Improved Influenza Vaccines: Integrating Pandemic and Seasonal Uses

Arnold S. Monto
University of Michigan
School of Public Health
Ann Arbor, Michigan
USA

Public Health Research Agenda for Influenza
Stream 3. Minimizing the impact of influenza

Areas of focus:
- Assessment of disease burden
  - Disease burden for epidemic influenza (developing regions, morbidity & mortality by age and epidemiological settings)
  - Evaluating influenza vaccine preventable disease burden using, for example vaccine demonstration projects
  - Using disease burden data for health resource utilization planning
- Pharmacological interventions to reduce impact of disease
  - Development of new-generation vaccines (immunogen design, new formulation, use of adjuvants)
  - Evaluation of vaccines (innovative clinical trial designs)
  - Increased global vaccine production capacity
  - Identification of correlates of protection
- Public health policies to reduce impact of disease
  - Best practices for under-resourced countries
  - Social, ethical and legal considerations in public health policies development

Topics Covered in Previous Meetings
1. Influenza vaccine design
   1.1 Novel influenza vaccines for antigen sparing and enhancement of immune response
   1.2 Vaccine delivery and approaches to vaccination
2. Influenza vaccine production
3. Influenza vaccine safety and regulation
4. Vaccine evaluation
5. Vaccine impact
6. Influenza disease burden
7. Influenza vaccine policy and implementation

Specific Needs in Vaccine Design
- Defining of minimal requirement for efficacy of novel vaccines
  - Are we preventing symptomatic infections?
  - Are we modifying disease expression?
- Defining immune targets of immunization, i.e. enhancing CD8 T cell responses for heterosubtypic immunity
- Assessing applicability of animal study results to humans
  - Can animal models of influenza prevention or treatment be improved?
Specific Needs in Vaccine Design – Continued

- Developing the ability to compare efficacy of one vaccine to another, avoiding the need in each case of large efficacy studies
  - Correlates of protection – how acceptable are they and can new ones be standardized for novel vaccines?
- Determining the effect on efficacy of different virus specific components
  - Efficacy trials will have to be carried out for any novel vaccine
  - Will traditional outcomes be appropriate?
- Examining regulatory pathways to facilitate licensure of successful candidate vaccines
  - New standards will have to be developed
- Will different vaccines be used for different population groups?

Integrating the Needs: Seasonal

- Our current seasonal influenza vaccines need to be improved; the PCR test has made it simple to identify failures
- Antigen sparing is not an issue. High dose vaccines being used.
- Match between vaccine and circulating strains remains a question, particularly in certain tropical regions. Broad response an advantage.
- Duration of protection and waning of immunity an issue. Longer duration of protection important.

Vaccine Effectiveness Studies with Virologic Outcomes

US Flu VE Network: Five Study Sites and Principal Investigators

Lisa Jackson
Mike Jackson
Ed Belongia
Arnold Monto
Suzanne Ohmit
Rick Zimmerman
Patricia Nowalk
Manju Gaglani
Adjusted1 Vaccine Effectiveness by Age Group, US Flu VE Network 2011-2012

Adjusted1 Vaccine Effectiveness by Influenza Type, A Subtype and B Lineage, US Flu VE Network 2011-2012

Adjusted Vaccine Effectiveness Against Influenza A/H3N2 by VE Network, 2011-2012

1: Models were adjusted for network center, subject age in months, sex, race/ethnicity categories, presence of high-risk health conditions, self-rated health status, time (days) between illness onset and specimen collection, and calendar time.


Influenza Vaccine Effectiveness by Type/Subtype and Year, US Flu VE Network 2009-2014

Models were adjusted for network center, subject age in months, sex, race/ethnicity categories, presence of high-risk health conditions, self-rated health status, time (days) between illness onset and specimen collection, and calendar time.


Jackson et al. MMWR 2013;62:119-23

Flannery et al. MMWR 2014;63:137-42


Castilla et al. Euro Surveill 2013;18:20388


Kelly et al. Influenza Other Respir Virus 2012;7:729-37

2009-10 2010-11 2011-12 2012-13

A H1N1 A H3N2 B

United States IMOVE-UK IMOVE-Spain IMOVE-Multicenter Canada Australia
Network Results 2011-2012

Adjusted1 Vaccine Effectiveness by Prior and Current Vaccination Status Among Subjects ≥9 years, US Flu VE Network 2011-2012

Vaccine Effectiveness (%)

Vaccinated 2011-2012 Only
Vaccinated 2011-2012 and 2010-2011
Vaccinated 2010-2011 Only
Unvaccinated

1: Models were adjusted for network center, subject age in months, sex, race/ethnicity categories, presence of high-risk health conditions, self-rated health status, time (days) between illness onset and specimen collection, and calendar time.

Reference

Mean Log2 HAI Titer of Subjects by Combined Vaccination Status in the 2011-2012 and 2012-2013 Seasons

Antigen

H1
H3
B Yam
B Vic

Integrating the Needs: Seasonal

- Our current seasonal influenza vaccines need to be improved, with the PCR test making it simple to identify failures
- Antigen sparing is not an issue. High dose vaccines being used.
- Broad response an advantage, especially in areas with different seasonality.
- Duration of protection and waning of immunity an issue. Longer duration of protection important.
- Correlates of failure are being developed

Geometric Mean HAI Titer of Placebo Cases and Non-Cases

Ohmit et al. J. Infect Diseases 2011;204:1879
Integrating the Needs: Pandemic

- The A(H5N1) threat focused attention on the need for broad immunity and long duration.
- Use of adjuvants in various ways a result; regulatory pathways developed.
- Heterosubtypic immunity and need to stockpile limited to pandemics. How to accomplish?
- Can vaccines produced for modification of disease be used for seasonal influenza?
Adjuvanted vaccine has proven broad immunity
Persistence of cross-reactive neutralizing antibodies Seropositivity (%) Human data

- Induce a broad cross clade and persistent immune responses
- Effective at very low antigen doses

**Adjuvanted H5N1/Vietnam vaccine prevents death from H5N1/Vietnam infection in ferrets**
- 2 immunizations on days 0 and 21 (Split virus H5N1 / AS)
- Homologous challenge (wild-type A/Vietnam, 10^7 TCID₅₀) on day 49

<table>
<thead>
<tr>
<th>Dose (µg)</th>
<th>Dead</th>
<th>Alive</th>
<th>% protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.8µg AS</td>
<td>3.8µg + AS</td>
<td>3.8µg + AS</td>
<td>3.8µg + AS</td>
</tr>
<tr>
<td>5 µg H5N1 – AS</td>
<td>0</td>
<td>6</td>
<td>100.00</td>
</tr>
<tr>
<td>15 µg H5N1 – AS</td>
<td>0</td>
<td>6</td>
<td>100.00</td>
</tr>
<tr>
<td>0.6 H5N1 – AS (saline or AS alone)</td>
<td>10</td>
<td>1</td>
<td>9.09</td>
</tr>
<tr>
<td>0.6 H5N1 – AS</td>
<td>1</td>
<td>4</td>
<td>66.67</td>
</tr>
<tr>
<td>1.7 µg H5N1 – AS</td>
<td>1</td>
<td>4</td>
<td>80.00</td>
</tr>
</tbody>
</table>


Conclusions

- Certain vaccine approaches will be suitable for seasonal use; some for pandemic use, some for both. How many approaches can be sustained?
- It will continue to be a problem to estimate the impact of vaccines for use only in pandemics. Correlates and animal studies will help.
- Randomized trials will continue to be necessary for novel seasonal regulatory approval. Are placebo controlled trials possible?
- What is the role of observational studies?
- How do we prioritize selection of approaches short of large-scale trials in humans?

Topics Covered in Previous Meetings

1. Influenza vaccine design
   1.1 Novel influenza vaccines for antigen sparing and enhancement of immune response
   1.2 Vaccine delivery and approaches to vaccination
2. Influenza vaccine production
3. Influenza vaccine safety and regulation
4. Vaccine evaluation
5. Vaccine impact
6. Influenza disease burden
7. Influenza vaccine policy and implementation