Influenza

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Colorado Children’s Immunization Coalition Education Event
October 11, 2016
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**
BACKGROUND
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
Antigenic Shift and Drift

Antigenic Drift: Accumulation of mutations in the genome

Human strain

Non-human strain

Antigenic Shift: Genome reassortment
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

Central
- Headache

Systemic
- Fever (usually high)

Muscular
- (Extreme) tiredness

Nasopharynx
- Runny or stuffy nose
- Sore throat
- Aches

Respiratory
- Coughing

Gastric
- Vomiting

Know the FLU
Fever
Aches
Chills
Tiredness
Sudden Onset
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

Asiatic or Russian flu
Other Pandemics

Influenza A virus subtypes in the human population

H3?
H3N2
H2N2
H1N1
H1N1

1889 1900 1918 1940 1960 1980 2000

Year

1918 Spanish Flu
Other Pandemics

Influenza A virus subtypes in the human population

- H1?
- H3?
- H2N2
- H1N1
- H1N1

Year:
1957  Asian Flu
Other Pandemics

Influenza A virus subtypes in the human population

1889  1900  1918  1940  1960  1980  2000

Year

H3?

H2N2

H1N1

H1N1

1968 Hong Kong Flu
Other Pandemics

Influenza A virus subtypes in the human population

- H3?
- H3N2
- H2N2
- H1N1
- H1N1
- H1N1

Year:

1889 1900 1918 1940 1960 1980 2000

1977 Russian Flu
Other Pandemics

Influenza A virus subtypes in the human population

H3?

H3N2

H2N2

H1N1

H1N1

1889 1900 1918 1940 1960 1980 2000

Year

2009  Swine Flu
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
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

**Back to School**

**THEN**
- #2 Pencil
- Box of Crayons
- Book covers
- Bottle of glue
- Three-ring binder

**NOW**
- #2 Flu shot
- Box of tissues
- Face covers
- Bottle of sanitizer
- Three-ring circlets
Influenza Disease Burden in the US

- Infections: 50-60 million
- Physician Visits: 25 million
- Hospitalizations: 117,000-816,000
- Deaths: 25-72,000

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

- **2012-2013**: Number of Deaths Reported = 171
- **2013-2014**: Number of Deaths Reported = 111
- **2014-2015**: Number of Deaths Reported = 148
- **2015-2016**: Number of Deaths Reported = 77
INFLUENZA VACCINATION
Trivalent Vaccine

A/Hong Kong/4801/2014 (H3N2)-like virus

A/California/7/2009 (H1N1)pdm09-like virus

B/Brisbane/60/2008-like virus
Quadrivalent Vaccine

- A/California/7/2009 (H1N1) pdm09-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus
- B/Phuket/3073/2013-like virus
Vaccine types

$IIV_{3/4}$

$LAIV_{4}$
Vaccine types 2016-2017

IIV$_{3/4}$

- Standard dose
- Cell culture
- High dose
- Intra-dermal

LAIV$_4$

- Adjuvant
- Recombinant
Vaccine types 2016-2017 - for children

- IIV$_{3/4}$
- LAIV$_4$

- Standard dose
- Cell culture
- High dose
- Intra-dermal
- Adjuvant
- Recombinant
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? 

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](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6430a3.htm#fig1)
Has the child received ≥ 2 total doses of trivalent or quadrivalent influenza vaccine before July 1, 2016? 

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

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Yes

1 dose of 2016-2017 influenza vaccine

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No

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No

2 doses\(^b\) of 2016-2017 influenza vaccine

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

\(^b\) Doses should be administered ≥ 4 weeks apart.

CDC ref: [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6430a3.htm#fig1](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6430a3.htm#fig1)
Has the child received $\geq 2$ total doses of trivalent or quadrivalent influenza vaccine before July 1, 2016? 

- **Yes**: 1 dose of 2016-2017 influenza vaccine 
- **No**: 2 doses of 2016-2017 influenza vaccine 

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

*b Doses should be administered $\geq 4$ weeks apart.

CDC ref: [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6430a3.htm#fig1](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6430a3.htm#fig1)
Has the child received ≥ 2 total doses of trivalent or quadrivalent influenza vaccine before July 1, 2016a?

- Yes
  - 1 dose of 2016-2017 influenza vaccine

- No
  - 2 dosesb of 2016-2017 influenza vaccine

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a The two doses need not have been received during the same season or consecutive seasons.
b Doses should be administered ≥ 4 weeks apart.

CDC ref: [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6430a3.htm#fig1](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6430a3.htm#fig1)
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

Ref: http://www.cdc.gov/vaccines/acip/meetings/downloads/
CDC panel recommends against using FluMist vaccine

By Susan Scutti, CNN

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

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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?

ACIP meeting June 2016.
# Influenza vaccine effectiveness estimates 2015-2016

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<td>63% (95%CI 52-72%)</td>
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<td><strong>Department of Defense</strong>²</td>
<td>53% (95% CI 28-70%)</td>
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<td><strong>AstraZeneca³</strong></td>
<td>46% (95% CI 7-69%)</td>
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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
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3. ICICLE vaccine effectiveness study - Presented at the Meeting of the advisory committee in immunization practices (ACIP). Atlanta, GA, June 22, 2016.
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.

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
Dilbert, I'd like you to meet one of our biggest customers. She has some technical questions.

Whoa! Get that disease-infested paw away from me!

Don't you follow the news? Shaking hands is so 2008.

No offense, but you look more like a virus incubator than a vigorous hand washer.

So why don't you pull that death stick back up your sleeve and we can pretend this ugly incident never happened.

And if it's not too much to ask, could you exhale toward things I'm unlikely to touch?

Okay, now that the pleasantries are out of the way, what can I tell you about our new product line?

We lost a customer, but I survived the meeting.

Next time, do it the other way.
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

<table>
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<tr>
<th>AGE</th>
<th>TREATMENT DOSE</th>
<th>PROPHYLAXIS DOSE</th>
</tr>
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<tbody>
<tr>
<td>2 weeks - 3 months</td>
<td>3 mg/kg/dose twice a day</td>
<td>Not recommended unless situation judged critical</td>
</tr>
<tr>
<td>Children 3-11 months</td>
<td>3 mg/kg/dose twice a day</td>
<td>3 mg/kg/dose once daily</td>
</tr>
<tr>
<td>Children 1-12 years old and weighing:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15 kg</td>
<td>30 mg/dose twice a day</td>
<td>30 mg once daily</td>
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<tr>
<td>&gt; 15-23 kg</td>
<td>45 mg/dose twice a day</td>
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<tr>
<td>&gt; 23-40 kg</td>
<td>60 mg/dose twice a day</td>
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<td>Children &gt; 13 years of age and adults</td>
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