ANTIVIRAUX ACTIFS SUR LES VIRUS RESPIRATOIRES

Enseignant : F. Van Bambeke

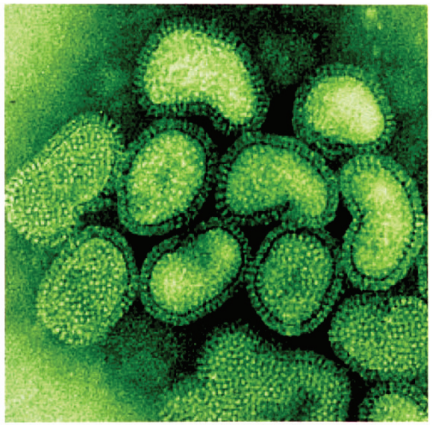
FARM2129 – année 2008-2009

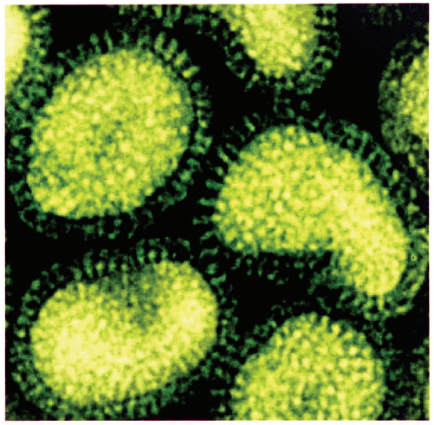
Médicaments des infections virales respiratoires

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

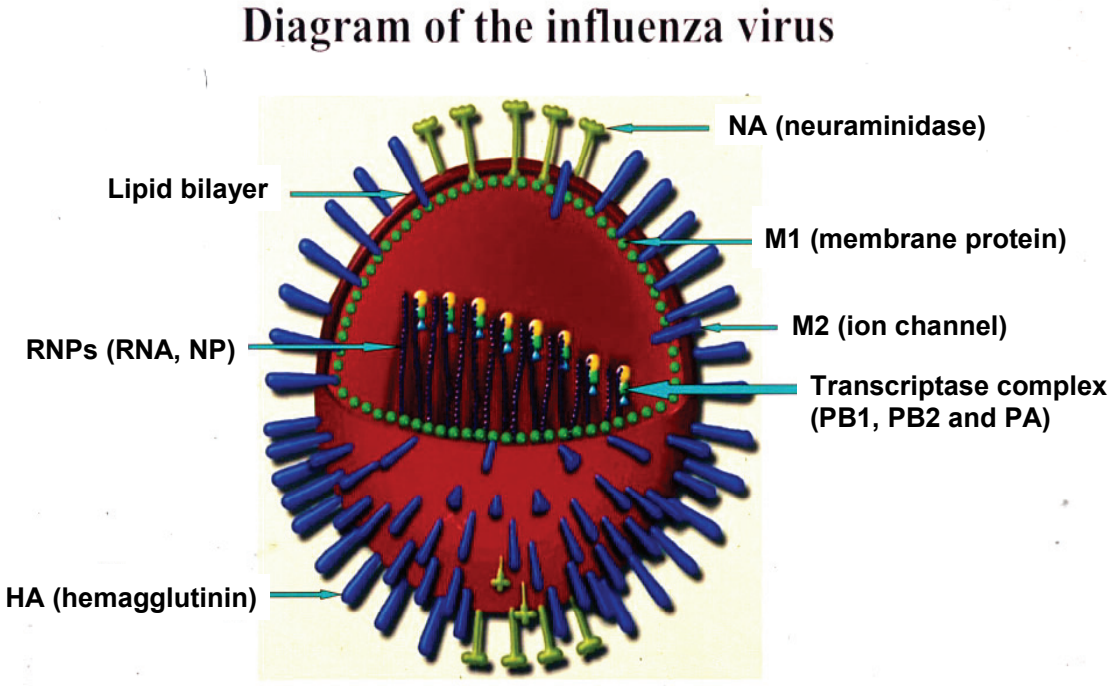
ANTIVIRAUX ACTIFS SUR LE VIRUS INFLUENZA

Le Virus de l'influenza: constituants

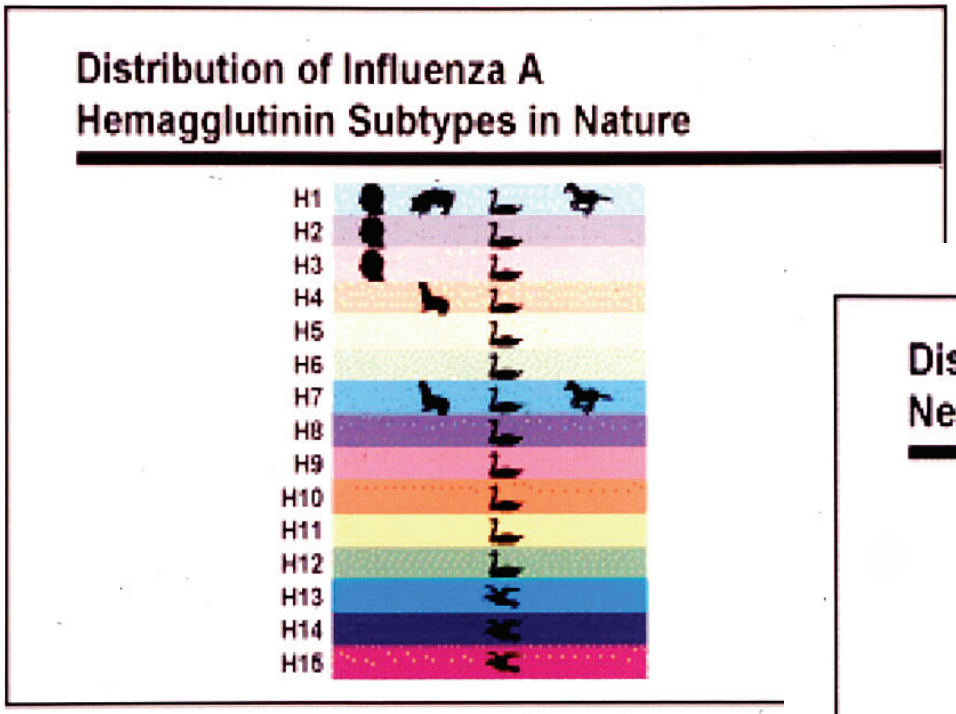


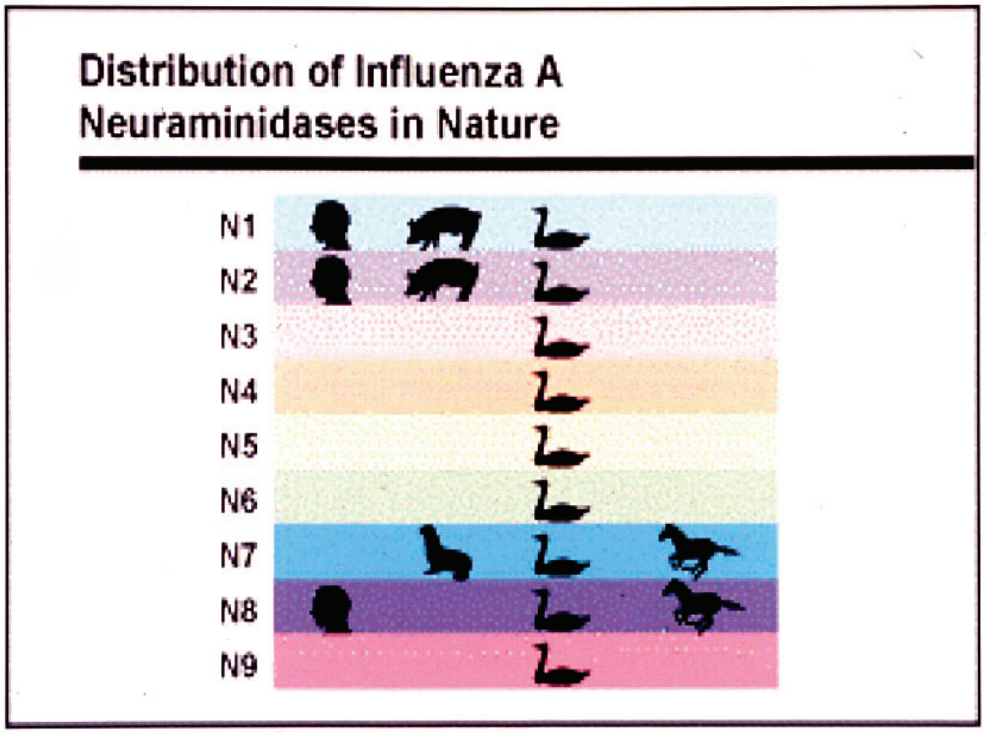


Electron micrographs of purified influenza virions. Hemagglutinin (HA) and neuraminidase (NA) can be seen on the envelope of viral particles. Ribonucleoproteins (RNPs) are located inside the virions.



Virus Influenza: Antigènes de surface

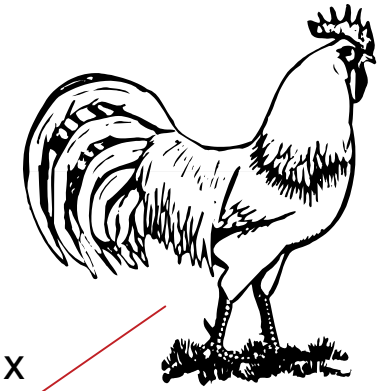




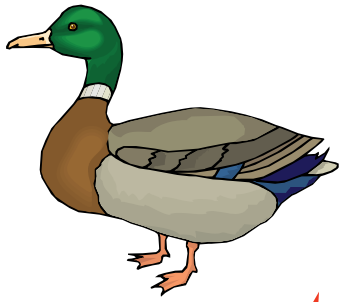
http://www.brown.edu/Courses/Bio_160/Projects1999/flu/mechanism.html

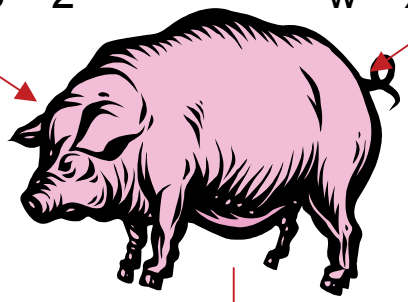
Influenza A Virus Shift

H_3N_2



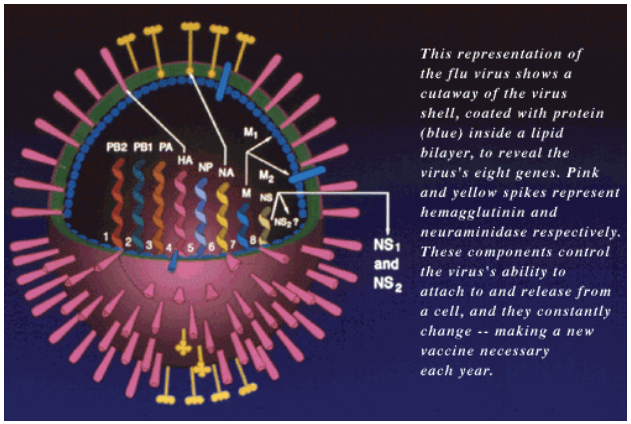
H_wN_x





H_5N_1

H_7N_7



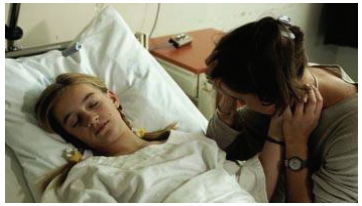
This representation of the flu virus shows a cutaway of the virus shell, coated with protein (blue) inside a lipid bilayer, to reveal the virus's eight genes. Pink and yellow spikes represent hemagglutinin and neuraminidase respectively. These components control the virus's ability to attach to and release from a cell, and they constantly change -- making a new vaccine necessary each year.

H_YN_Z

Commissariat
interministériel Influenza

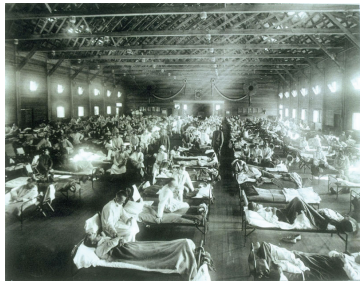
La Grippe

A distinguer :



Grippe saisonnière
(Maladie humaine) → Attendue chaque hiver

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

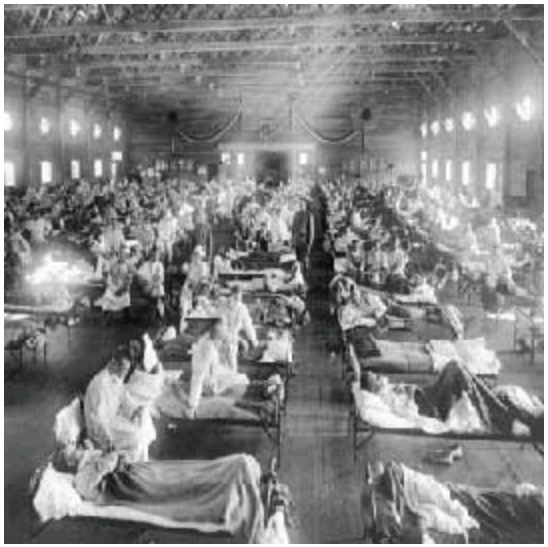


Pandémie de grippe

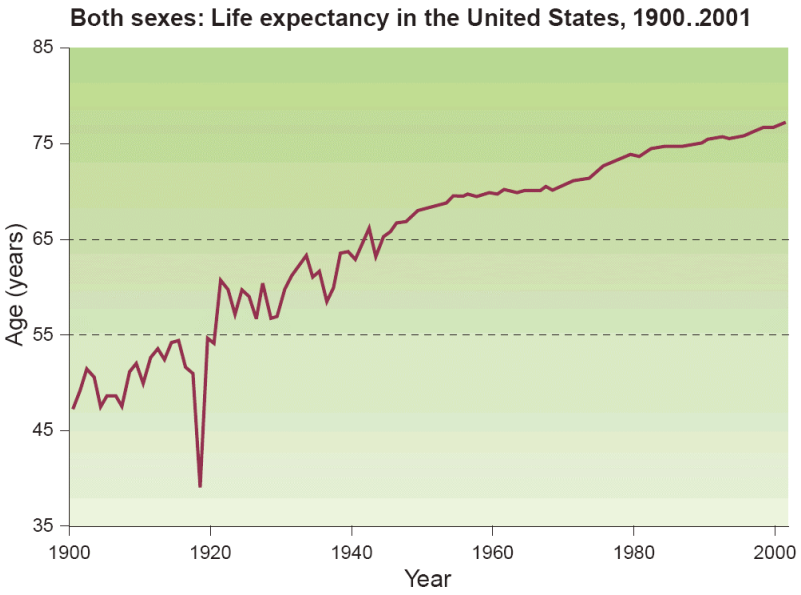
(Zoonose évoluant en
maladie humaine) → Pourrait émerger un jour

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*



Australian Red Cross 1918



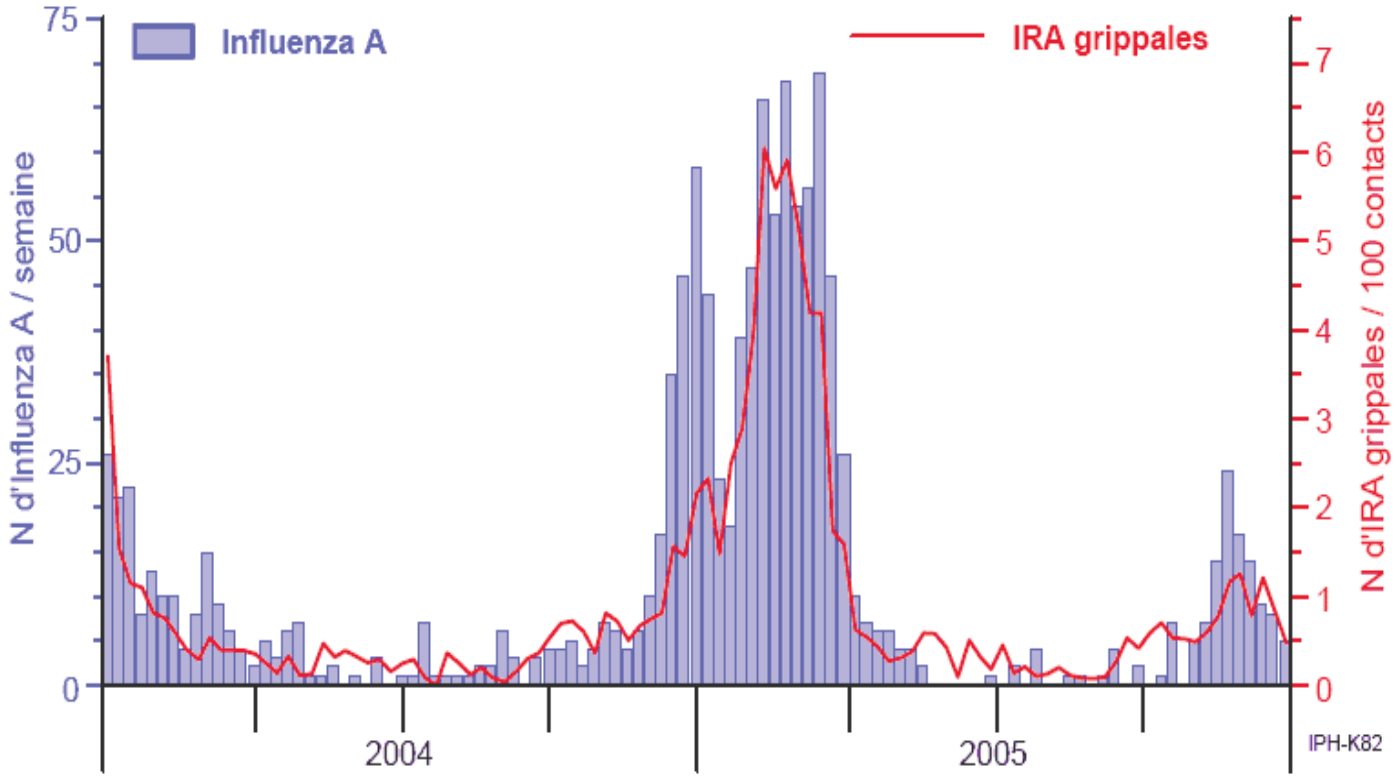
Life expectancy from 1900 to 2001 showing the impact of the 1918 influenza pandemic. Data are adapted from the National Vital Statistics Reports, Vol. 52, No. 14, February 18, 2004. (http://www.cdc.gov/nchs/data/dvs/nvsr52_14t12.pdf).

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

Laboratoires Vigies — **Influenza A**

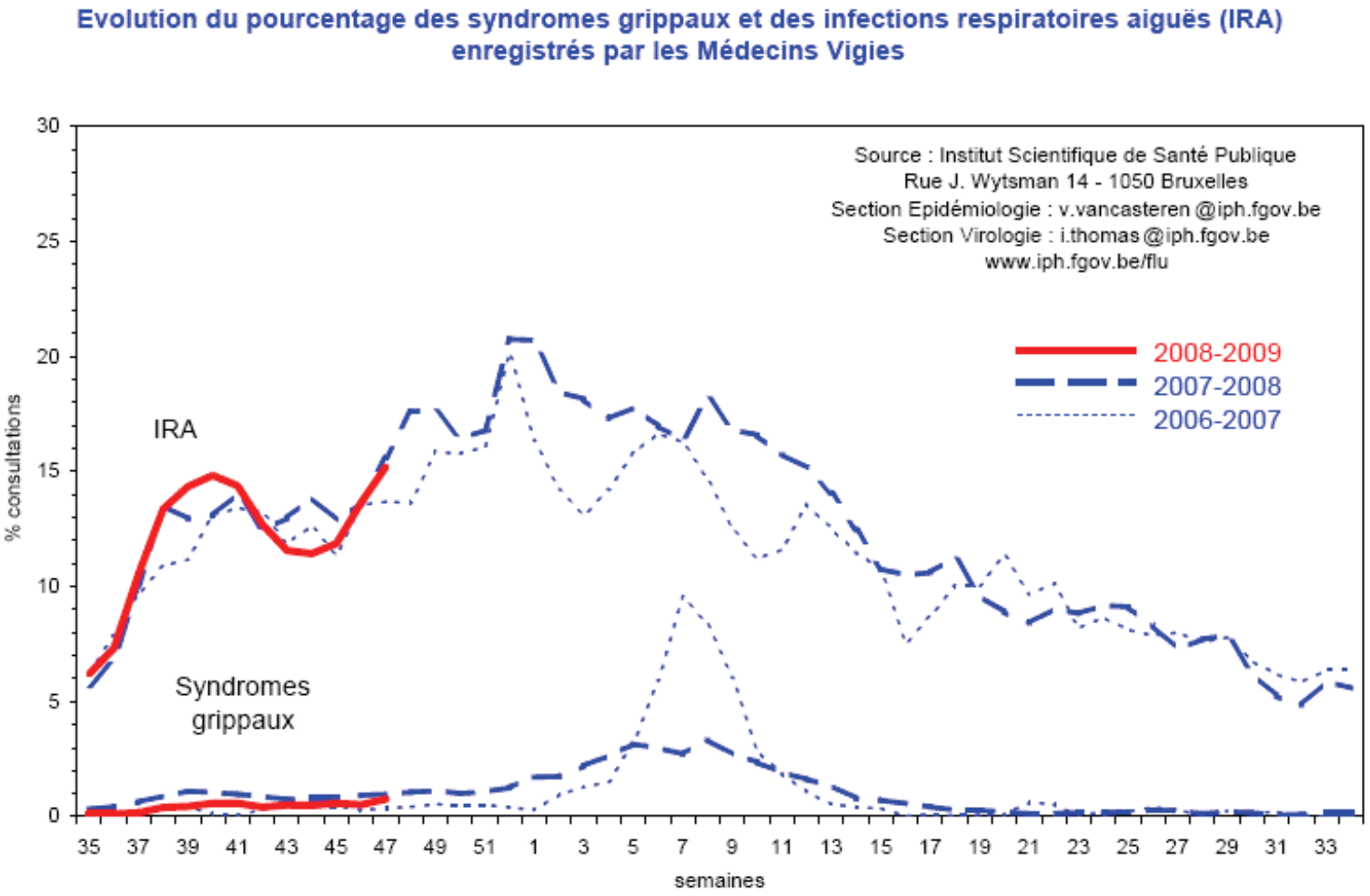
- l'évolution du nombre d'Influenza A est comparable à celle du nombre d'IRA grippales enregistrées par le réseau de médecins généralistes participant au programme de surveillance des IRA et de la grippe (figure 7).

Figure 7 : Influenza A : comparaison entre l'évolution par semaine du nombre d'Influenza A et celle des I.R.A. grippales (2004-2005)



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

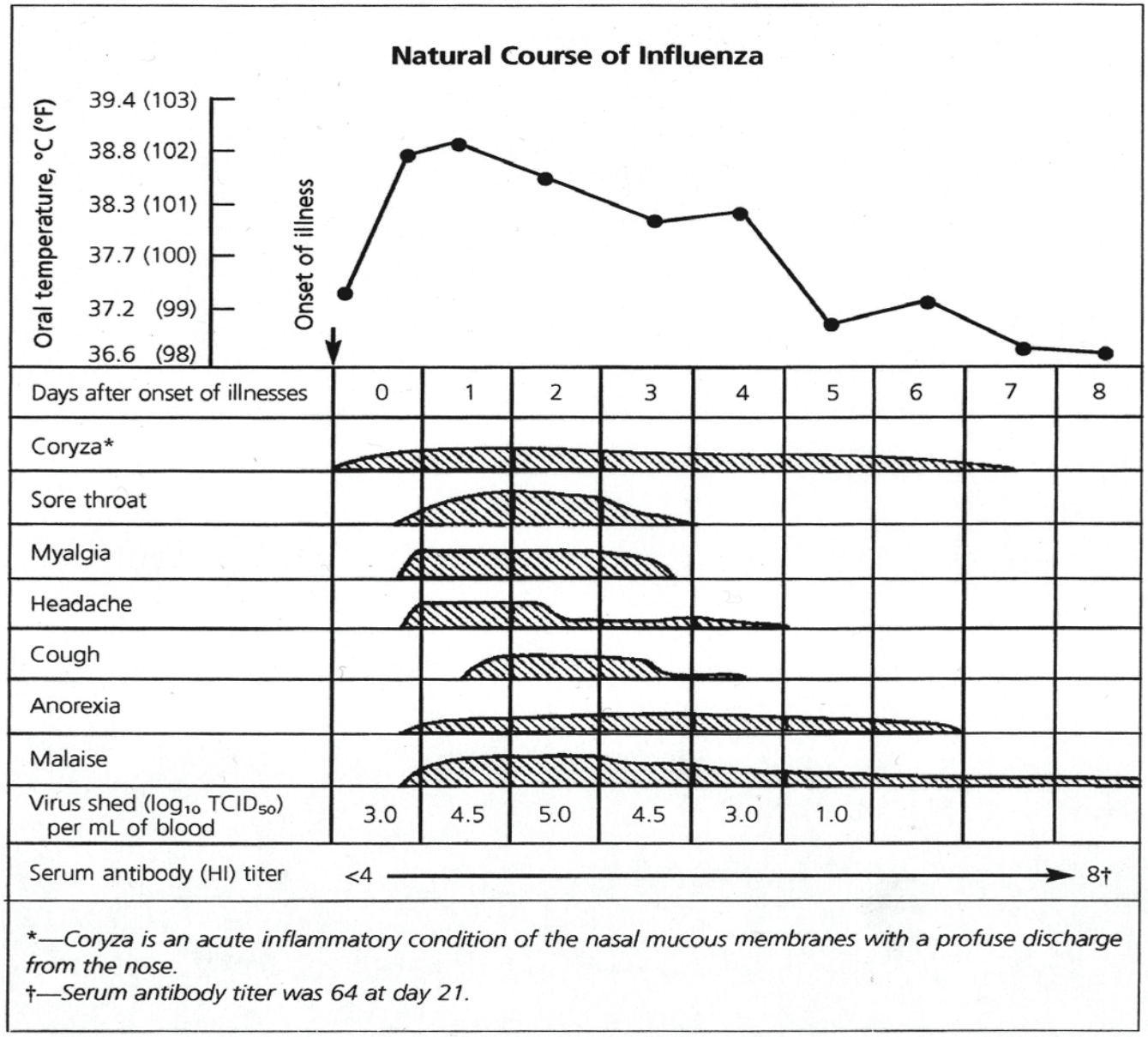
Voies de transmission

1. aérosolisation

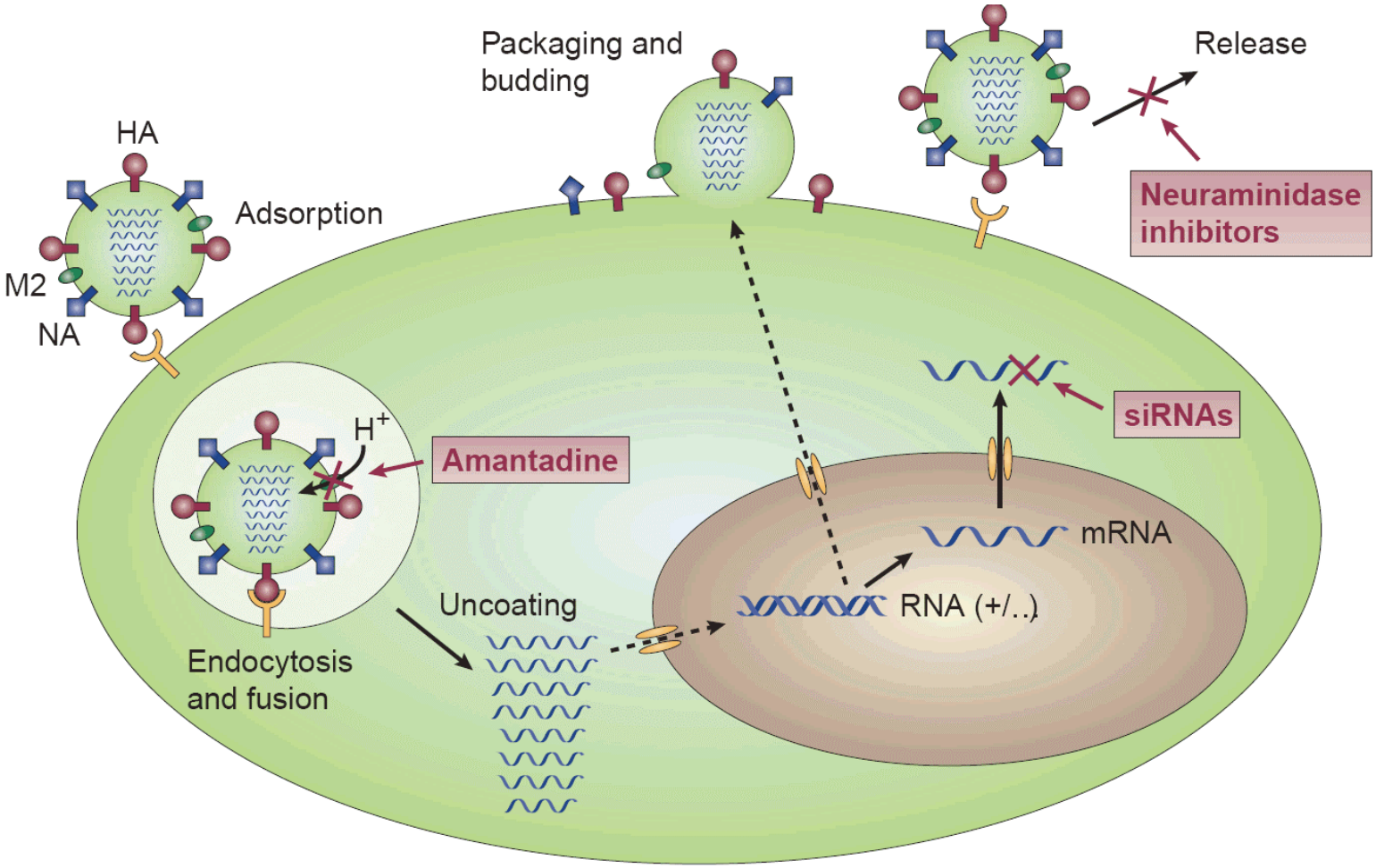
2. Voie aérienne

3. Objets contaminés

La grippe: signes cliniques



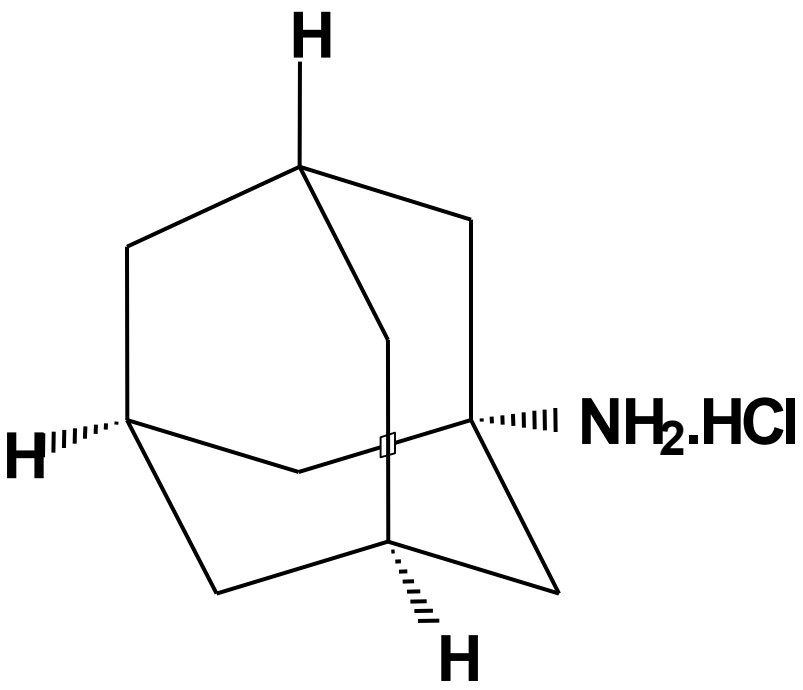
Cibles des antiviraux



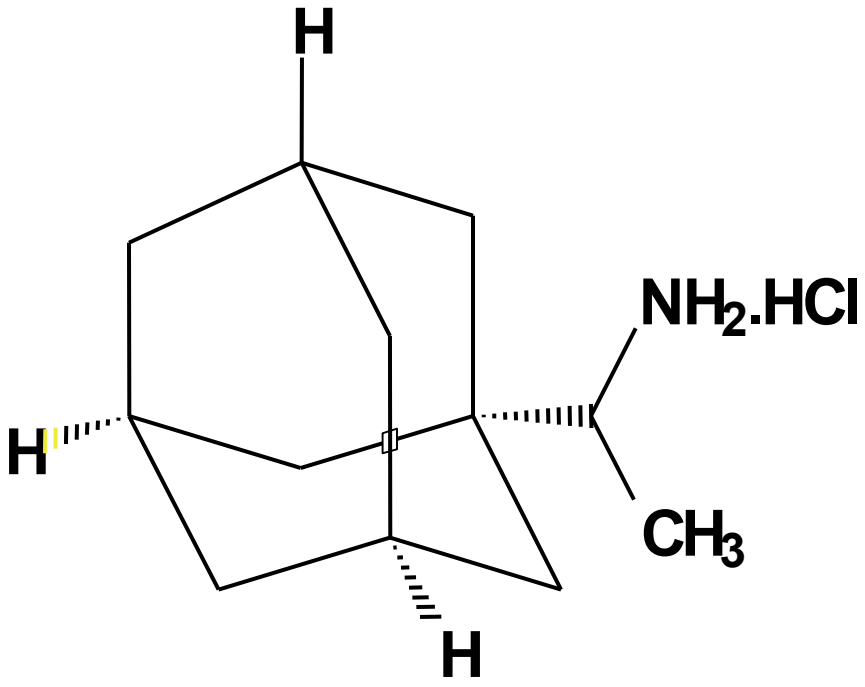
P. Palese Nature Medicine 10 : 2004

ADAMANTANES

Adamantanes



Amantadine

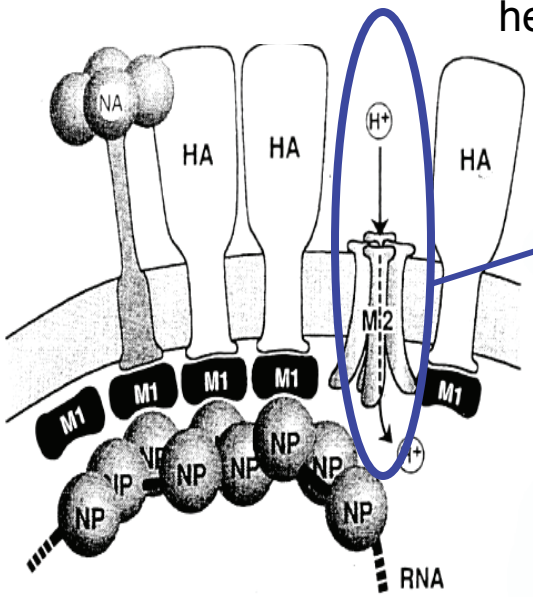


Rimantadine

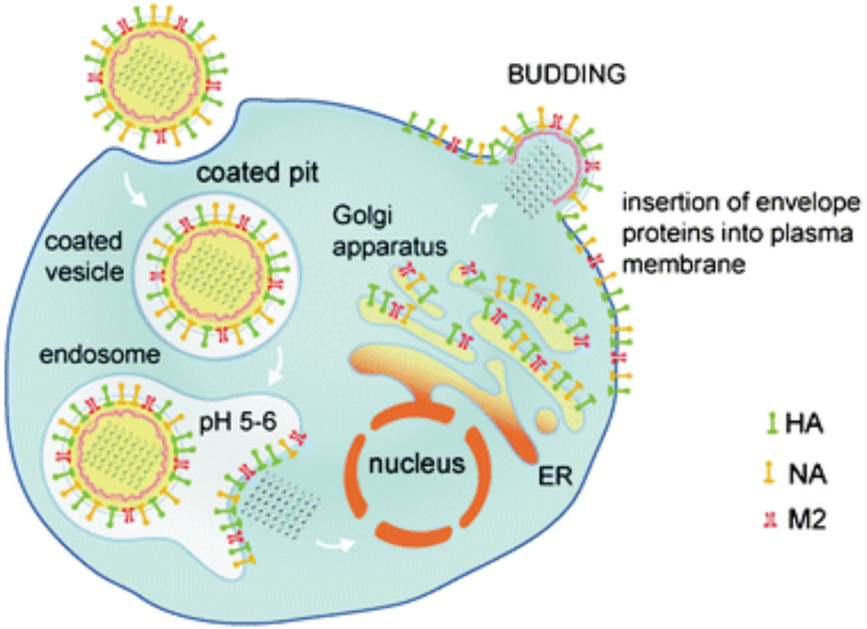
Mode d'action

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

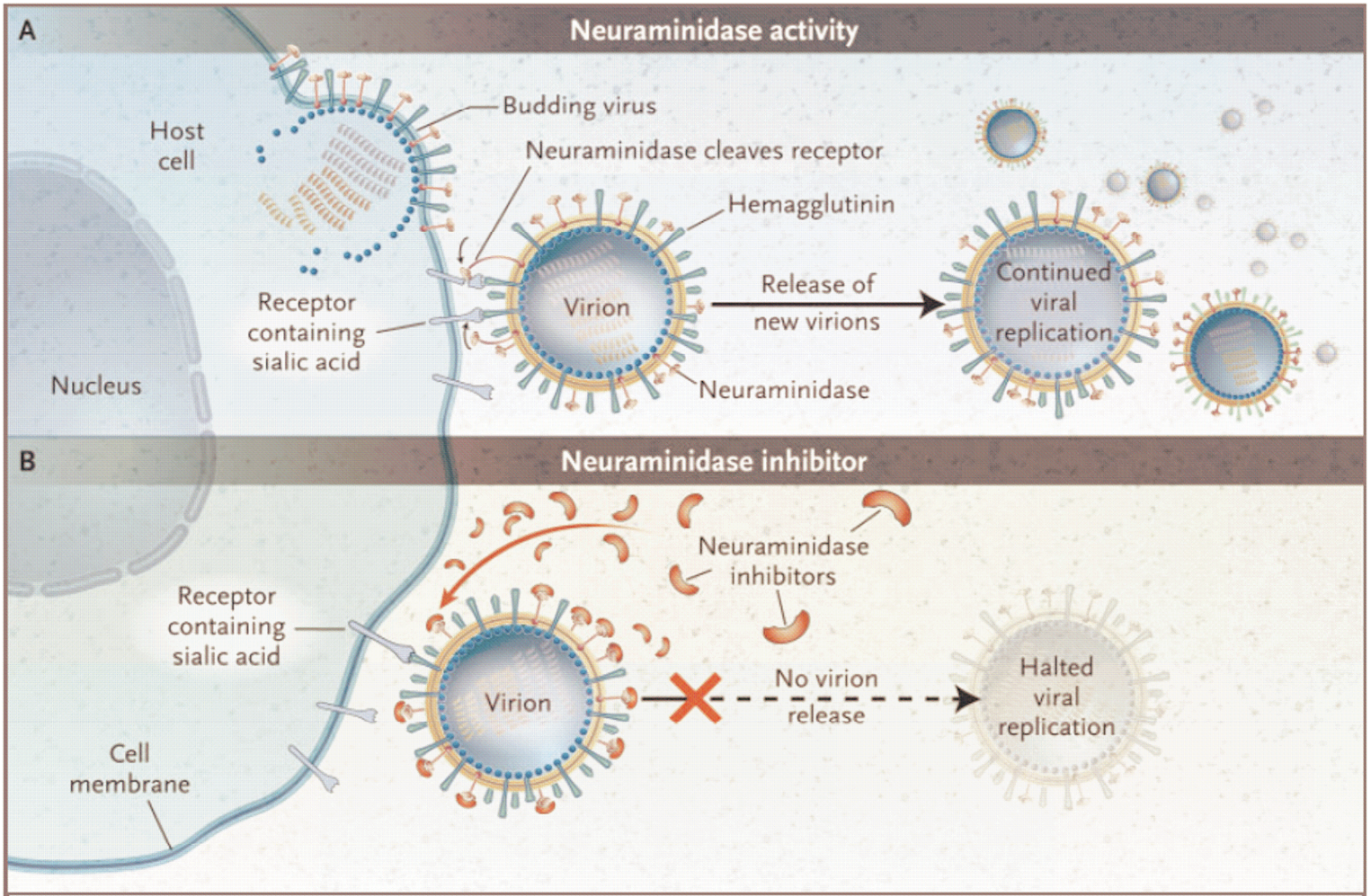
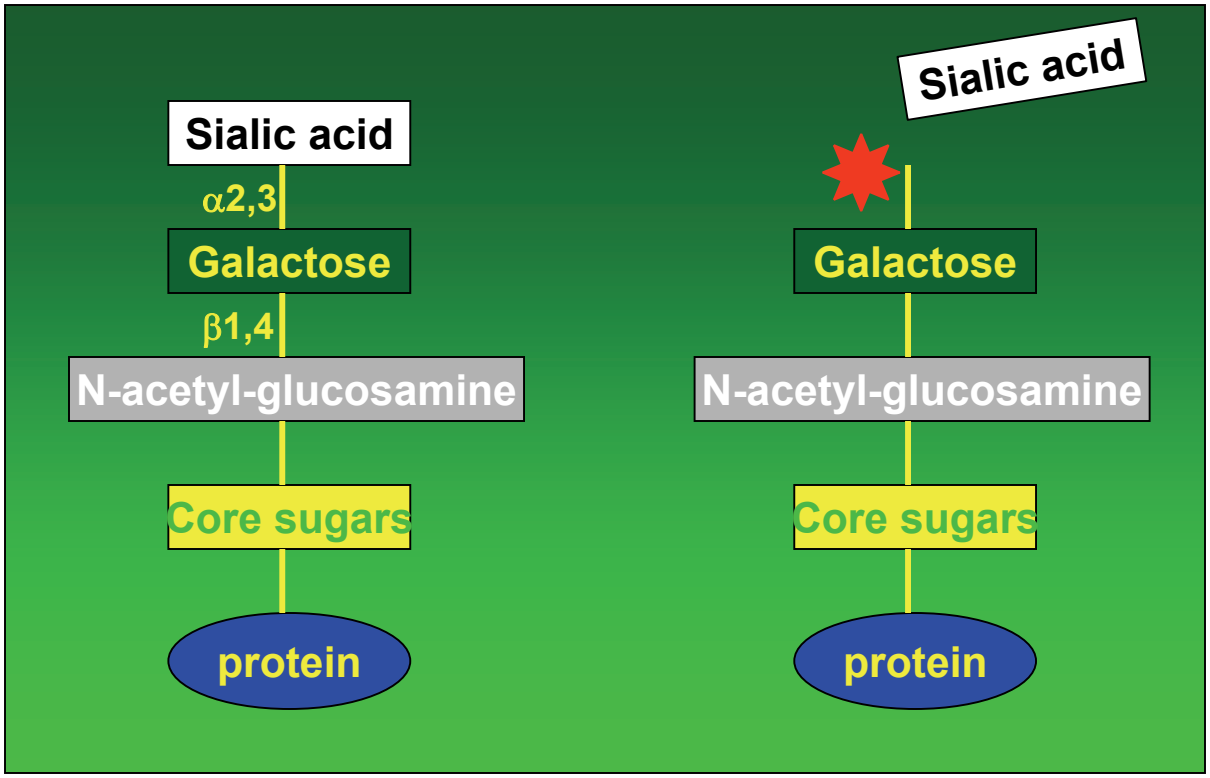


Figure 1. Mechanism of Action of Neuraminidase Inhibitors.

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



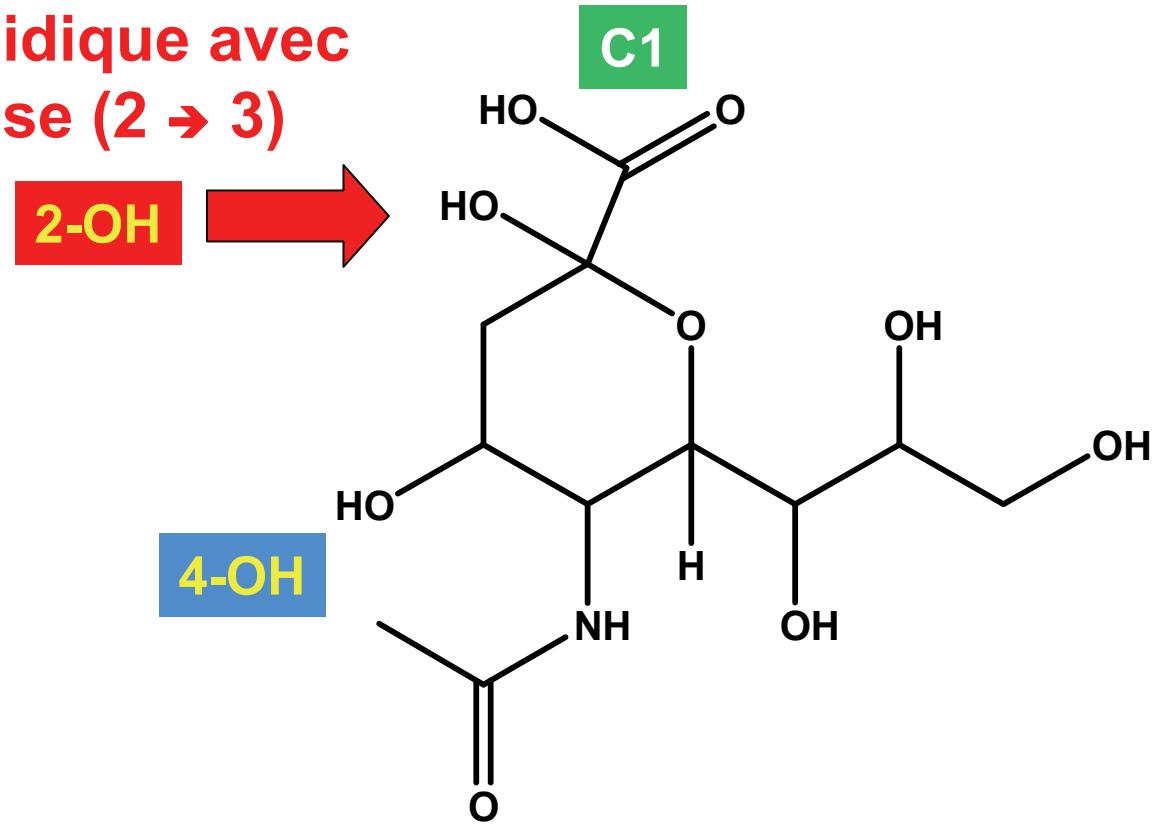
La neuraminidase clive l'acide sialique des glycoprotéines de surface cellulaire auquelles sont attachées les nouvelles particules virales

Functions:

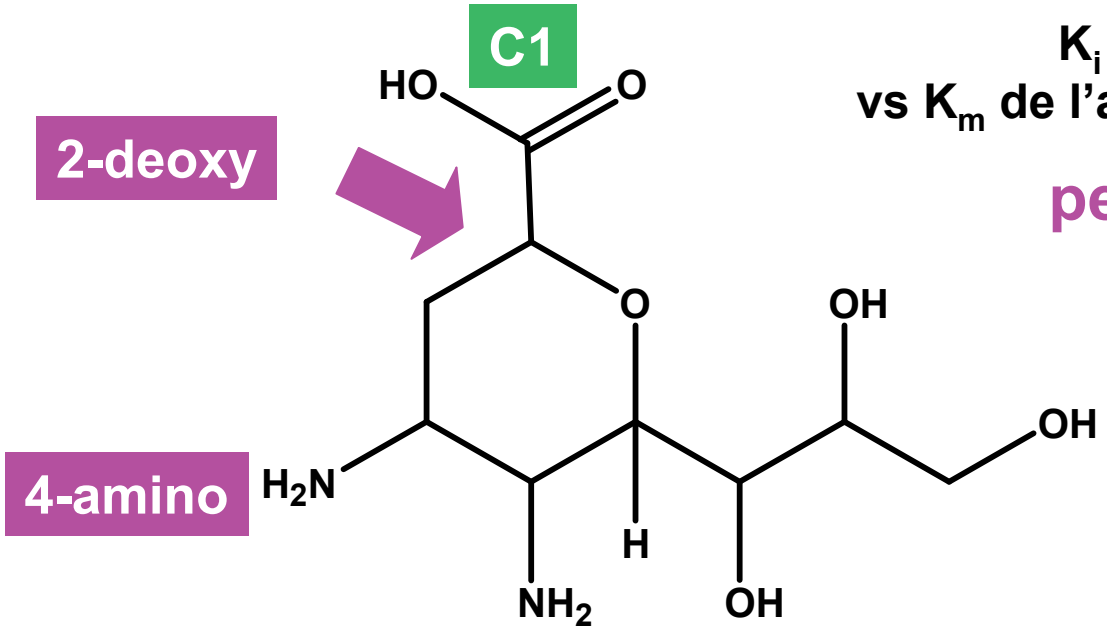
- favorise la libération des particules virales
- détruit les récepteurs de surface reconnus par les hémagglutinines
- prévient l'aggrégation des virus à la surface cellulaire
- prévient l'inactivation par le mucus respiratoire

L’acide sialique

Lien osidique avec galactose (2 → 3)



Découverte du premier inhibiteur … 1969 !



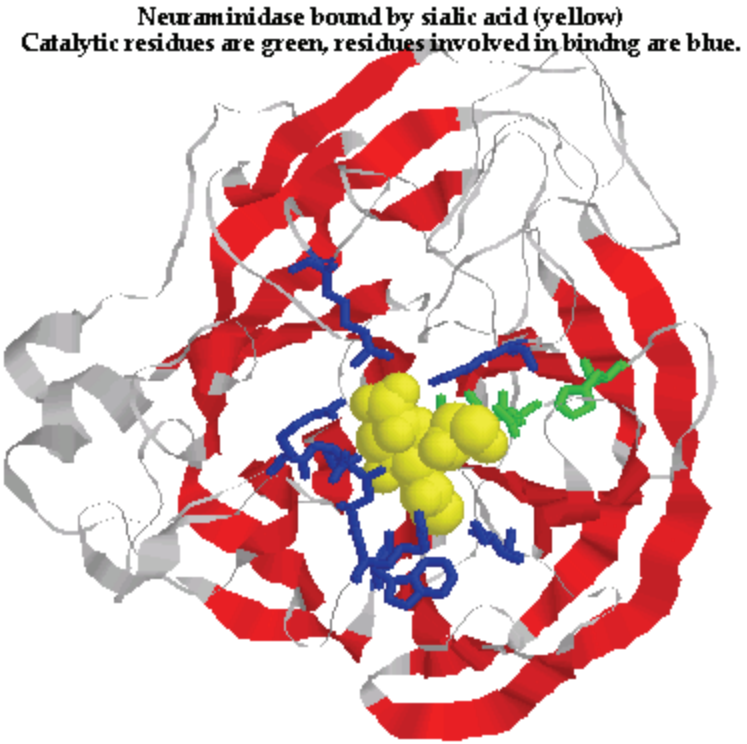
K_i ~ 0.01 mM
vs K_m de l'acide sialique ~ 1mM

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...



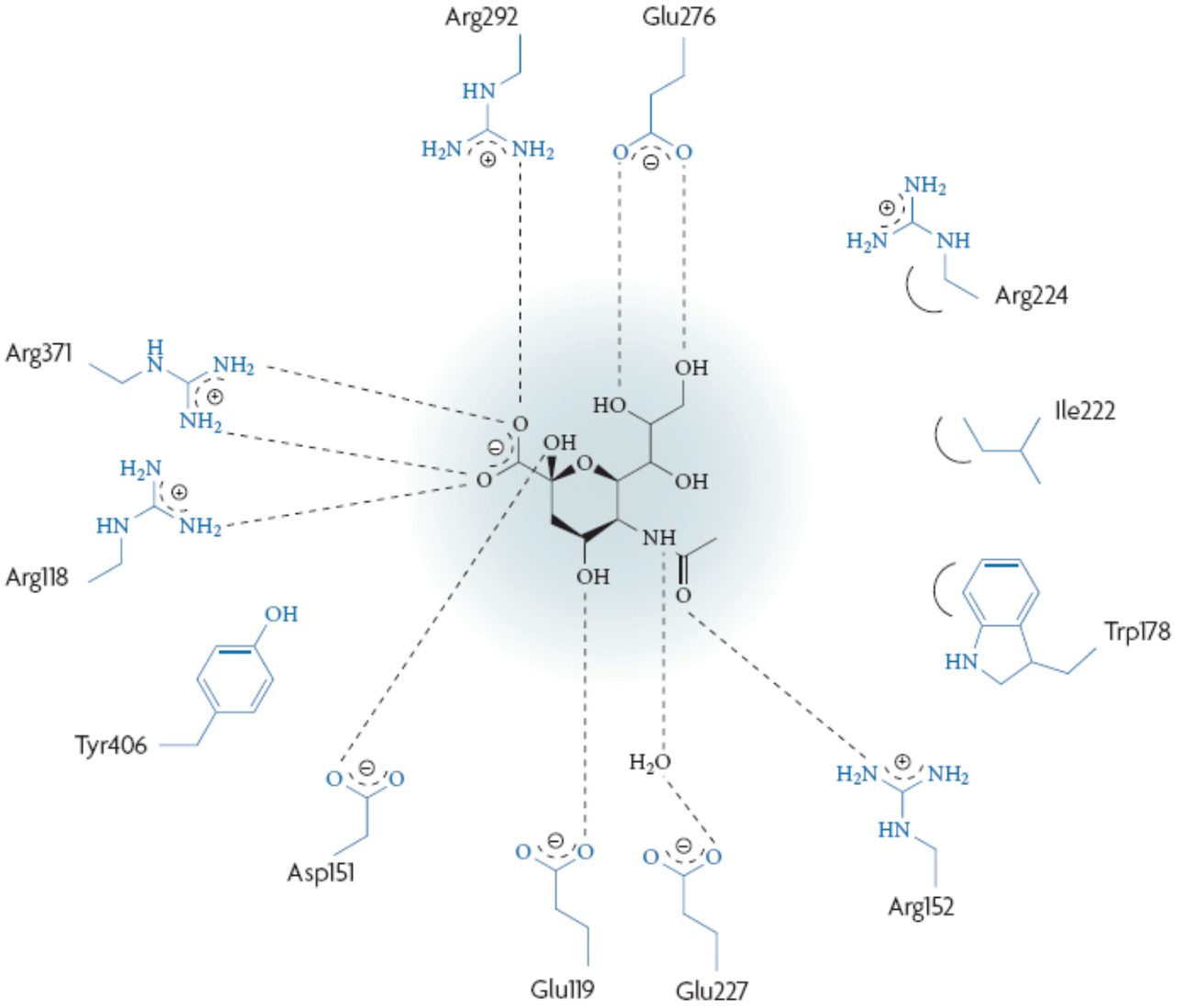
1983: structure of neuraminidase

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

→ place pour du drug design !

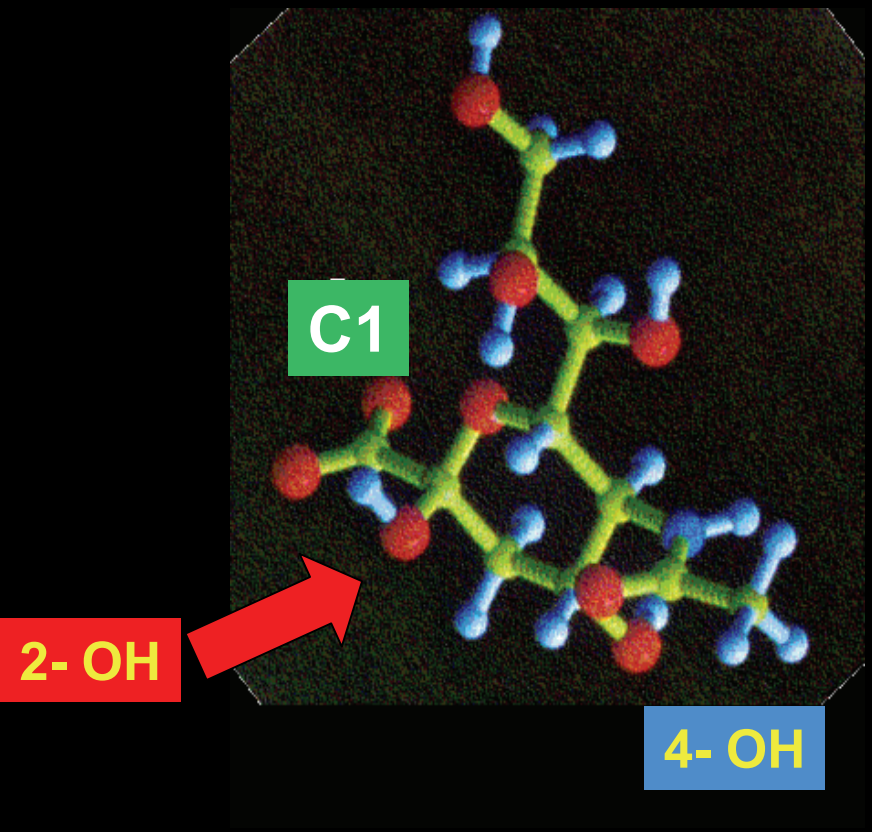
Colman et al., Nature (1983) 303: 41-44

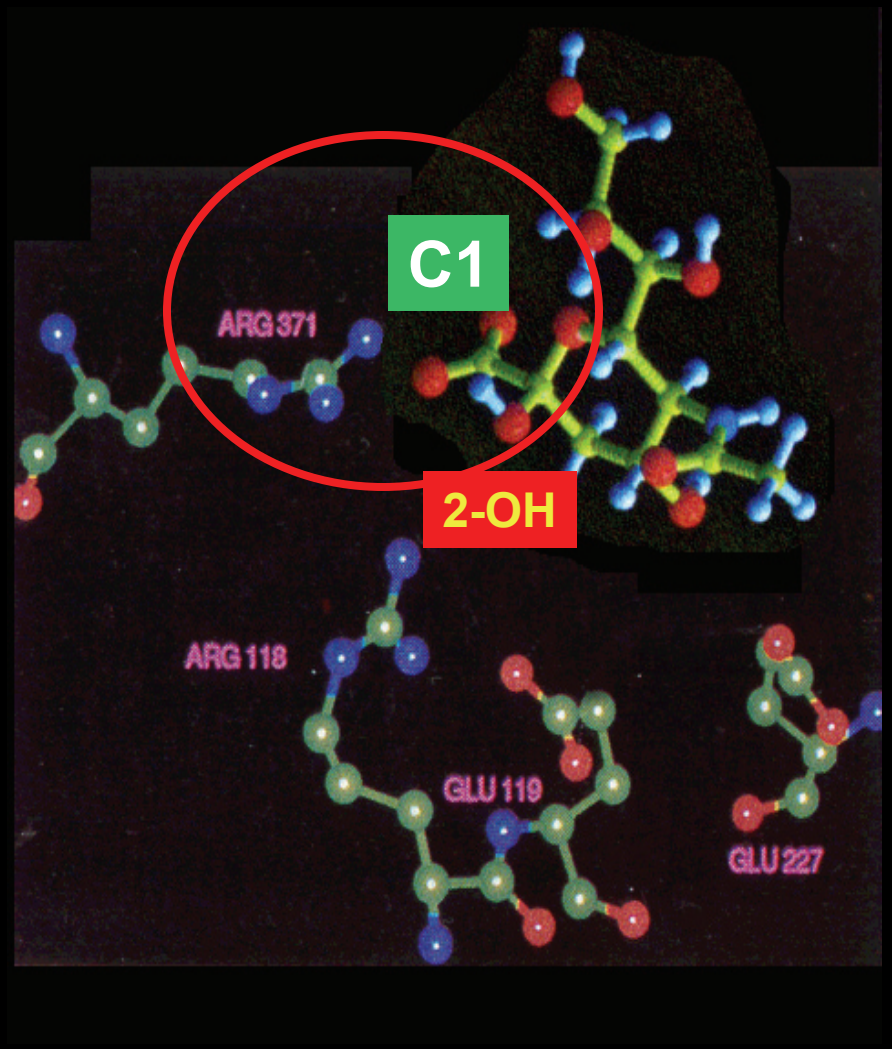
Site actif de la neuraminidase



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

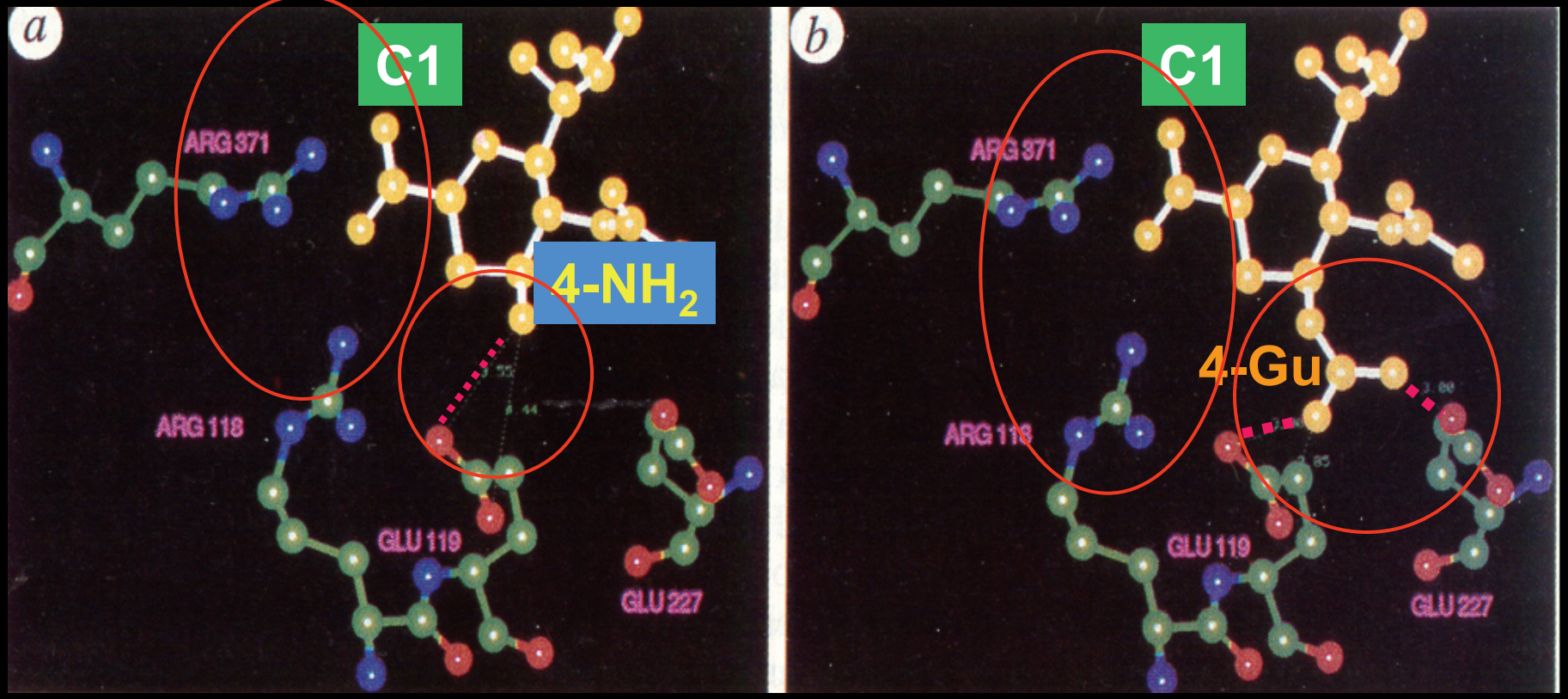
De l'acide sialique au zanamivir… (1)





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

De l'acide sialique au zanamivir… (2)

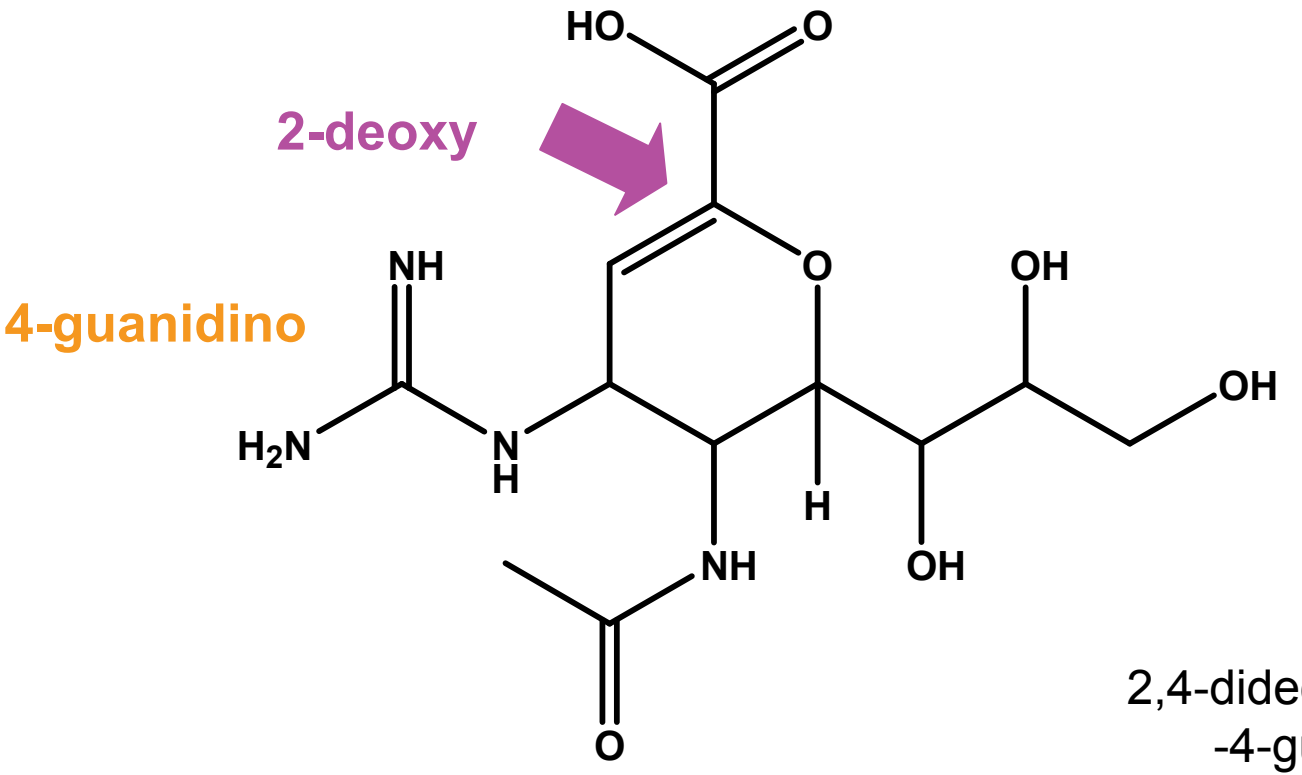


4-deoxy-4-amino ...

4-deoxy-4-guanidino...

interaction avec 1 puis 2 résidus conservés

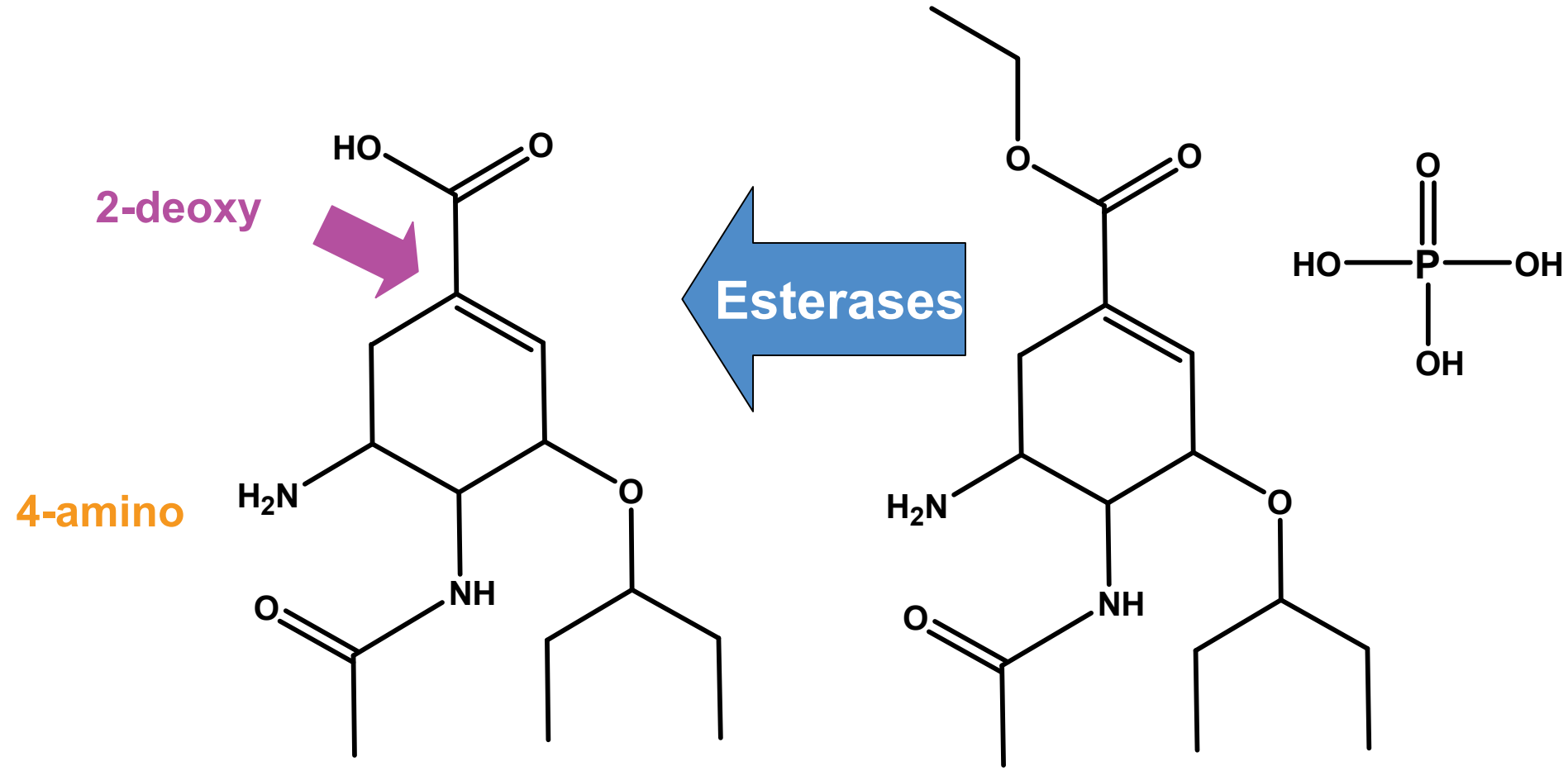
Le zanamivir



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

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

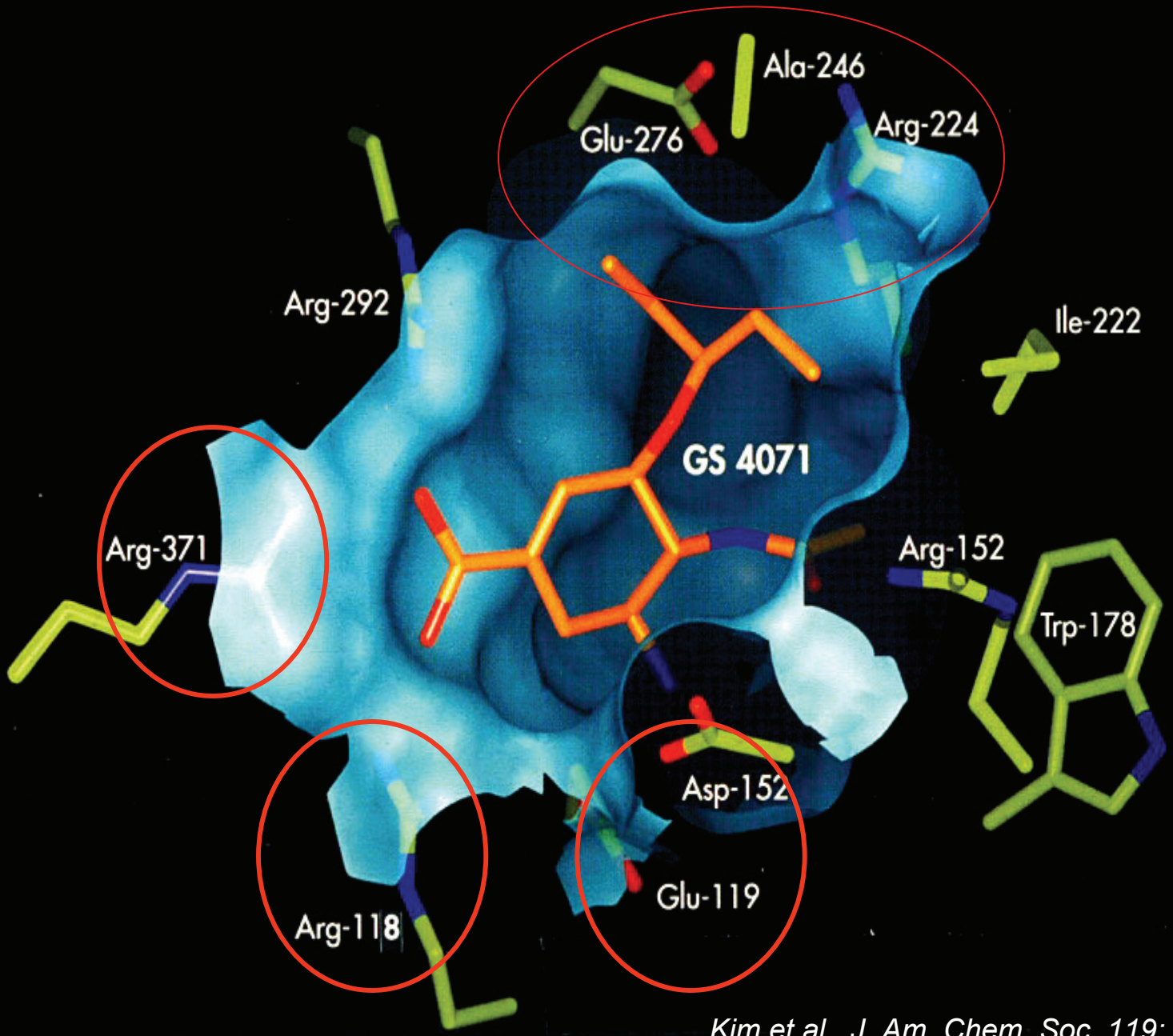
L'oseltamivir



oseltamivir

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

Oseltamivir dans le site actif



Kim et al., J. Am. Chem. Soc. 119: 681-690 (1997)

Résistance: mutation de la cible

Neuraminidase

119 Glu → Gly:

- Résistance au zanamivir
  (Glu 119 interagit avec guanidinium)

292 Arg → Lys (R292K)**:**

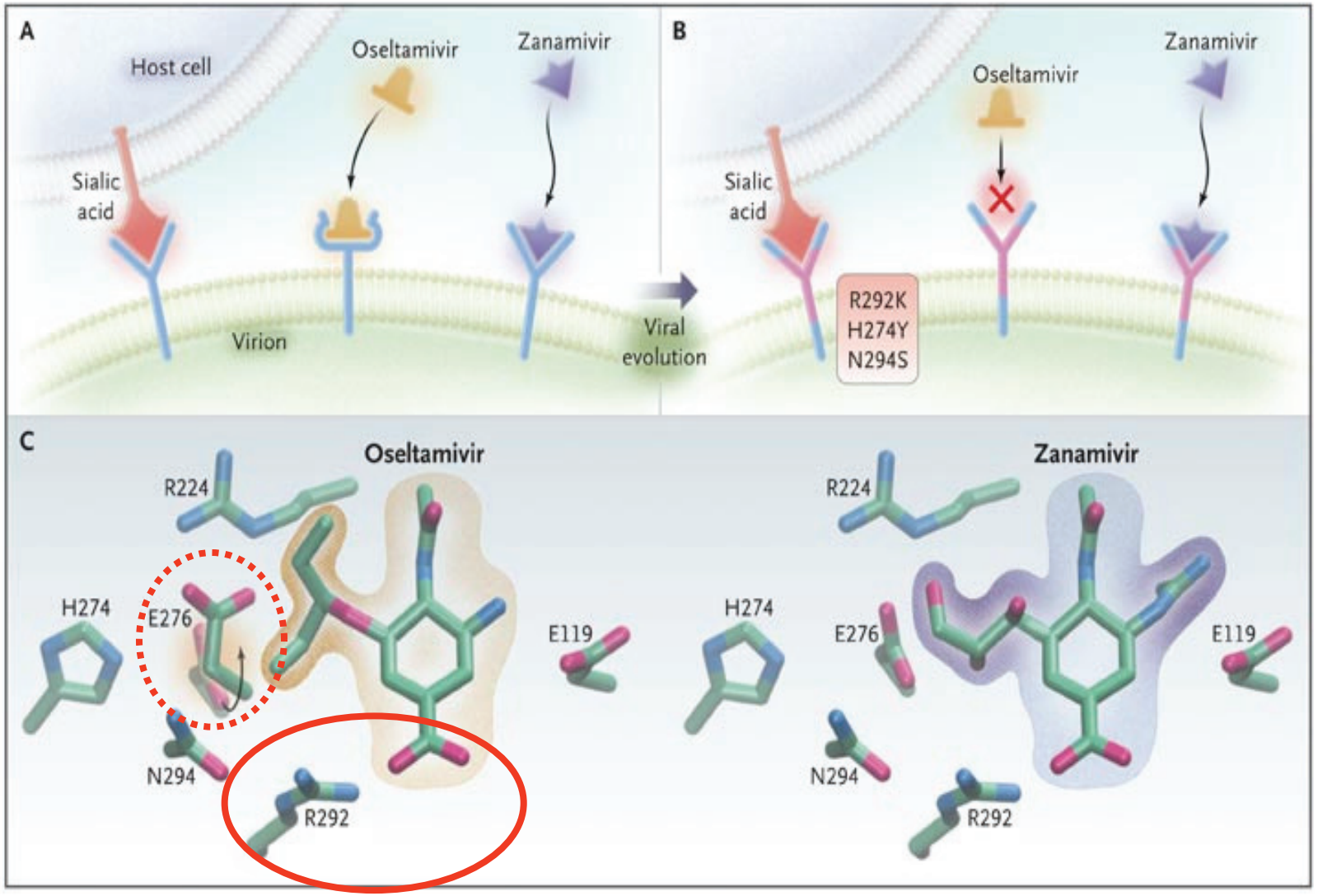
- Résistance à l'oseltamivir
  (Arg 292 interagit avec acide carboxylique mais conformation de la poche enzymatique adhoc pour le zanamivir)

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

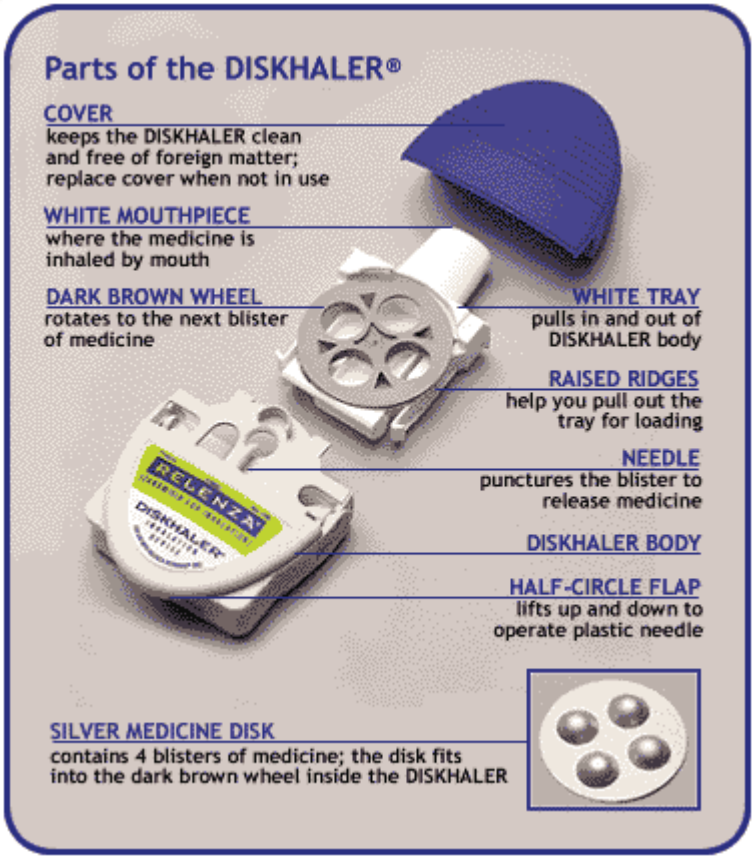
Mechanism of Resistance to Oseltamivir.

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 effiicace chez les patients contaminés	
tolérance	Bonne sauf path. respir.	bonne

Zanamivir: voie d'administration

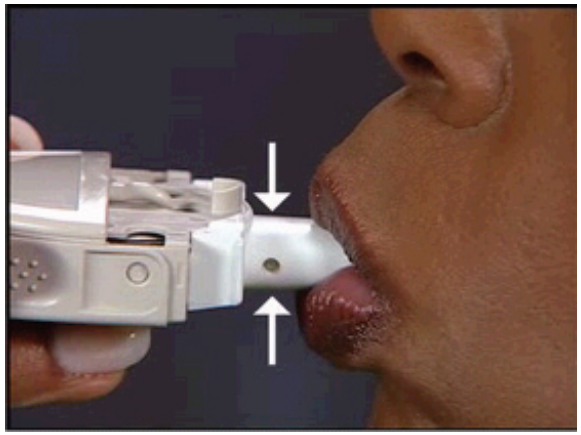


http://www.relenza.com/how-to-use-diskhaler.jsp?languages=French

Zanamivir: comment l'administrer correctement ?

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

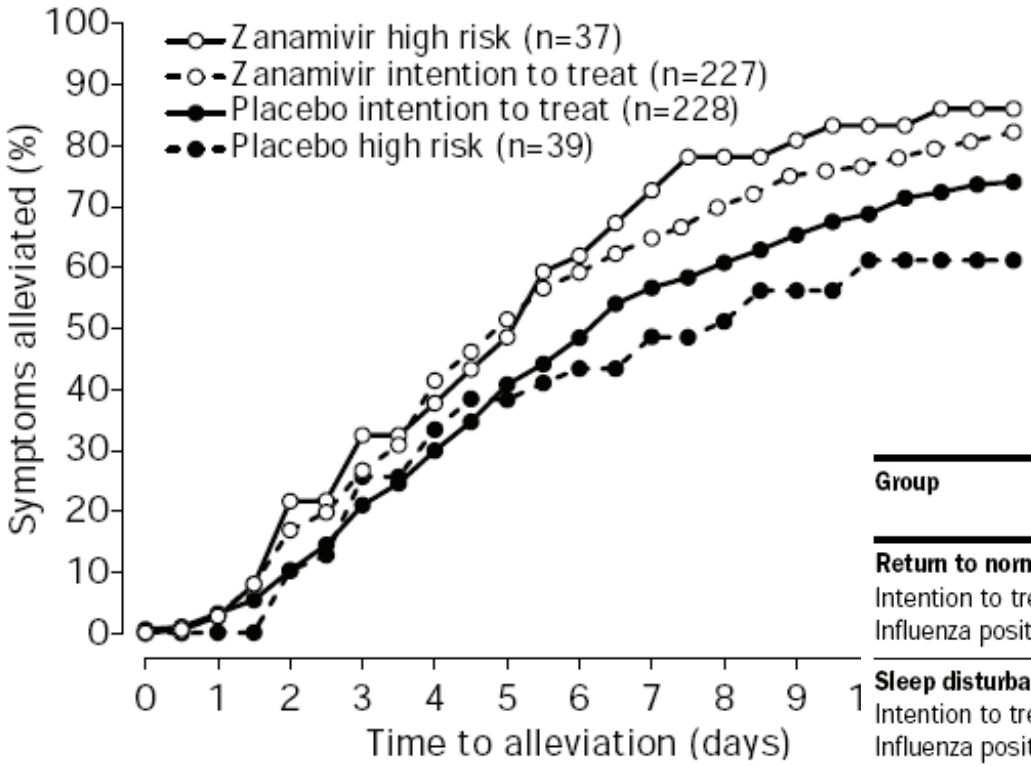
Zanamivir: comment l'administrer correctement ?



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*

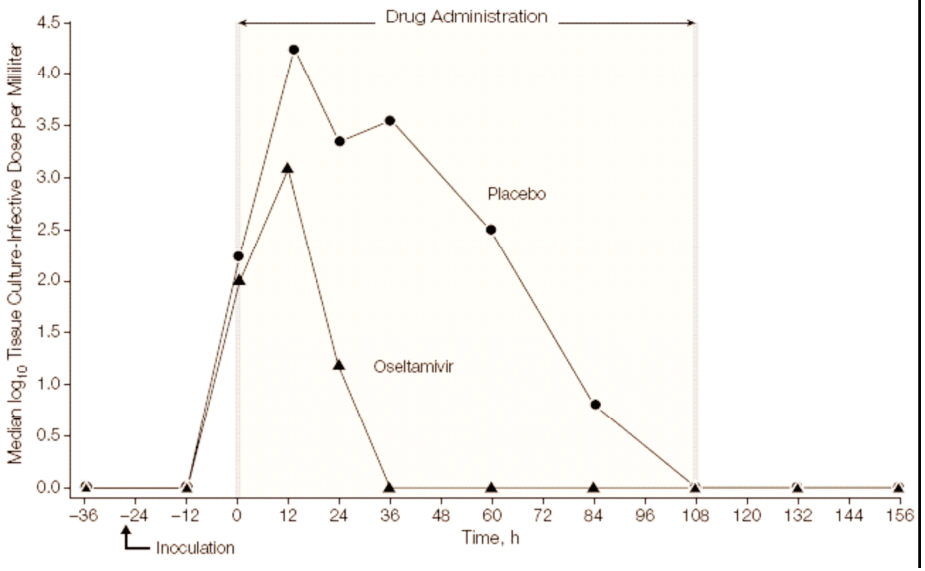
Outcome	Frequencies in Study Groups, No. (%)		Odds Ratio (95% CI)	Estimated Risk Ratio (95% CI)	Efficacy, 1 – Risk Ratio (95% CI), %
	Placebo (n = 554)	Zanamivir (n = 553)			
Laboratory-confirmed clinical influenza	34 (6)	11 (2)	0.31 (0.14-0.64)†	0.33 (0.17-0.61)	67 (39-83)
Laboratory-confirmed influenza 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 ?

Figure 3. Effect of Oral Oseltamivir Treatment on Vital Titers in Nasal Lavages Following Experimental Influenza A/Texas/36/91(H1N1) Infection

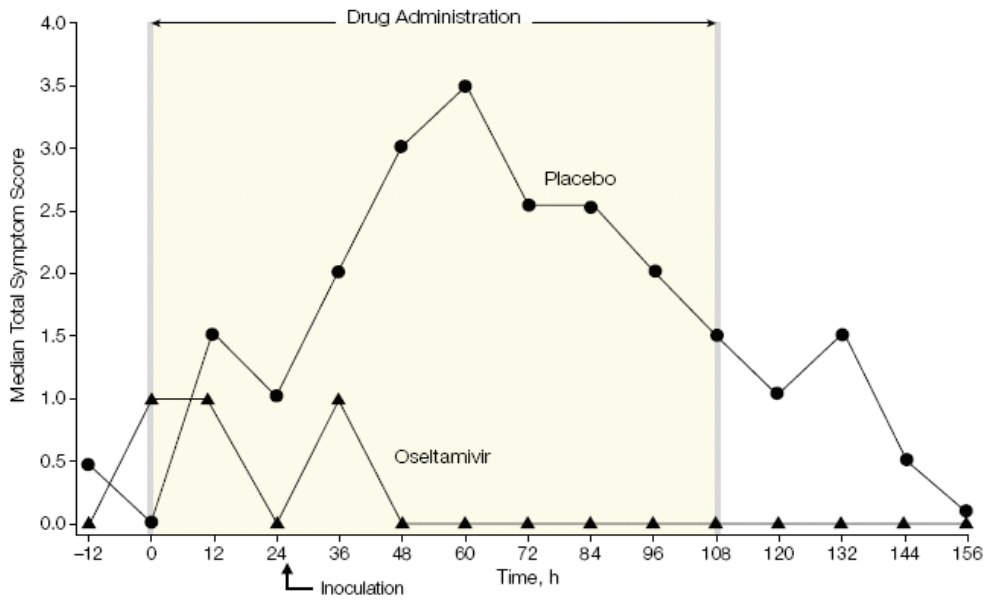


Traitement :
On gagne 1-2 jours …

JAMA (1999) 282:31-36

Prophylaxie :
efficace

Figure 2. Effect of Oral Oseltamivir Prophylaxis on Illness Following Experimental Influenza A/Texas/36/91(H1N1) Inoculation



The total symptom score area under the curve value was lower in the combined oseltamivir groups (n = 21) compared with placebo (n = 12); $P = .02$. Fourteen symptoms related to influenza were included in the score.

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:

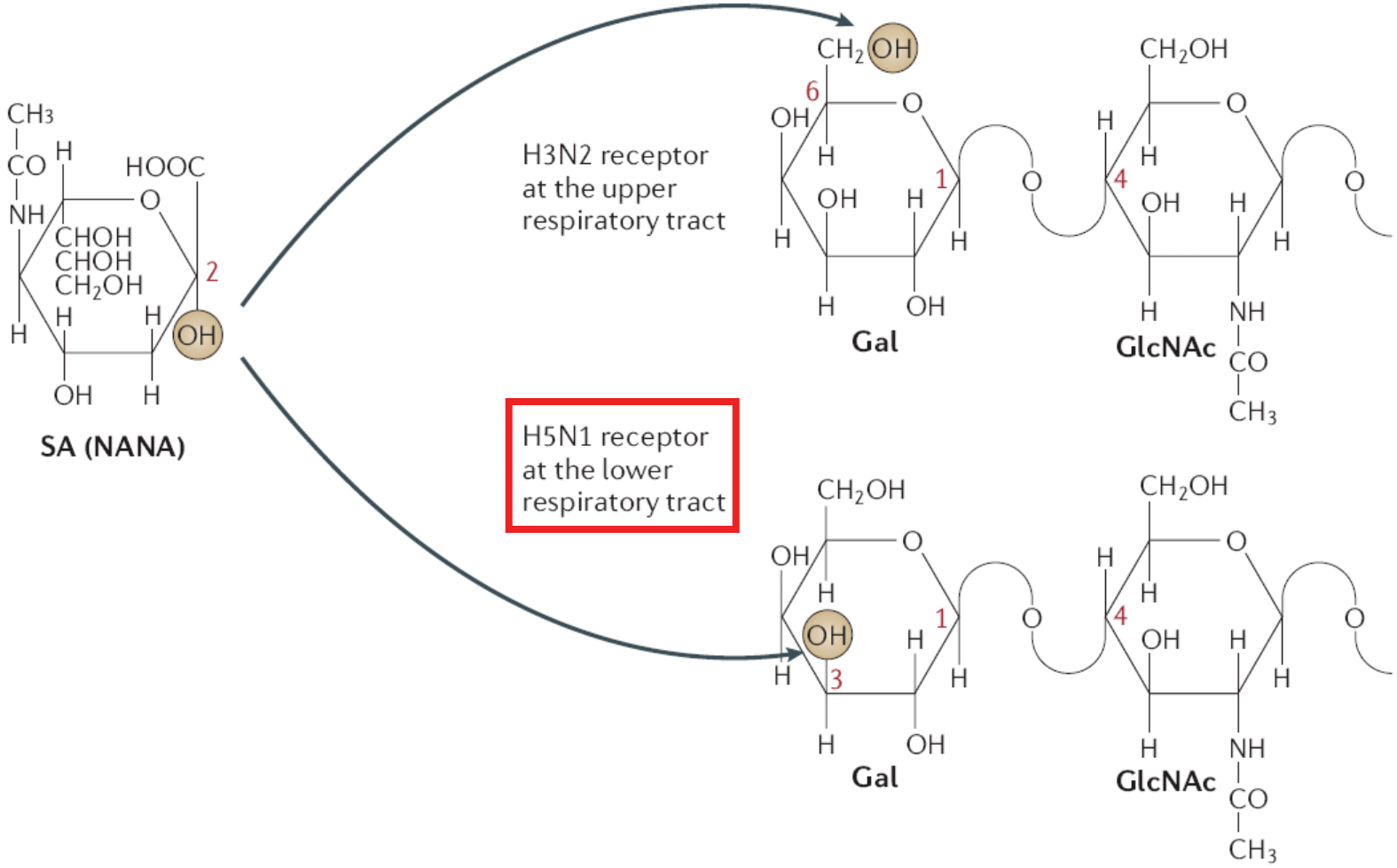
- ↘ durée des symptomes de 1-2 jours
- ↘ risque de transmission du virus
- ↘ risque de complications (sinusite, bronchite)
- ↘ usage d'antibiotiques

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 ?

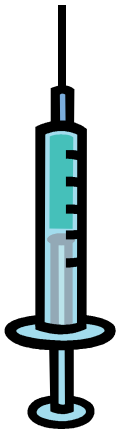
Conseils aux voyageurs

- 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

Pharmacothérapie de la grippe

- Traitement symptomatique
  - antipyrétiques
    - éviter aspirine chez les enfants (syndrôme de Reye)
  - selon les symptomes: 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 !

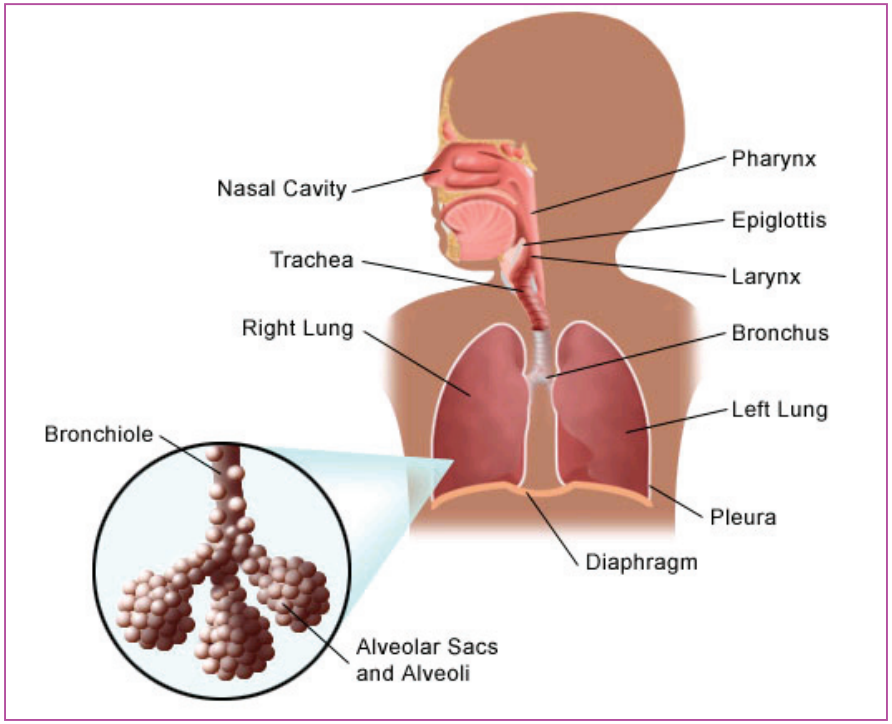
Recommandations de vaccination



- 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, …)

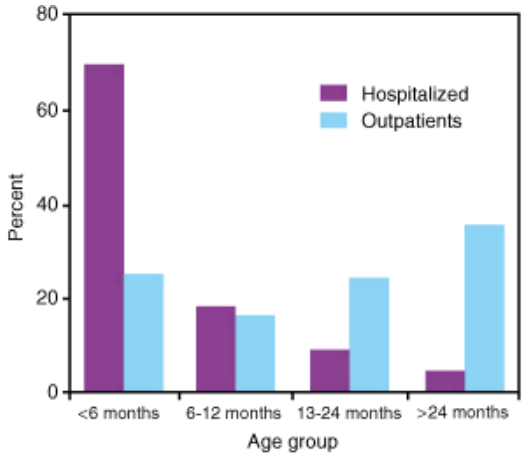
ANTIVIRAUX ACTIFS SUR RESPIRATORY SYNCYTIAL VIRUS (RSV)

Infections respiratoires à RSV



Respiratory Illnesses Caused by Respiratory Syncytial Virus (RSV)

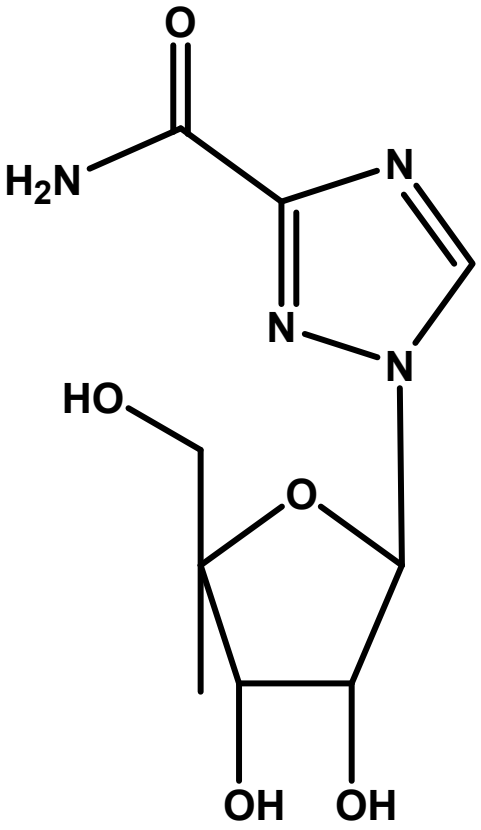
Syndrome	*PercentageCaused by RSV*
Bronchiolitis	43-90
Pneumonia	5-40
Tracheobronchitis	10-30
Croup	3-10
Asymptomatic	0.3



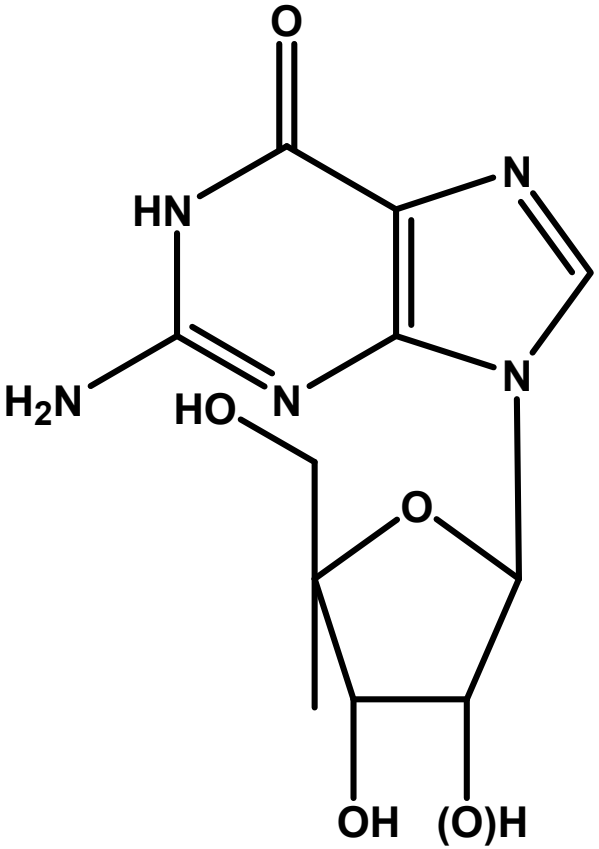
Difference in age distribution of inpatients and outpatients with respiratory syncytial virus infection in Rochester, NY.

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

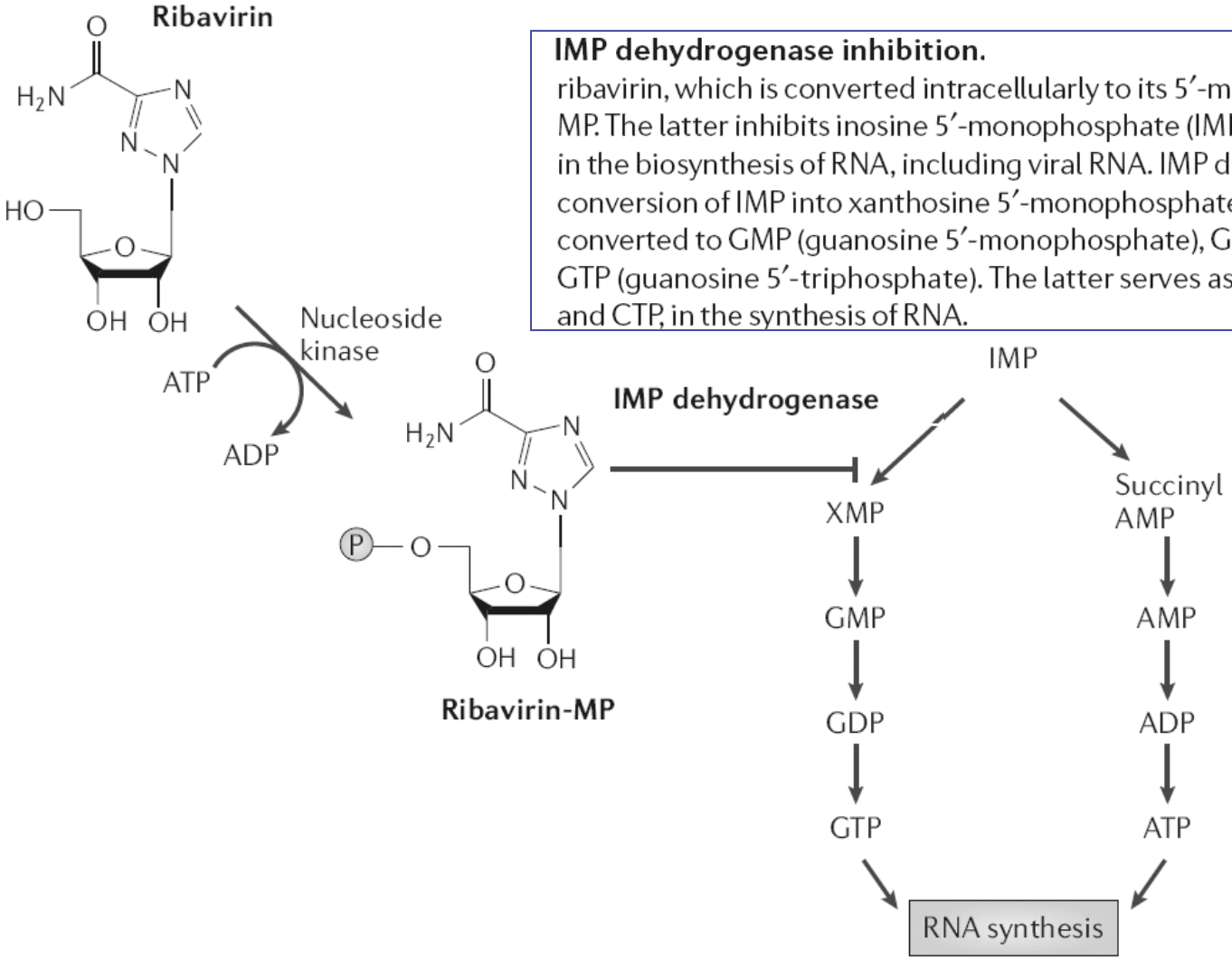


RIBAVIRINE



(deoxy)GUANOSINE

Mode d'action de la ribavirine



IMP dehydrogenase inhibition.
ribavirin, which is converted intracellularly to its 5′-monophosphate derivative, ribavirin-MP. The latter inhibits inosine 5′-monophosphate (IMP) dehydrogenase, a crucial enzyme in the biosynthesis of RNA, including viral RNA. IMP dehydrogenase is responsible for the conversion of IMP into xanthosine 5′-monophosphate (XMP) which, in turn, is further converted to GMP (guanosine 5′-monophosphate), GDP (guanosine 5′-diphosphate) and GTP (guanosine 5′-triphosphate). The latter serves as substrate, together with ATP, UTP and CTP, in the synthesis of RNA.

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:

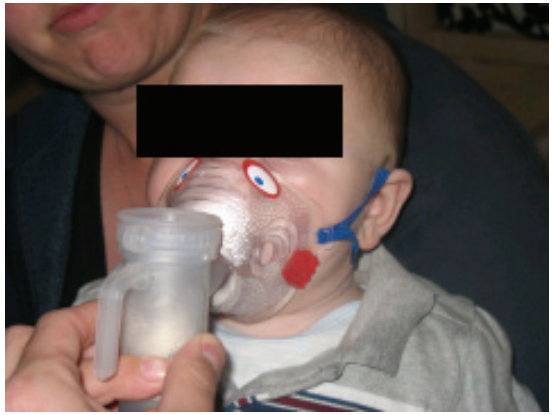
- Détérioration de la fonction respiratoire
- Anémie hémolytique + hypoplasie médullaire (Concentration dans les globules rouges)

Traitement des infections à RSV

Traitement symptomatique

- antipyrétique
- apport de fluides
- oxygène si nécessaire

- bronchodilatateurs
- cortocoïdes



Traitement antiviral

(ribavirine)