NOTHING TO SNEEZE AT: INFLUENZA UPDATES

A presentation for HealthTrust Members

January 29, 2020

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Speaker Disclosure

- The presenter has no real or perceived conflicts of interest related to this presentation.

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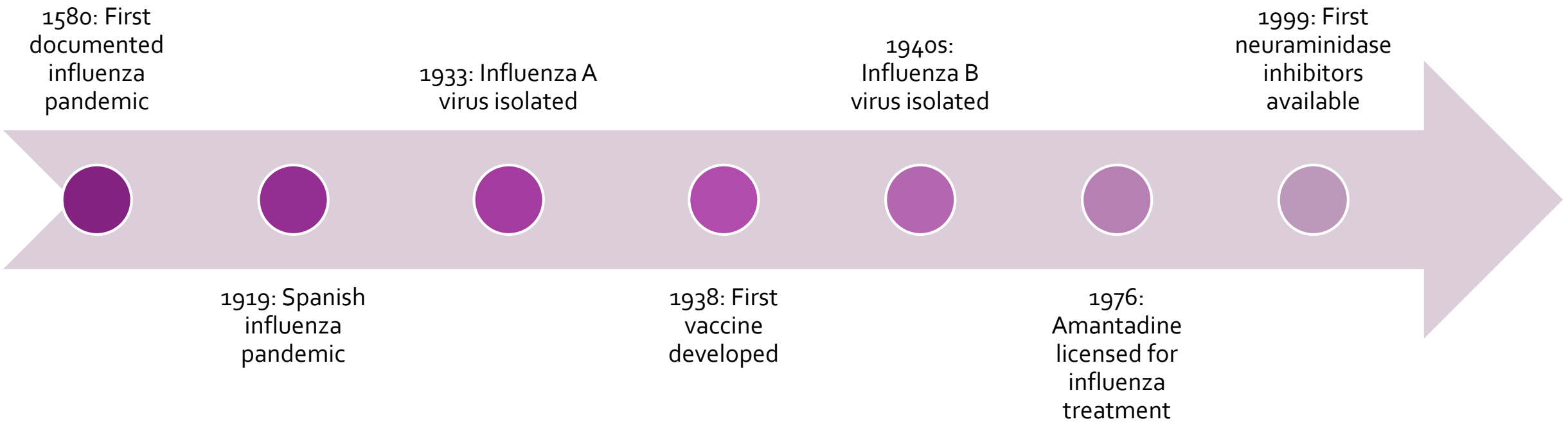
Learning Objectives for Pharmacists

- Apply current influenza vaccine recommendations to a variety of patient situations
- Recommend influenza treatment for a patient based on specific factors, including patient age and duration of illness
- Differentiate between currently available antiviral medications, their adverse effects and contraindications

Learning Objectives for Pharmacy Technicians

- Describe methods that can be taken to prevent the spread of influenza
- Identify patients who are eligible to receive an influenza vaccine

A Brief History



Source: Barberis I et al. *J Prev Med Hyg* 2016.

Influenza Virus

2 types that cause seasonal epidemics: A and B

Influenza A

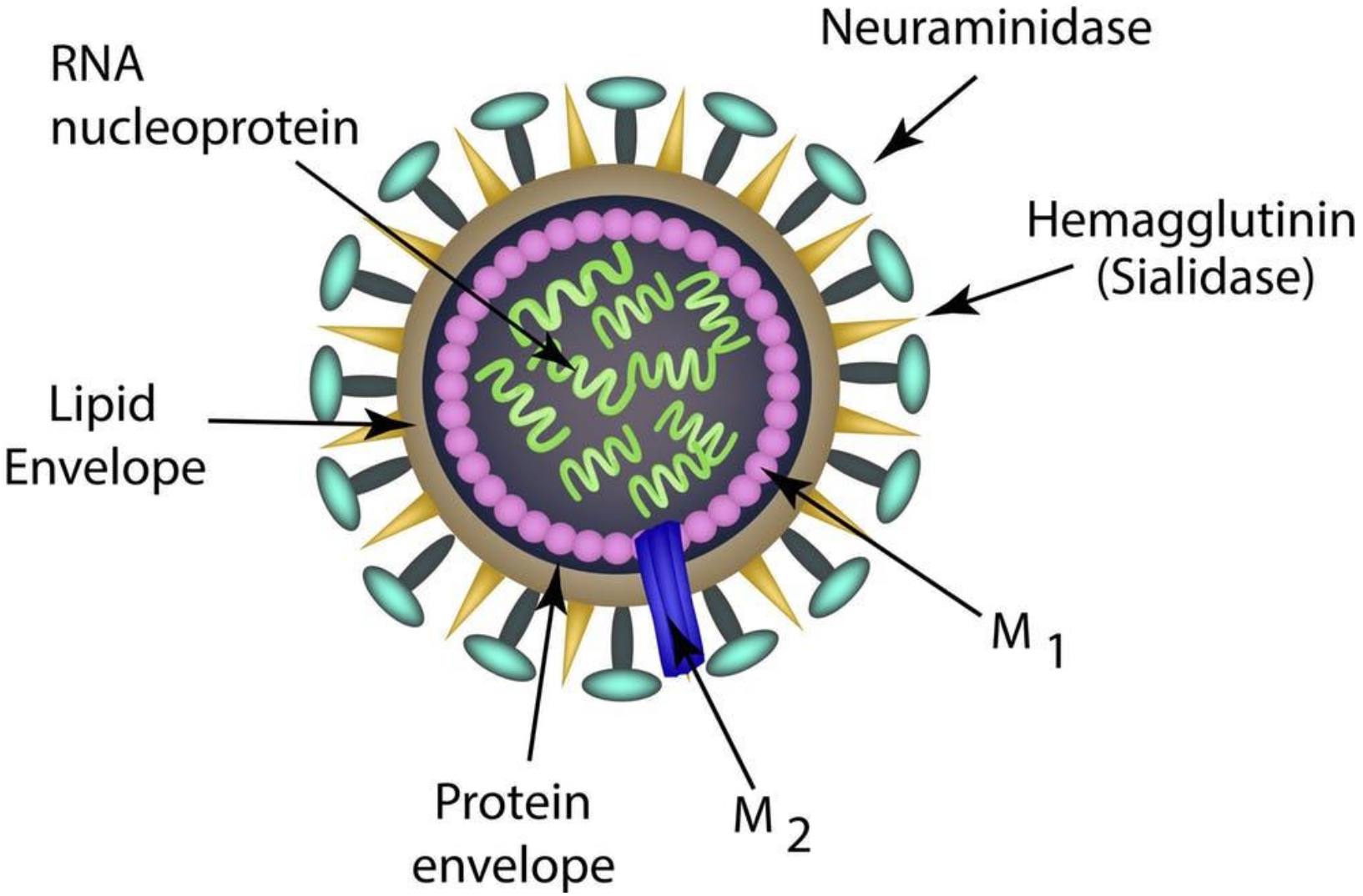
- Causes flu pandemics
- Divided into subtypes based on surface proteins hemagglutinin and neuraminidase
  - 18 hemagglutinin subtypes, 11 neuraminidase subtypes
  - "H1N1," "H3N2," etc.
  - Can be further classified into groups and subgroups

Influenza B

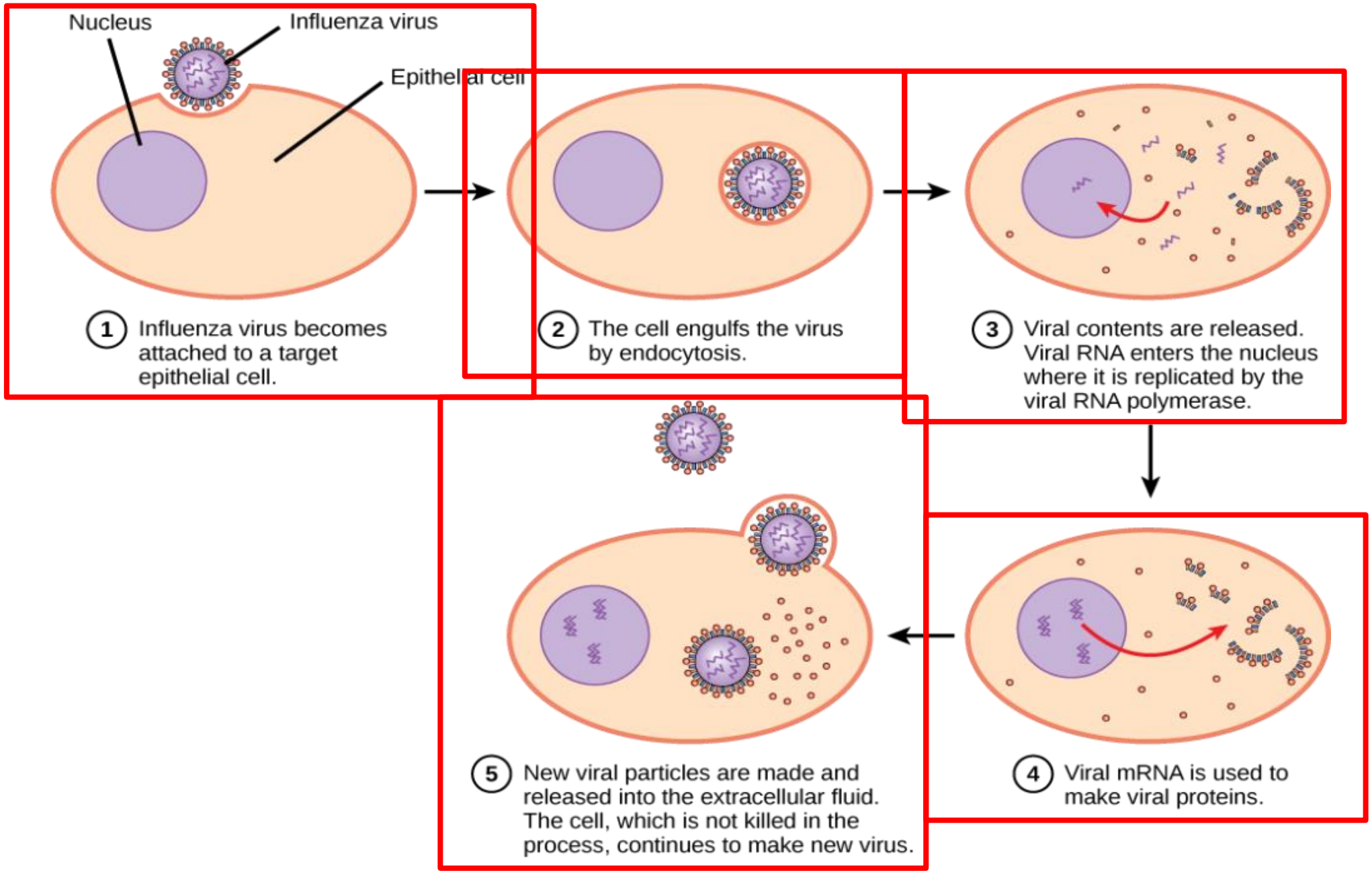
- Two lineages – Victoria and Yamagata

Vaccines contain H1N1, H3N2, and 1-2 influenza B viruses

Source: Dou D et al. *Front Immunol* 2018.



Source: https://theconversation.com/why-did-the-flu-kill-80-000-americans-last-year-105095



Source: https://courses.lumenlearning.com/suny-wmopen-biology2/steps-of-virus-infections-text-version/

Signs and Symptoms

- Fever/chills
- Cough
- Sore throat
- Muscle aches
- Headache
- Fatigue

Source: Influenza. Centers for Disease Control and Prevention. Accessed December 15, 2019.

Complications

- Secondary pneumonia
- Myocarditis
- Sinus infection
- Encephalitis
- Sepsis
- Multi-organ failure
- Death

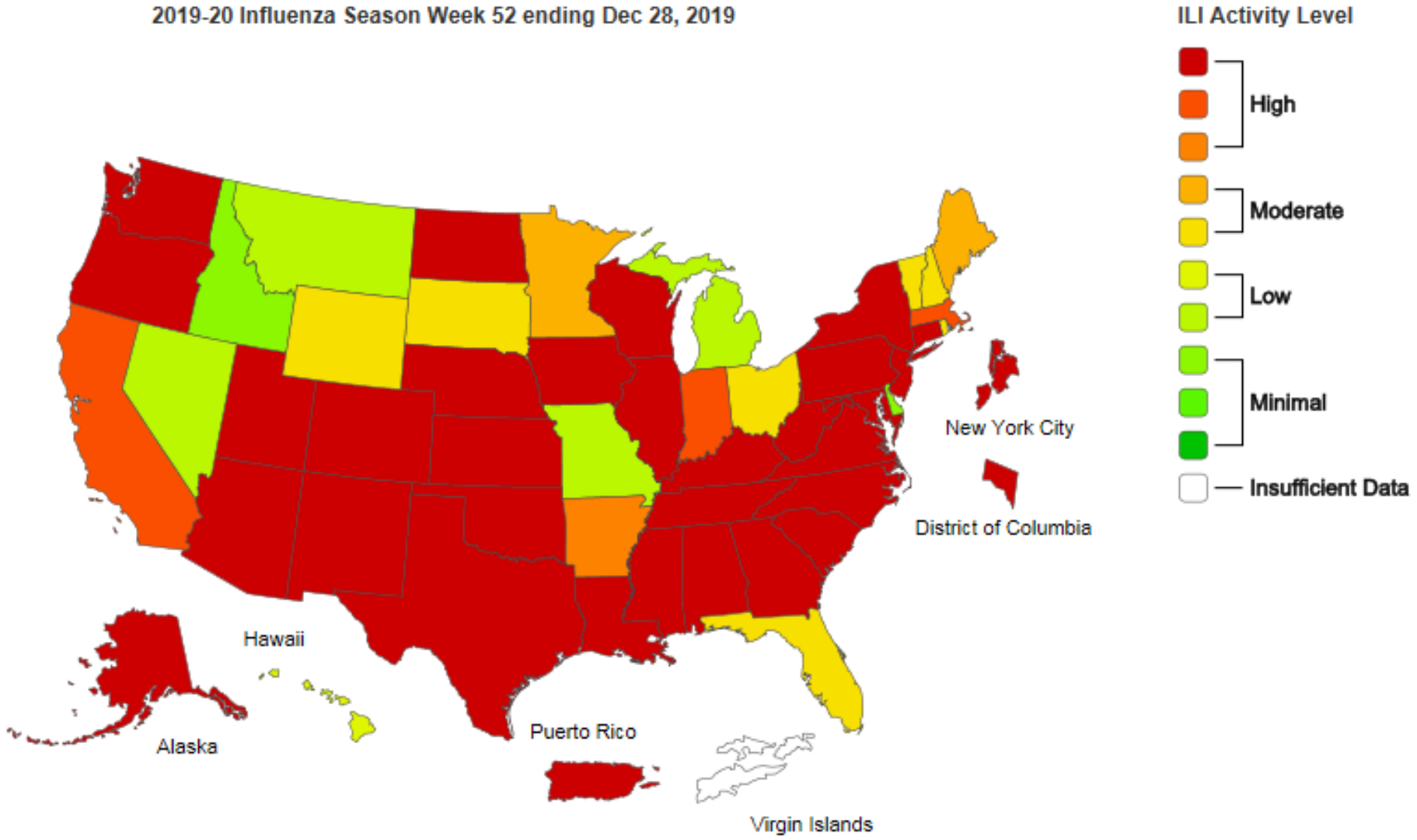
Source: Influenza. Centers for Disease Control and Prevention. Accessed December 15, 2019.

Patients at Highest Risk for Complications

- Children <2 years old
- Adults >65 years old
- Chronic conditions
  - Pulmonary, cardiovascular, renal, hepatic, hematologic, or metabolic disorders
  - Neurologic or neurodevelopment conditions including stroke and epilepsy
- Immunosuppression
  - May be caused by medications or HIV infection
- Pregnant women or women ≤ 2 weeks postpartum
- Children and adolescents up to 18 years old receiving aspirin- or salicylate-containing medications
- American Indian/Alaska Native people
- Extreme obesity (BMI >40 kg/m^2)
- Nursing home or other chronic care facility residents

Source: Uyeki TM et al. *Clin Infect Dis* 2018.

Current Influenza Activity



Source: Weekly U.S influenza surveillance report. Centers for Disease Control and Prevention. Accessed December 27, 2019.

Influenza Burden

2017-2018

- 45 million illnesses
- 21 million medical visits
- 810,000 hospitalizations
- 61,000 deaths

Vaccination prevented…

- 6.2 million illnesses
- 3.2 million medical illnesses
- 91,000 hospitalizations
- 5,700 deaths

Source: Influenza. Centers for Disease Control and Prevention. Accessed December 15, 2019.

Best Treatment: Prevention

Vaccination

Good hygiene

Pre-exposure prophylaxis

Post-exposure prophylaxis

Source: Influenza. Centers for Disease Control and Prevention. Accessed December 15, 2019.

ACIP* Recommendations for 2019-2020

Basically everybody older than 6 months

- Any age-appropriate flu vaccine
- Two doses, four weeks apart for those 6 months to 8 years who have never been vaccinated

Contraindications

- History of severe allergic reaction to any component of vaccine or a previous dose of influenza vaccine

Precautions

- Moderate or severe acute illness with or without fever
- History of Guillain-Barre Syndrome (GBS) within 6 weeks after receipt of influenza vaccine

Source: Grohskopf LA et al. *MMWR Recomm Rep* 2019.

*ACIP: Advisory Committee on Immunization Practices

Updates to ACIP* Recommendations for 2019-2020

Afluria®

- Indication age range updated
  - Formerly indicated for ages 5 years and older
  - Now approved for ages 6 months and up
- 0.25 mL dose for ages 6-35 months, 0.5 mL dose for ages 36 months and older
- Quadrivalent vaccine

Fluzone®

- Dosing information updated
  - Formerly 0.25 mL dose recommended for ages 6-35 months
  - Now 0.5 mL dose recommended for all children, including those younger than 35 months
  - Quadrivalent vaccine

*ACIP: Advisory Committee on Immunization Practices

Source: Grohskopf LA et al. *MMWR Recomm Rep* 2019.

Vaccines Available

Trivalent	Quadrivalent	Live	High-dose
Adjuvanted	Cell culture-based	Egg-based	Recombinant

Source: Centers for Disease Control and Prevention.

Vaccine Product	Virus	Egg-based, Cell culture-based, or Recombinant?	Trivalent or Quadrivalent?	Age Indication
Afluria®	Inactivated	Egg-based	Quadrivalent	≥6 months
Fluad®	Inactivated	Egg-based	Trivalent	≥65 years
Fluarix®	Inactivated	Egg-based	Quadrivalent	≥6 months
Flucelvax®	Inactivated	Cell culture-based	Quadrivalent	≥4 years
FluLaval®	Inactivated	Egg-based	Quadrivalent	≥6 months
Fluzone®	Inactivated	Egg-based	Quadrivalent	≥6 months
Fluzone High-Dose®	Inactivated	Egg-based	Trivalent	≥65 years
Flublok®	Inactivated	Recombinant	Quadrivalent	≥18 years
FluMist®	Live attenuated	Egg-based	Quadrivalent	2-49 years

Source: Grohskopf LA et al. *MMWR Recomm Rep* 2019.

Vaccine Product	Virus	Egg-based, Cell culture-based, or Recombinant?	Trivalent or Quadrivalent?	Age Indication
Afluria®	Inactivated	Egg-based	Quadrivalent	≥6 months
Fluad®	**Inactivated**	**Egg-based**	**Trivalent**	**≥65 years**
Fluarix®	Inactivated	Egg-based	Quadrivalent	≥6 months
Flucelvax®	Inactivated	Cell culture-based	Quadrivalent	≥4 years
FluLaval®	Inactivated	Egg-based	Quadrivalent	≥6 months
Fluzone®	Inactivated	Egg-based	Quadrivalent	≥6 months
Fluzone High-Dose®	**Inactivated**	**Egg-based**	**Trivalent**	**≥65 years**
Flublok®	Inactivated	Recombinant	Quadrivalent	≥18 years
FluMist®	Live attenuated	Egg-based	Quadrivalent	2-49 years

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Fluzone®	Inactivated	Egg-based	Quadrivalent	≥6 months
Fluzone High-Dose®	Inactivated	Egg-based	Trivalent	≥65 years
Flublok®	Inactivated	Recombinant	Quadrivalent	≥18 years
FluMist®	**Live attenuated**	**Egg-based**	**Quadrivalent**	**2-49 years**

Source: Grohskopf LA et al. *MMWR Recomm Rep* 2019.

Live Influenza Vaccine

Contraindications slightly different

- Concomitant aspirin or salicylate-containing therapy in children and adolescents
- Children ages 2-4 years with asthma or a wheezing episode in the last 12 months
- Immunocompromised patients of all ages
- Close contacts of a severely immunosuppressed person who requires a protected environment
- Pregnancy
- Receipt of influenza antivirals within the last 48 hours

Additional precautions

- Those with asthma
- Those with other chronic medical conditions (pulmonary, cardiovascular, renal, hepatic, neurologic, hematologic, or metabolic disorders)

Source: Grohskopf LA et al. *MMWR Recomm Rep* 2019.

Egg Allergy?

Not a contraindication!

- Patients with an egg allergy should receive any licensed, recommended influenza vaccine appropriate for their age and health status

Severe reaction (anaphylaxis)

- Supervise administration in inpatient or outpatient setting
- No set duration, but ACIP recommends observing all patients for 15 minutes after vaccination in the event of syncope

Vaccines that don't contain eggs

- Flucelvax®
- Flublok®

Source: Grohskopf LA et al. *MMWR Recomm Rep* 2019.

Knowledge Checkpoint 1:

RM is a 17-year-old healthy female who has not had her flu vaccine this season. Her current medications include budesonide-formoterol for asthma. She has no allergies and has never had a reaction to an influenza vaccine. Which of the following would be an appropriate choice for her this season?

- a. Afluria® - inactivated quadrivalent influenza vaccine
- b. FluMist® - live attenuated quadrivalent influenza vaccine
- c. Fluzone High-Dose® - inactivated trivalent influenza vaccine
- d. RM does not need an influenza vaccine this season

Knowledge Checkpoint 1 Response:

RM is a 17-year-old healthy female who has not had her flu vaccine yet. Her current medications include budesonide-formoterol for asthma. She has no allergies and has never had a reaction to an influenza vaccine. Which of the following would be an appropriate choice for her this season?

- a. **Afluria® - inactivated quadrivalent influenza vaccine**
- b. FluMist® - live attenuated quadrivalent influenza vaccine
- c. Fluzone High-Dose® - inactivated trivalent influenza vaccine
- d. RM does not need an influenza vaccine this season

Pre-Exposure Prophylaxis Candidates

For the duration of flu season:

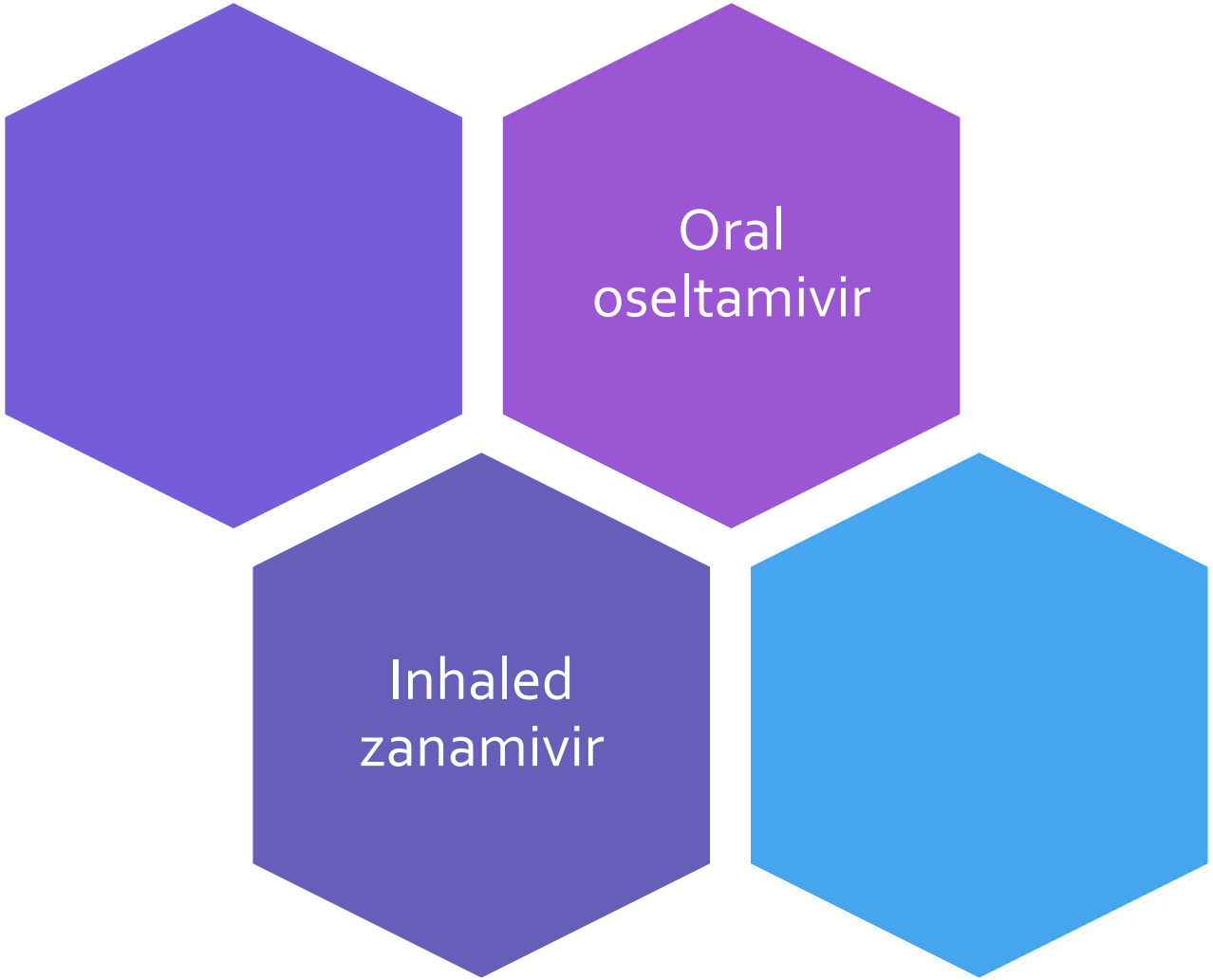
- ≥3 months old at highest risk of complications
  - Stem cell transplant recipients
  - Lung transplant recipient
- ≥3 months with very high risk of complications
  - Vaccine contraindicated or unavailable
  - Vaccine not expected to be effective

For short-term prophylaxis:

- ≥3 months old at high risk of developing complications
  - Vaccine has not yet been administered, but there is influenza activity in community
- Unvaccinated patients ≥3 months
  - If in close contact with people at high risk of developing complications
  - If those in close contact cannot take chemoprophylaxis

Source: Uyeki TM et al. *Clin Infect Dis* 2018.

Pre-Exposure Prophylaxis Drug Options



Source: Uyeki TM et al. *Clin Infect Dis* 2018.

Post-Exposure Prophylaxis Candidates

≥3 months with very high risk of complications

- Vaccine contraindicated or unavailable
- Vaccine not expected to be effective

Unvaccinated patients ≥3 months

- If household contacts include people at high risk of developing complications

Vaccinate when not contraindicated

Source: Uyeki TM et al. *Clin Infect Dis* 2018.

Post-Exposure Prophylaxis Drug Options

Inhaled zanamivir

Oral oseltamivir

Begin within 48 hours of exposure

Continue for 7 days after most recent exposure

Source: Uyeki TM et al. *Clin Infect Dis* 2018.

Knowledge Checkpoint 2:

Which of the following patients are eligible for influenza prophylaxis and why?

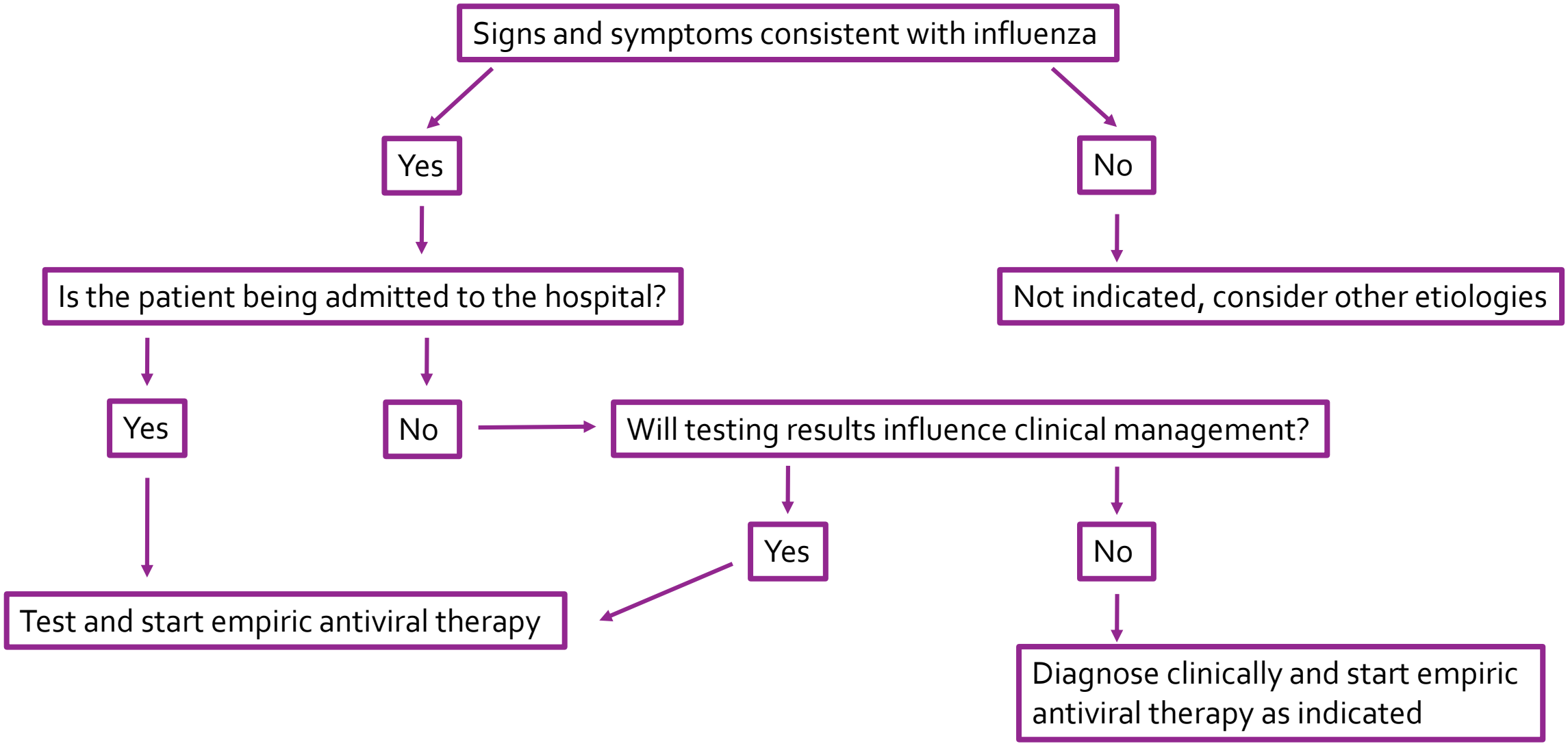
- a. A 45-year-old male with a history of a lung transplant on immunosuppression
- b. A 22-year-old male with no pertinent medical history who received a flu vaccine six weeks ago and has a roommate with influenza but no other close contacts
- c. A 67-year-old fully vaccinated female whose grandchild, who currently has the flu, visited three days ago

Knowledge Checkpoint 2 Response:

Which of the following patients are eligible for influenza prophylaxis and why?

- a. **A 45-year-old male with a history of a lung transplant on immunosuppression**
- b. A 22-year-old male with no pertinent medical history who received a flu vaccine six weeks ago and has a roommate with influenza but no other close contacts
- c. A 67-year-old fully vaccinated female whose grandchild, who currently has the flu, visited three days ago

When to Test for Influenza



Source: Influenza. Centers for Disease Control and Prevention. Accessed December 15, 2019.

Who to Treat?

All patients hospitalized with influenza	• Regardless of symptom duration
Outpatients with severe or progressive illness	• Regardless of symptom duration
Outpatients at high risk of complications	• Regardless of symptom duration

Source: Uyeki TM et al. *Clin Infect Dis* 2018.

Consider Treating…

Symptomatic outpatients with household contacts at high risk of developing complications

Symptomatic healthcare providers who care for patients at high risk of developing complications

Outpatients not at high risk of complications with symptom onset within 48 hours of presentation

Source: Uyeki TM et al. *Clin Infect Dis* 2018.

Influenza Treatment

Oseltamivir

Peramivir

Zanamivir

Baloxavir

Amantadine

Source: Uyeki TM et al. *Clin Infect Dis* 2018.

Influenza Treatment

Oseltamivir

Peramivir

Zanamivir

Source: Uyeki TM et al. *Clin Infect Dis* 2018.

Neuraminidase Inhibitors

Indications

- Oseltamivir, zanamivir: influenza treatment and prophylaxis
- Peramivir: influenza treatment only

Adverse effects

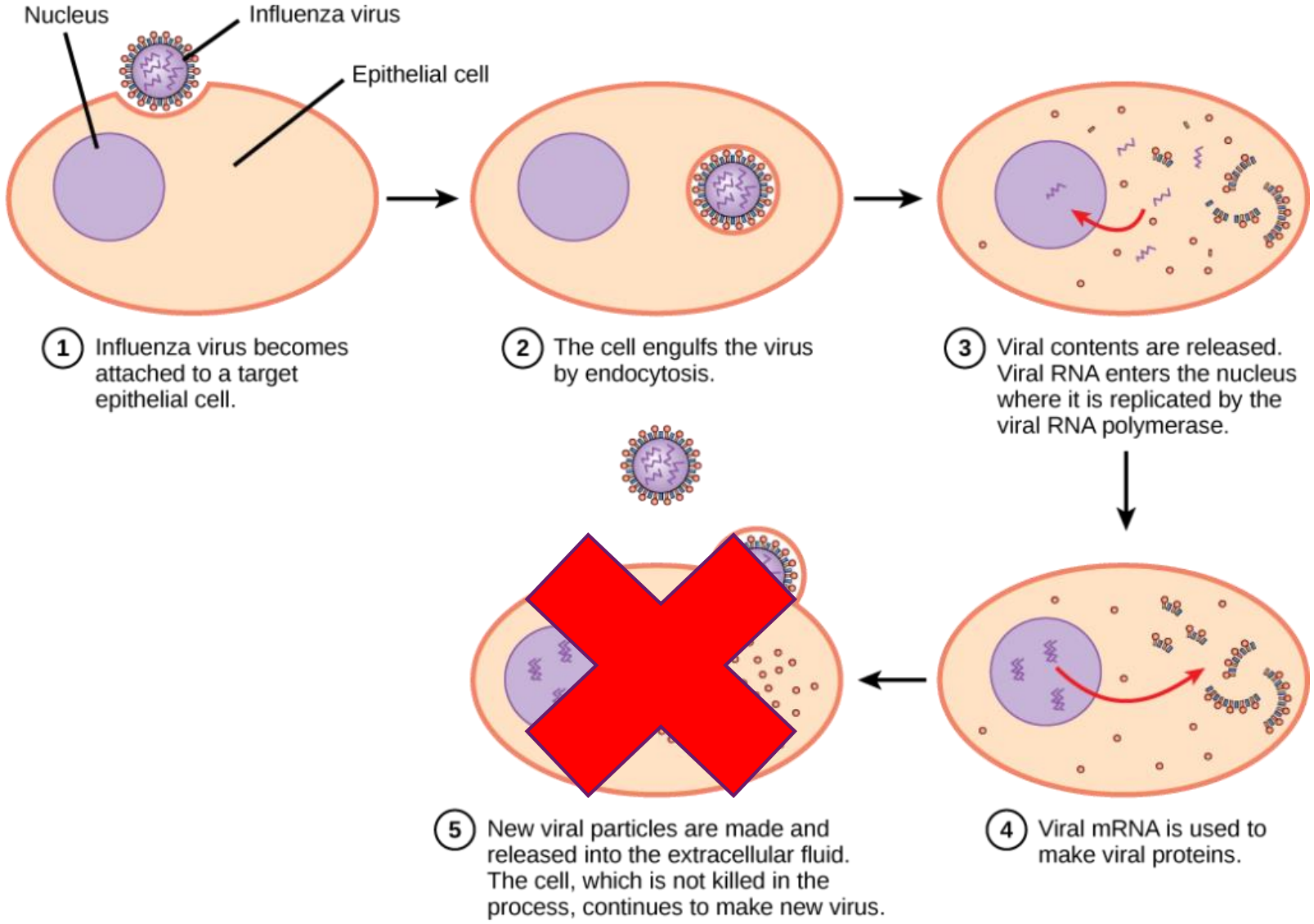
- Headache
- Sore throat
- Decreased appetite
- Vomiting
- Diarrhea

Warnings and precautions

- Allergic and skin reactions including Stevens-Johnson syndrome
- Neuropsychiatric events: abnormal behavior, delirium, hallucinations, self-harm

Sources: Oseltamivir [package insert]. South San Francisco, CA.
Peramivir [package insert]. Summit, NJ.
Zanamivir [package insert]. Research Triangle Park, NC.

Mechanism of Action



Source: https://courses.lumenlearning.com/suny-wmopen-biology2/steps-of-virus-infections-text-version/

Oseltamivir

- Administered orally
- Indicated for treatment in patients 2 weeks and older, prophylaxis in 1 year and older
- Renally adjusted (CrCl <60 mL/min)
- Prophylaxis: 75 mg once daily
- Treatment: 75 mg twice daily
- Treatment duration: 5 days
- Preferred agent for pregnant patients, <2 weeks postpartum

Source: Oseltamivir [package insert]. South San Francisco, CA.

Zanamivir

- Administered via inhalation
- Indicated for patients 5 years and older
- Prophylaxis: 10 mg (two inhalations) once daily
- Treatment: 10 mg (two inhalations) twice daily
- Treatment duration: 5 days

Source: Zanamivir [package insert]. Research Triangle Park, NC.

Peramivir

- Administered intravenously
- Indicated for patients 2 years and older
- Renally adjusted (CrCl <60 mL/min)
- Uncomplicated influenza: 600 mg once (12 mg/kg for ages 2-12)
- Hospitalized patients: 600 mg once daily for 5-10 days*

Sources: Peramivir [package insert]. Summit, NJ.
Peramivir. Lexicomp® Online.

Knowledge Checkpoint 3:

CM is a 67-year-old female with a BMI of 42 kg/m^2 and CrCl ~65 mL/min who has not received a vaccine yet this season. You determine that she requires post-exposure prophylaxis. Her most recent exposure was today. Which of the following regimens should CM receive?

- a. Peramivir 600 mg IV x 1 dose
- b. Oseltamivir 75 mg po daily for 7 days
- c. Oseltamivir 75 mg po BID for 5 days
- d. Zanamivir 10 mg inhalation BID for 7 days

Knowledge Checkpoint 3 Response:

CM is a 67-year-old female with a BMI of 42 kg/m^2 and CrCl ~65 mL/min who has not received a vaccine yet this season. You determine that she requires post-exposure prophylaxis. Her most recent exposure was today. Which of the following regimens should CM receive?

- a. Peramivir 600 mg IV x 1 dose
- **b. Oseltamivir 75 mg po daily for 7 days**
- c. Oseltamivir 75 mg po BID for 5 days
- d. Zanamivir 10 mg inhalation BID for 7 days

Baloxavir

Indication

- Influenza treatment only

Adverse effects

- Diarrhea
- Nasopharyngitis

Warnings and precautions

- Hypersensitivity
- Anaphylaxis
- Angioedema

No official recommendation from IDSA 2018 guidelines on influenza treatment for baloxavir, since it was approved after the guidelines were finalized

Sources: Baloxavir [package insert]. South San Francisco, CA.
Uyeki TM et al. *Clin Infect Dis* 2018.

Baloxavir

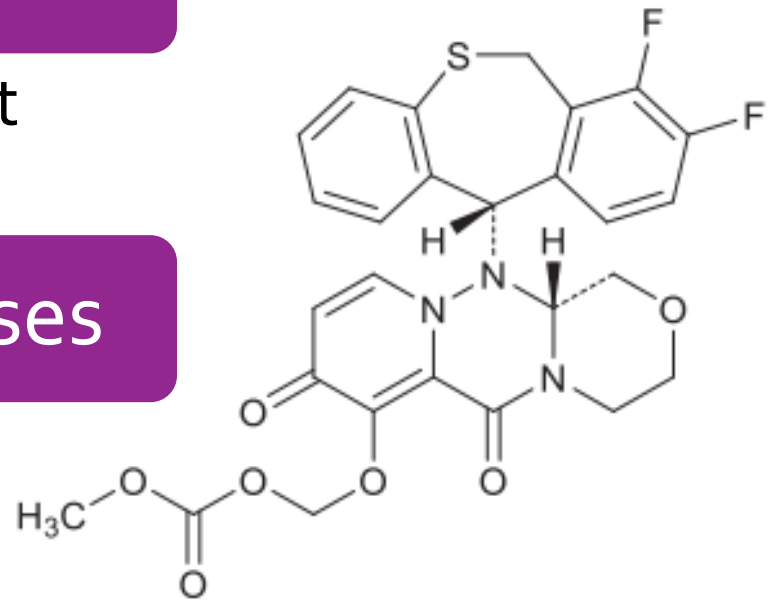
Prodrug (baloxavir marboxil)

Cap-dependent endonuclease inhibitor

- Inhibits polymerase acidic protein activity to inhibit virus replication

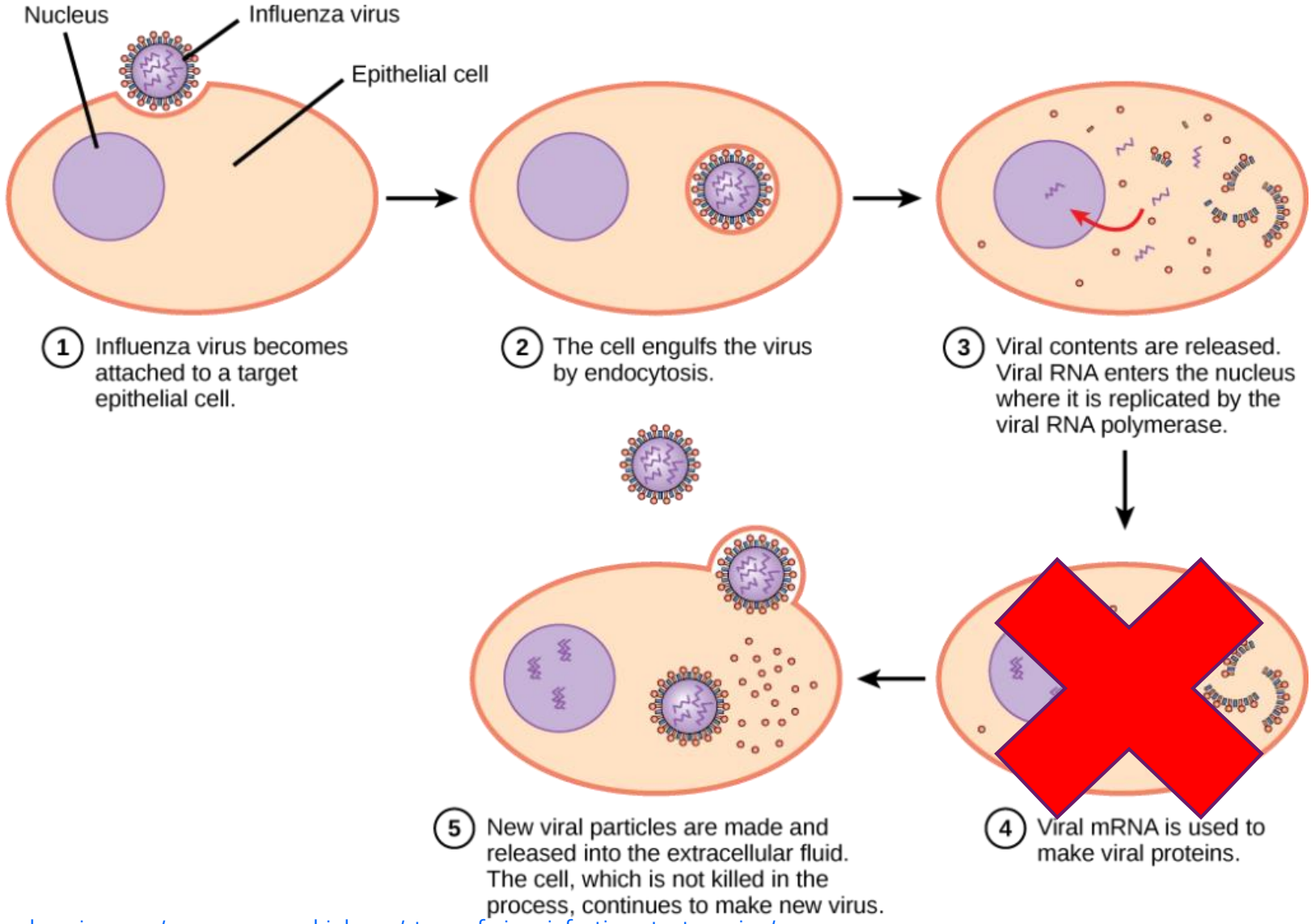
Has activity against influenza A and B viruses

- Even those resistant to other antivirals



Sources: Baloxavir [package insert]. South San Francisco, CA.
Ng KE. *P&T* 2019.

Mechanism of Action



Source: https://courses.lumenlearning.com/suny-wmopen-biology2/steps-of-virus-infections-text-version/

Baloxavir

- Administered orally
- For patients 40 to <80 kg: 40 mg x 1 dose
- For patients 80 kg or more: 80 mg x 1 dose
- Indicated for patients 12 years and older
- No renal or hepatic adjustments

Source: Baloxavir [package insert]. South San Francisco, CA.

CAPSTONE-1 Trial

Double-blind, placebo- and oseltamivir-controlled, randomized trial

Inclusion criteria

- Outpatients with influenza-like illness in the US and Japan from December 2016-March 2017
- Fever plus at least one systemic symptom and one respiratory symptom of influenza
- Symptom duration no longer than 48 hours

Exclusion criteria

- Patients receiving any other influenza treatment except acetaminophen (symptomatic management, antivirals, or antibiotics)

Source: Hayden FG et al. *N Engl J Med* 2018.

CAPSTONE-1 Trial

Adults 20-64 years old received:

- Baloxavir x 1 dose
- Oseltamivir 75 mg BID x 5 days
- Matching placebos

Patients 12-19 years old received:

- Baloxavir x 1 dose
- Matching placebo

Source: Hayden FG et al. *N Engl J Med* 2018.

CAPSTONE-1 Trial

Primary outcome: time to alleviation of symptoms

- Significantly shorter in baloxavir group compared to placebo
- No significant difference between baloxavir- and oseltamivir-treated patients
- Effect consistent among adolescents and adults
- Greater difference in patients who initiated therapy within 24 hours

Secondary outcomes

- Time to resolution of fever
- Time to return to usual health
- Newly occurring complications leading to antibiotic use

Source: Hayden FG et al. *N Engl J Med* 2018.

CAPSTONE-1 Trial

Outcome	Baloxavir	Placebo	Oseltamivir
Time to alleviation of symptoms	53.5 hours*	80.2 hours	53.8 hours*
Time to resolution of fever	24.5 hours*	42 hours	
Time to return to usual health	129.2 hours	168.8 hours	
Frequency of complications resulting in antibiotic treatment	3.5%	4.3%	2.4%
Duration of infectious virus detection	24 hours*	96 hours	72 hours
Rate of adverse events related to trial regimen	4.4%*	3.9%	8.4%

*statistically significantly different

Source: Hayden FG et al. *N Engl J Med* 2018.

CAPSTONE-1 Trial

- Single doses of baloxavir superior to placebo in reducing influenza symptoms
- Fewer clinically significant adverse effects
- Initiating therapy early resulted in faster symptom improvement compared to placebo
- Antiviral activity of baloxavir superior to oseltamivir

Source: Hayden FG et al. *N Engl J Med* 2018.

CAPSTONE-2 Trial

Randomized, double-blind, placebo- and oseltamivir-controlled study

- Included patients at high risk of influenza complications
- 2184 patients included
- Faster relief of symptoms with baloxavir over placebo, no difference compared to oseltamivir
- No difference in influenza complications among three groups

Full study has not yet been published

- Suggests baloxavir may be useful for patients at risk of influenza complications

Source: Ison MG et al. Presented at ID Week 2018; San Francisco, CA.

Baloxavir resistance

"Cause for concern"

- Decreased viral RNA levels at 24 hours
- Shorter duration of infectious virus detection
- Emergence of viral escape mutants with reduced susceptibility to the drug

Viral mutants appeared in up to 10% of patients studied

- Typically appeared at least 5 days after baloxavir treatment
- Duration of symptoms significantly longer when viral escape mutants were present

Source: Uyeki TM. *N Engl J Med* 2018.

Role of the Pharmacist

Appropriate vaccine selection

Identification of patients at high risk of complications

Appropriate prophylaxis and treatment selection

Summary

Vaccinate almost everybody

- Very few contraindications to the influenza vaccine
- Select an age-appropriate, ACIP-recommended vaccine

Prophylaxis should be initiated in patients at high risk of complications

- Depending on vaccine history, household contacts

Treat regardless of symptom duration for any patients that are hospitalized, have severe illness, or are at high risk of complications

- For outpatients not at high risk of complications, initiate within 48 hours of symptom onset

Baloxavir not included in 2018 IDSA guidelines, but is an option for influenza treatment for some patients

- Demonstrated superiority over placebo with fewer clinically significant adverse effects than oseltamivir

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THANK YOU!

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