fimp Federazione Italiana Medici Pediatri

FIRENZE, 15 DICEMBRE 2018
STARHOTELS MICHELANGELO

Farmaci anti-influenzali

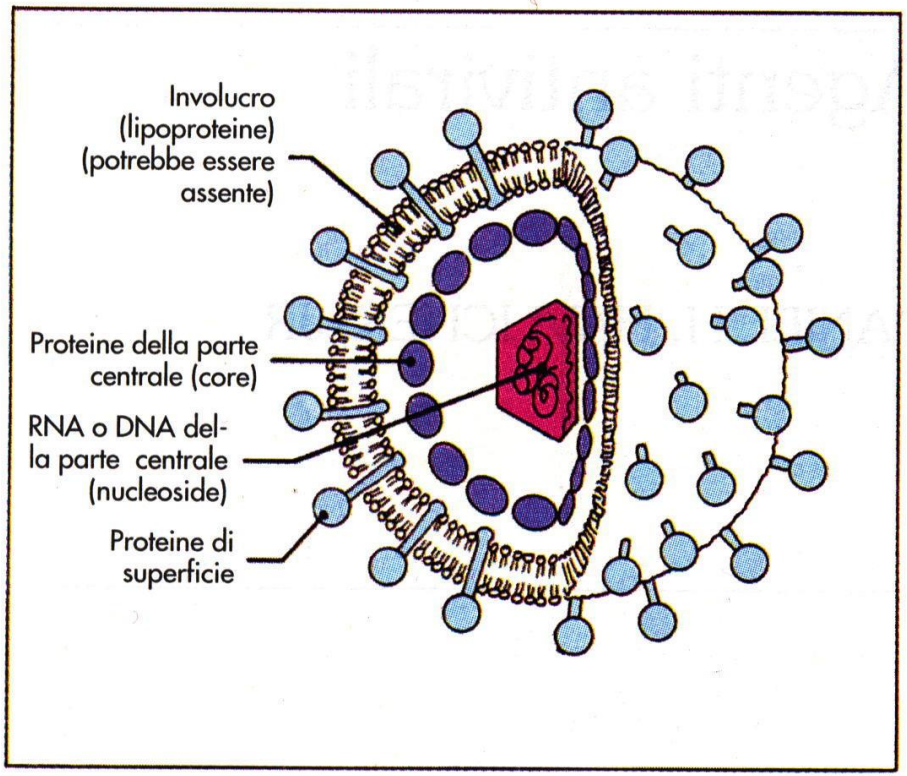
Elena Chiappini

Firenze 15 Dicembre 2018

INFLUENZA PERCHÉ AMMALARSI?

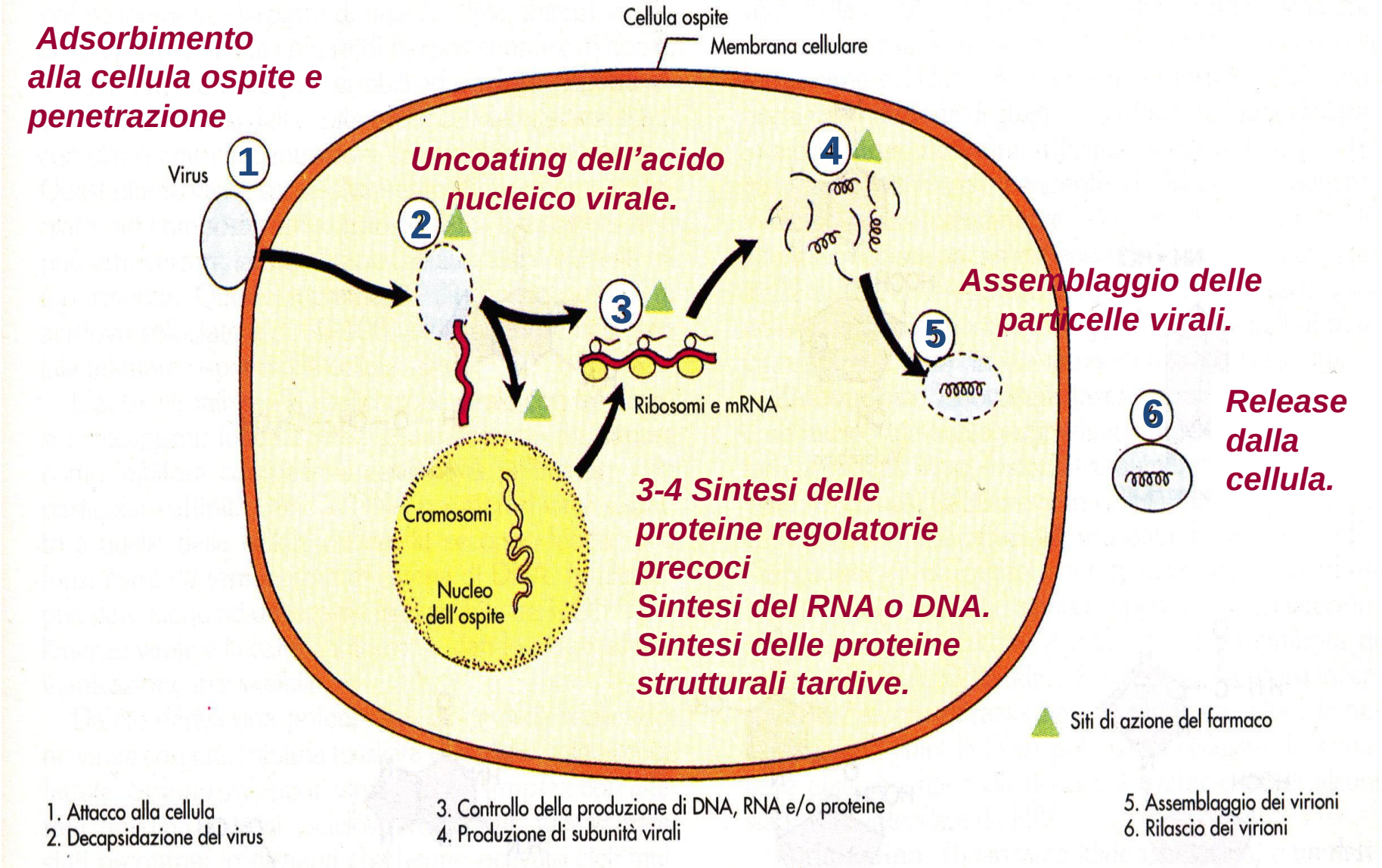
VIRUS *Parassiti intracellulari obbligati*

La loro replicazione dipende primariamente dai processi di sintesi della cellula ospite. I farmaci antivirali dovrebbero bloccare sia ***l'ingresso*** che ***l'uscita*** dalla cellula o essere ***attivi all'interno*** della cellula ospite.



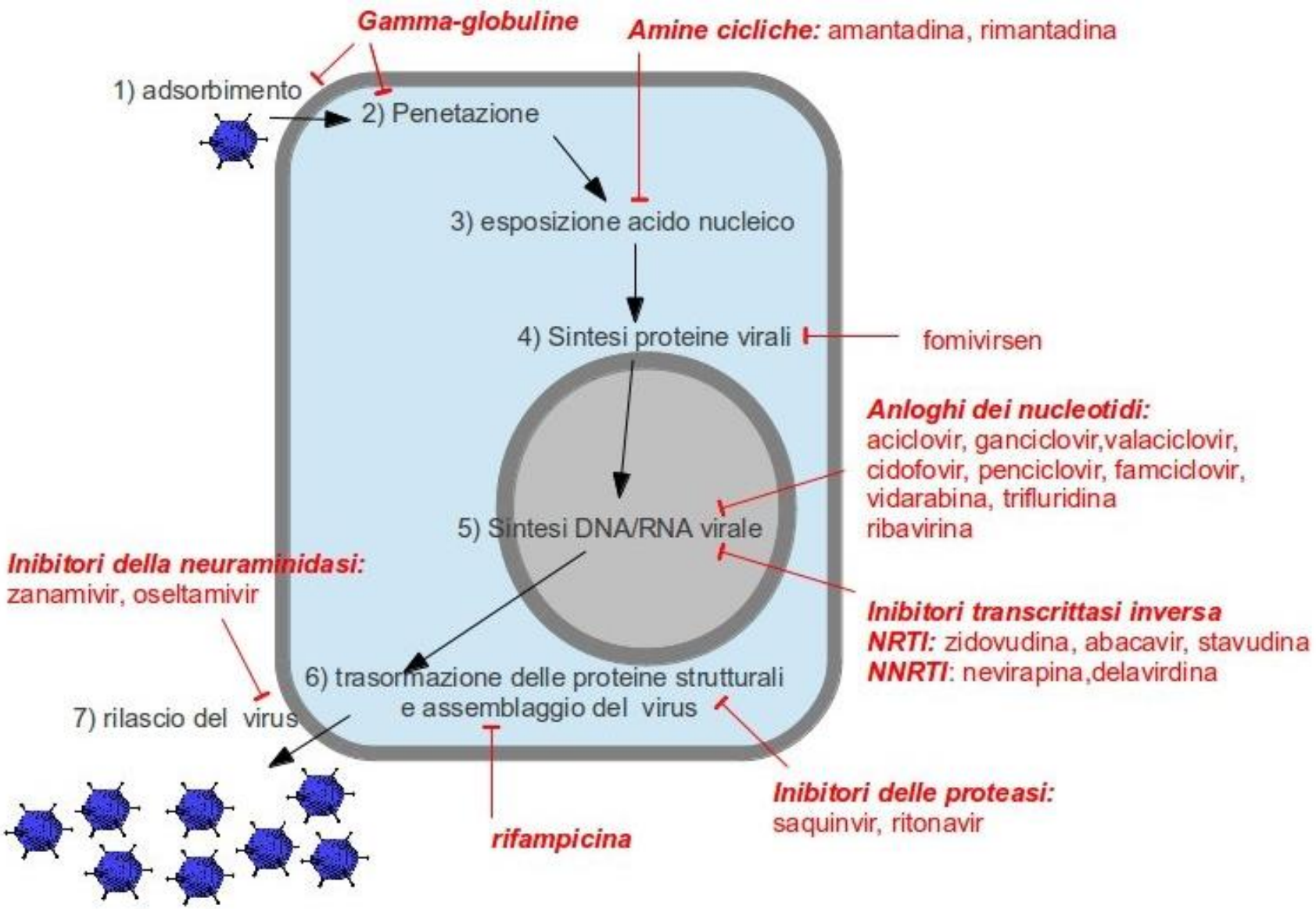
Doyle JD, Campbell AP. Curr Opin Pediatr. 2018 Dec 10

VIRUS – TAPPE DELLA REPLICAZIONE

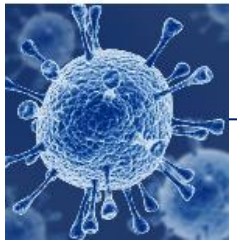


Doyle JD, Campbell AP. Curr Opin Pediatr. 2018 Dec 10

PRINCIPALI SITI D'AZIONE DEI FARMACI ANTIVIRALI

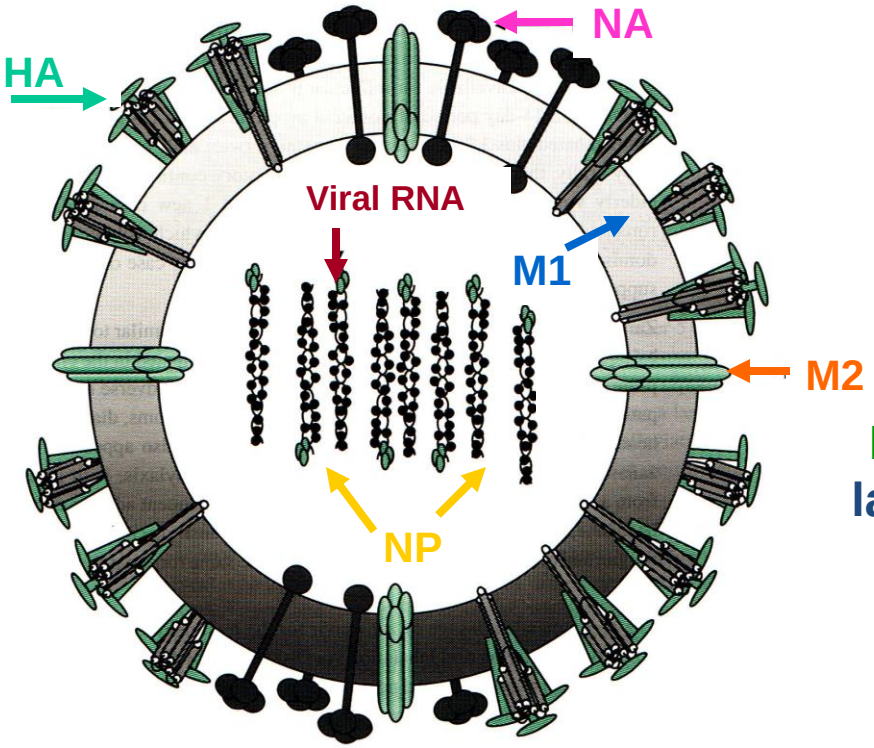


Doyle JD, Campbell AP. Curr Opin Pediatr. 2018 Dec 10



MIXOVIRUS – INFLUENZA VIRUS

Cavallazzi R, Ramirez JA. Clin Chest Med. 2018 ;39:703-721



Il virione dell'influenza contiene:
8 segmenti RNA
che codificano per 10 proteine

I **segmenti RNA** complessati con **Nucleoproteine (NP)** e con una **RNA-polimerasi**
RNA-dipendente trimerica costituiscono **la ribonucleoproteina core,** circondata da **uno strato di proteina matrice (M1)**

Emoagglutinina (HA) **Neuraminidasi** (NA) **M2** *(solo influenza tipo A)*

Sono tre proteine integrali immerse nel **guscio involucro (envelope) virale** derivato dalla membrana plasmatica delle cellule infette.

UNIVERSITÀ DEGLI STUDI FIRENZE

FARMACI ANTI-INFLUENZALI

- **INIBITORI DELLA PROTEINA M2**

Amantadina
Rimantadina

- **INIBITORI DELL'ENZIMA NEURAMINIDASI**

Zanamivir
Oseltamivir
Peramivir
Lanimavir

- **INIBITORI DELLA POLIMERASI RNA DIPENDENTE**

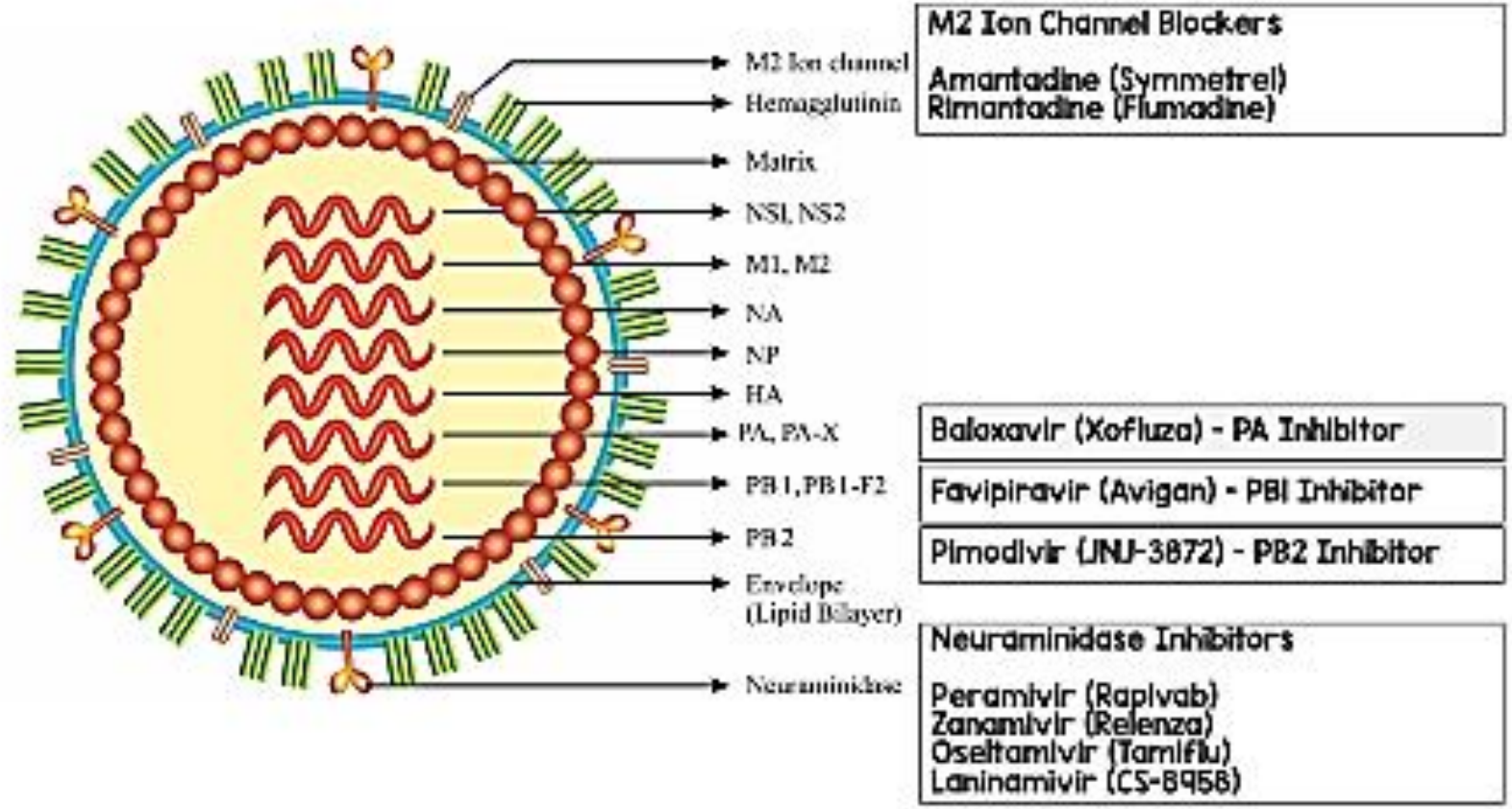
Favipiravir

- **INIBITORI DELLA ENDONUCLEASI CAP-DIPENDENTE**

Baloxavir

Cavallazzi R, Ramirez JA. Clin Chest Med. 2018 ;39:703-721

UNIVERSITÀ DEGLI STUDI FIRENZE



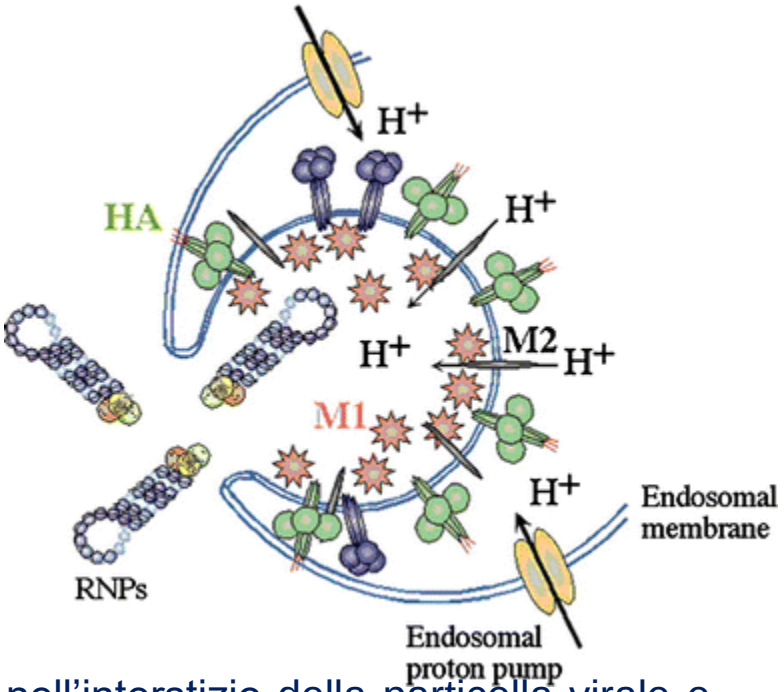
Beard KR, Brendish NJ, Clark TW. Curr Opin Infect Dis 2018;31:514-519

ADAMANTAMINE

AMANTADINA e RIMANTADINA
MECCANISMO D'AZIONE

- Agiscono bloccando un canale ionico formato dalla proteina M2 che attraversa la membrana virale.

- Durante lo stadio iniziale della replicazione virale il virus è captato in vescicole endocitotiche, in cui il pH si abbassa per l'ingresso di idrogenioni.



- Gli ioni idrogeno passano attraverso il canale M2 nell'interstizio della particella virale e promuovono la dissociazione della proteina M1 dai complessi ribonucleoproteine in modo che le ribonucleoproteine possono entrare nel nucleo cellulare e iniziare la replicazione.

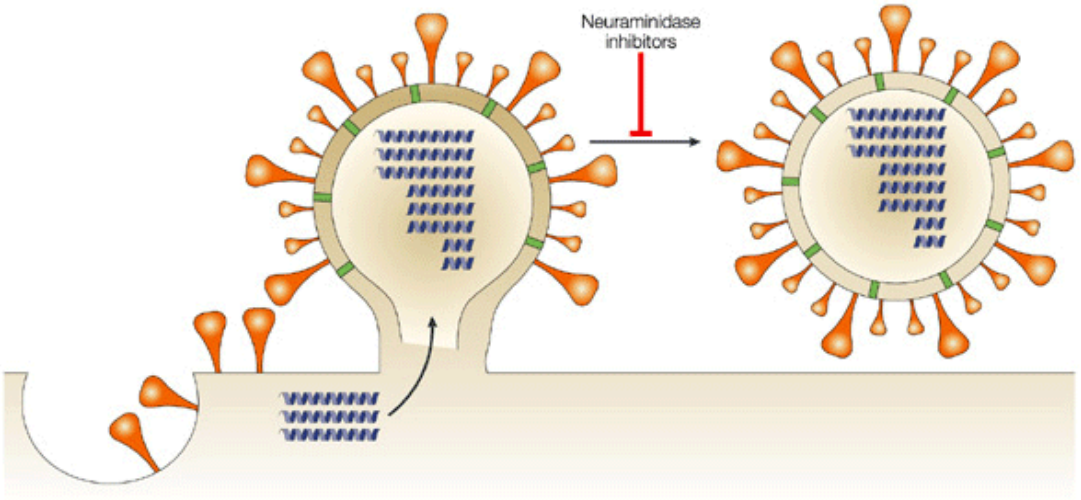
- Sia la AMANTADINA che la RIMANTADINA entrano nel canale ionico e bloccano la penetrazione degli ioni idrogeno che sono necessari per la dissociazione di M1 e ribonucleoproteine.

- ATTIVI SOLO VERSO I VIRUS A ----- RESISTENZE ELEVATE

Beard KR, Brendish NJ, Clark TW. Curr Opin Infect Dis 2018;31:514-519

NEURAMINIDASI

La **Neuraminidasi** catalizza il clivaggio virale dell'acido sialico terminale (acido N-acetilneuraminico) da vari glicoconiugati della superficie cellulare, facilitando la diffusione del virus influenzale nel tratto respiratorio e aumentando la virulenza di alcuni ceppi attraverso numerosi meccanismi:



Nature Reviews | Microbiology

⇒ ***Promuove il release del virione dalla cellula ospite infetta***
⇒ ***Previene la formazione di aggregati virali dopo il release***
⇒ ***Previene l'inattivazione virale da parte del muco respiratorio***
⇒ ***Promuove la penetrazione nelle cellule epiteliali respiratorie.***

⇒ ***Altera la parte carboidratica dell' Emoagglutinina.***

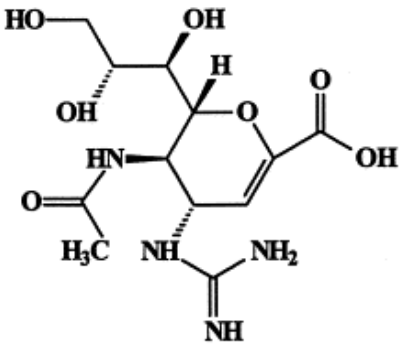
⇒ ***Promuove la produzione di IL-1 e TNF-alfa***
⇒ ***Attiva il TGF-β e induce apoptosi cellulare.***

Beard KR, Brendish NJ, Clark TW. Curr Opin Infect Dis 2018;31:514-519

ANALOGHI DI ACIDO SIALICO, CON SOSTITUZIONE AL 4' OH CON UN GRUPPO AMINICO O GUANIDINICO

MECCANISMO D'AZIONE

LEGANDOSI AL SITO ATTIVO DELLA PROTEINA NEURAMINIDASI (NA) VIRALE - REGIONE MOLTO CONSERVATA - INIBISCONO IL RILASCIO DEI VIRUS DELL'INFLUENZA A E B



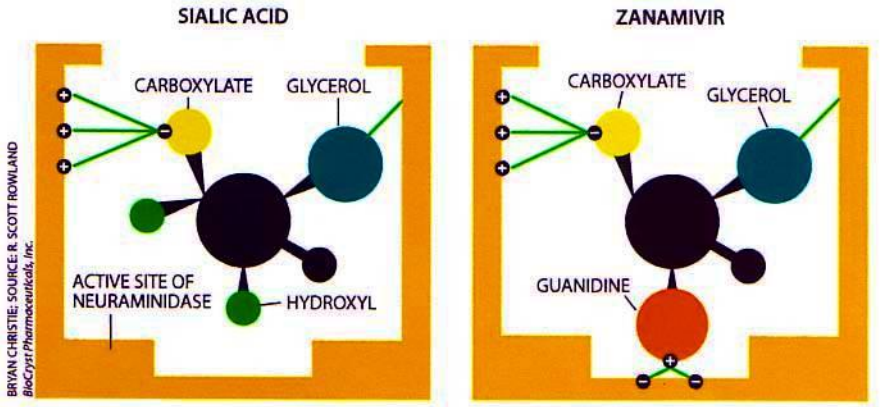
Zanamivir

SOMMINISTRAZIONE

Devono essere assunti molto precocemente

PROBLEMI TERAPEUTICI

emersione di mutanti virali



Beard KR, Brendish NJ, Clark TW. Curr Opin Infect Dis 2018;31:514-519

OSELTAMIVIR

SPETTRO ANTIVIRALE

Influenza virus A e B

MECCANISMO

Inibitore della neuraminidasi

RESISTENZA

Mutazione della neuraminidasi

FARMACOCINETICA

Somministrazione	*Orale: 75 mg x 2 /die per 5 giorni*
Assorbimento	Biodisponibilità orale: 75%
Distribuzione	Legame proteico: 42% Oseltamivir carbossilato: 3% Emivita plasm: 1-3 h Oseltamivir carbossilato): 6-10 h
Metabolismo	Epatico: idrolisi da *esterasi*: Oseltamivir carbossilato
Eliminazione	Renale: 90% (Oseltamivir carbossilato) FG+ST

INDICAZIONI

Trattamento e prevenzione dell'influenza A e B

TOSSICITA'

Nausea e Vomito

Beard KR, Brendish NJ, Clark TW. Curr Opin Infect Dis 2018;31:514-519

ZANAMIVIR

Analogo dell'acido sialico

SPETTRO ANTIVIRALE

Influenza virus A e B

MECCANISMO

Inibitore della neuraminidasi

RESISTENZA

Mutazione della neuraminidasi

FARMACOCINETICA

Somministrazione	*Inalazione: 10 mg x 2 /die per 5 giorni*
Assorbimento	Biodisponibilità orale: 2%
	Biodisponibilità inalatoria: 10-20 %
Distribuzione	Volume distribuzione 16 L
	Emivita plasmatica: 2 h (ev); 3-5 h (inalazione)
Eliminazione	Renale immodificata: 90%
	Respiratoria: 4%

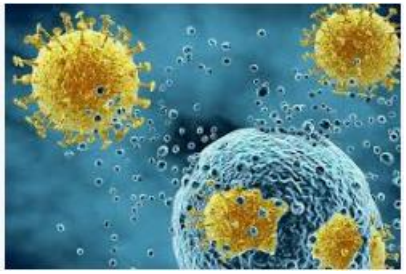
INDICAZIONI

Trattamento e prevenzione dell'influenza A e B

TOSSICITA'

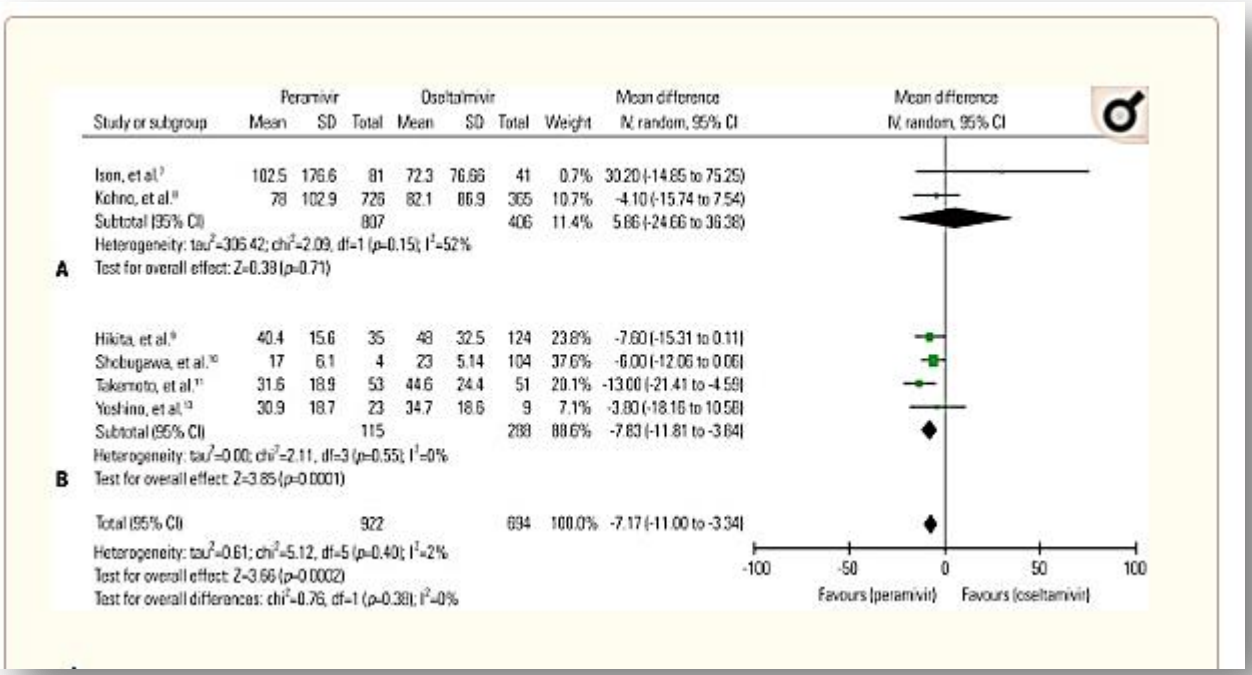
Ben tollerato

UNIVERSITÀ DEGLI STUDI FIRENZE



Comparison of Efficacy of Intravenous Peramivir and Oral Oseltamivir for the Treatment of Influenza: Systematic Review and Meta-Analysis. *LeeJ. Yonsei Med J. 2017;58:778-785*

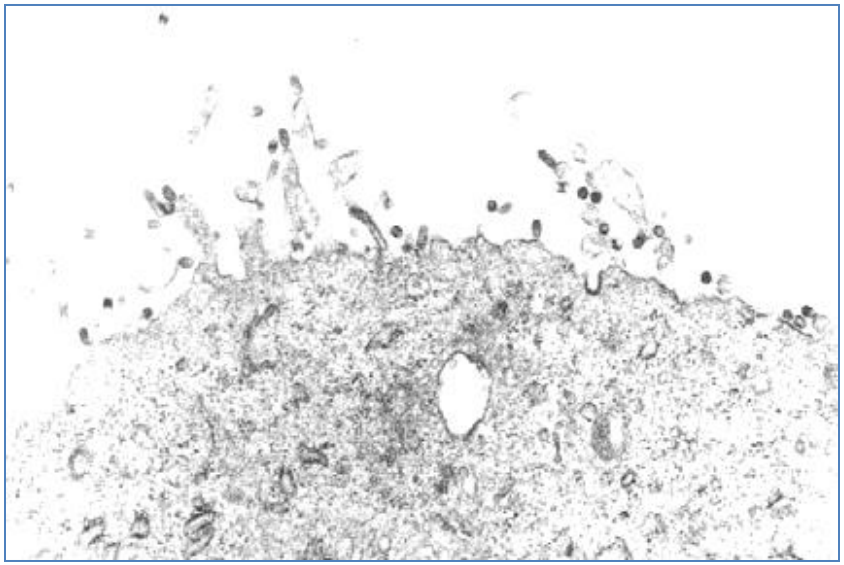
A total of seven trials [two RCTs and five non-randomized observational trials] involving 1676 patients were finally analyzed



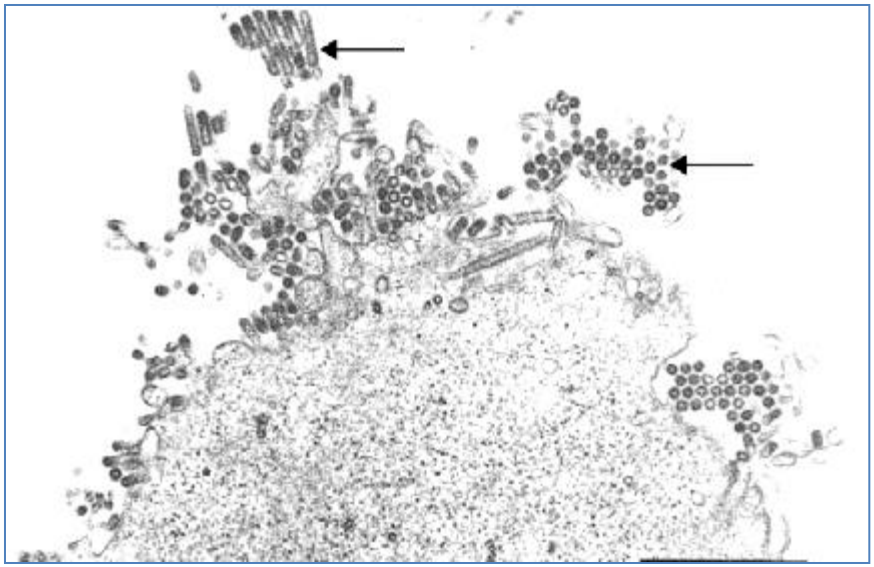
IV peramivir therapy might reduce the time to alleviation of fever in comparison with oral oseltamivir therapy in patients with influenza; however, we could not draw clear conclusions from a meta-analysis because of the few RCTs available and methodological limitations.

UNIVERSITÀ DEGLI STUDI FIRENZE

Sviluppo di inibitori della NA:
attività in vitro



Cellule non trattate.
Il virus viene assemblato e rilasciato normalmente

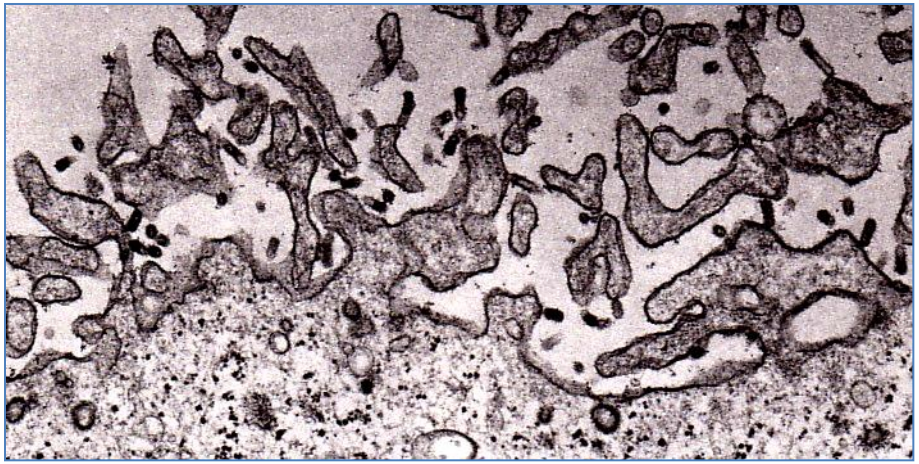


Cellule trattate con un inibitore NA.
Il virus è presente in grossi aggregati non infettivi

UNIVERSITÀ DEGLI STUDI FIRENZE

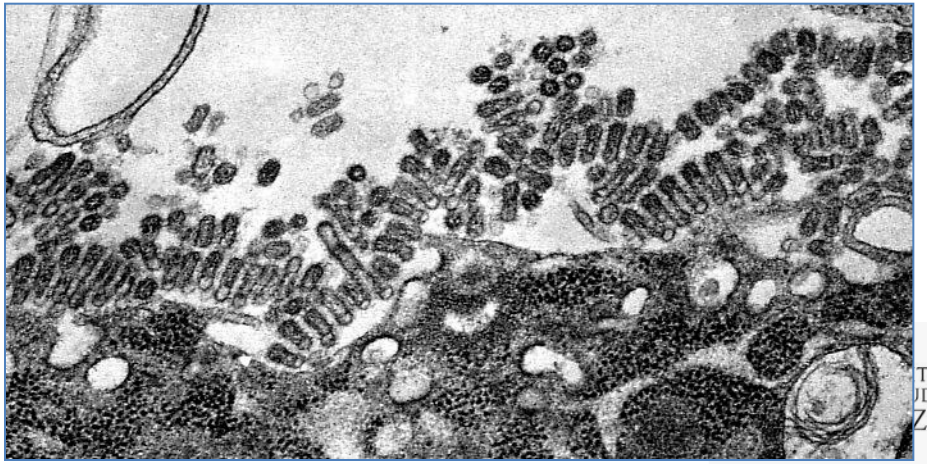
La Neuraminidasi: funzione

P. Palese, M. Ueda, K. Tobita, R.W. Compans. Characterization of temperature sensitive influenza virus mutants defective in neuraminidase. Virology 61:397–410 (1974).

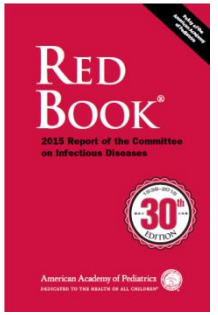


33° C
WT phenotype
Virioni liberi infettivi

39.5° C
NA- phenotype
Virioni aggregati
non infettivi



Red Book, 2018



Drug (Trade Name)	Virus	Administration	Treatment Indications	Chemoprophylaxis Indications	Adverse Effects
Oseltamivir (Tamiflu)	A and B	Oral	Birth or older[b]	3 mo or older	Nausea, vomiting
Zanamivir (Relenza)	A and B	Inhalation	7 y or older	5 y or older	Bronchospasm
Peramivir (Rapivab)	A and B[c]	Intravenous	2 y or older	N/A	Diarrhea; some reports of skin reactions
Amantadine[d] (Symmetrel)	A	Oral	1 y or older	1 y or older	Central nervous system, anxiety, gastrointestinal
Rimantadine[d] (Flumadine)	A	Oral	13 y or older	1 y or older	Central nervous system, anxiety, gastrointestinal

Oseltamivir in pregnancy and birth outcomes
Ehrenstein V. BMC Infect Dis. 2018 ;18:519.

The study included 946,176 pregnancies. Of these, 449 had first-trimester exposure and 1449 had second/third-trimester exposure to oseltamivir

The study does not provide evidence of risk associated with oseltamivir treatment additional to that associated with influenza infection.

Oseltamivir dosing in premature infants.
McPherson C. J Infect Dis2012 ;206:847-50.

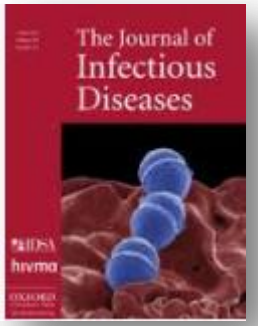
it was evidenced that exposure to oseltamivir was reduced from 31.5% to 11.7% when oseltamivir was dissolved in milk

Oseltamivir 1 mg/kg/dose twice daily in infants <38 weeks postmenstrual age (n=8) resulted in oseltamivir carboxylate exposure comparable to previously published pediatric data, which helps prospectively validate this regimen. Oseltamivir 3 mg/kg/dose once daily in premature infants >38 weeks postmenstrual age (born prematurely but chronologically past term, n=4) resulted in similar oseltamivir and oseltamivir carboxylate exposure

UNIVERSITÀ DEGLI STUDI FIRENZE

Oseltamivir pharmacokinetics, dosing, and resistance among children aged < 2 years with influenza.

Kimberlin DW. J Infect Dis 2013;207:709-720.

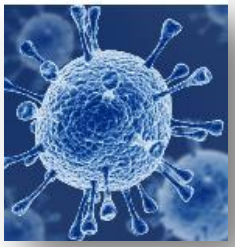


Kimberlin et al. recommended the administration of **3 mg/kg twice daily in infants from birth to 8 months of age** and a higher dose of **3.5 mg/kg in infants 9-11 months of age** to achieve appropriate exposure .

Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnant and breastfeeding women.

Tanaka T. CMAJ. 2009;181:55-8

UNIVERSITÀ DEGLI STUDI FIRENZE



Resistance to oseltamivir has been documented to be around 1% at most for any of the tested influenza viral samples during the past few years.

Esposito S. Expert Rev Respir Medicine 2015

Variations in the genetic characteristics of influenza virus neuraminidase can reduce the efficacy of oseltamivir.

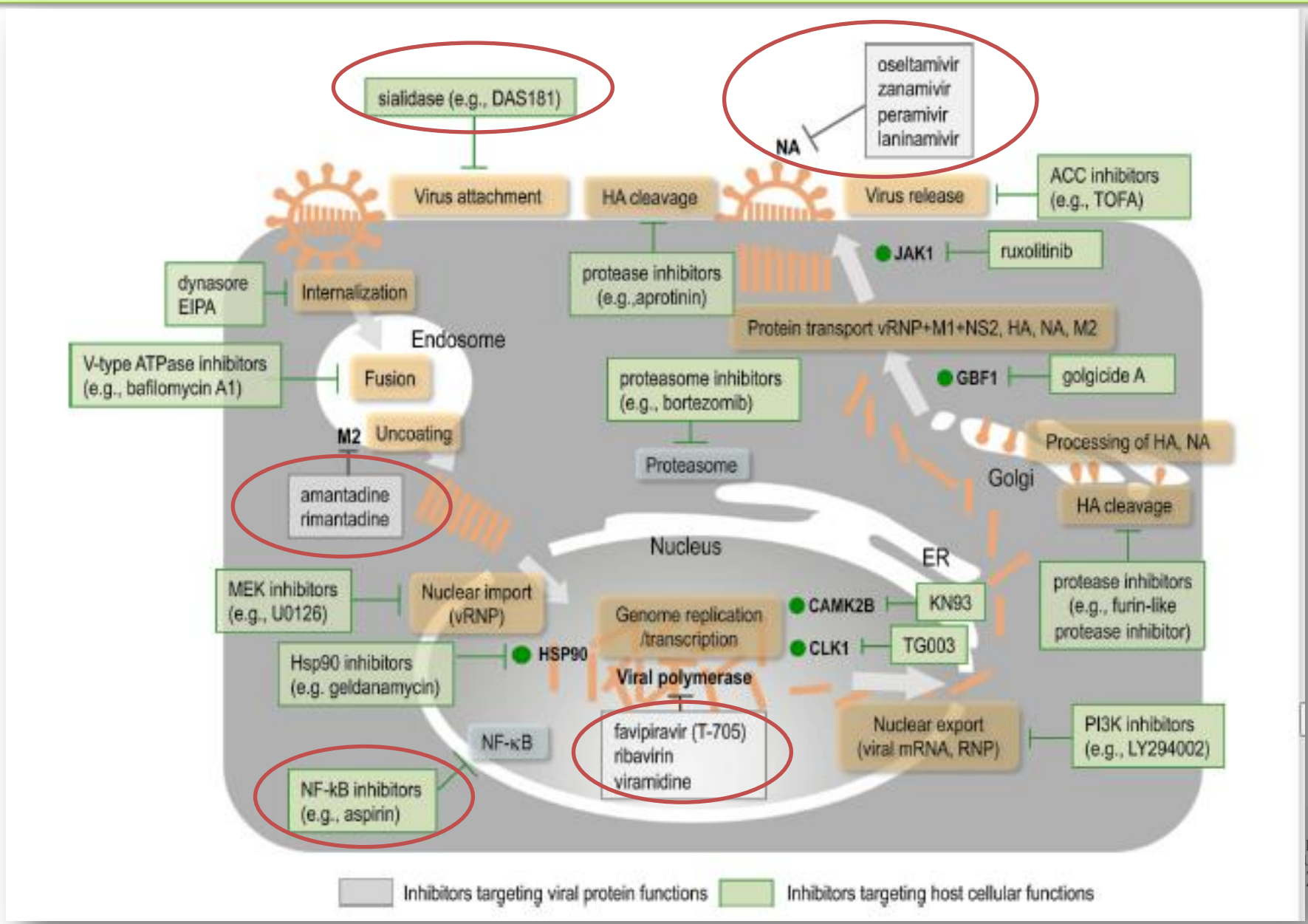
- H275Y mutations in influenza A/H1N1,
- R292K or E119V in influenza A/H3N2
- R152K or D198N in influenza B virus neuraminidase

are more frequently detected, mainly after prolonged treatment.

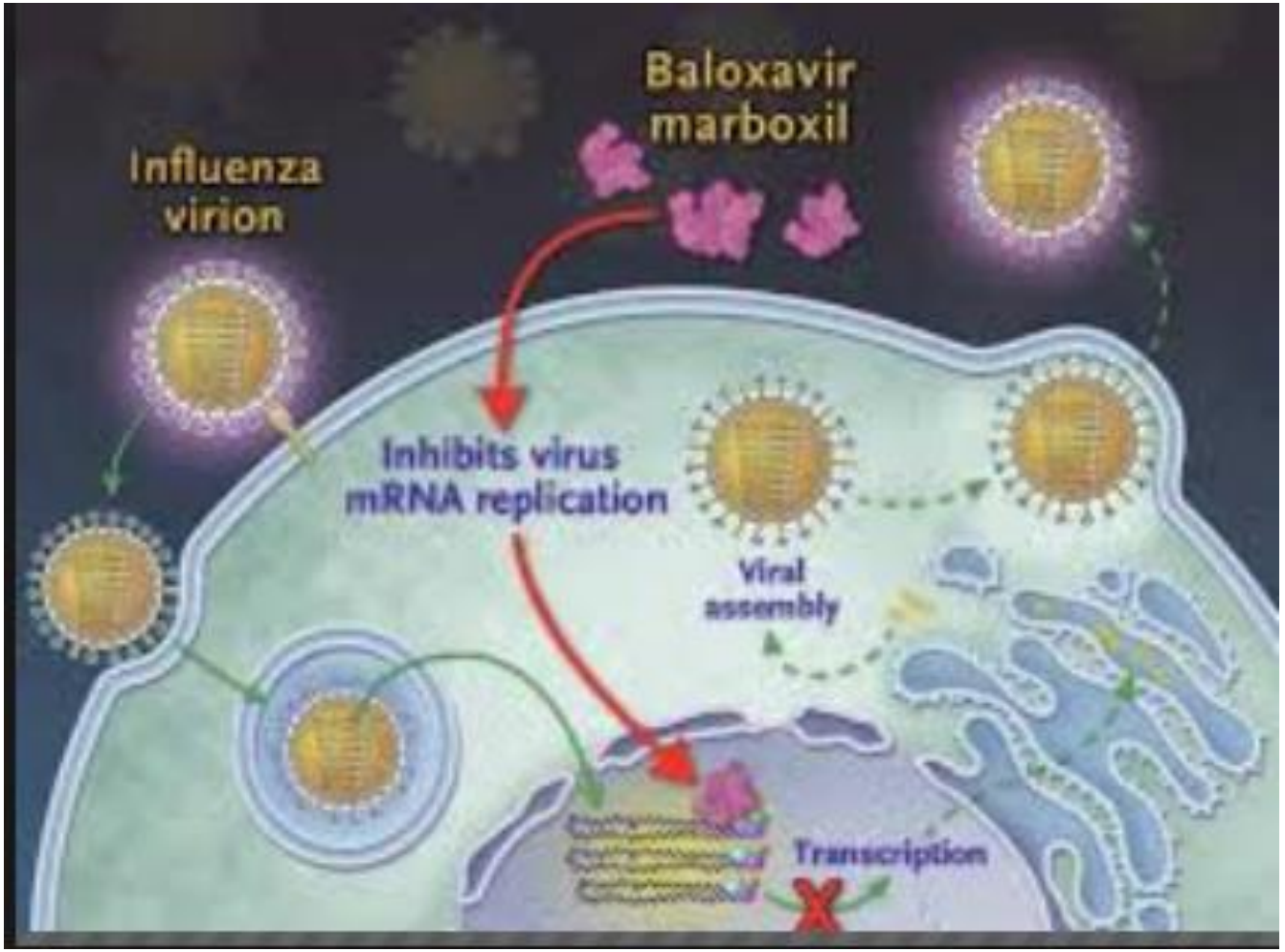
Emergence of resistance was also associated with the use of lower than recommended oseltamivir dosages

UNIVERSITÀ DEGLI STUDI FIRENZE

Influenza Virus-Host Interactomes as a Basis for Antiviral Drug Development.
Watanabe T , Kawaoka Y. Curr Opin Virol 2015; 14: 71–78.



Baloxavir


Baloxavir
marboxil
Influenza
virion
Inhibits virus
mRNA replication
Viral
assembly
Transcription

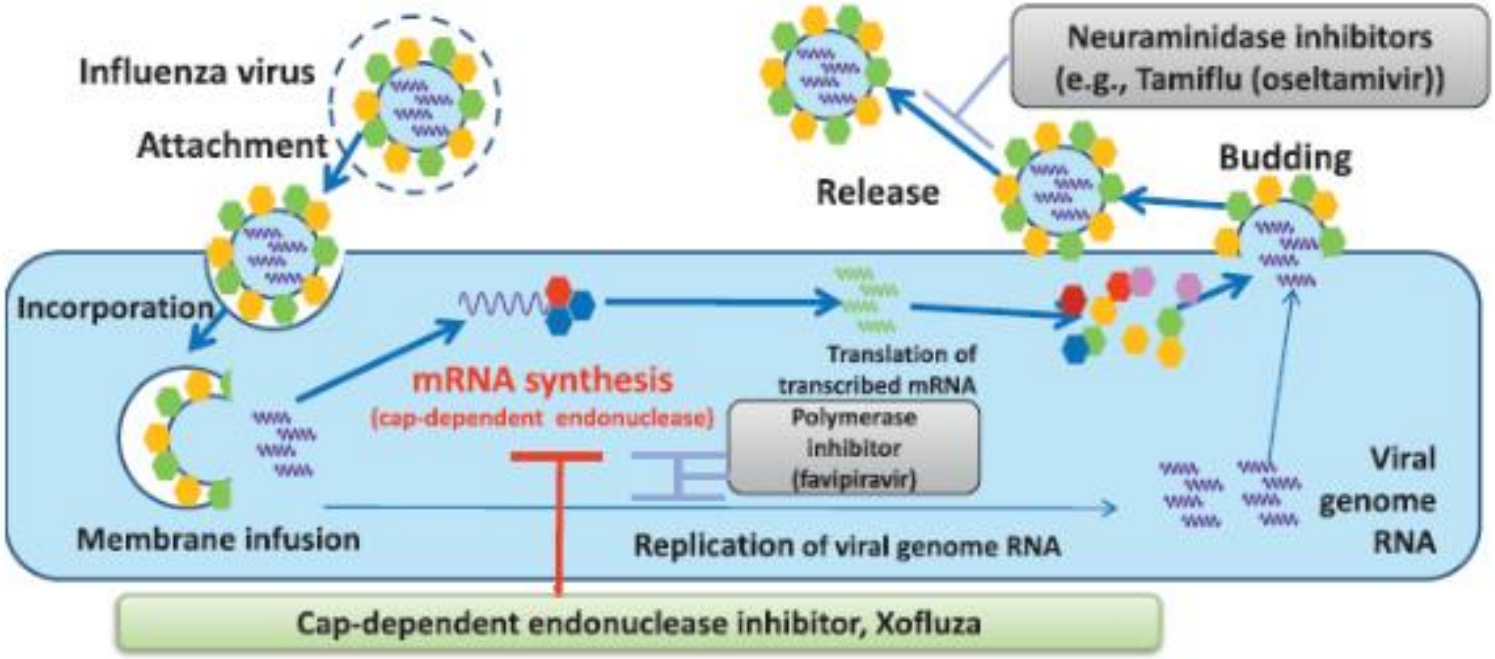


Fig. 1 | Novel mode of action of Xofluza (baloxavir marboxil). Xofluza is hydrolyzed in vivo to the active form that selectively inhibits cap-dependent endonuclease, a key enzyme involved in the initiation of influenza virus mRNA synthesis. Thus, proteins needed for the construction of new influenza virions cannot be synthesized in the presence of the drug.

EDITORIAL

A Step Forward in the Treatment of Influenza

…othy M. Uyeki, M.D., M.P.H., M.P.P.

The NEW ENGLAND JOURNAL of MEDICINE

Article Metrics

September 6, 2018
N Engl J Med 2018; 379:975-977
DOI: 10.1056/NEJMe1810815

6 References

2 trials in outpatients 12 to 64 years of age without underlying high-risk medical conditions who presented within 48 hours after the onset of laboratory-confirmed influenza in Japan and the United States.

In the phase 2 dose-ranging trial involving 389 Japanese adults, **a single baloxavir dose resulted in a significantly shorter time to alleviation of symptoms and greater reductions in levels of influenza virus at 1 and 2 days after administration** of the trial regimen than did placebo.

In the phase 3 trial in Japan and the United States, patients 20 to 64 years of age were randomly assigned to receive a single dose of **baloxavir or oseltamivir ,twice daily for 5 days, or placebo;** patients 12 to 19 years of age were assigned to receive either baloxavir or placebo. **Among the 1064 patients who had a diagnosis of influenza confirmed by a reverse transcriptase–polymerase chain reaction assay, baloxavir resulted in a significantly shorter time to alleviation of symptoms than did placebo in patients 20 to 64 years of age (median difference, 25.6 hours) and those 12 to 19 years of age (median difference, 38.6 hours).**

UNIVERSITÀ DEGLI STUDI FIRENZE

EDITORIAL

A Step Forward in the Treatment of Influenza

…othy M. Uyeki, M.D., M.P.H., M.P.P.

The NEW ENGLAND JOURNAL of MEDICINE

Article Metrics

6 References

September 6, 2018
N Engl J Med 2018; 379:975-977
DOI: 10.1056/NEJMe1810815

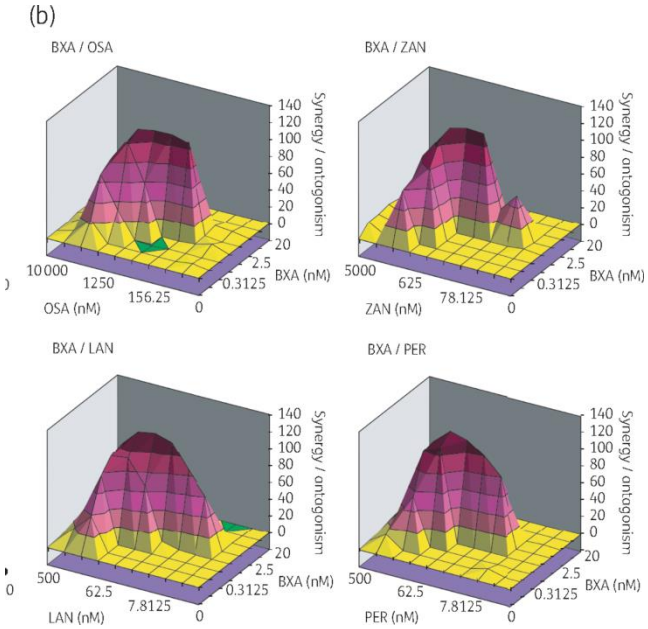
These findings indicate that baloxavir **has a clinical benefit that is similar to that with oseltamivir for the early treatment of otherwise healthy outpatients 12 to 64 years of age with uncomplicated influenza.**

Owing to its longer half-life, a single baloxavir dose provides the advantage of avoiding adherence concerns with treatment with 5 days of twice-daily oseltamivir.

in both trials, **baloxavir treatment induced the emergence of viral escape mutants with reduced susceptibility through changes from isoleucine to other amino acids at position 38 (I38) of the gene encoding PA.**

UNIVERSITÀ DEGLI STUDI FIRENZE

Journal of Antimicrobial Chemotherapy



Combination treatment with the cap-dependent endonuclease inhibitor baloxavir marboxil and a neuraminidase inhibitor in a mouse model of influenza A virus infection

Keita Fukao ✉, Takeshi Noshi, Atsuko Yamamoto, Mitsutaka Kitano, Yoshinori Ando, Takahiro Noda, Kaoru Baba, Kazumi Matsumoto, Naoko Higuchi, Minoru Ikeda, ... Show more

Journal of Antimicrobial Chemotherapy, dky462, https://doi.org/10.1093/jac/dky462

Published: 21 November 2018 **Article history** ▾

Therapy for influenza virus infection should be offered to any hospitalized child who has severe, complicated, or progressive respiratory illness that may be influenza related, regardless of influenza-immunization status or whether onset of illness has been greater than 48 hours before admission.

Outpatient therapy should be offered for influenza infection of any severity in children at high risk of complications of influenza infection, such as children younger than 2 years.

Treatment may be considered for any otherwise healthy child with influenza infection for whom a decrease in duration of clinical symptoms is believed to be warranted by his or her pediatrician.

the greatest impact on outcome will occur if treatment can be initiated within 48 hours of illness onset but treatment still should be considered if later in the course of illness, especially for hospitalized patients.

Antiviral treatment also should be considered for symptomatic siblings of children younger than 6 months or with underlying medical conditions that predispose them to complications of influenza.

Children with severe influenza should be evaluated carefully for possible coinfection with bacterial pathogens (eg, *S aureus*) that might require antimicrobial therapy.
Clinicians who want to have influenza isolates tested for susceptibility should contact their state health department.
If antiviral therapy is prescribed, treatment should be started as soon after illness onset as possible and should not be delayed while waiting for a definitive influenza test result, because early therapy provides the best outcomes.1
The duration of treatment is 5 days for the neuraminidase inhibitors (oseltamivir and zanamivir).

Only zanamivir, which is administered by inhalation, does not require adjustment for people with severe renal insufficiency.
The most common adverse effects of oseltamivir are nausea and vomiting

UNIVERSITÀ DEGLI STUDI FIRENZE

Indications for Chemoprophylaxis. Although immunization is the preferred approach to prevention of infection, chemoprophylaxis during an influenza outbreak, as defined by the CDC, is recommended:

• For children at high risk of complications from influenza for whom influenza vaccine is contraindicated.

• For children at high risk during the 2 weeks after IIV immunization.

• For family members or HCP who are unimmunized and are likely to have ongoing, close exposure to:

♦ unimmunized children at high risk; or

♦ unimmunized infants and toddlers who are younger than 24 months.

• For control of influenza outbreaks for unimmunized staff and children in a closed institutional setting with children at high risk (eg, extended-care facilities).

• As a supplement to immunization among children at high risk, including children who are immunocompromised and may not respond to vaccine.

• As postexposure prophylaxis for family members and close contacts of an infected person if those people are at high risk of complications from influenza.

• For children at high risk and their family members and close contacts, as well as HCP, when circulating strains of influenza virus in the community are not matched with seasonal influenza vaccine strains, on the basis of current data from the CDC and local health departments.

These recommendations apply to routine circumstances, but it should be noted that guidance may change on the basis of updated recommendations from the CDC together with antiviral availability, local resources, clinical judgment, recommendations from local or public health authorities, risk of influenza complications, type and duration of exposure contact, and change in epidemiology or severity of influenza. Chemoprophylaxis is not recommended for infants younger than 3 months, unless the situation is judged critical, because of limited safety and efficacy data in this age group.