Influenza Vaccine Innovation
New Vaccines Approved and on the Way

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The Biomedical Advanced Research and Development Authority

Develop and provide countermeasures for CBRN threats, pandemic influenza, and emerging infectious diseases through product development, stockpile acquisition/building, manufacturing infrastructure building, and product innovation.

Vaccines  Therapeutics  Diagnostics  Devices  Infrastructure

Requirements

• Requirements addressed by the BARDA Influenza Portfolio are derived from a number of documents that guide the US Government efforts to prepare for pandemics
  • National Strategy for Pandemic Influenza (Nov 2005)
  • HHS Pandemic Influenza Plan (Nov 2005)
  • Nation Strategy for Pandemic Influenza Implementation Plan (May 2006)
  • Public Health Emergency Medical Countermeasures Review (Aug 2010)
  • PCAST report on Reengineering the Influenza Vaccine Production Enterprise (Aug 2010)

Vaccine Challenges
Pandemic Response

**Vaccine Challenges**

**The Development Process**

<table>
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<tr>
<th>TIME</th>
<th>成本/阶段</th>
<th>3-7 yr</th>
<th>0.5-2 yr</th>
<th>1-2 yr</th>
<th>2-3.5 yr</th>
<th>2.5-4 yr</th>
<th>1-2 yrs</th>
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<tbody>
<tr>
<td></td>
<td>$100M-130M</td>
<td>$60-70M</td>
<td>$70M-100M</td>
<td>$130M-160M</td>
<td>$190M-220M</td>
<td>$18M-20M</td>
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</table>

**PHASE**
- 研究 | 预临床开发 | 临床I | 临床II | 临床III | 许可证 | 生产与交付

**TRLs**
- 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9

**PRODUCT PIPELINE**

- 1-3% | 5-17% | 10-25% | 18-35% | 45-70% | 90%

**PROBABILITY OF SUCCESS TO LICENSURE**

5 candidates here... → yield 1 product here

Sources: PRTM & Industry Data

**ASPR: Resilient People. Healthy Communities. A Nation Prepared.**

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**Vaccine Challenges**

**Financial Outlook**

<table>
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<tr>
<th>年份</th>
<th>费用</th>
<th>预2004</th>
<th>NGO</th>
<th>VC</th>
<th>INDUSTRY</th>
<th>GOV’T</th>
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<td>2005-2009</td>
<td>~$10B</td>
<td>NGO</td>
<td>VC</td>
<td>INDUSTRY</td>
<td>GOV’T</td>
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<td>Post-2009</td>
<td>~$1B</td>
<td>NGO</td>
<td>VC</td>
<td>INDUSTRY</td>
<td>GOV’T</td>
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</tr>
</tbody>
</table>

**Trends**
- 预算紧缩贯穿于各级政府
- 行业经济压力倾向于可靠的机会和更快的投资回报
- 更小的可用风险资本金额

**ASPR: Resilient People. Healthy Communities. A Nation Prepared.**
Influenza Vaccine Landscape

Current Influenza Vaccines

- Safe and efficacious, decades of experience
- Vulnerable to antigenic drifts and shifts
  - Antibodies target highly variable regions of HA and NA
  - Protection following vaccination or infection is limited to specific strains
  - Single site mutations can reduce efficacy
  - Host variations in immune response can reduce efficacy
- Non-adjuvanted vaccines provide minimal cross-protection within subtypes or against other subtypes
- Short duration of immunity, particularly in at-risk populations (e.g., pediatric, geriatric)

Ideal Attributes of Next-Generation Vaccines

- Effective in general and at-risk populations
- Broadly reactive against multiple strains
- Low cost per dose
- Safe for use in all populations
- Rapid, scalable production
- Long-lasting immunity

BARDA’s Approach to Vaccine Innovation

- **More**
  - Maximizing vaccine supply

- **Faster**
  - Minimizing the timeframe from pandemic virus identification to first vaccine dose

- **Better**
  - Driving generational improvements in manufacturability, speed, and effectiveness
Maximizing Near-Term Technologies

- Egg-based vaccines
  - Contracts to ensure year-round egg supply
  - Licensure of first H5N1 vaccine
  - Adjuvanted vaccines

- Cell-based vaccines
  - Advanced development of multiple technologies
  - Establish infrastructure for U.S.-based manufacturing

- International vaccine programs

First U.S. Cell-Based Facility

Landmark Public-Private Partnership
Global Influenza Vaccine Production

circa 2006

Licensed Influenza Vaccine Producers


Global Influenza Vaccine Production

circa 2012

Licensed/Active Influenza Vaccine Producers

BARDA/WHO Cooperative Agreement Grantees

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**Influenza Vaccine Virus Selection and Development Process**

Seasonal

1. Collection of specimens and disease/epidemiological data
2. Diagnosis, virus isolation in MDD, preliminary analysis
3. Virus isolation in eggs
4. Serological studies

H5N1

1. Ferret antiserum production
2. Thorough antigenic and genetic analysis
3. Review and selection of candidate viruses for vaccine use
4. Reassortment of high-growth viruses using reverse genetics (and full safety testing)

Antigenic and genetic characterization of reassortants
Development of standardized reagents for inactivated vaccines
Evaluation of growth property
Development of standardized reagents for inactivated vaccines
Antigenic and genetic characterization of reassortants

Availability of vaccine viruses and standardized reagents

who.int/influenza/resources/documents/influenza_vaccine-virus_selection
Traditional Egg-based Vaccine Manufacturing Processes


Influenza Vaccine Manufacturing Improvement Initiative

• Novel set of optimized donor viruses

• Faster sterility assays

• Reagent calibration and potency assays

**Synthetic Biology**

**Vaccine Seed Production**

Rapid synthesis process to assemble oligos into flu HA and NA segments in <1 day

- Pool overlapping oligos for HA or NA: 0.5 hr
- Assemble and amplify oligos: 2.5 hr
- Error-correct & reamplify: 3.0 hr
- Assemble oligos into linearized pKS10 vector to add essential reverse genetics promoter and terminator elements: 1.0 hr
- Amplify to get linear synthetic HA or NA segments: 2.0 hr
- Precipitate DNA and clean up reactions: 1.0 hr

**Final product is uncloned, synthetic linear HA or NA gene segment with regulatory control elements (promoters & terminators).**

**Total = 10-13 hours**

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**Synthetic Biology**

**Vaccine Seed Production**

Robust process to rescue influenza virus using synthetic gene segments in vaccine-approved MDCK cells

- Seed MDCK cells
- Transfect cells with DNA
- Remove serum, add feeder cells and trypsin *
- Monitor virus rescue daily by FFA**

**Confirmed viruses = 4 - 7 days**

* Replenish trypsin concentration every 48h if rescues take longer than 3 days.

** Focus-formation assay; based on immunological staining of viral nucleoprotein in infected cells**
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Recombinant Vaccine Production

Recombinant technologies provide vaccine sooner with less dependence on influenza virus strain properties

Flublok®
Influenza vaccine

New Vaccine Production Paradigm


Other Novel Approaches

- DNA vaccines
- Live-viral vectors (adenovirus, modified vaccinia)
- Other expression systems (*E. coli*, *Neurospora*)
- Synthetic vaccinology – from sequence to vaccine
Universal Influenza Vaccine

- Many definitions for a universal influenza vaccine
  - A single influenza vaccine that would provide “protection” against any given subtype of influenza A and/or B
  - Could be used for several influenza seasons before reformulation
    - Reduce annual “guesswork” for strain selection
    - Reduce production costs (thus vaccine costs/year round production)
    - Reduce vaccine “mismatches”
    - Reduce the potential for vaccine shortages
    - Increase the global supply of vaccine
- Could be stockpiled for epidemics/pandemics
- Surge capacity
  - Rapid scale-up, reduce production bottlenecks
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

- Location:
  - Intranasal, intradermal or intramuscular
  - Timing: Prime/boost
  - Regimen

HA1 (variable region)
HA2 (conserved region)

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

R. Rappuoli, F1000 Medicine Reports 3 (2011): 16

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

National Pandemic Influenza Vaccine Development Strategy: Multi-Step & Integrated Approach

“More and better vaccines sooner”

Universal Vaccines

Recombinant-based Vaccines

Flublok Licensed 01/16/13

Cell-based Vaccines

Flucelvax Licensed 11/20/12

Egg-based Vaccines

Antigen-Sparing Vaccine Technology

Manufacturing Improvements

Final Thoughts

• The landscape of new influenza vaccine development is active and rapidly evolving
• Significant technical challenges for innovative technologies
• Continued scientific discoveries provide greater opportunities for innovation
• Post-pandemic fatigue and economic challenges affect all partners
• Leveraging government, nonprofit and industry collaborations will be essential to continued public health success