Prevention of Influenza in High-Risk Groups: What Are the Vaccine Options and Strategies?

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Director, Mayo Vaccine Research Group
Mayo Clinic
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Search for: Jimmy Kimmel and Dr. Poland and Handwashing
The Goal

- Get influenza vaccine into the arms of the high-risk subject – *annually*
- Consider “cocooning” strategies whereby caretakers and those living in the home are also immunized
- Note that Medicare pays for annual influenza vaccine!
- *Sounds easy, so why doesn’t it work?*
Who is High-Risk?

- Everyone who, on the basis of epidemiological data or clinical experience, is at elevated risk of increased morbidity or mortality

- This can be due to:
  - Age
  - Co-morbid conditions (BMI > 40)
  - Medications or other treatments
  - Pregnancy
  - Other factors
High risk conditions

Respiratory disease
• Asthma
• Chronic bronchitis and emphysema
• Other pulmonary diseases

Cardiac disease
• Atherosclerotic heart disease
• Cardiomyopathy/CCF
• Congenital heart disease

Neurodevelopmental disorders
• Cerebral palsy
• Musculodystrophy
• Cognitive disorders

Metabolic disorders
• Diabetes

Haematological diseases
• Sickle cell anaemia
• Thalassemia major

Immunocompetency disorders
• HIV/AIDS
• Chemotherapy
• Transplant pts on immunosuppressants
• Chronic corticosteroid therapy

Chronic renal insufficiency on dialysis
Chronic liver disease, esp. with cirrhosis
Morbid obesity

Pregnancy
Position Statements – Mandatory Influenza Vaccination for HCPs

- AAFP: American Academy of Family Physicians
- AAP: American Academy of Pediatrics
- ACP: American College of Physicians
- AHA: American Hospital Association
- AMDA: American Medical Directors Association
- APhA: American Pharmacists Association
- APHA: American Public Health Association
- APIC: Association for Professionals in Infection Control and Epidemiology
- IDSA: Infectious Diseases Society of America
- NFID: National Foundation for Infectious Diseases
- NPSF: National Patient Safety Foundation
- SHEA: Society for Healthcare Epidemiology of America
Easiest Way To Remember

• Who should get influenza vaccine?

• EVERYONE $\geq$ 6 months of age benefits from flu vaccine, unless they have a contraindication
  • GBS within 6 weeks of flu vaccine
  • Anaphylactic reaction to flu vaccine component
  • Pregnancy is an *indication*, not a contraindication!

• Now official CDC/ACIP policy as of February 2010
1. Who needs a flu vaccine?
   a) You
   b) You
   c) You
   d) All of the above
Influenza Vaccine Doses Distributed in the United States, By Season

Graphic by CDC, data reported by influenza vaccine manufacturers and selected influenza vaccine distributors.
Figure 1. Seasonal Flu Vaccination Coverage, by Age Group and Season, United States, 2009-2014

Error bars represent 95% confidence intervals around the estimates. The 2009-10 estimates do not include the influenza A (H1N1) pdm09 monovalent vaccine. Starting with the 2011-12 season, adult estimates reflect changes in BRFSS survey methods: the addition of cellular telephone samples and a new weighting method.
# Influenza Immunization Rates

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Percent Coverage</th>
<th>Year</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥65 yrs</td>
<td>65%</td>
<td>2013–2014 season</td>
<td>BRFSS</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>52%</td>
<td>2013–2014 season</td>
<td>MMWR 2014</td>
</tr>
<tr>
<td>HCP</td>
<td>75%</td>
<td>2013–2014 season</td>
<td>MMWR 2014</td>
</tr>
</tbody>
</table>

**HP2020 goals:** 90% for seniors and HCPs, 80% for PG women
Influenza Vaccination Coverage Among Seniors

References:
Impact of Influenza

The “Silver Tsunami” Effect

<table>
<thead>
<tr>
<th>Discharge diagnosis</th>
<th>No. of Discharges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease (includes heart attack)</td>
<td>829,000 (372,000)</td>
</tr>
<tr>
<td>Injury</td>
<td>818,000</td>
</tr>
<tr>
<td>Heart failure</td>
<td>748,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>654,000</td>
</tr>
<tr>
<td>Cancer, all</td>
<td>621,000</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>618,000</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>592,000</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>542,000</td>
</tr>
<tr>
<td>Septicemia</td>
<td>483,000</td>
</tr>
<tr>
<td>COPD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>464,000</td>
</tr>
<tr>
<td>Complications of care and adverse effects</td>
<td>438,000</td>
</tr>
</tbody>
</table>

Influenza has clinical connections to 6 of the top 10 causes of hospitalization among seniors (in red)<sup>2,3</sup>

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>82 million</td>
</tr>
<tr>
<td>Illness</td>
<td>65 million</td>
</tr>
<tr>
<td>Medically attended</td>
<td>30 million</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>200,000</td>
</tr>
<tr>
<td>Death</td>
<td>12,000 - 36,000</td>
</tr>
</tbody>
</table>

Influenza virus infections: 33 per 100

Acute respiratory illness: 26 per 100

Medically attended illness: 12 per 100

ARD Hospitalizations: 12 per 10,000

Deaths: 1 per 10,000

Annual US Morbidity and Mortality
50% - 60% of all influenza-related hospitalizations²

90% of influenza-related deaths²
Flu-related deaths in the US

CDC MORBITIDITY AND MORTALITY WEEKLY REPORT

OVER 64 YEARS OLD

UNDER 65 YEARS OLD


45K

30K

Influenza in the Elderly

Seasonal Influenza (US 1976–2007)

- Serious complications from influenza
  - Secondary infections
  - Exacerbations of chronic diseases
  - Increased hospitalization and death

- Influenza vaccination
  - Reduced hospitalizations and death

Average Estimated Influenza-Associated Deaths

- < 19 yrs: 124
- 19–64 yrs: 2,385
- ≥ 65 yrs: 21,098

Influenza–Associated Hospitalization and Death (1976–2000)¹

A Disproportionate Share of the Disease Burden

Seniors Represent …

- Of the US population
- Of all hospital admissions
- Of influenza-related hospitalizations
- Of influenza-related deaths

References:
Influenza Vaccination and Its Impact on Major Cause–Specific Mortality

- Study in Taiwan in >100,000 residents ≥65 years of age
- Objective: “To understand more thoroughly whether influenza vaccination was effective for reducing major cause–specific mortality (other than lung diseases) in a county–wide population study with large sample sizes”
- Six of 8 major causes of mortality evaluated were not directly related to lung disease
- >10–month follow–up of 35,637 vaccinated and 67,061 unvaccinated persons ≥65 years of age
- High–risk was defined as having a chronic disease, residence in long–term care, or a history of recent (prior 3 years) hospital admission
  - 80% of the full study population were not classified as high–risk

Influenza vaccine is strongly associated with a lower mortality risk, not only for pneumonia and COPD, but also for other major cause-specific mortalities, which indicates that influenza vaccination might reduce the domino effects of complications from influenza in the elderly.

Influenza Vaccines

A New Era of Personalized Vaccinology
Why people don't get flu shots

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I don't need it</td>
<td>28</td>
</tr>
<tr>
<td>I didn't get around to it</td>
<td>16</td>
</tr>
<tr>
<td>I don't believe in flu vaccines</td>
<td>14</td>
</tr>
<tr>
<td>I might get sick/suffer side effects</td>
<td>14</td>
</tr>
<tr>
<td>Others need it more</td>
<td>6</td>
</tr>
<tr>
<td>I dislike needles</td>
<td>5</td>
</tr>
<tr>
<td>It costs too much</td>
<td>4</td>
</tr>
<tr>
<td>A doctor did not recommend it</td>
<td>3</td>
</tr>
<tr>
<td>No vaccine was available</td>
<td>3</td>
</tr>
</tbody>
</table>

Source: RAND Corporation
The Flu Vaccine Doesn’t Cause Flu!

HELLO, DR. MULLIGAN? THIS IS BRUTUS THORNAPPLE...

REMEMBER THAT FLU SHOT YOU GAVE ME?

WELL, IT WORKED!
# Influenza Vaccine Side Effects

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Vaccine (%)</th>
<th>Placebo (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>5.7</td>
<td>4.2</td>
<td>.68</td>
</tr>
<tr>
<td>Cough</td>
<td>6.6</td>
<td>5.1</td>
<td>.62</td>
</tr>
<tr>
<td>Coryza</td>
<td>13.2</td>
<td>10.2</td>
<td>.27</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8.0</td>
<td>7.7</td>
<td>.82</td>
</tr>
<tr>
<td>Malaise</td>
<td>7.2</td>
<td>6.3</td>
<td>.83</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4.8</td>
<td>4.2</td>
<td>.84</td>
</tr>
<tr>
<td>Headache</td>
<td>6.9</td>
<td>7.6</td>
<td>.99</td>
</tr>
<tr>
<td>Any symptom</td>
<td>27.7</td>
<td>22.9</td>
<td>.21</td>
</tr>
<tr>
<td>Sore arm</td>
<td>20.1</td>
<td>4.9</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

Newer Reasons to Get Flu Vaccine

• Increasingly virulent viral strains

• Increasing antiviral resistance
  • Seasonal (10% of H1N1 in 2007–2008, U.S. to oseltamivir)
  • H5N1

• Evidence of less severe H5N1 infection in those immunized with H1N1 seasonal vaccine

• (For HCWs) Professional ethics (often mandatory)
Influenza Vaccine and the Elderly

• Respond least well to flu vaccine with a significantly reduced antibody response

• Compared with younger subjects, elderly have seroconversion rates only 25% as robust for H1 and B antigens, and 50% for H3

• Only one randomized, double-blind, placebo-controlled trial in the elderly
  • 58% efficacy against serologically confirmed flu
  • 47% efficacy against clinical influenza
So persons age 65 years and older have among the highest rates of complications and death due to influenza; yet respond the least well to influenza vaccine.

What to do?
Option 1: High Dose Fluzone (HD–TIV)

- Licensed in US, Dec 2009
- Age 65 years and older
- Trivalent, inactivated
  - 60 mcg of each antigen (4x usual dose)
  - Does not contain thimerosal
  - Otherwise identical to TIV
HD–TIV Immunogenicity

- Randomized, placebo-controlled, double-blind, multicenter phase III clinical trial (2,575 vaccine vs 1,262 placebo) > 65 years

<table>
<thead>
<tr>
<th></th>
<th>SD</th>
<th>HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1</td>
<td>23.1%</td>
<td>48.6%</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>50.7%</td>
<td>69.1%</td>
</tr>
<tr>
<td>B/Malaysia</td>
<td>29.9%</td>
<td>41.8%</td>
</tr>
</tbody>
</table>

Superiority achieved for H1N1 and H3N2; noninferiority for B.

All comparisons, HD vs SD, $P < 0.0001$
Based on FDA criteria, the immunogenicity of Fluzone High-Dose vaccine was superior to Fluzone Standard-Dose vaccine

<table>
<thead>
<tr>
<th>Strain</th>
<th>GMT Ratios HD / SD (95% CI)</th>
<th>4-Fold Rise Rates HD – SD (95% CI)</th>
<th>Met Pre-Defined Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1</td>
<td>1.7 (1.6-1.8)</td>
<td>25% (22-28%)</td>
<td>Superiority</td>
</tr>
<tr>
<td>H3N2</td>
<td>1.8 (1.7-2.0)</td>
<td>18% (15-22%)</td>
<td>Superiority</td>
</tr>
<tr>
<td>B</td>
<td>1.3 (1.2-1.4)</td>
<td>12% (9-15%)</td>
<td>Noninferiority</td>
</tr>
</tbody>
</table>

Differences maintained for persons <75 yrs and ≥75 yrs of age, persons with or without a history of cardiovascular or respiratory disease, and both males and females
• No preference for dose type in persons age 65 yrs and older
  • Higher antibody levels
  • BUT, unknown level of efficacy compared to SD–TIV

• FDA mandated an efficacy study
  • 3 yr study of ≈ 30,000 elderly subjects
  • Randomized, blinded trial of HD–TIV vs SD–TIV
  • Active assessment for influenza (PCR and viral culture)
  • AE’s monitored for 180 days
Randomized, double-blind, active-controlled trial (n=31,989) over 2 flu seasons

Lab-confirmed influenza infection
- 1.4% in HD group
- 1.9% in SD group
- No difference in SAE

HAI titers (seroprotection rate):
- GMT’s approx. 2-fold higher in HD group

Take-home point: HD with 24% better relative efficacy!

Option 2: MF59–Adjuvanted Vaccine

- Trivalent, not quadrivalent vaccine
- Adjuvanted with MF59 (squalene in oil)
- Licensed in US November 2015
### MF59 Flu Vaccine Immunogenicity

<table>
<thead>
<tr>
<th>GMTs Against</th>
<th>FLUAD</th>
<th>AGRIFLU</th>
<th>GMT Ratio&lt;sup&gt;c&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/California/7/2009-like (H1N1)</td>
<td>GMT $N^b=3225-3227$ (95% CI)</td>
<td>GMT $N^b=3256-3259$ (95% CI)</td>
<td>1.4 (1.32-1.49)</td>
</tr>
<tr>
<td>A/Perth/16/2009-like (H3N2)</td>
<td>272 (257-288)</td>
<td>169 (159-179)</td>
<td>1.61 (1.52-1.7)</td>
</tr>
<tr>
<td>B/Brisbane/60/2008-like</td>
<td>28 (26-29)</td>
<td>24 (23-26)</td>
<td>1.15 (1.08-1.21)</td>
</tr>
</tbody>
</table>
Strategies to Improve Influenza Immunization Rates
Barriers to Adult Immunization

- Lack of coordination of adult immunization activities
- Lack of public knowledge
- Lack of provider recommendations for immunization
- Financial impediments to vaccinations
- Lack of access to, and utilization of, health care services by adults
- Lack of utilization of reminder or assessment systems
- Racial/ethnic disparities
- Health literacy
- Concern about adverse events
- Religious barriers
- Lack of trust of the scientific community
- Belief in misguided non-medical advice

Adapted from National Vaccine Advisory Committee. Public Health Reports. 2012;127(S1):1-127.
Strategies for Increasing Adult Vaccination Rates

- Standing Orders
- Computerized Record Reminder
- Chart Reminder
- Performance Feedback
- Home Visits
- Mailed/Telephoned Reminders
- Expanding Access in Clinical Settings
- Patient Education
- Personal Health Records
- Financial Incentives (HEDIS compliance)

4 Pillars of Successful Vaccination Programs

1. Convenience
2. Patient communication
3. Enhanced office vaccination systems
4. Motivation via an immunization champion

4pillarstoolkit.pitt.edu
Pillar 1: Convenient Vaccination Programs

• **Extended vaccination season**
  • Starts when influenza vaccine arrives
  • Continues into the influenza disease season for unvaccinated
    • Season unpredictable & some benefit possible
    • 2 waves of influenza may occur

• **Express vaccination services**
  • Vaccination only services:
    • Dedicated evening or weekend vaccine-only services
    • Walk-in vaccination station
    • Nursing vaccination visits
Pillar 2: Patient Communication

• Convenient Vaccination Services
• Notification Methods
  Autodialer; Email/text; Office posters/videos; Answering service “on–hold” messages; Mail
• Physician recommendation is essential

MMWR 1988;37:657-61
Pillar 3: Enhanced Office Vaccination Systems

• Assessment of vaccination as a routine part of the office visit by nursing staff at check-in/rooming:
  • Prompts in EMR
  • Health maintenance or immunization section review
  • Routinely address “Is vaccination status up to date?” as part of vital signs

• Empowering staff to vaccinate by standing orders

• Combination of assessment and SOPs should reduce missed opportunities
Pillar 4: Motivation

- Ongoing motivation is a key to success
  - Set goals for improving rates
  - Identify an Immunization Champion
  - Champion monitors weekly progress towards goals
  - Shares progress with team
  - Celebrate achievements
    - Consider rewards
## Interventions Increasing Vaccine Rates

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Odss Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organization change</td>
<td>16</td>
</tr>
<tr>
<td>Provider reminder</td>
<td>3.8</td>
</tr>
<tr>
<td>Patient financial incentive</td>
<td>3.4</td>
</tr>
<tr>
<td>Provider education</td>
<td>3.2</td>
</tr>
<tr>
<td>Patient reminder</td>
<td>2.5</td>
</tr>
<tr>
<td>Patient education</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Bridges et al. Vaccine 2015, 33:D114-120
Standing Orders Are Among the Most Effective Strategies

- Nonphysicians offer and administer vaccinations
- Established with physician approved policies and protocols
- Locations:
  - Clinics and hospitals
  - www.immunize.org/standingorders
  - www.immunizationed.org/standingorders

Provider Assessment and Performance Feedback

- Retrospectively assess the delivery of vaccine(s)
- Incorporates principles of continuous improvement
- AFIX
  - Assessment
  - Feedback
  - Incentives
  - eXchange
- Comprehensive Clinic Assessment Software Application (CoCASA)
- Immunization Information System (IIS)
A clinician’s recommendation for influenza vaccine is a strong predictive factor for immunizing patients of all ages\(^1,2\)

2014 Standards for Adult Immunization from the National Vaccine Advisory Committee call on all health care providers to\(^3,4\):

- Incorporate immunization needs assessment into every clinical encounter
- “Strongly recommend all immunizations that patients need” and
- Administer vaccines or refer the patient to a provider who can immunize

References:
Provider Recommendation Can Overcome Negative Attitudes Among Patients

Vaccination Rates Among High Risk Patients With Negative Attitudes

Editorial

Vaccine education spectrum disorder: the importance of incorporating psychological and cognitive models into vaccine education

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<table>
<thead>
<tr>
<th>Style</th>
<th>Examples</th>
<th>HCP Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denialist</td>
<td>“No data supporting vaccine safety” “No real risk of getting these diseases”</td>
<td>Provide materials, consistent messaging, avoid pressuring/persuading</td>
</tr>
<tr>
<td>Innumerate</td>
<td>Lack of understanding of probabilities and risks</td>
<td>Right brain communication methods, emotional appeals</td>
</tr>
<tr>
<td>Analytic</td>
<td>“What are the risks and benefits?”</td>
<td>Data-driven educational materials</td>
</tr>
<tr>
<td>Fear-based</td>
<td>“I’m just afraid that …”</td>
<td>Data, reassurance, personalize, strong HCP recommendation</td>
</tr>
<tr>
<td>Low complexity</td>
<td>Conspiracy theories, erroneous information</td>
<td>Cognitive–appropriate educational materials, strong HCP recommendation</td>
</tr>
<tr>
<td>Heuristic</td>
<td>“I heard of a case of …”</td>
<td>Face value appeals, strong HCP recommendation</td>
</tr>
</tbody>
</table>

Resources for Providers
Shots Immunization App – Free

- For iPhone/iPod, iPad, Android, Blackberry, and PC
- Select vaccine name for information on
  - High risk indications
  - Adverse reactions
  - Contraindications
  - Catch-up
  - Administration
  - Risk communication
  - Epidemiology
- www.ImmunizationEd.org
- Available at iTunes Store
  Content includes Childhood, Adolescent, and Adult Immunization Schedules for the US
ACP Immunization Advisor App by American College of Physicians

Free on iTunes

Receive Updates from the CDC via Email:
Email Updates from the Immunization Action Coalition: http://www.immunize.org/subscribe/

Immunization Action Coalition
Vaccination Information for Healthcare Professionals

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- Needle Tips
  - IAC's online publication for health professionals who provide vaccination services.
Staying Current

- [www.cdc.gov/emailupdates/index.html](http://www.cdc.gov/emailupdates/index.html)
  - Automatic notification of new information

- [www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)
  - Can download **Adult Scheduler**
  - Can download **Shots 2016**

- [www.immunizationed.org](http://www.immunizationed.org)

- [www.stfm.org](http://www.stfm.org)
  - Home site for **Shots 2016**

- [www.immunize.org](http://www.immunize.org)
  - Site for **Immunization Action Coalition**

- [www.cdc.gov/vaccines/recs/acip/default.htm](http://www.cdc.gov/vaccines/recs/acip/default.htm)
  - ACIP web site
Resources for Providers

- Immunization Schedules
  www.cdc.gov/vaccines/recs/schedules/
  www.immunizationed.org (point of care details; smartphone apps)

- ACIP recommendations & provisional recommendations
  www.cdc.gov/vaccines/pubs/ACIP–list.htm
  www.cdc.gov/vaccines/recs/provisional/default.htm

- The Immunization Action Coalition
  www.immunize.org/

- The Guide to Community Preventive Services. Vaccine recommendations
  www.thecommunityguide.org/vaccines/index.html

- Assessment, Feedback, Incentives, and Exchange (AFIX)
  www.cdc.gov/vaccines/programs/afix/index.html

- Comprehensive Clinic Assessment Software Application (CoCASA)
  http://www.cdc.gov/vaccines/programs/cocasa/index.html

- National Foundation for Infectious Diseases
  www.nfid.org

- Vaccine Adverse Event Reporting System (VAERS)
  vaers.hhs.gov/professionals/index
“Knowing is not enough; we must apply,
Willing is not enough; we must do”
- Goethe
Three Ingredients For Success:

1. I Can
2. I Will
3. I Q
Summary

- Older adults are at high risk of influenza–associated morbidity and mortality
- There are evidence–based ways to improve influenza vaccine coverage
- Educate adults about recommended vaccines
  - Address misconceptions and concerns about vaccine safety
  - Your recommendation makes a difference!
- Stay current with the immunization schedule and recommendations
- Establish an immunization champion in your practice
- Identify and address barriers
- Implement organizational and systems strategies
The Long Lost 11th Commandment:

“Thou shalt vaccinate!”

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