



United States Department of

Health & Human Services

Office of the Assistant Secretary for Preparedness and Response



Influenza Vaccines with Broader Strain Protection

BARDA INDUSTRY DAY

Ronald Reagan Building
International Trade Center
Washington, DC

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www.medicalcountermeasures.gov

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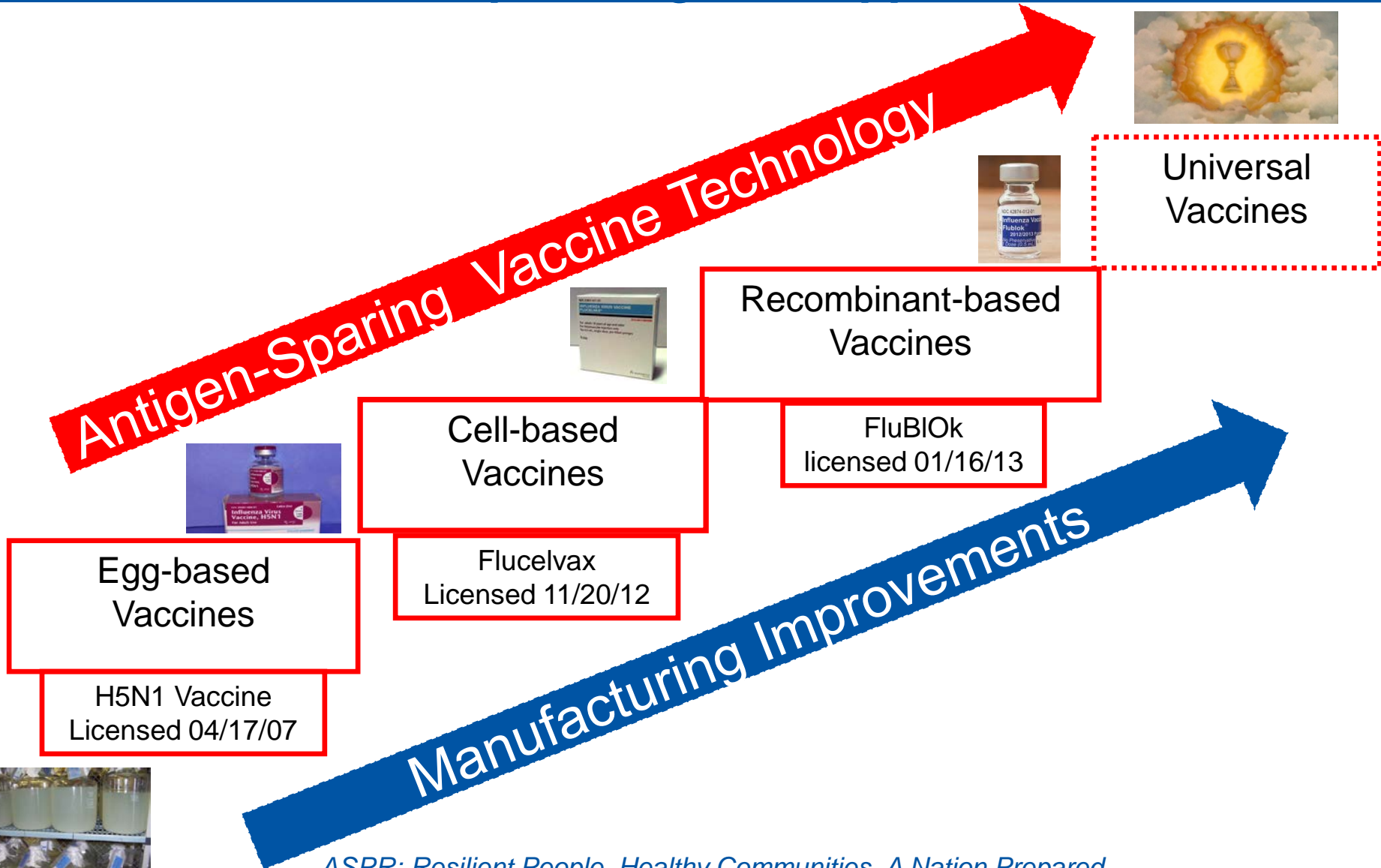
Influenza Vaccine Challenges



- Antigenic changes (drift and shift) represent a major challenge for current licensed vaccines
 - Annual immunization is required
 - Vaccine effectiveness is moderate in adults and less so in the elderly
- Current production processes are predominantly egg-based
 - Growth properties of human isolates in eggs (H3 isolation, yield)
 - Pandemic surge demands
- Pandemic-like candidate vaccines (H5 and H7) are poorly immunogenic in humans
 - 2 x 90 μ g dose for H5N1
 - Concerns about adjuvant safety and public perceptions
- Next generation influenza vaccines are needed



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



Influenza Vaccine Landscape

Pre Clinical | Phase 1 | Phase 2 | Phase 3 | Market Approval

Egg-based inactivated	Split w/ SPA03 Inactivated Cell Culture Split WIV Class II/SmithKline VIV Egg, Thailand	Split w/ iscomatrix Egg inactivated	H5N1, WIV H5N1 WIV w/ Adjuvant	Class II/SmithKline H5N1 A503	QIV VACCINE QIV, High dose, intradermal Class II/SmithKline Split Split Taiwan BIO-PHARMACEUTICALS Split WIV Japan EB66 Japan EB66 MOCK subunit (EU) US 2009/2010 Vero, Intijject/ Cevapan(EU) H1N1 Cell: HN-VAC (India) Vero, Intijject/ Cevapan(EU)
Cell-culture inactivated	Class II/SmithKline EB66 	Class II/SmithKline EB66, H5N1	PERC 6	Monkey Kidney Cell Japan EB66 Japan EB66	MOCK subunit (EU) US 2009/2010 Vero, Intijject/ Cevapan(EU) H1N1 Cell: HN-VAC (India) Vero, Intijject/ Cevapan(EU)
LAIV	Egg, Thailand dNS1 - Vero Egg H5N1/H5N2/H7N9	Egg, H6N2 dNS1- Vero HS Egg, Thailand	Egg	QIV, Egg HI Egg, Thailand	QIV, Egg Egg XEFL XEFL HI Egg, Thailand
Recombinant (VLPs)	VLP / HA VLP, Insect cells VLP, 293 cells rHA, Plants rHA, Insect cells Salmonella, Oral rHA, Plants Yeast, IN - Oral Salmonella, Oral Chimeric VLP + microneedles Molecular HAs rHA, Plants	VLP, Plants VLP, Insect Cells HA, Flagellin, e. coli rHA Insect Cells	rHA, Insect cells	rHA, Insect cells	rHA, Insect cells
Universal	M2e Liposome HA stalk; Chimeric SYN BIO LAIV UPNOC COBRA HA VLP Novel peptides Nanoparticle	NP & ISS Tech Peptide based Egg inactivated			
Vectors/ Adjuvant	MVA Based MVA Based Adenovirus M & NP Mass Gen Hospital Listeria Adenovirus Adenovirus, Oral Split MVA Mucosis	DNA / Vaxfectin DNA / snyCon w/ Electroporation			
DNA		DNA / Vaxfectin DNA / snyCon w/ Electroporation			

Seasonal

Pandemic

Seasonal & Pandemic

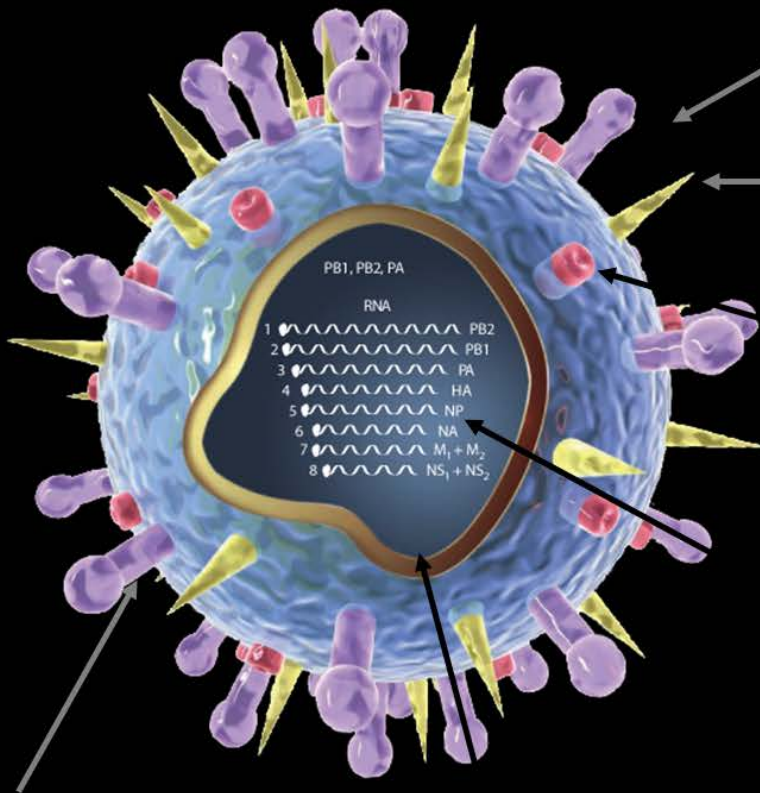
US License



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
 - 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



HA: surface, immunogenic
Highly variable. Drift. Shift.

NA: surface, immunogenic
Variable. Drift. Shift.

M2e: surface, immunogenic??
Fairly conserved. Ab-mediated.
Protective? Reduce severity.

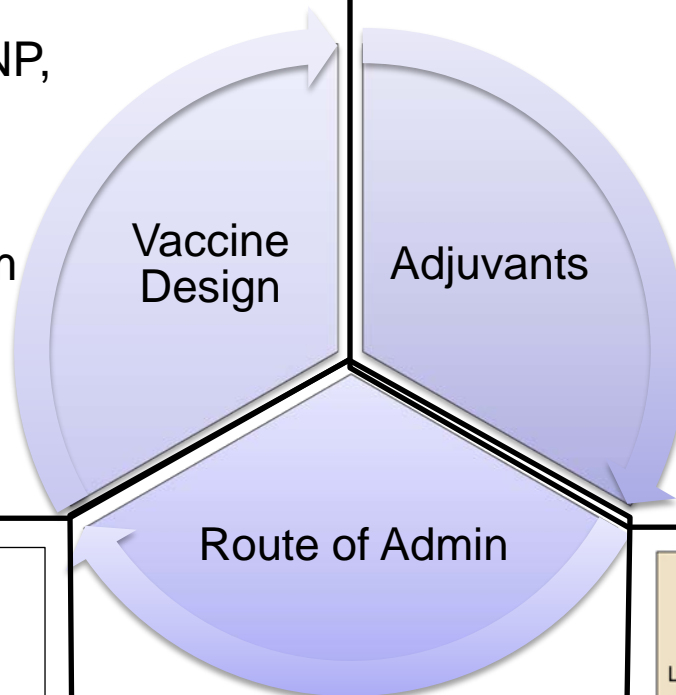
NP (nucleoprotein): internal
Highly conserved.
Induces CMI. Reduce severity?

HA Stalk
Highly conserved
Transiently accessible on
infected cell surface
Need to engineer a vaccine to target

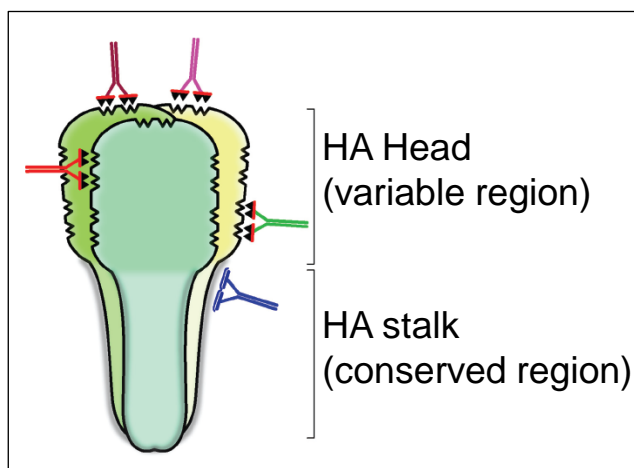
Matrix: internal
Highly conserved.
Induces CMI.

Universal Vaccine Strategies

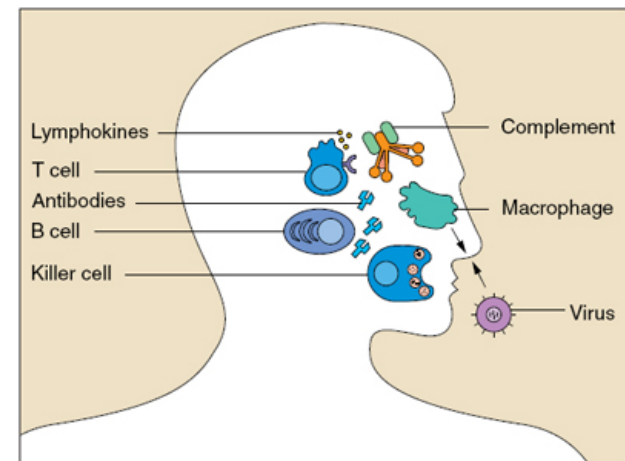
- Identify broadly reactive targets (HA Stalk, M2e, NP, M)
- Combination vaccines
- Vector expression system



- Broaden immune recognition
- Th1 vs Th2 responses
- Humoral and Cell-mediated



- Intranasal stimulation of mucosal immunity
- Intradermal delivery to target dendritic cells



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

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



Advanced Development of Universal Influenza Vaccine - Points to Consider



- Manufacturability and scalability
- Novel potency release assay
 - Most regulators are accustomed to SRID or SRH
- Clinical development
 - Non HI immune response
 - Current regulatory guidelines are based on HI
 - Potential safety concern/disease enhancement
 - Mono-specific immune response/drift potential
 - Will a single amino acid change render vaccine ineffective?
 - May require large scale efficacy trials over multiple seasons or other non-traditional clinical development plans
 - Challenge studies for cross protection



Universal Flu Vaccine Program at BARDA



- Collaborating within HHS to develop projects
- Current activities
 - Developing a Request for Information and/or sponsoring international symposium on universal influenza vaccine
 - Planning for an Acquisition Plan to support advanced development of promising programs demonstrating improved cross-reactivity and/or duration of effectiveness.
 - Foster public-private partnerships
 - BARDA Industry Day!



Pandemic Influenza

BAA-13-100-SOL-00019



- Novel influenza vaccine candidates that improve key vaccine attributes
 - dose schedule
 - time to onset of protection
 - induction of improved immunogenicity
 - broader cross-protection across influenza A virus subtypes,
 - duration of protection
- Use of approved or novel adjuvants may be a component of the advanced development program.
- Technology readiness level 6
 - Data demonstrating statistically relevant improvements in immunogenicity/efficacy as compared to existing vaccines.