STEFANIA MAGGI

La prevenzione vaccinale nelle infezioni da virus sinciziale respiratorio

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

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Disclosures

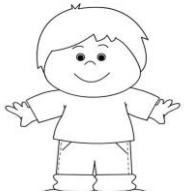
S. Maggi fa parte di advisory board e/o ha ricevuto fondi di ricerca da:

GSK, Pfizer, Merck, Sanofi, Takeda, Novavax and Janssen

Outline

- Epidemiology and clinical aspects of RSV infections in older adults
- RSV vaccines
- Future perspectives

Susceptibility to RSV infection



Virtually all children will have been infected by RSV by age 2

Immune response after natural infection is incomplete and short-lived:
reinfections occur throughout life

Older adults are at high risk of severe RSV infection and, as for all infections,
those with underlying medical conditions are at greater risk

Openshaw PJM *et al. Annu Rev Immunol* 2017;35:501–532; 3. Walsh E *et al*. *Clin Chest* Med 2017;38(1):29–36; 4. Branche AR *et al. Clin Infect Dis* 2022;74(6):1004-1011;

Clinical signs and symptoms

Common clinical symptoms are similar to other viral respiratory pathogens (cough, nasal congestion and rhinorrea, sore throat and dyspnea), but older frail patients might have atypical presentation:

Blunted or no fever

Unexplained hypoxia

Tachycardia, tachypnea

Delirium

Fatigue, functional decline or falls

Talbot et al. *Clinical Infectious Diseases*. 2010

Distribuzione di casi di ILI e RSV in pazienti ambulatoriali per sesso, età e presenza di patologie mediche.

	Total	
	ILI cases	RSV-positive
No. of cases; % (95% CI)	1047; 100%	135; 12.9% (11%-15.1%)
No. of males; % (95% CI)	551; 52.6% (49.6%-55.6%)	77; 13.9% (11.3%-17.1%)
Median age; IQR (range), y	36; 43.4 (10.1-.5)	8.3; 49 (3-52)
No. of cases with underlying medical conditions; % (95% CI)	224; 21.4% (19%-24.0%)	31; 13.8% (9.9%-19%)
No. of cases by age group; % (95% CI)		
0-5 y	183; 17.5% (15.3%-19.9%)	51; 27.8% (23.4%-35.3%)
6-15 y	158; 15.1% (13%-17.4%)	30; 18.9% (13.1%-25.1%)
16-45 y	332; 31.7% (28.9%-34.6%)	16; 4.8% (3%-7.7%)
46-65 y	249; 23.8% (21.3%-26.4%)	23; 9.3% (6.2%-13.5%)
>65 y	125; 11.9% (10.1%-14%)	15; 12% (7.4%-18.9%)

Dalla sorveglianza influenzale influnet di quattro stagioni invernali (dal 2014-15 al 2017-18) in Lombardia

A total of 12.9% (135/1047) of samples were positive to RSV that was mostly detected among children ≤5 years (51/183, 27.8%) and those aged 6 to 15 years (30/158, 18.9%), whereas elderly >65 years accounted for 12% of RSV cases (15/125).

The median start of RSV epidemic was in the end of November, with a peak in mid-February and a width of nearly 4 months, almost overlapping seasonal influenza epidemic·

L.Pellegrinelli et al. J Med Virol. 2020;92:2999–3006.

Disease burden estimates of RSV in adults with comorbidities:
A systematic review and meta-analysis

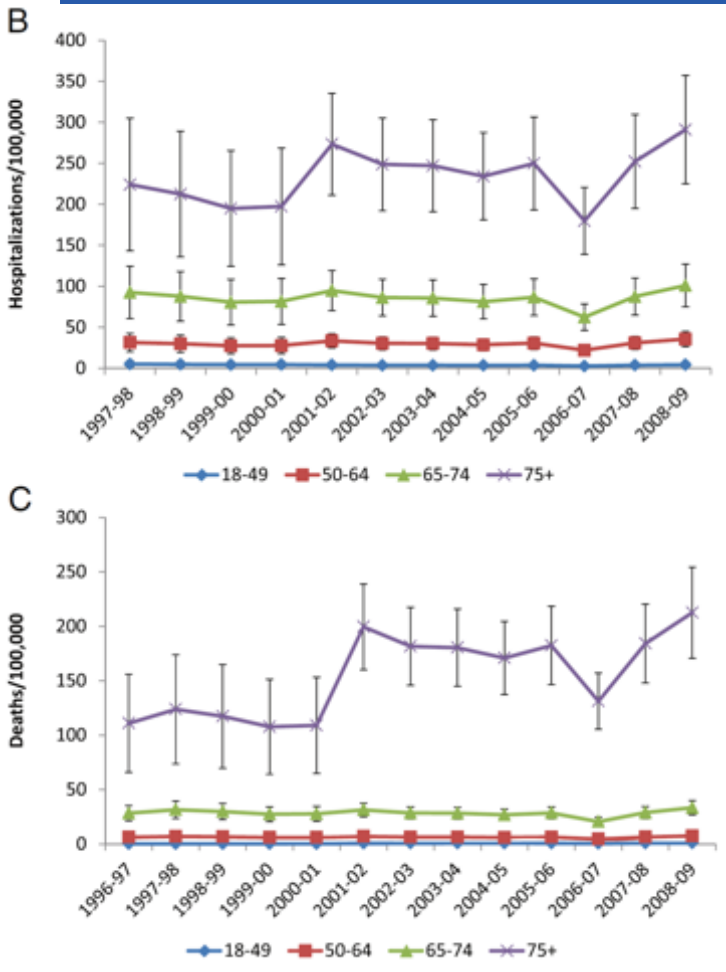
	Older Adults	OA with comorbidities
Annual incidence rates/1000	6.7	37.6
Hospitalisation rates/1000	4.8	13.2 (with COPD or HF)
In-hospital case fatality rate/100	1.6	11.7

Four-fold increase of experiencing RSV-ARI among patients with any comorbidity compared to those without, **RSV affects the most vulnerable**

- Adults age 65 and older, primarily institutionalised
- People of any age with underlying medical conditions, including: chronic lung disease or moderate to severe asthma, previous pneumonia, serious heart conditions, compromised immune function

ARI, acute respiratory infection; COPD, chronic obstructive ulmonary disease; HF, heart failure; OA, older adults; RSV, Shi et al. *JID*. 2021; Shi et al. *JID*. 2020

Modeling estimates of the burden of RSV infection in adults & elderly in UK



- 79% of hospitalization and 93% of deaths occurred in persons >65 yrs
- However, **older individuals at high risk** (due to chronic cardiac and respiratory diseases, diabetes, immune suppression, chronic liver disease, stroke) were four-fold more likely to be hospitalized for RSV and two-fold more likely to die compared to low-risk older individuals

Fleming et al. *BMC*. 2015

Incidence of RSV infection among hospitalized adults by underlying medical condition, 2017–2020

	Incidence Rate	Incidence Rate	Rate Ratio (95% CI)
Age-groups	COPD	No COPD	
18-49 years	24.87	7.83	3.18 (0.99-10.17)
50-64 years	204.76	32.25	6.35 (2.00-20.11)
≥ 65 years	1077.36	80.32	13.41 (4.29-41.98)
Age-groups	Diabetes	No Diabetes	
18-49 years	65.39	5.86	11.16 (3.45-36.13)
50-64 years	116.77	34.79	3.36 (1.06-10.63)
≥ 65 years	501.82	77.93	6.44 (2.06-20.17)
Age-groups	CHF	No CHF	
20-39 years	295.23	8.88	33.23 (10.14-108.90)
40-59 years	485.84	25.87	18.78 (5.92-59.55)
60-79 years	688.58	90.24	7.63 (2.43-23.93)

CHF, chronic heart failure; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; RSV, respiratory syncytial virus.
Branche et al. *CID*. 2022

Risk Factors for Hospitalization With RSV

Risk Factor	Odds Ratio	P Value
Male	2.4	0.17
Pulmonary disease	4.0	0.03
Coronary artery disease	1.0	NS
Congestive heart failure	1.9	NS
Diabetes	0.9	NS
Functional score (per integer 1–12)	1.7	0.001
Serum Neutralizing titer <10 $\log_2$	5.9	0.006

Walsh et al. *J Infect Dis*. 2004

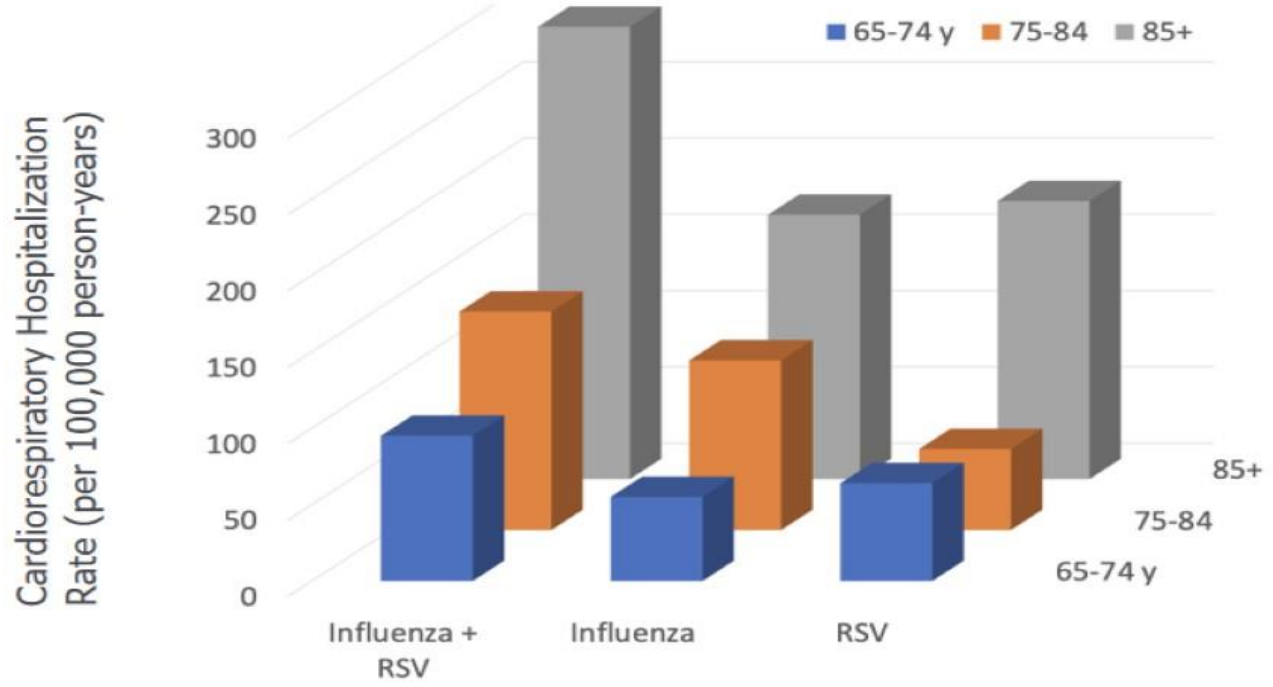
Burden of RSV in Older Adults

Retrospective cohort study

2,909,106 long-term care facility residents age ≥ 65 years

Follow-up period: 2011 to 2017 (6 respiratory seasons)

Attributable cardiorespiratory hospitalization burden from RSV and influenza was similar



y, years.

Bosco E, et al. JAMA Netw Open. 2021;4:e2111806.

RSV in Older Adults

- RSV and influenza are similar for ICU use and mortality

14 days vs 8 days	15% vs 12%	8% vs 7%
Longer length of stay	Similar rate of ICU use	Similar mortality rate

- RSV accounts for 11% of COPD and pneumonia admissions, 7% of asthma admissions, and 5% of CHF admissions
- RSV is similar to influenza in terms of the proportion of hospitalized patients who have a pneumonia diagnosis or require ventilator support

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

Falsey AR, et al. N Engl J Med. 2005;352:1749-1759.

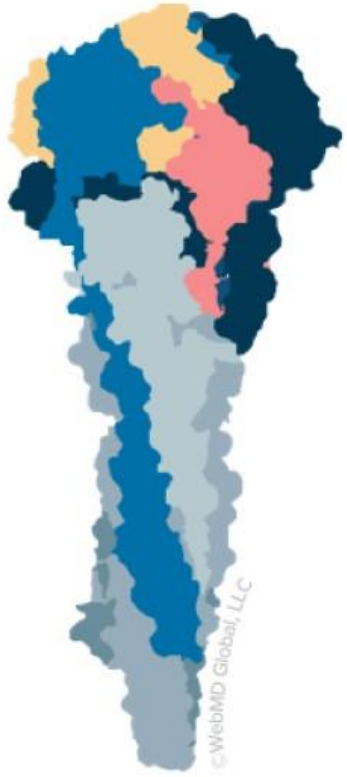
Outline

- Epidemiology and clinical aspects of RSV infections in older adults
- RSV vaccines
- Future persectives

Pre-Fusion Protein (cont)

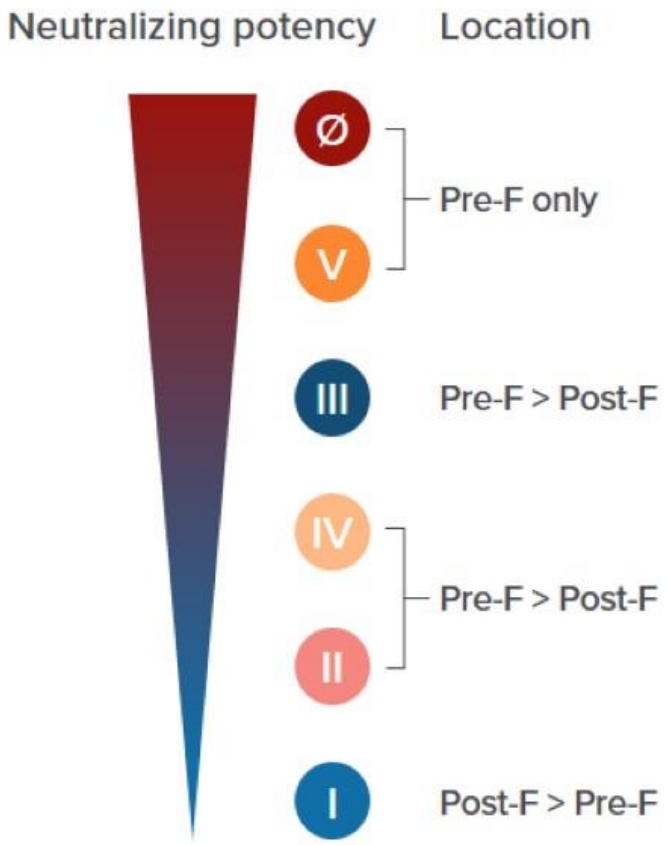
The **neutralization sensitivity** of each antigenic site is **directly related to** exclusive or preferential binding to **the pre-F conformation**[a]

Prefusion RSV F



Postfusion RSV F

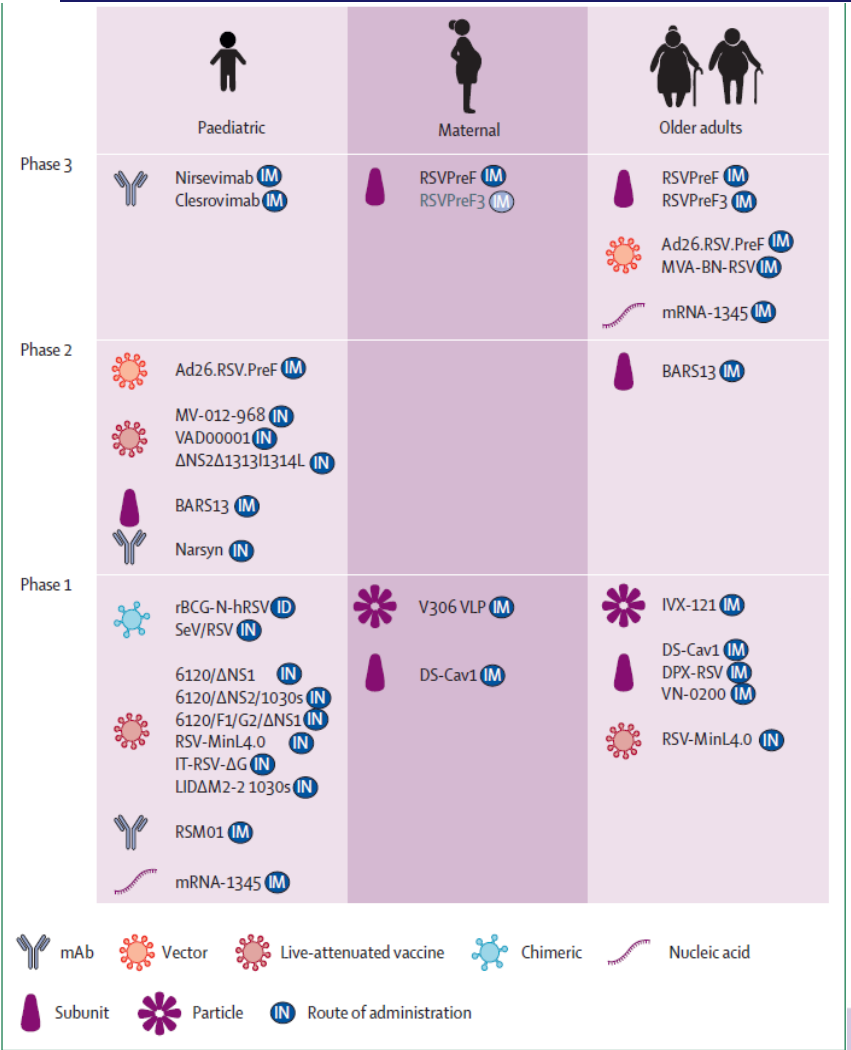
Current opinion in virology



F, fusion.

Graham BS. Curr Opin Virol. 2017;23:107-112.

RSV vaccines by target population



Older adults may have different levels of preexisting immunity to RSV,
therefore the use of a live-attenuated vaccine is not recommended

Subunit and vector-based are the preferable vaccine modalities,
because they allow for increased antigen dose compared to whole virus vaccines

Vaccines in phase 3:
Subunit-based vaccines are composed of purified viral protein (preF) administered alone or with adjuvant (Pfizer and GSK)
They boost Ab responses in seropositive populations (such as older adults)

Vector-based Vaccines are created from components of RSV inserted into a carrier (Bavarian Nordic and Janssen)
They induce immune responses to both the inserted and carrier sequences

mRNA vaccine (Moderna)

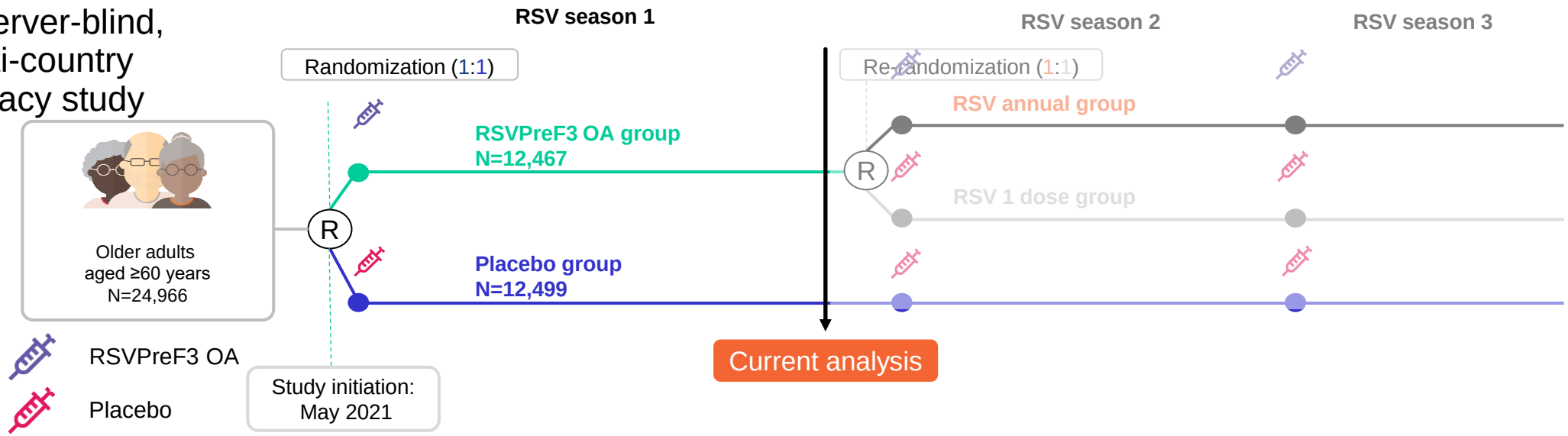
Mazur et al, Lancet 2022

How do these vaccines compare?

- All vaccines target preF
- Different mechanisms of action (subunit with/without adjuvant, vector, mRNA)
- Different stage of development (5 vaccines reach phase 3)
- Rich pipeline

Ongoing AReSVi-006 Phase 3 trial design

A randomized, placebo-controlled, observer-blind, multi-country efficacy study



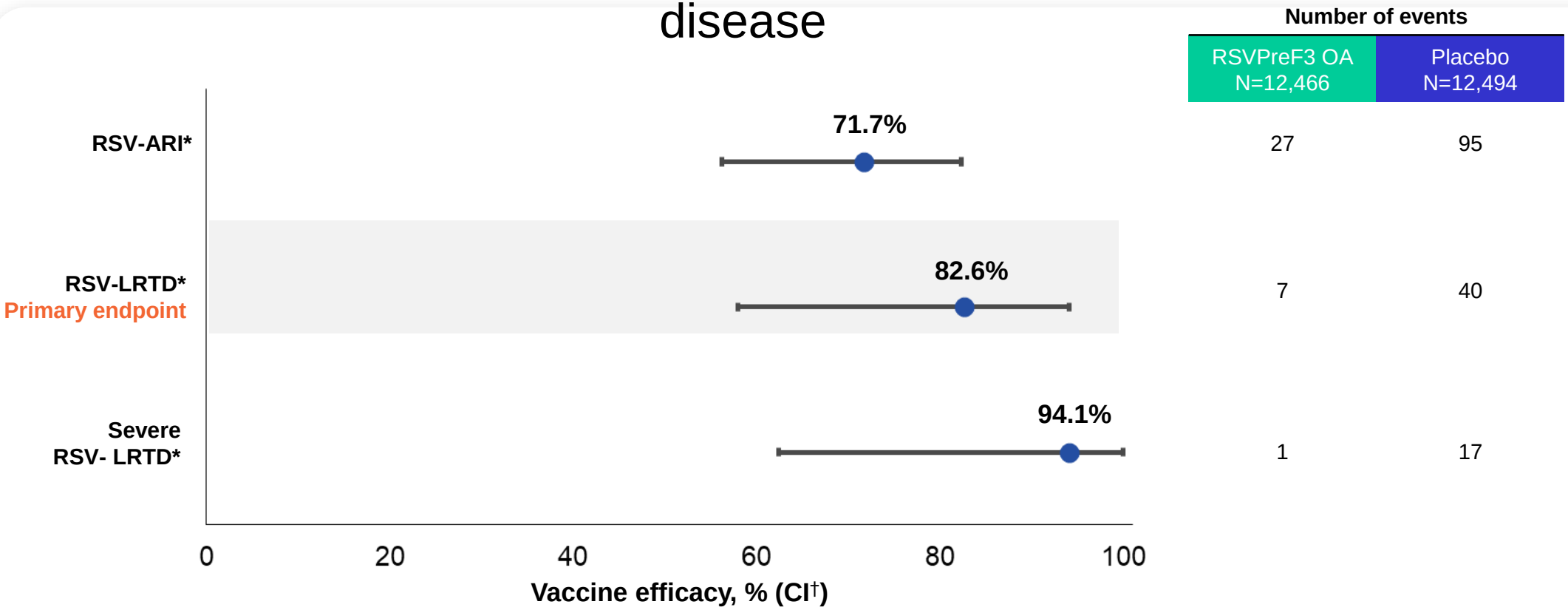
Primary endpoint: To demonstrate the efficacy of RSVPreF3 OA vaccine in the prevention of RSV† LRTD* in adults ≥60 years of age during the first season

All RSV-LRTD cases were adjudicated by an independent external adjudication committee

- LRTD defined as ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign OR ≥3 lower respiratory symptoms for ≥24 hours; †RT-PCR confirmed.. LRTD, lower respiratory tract disease; D, day.

https://www.cdc.gov/vaccines/acip/meetings/slides-2022-10-19-20.html

Consistently high vaccine efficacy across the full spectrum of RSV disease



*LRTD defined as ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign or ≥3 lower respiratory symptoms for ≥24 hours; severe LRTD defined as LRTD with ≥2 LRTD signs or assessed as severe by the Investigator; ARI defined as ≥2 respiratory symptoms/signs for ≥24 hours or ≥1 respiratory symptom/sign + 1 systemic symptom/sign for ≥24 hours; All RSV cases confirmed by RT-PCR; †96.95% CI for primary endpoint, 95% for all secondary endpoints. ARI, acute respiratory infection; CI, confidence interval; LRTD, lower respiratory tract disease; RT-PCR, reverse-transcriptase polymerase chain reaction

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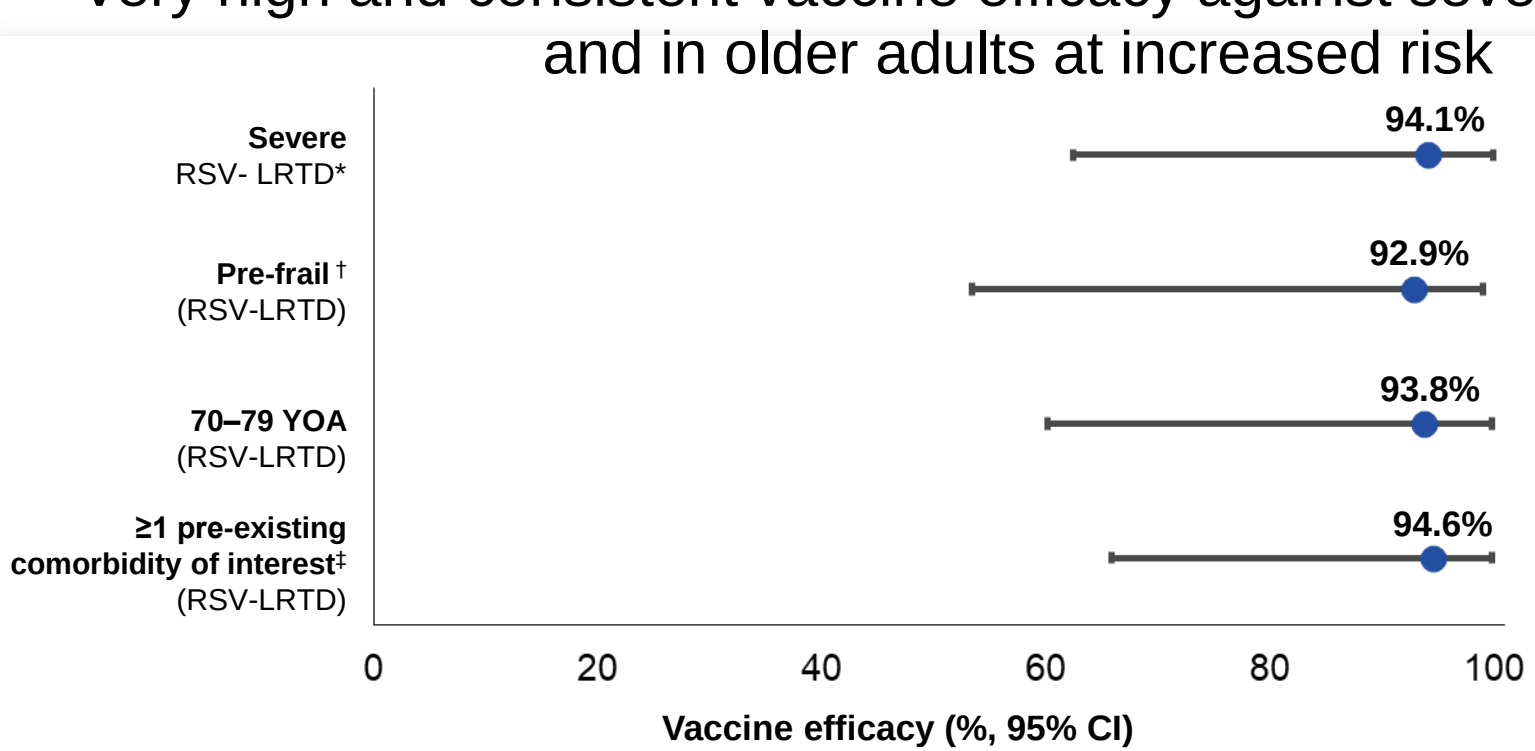
Very high and consistent vaccine efficacy against severe RSV disease and in older adults at increased risk



	Number of events / N	
	RSVPreF3 OA	Placebo
Severe RSV- LRTD*	1 / 12,466	17 / 12,494
Pre-frail † (RSV-LRTD)	1 / 4,792	14 / 4,778
70–79 YOA (RSV-LRTD)	1 / 4,487	16 / 4,487
≥1 pre-existing comorbidity of interest‡ (RSV-LRTD)	1 / 4,937	18 / 4,861

Due to too few cases observed in adults aged 80 years and older, and those considered frail we cannot conclude on VE.

- ≥80 YOA (number of events / N): **RSVPreF3 OA** (2 / 1,016); **Placebo** (3 / 1,028)
- Frail (number of events / N): **RSVPreF3 OA** (1 / 189); **Placebo** (1 / 177)

*LRTD defined as ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign or ≥3 lower respiratory symptoms for ≥24 hours; severe LRTD defined as LRTD with ≥2 LRTD signs or assessed as severe by the Investigator. All RSV cases confirmed by RT-PCR;†Frailty was assessed by a gait speed test.‡COPD, asthma, any chronic respiratory/pulmonary disease, diabetes type 1 or type 2, congestive heart failure, advanced liver or renal disease; CI, confidence interval; LRTD, lower respiratory tract disease; RT-PCR, reverse-transcriptase polymerase chain reaction; VE, vaccine efficacy;

https://www.cdc.gov/vaccines/acip/meetings/slides-2022-10-19-20.html

RENOIR Study Design I

240 study sites in 7 countries

Argentina
Canada
Finland
Japan
Netherlands
South Africa
U.S.

Targeted enrollment

Up to **40,000** participants
Adults **≥ 60 years**

Randomized 1:1 to receive RSVpreF 120 µg or placebo

Stratified by age group
60-69 years
70-79 years
≥ 80 years

Key inclusion/exclusion criteria

☑ Healthy or with stable chronic conditions

☒ Immunocompromised persons with serious chronic disorders (e.g., metastatic cancer, ESRD)

Abbreviations: ESRD, end-stage renal disease

https://www.cdc.gov/vaccines/acip/meetings/slides-2022-10-19-20.html

RSVpreF was highly efficacious against RSV-LRTI during the first season

Both primary efficacy endpoints met licensure criteria

Total cases ≥ 2 RSV-LRTI	Case split RSVpreF/Placebo	VE	96.66% CI[1]
44	11/33	66.7%	(28.8%, 85.8%)

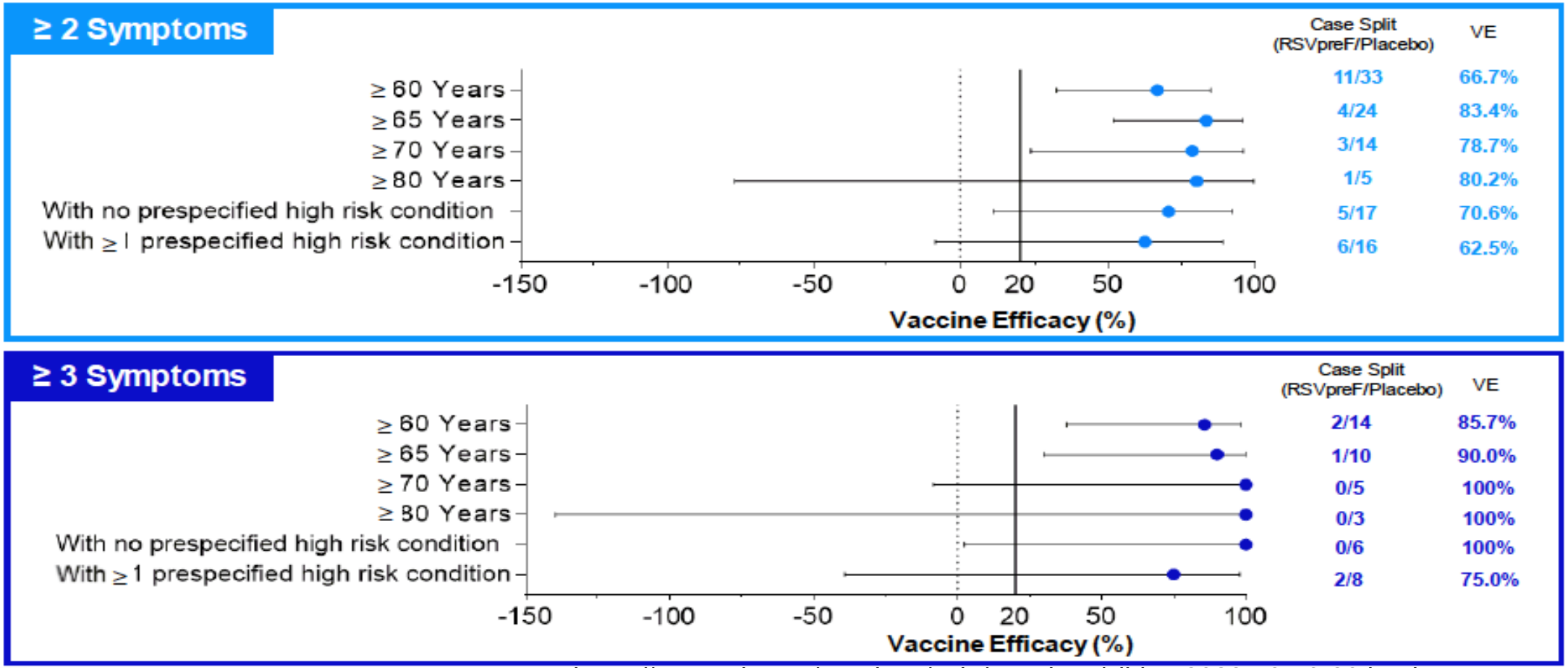
Total cases ≥ 3 RSV-LRTI	Case split RSVpreF/Placebo	VE	96.66% CI[1]
16	2/14	85.7%	(32.0%, 98.7%)

[1]CI obtained using the conditional exact test based on the binomial distribution of P, adjusted by Pocock error spending for interim analysis (alpha = 3.34%)

Abbreviations: CI, confidence interval; RSV-LRTI, lower respiratory tract illness due to respiratory syncytial virus; VE, vaccine efficacy

https://www.cdc.gov/vaccines/acip/meetings/slides-2022-10-19-20.html

Consistent efficacy was observed across population subgroup analyses



https://www.cdc.gov/vaccines/acip/meetings/slides-2022-10-19-20.html

Expect efficacy against more severe outcomes to be at least as high as efficacy against lower respiratory tract disease/illness

Increasing severity ↓

GSK		Pfizer	
Outcome	**Efficacy**	**Outcome**	**Efficacy**
RSV acute respiratory illness[a]	71.7%	RSV acute respiratory illness[b]	62.1%
RSV lower respiratory tract disease[c]	82.6%	RSV lower respiratory tract illness ≥2 symptoms[d]	66.7%
		RSV lower respiratory tract illness ≥3 symptoms[d]	85.7%
RSV lower respiratory tract disease with ≥2 lower respiratory **signs** or assessed as '**severe**' by investigator	94.1%		

[a] Acute respiratory illness: ≥2 respiratory symptoms/signs for ≥24 hours OR ≥1 respiratory symptom/sign +1 systemic sign for ≥24 hours
[b] Acute respiratory illness: ≥1 respiratory symptom lasting more than 1 day
[c] Lower respiratory tract disease: ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign OR ≥3 lower respiratory symptoms for ≥24 hours
[d] Lower respiratory tract illness: ARI with ≥2 or ≥3 lower respiratory signs/symptoms

https://www.cdc.gov/vaccines/acip/meetings/slides-2022-10-19-20.html

Both clinical trials showed significant efficacy against lower respiratory tract disease/illness caused by RSV

- Efficacy point estimates against the primary outcomes in both trials exceeded 60%
- Based on a small number of total events (<50 in each trial)

GSK			Pfizer		
Outcome	**n/N, vaccine**	**n/N, placebo**	**Outcome**	**n/N, vaccine**	**n/N, placebo**
RSV LRTD[a]	**7**/12,466	**40**/12,494	RSV LRTI ≥2 symptoms[b]	**11**/16,306	**33**/16,308
			RSV LRTI ≥3 symptoms[b]	**2**/16,306	**14**/16,308

[a] Lower respiratory tract disease: ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign OR ≥3 lower respiratory symptoms for ≥24 hours

[b] Lower respiratory tract illness: ≥2 or ≥3 lower respiratory signs/symptoms lasting more than 1 day

https://www.cdc.gov/vaccines/acip/meetings/slides-2022-10-19-20.html

Incidence of symptomatic RSV infection was low in both trials

Why?

- Clinical trials may enroll a healthier population, compared with the general U.S. population
- Both trials were conducted during periods of atypical RSV seasonality in the United States, attributable to the COVID-19 pandemic

https://www.cdc.gov/vaccines/acip/meetings/slides-2022-10-19-20.html

Future perspectives

- Prioritizing efforts in RSV awareness
- Understanding cost-effectiveness of RSV prevention in different parts of the world
- Defining efficacy and effectiveness in different at-risk subgroups
- Likely multiple immunization strategies with complementary value, unique advantages and personalized approaches will shape the RSV prevention landscape