Influenza Update

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What is Influenza?

- Contagious respiratory virus that infects the nose, throat, and lungs.
- Signs and symptoms
  - Fever or feeling feverish/chills
  - Not everyone will experience a fever
  - Cough
  - Sore throat
  - Runny or stuffy nose
  - Muscle or body aches
  - Headaches
  - Fatigue (very tired)
  - Vomiting and diarrhea (more common in children)

Influenza Virus

- Orthomyxoviridae family
  - A, B and C
- Influenza A and B viruses cause seasonal epidemics
- Influenza C viruses cause mild disease
- Influenza A viruses are classified into subtypes
  - Two surface glycoproteins
    - Hemagglutinin
      - H1-H16 (birds)
      - H17-H18 (bats)
    - Neuraminidase
      - N1-N19 (birds)
      - N10-N11 (bats)
- Influenza B
  - Two lineages:
    - Victoria
    - Yamagata

Nomenclature of Influenza Virus

- The antigenic type (e.g., A, B, C)
- The host of origin (e.g., swine, equine, chicken, etc.)
  For human-origin viruses, no host of origin designation is given.
- Geographical origin (e.g., Denver, Taiwan, etc.)
- Strain number (e.g., 15, 7, etc.)
- Year of isolation (e.g., 57, 2009, etc.)
- For influenza A viruses, the hemagglutinin and neuraminidase antigen description in parentheses e.g., (H1N1), (H5N1)
  - For example:
    - A/duck/Alberta/35/76 (H1N1) for a virus from duck origin
    - A/Perth/16/2009 (H3N2) for a virus from human origin
Introduction to Influenza

- Two forms of Influenza occur globally
  - Epidemic (seasonal or interpandemic) influenza caused by Influenza A and B
  - Sporadic Pandemics caused by Influenza A
- Antigenic Drift vs Antigenic Shift
  - Drift:
    - Continuous process that occurs in both influenza A and B virus, due to accumulation of point mutations in the viral hemagglutinin and neuraminidase genes
    - This allows the virus to escape immunity induced through previous exposure or vaccination resulting in seasonal epidemics
  - Shift:
    - Sporadic event, restricted to Influenza A
    - Introduction of human beings into a novel virus strain to which a large proportion of the population does not have immunity

Antigenic Shift (continued)

- If the novel influenza virus spreads efficiently and sustainably from person to person → global pandemic
- Four Influenza Pandemics:
  - 1918 Spanish Influenza (H1N1)
  - 1957 Asian Influenza (H2N2)
  - 1968 Hong Kong (H3N2)
  - 2009 Swine Influenza (H1N1)
- Most Severe Pandemic Occurred in 1918, led to 50 million deaths
- In the years following each pandemic, descendants of the pandemic strain established a new viral lineage in human beings and either replaced or co-circulated with previously circulating strains
- Currently:
  - Pandemic 2009 H1N1 (H1N1pdm09)
  - H3N2
  - Influenza B

Vaccination Strategies

- Since 1977, inactivated vaccines have contained three components – called this trivalent formulation (IIV3)
  - Recent H1N1 virus
  - H3N2 Virus
  - Influenza B Virus
- 1980:
  - Two antigenically distinct lineage of influenza B have co-circulated; and now we have a quadrivalent formulation (IIV4)
- Studies have demonstrated that the addition of the fourth component does not interfere with the immune response to the other three components
- Two vaccines which use substrates other than chicken eggs:
  - CCIIV4 – Mammalian Cell Culture
  - RIV3 – Recombinant Baculovirus – expressed HA proteins produced in insect eggs
- One Live Attenuated Vaccine
  - LAIV4 – Intranasal vaccine

Influenza Vaccine Composition 2019-2020

- 2019-2020 Trivalent Influenza Vaccine:
  - A(H1N1)pdm09 vaccine component
  - A/Brisbane/02/2018 (H1N1)pdm09-like virus
  - A(H3N2) vaccine component A/Kansas/14/2017 (H3N2)-like virus
  - B/Colorado/06/2017-like (Victoria lineage) virus
- 2019-2020 Quadrivalent Influenza Vaccine:
  - Includes all component of the Trivalent Influenza Vaccine
  - B/Phuket/3073/2013-like (Yamagata lineage) virus

### Influenza Vaccines—2019-2020

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Contraindications and conditions for which use is not recommended</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>- History of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine</td>
<td>Moderate or severe acute illness with or without fever History of Guillain-Barré syndrome within 6 weeks after receipt of influenza vaccine</td>
</tr>
<tr>
<td>RIV4</td>
<td>- History of severe allergic reaction to any component of the vaccine</td>
<td>Moderate or severe acute illness with or without fever History of Guillain-Barré syndrome within 6 weeks after receipt of influenza vaccine</td>
</tr>
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</table>

### Contraindications and Precautions to the Use of Influenza Vaccines—United States, 2019-2020 Influenza Season

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Contraindications or conditions for which use is not recommended</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAIV4</td>
<td>- History of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine</td>
<td>Moderate or severe acute illness with or without fever History of Guillain-Barré syndrome within 6 weeks after receipt of influenza vaccine</td>
</tr>
<tr>
<td></td>
<td>- Concomitant aspirin- or salicylate-containing therapy in children and adolescents</td>
<td>- Contact and caregivers of severely immunosuppressed persons who require a protected environment</td>
</tr>
<tr>
<td></td>
<td>- Children aged 2 through 4 years who have received a diagnosis of asthma or whose parents or caregivers report that a health care provider has told them during the past 12 months that their child had wheezing or asthma or whose medical record indicates a wheezing episode has occurred within the past 12 months Children and adults who are immunocompromised due to any cause (including immunosuppression caused by medications or HIV infection)</td>
<td>- Receipt of influenza antiviral medication within the past 48 hours</td>
</tr>
</tbody>
</table>

### Vaccine Effectiveness 2018-2019

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Influenza positive Total</th>
<th>Influenza positive (% Vaccinated)</th>
<th>Influenza negative Total</th>
<th>Influenza negative (% Vaccinated)</th>
<th>Adjusted VE %</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>2795</td>
<td>48</td>
<td>7246</td>
<td>56</td>
<td>29%</td>
<td>(21 to 35)</td>
</tr>
<tr>
<td>6 mos–8</td>
<td>759</td>
<td>40</td>
<td>1675</td>
<td>58</td>
<td>49%</td>
<td>(38 to 58)</td>
</tr>
<tr>
<td>9–17</td>
<td>493</td>
<td>45</td>
<td>772</td>
<td>41</td>
<td>6%</td>
<td>(-22 to 27)</td>
</tr>
<tr>
<td>18–49</td>
<td>831</td>
<td>39</td>
<td>2435</td>
<td>44</td>
<td>25%</td>
<td>(10 to 37)</td>
</tr>
<tr>
<td>50–64</td>
<td>448</td>
<td>60</td>
<td>1324</td>
<td>62</td>
<td>12%</td>
<td>(-12 to 31)</td>
</tr>
<tr>
<td>≥65</td>
<td>264</td>
<td>81</td>
<td>1040</td>
<td>83</td>
<td>12%</td>
<td>(-29 to 41)</td>
</tr>
</tbody>
</table>


### Influenza Specific Vaccine Effectiveness 2018-2019

#### Influenza A (H1N1) Viruses

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Influenza positive Total</th>
<th>Influenza positive (% Vaccinated)</th>
<th>Influenza negative Total</th>
<th>Influenza negative (% Vaccinated)</th>
<th>Adjusted VE %</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>1342</td>
<td>(43)</td>
<td>7246</td>
<td>(56)</td>
<td>44%</td>
<td>(36, 51)</td>
</tr>
</tbody>
</table>

#### Influenza A (H3N2) Viruses

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Influenza positive Total</th>
<th>Influenza positive (% Vaccinated)</th>
<th>Influenza negative Total</th>
<th>Influenza negative (% Vaccinated)</th>
<th>Adjusted VE %</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>1350</td>
<td>(52)</td>
<td>7246</td>
<td>(56)</td>
<td>9%</td>
<td>(-4, 20)</td>
</tr>
</tbody>
</table>


### Guidelines for Use In Specific Populations

#### Pregnant Women
- All women who are pregnant or who might be pregnant during the influenza season should receive influenza vaccine.
- An age-appropriate IIV or RIV4 may be used.
- LAIV4 should not be used during pregnancy.
- Influenza vaccine can be administered at any time during pregnancy

#### Adults Aged ≥65 years
- Persons aged ≥65 years may receive any age-appropriate IIV (standard- or high-dose, trivalent or quadrivalent, adjuvanted or unadjuvanted) or RIV4.
- High-dose IIV3 exhibited superior efficacy over a comparator standard-dose IIV3 in a large randomized trial, and may provide better protection than standard dose IIV3 for this age group.
- However, vaccination should not be delayed to find a particular product if an appropriate one is available.
### Guidelines for Use In Specific Populations

**Persons With Chronic Medical Conditions:**
- LAIV is not recommended for persons with some chronic medical conditions.

**Caregivers and Contacts of High-Risk Persons**
- Caregivers and contacts (including those of immunocompromised persons) may receive any age-appropriate IIV or RIV4.
- LAIV4 may be given to caregivers and contacts of persons who are not severely immunocompromised (i.e., who do not require a protected environment).
- Health care personnel or hospital visitors who receive LAIV4 should avoid providing care for severely immunocompromised persons requiring a protected environment for 7 days after vaccination.

**Persons with Egg Allergy**
- Persons who are able to eat lightly cooked egg (e.g., scrambled egg) without reaction are unlikely to be egg-allergic.
- Persons who have experienced only hives after exposure to egg should receive any licensed, recommended, age-appropriate influenza vaccine (i.e., IIV, RIV4, or LAIV4).
- Persons reporting symptoms other than hives after exposure to egg (such as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention) may also receive any licensed and recommended influenza vaccine that is otherwise appropriate.
  - Additionally, for these persons, vaccine should be administered in an inpatient or outpatient medical setting and supervised by a health care provider who is able to recognize and manage severe allergic reactions.
- A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of causing the reaction, is a contraindication to future receipt of the vaccine.

**Immunocompromised Persons**
- Immunocompromised persons should receive an age-appropriate IIV or RIV4.
- LAIV should not be used for immunocompromised persons.
- Immune response to vaccines might be blunted in immunocompromised persons, and might be reduced or minimal as a result of medications, chemotherapy, or transplant regimens.
Solid Organ Transplant Recipients

- Incidence varies among transplanted organ
  - In Liver Transplant Recipients:
    - 2.8 cases/1000 person years
  - In Lung Transplant Recipients:
    - 41.8 cases/1000 person years
- Population is high risk for influenza related complication
- Mortality 4-17%
- Influenza can lead to allograft dysfunction along with acute and chronic rejection in lung transplant recipients

Solid Organ Transplant Recipients

- Influenza vaccine:
  - Inactivated trivalent → Two Influenza A strains, and one Influenza B strain
  - Inactivated quadrivalent → Two Influenza A strains, and two Influenza B strains
- How do we know if Influenza vaccine is effective?
  - Check HAI titers
    - A titer of 1:40 is defined to be seroprotective (in nonimmunocompromised patient) and are associated with 50% strain-specific protection
    - However, it is not known if the titer of 1:40 provides the same degree of protection in immunocompromised individuals

Immunogenicity in SOTR

- Different Influenza Vaccines reviewed:
  - High Dose (unadjuvanted) inactivated influenza vaccine
  - Unadjuvanted inactivated influenza vaccine booster dose in same season
  - MF59 adjuvanted inactivated influenza vaccine

High Dose Vaccine

- Inactivated standard dose Influenza Vaccine contains 15ug of HA protein (in both trivalent or quadrivalent vaccine)
- Inactivated high dose vaccine contains 60 ug of HA
  - Approved for population age at least 65 years in North America
  - Demonstrated greater efficacy as well as reduced influenza mortality in this population
  - Demonstrated to be more immunogenic than standard-dose vaccine in pediatric and adult patients receiving chemotherapy
High Dose Vaccine

- 172 adults SOTR age 18-86 randomized to high-dose or trivalent standard dose vaccine
- Seroconversion rates significantly higher in HD vs SD:
  - Influenza A/H1N1 (40.5% vs 20.5%; P=0.007)
  - Influenza A/H3N2 (57.1% vs 32.5%; p = 0.002)
  - Influenza B (58.3 vs 40.6%; p = 0.002)
- Postvaccination geometric mean titers (GMTs) for influenza A/H1N1 and Influenza B were also higher in HD vs SD
- Current guidelines recommend to use standard dose vaccine
- However, high dose vaccines may be an alternative to standard-dose vaccine in SOTR even those younger than 65 years of age

Same-Season Booster Strategy

- Increasing evidence for immunological effectiveness of a same-season booster strategy, this approach maybe hampered by the fact that present overall vaccine coverage remains low
- Two-dose regimen may be difficult to implement due to lower compliance

Adjuvant Influenza Vaccine

- Adjuvant:
  - An oil-in-water emulsion that contains squalene, sorbitan trioleate and polysorbate-90 and acts via attracting inflammatory cells to the site of injection
- RCT of Adult Kidney Transplant (n=68); patients were either allocated to receive nonadjuvanted standard-dose influenza vaccine or MF59 adjuvanted vaccination
  - Neither the seroconversion or seroprotection rate or GMT were different in the two study groups
  - There was a questionable link to narcolepsy with the adjuvant 2009 H1N1 Vaccine in Europe, CDC published a study and found vaccination was NOT associated with an increased risk for narcolepsy

Diagnosis of Influenza
## Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Turnaround Time</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Cultures</td>
<td>Close to 100%</td>
<td>3-10 days</td>
<td>High sensitivity and specificity, virus available for characterization</td>
<td>Poor specimen quality might affect yield, results not available in time to inform clinical decision making, time and labor intensive, specialized labs required</td>
</tr>
<tr>
<td>Rapid Viral Culture</td>
<td>70-90%</td>
<td>1-3 days</td>
<td>Faster than traditional viral culture, less expertise needed than for traditional cell culture</td>
<td>Less sensitive than traditional viral culture, might miss divergent influenza viruses</td>
</tr>
<tr>
<td>Rapid Viral Detection: DFA</td>
<td>70-90%</td>
<td>1-4 days</td>
<td>Faster than traditional viral culture, less expertise needed than for traditional cell culture</td>
<td>Less sensitive than traditional viral culture, might miss divergent influenza viruses</td>
</tr>
<tr>
<td>Rapid Antigen Detection: Immunochromatogenic Assay</td>
<td>99-100%</td>
<td>5-30 min</td>
<td>No specialized equipment, rapid result</td>
<td>Least sensitive method</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Close to 100%</td>
<td>1-4 hours</td>
<td>High sensitivity and specificity, typing and subtyping possible</td>
<td>Expensive, potential for cross contamination</td>
</tr>
</tbody>
</table>

## Clinical Microbiology

- **Available tests:**
  - **Rapid**
    - Alerie I Influenza A & B
    - 1 hour turn around time
    - First line test
    - >95% sensitivity and specificity
  - **PCR**
    - Simplex Flu A, B, & RSV Direct assay
    - Reserved for negative rapid, but high clinical suspicion
    - 24 hour turn around time
    - >99% sensitivity and specificity
  - **Panel**
    - Immunosuppressed patients only
    - New bacterial targets included this year
    - Not a stat test
  - Proper collection is key

## Treatment

- **Six licensed AntiFour were recommended by U.S. FDA**
- Three neuraminidase inhibitors:
  - Oral Oseltamivir
  - Inhaled Zanamivir
  - Intravenous Peramavir
- Cap-dependent endonuclease inhibitor:
  - Oral Baloxavir
- Adamantanes:
  - Not recommended due to high level of resistance (>99%)
- Resistance:
  - Antiviral resistance and reduced susceptibility to the neuraminidase inhibitors and to baloxavir is low
  - Concern with emergence of viruses with molecular markers associated with reduced susceptibility to baloxavir viral Drugs approved in United States: following treatment
- Clinical data demonstrates best time to initiate therapy is within 48 hours of symptoms
Treatment

- Baloxavir was approved as a new antiviral treatment for influenza in October of 2018
- Blocks a different step in viral replication than neuraminidase inhibitors
- Is a single dose tablet vs five days of oral oseltamivir
- Shortened duration of influenza from a median of 80 to 54 hours
- Postmarket Adverse Event Data:
  - 382 reports received
  - All but 14 had serious or fatal outcome
  - 50 cases of anaphylactic shock
  - Concern for Hypersensitivity

Infection Control

- Prevention Strategies for Seasonal Influenza in Healthcare Settings
  - 5 to 20% of U.S. residents acquire influenza virus infection and will seek medical care in ambulatory health care settings
  - 200,000 persons are hospitalized each year for influenza-related complications
  - Healthcare-associated influenza can, and prevention measures must be implemented in all healthcare settings
- Mode of Transmission:
  - Large particle respiratory droplet transmission (travel short distance which is approximately six feet or less)
  - Indirect contact transmission via hand transfer

Infection Control

- Promote and administer seasonal influenza vaccine
- Take Steps to Minimize Potential Exposures
- Monitor and Manage Ill Healthcare Personnel
- Adhere to Standard Precautions
- Adhere to Droplet Precautions
- Use Caution when Performing Aerosol-Generating Procedures
- Manage Visitor Access and Movement Within the Facility
- Monitor Influenza Activity
Infection Control
• Implement Environmental Infection Control
• Implement Engineering Controls
• Train and Educate Healthcare Personnel
• Administer Antiviral Treatment and Chemoprophylaxis of Patients and Healthcare Personnel when Appropriate
• Consideration for Healthcare Personnel at Higher Risk for Complication of Influenza

Respiratory Hygiene/Cough Etiquette in Healthcare Settings
• Visual Alerts
  • Cover your Cough
• Respiratory Hygiene/Cough Etiquette
• Masking and Separation of Persons with Respiratory Symptoms
• Droplet Precautions

Interim Guidance for Influenza Outbreak Management in Long-Term Care and Post-Acute Care Facilities
• Institutions such as nursing homes and skilled nursing facilities that provide health care to people (including children) who are unable to manage independently in the community
• Preventing transmission of influenza virus requires a multi-faceted approach:
  • Influenza Vaccination
  • Influenza Testing
  • Infection Prevention and Control Measures
  • Antiviral Treatment
  • Antiviral Chemoprophylaxis

Post Exposure Prophylaxis
• Immunization is the best way to prevent influenza, and antiviral drugs should not be used as a substitute for influenza vaccination
• It is appropriate in certain target populations – outbreaks in nursing homes, hospitals, and other long-term care facilities
• Target Population for Prevention:
  • Residents of nursing homes and chronic care facilities
  • Adults > 65 years of age
  • Pregnant women and women up to two weeks postpartum
  • Chronic Medical Conditions
• Generally not recommended in instances patients who have been vaccinated during a season where there is a match between vaccine and circulating virus
Influenza Data 2018-2019

Patient Age at Time of IAH

OSU Wexner Medical Center
Influenza Data 2018-2019

Total IAH by Business Unit

12