Traitement antiviral au cours de la grippe : les enseignements de l'épidémie H1N1v (1)

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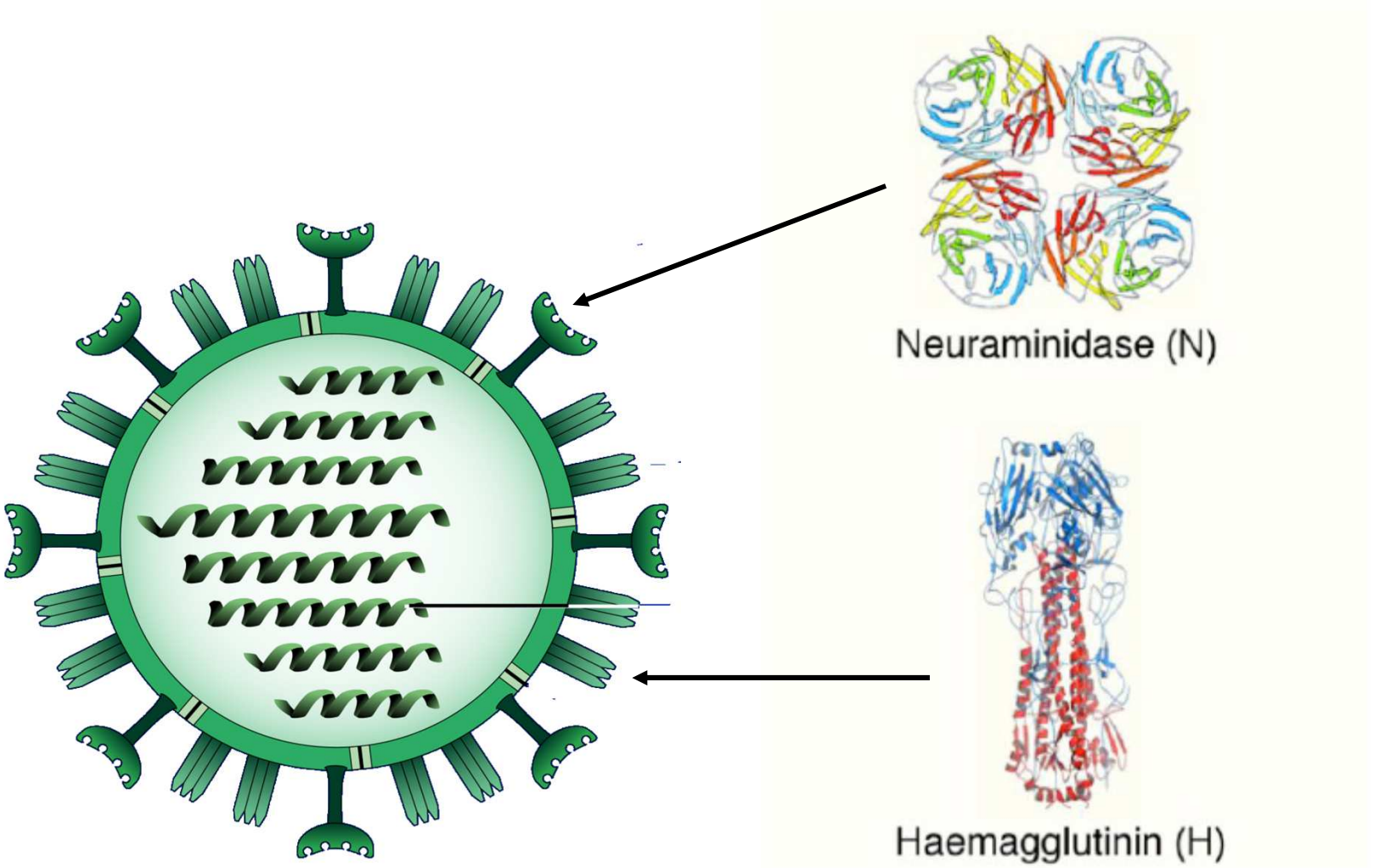
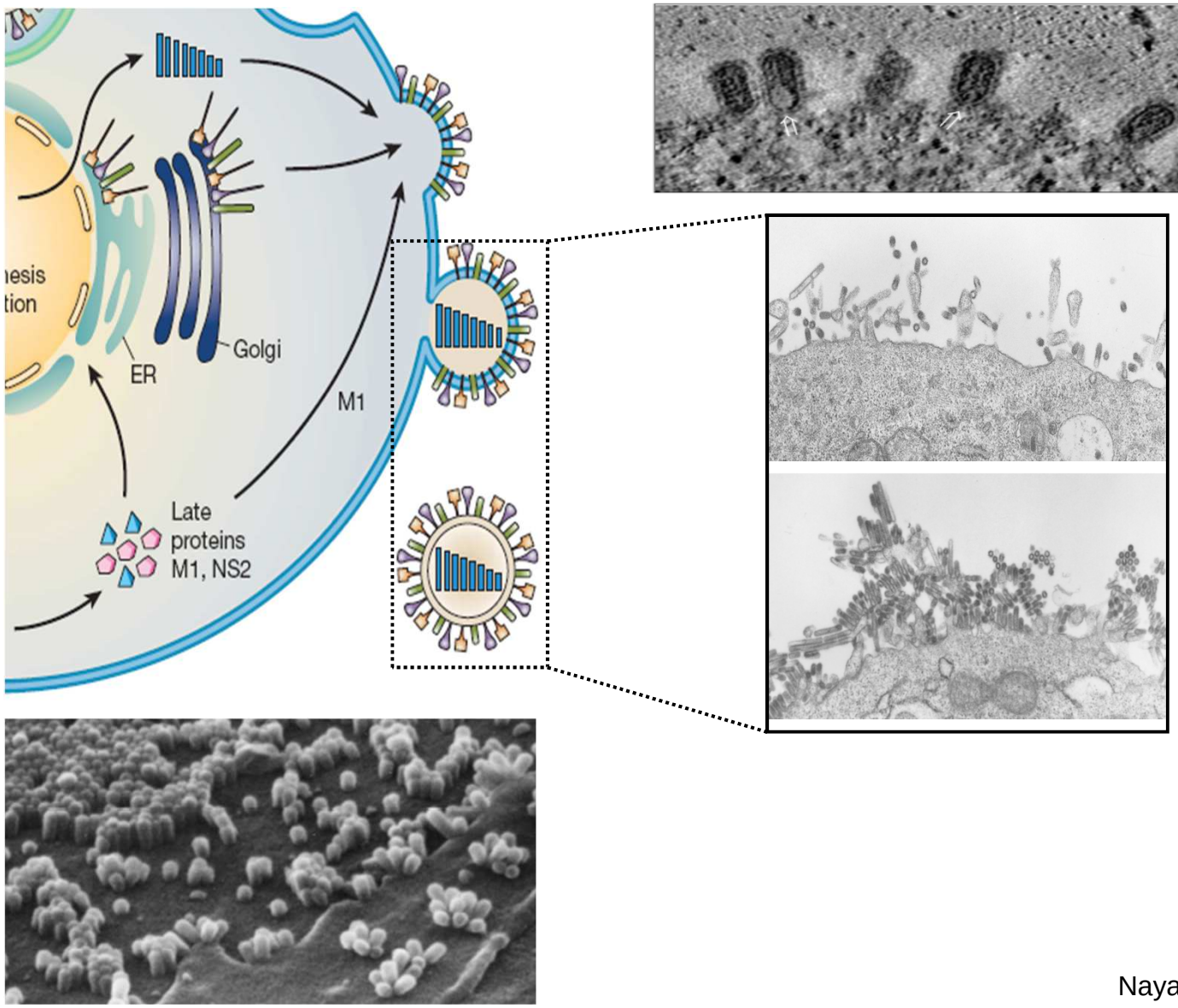
Liens d'intérêts : Roche, membre de ESWI

Représentation schématique d'un virus

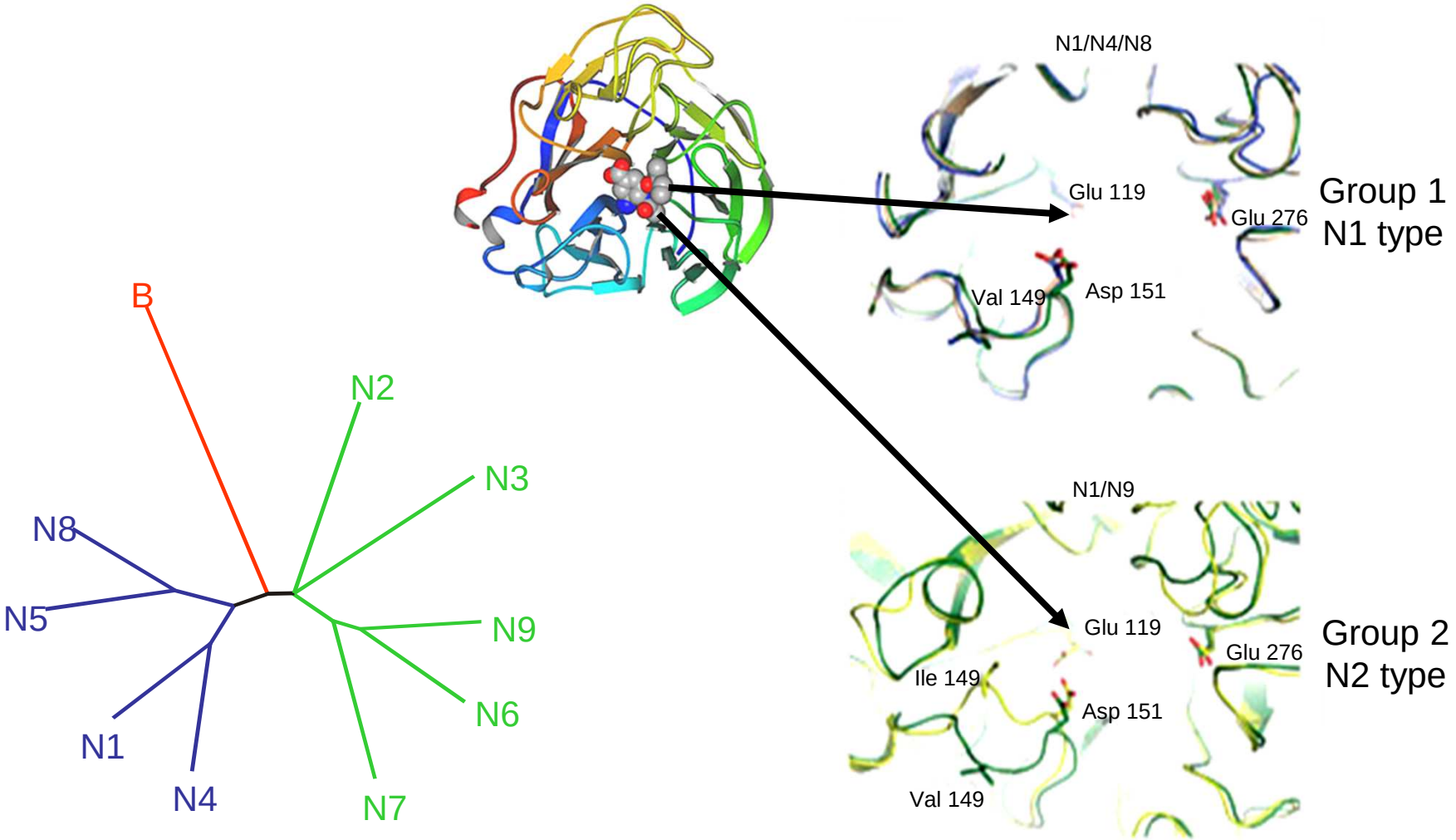


Mécanismes d’action des INA



Nayak et al 2009

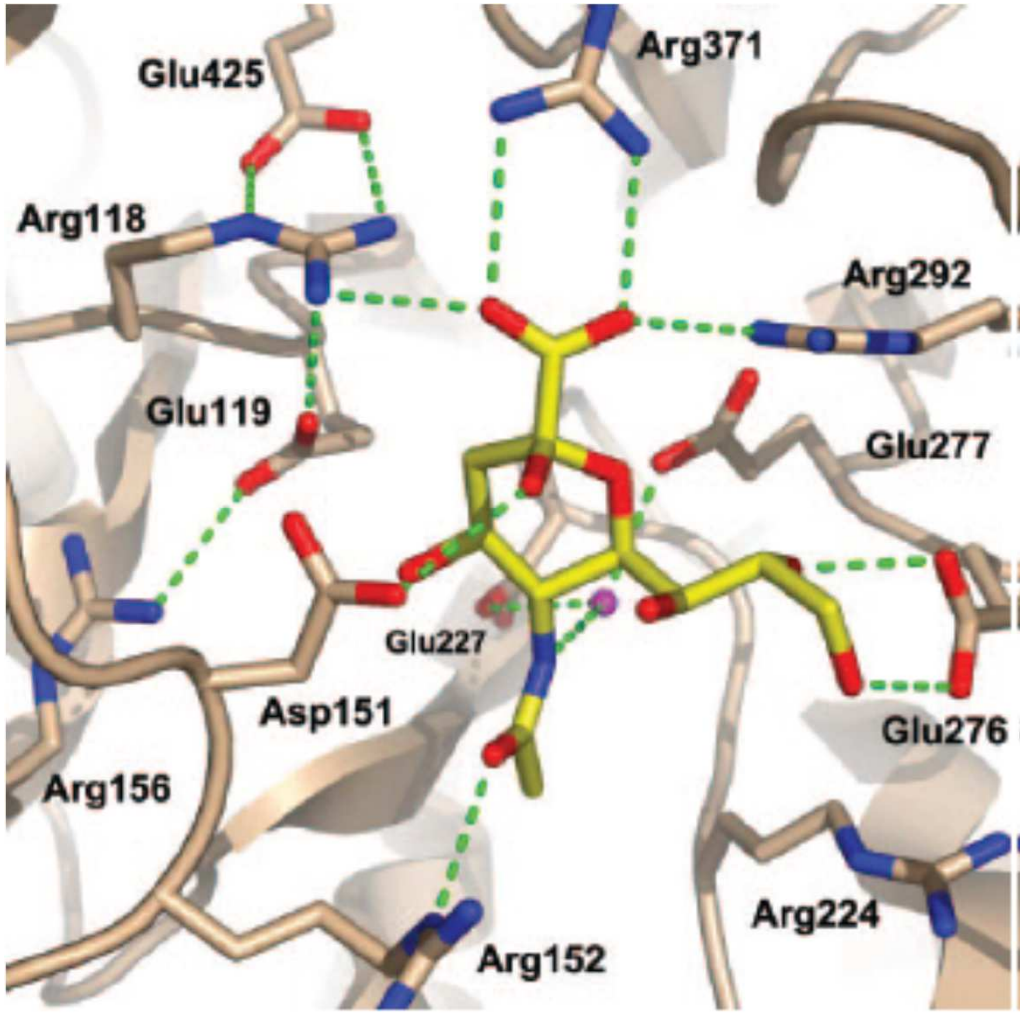
Différence de structure des Na en fonction des sous-types : incidence sur l'éfficacité



NA = neuraminidase

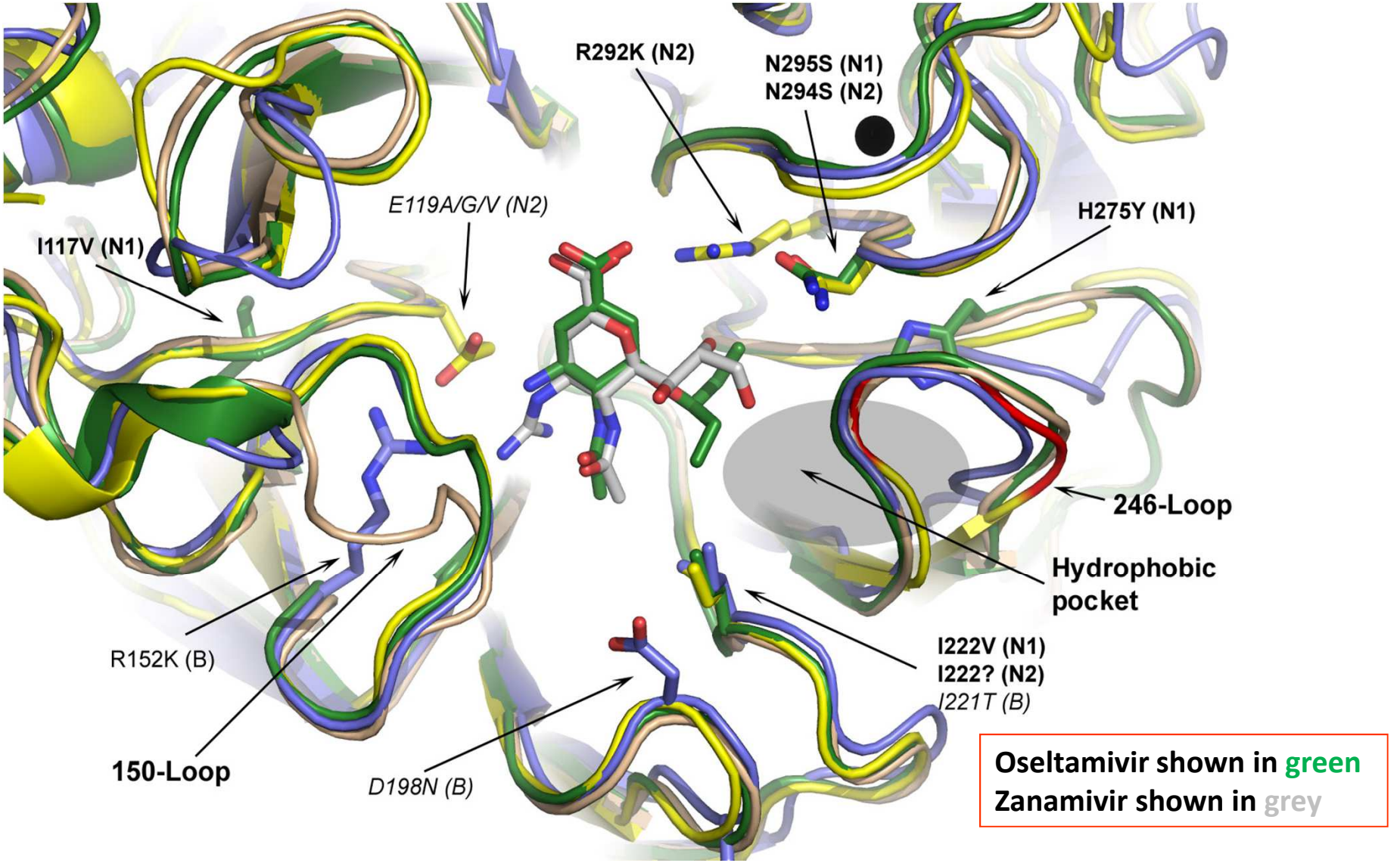
Russell et al. 2006

Site actif de la neuraminidase (numérotation N2)



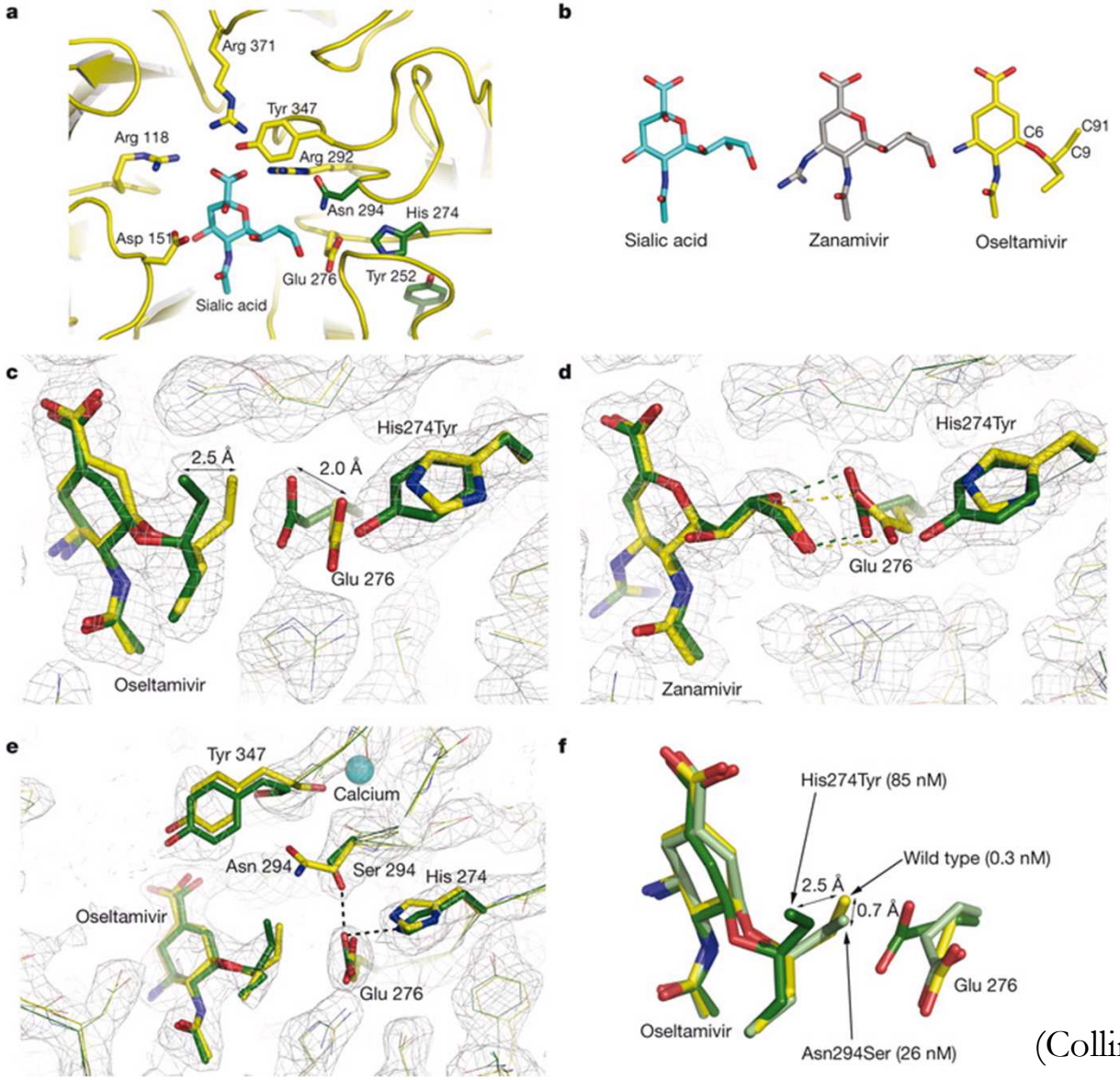
Yen et al. J Virol 2006

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



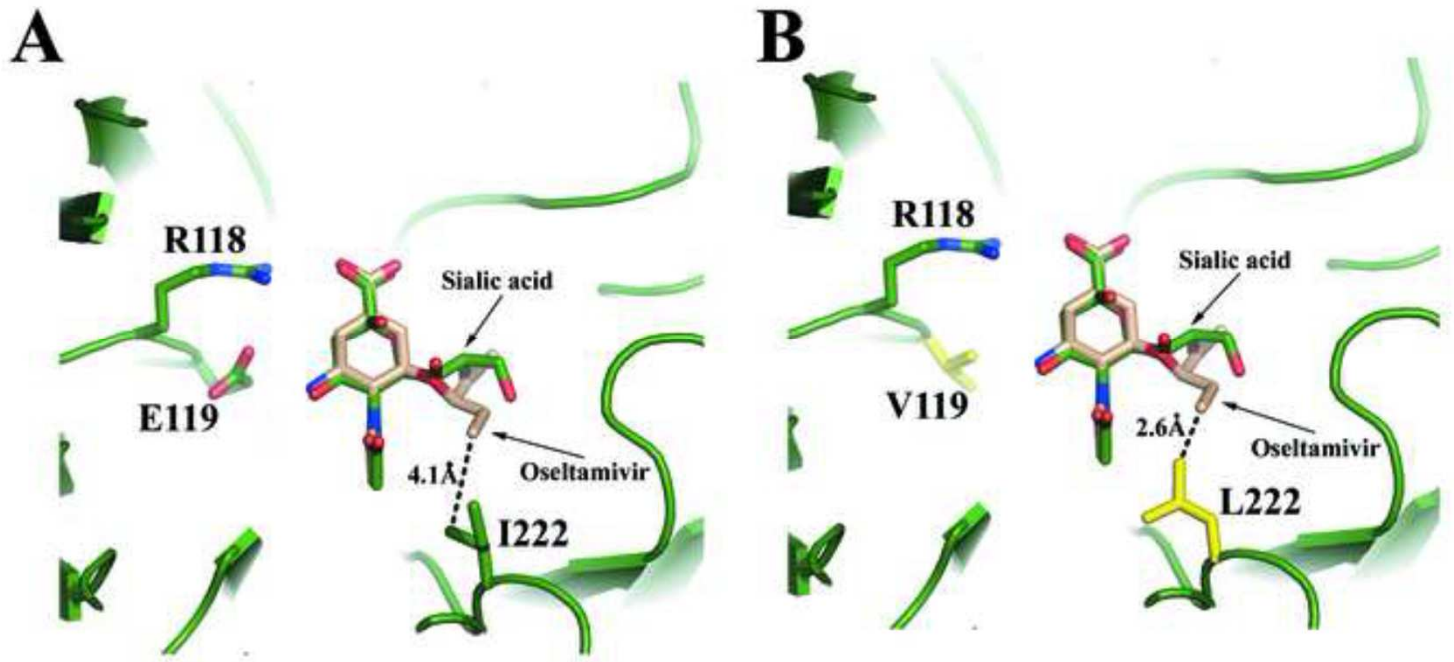
Chaine aliphatique

H275Y

N294S

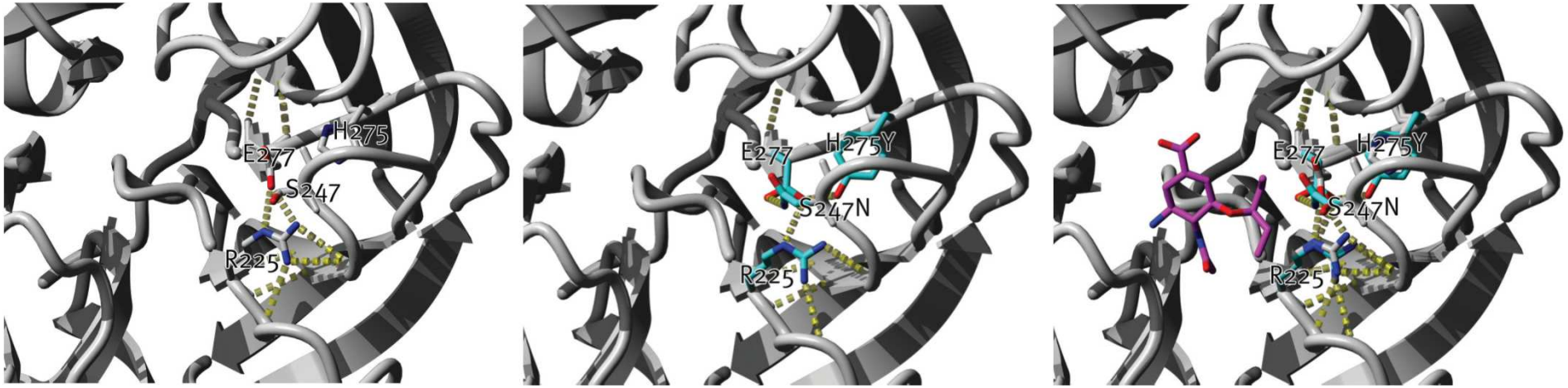
(Collins et al., Nature 2008)

Role possible de mutations additives (E119-I222)



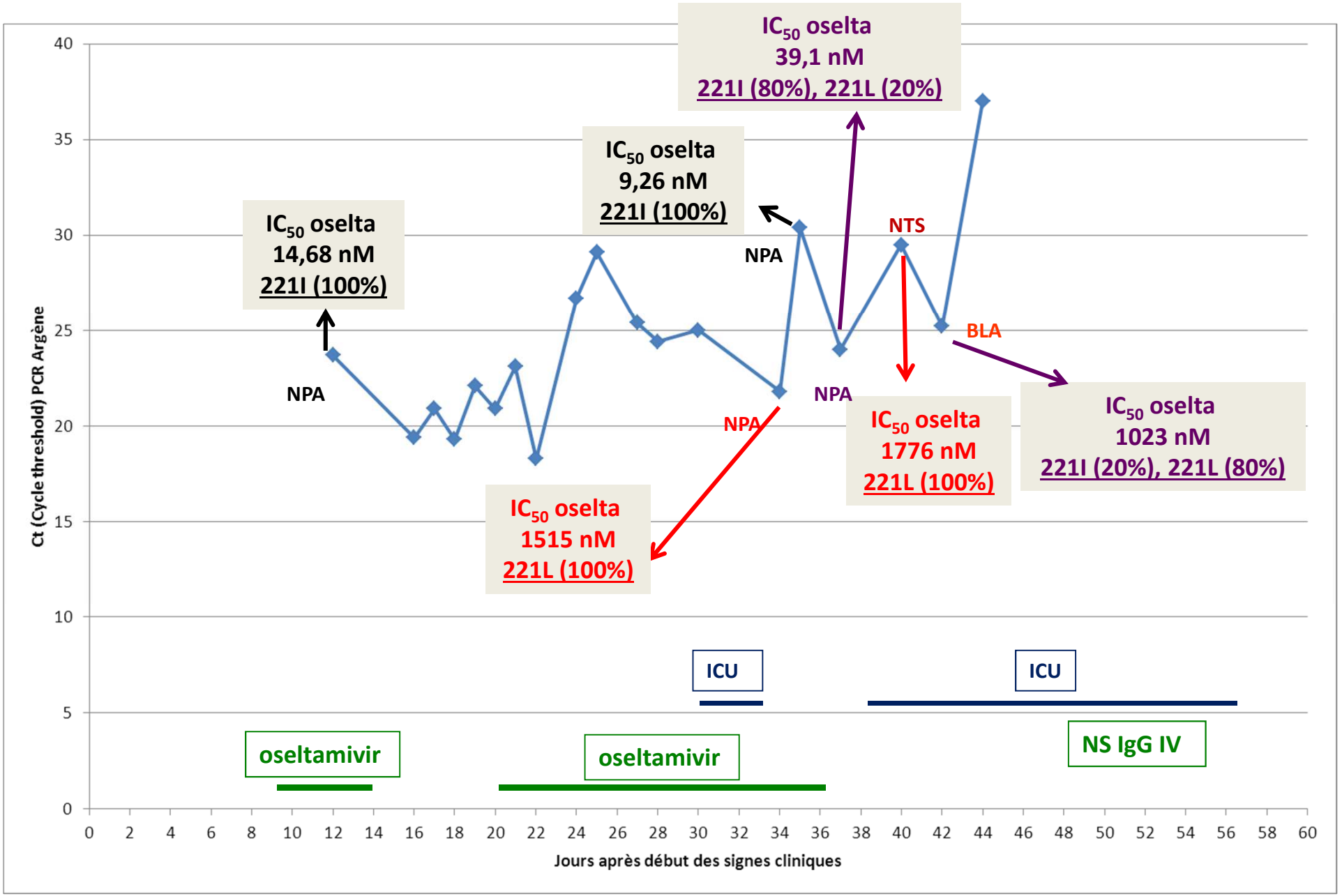
Richard et al, PLoS One 2012

Role possible de la S247N



AC Hurt et al, Eurosurveill, 2011

Probleme de l'émergence de resistance 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

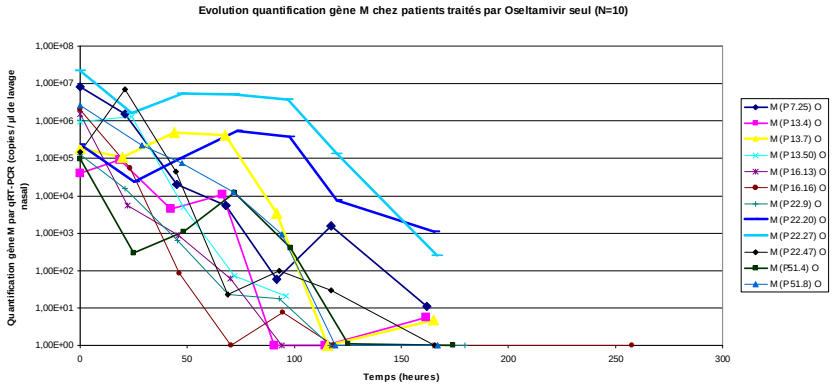
Détectés au cours des essais cliniques (IRIS)

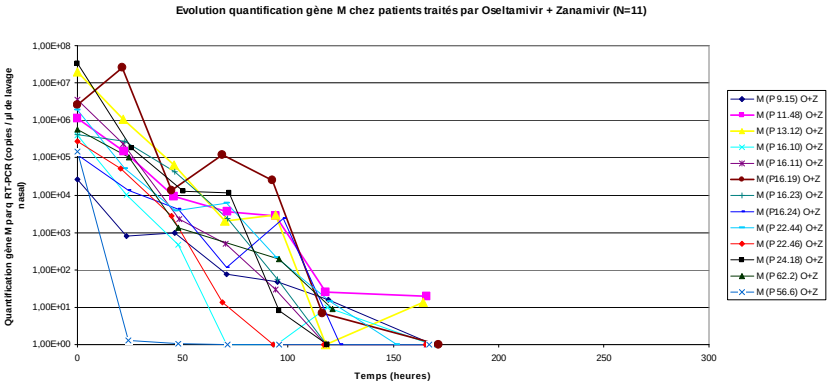
Différences entre H1N1v, H3N2 et B
Fréquence accrue chez les enfants traités (10% en cours de trt)
Les résistances apparaissent a J3 ou J6
Pas de notion de transmission

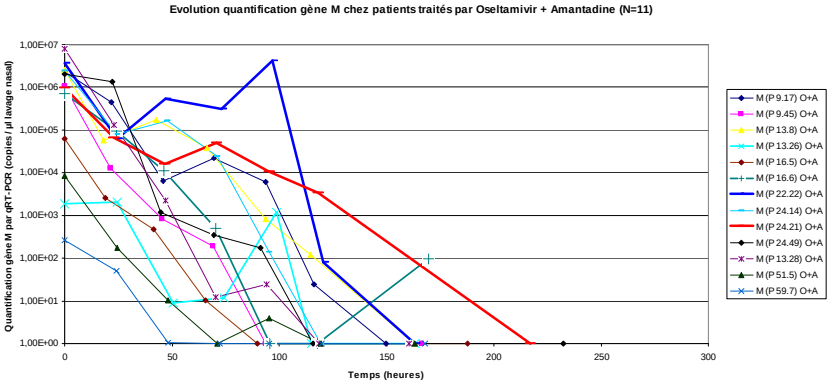
Impose la recherche d'alternatives thérapeutiques

Combinaisons d'INA (?) et des molécules existantes (A+INA+Riba)
Tests de nouvelles classes de molécules

L’usage des antiviraux conduit a une réduction des charges virales (données H1N1v)







Escuret et al, Antivir Res, 2012

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

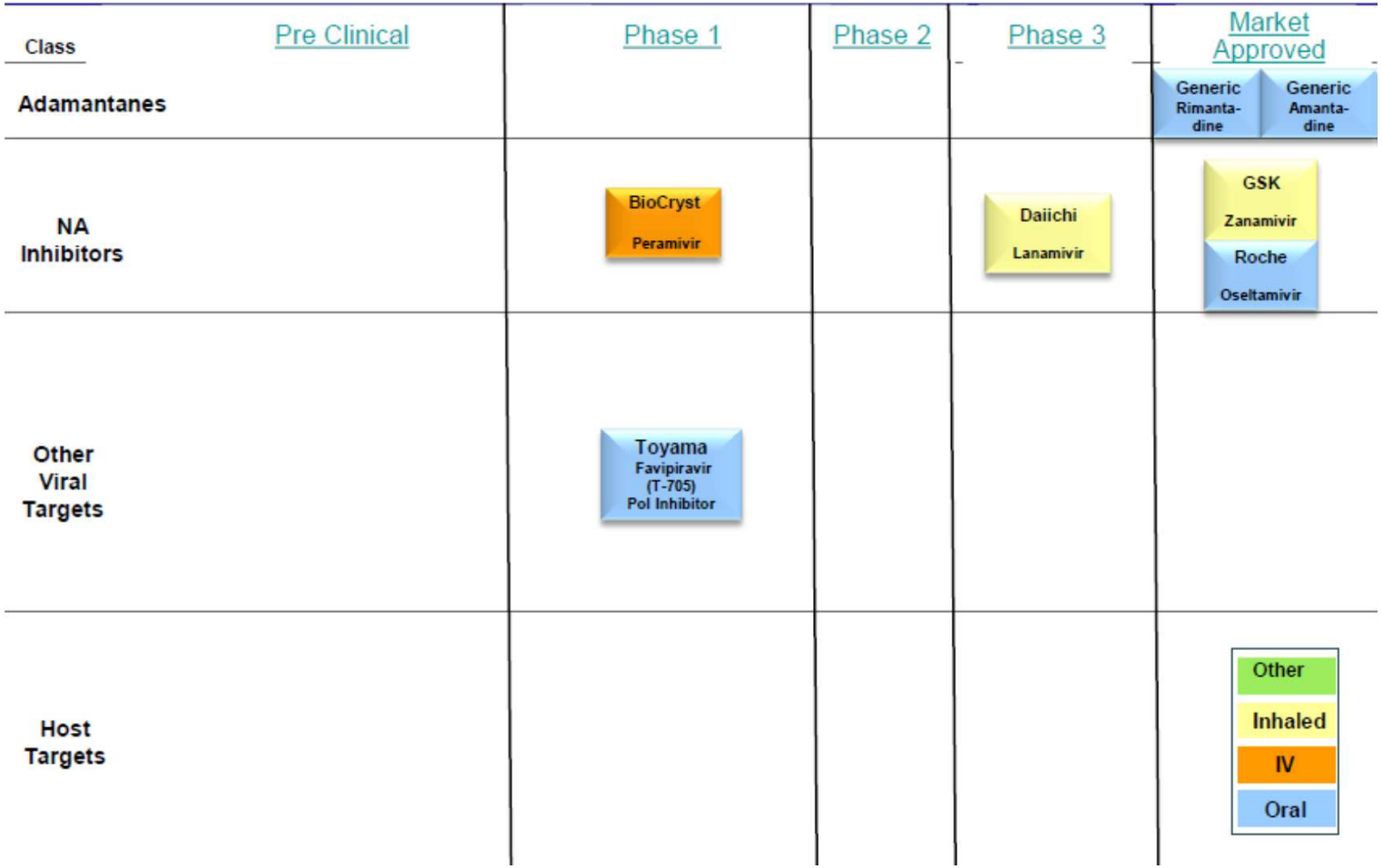
Type of Response	Virological and Clinical Response Variables	Combined Oseltamivir and Zanamivir	Oseltamivir Plus Placebo	O+Z versus O		Zanamivir Plus Placebo	O+Z versus Z		O versus Z
				p-Value	Difference [95% CI]		*p*-Value	Difference [95% CI]	Difference [95% CI][a]
	***n* patients**	**192**	**176**			**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]
	n (%) 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]
	n (%) 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%)		—	—

[a]Exploratory analysis.

doi:10.1371/journal.pmed.1000362.t002

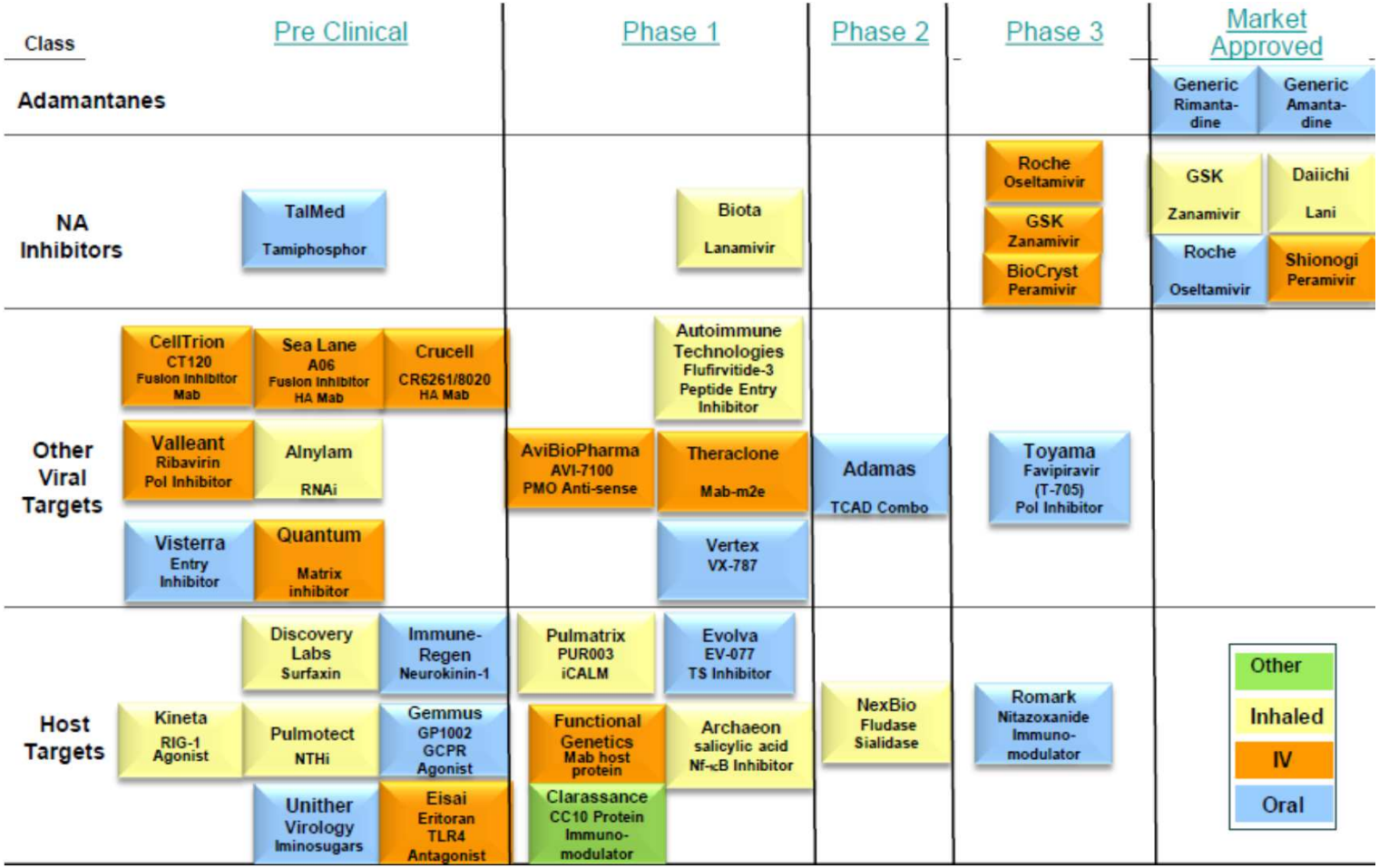
Duval X, van der Werf S, Blanchon T, Mosnier A, et al. (2010) Efficacy of Oseltamivir-Zanamivir Combination Compared to Each Monotherapy for Seasonal Influenza: A Randomized Placebo-Controlled Trial. PLoS Med 7(11): e1000362. doi:10.1371/journal.pmed.1000362
http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1000362

Antiviral development (2007)



Courtesy of MW Wathen, US Dept of HHS

Antiviral development (2012)



Courtesy of MW Wathen, US Dept of HHS

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