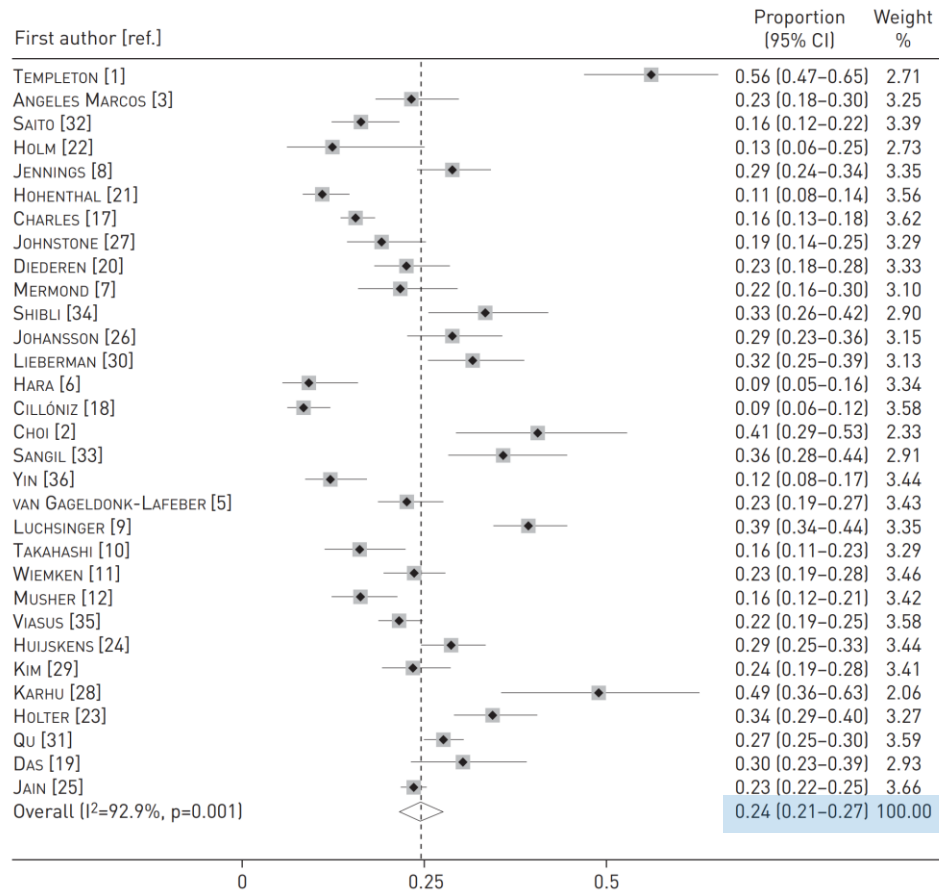


Up-to-date of respiratory viral infection

중앙대병원 호흡기내과

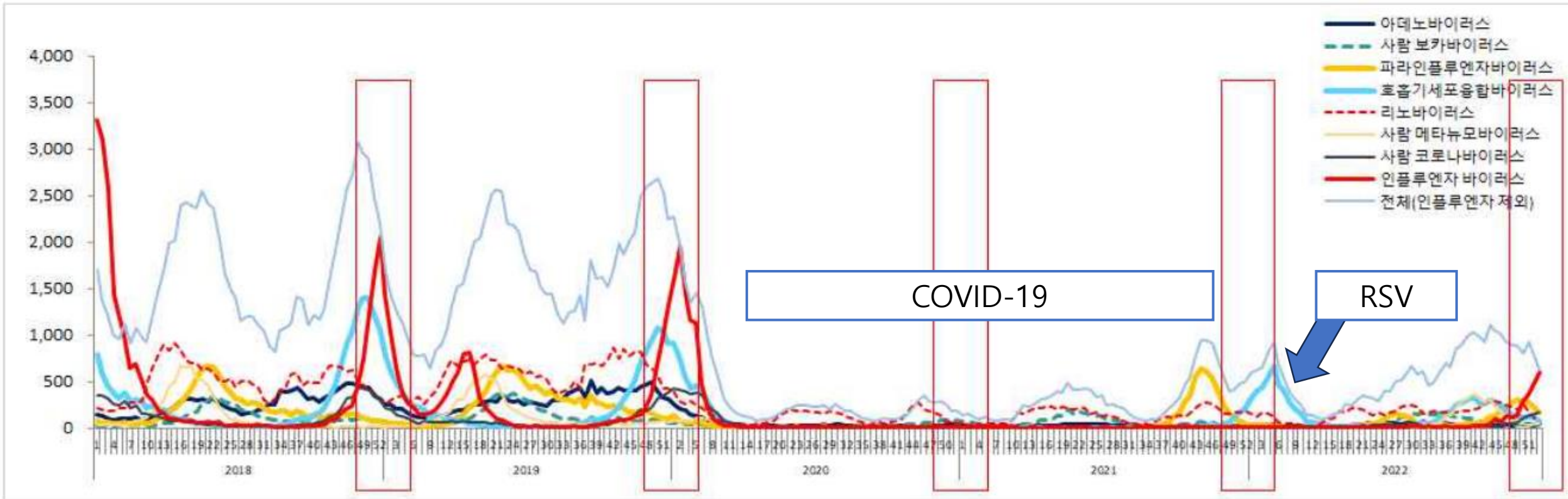
백문성

Respiratory viral infection in CAP



- CAP + PCR for viral pathogens
- ~ August 9, 2015 (31 studies, n=10,762)
- Pooled proportion
 - **24.5%** (95% CI 21.5–27.5%)
 - **44.2%** (95% CI 35.1–53.3%) in lower respiratory samples

급성호흡기감염증 입원환자 수 (2018-2022)



연도별 급성호흡기감염증 입원환자 수

연도	인플루엔자	급성호흡기감염증									
		계	리노바이러스	호흡기 세포융합 바이러스	아데노 바이러스	파라인플루엔자 바이러스	사람 메타뉴모 바이러스	사람 보카 바이러스	사람 코로나 바이러스	마이코플라즈마 폐렴균	클라미디아 페렴균
2017	8,723	70,442	21,467	14,450	6,663	7,971	4,388	4,581	3,825	6,902	195
2018	23,583	93,402	25,896	16,227	13,627	10,586	7,052	5,446	7,084	7,225	259
2019	14,000	101,083	29,653	11,897	15,162	12,804	6,951	6,426	4,376	13,479	335
2020	8,435	24,260	7,307	4,390	2,283	707	782	1,309	3,303	4,004	175
2021	206	18,004	6,929	743	1,092	4,415	34	3,216	126	1,265	184
2022	2,713	32,439	8,646	8,405	1,656	3,763	3,461	3,004	1,673	1,591	240
유행 전 ^{a)}	46,306	264,927	77,016	42,574	35,452	31,361	18,391	16,453	15,285	27,606	789
유행 후 ^{b)}	7,009	86,449	24,755	18,090	4,647	12,660	7,114	9,345	4,575	4,586	677
증감(%)	△84.9	△67.4	△67.9	△57.5	△86.9	△59.6	△61.3	△43.2	△70.1	△83.4	△14.2

단위: 명. ^{a)}코로나19 유행 전(2017-2019년), ^{b)}코로나19 유행 후(2020-2022년).

병원기반형 호흡기감염병 감시체계

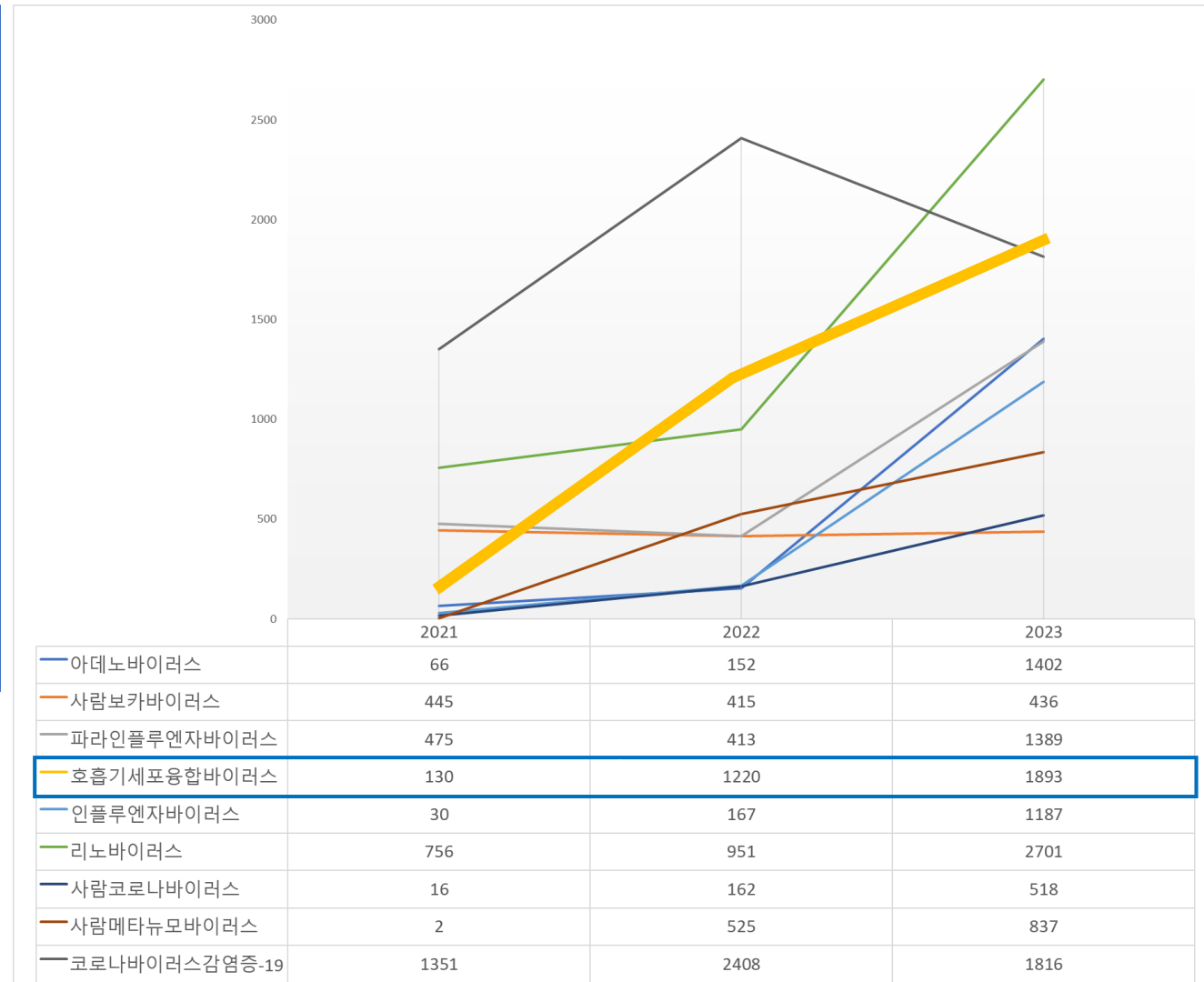
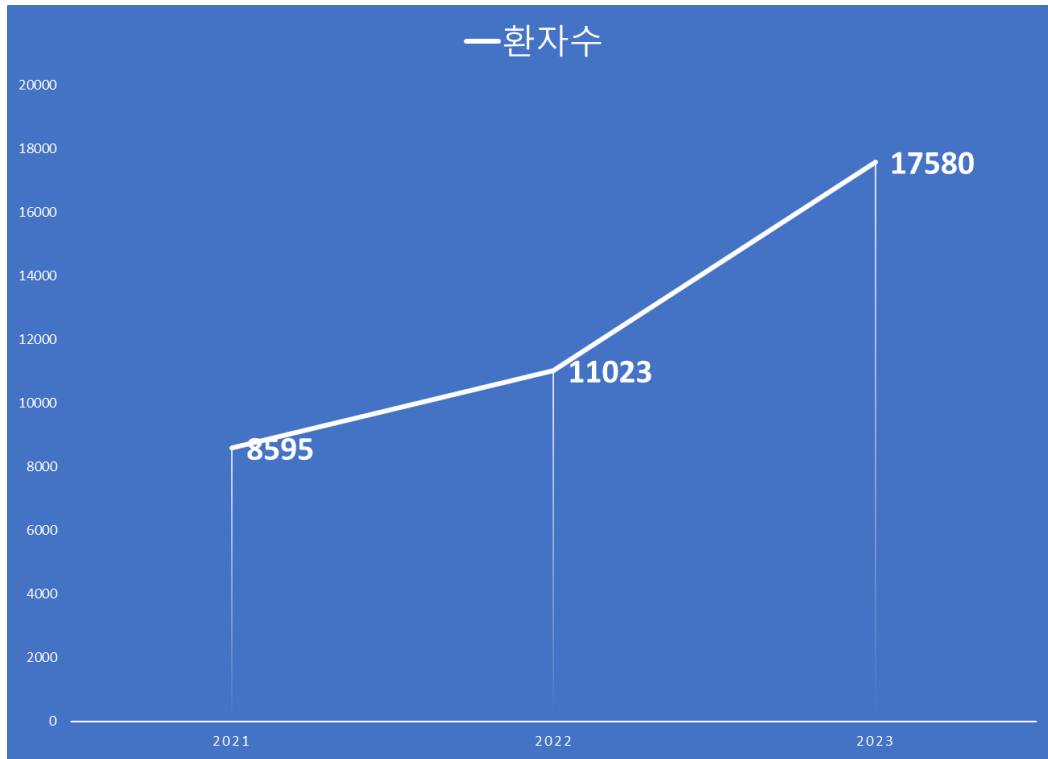
- 2022년 현재 42개 기관 참여



중증 급성 호흡기감염증
(**SARI**, Severe Acute Respiratory Infection)

- ① 발열 경험 또는 38도 이상의 고열과
- ② 기침이 있으며
- ③ 10일 이내 발생
- ④ 입원을 필요로 하는 경우

Respiratory virus in SARI



Influenza- and RSV-associated deaths

National viral surveillance data in the US
1990-1991 through 1998-1999 (17,200 RSV cases)

Table 4. Estimated Annual Age-Specific Influenza- and Respiratory Syncytial Virus-Associated Deaths for the 1990-1991 Through 1998-1999 Seasons

Age Group, y	No. of Influenza Deaths				No. of Total RSV Deaths
	A(H1N1)	A(H3N2)	B	Total	
Underlying Pneumonia and Influenza Deaths*					
<1	1	12	0	13	124
1-4	7	11	7	25	13
5-49	39	178	55	272	0
50-64	37	322	102	461	182
≥65	298	6089	939	7326	2388
Total	382	6612	1103	8097	2707

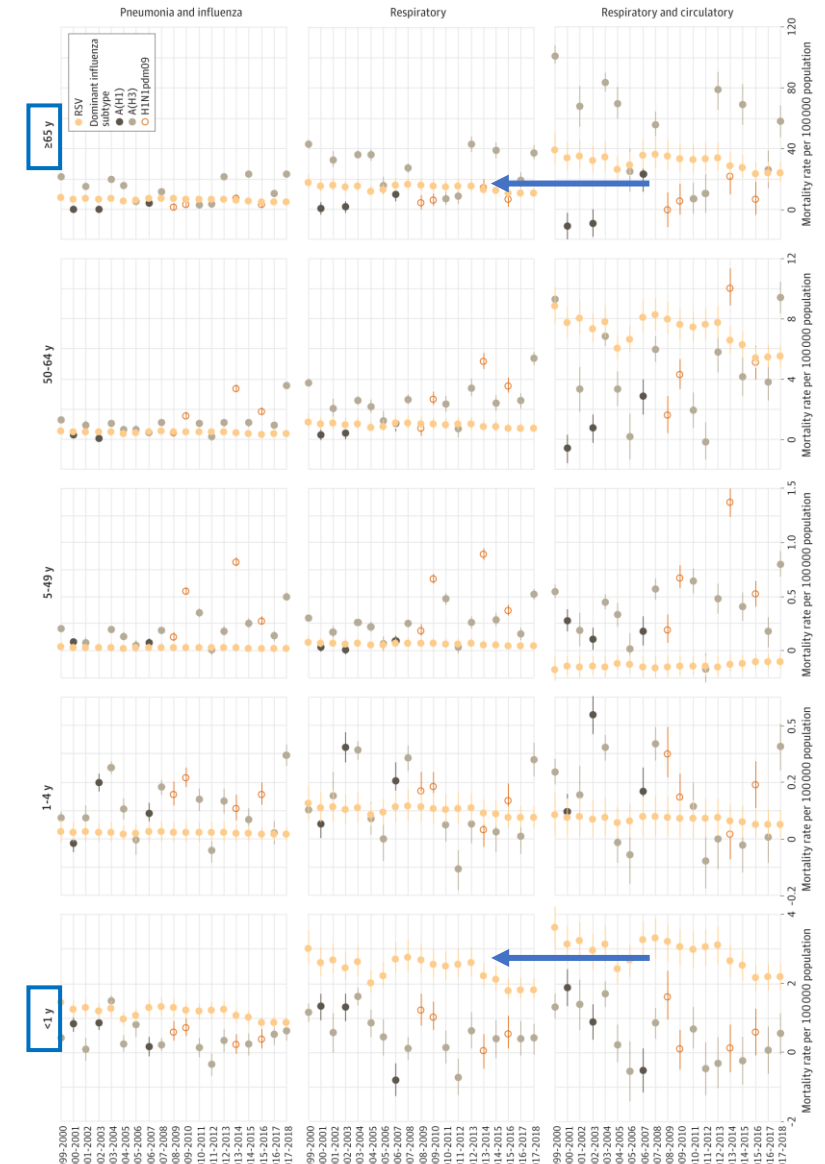
Table 5. Estimated Annual Influenza- and Respiratory Syncytial Virus-Associated Mortality Rates per 100 000 Person-Years for the 1990-1991 Through 1998-1999 Seasons

Age Group, y	Mortality Rate per 100 000 Person-Years	
	Influenza	RSV
Underlying Pneumonia and Influenza Deaths*		
<1	0.3	3.1
1-4	0.2	0.1
5-49	0.2	<.01
50-64	1.3	0.5
≥65	22.1	7.2
Total	3.1	1.0

Influenza viruses and RSV: substantial mortality among young children and elderly individuals

Mortality associated with influenza and RSV

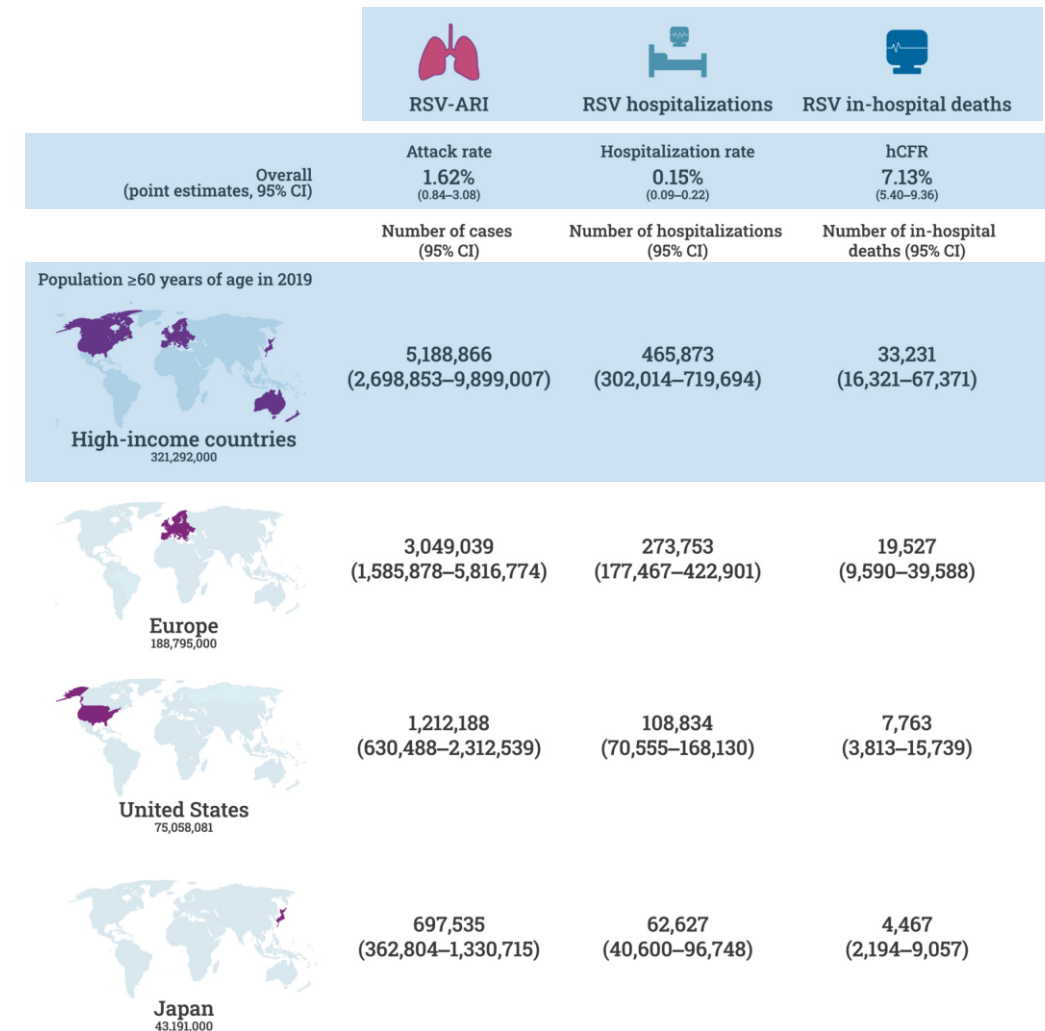
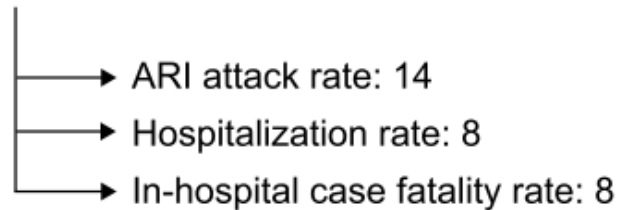
- National Center for Health Statistics (1999 ~ 2018, US)
- Cause of death classification (ICD 10th)
 - pneumonia and influenza (J09-J18)
 - **respiratory (J00-J99): RSV bronchitis**
 - respiratory and circulatory (I00-J99)
- 50.3 million death (1.0% [<1 yr], 73.4% [≥ 65 yr])
- RSV-associated mortality rate (respiratory)
 - ≥ 65 years: **14.7** per 100,000
 - <1 year: **2.4** per 100,000
- → RSV: substantial mortality among elderly individuals



RSV disease burden ≥ 60 -year-old adults

- In high-income countries (US, Canada, European countries, Japan, **South Korea**)
- January 1, 2000 ~ November 3, 2021
- RSV infections: PCR or seroconversion (≥ 4 -fold)

Total studies included: **21**



Rates of medically attended RSV

- 15 studies (RSV + epidemiology) in US
- 2007 ~ 2021
- Annual RSV-associated hospitalizations (≥ 65 y)
 - Pooled incidence: 178 per 100,000
 - After adjustment: 267 per 100,000
- True burden of RSV
 - underestimated
 - significantly higher among **older adults with chronic medical conditions**

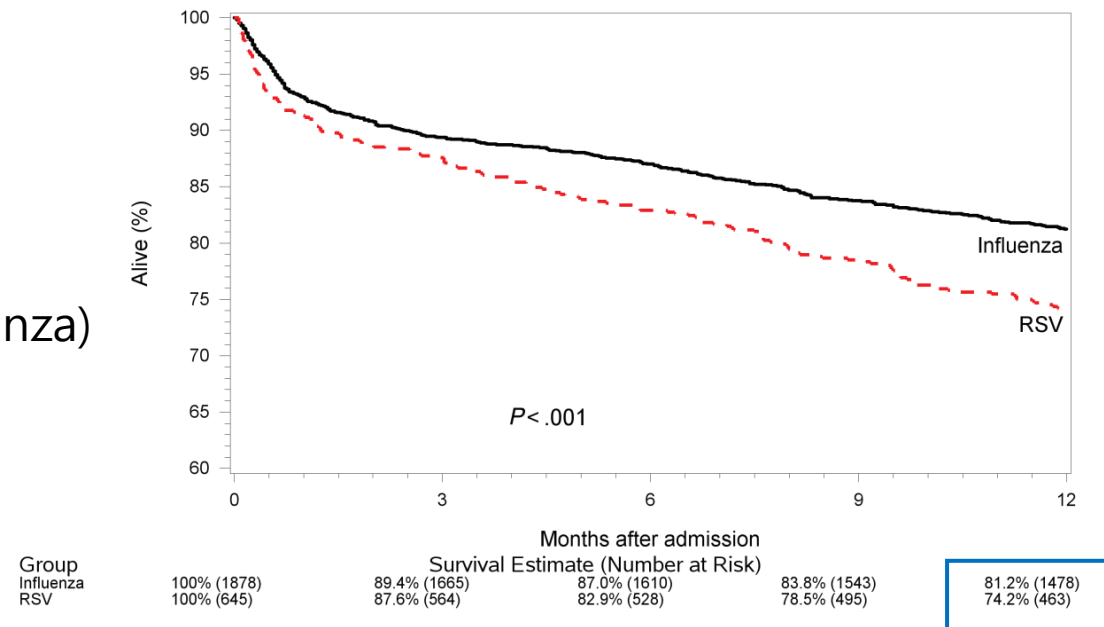
Table 2. Rates of Medically Attended RSV-Associated Illness per 100 000 US Adults by Chronic Conditions by Age Group

Study	Outcome	Chronic Condition	Age Group	Rate per 100 000 With Condition	Rate per 100 000 Without Condition	IRR
Branche et al. <i>Clin Infect Dis</i> (2021) [16] ^a	Hospitalizations	COPD	18–49	32	8	4.0
			50–64	207	33	6.3
			≥ 65	900	103	8.7
		Asthma	18–49	15	7	2.3
			50–64	97	36	2.7
			≥ 65	297	123	2.4
		Diabetes	18–49	71	6	11.3
			50–64	116	34	3.4
			≥ 65	444	97	4.6
		Obesity	18–49	9	7	1.3
			50–64	49	40	1.2
			≥ 65	158	127	1.2
		CAD	18–49	37	8	4.7
50–64	159		40	3.9		
≥ 65	529		102	5.2		
CHF	20–39	237	9	27.6		
	40–59	403	23	17.5		
	60–79	630	89	7.1		
	≥ 80	1131	254	4.5		
Belongia et al. <i>Open Forum Infect Dis</i> (2018) [5]	Medically attended	Cardiopulmonary	≥ 60	196	103	1.9
Matias et al. <i>BMC Public Health</i> (2017) [21]	Hospitalizations	High (COPD, diabetes, immunosuppression, stroke, or disorders of cardiovascular system, CNS, kidney, or liver)	18–49	8	3	2.7
			50–64	52	5	9.8
			≥ 65	242	42	5.7

Morbidity and mortality associated with RSV

- Observational, retrospective, cohort study
- Comprehensive prepaid health services (4.4 million members, 15 hospitals)
- Hospitalized adults ≥ 60 years
- 1 January 2011 ~ 30 June 2015 (645 RSV, 1878 influenza)

- Hospitalized older adults with RSV
 - ICU admission: 18%
 - 1-year mortality: 26%



Viral shedding of RSV infection

- 3 winters (2005 ~ 2008), in New York
- 111 RSV-infected adults (61 outpatients and 50 hospitalized)
 - 1st cohort: living in the community (≥ 21 years)
 - 2nd cohort: hospitalized with ARI (≥ 21 years)

Table 3. Viral and Antibody Comparisons for Respiratory Syncytial Virus (RSV)-Infected Outpatients Aged <65 Years or ≥ 65 Years

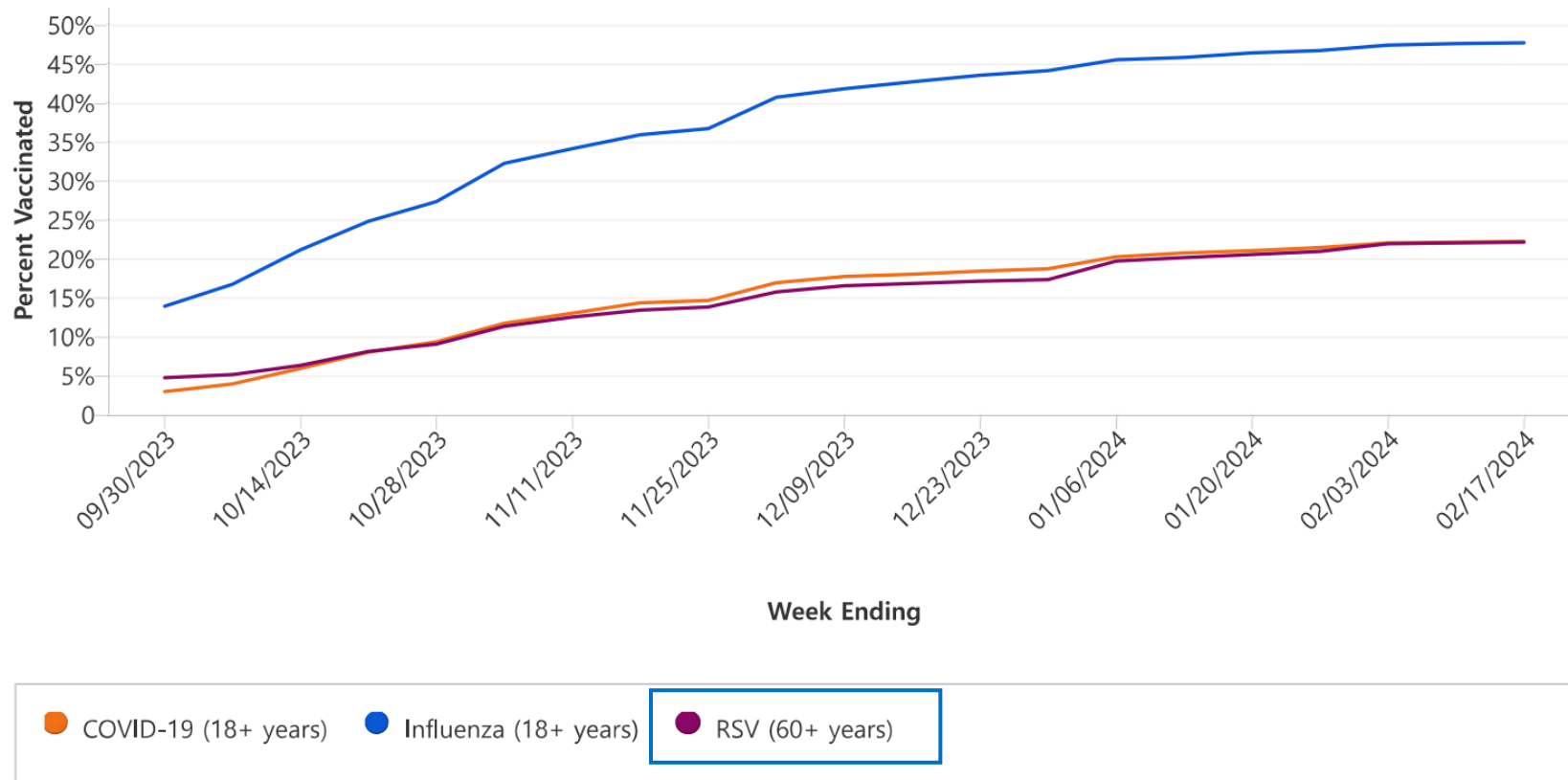
Variable	<65 years (n = 37)	≥ 65 years (n = 24)	<i>P</i>
RSV titer, log ₁₀ PFU/mL			
Nasal	2.0 ± 1.3	2.8 ± 1.0	.01
Sputum	2.3 ± 1.9	2.6 ± 1.8	NS
Duration of RSV shedding, d			
Nasal	8.7 ± 4.3	11.3 ± 5.2	.04
Sputum	7.2 ± 4.0	10.5 ± 3.8	.04

Table 4. Results of Multivariate Analysis of Factors Associated With Severe Disease in Adults




Variable	OR (95% CI)	<i>P</i>
Age, per 10 y increase	1.4 (.96–2.1)	.08
Nasal shedding duration >7 d	2.2 (1.0–4.9)	.03
Acute-phase ^a log ₂ IL-6 level	2.2 (1.2–4.2)	.01
MIP-1 α level ≥ 40 ng/mL	9.1 (.95–87.6)	.06
Underlying conditions	18.4 (5.1–65.9)	<.0001
Female sex	5.4 (1.2–23.8)	.03

Vaccination trends in the US

RSV disease burden in adults aged 60 years and older is higher
Need for RSV prophylaxis in this age group



New Immunizations to Protect Against Severe RSV

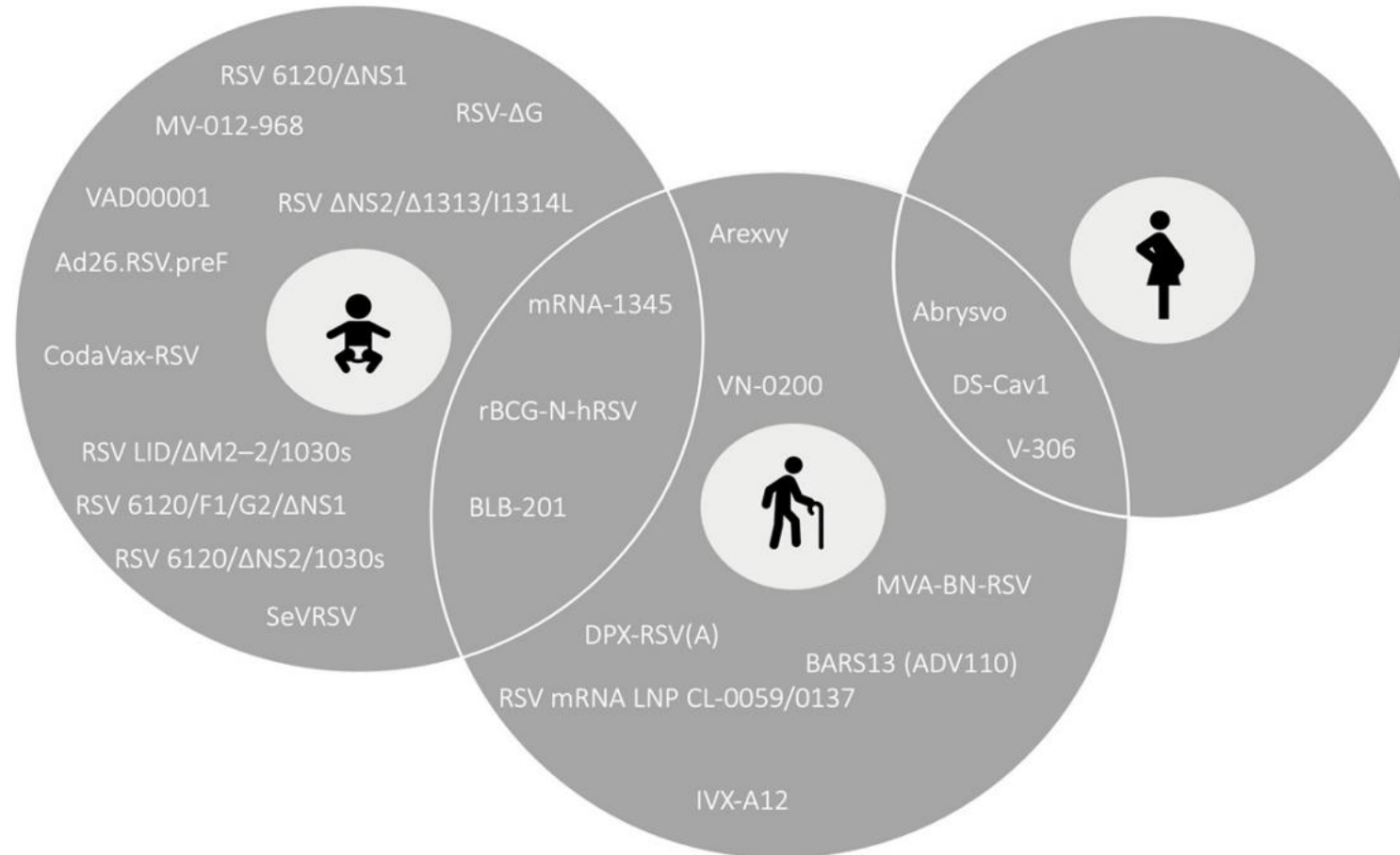
Who Does It Protect?	Type of Product	Is It for Everyone in Group?
 Adults 60 and over	RSV vaccine	Talk to your doctor first
 Babies	<p>RSV immunizations are recommended only for these groups:</p> <ul style="list-style-type: none">• Adults ages 60 and older: <u>Two RSV vaccines</u> (Arexvy by GSK and Abrysvo by Pfizer) have been licensed by FDA and recommended by CDC for adults ages 60 and older, using shared clinical decision-making.• Pregnant women: <u>One RSV vaccine</u> (Abrysvo by Pfizer) has been licensed and recommended during weeks 32 through 36 of pregnancy to protect infants.	
 Babies		

www.cdc.gov/rsv



RSV vaccine candidates

24 vaccines in the clinical stage of development



RSV vaccine candidates

1. mRNA Vaccines

- mRNA: vaccine platform carries genetic information exclusively for specific proteins
- higher safety, low interference and modification of the genetic material of the host
- **mRNA-1345: ongoing Phase II/III clinical trial (NCT05127434)**
- RSV mRNA LNP CL-0059 or RSV mRNA LNP CL-0137: Phase I/II (NCT05639894)

RSV vaccine candidates

2. Live-Attenuated/Chimeric Vaccines (LAVs)

- BLB-201: Phase I (NCT05281263)
- CodaVax-RSV: Phase I (NCT04295070)
- RSV- Δ G
- rBCG-N-hRSV1: Phase I (NCT03213405)
- SeVRSV: Phase I (NCT03473002)
- MV-012-968: Phase II (NCT04690335)
- VAD00001
- RSV Δ NS2/ Δ 1313/I1314L
- RSV LID/ Δ M2-2/1030s
- RSV 6120/ Δ NS2/1030s
- RSV 6120/F1/G2/ Δ NS1/RSV 6120/ Δ NS1

RSV vaccine candidates

3. Subunit/Virus-Like-Particle (VLP)-Based Vaccines

- Subunit vaccine: purified fragments of the desired pathogen → non-virulent, vaccine safety ↑
- VLP vaccine: subclass of subunit vaccine, suitable for use in older adults

- IVX-A12: Phase IIa (NCT05903183)
- V-306: Phase I (NCT04519073)
- DPX-RSV(A): Phase I (NCT02472548)
- VN-0200: Phase II (NCT05547087)
- BARS13 (ADV110): Phase II (NCT04681833)
- DS-Cav1 (VRC-RSVRGP084-00-VP)
- **Arexvy/RSVPreF3 OA (GSK3844766A): Phase III (NCT04886596) - licensed**
- **Abrysvo/RSVpreF: Phase III (NCT05035212) - licensed**

RSV vaccine candidates

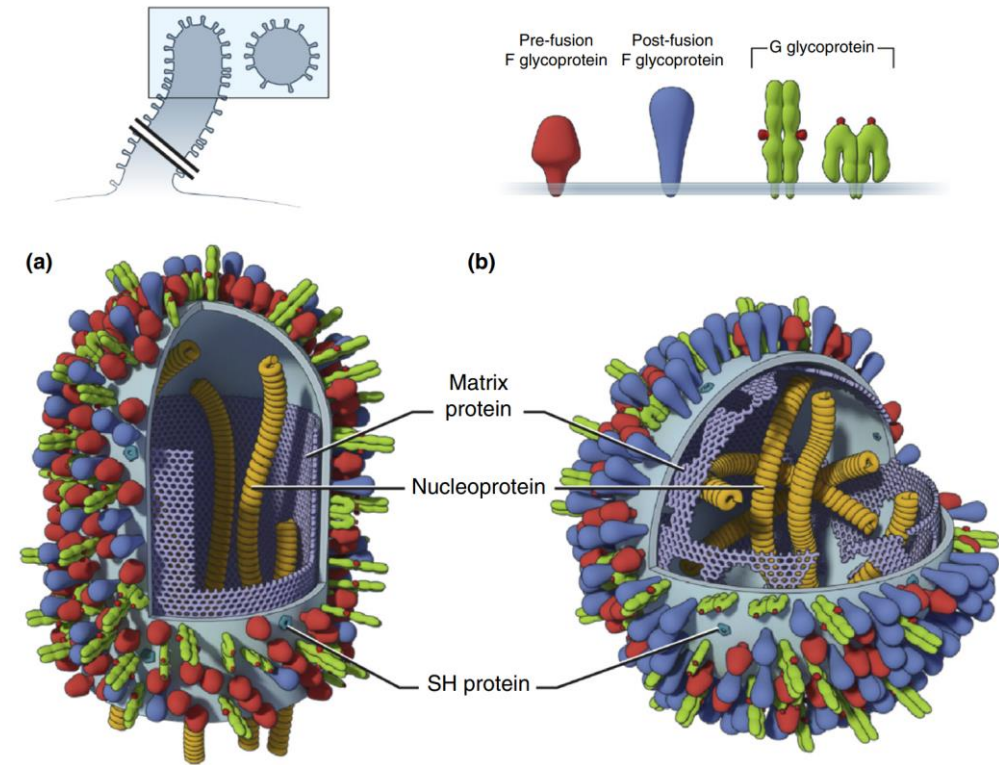
4. Recombinant Viral-Vector-Based Vaccines

- modifying the viruses by adding the desired genetic information → protein production using the virus as a delivery system
- Vector: key factor in the development of the vaccine (rapid production in shortened periods)

- MVA-BN-RSV: Phase III (NCT05238025)
- **Ad26.RSV.preF: Phase III (NCT04908683)**

Respiratory syncytial virus (RSV)

- Pneumovirus in the family *Paramyxoviridae*
- negative-sense single-stranded RNA virus
- 10 genes encode 11 proteins
- 2 major subtypes: A and B (by G glycoprotein)
- 3 viral envelope proteins
 - Small hydrophobic (SH): ion channel
 - G: attachment
 - **F (fusion): viral entry**
- **F glycoprotein**: unidirectional conformational change
 - **Metastable prefusion** conformation (**pre-F, functional**)
 - **Stable postfusion** conformation (**post-F, non-functional**)



F glycoprotein

- Major antigenic target for vaccine
 - Viral fusion and host-cell entry
 - transitioning to a stable postfusion state while mediating virus entry
 - elicits neutralizing antibodies
 - highly conserved across the two RSV subtypes (A and B)
 - antigenically divergent RSV G (determinant of A and B subgroups)
 - Palivizumab (neutralizing monoclonal antibody targeting RSV F)
 - RSV-related high-risk infant hospitalizations ↓

→ **Stabilized preF**: key vaccine antigen

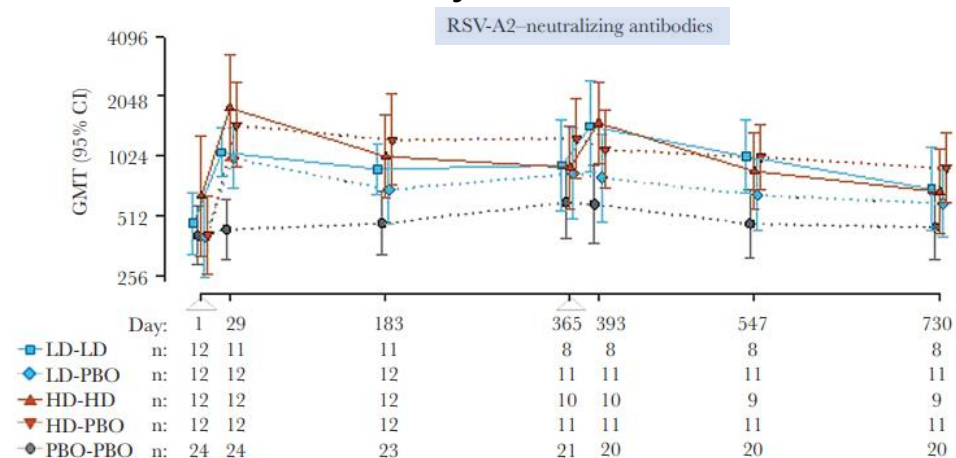
Recombinant Viral-Vector-Based Vaccines

Ad26.RSV.preF

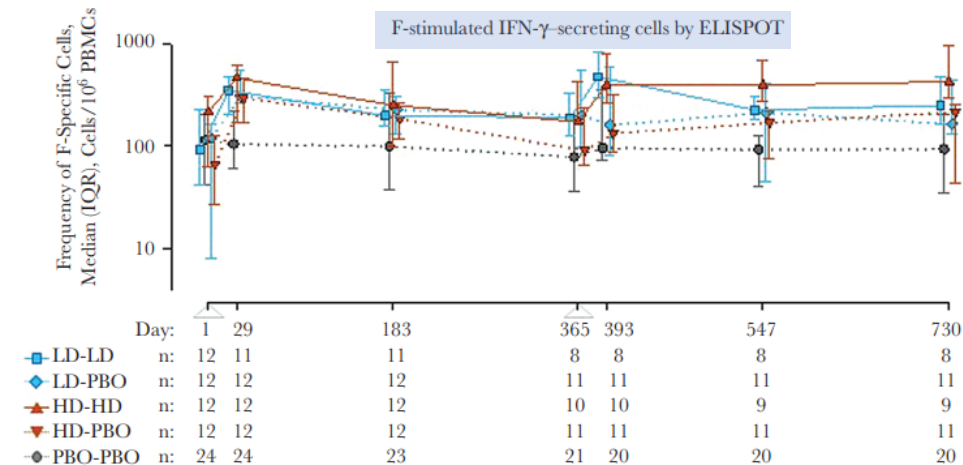
Ad26.RSV.preF

- Phase 1 trial
 - ≥ 60 years (n=72)
 - Ad26.RSV.preF vaccine (LD, HD) vs. saline placebo
 - 12 months between doses, 2-year follow-up
-
- Ad26.RSV.preF
 - well tolerated
 - acceptable safety profile
 - immunogenic after a single dose
 - durable for ≥ 2 years after vaccination

Humoral Immunity

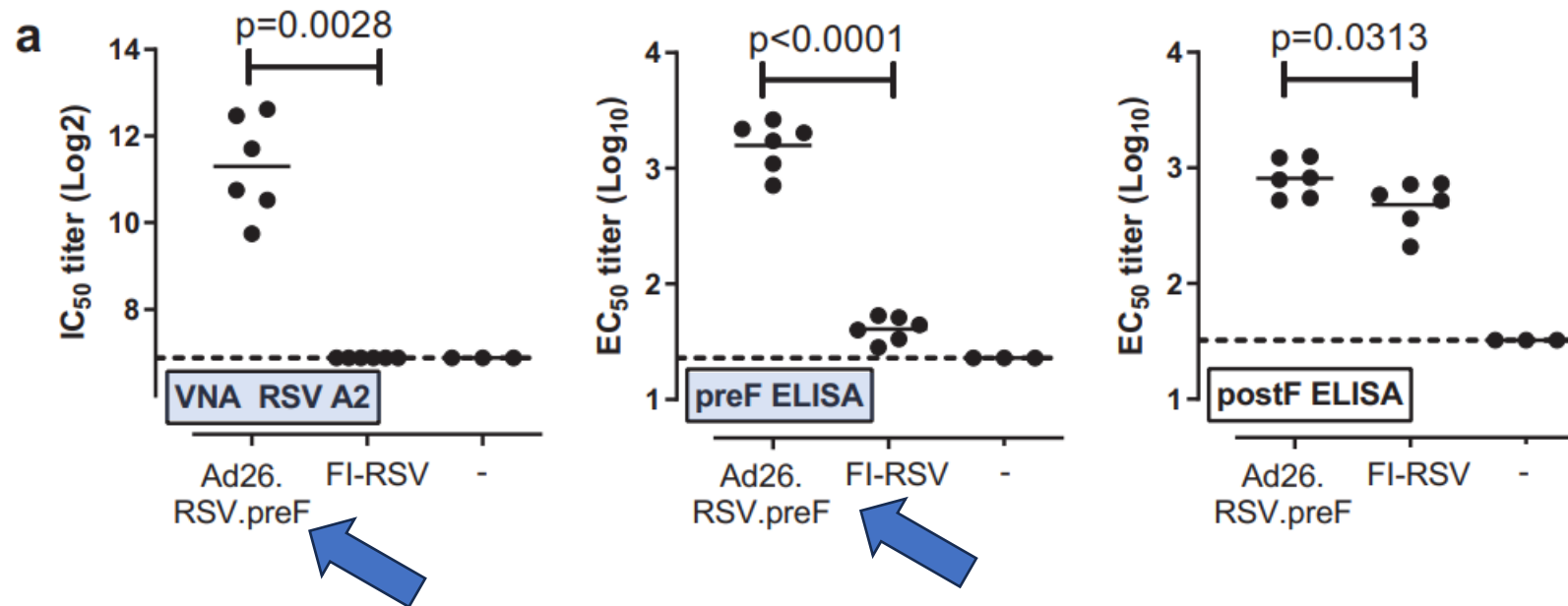


Cell-Mediated Immunity



Ad26.RSV.preF–RSV preF protein vaccine

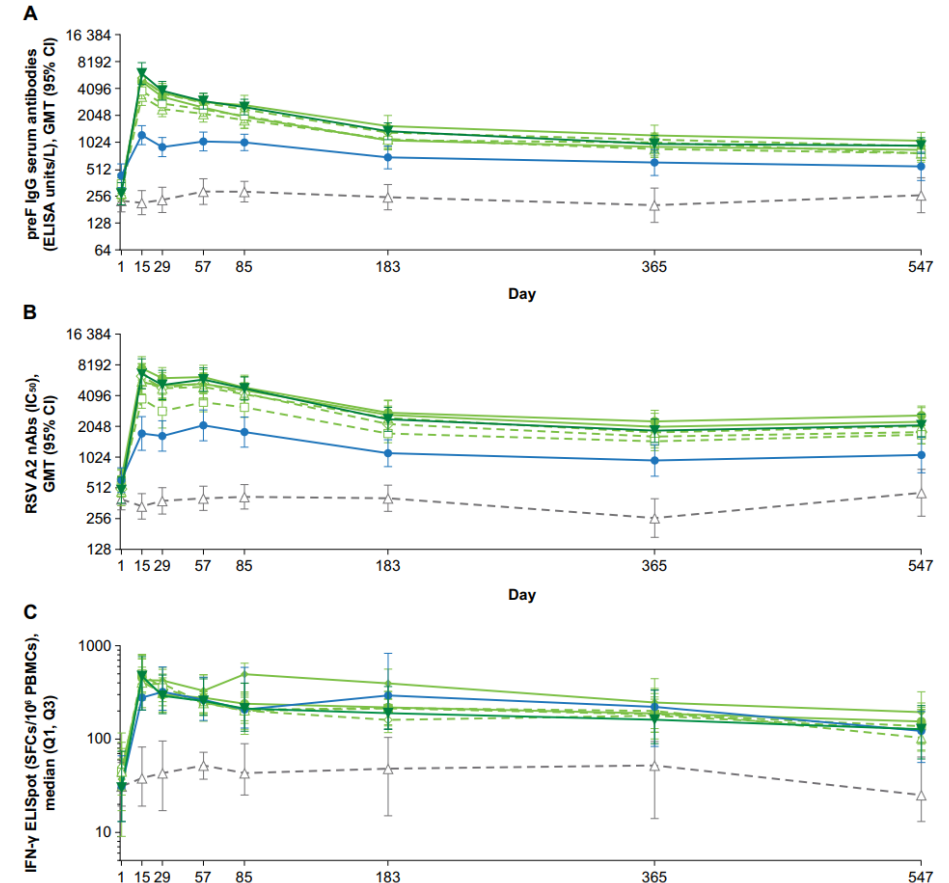
- Replication-incompetent serotype 26 adenovirus (Ad26)
 - Encoding a **conformation-stabilized RSV preF protein (Ad26.RSV.preF)** and **recombinant RSV preF protein**
 - Potent inducers of humoral and cellular Th1 responses



Adult mice
Ad26.RSV.preF vs. FI-RSV
Immune responses at 4, 8, 10 weeks

Ad26.RSV.preF–RSV preF protein

- phase 1/2a study
- Ad26.RSV.preF vs. Ad26.RSV.preF–RSV preF (LD, HD)
- ≥60 years
- cohort 1 (initial safety, n = 64)
- cohort 2 (regimen selection, n = 288)
- Ad26.RSV.preF–RSV preF protein
 - improved humoral immunogenicity
 - similar cellular immune responses
 - remained well for 1.5 years



	preF IgG	RSV A2 nAbs
Ad26 ^a + Placebo, ^b HD	2.1 (1.6, 2.6)	2.7 (2.0, 3.6)
Combo ^c + Placebo, ^b LD/LD	8.0 (6.1, 10.4)	5.4 (3.6, 8.0)
Combo ^c + Placebo, ^b HD/LD	8.7 (6.6, 11.5)	10.0 (6.9, 14.6)
Combo ^c + Placebo, ^b HD/HD	13.9 (10.0, 19.3)	10.5 (7.4, 15.1)

Ad26.RSV.preF–RSV preF protein vaccine

- **Efficacy and Safety of an Ad26.RSV.preF–RSV preF Protein Vaccine in Older Adults**
- CYPRESS trial (by Janssen)
- phase 2b
- Ad26.RSV.preF–RSV preF protein vaccine vs. saline placebo
- August 5, 2019 ~ November 13, 2019
- ≥ 65 years (n=5,782, 1:1 ratio)

Vaccine Efficacy Assessments

Efficacy Assessments

- Primary end point: 1st occurrence of RSV-mediated LRT disease
 - Definition 1: ≥ 3 symptoms of LRT infection
 - Definition 2: ≥ 2 symptoms of LRT infection
 - Definition 3: Definition 1 or 2 or ≥ 1 symptoms of LRT infection + ≥ 1 systemic symptom
- Secondary end point: 1st occurrence of any RSV-mediated ARI

Immunogenicity Assessments

- Blood samples: at days 1, 15, 85, 169
- RSV A2, RSV B neutralizing antibodies
- Serum preF IgG antibodies
- RSV-F-specific T-cell responses

Safety Assessments

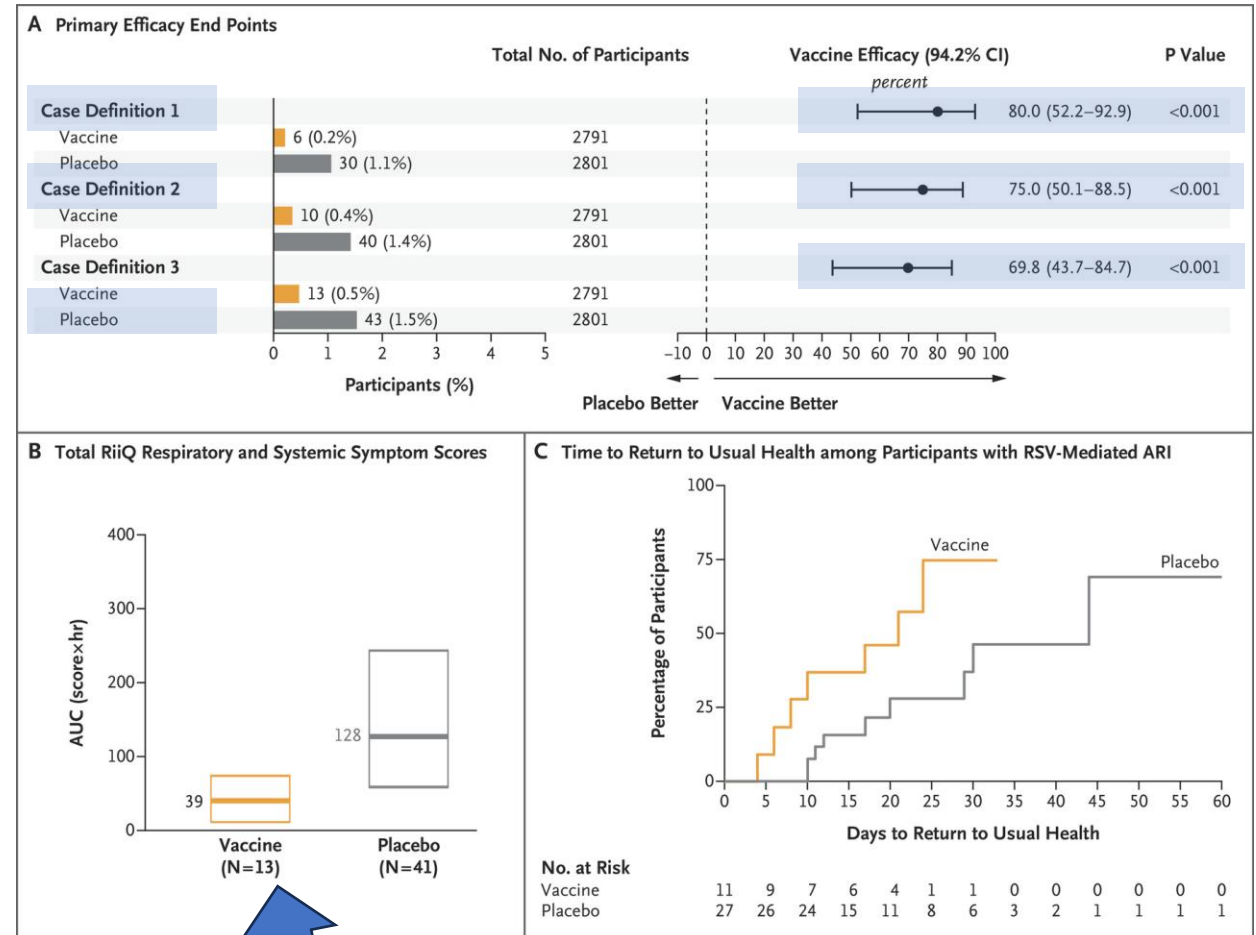
- serious adverse events and adverse events
- Solicited and unsolicited adverse events

CYPRESS trial

Table 1. Characteristics of the Participants at Baseline (Full Analysis Population).*

Characteristic	Vaccine (N=2891)	Placebo (N=2891)	Total (N=5782)
Median age (range) — yr	71 (65–94)	71 (65–98)	71 (65–98)
Age distribution — no. (%)			
65–74 yr	2126 (73.5)	2132 (73.7)	4258 (73.6)
75–84 yr	688 (23.8)	685 (23.7)	1373 (23.7)
≥85 yr	77 (2.7)	74 (2.6)	151 (2.6)
Sex — no. (%)			
Female	1640 (56.7)	1694 (58.6)	3334 (57.7)
Male	1251 (43.3)	1197 (41.4)	2448 (42.3)
Race or ethnic group — no. (%)†			
White	2658 (91.9)	2690 (93.0)	5348 (92.5)
Black	169 (5.8)	148 (5.1)	317 (5.5)
Asian	15 (0.5)	17 (0.6)	32 (0.6)
American Indian or Alaska Native	8 (0.3)	9 (0.3)	17 (0.3)
Native Hawaiian or other Pacific Islander	16 (0.6)	5 (0.2)	21 (0.4)
Multiple	9 (0.3)	14 (0.5)	23 (0.4)
Not reported, unknown, or missing data	16 (0.6)	8 (0.3)	24 (0.4)
Hispanic or Latino ethnic group			
Hispanic or Latino	84 (2.9)	97 (3.4)	181 (3.1)
Not Hispanic or Latino	2779 (96.1)	2773 (95.9)	5552 (96.0)
Not reported, unknown, or missing data	28 (1.0)	21 (0.7)	49 (0.8)
Smoking status — no. (%)			
Smoker	1297 (44.9)	1255 (43.4)	2552 (44.1)
Nonsmoker	1594 (55.1)	1635 (56.6)	3229 (55.8)
Not reported	0	1 (<0.1)	1 (<0.1)
Increased risk of severe RSV disease, narrower definition — no. (%)‡	740 (25.6)	727 (25.1)	1467 (25.4)
Congestive heart failure	58 (7.8)	54 (7.4)	112 (7.6)
Other chronic cardiac disease	330 (44.6)	330 (45.4)	660 (45.0)
Chronic obstructive pulmonary disease	219 (29.6)	208 (28.6)	427 (29.1)
Asthma	266 (35.9)	250 (34.4)	516 (35.2)
Other chronic pulmonary disease	30 (4.1)	37 (5.1)	67 (4.6)
Increased risk of severe RSV disease, broader definition — no. (%)§	1184 (41.0)	1136 (39.3)	2320 (40.1)

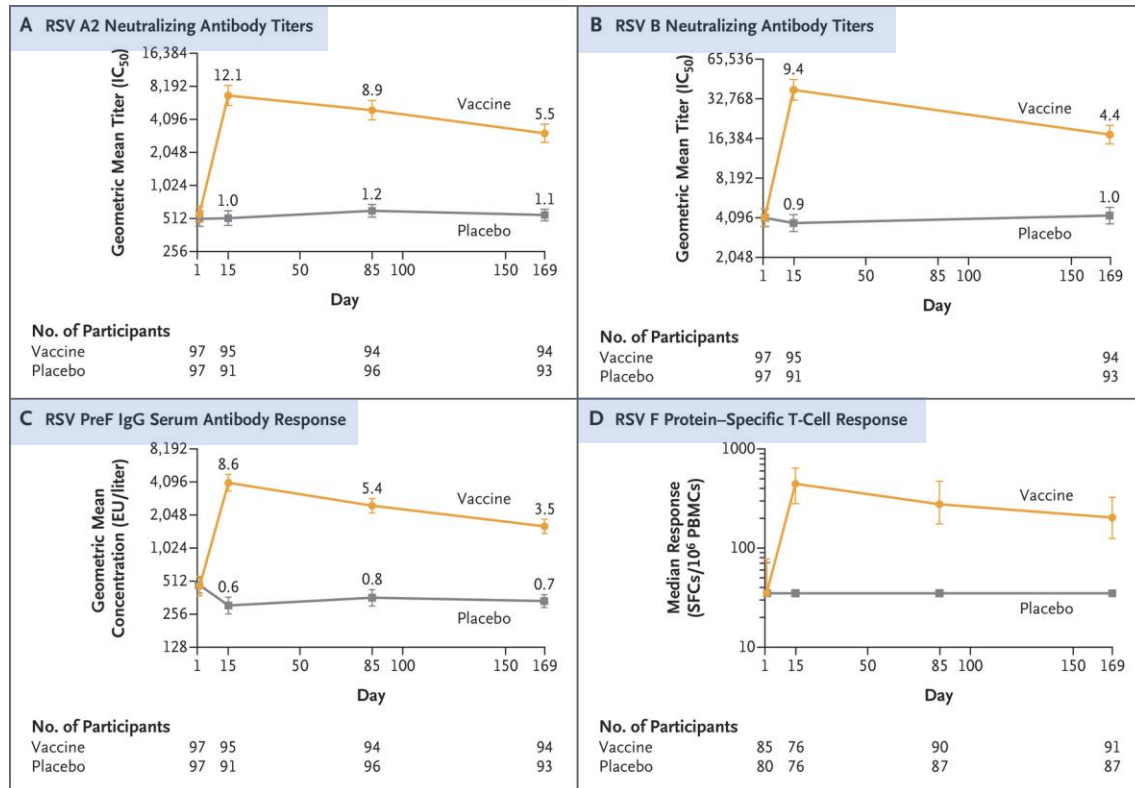
Efficacy



less severe in vaccine group

CYPRESS trial

Immunogenicity



Adverse Events

Table 2. Summary of Adverse Events.*

Adverse Event	Vaccine <i>no. of participants with event/total no. (%)</i>	Placebo <i>no. of participants with event/total no. (%)</i>
Solicited adverse events (safety subpopulation, within 7 days after injection)		
Any event	179/348 (51.4)	70/347 (20.2)
Event of grade ≥3	11/348 (3.2)	2/347 (0.6)
Local event†	132/348 (37.9)	29/347 (8.4)
Local event of grade ≥3†	6/348 (1.7)	1/347 (0.3)
Systemic event‡	144/348 (41.4)	57/347 (16.4)
Systemic event of grade ≥3‡	7/348 (2.0)	1/347 (0.3)
Unsolicited adverse events (safety subpopulation, within 28 days after injection)		
Any event	58/348 (16.7)	50/347 (14.4)
Event of grade ≥3	6/348 (1.7)	5/347 (1.4)
Event thought to be related to vaccine or placebo	18/348 (5.2)	8/347 (2.3)
Serious adverse events and adverse events leading to discontinuation of participation in trial (primary safety population)		
Serious adverse event	132/2891 (4.6)	136/2891 (4.7)
Serious adverse event thought to be related to vaccine or placebo	0	0
Adverse event with fatal outcome	8/2891 (0.3)	12/2891 (0.4)
Adverse event with fatal outcome thought to be related to vaccine or placebo	0	0
Adverse event leading to permanent discontinuation of participation in trial	10/2891 (0.3)	15/2891 (0.5)

A Study of an Adenovirus Serotype 26 Pre-fusion Conformation-stabilized F Protein (Ad26. RSV. preF) Based Respiratory Syncytial Virus (RSV) Vaccine in the Prevention of Lower Respiratory Tract Disease in Adults Aged 60 Years and Older (EVERGREEN)



The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT04908683

Recruitment Status : Completed
First Posted : June 1, 2021
Results First Posted : February 8, 2024
Last Update Posted : February 8, 2024

[View this study on the modernized ClinicalTrials.gov](#)

Study Description

Go to

Brief Summary:

The study will enroll up to 27,200 participants in order to demonstrate the efficacy of the active Ad26.RSV.preF-based study vaccine in the prevention of Reverse Transcription Polymerase Chain Reaction (RT-PCR) confirmed Respiratory Syncytial Virus (RSV)-mediated Lower Respiratory Tract Disease (LRTD) when compared to placebo in adults aged 60 years and above.

Condition or disease	Intervention/treatment	Phase
Respiratory Syncytial Viruses	Biological: Adenovirus serotype 26 (Ad26)-based respiratory syncytial virus (RSV). preF	Phase 3
Lower Respiratory Tract Disease	Biological: Placebo	

Study Design

Go to

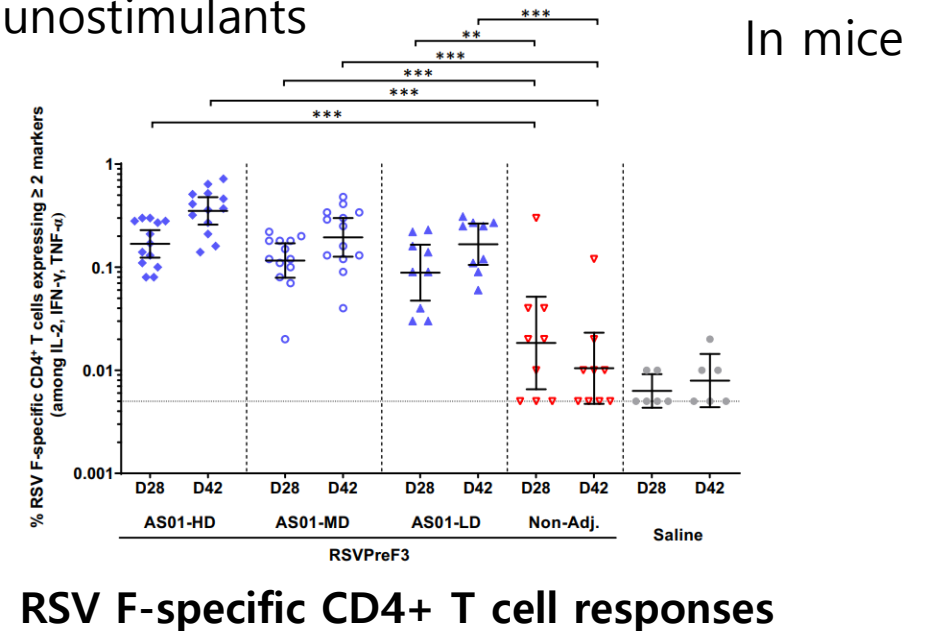
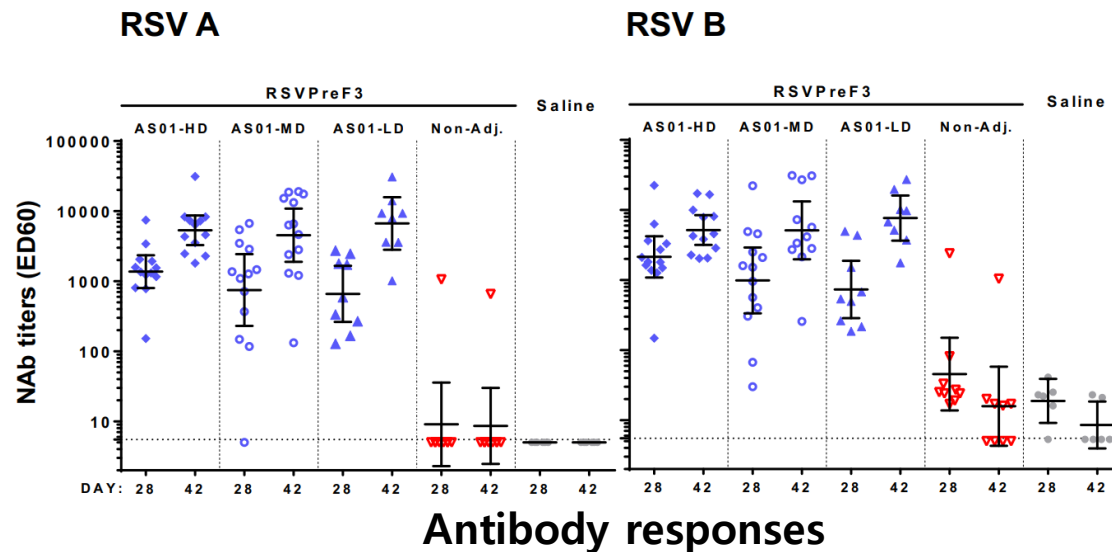
Study Type : Interventional (Clinical Trial)
Actual Enrollment : 25236 participants
Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Double (Participant, Investigator)
Primary Purpose: Prevention
Official Title: A Randomized, Double-blind, Placebo-controlled Phase 3 Efficacy Study of an Ad26.RSV.preF-based Vaccine in the Prevention of Lower Respiratory Tract Disease Caused by RSV in Adults Aged 60 Years and Older
Actual Study Start Date : July 21, 2021
Actual Primary Completion Date : July 21, 2023
Actual Study Completion Date : July 21, 2023

Subunit/VLP-Based Vaccines

RSVPreF3 OA (Arexvy)

AS01-adjuvanted RSVPreF3 vaccine

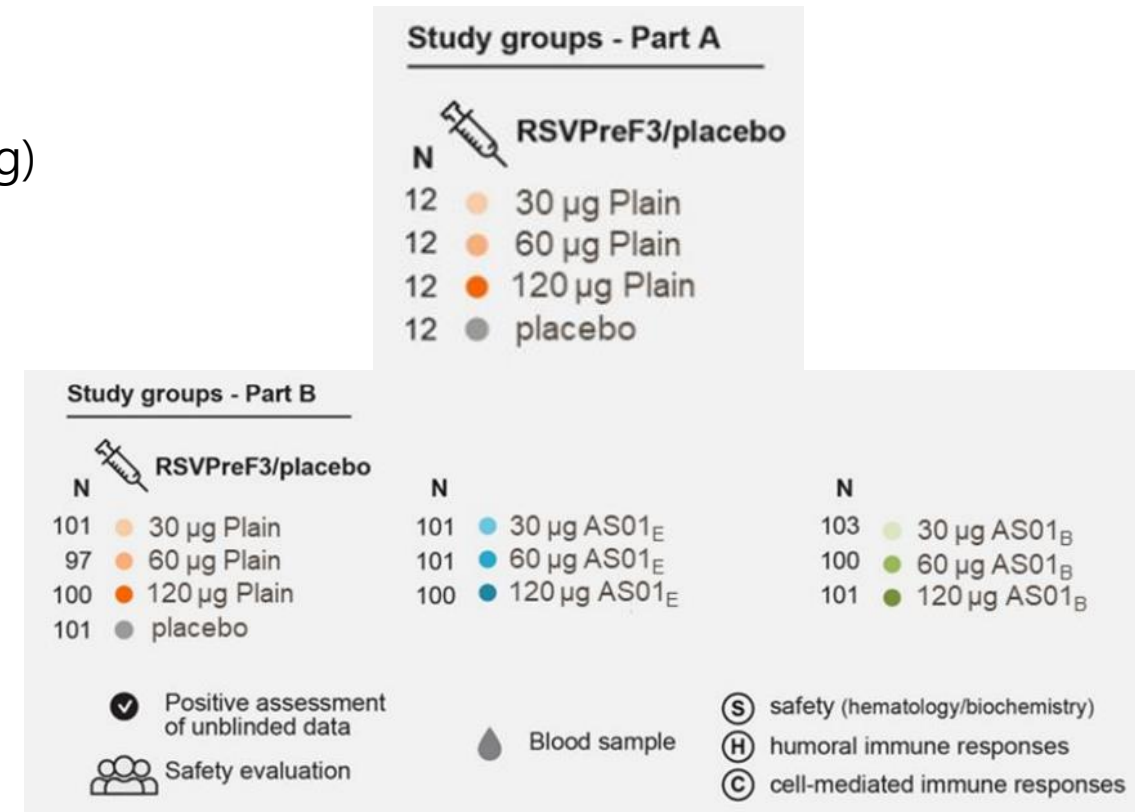
- RSVPreF3: recombinant subunit protein, engineered to preferentially maintain a PreF conformation
- Adjuvant System (AS)01: liposome-based adjuvant, immunostimulants



- RSVPreF3 antigen with AS01
 - better vaccine immunogenicity in immunologically impaired populations such as OA

RSVPreF3 Candidate Vaccine

- Phase 1/2 study
- RSVPreF3 formulations
 - RSVPreF3 antigen concentrations (30, 60, 120 μg)
 - AS01-based adjuvant (AS01E and AS01B)
- Participants
 - Part A (n=48, 18–40 years, YA)
 - part B (n=1005, 60–80 years, OA)
- IM 2 doses (2 months apart), vaccine vs. placebo



RSVPreF3 Candidate Vaccine

Table 1. Demographic Characteristics of Study Participants (Exposed Set)

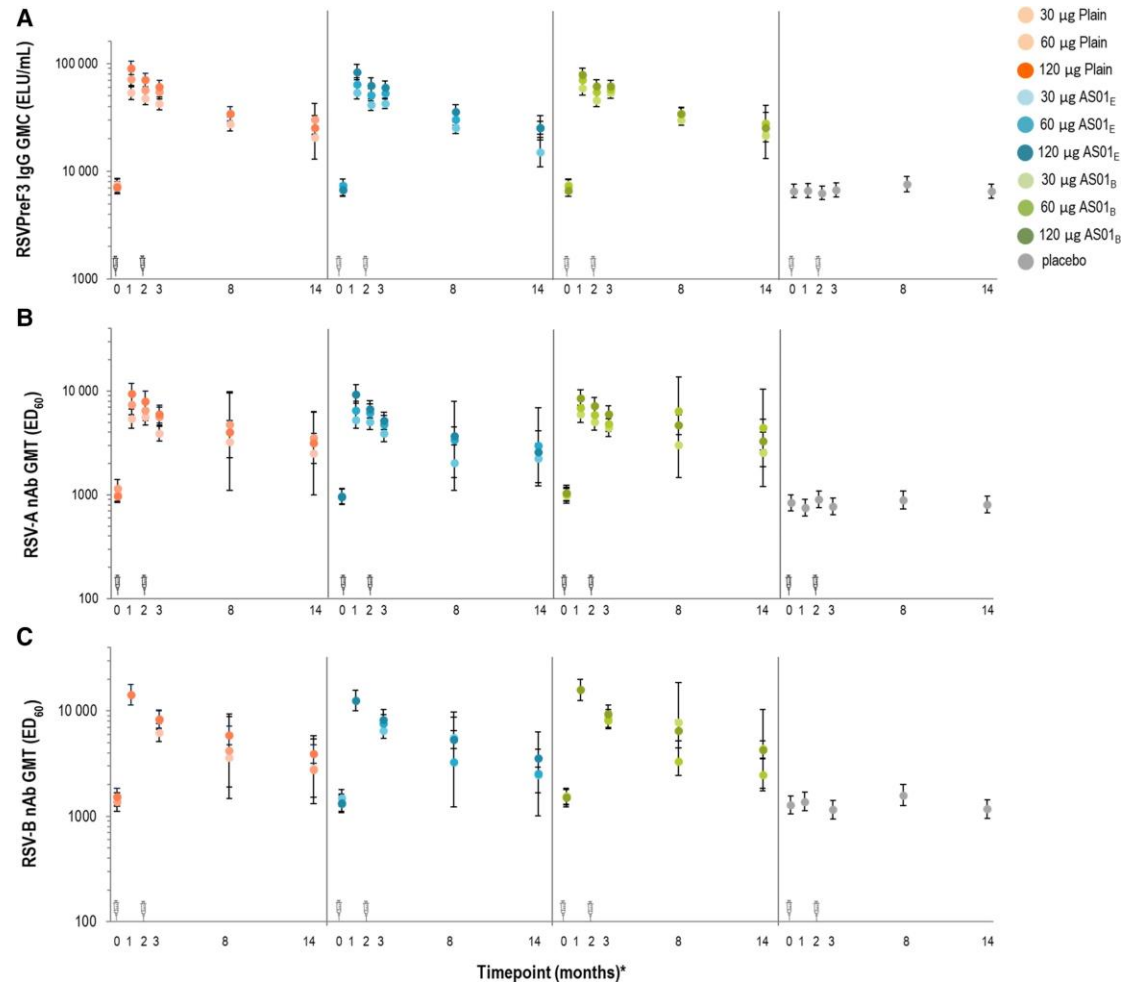
Participants	Adjuvant ^a	RSVPreF3 Antigen Concentration	No.	Age in Years at First Vaccination, Mean (SD)	Sex, No. (%)	Ethnicity, No. (%)	Race, No. (%)		
					Female	Not Hispanic or Latino	White	Black/African American	Other ^b
Young adults (18–40 y)	Plain	30 µg	12	31.2 (7.0)	8 (66.7)	12 (100)	10 (83.3)	2 (16.7)	0 (0.0)
		60 µg	12	26.5 (4.0)	7 (58.3)	11 (91.7)	10 (83.3)	1 (8.3)	1 (8.3)
		120 µg	12	29.9 (6.1)	7 (58.3)	11 (91.7)	10 (83.3)	2 (16.7)	0 (0.0)
		Placebo	12	31.6 (5.6)	9 (75.0)	12 (100)	11 (91.7)	1 (8.3)	0 (0.0)
Older adults (60–80 y)	Plain	30 µg	101	67.3 (5.6)	58 (57.4)	99 (98.0)	95 (94.1)	5 (5.0)	1 (1.0)
		60 µg	97	67.8 (5.6)	54 (55.7)	91 (93.8)	90 (92.8)	7 (7.2)	0 (0.0)
		120 µg	100	67.9 (4.9)	57 (57.0)	94 (94.0)	93 (93.0)	4 (4.0)	0 (0.0)
	AS01 _E	30 µg	101	67.8 (5.1)	58 (57.4)	98 (97.0)	88 (87.1)	12 (11.9)	1 (1.0)
		60 µg	101	67.1 (5.6)	57 (56.4)	98 (97.0)	94 (93.1)	7 (6.9)	0 (0.0)
		120 µg	100	67.6 (5.2)	57 (57.0)	97 (97.0)	93 (93.0)	5 (5.0)	1 (1.0)
	AS01 _B	30 µg	103	67.6 (4.9)	59 (57.3)	99 (96.1)	92 (89.3)	11 (10.7)	0 (0.0)
		60 µg	100	67.5 (4.9)	58 (58.0)	98 (98.0)	93 (93.0)	7 (7.0)	0 (0.0)
		120 µg	101	67.5 (4.9)	57 (56.4)	97 (96.0)	92 (91.1)	7 (6.9)	1 (1.0)
Plain	Placebo	101	68.1 (5.7)	58 (57.4)	98 (97.0)	97 (96.0)	4 (4.0)	0 (0.0)	

Abbreviations: RSVPreF3, prefusion conformation of the respiratory syncytial virus F protein; SD, standard deviation.

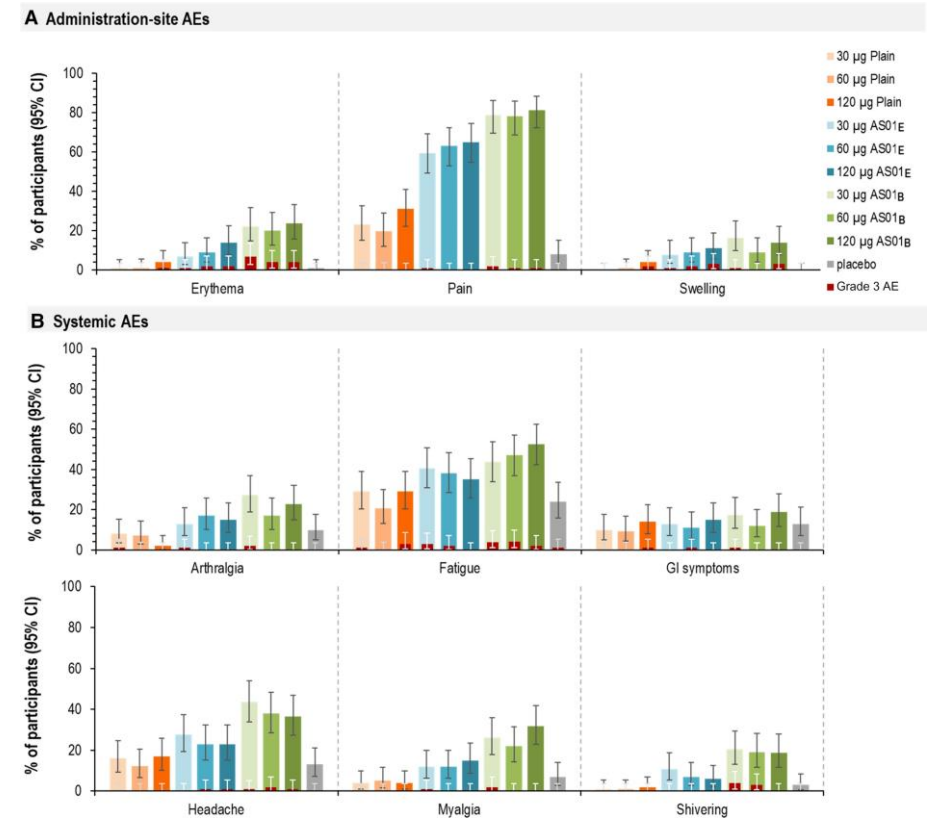
^aAS01_B and AS01_E, adjuvanted vaccine formulations with the corresponding vaccine adjuvant systems; Plain, unadjuvanted vaccine formulations.

^bIncludes American Indian/Alaska Native and Asian participants.

RSVPreF3 Candidate Vaccine



induced neutralizing antibody responses in older adults
 highest RSVPreF3 antigen level (**120 µg**)



higher reactogenicity of the AS01-based formulations (highest for **AS01B**)
 → less reactogenic **AS01E** adjuvant

RSVPreF3 OA

- **Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults**
- AReSVi-006 Study (by GSK)
- Phase 3 trial
- RSVPreF3 OA (**120 µg, AS01E-adjuvant**) vs. placebo
- May 25, 2021 ~ January 31, 2022
- ≥60 years (n=24,966, 1:1 ratio)

Vaccine Efficacy Assessments

Efficacy Assessments

- Primary end point: RSV-related **lower respiratory tract disease**
- Acute respiratory infection: ≥ 24 hours
 - ≥ 2 **respiratory** symptoms or signs
 - or ≥ 1 **respiratory** + 1 **systemic** symptom or sign
- Lower respiratory tract disease: ≥ 24 hours
 - ≥ 2 **lower respiratory symptoms or signs** (including at least one lower respiratory sign)
 - or ≥ 3 **lower respiratory symptoms**

→ Primary objective

- **lower limit of the confidence interval around the efficacy > 20%**

Immunogenicity Assessments

- Blood samples
 - before the injection
 - 1 month after the injection
- RSVPreF3-specific IgG enzyme-linked immunosorbent assay and RSV A and B neutralization assays

Safety Assessments

- Intensity of adverse events: mild (grade 1) ~ severe (grade 3)

AReSVi-006 Study

Efficacy

Table 1. Characteristics of the Participants at Baseline (Exposed Population).*

Characteristic	RSVPreF3 OA Group (N = 12,467)	Placebo Group (N = 12,499)
Age		
Mean — yr	69.5±6.5	69.6±6.4
Distribution — no. (%)		
≥70 yr	5,504 (44.1)	5,519 (44.2)
≥80 yr	1,017 (8.2)	1,028 (8.2)
60–69 yr	6,963 (55.9)	6,980 (55.8)
70–79 yr	4,487 (36.0)	4,491 (35.9)
Female sex — no. (%)	6,488 (52.0)	6,427 (51.4)
Frailty status — no. (%)§		
Frail	189 (1.5)	177 (1.4)
Prefrail	4,793 (38.4)	4,781 (38.3)
Fit	7,464 (59.9)	7,521 (60.2)
Unknown	21 (0.2)	20 (0.2)
Charlson comorbidity index¶		
Mean	3.2±1.2	3.2±1.2
Distribution — no. (%)		
Low or medium risk	8,235 (66.1)	8,368 (66.9)
High risk	4,232 (33.9)	4,131 (33.1)
Coexisting conditions of interest — no. (%)		
Any preexisting condition	4,937 (39.6)	4,864 (38.9)
Cardiorespiratory preexisting condition	2,496 (20.0)	2,422 (19.4)
Endocrine or metabolic preexisting condition	3,200 (25.7)	3,236 (25.9)

Table 2. Vaccine Efficacy against First Occurrence of RSV-Related Lower Respiratory Tract Disease and RSV-Related Acute Respiratory Infection (Modified Exposed Population).*

End Point	RSVPreF3 OA Group				Placebo Group				Vaccine Efficacy (CI)†
	No. of Participants	No. of Events	Follow-up participant-yr	Incidence Rate no. of events/1000 participant-yr	No. of Participants	No. of Events	Follow-up participant-yr	Incidence Rate no. of events/1000 participant-yr	%
RSV-related lower respiratory tract disease									
Overall	12,466	7	6,865.9	1.0	12,494	40	6,857.3	5.8	82.6 (57.9 to 94.1)
Severe‡	12,466	1	6,867.9	0.1	12,494	17	6,867.7	2.5	94.1 (62.4 to 99.9)
According to RSV subtype§									
RSV A	12,466	2	6,867.4	0.3	12,494	13	6,868.9	1.9	84.6 (32.1 to 98.3)
RSV B	12,466	5	6,866.7	0.7	12,494	26	6,862.3	3.8	80.9 (49.4 to 94.3)
RSV-related acute respiratory infection									
Overall	12,466	27	6,858.7	3.9	12,494	95	6,837.8	13.9	71.7 (56.2 to 82.3)
According to RSV subtype§									
RSV A	12,466	9	6,865.2	1.3	12,494	32	6,862.3	4.7	71.9 (39.7 to 88.2)
RSV B	12,466	18	6,861.7	2.6	12,494	61	6,849.4	8.9	70.6 (49.6 to 83.7)

primary objective was met (lower limit of CI >20%)

AReSVi-006 Study

Immunogenicity

Table S10. RSVPreF3-specific IgG and RSV-A and RSV-B neutralizing antibodies before and 1 month after RSVPreF3 OA or placebo administration, per-protocol set for immunogenicity

Antibody	RSVPreF3 OA				Placebo			
	Timepoint	N	GMC (95% CI), EU/mL	MGI (95% CI)	N	GMC (95% CI), EU/mL	MGI (95% CI)	
RSVPreF3 IgG								
Pre	885	7,041.1 (6,719.7–7,377.8)	13.1 (12.3–13.9)	892	7,090.1 (6,785.6–7,408.1)	1.0 (1.0–1.0)		
Post	848	91,729.9 (8,514.2–96,148.7)		846	7,044.5 (6,726.5–7,377.5)			
Neutralizing Ab								
	N	GMT (95% CI), ED60	MGI (95% CI)	N	GMT (95% CI), ED60	MGI (95% CI)		
RSV-A								
Pre	885	918.0 (865.7–973.5)	10.2 (9.5–11.0)	892	928.6 (877.5–982.6)	0.9 (0.9–1.0)		
Post	848	9,329.7 (8,699.3–10,005.8)		846	873.6 (822.6–927.8)			
RSV-B								
Pre	885	1,195.8 (1,130.5–1,264.8)	8.6 (8.0–9.2)	892	1,244.1 (1,174.4–1,317.9)	1.0 (1.0–1.1)		
Post	848	10,178.9 (9,564.1–10,833.1)		846	1,263.1 (1,185.0–1,346.3)			

Adverse Events

Table 3. Solicited and Unsolicited Adverse Events after Receipt of a Single Dose of the RSVPreF3 OA Vaccine or Placebo.*

Event	RSVPreF3 OA Group		Placebo Group	
	Participants	Incidence (95% CI)	Participants	Incidence (95% CI)
	no.	%	no.	%
Solicited safety population	879		878	
Solicited reactions				
Any solicited reaction	632	71.9 (68.8–74.9)	245	27.9 (25.0–31.0)
Any grade 3 solicited reaction	36	4.1 (2.9–5.6)	8	0.9 (0.4–1.8)
Solicited injection-site reactions				
Pain	535	60.9 (57.5–64.1)	81†	9.3 (7.4–11.4)
Erythema	66	7.5 (5.9–9.5)	7†	0.8 (0.3–1.6)
Swelling	48	5.5 (4.1–7.2)	5†	0.6 (0.2–1.3)
Solicited systemic reactions				
Fever‡	18	2.0 (1.2–3.2)	3	0.3 (0.1–1.0)
Headache	239	27.2 (24.3–30.3)	111	12.6 (10.5–15.0)
Fatigue	295	33.6 (30.4–36.8)	141	16.1 (13.7–18.7)
Myalgia	254	28.9 (25.9–32.0)	72	8.2 (6.5–10.2)
Arthralgia	159	18.1 (15.6–20.8)	56	6.4 (4.9–8.2)
Unsolicited adverse events				
Any unsolicited adverse event	131	14.9 (12.6–17.4)	128	14.6 (12.3–17.1)
Grade 3 unsolicited adverse event	12	1.4 (0.7–2.4)	12	1.4 (0.7–2.4)
Exposed population	12,467		12,499	
Unsolicited adverse events§				
Any adverse event	4,117	33.0 (32.2–33.9)	2,229	17.8 (17.2–18.5)
Any grade 3 adverse event	246	2.0 (1.7–2.2)	158	1.3 (1.1–1.5)
Adverse event related to vaccine or placebo	3,105	24.9 (24.1–25.7)	731	5.8 (5.4–6.3)
Grade 3 adverse event related to vaccine or placebo	112	0.9 (0.7–1.1)	25	0.2 (0.1–0.3)
Serious adverse events				
Any serious adverse event	522	4.2 (3.8–4.6)	506	4.0 (3.7–4.4)
Serious adverse event related to vaccine or placebo	10	0.1 (0.0–0.1)	7	0.1 (0.0–0.1)
Fatal serious adverse event	49	0.4 (0.3–0.5)	58	0.5 (0.4–0.6)
Fatal serious adverse event related to vaccine or placebo	3¶	—	3¶	—
Potential immune-mediated disease				
Any potential immune-mediated disease	40	0.3 (0.2–0.4)	34	0.3 (0.2–0.4)
Potential immune-mediated disease related to vaccine or placebo	7	0.1 (0.0–0.1)	5	<0.1 (0.0–0.1)

Subunit/VLP-Based Vaccines

RSVpreF (Abrysvo)

bivalent RSV prefusion F protein–based (RSVpreF) vaccine contains stabilized F from both subgroups A and B for maximal protection against circulating RSV strains

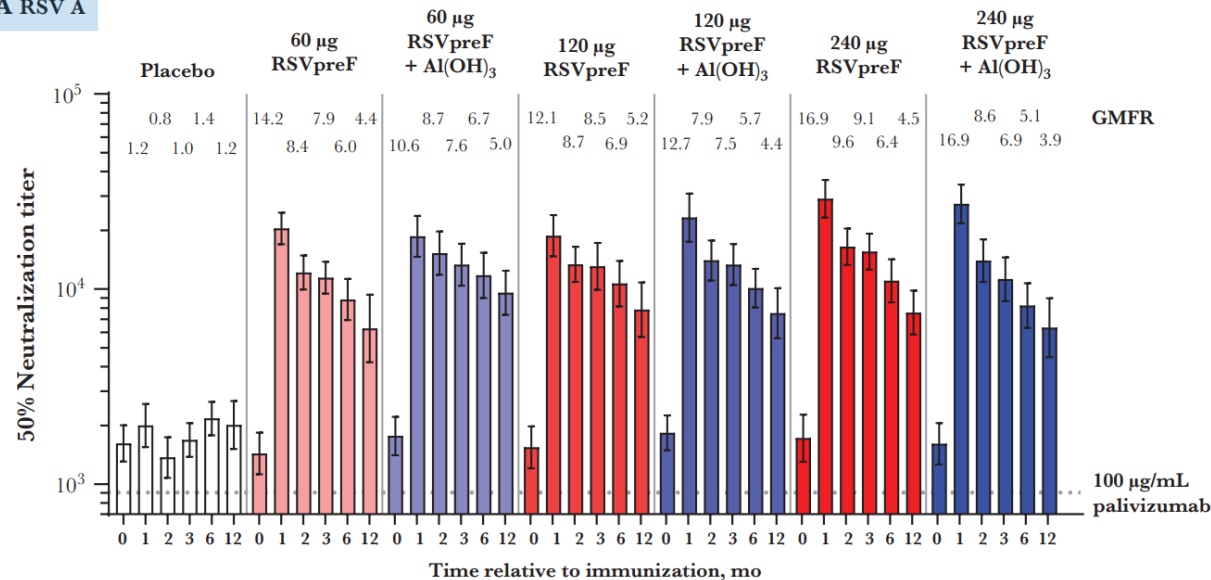
RSVpreF vaccine

- **A Randomized Phase 1/2 Study of a Respiratory Syncytial Virus Prefusion F Vaccine**
- April 2018 ~ November 2019 (US)
- Formulation: 60- μ g, 120- μ g, 240- μ g dose
- Phase 1, sentinel cohort (n=168): 18–49 or 50–85 years old
- Phase 2, expanded cohort (n=1014): 18–49 or 65–85 years old
- No serious adverse events related to vaccine

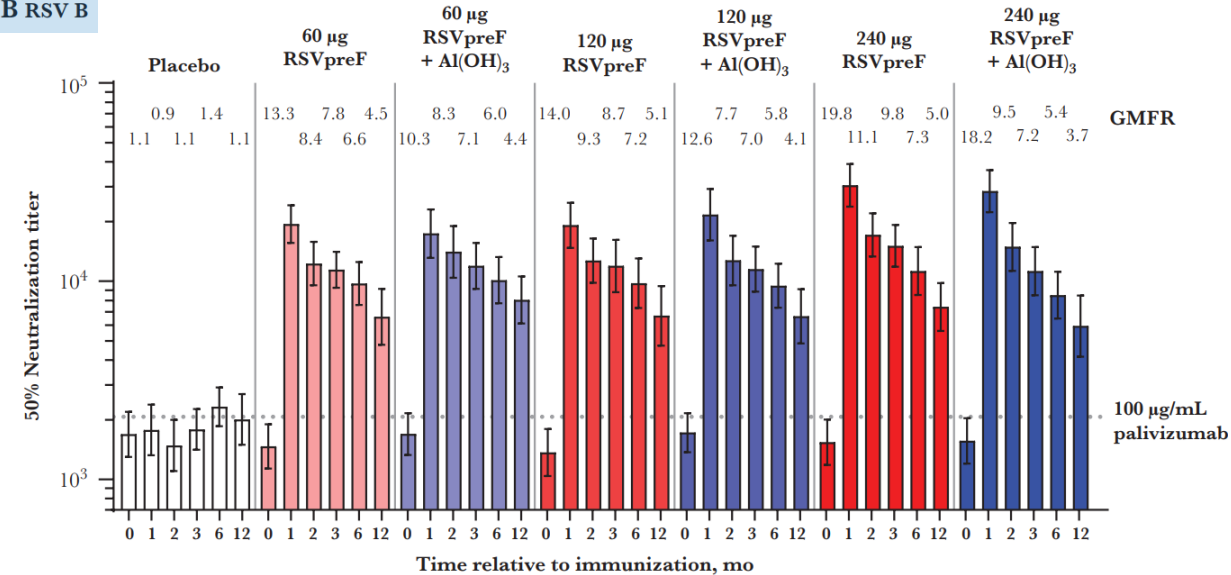
RSVpreF vaccine

- RSV neutralization titer through 12 months

A RSV A



B RSV B



RSVpreF formulations were safe, well tolerated, and induced robust neutralizing responses in adults.

RSVpreF vaccine

- **Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults**
- RENOIR trial (by Pfizer)
- **interim analysis**, ongoing, **phase 3**, multicenter, double-blind
- ≥ 60 years (n=34,284 , 1:1 ratio)
- 120 μg RSVpreF vaccine (A 60 μg and B 60 μg) vs. placebo
- August 31, 2021 ~ July 14, 2022

RENOIR trial

older population at risk for RSV-related illness

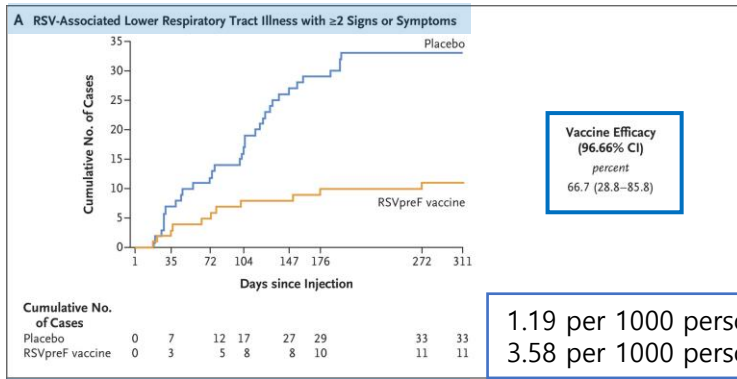
Efficacy Assessments

- 1st primary end point
 - preventing RSV-associated LRT illness with ≥ 2 signs or symptoms lasting more than 1 day and RSV infection
- 2nd primary end point
 - preventing RSV-associated LRT illness with ≥ 3 signs or symptoms lasting more than 1 day and RSV infection

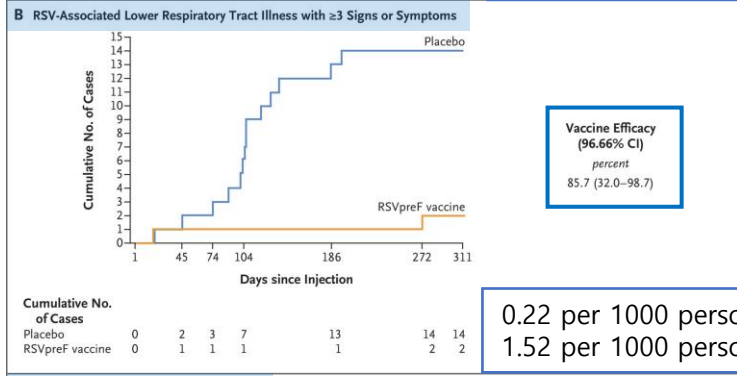
Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Safety Population).*

Characteristic	RSVpreF Vaccine (N=17,215)	Placebo (N=17,069)	Total (N=34,284)
Age			
Mean — yr	68.3±6.14	68.3±6.18	68.3±6.16
Median (range) — yr	67 (59–95)	67 (60–97)	67 (59–97)
Age group — no. (%)			
60–69 yr†	10,757 (62.5)	10,680 (62.6)	21,437 (62.5)
70–79 yr	5,488 (31.9)	5,431 (31.8)	10,919 (31.8)
≥ 80 yr	970 (5.6)	958 (5.6)	1,928 (5.6)
Male sex — no. (%)	8,800 (51.1)	8,601 (50.4)	17,401 (50.8)
Prespecified high-risk condition — no. (%)			
≥ 1 Prespecified high-risk condition	8,867 (51.5)	8,831 (51.7)	17,698 (51.6)
Current tobacco use	2,642 (15.3)	2,571 (15.1)	5,213 (15.2)
Diabetes	3,224 (18.7)	3,284 (19.2)	6,508 (19.0)
Lung disease‡	1,956 (11.4)	2,040 (12.0)	3,996 (11.7)
Heart disease¶	2,221 (12.9)	2,233 (13.1)	4,454 (13.0)
Liver disease	335 (1.9)	329 (1.9)	664 (1.9)
Renal disease	502 (2.9)	459 (2.7)	961 (2.8)
≥ 1 Chronic cardiopulmonary condition	2,595 (15.1)	2,640 (15.5)	5,235 (15.3)
Asthma	1,541 (9.0)	1,508 (8.8)	3,049 (8.9)
COPD	1,012 (5.9)	1,080 (6.3)	2,092 (6.1)
Congestive heart failure	293 (1.7)	307 (1.8)	600 (1.8)
No prespecified high-risk condition — no. (%)	8,348 (48.5)	8,238 (48.3)	16,586 (48.4)

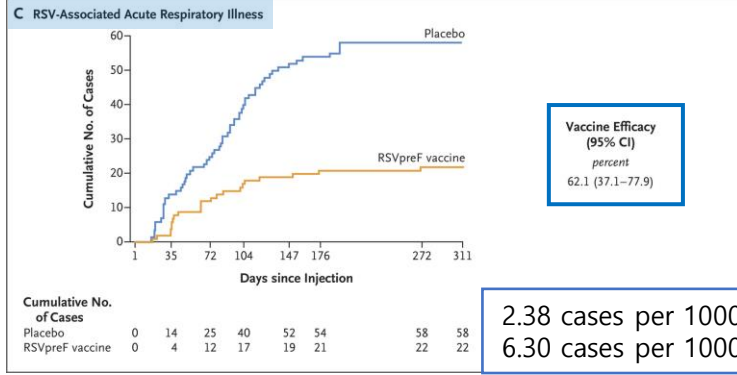
Vaccine Efficacy



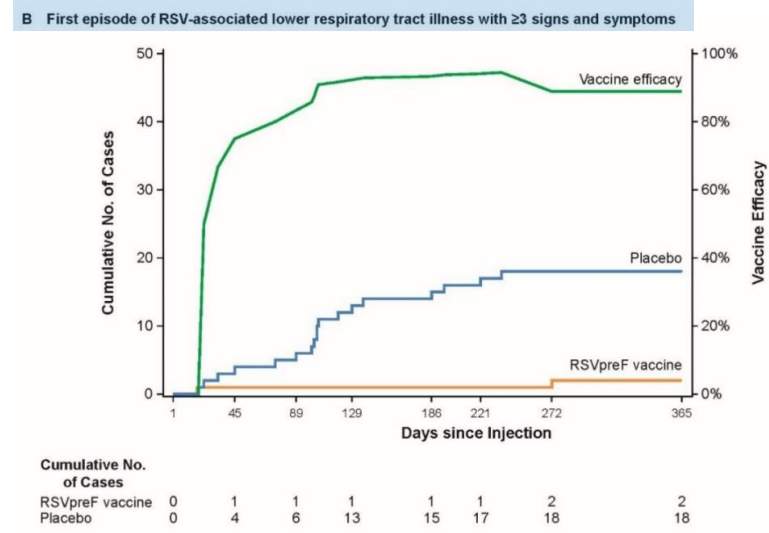
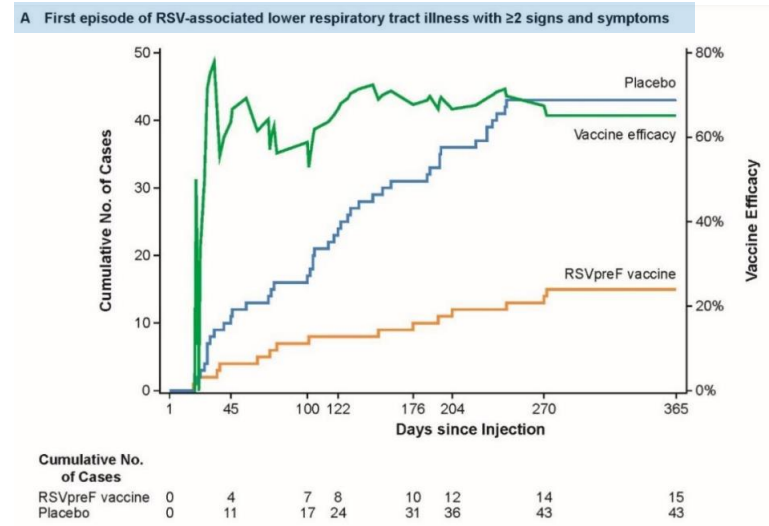
1.19 per 1000 person-years
3.58 per 1000 person-years



0.22 per 1000 person-years
1.52 per 1000 person-years



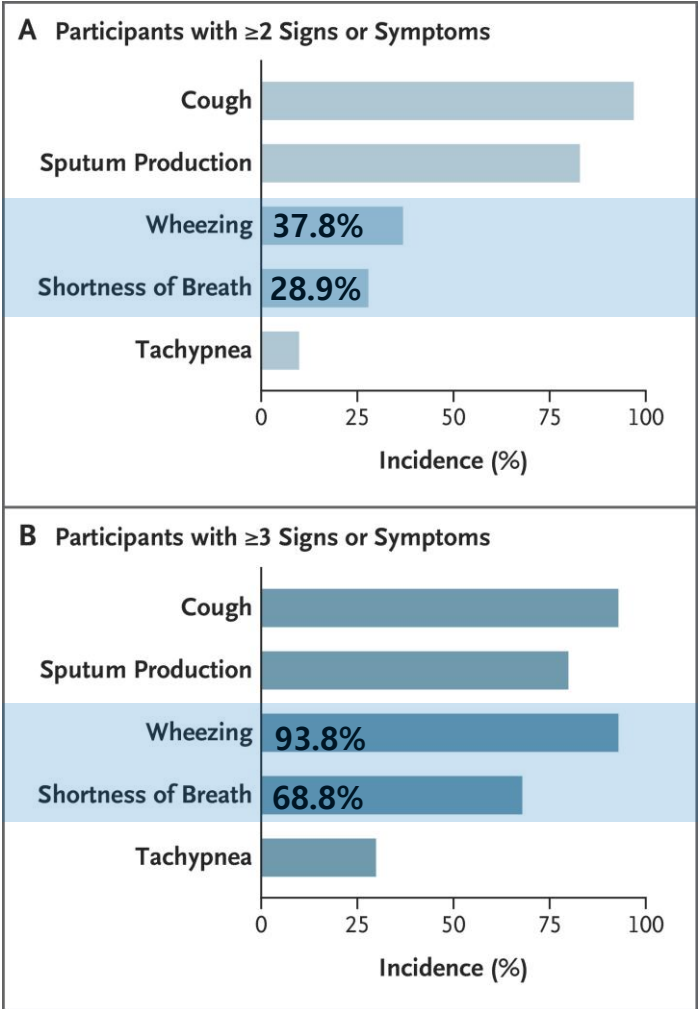
2.38 cases per 1000 person-years
6.30 cases per 1000 person-years



Vaccine efficacy: maintained through the end of the first RSV season

RENOIR trial

Incidence of signs or symptoms



Adverse Events

- More local reactions in vaccine group: 12% vs. 7%
- Similar systemic events: 27% vs. 26%

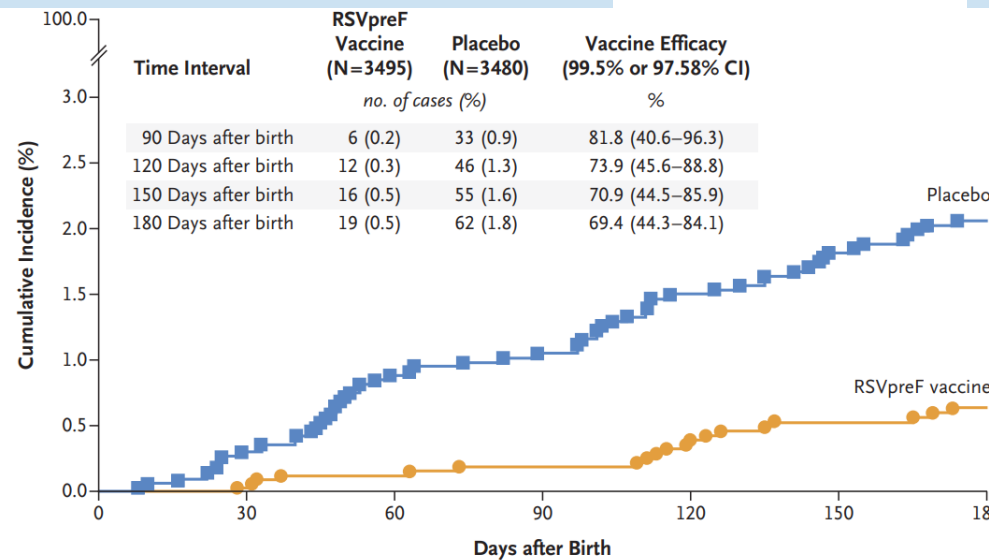
Table S7. Participants reporting at least 1 adverse event

Adverse event	RSVpreF	Placebo
	(N*=17,215)	(N*=17,069)
	n† (%)	n† (%)
Any adverse event (to 1 month after dose 1)	1544 (9.0)	1453 (8.5)
Related‡	239 (1.4)	163 (1.0)
Severe	65 (0.4)	51 (0.3)
Life-threatening	24 (0.1)	19 (0.1)
Immediate (within 30 minutes of vaccination)	37 (0.2)	31 (0.2)
Any serious adverse event (through data cutoff)§	396 (2.3)	387 (2.3)
Any adverse event leading to discontinuation (through data cutoff)	10 (<0.1)	6 (<0.1)
Related‡	0	0
Adverse event leading to death (through data cutoff)	52 (0.3)	49 (0.3)
Related‡	0	0
Newly diagnosed chronic medical condition (through data cutoff)¶	301 (1.7)	313 (1.8)

Maternal RSVpreF vaccination

- MATISSE trial (phase 3): maternal RSVpreF vaccination in preventing RSV-associated LRT illness in infants

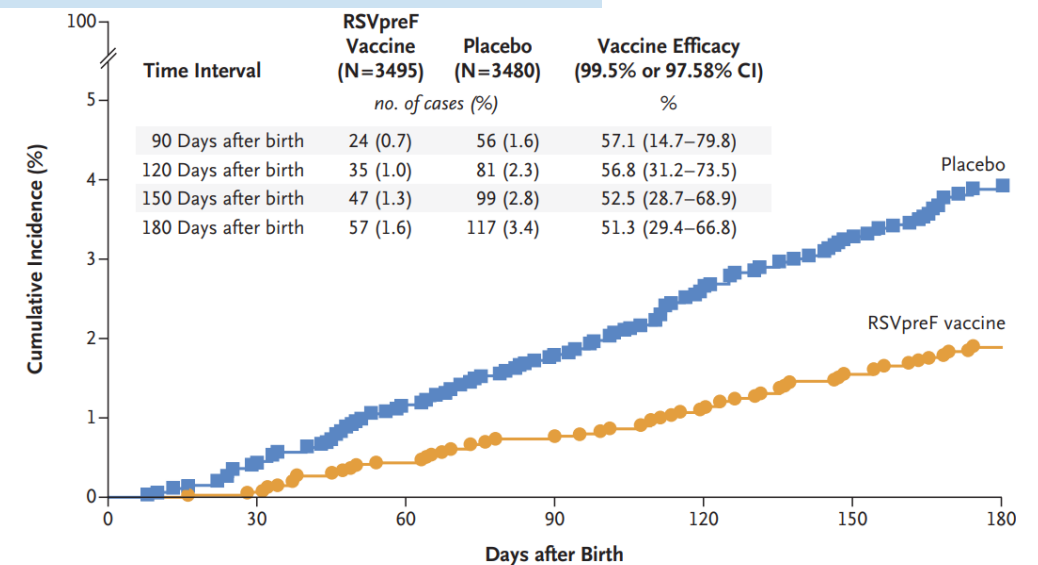
A Medically Attended Severe RSV-Associated Lower Respiratory Tract Illness



No. at Risk

	0	30	60	90	120	150	180
Placebo	3480	3292	2973	2899	2833	2776	274
RSVpreF vaccine	3495	3349	3042	2981	2916	2867	282

B Medically Attended RSV-Associated Lower Respiratory Tract Illness



No. at Risk

	0	30	60	90	120	150	180
Placebo	3480	3288	2964	2879	2804	2738	2700
RSVpreF vaccine	3495	3348	3035	2968	2898	2845	2792

mRNA Vaccines

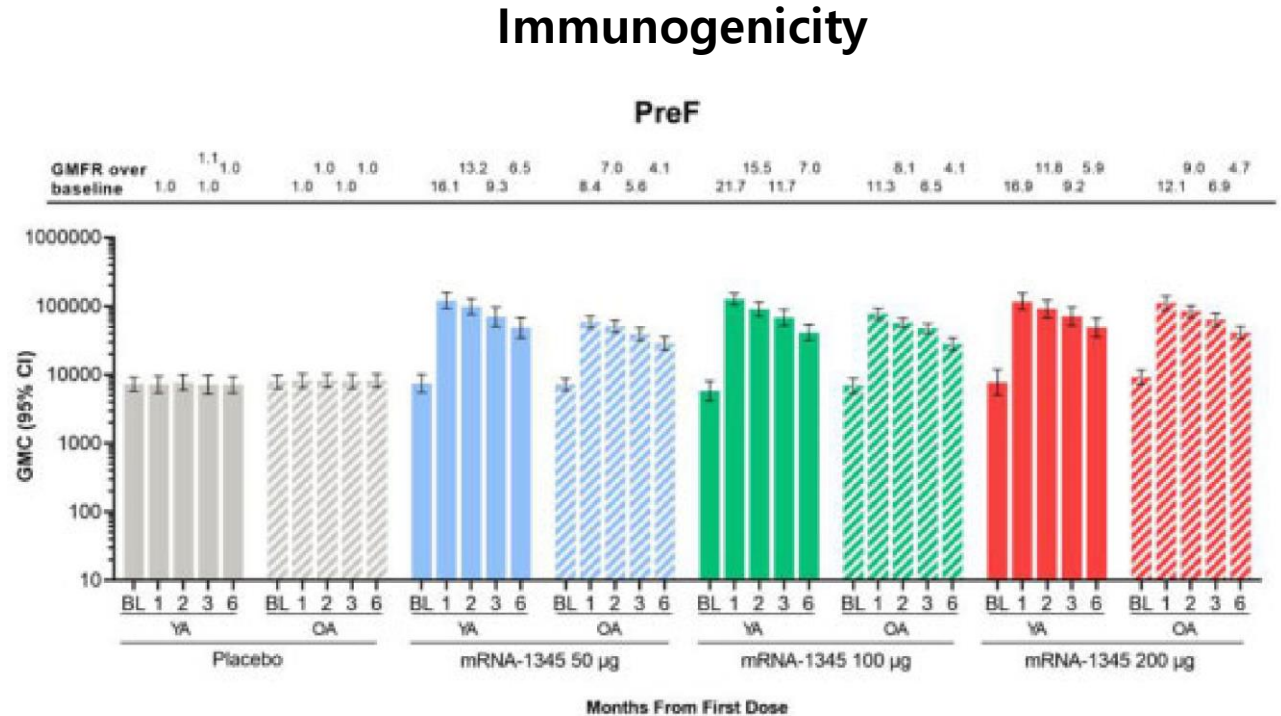
mRNA-1345

encoding the membrane-anchored RSV-F glycoprotein
derived from an RSV A strain

mRNA-1345

- phase 1
- Younger adults (YA; 18-49 years, n=74)
- Older adults (OA; 65-79 years, n=202)
- mRNA-1345 (50, 100, 200 µg) vs. placebo

- mRNA-1345
 - boosted antibody titers through month 1 in YA and OA
 - comparable immunogenicity observed across age groups
 - vaccine induced neutralizing antibodies persisted through 6 months



mRNA-1345

- **Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults**
- ConquerRSV (by Moderna)

- phase 2–3 trial
- mRNA-1345 (50 µg) vs. placebo
- November 17, 2021 ~ October 31, 2022
- ≥60 years (n=35,541, 1:1 ratio)

Vaccine Efficacy Assessments

Efficacy Assessments

Primary efficacy objectives

- 1st episode of RSV-associated LRT disease (~12 m)
 - with ≥ 2 lower respiratory signs or symptoms
 - with ≥ 3 lower respiratory signs or symptoms

Secondary objectives

- 1st episode of RSV-associated acute respiratory disease (~12 m) with ≥ 1 symptom
- 1st episode of RSV-associated LRT according to RSV subtype (A or B)

Success criterion for efficacy: lower boundary of the alpha-adjusted CI **>20%**

Safety Assessments

- solicited local and systemic adverse reactions for 7 days after injection
- Unsolicited adverse events: through 28 days after injection

ConquerRSV study

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Safety Analysis Population).*

Characteristic	mRNA-1345 (N=17,734)	Placebo (N=17,679)	Total (N=35,413)
Age at enrollment			
Mean — yr	68.1±6.2	68.1±6.2	68.1±6.2
Median (range) — yr	67 (60–95)	67 (60–96)	67 (60–96)
Distribution — no. (%)			
60–69 yr	11,281 (63.6)	11,222 (63.5)	22,503 (63.5)
70–79 yr	5,474 (30.9)	5,460 (30.9)	10,934 (30.9)
≥80 yr	979 (5.5)	997 (5.6)	1,976 (5.6)
Female sex — no. (%)	8,658 (48.8)	8,711 (49.3)	17,369 (49.0)
Race or ethnic group — no. (%)†			
White	11,240 (63.4)	11,216 (63.4)	22,456 (63.4)
Black	2,203 (12.4)	2,158 (12.2)	4,361 (12.3)
Asian	1,540 (8.7)	1,529 (8.6)	3,069 (8.7)
Other	2,682 (15.1)	2,671 (15.1)	5,353 (15.1)
Unknown or not reported	69 (0.4)	105 (0.6)	174 (0.5)
Frailty status — no. (%)‡			
Fit	13,512 (76.2)	13,354 (75.5)	26,866 (75.9)
Vulnerable	2,828 (15.9)	2,899 (16.4)	5,727 (16.2)
Frail	997 (5.6)	1,017 (5.8)	2,014 (5.7)
Missing data	397 (2.2)	409 (2.3)	806 (2.3)
No. of coexisting conditions of interest — no. (%)§			
0	12,496 (70.5)	12,551 (71.0)	25,047 (70.7)
≥1	5,238 (29.5)	5,128 (29.0)	10,366 (29.3)
Risk factors for lower respiratory tract disease — no. (%)			
Present	1,218 (6.9)	1,230 (7.0)	2,448 (6.9)
Congestive heart failure	205 (1.2)	201 (1.1)	406 (1.1)
COPD	960 (5.4)	978 (5.5)	1,938 (5.5)
Congestive heart failure and COPD	53 (0.3)	51 (0.3)	104 (0.3)
Absent	16,516 (93.1)	16,449 (93.0)	32,965 (93.1)

Efficacy

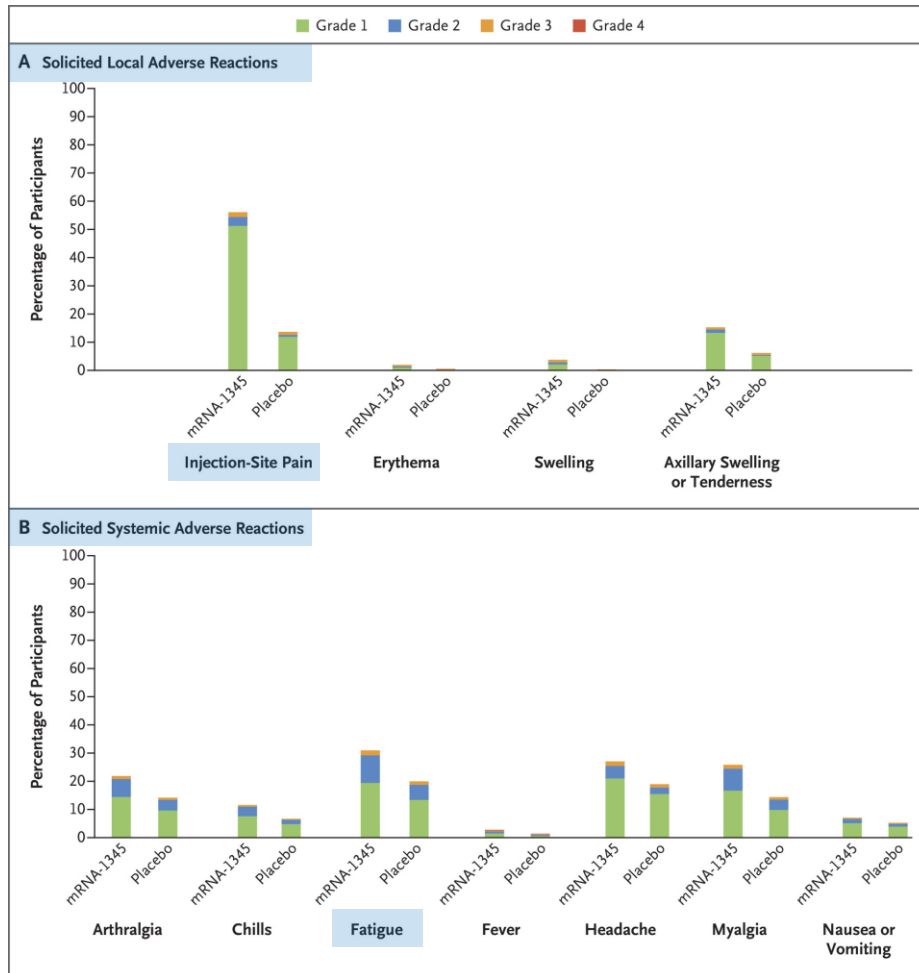
Table 2. Vaccine Efficacy against RSV-Associated Lower Respiratory Tract Disease with at Least Two or at Least Three Signs or Symptoms (Per-Protocol Efficacy Population).*

End Point	mRNA-1345		Placebo		Vaccine Efficacy (CI)†
	no. of participants	no. of events	no. of participants	no. of events	%
RSV-associated lower respiratory tract disease with ≥2 signs or symptoms‡					
Overall	17,572	9	17,516	55	83.7 (66.0 to 92.2)
RSV subtype					
RSV A	17,572	3	17,516	36	91.7 (73.0 to 97.4)
RSV B	17,572	6	17,516	19	68.5 (21.1 to 87.4)
Age group					
60–69 yr	11,168	8	11,118	33	76.0 (48.0 to 88.9)
70–79 yr	5,440	1	5,416	22	95.4 (65.9 to 99.4)
≥80 yr	964	0	982	0	NE (NE to NE)
RSV-associated lower respiratory tract disease with ≥3 signs or symptoms§					
Overall	17,572	3	17,516	17	82.4 (34.8 to 95.3)
RSV subtype					
RSV A	17,572	1	17,516	10	90.0 (22.0 to 98.7)
RSV B	17,572	2	17,516	7	71.5 (–37.0 to 94.1)
Age group					
60–69 yr	11,168	3	11,118	11	72.9 (2.8 to 92.4)
70–79 yr	5,440	0	5,416	6	100 (NE to 100)
≥80 yr	964	0	982	0	NE (NE to NE)

lower boundary of the CI >20%

ConquerRSV study

Adverse Events



- Solicited local adverse reactions
 - No grade 4
- Solicited systemic adverse reactions
 - grade 4 fever: 0.2% in each group

Summary

- Stabilized preF: key vaccine antigen for preventing RSV

- Arexvy (RSVPreF3 OA, GSK) ≥60 years
- Abrysvo (RSVpreF, Pfizer) ≥60 years, pregnant women
- mRNA-1345

