Viruses and Pediatrics – Part I
RNA Viruses

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Lecture Outline*

- Influenza
- Parainfluenza
- Mumps
- Respiratory Syncytial Virus

- Metapneumovirus
- Measles
- Rhinovirus
- Enteroviruses

* denote specific AAP content specifications
Influenza Viruses

• Orthomyxoviridae family
• Enveloped, negative sense RNA viruses
• Segmented genome
  – 8 RNA segments that encode 10 different proteins
• Classified into 3 types based on antigenic differences
  – Type A
  – Type B
  – Type C
Influenza: Epidemiology*

• Highly infectious, contagious virus
• Seasonal epidemics* during winter months
• Spread primarily by respiratory tract droplets*
  – Coughing, sneezing individuals
  – Contaminated surfaces
• Incubation period 1 - 4 days (mean = 2)
• Infectious from 24 hours before – 7 days after onset*
• Viral shedding peaks during first 3 days of illness
  – May be prolonged in young children and immunocompromised
Antigenic Drift vs. Shift

- **Drift**
  - Minor accumulations of point mutations in the predominant strains
  - Accounts for year to year appearance of new strains
  - Accounts for epidemic strains if sufficiently different

- **Shift**
  - Recombination between different types to give rise to an entirely new strain
  - Usually involves *nonhuman animal host*
  - Accounts for influenza pandemics
Influenza: Clinical Features*

• Sudden onset of fever
  – Chills, rigors, headache malaise, myalgia, nonproductive cough

• Progression of respiratory tract signs
  – Sore throat, nasal congestion, rhinitis, cough

• Variable presentations:
  – URI versus febrile illness with few respiratory symptoms
  – Sepsis-like picture
  – Croup, bronchiolitis, pneumonia
  – Acute myositis
  – Sudden death (in chronically ill and previously healthy)

• Gastrointestinal symptoms less common
Complications of Influenza
Clinical Case

• 14 year old previously-healthy male
• 8 days PTA developed fever, sore throat, headache, cough
• Symptoms progressed
• CXR: LLL pneumonia, respiratory failure, ARDS
• In ICU, developed hemodynamic instability
• Viral respiratory DFA: Influenza A
• MRSA isolated from ETT culture
Bacterial Pneumonia After Influenza

• Results primarily from disruption of mechanical host defenses
  – e.g. disruption of mucociliary ladder
• Common organisms
  – *S. pneumoniae*
  – *S. aureus*
  – *H. influenzae*
  • This bacteria was originally isolated from the lungs of individuals who died in the 1918 influenza epidemic
  • Mistakenly thought to have caused the flu, hence the name
Reye’s Syndrome

- Syndrome
  - Encephalopathy
  - Fatty infiltration of the liver
- Most common in children
- Occurs after viral illness
  - Almost entirely influenza
- Occurs when treated with aspirin and other salicylates
  - A few other drugs
- Avoid aspirin in children
Diagnosis of Influenza*

- Epidemiology and Clinical Presentation
- Nasopharyngeal specimens
  - Swab, aspirate or wash
  - Obtain within 1st 72 hours
- Rapid detection methods*
  - DFA and IFA – detect Influenza A and B antigens
- Viral Culture* – high sensitivity and specificity
- PCR assays* – high sensitivity and specificity
- Acute and Convalescent Serologies – less useful
Influenza: Who to Treat*

- “should be offered to any child with presumed influenza or severe, complicated or progressive disease, regardless of immunization status…”
- “…for influenza infection of any severity in children with a condition that places them at increased risk*”
  - Hemoglobinopathies
  - BPD, Asthma, Cystic Fibrosis
  - Malignancy
  - Congenital heart disease
  - Diabetes Mellitus
  - Chronic Renal Disease
M2 Inhibitors (“Amantadanes”)

- Amantadine* and Rimantadine*
- Inhibit M2 protein function
- Inhibit acidification of endosome, Golgi, ER, required for dissociation of viral genome from matrix
  - No uncoating of virus
- Acts only on influenza A virus*
- Can be used for prophylaxis and treatment*
  - Only if circulating influenza A resistant to oseltamivir, like occurred in 2007-2008 season
- Resistance with single point mutations
Neuraminidase Inhibitors*

- Oseltamivir* (Tamiflu) - oral
- Zanamivir* (Relenza) – inhaled
- Currently recommended influenza antiviral drugs*
- What is the function of Neuraminidase?
  - Allows virus to breakdown mucous and separate from cell
  - Prevents virus from clumping
- Effective against influenza A and B*
- Prophylaxis
- Treatment if given within 48 hours of onset of symptoms
# Influenza Antivirals: Side Effects*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Virus</th>
<th>Administration</th>
<th>Adverse Effects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>A &amp; B</td>
<td>Oral</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>A &amp; B</td>
<td>Inhalation</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Amantadine</td>
<td>A</td>
<td>Oral</td>
<td>CNS+, anxiety, GI</td>
</tr>
<tr>
<td>Rimantadine</td>
<td>A</td>
<td>Oral</td>
<td>CNS+, anxiety, GI</td>
</tr>
</tbody>
</table>

* increased incidence of seizures in children with epilepsy, Amantadine > rimantidine
Influenza Vaccine

• **Schedule**:  
  – Annually, as soon as available, but can give throughout flu season  
  – Children aged 6 months - 8 years receiving influenza vaccine for the first time require **two doses** administered ≥4 weeks apart  
  – Children **9 years or older** – **1 dose**

• **Inactivated vaccine** (subvirion or purified surface antigen, injectable)  
  – **Indications**:  
    • Ages 6 months or older  
    • Preferred for close contacts of severely immunosuppressed  
  – **Contraindications**:  
    • History of severe, life-threatening allergy to previous flu vaccine or any ingredient in the vaccine (precautions in egg-allergic)  
    • Infants < 6 months old
Live attenuated influenza vaccine (LAIV)

– NEW: For 2016-17 season, LAIV is **not recommended**

– **Indications*** (prior to 2016-17 season):
  • Healthy, nonpregnant, ages 2 - 49 years

– **Contraindications***:
  • History of severe allergic reaction to a component of the LAIV vaccine
  • History of severe allergic reaction to prior dose of any flu vaccine
  • Received other live vaccines within the last 4 weeks
  • Receiving salicylates
  • Known or suspected immune deficiency
  • Age 2 - 4 years with asthma or any history of wheezing within 12 months
  • Influenza antiviral medications within the previous 48 hours
  • < 2 years or ≥50 years; pregnancy
LAIV: What happened?

ACIP votes down use of LAIV for 2016-2017 flu season

CDC’s Advisory Committee on Immunization Practices (ACIP) today voted that live attenuated influenza vaccine (LAIV), also known as the “nasal spray” flu vaccine, should not be used during the 2016-2017 flu season. ACIP continues to recommend annual flu vaccination, with either the inactivated influenza vaccine (IIV) or recombinant influenza vaccine (RIV), for everyone 6 months and older.

June 22, 2016

ACIP is a panel of immunization experts that advises the Centers for Disease Control and Prevention (CDC). This ACIP vote is based on data showing poor or relatively lower effectiveness of LAIV from 2013 through 2016.

In late May, preliminary data on the effectiveness of LAIV among children 2 years through 17 years during 2015-2016 season became available from the U.S. Influenza Vaccine Effectiveness Network. That data showed the estimate for LAIV VE among study participants in that age group against any flu virus was 3 percent (with a 95 percent Confidence Interval (CI) of -49 percent to 37 percent). This 3 percent estimate means no protective benefit could be measured. In comparison, IIV (flu shots) had a VE estimate of 63 percent (with a 95 percent CI of 52 percent to 72 percent) against any flu virus among children 2 years through 17 years. Other (non-CDC) studies support the conclusion that LAIV worked less well than IIV this season. The data from 2015-2016 follows two previous seasons (2013-2014 and 2014-2015) showing poor and/or lower than expected vaccine effectiveness (VE) for LAIV.
Current Influenza Vaccines

2016-17

- A/California/7/2009 (H1N1)
- A/Hongkong/4801/2014 (H3N2)
- B/Brisbane/60/2008

- A/California/7/2009 (H1N1)
- A/Switzerland/9715293/2013 (H3N2)
- B/Brisbane/60/2008-like
- B/Phuket/3073/2013 virus

Antigen composition evaluated annually*

Trivalent

Quadrivalent
Paramyxoviridae

- **Parainfluenza group**
  - Parainfluenza virus 1-4
  - Mumps
- **Pneumovirus group**
  - Respiratory syncytial virus (RSV)
  - Metapneumovirus
- **Morbillivirus group**
  - Measles
Parainfluenza: Epidemiology

- **Predictable seasonal patterns**
  - Type 1: fall outbreaks of acute respiratory illness (croup)
  - Type 2: same as 1, but less severe and frequent
  - Type 3: spring and summer

- **Transmission:**
  - Direct contact and exposure to NP secretions

- **Incubation period 2-6 days**

- **Viral shedding**
  - up to 1 week before symptoms
  - 1-3 weeks after symptoms resolve
Parainfluenza: Clinical Features

- Major cause of laryngotracheobronchitis* (croup)
  - Types 1 and 2
- URI
- Type 3
  - Pneumonia and/or bronchiolitis*
  - Rare: Parotitis, aseptic meningitis, encephalitis
  - Severe, prolonged infections in immunocompromised*
- Infections do not confer complete protective immunity
Mumps

• Isolated in 1954
• Paramyxovirus
  – Negative sense, single-stranded RNA
• One antigenic type
• Most closely related to parainfluenza virus type 2
• World-wide distribution
• Winter/spring peak*
Mumps: Pathogenesis

- Respiratory transmission
  - Saliva and large respiratory droplets*
- Incubation period 16-18 days
- Replication in epithelial cells of nasopharynx
  - Lytic infection (no latent infection)
- Replication also occurs in regional lymph nodes
- Spread to Stensen’s duct (to parotid) directly or by viremia
- Viremia occurs 12-25 days after exposure
Mumps: Clinical Features*

- Up to 1/3 asymptomatic or with respiratory tract infection
- Prodrome of malaise, headache, low-grade fever
- Systemic disease with swelling of salivary gland(s)
- Parotitis* in 30-40%
- Only known cause of epidemic parotitis
- Virus in saliva from 6 days before to 9 days after parotitis
  - Infectious 3-5 days before symptoms
Mumps Parotitis*

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Mumps Complications*

- **CNS involvement**
  - CSF pleocytosis in > 50%
  - Symptomatic aseptic meningitis <10%
  - Encephalitis 2/100,000
  - Deafness 1 per 20,000 (CN VIII)

- **Orchitis**
  - 50% of postpubertal males
  - 50% of affected with some degree of testicular atrophy

- **Oophoritis**- only 5%; little long-term sequelae

- **Pancreatitis, arthritis, myocarditis, thyroiditis** - rare
Mumps: Management*

• Self-limited illness
• Supportive care
• Control measures
  – Isolation/exclusion of infected individual for 5 days after onset of parotid swelling
• For exposed individuals (without evidence of immunity)
  – MMR vaccine
  – If unable to receive vaccine, exclude for 26 days after mumps exposure
  – IG not effective as postexposure prophylaxis
Mumps Epidemic
New York, New Jersey; 2009 - 2010

• 11 year-old boy returned from UK on June 17, 2009
• He then attended a New York summer camp for tradition-observant Jewish boys
• He became symptomatic June 28
• Subsequently, other camp attendees and a staff member were reported to have mumps
• Transmission continued in multiple locations when the camp attendees returned home
• Approximately 3000 cases were reported
Respiratory Syncytial Virus (RSV)

- Large public health burden worldwide
- Half of all infants infected in the first year and 100% by 3 years of age
- Lower respiratory tract disease in 25 - 40% of infected infants
- 2 - 3% of infected infants hospitalized
- Most common cause of bronchiolitis and pneumonia in children under 1 year of age*
Annual epidemics during winter-early spring
Incubation period ranges 2-8 days
Spread by secretions and large particle droplets
  - Virus survives on hands usually for <1 hr and in secretions for 3-30 hrs
  - Inoculation primarily through nose or eyes, less frequently through mouth
Hand hygiene is important in controlling spread
Nosocomial spread is common
RSV: Clinical Features*

• Acute respiratory infection in all age groups
• Primary infection:
  – Pneumonia or bronchiolitis
  – Tracheobronchitis
  – URI + fever, otitis media
• Neonates may have minimal respiratory tract signs
  – Lethargy, poor feeding, apnea
• Asymptomatic infection is rare
• Reinfection throughout life common
RSV: Diagnosis*

- **Rapid diagnostic assays**
  - EIA, DFA of NP specimens to detect viral antigens
  - Sensitivity: most are 80 - 90%

- **Culture**
  - 3-5 days
  - Relatively labile virus
  - Requires optimal sample collection and transport

- **PCR assays**
  - Increased RSV detection rates
  - Interpret with caution: persistence of viral RNA in airway
RSV: Management*

• Mainly Supportive
  – Supplemental oxygen, hydration, suctioning

• Bronchodilators, corticosteroids
  – Not recommended

• Ribavirin
  – Not recommended for routine use
  – Consider in select populations with potentially life-threatening RSV infection
RSV Prevention

- No vaccine available
- Passive immunoprophylaxis: **Palivizumab**
  - Humanized mouse monoclonal antibody
    - Directed against the RSV Fusion protein
  - For high-risk infants and children
    - CLD, preterm birth congenital heart disease
  - Reduces the risk of RSV hospitalization
  - Typical RSV season duration 19 weeks (Nov – March)
  - 5 monthly doses provides > 20 weeks of protective serum antibody concentrations
Palivizumab Eligibility*

- **Premature Infants***
  - Recommended for infants born *before 29 weeks, 0 days* gestation

- **Infants and children with CLD***
  - Premature infants born *< 32 weeks gestation and < 12 months of age* and required *> 21% oxygen for a minimum of 28 days* after birth
  - Extend into the second year if still requiring medical treatment of chronic lung disease within 6 months of start of RSV season
Palivizumab Eligibility*

- Infants with Congenital Heart Disease*
  - $\leq$ 12 months old, with “hemodynamically significant” CHD
  - Most likely to benefit
    - Moderate to severe pulmonary HTN
    - Receiving medication to control CHF, awaiting surgery
- Infants with anatomic pulmonary abnormalities or neuromuscular disease* (that impair the ability to clear secretions from upper airway)
  - “may be considered” for prophylaxis in first year of life
- Immunocompromised children*
  - Consider if $< 24$ months old and “profoundly immunocompromised during the RSV season”
Human Metapneumovirus (HMPV)

- Ubiquitous RNA virus, Paramyxovirus family
- **Clinical manifestations**:  
  - URI* with otitis media  
  - Bronchiolitis* – a leading cause in infants  
  - Croup*  
  - Exacerbations of asthma* and COPD  
  - Pneumonia*  
  - Range from mild to severe; can be fatal in immunocompromised
Human Metapneumovirus (HMPV)

- **Epidemiology**: 
  - Transmission - contact with contaminated secretions
  - Annual epidemics - late winter and early spring
  - Incubation period 3-5 days
  - Children in US seropositive by age 5
  - Healthcare-associated infections
  - Co-infection with RSV

- Diagnosis by PCR in respiratory secretions
- No vaccine or specific antiviral treatment
ID in the News: Measles Outbreaks

Measles Cases and Outbreaks During 2014*

644 Cases
23 Outbreaks

representing 89% of reported cases this year

Number of measles cases by year since 2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
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<tbody>
<tr>
<td>2010</td>
<td>63</td>
</tr>
<tr>
<td>2011</td>
<td>220</td>
</tr>
<tr>
<td>2012</td>
<td>55</td>
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<td>2014</td>
<td>667</td>
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<tr>
<td>2015</td>
<td>188</td>
</tr>
<tr>
<td>2016*</td>
<td>70</td>
</tr>
</tbody>
</table>

*Cases as of December 31, 2016.

http://www.cdc.gov/measles/cases-outbreaks.html
Measles and Disneyland

Once the Orange County Health Care Agency notified us of this issue, we began working with them to inform our cast and raise awareness. A small number of cast members have tested positive and as they are medically cleared, they have been returning to work. In addition, cast members who may have come in close contact with those who tested positive are being tested for immunity to the virus. While awaiting results, they have been put on paid leave until medically cleared to return to work. We are also offering free vaccinations to all Disneyland Resort cast members.

As the California Department of Public Health has said: "Measles is highly contagious and highly preventable through vaccinations. CDPH is urging caution to individuals who are not vaccinated, especially infants under 12 months. Any place where large numbers of people congregate and there are a number of international visitors, like airports, shopping malls and tourist attractions, you may be more likely to find measles, which should be considered if you are not vaccinated. It is absolutely safe to visit these places, including the Disneyland Resort, if you are vaccinated. Therefore, CDPH recommends that anyone not already immunized against measles gets immunized at this time. Two doses of measles-containing vaccine (MMR vaccine) are more than 99 percent effective in preventing measles. If you are unsure of your vaccination status, check with your doctor to have a test to check for measles immunity or to receive vaccination." — Dr. Gil Chavez, State Epidemiologist and Deputy Director, Center for Infectious Diseases, California Department of Public Health
Measles

- RNA virus, Paramyxovirus family
- Highly infectious, respiratory illness
- Transmission
  - contact with infectious droplets*
  - airborne spread*
- Late winter and spring
- Incubation period 8-12 days (exposure to symptom onset)
- Contagious from 4 days before to 4 days after rash appears*
Measles: Clinical Features*

- Fever
- Cough
- Coryza
- Conjunctivitis
- Rash
  - Erythematous, maculopapular
- Koplik spots
  - Pathognomonic enanthem

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Measles: Complications*

- Otitis Media
- Bronchopneumonia
- Croup
- Diarrhea (common in young children)
- Subacute sclerosing panencephalitis (SSPE)
  - Rare degenerative CNS disease
  - Seizures and neurological deterioration 7-10 years after measles infection
Measles
Plan control measure to prevent spread*

• **Isolation**: Standard and Airborne
  – For 4 days after onset of rash
  – For *duration of illness in immunocompromised*

• **Immunization**
  – If given *within 72 hours of exposure*, provides protection in some cases

• **Immune globulin**
  – For select populations
Measles
Use of intramuscular immune globulin after exposure*

• **Within 6 days of exposure*** to prevent/modify measles

• **Who?**
  – *Susceptible* household/close contacts* (unimmunized), particularly those with highest risk of complications
    • < 12 months old*
    • Immunocompromised*
  – *Not* indicated for contacts who have received 1 dose of vaccine at 12 months of age or older *unless immunocompromised*

• **How much?**
  – 0.25 mL/kg IM for otherwise healthy children
  – 0.50 ml/kg IM for immunocompromised
Rhinoviruses

- Belong to the picornavirus family (*pico rna virus*)
- >100 serotypes identified
- Most common cause of common cold*
- Most commonly identified pathogens associated with wheezing exacerbations
Rhinovirus: Epidemiology*

- Found worldwide and occurs year-round
- Peaks in spring and autumn*
- Large number of distinct serotypes circulate each year
- Transmission via contaminated secretions*, aerosols
- Incubation period 2-3 days
- Infects the respiratory epithelium
- Viral shedding highest in first 2-3 days of infection
Rhinovirus: Clinical Manifestations*

- Sore throat
  - often first symptom
- Nasal discharge
  - Watery, then mucopurulent
  - May persist for 10-14 days
- Malaise, headache, fever
- Common cold*/rhinosinusitis
- Pharyngitis*
- Otitis Media*

  - Lower Respiratory Tract Illness
    - Bronchiolitis*
    - Pneumonia*
    - Acute wheezing episodes*
    - Asthma Exacerbations*

* See text for full definitions.
Enteroviruses: Epidemiology*

- Includes echo-, coxsackie-, numbered entero-, poliomyelitis
- **Transmission**
  - Fecal-oral, Respiratory, +/- Fomites
- **Seasonal pattern** in temperate climates (summer and fall)
- Incubation period usually 3-6 days
  - Exception: acute hemorrhagic conjunctivitis (24-72 hours)
- Infection incidence, disease severity in young children
- Fecal viral shedding persists for weeks-months
Enteroviruses

poliovirus infection

Echovirus type 9

Source: CDC Public Health Image Library ID#: 5578, 3175, 4482
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Enteroviruses: Clinical Features*

- **Nonspecific febrile illness**
- **Oropharyngeal**
  - Herpangina
  - Stomatitis
- **Respiratory**
  - Coryza, pharyngitis
  - Bronchiolitis, pneumonia
  - Pleurodynia
- **Skin**
  - Hand-foot-and-mouth disease
  - Nonspecific exanthems
- **Neurologic**
  - Aseptic meningitis
  - Encephalitis
  - Motor paralysis
- **GI/GU**
  - Vomiting, diarrhea, abd. pain
  - Hepatitis, pancreatitis
  - Orchitis
- **CV:** myopericarditis
- **Musculoskeletal:** myositis
Enteroviruses: Clinical Features*

- Neonates* at risk for severe disease
  - Sepsis, hepatitis, coagulopathy
  - Myocarditis
  - Meningoencephalitis
  - Pneumonitis
- Humoral and combined immune deficiencies*
  - Persistent CNS infections
  - Disseminated infection
Enterovirus: Age-Associations*

Hand-foot-and-mouth disease - usually affects infants and children < than 5
<table>
<thead>
<tr>
<th>Serotype</th>
<th>Disease(s)</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Enterovirus 71</td>
<td>Hand-foot-and-mouth disease</td>
<td>CNS disease rare, includes encephalomyelitis and paralytic disease</td>
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<tr>
<td></td>
<td>Herpangina</td>
<td></td>
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<tr>
<td></td>
<td>Severe neurologic disease</td>
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<td>Coxsackievirus A16</td>
<td>Hand-foot-and-mouth disease</td>
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<tr>
<td>Coxsackievirus A24&lt;sub&gt;v&lt;/sub&gt;</td>
<td>Acute hemorrhagic conjunctivitis</td>
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<tr>
<td>Enterovirus 70</td>
<td>Severe respiratory illness</td>
<td></td>
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<tr>
<td></td>
<td>Acute flaccid paralysis</td>
<td>2014 outbreak</td>
</tr>
<tr>
<td>Enterovirus 68</td>
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<tr>
<td>Coxsackieviruses B1-B5</td>
<td>Pleurodynia</td>
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<tr>
<td></td>
<td>Myocarditis</td>
<td></td>
</tr>
</tbody>
</table>
Enteroviruses: Laboratory Evaluation*

- **PCR assays** for detection of enterovirus RNA
  - CSF, Blood, Urine, Stool
  - Swabs from throat, conjunctiva, rectum
  - Tracheal aspirates
  - Tissue biopsy specimens

- **Culture**
  - Lower sensitivity (0-80%, depending on serotype)
  - Swab of throat, rectum
  - Vesicle fluid, CSF
Thank you!
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
Influenza-Like Illness (ILI) Activity Level Indicator Determined by Data Reported to ILINet

2016-17 Influenza Season Week 2 ending Jan 14, 2017

ILI Activity Level
- High
- Moderate
- Low
- Minimal
- Insufficient Data
Get out your phones, please

Web address: m.socrative.com

Room number: 515142
Extra Slide not Covered in Presentation
Influenza vaccine in Egg Allergic Individuals

People with egg allergy might tolerate egg in baked products (e.g., bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy. For people who have no known history of exposure to egg, but who are suspected of being egg-allergic on the basis of previously performed allergy testing, consultation with a physician with expertise in the management of allergic conditions should be obtained prior to vaccination. Alternatively, RIV may be administered if the recipient is age 18 years or older.

Recommendations for influenza vaccination of persons with egg allergy have been modified, including:

- Removal of the recommendation that egg-allergic recipients should be observed for 30 minutes postvaccination for signs and symptoms of an allergic reaction. Providers should consider observing all patients for 15 minutes after vaccination to decrease the risk for injury should they experience syncope, per the ACIP General Recommendations on Immunization (8).

- A recommendation that persons with a history of a severe allergic reaction to egg (i.e., any symptom other than hives) should be vaccinated in an inpatient or outpatient medical setting (including but not necessarily limited to hospitals, clinics, health departments, and physician offices), under the supervision of a health care provider who is able to recognize and manage severe allergic conditions.