ANTIVIRAUX ACTIFS SUR LES VIRUS RESPIRATOIRES

Enseignant : F. Van Bambeke

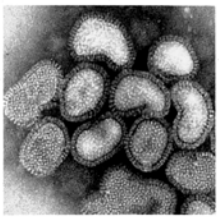
FARM2129 – année 2009-2010

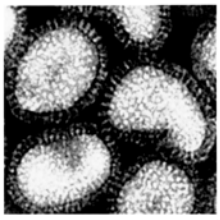
Médicaments des infections virales respiratoires

Adenovirus	**-**
Picornavirus	
Entero	**-**
Rhino	**-**
Orthomyxovirus	
Influenza	**inhibiteurs de neuraminidase : zanamivir, oseltamivir** **adamanatanes (influenza A)**
Paramyxovirus	
Parainfluenza	**-**
Respiratory syncytial virus	**ribavirine**
SARS virus	**-**

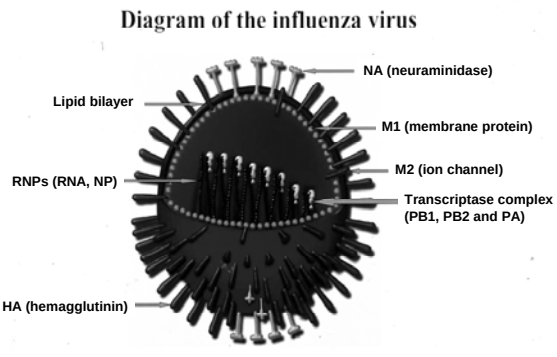
ANTIVIRAUX ACTIFS SUR LE VIRUS INFLUENZA

Le Virus de l'influenza: constituants

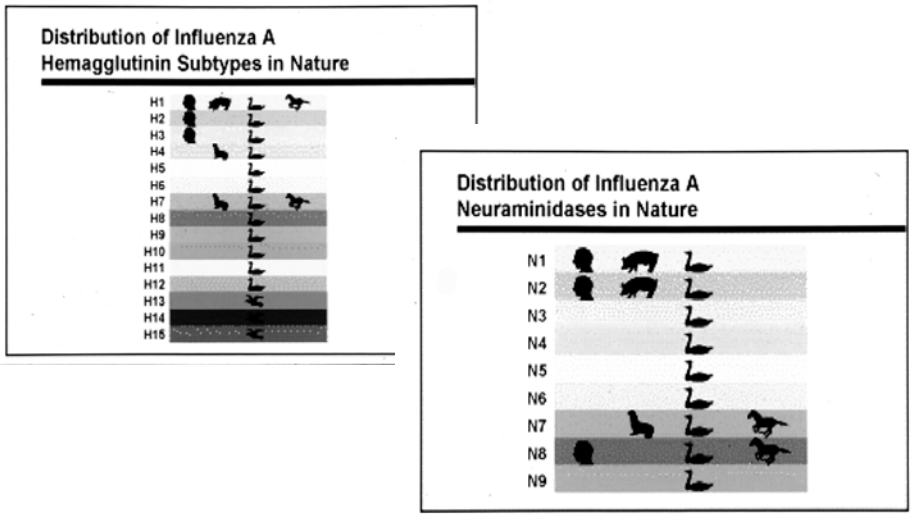




Electron micrographs of purified influenza virions. Hemagglutinin (HA) and neuraminidase (NA) can be seen on the envelope of viral particles. Ribonucleoproteins (RNPs) are located inside the virions.

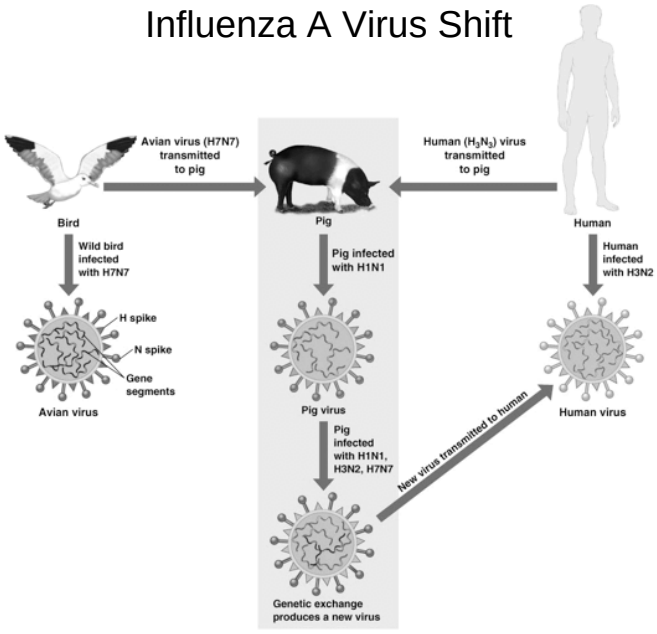


Virus Influenza: Antigènes de surface



http://www.brown.edu/Courses/Bio_160/Projects1999/flu/mechanism.html

Influenza A Virus Shift



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La Grippe

Commissariat
interministériel Influenza

A distinguer :

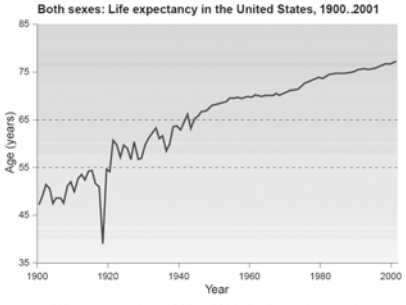
Grippe saisonnière (Maladie humaine) → Attendue chaque hiver

Cas humains de grippe aviaire (Zoonose) → Situation récente en Asie

Pandémie de grippe (Zoonose évoluant en maladie humaine) → Situation actuelle (H_1N_1)

Histoire des pandémies …

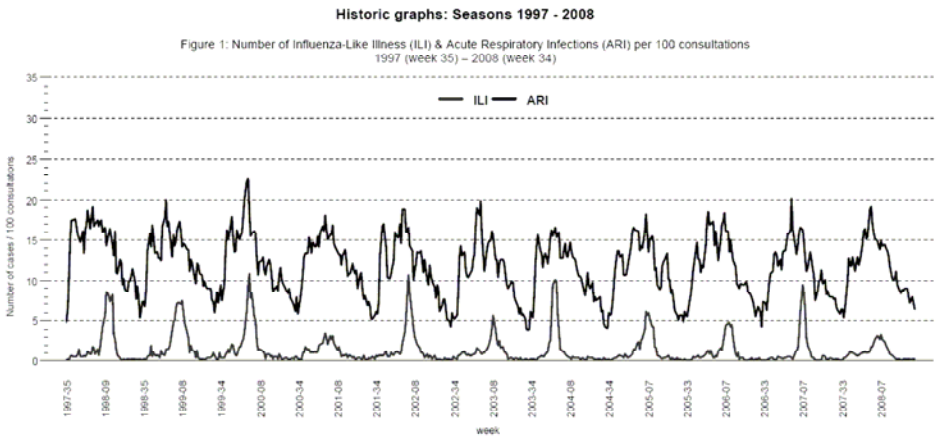
1889-90	A/H2N8	
1900-03	A/H3N8	
1918-19	A/H1N1	*Spanish Flu*
1957-58	A/H2N2	*Asian Flu*
1968-69	A/H3N2	*Hong Kong Flu*
(1977-78)	A/H1N1	*Russian Flu*
2009	A/H1N1	*Mexican Flu*



Life expectancy from 1900 to 2001 showing the impact of the 1918 influenza pandemic. Data are adapted from the National Vital Statistics Reports, Vol. 52, No. 14, February 18, 2004. (http://www.cdc.gov/nchs/data/dvs/nvsr52_14t12.pdf).

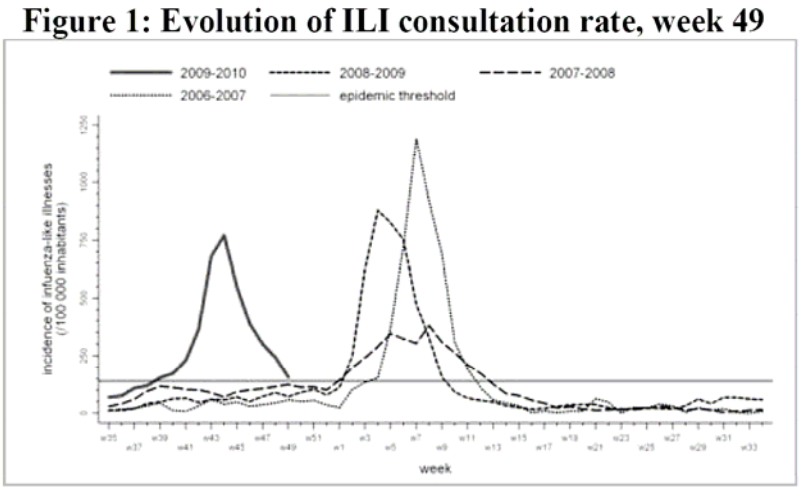
Australian Red Cross 1918

Evolution des "maladies grippales" et de l'isolement d'*Influenza A*



http://www.iph.fgov.be/epidemio/epifr/plabfr/plabanfr/05_082f_v.pdf

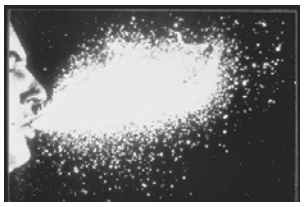
Epidémiologie annuelle des infections par *Influenza*



http://www.iph.fgov.be/flu/FR/22FR.htm

Voies de transmission

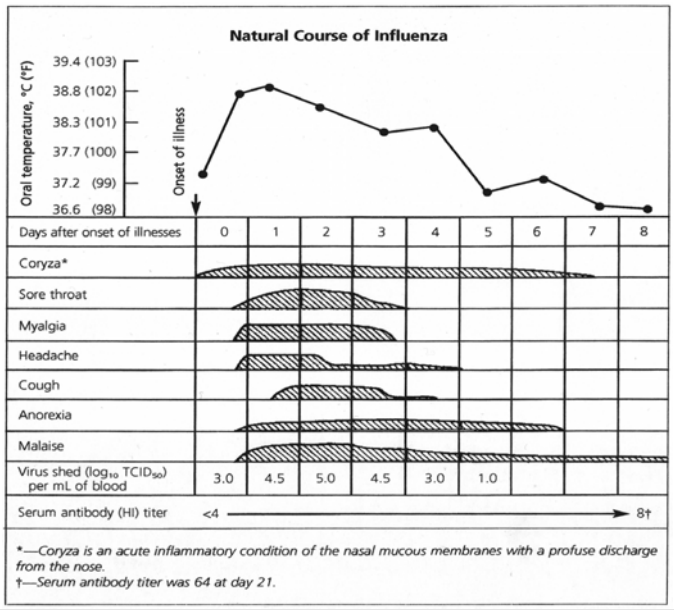
1. aérosolisation



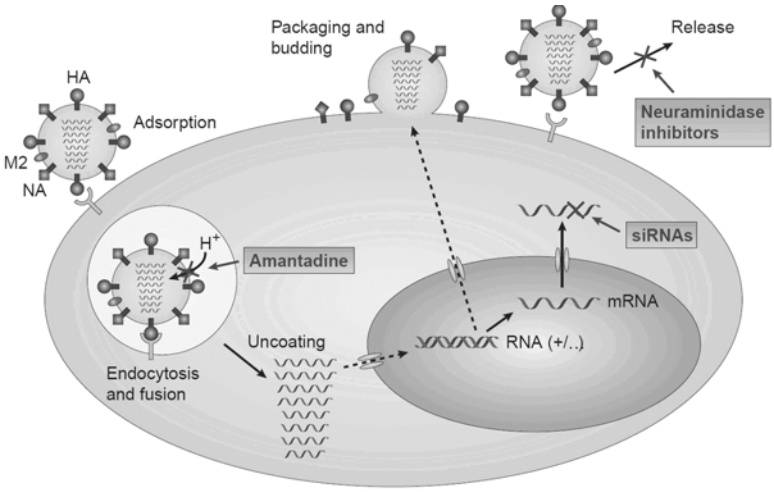
2. Voie aérienne

3. Objets contaminés

La grippe: signes cliniques



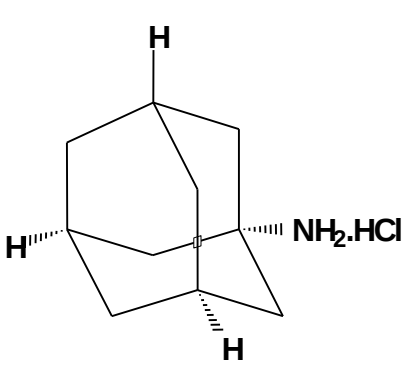
Cibles des antiviraux



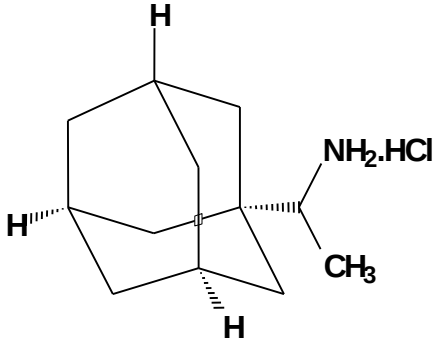
P. Palese Nature Medicine 10 : 2004

ADAMANTANES

Adamantanes



Amantadine

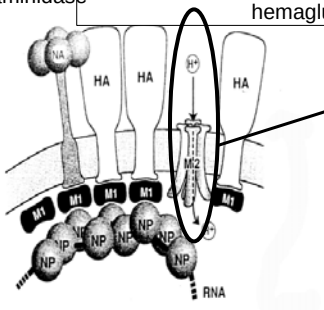


Rimantadine

Mode d'action

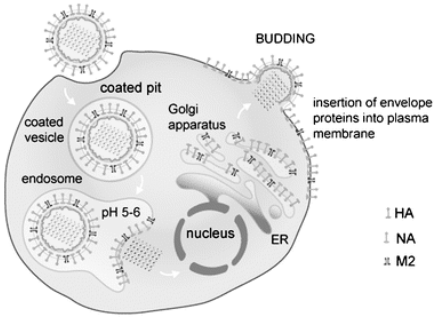
neuraminidase

hemaglutinine



Inhibiteurs de la protéine virale M2 du virus influenza A

- prévention du désassemblage du virus
- inhibition de l'acidification de l'endosome et prévention des fusions de membranes induites par les protéines virales



INHIBITEURS DE NEURAMINIDASE

La neuraminidase

Moscona, NEJM (2005) 353:1363-1373

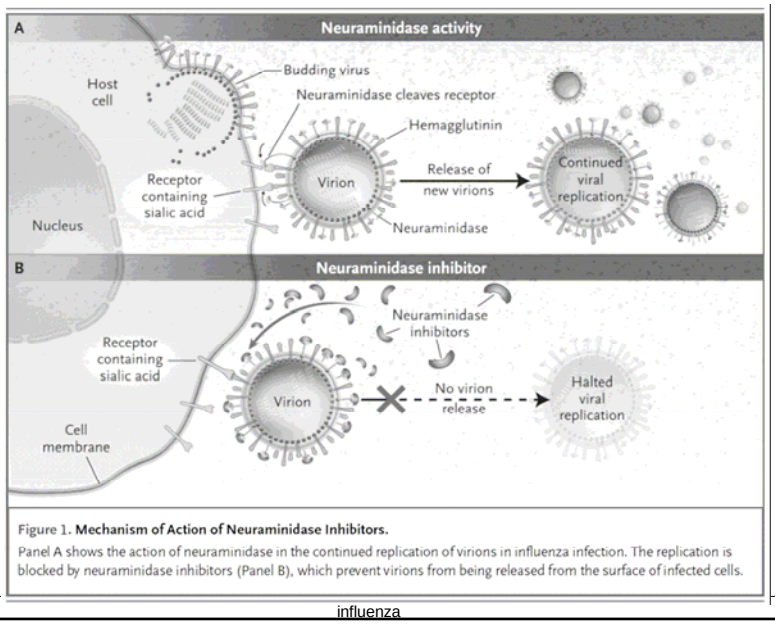
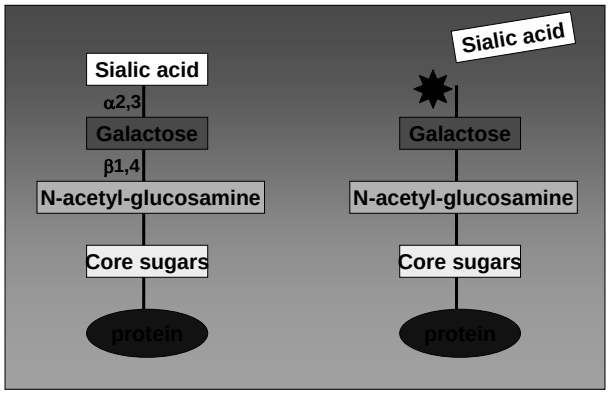


Figure 1. **Mechanism of Action of Neuraminidase Inhibitors.**
Panel A shows the action of neuraminidase in the continued replication of virions in influenza infection. The replication is blocked by neuraminidase inhibitors (Panel B), which prevent virions from being released from the surface of infected cells.

La neuraminidase



La neuraminidase clive l'acide sialique des glycoprotéines de surface cellulaire auquelles sont attachées les nouvelles particules virales

Functions:

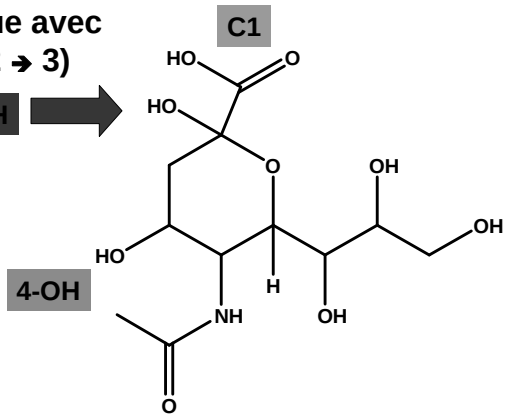
- favorise la libération des particules virales
- détruit les récepteurs de surface reconnus par les hémagglutinines
- prévient l'aggrégation des virus à la surface cellulaire
- prévient l'inactivation par le mucus respiratoire

L'acide sialique

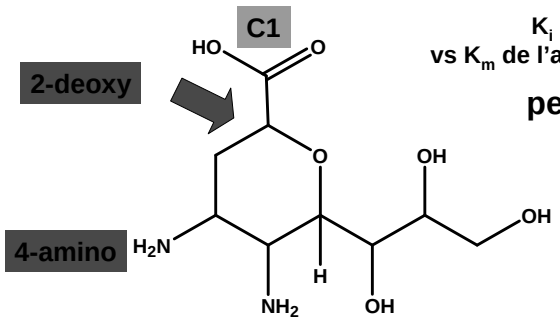
Lien osidique avec galactose (2 ➔ 3)

2-OH

4-OH



Découverte du premier inhibiteur … 1969 !

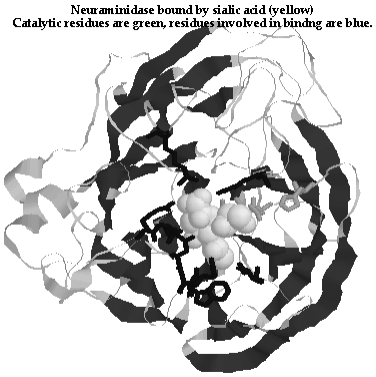


K_i ~ 0.01 mM
vs K_m de l'acide sialique ~ 1mM

peu efficace !

2,4-dideoxy-2,3-didehydro-4-amino-D-*N-acetylneuraminic acid*
Meindl et al., Hoppe-Seyler's Z. Physiol. Chem., 350:1088-1092, 1969

De 1969 à 1993...



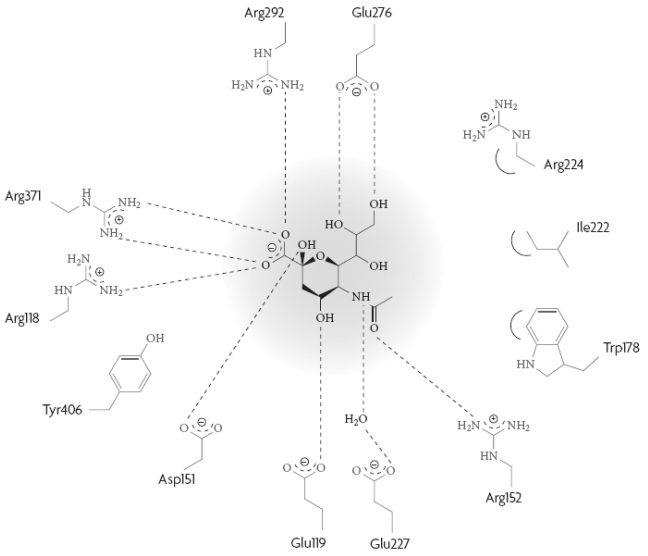
1983: structure of neuraminidase

- conservation des résidus du site actif
- variation des sites antigéniques

→ place pour du drug design !

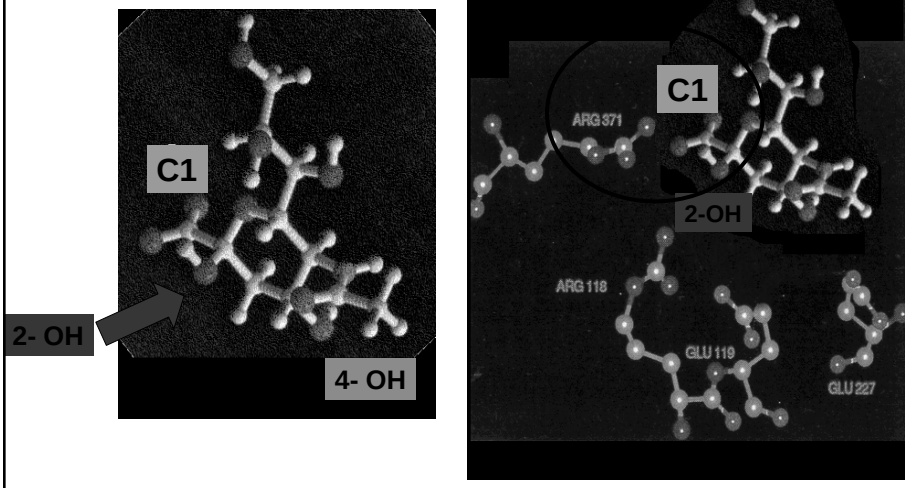
Colman et al., Nature (1983) 303: 41-44

Site actif de la neuraminidase



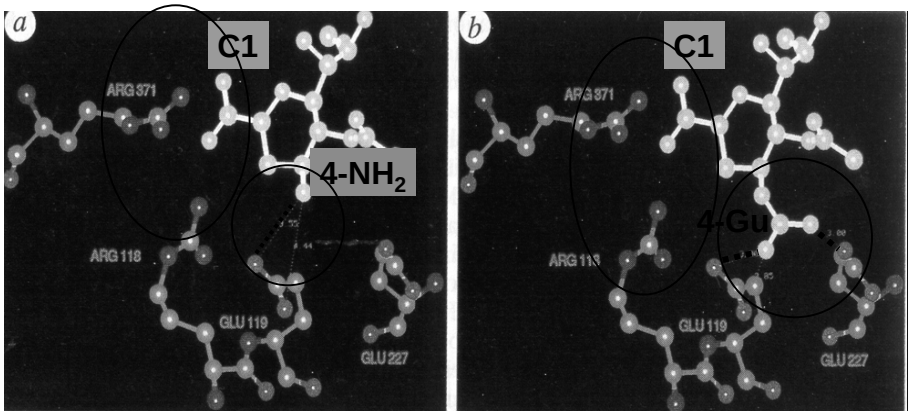
Von Itzstein., Nature Drug Discovery (2007) 6: 967

De l'acide sialique au zanamivir… (1)



acide sialique ou N-acétyl-neuraminique
interaction COOH avec Arg 371

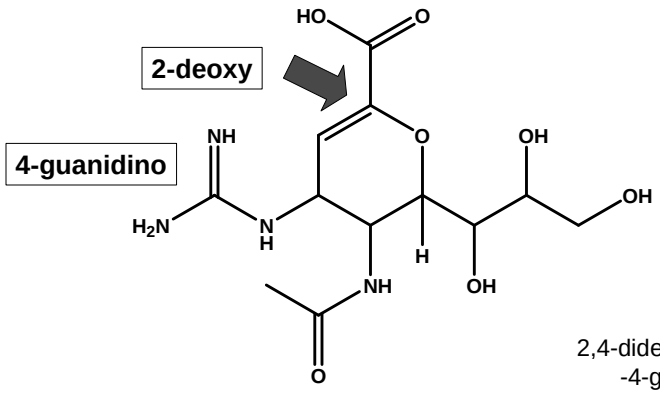
De l'acide sialique au zanamivir… (2)



4-deoxy-4-amino ... **4-deoxy-4-guanidino...**

interaction avec 1 puis 2 résidus conservés

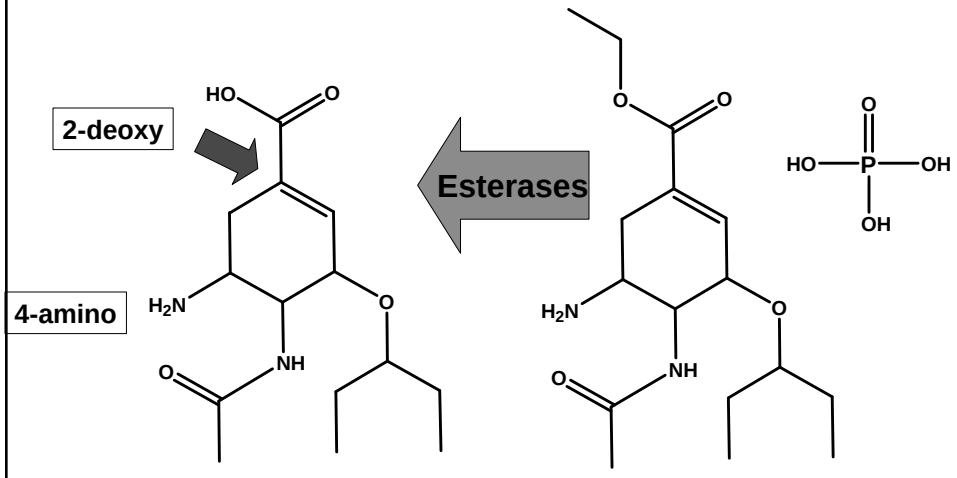
Le zanamivir



2,4-dideoxy-2,3-didehydro
-4-guanidino-D-N-
acetylneuraminic acid

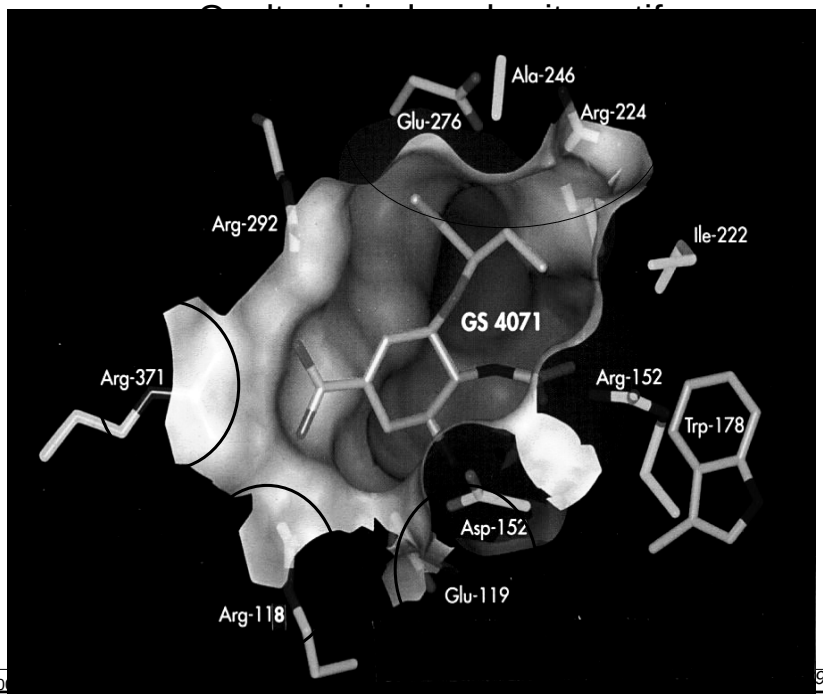
von Itzstein et al., Nature (1993) 363: 418-423, 1993

L'oseltamivir



oseltamivir

utilisé sous forme de sel (Phosphate)
de prodrogue résorbé par voie orale



90 (1997)

Résistance: mutation de la cible

Neuraminidase

119 Glu → Gly:

- Résistance au zanamivir
  (Glu 119 interagit avec guanidinium)

292 Arg → Lys (R292K)**:**

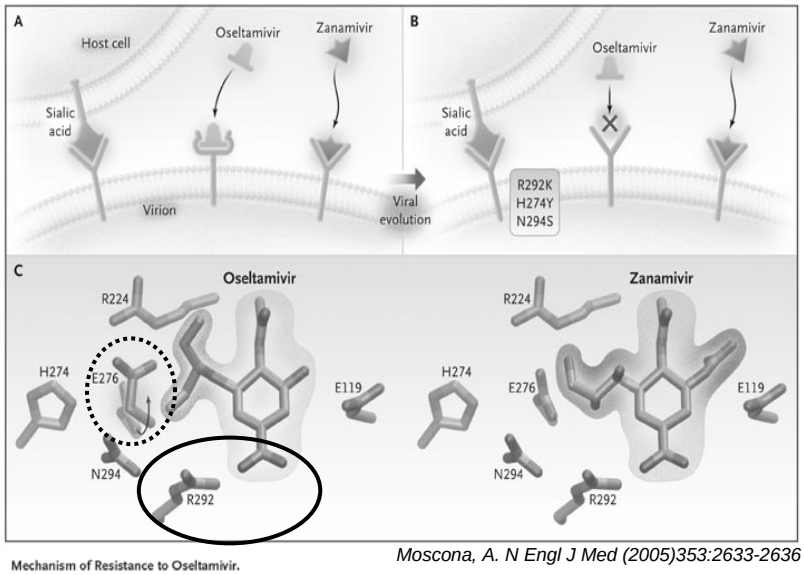
- Résistance à l'oseltamivir
  (Arg 292 interagit avec acide carboxylique mais conformation de la poche enzymatique adhoc pour le zanamivir)

274 His → Tyr (H274Y) **et 294 Asn → Ser** (N294S)

- Résistance à l'oseltamivir

Hemagglutinine

Certaines mutations (198 Thr → Ile) diminuent l'affinité pour le récepteur



Moscona, A. N Engl J Med (2005)353:2633-2636

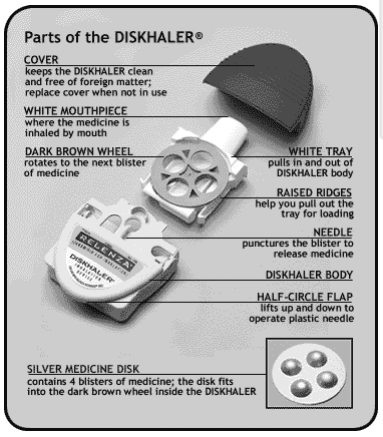
Mechanism of Resistance to Oseltamivir.

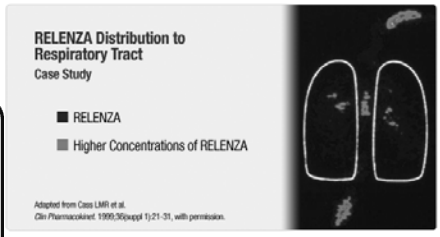
The neuraminidase active site changes shape to create a pocket for oseltamivir, whereas it accommodates zanamivir without such a change (Panel A). Any of several mutations may prevent the binding of oseltamivir by preventing the formation of this pocket (Panel B); the oseltamivir-resistant virus can nonetheless bind to the host-cell sialic acid receptor and to zanamivir. The pocket for oseltamivir, illustrated by key amino acids in Panel C, is created by the rotation of E276 and bonding of the amino acid to R224 — events that are prevented by the mutations R292K, N294S, and H274Y and therefore result in resistance to oseltamivir. An E119V mutation may permit the binding of a water molecule in the space created by the smaller valine, also interfering with oseltamivir binding. None of these mutations prevent the binding of zanamivir or of the natural sialic acid substrate.

Comparaison des inhibiteurs de neuraminidase

propriété	**zanamivir**	**oseltamivir**
spectre	Influenza A et B	
Voie d'administration	Inhalation 10 mg 2X/jour	Voie orale: 75-150 mg 2 X/jour
Traitement (5 jours)	↘ durée des symptômes – grippe saisonnière	
Prophylaxie	4 semaines: ↘ du nb de personnes malades	6 semaines: ↘ du nb de personnes malades
Activité sur H5N1	Peu efficace chez les patients contaminés	
tolérance	Bonne sauf path. respir.	bonne

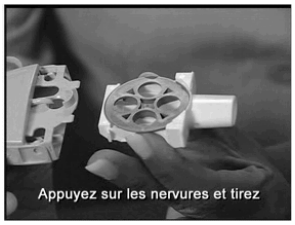
Zanamivir: voie d'administration

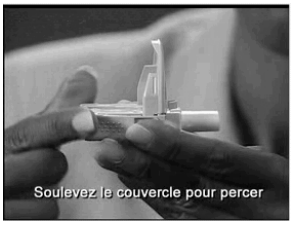




http://www.relenza.com/how-to-use-diskhaler.jsp?languages=French

Zanamivir: comment l'administrer correctement ?





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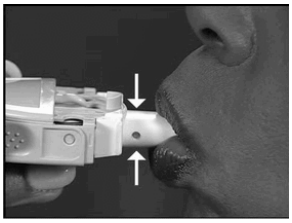
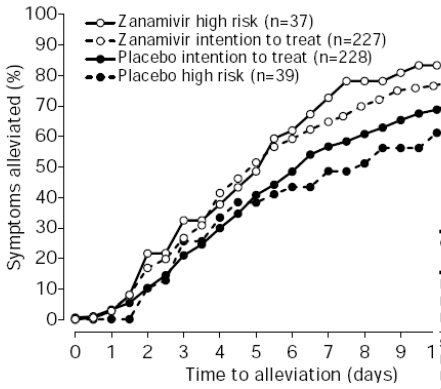
Zanamivir: comment l'administrer correctement ?



1 dose: = 2 cupules

http://www.relenza.com/how-to-use-diskhaler.jsp?languages=French

Zanamivir: efficacité clinique



On gagne 1-2 jours …

Group	No of patients	Median	No of patients	Median	Difference (95% CI)	p
Return to normal activities (days)						
Intention to treat	228	9·0	227	<7·0	2·0 (0 to 4·0)	<0·001
Influenza positive	160	9·0	161	<7·0	2·0 (0·25 to 4·0)	<0·001
Sleep disturbance (days of 13)						
Intention to treat	228	3	223	3·0	0 (–1·0 to 1·0)	0·088
Influenza positive	160	3·0	159	2·0	1·0 (0 to 1·5)	0·047
Number of paracetamol tablets (days 1–4)						
Intention to treat	228	12	224	14·0	–2 (–6 to 0)	0·291
Influenza positive	160	13	159	14·0	–1 (–5 to 2)	0·854
Number of cough mixture spoonfuls (days 1–14)						
Intention to treat	228	9	224	7·0	2 (–3 to 5)	0·738
Influenza positive	160	12	159	7·0	5 (–1 to 9)	0·045

Table 3: **Sleep disturbance, return to normal activities, and use of relief medications**

The Lancet (1998) 352: 1877-1881

Zanamivir: efficacité en prophylaxie

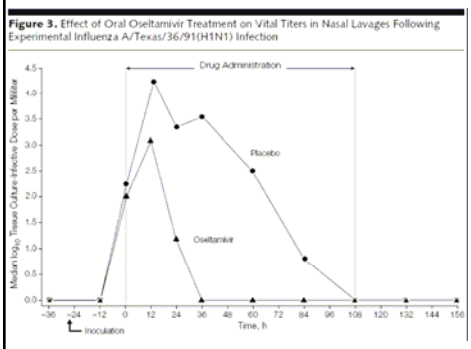
Table 2. Efficacy of Zanamivir in Prevention of Influenza Infection and Disease*

Outcome	Frequencies in Study Groups, No. (%)		Odds Ratio (95% CI)	Estimated Risk Ratio (95% CI)	Efficacy, 1 – Risk Ratio (95% CI), %
	Placebo (n = 554)	Zanamivir (n = 553)			
Laboratory-confirmed clinical influenza	34 (6)	11 (2)	0.31 (0.14-0.64)†	0.33 (0.17-0.61)	67 (39-83)
Laboratory-confirmed influenza with fever	19 (3)	3 (<1)	0.15 (0.03-0.53)†	0.16 (0.06-0.45)	84 (55-94)
All febrile illnesses	58 (10)	33 (6)	0.54 (0.34-0.86)‡	0.57 (0.38-0.86)	43 (14-62)
Influenza infection with or without illness	77 (14)	53 (10)	0.66 (0.44-0.97)§	0.69 (0.50-0.96)	31 (4-50)

*CI indicates confidence interval.
†$P \leq .001$.
‡$P = .009$.
§$P = .03$.

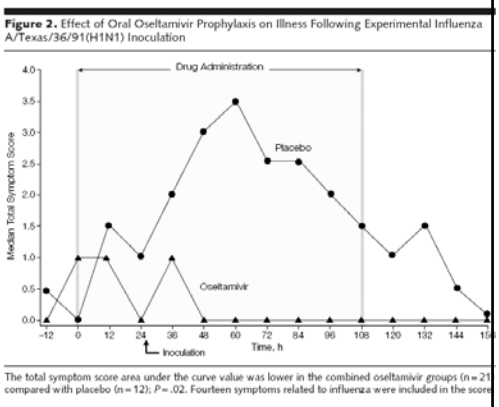
JAMA (1999) 282:31-35

Et l'oseltamivir ?



Traitement :
On gagne 1-2 jours …

Prophylaxie :
efficace



JAMA (1999) 282:31-36

Zanamivir: effets secondaires et contre-indications

Important Safety Information

RELENZA IS NOT RECOMMENDED FOR TREATMENT OR PROPHYLAXIS OF INFLUENZA IN INDIVIDUALS WITH UNDERLYING AIRWAY DISEASE (SUCH AS ASTHMA OR CHRONIC OBSTRUCTIVE PULMONARY DISEASE).

- **Serious cases of bronchospasm, including fatalities, have been reported during treatment with RELENZA in patients with and without underlying airway disease. Many of these cases were reported during postmarketing, and causality was difficult to assess**
- **RELENZA SHOULD BE DISCONTINUED IN ANY PATIENT WHO DEVELOPS BRONCHOSPASM OR DECLINE IN RESPIRATORY FUNCTION; immediate treatment and hospitalization may be required**
- RELENZA has not been proven effective for treatment of influenza in individuals with underlying airways disease.
- If treatment with RELENZA is considered for a patient with underlying airway disease, the potential risks and benefits should be carefully weighed. If a decision is made to prescribe RELENZA for such a patient, this should be done only under conditions of careful monitoring of respiratory function, close observation, and appropriate supportive care including availability of fast-acting bronchodilators
- Common adverse events in treatment and prophylaxis studies with RELENZA were nausea, diarrhea, sinusitis, viral respiratory infections, headaches, nasal signs and symptoms. The incidence of these adverse events was similar in both groups for RELENZA and placebo-treated groups

Bénéfice potentiel des inhibiteurs de neuraminidase

Thérapeutique:

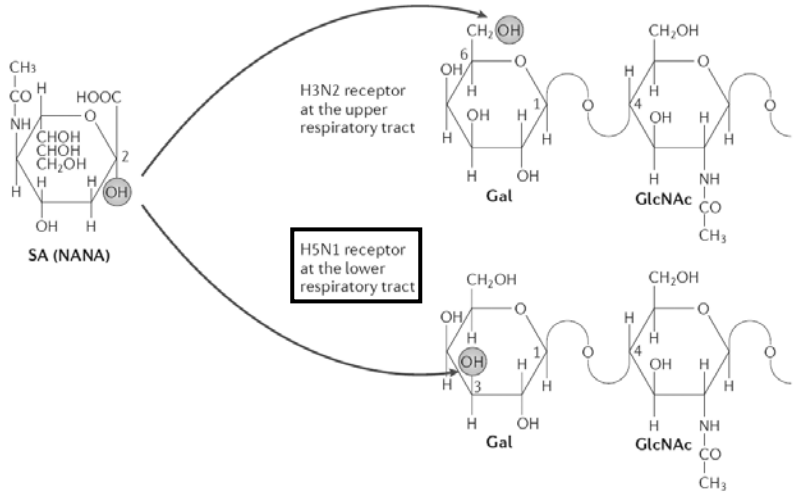
- ↘ durée des symptomes de 1-2 jours
- ↘ risque de transmission du virus
- ↘ risque de complications (sinusite, bronchite)
- ↘ usage d'antibiotiques

Prophylaxie:

- Prévention saisonnière de l'infection

Panique à bord: A quand la grippe aviaire ?

Pourquoi est-elle si redoutable ?



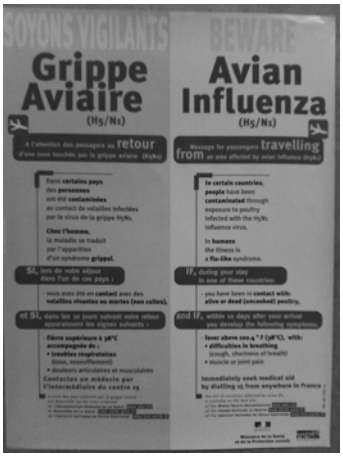
De Clercq, Nature Drug Discovery (2006) 5:1015-25

Panique à bord: A quand la grippe aviaire ?

Stockpiling of Antivirals

Objectif :
30% de la population belge devrait avoir accès au traitement dès 2008

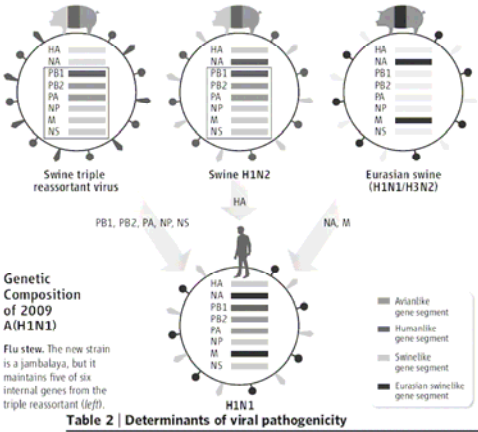
Panique à bord: A quand la grippe aviaire ?



Conseils aux voyageurs

- Vérifier la liste des pays concernés
- Éviter le contact avec la volaille
- Hygiène des mains en toutes circonstances
- Hygiène culinaire, dont la cuisson
- Pas d'antiviraux en préventif
- Consulter un médecin si fièvre < 7 jours après le retour

Nouvelle panique à bord: le H1N1



Science (2009) 325: 140 – 141
Nature (2009), 459: 931-939

Table 2 | Determinants of viral pathogenicity

Protein	Position	Pathogenicity		Swine-origin H1N1 viruses	Function
		Low	High		
PB2	627	Glu	Lys	Glu	Replicative ability in some mammals, including humans
	701	Asp	Asn	Asp	Nuclear import kinetics affecting replicative ability in mice
PB1-F2	66	Asn	Ser	Truncated (11 aa)	Induction of apoptosis
HA	Cleavage site	Single basic aa	Multiple basic aa	Single basic aa	HA cleavage
NS1	92	Asp	Glu	Asp	Unknown (interferon response?)
	C terminus	Arg-Ser-Glu-Val, deletion	Glu-Ser-Glu-Val	11 C-terminal aa truncated	Unknown

aa, amino acid(s).

Nouvelle panique à bord: le H1N1

CDC Estimates of 2009 H1N1 Cases and Related Hospitalizations and Deaths from April-October 17, 2009, By Age Group

2009 H1N1	Mid-Level Range*	Estimated Range *
Cases		
0-17 years	~8 million	~5 million to ~13 million
18-64 years	~12 million	~7 million to ~18 million
65 years and older	~2 million	~1 million to ~3 million
Cases Total	~22 million	~14 million to ~34 million
Hospitalizations		
0-17 years	~36,000	~23,000 to ~57,000
18-64 years	~53,000	~34,000 to ~83,000
65 years and older	~9,000	~6,000 to ~14,000
Hospitalizations Total	~98,000	~63,000 to ~153,000
Deaths		
0-17 years	~540	~300 to ~800
18-64 years	~2,920	~1,900 to ~4,600
65 years and older	~440	~300 to ~700
Deaths Total	~3,900	~2,500 to ~6,100

Seasonal Influenza-Associated Hospitalizations in the United States
An average estimated 200,000 flu-related hospitalizations occur in the United States each year, with about 60 percent of these hospitalizations occurring in people 65 years and older.
Seasonal Influenza-Associated Deaths
Flu-associated mortality varies by season because flu seasons often fluctuate in length and severity. CDC estimates that about 36,000 people died of flu-related causes each year, on average, with 90 percent of these deaths occurring in people 65 years and older

Nouvelle panique à bord: le H1N1

Mortality Associated with Influenza Pandemics and Selected Seasonal Epidemic Events, 1918–2009.*

Years	Circulating Virus (Genetic Mechanism)	Excess Deaths from Any Cause *no. per 100,000 persons/yr*
1918–1919	H1N1 (viral introduction), pandemic	598.0
1928–1929	H1N1 (drift)	96.7
1934–1936	H1N1 (drift)	52.0
1947–1948	H1N1 A′ (intrasubtypic reassortment)	8.9
1951–1953	H1N1 (intrasubtypic reassortment)	34.1
1957–1958	H2N2 (antigenic shift), pandemic	40.6
1968–1969	H3N2 (antigenic shift), pandemic	16.9
1972–1973	H3N2 A Port Chalmers (drift)	11.8
1975–1976	H3N2 (drift) and H1N1 ("swine flu" outbreak)	12.4
1977–1978	H3N2 (drift) and H1N1 (viral return)	21.0
1997–1999	H3N2 A Sydney (intrasubtypic reassortment) and H1N1 (drift)	49.5
2003–2004	H3N2 A Fujian (intrasubtypic reassortment) and H1N1 (drift)	17.1
2009	H3N2 and H1N1 (drift) and swine-origin H1N1 (viral introduction), pandemic	?

* Mortality data include deaths associated with all influenza A and B viruses combined. Many of these data have been calculated with the use of differing methods and may not be strictly comparable.[1,2] The 1934, 1951, and 1997 data span 2 years.

NEJM (2009) 361:225-229

Nouvelle panique à bord: le H1N1 en Belgique

Surveillance clinique

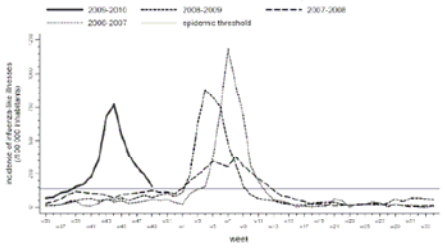


Figure 1: GP: Evolution of ILI incidence

Surveillance virologique

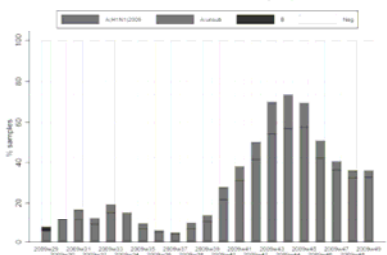


Figure 6: Virology: Evolution of the percentage of virus types among GPs samples

Mesures d'impact :

- *Absentéisme au travail* : Stable.
- *Absentéisme à l'école* : Stable
- *Admissions à l'hôpital* : En diminution
- *Suivi de la mortalité* : Pas d'excès de mortalité attribuable à la grippe.

http://www.iph.fgov.be/flu/FR/22FR.htm

Nouvelle panique à bord: le H1N1 en Belgique

a) **Evolution générale** :

En Belgique, l'épidémie de grippe A(H1N1)2009 a commencé à la semaine 40 (début du mois d'octobre). L'activité grippale a progressé jusqu'à la semaine 44 (fin du mois d'octobre) et diminue depuis la semaine 45. A la semaine 49, l'activité grippale répond tout juste aux critères épidémiques. Le virus circule toujours modérément dans la population et une réactivation de l'épidémie reste possible.

Pour rappel, les trois critères épidémiques sont :

1) taux de consultation > 141/100.000 habitants
2) > 20 % d'échantillons positifs collectés par les médecins vigies
3) Activité grippale dans les pays limitrophes ≥ activité moyenne

b) **Surveillance clinique** : Le taux de consultations pour syndromes grippaux a diminué pour atteindre 157/100.000 habitants [IC 95% : 135/100.000 - 182/100.000] sur la population générale. Notons que le seuil épidémique, estimé à 141/100.000 habitants, est inclus dans l'intervalle de confiance, ce qui confirme que nous sommes à la limite pour ce critère de l'épidémie.

c) **Surveillance virologique** : 36 % [IC 95 % : 24 % - 48 %] des échantillons prélevés par les médecins vigies sont positifs pour un virus Influenza A. Ce résultat, identique à la semaine précédente, est légèrement supérieur à la limite du critère épidémique qui est de 20 %. Le virus Influenza continue donc à circuler modérément dans la population.

Le virus Influenza circulant est toujours le virus A(H1N1)2009. Parmi les autres virus respiratoires, le VRS (virus respiratoire syncytial) présent parmi les enfants de 0 à 5 ans explique le taux d'infections respiratoires (ARI) dans ce groupe.

http://www.iph.fgov.be/flu/FR/22FR.htm

Nouvelle panique à bord: le H1N1 en Belgique

Table 1: Consultation rates per 100,000 inhabitants at three times: the peak of the last seasonal outbreak (week 4), the first peak of the current outbreak (week 44) and the week of reporting (49)

	Week 4 (2009)	Week 44 (2009)	Week 49 (2009)
Agegroup	*A(H3N2) seasonal peak*	*A(H1N1)2009*	*A(H1N1)2009*
< 5 years	1,268	1,328	340
5 - 14 years	1,192	2,076	278
15 - 64 years	934	662	141
≥ 65 years	363	153	65
Total	**881**	**774**	**157**

Table 1 shows that during this epidemic, the consultation rate among adults remained lower than in the last seasonal epidemic. An important group of adults remains potentially susceptible to contract and disseminate the disease.

Table 2 shows that, in week 49, the mean number of ILI consultations at GPs practices continues to decline, reflecting the decrease in the epidemic in the last 4 weeks.

Table 2: Mean number of cases reported per sentinel GPs during the A(H1N1)2009 epidemic at the start of the epidemic (week 40), at the first peak (week 44) and in the last 4 weeks.

Week	Number of reporting GPs	Number of ILI reported	Mean number of ILI per GP	Number of ARI reported	Mean number of ARI per GP
40 (start)	154	254	1.6	2,538	16
44 (peak)	153	1124	7.3	3,071	20
46	141	522	3.7	1,953	14
47	140	403	2.9	1,934	14
48	140	324	2.3	1,810	13
49	122	183	1.5	1,558	13

http://www.iph.fgov.be/flu/FR/22FR.htm

Nouvelle panique à bord: le H1N1 en Belgique

Figure 5: Weekly hospitalization rates per age groups

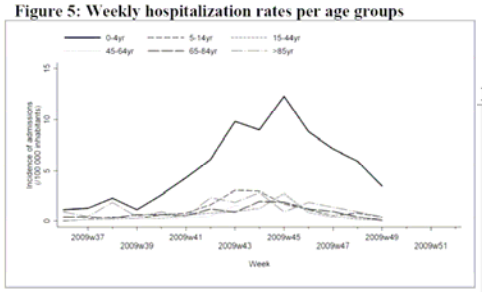


Figure 13: Absenteeism in Schools French-speaking community

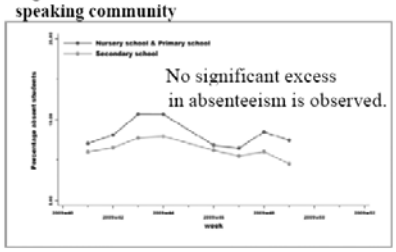
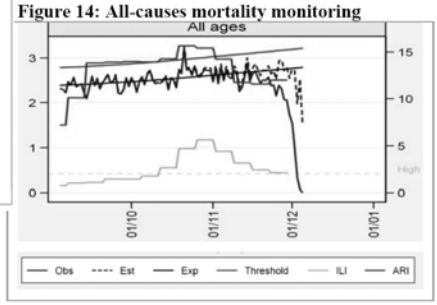


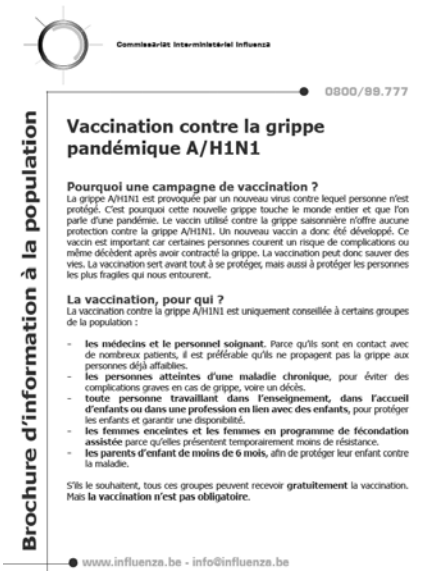
Figure 14: All-causes mortality monitoring



In November, no excess of mortality attributed to Influenza has been detected.

http://www.iph.fgov.be/flu/FR/22FR.htm

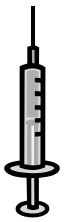
Nouvelle panique à bord: le H1N1



Pharmacothérapie de la grippe

- Traitement symptomatique
  - antipyrétiques
    - éviter aspirine chez les enfants (syndrôme de Reye)
  - selon les symptômes: décongestionnants, antitussifs
- Traitement antiviral
  - intérêt assez limité en traitement …
  - commencer < 36 heures après le début des symptômes
  - prophylaxie de l'environnement familial ?
- Suivre la survenue de complications (personnes à risque!)
- Vaccination !

Recommandations de vaccination (grippe saisonnière)



- Personnes à risque de complication:
  - > 65 ans
  - personnes vivant en institutions
  - co-morbidités
- Personnes susceptibles de transmettre la maladie à des personnes à risque (personnel médical, …)

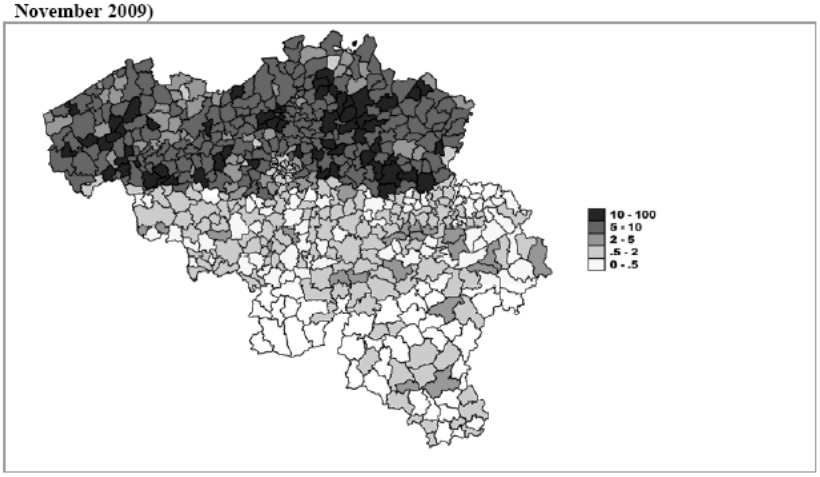
Recommandations de vaccination (grippe H1N1)

- médecins et les professionnels de santé
- personnes de plus de 6 mois qui courent un risque médical
- toute personne travaillant dans l'enseignement, dans l'accueil d'enfants ou dans une profession en lien avec des enfants
- femmes enceintes et femmes en programme de procréation médicalement assistée
- parents ayant des enfants de moins de 6 mois

Plus d'information sur <www.influenza.be>

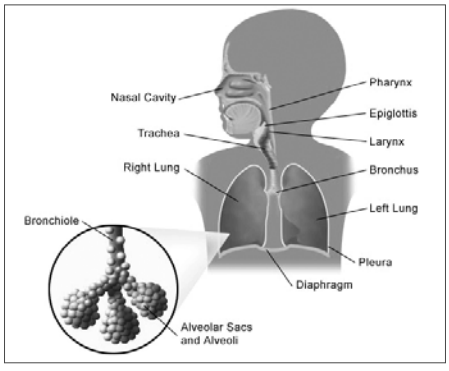
Recommandations de vaccination (grippe H1N1)

Figure 15: Map of the proportion of vaccinated populations as reported per communes (24 November 2009)



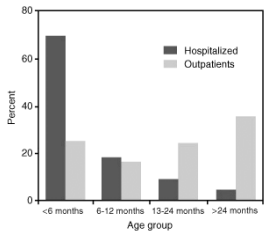
ANTIVIRAUX ACTIFS SUR RESPIRATORY SYNCYTIAL VIRUS (RSV)

Infections respiratoires à RSV



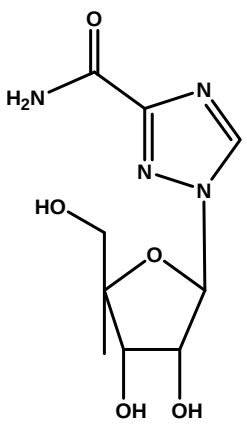
Respiratory Illnesses Caused by Respiratory Syncytial Virus (RSV)

Syndrome	*PercentageCaused by RSV*
Bronchiolitis	43-90
Pneumonia	5-40
Tracheobronchitis	10-30
Croup	3-10
Asymptomatic	0.3

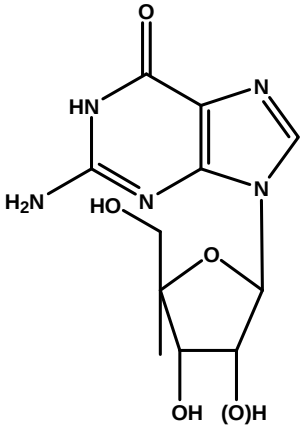


Difference in age distribution of inpatients and outpatients with respiratory syncytial virus infection in Rochester, NY. Of infants requiring hospitalization, 70% were younger than 6 months. In comparison, 25% of the children treated as outpatients were younger than 6 months and 38% were older than 2 years.

la ribavirine, un analogue de la guanosine

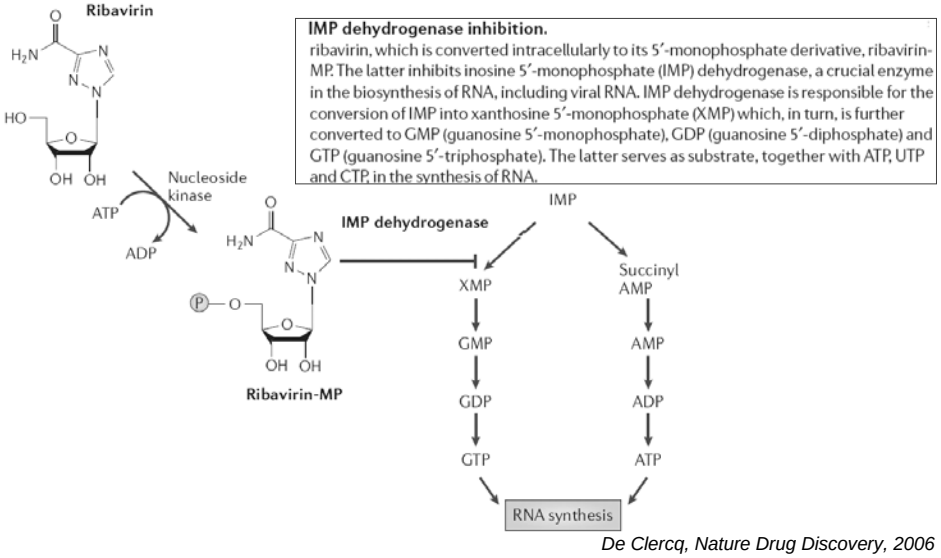


RIBAVIRINE



(deoxy)GUANOSINE

Mode d'action de la ribavirine



De Clercq, Nature Drug Discovery, 2006

Indications et propriétés pharmacologiques

Aérosol : traitement des infections à RSV
mais peu utilisé … affection bénigne

Voie générale: adjuvant dans le traitement de l'hépatite C

Effets secondaires:

- Détérioration de la fonction respiratoire
- Anémie hémolytique + hypoplasie médullaire
  (Concentration dans les globules rouges)

Traitement des infections à RSV

Traitement symptomatique

- antipyrétique
- apport de fluides
- oxygène si nécessaire

- bronchodilatateurs
- cortocoïdes

Traitement antiviral

(ribavirine)