FDA Approved Recombinant Hemagglutinin Influenza Vaccine Protects Against Drift Influenza Viruses

Flublok®
Influenza vaccine

Protein Sciences
CORPORATION

2nd International conference on **Flu**
October 31- November 02, 2016
San Francisco, California, USA

Protein Sciences
Manufacturing Vaccines

Flublok® Influenza vaccine

More, Faster, and Better ….

Meriden, CT



Pearl River, NY





Gifu, Japan (UNIGEN)
cGMP facility: 2x21,000L; adding 2 more

A New Approach to Vaccine Manufacture

Traditional

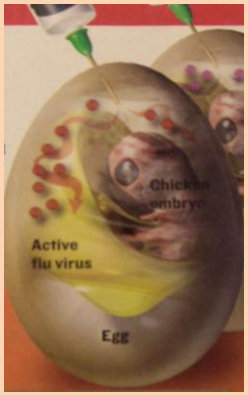
- Grow pathogen (in eggs)
- Inactivate pathogen
- Purify antigen (i.e., the active ingredient)
- Formulate vaccine

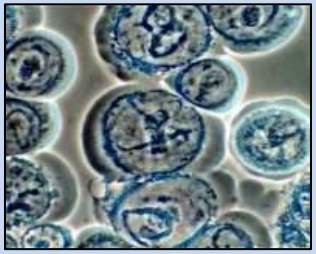
BEVS

- Produce antigen (in cell culture)
- Purify antigen
- Formulate vaccine

Fast ***Pure*** ***Egg-free***

TRADITIONAL METHOD







MODERN VACCINE



Baculovirus 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

From Gene to Production in 22 Days

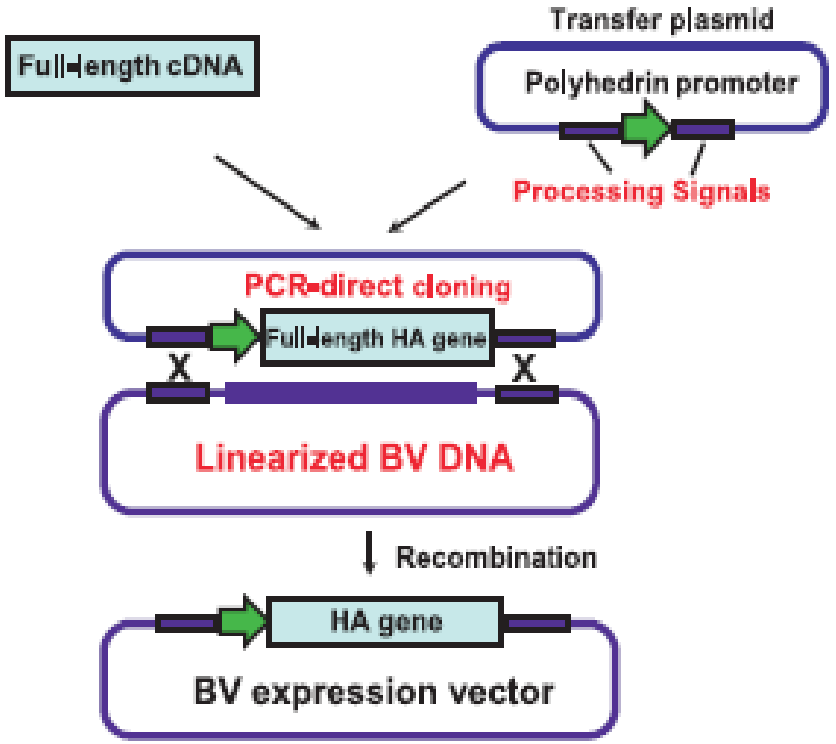


Fig. 1a. Schematic overview of the construction of the baculovirus vector.

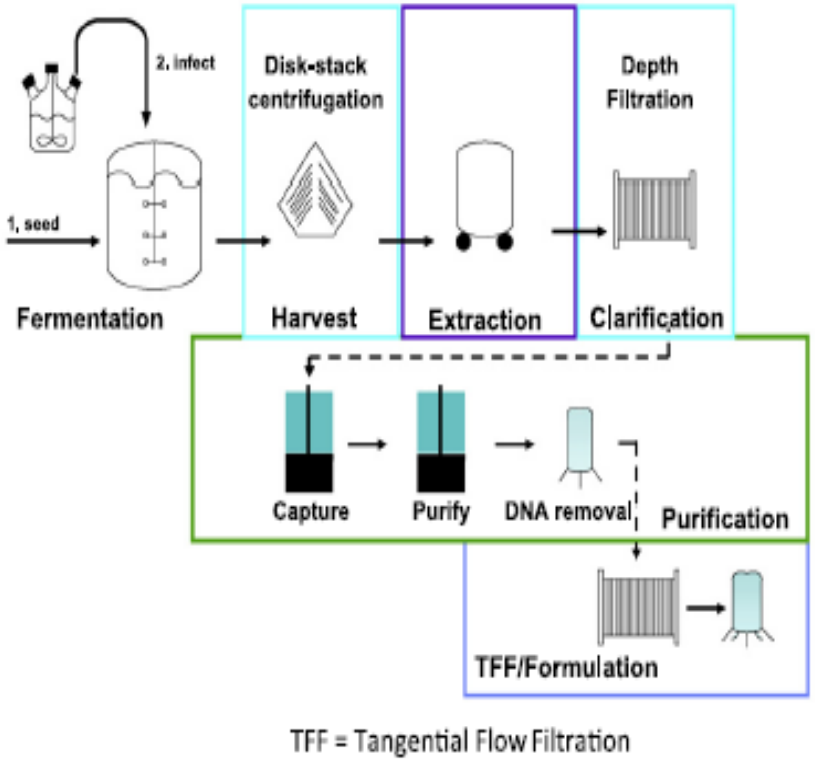


Fig. 1b. Schematic overview of the production process for the manufacturing of FluBlok.

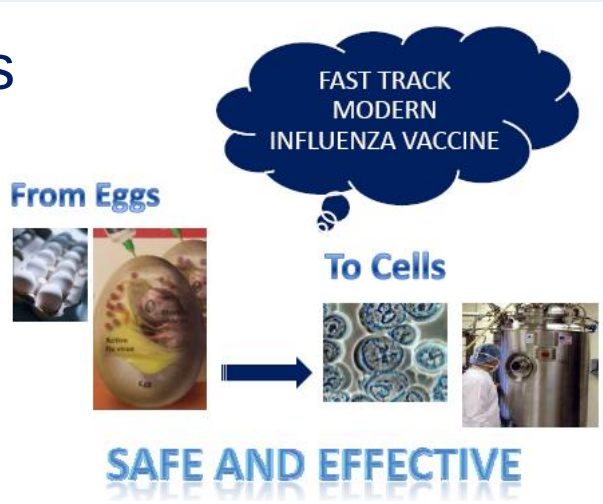
M.M.J. Cox, Y. Hashimoto / Journal of Invertebrate Pathology 107 (2011) S31–S41

From gene to production in 22 days

Flublok®

- First recombinant influenza vaccine
- FDA licensed for 18 years and above
- Pediatric age expansion underway
- Panblok: The pandemic solution

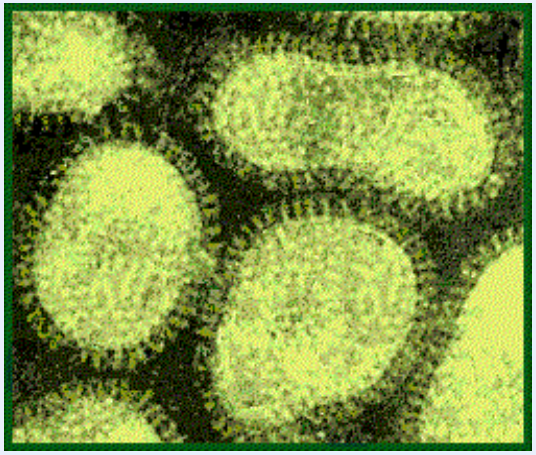
  Only pandemic vaccine that can be quickly manufactured and/or transferred to and manufactured in other countries

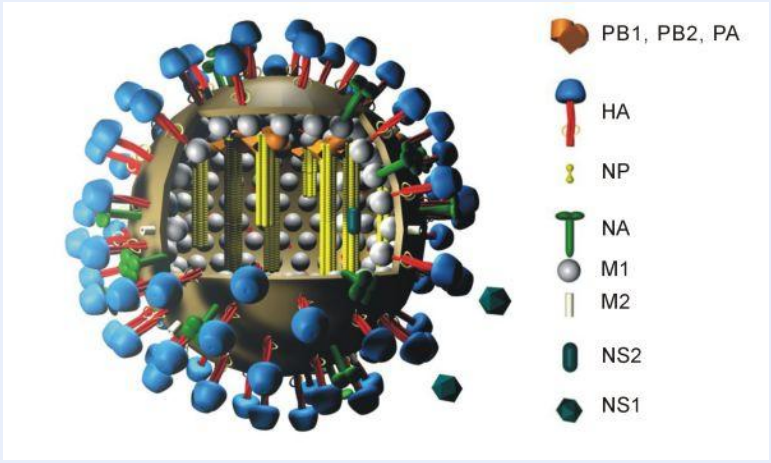


Influenza Vaccine: HA = Major Surface Protein

HA *(Hemagglutinin)*:

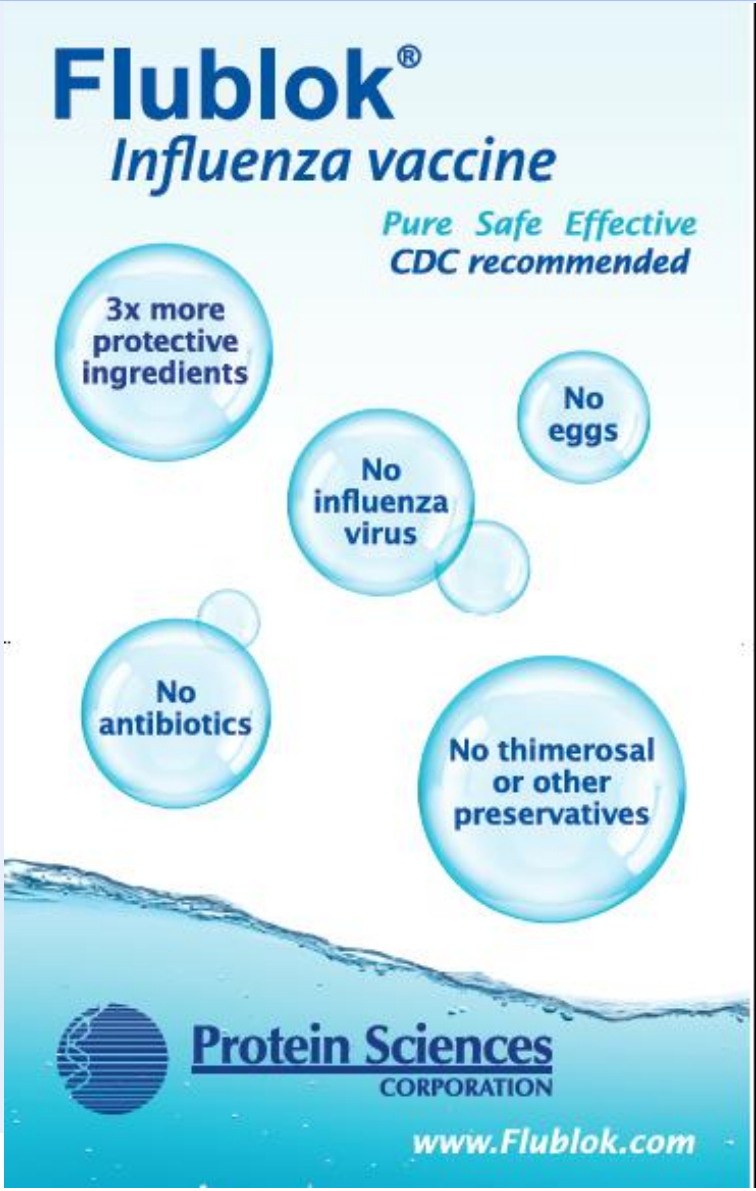
- Coat of the influenza virus
- Antibodies against HA protect against influenza
- Changes in HA require annual update of vaccine

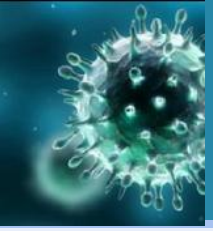




Flublok Features

- Pure protein vaccine – unique
- Matches circulating flu virus
- 3X more protein than conventional flu vaccines
- No
  - egg protein
  - influenza virus
  - thimerosal (mercury)
  - antibiotics
  - formaldehyde
  - latex
  - gelatin
  - gluten
  - endotoxins





Vaccine Characteristics - Purity

	EXACT MATCH	EGG	GELATIN	ANTIBIOTICS	LATEX	THIMEROSAL	FORMALDEHYDE	LIVE VIRUS
FLUBLOK	**X**							
AFLURIA		X		X		X		
FLUARIX		X		X	X		X	
FLUMIST		X	X	X				X
FLUVIRIN		X		X	X	X		
FLUZONE		X	X			X	X (INTRADERMAL)	
FLUCELVAX		X			X			
FLULAVAL		X				X	X	
AGRIFLU		X		X	X			

Flublok can “de-risk”

Flublok Protects Against Matched and Drifted Influenza Strains

Table 1. Efficacy of Flublok (Trivalent) vs Culture-Confirmed Influenza in Healthy Adults 18-49 Years of Age[8]

Case definition	Flublok Vaccine Efficacy (%)
Positive culture with a strain represented in the vaccine	
CDC-ILI: all matched strains	75.4
Any ILI: all matched strains	67.2
Positive culture with any strain, regardless of match to the vaccine	
CDC-ILI: all strains Subtype A Type B	44.6 54.4 23.1
Any ILI: all strains Subtype A Type B	44.8 49 37.2

ILI= influenza-like illness; CDC-ILI=ILI+fever ≥ 100°F

75% protection against matched strains

45% protection against *all* strains (including drifted)

And shows improved immunogenicity against the A strains and comparable responses to the B strains in adults ≥50 yr old

Influenza 2014-2015: The Longest Flu Season on Record

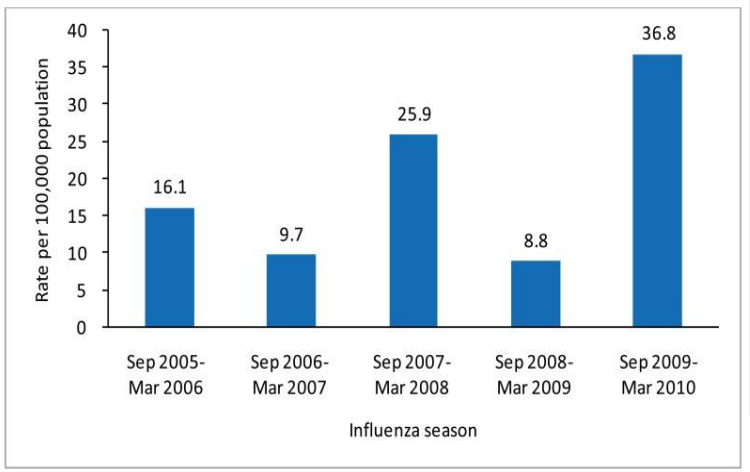
- Predominant circulating virus was H3N2
  - Causes worse disease and more complications than other influenza subtypes and can have mortality rates as high as 50,000
  - Highest hospitalization rate ever for people ≥65 (322/100,000) and 65.5/100,000 in all age groups

- Poor vaccine performance –
  - Approx. 35% effective in people over 65 years old (ACIP, June'15)
  - Some vaccines were associated with increased disease rates

- Why?

2 reasons for poor performance:

- Egg drift
- Seasonal drift



Immunogenicity Data
- Clinical -

Effectiveness: Non Inferiority Comparison
Flublok vs. 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

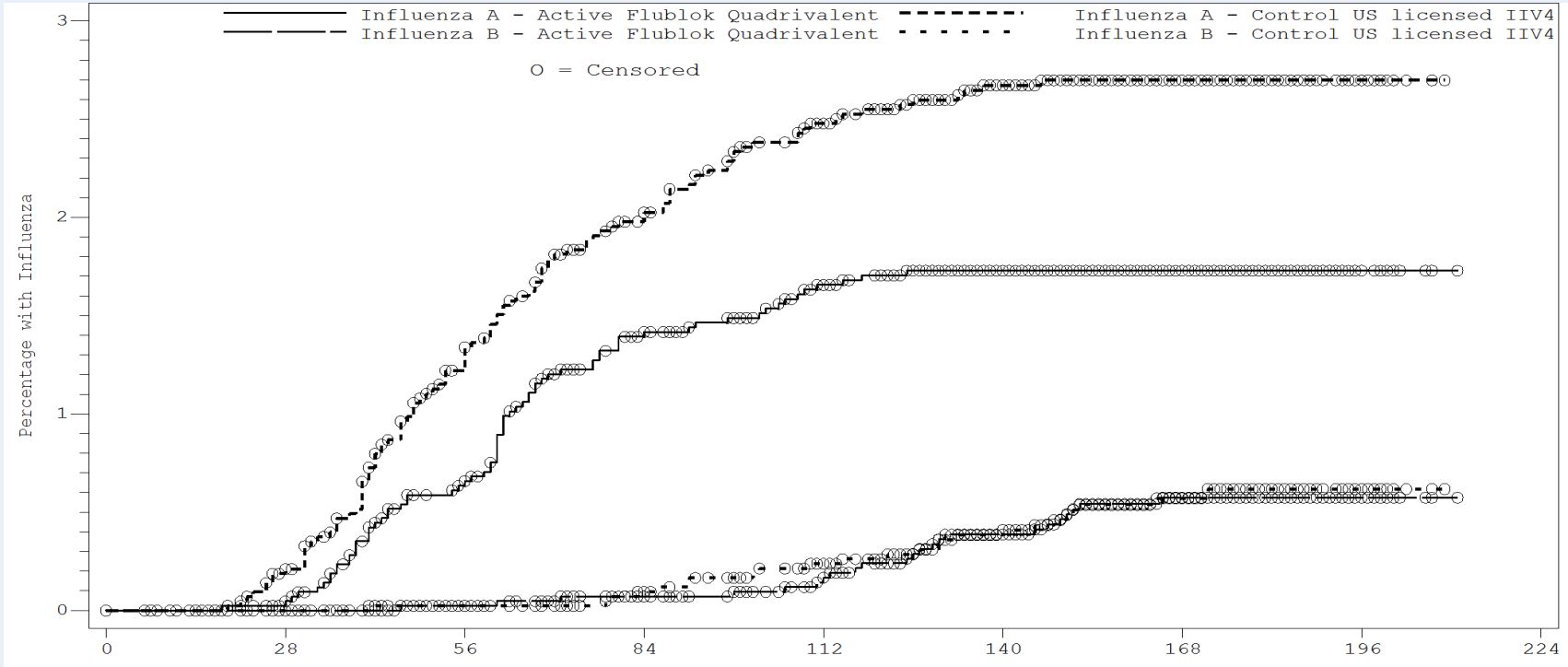
Topline Results
Quadrivalent Flublok [RIV4] vs. IIV

Efficacy of Flublok vs. PCR-confirmed Influenza in Adults 50 years and older in comparison to IIV		
	Flublok (n= 4303)	IIV (n=4302)
Overall RT-PCR Confirmed influenza	96	138
Attack rate	0.022	0.032

Conclusion: Relative Vaccine Efficacy = 0.31 (0.10, 0.47)

Flublok meets the exploratory superiority endpoint

Influenza Isolates by RT-PCR



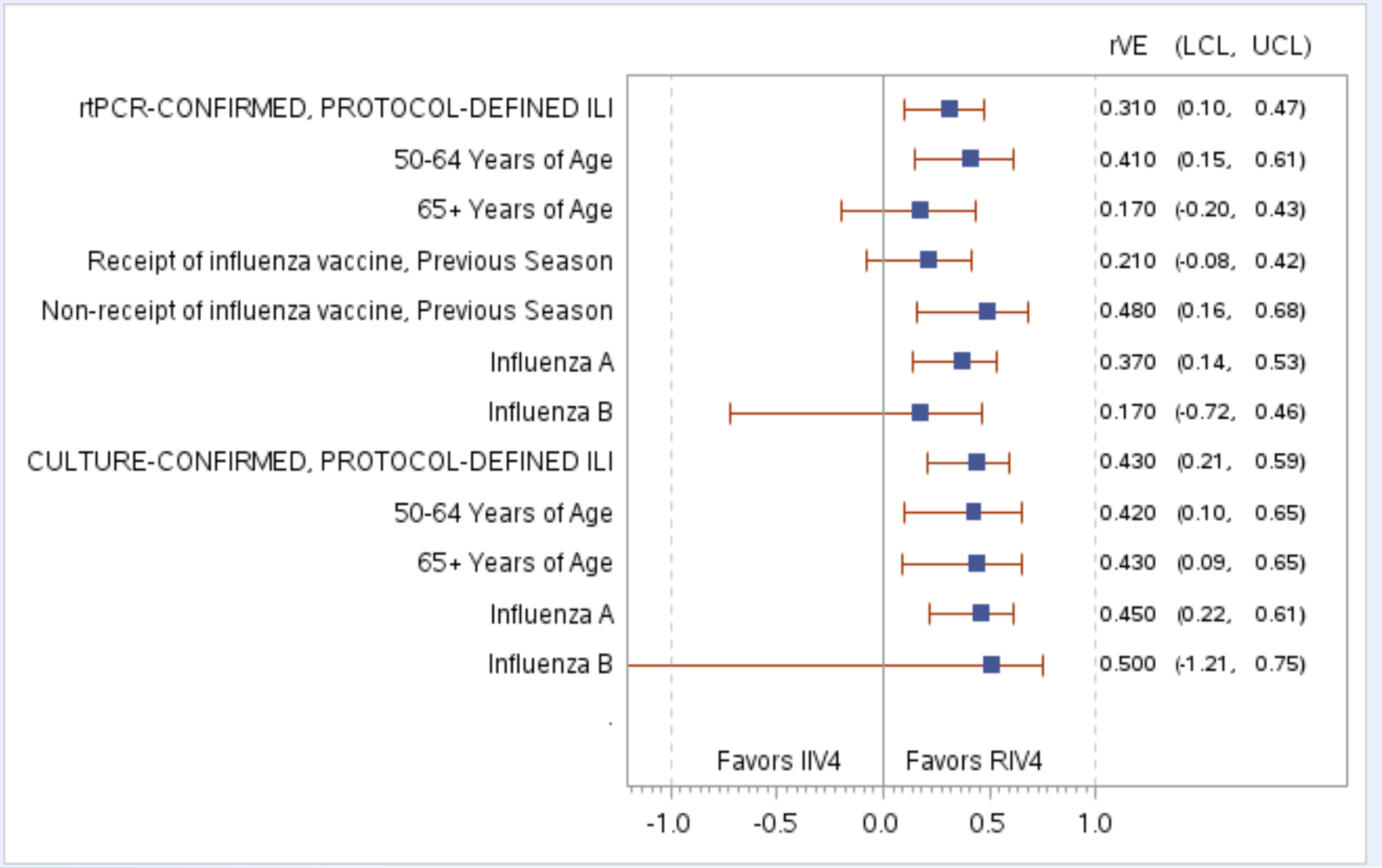
Flu A

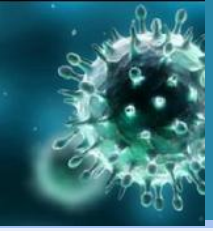
Flu B

Subjects Remaining at Risk (Cumulative Events)

Influenza A - Active Flublok Quadrivalent							
4303(0)	4266(2)	4201(28)	4127(60)	4081(70)	3859(73)	2339(73)	15(73)	0(73)
Influenza A - Control US licensed IIV4							
4301(0)	4261(9)	4177(57)	4120(86)	4073(105)	3832(113)	2336(114)	14(114)	0(114)
Influenza B - Active Flublok Quadrivalent							
4303(0)	4268(0)	4228(1)	4184(3)	4144(7)	3915(16)	2371(23)	16(23)	0(23)
Influenza B - Control US licensed IIV4							
4301(0)	4270(0)	4232(1)	4201(4)	4167(10)	3924(17)	2395(23)	14(24)	0(24)

Flublok Clinical Efficacy in Adults 50+ (protocol defined ILI)





ILI Related MAEs/ SAEs
During 6 months after vaccination

- Medical attended ILI
  - RIV4 = 6; IIV4 = 13
- Hospitalization for influenza
  - RIV4 = 1; IIV4 = 3

Most Common AEs (≥2%)

Preferred Term	Flublok [RIV4] N=4328	IIV4 N=4344
	N (%)	N (%)
Cough	226 (5.2)	253 (5.8)
Influenza like illness	186 (4.3)	199 (4.6)
Oropharyngeal pain	178 (4.1)	177 (4.1)
Headache	143 (3.3)	145 (3.3)
Upper respiratory tract infection	129 (3.0)	156 (3.6)
Fatigue	106 (2.4)	100 (2.3)
Myalgia	95 (2.2)	79 (1.8)
Productive cough	59 (1.4)	97 (2.2)

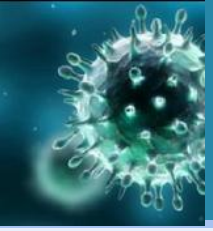
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Reactogenicity (%)

	RIV4 (Flublok Quadrivalent) N=4307			IIV4 N=4319			
	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4	P-value
≥1 event	48	1	<1	51	1	<1	0.006
≥1 local reaction	38	<1	0	40	<1	0	0.009
Local Pain	19	<1	0	22	<1	<1	<0.001
Local Tenderness	34	<1	<1	37	<1	<1	0.007
Erythema	3	<1	0	2	<1	0	0.014*
Induration	3	<1	0	3	<1	0	0.09

* Not significant after adjustment for four comparisons



PSC12 - Conclusions

- Flublok RIV4 met non-inferior clinical efficacy compared with IIV4
- Flublok RIV4 met pre-specified criterion for superiority over IIV4 clinical efficacy
  - Primary endpoint (non-inferiority) met for subgroups aged 50-64 and ≥65 years, despite smaller sample sizes
  - Efficacy most marked in subjects unvaccinated in 2013
- HAI responses to B/Brisbane were suboptimal for both vaccines
- Flublok RIV4 caused significantly less injection site pain and tenderness than IIV4
- No notable differences in SAEs or MAEs

Acknowledgement

Flublok is a reality thanks to support of BARDA contract HHSO100200900106C and the perseverance of the Protein Sciences team!

