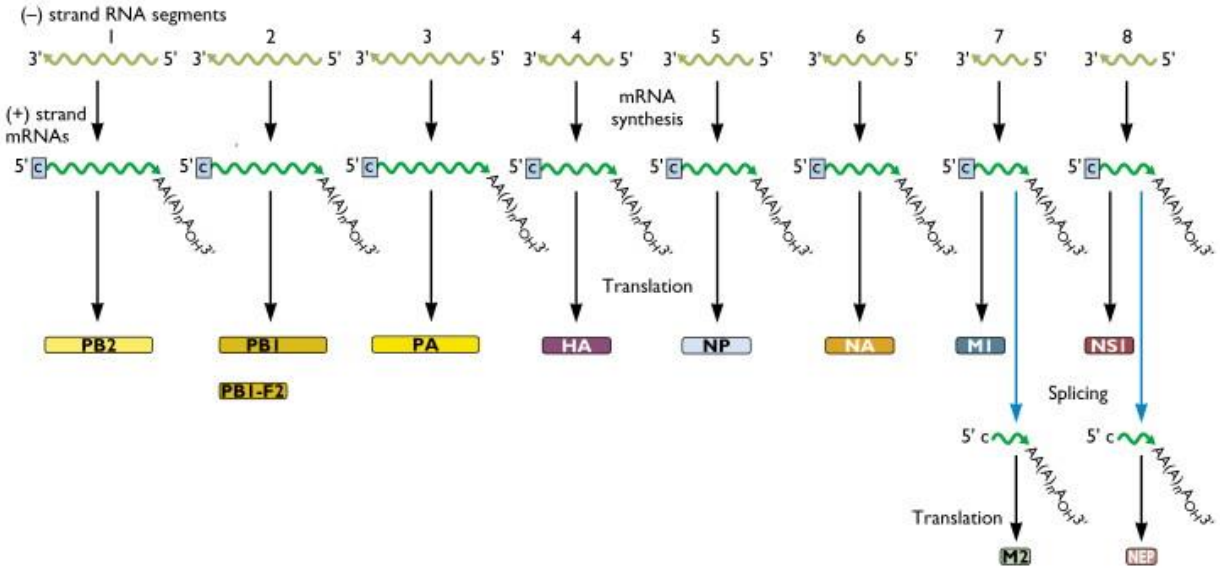
Influenza Virus

The influenza A, B, and C viruses, representing three of the five genera of the family *Orthomyxoviridae*, are characterized by **segmented, negative-strand RNA genomes.** Sequencing has confirmed that these viruses share a common genetic ancestry; however, they have genetically diverged, such that **reassortment** – the exchange of viral RNA segments between viruses – has been reported to occur within each genus, or *type*, but not across types. Influenza A viruses are further characterized by the *subtype* of their surface glycoproteins, the hemagglutinin (HA) and the neuraminidase (NA). Influenza viruses have a standard nomenclature that includes virus type; species from which it was isolated (if non-human); location at which it was isolated; isolate number; isolate year; and, for influenza A viruses only, HA and NA subtype. Thus, A/Panama/2007/1999(H3N2) was isolate number 2007 of a human influenza A virus taken in the country of Panama in 1999, and it has an HA subtype 3 and an NA subtype 2. While many genetically distinct subtypes – 16 for HA and 9 for NA – have been found in circulating influenza A viruses, only three HA (H1, H2, and H3) and two NA (N1 and N2) subtypes have caused human epidemics, as defined by sustained, widespread, person-to-person transmission. The particular structure of the influenza virus genome and function of its viral proteins enable *antigenic drift* and *antigenic shift*. These processes result in viruses able to evade the long-term adaptive immune responses in many hosts.

The influenza A and B virus genomes each comprise eight negative-sense, single-stranded viral RNA (vRNA) segments, while influenza C virus has a seven-segment genome. Eight RNAs are a total of about 14,000 nucleotides in length. The eight segments of influenza A and B viruses (and the seven segments of influenza C virus) are numbered in order of decreasing length. In influenza A and B viruses, segments 1, 3, 4, and 5 encode just one protein per segment: the PB2 (polymerase basic protein 2) , PA (Polymerase acidic protein), HA and NP (Nucleo protein) proteins. All influenza viruses encode the polymerase subunit PB1 on segment 2; in some strains of influenza A virus, this segment also codes for the accessory protein PB1-F2, a small, 87-amino acid protein with pro-apoptotic activity, in a +1 alternate reading frame. No analogue to PB1-F2 has been identified in influenza B or C viruses. Conversely, segment 6 of the influenza A virus encodes only the NA protein, while that of influenza B virus encodes both the NA protein and, in a −1 alternate reading frame, the NB matrix protein, which is an integral membrane protein corresponding to the influenza A virus M2 protein. Segment 7 of both influenza A and B viruses code for the M1 matrix protein. In the influenza A genome, the M2 ion channel is also expressed from segment 7 by RNA splicing, while influenza B virus encodes its BM2 membrane protein in a +2 alternate reading frame . Finally, both influenza A and B viruses possess a single RNA segment, segment 8, from which they express the interferon-antagonist NS1 protein and, by mRNA splicing, the NEP/NS2 , which is involved in viral RNP export from the host cell nucleus. The genomic organization of influenza C viruses is generally

similar to that of influenza A and B viruses; however, the HEF protein of influenza C replaces the HA and NA proteins, and thus the influenza C virus genome has one fewer segment than that of influenza A or B viruses.



Antigenic Drift

One way influenza viruses change is called “antigenic drift.” These are small changes (or mutations) in the genes of influenza viruses that can lead to changes in the surface proteins of the virus: HA (hemagglutinin) and NA (neuraminidase). The HA and NA surface proteins of influenza viruses are “antigens,” which means they are recognized by the immune system and are capable of triggering an immune response, including production of antibodies that can block infection. The changes associated with antigenic drift happen continually over time as the virus replicates. Most flu shots are designed to target an influenza virus’ HA surface proteins/antigens. The nasal spray flu vaccine (LAIV) targets both the HA and NA of an influenza virus.

The small changes that occur from antigenic drift usually produce viruses that are closely related to one another, which can be illustrated by their location close together on a phylogenetic tree. Influenza viruses that are closely related to each other usually have similar antigenic properties. This means that antibodies your immune system creates against one influenza virus will likely

recognize and respond to antigenically similar influenza viruses (this is called "cross-protection").

However, the small changes associated with antigenic drift can accumulate over time and result in viruses that are antigenically different (further away on the phylogenetic tree). It is also possible for a single (or small) change in a particularly important location on the HA to result in antigenic drift. When antigenic drift occurs, the body's immune system may not recognize and prevent sickness caused by the newer influenza viruses. As a result, a person becomes susceptible to flu infection again, as antigenic drift has changed the virus enough that a person's existing antibodies won't recognize and neutralize the newer influenza viruses.

Antigenic drift is the main reason why people can get the flu more than one time, and it's also a primary reason why the flu vaccine composition must be reviewed and updated each year (as needed) to keep up with evolving influenza viruses.

Antigenic shift

Antigenic shift occurs when a radical and abrupt change in influenza type A virus hemagglutinins occurs. In some cases, a 50% change occurs in the hemagglutinin structure. Antigenic shift can be the result of a direct jump from an unknown animal strain to humans or a reassortment of two or more influenza viruses within the same cell.
Evidence suggests that the 1918 influenza pandemic was the result of a direct jump from pigs to humans. The type A H1N1 pandemic flu killed 500,000 people in the United States. Worldwide, the death toll was estimated at 50 million.
Viral re-assortment is a more complex form of antigenic shift. It occurs when two viruses simultaneously infect the same animal. For example, pigs carry an endemic strain of influenza and can be infected with both human and avian influenza strains. Within an infected porcine cell, reassortment of genetic material from both viruses creates a new, hybrid virus. The virus that caused the 2009 pandemic influenza (type A H1N1) is a *quadruple reassortment virus.* It contains genes from pigs normally found in Europe and Asia, avian–swine influenza genes, and human influenza genes.

S.N.	Antigenic Shift	Antigenic Drift
1	Major Antigenic Change	Minor Antigenic Change
2	Forming new sub-type (Subtype A + Subtype B –> New Subtype)	Forming new strain of virus
3	One or Two Viruses are Involved	Only one virus is involve
4	Occurs once in a time	Occurs frequently
5	May jump from one species to another (animal-human)	May infect animals of the same species
6	Large change in nucleotides of RNA	Small mutation of RNA
7	Occurs as a results of genome reassortment between difference subtypes.	Occurs as a result of the accumulation of point mutations in the gene.
8	An antigenic change which results in drastic or dramatic alternation in HA (hemagglutinin) or NA (neuraminidase) subtypes.	An antigenic change can alter antigenic sites on the molecule such that a virion can escape recognition by the host's immune system.
9	Large and sudden mutation	Random and Spontaneous Mutation

Source – CDC, WHO.