Grandes endemias
Influenza

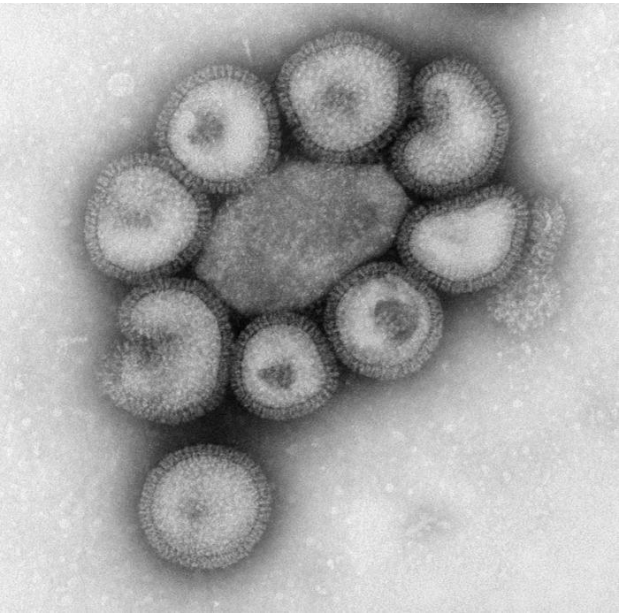
Dra. Charlotte Hársi Dömötör

Instituto de Ciências Biomédicas
Departamento de Microbiologia

O vírus Influenza

- Família - *Orthomyxoviridae*

- Gêneros
  - *Influenza virus A*
    - *Infecta aves, suínos, equinos, humanos*
  - *Influenza virus B*
    - *Infecta humanos*
  - *Influenza virus C*
    - *Infecta humanos e suínos*



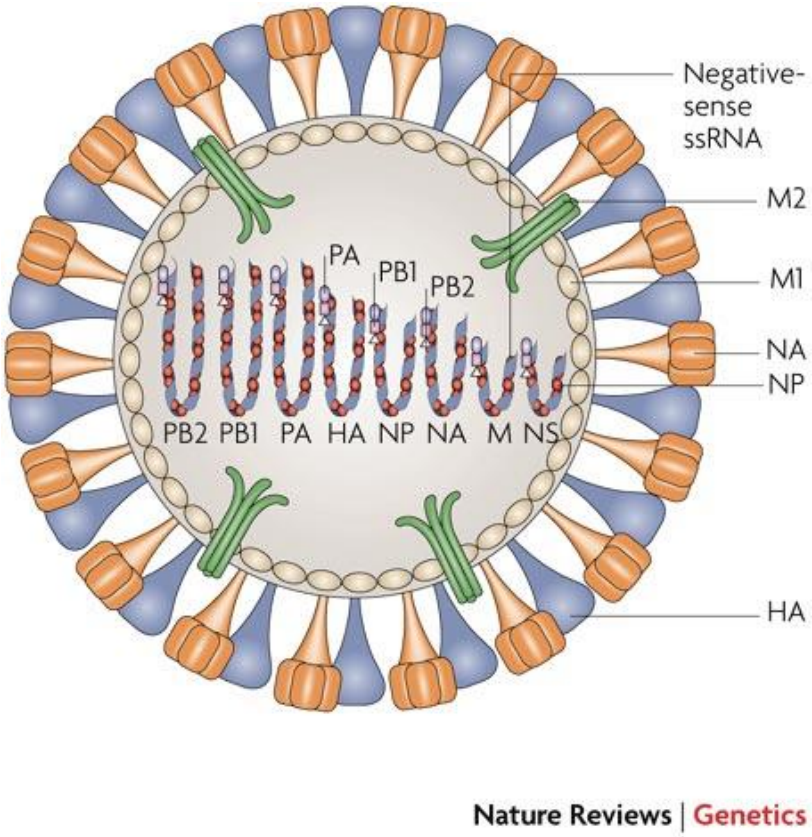
- Tipos – A/H1N1, A/H2N2, H3N2.....

Características da partícula viral

- **Estrutura**
- Vírus pleomórficos
- Nucleocapsídeo com simetria helicoidal
- Recoberto por membrana lipoprotéica
- Genoma RNA- segmentado (8 seg.)

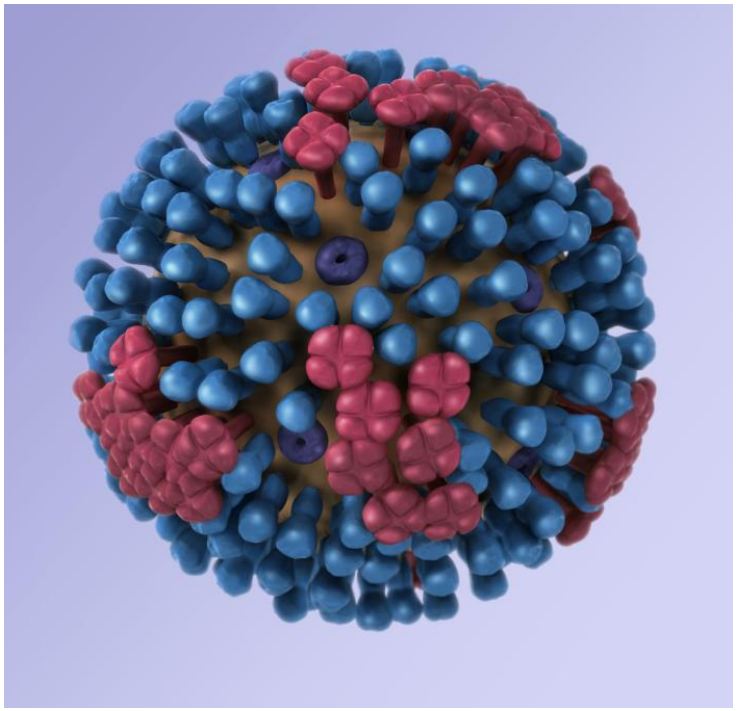
Proteínas

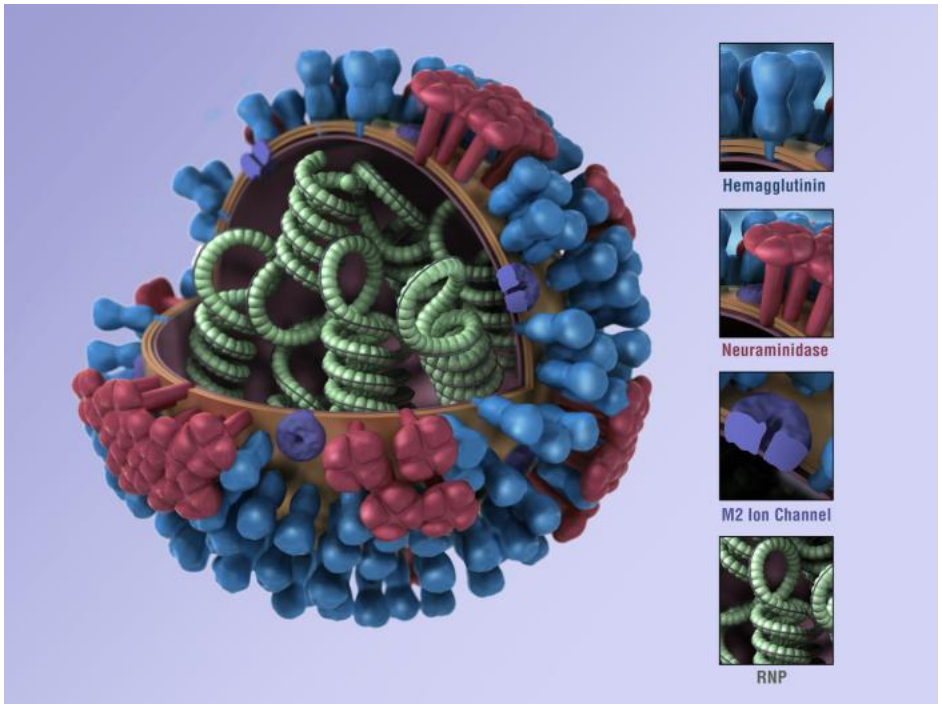
HA - hemaglutinina
NA - neuraminidase
M1 - Matriz
M2 – Montagem do vírus
NP – Nucleoproteína
PA, PB1, PB2 - polimerases



Nelson and Holmes *Nature Reviews Genetics* **8**, 196–205 (March 2007) | doi:10.1038/nrg2053

Características da partícula viral





HA – Hemaglutinina - reconhecimento da célula
NA – Neuraminidase - liberação viral e disseminação no trato respiratório
M2 – Montagem viral
RNP - ribonucleoproteína - genoma

Centers for Disease Control and Prevention
Public Health Image Library – 2009 – Dan Higgins

Classificação dos vírus *Influenza A*

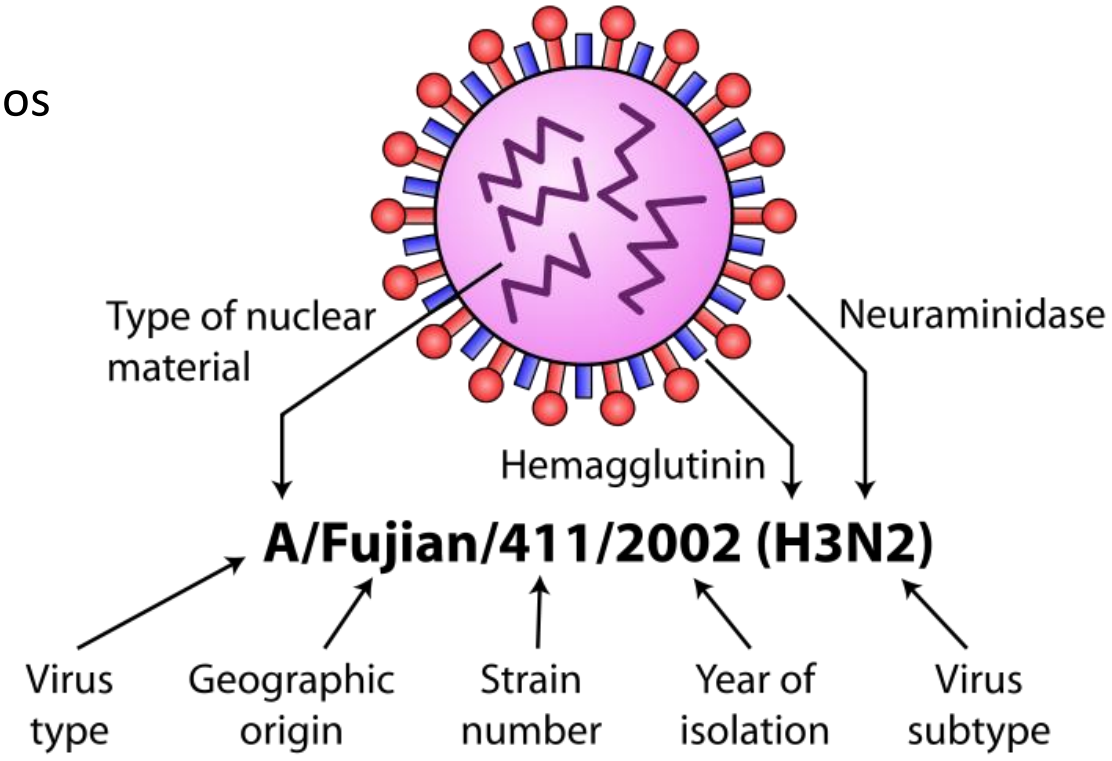
Proteína M1 e NP – gênero

Proteínas HA e NA – tipos

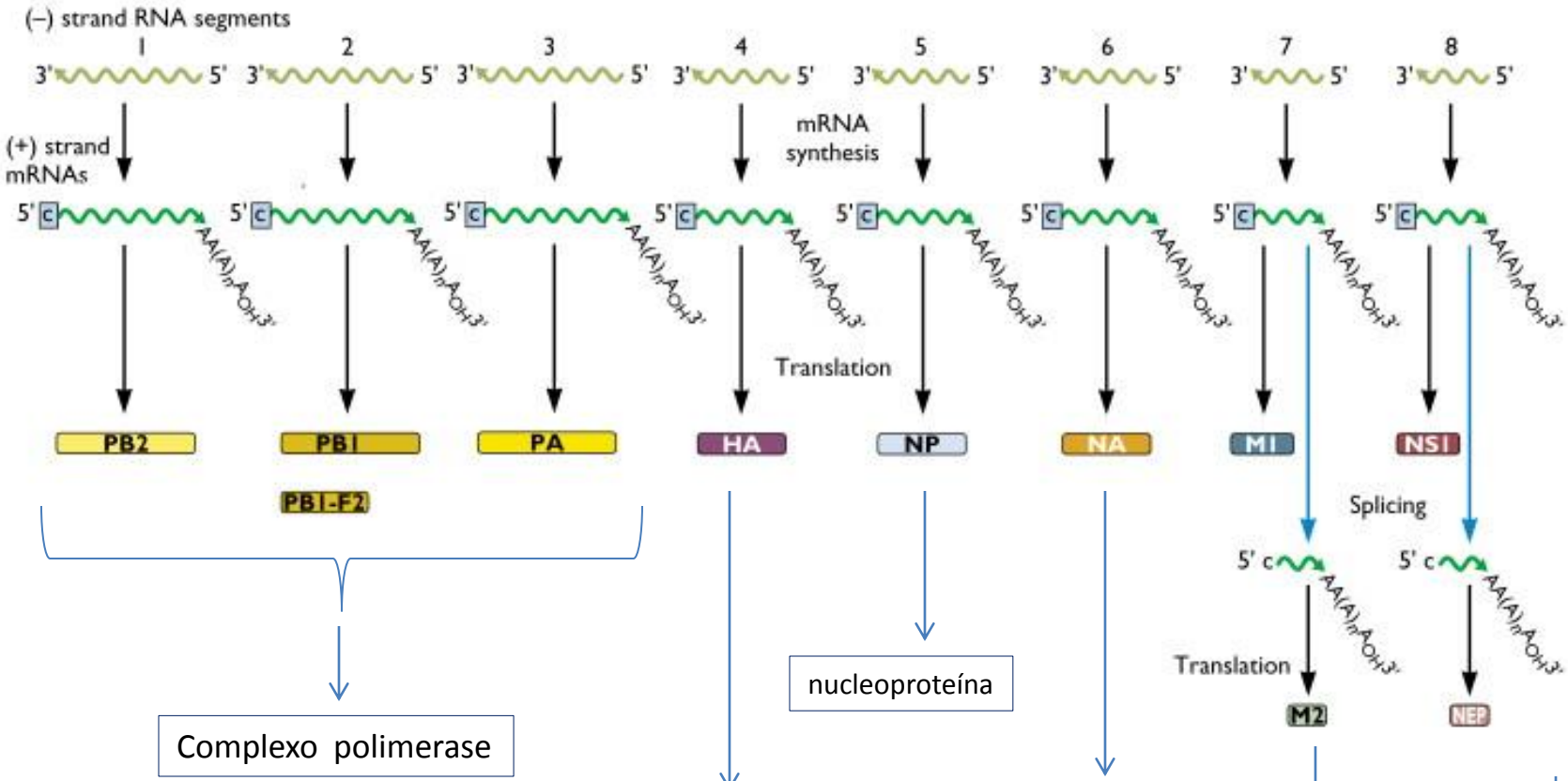
16 hemaglutininas
9 neuraminidases

H1N1
H1N2
H2N2
H3N2

H5N5
H9N1



Organização do genoma



Complexo polimerase

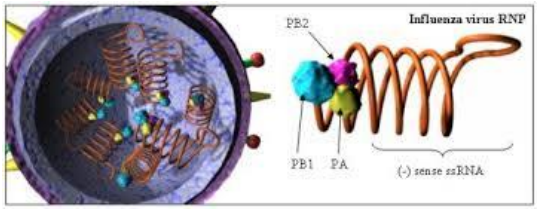
nucleoproteína

hemaglutinina

neuraminidase

Matriz e membrana 2

NS1 e Nuclear Export Protein



Replicação

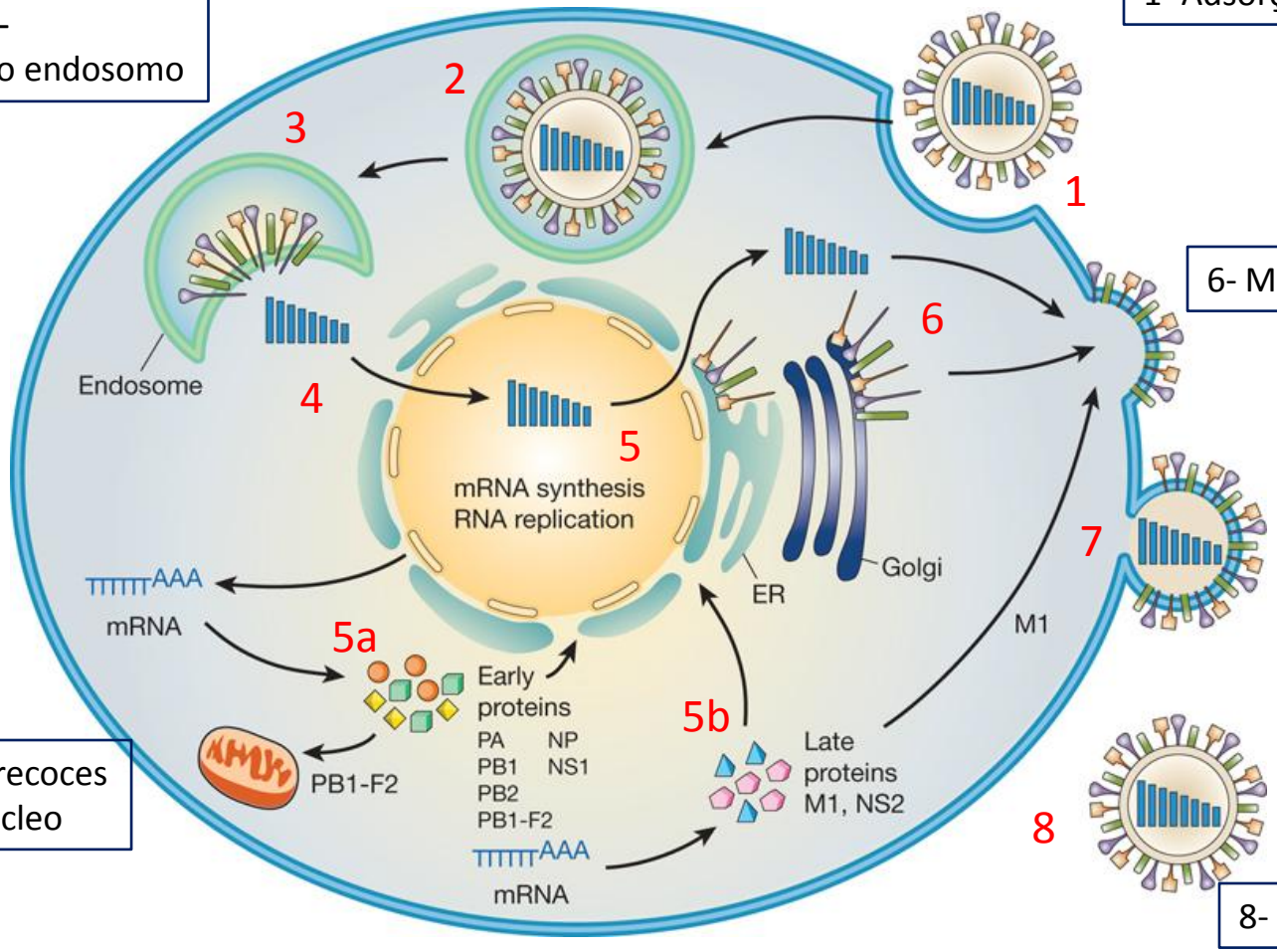
2- Penetração - endocitose

1- Adsorção

3 – Desnudação –
acidificação do endosomo

4- Transporte do nucleocapsídeo ao núcleo

5- Transcrição



6- Montagem

7 - Brotamento

8- Liberação

5a - proteínas precoces
Retornam ao núcleo

5b – proteínas tardias

G Neumann *et al. Nature* **459**, 931-939 (2009) doi:10.1038/nature08157

Hospedeiros conhecidos do Influenza A

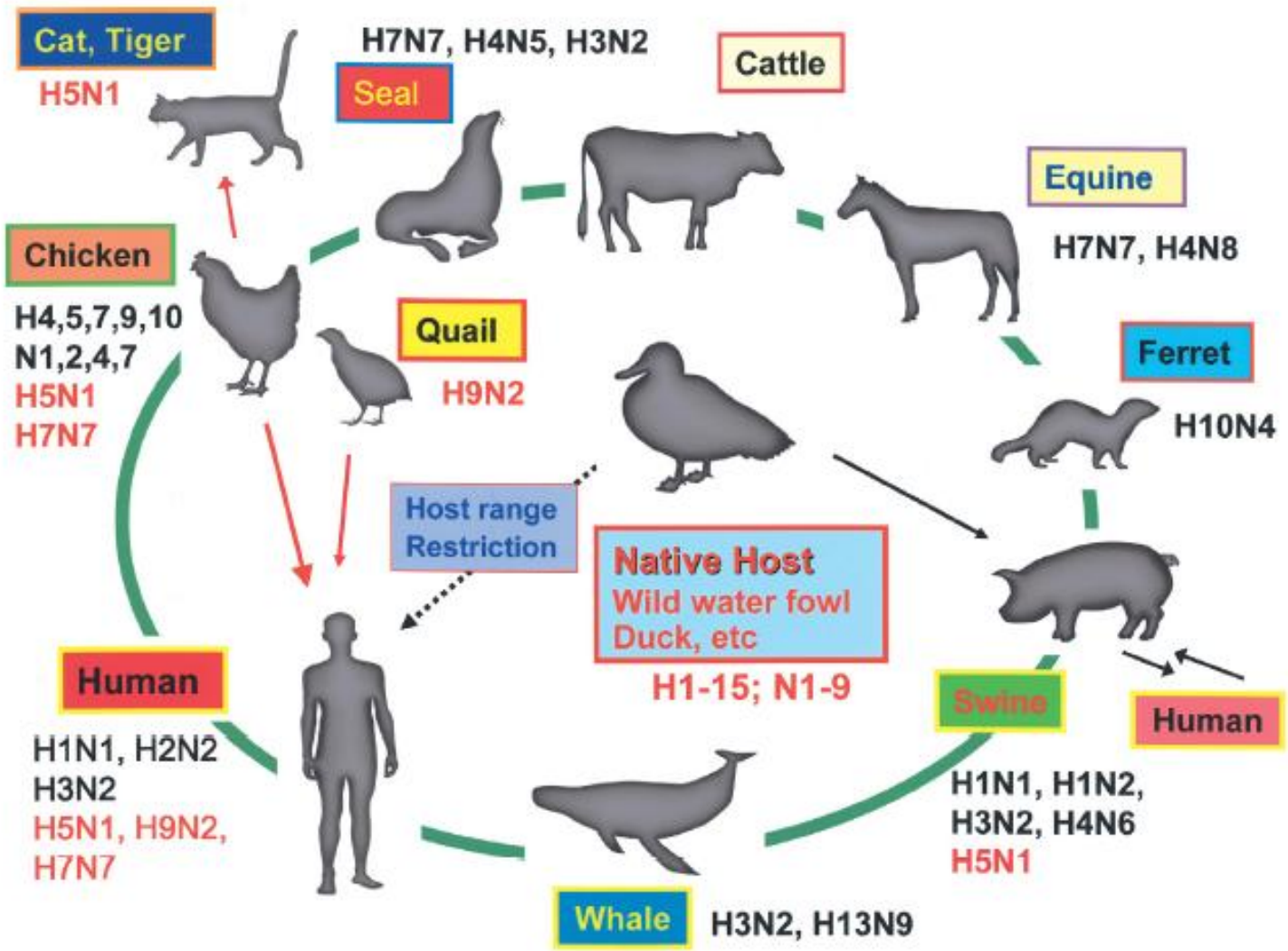
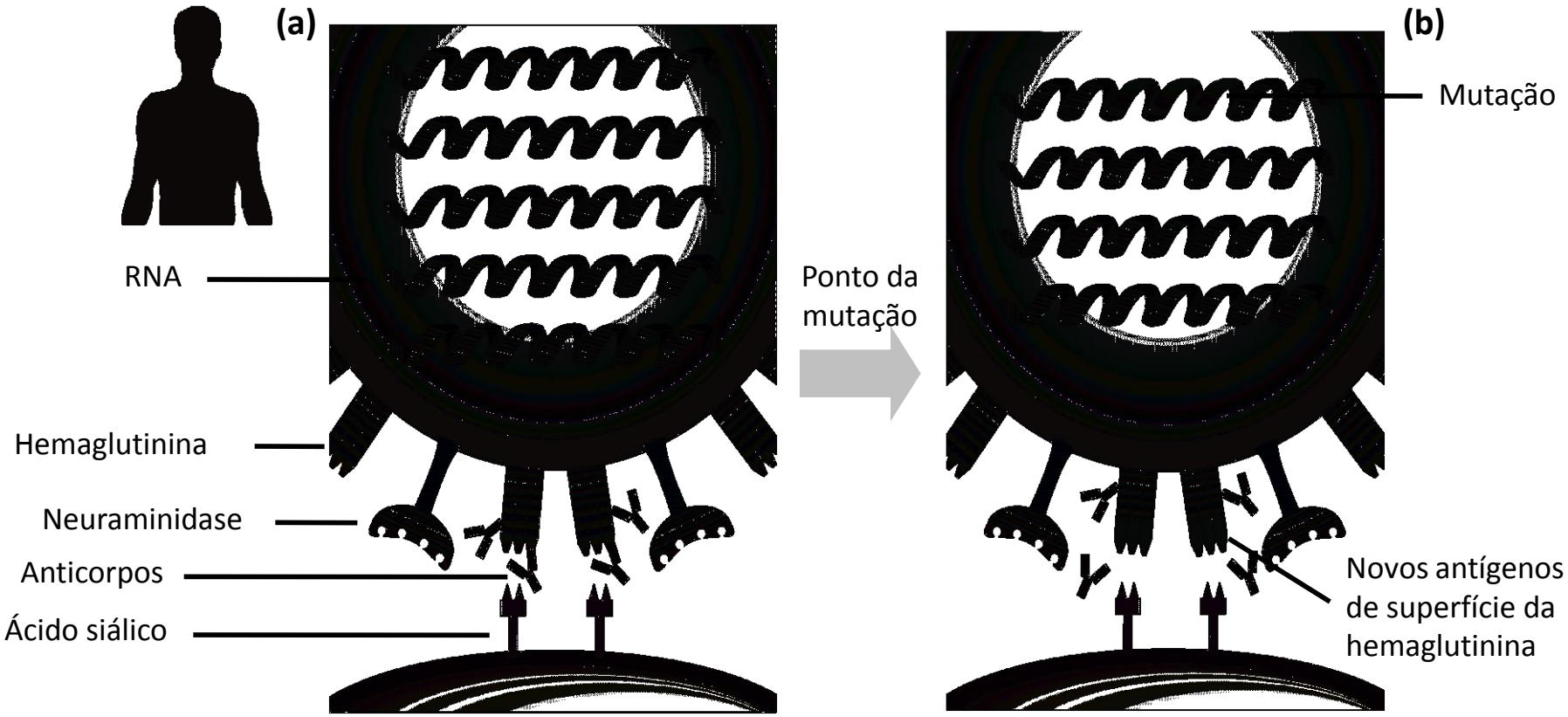


Fig. 1. Host Range of Influenza Viruses

Variabilidade Genética

Drifts Antigênicos (Variações Sazonais)

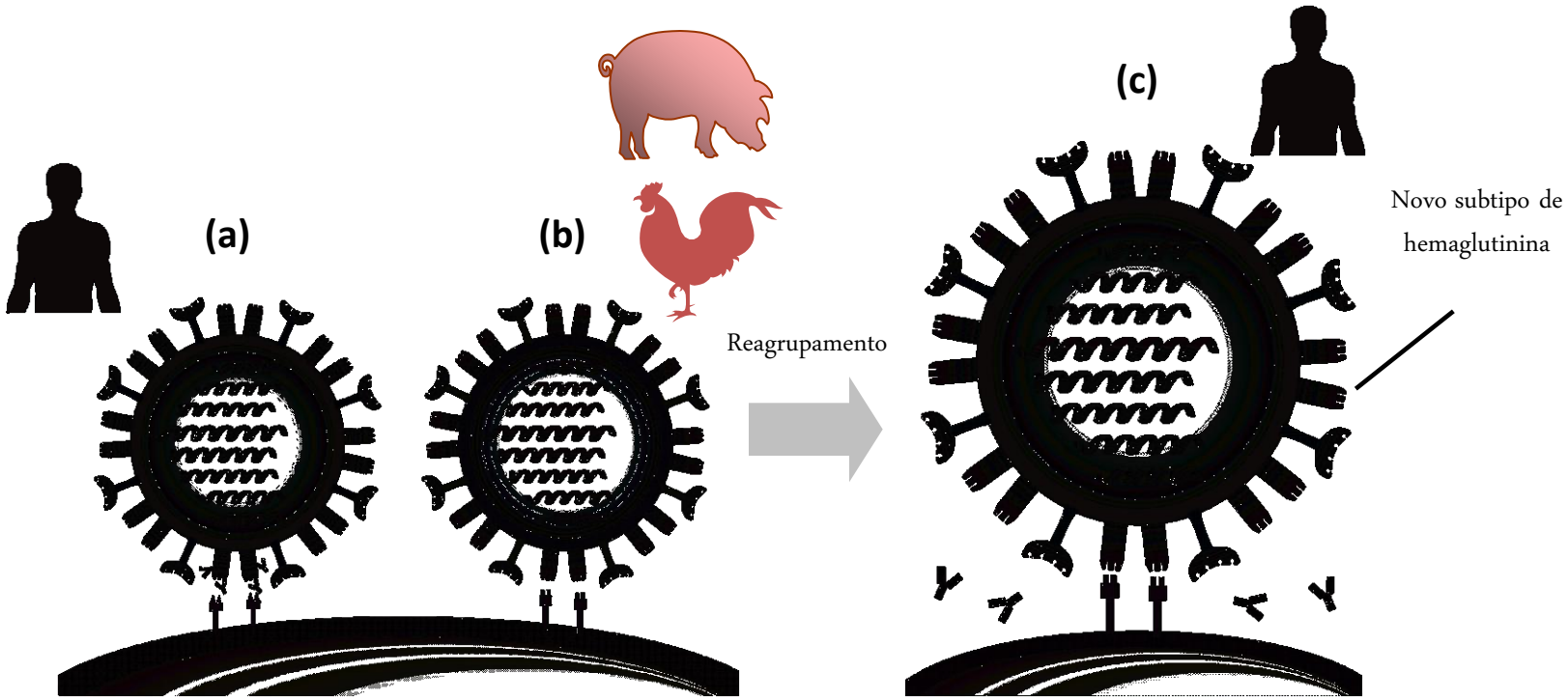


O lento acúmulo de mutações no vírus circulante (a) faz surgir uma 'nova' cepa antigênica com novos antígenos de superfície da hemaglutinina (b) que não são reconhecidos pelos anticorpos existentes

Cox and Fukuda. Infect Dis Clin North Am 1998;12:27–38. Laver et al. Sci Am 1999;280:78–87.

Variabilidade genética

Shifts Antigênicos(Candidatos Pandêmicos)

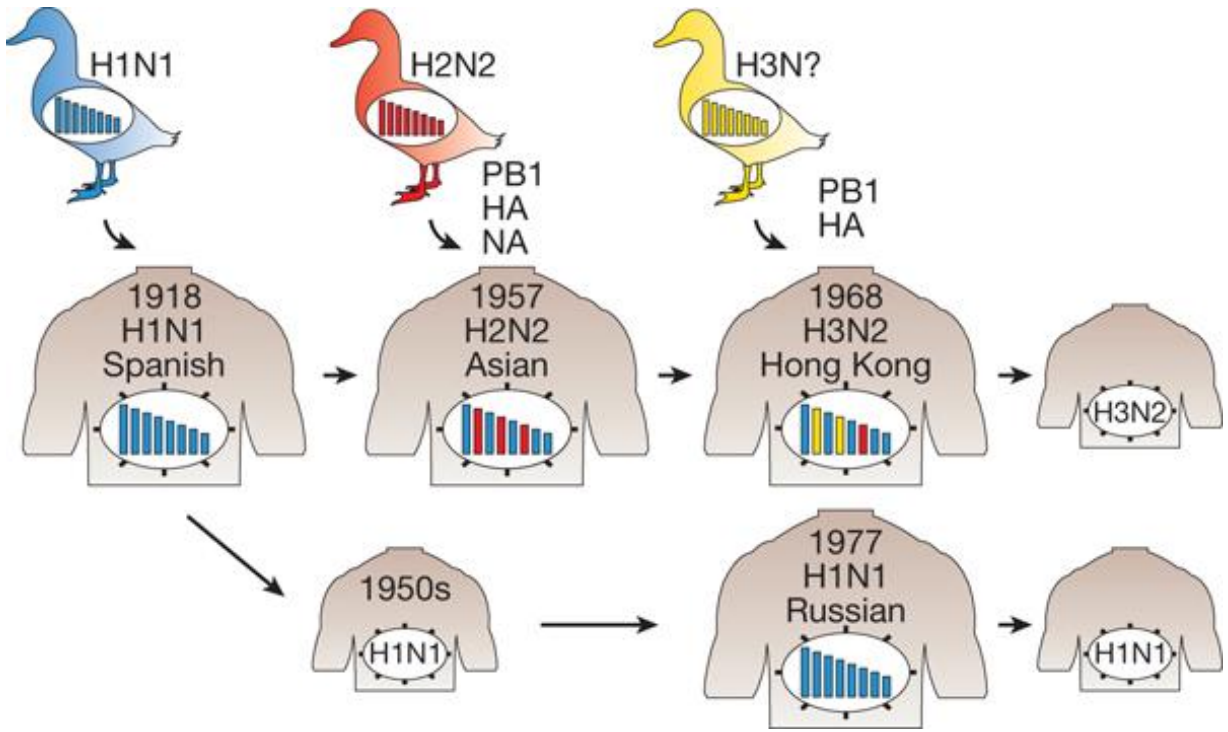


A ‘mistura’ de um vírus influenza que infecta humanos (a) com um vírus influenza que infecta somente outra espécie, p.ex. aves domésticas ou porco, (b) resulta em uma nova cepa (c) com um novo subtipo de hemaglutinina (ou neuraminidase) que pode levar a uma pandemia

Variabilidade genética

Shifts Antigênicos(Candidatos Pandêmicos)

Emergence of pandemic influenza viruses.

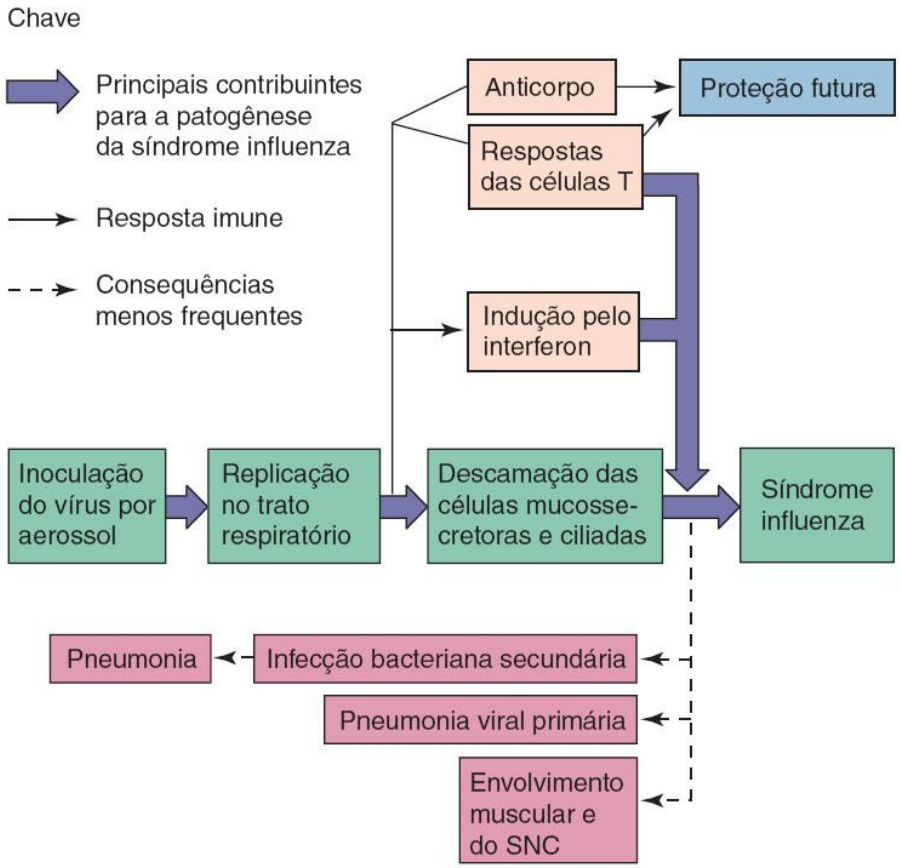


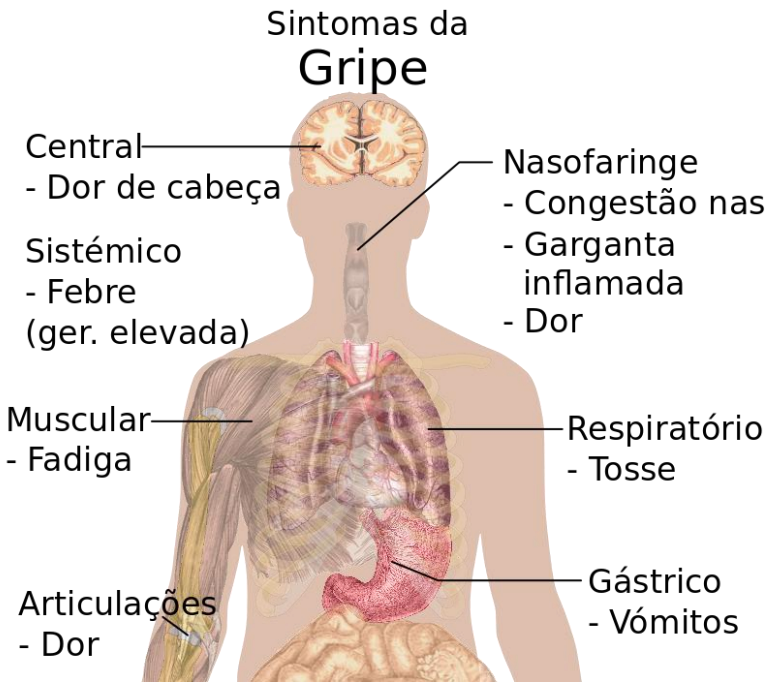
G Neumann *et al. Nature* **000**, 1-9 (2009) doi:10.1038/nature08157

nature

Patogenia

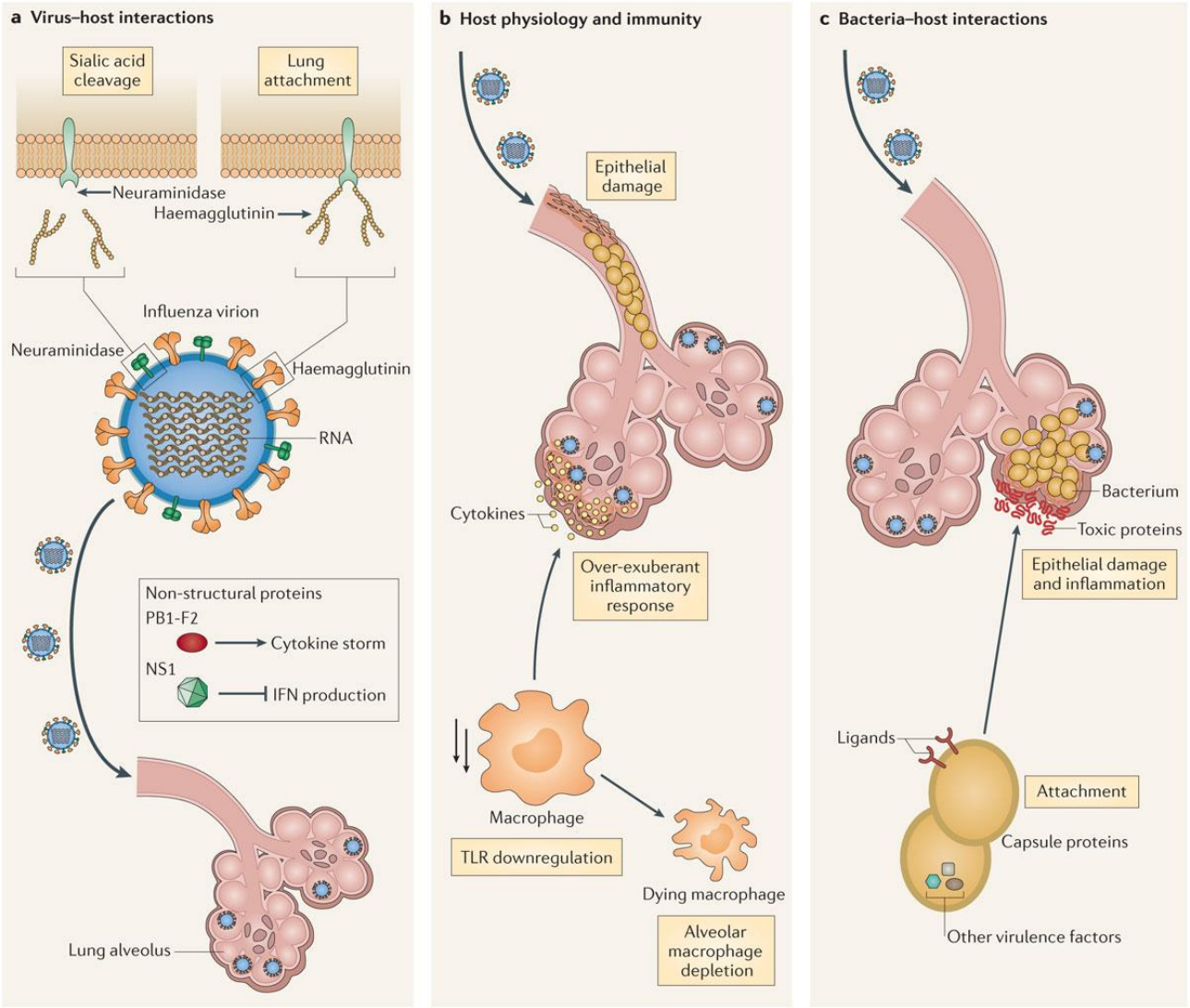
Microbiologia Médica - 6ª Edição
Murray & Rosenthal & Pfaller
ISBN: 9788535234466
Elsevier Editora





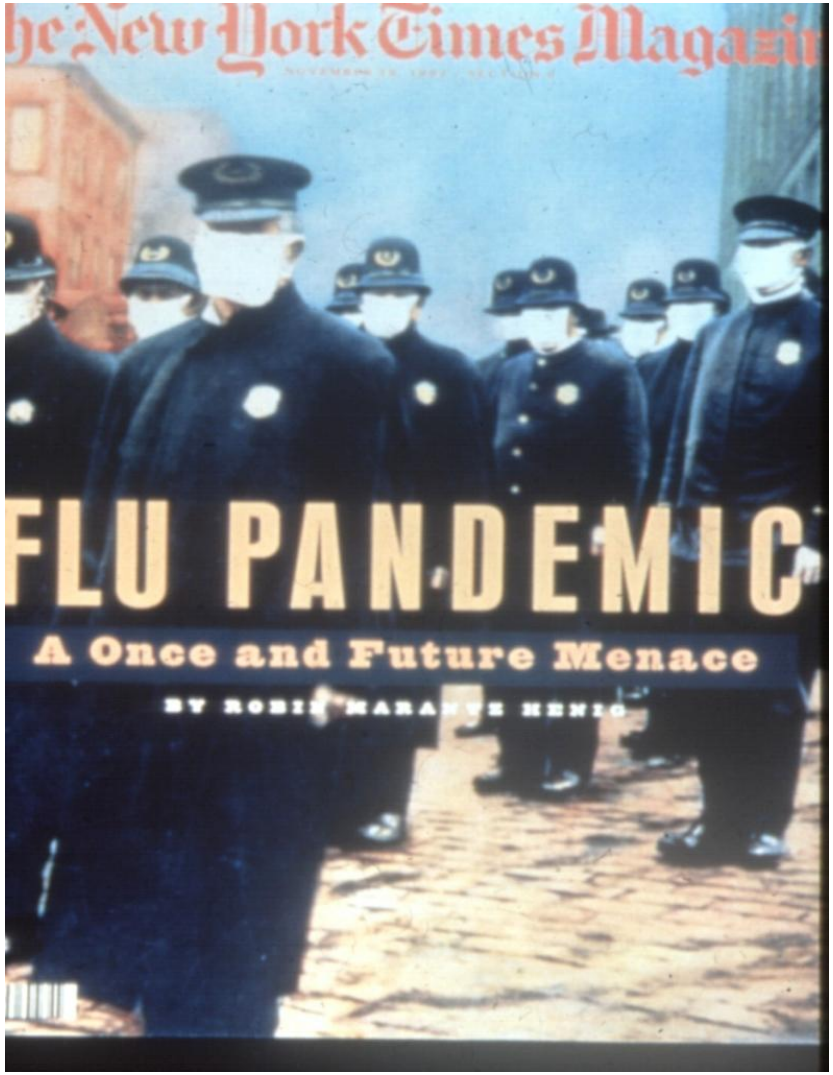
"Sintomas da gripe" por Mikael Häggström
tradução para o português

Patogenia



Nature Reviews | Microbiology

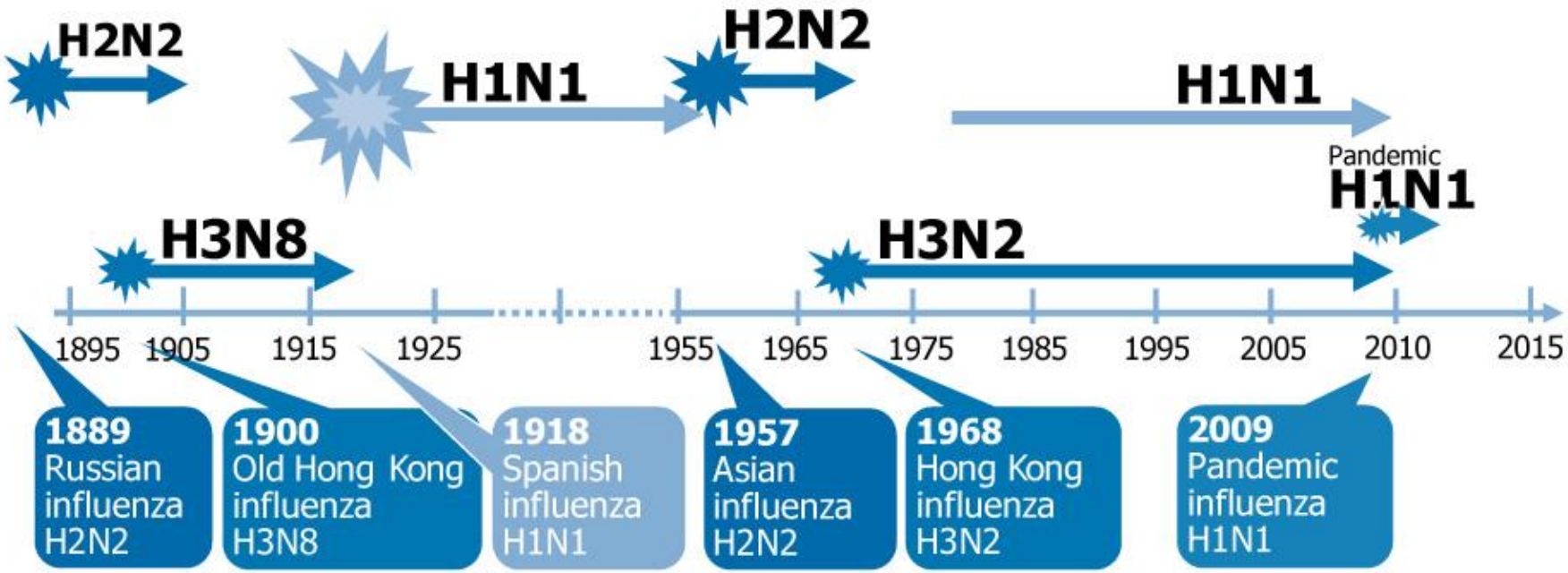
Pandemia de Influenza de 1918



Pandemias de *Influenza A*

FIGURE

Recorded human pandemic influenzas since 1885 (early sub-types inferred)



Source: European Centre for Disease Prevention and Control (ECDC) 2009

Reproduced and adapted (2009) with permission of Dr Masato Tashiro, Director, Center for Influenza Virus Research, National Institute of Infectious Diseases (NIID), Japan.

Influenza aviária

H5N1:

- 1997-2001:

contínua circulação em aves

- 2002:

H5N1 sofre *antigenic drift*

altamente patogênico em

patos e aves aquáticas

- 2003:

família infectada com H5N1 (pai vai a óbito)

- 2003-2004: Vietnã, Tailândia, Indonésia, Cambódia, Laos, Coréia,

Japão, China (e depois Malásia)

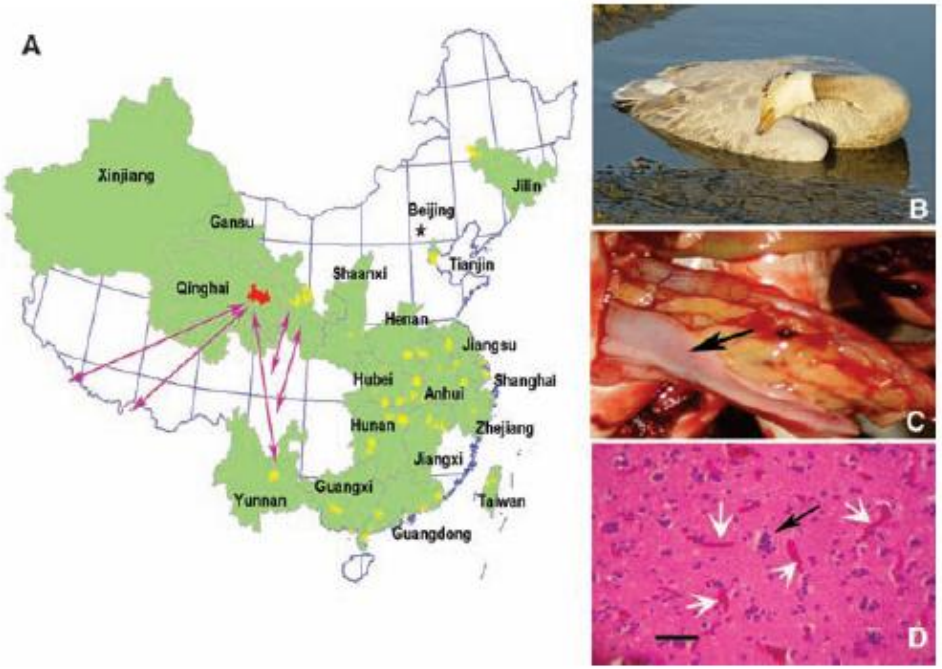


Fig. 1. (A) The reported H5N1 AIV prevalence sites during the 2004 outbreak in China are highlighted in yellow (*8*). Arrows indicate the migratory routes of the bar-headed goose (*A. indicus*) to Lake Qinghaihu. (B) A sick bar-headed goose showing typical opisthotonus before dying. (C) Bar-headed goose pancreas with pin-point necrotic lesions (arrow). (D) Microscopic lesions in bar-headed goose brain, showing congestion in the blood vessels (white arrows) and glial cell infiltration (black arrow). Hematoxylin and eosin ×25 (scale bar, 50 μm).

Liu et al, ago 2005 - Science

Influenza Aviária transmitida para humanos

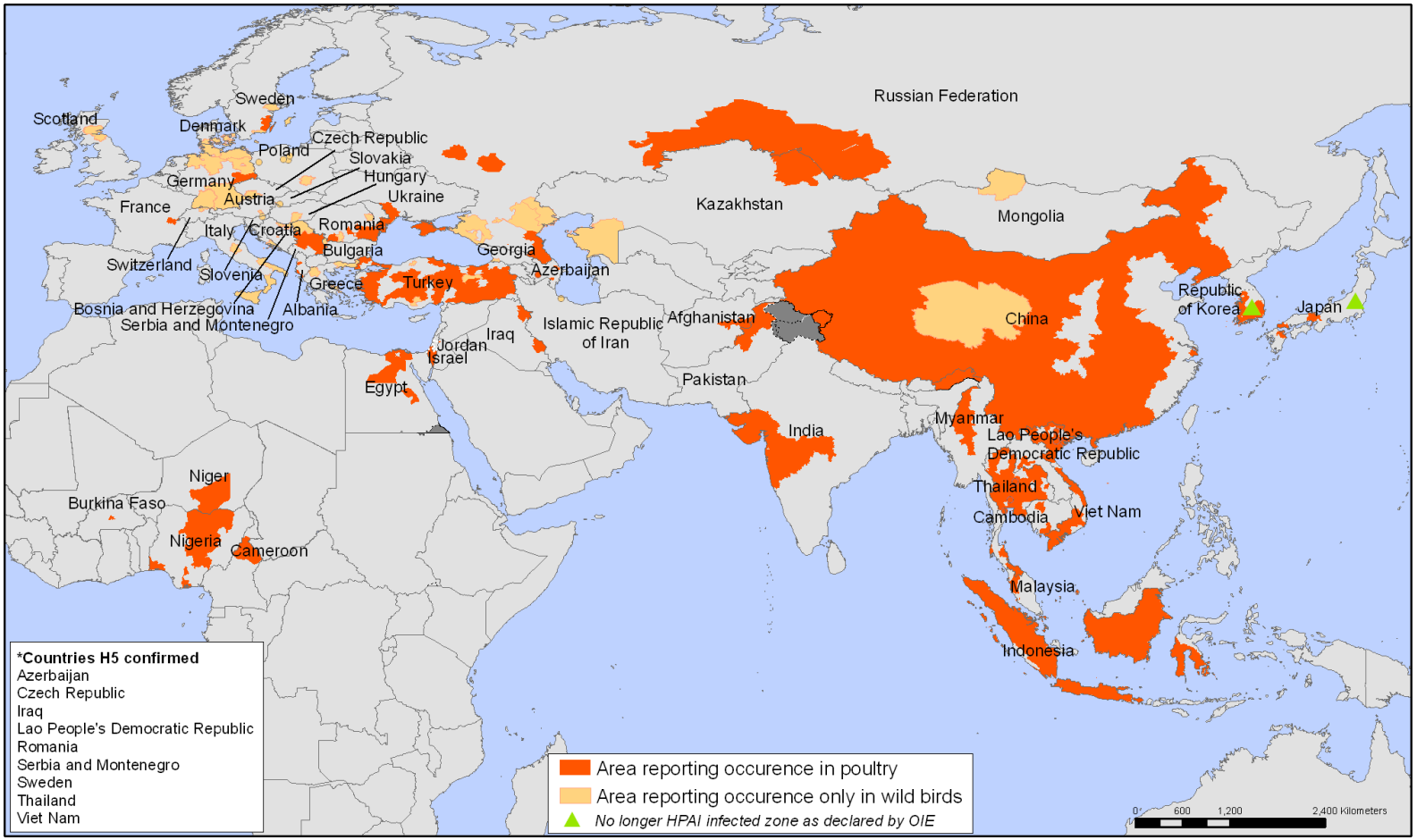
- 1997: H5N1 em Hong Kong
  18 hospitalizações, 6 mortes

- 1999: H9N2 em Hong Kong
  2 hospitalizações

- 2003: H5N1 na China
  2 hospitalizações , 1 morte
  H7N7 na Holanda
  80 casos com 1 morte
  (infecções respiratórias e oculares)

Areas reporting confirmed occurence of H5N1* avian influenza in poultry and wild birds since 2003

Status as of 07 April 2006



World Health Organization

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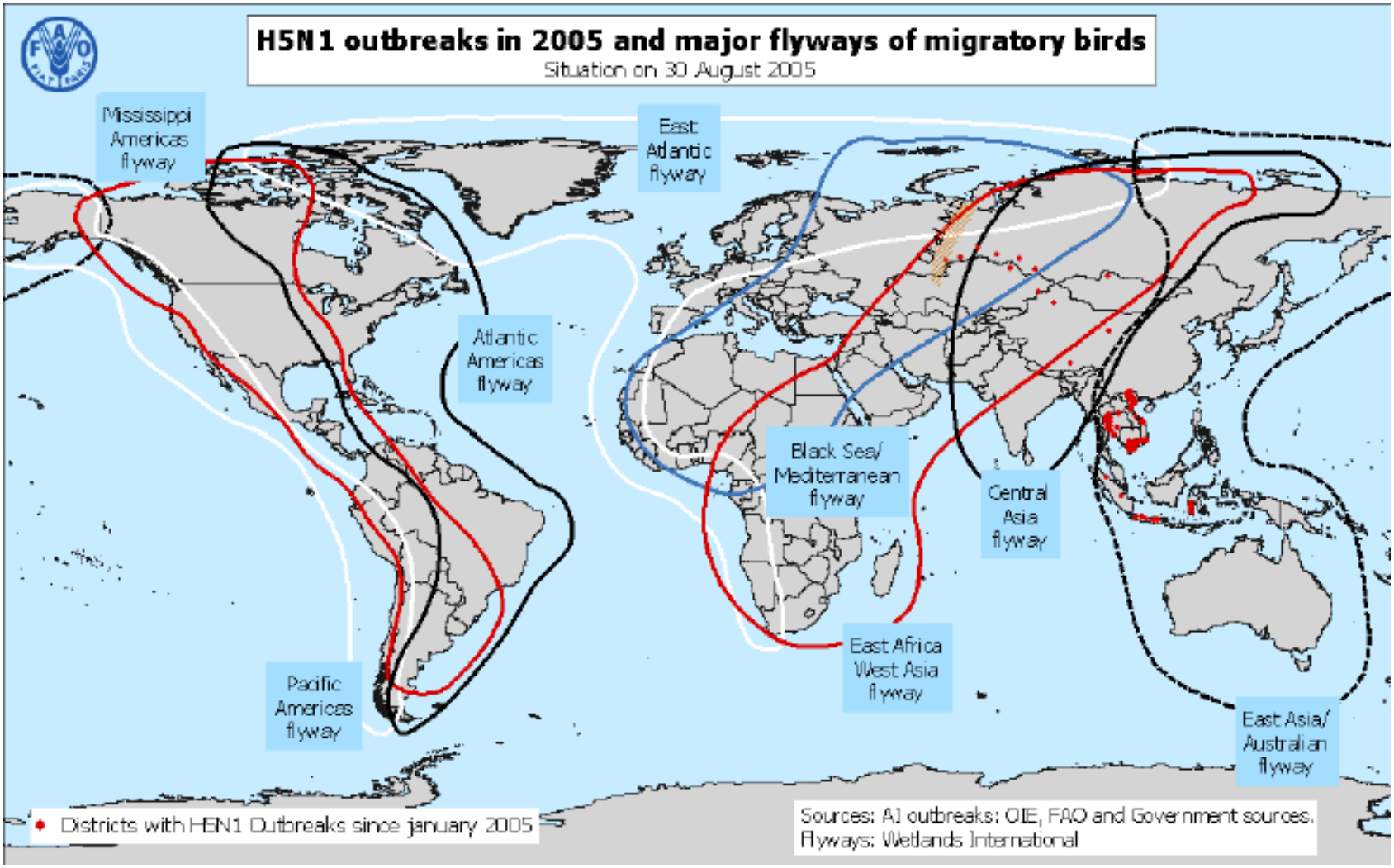
Data Source: World Organisation for Animal Health (OIE) and national governments

Map Production: Public Health Mapping and GIS
Communicable Diseases (CDS) World Health Organization


H5N1 outbreaks in 2005 and major flyways of migratory birds
Situation on 30 August 2005
Mississippi Americas flyway
East Atlantic flyway
Atlantic Americas flyway
Black Sea/ Mediterranean flyway
Central Asia flyway
East Africa West Asia flyway
Pacific Americas flyway
East Asia/ Australian flyway
Districts with H5N1 Outbreaks since january 2005
Sources: AI outbreaks: OIE, FAO and Government sources.
Flyways: Wetlands International

De 2003 até 24/06/2006

- Mais de 40 países relataram presença do vírus H5N1 nas aves;
- 203 pessoas adoeceram;
- 144 óbitos;
- 46 na Indonésia.

PERIGO!!

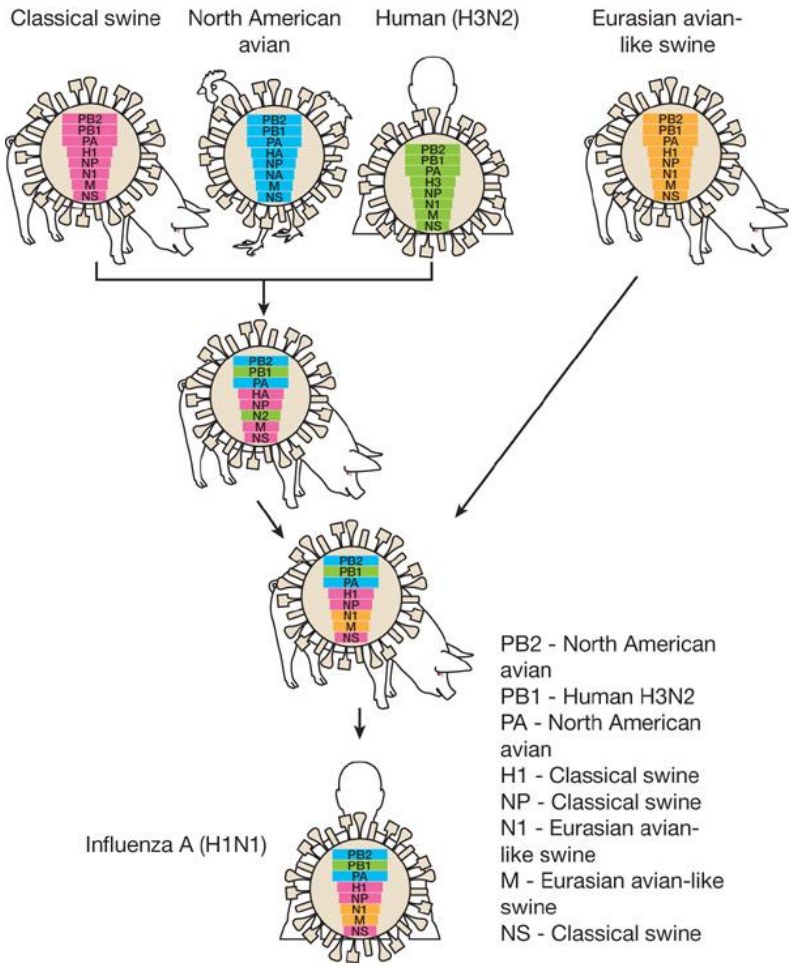
- Desde que surgiram os primeiros casos de contágio em humanos, no surto que começou em 2004, mais da metade das pessoas infectadas morreu.
- Quase todas as vítimas tinham contato direto com as aves.

Influenza Suína

Influenza Suína em humanos

- 1958 a 2005 (EUA) – total de 37 casos de influenza humana associada a influenza suína, com 4 óbitos.
  - 4 amostras eram H3N2 e o restante H1N1
- Transmissão descrita em outros países da Europa e Nova Zelandia
- 1974 – primeiro isolamento do vírus a partir de pulmão de um menino (Smith *et al*.1976)
- 1976 – surto em recrutas de Fort Dix (New Jersey, EUA) ~200 infectados
- 2005 – caso menino 17 anos com sinais clínicos – isolamento de H1N1 com um rearranjo triplo (circulante em suínos)

Genesis of swine-origin H1N1 influenza viruses.



- HA, NA e PB1 - vírus humanos
- M, NS e NP – vírus suínos
- PA e PB2 vírus aviários

G Neumann *et al. Nature* **000**, 1-9 (2009) doi:10.1038/nature08157

nature

Influenza Suína A/H1N1

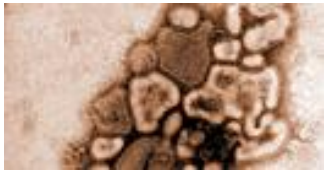
- H1N1 suína com recombinações humana e aviária.

- Casos iniciais México : Março?

- EUA: 17 Abril 2 casos confirmados em crianças na Califórnia.

CDC MMWR April 2009

Influenza Suína A/H1N1



- OMS: 29 Abril 19h
- 148 casos confirmados em 9 países
  - EUA: 91
  - México: 26
  - Áustria: 1
  - Canadá: 13
  - UK: 5
  - Alemanha: 3
  - Israel: 2
  - Nova Zelândia: 3
  - Espanha: 4
- 8 mortes confirmadas: 1 EUA e 7 México

www.who.int

New Influenza A (H1N1)
Number of laboratory confirmed cases and deaths

Status as of 5 May 2009
6:30 GMT

Canada
140 cases

US
286 cases
1 death

Mexico
590 cases
25 deaths

El Salvador
2 cases

Costa Rica
1 case

Colombia
1 case

Netherlands
1 case

Denmark
1 case

UK
18 cases

Germany
8 cases

Ireland
1 case

France
4 cases

Italy
2 cases

Portugal
1 case

Spain
54 cases

Switzerland
1 case

Austria
1 case

Israel
4 cases

Republic of Korea
1 case

China, Hong Kong SAR
1 case

New Zealand
6 cases

Total:
1124 cases
26 deaths

As reported by national health authorities

0 1,600 3,200 6,400 Kilometers

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Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

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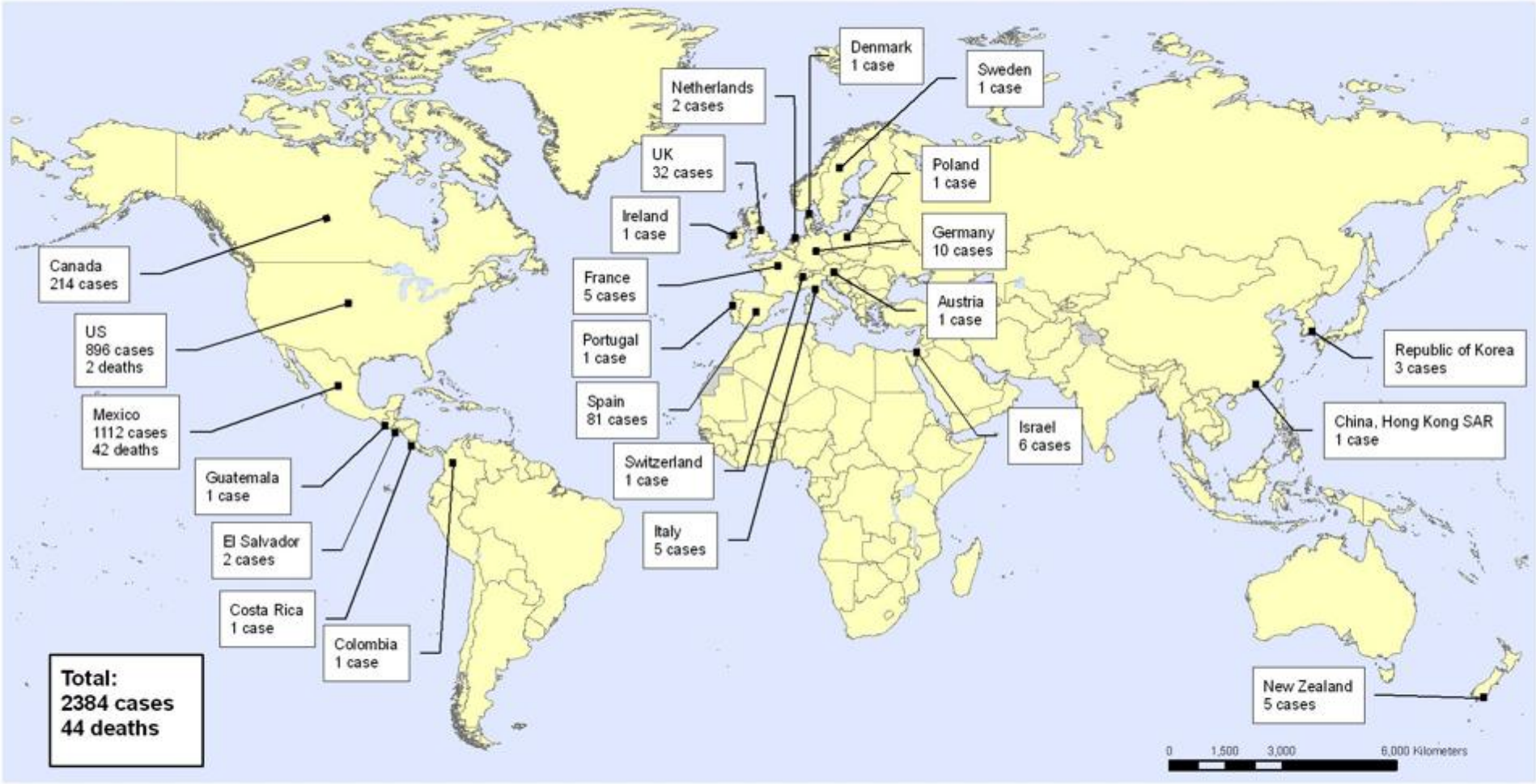
Map produced: 5 May 2009 6:30 GMT

New Influenza A (H1N1), Number of laboratory confirmed cases and deaths as reported to WHO

Status as of 8 May 2009 06:00 GMT



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Map produced: 8 May 2009 06:00 GMT

New Influenza A (H1N1), Number of laboratory confirmed cases and deaths as reported to WHO

Status as of 11 May 2009 06:00 GMT

Denmark 1 case
Norway 2 cases
Netherlands 3 cases
Sweden 2 cases
UK 47 cases
Poland 1 case
Ireland 1 case
Germany 11 cases
Canada 284 cases 1 death
France 13 cases
Austria 1 case
Japan 4 cases
US 2532 cases 3 deaths
Portugal 1 case
Republic of Korea 3 cases
Mexico 1626 cases 48 deaths
Spain 95 cases
Israel 7 cases
China 2 cases
Switzerland 1 case
Guatemala 1 case
Italy 9 cases
El Salvador 4 cases
Australia 1 case
Costa Rica 8 cases 1 death
Brazil 8 cases
Panama 15 cases
Argentina 1 case
New Zealand 7 cases
Colombia 3 cases

Total: 4694 cases 53 deaths

0 1,500 3,000 6,000 Kilometers

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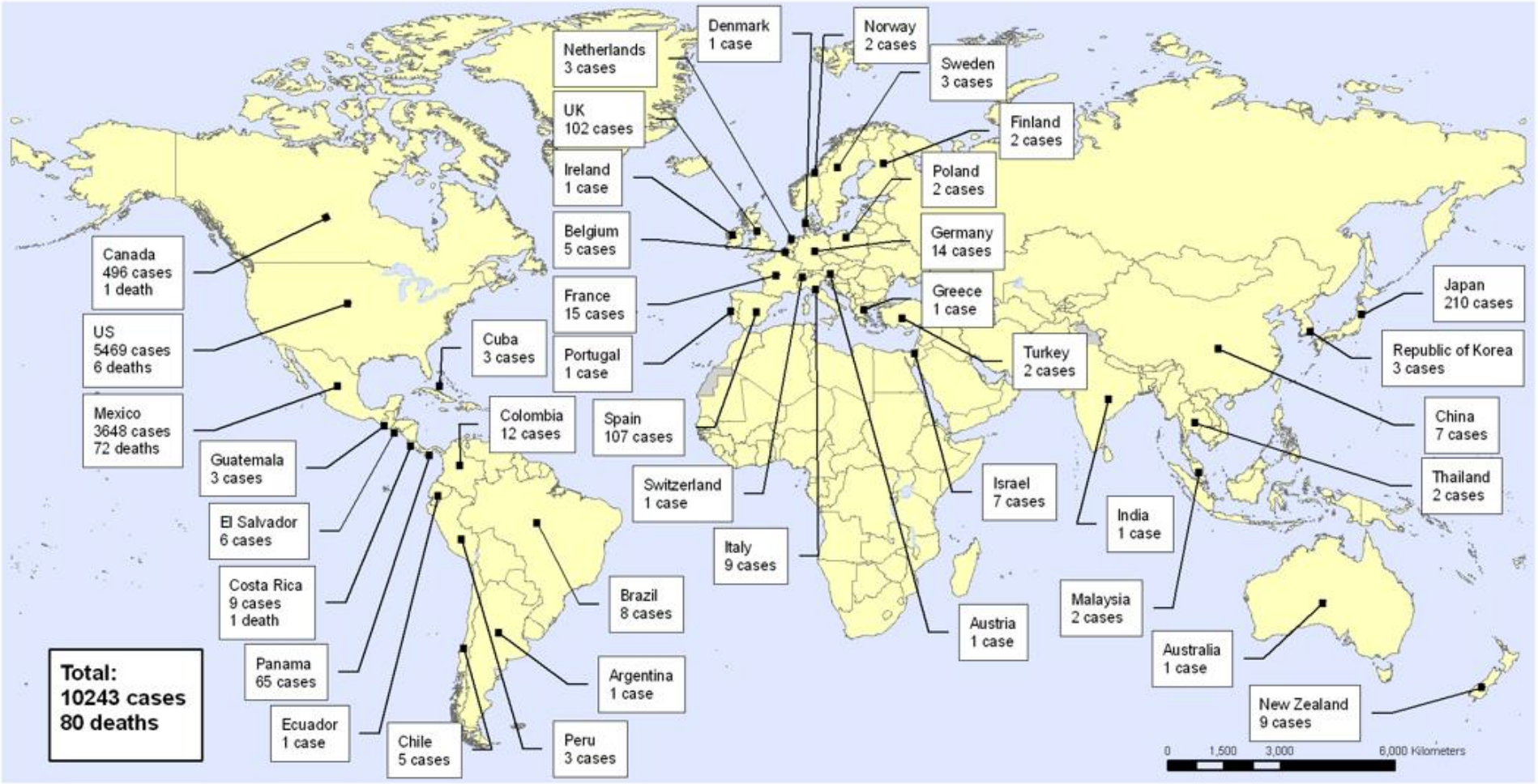
Map produced: 11 May 2009 06:00 GMT

New Influenza A (H1N1), Number of laboratory confirmed cases and deaths as reported to WHO

Status as of 20 May 2009 6:00 GMT



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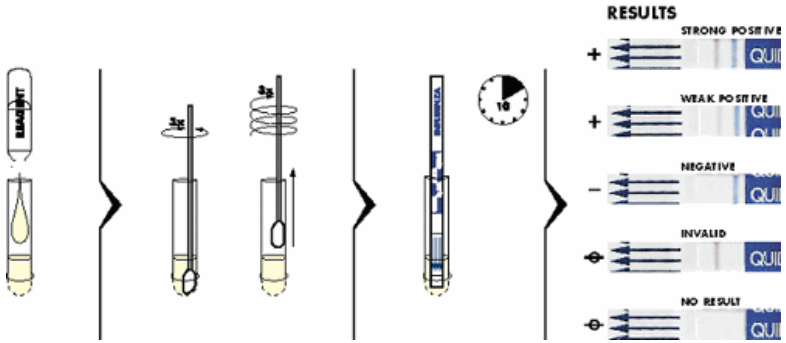
Map produced: 20 May 2009 6:00 GMT

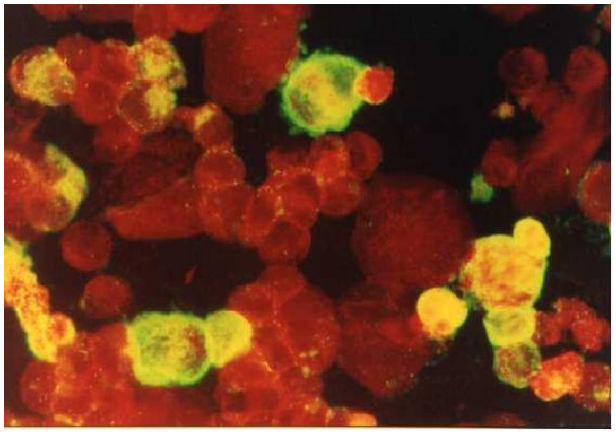
Influenza Suína A/H1N1
Diagnóstico

- Testes triagem: Influenza A/B



- Testes rápidos detecção antigênica

- Testes Imunofluorescência



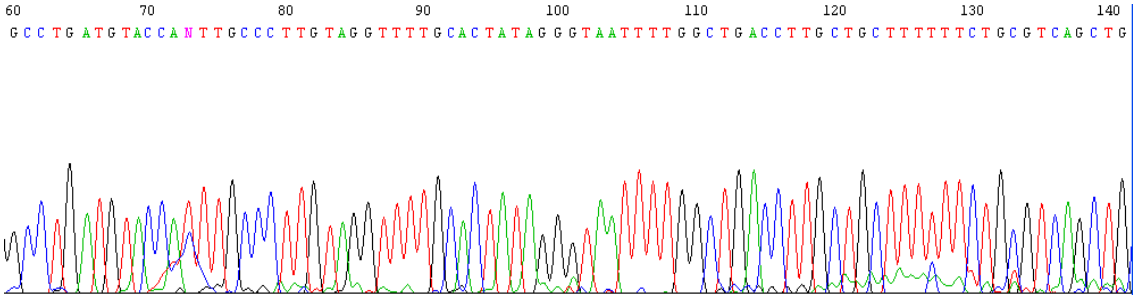
- PCR

Influenza Suína A/H1N1
Diagnóstico

- Confirmatório:

- RT- PCR com primer específico desenvolvido pelo CDC-EUA

- Cultura viral



www.cdc.gov/swineflu

Influenza Suína A/H1N1
Tratamento

- FDA: liberação Oseltamivir < 12 meses. Gestantes Categoria C
- Doses: cp 75mg, sol oral 12mg/ml
  - < 3 meses: 12mg 12/12h
  - 3 – 5 meses: 20mg 12/12h
  - 6 – 11 meses: 25mg 12/12h
  - <15 kg: 30mg 12/12h
  - 15 – 23kg: 45mg 12/12h
  - 23 – 40kg: 60mg 12/12h
  - >40kg: 75mg 12/12h

Influenza Suína A/H1N1
Tratamento

- Resistência aos antivirais:

- Não há resistência documentada ao oseltamivir e zanamivir.

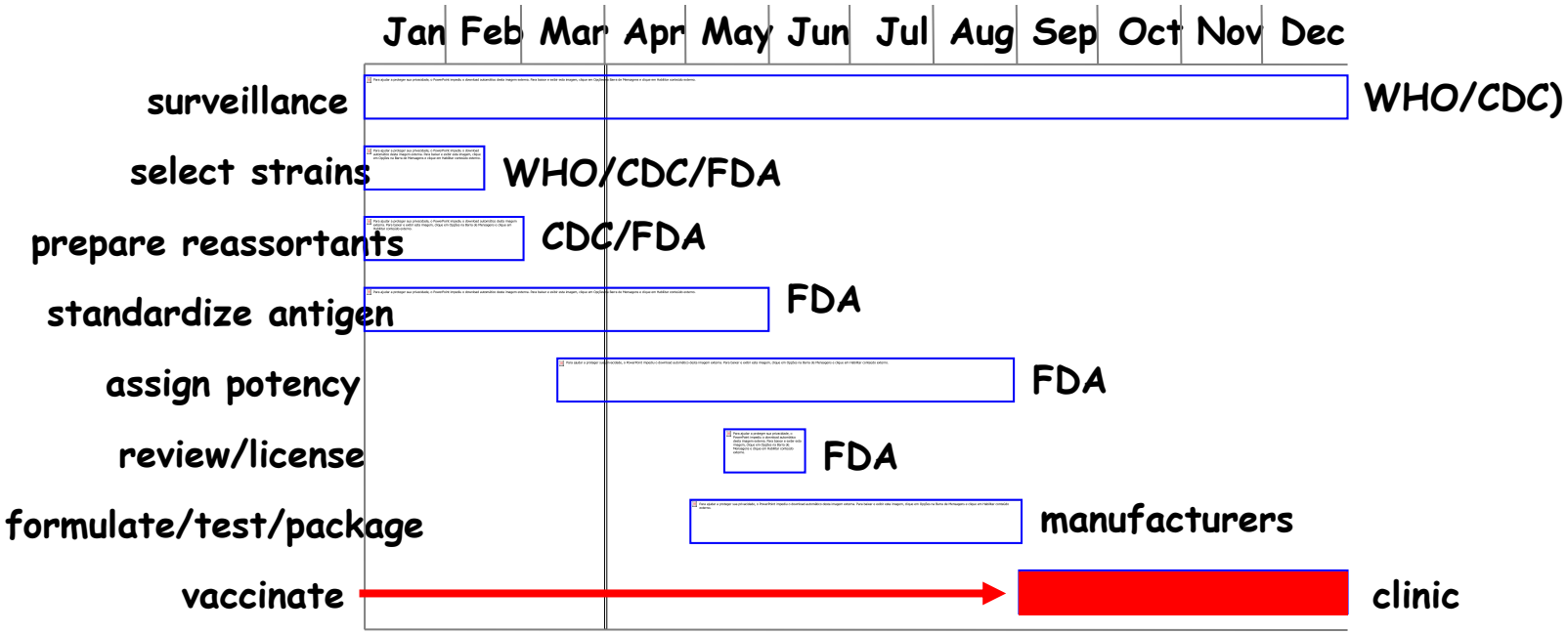
- Resistentes a Amantadina e Rimantadina

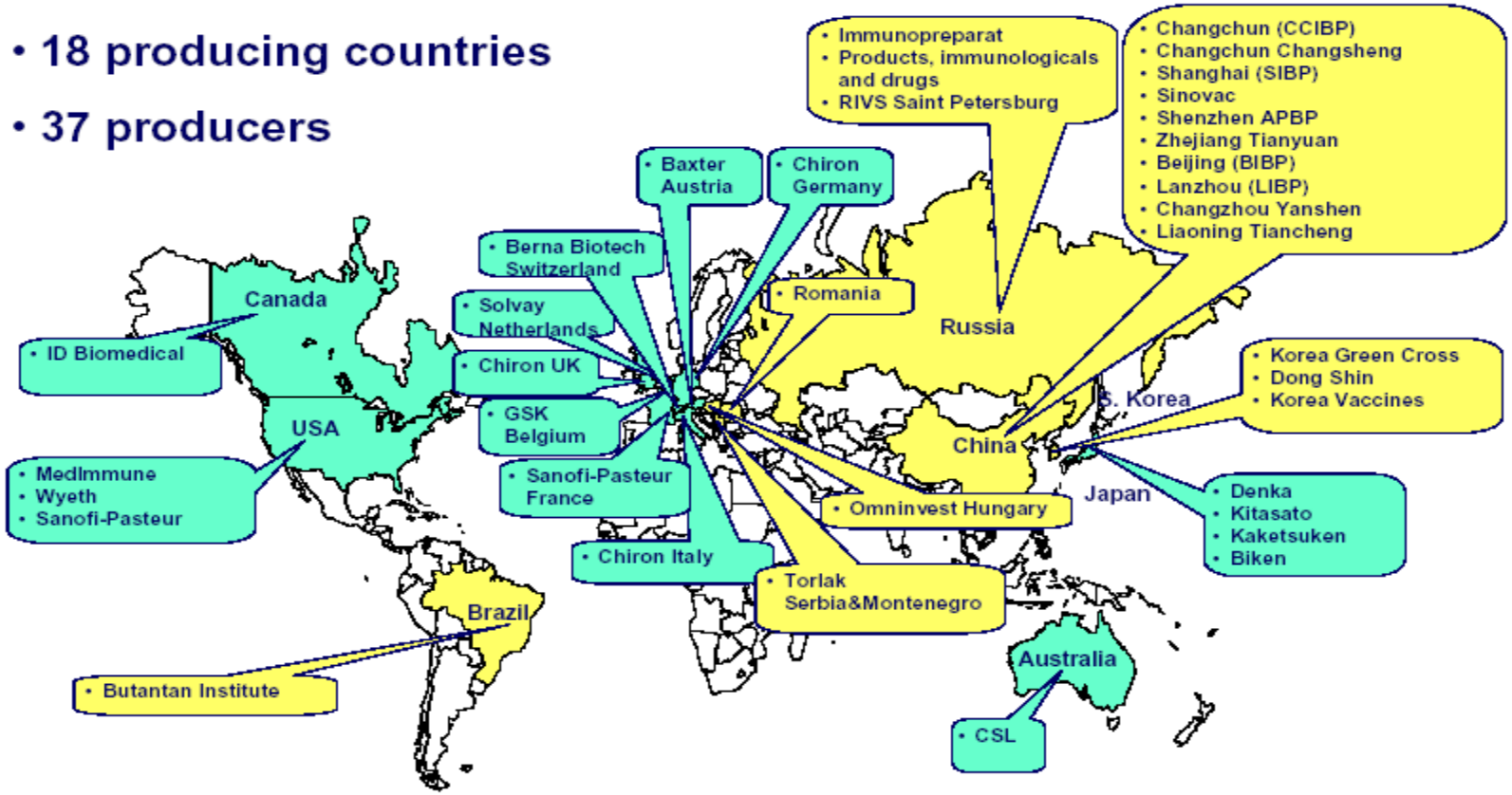
CDC MMWR April 2009

Influenza :Profilaxia

- Vacina Influenza Sazonal 2009
- Composição:
  - - A/Brisbane/59/2007 (H1N1)-like vírus*;
  - - A/Brisbane/10/2007 (H3N2)-like vírus**;
  - - B/Florida/4/2006-like vírus***.
  - Like-virus: *A/South Dakota/6/2007; **A/Uruguay/716/2007;
  - ***B/Brisbane/3/2007

Influenza :Profilaxia



Países produtores de vacinas

- 18 producing countries
- 37 producers