Update on Influenza 2018-19

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Plan

• How was last flu season?
  • Nationally and locally
  • Pediatric risk groups
• What makes flu dangerous
• Vaccines for this year
  • LAIV use
• Last year’s uptake and places dispensing vaccine
• Waning intra-seasonal protection?
• Kinds of flu vaccine – mostly now and 1 for future
• Pregnancy and flu
• Antivirals
• Effect of humidity on contagion
Severe 2017-18 Season

2017-2018 flu season:

- among most severe on record per CDC
  - Nov to Apr, peaked in Jan-Feb (19 wks)
  - ILI peaked at 7.5%, highest since pandemic (7.7%)
- 80,000 total deaths
  - Greater than usual 12,000-56,000 total deaths in flu season
    https://www.cdc.gov/flu/about/disease/2015-16.htm
    - 1918 pandemic had 500,000 deaths
- Many thousands children hospitalized with influenza
  - 180 pediatric influenza-associated deaths
  - ~80% of pediatric deaths unimmunized vs influenza
Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2017-2018 Season

Number of Positive Specimens

Week
Kansas ILI rates 2015-2018
Figure 9. Percentage of Emergency Department (ED) Visits for Influenza-like Illness (ILI) in ESSENCE Participating Hospitals, by Region and Statewide, 2017-2018 Influenza Season*
Figure 8. Percentage of Emergency Department (ED) Visits for Influenza-like Illness (ILI) in ESSENCE Participating Hospitals, by Age Group, Region and Statewide, Week 20, 2018

Percent of ED Visits

- CENTRAL
- EASTERN
- NORTHWEST
- SOUTHEAST
- SOUTHWEST
- STATEWIDE

Missouri Data
Number of Influenza-Associated Pediatric Deaths by Week of Death: 2014-2015 season to present

- **2014-2015**: Number of Deaths Reported = 148
- **2015-2016**: Number of Deaths Reported = 94
- **2016-2017**: Number of Deaths Reported = 110
- **2017-2018**: Number of Deaths Reported = 180

**Week of Death**

- **Deaths Reported Previous Week**
- **Deaths Reported Current Week**
Persons at High Risk for Severe Outcome or Complications from Influenza Infection

- Children <59 mo and adults ≥50 yo
- Women: are/will be pregnant during influenza season
- American Indians/Alaska Natives
- Extremely obese (BMI ≥40)
- <18 yo on ASA/salicylate-containing meds (Reye syndrome)
- Chronic lung (asthma too), cardiovascular (not isolated HTN), renal, hepatic, neurologic, hematologic, or metabolic disorders (including DM)
- Immunocompromised - any cause
- Nursing home and long-term care facility residents

Emphasis: Those who live with or care for higher risk patients need vaccine
Risk Factors for Influenza Pediatric Deaths 2017-18

- Asthma: 27%
- Cardio: 8.4%
- Lung: 6.7%
- Immune deficient: 8.2%
- Metabolic: 4.8%
- Neuro: 17%
- Neuro muscular: 3.7%
- Obesity: 10%
- Pregnancy: 1%
- Renal: 2.2%
- None: 45%
Vaccines can Prevent Death by Influenza

Immune System is the key – Goldilocks phenomenon

• Not too much to produce excess inflammation
• But enough to contain virus and secondary bacterial attacks

1. Primary viral infection - even in otherwise healthy
• Cytokine storm – high viral load + host genetics
• Severe lung injury

2. Viral disease increases physiologic load
• Chronic/metabolic/immune illness
• Pregnancy

3. Secondary bacterial infection – we can help
• Caused most deaths in 1917-18 pandemic
• Pneumococcus – there’s another vaccine for this
• S. aureus
Pain with no gain
Influenza as the Set-up Bug

- **Virus-mediated dysfunction of immune effectors, e.g. polys**
  - Compromises local immunity at normally sterile sites
  - Possible leukopenia = poor outcomes of secondary bacterial infection

- **Most secondary bacterial pneumonia assoc w leukocytosis**
  - Preponderance of polys and immature forms
  - Activated neutrophils and macrophages
    - Add to lung inflammation (mediators)
    - Synergizes with bacterial toxins

- **Despite sheets of polys/macrophages in lung**
  - Functional ability needed to clear bacteria altered
  - ↓ chemotaxis, phagocytosis, and bacterial killing
Other Influenza Factors

• Highly virulent strains (1918 and 1957, Bird flu strains)
  • Damage normally protective epithelia
    • Expose extracellular matrix molecules and basement membrane elements to which bacteria adhere

• Ciliary function compromised
  • Loss of large areas of cilia
  • Surviving cilia w decreased beat frequency & dyskinesia

• All strains create dead space and milieu for bacterial growth
  • Pulmonary function and diffusion capacity diminished
  • Obstruction of small airways
    • Disruption of surfactant
    • Increased mucous plus fibrin and edema fluid
  • Alveoli full of inflammatory cells
2018-19 Vaccines

• IIV3
  • 1st A H1N1: Michigan/45/2015pdm09–like virus
  • 2nd A H3N2–like Singapore/INFIMH-16-0019/2016 (updated)
  • 1st B Colorado/2017-like in Victoria lineage (updated)

• IIV4, RIV4, and LAIV4
  • 2nd B Phuket/2013–like in B/Yamagata lineage

• For adults – HD-IIV3 and a-IIV3 also available

• New lower age limit
  • Afluria Quadrivalent® (IIV4) down to 5 yo
  • Fluarix Quadrivalent® (IIV4) down to 6 mos
AAP Recommendations

• 1\textsuperscript{st} choice – IIV all >6mos old, preferably by Oct 31
  • IIV comes as trivalent (IIV3) or quadrivalent (IIV4)
  • Neither formulation preferred over the other

• 2\textsuperscript{nd} choice – (also ACIP) LAIV4 if would otherwise refuse influenza vaccine
  • >2 years old healthy (no underlying condition)

• Vaccine dose # depends on age and vaccine Hx
  • 6mos through 8yo = 2 doses in 1st year being vaccinated
  • >9yo need only 1 dose, regardless of prior vaccination Hx
Dosing for 6 through 35 Month Olds

IIVs

1. 0.5 mL FluLaval Quadrivalent®
   • 15 µg of HA per vaccine virus
2. 0.5 mL Fluarix Quadrivalent®
   • 15 µg of HA per vaccine virus
3. 0.25 mL Fluzone Quadrivalent®
   • 7.5 µg of HA per vaccine virus

LAIV4
• 0.2mL intranasally (0.1 mL each nostril)
Number of Doses <9 YO

- 2 dose requirement
  - ≥2 total prior doses
  - Any flu vaccine
  - >4 wks apart
  - Before 07/01/18
  - Even if 2 doses not in same or consecutive seasons

- Met 2 dose requirement
  - Yes - only 1 dose in 2018–19
  - No - 2 doses in 2018–19
    - Interval at least 4 wks
LAIV4 Option

  - LAIV not recommended in past 2 US seasons

- 2018-19 LAIV4 different than prior years
  - New seed strain
    - H1N1pdm09-like vaccine virus (A/Slovenia/2903/2015)
      - Induced higher immune response in pilot study

- VE of new LAIV not known yet
Other Influenza Recs from AAP/ACIP

• Pregnancy
  • Dose any time during pregnancy
  • Unless true contraindication

• Postpartum but no flu vaccine during pregnancy
  • Dose before hospital discharge

• Breastfeeding
  • Vaccine during safe for mothers and their infants

• Egg allergy - no added precautions above those for any other vaccine*
HCW Flu Vaccine Uptake Rising

CMH - >90% since 2012
Place of Vaccination 2017-18

- Doctor's Office: 34.7% (Children), 64.6% (Adults)
- Hospital, Emergency Department: 4.3% (Children), 5.9% (Adults)
- Clinic, Health Center or Other Medical Place: 8.6% (Children), 17.6% (Adults)
- Health Department: 1.9% (Children), 1.1% (Adults)
- Pharmacy/Store**: 4.9% (Children), 28.2% (Adults)
- Workplace: 0.4% (Children), 17.0% (Adults)
- Senior or Community Center: 0.0% (Children), 0.8% (Adults)
- School, College: 4.9% (Children), 1.0% (Adults)
- Other Place† †: 0.5% (Children), 2.8% (Adults)

*Percentage receiving vaccination at this type of place*
7.7 percentage point decrease in coverage among Hispanics

Flu Vaccine Uptake Inversely Related to Age Group, i.e. younger have higher uptake rates

~90% needed for herd immunity

* 7.7 percentage point decrease in coverage among Hispanics
Figure 2. Flu Vaccination Coverage by State, Children 6 Months—17 Years, United States, 2017–18 Season
Waning Intra-seasonal Protection

- “Balancing considerations of unpredictability of timing of influenza season onset and concerns that vaccine-induced immunity might wane over the season, it is recommended that vaccination should be offered by end of October.”
  MMWR Sept 2018

- Children needing 2 doses
  - 1\textsuperscript{st} dose as soon as available

- Should we revaccinate already fully vaccinated persons later in season?
  - Not recommended
Waning Intra-seasonal Vaccine Protection

- Delaying influenza vaccine
  - Might result in greater immunity later in the season
  - Likely results in some missed vaccination opportunities
    - More constrained time period and some may not return
- 8 studies - Conflicting results
  - Waning effects not observed consistently
- “Waning varies by:
  - Age (oldest and youngest), virus subtypes, and seasons
- ? partly due to unmeasured confounding bias or late season drift-variants not well-matched to vaccine strains
- May be greater with A(H3N2) than A(H1N1) or B viruses

- Refs at end of presentation
Original Immunological/antigenic Sin

• **1\textsuperscript{st} infection or 1\textsuperscript{st} vaccine**
  - Permanently imprints immune system
  - Persistent dominant immune memory and amnestic response for that influenza strain/s regardless of strain seen in future

• **When exposed to other strain/s**
  - Wild type virus in nature or other vaccine strains
  - Immune system not as effective in generating protective responses to new strains
Influenza Non-egg based Vaccine Formulation

- Preculture
- High density culture
- Virus infection
- Virus propagation
- Centrifugation
- DNA removal
- Whole virus
- Virus inactivation
- Virus disruption
- Split vaccine
- Subunit vaccine
- Formulation
- Polishing
Influenza Non-egg based Vaccine Formulation - 2

Baculovirus

WHO candidate virus

Insect cells high density culture

Cell infection

BEVS (HA cloning)

Virus replication

Centrifugation

Detergent extraction

Ion chromatography

Ultrafiltration

Chromatography

Membrane filtration

Formulation

HA protein
Best Protection: Antibody + Cellular Response

Neutralize free virus

Destroy the factory and its product!
Cell Culture-based IIV (cIIIV4) vs egg-based IIIV3

- Low 2017-18 VE (~24% overall)
  - Flu antigens from eggs drifted vs those in circulating strains
  - Cell derived flu antigens do not drift
  - ? cell-based vaccines have had higher VE last year
- Relative VE (cIIIV vs egg derived IIIV)
- Absolute VE of each vaccine alone

- Kaiser Permanente-North CA, 3 million 4-64 yo
  - ~1 million vaccinated; ~8.3% vaccinees got cIIIV
  - ~5,800 influenza A-positive
    - 70% unvaccinated
    - ~25% got egg-based IIIV3, 2.4% got cIIIV
Cell Culture-based IIV (cIIV4) vs egg-based IIV3

- Absolute VE for Flu A strains vs no vaccine
  - cIIV4 = 31.7%, 95% CI 18.7%-42.6%, \( P<0.0001 \)
  - egg-based IIV3 = 20.1%, 95% CI 14.5%-25.4%, \( P<0.0001 \)

- Relative VE cIIV vs IIV for flu A
  - Not significantly different
  - Overall (A+B strains) – \( P<0.01 \)
    - cIIV4 = 40.9%
    - IIV3 = 9.7%
  - But.....
    - Most flu in CA region was B Yamagata
    - B Yamagata not in IIV3 but is in cIIV4
Experimental Pediatric Nasal Influenza

• Goal: Protection even if vaccine mismatch for circulating strain
• New vaccine: H3N2 genetically altered to replicate only once in vivo
• Animal data
  • “single replication” virus did not cause disease
  • Robust immune response similar to natural influenza infection
• Phase 1 trial in healthy adults
  • As safe as seasonal vaccine and robust immune responses
• Ongoing
  • Phase 2 adult trial currently underway
  • Phase 1 double blind placebo-controlled clinical trial in healthy 9-17yo
    • Saint Louis University’s Vaccine and Treatment Evaluation Unit (VTEU)
    • N= 25 intranasal vaccine (FluGen Inc, Madison WI) and 25 placebo
    • All get licensed IIV4 3 months later
    • Metrics: Safety plus antibody and cell-mediated responses
M2 protein needed for ongoing replication

- Single-replication live-virus that has had M2 deleted produces robust immune response with extra benefit of providing cross-reactive immune response to strains not in vaccine
Why Pregnant Women Not Vaccinated (N=817)

Influenza and Tdap Vaccine in Pregnancy 2017-18

- 49.1% reported getting influenza vaccine; 54.4% Tdap
  - 32.8% got of both influenza and Tdap
- Lower uptake of influenza vaccine if:
  - Black non-Hispanics
    - 35.6% vs >50% for all other race/ethnicities
  - Less than a college degree
    - 57% vs 41%
  - Less provider visits
    - 18.1% (0 visits); 37% (1-5 visits); 50% (6-10 visits); 57% (>10 visits)
- No recommendation or offer
  - 9% no rec, no offer; 38% rec but no offer; 64% rec + offer
IIV Reduced Hospitalization Risk in Pregnancy by 40%

• From 2010-2016
  • 19,450 hospitalizations in influenza season
• Hospitalized pregnant women (other than delivery)
  • ~50% with pneumonia or influenza discharge Dx
• Influenza A or B detected in 598/1030 (58%) who were tested for respiratory virus
• Adjusted overall vaccine effectiveness
  • Against influenza-associated hospitalization during pregnancy
  • 40% (95% CI 12%-59%)

Antiviral medications

• Important in influenza Rx & control
  • But not substitute for vaccine

• Promptly identify influenza infected patients
  • Timely initiation of antiviral when indicated
  • Shared decision-making (medical + child caregiver)

• Best results if Rxed <48h post symptom onset

• BUT .... antiviral still considered >48h with
  • Hospitalization
  • Severe outpatient disease
  • Those at high risk of complications

CDC – MMWR 2018
Persons at High Risk for Severe Outcome or Complications from Influenza Infection

• Children <59 mo and adults ≥50 yo
• <18yo on ASA/salicylate-containing meds
  • Reye syndrome
• Women: are/will be pregnant during influenza season
• American Indians/Alaska Natives
• Extremely obese (BMI ≥40)
• Chronic Condition
  • Lung (asthma too), cardiovascular (not isolated HTN), renal, hepatic, neurologic, hematologic, or metabolic disorders (including DM)
• Immunocompromised - any cause
• Nursing home/long-term care facility
Baloxavir Marboxil (Xofluza®)

Influenza virus
Attachment

Incorporation

mRNA synthesis
(cap-dependent endonuclease)

Membrane infusion

Replication of viral genome RNA

Neuraminidase inhibitors (e.g., Tamiflu (oseltamivir))

Release

Budding

Translation of transcribed mRNA
Polymerase inhibitor (favipiravir)

Viral genome RNA

Cap-dependent endonuclease inhibitor, Xofluza
Oral Baloxavir marboxil for Influenza

• Novel action – endonuclease inhibitor
  • Blocks viral proliferation; inhibits start of mRNA synthesis
  • Approved in Japan Feb 2018 -under review by US FDA

• Phase III randomized US/Japan trial (N=1436)
  • 84% H3N2 influenza: single 40 or 80mg baloxavir dose
  • Otherwise healthy 12-64 yo

• Outcome - similar to 5d oseltamivir
  • Best if 1st dose within 24h post 1st Sx
  • Sx improve d2 vs d5 for placebo
  • Sx stop (54h) vs placebo (80 h)
    • Sx duration 26% shorter in adults, 39% shorter in teens
  • Shedding (1d) vs oseltamivir (3d) or placebo (4d)

• AEs same as placebo – diarrhea in 1.8% most common


2. Baloxavir presentations at ID Week Oct 2018, San Francisco
Variant Influenza Strains - Animals?

1. Kansas cattle with bovine respiratory disease
   - Influenza C detected by real-time PCR testing
   - Closely related to human -C strains (≈95%)

2. Migratory Birds w Eurasian-origin influenza in US
   - Wild birds in western Alaska
     - H1N2, H3N2, H3N2/N6 (mixed infection), H3N8, H4N6, H5N2, H6N2, H7N3, H8N4, and H12N2
   - Unusual A viruses to North America by migratory birds
   - Intercontinental dispersal not be as rare as once thought
17-year Molecular Epidemiologic Survey (Hong Kong)

- East Asia important contributor to influenza surveillance
  - but often mismatch of vaccine and circulating strains
- Most influenza A(H3N2) and B vaccine strains circulated in East Asia >1 year before being in US or Asian vaccines
- Yearly strain drift common
  - H3N2 = 41.2%; B = 35.3%

Flu on a Plane
– Sept 2018 Dubai Flight

• Commercial jets built since 1990
  • Recirculate 10%–50% of cabin air mixed with outside air
  • Filtered 20–30 times/h (HEPA filters)
  • Remove 99.9% of particles > 0.1–0.3 microns in diameter
    • Bacteria, fungi, and larger viruses or virus clumps
    • Cabin air environment not highly conducive to transmission
    • Influenza ~0.2 microns

• Highest risk on planes same as when not on planes
  • Contact with infected secretions
  • Ill person sneezes/coughs droplets that land on nose or eyes
  • Touching contaminated surface - then touching nose/eyes

Influenza Stable in Mucous at All Humidities

1. Rotating drum (1) set at desired RH
2. Bulk virus nebulized into drum (2)
3. Virus incubated: 1h w water + lung cell proteins
4. Samples extracted via port (3) onto gelatin filter over 15min
5. Filter dissolved to free virus for culture

Influenza Titer Loss w/o Lung Cell Protein
Recs with History of Egg Allergy

Unlikely to be allergic If no Rxn when eat lightly cooked egg (e.g., scrambled egg)
Still might be egg-allergic if tolerates egg in baked products (e.g., bread or cake)

How to confirm egg allergy if desired:
1. PMH
   - Consistent adverse Rxn to eggs/egg-containing foods
2. IgE to egg proteins
   - Skin and/or IgE blood test positive

Contraindication:
• Prior severe allergic Rxn to influenza vaccine, regardless of putative responsible component
**Recs with Egg Allergy Hx - 2**

Any licensed, recommended, age-appropriate vaccine

1. If only urticaria (hives) with eggs
2. Also if non-hive Sx, e.g. angioedema, resp distress, lightheadedness, or recurrent emesis
3. Also even if epi or other emergency intervention used for Rxn

   • **But......for 3.**
      
      • Vaccine in medical setting (inpt or outpt) supervised by health care provider able to recognize/manage severe Rxn
      
      • As with any vaccine, consider observing (seated or supine) for 15 min post-vaccine to lower syncope risk
Plan

• How was last flu season?
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• Waning intra-seasonal protection?
• Kinds of flu vaccine – mostly now and 1 for future
• Pregnancy and flu
• Antivirals
• Effect of humidity on contagion
Ref: Waning Intra-seasonal Protection


