Influenza

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Influenza

- Influenza, commonly known as the flu, is an infectious disease of human, birds and mammals
- caused by RNA viruses of the family Orthomyxoviridae, the influenza viruses.

Virology

In virus classification influenza viruses are RNA viruses that make up three of the five genera of the family Orthomyxoviridae:

- Influenzavirus A
- Influenzavirus B
- Influenzavirus C

These viruses are only distantly related to the human parainfluenza viruses, which are RNA viruses belonging to the paramyxovirus family that are a common cause of respiratory infections in children such as croup, but can also cause a disease similar to influenza in adults

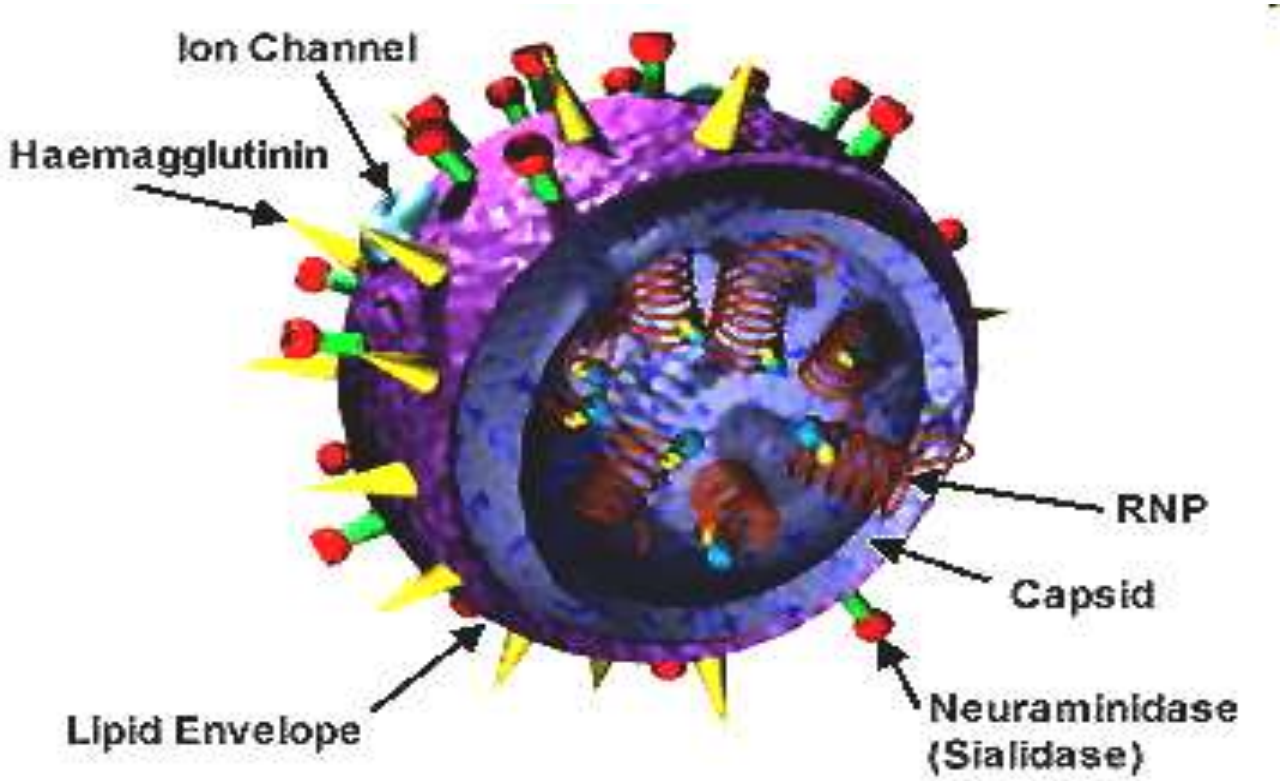
Structure, properties, and subtype nomenclature

- Influenzaviruses A, B and C are very similar in overall structure. The virus particle is 80–120 nanometers in diameter and usually roughly spherical, although filamentous forms can occur.
- These filamentous forms are more common in influenza C, which can form cordlike structures up to 500 micrometers long on the surfaces of infected cells.
- However, despite these varied shapes, the viral particles of all influenza viruses are similar in composition. These are made of a viral envelope containing two main types of glycoproteins, wrapped around a central core. The central core contains the viral RNA genome and other viral proteins that package and protect this RNA. RNA tends to be single stranded but in special cases it is double.
- Unusually for a virus, its genome is not a single piece of nucleic acid; instead, it contains seven or eight pieces of segmented negative-sense RNA, each piece of RNA containing either one or two genes, which code for a gene product (protein).
- For example, the influenza A genome contains 11 genes on eight pieces of RNA, encoding for 11 proteins: hemagglutinin (HA), neuraminidase (NA), nucleoprotein (NP), M1, M2, NS1, NS2(NEP: nuclear export protein), PA, PB1 (polymerase basic 1), PB1-F2 and PB2

Structure, properties, and subtype nomenclature

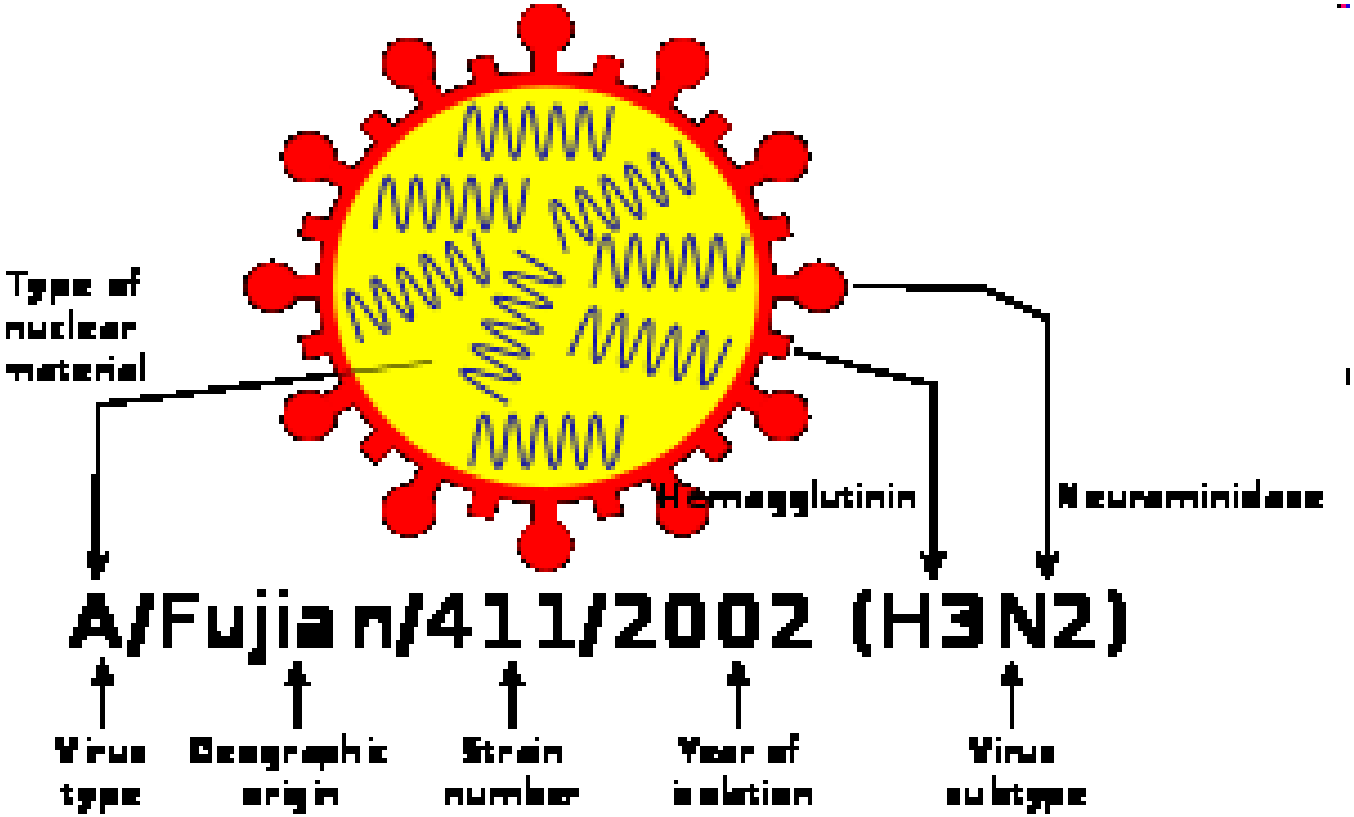
- Hemagglutinin (HA) and neuraminidase (NA) are the two large glycoproteins on the outside of the viral particles. HA is a lectin that mediates binding of the virus to target cells and entry of the viral genome into the target cell, while NA is involved in the release of progeny virus from infected cells, by cleaving sugars that bind the mature viral particles.
- Thus, these proteins are targets for antiviral drugs. Furthermore, they are antigens to which antibodies can be raised. Influenza A viruses are classified into subtypes based on antibody responses to HA and NA. These different types of HA and NA form the basis of the H and N distinctions in, for example, H5N1.
- There are 16 H and 9 N subtypes known, but only H 1, 2 and 3, and N 1 and 2 are commonly found in humans

Structure of the influenza virion

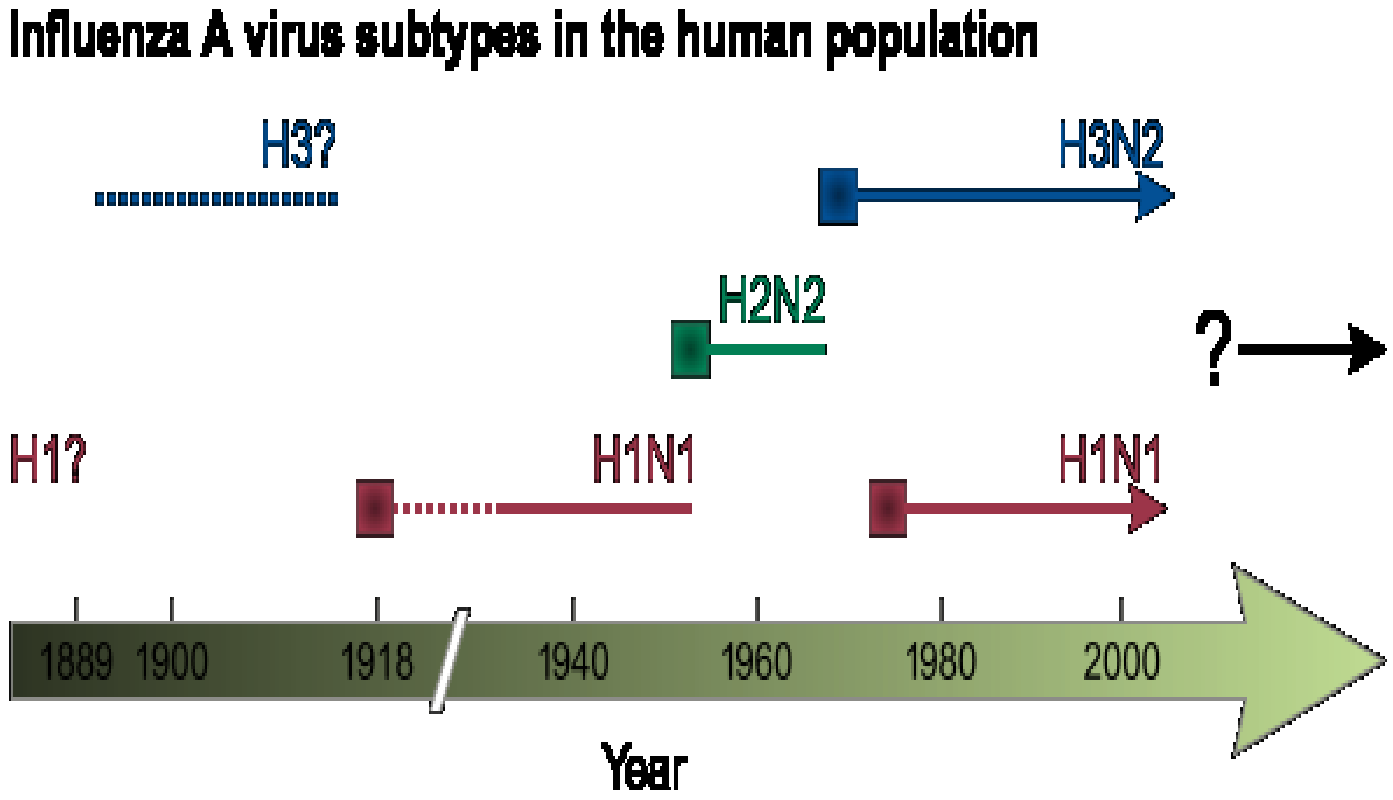


The hemagglutinin (HA) and neuraminidase(NA) proteins are shown on the surface of the particle. The viral RNAs that make up the genome are shown as red coils inside the particle and bound to Ribonuclear Proteins (RNPs)

Influenza virus nomenclature



The main types of influenza viruses in humans



Transmission

- Influenza virus shedding (the time during which a person might be infectious to another person) begins the day before symptoms appear and virus is then released for between 5 to 7 days, although some people may shed virus for longer periods. People who contract influenza are most infective between the second and third days after infection.
- The amount of virus shed appears to correlate with fever, with higher amounts of virus shed when temperatures are highest.
- Children are much more infectious than adults and shed virus from just before they develop symptoms until two weeks after infection.
- The transmission of influenza can be modeled mathematically, which helps predict how the virus will spread in a population

Transmission

Influenza can be spread in three main ways:

- by direct transmission (when an infected person sneezes mucus directly into the eyes, nose or mouth of another person);
- the airborne route (when someone inhales the aerosols produced by an infected person coughing, sneezing or spitting) and through hand-to-eye, hand-to-nose, or hand-to-mouth transmission, either from contaminated surfaces or from direct personal contact such as a hand-shake.

The relative importance of these three modes of transmission is unclear, and they may all contribute to the spread of the virus.

In the airborne route, the droplets that are small enough for people to inhale are 0.5 to 5 μm in diameter and inhaling just one droplet might be enough to cause an infection.

Although a single sneeze releases up to 40,000 droplets,most of these droplets are quite large and will quickly settle out of the air.

How long influenza survives in airborne droplets seems to be influenced by the levels of humidity and UV radiation: with low humidity and a lack of sunlight in winter aiding its survival.

Transmission

- As the influenza virus can persist outside of the body, it can also be transmitted by contaminated surfaces such as banknotes,doorknobs, light switches and other household items.
- The length of time the virus will persist on a surface varies, with the virus surviving for one to two days on hard, non-porous surfaces such as plastic or metal, for about fifteen minutes from dry paper tissues, and only five minutes on skin.
- However, if the virus is present in mucus, this can protect it for longer periods (up to 17 days on banknotes).
- Avian influenza viruses can survive indefinitely when frozen. They are inactivated by heating to 56 °C (133 °F) for a minimum of 60 minutes, as well as by acids (at pH <2)

Epidemiology

- Influenza reaches peak prevalence in winter, and because the Northern and Southern Hemispheres have winter at different times of the year, there are actually two different flu seasons each year.
- This is why the World Health Organization (assisted by the National Influenza Centers) makes recommendations for two different vaccine formulations every year; one for the Northern, and one for the Southern Hemisphere

Epidemiology

- A long-standing puzzle has been why outbreaks of the flu occur seasonally rather than uniformly throughout the year. One possible explanation is that, because people are indoors more often during the winter, they are in close contact more often, and this promotes transmission from person to person. Increased travel due to the Northern Hemisphere winter holiday season may also play a role.
- Another factor is that cold temperatures lead to drier air, which may dehydrate mucus, preventing the body from effectively expelling virus particles. The virus also survives longer on surfaces at colder temperatures and aerosol transmission of the virus is highest in cold environments (less than 5 °C) with low relative humidity.
- Indeed, the lower air humidity in winter seems to be the main cause of seasonal influenza transmission in temperate regions

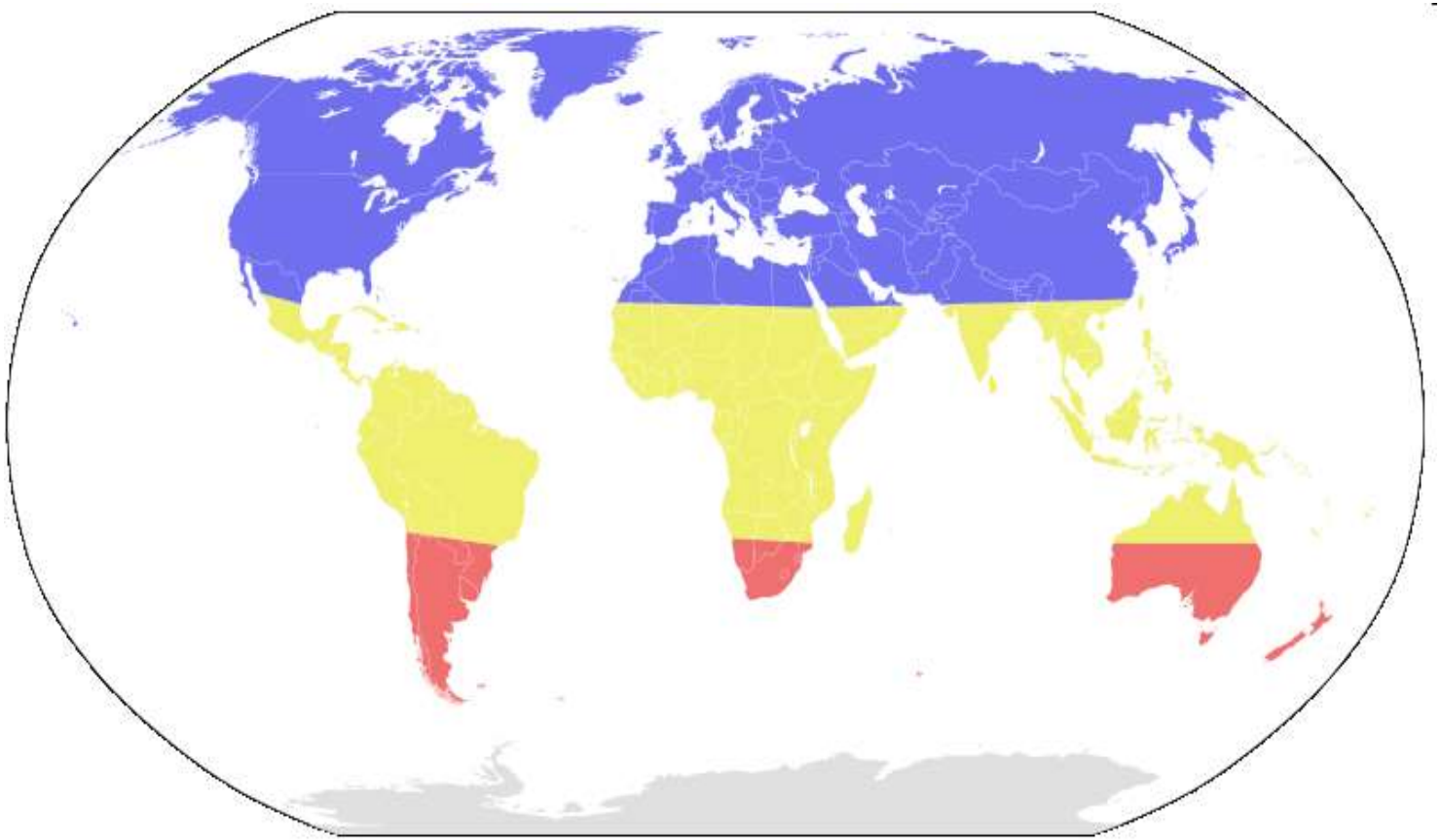
Epidemiology

- However, seasonal changes in infection rates also occur in tropical regions, and in some countries these peaks of infection are seen mainly during the rainy season.
- Seasonal changes in contact rates from school terms, which are a major factor in other childhood diseases such as measles and pertussis, may also play a role in the flu. A combination of these small seasonal effects may be amplified by dynamical resonance with the endogenous disease cycles.
- H5N1 exhibits seasonality in both humans and birds

Epidemiology

- An alternative hypothesis to explain seasonality in influenza infections is an effect of vitamin D levels on immunity to the virus.
- This idea was first proposed by Robert Edgar Hope-Simpson in 1965. He proposed that the cause of influenza epidemics during winter may be connected to seasonal fluctuations of vitamin D, which is produced in the skin under the influence of solar (or artificial) UV radiation.
- This could explain why influenza occurs mostly in winter and during the tropical rainy season, when people stay indoors, away from the sun, and their vitamin D levels fall

Seasonal risk areas for influenza: November–April (blue), April–November (red), and year-round (yellow)



Signs and symptoms

- Approximately 33% of people with influenza are asymptomatic.
- Symptoms of influenza can start quite suddenly one to two days after infection. Usually the first symptoms are chills or a chilly sensation, but fever is also common early in the infection, with body temperatures ranging from 38–39 °C (approximately 100–103 °F).
- Many people are so ill that they are confined to bed for several days, with aches and pains throughout their bodies, which are worse in their backs and legs.

Signs and symptoms

Symptoms of influenza may include:

- Fever and extreme coldness (chills shivering, shaking (rigor))
- Cough
- Nasal congestion
- Body aches, especially joints and throat
- Fatigue
- Headache
- Irritated, watering eyes
- Reddened eyes, skin (especially face), mouth, throat and nose
- Petechial Rash
- In children, gastrointestinal symptoms such as diarrhea and abdominal pain (may be severe in children with influenza B)

Signs and symptoms

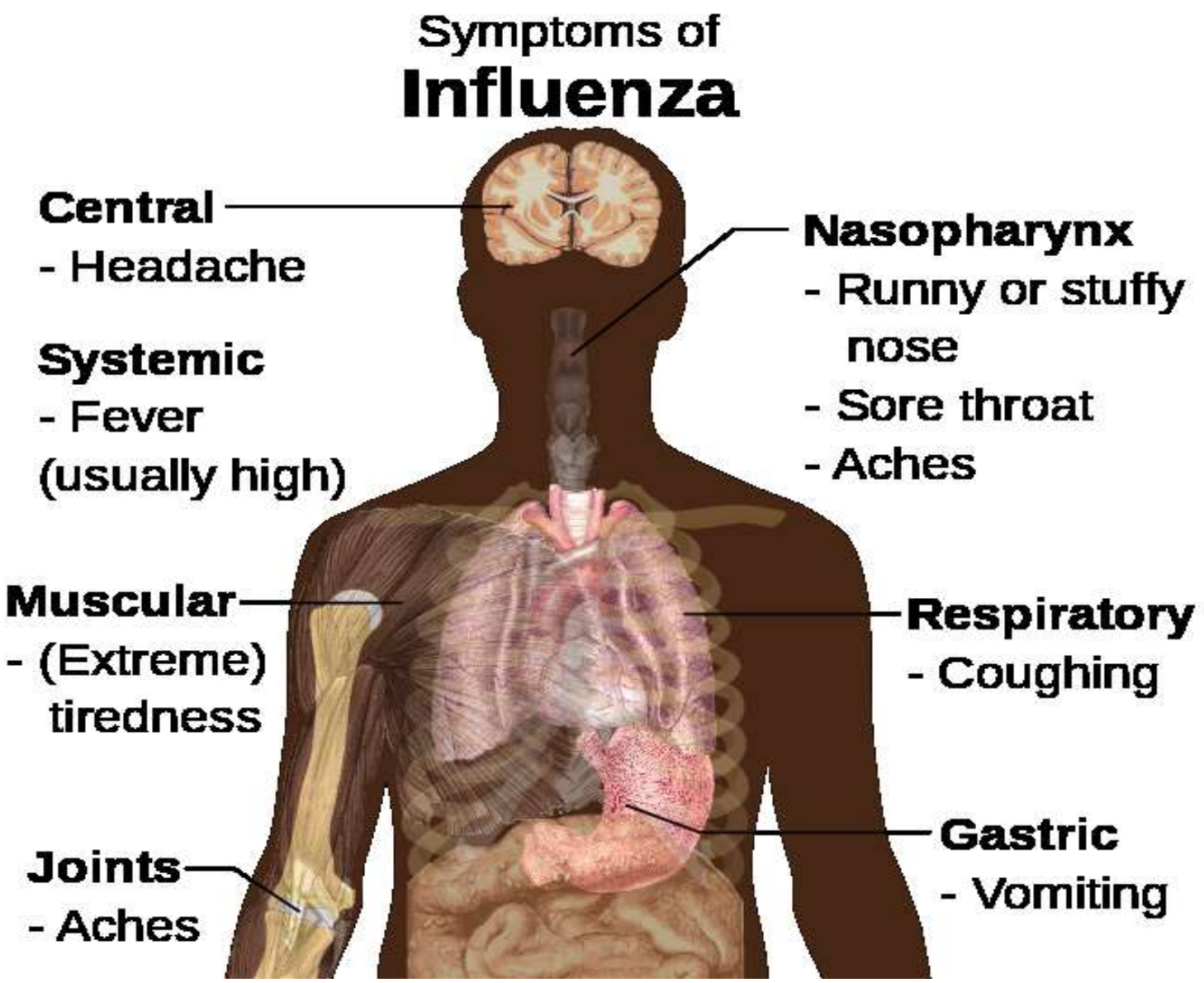
- It can be difficult to distinguish between the common cold and influenza in the early stages of these infections, but a flu can be identified by a high fever with a sudden onset and extreme fatigue. Diarrhea is not normally a symptom of influenza in adults, although it has been seen in some human cases of the H5N1 "bird flu" and can be a symptom in children. The symptoms most reliably seen in influenza are shown in the table to the right.
- Since antiviral drugs are effective in treating influenza if given early (see treatment section, below), it can be important to identify cases early. Of the symptoms listed above, the combinations of fever with cough, sore throat and/or nasal congestion can improve diagnostic accuracy.
- Two decision analysis studies suggest that during local outbreaks of influenza, the prevalence will be over 70%, and thus patients with any of these combinations of symptoms may be treated with neuraminidase inhibitors without testing. Even in the absence of a local outbreak, treatment may be justified in the elderly during the influenza season as long as the prevalence is over 15%

Signs and symptoms

- The available laboratory tests for influenza continue to improve. The United States Centers for Disease Control and Prevention (CDC) maintains an up-to-date summary of available laboratory tests. According to the CDC, rapid diagnostic tests have a sensitivity of 70–75% and specificity of 90–95% when compared with viral culture.
- These tests may be especially useful during the influenza season (prevalence=25%) but in the absence of a local outbreak, or peri-influenza season (prevalence=10%)

Signs and symptoms

- On the more serious side, influenza can occasionally cause either direct viral or secondary bacterial pneumonia.
- The obvious symptom is trouble breathing. In addition, if a child (or presumably an adult) seems to be getting better and then relapses with a high fever, that is a danger sign since this relapse can be bacterial pneumonia.
- For patients with influenza who show signs of pneumonia, a 2009 New England Journal of Medicine article recommends giving such patients both antivirals and antibiotics since it is difficult to make a differential diagnosis between viral and bacterial pneumonia


Symptoms of
Influenza
Central
- Headache
Systemic
- Fever
(usually high)
Nasopharynx
- Runny or stuffy nose
- Sore throat
- Aches
Muscular
- (Extreme) tiredness
Respiratory
- Coughing
Joints
- Aches
Gastric
- Vomiting

Treatment

- People with the flu are advised to get plenty of rest, drink plenty of liquids, avoid using alcohol and tobacco and, if necessary, take medications such as acetaminophen (paracetamol) to relieve the fever and muscle aches associated with the flu.
- Children and teenagers with flu symptoms (particularly fever) should avoid taking aspirin during an influenza infection (especially influenza type B), because doing so can lead to Reye's syndrome, a rare but potentially fatal disease of the liver.
- Since influenza is caused by a virus, antibiotics have no effect on the infection; unless prescribed for secondary infections such as bacterial pneumonia. Antiviral medication can be effective, but some strains of influenza can show resistance to the standard antiviral drugs.

Treatment

- The two classes of antiviral drugs used against influenza are neuraminidase inhibitors (oseltamivir and zanamivir) and M2 protein inhibitors (adamantane derivatives). Neuraminidase inhibitors are currently preferred for flu virus infections since they are less toxic and more effective.
- In a November 2009 press conference, the World Health Organization recommended that persons in high risk groups, including pregnant women, children under two, and persons with respiratory problems, begin taking antivirals as soon as they start experiencing flu symptoms.
- However, their effectiveness is controversial

Treatment

Neuraminidase inhibitors

- Antiviral drugs such as oseltamivir (Tamiflu) and zanamivir (Relenza).
- These drugs may be effective against both influenza A and B however the confidence of the research community in this conclusion is low as much of the trial data remains unpublished.
- Different strains of influenza viruses have differing degrees of resistance against these antivirals, and it is impossible to predict what degree of resistance a future pandemic strain might have. The FDA deems their effect to be modest.

Treatment

M2 inhibitors

- The antiviral drugs amantadine and rimantadine block a viral ion channel (M2 protein) and prevent the virus from infecting cells.
- These drugs are sometimes effective against influenza A if given early in the infection but are always ineffective against influenza B because B viruses do not possess M2 molecules.
- Measured resistance to amantadine and rimantadine in American isolates of H3N2 has increased to 91% in 2005.
- This high level of resistance may be due to the easy availability of amantadines as part of over-the-counter cold remedies in countries such as China and Russia,and their use to prevent outbreaks of influenza in farmed poultry.
- The CDC recommended against using M2 inhibitors during the 2005–06 influenza season due to high levels of drug resistance.

Prevention

Vaccination

- Vaccination against influenza with an influenza vaccine is often recommended for high-risk groups, such as children and the elderly, or in people who have asthma, diabetes, heart disease, or are immuno-compromised. Influenza vaccines can be produced in several ways; the most common method is to grow the virus in fertilized hen eggs.
- After purification, the virus is inactivated (for example, by treatment with detergent) to produce an inactivated-virus vaccine. Alternatively, the virus can be grown in eggs until it loses virulence and the avirulent virus given as a live vaccine.

Prevention

- The effectiveness of these influenza vaccines are variable. Due to the high mutation rate of the virus, a particular influenza vaccine usually confers protection for no more than a few years. Every year, the World Health Organization predicts which strains of the virus are most likely to be circulating in the next year (see Historical annual reformulations of the influenza vaccine), allowing pharmaceutical companies to develop vaccines that will provide the best immunity against these strains.
- Vaccines have also been developed to protect poultry from avian influenza. These vaccines can be effective against multiple strains and are used either as part of a preventative strategy, or combined with culling in attempts to eradicate outbreaks.

Prevention

- It is possible to get vaccinated and still get influenza. The vaccine is reformulated each season for a few specific flu strains but cannot possibly include all the strains actively infecting people in the world for that season.
- It takes about six months for the manufacturers to formulate and produce the millions of doses required to deal with the seasonal epidemics; occasionally, a new or overlooked strain becomes prominent during that time and infects people although they have been vaccinated (as by the H3N2 Fujian flu in the 2003–2004 flu season).
- It is also possible to get infected just before vaccination and get sick with the very strain that the vaccine is supposed to prevent, as the vaccine takes about two weeks to become effective.

Prevention

- The 2006–2007 season was the first in which the CDC had recommended that children younger than 59 months receive the annual influenza vaccine.
- Vaccines can cause the immune system to react as if the body were actually being infected, and general infection symptoms (many cold and flu symptoms are just general infection symptoms) can appear, though these symptoms are usually not as severe or long-lasting as influenza. The most dangerous side effect is a severe allergic reaction to either the virus material itself or residues from the hen eggs used to grow the influenza; however, these reactions are extremely rare.
- The cost-effectiveness of seasonal influenza vaccination has been widely evaluated for different groups and in different settings. It has generally been found to be a cost-effective intervention, especially in children and the elderly, however the results of economic evaluations of influenza vaccination have often been found to be dependent on key assumptions

Prevention

- In addition to vaccination against seasonal influenza, researchers are working to develop a vaccine against a possible influenza pandemic. The rapid development, production, and distribution of pandemic influenza vaccines could potentially save millions of lives during an influenza pandemic.
- Due to the short time frame between identification of a pandemic strain and need for vaccination, researchers are looking at non-egg-based options for vaccine production.
- Live attenuated (egg-based or cell-based) technology and recombinant technologies (proteins and virus-like particles) could provide better "real-time" access and be produced more affordably, thereby increasing access for people living in low- and moderate-income countries, where an influenza pandemic may likely originate. As of July 2009, more than 70 known clinical trials have been completed or are ongoing for pandemic influenza vaccines.

Prevention

- In September 2009, the US Food and Drug Administration approved four vaccines against the 2009 H1N1 influenza virus (the current pandemic strain), and expect the initial vaccine lots to be available within the following month.
- In 2011, there was some research success towards a "universal flu vaccine" that produces antibodies against proteins on the viral coat which mutate less rapidly, and thus a single shot could potentially provide longer-lasting protection