IMPROVING INFLUENZA VACCINES: CHALLENGES AND NEW DIRECTIONS

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2016 National Adult and Influenza Immunization Summit
Resilient People. Healthy Communities. A Nation Prepared.

Pandemic Influenza Response Capabilities Prior 2005

- Biomedical Advanced Research and Development Authority (BARDA)
  - 2005
  - US Department of Health and Human Services
- Support the advanced development of medical countermeasures for CBRN, pandemic influenza, and emerging infectious disease threats
Pandemic Influenza Response Capabilities Prior 2005

- No National Strategy for influenza pandemic preparedness
- No pre-pandemic vaccine or antiviral stockpile – federal or state
- Limited domestic manufacturing capability for pandemic response
- Lack of global vaccine supply for a pandemic response
- Candidate pandemic vaccines were poorly immunogenic
- All US licensed seasonal vaccines were egg-based (1940s-1950s technology)
  - No cell-based and no recombinant-based influenza vaccine licensed
  - No adjuvanted influenza vaccines licensed in U.S.
BARDA Pandemic Influenza Strategy

Reducing the Impact of Influenza Virus Infection

- Advanced development of antiviral drugs & therapeutics
- Therapeutics
- Develop rapid POC/ pre-symptomatic diagnostics
- Diagnostics
- Provide pandemic vaccine for U.S. within 6 months (or less) of a pandemic declaration (600M doses)
- Vaccines
- Develop influenza vaccines that induce broader, longer duration of immunity
- Vaccine & Adjuvant Stockpile
- Stockpile vaccines against influenza strains with pandemic potential
- International Vaccine Capacity Building
- Develop reusable masks and respirators to address surge need during a pandemic

More, Faster, & Better!

More Vaccines

Egg-based Vaccines

1st US FDA approved pandemic-ready site for cell-based vaccines & adjuvant

Centers for Innovation in Advanced Development and Manufacturing (CIADM)

sanofi pasteur – Swiftwater, PA

2013 ISPE Facility of the Year
Pandemic influenza vaccine target is two doses for everyone (~600M doses) within 4 months of pandemic onset.

Expanded Domestic Vaccine Manufacturing Surge Capacity

Changing Seasonal Vaccine Portfolio

Which Flu Vaccine is Right for You?

Get Vaccinated and Prevent the Spread of Infection

3-STRAIN: The standard for all

- Infants <6 months
- Healthy adults
- Pregnant women

HIGH-DOSE: Helps the elderly avoid complications like pneumonia or even death

- Elderly 65 or older

4-STRAIN: Protects against 3 new influenza subtypes, which affects young children

- Kids
- Healthy adults

NASAL SPRAY: Debuts this year

- Healthy kids
- Healthy people
- Ages 2-49

“NEEDLE-FREE”: Contains micro-needles that breach the surface of the skin

- Anyone afraid of needles
- Ages 16-64

EGG-FREE: Natural in composition and

- Anyone allergic to eggs
- Ages 18-64
More International Vaccine Manufacturing Capacity

Licensed/Active Influenza Vaccine Producers
BARDA/WHO Cooperative Agreement Grantees
BARDA/WHO Licensed Vaccine for Human Use (as of 2/2014)

Faster Response Capability

Recombinant-based Influenza Vaccine Flublok®
Protein Sciences
Licensed 01/16/2013

Influenza Vaccine Manufacturing Improvement Initiative

Fill Finish Manufacturing Network
Centers for Innovation in Advanced Development and Manufacturing (CIADM)
BARDA is Achieving National Pandemic Influenza Vaccine Goals

More Effective/Universal Vaccines

Advanced Development Initiative – FY15

Antigen-Sparing Vaccine Technology

More & Better Vaccines, Sooner!

Egg-based Vaccines

Cell-based Vaccines

Recombinant Vaccines

Flublok® Licensed 01/16/13

FLUCELVAX® Licensed 01/16/12

Q-Pan H5N1 Licensed 11/20/2013

HSN1 Vaccine Licensed 04/17/07

Challenges for Current Influenza 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
- Requires viral isolate for production
- Predominantly produced in chicken eggs
Limitations of Current Influenza Vaccines

"Vaccine improvements are needed to generate greater protection against H3N2 than with current vaccines."

![Image of chart showing limitations of current influenza vaccines](http://dx.doi.org/10.1016/S1473-3099(16)00129-8)
Recognized Need for Improved or Universal Influenza Vaccines

2010 PCAST Report “Because a universal vaccine would completely change the outlook on protecting the population against influenza virus infections, the Federal Government should support and encourage efforts to design a universal vaccine through various mechanisms.”

2012 PHEMCE Implementation Plan programmatic priority “Develop a novel antigen or “universal” flu vaccine that will eliminate the need for annual modifications to the influenza vaccine or annual boosters”

What is a More Effective/Universal Influenza Vaccine?

- A vaccine that provides safe, effective and long-lasting immunity against a broad spectrum of divergent influenza viruses in all ages and people in high risk groups
- Reduces need for annual vaccination against drifted influenza viruses
- Primes for single-dose vaccination against pandemic viruses
# More Effective/Universal Influenza Vaccine: Target Product Profile

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<thead>
<tr>
<th>Vaccine Property</th>
<th>Desired Primary Characteristics</th>
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<tr>
<td><strong>Breadth of Protection</strong></td>
<td>Protects against antigenically divergent influenza A viruses and viruses from both influenza B virus lineages</td>
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| **Efficacy**       | Shows 20% or greater efficacy above a licensed influenza vaccine comparator  
                      • Measured by clinical or surrogate endpoints (e.g. seroprotection or seroconversion rates) predictive of clinical benefit |
| **Duration of Immunity** | Protects for two years or more against influenza A subtypes and influenza B lineages |
| **Priming Immunity** | Primes for broad baseline immunity  
                      • A subsequent single dose of pandemic vaccine will elicit protection against the pandemic influenza virus |
| **Safety**         | Comparable to licensed vaccines                                                                 |

Source: https://www.fbo.gov/index?s=opportunity&mode=form&id=999926c9399641e9f8013454a0bdf78&tab=core&tabmode=list

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# Path to Industry Partnerships

- **Define the more effective candidate vaccine**
- **Provide data to support improved performance**
- **Phase I Clinical Trial Results**
- **Evidence of domestic manufacturing capability**
BARDA Funding Sources

- Title: Broad Agency Announcement for the Advanced Development of Medical Countermeasures for Pandemic Influenza
- BAA-16-100-SOL-00002 (FBO.GOV)
- Purpose: Identify innovative and promising technologies for advanced development of medical countermeasures for influenza and other emerging infectious diseases.
- Submission interim deadlines:
  - Round 1: 30-Jan-2016
  - Round 2: 30-Apr-2016
  - Round 3: 30-Jul-2016
  - Round 4: 30-Oct-2016
  - Round 5: 30-Jan-2017
  - Round 6: 30-Apr-2017
  - Round 7: 30-Jul-2017
  - Round 8: 30-Oct-2017

BARDA’s Core Service Assistance Programs

- Generate data to support existing animal models or establish new ones
- Develop MCM studies to support advancement of candidate products in the regulatory pathway for licensure
- Evaluate candidate products as MCMs through Proof of Concept studies

- Provide comprehensive, Phase 1 – IV clinical study services to evaluate safety, dosage, PK/PD, and efficacy of MCM candidates
BARDA Guidance to Developers

- Pre-clinical and clinical studies supporting the ability of your candidate vaccine to elicit:
  - Protective immunity against antigenically divergent viruses
  - Generic immunologic priming; i.e. protective responses upon single booster vaccine dose from divergent viruses
  - Increased duration of the immune response
  - Compared to currently licensed influenza vaccines

New Direction for Improved Influenza Vaccines:
Bringing it all together

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

- 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/500ap
Current Landscape of Novel Influenza Vaccine Candidates

**Pre Clinical**
- VLP-based Influenza vaccine
- KJ BioSciences LLC
- Self-assembling nanoparticles
- Avatar Medical, LLC

**Phase 1**
- Nanoemulsion T-cell vaccine
- DNA Vaccine construct with HA, NA, M2e
- VLP Influenza vaccine from tobacco plants
- Replication deficient hAd5 expressing HA/TRL 3 agonist
- Conformationally Locked Soluble Headless HA

**Phase 2**
- Conserved antigenic sites from previous seasons
- Ad4 Vector with H5 HA
- Nonneutralizing 3-cell vaccine
- Ad4 Vector constructed with HA, NA, M2e
- MVA Vector with NP, M1
- M2e + fusion peptide domain combined with nanoparticle carrier
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