Making Progress Toward Universal Influenza Vaccines

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Office of the Assistant Secretary for Preparedness & Response

8th WHO International Partners Meeting
Sao Paulo, Brazil, March 17-18, 2015
Public Health Impact of Influenza

- **1918 ‘Spanish’ Pandemic**
  - 20%-40% infected worldwide
  - 50M deaths worldwide
  - 675,000 deaths in US
  - 74 countries affected
  - 123,000-203,000 deaths worldwide
  - 60.8M infected worldwide
  - 50M deaths worldwide
  - 675,000 deaths in US

- **2009-2010 H1N1 Pandemic**
  - 74 countries affected
  - 274,304 hospitalizations in US
  - 12,469 deaths in US
  - 12,469 deaths in US

- **Seasonal Influenza Epidemic in US**
  - 5%-20% infected every year
  - >200,000 hospitalizations every year
  - 3,000-49,000 deaths every year
  - $87.1B economic burden every year
  - $10.4B medical costs every year

Influenza Viruses Constantly Evolve

H1N1, H1N1v
H2N2, H1N2v
H3N2, H3N2v
H5N1, H5N6
H9N2, H7N7
H7N9, H10N8
H6N1, H7N2
H7N3, H10N7

Photo Credits: Yasuo Suzuki & Avian Flu Diary
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 influenza 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
- Stockpile vaccines against influenza strains with pandemic potential
- Vaccine & Adjuvant Stockpile
- International Vaccine Capacity Building
- Diagnostics
- Respiratory Devices/Masks
- Therapeutics

Develop rapid POC/ pre-symptomatic diagnostics

Provide pandemic vaccine for U.S. within 6 months (or less) of a pandemic declaration (600M doses)

Develop influenza vaccines that induce broader, longer duration of immunity

More, Faster, & Better!

Develop low cost, easy to use respirators suitable for all ages with universal components

Develop reusable masks and respirators to address surge need during a pandemic

Enable 500M doses of pandemic vaccine production capacity in developing countries

More Vaccines

Egg-based Vaccines

sanofi pasteur – Swiftwater, PA

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

Centers for Innovation in Advanced Development and Manufacturing (CIADM)
Changing Seasonal Vaccine Portfolio

**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

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

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

**Egg-Free**
Collected in caterpillar cells
Great for:
- severe egg allergic adults
  ages 18–49

**"Needle-Free"**
Contains micro-needles that touch just the surface of the skin
Great for:
- anyone afraid of needles
  ages 18–64

njhealth.org
1.800.222 LUNG
(800.222.5864)
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)

Limitations of Current Influenza Vaccines

There is a need for improved, more effective influenza vaccines

<table>
<thead>
<tr>
<th></th>
<th>Influenza A and B</th>
<th>Overall</th>
<th>Influenza A</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO. vaccinated</td>
<td>Total sample (%)</td>
<td>NO. vaccinated</td>
<td>Total sample</td>
<td></td>
</tr>
<tr>
<td></td>
<td>465 (49)</td>
<td>1,371 (56)</td>
<td>407 (48)</td>
<td>1,371 (56)</td>
</tr>
<tr>
<td></td>
<td>771 (25)</td>
<td>1,371 (25)</td>
<td>771 (27)</td>
<td>1,371 (27)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(12–37)</td>
<td>(13–39)</td>
<td>(13–23)</td>
<td>(13–23)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(8–36)</td>
<td>(5–35)</td>
<td>(5–35)</td>
<td>(5–35)</td>
</tr>
</tbody>
</table>

Abbreviation: CI = confidence interval.
* Vaccine effectiveness was estimated as 100% x (1 - odds ratio [ratio of odds of being vaccinated among outpatients with influenza-positive test results to the odds of being vaccinated among outpatients with influenza-negative test results]); odds ratios were estimated using logistic regression.
## Influenza Vaccine Landscape

### Pre Clinical
- **Egg-based inactivated**
  - Split w/ SPA03
  - Proprietary Adjuvant
  - GPO
  - Egg, Thailand
  - Split w/ iscomatrix

- **Cell-culture inactivated**
  - EB66
  - HexoGen
  - QIV
  - WIV

- **LAIV**
  - Egg, H5N1
  - MedImmune
  - Egg, H5N2
  - Universal
  - H5N1 AS03

- **Recombinant (SUV & VLPs)**
  - VLP / HA
  - VLP, Insect cells
  - VLP, 293 cells
  - ASU
  - rHA, Plants
  - Molecular Has
  - rHA, Plants

- **Universal**
  - NYU / MSSM
  - HA stalk; Chimeric HAs
  - DynaVax
  - NIAID Nanoparticle

- **Vectors/Adjuvant**
  - MVA Based
  - Adenovirus
  - Inovio
  - DNA / Vaxfectin

### Phase 1
- CSL Biotechs
- Itay
- Universal
- HN1, WIV

### Phase 2
- SinoVac
- Novartis
- GlaxoSmithKline

### Phase 3
- CSL Biotechs
- Novartis
- Zydus

### Market Approval
- Sanofi Pasteur
- Novartis
- Zydus

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**Seasonal**
- NIBRC (China)
- NIBRG (Japan)
- Biocytum

**Pandemic**
- Novartis
- Zydus

**Seasonal & Pandemic**
- SinoVac
- GlaxoSmithKline

**US License**
- Sanofi Pasteur
- Novartis

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**DNA**
- Vical
- Inovio

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20MAR2014
BARDA is Achieving National Pandemic Influenza Vaccine Goals

**Universal Vaccines**
- Advanced Development Begins FY15

**Recombinant Vaccines**
- Flublok® Licensed 01/16/13

**Cell-based Vaccines**
- FLUCELVAX® Licensed 11/20/12

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

**Antigen-Sparing Vaccine Technology**
- Q-Pan H5N1 Licensed 11/20/2013

**Manufacturing Improvements**

**More, Faster, & Better Vaccines!**
A vaccine that provides safe, effective and long-lasting immunity against a broad spectrum of antigenically divergent influenza viruses in all ages and people in high risk groups
Transformative Approach: Bringing it all together

Universal Influenza Vaccine

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

Location:
Intranosal, intradermal or intramuscular
Timing: Prime/boost
Regimen

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

Toward a Universal Influenza Vaccine: Current Landscape

<table>
<thead>
<tr>
<th>Pre Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<tbody>
<tr>
<td></td>
<td>Protein Based</td>
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<tr>
<td>Chimeric HA Stalk Vaccine</td>
<td>M2e-VLPs</td>
<td>M2e + NP + M1 proteins</td>
</tr>
<tr>
<td>Self assembling nanoparticle</td>
<td>NPA + NPS + M1 + M2 + T-cell vaccine</td>
<td>Conserved epitopes from HA + NP + M1 proteins</td>
</tr>
<tr>
<td>Computationally Optimized Broadly Reactive Antigen (COBRA)</td>
<td></td>
<td>Fluorocarbon-inked conserved influenza peptide set T-cell vaccine</td>
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<table>
<thead>
<tr>
<th>Vectors</th>
<th>DNA</th>
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<tbody>
<tr>
<td>Listeria</td>
<td>DNA prime + TIV boost</td>
</tr>
<tr>
<td>Listeria Vector with HA and NP</td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td></td>
</tr>
<tr>
<td>MVA Vector with NP and M1</td>
<td></td>
</tr>
<tr>
<td>Ad5 Vector Expressing HA</td>
<td></td>
</tr>
<tr>
<td>Ad5</td>
<td></td>
</tr>
<tr>
<td>ad5 LAIV</td>
<td></td>
</tr>
<tr>
<td>FluGen</td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td></td>
</tr>
<tr>
<td>MVA Vector with NP and M1</td>
<td></td>
</tr>
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<td>Ad5 Vector Expressing HA</td>
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<tr>
<td>Ad5</td>
<td></td>
</tr>
<tr>
<td>Ad5 LAIV</td>
<td></td>
</tr>
<tr>
<td>VaxGen</td>
<td></td>
</tr>
<tr>
<td>DNA Vaccine construct with HA, NA, M2e-NP</td>
<td></td>
</tr>
</tbody>
</table>

No Phase 3 or Market Approved Universal Influenza Vaccines
Developmental Challenges for Universal Vaccines

• **New science**
  - New/alternate regulatory pathways
  - New markers of immunity
  - Alternate production/analytical methods
  - New antigen/adjuvant combinations
  - Large scale or adaptive clinical programs

• **New partnerships**
  - Public/private partnerships
  - New consortiums/collaborations/Mergers & Acquisitions

• **Funding**
  - Up to $1B per candidate from preclinical to licensure
BAA-13-100-SOL-00019 supports development of MCMs for pandemic influenza.

5.1 **Advanced development of novel influenza vaccine candidates which have achieved TRL 6 or greater.** Support for advanced development of novel influenza vaccine candidates with the potential to stimulate a broader and more effective immune response than currently available products. Data should be provided that demonstrates statistically-relevant improvements in immunogenicity/efficacy as compared to existing vaccines. Proposed activities should enable improvements to key vaccine attributes, including dose schedule, time to onset of protection, induction of improved immunogenicity, broader cross-protection across influenza A virus subtypes, and duration of protection. Use of approved or novel adjuvants to achieve enhanced or broadened immunogenicity may also be a component of the advanced development program.
Universal Influenza Vaccines: Draft Request for Proposal (RFP)

Draft Request for Proposals for Universal Influenza Vaccines

Solicitation Number: BARDA_Universal_Influenza_Draft_RFP
Agency: Department of Health and Human Services
Office: Office of the Secretary
Location: Acquisitions Management, Contracts, & Grants (AMCG)

Original Synopsis
Dec 19, 2014
5:43 pm

Solicitation Number:
BARDA_Universal_Influenza_Draft_RFP

Notice Type:
Presolicitation

Synopsis:
Added: Dec 19, 2014 5:43 pm

https://www.fbo.gov/index?s=opportunity&mode=form&id=0e8a2a57a94d08a6989e292485f8c65b&tab=core&cview=0
## Target Product Profile for More Effective Influenza Vaccines

### Transformative

<table>
<thead>
<tr>
<th>Property/Vaccine</th>
<th>Desired Primary Characteristics</th>
</tr>
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<tbody>
<tr>
<td>Breadth of Protection</td>
<td>Protects against antigenically divergent influenza A viruses and viruses from both influenza B virus lineages</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Shows 20% or greater efficacy above a licensed influenza vaccine comparator as measured by clinical endpoints or surrogate endpoints (e.g. seroprotection or seroconversion rates)</td>
</tr>
<tr>
<td>Duration of Immunity</td>
<td>Protects for two years or more against influenza A subtypes and influenza B lineages</td>
</tr>
<tr>
<td>Priming Immunity</td>
<td>Primes for baseline immunity such that a single dose of pandemic influenza vaccine will boost immune response to protective levels against the pandemic influenza virus</td>
</tr>
<tr>
<td>Safety</td>
<td>Comparable to licensed vaccines</td>
</tr>
</tbody>
</table>
Influenza: An Integrated Response

Vaccines

Therapeutics

Diagnostics

Early Detection  →  Early Response  →  Saving Lives

Website: https://www.medicalcountermeasures.gov/

- Information on the open influenza BAAs and RFPs
- Information on setting up a TechWatch meeting with BARDA to discuss your technology