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.
May 10-12, 2016 – Atlanta, GA

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.

3

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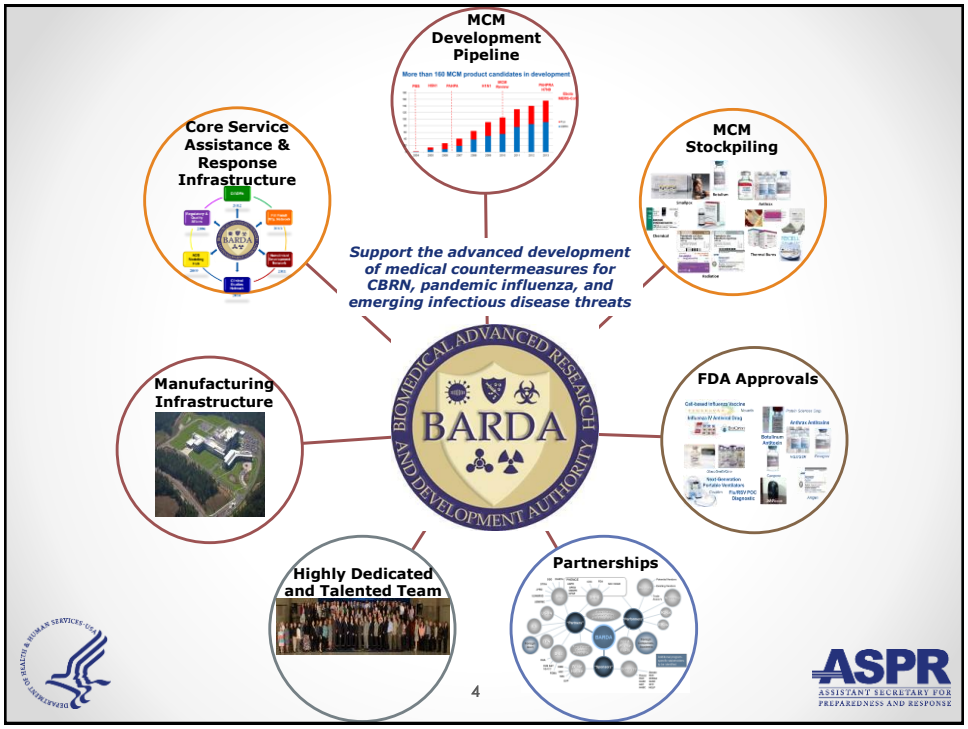

4

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BARDA Pandemic Influenza Strategy

Reducing the Impact of Influenza Virus Infection

Advanced development of antiviral drugs & therapeutics

Develop rapid POC/ pre-symptomatic diagnostics

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

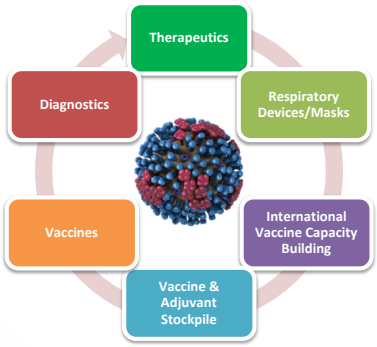
Develop reusable masks and respirators to address surge need during a pandemic

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

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

Develop influenza vaccines that induce broader, longer duration of immunity

More, Faster, & Better!



Stockpile vaccines against influenza strains with pandemic potential

5

More Vaccines

Egg-based Vaccines

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

2013 ISPE Facility of the Year

sanofi pasteur – Swiftwater, PA

Centers for Innovation in Advanced Development and Manufacturing (CIADM)

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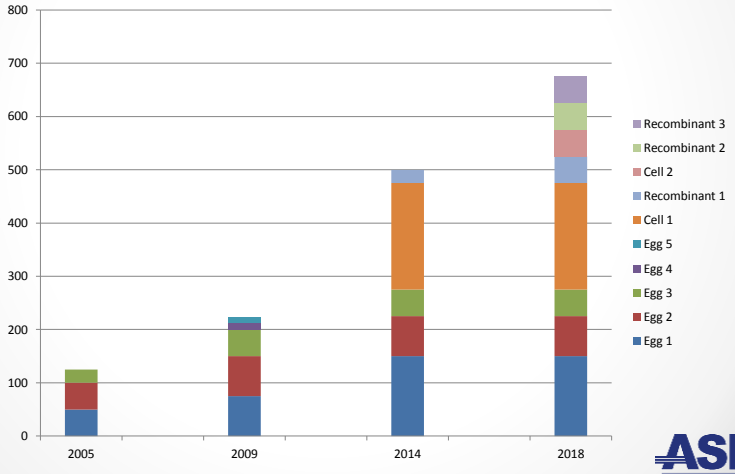
Expanded Domestic Vaccine Manufacturing Surge Capacity

Pandemic influenza vaccine target is two doses for everyone (~600M doses) within 4 months of pandemic onset



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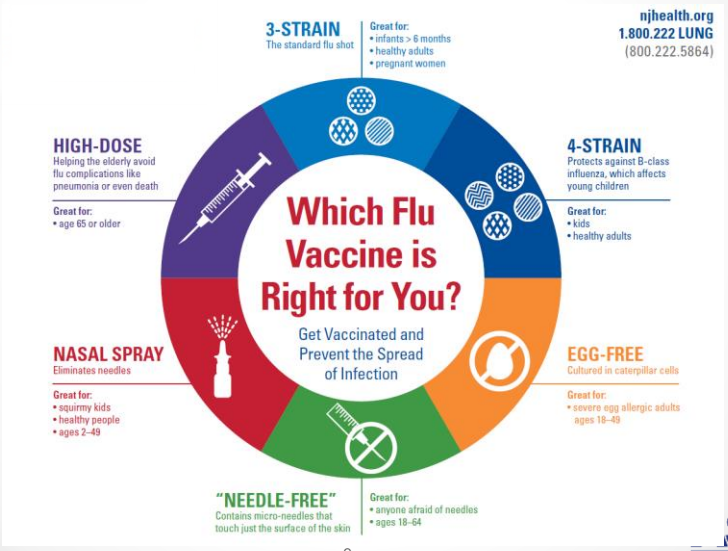
Changing Seasonal Vaccine Portfolio



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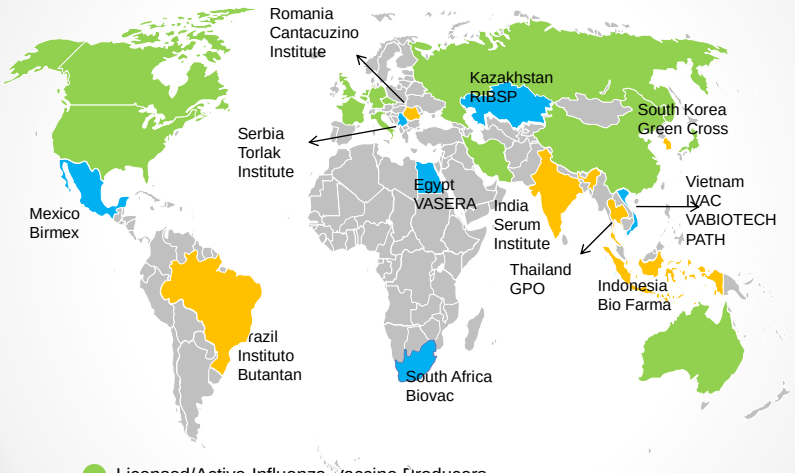
More International Vaccine Manufacturing Capacity



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

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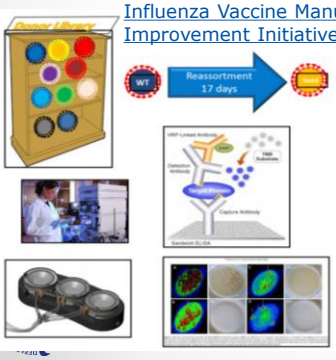
Faster Response Capability

Recombinant-based Influenza Vaccine Flublok®

Protein Sciences
Licensed 01/16/2013

Influenza Vaccine Manufacturing Improvement Initiative

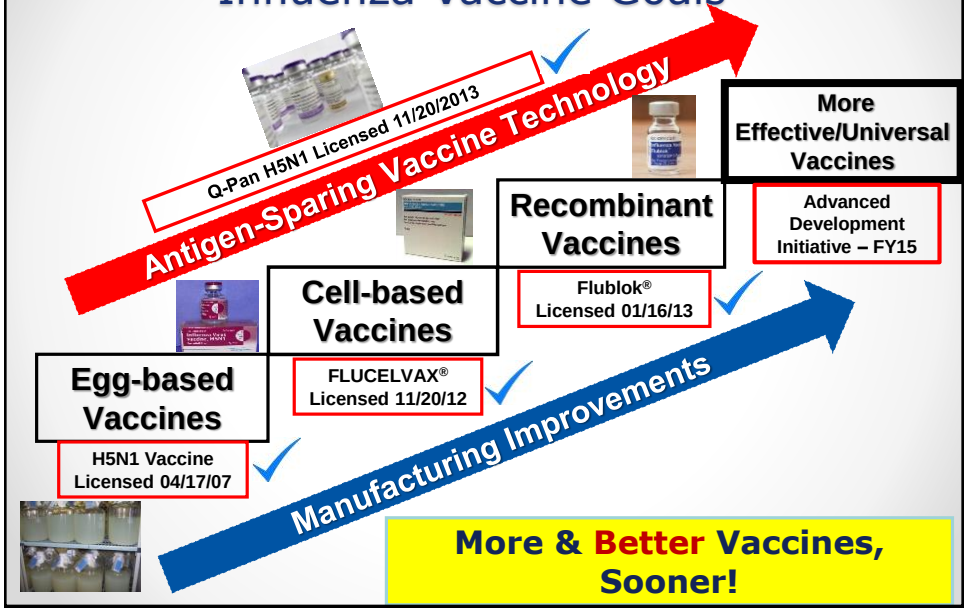


Fill Finish Manufacturing Network

Centers for Innovation in Advanced Development and Manufacturing (CIADM)

10

BARDA is Achieving National Pandemic Influenza Vaccine Goals



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

12

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Limitations of Current Influenza Vaccines

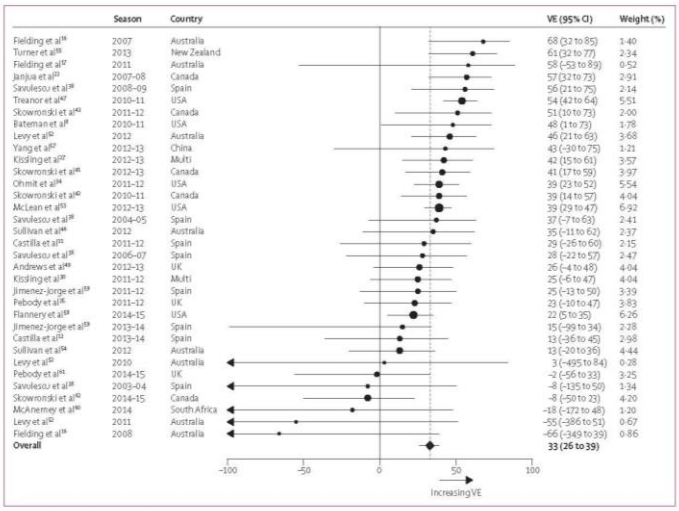

Figure 1: VE for H3N2 in studies without age restriction
The numbers of cases and controls for each VE estimate are provided in the appendix. VE=vaccine effectiveness.

Belongia 2016 Lancet http://dx.doi.org/10.1016/S1473-3099(16)00129-8

Limitations of Current Influenza Vaccines

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

Figure 1: VE for H3N2 in studies without age restriction
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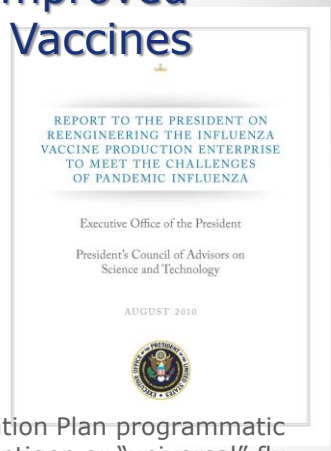
Recognized Need for Improved or Universal Influenza Vaccines

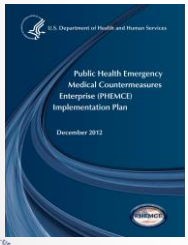
2010 PCAST Report "Because a universal vaccine would completely change the outlook on protecting the population against influenza virus infections, the Federal Government should support and encourage efforts to design a universal vaccine through various mechanisms."


REPORT TO THE PRESIDENT ON REENGINEERING THE INFLUENZA VACCINE PRODUCTION ENTERPRISE TO MEET THE CHALLENGES OF PANDEMIC INFLUENZA

Executive Office of the President

President's Council of Advisors on Science and Technology

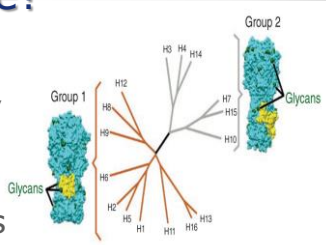
AUGUST 2010

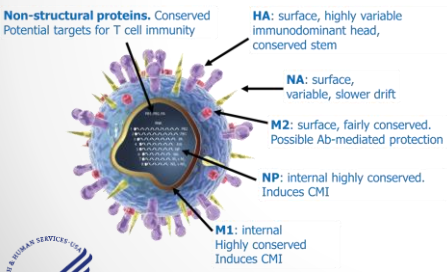


2012 PHEMCE Implementation Plan programmatic priority "Develop a novel antigen or "universal" flu vaccine that will eliminate the need for annual modifications to the influenza vaccine or annual boosters"

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

Vaccine Property	Desired Primary Characteristics
Breadth of Protection	*Protects against antigenically divergent influenza A viruses and viruses from both influenza B virus lineages*
Efficacy	*Shows 20% or greater efficacy above a licensed influenza vaccine comparator* • *Measured by clinical or surrogate endpoints (e.g. seroprotection or seroconversion rates) predicative 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*

https://www.fbo.gov/index?s=opportunity&mode=form&id=999926c9399641e86f001345a0bd8fd7&tab=core&tabmode=list&=

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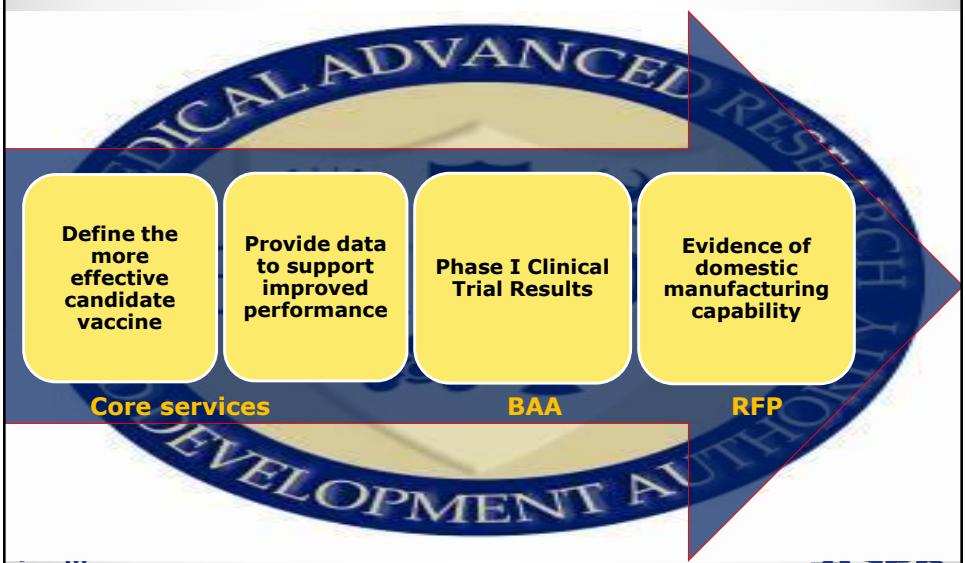
Path to Industry Partnerships



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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

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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

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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

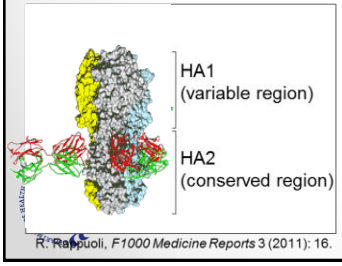
Vaccine Design

Adjuvants

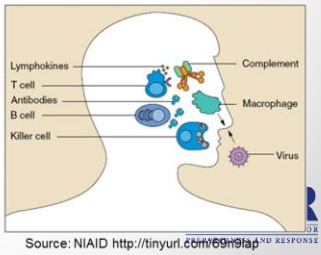
- Broaden B cell epitope recognition
- Th1 vs Th2 responses
- Humoral vs Cell-mediated

Administration

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

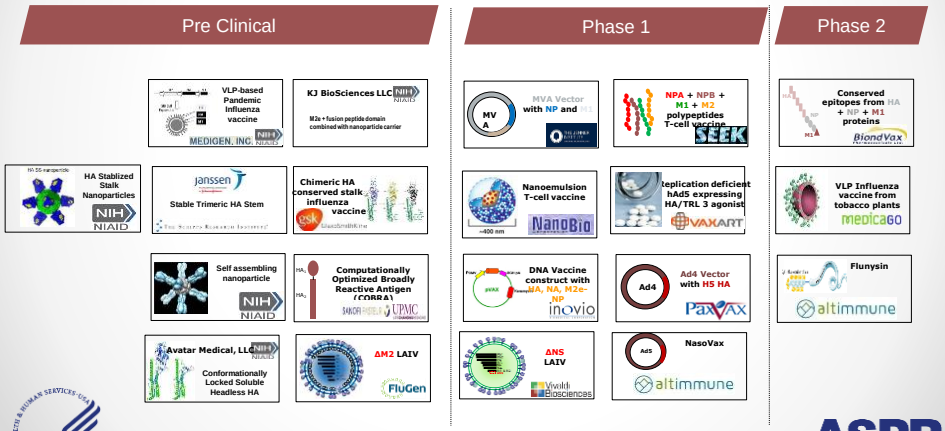


R. Rappuoli, *F1000 Medicine Reports* 3 (2011): 16.



Source: NIAID http://tinyurl.com/6bnslap

Current Landscape of Novel Influenza Vaccine Candidates



March 29, 2016

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Thank You!

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