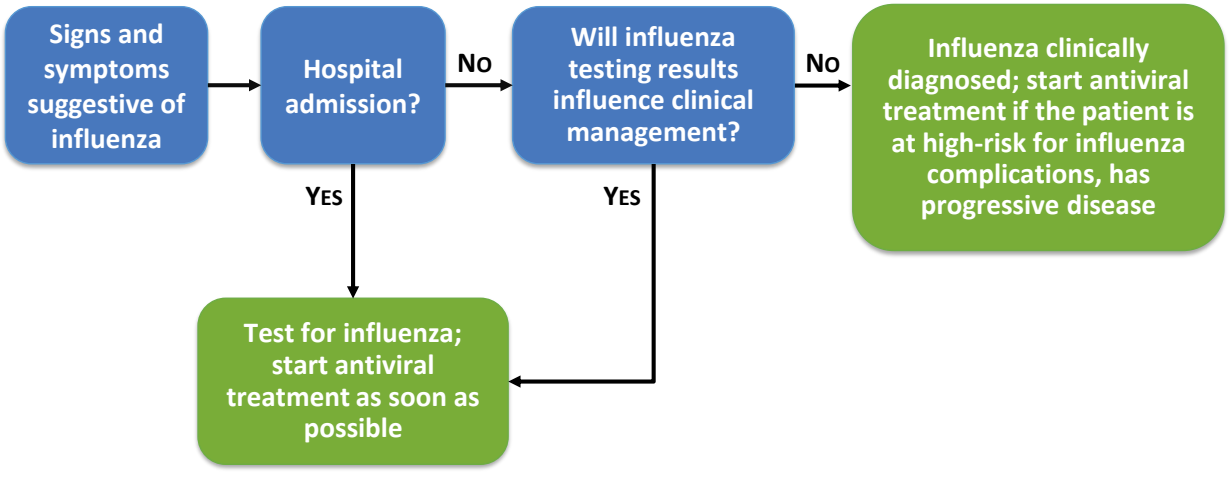
Differential Diagnosis (cont'd)

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.

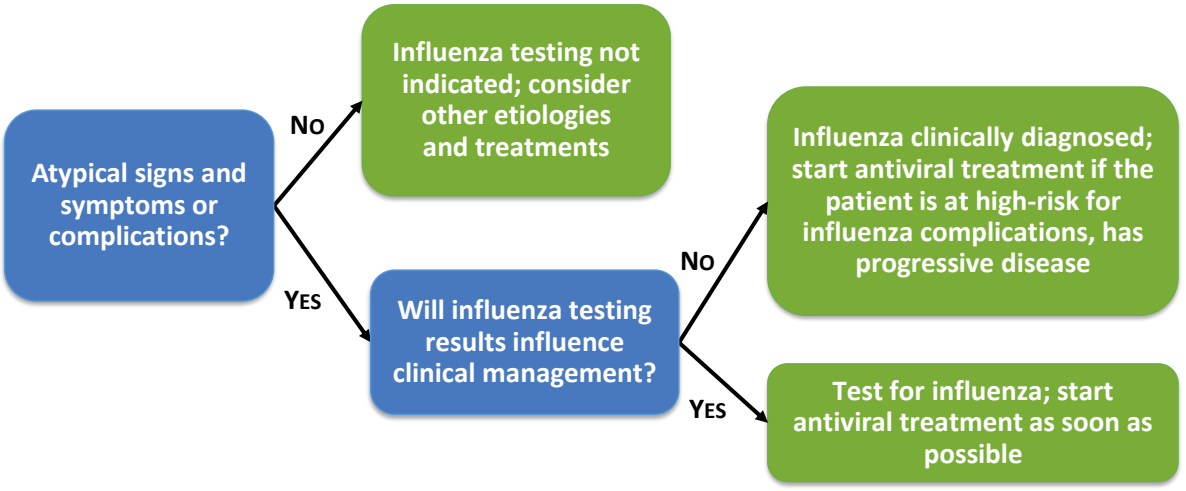
1. Centers for Disease Control and Prevention. Information on rapid molecular assays, RT-PCR, and other molecular assays for diagnosis of influenza virus infection. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm **2**. Centers for Disease Control and Prevention. Cold versus flu. 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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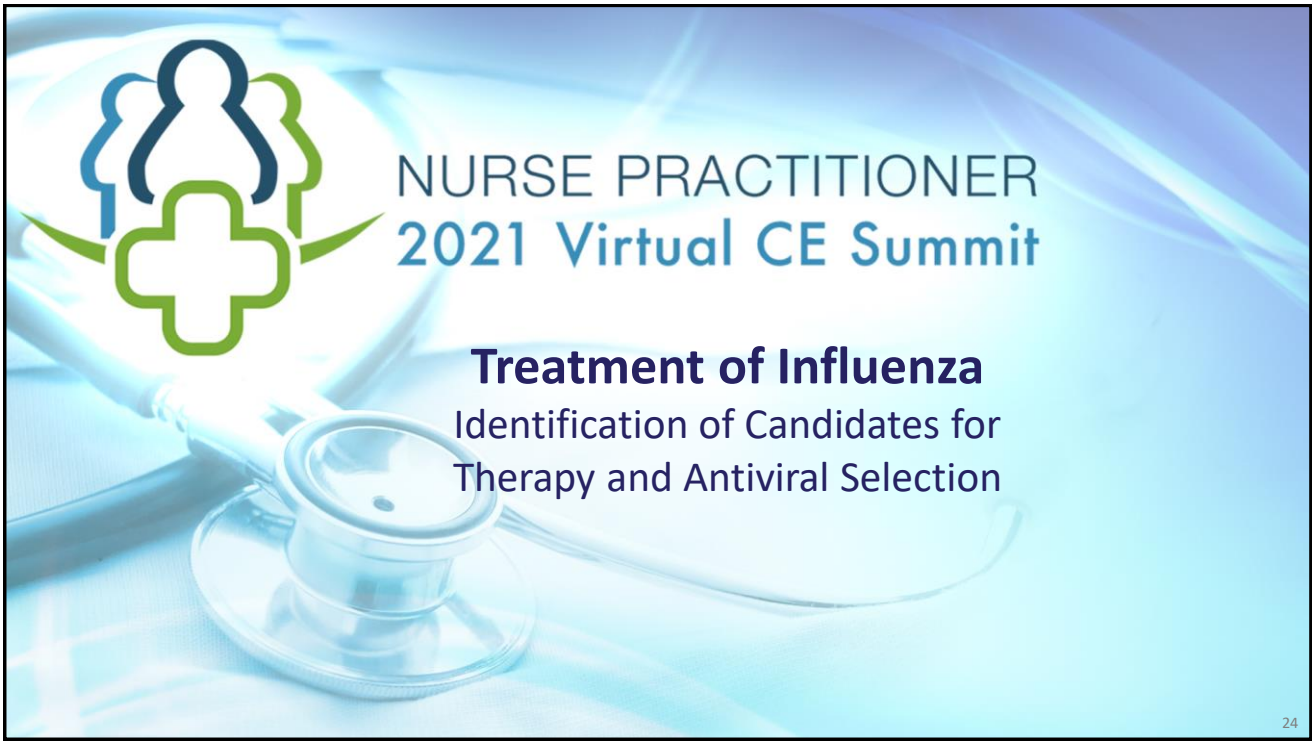

IDSA Guidelines for Influenza Treatment

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.

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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.

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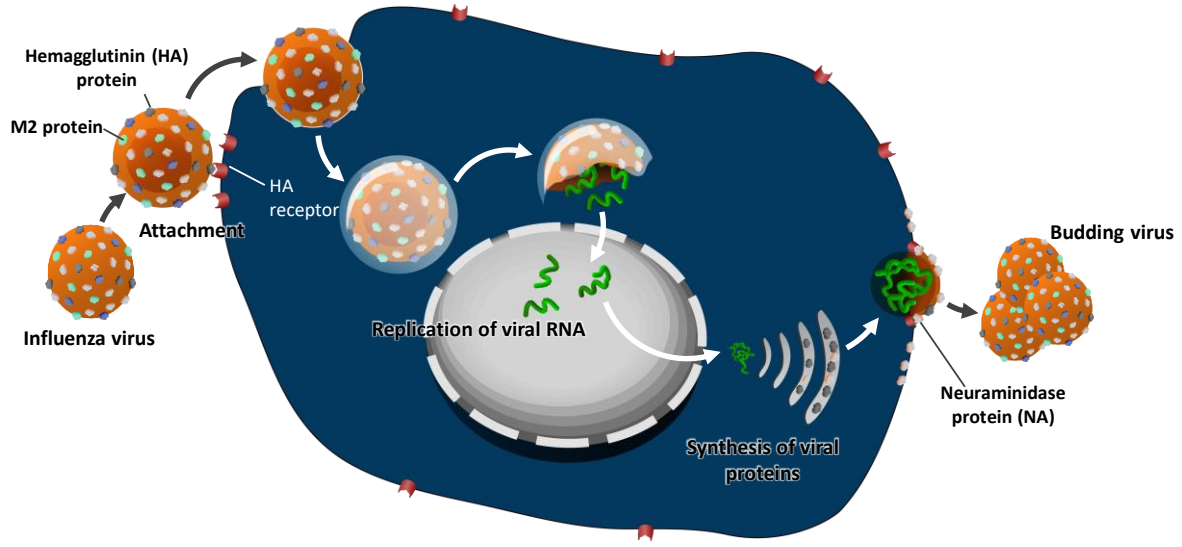
Mechanism of Action of Available Antivirals for Influenza



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

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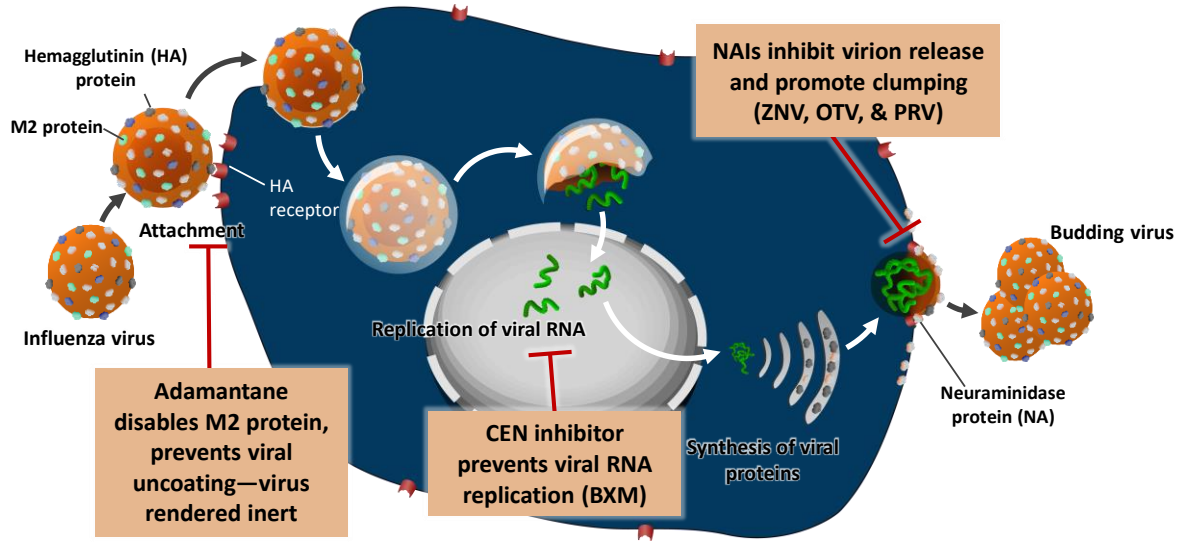
Mechanism of Action of Available Antivirals for Influenza



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

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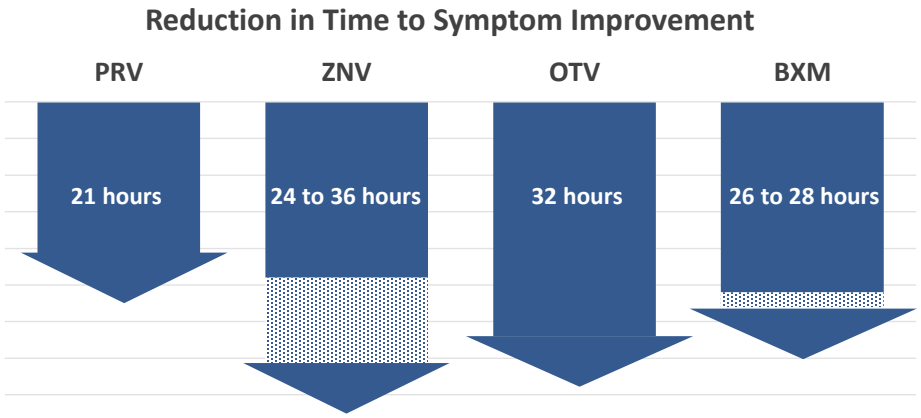
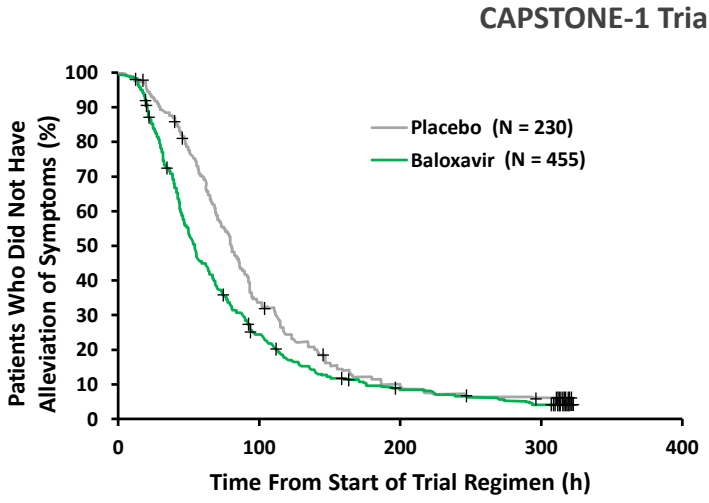
Overview of Antiviral Efficacy



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

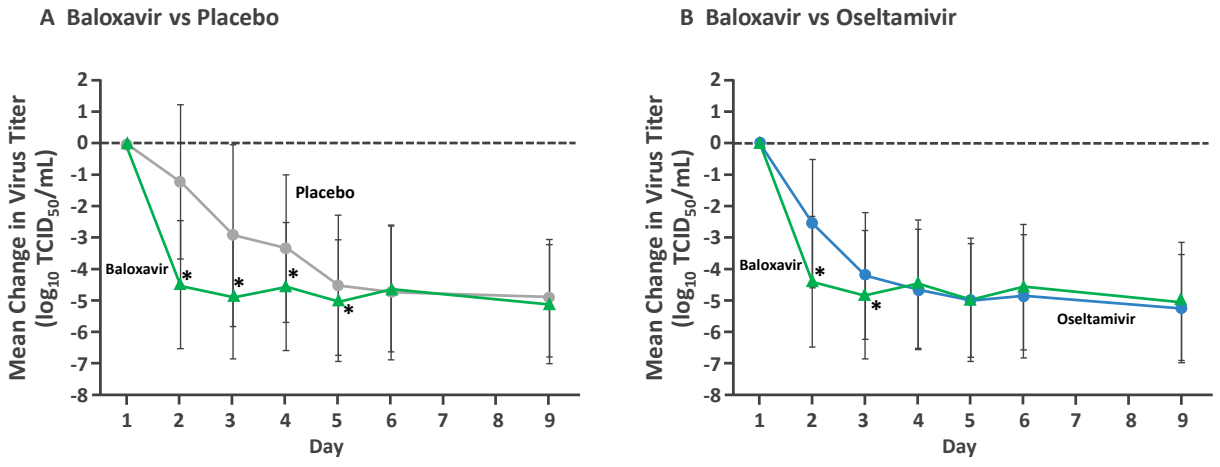


Treatment with baloxavir:

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

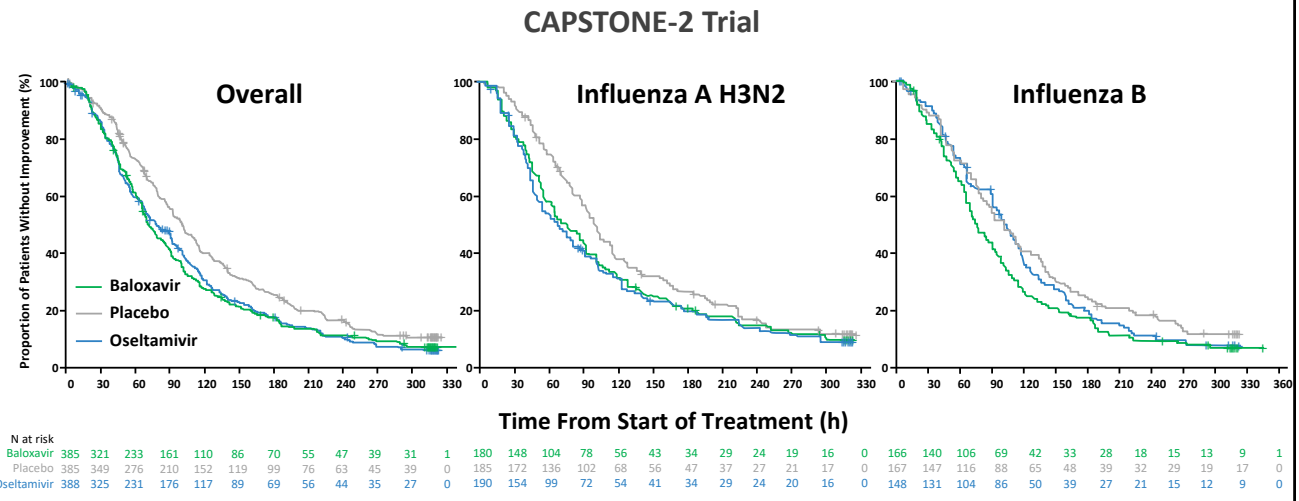
Hayden FG, et al. *N Engl J Med*. 2018;379(10):913-923.

Antiviral Therapy With Baloxavir Is Associated With a Rapid Decline in Infectious Viral Load



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

Baloxavir for the Treatment of Influenza in High-risk Patients

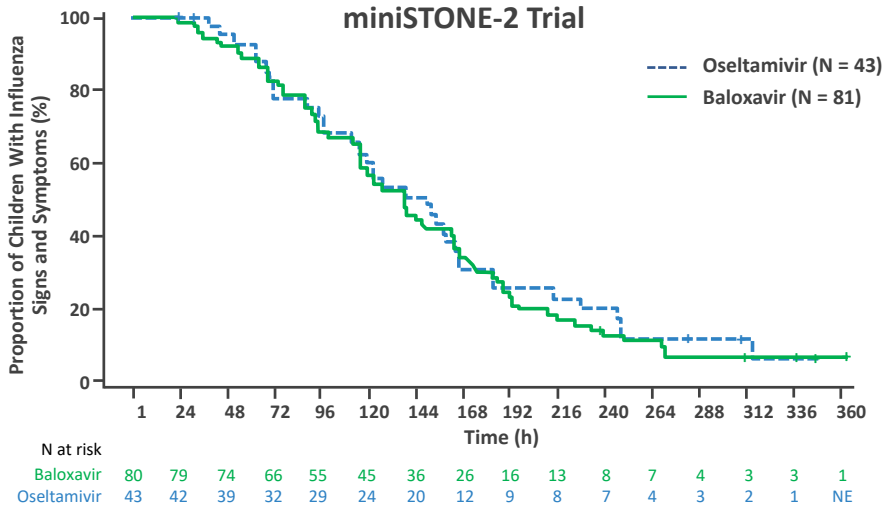


N at risk

Baloxavir	385	321	233	161	110	86	70	55	47	39	31	1	180	148	104	78	56	43	34	29	24	19	16	0	166	140	106	69	42	33	28	18	15	13	9	1
Placebo	385	349	276	210	152	119	99	76	63	45	39	0	185	172	136	102	68	56	47	37	27	21	17	0	167	147	116	88	65	48	39	32	29	19	17	0
Oseltamivir	388	325	231	176	117	89	69	56	44	35	27	0	190	154	99	72	54	41	34	29	24	20	16	0	148	131	104	86	50	39	27	21	15	12	9	0

Safety profile was similar across all groups.
Ison MG, et al. *Lancet Infect Dis*. 2020;20(10):1204-1214.

Efficacy of Baloxavir Marboxil in Children with Influenza



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

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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.

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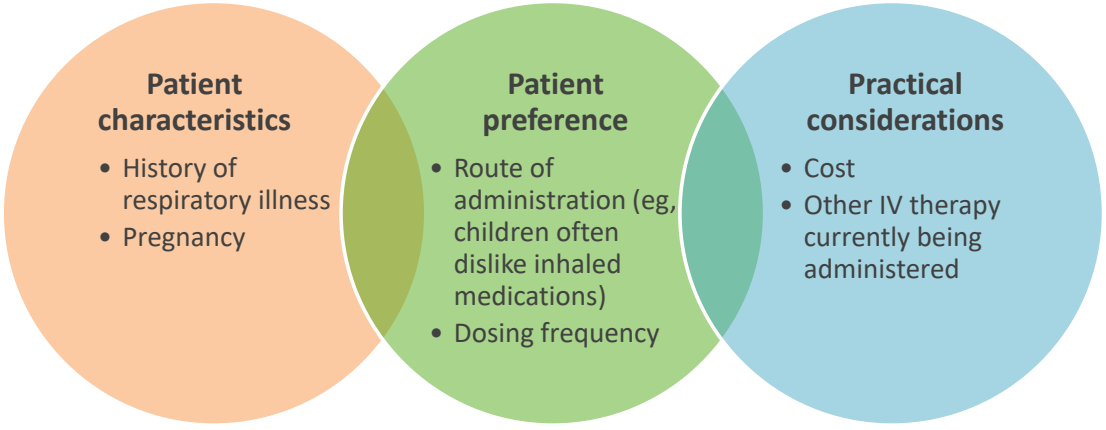
Considerations for Selecting an Antiviral Therapy



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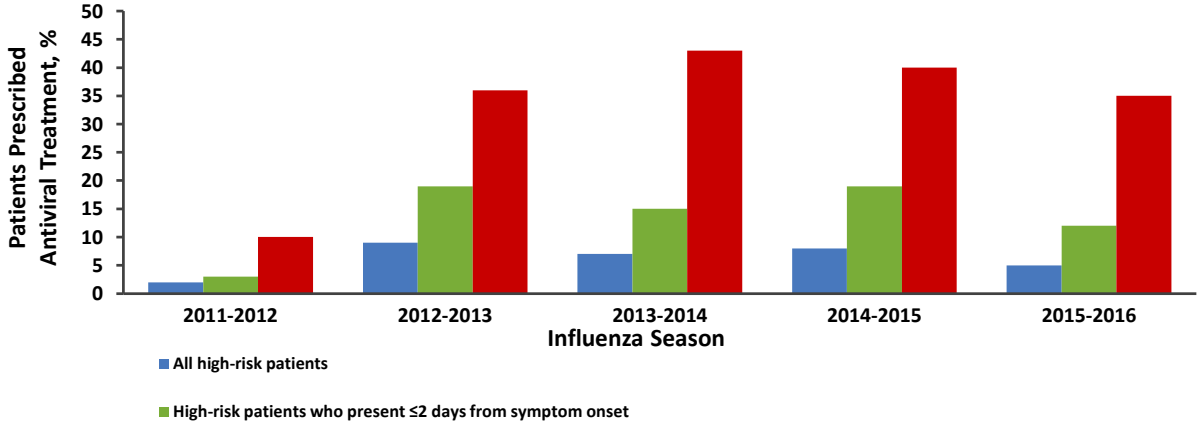
Antiviral Medications Don't Work if We Don't Use Them

Proportion of high-risk outpatients with an acute respiratory illness prescribed antiviral treatment, influenza seasons 2011-2012 through 2015-2016.



Stewart RJ, et al. *Clin Infect Dis*. 2018;66:1035-1041.

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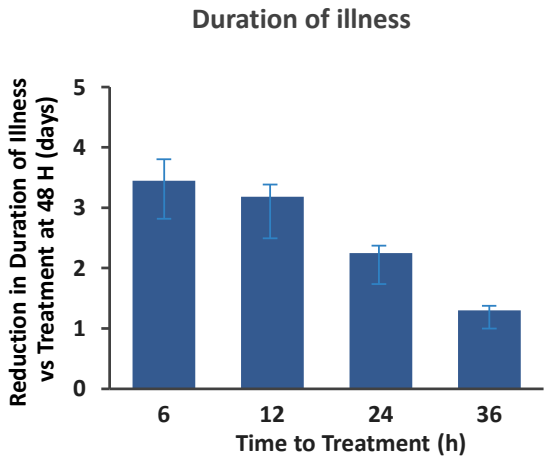
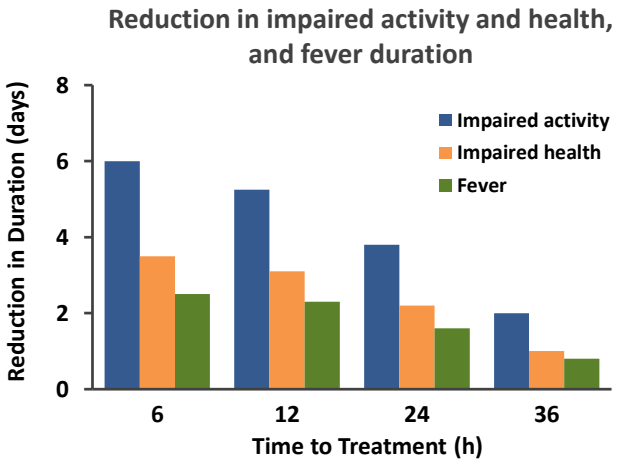
The Importance of Timing: Impact of Earlier vs Delayed Oseltamivir Treatment*





*Delayed treatment defined at 48 h.
Aoki FY, et al. *J Antimicrobial Chemotherapy*. 2003;51:123–129.

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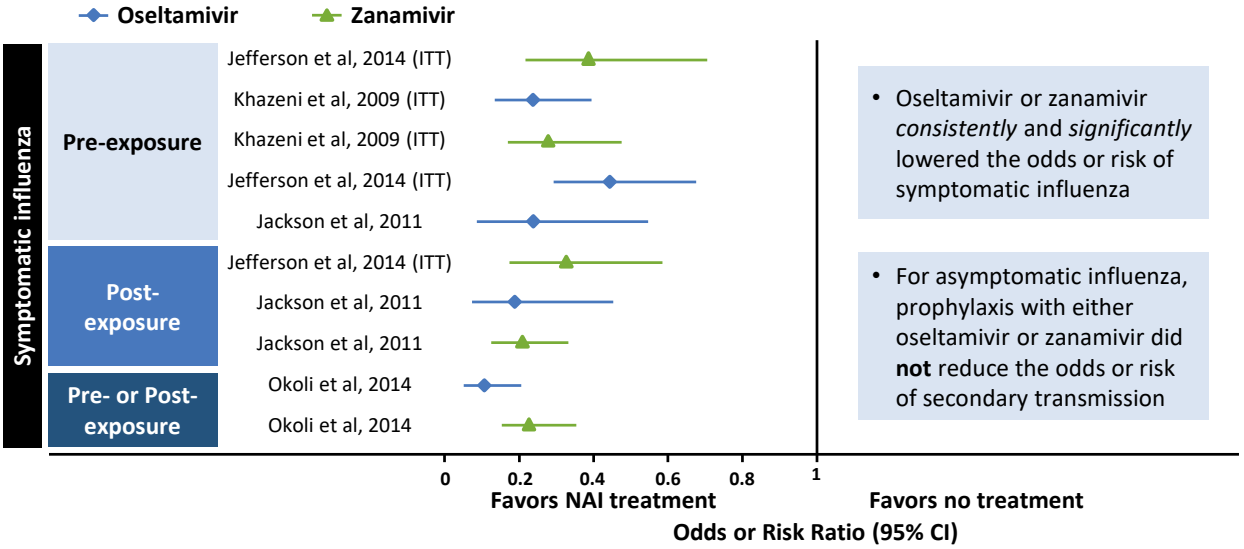
Prophylaxis with Oseltamivir and Zanamivir: Symptomatic Influenza



- 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.

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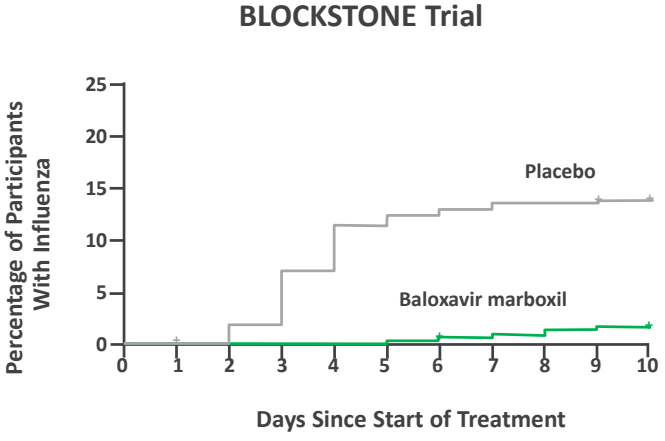
Efficacy of Baloxavir Marboxil for Postexposure Prophylaxis



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

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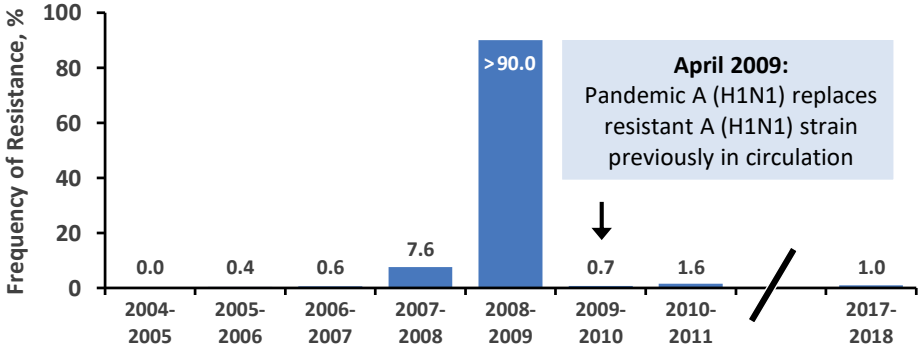
NAI-Resistant Strains May Emerge Again, Increasing Need for New Antiviral Treatments

Global Frequency of Oseltamivir-Resistant Influenza A (H1N1)

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



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

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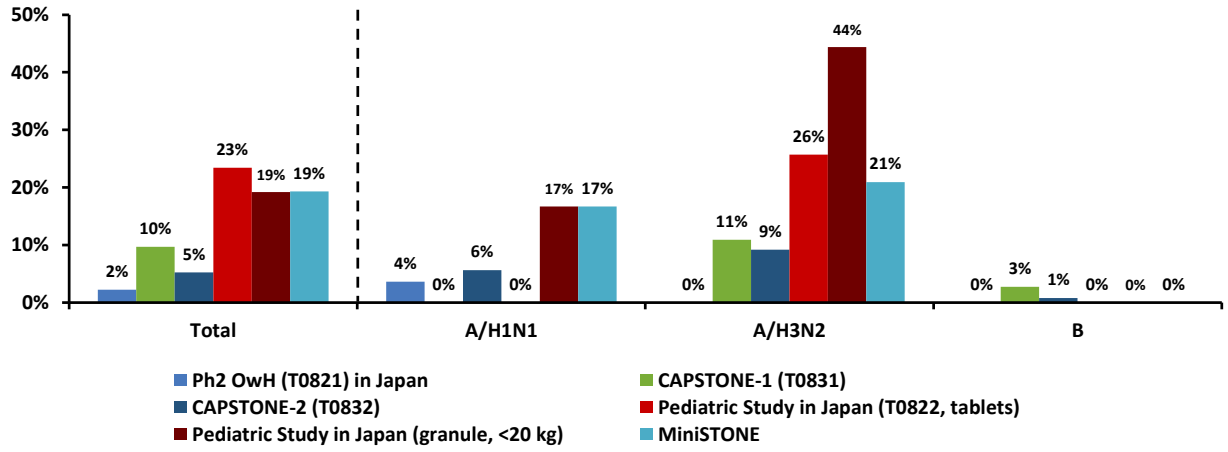
The Potential Challenge to Baloxavir: Resistance



Add reference

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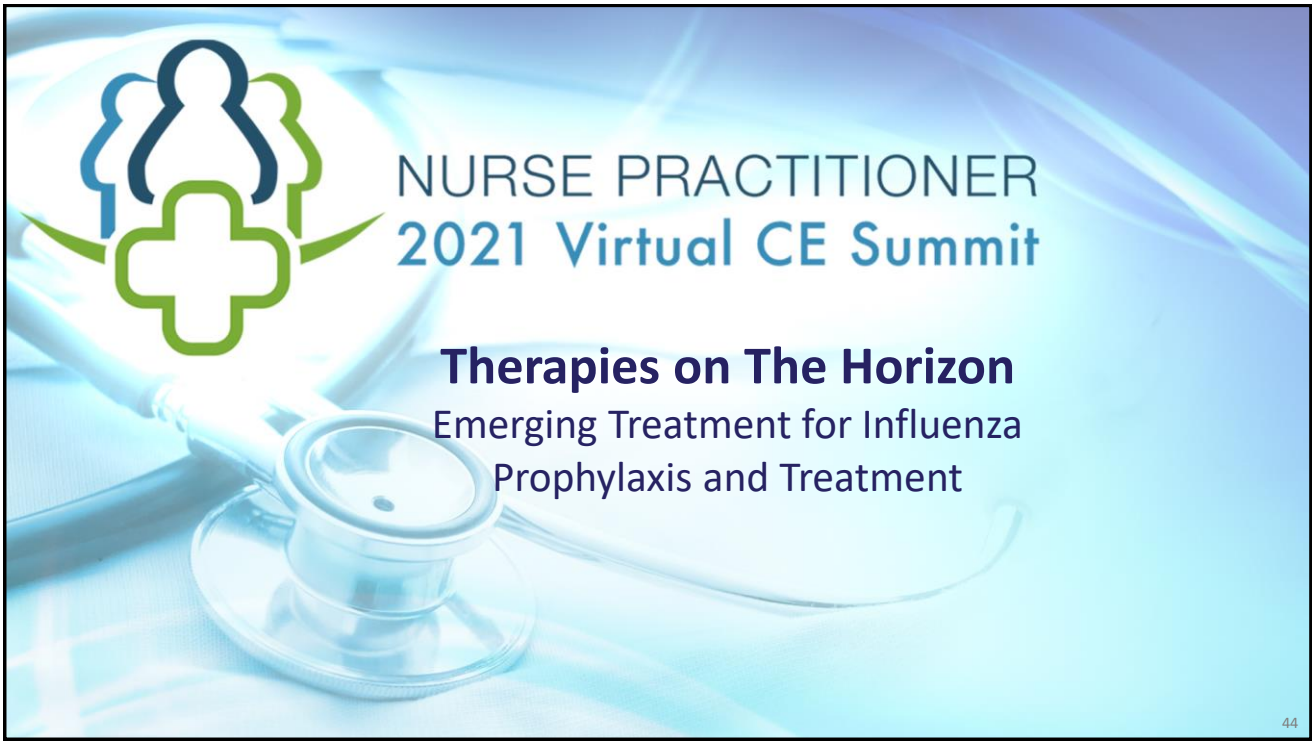

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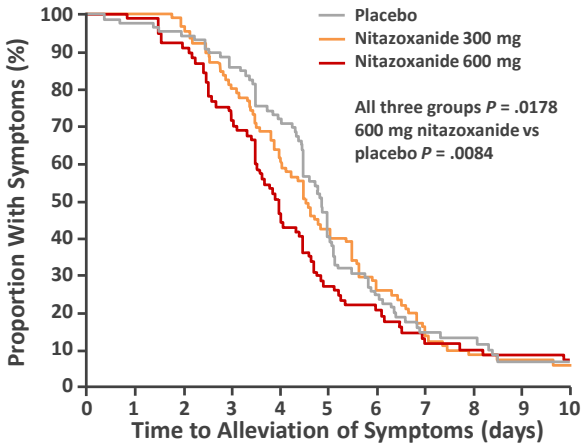
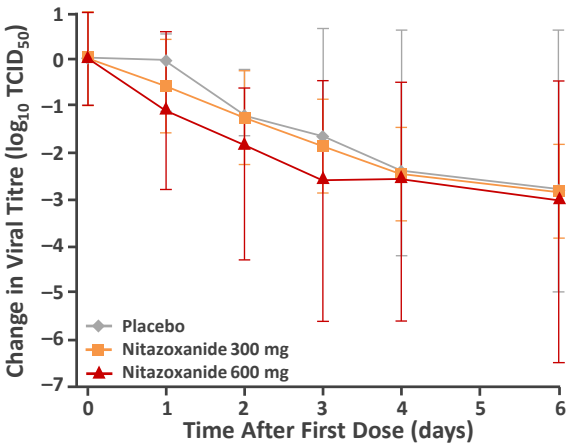
Antiviral Therapies for Influenza in Phase 3 Development: Nitazoxanide





Treatment with 600 mg BID of the thiazolide anti-infective nitazoxanide reduced median duration of symptoms vs PBO (116.7 hours vs 95.5 h; P = .0084)

Haffizulla J, et al. *Lancet Infect Dis*. 2014;14(7):609-618.

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Antiviral Therapies for Influenza in Phase 3 Development: Favipiravir

Efficacy as monotherapy

Phase 2

- Trial 1: No significant benefit
- Trial 2:
  - Faster ↓ in virus titers vs PBO
  - ↓ time to symptom resolution of 6 symptoms (not fever)

Phase 3

- ↓ time to undetectable virus
- ↓ time to symptom resolution by ~17%

Efficacy in combination with OTV

Phase 2a

- Patients critically ill with influenza
- No improvement in time to clinical improvement vs OTV monotherapy
- Secondary endpoints
  - ↓ rate of severe outcomes
  - ↑ rate of viral RNA clearance
  - No development of resistance

McKimm-Breschkin JL, et al. *Antiviral research*. 2018;149:118-142; Furuta Y, et al. *Antimicrob Agents Chemother*. 2002;46(4):977-98; Wang Y, et al. *EBioMedicine*. 2020;62:103125.

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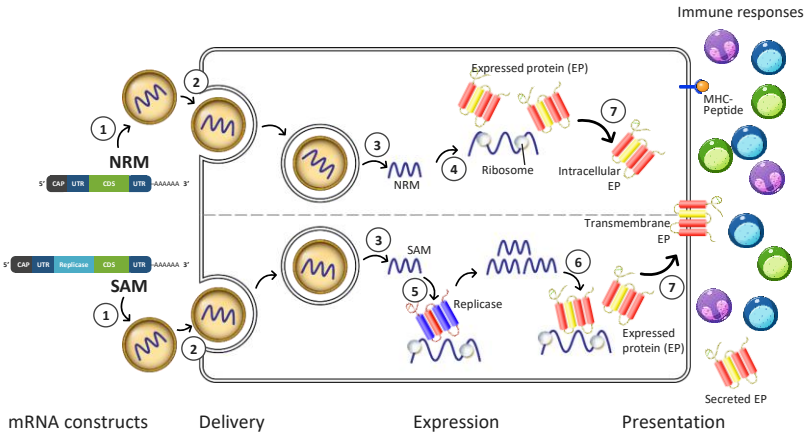
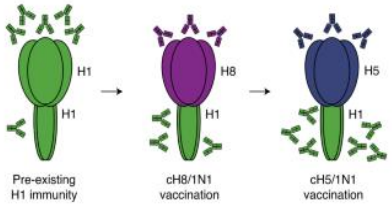
mRNA Vaccines Against Influenza

- Two **Phase 1** RCTs of H10N8 and H7N9 mRNA vaccines conducted in healthy adults
- **Primary endpoints**: Safety and tolerability
- **Secondary immunogenicity outcomes**: Humoral and cell-mediated responses
- **<u>Findings</u>**: Vaccines showed favorable safety and reactogenicity profiles



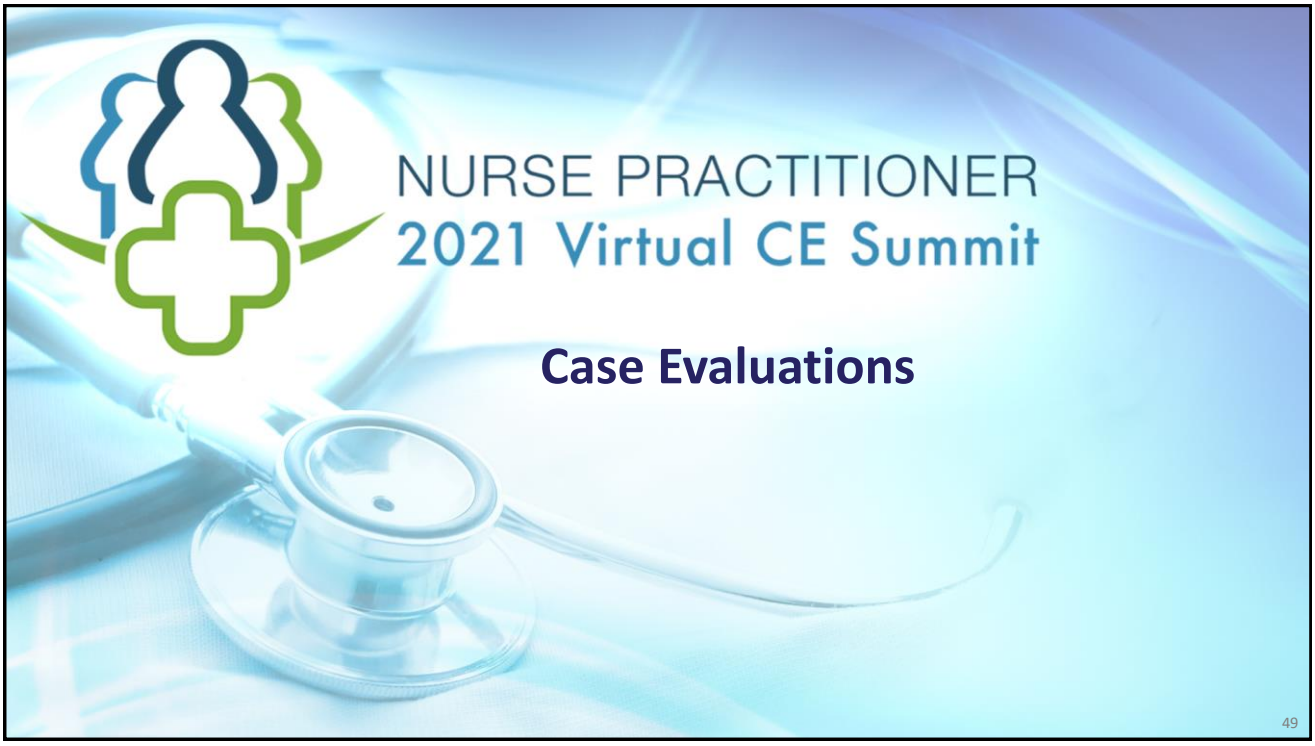
mRNA, messenger RNA; NRM, nonreplicating mRNA; SAM, self-amplifying mRNA.
Feldman RA, et al. *Vaccine*. 2019;37:3326-3334; Jackson NAC, et al. *Vaccines*. 2020;5:11.

Universal Influenza Vaccine: Targeting Broad and Long-lasting Immunity



- Influenza vaccines target the highly plastic head domain of the virus
- Targeting the more conserved HA stalk domain may induce broad, durable immunity
- **Phase 1 RCT** of chimeric HA-based vaccine conducted in healthy adults
- **Study goals**: Assess safety and immunogenicity against the stalk domain
- **<u>Findings</u>**: Favorable safety and induction of a broad, strong, durable and functional immune response against the stalk domain

Nachbagauer R, et al. *Nature Medicine*. 2021;27:106-114.



Case #1: Patient Description

Ilana is 27-year-old graduate student who also works part-time in an LTC facility for individuals with Alzheimer's disease. She presents with cough, nasal congestion, headache, fatigue, but no fever over the past 48 hours. She reports that she is in generally good health and that she was vaccinated against the flu prior to the start of the season. Her EMR indicates a history of mild atopic dermatitis and seasonal allergic rhinitis.

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Case #1: Discussion Question

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

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

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Case #1: Discussion Question

Based on the information presented, which of the following actions are most consistent with your approach to Ilana'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. Assess patient preferences and consider treatment with an antiviral
D. Do not treat with an antiviral

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Case #2: 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.

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Case #2: Discussion Question

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

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

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Case #2: 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

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Case #2: Discussion Question

Which antiviral agent would you prescribe for David?

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

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Case #2: 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

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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

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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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