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Influenza

Influenza (more commonly known as the “flu”) is an infection caused by a virus of which there are 4 known types: A, B, C, and D. Types A, B, and C can infect humans, but type D does not. The primary mode of transmission for the influenza virus is inhalation of virus-contained water/mucus droplets from an infected individual. Symptoms start around two days after being exposed to the virus. Adults are considered infectious the day before symptoms start up to 5-10 days after the first symptoms appear.

Common manifestations of influenza include fever, chills, malaise, muscle aches, headache, watery nasal discharge, nonproductive cough, and a sore throat. The rapid onset of malaise distinguishes the flu from other respiratory viral infections. The virus targets and kills mucous secreting cells, ciliated cells, and other epithelial cells. Because influenza is a viral infection, antibiotics are ineffective treatments and should not be prescribed. The optimal temperature for viral replication is 96 degrees F, so keeping warm helps to inhibit viral replication.

The influenza virus can cause 3 different types of infections. The first is an uncomplicated upper respiratory infection, the second is viral pneumonia, and the third is a bacterial infection (due to the effects of the virus). If viral pneumonia develops, it may become life threatening. Some manifestations of viral pneumonia include rapid onset of fever, tachycardia, tachypnea, cyanosis, and decreased blood pressure.

Pathophysiology of Influenza

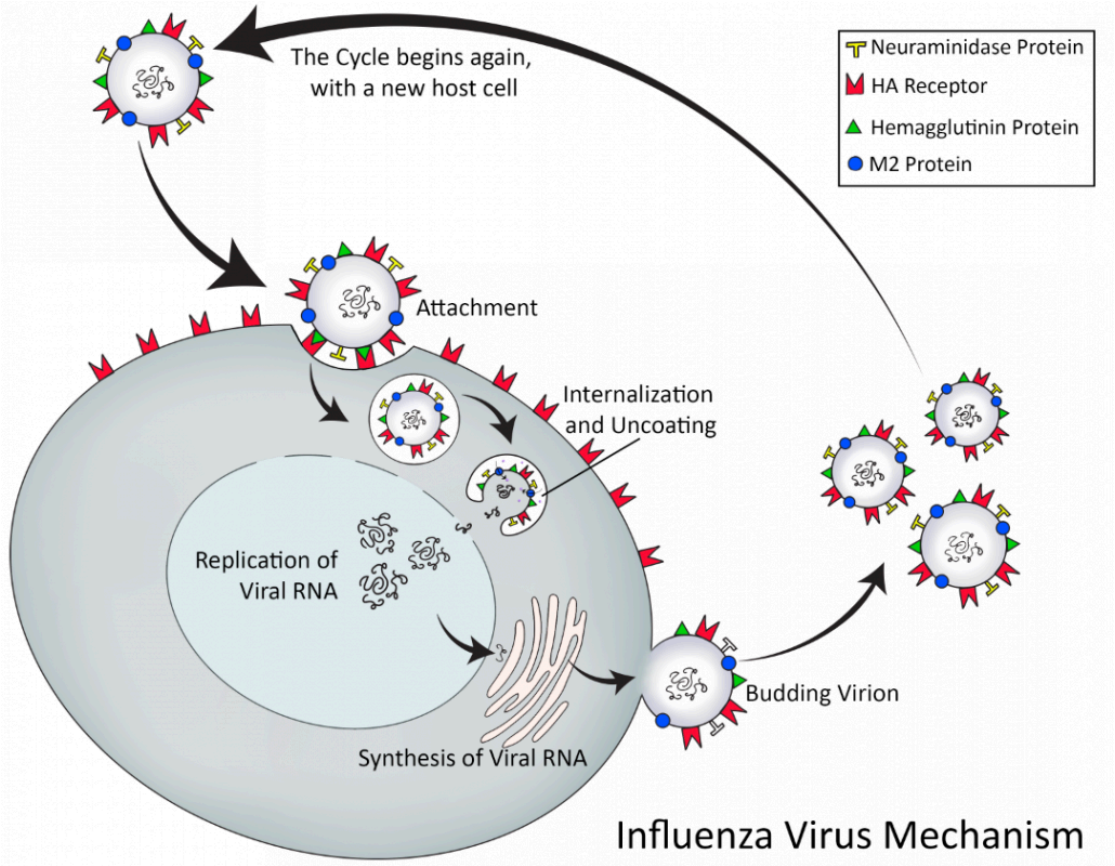

Image by Becky T. W20

Influenza A is capable of infecting both animals and humans. It can be further sub-categorized based on 2 glycoproteins called hemagglutinin and neuraminidase that are embedded in the virus lipid capsule:

Hemagglutinin (HA) allows the virus to anchor to the surface of epithelial cells in the respiratory tract. Hemagglutinin is a lectin, which is a protein that can selectively bind to certain carbohydrate groups. Epithelial cells of the respiratory tract contain an abundance of a 9 carbon carbohydrate called sialic acid that hemagglutinin binds in order to gain entry into epithelial cells. The membrane surface of the epithelial cells have many glycoproteins with different variants of sialic acid attached. Different hemagglutinin lectins can have a spectrum of binding affinities for a spectrum of sialic acid specific glycoproteins. This helps explain why different variants of influenza can have different virulent potentials. Virulence will depend, in part, on which hemagglutinin is expressed by the virus as well as which sialic acid glycoprotein is produced in the host. Once inside the cell, the virus causes replication and translation of viral RNA. This results in the formation of new virion particles that can “bud off” the epithelial cell to then infect other tissue. The infected epithelial cells generally do not survive and the tissue destruction causes an inflammatory response.

Neuraminidase is an enzyme that cleaves the glycosidic bond of sialic acid to proteins. This comes in handy for the virus after it enters the respiratory tract because the epithelial mucus contains a lot of glycoproteins with sialic acid. Hemagglutinin binds the sialic acid and could cause the virus to be stuck right there in the mucus with no access to the underlying healthy epithelial cells. No doubt this does happen a lot and is why mucus is an important part of our innate immune system. However, the virus has neuraminidase in its membrane and this enzyme can cleave the sialic acid residue off of the glycoprotein it is stuck to. This action would free the virus to move again and possibly find its way to an epithelial cell surface. Once the virus binds to an epithelial cell (via its hemagglutinin lectin), it will quickly be taken into the cell before the virus’ neuraminidase has a chance to cleave it off the cell surface. Neuraminidase is also important for the release of new virions. After new virions begin to accumulate and “bud” at the cell surface, they will

have their own hemagglutinin and their own neuraminidase. Neuraminidase will cleave the sialic acid residues that the hemagglutinins are bound to and will allow the new viral particles to be free of the epithelial cell so that they can travel and infect other tissues.

There are two more important viral proteins for the cycle of the influenza virus that you should be aware of. The first, **M1**, encircles the viral RNA core and binds the RNA together in the virus. The second, **M2**, forms a pore that can actively transport protons into the M1 shell. After entering an epithelial cell, the next task for the virus will be to release its encapsulated RNA so that replication and translation can begin. M2 will begin to pump protons found in the endosome into the M1 shell. This will lower the pH enough so that the M1 proteins will go through a conformational change that results in their "letting go" of the RNA fragments. Without the dissociation of M1, the RNA fragments would not be able to assume a state that allowed translation and replication.

This explanation of the pathophysiology of the influenza virus can help us understand the two current **antiviral drugs** that have been developed for influenza. The first type is a neuraminidase inhibitor with examples being oseltamivir, zanamivir, laninamivir and peramivir. These drugs block the ability of neuraminidase to cleave the sialic acid bond on the cell membrane glycoproteins. This causes the new virions to stay clumped and attached to the epithelial cells instead of budding off to infect other tissues. This greatly slows down the spread of the infection. The second class of drug is a M2 protein inhibitor such as amantadine. This drug blocks the ability of M2 protein channels to pump protons into the M1 shell. This results in an inability for the virus to release its RNA in a functional form that can be translated and replicated. This also greatly reduces the spread of the virus through the host tissues. There is concern that the influenza virus is mutating in ways that would make their neuraminidase or M2 proteins resistant to these drugs. If this happens, then these antivirals would not be very helpful. Antiviral drugs work best if they are started quickly after the onset of symptoms (within two days of the start of symptoms).

Nomenclature of the Influenza Virus

Type A influenza infects humans, pigs, horses, and birds and is the major cause of epidemics and pandemics (i.e. Spanish flu of 1918, bird flu of 2004, and swine flu of 2009). Type A has many different serotypes that are classified according to their unique and specific hemagglutinin (denoted as H) and neuraminidase (denoted as N) proteins. H has 18 variants and N has 11 variants. Mutations of these variants have allowed the virus to be more effective at escaping host defense mechanisms. The variants of the virus are named by listing H and N followed by the number that represents the variant. For example, it was a H1N1 variant that caused the swine flu pandemic of 1918 and 2009. H1, H2, and H3 along with N1 and N2 are the most common variants found in humans, but there are exceptions. It was the H5N1 strain that caused the bird flu scare of 2004.

Type B influenza infects only humans. The infections are not generally as severe as type A and mutations of this type occur at a much slower rate. Type B is not a high-risk virus for causing a pandemic. There are only a few known strains of type B and not nearly as many serotypes as there are for type A. For this reason, type B is not named by its H and N subtypes.

Type C influenza also only infects humans. It tends to cause a more mild form of the flu that resembles a cold. This type is also not known for its several serotypes and there are much fewer strains for this virus.

Influenza Vaccine

There are vaccines that try to prevent type A and B influenza infections, but type C has no vaccine. Immunity against various H and N antigens reduces the chance for an influenza infection and also reduces the severity of infections. Vaccines are developed to provide H and N antigens to individuals in hopes that they will develop antibodies against such antigens. It is difficult to know for sure which flu strain will be dominant in a population each year, so the CDC and other worldwide organizations compile data on the patterns of influenza infection. This data is used to make an "educated guess" as to the most likely strain of influenza to arise seasonally in the population centers. Traditionally, there have been two types of vaccines: a trivalent or quadrivalent vaccine. A trivalent contained two type A strains and

one type B strain. A quadrivalent contained two type A strains and two type B strains. Since the vaccination season of 2019-2020, all influenza vaccines are now quadrivalent.

There are three choices as to the way the antigen is developed and given in the vaccine:

1. An **inactivated influenza vaccine (IIV)** is a vaccine where the virus is grown in eggs and then the virus is killed (or inactivated) before being delivered to the body by injection. The immune system can then mount a response against the still present H and N antigens of the inactivated virus.
2. The **recombinant influenza vaccine (RIV3)** is a technique where genes for H and N are isolated and then the genes are combined with genes that are expressed in insects. The insects produce the antigen which can then be harvested for the vaccine. This is a good vaccine option for those who may have an egg allergy.
3. The **live attenuated influenza vaccine (LAIV)** is a live/active virus that has been adapted to function best in cooler temperatures. It is administered as a nasal spray. As the virus comes into contact with the nasal epithelium, it can survive there and cause the body to mount an immune response. However, when the virus tries to spread into tissues that are deeper and warmer, it cannot survive and dies. This vaccine allows the body to mount a strong immune response that will help ward off the flu if a regular circulating virus makes contact. LAIV is not recommended for individuals with a weakened immune system due to the fact that it is a live virus.

Each year, the CDC analyzes the flu season data and makes recommendations. Sometimes, one form of the vaccine or another may be taken off the market and re-evaluated or tweaked a little bit to increase safety and effectiveness. For example, in 2016, the nasal spray LAIV was taken off the market but then reintroduced in a future flu season.

If you would like to learn more about the flu, here are a couple of links that have a wealth of information. These are optional links and not part of your study guide.

https://www.cdc.gov/flu/

https://books.byui.edu/-qHo

Antigenic Drift and Antigenic Shift

Two major reasons that vaccines are notoriously hard to get right for the flu season each year are antigenic drift and antigenic shift.

Antigenic drift involves small mutations in the genes of the virus that can lead to changes in important proteins like hemagglutinin or neuraminidase. As you are well aware, the human body is capable of mounting a response to antigens by creating effective antibodies and cytotoxic T-cells. However, if the antigen changes enough, the immune cells and antibodies that work well for one strain of the virus may not work well for another mutated strain. On the one hand, small mutations may result in an antigenic drift that creates antigens quite similar to the ones a person is immune to. For this reason, we suspect that the flu vaccine can sometimes be at least partially effective even when the flu strain for the season is somewhat different than the predicted educated guess. On the other hand, sometimes antigenic drift creates an antigenic change that is just too different for the immune system to recognize and neutralize the virus. If this is the case, a person can become sick even if they have had the flu before or if they have been vaccinated recently.

Antigenic shift involves a change to the antigen that is relatively major and abrupt. This change can result in a new subtype of the virus from animals that can infect humans for the first time. Generally, humans are ill prepared for such an introduction as our population has not had to deal with that strain of the virus before. For example, an influenza virus that originally infected animals obtained the ability to infect humans in 2009 when an H1N1 virus strain acquired H and N genes from a strain that normally just infected animals. Armed with these new H and N genes, the virus attacked a relatively immune-absent human population and it spread quickly. Antiviral medications and flu vaccines to relatively close strains were our only weapons. It is a sobering thought to imagine an influenza virus that obtains both resistance to our antivirals as well as new antigenic components from another animal. If such a strain is particularly virulent and aggressive in its infection, we could witness a pandemic with very lethal consequences. This is why many in the medical community warn against ubiquitous use of antiviral medications.

Here are two full-page images that show a pictorial representation of antigenic drift and antigenic shift. These pictures will be very useful to help you understand what these concepts mean.

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