Considerations for Influenza Policy

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Objectives

• To understand the complexity of influenza vaccine policy
  • Unique characteristics of the vaccine
  • Delivery challenges
• To discuss tools and strategies that might facilitate better influenza prevention.
Why is delivering influenza vaccine so challenging?

- Influenza vaccine given every year.
- Influenza vaccine given on a seasonal schedule.
- Three different types of influenza vaccines licensed in US: TIV, LAIV, high-dose
- Vaccine supply and distribution: timing and availability of influenza vaccine uncertain.
- Need 2 doses in children the first year they receive vaccine.
- No vaccine licensed for children younger than 6 months
- Public perception.

Delivery challenges: low vaccination rates

CDC. Influenza Vaccination Coverage Among Children and Adults — United States, 2008–09 Influenza Season. MMWR 2009;58:1091-5

Goal: To prevent influenza virus infection and its complications

Need to consider factors related to disease, vaccine and implementation.

- Disease burden.
  - Absolute measure.
- Vaccine effectiveness
  - Relative measure.
- Vaccine safety
- Cost-effectiveness.
- Vaccine supply.
- Feasibility of sustained implementation.


*Preliminary data from 2007-08 influenza season
How can improved influenza prevention be accomplished?

• New strategies (e.g. higher coverage)
• New tools (e.g. better vaccines)
Evolution of seasonal influenza vaccination recommendations

Pre-2000: Persons aged 65 or older
- Persons with chronic medical conditions that make them more likely to have complications of influenza
- Pregnant women in the second or third trimester
- Contacts (household and out of home caregivers) of the above groups
- Health care workers

2000: Adults 50 and older

2004: Children aged 6 through 23 months
- Contacts (household and out of home caregivers) of children aged 0 through 23 months
- Women who will be pregnant during influenza season

2006: Children aged 6 through 59 months
- Contacts (household and out of home caregivers) of children aged 0 through 59 months

2008: All children 6 months through 18 years, if feasible

2009: All children 6 months through 18 years

2010: All persons 6 months and older

Decision to vaccinate young children

- Influenza is a nonspecific clinical disease.
- Manifestations and impact vary by age and risk group.
  - Youngest children at highest risk for serious disease.
  - Older children have significant outpatient illness, antibiotic use, missed school.
- Deaths are rare in children, but do occur.
- Efficacy is moderate in the youngest age groups.
Number of days from influenza onset until influenza-associated death: United States, 2004-2007

### New Recommendations, 2004-2006
**Advisory Committee on Immunization Practices**

<table>
<thead>
<tr>
<th>Program</th>
<th>Age Group</th>
<th>$/QALY*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td>Infants</td>
<td>Cost saving</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Adolescents</td>
<td>20,000</td>
</tr>
<tr>
<td>HPV</td>
<td>Adol girls</td>
<td>24,000</td>
</tr>
<tr>
<td>Influenza</td>
<td>2-4 yrs, non-high-risk</td>
<td>25,000</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>2 yrs</td>
<td>27,000</td>
</tr>
<tr>
<td>Varicella 2nd dose</td>
<td>5 yrs</td>
<td>105,000</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Adolescents</td>
<td>126,000</td>
</tr>
</tbody>
</table>

*Converted to 2003 dollars

*Presented at ACIP meetings 2006-07

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### Influenza vaccination recommendations — 2007

- Annual vaccination against influenza is specifically recommended for:
  - Persons at increased risk for severe complications (hospitalizations and death) from influenza.
    - Risk groups added as evidence became available — pregnant women, children aged 6-23 months, children with neurologic disorders.
  - “Or at higher risk for influenza-associated clinic, emergency department or hospital visits” (MMWR 2007):
    - Children through 4 years of age.
  - Persons who live with or care for persons at high risk of complications from influenza.
- Routine vaccination is also “permissive” for the general population.

*Presented at ACIP meetings 2006-07*
Limitations of risk-based recommendations

- The recommendations are complicated.
- Risk groups can be difficult to remember — in 2007, there were 12 specific influenza vaccination target groups.
  - More difficult for health care providers to identify patients by risk than by age.
  - More difficult for patients to self-identify based on risk conditions.
  - Coverage levels among the target groups vary, but in general are low.

Gulf Between Recommendations and Reality

- 220 million persons (73% of the population) should get vaccinated annually
- Fewer than 100 million get vaccinated

*Presented at ACIP meetings 2006-07
Potential Time-Frame for Modifying Influenza Vaccination Recommendations*

- **2007-2008**: Consider expanding recommendations to include school-age children
- **2010-2011**: Consider expansion of recommendations to include household contacts and caregivers of school-aged children
- **2012-2013**: Consider expansion to universal vaccination

*Presented to ACIP meetings 2006-07

Summary: Vaccinating school-age children against influenza*

- **Vaccine supply**: Adequate and improving, although local distribution issues remain problematic.
- **Vaccine safety**: Established, but need for continued vigilance and long-term studies.
- **Cost effectiveness**: Higher than many currently-recommended vaccines, but models do not fully account for potential indirect effects.
- **Disease burden**: Highest rates of influenza, but severe outcomes less common than in older or younger age groups.
- **Vaccine effectiveness**: Effective in reducing influenza illness, and increasing evidence for indirect effects.
- **Feasibility of sustained implementation**: Uncertain, but comprehensive efforts to vaccinate this large cohort are not likely to be established until a recommendation is made.

Based on CDC/CSTE consultation, September 2007.

*Presented at February 2008 ACIP meeting.
2008: Universal pediatric recommendation

Highlights of 2010 Influenza Vaccine Recommendations

- Influenza vaccine recommended for all persons 6 months and older
- Number of doses needed in children 6 months through 8 years
- Licensure of High-Dose Fluzone
Risk factors for complications of or severe illness with 2009 H1N1 virus infection

Healthcare Personnel Influenza Vaccination

- Prevent transmission to patients
  - Transmission of influenza in HC settings occurs; vaccination of patients and HCP reduces risk
  - Vulnerable populations with suboptimal response to vaccine
- Reduce risk that HCP will be infected with influenza
- Maintain critical workforce
- Set an example for the importance of vaccination for every person

New “tools” are needed

• Efficacy
  • Suboptimal, particularly in young children, elderly, immunocompromised

• Limited cross-protection
• Annual administration
• Cumbersome manufacturing process
• Supply and distribution

But translating to policy could be complicated…LAIV vs TIV

Laboratory-confirmed influenza illness by vaccine type, 6-59 months

Efficacy of influenza vaccine in young, healthy college students, 2007-2008

How do we protect children younger than 6 months? Effectiveness of maternal influenza immunization in mothers and infants

- Study participants and design:
  - Bangladesh, 2004-05.
  - Randomized controlled trial.
  - 340 pregnant women received either influenza vaccine or pneumococcal polysaccharide vaccine (control) during third trimester.
  - Follow-up through pregnancy and first 6 months after birth.

- Outcomes:
  - Febrile respiratory illness among infants and mothers.
  - Lab-confirmed influenza among infants.
Influenza vaccine reduced disease in mothers and babies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Episodes</th>
<th>Clinical Effectiveness (95% CI)</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Influenza Vaccine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Person-months</td>
<td>870</td>
<td>881</td>
</tr>
<tr>
<td>Infants:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any fever</td>
<td>151</td>
<td>110</td>
<td>-281 (-3.6 to 50.6)</td>
</tr>
<tr>
<td>Temperature &gt;58°C</td>
<td>77</td>
<td>56</td>
<td>-281 (-3.6 to 50.6)</td>
</tr>
<tr>
<td>Diarrheal disease</td>
<td>118</td>
<td>159</td>
<td>-281 (-3.6 to 50.6)</td>
</tr>
<tr>
<td>Clinic visit</td>
<td>92</td>
<td>54</td>
<td>-281 (-3.6 to 50.6)</td>
</tr>
<tr>
<td>Influenza test ordered</td>
<td>79</td>
<td>41</td>
<td>40.7 (29.4 to 64.7)</td>
</tr>
<tr>
<td>Influenza test positive</td>
<td>16</td>
<td>6</td>
<td>42.8 (9.0 to 86.4)</td>
</tr>
<tr>
<td>Mothers:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any fever</td>
<td>77</td>
<td>50</td>
<td>-35.8 (-37.7 to 57.2)</td>
</tr>
<tr>
<td>Temperature &gt;58°C</td>
<td>31</td>
<td>19</td>
<td>45.1 (-9.0 to 70.3)</td>
</tr>
<tr>
<td>Diarrheal disease</td>
<td>60</td>
<td>49</td>
<td>19.3 (-24.6 to 47.8)</td>
</tr>
<tr>
<td>Clinic visit</td>
<td>25</td>
<td>19</td>
<td>24.9 (-43.9 to 60.8)</td>
</tr>
</tbody>
</table>

High-dose influenza vaccine in adults 65 years and over

- A multicenter, randomized, double-blind controlled study was conducted to compare HD vaccine (which contains 60 mcg of HA per strain) with the licensed standard-dose (SD) vaccine (which contains 15 mcg HA per strain) in adults 65 years of age.
- HD vaccine was administered to 2575 subjects, and SD vaccine was administered to 1262 subjects.
- The immunogenicity of HD vaccine was assessed in terms of rates of seroconversion and ratio of GMTs for each virus strain, relative to the values obtained for the SD vaccine.
**Table 2. Comparison of responses to high dose (HD) and standard dose (SD) influenza vaccine.**

<table>
<thead>
<tr>
<th>Response, by antigen</th>
<th>HD vaccine recipients* (n = 2576)</th>
<th>SD vaccine recipients* (n = 1276)</th>
<th>HAI GMT 95% CI</th>
<th>HAI GMT ratio for HD and SD vaccine, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMTH1N</td>
<td>Day 0: 2963 29.5 (27.4–29.7)</td>
<td>Day 0: 1287 29.4 (27.3–31.1)</td>
<td>1.01 (0.96–1.06)</td>
<td></td>
</tr>
<tr>
<td>GMTH2N</td>
<td>Day 28: 2963 67.3 (63.7–71.1)</td>
<td>Day 28: 1287 67.3 (63.7–71.1)</td>
<td>1.01 (0.96–1.06)</td>
<td></td>
</tr>
</tbody>
</table>

**Vaccine efficacy of adjuvanted TIV against all strains and vaccine matched strains in Year 2 (6 to < 72 month old subjects)**


Summary

• Influenza causes substantial morbidity and mortality in many different populations; vaccine is cornerstone of influenza prevention

• Vaccine efficacy is only one of many considerations in making policy decisions
  • Burden of disease is critical
  • Absolute as well as relative prevention is important
  • Practical considerations

• The landscape of influenza vaccine development is rapidly evolving; policymakers will also need to be flexible