Stratégies thérapeutiques en période pandémique

Benoit Guery
Maladies Infectieuses
CHRU Lille

GEIG
Groupe d'Expertise et d'Information sur la Grippe

Vendredi 27 novembre 2009
Nice

Buts de la stratégie thérapeutique

- Diminuer la morbi-mortalité liée à la grippe
  - Diminuer la transmission et protéger les individus

    → Vaccination

  - Protéger les individus à « haut risque » de complication de s'infecter, ou s'ils sont infectés de développer une forme sévère…. Entre autre….

    → Tt médicamenteux antiviral

Stratégies thérapeutiques

Antiviraux

Lesquels?

Est ce utile?

Ciblée
Epargne
Limitation exposition

Population à risque

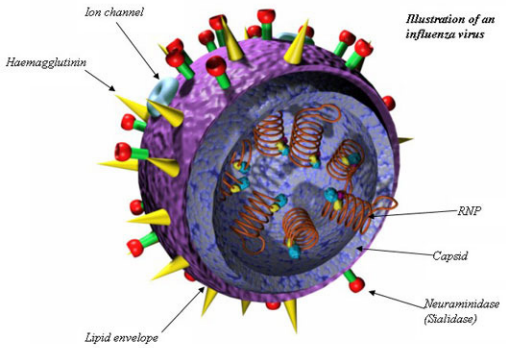
Population ILI

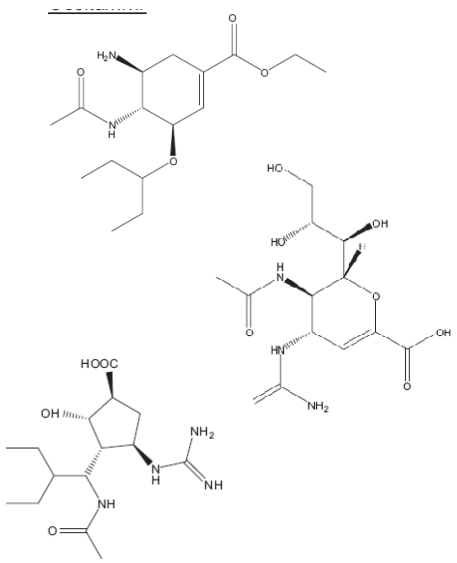
Présomptif

Diagnostic
Résistance
Effets secondaires
Cout/efficacité

Les molécules disponibles

- Adamantanes
  - Amantadine et rimantadine
  - Activité par le blocage du canal ionique M2
- Oseltamivir
  - Pro drug activée par une carboxylesterase dans le foie
  - Distribution systémique
- Zanamivir
  - 77.6% oropharynx
  - 13.2% bronches/poumons
- Peramivir
  - Quantité d'information limitées
  - Forme IV





The Emergency Use Authorization of Peramivir for Treatment of 2009 H1N1 Influenza

Debra Birnkrant, M.D., and Edward Cox, M.D., M.P.H.

Cross résistance

- Les sites de fixation des INA sont différents
  - Fixation au site catalytique (Smith et al, 2002)

- La plupart des souches résistantes à l'oseltamivir restent sensibles au zanamivir

McKimm-Breschkin et al, 2005
Mishin et al 2005

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Bénéfice d'un traitement antiviral

- Individuel
  - Réduction de la durée et de l'intensité des symptômes
  - Réduction des complications
  - Le recours précoce aux antiviraux est associé avec les formes moins graves
  - Collectif
  - Réduction de la transmission
  - Réduction des taux d'hospitalisation

Journal of Antimicrobial Chemotherapy (2003) **51**, 123–129
DOI: 10.1093/jac/dkg007

Early administration of oral oseltamivir increases the benefits of influenza treatment

F. Y. Aoki[1]*, M. D. Macleod[2], P. Paggiaro[3], O. Carewicz[4], A. El Sawy[5], C. Wat[6], M. Griffiths[6], E. Waalberg[7] and P. Ward[6] on behalf of the IMPACT Study Group†

Table 3. Duration of illness predicted by the AFT model[a] in patients treated with oseltamivir 75 mg twice daily for 5 days

	Time (h) from start of illness to treatment					
	0	6	12	24	36	48
Predicted median illness duration (h)	90.7	98.9	108	128.7	153.3	182.6
Reduction in illness duration (h)[b]	91.9	83.6	74.6	53.9	29.3	NA
(95% CI)	(78.4–107.7)	(72.2–96.8)	(65.0–85.6)	(47.2–61.5)	(25.3–33.9)	
Acceleration factor[b]	2.01	1.85	1.69	1.42	1.19	NA

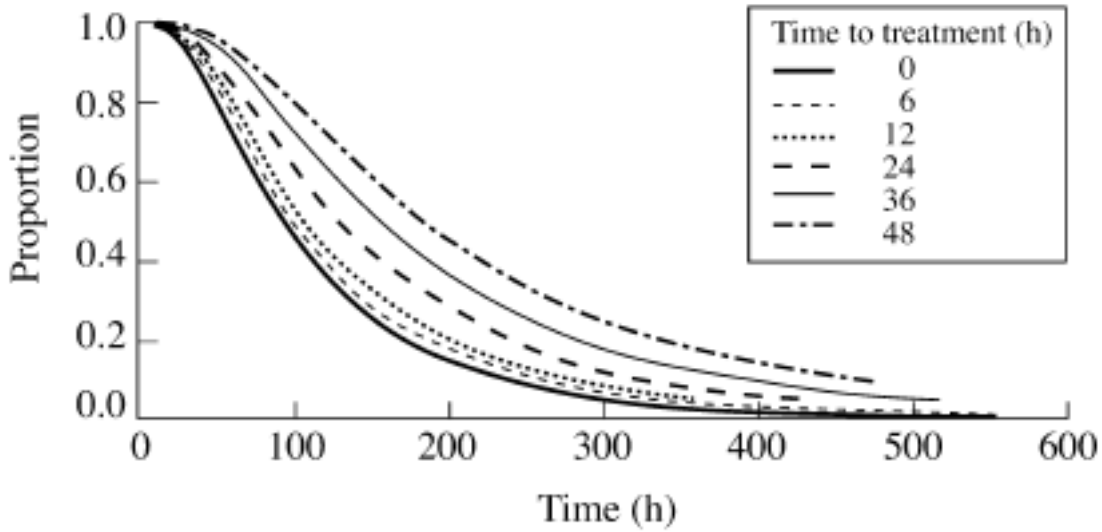

Figure 1. The duration of influenza illness is shorter the earlier that oseltamivir treatment 75 mg twice a day for 5 days is initiated (intent-to-treat infected population).

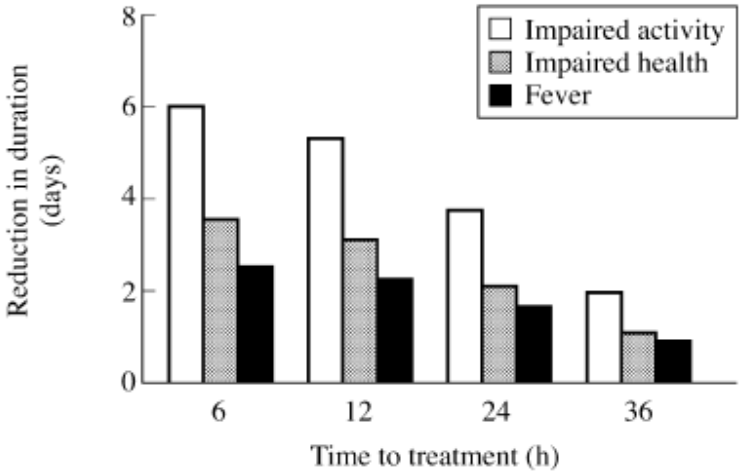

Figure 4. The median reduction in days of impaired activity and health and duration of fever with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h (intent-to-treat infected population).

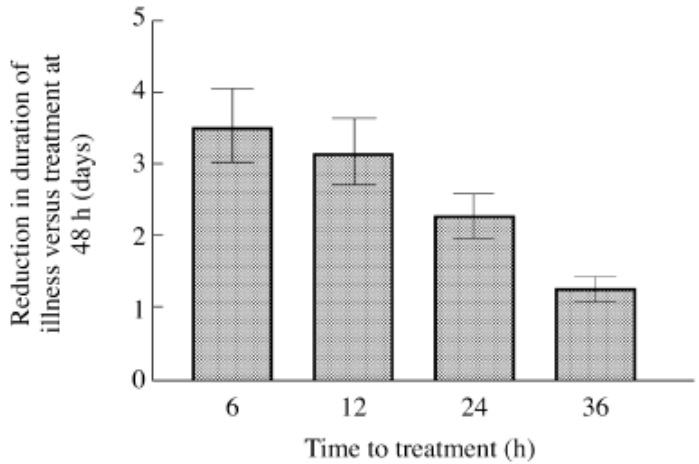

Figure 2. The reduction in days of illness duration with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h (intent-to-treat infected population). The data are median and 95% CI.

Prescription of anti-influenza drugs for healthy adults: a systematic review and meta-analysis

Jane Burch, Mark Corbett, Christian Stock, Karl Nicholson, Alex J Elliot, Steven Duffy, Marie Westwood, Stephen Palmer, Lesley Stewart

Study or subgroup	Zanamivir Median	Zanamivir SD	Total	Placebo Median	Placebo SD	Total	Weight (%)	Median difference (95% CI)
Boivin 2000[9]	5	3·67	363	5	5·14	305	24·3	0·00 (–0·69 to 0·69)
GlaxoSmithKline NAI30011[5]	4·5	5·21	229	4·5	3·88	237	20·0	0·00 (–0·84 to 0·84)
Hayden 1997[11]	3·5	3·22	132	4·5	3·36	144	21·6	–1·00 (–1·78 to –0·22)
Makela 2000[12]	5	4·44	161	6·5	7·79	163	10·2	–1·50 (–2·88 to –0·12)
MIST 1998[14]	5	4·82	190	6	4·54	189	17·3	–1·00 (–1·94 to –0·06)
Puhakka 2003[20]	2·2	15·23	293	2·7	4·02	295	6·5	–0·50 (–2·30 to 1·30)
Total (95% CI)			**1368**			**1333**	**100·0%**	**–0·57 (–1·07 to –0·08)**

Heterogeneity: τ^2=0·14; χ^2=8·08, df=5 (p=0·15); I^2=38%
Test for overall effect: Z=2·26 (p=0·02)

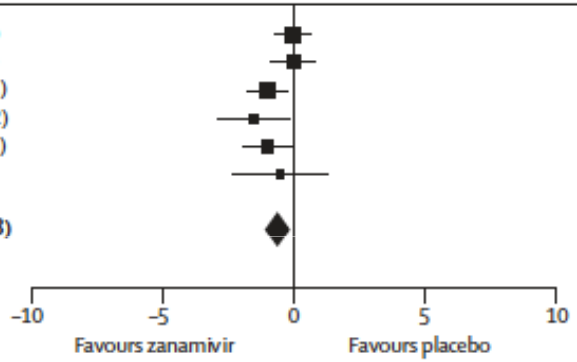

Figure 1: **Median number of days to symptom alleviation in the ITT population of healthy adults treated with zanamivir or placebo**

Study or subgroup	Oseltamivir Median	Oseltamivir SD	Total	Placebo Median	Placebo SD	Total	Weight (%)	Median difference (95% CI)
Li 2003[26]	83·5	80·39	216	87·7	78·79	235	44·9	–4·20 (–18·91 to 10·51)
Nicholson 2000[27]	97·6	154·95	243	116·1	117·46	239	16·2	–18·50 (–43·02 to 6·02)
Roche WV15730[5]	74·5	45·66	31	109·8	162·12	27	2·4	–35·30 (–98·53 to 27·93)
Treanor 2000[29]	76·3	93·15	210	97	76·52	209	36·5	–20·70 (–37·02 to –4·38)
Total (95% CI)			**700**			**710**	**100·0%**	**–13·29 (–23·15 to –3·43)**

Heterogeneity: χ^2=2·90, df=3 (p=0·41); I^2=0%
Test for overall effect: Z=2·64 (p=0·008)

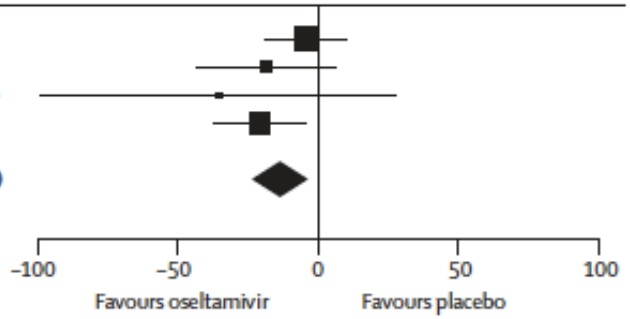

Figure 2: **Median number of hours to symptom alleviation in the ITT population of healthy adults treated with oseltamivir or placebo**

Study or subgroup	Oseltamivir Events	Oseltamivir Total	Placebo Events	Placebo Total	Weight (%)	Odds ratios (95% CI)
Overall complications						
Treanor 2000[29]	18	210	28	209	100·0	0·61 (0·32 to 1·13)
Subtotal (95% CI)		**210**		**209**	**100·0**	**0·61 (0·32 to 1·13)**
Total events	**18**		**28**			
Heterogeneity: Not applicable						
Test for overall effect: Z=1·57 (p=0·12)						
Complications requiring hospitalisation						
Deng 2004[33]	5	599	3	577	46·3	1·61 (0·38 to 6·77)
Nicholson 2000[7]	1	241	1	235	15·4	0·97 (0·06 to 15·68)
Treanor 2000[29]	0	210	2	209	38·2	0·20 (0·01 to 4·13)
Subtotal (95% CI)		**1050**		**1021**	**100·0**	**0·97 (0·33 to 2·90)**
Total events	**6**		**6**			
Heterogeneity: χ^2=1·53, df=2 (p=0·47); I^2=0%						
Test for overall effect: Z=0·05 (p=0·96)						
Pneumonia						
Kashiwagi 2000[32]	0	154	1	159	49·3	0·34 (0·01 to 8·46)
Nicholson 2000[7]	0	241	1	235	50·7	0·32 (0·01 to 7·99)
Subtotal (95% CI)		**395**		**394**	**100·0**	**0·33 (0·03 to 3·21)**
Total events	**0**		**2**			
Heterogeneity: χ^2=0·00, df=1 (p=0·98); I^2=0%						
Test for overall effect: Z=0·95 (p=0·34)						
Antibiotic use						
Deng 2004[33]	129	599	248	577	95·3	0·36 (0·28 to 0·47)
Nicholson 2000[7]	6	241	10	235	4·7	0·57 (0·21 to 1·61)
Subtotal (95% CI)		**840**		**812**	**100·0**	**0·37 (0·29 to 0·48)**
Total events	**135**		**258**			
Heterogeneity: χ^2=0·71, df=1 (p=0·40); I^2=0%						
Test for overall effect: Z=7·78 (p<0·00001)						

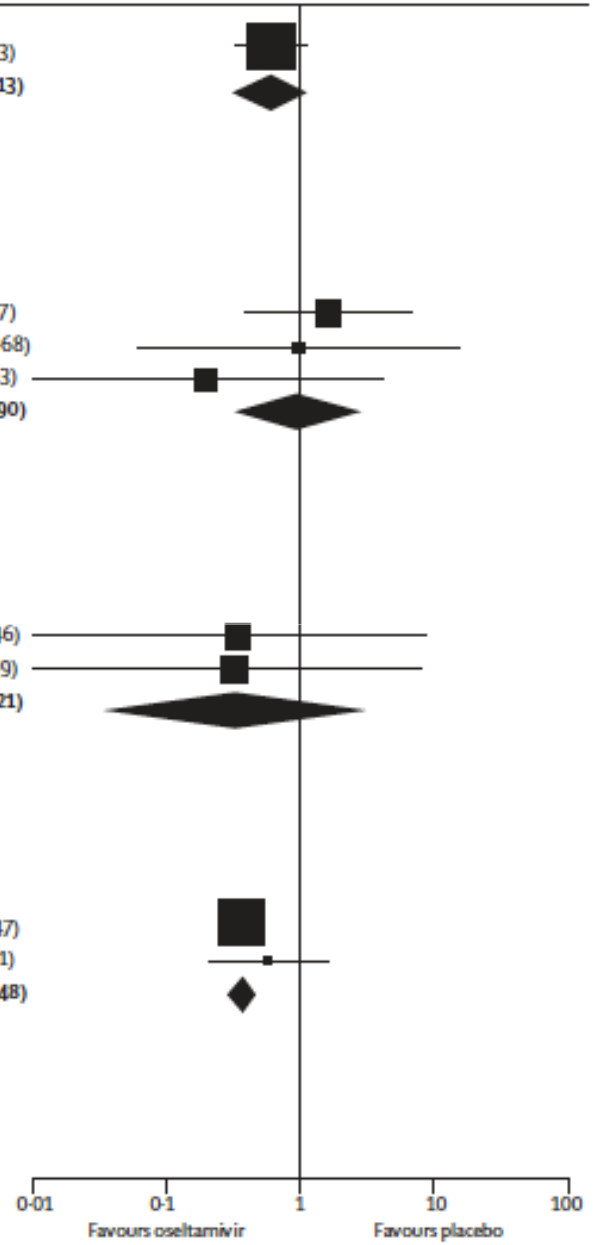

Figure 4: Complications in the ITT population of healthy adults treated with oseltamivir or placebo

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Original Contribution

Antiviral Effects on Influenza Viral Transmission and Pathogenicity: Observations from Household-based Trials

M. Elizabeth Halloran[1,2], Frederick G. Hayden[3], Yang Yang[1], Ira M. Longini, Jr.[1,2], and Arnold S. Monto[4]

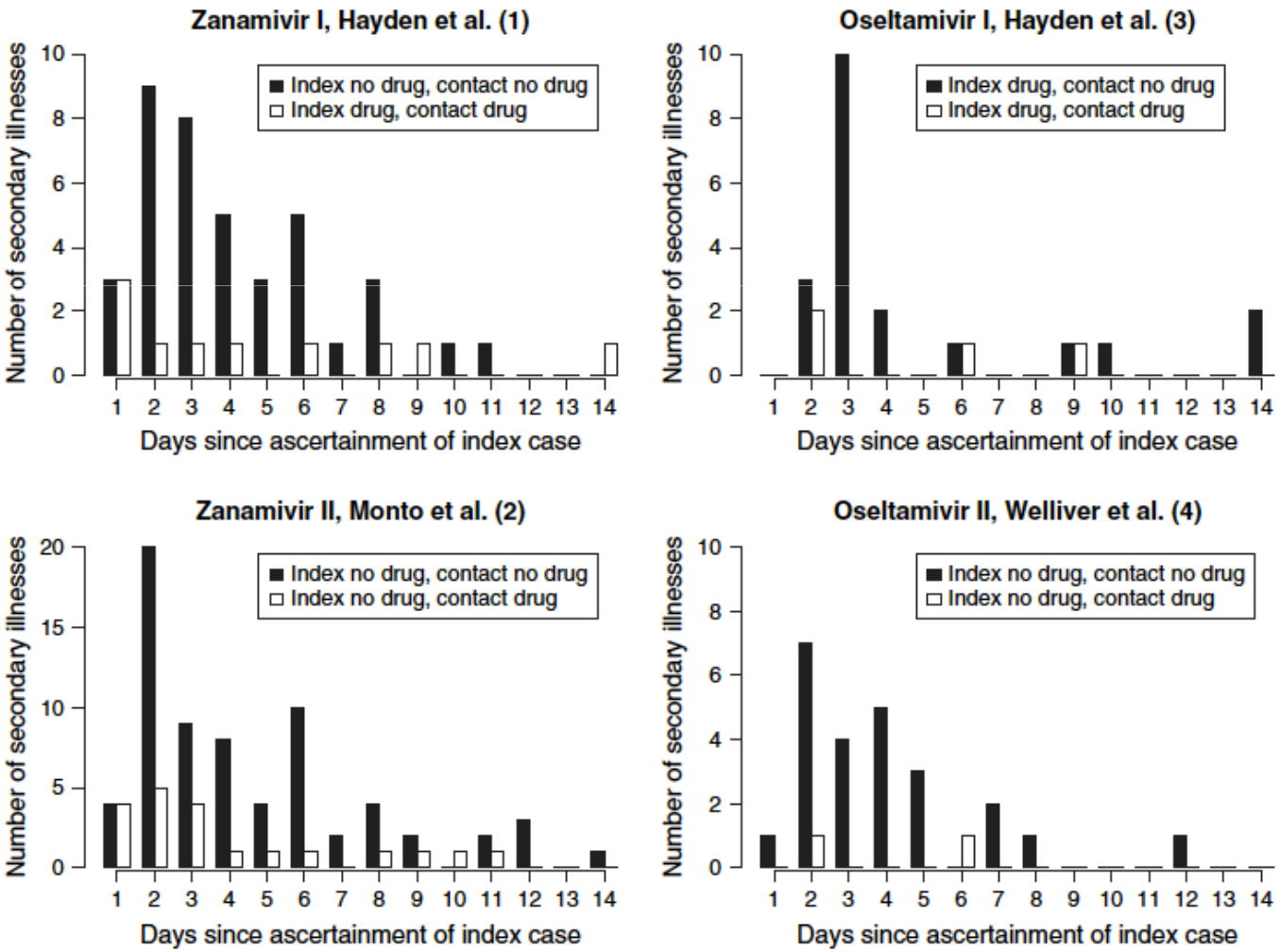

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TABLE 6. Estimates of pathogenicity, *P*, and the efficacy of antiviral prophylaxis to reduce pathogenicity, AVE_P, in the four studies*,†,‡

	Pathogenicity						Efficacy	
	Control			Drug				
	No.¶	*P* (%)	95% CI	No.¶	*P* (%)	95% CI	AVE_P (%)	95% CI§
Zanamivir studies								
Zan I, Hayden et al. (1)	40/66	66	48, 72	7/26	27	13, 47	56	14, 77
Zan II, Monto et al. (2)	55/105	52	43, 62	12/48	25	15, 39	52	19, 72
Oseltamivir studies								
Osel I, Hayden et al. (3)#	33/75	44	33, 55	10/46	22	12, 36	56	10, 73
Osel II, Welliver et al. (4)#	34/60	57	44, 69	4/33	12	5, 28	79	45, 92

$$AVE_P = 1 - \frac{\dfrac{\text{no. of symptomatic infected antiviral contacts}}{\text{no. of infected antiviral contacts}}}{\dfrac{\text{no. of symptomatic infected control contacts}}{\text{no. of infected control contacts}}}.$$

ORIGINAL INVESTIGATION

Impact of Oseltamivir Treatment on Influenza-Related Lower Respiratory Tract Complications and Hospitalizations

Laurent Kaiser, MD; Cynthia Wat, MBBS, MRCP; Tracy Mills, MSc; Paul Mahoney, MSc; Penelope Ward, MBBS; Frederick Hayden, MD

Table 3. Lower Respiratory Tract Complications (LRTCs) Leading to Antibiotic Use in Influenza-Infected and Uninfected Subjects With Influenzalike Illness

	Confirmed Influenza Illness						Influenza Uninfected			
	Overall		Otherwise Healthy (Age 13-65 y)		At Risk		Otherwise Healthy (Age 13-65 y)		At Risk	
LRTCs Leading to Antibiotic Use	Placebo (n = 1063)	Oseltamivir (n = 1350)	Placebo (n = 662)	Oseltamivir (n = 982)	Placebo (n = 401)	Oseltamivir (n = 368)	Placebo (n = 278)	Oseltamivir (n = 436)	Placebo (n = 200)	Oseltamivir (n = 237)
All LRTCs, No. (%)	109 (10.3)	62 (4.6)*	35 (5.3)	17 (1.7)*	74 (18.5)†	45 (12.2)‡	11 (4.0)	12 (2.8)	21 (10.5)	24 (10.1)
Bronchitis, No. (%)	87 (8.2)	53 (3.9)	25 (3.8)	15 (1.5)	62 (15.5)	38 (10.3)	8 (2.9)	11 (2.5)	13 (6.5)	19 (8.0)
Unspecified LRTCs, No. (%)	4 (0.4)	1 (0.1)	1 (0.2)	0	3 (0.7)	1 (0.3)	0	0	2 (1.0)	2 (0.8)
Pneumonia, No. (%)	19 (1.8)	9 (0.7)	9 (1.4)	2 (0.2)	10 (2.5)	7 (1.9)	3 (1.1)	1 (0.2)	6 (3.0)	3 (1.3)
Influenza A, No./total infected (%)	99/945 (10.5)	55/1168 (4.7)	31/579 (5.4)	15/840 (2.0)	68/366 (18.6)	40/328 (12.2)				
Influenza B, No./total infected (%)	10/112 (8.9)	7/172 (4.1)	4/77 (5.2)	2/133 (1.5)	6/35 (17.1)	5/39 (12.8)				

Arch Intern Med. 2003;163:1667-1672

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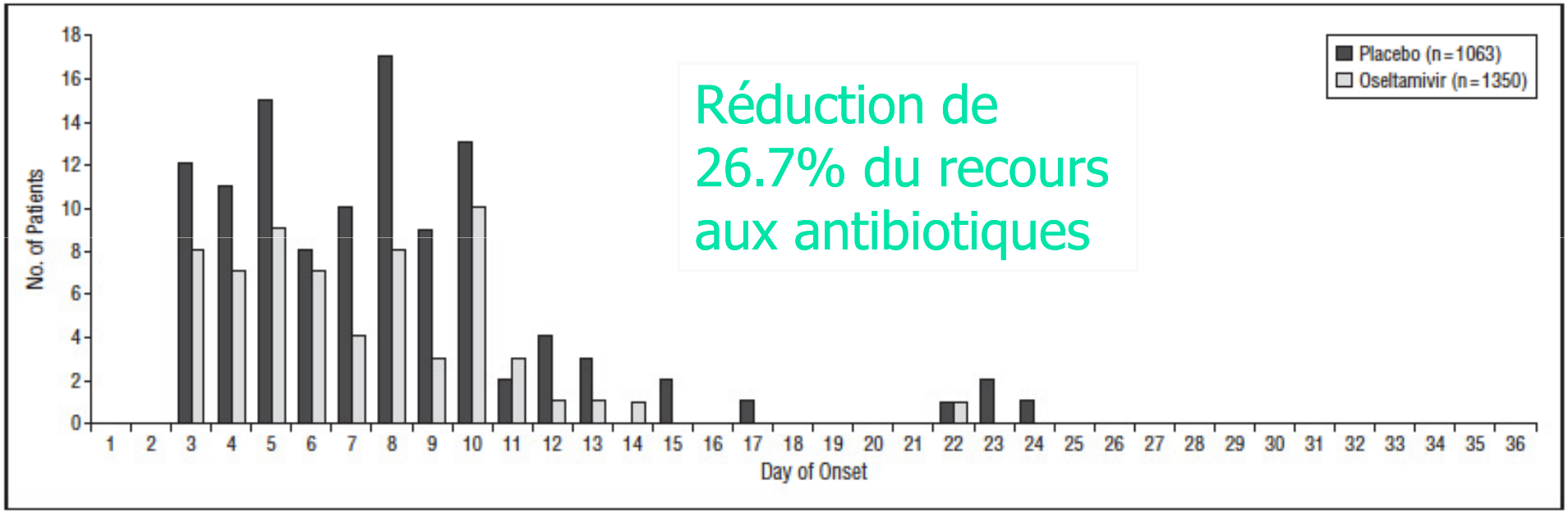

Figure 1. Day of onset of antibiotic therapy for lower respiratory tract complications in oseltamivir (75 mg twice daily) and placebo recipients with influenza infection. The analysis included prospectively specified complications (bronchitis, lower respiratory tract illness, and pneumonia) and was restricted to days 3 through 28 after enrollment. A patient is counted each time an antibiotic is taken for a new complication. Only the first of multiple antibiotics taken for a given complication is counted.

Arch Intern Med. 2003;163:1667-1672

ORIGINAL INVESTIGATION

Impact of Oseltamivir Treatment on Influenza-Related Lower Respiratory Tract Complications and Hospitalizations

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Table 4. Number of Hospitalizations in Influenza-Infected and Uninfected Subjects With Influenzalike Illness (ILI)

	Confirmed Influenza Illness						Influenza Uninfected			
	Overall		Otherwise Healthy (Age 13-65 y)		At Risk		Otherwise Healthy (Age 13-65 y)		At Risk	
Hospitalizations	Placebo (n = 1063)	Oseltamivir (n = 1350)	Placebo (n = 662)	Oseltamivir (n = 982)	Placebo (n = 401)	Oseltamivir (n = 368)	Placebo (n = 278)	Oseltamivir (n = 436)	Placebo (n = 200)	Oseltamivir (n = 237)
Possibly related to ILI, No. (%)	12 (1.1)	6 (0.4)*	3 (0.5)	1 (0.1)	9 (2.2)	5 (1.4)	0	3 (0.7)	6 (3.0)	4 (1.7)
All causes of hospitalizaitons, No. (%)	18 (1.7)	9 (0.7)†	5 (0.8)	3 (0.3)	13 (3.2)	6 (1.6)‡	2 (0.7)	7 (1.6)	6 (3.0)	6 (3.0)

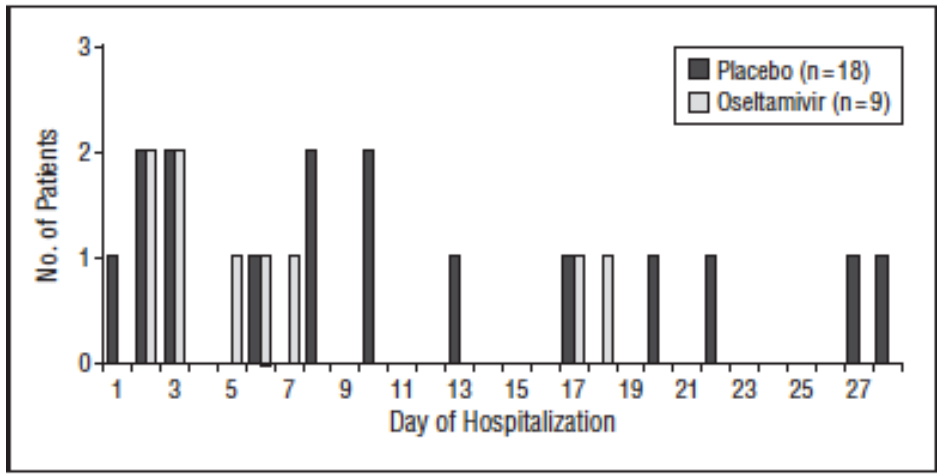

Figure 2. Day of hospitalization among placebo- or oseltamivir (75 mg twice daily)-treated adults with influenza infection.

Arch Intern Med. 2003;163:1667-1672

Stratégies thérapeutiques

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Population ILI

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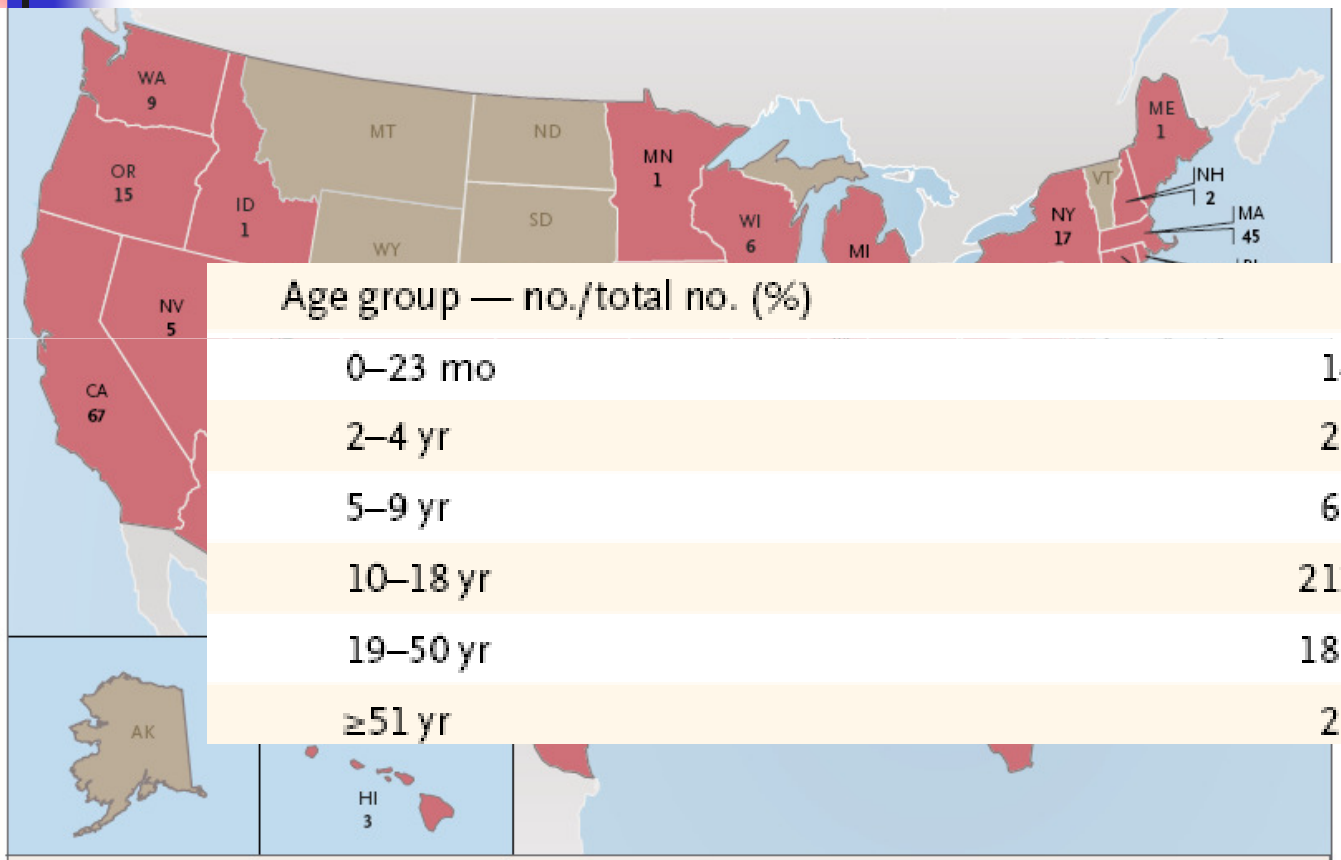
Cout/efficacité

Emergence of a Novel Swine-Origin Influenza A (H1N1) Virus in Humans

Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team*



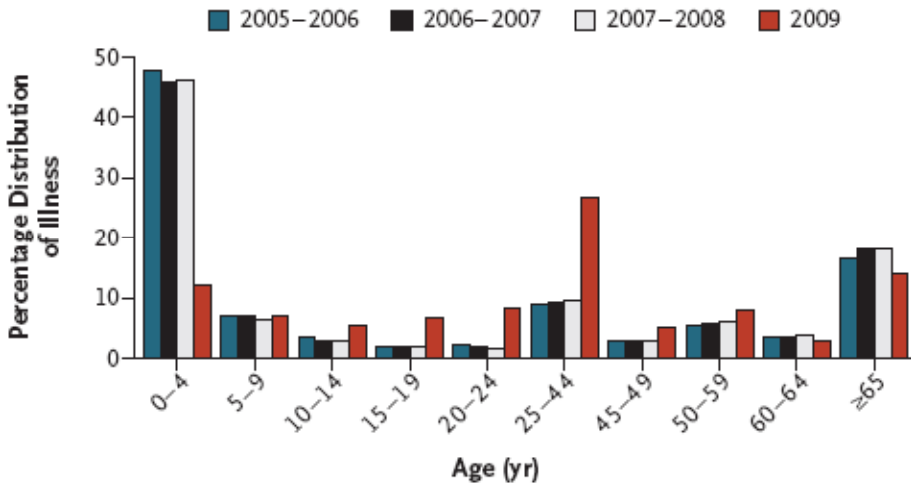
Age group — no./total no. (%)	
0–23 mo	14/532 (3)
2–4 yr	27/532 (5)
5–9 yr	65/532 (12)
10–18 yr	212/532 (40)
19–50 yr	187/532 (35)
≥51 yr	27/532 (5)

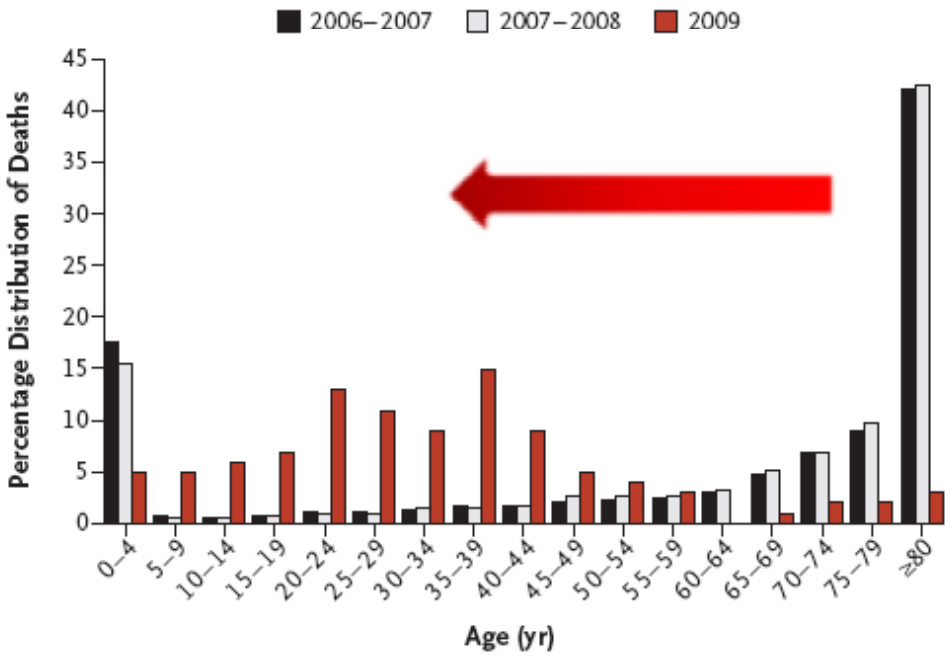
Figure 2. Distribution of 642 Confirmed Cases of Human Infection with Swine-Origin Influenza A (H1N1) Virus in the United States (May 5, 2009).

Severe Respiratory Disease Concurrent with the Circulation of H1N1 Influenza

Gerardo Chowell, Ph.D., Stefano M. Bertozzi, M.D., Ph.D.,
M. Arantxa Colchero, Ph.D., Hugo Lopez-Gatell, M.D., Ph.D.,
Celia Alpuche-Aranda, M.D., Ph.D., Mauricio Hernandez, M.D., Ph.D.,
and Mark A. Miller, M.D.

2155 cases of severe pneumonia, involving 821 hospitalizations and 100 deaths





N ENGL J MED 361;7 NEJM.ORG AUGUST 13, 2009

Research

Open Access

Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain

Jordi Rello[1], Alejandro Rodríguez[1], Pedro Ibañez[2], Lorenzo Socias[2], Javier Cebrian[3], Asunción Marques[4], José Guerrero[5], Sergio Ruiz-Santana[6], Enrique Marquez[7], Frutos Del Nogal-Saez[8], Francisco Alvarez-Lerma[9], Sergio Martínez[10], Miquel Ferrer[11], Manuel Avellanas[12], Rosa Granada[13], Enrique Maraví-Poma[14], Patricia Albert[15], Rafael Sierra[16], Loreto Vidaur[17], Patricia Ortiz[18], Isidro Prieto del Portillo[19], Beatriz Galván[20], Cristóbal León-Gil[21] for the H1N1 SEMICYUC working group

- 32 cas en 5 semaines (06-07/09).
- Age médian: 36 ans.
- Pneumonie virale:
  - 96,3% des cas.
- Délai traitement par Tamiflu® : 2-8 jours.
- 8 décès (25%).

Facteur de risque	Cas (n = 32)
Obésité	10
BMI > 40 / BMI 30/40	4 / 6
Asthme	5
BPCO	4
Grossesse	2
Insuffisance cardiaque	1
HTA	1
Diabète	1
VIH	1
Maladie neuro-musculaire	1
Hémopathie	1
Aucun	15

Critical Care 2009, **13**:R148

Pneumonia and Respiratory Failure from Swine-Origin Influenza A (H1N1) in Mexico

Rogelio Perez-Padilla, M.D., Daniela de la Rosa-Zamboni, M.D., Samuel Ponce de Leon, M.D., Mauricio Hernandez, M.D., Francisco Quiñones-Falconi, M.D., Edgar Bautista, M.D., Alejandra Ramirez-Venegas, M.D., Jorge Rojas-Serrano, M.D., Christopher E. Ormsby, M.Sc., Ariel Corrales, M.D., Anjarath Higuera, M.D., Edgar Mondragon, M.D., and Jose Angel Cordova-Villalobos, M.D., for the INER Working Group on Influenza*

Table 2. Survival and Death among the 18 Study Patients Who Had Confirmed Infection with Novel Swine-Origin Influenza A (H1N1) Virus.*

Variable at Admission	Patients Who Survived (N=11)	Patients Who Died (N=7)	Hazard Ratio or Odds Ratio for Death (95% CI)	P Value
Age — yr				0.81
Median	37	45	1.00	
Range	0.75–61	9–52	0.96–1.04	
Male sex — no./total no.	4/11	5/7	2.2 (0.4–11.5)	0.34
Hypotension that did not resolve after fluid administration — no./total no.	2/11	7/7		0.02
Orotracheal intubation required within first 24 hr after admission — no./total no.	3/11	7/7		0.06
Renal failure any time during follow-up — no./total no.	1/11	5/7	25 (1.3–1295)	0.01
Coexisting condition — no./total no.†	5/11	3/7	0.78 (0.2–3.6)	0.75

N Engl J Med 2009;361:680-9.

Factors Associated With Death or Hospitalization Due to Pandemic 2009 Influenza A(H1N1) Infection in California

Janice K. Louie; Meileen Acosta; Kathleen Winter; et al.

JAMA. 2009;302(17):1896-1902 (doi:10.1001/jama.2009.1583)

		Cases Aged 0-17 Years		Cases Aged ≥18 Years	
	All Cases (N = 1088)	Fatal (n = 8)	Nonfatal (n = 336)	Fatal (n = 110)	Nonfatal (n = 634)
Chronic comorbid illness associated with severe influenza[a]	741 (68)	6 (75)	199 (59)	83 (75)	453 (71)
Chronic lung disease	403 (37)	3 (38)	126 (38)	45 (41)	229 (36)
Asthma	257 (24)	1 (13)	99 (29)	18 (16)	139 (22)
Other/unknown[b]	146 (13)	2 (25)	27 (8)	27 (25)	90 (14)
Chronic cardiac disease[c]	167 (15)	2 (25)	25 (7)	25 (23)	115 (18)
Metabolic disease	223 (20)	2 (25)	23 (7)	38 (35)	160 (25)
Diabetes mellitus	116 (11)	0	4 (1)	20 (18)	92 (14)
Renal disease	72 (7)	0	8 (2)	18 (16)	46 (7)
Other/unknown[d]	59 (5)	2 (25)	11 (3)	7 (6)	39 (6)
Immunosuppressive conditions	205 (19)	3 (38)	55 (16)	36 (33)	111 (18)
Cancer/transplant/immunosuppressive drugs[e]	155 (14)	2 (25)	42 (13)	29 (26)	82 (13)
HIV/AIDS	22 (2)	0	0	4 (4)	18 (3)
Other/unknown	31 (3)	1 (13)	13 (4)	4 (4)	13 (2)
Neuromuscular disorder[f]	115 (11)	4 (50)	45 (13)	14 (13)	52 (8)
Pregnancy[g]	97/1012 (10)	0	5 (2)	6/104 (6)	86/587 (15)
Other chronic comorbid illness[a]	370 (34)	2 (25)	45 (13)	69 (63)	254 (40)
Obesity[g,h]	172/361 (48)	0	15 (19)	46/68 (66)	111/212 (52)
BMI 30-34.9	55 (35)			11 (24)	44 (40)
BMI 35-39.9	34 (22)			12 (26)	22 (20)
BMI ≥40	67 (43)			23 (50)	44 (40)
Gastrointestinal tract	109 (10)	2 (25)	29 (9)	12 (11)	66 (10)
GERD	34 (3)	1 (13)	5 (2)	4 (4)	24 (4)
Other/unknown[i]	75 (7)	1 (13)	24 (7)	8 (7)	42 (7)
Hyperlipidemia	33 (3)	0	0	2 (2)	31 (5)
Hypertension	176 (16)	0	2 (<1)	27 (25)	147 (23)

Hospitalized Patients with 2009 H1N1 Influenza in the United States, April–June 2009

Seema Jain, M.D., Laurie Kamimoto, M.D., M.P.H., Anna M. Bramley, M.P.H., Ann M. Schmitz, D.V.M., Stephen R. Benoit, M.D., M.P.H., Janice Louie, M.D., M.P.H., David E. Sugerman, M.D., M.P.H., Jean K. Druckenmiller, B.S., S.M.(N.R.M.), Kathleen A. Ritger, M.D., M.P.H., Rashmi Chugh, M.D., M.P.H., Supriya Jasuja, M.D., M.P.H., Meredith Deutscher, M.D., Sanny Chen, Ph.D., M.H.S., John D. Walker, M.D., Jeffrey S. Duchin, M.D., Susan Lett, M.D., M.P.H., Susan Soliva, M.P.H., Eden V. Wells, M.D., M.P.H., David Swerdlow, M.D., Timothy M. Uyeki, M.D., M.P.H., Anthony E. Fiore, M.D., M.P.H., Sonja J. Olsen, Ph.D., Alicia M. Fry, M.D., M.P.H., Carolyn B. Bridges, M.D., Lyn Finelli, Dr.P.H., for the 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team*

Table 1. Characteristics of 272 Hospitalized Patients Who Were Infected with the 2009 H1N1 Virus in the United States (April–June 2009).

Characteristic	No. (%)
Female sex	132 (49)
Age group*	
0–23 mo	23 (8)
2–4 yr	20 (7)
5–9 yr	29 (11)
10–17 yr	50 (18)
18–49 yr	104 (38)
50–64 yr	32 (12)
≥65 yr	14 (5)

N Engl J Med 2009;361.

Hospitalized Patients with 2009 H1N1 Influenza in the United States, April–June 2009

Seema Jain, M.D., Laurie Kamimoto, M.D., M.P.H., Anna M. Bramley, M.P.H., Ann M. Schmitz, D.V.M., Stephen R. Benoit, M.D., M.P.H., Janice Louie, M.D., M.P.H., David E. Sugerman, M.D., M.P.H., Jean K. Druckenmiller, B.S., S.M.(N.R.M.), Kathleen A. Ritger, M.D., M.P.H., Rashmi Chugh, M.D., M.P.H., Supriya Jasuja, M.D., M.P.H., Meredith Deutscher, M.D., Sanny Chen, Ph.D., M.H.S., John D. Walker, M.D., Jeffrey S. Duchin, M.D., Susan Lett, M.D., M.P.H., Susan Soliva, M.P.H., Eden V. Wells, M.D., M.P.H., David Swerdlow, M.D., Timothy M. Uyeki, M.D., M.P.H., Anthony E. Fiore, M.D., M.P.H., Sonja J. Olsen, Ph.D., Alicia M. Fry, M.D., M.P.H., Carolyn B. Bridges, M.D., Lyn Finelli, Dr.P.H., for the 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team*

Table 4. Characteristics of Hospitalized Patients Who Were Not Admitted to an Intensive Care Unit (ICU) and Survived and Patients Who Were Admitted to an ICU or Died.*

Characteristic	Patients Who Were Not Admitted to an ICU and Survived (N=205)	Patients Who Were Admitted to an ICU or Died (N=67)
Age		
Median — yr (range)	19 (21–80)	29 (1–86)
<18 Yr — no. (%)	98 (48)	24 (36)
Shortness of breath — no. (%)	104 (51)	58 (87)
Neurocognitive disorder — no. (%)	11 (5)	9 (13)
Neuromuscular disorder — no. (%)	10 (5)	9 (13)
Pneumonia seen on chest radiography on admission — no./total no. (%)	51/182 (28)	49/67 (73)
Antiviral treatment — no./total no. (%)		
Any — no./total no. (%)	144/203 (71)	56/65 (86)
≤2 Days after onset of symptoms — no./total no. (%)	62/139 (45)	13/56 (23)
Days from onset of symptoms to initiation — no. (range)	3 (0–29)	5 (0–24)
Antibiotic treatment — no./total no. (%)	144/195 (74)	62/65 (95)
Corticosteroid treatment — no./total no. (%)	57/183 (31)	29/56 (52)

N Engl J Med 2009;361.

Stratégies thérapeutiques

Antiviraux

Lesquels?

Est ce utile?

Ciblée
Epargne
Limitation exposition

Population à risque

Population ILI

Présomptif

Diagnostic
Résistance
Effets secondaires
Cout/efficacité

Distribution large ou confidentielle

- Comparaison Chili et Argentine
  - Chili
    - Usage intensif des antiviraux (4Tt/100 personnes)
    - Mortalité: 0.8/100 000 hbts
  - Argentine
    - Réservé aux hospitalisés puis élargissement secondaire
    - Mortalité: 1.44/100 000 hbts
  - Nombreux biais
    - Recueil de l'information
- Femmes enceintes Argentine
  - Avant élargissement: 31/174 décès (17.8%)
  - Après: 4/69 (5.8%)

Population à risque

- 8 septembre: CDC encourage le traitement des individus à haut risque
- Les patients présentant un tableau sans complications ne nécessitent pas de traitement

- Perte de chance des individus à faible risque ?

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RRN Home
About RRN
PLoS Currents Influenza

PLoS Currents Influenza. 2009 Oct 28:RRN1121.
See full citation
RRNID: RRN1121.1

Targeted vs. systematic early antiviral treatment against A(H1N1)v influenza with neuraminidase inhibitors in patients with influenza-like symptoms: Clinical and economic impact

Sylvie Deuffic-Burban,* Xavier Lenne,† Benoit Dervaux,* Julien Poissy, Xavier Lemaire, Caroline Sloan,* Fabrice Carrat, Jean-Claude Desenclos,†† Jean-Francois Delfraissy, and Yazdan Yazdanpanah

- Modélisation comparant 2 stratégies
  - Traitement de groupes à risques
  - Traitement de tout syndrome grippal
- Evaluation sur une cohorte de 64.300.000 personnes
  - Mortalité
  - Hospitalisation
  - Admission ICU
  - Coût, coût/efficacité

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- Résultats
  - Réduction de l'hospitalisation (2121)
  - Réduction du nombre d'hospitalisation en réanimation (249)
  - Réduction du nombre de décès (35)

  - Rapport cout efficacité: 4.100€/année de vie gagnée

Stratégies thérapeutiques

Antiviraux

Lesquels?

Est ce utile?

Ciblée
Epargne
Limitation exposition

Population à risque

Population ILI

Présomptif

Diagnostic
Résistance
Effets secondaires
Cout/efficacité

Predispensing of Antivirals to High-Risk Individuals in an Influenza Pandemic

- Schéma envisageable si la population cible ou en demande est inférieure au stock disponible
- Valable uniquement pour les pays les plus riches
- Pouvant être envisagé pour une population à risque (limiter le nombre de formes graves)
- Population à risque
  - Femmes enceintes
  - Obésité
  - Imunodéprimés

PLoS Currents: Influenza

Predispensing of Antivirals to High-Risk Individuals in an Influenza Pandemic

- La prédispensiation est, pour chacun de ces groupes, un bénéfice quelque soit le stock d'antiviraux disponible.
- Intérêt de la discussion de ce type de mesure en contexte pandémique

PLoS Currents: Influenza

Les limitations du présomptif large, de la prédispensiation

- Problème du diagnostic différentiel…

ELSEVIER MASSON

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Médecine et maladies infectieuses

Médecine et maladies infectieuses 39 (2009) 667–673

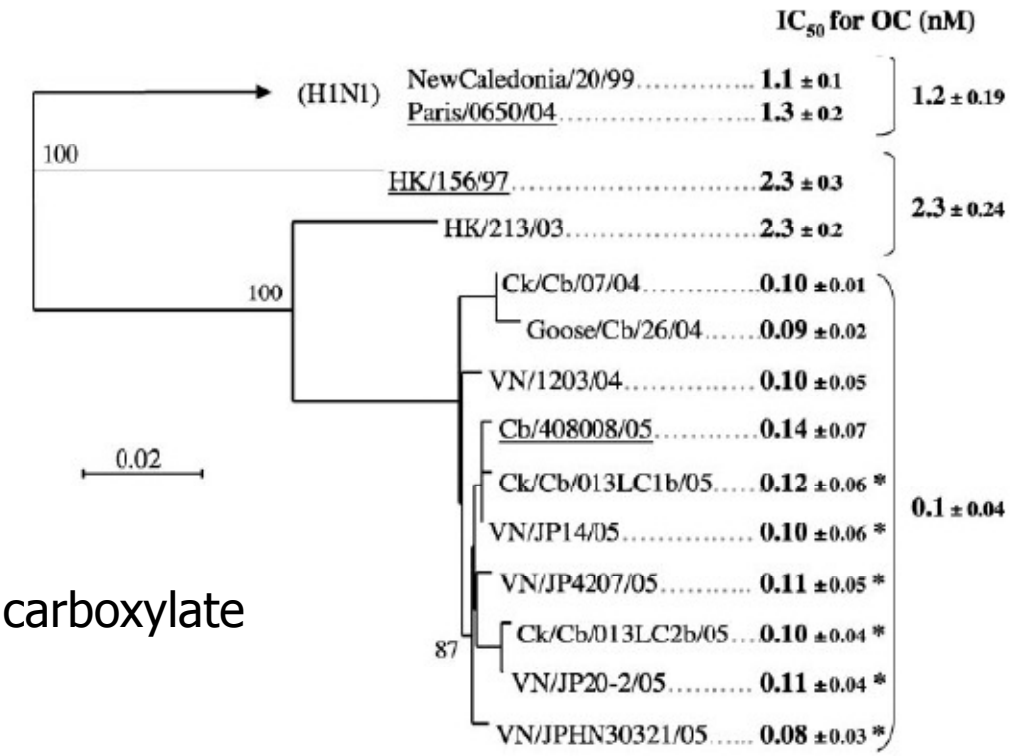
Éditorial

Les antiviraux de la grippe servent-ils à quelque chose ?

Do we really need antiflu virus medication?

- Mais cela reste vrai à toutes les étapes de la prise en charge de masse….

Variations naturelles de résistance



OC: oseltamivir carboxylate

Relevance clinique?

Rameix-Welti et al, AAC 2006

Region	Cumulative total as of 15 November 2009	
	Cases*	Deaths
WHO Regional Office for Africa (AFRO)	14950	103
WHO Regional Office for the Americas (AMRO) **	190765	4806
WHO Regional Office for the Eastern Mediterranean (EMRO)	28751	188
WHO Regional Office for Europe (EURO)**	over 79000	at least 350
WHO Regional Office for South-East Asia (SEARO)	45844	710
WHO Regional Office for the Western Pacific (WPRO)	166750	613
Total	over 526060	at least 6770

Résistance

- Faible niveau aux US, UK (usage intensif)
  - 0.17 à 0.5%

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Antiviral Resistance and the Control of Pandemic Influenza

Marc Lipsitch[1,2*], Ted Cohen[1,3], Megan Murray[1,3,4], Bruce R. Levin[5]

- Si la pandémie est avancée et même si l'utilisation est importante, la probabilité de voie émerger la résistance à haute fréquence est peu probable avant la fin de la vague
  - 1/50 000 traité 1/500 000 proph: prévalence de 10% de souches R en fin de pandémie
  - Mais coût en fitness? Mesures associées… autorisant la vaccination….

January 2007 | Volume 4 | Issue 1 |

Oseltamivir-Resistant Influenza A Pandemic (H1N1) 2009 Virus, Hong Kong, China

Honglin Chen, Chung Lam Cheung, Hung Tai, Pengxi Zhao, Jasper F.W. Chan, Vincent C.C. Cheng, Kwok-Hung Chan, and Kwok-Yung Yuen

Table. Quasi-species of 274H and 274 Y pandemic (H1N1) 2009 virus from NPA samples and subsequent virus isolate A/Hong Kong/2369/2009 from MDCK cells conferring resistance to oseltamivir, Hong Kong, China*

Sample	274H, no. samples positive/no. tested (%)	274Y, no. samples positive/no. tested (%)	IC_{50} for oseltamivir, nM	IC_{50} for zanamivir, nM
NPA	45/95 (47.37)	50/95 (52.63)	ND	ND
MDCK cell culture	2/96 (2.08)	94/96 (97.92)	197.5	0.8

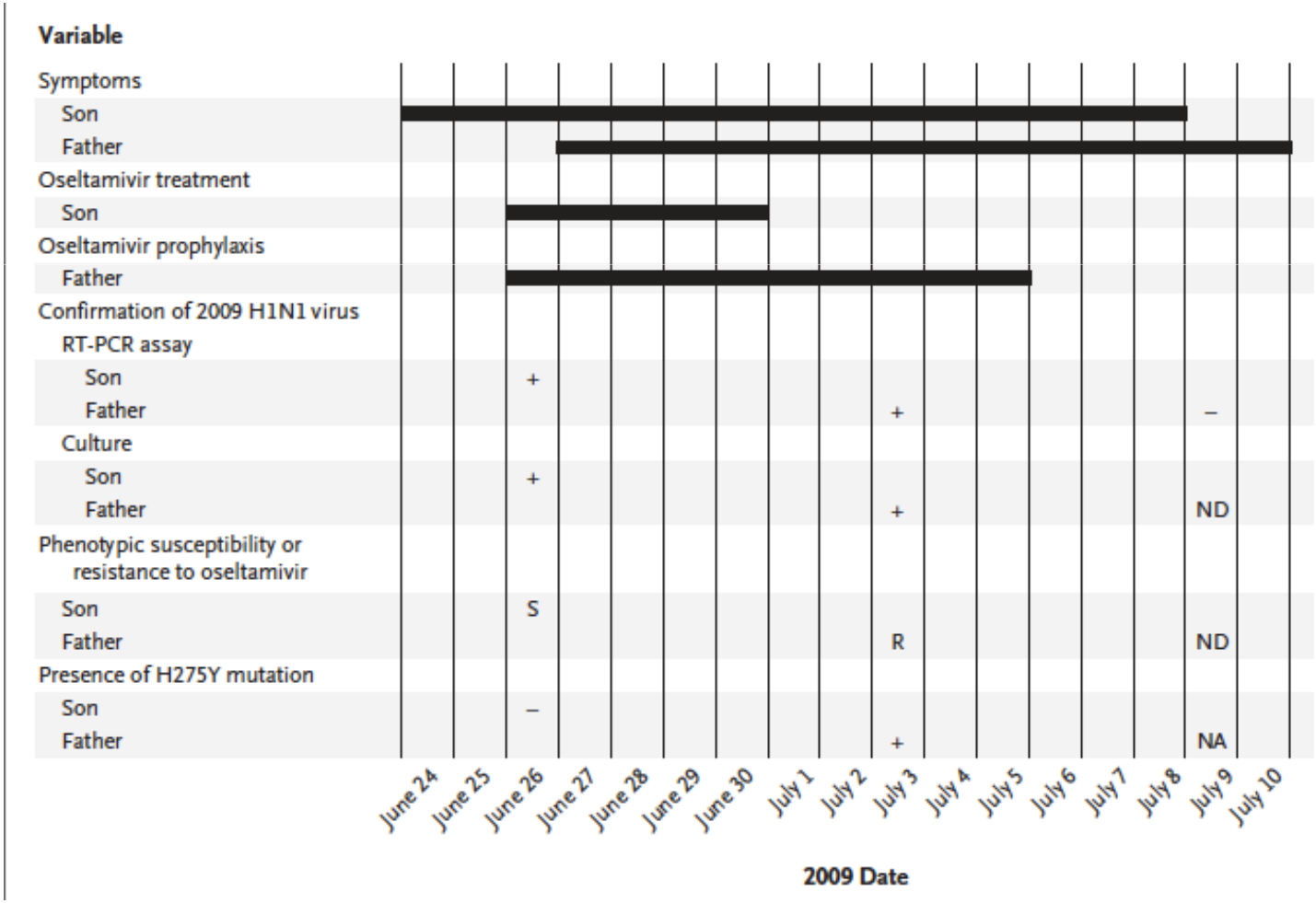
China. Emerg Infect Dis. 2009 Dec

- Sporadic incidents of H1N1 pandemic viruses that show resistance to the antiviral oseltamivir.
- To date, 57 oseltamivir resistant pandemic H1N1 influenza viruses have been detected.
- All of these viruses show the same H275Y mutation.
- All these viruses remain sensitive to zanamivir.
- Worldwide, more than 10,000 clinical specimens (samples and isolates) of the pandemic H1N1 virus have been tested and found to be sensitive to oseltamivir.

WHO update 75, 20 Novembre

Mariana Baz, M.Sc.
Yacine Abed, Ph.D.
Jesse Papenburg, M.D.
Xavier Bouhy, B.Sc.
Marie-Ève Hamelin, Ph.D.
Guy Boivin, M.D.

Emergence of Oseltamivir-Resistant Pandemic H1N1 Virus during Prophylaxis



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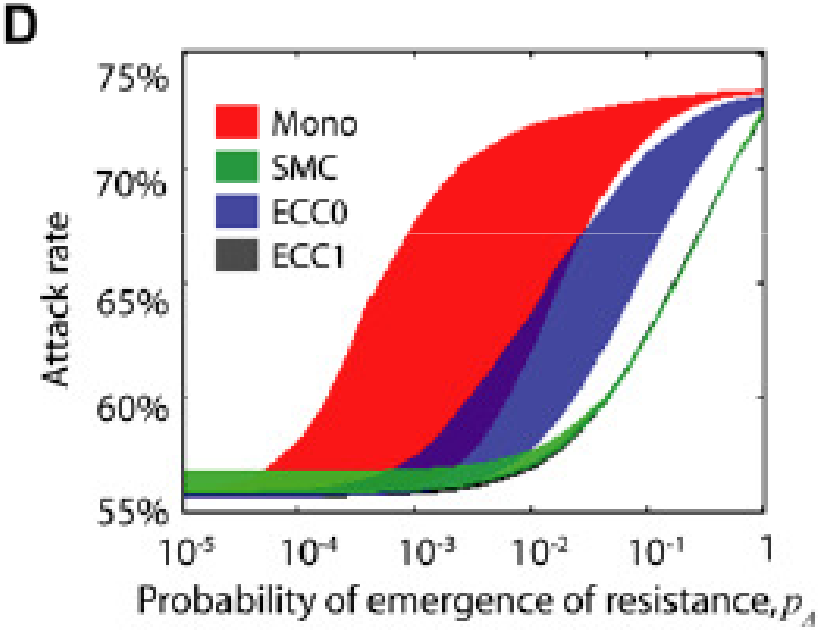
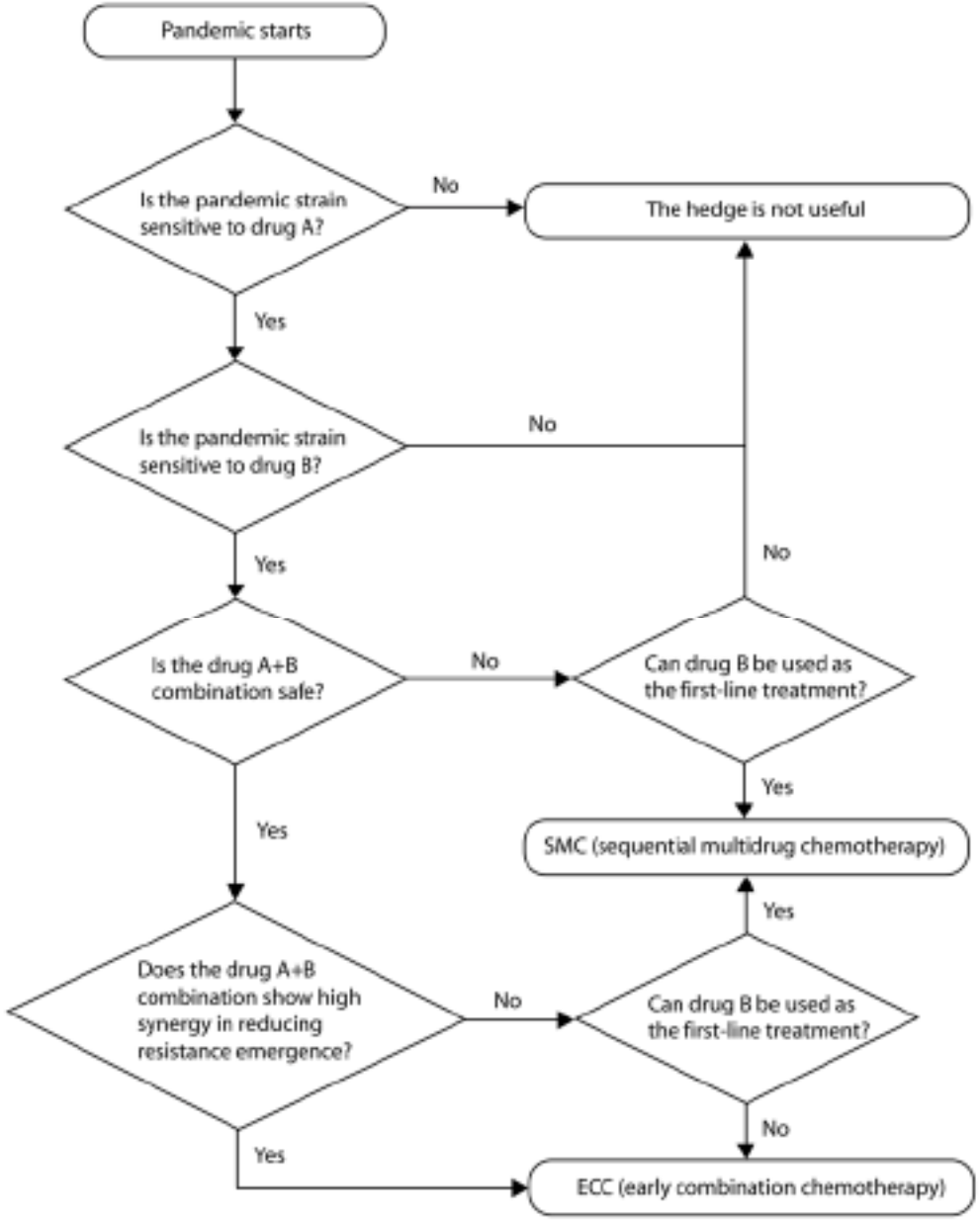
Hedging against Antiviral Resistance during the Next Influenza Pandemic Using Small Stockpiles of an Alternative Chemotherapy

Joseph T. Wu[1]*, Gabriel M. Leung[1], Marc Lipsitch[2], Ben S. Cooper[3], Steven Riley[1]

L'extension de la résistance peut être réduite par l'utilisation d'un stock alternatif (1% de la population) d'une seconde drogue à la phase précoce de l'épidémie

Mono: Monothérapie
SMC: utilisation de la drogue de seconde ligne jusqu'à « épuisement »… puis 1ere ligne
ECC: combinaison des deux initiale




Pandemic starts
Is the pandemic strain sensitive to drug A?
No
The hedge is not useful
Yes
Is the pandemic strain sensitive to drug B?
No
Yes
No
Is the drug A+B combination safe?
No
Can drug B be used as the first-line treatment?
Yes
Yes
SMC (sequential multidrug chemotherapy)
Yes
Does the drug A+B combination show high synergy in reducing resistance emergence?
No
Can drug B be used as the first-line treatment?
No
Yes
ECC (early combination chemotherapy)

Clinical Effectiveness of Oseltamivir and Zanamivir for Treatment of Influenza A Virus Subtype H1N1 with the H274Y Mutation: A Japanese, Multicenter Study of the 2007–2008 and 2008–2009 Influenza Seasons

Naoki Kawai,[1,a] Hideyuki Ikematsu,[1,2,a] Nobuo Hirotsu,[1] Tetsunari Maeda,[1] Takashi Kawashima,[1] Osame Tanaka,[1] Satoshi Yamauchi,[1] Kenichi Kawamura,[1] Shinro Matsuura,[1] Mika Nishimura,[2] Norio Iwaki,[1] and Seizaburo Kashiwagi[1]

Table 2. Duration of Fever for Patients with Influenza Virus A Subtypes H1N1 and H3N2 Treated with Oseltamivir or Zanamivir Therapy

	H1N1 virus			H3N2 virus	
Variable	2007–2008	2008–2009	P^a	2008–2009	P^b
Duration of fever after administration of the first dose, mean h ± SD					
Oseltamivir	32.0 ± 18.9 (n = 41)	49.1 ± 30.2 (n = 77)	<.001	33.7 ± 20.1 (n = 31)	<.01
Zanamivir	31.5 ± 14.9 (n = 27)	27.5 ± 18.5 (n = 87)	NS	30.1 ± 18.0 (n = 28)	NS
P value between oseltamivir and zanamivir	NS	<.001		NS	
Duration of fever from onset, mean h ± SD					
Oseltamivir	50.2 ± 21.4 (n = 41)	66.6 ± 31.1 (n = 77)	<.01	50.7 ± 22.6 (n = 31)	<.01
Zanamivir	48.1 ± 16.9 (n = 27)	43.9 ± 21.2 (n = 87)	NS	50.1 ± 19.9 (n = 28)	NS
P value between oseltamivir and zanamivir	NS	<.001		NS	

Centers for Disease Control and Prevention
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NOTE: On September 8, 2009, CDC issued Updated Interim Recommendations for the Use of Antiviral Medications in the Treatment and Prevention of Influenza for the 2009-2010 Season. (/h1n1flu/recommendations.htm) These updated recommendations are the most up-to-date guidance on the use of antiviral medications and apply to both 2009 H1N1 and seasonal influenza. The content of this web page will be revised to reflect the updated guidance shortly.

Antiviral Agents for Seasonal Influenza: Side Effects and Adverse Reactions

Effets secondaires

- Oseltamivir
  - Nausées, vomissements (10%)
  - Quelques cas d'évènements neuropsychiatriques (automutilation et délirium)
- Zanamivir
  - Données divergentes chez l'asthmatique et le BPCO
  - Comparable au placebo

Conclusion

- La stratégie d'utilisation des antiviraux doit être évolutive
  - Mortalité de la pathologie
  - Des populations touchées
  - Stade de la pandémie
  - Evolution de la résistance
- Nécessité d'une évaluation continue de ces différents paramètres avec ajustement en temps réel