

# Influenza Fact Sheet 2008

## Science:

Influenza, commonly known as ("the") flu, is an infectious disease of birds and mammals caused by RNA viruses of the family Orthomyxoviridae (the influenza viruses) which are comprised of five genera: Influenzavirus A, Influenzavirus B, Influenzavirus C, Isavirus, and Thogotovirus. The genus Isavirus affects primarily fish (Atlantic salmon, sea trout, etc.), and the genus Thogotovirus currently is made up of four "Old World" viruses: Thogoto, Dhori, Batken, and Araguari, the first three viruses are thought to be tick-transmitted, and can cause a rapidly fatal disease process in mice similar to Avian influenza A. [*Hey, we might be able to use that to model Avian influenza's effects and look for methods of treatment!*] All three influenzaviruses share certain features that are fundamental to their biologic behavior, including the presence of a host-cell derived envelope, envelope glycoproteins of critical importance in virus entry and egress from cells, and a segmented genome of negative sense (i.e., opposite of message sense), single-stranded RNA. The standard nomenclature for influenza viruses includes the influenza type, place of initial isolation, strain designation, and year of isolation. One of the unique and most remarkable features of influenza virus is the frequency with which changes in antigenicity occur; these changes are referred to as antigenic variation. Alteration of the antigen structure of the virus leads to infection with variants to which little or no resistance is present in the population at risk. The phenomenon of antigenic variation helps explain why influenza continues to be a major epidemic disease of humans. Antigenic variation involves principally the two external glycoproteins of the virus, HA (hemagglutinin) and NA (neuraminidase), and is referred to as **antigenic drift** or **antigenic shift**, depending on whether the variation is small or great.

Influenzavirus C genus has one species, influenza C. It causes upper respiratory illnesses routinely in humans, especially among children, but is not seasonal in occurrence and is mild generally in effect. It shows slow genetic drift and multiple lineages of influenza C virus cocirculate. It likely causes less severe infections because background antibody formation in the population (due to exposure to similar antigenic subtypes) limits the extent of an infection and its propagation to naïve populations.

The Influenzavirus A genus has one species, influenza A virus. Influenza A viruses infect a variety of species, including man, swine, horses, marine mammals, and in particular, birds. In fact, no less than 15 unique HA subtypes (H1 to H15) and nine NA subtypes (N1 to N9) have been identified in avian influenza viruses. Fortunately, avian influenza A viruses themselves appear to be relatively restricted in their ability to replicate in humans. The type A viruses are the most virulent human pathogens among the three influenza types and cause the most severe disease.

Influenzavirus B has one species, influenza B virus. Influenza B almost exclusively infects humans and is less common than influenza A. The only other animal known to be susceptible to influenza B infection is the seal. This type of influenza mutates at a rate 2–3 times lower than type A and consequently is less genetically diverse, with only one influenza

B serotype. As a result of this lack of antigenic diversity, a degree of immunity to influenza B is usually acquired at an early age. However, influenza B mutates enough that lasting immunity is not possible. This reduced rate of antigenic change, combined with its limited host range (inhibiting cross species antigenic shift), ensures that pandemics of influenza B do not occur.

Influenza A viruses have been studied the most and have been found to have eight structural proteins. At the surface there are spikes of glycoproteins that possess either hemagglutinin (HA) or neuraminidase (NA) activity. The HA is synthesized as a monomer (HA<sub>0</sub>), which is cleaved by host-cell proteases into HA<sub>1</sub> and HA<sub>2</sub> components that remain linked together. These proteases are found often in only very specific types of cells and the right protease can cleave the HA monomer into components that greatly increase the affinity/binding of the virus, and thus may increase its virulence. Antigenic sites and sites for binding to cells are located in the globular head of the molecule.

The viral NA is an enzyme that catalyzes the removal of terminal sialic acids (*N*-acetyl neuraminic acid) from sialic acid-containing glycoprotein, thus aiding in binding to the cell.

Genetic **drift** occurs frequently with influenza A and with a few amino acid changes in the surface proteins, the virus avoids host defenses in the population and it thus thrives (is selected). This selection supplants the prevalence of subtypes that humans in general have more immunity to, and thus enhances the possibility of further changes that the immune system doesn't recognize. This accounts for why you can get the influenza virus year after year! Genetic **shifts** occur when multiple amino acids change, usually by rearrangement of existing components of HAs or NAs from different reservoirs (but not always so). These major shifts can result in pandemics and depending on the subtype rearrangement, many deaths. At least 15 highly divergent, antigenically distinct HAs have been described in influenza A viruses (H1 to H15), as well as at least nine distinct NAs (N1 to N9).

A third integral membrane protein, the M2 protein, is also present in small amounts on the viral envelope, and is important to establish an ion channel that enables disrobing of the viral coat. Interior to the envelope is the matrix, or M1, protein. This protein is believed to provide stability to the virion. Within the envelope are eight physically discrete nucleocapsid segments. One of these, the NS gene, antagonizes the action of type-I interferons through an unknown mechanism, and absence of the NS1 protein renders the virus incapable of growth in interferon-competent systems. The NS gene of the H5 avian viruses appears to be especially potent in this regard, and this may provide a partial explanation for its enhanced virulence in mice. Recent reports have suggested that H5 viruses associated with fatal cases in humans have changes in nucleotide sequences in the NS1 gene that result both in increased resistance to the action of interferon and in the ability to induce proinflammatory cytokines.

## Disease prevention:

In the United States, annual epidemics of influenza occur typically during the late fall through early spring seasons. Influenza viruses can cause disease among persons in any age group, but rates of infection are highest among children. Rates of serious illness and death are highest among persons aged 65 years and older, children aged <2 years, and persons of any age who have medical conditions that place them at increased risk for complications from influenza. An annual average of approximately 36,000 deaths during 1990–1999 and 226,000 hospitalizations during 1979–2001 have been associated with influenza epidemics.

Annual influenza vaccination is the most effective method for preventing influenza virus infection and its complications. Influenza vaccine can be administered to any person aged 6 months and older (who does not have contraindications to vaccination) to reduce the likelihood of becoming ill with influenza or of transmitting influenza to others. Trivalent inactivated influenza vaccine (TIV) can be used for any person aged 6 months and older, including those with high-risk conditions. Live, attenuated influenza vaccine (LAIV) may be used for healthy, nonpregnant persons aged 2–49 years. If vaccine supply is limited, priority for vaccination is typically assigned to persons in specific groups and of specific ages who are, or are contacts of, persons at higher risk for influenza complications. Because the safety or effectiveness of LAIV has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications, these persons should only be vaccinated with TIV.

Influenza vaccine is generally very well tolerated in adults. Rates of mild local soreness after administration of inactivated influenza vaccine have been documented to be in the range of 60% to 80% in multiple studies. Local side effects are slightly more common in women than in men. Systemic reactions, including malaise, flulike illnesses, and fever, are relatively uncommon. Rates of transient, low-grade fever have varied from 2% to 10% of recipients in these studies; these rates are only marginally increased above the rates in placebo recipients. Although whole-virus and split-product vaccines are similarly reactogenic in adults, whole-virus vaccines are associated with fever in children and are no longer available in the United States. Fever occurs in approximately 8% to 11% of vaccinated children and may be associated with other systemic symptoms such as myalgia, arthralgia, headache, and malaise.

Severe, life-threatening, immediate hypersensitivity reactions to parenteral inactivated vaccine have been rare. However, hypersensitivity to hens' eggs, in which the vaccine virus is grown, is a contraindication to vaccination. Generally, if persons can eat eggs or egg-containing products, vaccination is safe. Although vaccine is usually not administered to patients with a genuine anaphylactic hypersensitivity to egg products, such individuals can be desensitized and safely vaccinated if necessary.

Influenza viruses are spread from person to person primarily through large-particle respiratory droplet transmission (e.g., when an infected person coughs or sneezes near a susceptible person). Transmission via large-particle droplets requires close contact between source and recipient persons, because droplets do not remain suspended in the air and generally travel only a short distance (less than or equal to 1 meter) through the air. Contact

with respiratory-droplet contaminated surfaces is another possible source of transmission. Airborne transmission (via small-particle residue [less than or equal to 5µm] of evaporated droplets that might remain suspended in the air for long periods of time) also is thought to be possible, although data supporting airborne transmission are limited. The typical incubation period for influenza is 1–4 days (average: 2 days). Adults shed influenza virus from the day before symptoms begin through 5–10 days after illness onset. However, the amount of virus shed, and presumably infectivity, decreases rapidly by 3–5 days after onset in an experimental human infection model. Young children also might shed virus several days before illness onset, and children can be infectious for 10 or more days after onset of symptoms. Severely immunocompromised persons can shed virus for weeks or months.

There are readily available tests for the detection of influenza virus antigen in mucosal secretions. A diagnosis can also be made on epidemiologic grounds. That is, when the presence of influenza virus is confirmed in a region or community, healthy adults with acute influenza-like illness most commonly have influenza. In fact, several studies have shown that the accuracy of a clinical diagnosis in healthy adults in the setting of an influenza outbreak is as high as 80% to 90%. In an analysis of symptoms in young adults being assessed for entry into studies of influenza virus treatment, the best multivariate predictors of laboratory-confirmed influenza virus infection were cough and fever, with an increasing predictive value with increasing levels of fever. However, the predictive value of such a symptom complex may be less in older adults and in children. In nursing homes, the presence of cocirculating pathogens (such as respiratory syncytial virus) that can result in identical symptoms can clearly complicate the ability to make a clinical diagnosis of influenza specifically.

Complications of influenza virus can include myositis, cardiac complications (pericarditis, myocarditis), a toxic shock-like syndrome, central nervous system complications (Guillain-Barre', transverse myelitis, encephalitis), and Reye's Syndrome.

## Treatment:

Four antiviral drugs are currently available for the prevention and treatment of influenza. Certain general principles apply regardless of the specific form of therapy chosen. It is important to recognize that individuals with an intact immune system who have had previous influenza infections rapidly limit the replication of these viruses. Therefore, the opportunity to impact viral replication with antiviral agents is limited, and effective use of these agents requires early initiation of therapy. No studies have ever demonstrated a benefit of antiviral therapy begun after 48 hours or more of symptoms, and the greatest effect is typically seen when therapy is started in the first 24 hours.

Amantadine and Rimantadine are M2 inhibitors and are active against all strains of **influenza A virus** in a variety of cell culture systems and animal models. The antiviral effect is primarily manifested in cell culture as inhibition of virus uncoating. Similar ion channels have been described for influenza B and C viruses; however, at clinically achievable levels, these drugs are active against only influenza A. Drug resistance has been a factor in limiting the more widespread use of these antiviral agents. Although resistant viruses are seen in less than 1% of unexposed individuals, they emerge fairly frequently in treated individuals, particularly children.

Zanamivir and Oseltamivir are neuraminidase inhibitors. Neuraminidase inhibitors are active against influenza viruses at millimolar concentrations or less. Activity against clinical isolates assessed in plaque inhibition tests ranges from concentrations of 0.01 to 16  $\mu$ M. Influenza B viruses are approximately 10-fold less sensitive than **influenza A viruses**, but they are still sensitive well within clinically achievable concentrations. Among the influenza viruses sensitive to neuraminidase inhibitors are avian viruses with all nine known neuraminidase subtypes. Because the neuraminidase inhibitors interact with highly conserved residues within the influenza virus neuraminidase, it has been hypothesized that antiviral resistance will be a relatively limited problem.

All four of the available antiviral agents are effective at preventing influenza prophylaxis provided the drug is administered continuously throughout the period of exposure. Several schemes for such prophylaxis have been evaluated, including seasonal prophylaxis, where drug is administered throughout the influenza epidemic season, generally 4 to 6 weeks; family prophylaxis, where drug is administered to family members for a short period of time after recognition of an index case in the family; and outbreak-initiated prophylaxis in institutions, which could be considered to be a variation on the theme of family prophylaxis. In addition, short term antiviral prophylaxis can be considered for high-risk individuals who are vaccinated during the influenza season.

Probably one of the most common uses of antiviral agents for influenza is to terminate the transmission of influenza within institutions such as nursing homes during outbreaks. Although this has not been subject to formal, placebo-controlled study, many anecdotal reports support the efficacy of amantadine, zanamivir, and oseltamivir in this setting. When M2 inhibitors are used for outbreak prophylaxis, individuals who are receiving treatment with amantadine should be isolated from those who are receiving prophylaxis. Failure to adhere to this practice is associated with the development and transmission of resistant viruses within the institution. One preliminary report has suggested that prophylactic administration of zanamivir was successful in terminating an outbreak of influenza in a nursing home in which cases continued to occur despite amantadine prophylaxis.

Prevention & Control of Influenza - Recommendations of the Advisory Committee on Immunization Practices (ACIP) 2008. MMWR 2008 Jul 17; Early Release:1-60.

The Viruses in Mandell, Bennett, & Dolin: Principles and Practice of Infectious Diseases, 6th ed.

Thanks to Wikipedia for getting me started with the Influenza genii so that they could be further searched. I HIGHLY recommend reading "1918 Influenza: the Mother of all Pandemics" in the Emerging Infectious Diseases web journal at the CDC website. The address is <http://www.cdc.gov/ncidod/EID/vol12no01/05-0979.htm> It has lots of connected articles related to the 1918 Swine flu epidemic and may put quite a scare into you regarding the possibilities of an Avian influenza pandemic.