Influenza Viruses

The influenza virus is a member of the Orthomyxoviridae family. As stated earlier, viruses are grouped by their similar characteristics and by the type of hosts they infect. Influenza viruses are RNA viruses that are further classified as A, B, or C. Influenza A is the most virulent (severe) of the three types and causes the most serious illness. It is the type A influenza that can cause deadly outbreaks and pandemics.

Influenza A viruses can cause influenza in birds and some mammals. All types of influenza A viruses have been found in wild birds, but it is rare that these produce illnesses in the birds. However, some variants of influenza A virus can cause severe sickness in domestic poultry and in humans. Occasionally, viruses are transmitted from wild birds to domestic poultry, sickening them.

Type B influenza does not have the ability to infect a wide range of hosts. It also mutates much slower, so it does not pose as much danger as type A influenza. Seasonal influenza outbreaks are caused by types A or B influenza viruses, and both can cause epidemics. Influenza C is less common than types A and B, and usually causes only mild illness.

Influenza (Flu)

Influenza, also known as the seasonal flu, is a highly contagious viral disease that tends to occur in epidemics during the colder and less humid months of the year. The symptoms are mainly fever, cough, sore throat, fatigue and body aches. Infection can be easily spread in airborne droplets from coughs and sneezes. Some people may also experience symptoms of nausea, vomiting and diarrhea. Complications can lead to pneumonia and dehydration.

Infections from influenza occur mainly in the upper respiratory tract. This is due to the fact that the upper respiratory tract epithelium (cells that lines cavities and covers surfaces) tissue contains receptors to which these viruses target and bond.

Most people have some immunity to circulating strains of influenza virus and, as a result, the severity and effect of seasonal influenza is substantially less than during pandemics. Each year, health officials study the circulating strains and predict which three will be the most likely to cause the most illness for the coming flu season. A trivalent influenza vaccine is prepared in advance of the anticipated seasonal outbreak, and it includes those strains (two type A and one type B).

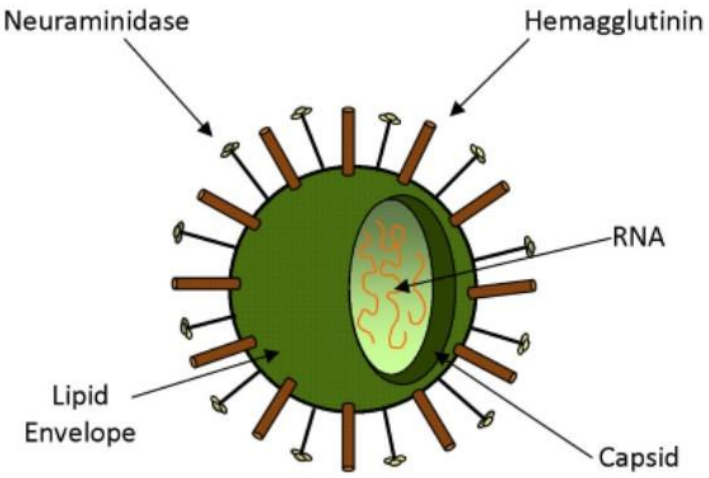
Structure of the Influenza Virus

Influenza viruses A and B are of a spherical shape, although type C viruses can be both spherical and filamentous. The outer layer is a lipid envelope that covers the sphere. Just beneath

the envelope is a protein shell that gives the virion its shape and rigidity. This protein shell, known as the capsid encapsulates the nucleic acid which consists of the genetic material DNA or RNA. The significance of DNA versus RNA will be discussed in the section "Viral Replication." At this time, it is important to know that it is these proteins that enable a virus to mutate and cross the species barrier (avian to animal or human).

Coming from the capsid are the proteins called *hemagglutinin* (H or HA) and *neuraminidase* (N or NA) that enable a virus to attach and invade host cells.

These proteins, also known as antigens, undergo mutation, or genetic variation. Mutation is the mechanism for the emergence of new strains. Type A in particular mutates frequently and can produce new strains to which few people are immune. This is how pandemics emerge.



Structure of an Influenza Virus

Influenza A viruses are categorized by the presence of these surface proteins, also known as antigens. It is the various combinations of the H's and the N's that determine the subtype strains, such as H5N1, H1N1. Three different subtypes of Influenza Type A have caused pandemics in the 20th century, H1N1, H2N2, and H3N2.

Currently there are at least seventeen different hemagglutinin antigens (H1-H17). The first three hemagglutinins, H1, H2, and H3, are found in human influenza viruses. The H1N1 was the cause of the pandemic in 2009. Currently world officials are watching the H5N1 and H7N9 anticipating these may develop into serious threats if they become easily transmitted between people.

Roles of Hemagglutinin and Neuraminidase

It is the hemagglutinin protein that is responsible for the virus attaching itself with the receptors of *sialic acid* (a sugar molecule) on the surface of upper respiratory cells. Once the virus attaches itself it penetrates the cell. The cells with specific receptors for the virus are called host cells. When the hemagglutinin spike touches the molecules of sialic acid sugars that

protrude from the surface of cells in the respiratory tract, they bind to the sialic acid receptor. Once these two shapes fit snuggly together, they bind allowing the virus to enter the cell. This is called *adsorption*, or adherence to the body of the target cell. The hemagglutinin's shape will determine its ability to bind to the epithelial cells (cells that line the tissue) of the upper or lower respiratory tract.

The neuraminidase protein enables the virus to be released from the host cell. At the top of each neuraminidase, under an electron microscope, it appears that there are propellers similar to those of a helicopter. These blades allow the neuraminidase to break up the sialic acid remaining on the cell surface. This is significant in that the virus would be trapped by the sialic acid when the new viruses burst from the cell after replication. The blades on the head of each spike destroy the acid's ability to bind to the newly formed, escaping influenza viruses. This ensures the new viruses can break free to invade other host cells.

In addition to the aiding in the release of new viruses, neuraminidase may also help during the binding process. The helicopter like blades on these proteins destroys the sialic acid in the mucus, enabling the hemagglutinin to bind to the receptor on the cell surface.

Viral Replication

It seems that a virus' only purpose is to replicate itself and they are only capable of reproducing inside a living host cell which they have invaded. This is because, as stated previously, they lack the needed components to reproduce on their own. Influenza viruses contain only RNA; unlike some other viruses whose genes consist of DNA. Once a virus has entered a host cell, the RNA takes over the functions of the cell in order to replicate new viruses. Eventually the cell dies and ruptures and the new viruses are released to find new host cells. In some cases, thousands of viruses are released, in other cases hundreds of thousands are released.

The mechanics involved in a virus taking over the metabolic machinery of the host cell have considerable medical significance. Some antiviral medications target the reproductive process in order to constrain further replication. Neuraminidase inhibitors such as Oseltamivir (Tamiflu), and Zanamivir (Relenza) work by blocking the function of neuraminidase and causing the newly formed viruses to stick together when escaping the host cell. Although this class of antiviral drugs do not actually kill the virus, they slow the disease process to allow the immune system to wage a fair fight against the invading antigen. The development of other antiviral drugs that would further interfere with viral replication would also interfere with the functions of the host cell and hence are too toxic for clinical use.

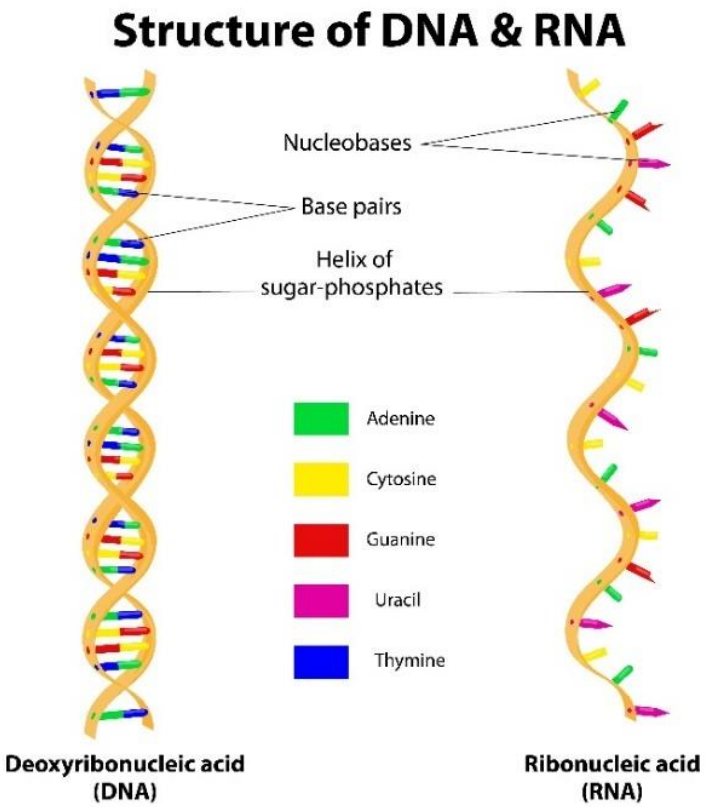
Significance of RNA vs. DNA

In most life forms, genes are made of DNA (deoxyribonucleic acid), which is a long filament type molecule. DNA usually exists as a double-stranded structure, with both strands coiled together to form its characteristic double-helix. Each single strand of DNA is a chain of four types of nucleotides having the bases: adenine, cytosine, guanine, and thymine (commonly noted as A, C, G, and T). DNA carries the information for making all of the cell's proteins. These proteins implement all of the functions of a living organism and determine the organism's characteristics.

When a cell reproduces, it has to pass all of this information on to the offspring cells. Before a cell can reproduce, it must first **replicate** or make a copy of its DNA. DNA contains deoxyribose; "deoxy" means there are no hydroxyl (-OH) groups. The absence of hydroxyl groups means that the chemical bonds between the molecules are not easily broken down into water (H2O).

RNA, conversely, consists of a single strand of nucleotides, that also contains ribose. The ribose contains a hydroxyl group that makes it more susceptible to hydrolysis. Hydrolysis means that the chemical bond between molecules can be easily broken into water. As a result, RNA is intrinsically fragile and its strands can be easily broken. Therefore, the presence of hydroxyl groups makes RNA less stable than DNA. Many viruses, including the influenza virus, encode their genes in RNA.

Whenever an organism reproduces, its genes contained in DNA or RNA attempt to make exact copies of themselves, but mistakes can happen. These mistakes are known as mutations. DNA has a kind of built in proofreading mechanism to prevent these alterations or mutations. During the replication process, DNA has an enzyme complex that moves along the new strand as it is being synthesized. This enzyme complex recognizes any errors and removes the nucleotide. It then returns to replace a correct nucleotide in its place.



DNA vs. RNA
Designua/Shutterstock.com [i]

RNA has no such proofreading mechanism, consequently, there is no protection against mutations. Even a virus produced from a single cell will include many variations of itself. Viruses that carry RNA mutate much faster than a DNA virus. Up to one million times faster. The influenza virus, HIV, and the coronavirus (SARS) are all among those that contain RNA and all mutate the fastest in the world of viruses.

Influenza Virus Mutation – "Drift" and "Shift"

The protein antigens, hemagglutinin and neuraminidase, are also important structures for the spread of the virus. The immune system recognizes viruses by these antigens. When viruses reproduce, the antigens on the new viruses may become slightly different to prevent the immune system from recognizing the virus. Slight changes are known as *antigenic drift*, and much larger changes that may result in epidemics is called *antigenic shift*. These changes, also known as mutations, can result in influenza viruses jumping between species of animals and even its ability to be transmitted from animals to humans.

Antigenic Drift

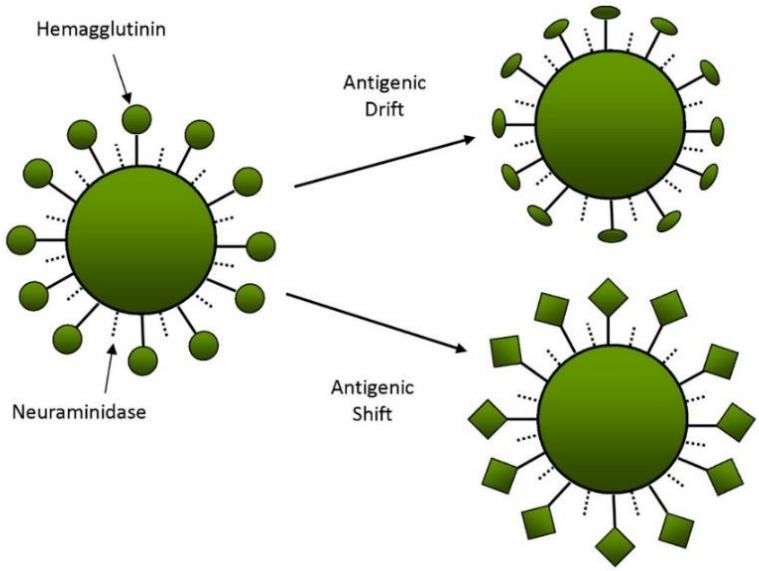
Antigenic drift are small changes in the virus that happen continually over time. This type of mutation produces new virus strains that may not be recognized by the body's immune system. The progression of antigen drift is a person becomes infected with a particular flu virus strain. Their immune system then makes antibodies against that virus according to the antigens presented on the virus' surface. When that virus replicates, the mutations lead to changes to the antigens and a new virus is introduced. The immune system no longer recognizes the new virus and reinfection can occur. This is why people are able to get the flu more than once, even in the same season. In addition, these mutations are the reason that people need to be vaccinated against the seasonal flu each year

Health officials predict the influenza strain most likely to cause the current seasonal flu epidemic then the flu vaccine is updated. However, as in the flu season of 2014-2015, the match to the circulating flu strain and the vaccine may not always be a good one.

Antigenic Shift

The second type of change is called antigenic shift. This is a significant change in the influenza A virus resulting in new hemagglutinin and/or new hemagglutinin and neuraminidase proteins. Antigenic shift results in a whole new influenza A subtype. When shift happens, most people have little or no protection against the new virus.

Antigenic shift occurred in the spring of 2009, when a new H1N1 virus with a new combination of genes emerged to infect people and quickly spread, causing a pandemic. While influenza viruses are changing by antigenic drift all the time, antigenic shift happens only occasionally. Type A viruses undergo both shift and drift types of changes; however, influenza type B viruses only undergo the more gradual process of antigenic drift.



Antigenic Drift vs. Antigenic Shift

Genetic Reassortment

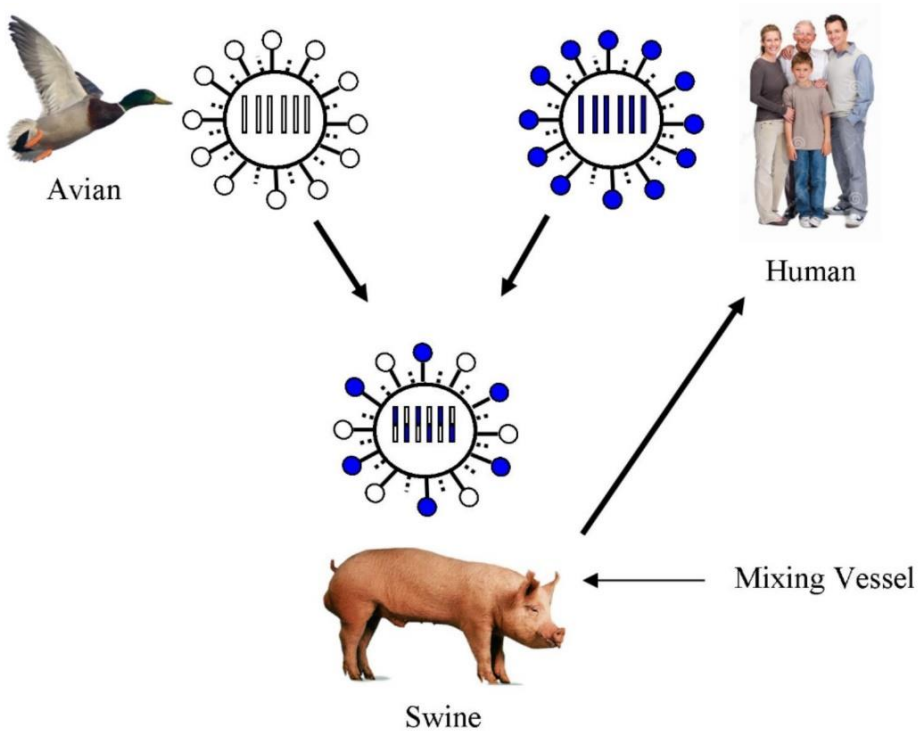
All categories of type A influenza viruses are constantly mutating, including those that regularly cause seasonal epidemics in humans. There are two consequences to this constant mutation. Antigenic drift, as stated above, allows the virus to genetically elude the host's immune system.

The second type of mutation, antigenic shift, as stated is of greater concern. Influenza viruses, including subtypes from different species, can swap or reassort genetic materials with the host and merge. This process is called *genetic reassortment*. Reassortment results in a new subtype different from both parent viruses.

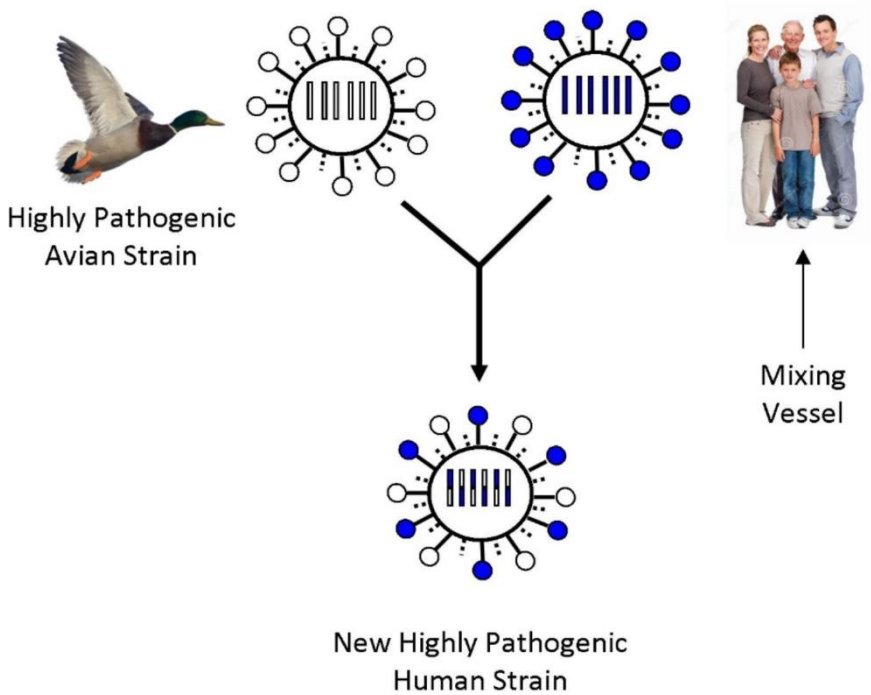
Pigs are susceptible to infection from both avian (bird) and mammalian (human) viruses, they can serve as a vessel for the mixing of genetic material from both type viruses. This can result in a new viral subtype. Due to the fact that humans live in close proximity to domestic pigs and poultry, it lends to favorable conditions for antigenic shift.

Evidence also shows that humans can also serve as a mixing vessel. This adds to the possibility of antigenic shift producing a deadly virus that can be transmissible from person-to-person.

The following are illustrations that demonstrate how both swine and humans can serve as "mixing vessels." By this exchange of genetic material of these animal and human species, new strains of influenza viruses are created.



Genetic Reassortment in Influenza Viruses with Swine as Mixing Vessels



Genetic Reassortment in Influenza Viruses with Humans as Mixing Vessels

Pathophysiology of Seasonal Influenza

The lifecycle of a virus was discussed earlier in the chapter titled Overview of a Virus. The replication processes the virus follows eventually destroys the host cell. During this cycle and the subsequent destruction of cells, the host becomes ill displaying signs and symptoms of the viral infection. An influenza virus that infects humans and attaches to receptors in the respiratory tract will cause a respiratory infection. When the host coughs or sneezes, viruses are expelled into the environment, this is called *shedding*.

Signs and Symptoms of Influenza

Dependent on the severity of a viral infection, or preexisting conditions, the level of illness can be mild to severe. At times, an influenza infection can lead to death. People can experience some or all of the following signs and symptoms of influenza:

- Sore throat
- Cough
- Muscle or body aches
- Headache
- Runny/stuffy nose/sinus congestion
- Fever
- Chills
- Fatigue
- Stomach upset
- Nausea/Vomiting
- Diarrhea

It may take a few days or even up to two weeks to recover; however, some people may develop complications resulting from their illness. These complications can lead to death. Some of these complications include:

- Bronchitis
- Pneumonia
- Sinus and ear infections

It is important to note that complications can arise with anyone no matter their health or their age. However, pregnant women, young children, the elderly, and people with preexisting medical conditions such as asthma, heart disease, or diabetes may be more at risk for developing complications (CDC, 2016). [ii]
Depending on the severity of the circulating seasonal influenza, estimates of flu-associated deaths in the United States range from a low of about 3,000 to a high of about 49,000 people.

During a regular flu season, about 90 percent of deaths occur in people 65 years and older (CDC, 2016).[iii]

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[i] Designua/Shutterstock.com, http://www.shutterstock.com/pic-124474282.html

[ii] Flu Symptoms and Severity, Influenza Symptoms, Centers for Disease and Control (CDC) website. Last modified May 2, 2016, accessed May 13, 2016. http://www.cdc.gov/flu/about/disease/symptoms.htm.

[iii] Estimating Seasonal Influenza-Associated Deaths in the United States: CDC Study Confirms Variability of Flu" Centers for Disease Control and Prevention. CDC Website, Last modified May 25, 2016, accessed June 23, 2016. http://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm.