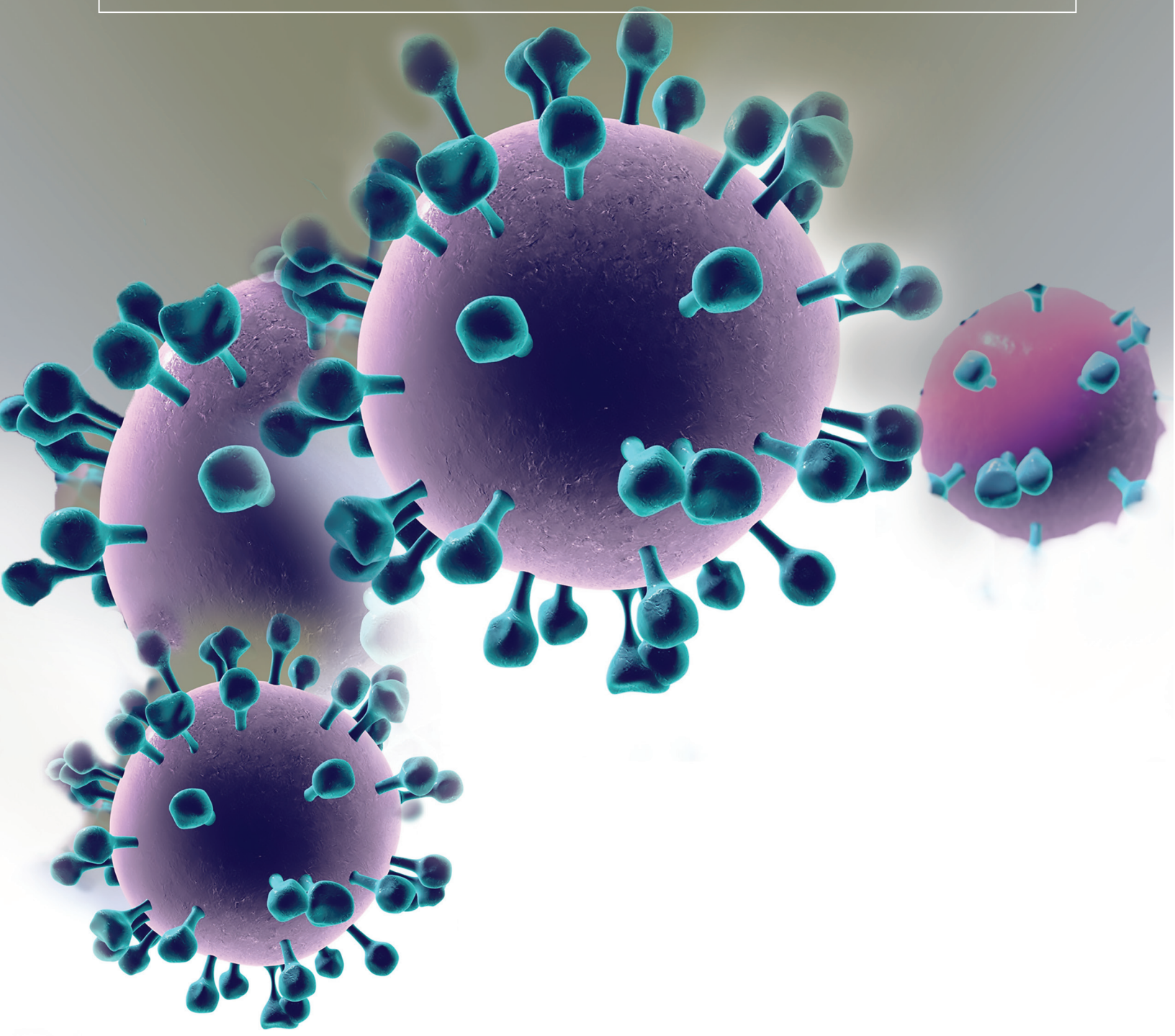
# TACKLING INFLUENZA INFECTION in the EMERGENCY DEPARTMENT:

## *Fast Help for Patients Through Point-of-Care Diagnostic Testing and the Use of Antiviral Agents*



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


**AGENDA**

**I. Overview of Influenza**

**II. Point-of-Care Influenza Infection Diagnostic Testing in the Emergency Department**

a. Types of POCTs and how they work

b. Evidence of benefits: potential to decrease patient LOS and staff time per patient by reducing unnecessary and time-consuming tests, as well as ineffective treatment

**III. Overview of Influenza Antiviral Medications**

a. MOAs of FDA-approved influenza antiviral medications

b. Clinical trial data for FDA-approved influenza antiviral medications

**IV. Guidance on the Use of Influenza Antiviral Medications in the Emergency Department**

a. Treating patients with low or high risk for influenza infection

b. Treating patients with low or high risk for complications of influenza infection

**V. Antiviral Treatment for Influenza Postexposure Prophylaxis**

a. Benefits of postexposure prophylaxis

b. Clinical trial data for FDA-approved influenza postexposure prophylaxis antiviral medications

**VI. Case studies**

**VII. Conclusions**

**VIII. Questions and answers**

***Tackling Influenza Infection in the Emergency Department:***
***Fast Help for Patients Through Point-of-Care Diagnostic Testing and the Use of Antiviral Agents***

**FACULTY**

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Irvine, CA

**PROGRAM OVERVIEW**

This case-based live activity will cover the pathophysiology, point-of-care testing, and antiviral therapy for treating patients who present to the Emergency Department.

**TARGET AUDIENCE**

This activity is intended for US-based emergency medicine and critical care professionals involved in the care of patients with influenza.

**LEARNING OBJECTIVES**

Upon the completion of this program, attendees should be able to:

- Integrate point-of-care testing methodologies in the emergency department to reduce unnecessary testing and the use of ineffective treatments
- Evaluate evidence from clinical trials assessing antiviral agents with different mechanisms of action and abilities to reduce viral shedding approved for the treatment of influenza infection
- Determine which patients infected with influenza are most likely to benefit from treatment with antiviral medications
- Assess the utility of antiviral treatment for influenza postexposure prophylaxis

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Purpose: This program would be beneficial for nurses involved in the treatment of patients with influenza. Credits: 1.0 ANCC Contact Hour.

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**CNE Content Review**
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# Tackling Influenza Infection in the Emergency Department

*Fast Help for Patients Through Point-of-Care Diagnostic Testing and the Use of Antiviral Agents*

## Disclosures

- **Dr. Vega** reports that he serves as a consultant for GlaxoSmithKline.
- During the course of this lecture, the presenter will discuss the use of medications for both FDA-approved and non-approved indications.

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

## Learning Objectives

1. Integrate point-of-care testing methodologies in the emergency department to reduce unnecessary testing and the use of ineffective treatments
2. Evaluate evidence from clinical trials assessing antiviral agents with different mechanisms of action and abilities to reduce viral shedding that are approved for the treatment of influenza infection
3. Determine which patients infected with influenza are most likely to benefit from treatment with antiviral medications
4. Assess the utility of antiviral treatment for influenza postexposure prophylaxis

## Overview of Influenza

## Common Signs and Symptoms of Influenza

- Fever or chills
- Cough
- Sore throat
- Runny or stuffy nose
- Muscle or body aches
- Headaches
- Fatigue
- Vomiting and diarrhea
  - More common in children than adults

Flu Symptoms & Complications. Centers for Disease Control and Prevention. Published 2020. https://www.cdc.gov/flu/symptoms/symptoms.htm, accessed 2/23/20.

## Complications of Influenza

Pneumonia

Myocarditis

Encephalitis

Myositis

Rhabdomyolysis

Multi-organ failure

Flu Symptoms & Complications. Centers for Disease Control and Prevention. Published 2020. https://www.cdc.gov/flu/symptoms/symptoms.htm, accessed 2/23/20.

## When Should I Test for Influenza?

### During influenza activity in the community:

- Immunocompromised people
- Testing will influence treatment or infection control decisions, such as whether a patient might return to a nursing home
- Testing is ***NOT*** needed among patients at high risk of influenza complications. Presumptive treatment is acceptable.

### During *low* influenza activity:

- Acute respiratory symptoms with or without fever, *especially* for immunocompromised and high-risk patients

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

## Point-of-Care Influenza Infection Diagnostic Testing in the Emergency Department

## The Value of Point-of-Care Diagnostic Testing for Influenza in the *Emergency Department*

- Guides diagnostic and treatment decisions more rapidly and avoids overcrowding in the ED
  - Improves efficiency of ED
  - Discharges patients from the ED more quickly
- Increases antiviral treatment in positive patients
- Decreases antibacterial/antiviral use in negative patients

Salway RJ, et al. *Rev Med Clin Condes*. 2017;28:213-219. Benirschke RC, et al. *J Clin Microbiol*. 2019;57(3):e01281-18.

## POC Diagnostic Tests for Influenza

| Test | Method | Time to Results | Performance | Sensitivity/Specificity |
|---|---|---|---|---|
| **Rapid diagnostic test (RIDT)** | Antigen detection | < 15 min | Low to moderate sensitivity; High specificity | Low/moderate sensitivity High specificity |
| **Rapid molecular assay*** | Viral RNA detection | 15-30 min | Moderate to high Sensitivity; High specificity | High sensitivity High specificity |
| **Immunofluo-rescence** | Antigen detection | 1-4 hours | Moderate sensitivity; High specificity | Moderate sensitivity High specificity |
| **RT-PCR and other molecular assays**** | Viral RNA detection | Varies (1-8 hrs) | High sensitivity; High specificity | High sensitivity High specificity |
| **Multiplex molecular assays**** | Virus isolation | 3-10 days | High sensitivity; High specificity | |

***Preferred for *outpatient* setting **Preferred for *inpatient* setting**

**Influenza Testing. CDC. Published 2020. https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm. Accessed 1/31/20 (2) Uyeki TM, et al. Clin Infect Dis. 2019;68(6):895-902.**

Click here to watch an animated video explaining how point-of-care tests work to diagnose influenza.

## Which Tests Should Be Used to Diagnose Influenza in the *Emergency Department*?

- ***Rapid molecular assays*** (ie, NAATs) preferred over RIDTs for *ambulatory* patients to improve detection of influenza virus infection
- ***RT-PCR or other molecular assays*** **are p**referred over other influenza tests in *hospitalized patients* to improve detection of influenza virus infection
- Do ***not*** use viral cultures for initial or primary diagnosis because results will not be available in a timely manner to inform clinical management
- Do ***not*** use serologic testing because results from a single serum specimen cannot be readily interpreted

**NAAT = nucleic acid amplification test; RIDT = rapid influenza diagnostic test; RT-PCR = reverse transcription polymerase chain reaction.**
**Uyeki TM, et al. *Clin Infect Dis*. 2019;68:e1-e47.**

## Overview of Influenza Antiviral Medications

## FDA-approved Drugs for Influenza Treatment

Neuraminidase inhibitors
- Oseltamivir phosphate
- Zanamivir
- Peramivir

Adamantanes
- Amantadine
- Rimantadine

**Not recommended*

Cap-dependent endonuclease inhibitor
- Baloxavir marboxil

Click here to watch an animated video explaining the mechanism of action of antiviral medications approved for the treatment of influenza.

## Zanamivir, FDA-Approved in 1999

- Inhaled zanamivir is associated with a significant improvement in time to alleviation of symptoms
  - –1 to 2 days in otherwise healthy adults[1-3]
  - –14.4 hours in adults with influenza-like illness[4]
  - –No significant difference in children[4]
  - –No reduction in complications of influenza[4]
  - –Insufficient data to evaluate the effect on hospitalization[4]

1. Hayden FG, et al. *N Engl J Med*. 1997;337:874-880. 2. Management of Influenza in the Southern Hemisphere Trialists (MIST) Study Group. *Lancet*. 1998;352:1877-1881. 3. Monto AS, et al. *J Infect Dis*. 1999;180:254-261. 4. Heneghan CJ, et al. *BMJ*. 2014;348:g2547.

## Oseltamivir Clinical Trials: *Ambulatory Patients*

| Study[1] | Characteristics | Time From Symptom Onset (h) | Reduction in Length of Illness (days) |
|---|---|---|---|
| Cooper et al[2] | Healthy adults with lab-confirmed influenza | <48 | 1.4 |
| Treanor et al[3] | Healthy adults with lab-confirmed influenza | <36 | 1.3 |
| Nicholson et al[4] | Healthy adults with lab-confirmed influenza | 24-36 | 1-2 |
| **Aoki et al[5]** | Healthy patients (aged 12-70 years) with lab-confirmed influenza | **0-6** | **4.1** |
| **Aoki et al[5]** | Healthy patients (aged 12-70 years) with lab-confirmed influenza | **6-12** | **3.1** |
| Cooper et al,[2] Kaiser et al[6] | Elderly and high-risk patients with lab-confirmed influenza | 36-48 | 0.5* |
| Whitley et al[7] | Children (1-12 years) with ILI (65% confirmed) | <48 | 1.5† |

*34% reduction in antibiotic for LRTI; †44% reduction in otitis media.

ILI = influenza-like illness; LRTI = lower respiratory tract infection.

1. Adapted from Moscona A. *N Engl J Med*. 2005;353(13):1363-1373. 2. Cooper NJ, et al. *BMJ*. 2003;326(7401):1235. 3. Treanor JJ, et al. *JAMA*. 2000;283(8):1016-1024. 4. Nicholson KG, et al. *Lancet*. 2000;355(9218):1845-1850. 5. Aoki FY, et al. *J Antimicrob Chemother*. 2003;51(1):123-129. 6. Kaiser L, et al. *Arch Intern Med*. 2003;163(14):1667-1672. 7. Whitley RJ, et al. *Pediatr Infect Dis J*. 2001;20(2):127-133.

## Oseltamivir vs Placebo: Meta-Analysis Findings

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

| Adverse Event | Oseltamivir (n = 2401) | Placebo (n = 1917) | *P*-Value | Risk Difference (95% CI) |
|---|---|---|---|---|
| **Gastrointestinal (GI) disorders** | 574 | 370 | 0.0019 | **4.0%** (1.4 to 6.9) |
| Nausea | 247 | 118 | <0.0001 | **3.7%** (1.8 to 6.1) |
| Vomiting | 201 | 63 | <0.0001 | **4.7%** (2.7 to 7.3) |
| Diarrhea | 147 | 147 | 0.016 | −1.9% (−3.1 to −0.4) |
| **Neurological disorders** | 124 | 93 | 0.97 | −0.0% (−1.2 to 1.5) |
| **Psychiatric disorders** | 11 | 13 | 0.27 | −0.3% (−0.5 to 0.3) |

AE = adverse event; CI = confidence interval.

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

## Oseltamivir in Hospitalized Population

- 5 years' worth of patient level data from a single urban center (N=699)
- Only 26% were treated with oseltamivir empirically (within 6 hours)
- Median time to first dose: 17.9 hours
- Early NAI was associated with shorter hospital length of stay (*P*<.001)
- No patients died in the early NAI group, compared to 18 deaths in the 399 patients receiving NAI after 6 hours (4.5%) and 4 deaths in the 116 patients not receiving NAI (3.4%)

Katzen J, et al. *Clin Infect Dis*. 2019;69(1):52-58.

## 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) |
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| 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) |

AE = adverse event
Dobson J, et al. *Lancet*. 2015;385(9979):1729-1737.

## Peramivir IV, FDA-Approved in 2014

***Uncomplicated influenza, single-dose***

- Peramivir, single-dosing, versus oseltamivir
  - Similar time-to-clinical resolution and virus titer reduction[1,2]
- Randomized, double-blind study of single-dose intravenous peramivir with oral oseltamivir[3]:

| Population and Treatment (n) | Median Time to Alleviation (h) | Hazard Ratio (97.5% CI) |
|---|---|---|
| Peramivir 300 mg (364) | 78.0 (68.4) | 0.946 (0.793) |
| Peramivir 600 mg (362) | 81.0 (72.7) | 0.970 (0.814) |
| Oseltamivir (365) | 81.8 (73.2) | 0.970 (0.814) |

1. de Jong MD, et al. *Clin Infect Dis*. 2014;59(12):e172-e185. 2. Nakamura S, et al. *Open Forum Infect Dis*. 2017;4(3):ofx129. 3. Kohno S, et al. *Antimicrob Agents Chemother*. 2011;55(11):5267-5276.

## Neuraminidase inhibitors

*Efficacy*

**Decrease the time to first alleviation of symptoms Of influenza-like illness by…**

**Oseltamivir (best evidence)**

- **Adults:** 16.8 - 17.8 hours[1,2]
- **Children:** 29 hours[2]

**Zanamivir (less robust evidence)**

- **Adults:** 14.4 hours[2]
- **Children**: Not significant[2]

(1) Dobson J, et al. Lancet. 2015;385:1729-1737. (2) Jefferson T, et al. Cochrane Database Syst Rev. 2014

# Neuraminidase inhibitors
## *Safety considerations*

| Oseltamivir | Zanamivir | NAIs |
|---|---|---|
| *Nausea and vomiting* does not generally result in discontinuation of therapy.<br>Taking the drug with food may minimize GI adverse effects. | *Bronchospasm and a decline in respiratory function* in patients with chronic respiratory disorders (i.e. asthma, COPD).<br>Should **NOT** be used in patients with underlying airway disease (manufacturer warning). | *Neuropsychiatric* events are **rare** and not proven to be associated with NAIs. |

NAI = neuraminidase inhibitor

Rasmussen SA, et al. Am J Obstet Gynecol. 2011 Jun;204(6 Suppl 1):S13-20. Graner S, et al. BMJ. 2017; 356: j629. (3) Dunstan HJ, et al. BJOG. 2014 Jun;121(7):901-6.

# Baloxavir Marboxil
## *CAPSTONE-1 Trial*

Phase 3, randomized, double-blind, placebo- and oseltamivir-controlled study
- Outpatients 12 to 54 years old
- Patients 12 to 19 years randomly assigned to baloxavir or placebo (Day 1 only)
- 1436 patients randomized; 1064 patients in ITT population

RANDOMIZED 2:1

- **Baloxavir single dose** (40 mg for BW < 80 kg; 80 mg for BW ≥ 80 kg)
- **Oseltamivir 75 mg twice daily** Days 1 to 5
- **Matching placebos**

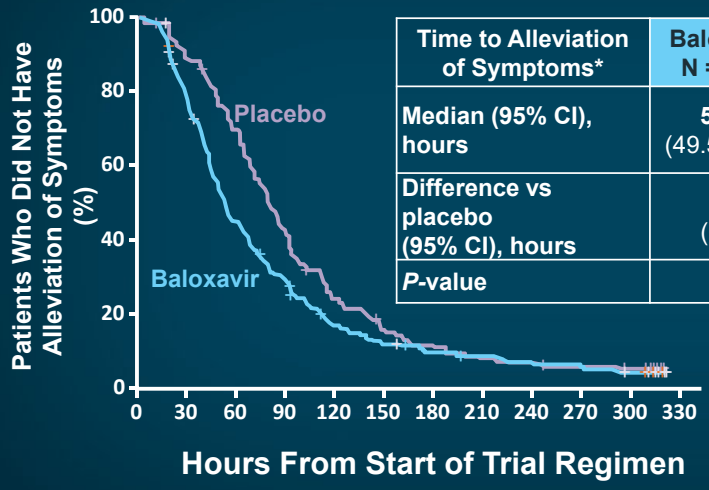
**Primary endpoint** Time to alleviation of influenza symptoms

BW = body weight , ITT = intention-to-treat

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

## Baloxavir Marboxil for Uncomplicated Influenza

### *CAPSTONE-1 Trial*




| Time to Alleviation of Symptoms* | 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 | < 0.0001 | |

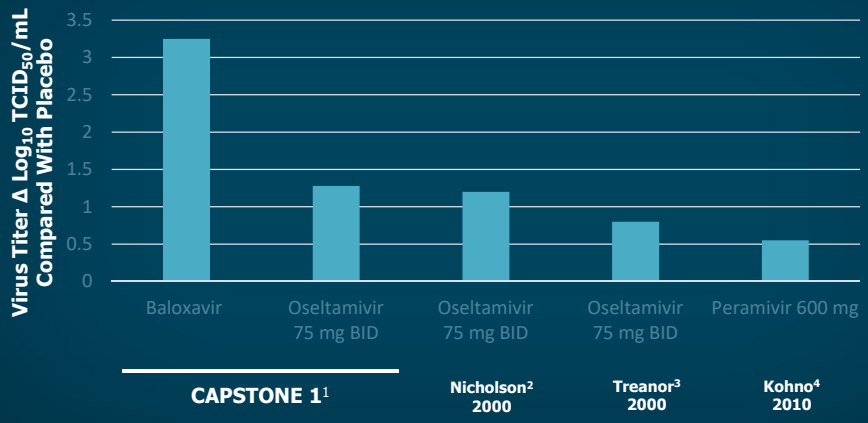
- Baloxavir significantly reduced duration of fever by ~1 day versus placebo
- Median time to alleviation of symptoms was similar for baloxavir and oseltamivir (~54 hours)

*Intention-to-treat infected population

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

## Baloxavir CAPSTONE-1 Study

**Virus titer change from baseline after 1 day of dosing**
**(Δ $Log_{10}TCID_{50}$/mL minus Δ placebo)**



## Baloxavir Marboxil for High-risk Adults

### *CAPSTONE-2: Study 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 years
  - Fever + influenza symptoms of ≤ 48 hours duration
  - **Presence of at least 1 higher risk factor (from CDC criteria)**
- 38% to 44% of patients had influenza B; 56% to 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 twice daily** Days 1-5 and placebo[b] on Day 1 (N = 389)
- **Placebo twice daily Days 1-5** Placebo to baloxavir on Day 1 (N = 386)

**Primary endpoint**
Time to improvement of influenza symptoms

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

[a]Placebo to oseltamivir; [b]Placebo to baloxavir.
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%)

BW = body weight.

Ison MG, et al. Presented at: IDSA Infectious Disease Week (IDWeek) 2018; Abstract LB16. ClinicalTrials.gov. 2016. (https://clinicaltrials.gov/ct2/show/NCT02949011). Ison MG, et al. *Lancet Infect Dis.* 2020;20(10):1204-1214. Baloxavir marboxil (XOFLUZA®). 2020 PI. (https://www.xofluza.com/).

## Baloxavir Marboxil in High-risk Adults

### *CAPSTONE-2: Outcome Summary*

**Baloxavir reduces time to clinical recovery**

| | |
|---|---|
| Baloxavir for influenza A | 73.2 h |
| Placebo for influenza A | 103.2 h |
| Baloxavir for influenza B | 74.6 h |
| Placebo for influenza B | 100.6 h |
| Oseltamivir for influenza B | 101.6 |

**Baloxavir reduces viral shedding**

- Reduced in baloxavir (n = 48) cohort vs oseltamivir (n = 96) or placebo (n = 96)

**Influenza-related complications**

- Reduced with either baloxavir or oseltamivir compared with placebo

**Safety**

- Similar incidence of AEs for baloxavir (25.1%) versus placebo (29.7%) or oseltamivir (28.0%),

ClinicalTrials.gov. Accessed January 15, 2021. https://clinicaltrials.gov/ct2/show/NCT02949011; Ison M, et al. Presented at: Infectious Disease Week (IDWeek) 2018; October 3-7, 2018; San Francisco. CA. Abstract #LB16; Ison MG, et al. *Lancet Infect Dis.* 2020;20(10):1204-1214; Baloxavir marboxil [Approval letter]. October 16, 2019. Accessed January 15, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/210854Orig1s001.pdf

# Baloxavir Marboxil
## *Safety*

Compared to oseltamivir…

Baloxavir marboxil is equally safe and potentially associated with ***fewer AEs***

| Adverse Event | Baloxavir marboxil (%) | Placebo (%) | Oseltamivir (%) |
|---|---|---|---|
| Diarrhea | 3 | 4.5 | 2.1 |
| Bronchitis | 2.6 | 5.5 | 3.5 |
| Nasopharyngitis | 1.5 | 0.6 | 0.8 |
| Nausea | 1.3 | 1.3 | 3.1 |
| Sinusitis | 1.1 | 2.6 | 1.0 |
| Increase in ALT | 1.0 | 1.3 | 1.4 |
| ANY ADVERSE EVENT | 20.7 | 24.6 | 24.8 |

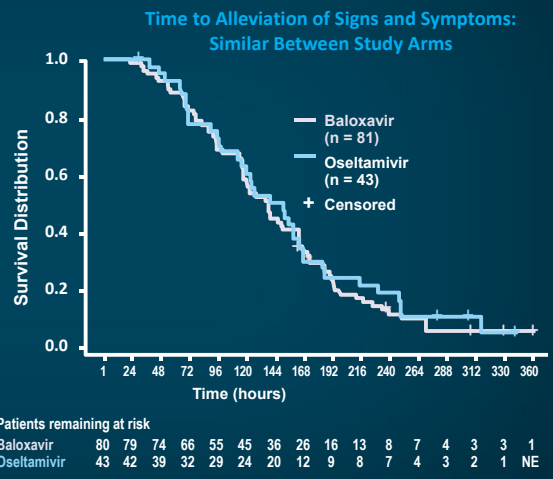
Hayden FG, Sugaya N, Hirotsu N, et al,. N Engl J Med. 2018 Sep 6;379(10):913-923. Taieb V, Ikeoka H, Ma F-F, et al., Curr Med Res Opin. 2019:1-1.

## 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 twice daily x 5 days; weight-based dosing
- Randomized 2:1, N = 112/57; 81/54 with confirmed influenza
- 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)




RCT = randomized control trial; sNDA = supplemental NDA; NDA = new drug application; NE = not evaluable.

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

## FLAGSTONE: Baloxavir + NAI in Hospitalized Patients With Severe Influenza

- Baseline characteristics were balanced in the baloxavir plus NAI versus placebo plus NAI

| | Baloxavir + NAI | Placebo + NAI | *P* Value |
|---|---|---|---|
| TTCI | 97.5 hours (75.9 – 117.2) | 100.2 hours (75.9 – 144.4) | .4666 |
| Median time to cessation of viral shedding | 23.9 hours | 63.7 hours | .0001 |
| ≥1 AE | 45.2% | 50.0% | |
| Serious AEs | 12.1% | 15.3% | |

AE = adverse event.

NCT03684044. (https://clinicaltrials.gov/ct2/show/NCT03684044).

Kumar D, et al. Presented at The Seventh European Scientific Working Group on Influenza (ESWI) Virtual Conference; December 6-9, 2020.

## Guidance on the Use of Influenza Antiviral Medications in the Emergency Department

## Which Patients Should Be Treated With Antiviral Therapy?

**ASAP regardless of vaccination history:**

- Any age with severe or progressive illness regardless of illness duration
- People at high-risk of complications from influenza
- Children younger than 2 years and adults ≥ 65 years
- Pregnant women and those within 2 weeks postpartum

**Consider treating the following patients:**

- Those with illness onset ≤ 2 days before presentation
- Symptomatic patients who are household contacts of people at high-risk of developing severe complications from influenza
- Symptomatic HCPs who care for people at high-risk of developing severe complications from influenza

## Neuraminidase inhibitors
## *Uncomplicated influenza*

| | Oseltamivir[1,2] (*Tamiflu*) | Zanamivir[2,3] (*Relenza*) | Peramivir[2,4] (*Rapivab*) |
|---|---|---|---|
| **Adult dosage** | 75 mg PO BID x 5 days | 2 inhalations BID x 5 days | 600 mg IV once |
| **Pediatric dosage** | ▪ **< 1yr:** 1.5-3.5 mg/kg BID x 5 days<br>▪ **1-12 yrs:** 30-75mg BID x 5 days **(**weight-based) | **≥ 7 yrs**: 2 inhalations BID x 5 days | ▪ **2-12 yrs**: 12 mg/kg (max 600 mg) IV once<br>▪ **≥ 13 yrs**: 600 mg IV once |
| **Renal Dosing** | **Adults**<br>CrCl >30-60 mL/min: 30 mg BID<br>CrCl >10-30 mL/min: 30 mg QD | No dosage adjustment required | **2-12 yrs**<br>CrCl 30-49 mL/min: 4 mg/kg once<br>CrCl 10-29 mL/min: 2 mg/kg once<br>**≥ 13 yrs**<br>CrCl 30-49 mL/min: 200 mg once<br>CrCl 10-29 mL/min: 100 mg once |

(1) Tamiflu (oseltamivir) prescribing information. Genentech, Inc; 2019 (2) American Academy of Pediatrics Committee on Infectious Diseases. *Pediatrics.* 2019;144(4):e20192478.(3) Relenza (zanamivir) prescribing information. GlaxoSmithKline; 2018. (4) Rapivab (peramivir) prescribing information. Seqirus; 2017.

## Baloxavir Marboxil

***Treatment*** and ***post-exposure prophylaxis*** for influenza A and B, including avian-origin H5N1 and H7N9

- ✓ ***Uncomplicated flu***
- ✓ ***High risk of flu-related complications***

***One-time oral dose***
*(total dose of 40 or 80mg, based on weight)*

Adults and children **≥ *12 years old***

*(currently under FDA review for ≥1 yr old)*

Symptomatic for **≤ *48 hours***

*More effective if given as soon possible (≤ 24 hrs of symptom onset)*

(1) Baloxavir marboxil (XOFLUZA). Prescribing Information. Genentech USA, Inc.; 2019. (2) FDA Expands Approval of Influenza Treatment to Post-Exposure Prevention. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-expands-approval-influenza-treatment-post-exposure-prevention. Published 2020. Accessed November 24, 2020.

## Antiviral Treatment for Influenza Postexposure Prophylaxis

## Chemoprophylaxis

NAIs and Baloxavir are

**~ 70% to 90%**

effective in preventing influenza,

*however…*

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

## …CDC does *NOT* recommend routine use except for…

- High-risk people in the first 2 weeks post-immunization
- High-risk people with no vaccine or expected poor response

**Other considerations:**

- Not recommended if ≥ 48 h after exposure
- The CDC and the American Academy of Pediatrics recommend the use of oseltamivir for prophylaxis in infants aged 3 months and older
- Oseltamivir has efficacy of 69% to 92% in preventing influenza

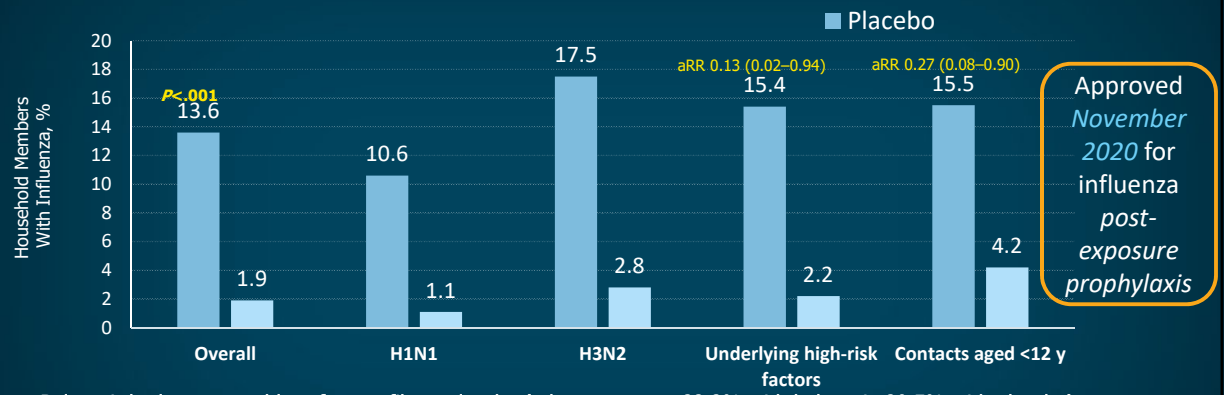
CDC = Centers for Disease Control and Prevention.
Centers for Disease Control and Prevention. Updated August 10, 2020. Accessed January 15, 2021. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm; Carey WA, et al. *Pediatrics*. 2018;141(3):e20173108; Moscona A. *N Engl J Med*. 2005;353(13):1363-1373.

## 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

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

## BLOCKSTONE: Preventative Treatment With Baloxavir After Exposure to an Infected Household Member – 86% Effective




Approved *November 2020* for influenza *post-exposure prophylaxis*

- 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.

## Case Study

## Sharon is a 62-year-old Female…

- 3-day history of cough and dyspnea
- Fatigue and myalgias, no fever, some sneezing
- ROS otherwise negative: esp GI and neuro
- Has generally been at home
- Daughter and her 2 kids come by twice per month – no illness
- Sees “a friend” routinely – mild cough only last week

COPD = chronic obstructive pulmonary disease; ER = extended release; HTN = hypertension; MDI = metered dose inhaler; OA = obstructive apnea; OAB = overactive bladder; ROS = review of systems; URI = upper respiratory tract infection

# Patient Case (continued)

**Medical history**

- COPD
- Hypertension
- Obstructive apnea
- Overactive bladder

**Medication**

- Fluticasone/salmeterol MDI
- Albuterol MDI
- Lisinopril/hydrochlorothiazide
- Naproxen
- Tolterodine ER

**Physical Exam**

- Temperature 99.7°F (37.6 °C)
- BP 164/90 mm Hg
- Pulse 96 bpm
- RR 18/min
- $O_2$ saturation 92% on room air
- Diffuse mild expiratory wheeze; otherwise unremarkable

COPD = chronic obstructive pulmonary disease; ER = extended release; HTN = hypertension; MDI = metered dose inhaler; OA = obstructive apnea; OAB = overactive bladder; ROS = review of systems; URI = upper respiratory tract infection

# Patient Case (continued)

- Rapid influenza diagnostic test is positive
- COVID-19 test sent, results usually in 1 to 2 days
- Patient prescribed baloxavir and told to take it right away
- The next day, RT-PCR test returns positive for COVID-19

RT-PCR = reverse transcription polymerase chain reaction

## What now?

## Patient Case (continued)

- Telehealth visit on day 5 of symptoms
- Energy slightly better, but dyspnea and cough same; afebrile
- Following isolation rules – staying in attic
- Difficulty climbing stairs at home

## What now?

## Patient Case (continued)

- Seen the next day in COVID-19 screening center
- Temperature 99.1 °F (37.3 °C), pulse 76 beats/minute, BP 154/86 mm Hg bilaterally, RR 14/minute; $O_2$ sat RA 94%

## What now?

## Patient Case (continued)

- Repeat telehealth visit 3 days later
- All symptoms resolved except mild dyspnea – improved
- On day 3 of 5-day burst of oral corticosteroid
- Wants to know if asymptomatic boyfriend should be tested for influenza, COVID-19
- Wants to know if she can go back to work (day 8 of symptoms)

## What now?

## Patient Case (continued)

- Repeat telehealth visit 3 days later
- Feels back to normal
- Some bloating with prednisone
- Will never remove mask again
- Letter completed for work; repeat COVID-19 test unnecessary and OK to return to work given CDC guidelines

## Questions & Discussion

# TACKLING INFLUENZA INFECTION in the EMERGENCY DEPARTMENT:

*Fast Help for Patients Through Point-of-Care Diagnostic Testing and the Use of Antiviral Agents*

## YOUTUBE VIRTUAL ANIMATIONS

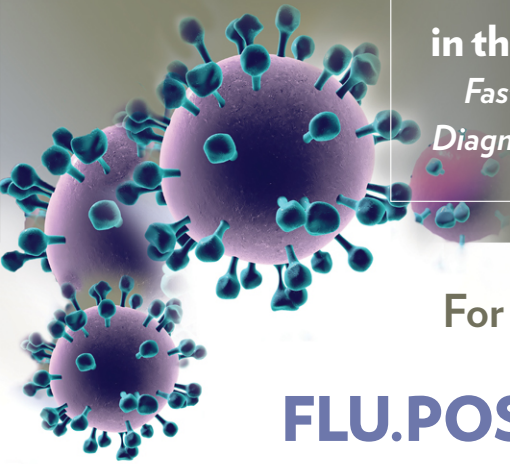
**MOA OF POCTs:** https://youtu.be/LvTgBLPlJXo

**MOA OF ANTIVIRAL TREATMENTS:** https://youtu.be/GJqU1pM1uFI

Use your device's QR code scanner to view this content in the **YOUTUBE APP!**

# TACKLING INFLUENZA INFECTION in the EMERGENCY DEPARTMENT:

*Fast Help for Patients Through Point-of-Care Diagnostic Testing and the Use of Antiviral Agents*



## Overview of Influenza

| Resource | Address |
|---|---|
| **Centers for Disease Control and Prevention (CDC). Flu symptoms & complications. Last reviewed April 12, 2021.** | https://www.cdc.gov/flu/symptoms/symptoms.htm |
| **Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):895-902.** | https://pubmed.ncbi.nlm.nih.gov/30834445/ |

## Point-of-Care Influenza Infection Diagnostic Testing in the Primary Care Setting

| Resource | Address |
|---|---|
| **Benirschke RC, McElvania E, Thomson RB Jr, Kaul KL, Das S. Clinical impact of rapid point-of-care PCR influenza testing in an urgent care setting: A single-center study. *J Clin Microbiol*. 2019;57(3):e01281-18.** | https://pubmed.ncbi.nlm.nih.gov/30602445/ |
| **Salway RJ, Valenzuela R, Shoenberger JM, Mallon WK, Viccellio A. Emergency department (ED) overcrowding: Evidence-based answers to frequently asked questions. *Rev Med Clin Condes*. 2017;28(2):213-219.** | https://www.elsevier.es/es-revista-revista-medica-clinica-las-condes-202-pdf-S0716864017300354 |
| **Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):895-902.** | https://pubmed.ncbi.nlm.nih.gov/30834445/ |

## Overview of Influenza Antiviral Medications

| Resource | Address |
|---|---|
| **Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases** | https://pubmed.ncbi.nlm.nih.gov/12493796/ |

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| **the benefits of influenza treatment. *J Antimicrob Chemother*. 2003;51(1):123-129.** | |
| **Baker J, Block SL, Matharu B, et al. Baloxavir marboxil single-dose treatment in influenza-infected children a randomized, double-blind, active controlled phase 3 safety and efficacy trial (miniSTONE-2). *Pediatr Infect Dis J*. 2020;39(8):700-705.** | https://pubmed.ncbi.nlm.nih.gov/32516282/ |
| **Centers for Disease Control and Prevention (CDC). Influenza virus testing methods. Last reviewed August 10, 2020.** | https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm |
| **Study to Assess Efficacy and Safety of Baloxavir Marboxil In Combination With Standard-of-Care Neuraminidase Inhibitor In Hospitalized Participants With Severe Influenza 2020. ClinicalTrials.gov identifier: NCT03684044. Updated January 6, 2021.** | https://ClinicalTrials.gov/show/NCT03684044 |
| **Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner D, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: Systematic review and meta-analyses of randomized controlled trials. *BMJ*. 2003;326(7401):1235.** | https://pubmed.ncbi.nlm.nih.gov/12791735/ |
| **Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: A meta-analysis of randomized controlled trials. *Lancet*. 2015;385(9979):1729-1737.** | https://pubmed.ncbi.nlm.nih.gov/25640810/ |
| **Dunstan HJ, Mill AC, Stephens S, Yates LM, Thomas SHL. Pregnancy outcomes following maternal use of zanamivir or oseltamivir during the 2009 influenza A/H1N1 pandemic: A national prospective surveillance study. *BJOG*. 2014;121(7):901-906.** | https://pubmed.ncbi.nlm.nih.gov/24602087/ |
| **Graner S, Svensson T, Beau AB, et al. Neuraminidase inhibitors during pregnancy and risk of adverse neonatal outcomes and congenital malformations: Population based European register study. *BMJ*. 2017;356:j629.** | https://www.bmj.com/content/356/bmj.j629 |
| **Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *N Engl J*** | https://www.nejm.org/doi/full/10.1056/NEJMoa1716197 |

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| ***Med*. 2018;379(10):913-923.** | |
| **Ison MG, Portsmouth S, Yoshida Y, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): A randomized, placebo-controlled, phase 3 trial. *Lancet Infect Dis*. 2020;20(10):1204-1214.** | https://pubmed.ncbi.nlm.nih.gov/32526195/ |
| **Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev*. 2014;2014(4):CD008965.** | https://pubmed.ncbi.nlm.nih.gov/24718923/ |
| **Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med*. 2003;163(14):1667-1672.** | https://pubmed.ncbi.nlm.nih.gov/12885681/ |
| **Katzen J, Kohn R, Houk JL, Ison MG. Early oseltamivir after hospital admission is associated with shortened hospitalization: A 5-year analysis of oseltamivir timing and clinical outcomes. *Clin Infect Dis*. 2019;69(1):52-58.** | https://pubmed.ncbi.nlm.nih.gov/30304487/ |
| **Kohno S, Kida H, Mizuguchi M, Shimada J. S-021812 Clinical Study Group. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrob Agents Chemother*. 2010;54(11):4568-4574.** | https://pubmed.ncbi.nlm.nih.gov/20713668/ |
| **Mor M, Waisman Y. Point-of-care testing: A critical review. *Pediatr Emerg Care*. 2000;16(1):45-48.** | https://pubmed.ncbi.nlm.nih.gov/10698145/ |
| **Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med*. 2005;353(13):1363-1373.** | https://pubmed.ncbi.nlm.nih.gov/16192481/ |
| **Nicholson KG, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: A randomized controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. *Lancet*.** | https://pubmed.ncbi.nlm.nih.gov/10866439/ |

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| **2000;355(9218):1845-1850.** | |
| **Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. *Am J Obstet Gynecol*. 2012;207(3 suppl):S3-S8.** | https://www.ajog.org/article/S0002-9378(12)00722-3/fulltext |
| **Taieb V, Ikeoka H, Ma FF, et al. A network meta-analysis of the efficacy and safety of baloxavir marboxil versus neuraminidase inhibitors for the treatment of influenza in otherwise healthy patients. *Curr Med Res Opin*. 2019;35(8):1355-1364.** | https://pubmed.ncbi.nlm.nih.gov/30810054/ |
| **Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza. *JAMA*. 2000;283(8):1016-1024.** | https://jamanetwork.com/journals/jama/fullarticle/192425 |
| **Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J*. 2001;20(2):127-133.** | https://pubmed.ncbi.nlm.nih.gov/11224828/ |

## Antiviral Treatment for Influenza Postexposure Prophylaxis

| Resource | Address |
|---|---|
| **Carey WA, Weaver AL, Mara KC, Clark RH. Inhaled nitric oxide in extremely premature neonates with respiratory distress syndrome. *Pediatrics*. 2018;141(3):e20173108.** | https://pediatrics.aappublications.org/content/141/3/e20173108 |
| **Ikematsu H, Hayden FG, Kawaguchi K, et al. Baloxavir marboxil for prophylaxis against influenza in household contacts. *N Engl J Med*. 2020;383(4):309-320.** | https://www.nejm.org/doi/full/10.1056/NEJMoa1915341 |
| **Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med*. 2005;353(13):1363-1373.** | https://pubmed.ncbi.nlm.nih.gov/16192481/ |