Influenza Vaccines: Pandemic, Seasonal, and Novel

23 February 2010

Frederick G. Hayden, M.D.
University of Virginia, Charlottesville, VA
and
Wellcome Trust, London, UK

Influenza Vaccines: Outline

• Pandemic H1N1
  – Immunogenicity
• Seasonal Vaccines
  – Intranasal, live-attenuated
  – Pregnancy
  – Universal immunization
  – Enhancing immunogenicity in elderly
• Novel vaccines
  – New antigens/adjuvants, delivery methods, and production technologies

Approved Influenza Vaccines

Whole virus  Split virus  Subunit (surface antigen)  Live attenuated
Circulation of Influenza A(H1N1) Viruses

Zimmer and Burke. NEJM 361:279, 2009

Neutralizing Antibody Titers against Pandemic H1N1 Virus according to Birth Decade

Hancock et al. NEJM 361; published 10 Sept 2009
Serologic Responses to A/New Jersey/8/79 (H1swN1) WV Vaccine

- Age (= prior exposure to H1N1 viruses) and, for unprimed, antigen dose were key variables in responding.


A Novel Influenza A (H1N1) Vaccine in Various Age Groups

- Single 15 μg dose of nonadjuvanted vaccine resulted in HAI titer ≥1:40 in
  - 74.5% of subjects between 3 and 11 yrs
  - 97.1% of subjects between 12 and 17 yrs
  - 97.1% of subjects between 18 and 60 yrs
  - 79.1% of subjects 61 yrs or older
- Alum adjuvant associated with poorer responses and more local reactogenicity

Zhu et al. NEJM, published 21 October 2009

Immunogenicity of Single Doses of Non-Adjuvanted Pandemic H1N1 Vaccine

<table>
<thead>
<tr>
<th>Group, age range</th>
<th>7.5 ug</th>
<th>15 ug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults, 18-60/64 yrs</td>
<td>90-95%</td>
<td>94-96%</td>
</tr>
<tr>
<td>Adults, &gt; 61/65 yrs</td>
<td>80-94%</td>
<td>79-93%</td>
</tr>
<tr>
<td>Children, 10/12-17 yrs</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>Children, 3-4/11 yrs*</td>
<td>69-77%</td>
<td>75-86%</td>
</tr>
<tr>
<td>Children, 6-35 mo*</td>
<td>45%</td>
<td>50-88%</td>
</tr>
</tbody>
</table>

*Low responses (25-36%) to single 15 μg doses in preliminary US study

Immunogenicity of Non-Adjuvanted, Egg-Grown Pandemic H1N1 Vaccine in Adults

Greenberg et al. NEJM, online 10 September 2009

ACIP Guidelines – Pandemic H1N1 Vaccine

• Recommended initial target groups:
  – Pregnant women
  – Individuals who live with or care for infants aged < 6 months (parents, sibs, daycare providers)
  – Health care and emergency medical services personnel
  – Individuals aged 6 months through 24 years of age
  – Adults aged 25 through 64 with health conditions associated with an increased risk of medical complications from influenza

http://www.cdc.gov/h1n1flu/vaccination/acip.htm
Black et al. Lancet, published online 31 October 2009

Based on USA 2003 population and using probabilistic modeling, annual influenza epidemics cause an average of:

- 610,660 life-years lost
- 3.1 million hospitalized days + 31.4 million outpatient visits
- Direct medical costs - $10.4 billion (95% CI, $4.1, $22.2)
- Projected lost earnings due to illness and loss of life - $16.3 billion (95% CI, $8.7, $31.0)
- Total economic burden using projected statistical life values - $87.1 billion (95% CI, $47.2, $149.5)


World Health Organization

Recommended viruses for influenza vaccines for use in the 2010-2011 northern hemisphere influenza season

February 2010

It is recommended that the following viruses be used for influenza vaccines in the 2010-2011 influenza season (northern hemisphere):
- an A/California/7/2009 (H1N1)-like virus;
- an A/Perth/16/2009 (H3N2)-like virus;
- a B/Brisbane/60/2008-like virus.

# A/Wisconsin/5/2009 is an A/Perth/16/2009 (H3N2)-like virus and is a 2010 southern hemisphere vaccine virus

The annual impact of seasonal influenza in the US: Measuring disease burden and costs

Necole-Angelique M. Molinari et al.

- Based on USA 2003 population and using probabilistic modeling, annual influenza epidemics cause an average of:
  - 610,660 life-years lost
  - 3.1 million hospitalized days + 31.4 million outpatient visits
  - Direct medical costs - $10.4 billion (95% CI, $4.1, $22.2)
  - Projected lost earnings due to illness and loss of life - $16.3 billion (95% CI, $8.7, $31.0)
  - Total economic burden using projected statistical life values - $87.1 billion (95% CI, $47.2, $149.5)
ACIP Guidelines—2009-2010
Seasonal Influenza Vaccination

• No changes in adult vaccination recommendations since last year
• Vaccinate all children aged 6 months through 18 years.
• Preference should be given to children aged 6 to 59 months and older children with underlying medical conditions at higher risk of complications.
  – 2 doses are critical for children aged 6 months to 8 years being vaccinated for the first time.

CDC. [press release]. February 27, 2008.

Vaccine Coverage Remains Low in the United States, Even in Priority Groups


Mandatory Influenza Vaccination of Health Care Workers: Translating Policy to Practice

• Introduction of mandatory immunization during 2008-09 season in large healthcare system.
• 25,561 (98.4%) of 25,980 active employees were vaccinated.
  – 0.3% received religious exemptions.
  – 1.2% received medical exemptions.
  – Eight employees (0.03%) were not vaccinated or exempted → termination.
Recent Seasonal Influenza Vaccine Studies

- Intranasal LAIV is superior to TIV in children (Belshe et al NEJM 356:685, 2007) but less effective than TIV in adults aged 18-49 yrs. (Monto et al. NEJM 361:13, 2009)
- Maternal immunization reduces influenza in infants + febrile ARI in mothers. (Zaman et al. NEJM 359, 2008)
- Universal vaccine program in Ontario reduced influenza-associated mortality, hospitalizations, healthcare visits, and antibiotic use by 40-60% compared to other provinces. (Kwong et al. CID 49:750, 2009)

Comparative Efficacy of Inactivated and Live Attenuated Influenza Vaccines

- Randomized, blinded study of LAIV vs TIV in 1952 subjects, 2007-2008 season (predominately H3N2)
  - Healthy adults aged 18-49 yrs
- Efficacies for laboratory-proven influenza illness:
  - 68% (95% CI, 46 to 81%) for TIV
  - 36% (95% CI, 0 to 59%) for LAIV
- Relative efficacy difference of 50% (95% CI, 20 to 69%)

Effectiveness of Maternal Influenza Immunization in Mothers and Infants

- Study 340 pregnant women, Bangladesh, 2004-5
  - Randomized to TIV or 23-valent pneumococcal vaccine
  - Followed to 24 weeks post delivery
- Vaccine effectiveness:
  - Laboratory-confirmed influenza in infants = 63% (95% CI, 5 to 85%).
  - Febrile respiratory illness in infants = 29% (95% CI, 7 to 46%)
  - Febrile respiratory illness in mothers = 36% (95% CI, 4 to 57%)
The Effect of Universal Influenza Immunization on Mortality and Health Care Use

• Universal influenza immunization program since 2000 in Ontario
• Outcomes: hospitalizations, ED and physician visits for P+I and of all-cause mortality 1997-2204
  – Comparisons of changes pre-post between Ontario and other provinces
  – Vaccine uptake from 1996 to 2005 increased in Ontario (18→38%) and other provinces (13→24%).

Effect of Universal Influenza Immunization Program (UIIP) in Ontario

• After UIIP, influenza-associated mortality decreased more in Ontario than in other provinces (relative ↓39%, p = 0.002).
• Similar differences between Ontario and other provinces were observed for influenza-associated
  • Hospitalizations (relative ↓42%, p < 0.001)
  • ED use (relative ↓55%, p < 0.001),
  • MD office visits (relative ↓59%, p < 0.001)
  • Antimicrobial use (relative ↓64%)


Mortality benefits of influenza vaccination in elderly people: an ongoing controversy

• 13 influenza H3N2 seasons
• ~1 influenza death per 1,000 elderly each season
• ? Frail elderly selection bias → less often immunized
Retrospective analysis of outcomes in community-dwelling elderly (≥ 65 yr) from 1990-2000 seasons
- 18 pooled cohorts from three HMOs in USA
- 713,872 person-years of observation

Primary outcomes were P&I hospitalizations (0.6-0.7% per season) and all-cause mortality (1.0-1.6% per season)
- Adjusted logistic regression analysis

Nichol et al. NEJM 357:1374, 2007

Vaccine effectiveness during season for
- P & I hospitalization = 27% reduction (adjusted OR = 0.73; 95% CI, 0.68 to 0.77)
- All-cause mortality = 48% reduction (adjusted OR = 0.52; 95% CI, 0.50 to 0.55)

Mortality benefit varied with season and match between vaccine and circulating A/H3N2 strain
- 37% reduction in 2 seasons of poor match
No evidence for healthy vaccinee bias in non-influenza periods.

Nichol et al. NEJM 357:1374, 2007

1173 cases and 2346 controls (aged 65–94 yr) enrolled in a Seattle HMO during 2000 – 02.
- Cases: those with outpatient or inpatient CAP episode
- Chart review to determine “frailty” status and adjusted for “pre-influenza” period
- Outcome: reduction in hospitalizations for X-ray confirmed pneumonia = 8% (95% CI, -10%; 23%)

By flow cytometry and intracellular cytokine staining of myeloid DCs (mDCs) and plasmacytoid DCs (pDCs), substantial ↓ in older compared with young individuals in TNF-α, IL-6, and/or IL-12 (p40) production in mDCs and in TNF-α and IFN-α production in pDCs in response to TLR stimuli. Defects in cytokine production were strongly associated with poor Ab responses to influenza immunization.

Strategies for Increasing Protection by Influenza Vaccines in Elderly

- Repeat same-season immunization - ineffective
- Increase immunogenicity of HA-based vaccines
  - Increase dose of HA antigen
  - Combination TIV + intranasal LAIV
  - Intradermal delivery
  - Adjuvants
    - Oil-in-water adjuvants
    - Sublingual interferon – ineffective
- Conserved antigen vaccines (M2e, NP)
- Reduce risk of influenza exposure
  - Immunization of household and other contacts

Randomized, Double-Blind Controlled Phase 3 Trial Comparing the Immunogenicity of High-Dose and Standard-Dose Influenza Vaccine in Adults 65 Years of Age and Older

- Randomized comparison of 15 vs 60 ug HA doses in ambulatory adults ≥65 yrs old
- Seroprotection (serum HAI ≥ 1:40) for all [≥ 75 yrs]
  - A(H1N1): 77% vs 90% [22 vs 48%]
  - A(H3N2): 97% vs 99% [53 vs 68%]
  - B: 68% vs 79% [25 vs 48%]
- More frequent local pain with high dose
Comparative Immunogenicity of Standard and High Dose TIV in Ambulatory Elderly

<table>
<thead>
<tr>
<th>HAI antibody responses (day 28)</th>
<th>High dose (60 ug HA) recipients (N = 2,576)</th>
<th>Standard dose (15 ug HA) recipients (N = 1,275)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM1</td>
<td>115.8</td>
<td>67.3</td>
</tr>
<tr>
<td>A/HIN2</td>
<td>608.9</td>
<td>332.5</td>
</tr>
<tr>
<td>B</td>
<td>69.1</td>
<td>52.3</td>
</tr>
<tr>
<td>% with HAI ≥ 1:40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/HIN1</td>
<td>89.9%</td>
<td>76.8%</td>
</tr>
<tr>
<td>A/HIN2</td>
<td>99.3%</td>
<td>96.5%</td>
</tr>
<tr>
<td>B</td>
<td>79.3%</td>
<td>67.6%</td>
</tr>
</tbody>
</table>

- Superiority in seroconversion rates for all 3 antigens (42-69% vs 23-51%) and in GMTs for 2 of 3 antigens
  Falsey et al. JID 200:174, 2009

Reactogenicity of Standard and High Dose TIV in Elderly

- No overall differences in systemic symptoms
  - Fever >38°C in 1.1% vs 0.3%
- Higher frequency of local pain with increased HA dose.
  Falsey et al. JID 200:174, 2009

Intradermal Influenza Vaccine Administered Using a New Microinjection System Produces Superior Immunogenicity in Elderly Adults: A Randomized Controlled Trial

- 1107 volunteers aged > 60 yrs randomized to intradermal TIV (15 or 21 ug HA per strain) or IM (15 ug) vaccine
- Seroprotection rates, seroconversion rates, and mean titer increases were superior for intradermally administered vaccine.
  Holland et al. JID 198:650, 2008
Immunogenicity of Candidate H5N1 Vaccines

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Adjuvant</th>
<th>HA dose (ug)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>rHA (baculovirus)</td>
<td>0</td>
<td>90</td>
<td>Treanor, 2001</td>
</tr>
<tr>
<td>Subvirion (eggs)</td>
<td>0</td>
<td>90</td>
<td>Treanor, 2006</td>
</tr>
<tr>
<td>Subvirion (eggs)</td>
<td>Alum</td>
<td>&gt;30</td>
<td>Bresson, 2006, Bernstein, 2008</td>
</tr>
<tr>
<td>Subvirion (eggs)</td>
<td>ASO3</td>
<td>3.8</td>
<td>Leroux-Roels, 2007</td>
</tr>
<tr>
<td>Whole virus (eggs)</td>
<td>Alum</td>
<td>10</td>
<td>Lim, 2006</td>
</tr>
<tr>
<td>Whole virus (Vero)</td>
<td>0</td>
<td>7.5</td>
<td>Ehlin, 2008</td>
</tr>
</tbody>
</table>

*Dose required to reach serologic endpoint. Endpoint varied by study.

Duration of Cross-Clade Antibody to ASO3-Adjuvanted Clade 1 H5N1 Vaccine

Duration of seroconversion rate and neutralizing antibodies following vaccination with ASO3-adjuvanted clade 1 H5N1 vaccine. Seroconversion was defined as a 4-fold increase in antibody titer. Neutralizing antibodies were measured using the 50% plaque reduction neutralization test (PRNT50).

Duration of Cross-Clade Antibody to ASO3-Adjuvanted Clade 1 H5N1 Vaccine

Potential Uses of H5N1 Vaccines


- Prototype pandemic vaccine
- True pandemic vaccine
### Examples of Investigational Influenza Vaccines

- Baculovirus-derived HA*
- Baculovirus* and lentivirus-derived virus-like particles*
- NS1-protein deleted (∆NS1)* and M2 tail deleted LAIV
- Vectored vaccines
  - DNA plasmids (gold particles, liposomes)*
  - Recombinant adenovirus [oral, intranasal]*
  - Vaccinia
- M2e vaccines (flagellin* and NP+ISS conjugates)
- Transdermal heat-labile enterotoxin (LT) patch*
- Nanoemulsion-adjuvanted inactivated nasal vaccines
- Production substrates- mammalian cells*, plants, fungi

*Clinical studies in progress

---

**DNA vaccination protects against an influenza challenge in a double-blind randomized placebo-controlled phase 1b clinical trial**

- Jennie Jones*, Kristen Evans*, 易丽宏* (Johns Hopkins), Ruth Lawrence, William* (Johns Hopkins), Julia Mori*, Maria Zamboni*, Joanna Ede*, John Read*, Peter F. Landers**

- 3 plasmids for HAs + plasmid for A + B subunits of *E. coli* heat labile enterotoxin as DNA adjuvant
  - Dose of 2 ug + adjuvant or 4 ug delivered by PMED™ (particle mediated epidermal delivery)
  - HAI antibody responses to 2 of 3 influenza HAs
- Laboratory confirmed influenza illness in 61.5% of placebo, 50% of 2ug, and 33.3% of 4ug subjects.
  - 4 ug dose with efficacy of 44% (P = 0.06) and 75% ↓ in nasal virus AUC compared to placebo

---

**4th Meeting on Influenza Vaccines that Induce Broad Spectrum and Long-Lasting Immune Responses**

Contributors: Wellcome Trust and World Health Organization

Welcome Trust, Euston Road, London, UK: 9-10 Nov (Monday-Tuesday)

Influenza Vaccines: Comments

- Diversification of seasonal influenza vaccines by target population:
  - Intranasal LAIV for children
  - Standard TIV for adults
  - High-dose TIV for elderly
- Policy issues
  - Mandatory immunization of HCWs
  - Universal immunization
  - Interpandemic use of H5N1 vaccines
  - Healthcare reform and vaccine coverage