RSV Vaccines: The Road to Licensure

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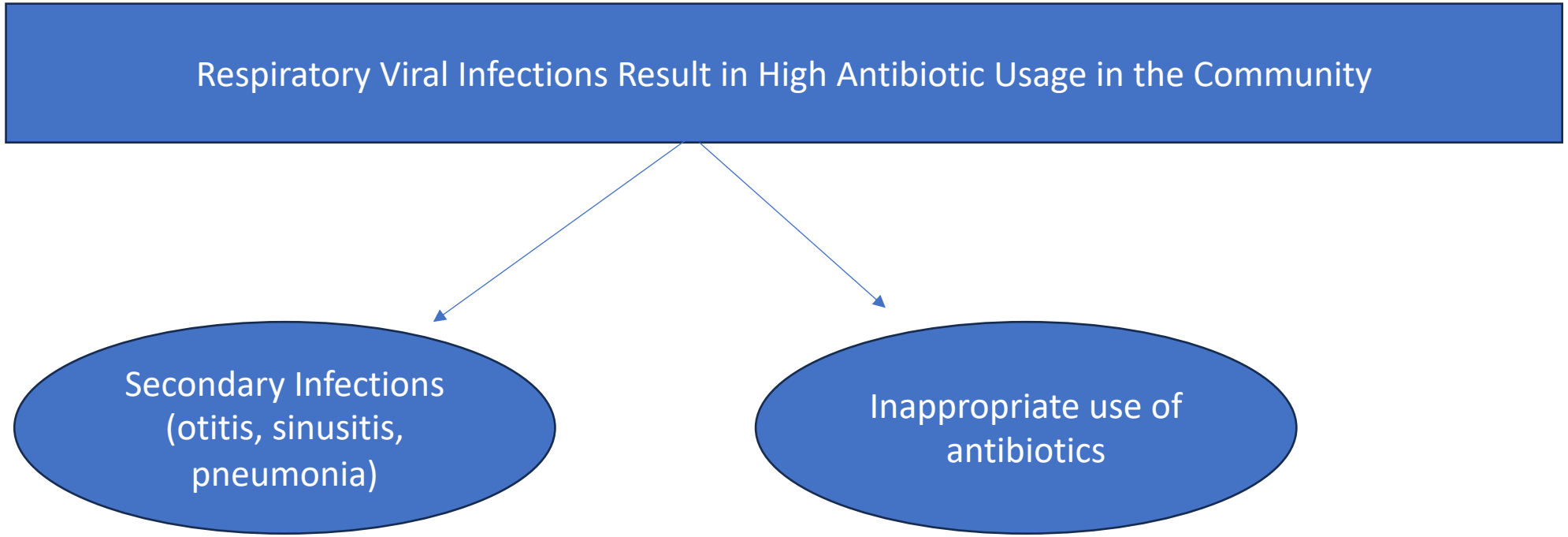
19January2024

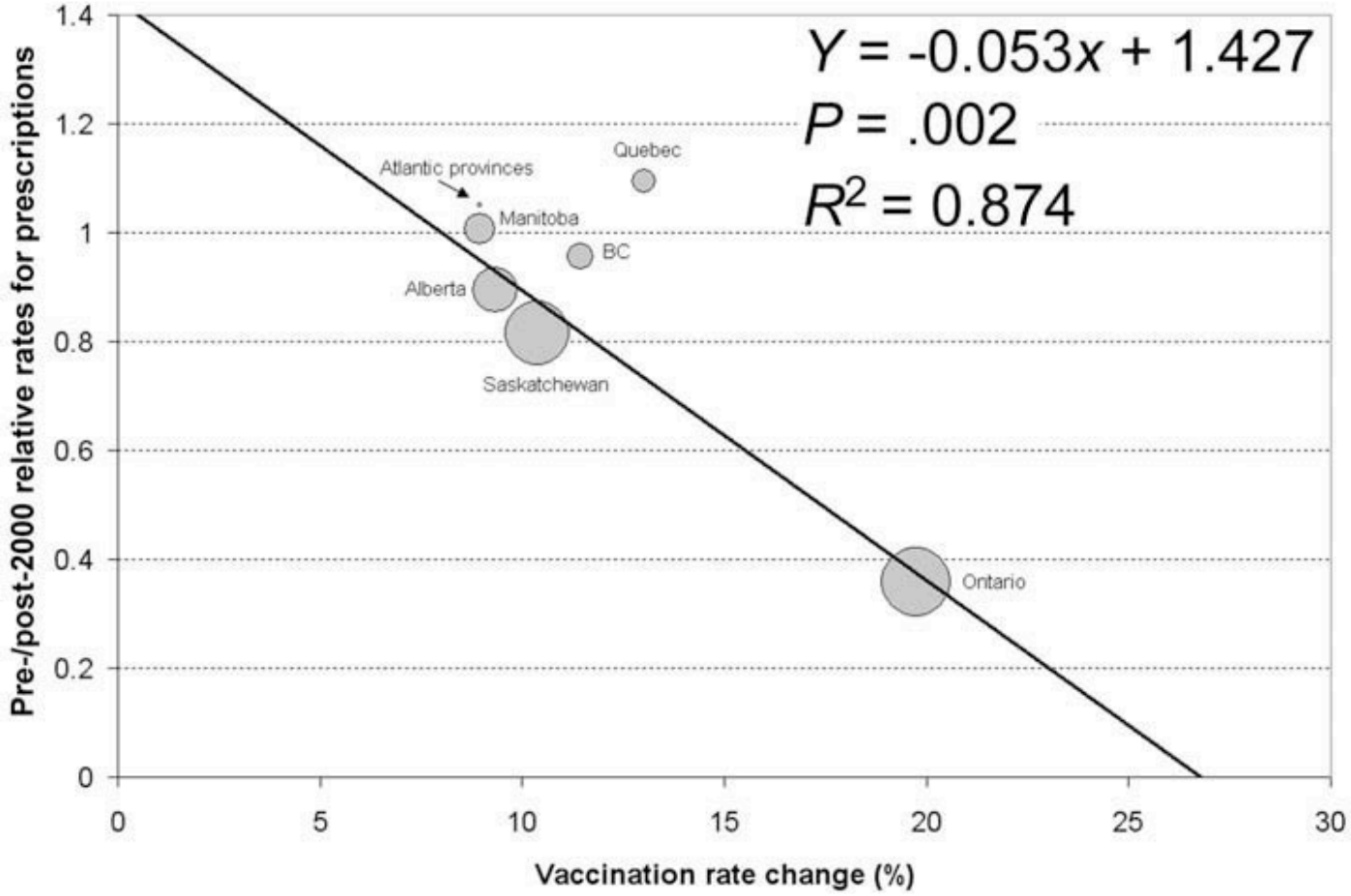
- I have no conflicts of interest to disclose

Viral Vaccines to Prevent Bacterial Drug Resistance?



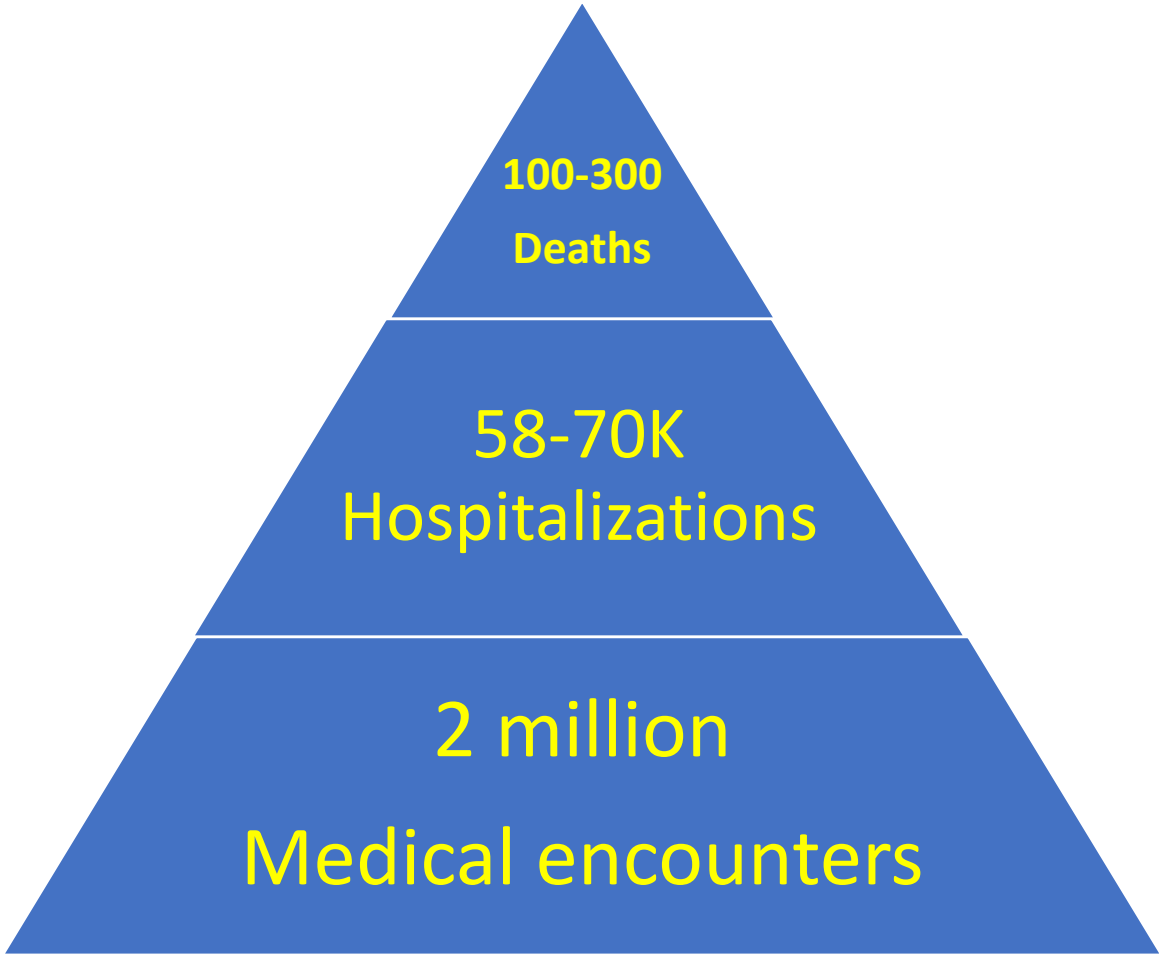
Viral Vaccines to Prevent Bacterial Drug Resistance?

- In 2000: Ontario implemented universal flu vaccination
- Other provinces: targeted flu vaccination
- Outcome: effect of flu vaccination strategy on antibiotic prescriptions

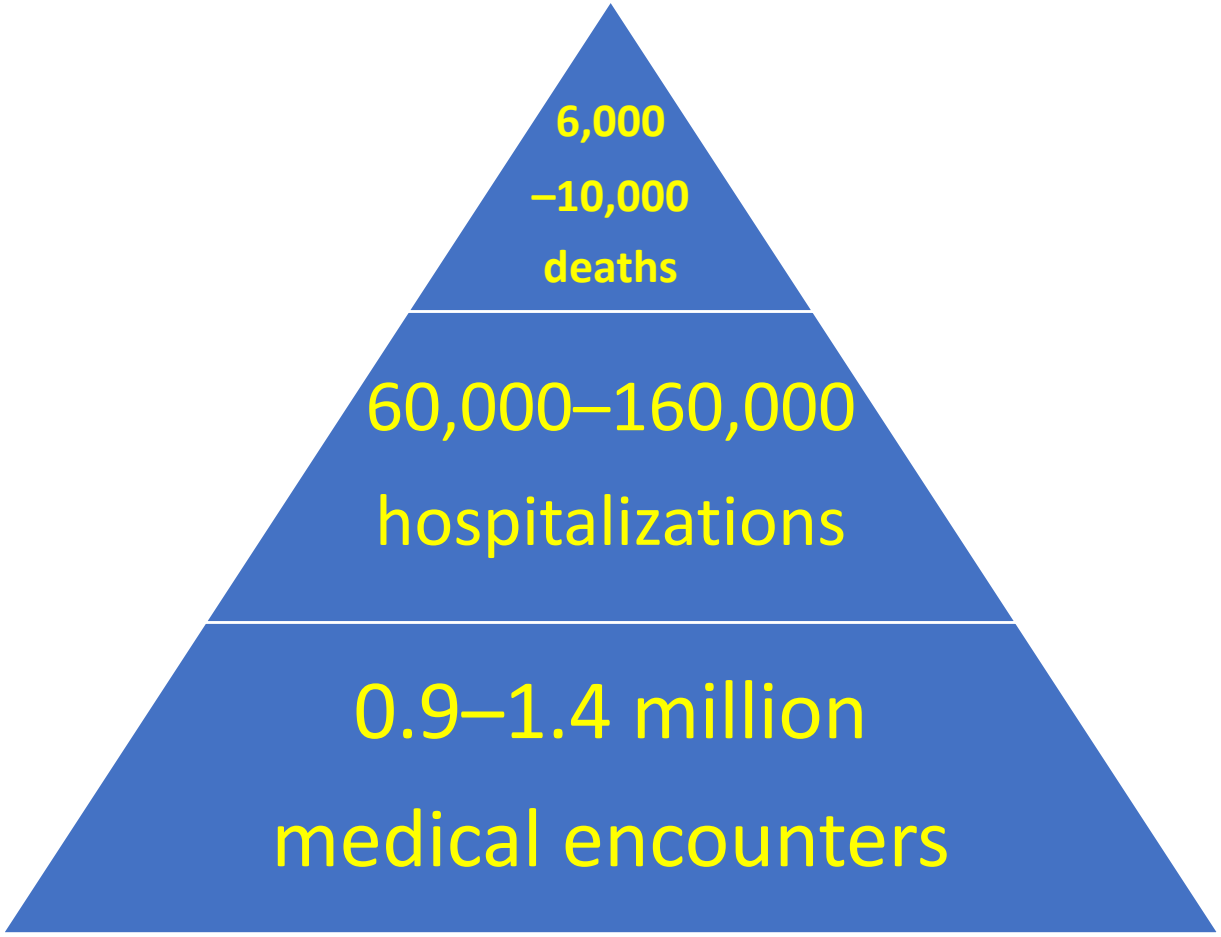


Kwong et al, Clin Infect Dis 2009

Morbidity and Mortality of RSV in the US



Children younger than 5 years of age



Adults aged ≥65 years

Thompson et al, JAMA 2003; Hansen et al JAMA Netw Open 2022; Hall et al, NEJM 2009; McLaughlin et al, J Infect Dis 2022.

Whole inactivated RSV vaccine The 1960s

- Population: infants 2-7m old
- Intervention 3 doses of RSV vaccine
- Control: parainfluenza virus vaccine
- Endpoint: immunogenicity and RSV infection

	RSV vaccine Group (N=31)	PIV Vaccine Group (N=40)
4fold rise in Neut Ab	43%	Not Done
4fold rise in Comp Fix Ab	91%	15%
RSV infection	65%	53%
Hospitalization (among RSV infected)	80%*	5%

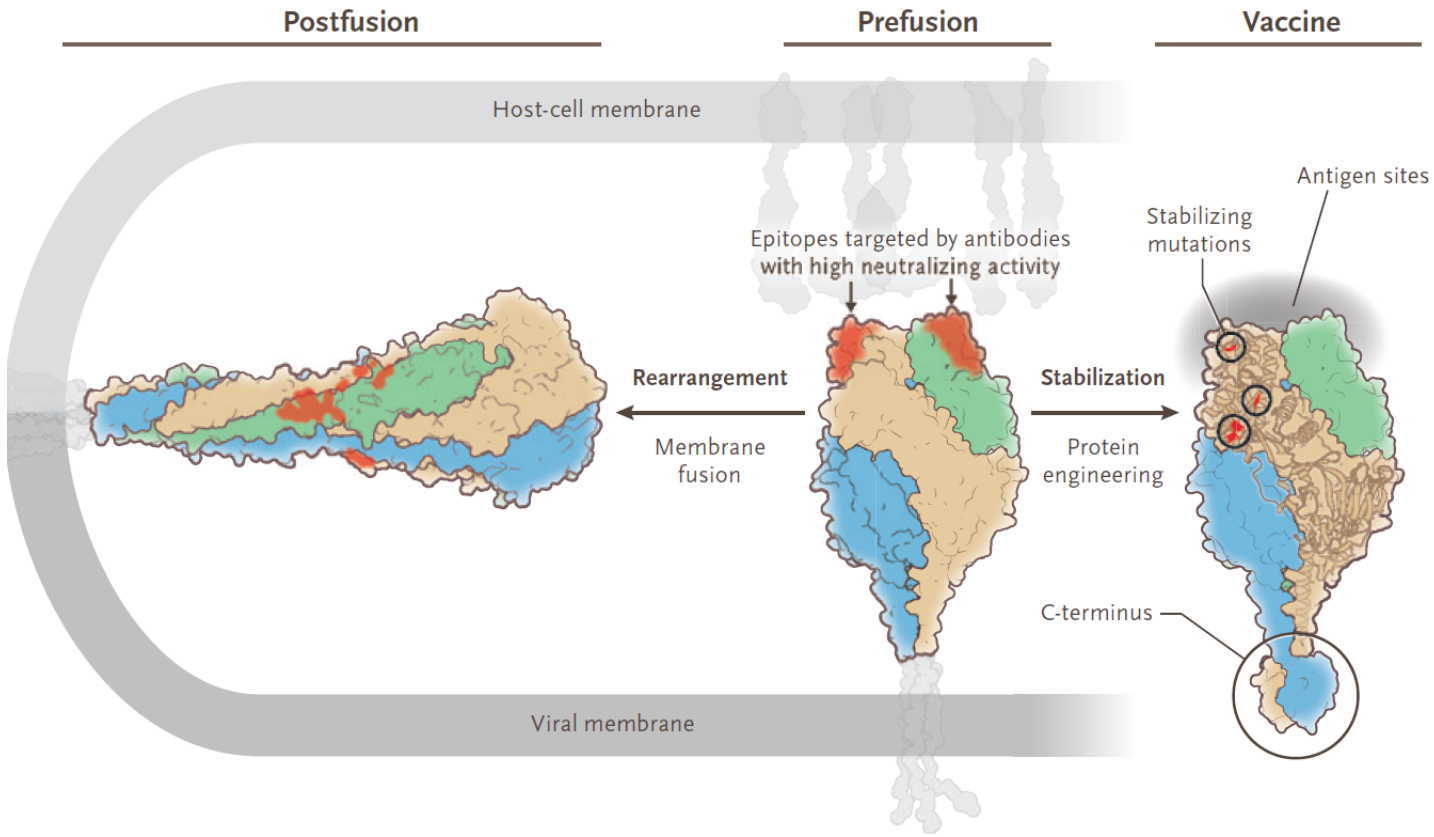
*2 deaths

Kim et al, Am J Epidemiol 1969

Road to RSV VACCINES WAS BLOCKED FOR DECADES

RSV vaccine development-Back to the Bench

- Majority of Neut Ab are targeted against preF
- The preF state can be locked via the introduction of specific mutations
- Vaccines based on preF antigen generated much higher levels of Neut Ab
- Implications for COVID-19 vaccines

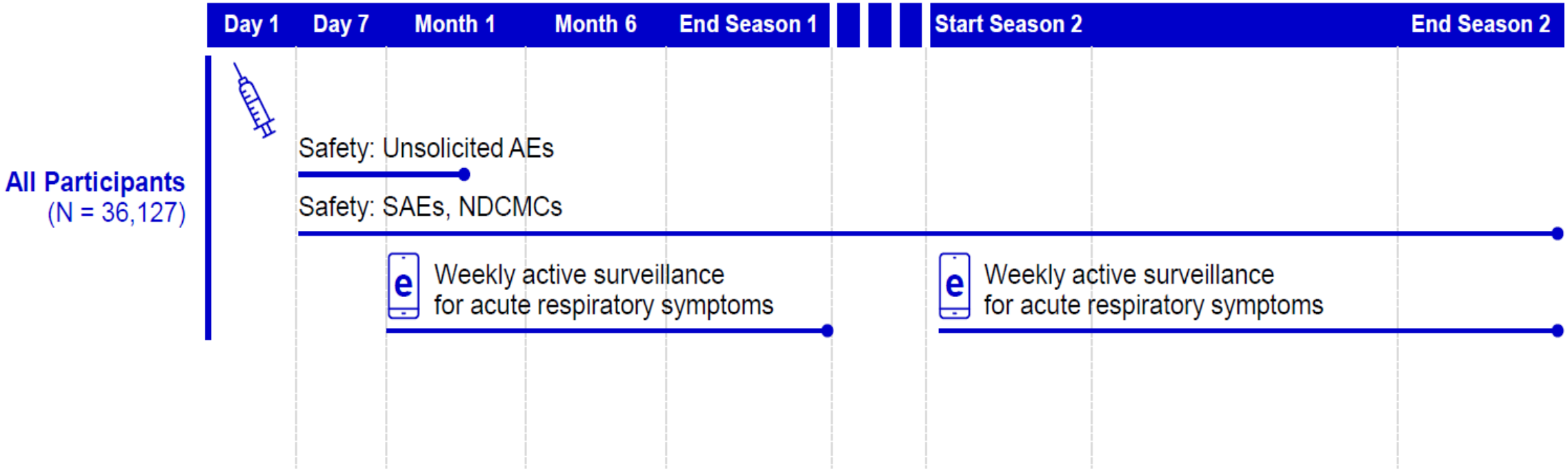


McLellan et al, Science 2013; Graham B, NEJM 2023

Ph3 clinical trials-RSV clinical trials

1. GSK: Prefusion-stabilized F protein adjuvanted with $AS01_{E,}$ 120 mcg, RSV A: **Elderly, and pregnancy study (aborted)**
2. Pfizer: Prefusion-stabilized F protein, bivalent 60mcg RSV A+60mcg RSV B. **(Elderly, pregnant women)**
3. Ad26-based product: development halted despite favorable VE data (?fallout from Covid-19 vaccine safety signal)
4. mRNA-1345: expresses Prefusion-stabilized F protein. Favorable VE data.

RSVpreF Ph3 Study Design



1. **Efficacy endpoints**:

Efficacy of the vaccine against RSV-related lower respiratory tract infection (LRTI) with 2 symptoms

Efficacy against RSV-related LRTI with 3 symptoms

2. **Tolerability and Safety Endpoints**

RSVpreF Ph3 Study Population

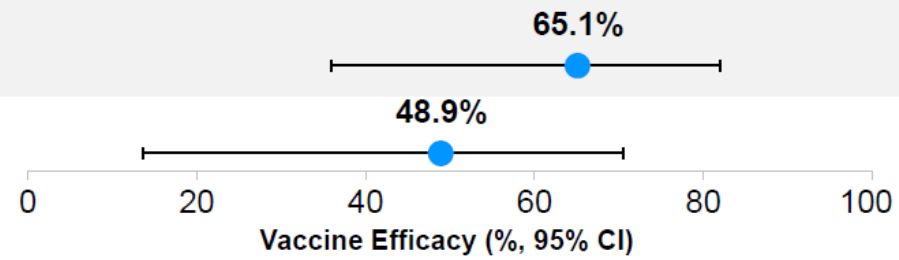
Characteristic	RSVpreF N=16306 n (%)	Placebo N=16308 n (%)
Sex	--	--
Male	8327 (51.1)	8225 (50.4)
Female	7979 (48.9)	8083 (49.6)
Age, years	--	--
60-69 years	10176 (62.4)	10191 (62.5)
70-79 years	5207 (31.9)	5196 (31.9)
≥80 years	923 (5.7)	921 (5.6)

With ≥1 prespecified significant condition: 51% (vaccine) vs 51.5% (placebo)
Chronic obstructive pulmonary disease (COPD): 5.6% (vaccine) vs 6.1% (placebo)
Congestive heart failure (CHF): 1.7% (vaccine) vs 1.8% (placebo)

Walsh et al, NEJM 2023; VRBPAC 28Feb2023
www.fda.gov

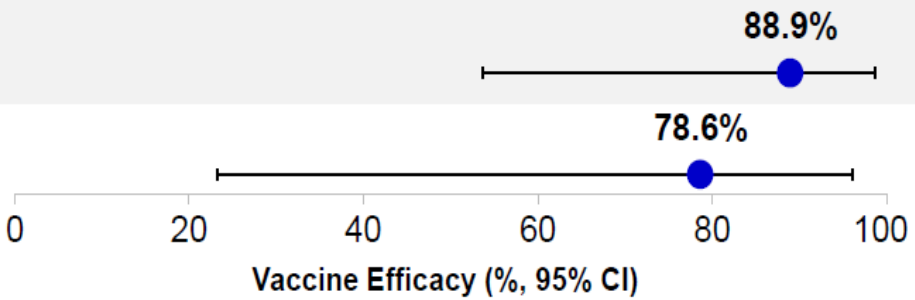
RSVpreF Ph3 Efficacy against LRTI through mid-season 2

RSV-LRTD with ≥ 2 symptoms



	Number of Events	
	RSVpreF	Placebo
Season 1 (N = 36,127)	15	43
Mid-Season 2 (n = 20,019)	23	45

RSV-LRTD with ≥ 3 symptoms



	Number of Events	
	RSVpreF	Placebo
Season 1 (N = 36,127)	2	18
Mid-Season 2 (n = 20,019)	3	14

Walsh et al, NEJM 2023, 21jun2023ACIP meeting
www.cdc.gov

RSVpreF Ph3 Safety and Tolerability

Solicited Adverse Reaction	RSVpreF N=3619-3621 n (%)	Placebo N=3532-3539 n (%)
Local reaction ≥ Grade 1	441 (12.2)	235 (6.6)
Grade 3	8 (0.2)	2 (<0.1)

Solicited Adverse Reaction	RSVpreF N=3619-3621 n (%)	Placebo N=3532-3539 n (%)
Systemic reaction ≥ Grade 1	994 (27.5)	909 (25.7)
Grade 3	27 (0.7)	20 (0.6)

RSVpreF Safety and Tolerability (20,255 participants)

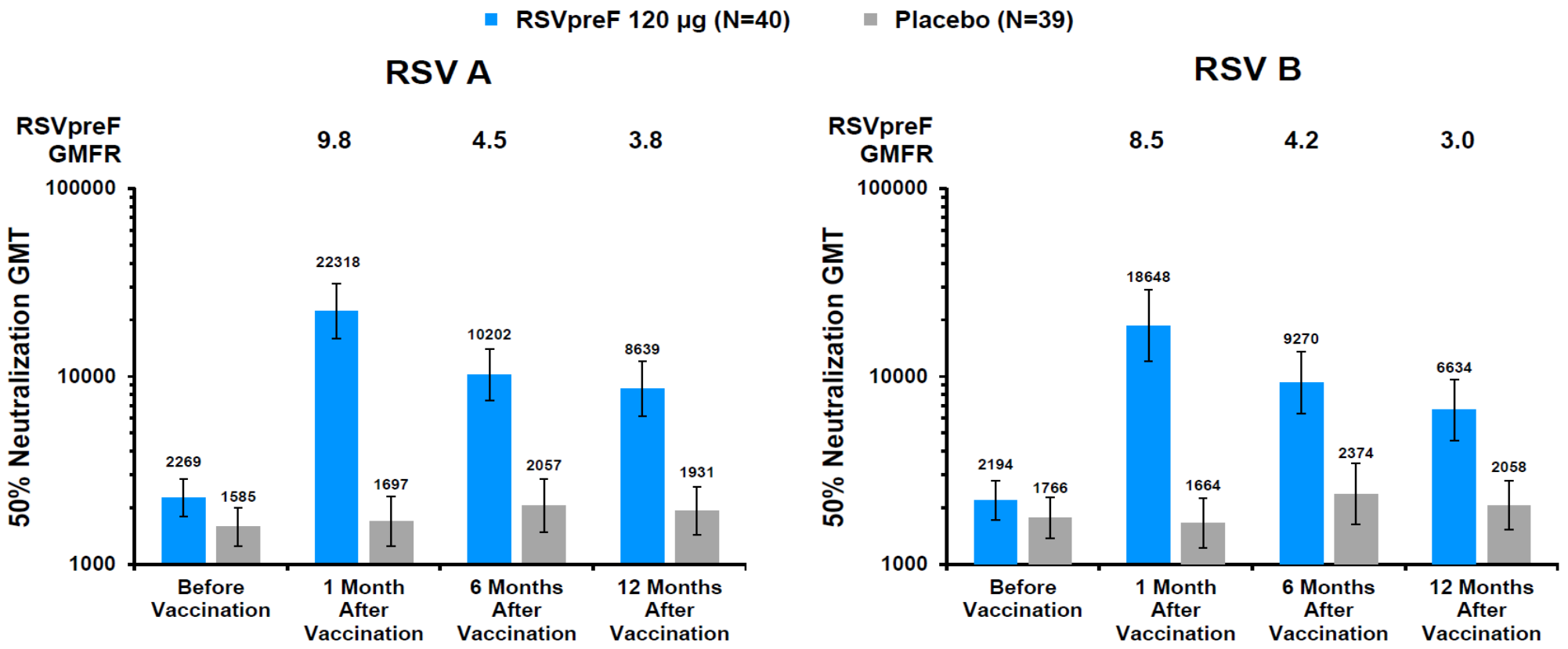
- Atrial fibrillation events in the vaccine (10) vs placebo (4) occurred between 18-30 days post injection
- Guillain-Barre Syndrome: 66 yoM, 7 days post-vaccination, hospitalized, resolving, 68 yo, 21 days post-vaccination
- Miller Fisher Syndrome: 66 yoF, 8 days post-vaccination; hospitalized, resolved by 3 month
- Motor-sensory axonal polyneuropathy: 68 yo, 21 days post-vaccination
- No cases in placebo
- Incidence of GBS in the general population: 1-3 per 100,000 (higher in older persons).

RSVpreF licensing status in the US

The RSVpreF vaccines was approved by the FDA on 31May2023 with a pharmacovigilance plan requirement to report on the following:

1. Full study data to FDA
2. Supraventricular arrhythmia events
3. Guillain Barré Syndrome and other demyelinating conditions

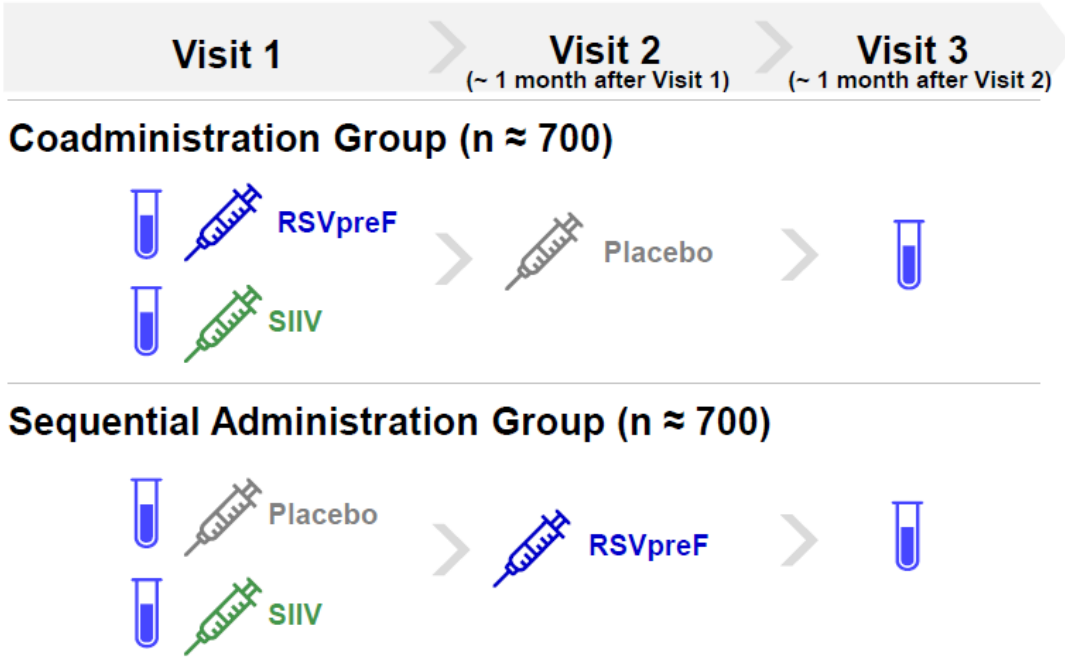
RSV PreF immunogenicity



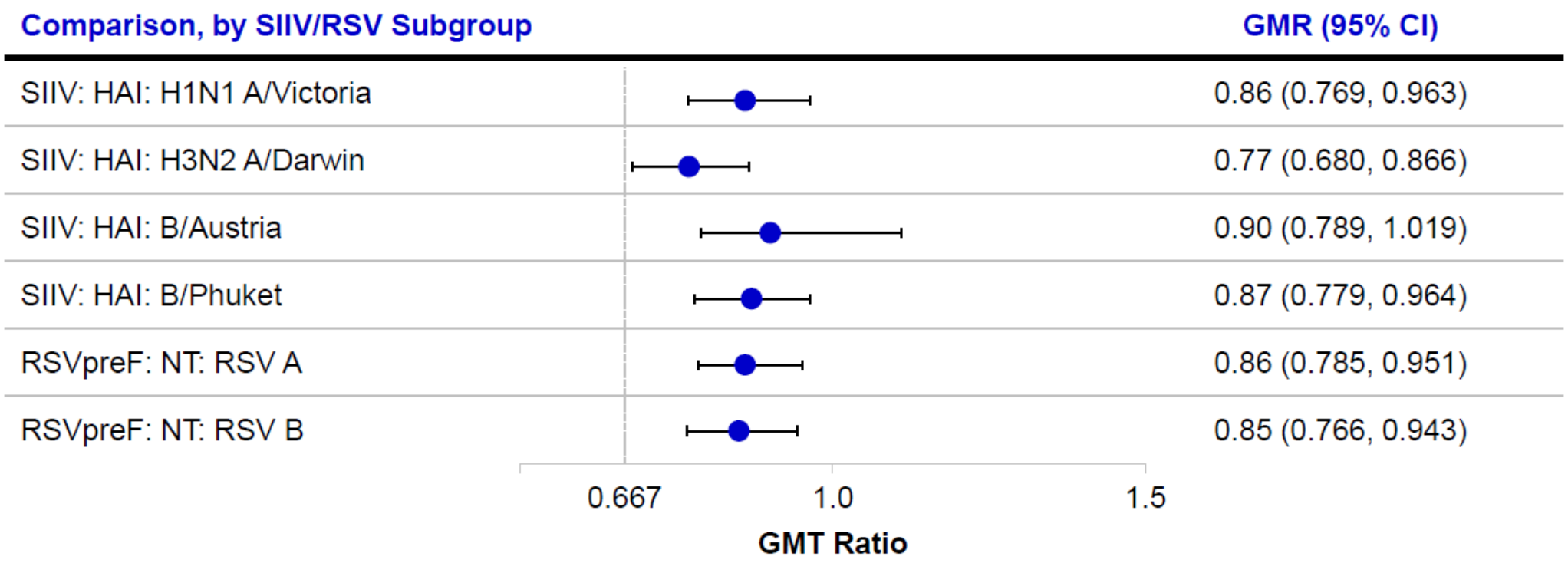
- No data on repeated dosing for the RSV PreF vaccine

RSVpreF co-administration with seasonal flu vaccine

- Placebo-controlled, double-blind study
- Assessing safety and immunogenicity (non-inferiority)
- Australia (31 sites)
- ~1,400 healthy participants ≥ 65 years of age
- Randomized 1:1
- SIIV: Fluad Quadrivalent
- Timeframe: April 13, 2022 – October 12, 2022

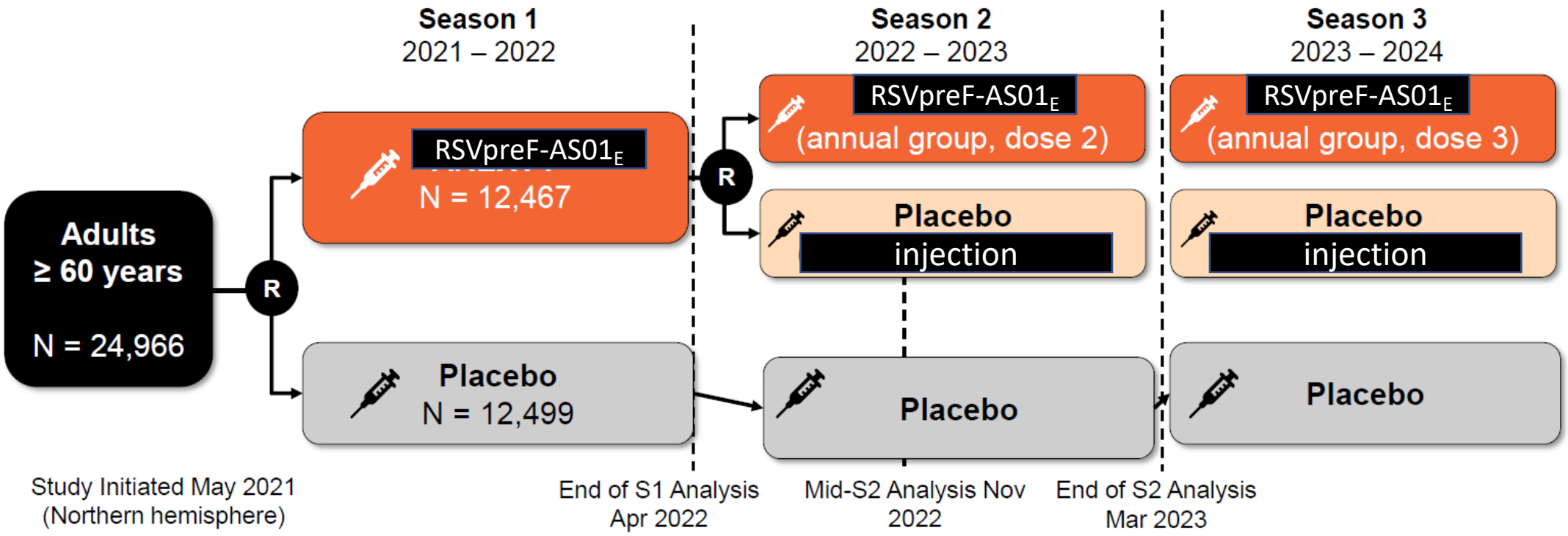


RSVpreF co-administration with seasonal flu vaccine



ACIP Presentation 21Jun2023 at www.cdc.gov;
Falsey et al, J Infect Dis 2022

RSVpreF-AS01$_E$ Ph3 Study Design



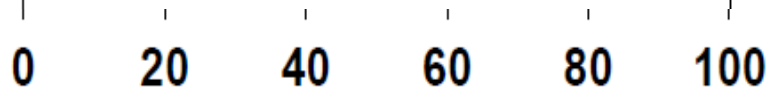
RSVpreF-AS01$_E$ Ph3 Study- Study Population

Characteristic	RSVpreF3-AS01$_E$ N=12467	Placebo N=12499
Sex, n (%)	--	--
Male	5979 (48.0)	6072 (48.6)
Female	6488 (52.0)	6427 (51.4)
Age, years	--	--
Mean age (SD)	69.0 (6.5)	69.6 (6.4)
Median age (min, max)	69.0 (59, 102)	69.0 (59, 98)
60-69 YOA	6963 (55.9)	6980 (55.8)
70-79 YOA	4487 (36.0)	4491 (35.9)
≥80 YOA	1017 (8.2)	1028 (8.2)
At least 1 pre-existing Cardiorespiratory condition	2496 (20.0)	2422 (19.4)

Papi et al, NEJM 2023; VRBPAC 01Mar2023 www.fda.gov

RSVpreF-AS01$_E$ Efficacy against RSV-LRTD

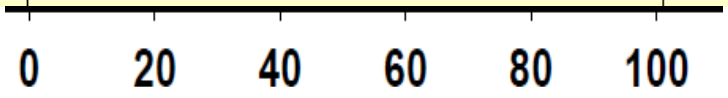
	Median Follow-Up (months)	Vaccine	Placebo	VE (95% CI)
		Number of events		
Single Dose				*W/o season as covariate#*
Season 1* VE 1	**6.7**	**7** / 12,466	**40** / 12,494	**82.6%** (57.9, 94.1)
Mid Season 2 Post dose 1	**14**	**15** / 12,469	**85** / 12,498	**80.9%#** (66.7, 89.8)
Season 2 Only Post dose 2	**6.4**	**20** / 4,991	**91** / 10,031	**56.1%** (28.2, 74.4)
Season 1 + 2**	**18**	**30** / 12,469	**139** / 12,498	**74.5%#** (60.0, 84.5)



Papi et al, NEJM 2023; ACIP presentation 21Jun2023

RSVpreF-AS01$_E$ Efficacy against severe RSV-LRTD

	Median Follow-Up (months)	Vaccine	Placebo	VE (95% CI)
		Number of events		
Single Dose				*W/o season as covariate#*
Season 1* VE 1	**6.7**	**1** / 12,466	**17** / 12,494	**94.1%** (62.4, 99.9)
Mid Season 2 Post dose 1	**14**	**4** / 12,469	**33** / 12,498	**86.8%#** (63.0, 96.6)
Season 2 Only Post dose 2	**6.4**	**5** / 4,991	**28** / 10,031	**64.2%** (6.2, 89.2)
Season 1 + 2**	**18**	**7** / 12,469	**48** / 12,498	**82.7%#** (61.6, 93.4)



Papi et al, NEJM 2023; ACIP presentation 21Jun2023

RSV PreF3-Ad Tolerability Data

	RSV Vaccine N = 879	Placebo N = 878
Any solicited AE (within 4 days)	**72%**	**28%**
Administration site AEs	**62%**	**10%**
Systemic AEs	**49%**	**23%**
Grade 3 AEs	**4%**	**0.9%**

	Exposed Set	
Within 30 days of vaccination	**RSV Vaccine** N = 12,467	**Placebo** N = 12,499
Any unsolicited AE*	**33%**	**18%**
Any medically attended AE	**6%**	**6%**

Papi et al, NEJM 2023; VRBPAC 01Mar2023 www.fda.gov

Adverse Events of concerns
~ 15000 participants

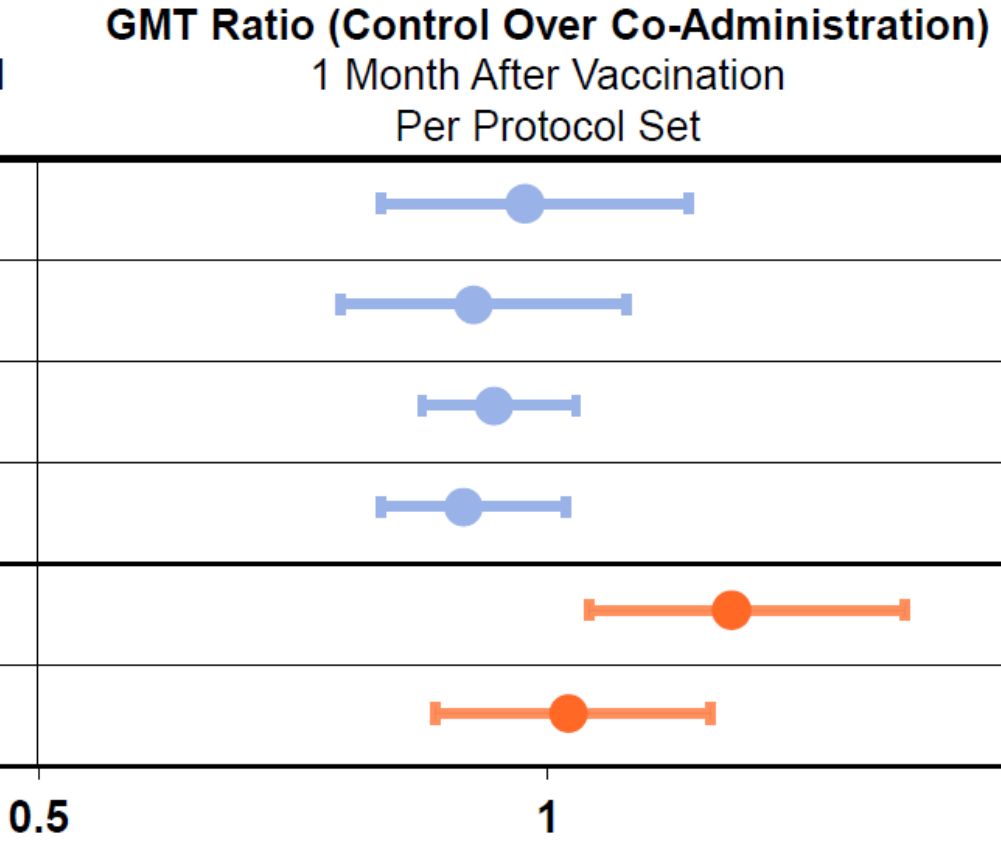
1. Numerical imbalance: atrial fibrillation within 30Days: Vaccine group=10 vs. placebo group=4.

2. Two cases of acute demyelinating encephalomyelitis (71 yo man/71yo woman), both occurred 22 days post vaccination, one fatal-Diagnosis ascertainment called into question.

3. One case of GBS: 78 yo woman, 9 days post vaccine. Required hosp for 6 months.

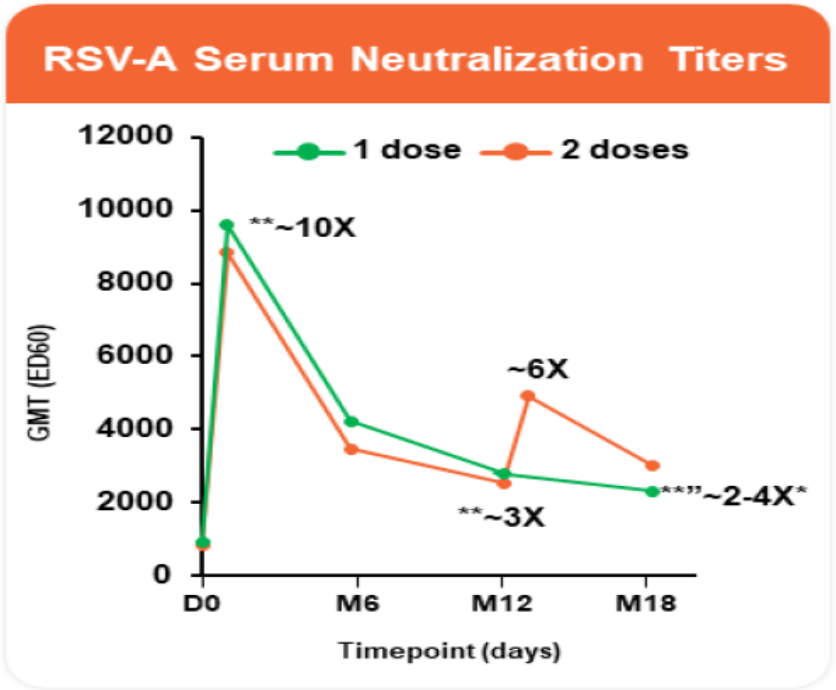
RSV PreF-AS01$_E$/Flu Vax High dose CoAdmin

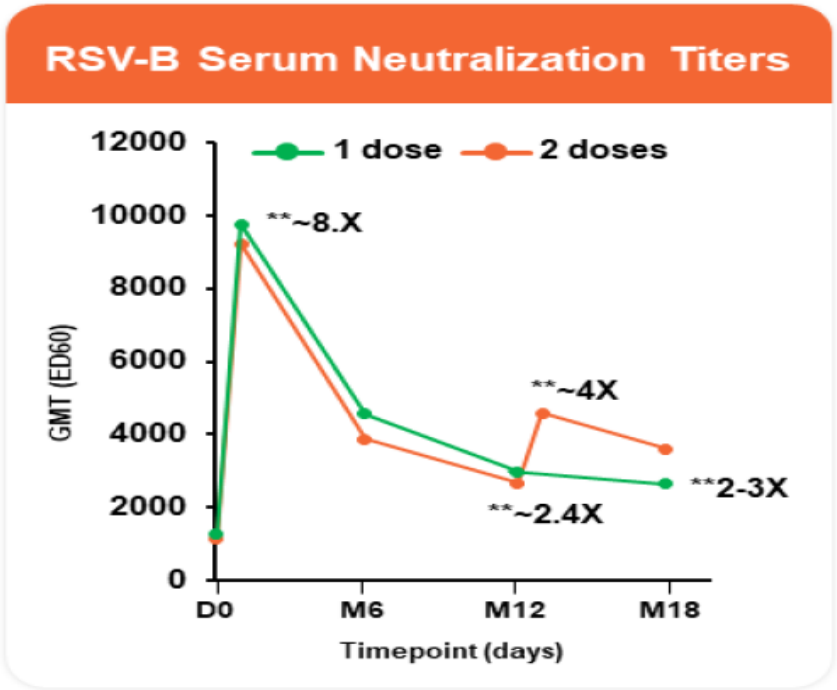
Antibody	Co-Ad N	Control N	GMT Ratio (95% CI)
Flu A/Darwin H3N2	458	441	**0.98** (0.84, 1.14)
Flu A/Victoria H1N1	452	435	**0.93** (0.80, 1.08)
Flu B/Austria/Victoria	458	441	**0.95** (0.88, 1.03)
Flu B/Phuket/Yamagata	456	441	**0.92** (0.84, 1.02)
RSV-A*	459	358	**1.18** (1.04, 1.35)
RSV-B	459	357	**1.02** (0.89, 1.16)



- N=1008, 65 years of age or older, randomized 1:1 high-dose flu vaccine vs RSV PreF-Ad
- When standard dose influenza vaccine was the comparator in younger adults, responses to influenza and RSV antigens were diminished.

RSVpreF-AS01$_E$: immunogenicity of repeated dosing





- A second dose of RSVPreF-AS01$_E$ did not boost antibody responses to levels comparable to first dose response: an unusual finding for protein-based vaccines.

RSVpreF-AS01$_E$ licensing status in the US

- RSVpreF-AS01$_E$ was approved on 03May2023 with a pharmacovigilance plan requirement to report to the FDA back on the following:

1. ADEM
2. Guillain Barré Syndrome and other demyelinating conditions
3. Supraventricular arrhythmia events

QUESTIONS?

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