



Influenza

Suchitra Rao

Assistant Professor

Pediatric Infectious Diseases,

Hospital Medicine and Epidemiology

Colorado Children's Immunization Coalition Education Event

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Conflict of Interest and Disclosures

- There are no conflict of interest or disclosures to report with regards to this presentation



Objectives

- Provide a **historic perspective** on influenza including lessons learned from past pandemics
- Describe the influenza virus **types**, subtypes and **epidemiology**
- Review **clinical manifestations** of influenza
- Summarize previous influenza season, including **vaccine effectiveness** and burden of disease
- Discuss the rationale for the **2016-2017 vaccine recommendations**
- Review recommendations for influenza **diagnosis** and **treatment**

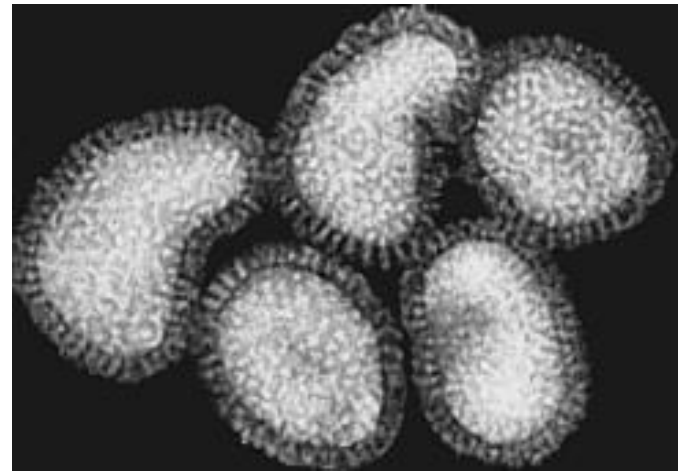
Influenza virus

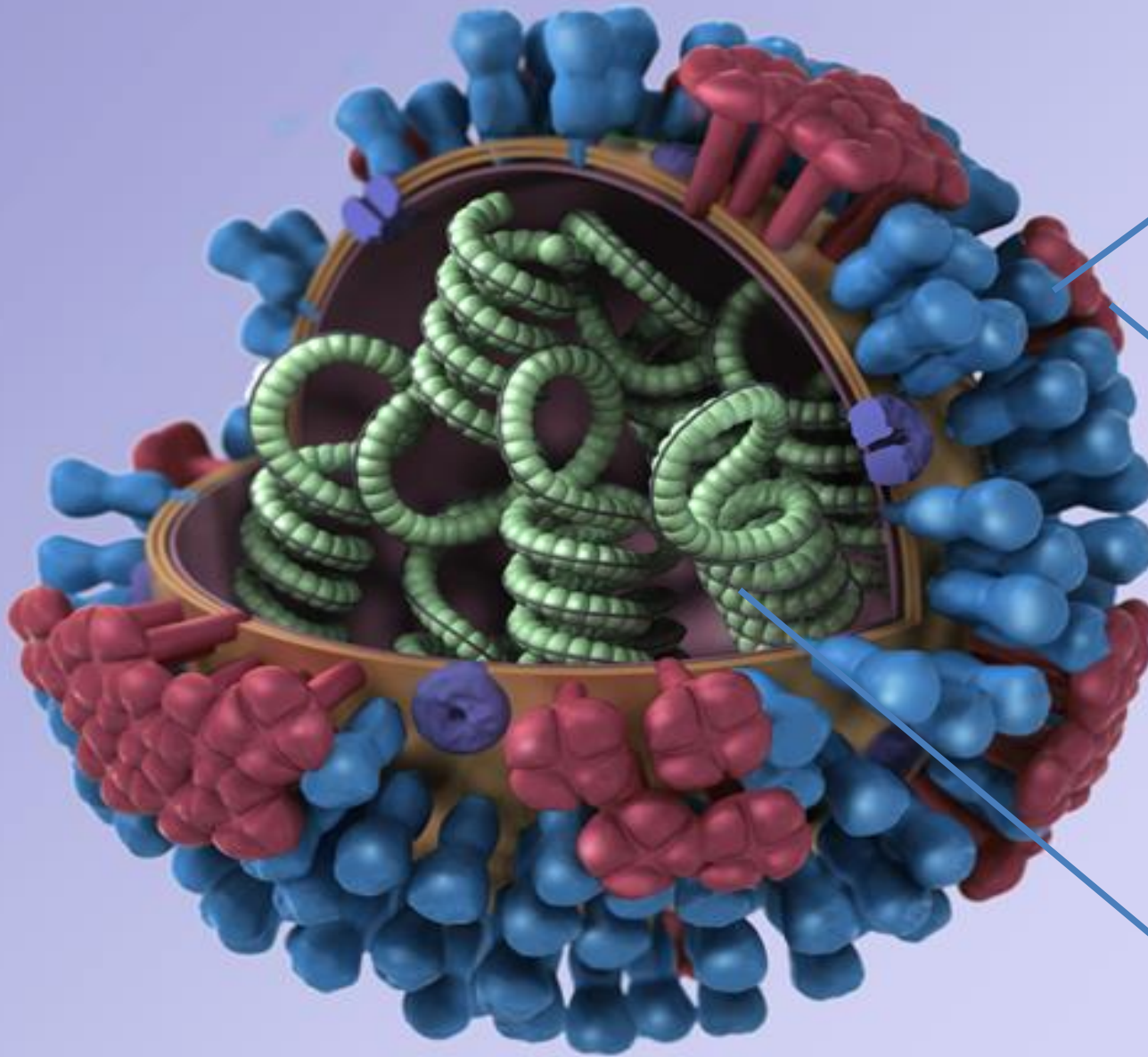
- RNA viruses
- Orthomyxoviridae family
- 3 virus subtypes



Influenza types

- **Type A:**
 - potentially severe illness
 - Epidemics and pandemics
 - Rapidly changing
 - Birds, swine, horses, seals, animals
- **Type B:**
 - Usually less severe illness
 - Epidemics
 - More uniform
 - Humans
- **Type C:**
 - Usually mild or asymptomatics
 - Minimal public health impact
 - Humans rarely, swine

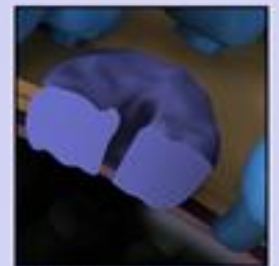




Hemagglutinin



Neuraminidase

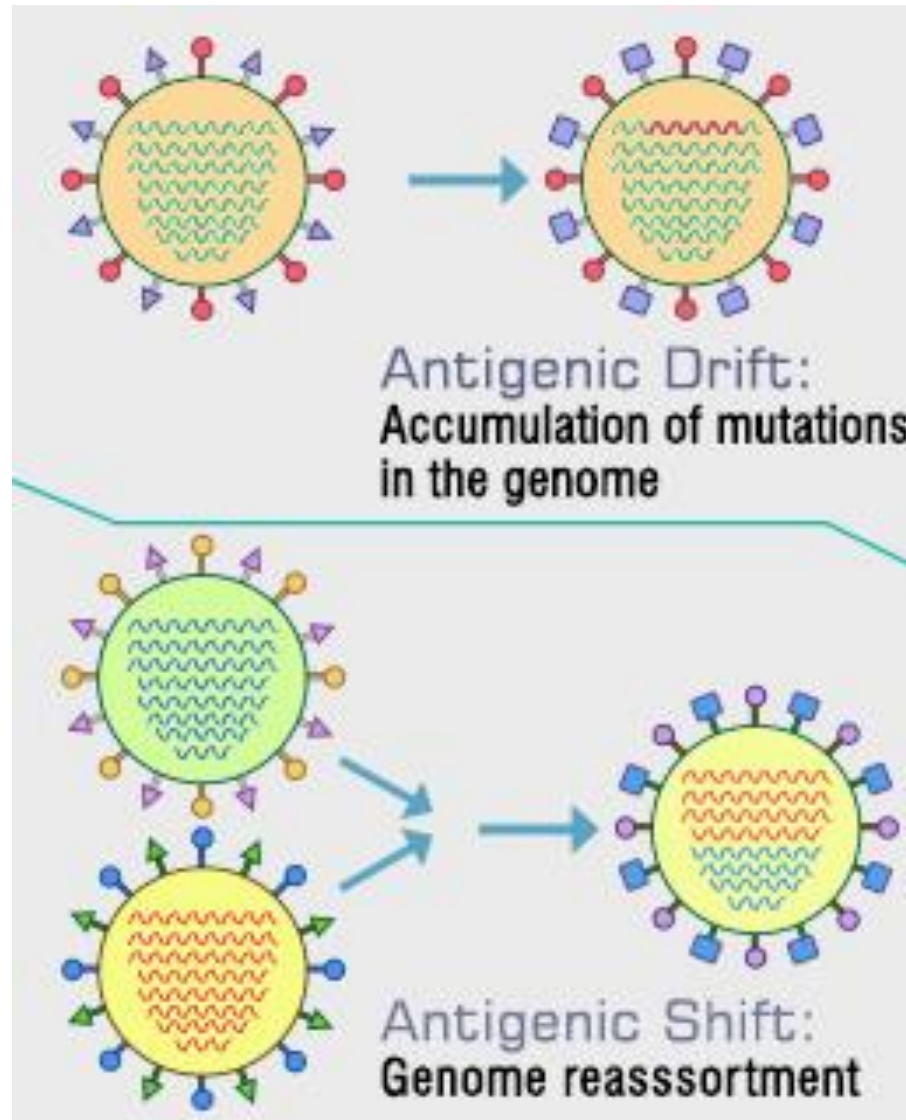


M2 Ion Channel



RNP

Antigenic Shift and Drift

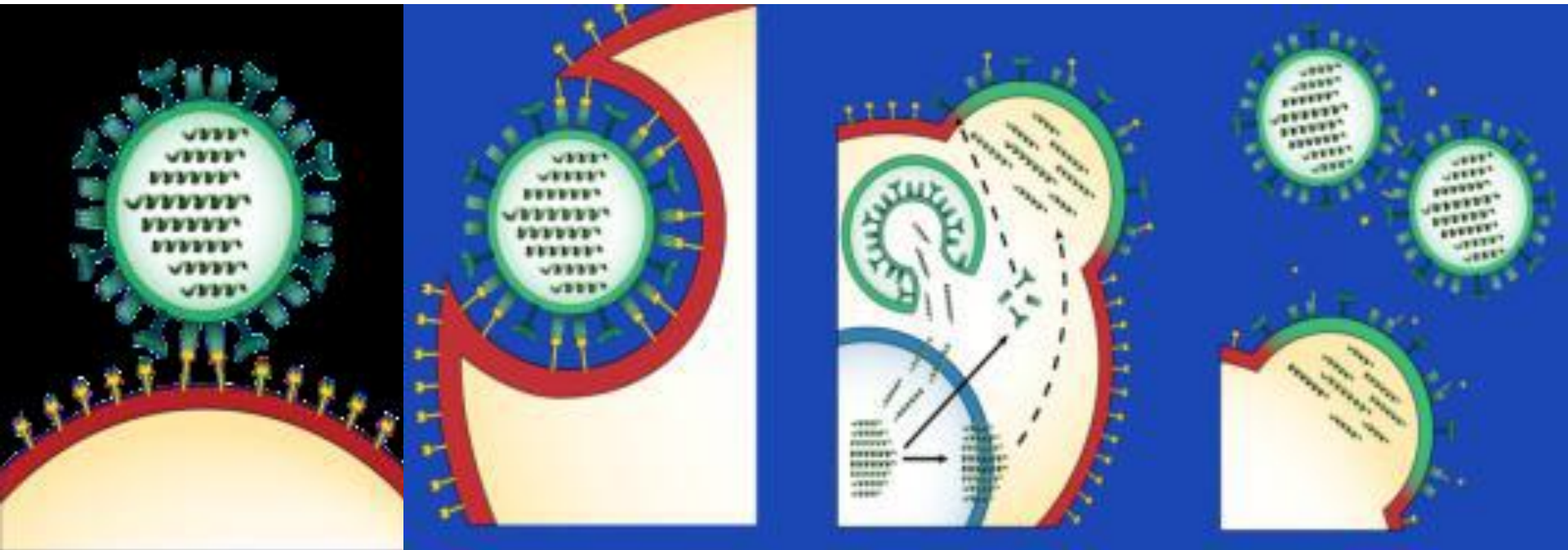


Why is all this important?

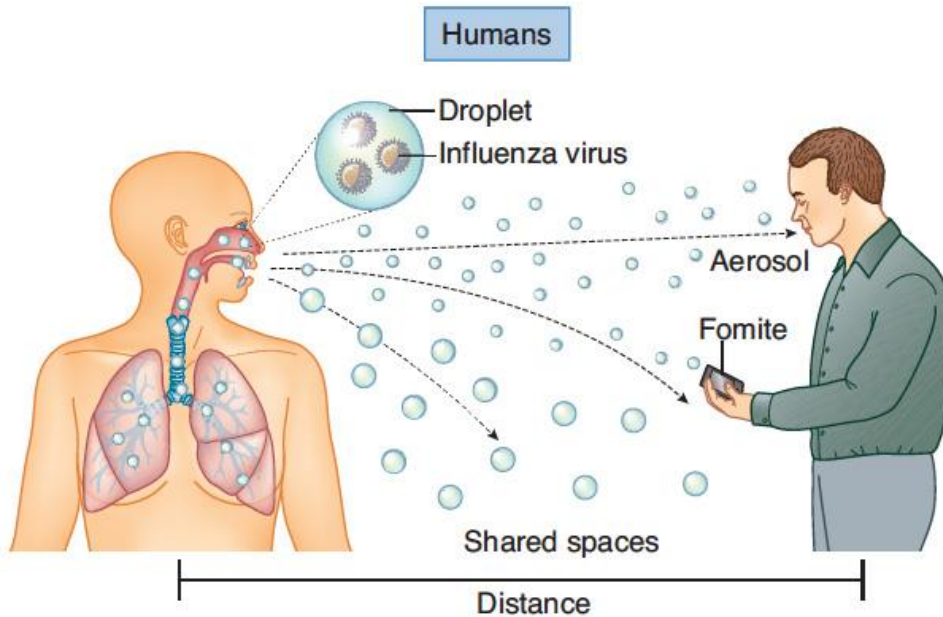
- Antigenic drift- why we need to change flu vaccine each year and get annual vaccine
- Antigenic shift- responsible for pandemics
- Segmented RNA- enables gene reassortment
- HA- novel subtypes contribute to pandemics, antibodies confer protection
- NA- target for antiviral drugs

Pathology of influenza infection

Binding to sialic acid Entering cell Replication Release from cell



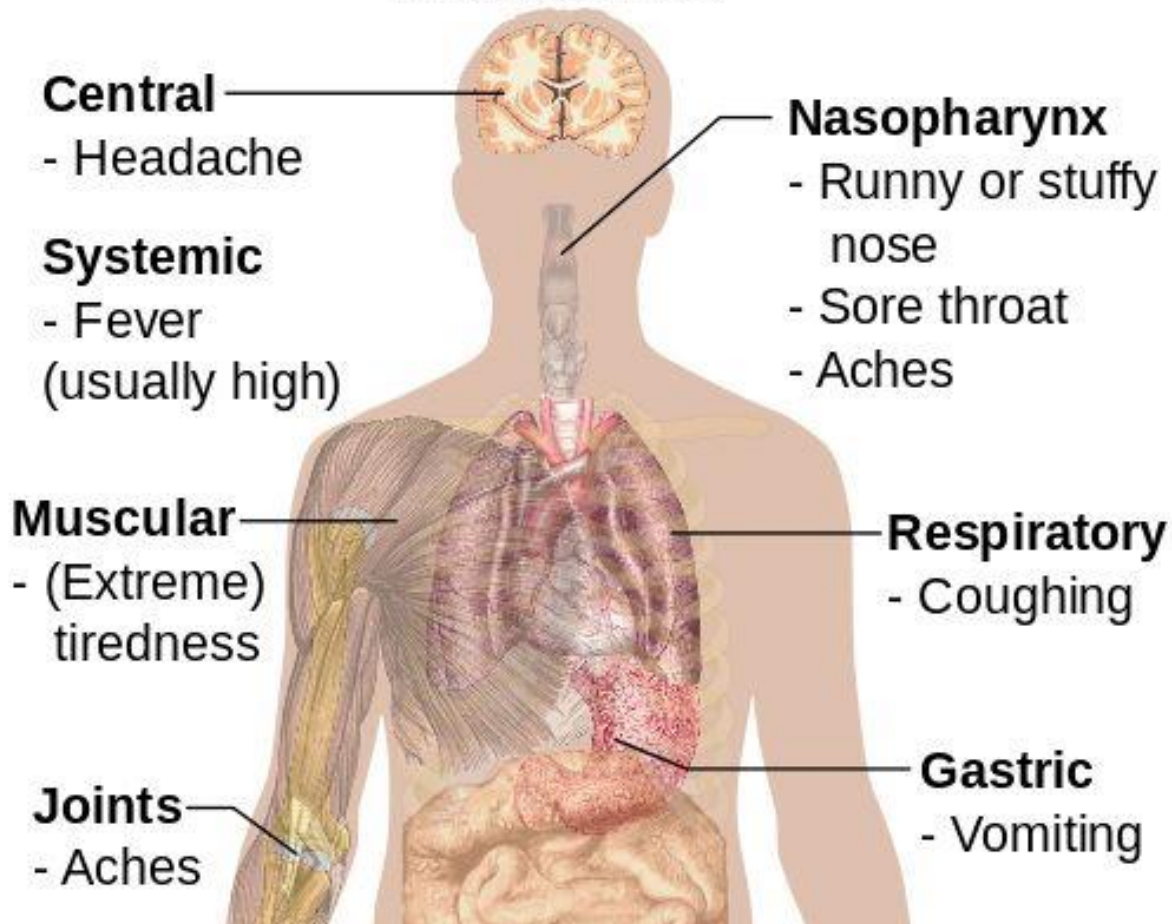
Epidemiology of influenza



- Small particle droplets, aerosols, or fomites
- Attacks epithelial cells of upper & lower respiratory tract
- Incubation period 2-3 days
- Shedding for 3-7 days

Clinical manifestations

Symptoms of Influenza



Know the FLU

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FEVER

ACHES

CHILLS

TIREDNESS

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United States, War-Department records show.

INFLUENZA KILLS 370,000 IN U. S.

About 350,000 Civilians
Victims of Grip Epidemic,

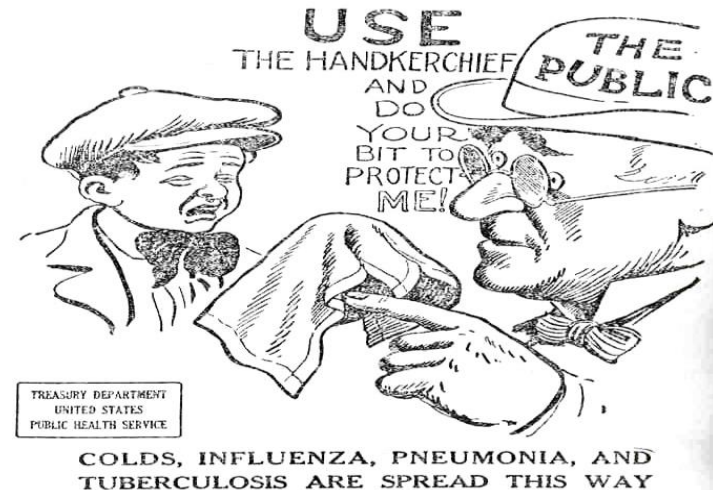
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Careless Spitting Spreads

CONSUMPTION
DIPHTHERIA
LA GRIPPE
BRONCHITIS
PNEUMONIA

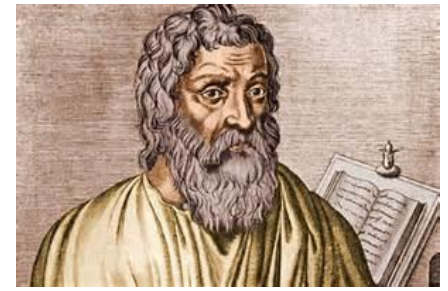
Stop Careless Spitting

Brooklyn Tuberculosis Committee
69 Schermerhorn Street



HISTORICAL CONTEXT

A brief history of influenza



- 412 BC – first mentioned by Hippocrates
- 1357 AD- term “influenza” coined
- 1485- “sweating sickness”: affects 100,000s in Britain
- 1580- first recorded influenza pandemic begins in Europe and spreads to Asia and Africa
- 1580-1900 - 28 pandemics
- 1918-1919- “Spanish flu”
- 1932- influenza A first isolated in the laboratory
- 1940- influenza B first isolated in the laboratory

Influenza epidemics

- Definition of epidemic
- Occur in winter months when cold, crowding of people
- Starts in Eastern or Southern Hemisphere countries, and later spread to Europe or North America
- More likely when a variant virus appears (drift)– showing antigenic changes (low cross-reacting antibody)

Influenza pandemics

- Definition of pandemic
- Outbreak of infection spreads throughout the world
- High percentage of individuals are infected resulting in increased mortality rates
- Caused by a new influenza A subtype, this subtype undergoes antigenic shift

1918-1919 pandemic- “the Spanish Flu”

- One of the most dramatic events in medical history
- Estimated to have affected 50% of world’s population
- 20-50 million deaths worldwide
- Infections developed into pneumonia
- US soldiers brought it to the world during WW1
- Preceded by a milder epidemic
- H1N1 strain

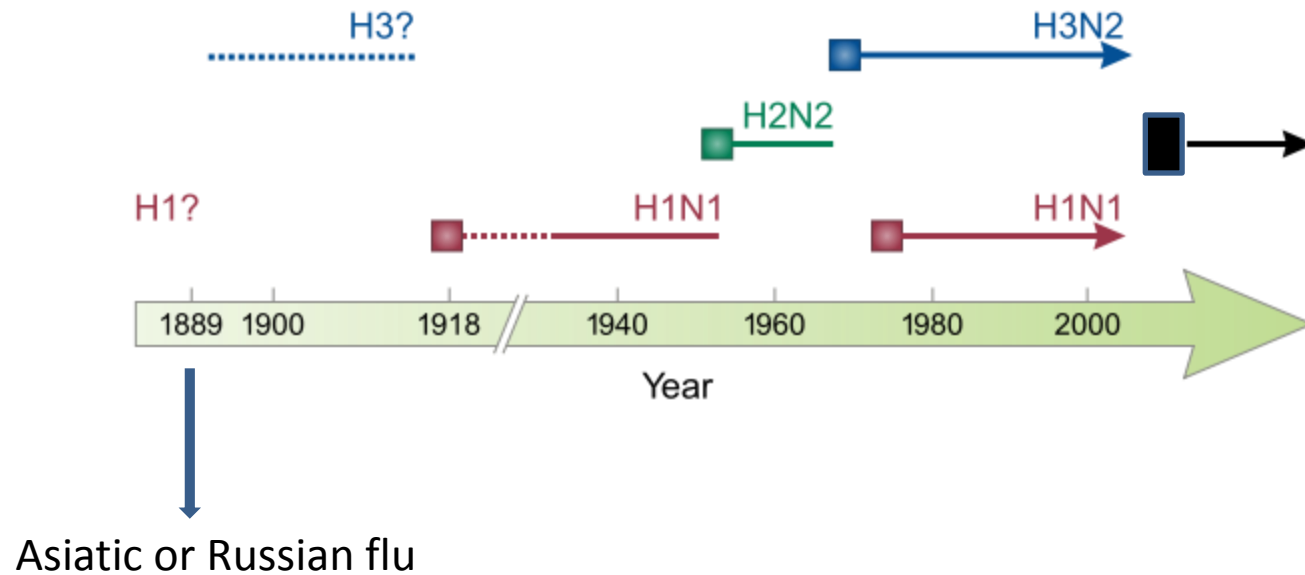


The Spanish Flu

- “Both individuals and governments were gripped with fear and took extreme measures to try to stop the disease from spreading. Some cities closed down theaters and schools. Some communities shut down completely until the worst had passed. Families with small children were in serious trouble if the parents were stricken, because friends and family members were often too frightened to enter the household to assist and care for the little ones...”

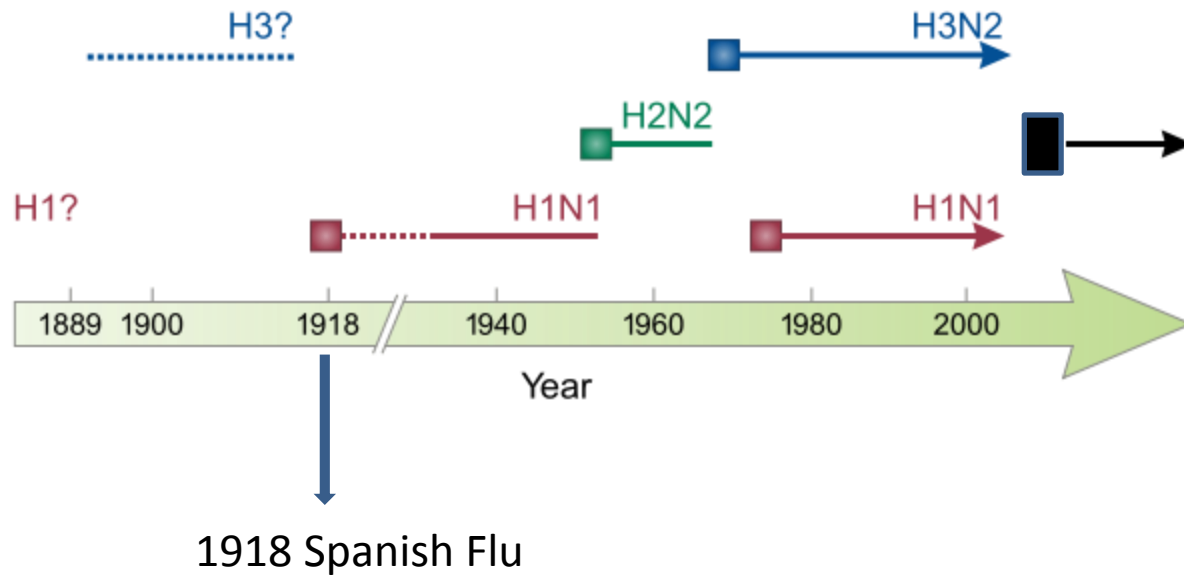
Other Pandemics

Influenza A virus subtypes in the human population



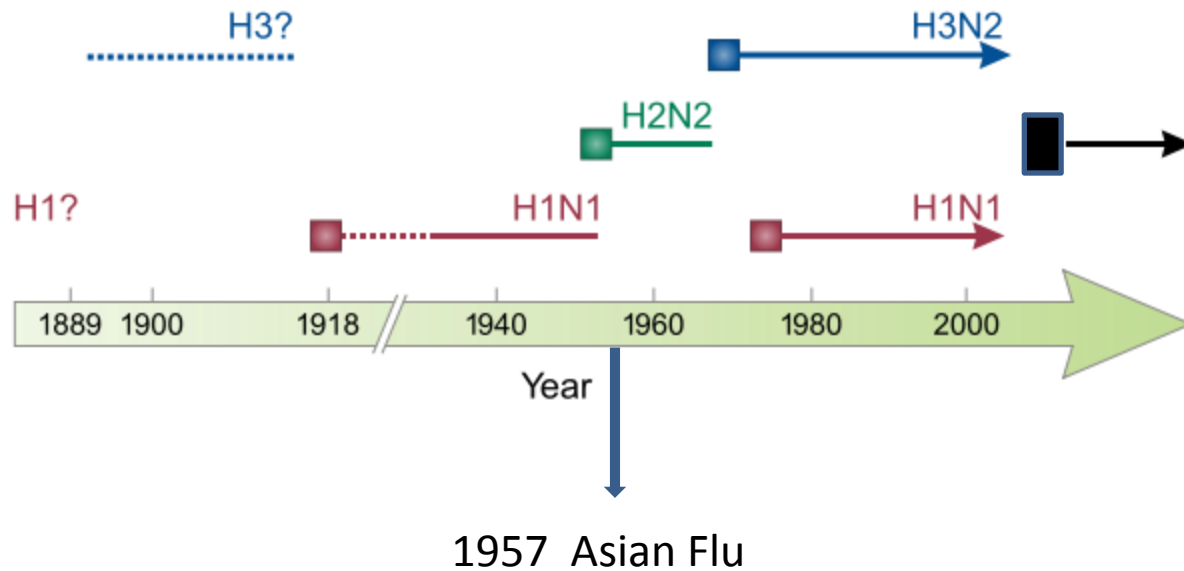
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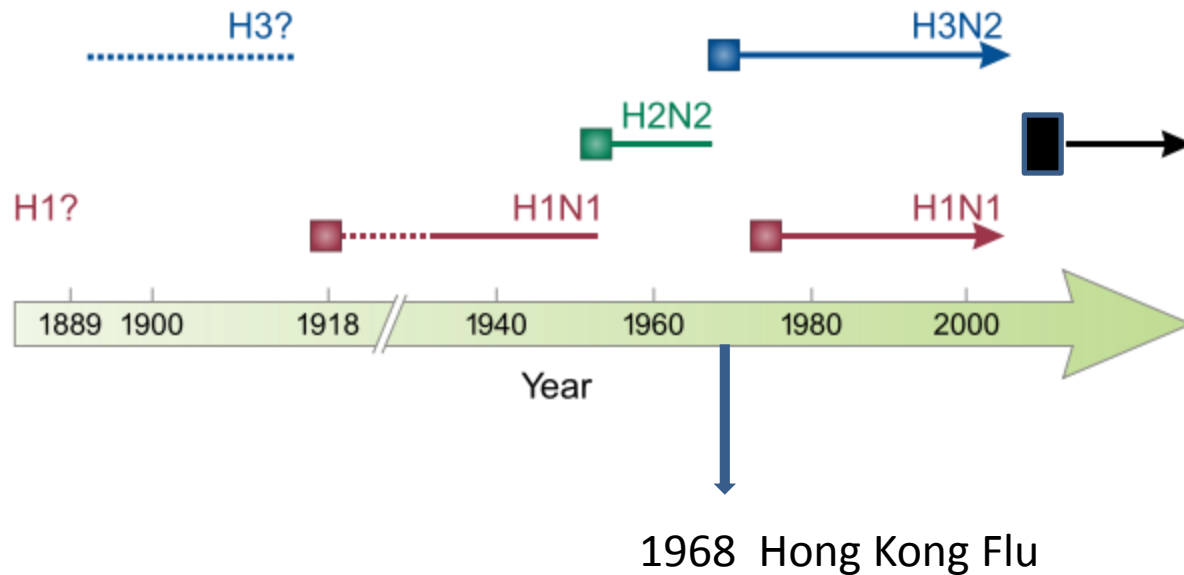
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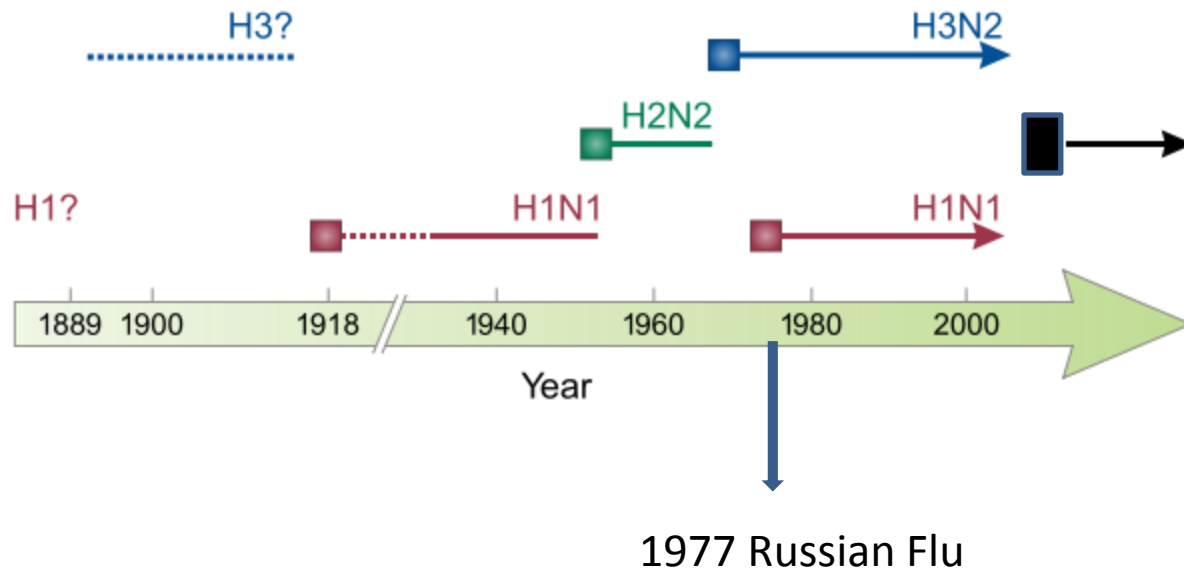
Other Pandemics

Influenza A virus subtypes in the human population



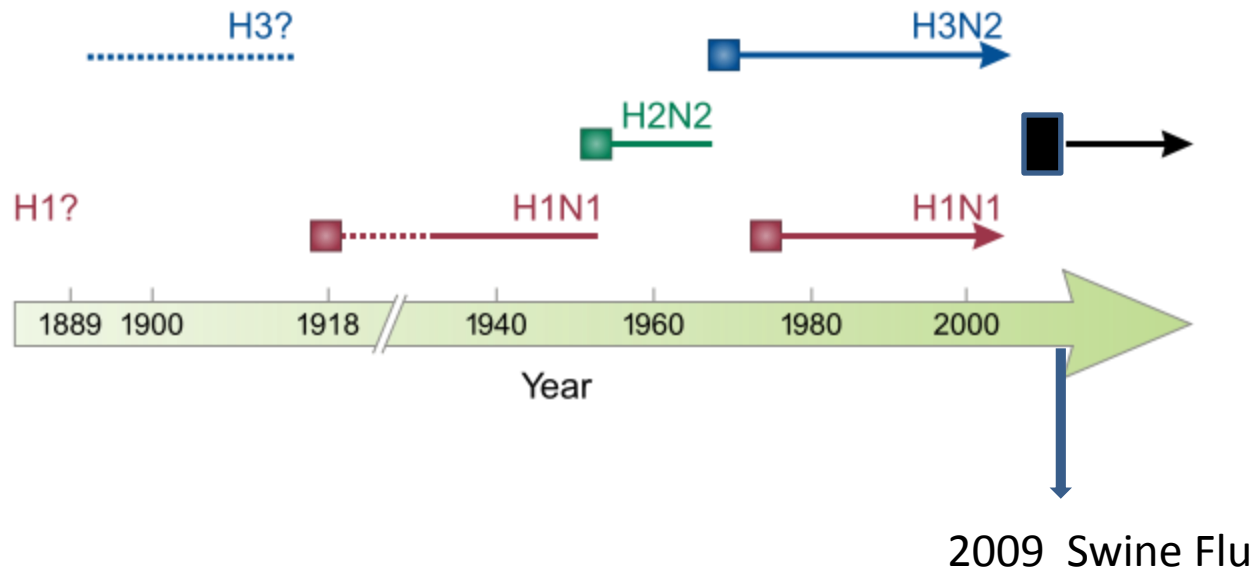
Other Pandemics

Influenza A virus subtypes in the human population



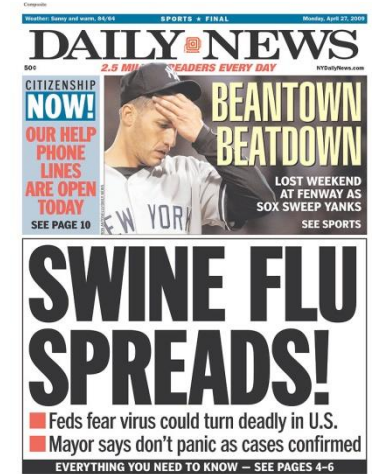
Other Pandemics

Influenza A virus subtypes in the human population



2009 H1N1 Pandemic

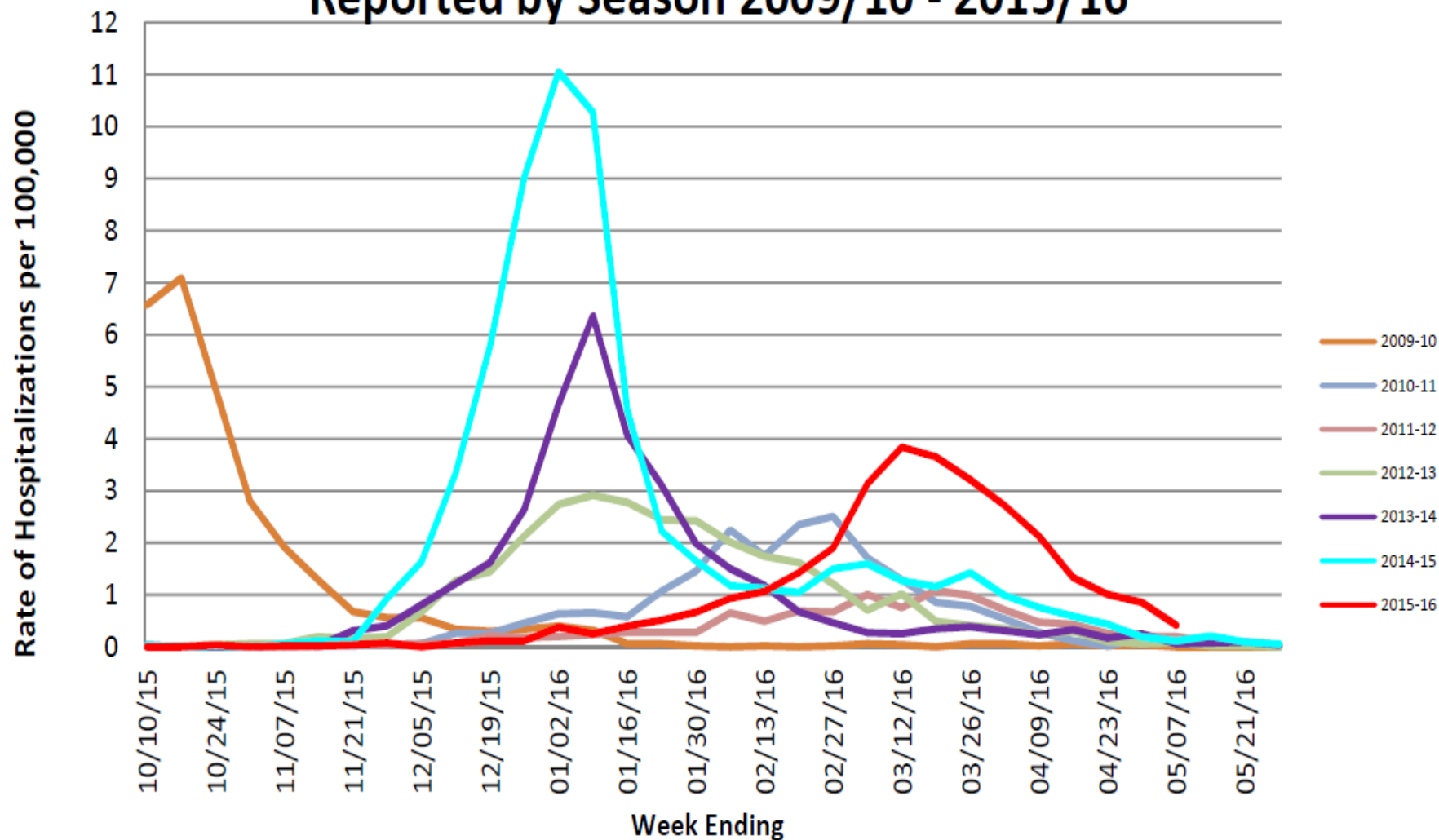
- First detected in North America
- Not a new subtype
- Infected children and adults, sparing over 65 years of age
- Relatively mild compared with 1918 flu
- But still significant mortality
- First in April-May, then peaked October-November
- 35 million cases - adults aged 18 to 64, 19 million in children, and 6 million in those older than 64.



Pandemics- lessons learned

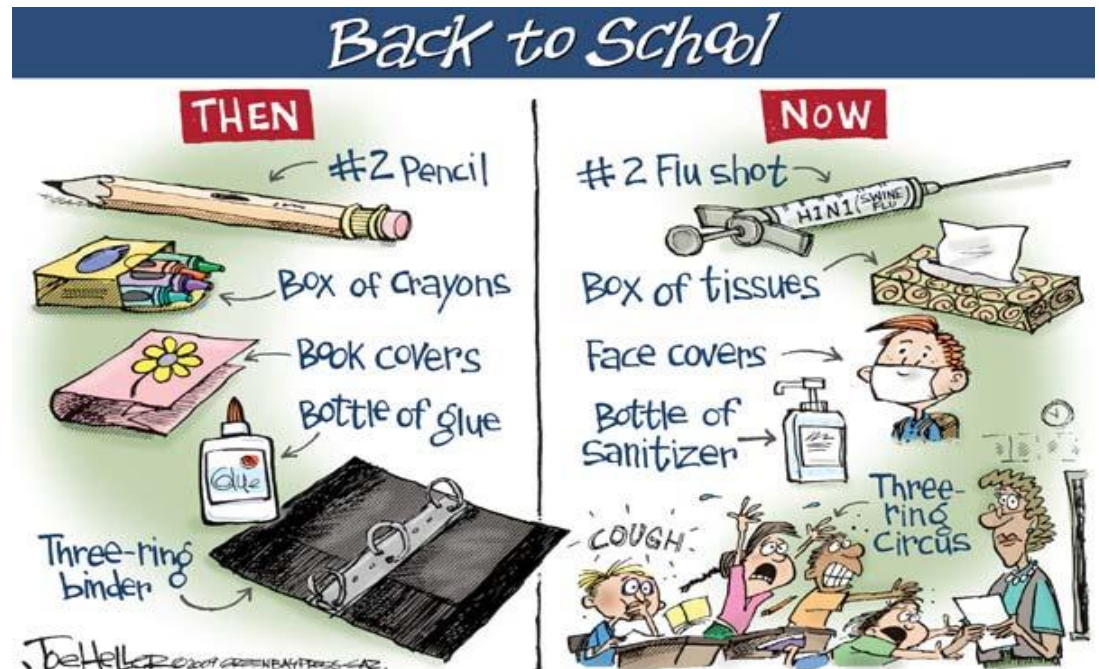
- Unpredictable, can occur at any time
- HA responsible for infectivity and lethality
- Obesity risk factor for severe flu
- Reinforced increased risk pregnant female
- Pandemic preparedness
- Value of early antiviral treatment
- Need for rapid, large scale influenza vaccine production

Rates of Influenza-Associated Hospitalizations Reported by Season 2009/10 - 2015/16

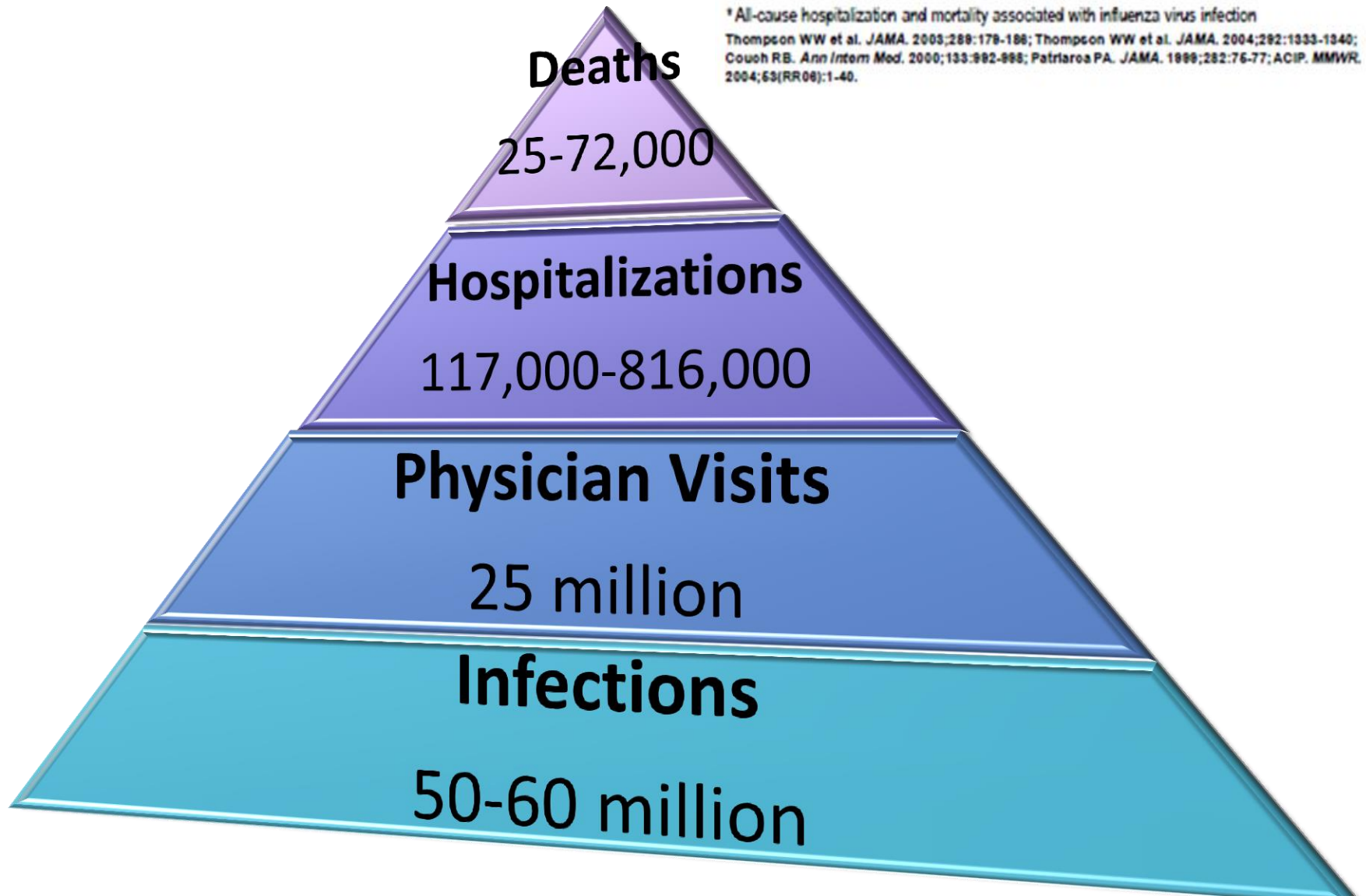


Children are the perfect vector for influenza

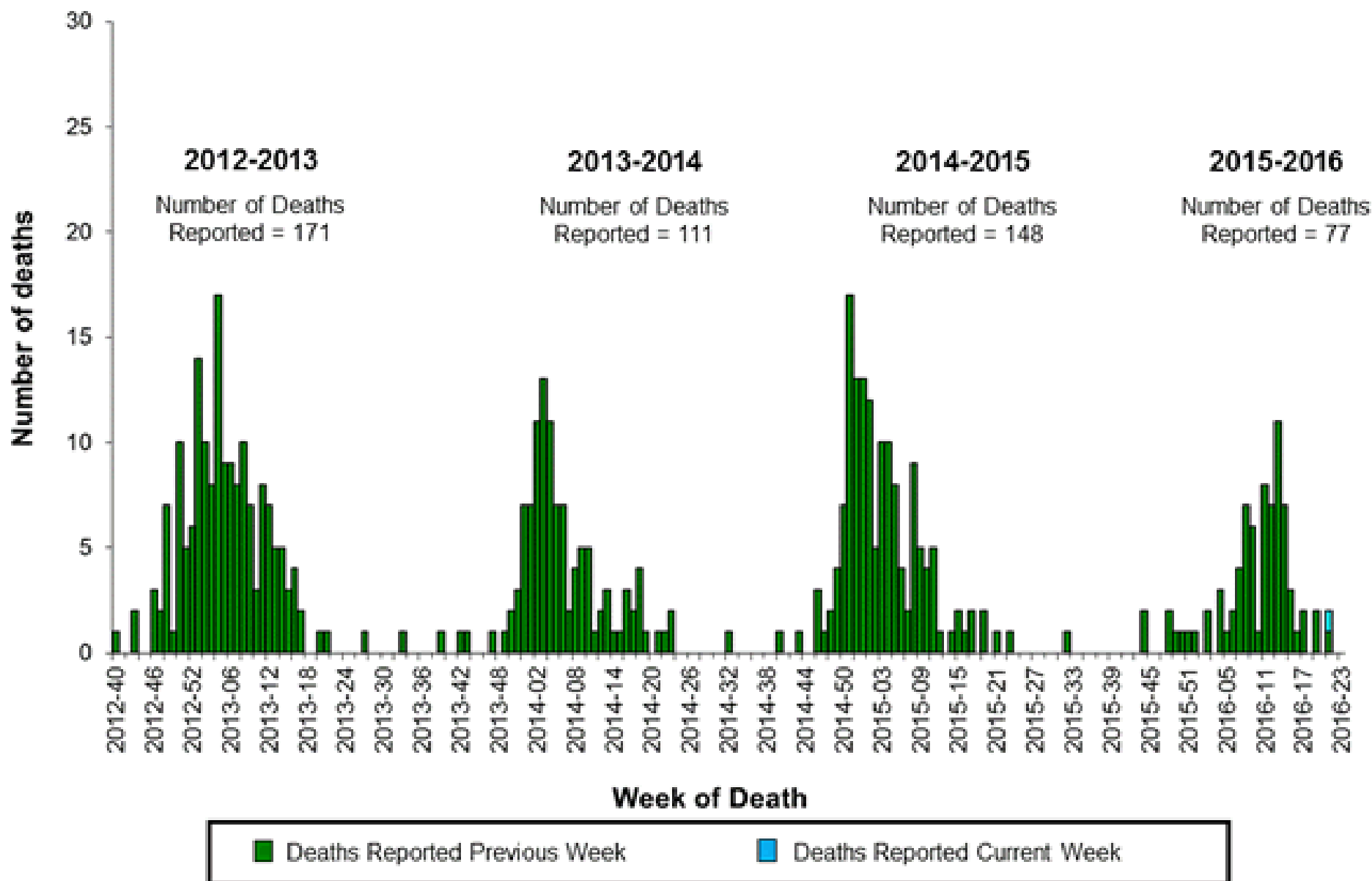
- Less sick than elderly, can spread virus effectively
- Have higher viral titers, longer viral excretion
- School-age children have highest attack rates
- Schools facilitate spread



Influenza Disease Burden in the US



Number of Influenza-Associated Pediatric Deaths by Week of Death: 2012-2013 season to present



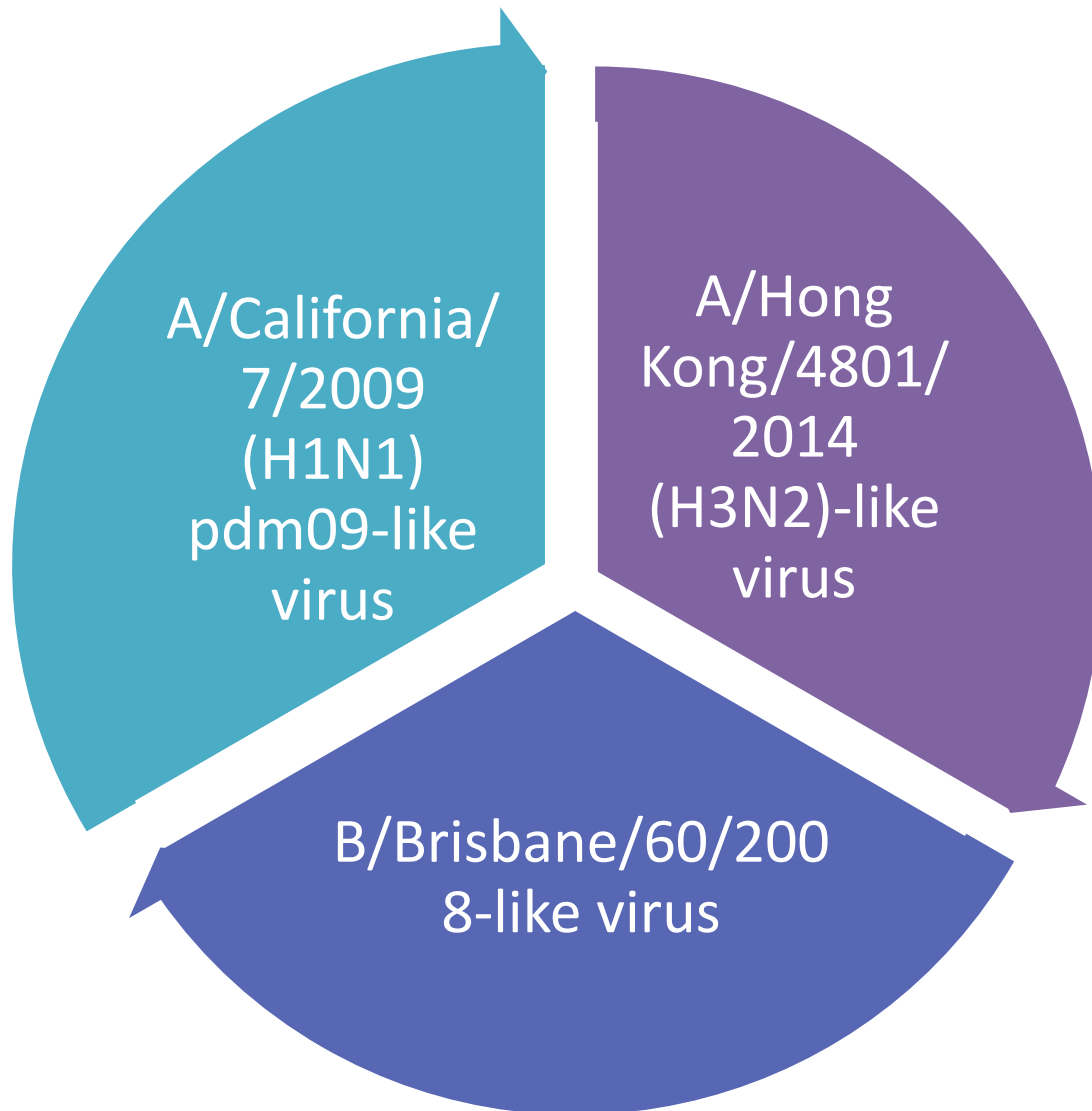
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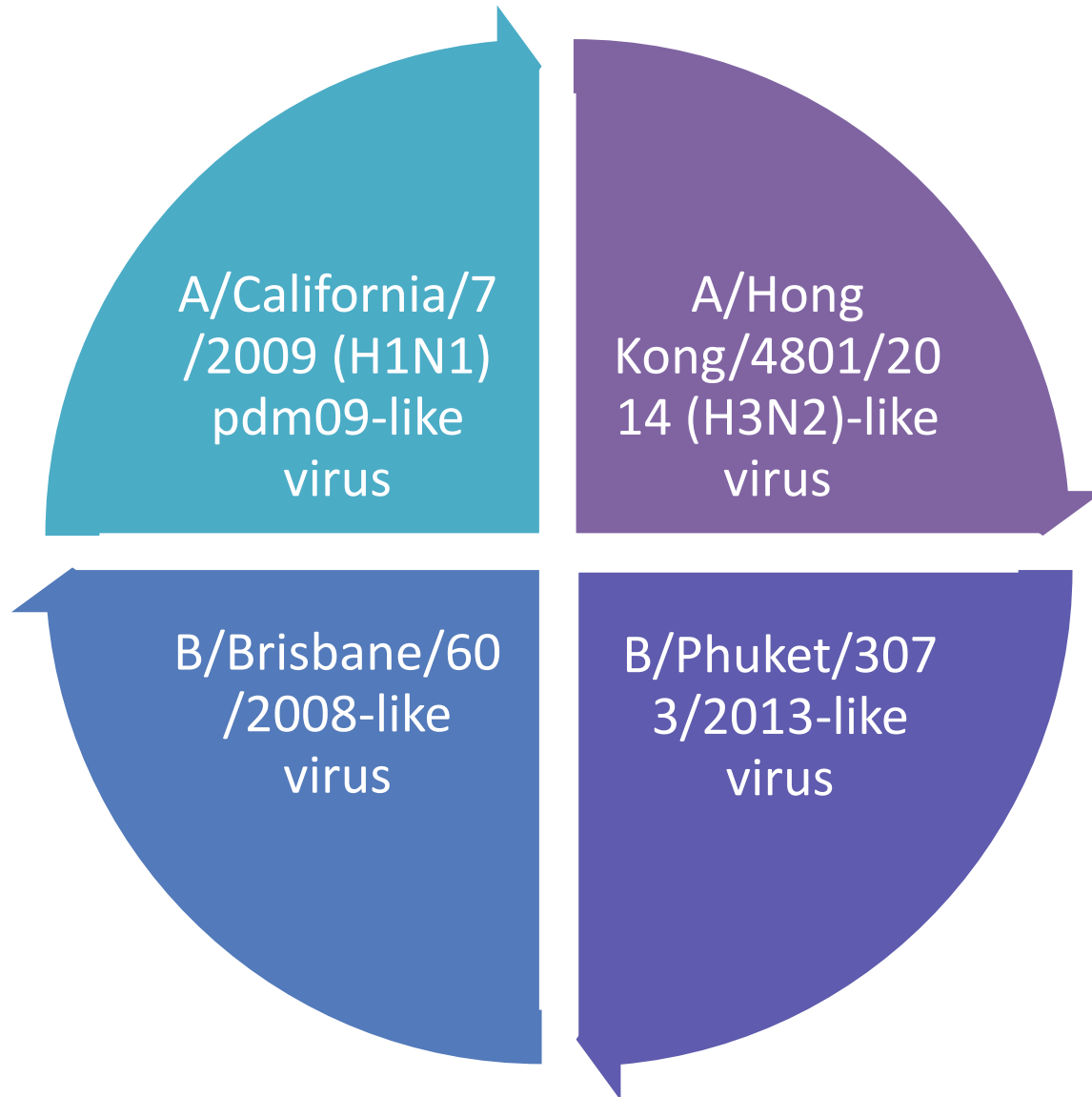
**“I can install this virus software if you bend over.
But a flu shot would be easier for both of us.”**

INFLUENZA VACCINATION

Trivalent Vaccine



Quadrivalent Vaccine



Vaccine types

IIV_{3/4}



LAIV₄



Vaccine types 2016-2017



Standard
dose

Cell
culture

High dose

Intra-
dermal

Adjuvant

Recomb-
inant

Vaccine types 2016-2017- for children



Standard
dose

Cell
culture

High dose

Intra-
dermal

Adjuvant

Recomb-
inant

Children who should NOT be vaccinated with IIV

- **Contraindications:**

- Infants younger than 6 months
- History of **severe** allergic reaction to any component of the vaccine, including egg protein, or after previous dose of any influenza vaccine.

- **Precautions:**

- Moderate to severe illness with or without fever.
- History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine.



**INFLUENZA VACCINE
RECOMMENDATIONS 2016-2017**

Definitions

- **IIV:** inactivated influenza vaccine
- **LAIV:** live attenuated influenza vaccine
- **Virus notation:** A/Moscow/10/99(H3N2): strain/place isolated/# virus isolated in that year/year isolated/subtype HA and NA
- **VE: Vaccine effectiveness** comparing the vaccination coverage in those who tested positive for influenza with those who tested negative and calculated as $100 \times (1 - \text{odds ratio})$ in logistic regression models
- **Man flu (*mæn flu*):** an illness that causes the male of the species to be helpless and sicker than other family members. In females; a *cold*.

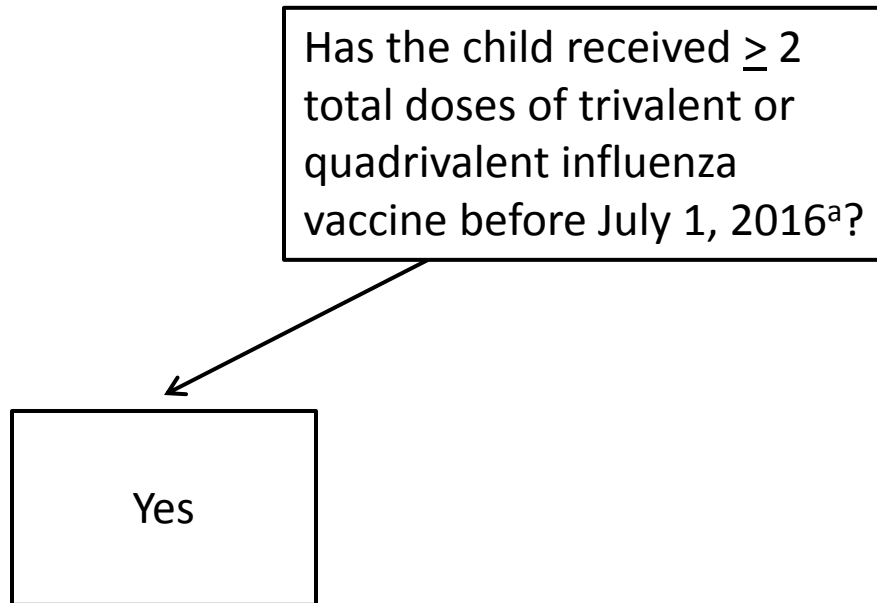
Influenza vaccine recommendations

- All people 6 months and older to be vaccinated against influenza
- Vaccination by the end of October is preferable
- A previous severe allergic reaction to influenza vaccine remains a contraindication to receiving the vaccine

Has the child received ≥ 2
total doses of trivalent or
quadrivalent influenza
vaccine before July 1, 2016^a?

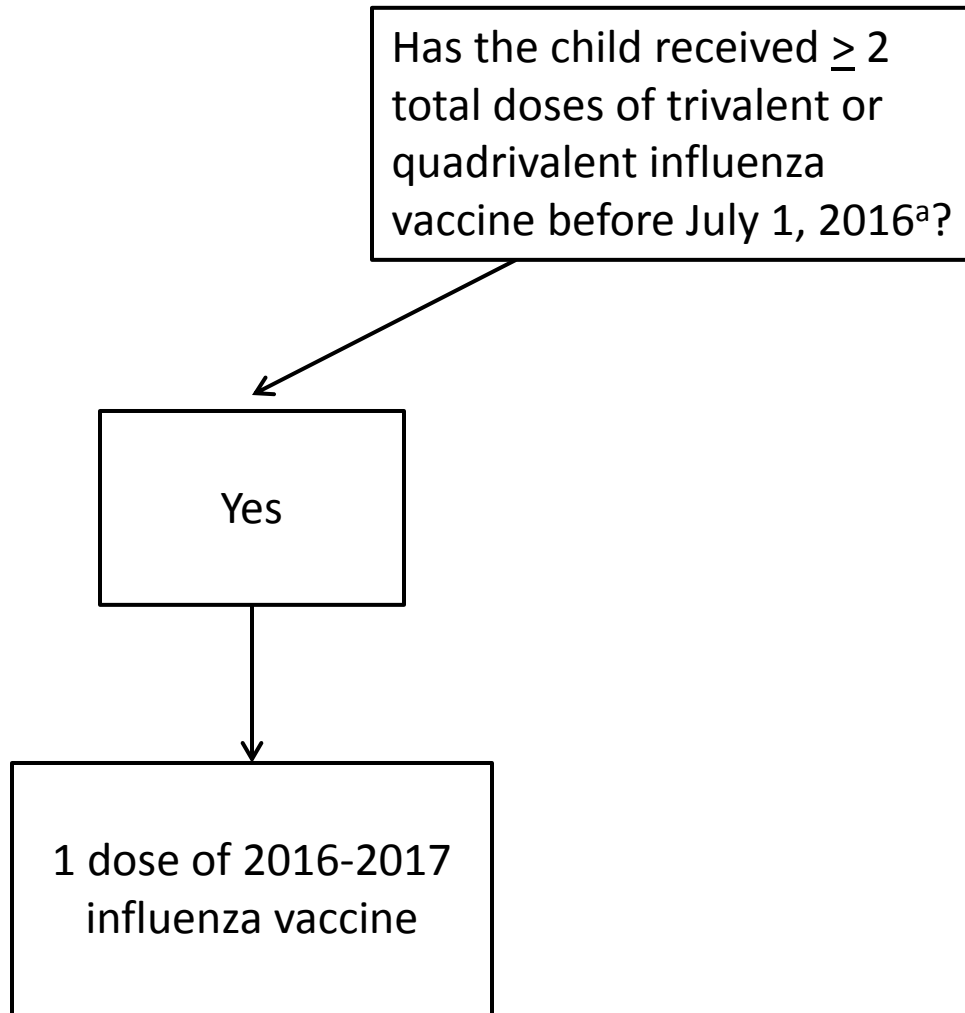
^a The two doses need not have been received during the same season or consecutive seasons.

CDC ref: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6430a3.htm#fig1>



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No

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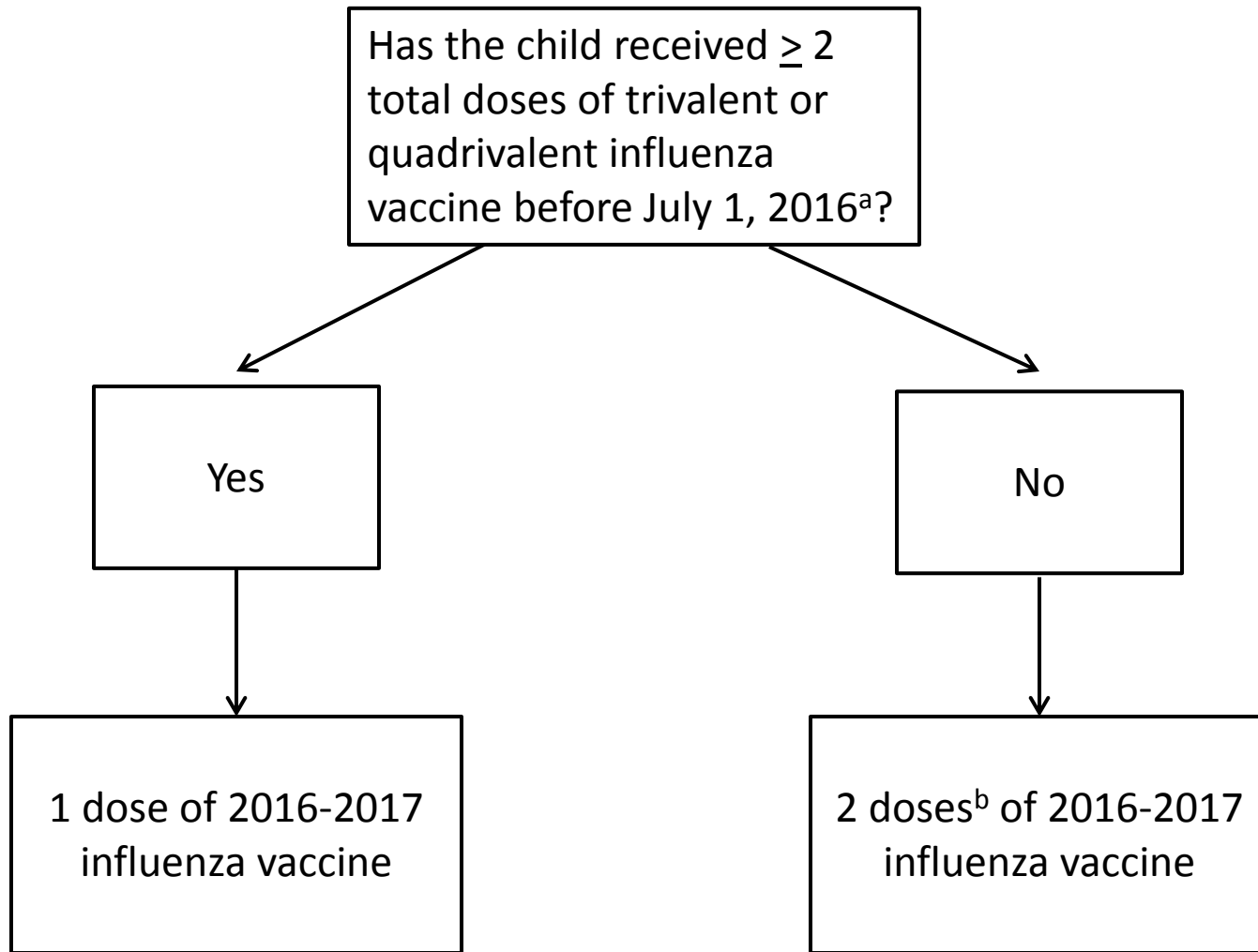
No

2 doses^b of 2016-2017
influenza vaccine

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^b Doses should be administered ≥ 4 weeks apart.

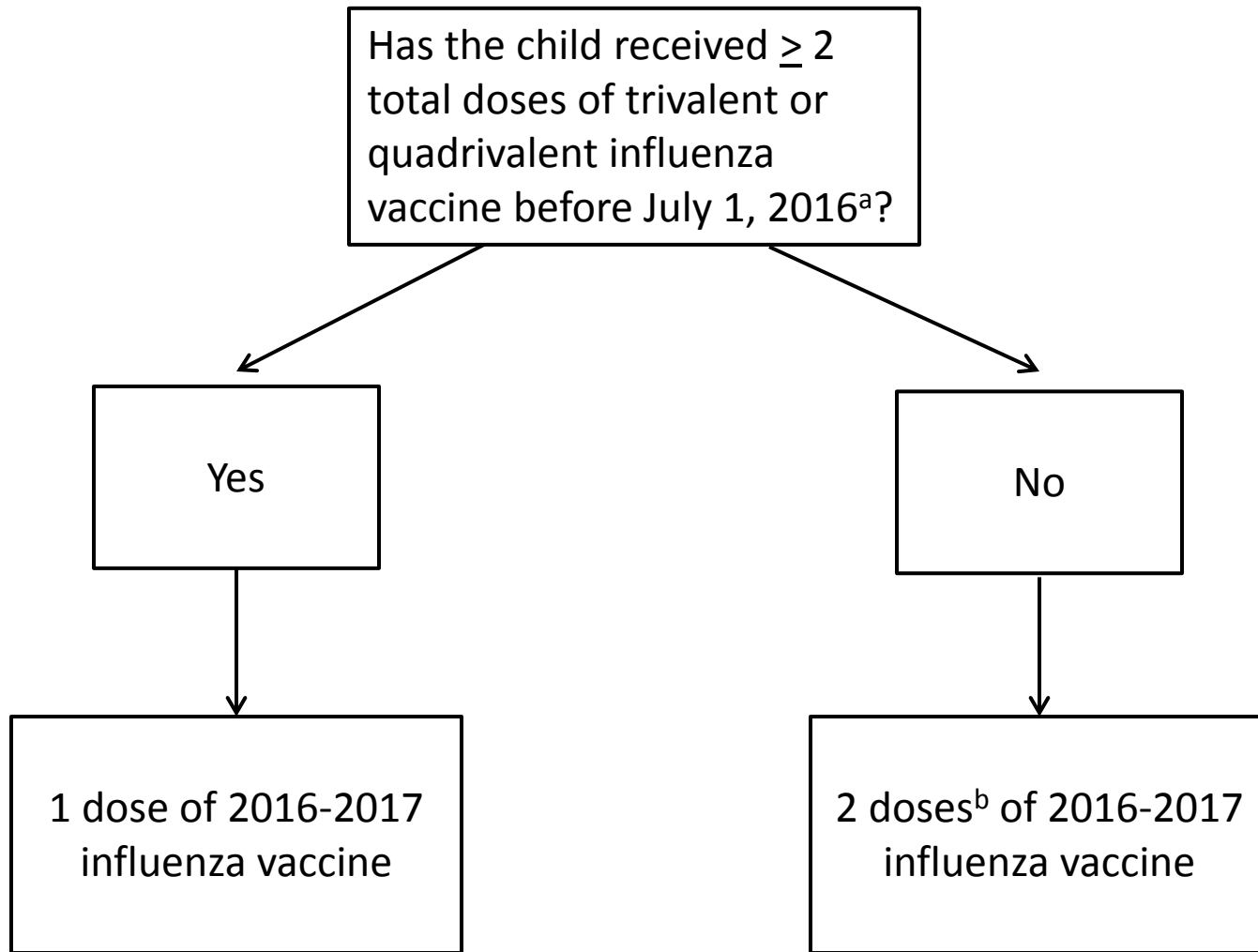
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ACIP recommendations

Egg allergy Feb 2016



- LAIV included as an option - egg allergy of any severity
- Eliminate algorithm regarding vaccinating such patients
- 15-minute post-vaccination observation period for patients with egg allergies, not 30 min
- If severe egg allergies -vaccinate in a setting with a physician trained to manage severe allergic conditions

After eating eggs or egg-containing foods, does the patient experience ONLY hives?

Yes

Administer any influenza vaccine formulation appropriate for recipient's age and health status

No

After eating eggs or egg-containing foods, does the patient experience other symptoms such as:

- **Cardiovascular changes**
- **Respiratory distress**
- **GI**
- **Reaction requiring epinephrine**
- **Reaction requiring emergency medical attention**

Yes

Administer any influenza vaccine formulation appropriate for recipient's age and health status
If a vaccine other than RIV is used, it should be administered in a medical setting in which a physician with experience in the recognition and management of severe allergic conditions is immediately available

THE CNN POLITICS APP:
WHO'S WINNING + WHY

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CDC panel recommends against using FluMist vaccine

By Susan Scutti, CNN

Updated 9:15 AM ET, Thu June 23, 2016



THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN ACADEMY OF PEDIATRICS

AAP News

Breaking News · June 22, 2016 · www.aapnews.org

AAP backs new ACIP recommendation on influenza vaccine

New ACIP recommendation on influenza vaccine June 2016

- LAIV should not be used during the 2016-2017 flu season
- Decreased VE of LAIV over the past 3 seasons
- IIV is more effective than LAIV against influenza A(H1N1)pdm09
- AAP in agreement
- Adult studies also poor vaccine effectiveness

Possible explanation for decreased efficacy

- Decreased replicative fitness of H1N1 in LAIV?
- Reduced thermal stability of the LAIV vaccine virus 2013-2014?
- Suboptimal performance of vaccine strain 2015-2016?
- Interference among viruses in vaccine?
- Effect of more highly vaccinated populations in recent years?

Influenza vaccine effectiveness estimates 2015-2016

	LAIV VE	LAIV- H1N1	IIV VE
CDC study ¹	3% (95% CI -47-39%)	-21% (95% CI -46-58%)	63% (95%CI 52-72%)
Department of Defense ²	53% (95% CI 28-70%)	15% (95% CI -20-50%)	66% (52-78%)
AstraZeneca ³	46% (95% CI 7-69%)	50% (95%CI -2-75%)	65% (95% CI 48-76%)
England ⁴	57.6% (95% CI 25-76%)	Not reported	Not reported
Finland ⁵ 24-35 months	46.2% (95% CI 22-63%)	46.7% (95% CI 20-65%) (for all Flu A)	59.7% (95% CI 27-78%)

1. Flannery B, Chung J. Influenza Vaccine Effectiveness, including LAIV vs IIV in children and adolescents, US flu VE network, 2015-16. Presented at the Meeting of the advisory committee in immunization practices (ACIP). Atlanta, GA, June 22, 2016.

2. US Department of Defense Study. Presented at the Meeting of the advisory committee in immunization practices (ACIP). Atlanta, GA, June 22, 2016. Confidence intervals estimated from CDC figures

3. ICICLE vaccine effectiveness study - Presented at the Meeting of the advisory committee in immunization practices (ACIP). Atlanta, GA, June 22, 2016

4. http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/530756/Influenza_vaccine_effectiveness_in_primary_care_in_children.pdf

5. Nohynek H. Seasonal childhood influenza vaccinations. Experiences from Finland. Presented at the Nordic Vaccine Meeting, Reykjavik, Iceland, April 28, 2016.

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Influenza Vaccine effectiveness 2015-2016

- CDC study- LAIV not effective
- Other studies- effectiveness 46% to 58%
- Overall effectiveness of LAIV lower than inactivated influenza vaccines (IIV)

Influenza vaccine recommendations 2015-2016

- Vaccine manufacturers have projected that as many as 171 million – 176 million doses of flu vaccine will be made for 2016-2017
- LAIV accounts for up to 14 million of those doses
- May disrupt school-based vaccine programs that primarily use LAIV
- Will affect evaluation of LAIV VE in future seasons



INFLUENZA TREATMENT

Who to treat for influenza?

- Confirmed or suspected influenza with severe, complicated, or progressive illness, or hospitalized
- Outpatients with confirmed or suspected influenza who are at higher risk for influenza complications
- Consider if < 48 hours symptoms

Source: CDC website <http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>

Why treat? RCT data

- Data from 10 clinical trials, 50% lower risk mortality among treated vs placebo, 34% lower among patients at risk for complications ($p < 0.05$)
- One RCT found a decreased incidence of otitis media among children treated with oseltamivir
- RCT in children with asthma- greater improvement in lung function & fewer asthma exacerbations among oseltamivir-treated children

Hsu et al 2012

Louie et al. CID 2012

Muthuri et al CID 2012

Why treat?

- One RCT of oseltamivir treatment among 408 children aged 1--3 years reported that when oseltamivir was started within 24 hours of illness onset, the median time to illness resolution was shortened by 3.5 days compared with placebo
- Minimal or no effect if started after 2 days of onset

Source: Heinonen S, et al. Clin Infect Dis 2010;51:887--94

Who to treat?



- Consider for outpatients with uncomplicated, suspected, or confirmed influenza at increased risk for developing severe or complicated illness if antiviral treatment can be initiated within 48 hours of illness onset
- Treatment should not be delayed while the results of diagnostic testing are awaited

Who is considered high risk?

- Children <2 years;
- Persons with chronic pulmonary (including asthma), cardiovascular, renal, hepatic, hematological (and sickle cell disease), metabolic disorders (and diabetes mellitus), neurologic and neurodevelopmental conditions, developmental delay, muscular dystrophy, or spinal cord injury); immunosuppression



Who is considered high risk?

- Women who are pregnant or postpartum (within 2 weeks after delivery);
- <19 years receiving long-term aspirin therapy;
- American Indians/Alaska Natives;
- Morbid obesity



Choosing an antiviral



- Oseltamivir 2 weeks and older (FDA)
- CDC and AAP approve < 2 weeks
- Inhaled zanamivir 7 years and older
- IV peramivir approved in 2014 for persons 18 years and older
- Oseltamivir is preferred for the treatment of pregnant women
- Rimantadine and amantadine not recommended for treatment or prevention of influenza

Oseltamivir

- Given orally for 5 days
- Experimental IV preparation
- Currently no issues with resistance
- Immunocompromised hosts more likely to develop resistance because of prolonged shedding



Zanamavir

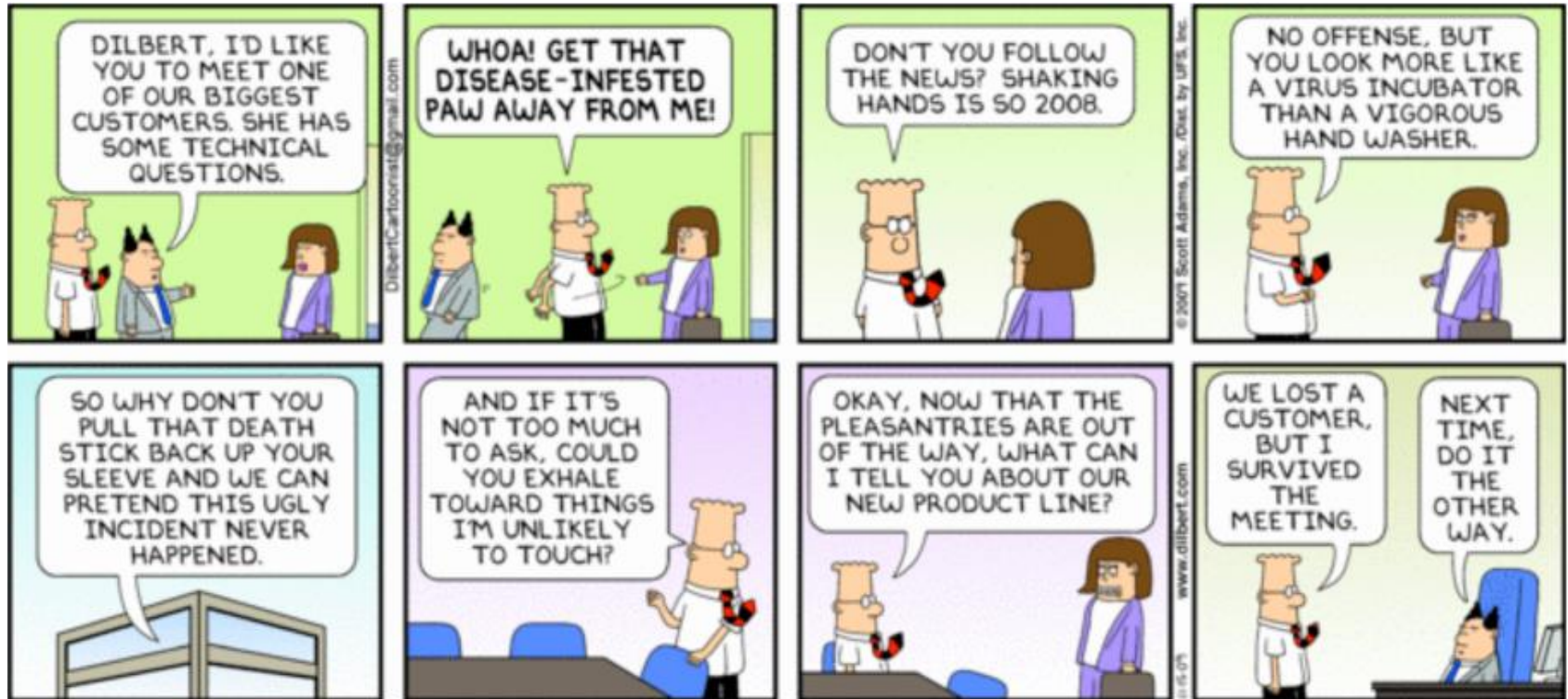


- Dry powder administered via oral inhalation
- Not FDA-cleared for children < 7 years of age
- Dose is 2 breath-activated inhalations twice daily for 5 days
- For prophylaxis, 2 inhalations once daily for 5 and older
- Not recommended for children with RAD
- Bronchospasm, decline in lung function

Chemoprophylaxis

- Not for widespread use due to the possibility of resistance
- Can consider for family members and close contacts considered high risk
- Chemoprophylaxis not recommended if >48 hours since last exposure
- Can be used for prophylaxis of influenza among infants < 6 months, AAP approves use for neonates
- For prophylaxis, antiviral must be taken each day for duration of potential exposure, and continue for 7 days afterwards

Questions?



Questions?



Children who should not be vaccinated with LAIV

- **Contraindications:**
- History of **severe allergic reaction** to any component of the vaccine, or after a previous dose of any influenza vaccine
- **Effectiveness or safety not established:**
- Children younger than 2 years
- Children with chronic underlying medical conditions, immunosuppression, on aspirin therapy

Children who should not be vaccinated with LAIV

- **Effectiveness or safety not established (contd.):**
- Children with asthma, or aged 2-4 years old with a history of recurrent wheezing or a wheezing episode in the previous 12 months
- Close contacts/ caregivers of severely immunosuppressed persons who require a protected environment;
- Pregnant women

Children who should not be vaccinated with LAIV

- **Precautions:**
- Guillain-Barré Syndrome (GBS) within 6 weeks of a previous dose of an influenza vaccine
- Children with moderate to severe acute illness with or without fever
- **Other considerations:**
- Children with nasal congestion that would notably impede vaccine delivery
- Children who have received other live virus vaccines within the past 4 weeks (although you can give LAIV at the same time as other live virus vaccines)
- Children taking an influenza antiviral medication should not receive LAIV until 48 hours after stopping the medication

Oseltamivir dosing

AGE	TREATMENT DOSE	PROPHYLAXIS DOSE
2 weeks - 3 months	3 mg/kg/dose twice a day	Not recommended unless situation judged critical
Children 3-11 months	3 mg/kg/dose twice a day	3 mg/kg/dose once daily
Children 1-12 years old and weighing:		
≤ 15 kg	30 mg/dose twice a day	30 mg once daily
> 15-23 kg	45 mg/dose twice a day	45 mg once daily
>23-40 kg	60 mg/dose twice a day	60 mg once daily
>40 kg	75 mg/dose twice a day	75 mg once daily
Children ≥ 13 years of age and adults	75 mg/dose twice a day	75 mg once daily

