

# Influenza

Tratamento  
Prevenção

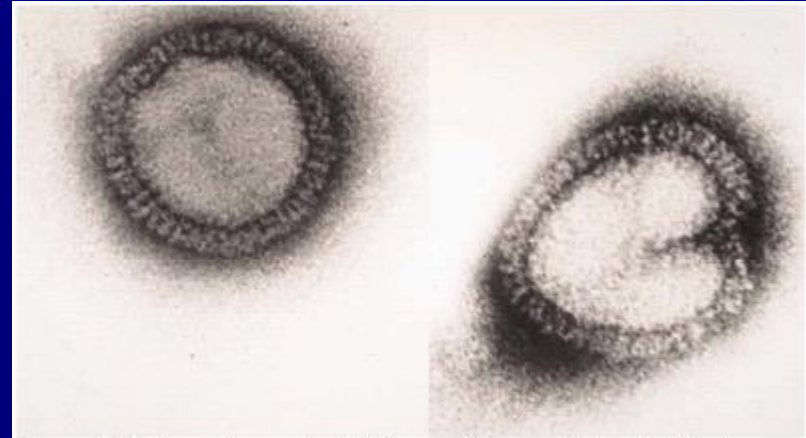
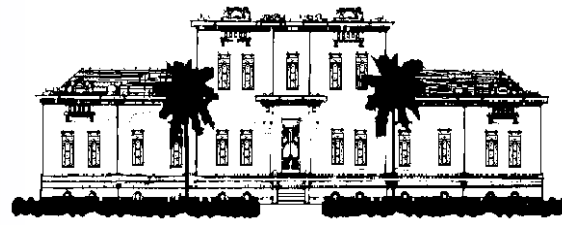
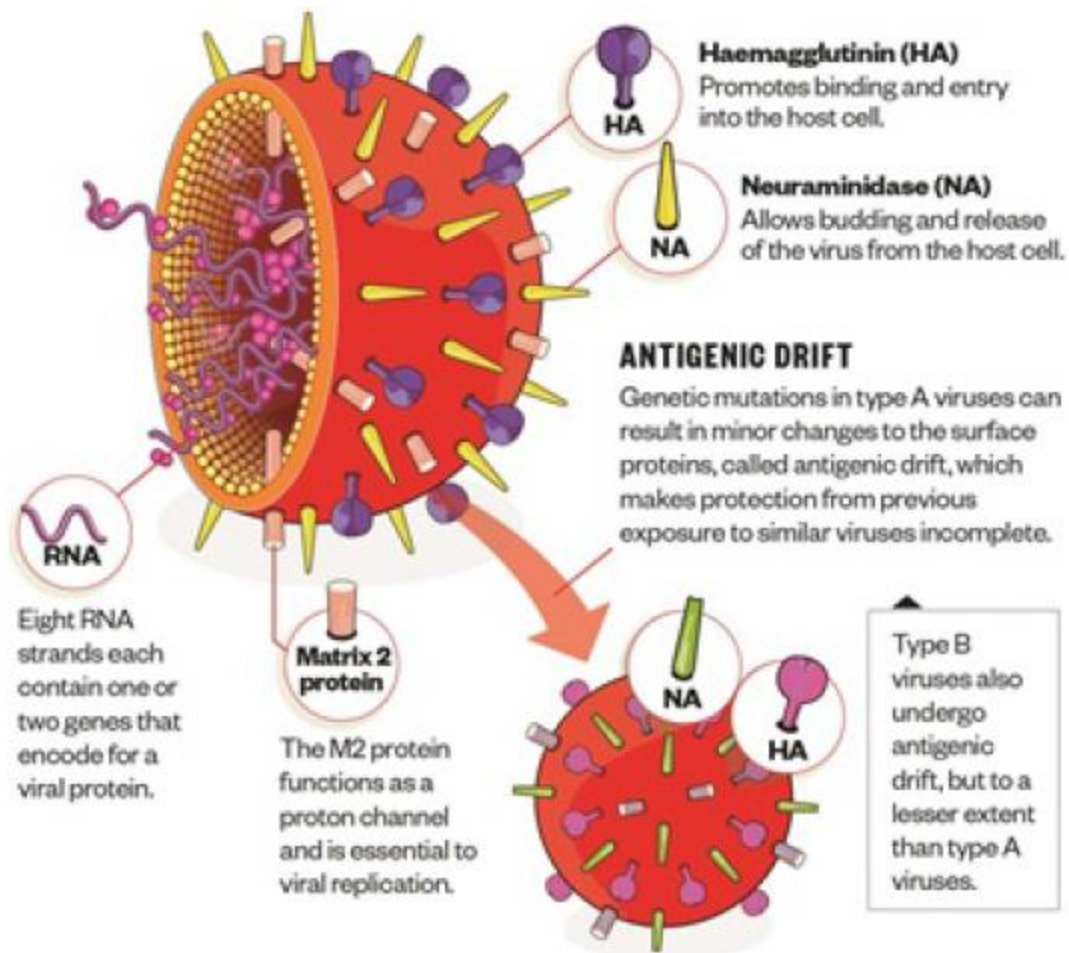


Figure 1 Electron micrograph of influenza A virus particles. Provided by M-T. Hsu and P. Palese.



INSTITUTO BUTANTAN

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### IMPACT OF FLU

The World Health Organization estimates that flu causes about

**3-5 MILLION**

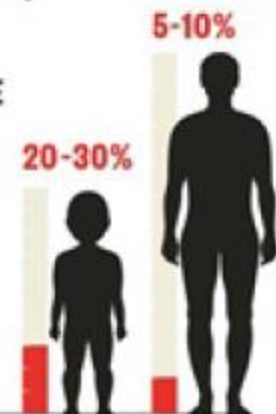
cases of severe illness, and about

**250K-500K**

deaths annually worldwide.

### ATTACK RATE

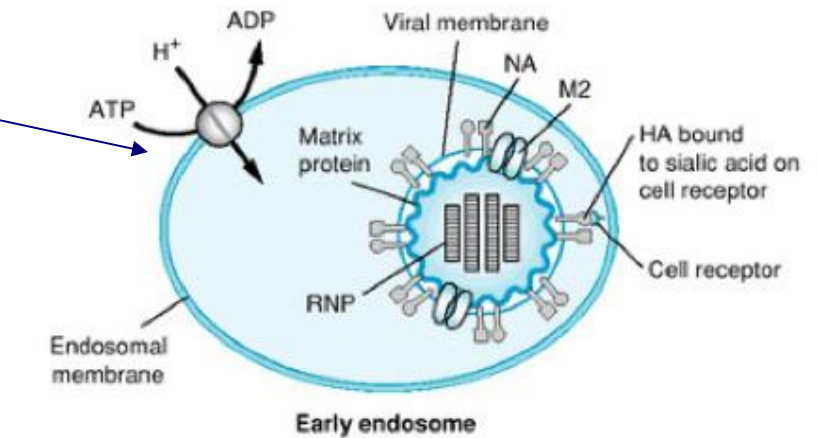
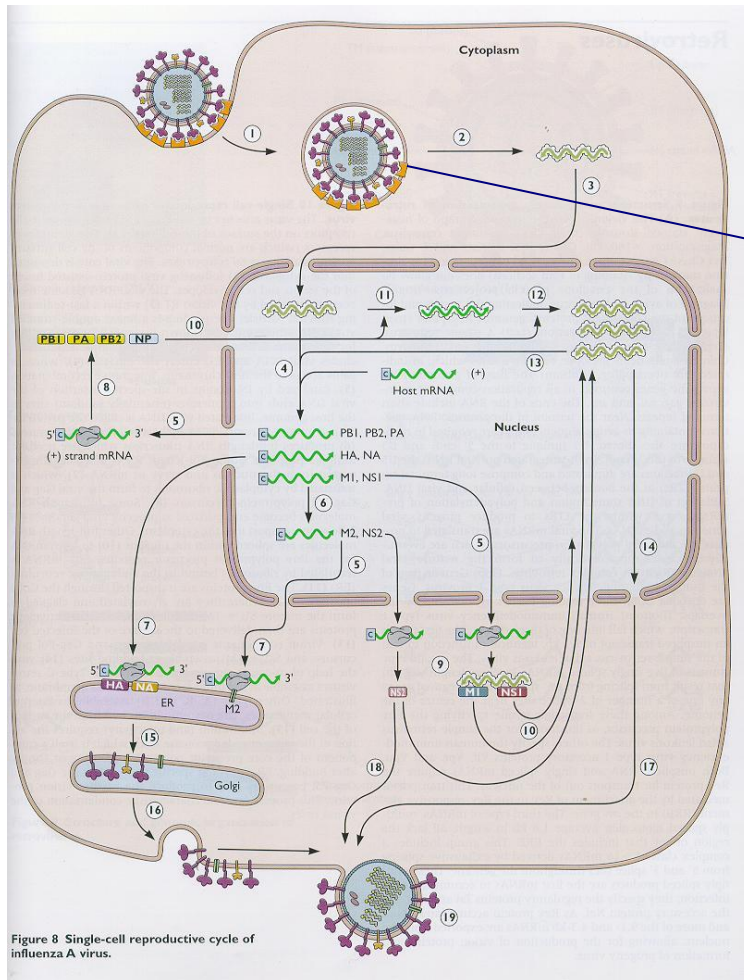
Influenza has an annual attack rate of about 5-10% in adults and 20-30% in children.



# Tratamento

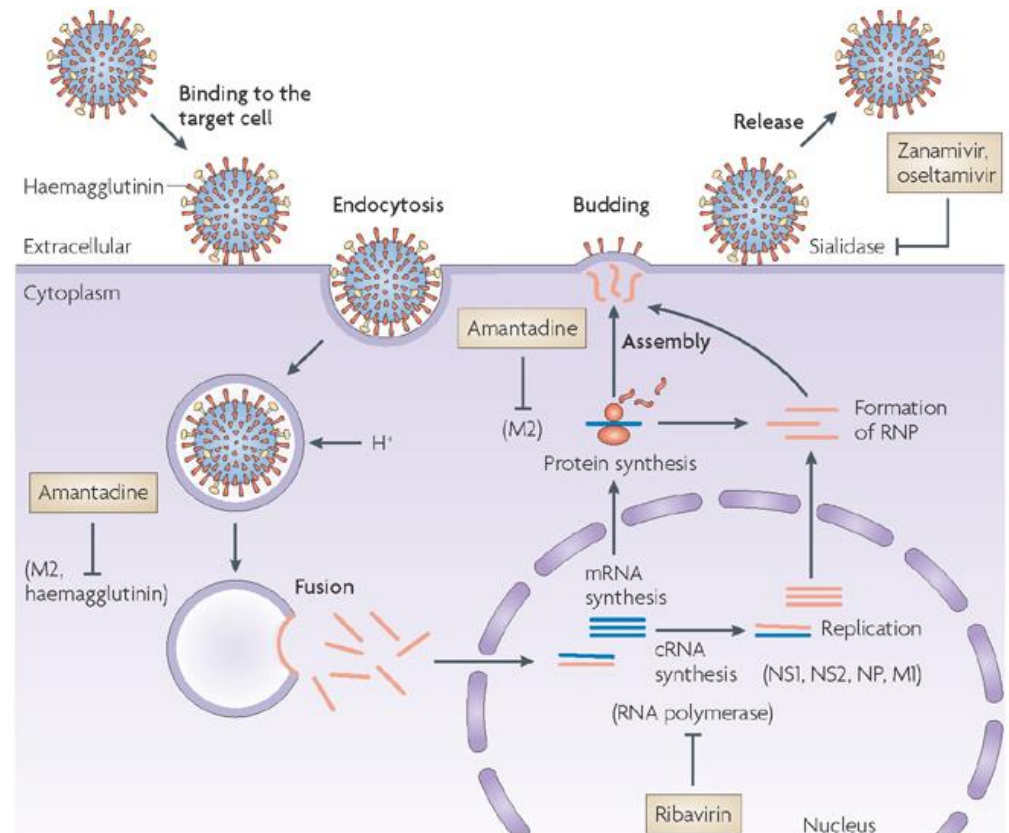


# Multiplicação do vírus da Influenza



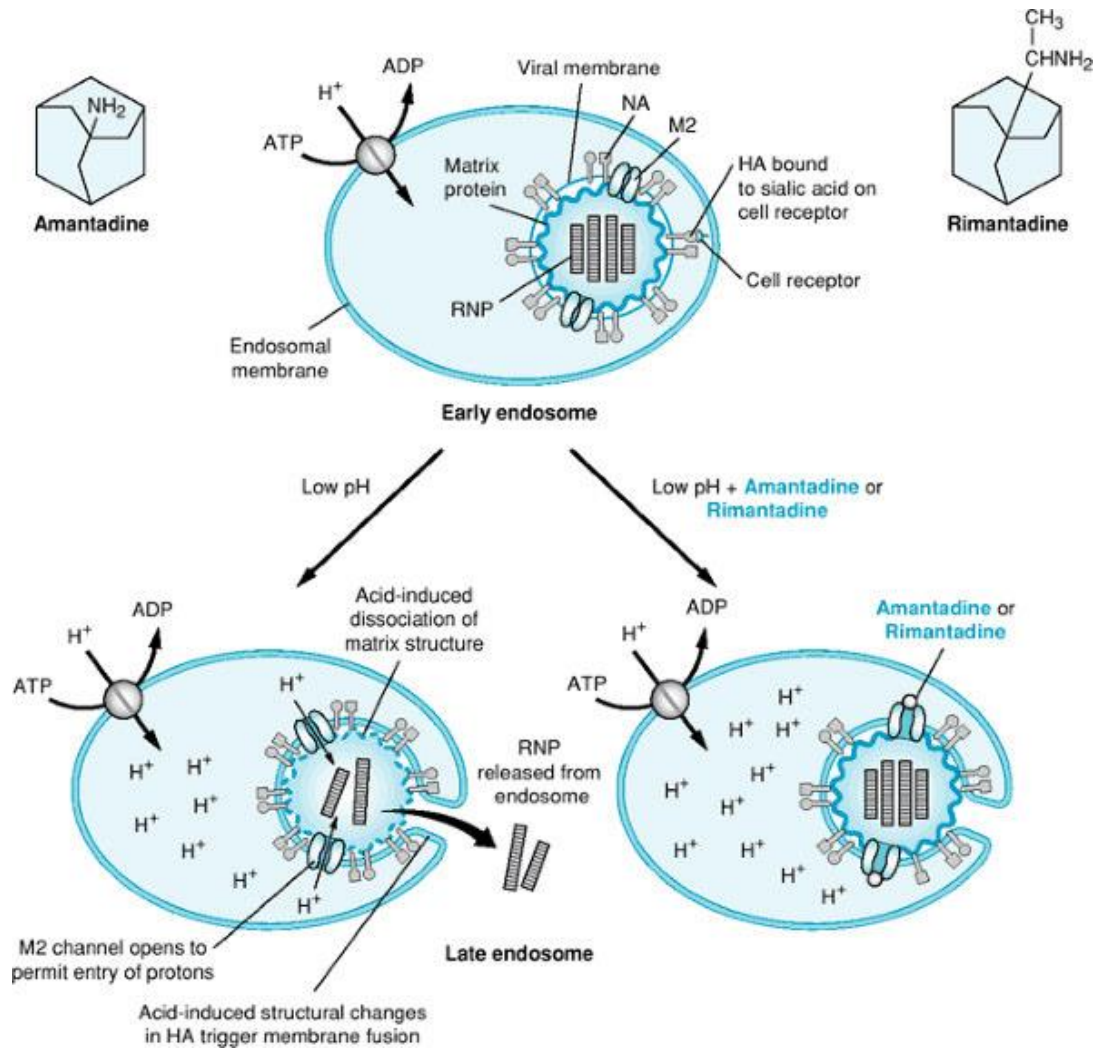
# Bloqueadores de canais iônicos

- Interfere no processo de modificação conformacional das proteínas HA recém-sintetizadas diminuindo a liberação de partículas infecciosas





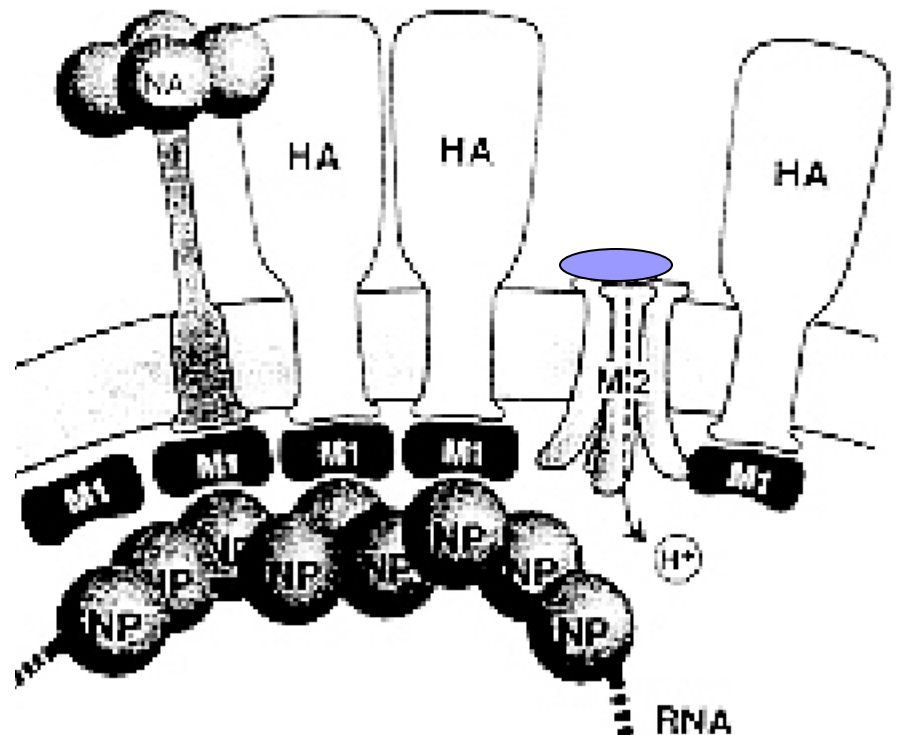
# Bloqueadores de canais iônicos



# Bloqueadores de canais iônicos

## Mecanismo de ação

- ↑ pH no interior do endossomo  
bloqueando a etapa de  
desnudamento viral





# Aplicação clínica e efeitos colaterais

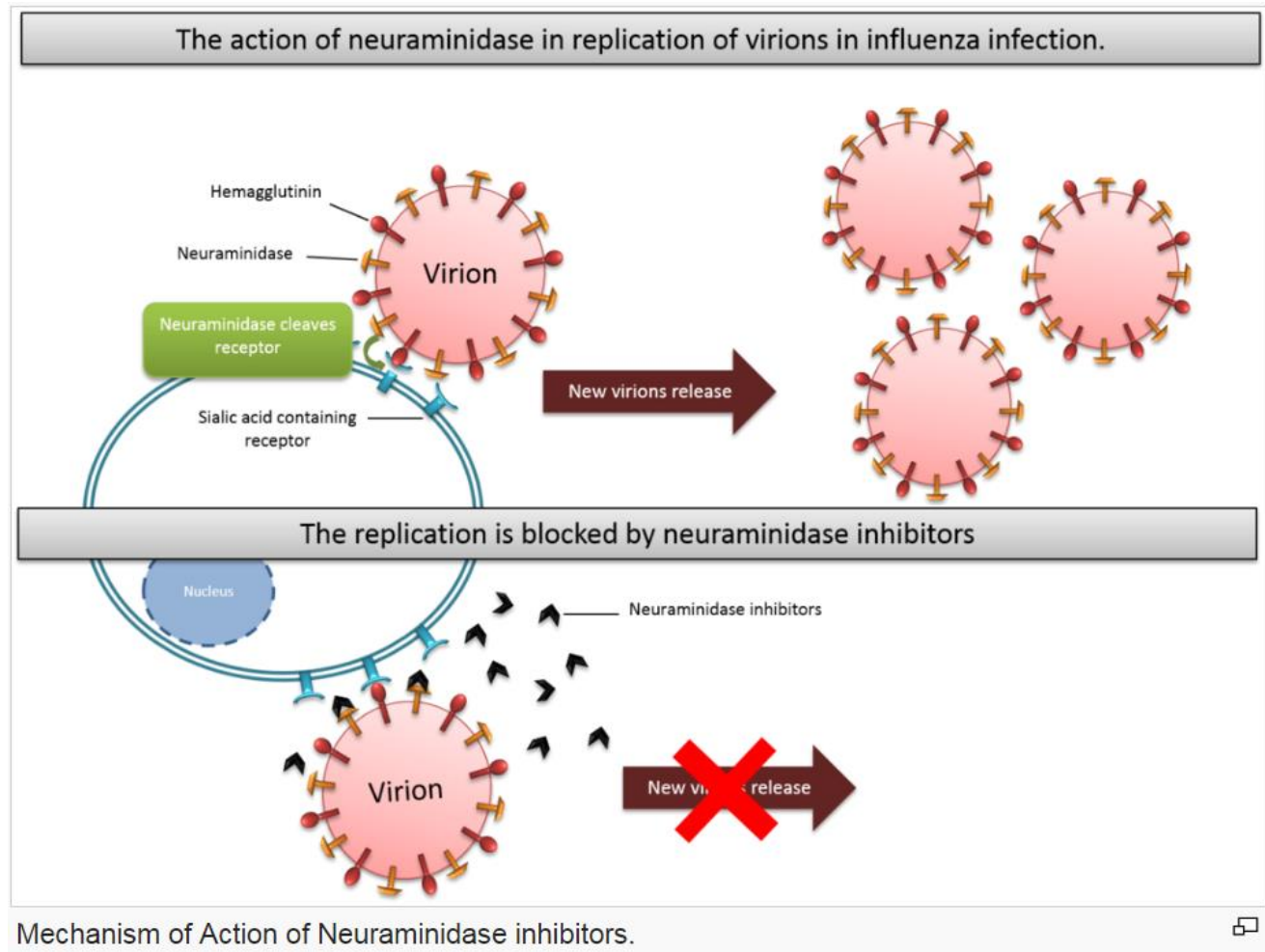
Redução da severidade dos sintomas de gripe em 50% dos casos

## Restrições

- eficácia sobre vírus da Influenza tipo A
- administração na fase inicial da doença
- efeitos colaterais: confusão, dores de cabeça, insônia
- Desenvolvimento de resistência - M2-S31N - 90% H3N2, H1N1 pdm 100%

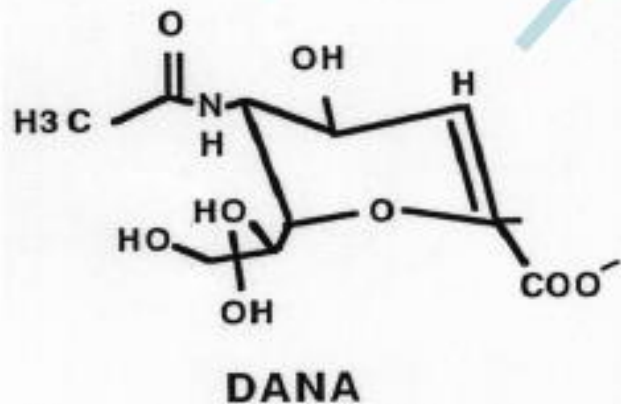
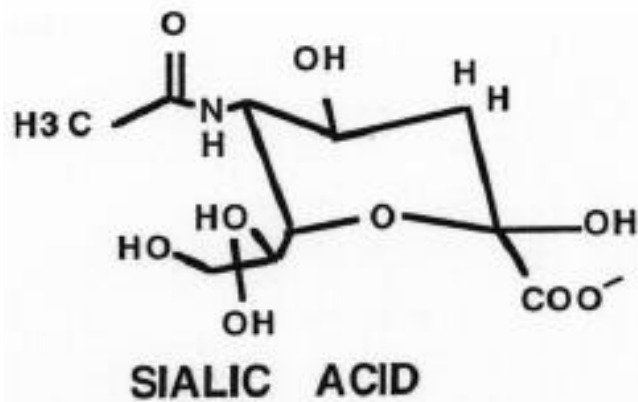


# Inibidores da Neuraminidase

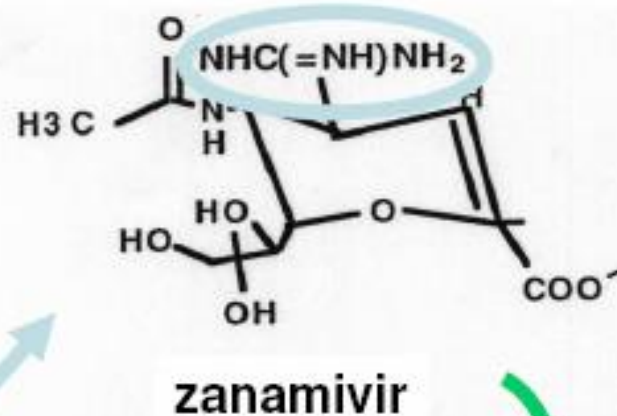


Neuraminidase que cliva o ácido siálico das glicoproteína da membrana celular

# Inibidores da Neuraminidase



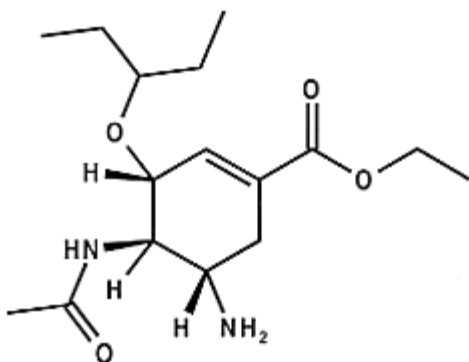
(ác. 2-deoxi-2,3-dehidro-N- acetilneuramínico)



esterificação  
com etanol  
(Via oral)

# Inibidores da Neuraminidase

## Oseltamivir



Of >4000 influenza A(H1N1)pdm09 viruses tested for susceptibility to the neuraminidase inhibitors, 69 carried an H275Y amino acid substitution in neuraminidase which conferred highly reduced inhibition by oseltamivir and peramivir.

- Forty-one of these viruses were detected in Japan (41/1467; 2.8%)
- Sixteen were detected in the United States of America (16/2331; 0.7%). The majority of

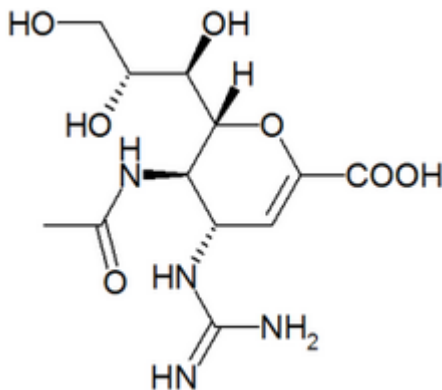
All of the A(H3N2) viruses tested were sensitive to neuraminidase inhibitors.

All but two influenza B/Yamagata/16/88 lineage viruses were sensitive to neuraminidase inhibitors.

One virus carried an I221V amino acid substitution in neuraminidase that resulted in reduced peramivir inhibition, while the other contained an I348T amino acid substitution in neuraminidase that conferred reduced oseltamivir inhibition.

All but four of the influenza B/Victoria/2/87 lineage viruses were sensitive to neuraminidase inhibitors. Both substitutions conferred reduced or highly reduced inhibition by all four neuraminidase inhibitors - oseltamivir, zanamivir, peramivir and laninamivir.

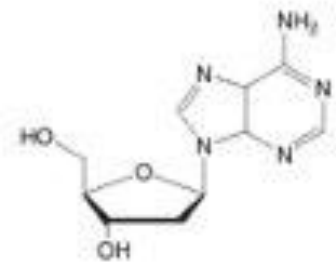
## Zanamivir



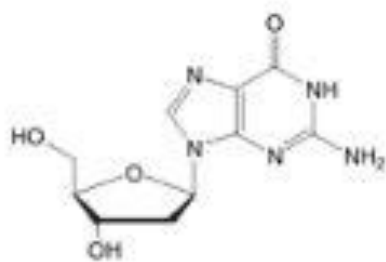
# Inibição da replicação do genoma viral

- Inibidores da RNA polimerase viral  
Análogos dos nucleosídeos

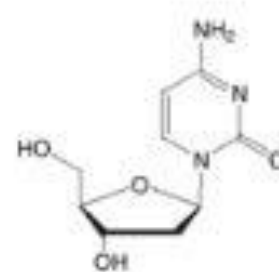
## A Native nucleosides



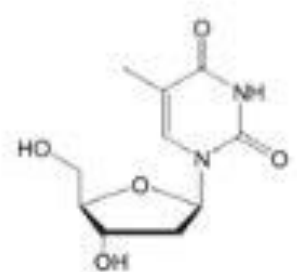
Deoxyadenosine



Deoxyguanosine



Deoxycytidine



Deoxythymidine

- **Favipiravir**

- Análogo sintético da adenosina/guanosina

- Mecanismo de ação:

- Inibe a iniciação e alongação pela RNA polimerase

- Teratogênico e embriotóxico.

- Aprovado no Japão para uso em emergências qdo outros anti-virais não foram efetivos

- **Ribavirin**

- Análogo sintético da guanosina

- Mecanismo de ação:

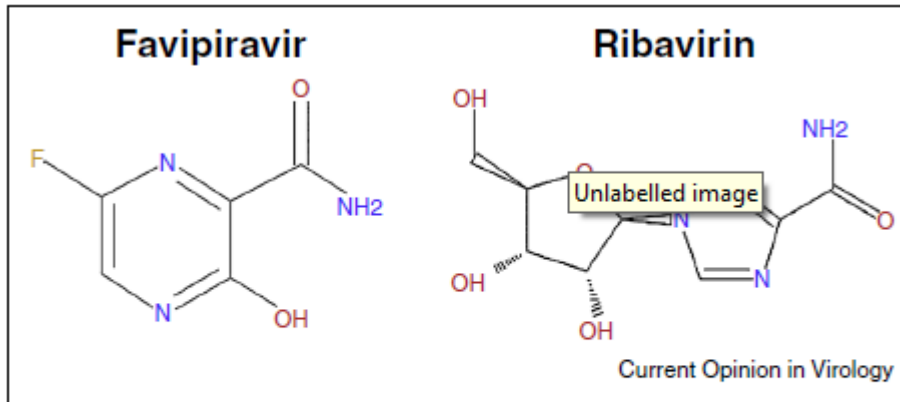
- Inibe a iniciação e alongação pela RNA polimerase

- Inibe a inosina monofosfato desidrogenase

- Inibe a guanililtransferase e adição de CAP

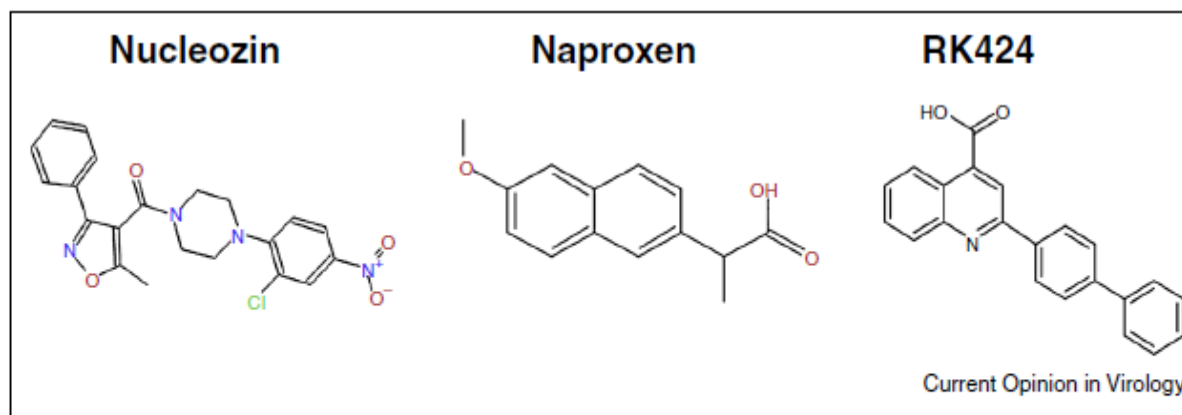
- Eficácia comprovada in vitro e animais

- Uso combinado



Nucleoside analogs that inhibit RNA-dependent RNA polymerase. Favipiravir and ribavirin are nucleoside analogs that shown broad-spectrum inhibitory activity for multiple RNA viruses.

# Novas drogas em estudo

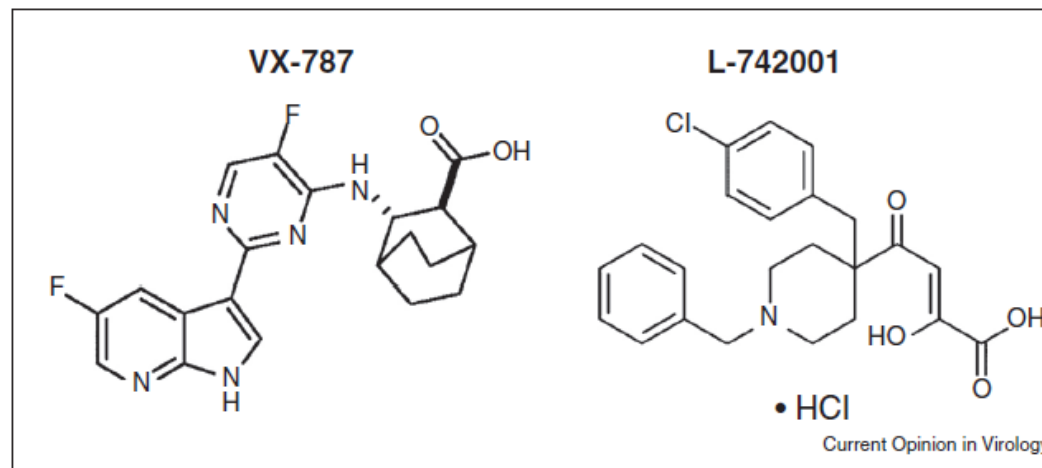


Inhibitors that interfere NP–NP or NP–RNA interactions. Nucleozin and RK424 were identified via high-throughput screening; naproxen that inhibits cyclooxygenase I and II were identified through virtual screening.

- Inibidor função da RNP
- Mecanismo - interferir na interação NP-NP, NP-RNA, NP-NES



# Novas drogas em estudo



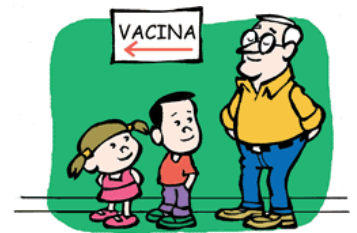
Small molecules that inhibits PB2 cap-binding and PA endonuclease activity.



# Prevenção - Vacinas

# Vacina contra Influenza

- Prevenção e redução da propagação da doença
- Vacina trivalente, 15 mcg/dose de cada HA
- Composição: Influenzavirus A (H1N1, H3N2) e B
- Uma dose anual, imunidade em 2 semanas
- Poucos efeitos colaterais e contra indicações
- Diminuição da gravidade e dos sintomas da doença com redução de morbidade e mortalidade
- Efetividade: 70 a 90%.
- Em idosos e portadores de doenças crônicas, induz proteção satisfatória contra complicações, hospitalizações e óbitos
- Redução de custos para o Sistema de Saúde
- +40 milhões de vacinados em 2016 (~89% dos idosos)



Regional Municipal:

Distrito Sanitário:

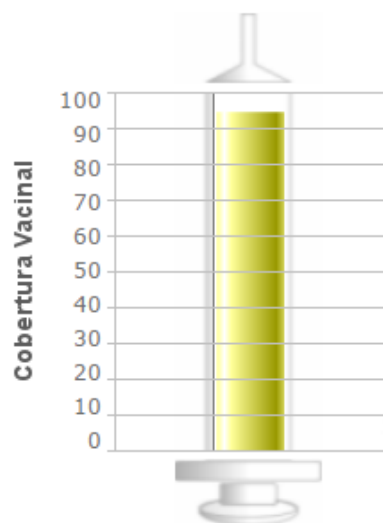
Unidade de Saúde:

#### Grupos Prioritários

Ano: \*



## Campanha Nacional de Vacinação Contra Influenza 2016 VACINÔMETRO

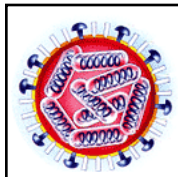


Desenvolvido por:  
Ministério da Saúde  
DATASUS - RJ

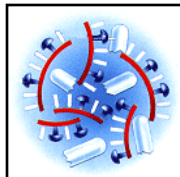
|                   |            |
|-------------------|------------|
| População         | 41.018.743 |
| Doses Aplicadas   | 38.735.927 |
| Cobertura Vacinal | 94,43%     |
| Grupo Prioritário | Todos      |
| Total Nacional    |            |

# Vacina contra Influenza

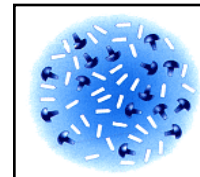
- 1933 - Isolamento do Vírus da Influenza
- 1935 - Primeira vacina de vírus inativado
- 1940' - Ensaios clínicos em grande escala  
Primeira vacinação em massa
- 1970' - Vacinas de vírus fragmentado e inativado,  
Vacinas de subunidades e Vírus atenuado
- 1990' - Desenvolvimento de vacinas em culturas de células
- 2003 - Vacina de vírus vivo atenuado (nasal)



Whole inactivated vaccine

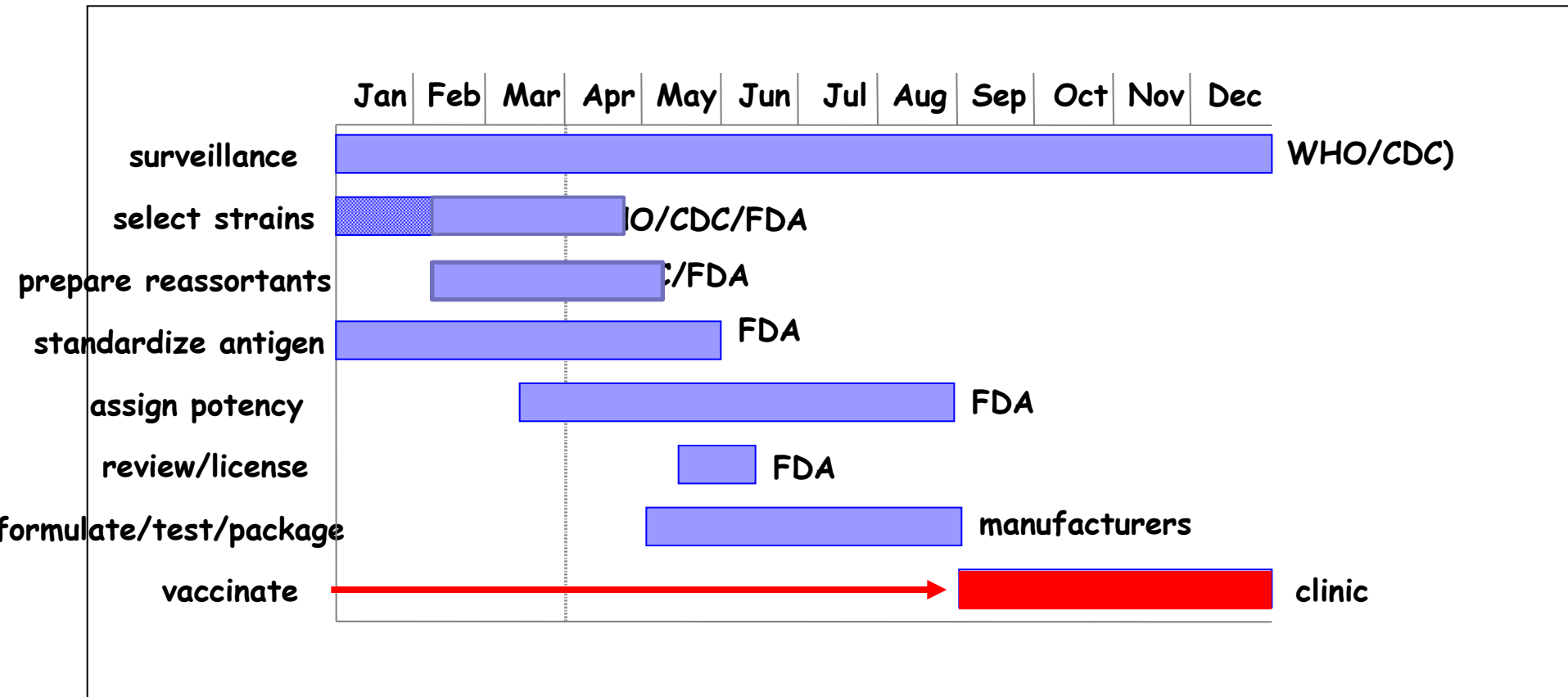


Split vaccine



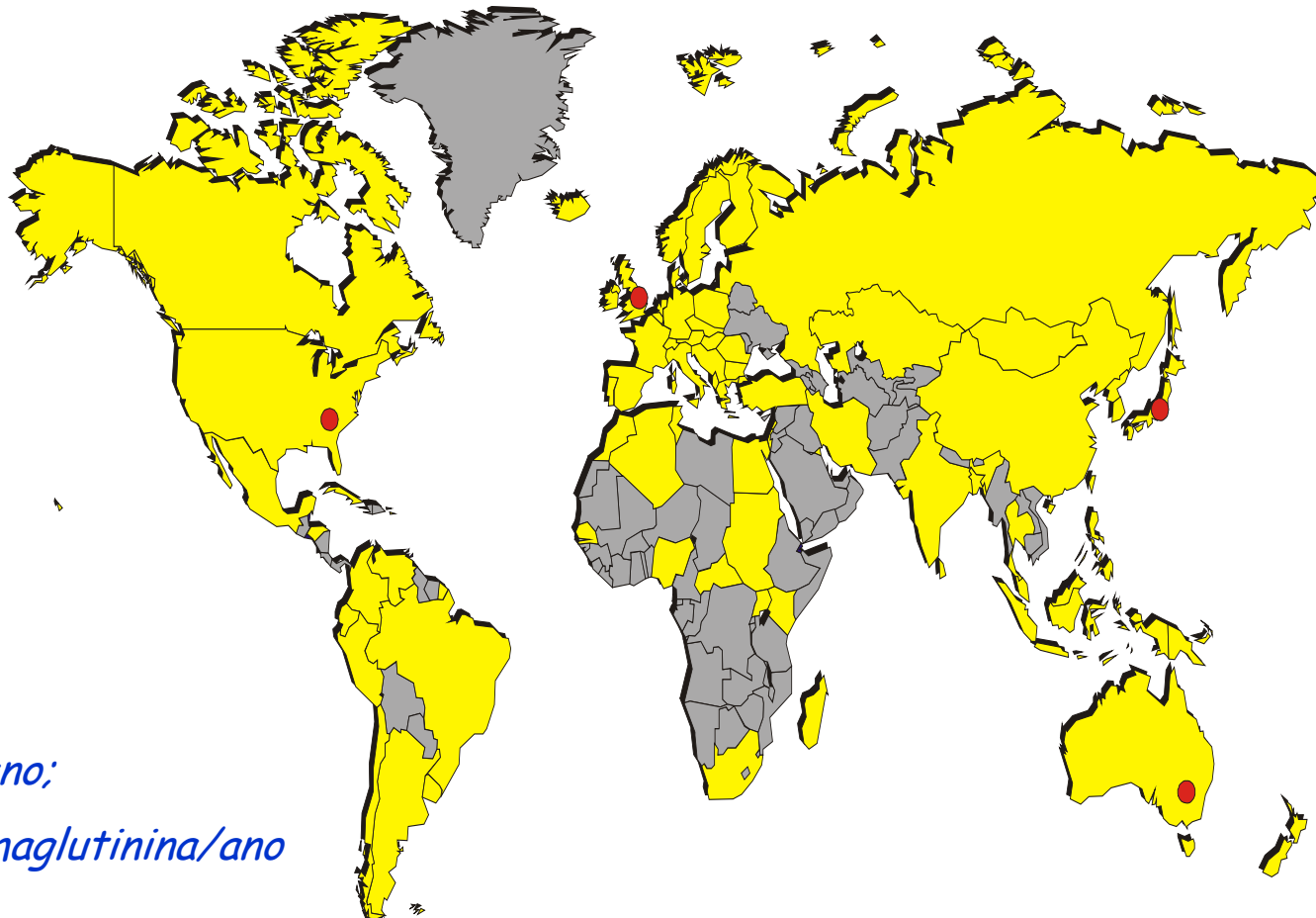
Subunit vaccine

# DESENVOLVIMENTO DA VACINA





# WHO Collaborating Centers for Influenza Worldwide



*8000 cepas/ano;*

*1000 seq hemaglutinina/ano*

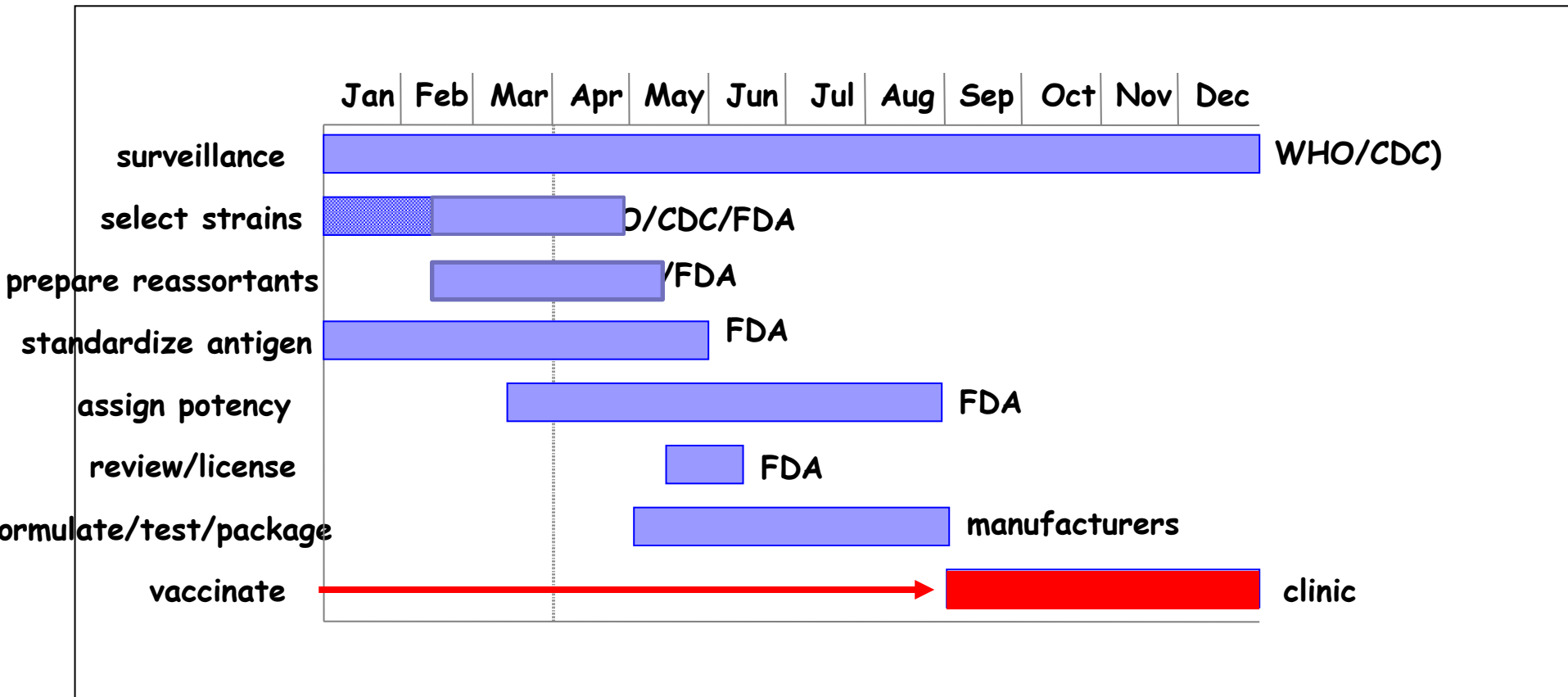
● WHO Collaborating Centers - Atlanta, London, Melbourne, and Tokyo

■ Countries containing at least 1 WHO influenza laboratory

# Centros Nacionais de Referência em Vírus Respiratórios



# DESENVOLVIMENTO DA VACINA



# Vacina contra Influenza

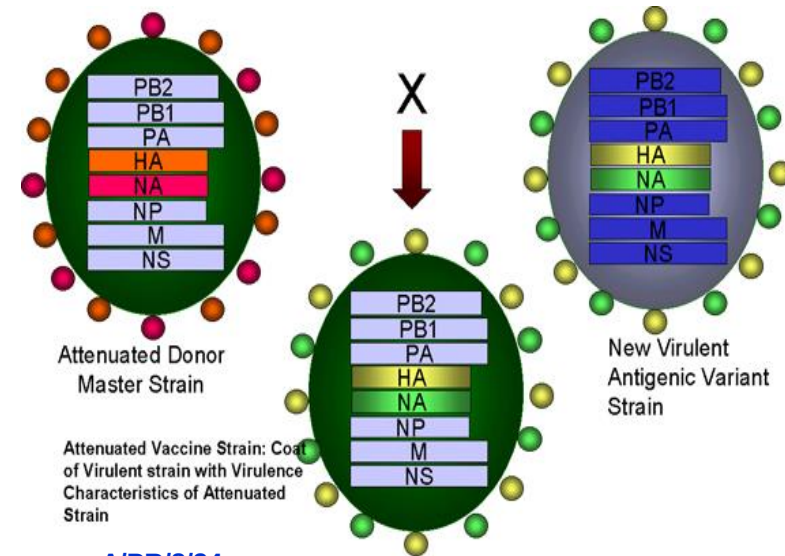
Recommended composition of influenza virus vaccines for use in the 2017 southern hemisphere influenza season

October 6 2016

It is recommended that trivalent vaccines for use in the 2017 influenza season (southern hemisphere winter) contain the following:

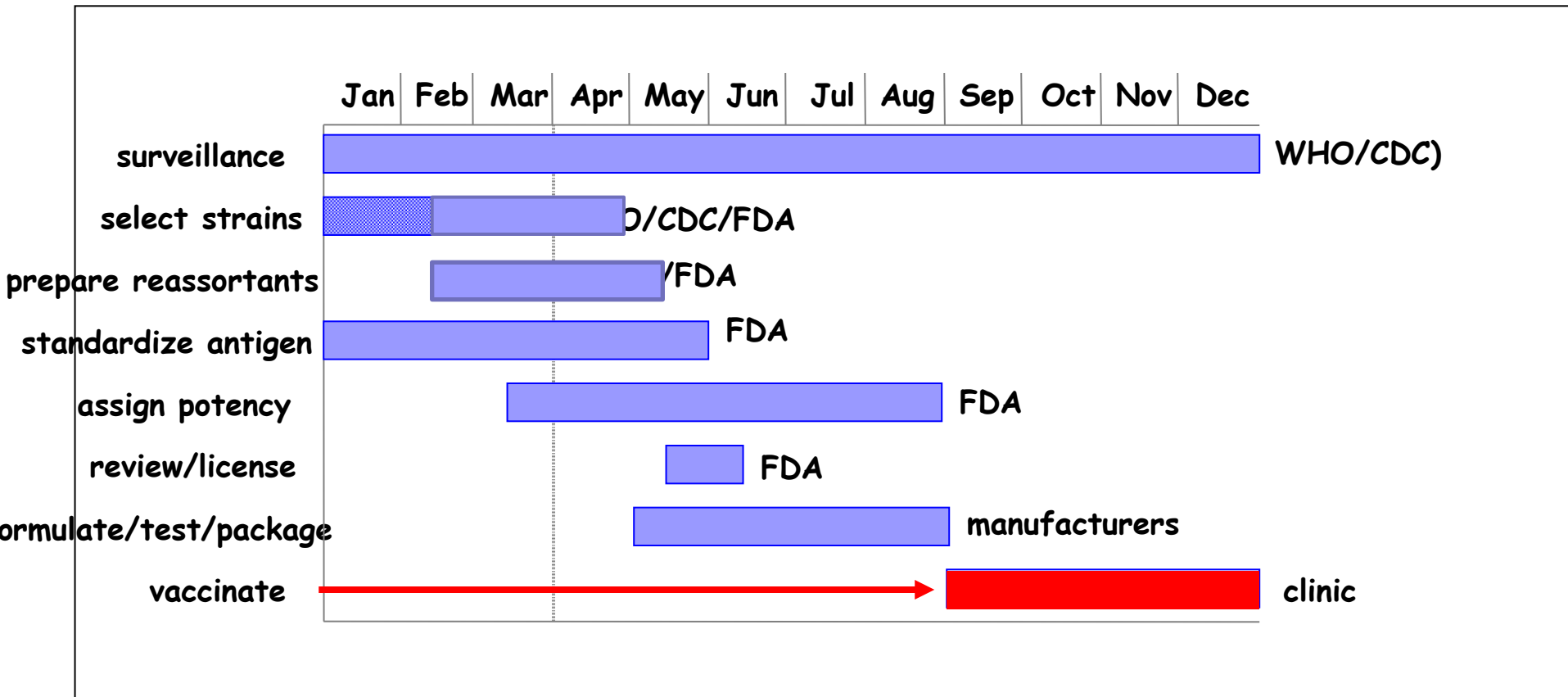
- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Hong Kong/4801/2014 (H3N2)-like virus;
- a B/Brisbane/60/2008-like virus.

It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013-like virus.



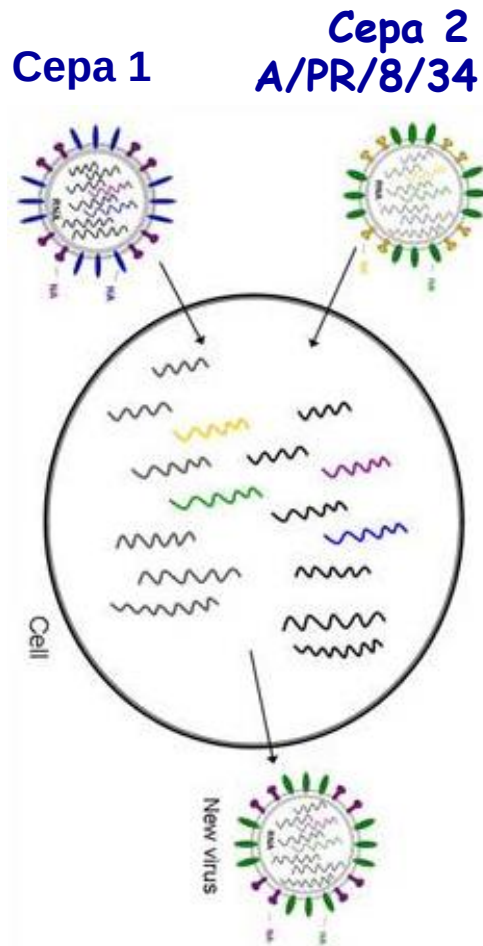
A/PR/8/34

# DESENVOLVIMENTO DA VACINA

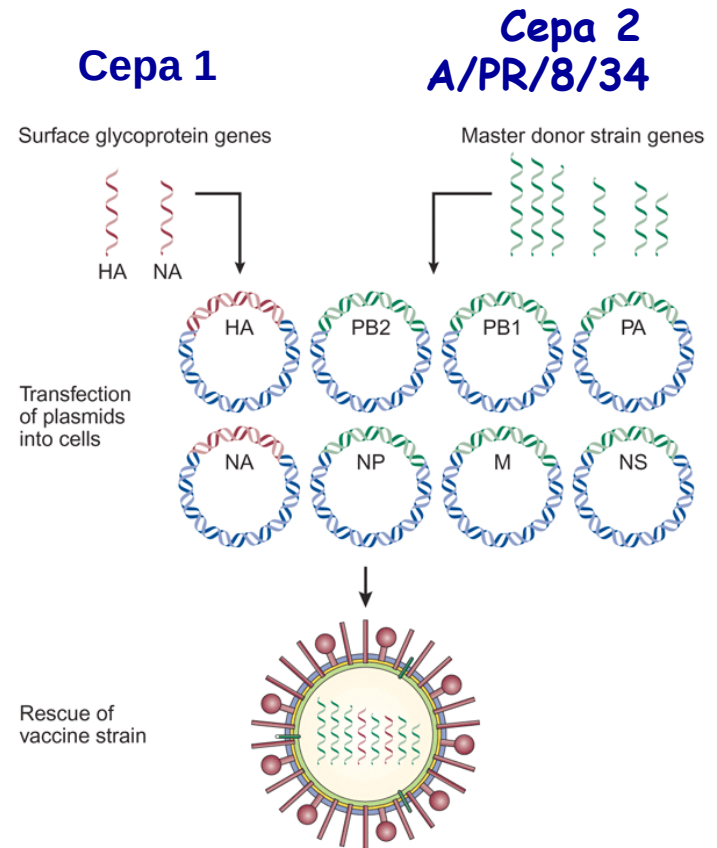


# VACINA CONTRA INFLUENZA

## Cepa vacinal

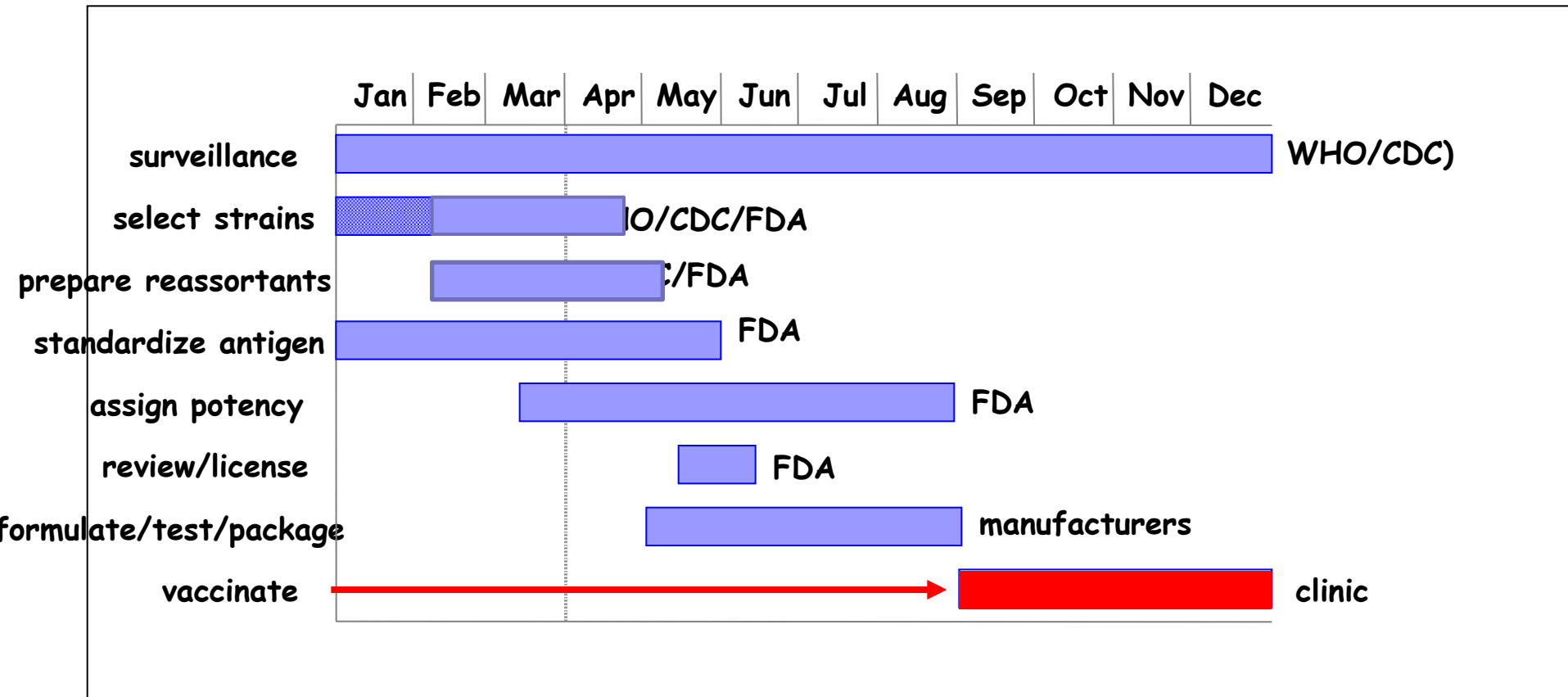


Rearranjo natural em ovos



Rearranjo e reversão genética  
em células

# DESENVOLVIMENTO DA VACINA





# Vacina contra Influenza

1. Rede Mundial de Vigilância (OMS)  
(1947 – 122 labs. , 94 países)

2. Seleção das cepas vacinais  
(4 Centros de Referência)

3. Produção (Agosto a Dezembro)

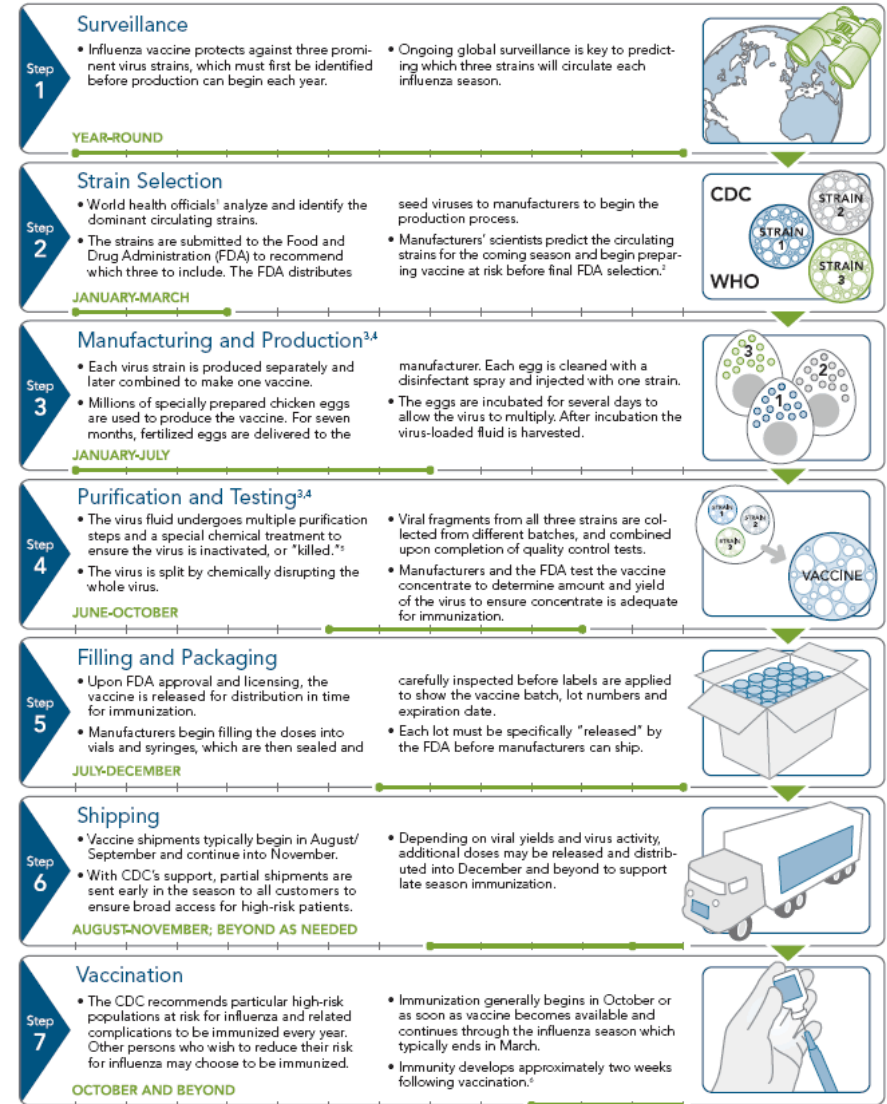
4. Controles

5. Envase e empacotamento

6. Distribuição

7. Vacinação (a partir de Abril)

## Annual Influenza Vaccine Production Timeline



# VACINA CONTRA INFLUENZA

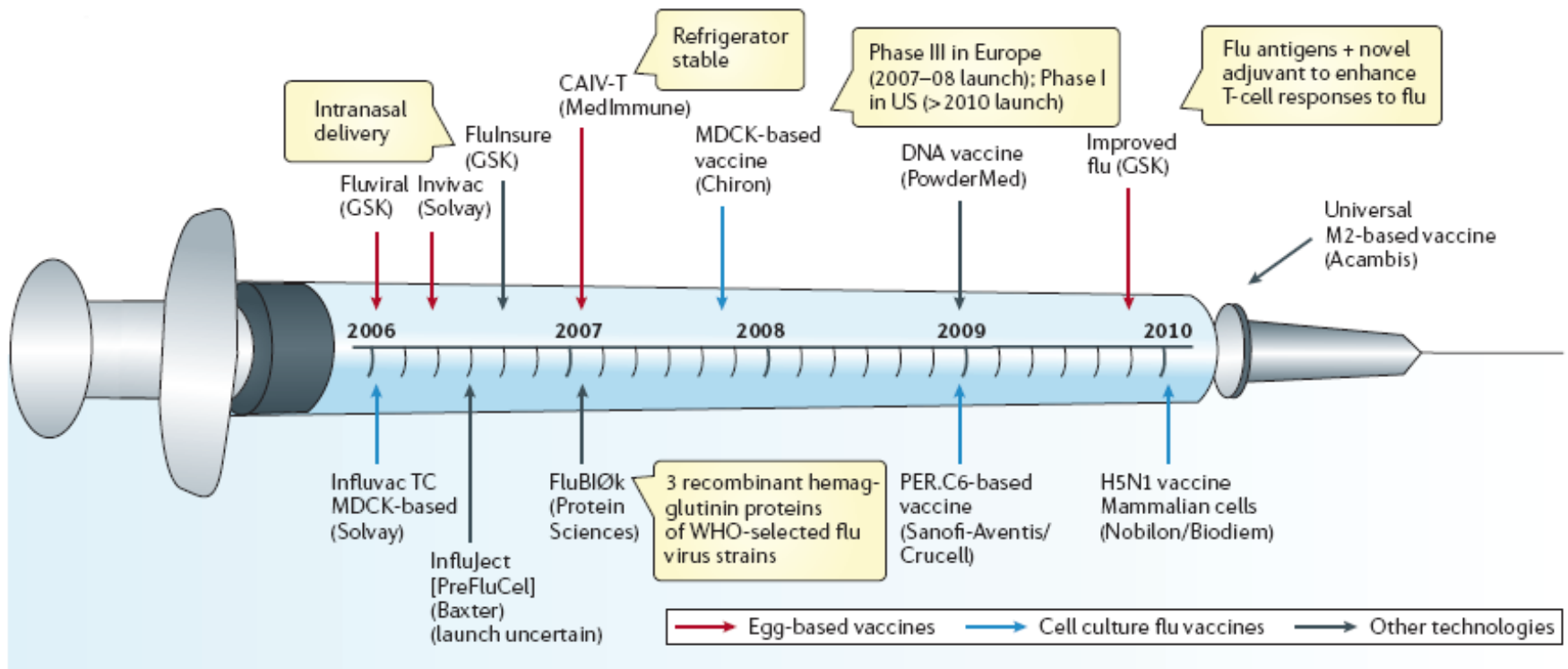


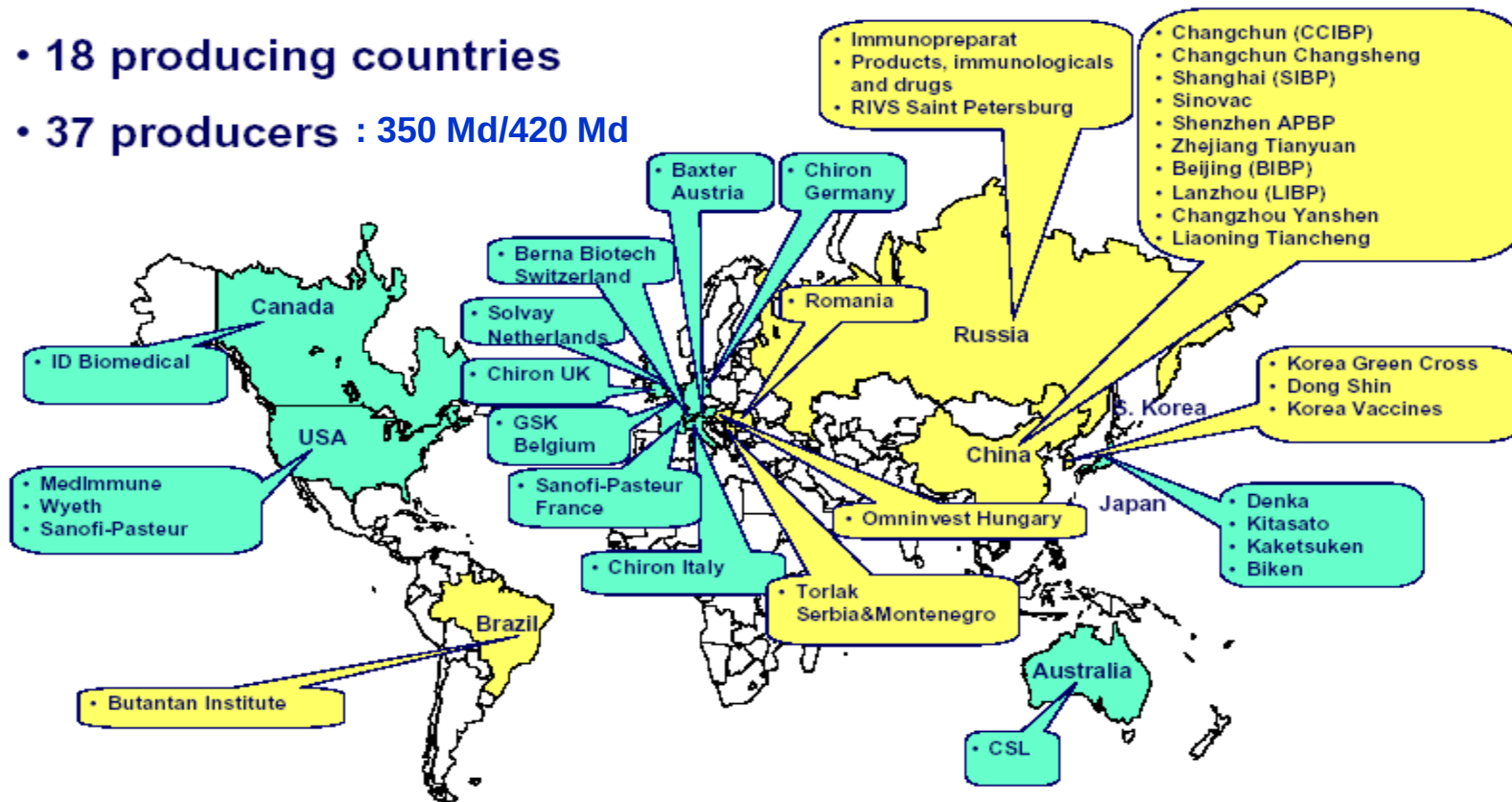
Figure 3 | Estimated US launch dates of developmental influenza vaccines. Source for data in all figures: Datamonitor and company-reported information.

Nature Reviews Drug Discovery 5: 183-184, 2006

# Vacina contra Influenza

## Laboratórios Produtores

- 18 producing countries
- 37 producers : 350 Md/420 Md



## U.S.-licensed Seasonal Influenza Vaccines

- Alfluria** - CSL - ovos,  $\beta$  propiolactone, split com sodium taurodeoxicholate,  
**Agriflu** - Novartis - ovos, formol, Split com cetyltrimethylammonium bromide (CTAB), T80  
**FluLaval** - Quebec - ovos, UV e formol, Split com sodium deoxycholate- triton, T80  
**Fluarix** - GSK - ovos, formol, Split com sodium deoxycholate - triton, T80, alfa tocoferol (vitamin E), hidro cortizona,  
**Flublok** - Protein Sciences - recombinante, cel de inseto - SF+ derivado de SF9, (Spodoptera frugiperda), vetor = baculovirus, extração do rHA com Triton, 45 ug de cada HÁ, contem T20, DNA e proteínas celular e de baculo vírus  
**Flucelvax** - Novartis - células MDCK,  $\beta$  propiolactone, Split com cetyltrimethylammonium bromide, cell protein, DNA cetyltr. e  $\beta$   
**Fluvirin** - Novartis - sub unidades, ovos,  $\beta$  propiolactone, split (remove proteínas internas) com nonylphenol ethoxylate,  
**Fluzone** - Sanofi - ovos, formol, Triton, gelatina 0,05%  
**Flumist** - quadrivalente - medimmune - intranasal, cold adapted (25° C), atenuado, ovos spf, resíduo de glutamato, gelatina, arginina, sacarose, 10x6,5-7,5 PFU  
**FluAd** - Novartis - com adjuvante, ovos, formol, CTAB, adjuvante= esqualeno na fase oleosa, estabilizado com o surfactante T80 e sorbitol trioleate em tampão citrato, 25 ug de cada HÁ, ova, formal, CTAB, bário.

MF59C.1 which is an exclusive adjuvant (Patent EP 0 399 843 B1): 9.75 mg squalene, 1.175 mg polysorbate 80, 1.175 mg sorbitan trioleate, 0.66 mg sodium citrate, 0.04 mg citric acid, and water for injections.  
Excipients: sodium chloride



# Muito Obrigada!!!

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