Ann Haley MacKenzie

Avian Flu

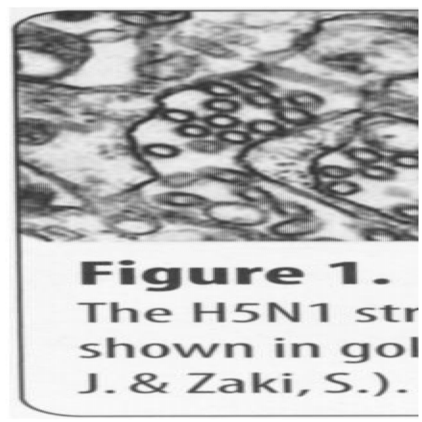
Bird flu. Avian flu. Pandemic. Global task force. Poultry industry. H5N1 virus. What do all these concepts have in common? They represent a potential human flu crisis that could affect 20% of the world's population this winter. Within a few months, an estimated 30 million individuals may need to be hospitalized and 25% of those may die.

Most flu epidemics begin in animal pools. Since human interactions with animals and the biology of animal ecology are increasingly complex, infections are spreading faster. In the case of avian flu, the virus is present among both wild bird populations and the poultry industry. Wild birds, particularly migratory ducks, geese, and shorebirds, are the natural holding spot for the influenza A virus that can infect other avian and mammalian species. Our knowledge about flu in wild birds is limited and our knowledge needs to be enhanced through more research in order to understand the dynamics of these viral infections and transmission routes.

As of this writing, the virus has been found in chickens throughout Asia and into Europe including Greece and Turkey. In the last two years, H5N1 has killed 140 million birds and infected 116 people. The chickens are generally gassed when an outbreak is located so as not to further pass the virus on to other organisms.

What do we know about the genome of H5N1?

The NIH Influenza Genome Sequencing Project intends to provide total sequencing data for selected human and avian influenza isolates. The project began in November 2004. The GenBank now includes sequences of 110 complete H5N1 genomes, four complete H2N2 genomes, and numerous other genomes from other viruses (see www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html). These data are critical to tracking viral evolution, transmission, mutation, and in helping drug manufacturers as they develop vaccines, drugs and diagnostics.



How was H5N1 discovered?

The scientists at St. Jude Children's Research Hospital in Tennessee traced the H5N1 outbreak in Asia back through a series of genetic reassortment events to a human outbreak that occurred in Hong Kong in 1997 (Li, 2004). The genetic reassortment resulted in a dominant H5N1 genotype infecting chickens and ducks in 2003 and 2004. Domestic ducks in southern China were the key players in harboring the virus during this time, with

migratory birds possibly carrying the virus and spreading it throughout southeast Asia.

What kind of medicines is H5N1 sensitive to?

H5N1 viruses are sensitive to the neuraminidase inhibitors oseltamivir, which is an oral drug, and zanamavir, an inhalable powder. These drugs act to prevent the hydrolysis of glycoproteins and glycolipids on the protein coat of the virus.

TIMELINE

1890: First recorded recent influenza pandemic.

1918: The "Spanish flu" pandemic caused by H1N1 influenza virus. Kills more than 40 million people. Origin unknown.

1957: Asian flu pandemic kills 100,000 people due to H2N2 influenza virus.

1968: Hong Kong flu pandemic kills 700,000 people due to H3N2 virus. Both the 1957 flu and 1968 flu are likely due to exchange of genes between avian and human flu viruses.

May 21, 1997: Bird flu H5N1 isolated from a human patient in Hong Kong.

1998: Trial results for two new influenza drugs are announced, Relenza and Tamiflu. They target the virus's neuraminidase enzyme.

1999: Two new flu drugs, Relenza and Tamiflu, are licensed in U.S. and Europe.

2001: The World Health Organization (WHO) outlines its new global laboratory proposal to improve the range, speed, and quality of influenza virus surveillance.

Feb. 2003: Two people in Hong Kong are infected by H5N1 virus, one fatally.

March 2004: Avian H5N1 flu virus becomes more widespread among bird flocks in Asia; 34 human cases, with 23 deaths.

Aug. 2004: H5N1 virus spreads throughout SE Asia, resulting in the deaths of over 100 million chickens. In Vietnam and Thailand, the virus has infected at least 37 people, with 26 deaths.

Nov. 2004: Warning that the H5N1 bird flu virus might spark a flu pandemic that could kill millions of people. WHO officials meet with vaccine makers, public-health experts, and government representatives in a bid to speed up the production of flu vaccines and avoid a global pandemic.

Jan. 2005: Chinese authorities state they developed a rapid test for bird flu that produces results in hours rather than days.

March 2005: Bird flu has spread to 10 countries and killed around 50 million chickens.

May 2005: WHO reports 53 deaths from bird flu since January 2004

Nov. 2005: Deaths from bird flu are up to 116 with over 140 million chickens dead.

How are vaccines made in preparation for a possible pandemic?

One of the first steps in making vaccines is to make a reference virus vaccine. A new technique called reverse genetics is now being used to create reference viruses that match the target flu strain exactly (Webby, 2004). Using this technique, an H5N1 reference virus was produced within weeks and an inactivated H5N1 vaccine was created. Preliminary results of Phase I clinical trial with 450 volunteers look promising. The government hopes to create 20 million doses.

NIH has also initiated the production and clinical testing of H9N2 candidates since this viral strain has been the most common subtype of avian flu circulating in Hong Kong and China and infecting at least eight individuals in the region. Generally it is less pathogenic to humans.

Are live vaccines still used?

Yes, immune responses to live attenuated vaccines develop more quickly than those produced by inactivated vaccines. These vaccines also tend to be more cross protective against variants of the same virus. Live attenuated H5N1 vaccines have been made.

As with any vaccines, the virus is grown inside chicken eggs. The problem is that this method does not allow for variations among the viruses. There is a current movement where scientists are trying to do more with using cell-culture methods for vaccine production to provide for more flexibility. Cell cultures would keep up with rapidly evolving viruses and provide more vaccines in the event of a possible pandemic.

What is another possible line of prevention against avian flu?

Antiviral drugs are another possibility when it comes to treating avian flu. Tamiflu, made by the Swiss drugmaker Roche, prevents daughter viruses from escaping to infect new cells. It has shown good results against H5N1 in cell cultures and in mice and works against milder forms of the flu in humans if taken early. Currently the United States has only enough Tamiflu to treat 2.3 million cases with 10 million more potentially available. Much of the Tamiflu being produced by Roche is going to other countries that ordered it much earlier than the U.S. did.

What exactly is gene swapping when it comes to avian flu?

Gene swapping occurs when a person is simultaneously infected by the avian flu virus and human influenza virus. These viruses can exchange genes and give rise to a completely new subtype of the influenza virus to which few, if any, humans would have natural immunity. The vaccines or drugs in use would have little effect on these subtypes. Transmission of this subtype of flu could occur from human to human and the conditions for the start of a new influenza pandemic will have been met. This is the situation that occurred in the Spanish flu pandemic of 1918-1919, when a completely new viral subtype emerged and spread among the soldiers of World War I, as well as the citizens around the globe.

How is the reconstruction of the 1918 Spanish flu virus important?

Scientists at the U.S. Centers for Disease Control reconstructed the genome of the 1918 flu virus recently, greatly enhancing our preparedness for the next pandemic. In reconstructing the 1918 influenza virus, scientists learned which genes were responsible for making the virus so harmful. This is important advance preparation for knowing which genes are responsible for causing severe illness and in helping develop vaccines and drugs.

The 1918 flu virus was sequenced from bits of lung tissue from two soldiers saved in an Army pathology warehouse and an Alaskan woman buried in permanently frozen ground who had died in the 1918 pandemic. The scientists think that changes in just 25 to 30 out of about 4400 amino acids in the viral proteins turned the virus into a killer. The 1918 virus acted much differently from ordinary viruses, infecting cells deep in the lungs such as the cells lining the air sacs that would normally not be affected by the flu. The bird flu acts much the same way and has a genome that is similar to the 1918 flu.

Is there any evidence of human-to human avian flu transmission at this time?

In Thailand during September 2004, officials concluded that a mother either contracted the avian flu from an environmental source or from her daughter. Evidence of human-to-human transmission seems limited to family clusters at this time.

Whether the avian flu will develop into a pandemic is yet to be seen, but we do know that the conditions are present for it to be possible. By becoming knowledgable of the biology behind avian flu and helping our students to be literate in the science of this virus, we create a sense of understanding when our students read news accounts, listen to stories on television, and hear their families talk about the avian flu. If just one student can respond with more knowledge about the biology behind the avian flu, then we as biology teachers can know that a small step has been taken toward responsible citizenry.

References

Fauci, A. (2005). Race against time. *Nature, 431,* 423-424.

Fouchier, R., Kuiken, T., Rimmelzwann, G. & Osterhaus, A. (2005). Global task force for influenza. *Nature, 431,* 419-420.

Kolata, G. (2005). Experts unlock clues to spread 1918 flu virus. Available online at: http://www.nytimes.com/2005/10/06/health/06flu.html?th&emc=th.

Li, K.S., Guan, Y., Wang, J., Smith, G.J.D., Xu, K.M., Duan, L, Rahardjo, A.P., Puthavathana, P., Buranathai, C., Nguyen, T.D., Estoepangestie, A.T.S., Chaisingh, A., Auewarakul, P., Long, H.T., Hanh, N.T.H., Webby, R.J., Poon, L.L.M., Chen, H., Shortridge, K.F., Yuen, K.Y., Webster, R.G. & Peiris, J.S.M. (2004). Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. *Nature, 430,* 209-213.

Webby, R.J., Perez, D., Coleman, J., Guan, Y., Knight, J., Govorkova, E., McClain-Moss, L., Peiris, J., Rehg, J., Tuomanen, E., Webster, R. (2004). Responsiveness to a pandemic alert: use of reverse genetics for rapid development of influenza vaccines. *The Lancet, 363,*1099-1103.

Web focus - Avian flu timeline. Available online at: http://www.nature.com/nature/focus/avianflu/timeline.html.