Improved/Universal Influenza Vaccine Prospects

Robert C Huebner, PhD
Branch Chief, Influenza Division
Biomedical Advanced Research and Development Authority (BARDA)
• Significant annual morbidity and mortality
  — Globally 3-5 million severe illnesses and 0.25-0.5 million deaths

• Groups at high risk of severe disease
  — Very young and very old
  — Chronic underlying cardio-pulmonary disease
  — Pregnant women
  — Immuno-compromised

• Vaccination is the cornerstone of prevention
  — Seasonal vaccines are reported to have 50%-70% efficacy in the general population
  — Global shortfall of vaccine supply for a pandemic
## Estimated Effectiveness of Current Influenza Vaccines (US)

<table>
<thead>
<tr>
<th>Season</th>
<th>Overall Adjusted Vaccine Effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 – 2012#</td>
<td>47% (36 to 56)</td>
</tr>
<tr>
<td>2012 – 2013*</td>
<td>56% (47 to 63)</td>
</tr>
<tr>
<td>2013 – 2014+</td>
<td>61% (52 to 68)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Season</th>
<th>Strain</th>
<th>Age Group</th>
<th>Vaccine Effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 – 2012#</td>
<td>A(H3N2)</td>
<td>18 – 49</td>
<td>33% (-5 to 57)</td>
</tr>
<tr>
<td></td>
<td>A(H3N2)</td>
<td>50 – 64</td>
<td>39% (-13 to 67)</td>
</tr>
<tr>
<td></td>
<td>A(H3N2)</td>
<td>&gt;9; Vaccinated prior to 2010-2011 only</td>
<td>-8% (-69 to 30)</td>
</tr>
<tr>
<td>2012-2013*</td>
<td>A(H3N2)</td>
<td>≥65</td>
<td>9% (-84 to 55)</td>
</tr>
</tbody>
</table>

* Interim adjusted estimates Feb 22, 2013 CDC *MMWR*
* Mid-season adjusted estimates Feb 21, 2014 CDC *MMWR*
Universal Influenza Vaccines

- **What is a “universal vaccine”***?
  - Idealized vaccine: single vaccine for any influenza A subtype
- **Could be used for several seasons**
  - Remove annual ‘guesswork’ for strain selection
  - Reduce production costs
  - Eliminate vaccine mismatches
  - Reduce potential for vaccine shortages
  - Increase global availability of vaccine
- **Stockpile of vaccine for epi/pandemics**
- **Year round production**
Universal Influenza Vaccine Target Characteristics

• **Vaccine Target:** All influenza A subtypes
  — Nasal > intramuscular > intradermal administration
  — Low antigen dose - safe and effective

• **Duration of response**
  — Single dose: annually < biannually < decennially

• **Target endpoint of efficacy with increased effectiveness?**
  — Reduction in morbidity and mortality in all groups
    • Reduction in spread of disease

• **Population targeted**
  — < 6mo – 85+ years of age
Nonstructural Proteins: infected cells
Highly conserved. Induces CMI. Reduce severity?

HA: surface, immunodominant
Highly variable head (shift, drift) conserved stem

NA: surface, immunogenic
Variable, slower drift

M2e: surface, immunogenic??
Fairly conserved. Ab-mediated. Protective? Reduce severity?

NP (nucleoprotein): internal
Highly conserved. Induces CMI. Reduce severity?

Matrix: internal
Highly conserved. Induces CMI.
### Dynamic Improved/Universal Influenza Vaccine Landscape

#### Protein Based
- **Chimeric HA Stalk Vaccine**
- **M2e Conjugatable Adjuvant Lipid Vesicle**
- **Computationally Optimized Broadly Reactive Antigen (COBRA)**
- **Self assembling nanoparticle**
- **Headless HA in VLP**
- **M2e-VLPs**

#### Vectors/ Adjuvant
- **MVA Vector with M2e**
- **PanAd3 Vector with M1 and NP**
- **MVA Vector with HA and NP**
- **MVA Vector with NP and M1**
- **DNA Vaccine construct with HA, NA, M2e-NP**
- **DNA prime + TIV boost**

#### DNA
- **Cationic lipid-DNA complex**
- **Nanoemulsion T-cell vaccine**
- **Fluorocarbon-linked conserved influenza peptide set T-cell vaccine**

*No Phase 3 or Market Approved universal influenza vaccines*
• Grounds for optimism
  — Discovery work over the past decade has advances in our understanding of influenza identifying a number of vaccine candidates that could contribute improved influenza vaccines
  — New adjuvants, vectors and industrialized expression systems have created further opportunities for the development of new influenza vaccines
  — This has stimulated the influenza vaccine development field with almost 100 products/candidates in the development landscape for influenza vaccines

• About a quarter of these candidates are designed to be improved or universal influenza vaccines
Grounds for Pessimism

- A lot of improved or universal influenza vaccine projects rely on a single technology
- Many projects are in early/pre-clinical development
- The regulatory pathway for influenza vaccines with novel mechanisms of action is unknown
- Large scale multi-year efficacy trials will likely be required
  - Three populations
- Funding is limited
  - Each promising candidate could cost up to $400M USD for development
What is needed for success

- Programs not projects
  - Combinations of technology that will result in the development of vaccines that stimulate broadened robust antibody, cellular and mucosal responses to influenza viruses
- New ways to evaluate and regulate these vaccines
  - Human challenge
  - New surrogates of immunity need to be identified
  - Alternate potency/release assays will be needed
- Financial commitment
  - Full development of new vaccine candidates with novel mechanisms of action will cost $100M-$200M USD
  - Phase 3 testing of these candidates will likely take several years costing $100M-$200M USD

Technology for improved/universal influenza vaccines is ready

• BARDA is ready
  — FY2014
    • Working with DMID to bring a promising universal vaccine candidate to the clinic
    • Open BAA
    • Market Research
  — FY2015
    • 1st RFP
      — With funding make base awards for promising programs
  — FY2016 and beyond
    • Additional RFPs
      — With funding made additional base awards
      — Exercise options on promising programs
• Technical advances over the last decade have created the opportunity to develop improved influenza vaccines
  — Expression systems, vectors, adjuvants, etc.
• Advances in our understanding of influenza have identified a number of vaccine candidates that could contribute improved influenza vaccines
• Improved/Universal influenza vaccine licensure will require a well planned campaign that addresses the technical, clinical and regulatory challenges of improved influenza vaccine advanced development
• A combination strategy will have the best chances of achieving our goals for improved influenza vaccines
Are You (and Your Team) Ready and Interested?

• Contact information
  Robert C Huebner, Ph.D.
  Improved/Universal Vaccine Branch Chief
  Phone 202-260-1179
  Email: robert.huebner@hhs.gov

• [Website URL]
  – Information on the open influenza BAA
  – Information on setting up a TechWatch meeting with BARDA to discuss your technology
  – Information on this year’s BARDA Industry Day when posted
  • Planned for October 15th-17 in Washington DC