Influenza A virus subtype H5N1

Influenza A virus subtype H5N1, also known as A(H5N1) or simply H5N1, is a subtype of the Influenza A virus which can cause illness in humans and many other animal species. A bird-adapted strain of H5N1, called HPAI A(H5N1) for "highly pathogenic avian influenza virus of type A of subtype H5N1", is the causative agent of H5N1 flu, commonly known as "avian influenza" or "bird flu". It is enzootic in many bird populations, especially in Southeast Asia. One strain of HPAI A(H5N1) is spreading globally after first appearing in Asia. It is epizootic (an epidemic in nonhumans) and panzootic (affecting animals of many species, especially over a wide area), killing tens of millions of birds and spurring the culling of hundreds of millions of others to stem its spread. Most references to "bird flu" and H5N1 in the popular media refer to this strain.

Overview

PAI A(H5N1) is an avian disease. There is no evidence of efficient human-to-human transmission or of airborne transmission of HPAI A(H5N1) to humans. In almost all cases, those infected with H5N1 had extensive physical contact with infected birds. Still, around 60% of humans known to have been infected with the current Asian strain of HPAI A(H5N1) have died from it, and H5N1 may mutate or reassort into a strain ca-
Pliable of efficient human-to-human transmission. In 2003, world-renowned virologist Robert Webster published an article titled "The world is teetering on the edge of a pandemic that could kill a large fraction of the human population" in American Scientist. He called for adequate resources to fight what he sees as a major world threat to possibly billions of lives. On September 29, 2005, David Nabarro, the newly-appointed Senior United Nations System Coordinator for Avian and Human Influenza, warned the world that an outbreak of avian influenza could kill anywhere between 5 million and 150 million people. Experts have identified key events (creating new clades, infecting new species, spreading to new areas) marking the progression of an avian flu virus towards becoming pandemic, and many of those key events have occurred more rapidly than expected.

Due to the high lethality and virulence of HPAI A(H5N1), its endemic presence, its increasingly large host reservoir, and its significant ongoing mutations, the H5N1 virus is the world's largest current pandemic threat, and billions of dollars are being spent researching H5N1 and preparing for a potential influenza pandemic. At least 12 companies and 17 governments are developing pre-pandemic influenza vaccines in 28 different clinical trials that, if successful, could turn a deadly pandemic infection into a nondeadly one. Full-scale production of a vaccine that could prevent any illness at all from the strain would require at least three months after the virus's emergence to begin, but it is hoped that vaccine production could increase until one billion doses were produced by one year after the initial identification of the virus.

H5N1 may cause more than one influenza pandemic as it is expected to continue mutating in birds regardless of whether humans develop herd immunity to a future pandemic strain. Influenza pandemics from its genetic offspring may include influenza A virus subtypes other than H5N1. While genetic analysis of the H5N1 virus shows that influenza pandemics from its genetic offspring can easily be far more lethal than the Spanish Flu pandemic, planning for a future influenza pandemic is based on what can be done and there is no higher Pandemic Severity Index level than a Category 5 pandemic which, roughly speaking, is any pandemic as bad as the Spanish flu or worse; and for which all intervention measures are to be used.

Genetics
The first known strain of HPAI A(H5N1) (called A/chicken/Scotland/59) killed two flocks of chickens in Scotland in 1959; but that strain was very different from the current highly pathogenic strain of H5N1. The dominant strain of HPAI A(H5N1) in 2004 evolved from 1999 to 2002 creating the Z genotype. It has also been called "Asian lineage HPAI A(H5N1)."
Asian lineage HPAI A(H5N1) is divided into two antigenic clades. "Clade 1 includes human and bird isolates from Vietnam, Thailand, and Cambodia and bird isolates from Laos and Malaysia. Clade 2 viruses were first identified in bird isolates from China, Indonesia, Japan, and South Korea before spreading westward to the Middle East, Europe, and Africa. The clade 2 viruses have been primarily responsible for human H5N1 infections that have occurred during late 2005 and 2006, according to WHO. Genetic analysis has identified six subclades of clade 2, three of which have a distinct geographic distribution and have been implicated in human infections: Map

Subclade 1, Indonesia
Subclade 2, Europe, Middle East, and Africa (called EMA)
Subclade 3, China"

A 2007 study focused on the EMA subclade has shed further light on the EMA mutations. "The 36 new isolates reported here greatly expand the amount of whole-genome sequence data available from recent avian influenza (H5N1) isolates. Before our project, GenBank contained only 5 other complete genomes from Europe for the 2004–2006 period, and it contained no whole genomes from the Middle East or northern Africa. Our analysis showed several new findings. First, all European, Middle Eastern, and African samples fall into a clade that is distinct from other contemporary Asian clades, all of which share common ancestry with the original 1997 Hong Kong strain. Phylogenetic trees built on each of the 8 segments show a consistent picture of 3 lineages, as illustrated by the HA tree shown in Figure 1. Two of the clades contain exclusively Vietnamese isolates; the smaller of these, with 5 isolates, we label V1; the larger clade, with 9 isolates, is V2. The remaining 22 isolates all fall into a third, clearly distinct clade, labeled EMA, which comprises samples from Europe, the Middle East, and Africa. Trees for the other 7 segments display a similar topology, with clades V1, V2, and EMA clearly separated in each case. Analyses of all available complete influenza (H5N1) genomes and of 589 HA sequences placed the EMA clade as distinct from the major clades circulating in People's Republic of China, Indonesia, and Southeast Asia."

As with other avian flu viruses, H5N1 has strains called "highly pathogenic" (HP) and "low-pathogenic" (LP). Avian influenza viruses that cause HPAI are highly virulent, and mortality rates in infected flocks often approach 100%. LPAI viruses have negligible virulence, but these viruses can serve as progenitors to HPAI viruses. The current strain of H5N1 responsible for the deaths of birds across the world is an HPAI strain; all other current strains of H5N1, including a North American strain that causes no disease at all in any species, are LPAI strains. All HPAI strains identified to date have involved H5 and H7 subtypes. The distinction concerns pathogenicity in poultry, not humans. Normally a highly pathogenic avian virus is not highly pathogenic to either humans or non-poultry birds. This current deadly strain of H5N1 is unusual in being deadly to so many species, including some, like domestic cats, never previously susceptible to any influenza virus.

**Genetic structure and related subtypes**

H5N1 is a subtype of the species Influenza A virus of the Influenzavirus A genus of the
Orthomyxoviridae family. Like all other influenza A subtypes, the H5N1 subtype is an RNA virus. It has a segmented genome of eight negative sense, single-strands of RNA, abbreviated as PB2, PB1, PA, HA, NP, NA, MP and NS.

HA codes for hemagglutinin, an antigenic glycoprotein found on the surface of the influenza viruses and is responsible for binding the virus to the cell that is being infected. NA codes for neuraminidase, an antigenic glycosylated enzyme found on the surface of the influenza viruses. It facilitates the release of progeny viruses from infected cells. The hemagglutinin (HA) and neuraminidase (NA) RNA strands specify the structure of proteins that are most medically relevant as targets for antiviral drugs and antibodies. HA and NA are also used as the basis for the naming of the different subtypes of influenza A viruses. This is where the H and N come from in H5N1.

Influenza A viruses are significant for their potential for disease and death in humans and other animals. Influenza A virus subtypes that have been confirmed in humans, in order of the number of known human pandemic deaths that they have caused, include:

- H1N1, which caused "Spanish flu" and currently causes seasonal human flu
- H2N2, which caused "Asian flu"
- H3N2, which caused "Hong Kong flu" and currently causes seasonal human flu
- H5N1, the world's major current pandemic threat
- H7N7, which has unusual zoonotic potential and killed one person
- H1N2, which is currently endemic in humans and pigs and causes seasonal human flu
- H9N2, which has infected three people
- H7N2, which has infected two people
- H7N3, which has infected two people
- H10N7, which has infected two people
Low pathogenic H5N1

Low pathogenic avian influenza H5N1 (LPAI H5N1) also called "North American" H5N1 commonly occurs in wild birds. In most cases, it causes minor sickness or no noticeable signs of disease in birds. It is not known to affect humans at all. The only concern about it is that it is possible for it to be transmitted to poultry and in poultry mutate into a highly pathogenic strain.

1975 – LPAI H5N1 was detected in a wild mallard duck and a wild blue goose in Wisconsin.
1981 and 1985 – LPAI H5N1 was detected in ducks by the University of Minnesota conducting a sampling procedure in which sentinel ducks were monitored in cages placed in the wild for a short period of time.
1983 – LPAI H5N1 was detected in ring-billed gulls in Pennsylvania.
1986 - LPAI H5N1 was detected in a wild mallard duck in Ohio.
2005 - LPAI H5N1 was detected in ducks in Manitoba, Canada.
"In the past, there was no requirement for reporting or tracking LPAI H5 or H7 detections in wild birds so states and universities tested wild bird samples independently of USDA. Because of this, the above list of previous detections might not be all inclusive of past LPAI H5N1 detections. However, the World Organization for Animal Health (OIE) recently changed its requirement of reporting detections of avian influenza. Effective in 2006, all confirmed LPAI H5 and H7 AI subtypes must be reported to the OIE because of their potential to mutate into highly pathogenic strains. Therefore, USDA now tracks these detections in wild birds, backyard flocks, commercial flocks and live bird markets."

Properties of H5N1

Infectivity

H5N1 is easily transmissible between birds facilitating a potential global spread of H5N1. While H5N1 undergoes mutation and reassortment, creating variations which can infect species not previously known to carry the virus, not all of these variant forms can infect humans. H5N1 as an avian virus preferentially binds to a type of galactose receptors that populate the avian respiratory tract from the nose to the lungs and are virtually absent in humans, occurring only in and around the alveoli, structures deep in the lungs where oxygen is passed to the blood. Therefore, the virus is not easily expelled by coughing and sneezing, the usual route of transmission.

H5N1 is mainly spread by domestic poultry, both through the movements of infected birds and poultry products and through the use of infected poultry manure as fertilizer or feed. Humans with H5N1 have typically caught it from chickens, which were in turn infected by other poultry or waterfowl. Migrating waterfowl (wild ducks, geese and swans) carry H5N1, often without becoming sick. Many species of birds and mammals can be infected with HPAI A(H5N1), but the role of animals other than poultry and waterfowl as disease-spreading hosts is unknown.

According to a report by the World Health Organization, H5N1 may be spread indirectly. The report stated that the virus may sometimes stick to surfaces or get kicked up in
fertilizer dust to infect people.

**Virulence**

H5N1 has mutated into a variety of strains with differing pathogenic profiles, some pathogenic to one species but not others, some pathogenic to multiple species. Each specific known genetic variation is traceable to a virus isolate of a specific case of infection. Through antigenic drift, H5N1 has mutated into dozens of highly pathogenic varieties divided into genetic clades which are known from specific isolates, but all currently belonging to genotype Z of avian influenza virus H5N1, now the dominant genotype. H5N1 isolates found in Hong Kong in 1997 and 2001 were not consistently transmitted efficiently among birds and did not cause significant disease in these animals. In 2002 new isolates of H5N1 were appearing within the bird population of Hong Kong. These new isolates caused acute disease, including severe neurological dysfunction and death in ducks. This was the first reported case of lethal influenza virus infection in wild aquatic birds since 1961. Genotype Z emerged in 2002 through reassortment from earlier highly pathogenic genotypes of H5N1 that first infected birds in China in 1996, and first infected humans in Hong Kong in 1997. Genotype Z is endemic in birds in Southeast Asia, has created at least two clades that can infect humans, and is spreading across the globe in bird populations. Mutations are occurring within this genotype that are increasing their pathogenicity. Birds are also able to shed the virus for longer periods of time before their death, increasing the transmissibility of the virus.

**Transmission and host range**

Infected birds transmit H5N1 through their saliva, nasal secretions, feaces and blood. Other animals may become infected with the virus through direct contact with these bodily fluids or through contact with surfaces contaminated with them. H5N1 remains infectious after over 30 days at 0 °C (32.0 °F) (over one month at freezing temperature) or 6 days at 37 °C (98.6 °F) (one week at human body temperature) so at ordinary temperatures it lasts in the environment for weeks. In Arctic temperatures, it doesn't degrade at all.

Because migratory birds are among the carriers of the highly pathogenic H5N1 virus, it is spreading to all parts of the world. H5N1 is different from all previously known highly pathogenic avian flu viruses in its ability to be spread by animals other than poultry.

In October 2004, researchers discovered that H5N1 is far more dangerous than was previously believed. Waterfowl were revealed to be directly spreading the highly pathogenic strain of H5N1 to chickens, crows, pigeons, and other birds, and the virus was increasing its ability to infect mammals as well. From this point on, avian flu experts increasingly referred to containment as a strategy that can delay, but not ultimately prevent, a future avian flu pandemic.

"Since 1997, studies of influenza A (H5N1) indicate that these viruses continue to evolve, with changes in antigenicity and internal gene constellations; an expanded host range in avian species and the ability to infect felids; enhanced pathogenicity in experimentally infected mice and ferrets, in which they cause systemic infections; and in-
creased environmental stability."

The New York Times, in an article on transmission of H5N1 through smuggled birds, reports Wade Hagemeijer of Wetlands International stating, "We believe it is spread by both bird migration and trade, but that trade, particularly illegal trade, is more important".

On August 22, 2007, a 28-year-old Indonesian chicken trader was the 2nd person to die of bird flu on the island of Bali, after 4 days of hospitalization, raising the death toll due to the disease in Indonesia to 84. Tests in 2 local laboratories were positive for the H5N1 strain of the disease. 194 people — the majority of them in Indonesia -- have died since 2003, according to the World Health Organization.

The H5N1 bird flu virus can also pass through a pregnant woman's placenta to infect the fetus, researchers reported on Thursday 27 September 2007. They also found evidence of what doctors had long suspected -- that the virus not only affects the lungs, but also passes throughout the body into the gastrointestinal tract, the brain, liver, and blood cells.

**High mutation rate**

Influenza viruses have a relatively high mutation rate that is characteristic of RNA viruses. The segmentation of its genome facilitates genetic recombination by segment reassortment in hosts infected with two different influenza viruses at the same time. A previously uncontagious strain may then be able to pass between humans, one of several possible paths to a pandemic.

The ability of various influenza strains to show species-selectivity is largely due to variation in the hemagglutinin genes. Genetic mutations in the hemagglutinin gene that cause single amino acid substitutions can significantly alter the ability of viral hemagglutinin proteins to bind to receptors on the surface of host cells. Such mutations in avian H5N1 viruses can change virus strains from being inefficient at infecting human cells to being as efficient in causing human infections as more common human influenza virus types. This doesn't mean that one amino acid substitution can cause a pandemic, but it does mean that one amino acid substitution can cause an avian flu virus that is not pathogenic in humans to become pathogenic in humans.

H3N2 ("swine flu") is endemic in pigs in China, and has been detected in pigs in Vietnam, increasing fears of the emergence of new variant strains. The dominant strain of annual flu virus in January 2006 was H3N2, which is now resistant to the standard antiviral drugs amantadine and rimantadine. The possibility of H5N1 and H3N2 exchanging genes through reassortment is a major concern. If a reassortment in H5N1 occurs, it might remain an H5N1 subtype, or it could shift subtypes, as H2N2 did when it evolved into the Hong Kong Flu strain of H3N2.

Both the H2N2 and H3N2 pandemic strains contained avian influenza virus RNA segments. "While the pandemic human influenza viruses of 1957 (H2N2) and 1968
(H3N2) clearly arose through reassortment between human and avian viruses, the influenza virus causing the 'Spanish flu' in 1918 appears to be entirely derived from an avian source”.

Humans and H5N1
The earliest infections of humans by H5N1 coincided with an epizootic (an epidemic in nonhumans) of H5N1 influenza in Hong Kong's poultry population. This panzootic (a disease affecting animals of many species, especially over a wide area) outbreak was stopped by the killing of the entire domestic poultry population within the territory.