Protein Sciences CORPORATION

Improved Efficacy of Recombinant Influenza Vaccine vs. Inactivated Vaccine During an Influenza Season Marked by a Vaccine Mismatch

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ACIP

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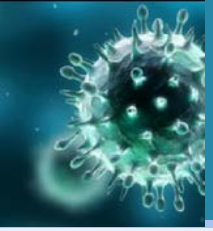
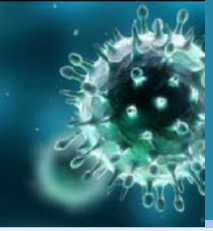


Background

- Flublok® (trivalent) is the first licensed recombinant hemagglutinin (HA) protein influenza vaccine
- Flublok hemagglutinins match the HAs chosen for seasonal influenza vaccine
- The North American influenza season of 2014-2015 was especially severe in adults ≥65 years of age:
  - Widespread circulation of an A/H3N2 strain not antigenically matched to the vaccine
- "Mismatch" led to low vaccine effectiveness:
  - estimated as <20% overall
  - high rates of lab confirmed hospitalizations for pneumonia and influenza
- During the 2014-2015 season, we conducted a randomized clinical trial:
  - Flublok Quadrivalent (RIV4) vs. quadrivalent inactivated (egg-grown) vaccine (IIV4, Fluarix® Quadrivalent)

Results Snapshot

- Flublok quadrivalent attack rates were significantly lower than IIV4 comparator (2.2 vs 3.3%)
- Lower attack rates persisted throughout the season
- Viral cultures did not yield sufficient titers to test for antigenic similarity. The “improved” efficacy in the face of a mismatch is inferred from the fact that >80% of the circulating H3N2 viruses in 2014-2015 were antigenically mismatched to the vaccines
- Local reactions (pain and tenderness) lower in Flublok quadrivalent group



Methods

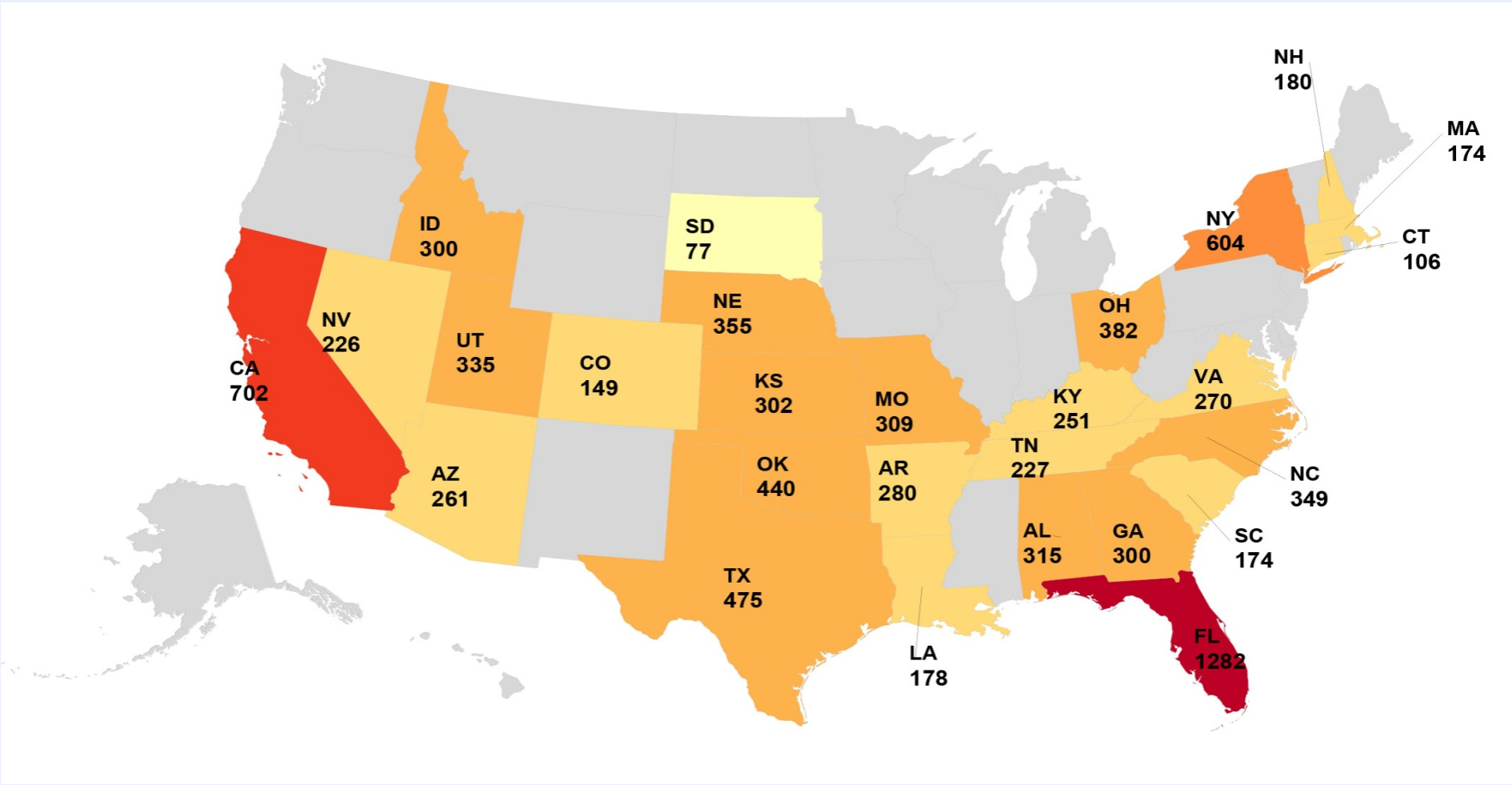
- **Hypothesis:** The relative vaccine efficacy (rVE) of Flublok Quadrivalent would be non-inferior to that of IIV4 in adults ≥ 50 years of age
  - rVE = 1-RR x 100 RR = RIV4 Attack rate/IIV4 Attack rate
- Non-inferiority = lower bound (LB) of 95% confidence interval (CI) for rVE > -20%.
- Superiority pre-specified exploratory analysis: LB of 95% CI for rVE > +9%.
- Sample size powered for 1^0 endpoint in entire study population
  - Pre-specified 2^0 analyses of sub-groups (age groups, flu type, Hx of flu vaccine)
- 9003 subjects vaccinated 22Oct – 23Dec2014; Followed thru 22May2015
- ILI symptomatic subjects had NP swabs for rtPCR and culture.
- HAI serology tested in 613 subjects
- Reactogenicity monitored for 7 days after vaccination
- Safety (SAEs and MAEs) monitored for 6 months after vaccination

Vaccine Antigenic Composition

Flublok Quadrivalent	IIV4
45 mcg per antigen	15 mcg per antigen
H1N1: A/California/07/2009	H1N1: A/ Christchurch/16/2010 (an A/California/7/2009-like virus)
H3N2: A/Texas/50/2012	H3N2: A/Texas/50/2012
B/Massachusetts/2/2012 (B/Yamagata-lineage)	B/Massachusetts/2/2012
B/Brisbane/60/2008 (B/Victoria-lineage)	B/Brisbane/60/2008.

Geographic Distribution of Enrollment

40 sites across US

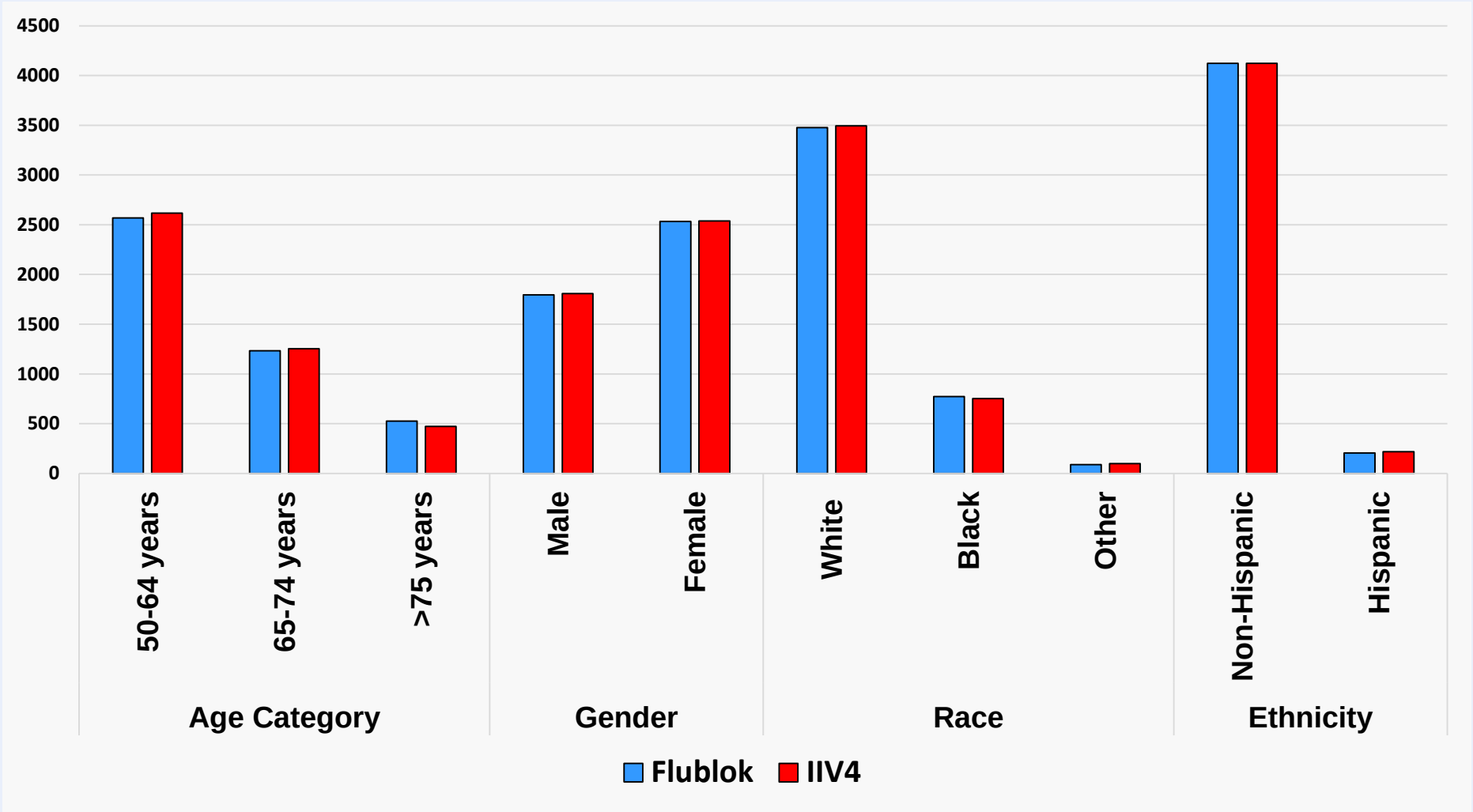


Subject Disposition

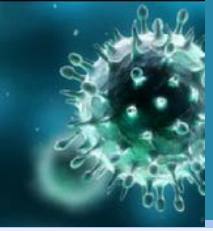
	RIV4 N=4474* n (%)	IIV4 N=4489* n (%)
Efficacy Population	**4303 (96.2)**	**4301 (95.8)**
Immunogenicity Population	**314 (7.0)**	**300 (6.7)**
Safety Population	**4328 (96.7)**	**4344 (96.8)**
Completed study	**4228 (94.5)**	**4236 (94.4)**
Primary Reason for Early Withdrawal		
Adverse Event	**9 (0.2)**	**8 (0.2)**
Investigator Decision	**1 (0.0)**	**2 (0.0)**
Lost to Follow-up	**176 (3.9)**	**172 (3.8)**
Sponsor Request	**0**	**0**
Voluntary withdrawal unrelated to AE	**53 (1.2)**	**61 (1.4)**
Other	**7 (0.2)**	**10 (0.2)**

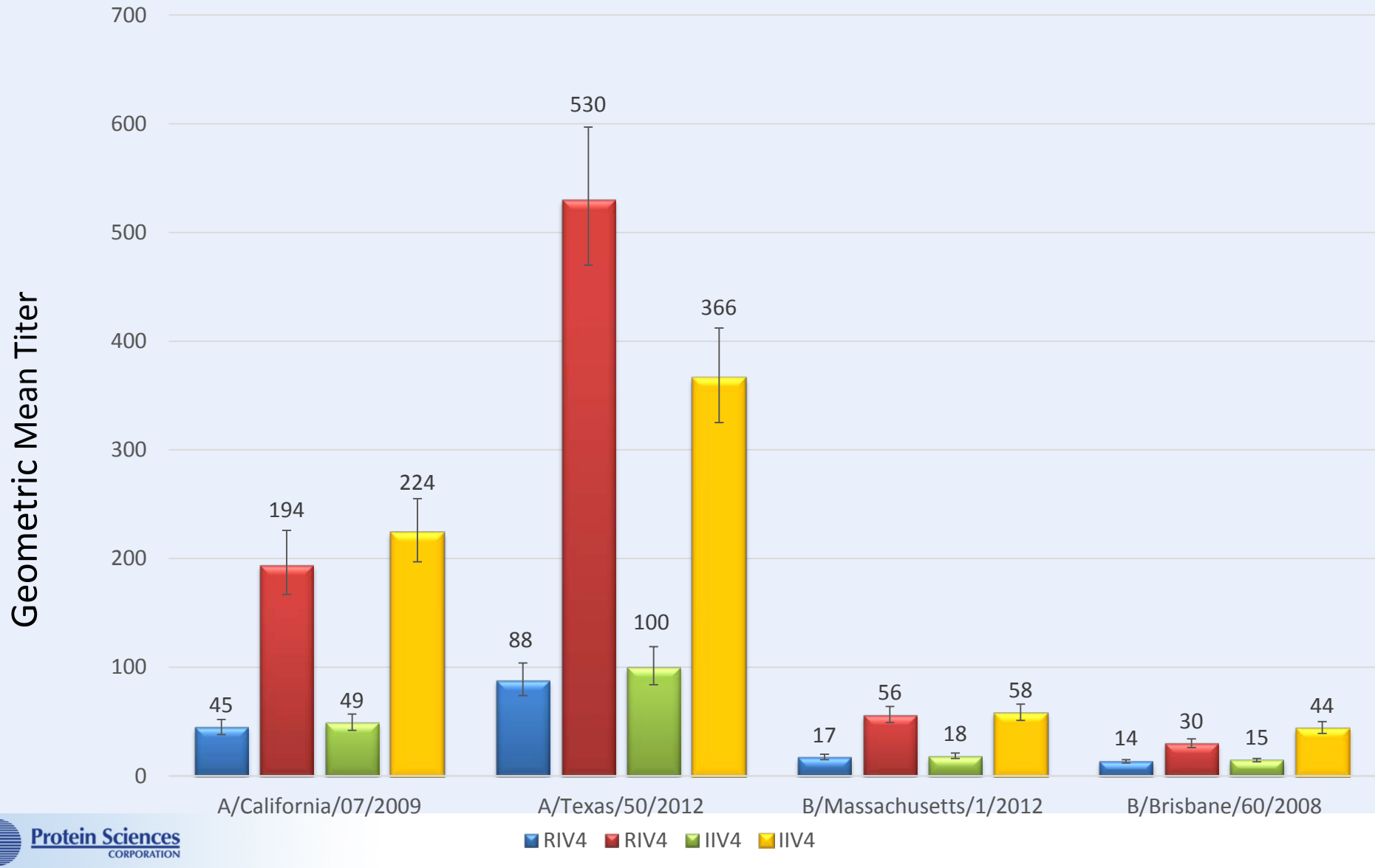
* **Excludes 40 subjects: 15 randomized, but never vaccinated, 25 vaccine unverified (12 RiV4 and 13 IIV4).**

Demographics – Safety Population



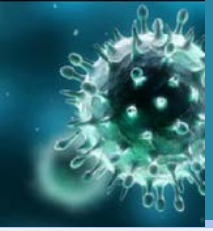
HAI Immune Responses – Day 0 and 28 GMTs





Influenza Attack Rates

	RIV4 (%)	IIV4 (%)
PCR-confirmed ILI	96 (2.2)	138 (3.3)
H3N2	73 (1.7)	114 (2.7)
B Strains	23 (0.5)	24 (0.6)
Culture confirmed ILI	38 (0.9)	64 (1.5)



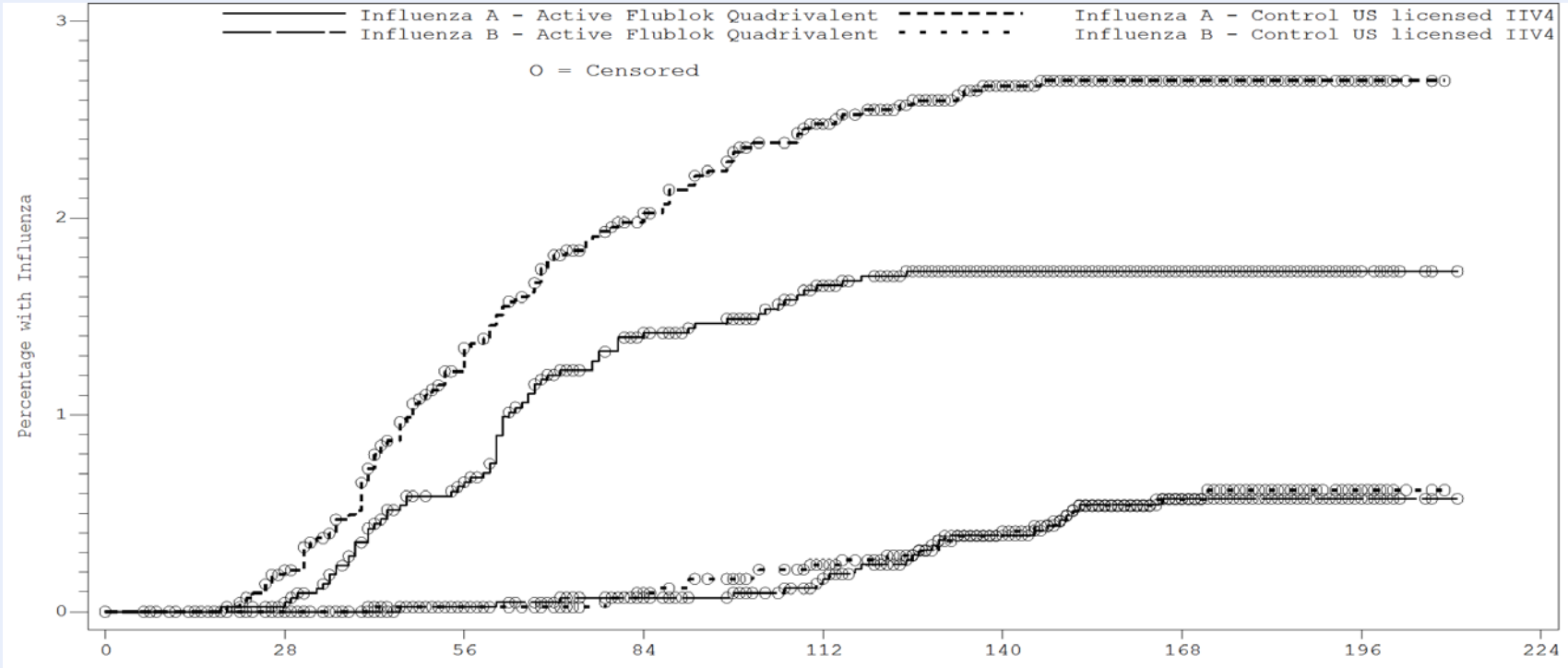
Relative Vaccine Efficacy RIV4 vs IIV4

- PCR Confirmed
  - All influenza: 31% (CI 95% 10, 47%) ★
  - Influenza A: 37% (CI 95% 14, 53%)
  - Influenza B: 17% CI 95% -72, +46%)
- Culture Confirmed
  - Influenza A: 43% (CI 95% 21, 59)
  - Influenza B: 50%R (CI 95% -121, +75%)

rVE = 1-RR x 100

★ MEETS NON-INFERIOR AND SUPERIORITY CRITERIA

Influenza Isolates by RT-PCR



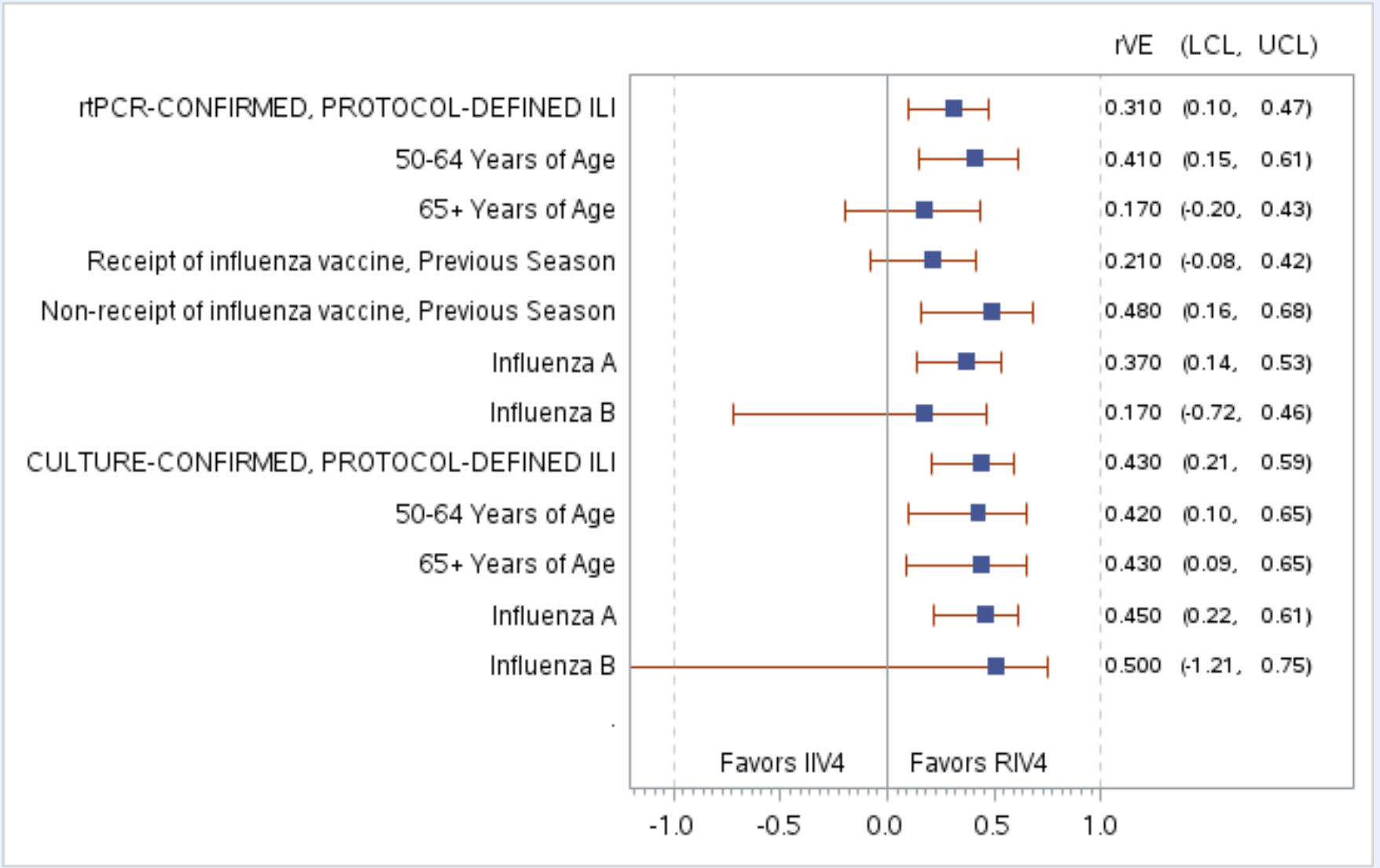
Flu A

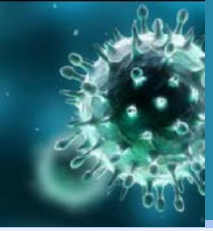
Flu B

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)



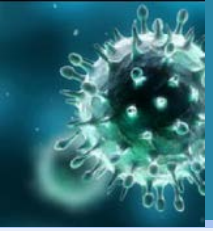


ILI Related MAEs/ SAEs
During 6 months after vaccination

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

Most Common AEs (≥2%)

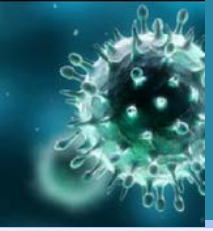
Preferred Term	Flublok [RIV4] N=4328	IIV4 N=4344
	N (%)	N (%)
Cough	226 (5.2)	253 (5.8)
Influenza like illness	186 (4.3)	199 (4.6)
Oropharyngeal pain	178 (4.1)	177 (4.1)
Headache	143 (3.3)	145 (3.3)
Upper respiratory tract infection	129 (3.0)	156 (3.6)
Fatigue	106 (2.4)	100 (2.3)
Myalgia	95 (2.2)	79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



Reactogenicity (%)

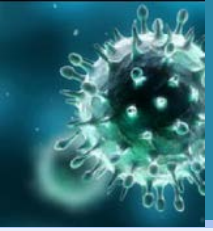
	RIV4 (Flublok Quadrivalent) N=4307			IIV4 N=4319			
	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4	P-value
≥1 event	48%	1	<1	51%	1	<1	0.006
≥1 local reaction	38%	<1	0	40%	<1	0	0.009
Local Pain	19%	<1	0	22%	<1	<1	<0.001
Local Tenderness	34%	<1	<1	37%	<1	<1	0.007
Erythema	3%	<1	0	2%	<1	0	0.014*
Induration	3%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

* Not significant after adjustment for four comparisons



Conclusions

- Flublok Quadrivalent met criterion for non-inferior efficacy against PCR-confirmed ILI
- Met pre-specified criterion for superior efficacy over IIV4
- Superiority possibly driven by efficacy against largely antigenically drifted influenza A
  - inferred >80% of the circulating H3N2 viruses in 2014-2015 were antigenically mismatched to the vaccines
- Efficacy against influenza B was similar to IIV4
- HAI antibody responses after Flublok were especially high for A/H3
- Both vaccines had similar safety profiles
- Injection site pain and tenderness significantly less with Flublok Quadrivalent
- No vaccine-related SAEs or medically-attended AEs



Acknowledgements

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