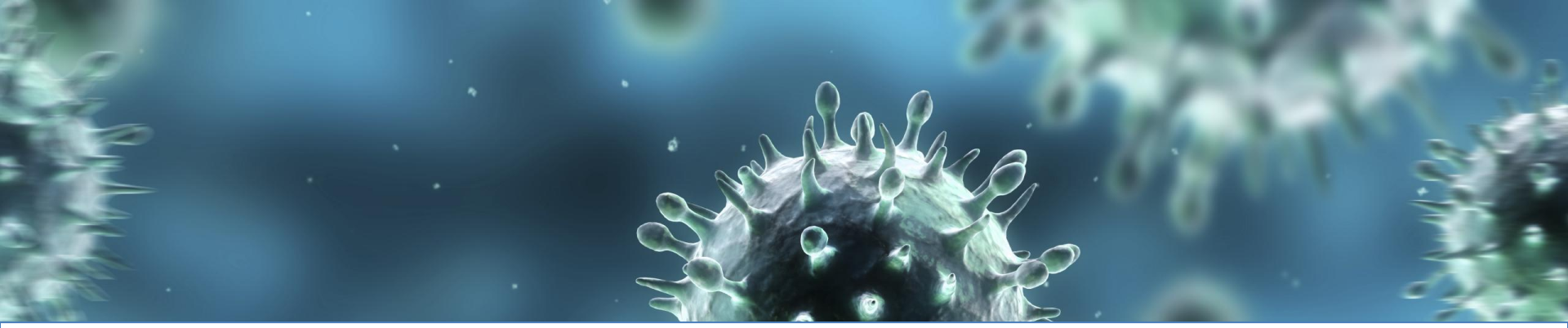
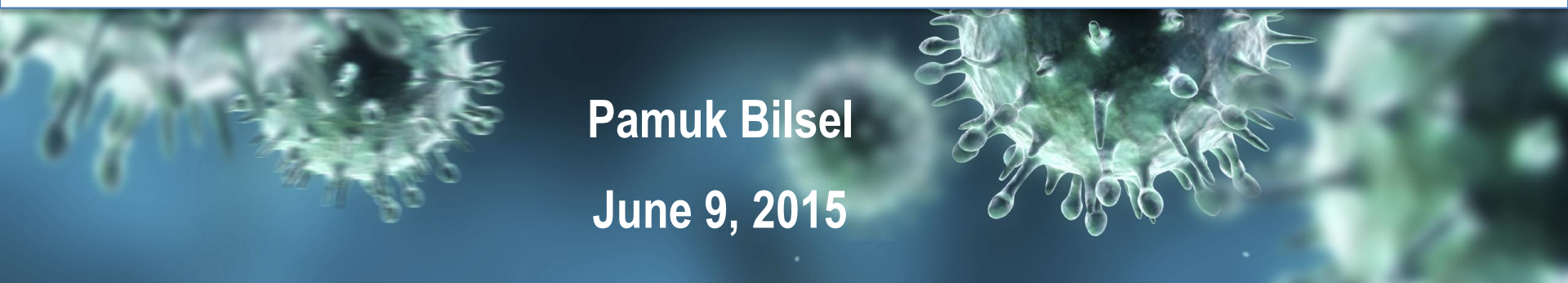


FluGen

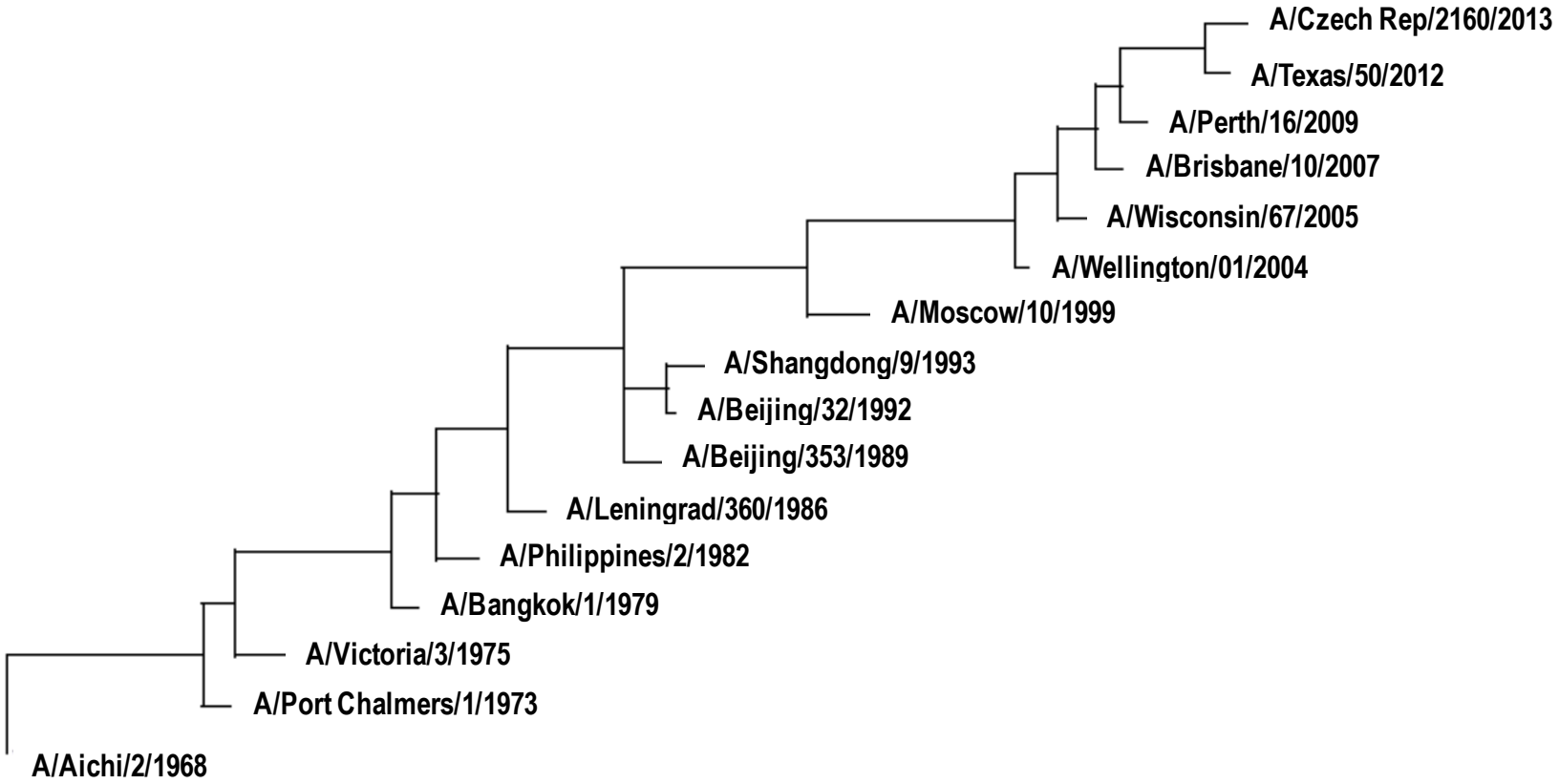
Challenges Associated with Developing Novel Flu Vaccines



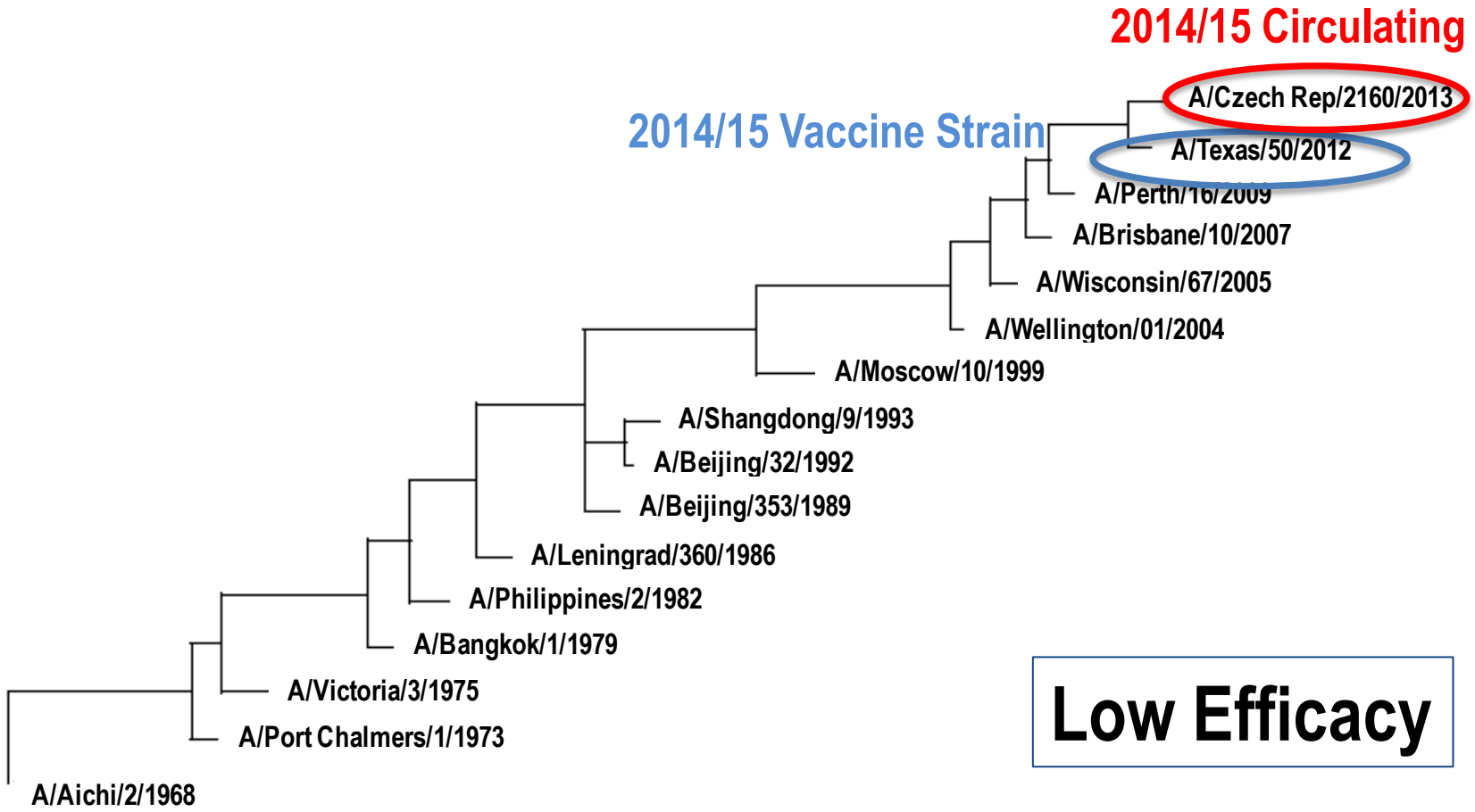
Pamuk Bilsel

June 9, 2015

Antigenic Drift of H3N2 HA Since 1968

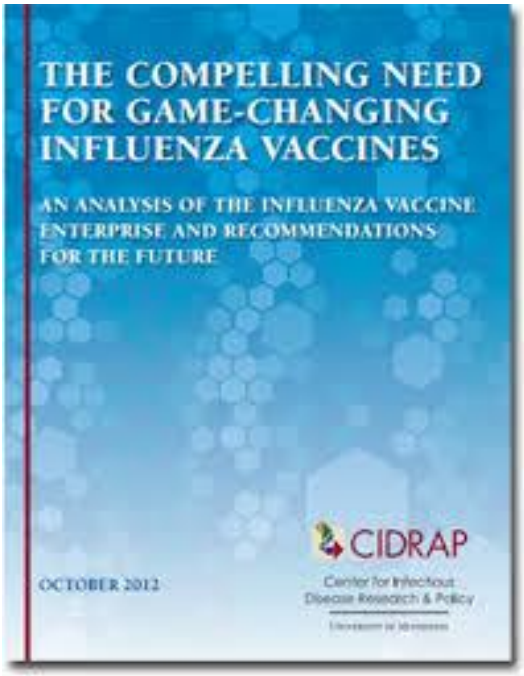


This Year's Vaccine is a Mismatch……..



Low Efficacy

Flu Vaccine Studies from 1967-2012 Show……

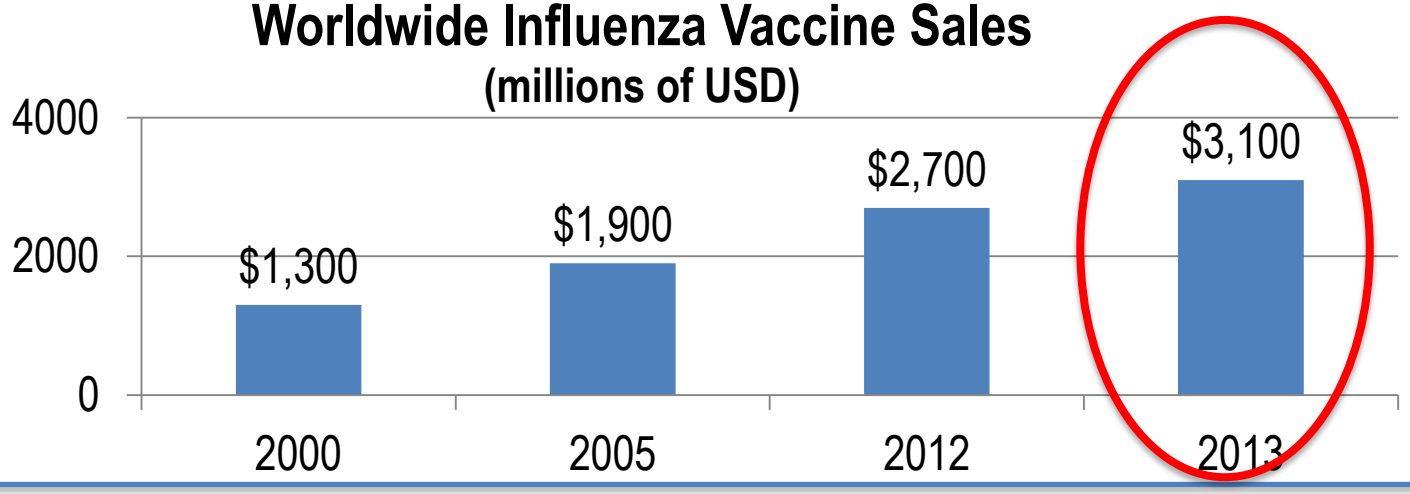


- Moderate coverage for adults 18-64 yrs. (59%)
- Inconsistent evidence of ***any*** protection for 2-17 yrs
- Virtually ***NO*** data for 65+ yrs

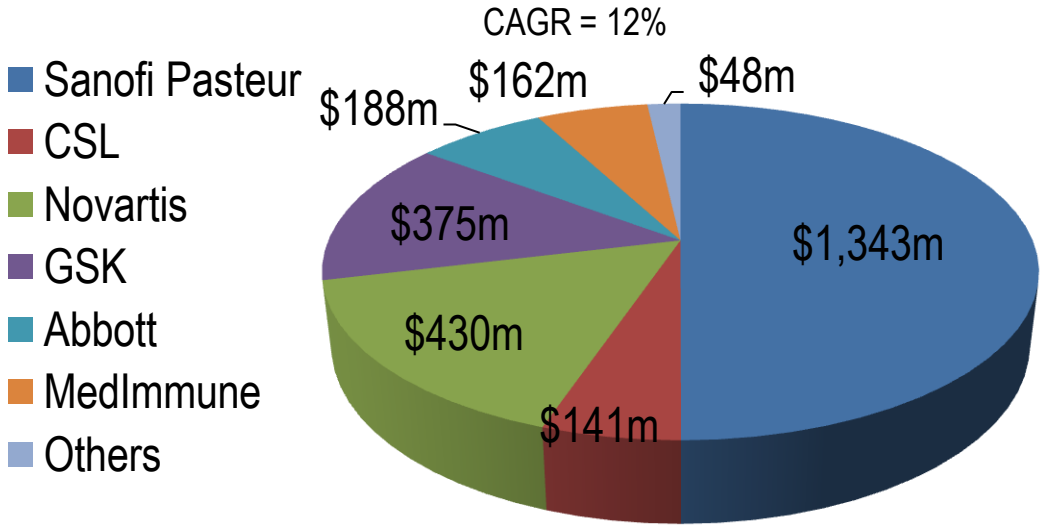
Flu Vaccine Efficacy Must Improve

CIDRAP Report , Oct 2012

Influenza: A $3 billion+ Market……..



TOTAL BRANDED MARKET 2011-2012 = $2.7 billion



With a vaccine that works less than half of the time

Strain	Effectiveness*
Polio	99%+
Measles	97%
Chicken Pox	88%-98%
All Flu 2012-13	56%
All Flu 2013-14	51%
All Flu 2014-15	**19%**
2014-15 H3N2	18%
2014-15 Flu B	45%

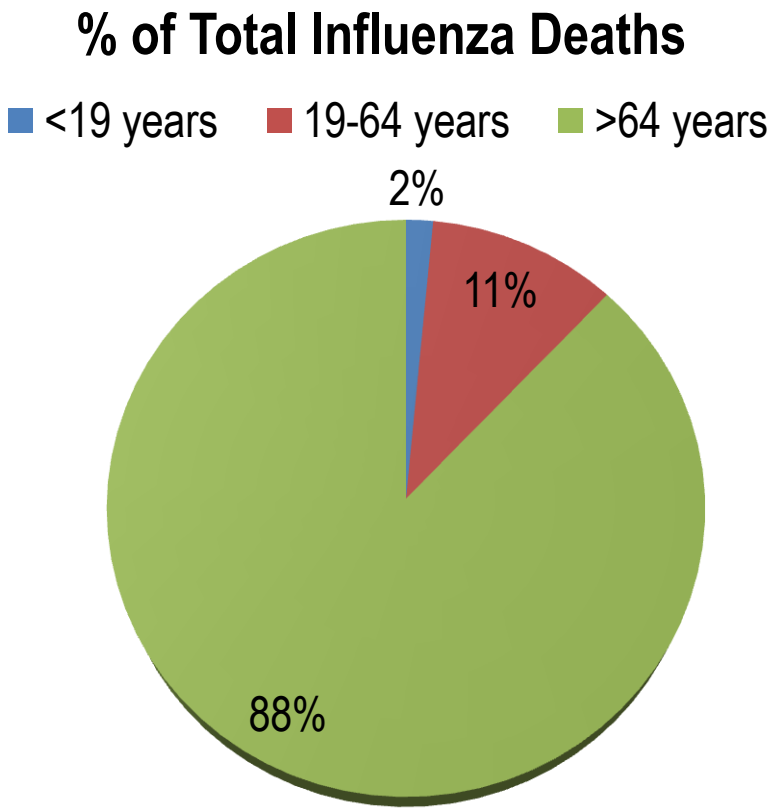
*http://www.cdc.gov/flu/news/updated-vaccine-effectiveness-2014-15.htm

The Annual Cost of Influenza in the US

- 610,660 life-years lost
- 3.1 million hospitalized days,
- 31.4 million outpatient visits
- $10.4 billion in direct medical costs
- $16.3 billion due to lost earnings/loss of life
- $87.1 billion in total economic burden

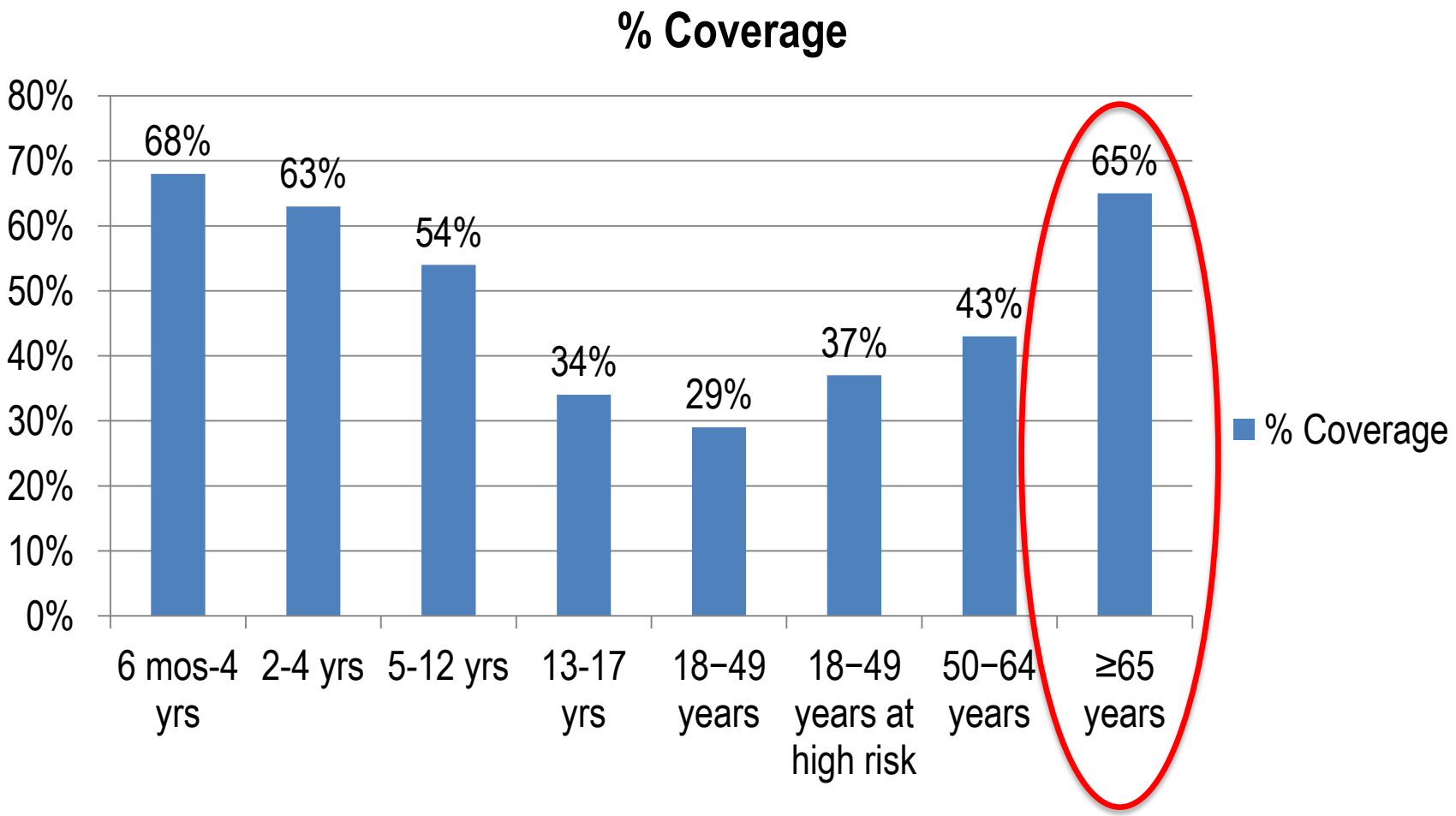
Molinari et al *Vaccine* 2007

Elderly Bear the Brunt of Influenza Deaths...



CDC Morbidity and Mortality Weekly Report Aug 2010

US Flu Vaccination Rates by Age 2011-12



Current Flu Vaccines Simply Don't Work Well

HA ANTIBODY RESPONSE

PRE-EXISTING IMMUNITY

FluMist Quadrivalent
Influenza Vaccine Live, Intranasal

Current Flu Vaccines: Variations on a Theme …..HA

FLUCELVAX
Influenza Virus Vaccine

Fluzone®
Quadrivalent
INFLUENZA VIRUS VACCINE

Flublok®
Influenza vaccine

Fluzone® High-Dose
INFLUENZA VIRUS VACCINE

Potent Immunity Develops Following Influenza Infection

Research article Related Commentary, page 3273

Memory T cells established by seasonal human influenza A infection cross-react with avian influenza A (H5N1) in healthy individuals

Laurel Yong-Hwa Lee,[1] Do Lien Anh Ha,[2] Cameron Simmons,[2] Menno D. de Jong,[2] Nguyen Van Vinh Chau,[2] Reto Schumacher,[1] Yan Chun Peng,[1] Andrew J. McMichael,[1] Jeremy J. Farrar,[2] Geoffrey L. Smith,[3] Alain R.M. Townsend,[4] Brigitte A. Askonas,[1] Sarah Rowland-Jones,[1] and Tao Dong[1]

[1]MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom. [2]Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam. [3]Department of Virology, Faculty of Medicine, Imperial College London, London, United Kingdom. [4]Molecular Immunology Group, Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom.

Prior H1N1 Influenza Infection and Susceptibility of Cleveland Family Study Participants during the H2N2 Pandemic of 1957: An Experiment of Nature

in

nology and Developmental Biology, Division of Cellular
s, Office of Cellular, Tissue, and Gene Therapies, Center
tion and Research, Food and Drug Administration,

Prior Infections With Seasonal Influenza A/H1N1 Virus Reduced the Illness Severity and Epidemic Intensity of Pandem in Healthy Adults

Robert B. Couch,[1,2] Robert L. Atmar,[1,2] Luis M. Franco,[2,3] John M. Quarles,[6] Sheree Cheung,[1] and John W. Belmont[3,4,5]

[1]Department of Molecular Virology and Microbiology, [2]Department of Medicine, [3]Departme
Pediatrics, and [5]Department of Pathology and Immunology, Baylor College of Medicine, Hou
Science Center, College Station

Cellular immune correlates of protection against symptomatic pandemic influenza

Saranya Sridhar[1], Shaima Begom[1], Alison Bermingham[2], Katja Hoschler[2], Walt Adamson[3], William Carman[4], Thomas Bean[5], Wendy Barclay[6], Jonathan J Deeks[7] & Ajit Lalvani[1]

The role of T cells in mediating heterosubtypic protection against natural influenza illness in humans is uncertain.

2009 Pandemic: T-cells Mitigate Illness

Nature Medicine, 2013 Oct;19(10):1305-12

Cellular immune correlates of protection against symptomatic pandemic influenza

Saranya Sridhar[1], Shaima Begom[1], Alison Bermingham[2], Katja Hoschler[2], Walt Adamson[3], William Carman[4], Thomas Bean[5], Wendy Barclay[6], Jonathan J Deeks[7] & Ajit Lalvani[1]

Presence of flu-specific $CD8^+$ T cells

Reduced disease symptoms

Mucosal IgA Key in Preventing Flu Infection

Relationship between pre-challenge antibody and infection

Pre-challenge Antibody Status		% Protected (# Protected/Total)
Serum HAI	Nasal αHA IgA	
−	−	28% (7/25)
−	+	67% (8/12)
+	−	79% (15/19)
+	+	96% (23/24)

Treanor , Vaccine 2000.18:899.

HAI Antibody Immune Response is a Surrogate Measure of Efficacy

Regulatory Path:

HAI antibody response *may be an acceptable* ***surrogate marker*** *of activity that is reasonably likely to predict clinical benefit.*

(2007 FDA "Guidance for Industry")

What defines “UNIVERSAL”?

- Broad HA coverage (multiple subtypes)
- Broad immune response (including CMI & Mucosal immunity)
- Highly conserved epitopes (HA2 Stalk, M2e)
- One dose for multiple seasons

What Would a Better Flu Vaccine Look Like?

Key Potential Attributes

- Protects from multiple flu A subtypes/ most B strains
- Superior efficacy in elderly
- 1 year+ duration of immunity
- One dose for all ages

BARDA Universal Influenza Vaccine RFP Target Product Profile Requirements Aug '14

In Pursuit of the Holy Grail:
Competitive Landscape

BiondVax Pharmaceuticals Ltd.
One • For All - The Universal Flu Vaccine

Mount Sinai Hospital

PaxVax

IMMUNE TARGETING SYSTEMS

BioDiem

Vivaldi Biosciences

THE SCRIPPS RESEARCH INSTITUTE

VAXART

ACCESS and AVAILABILITY

ACCEPTANCE and REACH

EASE and CONVENIENCE

NIH National Institute of Allergy and Infectious Diseases

THE JENNER INSTITUTE
DEVELOPING INNOVATIVE VACCINES

Pirbright INSTITUTE

UNIVERSITY OF OXFORD

vaxin

New Approaches: Categories

- Novel adjuvants (multiple)
- Live Attenuated
  - BioDiem, Vivaldi, NIAID
- Vector (Adeno or MVA)
  - Vaxin, Vaxart, PaxVax, Jenner
- T-cell
  - BiondVax, Immune Targeting Systems
- Other
  - VLP, HA stem, RNA, synthetic nanoparticle

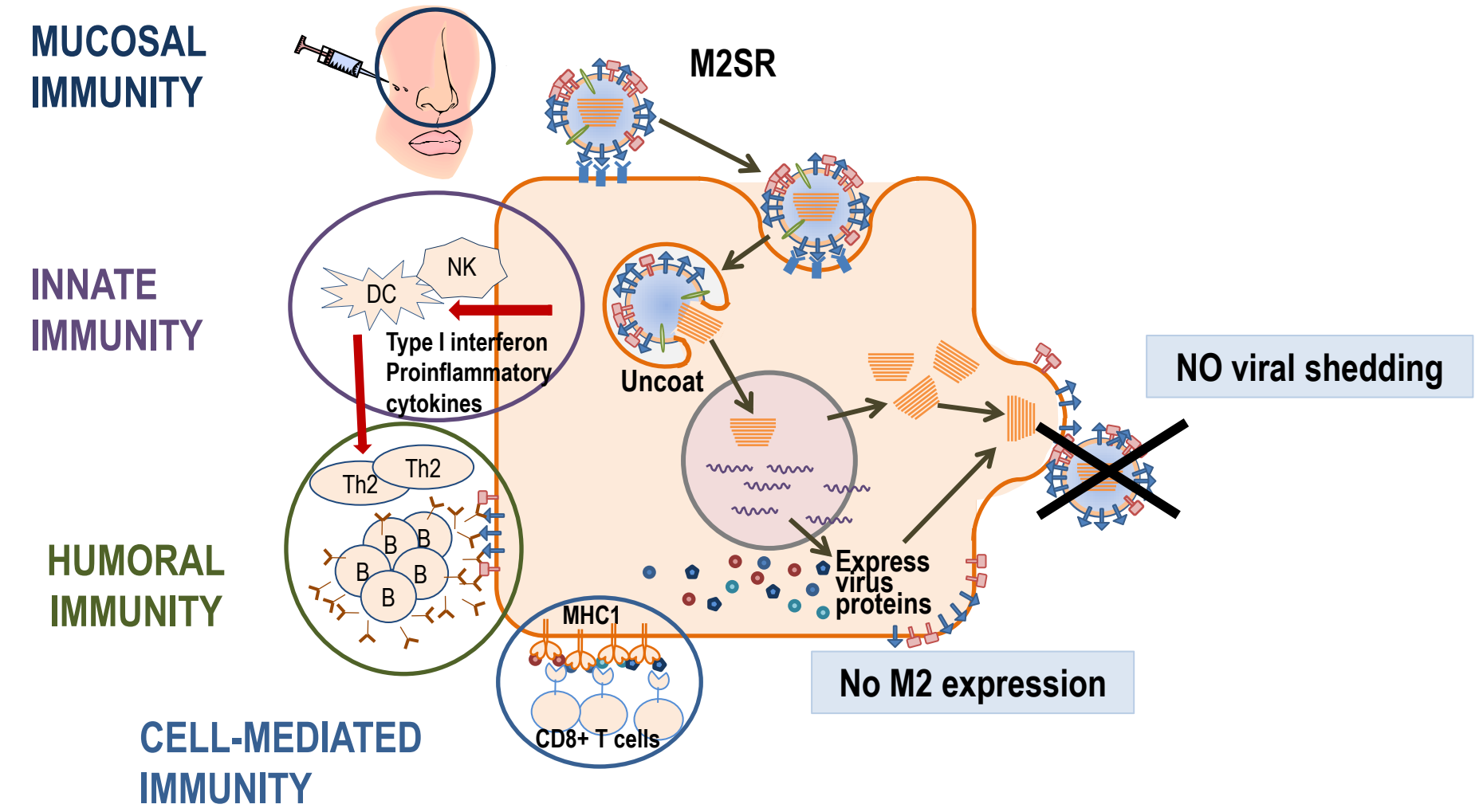
Features of Competing Technologies

Variable	Adju-vants	LAIV	Vector	T-cell	HA Stem
Proven technology?	+++	+++	+	+	-
Manufacturability?	+++	+++	++	++	+
Regulatory path straightforward?	++++	+	+	+	+++
Safety profile a major consideration?	++++	+++	+++	+	+
Elicitation of HAI antibody	++++	+	+	-	++++
Elicitation of other antibody	+	+	-	-	-
“Cross-protection” (within subtypes)	++	++	+	++++	++++
“Cross-protection” (across subtypes)	-	+	+	++++	++++
CMI	-	+++	+	++++	-

FluGen's Solution: M2SR Vaccine

- First in class single replication (SR) live flu vaccine
- Mimics true infection without symptoms
- Impacts all major immune system components
- Universal characteristics
  - Cross-protection against multiple strains
  - Generates antibodies to HA2 stem region
- Convenient intranasal delivery
- Cost competitive/ cell based manufacturing- no eggs

M2SR Elicits Broad Immune Responses



M2SR Influenza Vaccine: Key Targeted Attributes

- Seasonal vaccine with universal attributes
- Shows drifted strain and cross-protection
- Impacts all major immune systems
- Superior efficacy vs. standard of care
- Initial target >60 yrs.- largest patient segment

M2SR Development Approach

- M2SR is universal
  - H1N1 vaccine protects ferrets against deadly H5N1
  - H3N2/H1N1 cross protection in multiple models
  - H3N2 vaccine protects against drifted strains
  - Generates Humoral, Cell-Mediated, Mucosal and Innate immunity
- But, seasonal regulatory path is preferred
  - HAI titers are the only accepted correlate
  - Universal trials would take many years more than seasonal
  - Universal properties will be proven post licensure

Anticipated Phase 1 Immune Responses

HUMORAL

SERUM

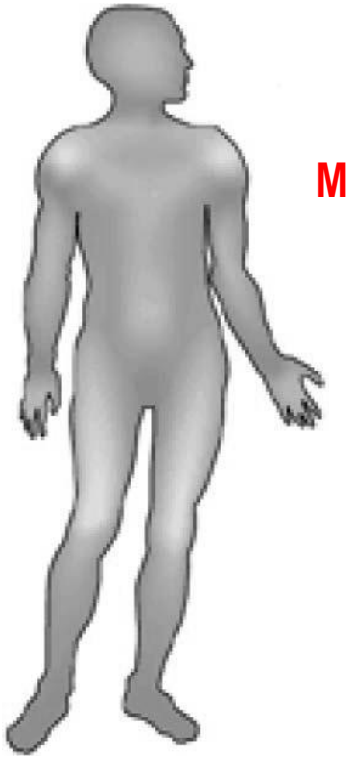
HAI Antibody

HA Stem/NA Antibody

Microneutralization

CELL MEDIATED

PBMC



MUCOSAL

NASAL SWAB

INNATE

Cell Subset Phenotypes
CD62L, CCR7lo, CD127,CD44, CD56, CD45RA

Mucosal IgA Antibody

Gene Expression
(Illumina HT-12v3 microarray)

CD4 and CD8 T-cell responses
IFNɣ, IL-2, IL-4, Gzmβ, perforin

Cytokines
IL-6, IFNα, TNF α, IL-8

Licensure Pathway for non-HAI vaccines

- If no HAI responses:

  Human challenge study to establish clinical POC and establish new correlate

  - Increasingly utilized by influenza vaccine and antiviral agent developers for clinical and/or virological POC studies
  - Challenge data was accepted by CBER as basis of approval for H1N1 component of FluMist

Influenza Challenge Studies

- Increasingly utilized by influenza vaccine and antiviral agent developers for clinical and/or virological POC studies
- hVivo (UK) = only provider up until recently because challenge strains not viewed as investigational medicinal products by the MHRA
- NIH and one other entity now have H1N1 challenge strains approved by CBER for intervention studies in the US
- In-patient evaluation and intensive clinical and virological monitoring substantially reduce study size
- Will not be accepted by CBER (or CDER) as a “true” efficacy trial, although challenge data was accepted by CBER as basis of approval for H1N1 component of FluMist

Summary

- establishment of appropriate correlates of protection
- improvement of assays for potency
- development of human challenge models
- novel-antigen vaccines → potential of lasting, broad, and potent protection