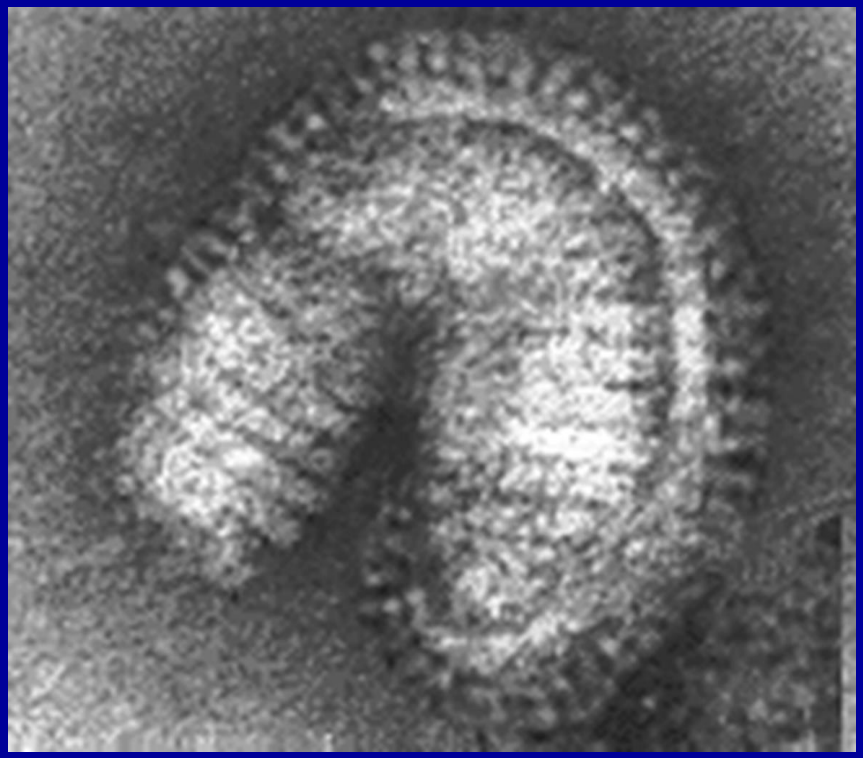
ORTHOMYXOVIRIDAE

INFLUENZA A, B, C

ssRNA (negative strand)



Some Flu Terms

- ***Epidemic or Seasonal (or common) flu*** **is a respiratory illness that can be transmitted person to person. Most people have some immunity, and a vaccine is available.**

- ***Pandemic flu*** **is virulent human flu that causes a global outbreak, or pandemic, of serious illness. Because there is little natural immunity, the disease can spread easily from person to person. Currently, there is no pandemic flu.**

- ***Avian (or bird) flu*** **is caused by influenza viruses that occur naturally among wild birds. The H5N1 variant is deadly to domestic fowl and can be transmitted from birds to humans. There is no human immunity and no vaccine is available.**

INTRODUCTION

- Influenza is an acute, usually self-limited, febrile illness
- It is caused by infection of influenza type A or B virus that occurs in outbreaks with different severity every winter
- Most common clinical manifestations are fever, malaise and cough
- Characteristic features are its epidemic nature and mortality that results in part from its pulmonary complications

HISTORY

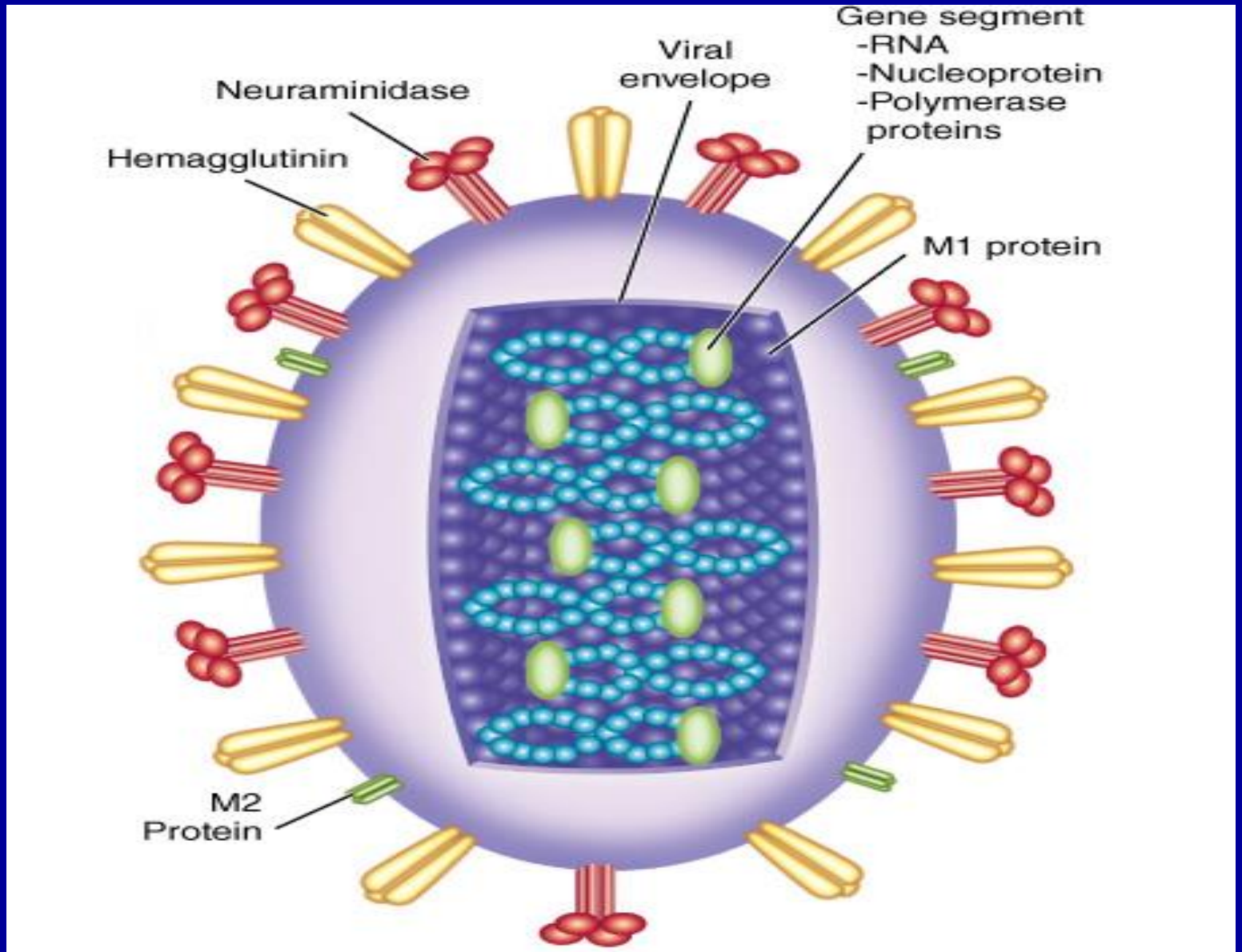
- Influenza virus has been causing recurrent epidemics of febrile respiratory disease every 1-3 years for the last 400 years (probably as old as cities.)
- The first recorded pandemic that fits the description of influenza occurred in 1580
- Since then, 31 pandemics have been described
- The greatest pandemic in recorded history occurred 1918-1919
  - Three waves of influenza
  - 50 - 100 million deaths globally!!!
  - In USA 549 000 deaths!!!

- **1933, influenza A isolated.**
- **1936, influenza A grown in embryonated hen's eggs allowing extensive studies of the virus and eventually vaccines.**
- **1939 Influenza B isolated**
- **1950 Influenza C isolated**
- **First animal cell cultures were developed 1950s**

- **Inactivated vaccines developed in the 1940s**
- **Inactivated vaccines has been in widespread use since then**
- **Use of live vaccines for influenza was first suggested when virus was discovered – first live vaccine licensed in USA 2003 (flumist)**
- **Five antiviral agents have been approved for treatment of influenza**
  - **M2 inhibitors: amantadine and rimantadine (type A)**
  - **Neuraminidase inhibitors: zanamivir, oseltamivir(Tamiflu) and peramivir (type A and B)**

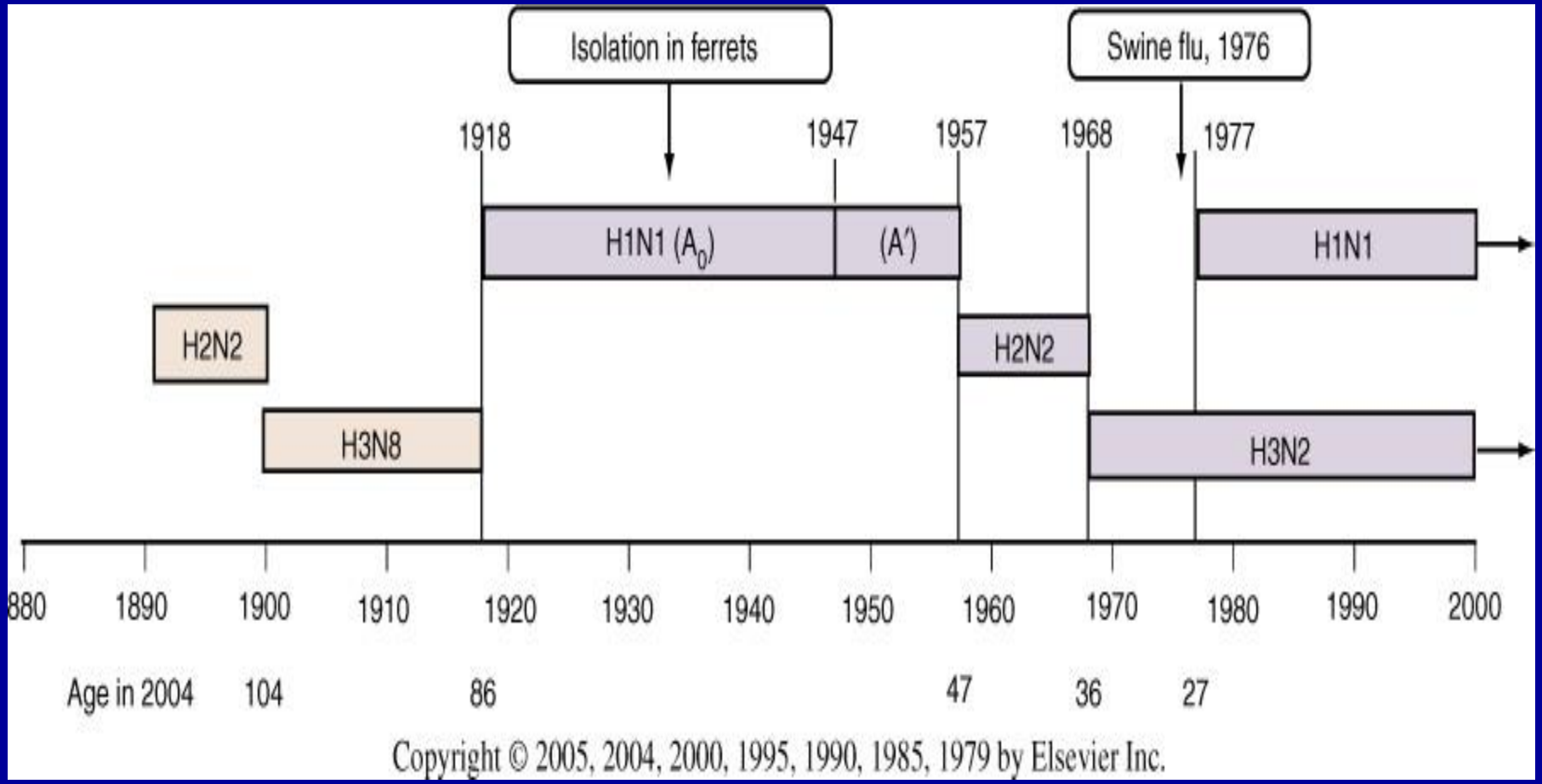
CLASSIFICATION

- Influenza A, B and C viruses belong to the family of Orthomyxoviridae
  - Segmented, RNA genome
  - Type A and B contains 8 segments
  - Type C contains 7 segments
- Sequence comparison indicates that all influenza types have common ancestor
- All strains cause classical influenza symptoms.



- **Influenza A can be subtyped (ie H1N1, H3N2)**

- **Subtyping influenza A is based on surface glycoproteins**
  - **Hemagglutinin (HA)**
    - **16 distinct HA subtypes**
    - **Only 3 HA subtypes (H1, H2, H3) have caused extensive outbreaks in humans**
  - **Neuraminidase (NA)**
    - **9 distinct NA subtypes**
    - **Only 2 NA subtypes (NA1 and NA2) has caused extensive outbreaks in humans**

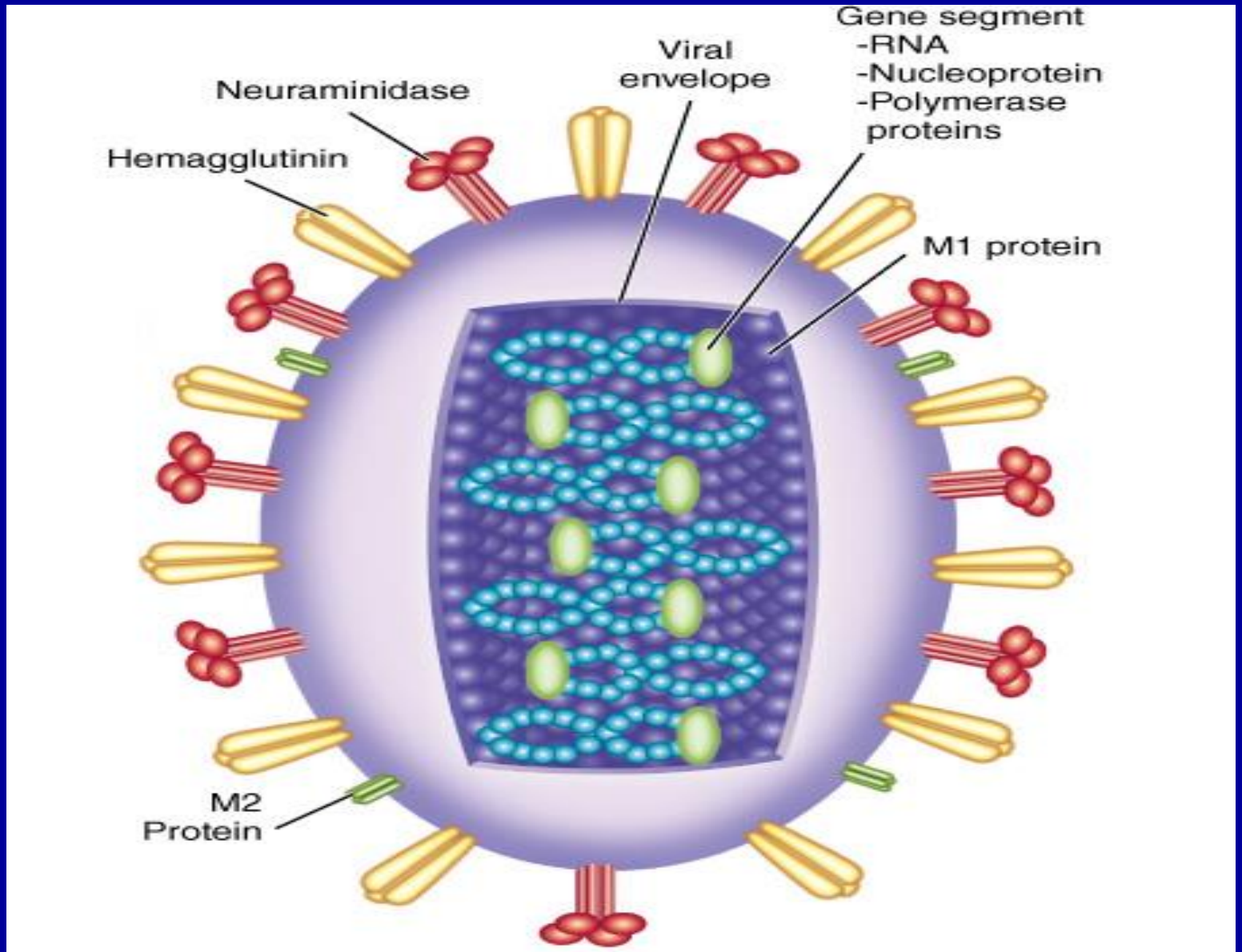


- **Virus strains are named on the basis of**
  - **type**
  - **location of isolation**
  - **serial number from that location**
  - **year of isolation**
  - **possible subtype in case of Influenza A**

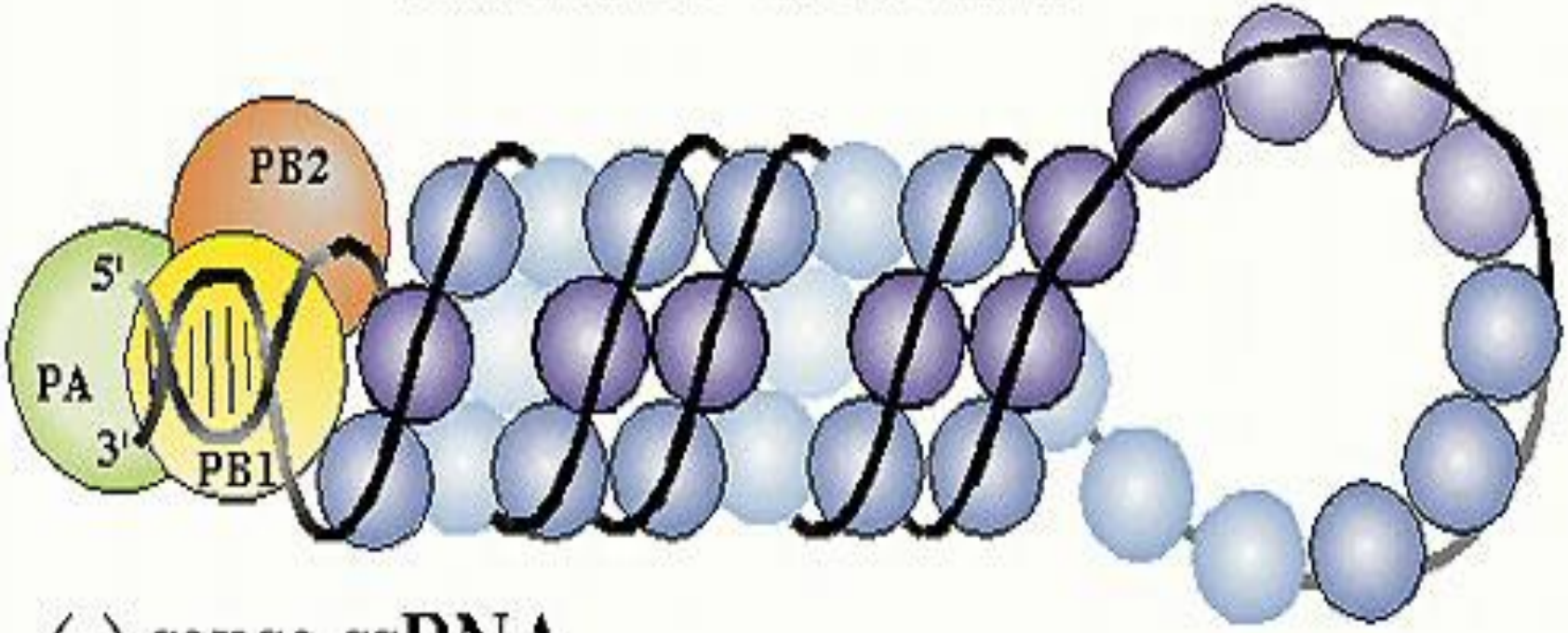
- **E.g.**

  - an A/California/7/2009 (H1N1)pdm09-like virus;
  - an A/Victoria/361/2011 (H3N2)-like virus;
  - a B/Wisconsin/1/2010-like virus (from the B/Yamagata lineage of viruses).

STRUCTURE



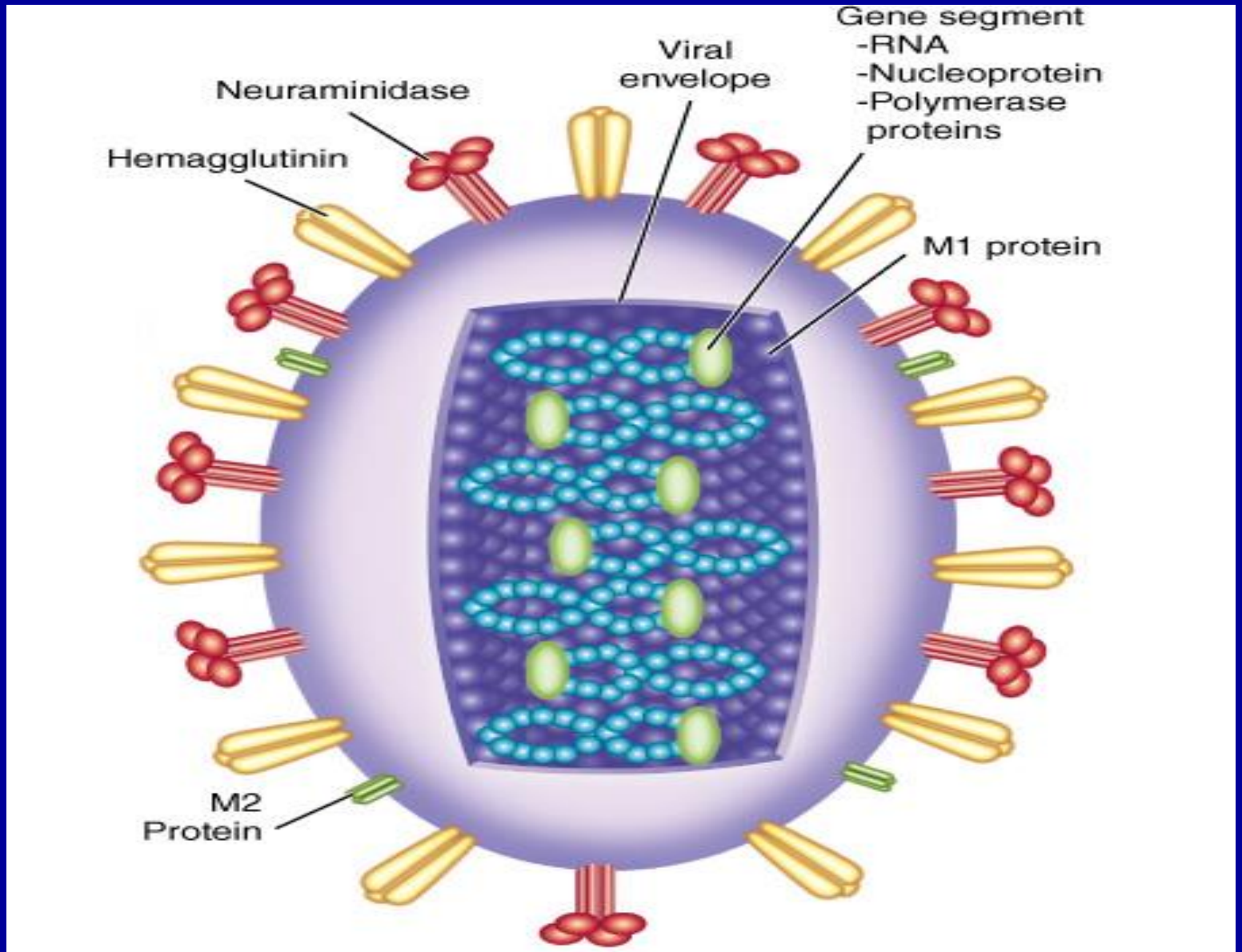
Influenza virus RNP

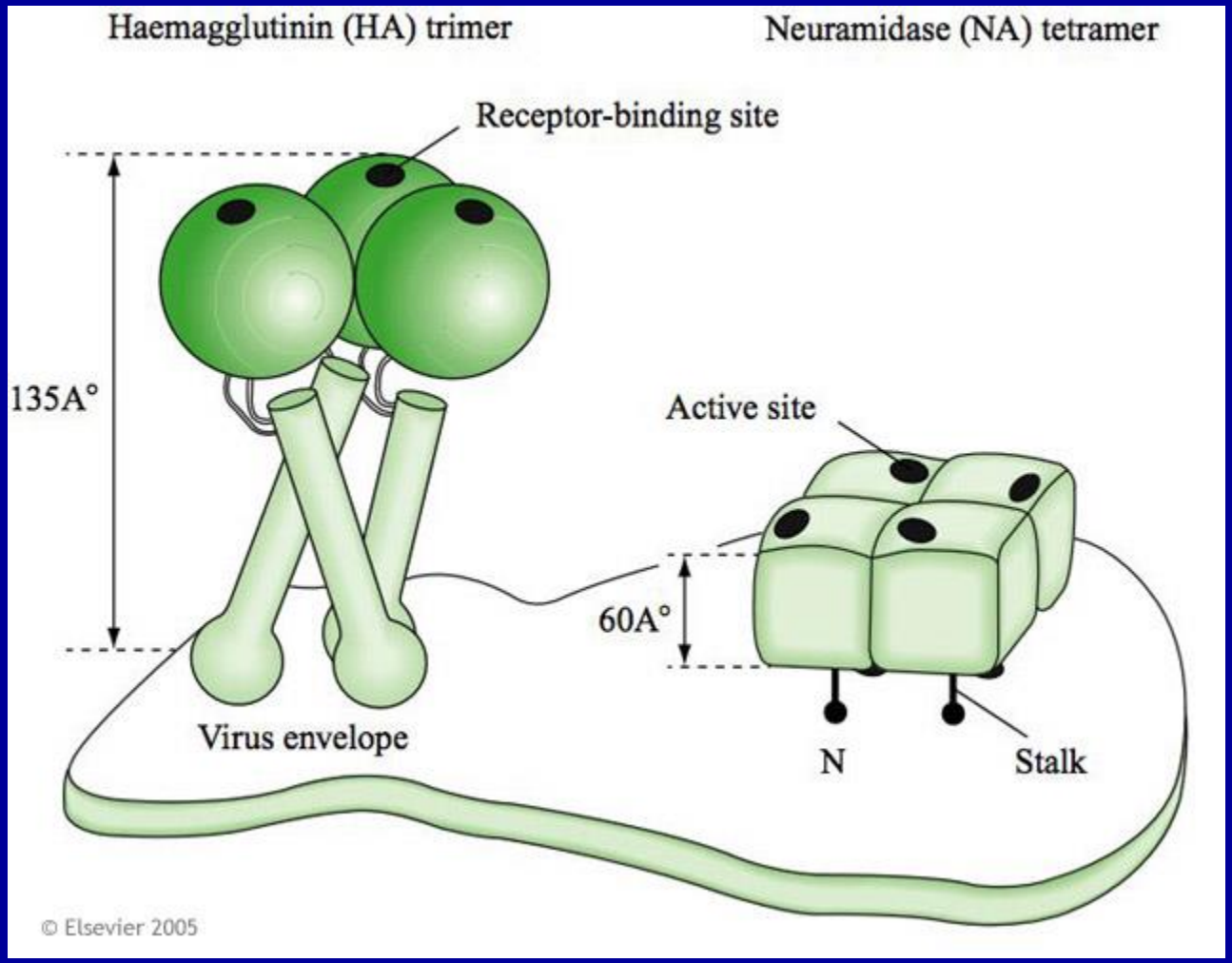


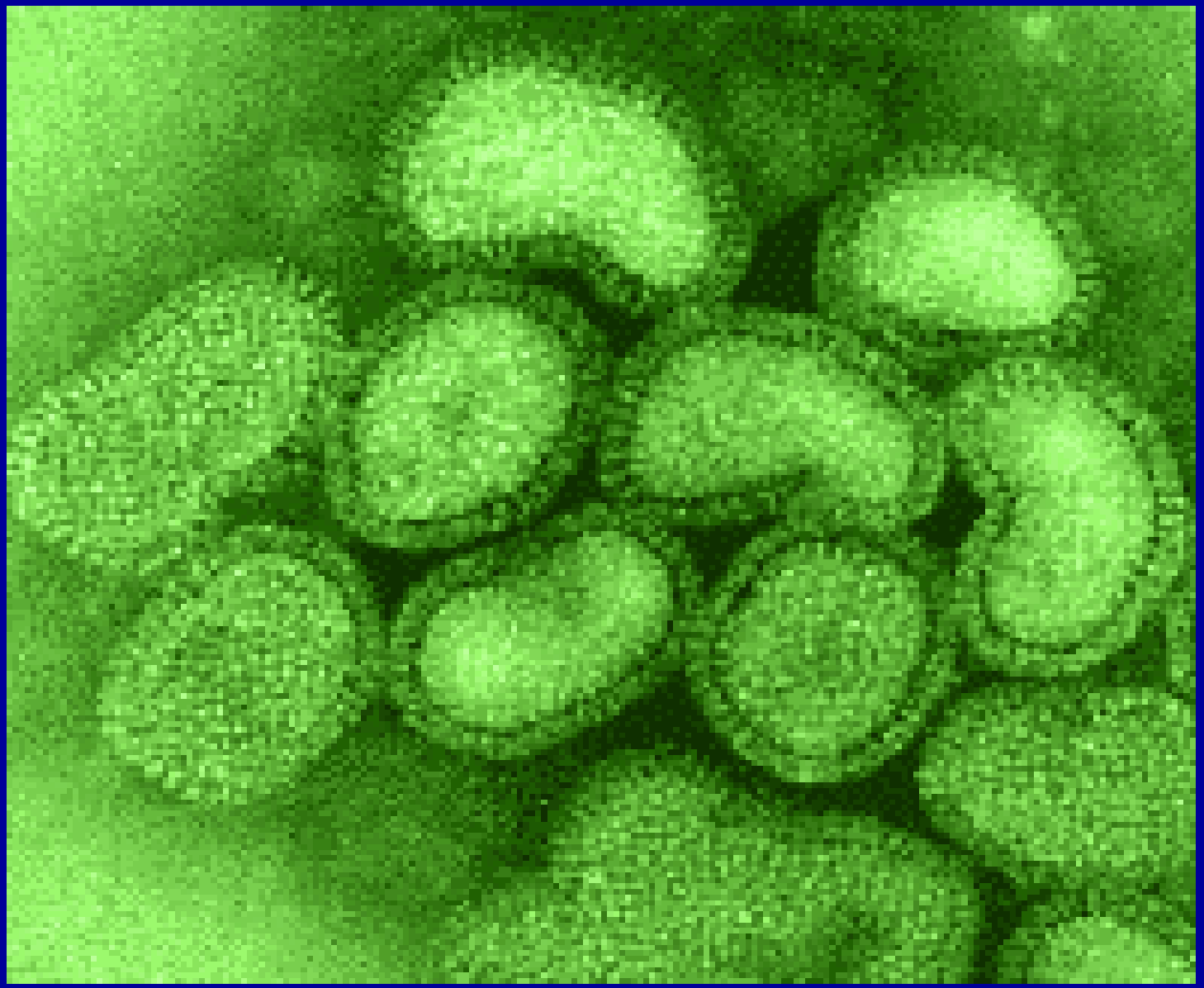
(-) sense ssRNA

3 polymerase subunits

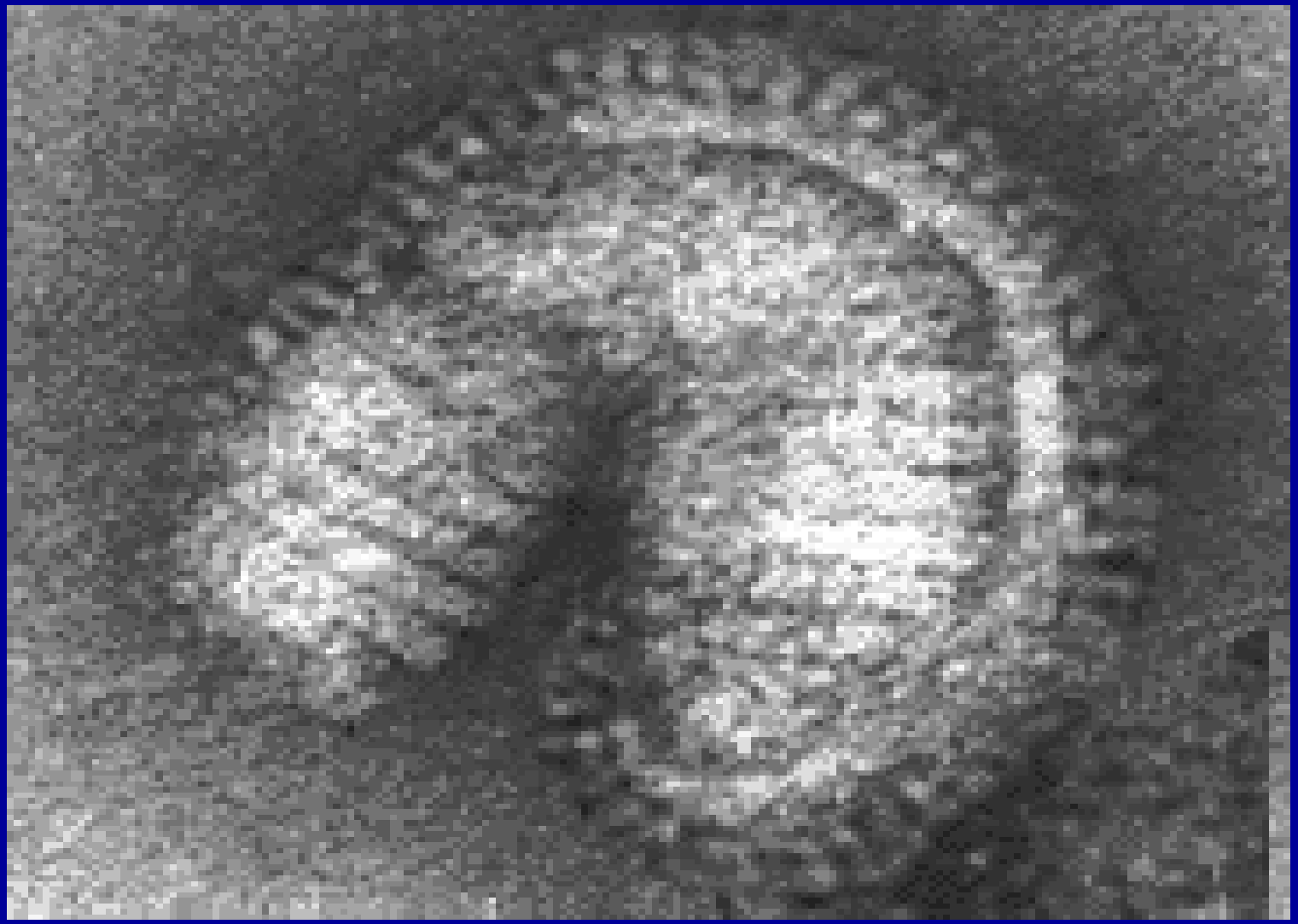
NP




Haemagglutinin (HA) trimer
Neuramidase (NA) tetramer
Receptor-binding site
135A°
Active site
60A°
Virus envelope
N
Stalk
© Elsevier 2005

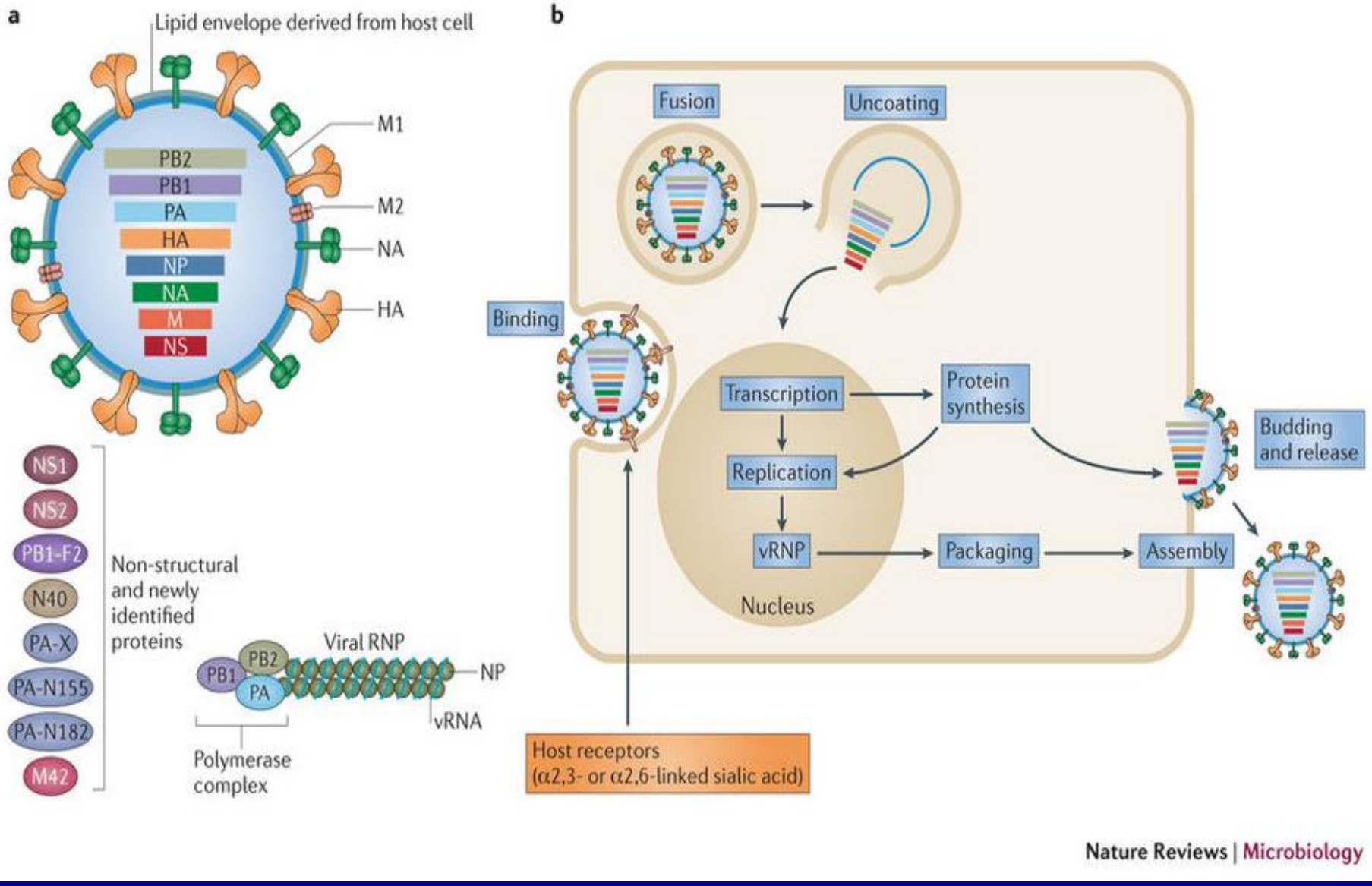


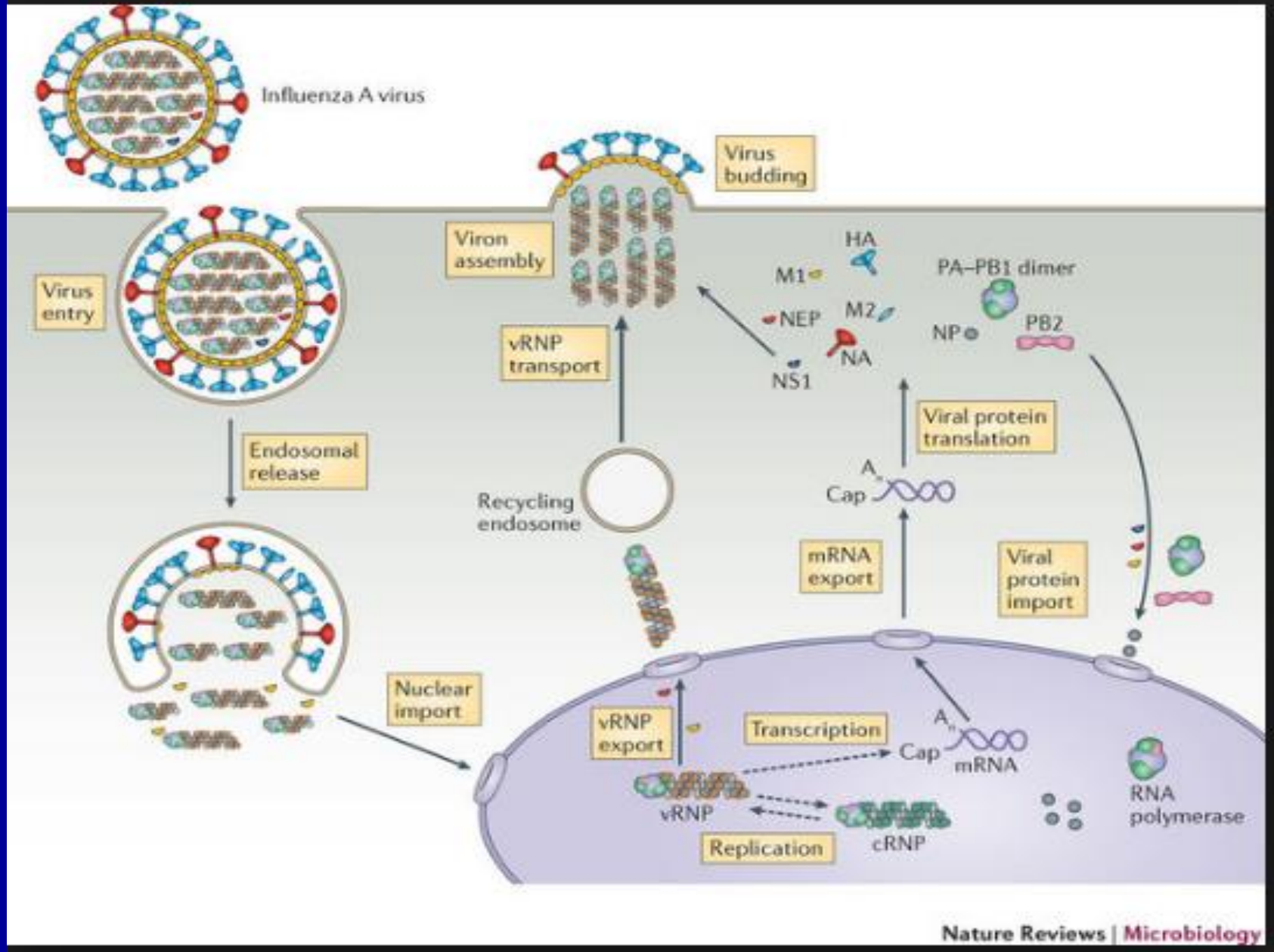
Courtesy of Linda Stannard,
Department of Medical Microbiology,
University of Cape Town



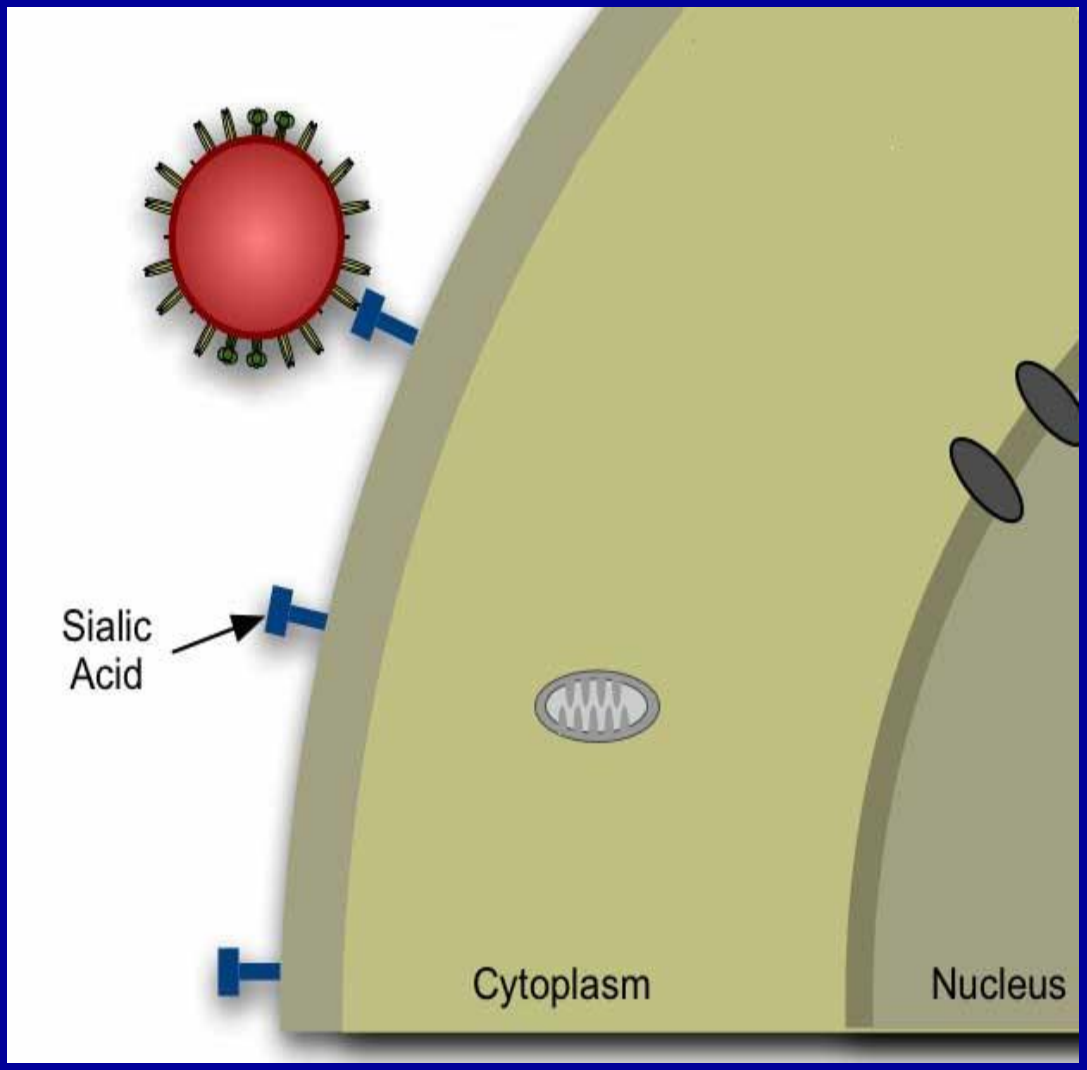
Courtesy of Linda Stannard,
Department of Medical Microbiology,
University of Cape Town

VIRUS LIFE CYCLE


a
Lipid envelope derived from host cell
M1
M2
NA
HA
PB2
PB1
PA
HA
NP
NA
M
NS
NS1
NS2
PB1-F2
N40
PA-X
PA-N155
PA-N182
M42
Non-structural and newly identified proteins
Viral RNP
PB2
PB1
PA
NP
vRNA
Polymerase complex
b
Fusion
Uncoating
Binding
Transcription
Protein synthesis
Replication
vRNP
Packaging
Assembly
Budding and release
Nucleus
Host receptors
(α2,3- or α2,6-linked sialic acid)
Nature Reviews | Microbiology


Influenza A virus
Virus budding
Viron assembly
Virus entry
HA
M1
PA–PB1 dimer
NEP
M2
NP
PB2
NA
NS1
vRNP transport
Viral protein translation
Endosomal release
Recycling endosome
Cap
mRNA export
Viral protein import
Nuclear import
vRNP export
Transcription
Cap
mRNA
RNA polymerase
vRNP
Replication
cRNP
Nature Reviews | Microbiology

RECEPTORS



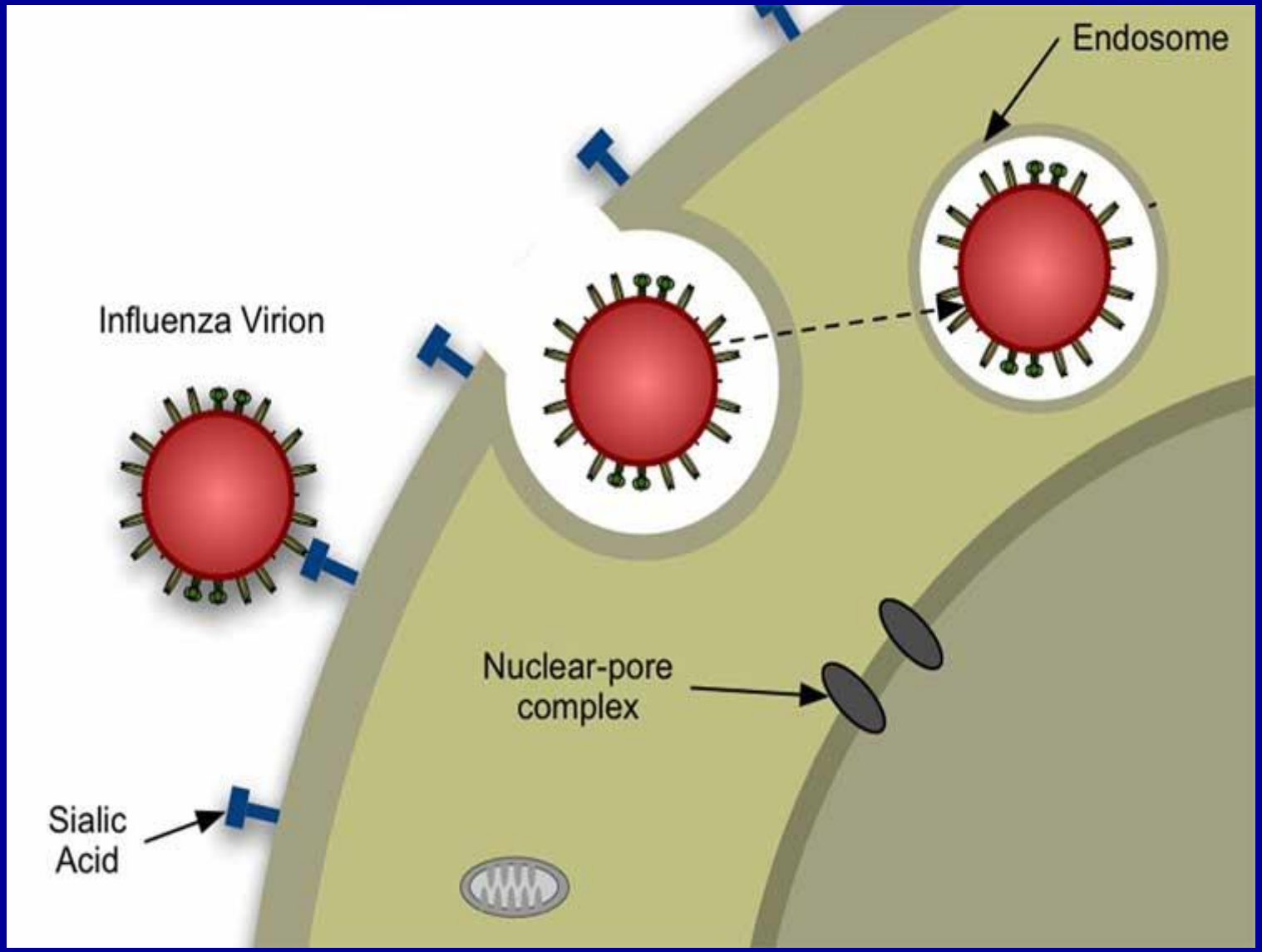
-Hemagglutinin binds to sialic acid
- glycolipids?
- specific proteins?

-Human cells – sialic acid in α2,6 linkage with galactose

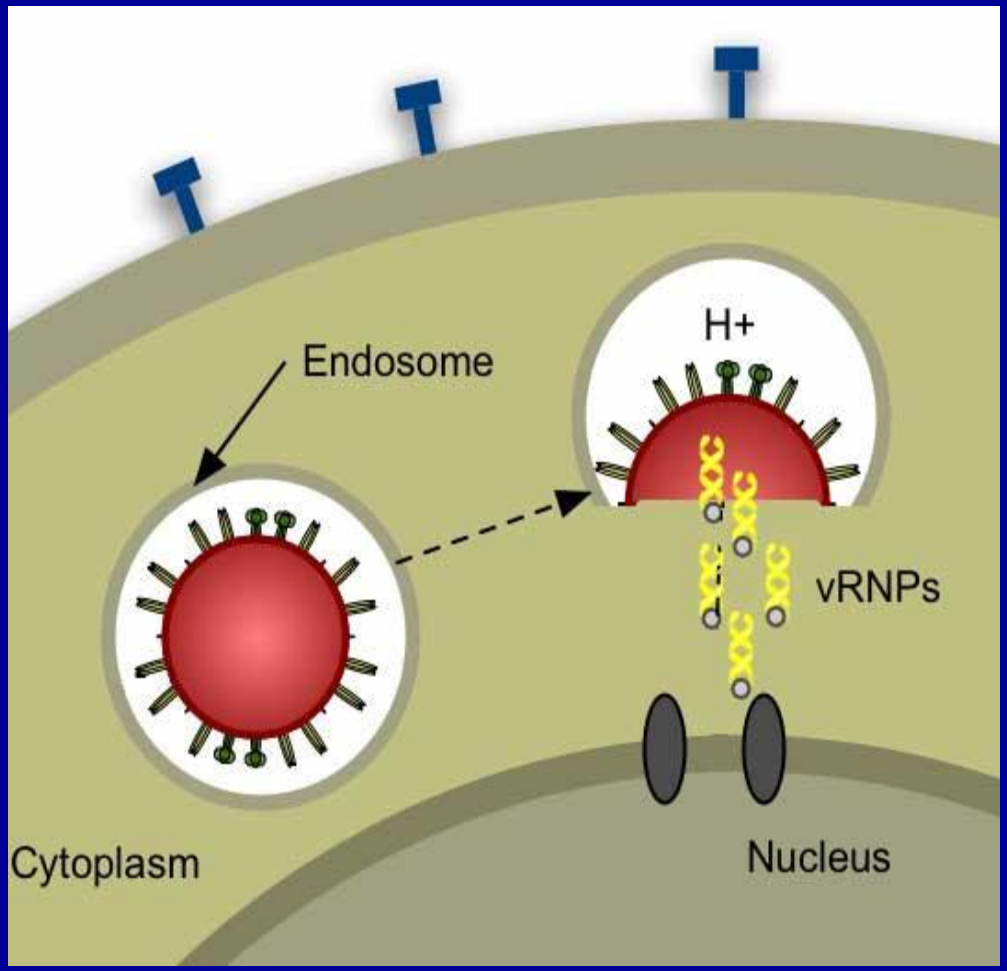
-In avian cells – sialic acid in α2,3 linkage with galactose

-In pig cells alpha 2,6 and α 2,3

INTERNALIZATION INTO ENDOSOMES



MEMBRANE FUSION

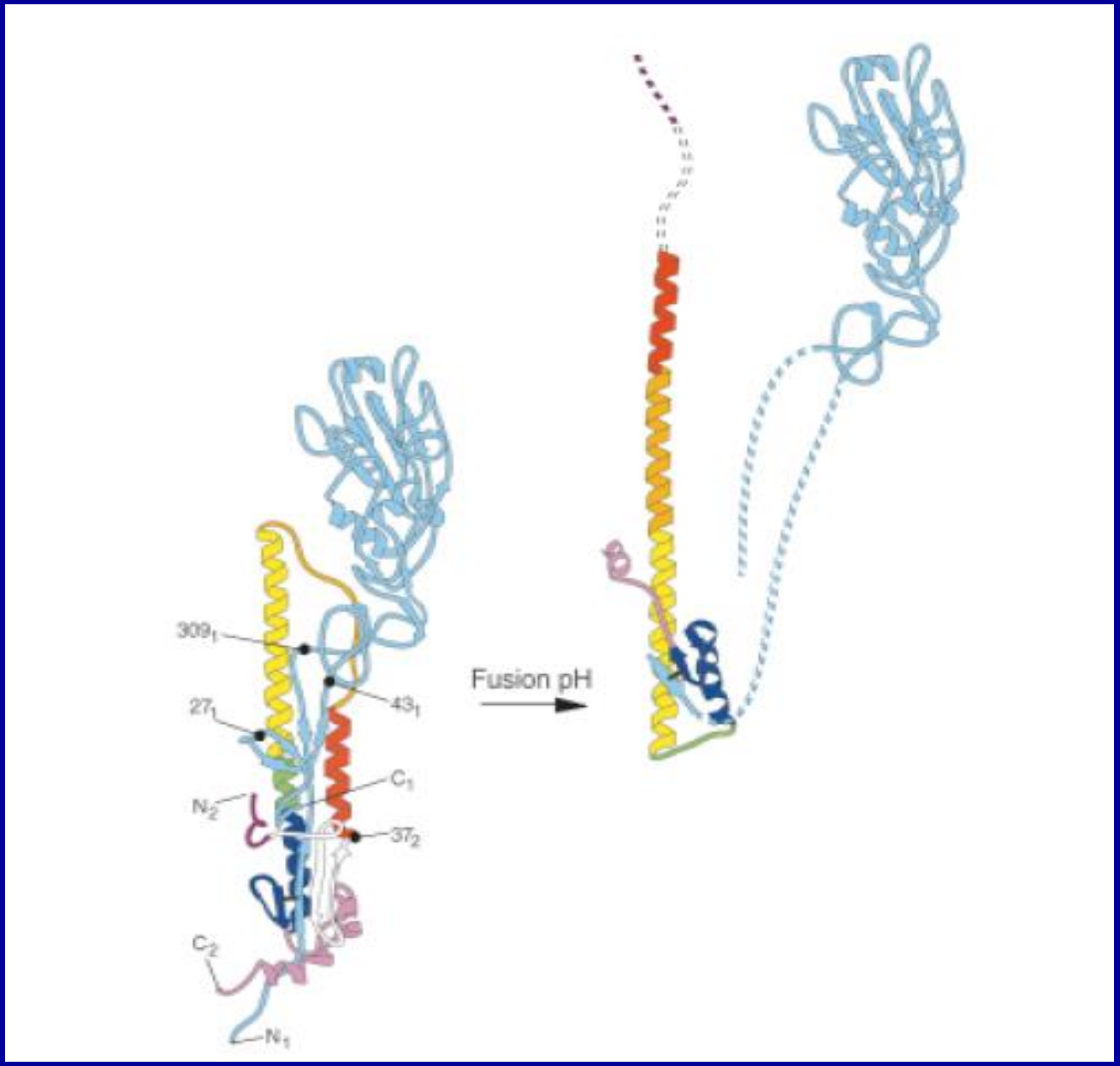


-Cleaved HA undergoes acidic-pH-triggered change and fuses membranes

-Ion channel in viral membrane composed of M2 proteins is activated by acidification

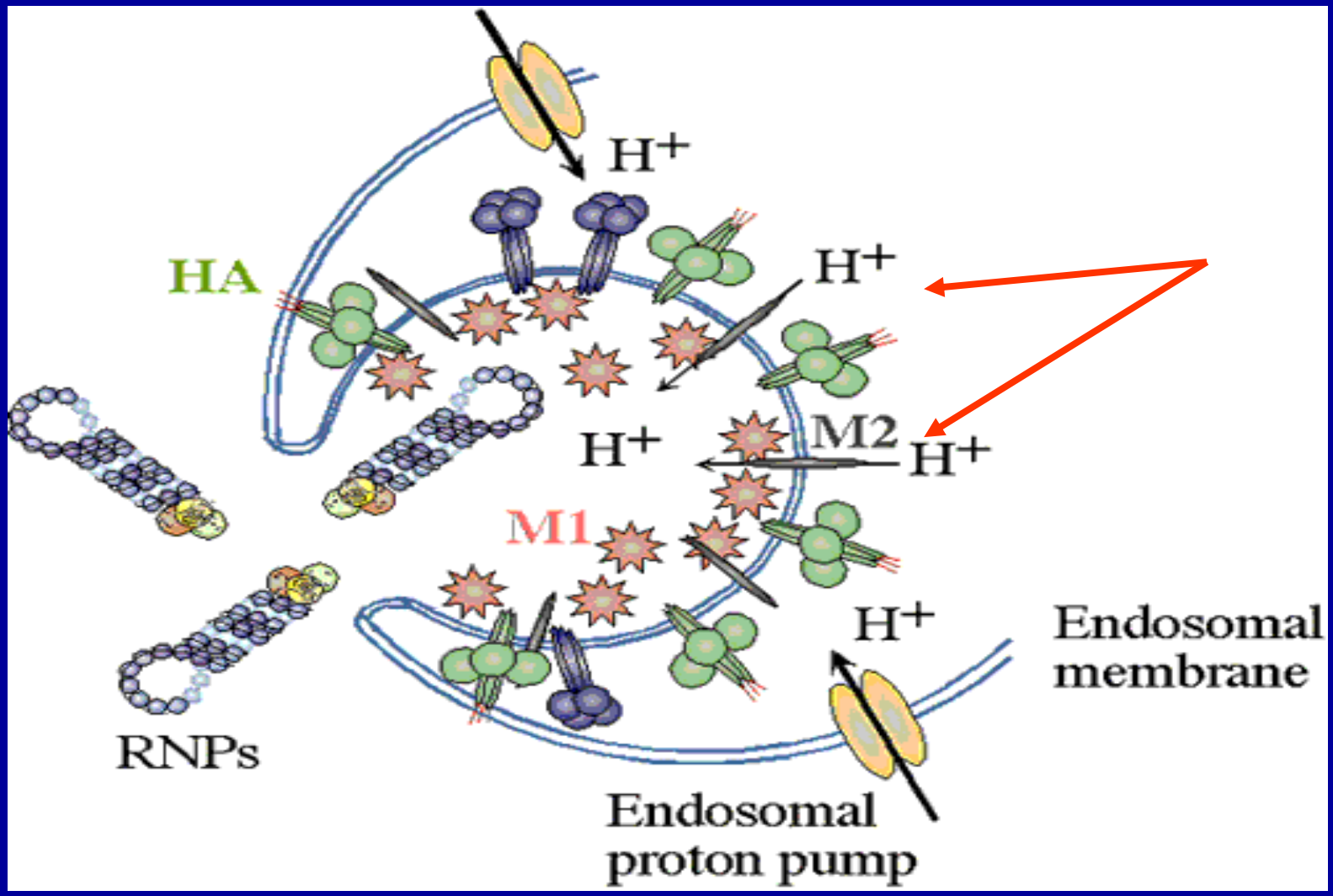
-Results in an influx of protons into virion interior facilitating uncoating of RNPs (ribonucleoproteins)

pH triggered conformational change of HA



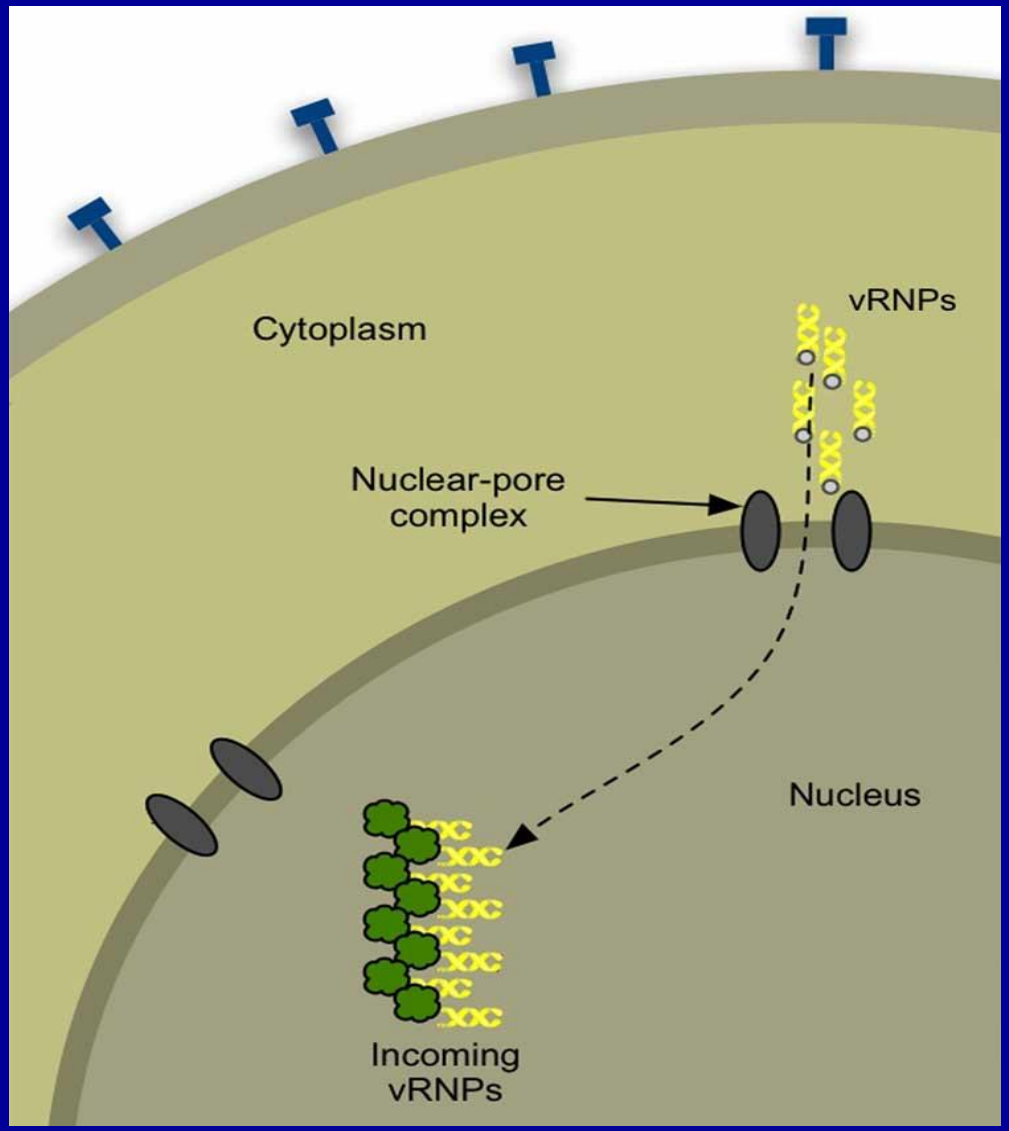
Skehel and Wiley
Ann. Rev. Biochem 2000

FUNCTION OF MP2 - PROTEIN CHANNEL IN VIRION

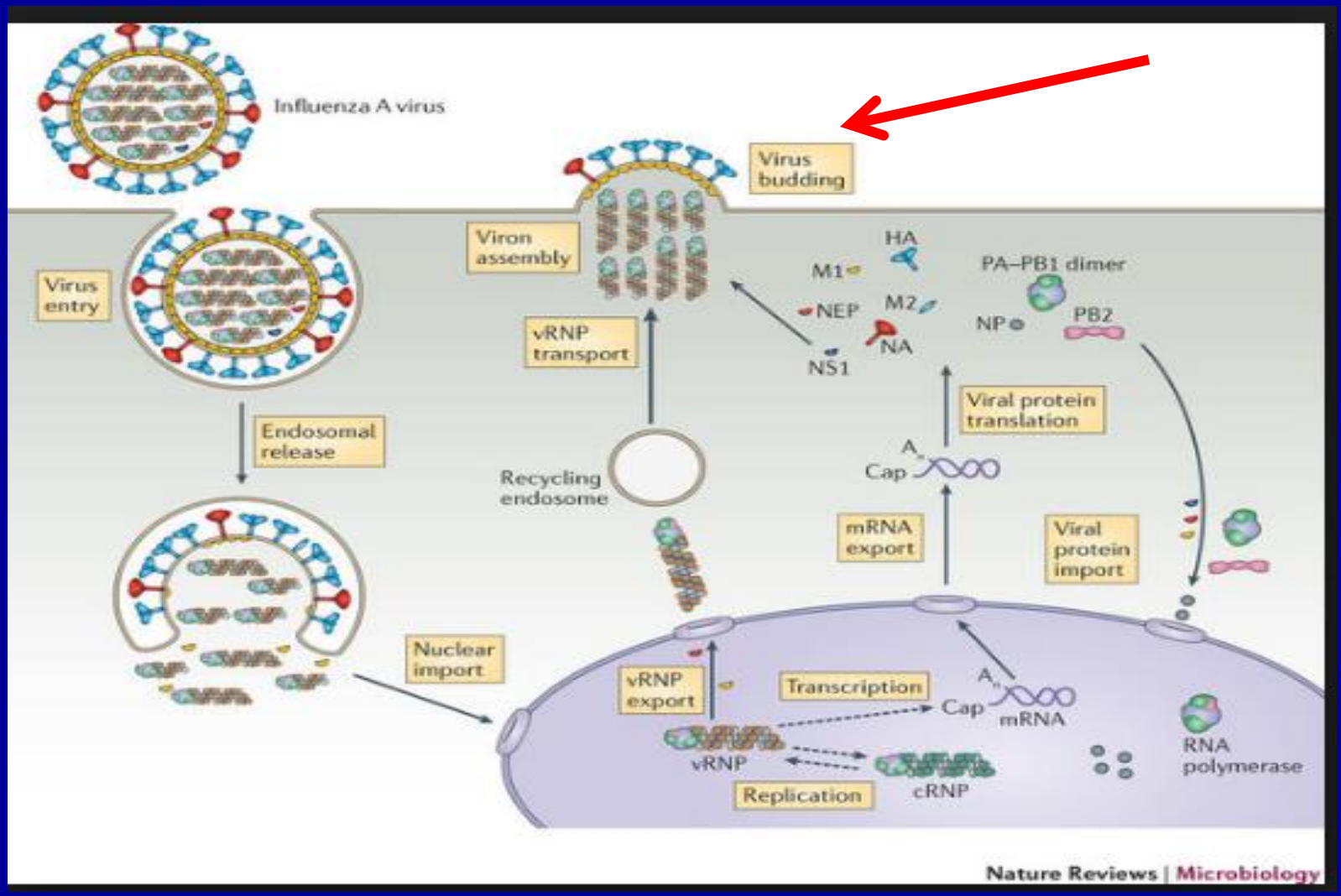


- M2 forms highly selective transmembrane ion channel
- Influx of protons facilitate uncoating of RNPs by weakening the matrix protein M1 and RNPs

TRANSPORT OF RNPs TO NUCLEUS

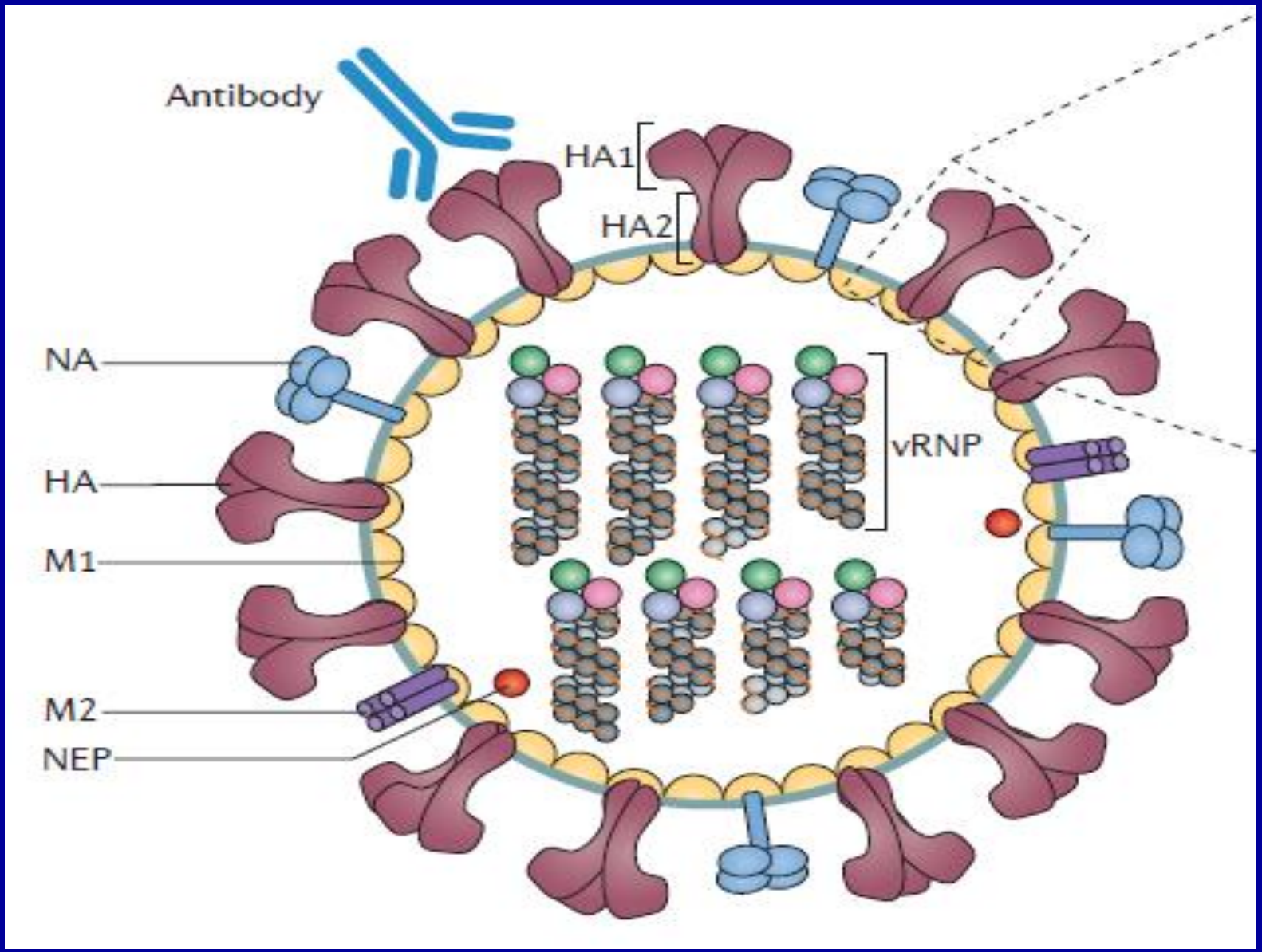


-Signals in NP protein guides the import of viral RNA into nucleus



-NA (neuraminidase) clears the virus and cell membrane from sialic acids:

- Without this the viruses stick to each other and the cell membrane. Virus can't get out.


Antibody
HA1
HA2
NA
HA
M1
M2
NEP
vRNP

PATHOGENESIS

- Once virus enters upper respiratory tract), it infects columnar epithelial cells and starts replicating causing cell death
- Virus replication and release initiates infection of nearby cells resulting in large numbers of cells releasing more virus and dying
- The incubation period (onset of illness and virus shedding)varies from 18-72 h depending on the initial virus inoculum. (Did somebody sneeze in the room or right on top of you.)

- **Virus replication causes**
  - **Expression of interferons, cytokines and other inflammatory agents leading to local and systemic inflammatory responses**
  - **Results flu-like symptoms: fever, headache, chills, malaise and muscle aches**

- **Influenza infection also damages bronchial epithelium and disrupts mucociliary clearance of bacteria increasing the risk of bacterial infections in pulmonary system (in lower respiratory tract)**
  - **In other words you are at greater risk of pneumonia (directly from the virus or from bacteria that are also present) and other lung infections. That is the real danger.**

TABLE 162-4 Comparative Features of Pulmonary Complications of Influenza

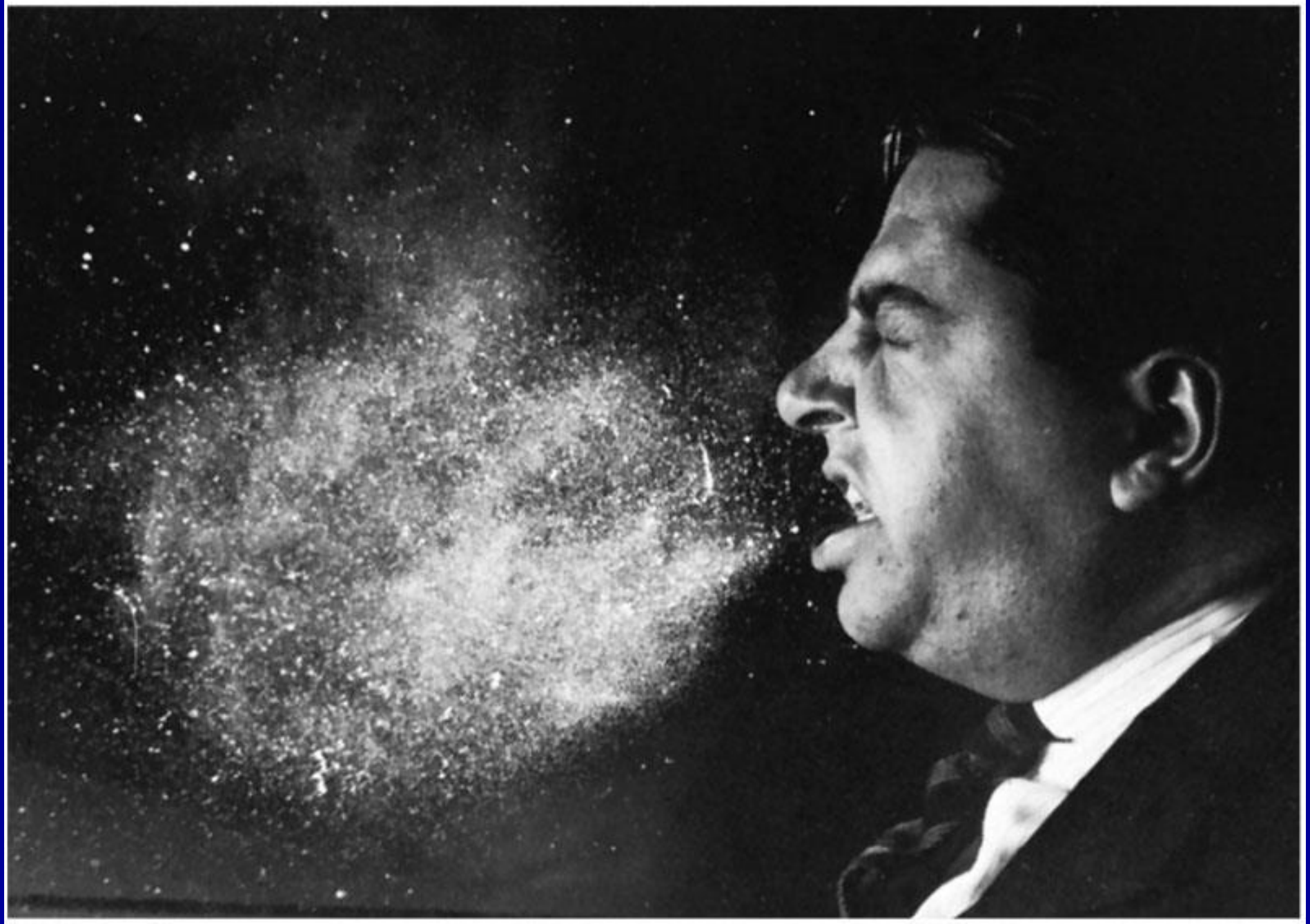
	Primary Viral Pneumonia	*Secondary Bacterial Pneumonia*	*Mixed Viral and Bacterial Pneumonia*	*Localized Viral Pneumonia*
Setting	Cardiovascular disease; pregnancy; young adult (Hsw1N1)	Age >65 yr; pulmonary disease	Any associated with A or B	?Normal
Clinical history	Relentless progression from classic 3-day influenza	Improvement, then worsening after 3-day influenza	Features of both primary and secondary pneumonia	Continuation of classic 3-day syndrome
Physical examination	Bilateral findings, no consolidation	Consolidation	Consolidation	Area of rales
Sputum bacteriology	Normal flora	*Pneumococcus, Staphylococcus, Haemophilus influenzae*	*Pneumococcus, Staphylococcus, H. influenzae*	Normal flora
Chest radiography	Bilateral findings	Consolidation	Consolidation	Segmental infiltrate
White blood cell count	Leukocytosis with a shift to the left	Leukocytosis with a shift to the left	Leukocytosis with a shift to the left	Usually normal
Isolation of influenza virus	Yes	No	Yes	Yes
Response to antibiotics	No	Yes	Often	No
Mortality	High	Low	Variable	Very low

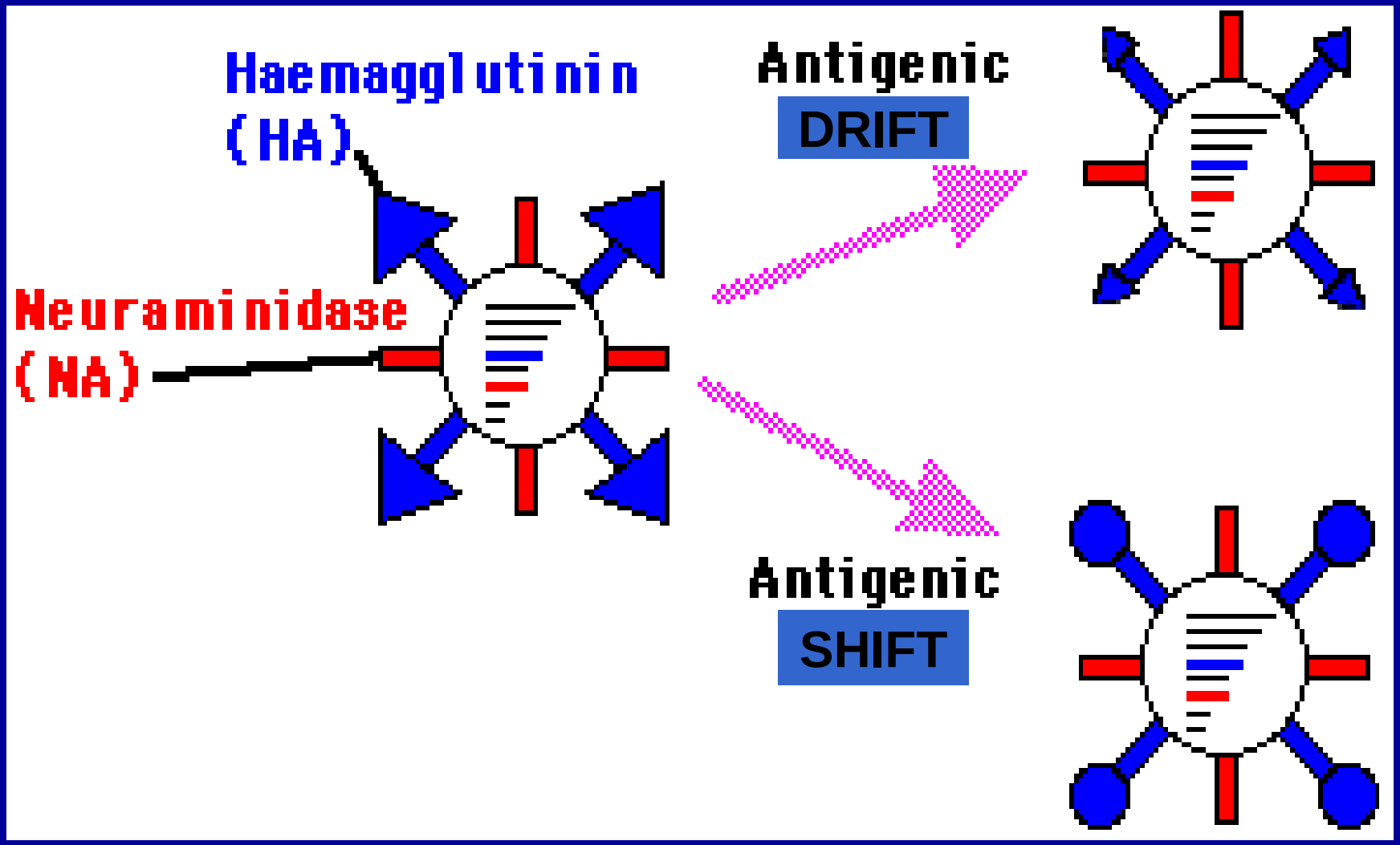
Pulmonary consolidation: A pulmonary consolidation is a region of (normally compressible) lung tissue that has filled with liquid instead of air. The condition is marked by induration (swelling or hardening of normally soft tissue) of a normally aerated lung.

EPIDEMIOLOGY

Transmission

- Influenza viruses have a worldwide distribution and cause outbreaks of variable intensity annually
- Virus spreads from person to person by airborne droplets during coughing, sneezing or speaking
- Zoonotic influenza is also spread by the respiratory route
- Remain infectious for 24 hours after aerosolization under low level of humidity (Winter)
- Becomes noninfectious after 1 hour at high humidity
- (Summer)




Haemagglutinin
(HA)
Neuraminidase
(NA)
Antigenic
DRIFT
Antigenic
SHIFT

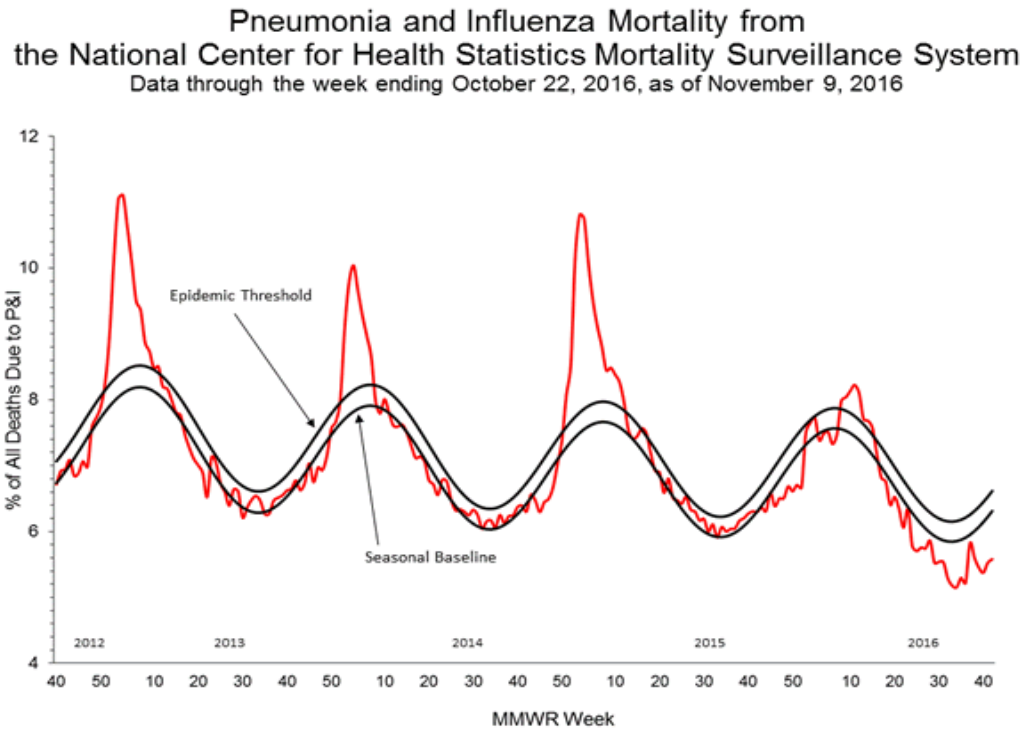
Antigenic drift

Pneumonia and Influenza (P&I) Mortality Surveillance:

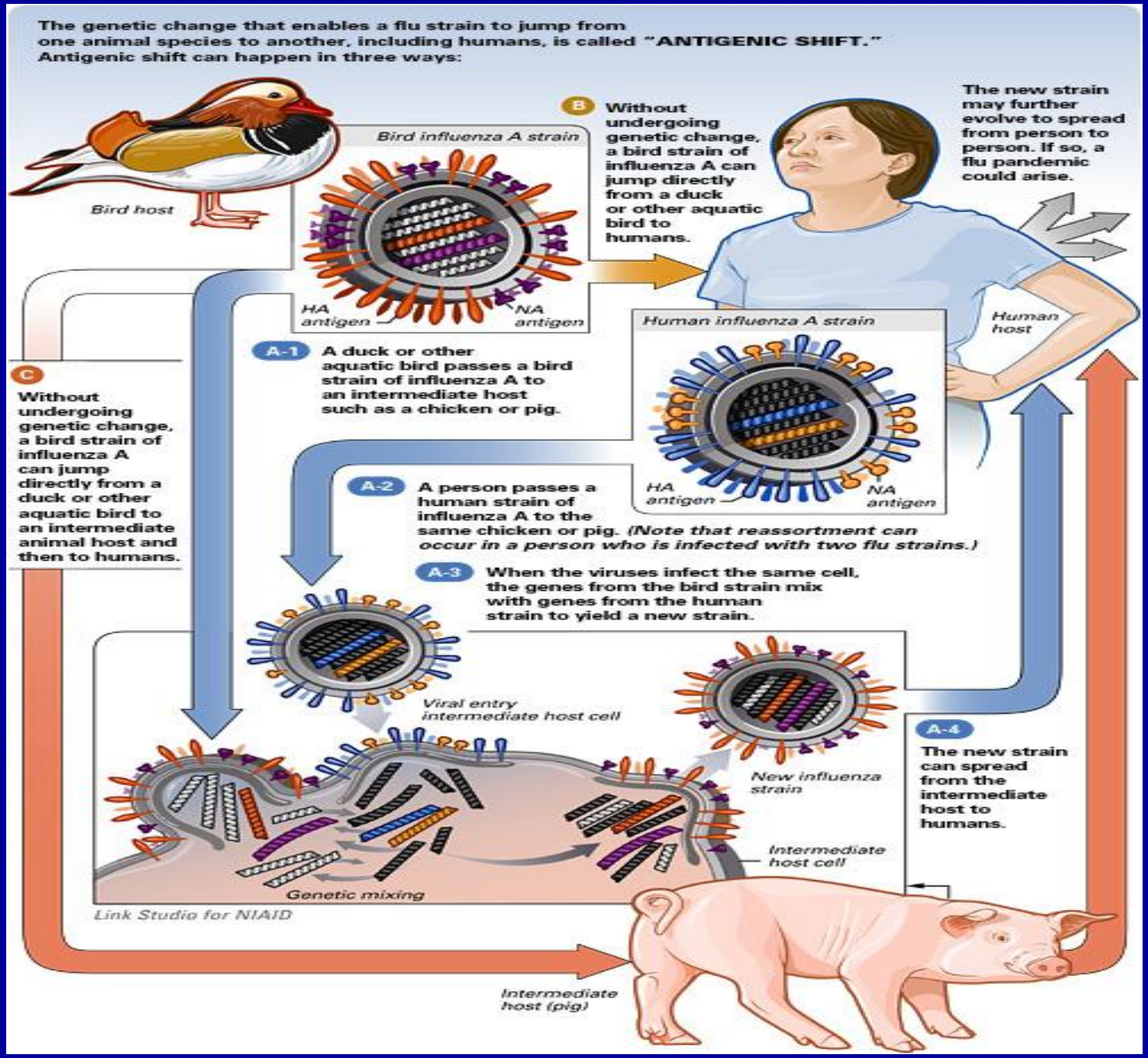
Based on National Center for Health Statistics (NCHS) mortality surveillance data available on November 9, 2016, 5.6% of the deaths occurring during the week ending October 22, 2016 (week 42) were due to P&I. This percentage is below the epidemic threshold of 6.6% for week 42.

P&I percentages for recent weeks may be artificially low due to a backlog of records requiring manual processing. Percentages will likely increase to levels more similar to the baseline as more data becomes available.

Region and state-specific data are available at http://gis.cdc.gov/grasp/fluview/mortality.html.



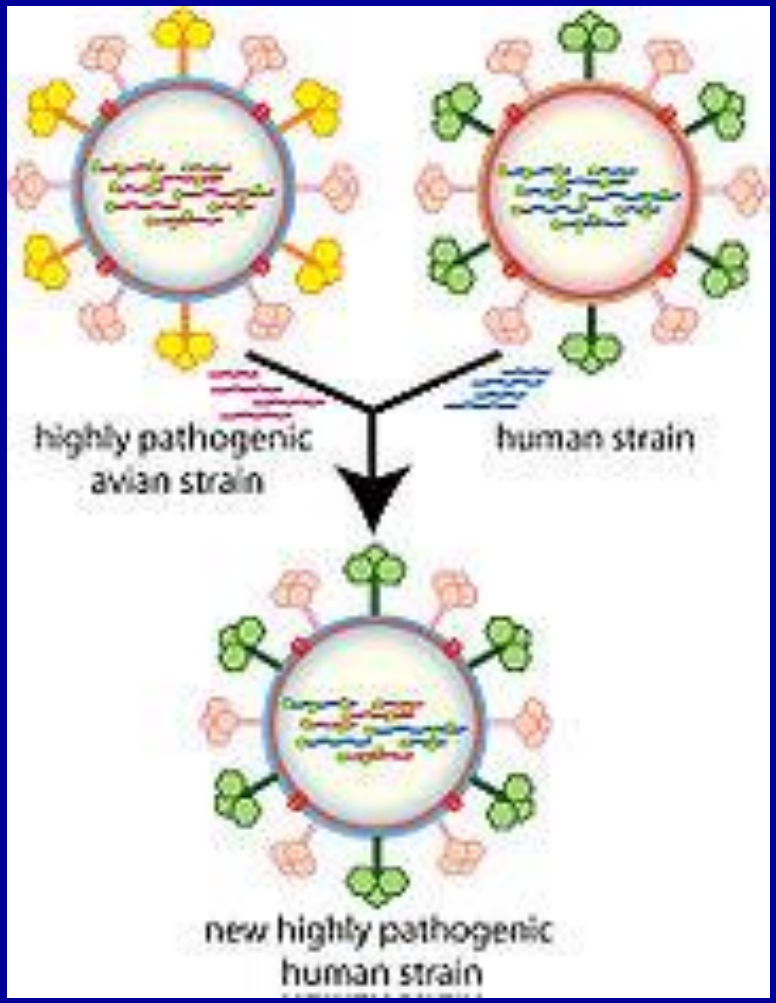
The influenza season reaches an epidemic level when the proportion of deaths attributed to pneumonia and influenza exceeds 6.6%



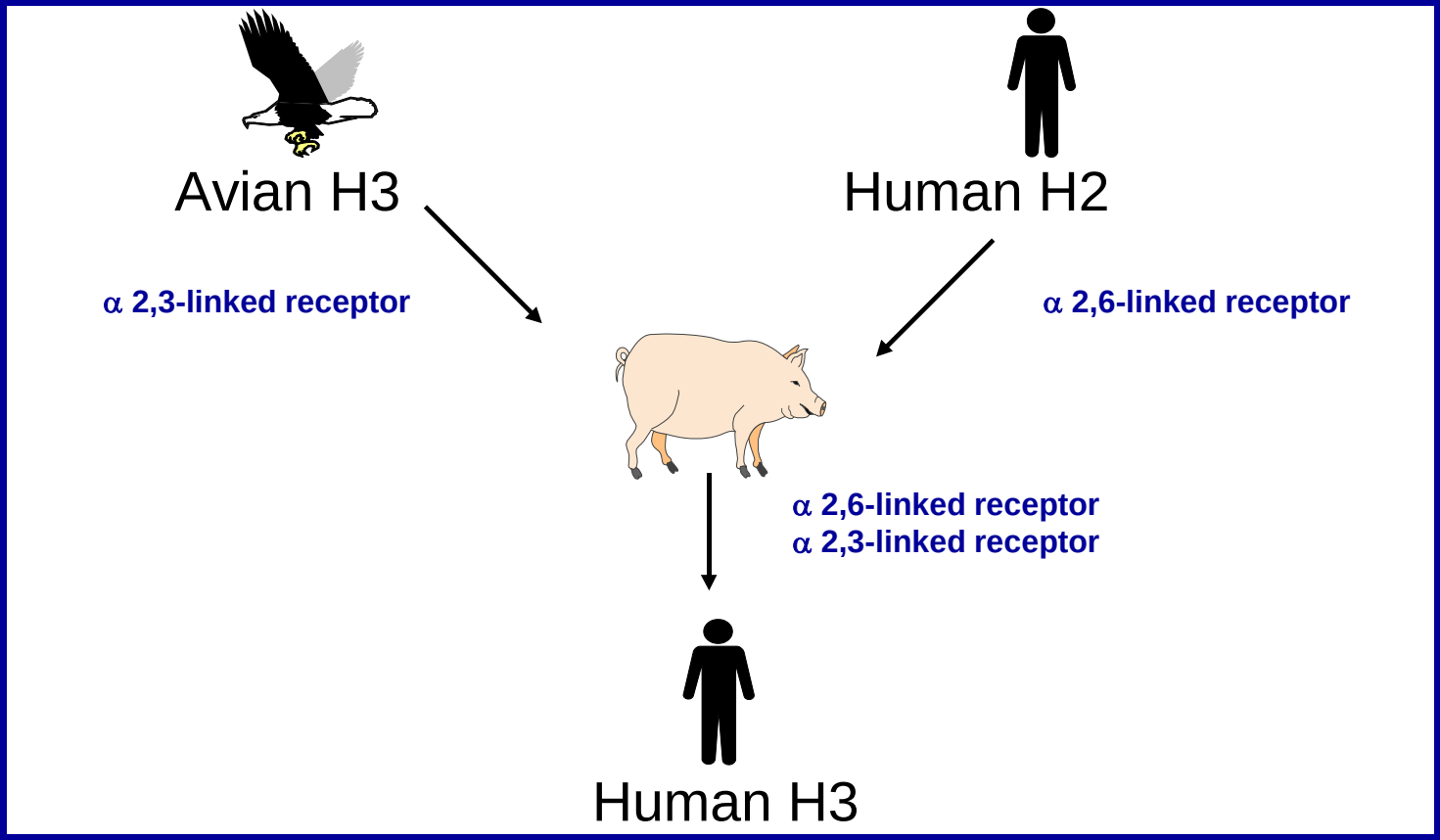
Courtesy of NIAID

Antigenic Shift

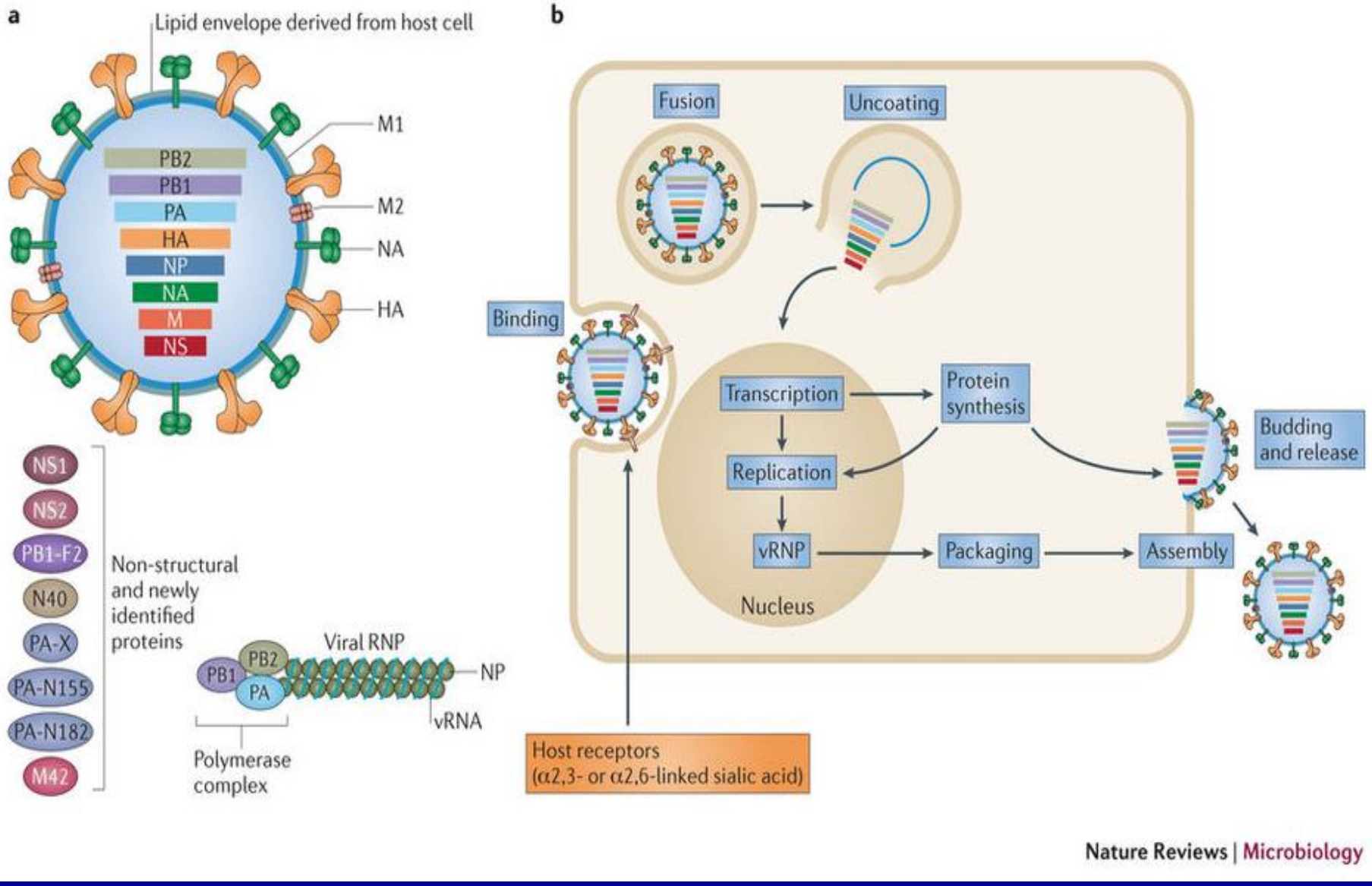
- Two or more types of virus can infect the same cell at the same time.
- This results in packaging viruses with different vRNPs making a new variant.



ANTIGENIC SHIFT
Reassortment



See next slide!

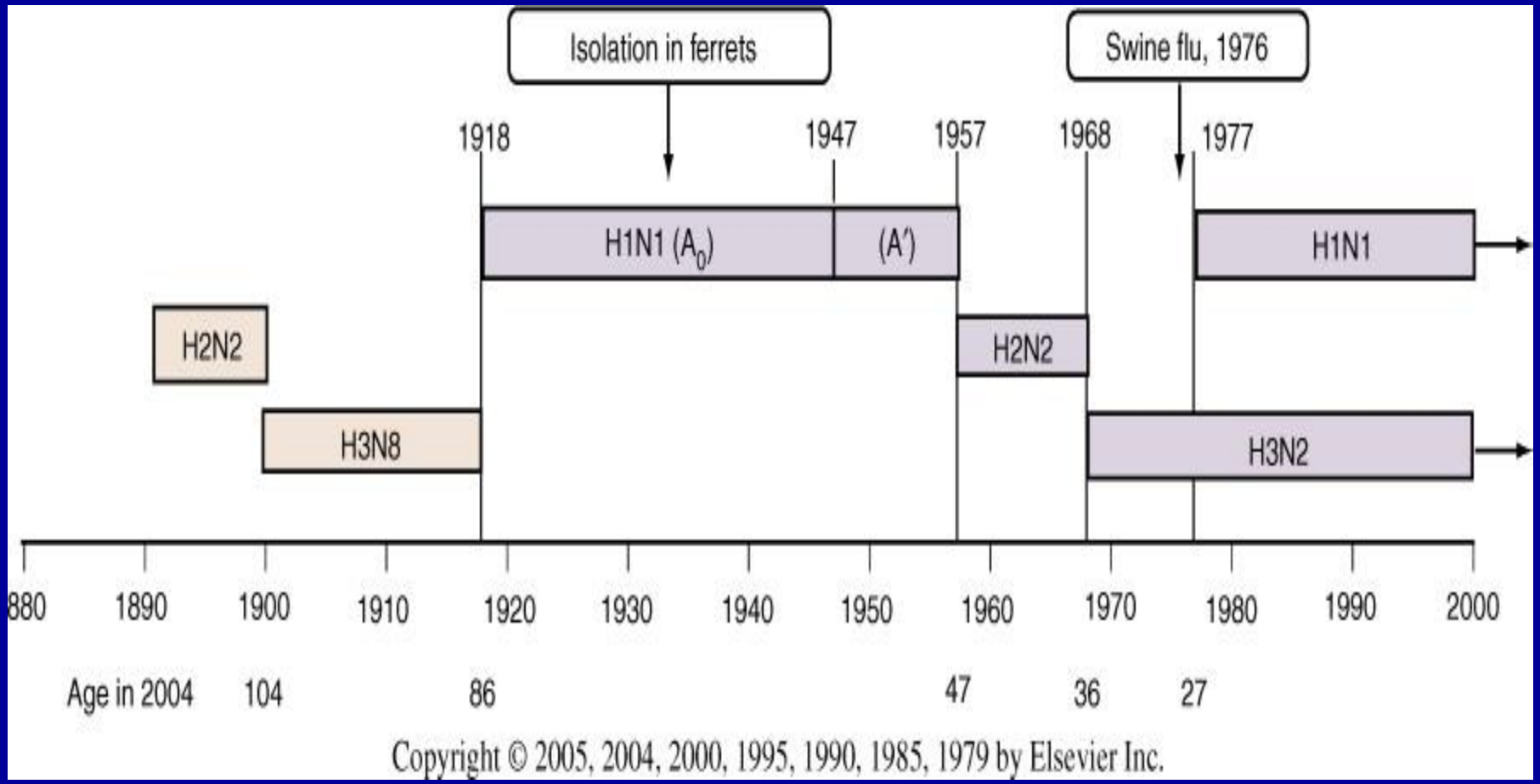

a
Lipid envelope derived from host cell
M1
M2
NA
HA
PB2
PB1
PA
HA
NP
NA
M
NS
NS1
NS2
PB1-F2
N40
PA-X
PA-N155
PA-N182
M42
Non-structural and newly identified proteins
Viral RNP
PB2
PB1
PA
NP
vRNA
Polymerase complex
b
Fusion
Uncoating
Binding
Transcription
Protein synthesis
Replication
vRNP
Packaging
Assembly
Budding and release
Nucleus
Host receptors
(α2,3- or α2,6-linked sialic acid)
Nature Reviews | Microbiology

Epidemiology

- Pandemics - influenza A pandemics arise when a virus with a new haemagglutinin subtype (with or w/o NA) emerges as a result of antigenic shift. As a result, the population has no immunity against the new strain. Antigenic shifts had occurred 3 times in the 20th century.

- Epidemics - epidemics of influenza A and B arise through more minor antigenic drift as a result of mutation.

PANDEMICS

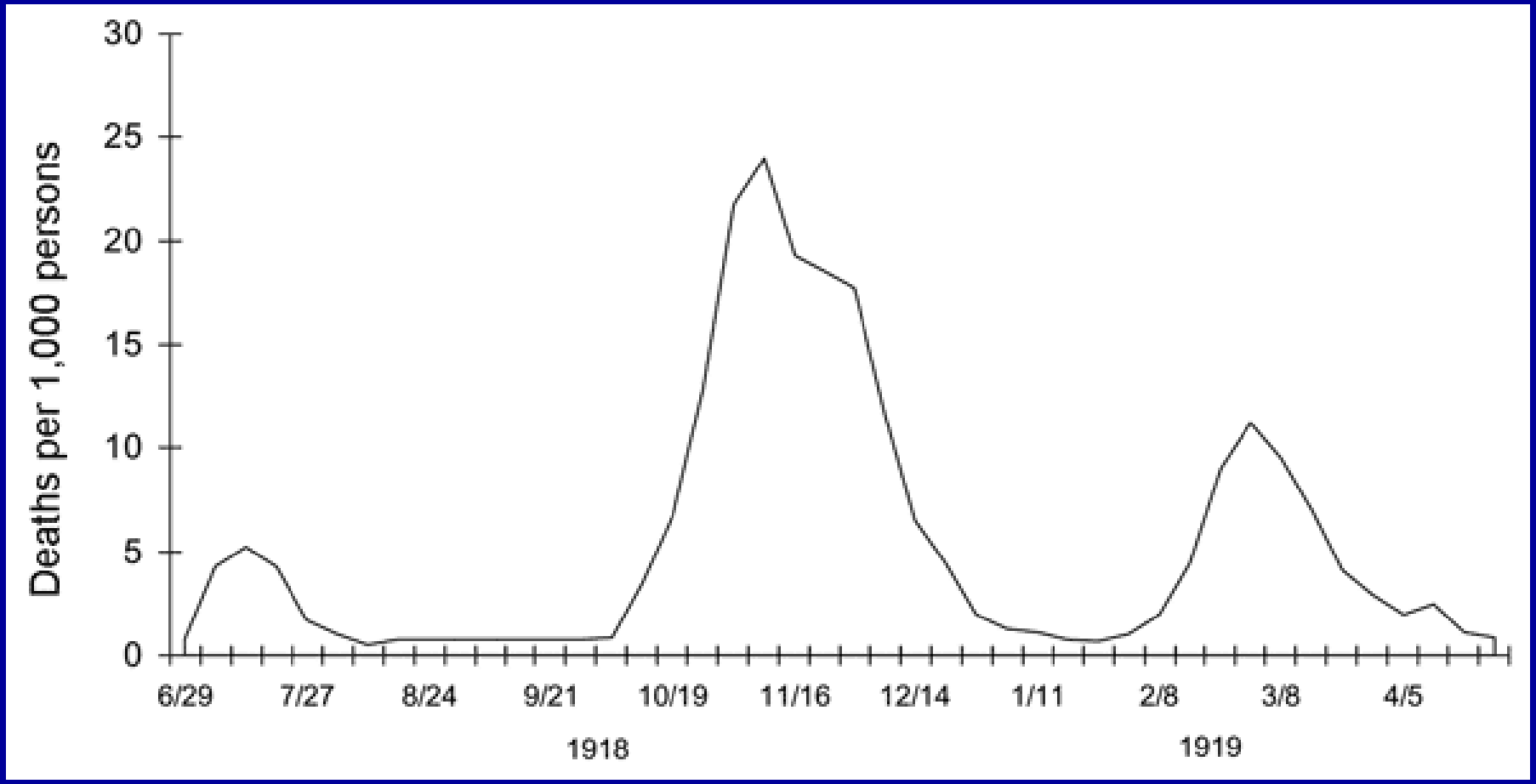


-1918 H1N1 gradually adapted from avian influenza to human transmission (direct)
-1957 H2N2 virus resulted from H1N1 acquiring new segments (NA,HA, PB1) from avian origin (through swine)
-1968 H3N2 was formed by acquisition of HA and PB1 from avian virus (through swine)
-1977 H1N1 reintroduction by unknown mechanism

1918 INFLUENZA

H1N1 Pandemic

Figure 1. Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919



Jeffery K. Taubenberger* and David M. Morens
Volume 12, Number 1, January 2006
Emerging infectious diseases

"Emergency hospital during 1918 influenza epidemic, Camp Funston, Kansas"

Courtesy of the National Museum of Health and Medicine,

Armed Forces Institute of Pathology, Washington, D.C., Image NCP 1603

U.S. Army Camp Hospital No. 45, Aix-Les-Bains, France, Influenza Ward No. 1, 1918"

Courtesy of the National Museum of Health and Medicine,

Armed Forces Institute of Pathology, Washington, D.C., Image Reeve 14682

"U.S. Army Field Hospital No. 29, Hollerich, Luxembourg, Interior View - Influenza Ward, 1918"

Courtesy of the National Museum of Health and Medicine,

Armed Forces Institute of Pathology, Washington, D.C., Image Reeve 15183

"Influenza Avenue, 1918 influenza epidemic"

Courtesy of the National Museum of Health and Medicine,

Armed Forces Institute of Pathology, Washington, D.C., Image Smith 18

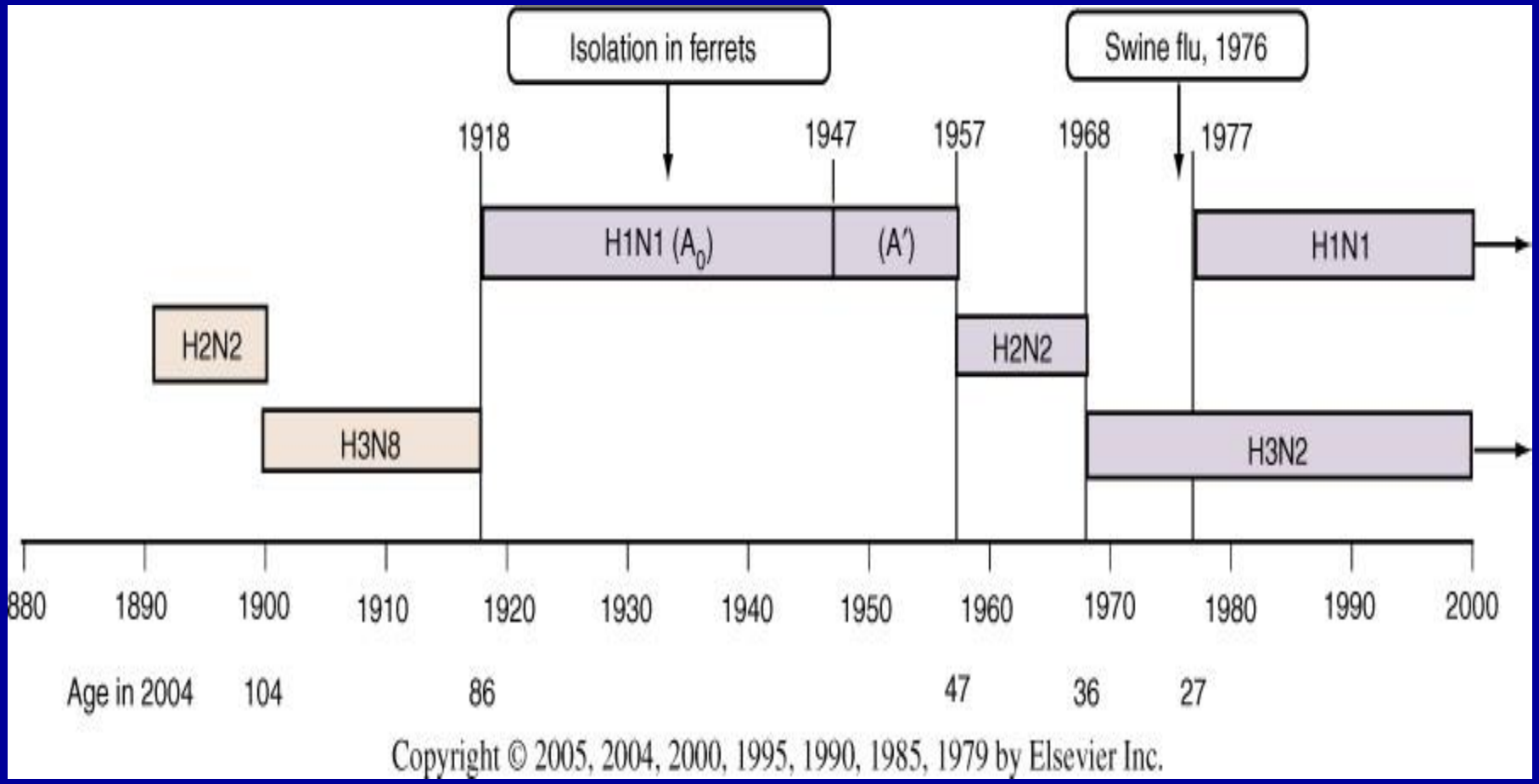
"Convalescing, 1918 influenza epidemic"

Courtesy of the National Museum of Health and Medicine,

Armed Forces Institute of Pathology, Washington, D.C., Image Smith 3

Past Antigenic Shifts

1918	**H1N1**	**“Spanish Influenza”**	**~ 50-100 million deaths**
1957	**H2N2**	**“Asian Flu”**	**1-2 million deaths**
1968	**H3N2**	**“Hong Kong Flu”**	**700,000 deaths**
1977	**H1N1**	**Re-emergence**	**No pandemic**



-H1N1 resurfaced at 1977 affecting mostly people under age of ~25 yrs. (borne after 1957) since they did not have immunity

-similarly H2N2 surfaced 1957 and disappeared 1968 – thus, if H2N2 resurfaces (like H1N1 did), people who have borne after 1968 do not have immunity against it

WHO STAGES OF PANDEMIC

March 2009

ALERT: PHASE 3

Inter-pandemic phase New virus in animals, no human cases	Low risk of human cases	1
	Higher risk of human cases	2
Pandemic alert New virus causes human cases	No or very limited human-to-human transmission	3
	Evidence of increased human-to-human transmission	4
	Evidence of significant human-to-human transmission	5
Pandemic	Efficient and sustained human-to-human transmission	6

WHO STAGES OF PANDEMIC

Thursday 5.6.2010

ALERT: PHASE 6

(Because of 2009 H1N1)

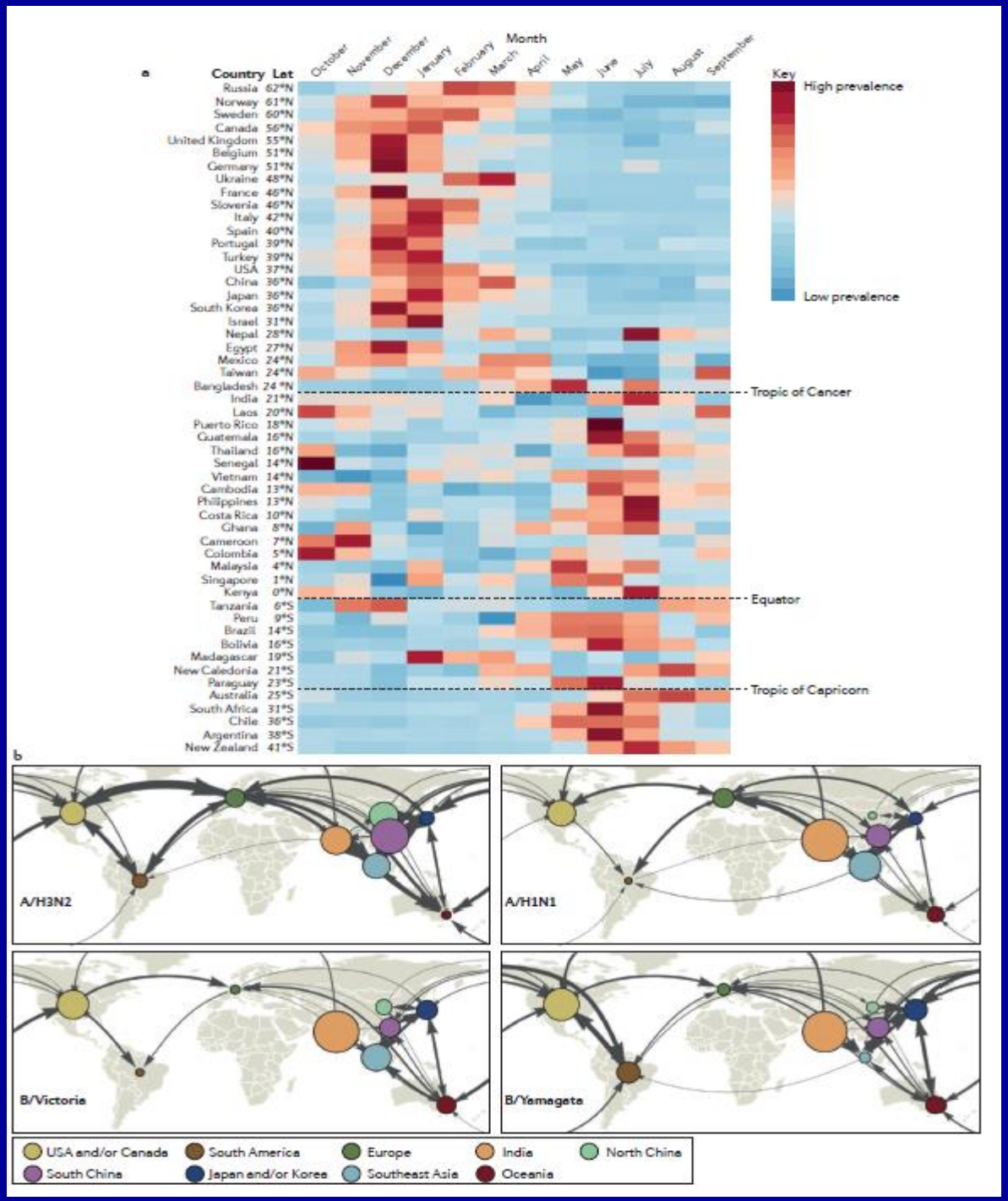
A Novel H1N1

- A quadruple reaasortment virus combo of swine, avian, and human (Asian and NA)
- Started in US/MEX in April 2009; pig to person then person to person. 41% hospitalization rate and hit all ages evenly – unusual.
- There was much media attention caused by the CDC (huge and expensive preparedness and vaccine production) but it did not turn out to be more lethal than the regular yearly epidemics
- Worldwide, from April 2009 to 2010 there were 10 - 200 million infected and 18K to 280K deaths.
- Huge variation in the estimates is because it is very hard to determine if a pneumonia death is also a flu death.
- The British Medical Journal and others have pointed out many WHO experts who declared the pandemic are on the payroll of Big Pharma. Direct conflict of interest. Hard to find experts that don't work for Big Pharma.

EPIDEMIC INFLUENZA

EPIDEMIC INFLUENZA

- Occurs annually most often during the winter and early spring
- Seasonal (low humidity, enclosed spaces)
  - Reintroduction of virus each season
  - Behavioral factors influencing exposure (school attendance, indoor crowding, air travel on the holidays)
- In Northern hemisphere typically between October to April: peak December-March
- In Southern hemisphere typically peaks between May to August (If they have a bad winter, we probably will too.)


a
Country Lat
Month
October
November
December
January
February
March
April
May
June
July
August
September
Key
High prevalence
Low prevalence
Russia 62°N
Norway 61°N
Sweden 60°N
Canada 56°N
United Kingdom 55°N
Belgium 51°N
Germany 51°N
Ukraine 48°N
France 46°N
Slovenia 46°N
Italy 42°N
Spain 40°N
Portugal 39°N
Turkey 39°N
USA 37°N
China 36°N
Japan 36°N
South Korea 36°N
Israel 31°N
Nepal 28°N
Egypt 27°N
Mexico 24°N
Taiwan 24°N
Bangladesh 24 °N
Tropic of Cancer
India 21°N
Laos 20°N
Puerto Rico 18°N
Guatemala 16°N
Thailand 16°N
Senegal 14°N
Vietnam 14°N
Cambodia 13°N
Philippines 13°N
Costa Rica 10°N
Ghana 8°N
Cameroon 7°N
Colombia 5°N
Malaysia 4°N
Singapore 1°N
Kenya 0°N
Equator
Tanzania 6°S
Peru 9°S
Brazil 14°S
Bolivia 16°S
Madagascar 19°S
New Caledonia 21°S
Paraguay 23°S
Tropic of Capricorn
Australia 25°S
South Africa 31°S
Chile 36°S
Argentina 38°S
New Zealand 41°S
b
A/H3N2
A/H1N1
B/Victoria
B/Yamagata
USA and/or Canada
South America
Europe
India
North China
South China
Japan and/or Korea
Southeast Asia
Oceania

- **In a given region outbreaks usually peak in ~ 3 weeks and are short duration, 6-10 weeks**

- **Successive or overlapping waves of infection by different type A and type B viruses may prolong the season**

- **The isolation of an antigenically drifted virus late in the spring months during limited outbreaks may foreshadow an epidemic in the next season (impact on decision of vaccine components)**

IN USA

TABLE 162-3 Estimated Excess Pneumonia- and Influenza-Related Deaths and Excess Mortality of All Causes during Influenza Epidemics

Year	Percent of Isolates That Were of the Following (Sub) Type			Pneumonia- and Influenza-Related Excess Deaths (Range)	All-Cause Excess Deaths (Range)
	H3N2	H1N1	B		
1972/73	90	0	10	7900 (5500-10,300)	18,300 (1200-35,000)
1973/74	20	0	80	0 0	0 0
1974/75	100	0	0	6500 (4100-8900)	15,100 (0-32,100)
1975/76	70	0	30	11,800 (9200-14,400)	24,600 (3400-45,900)
1976/77	5	0	95	0 0	0 0
1977/78	60	26	14	8300 (6000-10,500)	46,200 (19,800-72,700)
1978/79	0	98	2	0 0	0 0
1979/80	2	1	97	5100 (3500-6700)	17,300 (600-34,100)
1980/81	77	23	0	11,700 (9100-14,200)	47,200 (27,800-66,600)
1981/82	1	24	75	2100 (600-3700)	0 0
1982/83	79	10	11	4700 (2800-6700)	9600 (0-19,200)
1983/84	5	50	45	3500 (1600-5400)	8200 (0-17,600)
1984/85	97	0	3	8100 (6600-9600)	36,200 (17,700-54,700)
1985/86	24	0	76	6700 (4900-8500)	34,000 (6800-61,200)
1986/87	—	—	—	1800 (1100-2500)	16,800 (1900-31,700)
1987/88	0	80	20	7400 (5600-9100)	33,400 (12,900-53,800)
1988/89	45	45	10	5100 (3600-6600)	10,500 (800-20,200)
1989/90	90	1	9	10,100 (8500-11,700)	43,600 (27,600-59,600)
1990/91	4	3	93	4200 (2400-6100)	23,000 (0-46,000)
1991/92	19	81	0	6600 (5600-7700)	41,700 (19,600-63,700)

Data from Table 153-3 in Treaner JL. Influenza virus. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, ed. 5. Philadelphia: Saunders; 2000:1826; and Simonsen L, Clarke MJ, Williamson DW, et al. The impact of influenza epidemics on mortality. Introducing a severity index. Am J Public Health. 1947;87:1944-1950.

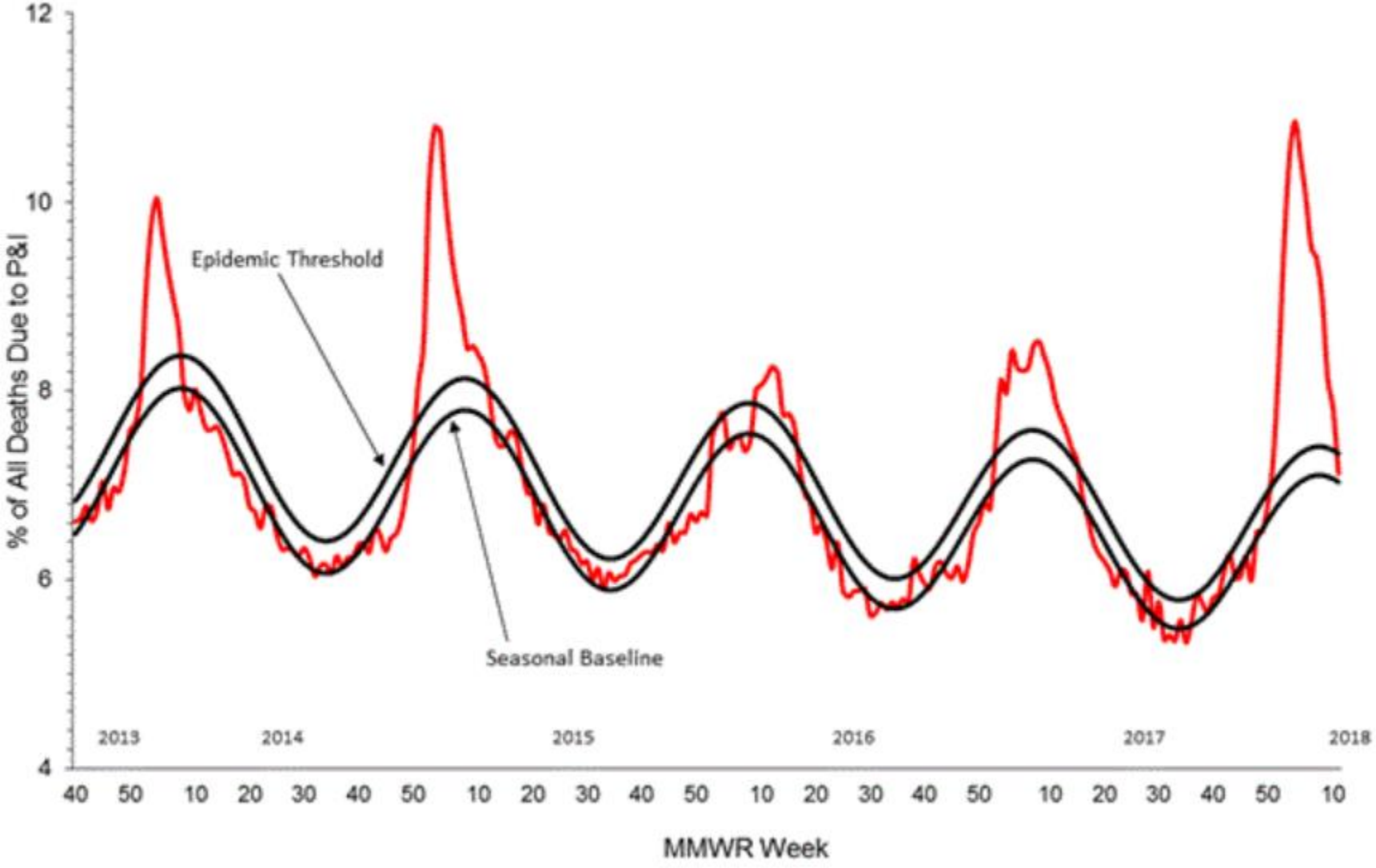
-Recent studies estimate that influenza-related deaths might be as high as ~ 60 000/year

- World wide causes hundreds of thousands of deaths

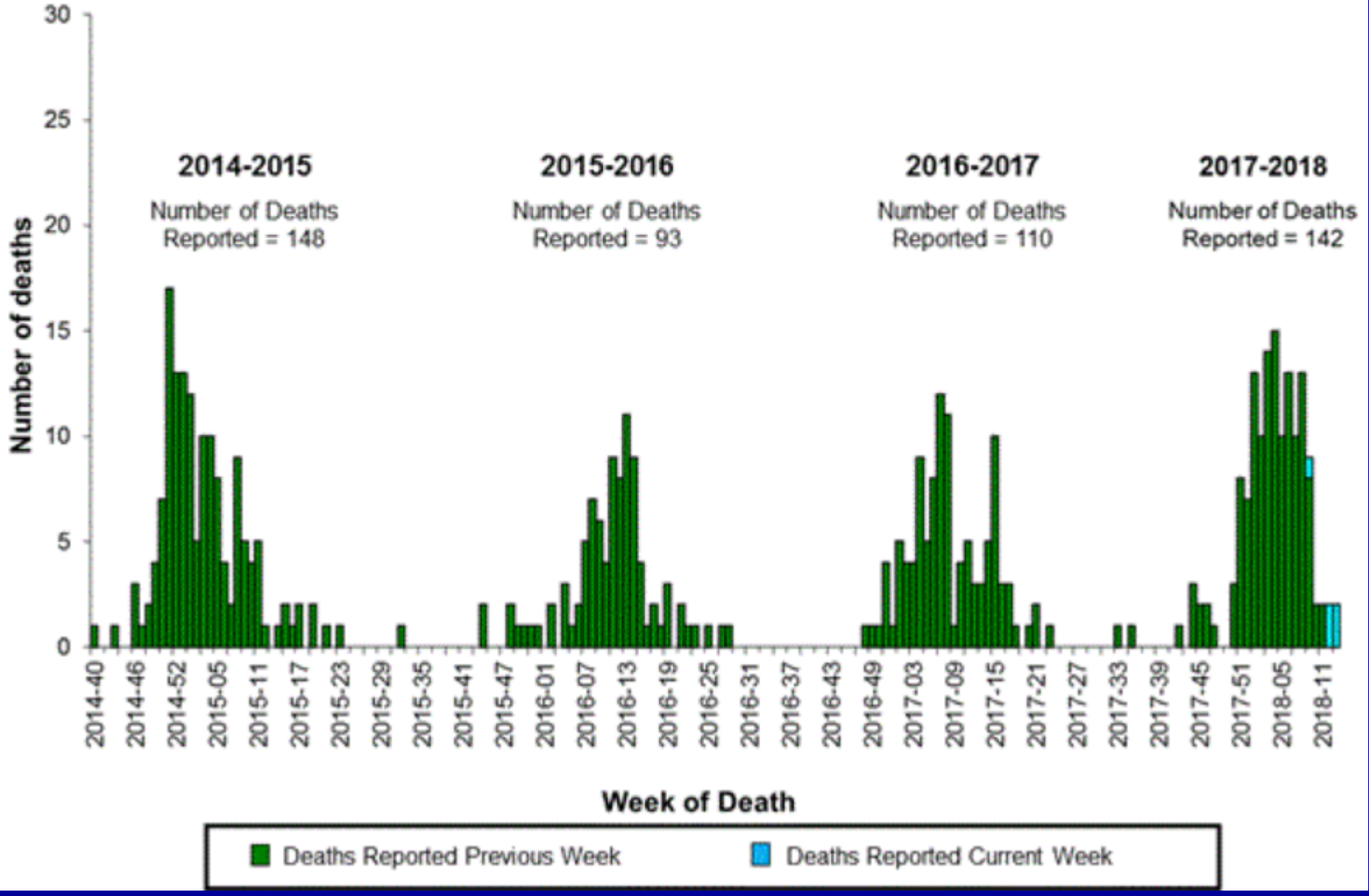
2017 to 2018 SEASON

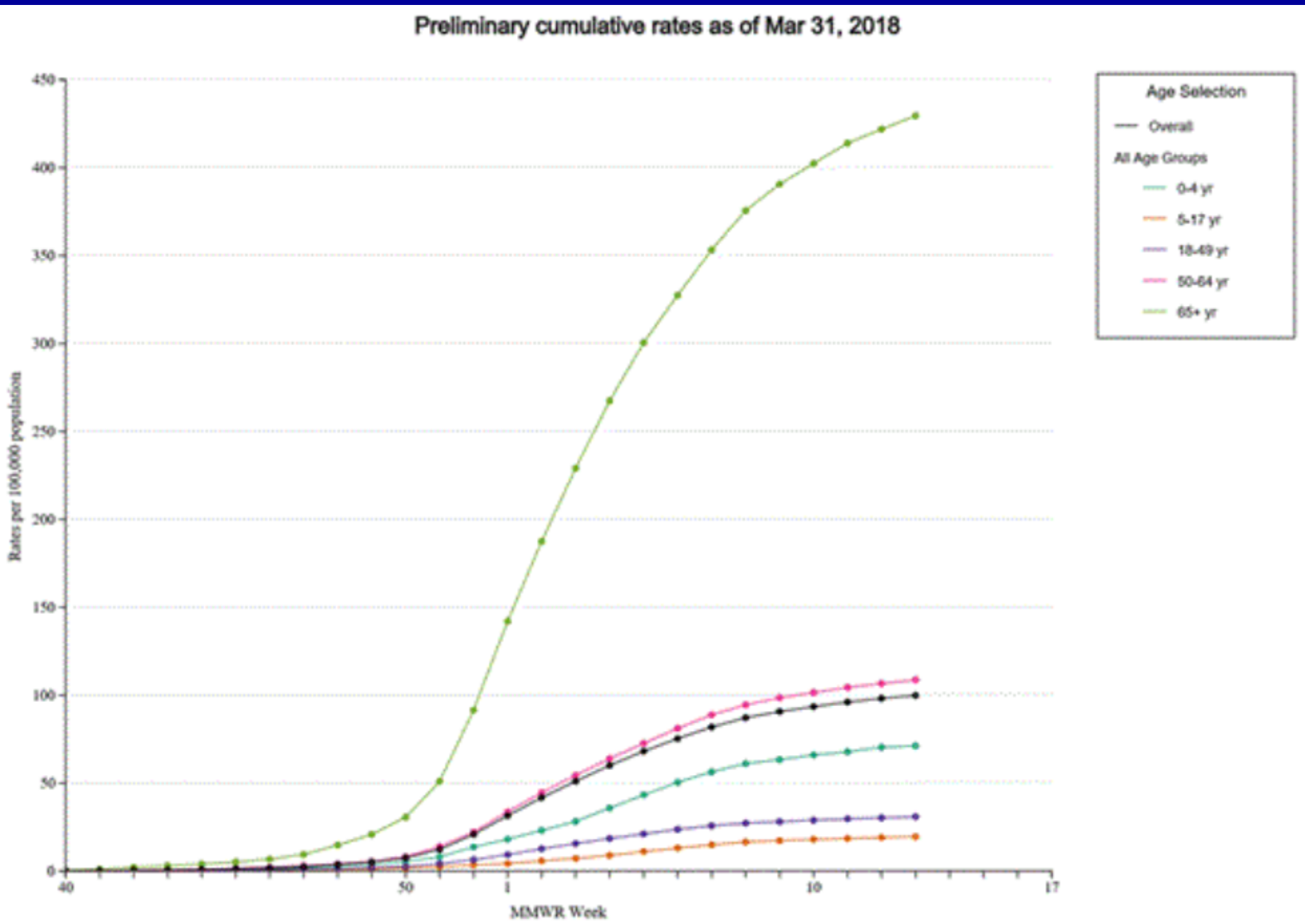
Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System

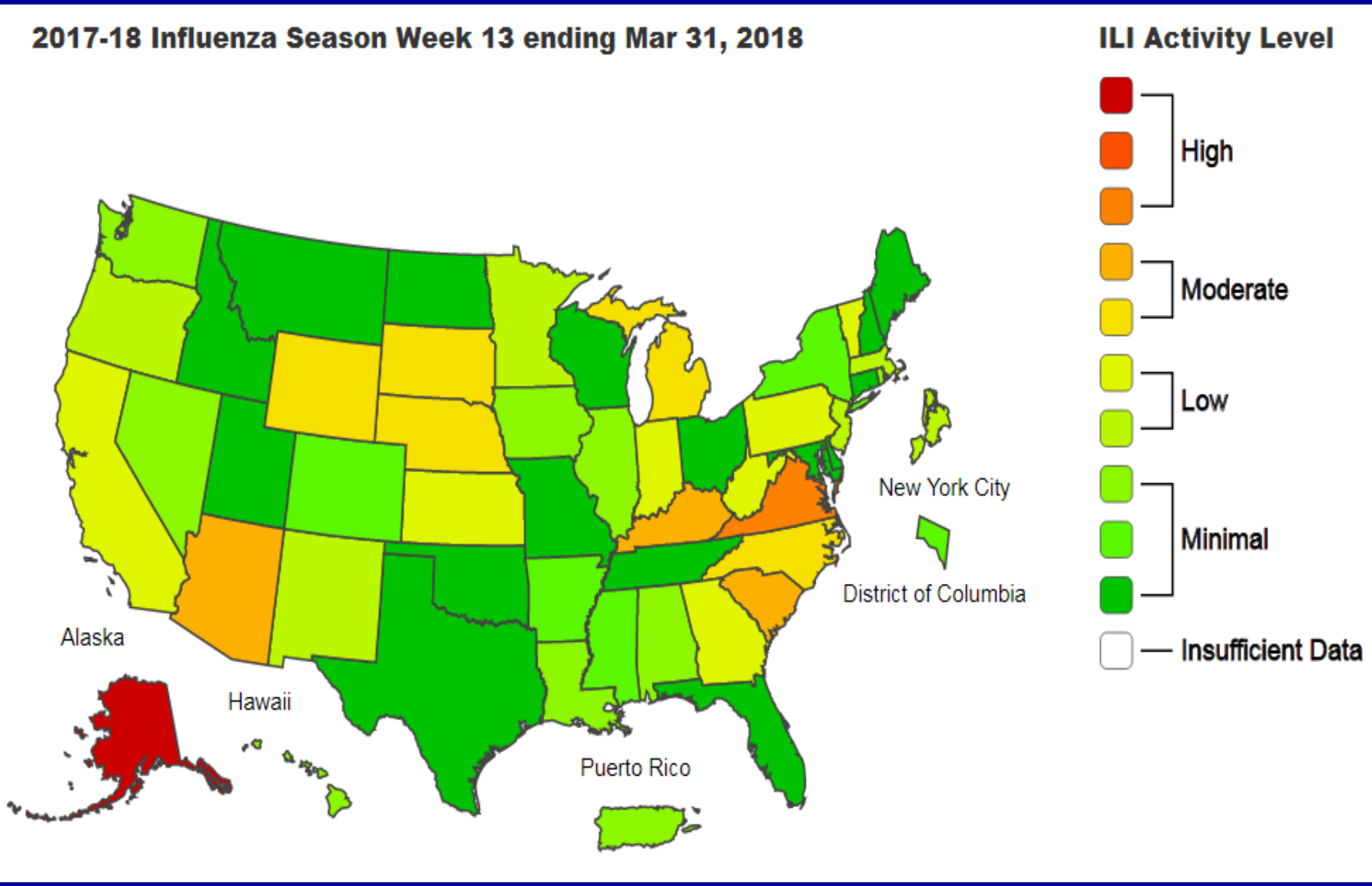
Data through the week ending March 17, 2018, as of April 5, 2018



Number of Influenza-Associated Pediatric Deaths by Week of Death: 2014-2015 season to present



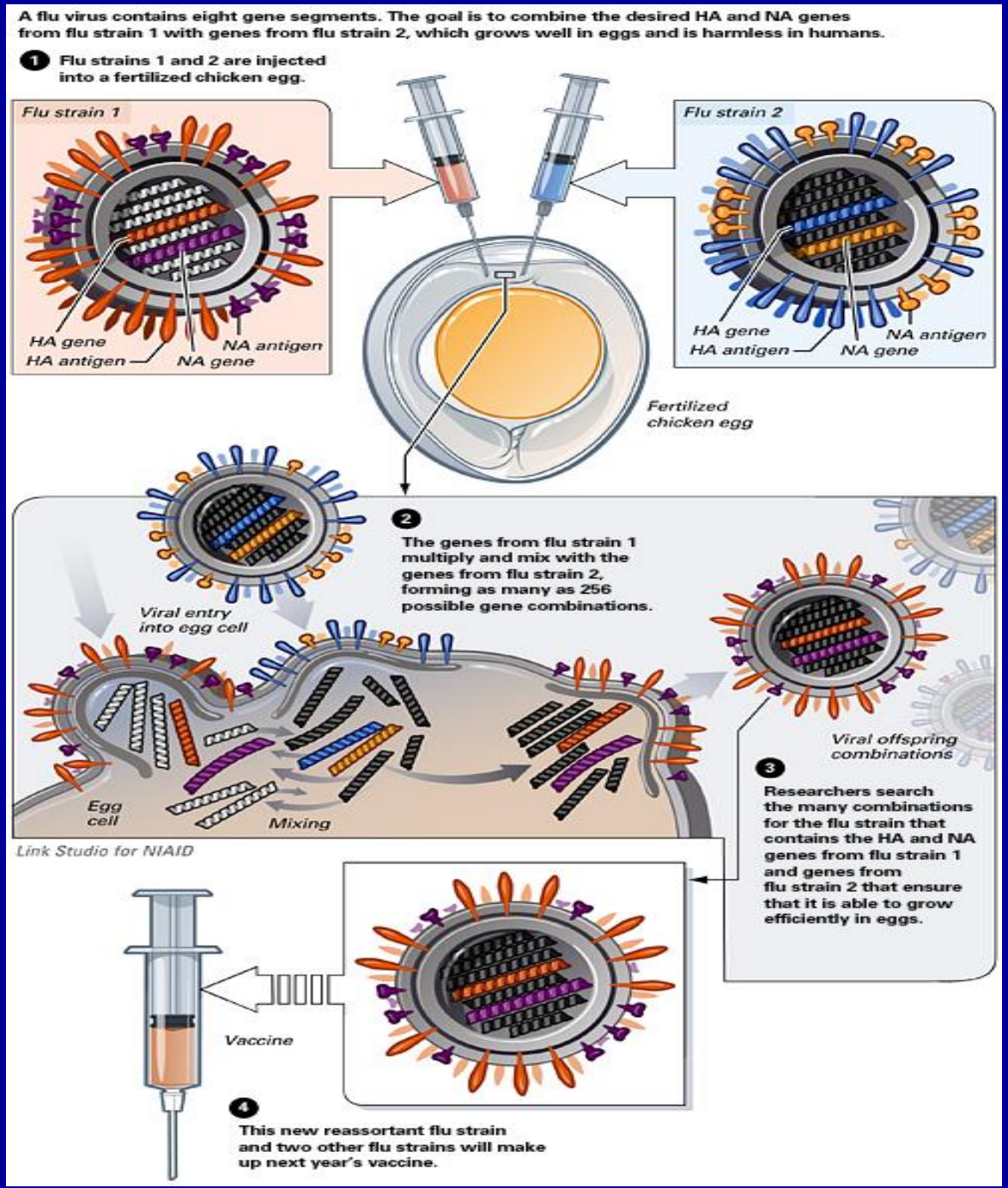

Preliminary cumulative rates as of Mar 31, 2018
Rates per 100,000 population
MMWR Week
40
50
1
10
17
0
50
100
150
200
250
300
350
400
450
Age Selection
Overall
All Age Groups
0-4 yr
5-17 yr
18-49 yr
50-64 yr
65+ yr


2017-18 Influenza Season Week 13 ending Mar 31, 2018
ILI Activity Level
High
Moderate
Low
Minimal
Insufficient Data
New York City
District of Columbia
Alaska
Hawaii
Puerto Rico

Vaccine Effectiveness Lower Than Expected

Interim results for this season show that vaccination lowered the number of cases of medically attended influenza illness by 36%. Vaccine effectiveness against influenza A(H3N2) was 25% for all ages and 51% for children aged 6 months to 8 years. There were no statistically significant estimates of vaccine effectiveness against influenza A(H3N2) for other age groups. The vaccine was 67% effective against A(H1N1)pdm09 and 42% effective against influenza B (mostly B/Yamagata, not in inactivated influenza vaccine, trivalent).

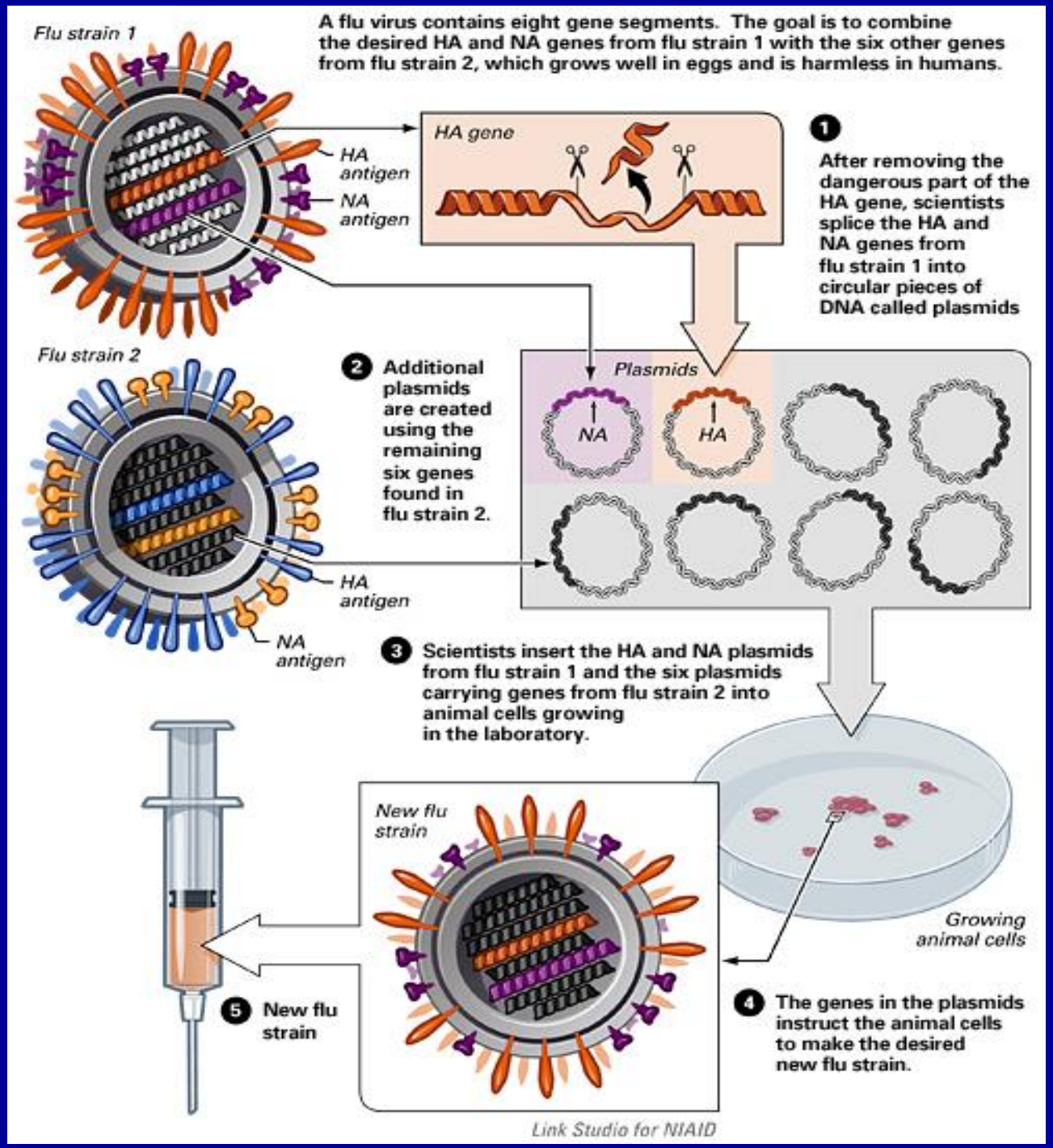
VACCINATION AND TREATMENT



Usual method
Genetic re-assortment

Courtesy of NIAID

NEW method
Split virus

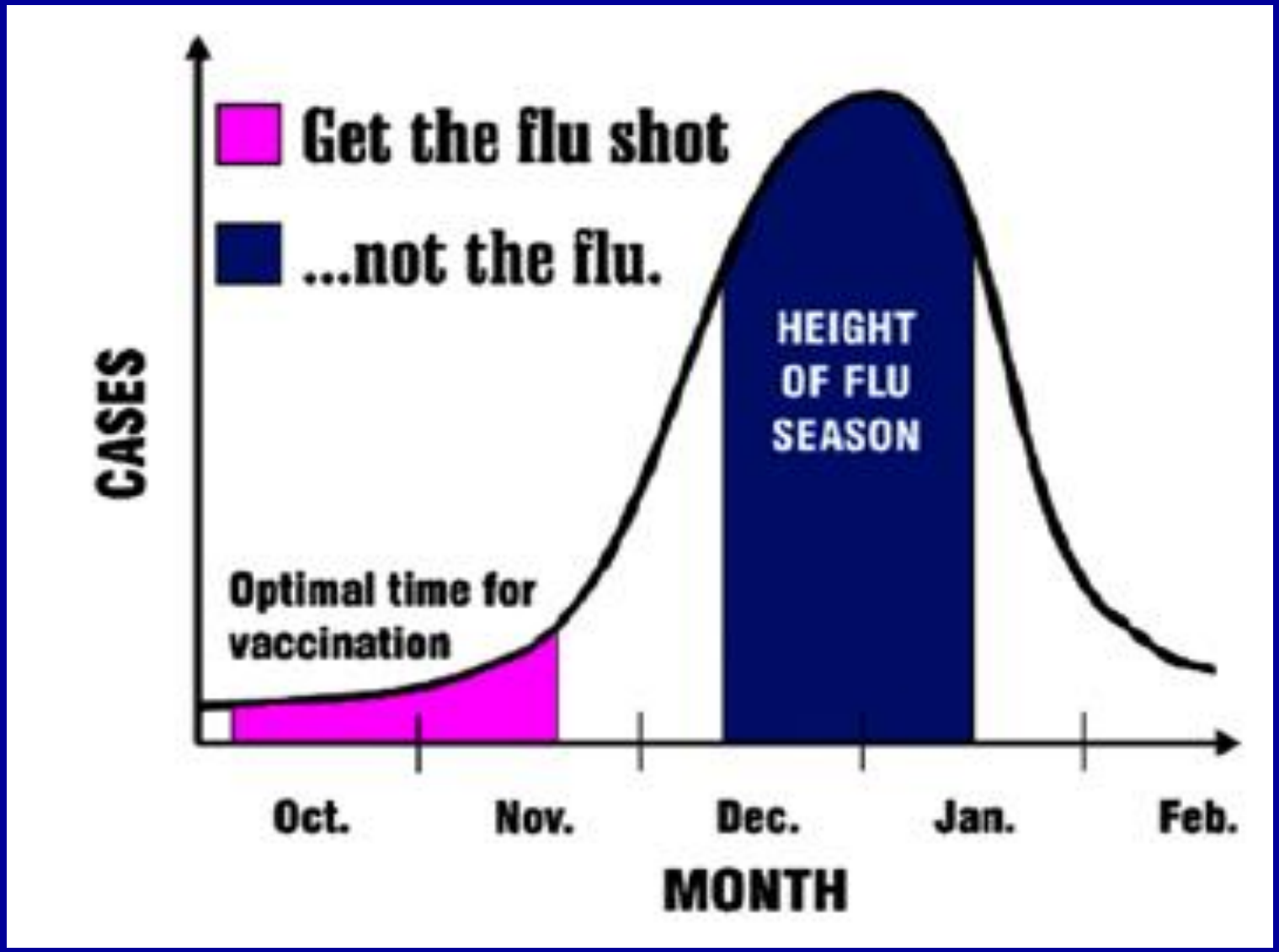


Courtesy of NIAID

Vaccines

- Current vaccines are
  - formalin-inactivated whole-virus
  - Chemically disrupted (split-virus vaccine)
  - Purified surface antigen preparations

- In addition recently FDA has approved of usage of live-attenuated virus vaccine for age groups of 5 to 49 years which is administered intranasally
  - Might be preferable in a future due to induction of mucosal immune response (that's the way you get it in real life)
  - Protect upper respiratory tract
  - Route of administration might be more preferable, at least certain age groups



Courtesy of CDC

Vaccine strains for 2018

Vaccine Strains

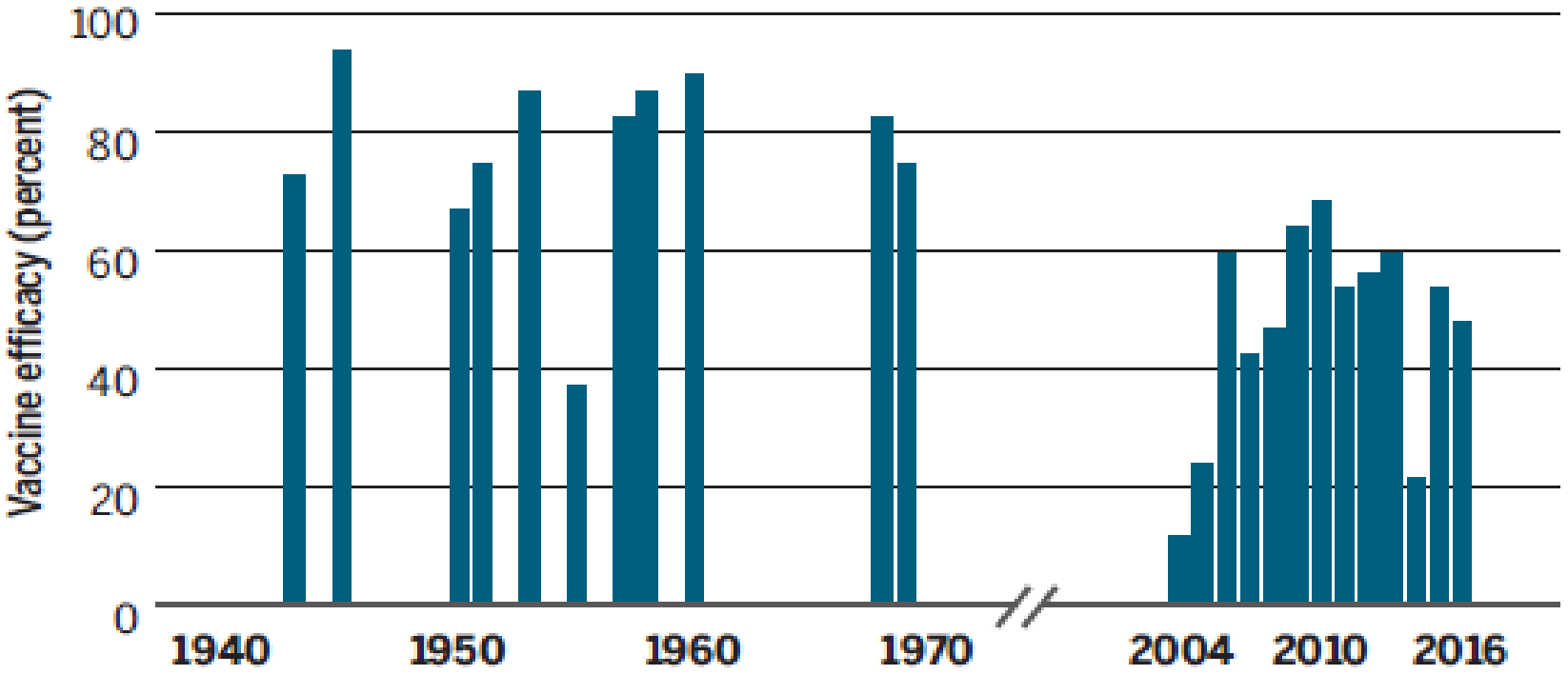
For the trivalent vaccine, the committee voted unanimously (12 yes, 0 no) to include an A/Michigan/45/2015 (H1N1)pdm09-like virus. The panel voted unanimously to include an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, which is a change from the 2017-2018 vaccine.

The group voted by a large margin (11 yes, 1 abstain) to include a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage), which is a change from this season's vaccine.

The committee also voted unanimously to include a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) as the second influenza B strain in the quadrivalent vaccine.

Loss of confidence

For decades, tests suggested the flu vaccine worked extremely well, but in the past 15 years a better test revealed many infections in vaccinated people who would previously have been deemed protected.



It takes a long time to develop a vaccine. Therefore you have to predict what is coming long in advance. This increases the possibility of mistakes:

The suspected virus could be replaced by another.

Even if the CDC is right, genetic changes in the virus over 6 months makes the vaccine less effective.

Work is under way to decrease development time or make a multivalent vaccine against more strains.

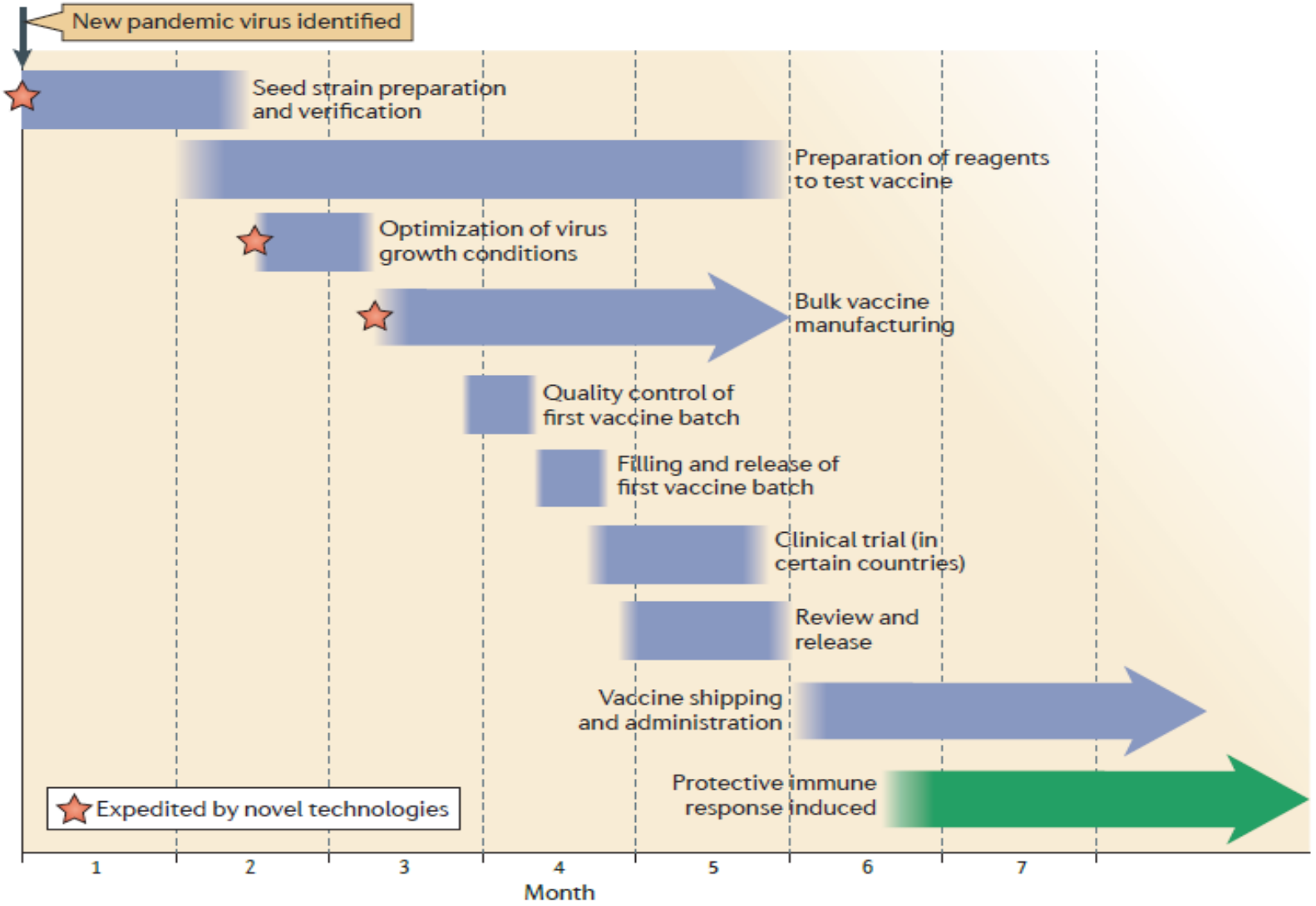


Figure 1 | **Advances in the pandemic influenza virus vaccine production process.** This figure shows the vaccine production process in response to a new pandemic. Orange stars indicate steps that could be accelerated by using novel technology. For example, seed strain preparation and verification can be facilitated by using gene synthesis, reverse genetics and deep sequencing. Once seed strains are prepared, viruses can be rescued in a backbone that has been optimized for growth on the selected substrate. This strategy can reduce the time required for growth optimization. Bulk manufacturing can be expedited by using novel production technologies that are easy to scale up (for example, cell culture or recombinant protein technologies). Adapted from REF. 227, World Health Organization.

TREATMENT

- There are altogether 5 antiviral drugs against influenza for prevention and treatment

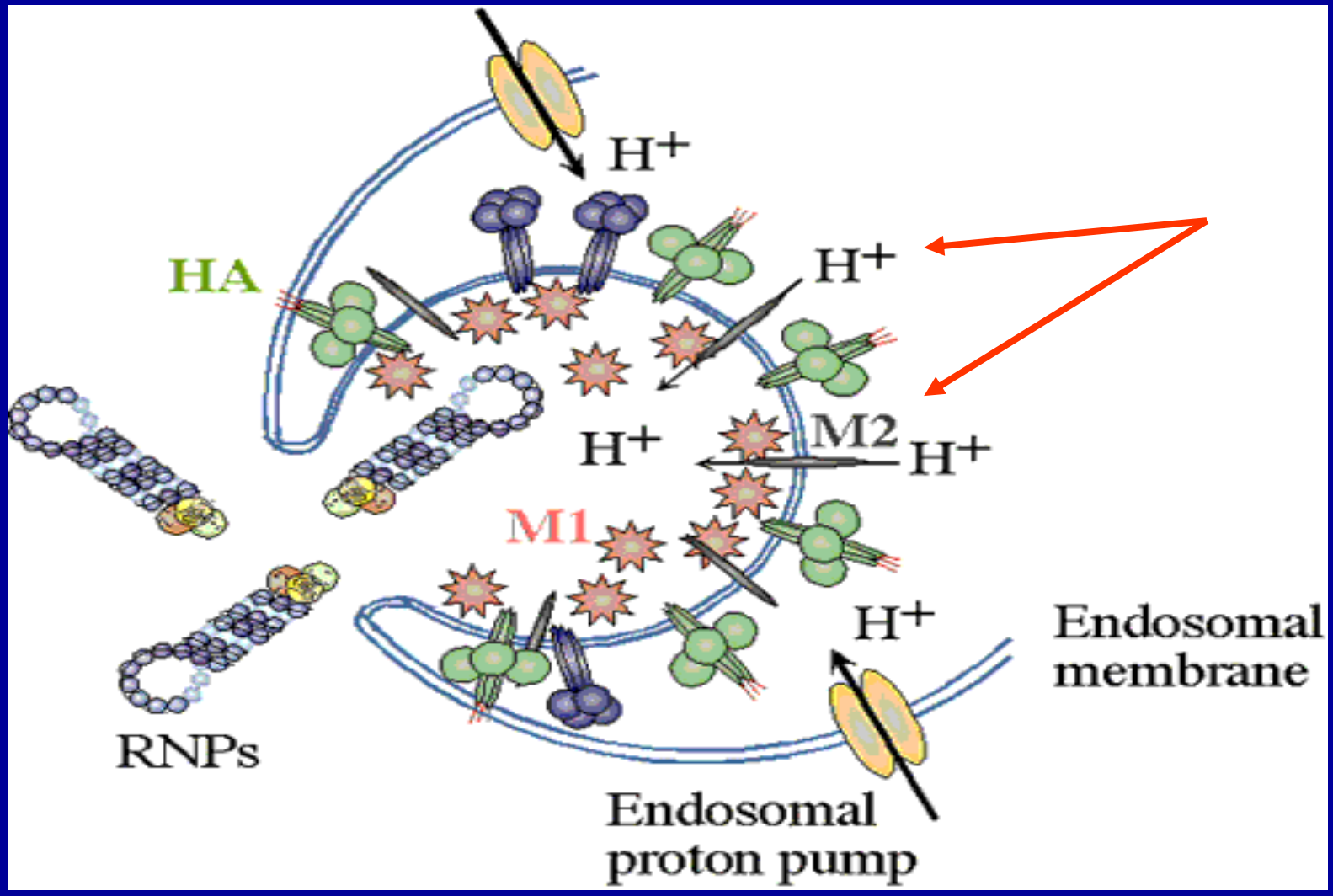
- M2 inhibitors
  - Amantadine
  - Rimantadine

- Neuraminidase inhibitors
  - Zanamivir
  - Oseltamivir
  - Peramivir

M2 inhibitors: amantadine and rimantadine

- **Mode of action:** inhibit the M2 ion channel activity of susceptible viruses – inhibit viral uncoating
- Similar ion channels has been described for type B and C, BUT at clinically achievable levels, these drugs are active only against influenza type A
- **Side effects:** insomnia, dizziness and difficulty concentrating
- **Efficacy:** treatment within the first 48 h of illness was associated with decrease in the duration of fever by about 24 h – great portion appear to be “rapid resolvers”
- **Drug resistance:** GREAT FACTOR - emerge fairly frequently in treated individuals (result from a single point mutation in the M2 protein)

FUNCTION OF MP2-PROTEIN CHANNEL IN VIRION



NA inhibitors: Zanamivir, Oseltamivir and Peramivir

- Inhibit the functioning of neuraminidase resulting that virus remains attached to the host cell and to the other virions
- Against influenza type A and B
  - B-viruses typically 10-fold less sensitive than type A
  - ALSO works against all 9 known NA subtypes of AVIAN influenza viruses!!
- Side effects: gastrointestinal upset, nausea (reduced if taken with food)
- Efficacy: treatment started after first 36 h of symptoms resulted 30-40% decrease of duration of symptoms and severity of illness and reduced rates of prolonged coughing
- Drug resistant viruses rare (1% of adult and 5.5% of pediatric recipients)
- Resistant viruses have reduced fitness: reduced level of replication and ability to be transmitted from animal to animal

Table 1. Antiviral Medications Recommended for Treatment and Chemoprophylaxis of Influenza

Antiviral Agent	Activity Against	Use	Recommended For	Not Recommended for Use in	Adverse Events
Oseltamivir (Tamiflu®)	**Influenza A and B**	**Treatment**	Any age[1]	N/A	**Adverse events**: nausea, vomiting. Postmarketing reports of serious skin reactions and sporadic, transient neuropsychiatric events (self-injury or delirium; mainly reported among Japanese adolescents and adults).
		Chemo-prophylaxis	3 months and older[1]	N/A	
Zanamivir (Relenza®)	**Influenza A and B**	**Treatment**	7 yrs and older	people with underlying respiratory disease (e.g., asthma, COPD)[2]	**Allergic reactions**: oropharyngeal or facial edema. **Adverse events**: diarrhea, nausea, sinusitis, nasal signs and symptoms, bronchitis, cough, headache, dizziness, and ear, nose and throat infections.
		Chemo-prophylaxis	5 yrs and older	people with underlying respiratory disease (e.g., asthma, COPD)[2]	
Peramivir (Rapivab®)	**Influenza A and B[3]**	**Treatment**	18 yrs and older	N/A	**Adverse events**: diarrhea. Postmarketing reports of serious skin reactions and sporadic, transient neuropsychiatric events (self-injury or delirium; mainly reported among Japanese adolescents and adults).
		Chemo-prophylaxis	N/A	N/A	

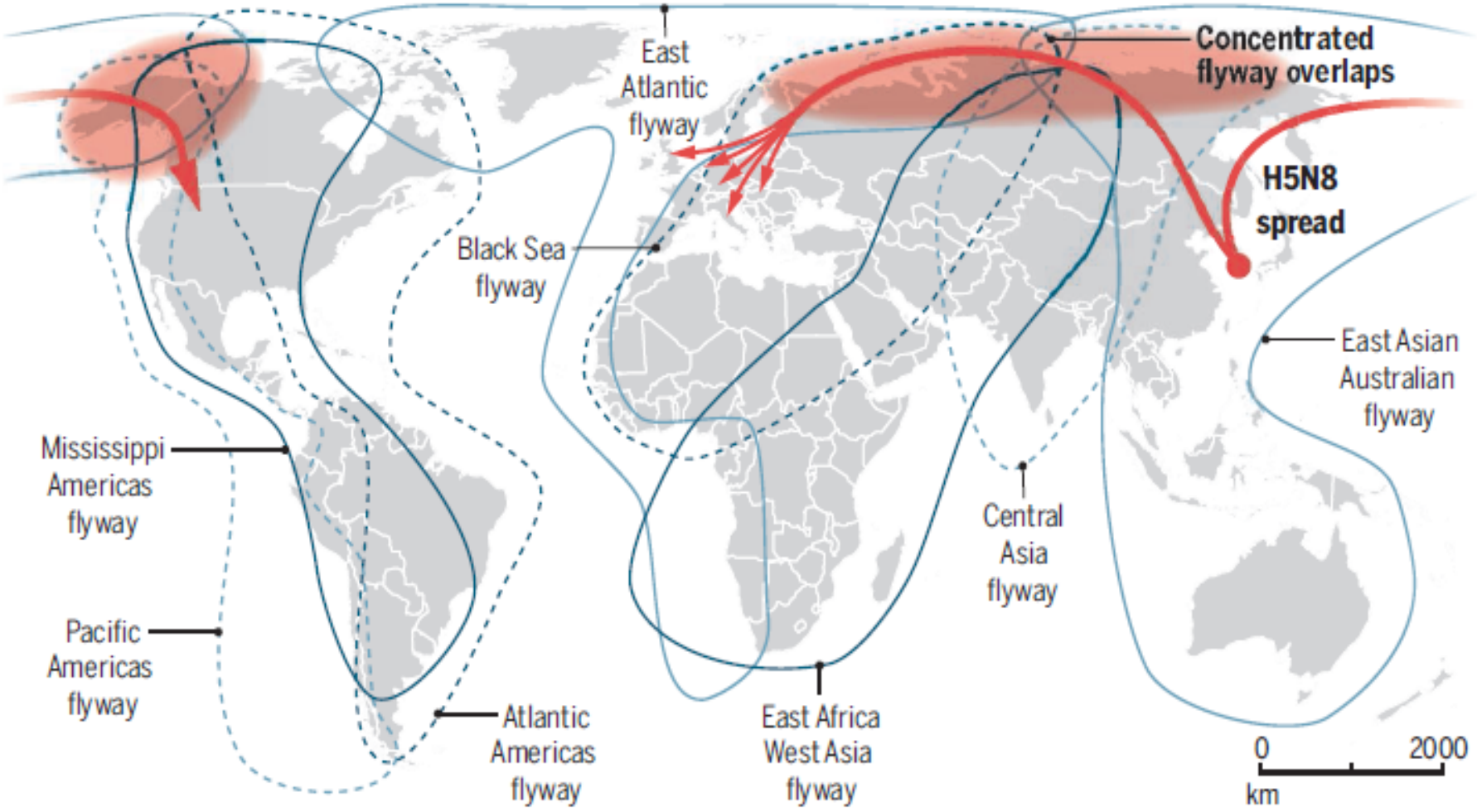
FDA ALERT TO TAMIFLU

- **Note:** On November 13, 2006, FDA approved a labeling supplement for Roche Laboratories' Tamiflu (Oseltamivir Phosphate) to include a precaution about neuropsychiatric events. The revision is based on postmarketing reports (mostly from Japan) of self-injury and delirium with the use of Tamiflu in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. However, people with the flu, particularly children, may be at an increased risk of self-injury and confusion shortly after taking Tamiflu and should be closely monitored for signs of unusual behavior. A healthcare professional should be contacted immediately if the patient taking Tamiflu shows any signs of unusual behavior. Visit http://www.fda.gov/medwatch/safety/2006/safety06.htm#tamiflu for more information.

AVIAN FLU

Global movement of wild birds

The complex overlap of flyways [adapted from (6)] provides numerous opportunities for long-distance virus spread by migratory birds. The Global Consortium for H5N8 and Related Influenza Viruses shows that these flyway overlaps were key to the spread of H5N8 viruses into North America and Europe.



RECENT “BIRD FLUs”

Birds are very effected by the flu and sometimes it spreads to us.

Bird flus are worldwide. Many are in the US.

If a random recombination manages to spread well from person to person, we could have a pandemic.

Avian Influenza (from NIAID)

H5N1

- **An outbreak occurred in Hong Kong in 1997 where 18 persons were infected of which 6 died.**
- **The source of the virus was probably from infected chickens and the outbreak was eventually controlled by a mass slaughter of chickens in the territory.**
- **However, the strains were highly virulent for their avian hosts.**

H9N2

- **Several cases of human infection with H9N2 virus occurred in Hong Kong and Southern China in 1999.**
- **The disease was mild and all patients made a complete recovery.**

- **2002: H5N1**
  - **H7N2: evidence of infection in one person in Virginia following poultry outbreak**

- **2003: H5N1**
  - **H7N7: first reported cases of this strain in humans**
    - **89 people in Holland**
    - **Poultry workers, became ill with eye-infections or flu-like symptoms**
    - **A veterinarian who visited affected farms died**
  - **H7N2: person hospitalized in New York**
  - **H9N2: caused illness in one child in Hong Kong**

- **2004: H5N1**
  - **H7N3: infection reported first time in humans**
    - **Caused illness in two poultry workers in Canada**
  - **H10N7: infection reported first time in humans**
    - **Caused illness in two infants in Egypt. One child's farther is a poultry merchant**

Three prominent subtypes of avian influenza A viruses that are known to infect both birds and people are:

- **Influenza A H5**
- Nine potential subtypes of H5 viruses are known (H5N1, through H5N9) in wild birds and poultry. Sporadic H5 virus infection of humans, from strains circulating among poultry in Asia and the Middle East have been reported in 15 countries, often resulting in severe pneumonia with approximately 60% mortality worldwide.

- **Influenza A H7**
- **Nine potential subtypes of H7 viruses are known (H7N1 through H7N9). H7 virus infection in humans is uncommon, occurring in persons who have direct contact with infected birds, poultry.**
- **In humans, (H7N2, H7N3, H7N7) virus infections have caused mild to moderate illness, and (H7N3, H7N7) virus infections have caused mild to fatal illness.**

- **Influenza A H9**
- Nine potential subtypes of H9 are known (H9N1 through H9N9); in wild birds and poultry.
- Worldwide
- Rare, sporadic H9N2 virus infections of humans have been reported to cause generally mild upper respiratory tract illness.

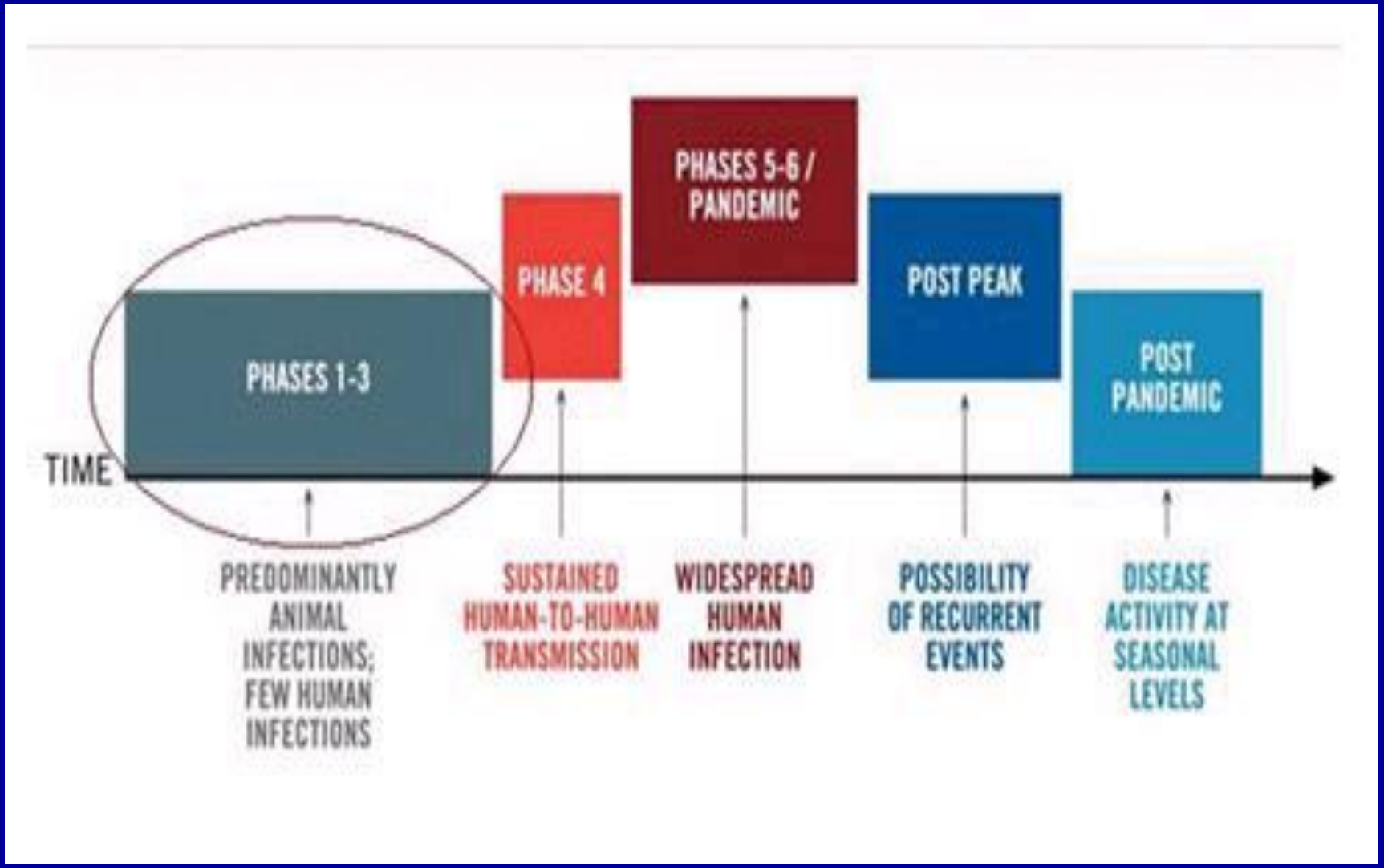
- Human infection with avian influenza A(H5N6) viruses
- In April 2014, A(H5N6) virus was detected in a respiratory tract sample from a patient who died of severe pneumonia in China. The likely source of infection was exposure to infected poultry. No further cases were reported.

- Outbreaks of illness and deaths in poultry due to highly pathogenic A(H5N6) avian influenza viruses have been reported in China, Laos and VietNam.

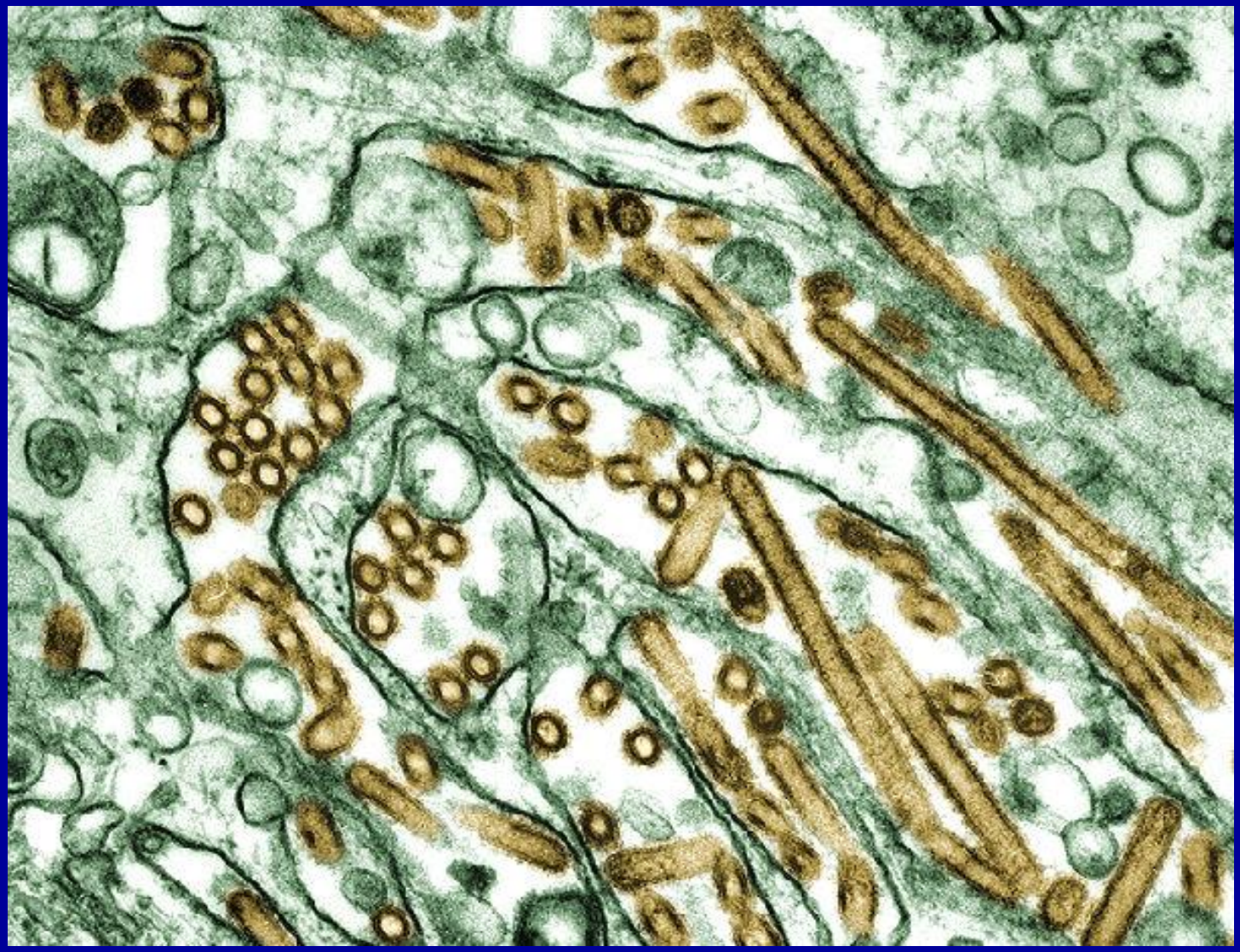
- This human case appears to be isolated, but given that the disease is widespread in poultry, further sporadic human cases or small clusters of infection would not be unexpected.

H5N1

PANDEMIC ALERT: NOVEMBER 19, 2014



EM picture of H5N1 Avian influenza virus

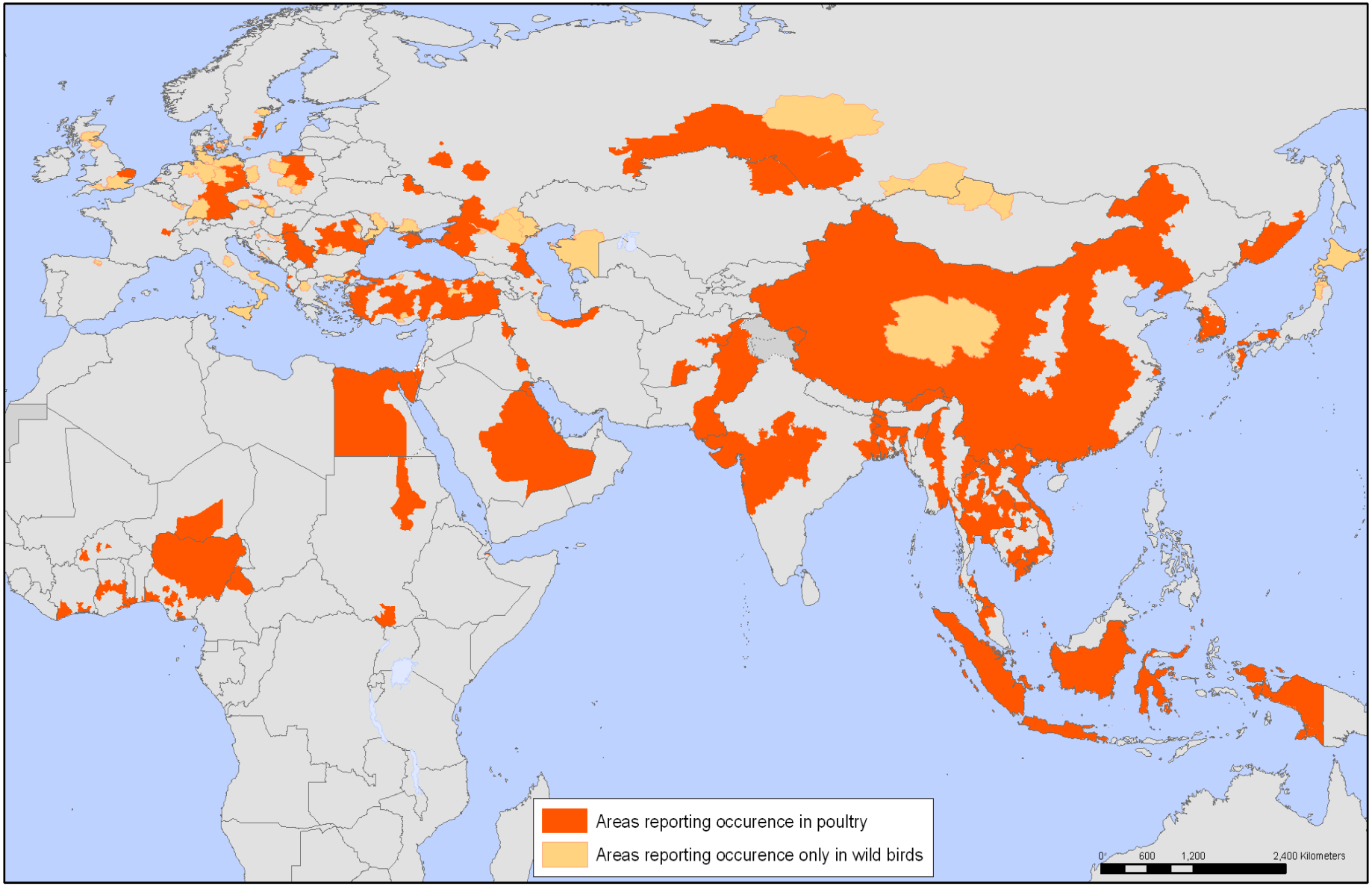


Courtesy of CDC

H5N1 in Poultry

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

Status as of 03 October 2008
Latest available update



World Health Organization

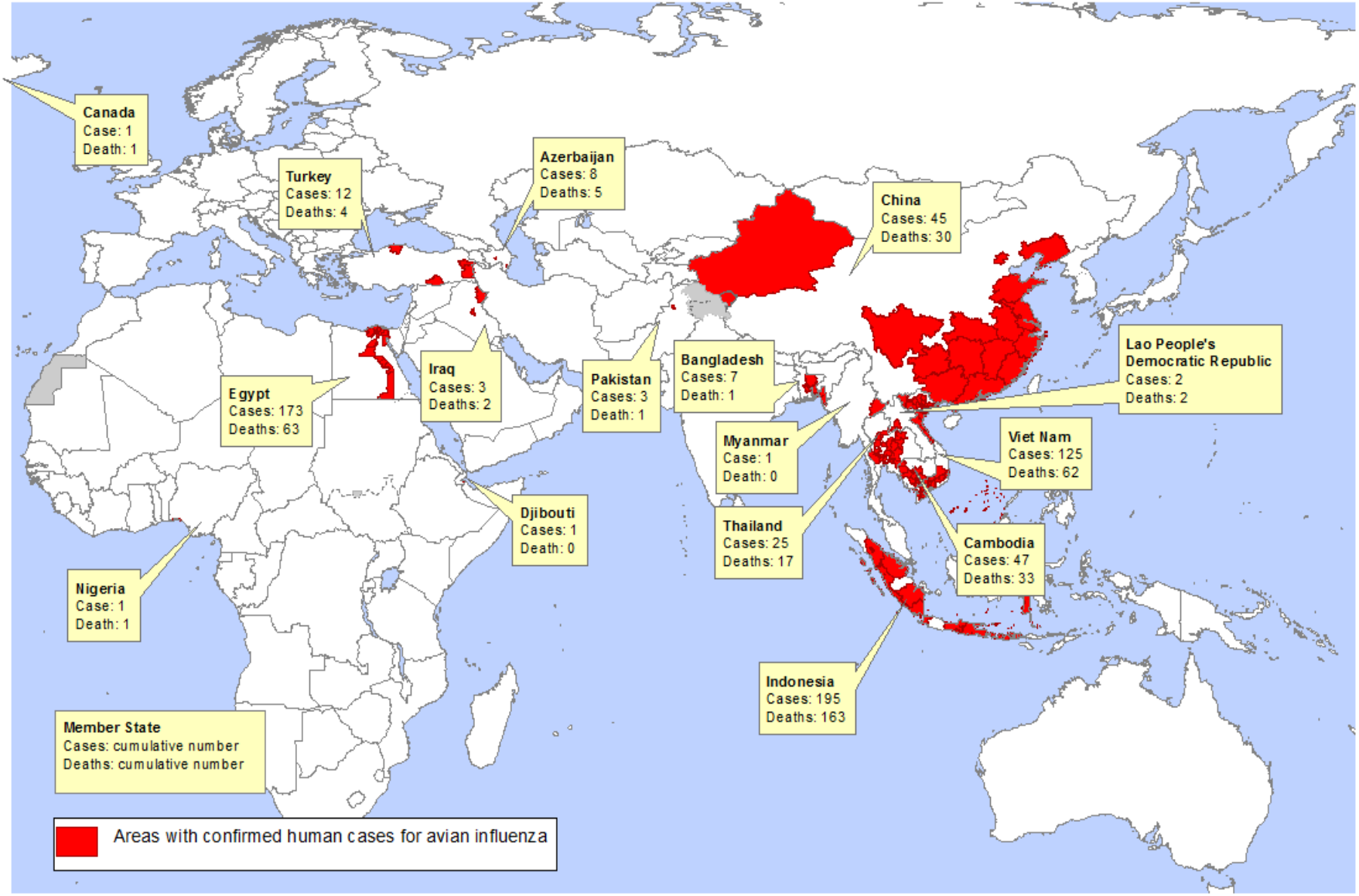
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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

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

H5N1 infections in humans

Areas with confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2013*



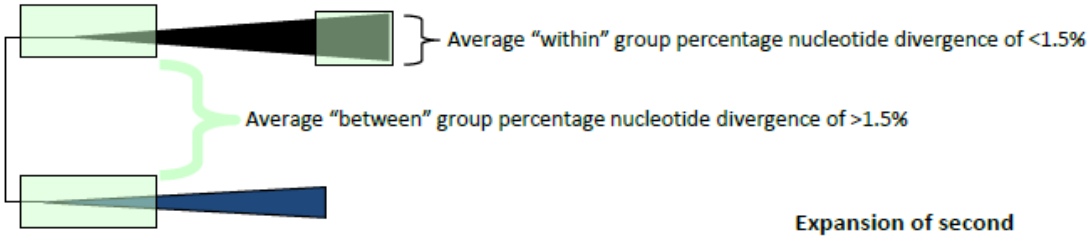
*All dates refer to onset of illness
Data as of 24 January 2014
Source: WHO/GIP

Total Cases (October 2, 2014)
Laboratory-confirmed cases

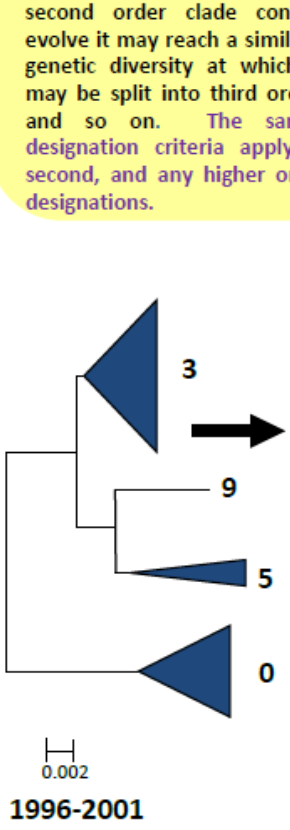
- Confirmed cases 688
- Deaths 393

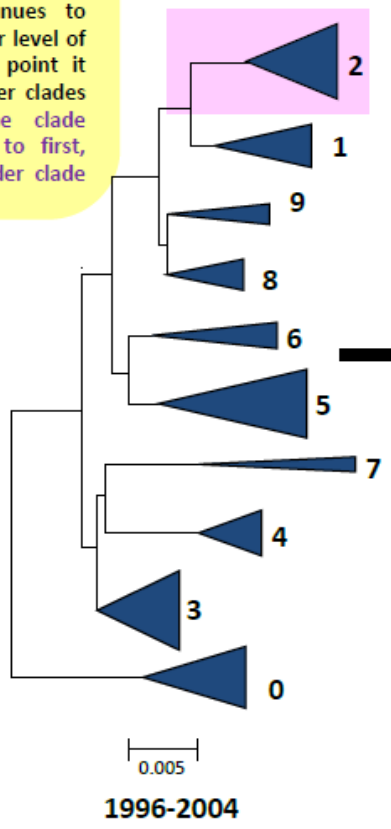
- In addition, H5N1 viruses have diversified both genetically and antigenetically

Evolution of the Asian H5 Hemagglutinin

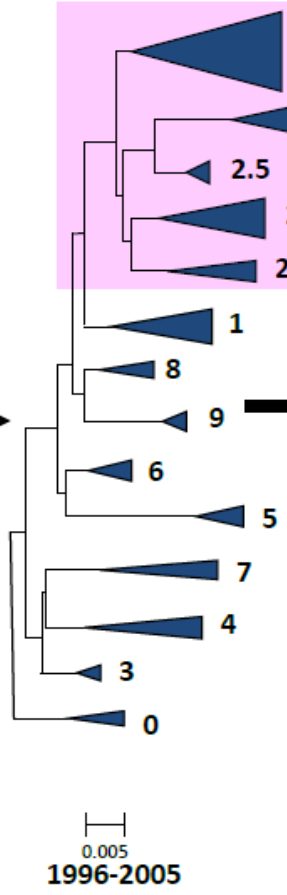


When discrete monophyletic groups begin to appear within a specific clade and those groups meet the nucleotide divergence criteria (as well as having bootstrap values >60), they are split into second order clades (but still considered part of the original first order clade). As a second order clade continues to evolve it may reach a similar level of genetic diversity at which point it may be split into third order clades and so on. The same clade designation criteria apply to first, second, and any higher order clade designations.

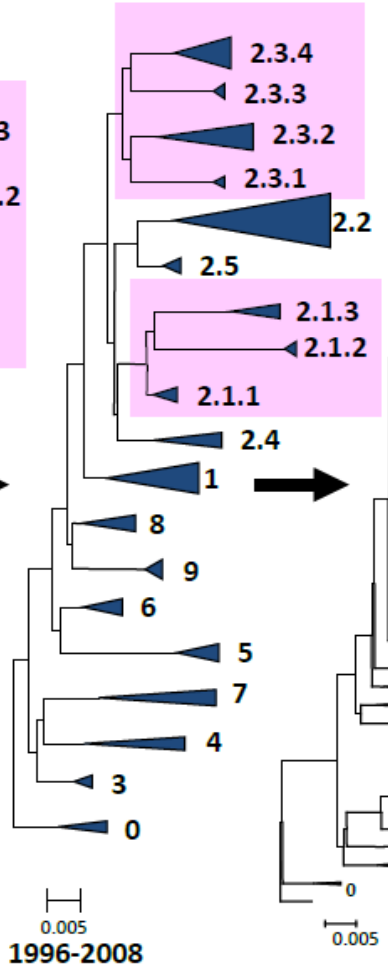




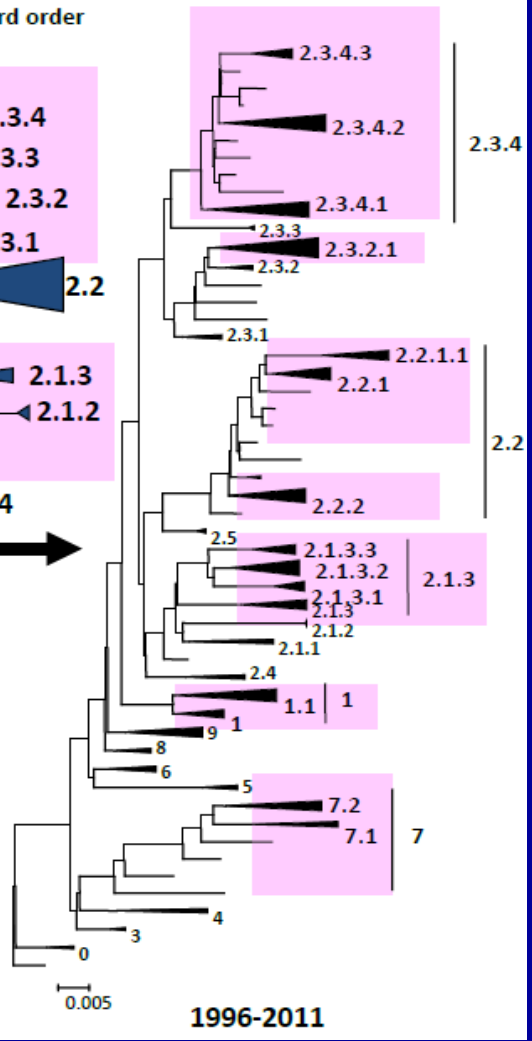
Expansion of clade 2 into five second order clades



Expansion of second order clades into additional third order clades



Expansion of first, second and third order clades into additional second, third and fourth order clades



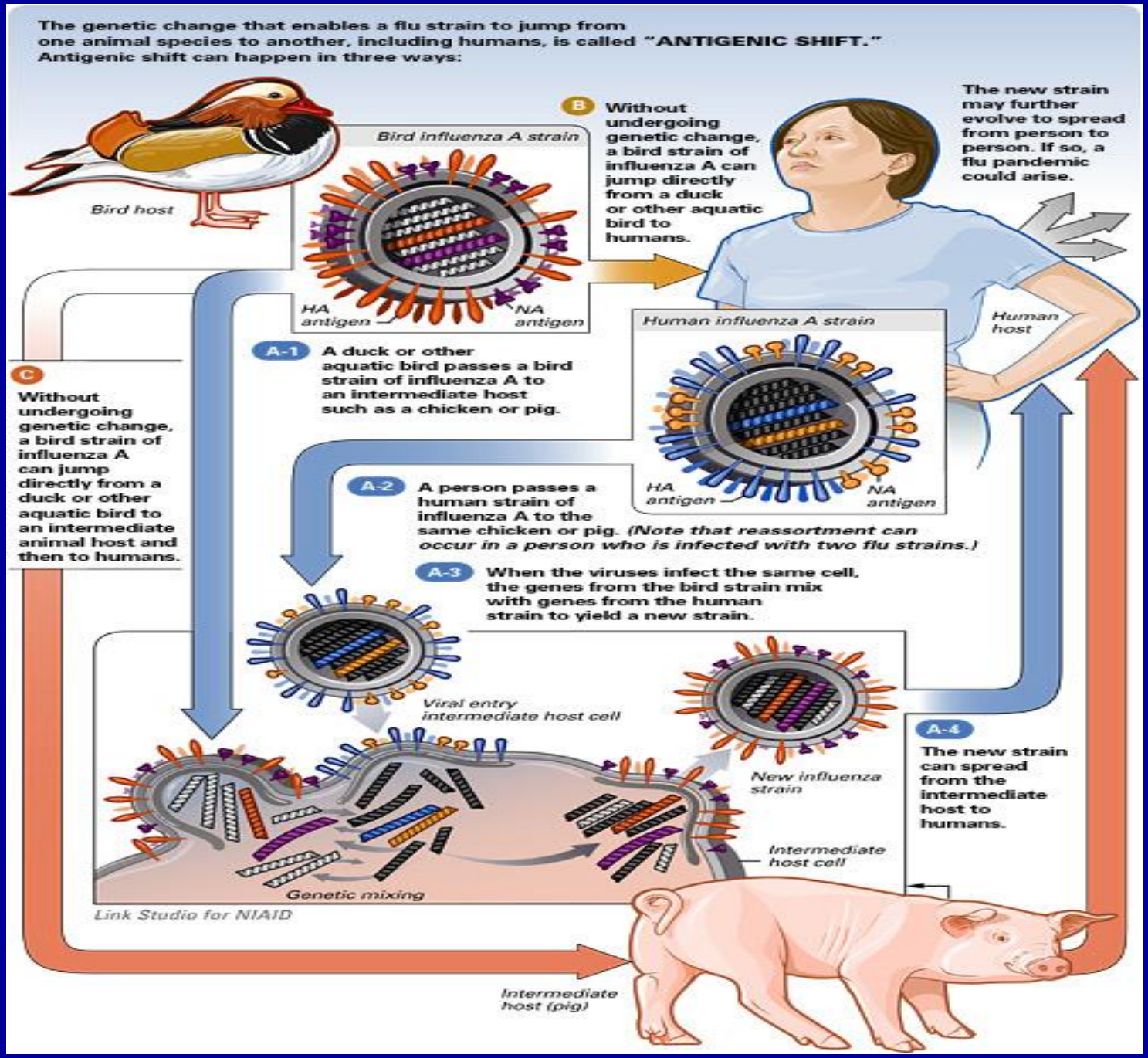
Availability of a new recombinant A(H5N1) vaccine virus

- **03 August 2010 -**A new recombinant A(H5N1) vaccine virus has been developed by the WHO and the CDC. The new recombinant vaccine virus named **A/Egypt/3300-NAMRU3/2008 (H5N1)-PR8-IDCDC-RG13.**

- The Global Influenza Surveillance Network (GISN) has been closely monitoring the antigenic and genetic evolution of the circulating viruses, especially viruses that infect humans. Countries are encouraged to share with WHO their specimens and/or isolates, both from humans and animals, in order to be included in the WHO H5N1 vaccine virus selection and development program.

- **2012 another vaccine, IDCDC-RG-30, created.**

Swine flu



Courtesy of NIAID

Swine influenza viruses are most commonly of the H1N1 subtype, but other subtypes are also circulating in pigs (e.g., H1N2, H3N1, H3N2).

Swine flu in pigs

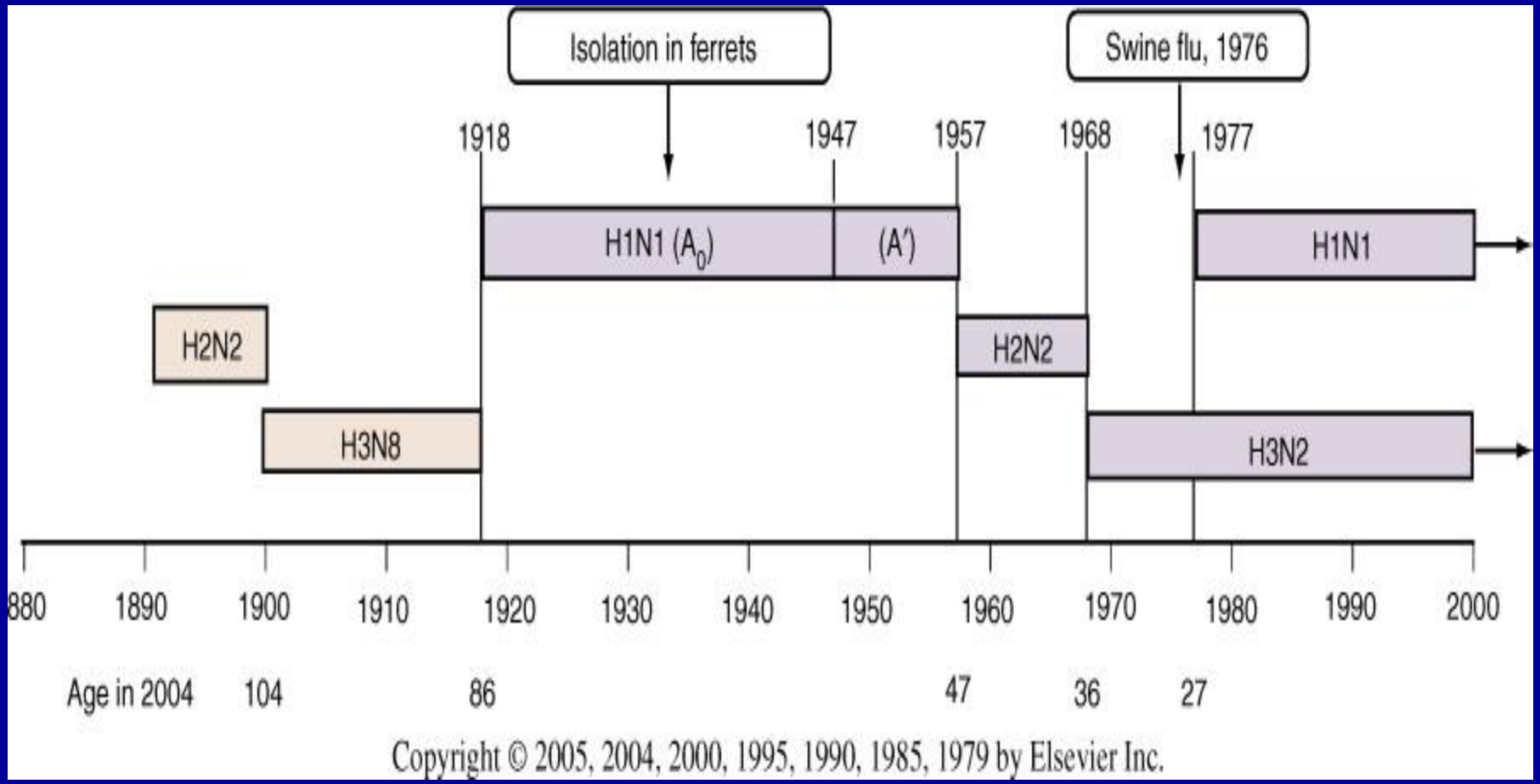
- **Swine influenza is an upper respiratory disease that causes outbreaks in herds. The incubation period in swine is usually 1 to 3 days.**

- **Clinical signs in pigs very similar to humans.**

- **The mortality rate is relatively low (1% to 3%), and most affected animals recover within 5 to 7 days after illness onset. Some pigs exhibit severe viral pneumonia, which is the major cause of death. Secondary bacterial or viral infections also can occur.**

- **Pigs begin excreting the virus within 24 hours after infection, and may shed the virus for 7 to 10 days. A carrier state can exist for up to 3 months.**

PANDEMICS



-1918 H1N1 gradually adapted from avian influenza to human transmission (direct)
-1957 H2N2 virus resulted from H1N1 acquiring new segments (NA,HA, PB1) from avian origin (through swine)
-1968 H3N2 was formed by acquisition of HA and PB1 from avian virus (through swine)
-1977 H1N1 reintroduction by unknown mechanism

Swine flu 1976

- New Jersey army basic training camp in Fort Dix
- January – February 1976
- ~200 soldiers became sick: four soldiers had pneumonia and one died
- Virus was identified as a H1N1 swine flu - named A/New Jersey/76 (Hsw1N1).
- nationwide vaccination campaign, which was announced by President Gerald Ford in March.
- By the end of the year, 48 million people had been vaccinated

- **But the feared pandemic never occured.**

- **From CDC: "The virus is thought to have circulated for a month and disappeared. The Fort Dix outbreak may have been an animal anomaly caused by introduction of an animal virus into a stressed human population in close contact in crowded facilities during the winter."**

- Health officials suspended the vaccination campaign on Dec 16, 1976, after receiving numerous reports of Guillian-Barre syndrome (GBS), a paralyzing neurologic illness, after vaccination, according to an August 1979 report in the *American Journal of Epidemiology*.

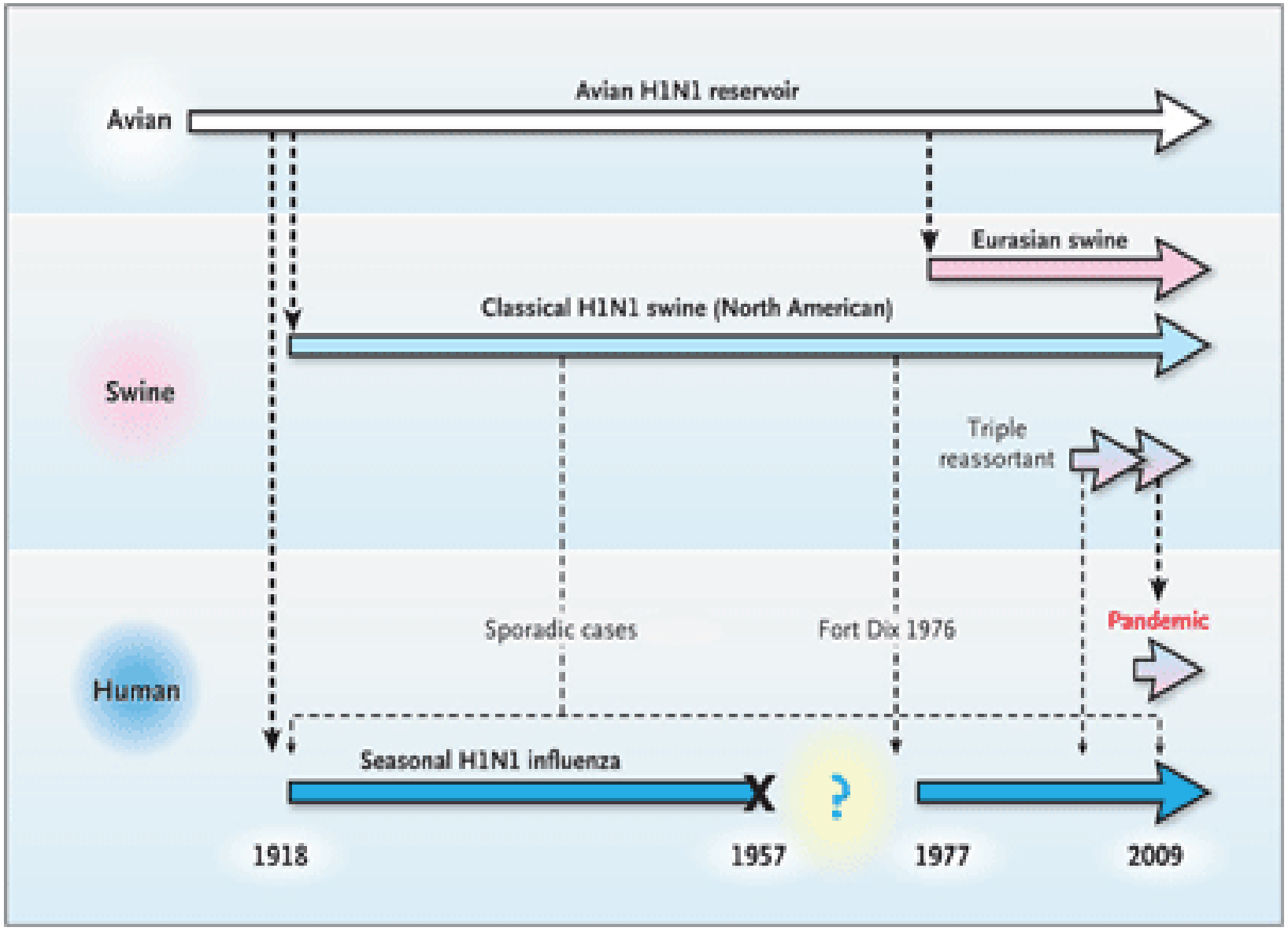
- Nationwide surveillance detected 1,098 patients with GBS onset from October 1976 through January 1977.

- Epidemiologic evidence suggested that many cases were related to vaccination, with an estimated risk of 1 case for every 100,000 vaccinations.

- Resulted ~25 deaths due to pulmonary complications

- Experts still don't know what caused the GBS cases after the swine flu vaccination.
- One theory was that bacterial antigens from contaminated eggs used in vaccine production could have elicited GBS.
- (bacteria in the vaccine damaged the immune system, which is why they use preservatives like formalin and formerly, mercury.)

2009 H1N1


Avian H1N1 reservoir
Avian
Eurasian swine
Classical H1N1 swine (North American)
Swine
Triple
reassortant
Pandemic
Sporadic cases
Fort Dix 1976
Human
Seasonal H1N1 influenza
?
1918
1957
1977
2009

2009 Novel H1N1 Virus history

- The NA and M gene segments are in the Eurasian swine lineage; they were originally derived from a wholly avian influenza virus and likely entered the Eurasian swine population in 1979.

- The HA, NP, and NS gene segments are in the classical swine lineage; they likely entered the swine population around 1918 and are common in North America.

- The PB2 and PA gene segments are in the swine triple reassortant lineage; viruses of this lineage entered pigs in North America around 1998. Viruses that seeded this lineage were originally of avian origin.

Updated Estimates from April 2009 – February 13, 2010

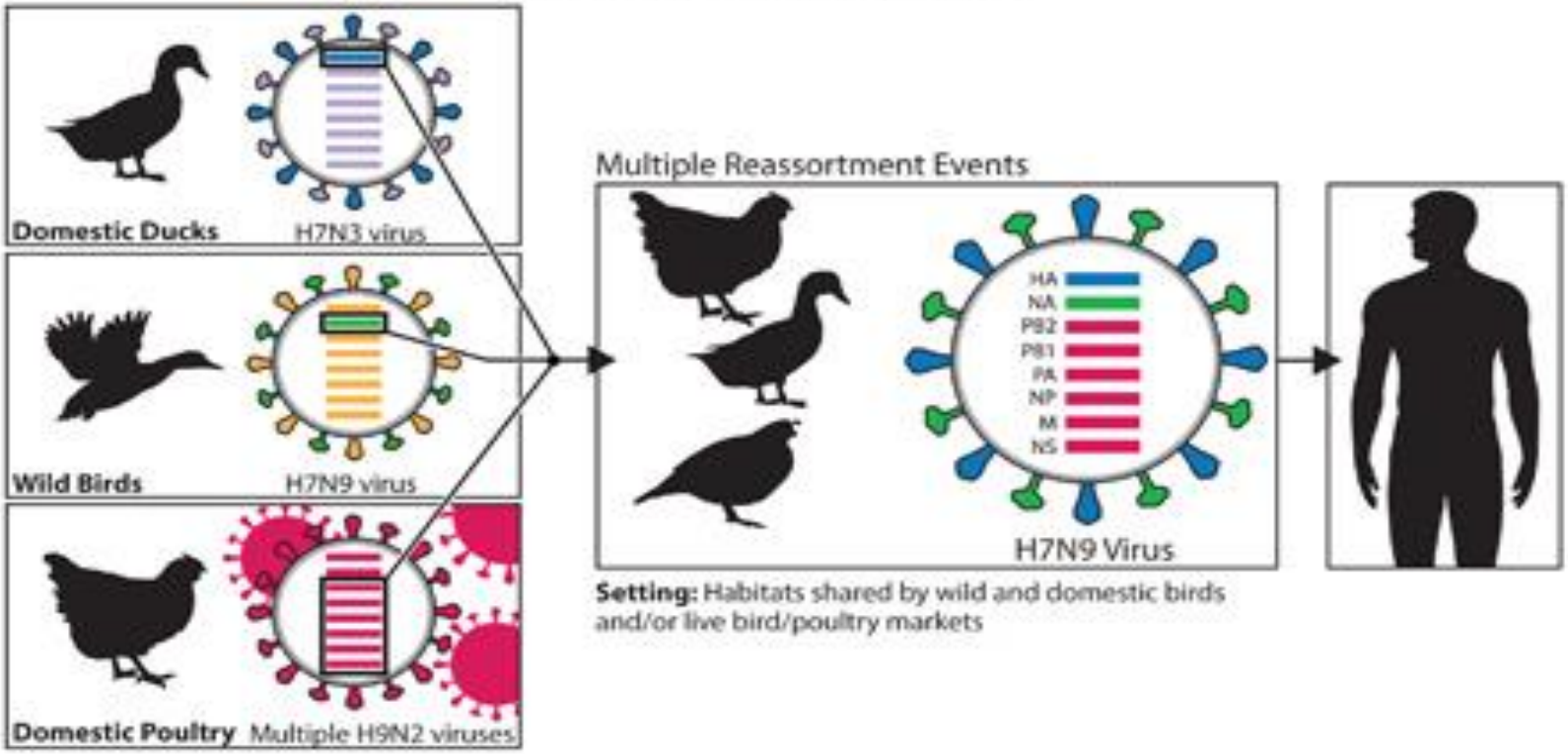
- CDC estimates:
- About 59 million people infected with 2009 H1N1.
- About 265,000 2009 H1N1-related hospitalizations.
- About 12,000 deaths.

Avian influenza A(H7N9) virus

- Avian influenza A(H7N9) is a subtype of influenza viruses that have been detected in birds in the past. This particular A(H7N9) virus had not previously been seen in either animals or people until it was found in March 2013 in China.

  However, since then, infections in both humans and birds have been observed. The disease is of concern because most patients have become severely ill with a 30% mortality rate. Most of the cases of human infection with this avian H7N9 virus have reported recent exposure to live poultry or potentially contaminated environments, especially markets where live birds have been sold. This virus does not appear to transmit easily from person to person.

Genetic Evolution of H7N9 Virus in China, 2013



The eight genes of the H7N9 virus are closely related to avian influenza viruses found in domestic ducks, wild birds and domestic poultry in Asia. The virus likely emerged from "reassortment," a process in which two or more influenza viruses co-infect a single host and exchange genes. This can result in the creation of a new influenza virus. Experts think multiple reassortment events led to the creation of the H7N9 virus. These events may have occurred in habitats shared by wild and domestic birds and/or in live bird/poultry markets, where different species of birds are bought and sold for food. As the above diagram shows, the H7N9 virus likely obtained its HA (hemagglutinin) gene from domestic ducks, its NA (neuraminidase) gene from wild birds, and its six remaining genes from multiple related H9N2 influenza viruses in domestic poultry.

CDC
Centers for Disease Control and Prevention
National Center for Immunization and Respiratory Diseases

Figure 1: Epidemiological curve of avian influenza A(H7N9) cases in humans by week of onset, 2013-2018.