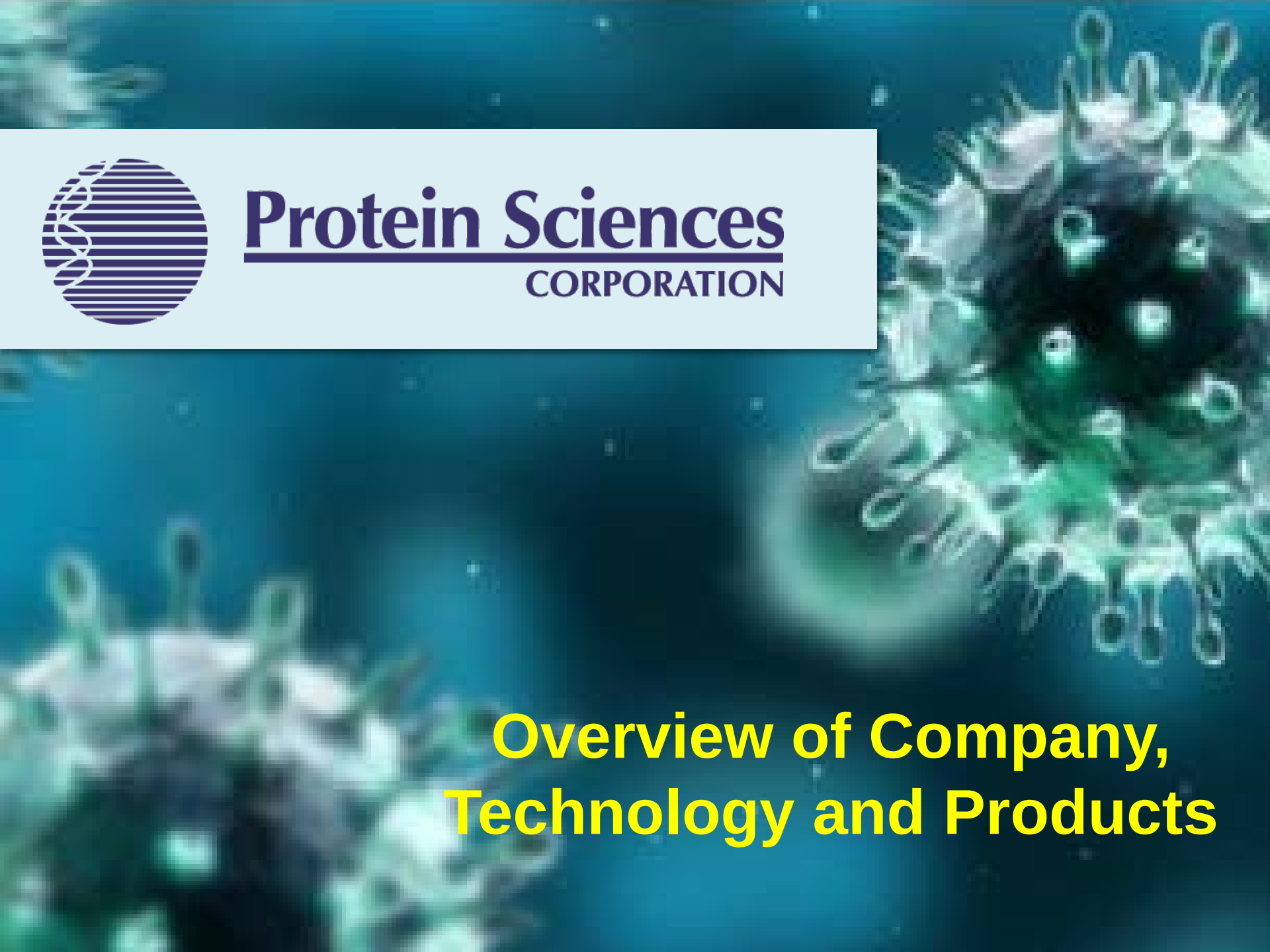
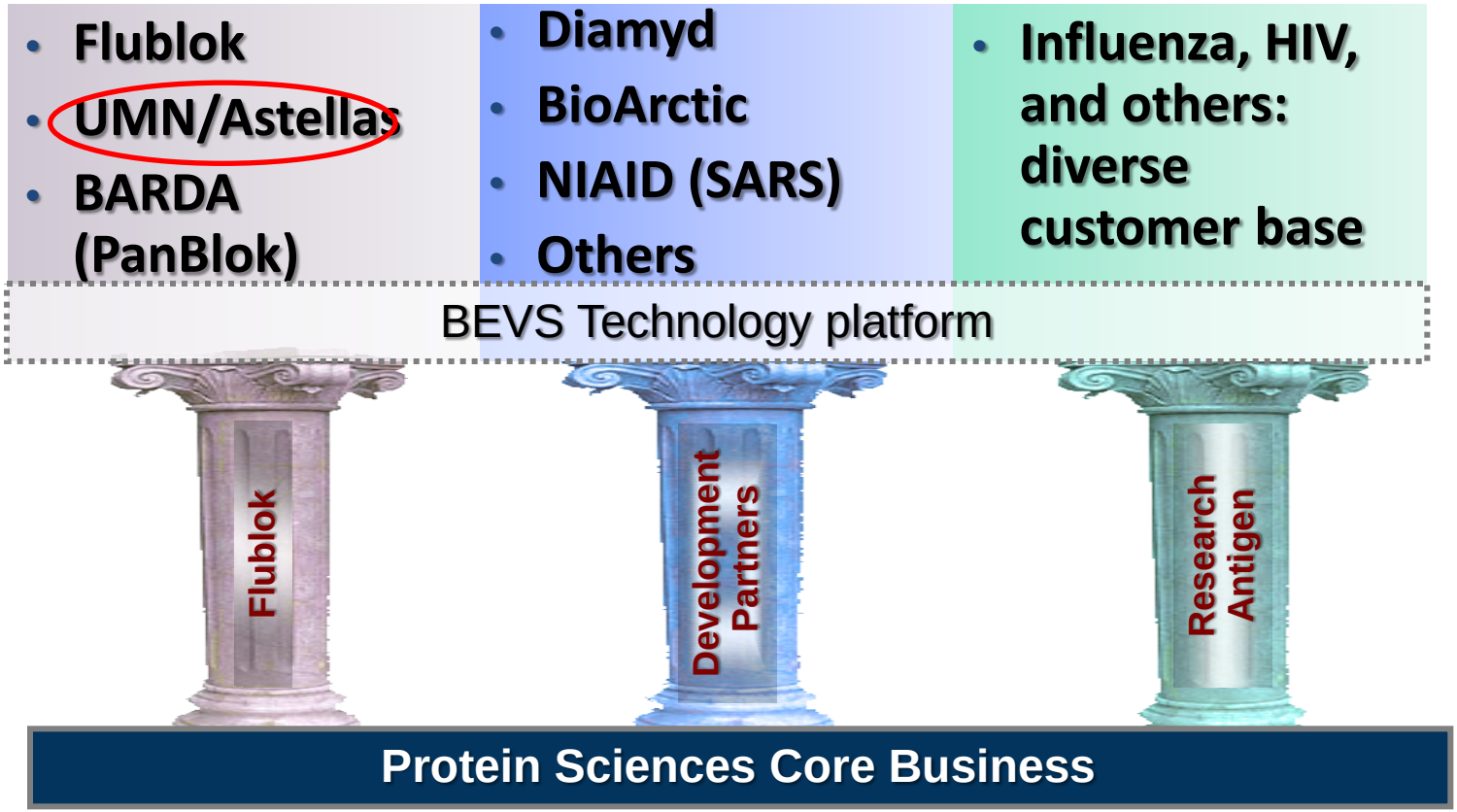

Protein Sciences
CORPORATION
Overview of Company,
Technology and Products

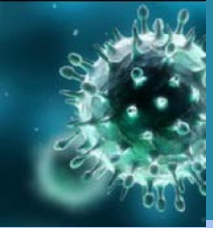
Overview

Flublok® received FDA approval on 16JAN2013

BARDA contract award 2009 to support Panblok® & Flublok

Merck and B. Ingelheim cell line licenses





PCAST Report – Issued following H1N1 pandemic

Fault was not with the execution of the response, but in inherent shortcomings of current technologies for development & production of influenza vaccines"

Most US influenza vaccines are currently produced in embryonated chicken eggs:

- Delayed response time
- Limited capacity
- Limited flexibility

PCAST recommended short-term improvements in surveillance, strain development, testing & fill/finish.

"The greatest potential for substantially shortening the time and increasing the reliability of influenza vaccine production lies in the use of recombinant DNA technologies" - PCAST

Flublok

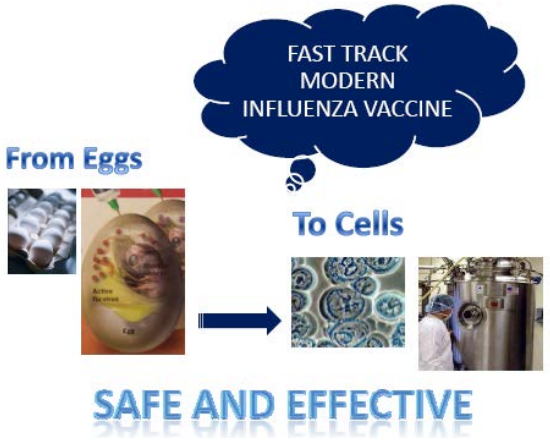
- On 16JAN2013 FDA approves Flublok for the prevention of influenza in adults 18 - 49 years old

“The Evolution, and Revolution, of Flu Vaccines”

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm336267.htm

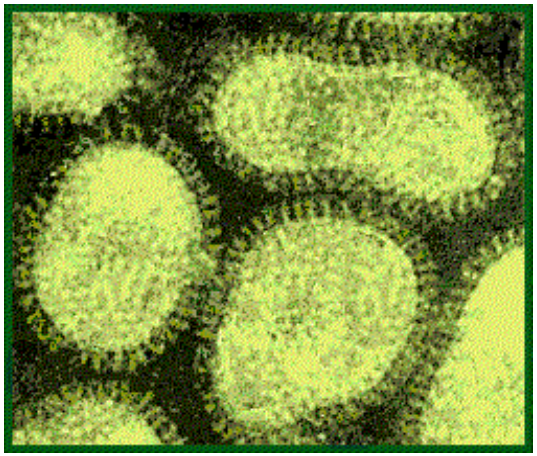
- First recombinant influenza vaccine
- The pandemic solution

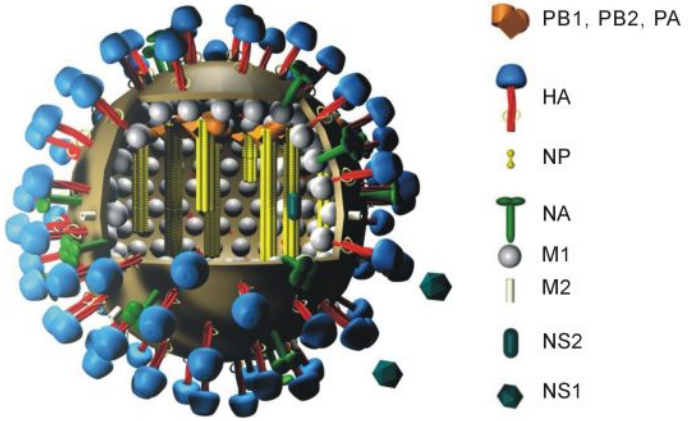
Only vaccine platform that can be manufactured quickly and/or transferred to and manufactured in other countries



Influenza Vaccine:
HA = Major Surface Protein

- **HA *(Hemagglutinin)*:**
  - Coat of the influenza virus
  - Antibodies against HA protect against influenza
  - Changes in HA require annual update of vaccine



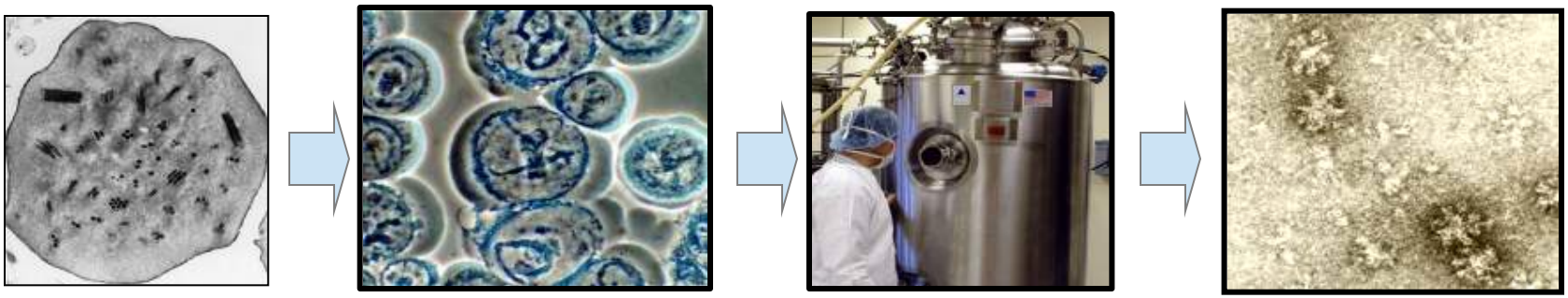


Baculovirus Expression Vector Technology Platform (BEVS)

BEVS Technology

"Enabling products where speed, cost and safety matter"

Baculovirus Expression Vector System (BEVS)



- Engineer baculovirus with the gene of interest (e.g. Hemagglutinin)
- Baculoviruses highly specific to insect cells
- Powerful promoter generates high yield of protein of interest

- Culture expression of insect cells in a fermenter
- Infect cells with engineered virus
- Incubate infection for ~48 - 72 hours

- Protein forms rosettes
- Purify protein to > 90% into final product
- Formulate with PBS into vaccine

Flublok® Approval → Validation

Universal “Plug and Play” Process

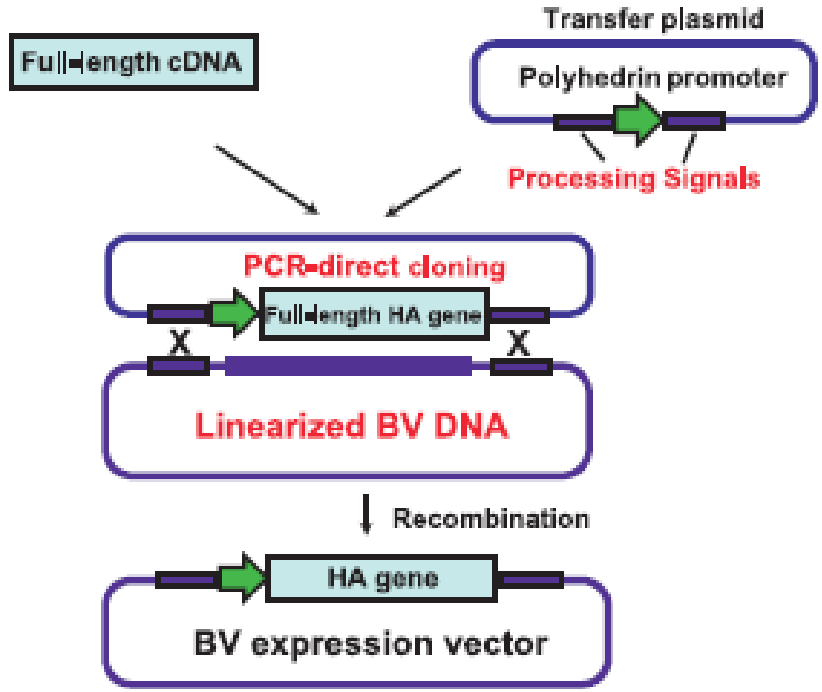


Fig. 1a. Schematic overview of the construction of the baculovirus vector.

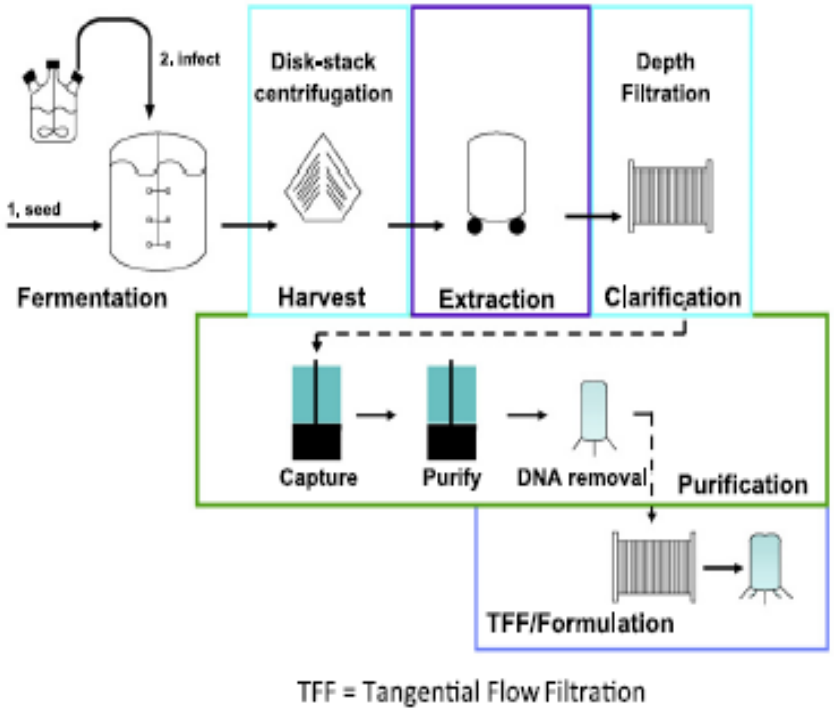
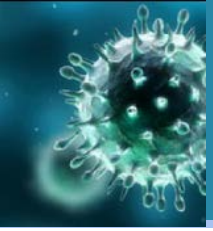


Fig. 1b. Schematic overview of the production process for the manufacturing of FluBlok.

From gene to production in 21days

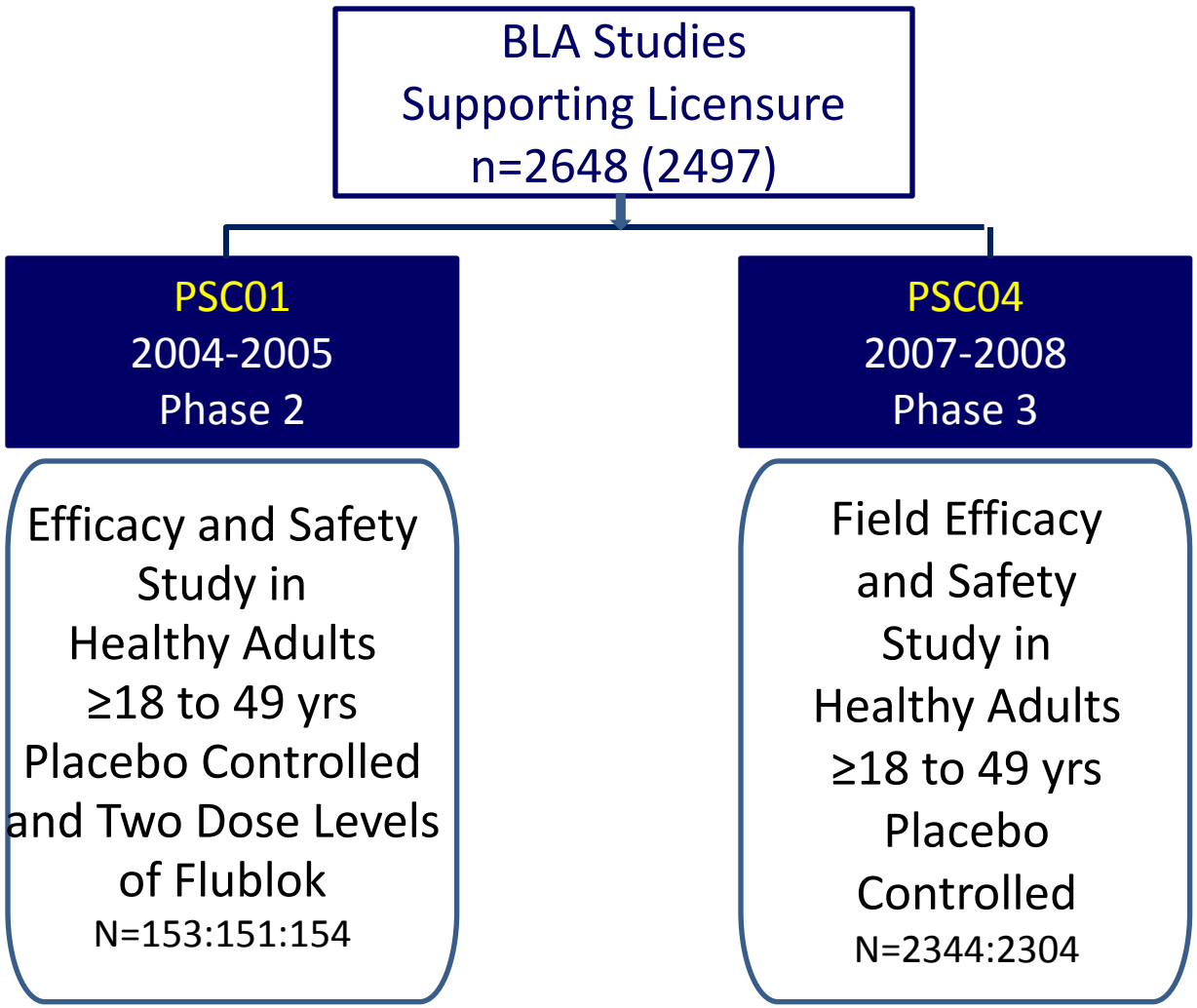
M.M.J. Cox, Y. Hashimoto/Journal of Invertebrate Pathology 107 (2011) S31–S41



Flublok
Recombinant Hemagglutinin

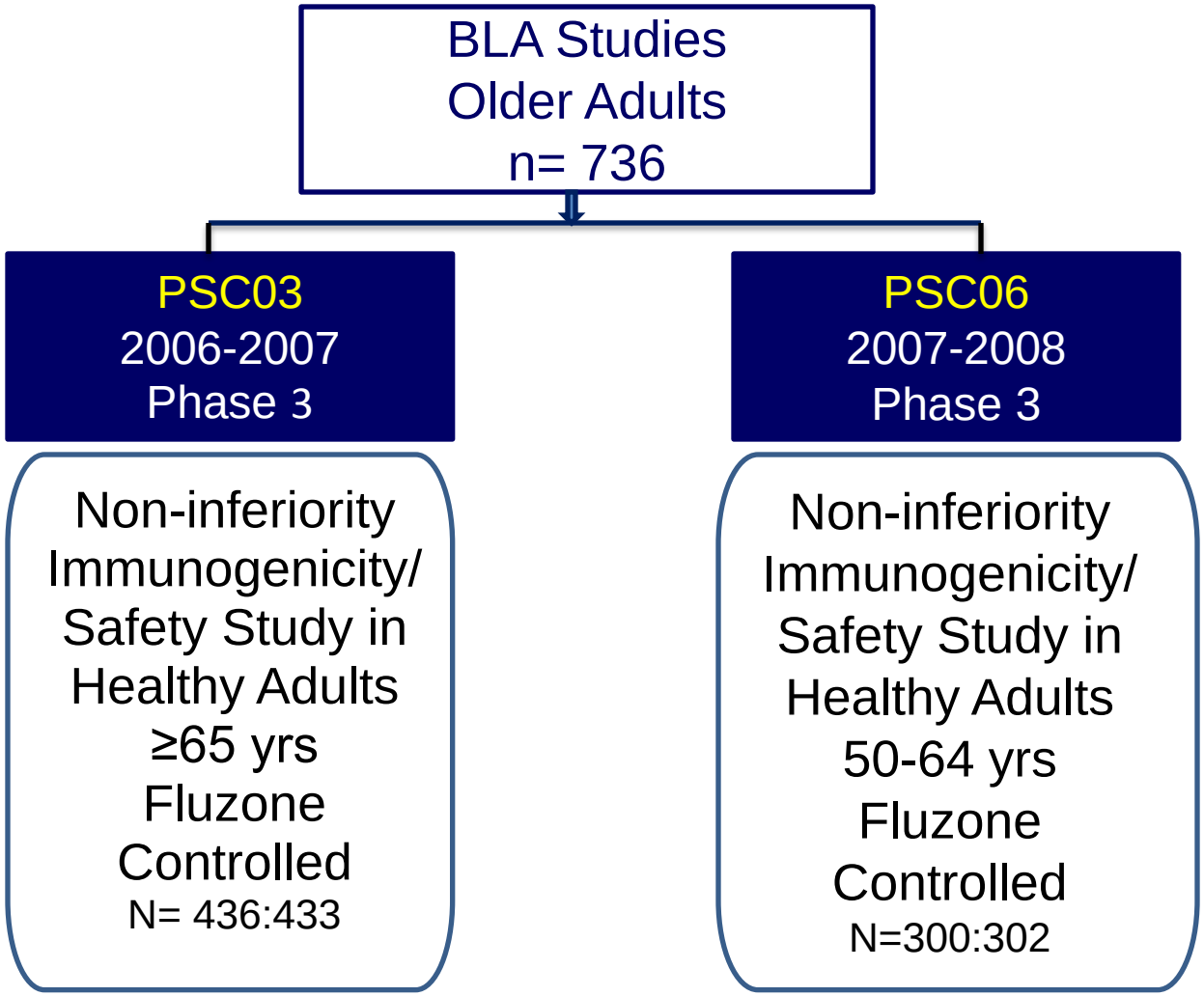
Product	Recombinant hemagglutinin protein Dose: 135µg rHA (45µg/rHA antigen) No adjuvant, preservative, antibiotic or latex
Process	Insect cell culture (Baculovirus-vector)
Features	Purified protein: high dose is feasible, No egg protein, low endotoxin content Short production cycle, no live influenza viruses or eggs, no biocontainment High yield process allows increased HA content to enhance immunogenicity

Flublok Registration Trials

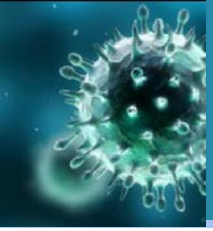


n = number of subjects vaccinated with Flublok
( ) = number of subjects receiving commercial formulation of Flublok

Flublok Supportive Trials

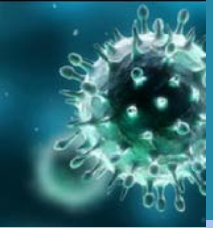


n = number of subjects vaccinated with Flublok



Clinical Studies Supporting Licensure

- Unless specified otherwise, trials were:
  - Randomized
  - Modified double-blind design (i.e. all subjects, site staff, and laboratory personnel blinded, except for vaccine administrator)
  - Multicenter studies, all conducted in US
  - Included healthy adults age 18-49 yrs
- Supportive studies:
  - PSC03 and PSC06
  - Medically stable adults age ≥65 and 50-64, respectively

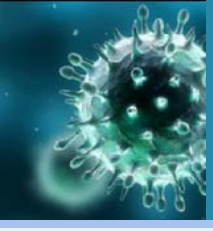


Clinical Study Designs – Common Features
PSC01, PSC03, PSC04 and PSC06

- SAFETY
  - Standardized Memory Aid for ARs days 0-7
  - Unsolicited AEs through Day 28
  - Final safety follow-up at Day ~180
  - Standardized definitions/MedDRA coding
- IMMUNOGENICITY
  - Validated hemagglutinin inhibition (HI) antibody assay performed at central laboratory
  - Serological endpoint criteria specified in FDA and EMA Guidances

Overall Demographics

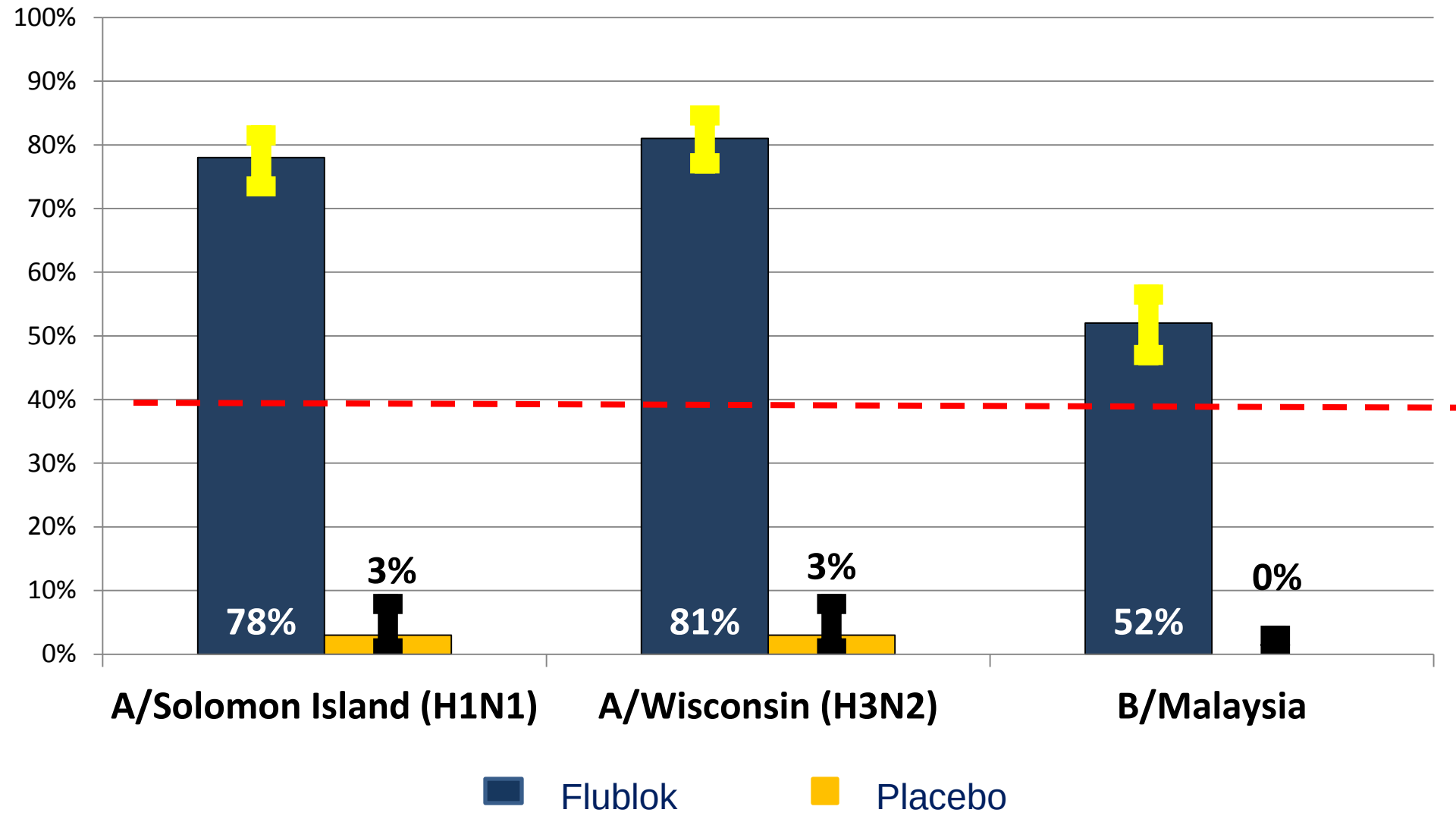
- Age:
  - 18 – 49 y/o: mean ~32 years
  - 50 – 64 y/o: mean ~56 years
  - ≥ 65 y/o: mean ~ 73 years
- Gender: ~40% male: ~60% female
- Ethnicity: ~70-80% Caucasian; ~20 – 25% black, Asian or Latino; ~5% other



PSC04: Protective Efficacy of Flublok

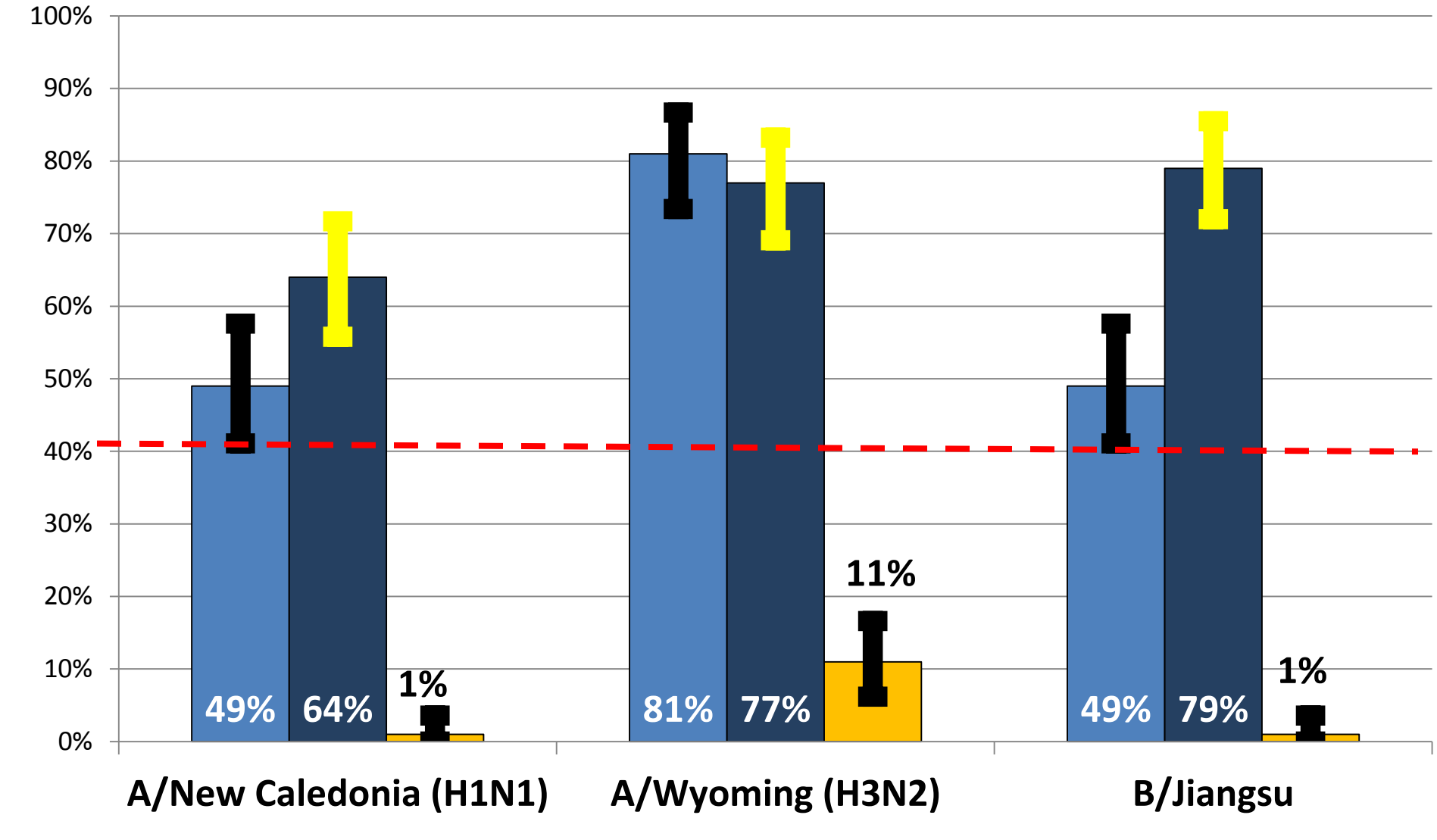
	Flublok (N=2344)		Placebo (N=2304)		Flublok Protective Efficacy, %	95% Confidence Interval
	Cases, n	Rate, %	Cases, n	Rate, %		
Positive culture due to a strain represented in the vaccine						
CDC-ILI, all matched strains	1	0.04	4	0.2	75.4	(-148.0, 99.5)
All matched strains	2	0.1	6	0.3	67.2	(-83.2, 96.8)
Positive culture due to any strain, regardless of match to the vaccine						
CDC-ILI, all strains	44	1.9	78	3.4	44.6	(18.8, 62.6)
Type A	26	1.1	56	2.4	54.4	(26.1, 72.5)
Type B	18	0.8	23	1.0	23.1	(-49.0, 60.9)
All strains	64	2.7	114	4.9	44.8	(24.4, 60.0)
Type A	41	1.7	79	3.4	49.0	(24.7, 65.9)
Type B	23	1.0	36	1.6	37.2	(-8.9, 64.5)

PSC04 - Seroconversion

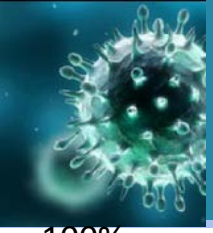


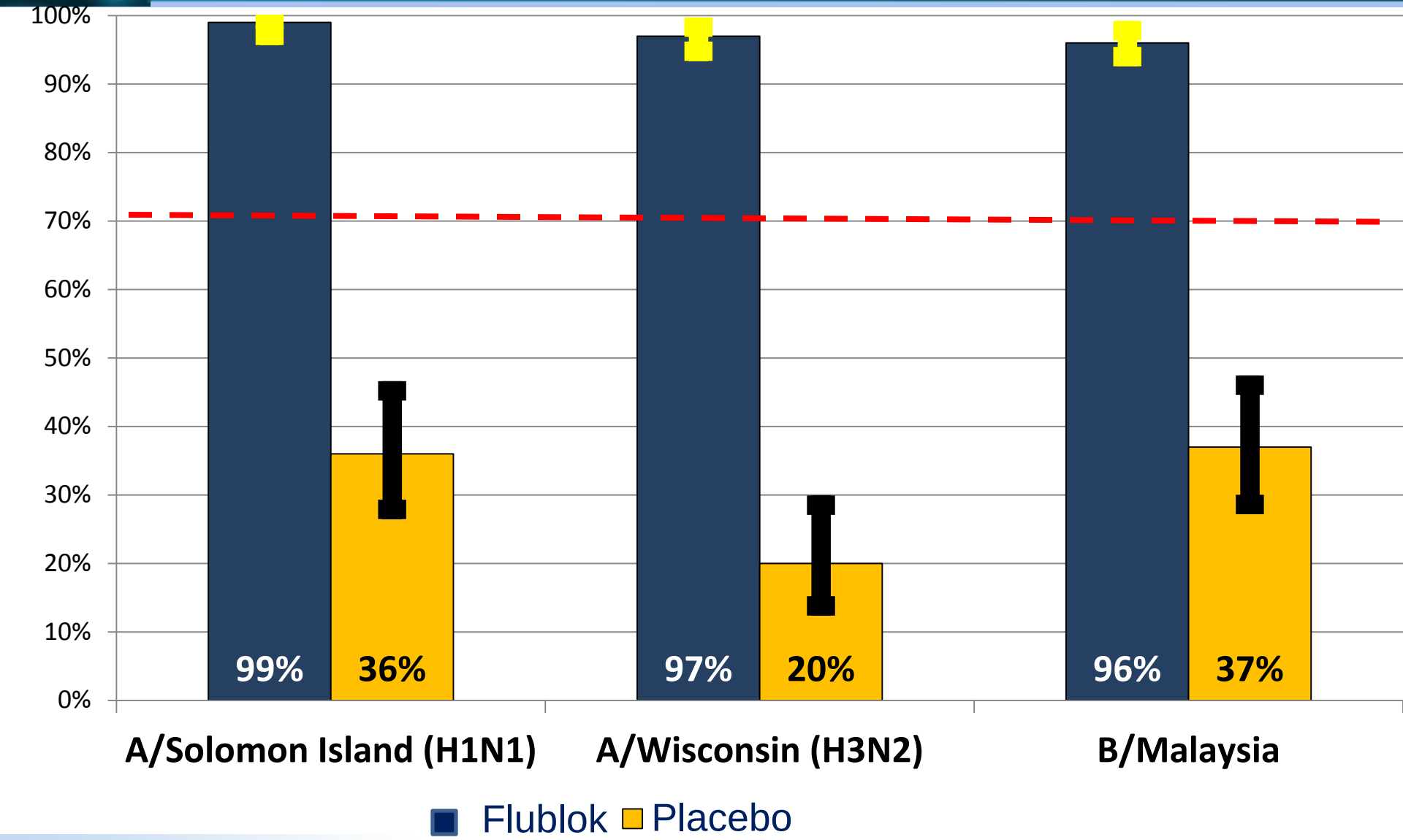
2-sided 95% Confidence Intervals represented as error bars

PSC01: Seroconversion Day 28 Titer ≥32

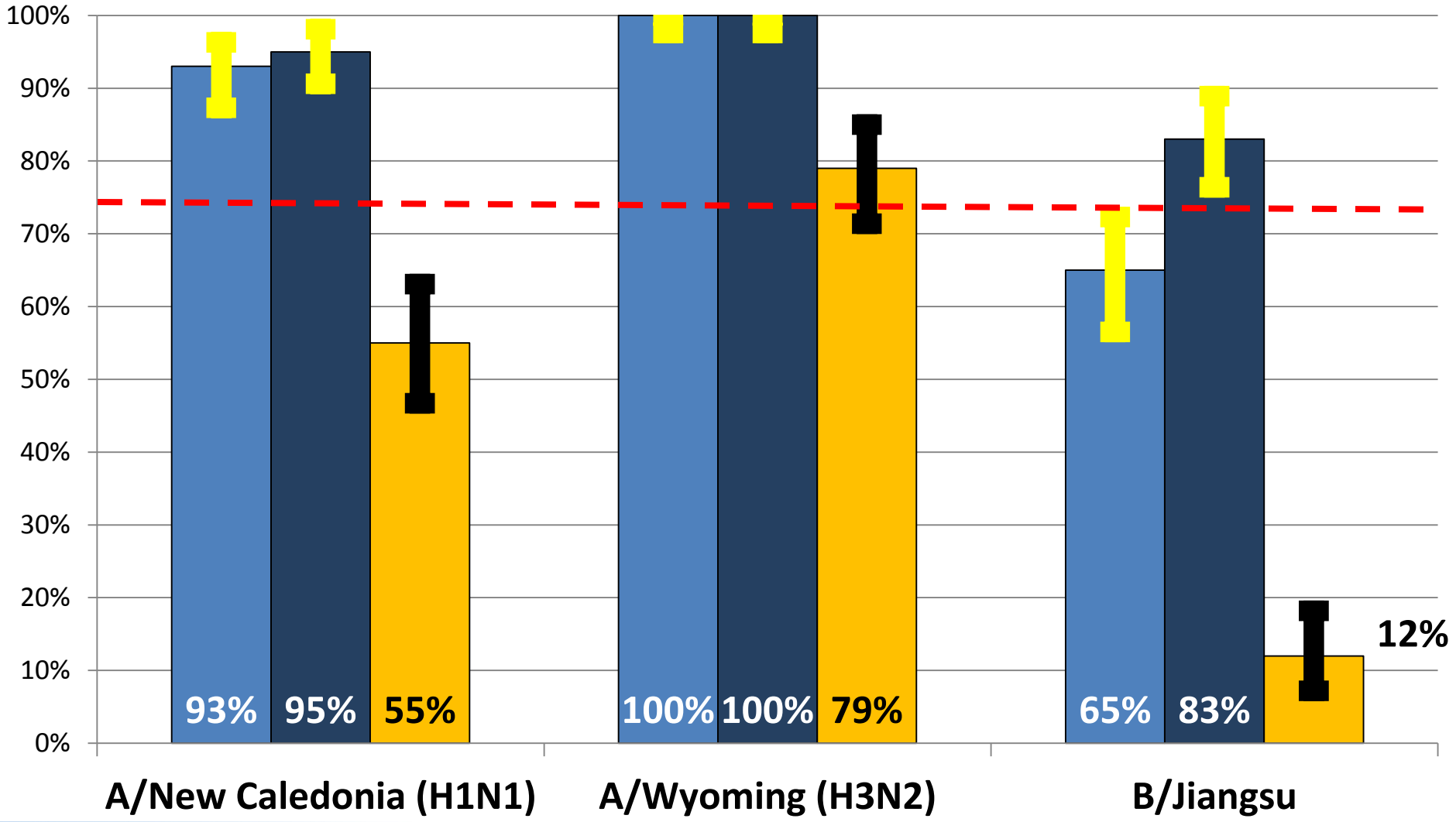


PSC04: Seroprotection





PSC01: HI Titer ≥32



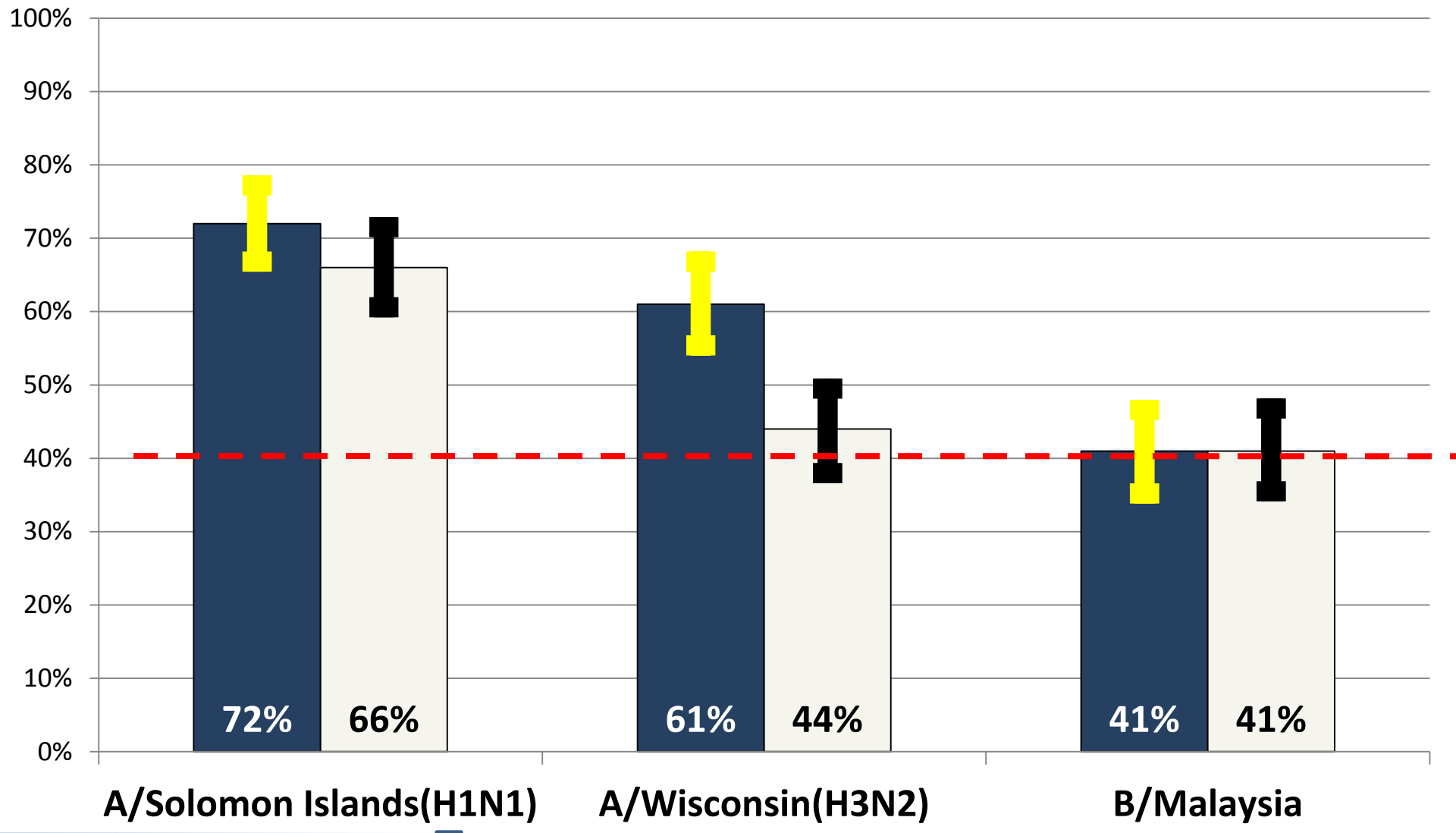
Serum HI Antibody Response Summary

	PSC01	PSC04
	18-49 yrs	18-49 yrs
	Flublok	**Flublok**
A/H1N1	***A/New Caledonia***	***A/Solomon Islands***
% Seroprotected		
%Seroconversion		
A/H3N2	***A/Wyoming***	***A/Wisconsin***
% Seroprotected		
%Seroconversion		
B	***B/Jiangsu***	***B/Malaysia***
%Seroprotected		
%Seroconversion		

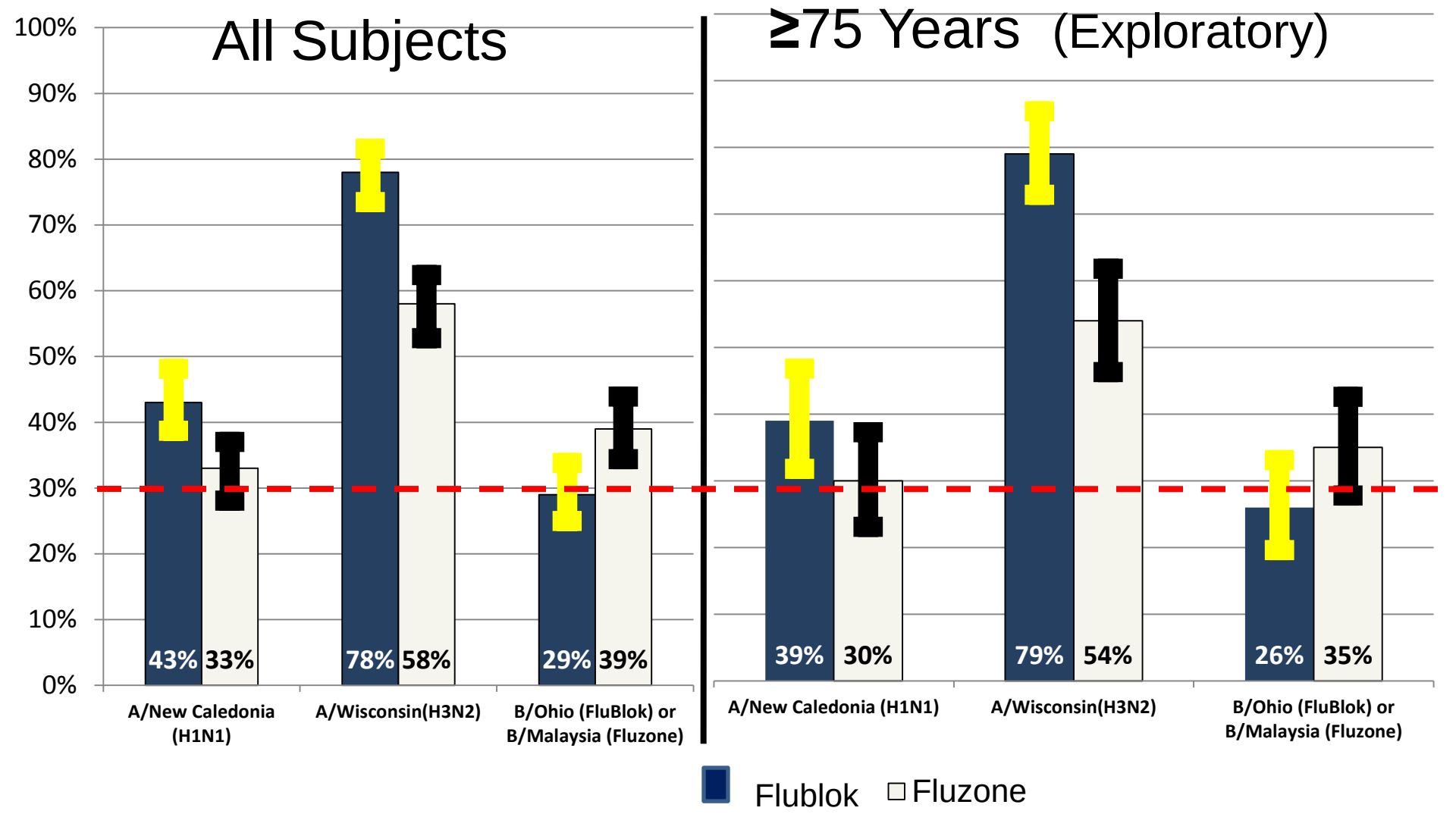
Green = meets licensure criteria

Red = fails to meet criteria

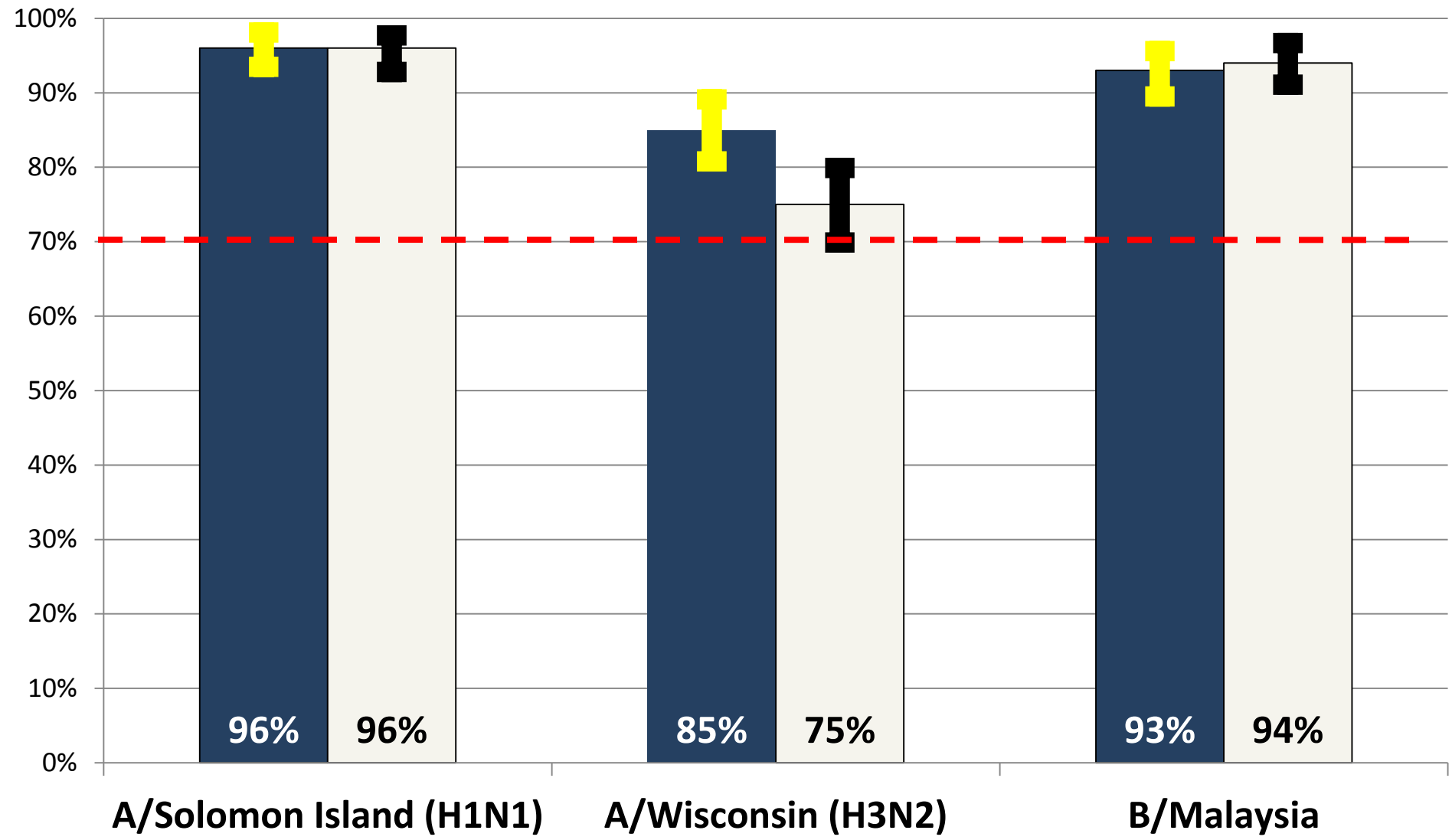
PSC06: Seroconversion



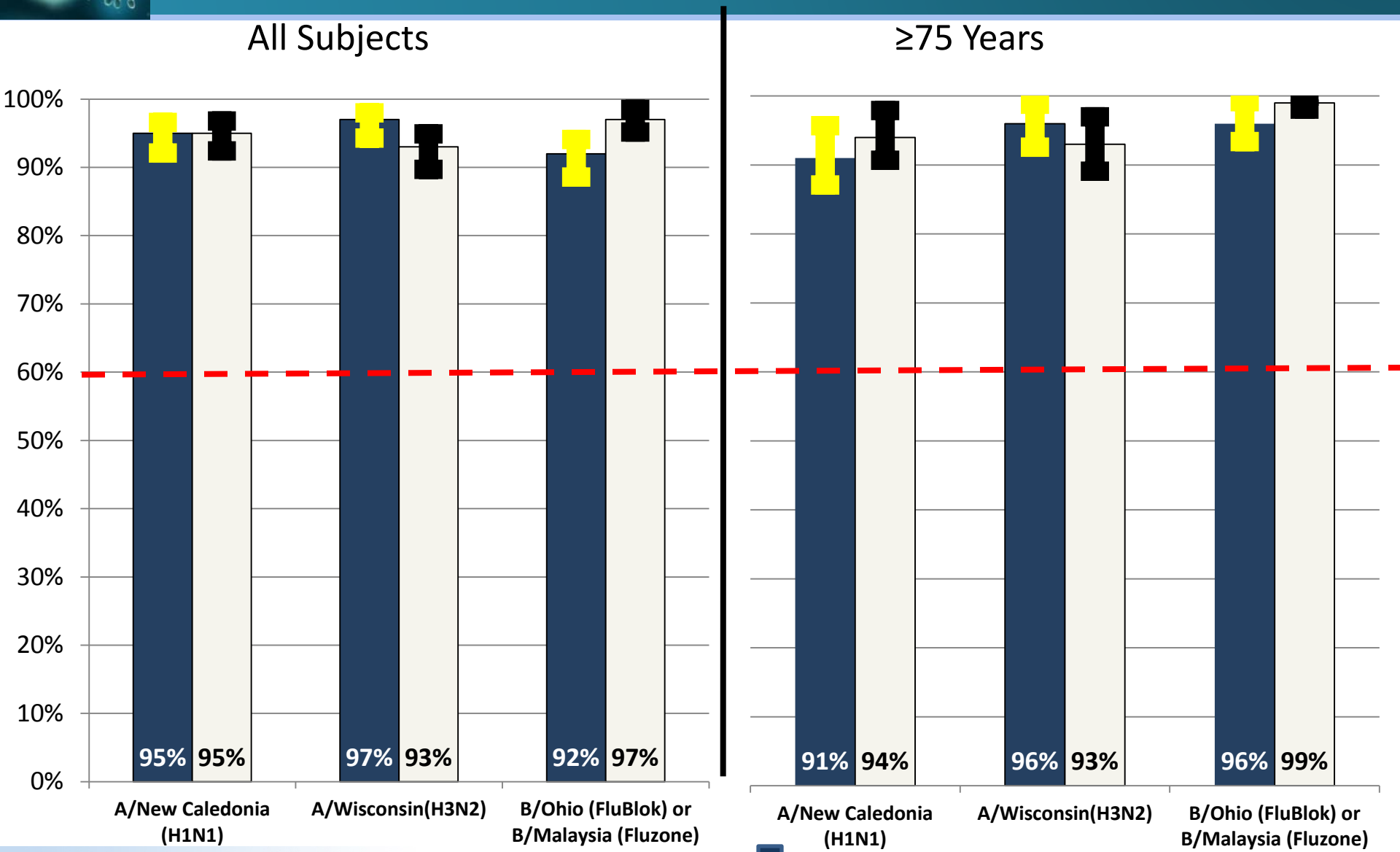
PSC03: Seroconversion



PSC06: Seroprotection (HI Titer ≥40)



PSC03: Seroprotection (HI Titer ≥40)



Non-Inferiority Comparison: Flublok Compared to Fluzone

		H1	H3	B
GMT	06	FB>Fz	FB>Fz	
	03	FB>Fz	FB>Fz	
% SCR	06		FB>Fz	
	03	FB>Fz	FB>Fz	Fz>FB

NI		Not NI

FB>Fz :Flublok significantly higher $p<0.05$
Fz>FB :Fluzone significantly higher $p< 0.05$

Local Adverse Reactions - Overview

	PSC01		PSC04	
	Adults age 18-49 yrs		Adults age 18-49 yrs	
	Flublok	Placebo	Flublok	Placebo
Number of Subjects	153	154	2344	2304
Local Adverse Events				
Pain	61%*	17%*	37%	8%
Redness	5%	2%	4%	2%
Swelling	10%	3%	3%	2%
Bruising	7%	4%	3%	3%

* Includes additional clinical evaluation on Day 3

Systemic Adverse Reactions - Overview

	PSC01		PSC04	
	Adults age 18-49 yrs		Adults age 18-49 yrs	
	Flublok	Placebo	Flublok	Placebo
Number of Subjects	153	154	2344	2304
Systemic Adverse Events				
Headache	42%*	41%*	15%	16%
Fatigue	16%	18%	15%	15%
Muscle Pain	20%	12%	11%	7%
Fever	0%	1%	<1%	<1%
Joint pain	5%	5%	4%	4%
Nausea	8%	6%	6%	5%
Chills	3%	2%	3%	3%
Sweating	3%	5%	NA	NA

* Includes additional clinical evaluation on Day 3

Spontaneous AEs - Overview

Category	PSC04		PSC01	
	Flublok	Pbo	Flublok	Pbo
Non-serious (%)	17	17	35	42
SAE (%)	1.3	1.5	1	0
Pregnancy (n)	20	17	3	0

- Most common non-serious reports were headache, URI, cough, injection site reactions
  - Most mild; all self-limited
- SAEs largely judged not related to study vaccine
  - One episode of “pericarditis” considered “possibly related”
- Most pregnancies had normal outcomes; miscarriages judged “not related”; no congenital defects

FDA Assessment: Hypersensitivity-type Events

Unsolicited AE by MedDRA Preferred Term	Flublok N=3233	Placebo N=2188	Fluzone n=735
	n (%)	n (%)	n (%)
Pleuropericarditis	1	-	-
Hypersensitivity	4 (0.1)	1 (0.04)	-
Urticaria	1	-	-
Rash	9 (0.3)	3 (0.1)	6 (0.8)
Swelling face	1	-	-

- Rash:
  - Rates appear lower in Flublok group compared to Fluzone.
  - None in the Flublok recipients were serious or severe.
  - Majority appeared unrelated to Flublok.

Flublok in Pregnancy

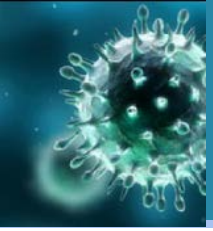
- 20 women in PSC04 on Flublok became pregnant
  - No birth defects in live births (75% follow-up)
  - No vaccine-related AEs
- Full battery of reproductive tox in rats
  - 135 µg injected x2 prior to and x1 during gestation
  - No effect on fertility
  - No effect on implantation or fetal growth
  - No birth defects
  - No effect on pups through weaning
- Formal pregnancy registry planned to initiate 2014

Summary of Safety Data

- Commercial formulation evaluated in a total of 3,233 adults in 4 randomized, controlled trials
  - 2497 adults age 18-49 yrs
  - 736 adults ≥50 years not included in indication
- Excellent tolerability and safety profile, with AE rates generally similar to the active comparator, Fluzone in two studies
- Only one treatment-related SAE (vasovagal syncope) and one possibly-related SAE (pericardial/pleural effusion) reported

Availability of Flublok

- 15FEB2013:
  - ~100,000 – 150,000 doses available
  - Target recipients: self-identified egg-allergic individuals
  - Target college-age groups
  - Most currently registered with PSC
- 2013-2014 season:
  - New expanded manufacturing facility
  - Expect 3-5 million doses
  - Distributor(s) to be identified

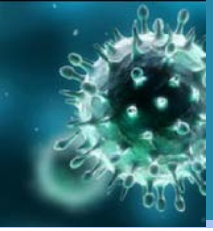


Clinical Trials 2013/2014

- Age indication expansion – Older adults:
  - 30-day safety study in 2500 adults ≥50 years old
    - Being conducted in 2Q2013
    - TIV-controlled assessment of hypersensitivity
    - Expected to support approval for 2013-2014

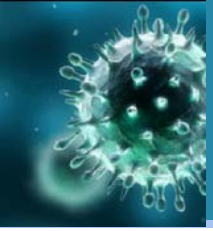
Clinical Trials - 2

- Age indication expansion – Pediatrics:
  - Safety/immunogenicity study in ~700 6–17 yo
    - First of PREA-required studies
    - TIV-controlled non-inferiority study
    - To initiate by October, 2013
    - 6-12 months safety follow-up



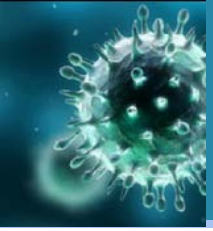
Clinical Trials - 3

- Post-marketing commitments:
  - Pregnancy registry:
    - To initiate 2014
    - To enroll 600 pregnant women, at least 300 Flublok recipients
    - Follow for pregnancy complications & outcome
    - Follow live newborns to 1st well-baby visit
    - Concurrent non-Flublok recipient controls
    - May take up to 5 years to enroll



Clinical Trials - 4

- Post-marketing commitments:
  - Observational safety study of 25,000 Flublok recipients
  - Controls will be non-Flublok recipients
  - To initiate in fall, 2013
  - Follow for MAEs, AEs and AEs of special interest
  - Expected to be completed in single flu season



Conclusions

- Flublok is the first purified, recombinant HA protein flu vaccine
  - No influenza virus is used in the manufacturing process
- Contains 45µg each HA to improve immunogenicity
- Safety and protective efficacy shown in adults 18-49
- Contains no egg protein, preservative, antibiotics or latex
- Full battery of reproductive toxicology studies were negative
  - Pregnancy monitoring on-going; formal Registry to begin 2014
- Single-dose vials available for targeted populations in 2013
  - 3-5 million doses expected in 2013-2014 season
- Additional studies being conducted to expand age range
  - Approval for ≥50 yo adults expected for 2013-2014 season
  - Immunogenicity in 6-17 yo being studied in 2013-2014