HOSPITAL & INTERNAL MEDICINE FORUM

What's Your InFLUence?

The Evolving Role of Antiviral Therapy and Your Role in Management and Prevention of Seasonal Influenza

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Disclosures

- Speaker: Genentech

Learning Objectives

- Explain the importance of vaccination in preventing the spread of influenza and minimizing morbidity and mortality outcomes
- Integrate guideline recommendations for the diagnosis of influenza into clinical practice
- Apply knowledge of antiviral therapy and guideline recommendations to administer chemoprophylaxis to individuals at risk of influenza and associated complications
- Appraise current and emerging antiviral agents for use in patients with influenza

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The Importance of Influenza Prevention

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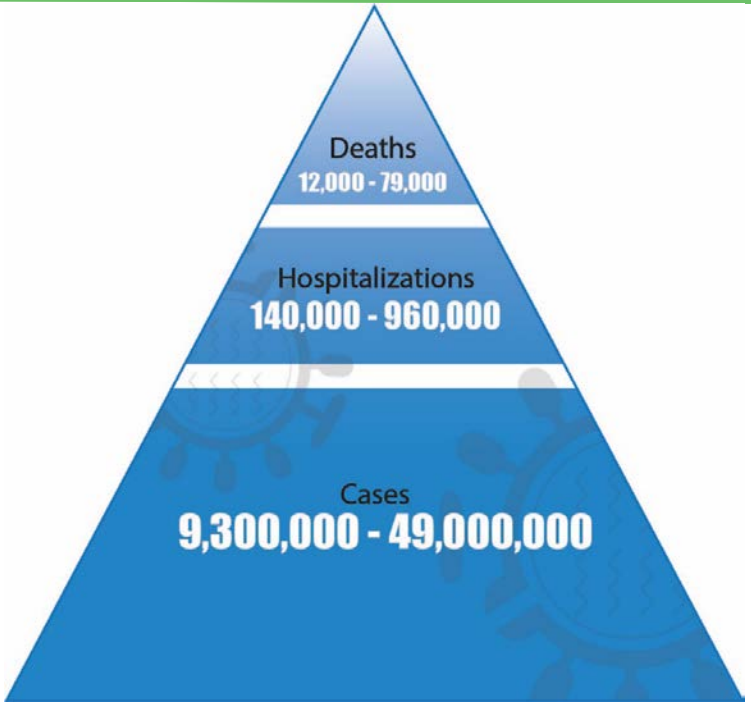
Influenza – A Recurring and Significant Threat
United States, 2010-11 Through 2017-18 Influenza Seasons

Burden of influenza disease in the United States can vary widely and is determined by a number of factors, including characteristics of circulating viruses, timing of the season, how well the vaccine is working to protect against illness, and how many people got vaccinated.

While the impact of flu varies, it places a substantial burden on the health of people in the United States each year.



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Estimated Influenza Disease Burden, by Season
United States, 2010-11 Through 2018-19 Influenza Seasons

	Symptomatic Illnesses		Medical Visits		Hospitalizations		Deaths	
Season	**Estimate**	**95% Cr I**	**Estimate**	**95% Cr I**	**Estimate**	**95% Cr I**	**Estimate**	**95% Cr I**
2010-2011	21,000,000	(20,000,000 – 25,000,000)	10,000,000	(9,300,000 – 12,000,000)	290,000	(270,000 – 350,000)	37,000	(32,000 – 51,000)
2011-2012	9,300,000	(8,700,000 – 12,000,000)	4,300,000	(4,000,000 – 5,600,000)	140,000	(130,000 – 190,000)	12,000	(11,000 – 23,000)
2012-2013	34,000,000	(32,000,000 – 38,000,000)	16,000,000	(15,000,000 – 18,000,000)	570,000	(530,000 – 680,000)	43,000	(37,000 – 57,000)
2013-2014	30,000,000	(28,000,000 – 33,000,000)	13,000,000	(12,000,000 – 15,000,000)	350,000	(320,000 – 390,000)	38,000	(33,000 – 50,000)
2014-2015	30,000,000	(29,000,000 – 33,000,000)	14,000,000	(13,000,000 – 16,000,000)	590,000	(540,000 – 680,000)	51,000	(44,000 – 64,000)
2015-2016 *	25,000,000	(24,000,000 – 28,000,000)	12,000,000	(11,000,000 – 13,000,000)	310,000	(290,000 – 340,000)	25,000	(21,000 – 31,000)
2016-2017 *	30,000,000	(28,000,000 – 32,000,000)	14,000,000	(13,000,000 – 16,000,000)	580,000	(520,000 – 660,000)	51,000	(44,000 – 64,000)
2017-2018 *	49,000,000	(46,000,000 – 53,000,000)	23,000,000	(21,000,000 – 25,000,000)	960,000	(870,000 – 1,100,000)	79,000	(69,000 – 99,000)
2018-2019*	*Preliminary Burden Estimates*	37,400,000 – 42,900,000)		(17,300,000 – 20,100,000)		(531,000 – 647,000)		(36,400 – 61,200)

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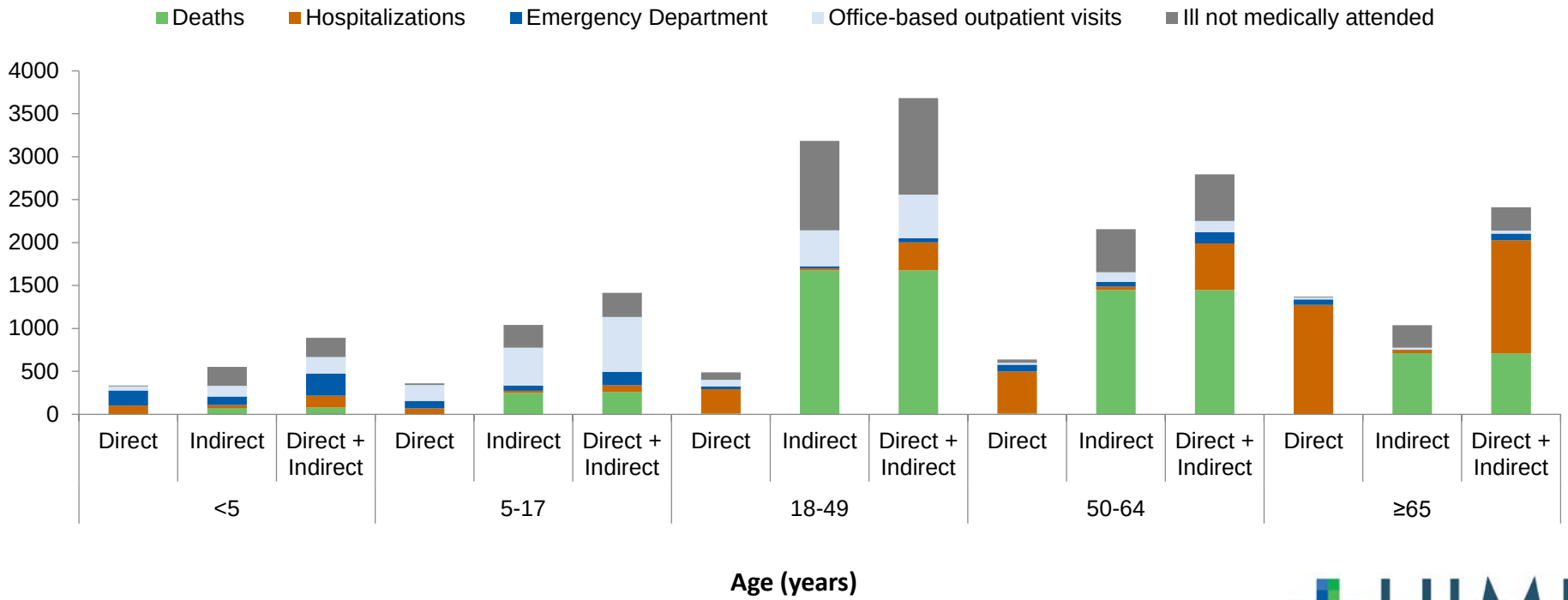
The Economic Burden of Influenza



Putri, et al. *Vaccine*. 2018 Jun 22;36(27):3960-3966.

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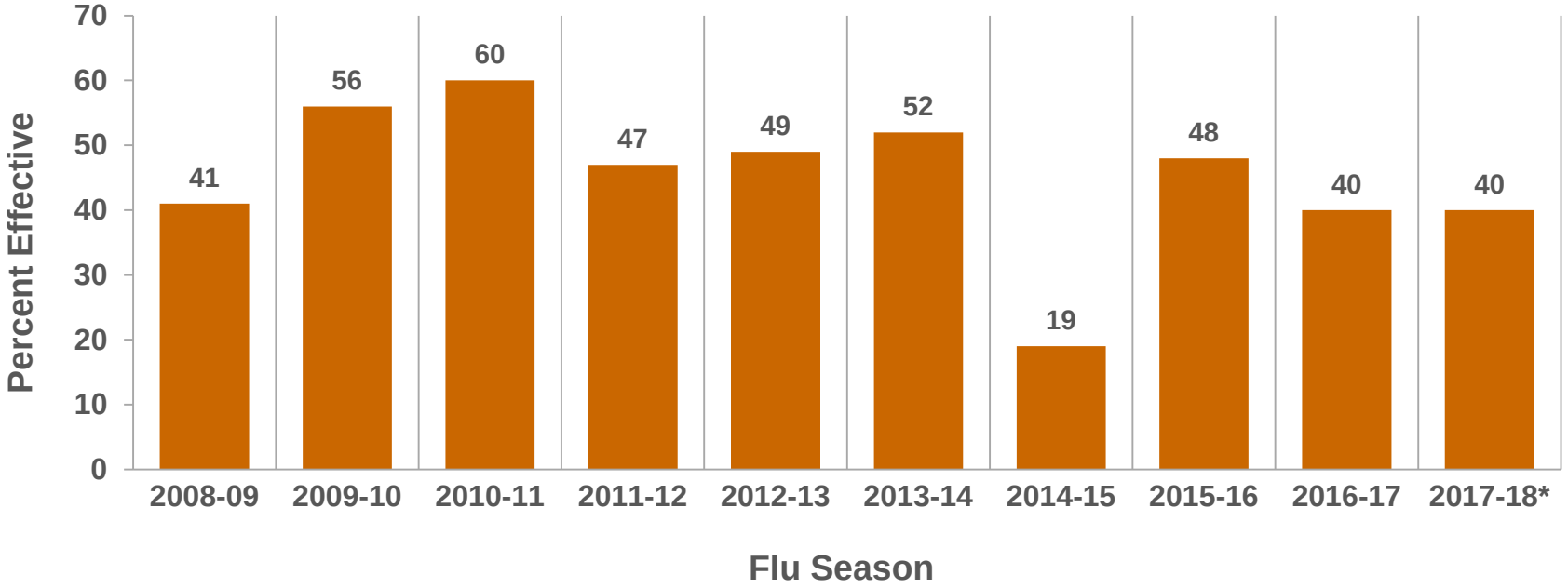
Effectiveness of Seasonal Flu Vaccines From the 2008-2018 Flu Seasons



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Impact of Influenza Vaccination on Disease Severity

Characteristics	ICU/death (n = 692)		Non-ICU/death (n = 1,035)		Adjusted OR	95% CI	p value
	n	%	n	%			
Seasonal vaccine							
Yes	146	21.3	304	29.7	0.78	(0.61 to 0.99)	0.048
No	540	78.7	721	70.3	Ref		
Age							
18-64 years	386	55.8	422	40.8	Ref		
≥ 65 years	306	44.2	613	59.2	0.56	(0.45 to 0.68)	< 0.001
Comorbidities							
Yes	520	75.1	765	73.9	1.36	(1.07 to 1.73)	0.011
No	172	24.9	270	26.1	Ref		

Catalonia, Spain, influenza seasons 2010/11–2015/16 (n = 1,727)

CI: confidence interval; ICU: intensive care unit; OR: odds ratio; Ref: reference.

Godoy P et al. *Euro Surveill.* 2018;23(43).

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Benefits of Influenza Vaccination

Effects of Influenza Vaccination During the 2017–2018 Influenza Season

The estimated number of flu **illnesses prevented by vaccination** during the 2017-2018 season**:**

7 MILLION

About the population of New York City

The estimated number of flu **hospitalizations prevented by vaccination** during the 2017-2018 season**:**

109,000

About the number of vehicles crossing the Golden Gate Bridge each day

The estimated number of flu **deaths prevented by vaccination** during the 2017-2018 season**:**

8,000

Twice the number of hospitals in the United States

Available at: https://www.cdc.gov/flu/vaccines-work/averted-estimates.htm?CDC_AA_refVal=https%3A%2F%2F www.cdc.gov%2Fflu%2Fabout%2Fburden-averted%2Faverted-estimates.htm

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Diagnosis of Influenza

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Signs and Symptoms of Influenza

General	Head, Eyes, Ears, Nose, Throat	Neuromuscular	Gastrointestinal[b]	Pulmonary
• Fever[c,d] • Chills • Malaise • Fatigue	• Headache • Nasal congestion[d] • Rhinorrhea[d] • Sore throat/ hoarseness	• Myalgia, arthralgia • Weakness • Chest pain	• Abdominal pain • Vomiting • Diarrhea[d]	• Nonproductive cough • Pleuritic chest pain

[a]Abrupt onset of respiratory and systematic signs and symptoms, with or without fever.
[b]Gastrointestinal symptoms vary with age: diarrhea is more common among infants, young children, and school-aged children; abdominal pain may be present among school-aged children; vomiting may be present among adults.
[c]Fever can be age-specific: high fever or fever alone may be the only sign in infants and young children; fever may be absent or low grade in infants and the elderly.
[d]Fever, nasal congestion, rhinorrhea, and diarrhea may be present among infants and young children.

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

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Differential Diagnosis

Condition	Clinical Presentation	Fever?	Diagnostic Tests	Onset	Duration
Influenza	Myalgia, arthralgia, anorexia, headache, dry cough, malaise, fatigue, weakness, and chest discomfort.	Yes	Rapid antigen detection testing, reverse transcriptase-polymerase chain reaction, and viral culture.	Sudden; usually over 3-6 hours	Approximately 5-7 days
Upper Respiratory Infection	Nasal congestion, rhinorrhea, cough, sneezing, and pharyngitis.	Rare	None	Gradual; usually over a few days	Approximately 2-3 weeks
Infectious Mononucleosis	Pharyngitis and posterior cervical lymphadenopathy.	Yes	Heterophile antibody testing and Epstein-Barr virus–specific serologies.	Gradual; usually over 1-2 weeks	Approximately 2-3 weeks

Available at: https://contemporaryclinic.pharmacytimes.com/journals/issue/2015/2015-vol1-n3/influenza-differential-diagnosis-and-treatment/p-2

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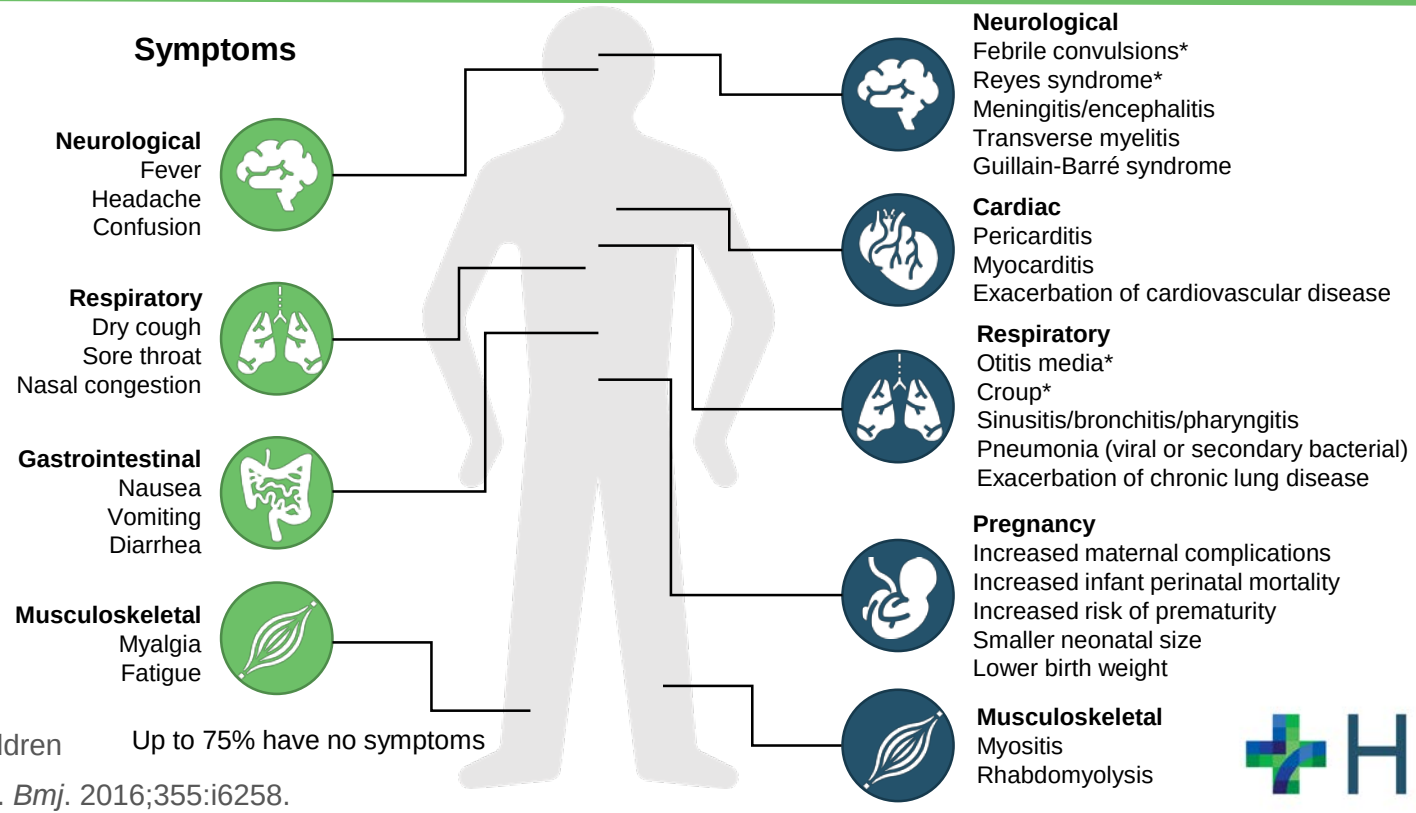
Complications of Influenza



*More common in children

Ghebrehewet S, et al. *Bmj*. 2016;355:i6258.

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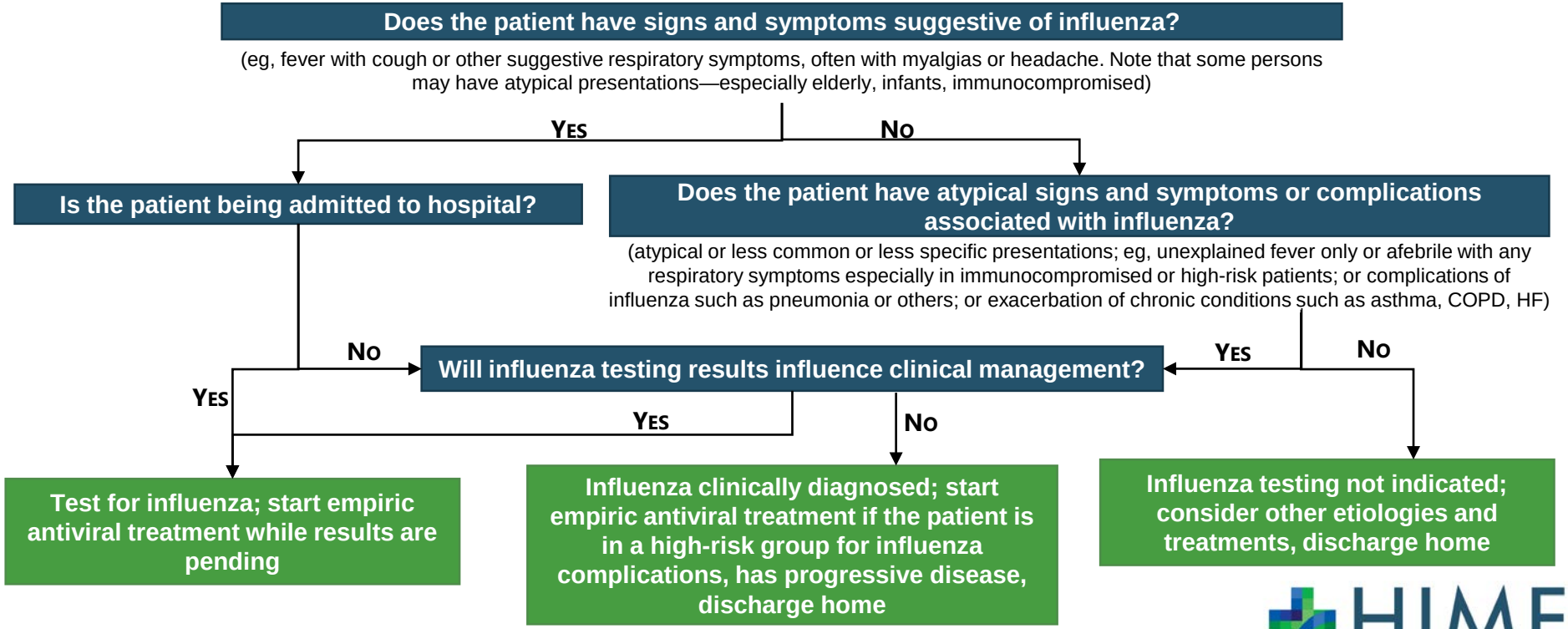
IDSA Guidelines for the Diagnosis of Influenza



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

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Diagnostic Tests for Influenza

Testing category	Method	Influenza viruses detected	Distinguishes influenza A subtypes	Time to results	Performance
Rapid molecular assay	Nucleic acid amplification	Influenza A or B viral RNA	No	15–30 minutes	High sensitivity; high specificity
Rapid influenza diagnostic test	Antigen detection	Influenza A or B virus antigens	No	10–15 minutes	Low to moderate sensitivity (higher with analyzer device); high specificity
Direct and indirect immunofluorescence assays	Antigen detection	Influenza A or B virus antigens	No	1–4 hours	Moderate sensitivity; high specificity
Molecular assays (including RT-PCR)	Nucleic acid amplification	Influenza A or B viral RNA	Yes, if subtype primers are used	1–8 hours	High sensitivity; high specificity
Multiplex molecular assays	Nucleic acid amplification	Influenza A or B viral RNA, other viral or bacterial targets (RNA or DNA)	Yes, if subtype primers are used	1–2 hours	High sensitivity; high specificity
Rapid cell culture (shell vial and cell mixtures)	Virus isolation	Influenza A or B virus	Yes	1–3 days	High sensitivity; high specificity
Viral culture (tissue cell culture)	Virus isolation	Influenza A or B virus	Yes	3–10 days	High sensitivity; high specificity

RT-PCR, reverse-transcriptase polymerase chain reaction.

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

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Current and Emerging Therapies for Influenza

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Who Should be Treated?

- **Aim**:
  shorten duration of illness, reduce complications, hospitalizations, and adverse outcomes

- Treatment is recommended in confirmed/suspected influenza if:
  - Patient is hospitalized
  - Outpatient with severe, complicated, or progressive illness
  - Outpatient at high risk for influenza complications
  - Older adults (>65 years) young children (<5 years)

AND

- Clinicians can consider antiviral treatment for confirmed/suspected patients not at high risk of influenza complications if:
  - Illness onset of 2 days or less prior to presentation
  - Symptomatic outpatient with high-risk home contact
  - Symptomatic healthcare provider

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

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Patients at High Risk for Influenza-Related Complications

- Adults ≥65 YOA
- All children ≤5 YOA
  - Highest risk is for those <2 YOA
  - Highest hospitalization and death rates among infants <6 months old
- Pregnant women and women up to 2 weeks after the end of pregnancy
- American Indians and Alaska Natives
- People living in nursing homes and other LTC facilities

YOA, years of age; LTC, long-term care.

Available at: https://www.cdc.gov/flu/highrisk/index.htm

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Additional Risk Factors for Complications

- Asthma
- Neurologic and neurodevelopment conditions
- Blood disorders (eg, sickle cell disease)
- Chronic lung disease (eg, COPD, CF)
- Endocrine disorders (eg, DM)
- Heart disease (eg, CHD, CHF, CAD)
- Kidney disorders
- Liver disorders
- Metabolic disorders
- Obesity (ie, BMI≥40)
- <19 YOA on long-term aspirin- or salicylate-containing medications
- Weakened immune system due to disease or medications

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

Available at: https://www.cdc.gov/flu/highrisk/index.htm

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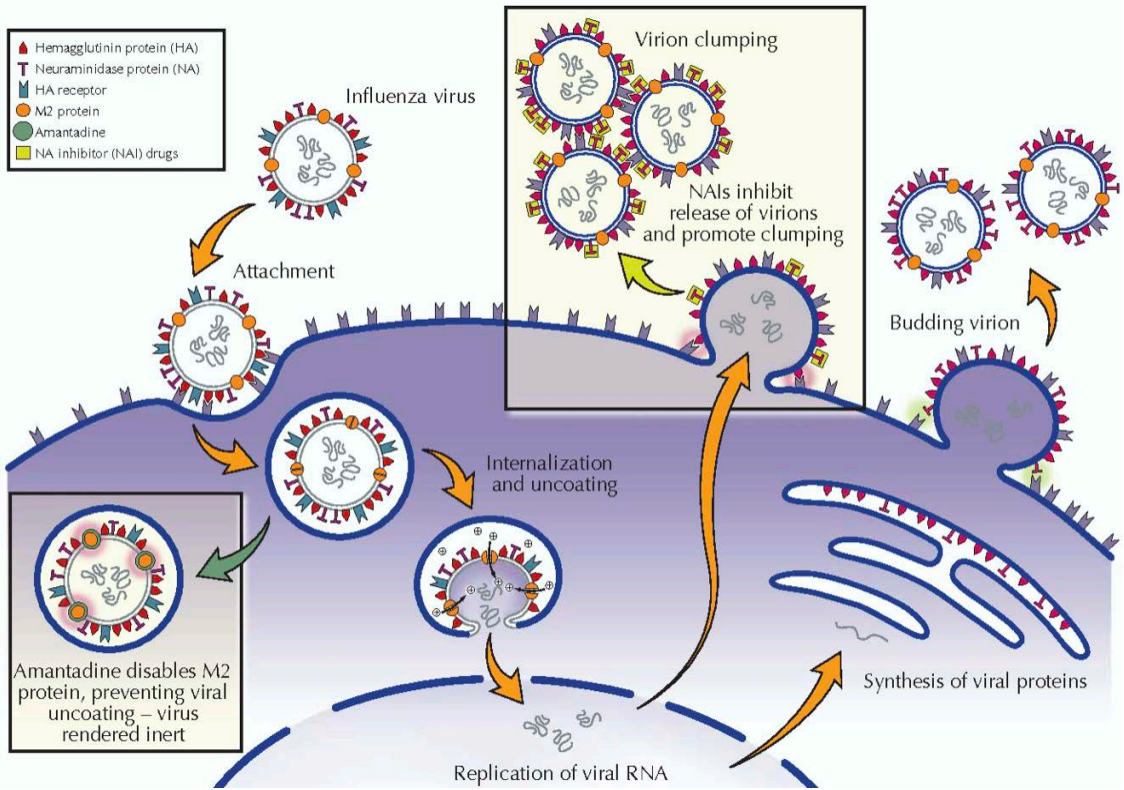
Available Antivirals for Influenza



- Adamantanes
- Neuraminidase inhibitors (NAIs)
  - Oseltamivir (>2 weeks of age)
    - 75 mg PO twice daily × 5 days
  - Zanamivir (≥7 years of age)
    - 10 mg inhalation every 12 hrs × 5 days
  - Peramivir (>12 years of age)
    - 600 mg IV × 1
- Cap-dependent nuclease inhibitor (CEN)
  - Baloxavir (≥ 12 years of age)
    - 40 to <80 kg 40 mg PO × 1
    - >80 kg 80 mg PO × 1

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Available Antiviral Therapies: Indications and Administration

AGENT	ROUTE AND DOSING FREQUENCY	INDICATED AGE	
		Acute uncomplicated influenza with symptoms present ≤48 hours	Prophylaxis
Oseltamivir (NAI)	• PO • BID x 5 days • QD x 7 days (prophylaxis)	• ≥2 weeks old	• ≥1 years old
Peramivir (NAI)	• IV • Single infusion over 15-30 minutes	• ≥18 years old	
Zanamivir* (NAI)	• INH • 2 inhalations BID x 5 days • 2 inhalations QD x 7 days (prophylaxis)	• ≥7 years old	• ≥5 years old
Baloxavir marboxil (CEN inhibitor)	• PO • Single dose	• ≥12 years old	

*Should not be used in patients with underlying respiratory disease and is contraindicated in patients with a history of milk protein allergy.

CEN, cap-dependent endonuclease; IV, intravenous; INH, inhaled; BID, once every 2 days; QD, once a day.

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Overview of Antiviral Efficacy and Safety

	Reduction in Time to Improvement vs PBO	Adverse Effects
Peramivir	21 hours	• Nausea and vomiting; taking with food may minimize GI AEs • Headaches • Serious skin reaction, sporadic, transient neuropsychiatric events
Zanamivir	1 day – 1.5 days	• Diarrhea • Neutropenia • Serious skin reaction, sporadic, transient neuropsychiatric events
Oseltamivir	1.3 days	• Diarrhea, nausea, sinusitis, fever, and arthralgia • Potential for bronchospasm • Serious skin reaction, sporadic, transient neuropsychiatric events
Baloxavir marboxil	26 – 28 hours	• Well tolerated; none more common vs placebo

GI AES, gastrointestinal adverse effects.

Rapivab [prescribing information]. Durham, NC: BioCryst Pharmaceuticals; 2014; Relenza [prescribing information]. Research Triangle Park, NC GlaxoSmithKline; 2018; Tamiflu [prescribing information]. San Francisco, CA: Genentech; 2016; Xofluza [prescribing information]. San Francisco, CA: Genentech; 2018.

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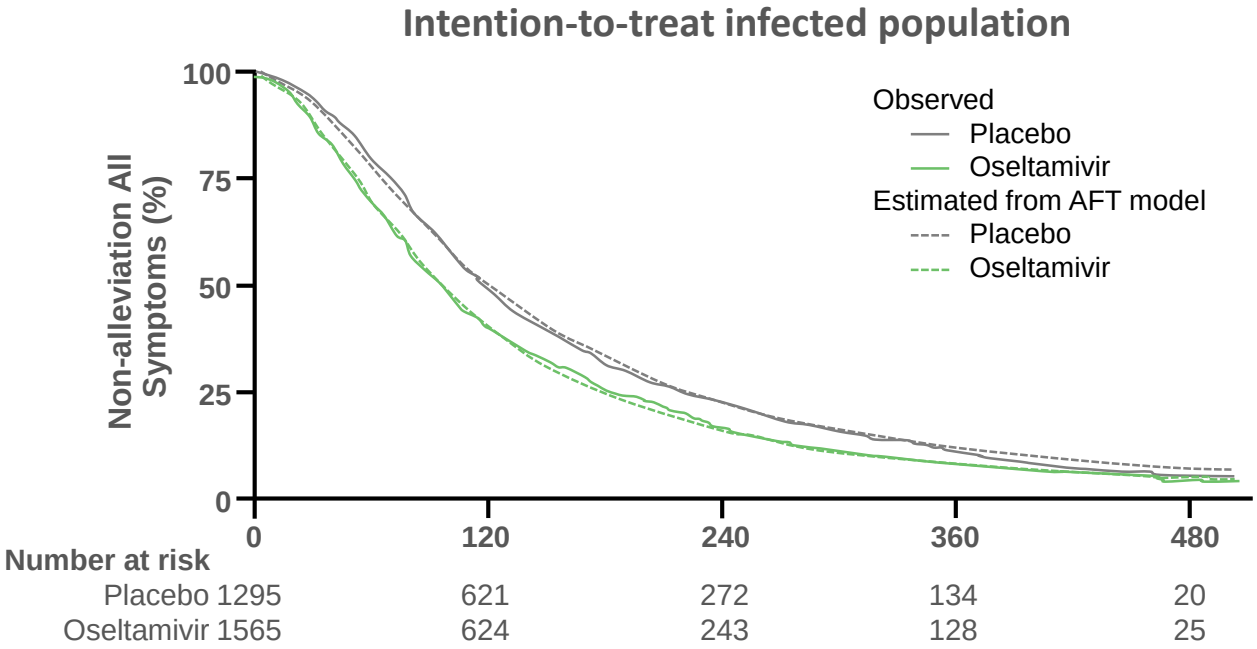
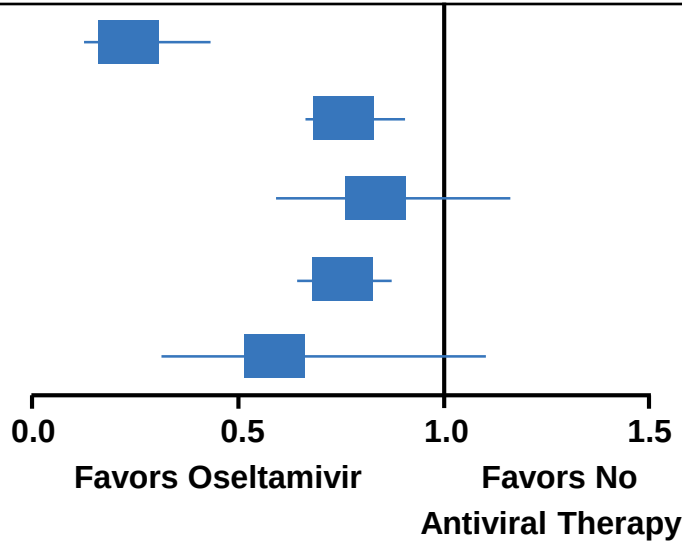
Available Agents: Neuraminidase Inhibitors

- Reduction in time to improvement by ~1 day
- Median time to alleviation
  - O: 97.5 hours
  - Placebo: 122.7



Available Agents: Neuraminidase Inhibitors

Outcome	Patients (Studies), n	Pooled Odds Ratio (95% CI)
Mortality	681 (3)	0.23 (0.13-0.43)
Hospitalization	150 710 (4)	0.75 (0.66-0.89)
Pneumonia	150 466 (3)	0.83 (0.59-1.16)
Otitis media	78 407 (2)	0.75 (0.64-0.87)
Cardiovascular events	100 830 (2)	0.58 (0.31-1.10)



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NAI Treatment at Admission Reduces Length of Hospital Stay

Variable	Unadjusted, IRR (95% CI)	Adjusted, IRR (95% CI)
Primary analysis: NAI treatment on day of hospital admission vs later/no NAI treatment		
Overall	0.83 (.79–.87)	0.81 (.78–.85)
Laboratory-confirmed A(H1N1)pdm09 infection	0.83 (.79–.86)	0.81 (.77–.85)
Children (age <16 y)	0.90 (.83–.97)	0.85 (.78–.92)
Elderly (age ≥65 y)	0.78 (.67–.91)	0.78 (.67–.91)
Patients requiring standard ward-based care only	0.81 (.77–.85)	0.81 (.78–.86)
ICU-admitted patients only	0.80 (.73–.88)	0.79 (.72–.87)
Confirmed absence of influenza-related pneumonia	0.71 (.66–.77)	0.73 (.68–.79)
Confirmed presence of influenza-related pneumonia	0.91 (.84–.98)	0.85 (.79–.93)

Venkatesan S, et al. *J Infect Dis*. 2019.

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Meta-analysis of RCTs of Zanamivir: Time to Alleviation of Symptoms

- Inhaled zanamivir associated with a significant improvement in time to alleviation of symptoms by:
  - 1 to 2 days in otherwise healthy adults
- Meta-analysis of unpublished manufacturer studies of ILI
  - 14.4 hours in adults with Influenza-like Illness
  - No significant difference in children
  - No reduction in complications of influenza
  - Insufficient data to evaluate the effect on hospitalization

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Peramivir IV, Approved in 2014: Uncomplicated Influenza, Single-dose

RCT: Peramivir (single dosing) versus oseltamivir (SOC): Similar time-to-clinical resolution (TTCR) and virus titer reduction

Population and Treatment (n)	Median Time to Alleviation (h) (95% CI)	Hazard Ratio (97.5% CI)[a]
Overall		
Peramivir		
300 mg (364)	78.0 (68.4, 88.6)	0.946 (0.793, 1.129)
600 mg (362)	81.0 (72.7, 91.5)	0.970 (0.814, 1.157)
Oseltamivir (365)	81.8 (73.2, 91.1)	

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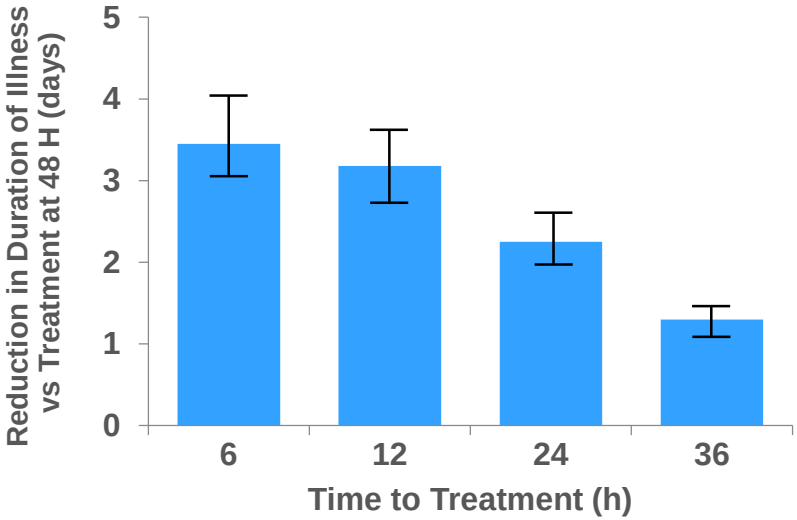
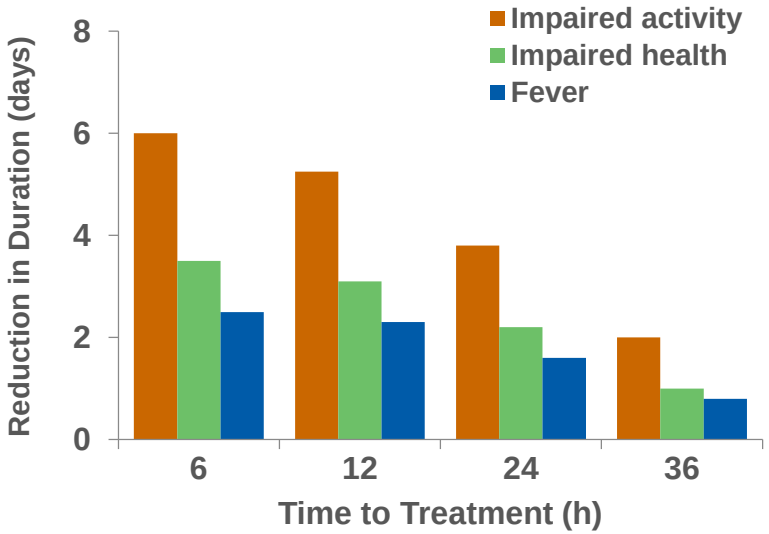
Importance of Timing: Ambulatory



Reduction in days of illness duration with earlier treatment with oseltamivir 75 mg twice per day in comparison with delayed treatment at 48 h



Median reduction in days of impaired activity and health and duration of fever with earlier treatment with oseltamivir 75 mg twice per day in comparison with delayed treatment at 48 h

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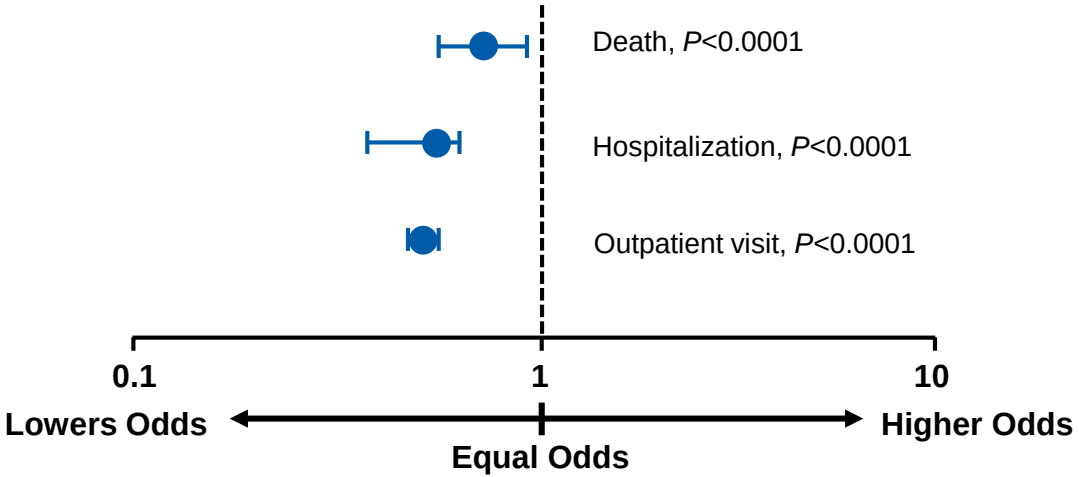
Interventions With Antivirals Up to 1 Week After Symptoms Can Reduce the Risk of Complications and Mortality

Compared With Late Initiation, Early Initiation of Antiviral Treatment Lowers the Risk of Death, Hospitalization, and Outpatient Visits



Early initiation was defined as treatment starting **<1 week** from symptom onset

Late initiation was defined as treatment starting ≥**1 week** from symptom onset

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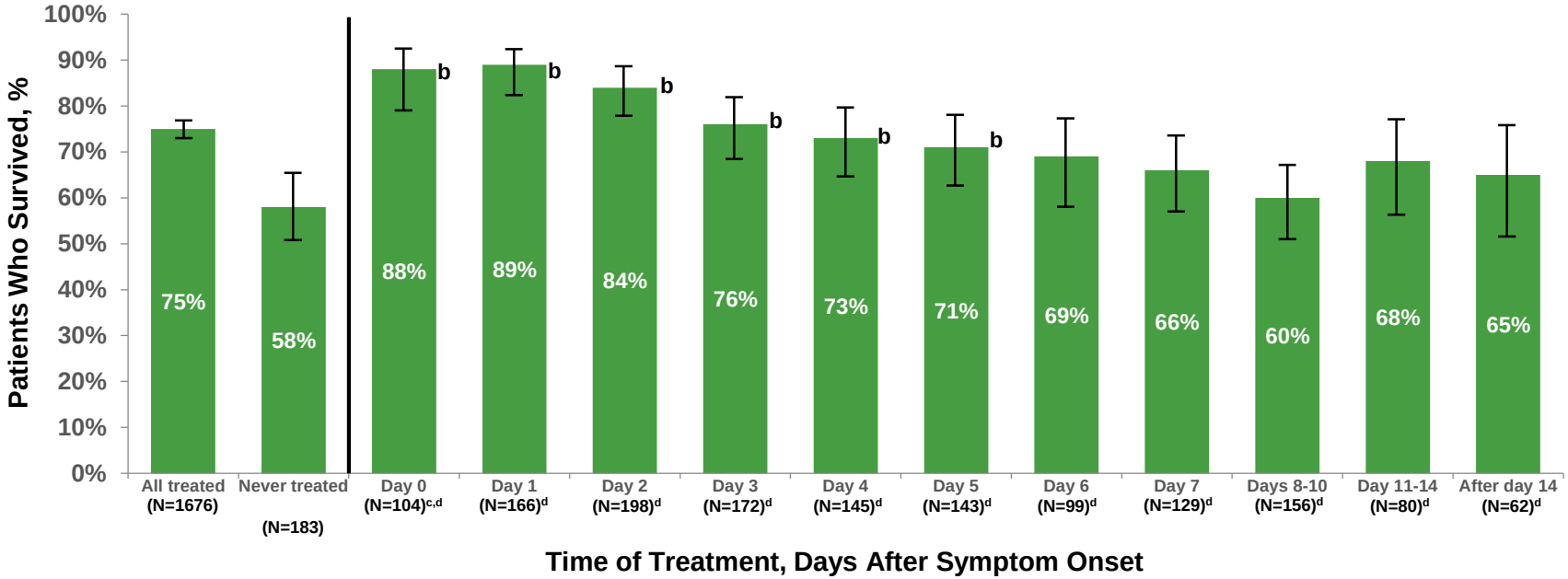
Survival Among ICU Patients With H1N1pdm by Time to NAI Treatment



Impact of Antiviral Treatment Timing on Outcomes of Pregnant Women with H1N1

Treatment		No. (%) of Women							
		Hospital Admission		ICU Admission Among Hospitalized Patients		Mechanical Ventilation Among Hospitalized Patients		Maternal Death	
		Yes (n = 509)	No (n = 263)	Yes (n = 115)	No (n = 350)	Yes (n = 77)	No (n = 332)	Yes (n = 30)	No (n = 662)
Timing after symptom onset, d									
≤2		148 (67.6)	71 (32.4)	13 (9.4)	125 (90.6)	6 (4.6)	125 (95.4)	1 (0.5)	197 (99.5)
3-4		66 (78.6)	18 (21.4)	15 (22.7)	51 (77.3)	10 (17.2)	48 (82.8)	4 (5.0)	76 (95.0)
>4		67 (82.7)	14 (17.3)	37 (56.9)	28 (43.1)	32 (56.1)	25 (43.9)	20 (27.0)	54 (73.0)
No treatment		45 (57.7)	33 (42.3)	15 (34.9)	28 (65.1)	9 (21.4)	33 (78.6)	5 (6.9)	67 (93.1)
Treated, timing unknown		73	52	17	47	10	41	0	115
Unknown treatment status		110	75	18	71	10	60	0	153
Treatment Timing Comparisons									
3-4 vs ≤2 d	Relative risk (95% CI)	1.2 (1.0-1.3)		2.4 (1.2-4.8)		3.8 (1.4-9.9)		9.9 (1.1-87.2)	
	P Value	.06		.01		.008		.03	
>4 vs ≤2 d	Relative risk (95% CI)	1.2 (1.1-1.4)		6.0 (3.5-10.6)		12.3 (5.4-27.7)		53.5 (7.3-391.7)	
	P Value	.01		.001		.001		.001	
None vs ≤2 d	Relative risk (95% CI)	0.8 (0.7-1.0)		3.7 (1.9-7.2)		4.7 (1.8-12.4)		13.8 (1.6-115.7)	
	P Value	.12		.001		.002		.006	

Among pregnant women with 2009 H1N1 influenza, early antiviral treatment was associated with fewer admissions to an ICU and fewer deaths

Siston AM, et al. *Jama*. 2010;303(15):1517-1525.

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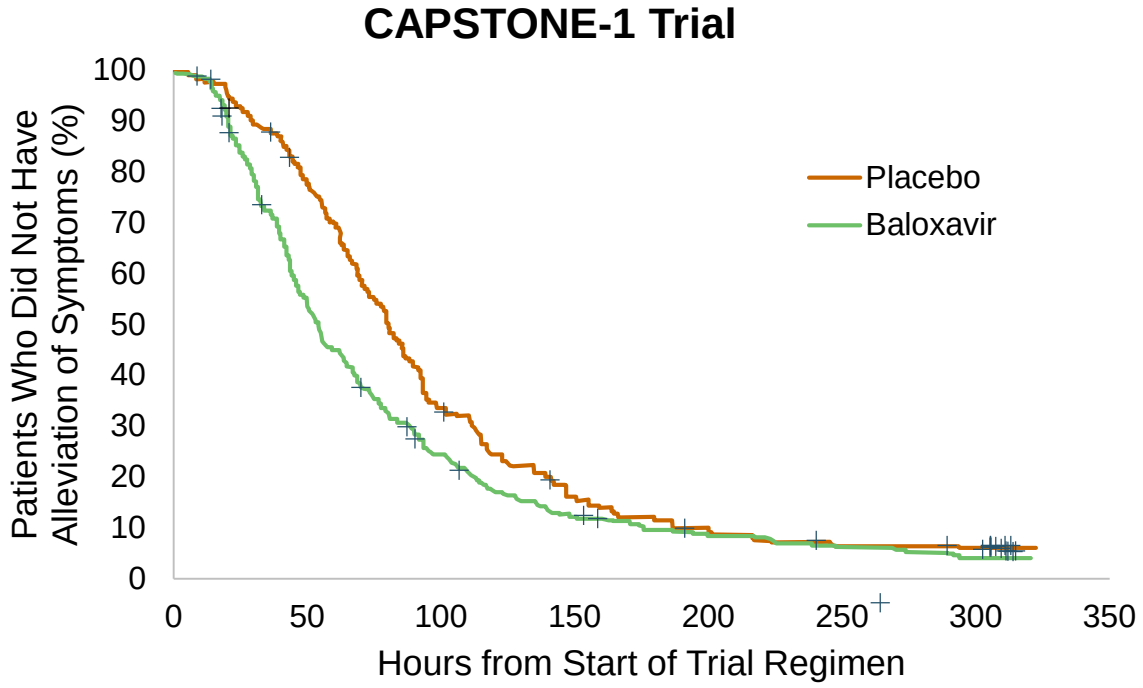
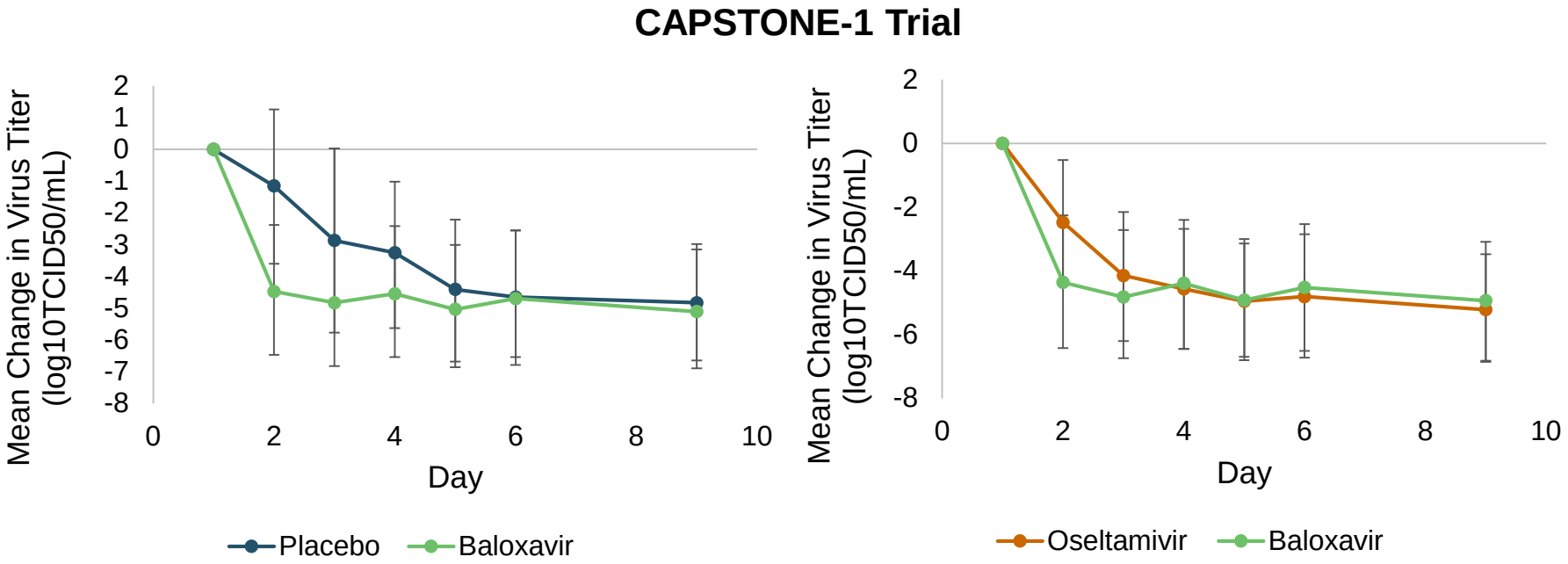
Baloxavir Marboxil Reduces Time to Symptom Alleviation vs PBO



PBO, placebo.

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

Baloxavir Marboxil Is Associated with a Faster Decline in Viral Load vs PBO and Oseltamivir



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

Baloxavir Marboxil for the Treatment of High Risk Influenza Patients: CAPSTONE-2

- BXM treatment was associated with the following:
  - Faster recovery and reduced risk of complications vs placebo in high-risk influenza patients (*Table*)
  - Superiority vs oseltamivir and placebo in resolving influenza B illness (*Table*)
  - Superiority vs oseltamivir in decreasing duration of virus replication (48 hours vs 96 hours) in patients with influenza B
- Safety profile was similar across all groups

	Time to Symptom Resolution (h)		
	ITT	**Influenza B**	**A/H3N2**
Placebo	102.3	100.6	100.4
Oseltamivir	81.0	101.6	68
Baloxavir	73.2	74.6	75.4

Available at: https://idsa.confex.com › idsa › webprogram › Paper74204

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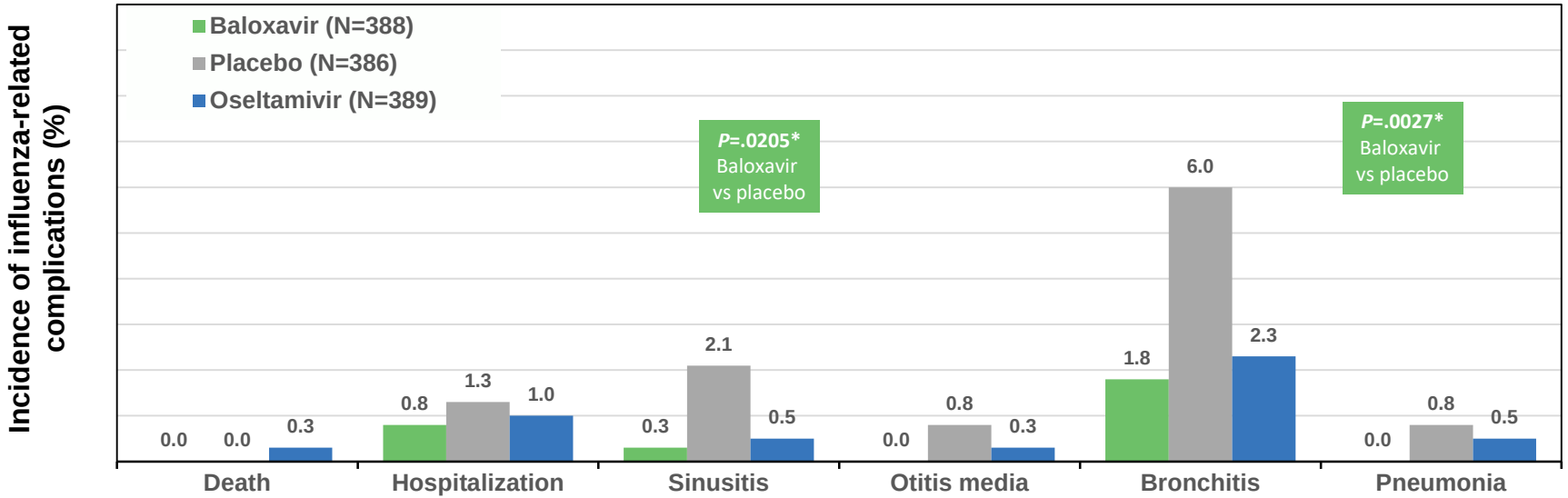
Available Agents: Baloxavir

CAPSTONE 2: Fewer Complications With Treatment Compared to Placebo

	Baloxavir N=388	Placebo N=386	Oseltamivir N=389
Patients with any complications	**2.8%*** (11/388)	**10.4%** (40/368)	**4.6%** (18/389)



The Safety and Efficacy of Baloxavir Marboxil in Children with Influenza: miniSTONE-2

- Patient population: Otherwise healthy children 1 to <12 with a positive influenza test
- Primary outcome results: No serious AEs, deaths, or AEs of special interest observed over 29-day follow-up
- Secondary outcome results:

	Baloxavir marboxil (N=43)	Oseltamivir (N=81)
Time to resolution of signs and symptoms (hours)	138 (116.6,163.2)	150 (115.0,165.7)
Time to cessation of viral shedding (hours)	24.2 (23.5,,24.6)	75.8 (68.9,97.8)

Baker, et al. Options X 2019. Abstract 11756.

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Emerging Antiviral Therapies for Influenza

Agent	Mechanism of Action	Developer	Clinical Trial Status
Nitazoxanide	Inhibits assembly of hemagglutinin	Romark	Phase 3
Favipiravir	Selective inhibition of viral RNA-dependent RNA polymerase	MediVector	Phase 3
Pimodivir	Inhibits PB2 subunit of influenza A polymerase	Janssen	Phase 3

RNA, ribonucleic acid.

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Considerations for Selecting an Antiviral Therapy

Patient characteristics	• History of respiratory illness • Pregnancy
Patient preference	• Route of administration (eg, children often dislike inhaled medications) • Dosing frequency
Practical considerations	• Cost • Other IV therapy currently being administered

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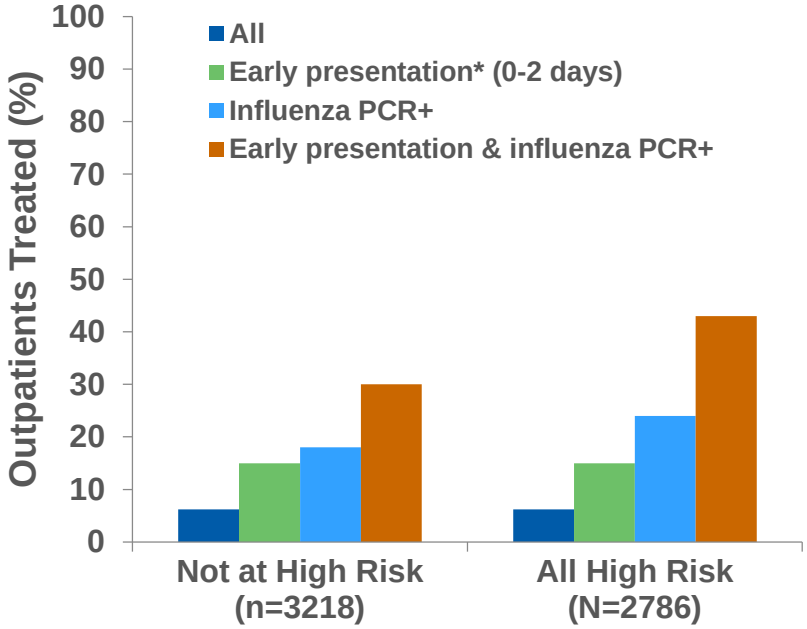
Antiviral Medications Don't Work if We Don't Use Them

- US Flu Vaccine Effectiveness Network (2013-2014)
- Only 30% of patients "Not at high risk" with early presentation and influenza PCR + were treated



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Influenza Prophylaxis

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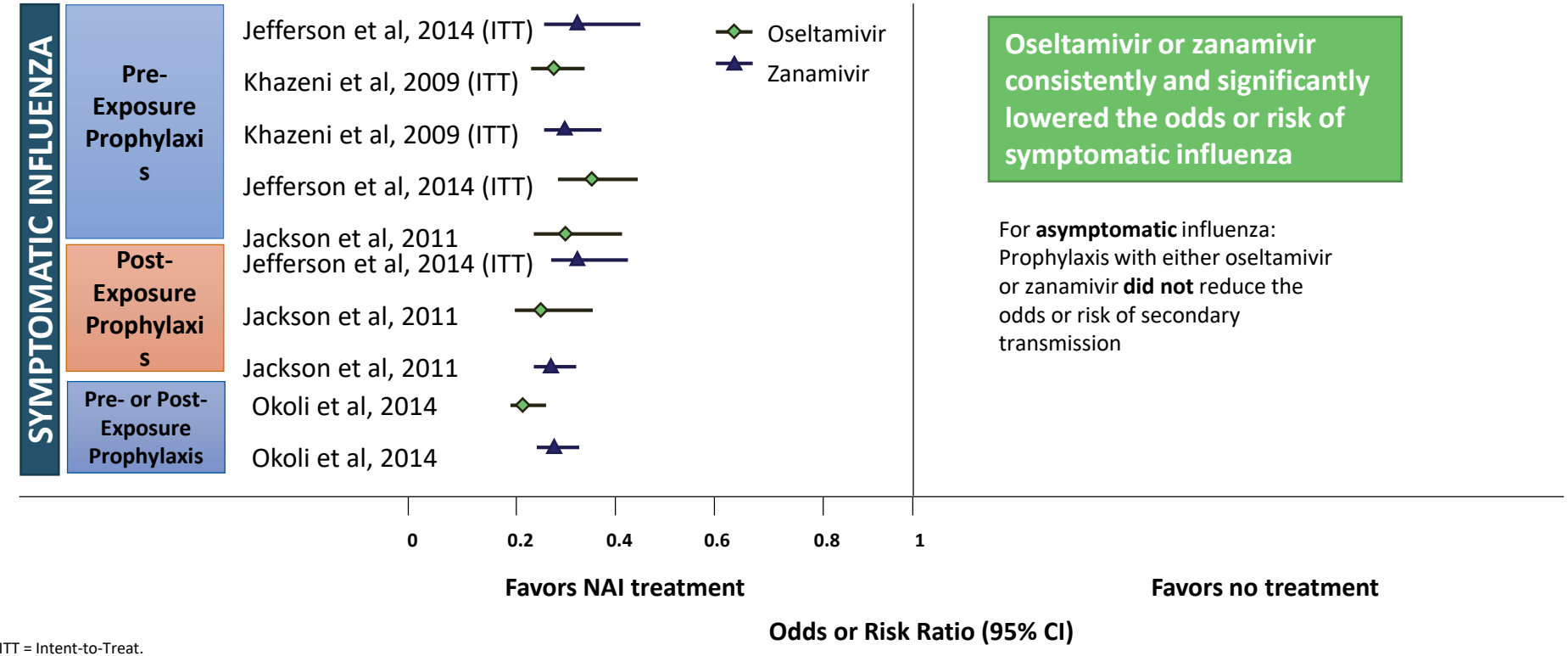
Prophylaxis With Oseltamavir and Zanamivir: Symptomatic Influenza



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

ITT = Intent-to-Treat.

Doll MK, et al. ***J Antimicrob Chemother.*** **2017;72:2990–3007.**

Baloxavir Marboxil Treatment Reduces the Risk of Influenza Infection in Household Contacts

BLOCKSTONE Trial

Patients	PBO	Baloxavir	p-value
All study participants	13.6%	1.9%	<0.0001
Patients with H1N1	10.6%	1.1%	0.0023
Patients with H3	17.5%	2.8%	<0.0001
Contacts at high risk for complications	15.4%	2.2%	0.0435
Children < 12 YOA	15.5%	4.2%	0.0339

- Compared with PBO, treatment with baloxavir marboxil resulted in a significantly smaller rate of positive test for flu, fever, and ≥1 respiratory symptom
- AE incidence was 22.2% for baloxavir vs 20.5% with PBO
- No serious AEs were observed

Ikematsu, et al. Options X for the Control of Influenza 2019. Abstract 11718.

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Factors Contributing to Antiviral Resistance

Virus-driven Factors		Host-contributed Factors	
Issue	**Potential Solution**	**Issue**	**Solution**
Error-prone viral polymerase, quasispecies, antigenic drift	Target host pathways	Chemoprophylaxis, use of sub-therapeutic doses	Confined and checked use of chemoprophylaxis with full dosage
Antigenic shift	Vigilant surveillance	Prolonged shedding due to virulent strain or infection of high-risk group	Hospitalized isolation, treatment and maintenance to prevent nosocomial transmission

Han J, et al. *Curr Med Chem*. 2018;25(38):5115-5127.

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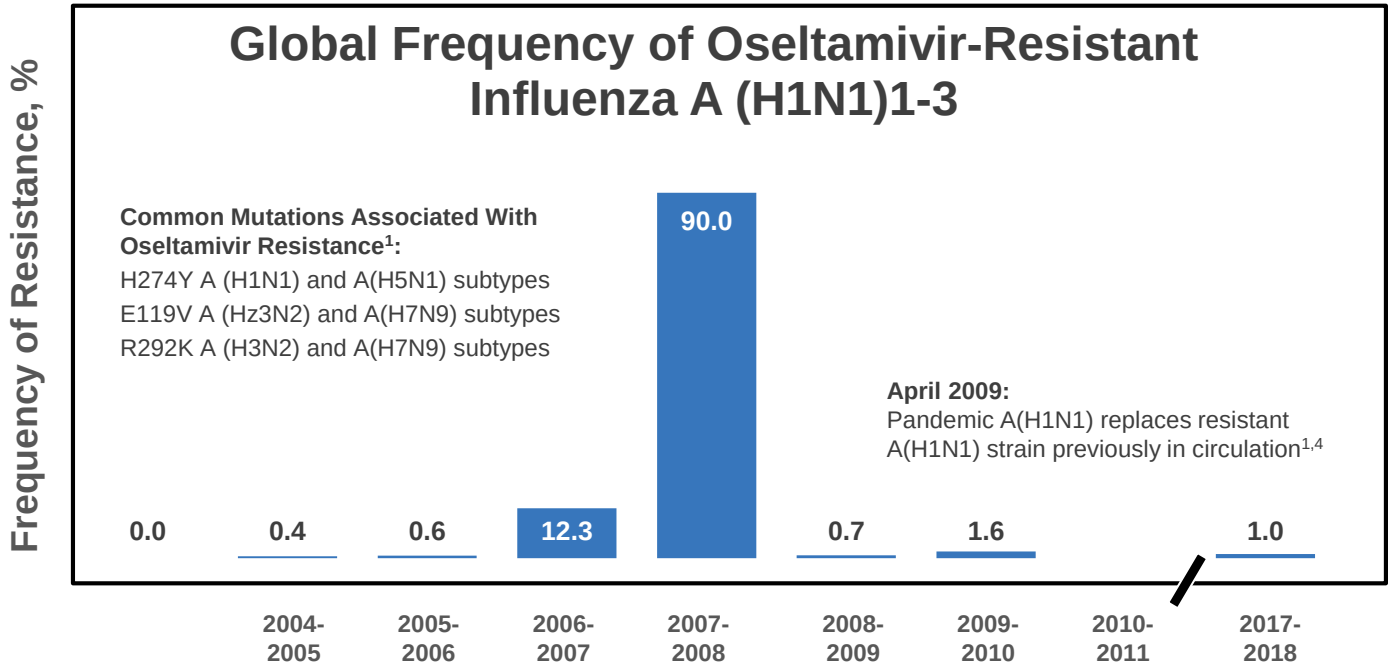
NAI-Resistant Strains May Emerge Again, Increasing Need for New Antiviral Treatments



The Potential Challenge to Baloxavir: Resistance

Proportions of I38X Variant Emergence	Total	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% 36/330	2.7% 1/37
CAPSTONE-2 (T0832)	5.2% 15/290	5.6% 1/18	9.2% 13/141	0.8% 1/131
Pediatric Study in Japan (T0822, tablets)	23.4% 18/77	0% 0/2	25.7% 18/70	0% 0/6
Pediatric Study in Japan (granule, <20 kg)	19.2% 5/26	16.7% 1/6	44.4% 4/9	0% 0/11
MiniSTONE	19.3% 11/57	16.7% 2/12	20.9% 9/43	0% 0/2

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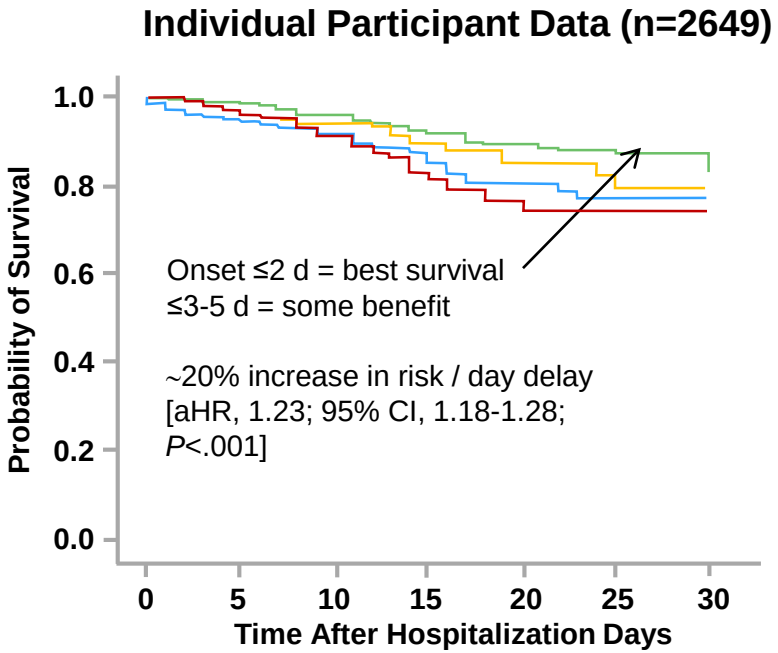
Neuraminidase Inhibitors, Superinfection, and Corticosteroids Affect Survival of Flu Patients

- ↓ **Mortality** (NAI vs nil)
  - 5.3% vs 7.6%
  - aHR, 0.28 (95% CI, 0.19-0.43)
- ↑ **Secondary infection with corticosteroids**
  - 9.7% vs 2.7%
  - Death HR 1.73 95% CI 1.14-2.62



Based on both conventional and time-dependent Cox proportional hazards models, adjusted for patient characteristics and treatment propensity score

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Case Evaluations

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Case Evaluation #1: Patient Description

A 65-year-old woman presents to the ED for symptoms over the past day that include fever, cough, sneezing, nasal congestion, and generalized muscle pain. The patient has a history of mild asthma that is well-controlled but is otherwise healthy. She reports that she received a flu vaccination earlier during the season. Evaluation of her vital signs reveal an SpO2=97%, a temperature=101.5°F, HR=100, RR=22 and BP=140/90. Results of her physical examination are normal.

Case Evaluation #1: Discussion Question 1

What would you do next for this patient?

A. Administer antiviral therapy
B. Test the patient for influenza
C. Both A and B simultaneously
D. Neither A nor B

This is an outpatient who is generally healthy and has been symptomatic for ≤48h. She does not appear to be high risk.

I think that there is some degree of judgement involved for this patient profile. I have to double-check.

Case Evaluation #1: Discussion Question 1

Upon further questioning, you find out that the patient lives with her sister, who is currently undergoing chemotherapy for breast cancer. Given this additional information, what would you do next for this patient?

A. Administer antiviral therapy
B. Test the patient for influenza
C. Both A and B simultaneously
D. Neither A nor B

The patient herself is not high risk. However, she lives with her sister who is at very high risk.

Case Evaluation #1: Discussion Question 2

Which of the following antiviral therapies would you consider prescribing for the patient?

A. Baloxavir
B. Zanamivir
C. Oseltamivir

Baloxavir due to superiority at reducing viral load in uncomplicated influenza

Case Evaluation #2: Patient Description

A 49-year-old man is currently in the hospital following a myocardial infarction. Two days ago, he began to demonstrate a cough and fever, and 4 hours ago he also began vomiting. The patient has a history of T2DM and HT and reports that has not received a flu vaccination this year. His vital signs are as follows: SpO2=97%, temperature=102°F, HR=102, RR=22, and BP=150/80. A physical examination reveals the presence of dry mucous membranes and hot dry skin.

T2DM, type 2 diabetes; HT, hypertension.

Case Evaluation #2: Discussion Question 1

What would you do next for this patient?

A. Administer antiviral therapy
B. Test the patient for influenza
C. Both A and B simultaneously
D. Neither A nor B

Case Evaluation #2: Discussion Question 2

Which of the following antiviral therapies would you consider prescribing for the patient?

A. Baloxavir
B. Peramivir
C. Oseltamivir

Because of his risk, oseltamivir would be a recommended choice. Oral oseltamivir is the CDC-recommended antiviral for patients with severe, complicated, or progressive illness who are not hospitalized, and for hospitalized influenza patients.

Summary

- Seasonal influenza epidemics are associated with significant morbidity and mortality, particularly among high-risk individuals.
- Vaccination is essential for reducing the likelihood of illness and poor outcomes in the event of infection.
- A number of antiviral therapies are currently available for influenza treatment and prophylaxis.
- All of these therapies have demonstrated good safety and efficacy in shortening illness duration, as well as reducing complications and the need for hospitalization.

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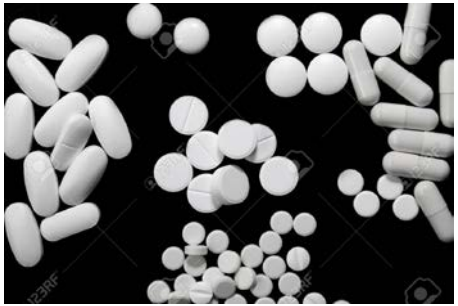
Clinical Pearls



- All patients should be vaccinated against influenza.
- Antiviral therapy should be initiated as soon as possible for patients with influenza.
- Clinicians should not wait for diagnostic test results to begin antiviral treatment for hospitalized patients suspected of having influenza.
- Antiviral selection should be based upon patient characteristics, circumstances, and preferences.

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Thank You!

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