



Session 2 Webinar "RSV Insights" GenEpi-BioTrain

RSV Treatment and Vaccine Development

13/12/2024

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Head of the Research Unit on Molecular Mechanisms of Pneumovirus Multiplication
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Head of the National Reference Laboratory for Respiratory Viruses at the Pasteur
Institute (associated laboratory)



Intended Learning Objectives

Specific aims of this session

- Learn about preventive strategies for RSV infection
- Learn about curative strategies for RSV infections
- Learn how to adapt surveillance to new therapeutics

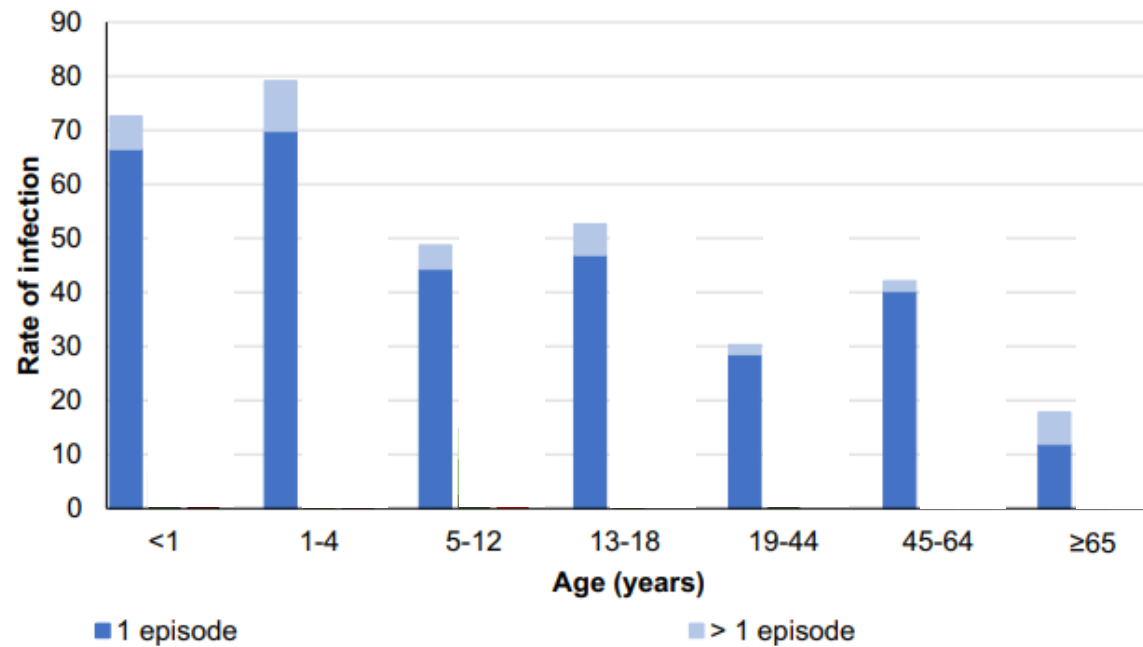
Outline

This session will consist of the following elements

1. Introduction to RSV replication and therapeutic targets
2. Description of prevention tools
3. Description of antivirals in development
4. Risk of viral escape : illustration of a viral surveillance study

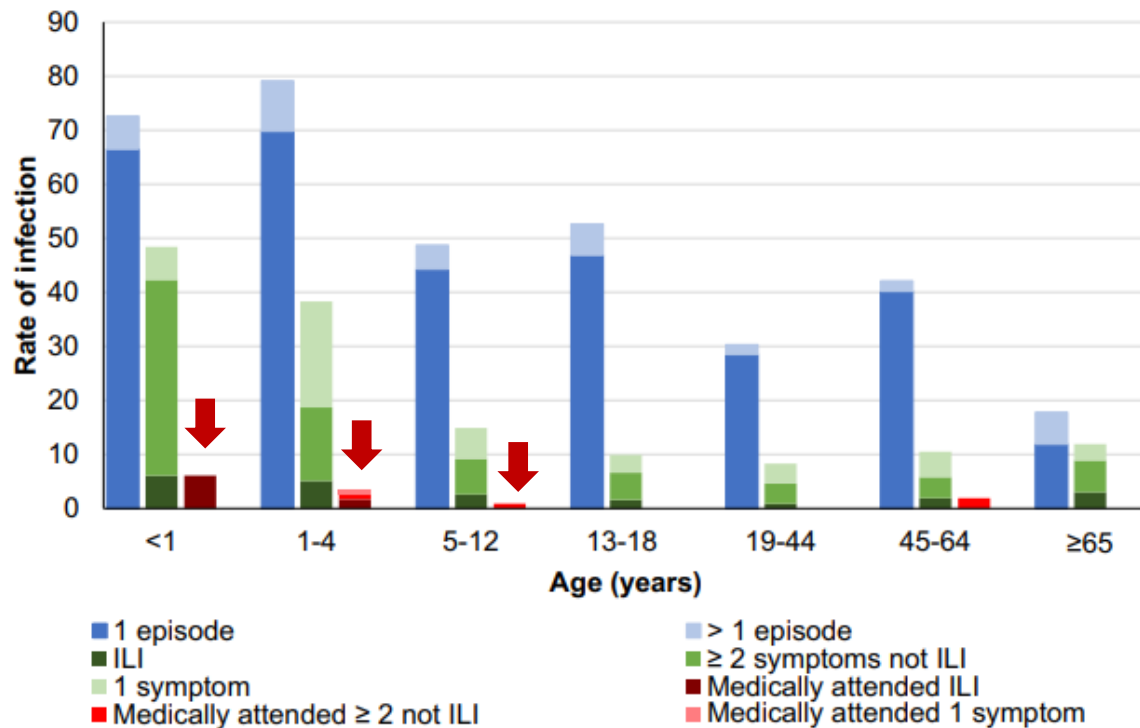
RSV highly prevalent

PHIRST study: 81,430 samples from 1,116 participants in 225 households (follow-up 90%).

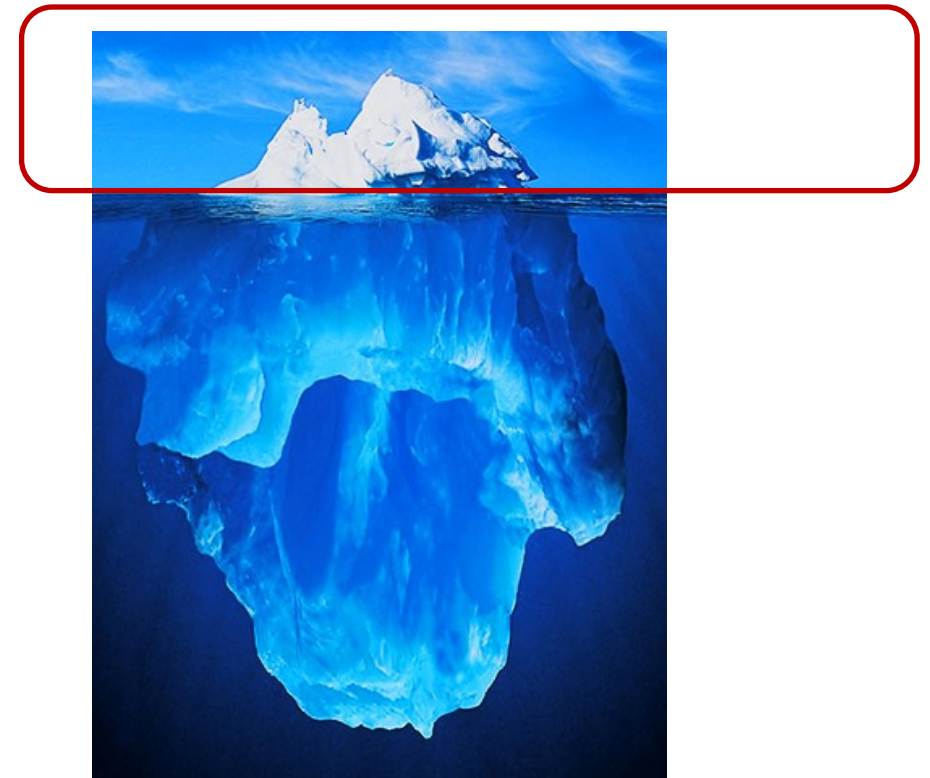


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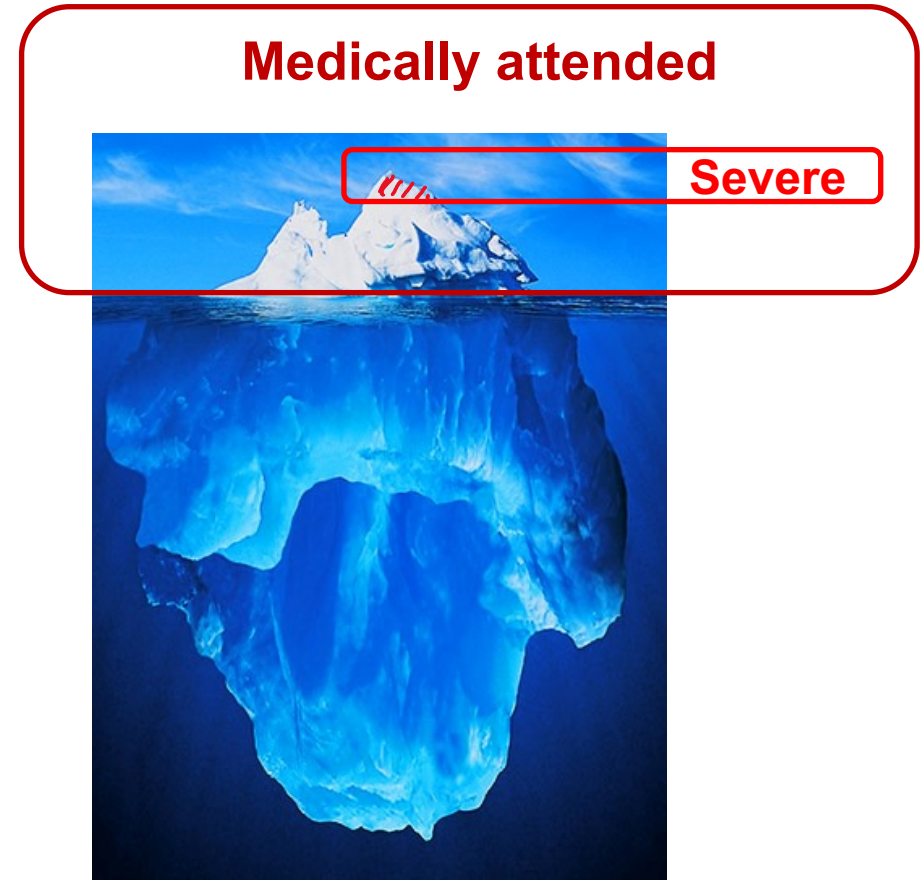
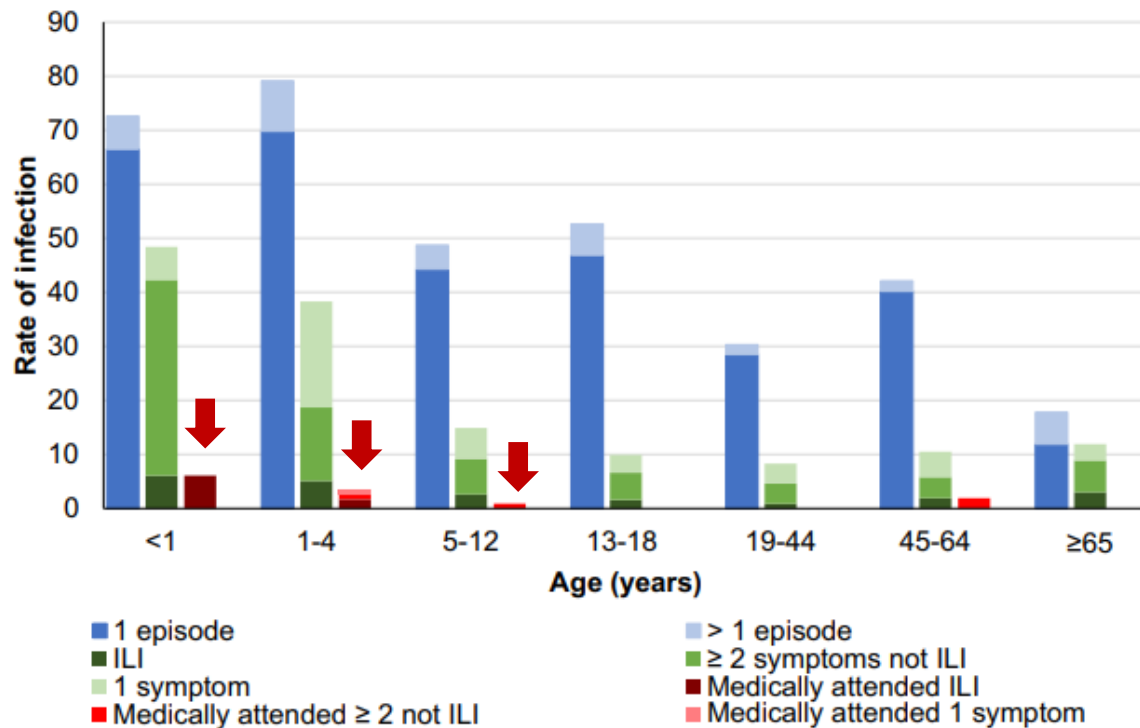


Medically attended



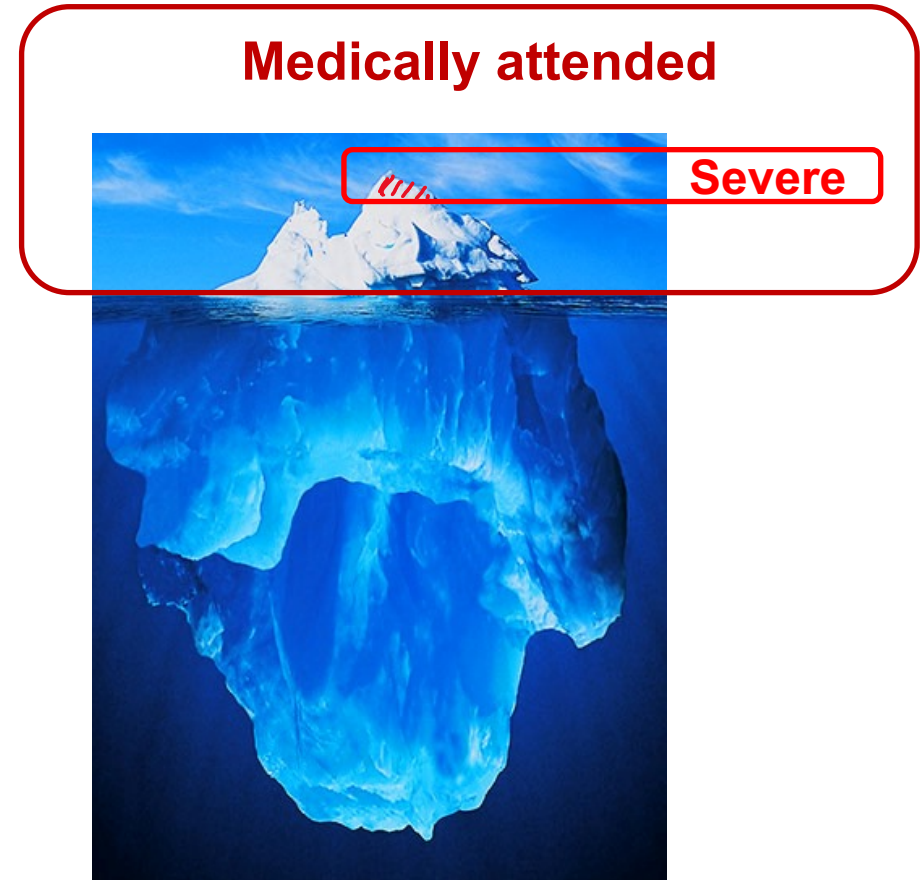
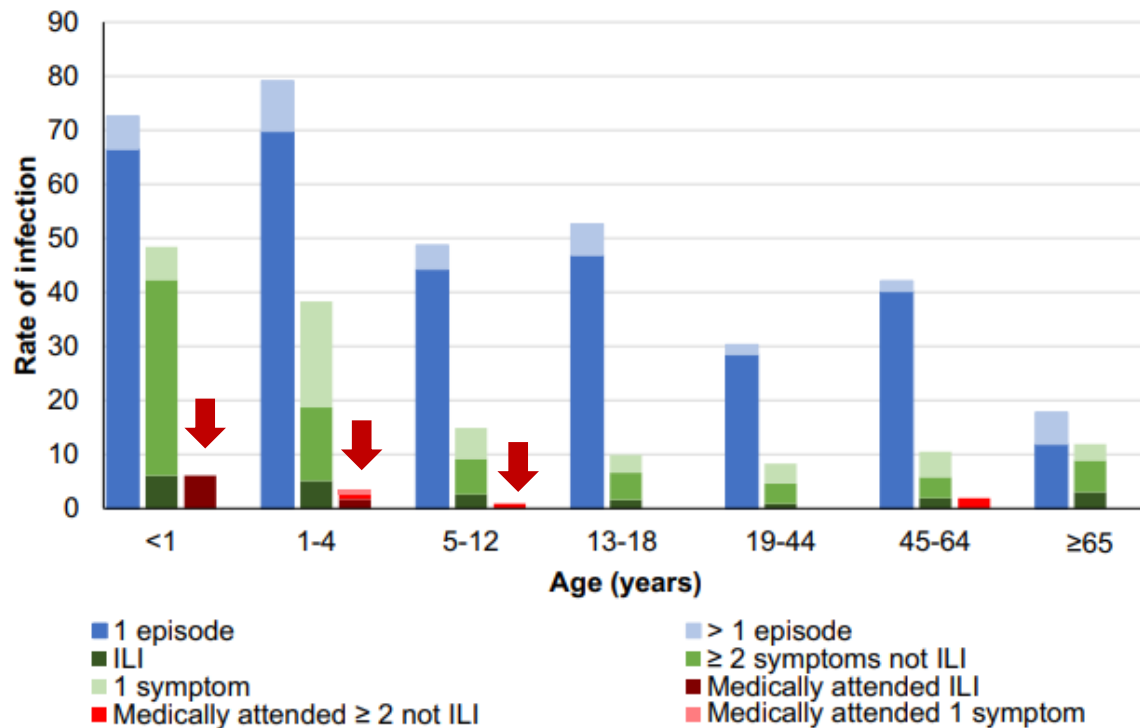
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Target population for RSV infection treatment and prevention

Infants



Elderly



Others ?

Immunosuppressed

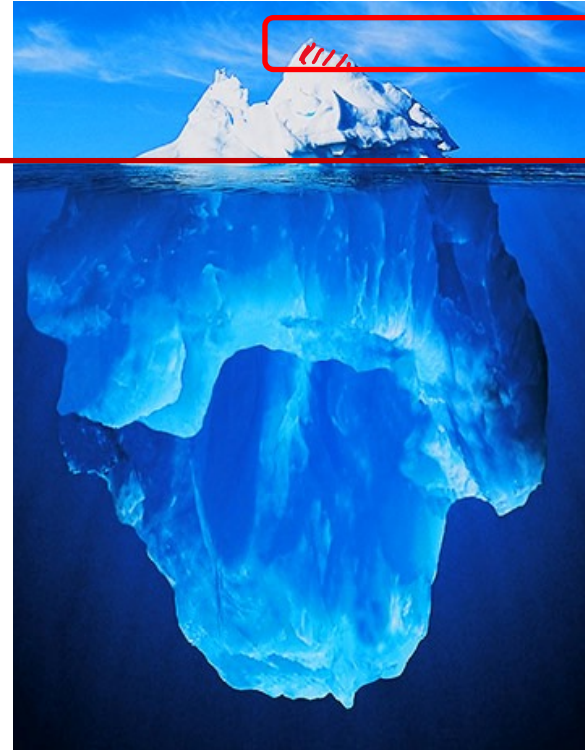


Chronic respiratory conditions



Medically attended

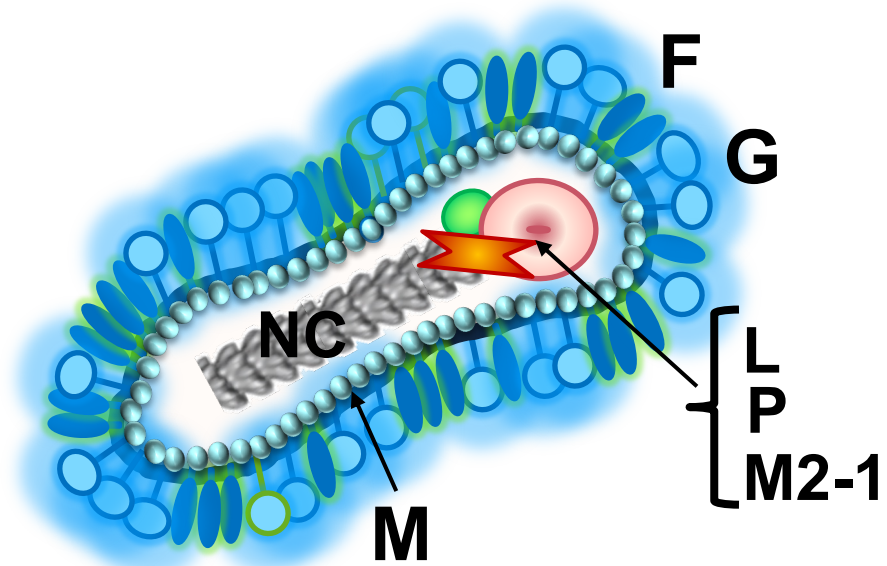
Severe



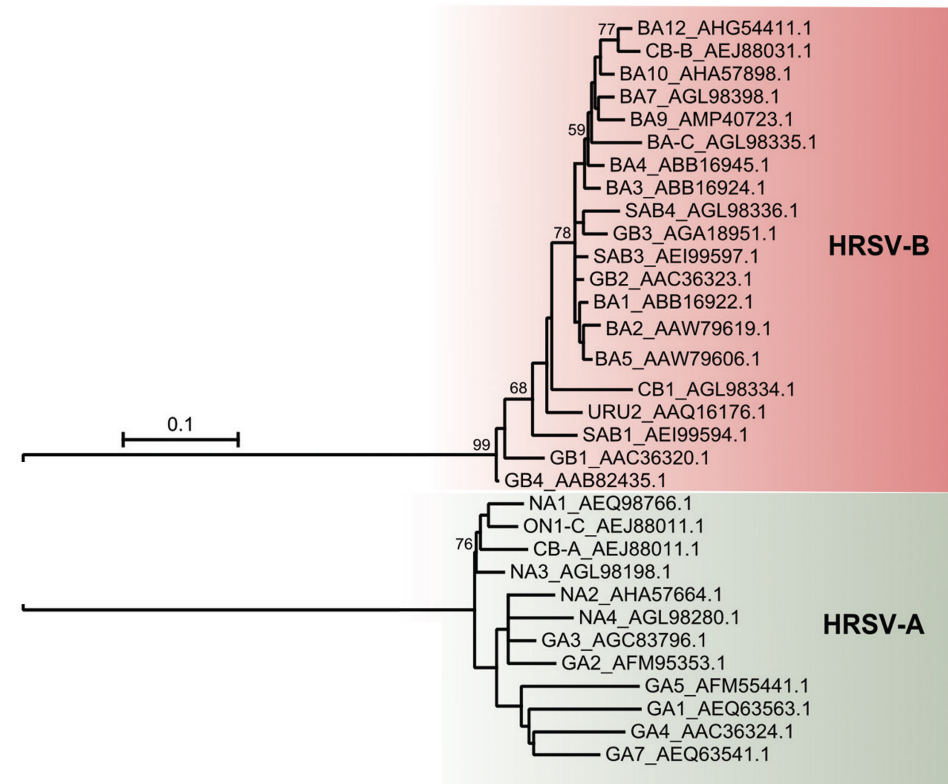
Respiratory syncytial virus

Negative strand RNA virus

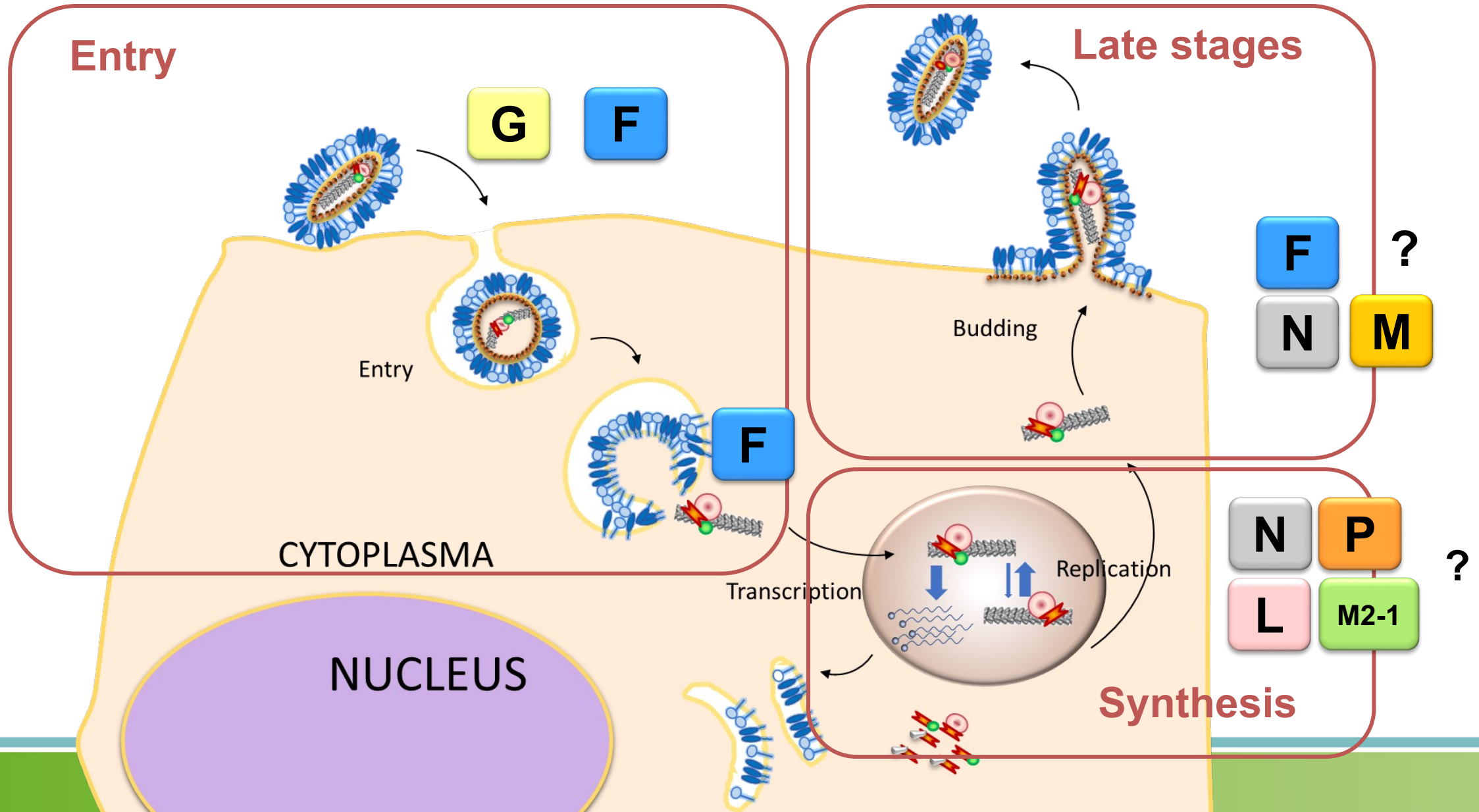
Enveloped



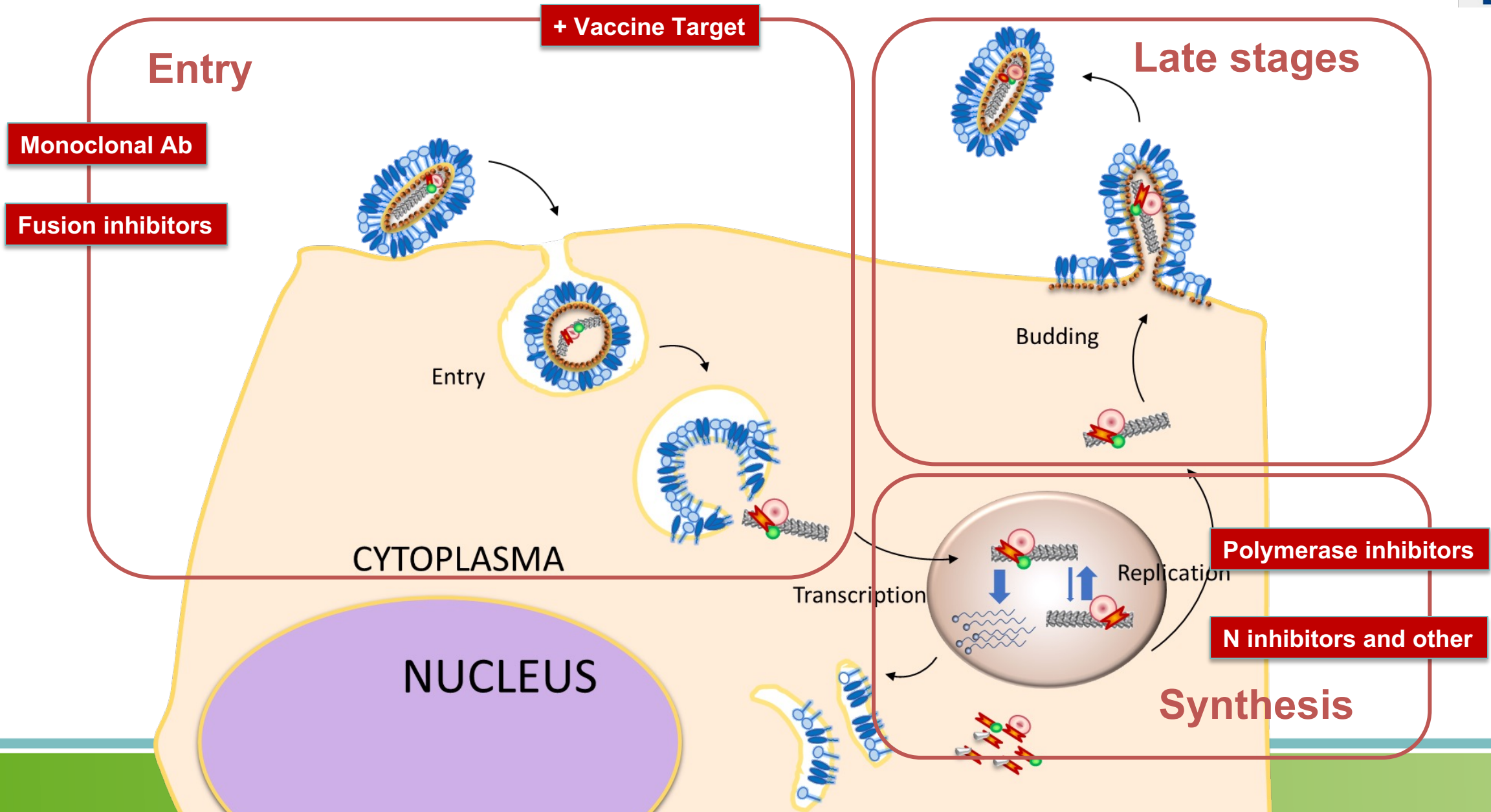
2 groups RSV-A et RSV-B



Respiratory syncytial virus replication cycle



Respiratory syncytial virus replication cycle



Targeting attachment: RSV surface glycoproteins

Glycoprotein **G**

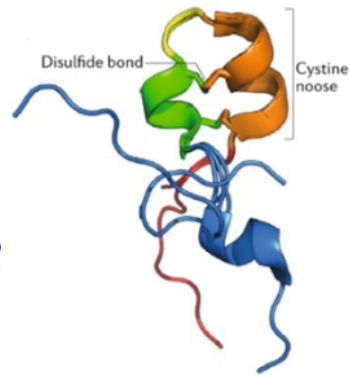
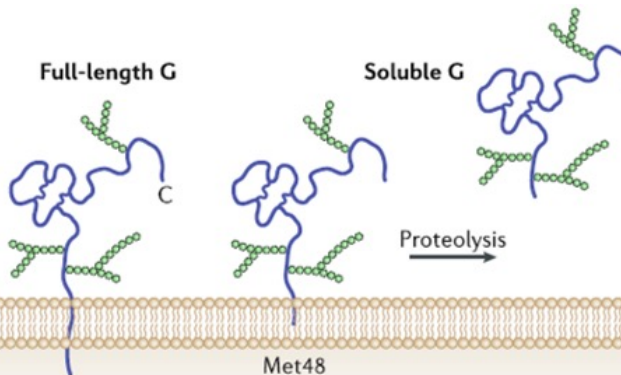
Highly variable ($50\% < \text{inter-group identity}$)

Dispensable

- Attachment
- Immune escape

Unknown structure:

- 2 highly glycosylated region
- Conserved cysteine nose



Battles MB, McLellan JS. Nat Rev Microbiol. 2019 Apr;17(4):233-245.

Targeting attachment: RSV surface glycoproteins

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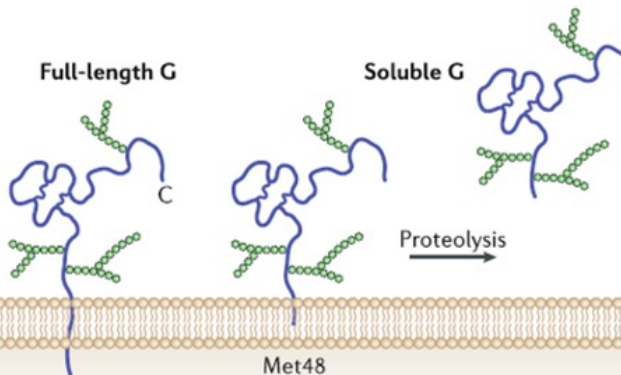
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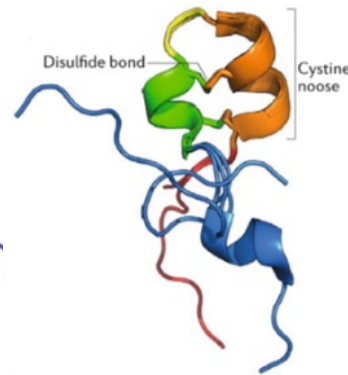


Fusion protein **F**

Conserved ($95\% \text{ inter-group identity}$)

Not Dispensable

- Attachment
- Fusion



Battles MB, McLellan JS. Nat Rev Microbiol. 2019 Apr;17(4):233-245.

Targeting attachment: RSV surface glycoproteins

Glycoprotein **G**

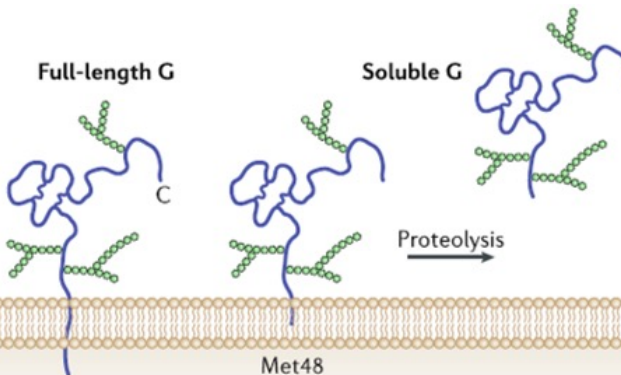
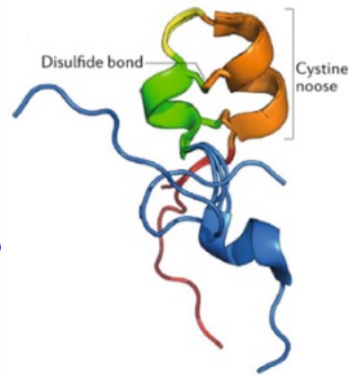
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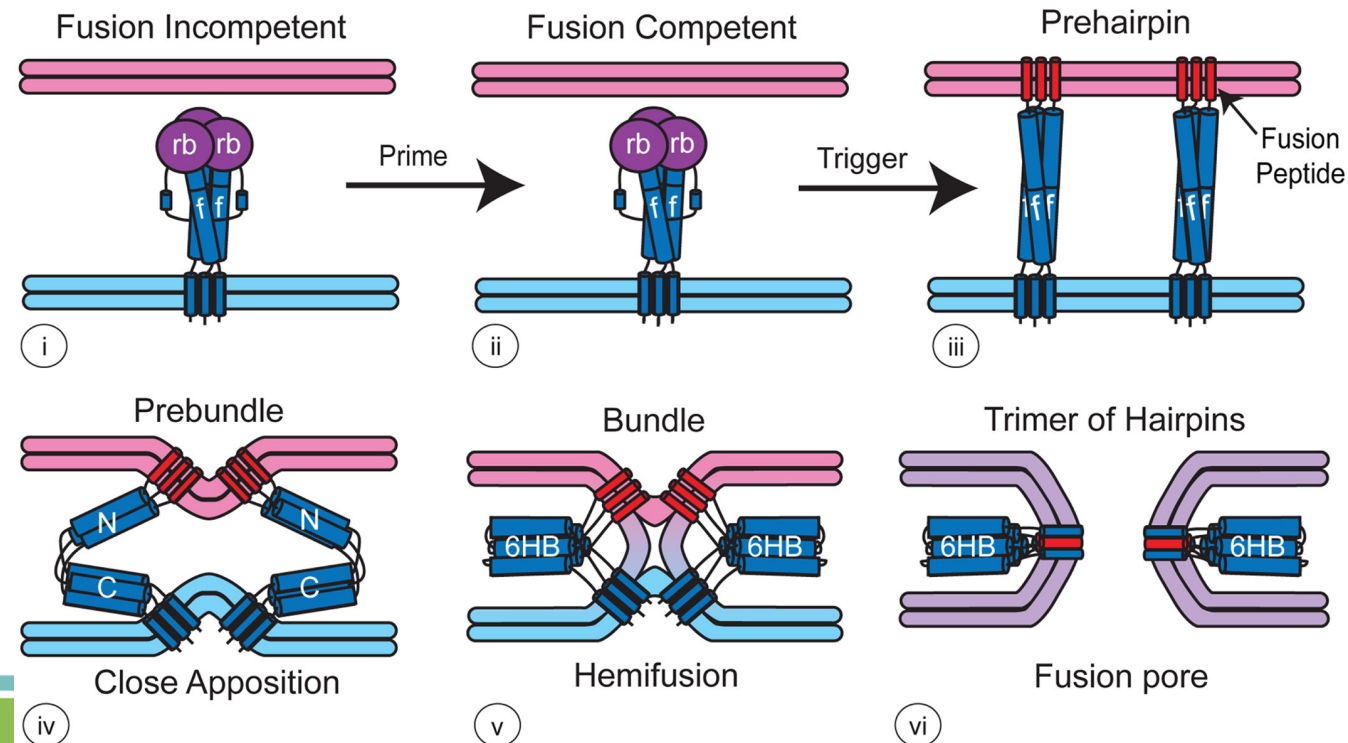
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Fusion protein **F**

Conserved ($95\% \text{ inter-group identity}$)

Not Dispensable



Targeting attachment: RSV surface glycoproteins

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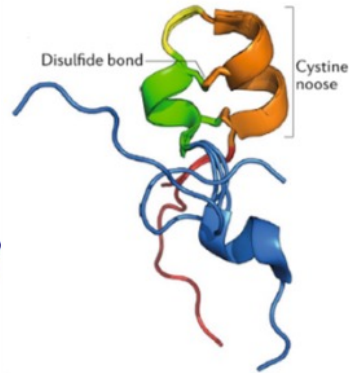
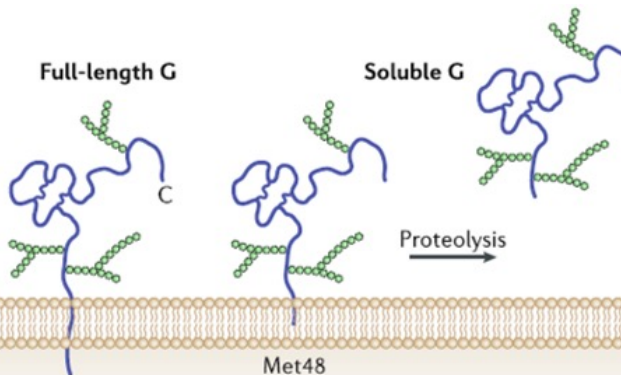
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Fusion protein **F**

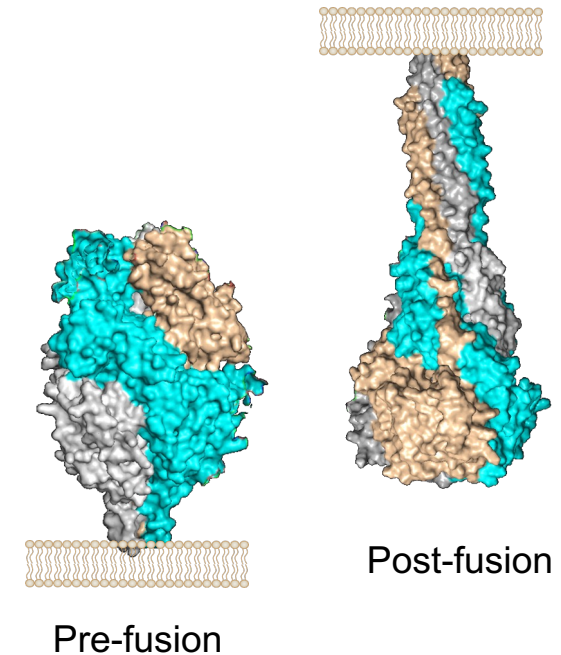
Conserved ($95\% \text{ inter-group identity}$)

Not Dispensable

- Attachment
- Fusion

Two known structures:

- *pre-fusion form*
- *post-fusion form*



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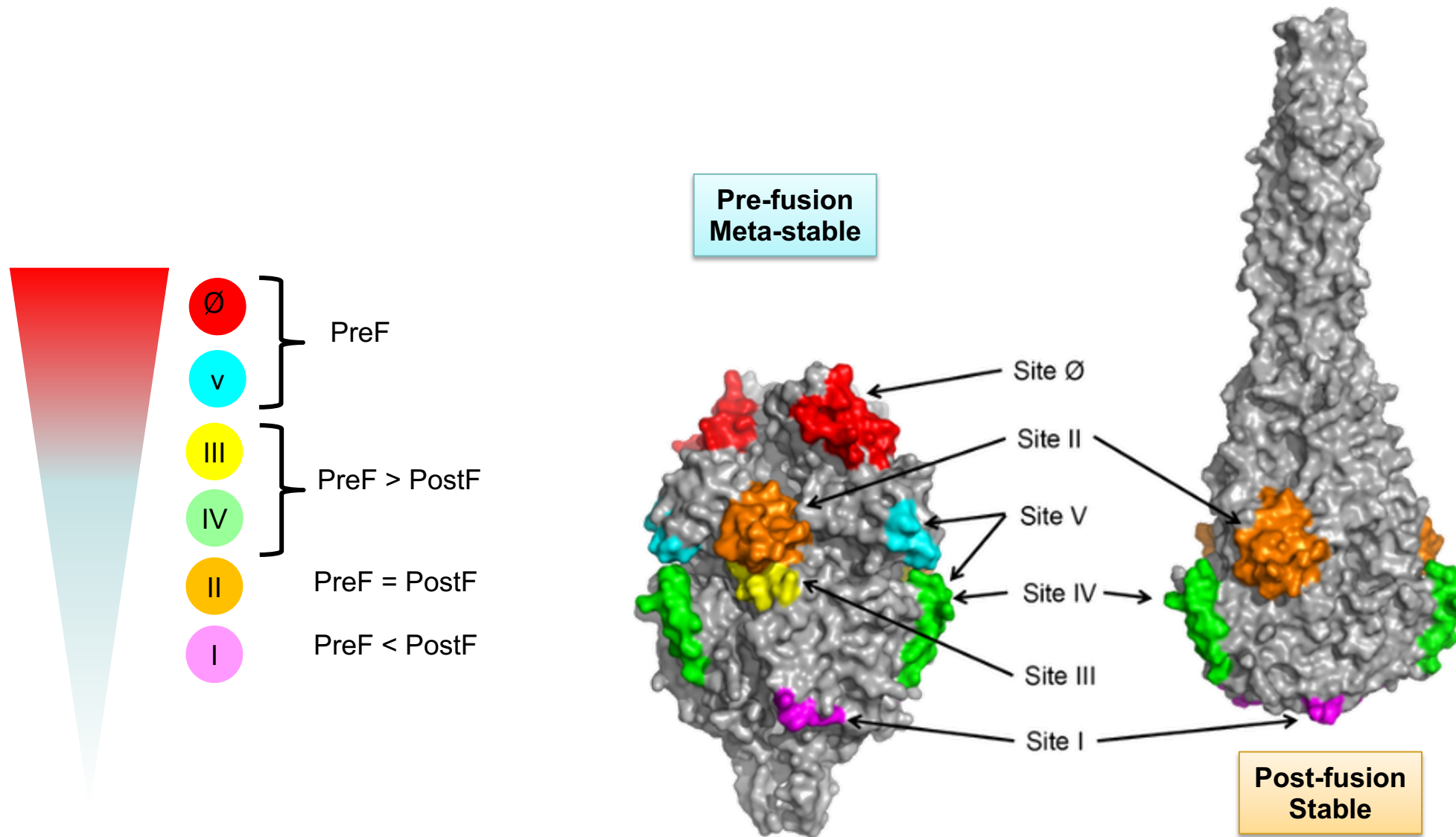
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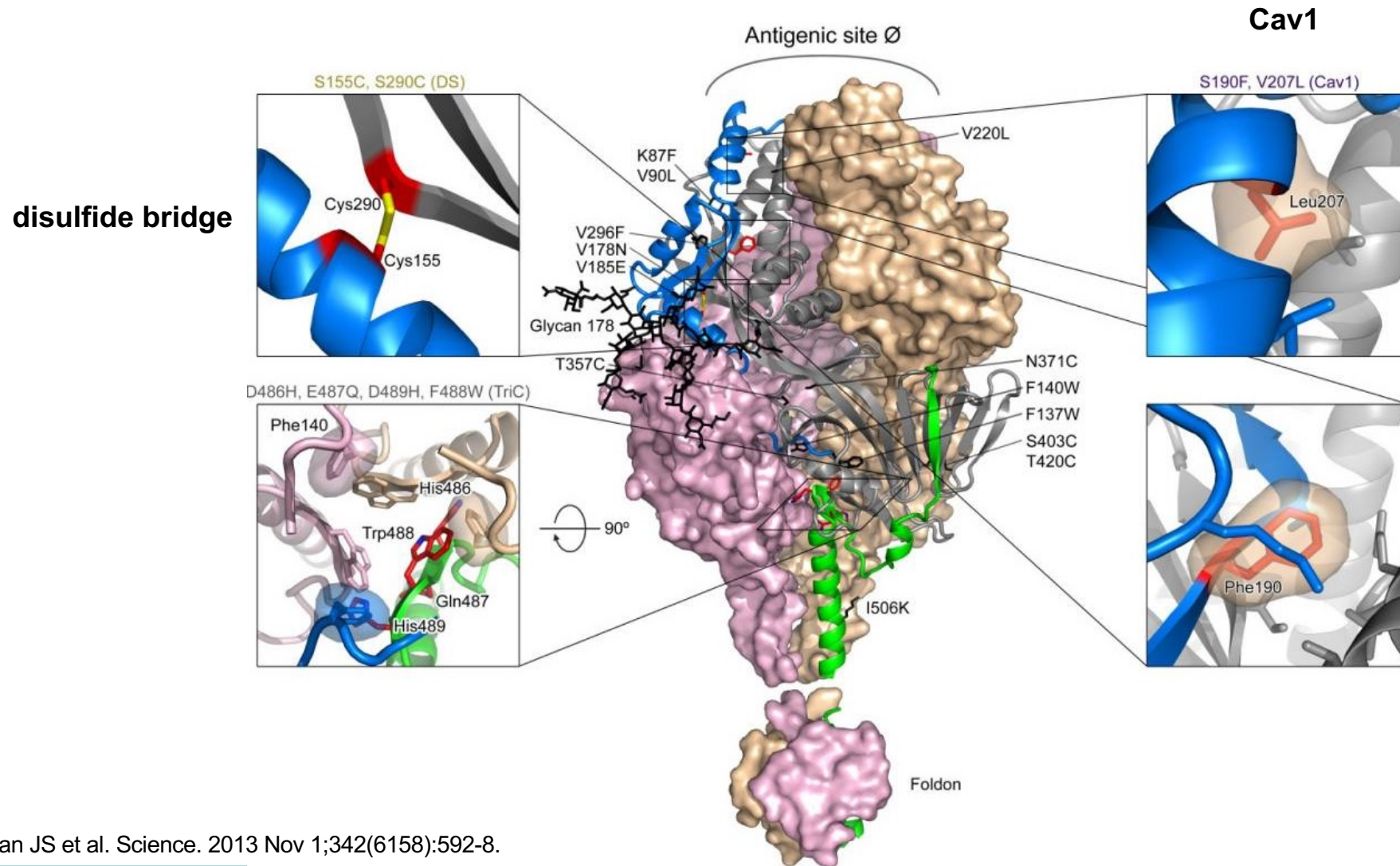
Which protein is mandatory for RSV entry ?

① Start presenting to display the poll results on this slide.

The most potent antigenic sites are only on pre-fusion F



Stabilised pre-fusion F: a new generation of vaccines






➔ **DS-Cav1
Vaccine Candidate**



Approved pre-fusion F vaccines



Vaccine	technology	Population target	Efficacy (Phase III)
 RSVpreF3 (GSK) AREXVY	RSV A2 Recombinant adjuvant vaccine	Adults aged >60 (AReSVi-006)	82.6% efficacy against LRTD ¹ 94.1% effective in protecting against severe LRTD ²
 RSVpreF (Pfizer) ABRYSVO	Bivalent Recombinant vaccine	Adults aged >60 (RENOIR) Pregnant women (MATISSE)	85.7% efficacy against LRTD ³ 81,8% efficacy against severe LRTD within 3M after birth. <i>Safety ??</i>
 mRNA-1345 (Moderna) mRESVIA	mRNA	Adults aged >60	83,7% efficacy against LRTD ⁴

(¹) ≥ 2 lower resp. symptoms or signs > 24h (²) ≥ 3 lower resp. symptoms (³) ≥ 3 signs or symptoms; (⁴) ≥ 2 symptoms

Limitations

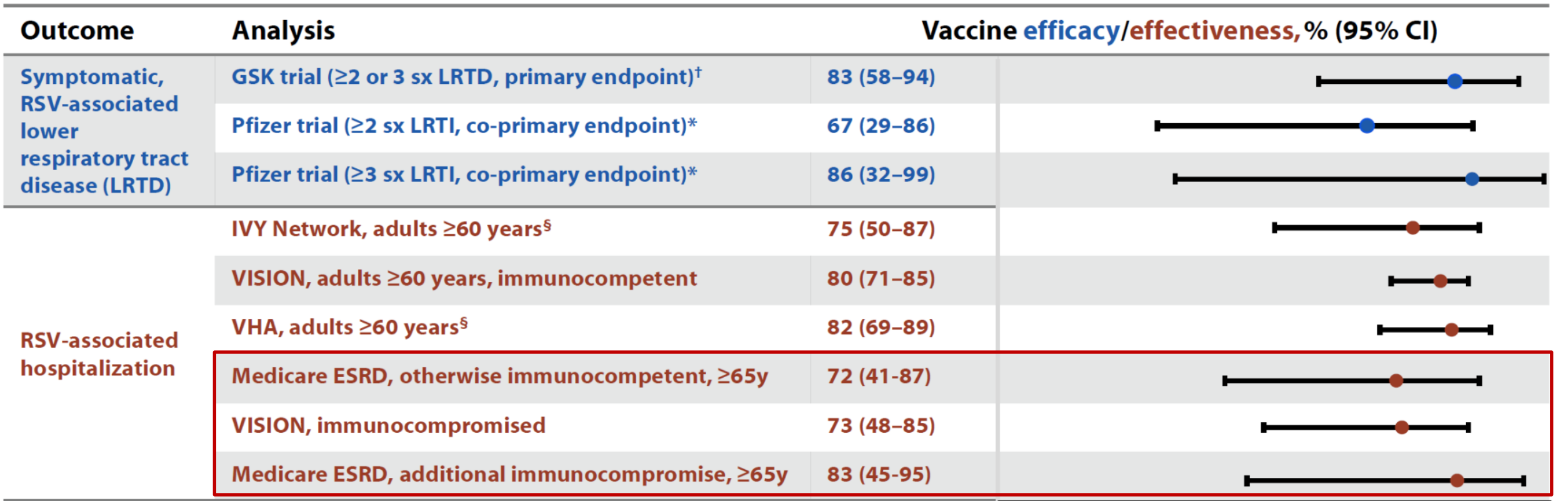
- Efficacy not proven in severe forms due to lack of events
- Efficacy not proven in ≥ 80 years due to lack of events (only 5-8%)
- Immunosuppressed patients not included

Severe RSV infection prevention in elderly



Vaccine	EMA approved Adults >60 years	EMA approved Adults 50-59 years
RSVpreF3 (GSK) AREXVY	YES	YES
RSVpreF (Pfizer) ABRYSVO	YES	NO
mRNA-1345 (Moderna) mRESVIA	YES	NO

Real life data



Abbreviations: LRTI = lower respiratory tract infection; LRTD = lower respiratory tract disease; sx = symptoms or signs; y = years

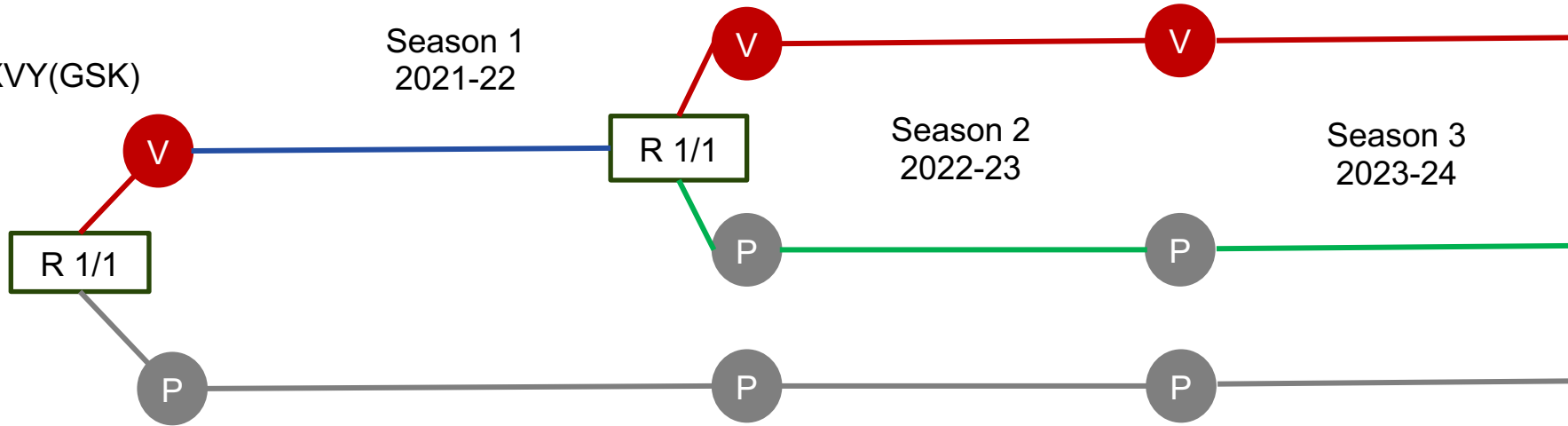
Surie ACIP June 2024

[†] Papi A, et. al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. *N Engl J Med.* 2023;388:595–608. See slide
^{*} Walsh E, et. al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. *N Engl J Med.* 2023;388:1465–77. See sl
[§] Includes patients with immunocompromising conditions in the displayed VE estimate.

Observational VE studies	Methods
IVY Network (CDC)	Test-negative design ^{1,2,3}
VISION (CDC)	
Veterans Health Administration (VHA)	Target trial emulation ^{4,5}
Medicare/end stage renal disease (ESRD) patients	Retrospective cohort

Duration of protection ???

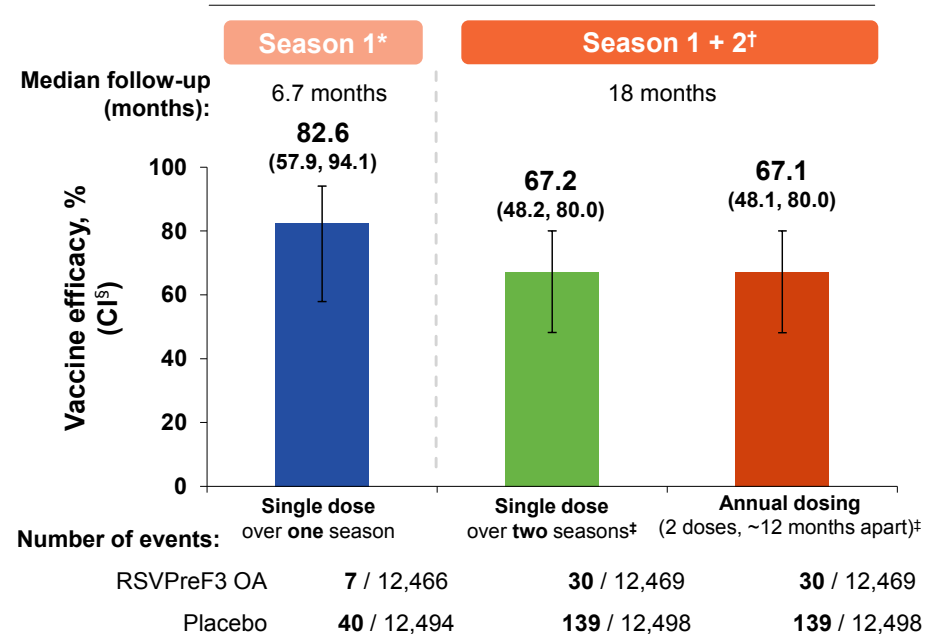
RSVpreF3 AREXVY(GSK)



Revaccination at 1 year of age does not appear to provide additional clinical benefit

Arexvy vaccine

RSV-LRTD



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Approved vaccines for RSV

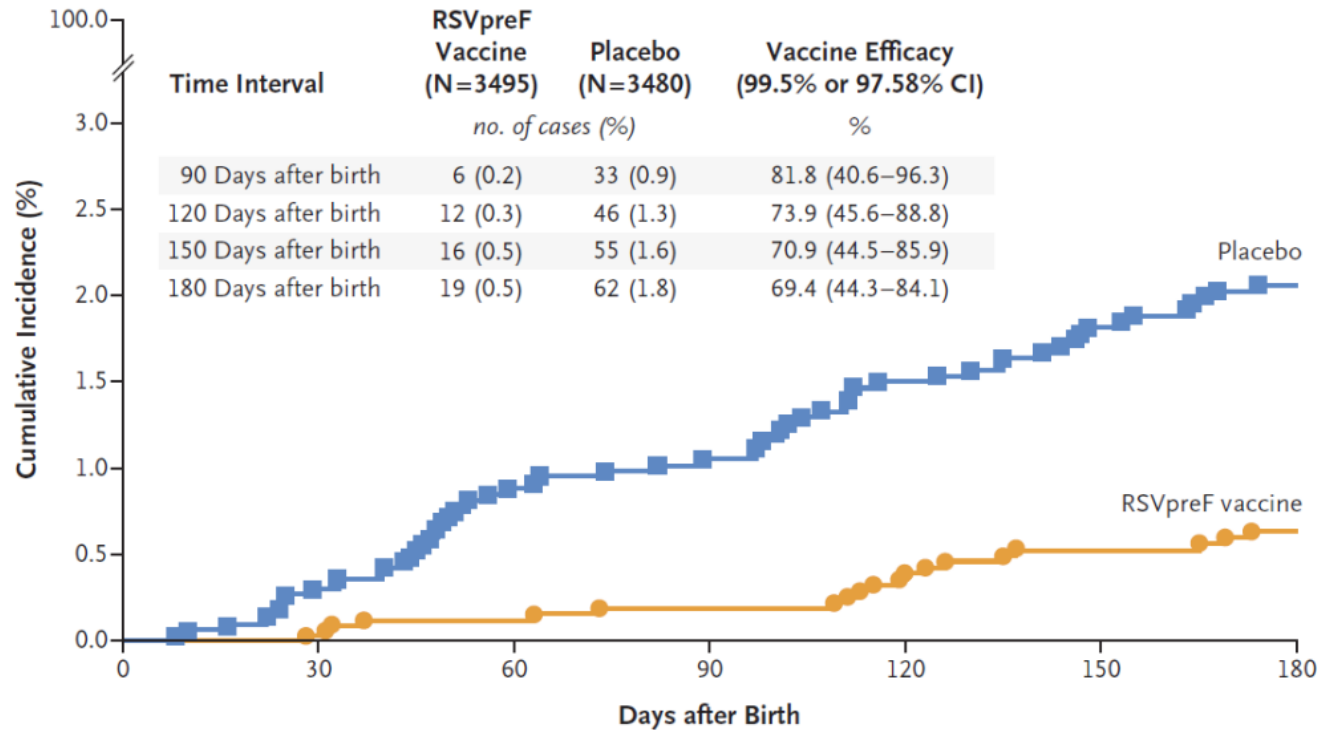
① Start presenting to display the poll results on this slide.

Strategies to prevent severe RSV infection in children

Maternal vaccination



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	2749
RSVpreF vaccine	3495	3349	3042	2981	2916	2867	2820

	Regulatory approval	NITAG recommendations
Australia	24–36 weeks	Yes (28–36 weeks and beyond)
Argentina	32–36 weeks	Yes (32–36 weeks)
Bahrain	24–36 weeks	Unknown or not yet available
Brazil	24–36 weeks	Unknown or not yet available
Canada	32–36 weeks	Yes (32–36 weeks)
EU*	24–36 weeks	Austria (24–26 weeks), Belgium (28–36 weeks), France (32–36 weeks), Luxembourg (32–36 weeks)
Hong Kong	32–36 weeks	Unknown or not yet available
Japan	24–36 weeks	Unknown or not yet available
Macau	32–36 weeks	Unknown or not yet available
Qatar	24–36 weeks	Unknown or not yet available
Saudi Arabia	24–36 weeks	Unknown or not yet available
United Arab Emirates	24–36 weeks	Unknown or not yet available
UK	28–36 weeks	Yes (28–36 weeks)
USA	32–36 weeks	Yes (32–36 weeks)
Uruguay	32–36 weeks	Yes (32–36 weeks)

Information is accurate as of July 19, 2024 (Snow V, Pfizer, personal communication). NITAG=National Immunization Technical Advisory Group. RSVpreF=respiratory syncytial virus prefusion F. *European Medicines Agency authorisation applies to all EU countries and to Iceland, Norway, and Lichtenstein.

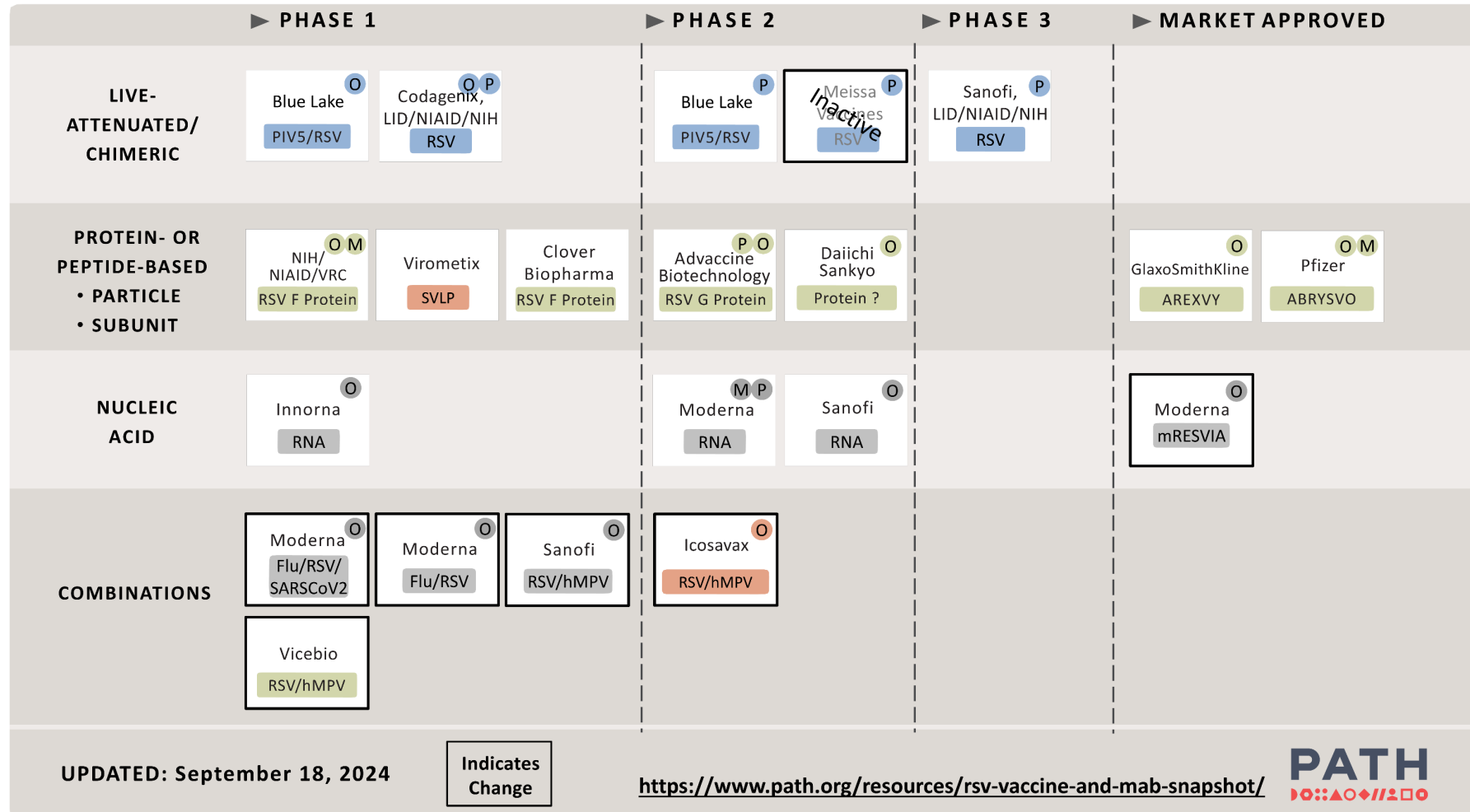
Table 1: Gestational age windows for RSVpreF maternal vaccine

New vaccines in development



RSV Vaccine and mAb Snapshot

TARGET INDICATION: **P** = PEDIATRIC **M** = MATERNAL **O** = OLDER ADULT
 PLATFORM KEY: **Blue** = LIVE/CHIMERIC **Orange** = PARTICLE **Green** = SUBUNIT
Grey = NUCLEIC ACID **Purple** = mAb

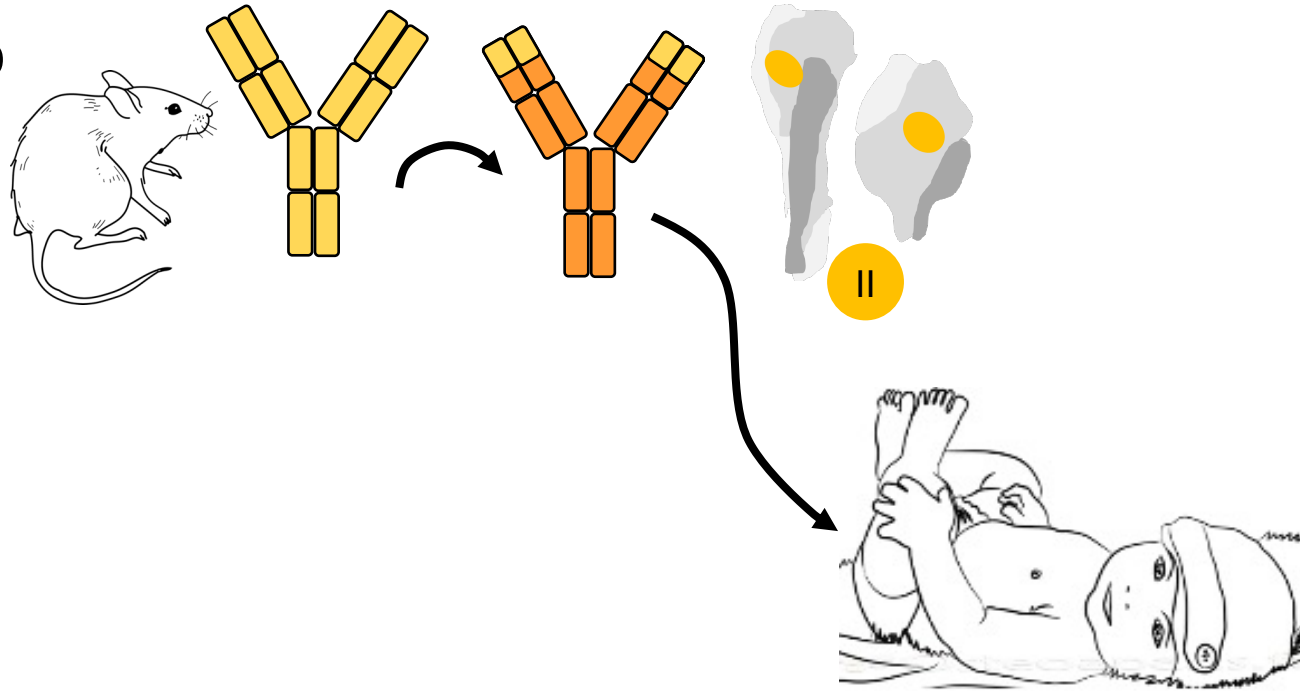


Monoclonal antibodies targeting F

Palivizumab

Poor benefit
risk ratio

Motavizumab

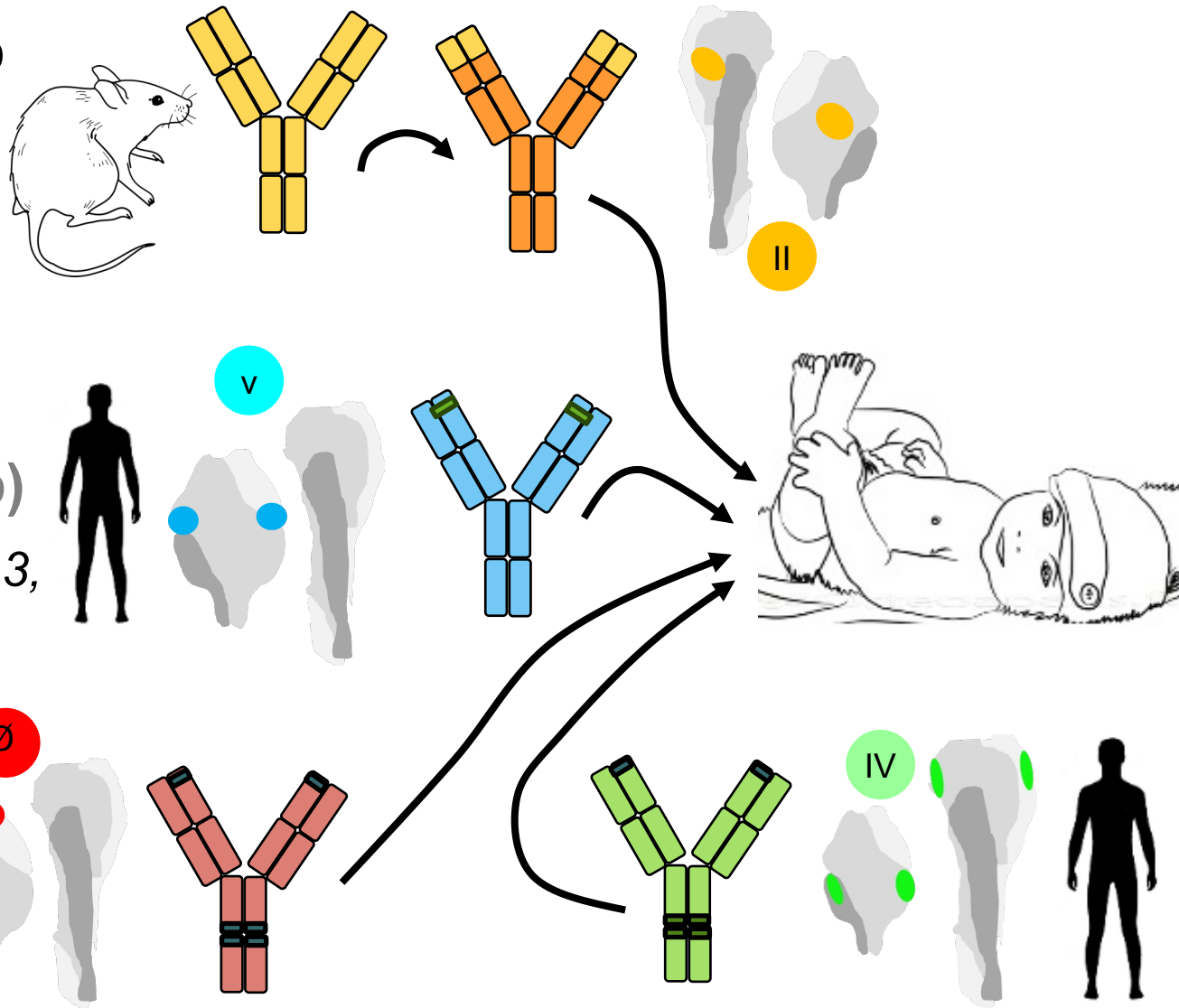


Monoclonal antibodies targeting F

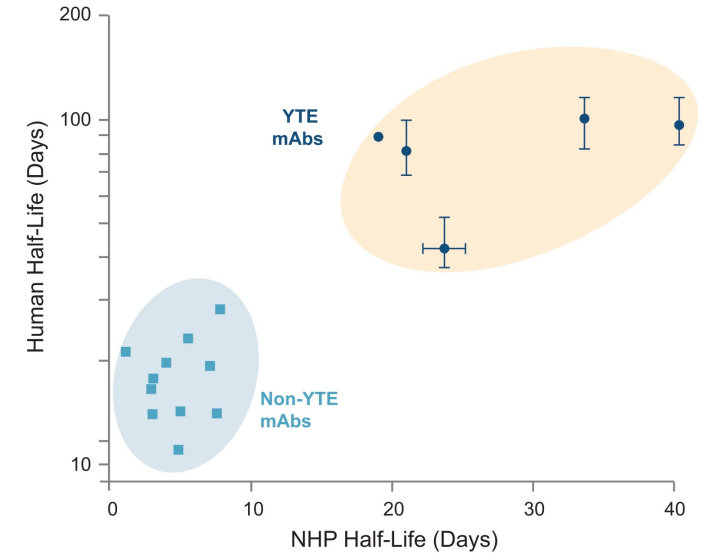
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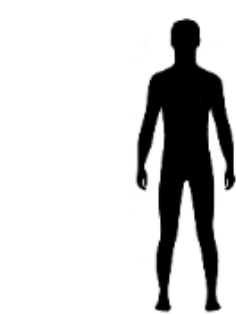


YTE mutation in Fc fragment to
increase half life Oganessian V, et
al. Mol Immunol. 2009



REGN2222 (Suptavumab)

Failure in Phase 3,
resistance



MED8897

Nirsevimab Beyfortus : Autorised

MK-1654 (Clesrovimab)

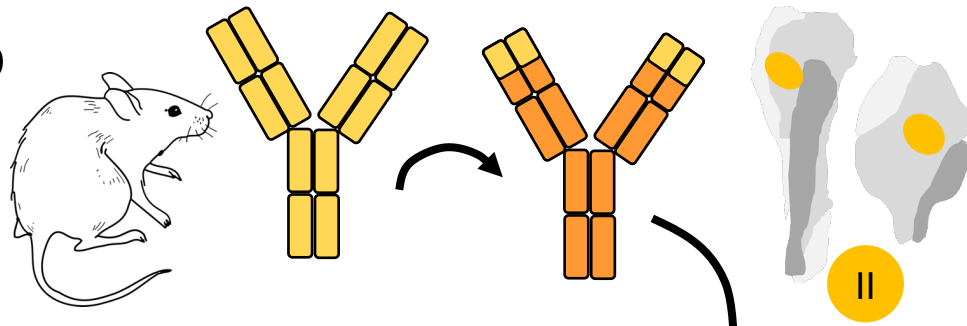
Phase 3

Monoclonal antibodies targeting Fc

Palivizumab

Poor benefit
risk ratio

Motavizumab

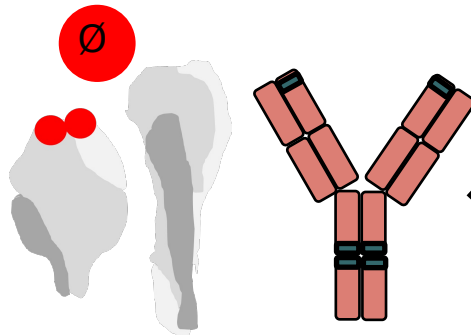
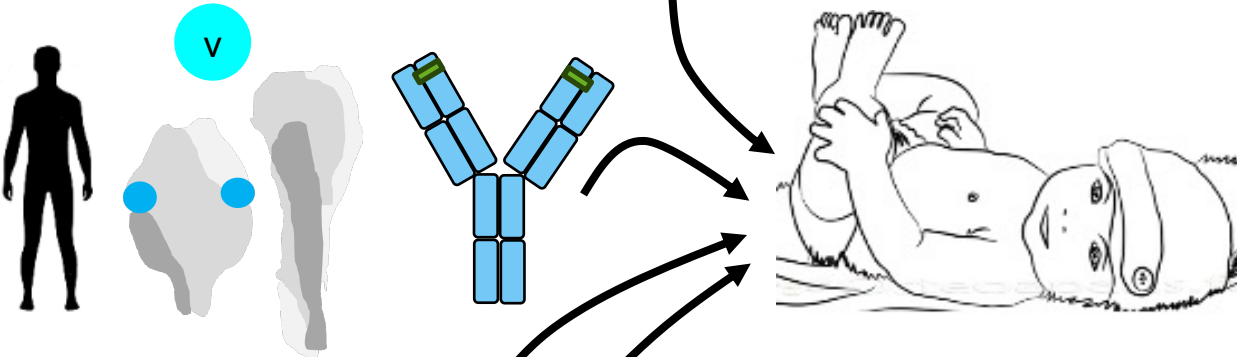


YTE mutation in Fc fragment to increase half life Oganessian V, et al. Mol Immunol. 2009

TNM001
Zhuhai Trinomab
Phase 2

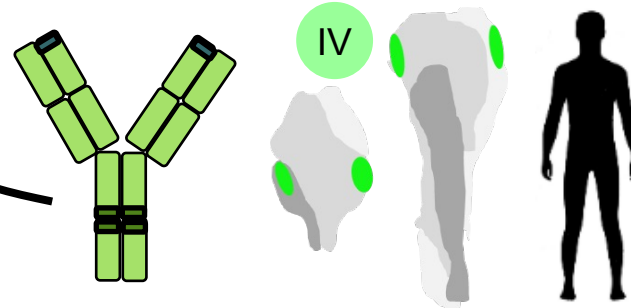
REGN2222 (Suptavumab)

*Failure in Phase 3,
resistance*



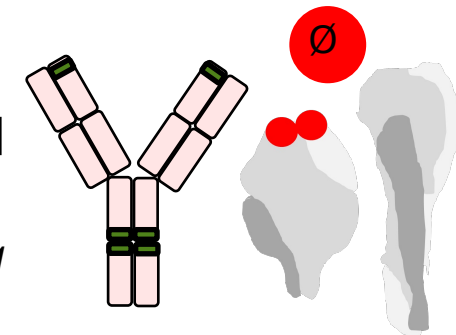
MED8897

Nirsevimab Beyfortus : Autorised

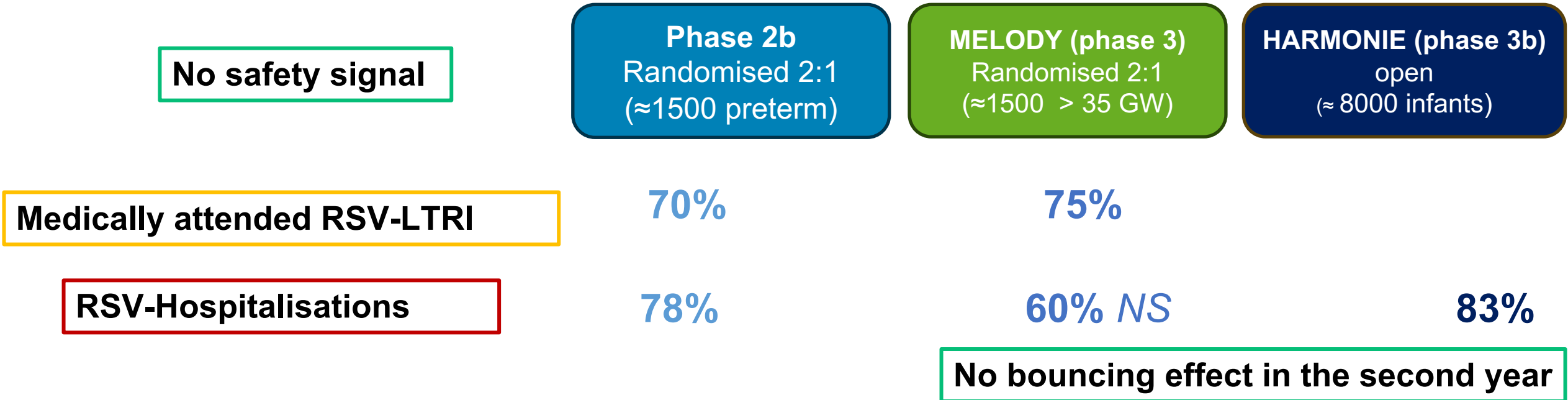


MK-1654 (Clesrovimab)
Phase 3

RSM01
Gates
Phase 1



Nirsevimab: Prevention of severe RSV infection in all newborn for their first RSV season



EMA (oct 2022) and FDA (july 2023) approved for prevention of RSV severe infection in all infants

First year real life data



In France

Good safety profile
(ANSM 30/09/24)

ENVIE
Prospective observational
multicenter case-control



RSV Hospitalisation: 83,0%

PARI Network

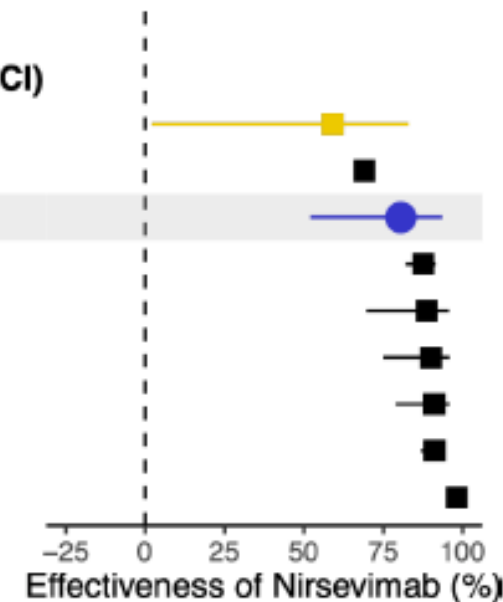


Medically attended RSV-LTRI: 26-53%

Same data in other countries

RSV-associated hospitalization

Study	Design	Country	Time	Effectiveness (95%CI)
Hammitt 2022	trial	Multi-country	19/20 season	59 (2.1–82.9)
Ernst 2024	observational	Luxembourg	Oct–Dec	69 (NA–NA)
Current study	observational	US	Oct–May	80.5 (52–93.5)
Coma 2024	observational	Spain	Oct–Jan	87.6 (82.1–91.4)
Ezpeleta 2024	observational	Spain	Oct–Jan	88.7 (69.6–95.8)
Moline 2024	observational	US	Oct–Feb	90 (75–96)
NVSN study	observational	US	Oct–Mar	91 (79–96)
Barbas del Buey 2024	observational	Spain	Oct–Feb	91.1 (86.9–94)
VISION study	observational	US	Oct–Mar	98 (95–99)



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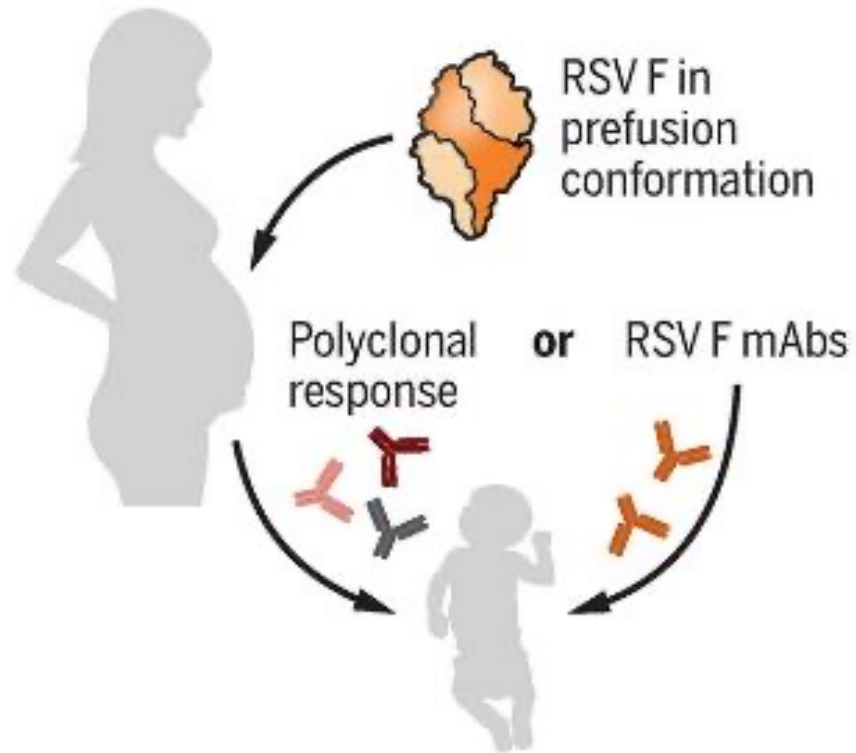


Nirsevimab (Beyfortus)

① Start presenting to display the poll results on this slide.

Strategies to prevent severe RSV infection in children

Passive immunisation of newborn babies



2024-2025 Season: maternal vaccine or nirsevimab ?

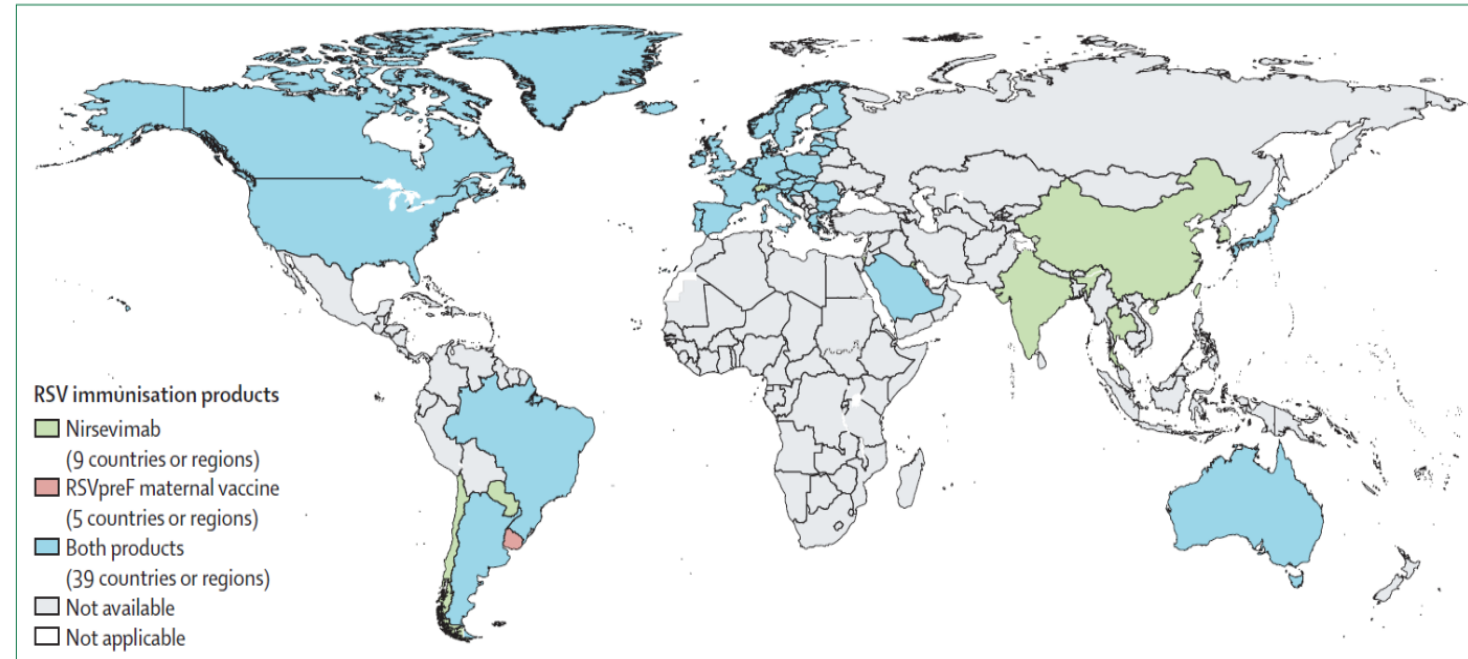
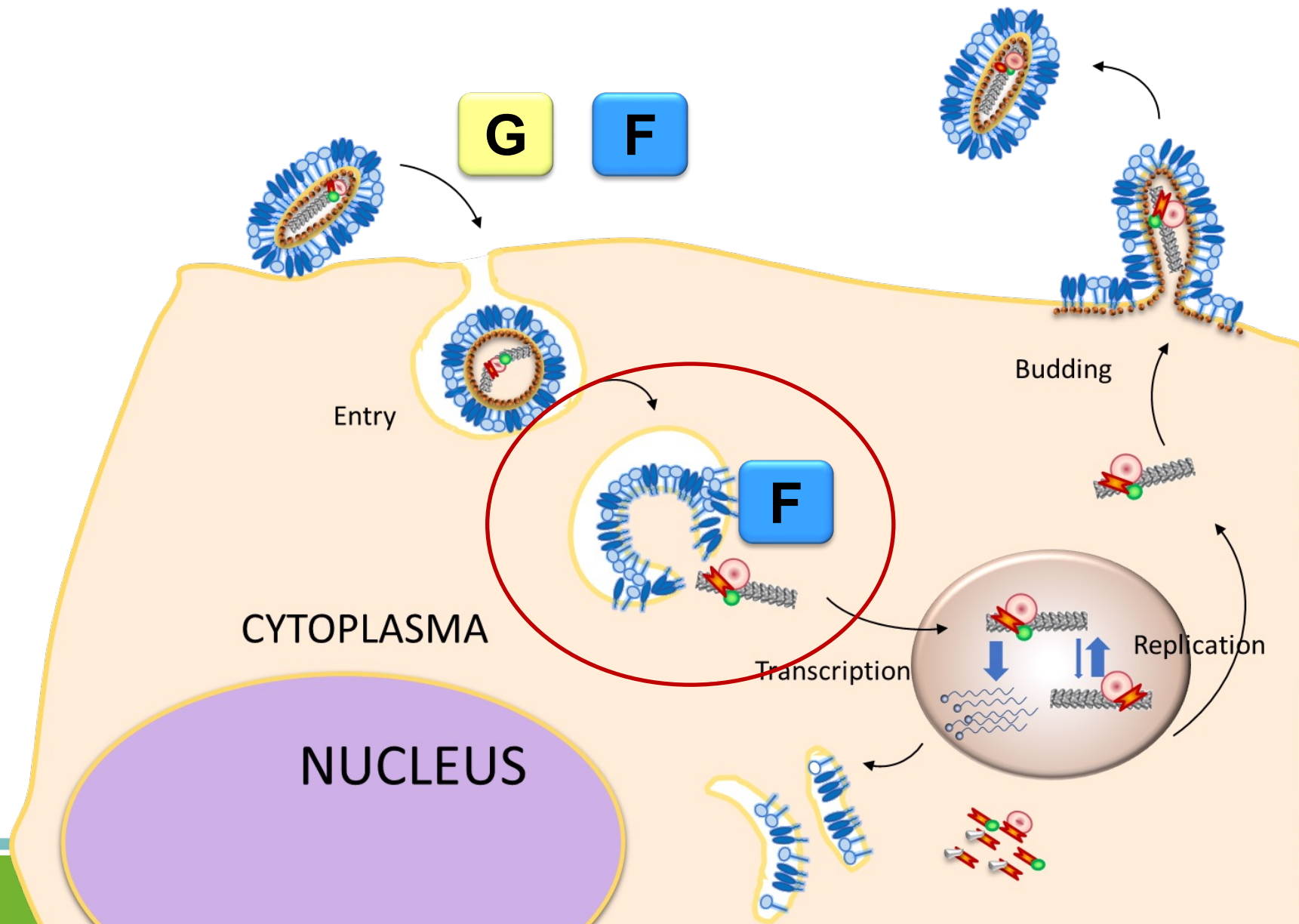


Figure 1: Global market authorisations of RSV immunisation products to protect infants

Information is accurate as of July 19, 2024 (Snow V, Pfizer, personal communication; Villafana T, AstraZeneca, personal communication). RSV=respiratory syncytial virus. RSVpreF=respiratory syncytial virus prefusion F.

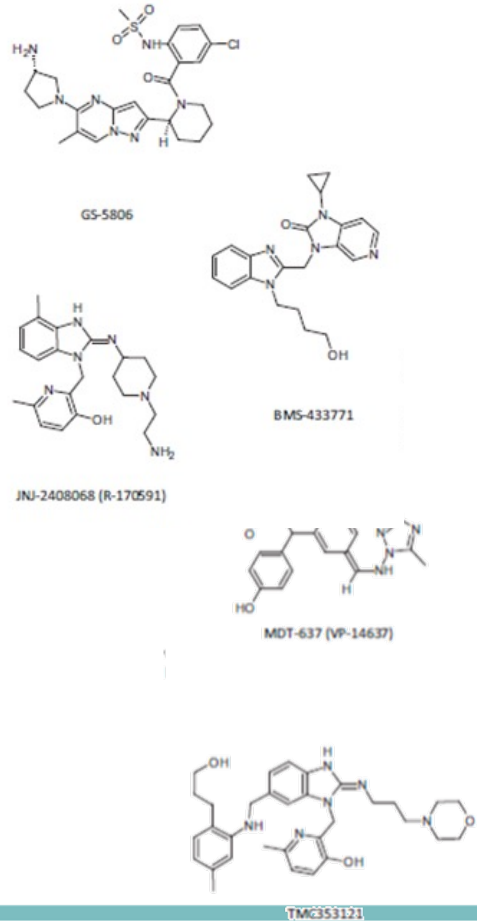
Pediatric vaccination to come ?

Respiratory syncytial virus replication cycle

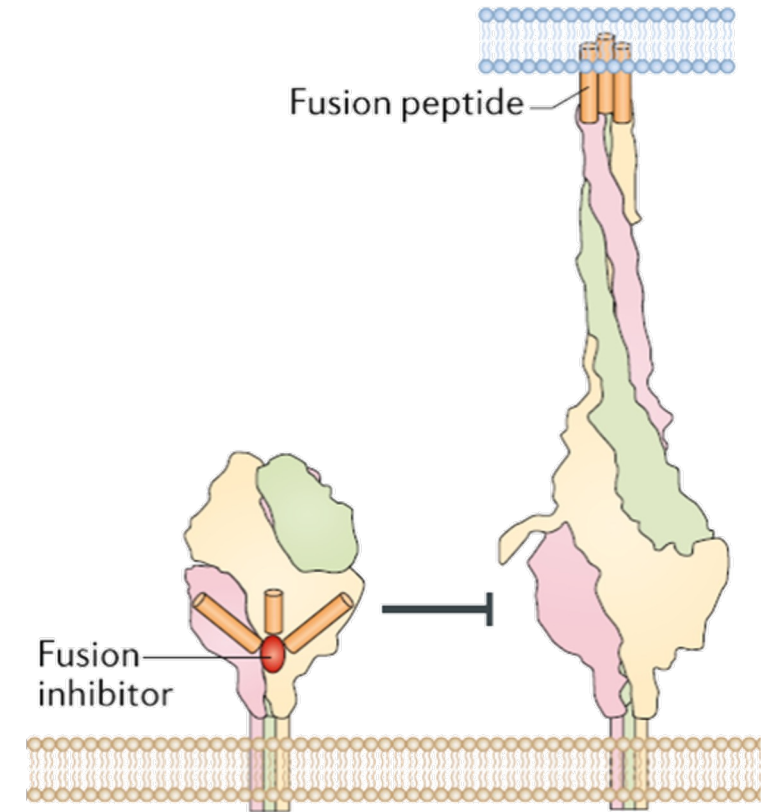
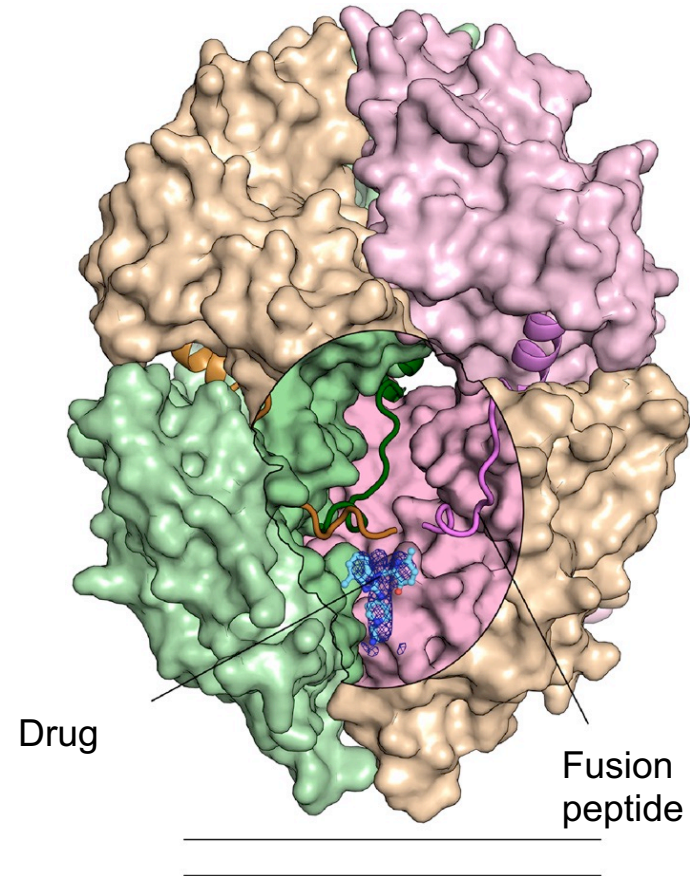


Targeting fusion: fusion inhibitors

Small molecules



Binding to pre-fusion F



Molecules tested in clinical trials

Phase I

Biota Pharmaceuticals, Inc. **A**

BTA9881

MicroDose Therapeutx, Inc **A**

MDT-637

A = Adults
O = Older
C = Childs

Phase II

Pfizer **O A C**

RV521 = Sisunatovir

Biota Pharmaceuticals **A**

BTA-C585 =Enzaplatovir

Gilead Sciences **A O**

Presatovir

Ark Biosciences Inc **A C O**

AK0529 = Ziresovir

Janssen Research & Development, LLC **A C O**

JNJ53718678=Rilematovir

Phase III

Pfizer **O A**

RV521 = Sisunatovir

Ark Biosciences Inc **C**

AK0529 = Ziresovir

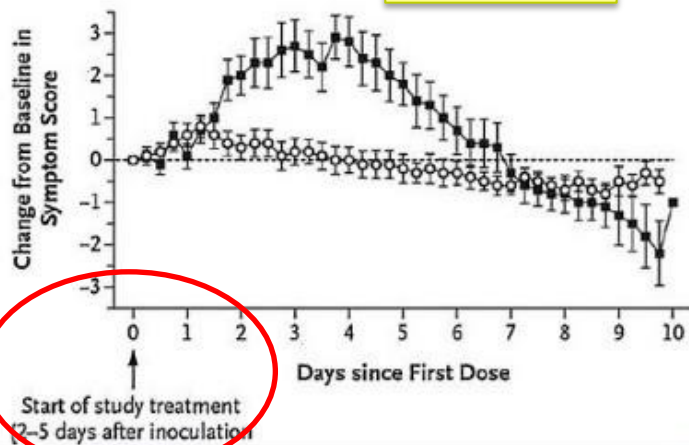
Janssen Research & Development, LLC **C**

JNJ53718678=Rilematovir

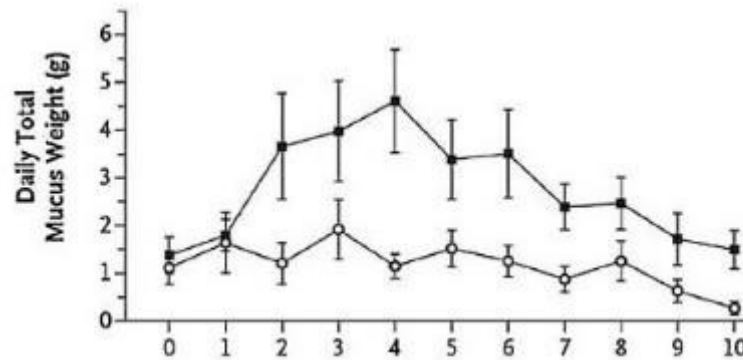
Promising results in experimental human infection model

GS-5806 Presatovir

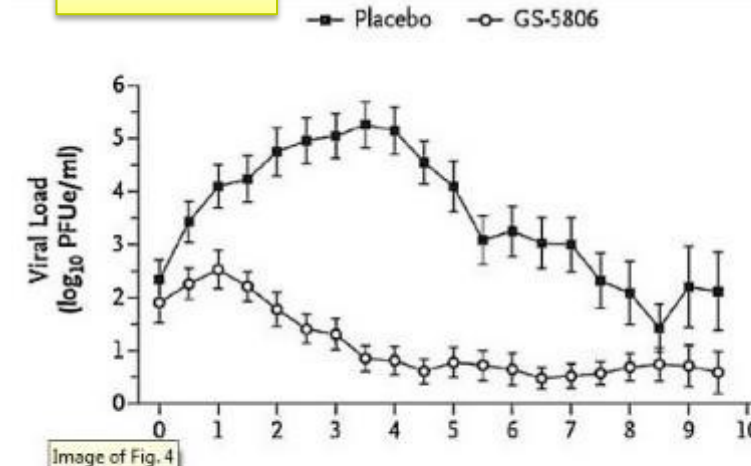
Symptoms



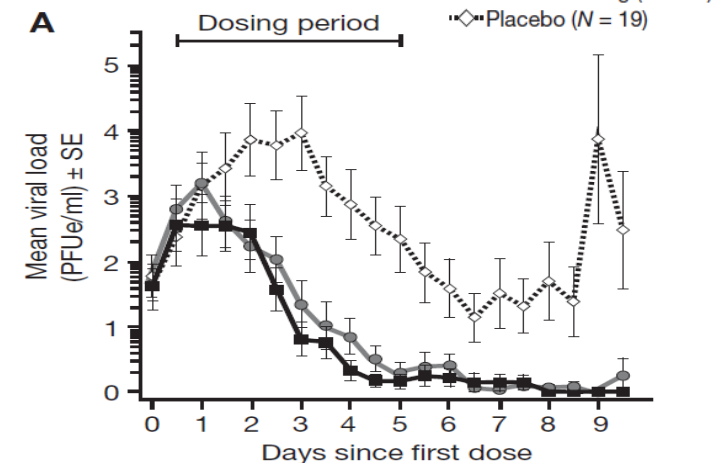
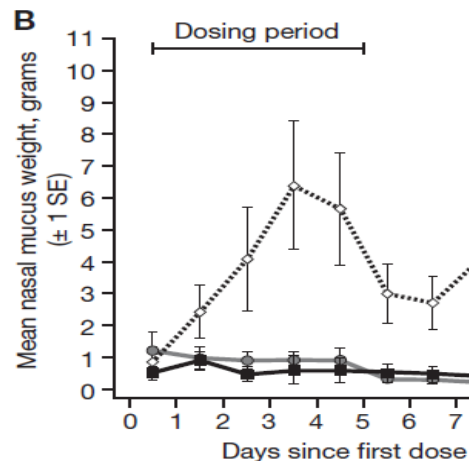
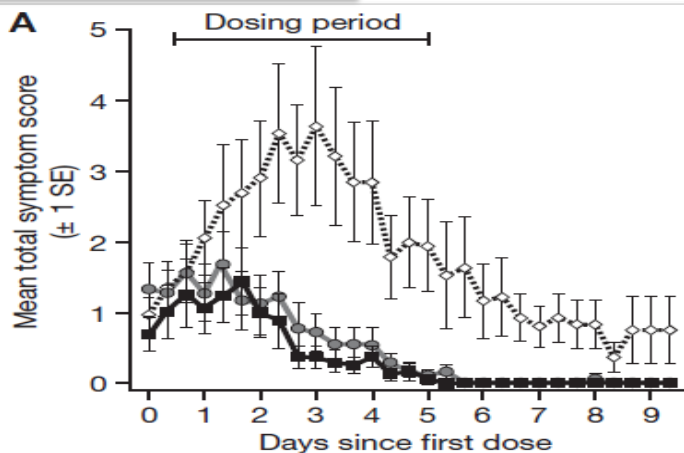
Mucus



Viral Load



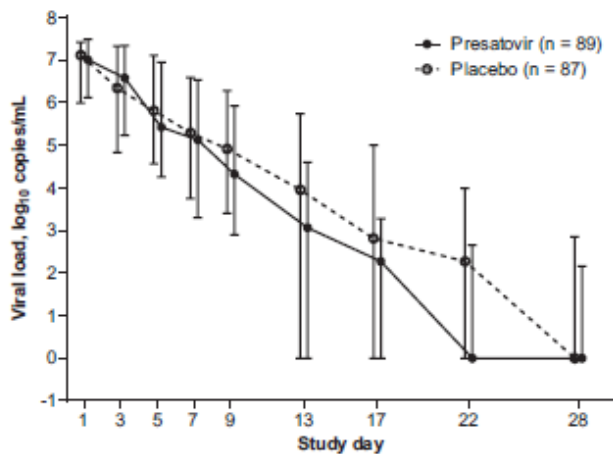
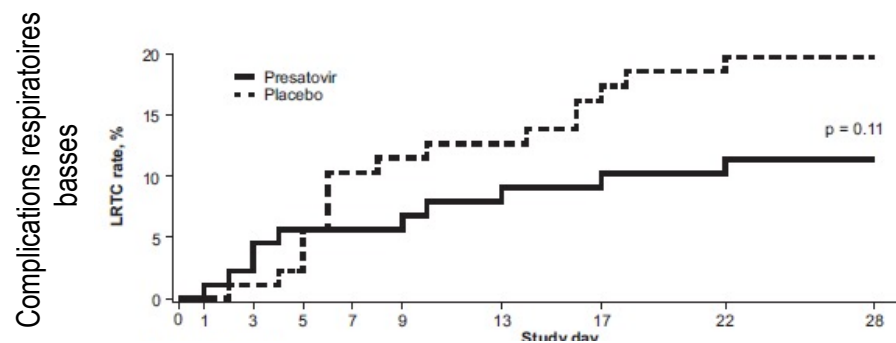
RV521 Sisunatovir



but failure of clinical trials in the real world

GS-5806 Presatovir

Non significant effects



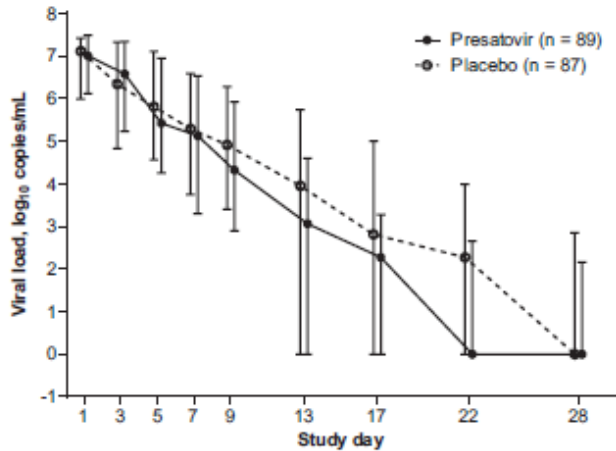
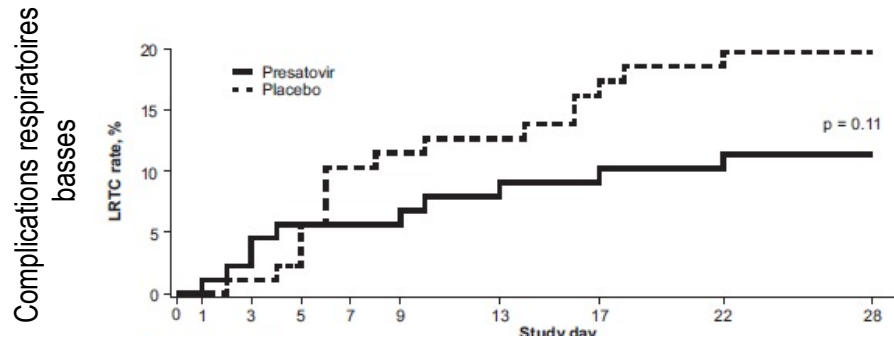
2 others trials with similar results

Gottlieb et al. J Heart Lung Transplant. 2023 Jul;42(7):908-916; Marty et al. Clin Infect Dis. 2020 Dec 31;71(11):2787-2795; Chemaly et al. Clin Infect Dis. 2020 Dec 31;71(11):2777-2786; Nilsson et al. Clin Microbiol Infect. 2023 Oct;29(10):1320-1327

but failure of clinical trials in the real world

GS-5806 Presatovir

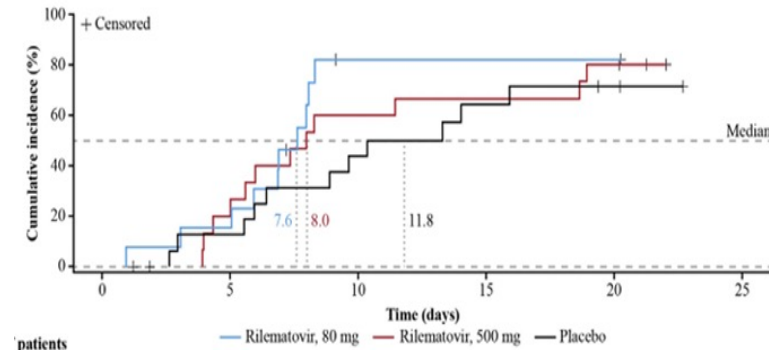
Non significant effects



2 others trials with similar results

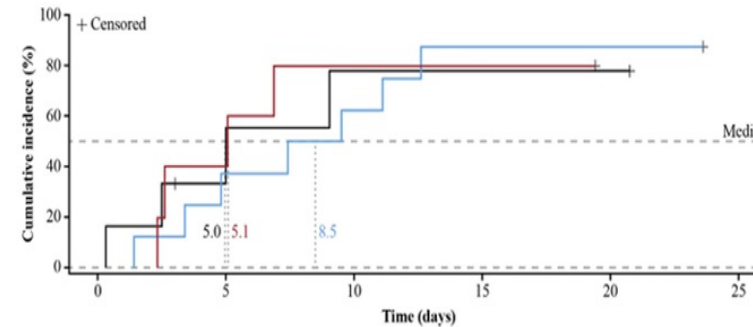
JNJ-53718678 = Rilematovir

Associated with delay between onset of symptoms and treatment



Ttt < 3 days post-symptoms onset

patients



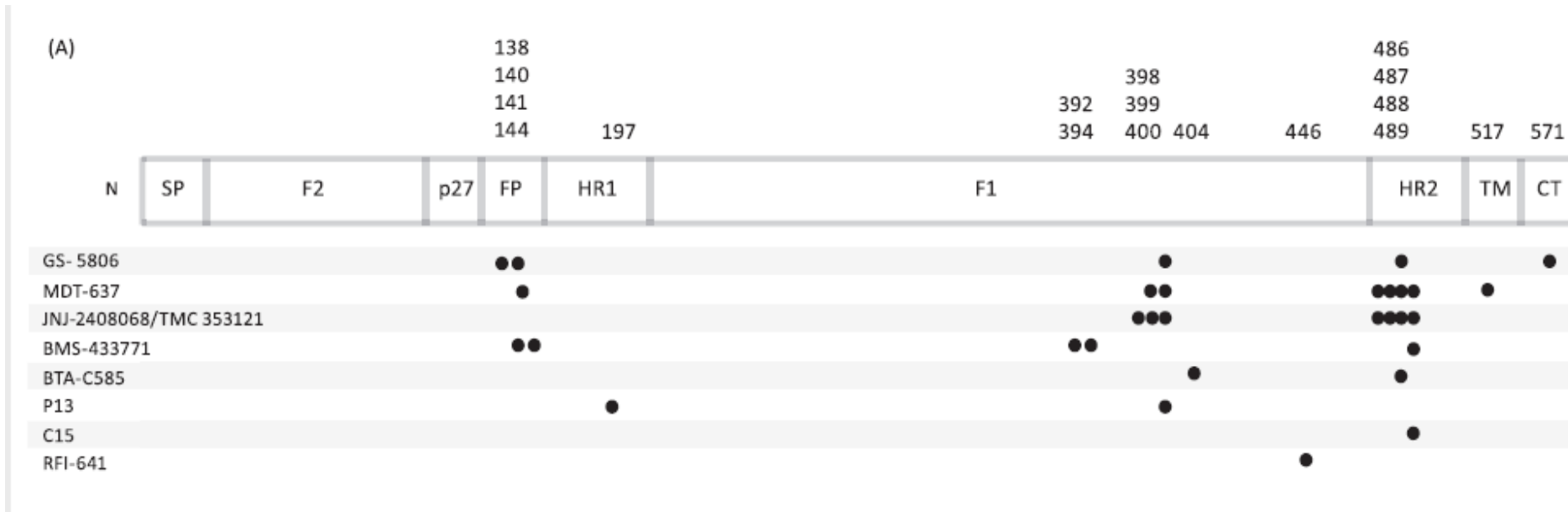
Ttt > 3 days post-symptoms onset

Resistance to fusion inhibitors

Common: from 1-1.5% in immunocompetent patients to 10-15% in immunocompromised patients

Cross-resistance

Mutations in the fusion peptide and HR2 helix



slido

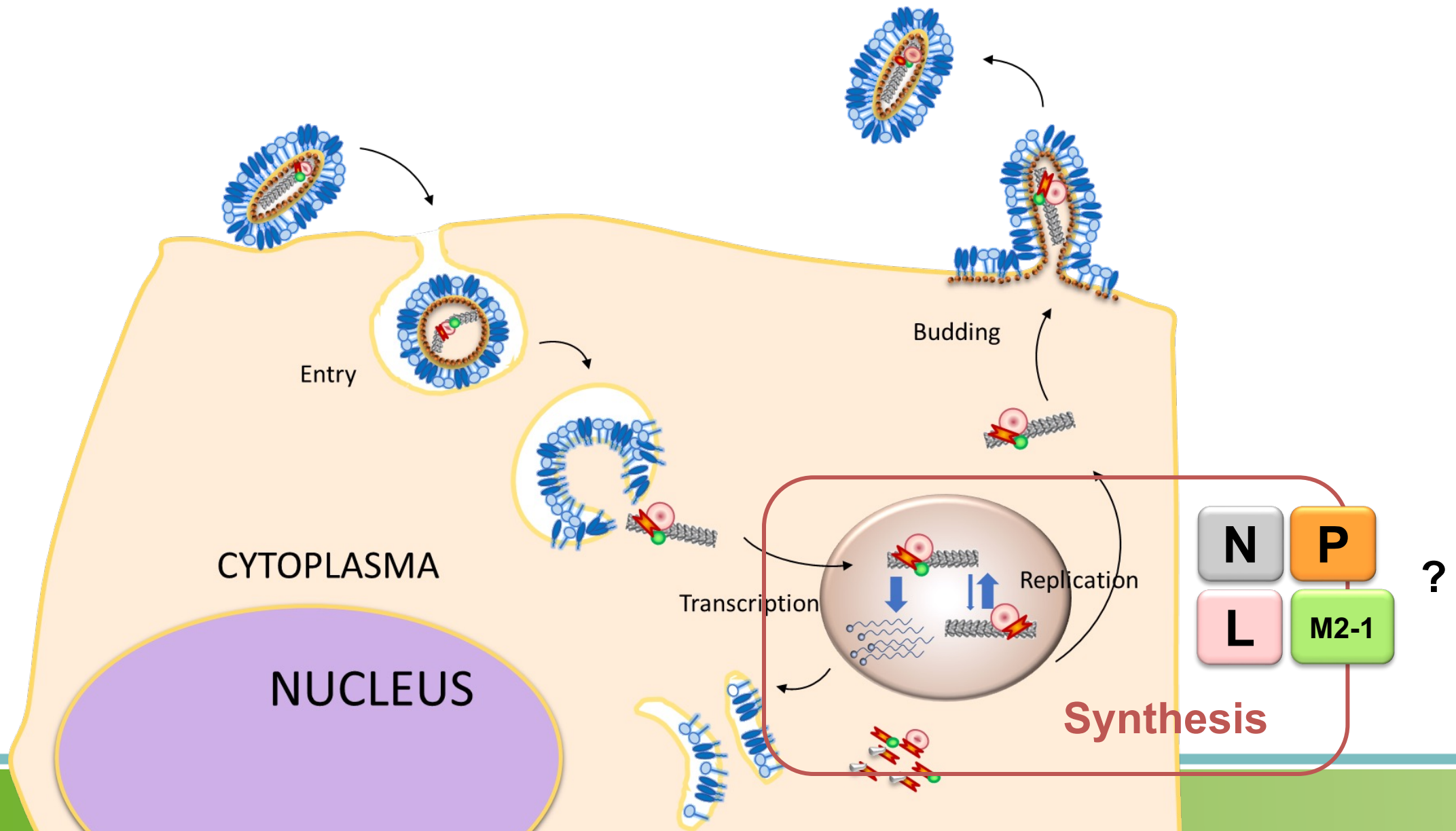
Please download and install the Slido app on all computers you use



RSV Fusion inhibitors

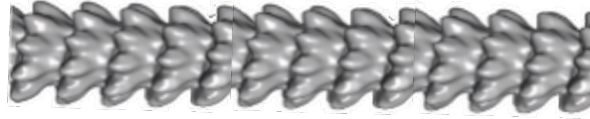
① Start presenting to display the poll results on this slide.

Respiratory syncytial virus replication cycle

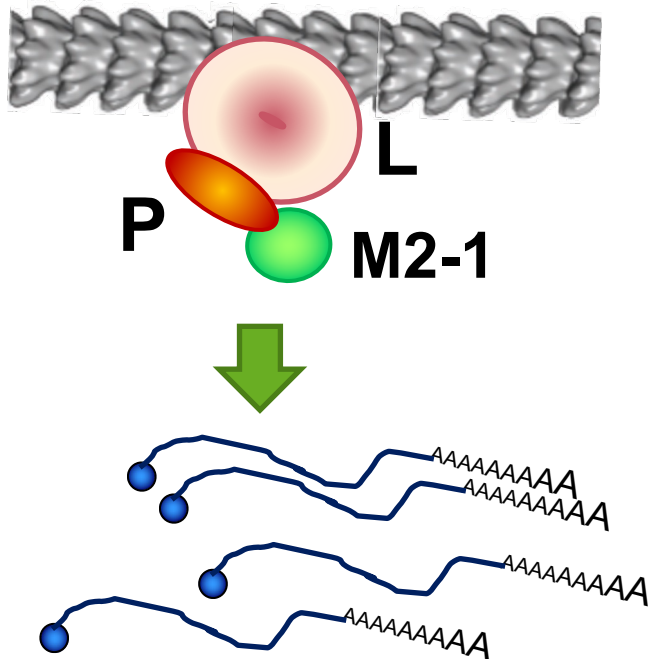


Targeting viral RNA synthesis

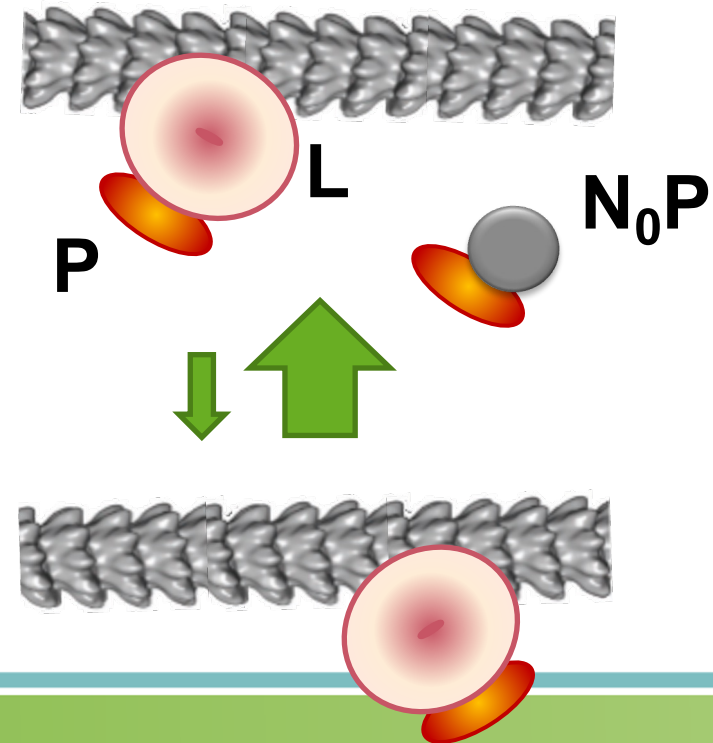
Matrix N + RNA



Transcription



Replication



RSV polymerase activities



RNA polymerase RNA-dependent

Polyadenylation of viral mRNA

Capping of viral mRNAs

involving 3 enzymatic activities:

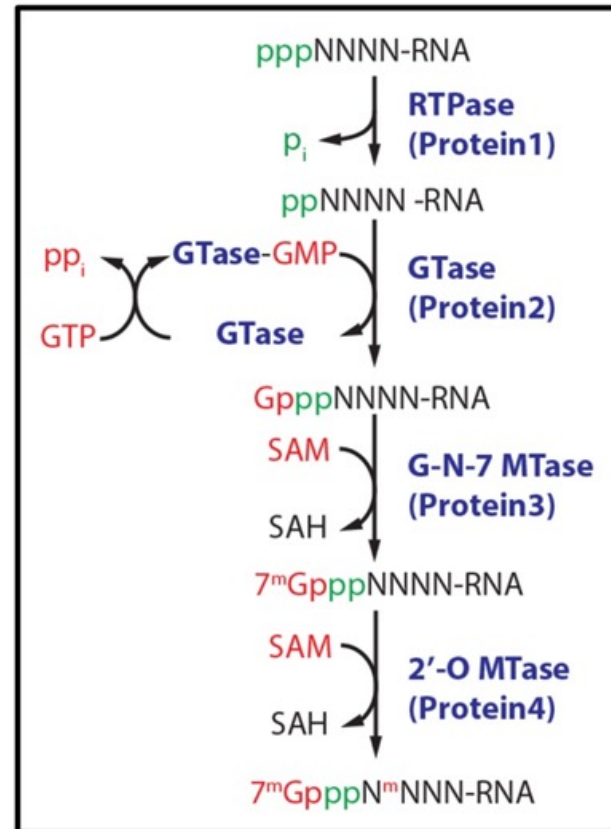
-Polyribonucleotidyl transferase

-G-N-7 methyltransferase

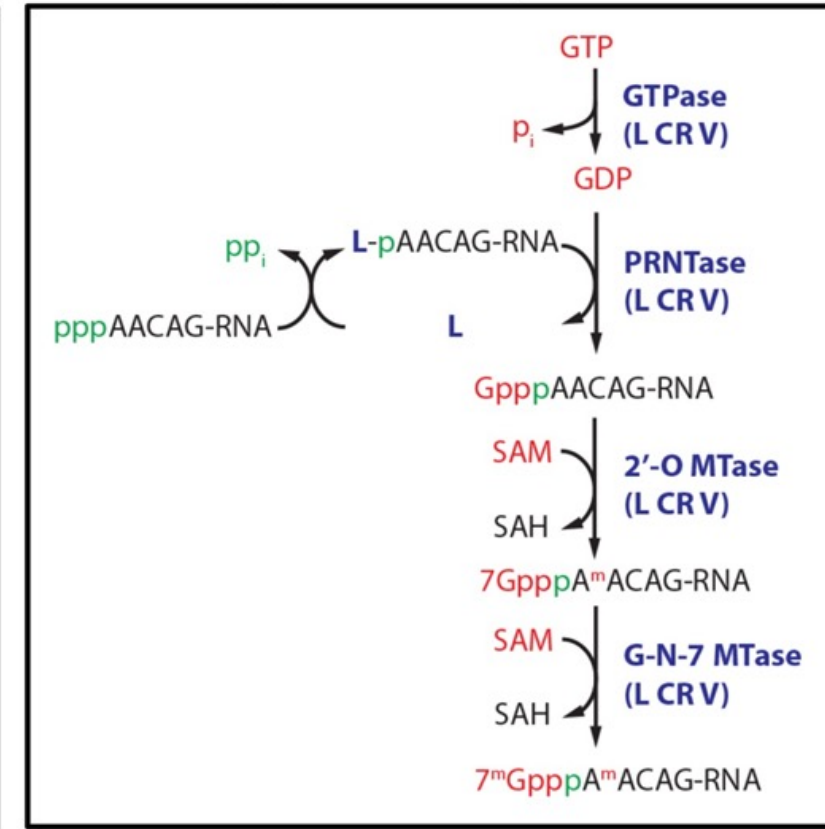
-2'-O-methyltransferase

Encapsidation ???

(A) Cellular mRNA cap formation



(C) VSV mRNA cap formation

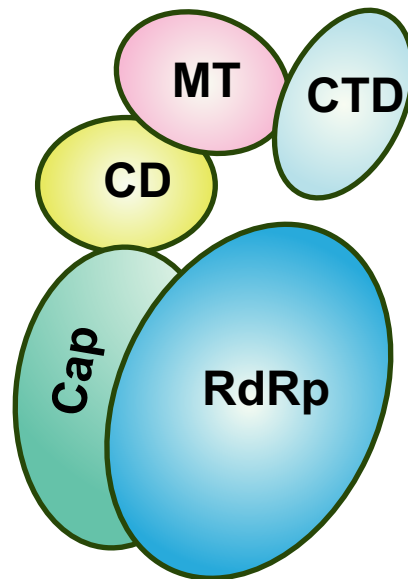


RSV-polymerase structure

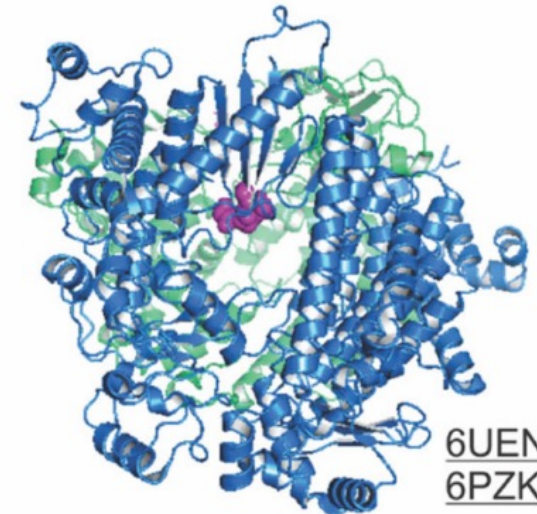
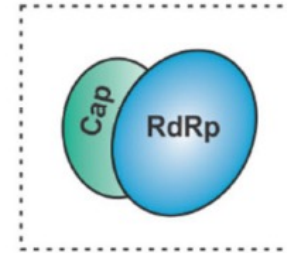
L



Multifunctional enzyme - monomeric L



Cryo EM structures



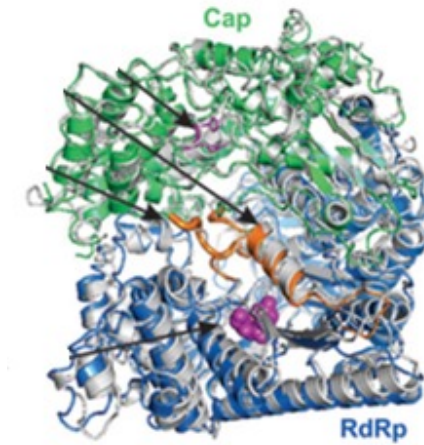
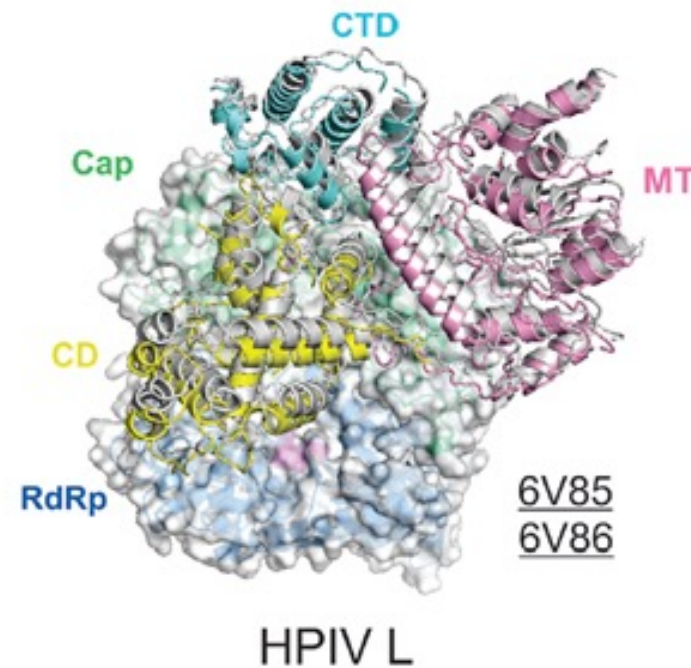
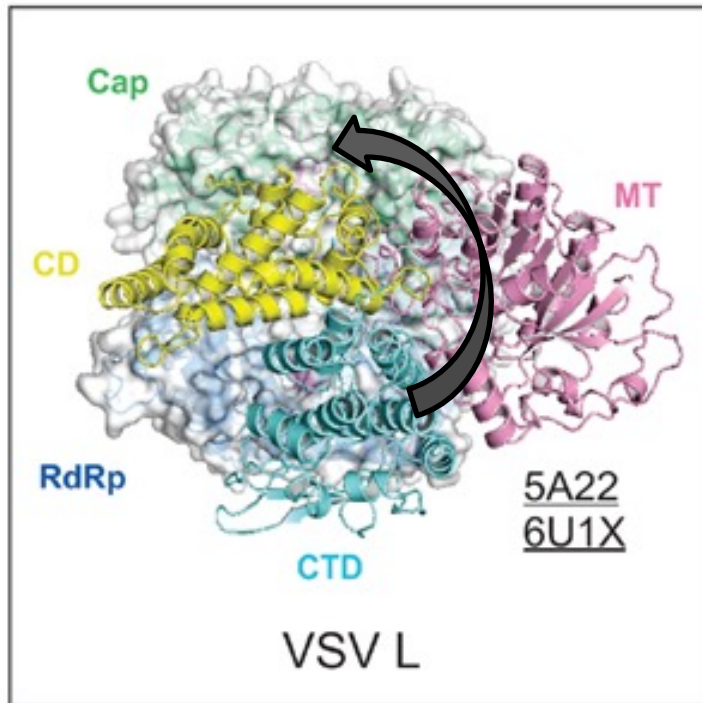
RSV L



VSV L

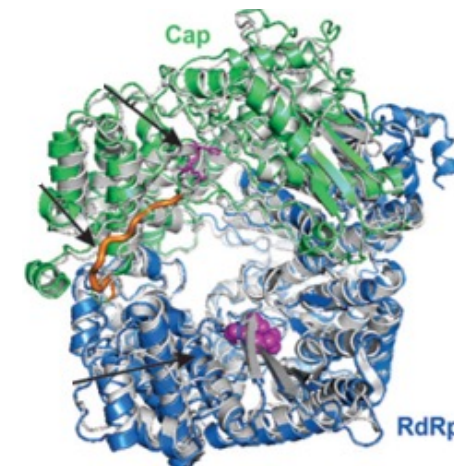
L: multifunction – multiconformation protein

Top View



VSV Rabies

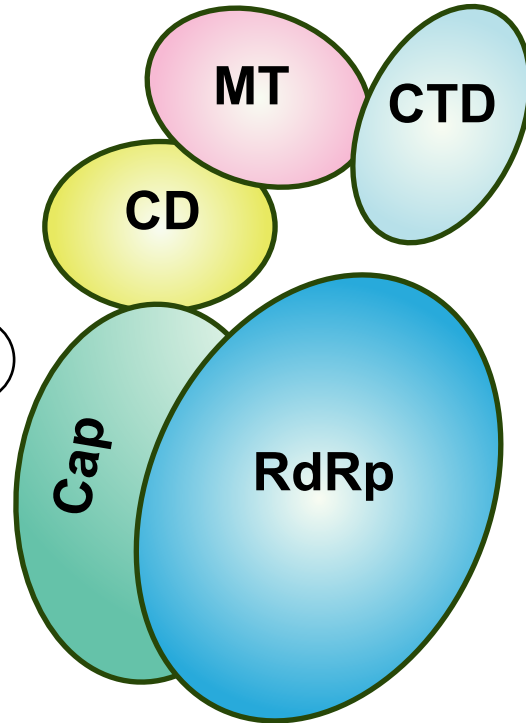
Initiation ?



RSV hMPV

Elongation ?

Targeting the polymerase... first molecules



Phase 1 (A) 

Janssen Research & Development, LLC


JNJ-6447184

Phase 1 (A) (O)

ata Pharmaceuticals


EDP 323

SiRNA

Phase 2 (A) (O) 

Alnylam Ph

ALN-RSV01 (inhalé)

Phase 2 (A) (O) 

Arrow Thx

A-60444

Phase 2 (A) (C) (O)


Enanta Pharmaceuticals

EDP-938

Phase 1 (A)


Pfizer

RV299

Phase 2 (A) (C) (O) 

Alios Biopharma, Janssen

Lumicitabine = ALS-8176

Phase 2 (A) (O) 

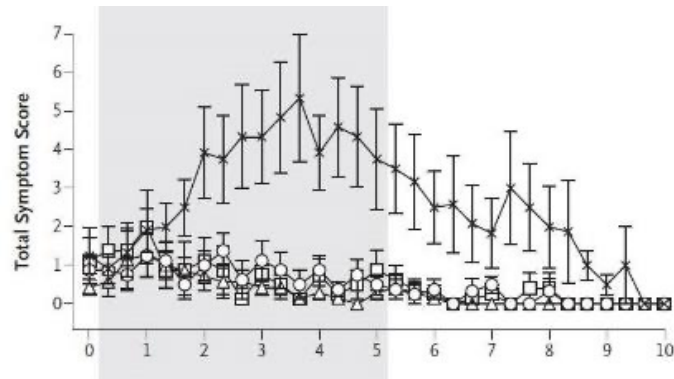
Pulmocide Ltd

PC786 (inhalé)

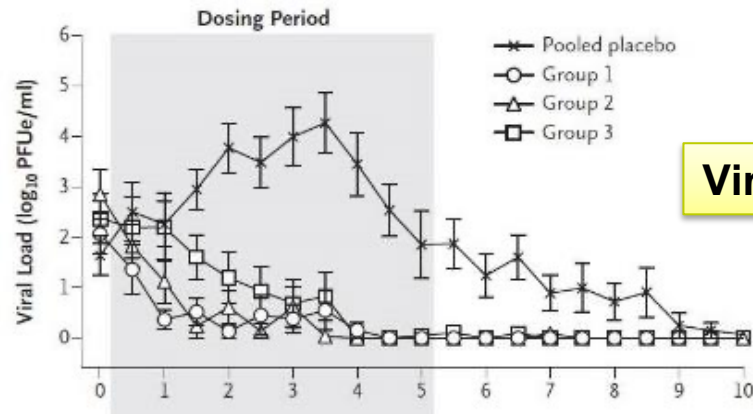
N

Good results in experimental human infection model, but....

ALS-8176 Lumicitabine

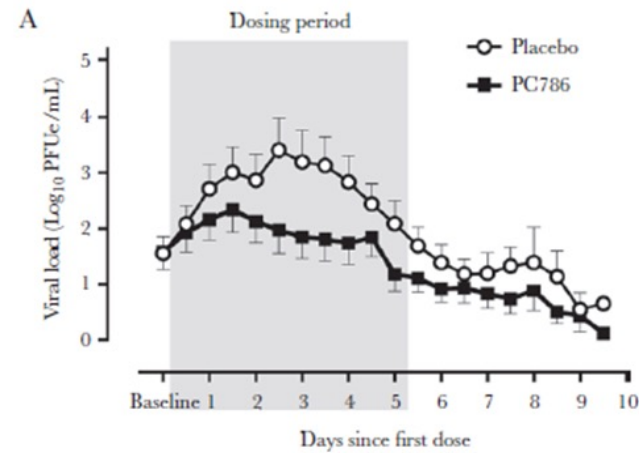
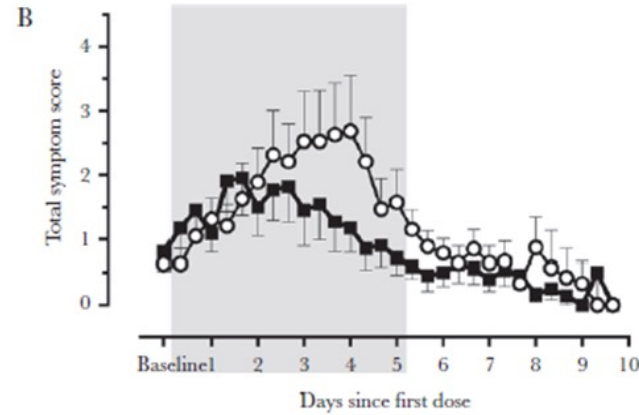


Symptoms



Viral Load

PC786 (inhaled)



Phase 2b trials discontinued July 2019

DeVincenzo et al. N Engl J Med. 2015 Nov 19;373(21):2048-58; DeVincenzo et al. J Infect Dis. 2022 Jun 15;225(12):2087-2096

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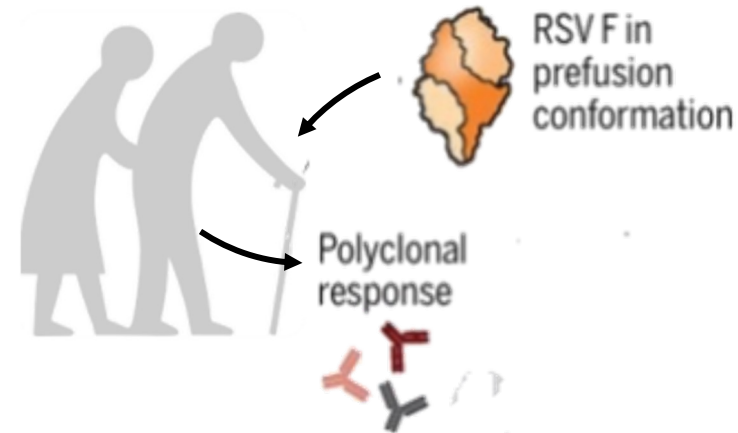
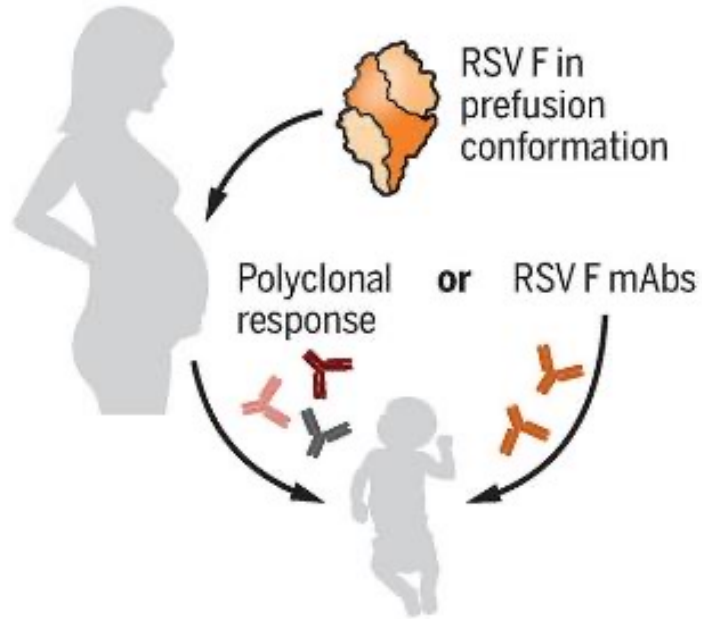


RSV polymerase

① Start presenting to display the poll results on this slide.

In summary

Major advances in prevention thanks to prefusion F stabilisation



Specify indications

What about other at-risk populations ?

Viral escape ????



In summary

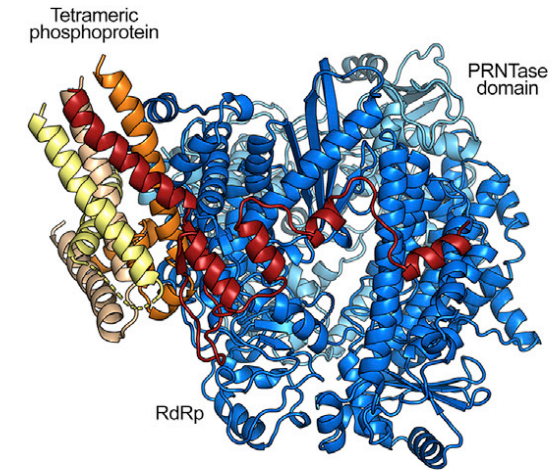
Major efforts to develop antivirals

More to come with recent structures...

Challenges to overcome

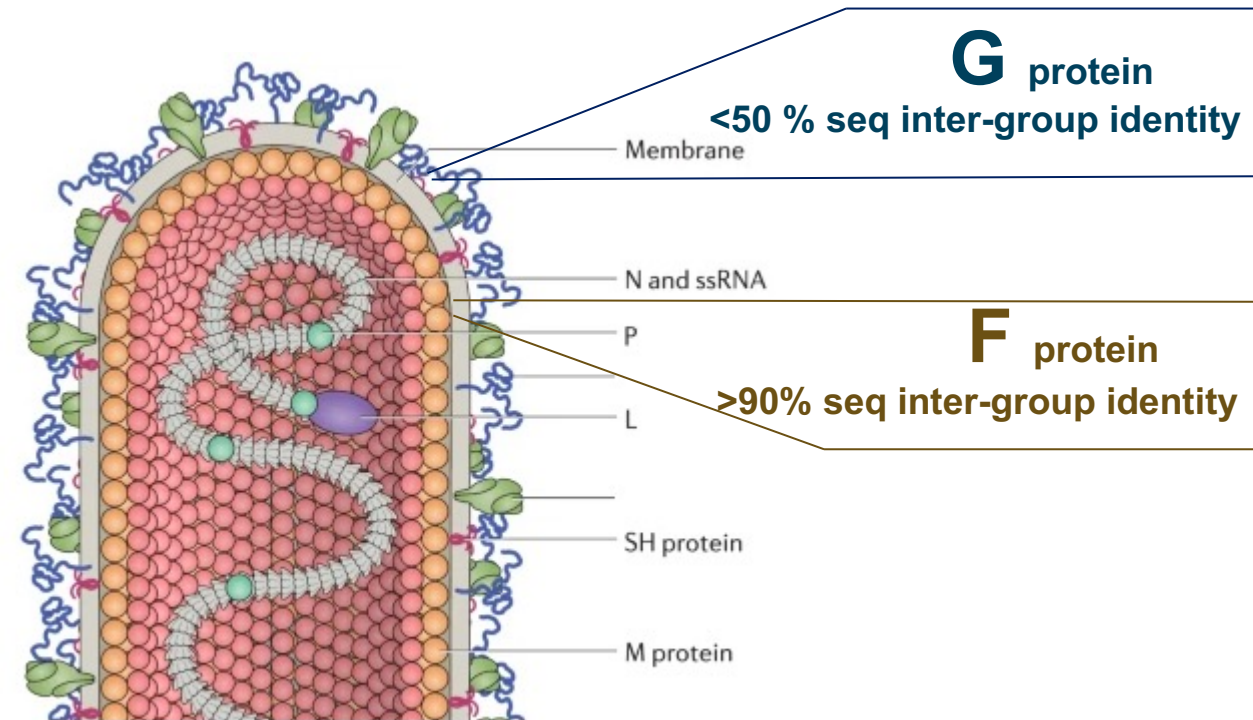
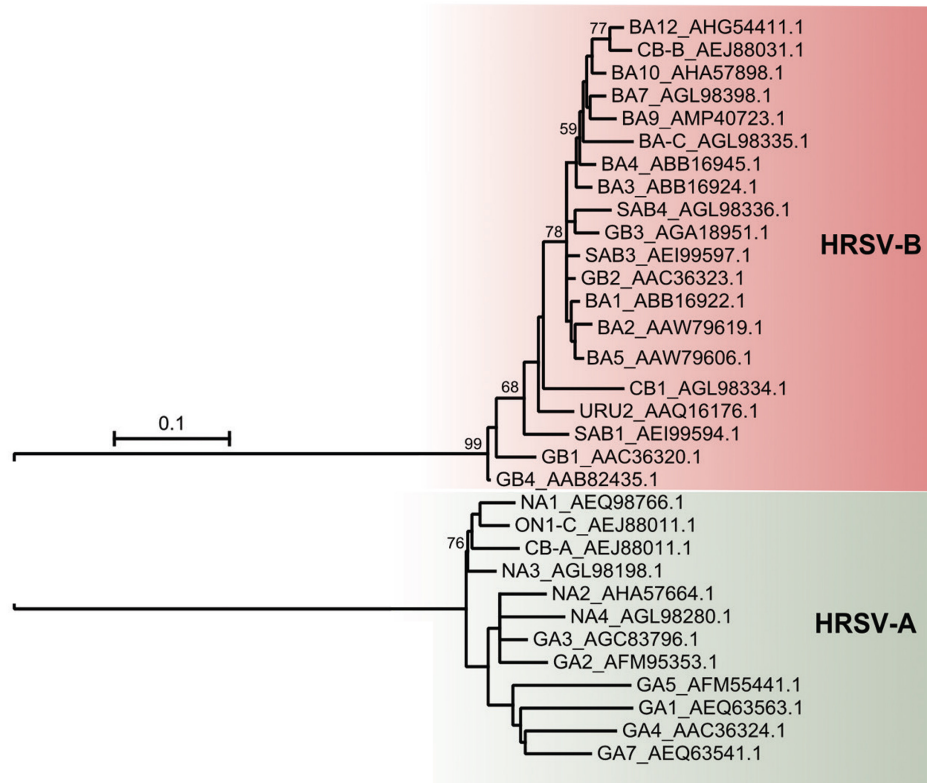
Early administration

Resistance, particularly in immunocompromised patients



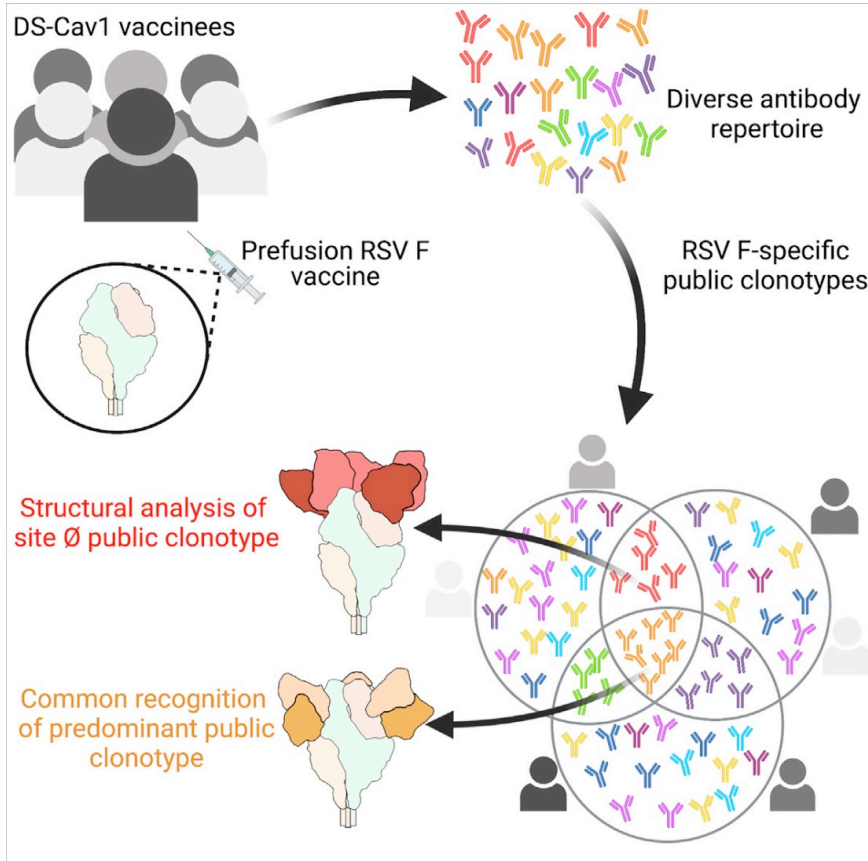
Viral escape to vaccines and monoclonal antibodies ?

RNA virus with 7.10^{-4} sub/site/year



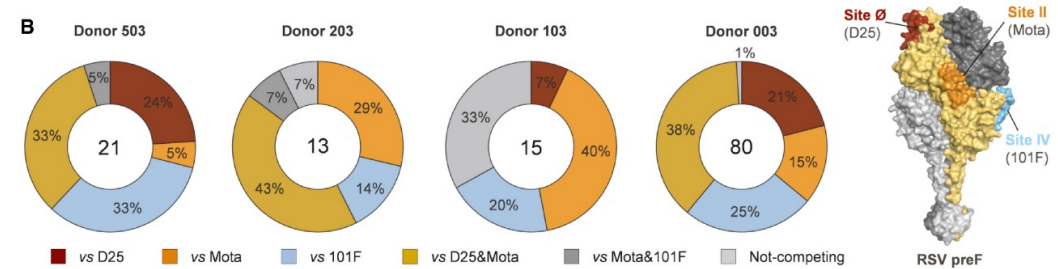
Response to F vaccine and F variability

F response is polyclonal



*Diverse pre- and post-vaccination repertoire
Vaccine increases neutralising antibodies and
"Public" antibodies*

Broad efficacy of vaccine : GSK vaccine only (A2 strain)



Sera from vaccinated patients still neutralise escape monoclonal variants

Nirsevimab escape ?

Of concern because

- RNA virus ($7 \cdot 10^{-4}$ sub/site/year)
- Single mutation sufficient (monoclonal)
- Mass administration

Natural escape ?

e.g. emergence of escape variants independent of selection pressure



Uncommon (<1%)

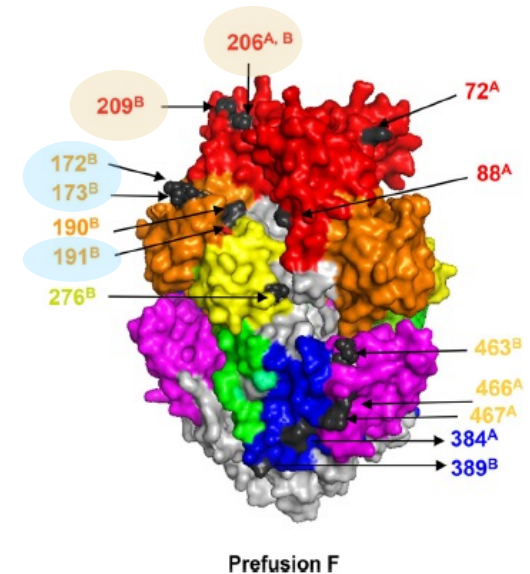
5600 sequences from 2015-2021

INFORM 2017-2018

Large-scale sequencing study of 410 G-F RSVs from 8 countries on different continents

Emergence in 2015-2019: no impact on nirsevimab susceptibility

Emergence 2014: Escape to Suptavumab



- ∅ Nirsevimab
- I
- II Palivizumab
- III
- IV MK1654
- V Suptavumab

Nirsevimab escape ?

Of concern because

- RNA virus ($7 \cdot 10^{-4}$ sub/site/year)
- Single mutation sufficient (monoclonal)
- Mass administration

Selection in treated patients ?

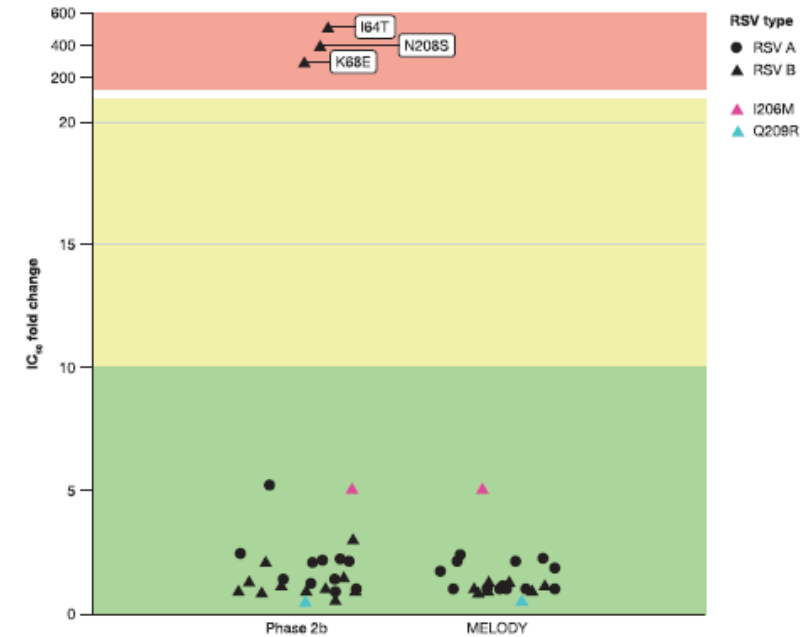
e.g. emergence of escape variants under selection pressure

Phase 2b and MELODY

0/24 RSV-A

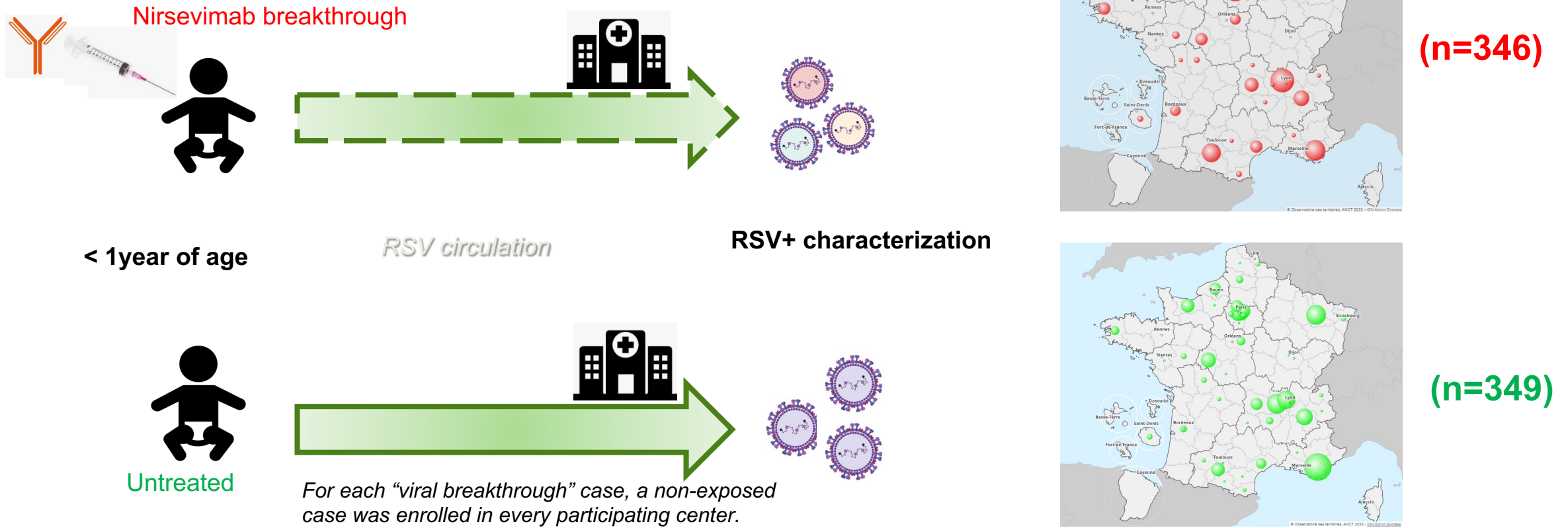
2/24 RSV-B

Uncommon ? but very few data



RSV National Genomic Observatory

Multicentric observational study season 2023-2024 in the clinical virologist network of ANRS (national health research agency)



Respiratory samples and analysis

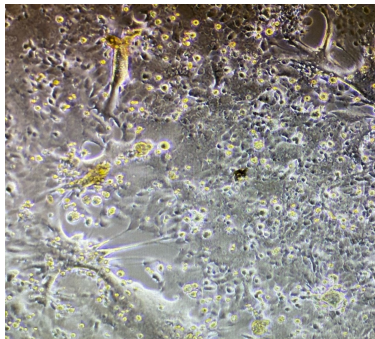
RSV full-length genome sequencing



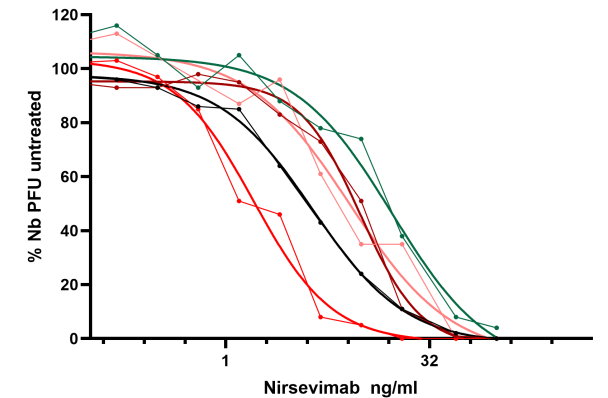
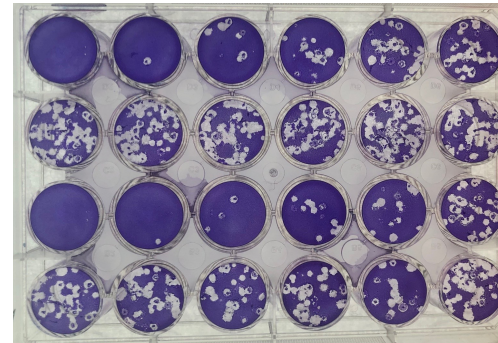
Lineages

Mutations in F epitop Ø

Viral isolation on HEp-2 cells



Neutralisation assay on HEp-2 cells



Assessment of the effect of unknown mutations

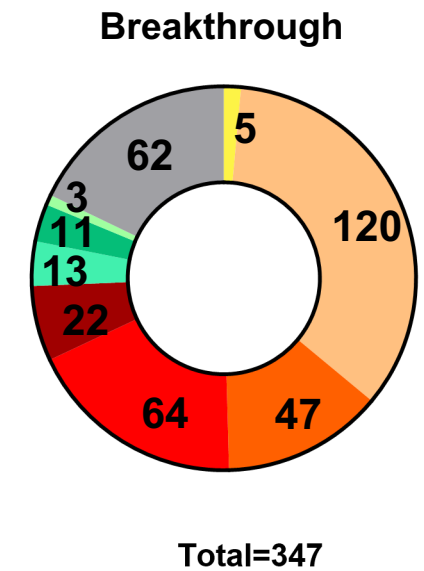
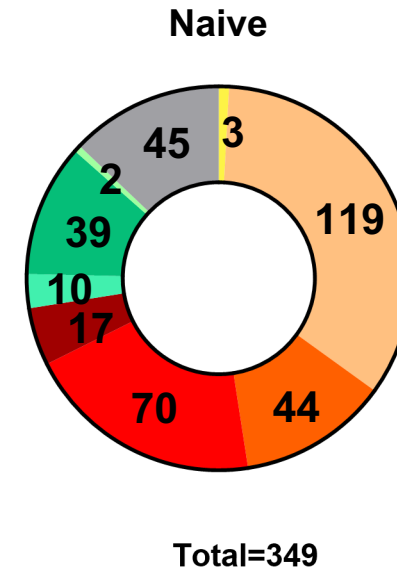
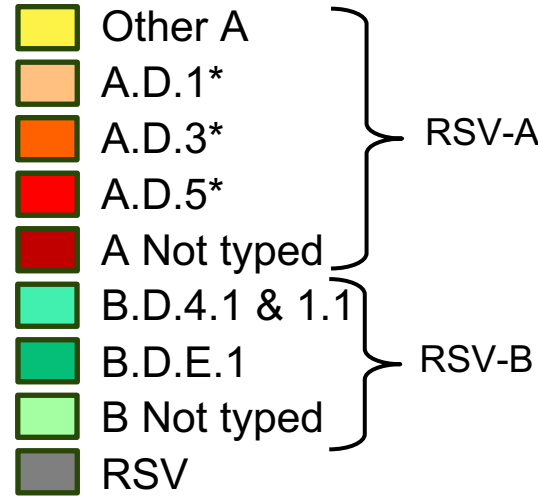


Fusion inhibition assay

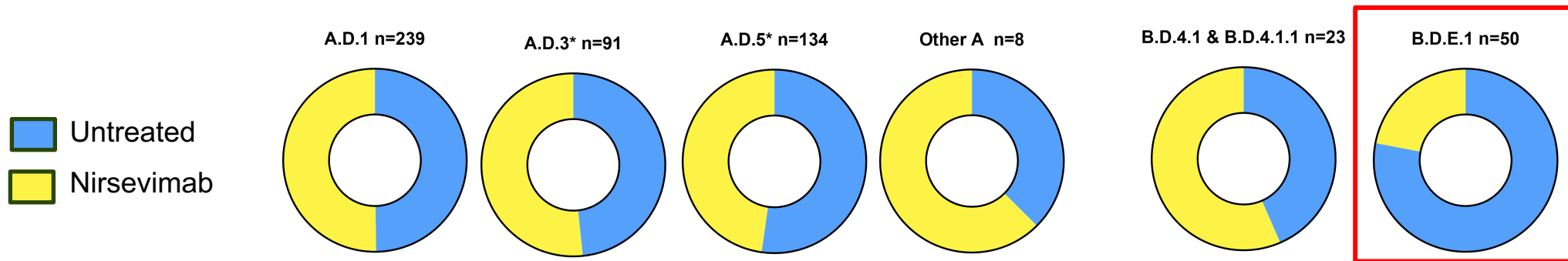
Virological data: Breakthrough infections observed with all lineages in similar proportions (?)

695 samples
 RSV-A
 RSV-B
 Untyped

=> 545 high quality sequences



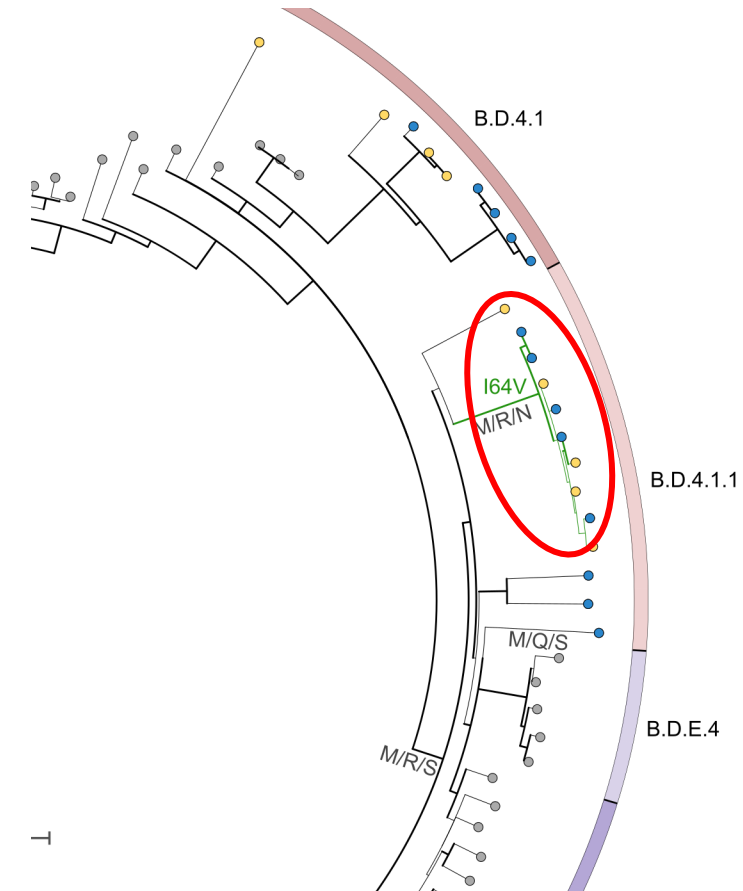
Proportions of breakthrough identical in all lineages except for B.D.E.1



Analysis of mutations in site Ø

RSV-A	N63S	E66G	K209R	S211R
Breakthrough infection n=236	4		1	1
Untreated n=236	3	1		
Previously described	YES no effect	NO	NO	NO

RSV-B	N63D 5%	I64M K65E 5%	I64V	N208D
Breakthrough infection n=24		1	5	1
Untreated n=49	1		3	
Previously described	NO	NO	NO	YES R

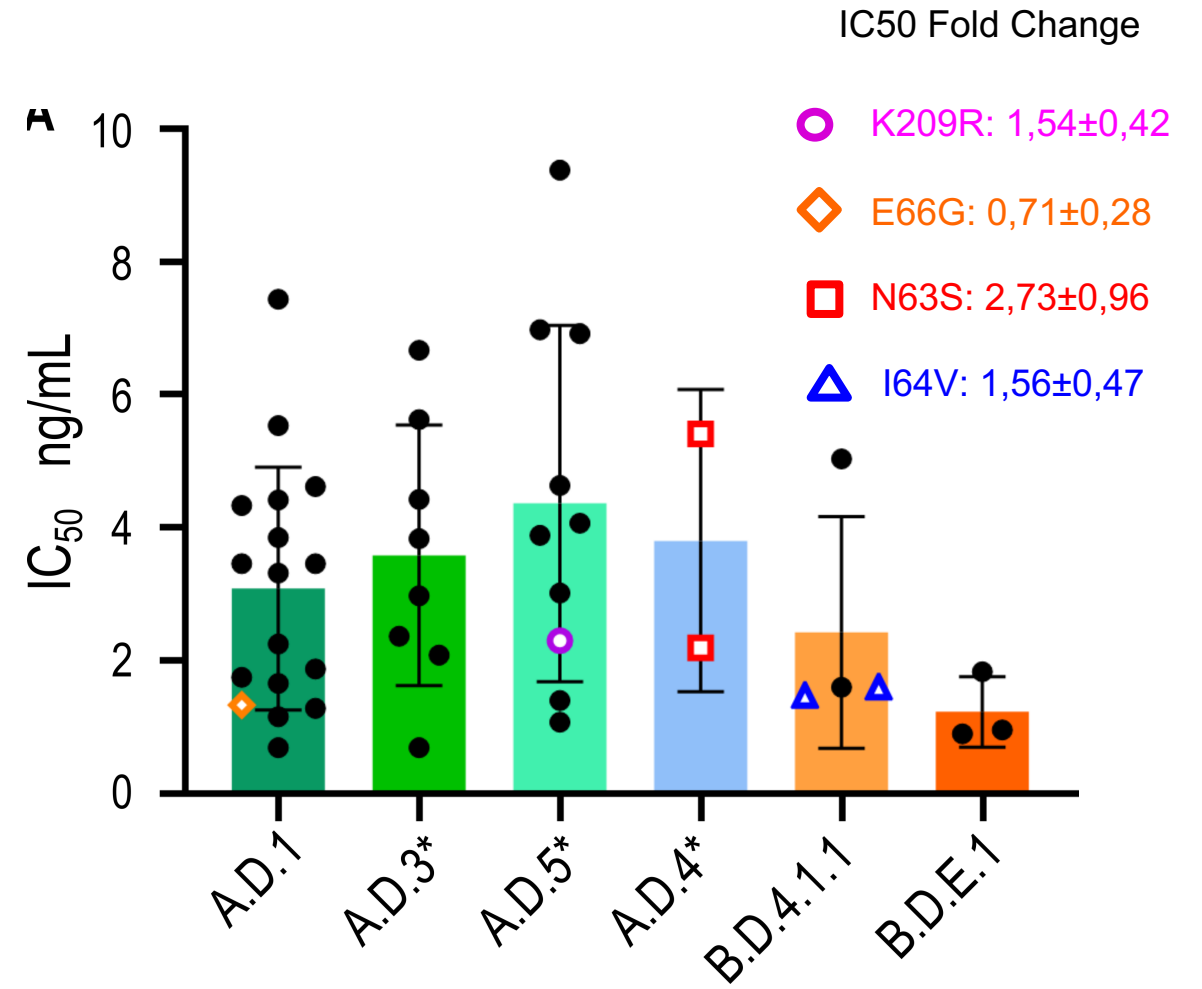
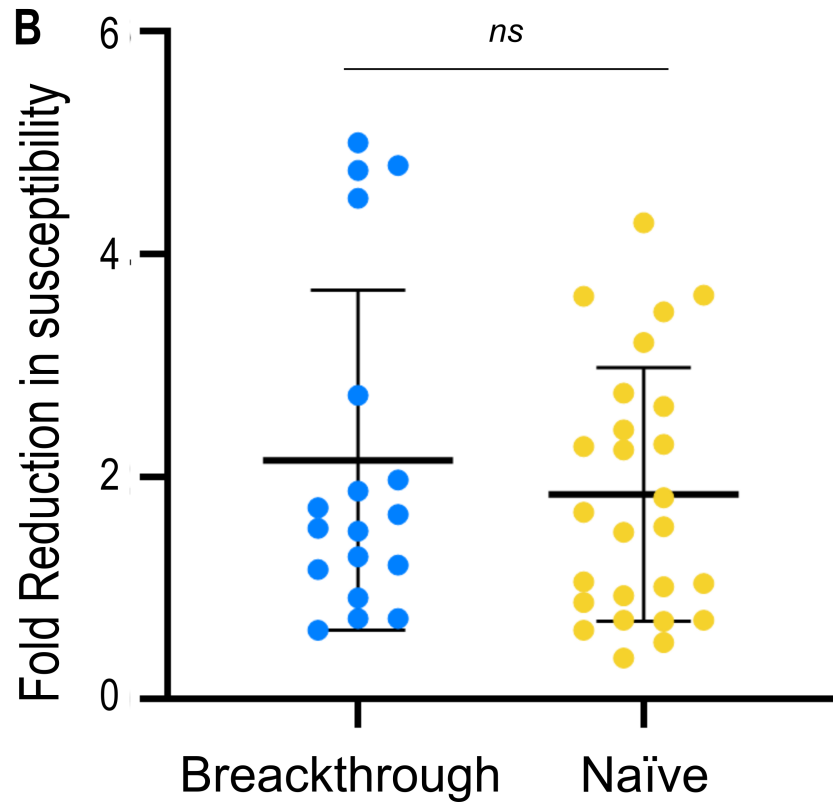


-1

Phenotypic assay

44 isolates tested

Plaque reduction assay to assess susceptibility to nirsevimab (1 to 4 replicates)



No differences between « breakthrough » and « naive » viruses

Effects of mutations in site Ø

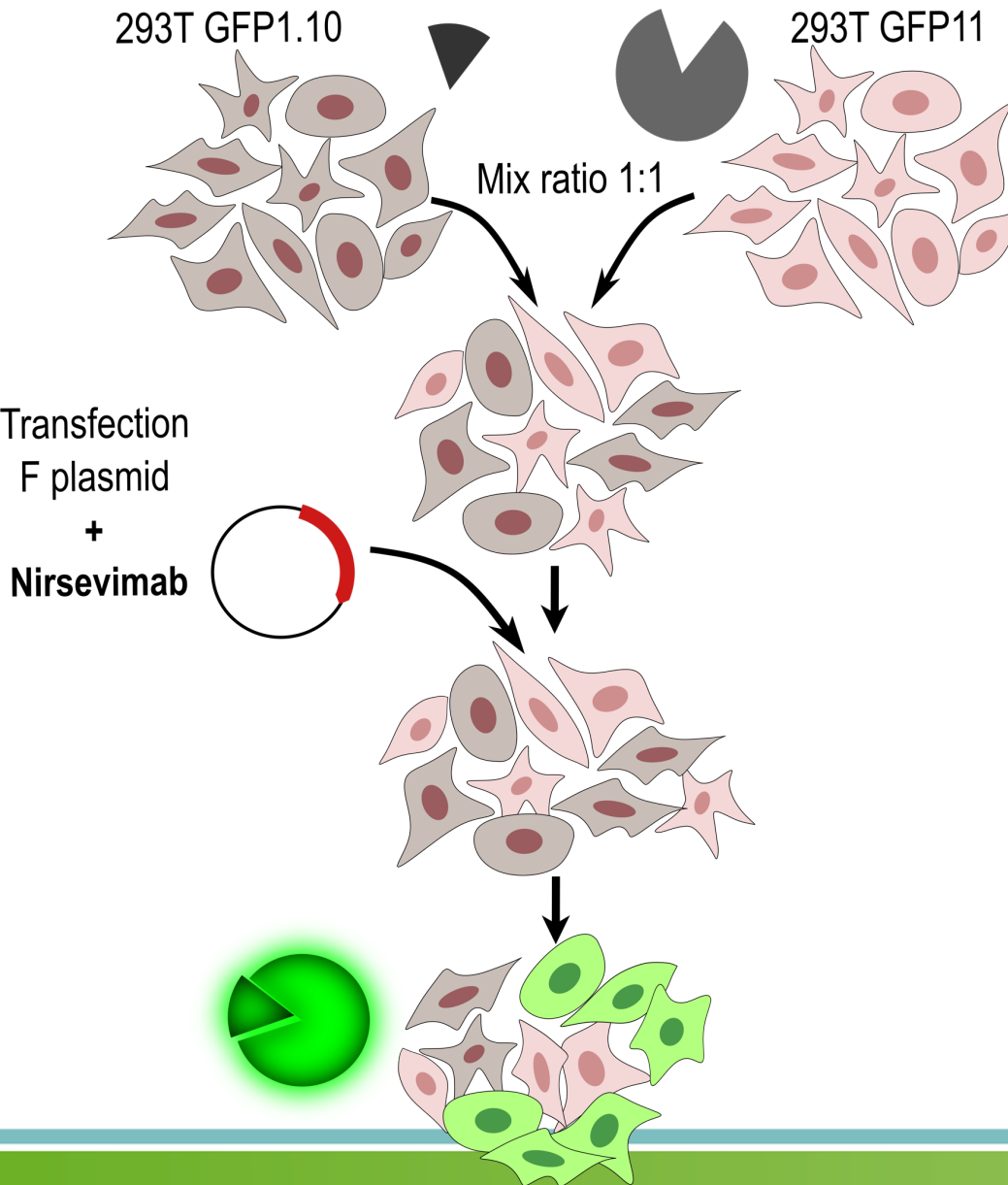
RSV-A	N63S	E66G	K209R	S211R
Breakthrough infection n=236	4		1	1
Untreated n=236	3	1		
Previously described	YES no effect	NO	NO	NO
IC50 FC Ctrl (mean, sd)	2,73±0,96	0,71±0,28	1,54±0,42	NA



RSV-B	N63D 5%	I64M K65E 5%	I64V	N208D
Breakthrough infection n=24		1	5	1
Untreated n=49	1		3	
Previously described	NO	NO	NO	YES R
IC50 FC Ctrl (mean, sd)	NA	NA	1,56±0,47	NA



Fusion assay to assess impact of unknown mutations



RSV-A	N63S	E66G	K209R	S211R
Breakthrough infection	4		1	1
Untreated	3	1		
Previously described	YES no effect	NO	NO	NO
IC50 FC Ctrl (mean, sd)	2,73±0,96	0,71±0,28	1,54±0,42	NA
Fusion inhibition FC (mean, sd)	1,05±0,53	0,62±0,21	1,32±0,60	0,98±0,87

RSV-B	N63D 5%	I64M K65E 5%	I64V	N208D
Breakthrough infection		1	5	1
Untreated	1		3	
Previously described	NO	NO	NO	YES R
IC50 FC Ctrl (mean, sd)	NA	NA	1,56±0,47	NA
Fusion inhibition FC (mean, sd)	0,81±0,35	>500	NA	>500

Conclusion

- RSV-A: 100% (236 from breakthrough) of RSV-A viruses tested are susceptible
- RSV-B: 2 RSV-B resistance profiles identified in breakthrough patients. None in naïve patients

2/24 breakthrough with escape mutations (+ 2/24 in trials)

=>Need for close monitoring of nirsevimab susceptibility in the future

- Unanswered questions

Fitness of RSV with resistance mutations

Selective pressure

Fourati S
Reslan A

Bourret J,
Rahou Y,
Simon-Loriere E,
Schwartz O,
Buchrieser J,

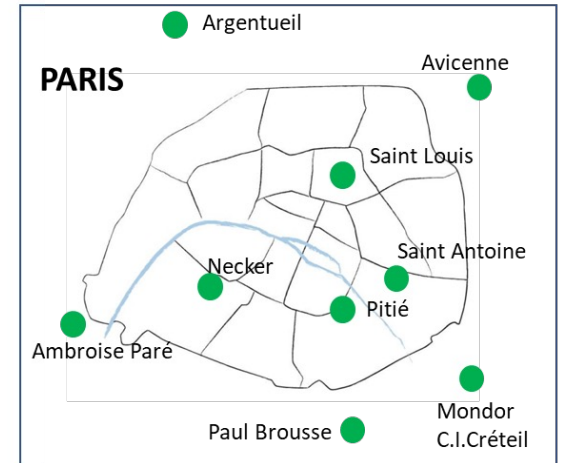
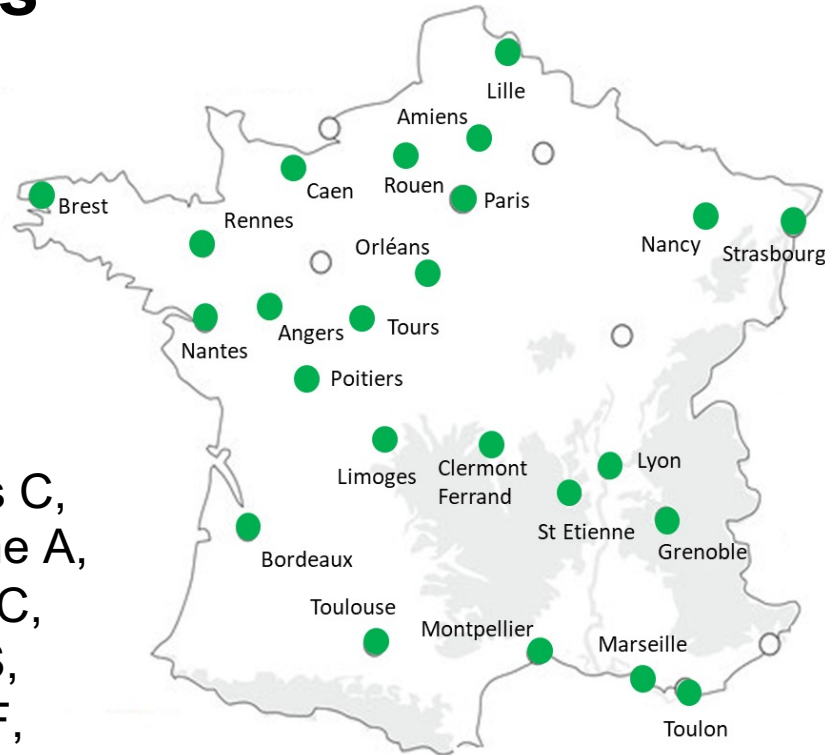
Pawlotsky J-M,
Lemoine F,
Audureau E,
Ly A,
Rodriguez C

POLYRES investigators

Casalegno J,
Chollet L,
Pillet S,
Tremeaux P,
Dossou NC,
Gault E,
Salmona M,
Imbert-Marcille B,
Mirand A,
Larrat S,
Moisan A,
Marot S,
Schnuriger A,

Veyrenche N,
Engelmann I,
Handala L,
Henry A,
Stephan V,
Brichler S,
Avettand-Fenoel V,
Zemali N,
Lefeuvre C,
Pronier C,
Deroche L,
Jaffar-Bandjee M,
Mouna L

Francois C,
Regueme A,
Hartard C,
Rogez S,
Gallais F,
Dos Santos G



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What is true about RSV resistance to nirsevimab?

① Start presenting to display the poll results on this slide.

**Thanks for your attention
Questions ?**



Surveillance of bronchiolitis and RSV infections



Surveillance of bronchiolitis (< 2 years) – weekly data



Surveillance of RSV infection in adults

Virological surveillance

Surveillance of bronchiolitis (< 2 years) – weekly data



Community
Sentinelles
SOS Med



Consultations of outpatients for bronchiolitis



Hospital
Réseau OSCOUR®



Consultation in an emergency department for bronchiolitis
Hospitalisation for bronchiolitis
Hospitalisation for bronchiolitis in PICU



ICU
PICURe



Surveillance of cases of bronchiolitis hospitalized in PICU (< 2 years)

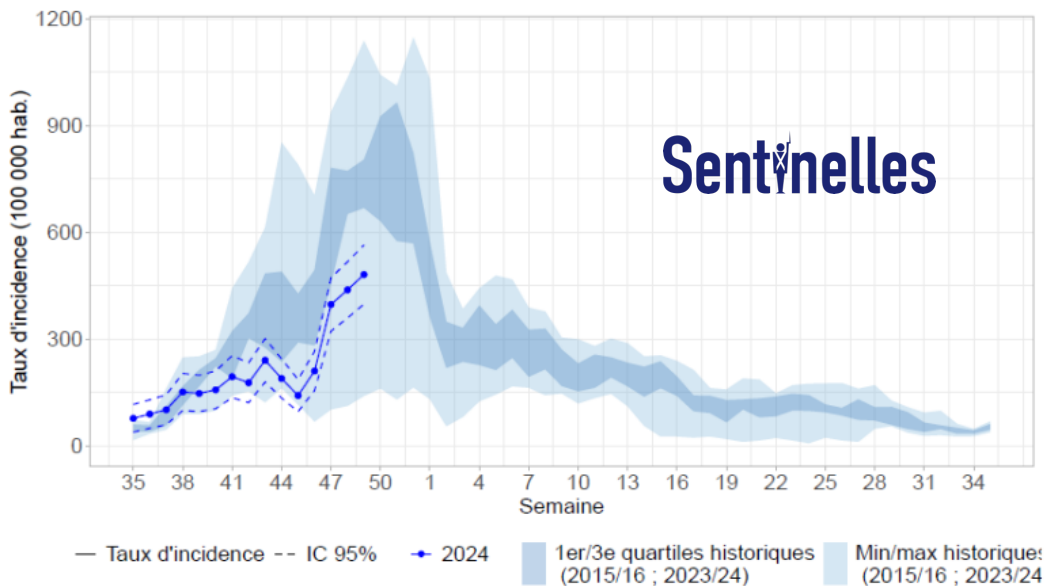
Surveillance of bronchiolitis (< 2 years) – weekly data



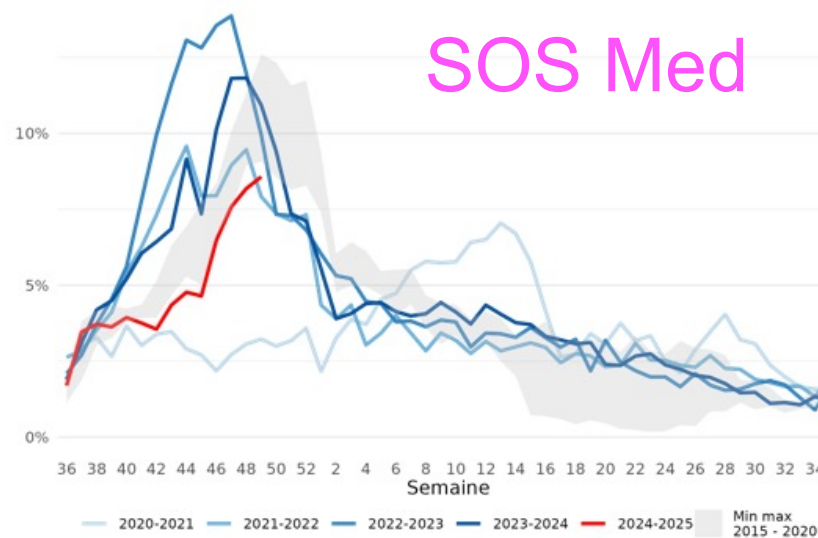
Community



Estimated incidence



Consultations of outpatients



Regional warning levels, W49-2024



Source : SOS Médecins

<https://www.sentiweb.fr/document/6453>

<https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/grippe/documents/bulletin-national/infections-respiratoires-aigues-grippe-bronchiolite-covid-19-.-bulletin-du-11-decembre-2024>

Adapted from a presentation by Sophie VAUX Spf

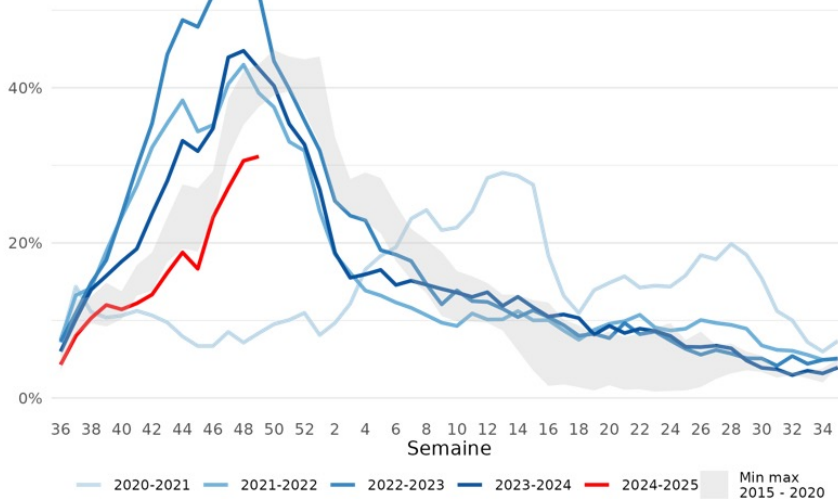
Surveillance of bronchiolitis (< 2 years) – weekly data



Hospital

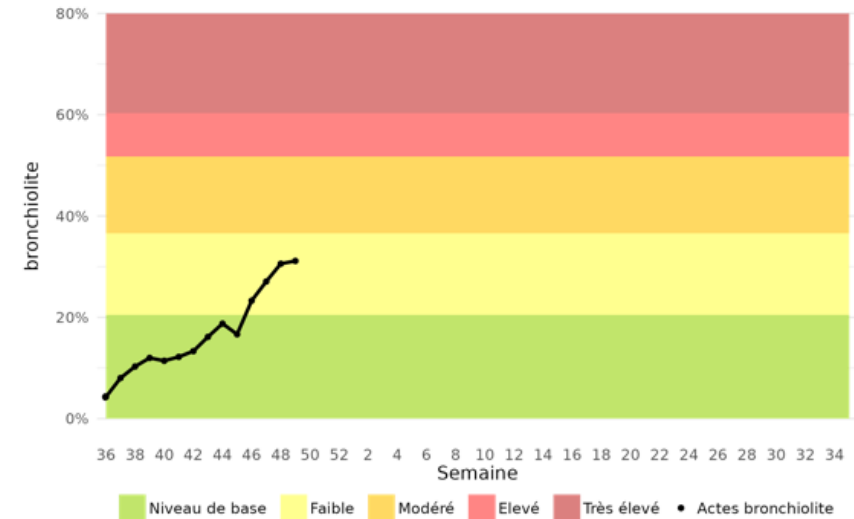
Réseau OSCOUR®

Hospitalisation for bronchiolitis after ER visit



Source : réseau OSCOUR®

Intensity level (Hospitalisation for bronchiolitis after an emergency visit)



Source : réseau OSCOUR®. * Méthodologie en [annexe](#)

Moving Epidemic Method (MEM)

<https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/grippe/documents/bulletin-national/infections-respiratoires-aigues-grippe-bronchiolite-covid-19-.-bulletin-du-11-decembre-2024>

Surveillance of bronchiolitis and RSV infections



Surveillance of bronchiolitis (< 2 years) – weekly data



Surveillance of RSV infection in adults

Surveillance of cases of RSV infections hospitalized in PICU

Virological surveillance

Overview of the French National Reference Center for respiratory viruses

Surveillance of Influenza, SARS-CoV-2 and RSV *and other respiratory viruses*



French virological surveillance

Networks providing information and/or samples to the CNR



Community

Sentinelles

RELAB



RELAB
Laboratoires

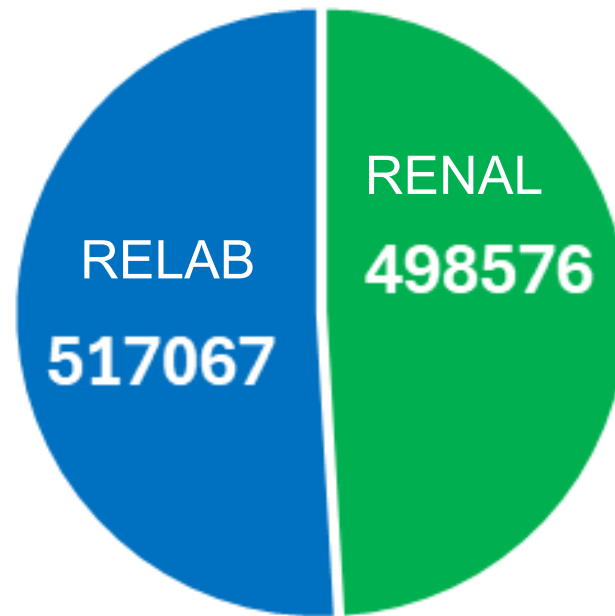
SOS Med



Hospital

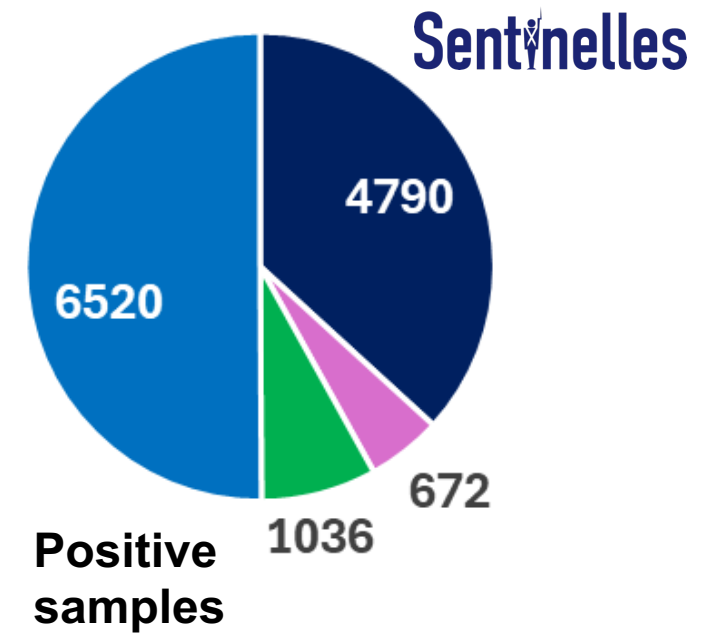
RENAL

Virological data



2023-24 numbers

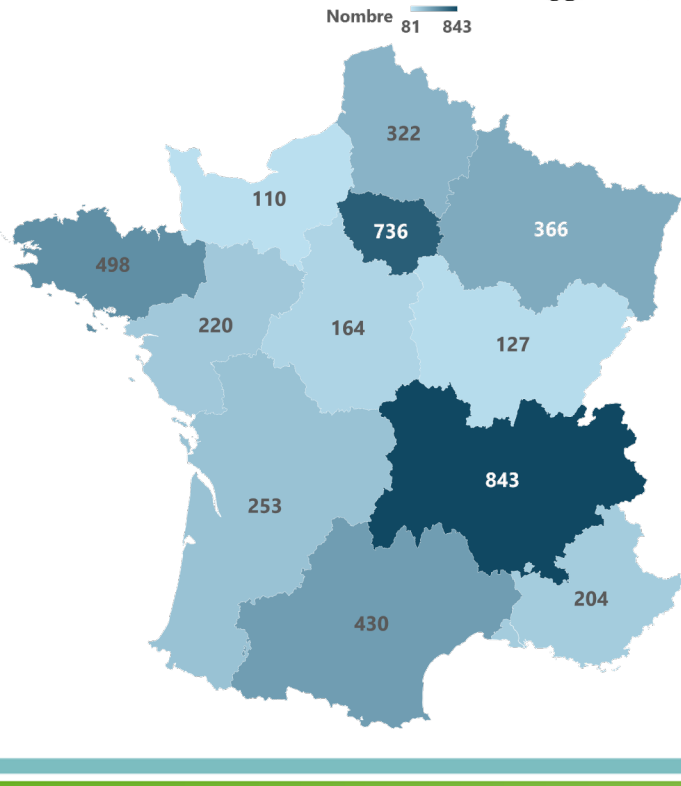
Respiratory Samples



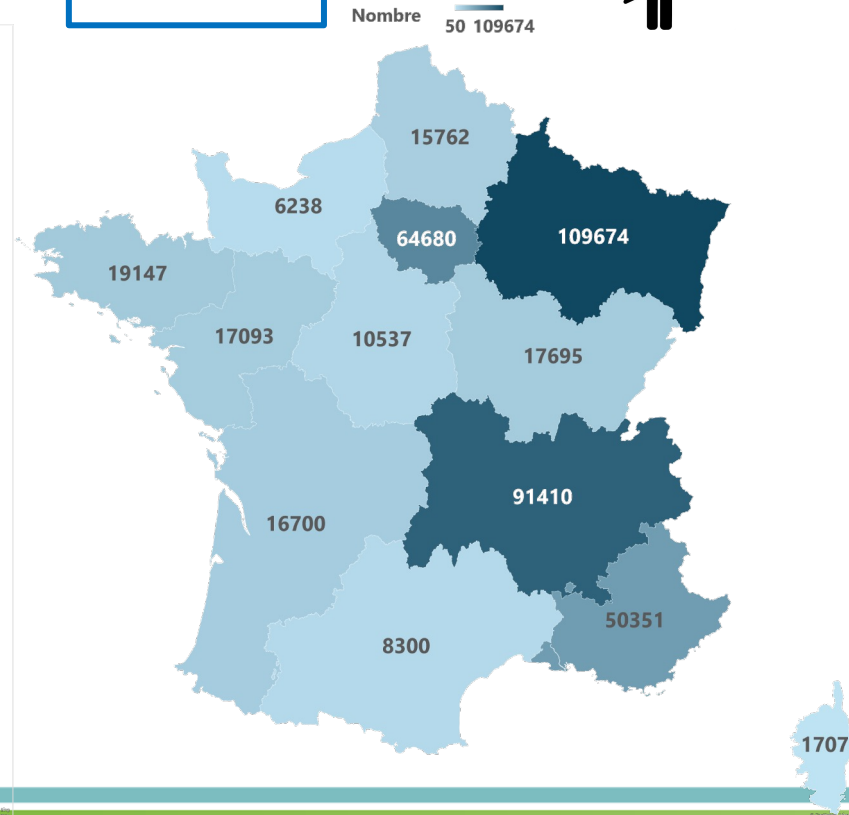
Good geographical coverage, although there are some regional differences

Number of samples tested (for SARS-CoV-2) per region in the 2023-24 season

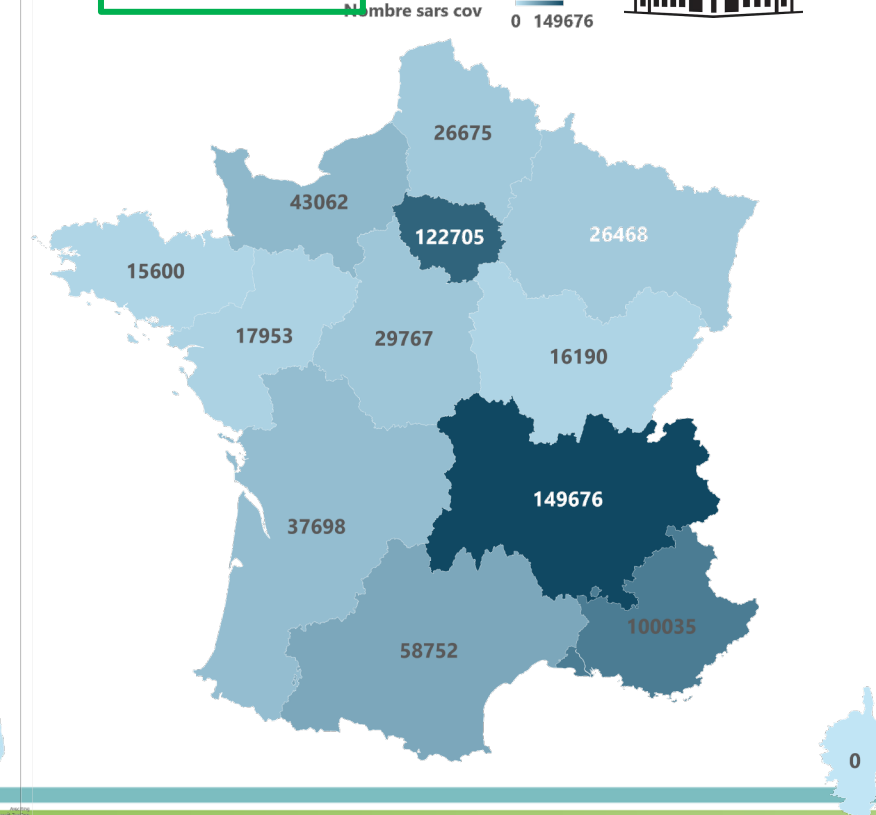
Sentinelles



RELAB



RENAL



French virological surveillance Reporting



➤ **Weekly publication of the NRC report (open access)**

➤ Weekly reporting to



➤ **Biennial report on influenza to WHO and virus transmission to WHO Collaborating Centre**

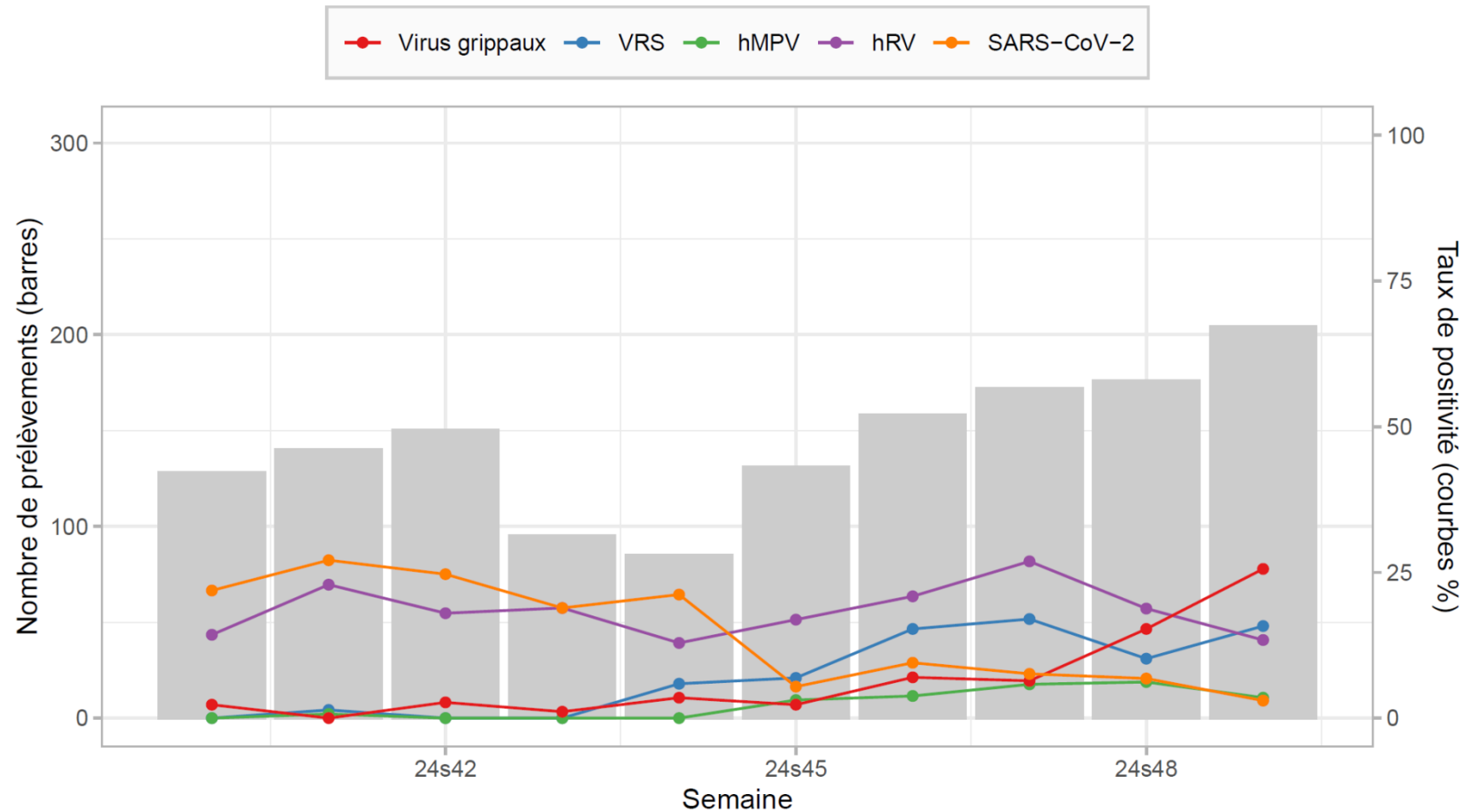


Covinet ?

French virological surveillance: Weekly report

Sentinelles

RT-PCR by NRC



French virological surveillance: Weekly report



Centre National de Référence Virus des Infections
Respiratoires (dont la grippe et le SARS-CoV-2)



SEMAINE 49/2024

● Saison 2023/2024

● Saison 2024/2025



RELAB
Laboratoires

Taux de détection

7,85%

vs 48/2024 ▲ +1,0%

vs 49/2023 ▲ +2,77%

Prélèvements positifs

555

vs 48/2024 ▲ +102

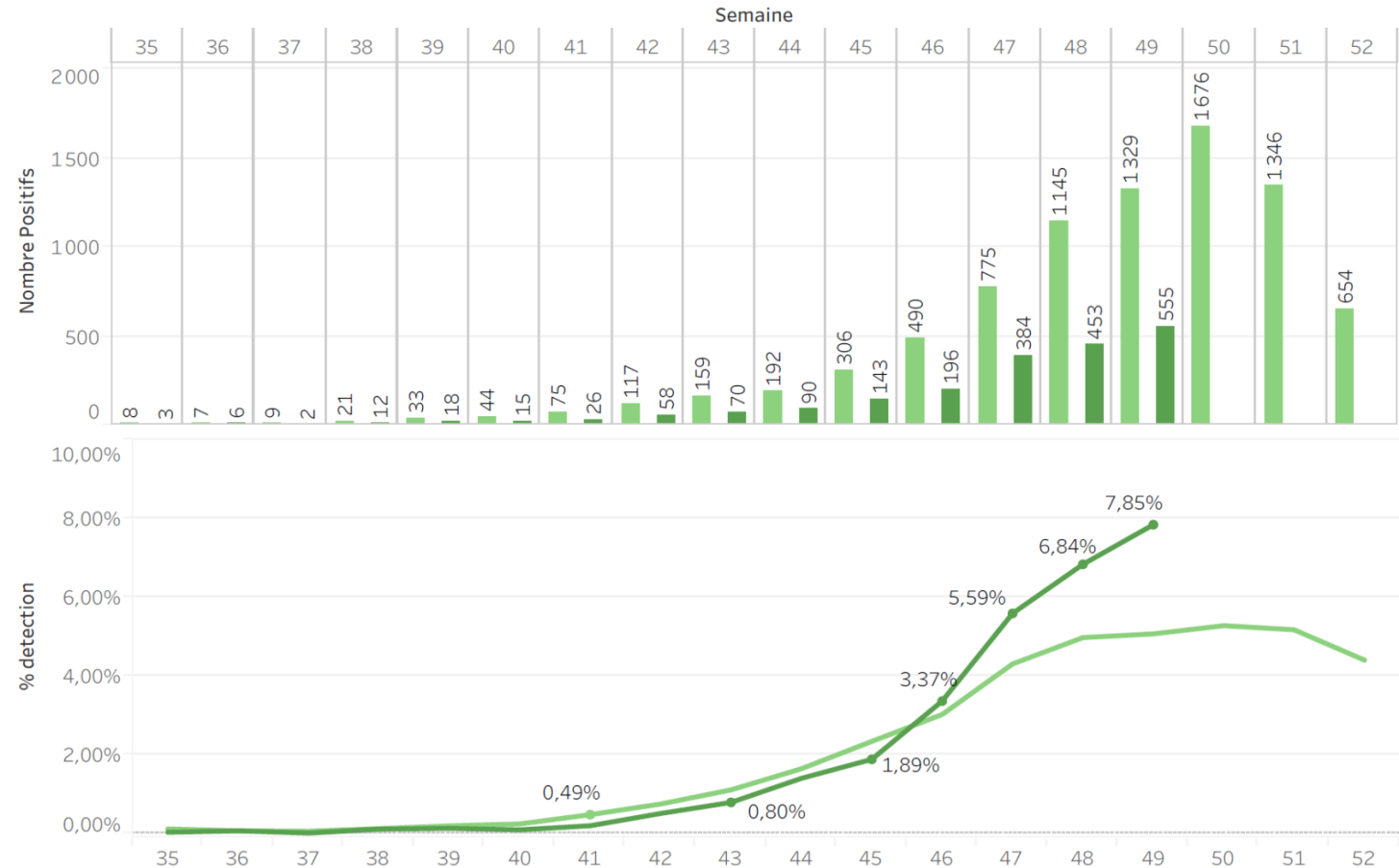
vs 49/2023 ▼ -774

Spécimens testés

7074

vs 48/2024 ▲ +452

vs 49/2023 ▼ -19108



https://www.pasteur.fr/sites/default/files/rubrique_pro_sante_publicque/les_cnr/virus_des_infections_respiratoires_dont_grippe/bnhvir_france_2024_s48.pdf

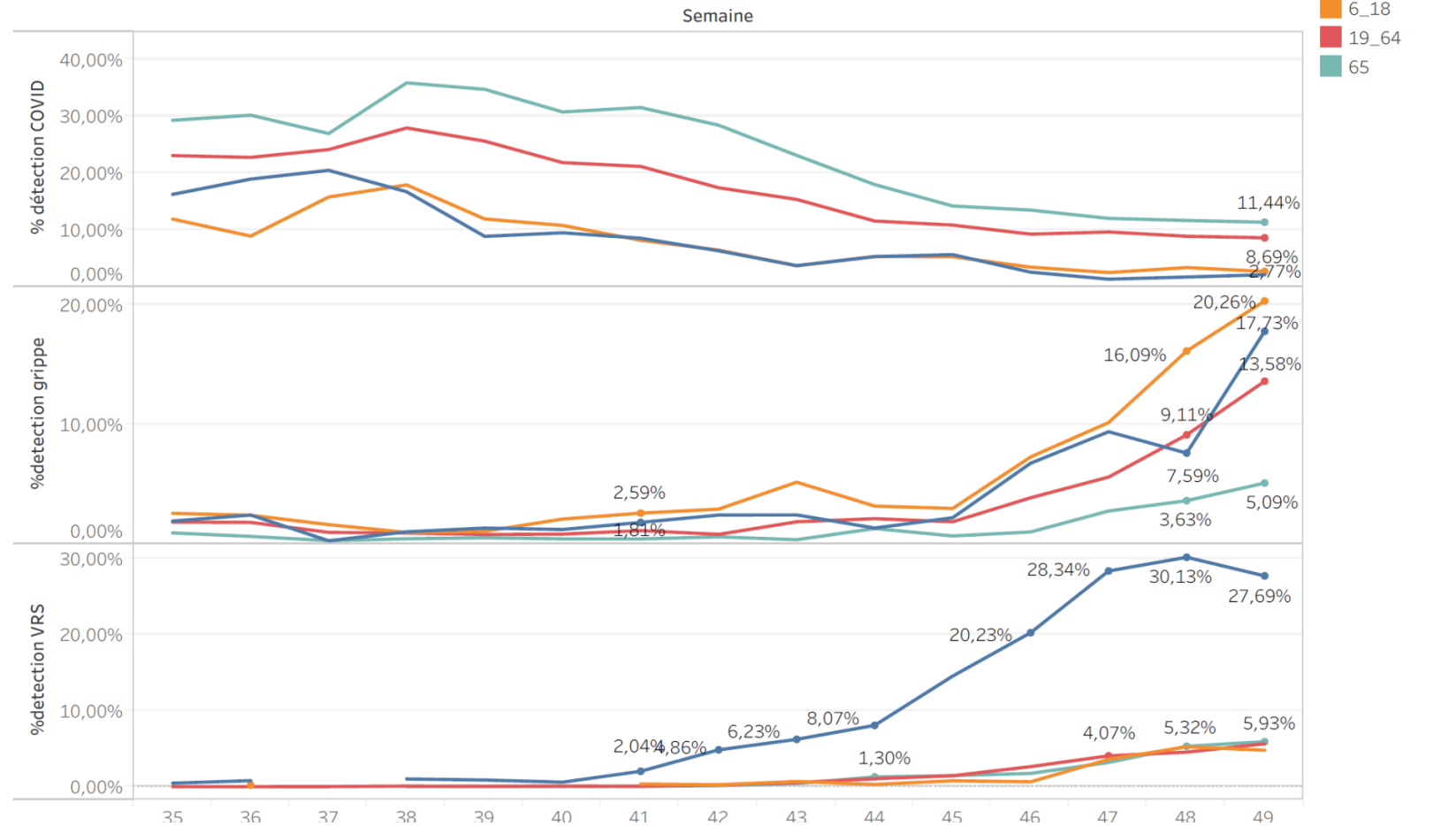
French virological surveillance: Weekly report



Centre National de Référence Virus des Infections
Respiratoires (dont la grippe et le SARS-CoV-2)



% détection COVID, Grippe et VRS par classe d'âge



French virological surveillance: Weekly report



Centre National de Référence Virus des Infections
Respiratoires (dont la grippe et le SARS-CoV-2)



RENAL

SEMAINE 49/2024

Taux de détection

11,78%

vs 48/2024 ▲ +1,97%

vs 49/2023 ▼ -1,05%

Prélèvements positifs

911

vs 48/2024 ▼ -107

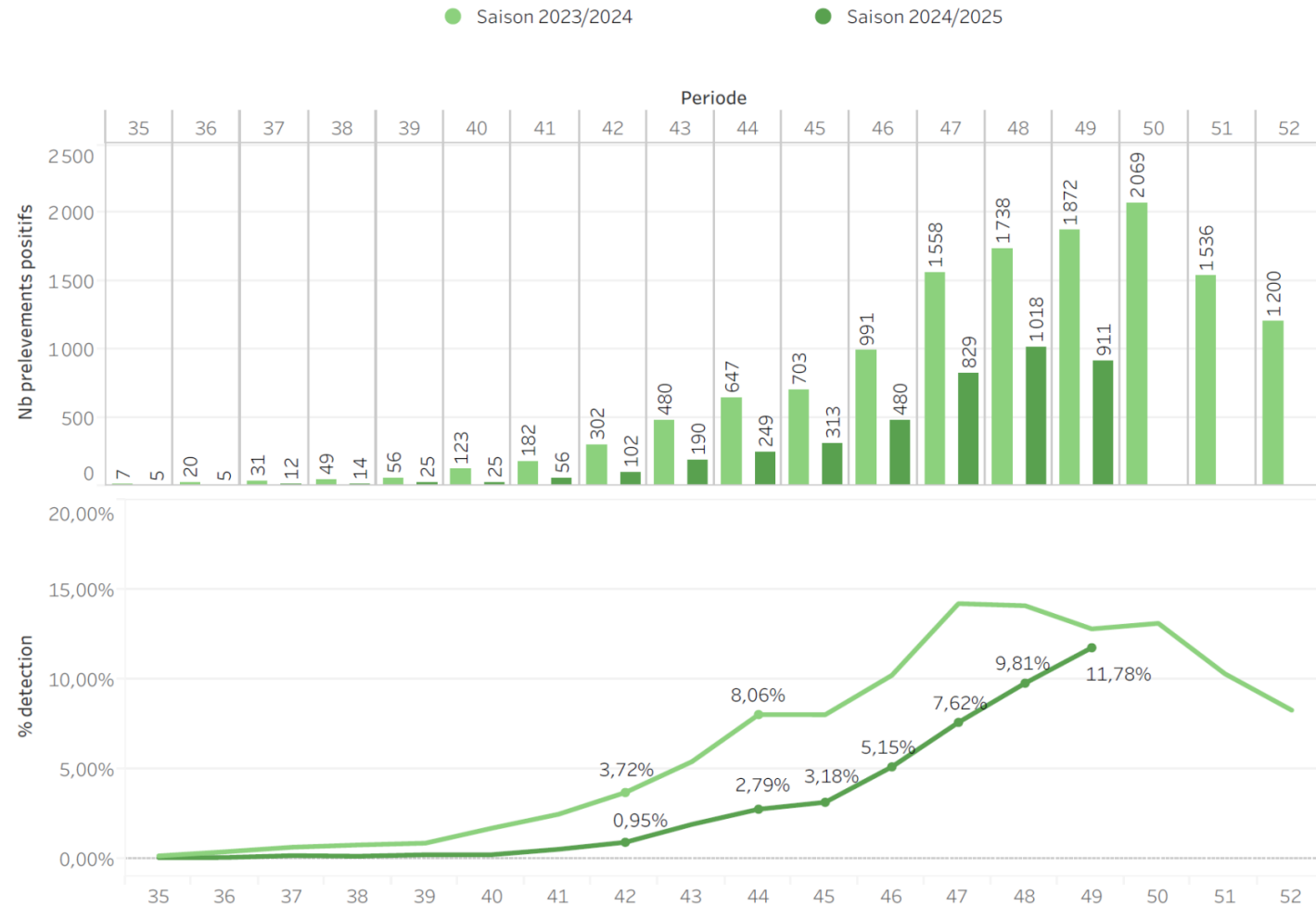
vs 49/2023 ▼ -961

Spécimens testés

7733

vs 48/2024 ▼ -2648

vs 49/2023 ▼ -6861



French virological surveillance: Weekly report

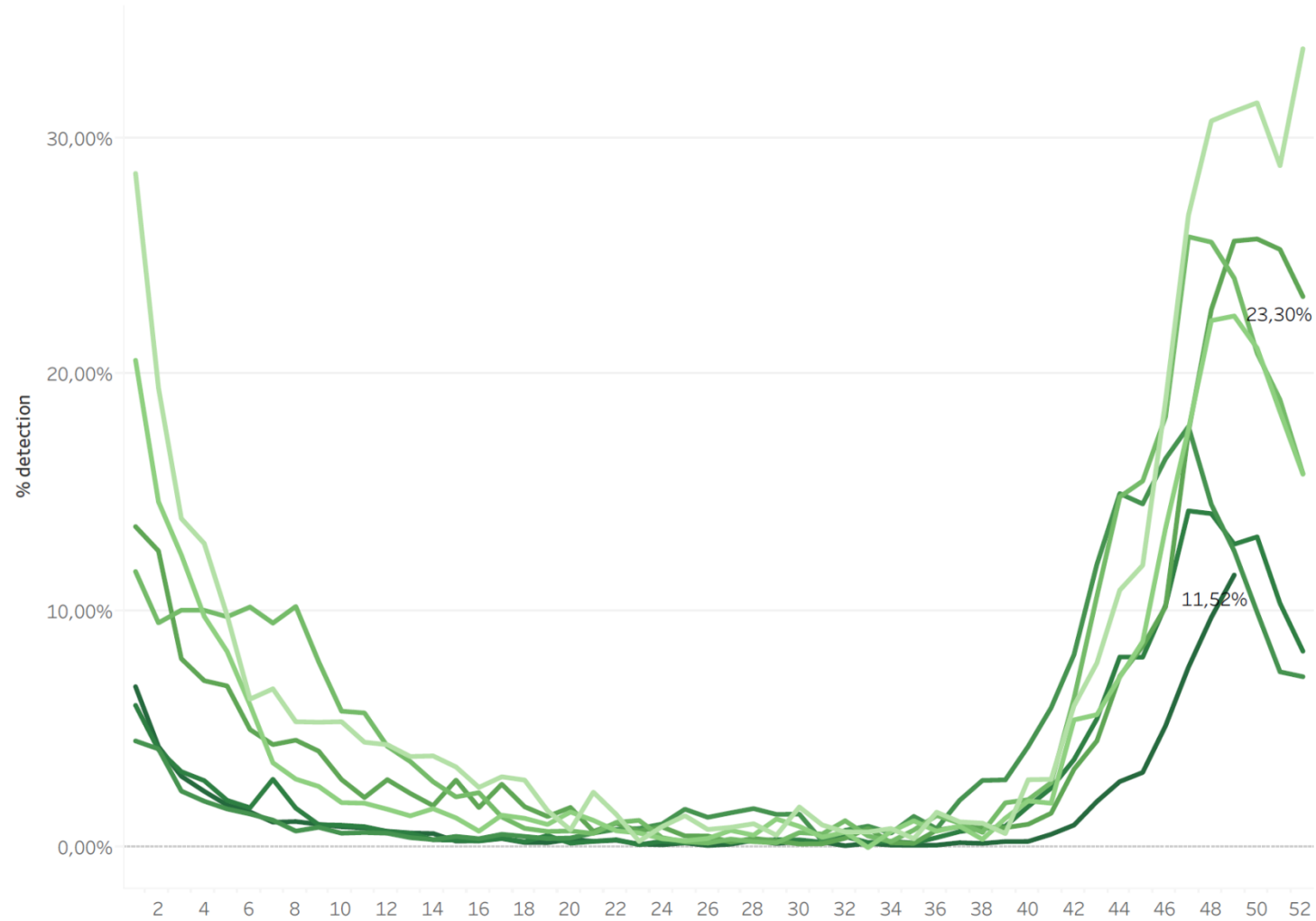
RENAL



Saisons

- Saison 2015/2016
- Saison 2016/2017
- Saison 2017/2018
- Saison 2018/2019
- Saison 2022/2023
- Saison 2023/2024
- Saison 2024/2025

Historical data from RENAL



French virological surveillance: Weekly report



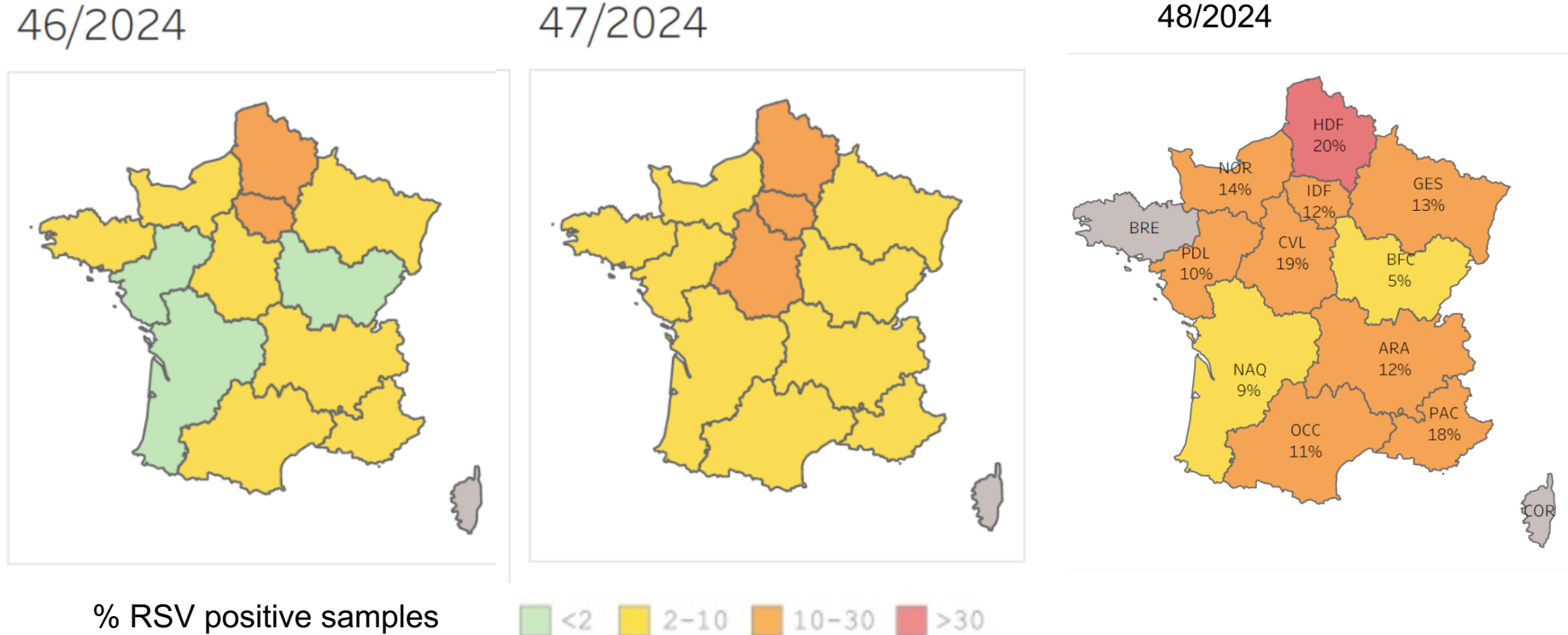
Centre National de Référence Virus des Infections
Respiratoires (dont la grippe et le SARS-CoV-2)



RENAL



Regional circulation



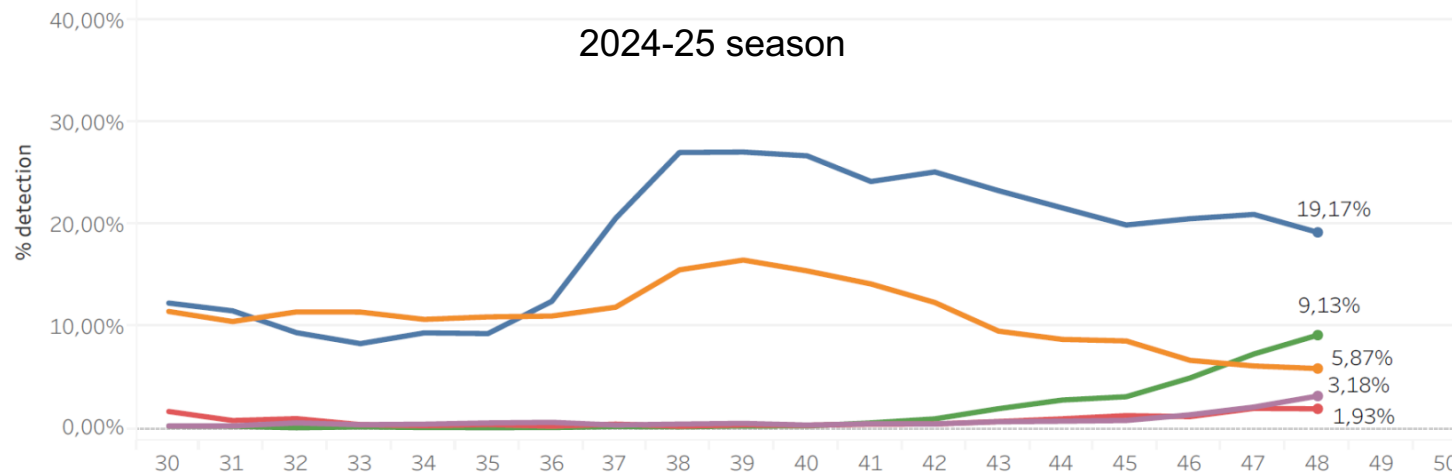
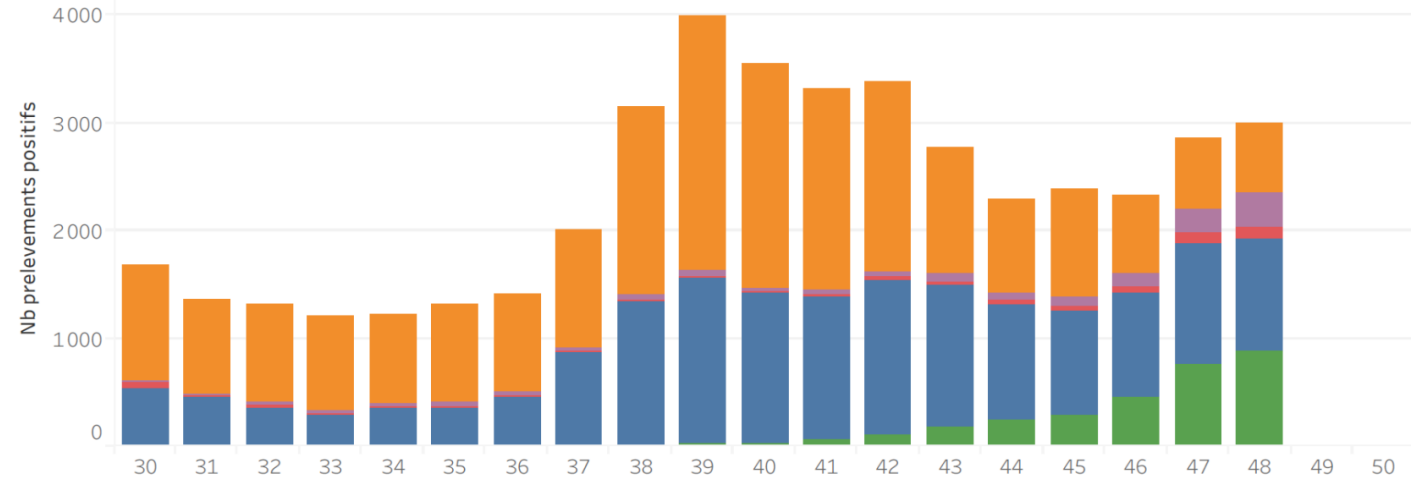
French virological surveillance: Weekly report



Centre National de Référence Virus des Infections
Respiratoires (dont la grippe et le SARS-CoV-2)



RENAL



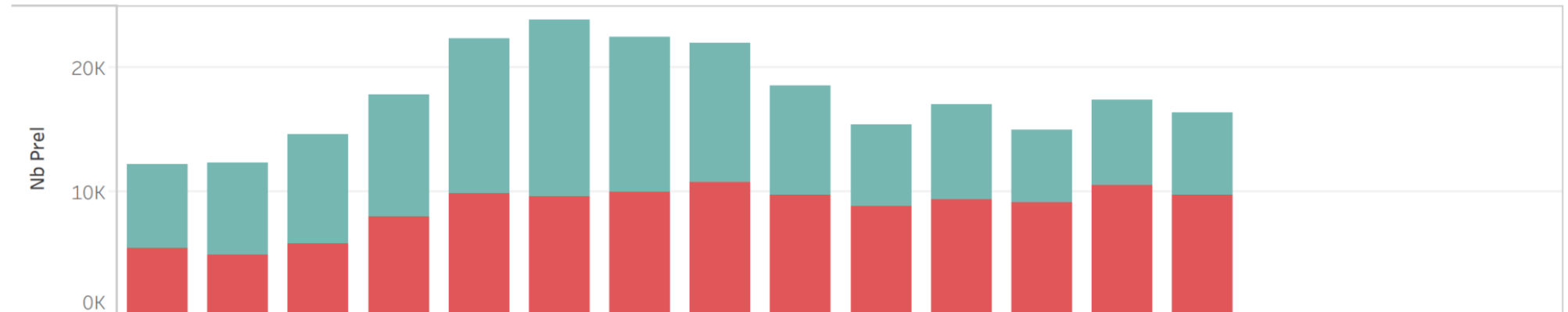
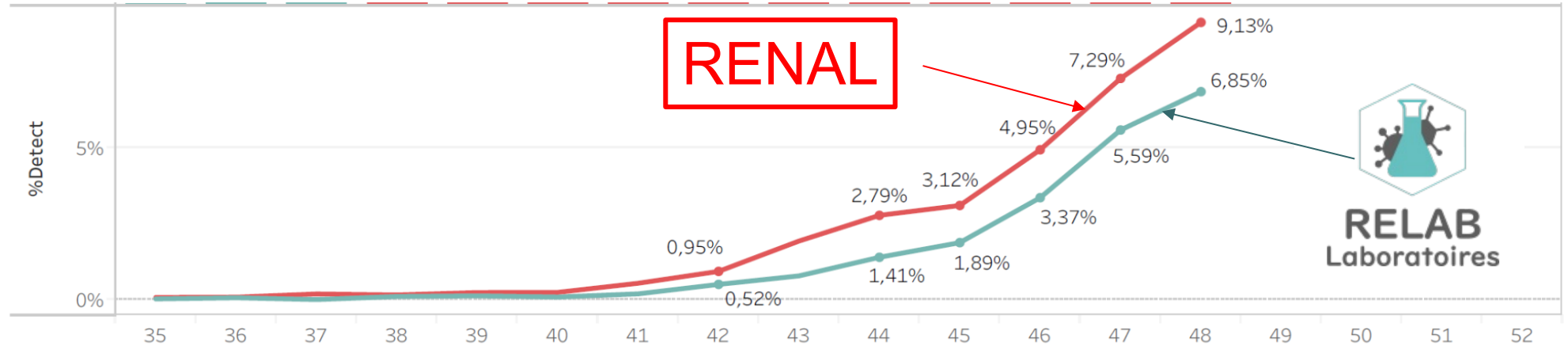
https://www.pasteur.fr/sites/default/files/rubrique_pro_sante_publique/les_cnr/virus_des_infections_respiratoires_dont_grippe/bnhvir_france_2024_s48.pdf

French virological surveillance: Weekly report

RENAL



RELAB
Laboratoires



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French virological surveillance:

① Start presenting to display the poll results on this slide.

RSV genomic surveillance in France



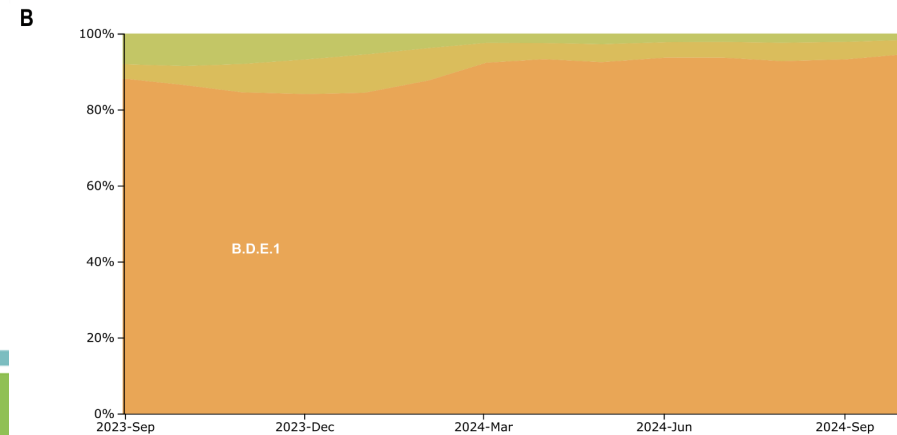
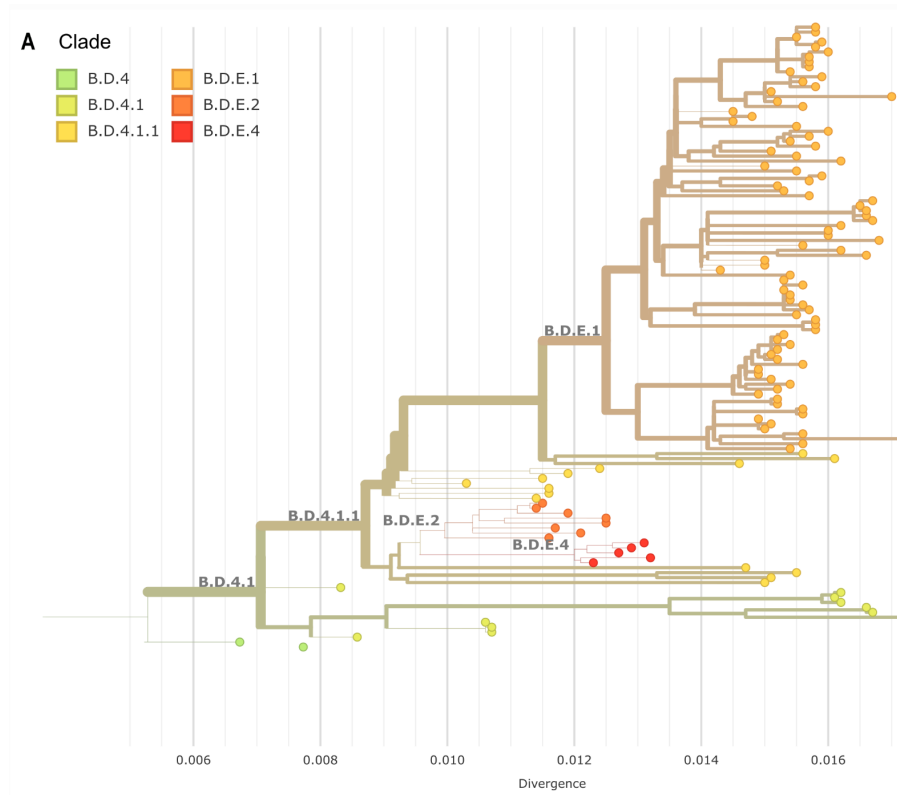
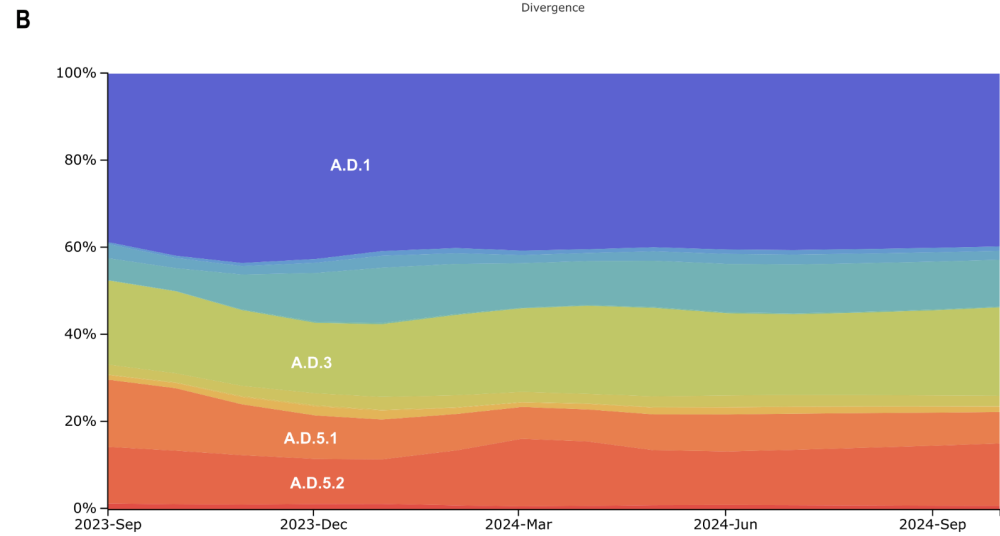
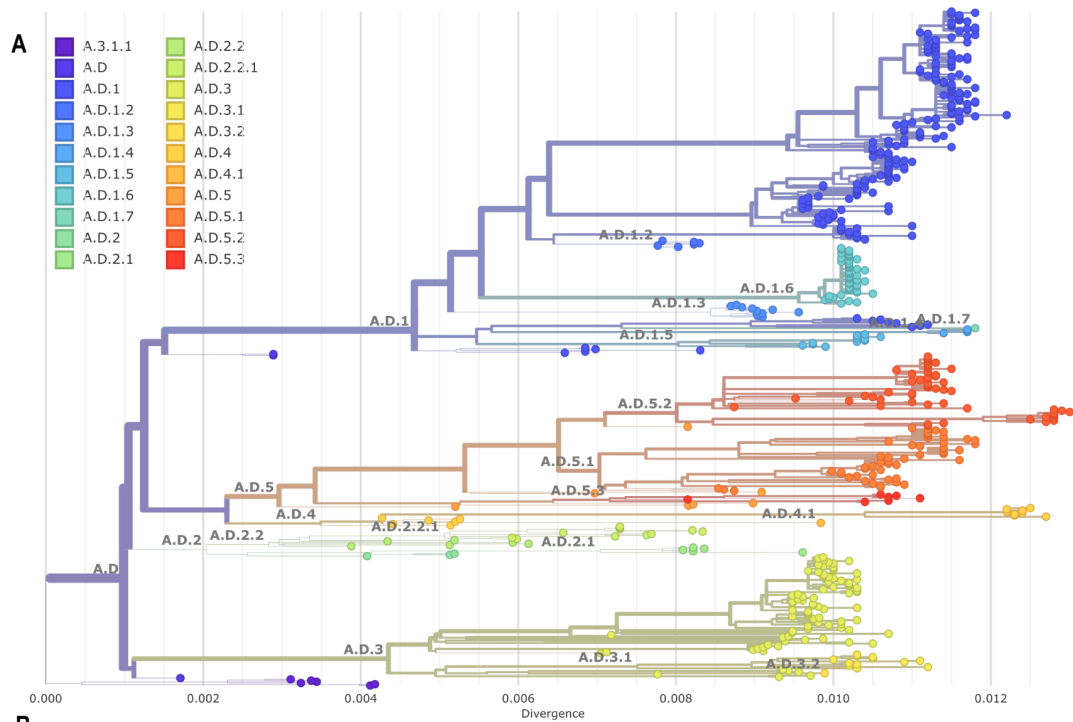
Objectives:

- **Description of circulating variants**
- **Detection of new lineages**
- **Detection of lineages circulating in specific population (age, hospital, region)**
- **Detection of nirsevimab escape mutations**



- ✓ **Whole genome sequencing using in-house amplicon method**
- ✓ **Lineage assignment**
- ✓ **Analysis of lineages in specific populations**
- ✓ **Screening for mutation in site O**

RSV genomic surveillance in France



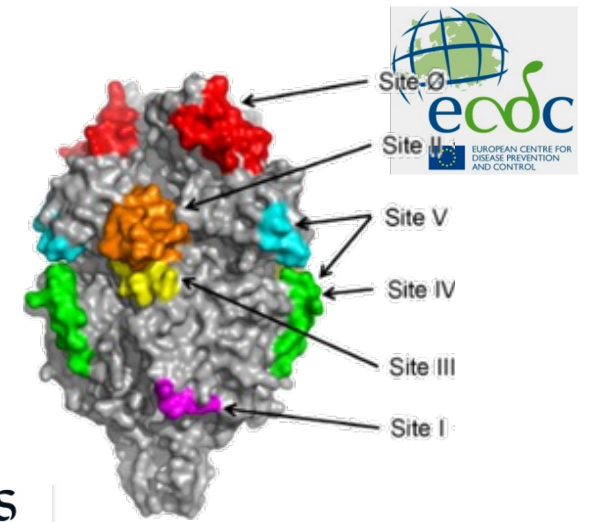
Escape mutations to nirsevimab

Description of mutations in the literature

ANRS (French National Agency for Health Research)

Website with list of mutations

<https://virusfrenchresistance.org/>



VIRUS French Resistance | VIRAL RESISTANCE INTERPRETATION ALGORITHMS | **anrs** MALADIES INFECTIEUSES ÉMERGENTES | Inserm

HOME WHO ARE WE? TABLES OF RULES LINKS

RSV

RSV-A genotypic drug resistance interpretation's algorithm (October 2023 – Version n°1)

ANRS-MIE – Respiratory viruses group
GENOTYPE INTERPRETATION: MONOCLONAL ANTIBODIES TO RSV F PROTEIN

	Mutations associated with resistance	Mutations associated with « possible resistance »	Described polymorphisms in epitope Ø without impact on sensitivity (fold change <5)
Nirsevimab	▪ N67I + N208Y [4] *Note that N67I or N208Y alone are not associated with resistance.	▪ K68E [1]	N63T/S [3] I64V [1] V650 I [1]

Systematic analysis with in-house pipeline of AA substitutions at the FØ site

RSV phenotypic surveillance in France



Objectives:

- **Susceptibility to nirsevimab**
- **Specific phenotypic traits**
- **To come: escape to vaccinated sera ?**



- ✓ **RSV isolation and amplification**
- ✓ **Nirsevimab susceptibility assay**

Isolation of RSV

Inoculation onto HEp-2
confluent cells in P12 wells



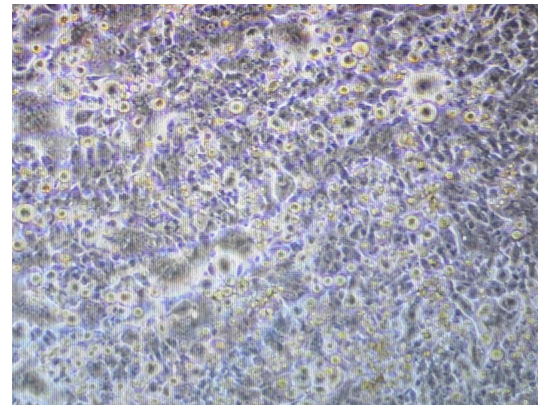
Respiratory sample



Viral growth 6 days max



Check for cytopathic
effect every 72h

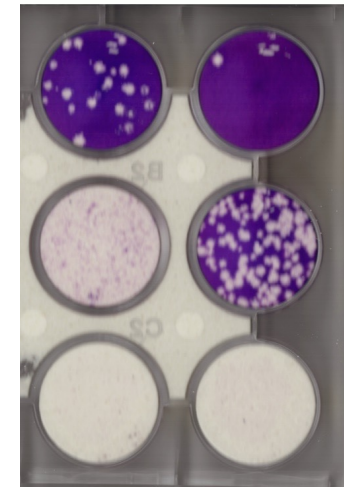


Harvest virus



➔ Sequencing
NGS metagenomic

➔ Titration

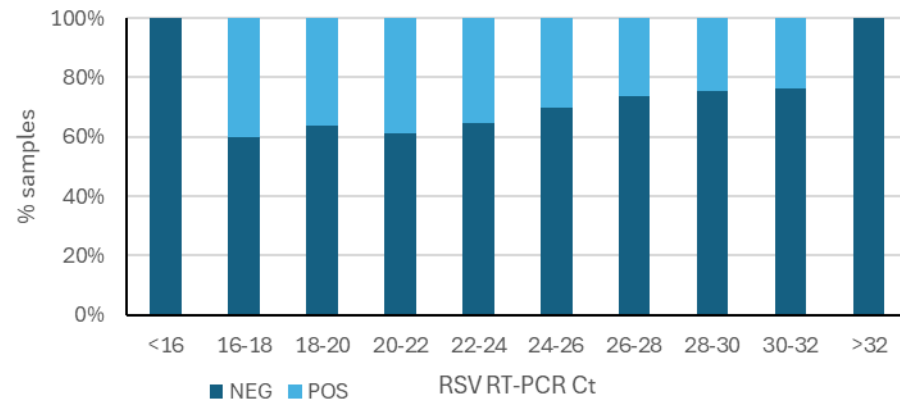
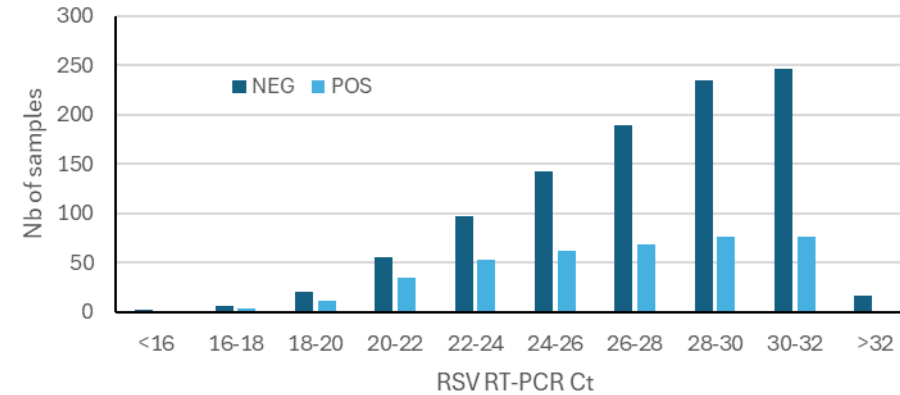
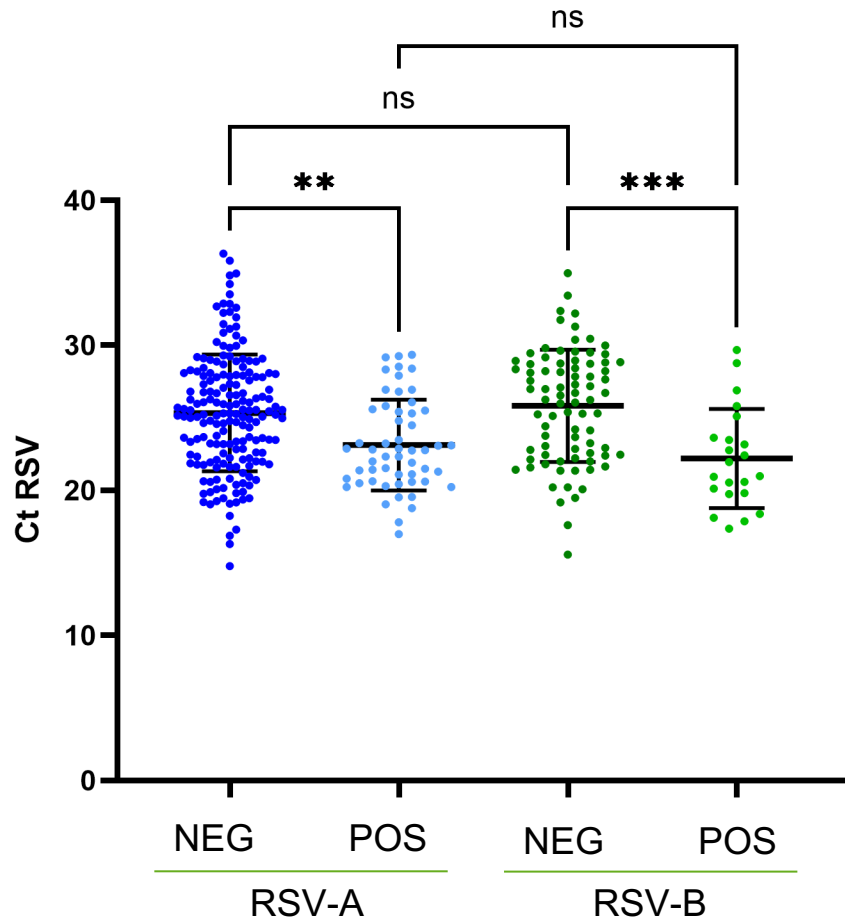


Still difficult : Isolation success around 20-25%

Does RT-PCR Ct value predicts isolation success ?

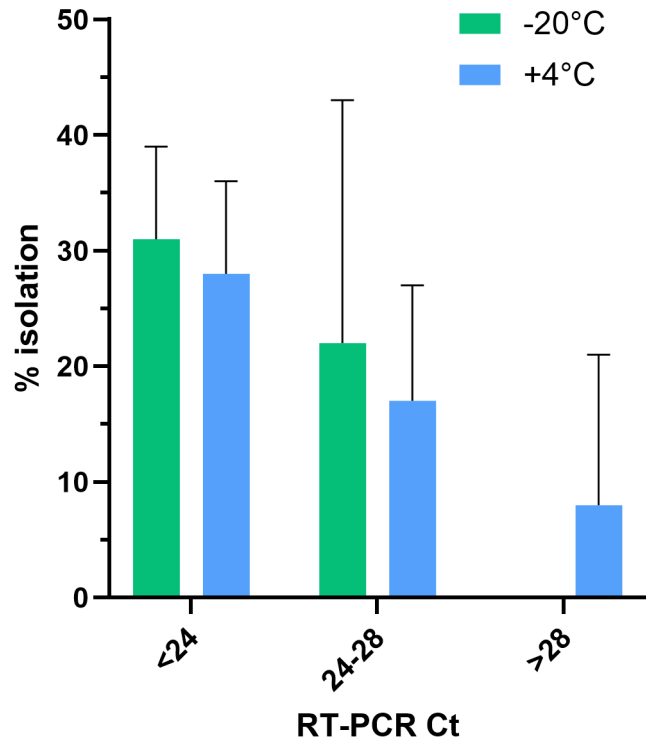
No differences in isolation success between A/B

Isolation efficiency decreases with Ct, but it is difficult to establish a threshold.

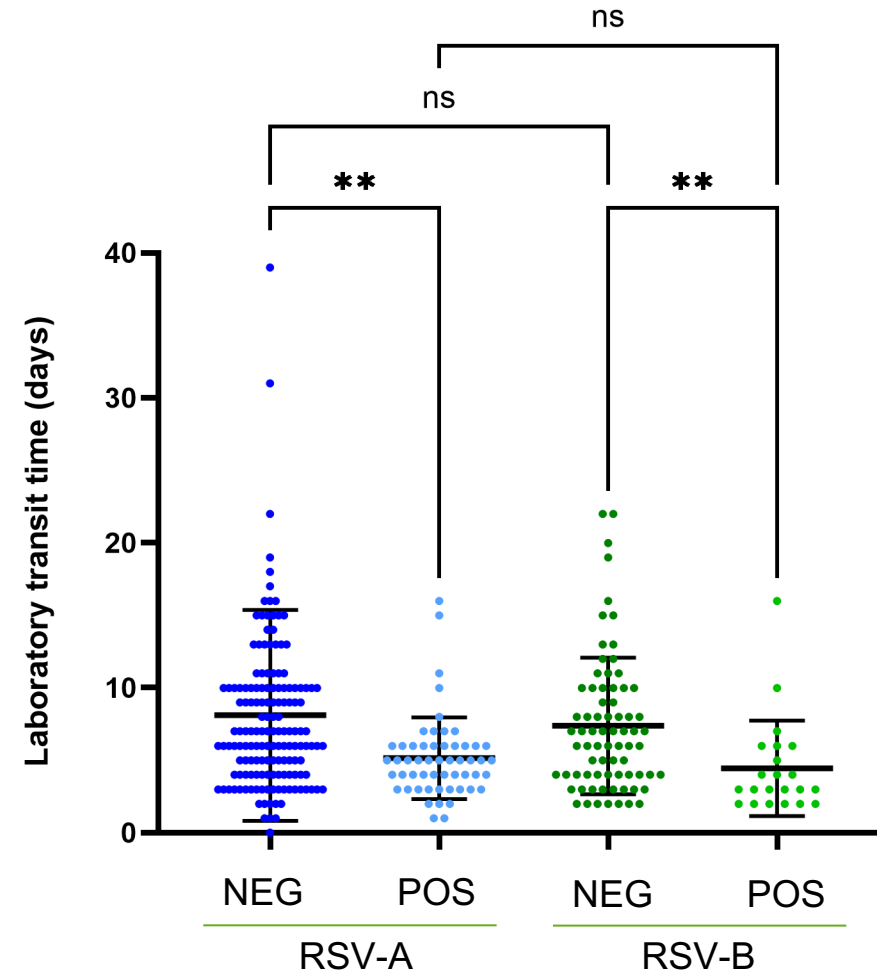


Conservation ?

Limited effect of freezing ?
Bias for +4°C preservation

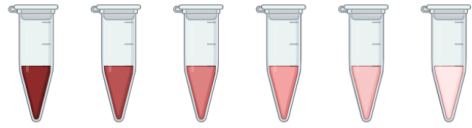


Still under investigation

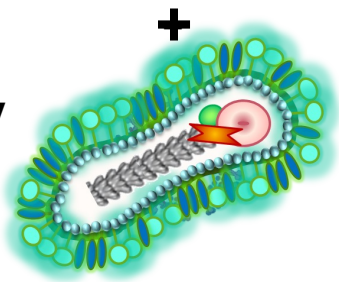


Nirsevimab neutralisation Assay

Serial dilutions of nirsevimab

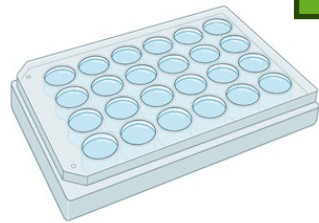


RSV



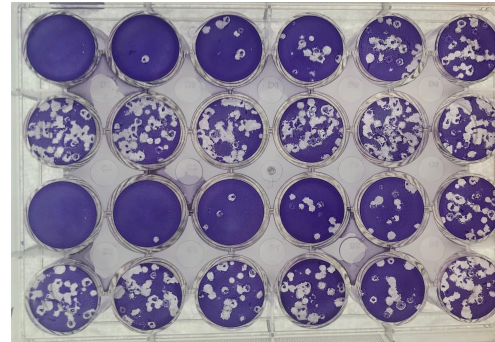
Incubation
60 min 37°C

Infection HEp-2
+ overlay

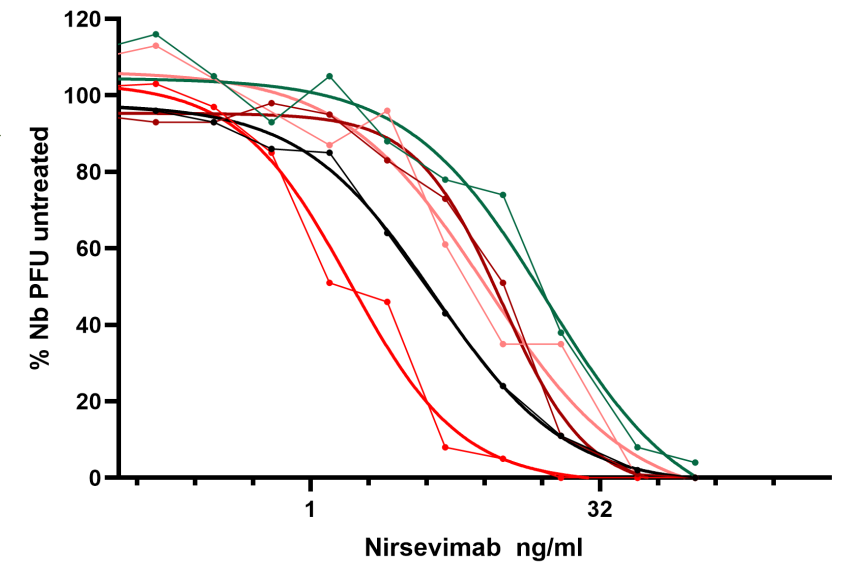


Incubation 6 days
CO₂ 37°C

Revelation



EC50 calculation



Challenges:

- Long and tedious
- Unstable titers
- Need for internal standard

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The following statements apply to RSV

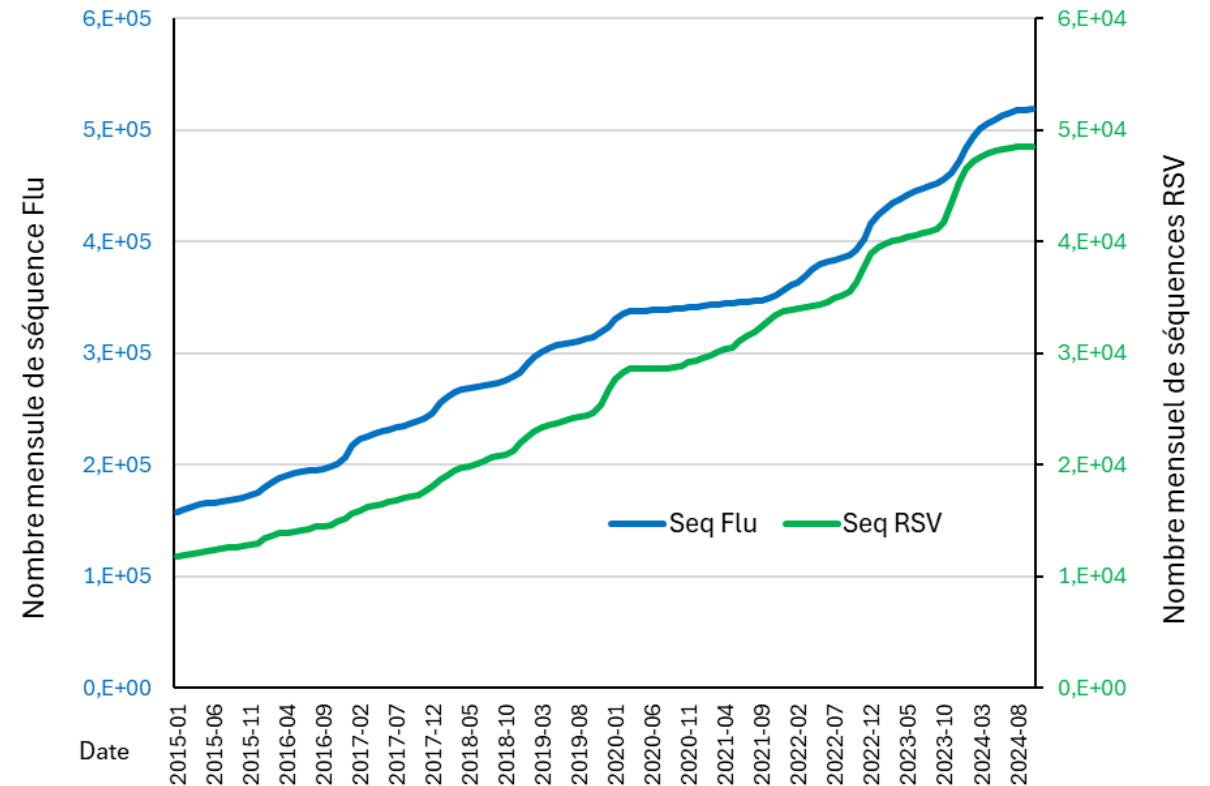
① Start presenting to display the poll results on this slide.

RSV surveillance

Sequencing still challenging

**Isolation difficult,
neutralisation assay to
improve**

Séquences déposée sur GISAID - Monde (4-11-2024)



**Thanks for your attention
Questions ?**

