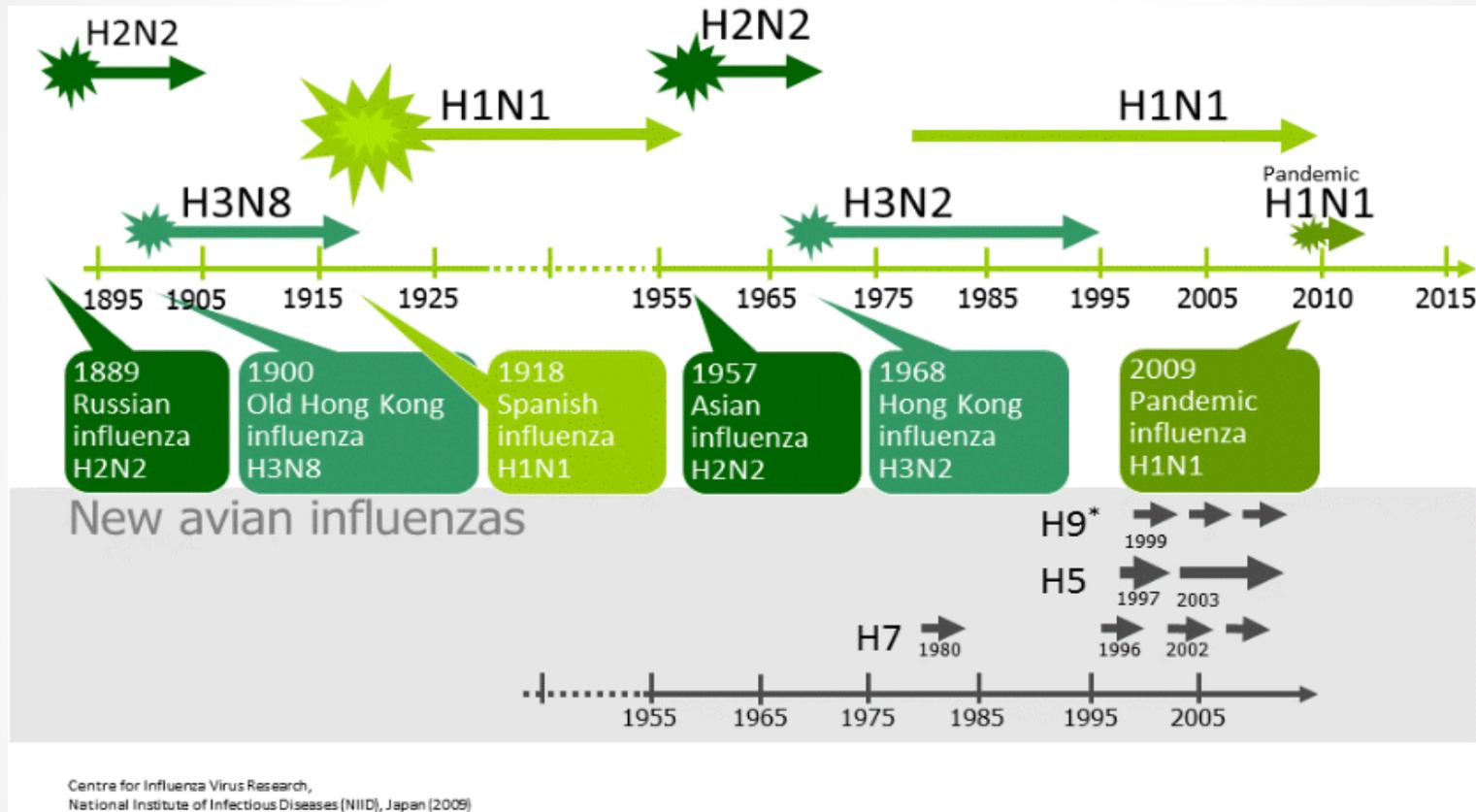




# MORE EFFECTIVE INFLUENZA VACCINES

Armen Donabedian, Ph.D.  
Chief, Influenza Vaccine Advanced  
Development Branch  
October 18, 2016

# Perpetual challenge of responding to influenza



## 1918 'Spanish' Pandemic

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

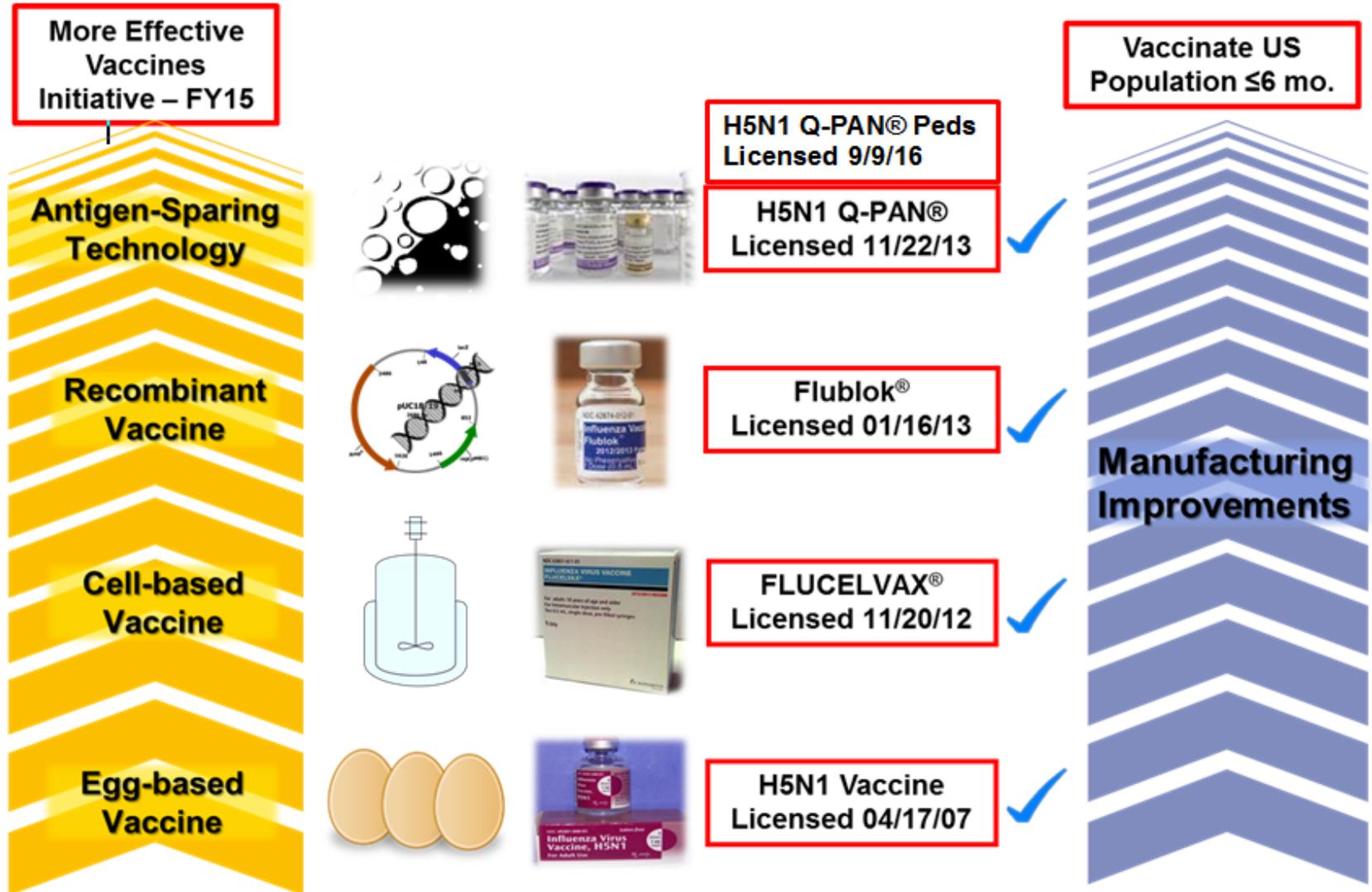
## 2009-H1N1 Pandemic

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 US

5%-20% of population infected year  
 3,000-49,000 deaths every year  
 >200,000 hospitalizations  
 \$87.1B economic burden every year  
 \$10.4B medical costs every year

# BARDA is achieving national pandemic vaccine goals



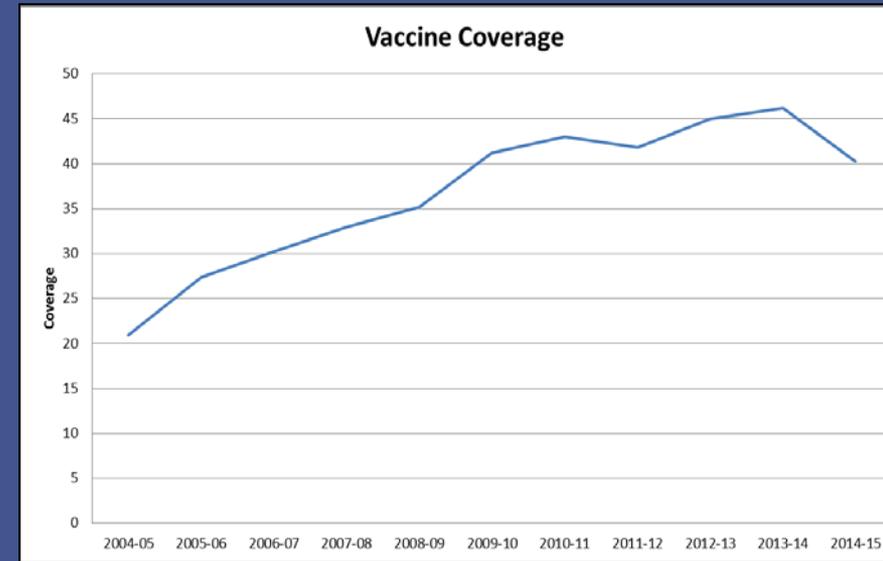
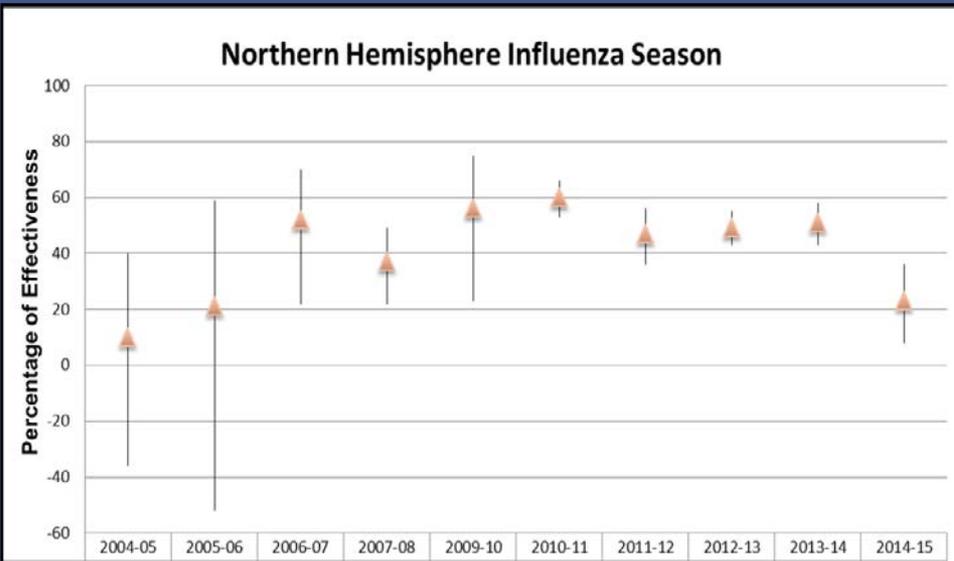
**More, faster to More, faster & better!**

# Limitations of 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, particularly in at-risk populations (e.g., pediatric, geriatric)
- Requires viral isolate for production
- Predominantly produced in chicken eggs
- Avian influenza strains will likely require adjuvant
- Vaccine efficacy is modest



# Limitations of current influenza vaccines

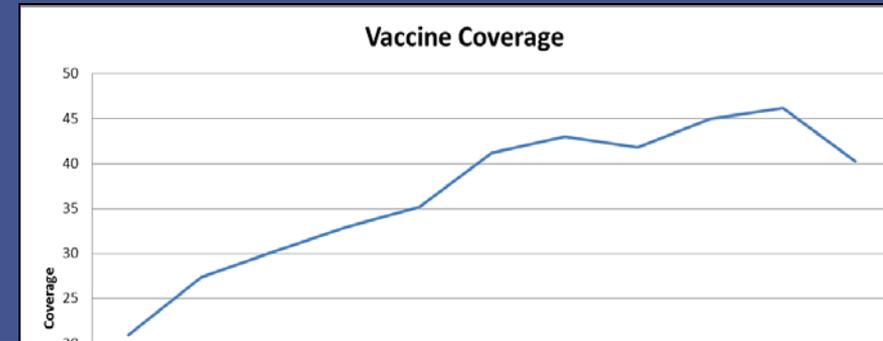
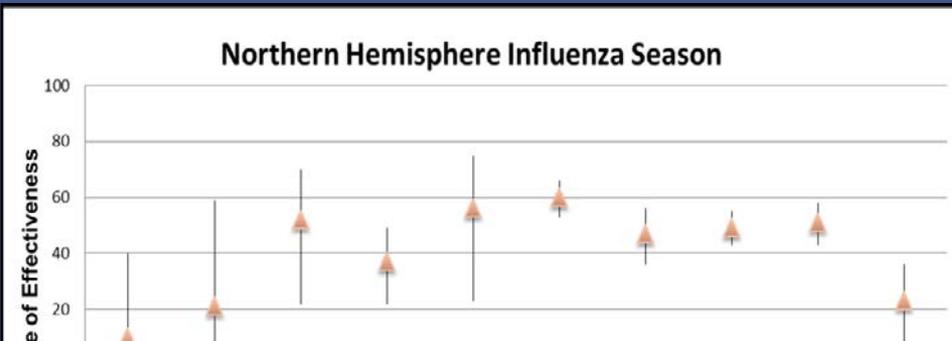


## Adjusted VE for influenza vaccination by influenza A subtype and B virus lineage, US Flu VE Network, 2014-15

	Influenza -Positive	% vaccinated	Influenza- negative	% vaccinated	Adjusted VE	(95% CI)
Influenza A (H3N2)	941/1821	(52)	3866/7072	(55)	13%	(2 to 23)
Influenza B (Yamagata)	125/340	(37)	3866/7092	(55)	55%	(43 to 65)
Influenza B (Victoria)	12/47	(26)	3866/7092	(55)	63%	(26 to 81)

\* Data is for all ages and adjusted for study site, age, sex, race/Hispanic ethnicity, self-rated health status, days from illness onset to enrollment, and calendar time (biweekly intervals).

# Limitations of current influenza vaccines



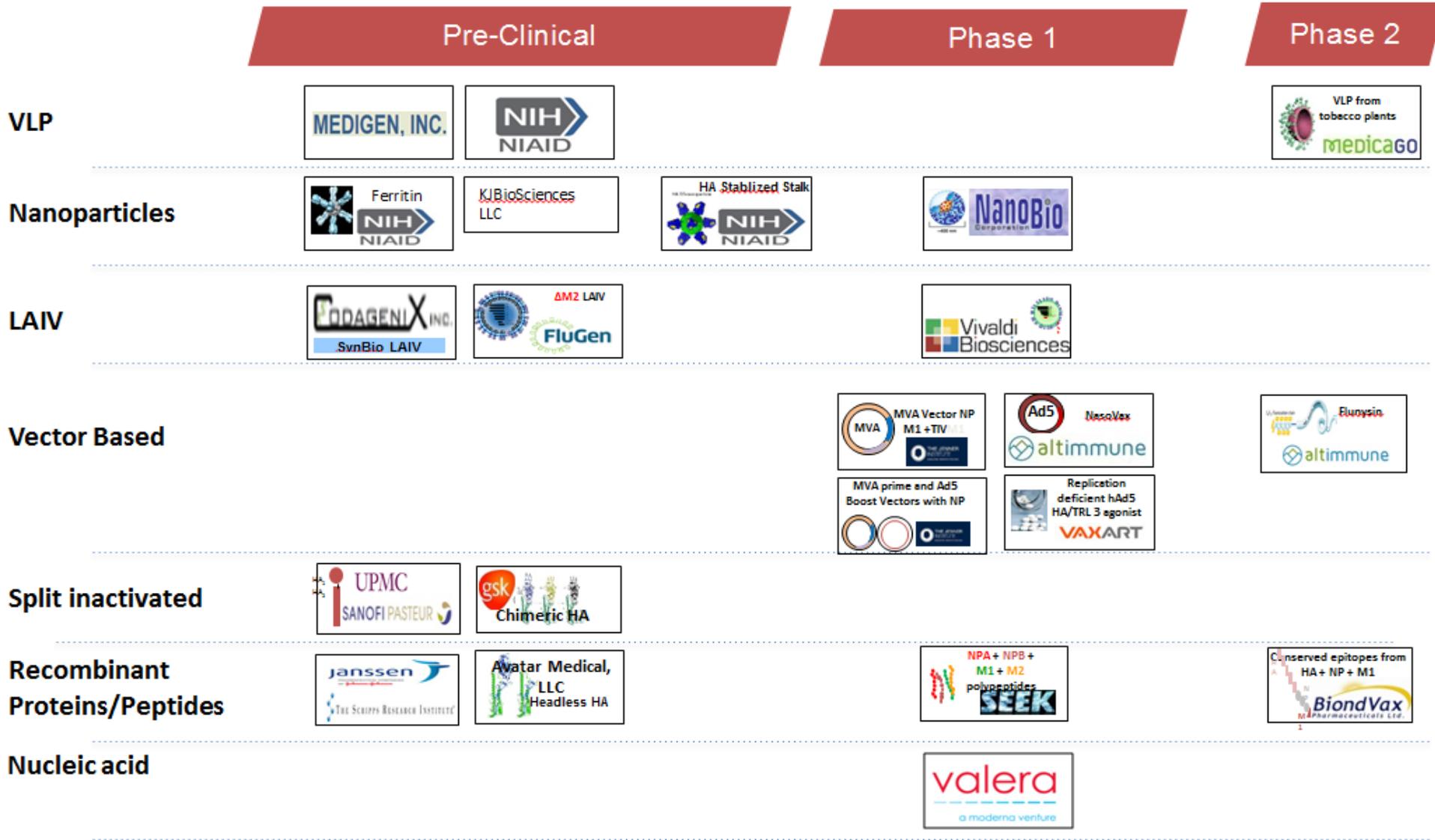
There is need for more effective influenza vaccines

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# Landscape of more effective influenza vaccine candidates



# Landscape of more effective influenza vaccine candidates



# Landscape of more effective influenza vaccine candidates

? Data is lacking  
■ Presence of desirable immune response

Immunological compartment		Humoral		Cell-mediated			Mucosal
Platform	Responses	HAI/MN	Stem	CD4	CD8 to HA	CD8 to conserved Ag	Tissue-resident memory cells
TIV or QIV +/- MF59, AS03	Candidate examples		?				
	potential						
Vector	LAIV or dM2, dNS wt		?	?	?	?	
	MVA-NP, M1, PB1	?	?	?	?		?
	Ad - HA, IN	?	?			?	
	Ad -HA, Oral		?			?	
	Plant VLP		?			?	?
Peptides	potential						
	M-100						
	NP, PB1, PB2, M			?	?		
Nucleic Acid	potential						
	RNA + delivery		?			?	
Stem-based	Exotic, headless Stalk						

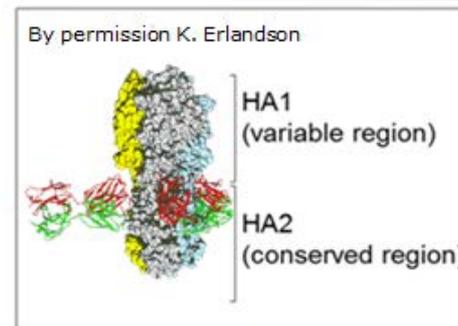
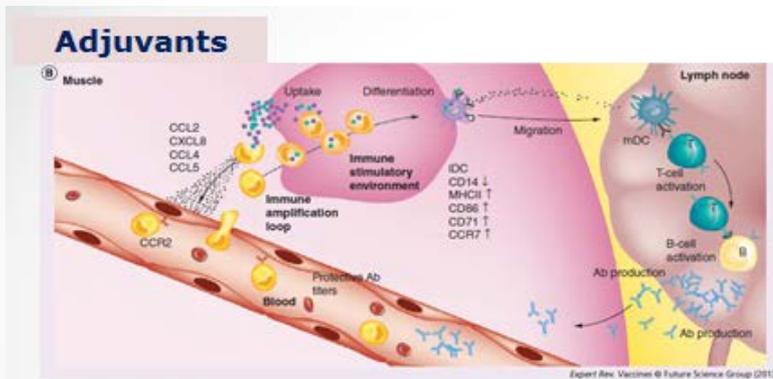
# Overview Information

- 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.
- Technical Point of Contact:
  - Aaron Bandremer, [Aaron.Bandremer@hhs.gov](mailto:Aaron.Bandremer@hhs.gov)

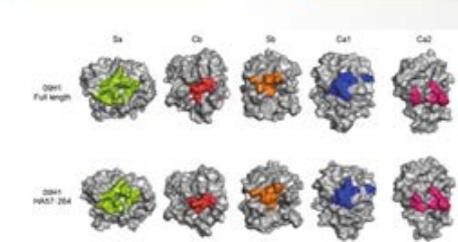


# Influenza Vaccine Development Priorities

- Vaccines that induce broad immunity so as to protect against antigenically divergent influenza A viruses and viruses from both influenza B virus lineages



### Cross-reactive stalk-based epitopes

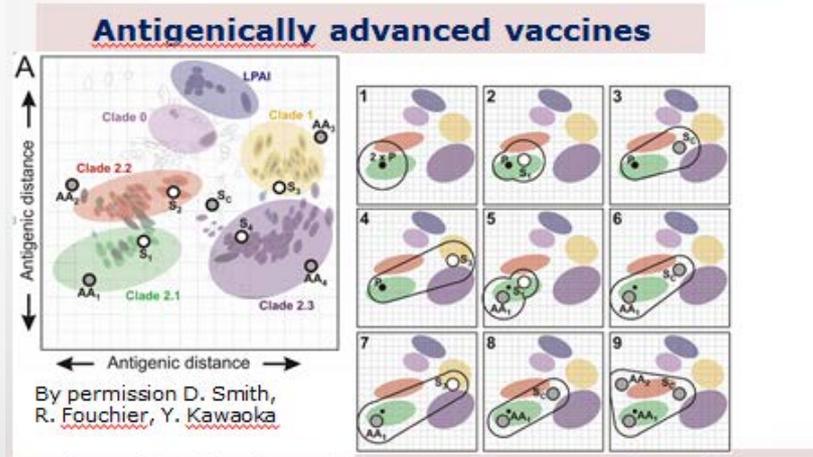


### Structure-based modification of HA specificity

Protein Cell 2011, 2(12): 997-1005  
DOI 10.1007/s13238-011-1134-y

Structural vaccinology: structure-based design of influenza A virus hemagglutinin subunit-specific subunit vaccines

Protein & Cell

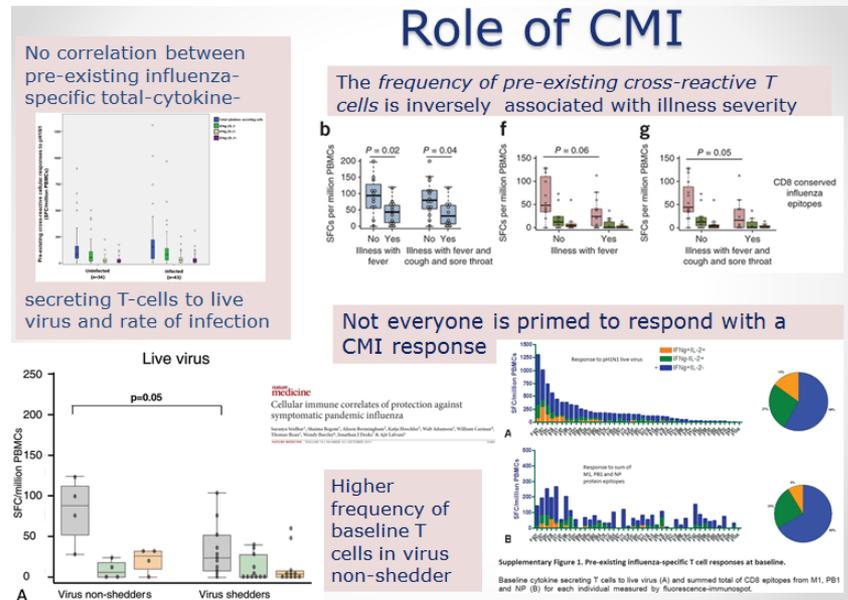
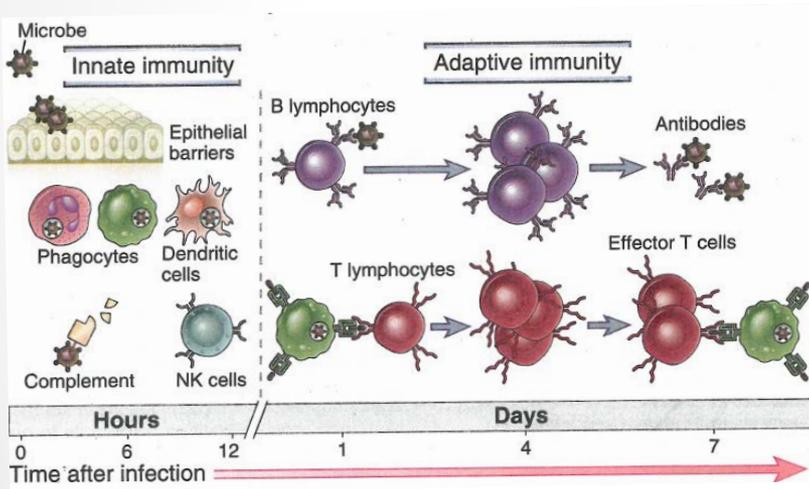


### Rationally designed heterologous prime boost



# Influenza Vaccine Development Priorities (2)

- Vaccines that induce broad immunity so as to prime the population against newly emerging influenza viruses or other respiratory viruses of pandemic potential

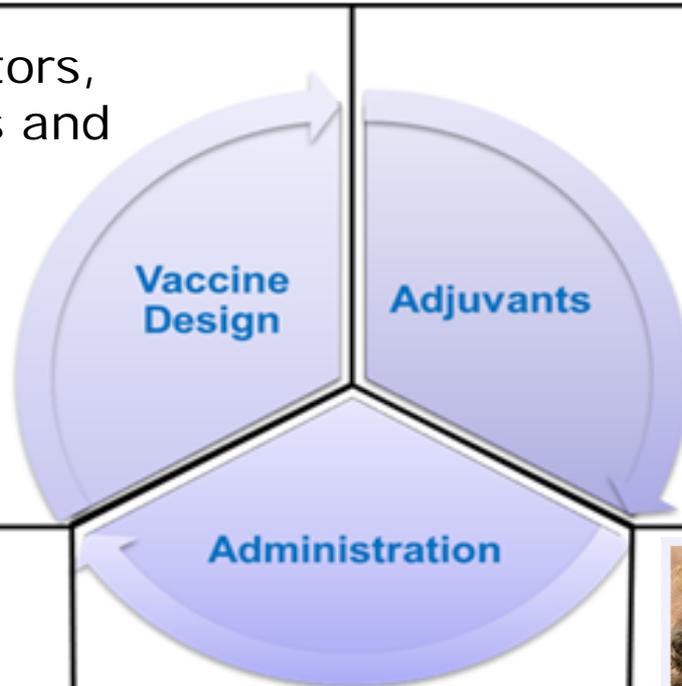


- Vaccines that induce long-lasting immunity in all populations compared to licensed influenza vaccines

# Influenza Vaccine Development Priorities (3)

- Influenza vaccines that have greater efficacy in all populations compared to licensed vaccines as measured by clinical surrogate endpoints predicative of clinical benefit

- ❖ IIV, attenuated vectors, recombinant – VLPs and nanoparticles, nucleic acid
- ❖ Epitope content, structure
- ❖ Humoral, CMI, mucosal, innate



- ❖ MF59, AS03, poly IC, Resiquimod, other TRL agonists
- ❖ Innate immunostimulators?



- ❖ Oral, intranasal, injection
- ❖ HtPB
- ❖ Boost regimen



# More effective influenza vaccine: Target Product Profile

Property/Vaccine	Desired Primary Characteristics
<b>Breadth of Protection</b>	<i>Protects against antigenically divergent influenza A viruses and viruses from both influenza B virus lineages</i>
<b>Efficacy</b>	<i>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) predicative of clinical benefit</i>
<b>Duration of Immunity</b>	<i>Protects for two years or more against influenza A subtypes and influenza B lineages</i>
<b>Priming Immunity</b>	<i>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</i>
 <b>Safety</b>	<i>Comparable to licensed vaccines</i>

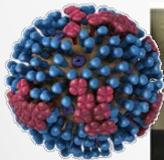
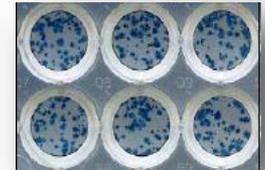
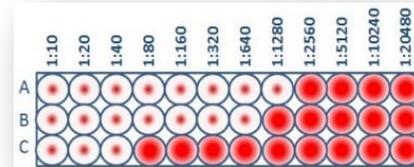
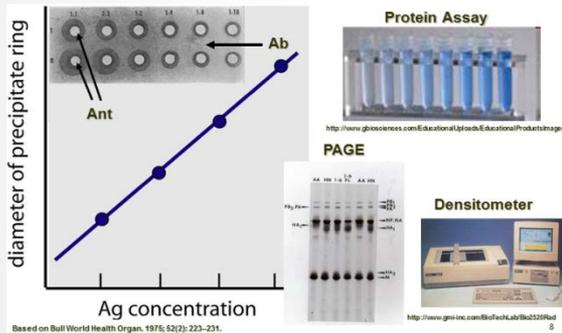
# Data Expectations

- Pre-clinical and clinical studies supporting the ability of your candidate vaccine to elicit cross-reactive immune responses against antigenically diverse influenza A viruses
- Data that demonstrate improvements in immunogenicity/efficacy as compared to licensed vaccines
- Pre-clinical and/or clinical data regarding the duration of the immune response
- Data to support priming immunity against pandemic influenza
- Evidence of TRL6 of your proposed candidate or approach, including evidence of an in-effect US IND
- All communications with the FDA for your candidate
- Information on the immunological assays used to evaluate immune responses in clinical trials. Include where assays were performed, qualification/validation state of the assay, and all data that may be used to correlate specific immune responses with clinical benefit

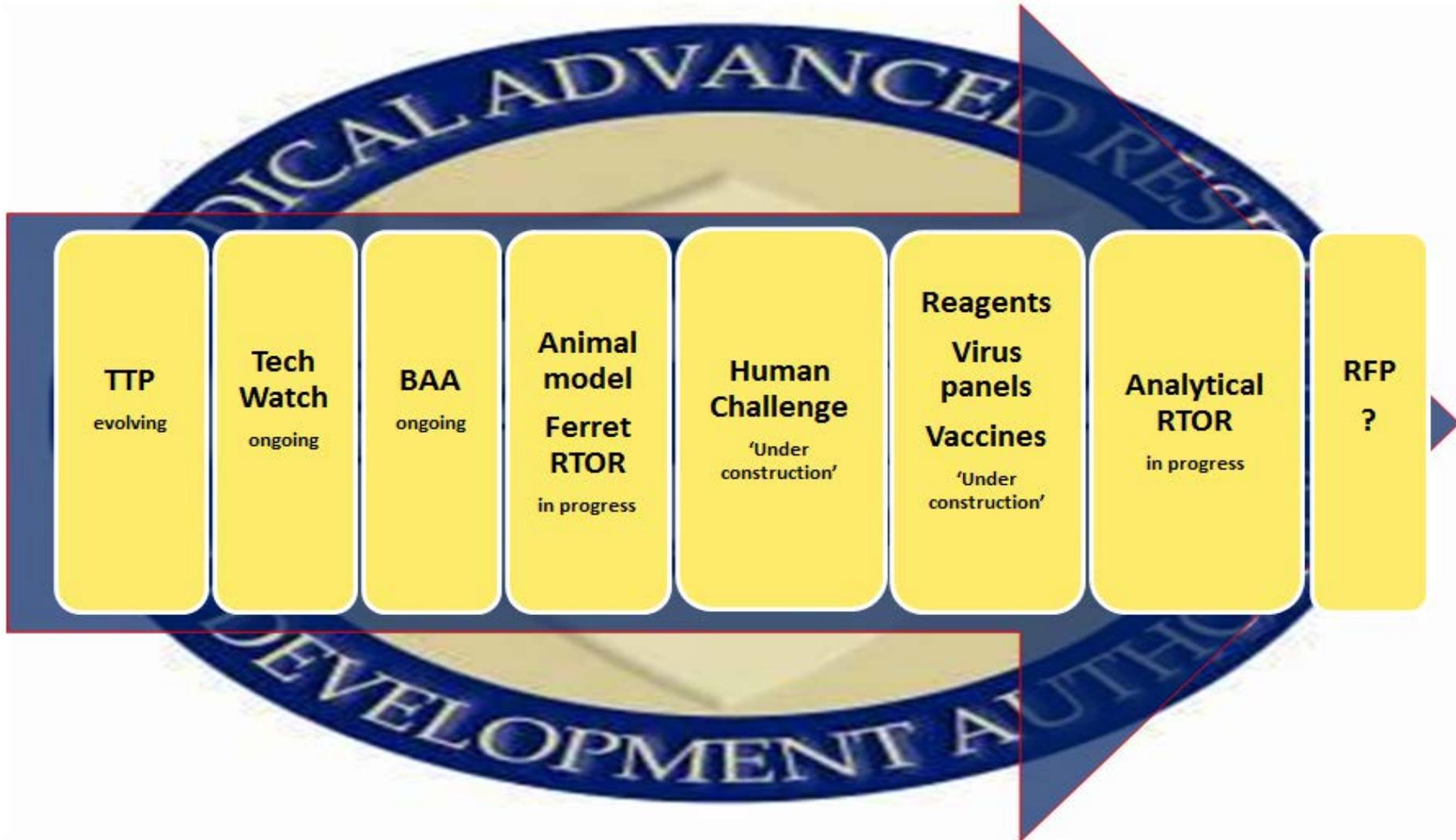


# Influenza Vaccine Development Priorities (4)

- Improvements in vaccine production methods that accelerate the availability of vaccines against viruses with pandemic potential



# More effective influenza vaccine development pipeline at BARDA





## MORE EFFECTIVE INFLUENZA VACCINES .... ....NEXT STEPS



Medical  
**Countermeasures.gov**



### Broad Agency Announcement (BAA) for the Advanced Development of Medical Countermeasures for Pandemic Influenza

Solicitation Number: BAA-16-100-SOL-00002

Agency: Department of Health and Human Services

Office: Office of the Secretary

Location: Acquisitions Management, Contracts, & Grants (AMCG)