Towards a Universal Influenza Vaccine

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Key Facts

• Influenza virus first identified in the 1930s
• First influenza vaccine developed in 1945
• Human strains classified as types A, B, or C
  – Type A is the most common and usually most severe (18 HA; 9 NA)
    • Two groups based on sequence & structure. HAs associated with human infection:
      • Group 1: H1, H2, H5, H9
      • Group 2: H3, H7, H10
  – Type B can also cause epidemics, but tends to be milder
  – Type C viruses have never caused a large epidemic
Global Disease Burden

- 3-5 million cases of severe illness
- 250,000 to 500,000 deaths globally/year
- Industrialized countries, most influenza deaths occur in elderly
  - TIV effectiveness is as low as 9% in this population
- Severity of influenza may be higher in developing countries
- High mortality in children under 5
  - An estimated 28,000 to 111,500 child deaths due to causes attributable to influenza-associated acute lower respiratory infections

Prevention and Treatment

- Seasonal Vaccination
  - Conventional TIV (A group 1, A group 2, and B)
    - 50-70% in the overall population when vaccine strains and outbreak strains are well matched
  - LAIV
    - Tends to be more effective in children
    - Theoretical advantage over TIV because of delivery of more NA and M2 antigens, mucosal responses including IgA, and potential for induction of CD8 T cell responses
  - HA subunit
    - Produced by baculovirus
- Antivirals (NA inhibitors)
  - Short window of effectiveness
  - mAbs in development

Unmet Public Health Need

• Improved seasonal influenza vaccine-induced immunity
  – Magnitude or quality of response
  – Durability of protection extended beyond 1 year

• Development of a more universal influenza vaccine
  – Protection within subtype
  – Protection within HA group
  – Protection against all known HAs
  – Protection against future pandemic strains

• Limited if any influenza vaccine production capacity in the WHO African Region or the WHO Eastern Mediterranean Region

Influenza HA Diversity

Adapted from Volz, E.M. et al. (2013)
Degrees of Universality for Influenza Vaccine Concepts

Global Distribution of Influenza Vaccine

<table>
<thead>
<tr>
<th>Region</th>
<th>Populationa (百万)</th>
<th>Provided information on vaccine distribution, %</th>
<th>Doses of vaccine distributed</th>
<th>Increase from 1999b, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe</td>
<td>387,182,000</td>
<td>100</td>
<td>65,972,000</td>
<td>17</td>
</tr>
<tr>
<td>North America</td>
<td>306,148,000</td>
<td>100</td>
<td>81,200,000</td>
<td>–2</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>22,981,000</td>
<td>100</td>
<td>4,163,000</td>
<td>10</td>
</tr>
<tr>
<td>Subtotal</td>
<td>716,311,000</td>
<td>100</td>
<td>151,365,000</td>
<td>5</td>
</tr>
<tr>
<td>Central and eastern Europe</td>
<td>480,092,000</td>
<td>74</td>
<td>26,064,000</td>
<td>95</td>
</tr>
<tr>
<td>Latin America</td>
<td>522,353,000</td>
<td>84</td>
<td>24,991,000</td>
<td>29</td>
</tr>
<tr>
<td>Western Pacificd</td>
<td>1,696,937,000</td>
<td>95</td>
<td>26,877,000</td>
<td>41</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>1,555,081,000</td>
<td>83</td>
<td>64,000</td>
<td>231</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>518,602,000</td>
<td>73</td>
<td>998,000</td>
<td>23</td>
</tr>
<tr>
<td>Africa</td>
<td>672,176,000</td>
<td>23</td>
<td>2,409,000</td>
<td>10</td>
</tr>
<tr>
<td>Subtotal</td>
<td>5,457,210,000</td>
<td>78</td>
<td>81,200,000,000</td>
<td>48</td>
</tr>
<tr>
<td>World total</td>
<td>6,173,521,000</td>
<td>80</td>
<td>222,598,000</td>
<td>16</td>
</tr>
</tbody>
</table>

a Regions are those defined by the World Health Organization.
b Population data were obtained from the Division of Health Situation and Trend Assessment, World Health Organization [18].
c Data on vaccine distribution by all companies were gathered by Aventis Pasteur MSD and Aventis Pasteur.
d Excludes Australia and New Zealand.

Fedson D S Clin Infect Dis. 2003;36:1552-1561. © 2003 by the Infectious Diseases Society of America
Target Groups

- Pregnant women
- School age children
- Children aged 6 months to 5 years
- Elderly (≥65 years of age)
- Individuals with chronic medical conditions
- Health-care workers

Commercial Influenza Vaccine Research and Development (partial list)

**Quadrivalent Vaccine Manufacturers**
- MedImmune (FluMist)
- GlaxoSmithKline (GSK) (Fluarix) (also trivalent)
- Sanofi Pasteur (Fluzone) (also trivalent)
- Merck/CSL (Afluria) (also trivalent)
- ID Biomedical (FluLaval) (also trivalent)

**Trivalent and Cell-based Vaccine Manufacturers**
- Novartis (Flucelvax, Fluvirin, Agriflu)
- Protein Sciences Corp (Flublok)

**Vaccine Products in Various Research Stages**
- Alphavax
- Okairos
- GenVec
- Novavax
- Mymetics
- TechnoVax
- Mucosis
- Takeda
- AmiVac
- Visterra
- Inovio Pharmaceuticals
- Emergent BioSolutions
- VaxInnate
- Liquidia Technologies
- Aphios
- Baxter
- NanoBio Corp. (Merck)
- Southern Research Institute
- Vaxin, Inc.
- Sarepta Therapeutics
- Abbott Laboratories
- Scripps Research Institute
- Johnson & Johnson/Janssen/Crucell
## Vaccine Development: Animal Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Mouse</th>
<th>Ferret</th>
<th>Guinea Pig</th>
<th>NHP</th>
<th>Pig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reagent availability</td>
<td>Excellent</td>
<td>Poor</td>
<td>Good</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Ease/Cost of housing, breeding</td>
<td>Excellent</td>
<td>Poor</td>
<td>Good</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Infectable with human strains</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (less susceptible)</td>
<td>Yes</td>
</tr>
<tr>
<td>Visible clinical signs</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes (marmosets)</td>
<td>Yes</td>
</tr>
<tr>
<td>Transmissible</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Variable</td>
<td>Yes</td>
</tr>
<tr>
<td>Most useful for:</td>
<td>Screening immunogenicity, basic immunology</td>
<td>Transmission, symptom scores, treatment, vaccines</td>
<td>Transmissio n</td>
<td>Advanced vaccine immunogenicity</td>
<td>Transmission, pathology</td>
</tr>
<tr>
<td>Applicable disease severity, tissue tropism</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

## Vaccine Development: In Vitro Assays

### Serology
- Hemagglutination Inhibition (HAI)
- Microneutralization, pseudotyped lentivirus reporter
- ELISA (protein, region, or epitope specific)
- Phage display epitope mapping
- Avidity measurement by surface plasmon resonance
- NA or M2 specific assays

### T cell assays
- ELISpot
- Flow cytometry / intracellular cytokine staining (ICS)
- HAΔSA probes for B cell isolation and phenotyping
Vaccine Development: Endpoints for Licensure

- An advantage for influenza vaccine development is ability to license based on achieving a threshold HAI response.
- Otherwise a large field trial to prove efficacy is required. Complicated by need to include and control for available seasonal vaccines.

Targeting Viral Surface Glycoproteins

<table>
<thead>
<tr>
<th></th>
<th>RSV F</th>
<th>Flu HA</th>
<th>HIV-1 Env</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine-induced NT Ab</td>
<td>Easy (structure-dependent)</td>
<td>Easy (strain-specific)</td>
<td>Very difficult (even autologous)</td>
</tr>
<tr>
<td>Genetic diversity</td>
<td>Low</td>
<td>High</td>
<td>Very High</td>
</tr>
<tr>
<td>Glycosylation</td>
<td>Low</td>
<td>High</td>
<td>Very High</td>
</tr>
<tr>
<td>Conformational evasion</td>
<td>High</td>
<td>Low</td>
<td>Very High</td>
</tr>
<tr>
<td>Immunodominance</td>
<td>Minor</td>
<td>Major</td>
<td>Major</td>
</tr>
</tbody>
</table>
Universal Influenza Vaccine Options

• Improving current vaccines
  – DNA or LAIV prime with conventional boost
  – Novel adjuvant formulations

• Approaches to increase breadth
  – Consensus or chimeric HA head designs
  – Improved formulations and delivery of HA antigens (e.g. nanoparticle or VLP delivery)
  – Multi-valent or multi-epitope designs
  – Induce broadly neutralizing HA stem-specific antibodies
  – Use of NA or M2 antigens (ADCC)
  – Induction of CD8 T cell responses using gene-based approaches (e.g. RNA, DNA, live or replication-defective viral vectors)

Weaknesses in the universal influenza vaccine pipeline

• Commercialization unlikely if strategy does not use the HAI endpoint for licensure. Focus on HA head region limits universality

• Many vaccination strategies are too complex for real-world deployment
  – More than one product used in multiple-administration combinations
  – Novel delivery platforms and formulations
  – Difficult to achieve low-cost, large-scale manufacturing
Approaches to Elicit HA Stem Response

Assessment: Potential Opportunities for Licensure

- For Improving Current Products
  - New adjuvant formulations and cell-grown products are available and should proceed

- For Universal Influenza Vaccines
  - No universal vaccine candidate sufficiently advanced to discuss licensure
  - Will be a long-term iterative process relying on human clinical data and novel immunological endpoints
Assessment: Potential Role for WHO

• Define interim goals for universal vaccine development
  – Encourage developing sites for field testing in LMIC
• Consensus building and guidance for using and expanding access to existing vaccines
  – Encourage use of more LAIV
  – Promote vaccination of pregnant women and children
  – Expand cell-based manufacturing capacity
  – Expand manufacturing capacity in LMIC
• Support surveillance and pandemic preparedness

Discussion