What is the ‘flu?

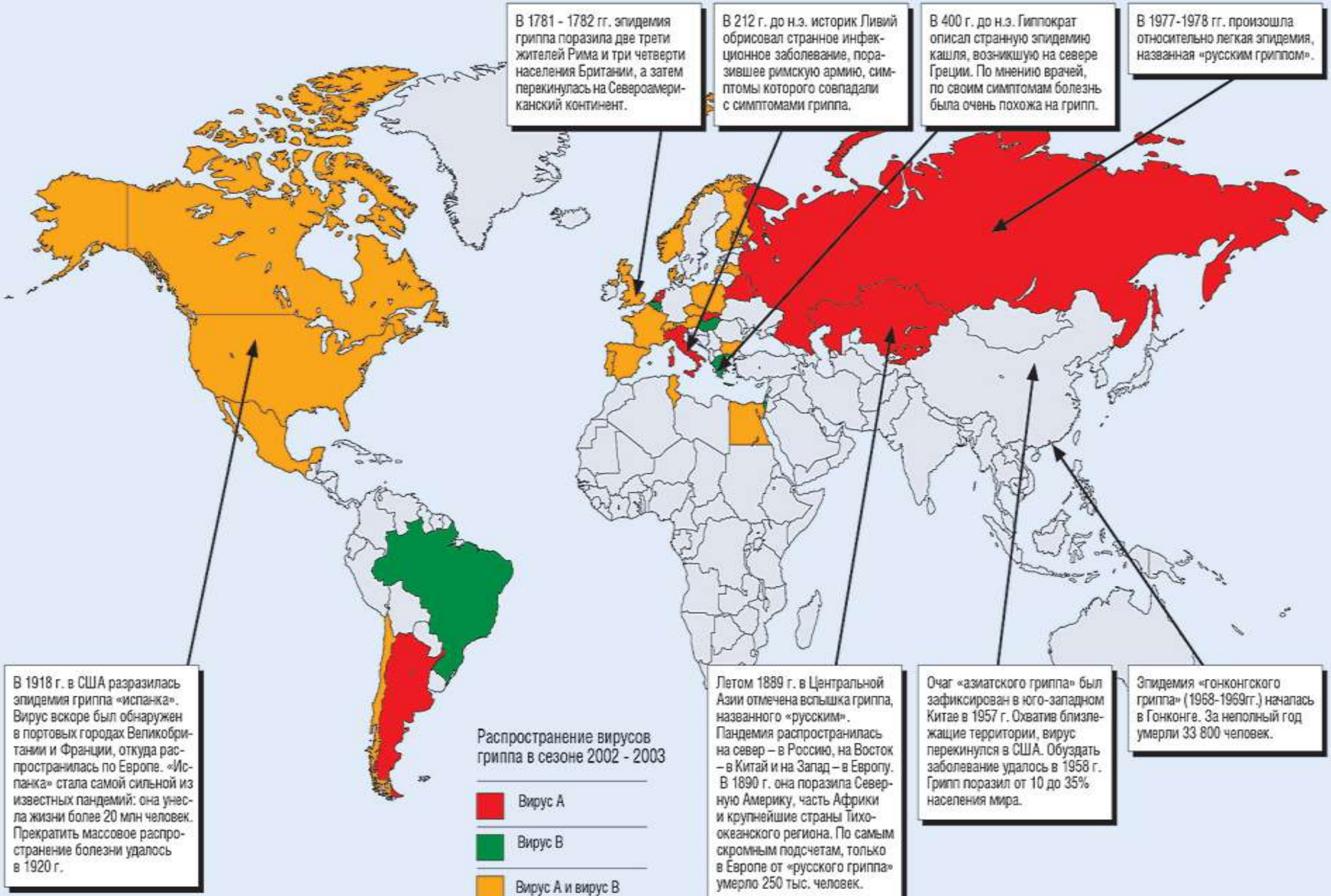
- Influenza (the flu) is a contagious respiratory illness caused by influenza viruses. It can cause mild to severe illness, and at times can lead to death.

- Seasonal influenza epidemics are annually responsible for between 3 million and 5 million cases of severe illness and between 250,000 and 500,000 deaths worldwide*

- Older people, young children, and people with certain health conditions, are at high risk for serious flu complications.

Source: CDC http://www.cdc.gov/flu/about/disease/index.htm

*http://www.medscape.com/resource/influenza


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.

- „Historically has caused pandemics,with millions of deaths worldwide
- Epidemics occur despite effective vaccine and antiviral drugs
- Influenza A virus is a highly mutable virus with frequent antigenic drift and occasional antigenic shift

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

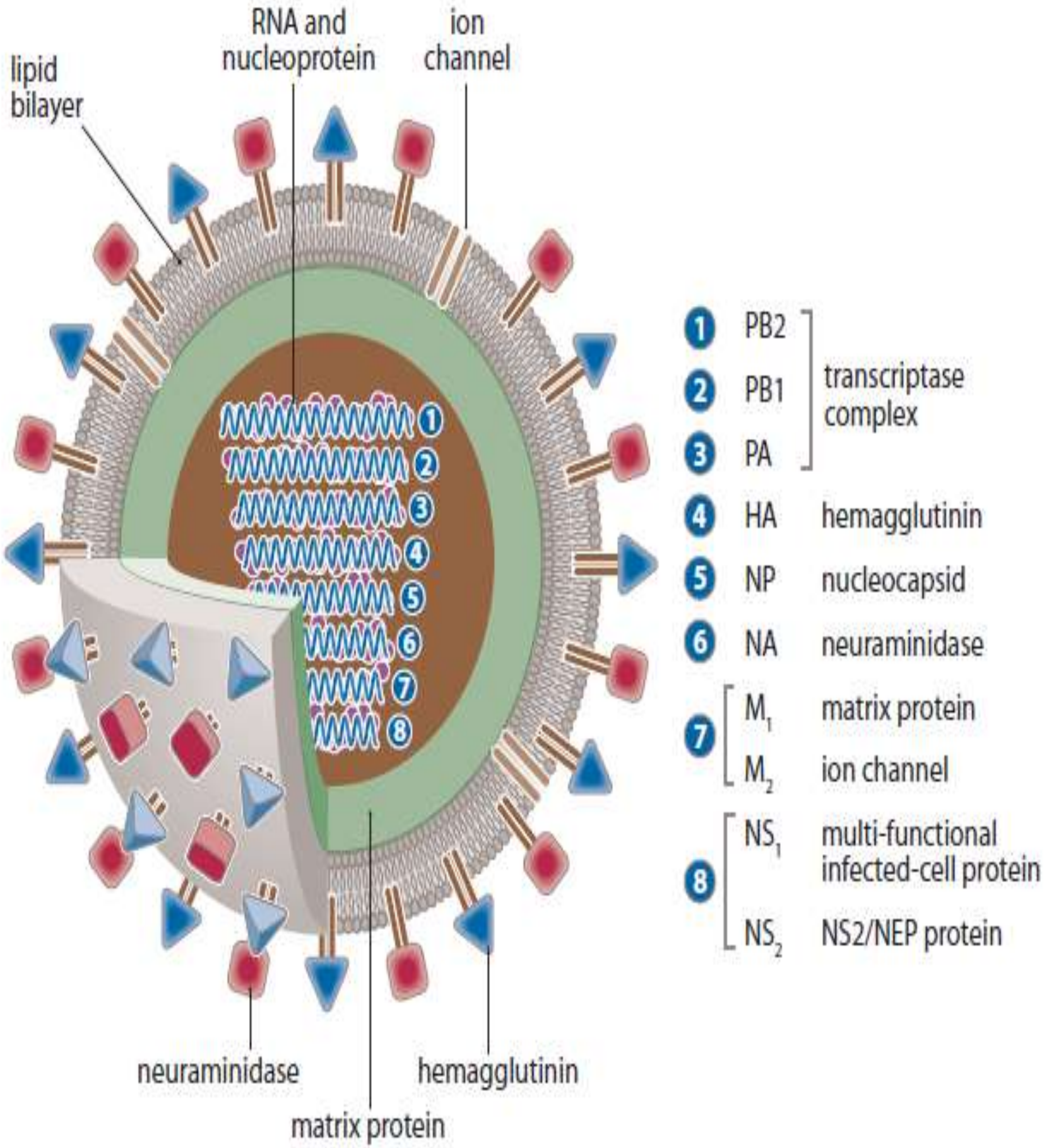


Figure 1. Schematic diagram of an influenza virus. The eight segments of RNA are enclosed within a nucleocapsid, which is in turn surrounded by a lipid envelope into which are inserted two surface glycoproteins, the hemagglutinin and neuraminidase. The helical nucleocapsid contains eight segments of 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 viruses are grouped in one of three antigenic forms, A, B, or C influenza viruses.
- Influenza type A viruses are widespread in nature, infecting many avian species, but also humans, pigs, horses, and occasionally other species such as cats.
- Influenza B virus is an exclusively human pathogen, while influenza C viruses are not serious pathogens in humans.

16 distinct hemagglutinins and nine different neuraminidases have been identified.

When referring to an influenza A virus isolate, it is necessary to specify which subtype it is, for example influenza A/H1N1 or influenza A/H7N7.

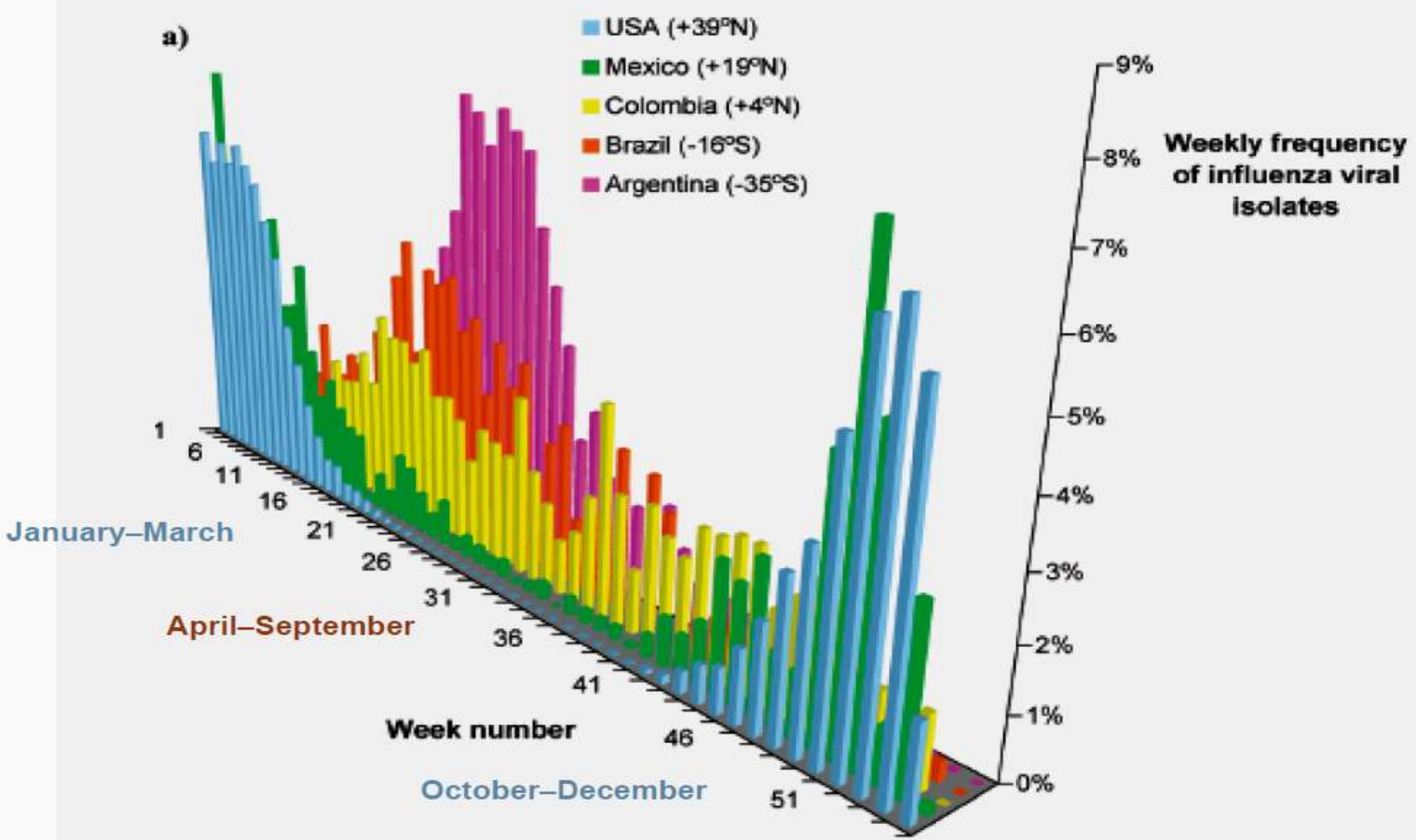
Influenza Virus Nomenclature

- 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



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

Epidemiology

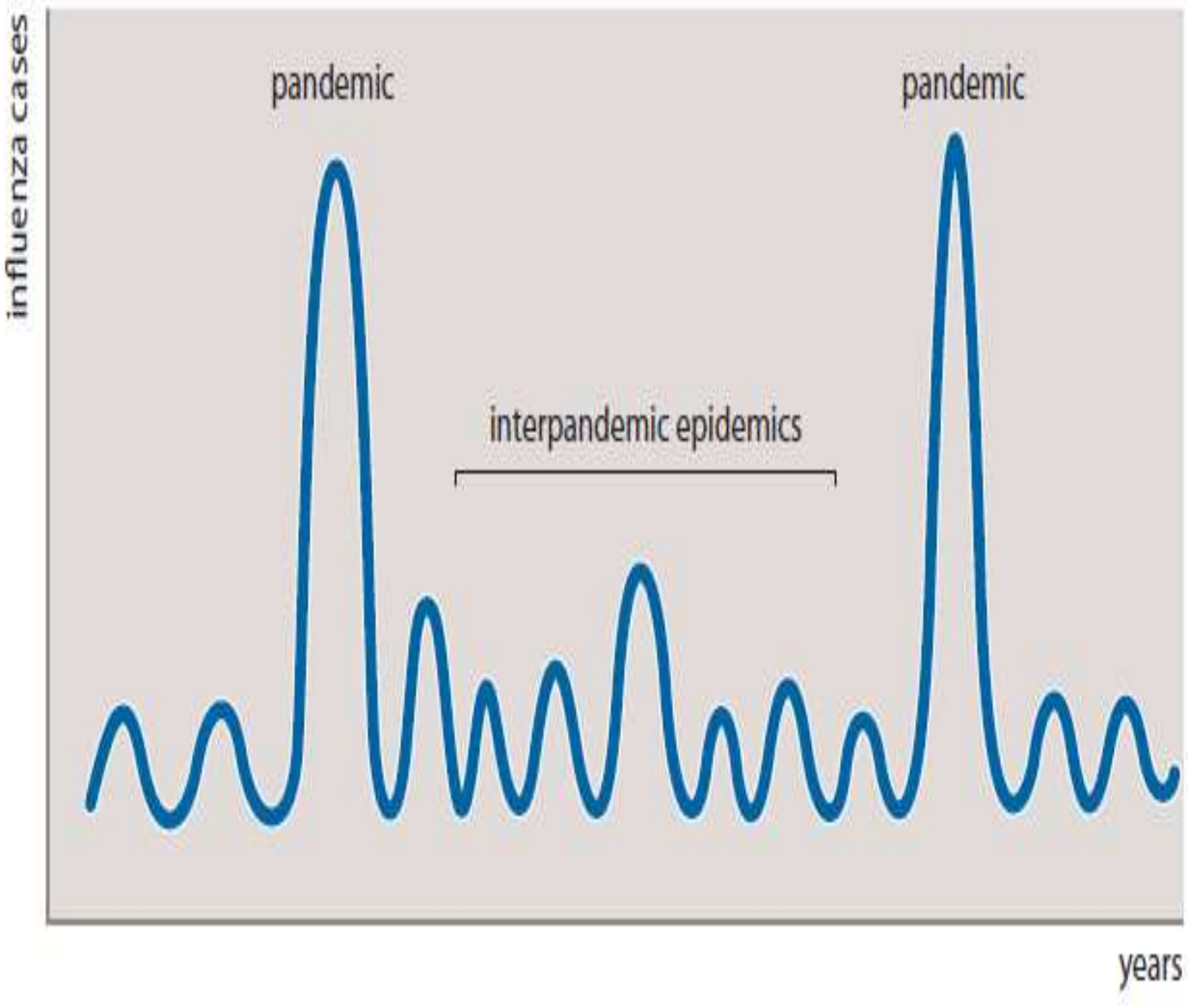
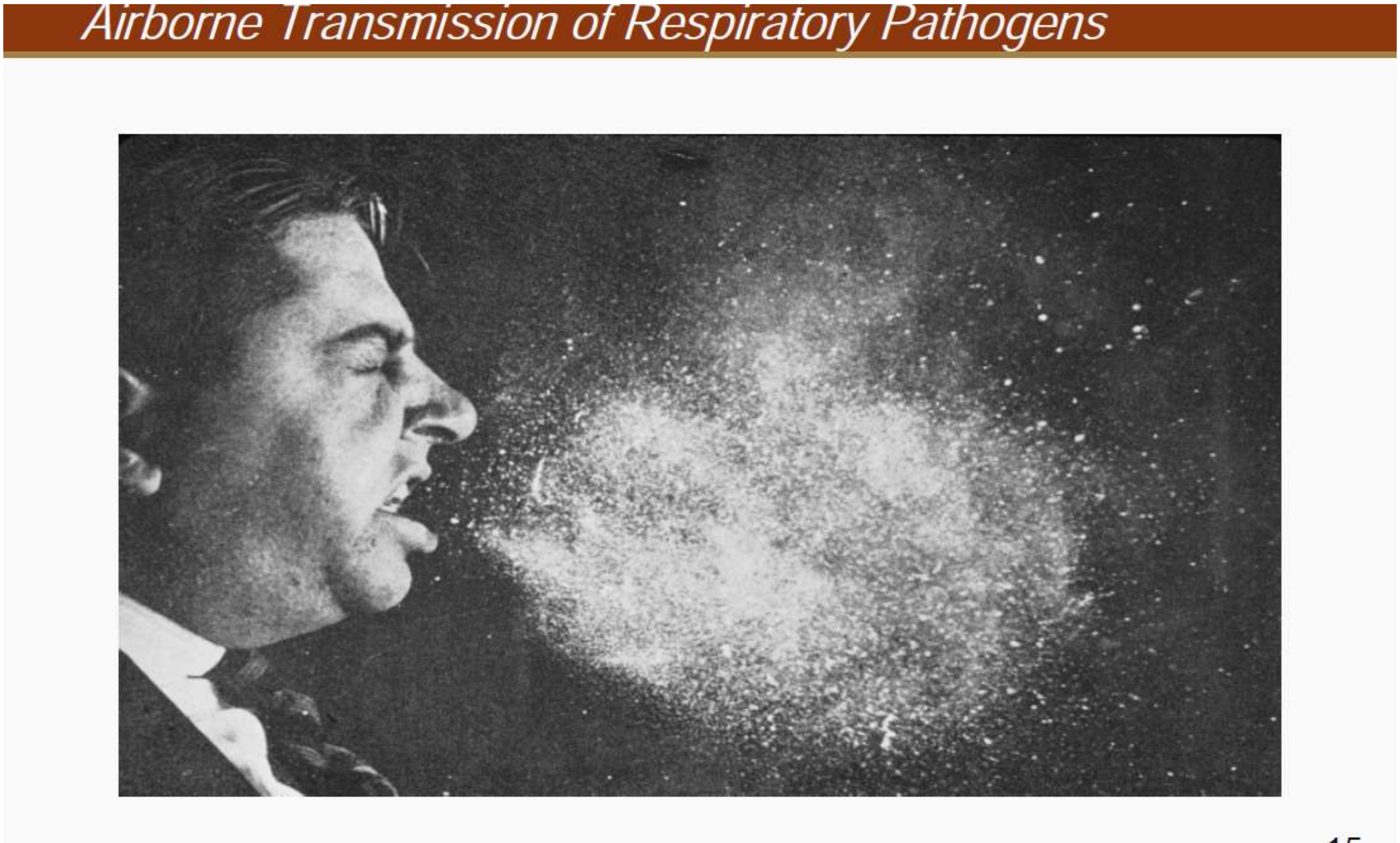


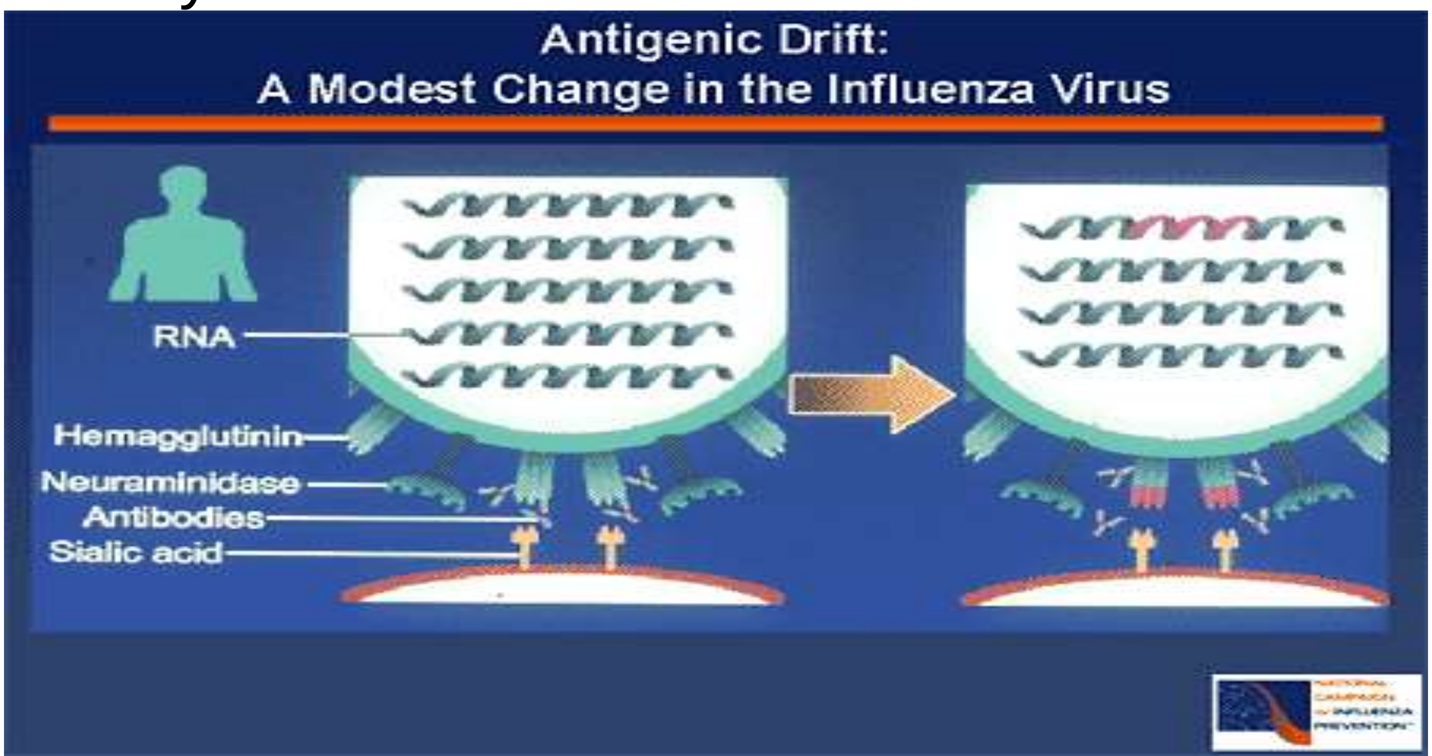
Figure 2. Epidemiology of influenza. This diagram shows the number of cases of influenza occurring over time. Each peak corresponds to a winter season, illustrating the annual epidemics. Superimposed on that, at irregular intervals averaging about once every 30–40 years, there is a massive peak corresponding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

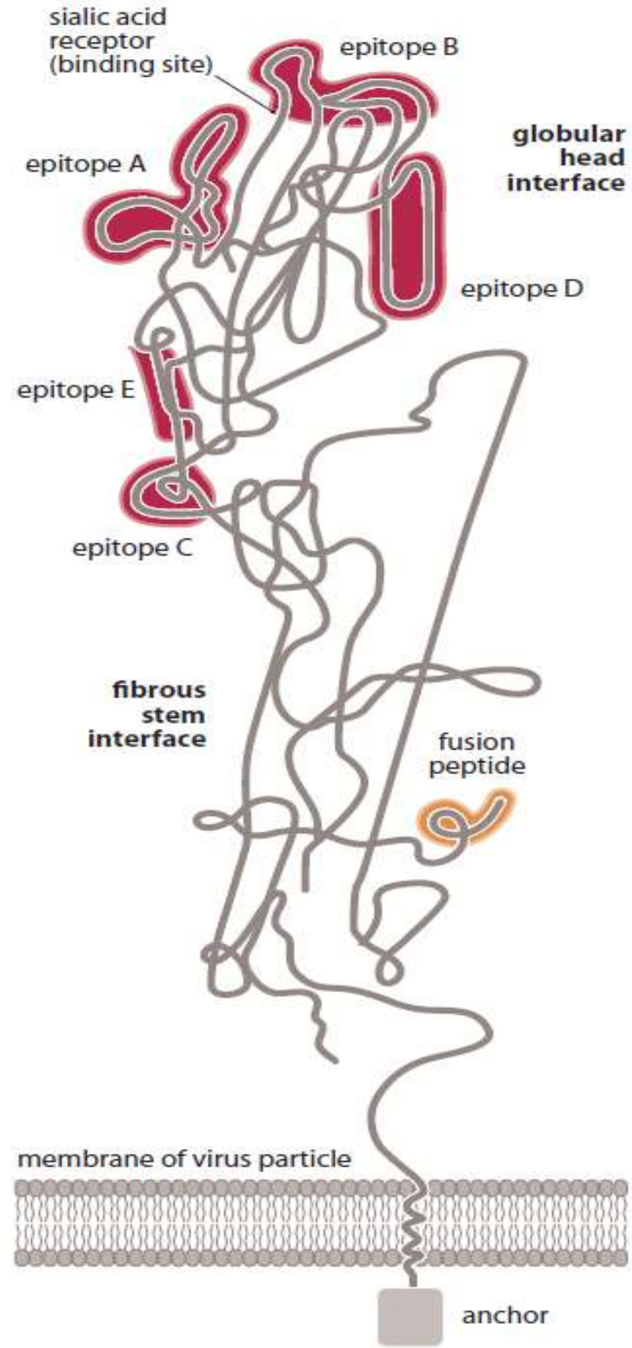


- Influenza epidemics and pandemics arise from the processes of antigenic drift and antigenic shift, respectively.

- Antigenic drift results in the emergence of new strains each year. It arises from random spontaneous mutation occurring within the influenza virus genome as it replicates. Virus causing an outbreak in a particular year will have up to 1% genome sequence difference from virus that caused the previous year's outbreak.



The HA protein contains five highly immunogenic regions to which the antibody response to infection is directed. Mutations within these epitopes may therefore allow virus to escape the inhibitory effects of antibodies that would bind to these regions and prevent virus–cell interactions.
Drift occurs in both influenza A and B viruses.



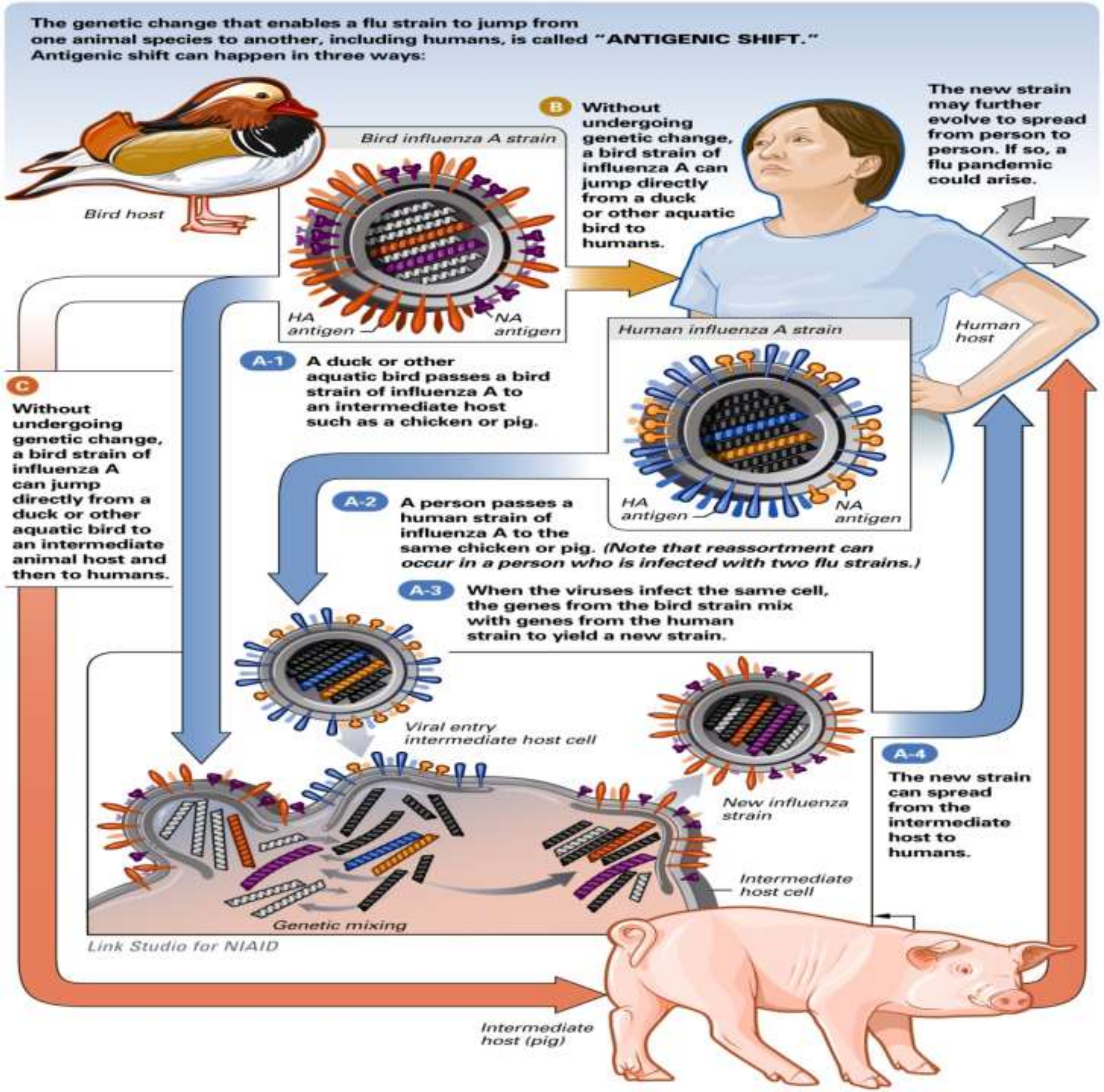
- Antigenic shift, which generates the new pandemic strains, is an altogether different process. The viruses causing the influenza pandemics of the 20th century are shown in Table . Each pandemic arose from the emergence of a new influenza A subtype into the human population. As the new pandemic strain appeared, so the old circulating strain disappeared – thus, in 1956–57, H2N2 completely replaced H1N1, only to be replaced itself by H3N2 virus in 1968. There are two possible underlying mechanisms that can give rise to new pandemic strains, as described below.

Table 1. Pandemic influenza viruses of the 20th century

Year	*Virus*	*Name*
1918–19	H1N1	Spanish flu
1956–57	H2N2	Asian flu
1968	H3N2	Hong Kong flu

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.



There is a worry, however, that as it replicates within human cells, this virus may acquire mutations that could result in adaptation to efficient replication within human cells, at which point person to person spread will become more likely.

There is some evidence that the H1N1 virus that caused the 1918–19 pandemic was entirely avian in origin, and that it had been causing sporadic infections within humans for several years before its emergence as a pandemic virus in 1918.

The presumption is that during those preceding years the virus acquired the necessary mutations to allow adaptation to increased replication within human cells.

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

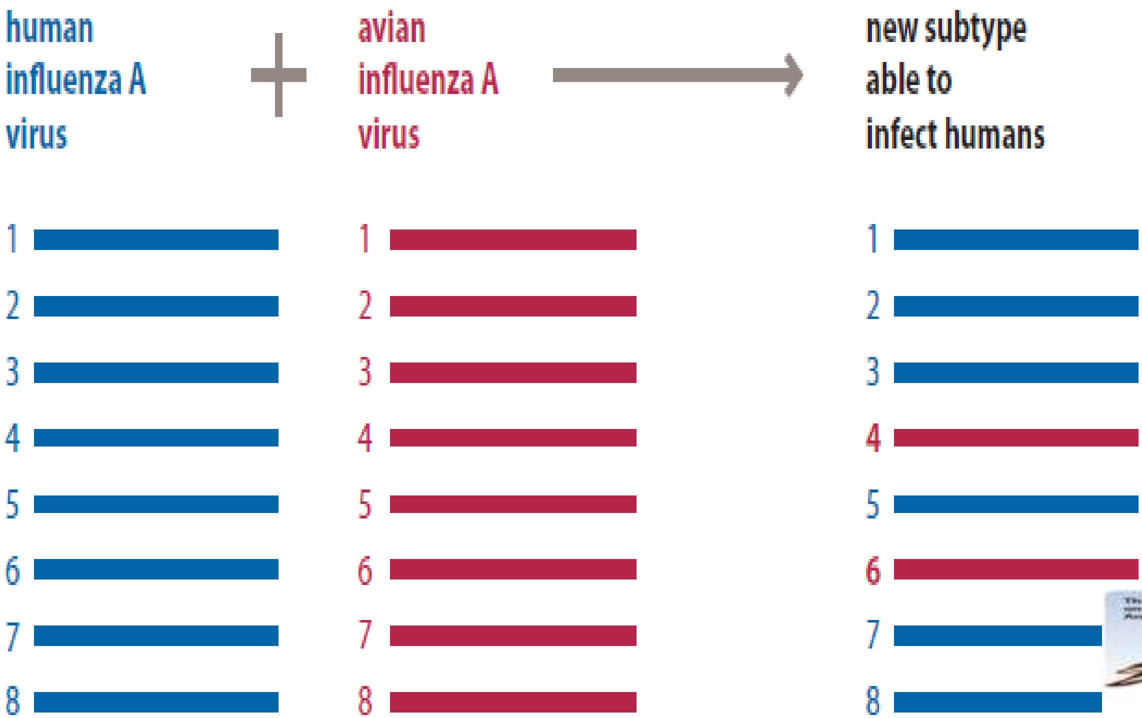
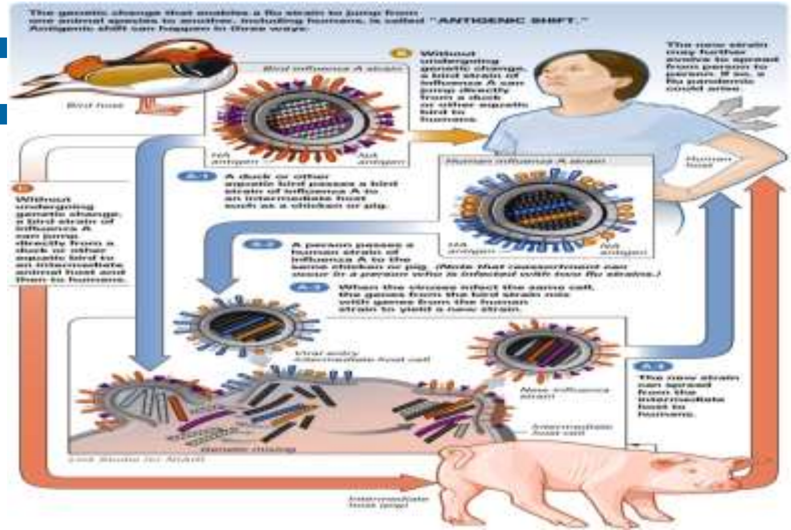


Figure 4. Genetic reassortment. Each RNA segment (numbered 1–8) is represented by a horizontal line. The human virus is blue, the avian virus is red. When co-infecting the same cell, emergent viruses may possess RNA segments from either 'parent' virus.



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

Entry and spread within the body

- Influenza virus enters via the nasal or oral mucosa. In humans and other mammalian species, the virus is pneumotropic (in avian species, the virus infects a variety of tissues and is primarily spread through the fecal–oral route), that is it preferentially binds to, and infects, respiratory epithelial cells, all the way from the oropharynx and nasopharynx right down to the alveolar walls.

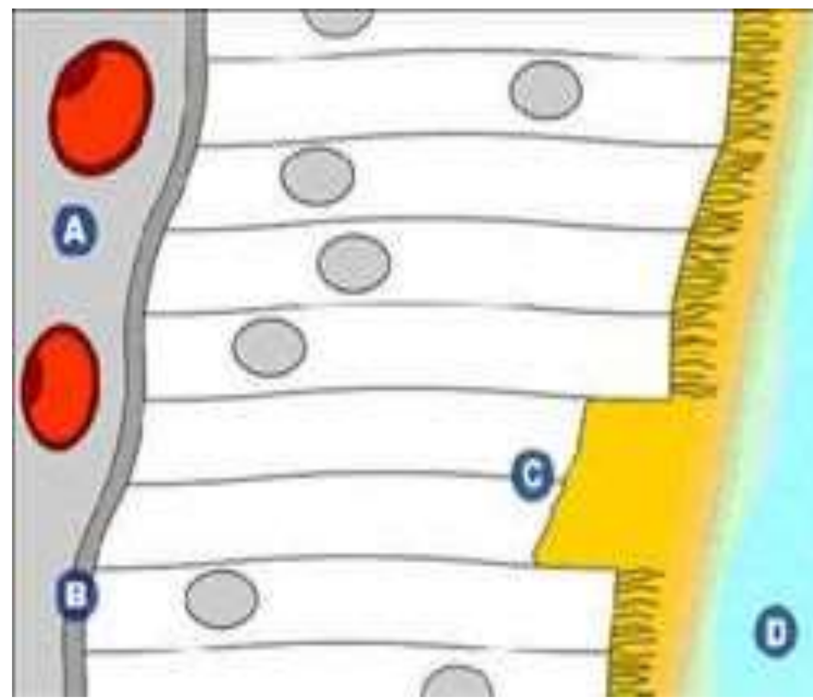
- Influenza virus attaches to target cells via an interaction between the viral ligand, hemagglutinin, and a cellular receptor, comprising sialic acid on the surface of respiratory epithelial cells.

- The virus then replicates and new virions are released by the infected cells by budding at the plasma membrane of the host cell. With infections of the lower respiratory tract, direct infection of pneumocytes and macrophages can occur.

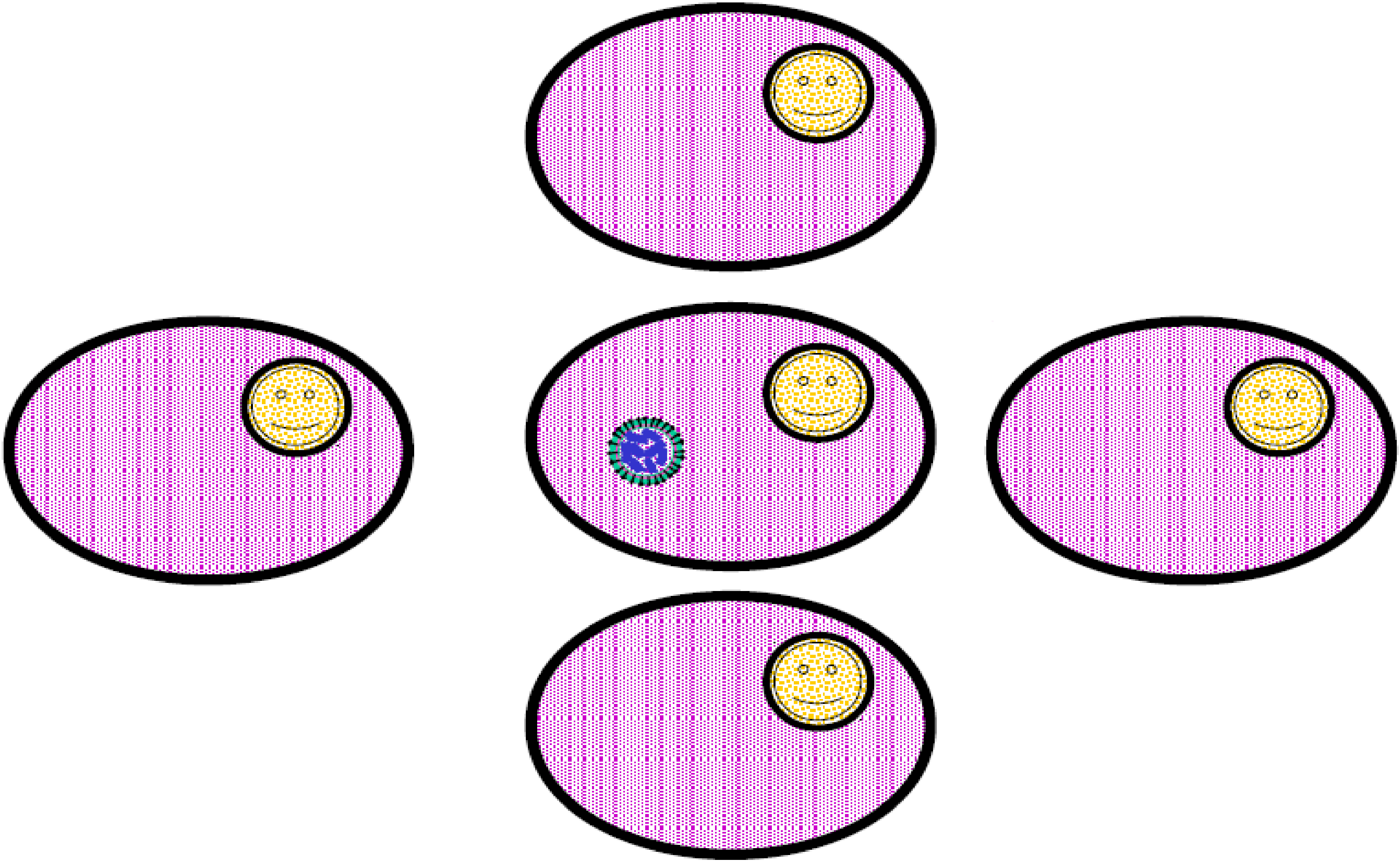
What is the host response to the infection and what is the disease pathogenesis?

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.

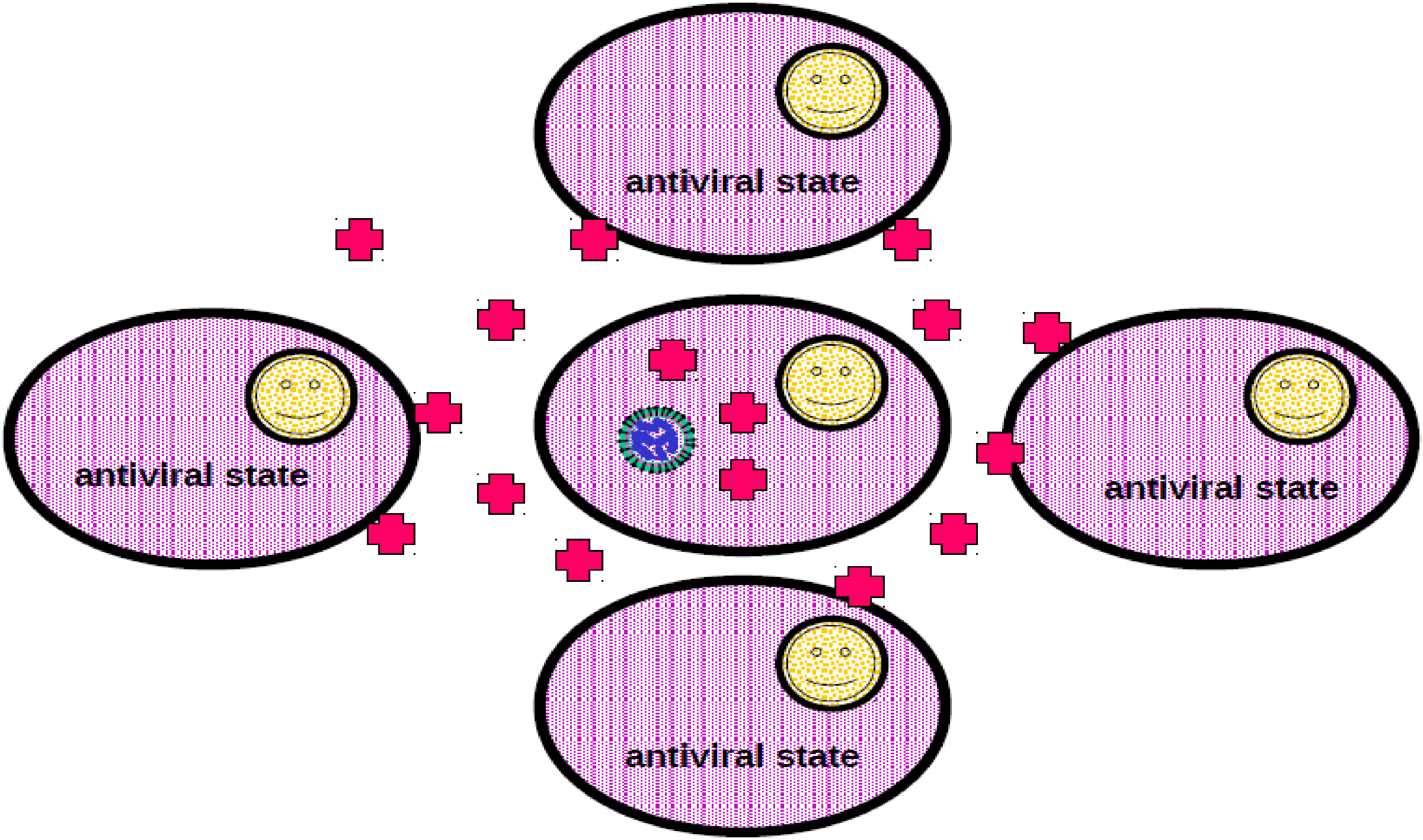
The muco-ciliary escalator then transports any inhaled particulate matter towards the pharynx, to be coughed out in sputum or swallowed. Removal of these defenses, results in potential exposure of the lower respiratory tract to inhaled particulate matter, such as bacteria.



INTERFERON

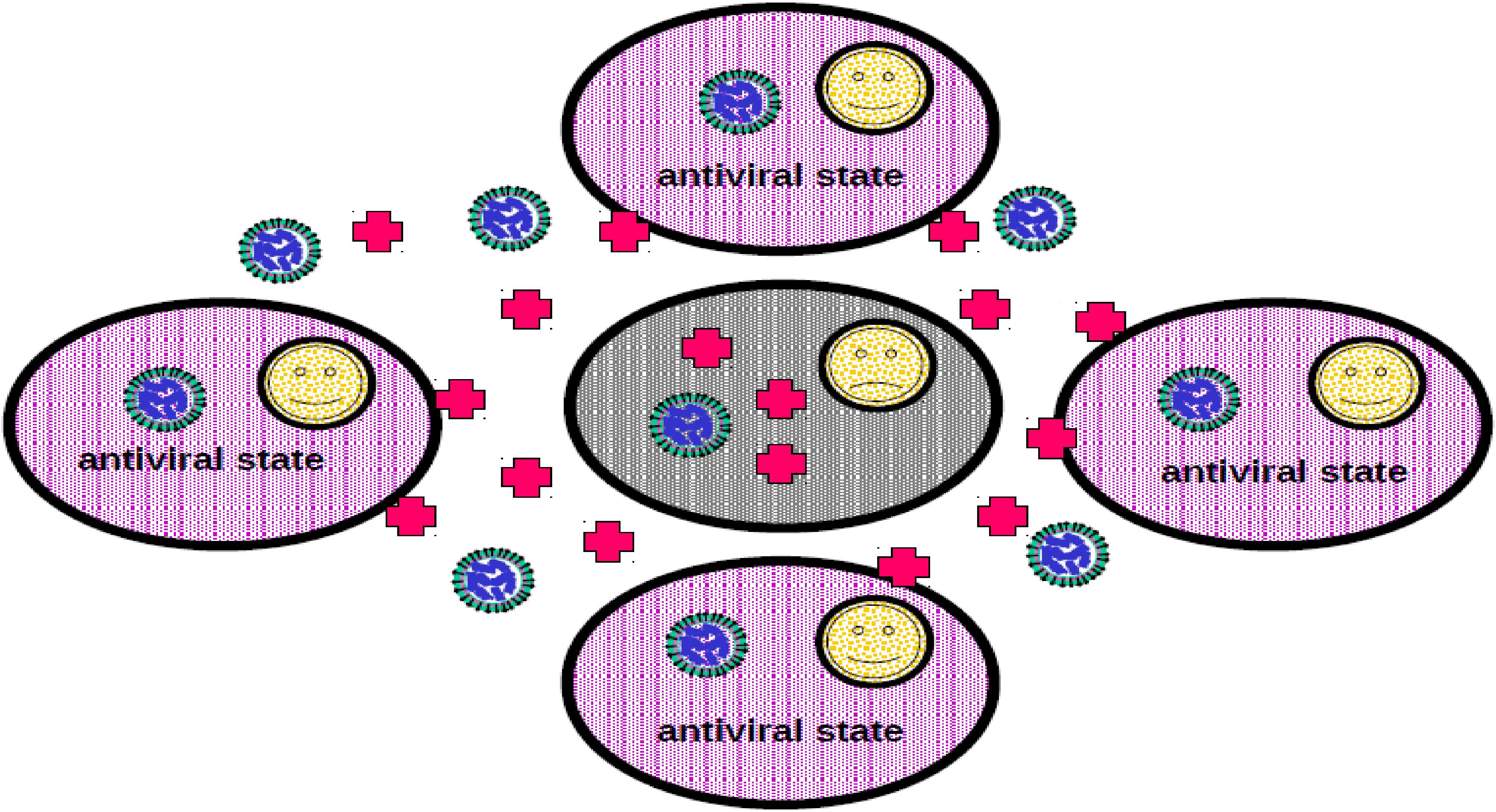


INTERFERON



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

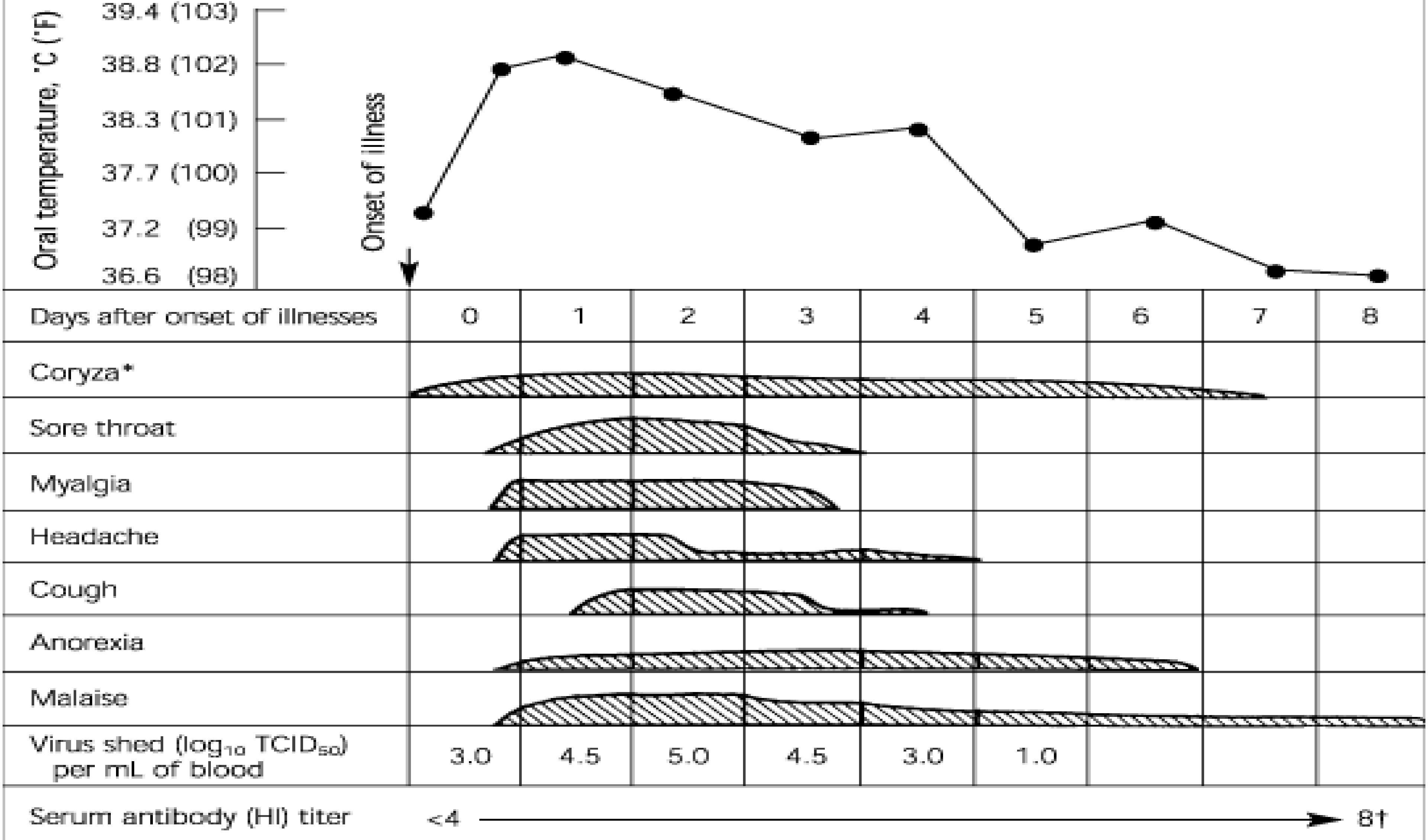
- So, influenza viruses are potent inducers of cytokines such as interferon-a (IFN-a) and interleukin (IL)-6, and it is these cytokines, not the virus, that circulate in the bloodstream and give rise to the systemic manifestations of fever, headache, muscle aches and pains, and severe malaise.
- Administration of IFN reproduces this symptomatology.

- In addition to this innate immune response to infection, adaptive humoral and cellular immune responses are also stimulated. Antibodies to the surface proteins, particularly hemagglutinin, may be neutralizing, that is they can prevent the interaction of the HA protein with cellular sialic acid residues and thereby prevent infection. However, antigenic drift results in the generation of strains of virus that can escape this protective immunity.
- T-cell responses to influenza virus are mostly directed against antigens derived from the internal viral proteins, for example the nucleoprotein. These proteins are much more conserved within influenza types than the surface proteins, so T-cell immunity may offer some protection each year to emerging drifted viruses.

What is the typical clinical presentation and what complications can occur?

- There are two distinct components to the illness that arises following infection with influenza virus – a respiratory tract component, plus a marked systemic illness characterized by fever, headache, and myalgia.
- Infection does not necessarily result in clinical disease – this will be dependent on the pre-existing state of the patient's lung function, the infecting dose of virus, the presence of pre-existing immunity and the extent to which that immunity is able to cross-react with a new viral strain.

Natural Course of Influenza



*—*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.

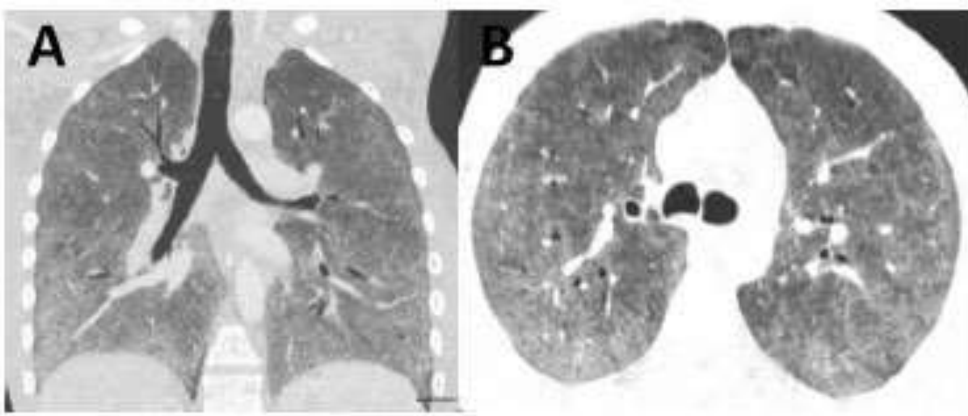
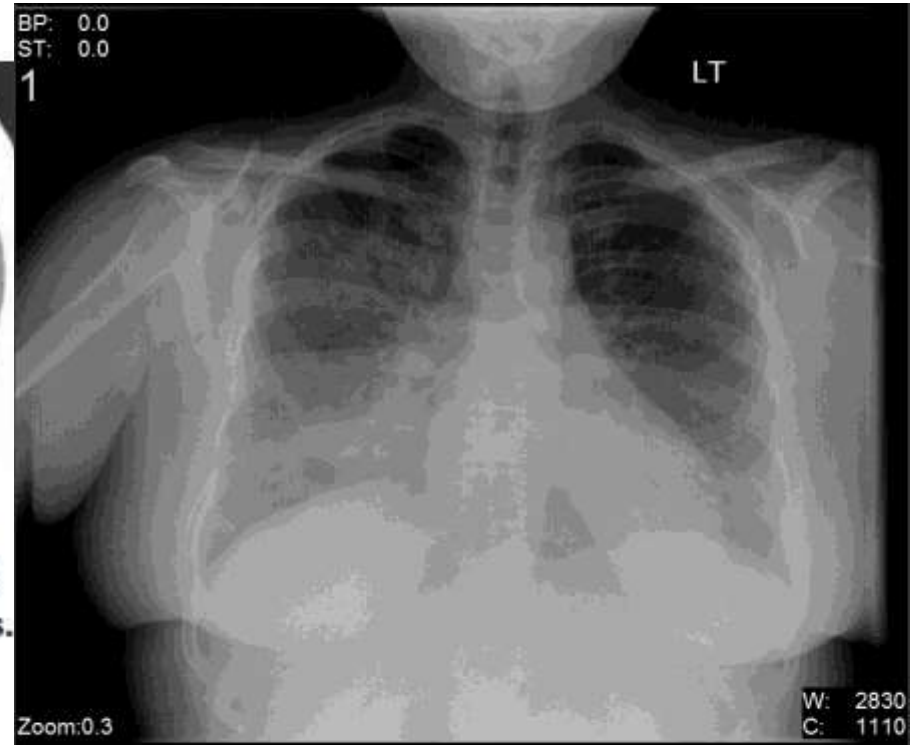
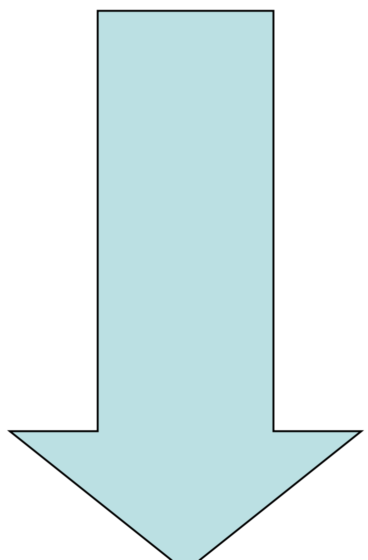


Fig. 1 - Coronal (A) and axial (B) views of chest CT scan in a patient with pneumonia caused by seasonal influenza A virus, showing diffusely distributed ground-glass opacities.



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

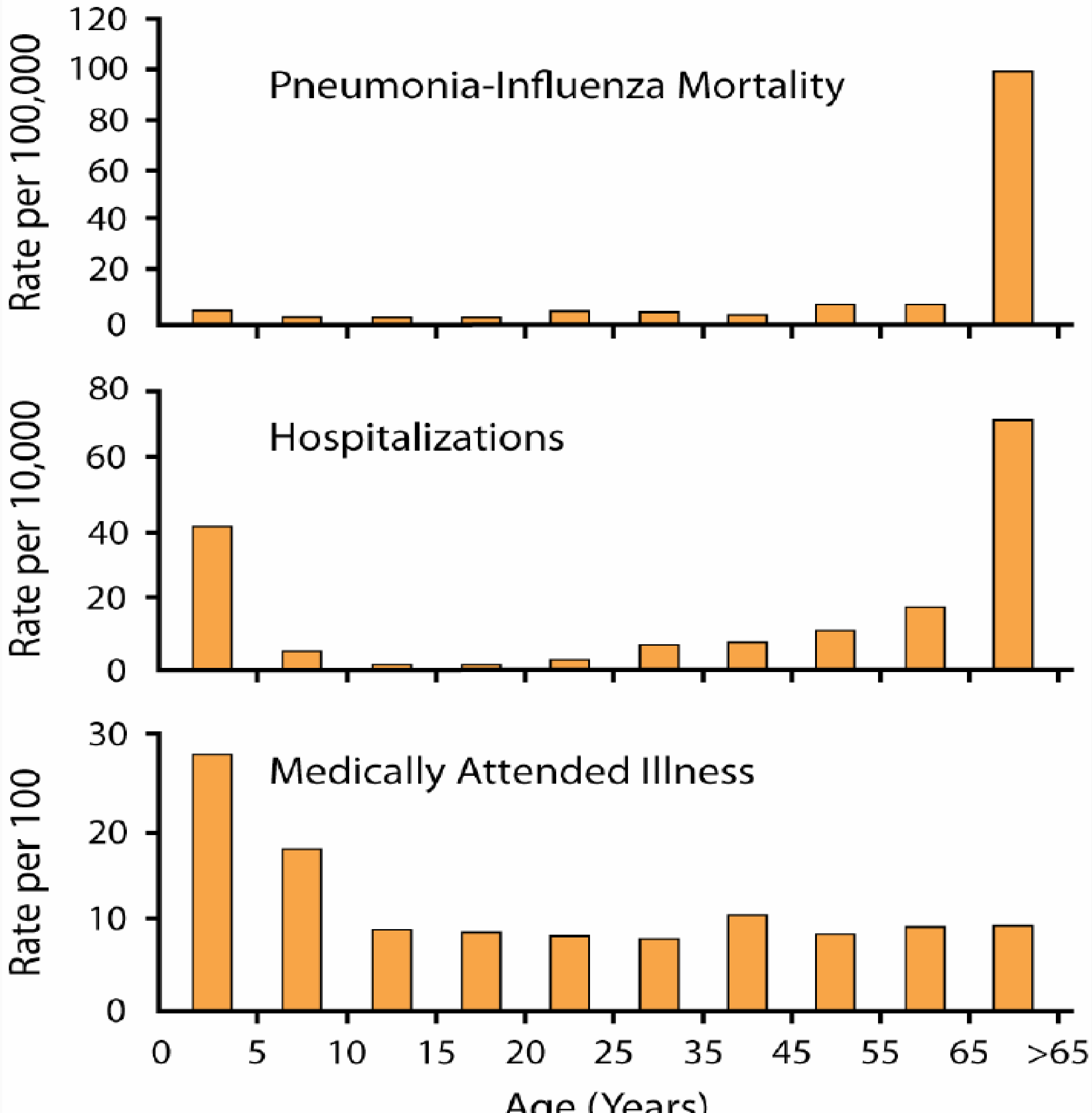
- 2.Secondary bacterial pneumonia. In recent years, this has been considerably more common than viral pneumonia. Bacteria gain access to the lower respiratory tract for reasons explained above. There is a polymorphonuclear cell infiltrate into the alveoli. This complication is more common in



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



Differential Diagnosis of Influenza

Disease	*Characteristics*	*Notes*
Common cold	Upper respiratory symptoms dominated by rhinitis; fever usually absent or mild.	Fever is a negative predictor of rhinovirus infection in adults.
Streptococcal pharyngitis	Sore throat with accompanying nasal symptoms is typical of viral pharyngitis. Presence of tender unilateral adenopathy and exudate is typical of streptococcal pharyngitis.	Severe sore throat is evidence against influenza.
Acute mononucleosis	Presence of elevated liver function test results, splenomegally, and atypical lymphocytes on peripheral smear; positive monospot test.	
Bacterial pneumonia	Classic association with pleuritic chest pain and productive sputum.	Bacterial pneumonia may be concurrent with viral pneumonia or may occur up to 2 wk after recovery from influenza.
Bacterial meningitis	In general, will present with clouded sensorium, prominent headache, and stiff neck, but early presentation may be confused with influenza.	Patients with influenza should have some improvement within 48 h. Influenza is associated with increased risk for invasive meningococcal disease.
Encephalitis	Fever, change in mental status, stiff neck, headache.	
Febrile seizures	Generalized seizure activity associated with rising body temperatures. Lasts <15 min without residual weakness or mental changes.	
Other diseases	A large list of relatively rare conditions can present with influenza-like symptoms.	Inhalational anthrax can present initially with influenza-like illness.

Table 9 — Clinical presentations and diagnostic findings of influenza A in adults

	Swine, avian, and human influenza pneumonia	Influenza pneumonia with *simultaneous* MSSA/MRSA CAP	Influenza pneumonia followed by *subsequent* CAP
Presentation	Acute	Acute	Influenza pneumonia followed by interval (~1 week) of clinical improvement followed by bacterial CAP
Symptoms	Severe myalgias (neck/back); extreme fatigue; retro-orbital pain; dry cough; shortness of breath	Same as for influenza **plus** productive cough/ purulent sputum ± pleuritic chest pain	After improvement following influenza, reappears with new fevers and productive cough/ purulent sputum ± pleuritic chest pain
Signs	Fever; conjunctival suffusion ± dyspnea; no rales	Same as influenza **plus** high spiking fevers; localized rales ± cyanosis; hypotension	Reappearance of fever ~1 week after improvement following influenza pneumonia; localized rales ± consolidation ± unilateral costophrenic angle dullness (*Haemophilus influenzae*)
Laboratory tests	Hypoxemia (increased A-a gradient, >35); relative lymphopenia; thrombocytopenia; leukopenia; sputum: WBCs with normal/or no flora	Hypoxemia (increased A-a gradient, >35); leukocytosis; sputum: WBCs with gram-positive cocci (in clusters)	Minimal/no hypoxemia (A-a gradient <35); leukocytosis; sputum: WBCs with gram-positive cocci (in pairs) or GNB
Chest film	No infiltrates (early, <48 h); bilateral interstitial patchy infiltrates (later, >48 h); no pleural effusions	Focal segmental/lobar infiltrates (with rapid cavitation <72 h)	Focal segmental/lobar infiltrates (without cavitation) ± pleural effusion ± consolidation

- **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

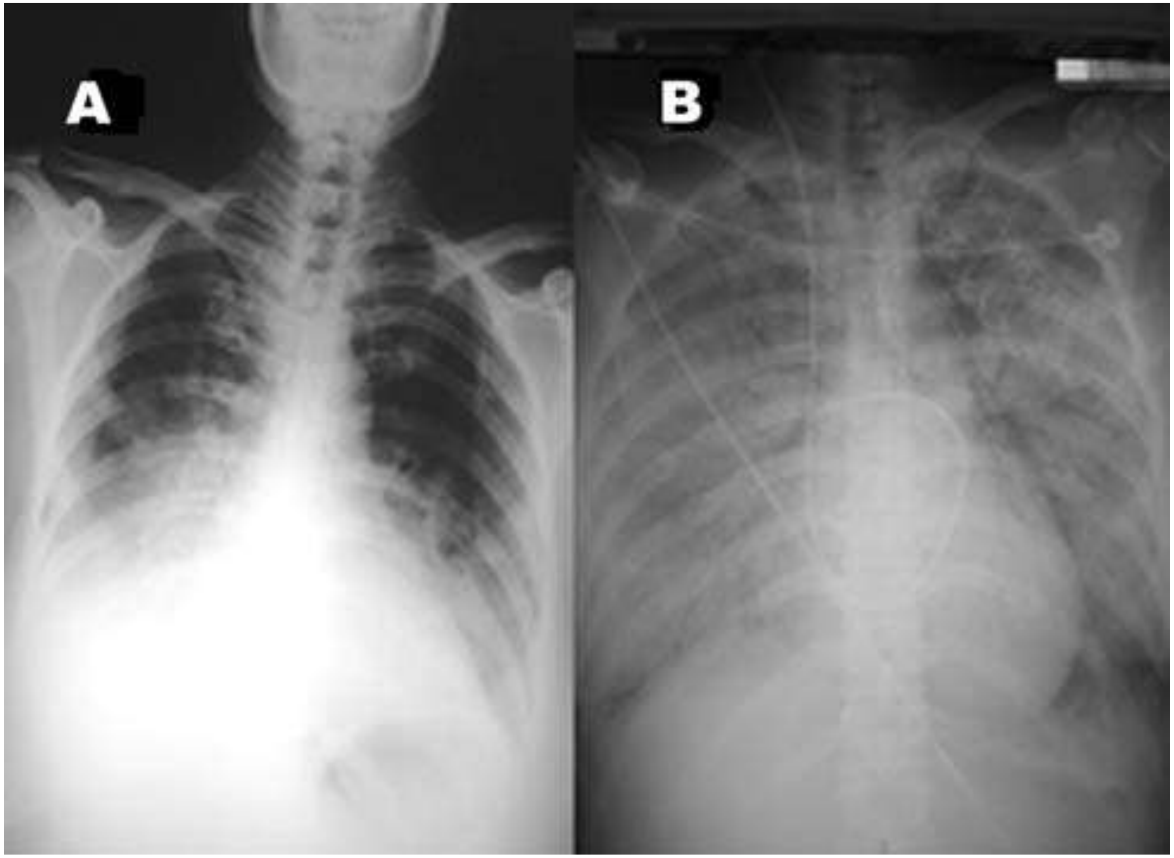


Table 12.1 Options for laboratory confirmation of influenza virus infection

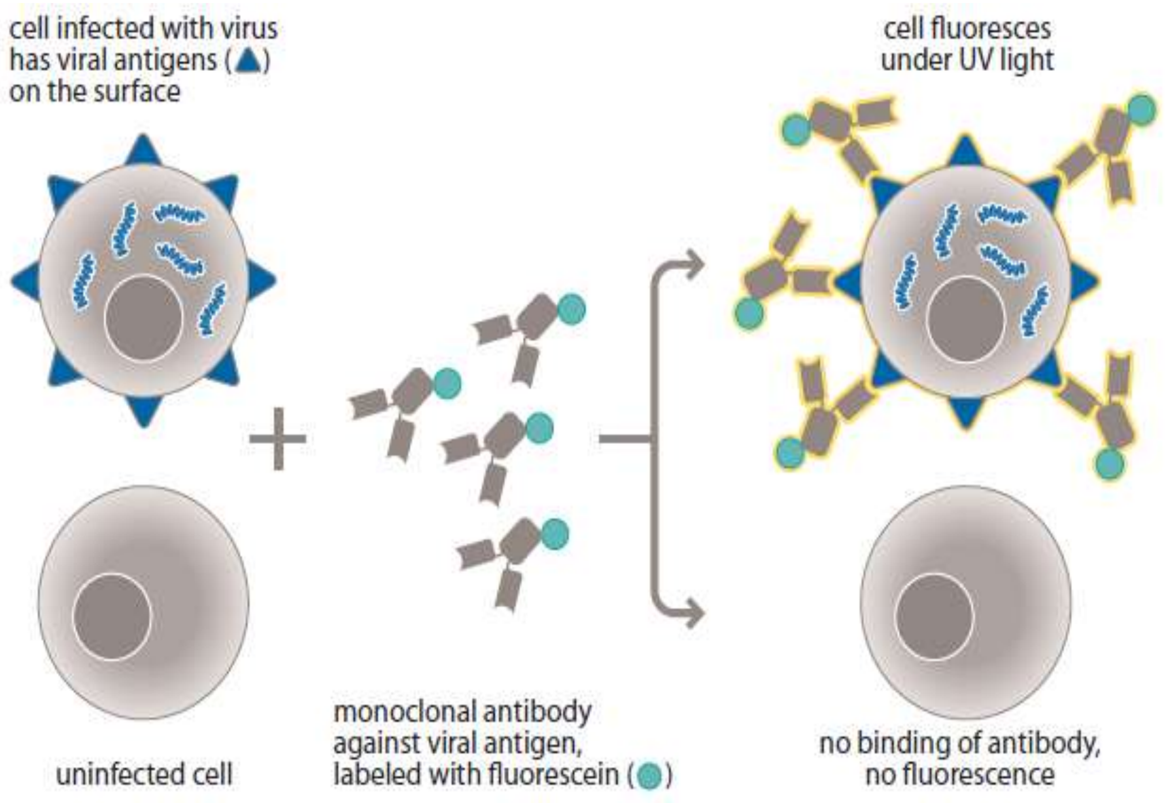
Source of specimen	Diagnostic test	Time to test result	Test characteristics
Respiratory tract (NP aspirate, NP swab/wash, throat swab)			
	Rapid antigen detection	<30 minutes	Less sensitive than other respiratory tract tests
	Immunofluorescence microscopy	~1–4 hours	Immunofluorescent antibody detection 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.

- There are two main approaches to the rapid diagnosis of influenza virus infection. Historically, most laboratories relied on immunofluorescent (IF) antigen detection using monoclonal anti-influenza antibodies

Figure 5. Detection of influenza virus by immunofluorescence. A throat swab (or ideally, a nasopharyngeal aspirate) is spotted onto a glass slide, and a fluorescently tagged monoclonal antibody is added. The antibody binds to cells infected with virus, but not to uninfected cells. After an incubation period, any unbound antibody is washed off, and the cells are examined under ultraviolet light. The presence of brightly fluorescent cells is a positive result indicating that the patient is infected with the virus to which the monoclonal antibody was raised. The whole process takes about 2 hours.



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).

Administer Rapivab (peramivir) within 2 days of onset of symptoms of influenza.

Adults and Adolescents (13 years of age and older)

The recommended dose of Rapivab in adult and adolescent patients 13 years of age or older with acute uncomplicated influenza is a single 600 mg dose, administered via intravenous infusion for 15 to 30 minutes.

Pediatric Patients (2 to 12 years of age)

The recommended dose of Rapivab in pediatric patients 2 to 12 years of age with acute uncomplicated influenza is a single 12 mg/kg dose (up to a maximum dose of 600 mg), administered via intravenous infusion for 15 to 30 minutes.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XOFLUZA safely and effectively. See full prescribing information for XOFLUZA.

XOFLUZA™ (baloxavir marboxil) tablets, for oral use
Initial U.S. Approval: 2018

----------------------------INDICATIONS AND USAGE----------------------------

XOFLUZA™ is a polymerase acidic (PA) endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. (1)
Limitations of Use: Influenza viruses change over time, and factors such as the virus type or subtype, emergence of resistance, or changes in viral virulence could diminish the clinical benefit of antiviral drugs. Consider available information on drug susceptibility patterns for circulating influenza virus strains when deciding whether to use XOFLUZA. (1)

-----------------------DOSAGE AND ADMINISTRATION-----------------------

Take a single dose of XOFLUZA orally within 48 hours of symptom onset with or without food. Avoid co-administration of XOFLUZA with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc). The dose of XOFLUZA depends on weight. (2)

Patient Body Weight (kg)	Recommended Oral Dose
40 kg to less than 80 kg	Single dose of 40 mg
At least 80 kg	Single dose of 80 mg

---------------------DOSAGE FORMS AND STRENGTHS---------------------

Tablets: 20 mg and 40 mg (3)

- For the more seriously ill patients there are two classes of anti-influenza agents shown to be effective. The first of these include amantadine and rimantadine. These drugs work by preventing the uncoating of influenza virions that have entered a target cell. They do this by binding to the viral matrix M2 protein and there by blocking ion channels, whose function is essential for the pH-mediated dissolution of the viral capsid, that is uncoating.

- But amantadine and rimantadine only work against influenza A viruses and therefore are of no benefit in a patient infected with influenza B virus.

- Secondly, these drugs are also dopamine agonists and therefore have marked central nervous system stimulatory activity – in fact, amantadine was originally developed for the treatment of Parkinson’s disease. Thus, it is very poorly tolerated in the elderly, the precise group of patients who are most likely to require antiviral therapy, giving rise to hallucinations, insomnia, and agitation.

- Thirdly, resistance to amantadine emerges within a few days of onset of therapy, due to point mutations in the M2 protein. Finally, many of the avian influenza viruses, including H5N1 strains, are inherently resistant to amantadine.

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

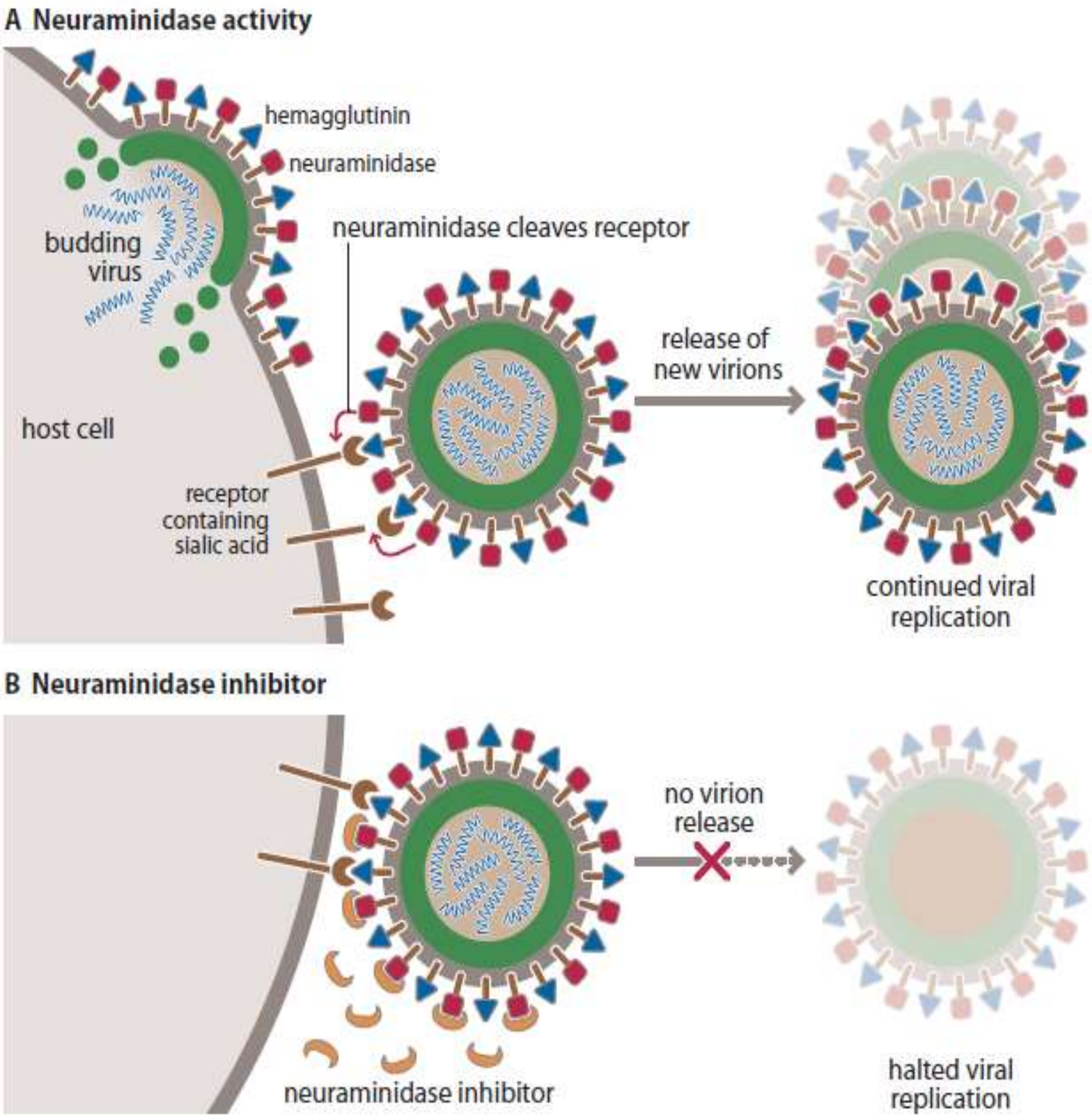
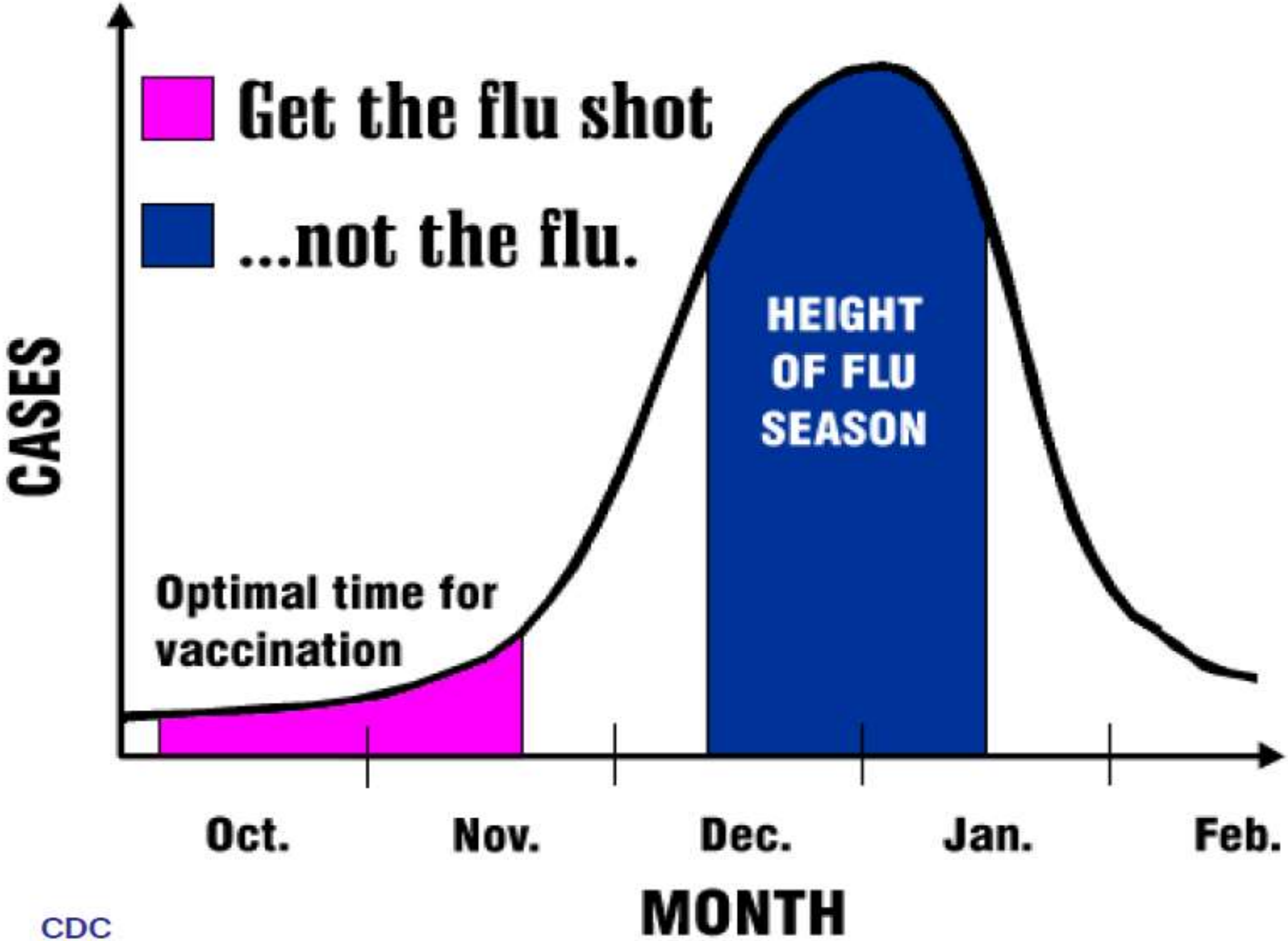


Figure 6. Neuraminidase on the surface of the virus fulfills an essential role in the life cycle of the virus. As newly formed viral particles bud out of an infected cell (A), the hemagglutinin on the viral surface would naturally bind to sialic acid receptors on the surface of the cell. Thus, it would 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.

Vaccines

- Each year, the WHO (based on monitoring current strains in its reference laboratories) announces which particular A/H1N1, A/H3N2, and B viral strains should be used for ***vaccine***
  being manufactured for the following influenza season.
- The protection offered by these vaccines depends to a large extent on the degree of antigenic match between the vaccine strains and the strains actually circulating during the season – some years this is better than others!



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

CDC

The availability of a vaccine then begs the question of who should be vaccinated. Most countries adopt a selective policy, that is the recommendation is to vaccinate those subgroups within the population who will fare badly should they acquire infection.

Table 2. Target groups for influenza vaccination

UK – Department of Health recommendations

- Patients aged 6 months or older with underlying:
  - chronic respiratory disease (including asthma)
  - chronic heart disease
  - diabetes requiring insulin or oral hypoglycemic drugs
  - chronic renal disease
  - immunosuppression
  - chronic liver disease
- Individuals over the age of 65
- Health and social care staff directly involved in patient care
- People who live in nursing homes and other long-term care facilities

USA – Centers for Disease Control and Prevention recommendations

- Children aged 6 months to 5 years
- Pregnant women
- Individuals over the age of 50
- Patients with certain chronic medical conditions (see list above)
- People who live in nursing homes and other long-term care facilities
- Household contacts of individuals who fall within the groups above
- Household contacts of children less than 6 months of age
- Health-care workers