Advanced Concepts:
Influenza Vaccination, Respect and Understanding for a Powerful Tool

William Sonnenberg, MD, FAAFP

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Dr. Sonnenberg earned his medical degree from the University of Pittsburgh and completed his family medicine residency at McKeesport Hospital in Pennsylvania. A past president of the Pennsylvania Academy of Family Physicians, he has been in private practice in the Titusville area since 1983. In 2017, he was a featured speaker about pneumonia and inflammatory bowel disease in three editions of the AAFP’s FP Audio™. His lectures at national meetings have been selected for publication by Audio-Digest seven times. 2019 marks his 12th time presenting at the AAFP’s annual meeting.
Learning Objectives

1. Learn the benefits and safety of Influenza vaccination.

2. Obtain effective tools to deal with objections to Influenza vaccination.

3. Getting the best payment for providing this service.

Audience Engagement System

Step 1

Step 2

Step 3
Goals

• Benefits and safety of Influenza vaccination
• Dealing with objections to Influenza vaccination
• Best payment for providing this service

History of Influenza Vaccination

• 1918 flu kill more USA troops in WWI than battle, reduces life span in USA by 12 years
• Type A isolated in 1933, Type B in 1936
• 1936, ability to grow in eggs.
• First vaccine for troops in WWII, reduced fever from flu
• Zonal ultracentrifugation in 60’s
Creation of the Annual Vaccine

- Egg-based vaccine production takes 6 months
  - VPL take 3 months
- Mutation rate of 99%
- International monitoring for strains
- Predicted strains announce in February or March
- China much human-poultry contact, epicenter
  - Only 2% of Chinese get flu vaccines

Melinda Liu, Smithsonian Magazine, November 201

Benefits of Annual Flu Vaccination

- 41% reduction in mortality
  - 75% reduction in previously vaccinated
  - 9% in newly vaccinated
- 24% reduction in elderly
  - No reduction in newly vaccinated

Vaccine Contribution
2017-2018 Season

• Prevented;
  • 7.1 million illnesses
  • 3.7 million office visits
  • 109,000 hospitalizations
  • 8,000 deaths
• 6% decline in adult vaccinations from 2009-2010 season


High Priority

• Children <5 years; especially those <2 years
• Adults >50 years; especially those >65
• Pregnancy
• Chronic illness, immunocompromised
• Health care workers
• Household contacts of high risk groups
• American Indians and Alaskan natives
• Asplenic?

Flu Vaccine and CV Mortality

• 4 trials of secondary prevention (n=1682) with established CAD
• RR of CV mortality 0.45 (95% CI 0.26 to 0.76)

Heart Failure and Influenza Vaccination

• 50% drop in death rate during flu season
• 20% drop rest of year
Vaccine Administration

• By end of October
• Can be given with minor respiratory illness
  • Avoid using LAIV with respiratory infections
• Can give inactivated vaccines with other vaccines
  • Don’t give LAIV with other live virus vaccines on the same day

Duration of Effect

• Ages 18-49, time for twofold decrease in titer is >600 days
• Ages >60 yrs, 8 studies all showed efficacy of at least 4 months
• Possible older adults are better protected closer to time of vaccination

Timing of Flu Vaccine

• By the end of October
• Continue to offer till January
• Topics throughout year

Effect of Statin

• Statins have known immunomodulatory effects
• Study of pts > 65 years have post-vaccine titers 38-67% lower
• Vaccine efficacy lower in statin users (14.% v. 22.9%)
• Consider high dose vaccine

Effect of Glucocorticoids

- Response not affected by brief (<14 day) courses or every other day steroids
- May be impaired by high doses (prednisone 20 mg) prolonged administration (≥14 days)
- May want to defer if possible

Effect of Prior Influenza Vaccination on Efficacy, 2011-2012

<table>
<thead>
<tr>
<th></th>
<th>Vaccine Efficacy</th>
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<tbody>
<tr>
<td>Current year only (2011-2012)</td>
<td>56%</td>
</tr>
<tr>
<td>Current (2011-2012) and prior years</td>
<td>45%</td>
</tr>
<tr>
<td>Vaccinated prior years only</td>
<td>18%</td>
</tr>
</tbody>
</table>
Vaccine Formulations

- Standard-dose trivalent and quadrivalent inactivated
- High-dose trivalent - ≥65 years, 4 times HA antigen
- Adjuvanted trivalent inactivated - ≥65 years
- Quadrivalent inactivated produced in cultured cells
- Inactivated produced with recombinant DNA
- Standard-dose quadrivalent live attenuated - ages 2-49, cold adapted

Audience Engagement Question #1

- Specially formulated vaccines for older adults do not have
  a. Polymerized, monovalent virus fragments
  b. Squalene adjuvant
  c. Quadrupled viral particles
<table>
<thead>
<tr>
<th>Types of Flu Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard-dose trivalent and quadrivalent inactivated</td>
</tr>
<tr>
<td>Quadrivalent inactivated produced in cultured cells</td>
</tr>
<tr>
<td>Inactivated produced with recombinant DNA</td>
</tr>
<tr>
<td>High-dose trivalent - ≥65 years, 4 times HA antigen</td>
</tr>
<tr>
<td>Adjuvanted trivalent inactivated - ≥65 years</td>
</tr>
<tr>
<td>Standard-dose quadrivalent live attenuated - ages 2-49, cold adapted</td>
</tr>
</tbody>
</table>

**Standard-dose Tri-and Quadrivalent Inactivated**

- Inactivated, split or subunit vaccines
- 15 mcg of hemagglutinin per dose
- Produced in embryonated chicken eggs
Trivalent v. Quadrivalent?

- Influenza B more stable
- 26% of all typed viruses
- 12 seasons (1999-2012) 42% of B infections caused by the extra strain in the quadrivalent
- May cost more

High-Dose Trivalent Inactivated

- 60 mcg v. 15 mcg of hemagglutinin per dose
- ≥65 years of age
- Efficacy – 3 studies
  - Confirmed cases 1.4% v. 1.9% (24.3% relative efficacy)
  - Mortality advantage 0.028 v. 0.038 per 10,000 person-weeks
  - 823 nursing homes relative risk 0.87
Trivalent Produced in Cultured Cells

- Trivalent inactivated produced in cultured mammalian cells
- Efficacy similar to egg-based vaccine
- ≥ 18 years
- Less laborious, shorter production time, not reliant on egg supply
- HA structure preserved
- Some strains don’t reproduce well in eggs

Recombinant DNA

- Trivalent and quadrivalent hemagglutinin
- Recombinant DNA and a baculovirus
  - Virus infecting invertebrates
  - Produces virus-like particles
- 18 years and older
- 45 mcg of HA
- PCR confirmed flu-like illness 30% lower than inactivated vaccine in 50 years and older
- 6-8 week lead time v. 6 months for inactivated

Adjuvanted Trivalent Inactivated Super-Charged with Shark Oil

• ≥65 years
• Adjuvant Oil-in-water emulsion of squalene oil
• No comparison studies with HD Flu vaccine
• Observational study in Canada of 282 patients showed 63% higher efficacy compared to SD flu vaccine

CDC, December 10, 2018

Audience Engagement Question #2

• Who can receive the live attenuated nasal vaccine?
  a. Senior citizen residents of nursing homes
  b. Pregnant women over 35 years of age
  c. Teenagers
  d. Transplant patients
Live Attenuated Quadrivalent Nasal

- Live, but weakened and cold-adapted
  - Can only multiple in nose
- Reintroduced with better H1N1 strain
- Ages 2-49 (59 in Canada)
- Contraindicated in pregnancy
- Poor efficacy in children in previous seasons, not to be used 2016-17, 2017-18

Nasal Flu Vaccine Restrictions

**Should Not Receive**
- Younger than age 2
- 50 and older
- Pregnant
- Age 2-17 on aspirin
- Immunosuppressed
- Asthma, ages 2-4
- Wheezing in past 12 months
- Antivirals in past 48 hours
- Caretakers of immunocompromised

**Use with Precaution**
- Asthma age 5 and older
- Lung, heart, kidney, liver, neurologic, neuromuscular, or metabolic disease
- Moderate or severe acute illness
- Hx of Guillain-Barré syndrome
Pregnancy and Influenza Vaccination

Administration

• **All women** pregnant or potentially pregnant during flu season should receive the inactivated flu vaccine
• No live virus vaccine
• 49% coverage during 2017-18 season

Vaccination in Pregnancy

• Risk of hospitalization more than 4 times higher than among nonpregnant women
• Risk of complications comparable to nonpregnant women with high-risk medical conditions
• ACIP recommends vaccination with inactivated influenza vaccine for ALL women who will be pregnant during influenza season
• Any trimester
• No live virus vaccination

Maternal Vaccination

• Randomized study of 340 mothers
  • Influenza
  • Pneumococcal vaccine (control)
• Infant benefit
  • 6 v. 16 cases of influenza, 63% effective
  • 29% reduction in URI with fever
• Maternal benefit
  • 36% reduction in URI with fever

Infant Influenza Hospitalizations

• 1510 hospitalized infants < 6 months
• Infants of vaccinated mothers during pregnancy were 45-48% less likely to be hospitalized


Hospitalization Risk and Vaccination

### Infants

• 1510 hospitalized infants < 6 months
• Infants of vaccinated mothers during pregnancy were 45-48% less likely to be hospitalized

### Mothers

• Pregnant women 18-50 from 2010 thru 2016
• 40% reduction in hospitalization


Clinical Infectious Diseases, Volume 68, Issue 9, 1 May 2019, Pages 1444-1453
Influenza Vaccination in Children

Children 6 Months through 8 Years

- **Two doses** first season of influenza vaccination or if status unknown
- First dose given as soon as vaccine first available
- Separate by at least 28 days
### Dose?

<table>
<thead>
<tr>
<th>6 months through 35 Months</th>
<th>Children ≥ 36 Months</th>
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<tbody>
<tr>
<td>• Afluria – 0.25 cc</td>
<td>• 0.5 cc</td>
</tr>
<tr>
<td>• Fluzone – 0.5 cc (new this year)</td>
<td></td>
</tr>
<tr>
<td>• Fluarix – 0.5 cc</td>
<td></td>
</tr>
<tr>
<td>• FluLaval – 0.5 cc</td>
<td></td>
</tr>
</tbody>
</table>

**Egg Allergy**
Audience Engagement Question #3

- Precautions for influenza vaccination for the egg allergic patients include
  a. Skin testing
  b. Referral to allergist
  c. Pretreatment with diphenhydramine
  d. Observation in office

Risk of Anaphylaxis

- 12 adverse events reported to VAERS with egg-free vaccine in self-reported egg allergic patients
- Survey of 9 HMOs years 2009-2011 show rate of anaphylaxis of 1.35 per million doses
- Testing of lots shows all vaccines < 0.17 mcg of ovalbumin per dose
- Study of 500 patients with anaphylaxis to egg ingestion – none had serious reaction

Woo EJ. Clin Infect Dis. 2015;60(5):777
Risk of Anaphylactic Death?

- 15 years of VAERS data, 1990 to 2005
- 747 million doses in USA
- 4 reported anaphylactic deaths shortly after flu vaccines
  - No information on egg allergy in patients

Vaccine. 2009;27(15):2114

Egg-Free Flu Vaccines

- Cultured mammalian cell (Flucelvax)
  - Minuscule amounts of egg protein
  - Efficacy compatible with standard flu vaccines
- Recombinant hemagglutinin protein (Flublok)
  - Similar efficacy
  - Less immunogenic <3 years of age
Approach to Patient with Egg Allergy

• Skin testing not predictive of vaccine reaction – no longer recommended
• AAP, ACIP, and CDC recommend patients with egg allergy receive egg-based flu vaccine
• Need not screen for egg allergy
• Hx of reactions worse than hives be supervised by health care provider
• Anyone administrating vaccines be ready for potential anaphylaxis

MMWR Recomm Rep. 2017;66(2)

Fighting Flu Fallacies
Arguing with idiots is like playing chess with a pigeon... No matter how good you are, the bird is going to s--- on the board and strut around like it won anyway.

Formaldehyde

- Human body produces and uses formaldehyde, 1,000,000 times more
- Total 1.1 mg formaldehyde in blood of 2 month infant, total in any vaccine < 0.1 mg
- Pear contains 50 times more formaldehyde than any vaccine
- 10 million flu vaccines would make a lethal dose

Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, University of Oxford, OX3 7LE.
Aluminum Salts

- Adjuvant, used in vaccines for 80 years
- Infant aluminum consumption in first 6 months
  - 4.4 mg from routine vaccinations
  - 7 mg from breast milk
  - 37 mg formula
  - 117 mg from soy formula
- Alzheimer’s link disproved

2019 The Children’s Hospital of Philadelphia
Aluminum Alzheimer’s Disease?

• 1965 rabbits injected with extremely high amounts of aluminum developed tau tangles
• Third most abundant element on Earth
• 1% absorption, most cleared by kidney

Ingredients?

INGREDIENTS: AQUA (84%), SUGARS (10%) (FRUCTOSE (48%), GLUCOSE (40%), SUCROSE (2%), FIBRE E440 (2.4%), AMINO ACIDS (<1%) (GLUTAMIC ACID (23%), ASPARTIC ACID (18%), LEUCINE (17%), ARGinine (8%), ALANINE (4%), VALINE (4%), GLYCINE (4%), PROLINE (4%), ISOLEUCINE (3%), SERINE (3%), THREONINE (3%), PHENYLALANINE (2%), LYSINE (2%), METHIONINE (2%), TYROSINE (1%), HISTIDINE (1%), CYSTINE (1%), TRYPTOPHAN (<1%)), FATTY ACIDS (<1%) (OMEGA-6 FATTY ACID: LINOLEIC ACID (30%), OMEGA-3 FATTY ACID: LINOLENIC ACID (10%), OLEIC ACID (18%), PALMITIC ACID (8%), STEARIC ACID (2%), PALMITOLEIC ACID (<1%), ASH (<1%), PHYTOESTEROLS, OXALIC ACID, E330, E336 (TOCOPHEROL), THIAMIN, COLOURS (E101a, E102, E160a, E160f, E160n). FLAVOURS (ETHYL ETHANOATE, 3-METHYL BUTYRALDEHYDE, 2-METHYL BUTYRALDEHYDE, PENTANAL, METHYLBUTYRATE, OCTANE, HEXANAL, DECANAL, 3-CARENE, LIMONENE, STYRENE, NONANE, ETHYL-3-METHYLBUTANOATE, NON-1-ENE, HEXAN-2-ONE, HYDROXYLINALOOL, LINALOOL, TERPINYL ACETATE, CARYOPHYLLENE, ALPHA-TERPINENE, ALPHA-TERPINENe, 1,8-CINEOLE, CITRAL, BENZALDEHYDE), METHYLPARABEN, 1510, E300, E440, E421 and FRESH AIR (E941, E948, E290).

[jameskennedymonash.wordpress.com]
Guillain-Barré Syndrome

• 11 cases in China with 100 million vaccines – lower than normal rate of disease
• Risk of GBS syndrome 10 times greater with influenza than the worst vaccine rate of GBS
• No evidence of increased risk


Preparation of Oscillococcinum

Decapitate duck
Remove 35 grams of heart and 15 grams of liver
Mix with pancreatic juice and glucose
Allow to ferment for 40 days
Dilute, dilute, dilute ...
Table of Dilution

<table>
<thead>
<tr>
<th>Dilution</th>
<th>Ratio</th>
<th>Notes</th>
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<tbody>
<tr>
<td>1C</td>
<td>1:100</td>
<td></td>
</tr>
<tr>
<td>3C</td>
<td>$10^{-6}$</td>
<td></td>
</tr>
<tr>
<td>12C</td>
<td>$10^{-24}$</td>
<td>Unlikely single molecule remains</td>
</tr>
<tr>
<td>30C</td>
<td>$10^{-50}$</td>
<td>Standard homeopathic dilution, to get single molecule, 2 billion doses per second to 6 billion people for 4 billion years</td>
</tr>
<tr>
<td>200C</td>
<td>$10^{-400}$</td>
<td>Dilution of Oscillococcinum</td>
</tr>
</tbody>
</table>

“I never get the flu”?  

- Drop fire insurance too?  
- 75% of infections may be asymptomatic  

Religious Objections

- Almost no religions object to vaccination
  - Congregation of Universal Wisdom (chiropractic and universal intelligence)
- EEOC defines “religion” as moral or ethical beliefs as to what is right and wrong which are sincerely held with the strength of traditional religious views.” i.e. vegan lifestyle
- Can’t be, “personal moral code”
- Must address ultimate questions, not just vaccines

“Your right to swing your arms ends just where the other man’s nose begins.”

Zechariah Chafee, Jr.
Becoming immune to a disease by catching the disease is like using pregnancy as contraception.
Why Flu Vaccine for HCW?

- Up to 25% are infected each season
- More likely to work sick than other workers
- Half may not have classic symptoms yet shed for 5-10 days
- Admissions and absenteeism are higher during flu season
- Care for high risk patients; elderly, pregnant, heart, lung disease


Does Masking Unvaccinated Workers Help?

- Evidence lacking for reducing transmission
- One study showed increase in vaccination from 33% to 52% within 10 days
Benefits for Health Professionals

- Influenza Infection: -88%
- Sick Day due to Respiratory Infection: -28%
- Lost Days from work: -41%
- Patient Mortality: -41%


Neonatal ICU Event

- 19 babies in Ontario NICU, one died in 2000
- Only 15% of the workers vaccinated

Infect Control Hosp Epidemiol. 2000 Jul;21(7):449-54
AAFP Policy – June 2011

• All health care personnel to receive the vaccine each year
• Exceptions based only on medical or religious reasons, not on personal preference
• Refusers should wear masks or refrain from patient contact

Influenza Vaccine Reimbursement
Coding for Refusal

| Refusal for documented reasons | G8483 |
| Religious or group pressure | Z28.1 |
| Patient refusal | Z28.21 |
| Caregiver refusal | Z28.82 |

Administration Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>90460</td>
<td>≤18 years, with qualified counseling, first vaccine/toxoid component</td>
</tr>
<tr>
<td>90461</td>
<td>≤18 years, with qualified counseling, each additional vaccine/toxoid component</td>
</tr>
<tr>
<td>90471</td>
<td>First vaccine (percutaneous, intradermal, IM)</td>
</tr>
<tr>
<td>90472</td>
<td>Each additional vaccine (percutaneous, intradermal, IM)</td>
</tr>
<tr>
<td>90473</td>
<td>First vaccine, nasal or oral</td>
</tr>
<tr>
<td>90474</td>
<td>Each additional, nasal or oral</td>
</tr>
<tr>
<td>G0008</td>
<td>Influenza vaccination, Medicare</td>
</tr>
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</table>
Improving Flu Vaccination Rates

- Have a champion
- Standing orders
- Documentation
  - Document refusals (allergy, already received, refusal, shortage)
- Reminders
- Ongoing feedback

Cunningham A, Stoeckle J, Diaz V, Valko G, Arenson C. Back to basics: five steps to better influenza vaccination rates. FPM. 2017;24(6):30-33.

Elements of a Standing Order

- Who is targeted
- Determine need (indications, contraindications, precautions)
- Procedures (route, dose, needle size)
- Vaccine information sheet
- How to document
- Protocol for emergencies
- How to report adverse events

www.immunize.org/catg.d/p3066.pdf • Item #P3066 (12/18)
A Better Influenza Vaccine?

Room for Improvement

- Technology from the 1940’s
- Could be more effective
  - 47% overall last year
- Slow production time in eggs
- Need for annual vaccination
- Dependent on supply of eggs

MMWR, February 15, 2019 / 68(6):135–139
Non-Egg Production

- Shorter production time, less laborious
- Virus adapts to chickens, no humans
- No egg supply issues
- Mammalian cell line vaccines preserve structure of HA site
  - More robust antibody response
  - Broader response, variant strains
  - Some strains (Avian H5N1) don’t replicate well in eggs

Need More of a Head Start

- Prediction of strains 6 months
- 2004-2005 season, antigen fit was 5%
  - 10% effective
- 2006-2007 season, antigen fit was 91%
  - 52% effective
- 2014-15 season 19% antigen
  - 6% efficacy
Target Neuraminidase Too

- Vaccines prompt antibody response to hemagglutinin
- Natural flu induces antibody response to HA and NA
- NA antibodies may give broader response across more stains


Universal Vaccines

- Antibodies against conserved viral proteins
  - M2 protein
  - Conserved antigen sites of M1, HA, and NP
Intradermal Delivery

- Similar immunogenicity at reduced doses
- Stimulated dendritic cells, antigen-presenting
- More site reactions


Practice Recommendations

- For egg allergy, use an egg-free vaccine, or give under supervision. Skin testing not useful
- Vaccination in pregnancy is a priority in any trimester
- Practice responses to objections to flu vaccination and be steadfast in the mission of saving our patients from influenza
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Questions