

Infection VRS de l'adulte

Atelier GREPI 2023

Orateurs:

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HOPITAL
FOCH

Pour votre santé, Foch s'engage



Infection VRS de l'adulte - données cliniques -

GREPI 2023
16/11/2023

Dr Benjamin Zuber
-Réanimation-



Quels patients sont concernés?

Original article

Prognosis of hospitalised adult patients with respiratory syncytial virus infection: a multicentre retrospective cohort study

Héloïse Celante^{1,2}, Nadia Oubaya^{3,4}, Slim Fourati^{5,6}, Sébastien Beaune⁷, Mehdi Khellaf^{8,9}, Enrique Casalino¹⁰, Jean-Damien Ricard¹¹, Antoine Vieillard-Baron^{12,13}, Nicholas Heming¹⁴, Armand Mekontso Dessap^{1,2,3}, Etienne de Montmollin¹⁵, Sarah Benghanem¹⁶, Nicolas Epaillard¹⁷, Richard Layese^{3,18}, Nicolas de Prost^{1,2,*}, on behalf of Prono-RSV study group of the clinical data warehouse of Greater Paris University Hospitals



2023

- Patients âgés
- FDR cardiovasculaire
- BPCO
- Immunodépression

Table 1

Baseline characteristics, management, and outcomes of patients with RSV infection

	Total population (n = 1168)
Demographics, comorbidities, and co-infection at hospital admission	
Age, y	75 (63–85)
Female sex	631 (54.0)
BMI ≥ 30 kg/m ²	244 (20.9)
Diabetes	252 (21.6)
Hypertension	542 (46.4)
Chronic heart failure	402 (34.4)
COPD	334 (28.6)
Respiratory chronic failure	185 (15.8)
Cirrhosis	12 (1.0)
Chronic alcoholism	36 (3.1)
Chronic haemodialysis	45 (3.9)
Immunosuppression	345 (29.5)
Cancer	118 (10.1)
Solid organ transplant ^a	75 (6.4)
HIV infection	25 (2.1)
Allogeneic HSCT	35 (3)
Neutropenia	26 (2.2)
Haematologic disease	130 (11.1)
Co-infection	213 (18.2)

L'infection VRS de l'adulte est elle moins grave que la grippe?



Contents lists available at ScienceDirect

Journal of Clinical Virology

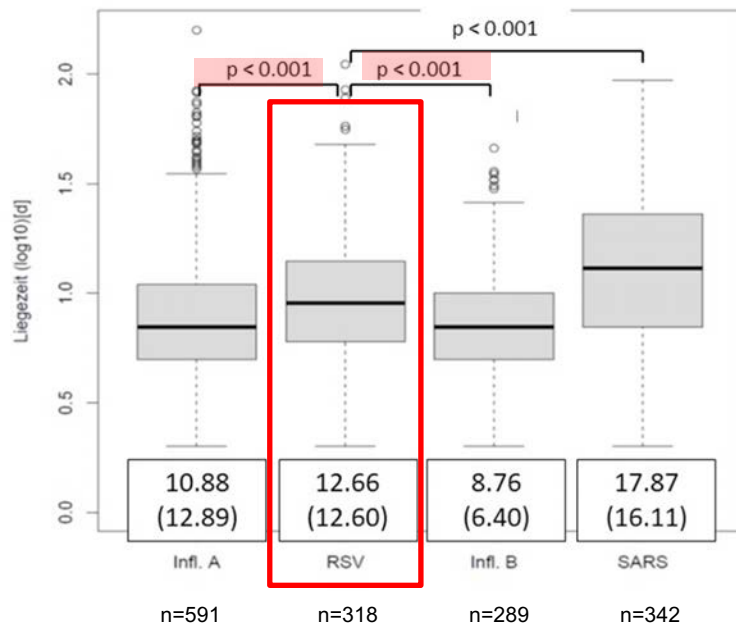
journal homepage: www.elsevier.com/locate/jcv



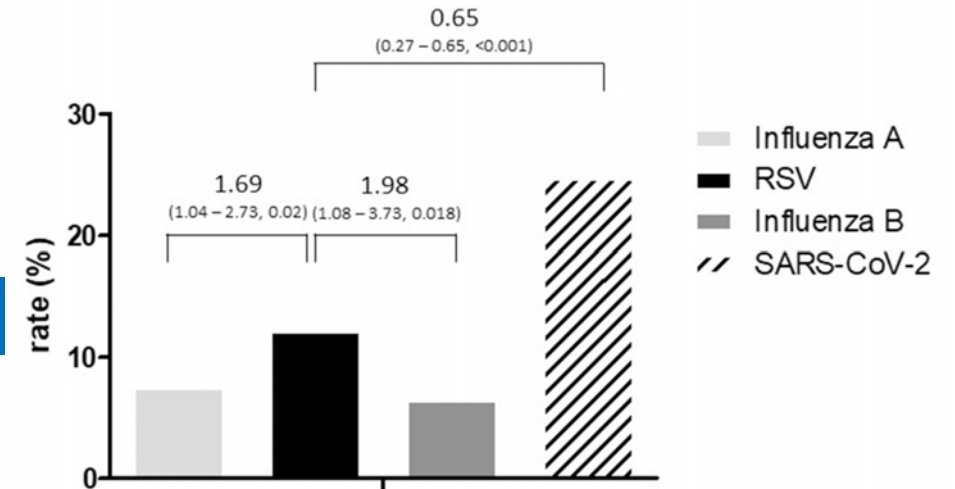
2023

Focusing on severe infections with the respiratory syncytial virus (RSV) in adults: Risk factors, symptomatology and clinical course compared to influenza A / B and the original SARS-CoV-2 strain

Andreas Ambrosch^{a,*}, Doris Lubert^a, Frank Klawonn^{b,c}, Michael Kabesch^{d,e}



Plus d'admission en réa



OR (95%CI, p)	Pneumonia	Bacterial superinfection	Mechanical ventilation	Mortality
RSV / Influenza A	1.39 (1.01 - 1.93; 0.035)	1.12 (0.73 - 1.69, 0.60)	1.59 (0.93 - 2.69, 0.05)	1.65 (0.98 - 274, 0.05)
RSV / Influenza B	1.09 (0.77-1.57, 0.60)	1.64 (1.02- 2.64, 0.04)	2.33 (1.15 - 4.96, <0.001)	1.42 (0.78 - 2.61, 0.26)

Durée d'hospitalisation plus longue

Plus de pneumonie et mortalité supérieure

L'infection VRS de l'adulte est elle moins grave que la grippe?

Original article

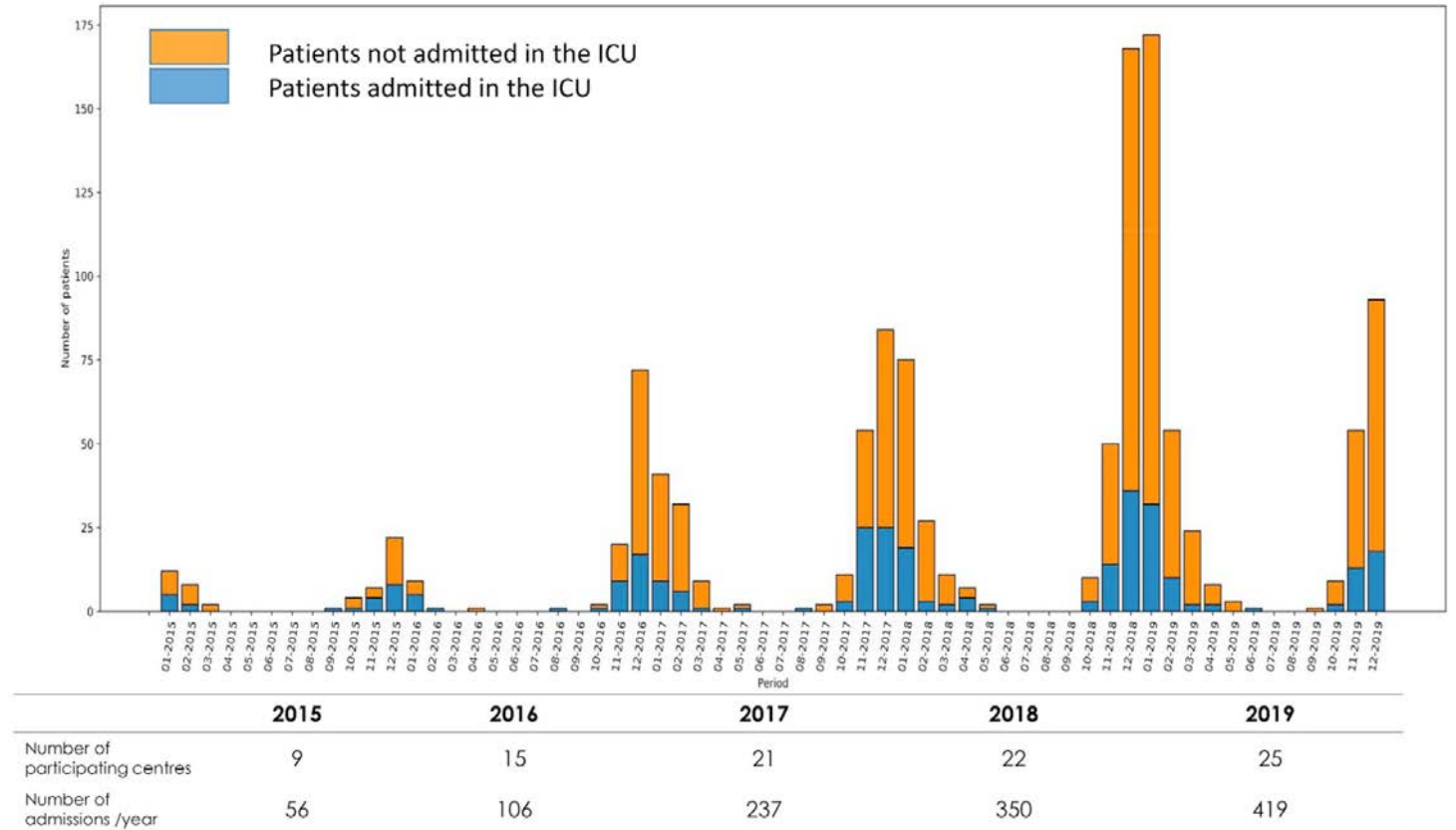
Prognosis of hospitalised adult patients with respiratory syncytial virus infection: a multicentre retrospective cohort study

Héloïse Celante ^{1,2}, Nadia Oubaya ^{3,4}, Slim Fourati ^{5,6}, Sébastien Beaune ⁷, Mehdi Khellaf ^{8,9}, Enrique Casalino ¹⁰, Jean-Damien Ricard ¹¹, Antoine Vieillard-Baron ^{12,13}, Nicholas Heming ¹⁴, Armand Mekontso Dessap ^{1,2,3}, Etienne de Montmollin ¹⁵, Sarah Benghanem ¹⁶, Nicolas Epaillard ¹⁷, Richard Layese ^{3,18}, Nicolas de Prost ^{1,2,*}, on behalf of Prono-RSV study group of the clinical data warehouse of Greater Paris University Hospitals



2023

Admission en réanimation: 24,7%
Mortalité hospitalière (ts patients): 6,6%
Mortalité patients admis en réa: 12,8%



L'infection VRS de l'adulte est elle moins grave que la grippe?

Characteristics and Outcomes of Patients in the ICU With Respiratory Syncytial Virus Compared With Those With Influenza Infection

A Multicenter Matched Cohort Study

Julien Coussement, PhD; Benjamin Zuber, MD; Eve Garrigues, MD; Antoine Gros, MD; Charlotte Vandueren, MD; Nicolas Epailard, MD; Guillaume Voiriot, PhD; Yacine Tandjaoui-Lambiotte, MD; Jean-Baptiste Lascarrou, PhD; Florence Boissier, PhD; Virginie Lemiale, MD; Damien Contou, MD; Sami Hraiech, PhD; Anne-Pascale Meert, PhD; Bertrand Sauneuf, MD; Aline Munting, MD; Sylvie Ricome, MD; Jonathan Messika, PhD; Gregoire Muller, MD; Hassane Njimi, PhD; and David Grimaldi, PhD



2022

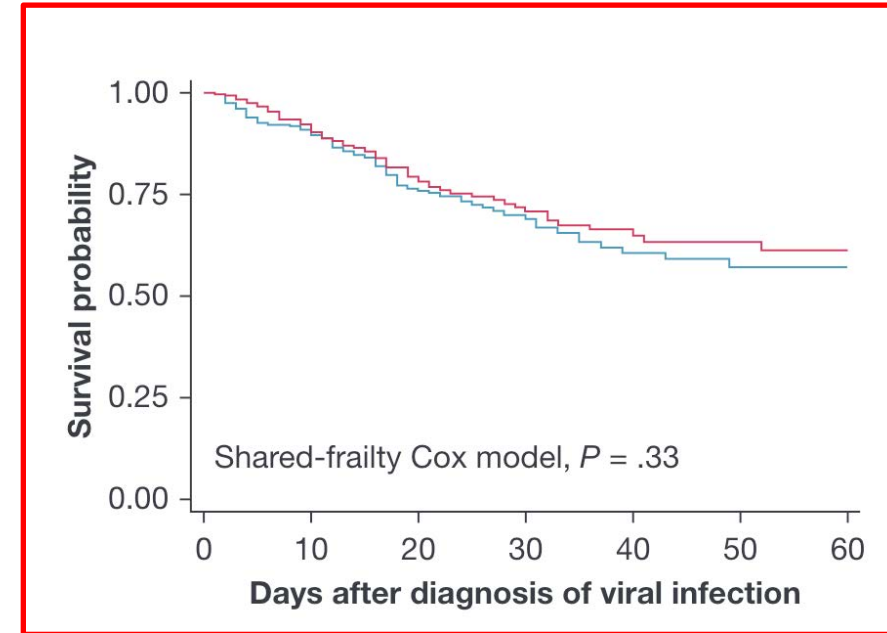


TABLE 2 | Patient Outcomes According to Type of Viral Infection (RSV vs Influenza)

Variable	RSV Infection (n = 309)	Influenza Infection (n = 309)	P Value
In-hospital mortality	74 (23.9)	79 (25.6)	.63
Hospital length of stay (for overall cohort), d	16 (10-28)	15 (8-28)	.35
Hospital length of stay (for survivors), d, n = 465	17 (10-29)	16 (9-29)	.87
In-ICU mortality	60 (19.4)	63 (20.4)	.75
ICU length of stay (for survivors), d, n = 495	6 (3-11)	6 (3-11)	.99
Length of mechanical ventilation (for survivors), d, n = 296	5 (2-11)	5 (3-12)	.59
ARDS during ICU stay	63 (20.4)	88 (28.5)	.01
Maximum form of respiratory support during ICU stay			.001
Low-flow oxygen therapy	66 (21.4)	82 (26.6)	
High-flow nasal cannula	20 (6.5)	30 (9.7)	
Noninvasive ventilation	71 (23)	52 (16.9)	
Invasive ventilation	152 (49.2)	144 (46.8)	
Including prone position	5 (1.6)	12 (3.9)	
Including ECMO	8 (2.6)	23 (7.5)	

**Patients VRS vs Grippe en réanimation:
Moins de SDRA
Plus de recours à ventilation mécanique
Mortalité équivalente:
- réanimation 20%
- hospitalière 25%**

Infection VRS de l'adulte: quels traitements?

Traitement essentiellement symptomatique+++

Oxygénothérapie
+/- ventilation
mécanique

Nébulisations BD

Corticoides
systémiques

Antibiothérapie
systémique

Bénéfices??

Si suspicion
de coinfection

Infection VRS de l'adulte: quels traitements?

Place du traitement antiviral chez l'immunodéprimé?

Patients transplantés d'organes solides

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

WILEY  Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

2019

RNA respiratory viral infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Oriol Manuel¹ | Michele Estabrook² | on behalf of the American Society of Transplantation Infectious Diseases Community of Practice

- Treatment with aerosolized or oral ribavirin is recommended for lung transplant recipients with upper or lower respiratory tract infection (weak, moderate)
- Addition of corticosteroids and IVIG to ribavirin can be considered for lung transplant recipients with upper or lower respiratory tract infection (weak, low)
- Treatment with aerosolized or oral ribavirin of non-lung solid organ recipients with lower respiratory tract disease can be considered (weak, low)

Oral or intravenous ribavirin maximal dosing 10 mg/kg body weight every 8 h for adults

Day 1: Start with 600 mg loading dose, then 200 mg every 8 h

Day 2: 400 mg every 8 h

Day 3: Increase the dose to a maximum of 10 mg/kg body weight every 8 h

In case of adverse events:	Decrease dose or discontinue ribavirin
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Creatinine clearance:	Oral or intravenous administration
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30–50 mL/min	Maximal 200 mg every 8 h
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10–30 mL/min	No recommendation can be given ^b
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Patients d'hématologie

Clinical Infectious Diseases 2014

Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for Diagnosis and Treatment of Human Respiratory Syncytial Virus, Parainfluenza Virus, Metapneumovirus, Rhinovirus, and Coronavirus

- Patients with RSV URTID undergoing allogeneic HSCT or recipients of allogeneic HSCT with risk factors for progression to RSV LRTID and death should be treated with aerosolized or systemic ribavirin and IVIG (**BII**)

Infection VRS de l'adulte: quels traitements?

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Ribavirine et IgIV recommandés avec faible niveau de preuve

Infection VRS de l'adulte: quels traitements?

Dans la vraie vie en France?

Original article

Prognosis of hospitalised adult patients with respiratory syncytial virus infection: a multicentre retrospective cohort study

Héloïse Celante^{1,2}, Nadia Oubaya^{3,4}, Slim Fourati^{5,6}, Sébastien Beaune⁷, Mehdi Khellaf^{8,9}, Enrique Casalino¹⁰, Jean-Damien Ricard¹¹, Antoine Vieillard-Baron^{12,13}, Nicholas Heming¹⁴, Armand Mekontso Dessap^{1,2,3}, Etienne de Montmollin¹⁵, Sarah Benghanem¹⁶, Nicolas Epailard¹⁷, Richard Layese^{3,18}, Nicolas de Prost^{1,2,*}, on behalf of Prono-RSV study group of the clinical data warehouse of Greater Paris University Hospitals



2023





Management and outcomes during hospital stay

Oxygen therapy ^b	213 (18.2)
Non-invasive mechanical ventilation	177 (15.2)
Invasive mechanical ventilation	86 (7.4)
Vasopressor	66 (5.7)
Renal replacement therapy	4 (0.3)
Antibiotics	959 (82.1)
Corticosteroids	507 (43.4)
Ribavirin	48 (4.1)
Pavilizumab	0
Intravenous immunoglobulins	5 (0.4)

	Total population (n = 1168)	Exposed to ribavirin (n = 48)
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Immunodeficiency	345 (29.5)	46 (95.8)
Cancer	118 (10.1)	4 (8.3)
Solid organ transplant ^b	75 (6.4)	20 (41.7)
HIV infection	25 (2.1)	2 (4.2)
Allogeneic HSCT	35 (3)	18 (37.5)
Neutropenia	26 (2.2)	4 (8.3)
Haematologic disease	130 (11.1)	21 (43.8)

Infection VRS de l'adulte: -Peut être demain des antiviraux efficaces??-

Gène cible du VRS	antiviral	« Design » de l'étude	population	Efficacité viro-clinique (Phase II)	
Fusion (PreF)	Sisunatovir (RV521)	randomisé, en double aveugle, contrôlé vs placebo	« Human challenge » (adultes sains infectés de manière expérimentale)	-diminution de la charge virale (AUC) -diminution (ou tendance) de la production de mucus et des symptômes	
L polymerase (Non-nuc)	PC786				
N Nucloproteine	EDP-938				
Fusion (PreF)	Rilematovir (JNJ-53718678)	randomisé, en double aveugle, contrôlé vs placebo (pilote)	adultes non hospitalisés âgés de ≥18 ans avec une infection à VRS diagnostiquée dans les 5 jours suivant l'apparition des symptômes	- réduction du délai d'indélectabilité de la CV (ENP) - impact favorable sur l'évolution clinique (preuve de concept. Consolidation des données nécessaires)	
Fusion (nanobody)	ALX 0171	randomisé, en double aveugle, contrôlé vs placebo	Nourrissons hospitalisés (<2 ans) pour bronchiolite à VRS	-réduction du délai d'indélectabilité de la CV (ENP) -Pas d'impact sur les résultats cliniques (délai de réponse / amélioration des symptômes respiratoires)	
Fusion (PreF)	Presatovir	randomisés, en double aveugle, contrôlé vs placebo	Adultes ID (transplanté pulm/ GSH) avec infection respiratoire basse	-Pas de réduction de la CV (ENP) -Pas d'impact sur les résultats cliniques (délai de réponse / amélioration des symptômes respiratoires)	

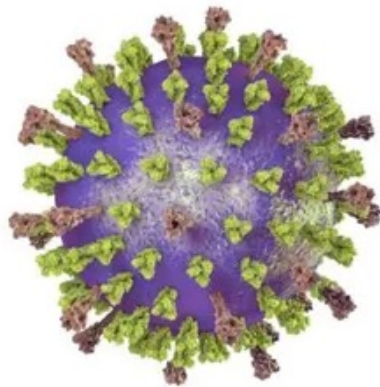
Anna C. Nilsson et al. CMI 2023; John DeVincenzo et al. Antimicrob Agents Chemother 2020 Jan 27;64(2):e01884-19 ; DeVincenzo et al. J. Inf. Dis 2022 Jun 15; 225(12): 2087–2096. Alaa Ahmad et al. NEJM 2022;386:655-66. Cunningham S et al. Lancet Respir Med 2021; 9:21-32; Roy F. Chemaly, Clinical Infectious Diseases 2020;71(11):2777–86; Gottlieb J et al. The Journal of Heart and Lung Transplantation 2023; Marty FM Clinical Infectious Diseases 2020;71(11):2787–95

Infection VRS de l'adulte

- **Concerne patients âgés, avec comorbidités cardio respiratoires et patients immunodéprimés**
 - **Associée à une importante morbi mortalité hospitalière**
 - **Traitement antiviral recommandé sur population patients vulnérables très sélectionnés mais niveau de preuve très bas**
 - **Pas de nouveau traitement antiviral commercialisé prochainement**
 - **Mieux vaut prévenir que guérir!!**
- 

Infection VRS de l'adulte: quelles perspectives thérapeutique?

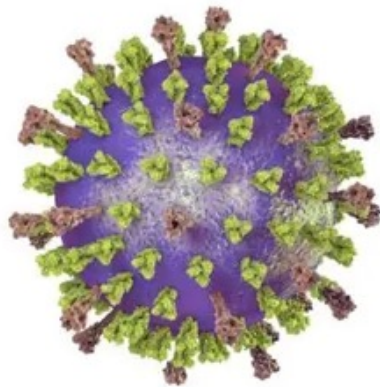
Le point de vue du virologue



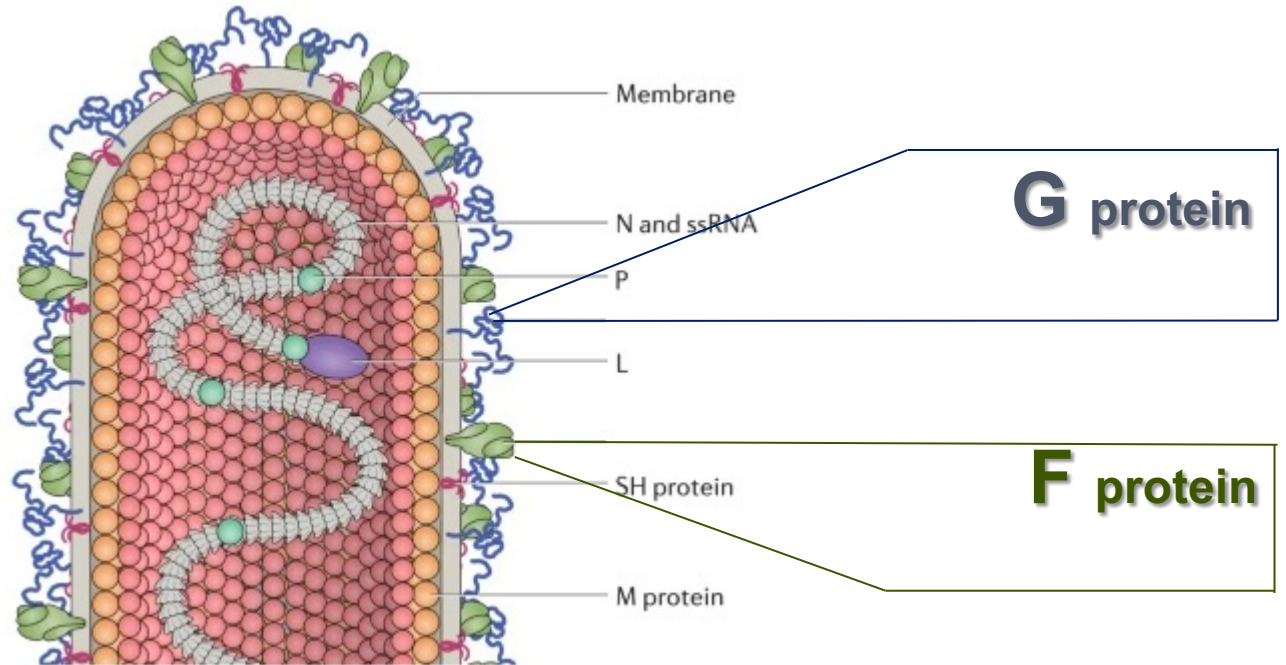
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Infection VRS de l'adulte: quelles perspectives thérapeutique?

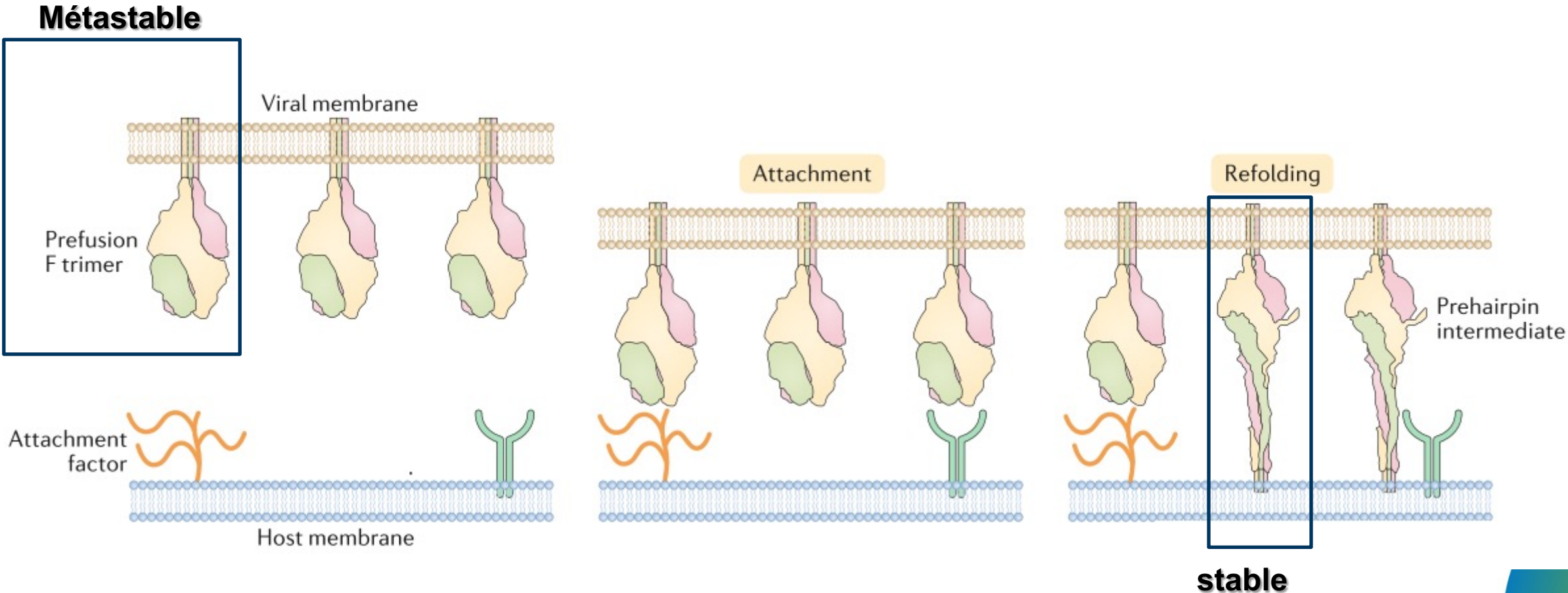
Le point de vue du virologue



Structure du RSV

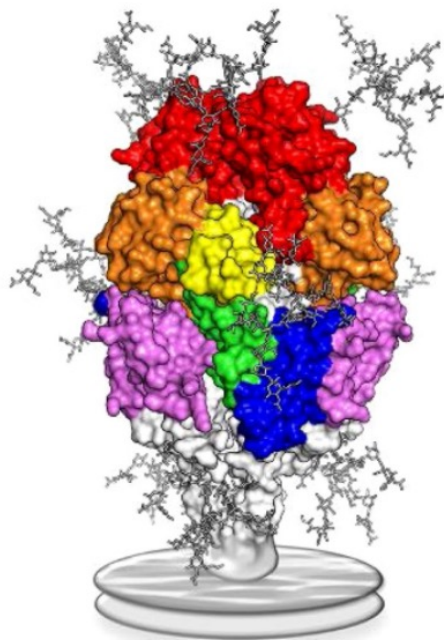


Entrée virale : clé pour la mise en place l'immunoprophylaxie



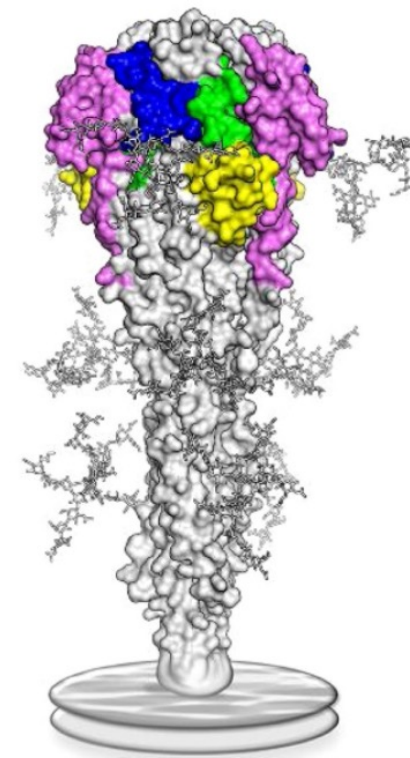
Structure et antigénicité de la conformation Pré-fusion et post-fusion

Conformation **pré-fusion**
métastable



- Site Ø
- Site I
- Site II
- Site III
- Site IV
- Site V

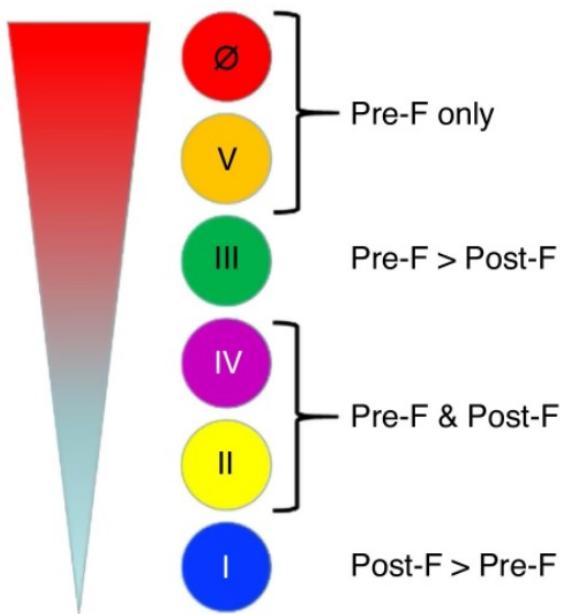
Conformation **post-fusion**
stable



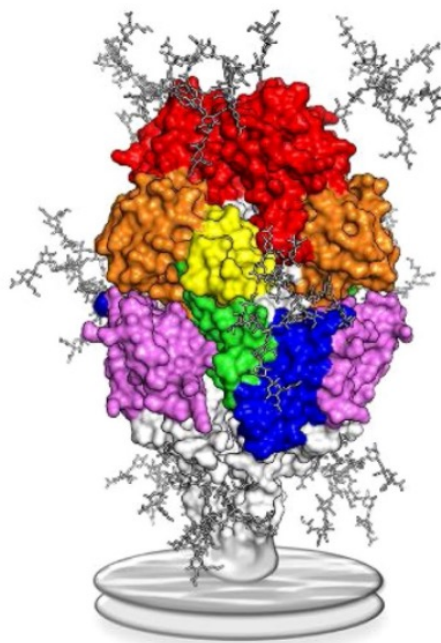
Révolution dans l'approche vaccinale anti-VRS : stabilisation de la conformation préF

Pouvoir neutralisant des Ac dirigés contre les sites Ag

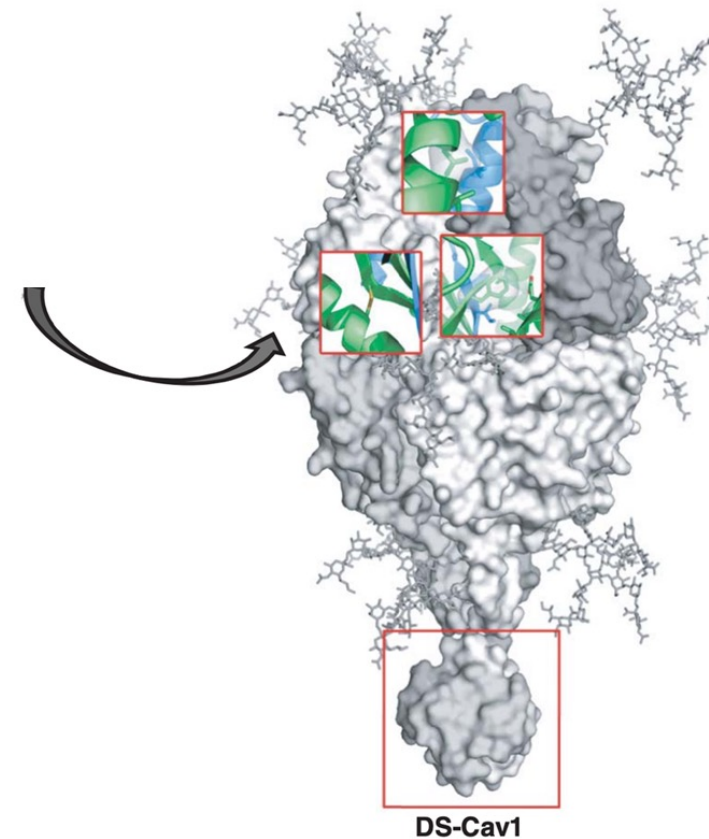
Localisation



Conformation pré-fusion



- Site Ø
- Site I
- Site II
- Site III
- Site IV
- Site V



Stabilisation de la conformation pré-fusion candidat vaccinal +++







EDITORIALS



RSV Illness in the Young and the Old — The Beginning of the End?

Vaccins Pre-F bientôt commercialisés?

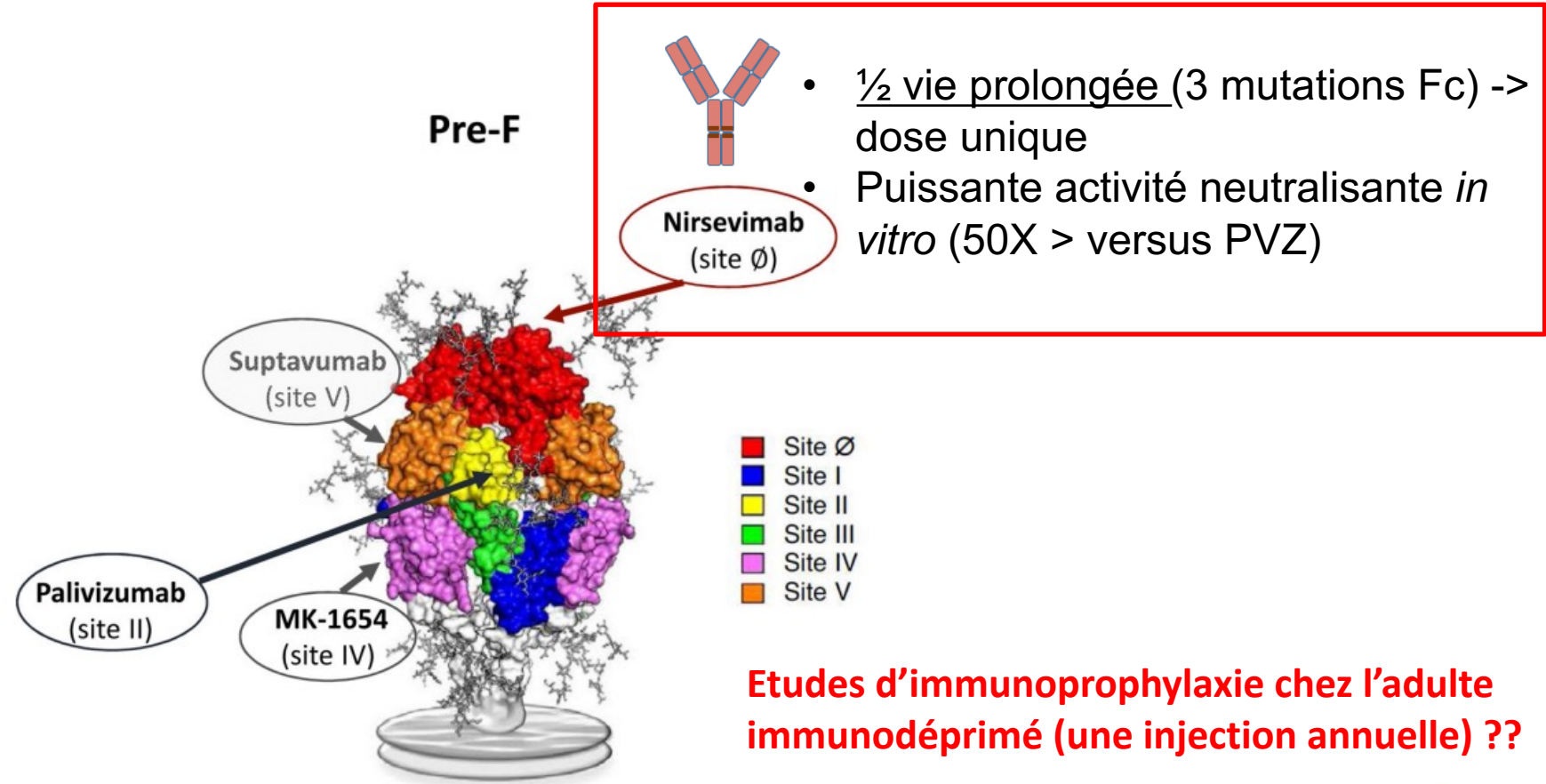


Vaccin	Technologie	Population cible (Phase III)	Efficacité (Phase III)
 RSVpreF3 AREXVY(GSK) FDA/EMA approuvé	RSV A2 Recombinant adjuvant vaccine	Adultes >60 ans (ARESVi-006)	82.6% protection contre LRTD ¹ 94.1% protection contre LRTD sévères ²
 RSVpreF (Pfizer) FDA/EMA approuvé	Bivalent Recombinant vaccine	Adultes >60 ans (RENOIR)	85.7% protection LRTD ³
 RSVpreF (Pfizer)	Bivalent Recombinant vaccine	Femme enceinte (MATISSE)	81,8% protection LRTD sévères dans les 3 premiers mois de vie. Effets secondaires à surveiller
 mRNA-1345 (Moderna)	mRNA	Adultes >60 ans	83,7% protection contre LRTD ⁴

Critères de definition :

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

Immunoprophylaxie passive par Ac monoclonaux visant la protéine F



Conclusion – Révolution de l'immunoprophylaxie anti-RSV

- La glycoprotéine d'enveloppe F (conservée) : conformation « pré-F » comporte les épitopes les plus immunogènes
- Stabilisation de l'antigène F dans sa conformation préF (pont S-S ; « cavity-filling » mutations) -> Approche vaccinale efficace anti- RSV
- Efficacité de plusieurs candidats vaccins. Mais des études complémentaires (durée de protection/ impact des variants) sont à conduire.
- Immunoprophylaxie passive par anticorps monoclonaux : approche nouvelle pour la prophylaxie des patients immunodéprimés ?

