BARDA INFLUENZA PROGRAM OVERVIEW

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Vaccines and Therapeutics

Resilient People. Healthy Communities. A Nation Prepared.
BARDA Overview

Support the advanced development of medical countermeasures for CBRN, pandemic influenza, and emerging infectious disease threats.

- Core Service & Response Infrastructure
- MCM Development Pipeline
- MCM Stockpiling
- Manufacturing Infrastructure
- FDA Approvals
- Highly Dedicated and Talented Team
- Partnerships
Perpetual challenge of responding to influenza

1918 'Spanish' Pandemic
- All countries affected
- 20%-40% infected worldwide
- 50M deaths worldwide
- 675,000 deaths in US

2009-H1N1 Pandemic
- 74 countries affected
- 60.8M infected in U.S.
- 123,000-203,000 deaths worldwide
- 12,469 deaths in US
- 274,304 hospitalizations in US

Seasonal Influenza Epidemic in U.S.
- 5%-20% of population infected each year
- 3,000-49,000 deaths every year
- >200,000 hospitalizations
- $87.1B economic burden every year
- $10.4B medical costs every year
### Landscape of Next Generation Influenza Vaccine Candidates

<table>
<thead>
<tr>
<th>Category</th>
<th>Pre Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLP</td>
<td>MEDiGEN, INC</td>
<td>NIH NIAID</td>
<td>VLP from tobacco plants Medicago</td>
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<tr>
<td>Nanoparticle</td>
<td>Ferritin NIH NIAID</td>
<td>NIH NIAID</td>
<td>NanoBio</td>
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<tr>
<td>LAIV</td>
<td>CodagenX Inc</td>
<td>SynBio LAIV</td>
<td>ΔM2 LAIV FluGen Vivaldi Biosciences</td>
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<tr>
<td>Vector Based</td>
<td>UPMC</td>
<td>Chimeric HA</td>
<td>MV Vector NP M1 + vaco tech Ad NacoVa altimmune</td>
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<tr>
<td>Split inactivated</td>
<td>Sanofi Pasteur</td>
<td>Chimeric HA</td>
<td>MVA prime and Ad5 Boost Vector with NP VivaTec</td>
</tr>
<tr>
<td>Recombinant</td>
<td>Janssen</td>
<td>Avatar Medical LLC Haddara IIA</td>
<td>Sanofi Pasteur M2 - hepB core NPV RCV INOVIO Pharmaceuticals</td>
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<tr>
<td>Protein/Peptide</td>
<td>Merck</td>
<td>Inovio Pharmaceuticals</td>
<td>Conserved epitopes from HA + NP + M1 BiondVax Bioscience PepTcell</td>
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Landscape of Next Generation Influenza Vaccine Candidates

Need more convincing immunological data
### Immune-Landscape of Influenza Vaccines

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<tr>
<th>Immunological compartments</th>
<th>Humoral</th>
<th>Cell-mediated</th>
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<td><strong>Platform</strong></td>
<td><strong>Responses</strong></td>
<td><strong>HA/MN</strong></td>
<td><strong>Stem</strong></td>
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<td>---------------------------</td>
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<tr>
<td>TIV or QIV MF59, AS03</td>
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<td>?</td>
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<td><strong>Vectors</strong></td>
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<td>MVA-NP,M1,</td>
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<td>Ad – HA, IN</td>
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<td>Ad – HA, Oral</td>
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<td>Plant VLP</td>
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<td>M-100</td>
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<td></td>
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<tr>
<td>conserved Ag</td>
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- **Theoretical potential**
- **Demonstrated immune response**
- ? Data lacking
- Not expected
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## Need convincing immunological data

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More Effective Influenza Vaccine Development Pipeline at BARDA
The program is investing in next-generation portfolio of improved influenza vaccines

Next-Generation Influenza Vaccines

**Leverage licensed influenza platforms**
- Design ‘antigenically advanced’ vaccines
- Heterologous prime-boost (HtPB) vaccination

**Innovative antigen delivery platforms**
- Orally administered temperature-stable vaccine
- HA-stem recombinant or vectored
- mRNA vaccines

**Promote industry partnerships & interagency efforts**
- Phase 1b (human challenge) studies
- Leverage HHS technology pipeline
Current Development Efforts

Adjuvants

Antigenically advanced HA vaccines

Mucosal delivery

Targeting Stem HA

T-cells to conserved Ag

Graphs (b, f, g) with statistical data.
Influenza: An Integrated Response
Influenza HA and Stalk mAbs
• Target the HA stalk
  – Highly conserved
  – Novel target
  – Broad spectrum – Group 1 and 2 of Influenza A

• Unique properties
  – Extended treatment window
  – Long half life resulting in single dose administration
  – Large binding surface reducing likelihood for resistance
Antibody Therapies in Development
Clinical Trial Challenges for Hospitalized Influenza Patients

- Trial enrollment
- Heterogeneous population
- ENDPOINTS
- Trial design
How Can We Improve Enrollment?

• 2015-2016 season - 1 ED enrolled 58 subjects in BARDA sponsored study evaluating enrollment
  — 24 hospitalized subjects
  — 34 outpatients

• Recommendations
  — Identify subjects in the ED for early enrollment and treatment
  — Include ED clinicians on clinical site contracts
  — Find sites that have rapid influenza PCR testing as SOC in the ED with 24/7 coverage
Current Endpoints

• FDA Guidance for Industry – Influenza: Developing Drugs for Treatment and/or Prophylaxis (2011)
  – Primary Endpoint should include:
    • Clinical signs and symptoms
    • Duration of hospitalization
    • Time to normalization of vital signs
      – Fever
      – Respiratory status
      – Heart rate
      – Systolic blood pressure
    • Supplemental oxygenation requirements
      – “Proposed endpoint [should] directly measure how a patient feels, functions, or survives…”
Clinical Endpoints Working Group

• Government and academic working group
  • WG has looked at therapeutic sponsor, research and hospital databases

• Ordinal Scale
  — Discrete categories for classifying hospitalized subjects over time could include:
    • Death
    • ICU on mechanical ventilation
    • ICU
    • Hospital floor receiving supplemental oxygen
    • Hospital floor without supplemental oxygen
    • Discharge but has not returned to normal activity
    • Discharge returned to normal activity
Relative Frequency Distribution of Ordinal Scale

≤ 48 Hours (n=58)

> 48 Hours (n=157)

Day from Admission

Discharged → Hospitalized → ICU → Ventilator → Death
Program Goal: Reduce morbidity and mortality in all patient populations during an influenza pandemic

Critical unmet medical needs:

- Severely ill, hospitalized influenza patients
- More effective treatment options, suitable for all populations

• Critical Properties for Target Product Profile
  - Novel mechanism of action
  - Superior efficacy compared to neuraminidase inhibitors (NAIs)
  - Inhibits all Influenza A strains tested
  - Expanded treatment window beyond 48 hours
  - Suitable for combination therapy with existing NAI or other therapies
  - IV formulation for seriously ill