



United States Department of

Health & Human Services

Office of the Assistant Secretary for Preparedness and Response



The Next Phase of Influenza Vaccine Development

Development of Universal Influenza Vaccines

**Robert C. Huebner, PhD
Branch Chief
BARDA Influenza Division**

**BARDA Industry Day
October 15, 2014**



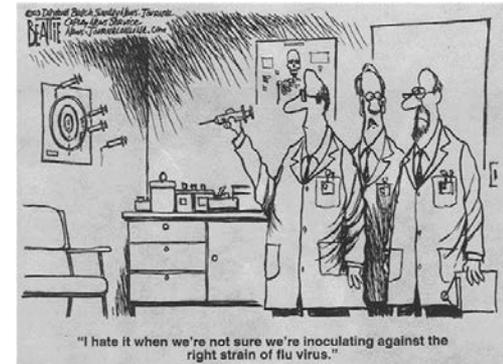
Current Influenza Vaccines Have Limitations



- Moderately effective (overall 50%-70%)
 - Annual immunization
 - Dependent on vaccine match and virus
 - Lower effectiveness in high risk populations

Season	Strain	Age Group	Vaccine Effectiveness (95% CI)
2011 – 2012 [#]	A(H3N2)	18 – 49	33% (-5 to 57)
	A(H3N2)	50 – 64	39% (-13 to 67)
2012-2013 [*]	A(H3N2)	≥65	9% (-84 to 55)

* Interim adjusted estimates Feb 22, 2013 CDC *MMWR*
Clin Infect Dis. (2014) 58 (3): 319-327. doi: 10.1093/cid/cit736



... And They Don't Provide Immunity to Novel Viruses



Credit: US National Museum of Health and Medicine

1918: "Spanish Flu"
 A(H1N1)
 20-100 m deaths
 ~500,000 in US

1957: "Asian Flu"
 A(H2N2)
 1-4 m deaths
 60-80,000 in US

1968: "Hong Kong Flu"
 A(H3N2)
 1-4 m deaths
 ~30,000 in US

2009 "H1N1 Pandemic"

Recent scares H5N1, 2012 H3N2v, 2013 H7N9, 2013 H10N8

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





United States Department of

Health & Human Services

Office of the Assistant Secretary for Preparedness and Response



We need better influenza vaccines!

We need universal influenza vaccines

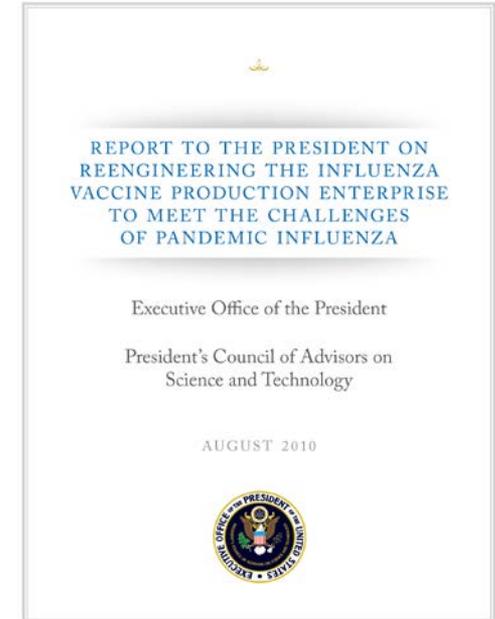
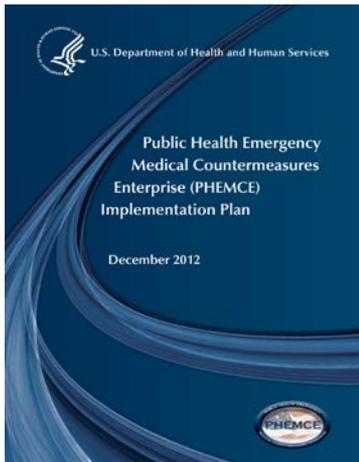
Universal influenza vaccines elicit lasting, broad spectrum immunogenicity and efficacy in humans against the widest range of antigenically divergent influenza strains within and across subtypes.



Universal Influenza Vaccine - Mission Call



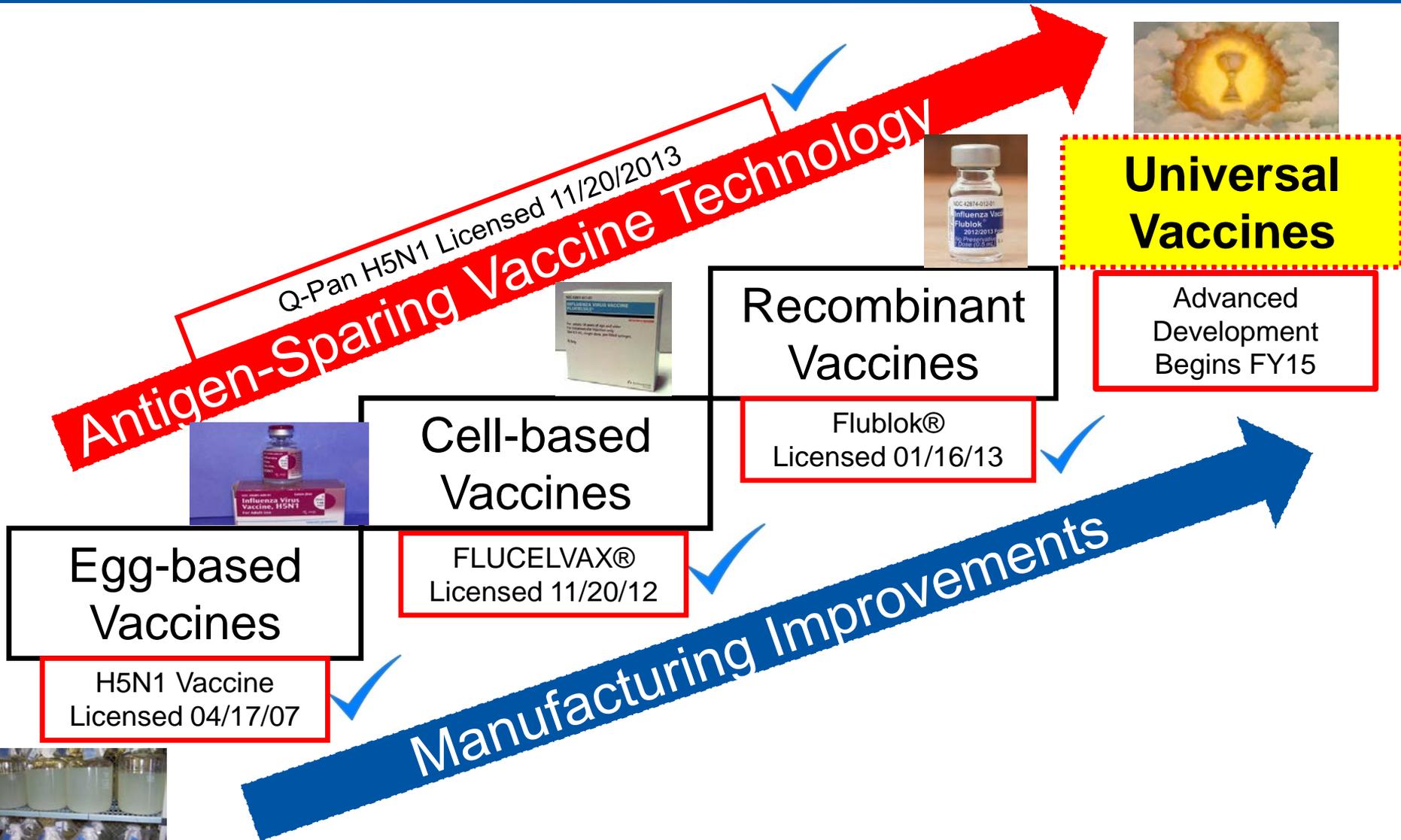
2010 PCAST Report “Because a universal vaccine would completely change the outlook on protecting the population against influenza virus infections, the Federal Government should support and encourage efforts to design a universal vaccine through various mechanisms.”



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”



New Technologies are Now Available for Influenza Vaccine Production





Infrastructure & Core Services



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

Viral Targets for Universal Vaccine Development

Non-structural proteins. Conserved
Potential targets for T cell immunity

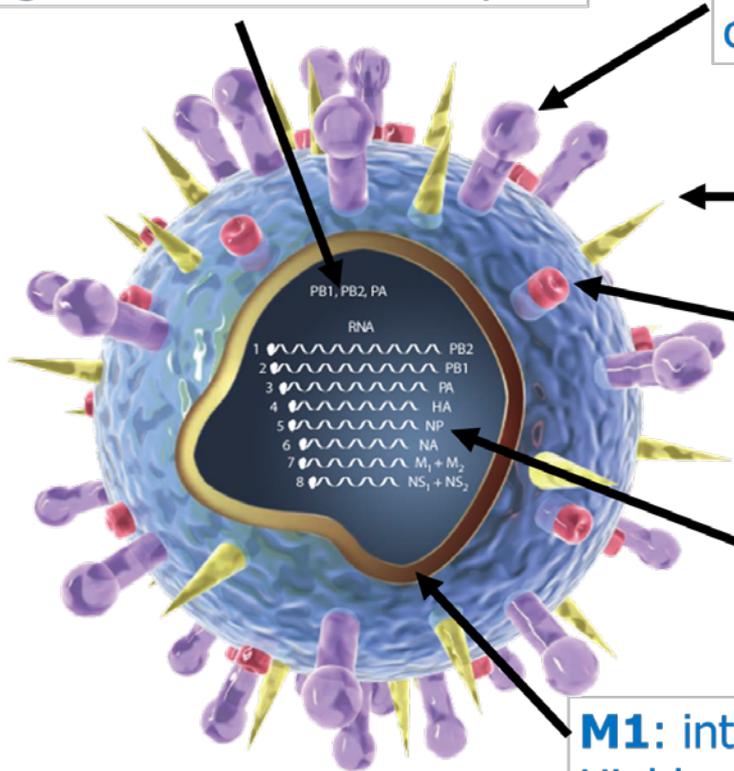
HA: surface, highly variable
immunodominant head,
conserved stem

NA: surface,
variable, slower drift

M2: surface, fairly conserved.
Possible Ab-mediated protection

NP: internal highly conserved.
Induces CMI

M1: internal
Highly conserved
Induces CMI



Adapted from: Paul Lewis, MD
Oregon State Public Health

Approach to Universal Vaccine Development

- This is a new vaccine – approach as if current influenza vaccines do not exist
 - 1/40 HAI titer (nice to have, but what else is needed?)
 - Think about other targets, other correlates, other types of immunity to improve effectiveness and duration of immunity
 - Multiple approaches will need to be investigated so a few can reach our target

Candidates



<http://www.niarchery.co.uk/history.php>

<http://heatherfuture.blogspot.com/>

<http://celindareyesblog.buzznet.com/user/journal/17433956/top-10-reasons-why-s/>

Phase 1



Phase 2



Phase 3



BLA!



Pre Clinical

Phase 1

Phase 2

Protein Based

Chimeric HA Stalk Vaccine
MSM

Computationally Optimized Broadly Reactive Antigen (COBRA)
SANOFI PASTEUR UPMC

Self assembling nanoparticle
NIH NIAID

M2e + NP + Immunostimulatory Sequence (ISS)
DYNAXX DYNAXX TECHNOLOGIES

NPA + NPB + M1 + M2 polypeptides T-cell vaccine
SEEK

Conserved epitopes from HA + NP + M1 proteins
BiondVax Pharmaceuticals Ltd.

M2e Conjugatable Adjuvant Lipid Vesicle
Molecular Express, Inc.

Headless HA in VLP
TechnoVax

M2e-VLPs
SANOFI PASTEUR

LI-Key H5 Hybrid T-cell vaccine
Generex

Fluorocarbon-linked conserved influenza peptide set T-cell vaccine
IMMUNE TARGETING SYSTEMS

Vectors/ Adjuvant

MVA Vector with M2e
emergent

PanAd3 Vector with M1 and NP
GSK

Listeria Vector with NP
MGH 1811

Ad4 Vector with H5 HA
PaxVAX

Nanoemulsion T-cell vaccine
-400 nm
NanoBio Corporation

MVA Vector with HA and NP
Inviragen

ΔM2 LAIV
FluGen

ΔNS LAIV
Vivaldi Biosciences

MVA Vector with NP and M1
THE JENNER INSTITUTE

DNA

Cationic lipid-DNA complex
JUVARIS BIOTHERAPEUTICS, INC.

DNA Vaccine construct with HA, NA, M2e-NP
inovio

DNA prime + TIV boost
NIH NIAID

*No Phase 3 or Market Approved universal influenza vaccines



Universal Influenza Vaccine

Target Product Profile – 5 Key Features



Property/Vaccine	Acceptable Primary Characteristics	Desired Primary Characteristics
Breadth of Protection	<i>Protection against most influenza A strains of the same subtype</i>	<i>Protection against multiple influenza A subtypes and most influenza B strains</i>
Efficacy**	<i>70% or greater in healthy adult, young and elderly</i>	<i>80% or greater in healthy and special populations</i>
Duration of Immunity	<i>One full year</i>	<i>Five years or more</i>
Age Indication	<i>6 months and above</i>	<i>2 months and above</i>
Safety	<i>Reactogenicity similar to licensed influenza vaccines</i>	<i>Reduced reactogenicity compared to licensed influenza vaccines</i>



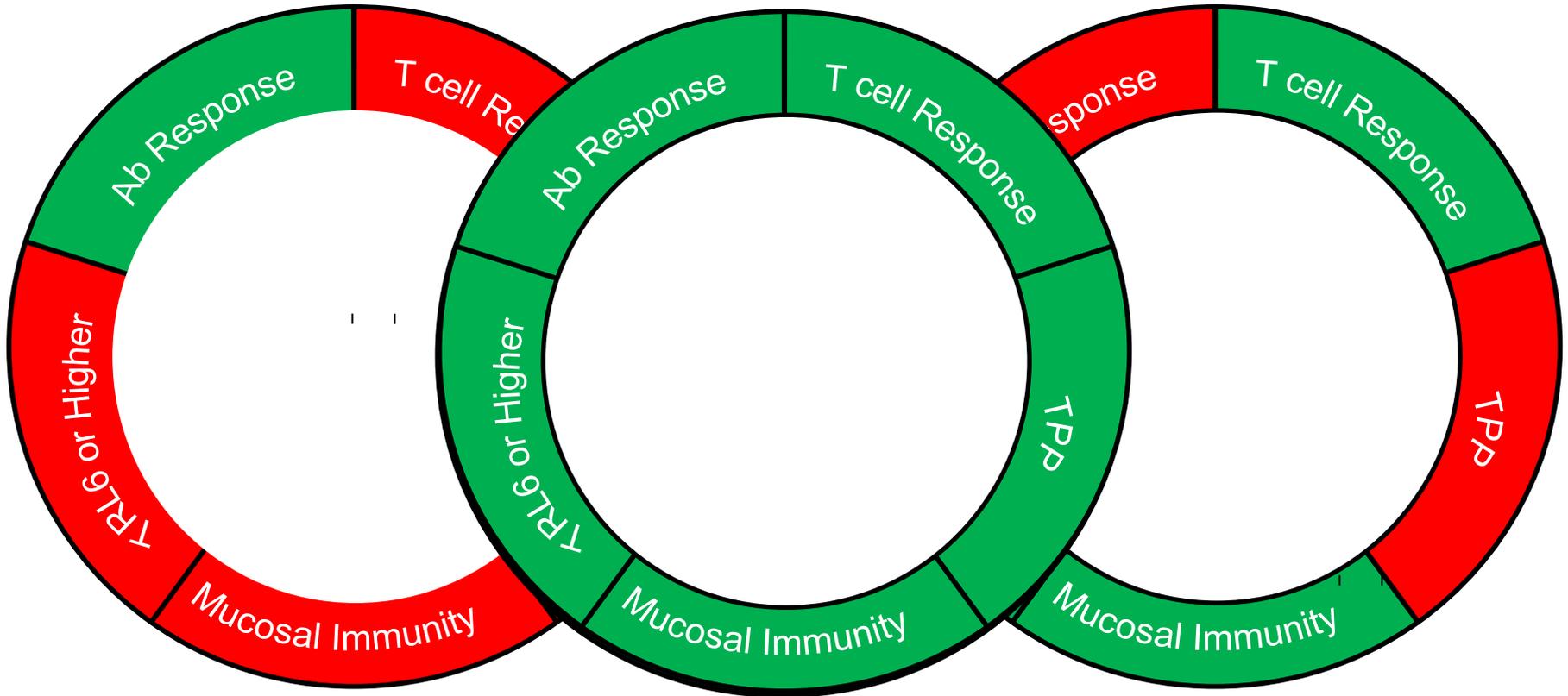
Universal Influenza Vaccine Challenges



- Most improved or universal influenza vaccine candidates rely on a single technology or immunological target
 - Many will be unable to meet TPP for universal vaccines by themselves
- Many projects are in early/pre-clinical development
- Large scale multi-year efficacy trials may be required
 - Young, healthy adult, elderly populations
- Funding is limited
 - Each promising candidate could cost over \$100 M USD for development



Technology Combinations?





Universal Influenza Vaccine – Needs for Success



- New partnership and a different way of thinking
 - Programs not projects
 - Combinations of technologies that will result in the development of vaccines that stimulate broadened, long lasting antibody, cellular and/or mucosal responses to influenza viruses that meet the universal TPP
 - New ways to design, evaluate and regulate these vaccines
 - New vaccine approaches and targets
 - Human challenge
 - New surrogates of immunity need to be identified
 - Validated assays will need to be developed
 - Alternate potency/release assays will be needed
 - Financial commitment
 - High development costs





BARDA Universal Vaccine Forecast





Parting Thoughts



- *Don't let currently licensed vaccines constrain your thinking!*
- Technical advances over the last decade have created the opportunity to develop universal influenza vaccines
 - Expression systems, vectors, adjuvants, etc.
- Advances in our understanding of influenza have identified a number of vaccine candidates that could contribute to the development of a universal influenza vaccine
- Universal influenza vaccine licensure will require a well-planned and executed program that addresses the technical, clinical and regulatory challenges of universal influenza vaccine advanced development
- **A combination strategy will likely have the best chances of achieving the HHS goals for universal influenza vaccines**



Are You (and Your Team) Ready and Interested?



- Contact information

Robert C Huebner, Ph.D.

Chief, Universal Influenza Vaccines

Phone 202-260-1179

Email: robert.huebner@hhs.gov

- www.medicalcountermeasure.gov

- Information on the open influenza funding opportunities
- Information on setting up a TechWatch meeting with BARDA to discuss your technology