Treating the Influenza Virus and Improving Outcomes in the Health System

Faculty Information

Content for this program was developed and reviewed by:

Lucas Schulz, PharmD, BCIDP
Clinical Coordinator – Infectious Diseases
UW Health
Madison, Wisconsin

Joshua Vanderloo, PharmD, BCPS
Clinical Pharmacist, Drug Policy Program
UW Health
Madison, Wisconsin

Content for this program was also reviewed by:

James Lewis, PharmD, FIDSA
Infectious Diseases Clinical Pharmacy Supervisor
Oregon Health & Science University
Portland, Oregon

Rupal Mansukhani, PharmD, FAPhA, CTTS
Clinical Associate Professor
Ernest Mario School of Pharmacy
Rutgers University, The State University of New Jersey
Piscataway, New Jersey

PTce

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

Educational Objectives

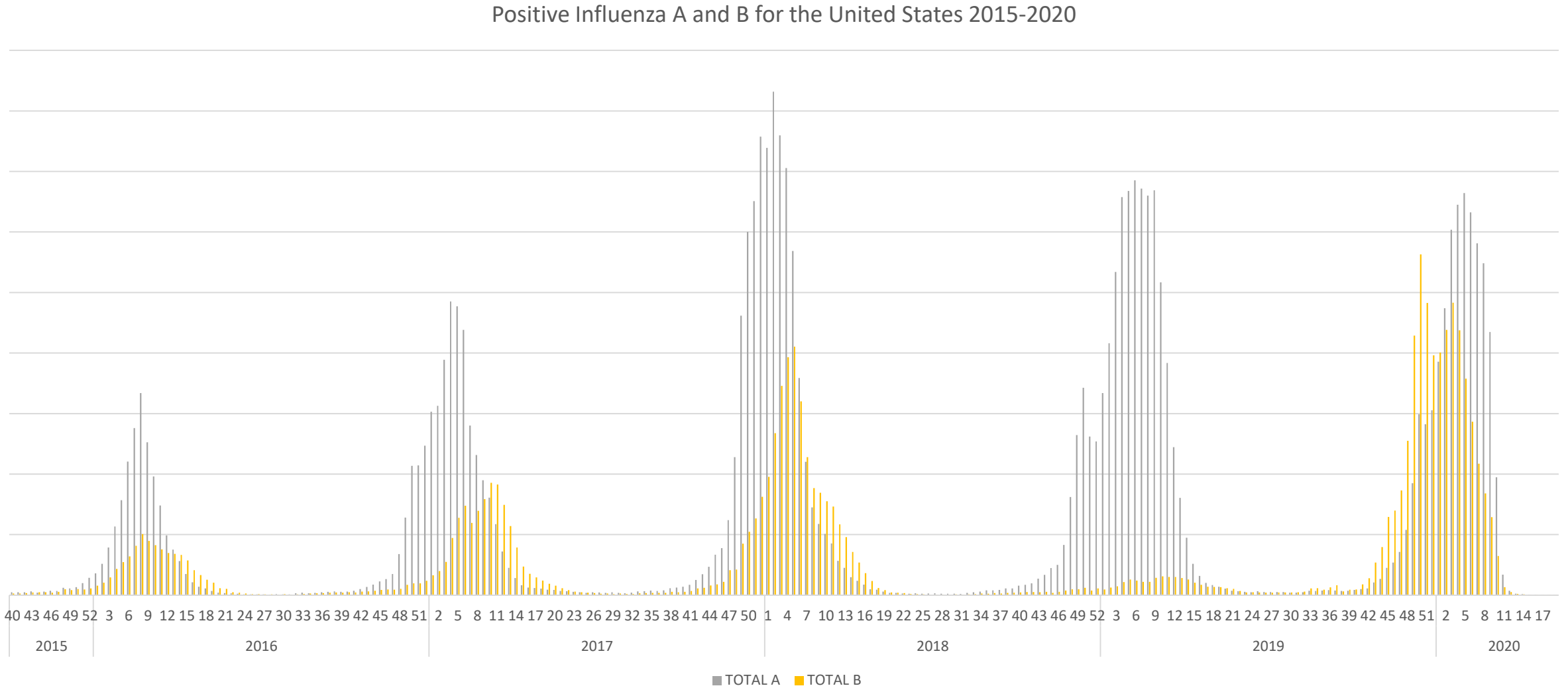
After completion of this activity, participants will be able to:

- Examine the pathogenesis and modes of transmission of influenza, as well as factors contributing to greater risk of influenza-related complications in certain patient populations
- Compare the mechanisms of action, dosing, clinical benefits, and adverse effects associated with the antivirals recommended by the CDC for the influenza season
- Identify the role of health-system pharmacists in making clinical recommendations and in counseling patients about the use of antivirals for the prevention and treatment of the influenza virus

What Time Is It?

- 35-year-old mother of 3 school-aged children presents to your clinic pharmacy and requests help finding an OTC medication to treat a low-grade fever and generalized aches and pains. It is late November 2019. PMH unremarkable
- 83-year-old man with a history of diabetes is hospitalized on your general care floor and is requiring 6L O_2 per nasal canula to maintain PaO_2 sats above 94%
- 53-year-old woman is intubated and receiving extracorporeal membrane oxygenation in your medical intensive care unit

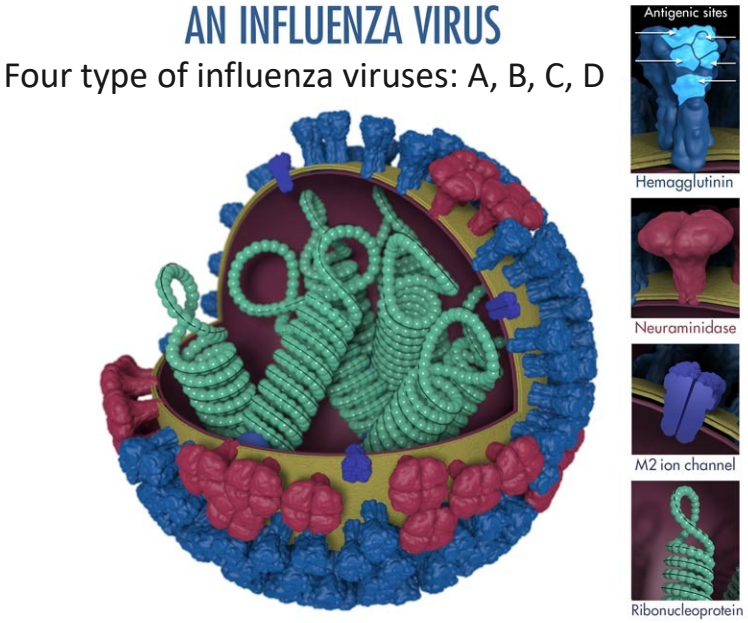
It’s Influenza Season!



National, regional, and state level outpatient illness and viral surveillance. Fluview Interactive. Accessed June 2, 2020. gis.cdc.gov/grasp/fluview

Pathophysiology

- Strains causing most human disease: A, B
- Acute illness with varying severity of symptoms: mild fatigue to respiratory failure and death



CDC. Cold Versus Flu. Accessed August 27, 2020. cdc.gov/flu/symptoms/coldflu.htm; CDC. Flu Symptoms & Complications. Accessed August 27, 2020. cdc.gov/flu/symptoms/symptoms.htm. World Health Organization. Coronavirus. Accessed September 2, 2020. who.int/health-topics/coronavirus

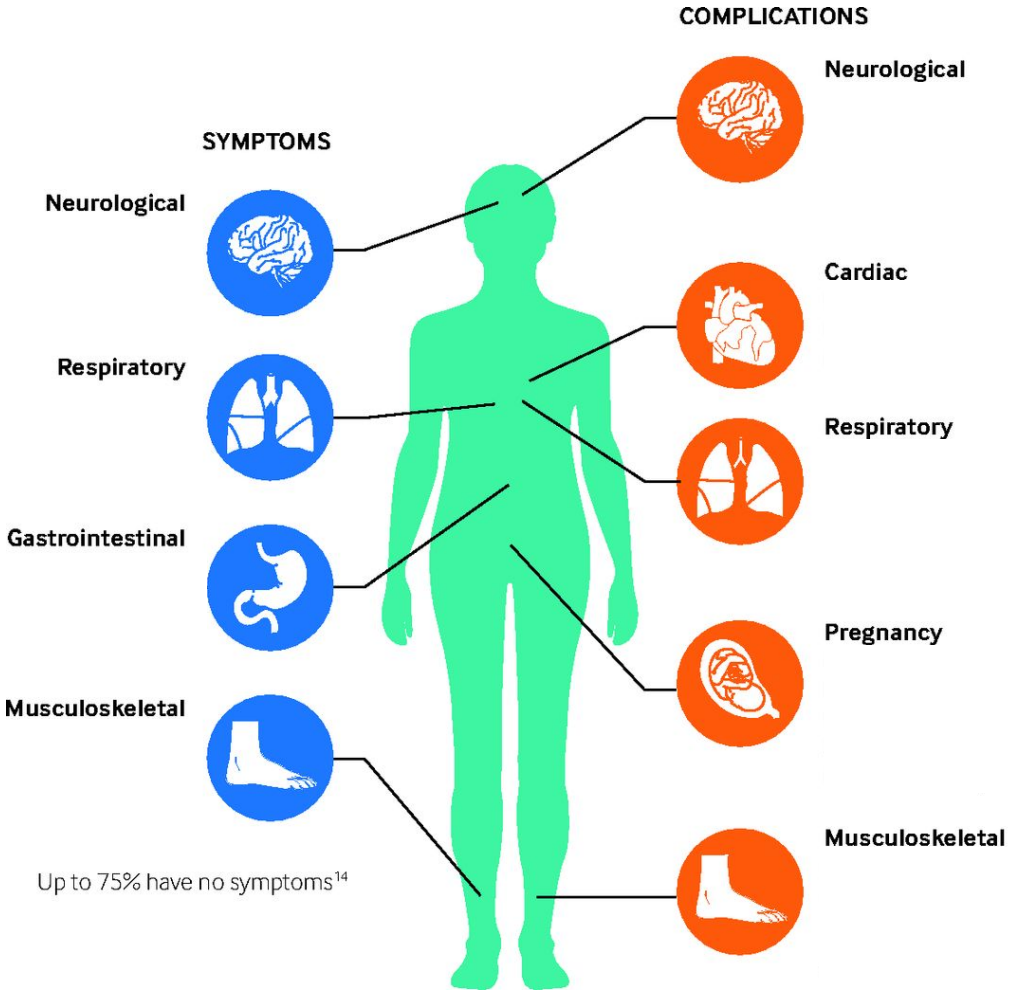
Comparison of Respiratory Illnesses

	Influenza	COVID-19	Cold
Incubation period	1-4 days	2-14 days	1-3 days
Symptom onset	Abrupt	Gradual	Gradual
Fever	Common	Common	Rare
Cough	Common	Common	Common
Sore throat	Sometimes	Sometimes	Common
Shortness of breath	Common	Sometimes	No
Fatigue	Common	Common	Sometimes
Aches and pain	Common	Sometimes	No
Headaches	Common	Sometimes	Common
Runny or stuffy nose	Sometimes	Sometimes	Common
Diarrhea	Sometimes	Rare	No
Sneezing	No	No	Common

Adapted from content produced by WHO and CDC.

Note: Information is evolving. This list is not all-inclusive of all potential symptoms.

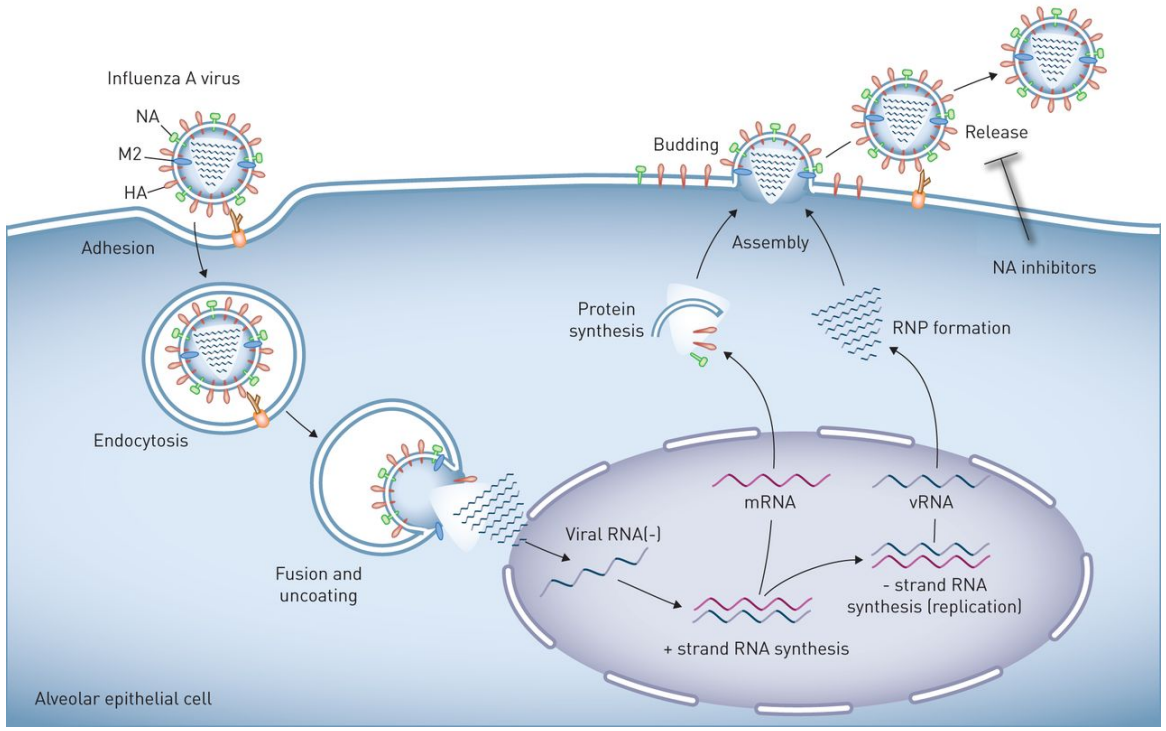
Pathophysiology

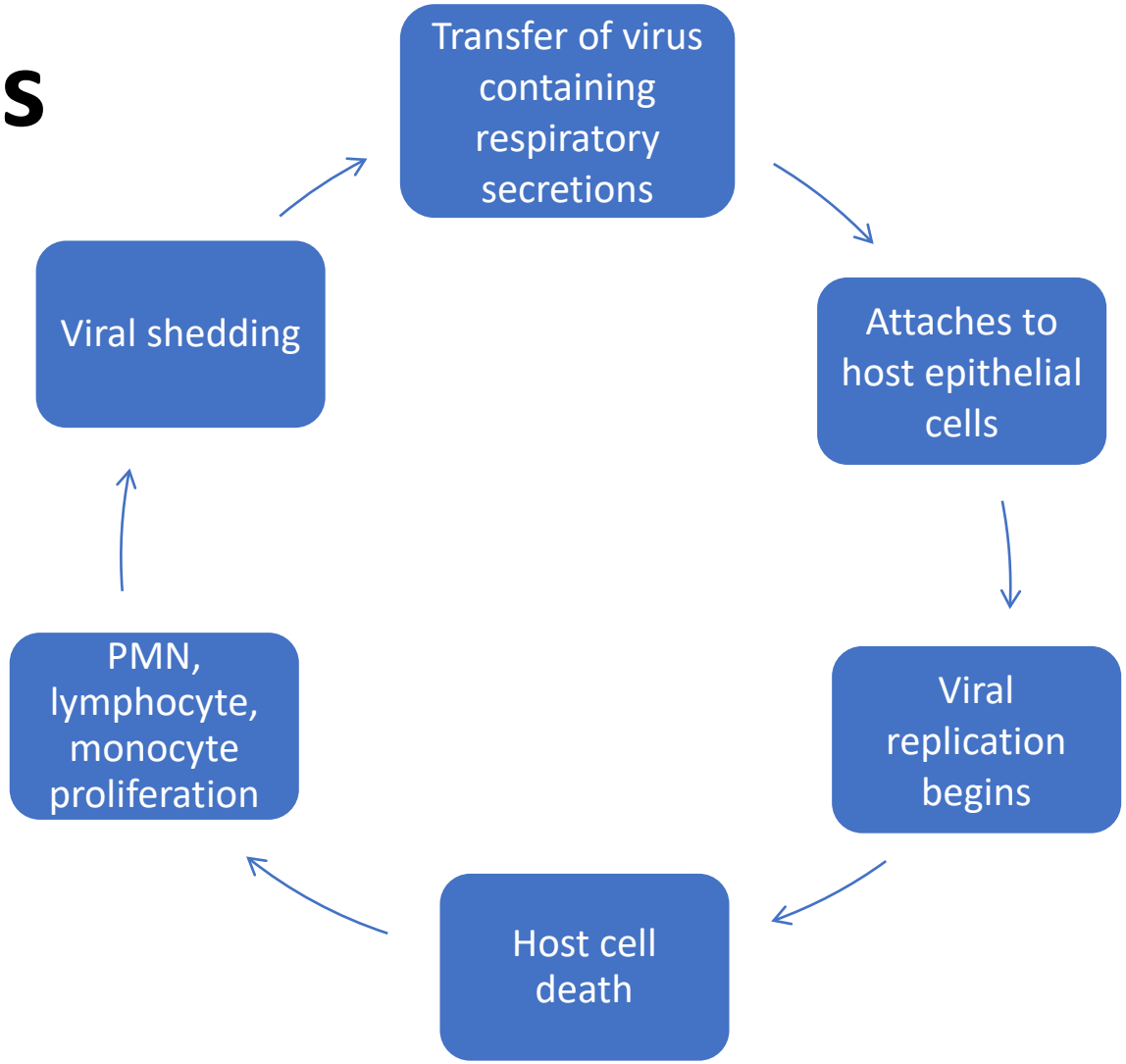


- Most patients = recovery without sequelae
- Some patients progress to severe and fatal influenza
  - Risk factors—more to come
  - Pneumonia
- Nonpulmonary complications
  - Exacerbation of chronic disease states
  - Myocardial infarction

IDSA Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. Figure republished from Ghebrehewet S, et al. *BMJ.* 2016;355:i6258, in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) License (creativecommons.org/licenses/by-nc/3.0/).

Cellular Pathogenesis





PMN, polymorphonuclear cells. Figure reproduced with permission of the © ERS 2020: European Respiratory Journal 45 (5) 1463-1478 doi: 10.1183/09031936.00186214. Published April 30, 2015; Bennett JE, et al. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Elsevier Inc; 2014.

Who Is at High Risk for Influenza Complications?

Individuals ≥50 years	**Asthma and chronic pulmonary disorders** (COPD, cystic fibrosis)	**Cardiovascular disorders** (congenital heart disease, congestive heart failure, coronary artery disease)
Individuals 6 through 59 months	**Immunocompromised** (disease state, iatrogenic)	**Renal or hepatic disorders**
Nursing home and long-term care residents	**Hematologic disorders** (sickle cell disease)	**Metabolic disorders** (inherited metabolic disorders, mitochondrial disorders)
BMI ≥40	**Neurologic and neurodevelopment conditions**	**Endocrine disorders** (diabetes mellitus)
American Indians, Alaska Natives	**Individuals 6 months through 18 years taking long-term aspirin- or salicylate-containing medications**	**Pregnancy or up to 2 weeks postpartum**

…Or, Who Is Not at Risk for Influenza Complications?

Grohskopf LA, et al. *MMWR Recomm Rep*. 2019;68(3):1-21.

Immunocompromised and Aged Populations

Immunocompromised disease states

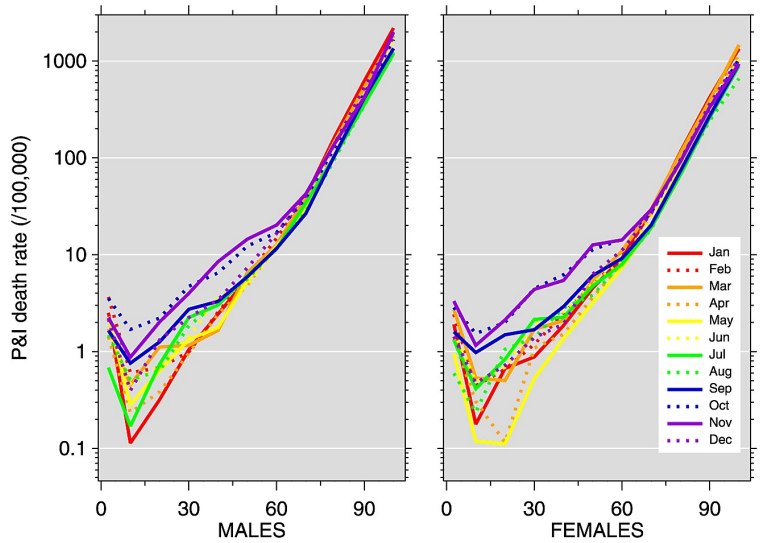
- HIV/AIDS
- Some cancers (eg, leukemia)

Iatrogenic immunosuppression

- Chemotherapy
- Radiation treatment for cancer
- Chronic corticosteroids
- Other medications

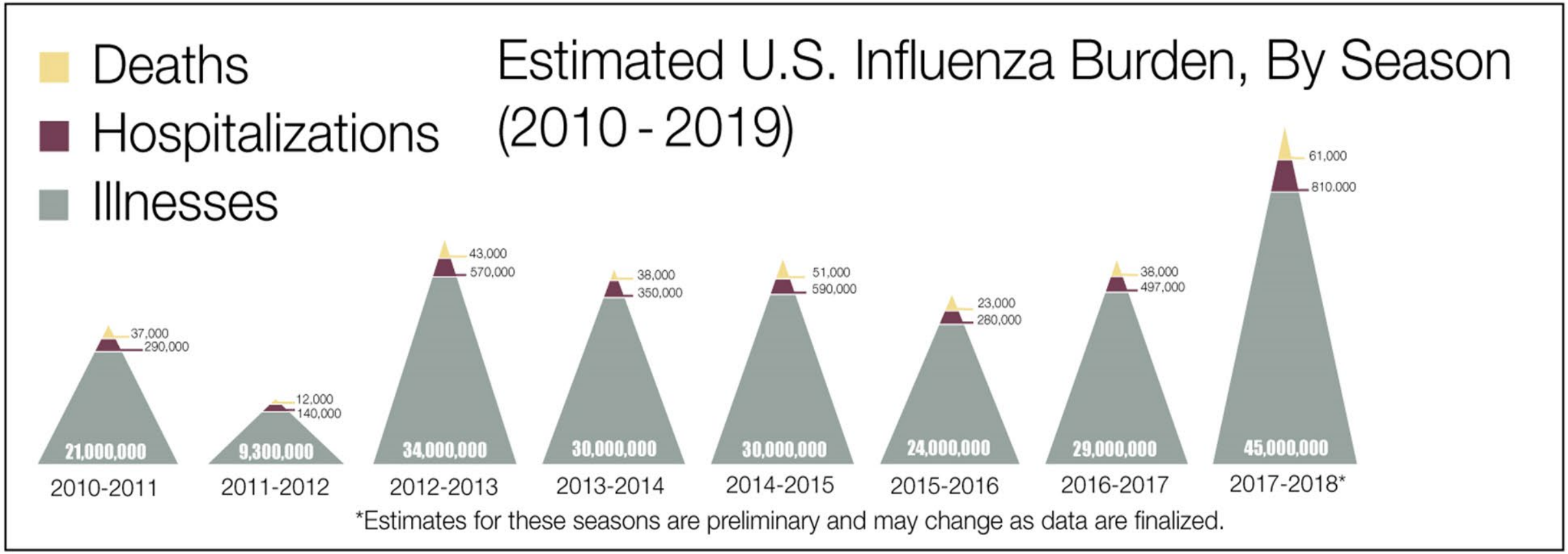
Age

- Influenza mortality is highest in the very young and the very old
- U-shaped mortality curve



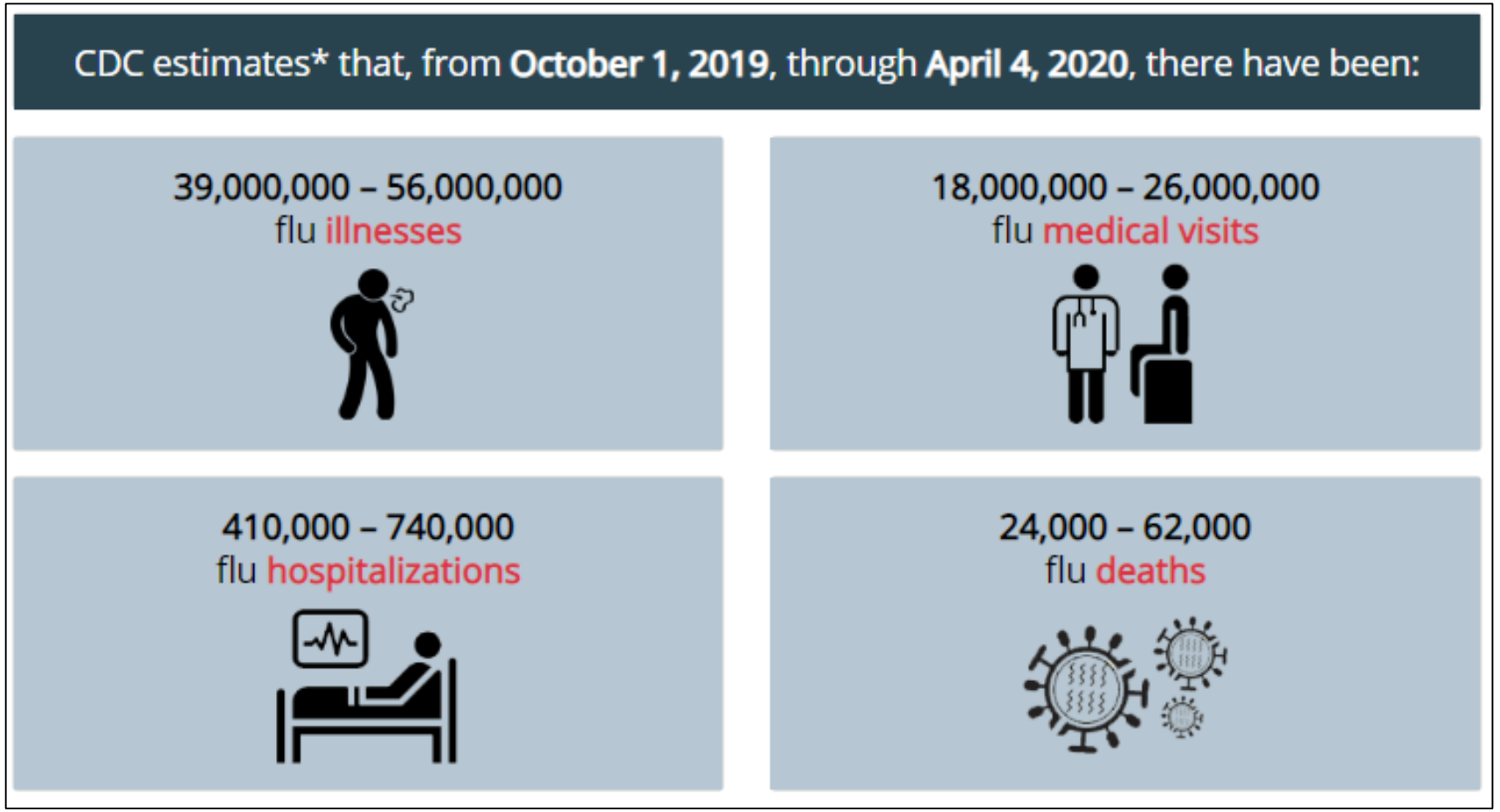
Grohskopf LA, et al. *MMWR Recomm Rep*. 2019;68(3):1-21; Figure republished from Nguyen AM, Noymer A. PLoS ONE. 2013;8(5):e64198, under the terms of the Creative Commons Attribution License.

Influenza Disease Burden



Disease burden of influenza. CDC. Reviewed April 17, 2020. Accessed August 27, 2020. cdc.gov/flu/about/burden/index.html

Influenza Disease Burden: 2019-2020



- Estimated average annual total economic burden in 2018 of influenza to the health care system and society was $11.2 billion ($6.3–$25.3 billion)
- Direct medical costs estimated to be $3.2 billion ($1.5–$11.7 billion)
- Indirect costs: $8.0 billion ($4.8–$13.6 billion)

CDC. Accessed August 27, 2020. cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm; Putri WC, et al. *Vaccine*. 2018:36(27):3960-3966.

Influenza Disease Burden: Pediatric Patients

- Half of influenza-related pediatric deaths occurred in otherwise healthy children
  - Antiviral given in approximately 50% of deaths
  - Two-thirds of deaths within 7 days of developing symptoms

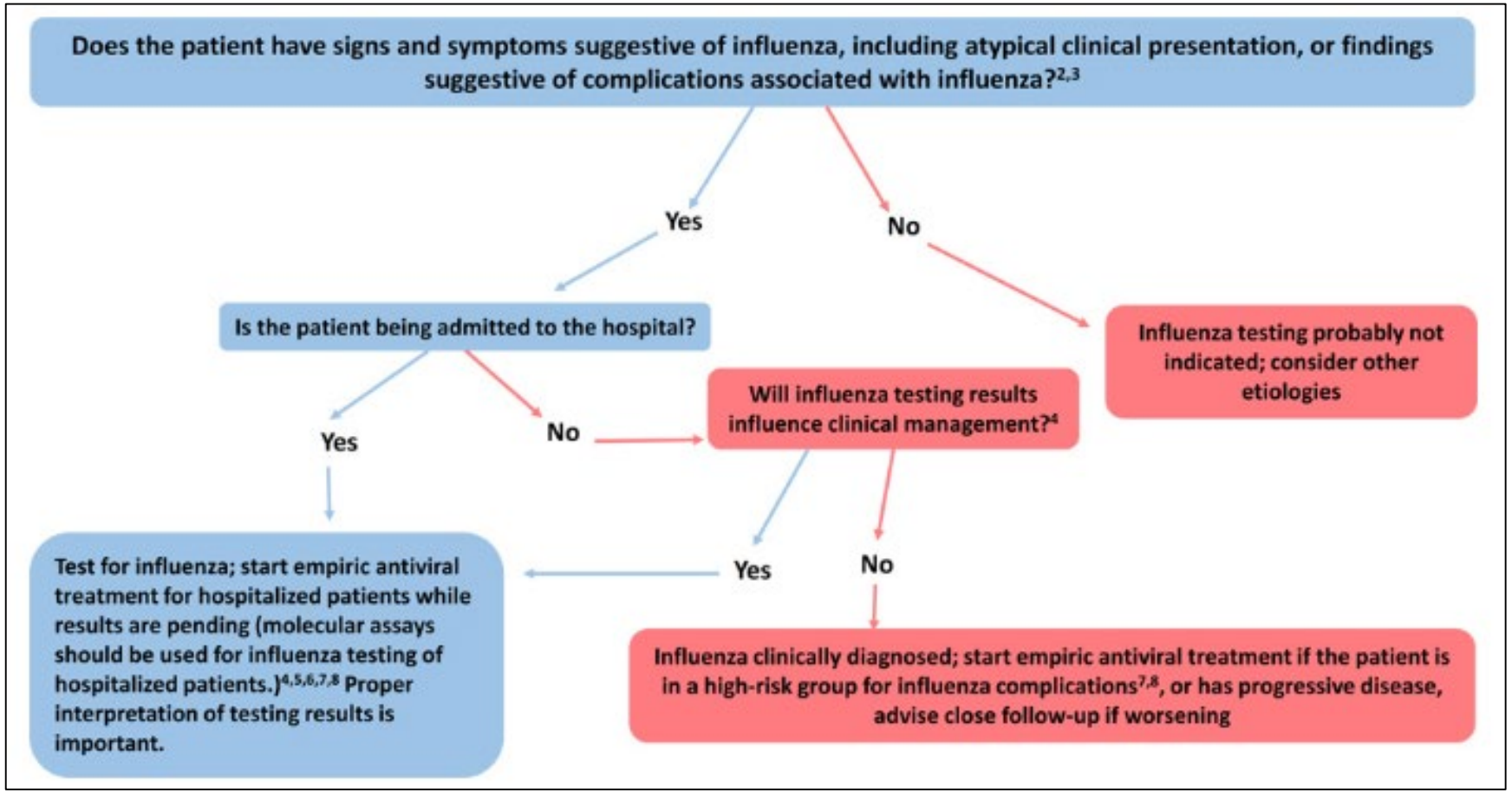
Season	Total Influenza-associated Pediatric Mortality
2016-2017	110
2017-2018	188
2018-2019	144
2019-2020	185

CDC Fluview Interactive. Accessed June 24, 2020. gis.cdc.gov/grasp/fluview/pedfludeath.html; Shang M, et al. *Pediatrics*. 2018;141(4):e20172918.

Influenza Testing and Treatment

CDC Guide When Influenza Viruses Are Circulating in the Community

Decisions about starting antiviral treatment ***should not wait for laboratory*** confirmation of influenza.



Influenza antiviral medications: summary for clinicians. CDC. Updated July 12, 2020. cdc.gov/flu/professionals/antivirals/summary-clinicians.htm; Guide for considering influenza testing when influenza viruses are circulating in the community. CDC. Updated March 4, 2019. Accessed August 27, 2020. cdc.gov/flu/professionals/diagnosis/consider-influenza-testing.htm

Which Patients Should Be Treated With Antivirals?

SHOULD start antiviral therapy **as soon as possible** for adults and children

- Hospitalized patients regardless of illness duration prior to hospitalization
- Outpatients with severe or progressive illness, regardless of illness duration
- Outpatients who are at high risk of complications (chronic medical conditions and immunocompromised)
- Children <2 years and adults ≥65 years
- Pregnant women and those within 2 weeks postpartum

CONSIDER antiviral therapy

- Outpatients (clinically stable and low risk for complications) with illness onset ≤2 days
- Outpatients who are household contacts of high-risk people
- Outpatients who are caregivers for high-risk people

Next, which antiviral should my patient receive?

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

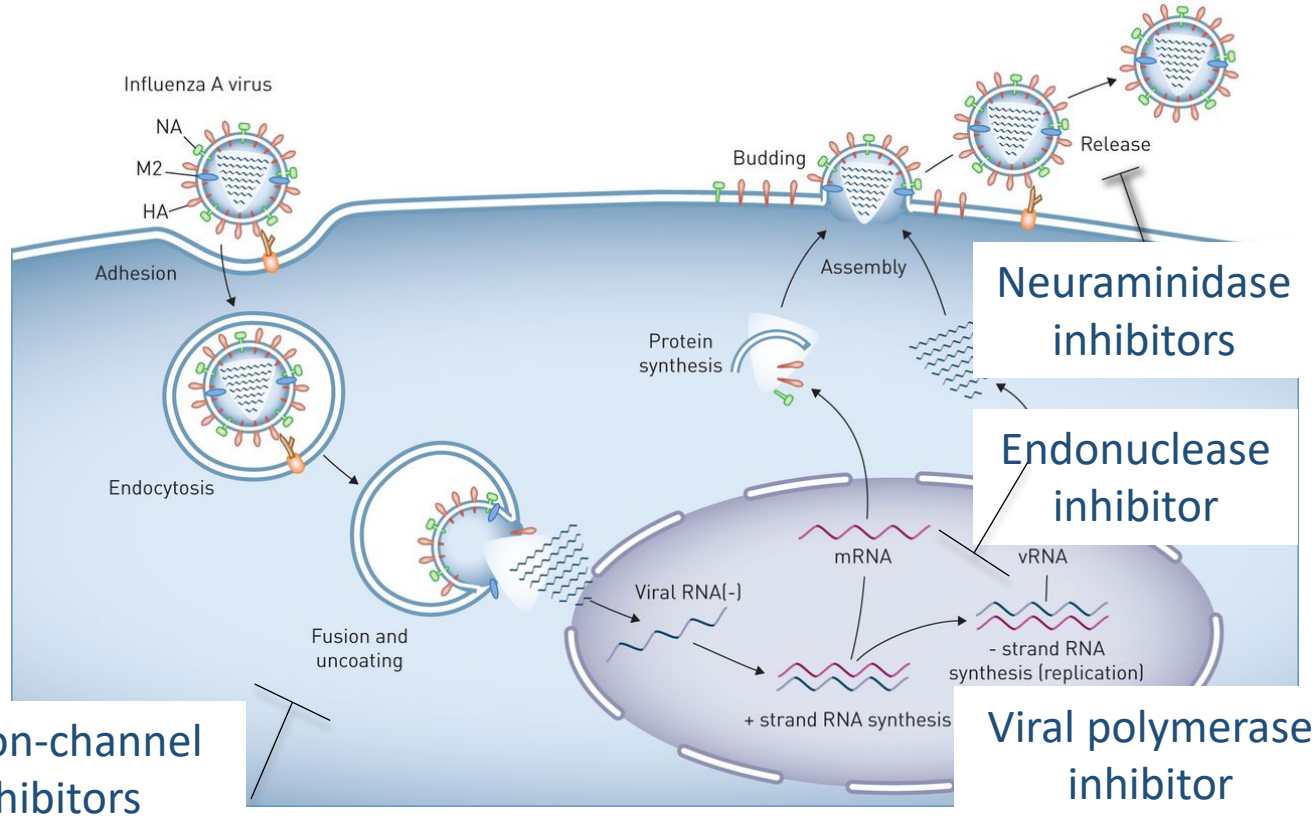
Influenza Antiviral Targets

FDA-approved therapies

- **Neuraminidase (NA) inhibitors:** oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapivab)
- **M2 ion-channel inhibitors:** amantadine (Symmetrel) and rimantadine (Flumadine)
- **Endonuclease inhibitor:** baloxavir (Xofluza)

Not FDA approved for influenza

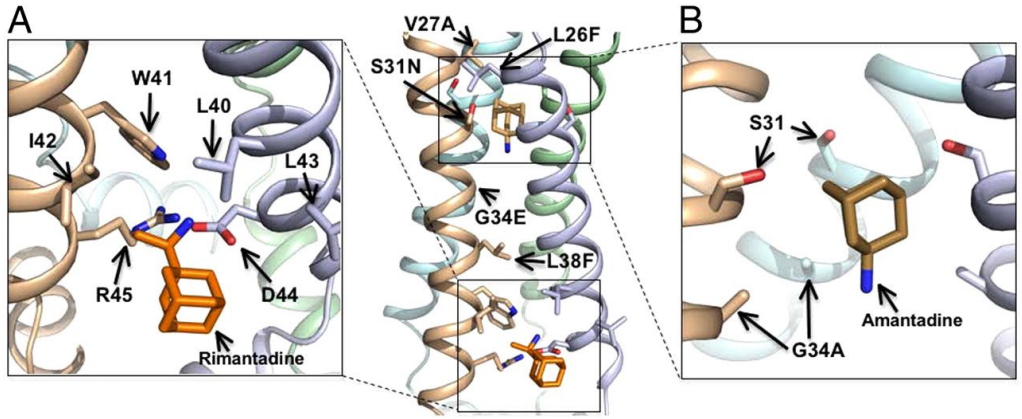
- **Viral polymerase inhibitor:** favipiravir



Herold S, et al. *Eur Respir J*. 2015;45(5):1463-1478; Xofluza. Prescribing information. Genentech; 2019.

M2 Ion Channel Inhibitors: Amantadine and Rimantadine

- Mechanism of action: prevent M2 channel from opening and subsequent fusion and uncoating to prepare for replication
- High rates of resistance in influenza A
  - 0.4% during 1994-1995
  - 12.3% during 2003-2004
  - 92% in 2005-2006
- No activity against influenza B
- Not recommended in current influenza treatment or chemoprophylaxis guidelines



Shin WJ, Seong BL. *Expert Opin Drug Discov*. 2019;14:153-168;

Figure reproduced from Rafal M, et al. *Proc Natl Acad Sci*. 2009;106(18):7379-7384, with permission from *PNAS*.

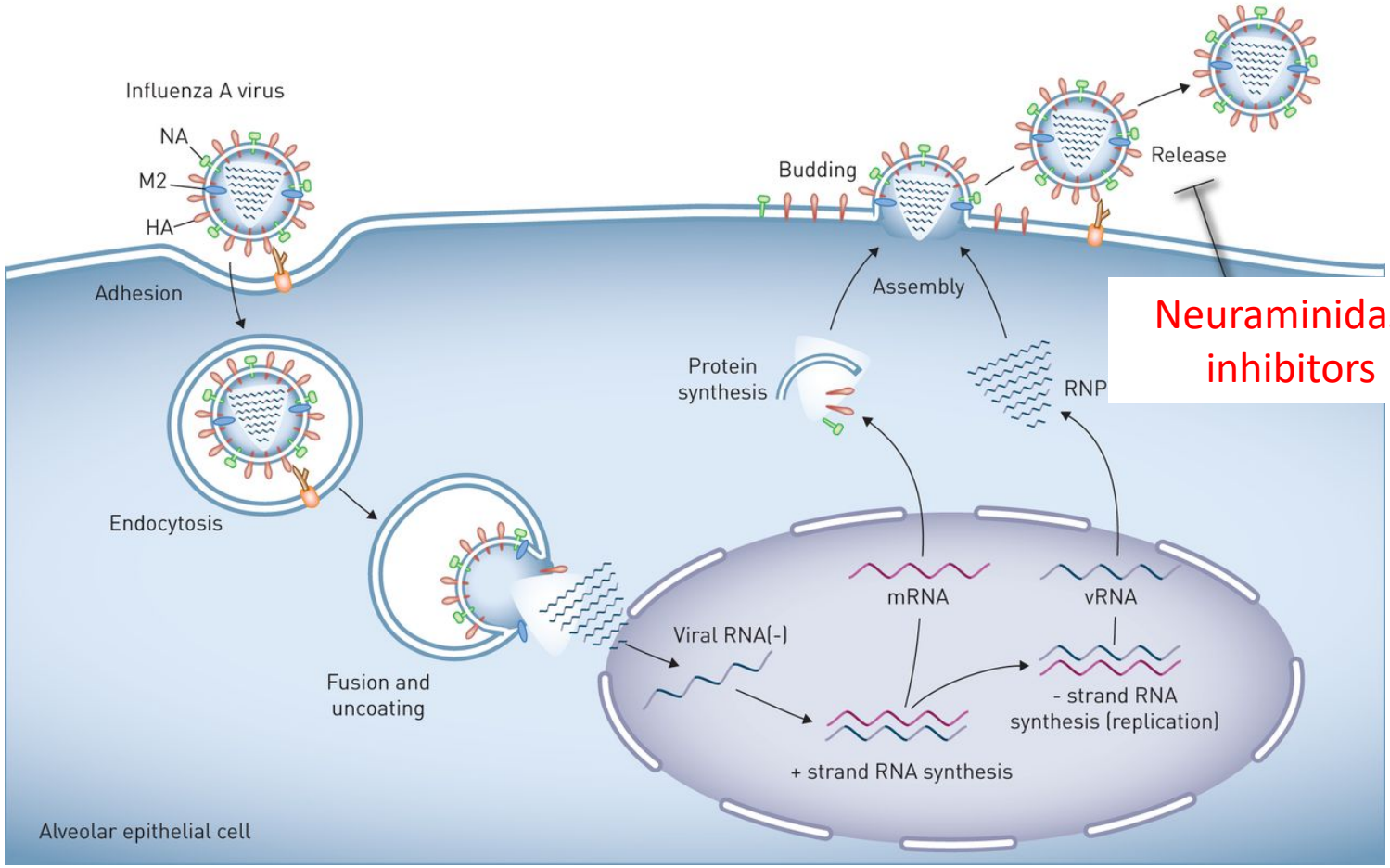
M2 Ion Channel Inhibitor Pharmacokinetics: Amantadine and Rimantadine

	Amantadine	Rimantadine
Dosing (adult, treatment)	200 mg daily OR 100 mg BID x 5 days Start within 48 hours of symptom onset	100 mg BID x 5-7 days Start within 48 hours of symptom onset
Absorption	Oral, well absorbed	Oral, well absorbed
Metabolism	None	Extensive hepatic metabolism
Excretion	Urine (90% unchanged drug)	Urine (<25% unchanged drug)
Drug interactions	Antihistamines, anticholinergics	None
Adverse effects	CNS (13%); GI (3%)	GI (9%)
Dose adjustments	Renal function <60 mL/min	Age ≥65 years Renal function <30 mL/min Severe liver impairment
Contraindications	Untreated acute angle glaucoma Hypersensitivity	Hypersensitivity
Special populations	FDA approval down to 1 year of age	FDA approval down to 1 year of age

Amantadine. Prescribing information. Vensun Pharmaceuticals; 2019; Flumadine. Prescribing information. Forest Pharmaceuticals; 2010.

NA Inhibitors: Oseltamivir, Zanamivir, Peramivir

- Mechanism of action: prevent neuraminidase cleavage and subsequent release of new virus
- NA is present in both influenza A and B subtypes
- Drug resistance is rare
  - May exhibit reduced virulence
  - Zanamivir may work for oseltamivir-resistant strains



Herold S, et al. *Eur Respir J*.2015;45(5):1463-1478; CDC. Accessed June 2, 2020. cdc.gov/flu/antivirals; McKimm-Breschkin JL, et al. *J Virol*. 1998;72:2456-2462; Goto H, et al. *Virology*. 1997;238:265-272; CDC. Accessed August 27, 2020. cdc.gov/flu/treatment/antiviralresistance.htm

Figure reproduced with permission of the © ERS 2020: European Respiratory Journal 45 (5) 1463-1478 doi: 10.1183/09031936.00186214. Published April 30, 2015.

NA Inhibitors: Oseltamivir, Zanamivir, Peramivir

	Oseltamivir	Zanamivir	Peramivir
Dosing (adult, treatment)	75 mg** BID x 5 days*	10 mg BID x 5 days*, space doses ≈12 hours	600 mg x 1
Absorption	Oral, well absorbed	Poor, must inhale	Poor, only intravenous
Metabolism	Hepatic to active metabolite	None	Minimal
Excretion	Urine	Urine	Urine
Drug interactions	None	None	None
Adverse effects	GI (15%) CNS (17%)	Sore throat (11%) Cough (16%)	Neutropenia (8%) Diarrhea (8%) Hyperglycemia (5%)
Dose adjustments	Renal ≤29 mL/min	None	Renal <49 mL/min
Contraindications	Hypersensitivity	Hypersensitivity, intubated patients—incompatibility	Hypersensitivity
Special populations	Peds ≤8 months	Peds ≥7 years	Peds ≥2 years

*Consider longer duration in severely ill or immunocompromised patients.

**Higher doses (150 mg BID) are NOT currently recommended even in severely ill or immunocompromised patients.

Tamiflu. Prescribing information. Genentech; 2019; Relenza. Prescribing information. GlaxoSmithKline; 2018; Rapivab. Prescribing information]. BioCryst Pharmaceuticals; 2020.

Oseltamivir Dosing Considerations in Special Populations

Pediatrics	• Weight-based dosing
Obesity	• 150 mg vs 75 mg BID studied in 155 adult patients • Oseltamivir carboxylate trough concentrations higher (501 ± 237 vs 342.6 ± 193 ng/mL) in 150 mg group • Viral clearance at day 5 were the same (44.7% vs 40.2%) • Culture negativity, RNA decline rate, fever duration, O_2 supplementation need, and hospitalization similar
CRRT	• Filtration of oseltamivir carboxylate estimated from ultrafiltration rate • Appears to be increased exposure in patients receiving CRRT (117 vs 282 ng/mL) • Antiviral efficacy did not equate to clinical efficacy
ECMO	• 150 mg vs 75 mg BID studied in 7 patients receiving venovenous ECMO • Comparable oseltamivir carboxylate trough and AUC (1029 ± 478 ng/mL and 9.0 ± 4.5 mcg*h/mL, respectively) to non-critically ill patients

Lee N, et al. *Clin Infect Dis*. 2013;57(11):1511-1519; Ariano RE, et al. *CMAJ*. 2010; 82(4):357-363; Lemaitre F, et al. *Ther Drug Monit*. 2012;34(2):171-175; Tamiflu. Prescribing information. Genentech; 2019.

Zanamivir and Peramivir Considerations

Zanamivir

- Caution if patient has underlying respiratory disease due to risk of bronchospasm
- Disk inhaler requires good inspiratory technique
- Postmarketing reports of sporadic, transient neuropsychiatric events
- May be considered for oseltamivir-resistant virus serotypes
  - Defined by epidemiology of circulating strains

Peramivir

- 2009 influenza season
  - Emergency Use Authorization in the US for patients with pandemic A (H1N1) virus
  - Dosed 600 mg daily for a median duration of 6 days
- Studied in hospitalized patients and/or patients with complicated influenza, but a clinical benefit could not be demonstrated
- Some clinicians may consider, particularly in patients unable to tolerate or absorb oral oseltamivir

Relenza. Prescribing information. GlaxoSmithKline; 2018; Yu Y, et al. *Clin Infect Dis*. 2012;55(1):8-15; de Jong MD, et al. *Clin Infect Dis*. 2014;59(12):e172-e185; Yeh CY, et al. *J Microbiol Immunol Infect*. 2018;51(6):697-704; Yoo JW, et al. *J Med Virology*. 2015;2015;87:1649-1655; Noel ZR, et al. *J Intens Care Med*. 2017;32(10):574-577.

NA Inhibitors: Oseltamivir, Zanamivir, Peramivir

- Demonstrated mortality benefit and reduces risk of hospitalization
- Oseltamivir preferred at a dose of 75 mg PO BID x 5 days
  - Most clinical experience
  - Widest age range
- Peramivir for critically ill patients who cannot take oseltamivir
- Zanamivir for patients unable to take oral oseltamivir
  - Consider if concern for oseltamivir resistance (very rare)

Meta-analyses demonstrate benefit in treatment with NA inhibitors versus no treatment among individuals with influenza

Decreased odds of mortality in hospitalized patients

- ✓ General population
- ✓ Children
- ✓ Pregnant women

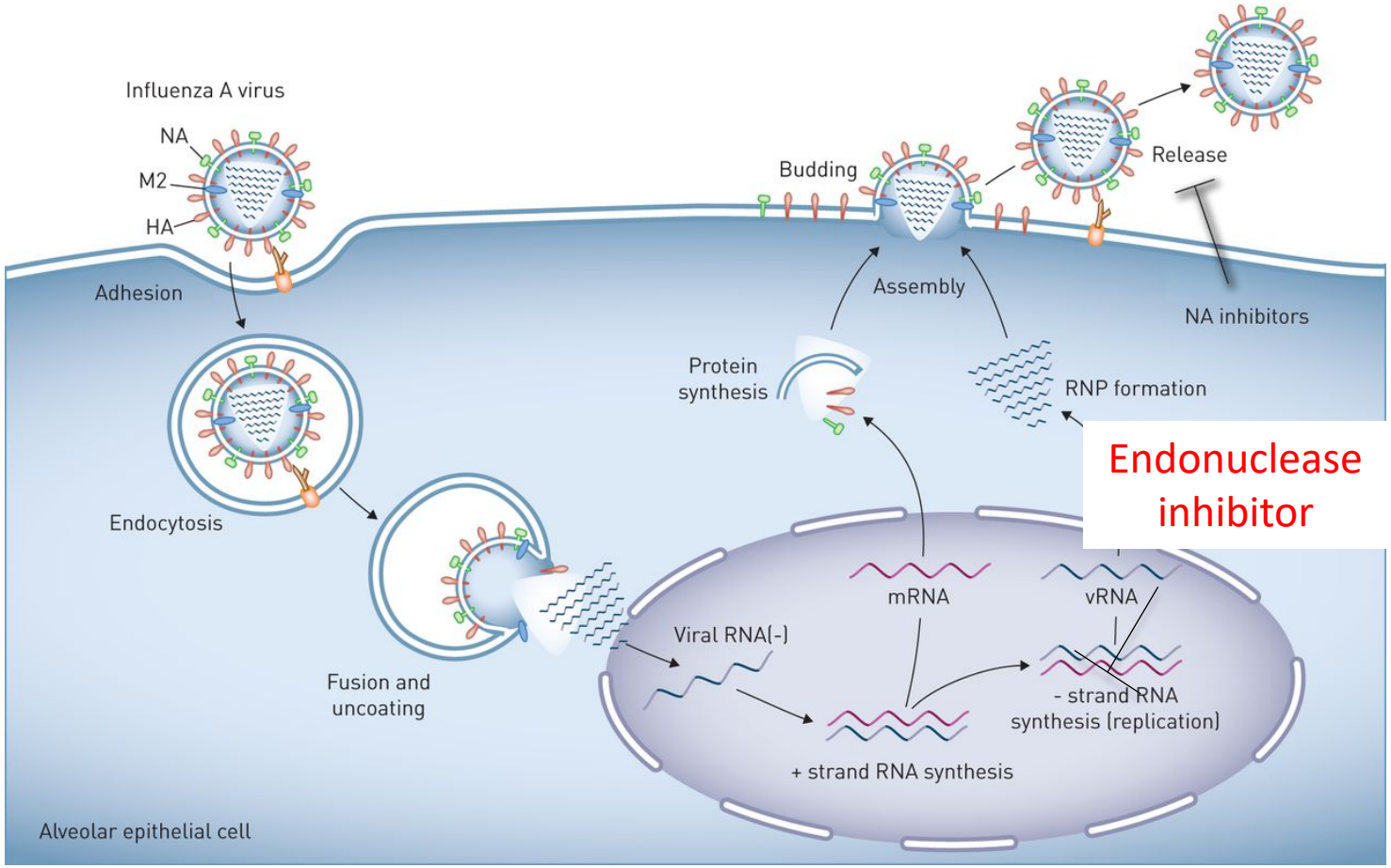
Decreased hospitalization risk

- ✓ General population

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

Baloxavir

- Mechanism of action: Endonuclease inhibitor ➔ RNA transcription, virus replication interrupted
- Activity against wide range of influenza viruses (susceptibility to A, B, C and D), including NA-resistant strains and avian strains (H7N9 and H5N1)
- Single-dose therapy for uncomplicated influenza pneumonia and high-risk patients



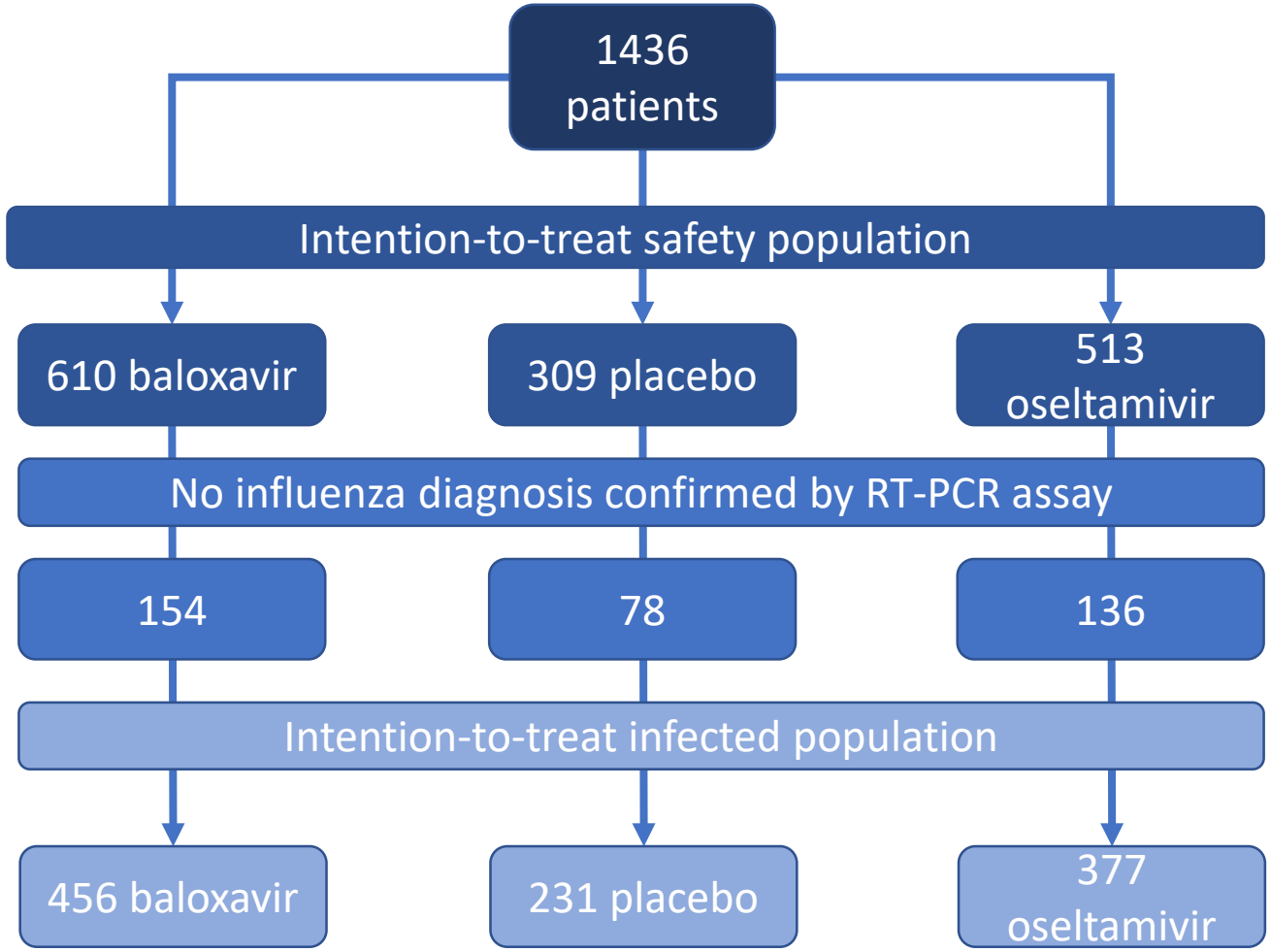
Herold S, et al. *Eur Respir J*. 2015;45(5):1463-1478; Taniguchi K, et al. Scientific reports 9.1 (2019): 1-12; Taniguchi K, et al. Inhibitory Effect of S-033188/S-0a33447, a novel inhibitor of influenza virus cap-dependent endonuclease, against highly pathogenic avian influenza virus A/H5N1. Poster presentation at ECCMID, April 2017. Xofluza. Prescribing information. Genentech; 2019. Mishin V, et al. *Emerging Infectious Diseases*. 2019;25(10):1969-1972. Figure reproduced with permission of the © ERS 2020: European Respiratory Journal 45 (5) 1463-1478 doi: 10.1183/09031936.00186214. Published April 30, 2015.

Baloxavir

Dosing (adult, treatment)	40 mg (weight 40 to <80 kg), 80 mg (≥80 kg) single dose (2 tablets taken at the same time)
Absorption	Oral, well absorbed
Metabolism	Hepatic to active metabolite
Excretion	Feces (80%) and urine (14%)
Drug interactions	Avoid administration with dairy, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (eg, calcium, iron, magnesium, selenium, zinc)
Adverse effects	GI (1%-10%)
Dose adjustments	None
Contraindications	Hypersensitivity (eg, anaphylaxis, angioedema, urticaria, erythema multiforme) to baloxavir or any component of the formulation • Hypersensitivity reactions have been reported

Xofluza. Prescribing information. Genentech; 2019.

Baloxavir: CAPSTONE-1



- Enrolled outpatients 12-64 years old with influenza-like illness (ILI)
  - ILI = fever + one systemic symptom and one moderate-severity respiratory symptom
  - Symptom duration ≤48 hours
- Randomized 2:2:1 to baloxavir, oseltamivir, or matching placebos
  - All patients received 5-day regimen
- Primary end point: time to symptom resolution
- Significant secondary end points: time to cessation of viral shedding

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

Baloxavir: CAPSTONE-1

Time to alleviation of influenza symptoms

- The median time to alleviation of symptoms was 53.7 hours (95% CI, 49.5-58.5) with baloxavir, as compared with 80.2 hours (95% CI, 72.6-87.1) with placebo (*P* <0.001)

Rapid viral suppression

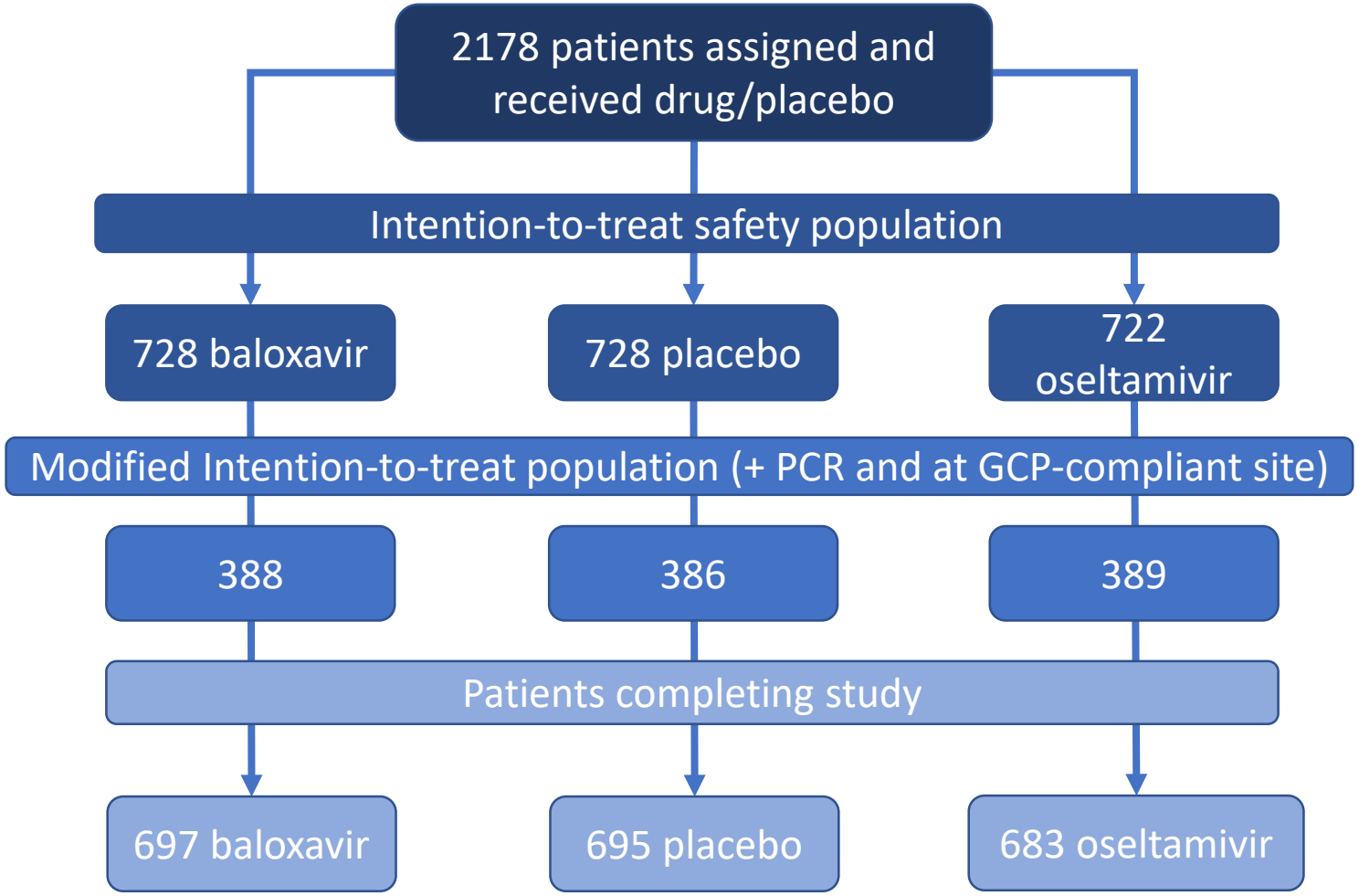
- Change from baseline in influenza infectious viral load over time
- Baloxavir was associated with significantly more rapid declines in infectious viral load than placebo or oseltamivir

Reduced viral shedding

- Time to cessation of infectious virus detection over time
- The median duration of infectious virus detection was shorter in the baloxavir (24 hours) than oseltamivir (72 hours, *P* <0.001) groups

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

Baloxavir: CAPSTONE-2

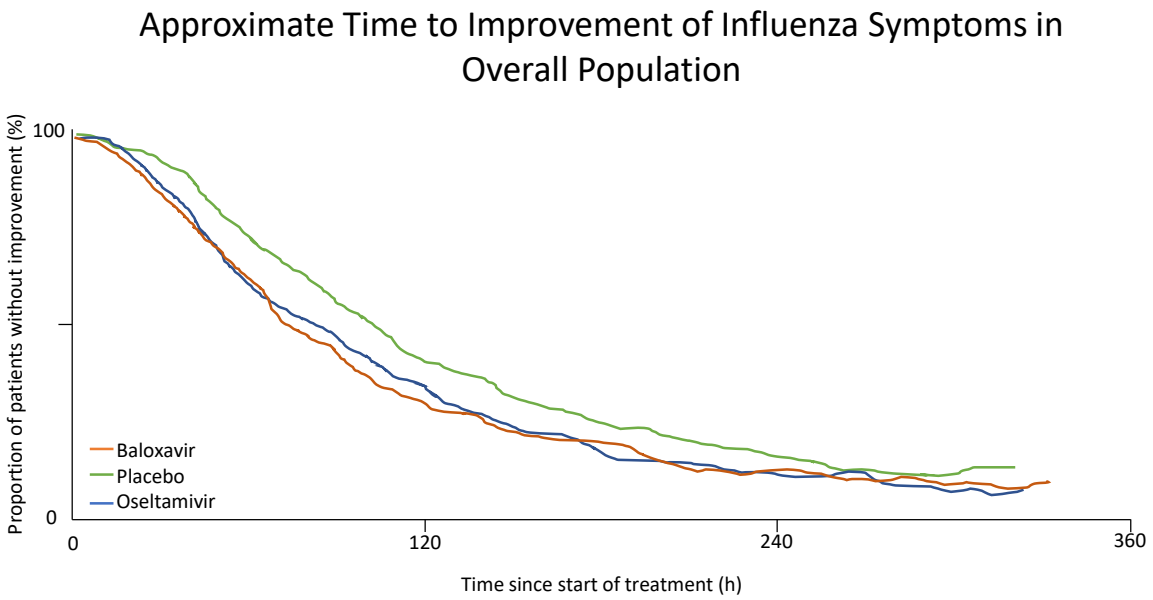


GCP, good clinical practice.

Ison MG, et al. *Lancet Infect Dis*. 2020;S1473-3099(20)30004-9.

- Enrolled outpatients 12 years or older with influenza-like illness (ILI) who were at **high risk of developing influenza complications**
  - ILI = fever + one systemic symptom and one moderate severity respiratory symptom
  - Symptom duration ≤48 hours
  - **Notable high-risk complications: asthma, chronic lung disease, and age >65 years**
- Randomized 1:1:1 to baloxavir, oseltamivir, or matching placebos
  - All patients received 5-day oseltamivir regimen
- Primary end point: time to symptom resolution of baloxavir vs placebo
- Significant secondary end points:
  - Time to symptom resolution: baloxavir vs oseltamivir
  - Time to cessation of viral shedding
  - Frequency of baloxavir resistance mutations

Baloxavir: CAPSTONE-2



- 48% (557/1163) patients with influenza A, 42% (484/1163) patients with influenza B
- Asthma or CLD in 39% (456/1163), endocrine disorders in 33% (382/1163), and age >65 years in 37% (319/1163) patients
- Time to symptom relief was shorter in baloxavir than placebo by 29.1 h (*P* <0.001)
  - Difference significantly different up to 36 hours of drug initiation
- Time to symptom relief similar between baloxavir and oseltamivir overall (≈81 hours)
  - Baloxavir shorter time to symptom relief in influenza B (27.1 hours shorter, *P* = 0.025)

CLD, chronic lung disease.

Ison MG, et al. *Lancet Infect Dis*. 2020;S1473-3099(20)30004-9. Figure is an approximate recreation.

Baloxavir: CAPSTONE-2

- Baloxavir was associated with a significantly faster decline in infectious virus titers than were placebo and oseltamivir
- Time to cessation of infectious virus detection shorter in baloxavir group than placebo and oseltamivir by 48 hours
- Emergence of resistant mutant occurred in subset of patients (9% influenza A and 1% influenza B)
  - Unknown if clinical significance of this resistance since not associated with emergence of symptoms
  - Occurred between day 6 and 9 when baloxavir concentrations lowest
  - Further investigation is needed to determine if clinically significant, additional baloxavir is necessary, or if dual-mechanism therapy is important

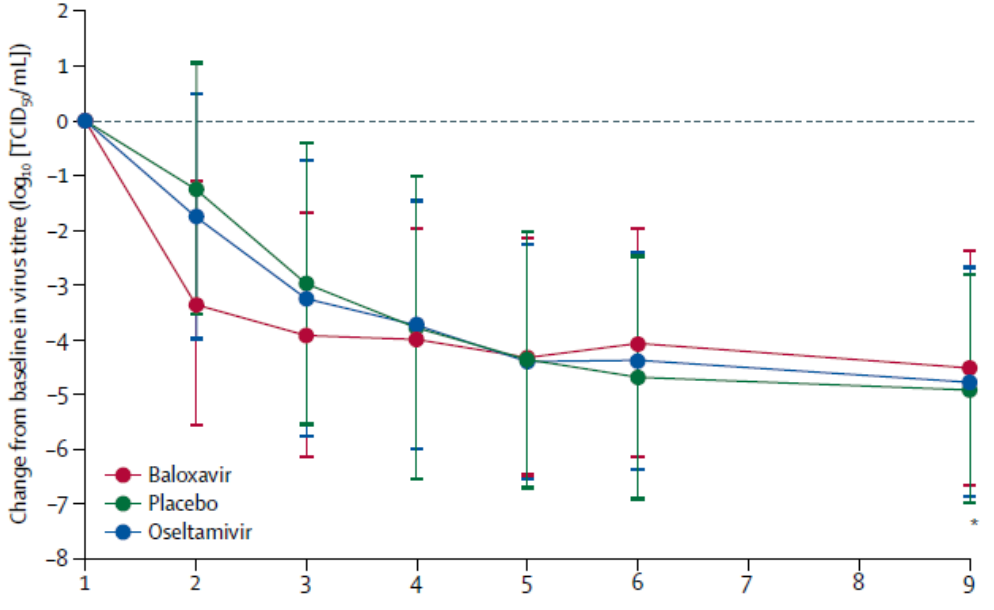


Figure 3: **Change from baseline in virus titre in the modified intention-to-treat population**
Data are mean reduction with error bars indicating SD. Days 4 and 6 were optional visits, and there were no visits on days 7 and 8 Day 2: p<0·0001 for baloxavir versus placebo and p<0·0001 for baloxavir versus oseltamivir. Day 3: p<0·00001 for baloxavir versus placebo and p<0·0024 for baloxavir versus oseltamivir. $TCID_{50}$=50% tissue culture infectious dose.

Baloxavir in Pediatrics

miniSTONE-2 (multicenter, randomized, double-blind, placebo-controlled phase 3 study of oral baloxavir in influenza)	
Study population	Children aged 1-<12 years, otherwise healthy, with influenza
Intervention	Baloxavir 2 mg/kg for wt <20 kg and 40 mg for wt ≥20 kg
Comparator	Oseltamivir per package insert x 5 days
Enrollment	Fever and one respiratory symptom (cough or nasal congestion) within 48 hours
Exclusion	Severe symptoms requiring hospitalization and no comorbidities
Primary end point	Adverse effects related to the treatment medication
Secondary end point	Time to symptom alleviation and return to afebrile state
Results: Safety	Baloxavir 2.6% (3/115) vs oseltamivir 8.6% (5/58) (*P* >0.05) Most common: vomiting and diarrhea (10.4% baloxavir vs 17.2% oseltamivir)
Results: Efficacy	138.1 hours for baloxavir vs 150.0 hours for oseltamivir (*P* >0.05) time to symptom resolution 41.2 hours for baloxavir vs 46.8 hours for oseltamivir (*P* >0.05) for fever resolution

Open-label phase 3 study with granule formulation

- 33 patient case series for children 10- <20 kg (n=21) and <10 kg (n=12) receiving 1 mg/kg baloxavir
- No deaths, serious adverse effects, or adverse drug reactions reported
- Time to illness alleviation = 45.3 (28.5-64.1) hours with rapid viral reduction (4-log decrease by day 2)

Baker J, et al. *Pediatr Infect Dis J.* 2020;39(8):700-705; Yokoyama T, et al. *Pediatr Infect Dis J.* 2020;39(8):706-712.

Baloxavir: BLOCKSTONE and Influenza Prophylaxis

- Enrolled household contacts of influenza-positive index patients in Japan
  - Excluded pregnant, immunocompromised household contacts
- Randomized 1:1 to receive single-dose baloxavir or placebo

  >95% of index cases = influenza A
- Primary end point: laboratory-confirmed clinical influenza (RT-PCR, fever, and 1 respiratory symptom)
  - >75% of household contacts received baloxavir within 24 hours
  - Adjusted risk ratio = 0.14 (95% CI, 0.06-0.30); *P* <0.001)

	Baloxavir	Placebo
Laboratory-confirmed influenza	7/374 (1.9%)	51/375 (13.6%)

  - NNT = 9 ➔ Treat 9 patients to prevent 1 additional influenza case
- Similar safety profile

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

Baloxavir Summary

- Novel mechanism of action with activity against wide range of influenza viruses, including NA-resistant strains and avian strains (H7N9 and H5N1)
- Single-dose therapy for uncomplicated influenza pneumonia and for patients with high risk for complications from influenza infection
- Similar time to clinical symptom resolution as oseltamivir
- May reduce time to viral shedding by rapidly reducing viral load
- New clinical trial demonstrating prophylaxis efficacy compared to placebo
- FDA has accepted NDA and sNDAs for baloxavir in the treatment of children, new granules for oral suspension formulation, and postexposure prophylaxis indication
- CDC treatment guidance: Oral oseltamivir is the recommended antiviral for patients with severe, complicated, or progressive illness who are not hospitalized, and for hospitalized influenza patients

FDA accepts Roche's New Drug Application for Xofluza (baloxavir marboxil) for the treatment of influenza in children. News release. Roche; March 27, 2020. Accessed April 14, 2020. roche.com/investors/updates/inv-update-2020-03-27.htm

Summary of Treatment Options

	Route	Indication for treatment of acute, uncomplicated influenza	Indication for prophylaxis
Oseltamivir*	Oral capsules or suspension	Aged **≥2 weeks**; symptomatic ≤48 hours	Aged **≥1 year**
Zanamivir	Oral inhalation	Aged **≥7 years**; symptomatic ≤2 days	Aged **≥5 years**
Peramivir	IV	Aged **≥2 years**; symptomatic ≤2 days	N/A
Baloxavir	Oral tablets	Aged **≥12 years**; symptomatic ≤48 hours Patients otherwise healthy, or at high risk of developing influenza-related complications	N/A

*CDC and the American Academy of Pediatrics recommend use for treatment in infants aged <14 days and for prophylaxis in infants aged 3 months to 1 year.

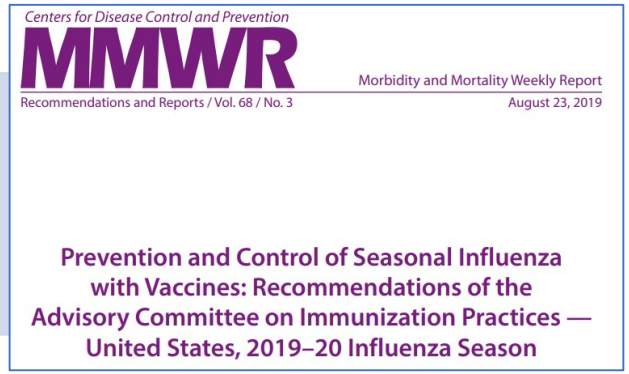
Tamiflu. Prescribing information. Genentech; 2019; Relenza. Prescribing information. GlaxoSmithKline; 2018; Rapivab. Prescribing information. BioCryst Pharmaceuticals, Inc; 2020; Xofluza. Prescribing information. Genentech; 2019.

Summary of Treatment Options

	Adult Dosing	Usual Treatment Duration	Dose Adjustments	Adverse Effects
Oseltamivir	75 mg enterally twice daily	5 days	Renal impairment dose adjustments	Nausea, vomiting, headache Postmarketing reports of serious skin reactions and sporadic, transient neuropsychiatric events
Zanamivir	2 inhalations twice daily	5 days	Not recommended for use with underlying respiratory disease	Bronchospasm, sinusitis, dizziness Postmarketing reports of serious skin reactions and sporadic, transient neuropsychiatric events
Peramivir	600 mg IV	Once	Renal impairment dose adjustments	Diarrhea Postmarketing reports of serious skin reactions and sporadic, transient neuropsychiatric events
Baloxavir	40-80 kg: 40 mg orally ≥80 kg: 80 mg orally	Once	None	Diarrhea No adverse effects more common than placebo in clinical trials

Influenza antiviral medications: summary for clinicians. CDC. Updated August 10, 2020. Accessed August 27, 2020. cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Influenza Prophylaxis



Vaccinate

- All patients 6 months and older without contraindication (this does not include an egg allergy)

CDC Guidance

- May consider for high-risk patients following exposure who cannot receive vaccine (or within first 2 weeks following vaccine); severe immune deficiencies who might not respond to vaccine following exposure
- Oseltamivir or zanamivir

IDSA Guidance

- Duration of season: May consider for high-risk and highest-risk (eg, transplant, hematopoietic stem cell transplant) patient who cannot receive vaccine
- Short term: May consider for high-risk patients for whom vaccine not yet administered when influenza activity detected; close contacts of high-risk patients unable to take chemoprophylaxis
- Oseltamivir or zanamivir

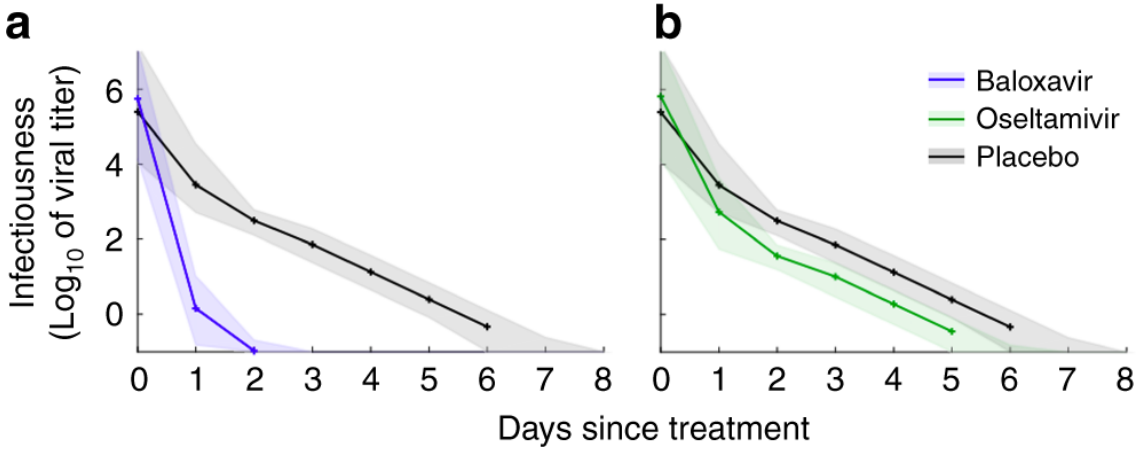
Grohskopf LA, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2019–20 Influenza Season. *MMWR Recomm Rep.* 2019;68(No. RR-3):1-21; Influenza antiviral medications: summary for clinicians. CDC. Updated August 10, 2020. Accessed August 27, 2020. cdc.gov/flu/professionals/antivirals/summary-clinicians.htm; Uyeki TM, 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):e1-e47.

Benefits of Antiviral Therapy

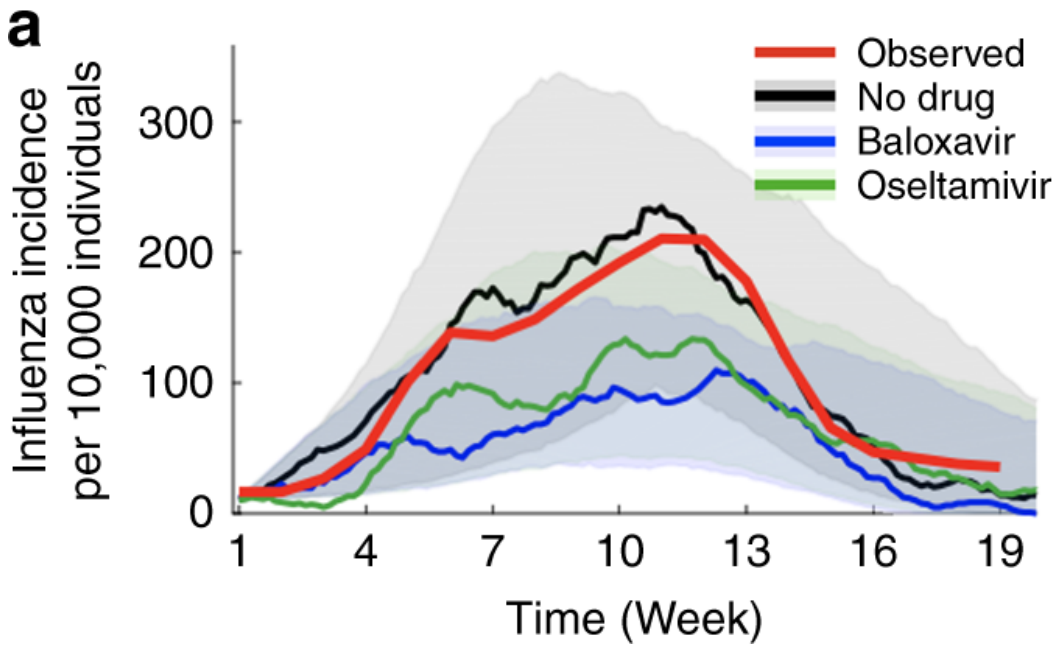
- Reduces duration of fever and symptoms
- Reduces risk of complications
  - Bronchitis
  - Pneumonia
  - Respiratory failure
- Reduces hospital admissions
- Reduces mortality in high-risk populations
- Reduces shedding and slows transmission

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

Antiviral Therapy Mitigating a Pandemic



Reduction of infectiousness model.
(A) with baloxavir and (B) with oseltamivir compared with placebo. Model assumes patients treated within 48 hours of symptom onset



Mitigation of influenza epidemic through treatment. Model of influenza incidence based on 2017/18 US surveillance data with and without treatment of 30% of cases with baloxavir (blue) or oseltamivir (green)

The Role of the Health-System Pharmacist

- Identifying patients at risk for influenza and influenza-like illness
  - Challenge in 2020-2021 influenza season with overlap of COVID-19 illness
- Initiating early antiviral therapy
  - Antivirals are indicated for symptoms less than 48 hours, but may be used beyond that time in select patients
- Oseltamivir vs baloxavir
  - Oseltamivir and baloxavir data available in hospitalized patients
  - Convenience and compliance with single-dose baloxavir
  - Location of treatment (inpatient vs outpatient vs ED vs community pharmacy?)
    - Testing location and pharmacist testing capabilities
    - Reducing interaction between patient and health care providers/health care site
- Oseltamivir PLUS baloxavir?
  - 2 patient case series where both were given in critically ill patients
  - Ongoing trials to evaluate this

Ntem-Mensah AD, et al. *Open Forum Infect Dis.* 2019;6(suppl 2):772.
Shah S, et al. *J Antimicrob Chemother*. 2020;dkaa252. doi:10.1093/jac/dkaa252

Counseling Patients

- Antivirals are not a replacement for influenza vaccination; antivirals do not stop the spread of influenza to others
- Initiate therapy as soon as possible
- Counseling pearls:

	Oseltamivir	Baloxavir
Medication administration	May be taken with or without food; take with food if causing nausea	Avoid administration with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements
Common adverse effects	Nausea, vomiting, diarrhea; headache	Diarrhea
Special patient population considerations	Elderly patients may have more pronounced adverse effects Oral capsules may be opened and mixed with sweetened liquid	Elderly patients may have more pronounced adverse effects

Tamiflu. Prescribing information. Genentech; 2019; Xofluza. Prescribing information. Genentech; 2019.

Conclusion

- Influenza disease causes significant morbidity and mortality
- Heightened awareness of the infectious nature of respiratory diseases will likely drive more patients to seek care and treatment
- Treatment with neuraminidase inhibitors is often delayed but works best when given early
- Oral oseltamivir, inhaled zanamivir, IV peramivir, and oral baloxavir recommended for the treatment of influenza
- Initiating treatment reduces mortality, hospitalization, viral replication, and viral shedding with important implications to health care systems
- Pharmacists play an important role in ensuring the appropriate use of these antiviral medications and counseling patients
- Complexities with COVID-19… be aware coinfection can occur, test for both, and treat early if you have a suspicion

Additional Resources

- CDC Influenza Resources
  - cdc.gov/flu
- IDSA Influenza Treatment Guidelines
  - 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 [published correction appears in *Clin Infect Dis*. 2019;68(10):1790]. *Clin Infect Dis*. 2019;68(6):e1-e47.
- Influenza Review Article
  - Krammer F, Smith GJD, Fouchier RAM, et al. Influenza. *Nat Rev Dis Primers.* 2018;4(1):3.

Thank you!