



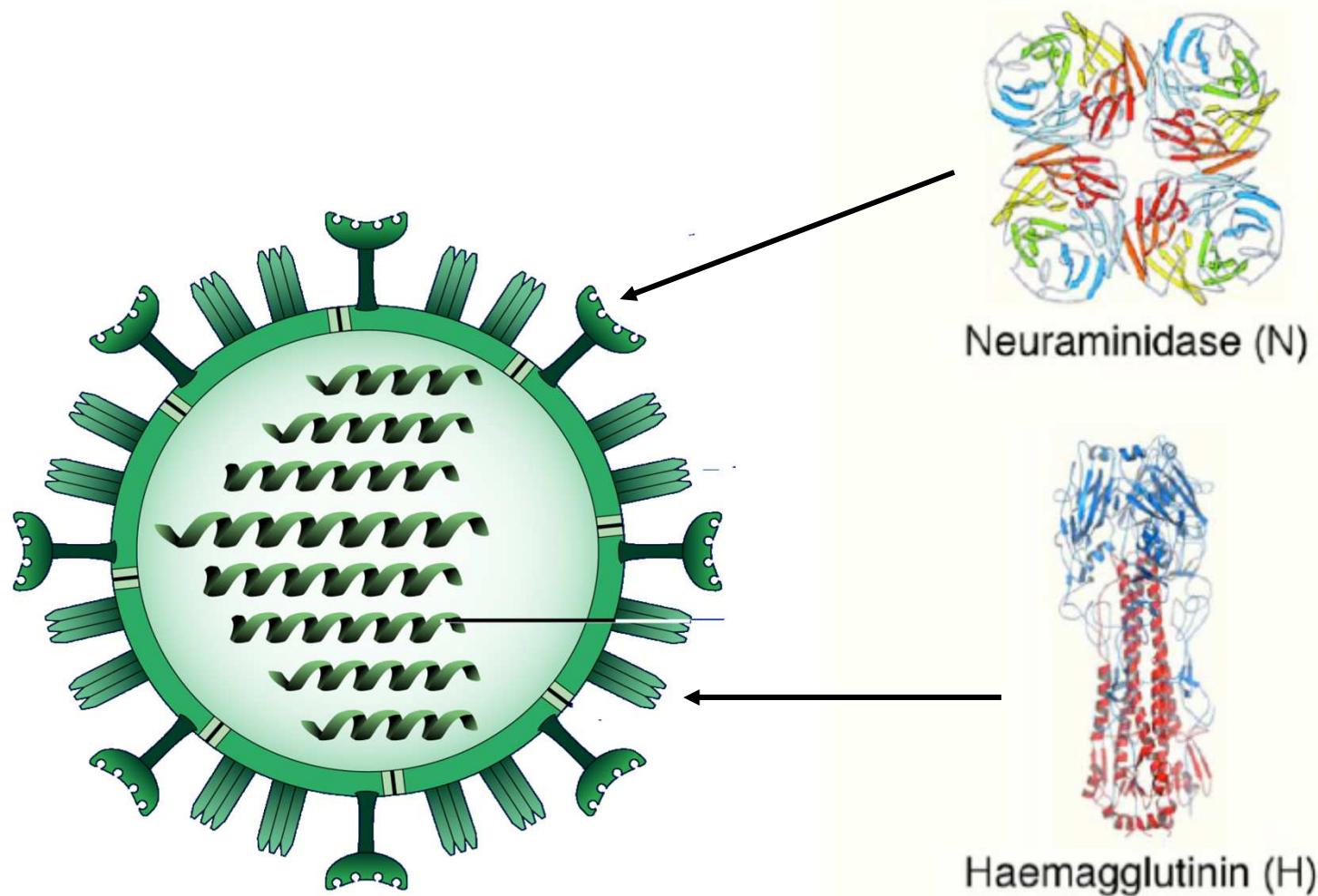
Traitements antiviraux au cours de la grippe : les enseignements de l'épidémie H1N1v (1)

Bruno Lina

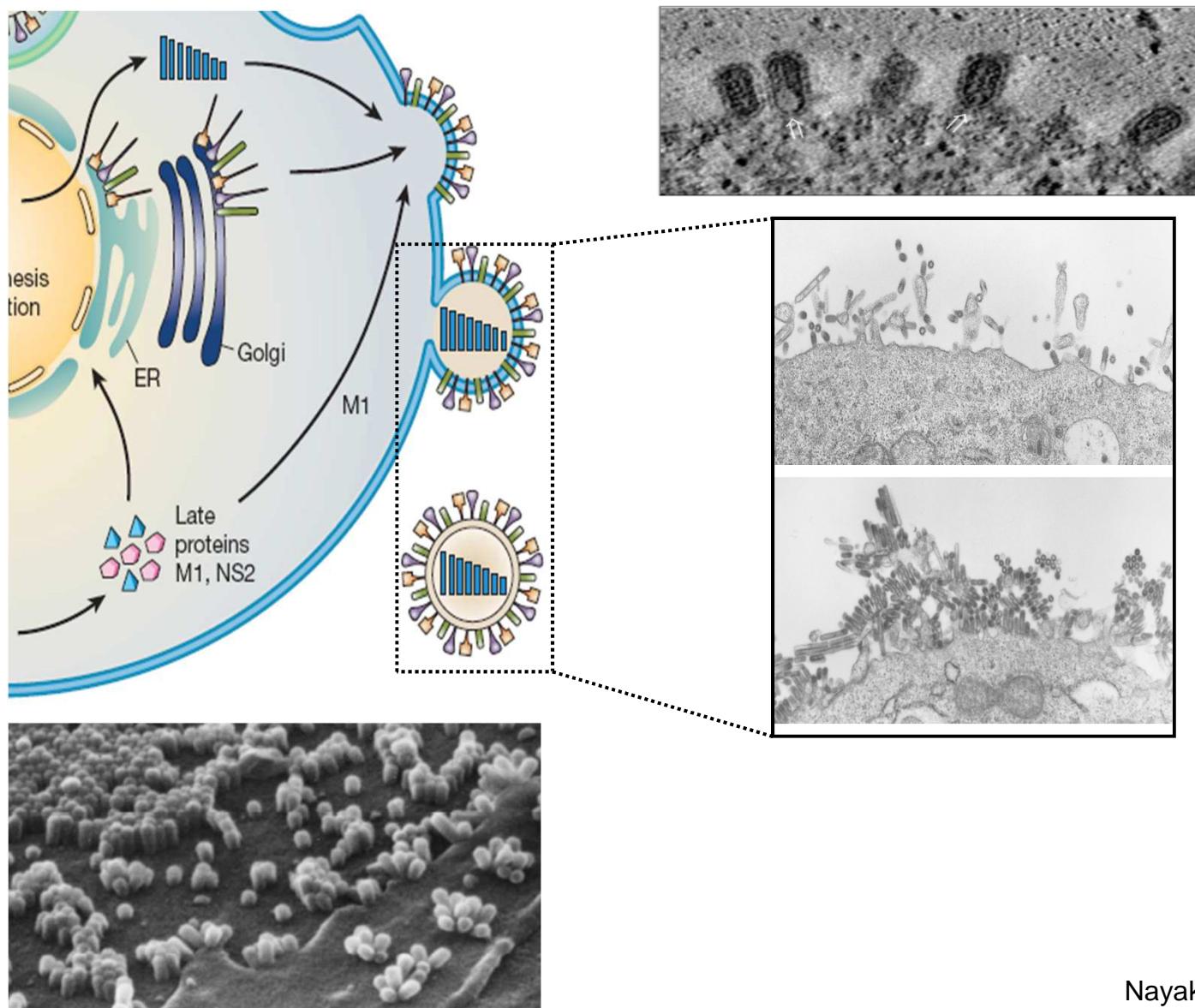
Hospices Civils de Lyon, CNR des virus influenza (Sud), F69677, Bron
Virpath, Université de Lyon, Université Lyon 1, F69372, Lyon

Liens d'intérêts : Roche, membre de ESWI

Représentation schématique d'un virus

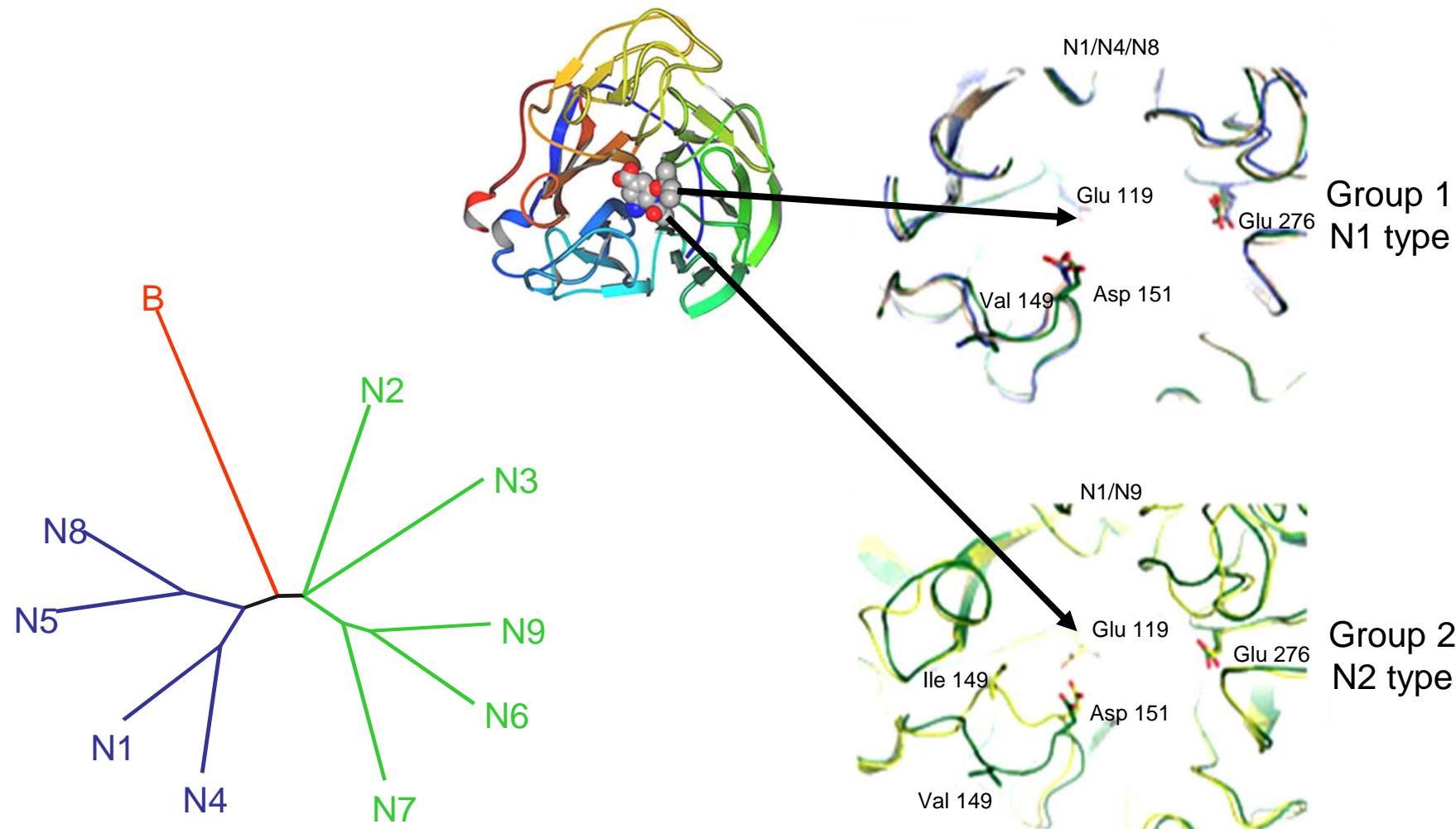


Mécanismes d'action des INA



Nayak et al 2009

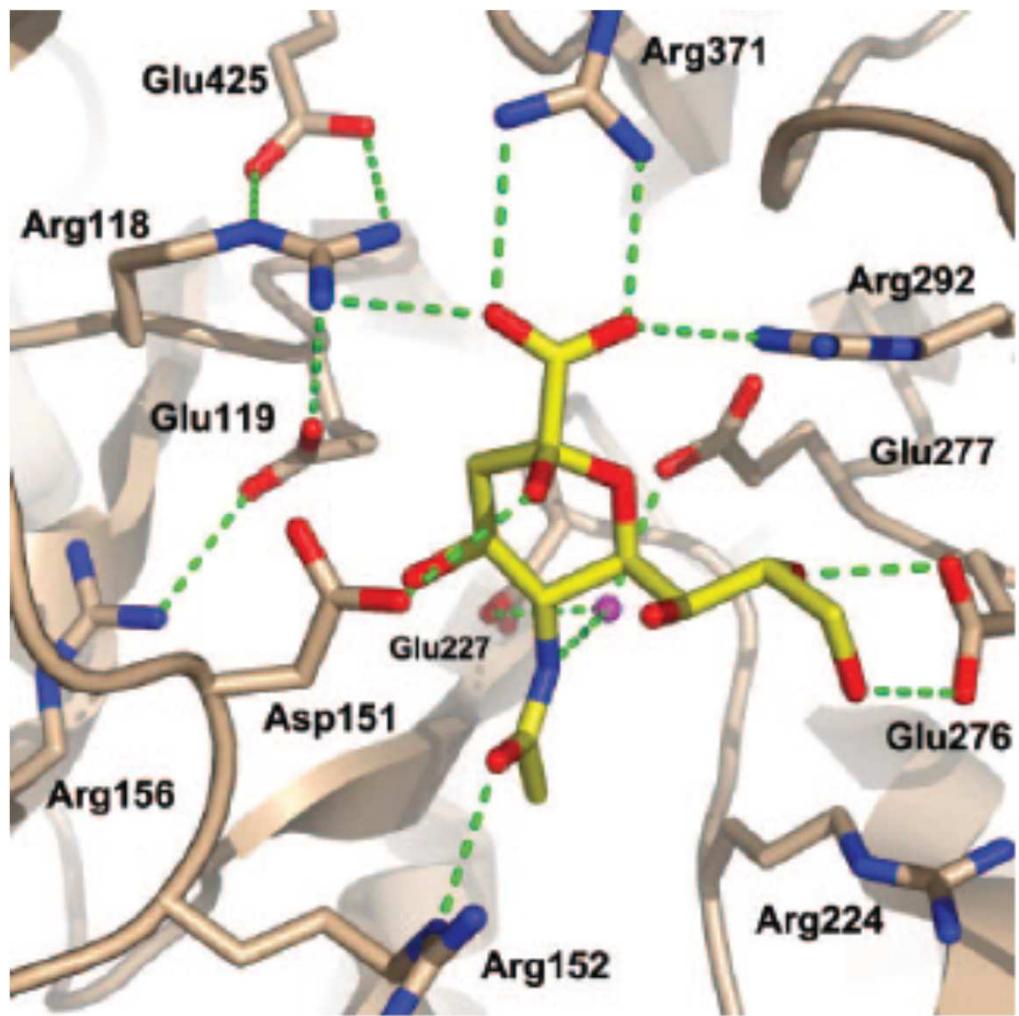
Différence de structure des Na en fonction des sous-types : incidence sur l'efficacité



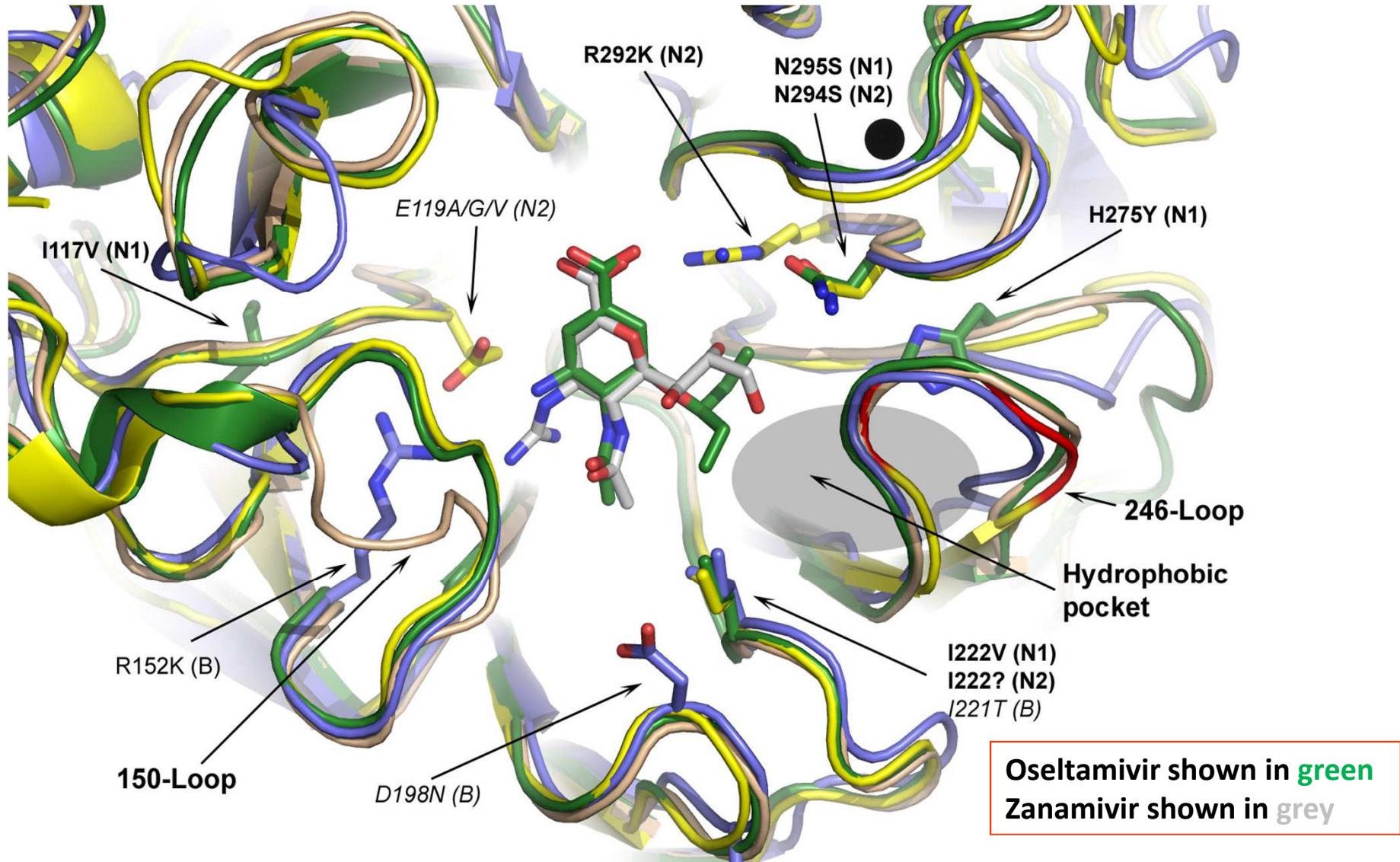
NA = neuraminidase

Russell et al. 2006

Site actif de la neuraminidase (numérotation N2)



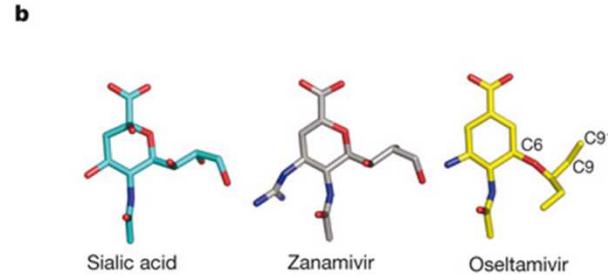
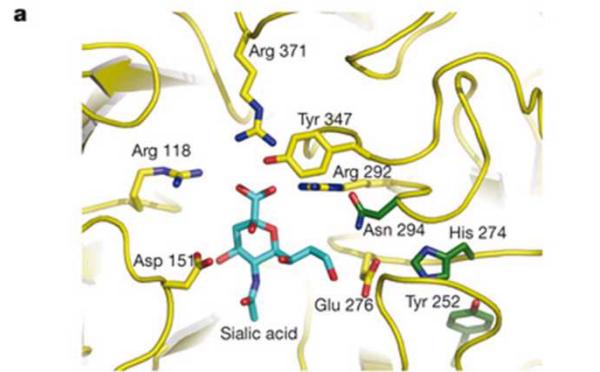
Site catalytique des neuraminidases et interactions avec les INA



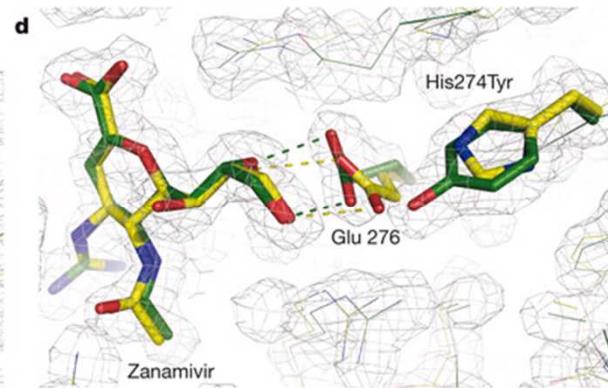
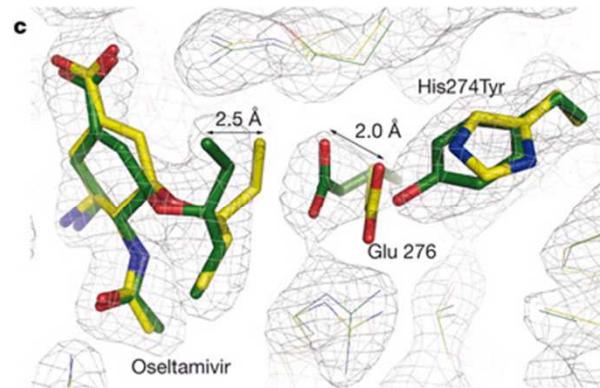
Sites of substitution associated with reduced inhibition
by oseltamivir and/or zanamivir in N1, N2 and Influenza B NAs are shown

Comprendre les mécanismes de résistance

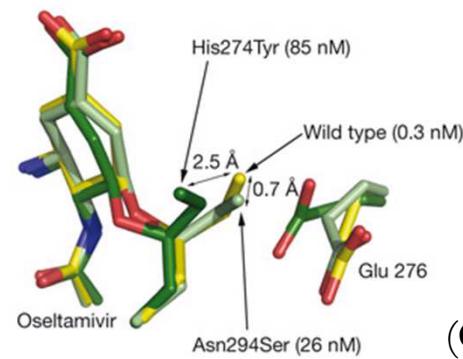
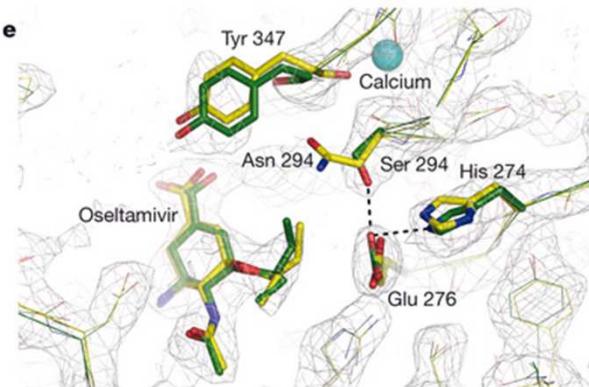
H275Y



Chaine aliphatique

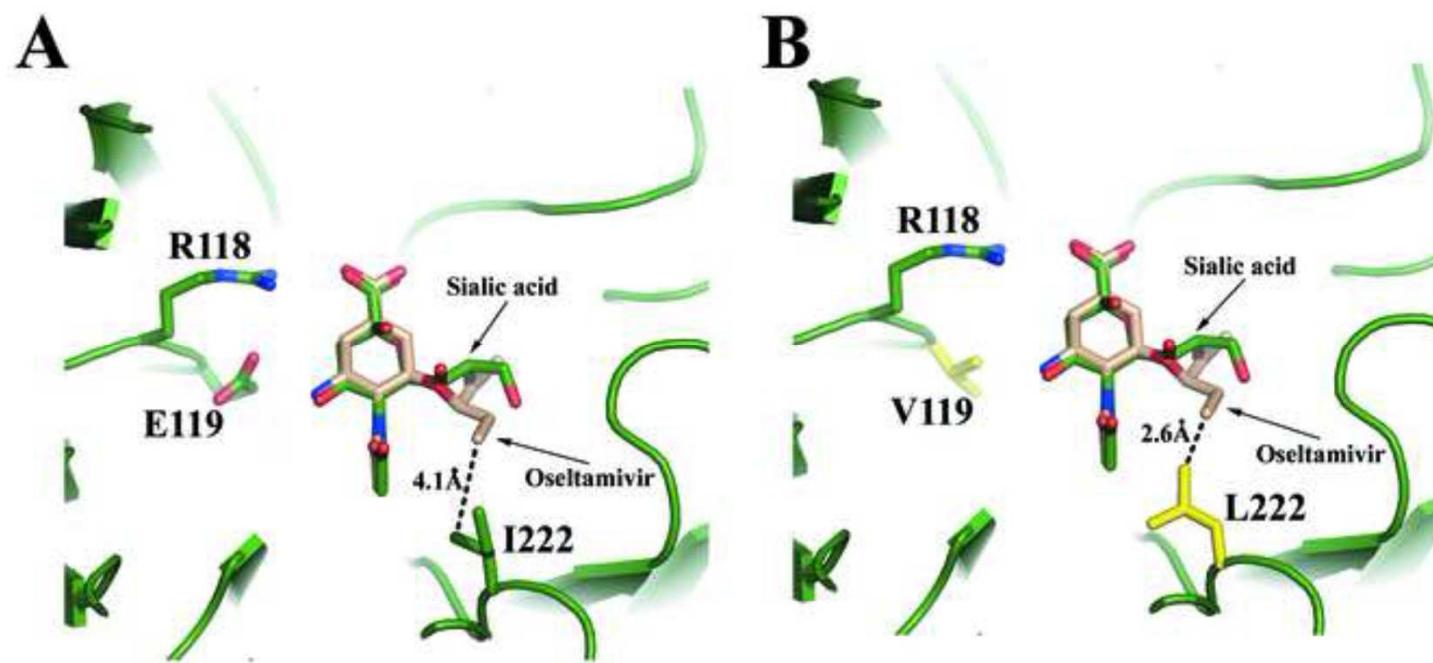


N294S

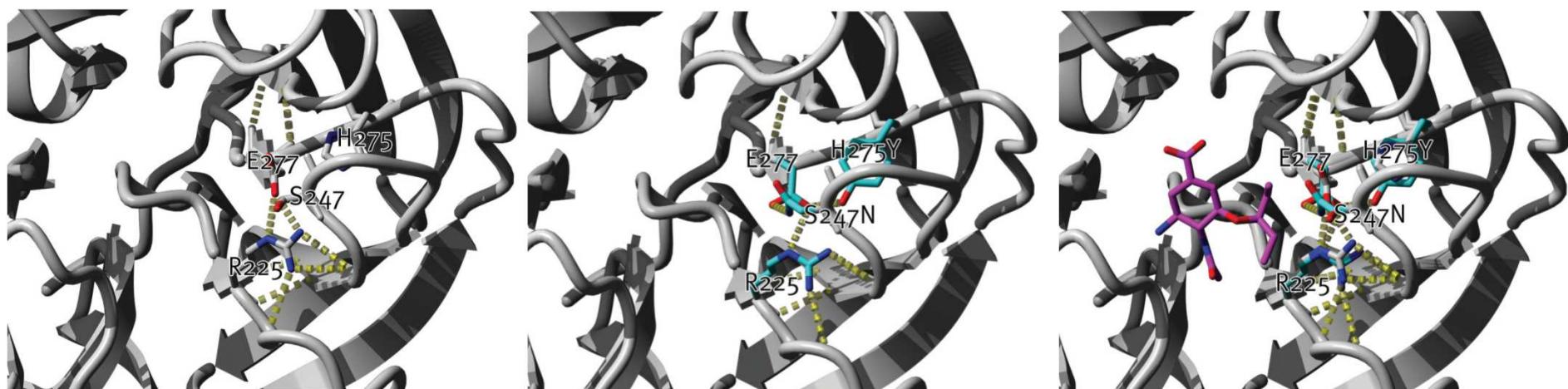


(Collins et al., Nature 2008)

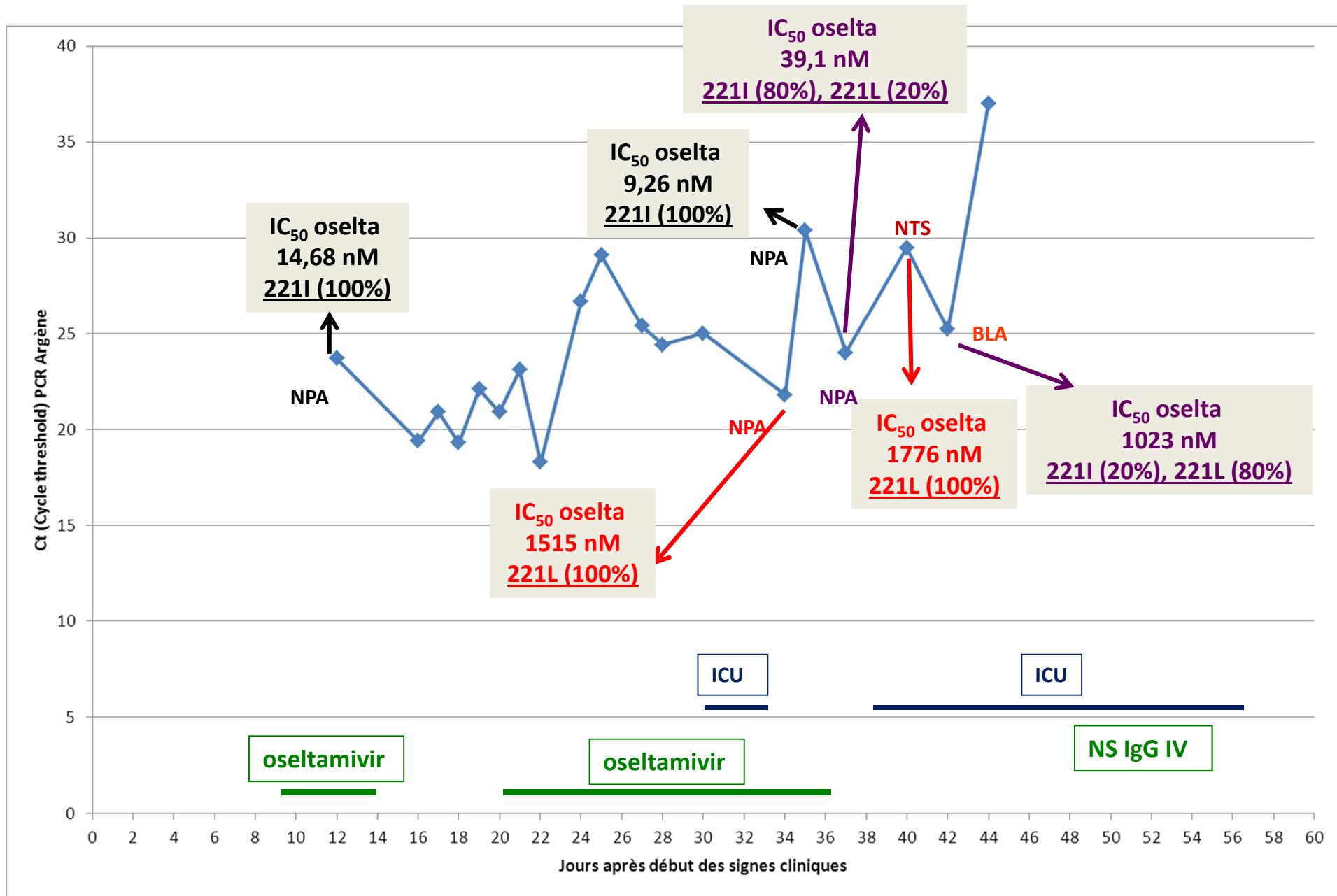
Role possible de mutations additives (E119-I222)



Role possible de la S247N



Probleme de l'émergence de résistance chez les immunodéprimés



Emergence des résistances

DéTECTÉS VIA LES RÉSEAUX DE SURVEILLANCE (ECDC, WHO, ETC)

rare cas de résistance détectés

Identification de foyer (ex Australie)

description de nouveau mécanismes chez les immunodéprimés

DÉTECTÉS AU COURS DES ESSAIS CLINIQUES (IRIS)

Différences entre H1N1v, H3N2 et B

Fréquence accrue chez les enfants traités (10% en cours de trt)

Les résistances apparaissent à J3 ou J6

Pas de notion de transmission

IMPOSE LA RECHERCHE D'ALTERNATIVES THÉRAPEUTIQUES

Combinaisons d'INA (?) et des molécules existantes (A+INA+Riba)

Tests de nouvelles classes de molécules

L'usage des antiviraux conduit à une réduction des charges virales (données H1N1v)

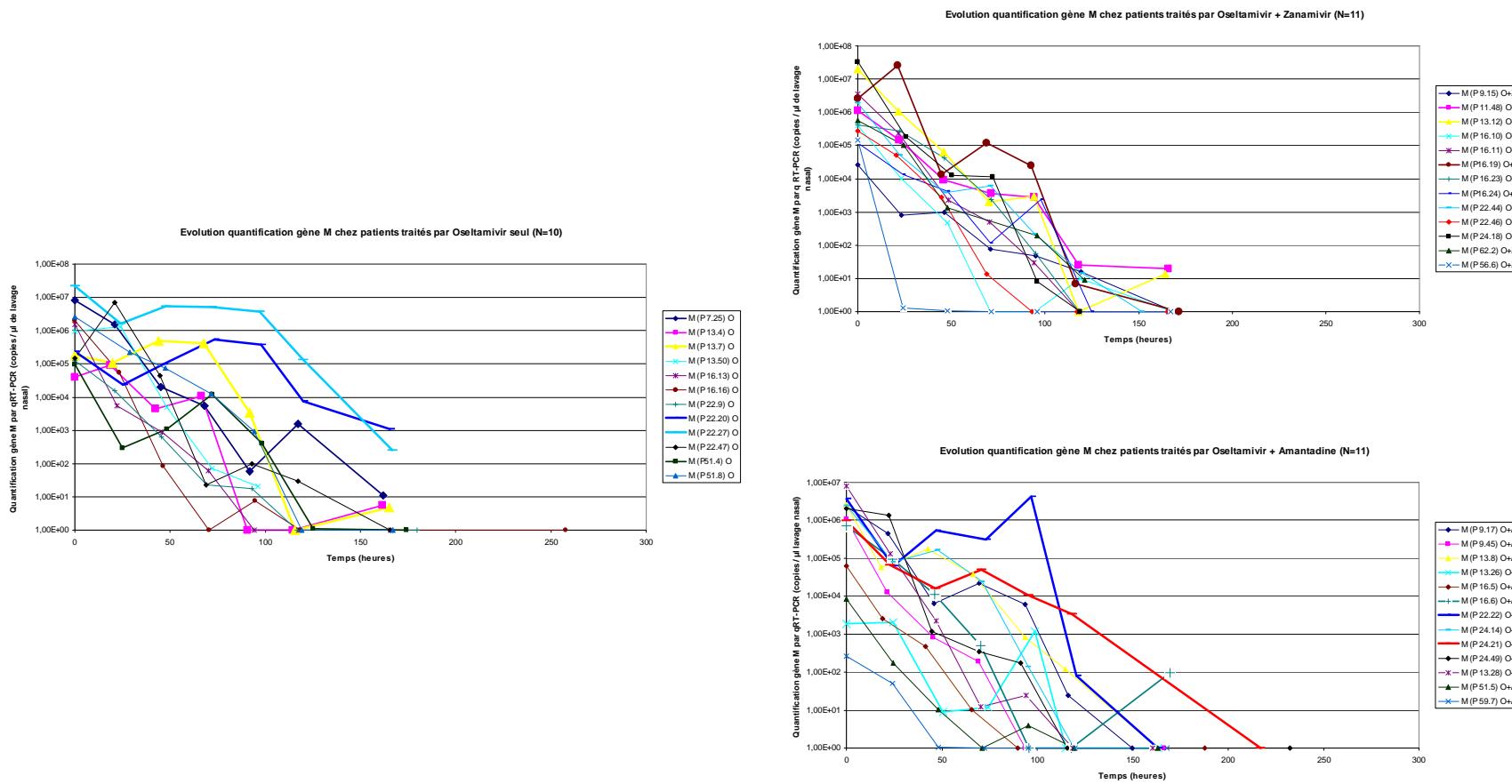


Table 2. Virological and clinical response according to treatment arms in the 541 enrolled patients, between day 0 and day 2 (ITT analysis).

Type of Response	Virological and Clinical Response Variables	Combined Oseltamivir and Zanamivir	Oseltamivir Plus Placebo		Zanamivir Plus Placebo		P-Value	Difference [95% CI]	P-Value	Difference [95% CI]	Difference [95% CI] ^a
			O+Z versus O	O+Z versus Z							
	<i>n</i> patients	192	176			173					
Virological											
	Primary virological endpoint										
	Day 2 influenza RT-PCR<200 cgeq/μl (% patients)	52.6%	62.5%	0.055	-9.9% [-19.9 to 0.2]	40.5%	0.020	+12.1% [2.02–22.3]	+22.0% [12.1–32.0]		
Clinical											
	Time to resolution of illness in days (median, IQR)	3.5 [2.5–14]	3.0 [2–7]	0.015	+0.5 [0.0–1.5]	4.0 [2.5–14]	0.78	-0.5 [-1.0 to 0.5]	-1.0 [-1.5 to -0.5]		
	<i>n</i> (%) of patients with alleviation of symptoms at end of treatment	111 (57.8%)	122 (69.3%)	0.023	-11.5% [-21.3 to -1.7]	100 (57.8%)	1.00	+0.0% [-10.1 to 10.1]	+11.5% [1.7–21.3]		
	Symptoms score at end of treatment (median, IQR)	3 [2–5]	2 [1–4]	0.0006	+1.0 [0.0–1.0]	3 [1–6]	0.79	+0.0 [-1.0 to 0.0]	-1.0 [-2.0 to -1.0]		
	<i>n</i> (%) of patients with clinical event during treatment	26 (13.5%)	15 (8.5%)	0.14	+5.0% [-1.3 to 11.4]	23 (13.3%)	1.00	+0.3% [-6.7 to 7.2]	-4.8% [-11.2 to 1.6]		
	Initiation of antibiotics	17 (8.9%)	10 (5.7%)		—	13 (7.5%)		—	—		
	Pneumonia	2 (1.0%)	1 (0.6%)		—	0 (0.0%)		—	—		
	Other	21 (10.9%)	14 (8.0%)		—	22 (12.7%)		—	—		

^aExploratory analysis.

doi:10.1371/journal.pmed.1000362.t002

Duval X, van der Werf S, Blanchon T, Mosnier A, et al. (2010) Efficacy of Oseltamivir-Zanamivir Combination Compared to Each Monotherapy for Seasonal Influenza: A Randomized Placebo-Controlled Trial. PLoS Med 7(11): e1000362. doi:10.1371/journal.pmed.1000362

<http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1000362>

Antiviral development (2007)

<u>Class</u>	<u>Pre Clinical</u>	<u>Phase 1</u>	<u>Phase 2</u>	<u>Phase 3</u>	<u>Market Approved</u>
Adamantanes					Generic Rimantadine Generic Amantadine
NA Inhibitors		BioCryst Peramivir		Daiichi Lanamivir	GSK Zanamivir Roche Oseltamivir
Other Viral Targets		Toyama Favipiravir (T-705) Pol Inhibitor			
Host Targets					Other Inhaled IV Oral

Courtesy of MW Wathen, US Dept of HHS

Antiviral development (2012)

Class	Pre Clinical	Phase 1	Phase 2	Phase 3	Market Approved
Adamantanes					
NA Inhibitors	TalMed Tamiphosphor	Biota Lanamivir	Roche Oseltamivir GSK Zanamivir BioCryst Peramivir	GSK Zanamivir Lani Roche Oseltamivir Shionogi Peramivir	Generic Rimantadine Generic Amantadine
Other Viral Targets	CellTrion CT120 Fusion Inhibitor Mab Valleant Ribavirin Pol Inhibitor Visterra Entry Inhibitor	Sea Lane A06 Fusion Inhibitor HA Mab Alnylam RNAi Quantum Matrix inhibitor	Crucell CR6261/8020 HA Mab Autoimmune Technologies Fluirivitide-3 Peptide Entry Inhibitor AviBioPharma AVI-7100 PMO Anti-sense Theracclone Mab-m2e Vertex VX-787	Adamas TCAD Combo Toyama Favipiravir (T-705) Pol Inhibitor	
Host Targets	Kineta RIG-1 Agonist Pulmotect NTHi Unither Virology Iminosugars	Discovery Labs Surfaxin Immune-Regen Neurokinin-1 Gemmus GP1002 GCPR Agonist Eisai Eritoran TLR4 Antagonist	Pulmatrix PUR003 iCALM Functional Genetics Mab host protein Clarassance CC10 Protein Immuno-modulator Archaeon salicylic acid Nf- κ B Inhibitor	NexBio Fludase Sialidase Romark Nitazoxanide Immuno-modulator	Other Inhaled IV Oral

Courtesy of MW Wathen, US Dept of HHS

Remerciements

Rupert Russell

University of St Andrews

- **HCL, NIC, Lyon**

- V Escuret,
- JS Casalegno
- G Burfin
- R Fanget
- M Valette



- **Virpath, Université de Lyon**

- C Picard
- M Ottmann
- M Sabatier
- O Ferraris



- **Virology Division, MRC, NIMR, Mill Hill, London**

- P Collins,
- S Vachieri
- JJ Skehel
- S Gamblin



- **WHOCC, NIMR, Mill Hill, London**

- N Cattle,
- J McCauley
- R Daniels

