



# JNI

14<sup>es</sup> Journées  
Nationales  
d'Infectiologie

Clermont-Ferrand  
et l'interrégion Rhône-Alpes Auvergne

Du mercredi 12 au  
vendredi 14 juin 2013  
Polydome, centre d'expositions  
et des congrès



## Viroses Respiratoires Emergentes :

# Grippes à Virus Aviaires : Aspects Cliniques H5N1 *versus* H9N7



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# Grippe à Virus A(H5N1). Cas Cumulés au 03 juin 2013 selon OMS

Country	2003-2009*		2010		2011		2012		2013		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	0	0	2	0	3	0	1	1	7	1
Cambodia	9	7	1	1	8	8	3	3	11	8	32	27
China	38	25	2	1	1	1	2	1	2	2	45	30
Djibouti	1	0	0	0	0	0	0	0	0	0	1	0
Egypt	90	27	29	13	39	15	11	5	4	3	173	63
Indonesia	162	134	9	7	12	10	9	9	0	0	192	160
Iraq	3	2	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	12	4
Viet Nam	112	57	7	2	0	0	4	2	2	1	125	62
<b>Total</b>	<b>468</b>	<b>282</b>	<b>48</b>	<b>24</b>	<b>62</b>	<b>34</b>	<b>32</b>	<b>20</b>	<b>20</b>	<b>15</b>	<b>630</b>	<b>375</b>

Mortalité : 59 %



# The NEW ENGLAND JOURNAL *of* MEDICINE

**REVIEW ARTICLE**

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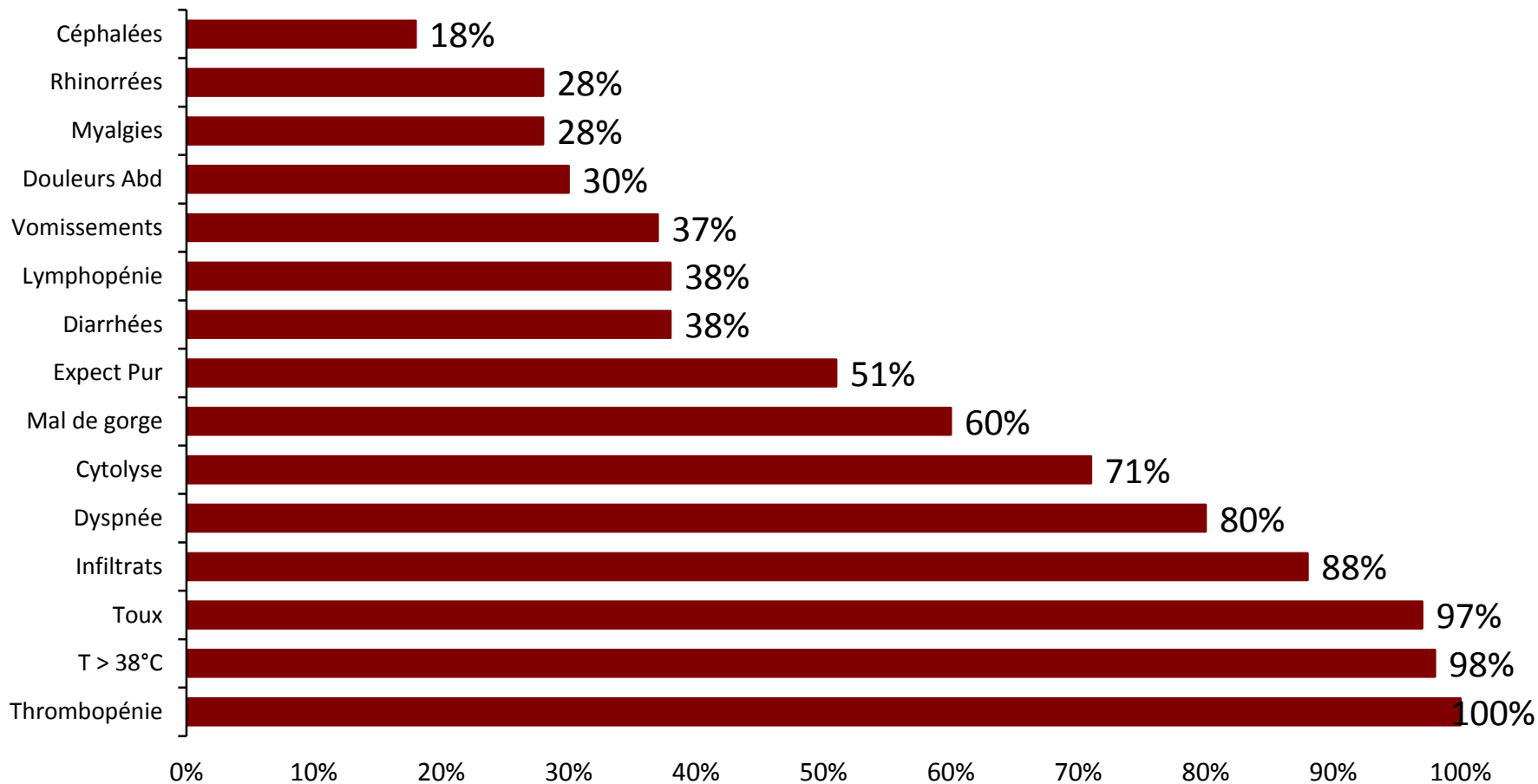
## **Avian Influenza A (H5N1) Infection in Humans**

*The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5*

## Caractéristiques des pts H5N1 (n=59) (I)

	Hong Kong 1997	Thaïlande 2004	Vietnam 2004	Ho Chi Minh 2005	Cambodge 2005
n	18	17	10	10	4
Age	9,5 1-60	14 2-58	13,7 5-24	19,4 6-35	22 8-28
Sexe M : n (%)	8 (44)	9 (53)	6 (60)	3 (30)	1 (25)
Incubation	-	4 2 - 8	3 2 - 4	-	-
Clusters familiaux		1	2	1	1
Exposition volailles malades	11/16 (70)	14/17 (82)	8/9 (89)	6/6 (100)	3/4 (75)
Délai symptômes/H	3 1-7	- -	6 3-8	6 4-7	8 5-8

# Caractéristiques des Patients avec Grippe H5N1, n = 59 (II)



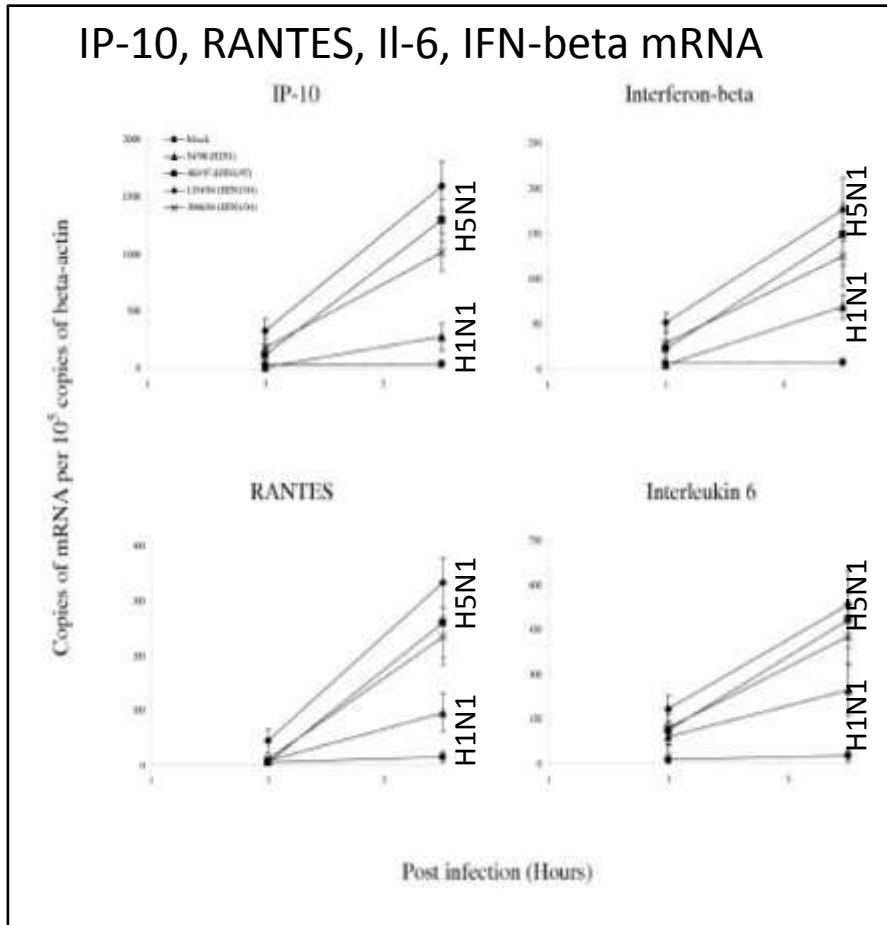
## Caractéristiques des pts H5N1 (n = 59) (III)

	Hong Kong 1997	Thaïlande 2004	Vietnam 2004	Ho Chi Minh 2005	Cambodge 2005
<b>n</b>	18	17	10	10	4
<b>Ins.respiratoire</b>	8 (44)	13 (76)	9 (90)	7 (70)	4 (100)
<b>Ins. cardiaque</b>	-	7 (41)	-	0	-
<b>Ins. rénale</b>	4 (22)	5 (29)	1 (10)	2 (20)	-
<b>Traitement</b>					
<b>Amantadine</b>	10 (56)	0	0	0	-
<b>Ribavirine</b>	1 (6)	0	2 (20)	0	-
<b>Oseltamivir</b>	0	10 (59)	5 (50)	10 (100)	-
<b>Corticoïdes</b>	5 (28)	8 (47)	7 (70)	5 (50)	-
<b>Inotropes</b>	-	8 (47)	2 (20)	-	-

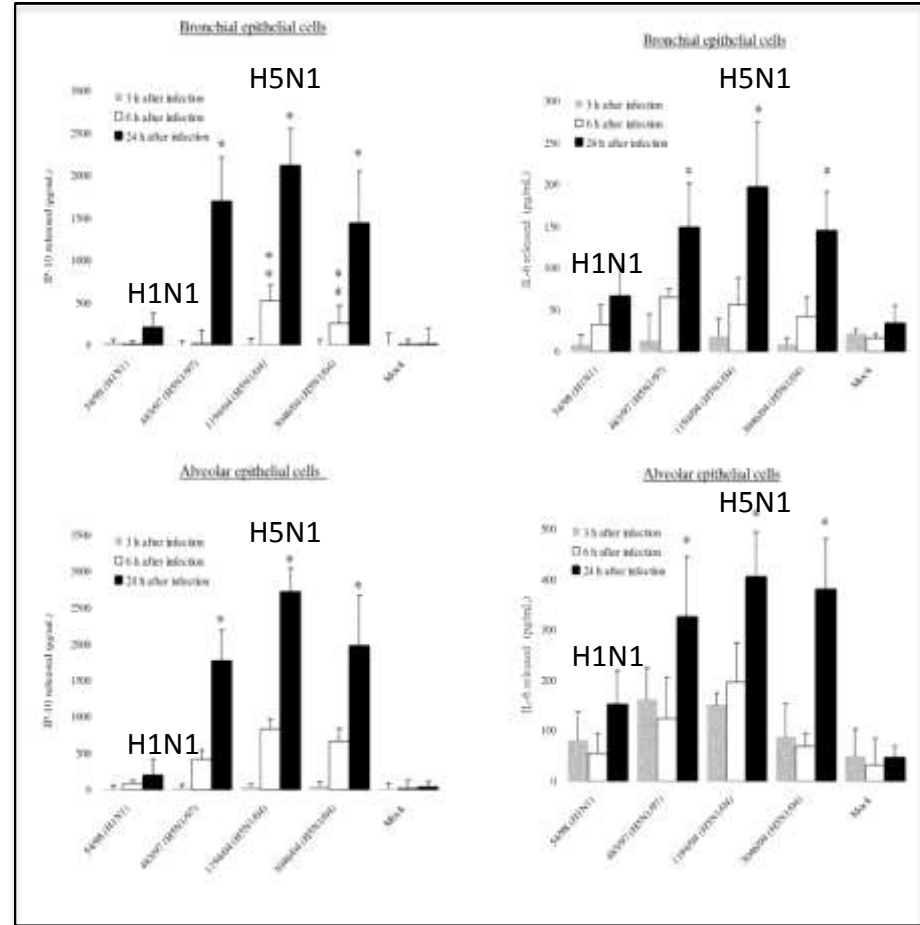
# Synthèse

- Exposition : volailles +++
- Incubation plus longue que grippe « normale »
- Fièvre élevée, et ILI +++
- Diarrhée liquidienne plus fréquente
- Symptômes respiratoires et signes radiologiques marqués
- Défaillance multiviscérale fréquente
- Délai début signes/décès : long
- Décès liés à la défaillance respiratoire
- Mortalité importante  $\geq 50\%$
- Résistance aux inhibiteurs de M2

# Hyper Induced Cytokine and Chemokine Gene Expression in Primary Human type II Pneumocytes



Gene expression in type II pneumocytes

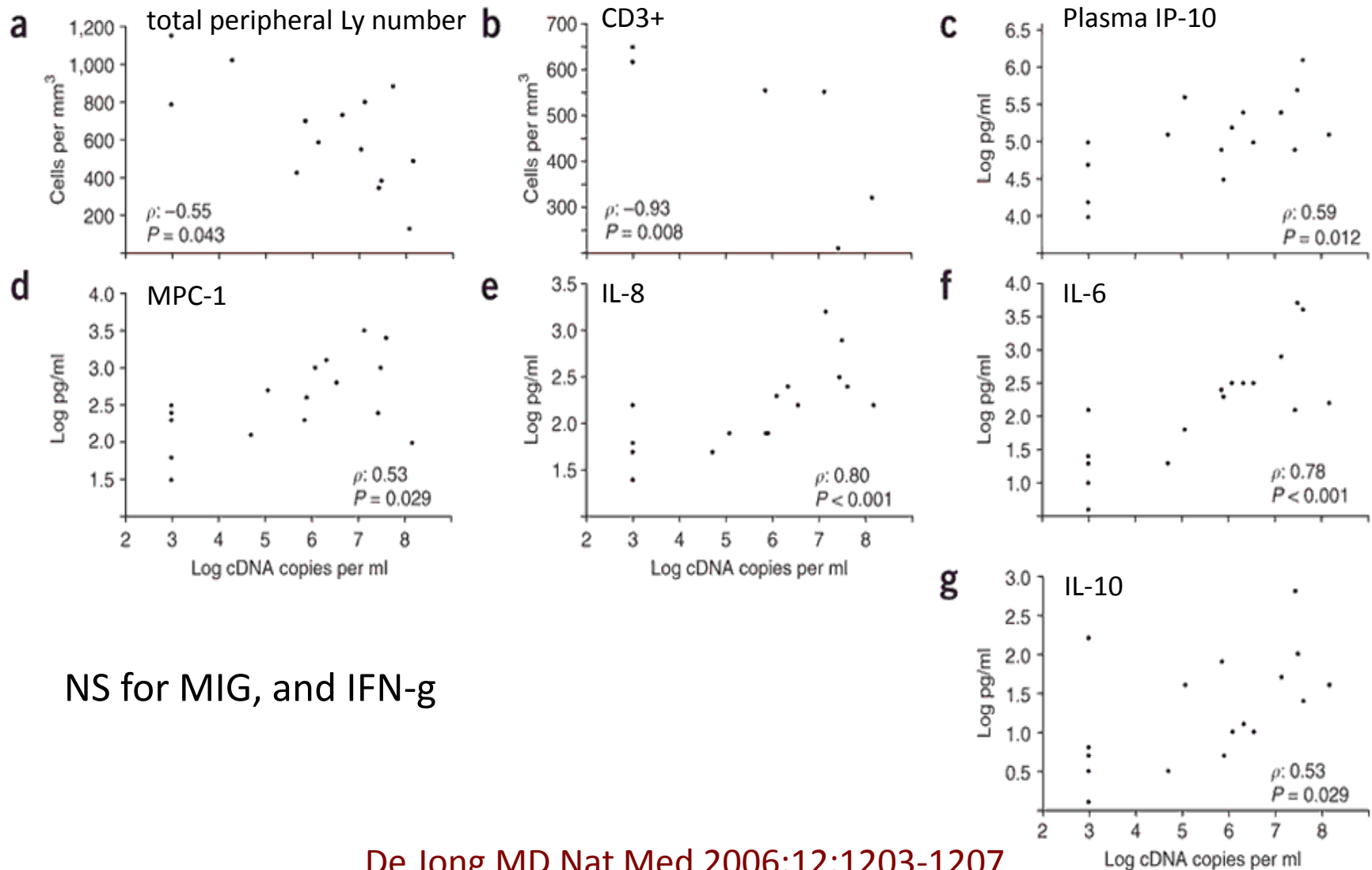


Cytokine production by bronchial and alveolar epithelial cells

RANTES : Regulated on Activation, Normal T cell Expressed and Secreted

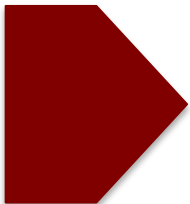


# Correlations Between Pharyngeal Virus Load and Immunological Parameters in H5N1 Infection



# Efficacité de l'Oseltamivir sur H5N1

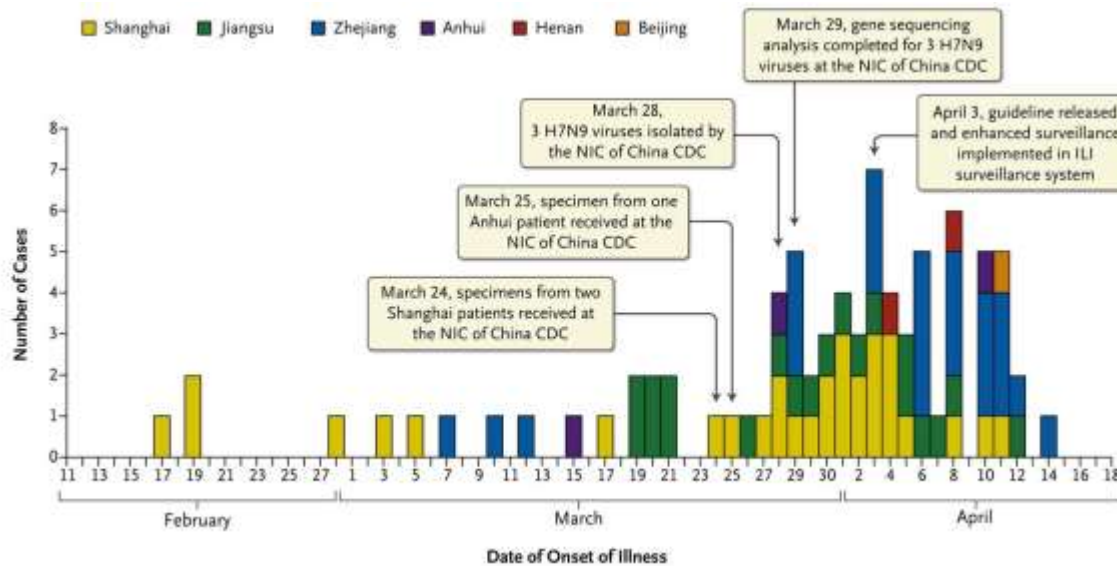
- *In vitro* :
  - Leneva JA, Antiviral Res 2000;48:101-15
  - Govorkova EA, Antimicrob Agents Chemother 2001;45:2723-32.
- **Expérimental** :
  - modèle furet (Govorkova EA, 2006)
  - 100% de survie (dose et durée de traitement recommandées)
- **Clinique : absence de données fiables pour l'évaluation**
  - WHO (NEJM 2005) :
    - Disparition du virus en 3 j de traitement
    - Effectif limité (25), traitement tardif, gravité : évaluation difficile
  - De Jong :
    - 4/8 pts traités survivants
    - 2/4 échecs porteur résistance H274Y
  - Expérience Turque :
    - 4/13 échecs pts traités précocement

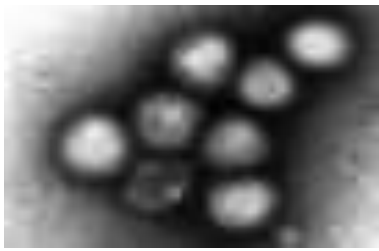


Challenge : optimisation de l'utilisation de l'oseltamivir  
« Frapper vite.... et fort (?) »

# H7N9

Au 30 mai 2013  
 132 cas; 37 décès  
 Mortalité :28%





# Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection

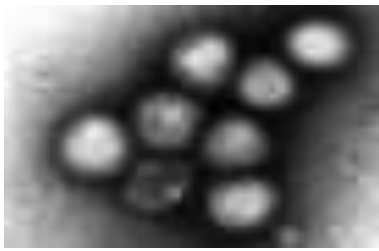
Characteristic	Value
<b>Age</b>	
Median (range) - Yr	61 (3-88)
Subgroup – no. (%)	
0-4	1 (0,9)
5-14	1 (0,9)
15-49	28 (25,2)
50-64	34 (30,6)
≥ 65	47 (42,3)
<b>Female sex – no. (%)</b>	35 (31,5)
<b>Current smoker</b>	27 (24,3)
<b>Exposure to live poultry</b>	
In previous 14 days – no (%)	62 (55,9)
Median incubation time since exposure (interquartile range) - days	5 (2-8)
<b>Hospitalization – no. (%)</b>	109 (98,2)

Characteristic	Value
<b>Coexisting condition – no. (%)</b>	
Any	68 (61,3)
Hypertension	51 (45,9)
Diabetes	18 (16,2)
Coronary heart disease	11 (9,9)
Immunosuppression	10 (9,0)
COPD	8 ((7,2)
Cancer	6 (5,4)
Cerebrovascular disease	4 (3,6)
Hepatitis B infection	4 (3,6)
Chronic renal disease	2 (1,8)
Pregnancy	2 (1,8)

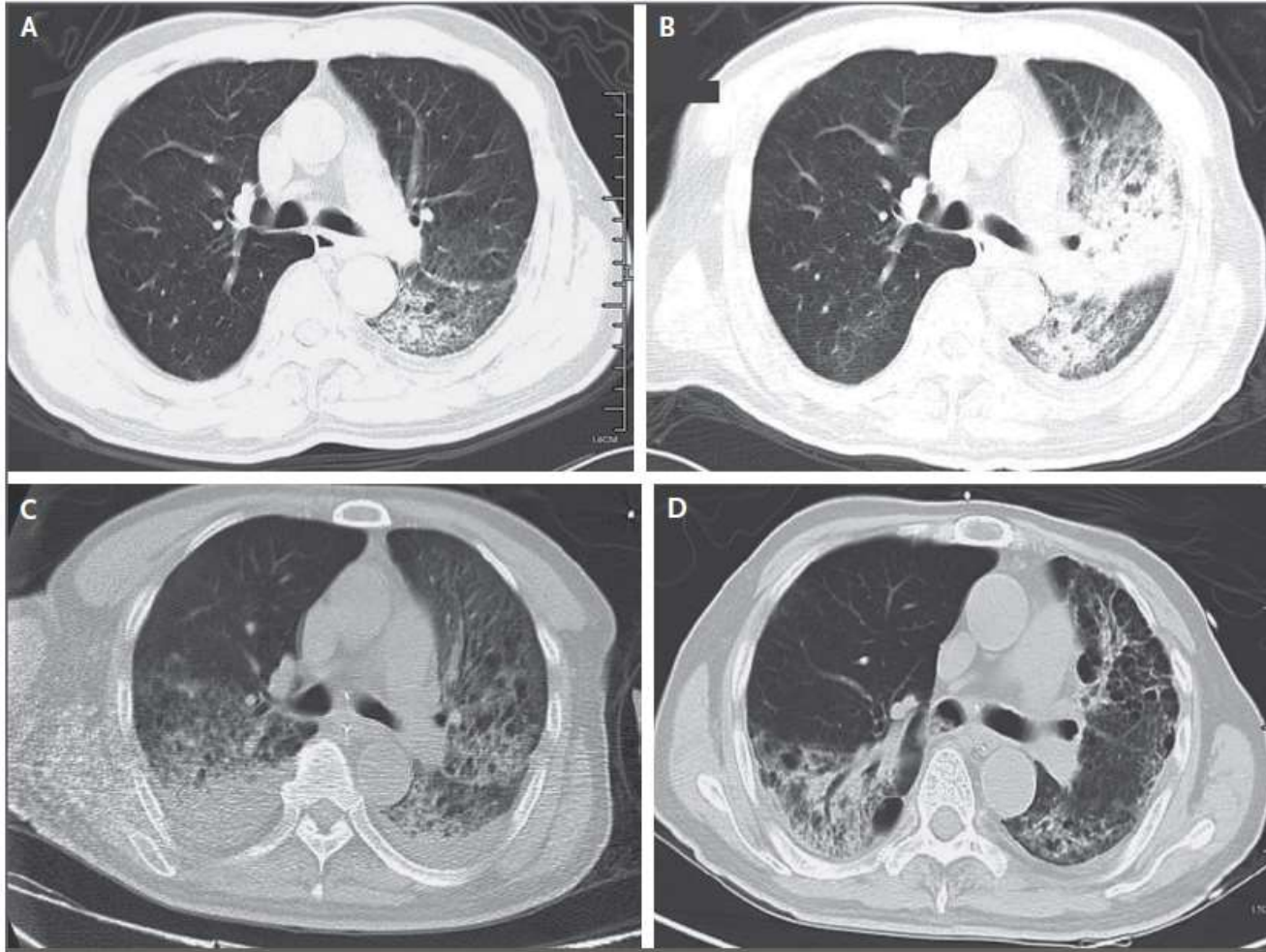
## Clinical Characteristics and Selected Laboratory Abnormalities of 111 Patients Infected with H7N9 Virus

Characteristic	Value
<b>Fever</b>	
Any – no. (%)	111 (100)
Maximal temperature - °C	39,2 ± 0,8
Subgroup – no. (%)	
37-3 – 38,0°C	11 (9,9)
38,1 – 39,0°C	43 (38,7)
> 39°C	57 (51,4)
<b>Fatigue</b> – no. (%)	10 (36,0)
<b>Conjunctivitis</b> – no. (%)	0
<b>Cough</b> – no. (%)	100 (90,1)
<b>Sputum production</b> – no. (%)	62 (55,9)
<b>Hemoptysis</b> – no. (%)	27 (24,3)
<b>Shortness of breath</b> – no. (%)	62 (55,9)
<b>Diarrhea or vomiting</b> – no. (%)	15 (13,5)
<b>White cells</b>	
Median – per mm <sup>3</sup>	4450
Interquartile range – per mm <sup>3</sup>	2900-6320
Subgroup	
> 10 000 per mm <sup>3</sup>	5 (4,5)
< 4 000 per mm <sup>3</sup>	51 (45,9)
<b>Lymphocytes – per mm<sup>3</sup></b>	
Median	460
Interquartile range	320-700

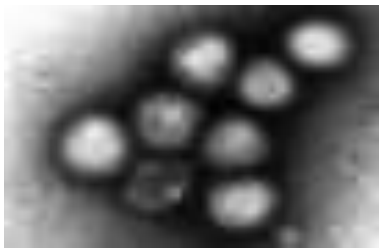
Characteristic	Value
<b>Lymphocytopenia</b> – no. (%)	98 (988,3)
<b>Hemoglobin</b> – g/dl	12,9 ± 3,1
<b>Platelets– per mm<sup>3</sup></b>	
Median	115 500
Interquartile range	82 000 – 149 500
<b>Thrombocytopenia</b> – no. (%)	81 (73,0)
<b>C-reactive protein &gt;10mg/liter</b>	85 (76,6)
<b>Procalcitonin &gt; 0,5 ng/ml</b> – no. (%)	28 (37,3)
<b>Aspartate amino transferase &gt; 40 U/liter</b> – no. (%)	73 (65,8)
<b>Creatine kinase &gt; 200 U/liter</b> – no. (%)	49 (44,1)
<b>Myoglobin &gt; 80 µg/ml</b> – no. (%)	16 (55,2)
<b>PaO<sub>2</sub>:FiO<sub>2</sub></b>	
Median	144,0
Interquartile range	107,1-226,9
<b>Potassium</b> – mmol/liter	3,8 ± 0,5
<b>Sodium</b> – mmol/liter	136,8 ± 6,0
<b>D-dimer &gt; 0,5 mg/liter</b> – no. (%)	47 (90,4)
<b>Chest radiologic findings</b> – no. (%)	
Involvement of both lungs	60 (54,1)
Ground-glass opacity	62 (55,9)
Consolidation	99 (89,2)



# Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection



# Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection



Variable	Value no. (%)	Variable	Value no. (%)
<b>Complications</b>		Admission to an ICU	85 (76,6)
Pneumonia	108 (97,3)	ECMO	20 (18)
ARDS	79 (71,2)	Continuous renal replacement therapy	29 (26,1)
Shock	29 (26,1)	Artificial-liver-support-system therapy	17 (15,3)
Acute kidney injury	18 (16,2)	Antibiotics	79 (71,2)
Rhabdomyolysis	11 (9,9)	Antifungal drugs	1 (0,9)
<b>Treatment</b>		Glucocorticoids	69 (62,2)
Bacteria isolation from culture	29 (26,1)	Intravenous immune globulin	59 (53,2)
Administration of oseltamivir or peramivir	108 (97,3)	<b>Clinical outcome</b>	
Timing from onset of illness to antiviral therapy		Death	30 (27)
0-2 days	11 (9,9)	Cause of death	
3-5 days	32 (28,8)	Refractory hypoxemia	22 (73,3)
≥ 6 days	65 (58,6)	Shock	1 (3,3)
Oxygen therapy	111 (100)	Acute heart failure	2 (6,7)
Mecanical ventilation		Secondary bacterial or fungal infection	3 (10)
Non invasive	31 (27,9)	Arrythmia	2 (6,7)
Invasive	65 (58,6)	Discharge from hospital	49 (44,1)

Adapté de GAO HN N Engl J Med 2013 DOI : 10.1056/NEJMoa1305584



# Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection

## Multivariate Analysis of Risk Factors for the 79 Patients with the Acute Respiratory Distress Syndrome

Risk factor	Ods ratio (95% CI)	P value
Age $\geq$ 65 Yr	1,01 (0,99-1,03)	0,30
Coexisting medical condition	3,42 (1,21-9,70)	<b>0,02</b>
Lymphocyte count $<$ 1000 cells/mm <sup>3</sup>	2,73 (0,60-12,52)	0,20
Aspartate aminotransferase level $>$ 40 U/liter	1,37 (0,42-4,43)	0,60
Creatine kinase level $>$ 200 U/liter	1,80 (0,59-5,48)	0,30
Time from symptoms to NI $>$ 3 days	2,42 (0,49-11,99)	0,28



# Grippe AH7N9 : Évolution Défavorable, Portage Viral Prolongé & Résistance

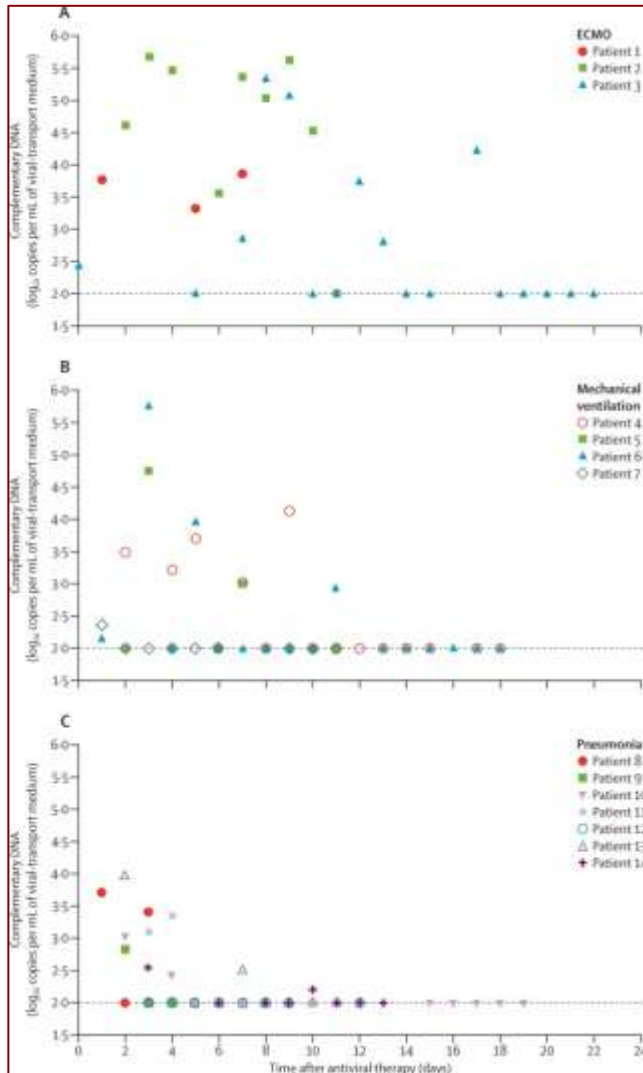
- Méthodes :

- 14 patients, hospitalisés (Shanghai), 4-20 Avril 2013,
- Traités par oseltamivir ou peramivir < 2 j avant admission
- Exploration répétée de la CV pharyngée, fécès, sérum, urines
- Séquençage ARN viral : mutations associées à R aux INA?
- Corrélation à l'évolution clinique

- Résultats :

- 14 pts avec pneumonie, 7/14 VM, 3/14 ECMO, 2/14 décès.
  - 11 pts survivants : INA associés à réduction de la CV pharyngée
  - 3 pts ECMO dépendant : persistance CV élevée sous INA
    - Mutation Arg292Lys chez 2/3pts
    - Traités par CS
    - 1pt : Arg292 à J2 du tt
    - 1 pt : Lys292 à 9 j du tt

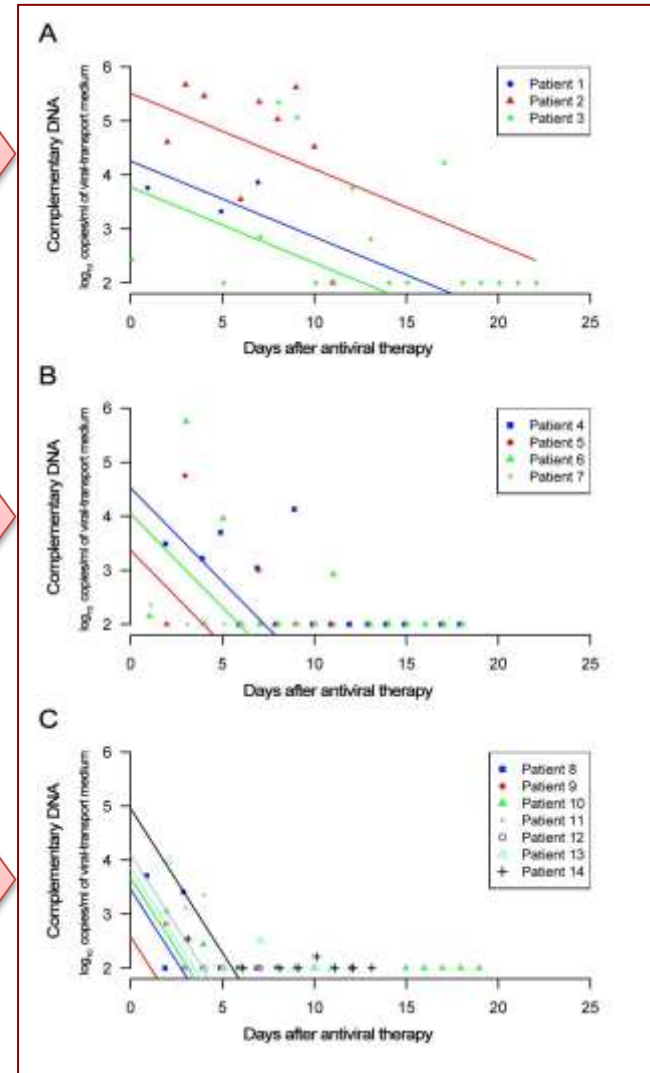
# Grippe AH7N9 : Évolution Défavorable, Portage Viral Prolongé & Résistance



ECMO

Mechanical Ventilation

Pneumonia



# Grippe AH7N9 : Évolution Défavorable, Portage Viral Prolongé & Résistance

	CV admission		
	Médiane	Extrêmes	IQR
ECMO	3,76	2,43 – 4,61	52,43 – 4,61
VM	2,26	2,00 – 3,49	2,04 – 3,21
Pneumonie	3,05	2,00 – 3,97	0,68

- Pic moyen de CV :
  - CV ECMO > CV Pneumonie,  $P = 0,033$
- Modèle de régression linéaire :
  - CV ECMO > CV Pneumonie,  $p = 0,047$
  - CV ECMO > CV VM + pneumonie,  $P = 0,02$

# Grippe AH7N9 : Évolution Défavorable, Portage Viral Prolongé & Résistance

Group	Patient No.	Days after antiviral therapy	NA R292, Wild type CT value* (percentage†)	NA R292K, Mutant CT value* (percentage†)
ECMO	2	3	37.42 (32.42%)	36.36(67.58%)
		4	40.4(17.87%)	38.2(82.13%)
		7	39.57(3.68%)	34.86(96.32%)
		9	40.61(2.87%)	35.53(97.13%)
	3	2	36.81(100%)	Und‡
		9	Und	36(100%)
Mechanical Ventilation	4	2	Und	Und
		9	Und	Und
	6	2	39.14(100%)	Und
		4	Und	Und
Pneumonia	9	2	Und	Und
	11	3	Und	Und

\*CT value indicates the threshold cycles of PCR  
†Percentage indicates the ratio of detected molecules among the whole population. The method of calculation is given in the supplementary materials. ‡Und=below detection limit.

*Table S4: Differentiation of NA 292R and 292K population in patients by genotype specific Taqman assay*



# WHO Provisional Recommendation on Influenza A(H7N9) Vaccine Virus 31 05 13

- Critical insights into the evolution and biological properties of this novel influenza virus :
  - The virus is “low-pathogenic” for chickens, notwithstanding the capacity of these viruses to cause severe and fatal infections in people.
  - The virus appears to have acquired mutations associated with:
    - Adaptation of avian viruses to humans, swine and terrestrial poultry;
    - Increased transmissibility in experimentally infected ferrets; and
    - Enhanced replication at the temperature of the upper airway of mammalian hosts and possibly humans.
  - The virus is resistant to M2 inhibitors.
  - In general, the virus is sensitive to neuraminidase inhibitors (NI), although resistance may emerge during treatment.
  - Humans have very little or no existing cross protective immunity

# Grippe A(H7N9) et Antiviraux

- Points à considérer :
  - Absence de vaccin
  - Sévérité des cas, mortalité substantielle
  - Transmission interhumaine limitée, mais potentialités de transmission
  - Sensibilité *in vitro* aux INA, inefficacité des adamantanes
  - Absence de données concernant traitement précoce par INA dans la grippe A(H7N9)
  - Mais leçons de la pandémie A(H1N1)
- Recommandations thérapeutiques (CDC)
  - Traiter le plus tôt possible par INA
  - Tous cas confirmés, probables, en investigation
  - Formes non compliquées, non sévères : oseltamivir ou zanamivir
  - Formes compliquées ou sévères : oseltamivir PO
    - Voire oseltamivir ou zanamivir IV

