Influenza and Influenza Vaccines

Epidemiology and Prevention of Vaccine-Preventable Diseases (Pink Book) Webinar Series

October 3, 2018
Influenza

- Highly infectious viral illness
- First pandemic in 1580
- At least 4 pandemics in 19th century
  - Pandemics of 1957 and 1968 of lesser severity
- Most recent pandemic (H1N1) in 2009-2010
- Estimated 50 million deaths worldwide in pandemic of 1918-1919
- Virus first isolated in 1933
Influenza Virus

- Single-stranded RNA virus
- Orthomyxoviridae family
- 3 types: A, B, C
- Subtypes of type A are determined by hemagglutinin and neuraminidase
Influenza Virus Strains

- **Type A**
  - Moderate to severe illness
  - All age groups
  - Humans and other animals

- **Type B**
  - Milder epidemics
  - Primarily affects children
  - Humans only

- **Type C**
  - Rarely reported in humans
  - No epidemics
Influenza Type A Subtypes

Subtypes of type A determined by hemagglutinin (H) and neuraminidase (N)

A/California/7/2009 (H1N1)
Influenza Antigenic Changes

- **Antigenic Drift**
  - minor change, same subtype
  - caused by point mutations in gene
  - may result in epidemic

- **Antigenic Shift**
  - major change, new subtype
  - caused by exchange of gene segments
  - may result in pandemic
WHO declares first flu pandemic in 41 years

By Steve Sternberg, USA TODAY

The World Health Organization scaled up its flu warning to its highest level Thursday, declaring the first global influenza pandemic in 41 years as cases of H1N1 continued to mount in the USA, Europe, Latin America and Australia.

"The scientific criteria for a pandemic have been met," said Margaret Chan, director general of the WHO. "The world is now at the start of the 2009 influenza pandemic."

PHOTOS: Schools closed in Hong Kong, Vermont (and more)
INTERACTIVES: World map, how H1N1 strain emerged
FAQ: What you should know about swine flu
VIDEO: Reporters answer your questions

The decision marks the agency's formal recognition of the magnitude of the challenge posed by a novel H1N1 flu virus now spreading unchecked among people who, because the virus is new, are virtually all susceptible to it.

The WHO is working closely with vaccine makers, who are just wrapping up production of seasonal flu vaccine for fall and gearing up to produce the first doses of an H1N1 vaccine by September. The agency urged member nations to maintain their vigilance to detect ominous changes in the virus’s
Influenza Pathogenesis

- Respiratory transmission of virus

- Replication in respiratory epithelium with subsequent destruction of cells

- Viremia rarely documented

- Virus shed in respiratory secretions for 5-10 days
Influenza Clinical Features

- Incubation period 2 days (range 1-4 days)

- 50% of infected persons develop classic symptoms

- Abrupt onset of fever (usually 101° - 102°F), myalgia, sore throat, nonproductive cough, headache
Influenza Complications

- Pneumonia
  - Primary influenza pneumonia
  - Secondary bacterial pneumonia

- Reye syndrome

- Myocarditis

- Death reported in <1 per 1,000 cases
Impact of Influenza – United States, 2010-2014

- Number of influenza-associated deaths varies substantially by year, influenza virus type and subtype, and age group.

- Annual influenza-associated deaths ranged from 12,000 to 56,000 between 2010 and 2014, with an average of 23,607 annual deaths.

- Persons 65 years of age and older account for 70% to 85% of deaths.

- 2.7 times more deaths during seasons when A(H3N2) viruses were prominent.

Impact of influenza, 2010-2016 - United States

- Highest rates of complications and hospitalization among persons 65 years and older, young children, and persons of any age with certain underlying medical conditions

- 2010-2011 to 2015-2016:
  - Flu-related hospitalizations in the United States ranged from a low of 140,000 (during 2011-2012) to a high of 710,000 (during 2014-2015).
  - During the 2015-2016 flu season, CDC estimated 310,000 people were hospitalized for flu-related illness.

- About 50% of hospitalizations among persons younger than 65 years of age

- Greater number of hospitalizations during years that A(H3N2) is predominant
Influenza Among School-Aged Children

- School-age children
  - typically have the highest attack rates during community outbreaks of influenza
  - serve as a major source of transmission of influenza within communities
Influenza Epidemiology

- Reservoir
  - human, animals (type A only)

- Transmission
  - respiratory, probably airborne

- Temporal pattern
  - peak December – March in temperate climate
  - may occur earlier or later

- Communicability
  - 1 day before to 5 days after onset (adults)
Influenza Diagnosis

- Clinical and epidemiological characteristics

- Isolation of influenza virus from clinical specimens (e.g., throat, nasopharynx, sputum)

- Significant rise in influenza IgG by serologic assay
## Influenza Virus Testing Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Types Detected</th>
<th>Test Time</th>
</tr>
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<tbody>
<tr>
<td>Viral tissue cell culture</td>
<td>A and B</td>
<td>3-10 days</td>
</tr>
<tr>
<td>Rapid cell culture (shell vials; cell mixtures; yields live virus)</td>
<td>A and B</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Immunofluorescence, Direct (DFA) or Indirect (IFA) Fluorescent Antibody Staining</td>
<td>A and B</td>
<td>1-4 hours</td>
</tr>
<tr>
<td>Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and other molecular assays [influenza viral RNA or nucleic acid detection]</td>
<td>A and B</td>
<td>Varies by assay (Generally 60-80 minutes and 4-8 hours)</td>
</tr>
<tr>
<td>Rapid Molecular Assay [influenza viral RNA or nucleic acid detection]</td>
<td>A and B</td>
<td>15 to 30 minutes</td>
</tr>
<tr>
<td>Rapid Influenza Diagnostic Tests (antigen detection)</td>
<td>A and B</td>
<td>&lt;15 min.</td>
</tr>
</tbody>
</table>

Adapted from [https://www.cdc.gov/flu/professionals/diagnosis/overview-testing-methods.htm](https://www.cdc.gov/flu/professionals/diagnosis/overview-testing-methods.htm)
Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System

Data through the week ending September 8, 2018, as of September 27, 2018
Influenza Surveillance

- Monitor prevalence of circulating strains and detect new strains
- Estimate influenza-related morbidity, mortality and economic loss
- Rapidly detect outbreaks
- Assist disease control through rapid preventive action
Inactivated Influenza Vaccine Efficacy

- About 60% effective among healthy persons younger than 65 years of age
- 50%-60% effective in preventing medically attended illness and hospitalization among elderly persons
- 60% or greater effectiveness in preventing medically attended illness in children, with either IIV or LAIV

https://www.cdc.gov/flu/professionals/vaccination/effectivenessqa.htm
2018-19 Influenza Vaccine Recommendations
2018-19 ACIP Influenza Statement--Overview

- Published in MMWR August 24, 2018*
- Continues 2017 Format
  - MMWR document focuses on recommendations and selected references; contains figure and tables
  - Background Document with additional references and a Summary of recommendations available on ACIP web pages
  - Core recommendation remains the same: annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications

https://www.cdc.gov/mmwr/volumes/67/rr/rr6703a1.htm?s_cid=rr6703a1_w
There are Still Many Different Vaccines

- ACIP Statement, Table 1
- 10 distinct products
- More than one might be appropriate for any given recipient
  - ACIP/CDC express no preferences for any one type of influenza vaccine over another, where more than one is appropriate and available
  - Vaccination should not be delayed in order to obtain a specific product.
Abbreviations

- IIV = Inactivated influenza vaccine
- LAIV = Live attenuated influenza vaccine
- RIV = Recombinant influenza vaccine
- Prefixes: SD = standard dose
  HD = high dose
  a = adjuvanted
  cc = cell culture-based
- Numeric suffixes (e.g., RIV3, IIV4) indicate trivalent or quadrivalent, respectively
Influenza Vaccines

- **IIV:**
  - Contain inactivated virus, split or subunit
    - High Dose or Standard Dose
    - Trivalent or quadrivalent
    - Unadjuvanted or adjuvanted
    - Egg- or cell culture-based
  - Many brands, some approved for those as young as 6 months of age
  - Most are intramuscular

- **RIV**
  - Contain recombinant HA
  - Egg-free
  - Trivalent or (starting in 2017-18) quadrivalent

- **LAIV**
  - Live attenuated virus
  - Recommended again in 2018-19

[Links](https://www.cdc.gov/mmwr/volumes/67/wr/mm6722a5.htm?s_cid=mm6722a5_w and https://www.cdc.gov/mmwr/volumes/67/rr/pdfs/rr6703a1-H.pdf)
2018-19 ACIP Influenza Statement

- Principal changes and updates for 2018-19
  - Influenza vaccine composition for 2018-19

  - LAIV4 is an option for influenza vaccination of persons for whom it is appropriate

  - a recommendation that persons with a history of egg allergy may receive any licensed, recommended, and age-appropriate influenza vaccine (IIV, RIV4, or LAIV4)

  - new vaccine licensures and labeling changes for previously licensed vaccines
2018-19 Influenza Vaccine Composition

- **Trivalent vaccines:**
  - A/Michigan/45/2015 (H1N1) pdm09–like virus
  - A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus*
  - B/Colorado/06/2017–like virus (Victoria lineage)*

- **Quadrivalent vaccines:**
  - The above three viruses, and
  - B/Phuket/3073/2013–like virus (Yamagata lineage).

*New vaccine virus for 2018-19
Live Attenuated Influenza Vaccine, 2018-19

- Following two seasons (2016–17 and 2017–18) during which ACIP recommended that LAIV4 not be used, providers may choose to administer any licensed, age-appropriate influenza vaccine (IIV, RIV4, or LAIV4). LAIV4 is an option for those for whom it is appropriate.

- Licensed for persons 2 years through 49 years.

- Numerous precautions and contraindications to vaccination to be aware of, to be presented shortly.
Vaccinating Persons with Egg Allergy

- Persons with a history of egg allergy of any severity may receive any licensed, recommended, and age-appropriate influenza vaccine (IIV, RIV4, or LAIV4). IIV and RIV4 have been previously recommended.

- Persons who report having had reactions to egg involving symptoms other than urticaria (hives), possibly related to anaphylaxis; or who required epinephrine or another emergency medical intervention, may receive any licensed, recommended, and age-appropriate influenza vaccine appropriate for their health status. Vaccine should be administered in an inpatient or outpatient medical setting, and be supervised by a health care provider able to recognize and manage severe allergic reactions.
Vaccinating Persons with Egg Allergy - 2

- Persons who report having had reactions to egg involving symptoms other than urticaria (hives), possibly related to anaphylaxis; or who required epinephrine or another emergency medical intervention, may receive any licensed, recommended, and age-appropriate influenza vaccine appropriate for their health status. **Vaccine should be administered in an inpatient or outpatient medical setting**, and be **supervised by a health care provider able to recognize and manage severe allergic reactions**.

- No postvaccination observation period is recommended specifically for egg-allergic persons. However, ACIP recommends providers consider observing patients (seated or supine) for 15 minutes following administration of any vaccine to decrease risk for injury should syncope occur.
Afluria Quadrivalent

- Standard-dose IIV 3 and IIV4 (Seqirus)

- Licensed in August 2016,
  - Initially for persons aged ≥18 years
  - Now for persons aged ≥5 years

- Intramuscular

- Trivalent formulation of Afluria also available this season
  - Both Afluria and Afluria Quadrivalent are licensed for ≥5 years
Age Recommendation for Afluria (IIV3 and IIV4)

- Afluria is licensed by FDA for persons aged ≥5 years.
- From 2010-11 through 2016-17 ACIP recommended only for ≥9 years
  - Febrile seizures/reactions in Australia during 2010 season
- February 2017: ACIP reviewed manufacturer data concerning investigation and resulting manufacturing changes
- FDA approved an expanded age indication for Afluria Quadrivalent (IIV4) in August, 2017
- For 2018-19, ACIP recommends Afluria for ≥5 years
Fluarix Quadrivalent

- January 2018, FDA approved an expanded age indication for Fluarix Quadrivalent (IIV4).

- Previously licensed for persons age ≥3 years

- Fluarix Quadrivalent now licensed for persons age ≥6 months.

- Children aged 6 through 35 months may receive Fluarix Quadrivalent at the same 0.5 mL per dose (containing 15 μg of hemagglutinin [HA] per vaccine virus) as is used for older children and adults.
Fluarix Quadrivalent

- Potential for confusion
  - The other products licensed for 6-through 35 month olds are 0.25mL Fluzone—dose volumes are different for this age group, and
  - FluLaval, also 0.5mL dose

- *Dose volume* is distinct from *number of doses* needed:
  - A child aged 6 months through 8 years who needs 2 doses—
  - (for example, if a first-time vaccinee)—
  - and who gets 0.5mL Fluarix Quadrivalent for a first dose—
  - Still needs a second dose of influenza vaccine, ≥4 weeks late
Influenza Vaccination of Pregnant Women

- Influenza vaccination recommended by ACIP for women who will be pregnant during influenza season since 2004
  - Increased risk for severe influenza illness in pregnant women, particularly during second and third trimesters;

- Previous language stated pregnant women should receive inactivated influenza vaccine (IIV)

- For 2018-19, pregnant women may receive any licensed, recommended, age-appropriate influenza vaccine
  - IIV or RIV
  - LAIV not recommended for pregnant women
2018-19 ACIP Influenza Statement

- Recommendations for which there are no changes for 2018-19
  - Groups Recommended for Vaccination
  - Groups at Increased Risk for Influenza Complications and Severe Illness
  - Inactivated Influenza Vaccine Schedule
Groups Recommended for Vaccination

- Routine annual influenza vaccination is recommended for all persons ≥6 months of age who do not have contraindications.

- While vaccination is recommended for everyone in this age group, there are some for whom it is particularly important—
  - People aged ≥6 months who are at high risk of complications and severe illness
  - Contacts and caregivers of these people, and of infants under age 6 months (because there is no vaccine approved for children this age)
Groups at Increased Risk for Influenza Complications and Severe Illness

- Children aged 6 through 59 months and adults aged ≥50 years (children under 6 months of age are also at high risk, but cannot be vaccinated);
- Persons with chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus);
- Immunocompromised persons;
- Women who are or will be pregnant during the influenza season;
- Children and adolescents (aged 6 months–18 years) who are receiving aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection;
- Residents of nursing homes and other long-term care facilities;
- American Indians/Alaska Natives; and
- Persons who are extremely obese (BMI ≥40).
Egg Allergy Algorithm

- No longer printed in the MMWR
## Inactivated Influenza Vaccine Schedule

<table>
<thead>
<tr>
<th>Group Age</th>
<th>Dose</th>
<th>No. Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-35 mos</td>
<td>0.25 mL or 0.50 mL*</td>
<td>1 or 2</td>
</tr>
<tr>
<td>3-8 yrs</td>
<td>0.50 mL</td>
<td>1 or 2</td>
</tr>
<tr>
<td>9 yrs and older</td>
<td>0.50 mL</td>
<td>1</td>
</tr>
</tbody>
</table>

*Depending on vaccine product*
Dosing Algorithm for Children aged 6 months through 8 years, 2018-19

Similar to past seasons

If two cumulative doses received prior to July 1, 2018, only one dose needed for 2018-19

FIGURE. Influenza vaccine dosing algorithm for children aged 6 months through 8 years — Advisory Committee on Immunization Practices, United States, 2018–19 influenza season

Has the child received ≥2 doses of trivalent or quadrivalent influenza vaccine before July 1, 2018 (Doses need not have been given during same or consecutive seasons)

Yes

No / Don’t know

1 dose of 2018–19 influenza vaccine

2 doses of 2018–19 influenza vaccine (administered ≥4 weeks apart)
Inactivated Influenza Vaccine (IIV) and RIV
Contraindications and Precautions

- Severe allergic reaction (e.g., anaphylaxis) to a vaccine component or following a prior dose of inactivated influenza

- Moderate or severe acute illness

- History of Guillain-Barré syndrome (GBS) within 6 weeks following a previous dose of influenza vaccine
## LAIV Contraindications and Precautions

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• History of severe allergic reaction to any component of the vaccine or after a previous dose of any influenza vaccine</td>
<td>• Moderate-to-severe acute illness with or without fever</td>
</tr>
<tr>
<td>• Concomitant aspirin or salicylate-containing therapy in children and adolescents</td>
<td>• History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine</td>
</tr>
<tr>
<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 preceding 12 months that their child had wheezing or asthma or whose medical record indicates a wheezing episode has occurred during the preceding 12 months</td>
<td>• Asthma in persons aged ≥5 years</td>
</tr>
<tr>
<td>• Children and adults who are immunocompromised due to any cause (including immunosuppression caused by medications or by HIV infection)</td>
<td>• Other underlying medical conditions that might predispose to complications after wild-type influenza infection (e.g., chronic pulmonary, cardiovascular [except isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic disorders [including diabetes mellitus])</td>
</tr>
<tr>
<td>• Close contacts and caregivers of severely immunosuppressed persons who require a protected environment</td>
<td>• Receipt of influenza antiviral medication within the previous 48 hours</td>
</tr>
</tbody>
</table>
Inactivated Influenza Vaccine (IIV) Adverse Reactions

- Local reactions (soreness, redness)
  - 15% - 20%

- Fever, malaise, myalgia
  - Less than 1%

- Allergic reactions (hives, angioedema, anaphylaxis)
  - Rare

- Guillain Barre Syndrome
Live Attenuated Influenza Vaccine (LAIV)
Adverse Reactions

- **Children**
  - No significant increase in URI symptoms, fever, or other systemic symptoms
  - Increased risk of wheezing in children 6-23 months of age

- **Adults**
  - Significantly increased rate of cough, runny nose, nasal congestion, sore throat, and chills reported among vaccine recipients
  - No increase in the occurrence of fever

- No serious adverse reactions identified
Influenza Antiviral Agents*

- Amantadine and rimantadine
  - Not recommended because of documented resistance in U.S. Influenza isolates

- Zanamivir, oseltamivir, and peramivir
  - Neuraminidase inhibitors
    - Effective against influenza A and B
    - Oseltamavir and zanamavir approved for prophylaxis
    - Peramivir (intravenous preparation only) approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in persons aged 2 years and older.

*https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
CDC website on influenza:
https://www.cdc.gov/flu/index.htm
Influenza Resources

- ACIP’s Influenza Recommendations web page
  www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html

- CDC’s Influenza web page
  www.cdc.gov/flu/index.htm

- Immunization Action Coalition Influenza web page
  www.immunize.org/influenza/

- Children’s Hospital of Philadelphia Vaccine Education Center Influenza web page
  http://www.chop.edu/centers-programs/vaccine-education-center/vaccine-details/influenza-vaccine#.VgHMa3YpCAU
...and get a flu vaccination!