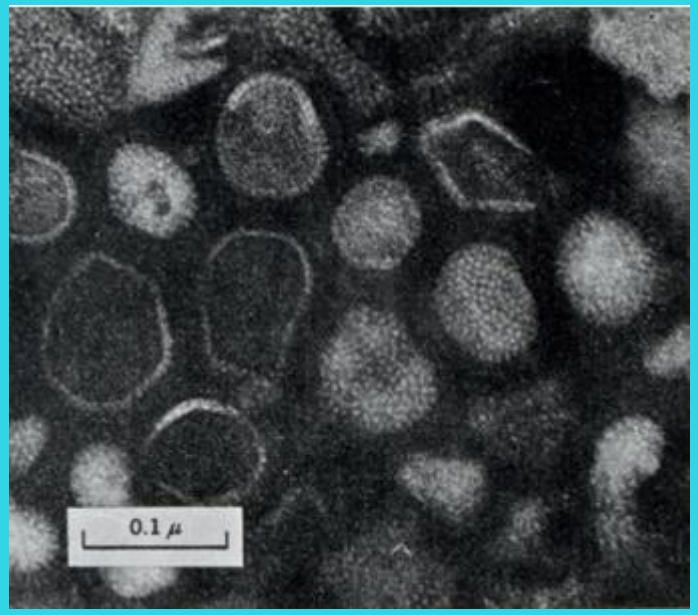
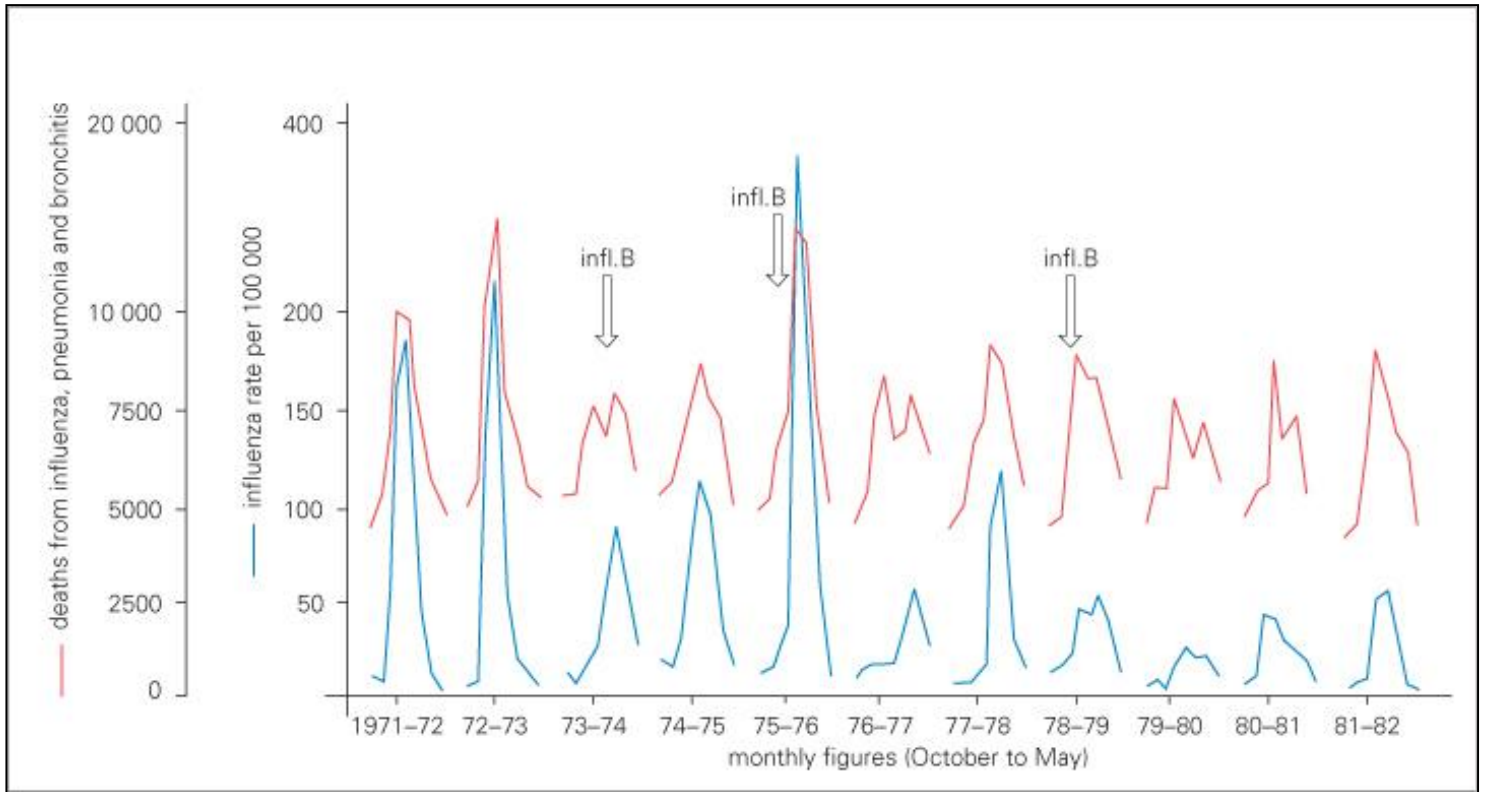
Influenza virus

- **Influenza is an acute viral infection that spreads easily from person to person.**
- **It is caused by a virus belonging to the genus Influenzavirus (Family Orthomyxoviridae = viruses that have an affinity for mucoproteins).**
- **This infection affects the respiratory system and may also cause serious complications.**



Outbreaks of influenza within a community are reflected by a general increase in deaths from acute respiratory disease



England and Wales (1971-83) The peaks are due to the spread of different strains of influenza A (H3N2 and H1N1) and influenza B (arrows) viruses in the community. (Data from the Office of Population, Censuses and Surveys.)

World Health Organization

Influenza (Seasonal)

3 October 2023

Key facts

- There are around a billion cases of seasonal influenza annually, including 3–5 million cases of severe illness.
- It causes 290 000 to 650 000 respiratory deaths annually.
- Ninety-nine percent of deaths in children under 5 years of age with influenza-related lower respiratory tract infections are in developing countries.
- Symptoms begin 1–4 days after infection and usually last around a week.

AVIAN INFLUENZA VIRUSES

Avian influenza subtype A(HxNy) normally spreads in birds but can also infect humans. Human infections are primarily acquired through direct contact with infected poultry or contaminated environments. While avian influenza viruses do not currently transmit easily from person to person, the ongoing circulation of these viruses in poultry is concerning, as these viruses can result in mild to severe illness and death, and also have the potential to mutate to become more contagious.

Human infection with avian influenza A(H5N1) virus: From 1 January 2003 to 21 December 2023, a total of 248 cases of human infection with avian influenza A(H5N1) virus were reported from four countries within the Western Pacific Region (Table 1). Of these cases, 139 were fatal.

Human infection with avian influenza A(H5N6) virus: As of 31 January 2024, a total of 90 laboratory-confirmed cases of human infection with influenza A(H5N6) virus including 35 deaths were reported to WHO in the Western Pacific Region since 2014. The last case was reported from China on 25 November 2023.

Human infection with avian influenza A(H3N8) virus: As of 31 January 2024, a total of three laboratory-confirmed cases of human infection with influenza A(H3N8) virus with one death were reported to WHO in the Western Pacific Region. The last case was reported from China on 22 February 2023.

Human infections with avian influenza A (H7N4) virus in China: As of 31 January 2024, only one laboratory-confirmed case of human infection with influenza A(H7N4) virus was reported to WHO. This case was reported from China on 14 February 2018.

Human infection with avian influenza A(H7N9) virus in China: As of 31 January 2024, a total of 1568 laboratory-confirmed human infections with avian influenza A(H7N9) virus, including 616 fatal cases, were reported to WHO since early 2013. The last case of human infection with avian influenza A(H7N9) reported to WHO in the Western Pacific Region was in 2019.

Human infection with avian influenza A(H9N2): As of 31 January 2024, a total of 94 cases of human infection with avian influenza A(H9N2), including two deaths (both with underlying conditions), were reported to WHO in the Western Pacific Region since December 2015. Of these, 92 were reported from China and two were reported from Cambodia. The last two cases were reported from Sichuan Province, China, with onset dates of 5 November 2023 and 14 November 2023, respectively.

Human infection with avian influenza A(H10N3) in China: As of 31 January 2024 two cases of avian influenza A(H10N3) virus have been reported globally. The last case was reported from Zhejiang, China with an onset date of 11 June 2022.

CORRESPONDENCE

Highly Pathogenic Avian Influenza A(H5N1) Virus Infection in a Dairy Farm Worker

This letter was published on May 3, 2024, at NEJM.org.

TO THE EDITOR: Sporadic human infections with highly pathogenic avian influenza (HPAI) A(H5N1) virus, with a wide spectrum of clinical severity and a cumulative case fatality of more than 50%, have been reported in 23 countries over more than 20 years.[1] HPAI A(H5N1) clade 2.3.4.4b viruses have spread widely among wild birds worldwide since 2020–2021,[2,3] resulting in outbreaks in poultry and other animals.[2] Recently, HPAI A(H5N1) clade 2.3.4.4b viruses were identified in dairy cows, and in unpasteurized milk samples, in multiple U.S. states.[4,5] We report a case of HPAI A(H5N1) virus infection in a dairy farm worker in Texas.

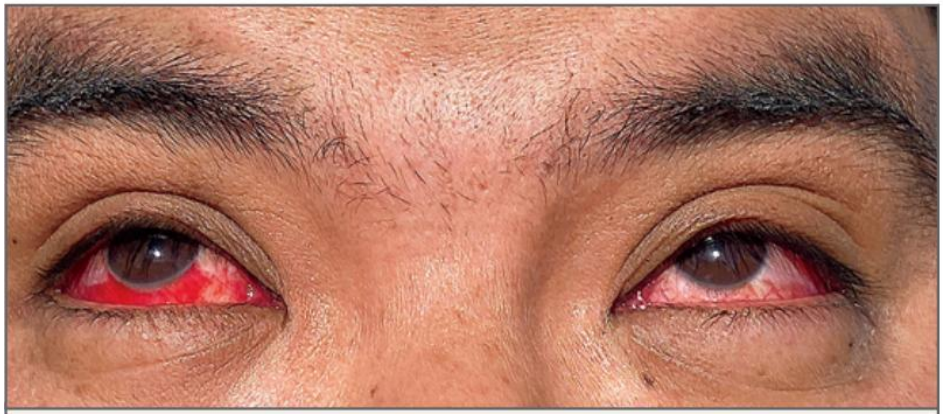
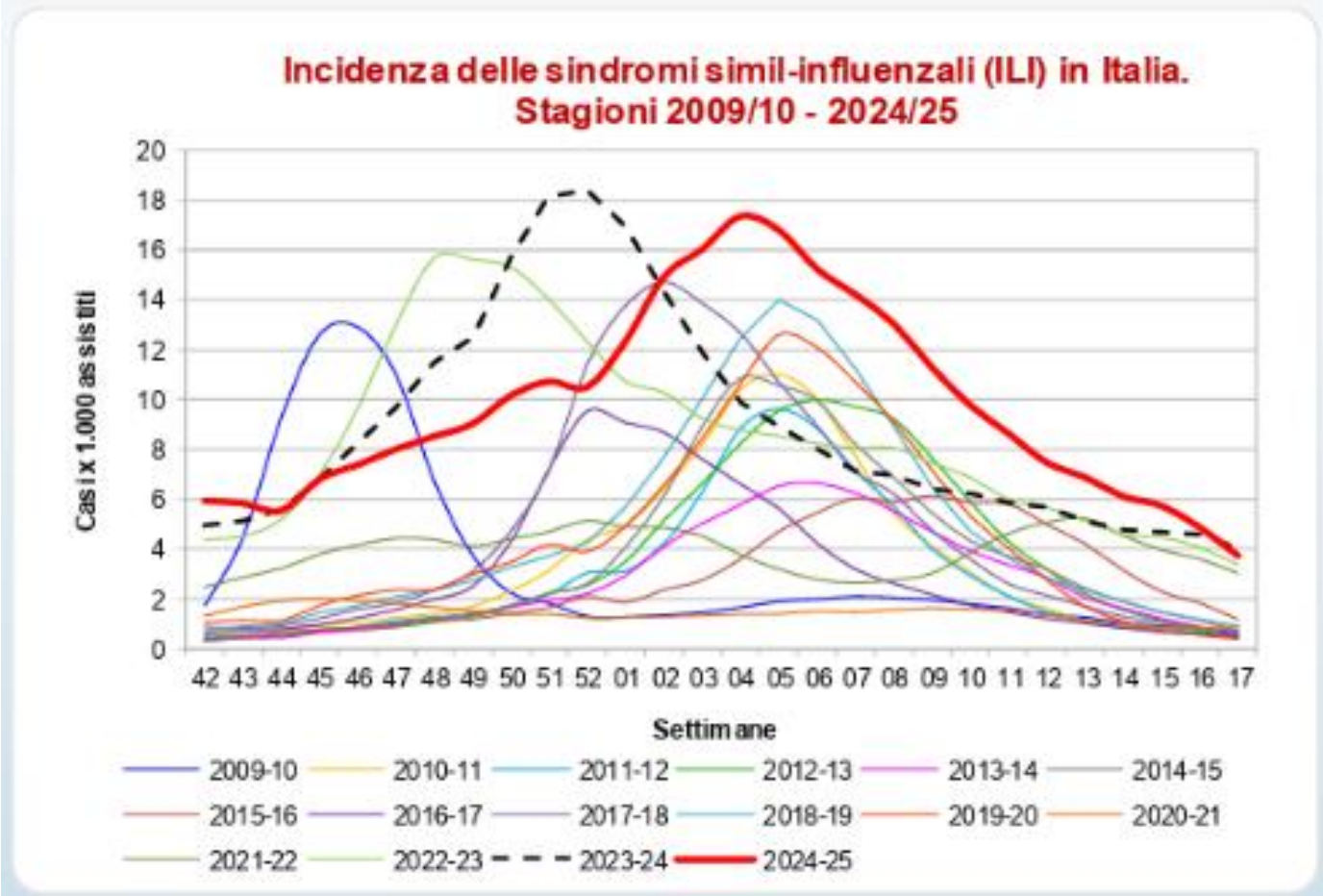


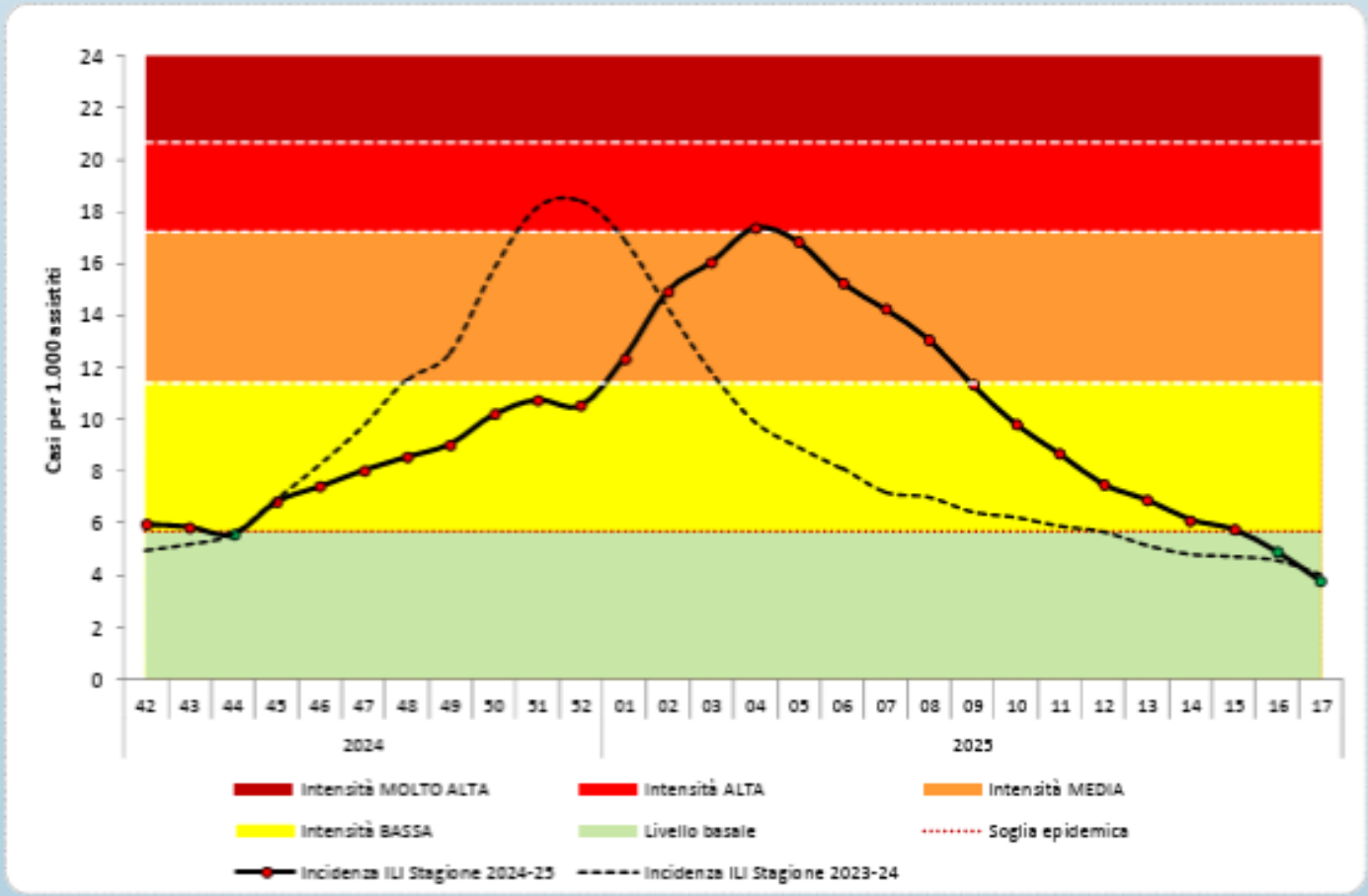
Figure 1. Conjunctivitis with Subconjunctival Hemorrhage in Both Eyes.



Rapporto N. 25 del 5 maggio 2025

Rapporto Epidemiologico RespiVirNet

Stagione 2024 - 2025



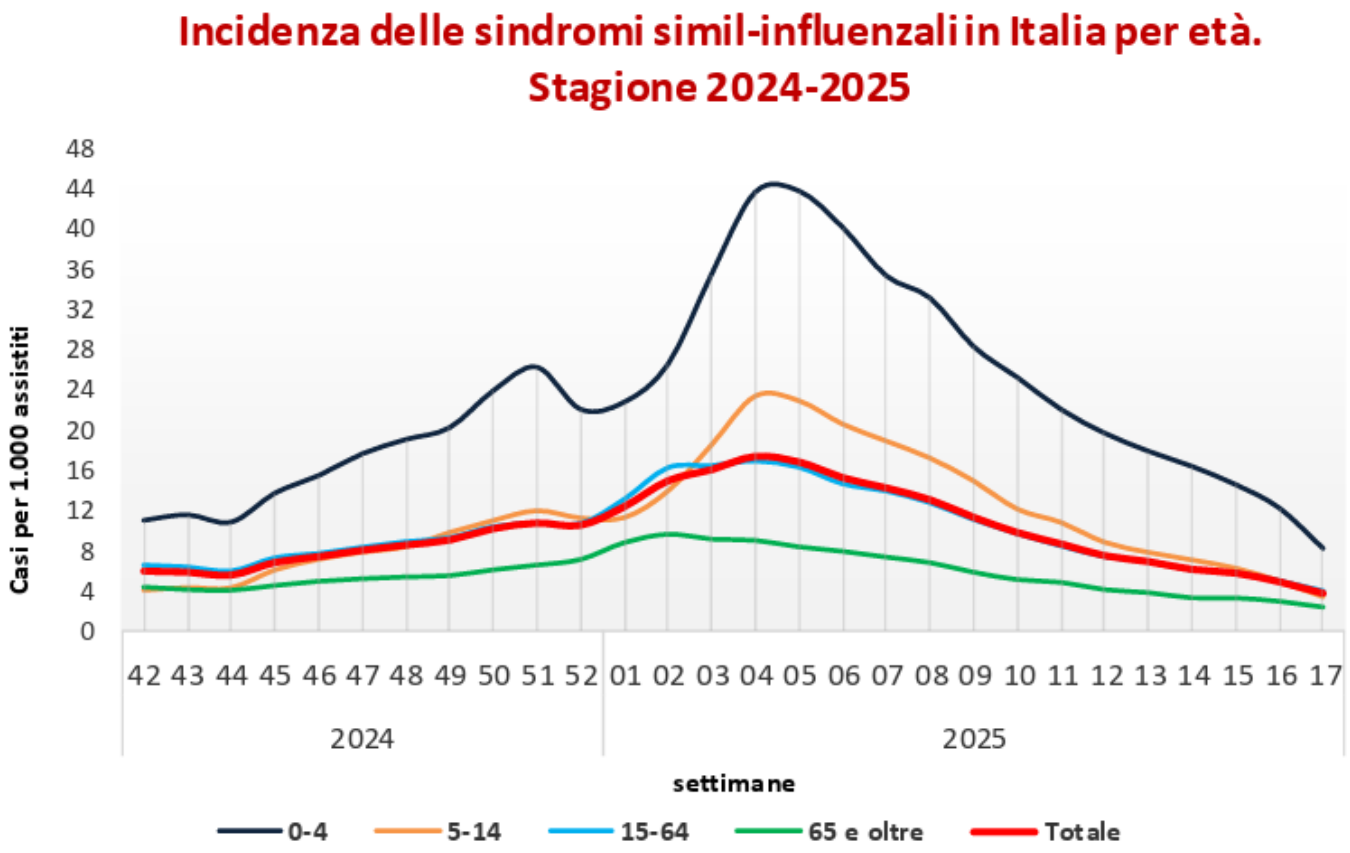
Dipartimento Malattie Infettive - Istituto Superiore di Sanità

Rapporto N. 25 del 5 maggio 2025

Rapporto Epidemiologico RespiVirNet

Stagione 2024 - 2025

Risultati Nazionali



Rapporto N. 25 del 5 maggio 2025

Rapporto Epidemiologico

RespiVirNet

Stagione 2024 - 2025

Orthomyxovirus

Coronavirus

Togavirus

Adenovirus

Reovirus

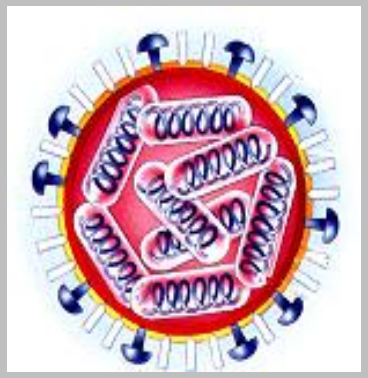
Papovavirus

Picornavirus

Parvovirus

100 nm

Classification and Nomenclature



Family: **ORTHOMYXOVIRIDAE**

Genera (type):

- **Influenza A virus** → **Human Animal**
- **Influenza B virus** → **Human**
- **Influenza C virus** → **Human**

Clinically Relevant Influenza Viruses

Type A	Potentially severe illness
	Epidemics and pandemics
	Rapidly changing
Type B	Usually less severe illness
	Epidemics
	More uniform
Type C	Usually mild or asymptomatic illness
	Minimal public health impact

Available at: http://www.cdc.gov/ncidod/diseases/flu/fluinfo.htm.

There are 4 types of influenza viruses, types A, B, C and D. Influenza A and B viruses circulate and cause seasonal epidemics of disease.

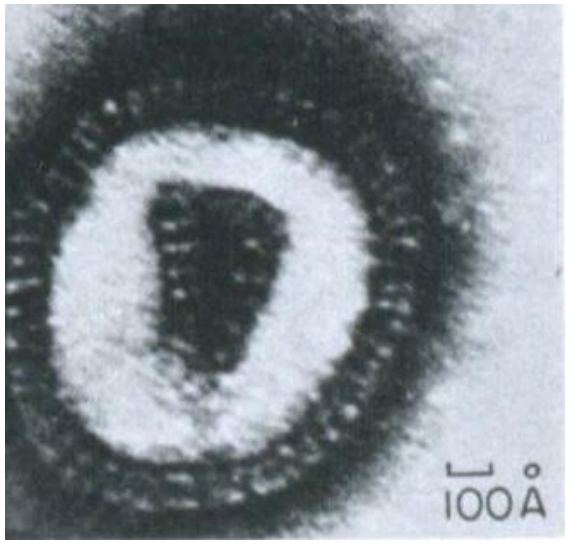
Influenza A viruses are further classified into subtypes according to the combinations of the proteins on the surface of the virus. Currently circulating in humans are subtype A(H1N1) and A(H3N2) influenza viruses. The A(H1N1) is also written as A(H1N1)pdm09 as it caused the pandemic in 2009 and replaced the previous A(H1N1) virus which had circulated prior to 2009. Only influenza type A viruses are known to have caused pandemics.

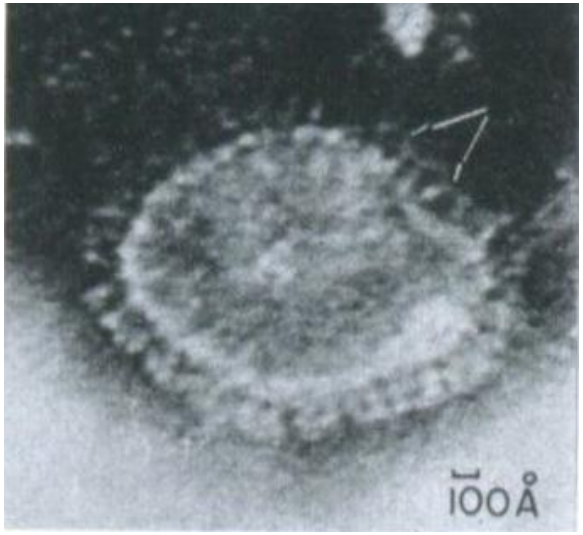
Influenza B viruses are not classified into subtypes but can be broken down into lineages. Influenza type B viruses belong to either B/Yamagata or B/Victoria lineage.

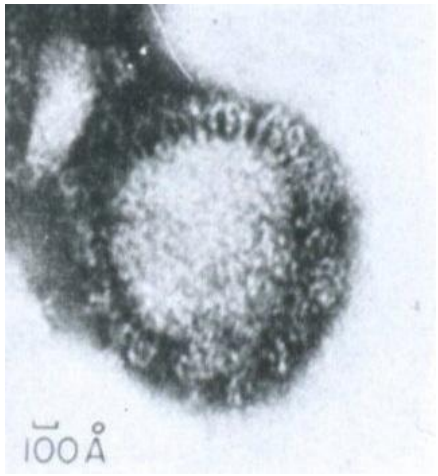
Influenza C virus is detected less frequently and usually causes mild infections, thus does not present public health importance.

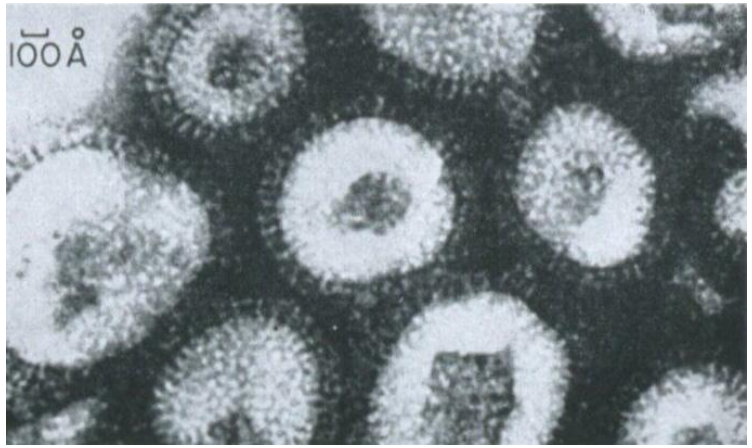
Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people.

World Health Organization

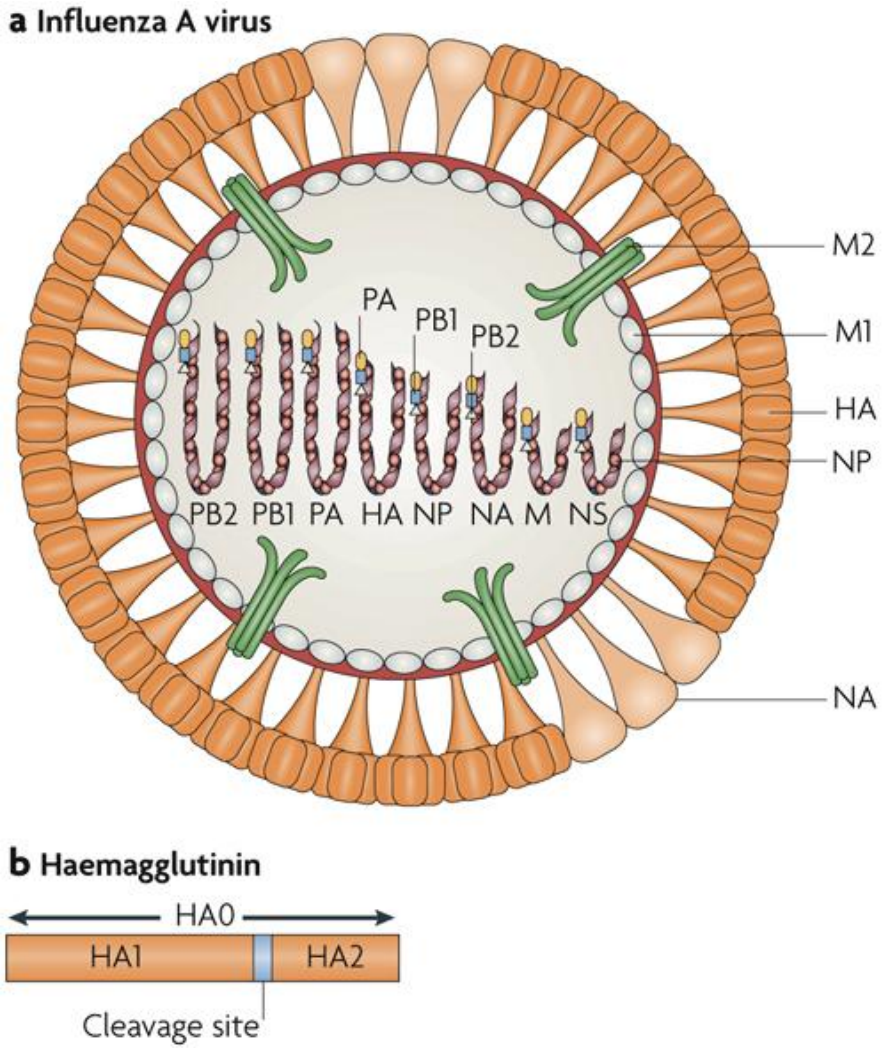

100 Å


100 Å


100 Å

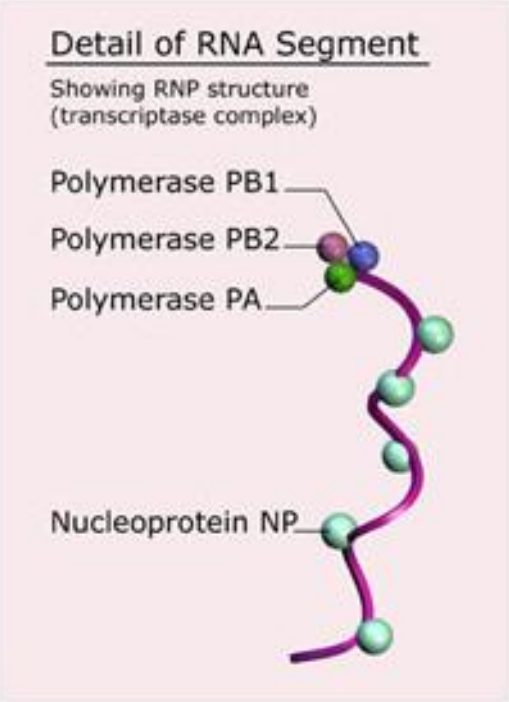

100 Å

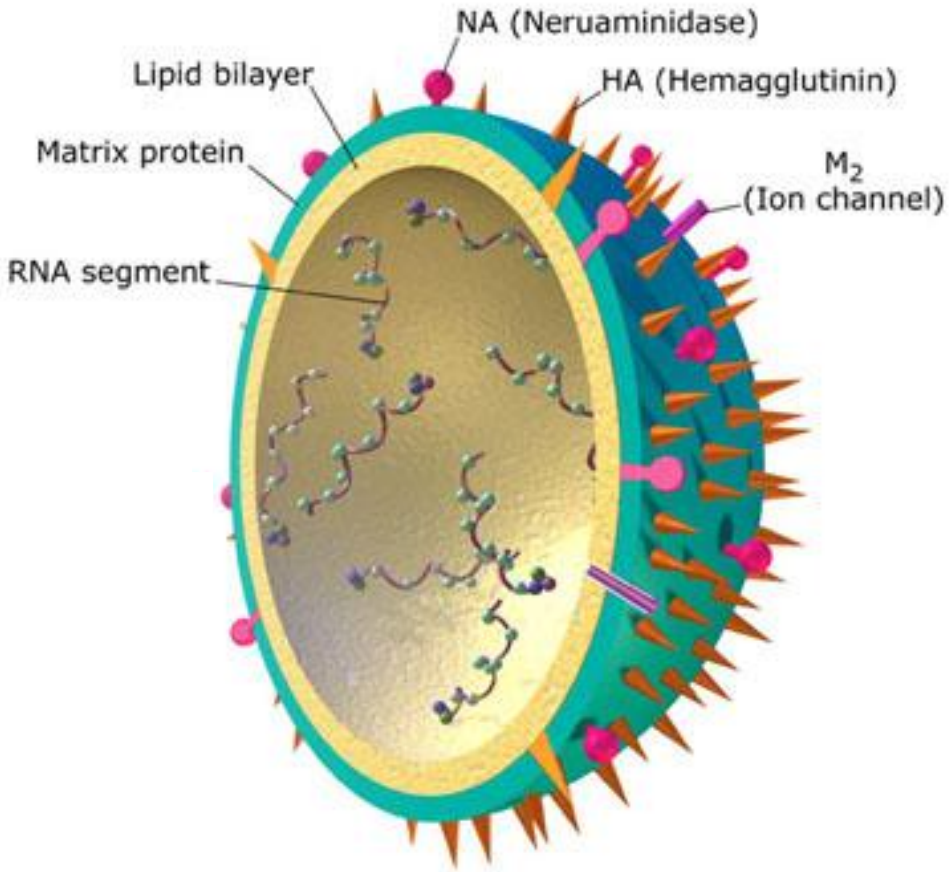
Schematic view of Influenza A virus



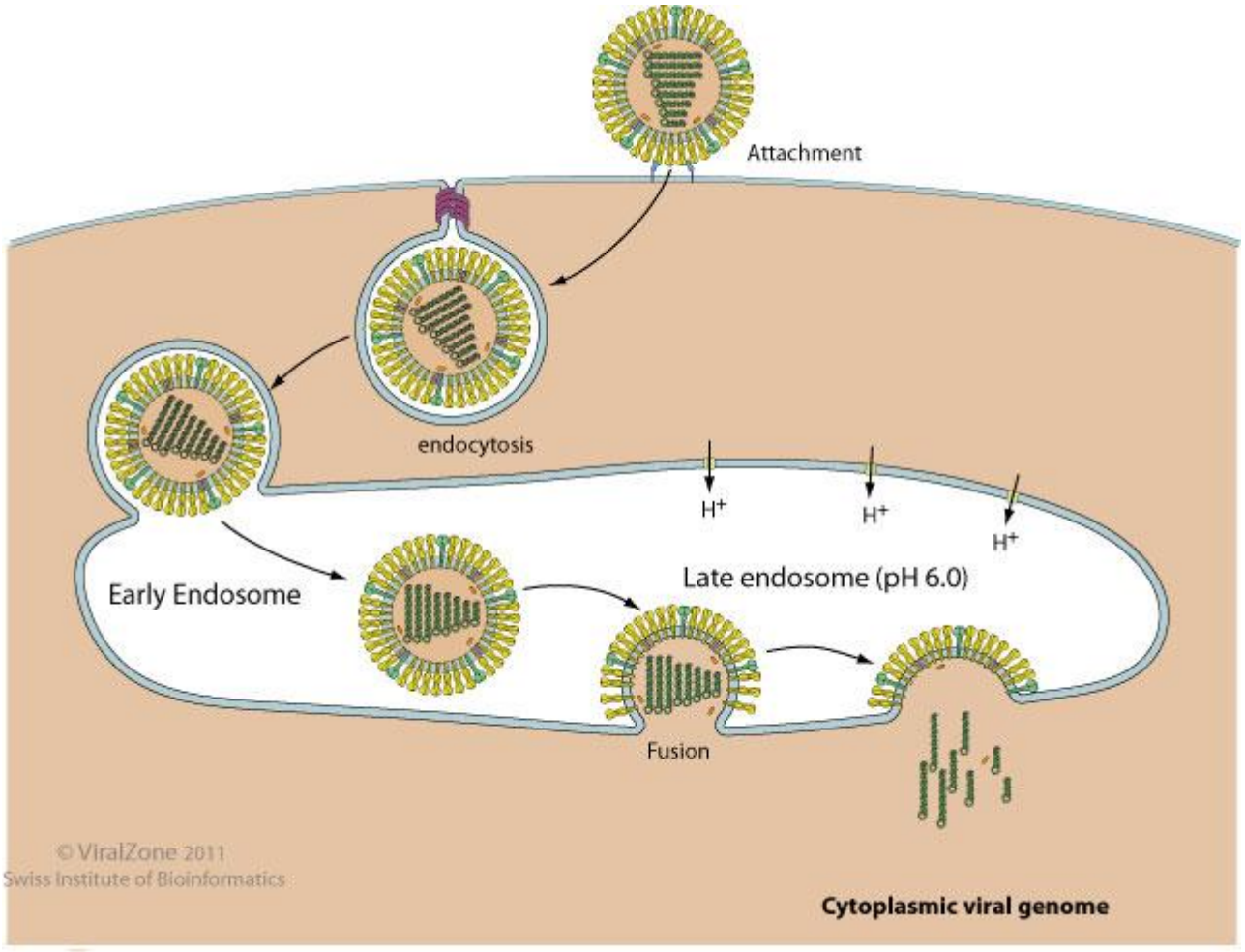
Nature Reviews | Immunology 2007

Influenza virus

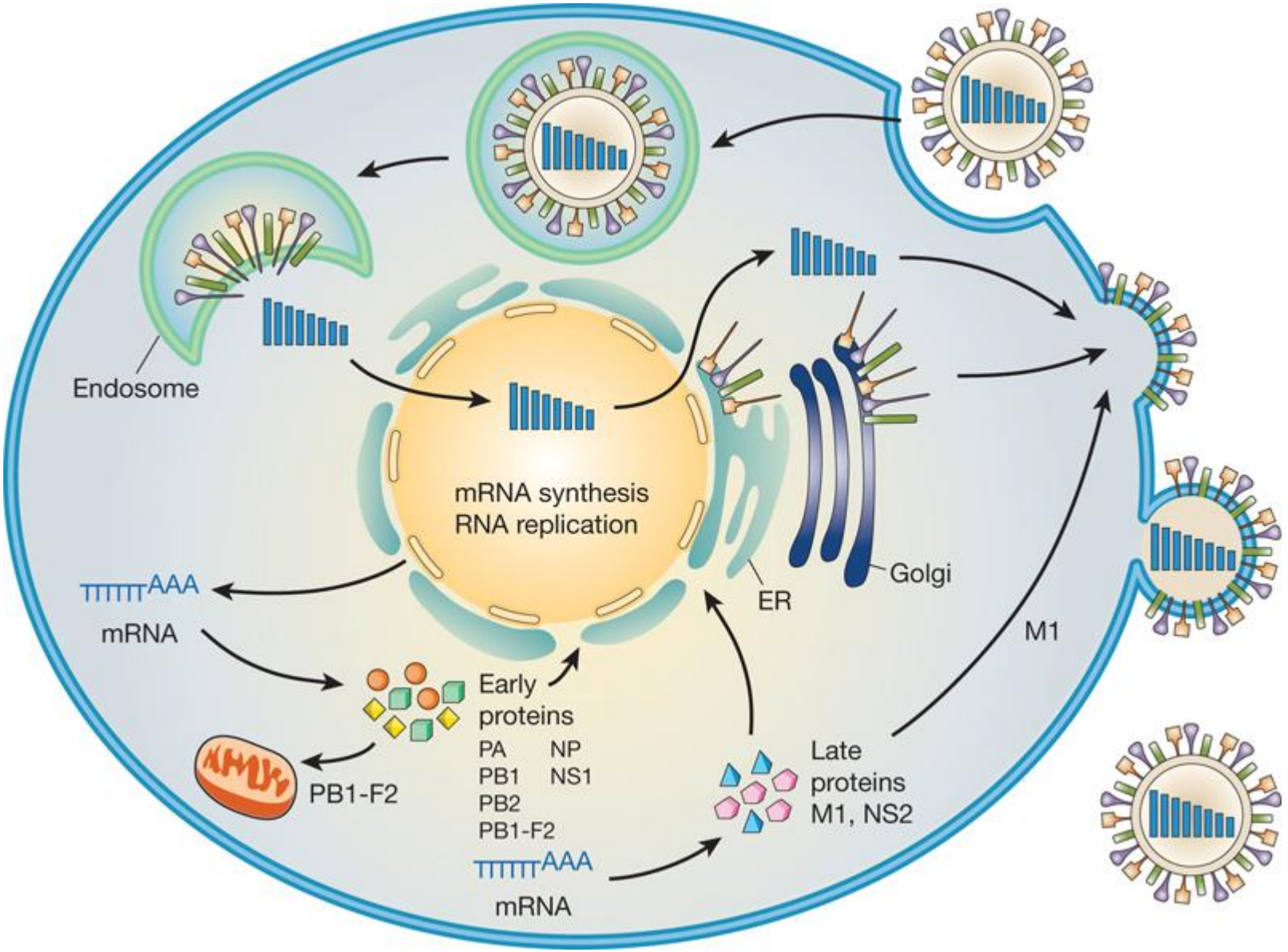




Fusion of virus membrane with host endosomal membrane

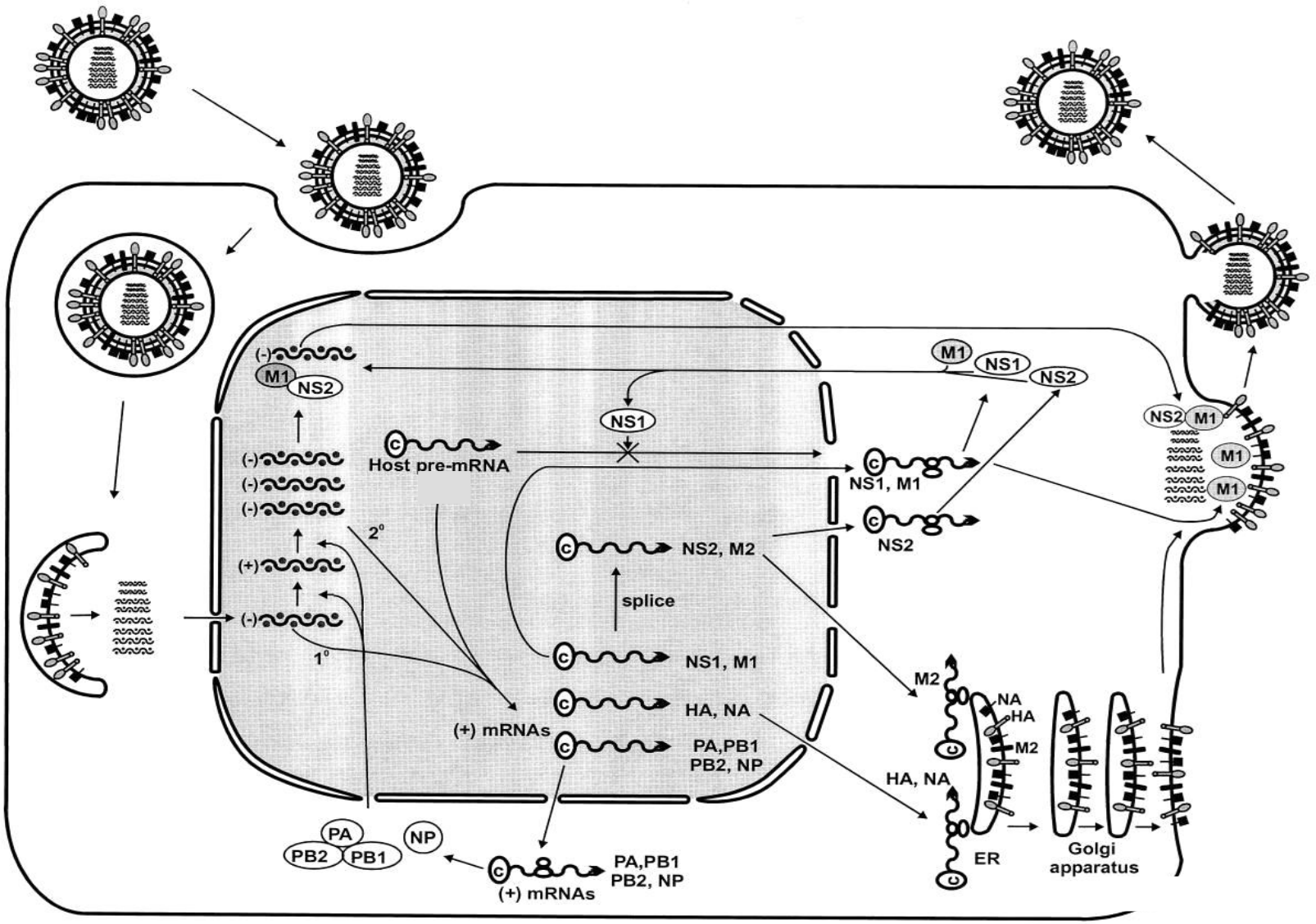


Schematic diagram of the influenza viral life cycle

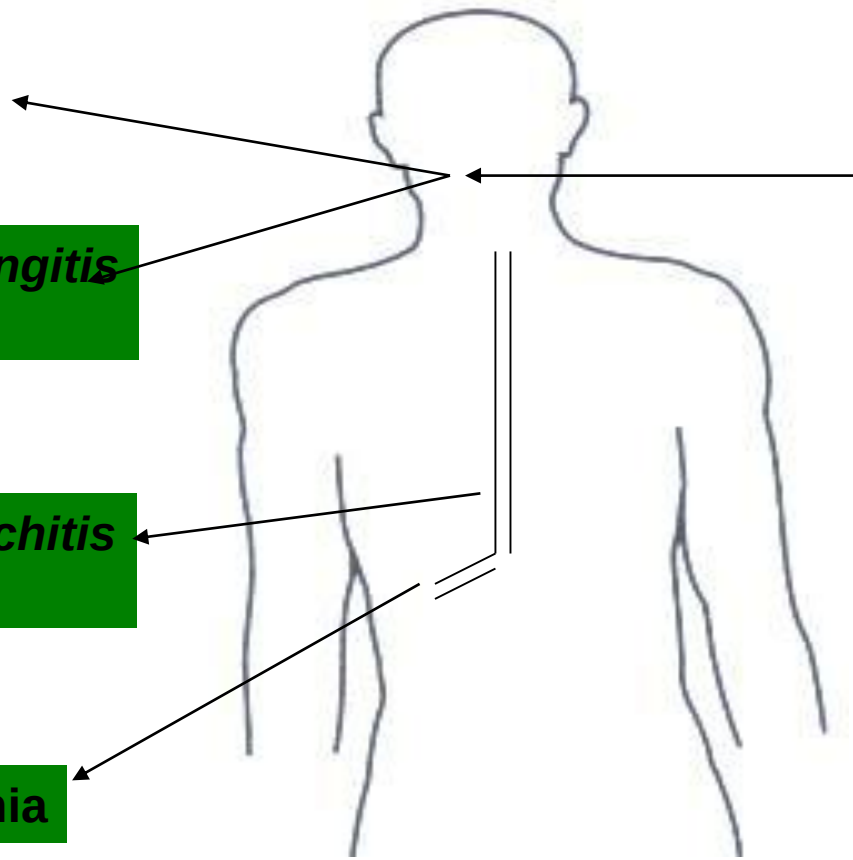


Nature , 2009

Schematic diagram of the influenza viral life cycle



Pathogenesis



3. Shedding

1. Entry

Nasopharyngitis
Laryngitis

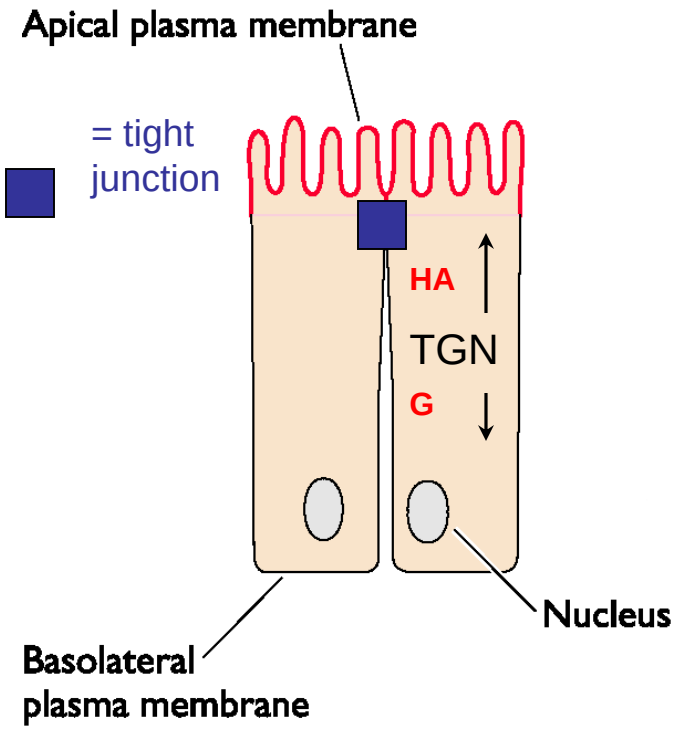
2. Desease

Tracheobronchitis
Bronchitis

Pneumonia

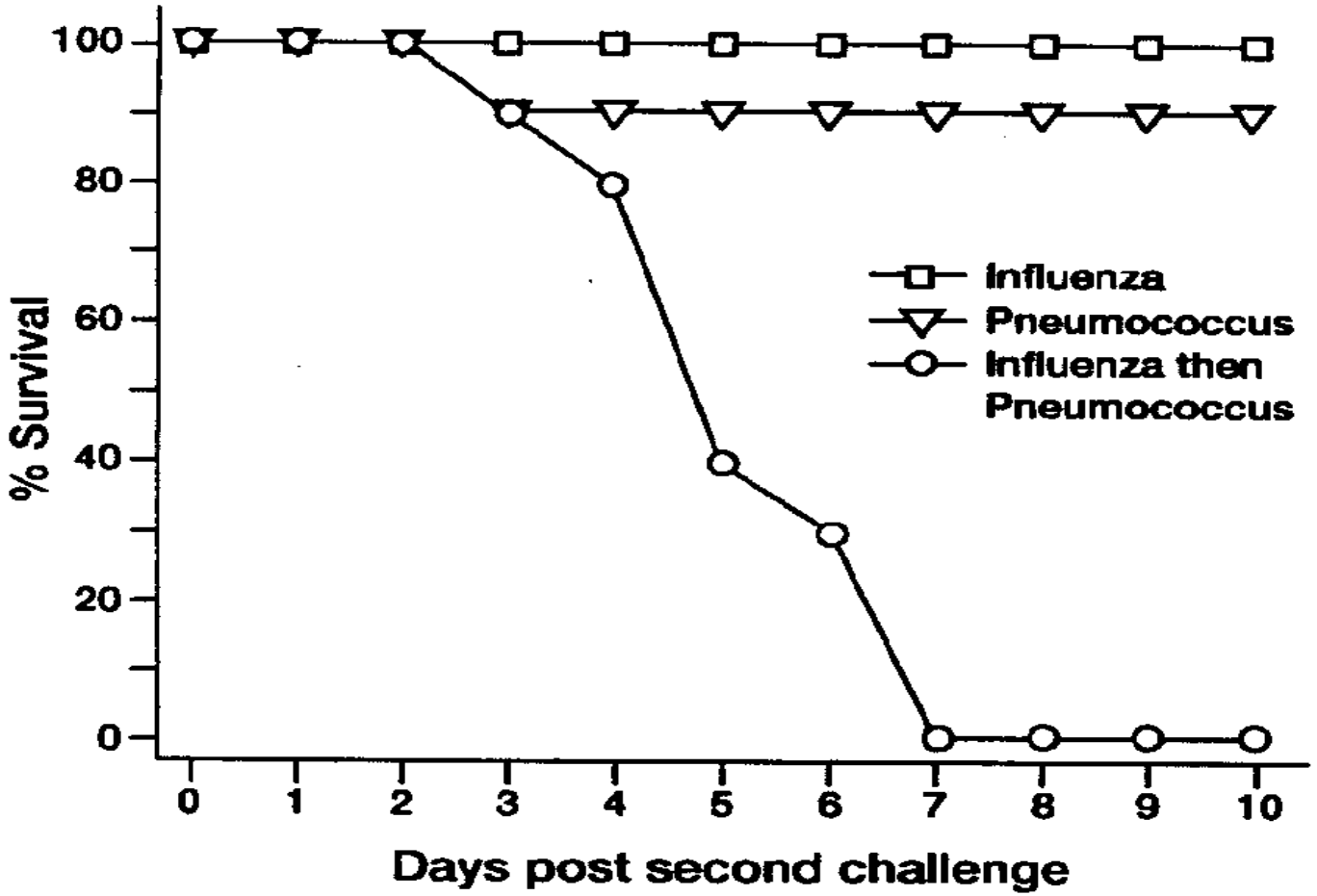
Polarized cells and virus spread

- At a cellular level directional release is very important for virus spread
  - ***Apical*** release is back to where it all started
  - ***Basolateral*** release is inwards away from lumenal defences
  - Apical/basolateral targeting is mediated by virus glycoproteins that determine the site of budding ;
  - ***classic e.g. -***
    - ***Influenza HA (apical)***
    - ***Sendai virus (basolateral)***



Modified from Flint et al Principles of Virology ASM Press

INFLUENZA VIRAL INFECTION LEAD TO BACTERIAL SUPERINFECTIONS



V.T. Peltola et al., Pediatr Infect Dis J 2004

Laboratory Diagnosis

- Virus isolation from respiratory secretions serotyping
- Detection of specific antibodies against influenza virus antigens in the serum of patients
- Detection of viral antigens or viral RNA in respiratory secretions

Laboratory Diagnosis

Differential diagnosis is required
to exclude other more common infectious agents:

Bacteria

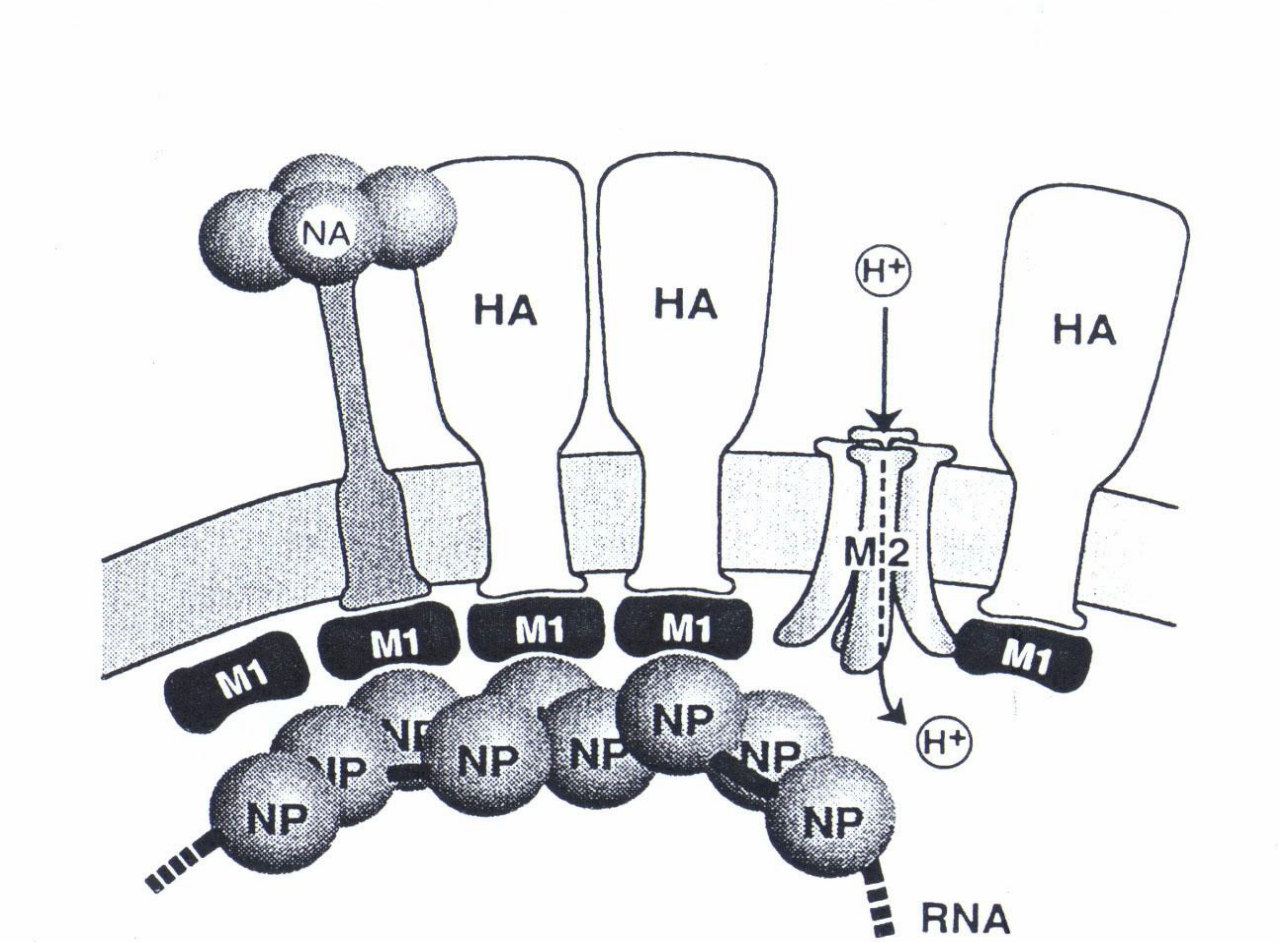
Fungi

Other respiratory viruses

Management. THE ANTIVIRAL AGENTS AVAILABLE FOR TREATMENT AND CHEMOPROPHYLAXIS OF INFLUENZA IN THE US

Antiviral agent	Mode of action	Activity
Amantadine	M2 inhibitor	Influenza A
Rimantadine	M2 inhibitor	Influenza A

Amantadine and rimantandine interfere with the release of infectious viral nucleic acid into the host cell through interaction with the transmembrane domain of the M2 protein of the virus.



Management. THE ANTIVIRAL AGENTS AVAILABLE FOR TREATMENT AND CHEMOPROPHYLAXIS OF INFLUENZA IN THE US

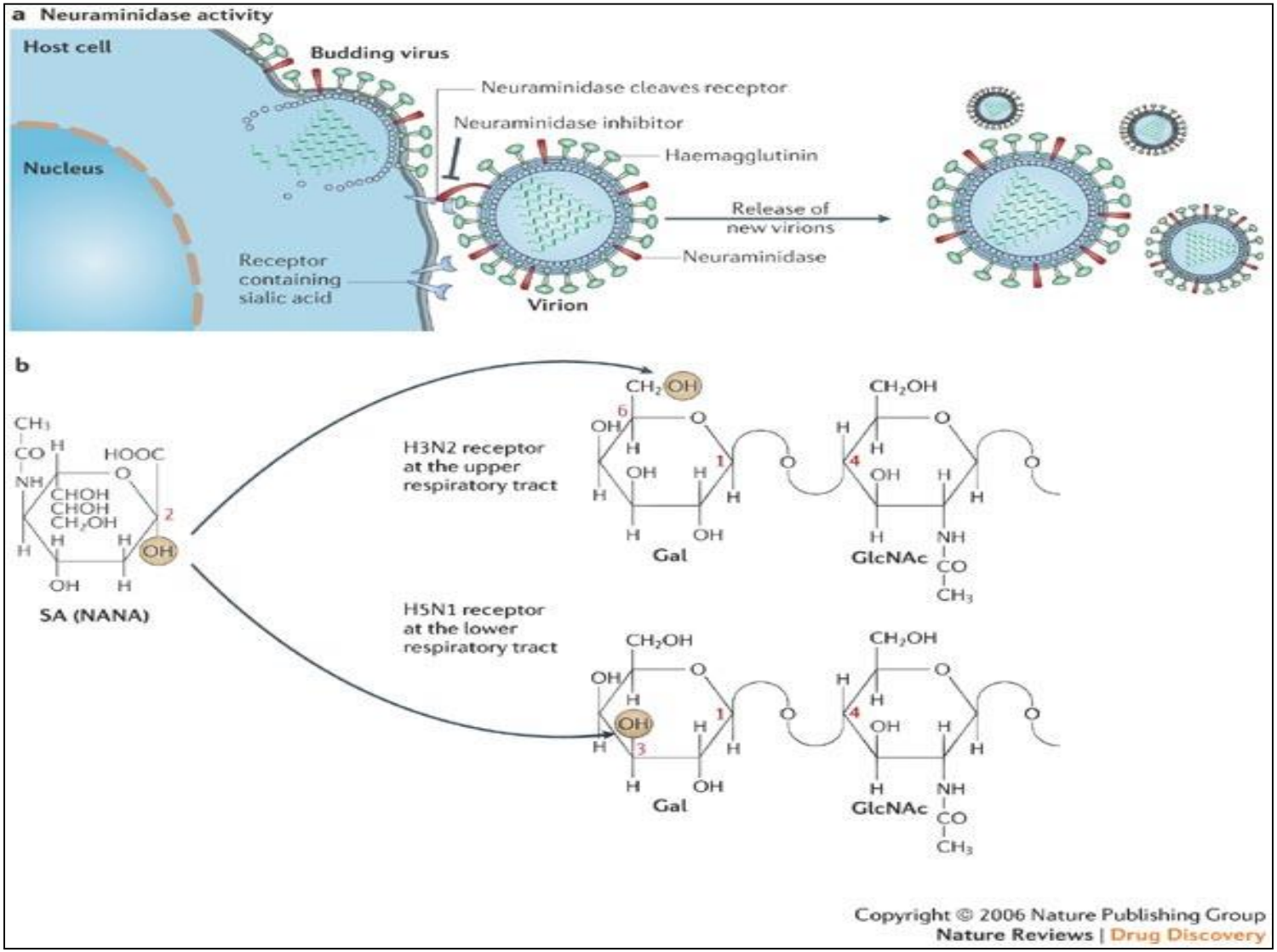
There are four FDA-approved antiviral drugs recommended by CDC to treat flu virus.

- **oseltamivir** phosphate (available as a generic version or under the trade name Tamiflu®),
- **zanamivir** (trade name Relenza®)
- **peramivir** (trade name Rapivab®), and
- baloxavir marboxil (trade name Xofluza®).

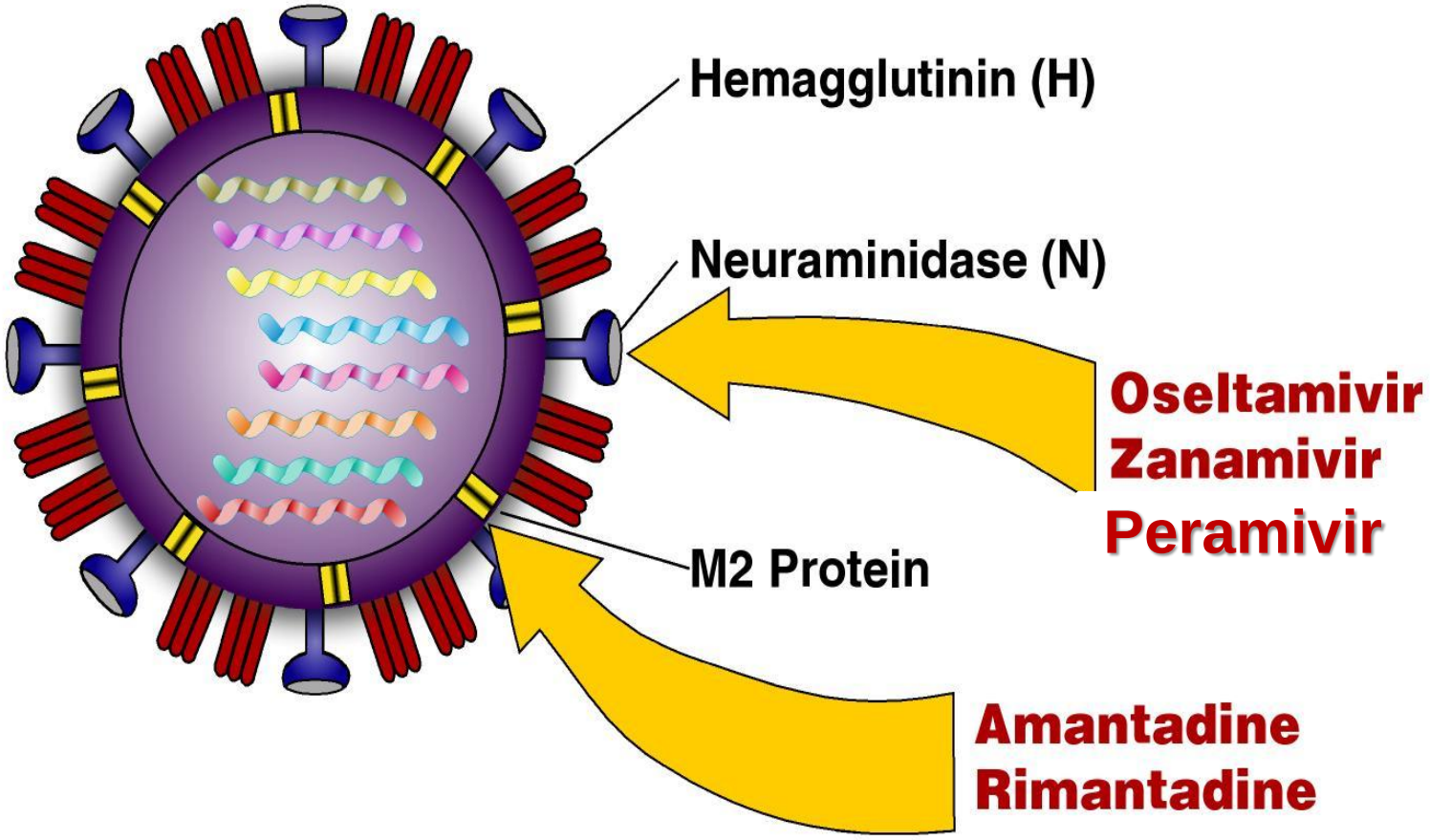
Oseltamivir, zanamivir and peramivir are inhibitors of the neuraminidase enzyme, which is expressed on the viral surface. The enzyme promotes release of virus from infected cells and facilitates viral movement within the respiratory tract.

Baloxavir marboxil was developed as a prodrug strategy, with its metabolism releasing the active agent, baloxavir acid (BXA). BXA then functions as enzyme inhibitor, targeting the influenza virus' cap-dependent endonuclease activity CEN), used in "cap snatching" by the virus' polymerase complex, a process essential to its life-cycle.

Viral neuraminidase inhibition

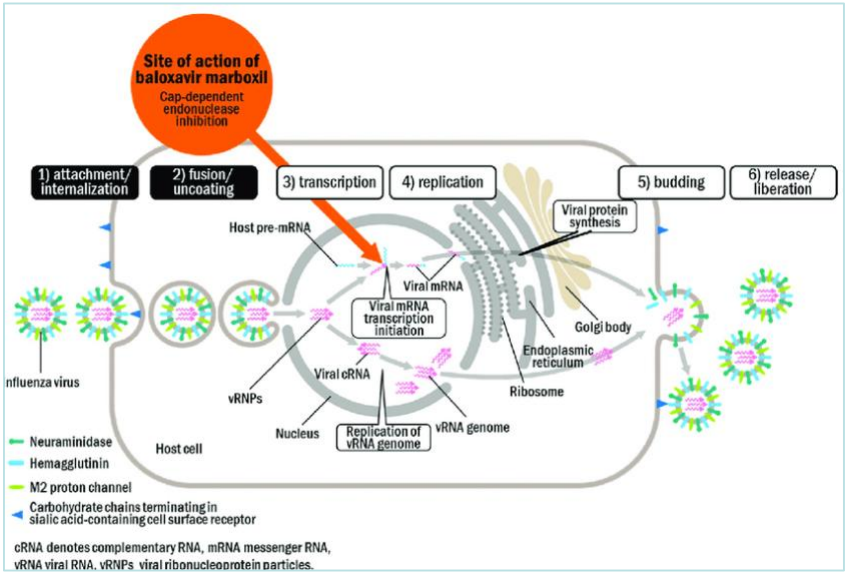


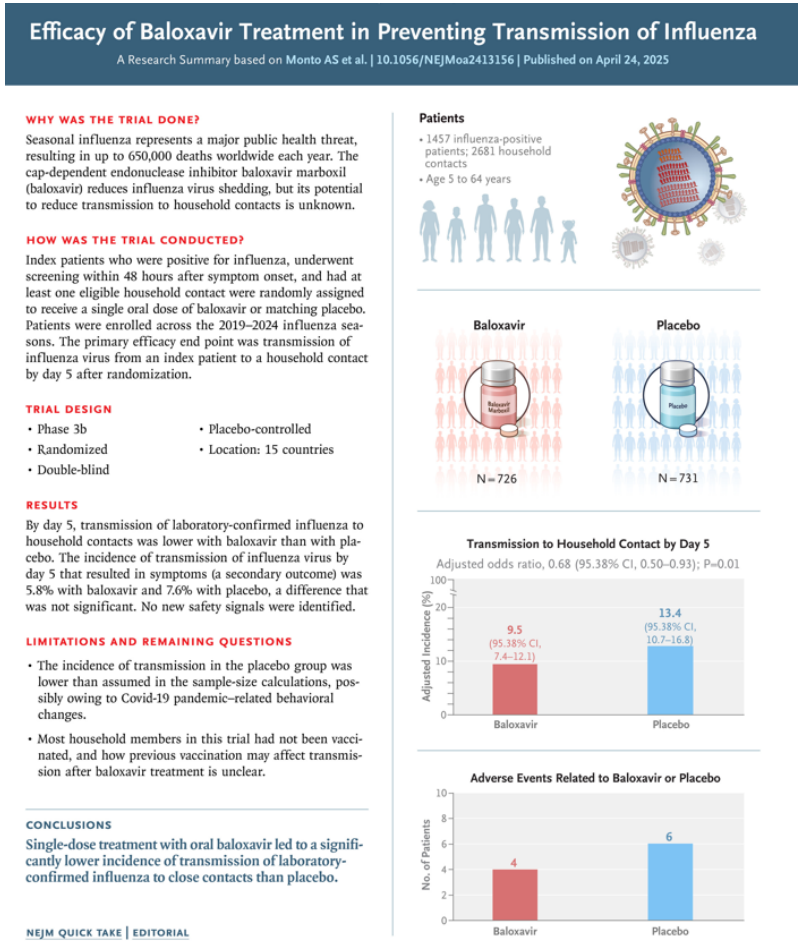
Antiviral Therapies for Influenza

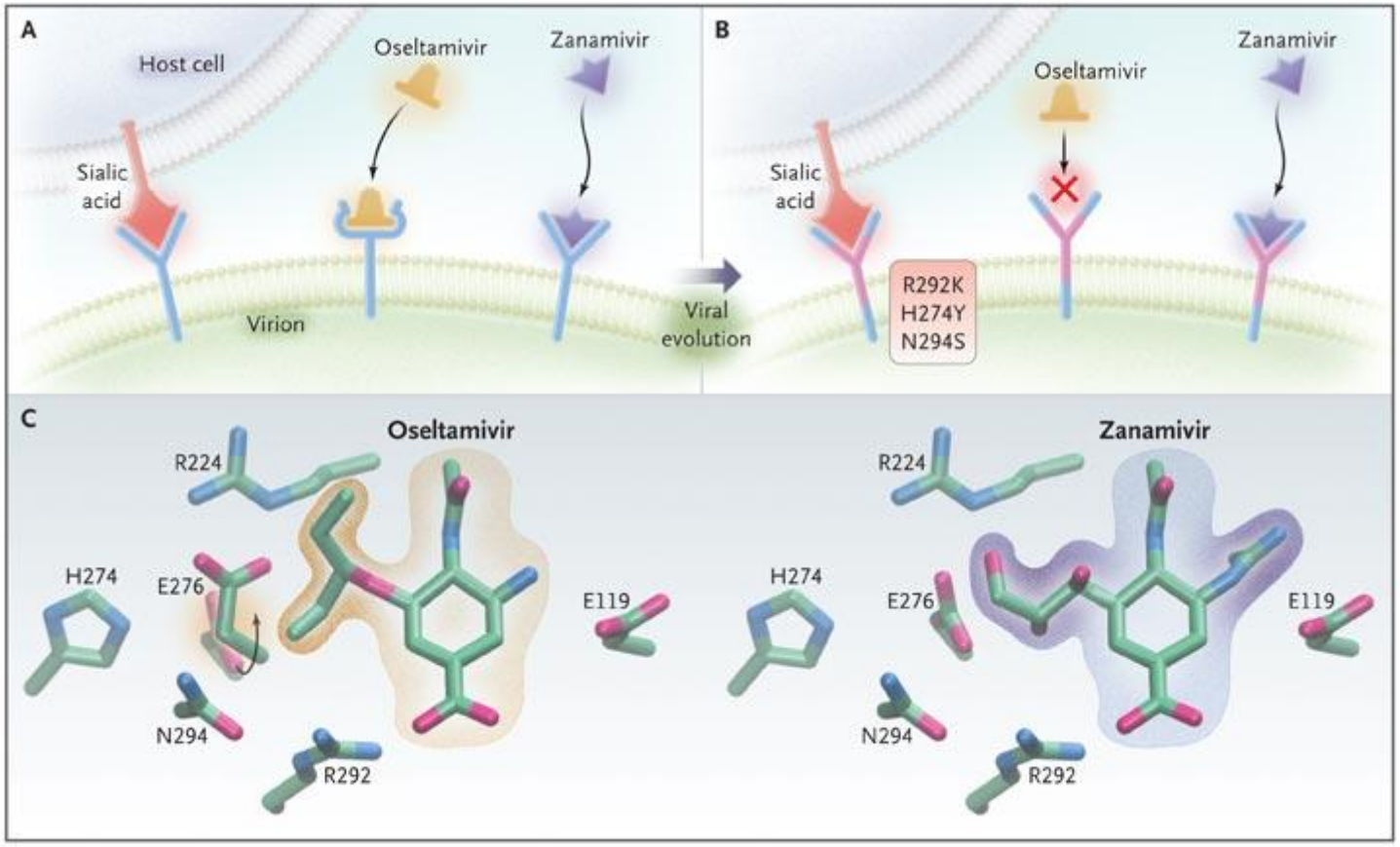


Mechanism of action – Baloxavir marboxil

Baloxavir marboxil is the prodrug of baloxavir acid (BXA), a potent and selective inhibitor of the Cap dependent endonuclease (CEN) in PA subunit of RNA dependent RNA polymerase (RdRP) of both influenza A and B.[16] CEN is vital for transcription of viral RNA, as RdRP lacks the ability to cap the 5' end of mRNA generated from the viral RNA.[12–15] Endonuclease by binding to the host RNA polymerase (Pol II segment) with the help of PB2 subunit cleaves 10–13 capped RNA fragment from pre mRNA/mRNA, that acts as a primer for generation of 7-methyguanosine capped mRNA from viral RNA (Cap Snatching mechanism).[12–15] BXA thus prevents transcription of viral RNA and further spread of the virus.







Moscona A, NEJM 2005

Prevention

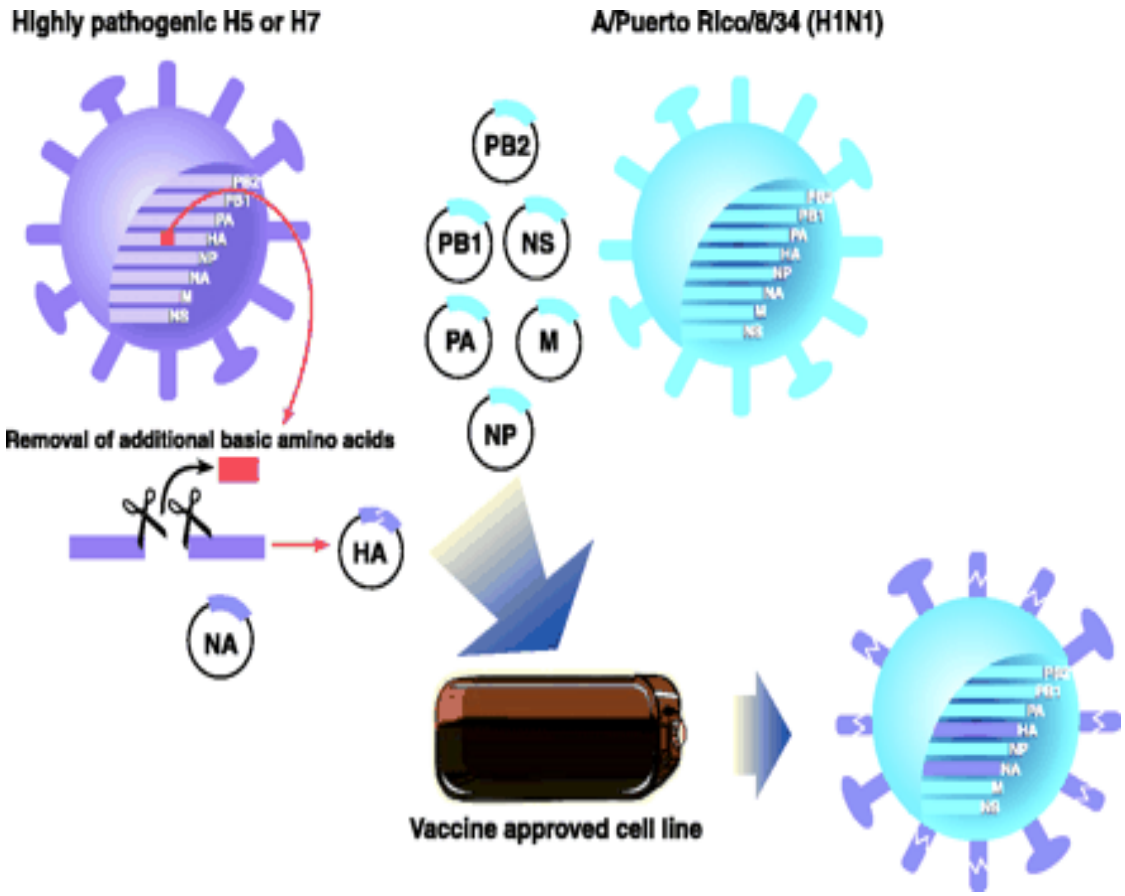
- Inactivated split/subunit vaccines are available against influenza A and B.
- The vaccine is normally trivalent or quadrivalent, consisting of one A H3N2 strain, one A H1N1 strain, and one B strain.
- The strains used are reviewed by the WHO each year.
- The vaccine should be given to debilitated and elderly individuals who are at risk of severe influenza infection.
- Amantidine can be used as a prophylaxis for those who are allergic to the vaccine or during the period before the vaccine takes effect.

	Quadrivalent *vs* trivalent*	Route	Approved age group	Comments
Inactivated	Quadrivalent or trivalent	Intramuscular	≥6 months	Contains 15 μg of each haemagglutinin
Inactivated: intradermal	Quadrivalent	Intradermal	18–64 years	Contains 9 μg of each haemagglutinin
Inactivated: derived from cell culture	Trivalent	Intramuscular	≥18 years	Contains 15 μg of each haemagglutinin; contains egg protein; manufacturing does not rely on eggs
Inactivated: high dose	Trivalent	Intramuscular	≥65 years	Contains 60 μg of each haemagglutinin
Live attenuated†	Quadrivalent	Intranasal	2–49 years	Cold adapted; uses a master donor virus plus the haemagglutinin and neuraminidase of the circulating viruses; generates a broader immune response (T-cell, mucosal); not approved for use in immunocompromised patients or pregnant women
Recombinant	Trivalent	Intramuscular	≥18 years	Made with recombinant DNA technology to produce full-length haemagglutinin; shorter manufacturing time than for egg-derived or cell-culture-derived vaccines; can be used in individuals with egg allergy

*Trivalent vaccines contain antigens from the circulating H1N1 and H3N2 influenza A viruses and the dominant influenza B virus circulating at the time of vaccine strain selection. Quadrivalent vaccines contain antigens from the circulating H1N1 and H3N2 influenza A viruses and both lineages of influenza B. †Live attenuated vaccine not recommended by the US Advisory Committee on Immunization Practices for the 2016–17 season; this table represents the 2015–16 influenza season.

Table 4: **Types of influenza vaccine licensed for use in the USA 2015–16 influenza season**[40,93-97]

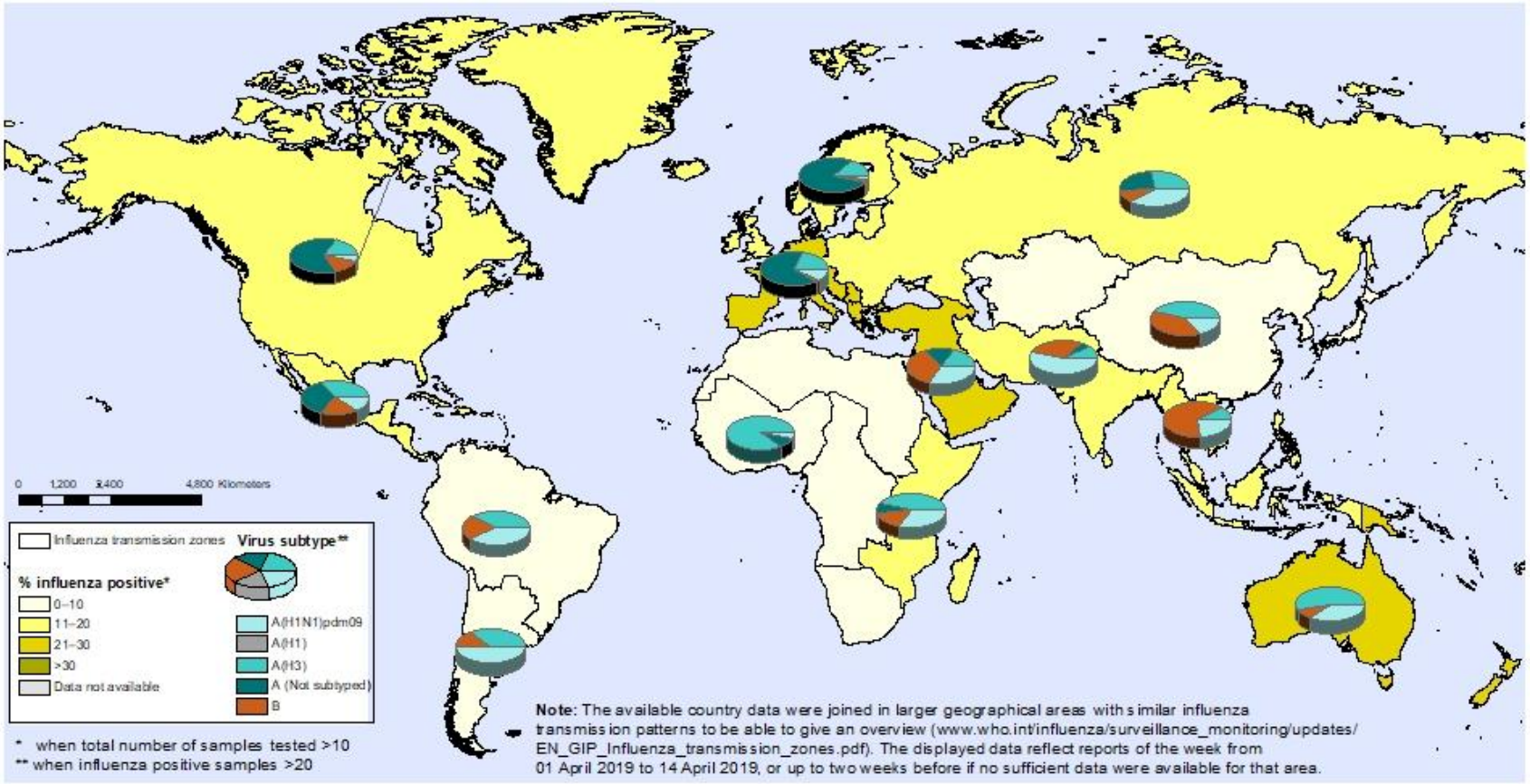
PROPOSED METHOD OF INFLUENZA VACCINE SEED VIRUS PRODUCTION USING THE EIGHT-PLASMID REVERSE GENETICS SYSTEM



(Webby RJ et al., Science 2003)

Percentage of respiratory specimens that tested positive for influenza
By influenza transmission zone

Status as of 26 April 2019



* when total number of samples tested >10
** when influenza positive samples >20

Note: The available country data were joined in larger geographical areas with similar influenza transmission patterns to be able to give an overview (www.who.int/influenza/surveillance_monitoring/updates/EN_GIP_Influenza_transmission_zones.pdf). The displayed data reflect reports of the week from 01 April 2019 to 14 April 2019, or up to two weeks before if no sufficient data were available for that area.

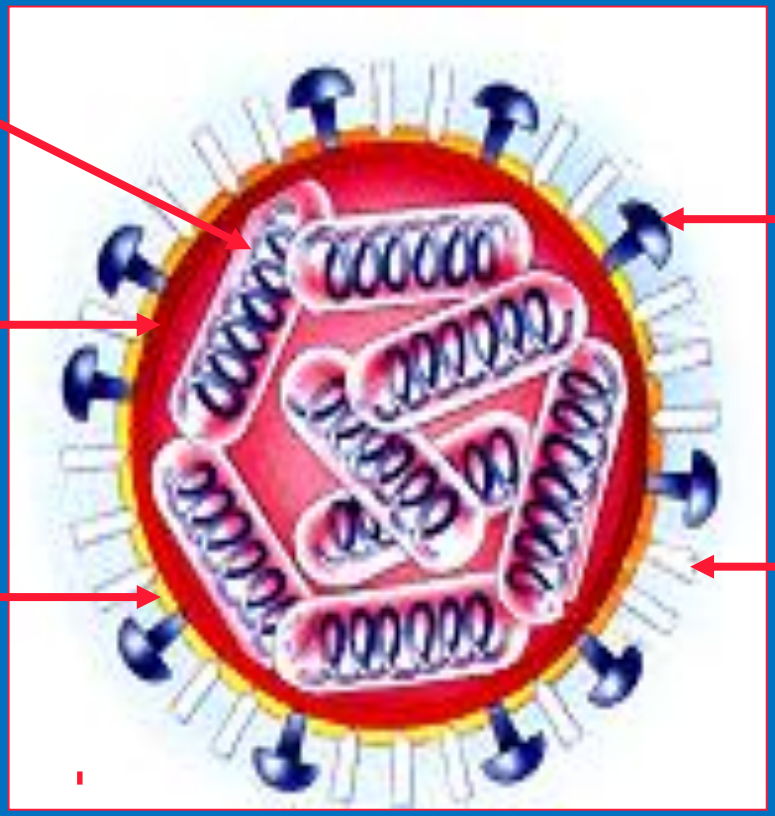
Data Source:
Global Influenza Surveillance and Response System (GISRS),
FluNet (www.who.int/flunet)

World Health Organization

VARIABILITY OF INFLUENZA VIRUSES

Genomic RNA : 7-8 segments

Nucleocapsid:
Nucleoprotein (NP) -RNA (7 or 8 segments)



Neuraminidase (NA)

Matrix protein (M)

Lipid layer

Hemagglutinin (HA)

80 - 120 nm

Internal antigens

Surface antigens

Nomenclature system for influenza A viruses

The current nomenclature system for influenza A viruses includes the species from which the virus was isolated (omitted if human), geographic location of first isolation, strain number and year of isolation, the HA and NA subtype

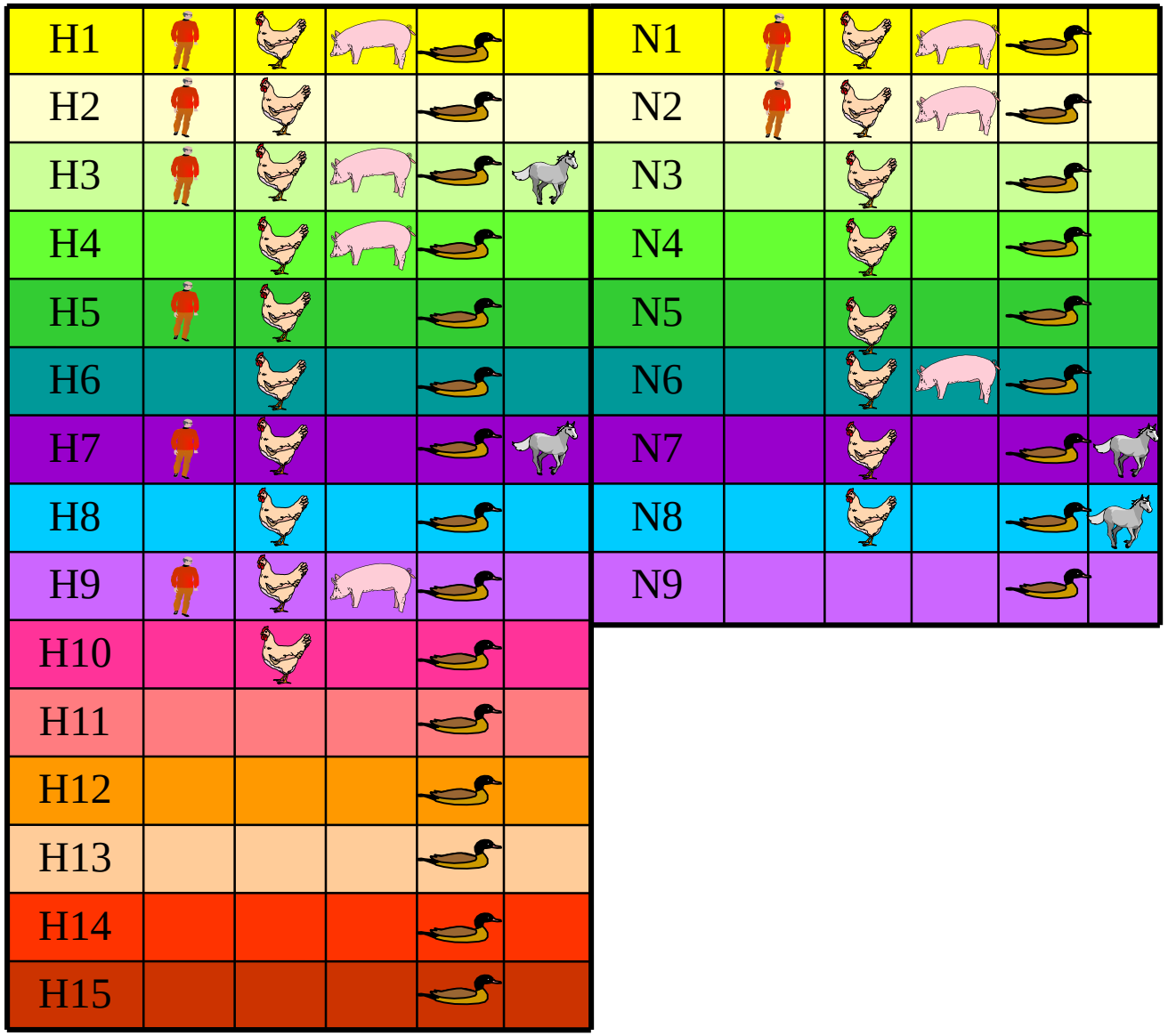
Eg. A/chicken/Hong Kong/220/97(H5N1) or

A/New Caledonia/20/99 (H1N1).

The current nomenclature system for influenza A viruses includes geographic location of first isolation, strain number and year of isolation.

Eg. B/Shanghai/361/02.

Subtypes of hemagglutinin (H) and neuraminidase (N)



Antigenic variation

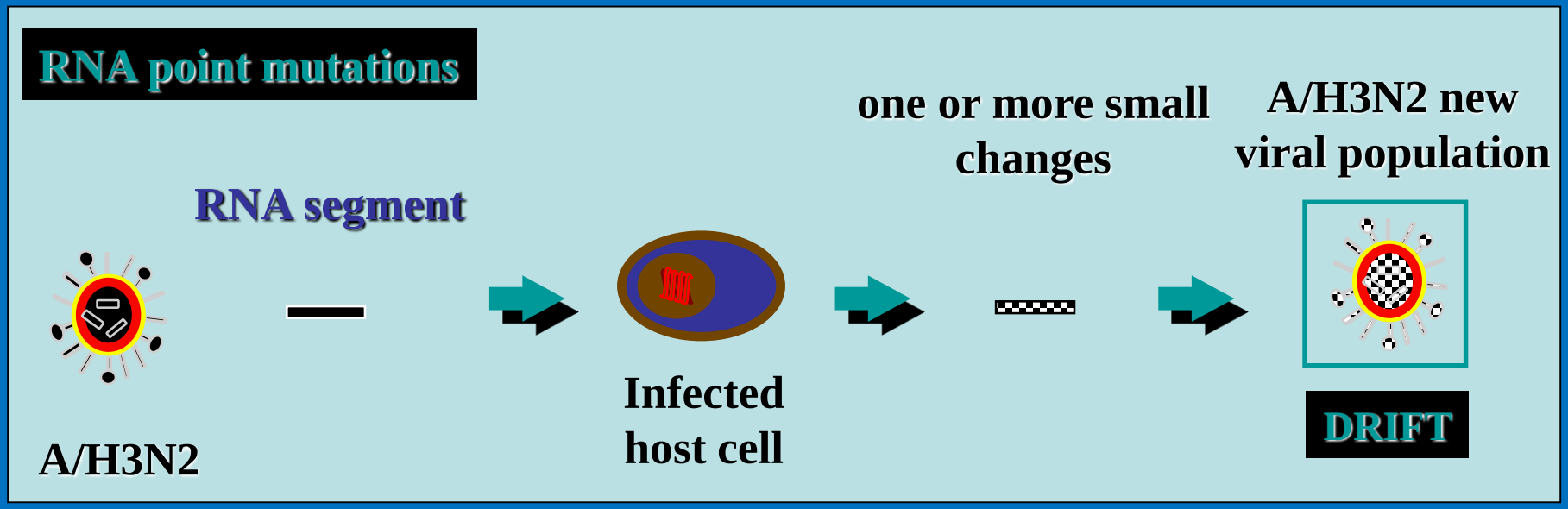
- It occurs frequently in Influenza A, less frequently in type B than A and does not exist for the type C
- It makes influenza virus resistant to population immunity
- It involves the surface antigens : HA and NA

- There are two types of mutations :
  - **Antigenic Drift**
  - **Antigenic Shift**

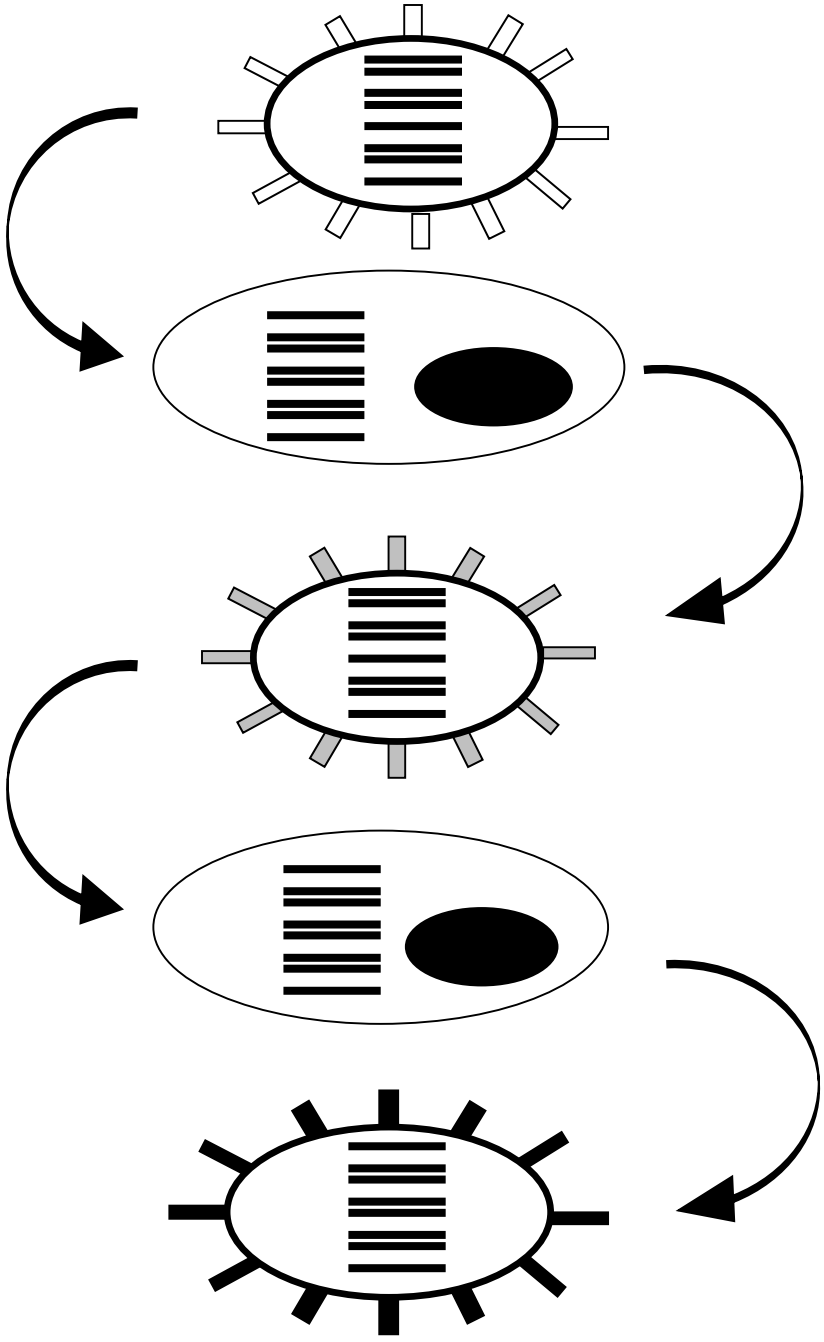
Each year, this mechanism may create a different virus

Antigenic drift: minor changes in HA or NA

- Minor modifications of the genome (RNA mutations) which lead to small changes in the surface antigens
- Affects Influenza A and B viruses
- Occurs every year or every few years within an influenza subtype
- Does not result in new subtype but can result in significant epidemics

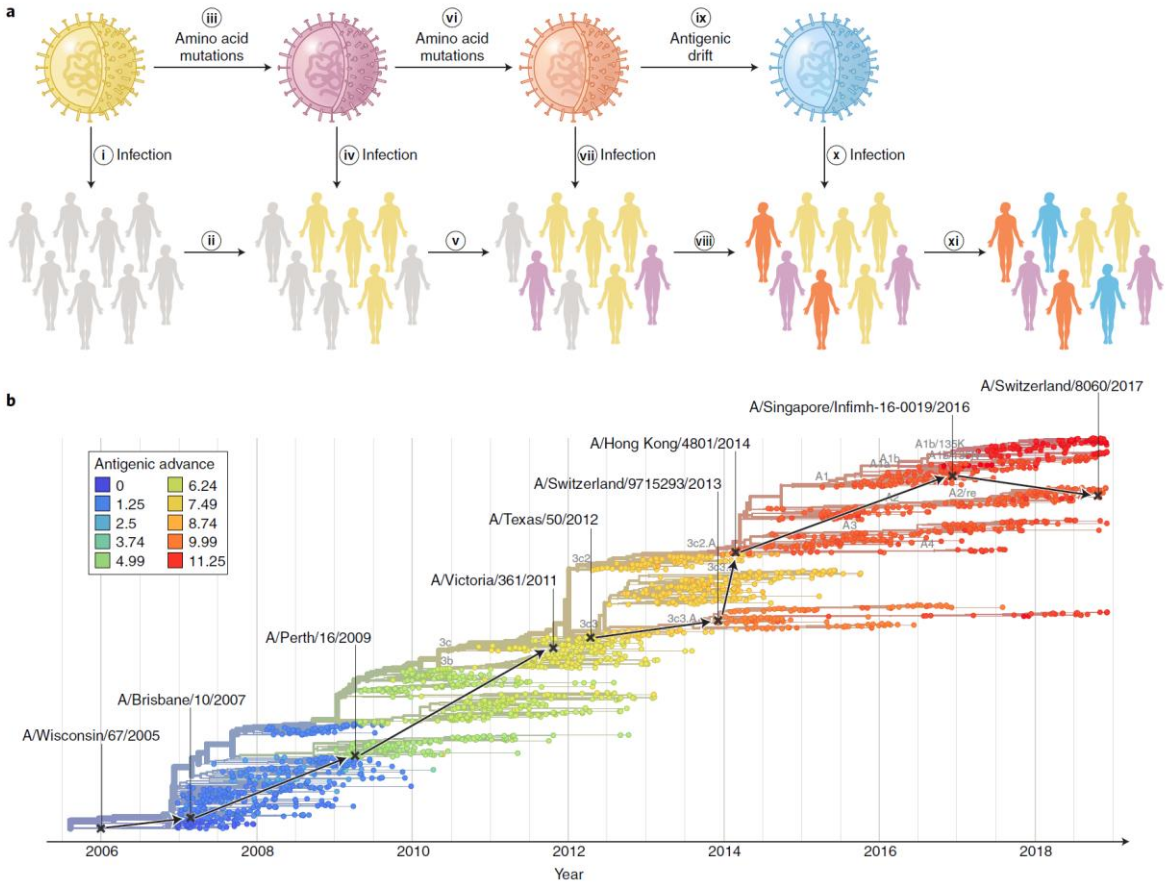


Betts FR, Douglas RG, Mandell GL, Douglas RG, Bennett JE. Principles and practice of infectious diseases, 3rd ed.; 1990;39:1306-25.



ANTIGENIC DRIFT

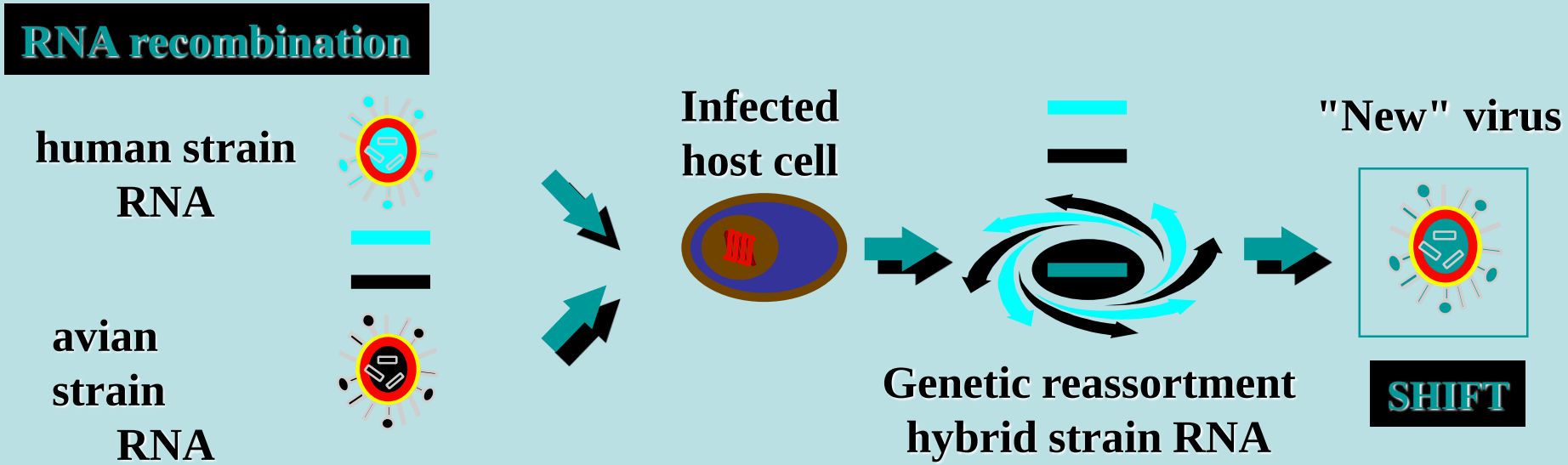
Antigenic drift



NATURE MEDICINE | VOL 25 | FEBRUARY 2019 | 212–220 |

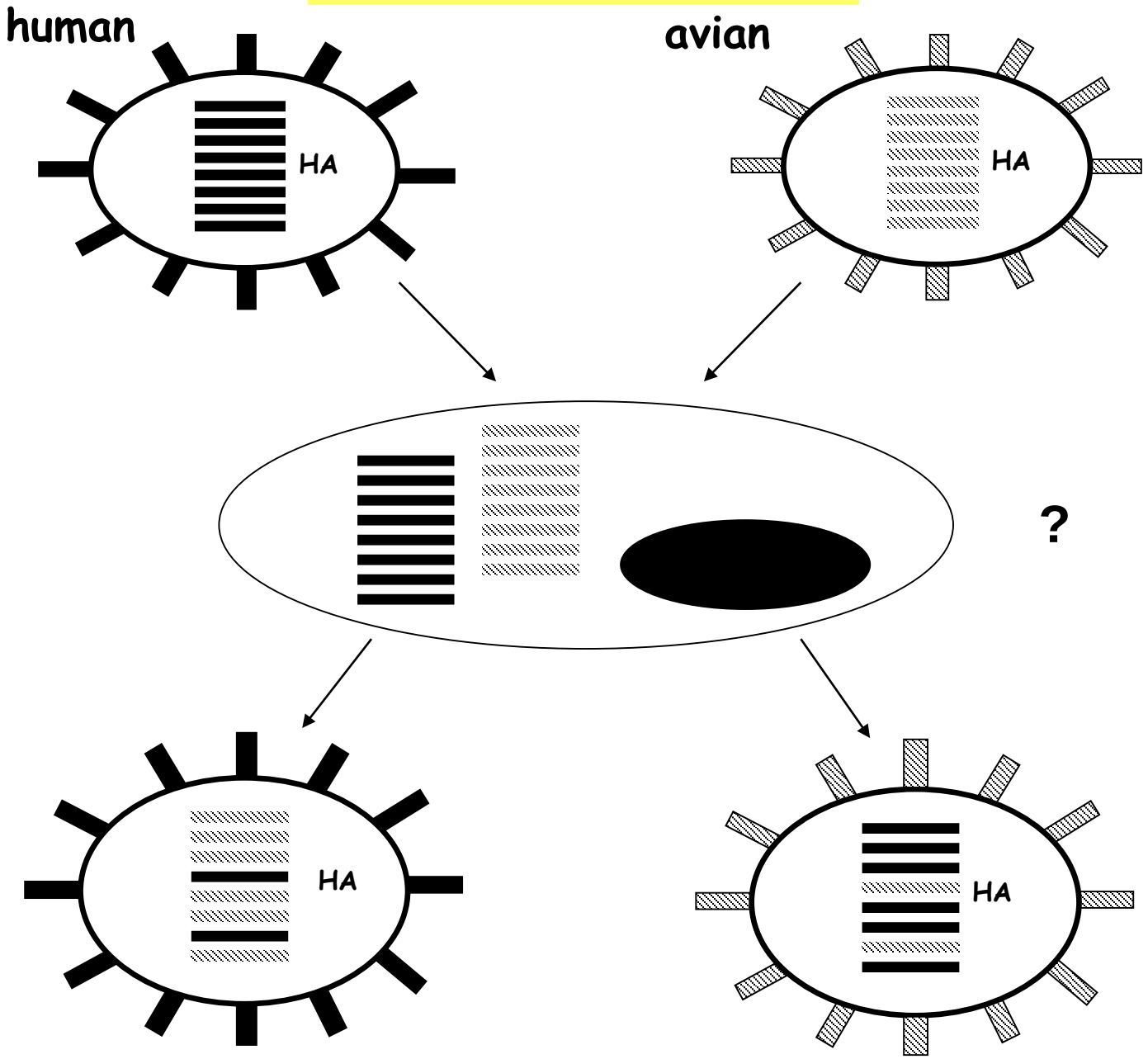
Antigenic shift: emergence of a "new" virus worldwide

- Affects only Influenza A virus
- Major and sudden genetic variations which lead to replacement of a whole piece of HA and/or NA
- No immunity in population ⇨ results in pandemics

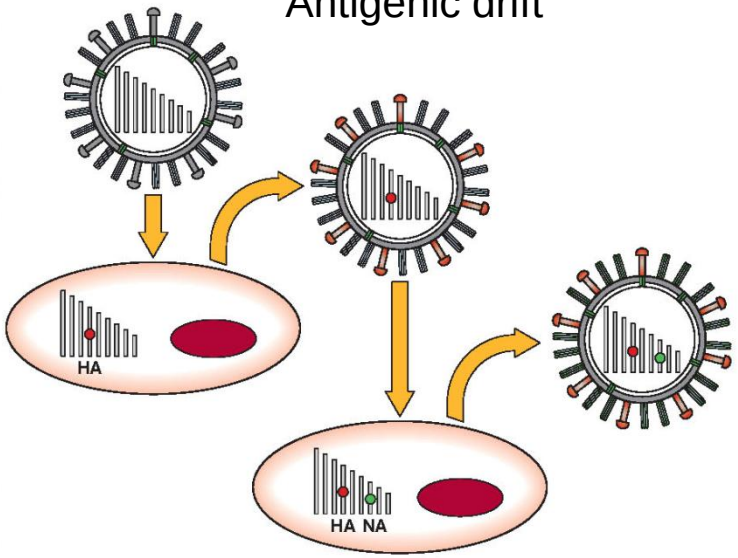


Betts FR, Douglas RG, Mandell GL, Douglas RG, Bennett JE. Principles and practice of infectious diseases, 3rd ed.; 1990;39:1306-25.

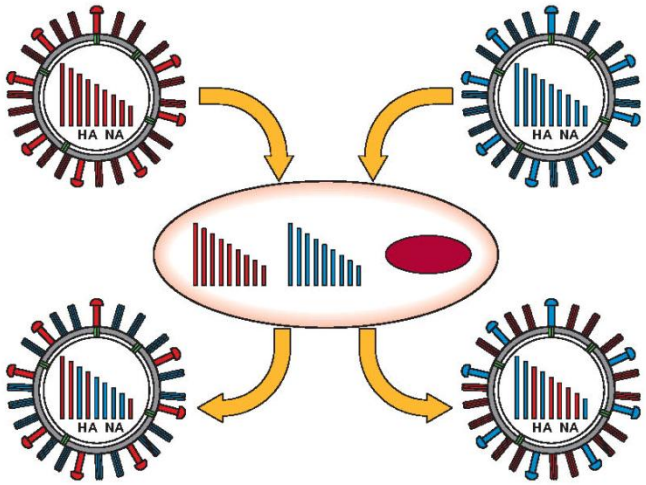
ANTIGENIC SHIFT



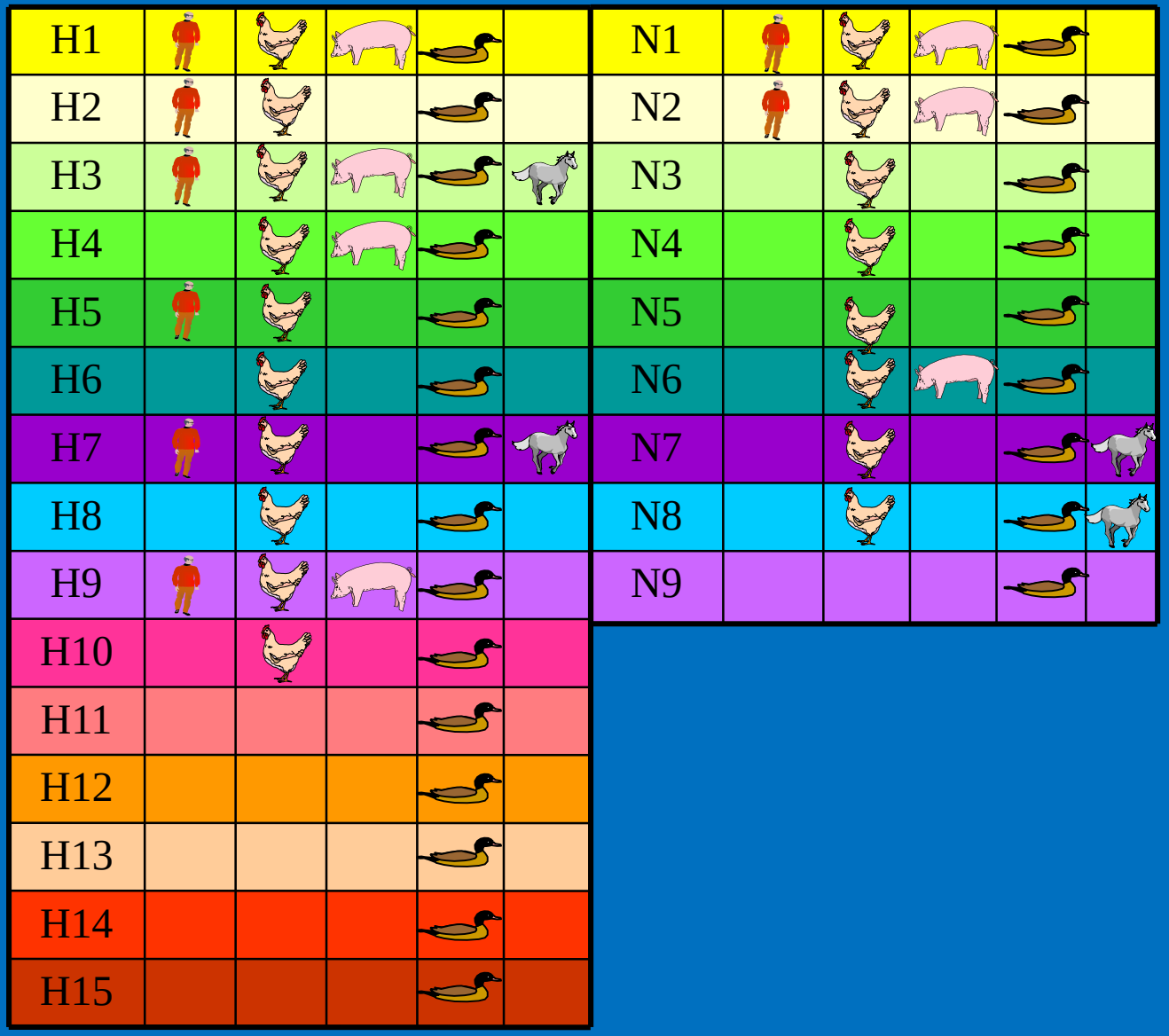
Antigenic drift



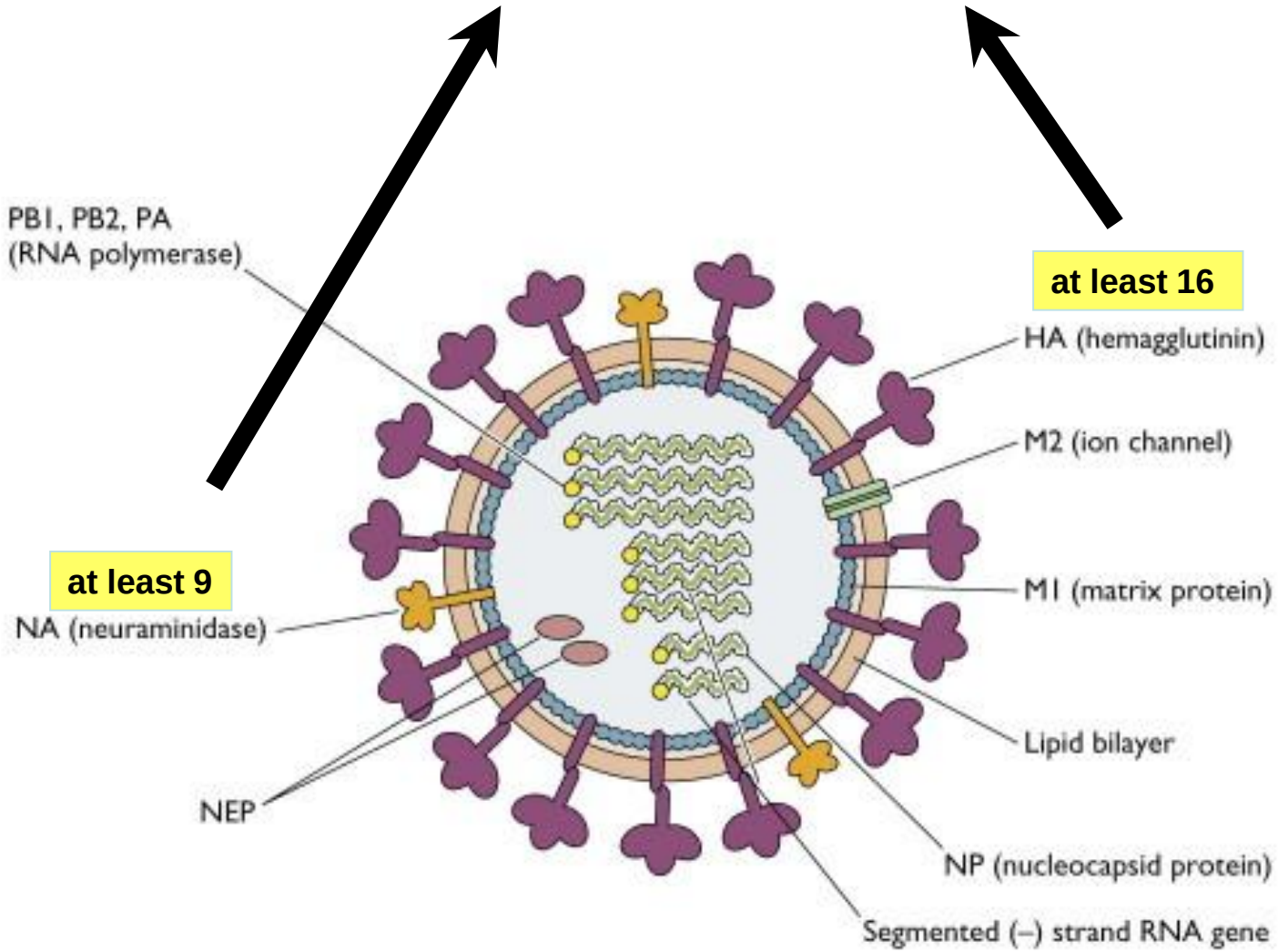
Antigenic shift



Subtypes of hemagglutinin (H) and neuraminidase (N)



At least 144 type A influenza A virus HA-NA combinations

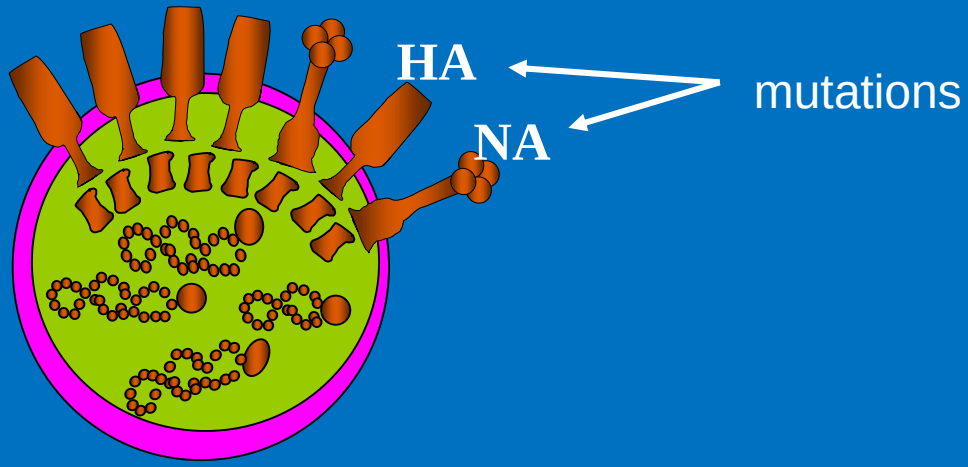


Influenza Antigenic Changes

- Structure of hemagglutinin (H) and neuraminidase (N) periodically change

- **Drift:** **Minor change, same subtype**
  Point mutations in gene
  May result in epidemic

- **Shift:** **Major change, new subtype**
  Exchange of gene segment
  May result in pandemic



Epidemic variants

-They are consequences of point mutations, antigenic drift
-Selective immunological pressure present in the population

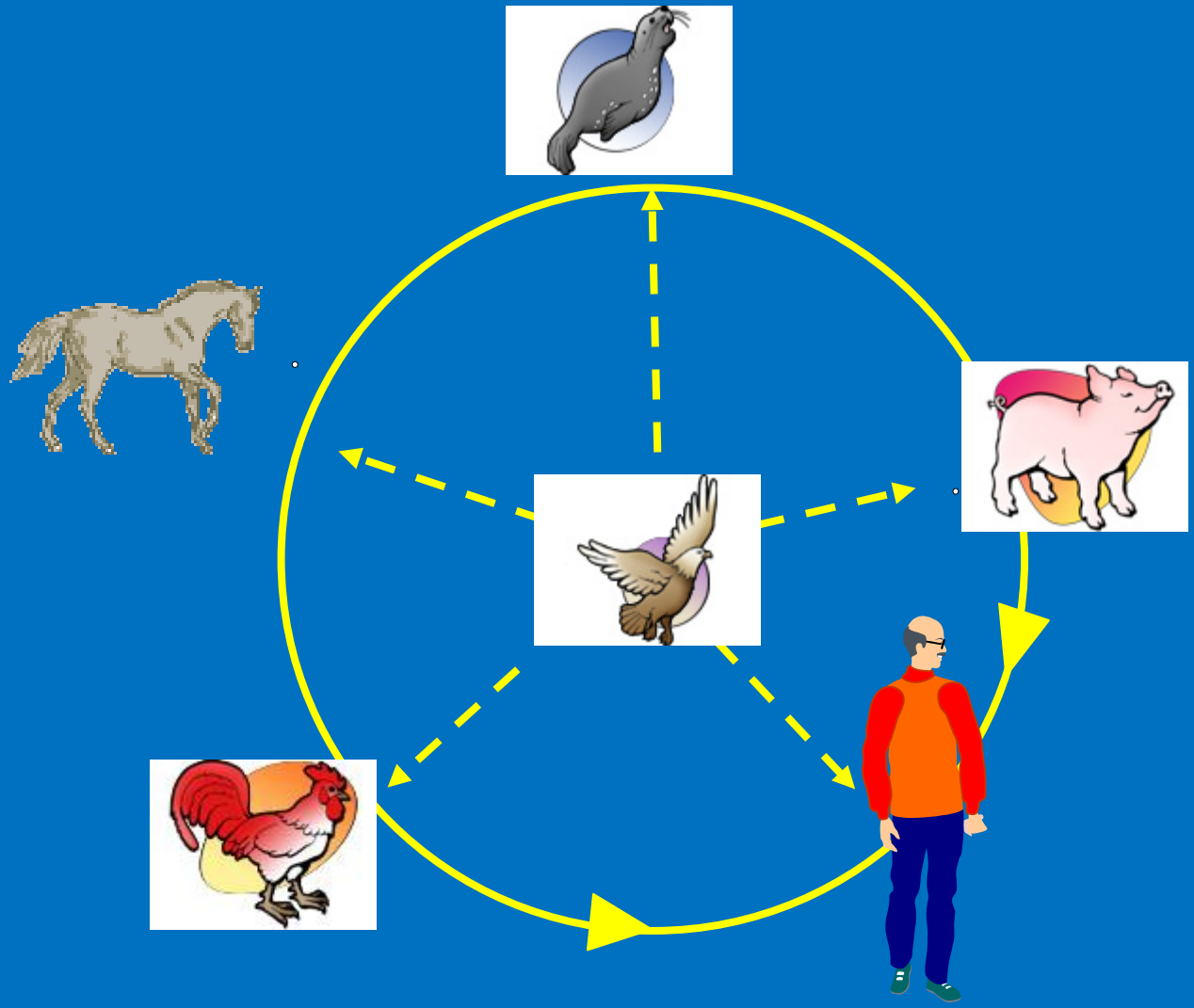
Pandemic variants

-They are consequences of appearance of new subtypes of HA and NA, antigenic shift
-Transmission from other animal species (birds, pigs, horses, etc.) to humans

Characteristics of influenza A, B and C virus

	A	B	C
disease severity	++++	++	+
animal reservoirs	Yes	No	No
pandemics	Yes	No	No
epidemics	Yes	Yes	No (only sporadic)
antigenic variability	Shift, drift	Drift	Drift
number of genomic segments	8	8	7
surface glycoproteins	2	2	1
sensitivity to: - amantadine - rimantadine - neuraminidase inhibitors	 Yes Yes Yes	 No No Yes	 No No ?

Animal species infected by Influenza virus



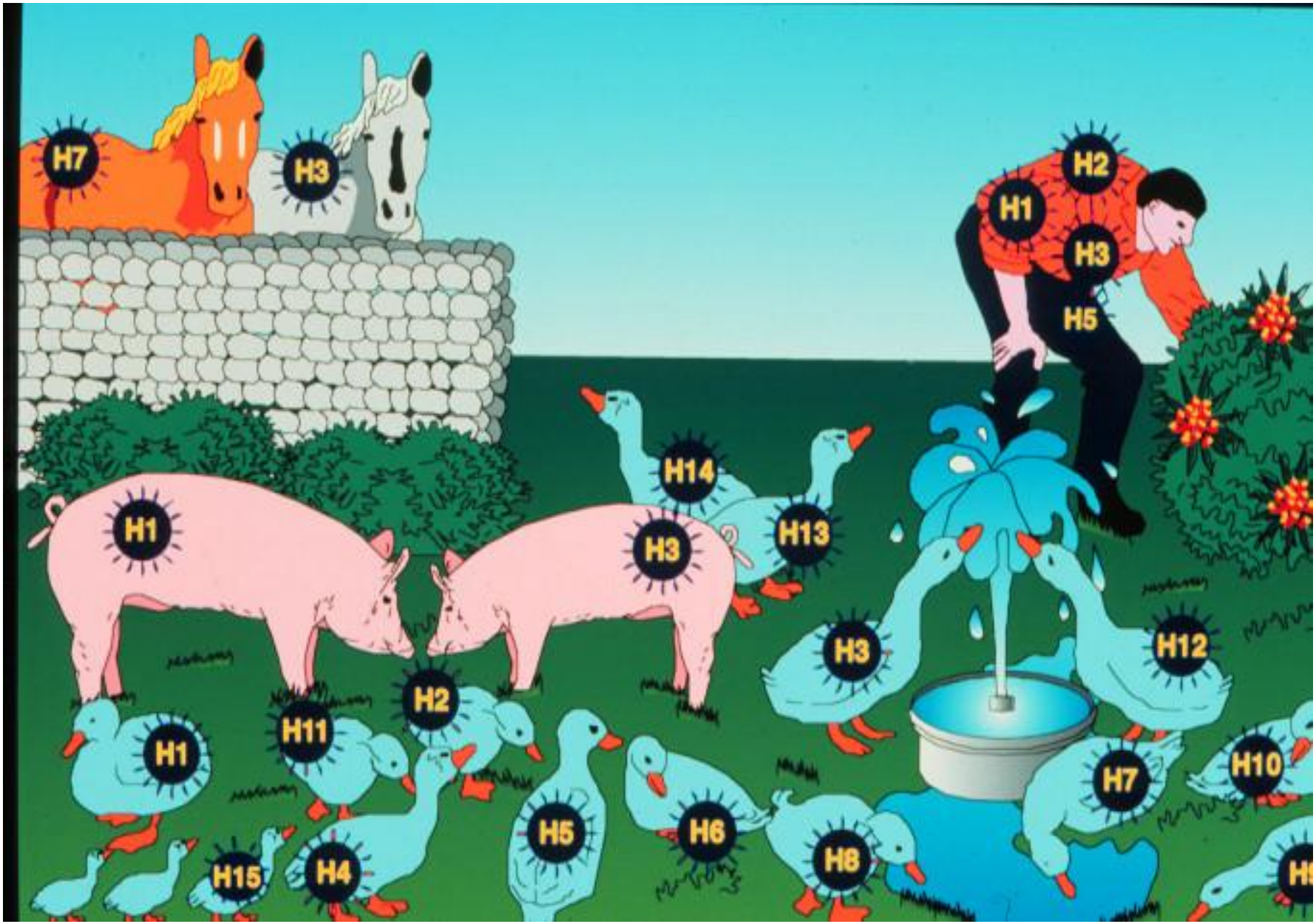
Reservoir of influenza A viruses

- Important reservoirs of influenza A viruses are represented by water birds (in some cases subclinical infections occur); many strains until now have never caused human infection

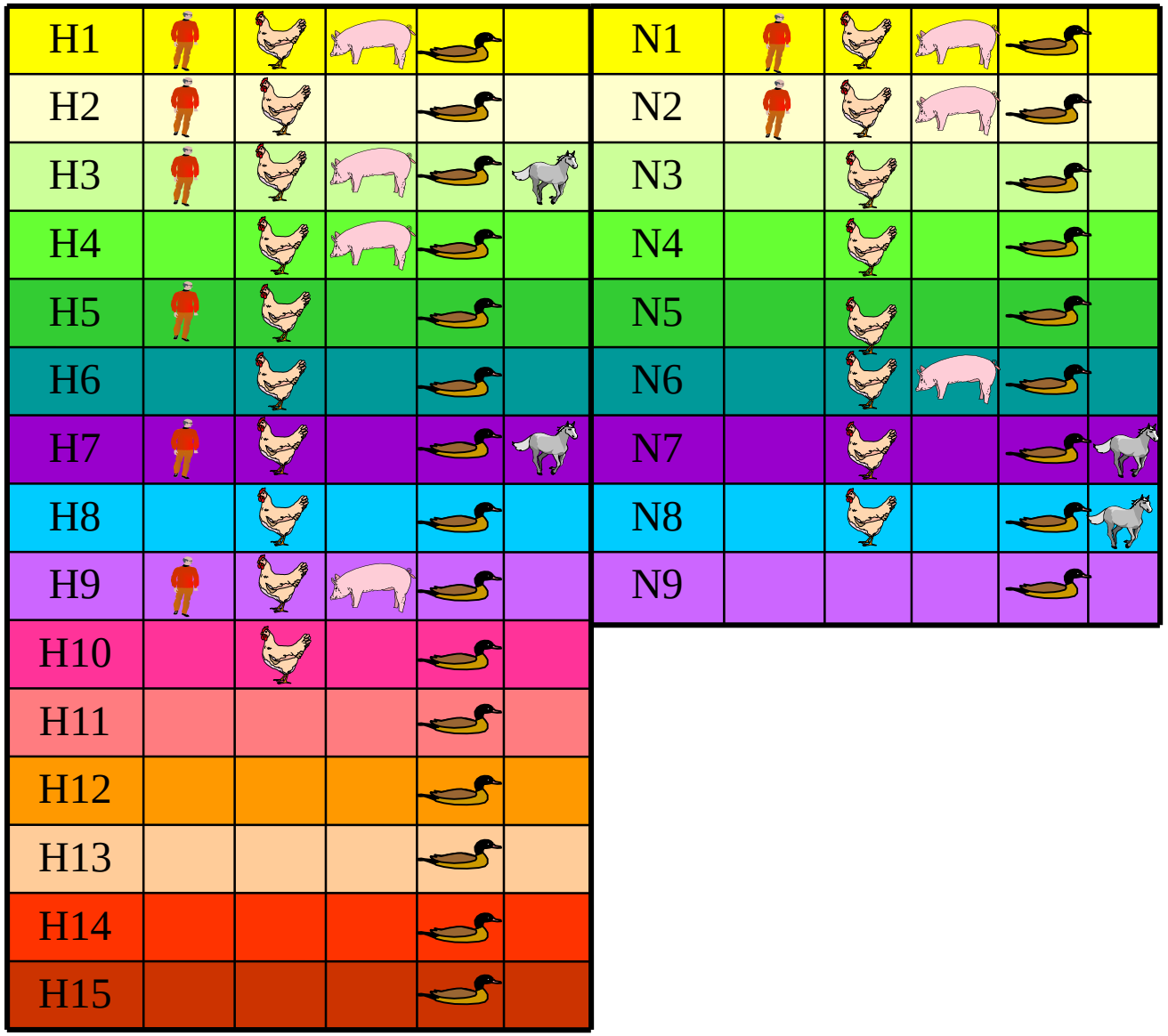
- Viruses can sometimes spread to terrestrial bird species, wild or domestic, and subsequently to large mammals, including pigs, horses and man

- Main avian species are quail, ducks, poultry, turkeys and geese.

- However, many strains also infect small mammals but it is unlikely that they overcome species barriers and affect humans


H7
H3
H2
H1
H3
H5
H14
H1
H3
H13
H3
H12
H2
H11
H1
H7
H10
H5
H6
H8
H15
H4

Subtypes of hemagglutinin (H) and neuraminidase (N)



Past pandemics

1918 H1N1 "Spanish Flu" 20-50 million deaths

- 8 genes from unusual avian precursor

1957 H2N2 "Asian Flu" 1-2 million deaths

- HA, NA and PB1 genes from avian virus

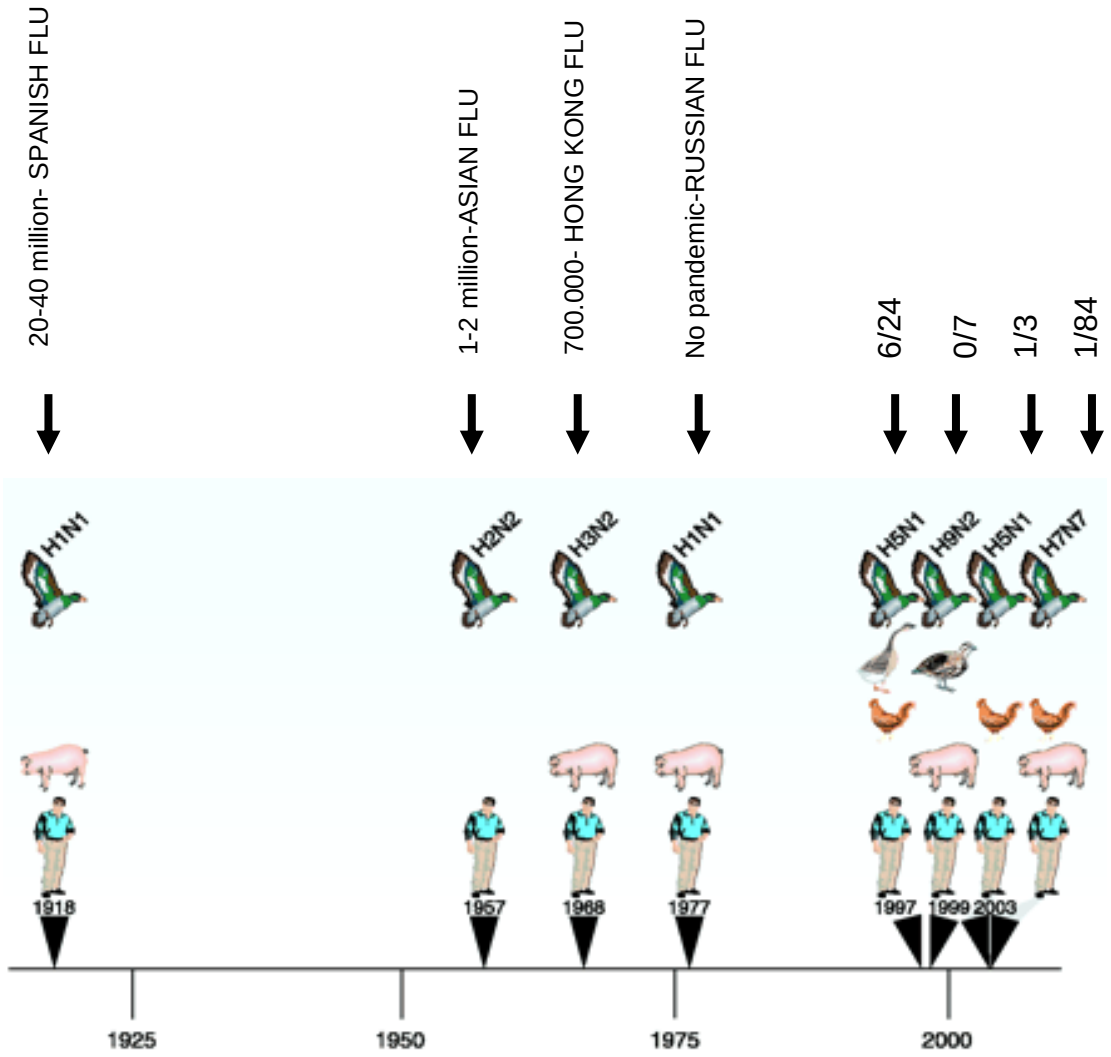
1968 H3N2 "Hong Kong Flu" 700,000 deaths

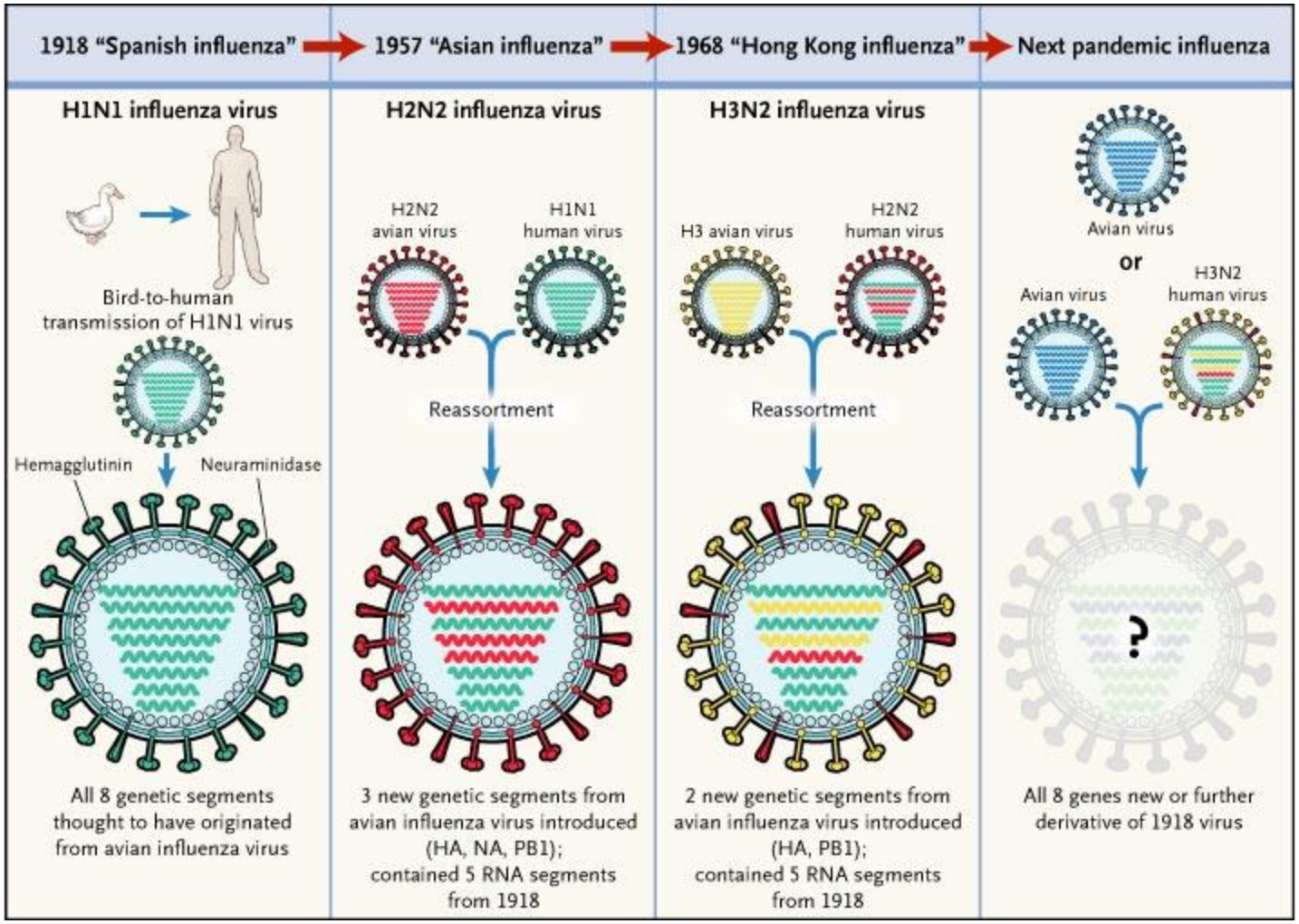
- HA and PB1 genes from avian virus

1977 H1N1 "Russian Flu"

- All human genes (almost identical to a strain that circulated in humans in 1950)

TIMELINE OF HUMAN INFLUENZA OVER THE PAST 100 YEARS (Webby RJ et al.,Science 2003)





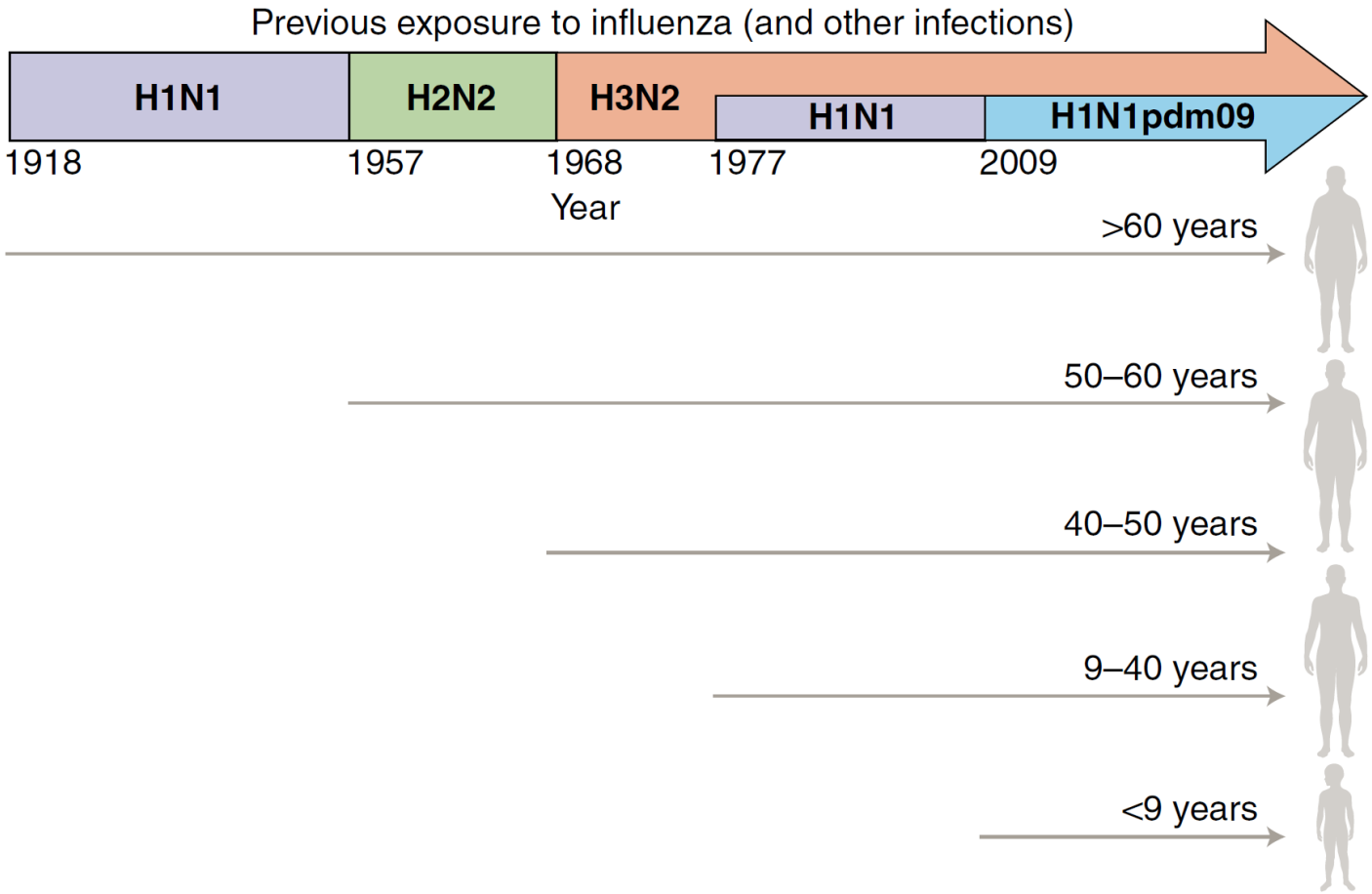
From Belshe RB, NEJM 2005

What makes a new influenza virus “pandemic”?

- It is antigenically novel (population is immunological naïve)
- It’s pathogenic to humans
- It transmits easily from person to person

Past pandemics

Pandemics	Year	Viral subtype	Transmission
Spanish Flu	1918	H1N1	Directly transmitted from birds to humans
Asian Flu	1957	H2N2	Reassortment between human (5 segments) and avian (3 segments) strains
Hong Kong Flu	1968	H3N3	Reassortment between human (6 segments) and avian (2 segments) strains
Swine Flu	2009	H1N1	Reassortment between a human strain (1 segments) , an avian strain (2 segments) and two strains of pigs (3 segments of American swine virus and 2 segments of Eurasian swine virus)


Previous exposure to influenza (and other infections)
H1N1
H2N2
H3N2
H1N1
H1N1pdm09
1918
1957
1968
1977
2009
Year
>60 years
50–60 years
40–50 years
9–40 years
<9 years

AVIAN INFLUENZA

Avian influenza is transmitted by strains of influenza viruses originated from birds; in humans, initial symptoms aresimilar to those of classical influence, but much more severe evolution and greater tendency to cause complications, especially in lower respiratory tract. A characteristic element in some cases may be conjunctivitis (eg H7N7), but also the gastrointestinal manifestations (H5N1)

Confirmed human cases of Avian Influenza H5N1
November 24, 2005 - source: WHO

Date of onset	Indonesia		VietNam		Thailand		Cambodia		China		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
26.12.03-10.03.04	0	0	23	16	12	8	0	0	0	0	35	24
19.07.04-08.10.04	0	0	4	4	5	4	0	0	0	0	9	8
16.12.04- to date	11	7	65	22	4	1	4	4	4	2	86	35
Total	11	7	92	42	21	13	4	4	2	1	132	68

Mortality = 51,5%

The genetic sequences of the 1997 Hong Kong H5N1 virus and the 2004 Vietnam H5N1 virus revealed that several human isolates of these viruses contain one of the five amino acid changes in PB2 that have been identified as important to the ability of the 1918 virus to infect humans.

This finding suggests that several additional genetic changes must occur before these viruses will begin to spread efficiently from person to person.

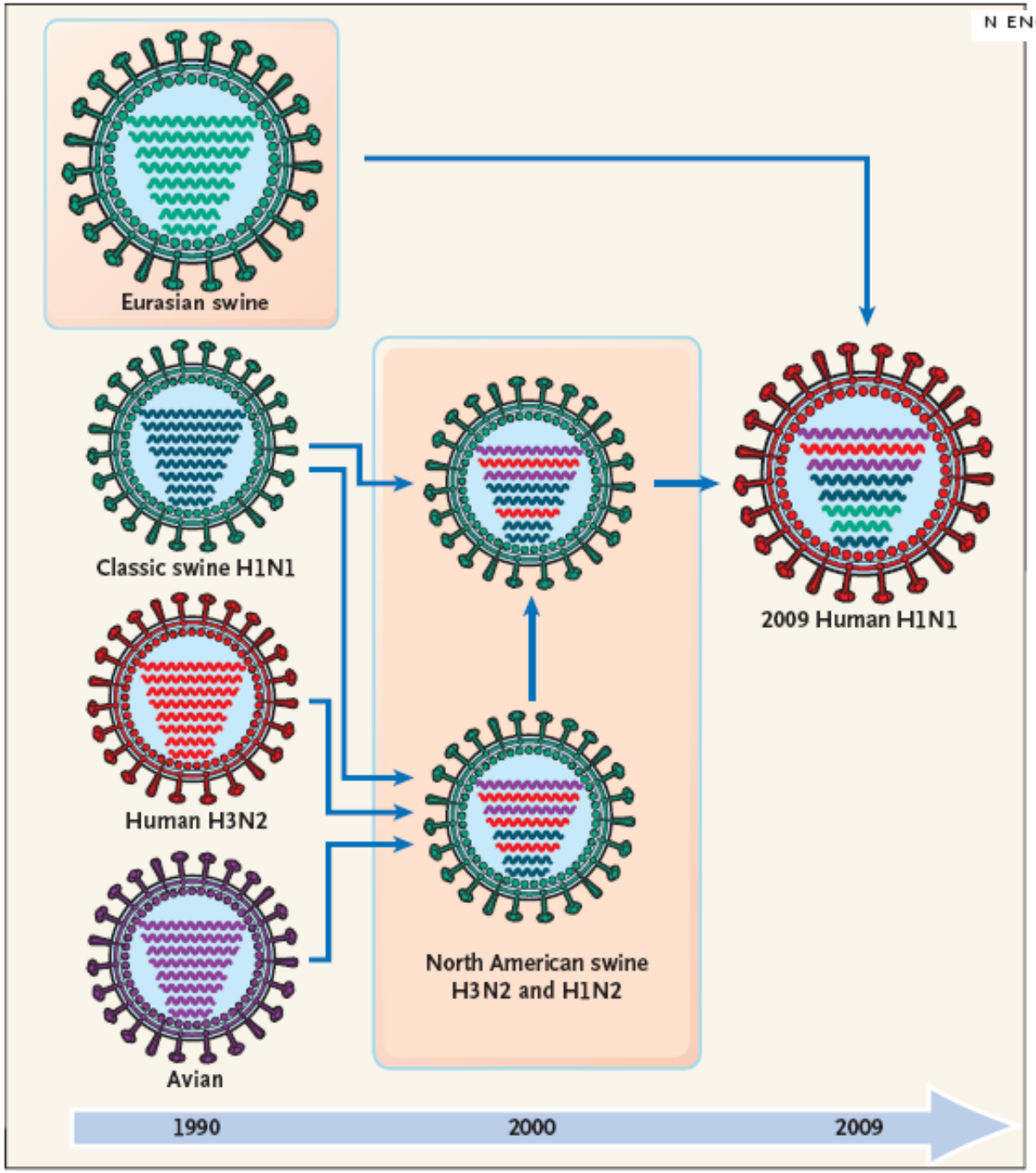
Documented changes are needed but not enough

Avian influenza polymerase genes had been circulating in humans as early as 1900.

If this estimate is correct, then monitoring of the sequences of viruses isolated in instances of bird-to-human transmission for genetic changes in key regions may enable us to track viruses years before they develop the capacity to replicate with high efficiency in humans.

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	?

2009 pandemic H1N1



Top to bottom
PB1
PB2
PA
HA
NP
NA
MP
NSP

WHO - Pandemic (H1N1) 2009 - update 68

Weekly update

As of 27 September 2009, worldwide there have been more than
340,000 laboratory confirmed cases
of pandemic influenza H1N1 2009
and over 4100 deaths reported to WHO.

4100/340.000= 0.012

Conclusions

- An influenza pandemic will most likely occur in the near future
- Widespread illness will occur
- All countries will be affected
- Medical supplies will be inadequate
- A large number of deaths will occur
- Economic and social disruption will be great
- Everyone must be prepared
- The most important players in the response will be people at the local level