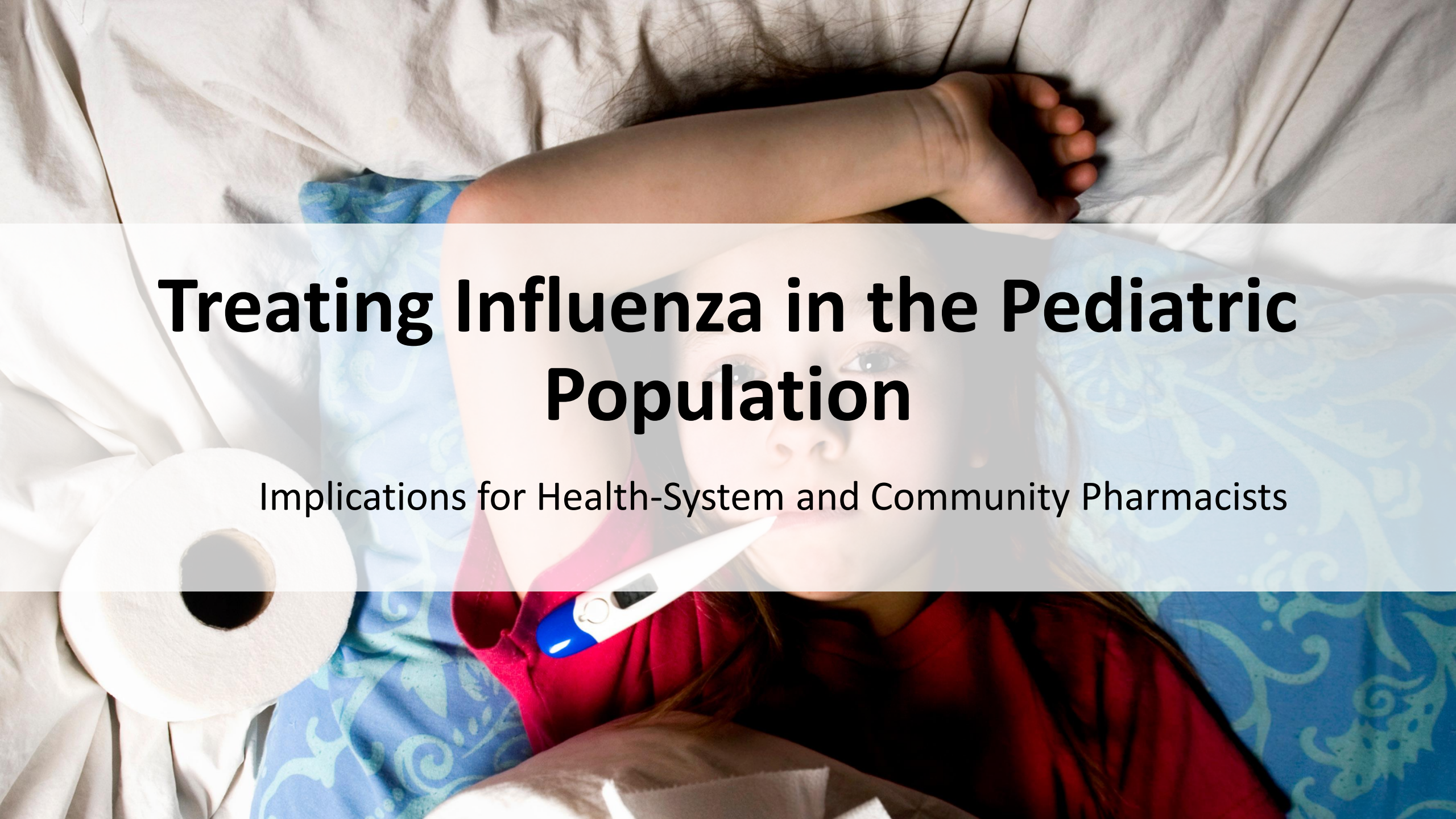

Treating Influenza in the Pediatric Population

Implications for Health-System and Community Pharmacists

This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by an educational grant from Genentech, Inc.

Faculty

Molly Hayes, PharmD, BCPS
Infectious Disease Clinical Pharmacist
Children's Hospital of Philadelphia
Philadelphia, PA

Dr. Hayes is a clinical pharmacy specialist in Infectious Diseases. She currently works for the Antimicrobial Stewardship Program as a part of the Center for Healthcare Quality and Analytics at the Children's Hospital of Philadelphia. Dr. Hayes works closely with the Infectious Diseases consult services and participates in multiple clinical research projects. She also leads several quality improvement initiatives aimed at improving antimicrobial use in children.
Dr. Hayes received her Bachelor of Science in Biology and Doctor of Pharmacy degrees from Temple University. She completed her Pharmacy Practice and Infectious Diseases residencies at Thomas Jefferson University Hospital. Dr. Hayes is a Board Certified Pharmacotherapy Specialist and a member of the Pediatric Infectious Diseases Society.

Faculty

Talene Metjian, PharmD

Manager, Antimicrobial Stewardship Program
Infectious Disease Clinical Pharmacist
Children's Hospital of Philadelphia
Philadelphia, PA

Dr. Metjian is the manager of the Antimicrobial Stewardship Program and a clinical specialist in Pediatric Infectious Diseases at the Children's Hospital of Philadelphia. She received her Bachelor of Science in Pharmacy and Doctor of Pharmacy degrees from the Philadelphia College of Pharmacy/University of the Sciences in Philadelphia. Dr. Metjian completed a residency in Pediatric Pharmacy Practice at the Children's Hospital of Philadelphia. Dr. Metjian develops and maintains antimicrobial treatment guidelines, monitors antimicrobial use within the institution, performs quality improvement projects, and provides education on the appropriate use of antimicrobials to patients, families, and employees. Dr. Metjian sits on numerous committees, including the Influenza Vaccine Taskforce, and co-chairs the Antibiotic Drug Use Evaluation Subcommittee Meeting. Dr. Metjian is a member of the Pediatric Infectious Diseases Society and the Society of Infectious Disease Pharmacists.

Acknowledgement

The faculty wishes to acknowledge the contribution of Jordan Serio, PharmD (Resident)

Disclosures

Drs. Metjian and Serio have disclosed that they have no relevant affiliations or financial relationships with a commercial interest to disclose.

Dr. Hayes has disclosed that she has received grant/research support from Merck.

The following clinical reviewer, **Kyle A. Davis, PharmD**, hereby states he has no relevant affiliation or financial relationship or relationship to products or devices with a commercial interest related to the content of this activity to disclose.

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UAN: **0430-0000-20-100-H01-P**
Credits: 1.5 hour (0.15 CEU)
Type of Activity: Application

Learning Objectives

- **Describe** the burden of influenza in pediatric patients, including the risk of severe complications
- **Apply** knowledge of FDA-approved antiviral therapies to the treatment of influenza in pediatric patients
- **Integrate** safety and efficacy outcomes from recent clinical trials into the treatment of influenza in pediatric patients
- **Demonstrate** effective communication strategies to educate children and their parents about influenza treatment options

ARS Question #1

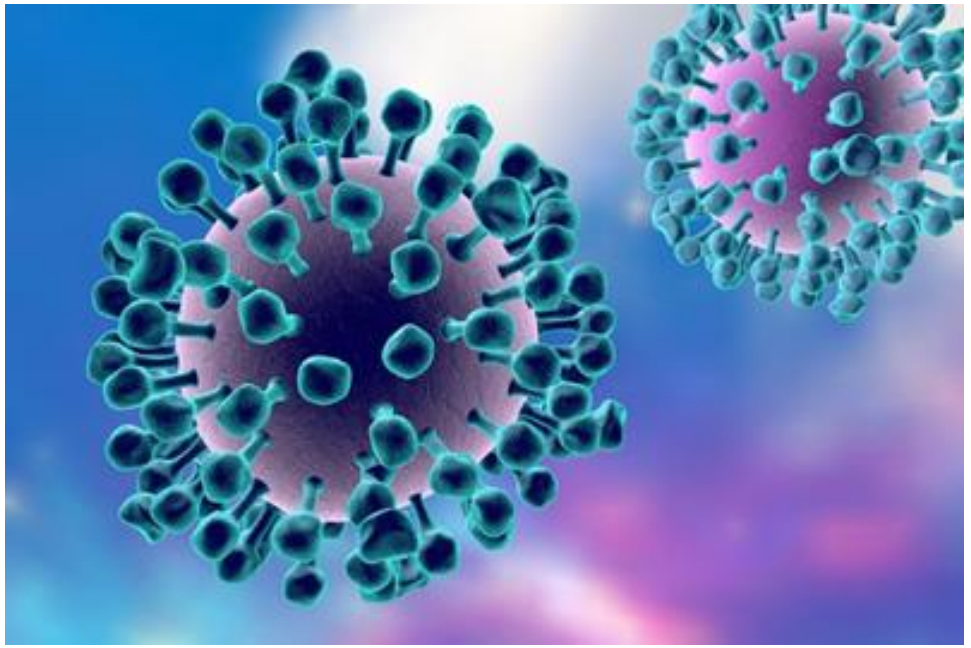
Yes or No?

Are you comfortable in the management of pediatric patients diagnosed with influenza?

Background

Etiology – The Influenza Virus

- “Influence of the stars”
- 1580 was the first described pandemic
- Influenza A virus was first isolated in 1933 from ferrets
- Orthomyxoviridae family
  - Single-stranded, helically shaped, RNA virus
  - Spherical
  - Types A, B, C, and D



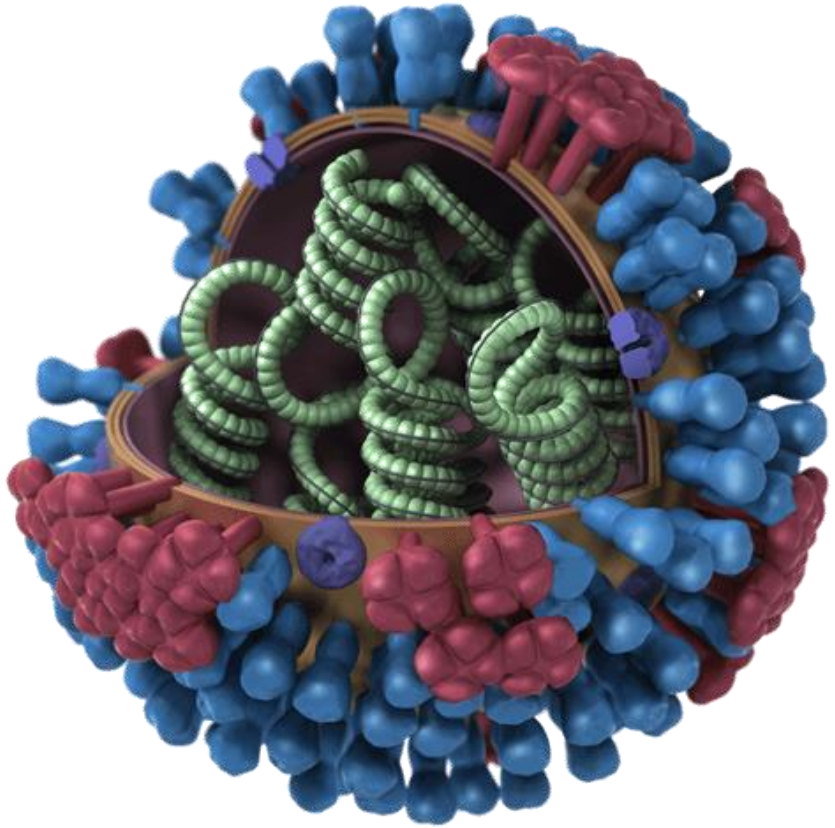
Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/pubs/pinkbook/flu.html.

Pathogen

- Influenza A
  - Classified according to subtype based on 2 proteins
    - Hemagglutinin (H) – 18 (H1 – H18)
    - Neuraminidase (N) – 11 (N1 – N11)
    - Example: A(H1N1)

- Infects humans and other animals
  - Moderate to severe illness
  - Affects all age groups

Influenza A



Centers for Disease Control and Prevention. https://www.cdc.gov/flu/about/viruses/types.htm#:~:text=There%20are%20four%20types%20of,global%20epidemics%20of%20flu%20disease.;
Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/pubs/pinkbook/flu.html.

Pathogen

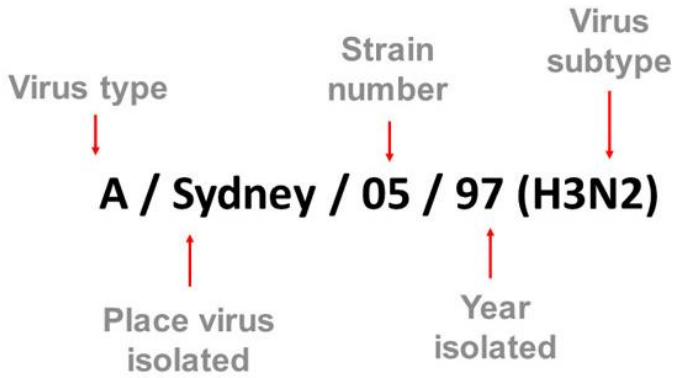
Influenza B

- Two lineages
  - B/Yamagata
  - B/Victoria
- Affects humans
  - Milder disease than influenza A
  - Primarily affects children

- Influenza A and B are responsible for seasonal epidemics and make up the influenza vaccine

Nomenclature

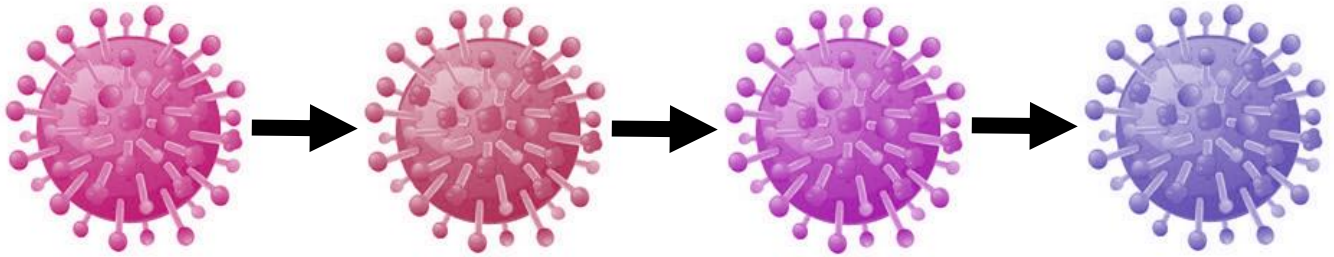
1. Name starts with the virus type
2. Place the virus was isolated
3. Virus strain number
4. Year isolated
5. Virus subtype



Centers for Disease Control and Prevention. https://www.cdc.gov/flu/about/viruses/types.htm#:~:text=There%20are%20four%20types%20of,global%20epidemics%20of%20flu%20disease.; Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/pubs/pinkbook/flu.html.

Antigenic Changes

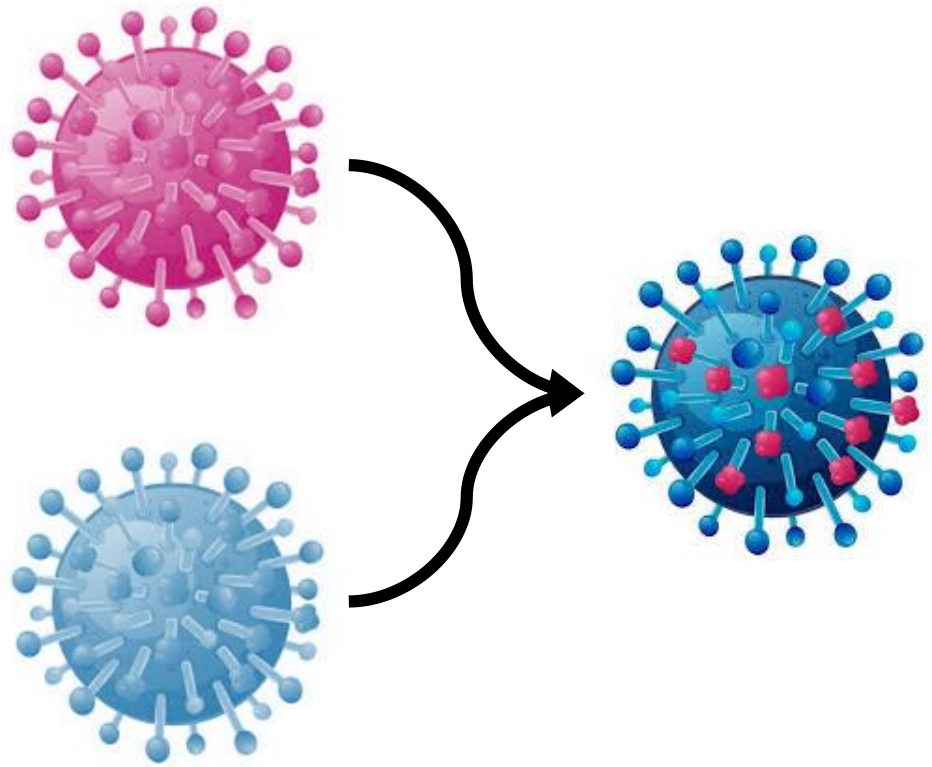
- Antigenic drift
  - Small point mutations or minor changes in influenza virus A or B
    - Lead to changes in the surface proteins hemagglutinin and neuraminidase
  - Viruses are closely related
    - Incomplete immunity from exposures or vaccines
  - Associated with epidemics
    - 1997–1998 a variant of the circulating A/Wuhan/359/95 (H3N2) appeared named A/Sydney/5/97
  - Reason for variation in the influenza vaccine composition each year



American Academy of Pediatrics. *Red Book.* 2018;476-90.;
Centers for Disease Control and Prevention. https://www.cdc.gov/flu/about/viruses/change.htm#:~:text=When%20shift%20happens%2C%20most%20people,in%20the%20past%20100%20years.;
Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/pubs/pinkbook/flu.html.

Antigenic Changes

- Antigenic shift
  - Abrupt, major change likely due to genetic recombination of influenza A
  - Change in 1 or both surface antigens (H or N)
  - Most people will have little or no pre-existing immunity
  - Associated with pandemics
    - 2009 H1N1 pandemic (A(H1N1)pdm09)

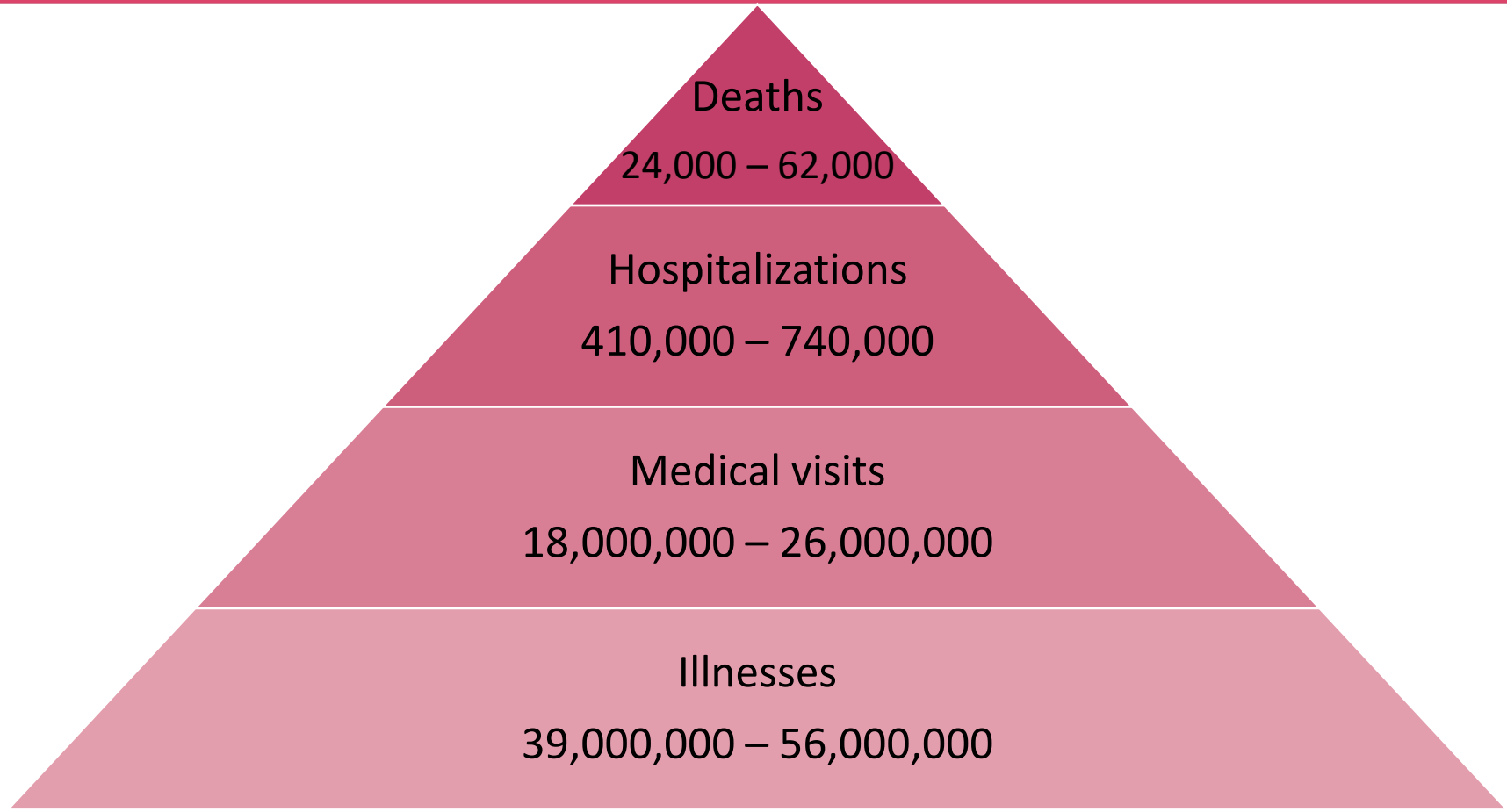


American Academy of Pediatrics. *Red Book.* 2018;476-90.;
Centers for Disease Control and Prevention. https://www.cdc.gov/flu/about/viruses/change.htm#:~:text=When%20shift%20happens%2C%20most%20people,in%20the%20past%20100%20years.;
Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/pubs/pinkbook/flu.html.

Burden of Influenza in the Pediatric Population

Epidemiology

- Highly contagious respiratory illness prevalent during winter months
- Spread person to person
  - Respiratory droplet and less commonly via contact



Estimated burden of influenza in the U.S.: 2019–2020

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm.;
Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/pubs/pinkbook/flu.html.

Pediatric Morbidity and Mortality (U.S.)

- Hospitalization and mortality rates highest in patients < 6 months old
- Hospitalizations (2019–2020 flu season)
  - Ages 0–4 years: 93.3 per 100,000 population
  - Ages 5–17 years: 24.3 per 100,000 population
  - Ages 18–49 years: 34.8 per 100,000 population
- Mortality
  - 188 pediatric deaths in U.S. (2019–2020 flu season)
  - 2011 meta-analysis estimated between 28,000 and 111,500 aged < 5 years old die each year globally
- Pandemics lead to increased rates of morbidity and mortality
  - 2009 pandemic: 288 pediatric deaths

Centers for Disease Control and Prevention. https://gis.cdc.gov/grasp/fluview/fluhosprates.html.;
Centers for Disease Control and Prevention. https://gis.cdc.gov/grasp/fluview/pedfludeath.html.;
Ruf B, et al. *Eur J Pediatr.* 2014;173(3):265-76.

Pathogenesis

- Incubation period: 1–4 days
- Contagious via viral-shedding cough or sneeze
  - May be contagious 24 hours before symptom onset
  - Peaks during the first 3 days of illness
  - Duration: 5–7 days illness onset in adults and up to 10 or more days in young children
  - Viral shedding is correlated directly with degree of fever
- Majority of pediatric patients recover after 3–7 days

American Academy of Pediatrics. *Red Book.* 2018;476-90.;
Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/pubs/pinkbook/flu.html.

ARS Question #2

Emily is a 2-year-old with a 24-hour history of chills, headache, lethargy, stuffy nose, sore throat, and fever. Emily's mother states that her symptoms have progressed very abruptly. What is Emily's likely diagnosis?

- Influenza
- The common cold

Influenza Signs and Symptoms

Can range from mild to severe with a sudden onset

- Fever or feeling feverish/chills
- Cough (non-productive)
- Sore throat
- Rhinorrhea, nasal congestion
- Myalgia
- Headache
- Malaise
- Vomiting and diarrhea (more common in children than adults)

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/index.htm.;
Ruf BR, et al. *Eur J Pediatr.* 2014;173(3):265-76.

Cold vs. Flu

Signs and symptoms	Cold	Influenza (flu)
Symptom onset	Gradual	Abrupt
Fever	Rare	Usual
Aches	Slight	Usual
Chills	Uncommon	Common
Fatigue, weakness	Sometimes	Usual
Sneezing	Common	Sometimes
Chest discomfort, cough	Mild to moderate	Common; can be severe
Stuffy nose	Common	Sometimes
Sore throat	Common	Sometimes
Headache	Rare	Common

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/symptoms/symptoms.htm.

Risk Factors for Influenza Complications

Diseases

- Blood disorders
- Chronic respiratory diseases
- Endocrine disorders
- Heart disease
- Kidney disease
- Liver disorders
- Metabolic disorders
- Neurologic and neurodevelopmental conditions

People

- Adults > 65 years old
- American Indians and Alaska Natives
- Children < 2 years old
- Immunosuppressed
- People < 19 years old on long-term aspirin or salicylates
- Pregnant women
- Obese with BMI ≥ 40 kg/m^2
- Residents in long-term care facilities or nursing homes

BMI, body mass index.

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/highrisk/index.htm.

Complications

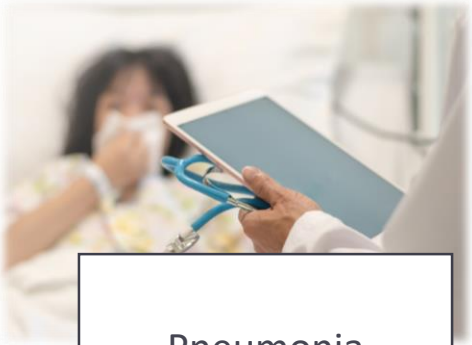
- Acute otitis media
- Dehydration
- Encephalitis/encephalopathy
- Exacerbation of chronic illness
- Sinus infection
- Myocarditis or pericarditis
- Myositis or rhabdomyolysis
- Pneumonia or bronchitis

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/symptoms/symptoms.htm.

Complications in Children < 5 Years Old

Acute otitis media

Sinus infections



Pneumonia

Exacerbation of chronic illnesses

Dehydration

Encephalopathy

Kondrich J, et al. *Curr Opin Pediatr*. 2017;29(3):297-302.;
Ruf BR, et al. *Eur J Pediatr.* 2014;173(3):265-76.

Emergency Warning Signs in Children

- Fast or trouble breathing
- Bluish lips or face
- Ribs pulling in with each breath
- Chest pain
- Severe muscle pain (child refuses to walk)
- Dehydration (no urine for 8 hours, dry mouth, no tears when crying)
- Not alert or interacting when awake
- Seizures
- Fever above 104°F
- In children younger than 12 weeks old, any fever
- Fever or cough that improve but then return or worsen
- Worsening of chronic medical conditions

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/symptoms/symptoms.htm.

Prevention of Influenza in Children and Adolescents

Preventative Measures

- Vaccination
- Infection prevention and control
- Chemoprophylaxis

Preventative Measures

- Vaccination
- Infection prevention and control
- Chemoprophylaxis

Vaccines

- Vaccination is the number one recommendation for prevention!

- Vaccine → anti-body production against the influenza viruses
  - Research indicates which virus will be most common during the upcoming flu season

- Influenza vaccine recommendations
  - Children aged 6 months – 8 years
    - Received fewer than 2 influenza vaccines before July 1, 2019: 2 doses, separated by at least 4 weeks
    - Received at least 2 influenza vaccines before July 1, 2019: 1 dose
  - All persons ≥ 9 years old: 1 dose yearly

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/prevent/how-fluvaccine-made.htm.;
Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html.

Vaccines

Egg-based	• Influenza viruses grown in hens' eggs
Cell-based	• Influenza viruses grown in cultured animal cells
Recombinant	• Synthetic production of influenza virus
Live attenuated	• Weakened but still able to replicate to produce immunity
Inactivated	• Whole or fractions of killed virus
Adjuvant	• Ingredient of a vaccine that helps promote a better immune response

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/prevent/how-fluvaccine-made.htm.

Vaccines

- Trivalent
  - 3 different influenza viruses: 2 influenza A viruses and 1 influenza B virus
- Quadrivalent
  - 4 different influenza viruses: 2 influenza A viruses and 2 influenza B viruses
  - *Aims to give broader protection against circulating influenza viruses*
- High-dose
  - Trivalent, inactivated
  - Specifically for people ≥ 65 years old
  - 4 times the antigen of standard dose
  - *Intended to give older individuals a stronger immune response*

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/prevent/how-fluvaccine-made.htm.

Vaccines

Individuals with egg allergies:

Can receive any licensed, recommended age-appropriate influenza vaccine

History of severe egg allergy:

Vaccination in a medical setting, supervised by a healthcare provider who can recognize and manage severe allergic reactions

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/professionals/vaccination/index.htm.

Vaccines

Influenza injection

- *Recommended:* children ≥ 6 months old
- *Not recommended:*
  - Children < 6 months old
  - Severe, life-threatening allergies to flu vaccine or any ingredient

Nasal spray – live attenuated influenza vaccine

- *Recommended:* 2–49 years old
- *Not recommended:*
  - Children < 2 years old, adults ≥ 50 years old
  - Pregnant women
  - History of severe allergic reaction
  - Children 2–17 years old receiving aspirin- or salicylate-containing medications
  - Immunosuppressed persons or those taking care of immunosuppressed persons
  - Children 2–4 years old who have asthma
  - Patients cochlear implants, CSF leaks, or asplenia
  - Antiviral exposure (check timing)

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/prevent/how-fluvaccine-made.htm.;
Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html.

Preventative Measures

- Vaccination
- Infection prevention and control
- Chemoprophylaxis

Infection Prevention and Control

Avoid close contact with sick individuals

Stay at home

Use your elbow or a tissue

Handwashing

Avoid touching eyes and mouth

Practices good health habits

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/prevent/index.html.

Preventative Measures

- Vaccination
- Infection prevention and control
- Chemoprophylaxis

Chemoprophylaxis

- Vaccination is still the best way to prevent influenza
- The antiviral class of neuraminidase inhibitors (NAIs) are approximately 70%–90% effective in preventing influenza
- Widespread or routine use of antiviral medications for chemoprophylaxis is not recommended

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.; Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).

Chemoprophylaxis

- ≥ 3 months old who have highest risk of influenza associations

- Pre-exposure
  - Recommended as soon as influenza activity is detected in the community
  - Continued for the duration of influenza season

- Post-exposure
    - Recommended for 7-10 days after last known exposure
    - Longer durations recommended for outbreaks in institutional settings

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.;
Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).

Chemoprophylaxis

Children at high risk for whom influenza vaccine is contraindicated

Children at high risk during the 2 weeks after immunization or as a supplement to immunization

Unvaccinated family members/HCP with exposure to unvaccinated children at high risk or < 24 months

Children at high risk (and close contacts) when circulating strains of virus are not well matched by the seasonal vaccine

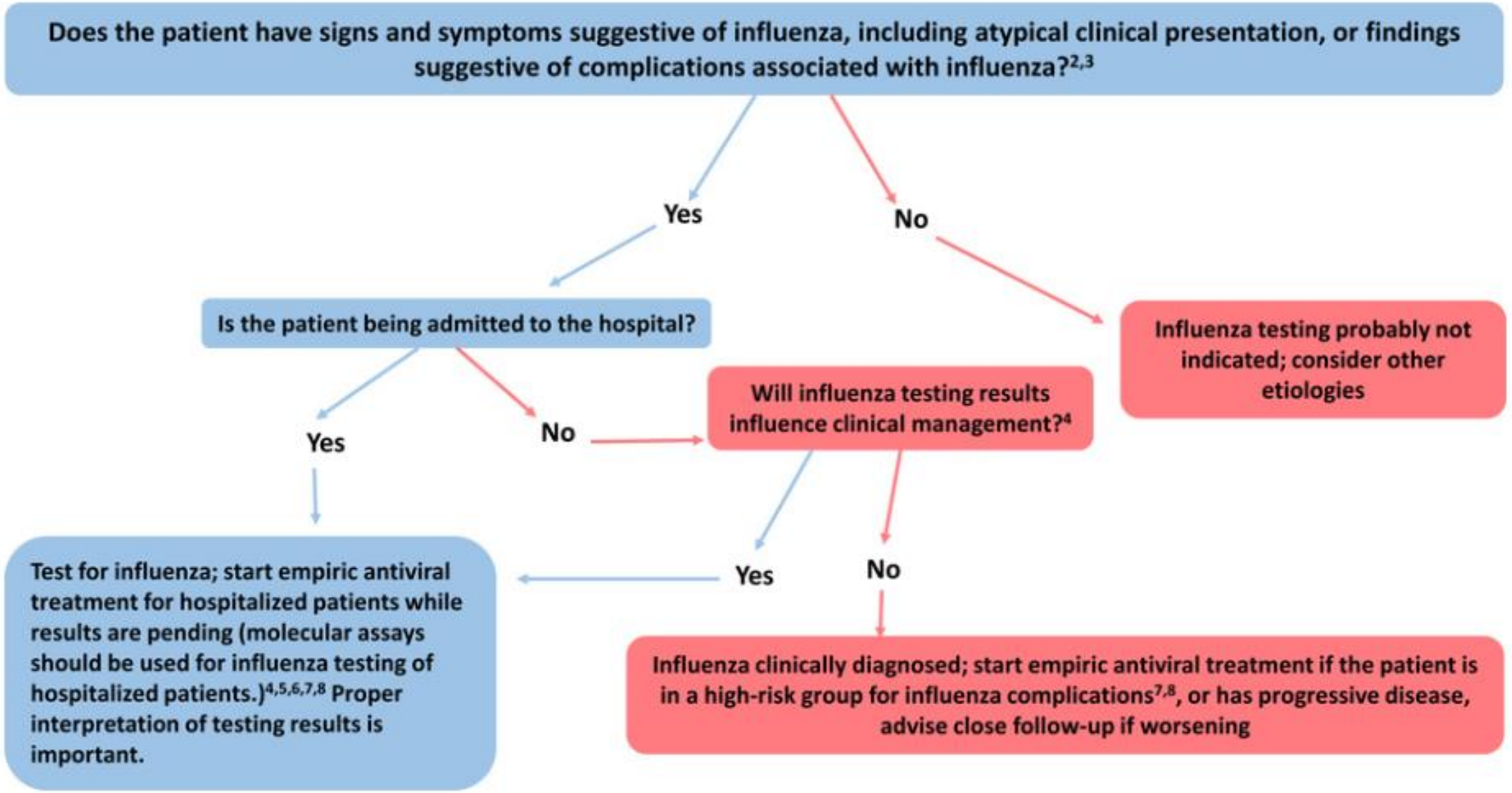
Control of influenza outbreaks for unimmunized staff and children in a closed institutional setting with children at high risk

Post-exposure prophylaxis for family members and close contacts of high-risk individuals

Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).

Testing

Influenza Testing and Treatment Algorithm



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

Treatment of Influenza in Children and Adolescents

Treatment Recommendations

- Treatment for influenza
  - Hospitalized patient with suspected or confirmed influenza
  - Outpatient with progressive, symptomatic illness
  - Patients at high risk of complications
  - To be considered based on clinical judgement
    - Otherwise healthy outpatient with presumed influenza ≤ 2 days after onset
    - Symptomatic outpatients in close contact with individuals at high risk

- If prescribed, treatment should be start as early as possible without waiting for confirmatory influenza testing

American Academy of Pediatrics. *Red Book.* 2018;476-90.;
Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.

Early > Delayed Treatment

- Systematic reviews and meta-analyses have shown the greatest clinical benefit of antiviral treatment within 48 hours of symptom onset
  - Reduce the duration of fever and symptoms
  - Lower the risk of otitis media in children
  - Decrease the risk of lower respiratory tract complications requiring antibiotics and of hospitalization in adults
- Benefit still seen in most patients even when treatment initiated 4–5 days after illness onset

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

Beneficial Outcomes of Antiviral Therapy

- Reduction in symptom duration
- Decreased mortality
- Reduce influenza complications
- Decrease in hospitalizations
- Help control community outbreaks

American Academy of Pediatrics. *Red Book.* 2018; 476-90.;
Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47.

Antiviral Medications

Antiviral Agents for Influenza

Adamantanes

- Amantadine (Symmetrel®)
- Rimantadine (Flumadine®)

Neuraminidase inhibitors

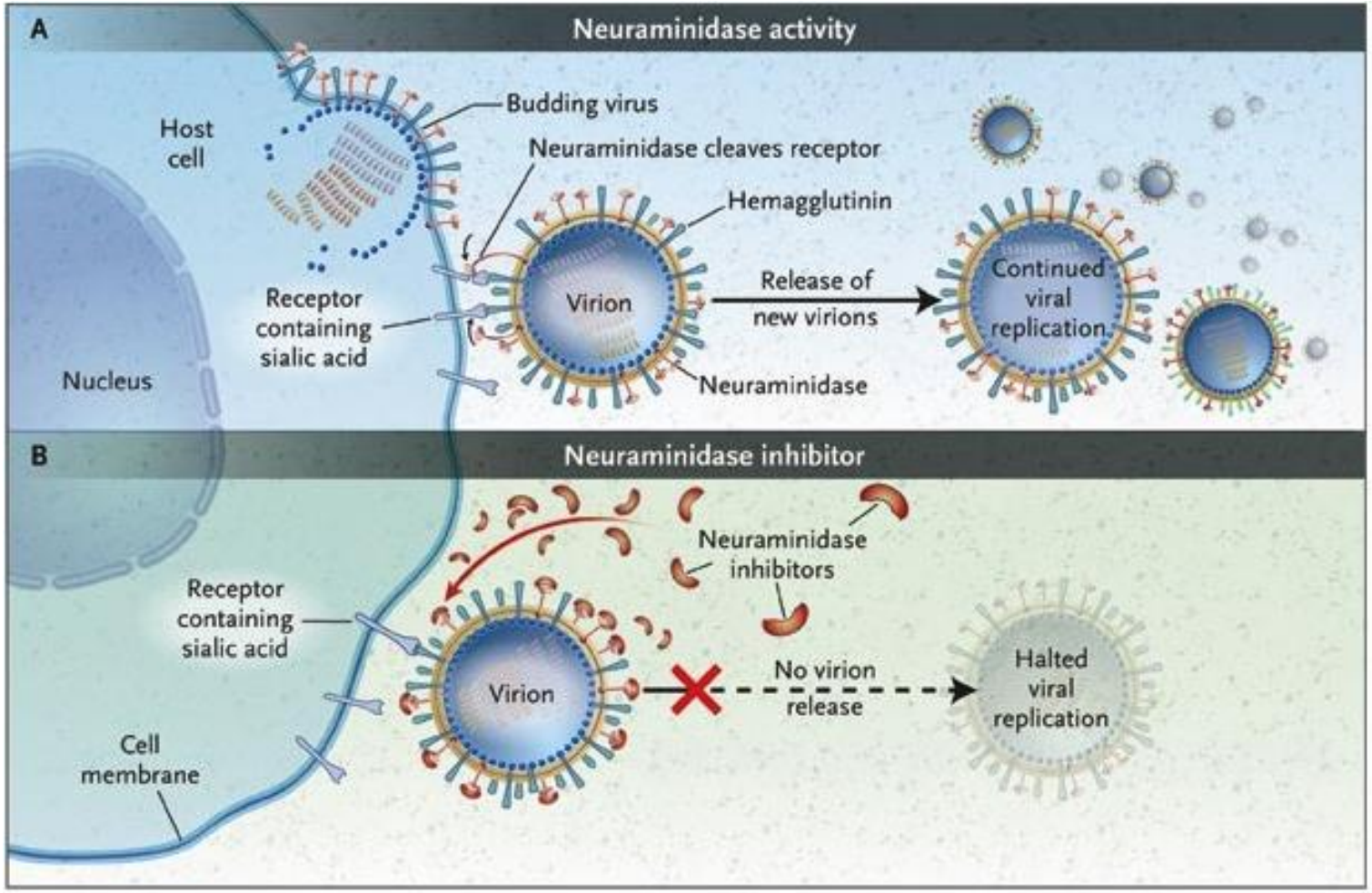
- Oseltamivir (Tamiflu®)
- Zanamivir (Relenza Diskhaler®)
- Peramivir (Rapivab®)

Cap-dependent endonuclease inhibitor

- Baloxavir marboxil (Xofluza®)

Neuraminidase Inhibitors

- Mechanism
  - Inhibits influenza virus neuraminidase
  - Neuraminidase enzyme cleaves the budding virus just prior to release
  - Blocks release of progeny influenza virus
- Activity against influenza A and B



Moscona A. *N Engl J Med.* 2005;353(13):1363-73.

Oseltamivir

Oseltamivir

- FDA approved for treatment in patients ≥ 14 days old
  - Prophylaxis: ≥ 3 months old
- Available as oral capsule and suspension
- Numerous studies evaluating safety and efficacy
  - No severe adverse effects
  - Typical side effects: nausea (8%–10%), vomiting (2%–16%), and headache (2%–17%)
  - Precautions: cardiovascular disease, respiratory disease, hepatic impairment, and renal impairment
- Treatment was efficacious in seasonal influenzas, epidemics, and 2009 H1N1 pandemic for both adults and pediatrics
- Post-exposure prophylaxis prevented outbreaks in household contacts and was well tolerated
  - Oseltamivir was effective for 89% of individuals

Aoki FY, et al. *J Antimicrob Chemother*. 2003;51(1):123-9.; Hiba V, et al. *J Antimicrob Chemother.* 2011;66(5):1150-5.; Lytras T. *Clin Infect Dis*. 2019;69(11):1896-902.; Tamiflu (oseltamivir) [package insert]. 2012.; Welliver R, et al. *JAMA.* 2001;285(6):748-54.

Oseltamivir

Whitley RJ, et al. and *Heinonen S, et al.*

- Randomized, placebo-controlled trials
- Clinically significant reduction in time to resolution of symptoms (fever, cough, and coryza)
  - *Whitley RJ, et al.* — Children 1–12 years old with uncomplicated pediatric influenza
  - *Heinonen S, et al.* — Children 1–3 years old with laboratory-confirmed influenza

Coffin SE, et al.

- Retrospective chart review of 257 children admitted to pediatric ICU

(oseltamivir to non-treated)

  - Primary: treatment within 24 hours of hospitalization was associated with a shorter duration of hospital days (18% shorter time)
  - No difference found in ICU stay, in-hospital mortality, or readmission rates

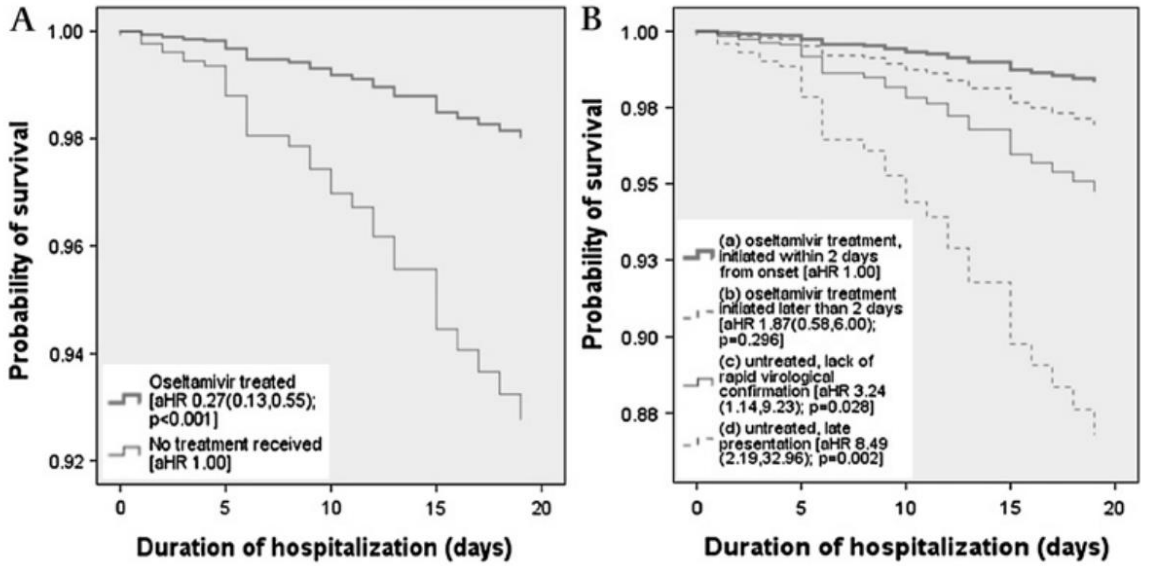
ICU, intensive care unit.

Whitley RJ, et al. *Pediatr Infect Dis J.* 2001;20:127-33.
Heinonen S, et al. *Clin Infect Dis.* 2010;51(8):887-94.
Coffin SE, et al. *Pediatr Infect Dis J.* 2011;30(11):962-6.

Oseltamivir

Lee, et al.

- Prospective, observational study in adult hospitalized patients
- Antiviral treatment was associated with reduced risk of death
  - Mortality rate: 4.56 (treated) and 7.42 (untreated) per 1000 patient-days
  - Multivariate analysis showed antiviral use was associated with reduced risk of death (adjusted HR 0.27 [95% CI: 0.13–0.55]; p<0.001)



CI, confidence interval; HR, hazard ratio.

Lee N, et al. *Thorax*. 2010;65(6):510-5.

Oseltamivir

Age/weight	Treatment*		Prophylaxis*
0–8 months old	3 mg/kg/dose BID		3 mg/kg/dose once daily+
9–11 months old	3.5 mg/kg/dose BID		3.5 mg/kg/dose once daily
Children ≥ 1 year old	≤ 15 kg	30 mg BID	30 mg daily
	15–23 kg	45 mg BID	45 mg daily
	23–40 kg	60 mg BID	60 mg daily
	> 40 kg	75 mg BID	75 mg daily
Adults		75 mg BID	75 mg daily

*Dosing adjustment is necessary in renal impairment
+ Not recommended for infants < 3 months of age

Duration of therapy:

- Treatment: 5 days
- Post-exposure prophylaxis: 10 days
  - AAP recommendation

BID, twice daily.

Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).;
Tamiflu (oseltamivir) [package insert]. 2012.

Oseltamivir: Counseling Points

- Side effects
  - Headache, nausea, pain, and vomiting
- Oral suspension
  - May not be palatable to some patients
- Capsules: can be opened and mixed with sweetened liquid
  - Chocolate syrup, corn syrup, caramel topping, brown sugar
- May be administered with or without meals
  - Taking with meals may help with GI upset

GI, gastrointestinal.

Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).;
Tamiflu (oseltamivir) [package insert]. 2012.

Zanamivir

Zanamivir

- FDA approved for treatment in patients ≥ 7 years old
  - Prophylaxis: ≥ 5 years old
  - Not recommended in patients with underlying airway disease
- Available as oral dry powdered inhalation, Diskhaler®
  - More difficult to administer than enteral NAI
  - Option for patients with absorption concerns or difficulty with enteral administration
- Safety and efficacy have shown zanamivir is well tolerated and is effective as treatment and prophylaxis
  - Typical side effects: cough (16%), fever/chills (5%), sore throat (11%), and nasal symptoms (20%)
  - Precautions: chronic respiratory conditions due to risk of bronchospasm

Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).;
Hedrick JA, et al. *Pediatr Infect Dis J.* 2000;19(5):410-7.;
Monto AS, et al. *J Antimicrob Chemother*. 1999;44(Suppl B):23-9.;
Relenza (zanamivir) [package insert]. 2018.

Zanamivir

- Treatment was efficacious for seasonal influenza in adults and pediatrics
  - Clinically significant decrease in time to symptom resolution, decrease in relief medication usage, complications, and concomitant antibiotic use
    - *Hendrick JA, et al.* — children 5–12 years of age with uncomplicated influenza A and B
    - *Monto AS, et al.* — pooled analysis in adults; median time to symptom alleviation was 1 day sooner than placebo ($P<0.001$)
  - Limited data for use inpatient

- Effective post-exposure prophylaxis
  - *Monto AS, et al.* — treatment of all household members (contacts) ≥ 5 years old
    - 81% protective efficacy (4% zanamivir vs. 19% placebo [$P<0.001$])

Hedrick JA, et al. *Pediatr Infect Dis J.* 2000;19(5):410-7.;
Monto AS, et al. *J Antimicrob Chemother*. 1999;44(Suppl B):23–9.;
Monto AS, et al. *J Infect Dis*. 2002;186(11):1582-8.

Zanamivir

- Duration of therapy
  - Treatment: 5 days
  - Post-exposure prophylaxis: 10 days
    - AAP recommendation

	Treatment	Prophylaxis
Children (≥ 7 years)	10 mg twice daily	10 mg daily
Adults	10 mg twice daily	10 mg daily
10 mg = 2 x 5-mg inhalations		

- Counseling points
  - Side effects
    - Cough, dizziness, fever/chills, GI upset, nasal symptoms, and sore throat
  - Provide instruction on proper administration technique
  - Should not be used in a nebulizer; only use device provided
  - Immediately report signs or symptoms of bronchospasm and respiratory depression

Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).;
Relenza (zanamivir) [package insert]. 2018.

Peramivir

Peramivir

- FDA approved for treatment in patients ≥ 2 years old
  - Not indicated for prophylaxis
  - Symptomatic < 2 days
- Available as intravenous solution
- Shown to be safe, well tolerated, and effective in the treatment of influenza
  - Typically mild, the most common side effects are diarrhea (8%) and vomiting (3%)
  - Rare but serious side effects include skin reactions (including Stevens-Johnson syndrome) and transient neuropsychiatric events
    - No severe adverse events reported in critically ill pediatric patients admitted to the PICU
  - Precautions: patients with renal impairment (dose adjustment required)

PICU, pediatric intensive care unit.

Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).;
Randolph AG, et al. *Pediatrics.* 2011;128(6):e1450-8.;
Rapivab (peramivir) [package insert]. 2018.

Peramivir

- Multiple studies have shown efficacy in acute uncomplicated influenza and hospitalized patients
  - Time to alleviation of symptoms was greater than placebo
  - Symptom alleviation was comparable to oseltamivir (non-inferior)

- *Sugaya N, et al.*
  - Open-label, uncontrolled study in children
  - Pharmacokinetic exposure in children was within the range of levels similar to adults
  - Considered safe and effective in children during H1N1 virus A pandemic

- *Komeda T, et al.*
  - Post-marketing surveillance of peramivir in pediatric patients < 15 years old with influenza
  - Median time to alleviation of both influenza symptoms and fever was 3 days
  - Adverse reactions: diarrhea (2.50%) and abnormal behavior (2.25%)

Hata A, et al. *Drug Des Devel Ther*. 2014;8:2017-38.; Ison MG, et al. *Antivir Ther (Lond).* 2014;19(4):349-61.; Kohno S, et al. *Antimicrob Agents Chemother.* 2010;54(11):4568-74.; Komeda T, et al. *J Infect Chemother*. 2016;22(10):677-84.; Sugaya N, et al. *Antimicrob Agents Chemother.* 2012;56(1):369-77.; Wester A, et al. *Infect Drug Resist.* 2016;9:201-14.

Peramivir

- 1-time dose recommended in uncomplicated influenza

Age	Treatment dose*
2–12 years of age	One dose of 12 mg/kg (max 600 mg)
≥ 13 years of age	One 600-mg dose

*Dosing adjustment is necessary in renal impairment

- Age-directed dosing and longer treatment durations utilized during 2009 H1N1 Emergency Use Authorization (EUA)

Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).;
Rapivab (peramivir) [package insert]. 2018.

Emergency Use Authorization

- In 2009, the FDA issued an EUA for peramivir for certain hospitalized adult and pediatric patients with known or suspected 2009 H1N1 influenza
  - EUA was restricted to patients not responding or unable to take oral or inhaled therapy with potentially life-threatening illness
  - Pediatric dosing was based on modeling

Age	Recommended dose (duration 5–10 days)
Birth – 30 DOL	6 mg/kg
31–90 DOL	8 mg/kg once daily
91–180 DOL	10 mg/kg once daily
181 DOL – 5 years	12 mg/kg once daily Maximum daily dose: 600 mg/day
6–17 years	10 mg/kg once daily Maximum daily dose: 600 mg/day
≥ 18 years	600 mg once daily

DOL, days of life.

Birnkrant D, et al. *N Engl J Med.* 2009;361(23):2204-7.;
Hata A, et al. *Drug Des Devel Ther*. 2014;8:2017-38.;
U.S. Food and Drug Administration. https://www.fda.gov/media/77787/download.

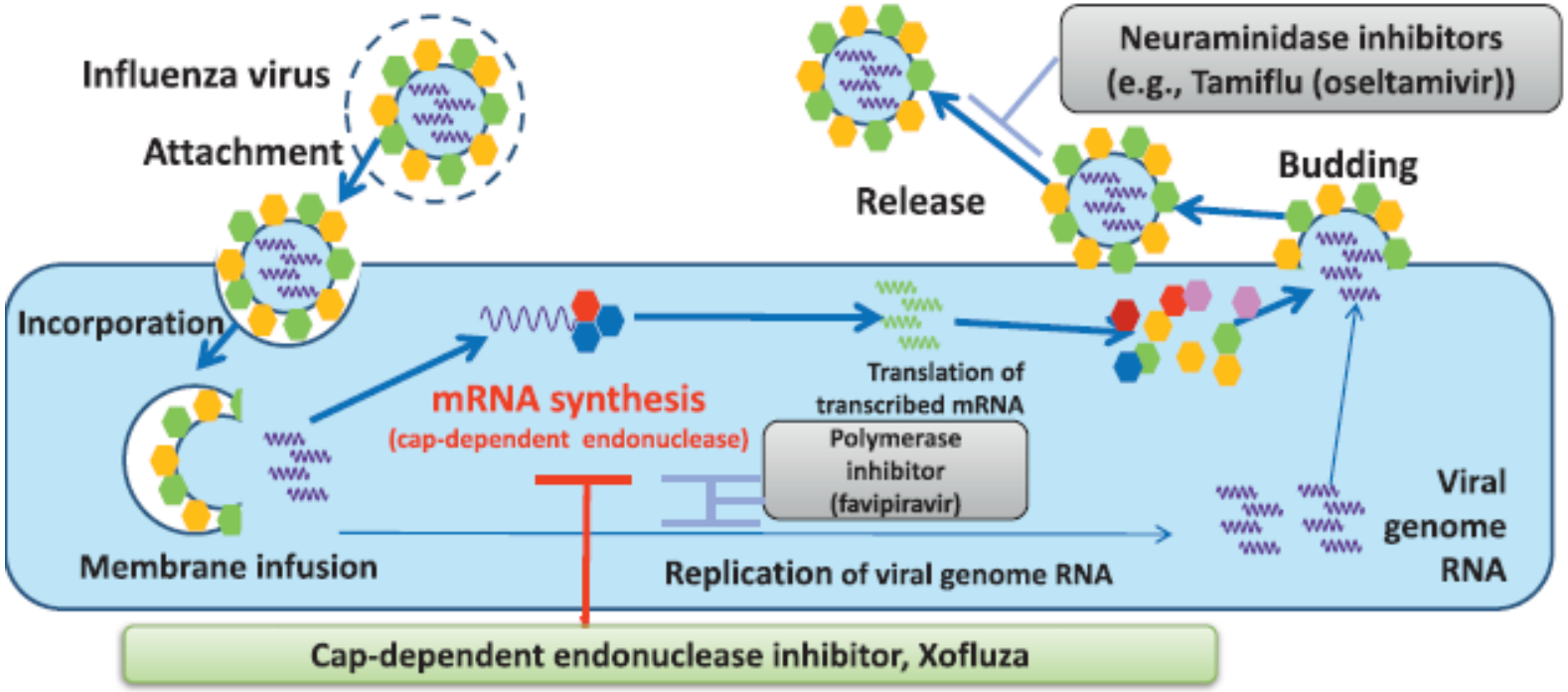
Peramivir: Counseling Points

- Side effects
  - GI upset (diarrhea, constipation), insomnia, hypertension, skin reactions (Stevens-Johnson syndrome), and neuropsychiatric events
- Report any signs of skin reactions or abnormal behavior

Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).;
Rapivab (peramivir) [package insert]. 2018.

Cap-dependent Endonuclease Inhibitor

- Inhibitor of cap-dependent endonuclease (CEN)
  - Required for viral mRNA biosynthesis



https://biopharmadealmakers.nature.com/posts/37749-shionogi-s-growing-anti-infectives-portfolio.

Baloxavir Marboxil

Baloxavir Marboxil

- FDA approved for treatment in patients ≥ 12 years old weighing ≥ 40 kg
  - Acute, uncomplicated influenza
  - No more than > 48 hours after symptom onset

- Available as a tablet therapy pack

- Clinical trials and studies have shown safety and efficacy for use in influenza
  - Common side effects: diarrhea (3%), bronchitis (2%), nasopharyngitis (1%), headache (1%), and nausea (1%)

Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).;
Hayden FG, et al. *N Engl J Med.* 2018;379(10):913-23.;
Ikematsu H, et al. *N Engl J Med*. 2020;383:309-20.;
Ison M, et al. *Lancet Infect Dis*. 2020;S1473-3099(20)30004-9.;
Xofluza (baloxavir marboxil) [package insert]. 2018.

Baloxavir Marboxil

- Demonstrated efficacy and safety in the treatment of influenza in uncomplicated healthy patients ≥ 12 years old and those at risk for complications
  - *Hayden FG, et al.* and *Ison MG, et al.*
    - Clinically significant decrease in time to symptom resolution compared to placebo
    - Similar time to symptom resolution compared to oseltamivir
    - Adverse reactions were similar: nausea, diarrhea, and bronchitis
    - Evidence of reemergence of resistance to baloxavir
      - Not recommended as monotherapy for immunosuppressed patients

- Effective post-exposure prophylaxis
  - *Ikematsu H, et al.*
    - Decreased risk of influenza in household contacts
    - Similar safety profiles compared to placebo
    - Resistance: 2.7% baloxavir and 1.3% placebo

Hayden FG, et al. *N Engl J Med.* 2018;379(10):913-23.;
Ikematsu H, et al. *N Engl J Med*. 2020;383:309-20.;
Ison M, et al. *Lancet Infect Dis*. 2020;S1473-3099(20)30004-9.

Baloxavir Marboxil

- *Hirotsu N, et al.*
  - 1 weight-adjusted dose of baloxavir in 107 children aged 1–11 years
  - 44.56 hours to symptom alleviation and 21.4 hours to fever resolution
  - Reported adverse drug events: 34.6%
    - GI (15%) most common with vomiting (7.5%)
  - Resistance detection: 23.4%

- *Baker J, et al.*
  - Double-blind, randomized, active control trial
  - Single-dose baloxavir (n=115) vs. oseltamivir (n=58) twice daily for 5 days
  - Primary objective of safety: adverse drug reactions were similar with baloxavir (46.1%) and oseltamivir (53.4%)
    - Vomiting/diarrhea
  - Secondary objective of efficacy
    - Median time to alleviation of influenza symptoms were similar
    - Emergent resistance was detected in 19.3% (11/57) of patients who received treatment

Baker J, et al. *Pediatr Infect Dis J.* 2020;39(8):700-5.;
Hirotsu N, et al. *CID* 2019. ciz908. https://doi.org/10.1093/cid/ciz908.

Baloxavir Marboxil

Upcoming

- An industry-sponsored study to assess the safety and efficacy of baloxavir in combination with standard-of-care NAI in hospitalized patients with severe influenza has been completed (NCT03684044)
  - ≥ 12 years old
  - Awaiting publication of results
- An industry-sponsored study to assess the safety, pharmacokinetics, and efficacy of baloxavir in healthy pediatric participants from birth to < 1 year old with influenza-like symptoms (NCT03653364)
  - Recruiting

https://clinicaltrials.gov/ct2/show/NCT03653364.; https://www.clinicaltrials.gov/ct2/show/NCT03684044?cond=baloxavir&draw=2&rank=7.

Baloxavir Marboxil

- Oral 1-time dose
  - 40 to < 80 kg: 40 mg once
  - ≥ 80 kg: 80 mg once

- Counseling points
  - Common side effects: diarrhea, bronchitis, nausea, nasopharyngitis, and headache
  - Do not take with dairy products or products containing calcium, iron, magnesium, selenium, or zinc

Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).;
Xofluza (baloxavir marboxil) [package insert]. 2018.

Resistance

- Adamantanes
  - Amino acid mutations of the M2 protein
  - Increased resistance of H3N2 and H1N1 since 2003
- NAIs: ~ 1%
  - 2 mechanisms of resistance
    - Amino acid substitutions at the active site of the neuraminidase
    - Mutations in the hemagglutinin
- Baloxavir
  - Amino acid substitutions
  - Reduced susceptibility
    - H3N2
    - Children
    - Human-to-human transmission
- CDC surveillance on resistance informs treatment and prophylaxis yearly

CDC, Centers for Disease Control and Prevention.

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/treatment/antiviralresistance.htm#anchor_1543591709173.;
Lackenby A, et al. *Antiviral Res*. 2018;157:38-46.;
Takashita E, et al. *Emerging Infect Dis*. 2019;25(11):2108-11.

Antivirals: Treatment

		Oseltamivir	Zanamivir	Peramivir	Baloxavir
Route of administration		Oral	Inhaled	Intravenous	Oral
Approved age for therapy		≥ 14 days old	≥ 7 years old	≥ 2 years old	≥ 12 years old weighing at least 40 kg
Duration of therapy		5 days	5 days	1 day	1 day
Renal dose adjustment recommendations?		Yes	No	Yes	No
Cost of treatment	20-kg child	$210	$70.80	$228	$90
	Adult	$140	$70.80	$1440	$180

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

Antivirals: Chemoprophylaxis

		Oseltamivir	Zanamivir	Peramivir	Baloxavir
Route of administration		Oral	Inhaled	Intravenous	Oral
Approved age for therapy		≥ 3 months old	≥ 5 years old	Not recommended	
Duration of therapy	Pre-exposure	Duration of influenza season			
	Post-exposure	Adults: 7 days Pediatrics: 10 days*			
Cost of treatment (7 days)	20-kg child	$147	$49.56		
	Adult	$98	$49.56		

*Duration of prophylaxis recommended by the CDC is 7 days, or longer if part of an institutional outbreak.

Centers for Disease Control and Prevention. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.;
Committee on Infectious Diseases. *Pediatrics*. 2019;144(4).

Pharmacist Implications

Counseling Points for Patients

- Recommend influenza prevention
  - Vaccination
  - Infection prevention and control
- Influenza recognition
  - Common: abrupt onset, fever, aches, fatigue, and headache
- Importance of early intervention
  - Reduction in symptom duration, complications, hospitalizations, and mortality
- Inhalation technique for zanamivir
- Possible adverse effects of medications
- Complete entire course of antivirals

ARS Question #3

Which antiviral is appropriate for use in a 15-month-old patient with suspected influenza?

- Oseltamivir
- Zanamivir
- Peramivir
- Baloxavir

Best choice for a particular patient?

Consider:

- Age
- Weight
- Allergies
- Route
- Renal function
- Comorbidities
- Indications for use
- Drug interactions

Questions & Answers

Thank You!

References

1. Hamborsky J, Kroger A, Wolfe S, eds. Epidemiology and Prevention of Vaccine-Preventable Diseases. 13th ed. Centers for Disease Control and Prevention; Washington D.C. Public Health Foundation; 2015.
2. Centers for Disease Control and Prevention. Types of Influenza Viruses. 2019. https://www.cdc.gov/flu/about/viruses/types.htm#:~:text=There%20are%20four%20types%20of,global%20epidemics%20of%20flu%20disease.
3. Samji T. Influenza A: understanding the viral life cycle. *Yale J Biol Med.* 2009;82(4):153-9.
4. Centers for Disease Control and Prevention. How the Flu Virus Can Change: "Drift" and "Shift". 2019. https://www.cdc.gov/flu/about/viruses/change.htm#:~:text=When%20shift%20happens%2C%20most%20people,in%20the%20past%20100%20years.
5. Centers for Disease Control and Prevention. 2019-2020 U.S. Flu Season: Preliminary Burden Estimates. 2020. https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm.
6. Influenza. In: Kimberlin DW, Brady MT, Jackson MA, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* American Academy of Pediatrics; 2018; 476-90.
7. Ruf BR, Knuf M. The burden of seasonal and pandemic influenza in infants and children. *Eur J Pediatr.* 2014;173(3):265-76.
8. Centers for Disease Control and Prevention. Laboratory-Confirmed Influenza Hospitalizations. 2020. https://gis.cdc.gov/grasp/fluview/fluhosprates.html.
9. Centers for Disease Control and Prevention. Influenza-Associated Pediatric Mortality. 2020. https://gis.cdc.gov/grasp/fluview/pedfludeath.html.
10. Centers for Disease Control and Prevention. Flu Symptoms & Complications. 2019. https://www.cdc.gov/flu/index.htm.
11. Kondrich J, Rosenthal M. Influenza in children. *Curr Opin Pediatr*. 2017;29(3):297-302.
12. Centers for Disease Control and Prevention. How Influenza (Flu) Vaccines Are Made. 2019. https://www.cdc.gov/flu/prevent/how-fluvaccine-made.htm.
13. Centers for Disease Control and Prevention. Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States. 2020. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html.
14. Centers for Disease Control and Prevention. Seasonal Influenza Vaccination Resources for Health Professionals. 2020. https://www.cdc.gov/flu/professionals/vaccination/index.htm.
15. Centers for Disease Control and Prevention. Heathy Habits to Help Prevent Flu. 2020. https://www.cdc.gov/flu/prevent/index.html.
16. Committee on Infectious Diseases. Recommendations for Prevention and Control of Influenza in Children, 2019-2020. *Pediatrics*. 2019;144(4):e20192478.
17. Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.

References

18. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal Influenza. *Clin Infect Dis*. 2019;68(6):e1-e47.
19. Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med.* 2005;353(13):1363-73.
20. Tamiflu (oseltamivir) [package insert]. South San Francisco, CA: Genentech, Inc.; 2012.
21. Hiba V, Chowers M, Levi-vinograd I, et al. Benefit of early treatment with oseltamivir in hospitalized patients with documented 2009 influenza A (H1N1): retrospective cohort study. *J Antimicrob Chemother.* 2011;66(5):1150-5.
22. Lytras T, Mouratidou E, Andreopoulou A, et al. Effect of early oseltamivir treatment on mortality in critically ill patients with different types of influenza: a multiseason cohort study. *Clin Infect Dis*. 2019;69(11):1896-902.
23. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Chemother*. 2003;51(1):123-9.
24. Coffin SE, Leckerman K, Keren R, et al. Oseltamivir shortens hospital stays of critically ill children hospitalized with seasonal influenza: a retrospective cohort study. *Pediatr Infect Dis J.* 2011;30(11):962-6.
25. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J.* 2001;20:127-33.
26. Heinonen S, Silvennoinen H, Lehtinen P, et al. Early oseltamivir treatment of influenza in children 1-3 years of age: a randomized controlled trial. *Clin Infect Dis.* 2010;51(8):887-94.
27. Lee N, Choi KW, Chan PK, et al. Outcomes of adults hospitalised with severe influenza. *Thorax.* 2010;65(6):510-5.
28. Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA.* 2001;285(6):748-54.
29. Pannaraj PS, Tam B, Akan D. Oseltamivir treatment and prophylaxis in a neonatal intensive care unit during a 2009 H1N1 influenza outbreak. *J Perinatol*. 2011;31(7):487-93.
30. Relenza (zanamivir) [package insert]. Research Triangle Park, NC: GlaxoSmithKline LLC.; 2018.
31. Hedrick JA, Barzilai A, Behre U, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. *Pediatr Infect Dis J.* 2000;19(5):410-7.
32. Monto AS, Webster A, Keene O. Randomized, placebo-controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. *J Antimicrob Chemother*. 1999;44(Suppl B):23-9.
33. Monto AS, Pichichero ME, Blanckenberg SJ, et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J Infect Dis.* 2002;186(11):1582-8.

References

34. Rapivab (peramivir) [package insert]. Summit, NJ: Seqirus USA, Inc.; 2018.
35. Randolph AG, Vaughn F, Sullivan R, et al. Critically ill children during the 2009-2010 influenza pandemic in the United States. *Pediatrics*. 2011;128(6):e1450-8.
36. Wester A, Shetty AK. Peramivir injection in the treatment of acute influenza: a review of the literature. *Infect Drug Resist.* 2016;9:201-14.
37. Hata A, Akashi-Ueda R, Takamatsu K, Matsumura T. Safety and efficacy of peramivir for influenza treatment. *Drug Des Devel Ther*. 2014;8:2017-38.
38. Kohno S, Kida H, Mizuguchi M, et al. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrob Agents Chemother.* 2010;54(11):4568-74.
39. Ison MG, Fraiz J, Heller B, et al. Intravenous peramivir for treatment of influenza in hospitalized patients. *Antivir Ther (Lond).* 2014;19(4):349-61.
40. Sugaya N, Kohno S, Ishibashi T, et al. Efficacy, safety, and pharmacokinetics of intravenous peramivir in children with 2009 pandemic H1N1 influenza A virus infection. *Antimicrob Agents Chemother.* 2012;56(1):369-77.
41. Komeda T, Ishii S, Itoh Y, et al. Post-marketing safety evaluation of the intravenous anti-influenza neuraminidase inhibitor peramivir: a drug-use investigation in patients with high risk factors. *J Infect Chemother*. 2016;22(10):677-84.
42. Birnkrant D, Cox E. The Emergency Use Authorization of peramivir for treatment of 2009 H1N1 influenza. *N Engl J Med.* 2009;361(23):2204-7.
43. U.S. Food and Drug Administration. Peramivir emergency use authorization, fact sheet for health care providers. 2009. https://www.fda.gov/media/77787/download.
44. Louie JK, Yang S, Samuel MC, et al. Neuraminidase inhibitors for critically ill children with influenza. *Pediatrics*. 2013;132(6):e1539-45.
45. Xofluza (baloxavir marboxil) [package insert]. San Francisco, CA: Genentech, Inc.; 2018.
46. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *N Engl J Med.* 2018;379(10):913-23.
47. Ison M, Portsmouth S, Yoshida Y, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. *Lancet Infect Dis*. 2020;S1473-3099(20)30004-9.
48. Ikematsu H, Hayden FG, Kawaguchi K, et al. Baloxavir marboxil for prophylaxis against influenza in household contacts. *N Engl J Med*. 2020;383(4):309-20.
49. Baker J, Block SL, Matharu B, et al. Baloxavir marboxil single-dose treatment in influenza-infected children: a randomized, double-blind, active controlled phase 3 safety and efficacy trial (miniSTONE-2). *Pediatr Infect Dis J.* 2020;39(8):700-5.
50. Hirotsu N, Sakaguchi H, Sato C, et al. Baloxavir marboxil in Japanese pediatric patients with influenza: safety and clinical and virologic outcomes, *Clinical Infectious Diseases.* 2020;71(4):971-81.
51. Takashita E, Ichikawa M, Morita H, et al. Human-to-human transmission of influenza A(H3N2) virus with reduced susceptibility to baloxavir, Japan, February 2019. *Emerging Infect Dis*. 2019;25(11):2108-11.
52. Centers for Disease Control and Prevention. Influenza Antiviral Drug Resistance. 2020. https://www.cdc.gov/flu/treatment/antiviralresistance.htm#anchor_1543591709173.
53. Lackenby A, Besselaar TG, Daniels RS, et al. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors and status of novel antivirals, 2016-2017. *Antiviral Res*. 2018;157:38-46.