« Best of » en Infectiologie

Actualité bibliographique 2006 – Poumons

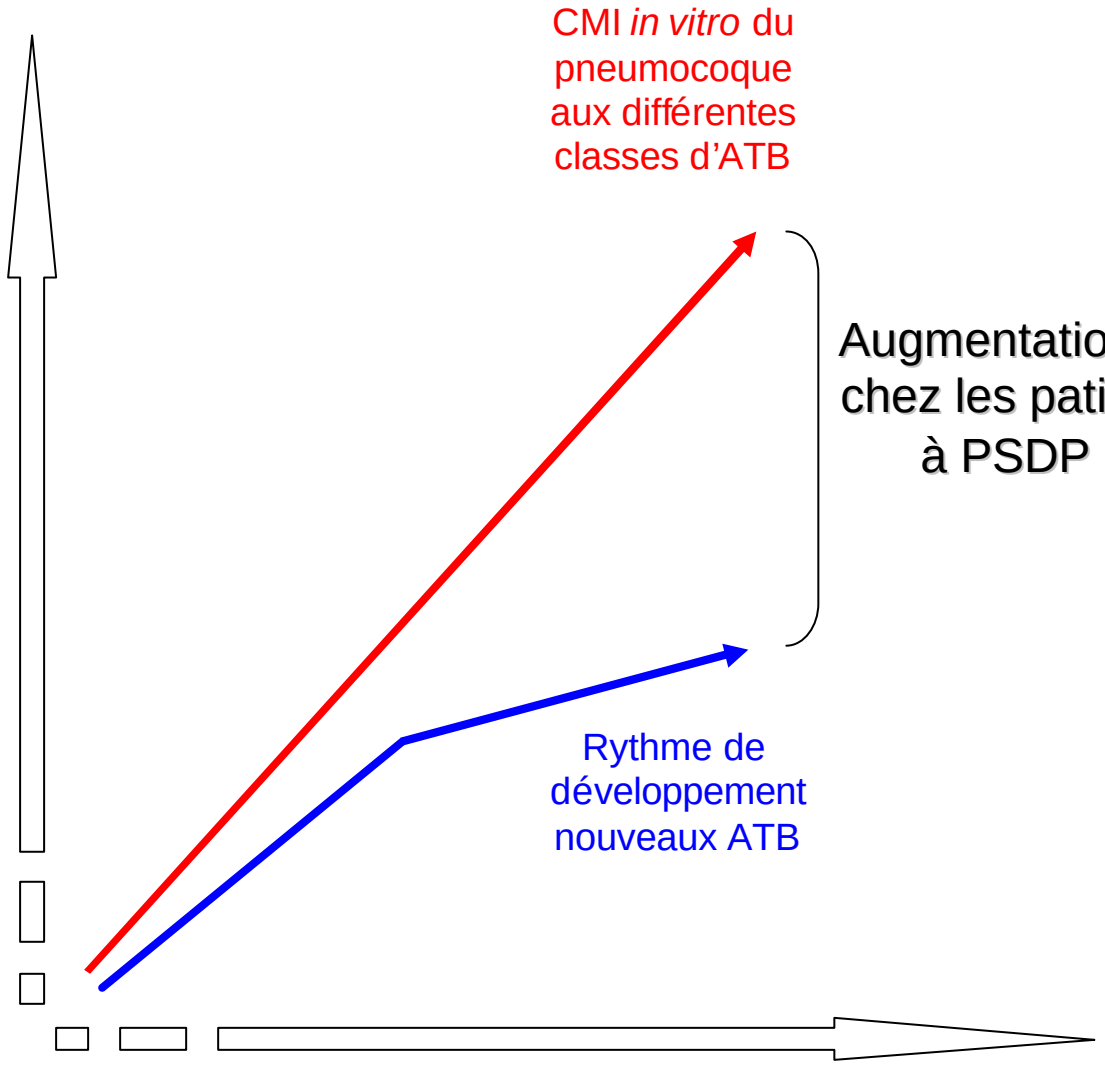
F. Ader – C. Chidiac

VIEWPOINTS

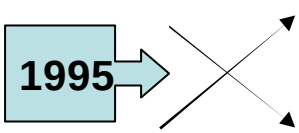
Penicillins for treatment of peumococcal pneumonia: does *in vitro* resistance really matter ?

Peterson LR

Clinical Infectious Diseases 2006;42:224-233



Augmentation des échecs de traitement chez les patients atteints de pneumonie à PSDP ou PRP et traités par β-lactamines?



Mortalité des PAC

Sensibilité du pneumocoque à la pénicilline

Mais,

- Souvent obsolète si pondération à l'âge et aux comorbidités
- Manque de corrélation entre un traitement spécifique et succès ou échec dans les études pronostiques des PAC à PSDP

D'où revue au cas par cas

ATB Voie IV	Documentation échec	Contexte	CMI	Remarque de l'auteur
Aminopénicilline	1 cas	Empyème	8 µg/mL	**Documentation d'échecs avec l' aminopénicilline virtuellement NON existant**
Cefamandole	1 cas	Etude prospective 75 patients/vs Amox + Sulbactam		
Cefotaxime	1 cas	Empyème		
Ceftazidime	Qq cas	Patients hémato neutropéniques, bactériémiques		Cas particulier d'immunodéprimés^{++}
Inhibiteurs de b-lactamases ?	∅	Etude de 97 patients: Amox + Ac clavulanique Pipé + Tazobactam		Ni mieux ni moins bien Patients hospitalisés
b-Lactamines voie orale	Cas d'échecs = concentrations ATB sub-optimales/biodisponibilité			

- PAC hospitalisée = ECBC – HC recommandés
- PACC pour la PAC = Penicilline, Aminopénicilline, Cefotaxime, Ceftriaxone
- Dépistage drastique localisations extra-pulmonaires

Agent	Dosage	Comments
Penicillin	2 g (3.2 mU) iv every 4 h	Should be adequate for strains with an MIC of ≤8 μg/mL; not always available; adjust dose for renal impairment
Ampicillin	2 g iv or im every 6 h	Should be adequate for strains with an MIC of ≤8 μg/mL; not always available; adjust dose for renal impairment
Ampicillin/sulbactam	2 g ampicillin and 1 g sulbactam iv or im every 6 h	Should be adequate for strains with an MIC of ≤8 μg/mL; adjust dose for renal impairment
Amoxicillin	1 g iv every 6 h	Should be adequate for strains with an MIC of ≤4 μg/mL; not available parenterally in the United States; adjust dose for renal impairment
Amoxicillin/clavulanate	1 g amoxicillin and 0.125 g clavulanate iv every 6 h	Should be adequate for strains with an MIC of ≤4 μg/mL; not available parenterally in the United States; adjust dose for renal impairment
Piperacillin	4 g iv every 6 h	Should be adequate for strains with an MIC of ≤16 μg/mL; not always available; adjust dose for renal impairment
Piperacillin/tazobactam	4 g piperacillin and 0.5 g tazobactam iv every 6 h	Should be adequate for strains with an MIC of ≤16 μg/mL; adjust dose for renal impairment
Cefotaxime	2 g iv or im every 6 h	Should be adequate for strains with an MIC of ≤8 μg/mL
Ceftriaxone	1 g iv or im every 12 h	Should be adequate for strains with an MIC of ≤8 μg/mL

Revue proposée par l'auteur des β-lactamines parentérales disponibles pour les PAC à pneumocoque hospitalisés

MAJOR ARTICLE

The impact of penicillin resistance on short-term mortality in hospitalized adults with peumococcal pneumonia: a systematic review and meta-analysis

Tleyjeh IM, Tlaygeh HM, Hejal R, Montori VM, Baddour LM

Clinical Infectious Diseases 2006;42:778-797

Pneumonie communautaire à pneumocoque (PCP) hospitalisée

↕

Diminution de sensibilité à la pénicilline

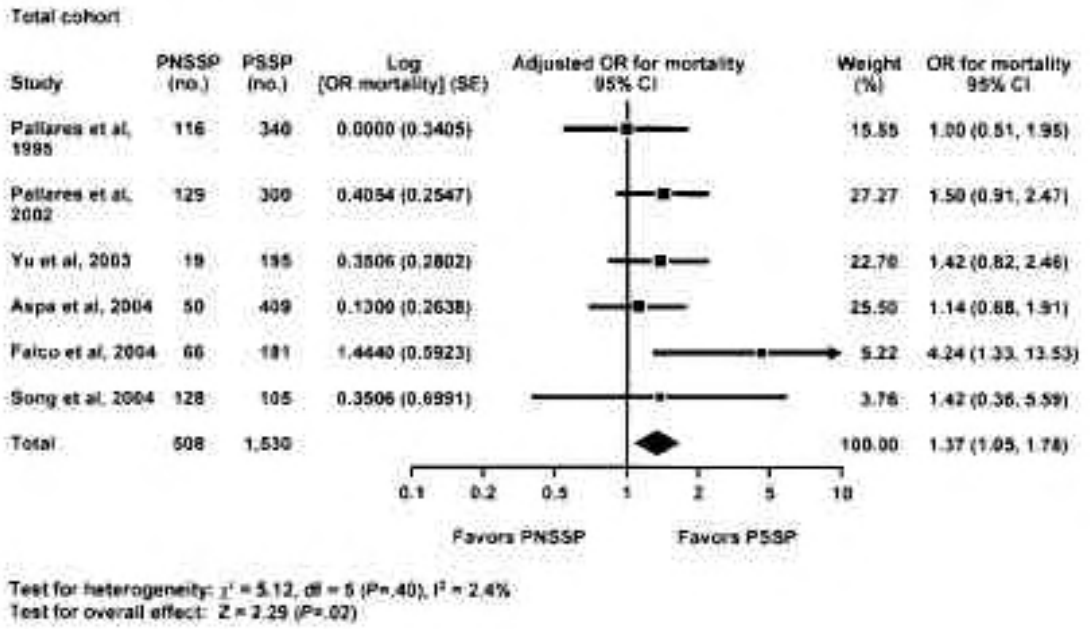
↕

mortalité court terme

10/1144 études prospectives

6 études aux variables ajustées pour l'analyse uni/multivariée

Méta-analyse



Résistance pénicilline =
Petit impact mortalité court terme des PCP

Reference	Period	Country	Inclusion criteria[a]	Age, mean years	No. of patients	Percentage of isolates			Bacteremia, % of patients	Mortality definition	Mortality rate, %
						PISP	PRSP	HPRSP			
Jehl et al. [18]	1998–2000	France	Invasive and noninvasive pneumococcal pneumonia	65	465	32.9	10.5	0	47.5	30-day	16.3
Pallares et al. [8]	1984–1993	Spain	Invasive pneumococcal pneumonia	...	456	15.1	10.3	2.6	78	In-hospital	23.5
Yigla et al. [20]	1989–1990	Israel	Invasive and noninvasive pneumococcal pneumonia	60.2	22	13.6	0	0	68	In-hospital	36.4
Ewig et al. [17]	1996–1998	Spain	Invasive and noninvasive pneumococcal pneumonia	...	101	2	5.9	0	55	In-hospital	10.9
Pallares et al. [9]	1994–2000	Spain and Switzerland	Invasive nonmeningeal pneumococcal infection	...	429	12.1	17.9	0	> 50%	30-day	16.8
Sangthawan et al. [10]	1998–2001	Thailand	Invasive and noninvasive pneumococcal pneumonia	52.5	46	37	4.3	2.2	...	In-hospital	26.1
Yu et al. [12]	1998–2001	International	Pneumococcal bacteremia	52.1	793	15	9.6	1.6	100	14-day in-hospital	17
Aspa et al. [6]	1999–2000	Spain	Invasive pneumococcal pneumonia	61.5	638	25.7	10.2	0.5	73.6	30-day	14.4
Falco et al. [7]	1997–2001	Spain	Invasive pneumococcal pneumonia	62.8	247	20.6	6.1	0	95	In- hospital	15.8
Song et al. [19]	2000–2001	9 Asian countries	Invasive pneumococcal pneumonia	60.8	233	25.3	29.6	3.4	31	30-day	13.3

Mais, …

- Limitation(s):
  - Biais
    - Disparité durées d'hospit
    - Études sans CMI
    - Multicolonisation
  - Facteurs confondants
    - Comorbidités
    - Pas d'ajustement pour les ATB hors pénicillines
  - Patients hospitalisés uniquement, imprécisions sur éradication bactérienne, complications liées à l'infection, réponse clinique.

- Mécanisme(s) ?
  - Virulence/résistance
  - Comorbidités hôte
  - Sévérité infection
  - ATB inadéquate

- Implication:

  Limiter la séquence **émergence-diffusion**

  (concordance méta-analyse bactériémies SARM/ERV)

MAJOR ARTICLE

Indirect effect of conjugate vaccine on adult carriage of *Streptococcus pneumoniae*: an explanation of trends in invasive peumococcal disease

Hammit LL, Bruden DL, Butler JC, Baggett HC, Hurlburt DA, Reasonover A, Hennessy TW

Clinical Infectious Diseases 2006;193:1487-1494

2000 : vaccin conjugué heptavalent (**VC7**) =
↓ infections invasives par sérotypes VC7 :
- enfants vaccinés
- Adultes

Alaska 2001-2003
↓ 86%
↓ 40%

Caractérisation de l'effet **INDIRECT** du VC7 sur infections de l'adulte

Colonisation NASOPHARYNGÉE pneumococcique
Enfant + adultes
Avant + après

8 villages ruraux (pop° ~ 4000) – 1998/2004 – Ouvert – E < 5a/A>18a
Ecouvillon naso-pharyngé: culture/sensibilité /sérotypage

Household characteristic	Adults with PCV-type pneumococcal carriage, *n/N* (%)[a]					Adjusted OR[c] (95% CI)	*P*
	At baseline[b]	In 2001	In 2002	In 2003	In 2004		
Children <5 years of age in household	47/149 (32)	32/133 (24)	25/142 (18)	15/198 (8)	11/162 (7)	1.81 (1.31–2.50)	.0003
No children <5 years of age in household	31/126 (25)	15/133 (11)	11/124 (9)	9/215 (4)	6/215 (3)	Referent	...

Relation présence enfant < 5 ans - colonisation des adultes

Vaccination status of children in household	Adults with PCV-type pneumococcal carriage, *n/N* (%)[a]				Adjusted OR[b] (95% CI)	*P*
	In 2001	In 2002	In 2003	In 2004		
Age-appropriately vaccinated[c]	8/41 (20)	18/114 (16)	6/144 (4)	9/143 (6)	0.49 (0.28–0.83)	.007
Not age-appropriately vaccinated[d]	24/92 (26)	7/28 (25)	9/54 (17)	2/19 (11)	Referent	...

Relation statut vaccinal des enfants - colonisation des adultes

Antimicrobial agent, susceptibility	No. (%) of isolates that were nonsusceptible to antimicrobial agents					*P*[b]	OR[c] (95% CI)
	At baseline[a] (*n* = 275)	In 2001 (*n* = 266)	In 2002 (*n* = 266)	In 2003 (*n* = 413)	In 2004 (*n* = 377)		
Penicillin							
Resistant	36 (13)	19 (7)	20 (8)	27 (7)	24 (6)	.002	0.45 (0.26– 0.78)
Intermediate	32 (12)	26 (10)	24 (9)	57 (14)	72[d] (19)	.003	1.79 (1.14– 2.80)

Profil des PRP ou PSDP chez les adultes

d: 26 isolats 19A

MAJOR ARTICLE

Pneumococcal coinfection with human metapneumovirus

Madhi SA, Ludewick H, Kuwanda L, van Niekerk N, Cutland C, Little T, Kluman KP

Clinical Infectious Diseases 2006;193:1236-1243.

Phase III (1998/2000) - vaccin conjugué 9 valences anti-pneumococcique – 39 836 enfants – Afrique du Sud

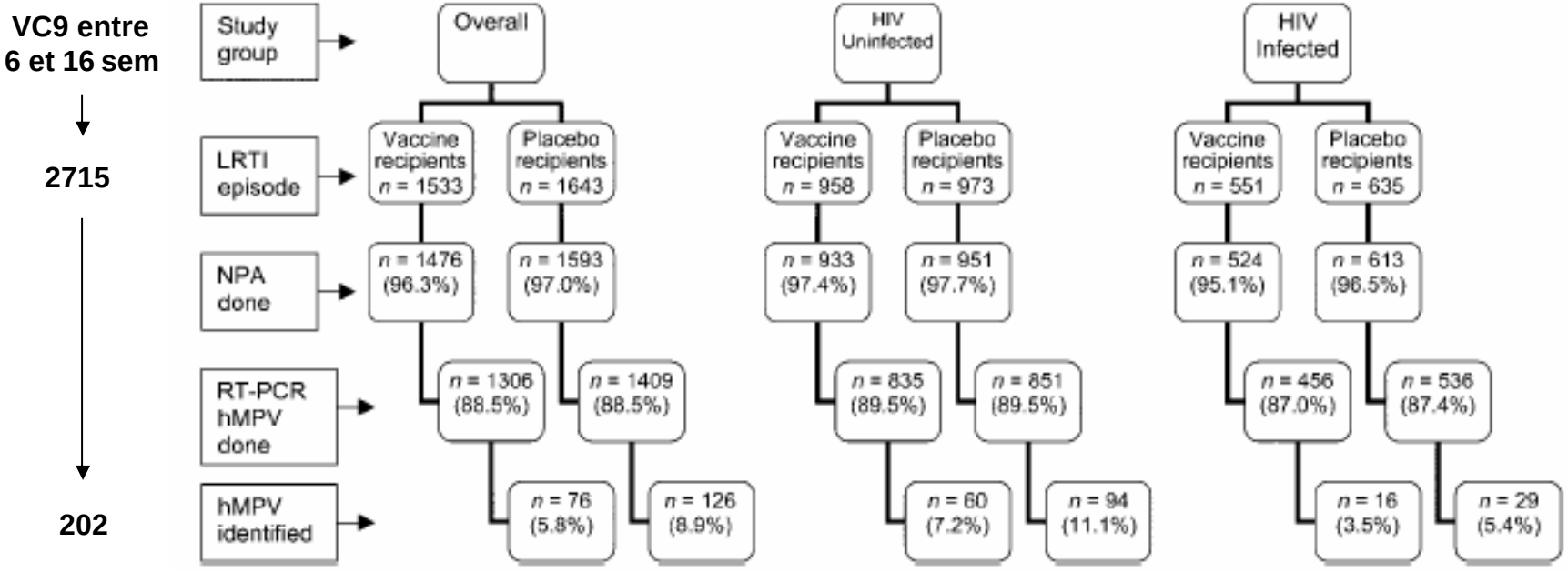
2 questions corollaires

Prévention vaccinale par VC9 a-t-elle un effet sur l'incidence des pneumonies associées au hMPV ?

⟺

Rôle de la co-infection pneumococcique dans la pneumonie associée au hMPV ?

Cohorte randomisée



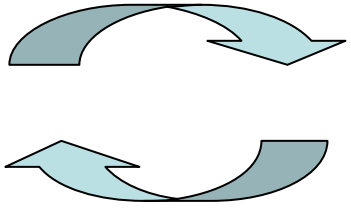
	Overall				HIV uninfected				HIV infected			
hMPV-associated outcome	Vaccine recipients	Placebo recipients	Efficacy (95% CI), %	*P*	Vaccine recipients	Placebo recipients	Efficacy (95% CI), %	*P*	Vaccine recipients	Placebo recipients	Efficacy (95% CI), %	*P*
LRTI	72	123	42 (22 to 56)	.0002	57	92	38 (14 to 56)	.004	15	28	47 (1 to 72)	.04

% d'efficacité du vaccin conjugué anti-pneumoccique dans la prévention des infections respiratoires basses liées à l'hMPV

Diminution d'incidence estimée globale **= 58%**

↓

Suggère un rôle des co-infections bactériennes, en particulier à pneumocoque, dans la pathogénèse des infections respiratoires basses à hMPV du petit enfant

Facilitation pneumocoque  hMPV

Insights into the interaction betwen Influenza virus ans Pneumococcus
McCullers JA. *Clin Microbiol Rev* 2006; 19(3): 571-582.

MAJOR ARTICLE

Emergence of *Legionella pneumophila* pneumonia in patients receiving Tumor Necrosis Factor-α antagonists

Tubach, F, Ravaud, P, Salmon-Ceron, D, Petitpain, N, Brocq, O, Grados, F, Guillaume, J.C, Leport, J, Roudaut, A, Solau-Gervais, E, Lemann, M, Mariette, X, Lortholary, O for the Recherche Axée sur la Tolérance des Biothérapies (RATIO) group

Clinical Infectious Diseases Nov 2006; **43**:e95-100

Rôle agoniste
path infl chnq

TNF-α

Rôle antagoniste
croissance bactérienne

ANTI-TNF-α
Infliximab
Etanercept
Adalimumab

486 centres - 1 an

Étude Épidémiologique

Descriptive - 10 cas consécutifs

38,5 sem (**8/10 < 1 an de traitement**)
Communautaire - Sporadique
8/10 PR
4/10 tabac et/ou BPCO
6/10 sous CC – 8/10 sous MTX
9/10 *L. pneumophila* sg 1
Présentation clinique classique
Æ **mortalité**

Incidence/Risque Relatif

Legionellose/an: 2/100 000
Anti-TNF-α/an: fourchette 24 000 – 30 000
Légionellose sous anti-TNF-α/an: 10

33 à 42/100 000
RR 16,5 à 21

MAJOR ARTICLE

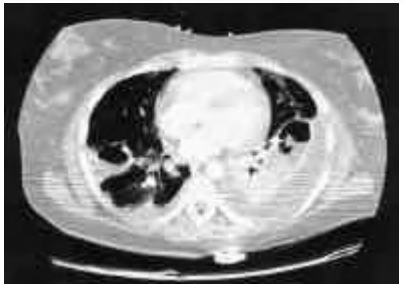
Severe community-onset pneumonia in healhy adults caused by methicillin-resistant *Staphylococcus aureus* carrying the Panton-Valentine leukocidine genes

Francis JS, Doherty MC, Lopatin U, Johnston CP, Sinah G, Ross T, Cai M, Hansel NN, Perl T, Ticehurst JR, Carroll K, Thomas DL, Nuermberger E, Bartlett JG

Clinical Infectious Diseases 2005;40:100-107

MRSA + PVL

Patient	Age, years	Peak temperature, °C	Hemoptysis	Shock	Cavitary lesions	Duration of hospitalization, days	Nadir WBC count, cells/mm³	Influenza A titer[a]
1	31	39.7	+	+	+	41	7400	<1:10 to 1:80
2	52	41.0	+	+	+	2[b]	1020	ND
3	20	39.9	−	+	+	109	380	1:32 to 1:512
4	33	40.2	+	+	+	102	800	ND



		DNA analysis			Antibacterial susceptibility[a]						
Patient	Source of MRSA	PFGE pattern	SCC*mec* type IV	PVL	Vm	C	Em	TMP-SMZ	Tet	Gm	Gat
1	Blood, sputum	Same	+	+	S	S	R	S	S	S	S
2	Sputum	Similar	+	+	S	S	R	S	R	S	I
3	BAL, blood	Same	+	+	S	S	R	S	R	S	I
4	BAL, blood	Same	+	+	S	S	R	S	S	S	I

Detection of influenza viruses resistant to neuraminidase inhibitors in global surveillance during the first 3 years of use

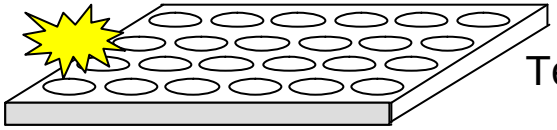
Monto AS, McKimm-Breschkin JL, Macken C, Hampson AW, Hay A, Klimov A, Tashiro M, Webster RG, Aymard M, Hayden FG, Zambon M

Antimicrobial Agents and Chemotherapy 2006;50(7):2395-2402

Avant commercialisation (1999)
pas de résistance primaire à cette classe

Neuraminidase Inhibitor Susceptibility Network (NISN)

Post-commercialisation : sensibilité à 3 ans ?



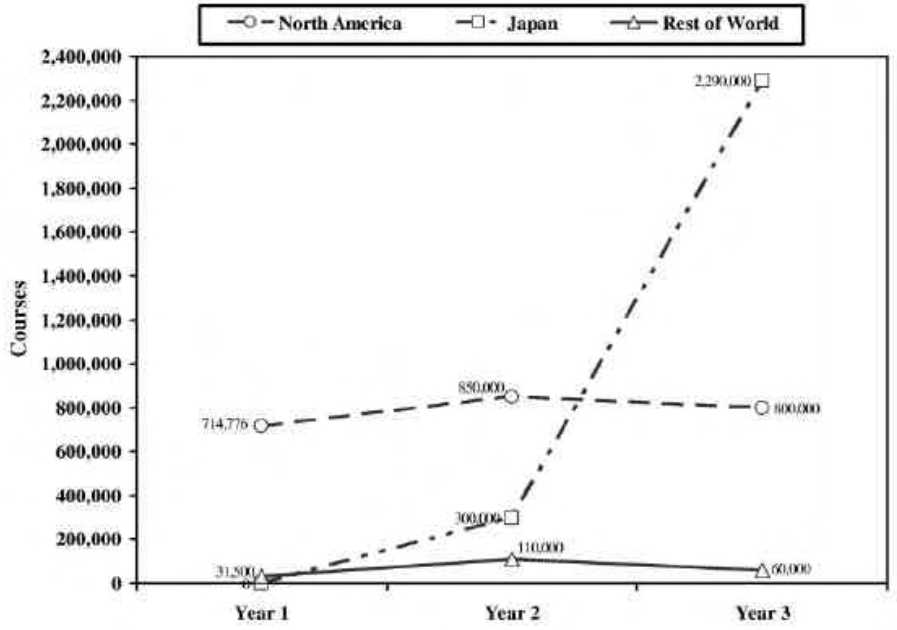
Test d'inhibition de la NA par Oseltamivir et Zanamivir

↓

Concentration Inhibitrice 50% (IC_{50})
(n=2287)

↓

Séquençage NA des souches avec IC_{50} élevées ou extrêmes (n=63)



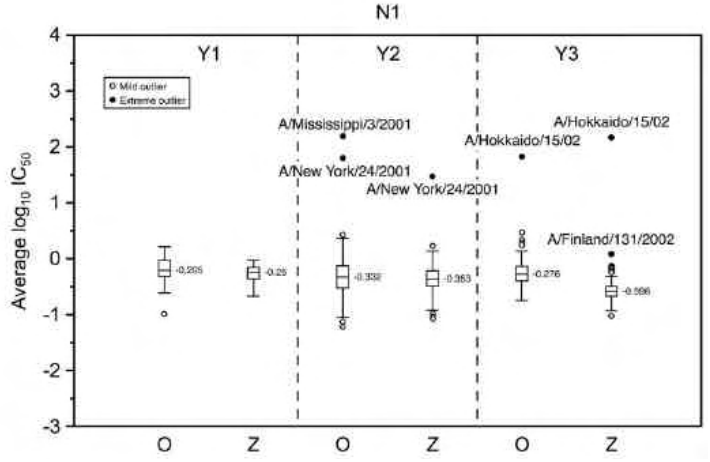
Traitement 5 j
Oseltamivir

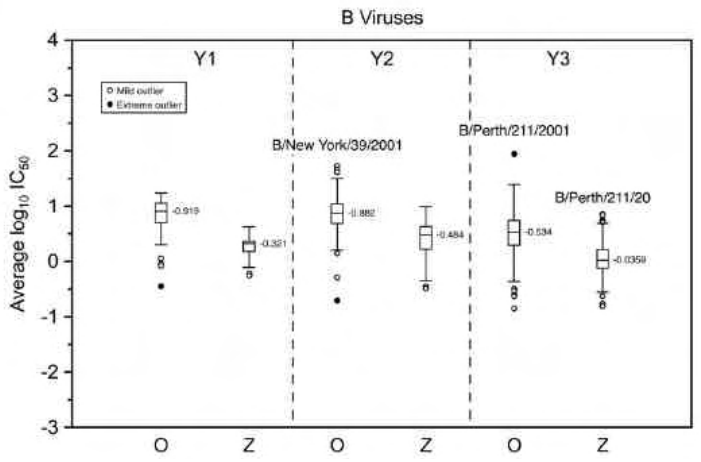
	Types A						Type B		
	H1N1			H1/3N2					
	1	2	3	1	2	3	1	2	3
n =	54	402	166	46	54	115	18	109	160
Oseltamivir	0.64	0.48	0.56	0.43	0.34	0.35	6.40	7.54	3.26
Zanamivir	0.54	0.44	0.27	1.55	1.34	1.25	1.84	2.61	1.16

Moyennes des IC_{50} pour Oseltamivir et Zanamivir selon les types, sous-types et années

Mais, …

63





Virus subtype and strain	Sequence change(s)	Oseltamivir IC_{50} (nM)[a]		Fold difference	Zanamivir IC_{50} (nM)[a]		Fold difference
		Wild type	Variant		Wild type	Variant	
H1N1 outliers							
Reference strain A/Texas/36/91[b]	H274Y	0.4	253.9	632	0.75	0.7	1
A/Mississippi/3/2001	H274Y	0.48	**157**	327	0.44	0.47	1
A/New York/24/2001	G248R I266V	0.48	**64**	133	0.44	**30**	68
A/Hokkaido/15/2002	Y155H	0.56	**69**	123	0.27	**150**	555
H3N2/H1N2 outliers							
Reference strain A/Wuhan/359/95[b]	E119V	0.3	15.6	52	0.7	1.3	2
Reference strain A/Sydney/5/97[b]	R292K	0.4	3,877	9,692	1.8	6.7	3.7
A/Greece/110/2000	E41G	0.43	**5.07**	11.7	1.55	1.67	1.1
A/Denmark/25/2002	Drift only	0.35	**4.91**	14.0	1.26	1.76	1.39
A/Belgium/969/2002	Q226H	0.35	**4.74**	13.5	1.26	0.96	0.76
B outliers							
Reference strain B/Memphis/20/96[b]	R152K	6.7	509.2	76	3.5	33.7	9.6
B/New York/39/2001[c]	I222T	7.44	**100** (55)	13.4 (7.3)	2.6	**17** (6)	6.5 (2.3)
B/Perth/211/2001	D198E	3.26	**90**	26.3	1.16	**7.36**	6.7

Avian flu: influenza virus receptors in the human airway

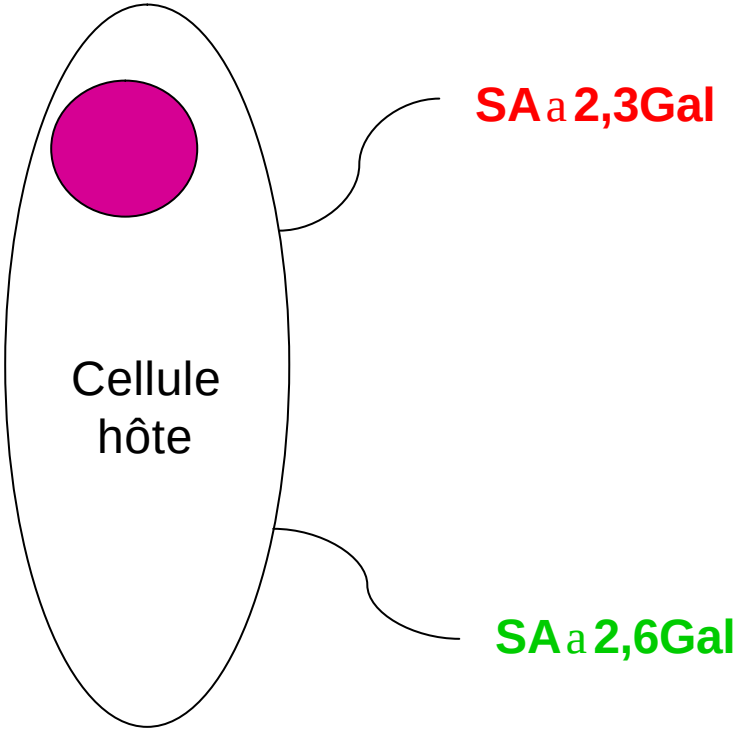
Shinya K, Ebina M, Yamada S, Ono M, Kasai N, Kawaoka Y

Nature 2006 23;440(7083):435-436

«What are the molecular barriers limiting human-to-human transmission? »

HA/cellule hôte =
liaison via un Acide Sialique (SA) + Galactose (Gal)
2 conformations

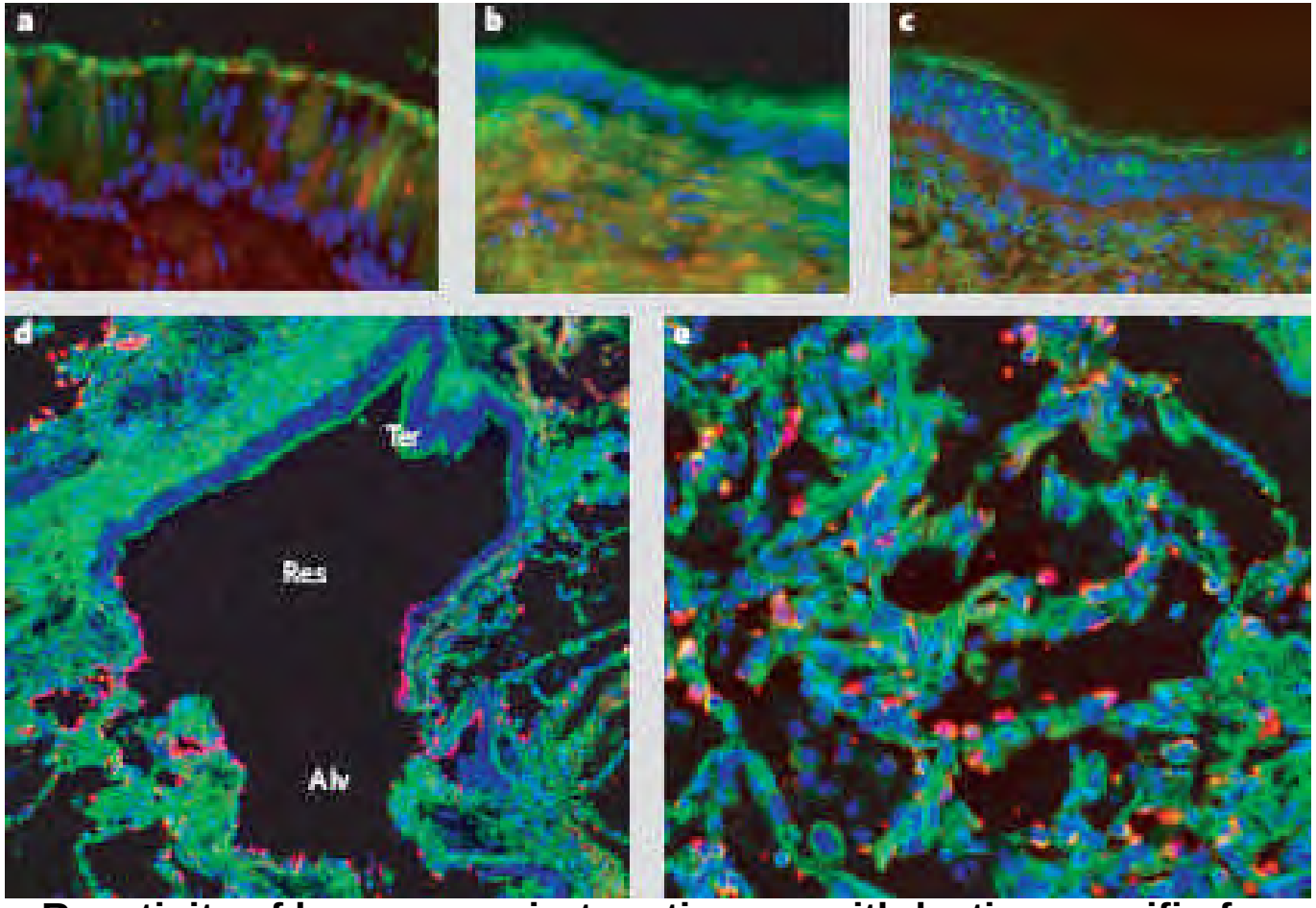
Hemaglutinine (HA)



Cellules du tractus respiratoire humain?

Paranasal sinuses

Nasal mucosa



Bronchus

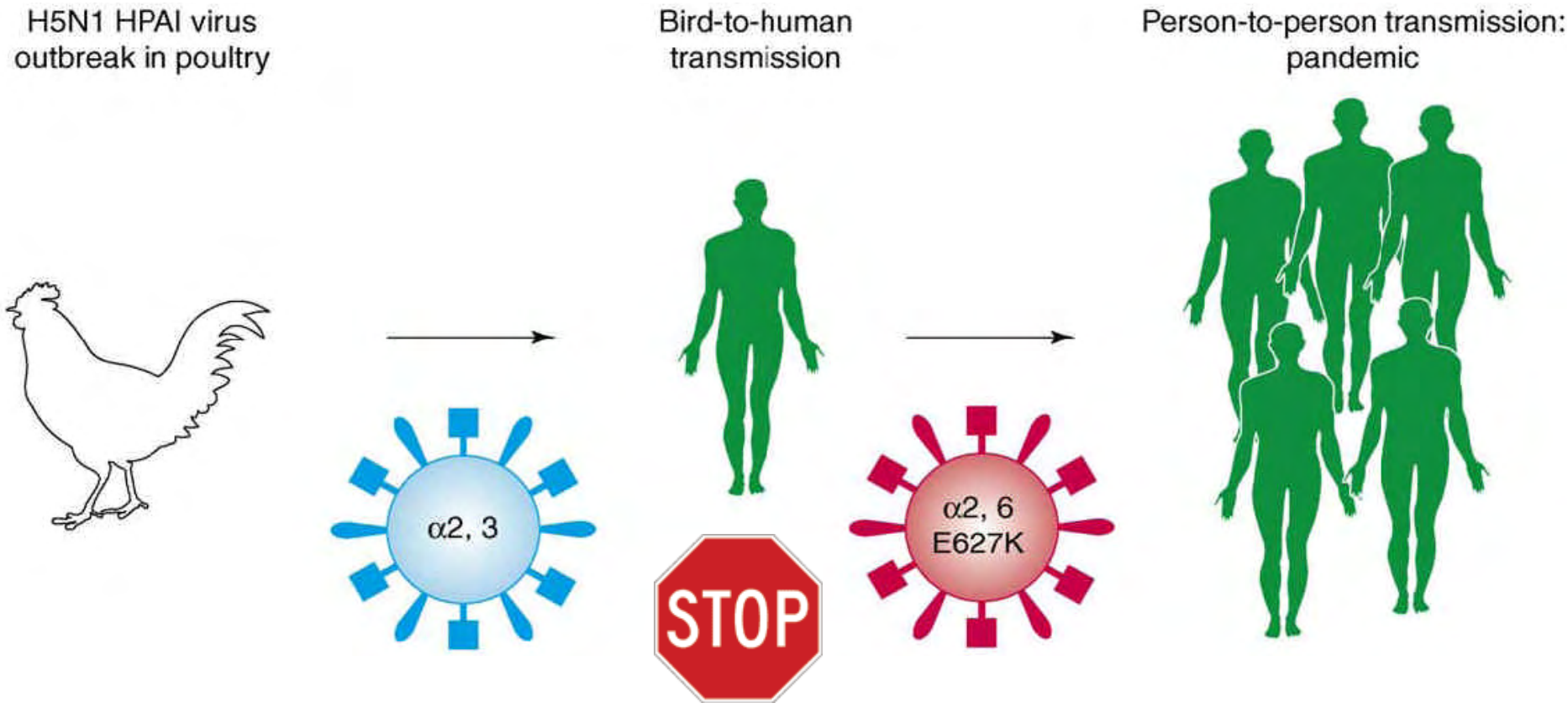
Bronchiole

Alveolus

Reactivity of human respiratory tissues with lectins specific for different sialic acid linkages

Green = SAα2,6Gal linkage

Red = SAα2,3Gal linkage

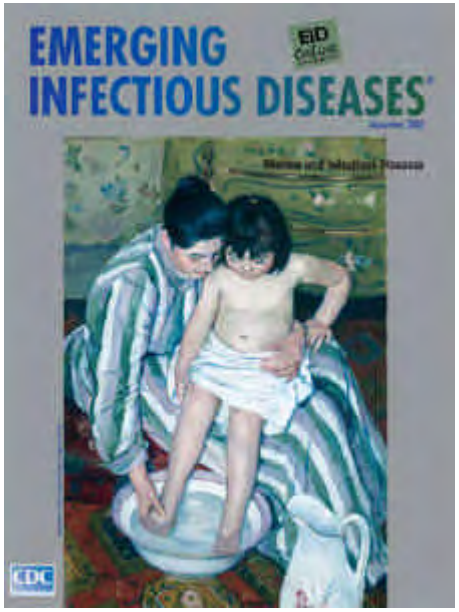

H5N1 HPAI virus outbreak in poultry
Bird-to-human transmission
Person-to-person transmission: pandemic
α2, 3
STOP
α2, 6 E627K

! AEROSOL !

Review of Aerosol Transmission of Influenza A Virus

Raymond Tellier*†

Volume 12, Number 11 – November 2006



Published evidence indicates that aerosols transmission of Influenza can be an important mode of transmission, which has obvious implications for pandemic influenza planning and in particular for recommandations about the use of N95 respirators as a part of personnal protective equipment.

Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: phase I randomized trial

Bresson JL, Perronne C, Launay O, Gerdil C, Saville M, Wood J, Höschler K, Zambon MC

The Lancet 2006 367:1657-1664

Thai dogs carry bird-flu virus, but wil they spread it ?

Butler D

Nature 2006 439:773

	Chiens de village	Chats de village
n	629	111
Ac anti-H5N1	160 (25%)	8 (7%)