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Managing Influenza:

The Struggle is Real!

This continuing education activity is provided by

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

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Learning Objectives

Upon successful completion of this activity, participants should be better able to:

- Differentiate influenza from other respiratory illnesses by utilizing evidence-based diagnostic recommendations and best practices.
- Implement the use of antivirals for the treatment of influenza based on patient characteristics, as well as the treatment's efficacy and safety.
- Examine how the use of antiviral prophylaxis can reduce the spread of influenza infection.

Update on Flu Epidemiology

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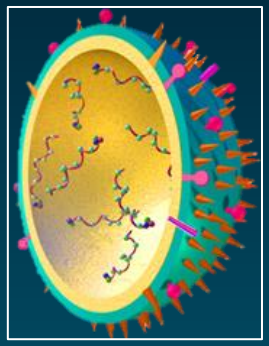
Disclosures

- *Consulting Fee:* Bayer, GlaxoSmithKline, Sanofi Pasteur
- *Speakers Bureau:* Sanofi Pasteur

History of Influenza



- **Felt to be due to the "influence of the stars"**
- **Epidemics every 1 to 3 years for the past 400 years**
- **Pandemics ("worldwide epidemics")**
  - Occur less often
  - First in 1590, 31 since then; last major pandemic occurred in 1977 (H1N1 in 2009)
  - 1918-1919: 21 million deaths worldwide; >500,000 deaths in the United States alone

The College of Physicians of Philadelphia. Accessed March 22, 2021. https://www.historyofvaccines.org/content/articles/influenza-pandemics

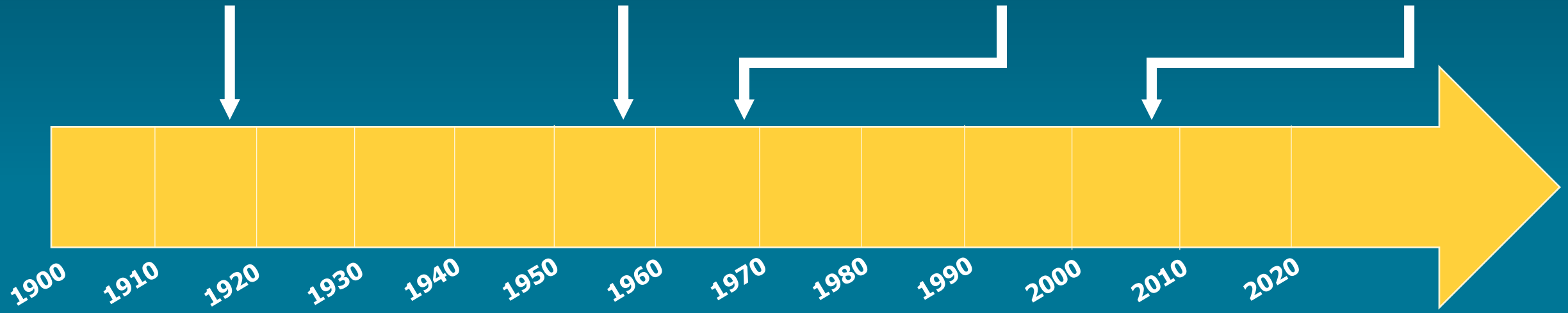
Flu Pandemics in the 20th and 21st Centuries

1918 – H1N1
~50-100 million deaths

1957 – H2N2
~1-2 million deaths

1968 – H3N2
~1 million deaths

2009 – H1N1
>12,700 deaths



Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/pandemic-resources/basics/past-pandemics.html

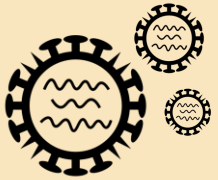
2019-2020 US Influenza Season*: Preliminary Burden Estimates

39 to 56 million
flu illnesses

18 to 26 million
flu medical visits

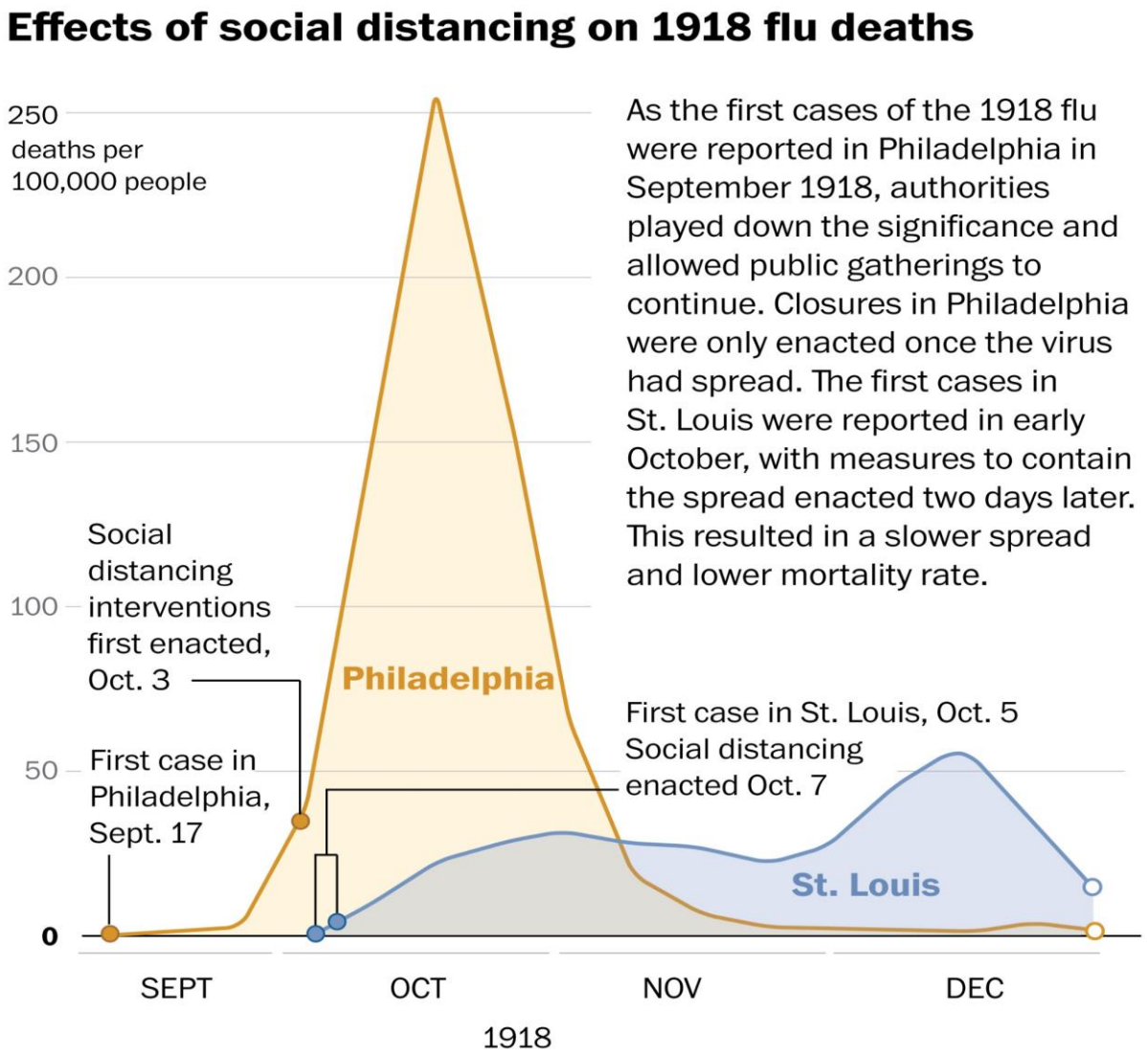
410,000 to 740,000
flu hospitalizations

24,000 to 62,000
flu deaths

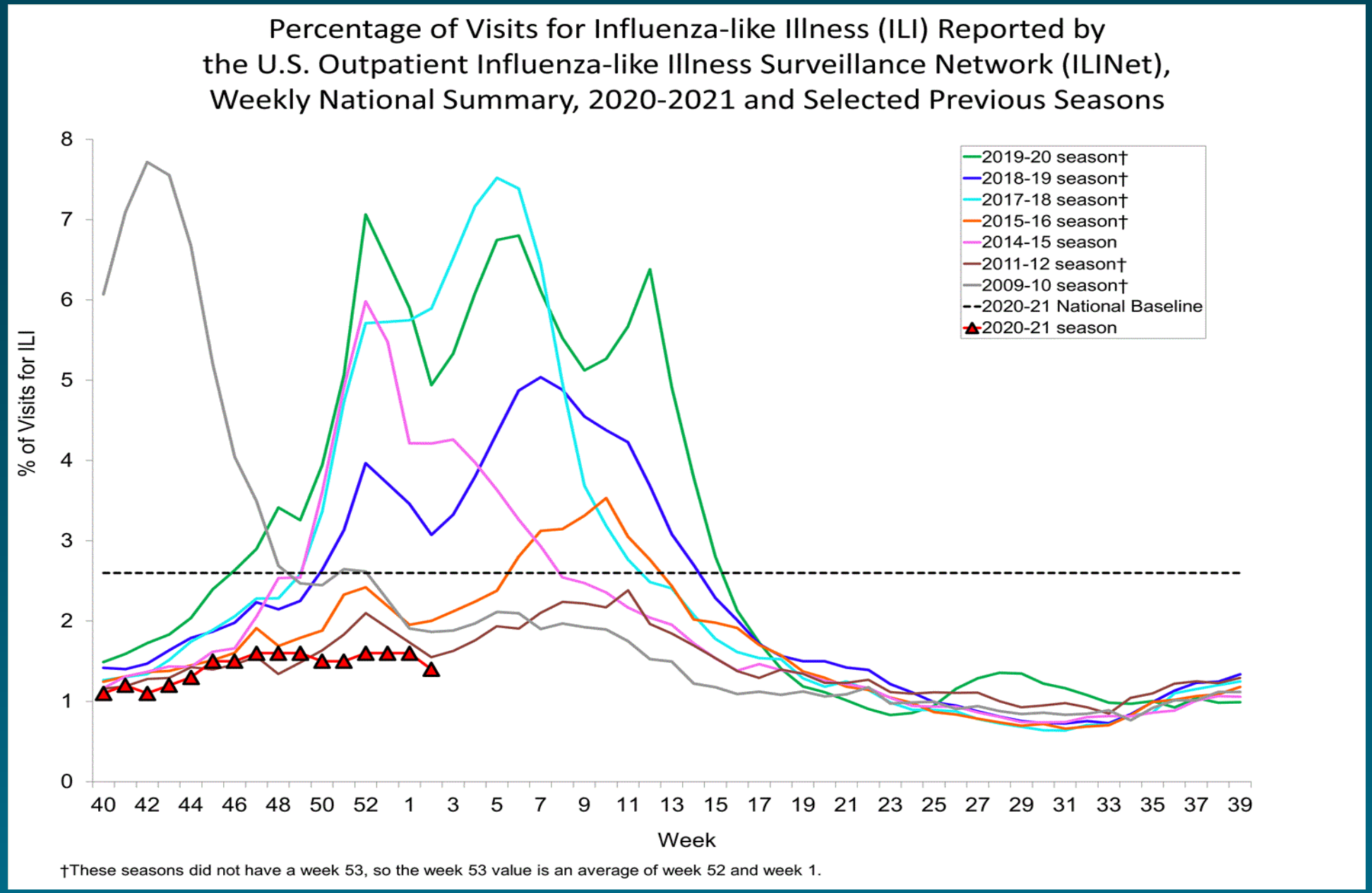


*Data from October 1, 2019 to April 4, 2020.
Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm
Images created by Gan Khoon Lay, Thuy Ghuyen, and Léa Lortal from the Noun Project.

Flattening the Curve

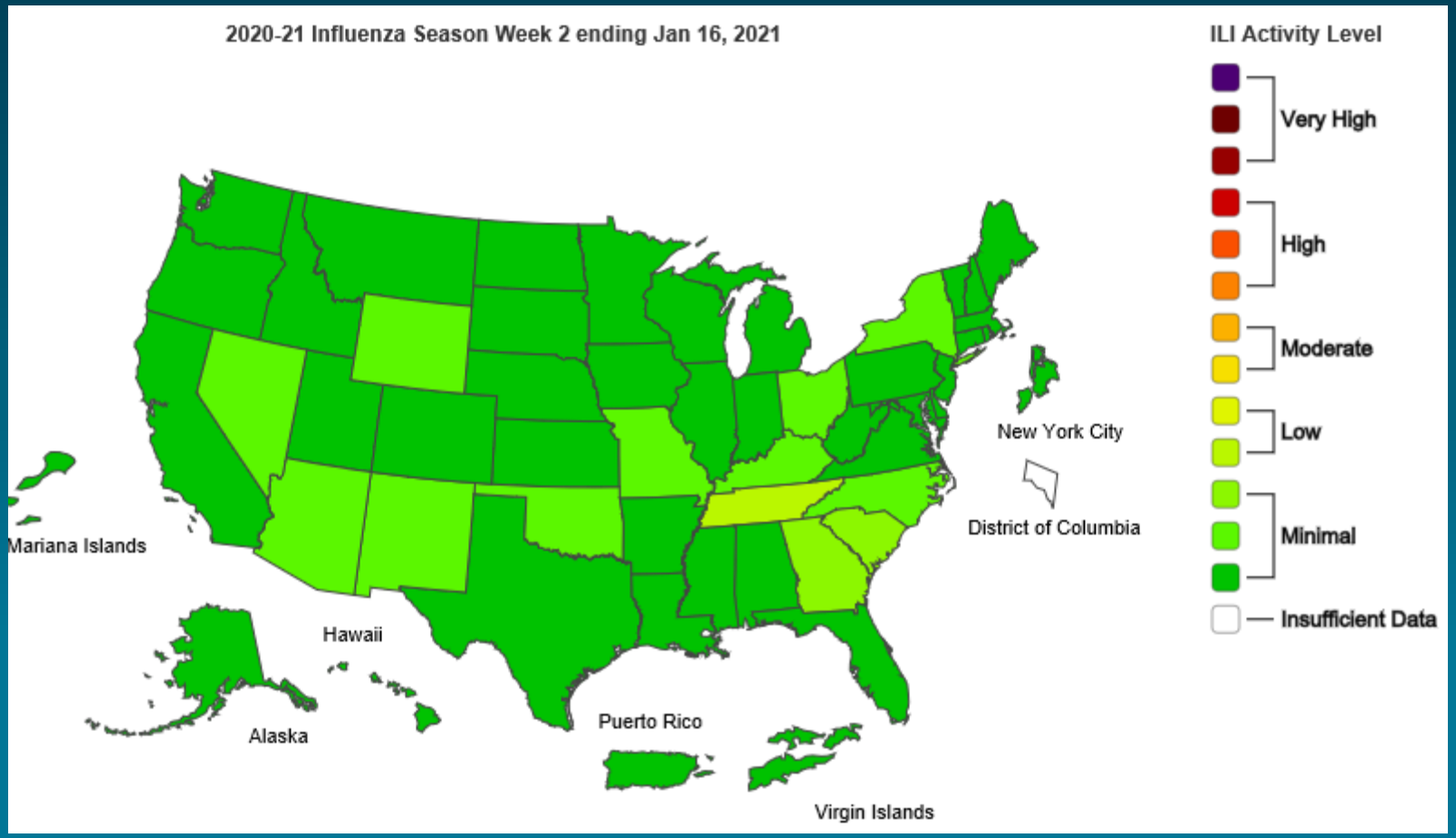


Sources: "Public health interventions and epidemic intensity during the 1918 influenza pandemic" by Richard J. Hatchett, Carter E. Mecher, Marc Lipsitch, Proceedings of the National Academy of Sciences May, 2007. Data derived from "Public health interventions and epidemic intensity during the 1918 influenza pandemic" by Richard J. Hatchett, Carter E. Mecher, Marc Lipsitch, Proceedings of the National Academy of Sciences May, 2007.



Centers for Disease Control and Prevention. Accessed January 16, 2021.
https://www.cdc.gov/flu/weekly/index.htm#ILIActivityMap

2020-2021 Influenza Season



Centers for Disease Control and Prevention. Accessed January 16, 2021. https://www.cdc.gov/flu/weekly/index.htm#ILIActivityMap

Incorporating Tools for Patient Assessment and Diagnostic Testing

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Disclosures

- *Consulting Fee:* AstraZeneca, Pfizer, Sanofi Pasteur
- *Contracted Research:* Sanofi Pasteur

Why Adults With Chronic Health Conditions Need to Get Vaccinated

During the 2017-2018 flu season, highest hospitalization rates were among **adults age 50-64 and 65+**

US adults with chronic health conditions are at high risk for flu-related complications

- Exacerbation of chronic health conditions
- Permanent physical decline
- Risk of heart attack or stroke
- Death

90% of flu-related deaths occur in adults 65+

15+ million have heart disease and are **10x** more likely to have a heart attack within **3 days** of flu infection

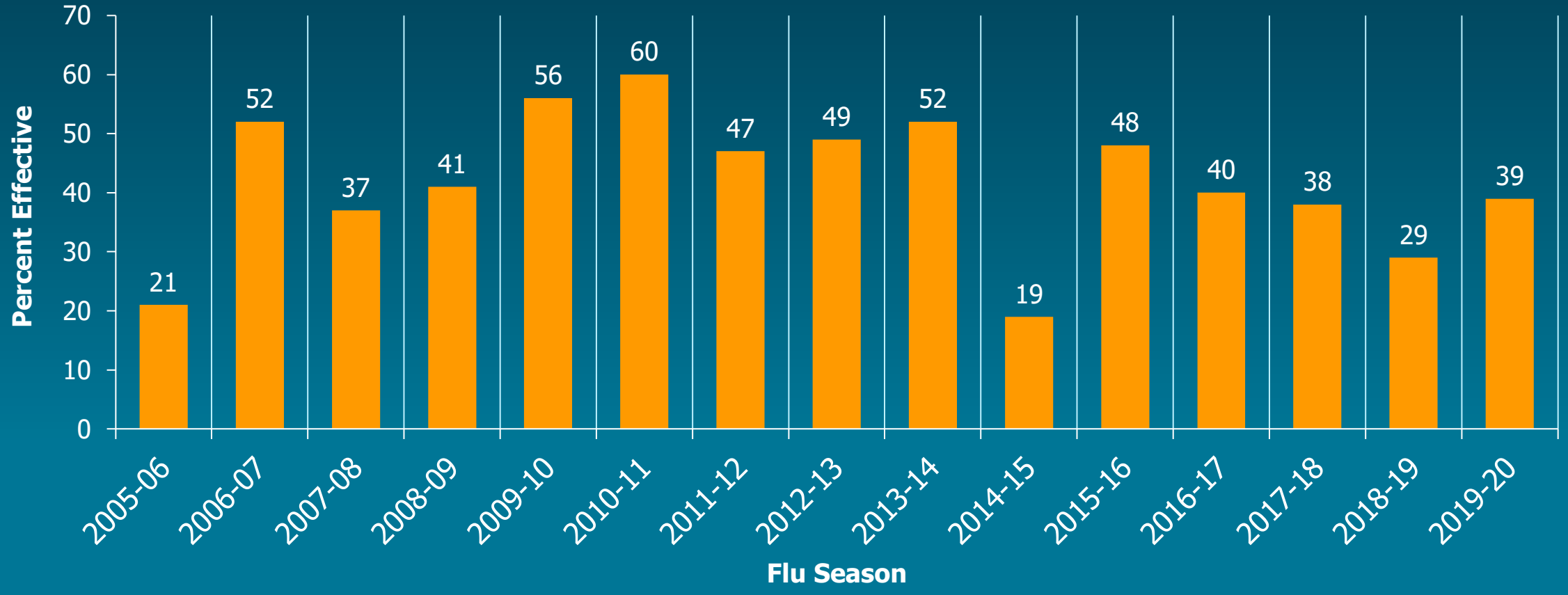
31+ million have asthma and/or COPD putting them at greater risk of serious flu-related complications

30+ million **have diabetes** and are at **6x increased risk** of flu-related hospitalization

Annual flu vaccination is the best way to protect patients with chronic health conditions from serious long-term complications of flu.

National Foundation for Infectious Diseases (NFID). September 2018.
Accessed March 21, 2021. https://www.nfid.org/wp-content/uploads/2019/08/cta-dangers-of-influenza-in-adults-with-chronic-health-c.pdf

Effectiveness of Seasonal Flu Vaccines: 2008-2020 Flu Seasons



Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm
Flannery B, et al. *J Infect Dis.* 2020;221(1):8-15.

Vaccine Coverage – How Are We Doing?

	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018	2018-2019	2019-2020
6 months-4 years	70.4%	70.4%	70.0%	70.4%	67.8%	73.4%	**75.5%**
5-12 years	61.0%	61.8%	61.8%	59.9%	59.5%	63.6%	**64.6%**
13-17 years	46.4%	46.4%	46.8%	48.8%	47.4%	52.2%	**53.3%**
18-49 years with high-risk condition	38.7%	39.3%	39.5%	39.3%	31.3%	40.4%	**44.4%**
18-49 years without high-risk condition	31.1%	32.6%	31.5%	32.6%	26.1%	33.8%	**37.5%**
50-64 years	45.3%	47.0%	43.6%	45.4%	39.7%	47.3%	**50.6%**
65+ years	65.0%	66.7%	63.4%	65.3%	59.6%	68.1%	**69.8%**

Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/fluvaxview/

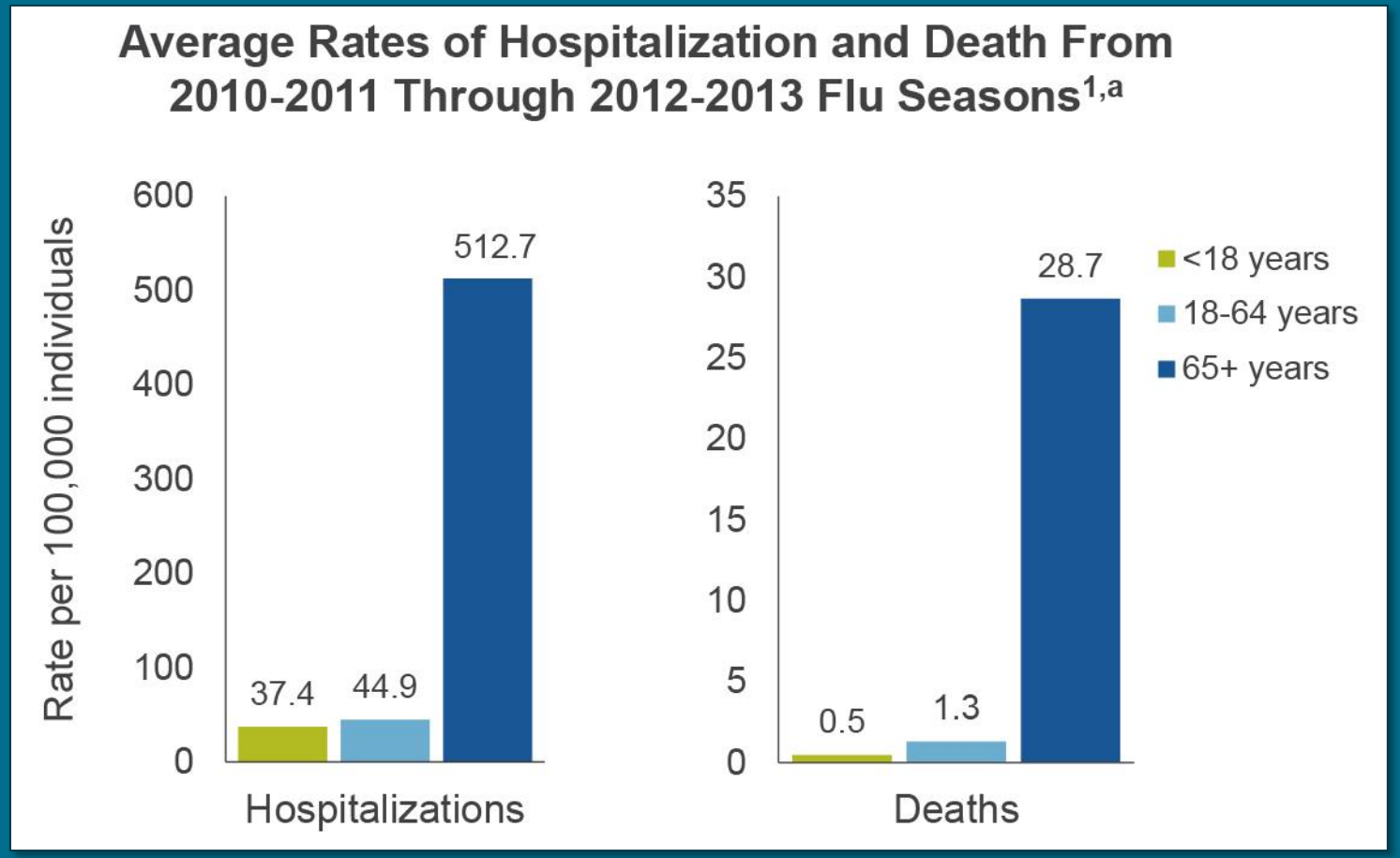
Factors Affecting the Burden of Influenza

- Burden of disease varies widely and determined by:
  - Characteristics of circulating viruses
  - Timing of the season
  - Vaccine efficacy
    (may be poor match for circulating strains in some years)
  - How many people were vaccinated
  - Social distancing/use of PPE

PPE = personal protective equipment.

Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/about/burden/index.html

Burden of Flu Is Greater in Elderly Patients



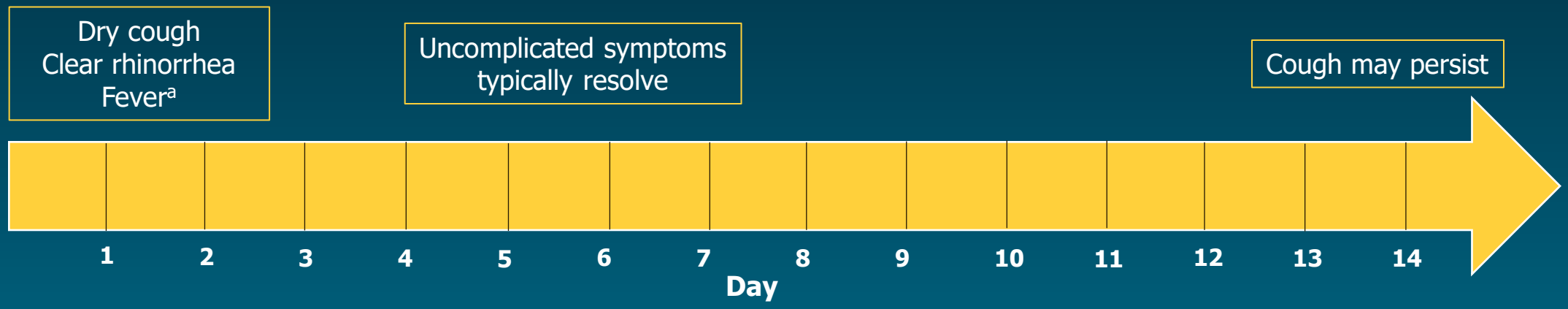
Older adults aged 65+ years accounted for **54% to 70% of hospitalizations** and **73% to 85% of deaths** depending on the season[1]

$1.3 billion in direct costs among adults ≥65 years old represents the largest share of direct medical costs, primarily due to the cost of hospitalization[2]

[a]Data shown are averaged across seasons (2010-2011, 2011-2012, and 2012-2013).

1. Reed C, et al. *PLoS One.* 2015;10(3):e0118369; 2. Putri WCWS, et al. *Vaccine.* 2018;36(27):3960-3966.

Influenza Clinical Course



- Abrupt onset of constitutional and upper respiratory tract symptoms:

Fever[b]/chills	Nonproductive cough
Myalgia	Sore throat
Headache	Rhinitis
Malaise	Vomiting and diarrhea (more common in children)

- Nausea, vomiting, diarrhea may occur with respiratory symptoms in children
- Atypical signs/symptoms can occur in frail and institutionalized elderly patients

[a]Increases to 104 °F within 12 hours, then decreases 0.5 to 1.0 °F/day.
[b]Elderly and immunosuppressed patients may not have fever.

Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/acip/clinical.htm

Populations at Higher Risk for Complications Attributable to Severe Influenza

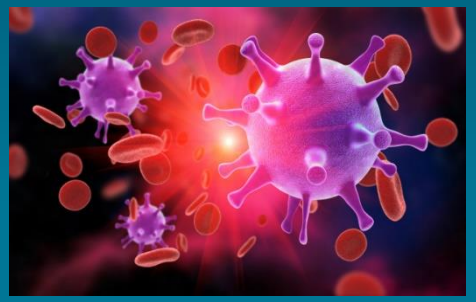
Children <5 years, especially <2 years

Children/adolescents on aspirin or salicylate-containing medications

Chronic disorders/disease (eg, diabetes, heart, liver, renal disease, COPD)

Neurologic conditions or disorders

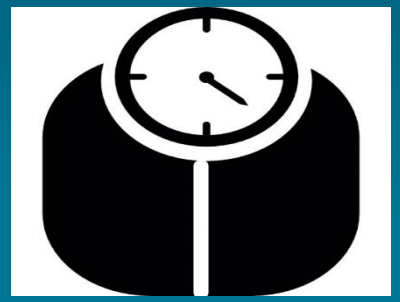
Adults ≥65 years



Immunosuppressed, HIV+

Pregnant or postpartum (2 weeks after delivery)

American Indians/ Alaska Natives



Extreme obesity (BMI ≥40 kg/m^2)

Nursing home residents

BMI = body mass index; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.

Grohskopf LA, et al. *MMWR Recomm Rep*. 2017;66(2):1-20;
Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/highrisk/index.htm

Potential Complications of Influenza

DIRECT effects: Respiratory

Asthma, COPD exacerbations

Sinus Infection

Bronchitis and Pneumonia

INDIRECT effects: Multi-Organ Systems

TRIGGER for:

Acute Myocardial Infarction, Ischemic Heart Disease, and Cerebrovascular Disease

EXACERBATION of:

Renal Disorder and Diabetes

National Foundation for Infectious Diseases (NFID). September 2018.
Accessed March 22, 2021. https://www.nfid.org/wp-content/uploads/2019/08/cta-dangers-of-influenza-in-adults-with-chronic-health-c.pdf

Influenza Diagnosis: Challenges and Opportunities

Challenges

- Signs and symptoms can vary with:
  - Age
  - Immune status
  - Underlying comorbidities
- Influenza immunization provides incomplete protection (although still very helpful)
  - 2019-2020 vaccine effectiveness ~45%
- **Potential overlap of influenza, COVID-19, and pneumonia symptoms**

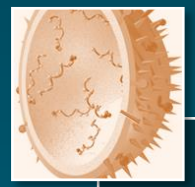
Opportunities

- Timely influenza diagnosis can help to:
  - Decrease further unnecessary workups
  - Reduce unnecessary antibiotic use
  - Improve use of infection prevention measures
  - Increase appropriate use of antivirals

COVID-19 = coronavirus disease 2019.

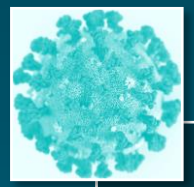
Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-47;
Rolfes MA, et al. *Clin Infect Dis*. 2019;69(11):1845-1853;
Dawood FS, et al. *MMWR Morb Mortal Wkly Rep.* 2020;69(7):177-182; Auwaerter PG. Accessed March 22, 2021. https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2_;
Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

Symptoms of Co-circulating Respiratory Illnesses and Allergies



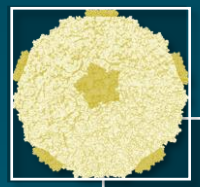
Influenza

- **COMMON**: Abrupt onset, fever (can be high grade), body aches, fatigue, cough, and headache
- LESS COMMON: Sore throat, sinus congestion, gastrointestinal (GI) upset, dyspnea, sneezing



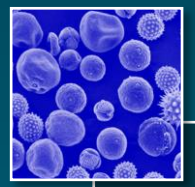
COVID-19*

- Fever, cough, shortness of breath or difficulty breathing, chills, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell



Colds

- **COMMON**: Gradual onset, sinus congestion, sneezing, sore throat, mild to moderate cough
- LESS COMMON: Fatigue, aches
- RARE: Fever, dyspnea, GI upset



Allergies

- **COMMON**: Rhinitis, sneezing, sinus congestion, mild cough, sore throat
- RARE/NEVER: Fever, dyspnea, body aches, GI upset

***Information is still evolving. Symptoms can vary and range from mild to severe.**

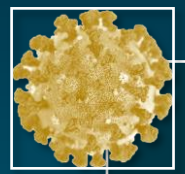
Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/symptoms/coldflu.htm
Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html
National Institute of Allergy and Infectious Diseases. Accessed March 22, 2021. https://www.niaid.nih.gov/diseases-conditions

Differentiating Influenza From COVID-19

Influenza[1]

- Transmission: Respiratory droplets, contaminated surfaces
- Incubation period: Mean 2 days, range 1 to 4 days
- Overall hospitalization rate: 2%
- Overall fatality rate: ~0.1%

vs



COVID-19*

- Transmission: Respiratory droplets, contaminated surfaces
- Incubation period: Mean 5-6 days, range 2 to 14 days[2]
- Hospitalization rate: 1.1% (ages 20–29 years) to 18.4% (ages ≥80 years)[3]
- Estimated fatality rate[3,4]:
  - Approximately 6 to 12× greater than seasonal influenza, but it has an extremely steep age gradient
  - Current data suggest a range (0.66% to >4%)†
- Children less symptomatic with infection and much less prone to severe illness[2]

To be determined…

- How common is asymptomatic infection and transmission?
- Rates of symptomatic infection/complication in the pediatric population?

*Information is rapidly evolving and subject to change. †The case fatality rate is likely higher than seasonal influenza (≤0.1%) but may be lower than initially reported (~2% to 4%), epidemiology surveys are in progress. Results may vary in some countries, depending on health practices. Current estimates suggest COVID-19 is ~6 to 12 × worse than influenza with a steep age gradient.

1. Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/about/disease/spread.htm; 2. Auwaerter PG. Accessed March 22, 2021. https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2_; 3. Verity R, et al. *Lancet Infect Dis*. 2020;20(6):669-677; 4. Johns Hopkins Coronavirus Resource Center. Accessed March 22, 2021. https://coronavirus.jhu.edu/map.html

Influenza Testing – RIDT

Rapid Influenza Diagnostic Tests (RIDTs):

- Office-based, point-of-care tests
- Immunochromatographic assays detect specific influenza viral antigens in a respiratory specimen
- Have inconsistent accuracy; historically, sensitivity has ranged from 10% to 80%, with specificity above 90%
- Meta-analysis[1] had pooled sensitivity of 62.3%; specificity was 98.2%
- Sensitivity was 13% higher in children
- In 2017, the FDA reclassified RIDTs to meet minimum specific criteria for sensitivity/specificity[2]

FDA = US Food and Drug Administration.

1. Chartrand C, et al. *Ann Intern Med*. 2012;156(7):500-511.
2. Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

Influenza Rapid Molecular Assays

- Tests for nucleic acid
- Tests for influenza A or B
- Does not distinguish strain of influenza
- Results in 15 to 30 minutes
- High sensitivity
- High specificity

Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.
Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

Influenza RT-PCR Testing

- RT-PCR is a highly sensitive, highly specific testing modality for detection of influenza A and B viral RNA in respiratory specimens:
  - Results may take 4 to 6 hours or more once testing is started; some of the newer cartridge-based RT-PCR assays can yield results in 60 to 80 minutes
  - RT-PCR can be useful as a confirmatory test and identify influenza virus types and influenza A virus subtypes
  - *Recommended* test by IDSA for hospitalized patients
- 3 multiplex RT-PCR assays target a panel of microorganisms – multiplex respiratory pathogen panels range from narrow (targeting influenza A and B viral and RSV RNA) to broad (targeting more than a dozen respiratory viruses and other pathogens in respiratory specimens):
  - Turnaround times to results range from 1 to 8 hours
  - Multiplex assays are preferred for immunocompromised patients and may be useful for other hospitalized patients
  - Now available in combination with COVID testing

IDSA = Infectious Disease Society of America; RNA = ribonucleic acid; RSV = respiratory syncytial virus; RT-PCR = reverse transcription polymerase chain reaction.

Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.
Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

Office-based PCR Tests

- Real-time PCR testing
- Closed system
- CLIA-waived
- Less than 5 minutes of hands-on time; 20 minutes total
- Compared with routine PCR, sensitivity is 99.2% and specificity is 100%
- Other CLIA-waived, point-of-care FDA-cleared nucleic acid amplification tests:

ID NOW:	sensitivity 96.3%; specificity 97.4% (influenza A)
	sensitivity 100%; specificity 97.15% (influenza B)
cobas Liat:	sensitivity 100%; specificity 100%

CLIA = Clinical Laboratory Improvement Amendments; PCR = polymerase chain reaction.

Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm
Binnicker MJ, et al. *J Clin Microbiol*. 2015;53(7):2353-2354; Nolte FS, et al. *J Clin Microbiol*. 2016;54(11):2753-2766.
Abbott. ID NOW INFLUENZA A & B 2. Accessed March 22, 2021. https://www.globalpointofcare.abbott/en/product-details/id-now-influenza-ab-2.html

Available Influenza Diagnostic Tests

Type of Test	Acceptable Specimens	Time to Results	Sensitivity/ Specificity
Rapid Influenza Diagnostic Test (RIDT)	NP swab, nasal swab, throat swab, aspirate or wash	10-15 minutes	Low to moderate sensitivity High specificity
Rapid Molecular Assay (viral RNA detection or nucleic acid amplification tests)	NP swab, nasal swab	15-30 minutes	High sensitivity High specificity
Direct and indirect immunofluorescence assays	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours	Moderate sensitivity High specificity
Molecular assays (including RT-PCR)	NP or throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	1-8 hours	High sensitivity High specificity
Multiplex molecular assays	NP or throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	1-2 hours	High sensitivity High specificity
Rapid cell culture (shell vial and cell mixtures)	NP or throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	1-3 days	High sensitivity High specificity
Viral culture (tissue cell culture)	NP or throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 days	High sensitivity High specificity

Preferred for outpatient setting

Preferred for inpatient setting

Inpatient use for immunocompromised patients or if results might influence care

Grey text = Not recommended for hospitalized patients except when more sensitive molecular assays are not available; follow-up testing with RT-PCR or other molecular assays should be performed to confirm negative immunofluorescence test results.

NP = nasopharyngeal.

Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm
Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.

Which Tests Should Be Used to Diagnose Influenza?

Guidelines from the Infectious Diseases Society of America

In ***outpatients***, clinicians should use rapid molecular assays (ie, NAATs) over RIDTs to improve detection of influenza virus infection.

In ***hospitalized patients***, clinicians should use RT-PCR or other molecular assays over other influenza tests to improve detection of influenza virus infection.

For initial or primary diagnosis of influenza, clinicians should ***not*** use viral cultures, because results will not be available in a timely manner to inform clinical management.

For diagnosis of influenza, clinicians should ***not*** use serologic testing, because results from a single serum specimen cannot be reliably interpreted.

NAAT = nucleic acid amplification test; RIDT = rapid influenza diagnostic test; RT-PCR = reverse transcription polymerase chain reaction.

Infectious Diseases Society of America. Accessed March 22, 2021. https://www.idsociety.org/practice-guideline/influenza/
Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.

Influenza Prevalence and Predictive Value of Testing

Positive predictive value (PPV) = probability that patients with a positive screening test truly have the disease

Negative predictive value (NPV) = probability that patients with a negative screening test truly do not have the disease

When influenza prevalence is relatively low, the PPV is low and **false-positive test results more likely**

When influenza prevalence is low, the NPV is high and **negative results more likely to be true**

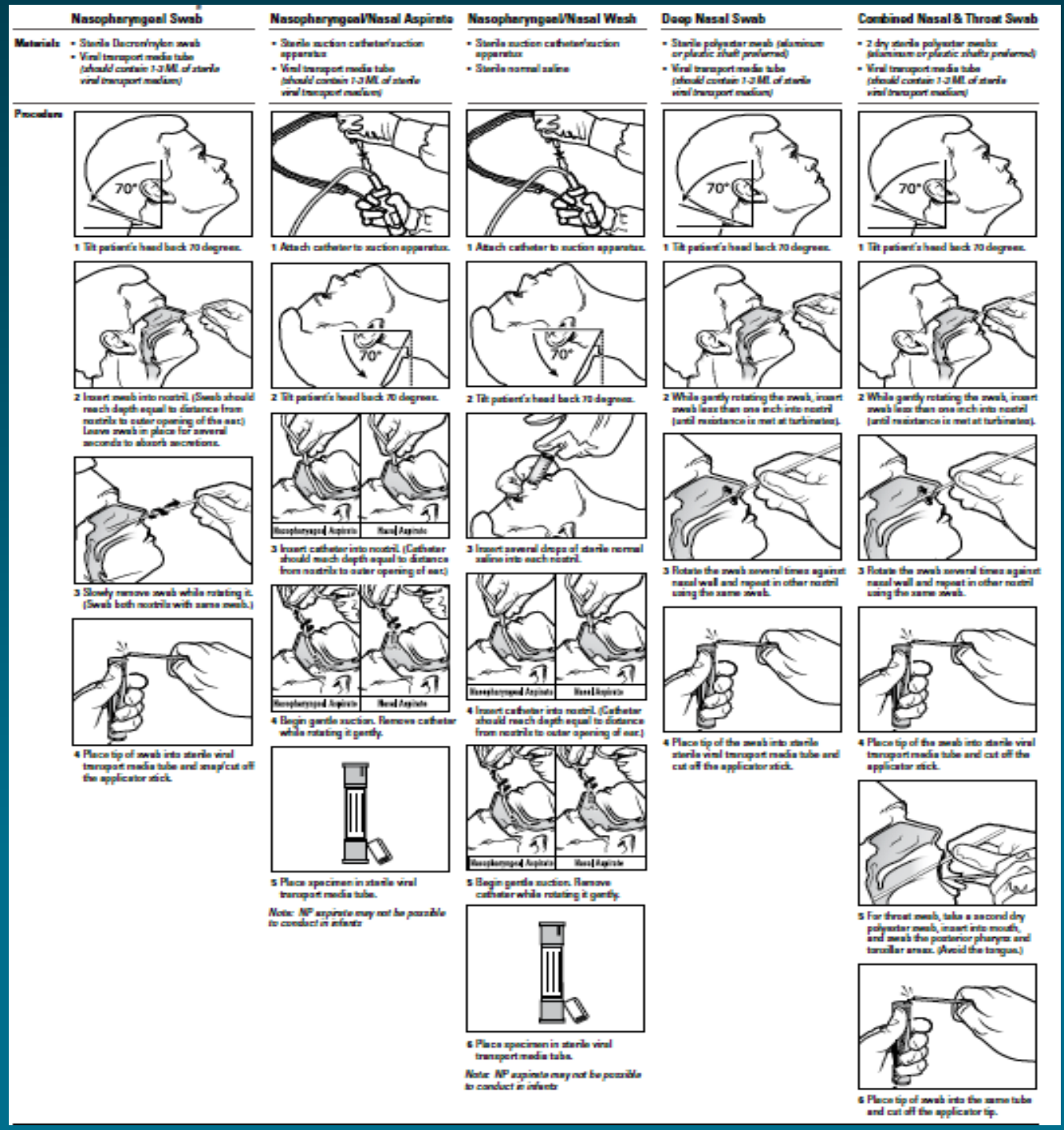
When influenza prevalence is relatively high, the NPV is low and **false-negative test results more likely**

When influenza prevalence is high, the PPV is high and **positive results more likely to be true**

Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm

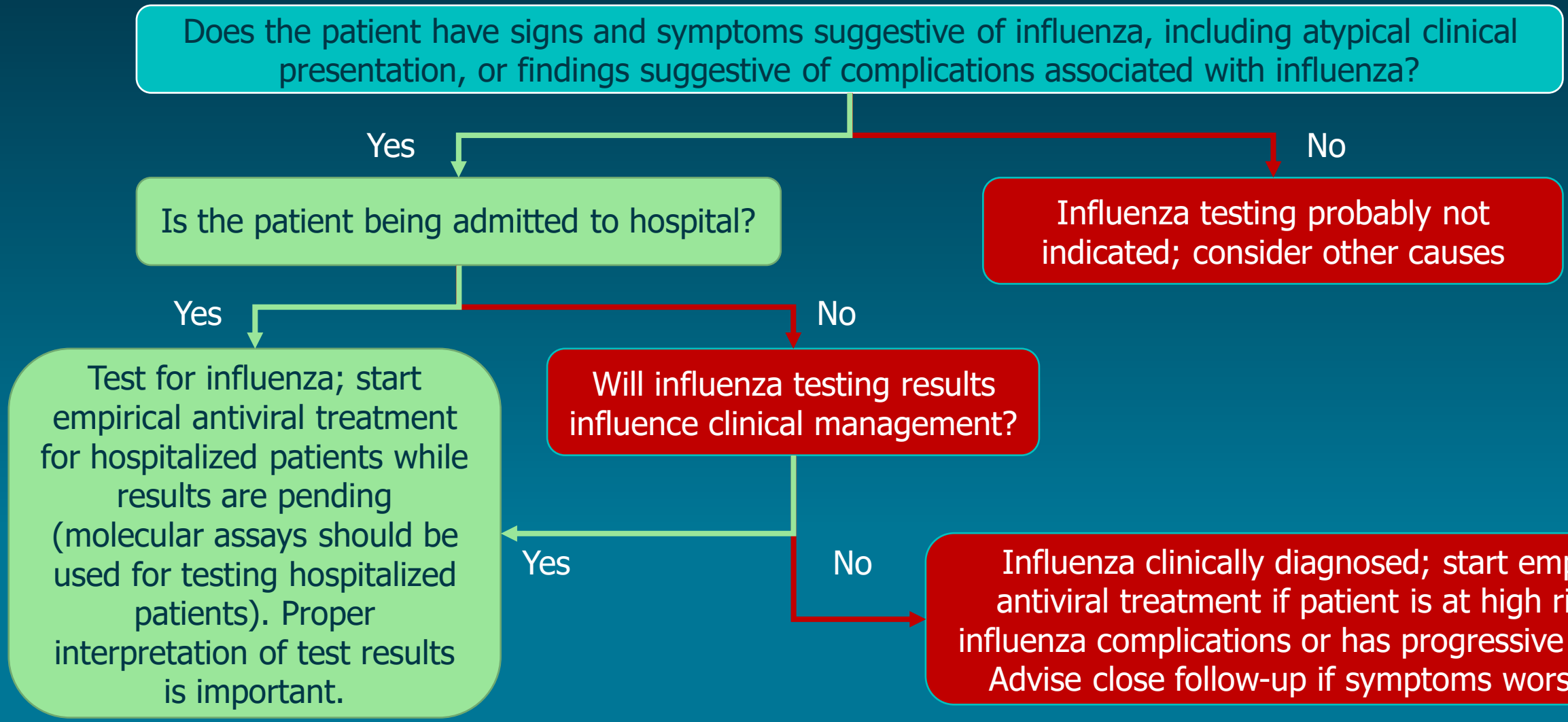
Influenza Specimen Collection Techniques

- Centers for Disease Control and Prevention resources for specimen collection



Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/pdf/professionals/flu-specimen-collection-poster.pdf

Influenza Antiviral Treatment Guideline



Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm#summary

Case Discussion

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Disclosures

- No relevant financial relationships to disclose.

Case 1: Dawn

- 43-year-old woman with 3-day history of fever to 104 °F is sent to ED from primary care physician
- Mild nasal congestion, moderate myalgia, no dyspnea, no gastrointestinal symptoms, sense of taste and smell still intact
- Potential exposure to COVID-19–positive patient in the past week
- *Medical history:* non-contributory
- *Vitals:* Temperature 103.2 °F; BP 95/65 mm Hg bilaterally; pulse 103 beats/minute; RR 15/minute; O_2 saturation 89% room air
- *Exam:* Hyperemia of the oropharynx, otherwise unremarkable

BP = blood pressure; ED = emergency department; RR = respiration rate.

Dawn

- Test for COVID-19/influenza is sent – estimated turnaround: 2 days
- *Other tests?*
  - *Chest x-ray?*
  - *Complete blood count?*
  - *Inflammatory markers?*
  - *Other viral molecular testing?*
- Which treatment should be offered?

Dawn

- Patient is admitted to the hospital and given intravenous fluids, nasal oxygen, and a 5-day course of oseltamivir is started
- Combination flu/COVID RT-PCR test comes back positive for flu on day 2
- After 3 days, patient is discharged from the hospital when vital signs return to normal

Challenges in Flu Treatment

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Key Treatment Points: When Should Treatment Be Considered?

IDSA Guidelines

Criteria for *considering* antiviral treatment[a]:
Outpatients with illness onset ≤2 days before presentation
Symptomatic outpatients who are household contacts of persons who are at high risk for complications from influenza, particularly those who are severely immunocompromised
Symptomatic health care providers who care for patients who are at high risk for complications from influenza, particularly those who are severely immunocompromised

[a]Regardless of influenza vaccination history.

Guidelines are paraphrased from the article cited below.

IDSA = Infectious Diseases Society of America.

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

Key Treatment Points:
Who Should Be Treated for a Positive Influenza Test?

IDSA Guidelines

Criteria for initiating antiviral treatment as soon as possible[a]:
Persons (any age) who are hospitalized with influenza, regardless of illness duration before hospitalization
Outpatients (any age) with severe or progressive illness, regardless of illness duration
Outpatients who are deemed at high risk for complications from influenza (ie, those with chronic medical conditions and immunocompromised patients)
Children aged <2 years and adults aged ≥65 years of age
Pregnant women and those within 2 weeks postpartum

[a]Regardless of influenza vaccination history.

Guidelines are paraphrased from the article cited below. For items indicated in parentheses, see Table 1 of the cited article for category, grade, and definition for ranking recommendations.

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

6 FDA-Approved Drugs for Influenza

- **4 recommended for influenza A + B:**
  - Neuraminidase inhibitors:
    1. Oseltamivir phosphate (oral)
    2. Zanamivir (inhaled)
    3. Peramivir (IV)
  - Cap-dependent endonuclease inhibitor:
    4. Baloxavir marboxil (oral)

Not recommended:

- Adamantanes (M2 ion channel):
  - Amantadine
  - Rimantadine
    - High levels of drug resistance to circulating influenza A, ineffective for influenza B

Current FDA indications for recommended oral agents:

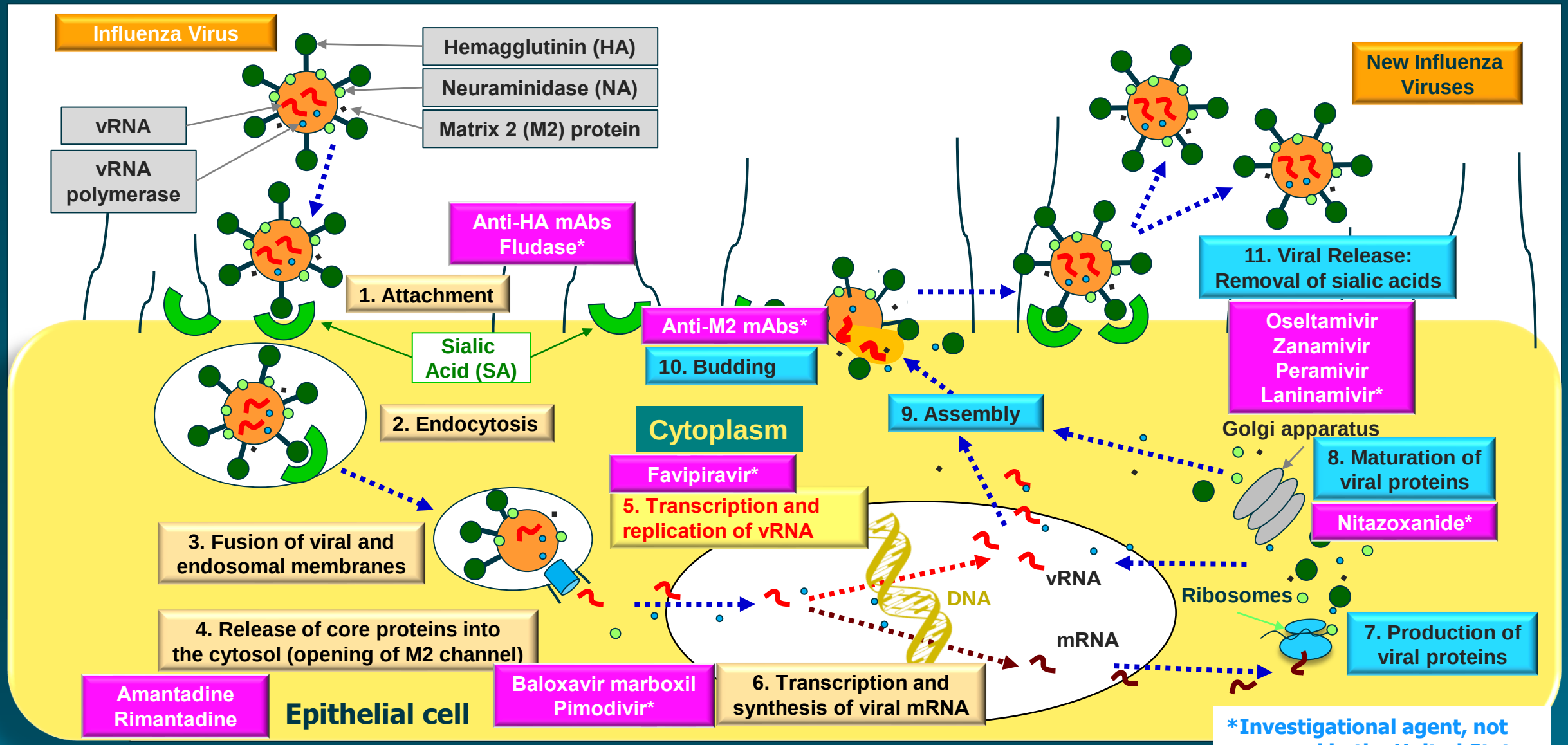
Oseltamivir: for treating influenza in patients ≥1 year who have been symptomatic for no more than 2 days, and for prophylaxis of influenza in patients ≥1 year

Baloxavir: for treating acute uncomplicated influenza within 2 days of illness onset in people ≥12 years who are otherwise healthy, postexposure prophylaxis in people aged ≥12 years, *or at high risk for flu-related complications*

FDA = US Food and Drug Administration; IV = intravenous; M2 = matrix protein 2.

Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Influenza: Lifecycle and Antiviral Mechanisms of Action



mAb = monoclonal antibody; mRNA = messenger RNA; vRNA = viral RNA.

Ramirez J. *The University of Louisville Journal of Respiratory Infections*. 2019;3(1):Article 9. https://ir.library.louisville.edu/jri/vol3/iss1/. Open Access.

FDA-Approved Drugs for Influenza Treatment

Antivirals	Mechanism of Action	Route of Administration	Dosing (Adults)
Neuraminidase inhibitors Oseltamivir phosphate Zanamivir Peramivir	Block viral neuraminidase enzyme; active against influenza A and B	Oral (capsules, suspension) Inhaled Intravenous	**75 mg BID x 5 days** **10 mg BID x 5 days** **600 mg IV (1 dose)**
Cap-dependent endonuclease inhibitor Baloxavir marboxil	Interferes with viral RNA transcription and blocks virus replication; active against influenza A and B	Oral (tablets) 20 mg and 40 mg (blister card contains two tablets)	40 to <80 kg (88 lb to <176 lb): **One 40-mg dose** (Two 20-mg tablets taken at the same time) ≥80 kg (≥176 lb): **One 80-mg dose** (Two 40-mg tablets taken at the same time)
Adamantanes Amantadine Rimantadine	Target M2 ion channel protein of influenza A viruses; active against influenza A, not B	**As in past seasons, high levels of resistance (>99%) to adamantanes** **Not recommended for treatment or prophylaxis of influenza A**	

BID = twice daily; IV = intravenous.

Baloxavir marboxil. Package insert. Genentech USA, Inc; 2020.
Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm#overview

Side Effects of Available Antivirals

Drug	Side Effects
Oseltamivir	• **AEs:** nausea, vomiting, headache • **Postmarketing reports:** serious skin reactions, sporadic neuropsychiatric events[a]
Peramivir	• **AEs:** diarrhea • **Postmarketing reports:** serious skin reactions; sporadic, transient neuropsychiatric events[a]
Zanamivir	• **Allergic reactions:** oropharyngeal or facial edema, skin rash • **AEs:** risk for bronchospasm, especially in those with underlying airways disease; dizziness; ear, nose, and throat infections • **Postmarketing reports:** sporadic, transient neuropsychiatric events[a]
Baloxavir	• **AEs:** diarrhea, bronchitis, nasopharyngitis, headache, nausea

[a]Self-injury or delirium, mainly reported among Japanese adolescent and adults, may be due to the viral infection itself.

AEs = adverse events.

Centers for Disease Control and Prevention. Accessed March 22, 2021. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Oseltamivir Trials: Ambulatory Patients

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

[a]34% reduction in antibiotic for LRTI; [b]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.

Meta-analysis of Oral Oseltamivir vs No Antiviral Therapy

Outcome	Number of Patients (Studies)	Pooled Odds Ratio (95% CI)
Mortality	681 (3)	0.23 (0.13-0.43)
Hospitalization	150,710 (4)	0.75 (0.66-0.89)
Otitis media	78,407 (2)	0.75 (0.64-0.87)
Pneumonia	150,466 (3)	0.83 (0.59-1.16)
Cardiovascular events	100,830 (2)	0.58 (0.31-1.10)
		<1.0: favors oseltamivir; >1.0 favors no antiviral

- Observational studies of hospitalized patients, no RCTs
- Studies of both seasonal influenza and pandemic influenza

- **Findings suggest that neuraminidase inhibitors decrease mortality**
  - **Odds ratio 0.23 for oral oseltamivir (95% CI, 0.13-0.43)**
  - **Mortality effect mostly derived from use in patients with <3 days of symptoms**
- Low-quality evidence and many unmeasured confounders

RCTs = randomized controlled trials.

Hsu J, et al. *Ann Intern Med*. 2012;156(7):512-524.

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)
Nausea	247	118	<.0001	**3.7%** (1.8 to 6.1)
Vomiting	201	63	<.0001	**4.7%** (2.7 to 7.3)
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)

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

Oseltamivir in Hospitalized Population

- 5 years of patient-level data from 1 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 length of hospital stay ($P<.001$)
- No patients died in the early NAI group, compared with 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%)

NAI = neuraminidase inhibitor.

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

Efficacy and Safety of Oseltamivir in Children

- Systematic review identified RCTs of oseltamivir in children
  - Examined protocol-defined outcomes based on individual patient data
  - 2-stage, random-effects meta-analysis conducted to determine efficacy of treatment in reducing duration of illness (differences in RMST by treatment group)
- Data from 5 trials included
  - ITT: N=2561; ITT infected (ITTI): N=1598

Findings:

- **Oseltamivir significantly reduced duration of illness in the ITTI population**
  - RMST difference −17.6 hours (95% CI, −34.7 to −0.62)
  - Reduction larger in trials that enrolled patients **without asthma** −29.9 hours (95% CI, −53.9 to −5.8)
- Risk for otitis media 34% lower in ITTI population
- Vomiting was the only AE with significantly higher risk in treatment group

ITT = intention-to-treat; RMST = restricted mean survival time.

Malosh RE, et al. *Clin Infect Dis*. 2018;66:1492-1500.

Other NAIs: Peramivir

- Parenteral agent
  - Single dose
- FDA approved for uncomplicated influenza, <48 hours from symptom onset
- Mostly used off-label:
  - ICU
  - Lack of GI absorption

RCT of Peramivir
N=398 **hospitalized patients**
Over half were >48 hours from symptom onset
Peramivir + SOC vs placebo + SOC • The primary efficacy analysis included 121 patients who did not receive a concurrent NAI as part of the SOC
Endpoints: median time to clinical resolution and change in viral shedding
No significant clinical benefit demonstrated for peramivir + SOC compared with placebo + SOC

GI = gastrointestinal; ICU = intensive care unit; SOC = standard of care.

deJong MD, et al. *Clin Infect Dis*. 2014;59(12):e172-e185.

Baloxavir: CAPSTONE-1 Study

Phase 3, randomized, double-blind, placebo- and oseltamivir-controlled study:

- Outpatients 12-54 years old
- Patients 12-19 years randomly assigned to baloxavir or placebo (day 1 only)
- 1436 randomized; 1064 intention-to-treat population

RANDOMIZED

2:1

Baloxavir single dose
(40 mg for BW <80 kg;
80 mg for BW ≥80 kg)

Oseltamivir 75 mg BID
Days 1-5

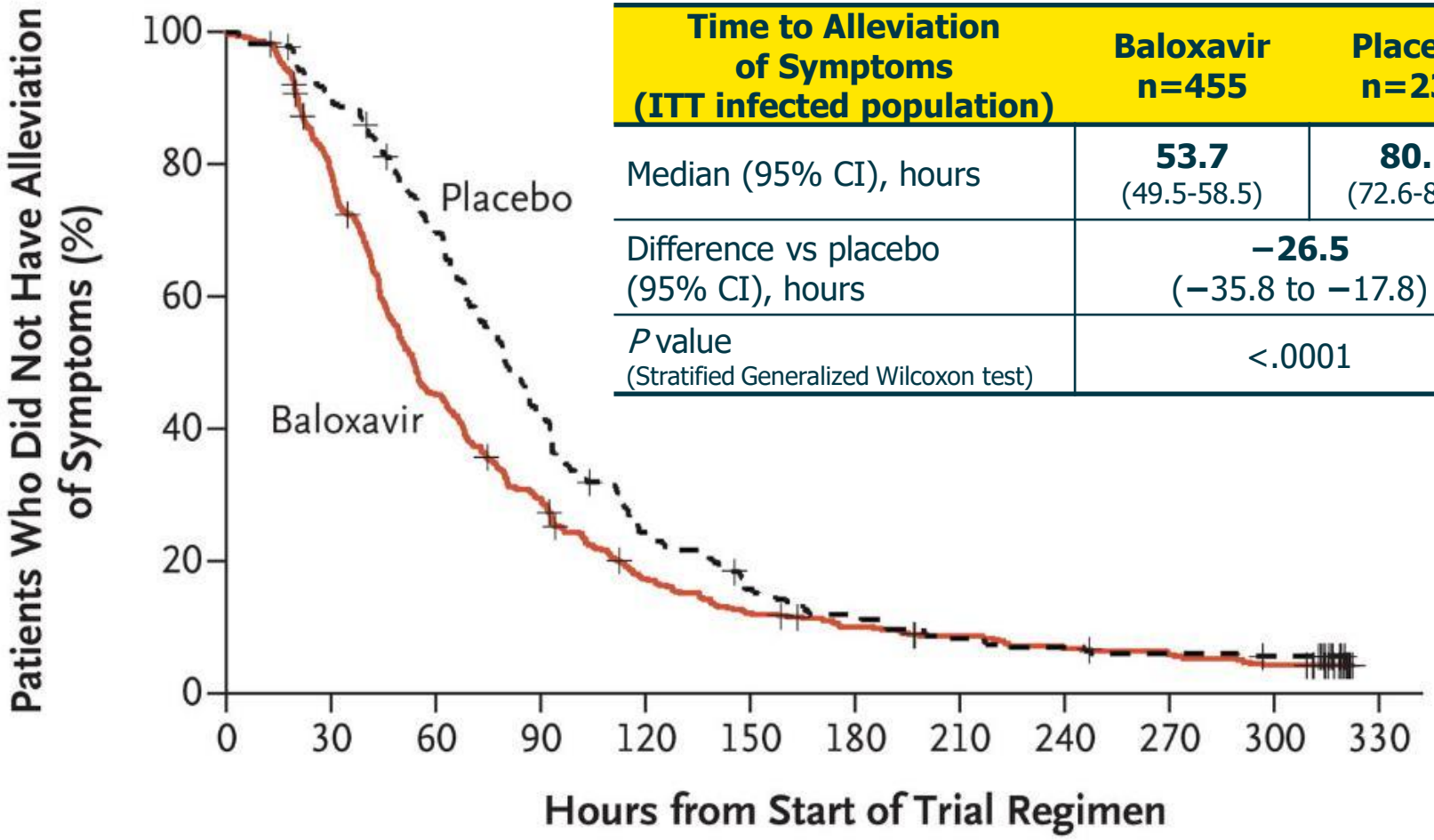
Matching placebos

Primary endpoint
Time to alleviation of influenza symptoms

BID = twice daily; BW = body weight.

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

CAPSTONE-1: Baloxavir for Uncomplicated Influenza



Time to Alleviation of Symptoms (ITT infected population)	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 (Stratified Generalized Wilcoxon test)	<.0001	

- Baloxavir significantly reduced duration of fever by ~1 day versus placebo (median time: 24.5 hours versus 42 hours; *P*<.0001)
- Median time to alleviation of symptoms was similar for baloxavir and oseltamivir (~54 hours)

Overall incidence of AEs:

- **Baloxavir:** 20.7%
- **Oseltamivir:** 24.8%
- **Placebo:** 24.6%

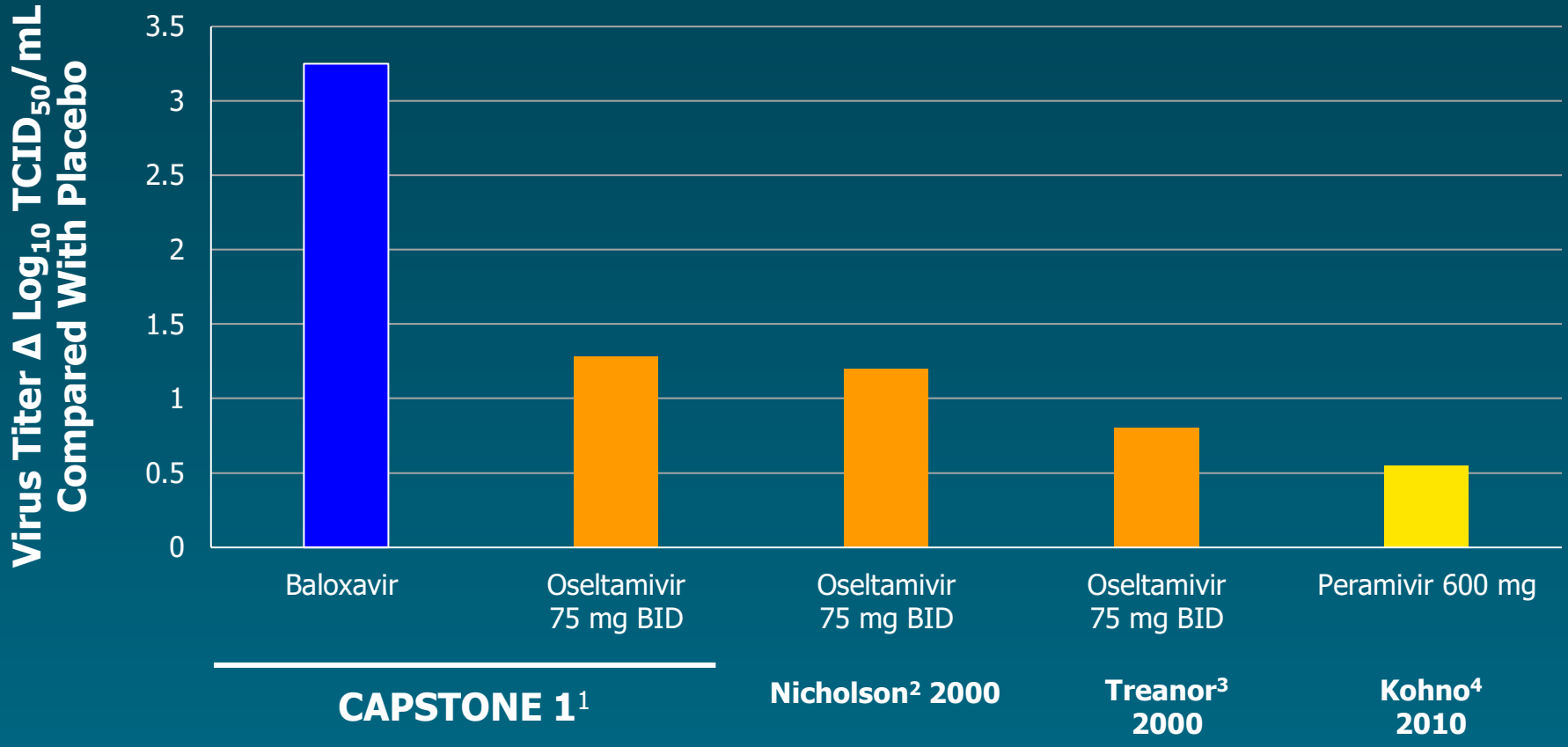
Baloxavir has a similar overall AE incidence, with a potentially lower rate of nausea and vomiting than oseltamivir

AE = adverse event; ITT = intent-to-treat.

From 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)



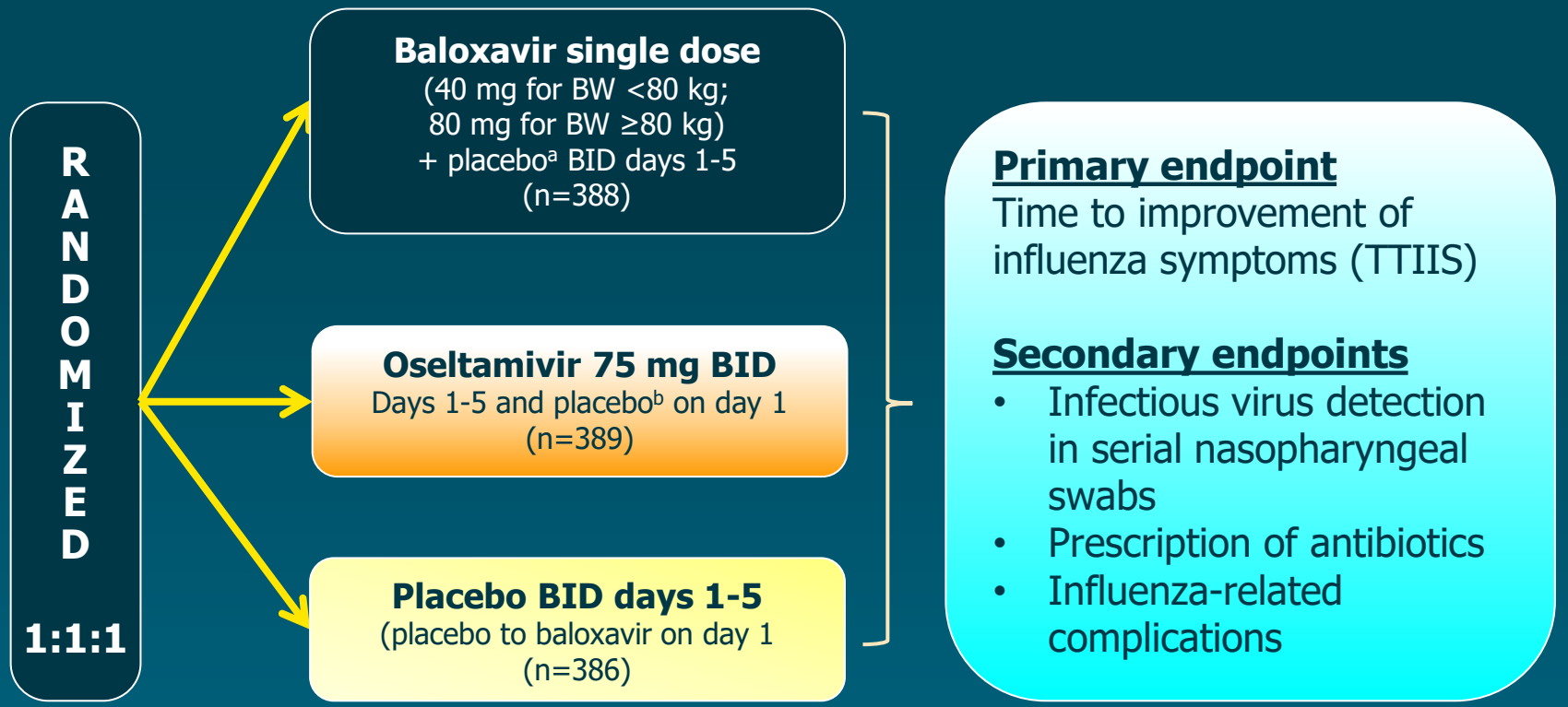
TCID = median tissue culture infectious dose.

1. Hayden FG, et al. *N Engl J Med*. 2018;379(10):913-923.
2. Nicholson KG, et al. *Lancet*. 2000;355(9218):1845-1850.
3. Treanor JJ, et al. *JAMA*. 2000;283(8):1016-1024.
4. Kohno S, et al. *Antimicrob Agents Chemother*. 2010;54(11):4568-4574.

Baloxavir CAPSTONE-2 Design

Phase 3, multicenter, randomized, double-blind, placebo- and oseltamivir-controlled study:

- Patients with influenza at **higher risk for 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%-44% of patients had influenza B; 56%-62% had influenza A



Primary endpoint
Time to improvement of influenza symptoms (TTIIS)

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

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%)

[a]Placebo to oseltamivir; [b]Placebo to baloxavir

BID = twice daily; BW = body weight.

Ison MG, et al. Presented at: Infectious Disease Week (IDWeek) 2018; October 3-7, 2018; San Francisco, CA. Abstract #LB16; ClinicalTrials.gov. Accessed March 22, 2021. https://clinicaltrials.gov/ct2/show/NCT02949011; Ison MG, et al. *Lancet Infect Dis.* 2020;20(10):1204-1214; Baloxavir marboxil. Package insert. Genentech USA, Inc. 2020.

CAPSTONE-2: Baloxavir Marboxil in High-risk Adults

CAPSTONE-2 Outcomes (1163 patients)	
Time to clinical recovery	**Reduced time to clinical recovery for:** • Baloxavir vs placebo (73.2 vs 102.3 hrs; *P*<.0001); difference of 29.1 hours • Baloxavir for influenza A vs placebo (75.4 vs 100.4 hours; *P*=.014) • Baloxavir for influenza B vs placebo (74.6 vs 100.6 hours; *P*=.0138) • Baloxavir for influenza B vs oseltamivir (74.6 vs 101.6 hours; *P*=.0251) **Similar time to clinical recovery:** • Baloxavir for influenza A vs oseltamivir (75.4 vs 68.2 hours; *P*=NS)
Viral shedding	Reduced in patients who received baloxavir vs oseltamivir or placebo (48 vs 96 and 96, respectively; *P*<.0001)
Influenza-related complications	Treatment with either baloxavir or oseltamivir was associated with reduced risk for complications compared with placebo
Safety	Similar incidence of AEs for baloxavir (25.1%) versus placebo (29.7%) or oseltamivir (28.0%)

FDA approved a supplemental New Drug Application for baloxavir marboxil for the treatment of acute, uncomplicated influenza, or flu, in people 12 years of age and older who have been symptomatic for no more than 48 hours and ***who are at high risk for flu-related complications***. (October 2019)

NS = not significant.

ClinicalTrials.gov. Accessed March 22, 2021. https://clinicaltrials.gov/ct2/show/NCT02949011; Ison M, et al. Presented at: 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 March 22, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/210854Orig1s001.pdf

FLAGSTONE: Baloxavir + NAI in Hospitalized Patients With Severe Influenza

Study Characteristics	
Trial Design:	**Phase 3, multicenter, double-blind, placebo-controlled trial**
Participants:	**Hospitalized patients at least 12 years of age with severe influenza** N=366, Participants randomized 2:1 to receive baloxavir or matching placebo

Treatment Groups:	• **Baloxavir + NAI (n=208)**
	  • Weight-based dose of baloxavir given on days 1, 4, and 7 (if no improvement by day 5)
	  • NAI therapy given in accordance with local practice (at least 5 days)
	• **Placebo + NAI (n=144)**
	  • Matching placebo
	  • NAI therapy given in accordance with local practice (at least 5 days)

Outcome Measures:	• **Primary: time to clinical improvement**
	  • Time to hospital discharge *OR*
	  • Time to NEWS2 (National Early Warning Score 2) of ≤2 maintained for 24 hours
	• **Secondary:**
	  • AEs; ICU stay/duration; mechanical ventilation (need/duration); time to discharge; viral shedding; mortality; etc.

ClinicalTrials.gov. Accessed March 22, 2021. 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.

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%	

TTCI = time to clinical improvement.

ClinicalTrials.gov. Accessed March 22, 2021. 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.

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 BID 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

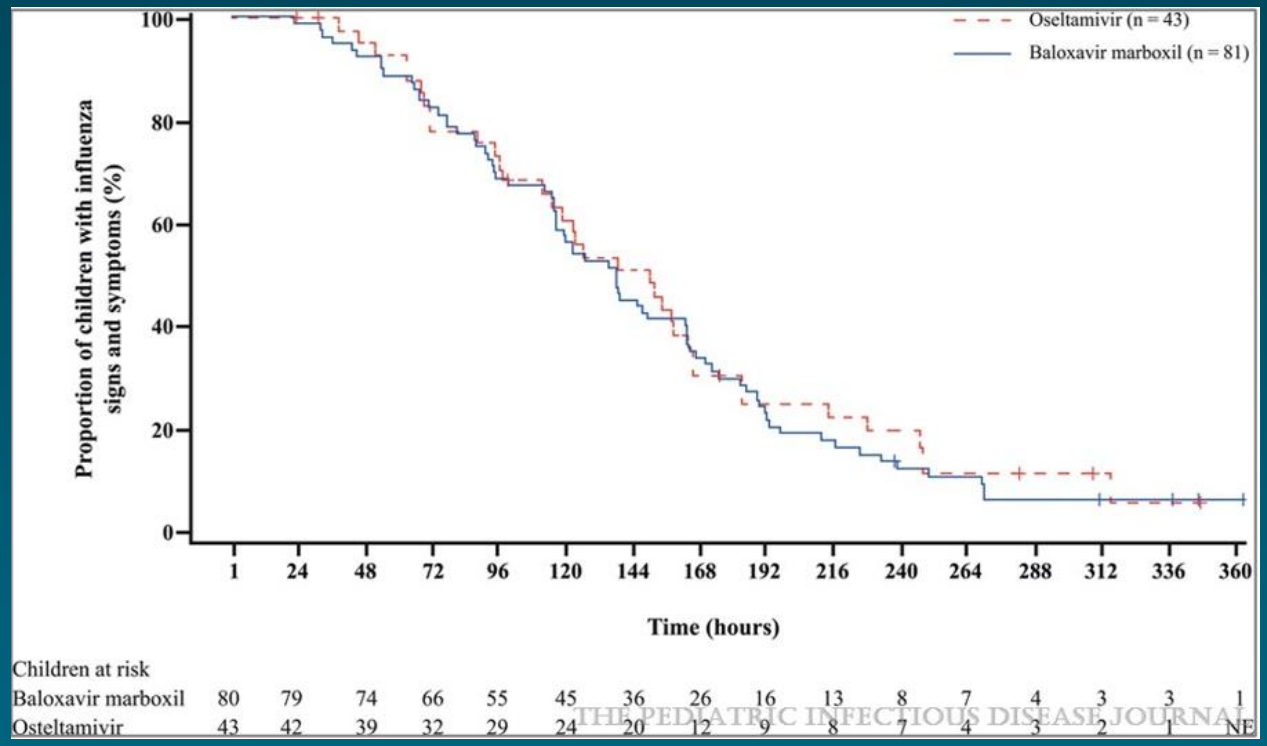
	Baloxavir (hours, 95% CI)	Oseltamivir (hours, 95% CI)
Time to alleviation of symptoms	138 (117-163)	150 (115-165)
Time to culture negativity	24.2 (23.5-24.6)	75.8 (68.9-97.8)

- 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)

BID = twice daily; NDA = new drug application; sNDA = supplemental NDA.

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

Time to Alleviation of Signs and Symptoms: Similar Between Study Arms



Resistance to Baloxavir: PA-I38X Emergence

Proportions of PA-I38X variant emergence	Total	Virus type/subtype		
		A/H1N1	A/H3N2	B
Phase 2 in Japan[1]	**2.2%** 4/182	3.6% 4/112	0% 0/14	0% 0/56
CAPSTONE-1[2]	**9.7%** 36/370	0% 0/4	10.9% 35/330	2.7% 1/37
Pediatric Study in Japan[3]	**23.4%** 18/77	0% 0/2	25.7% 18/70	0% 0/6
CAPSTONE-2[4]	**5.2%** 15/290	5.6% 1/18	9.2% 13/141	0.8% 1/131

1. Uehara T, et al. *J Infect Dis.* 2020;221(3):346-355; 2. Hayden FG, et al. *N Engl J Med*. 2018;379(10):913-923; 3. Hirotsu N, et al. *Clin Infect Dis.* 2020;71(4):971-981; 4. Ison GM, et al. *Lancet Infect Dis*. 2020;20:1204-1214.

Chemoprophylaxis

- The CDC does *not* recommend routine use
  - **Exceptions include:**
    - High-risk persons in the first 2 weeks postimmunization
    - Unvaccinated high-risk persons or those with expected poor response (immunosuppressed)
- Not recommended if ≥48 hours after exposure
- The CDC and the American Academy of Pediatrics recommend 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.

Prophylaxis: Oseltamivir and Zanamivir

Systematic review of data on NAIs for prophylaxis of influenza[1]	
Studies examining secondary transmission of **symptomatic** influenza	• Jackson et al, 2011[2] • Jefferson et al, 2014[3] • Khazeni et al, 2009[4] • Okoli et al, 2014[5]
Studies examining secondary transmission of **asymptomatic** influenza	• Jefferson et al, 2014[3] • Khazeni et al, 2009[4]
Data were classified by **pre-exposure prophylaxis**, **post-exposure prophylaxis**	

Findings

In situations of pre-exposure and post-exposure prophylaxis, 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

1. Doll MK, et al. *J Antimicrob Chemother*. 2017;72(11):2990-3007; 2. Jackson RJ, et al. *J Infect.* 2011;62(1):14-25; 3. Jefferson T, et al. *Cochrane Database Syst Rev.* 2014;2014(4):CD008965; 4. Khazeni N, et al. *Ann Intern Med.* 2009;151(7):464-473; 5. Okoli GN, et al. *PLoS One.* 2014;9(12):e113633.

Neuraminidase Inhibitors Reduce Influenza by 69% to 92%

- Several large, controlled studies of prophylaxis showed 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: Baloxavir Prophylaxis in Households

Study of baloxavir prophylactic efficacy among HHCs with influenza

Multicenter, double-blind, placebo-controlled study of HHCs in Japan during the 2018-2019 season

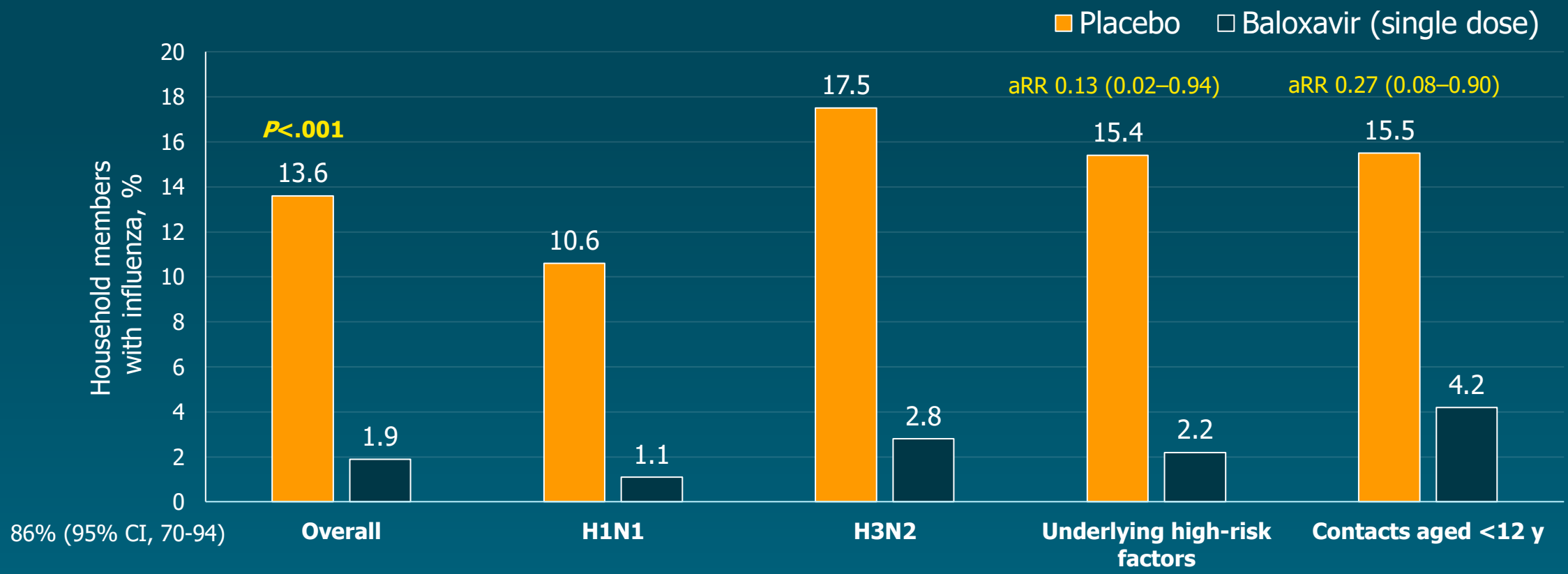
- All index patients were treated
- Asymptomatic HHCs randomized to baloxavir or placebo

Endpoint: Proportion of HHCs who developed clinical influenza over a 10-day observation period

HHCs = household contacts.

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

BLOCKSTONE: Preventative Treatment With Baloxavir After Exposure to an Infected Household Member



- Baloxavir had a comparable safety profile to placebo (adverse events: 22.2% with baloxavir, 20.5% with placebo)
- November 2020: Baloxavir is FDA-approved for postexposure prophylaxis in patients 12 years and older

aRR = adjusted risk ratio.

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

Antiviral Chemoprophylaxis

Antiviral	Indication	Age	Routine Duration[1]	Dosing
Baloxavir[2,3]	Yes	≥12 years	Single dose	• **<80 kg:** Two 20 mg tablets taken at the same time for a total single dose of 40 mg (blister card contains two 20 mg tablets) • **≥80 kg:** Two 40 mg tablets taken at the same time for a total single dose of 80 mg (blister card contains two 40 mg tablets)
Oseltamivir	Yes	≥3 months	7 days	**Adults: 75 mg orally once daily** Children 3 months to <1 year old: • 3 mg/kg/dose once daily Children >1 year old: • 15 kg or less: 30 mg once daily • >15 to 23 kg: 45 mg once daily • >23 to 40 kg: 60 mg once daily • >40 kg: 75 mg once daily
Peramivir	Chemoprophylaxis not recommended			
Zanamivir	Yes	≥5 years	7 days	**Adults and children: 10 mg** (two 5-mg inhalations daily)

See CDC guidance for special institutionalized settings with an outbreak.[4]

1. Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm;
2. Ikematsu H, et al. *N Engl J Med.* 2020;383(4):309-320; 3. Baloxavir marboxil. Package insert. Genentech USA, Inc. 2020;
4. Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/infectioncontrol/ltc-facility-guidance.htm

Treatment of Community-acquired Pneumonia (CAP) Considerations

- Should patients with CAP diagnosed with influenza get antibacterial treatment?
  - Yes
  - If nonsevere, β-lactam + macrolide OR respiratory fluoroquinolone
    - If no risk factors for MRSA or *Pseudomonas aeruginosa*
- Should patients with CAP receive antivirals for influenza?
  - Yes (strong recommendation, moderate quality of evidence)

MRSA = methicillin-resistant *Staphylococcus aureus.*

Centers for Disease Control and Prevention. Accessed March 22, 2021. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
Metaly JP, et al. *Am J Respir Crit Care Med.* 2019;200(7):e45-e67.
Uyeki TM, et al. *Clin Infect Dis.* 2018;68(6):e1-e47.

Treatment: Key Take-home Points

- Start therapy early for best outcomes
- Antiviral treatment for influenza recommended within 48 hours of symptom onset
  - Shorter duration of clinical illness
  - Fewer complications and need for antibiotics
  - Reduced mortality and length of stay for hospitalized patients
- Newer therapies and new indications are on the horizon

Case Discussion

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Case 2: Roger

- Patient is a 44-year-old male who is HIV+, who presents to outpatient clinic with 12 hours of fever, chills, and muscle aches
- Reports being at a party recently where a few people "were getting over the flu"
- Did not get the flu vaccine this year
- Current medications include triple therapy consisting of dolutegravir + abacavir + lamivudine

Roger

- HIV infection diagnosed at age 32 years
- Has family history of severe obesity; body mass index is 41 kg/m^2
- No known drug allergies
- Medications also include lisinopril for hypertension
- Lives with husband, also HIV+ and on the same triple therapy

Roger

- Vital signs: pulse 88 beats/minute; BP 130/88 mm Hg bilaterally; RR 16/minute; O_2 saturation 96%; temperature 102.8 °F; weight 100 kg
- Nontoxic appearing, no respiratory distress
- Tympanic membranes clear, pharynx clear, has some nasal congestion
- Heartbeat regular, without murmur
- Lungs – clear to auscultation bilaterally
- Abdomen: positive bowel sounds, nontender, no masses
- No edema

Roger

- Results of in-office testing are positive for influenza B.
- The husband has not been vaccinated this flu season.
- Treatment options such as baloxavir and oseltamivir were discussed for the patient and his husband.