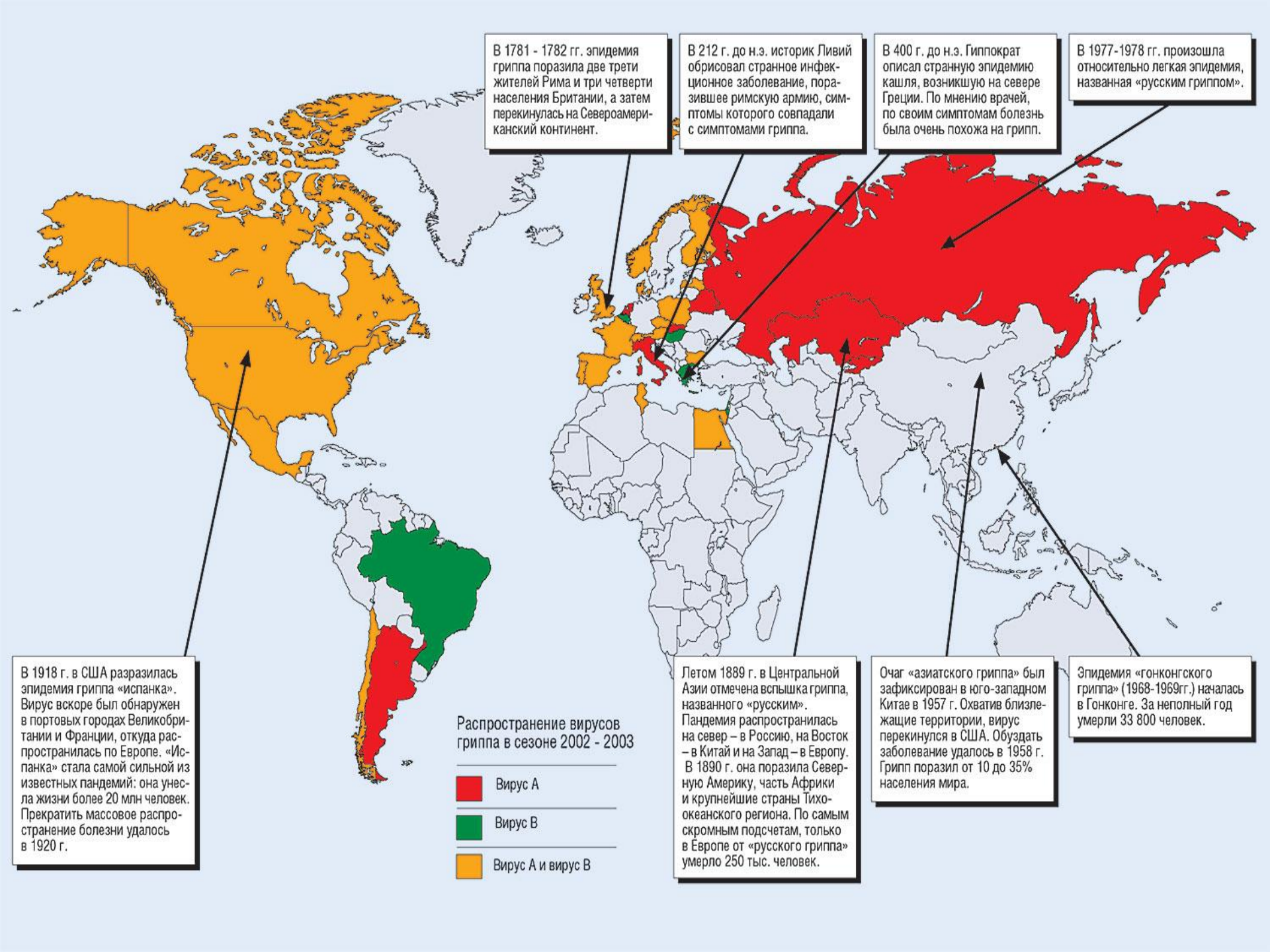
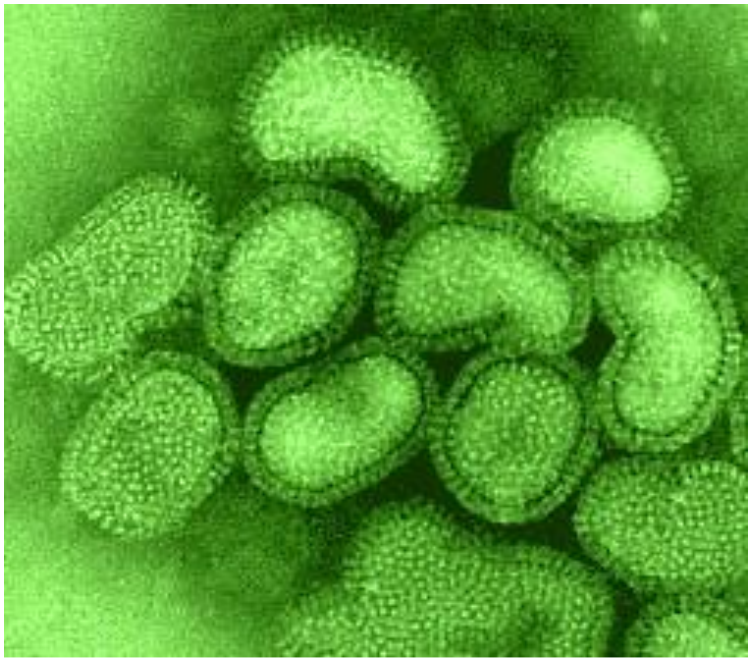

В 1781 - 1782 гг. эпидемия гриппа поразила две трети жителей Рима и три четверти населения Британии, а затем перекинулась на Североамериканский континент.
В 212 г. до н.э. историк Ливий обрисовал странное инфекционное заболевание, поразившее римскую армию, симптомы которого совпадали с симптомами гриппа.
В 400 г. до н.э. Гиппократ описал странную эпидемию кашля, возникшую на севере Греции. По мнению врачей, по своим симптомам болезнь была очень похожа на грипп.
В 1977-1978 гг. произошла относительно легкая эпидемия, названная «русским гриппом».
В 1918 г. в США разразилась эпидемия гриппа «испанка». Вирус вскоре был обнаружен в портовых городах Великобритании и Франции, откуда распространилась по Европе. «Испанка» стала самой сильной из известных пандемий: она унесла жизни более 20 млн человек. Прекратить массовое распространение болезни удалось в 1920 г.
Распространение вирусов гриппа в сезоне 2002 - 2003
Вирус А
Вирус В
Вирус А и вирус В
Летом 1889 г. в Центральной Азии отмечена вспышка гриппа, названного «русским». Пандемия распространилась на север – в Россию, на Восток – в Китай и на Запад – в Европу. В 1890 г. она поразила Северную Америку, часть Африки и крупнейшие страны Тихоокеанского региона. По самым скромным подсчетам, только в Европе от «русского гриппа» умерло 250 тыс. человек.
Очаг «азиатского гриппа» был зафиксирован в юго-западном Китае в 1957 г. Охватив близлежащие территории, вирус перекинулся в США. Обуздать заболевание удалось в 1958 г. Грипп поразил от 10 до 35% населения мира.
Эпидемия «гонконгского гриппа» (1968-1969гг.) началась в Гонконге. За неполный год умерли 33 800 человек.

Causative agent

- Influenza A virus belongs to the *Orthomyxoviridae* virus family (myxo means affinity for mucin). The viral genome consists of 8 segments.
- RNA, which collectively encode 10 (or possibly 11) viral proteins



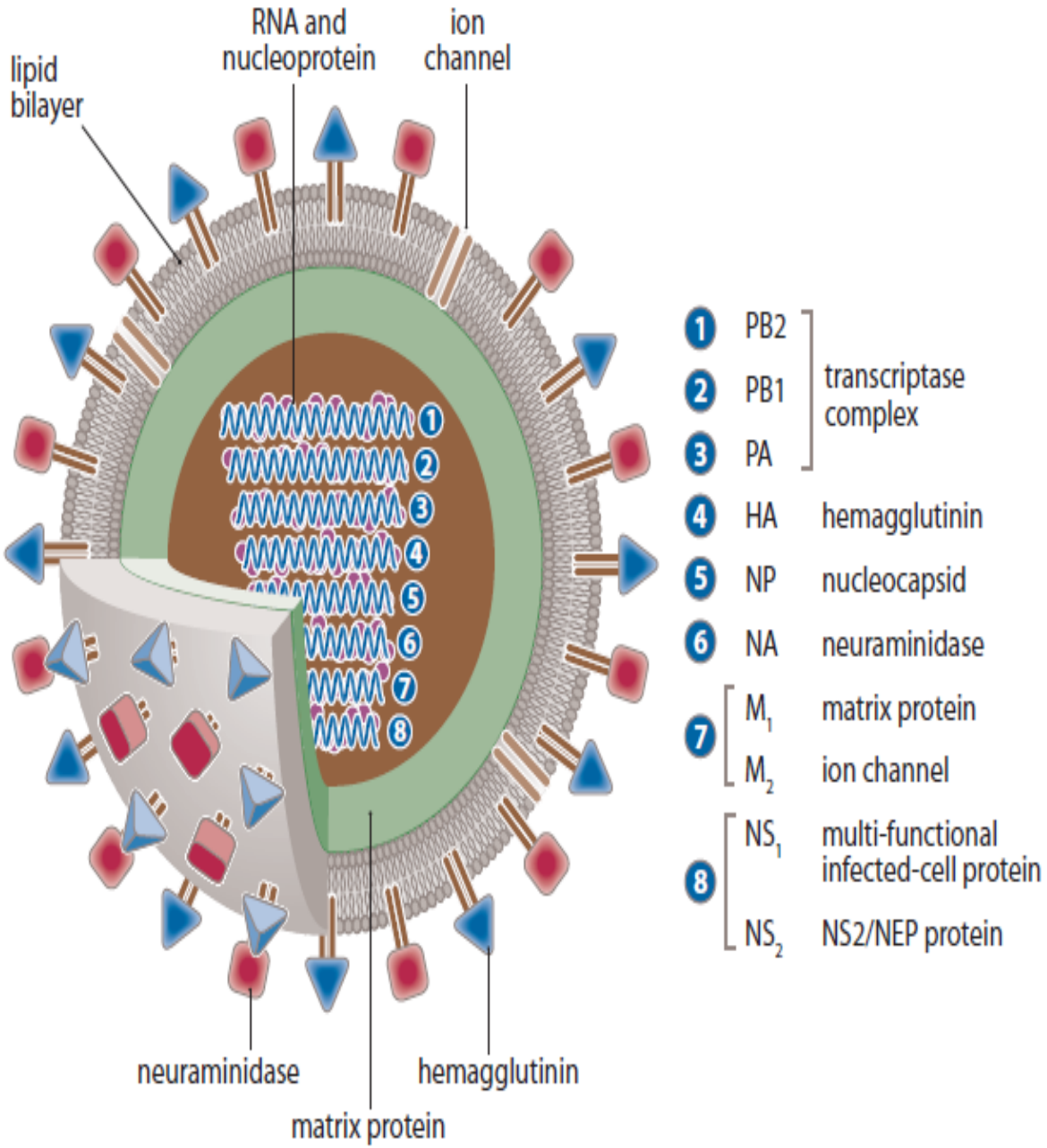


Figure 1. Schematic diagram of an influenza virus. The eight segments of RNA are enclosed within a nucleocapsid, which is in turn surrounded by a lipid envelope into which are inserted two surface glycoproteins, the hemagglutinin and neuraminidase. The helical nucleocapsid contains eight segments of ssRNA each coated with nucleoprotein. This is surrounded by a layer of M1 (membrane or matrix) protein, which in turn is surrounded by a lipid envelope into which are inserted two viral glycoproteins (hemagglutinin and neuraminidase) and a small amount of the M2 ion channel protein.

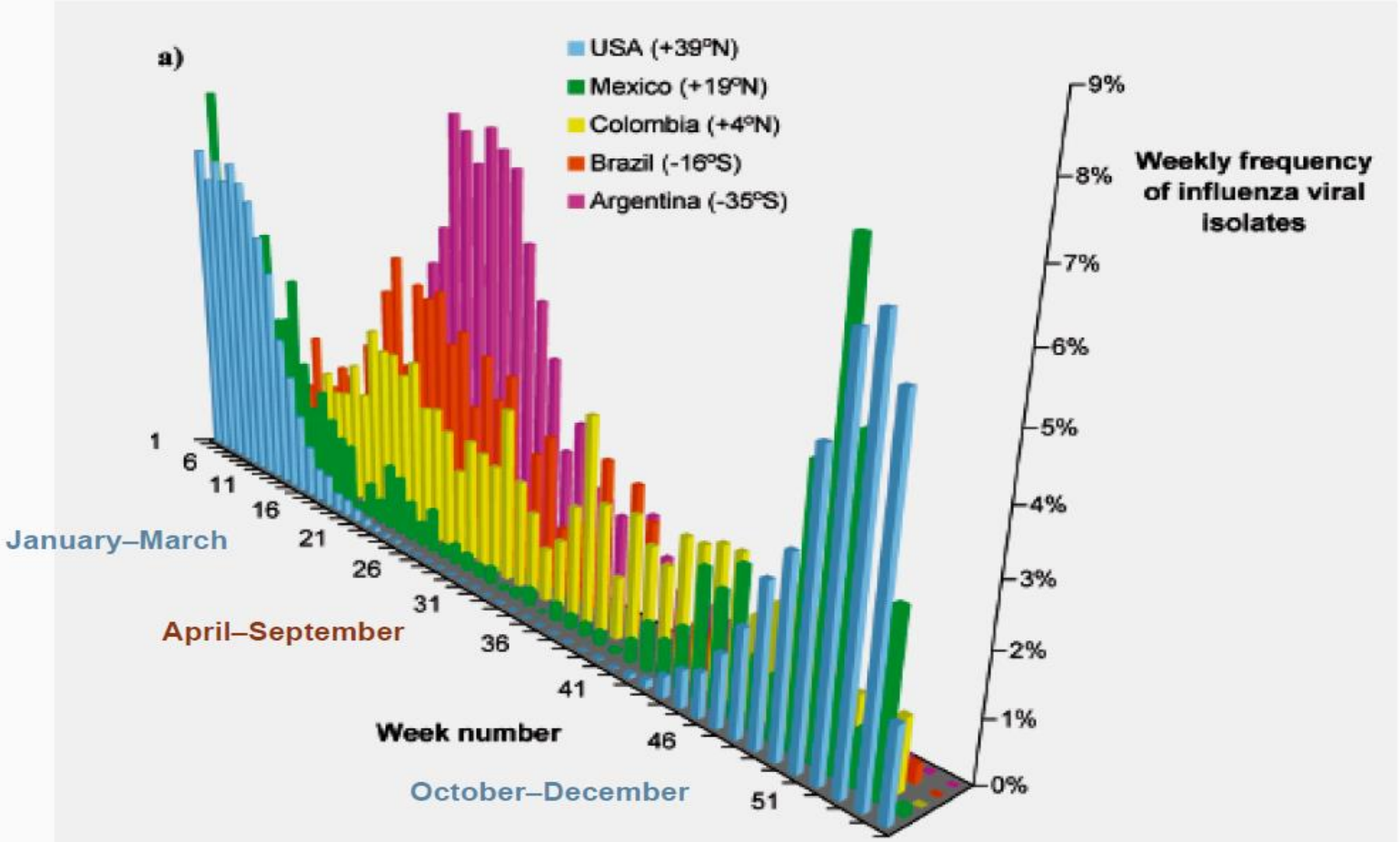
Influenza Virus Nomenclature

- Three levels of nomenclature
  1. Type—influenza "A, B, or C"
  2. Subtype—specific HA, NA: influenza A "H3N2" (defines major surface antigens)
  3. Strain—specific site and year of isolation: "A/Victoria/75 (H3N2)" (defines specific minor antigens)

Epidemiology

Reservoir	Humans, animals (type A only)
Transmission	Respiratory route; Airborne and direct contact
Temporal pattern	Peak: December–March in northern temperate areas
Communicability	1–2 days before to 4–5 days after onset of illness

Seasonality Is Related to Latitude



Source: Viboud, C., Alonso, W. J., Simonsen, L. (2006, April). Influenza in tropical regions. *Plos Med, 3(4)*, e89.

Epidemiology

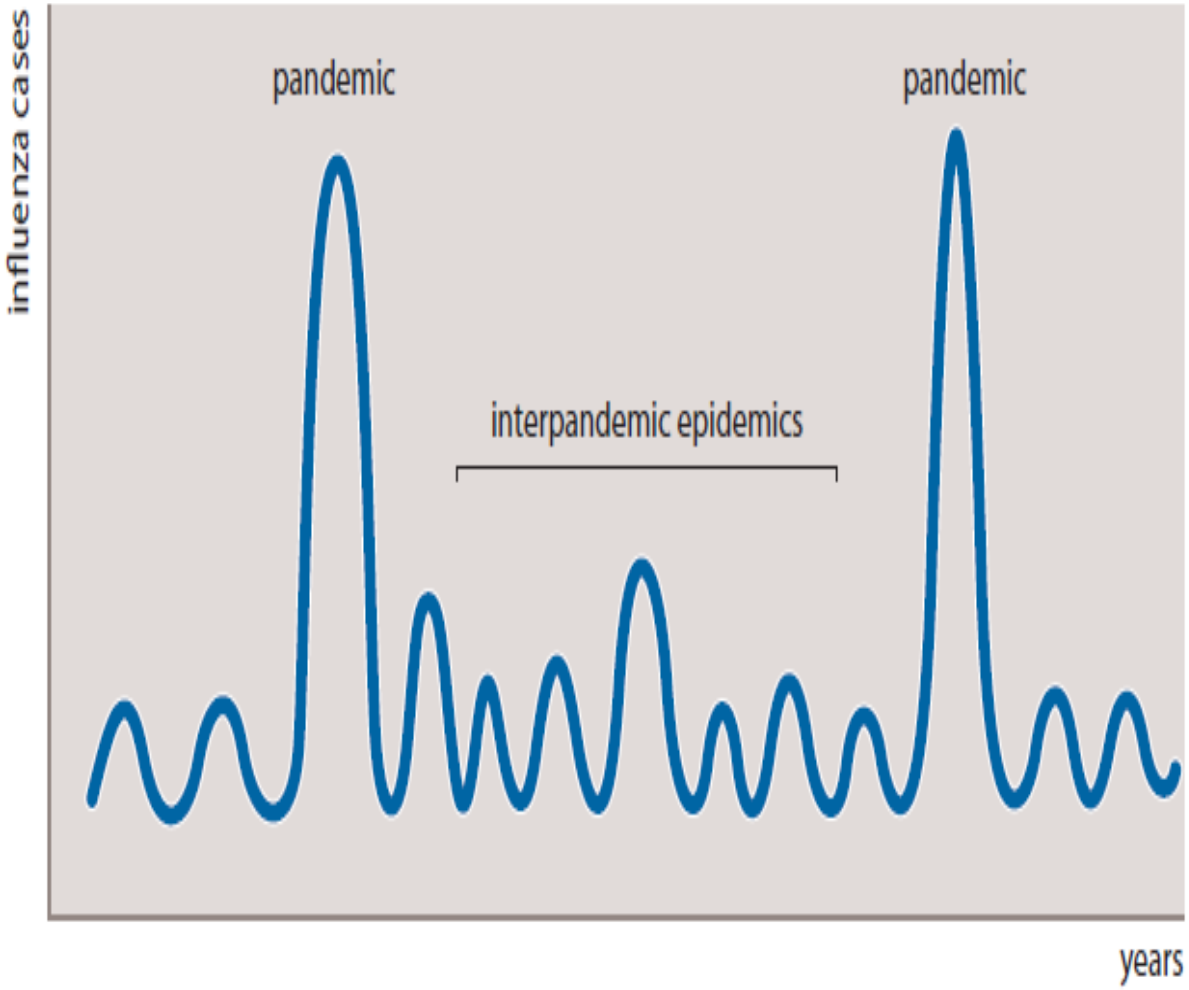
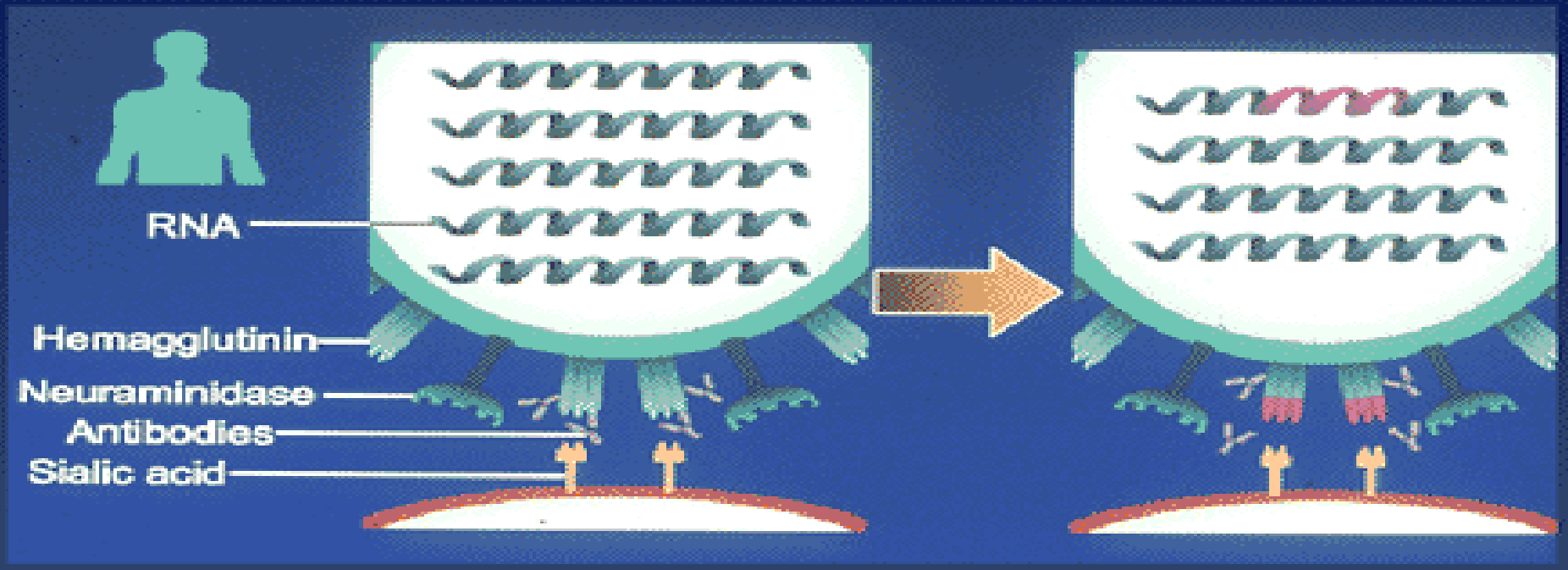


Figure 2. Epidemiology of influenza.
This diagram shows the number of cases of influenza occurring over time. Each peak corresponds to a winter season, illustrating the annual epidemics. Superimposed on that, at irregular intervals averaging about once every 30–40 years, there is a massive peak corresponding to an influenza pandemic.

Transmission of influenza viruses from person to person is believed to be via large droplets (=5 mm diameter) – 100,000 TO 1,000,000 VIRIONS PER DROPLET

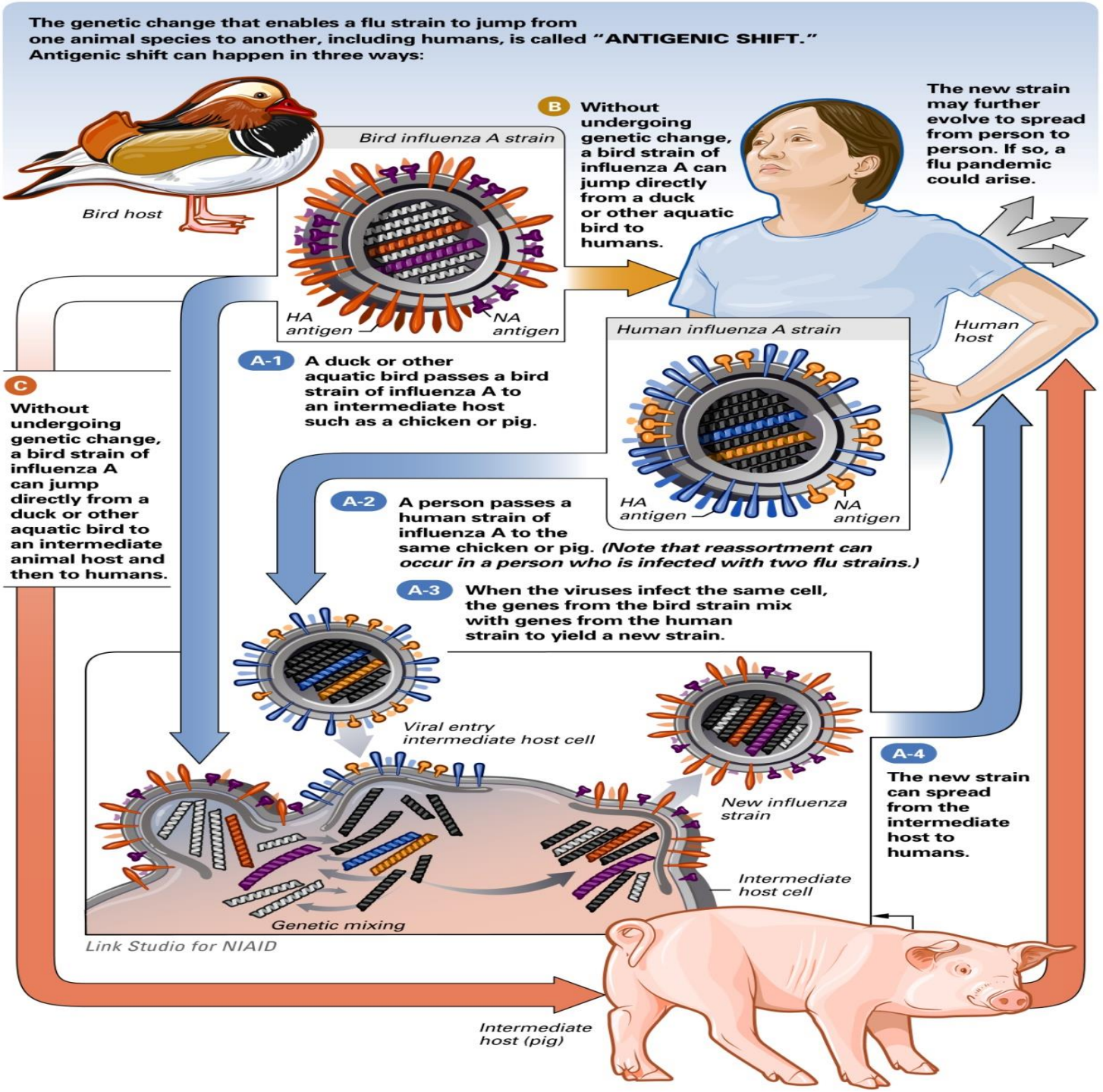
Airborne Transmission of Respiratory Pathogens

Antigenic Drift:
A Modest Change in the Influenza Virus



1.Direct transfer of an **avian** influenza A virus into humans. This process is undoubtedly happening at the moment, with an increasing number of human infections with the avian virus (responsible for large avian epidemics, particularly among chickens) being reported worldwide.

2.The new strain can spread from **the intermediate host** to humans.



- 2. Genetic reassortment of human and avian viruses within a co-infected host.

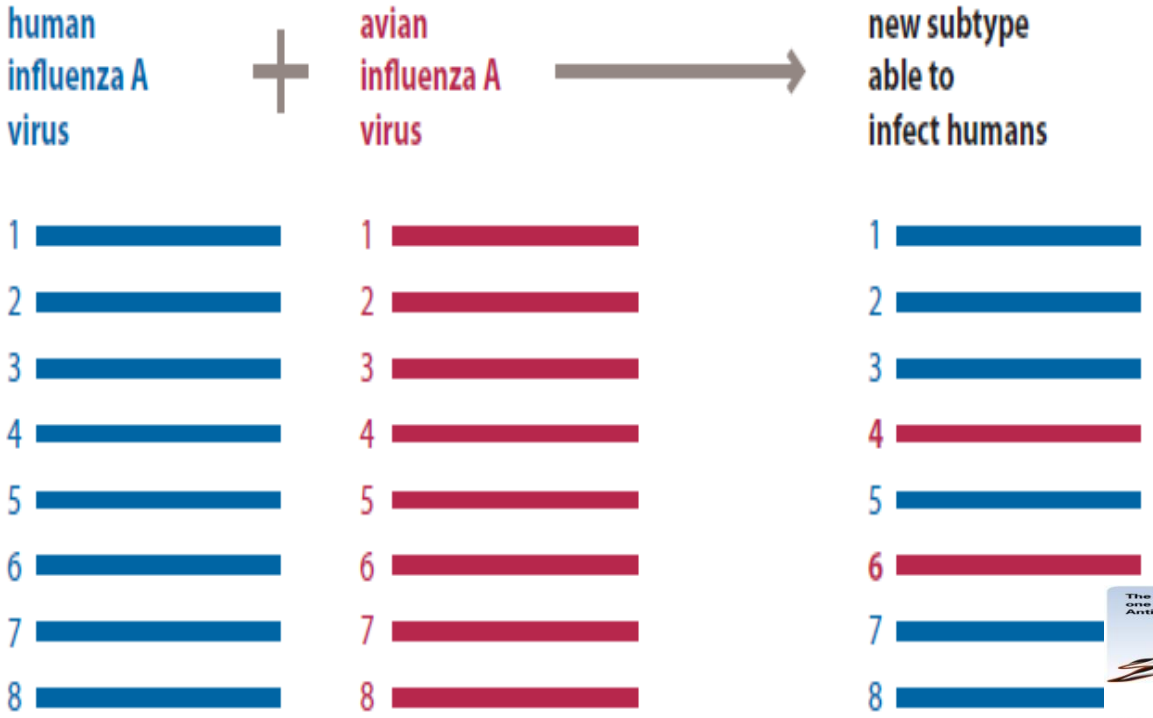
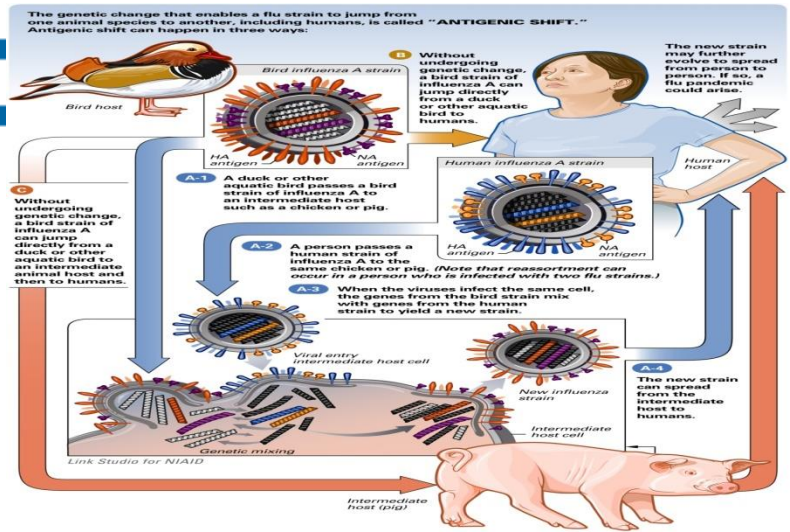


Figure 4. Genetic reassortment.
Each RNA segment (numbered 1–8) is represented by a horizontal line. The human virus is blue, the avian virus is red. When co-infecting the same cell, emergent viruses may possess RNA segments from either 'parent' virus.



Current WHO phase of pandemic alert

November 2005

CURRENT PHASE OF ALERT IN THE WHO GLOBAL INFLUENZA PREPAREDNESS PLAN

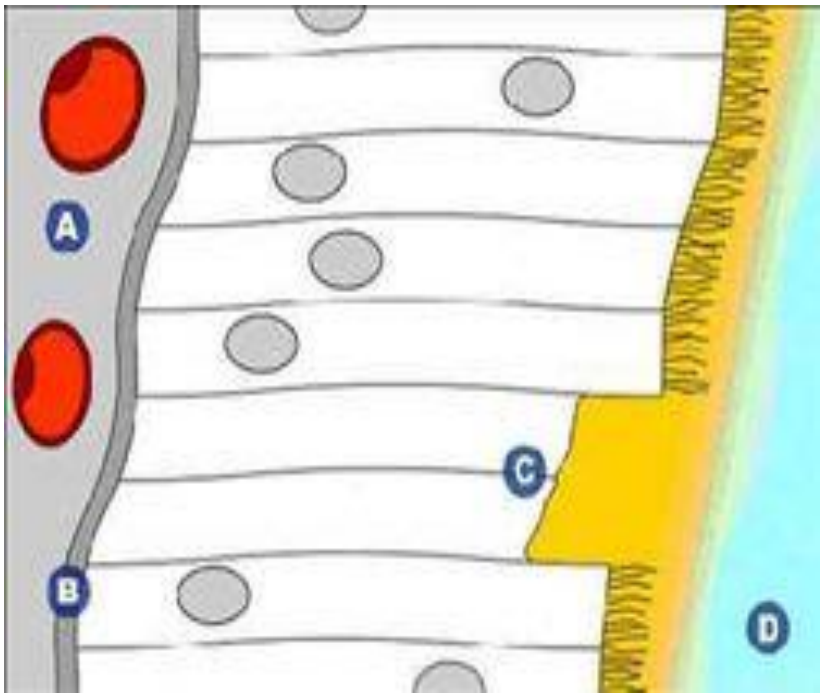
- WHO global influenza preparedness plan

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

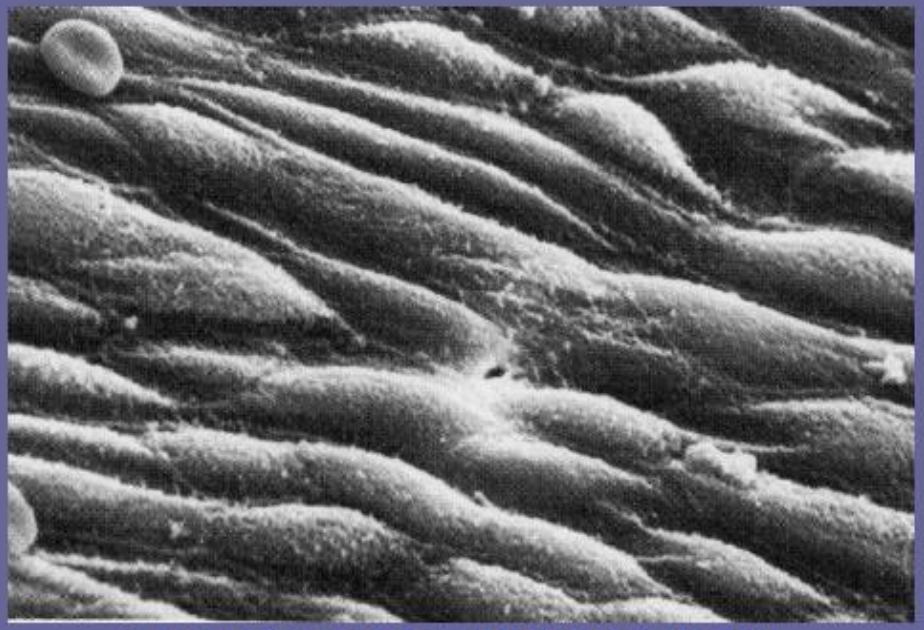
What is the host response to the infection and what is the disease pathogenesis?

Damage to the respiratory epithelial surface occurs due to the cytolytic interaction of the virus and the host cell, that is the infected host cells undergo acute cell death. In effect, the virus strips off the inner lining of the respiratory tract, and in so doing, removes two important innate immune defence mechanisms – mucus-secreting cells, and the muco-ciliary escalator.

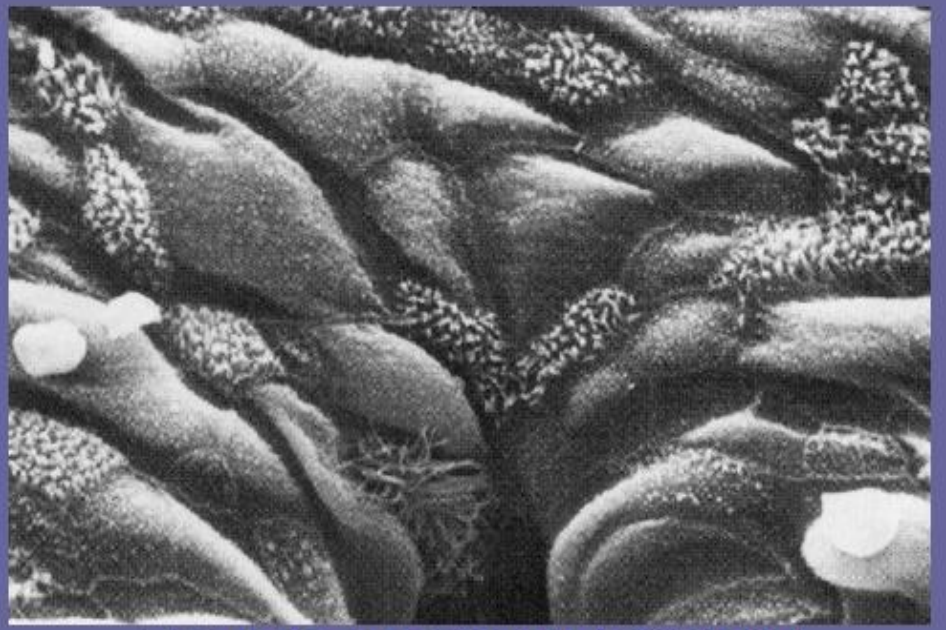
The muco-ciliary escalator then transports any inhaled particulate matter towards the pharynx, to be coughed out in sputum or swallowed. Removal of these defenses, results in potential exposure of the lower respiratory tract to inhaled particulate matter, such as bacteria.



NORMAL TRACHEAL MUCOSA

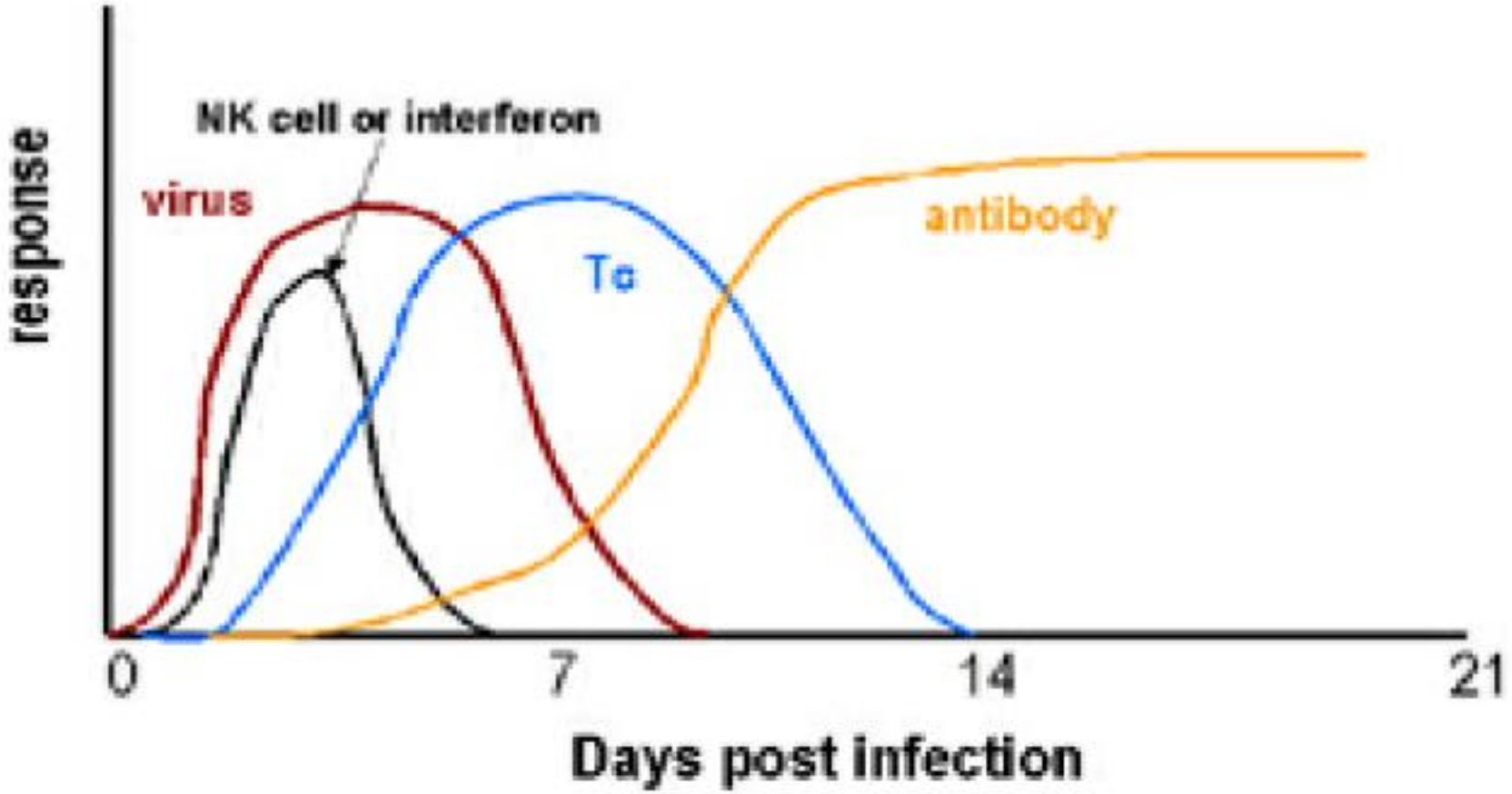


3 DAYS POST-INFECTION



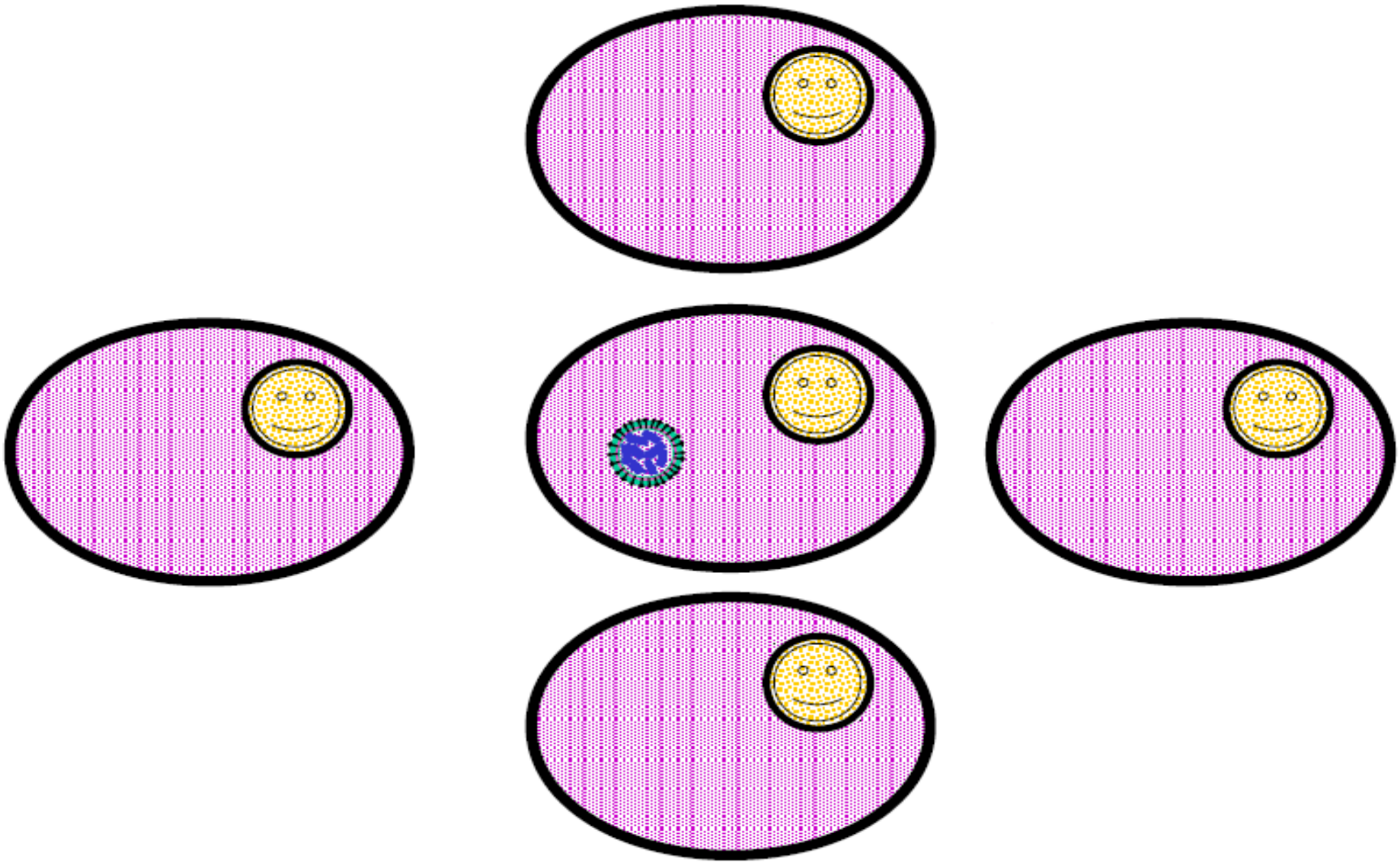
7 DAYS POST-INFECTION

INTERFERON

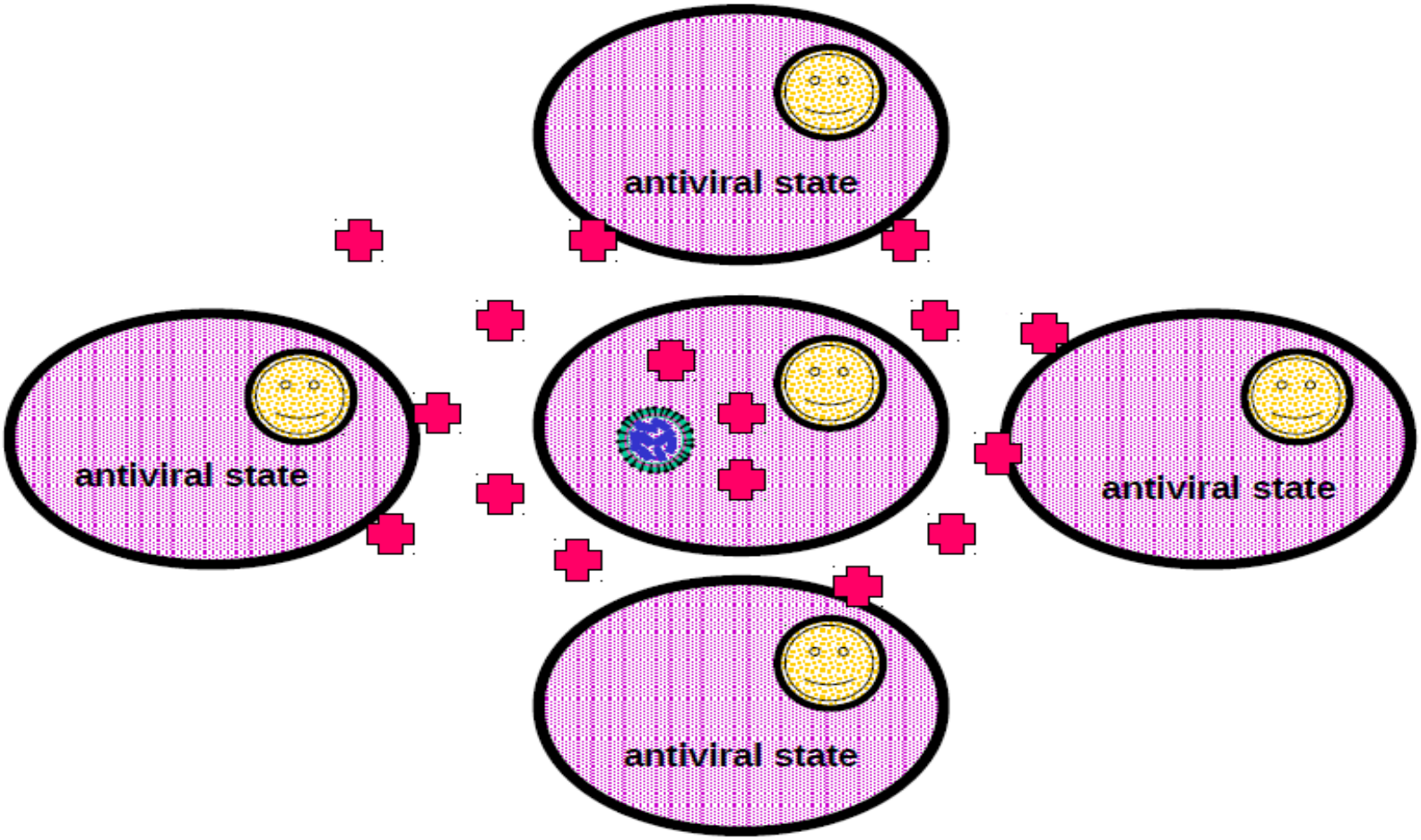


Typical response to an acute virus infection

INTERFERON

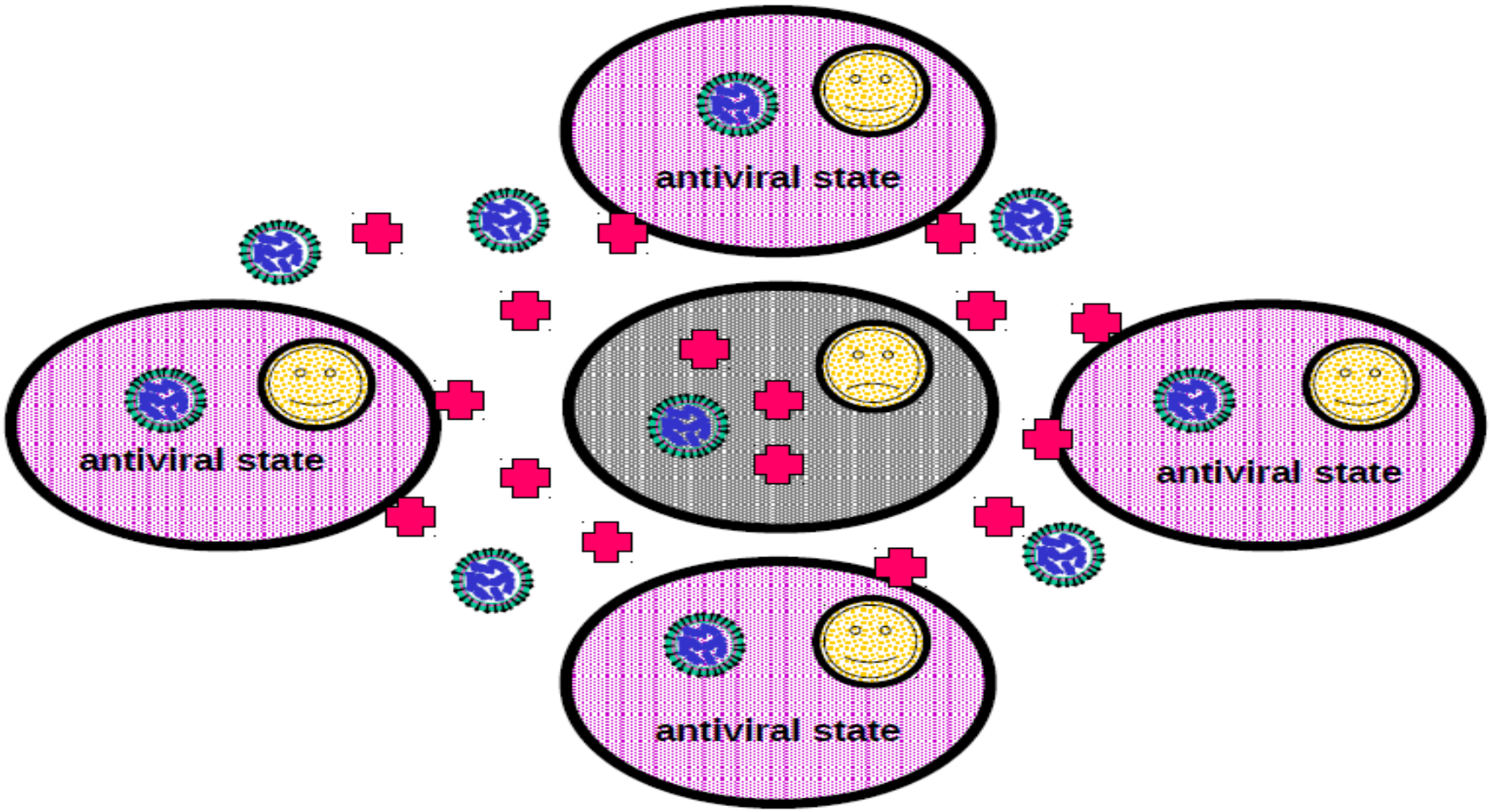


INTERFERON

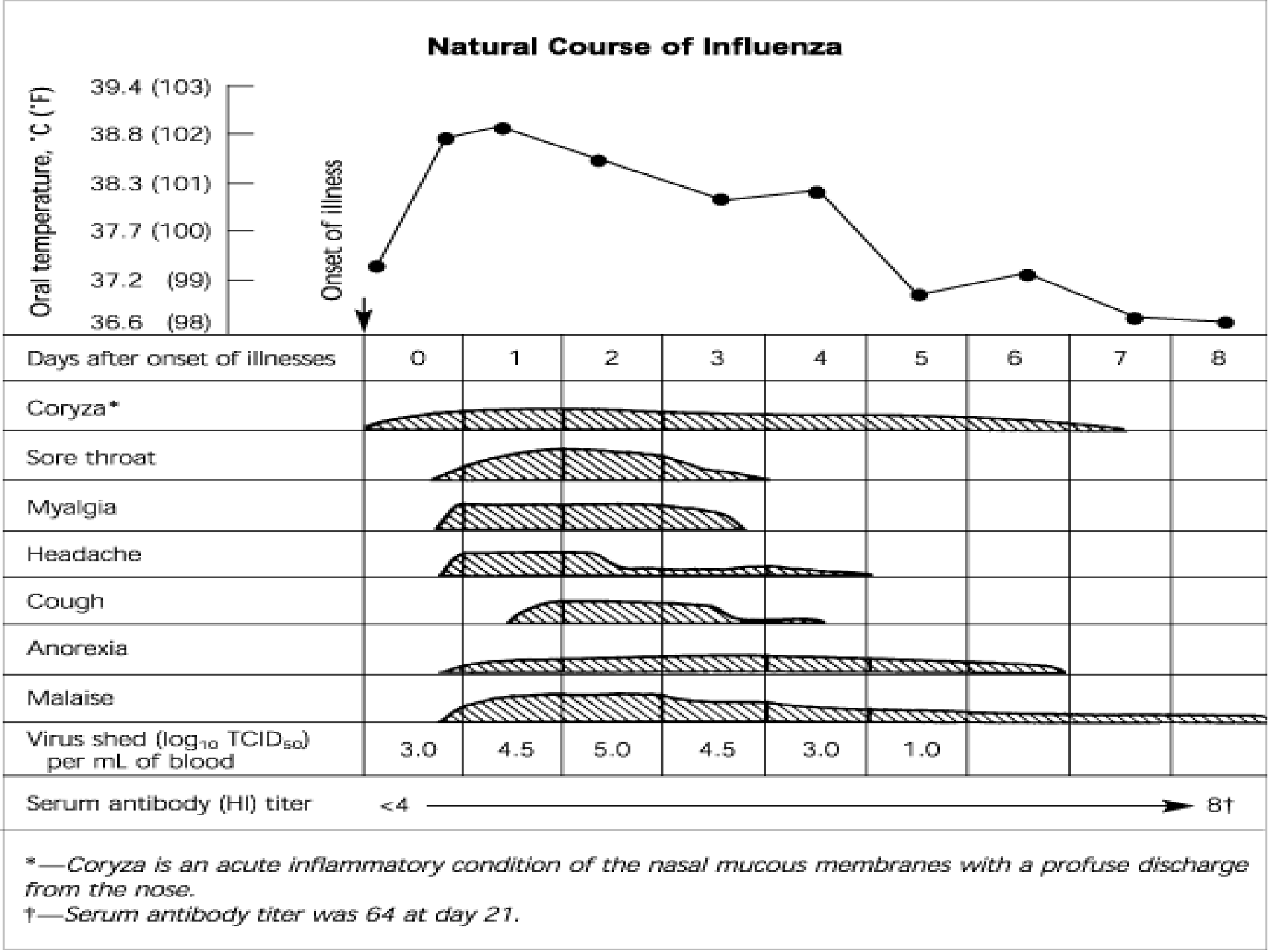


Cells that have been infected with a virus produce interferon, which sends a signal to other cells of the body to resist viral growth.

INTERFERON



Thus, we see the primary infected cell lysis
and resistance to other protected cell by interferon induction



*—*Coryza is an acute inflammatory condition of the nasal mucous membranes with a profuse discharge from the nose.*

†—*Serum antibody titer was 64 at day 21.*

- The commonest life-threatening complication of influenza virus infection is pneumonia, of which there are two pathological types:
- 1.Primary influenzal pneumonia. The virus itself infects right down to the alveoli. There is a mononuclear cell infiltrate into the alveolar walls, and the airspaces become filled with fibrinous inflammatory exudates.

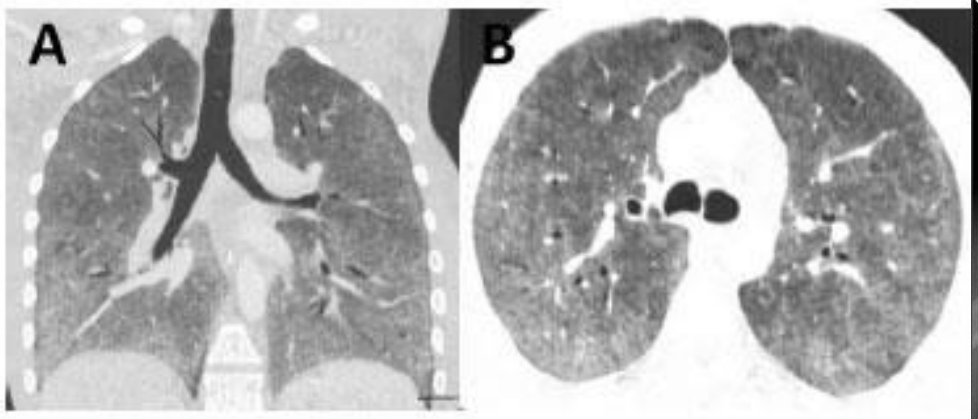
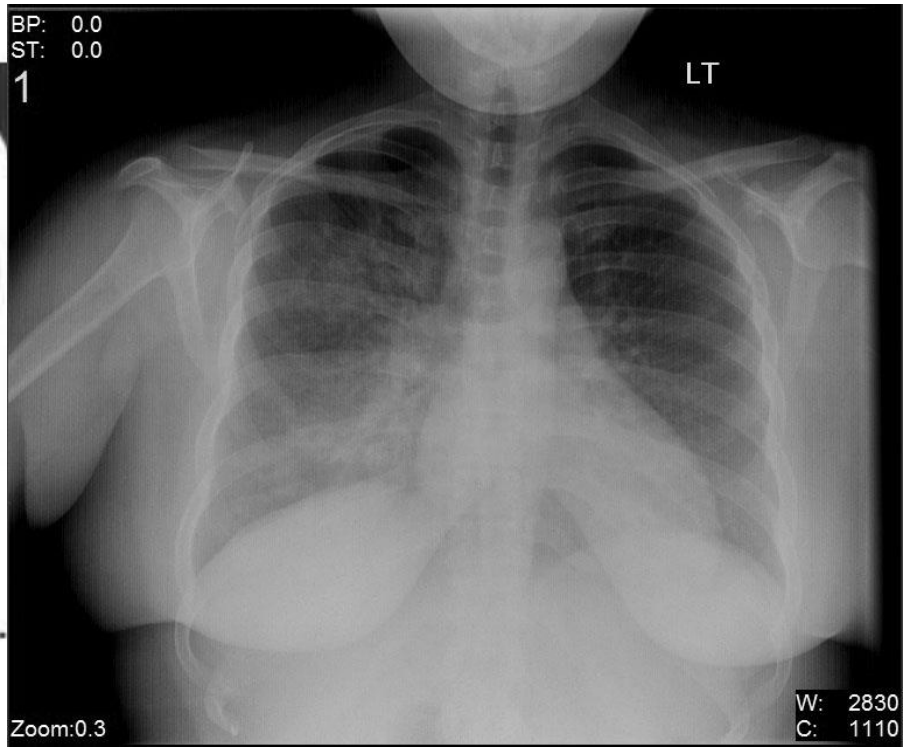


Fig. 1 - Coronal (A) and axial (B) views of chest CT scan in a patient with pneumonia caused by seasonal influenza A virus, showing diffusely distributed ground-glass opacities.

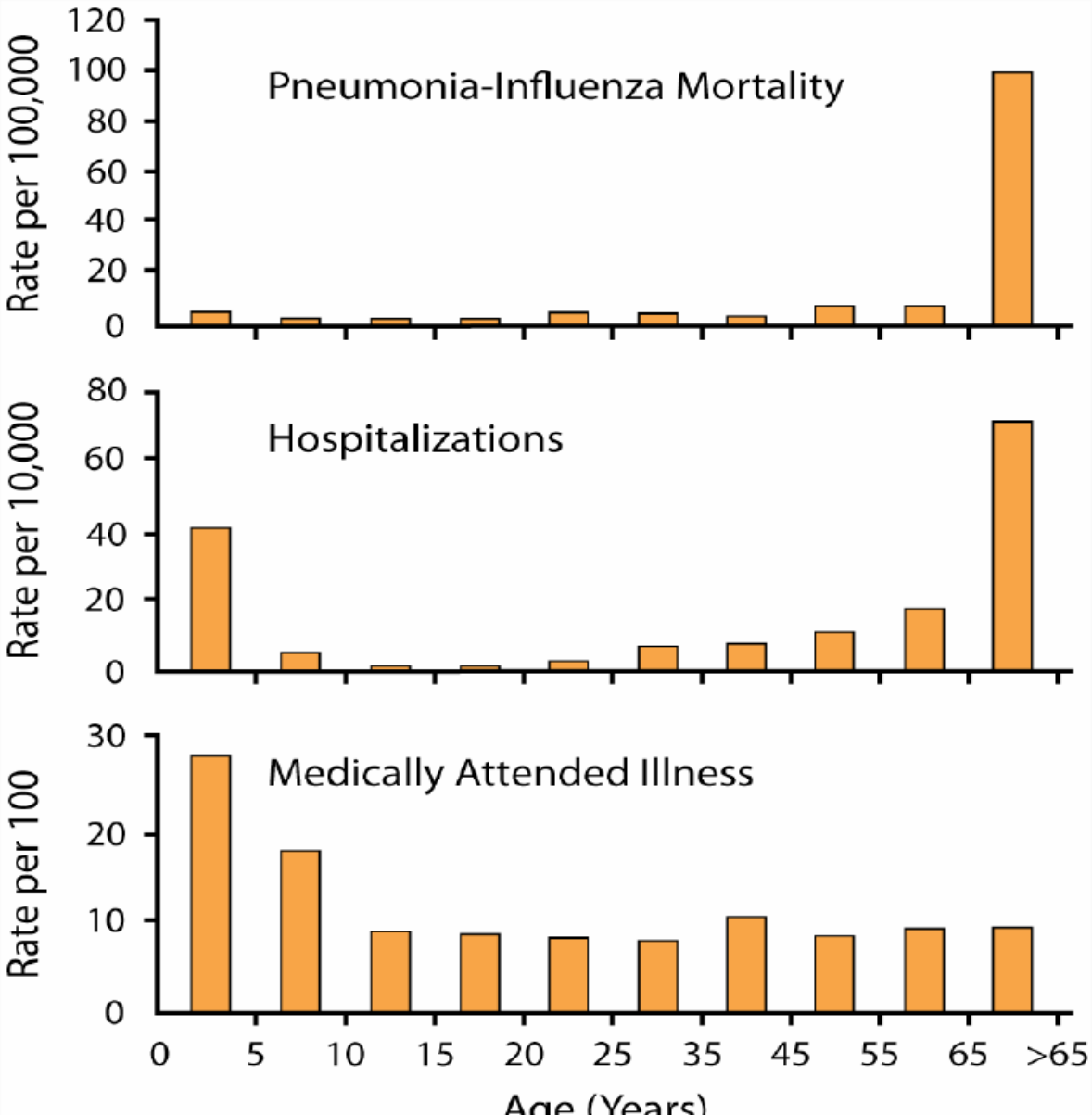


Bilateral interstitial infiltrates in a 31-year-old patient with influenza pneumonia.

Risk Factors for Severe Influenza

- Chronic pulmonary or cardiac disease
- Immunosuppression, HIV
- Sickle cell anemia, hemoglobinopathy
- Aspirin therapy: rheumatoid arthritis, Kawasaki disease
- Diabetes, renal and metabolic disease
- Pregnancy (if >14 weeks during flu season)
- Age greater than 65 years, [now 50 years]

Age-Specific Rates of Influenza Morbidity and Mortality



- **Radiology**
- The radiologic pattern of viral pneumonia is usually less confluent and homogenous than bacterial pneumonia.
- The picture in viral infection may be one of air-space nodules (of 4–10 mm), patchy peribronchial ground glass opacity, or air-space consolidation

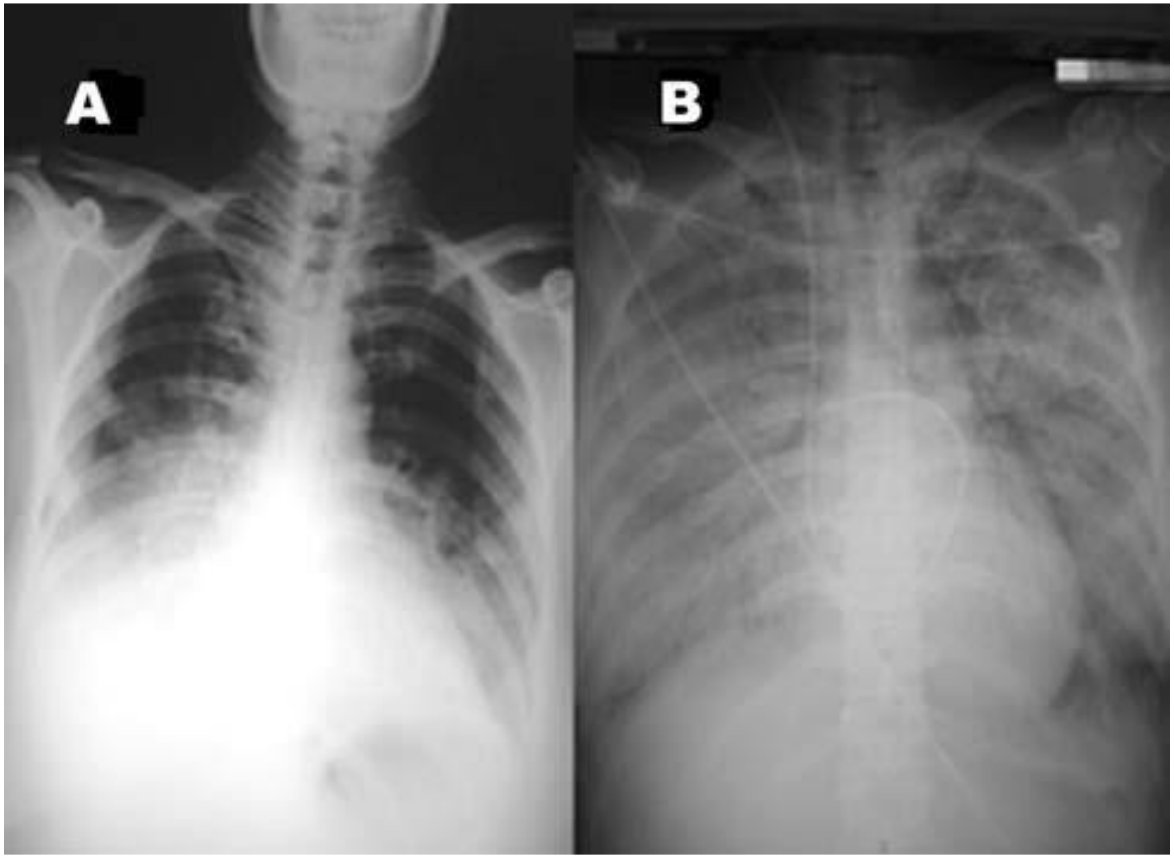


Table 12.1 Options for laboratory confirmation of influenza virus infection

Source of specimen	Diagnostic test	Time to test result	Test characteristics
Respiratory tract (NP aspirate, NP swab/wash, throat swab)			
	Rapid antigen detection	<30 minutes	Less sensitive than other respiratory tract tests
	Immunofluorescence microscopy	~1–4 hours	Immunofluorescent antibody detection more sensitive but slower than direct fluorescent antibody detection
	Nucleic acid testing (e.g. RT-PCR)	4–6 hours	Most sensitive and specific tests for influenza
	Virus isolation – by shell vial culture – by conventional culture	 18–48 hours 3–14 days	 Shell vial method more sensitive
Serum			
	Neutralization test Hemagglutination-inhibition Enzyme immunoassay Complement fixation	Paired serum samples taken during acute and convalescent (2–3 weeks later) phases required	

Adapted from Petric M et al., Role of the laboratory in diagnosis of influenza during seasonal epidemics and potential pandemics [7] and Cox N et al., Manual of Clinical Microbiology [45].

NP, nasopharyngeal; RT-PCR, reverse-transcription polymerase chain reaction.

How is the disease managed and prevented?

Table 2 – Main drugs used to treat the principal viruses that cause community-acquired pneumonia

Action mechanism	Drugs	Posology	Virus
Neuraminidase Inhibitors	Oseltamivir	75-150 mg twice a day for five days (oral route)	Influenza A and B
	Zanamivir	10 mg twice a day for five days (aerosol)	
M2 protein inhibitors	Amantadine	100 mg twice a day for five days (oral route)	Influenza A
	Rimantadine	200 mg once a day for five days (oral route)	
Unknown	Ribavirin (20 mg/mL)	18 hrs/day (aerosol) for three to six days with a nebulizer	RSV Adenovirus[a] Parainfluenza

RSV, respiratory syncytial virus.
[a]For adenovirus, consider the association with cidofovir (5 mg/Kg – once a week, IV route).

The second class of anti-influenzal drugs comprise the neuraminidase inhibitors.

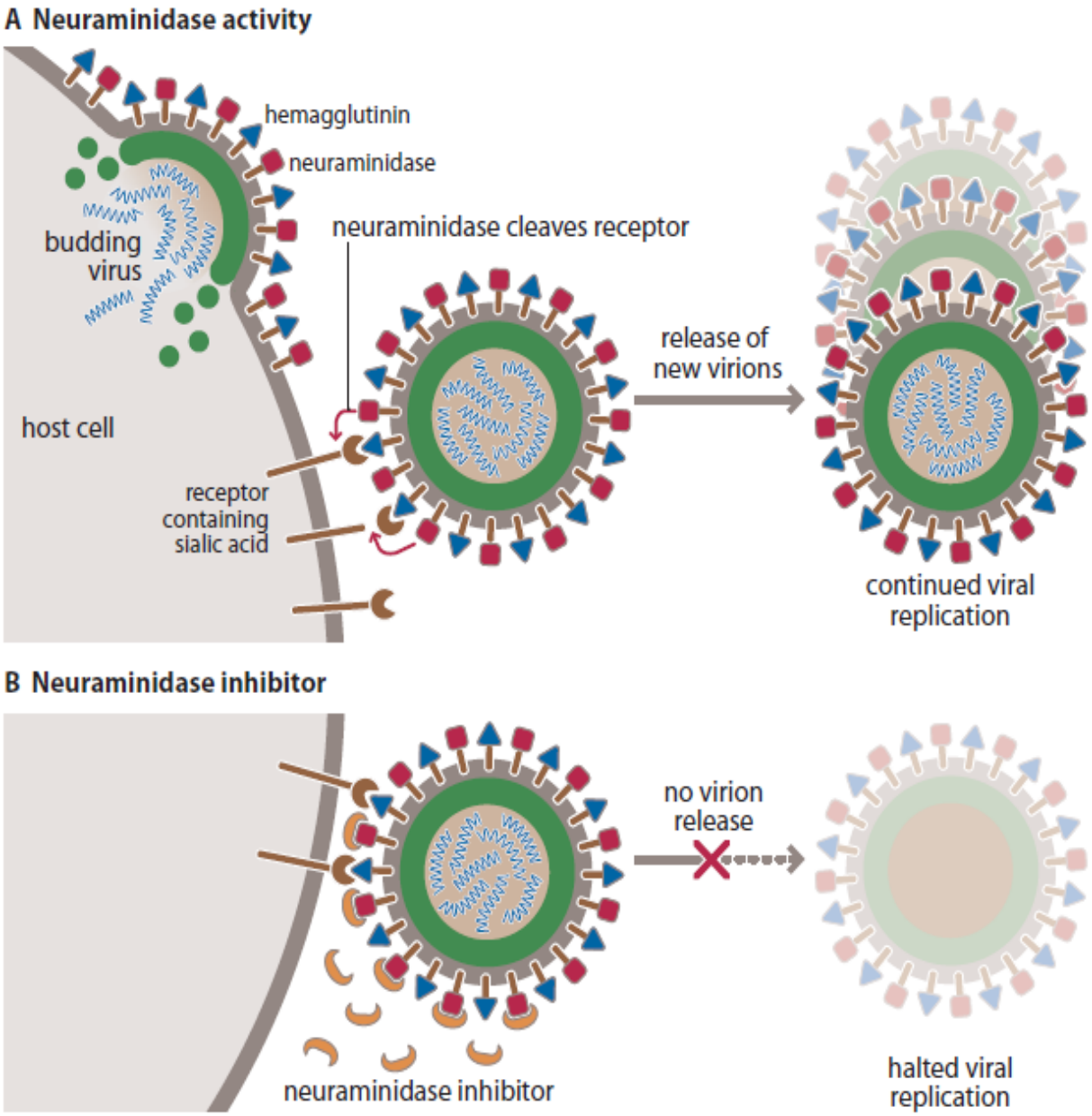


Figure 6. Neuraminidase on the surface of the virus fulfills an essential role in the life cycle of the virus. As newly formed viral particles bud out of an infected cell (A), the hemagglutinin on the viral surface would naturally bind to sialic acid receptors on the surface of the cell. Thus, it would not be possible for these new virus particles to move away from the cell and infect other cells, were it not for the fact that the neuraminidase is there to remove the sialic acid residues and release the viral particles. Thus, inhibition of the viral neuraminidase by small molecule inhibitors (B) prevents virus release from the cell and therefore also prevents any downstream viral infection of and replication within other cells.

Adapted with kind permission from the New England Journal of Medicine Volume 353: 1363 – 1373, Page 1364, Figure 1. © 2005 Massachusetts Medical Society.

Rapivab (peramivir) se administrează după 2 zile de la debutul simptomelor de gripă.

Adulți și adolescenți (vîrsta > 13 ani)

Doza recomandată de Rapivab pentru adulți și adolescenții de 13 ani sau mai mari cu gripă acută necomplicată este o doză unică de 600 mg, administrată prin perfuzie intravenoasă timp de 15 – 30 minute.

Pacienți pediatrici (cu vîrsta de la 2 la 12 ani)

Doza recomandată de Rapivap pentru copii cu vîrsta cuprinsă între 2 și 12 ani ce suportă gripă acută necomplicată este o doză unică de 12 mg/kg (pînă la doza maximă de 600 mg), administrată prin perfuzie intravenoasă timp de 15-30 minute.

Esențialul din informația pentru prescriere

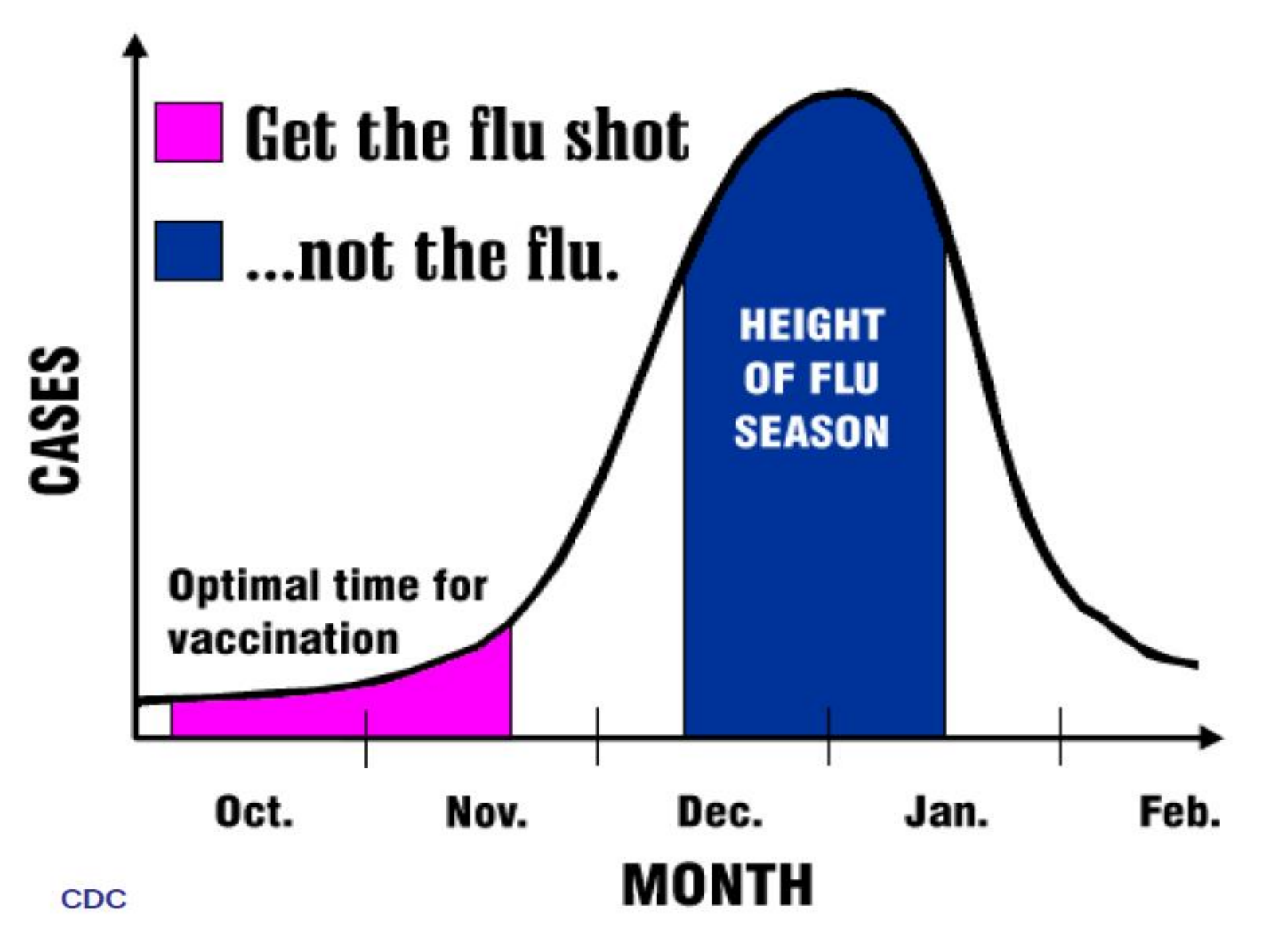
Xofluza (baloxavir marboxil) – comprimate pentru uz oral.
Aprobarea inițială în SUA: 2018

Indicații și utilizare
Xofluza este un inhibitor al endonucleazei polimerazei virale indicat pentru tratamentul gripei acute necomplicate la pacienți cu vîrsta > 12 ani la care simptomele au debutat în ultimele 48 ore.
Limitări în întrebuințare: Virusurile gripale se schimbă tot timpul și factorii precum tipul sau subtipul virusului, apariția rezistenței sau modificări ale virulenței virale pot diminua beneficiul clinic al preparatului antiviral.
Înainte să începeți tratamentul luați în calcul în baza informației prezente despre patternul de acțiune a preparatului dat asupra tipului de virus care circulă.

Dozaj și modul de administrare
Administrați o singură doză de Xofluza per os nu mai tîrziu de 48 ore de la debutul bolii, independent de alimentare. Evitați administrare concomitentă a prepartului cu produsele lactate, produse cu conținut sporit de calciu, laxative policationice, antiacide, suplimente orale (calciu, fier, magneziu, seleniu, zinc).
Doza de Xofluza depinde de masa corporală.

Masa corporală a pacientului	Doza recomandată
40 – 80 kg	doză unică 40 mg
> 80 kg	doză unică 80 mg

Forme de administrare: comprimate 20 și 40 mg


Get the flu shot
...not the flu.
CASES
HEIGHT OF FLU SEASON
Optimal time for vaccination
Oct.
Nov.
Dec.
Jan.
Feb.
MONTH
CDC