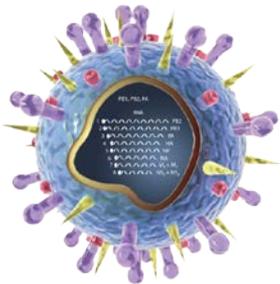




United States Department of
Health & Human Services
Office of the Assistant Secretary for Preparedness and Response



U.S. Influenza Vaccine Development and Pandemic Preparedness: Past, Present and Future



Rick Bright, PhD

Acting Director, Influenza Division

Biomedical Advanced Research and Development Authority (BARDA)

Office of the Assistant Secretary for Preparedness & Response

National Vaccine Advisory Committee Meeting

June 10, 2014



A Nation Unprepared: US Influenza Vaccines in 2004



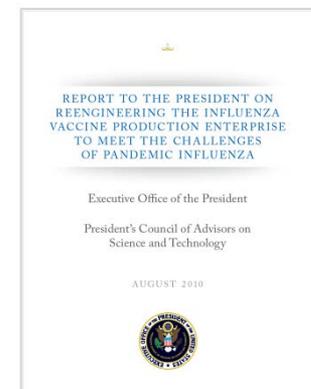
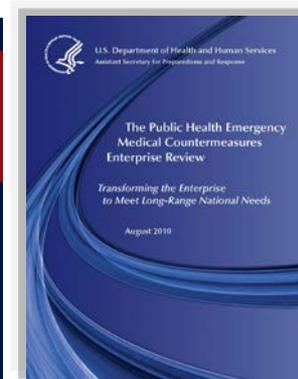
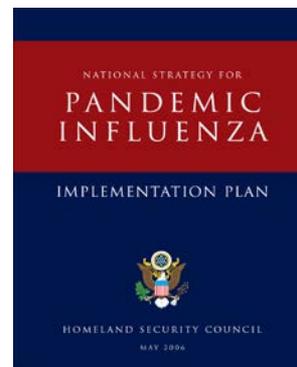
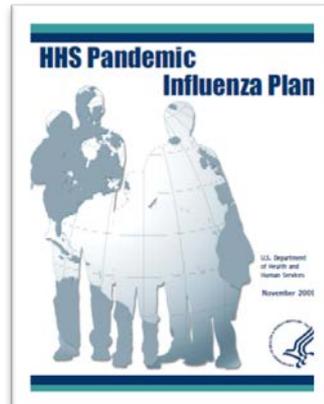
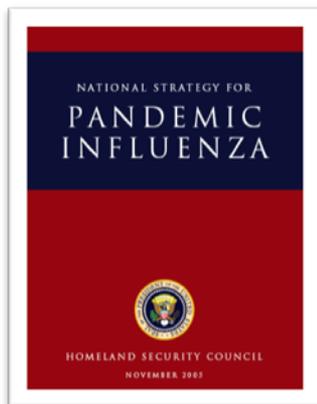
- All licensed seasonal vaccines are egg-based (1940s-1950s technology)
- Vaccine is produced in a six month production window (January-June each year); no production capability outside of that window
- Annual immunization is required
 - Vaccine effectiveness estimated at 50-70% in healthy adults
- Severe shortage of seasonal influenza vaccine in fall 2004 due to production failure at one facility highlighted US vulnerability
- Limited domestic manufacturing capacity to respond to a pandemic



Establishing Pandemic Influenza Vaccine Capabilities: USG Requirements



- In 2005, the USG launched an national effort to improve US pandemic preparedness, called for 300+ preparedness actions
- The requirements addressed by the BARDA Influenza Portfolio are derived from a number of documents that guide the US Government efforts to prepare for pandemic, including:
 - Establish and maintaining a dynamic pre-pandemic vaccine stockpile
 - Establish domestic manufacturing capacity to produce sufficient vaccine for the entire U.S. population within 6 months of pandemic declaration
 - Improve, optimize and/or innovate vaccine production technologies
- Goal: More and better influenza vaccine, faster





BARDA's Mission



Enhance national preparedness for CBRN threats, pandemic influenza, and emerging infectious diseases by supporting innovation, developing and acquiring medical countermeasures, and building manufacturing infrastructure.



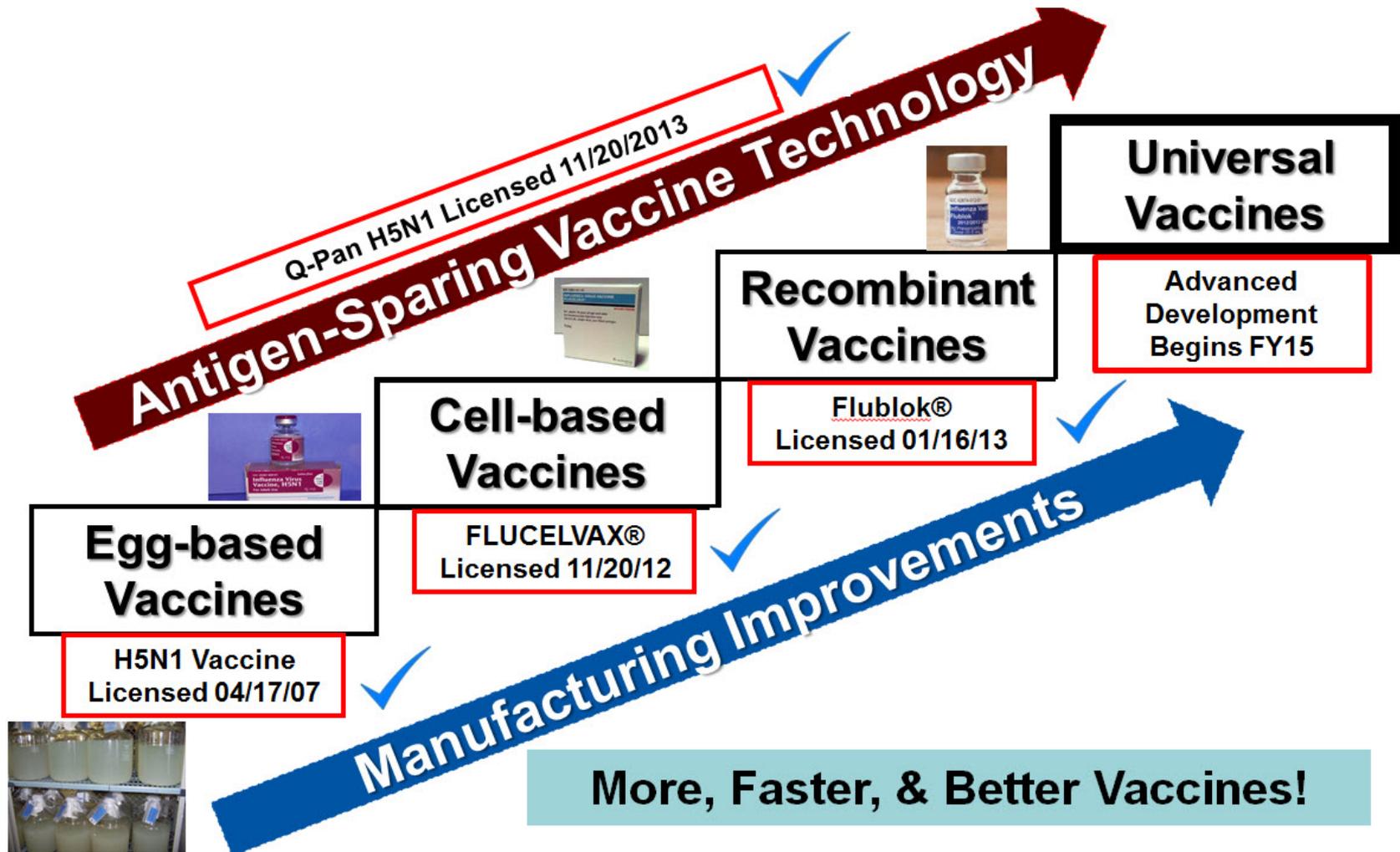


BARDA Approach to Making Medical Countermeasures Available





BARDA is Achieving National Pandemic Influenza Vaccine Goals





BARDA: Enhancing Domestic Vaccine Manufacturing Capacity



- Expanding Existing Capacity by Retrofitting Vaccine Manufacturing Infrastructure



sanofi pasteur – Swiftwater, PA

- Changing Flu Vaccine Industry
2013 ISPE Facility of the Year



Novartis – Holly Springs, NC



Centers for Innovation in Advanced Development and Manufacturing

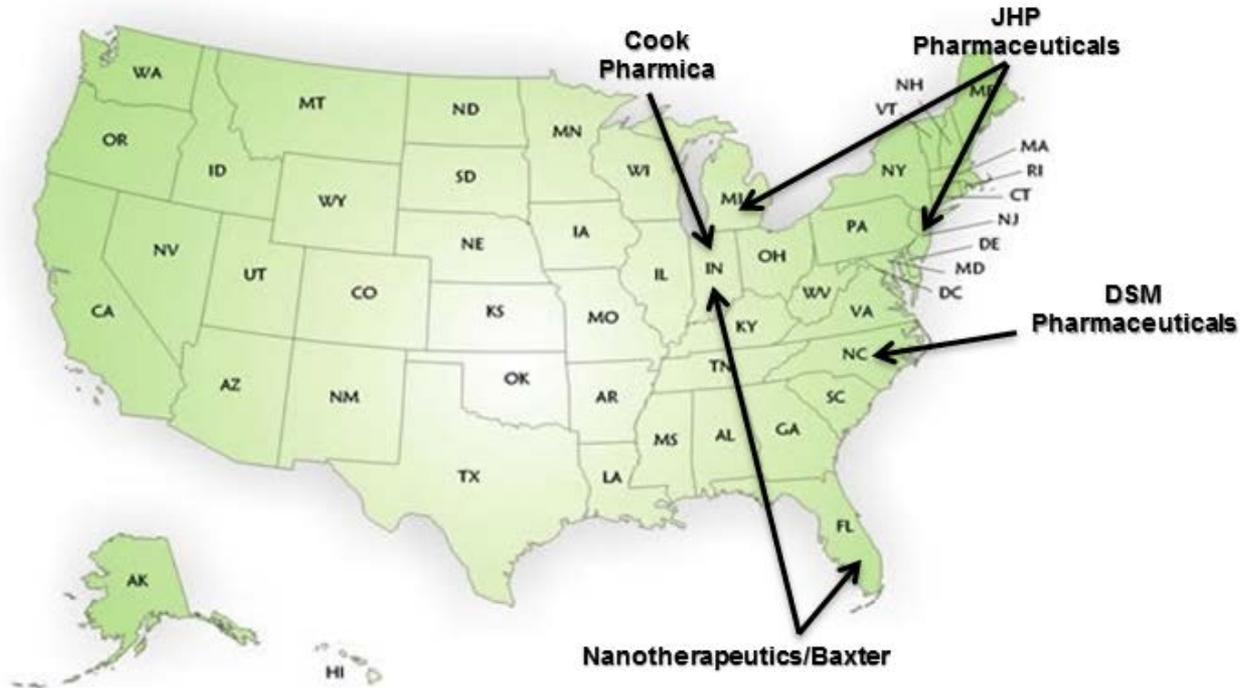






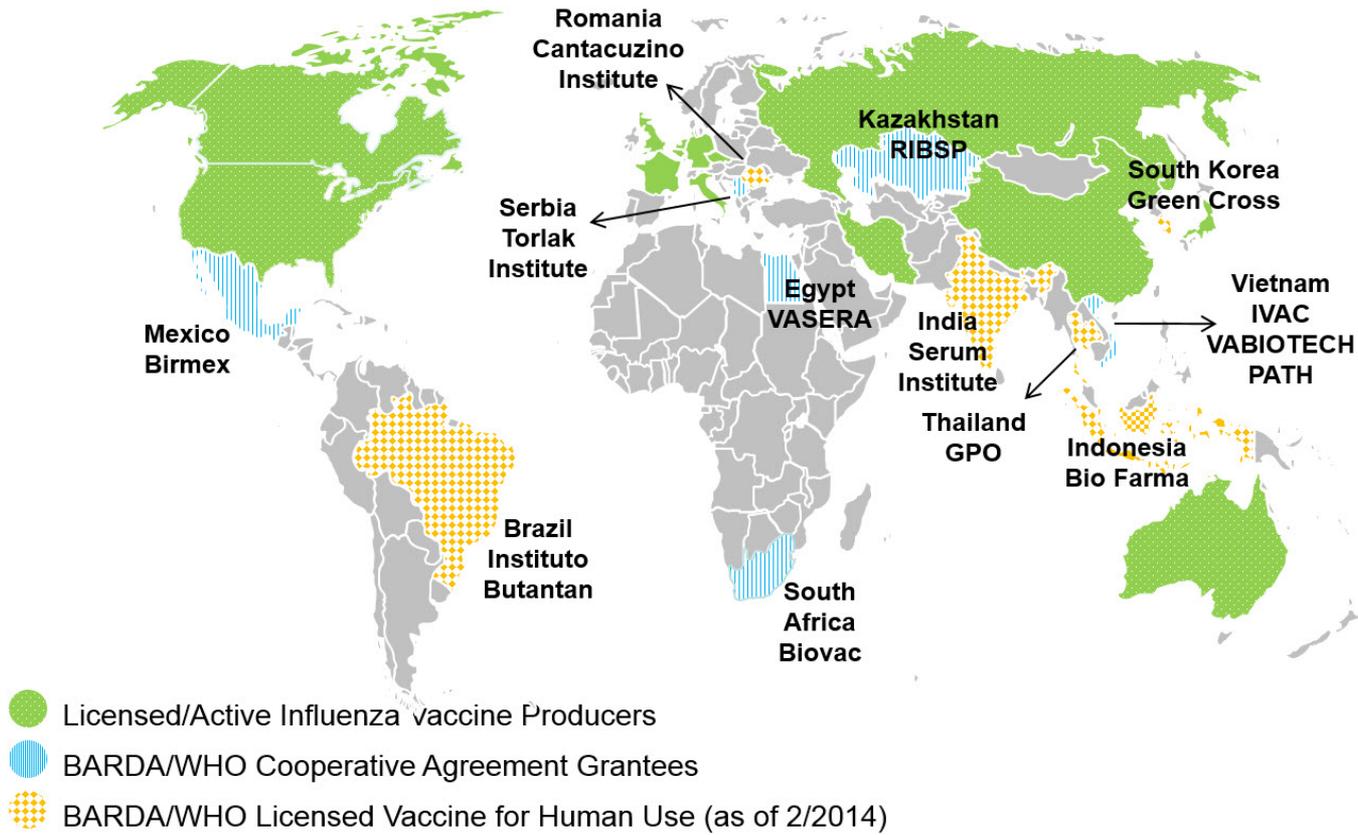
Contract Awardees:

Emergent Manufacturing Operations Baltimore LLC
Novartis Vaccines & Diagnostics, Inc.
The Texas A&M University System (TAMUS)



Cook Pharmica (IN)
JHP Pharmaceuticals (MI and NJ)
DSM Pharmaceuticals (NC)
Nanotherapeutics/Baxter (FL and IN)

Current Geographical Distribution of Influenza Vaccine Production



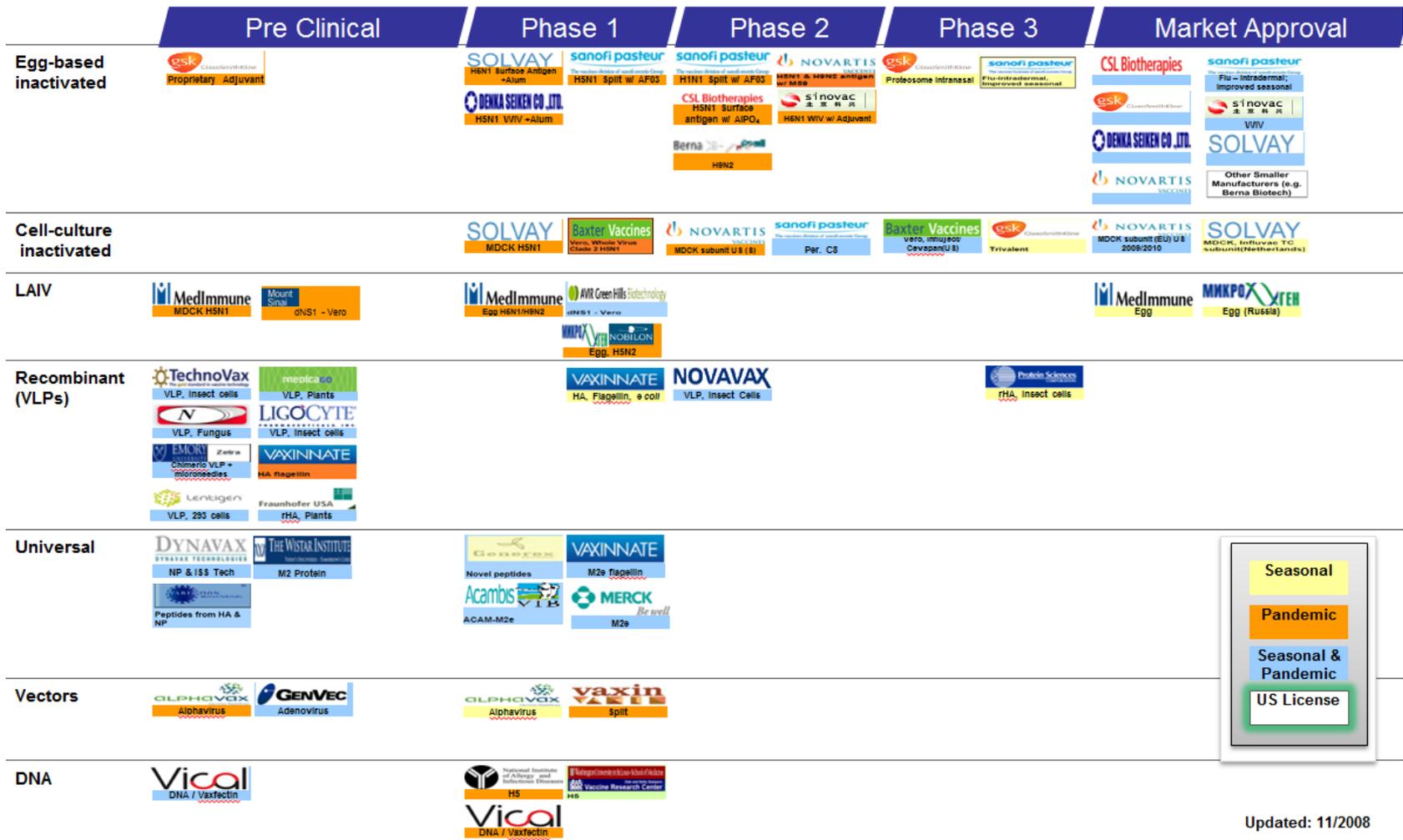


Influenza Vaccine Landscape

	Pre Clinical	Phase 1	Phase 2	Phase 3	Market Approval
Egg-based inactivated					
Cell-culture inactivated					
LAIV					
Recombinant (VLPs)					
Universal					
Vectors					
DNA					

- Seasonal
- Pandemic
- Seasonal & Pandemic
- US License

2008 Influenza Vaccine Landscape



Seasonal

Pandemic

Seasonal & Pandemic

US License

Updated: 11/2008

2009 Influenza Vaccine Landscape

	Pre Clinical	Phase 1	Phase 2	Phase 3	Market Approval
Egg-based inactivated	Proprietary Adjuvant <small>Classroom/MSD/Novartis</small>	HSN1 Surface Antigen + Alum HSN1 WVIV + Alum HSN2 virosomal & whole	HSN1 Split w/ AF03 HSN1 Split w/ AF03 HSN1 Surface antigen w/ AIPO₂ HSN1, WVIV	HSN1 & HSN2 Antigen w/ ASB HSN1 WVIV w/ Adjuvant Classroom/MSD/Novartis Protosome Intranasal	HSN1 intranasal, improved seasonal Fig - Intradermal, improved seasonal HSN1 WVIV SOLVAY Other Smaller Manufacturers (e.g. Berna Biotech)
Cell-culture inactivated	MDCK, Adjuvanted	MDCK HSN1 vero, whole virus, double 2 HSN1	MDCK subunit U & (B) Per. CS	vero, mfu, ego, Cevaxan(U8) Trivalent, Classroom/Novartis	MDCK subunit (EU) U8 2009/2010 MDCK, Influvax TC subunit (Netherlands)
LAIV	MDCK HSN1 dNS1 - Vero Batmonetta, Oral	Egg HSN1/HSN2 dNS1 - Vero Egg, HSN2			Egg Egg (Russia)
Recombinant (VLPs)	VLP, Insect cells VLP / HA Chimeric viral microproteins VLP, Fungus Yeast, IN - Oral rHA, Plants HA flagellin VLP, Plants VLP, Insect cells	HA, Flagellin, a coil VLP, Insect Cells rHA, Insect cells			rHA, Insect cells
Universal	NP & ISS Tech M2 Protein Peptides from HA & NP	ACAM-M2e M2e Novel peptides M2e flagellin Peptide based			
Vectors	Alphavirus Adenovirus Adenovirus, Oral	Adenovirus, Oral Split Alphavirus			
DNA	DNA / Vaxfectin	HS DNA / Vaxfectin DNA	HS HS		

Seasonal

Pandemic

Seasonal & Pandemic

US License

Updated: 08/2009

2010 Influenza Vaccine Landscape

	Pre Clinical	Phase 1	Phase 2	Phase 3	Market Approval
Egg-based inactivated					
Cell-culture inactivated					
LAIV					
Recombinant (VLPs)					
Universal					
Vectors					
DNA					

Seasonal

Pandemic

Seasonal & Pandemic

US License

Updated: 11/09/2010

2011 Influenza Vaccine Landscape

	Pre Clinical	Phase 1	Phase 2	Phase 3	Market Approval
Egg-based inactivated	Whole Virion Proprietary Adjuvant Egg inactivated VIV Split VIV H2N2 virosome/whole VIV Split H2N1 surface Antigen + Alum H2N1 VIV + Alum Split	H2N1 Split w/ AF03 H2N1 Split w/ AF03 H2N1 surface antigen w/ AIPO ₄ H2N1, VIV H2N1 VIV w/ Adjuvant Proteosome intranasal H2N1 A 803	H2N1 A 803 H1N1 intradermal; Improved seasonal H1N1 Cell; HN-VAC (India) H2N1 VIV + Alum Split Split Adimmune-Taiwan BIO-PHARMA 天源生物 华兰生物 VIV SK chemicals qingdao 北里研究所 (주)한국백신		
Cell-culture inactivated	H2N1 MDCK H2N1 dN S1 - Vero MDCK H2N1 EB 65 Cells MDCK Influenza TC subunit (Netherlands) Monkey Kidney Cell MDCK subunit U & B Vero, Influenza Covapan (U.S.) MDCK subunit (EU) U & B 2009/2010 Vero, Influenza Covapan (EU) H2N1 Cell; HN-VAC (India)	MDCK H2N1 dN S1 - Vero MDCK H2N1 EB 65 Cells MDCK Influenza TC subunit (Netherlands) Monkey Kidney Cell MDCK subunit U & B Vero, Influenza Covapan (U.S.) MDCK subunit (EU) U & B 2009/2010 Vero, Influenza Covapan (EU) H2N1 Cell; HN-VAC (India)	MDCK H2N1 dN S1 - Vero MDCK H2N1 EB 65 Cells MDCK Influenza TC subunit (Netherlands) Monkey Kidney Cell MDCK subunit U & B Vero, Influenza Covapan (U.S.) MDCK subunit (EU) U & B 2009/2010 Vero, Influenza Covapan (EU) H2N1 Cell; HN-VAC (India)	MDCK H2N1 dN S1 - Vero MDCK H2N1 EB 65 Cells MDCK Influenza TC subunit (Netherlands) Monkey Kidney Cell MDCK subunit U & B Vero, Influenza Covapan (U.S.) MDCK subunit (EU) U & B 2009/2010 Vero, Influenza Covapan (EU) H2N1 Cell; HN-VAC (India)	MDCK H2N1 dN S1 - Vero MDCK H2N1 EB 65 Cells MDCK Influenza TC subunit (Netherlands) Monkey Kidney Cell MDCK subunit U & B Vero, Influenza Covapan (U.S.) MDCK subunit (EU) U & B 2009/2010 Vero, Influenza Covapan (EU) H2N1 Cell; HN-VAC (India)
LAIV	MDCK H2N1 dN S1 - Vero MDCK H2N1 EB 65 Cells MDCK Influenza TC subunit (Netherlands) Monkey Kidney Cell MDCK subunit U & B Vero, Influenza Covapan (U.S.) MDCK subunit (EU) U & B 2009/2010 Vero, Influenza Covapan (EU) H2N1 Cell; HN-VAC (India)	MDCK H2N1 dN S1 - Vero MDCK H2N1 EB 65 Cells MDCK Influenza TC subunit (Netherlands) Monkey Kidney Cell MDCK subunit U & B Vero, Influenza Covapan (U.S.) MDCK subunit (EU) U & B 2009/2010 Vero, Influenza Covapan (EU) H2N1 Cell; HN-VAC (India)	MDCK H2N1 dN S1 - Vero MDCK H2N1 EB 65 Cells MDCK Influenza TC subunit (Netherlands) Monkey Kidney Cell MDCK subunit U & B Vero, Influenza Covapan (U.S.) MDCK subunit (EU) U & B 2009/2010 Vero, Influenza Covapan (EU) H2N1 Cell; HN-VAC (India)	MDCK H2N1 dN S1 - Vero MDCK H2N1 EB 65 Cells MDCK Influenza TC subunit (Netherlands) Monkey Kidney Cell MDCK subunit U & B Vero, Influenza Covapan (U.S.) MDCK subunit (EU) U & B 2009/2010 Vero, Influenza Covapan (EU) H2N1 Cell; HN-VAC (India)	MDCK H2N1 dN S1 - Vero MDCK H2N1 EB 65 Cells MDCK Influenza TC subunit (Netherlands) Monkey Kidney Cell MDCK subunit U & B Vero, Influenza Covapan (U.S.) MDCK subunit (EU) U & B 2009/2010 Vero, Influenza Covapan (EU) H2N1 Cell; HN-VAC (India)
Recombinant (VLPs)	VLP / HA VLP, Insect cells VLP, 293 cells rHA, Plants rHA, Insect cells VLP, Insect Cells rHA, Insect cells Influenza, Oral Yeast, IN - Oral Salmonella, Oral Molecular HA rHA, Plants rHA, Plants VLP, Fungus Yeast, IN - Oral Influenza VLP + microencapsules VLP, Insect cells VLP, Plants HA, Flagellin, e coli rHA, Insect Cells	VLP / HA VLP, Insect cells VLP, 293 cells rHA, Plants rHA, Insect cells VLP, Insect Cells rHA, Insect cells Influenza, Oral Yeast, IN - Oral Salmonella, Oral Molecular HA rHA, Plants rHA, Plants VLP, Fungus Yeast, IN - Oral Influenza VLP + microencapsules VLP, Insect cells VLP, Plants HA, Flagellin, e coli rHA, Insect Cells	VLP / HA VLP, Insect cells VLP, 293 cells rHA, Plants rHA, Insect cells VLP, Insect Cells rHA, Insect cells Influenza, Oral Yeast, IN - Oral Salmonella, Oral Molecular HA rHA, Plants rHA, Plants VLP, Fungus Yeast, IN - Oral Influenza VLP + microencapsules VLP, Insect cells VLP, Plants HA, Flagellin, e coli rHA, Insect Cells	VLP / HA VLP, Insect cells VLP, 293 cells rHA, Plants rHA, Insect cells VLP, Insect Cells rHA, Insect cells Influenza, Oral Yeast, IN - Oral Salmonella, Oral Molecular HA rHA, Plants rHA, Plants VLP, Fungus Yeast, IN - Oral Influenza VLP + microencapsules VLP, Insect cells VLP, Plants HA, Flagellin, e coli rHA, Insect Cells	VLP / HA VLP, Insect cells VLP, 293 cells rHA, Plants rHA, Insect cells VLP, Insect Cells rHA, Insect cells Influenza, Oral Yeast, IN - Oral Salmonella, Oral Molecular HA rHA, Plants rHA, Plants VLP, Fungus Yeast, IN - Oral Influenza VLP + microencapsules VLP, Insect cells VLP, Plants HA, Flagellin, e coli rHA, Insect Cells
Universal	HA Fusion Peptide M2 Protein Peptides from HA & NP M2s NP & 18S Tech M2s flagellin Novel peptides M2s Peptide based	HA Fusion Peptide M2 Protein Peptides from HA & NP M2s NP & 18S Tech M2s flagellin Novel peptides M2s Peptide based	HA Fusion Peptide M2 Protein Peptides from HA & NP M2s NP & 18S Tech M2s flagellin Novel peptides M2s Peptide based	HA Fusion Peptide M2 Protein Peptides from HA & NP M2s NP & 18S Tech M2s flagellin Novel peptides M2s Peptide based	HA Fusion Peptide M2 Protein Peptides from HA & NP M2s NP & 18S Tech M2s flagellin Novel peptides M2s Peptide based
Vectors	MVA Based MVA Based Adenovirus, M & NP Adenovirus Adenovirus, Oral Adenovirus, Oral MVA Adenovirus Adenovirus Alphavirus Adenovirus, Oral	MVA Based MVA Based Adenovirus, M & NP Adenovirus Adenovirus, Oral Adenovirus, Oral MVA Adenovirus Adenovirus Alphavirus Adenovirus, Oral	MVA Based MVA Based Adenovirus, M & NP Adenovirus Adenovirus, Oral Adenovirus, Oral MVA Adenovirus Adenovirus Alphavirus Adenovirus, Oral	MVA Based MVA Based Adenovirus, M & NP Adenovirus Adenovirus, Oral Adenovirus, Oral MVA Adenovirus Adenovirus Alphavirus Adenovirus, Oral	MVA Based MVA Based Adenovirus, M & NP Adenovirus Adenovirus, Oral Adenovirus, Oral MVA Adenovirus Adenovirus Alphavirus Adenovirus, Oral
DNA	LNA / in vivo w/ Electroporation DNA / Vaxfectin H5 LNA / in vivo w/ Electroporation DNA / Vaxfectin DNA	LNA / in vivo w/ Electroporation DNA / Vaxfectin H5 LNA / in vivo w/ Electroporation DNA / Vaxfectin DNA	LNA / in vivo w/ Electroporation DNA / Vaxfectin H5 LNA / in vivo w/ Electroporation DNA / Vaxfectin DNA	LNA / in vivo w/ Electroporation DNA / Vaxfectin H5 LNA / in vivo w/ Electroporation DNA / Vaxfectin DNA	LNA / in vivo w/ Electroporation DNA / Vaxfectin H5 LNA / in vivo w/ Electroporation DNA / Vaxfectin DNA

Seasonal

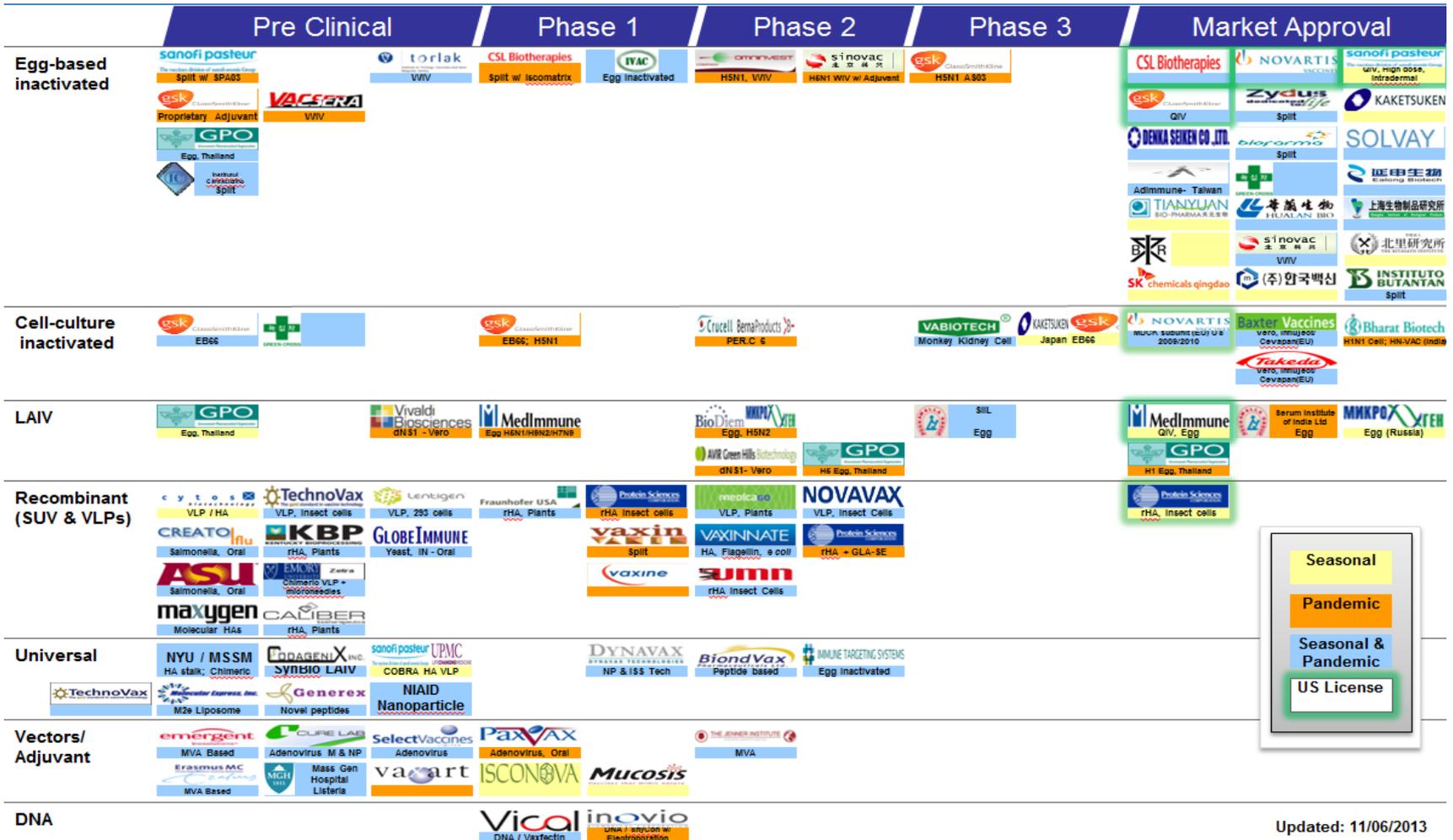
Pandemic

Seasonal & Pandemic

US License

Updated: 07/29/2011

2013 Influenza Vaccine Landscape



Seasonal

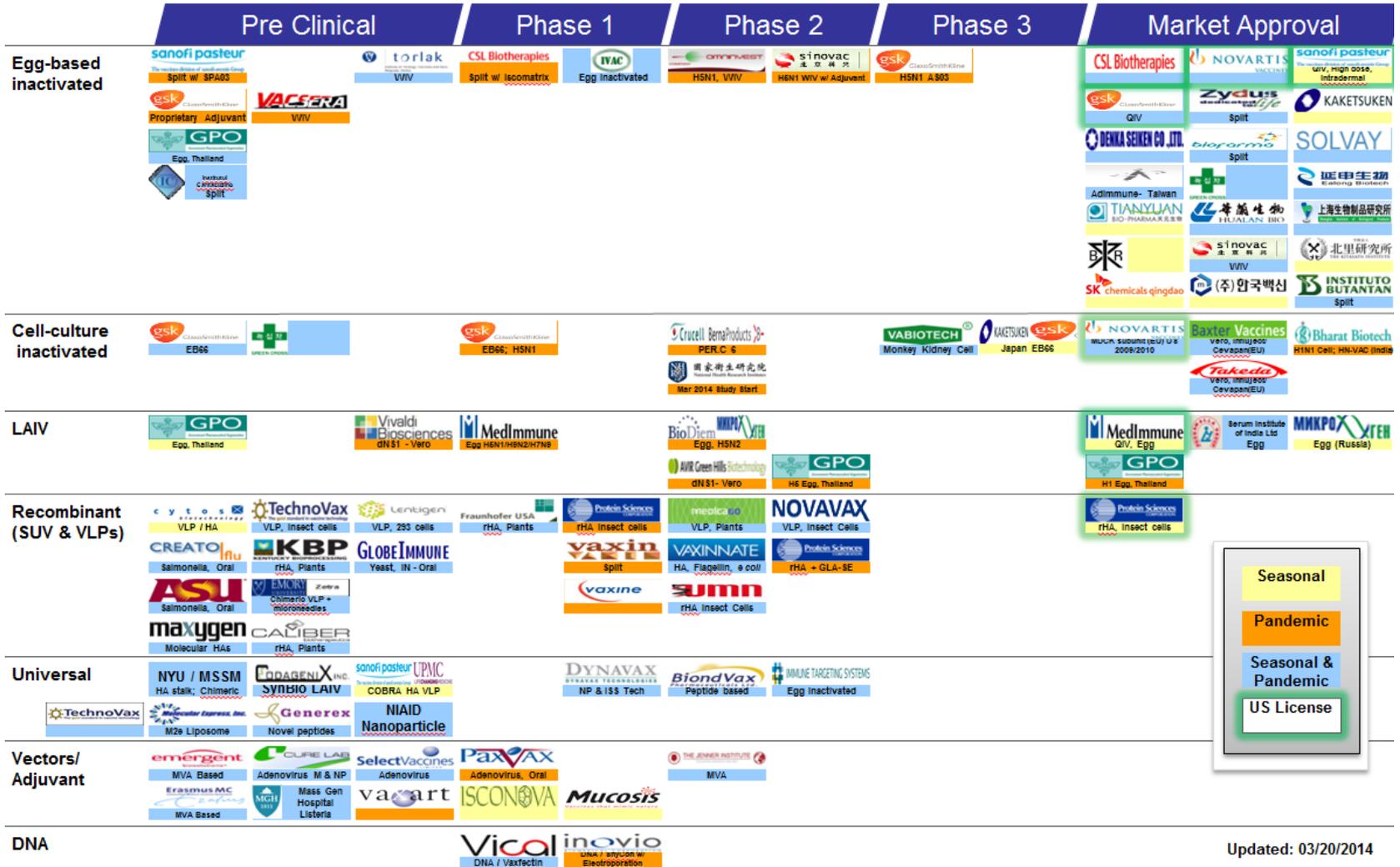
Pandemic

Seasonal & Pandemic

US License

Updated: 11/06/2013

2014 Influenza Vaccine Landscape



Seasonal

Pandemic

Seasonal & Pandemic

US License

Updated: 03/20/2014



Which Flu Vaccine is Right for You?



Which Flu Vaccine is Right for You?

Get Vaccinated and Prevent the Spread of Infection

HIGH-DOSE - Helping the elder avoid flue complications like pneumonia or even death

Great for:

- age 65 or older

NASAL SPAY – Eliminates needles

Great for:

- squirmy kids
- healthy people
- age 2-49

“NEEDLE-FREE” - Contains micro-needles that touch just the surface of the skin

Great for:

- anyone afraid of needles
- age 18-64

EGG-FREE – Cultured in caterpillar cell

Great for:

- egg allergic people

4-STRAIN – Protect against B-class influenza, which affect young children

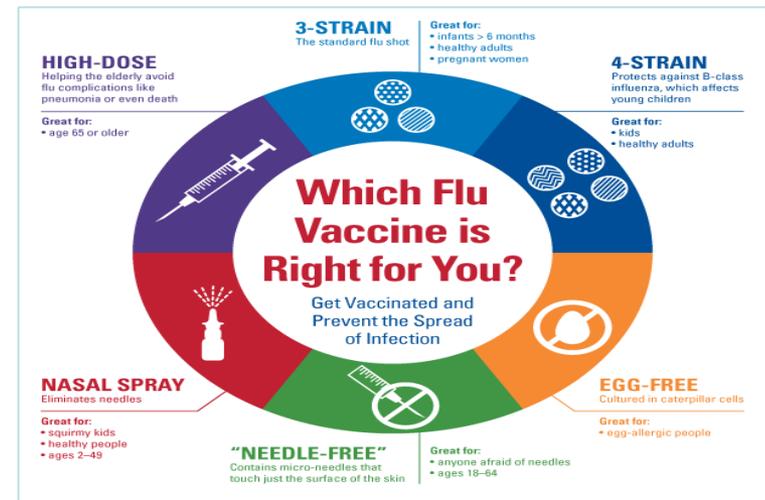
Great for:

- Kids
- healthy adults

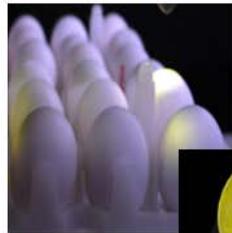
3-STRAIN – The standard flu shot

Great for:

- infants > 6 month
- healthy adults
- pregnant women

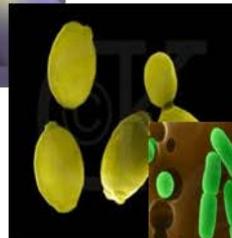


Need for New High Performance Platform Technologies

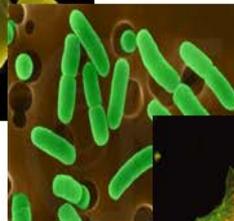


Safety

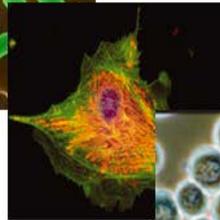
Goal: Develop technologies to address unmet needs



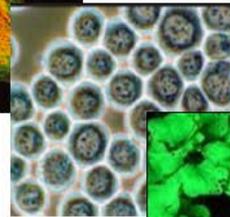
Capacity



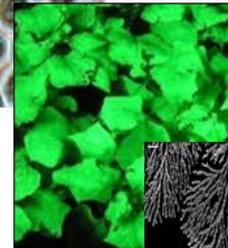
Low Cost



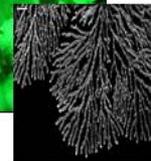
Broadly Reactive



Rapid Response



Simple Manufacture





Universal Influenza Vaccines



- **What is a “universal vaccine”?**
 - Idealized vaccine: single vaccine for any influenza A subtype
- **Could be used for several seasons**
 - Remove annual ‘guesswork’ for strain selection
 - Reduce production costs
 - Eliminate vaccine mismatches
 - Reduce potential for vaccine shortages
 - Increase global supply of vaccine
- **Stockpile of vaccine for epi/pandemics**
- **Year round production**

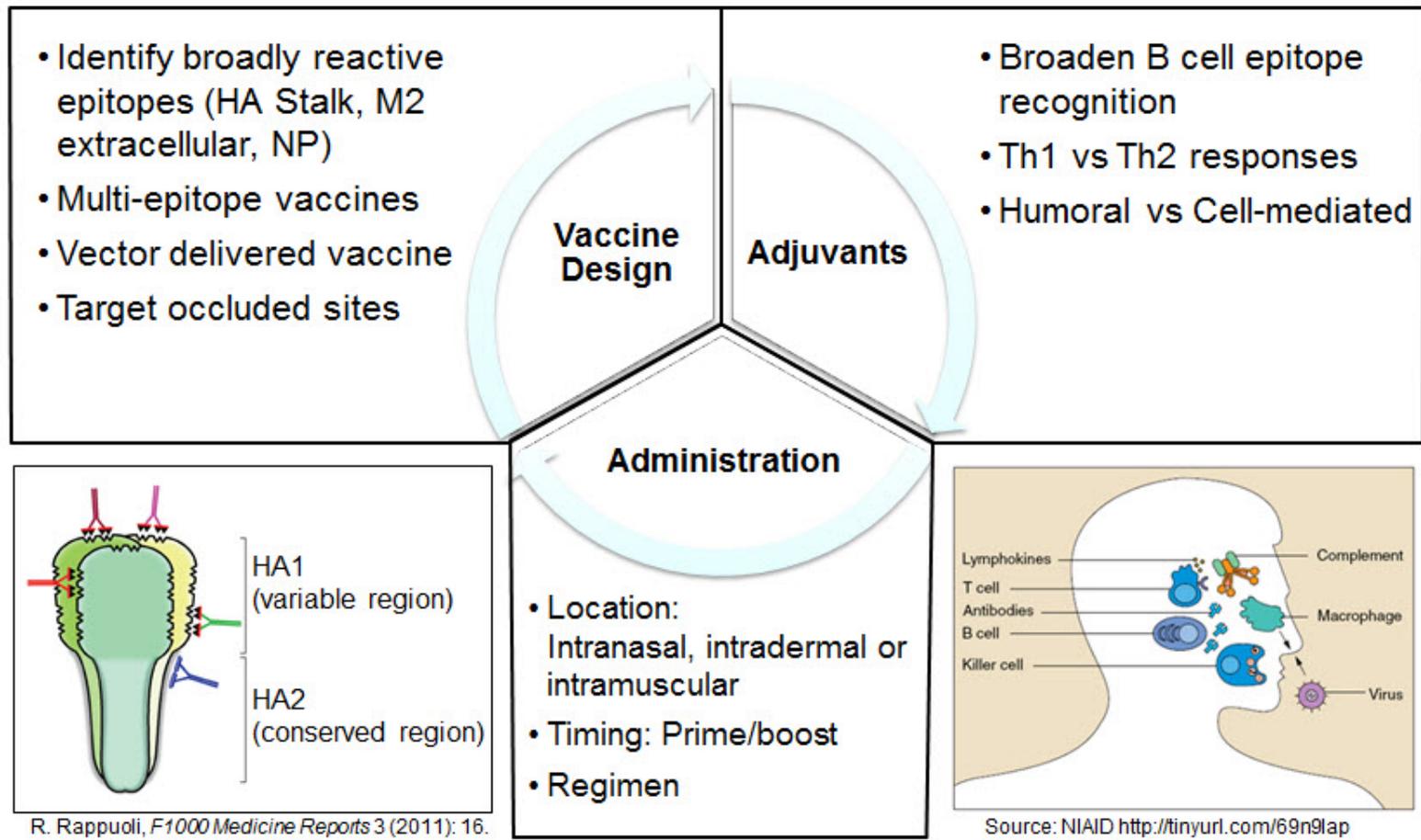


Universal Influenza Vaccine Target Characteristics



- **Vaccine Target: All influenza A subtypes**
 - Nasal > intramuscular > intradermal administration
 - Low antigen dose - safe and effective
- **Duration of response**
 - Single dose: annually < biannually < decennially
- **Target morbidity or mortality as endpoint of efficacy?**
 - Reduction in spread of disease
- **Population targeted**
 - < 6mo – 85+ years of age
- **Storage conditions**
 - Room temperature

Universal Vaccine Strategies Leveraging Old and New Discoveries





Closing Thoughts



- There has never been a greater variety of influenza vaccines available to address population variety than there are today
- The landscape of new influenza vaccine development is active and rapidly evolving – 94+ products/candidates
- Technical and regulatory challenges exist for innovative technologies
- Continued scientific discoveries provide greater opportunities for innovation
- While the field of influenza vaccine types appear to be moving towards a variety of niche vaccines in the near term, it is apparent from the landscape that the ultimate aim is to develop a single, more effective vaccine that could be used by all populations

Rick Bright, PhD

Acting Director

Influenza Division

BARDA

U.S. Department of Health and Human Services

Rick.Bright@HHS.GOV