Global Vaccine Development Pipeline

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Biomedical Advanced Research and Development Authority (BARDA)

7th Meeting with International Partners on Prospects for Influenza Vaccine Technology Transfer To Developing Country Vaccine Manufacturers
25-26 March 2014
Dubai, UAE
Public Health Impact of Influenza

• 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
  – Immunocompromised

• Vaccination is the cornerstone of prevention
  – Seasonal vaccines only 30% to 50% efficacy in older adults
  – Global shortfall of vaccine supply for a pandemic
Influenza Vaccine Challenges:
Limitations of Current Vaccines

- Vulnerable to antigenic drift and shift
  - Antibodies target highly variable regions of HA and NA
  - Single site mutations can impact immunogenicity
- Provide minimal cross-protection within subtypes or against other subtypes of influenza
- Short duration of immunity, particularly in at-risk populations (e.g., pediatric, geriatric)
- Requires viral isolate for production
- Predominantly produced in chicken eggs
- Avian influenza strains will likely require adjuvant
- Vaccine efficacy is modest

There is a need for improved, more effective influenza vaccines.
### Estimated Effectiveness of Current Influenza Vaccines (US)

**Season** | **Overall Adjusted Vaccine Effectiveness (95% CI)**
--- | ---
2011 – 2012* | 47% (36 to 56)
2012 – 2013* | 56% (47 to 63)
2013 – 2014+ | 61% (52 to 68)

### Strain and Age Group

**Season** | **Strain** | **Age Group** | **Vaccine Effectiveness (95% CI)**
--- | --- | --- | ---
2011 – 2012* | A(H3N2) | 18 – 49 | 33% (-5 to 57)
 | A(H3N2) | 50 – 64 | 39% (-13 to 67)
 | (H3N2) | ≥9; Vaccinated prior to 2010-2011 only | -8% (-69 to 30)
2012-2013* | A(H3N2) | ≥65 | 9% (-84 to 55)

* Interim adjusted estimates Feb 22, 2013 CDC *MMWR*
* Mid-season adjusted estimates Feb 21, 2014 CD *MMWR*
# Influenza Vaccine Landscape

## Pre Clinical

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## Recombinant (SUV & VLPs)

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## Seasonal

- Vical
- inovio

## Pandemic

- DNA
- Vical
- inovio

## Seasonal & Pandemic

- DNA
- Vical
- inovio

## US License

- DNA
- Vical
- inovio

20MAR2014
Which Flu Vaccine is Right for You?

Get Vaccinated and Prevent the Spread of Infection

**3-STRAIN**
- The standard flu shot
- Great for:
  - infants > 6 months
  - healthy adults
  - pregnant women

**HIGH-DOSE**
- Helping the elderly avoid flu complications like pneumonia or even death
- Great for: age 65 or older

**4-STRAIN**
- Protects against B-class influenza, which affects young children
- Great for:
  - kids
  - healthy adults

**NASAL SPRAY**
- Eliminates needles
- Great for:
  - squimmy kids
  - healthy people
  - ages 2–49

**“NEEDLE-FREE”**
- Contains micro-needles that touch just the surface of the skin
- Great for:
  - anyone afraid of needles
  - ages 18–64

**EGG-FREE**
- Cultured in caterpillar cells
- Great for:
  - egg-allergic people

U.S. Pandemic Influenza Vaccine Development Strategy: Multi-Step & Integrated Approach

Cell-based Vaccines
- FLUCELVAX® Licensed 01/16/13
- Q-Pan H5N1 Licensed 11/20/2013

Egg-based Vaccines
- H5N1 Vaccine Licensed 04/17/07

Recombinant Vaccines
- Flublok® Licensed 01/16/13

Antigen-Sparing Vaccine Technology

Universal Vaccines
- Advanced Development Begins FY15

Manufacturing Improvements

Influenza Vaccine Manufacturing Improvement Initiative

• Novel set of optimized donor viruses
• Faster sterility assays
• Reagent calibration and potency assays

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 supply 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 morbidity or mortality as endpoint of efficacy?**
  – Reduction in spread of disease

• **Population targeted**
  – < 6mo – 85+ years of age

• **Storage conditions**
  – Room temperature
Universal Vaccine Strategies
Leveraging Old and New Discoveries

- Identify broadly reactive epitopes (HA Stalk, M2 extracellular, NP)
- Multi-epitope vaccines
- Vector delivered vaccine
- Target occluded sites

- Broaden B cell epitope recognition
- Th1 vs Th2 responses
- Humoral vs Cell-mediated

Vaccine Design
Adjuvants
Administration

HA1 (variable region)
HA2 (conserved region)

Source: NIAID http://tinyurl.com/69n9lap


### Example Approaches to Develop More Effective Influenza Vaccines

<table>
<thead>
<tr>
<th>Company</th>
<th>Clinical Data</th>
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<td>PaxVax</td>
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<td>Computationally Optimized Broadly Reactive Antigen</td>
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Developmental Challenges for Universal Vaccines

• No universal definition or target product profile
• Regulatory science will need to evolve with the technical science development
  — Protective immune responses may be to something other than the HA protein (non-HAI)
  — New surrogates of immunity may need to be identified
  — Alternate potency/release assays will be needed
• Large scale efficacy trials or other “creative” clinical development approaches may be required
• Funding is limited
  — Most candidates are in preclinical development stage
  — Each promising candidate could cost up to $1B USD for development

Final Thoughts

• There has never been a greater variety of influenza vaccines available to address population variety than there are today.

• The landscape of new influenza vaccine development is active and rapidly evolving – 94+ products/candidates.

• Technical and regulatory challenges exist for innovative technologies.

• Continued scientific discoveries provide greater opportunities for innovation.

• While the field of influenza vaccine types appear to be moving towards a variety of niche vaccines in the near term, it is apparent from the landscape that the ultimate aim is to develop a single, more effective vaccine that could be used by all populations.
US H7N9 Vaccine Clinical Trials

- HHS/BARDA-supported H7N9 vaccines in clinical trials:
  - Novavax (recombinant-based VLP +/- Iscomatrix) (Matrix M)
  - Novartis (cell-based inactivated, subunit +/- MF59)
  - MedImmune (egg-based LAIV) – with NIH
  - GSK (egg-based inactivated, subunit +/- AS03)
    - H7N1 vaccine study - initial dose finding studies
    - H7N9 vaccine Phase 2 study
  - sanofi pasteur (egg-based inactivated, subunit) (Mix & Match Studies conducted by NIH)

- In general, all vaccines well tolerated

- Limited preliminary data indicate that two doses of vaccine delivered with adjuvant are needed to induce sufficient immunity as measured by HAI or MN
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