Antigen Surveillance: from Evolution to Immune Escape”

RSV immunoprophylaxis tools and immune escape from monoclonal antibodies

March 23rd 2026

Outline

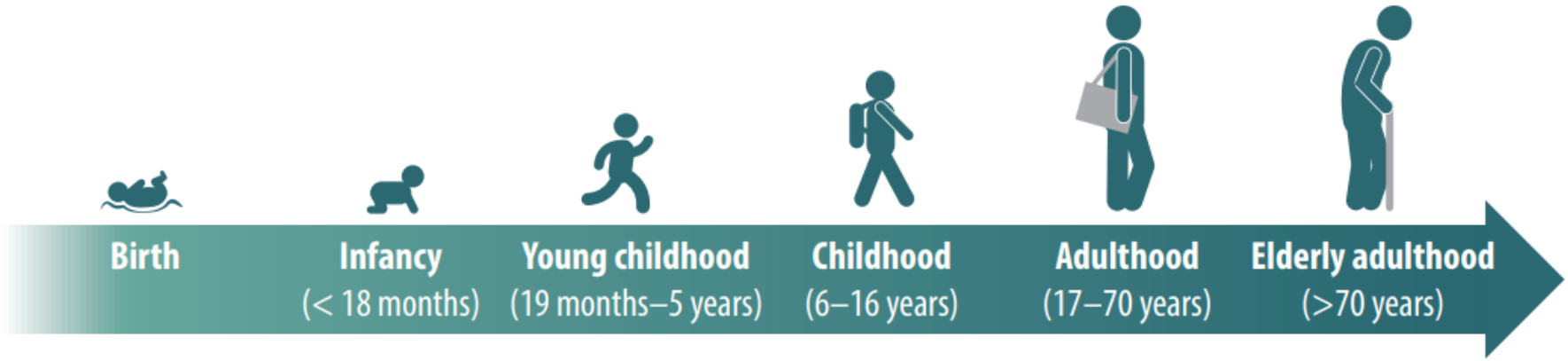
This session will cover the following elements

1. RSV disease burden

2. Immunoprophylactic strategies against RSV

3. Genetic variation and its impact on escape from monoclonal antibodies

RSV disease burden



RSV bronchiolitis

Postbronchiolitic wheeze

age >2 : all infants had an episod of RSV infection

Exacerbation of asthma/COPD

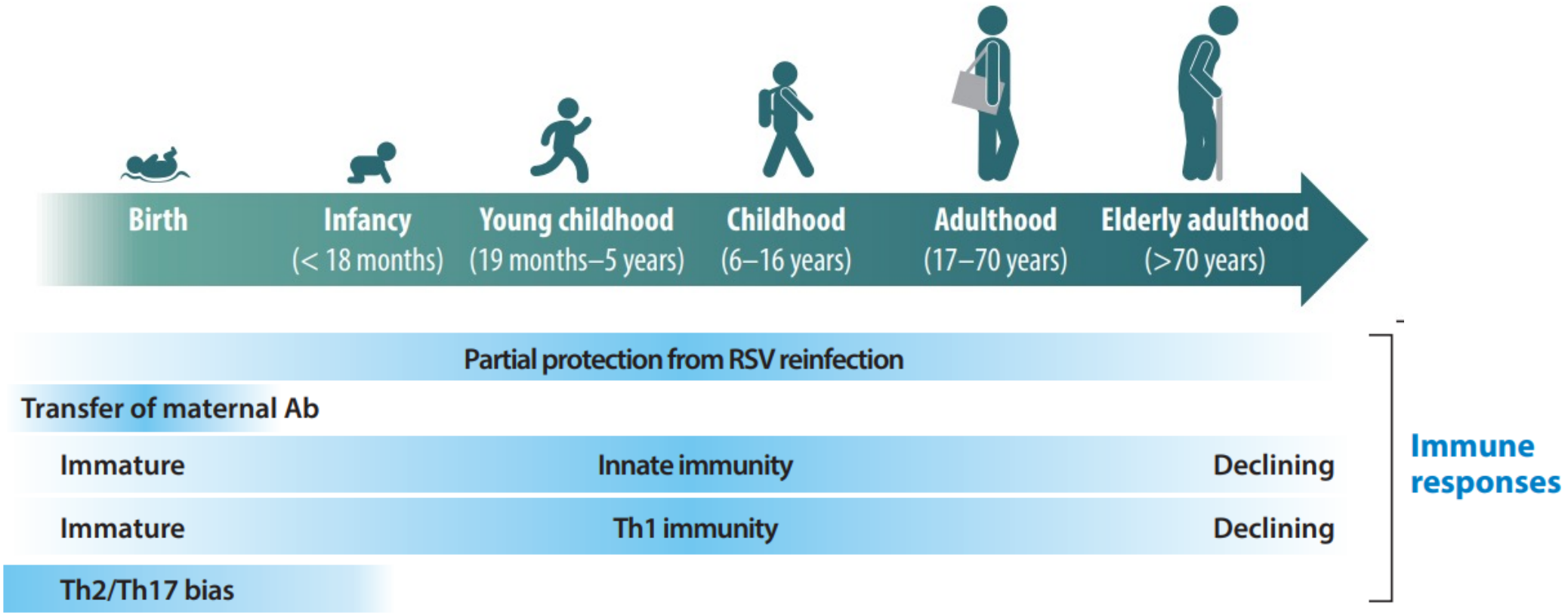
Insidious respiratory illness

Colds due to infection or reinfection

Clinical features

Peter J.M. Openshaw et al. Annu. Rev. Immunol. 2017. 35:501–32; Recto C et al. JID 2024

RSV disease burden

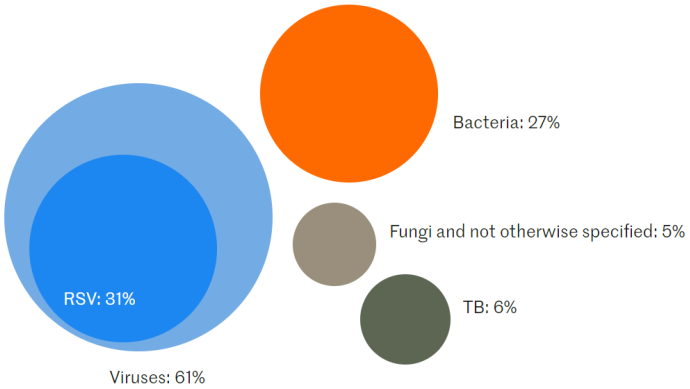


Peter J.M. Openshaw et al. Annu. Rev. Immunol. 2017. 35:501–32; Recto C et al. JID 2024

RSV disease burden

at high risk of severe disease

Infants < 1 year



Severe respiratory infections (1m – 5 years)

- >3 millions hospitalisations/year worldwide
- >100,000 deaths/y worldwide

Older adults

- 5,1 millions RSV-ARI/y
- 465 000 hospitalisations/y
- 33,000 deaths/y

Immunocompromised

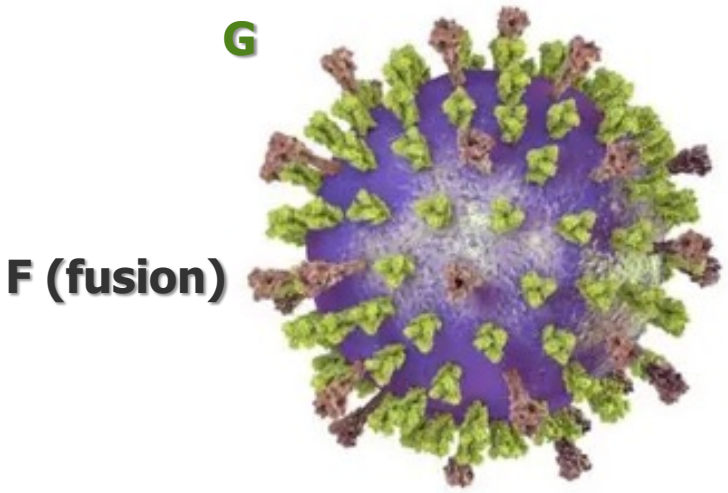
COPD exacerbations, cardiac diseases

- 174 millions dans le monde
- RSV second leading cause of hospitalizations for COPD exacerbations and acute heart failure.

Influenza Other Respir Viruses. 2023 Jan;17(1):e13031 ; PERCH study Lancet 2019 (http://perchresults.org/)

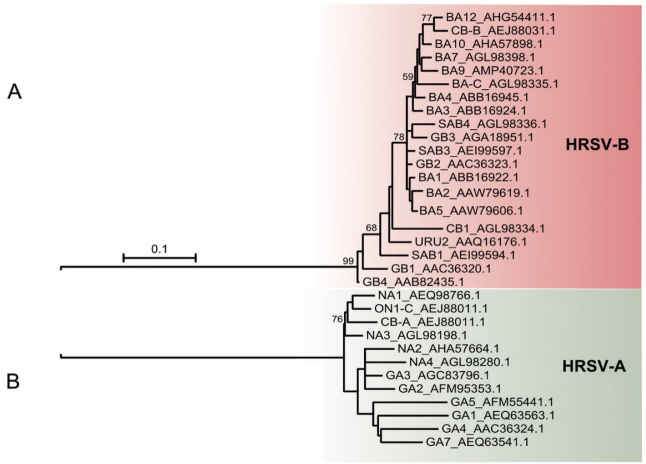
Due to the significant burden, the development of anti-RSV immunoprophylaxis tools is crucial

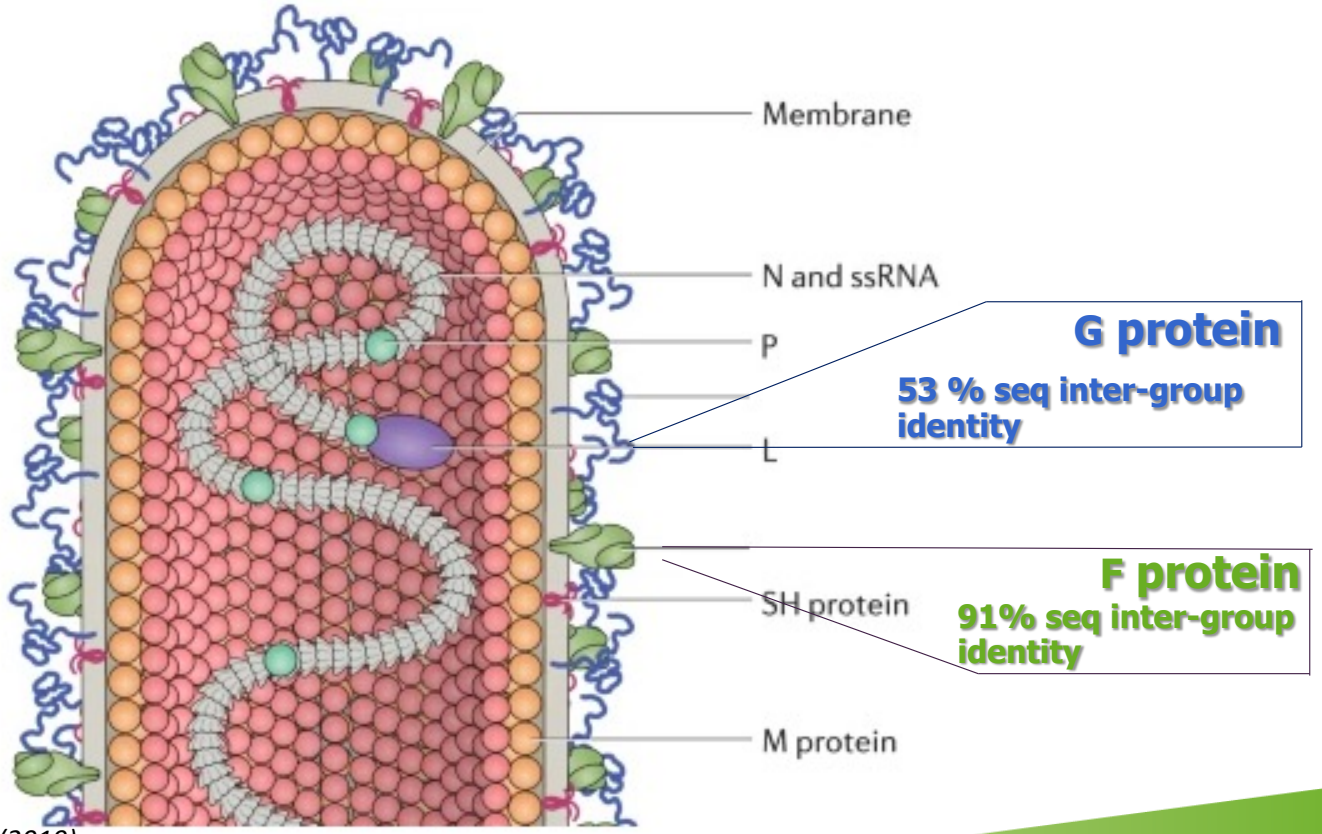
Let's focus on a key viral protein: the fusion (F) protein



RSV classification & structure

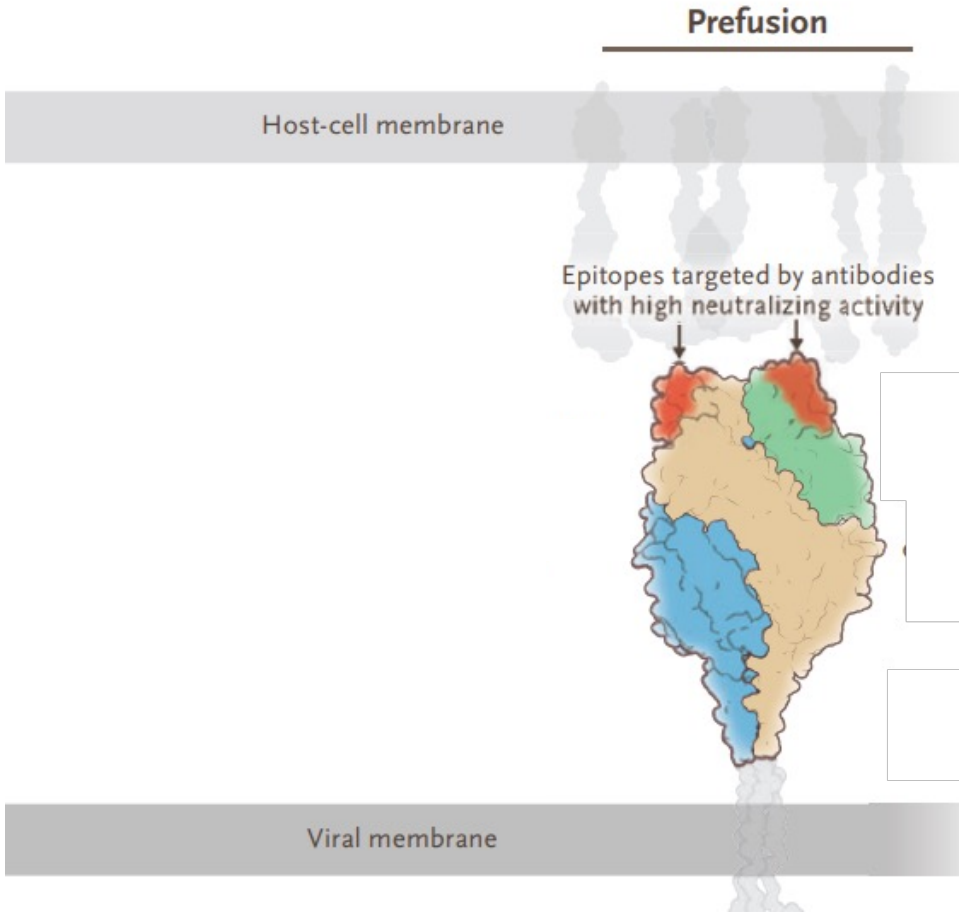
Two major antigenic subgroups (co-circulate) : RSV-A & RSV-B
with multiple lineages within each of them





Battles, M.B., McLellan, J.S. Nat Rev Microbiol 17, 233–245 (2019)

F involvement in viral entry (Type I viral fusion protein)



Barney S. Graham, nejm 388;7 February 16, 2023

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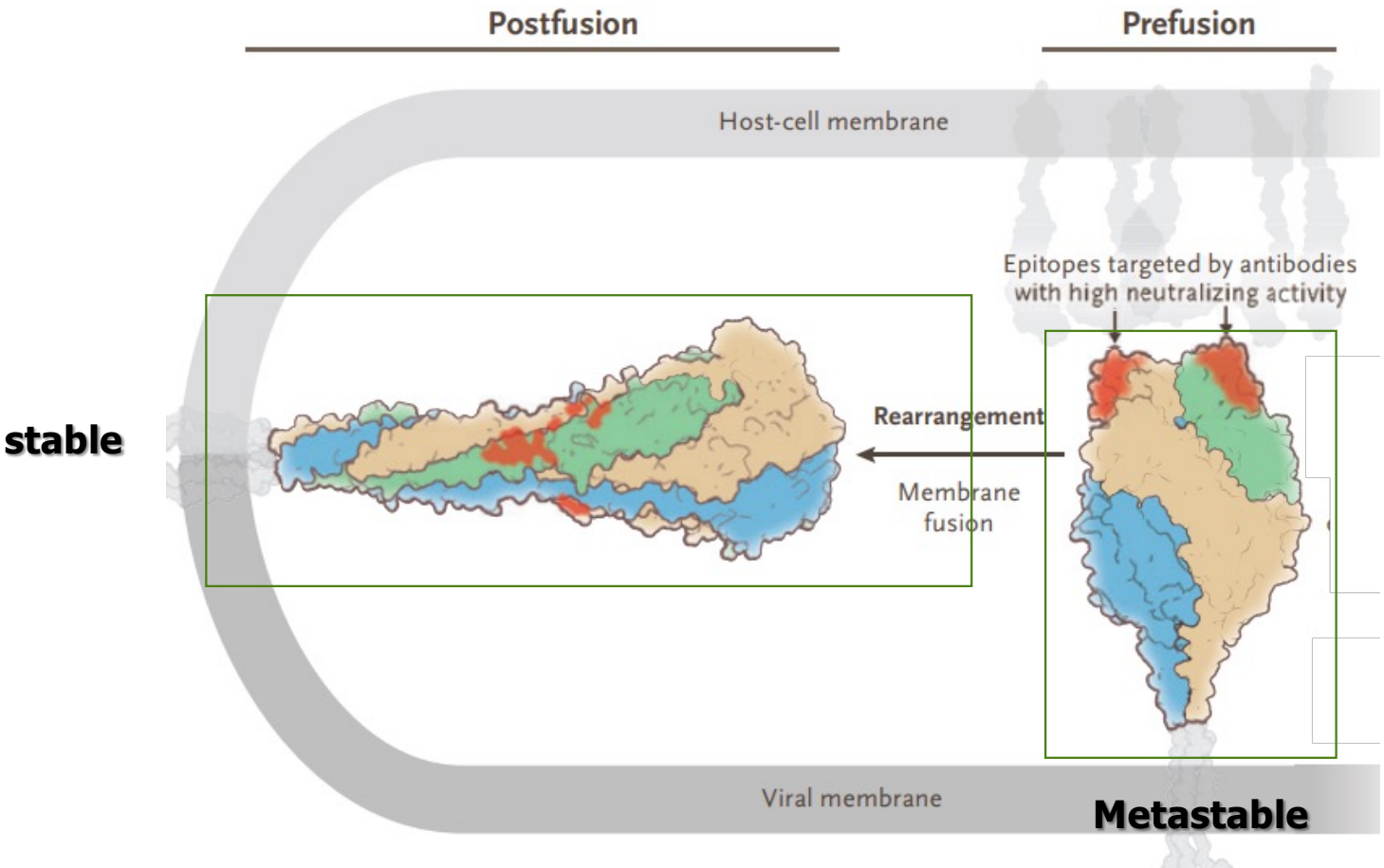
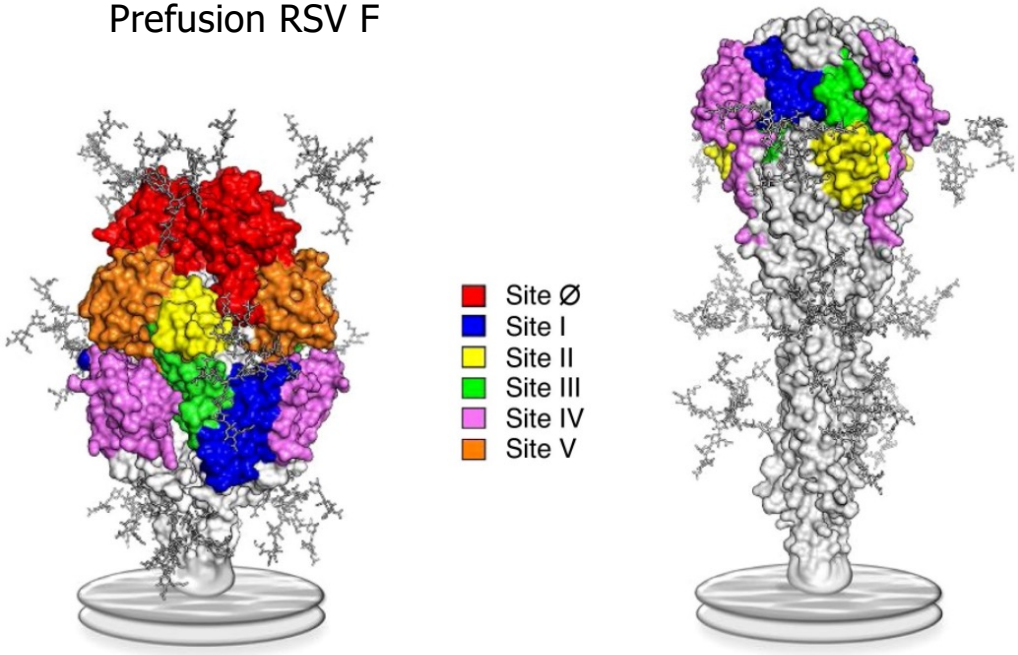


Barney S. Graham, nejm 388;7 February 16, 2023

Structure and antigenicity of the fusion (F) glycoprotein

Postfusion RSV F

Prefusion RSV F

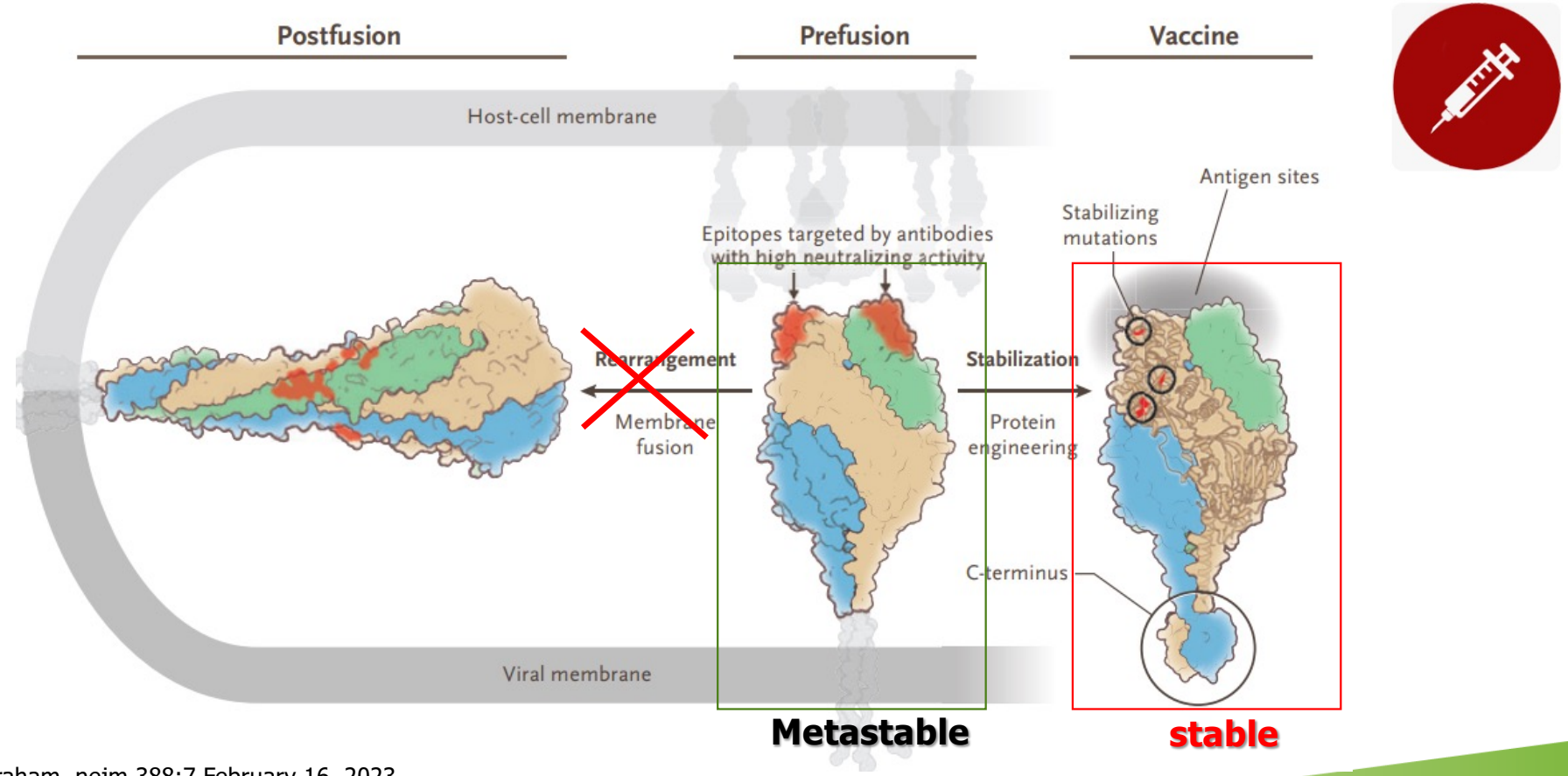


Metastable

stable

McLellan JS et al. Science. 2013 Nov 1;342(6158):592-8. S Graham B. Current Opinion in Virology 2017

Designing potent anti-RSV vaccine: stabilize the pre-fusion conformation to make transitioning to the post-fusion less favorable



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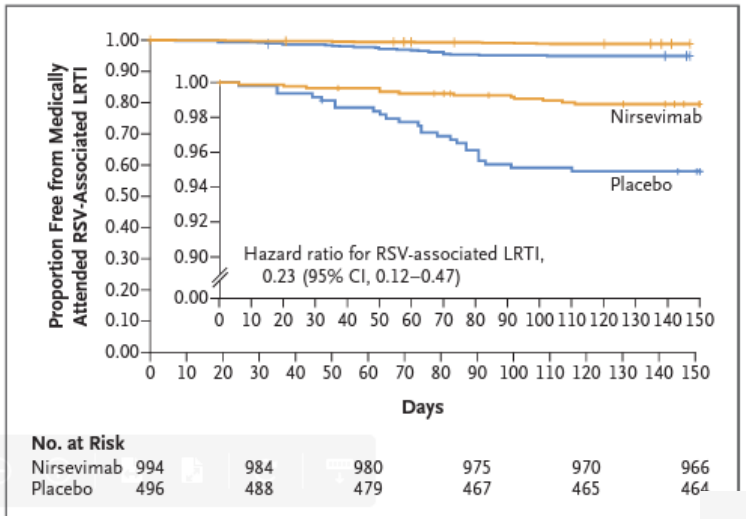
RSV prophylaxis: two complementary revolutionary approaches

PreF stabilisation is the basis for all vaccines that have been developed

This approach is the basis for three vaccines currently on the market.

Monoclonal antibodies



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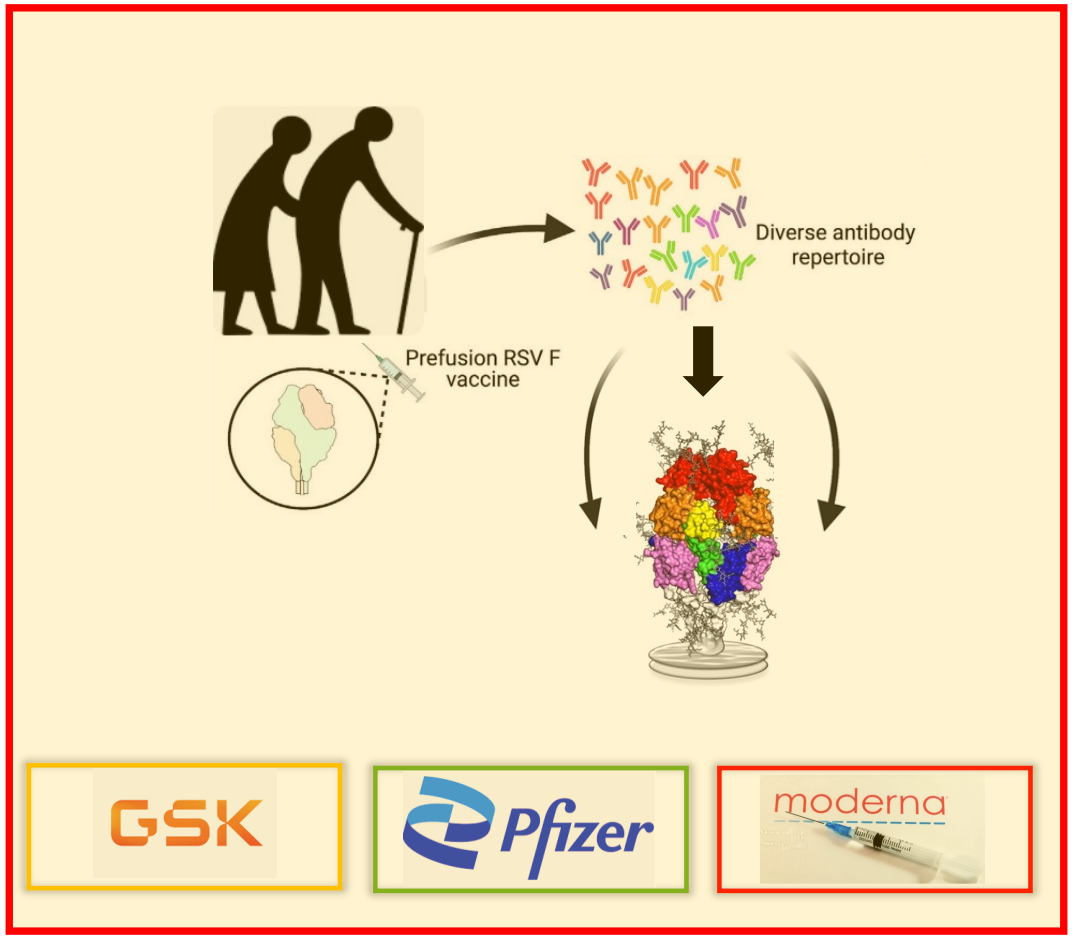
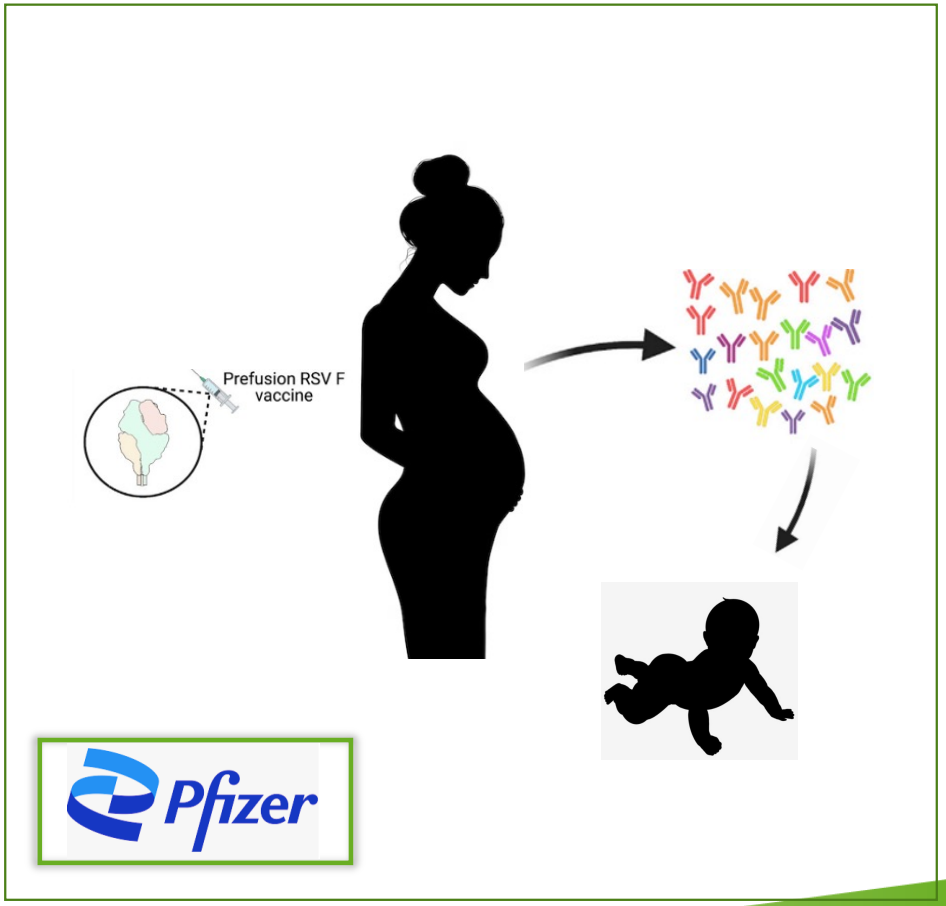
The EMA/FDA approved Pre-F Vaccines





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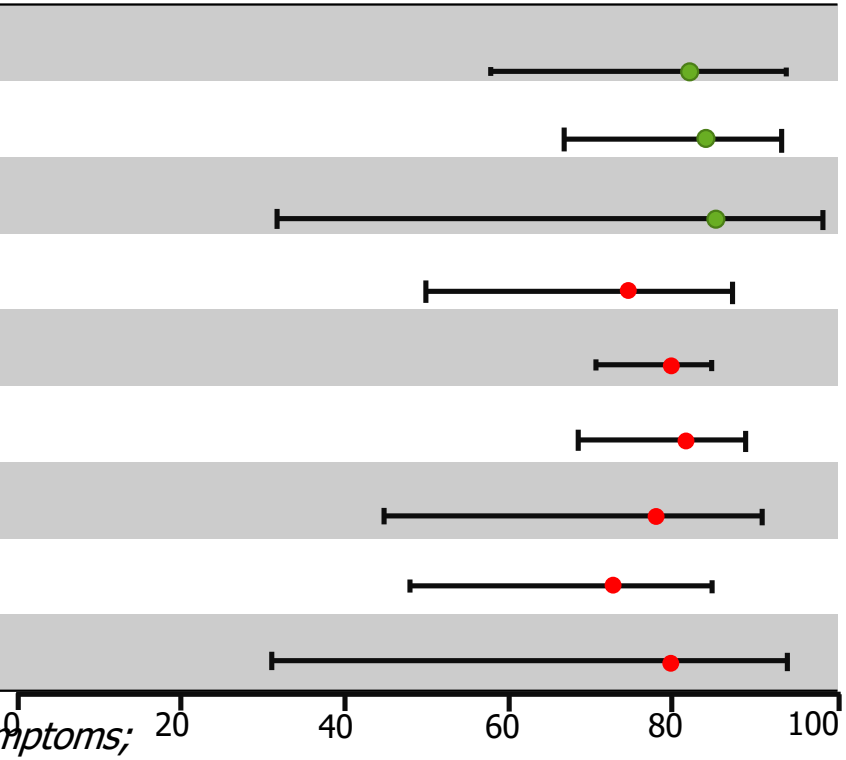
Which elderly population may not be protected by vaccines

Real world effectiveness similar to clinical trial efficacy results (although different endpoints)

endpoint	Study	Vaccine efficacy /effectiveness % (95% CI)
RSV lower respiratory tract infection (LRTI)	GSK trial [1] (AReSVi-006) (≥60 ans)	83 (58-94)
	Moderna trial [2] (≥60 y)	84 (66-92)
	Pfizer trial [3] (RENOIR) (≥60 y)	86 (32-99)
RSV hospitalisation	IVY network (20 US states) (≥60 y)	75 (50-87)
	VISION, immunocompetent ≥60 y*	80 (71-85)
	Veterans US cohort, adults *≥ 60 y*	82 (69-89)
	Dialysis cohort (Medicare) >65 y	78 (45-91)
	VISION, immunocompromised ≥60 y*	73 (48-85)
	Dialysis and other IC conditions > 65 y	80 (31-94)

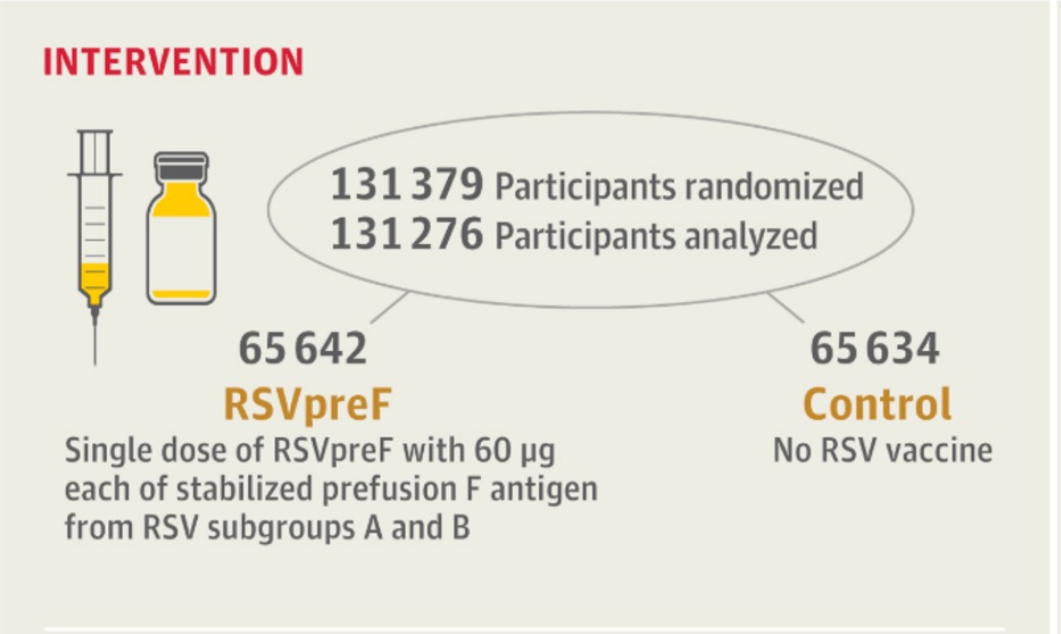


(1) ≥ 2 lower resp. symptoms or signs > 24h (2) ≥2 symptoms (3) ≥ 3 signs or symptoms;

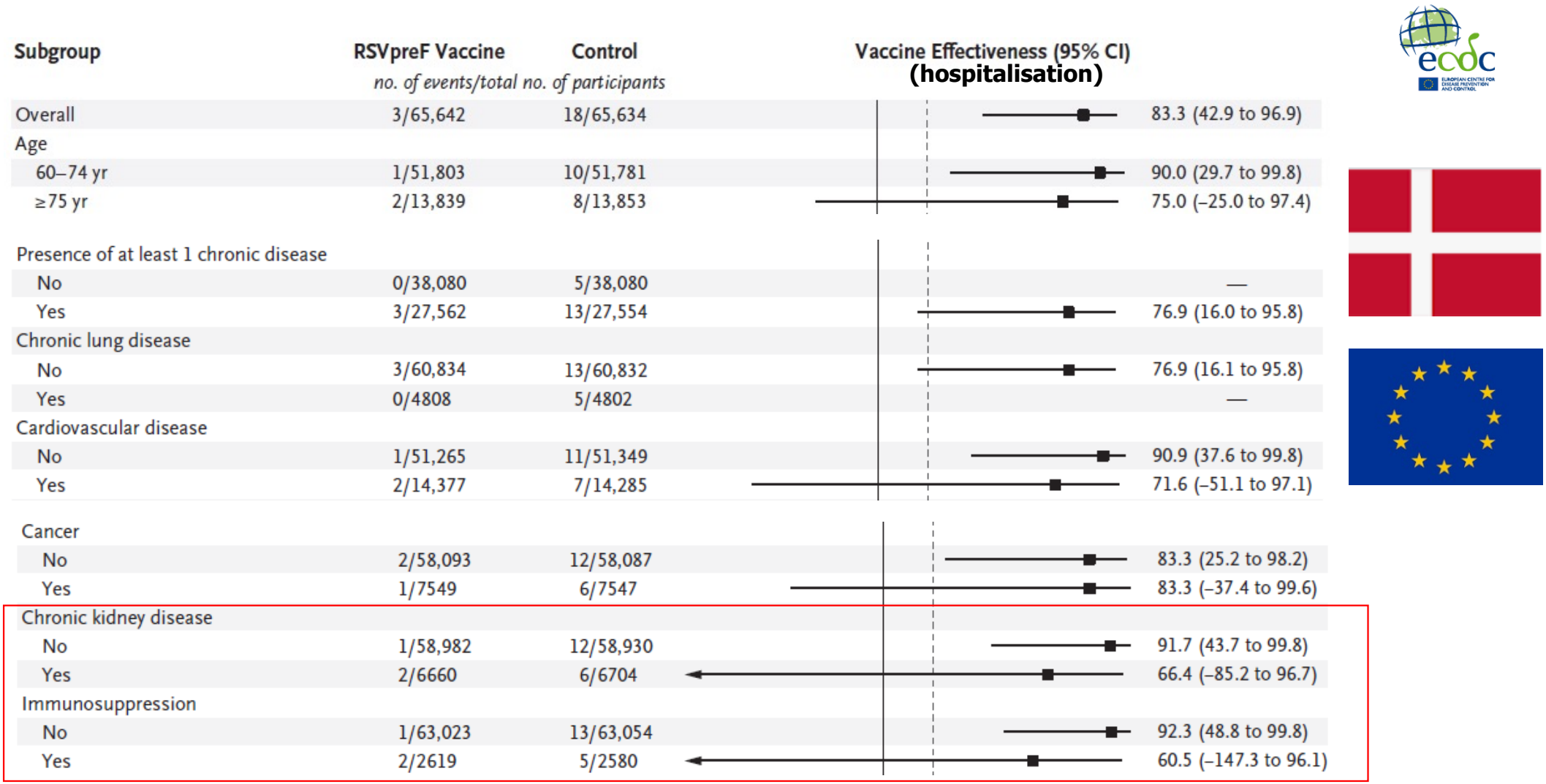
Papi A et al. N Engl J Med 2023; 388:595-608; Beate Kampmann et al. N Engl J Med 2023; 388:1451-1464; E.E. Walsh et al. N Engl J Med 2023;388:1465-77. Wilson E 7th ReSViNET Conference (RSVVW 2023), Payne et al. Lancet 2024;404(10462):1547-59.

Randomized clinical trial

participants ≥ 60 years were assigned to receive the RSVpreF vaccine (the RSVpreF group) or no vaccine (the control group) during the 2024–2025 winter season.



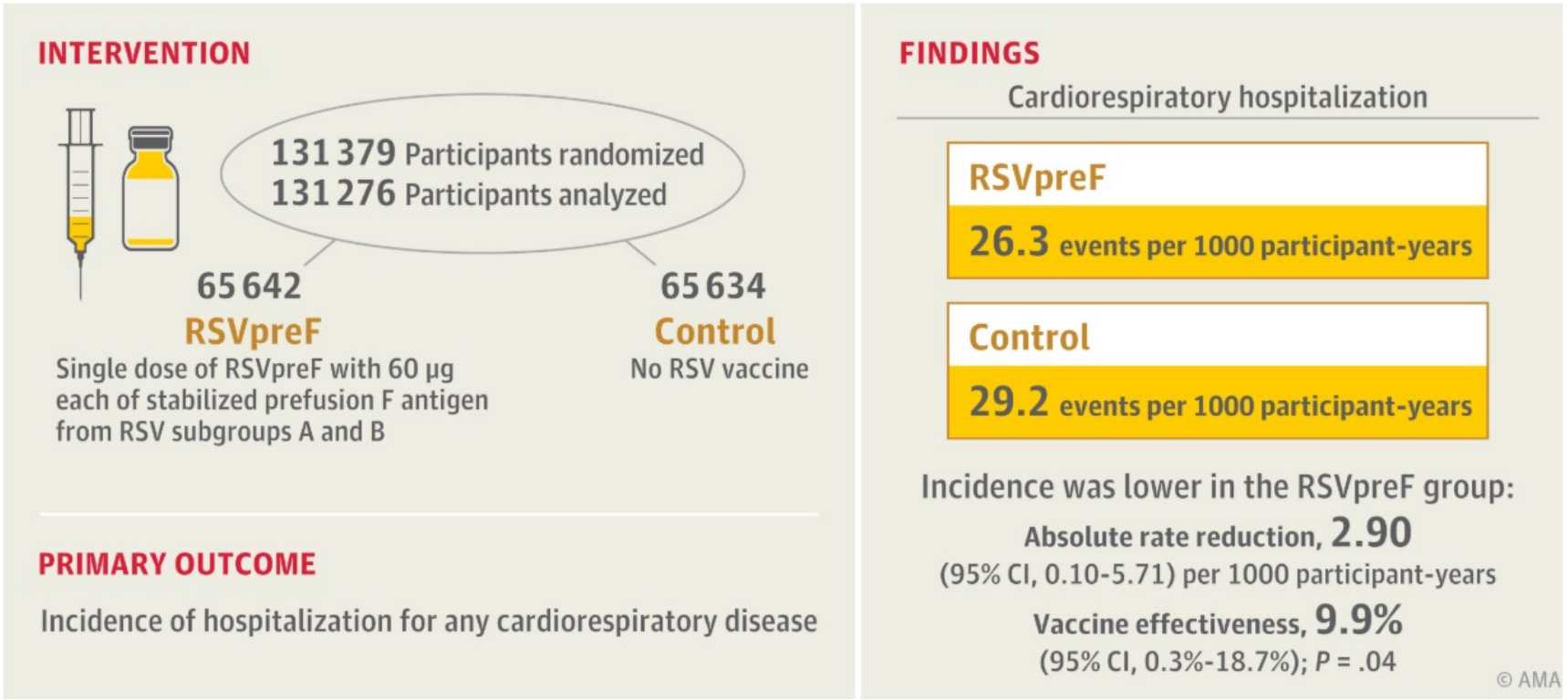
M.C.H. Lassen et al. JAMA Network August 2025



Subgroup	RSVpreF Vaccine	Control	Vaccine Effectiveness (95% CI) (hospitalisation)
	no. of events/total no. of participants		
Overall	3/65,642	18/65,634	83.3 (42.9 to 96.9)
Age			
60–74 yr	1/51,803	10/51,781	90.0 (29.7 to 99.8)
≥75 yr	2/13,839	8/13,853	75.0 (–25.0 to 97.4)
Presence of at least 1 chronic disease			
No	0/38,080	5/38,080	—
Yes	3/27,562	13/27,554	76.9 (16.0 to 95.8)
Chronic lung disease			
No	3/60,834	13/60,832	76.9 (16.1 to 95.8)
Yes	0/4808	5/4802	—
Cardiovascular disease			
No	1/51,265	11/51,349	90.9 (37.6 to 99.8)
Yes	2/14,377	7/14,285	71.6 (–51.1 to 97.1)
Cancer			
No	2/58,093	12/58,087	83.3 (25.2 to 98.2)
Yes	1/7549	6/7547	83.3 (–37.4 to 99.6)
Chronic kidney disease			
No	1/58,982	12/58,930	91.7 (43.7 to 99.8)
Yes	2/6660	6/6704	66.4 (–85.2 to 96.7)
Immunosuppression			
No	1/63,023	13/63,054	92.3 (48.8 to 99.8)
Yes	2/2619	5/2580	60.5 (–147.3 to 96.1)

M.C.H. Lassen et al. NEJM August 2025

Reduction in all-cause cardiorespiratory hospitalizations among vaccinated individuals



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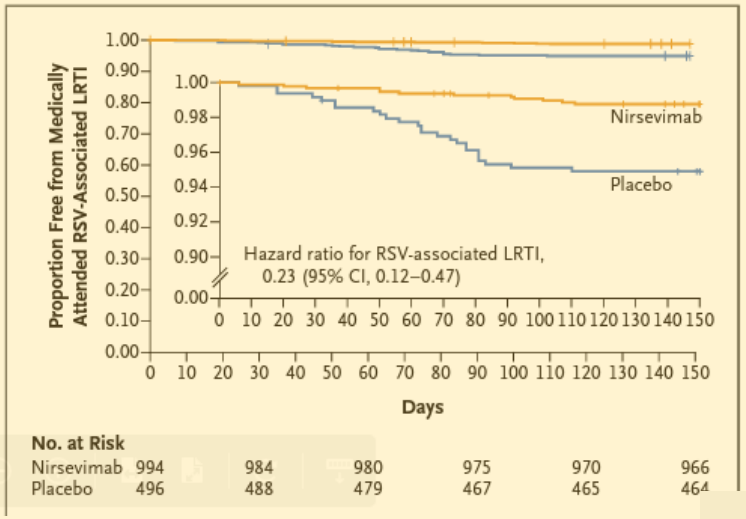
This approach is the basis for three vaccines currently on the market.

Monoclonal antibodies



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New generation of available monoclonal antibodies targeting RSV ...

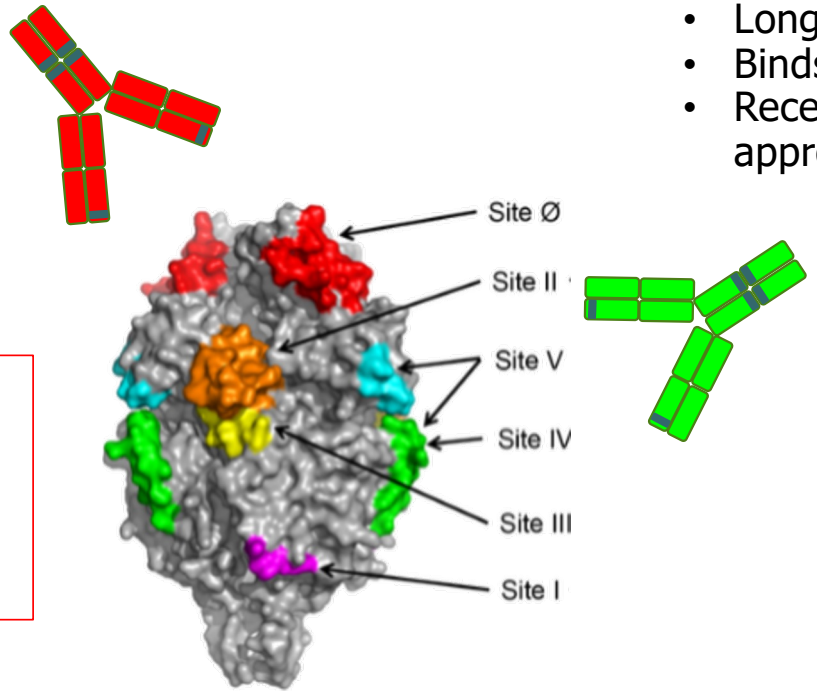
The key breakthrough of new monoclonal antibodies is their long-acting activity

Nirsevimab

- Human IgG1 monoclonal antibody
- Long-acting
- Binds antigenic site Ø
- In use since 2023 in multiple countries for infant prophylaxis

Clesrovimab

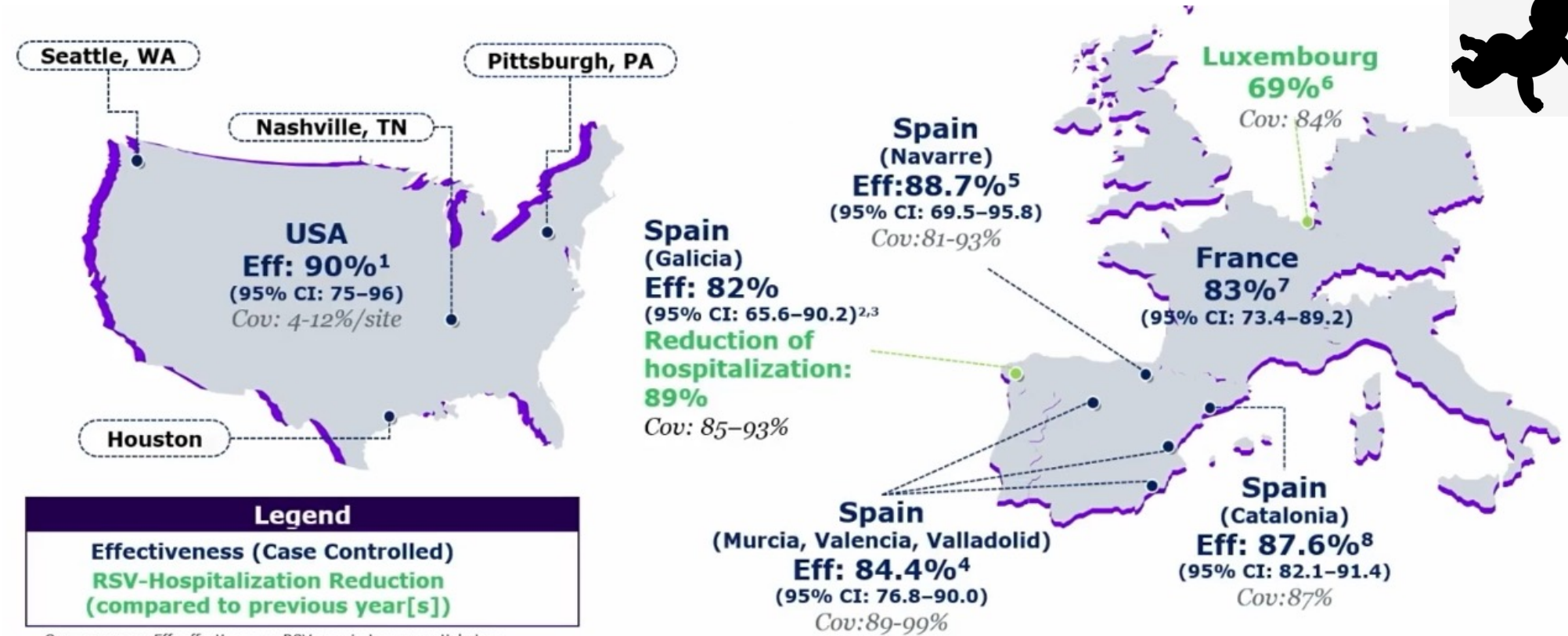
- Human IgG1 monoclonal antibody
- Long-acting
- Binds antigenic site IV
- Recently developed (EMA and FDA approval in 2025)



a single injection at birth or in early infancy can protect infants against RSV bronchiolitis for an entire season, with an efficacy around 80%.

Adapted from Flynn et al, 2016

Summary of Real-World Effectiveness and Reduction of RSV-Hospitalisation Estimates 2023/2024



Cov, coverage; Eff, effectiveness; RSV, respiratory syncytial virus.

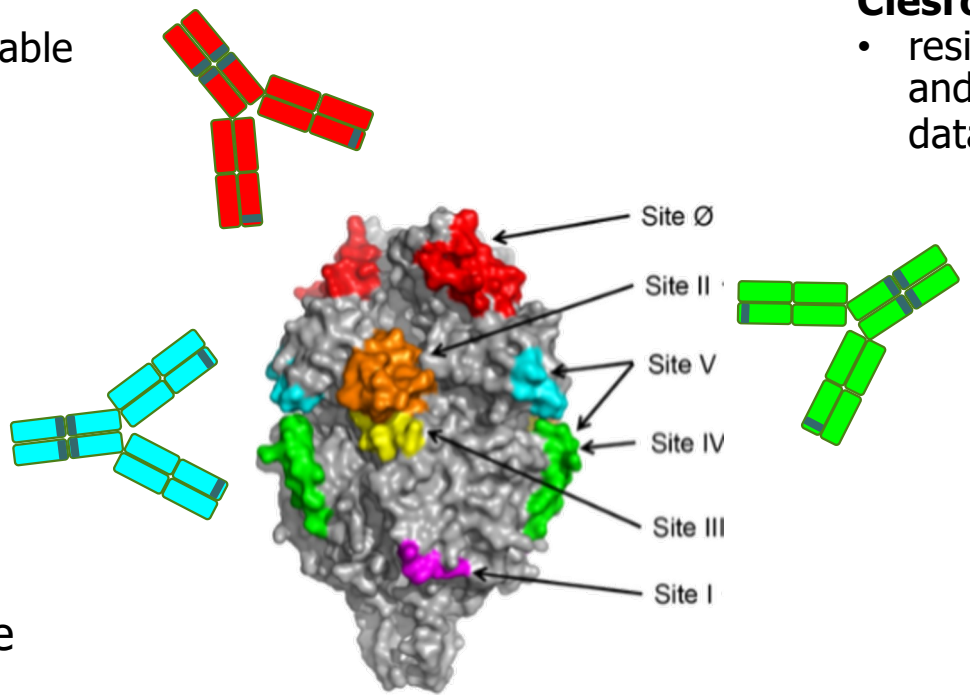
References: 1. Moline HL, et al. *MMWR Morb Mortal Wkly Rep*. 2024;73:209-214. 2. NIRSE-GAL research team. Results of implementation of nirsevimab in Galicia. Accessed 23 April 2024. https://www.nirsegal.es/en 3. Martinon-Torres et al. ESWI Respiratory Virus Summit 2024 | ESWI, 5 March 2024. https://eswi.org/cnt/activity/eswi-summit-2024#activity-programme 4. López-Lacort M, et al. *Euro Surveill*. 2024;29(6):pii=2400046. 5. Ezpeleta G, et al. *Vaccines*. 2024;12:383 6. Ernst C, et al. *Euro Surveill*. 2024;29(4):pii=2400033 7. Haute Autorité de santé. Recommandation vaccinale contre les infections à VRS chez les femmes enceintes. Accessed 27 March 2024. https://www.has-sante.fr/upload/docs/application/pdf/2024-03/recommandation_vaccinale_contre_les_infections_a_vrs_chez_les_femmes_enceintes_-_version_provisoire.pdf 8. Coma E, et al. Preprints with *The Lancet*. Accessed 23 April 2024. https://ssrn.com/abstract=4749763

What immunoprophylaxis strategy in infants is used in your country for the prevention of RSV?

Resistance to Long-acting monoclonal antibodies?

Nirsevimab
- In use since 2023 in multiple countries for infant prophylaxis

-> Real-world surveillance genomic is becoming available



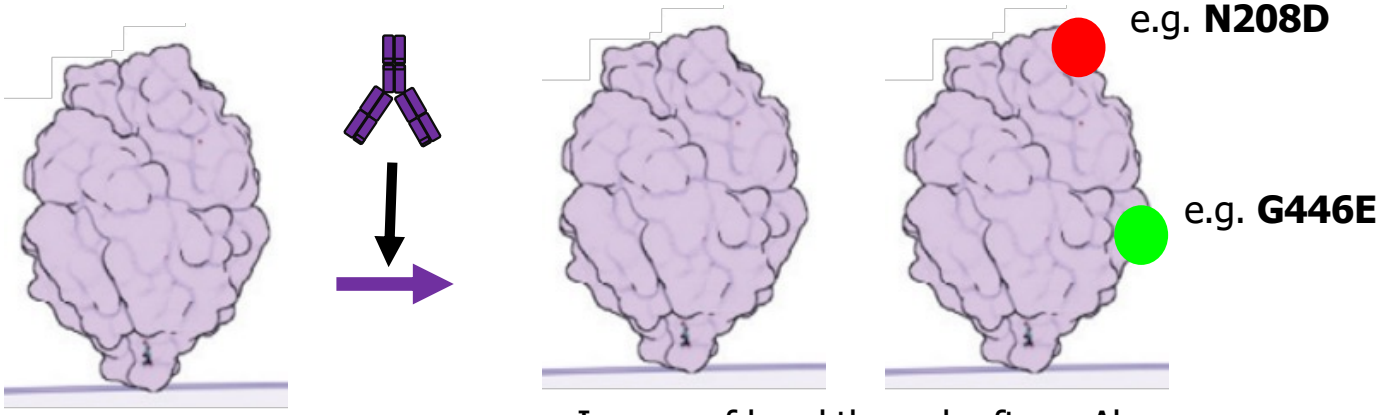
Clesrovimab
- resistance data only from *in vitro* and clinical trials; no real-world data available

Suptavumab
- Humanized monoclonal antibody
- Binds antigenic site V
- NOT USED / failure because of natural emergence of resistance

Adapted from Flynn et al, 2016

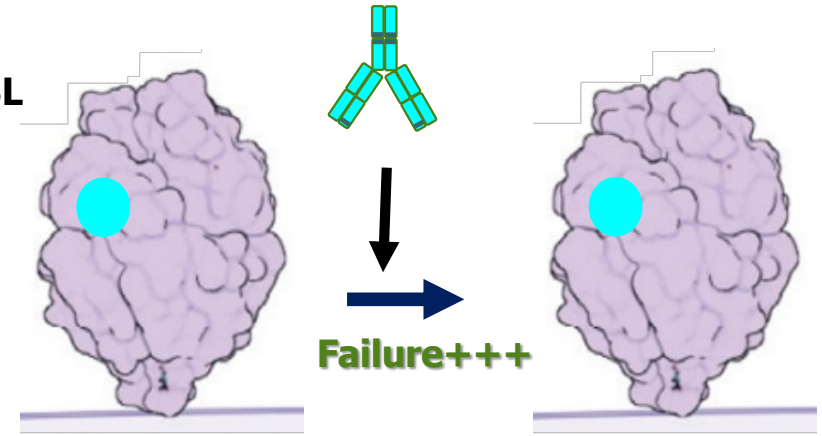
What do we mean by resistance to RSV monoclonal antibodies?

Nirsevimab
Clesrovimab



Suptavumab

RSV-B
L172Q/S173L

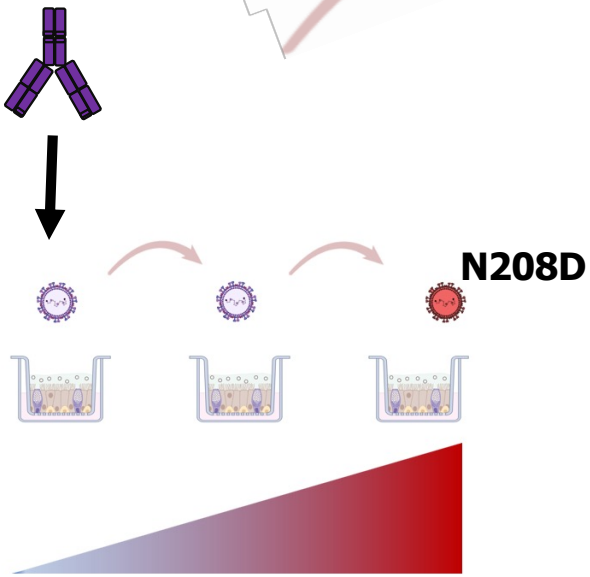


What is "resistance"?

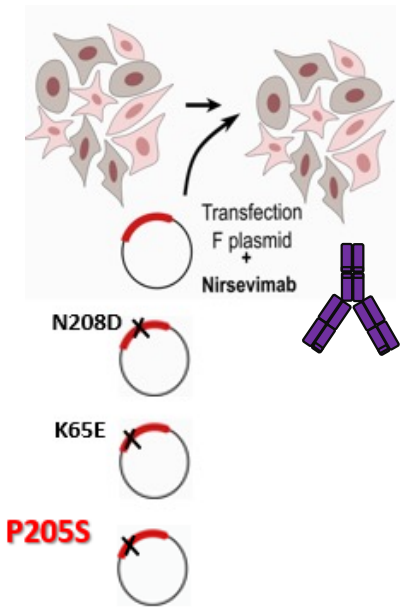
- **Amino acid substitutions** in the monoclonal antibody–targeted epitope (**RAS**)
- Reduced antibody binding and/or neutralization activity

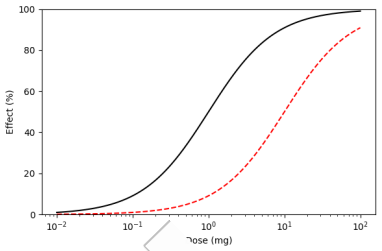
Adapted from Terstappen et al. 2024

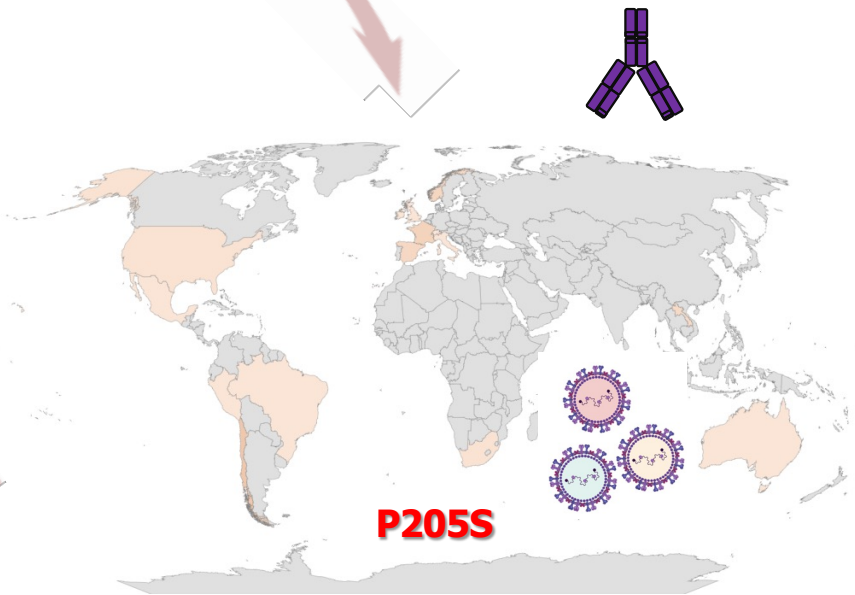
How can we identify resistance-associated substitutions?



In vitro selection experiments



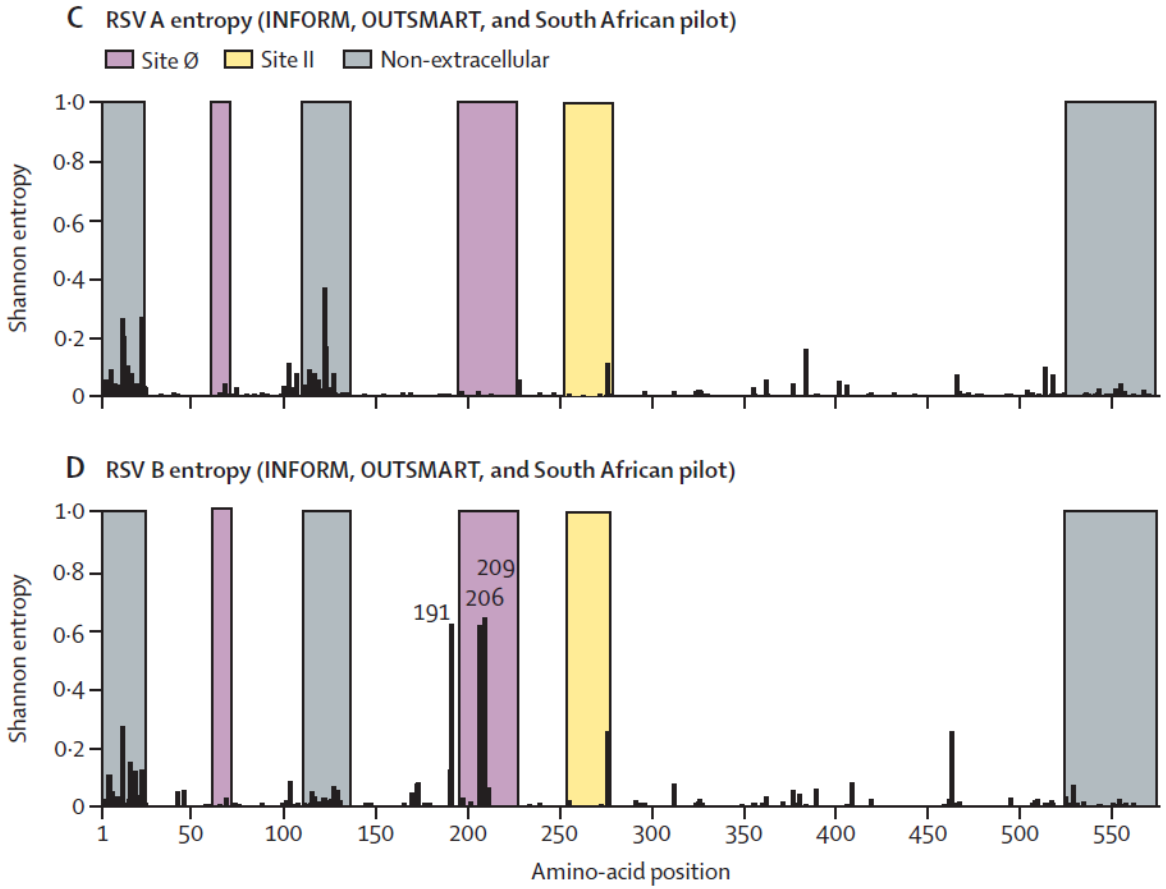




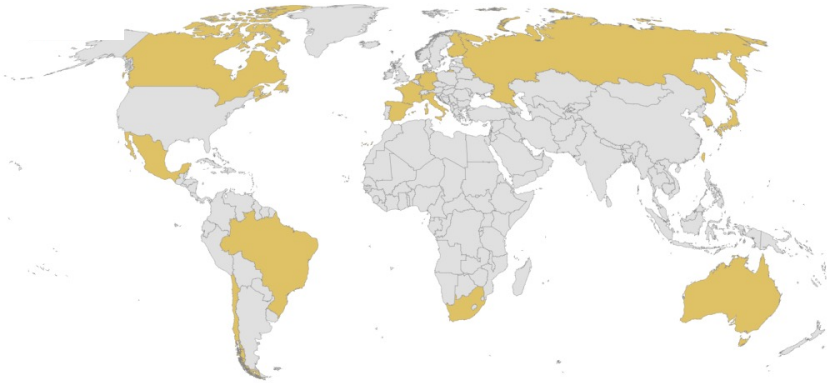
Clinical validation

How frequent are resistant variants before nirsevimab introduction ?

Comprehensive analysis of >5000 RSV A and RSV B sequences collected from three surveillance studies (2015–2021).



Wilkins et al. Lancet Inf Dis 2022

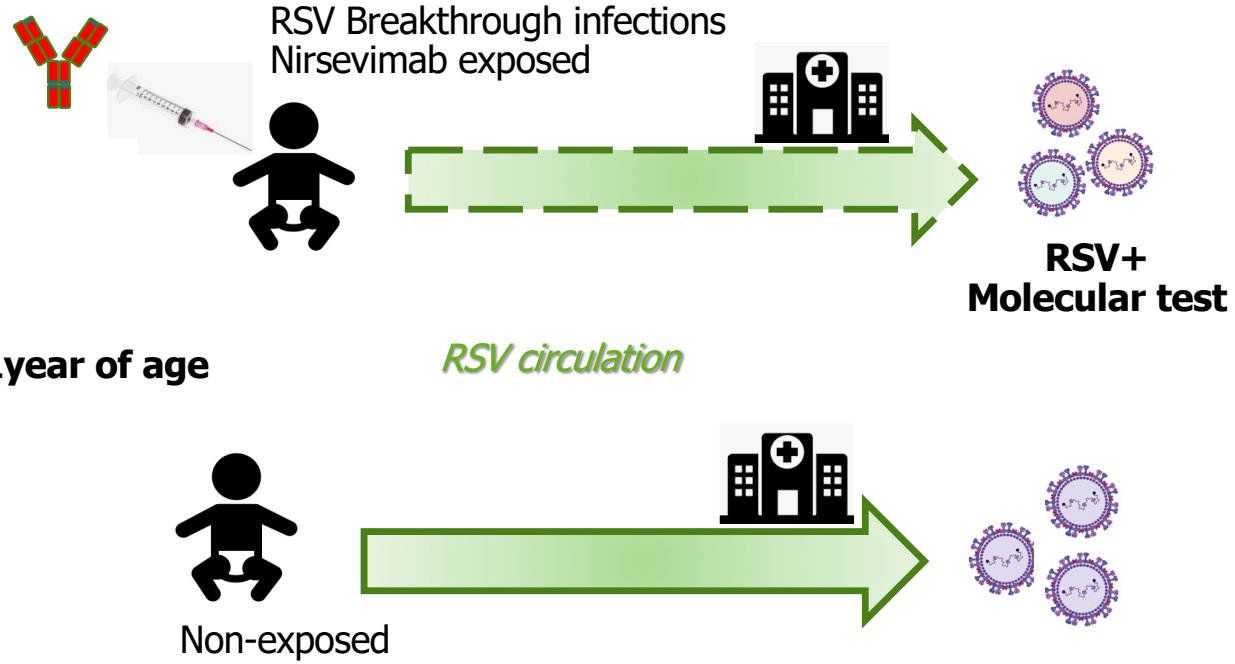


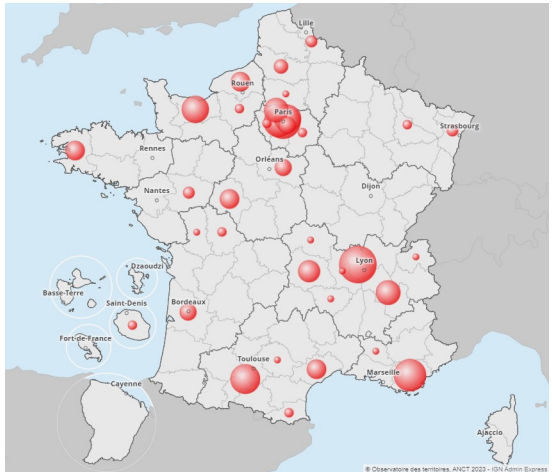
Across both RSV-A and RSV-B, <1% of sequences harboured any resistance-associated substitution (RAS)

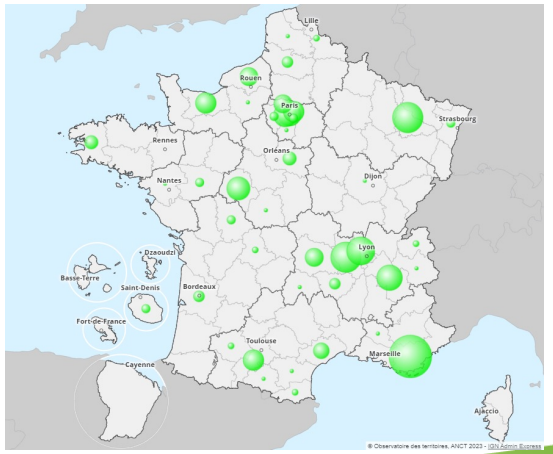
genetic stability of nirsevimab-binding site

How frequent are resistant variants after nirsevimab introduction ?

POLYRES study : Prospective observational study since 2023 (>30 hospitals)







For each "viral breakthrough" case, one non-exposed case was enrolled in each participating center.

Fourati S et al. Lancet Inf Dis 2025; Fourati S et al. http://dx.doi.org/10.2139/ssrn.5427106

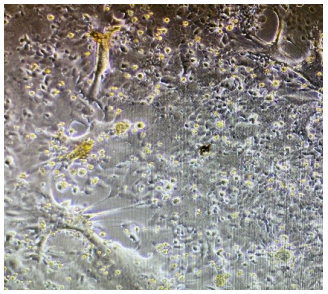
Methods

RSV full-length genome sequencing

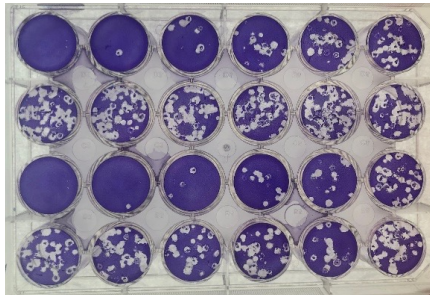
high-quality sequences
> 90% of the viral genome
> 90% of the F protein

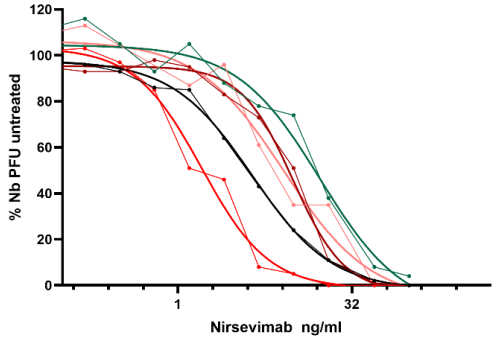
RSV Lineages*
Phylogenetic analysis (IQ-TREE)
Identification of F- site Ø amino acid substitutions

sample inoculated onto Hep-2 cells (37°C, 5% CO2)



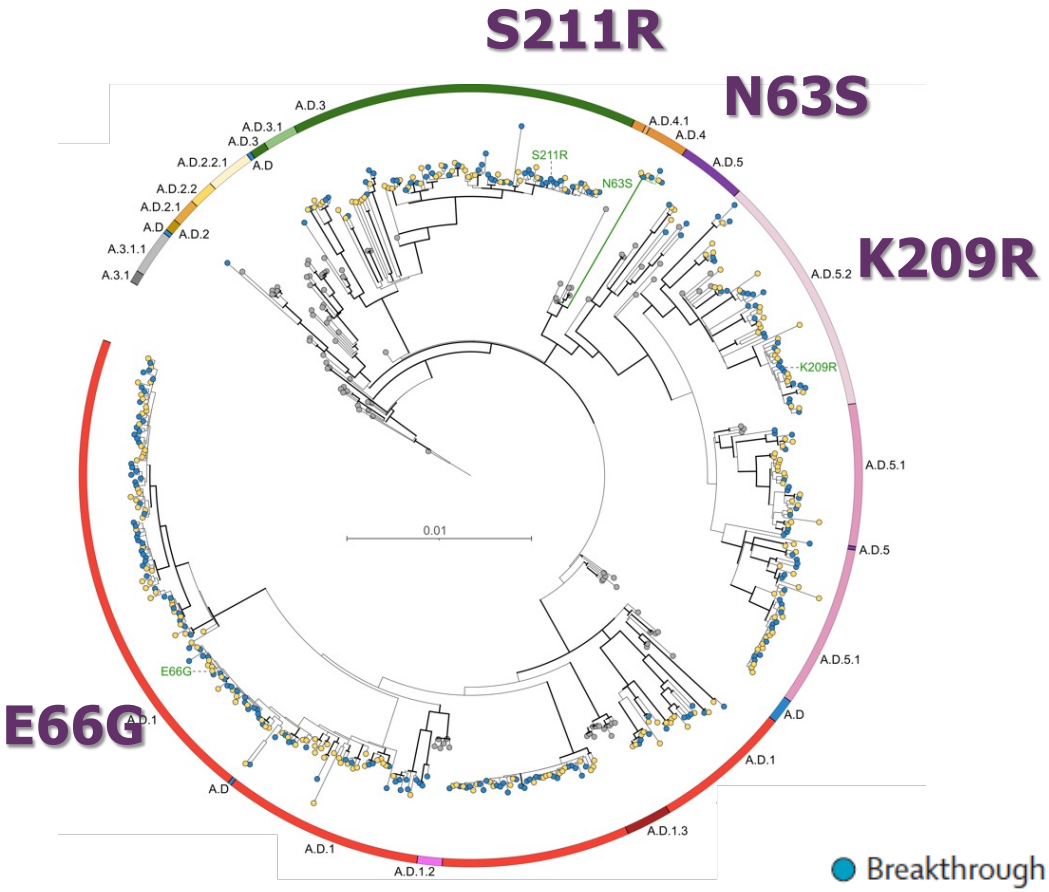
Assess the susceptibility of isolates to nirsevimab by PRNTs

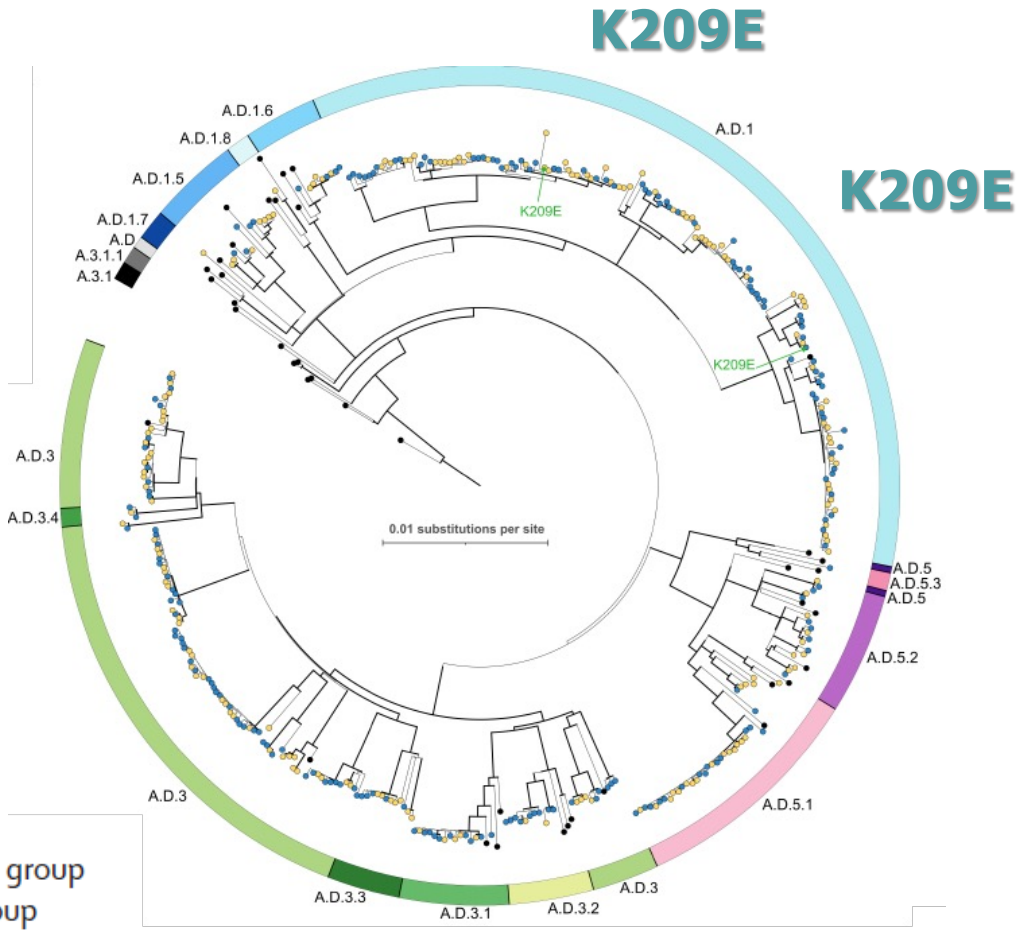




** According to Goya S, Ruis C, Neher RA, et al. The unified proposal for classification of human respiratory syncytial virus below the subgroup level.*

RSV-A sequences during 2023-24 and 2024-25 seasons



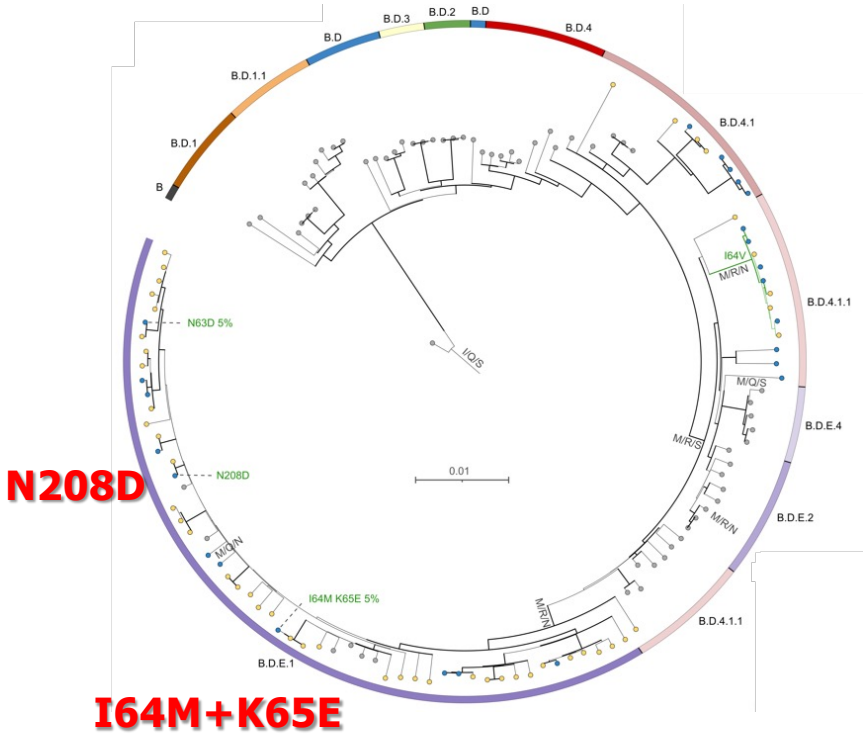


Breakthrough group
Untreated group

2023/24 season
N (breakthrough)= 236 (no resistance)

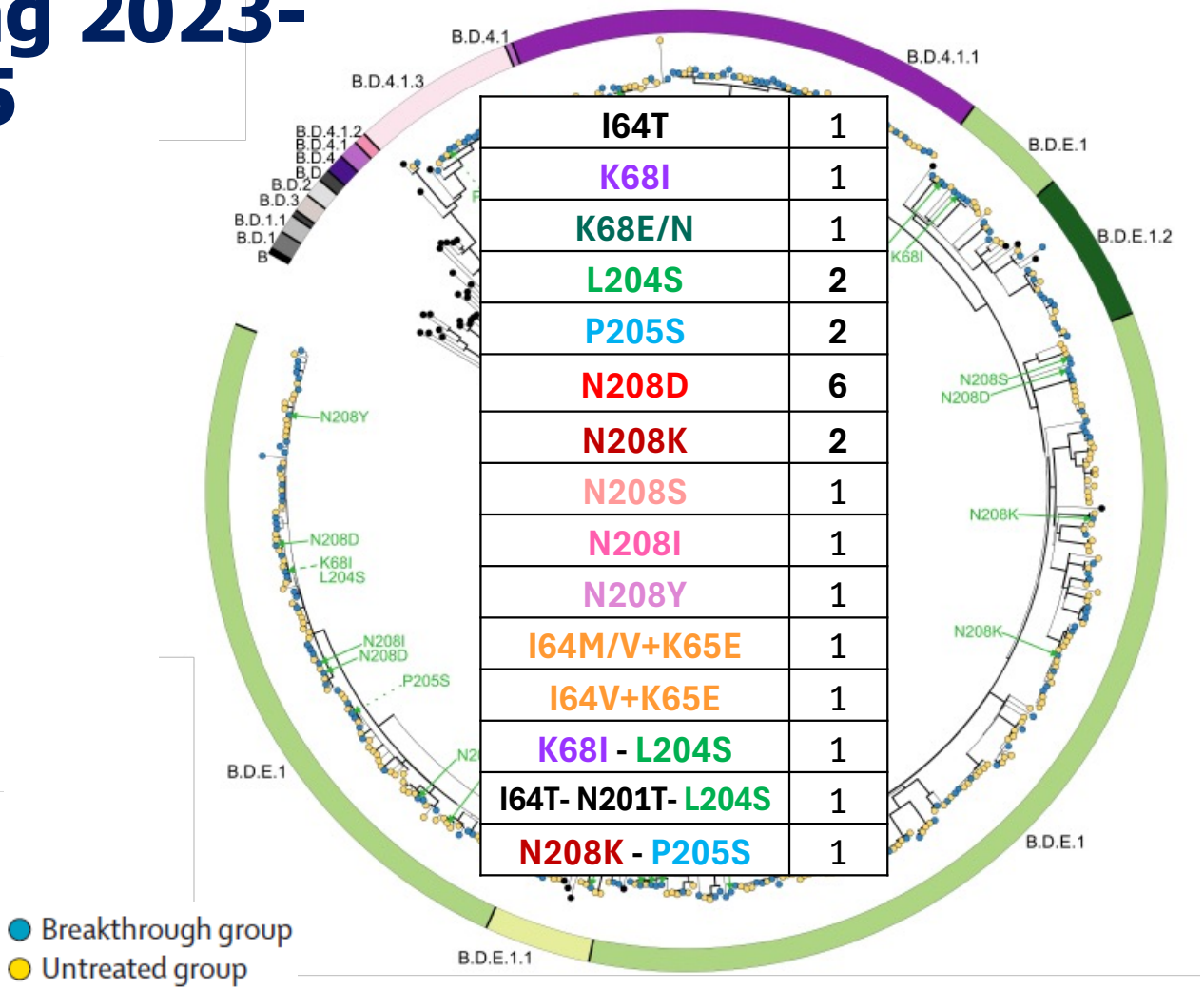
2024/25 season
N (breakthrough)= 195 (2 resistant variants)

RSV-B viruses during 2023-2024 and 2024-2025 seasons



N208D

I64M+K65E



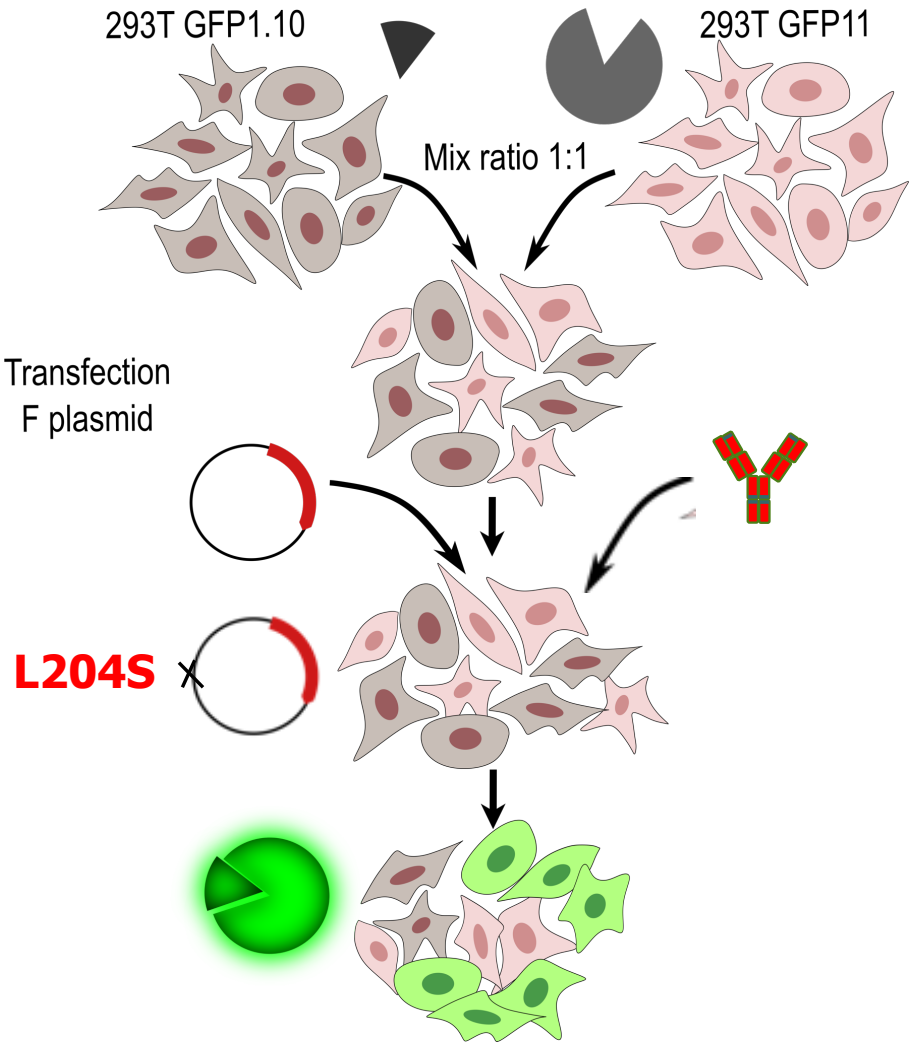
I64T	1
K68I	1
K68E/N	1
L204S	2
P205S	2
N208D	6
N208K	2
N208S	1
N208I	1
N208Y	1
I64M/V+K65E	1
I64V+K65E	1
K68I - L204S	1
I64T- N201T- L204S	1
N208K - P205S	1

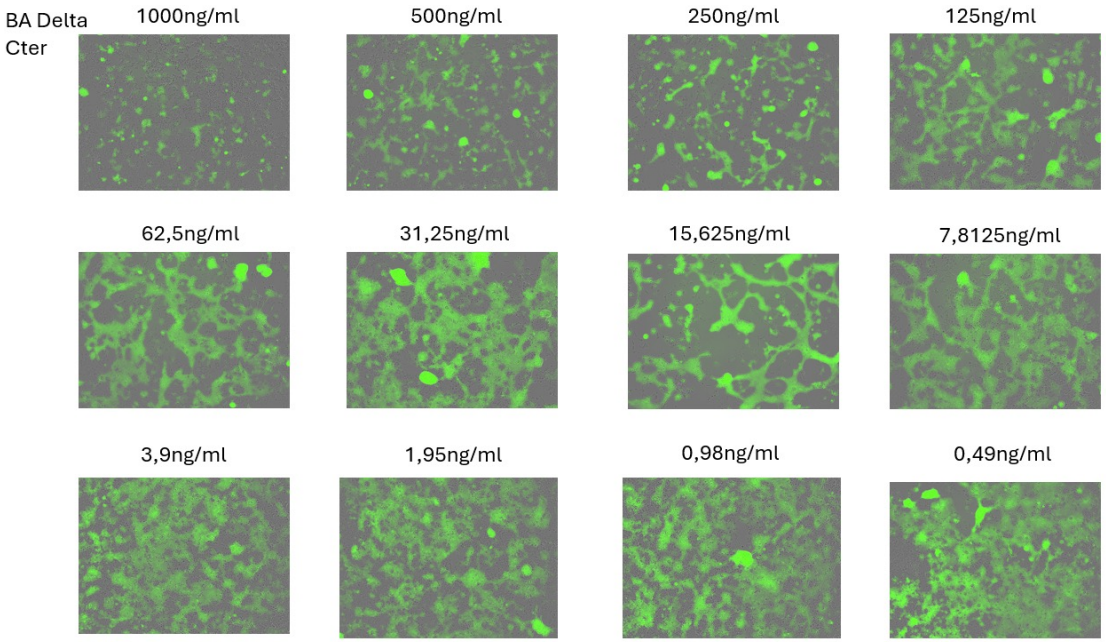
Breakthrough group
Untreated group

2023/24 season
N(breakthrough)= 24 (2 resistant variants)

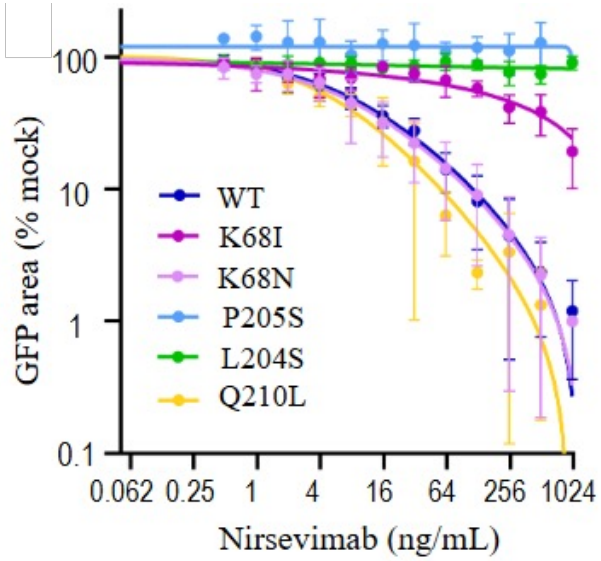
2024/25 season
N (breakthrough)= 184 (23 resistant variants)

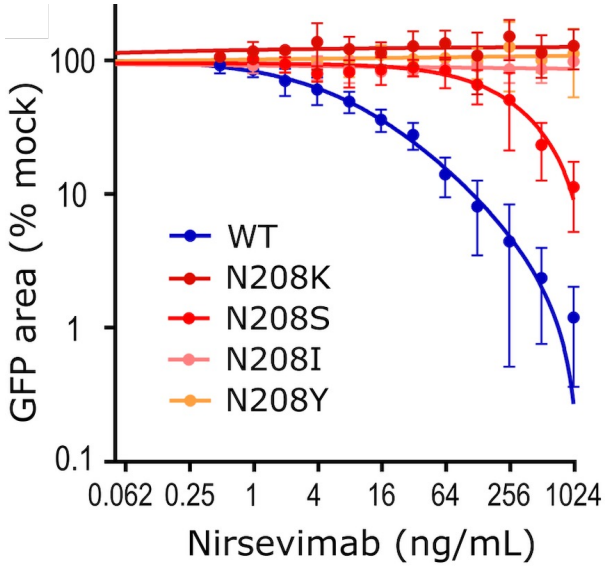
Fusion inhibition assay to assess impact of identified substitutions

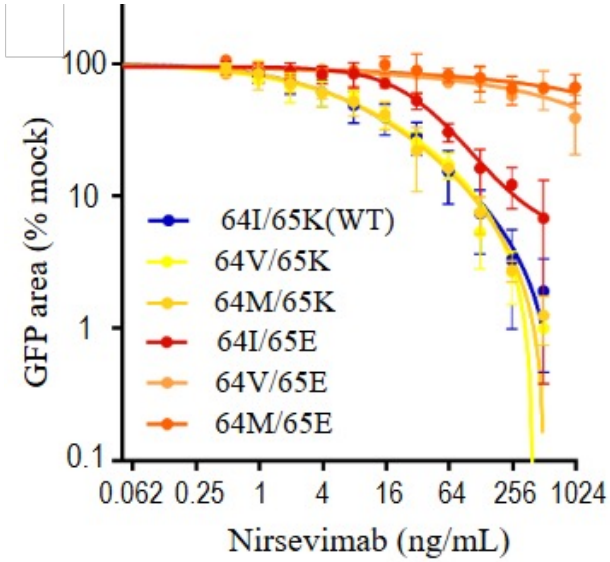




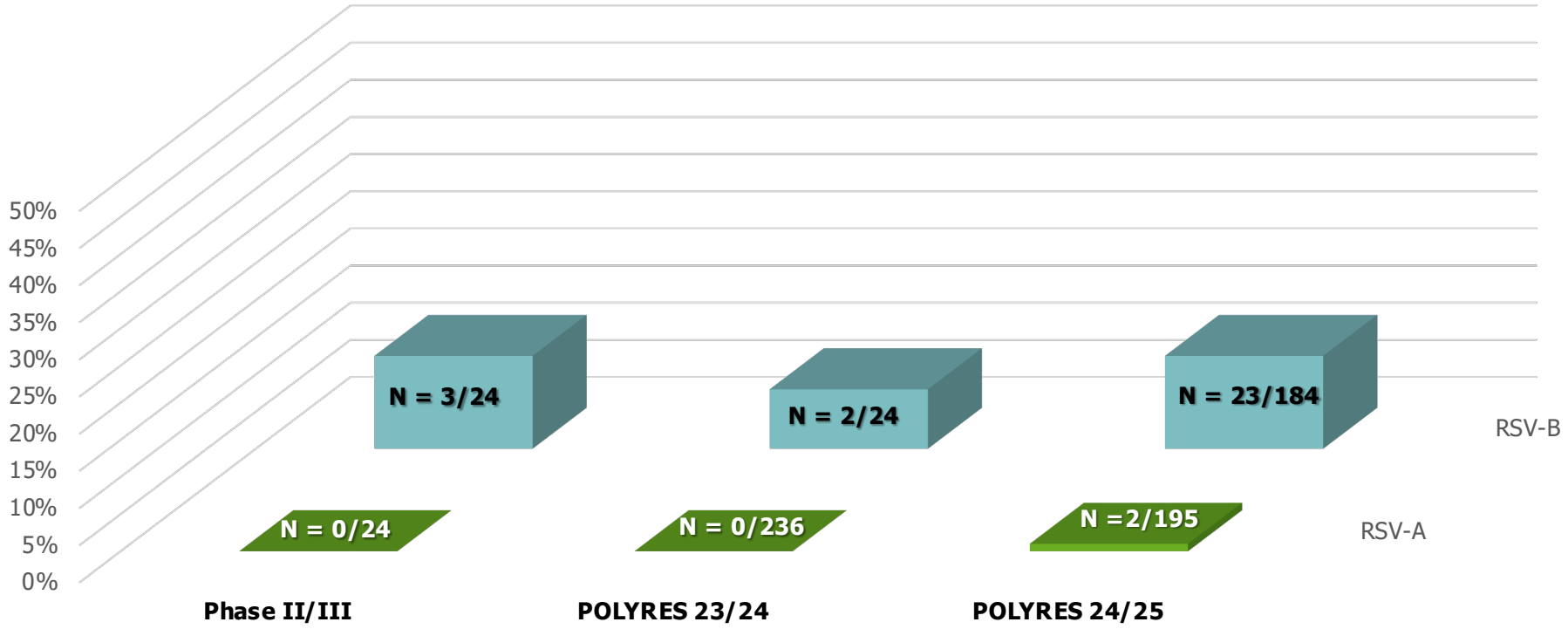
Fusion inhibition assay to assess impact of identified substitutions



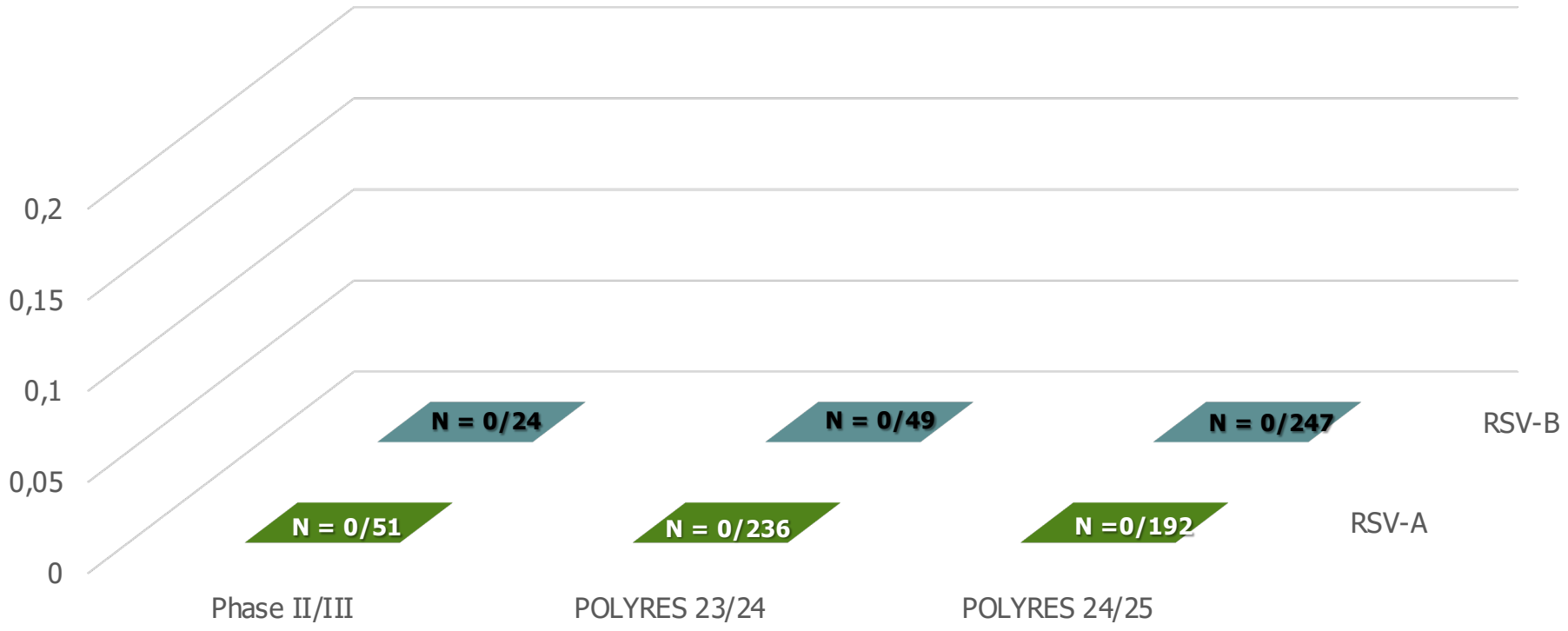




Prevalence of RSV-A and RSV-B Nirsevimab Resistant variants among breakthrough cases



Prevalence of RSV-A and RSV-B Resistant variants among unexposed cases in areas where Nirsevimab was delivered



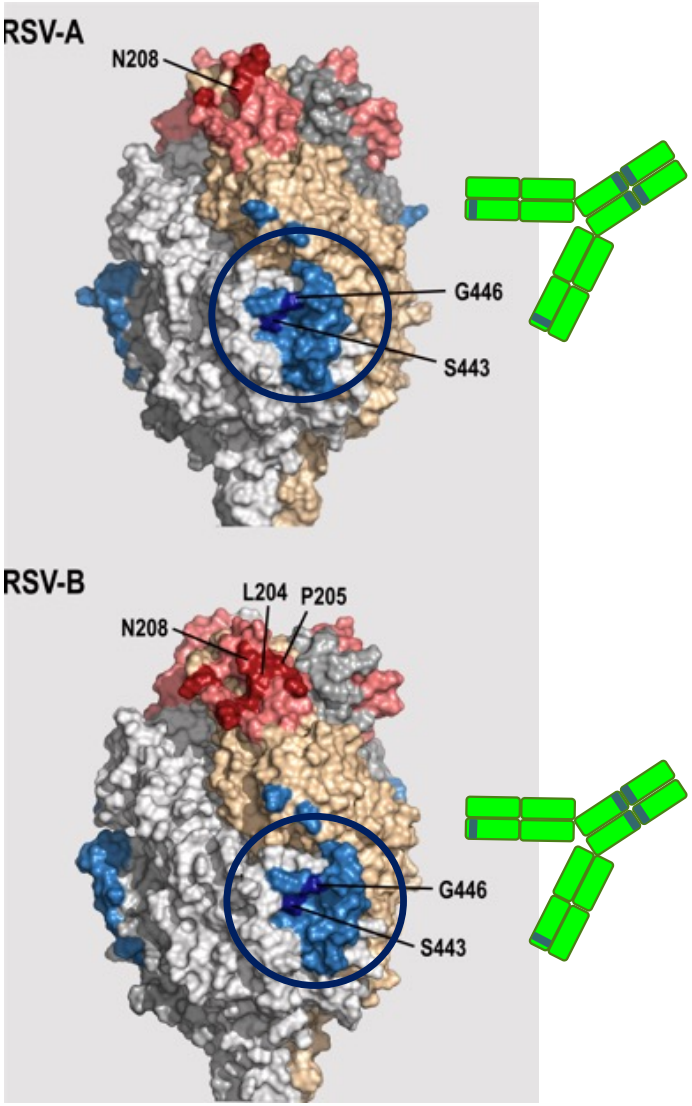
Resistance to clesrovimab

- The amino acid region of site IV (defining the clesrovimab binding site) is highly conserved (>99%)

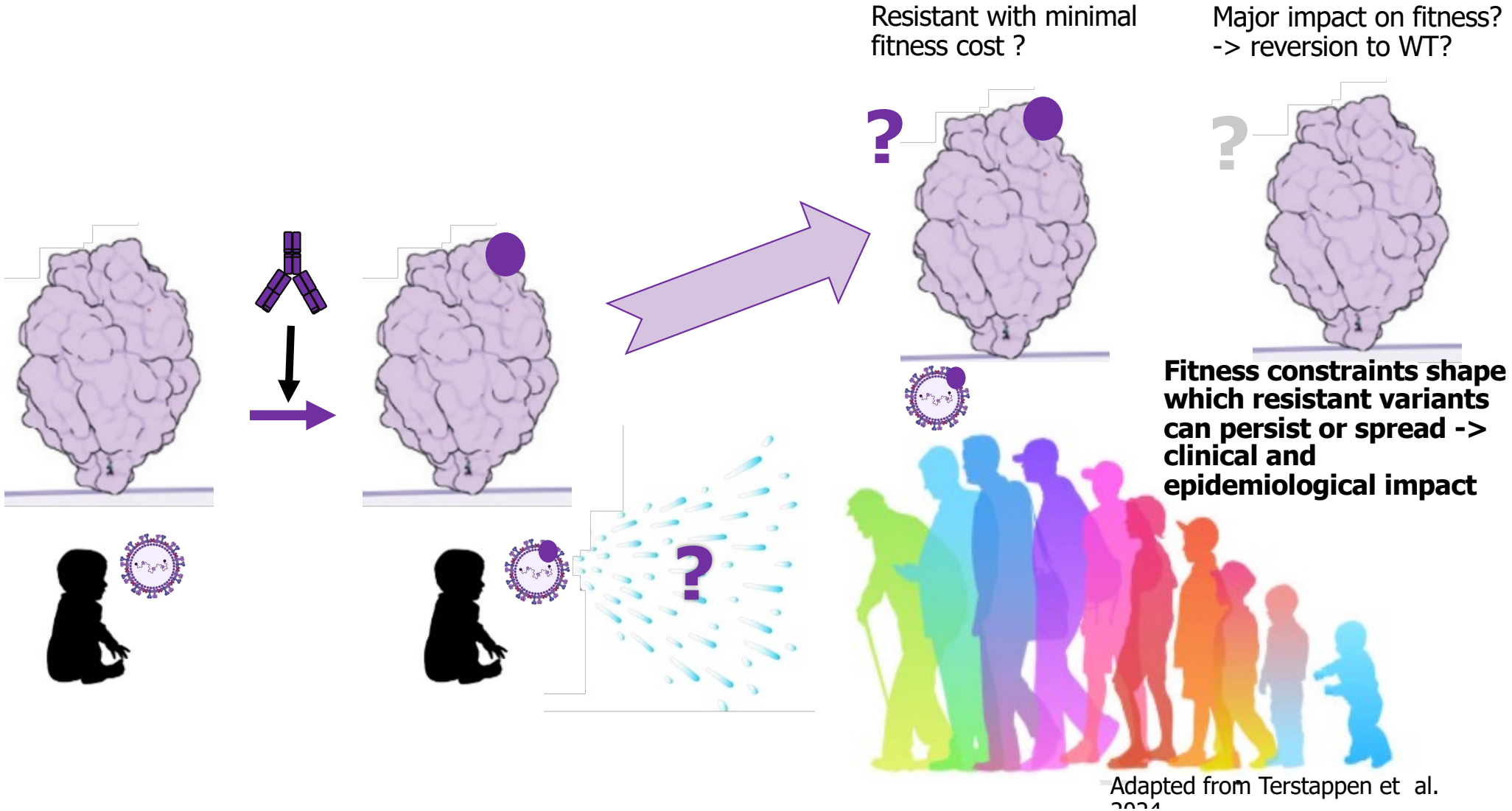
- *In vitro* selection experiments identified several substitutions within the clesrovimab epitope (site IV)

- Some of these substitutions also identified during pivotal phase IIb/III and III clinical trials in patients failing clesrovimab (substitutions G446E/R/W).

- Prospective post-licensure molecular surveillance will be essential to establish resistance frequencies under real-world selective pressure



Are resistant variants transmitted to the community ?



In summary

- The emergence of resistant RSV variants to prophylactic long-acting mAbs is rare so far; no widespread emergence of resistance despite the universal use of nirsevimab in several countries
  - *-> Resistance does not currently compromise their clinical or public health impact.*

- For Nirsevimab : Resistance profiles have been identified among RSV-B breakthrough infections

- For Clesrovimab, resistance data are currently limited to clinical trials with no real-world data yet available.

What do we need for the future ?

Continued integrated molecular and phenotypic surveillance, alongside global data sharing

- long-term persistence and evolutionary potential of resistance remain not documented:
  - clinical longitudinal follow-up of breakthrough infections should be implemented to determine whether RASs persist within hosts
  - experimental fitness studies are needed to quantify the relative replication efficiency of resistant versus non-resistant contemporary RSV variants.

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