

### Don't Count Your Chickens

From dying swans in Scotland to unhealthy chickens in Norfolk, it seems that the UK is being threatened on all sides from "bird flu". Politicians and poultry are competing for space in the newspapers. Feathers are indeed ruffled.

What is Avian or "Bird Flu", what threat does it pose to the man in the street and heaven forbid but must we stop eating roast chicken or travelling to areas known to harbour Avian flu? Is fowl still fair and fair is fowl?

This article addresses these issues. In order to better understand the description of Avian flu it is important to learn a few basic facts about the influenza virus.

#### Types of Influenza Virus

Influenza is caused by a virus called orthomyxovirus and is readily spread by aerosol droplets that occur in coughing and sneezing.

There are three main types of flu virus, types A, B and C. Type A is a moderate to severe illness affecting humans and animals of all age groups and this is the type we will concentrate on. Type A Influenza virus is further sub divided into groups that have a specific "H" number and "N" number. The "H" number and the "N" number refer to two major proteins on the outside coating or the envelope of the virus and are known respectively as haemagglutinin (H) and neuraminidase (N) proteins. There are 15 major subtypes of H and 9 major subtypes of N. For example the 1997 Avian flu in Hong Kong and the present "bird flu" threat is a Type A, H5N1. Research has been performed on autopsy specimens from the 1914-1918 pandemic and it has been determined that this pandemic was caused by a Type A, H1N1 strain of the influenza virus. The various subtypes have different capabilities to cause disease in humans and animals and so it is

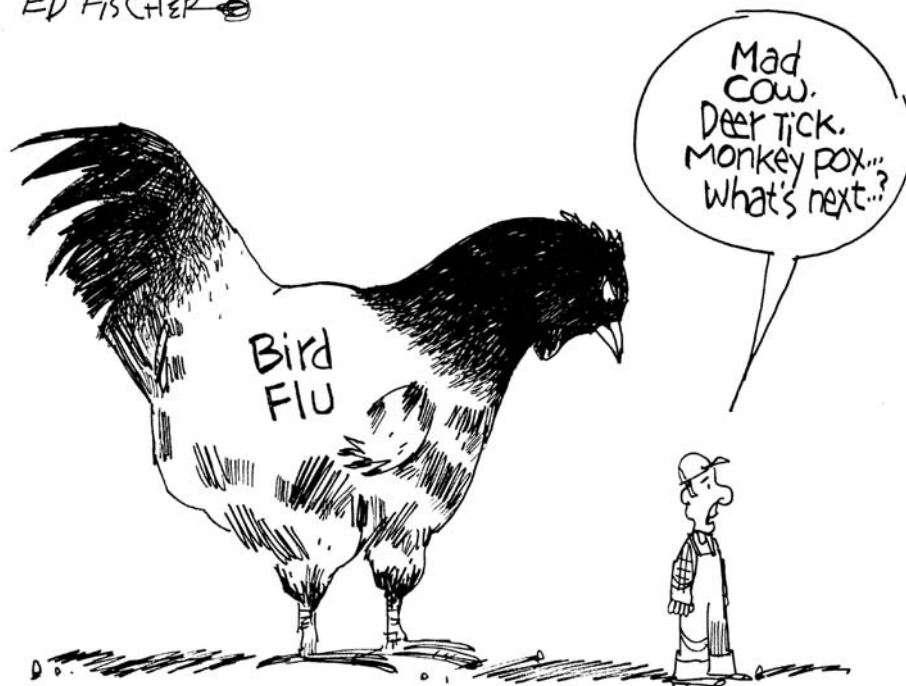
important to know these "H" and "N" numbers. The H5N1 or "bird flu" subtype appears to be capable of causing severe disease. Whether it will be as severe as the dreaded H1N1 Spanish flu of 1914-1918 remains to be seen.

#### Changes in the virus over time

The virus itself has been described as sloppy and capricious. It makes billions of copies of itself in the person or animal it is infecting and occasionally makes mistakes when replicating itself. Unfortunately the Influenza virus lacks mechanisms for the "proofreading" and repairs of errors that occur during replication and so the genetic make up of the virus tends to change over time. Slow and minor genetic changes are known as antigenic drift while large and abrupt changes are known as antigenic shift. These ongoing changes in the genetic make up of the virus are the reason why we have to have a new flu shot every year.

Researchers have to create a new flu vaccine every year to match the changes in the virus. When there is a very large genetic change in the virus, our bodies do not recognise it as something we have encountered before and our bodies can not mount a proper immune response. In this scenario the mortality rate increases as we can not effectively fight the influenza infection. When such a major genetic change occurs, the death rate in the population usually doubles. This happened between 1957-1960 and 1968-1972 when 1 million people worldwide died in each of these pandemics. The 20-fold increase in the death rate in the 1914-1918 pandemic was highly unusual. Scientists feel that "bird flu" will increase influenza mortality above the average annual rate but whether it will double the annual influenza mortality rate or increase it by 20 fold is the burning question.

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In reality mortality from influenza is usually low (0.1%) but because the number of infected people is high, there is usually significant excess mortality, mainly due to pneumonia and other secondary pulmonary complications. In England and Wales there are currently 12,000 deaths per year attributed to influenza outbreaks. These deaths occur predominantly in the elderly. When the virus changes and mutates as in the 1969 flu pandemic the death rate increases above this average level. In 1969 there were 47,000 deaths attributed to influenza in the UK and in the worst known flu pandemic to date there were over 200,000 deaths in the UK due to influenza in the 1914-1918 Spanish flu.

### The Influenza Virus and the Spanish Flu

The Influenza pandemic of 1914-1918 killed at least 20 million people globally. It is estimated that 20% of the worldwide population became ill from this pandemic. This "Spanish Flu" Pandemic is the catastrophe against which all modern pandemics are measured. Annual influenza epidemics are virtual disaster drills for the next pandemic, an event that is likely to wreak more havoc than most scenarios of bioterrorism.

### Avian Influenza or "Bird Flu".

#### The impending pandemic

In 1997 there was concern that a pandemic may occur from an Avian flu virus known as Type A H5N1. Several hundred people became infected with this strain and 18 people were hospitalised. Six of these people died. This virus was different as it moved directly from chickens to people, rather than having been altered by infecting pigs as an intermediate host. In addition, many of the most severe illnesses occurred in young adults similar to the 1914-1918 pandemic. To prevent the spread of this virus, all chickens (approximately 1.5 million) in Hong Kong were slaughtered. The avian flu did not spread easily from one person to another, and after the poultry slaughter, no new human infections were identified.

Avian influenza ("Bird Flu") is an infectious disease of birds caused by type A strains of the influenza virus. The disease, which was first identified in Italy more than 100 years ago, occurs worldwide. Fifteen subtypes of Influenza virus are known to infect birds, thus providing an extensive reservoir of influenza virus potentially circulating in bird populations. Ducks are the natural reservoir of avian influenza viruses, and these birds are also the most resistant to infection.

### A Human time bomb

Besides the alteration in the genetic make up of the Influenza virus due to lack of "proofreading", there is another very concerning characteristic of the Influenza virus. This virus can swap or reassort and merge genetic material from different species and subtypes. This will result in new subtypes where no person will have any immunity and existing vaccines will be useless. What this new subtype will have to have is genes from a human influenza virus that makes it readily transmissible from person to person for a sustainable period. Once this occurs, all the makings are there for a lethal pandemic. 1997 saw the beginning of "Bird flu"

infecting humans. All that is needed now is for a human to act as a mixing bowl to produce an avian flu that is transmissible from person to person. Extensive investigation of this 1997 outbreak determined that close contact with live infected poultry was the source of the human infection. Studies at the genetic level further determined that the virus had jumped directly from birds to humans. The destruction of Hong Kong's entire poultry population may well have averted a pandemic. This was an alarming event as the avian flu caused severe illness with high mortality. Alarm bells rang again in 2003 when an outbreak of H5N1 avian flu caused illness and 1 death in a family that had recently traveled to China. H5N1 has also caused severe respiratory disease in patients in Vietnam in January 2005. Experts agree that another influenza pandemic such as the likes of the pandemics of 1914, 1957 and 1968 is inevitable and imminent. At least four months would be required to produce a new vaccine, in significant quantities, capable of conferring protection against a new virus subtype.

### Excess Mortality from Avian Flu

It would appear that the H5N1 strain may be more virulent than the H1N1 strain that caused the 1914-1918 pandemic. It has been calculated that 2.5 % of Americans infected in the Spanish Flu pandemic died. If "bird flu" has a mortality rate equal to or above this figure, the consequences will be dire. In the 8th version of the British Influenza Pandemic contingency plan dated October 2005 Epidemiologists have projected some figures for the excess mortality in the UK if Avian flu was to strike. They are as follows:

Range of possible excess deaths based on various permutations of case fatality rates and clinical attack rate for the UK

Overall case fatality rate	Clinical attack rate		
	10%	25%	50%
0.37%	21,500	53,700	107,500
1.00%	56,700	141,800	283,700
1.5%	85,100	212,800	425,500
2.5%	141,800	354,600	709,300

Taken from Influenza Pandemic Contingency Plan - Health Protection Agency Pandemic Plan for Influenza version / October 2005

The clinical attack rate is the number of people that will become infected in the population from the "bird flu" and who develop symptoms of influenza. In the last 3 pandemics the clinical attack rate has been approximately 25%. The fatality rate in the 1957 pandemic was 0.37% and 2.5% in the 1914-1918 Spanish flu pandemic. Obviously there were no vaccines, antibiotics, antiviral drugs and ventilators available in 1914 so one would hope that the mortality rate would not be as severe as this 'worse case' scenario.

It is estimated that 1/3 of these excess deaths would occur in persons younger than 65 years of age. (In the Spanish Flu 98% of the excess deaths occurred in persons under the age of 65).

The press is currently awash with articles relating to "Bird flu" and the projected deaths vary greatly. The reason for this is that no one is sure of what the clinical attack rate will be nor of the case fatality rate. The pessimists are projecting alarming figures which is already causing panic and a rush on drugs used to treat a flu pandemic.

The authors of the table on page 2 speculate that an attack rate of 25% with a case fatality rate of 0.37% is likely with a projected figure of 53,700 excess deaths in the UK. I have seen figures of 700,000 excess deaths for the UK in the popular press. This would be equal to a 50% clinical attack rate with a case fatality rate equal to the Spanish flu. This seems unlikely. The UK Government is certainly taking this seriously though and has spent £200 million on 14 million courses of drugs that are presently available to treat an influenza outbreak. They are modeling a 25% attack rate and have ordered enough drugs for a quarter of their population. Modelling studies suggest that after a case occurs in the Far East, it will probably take less than one month for the virus to reach the UK. Once cases begin to occur in the UK it will take only a few weeks before activity is widespread. Britain announced recently that when a vaccine becomes available the entire population will be supplied with the vaccine. The Royal family has supposedly already received their stock of anti flu drugs known as Tamiflu.

#### Drug treatment for Bird Flu- Tamiflu

Tamiflu will become a household word. It is presently the drug treatment of choice for "Bird Flu". It belongs to a class of drugs known as the Neuraminidase Inhibitors.

Approximately 20% of the World's population develops influenza annually and many are accustomed to going for an annual flu injection. The trouble with flu vaccines is that vaccine production by current methods cannot be carried out with the speed required to halt the progress of a new strain of influenza virus therefore antiviral drugs such as Tamiflu become important in combating an influenza pandemic.

Four drugs are presently available for the treatment and prophylactic treatment of influenza. They are the amantidines (amantadine and rimantadine) and the newer class of neuraminidase inhibitors (Zanamivir (Relenza) and Oseltamivir (Tamiflu))

The Amantidines interfere with viral uncoating inside the cell and are only effective against Influenza A. The trouble is they do have toxic side effects and there is the rapid emergence of drug resistance. The Avian H5N1 virus seems to be resistant to Amantadines.

The neuraminidase inhibitors (Tamiflu) interfere with the release of progeny influenza viruses from the infected host cell. These drugs have very little toxicity and are less likely to promote resistance.

They are effective against all strains of influenza. The sooner they are started (preferably within 12 hours) the better. In a recent conference in Malta it was reported that Tamiflu appears to cause a 38% reduction in severity of flu symptoms, a 67% reduction in secondary complications such as pneumonia and a 37% reduction in the duration of symptoms. It also has been reported to provide an 89% overall protective efficacy against clinical influenza in adults and adolescents who have been in close contact with influenza infected patients.

The whole world is now clamoring to stockpile this drug.

#### Stockpiling of Tamiflu

At the time of writing this article 30 countries had ordered stockpiles of Tamiflu. France, Finland, Iceland, Ireland, Luxembourg, Netherlands, New Zealand, Norway, Switzerland and the UK have been the most aggressive in ordering Tamiflu and have ordered stocks to cover 20-40% of their population. This is where we can gauge how prepared countries are for the pandemic, the difference between 1st and 3rd world countries, the haves and the have nots. In my own country South Africa, which is one of the most advanced countries in Africa Tamiflu has only just been registered for use. No stockpiles are available. What we are now seeing is the stockpiling of the drug by private enterprises and demand is certainly going to outstrip supply. The good news for the UK is that the government appears to be well prepared for an outbreak of "bird flu".

#### What about the Roast Chicken and the trip to Hong Kong?

The Department of Health as of April 2006 does not presently recommend any restrictions on travel to any country experiencing outbreaks of "bird flu" in poultry stocks. Presently "bird flu" does not transmit from person to person and so you can only really contract the infection from birds. Bearing this in mind the Department of Health does recommend that you:

- Do not visit bird or poultry farms or live animal markets
- Avoid close contact with live or dead poultry
- Do not eat raw or poorly cooked poultry or poultry products, including blood

#### Pandemics and pandemic threats of the 20th century

• 1918-19	"Spanish flu"	H1N1
• 1957	"Asian flu"	H2N2
• 1968	"Hong Kong flu"	H3N2
• 1976	"Swine flu" episode	H1N1
• 1977	"Russian flu"	H1N1
• 1997	"Bird flu" in HK	H5N1
• 1999	"Bird flu" in HK	H9N2
• 2003	"Bird flu" in Netherlands	H7N7
• 2004	"Bird flu" in SE Asia	H5N1

Slide taken from presentation by David K Shay "Influenza Pandemics of the 20th Century" Influenza Branch National Center for Infectious Diseases Center for Disease Control and Prevention

The good news therefore is that you can continue to have your roast chicken as long as it is cooked well, you can still travel to the countries with outbreaks of "bird flu" in poultry but perhaps you should hold off from feeding the Wild Swans at Coole.

The Swiss based drug company that manufactures Tamiflu has seen sales of the drug Tamiflu climb by 17% in 2005 and they have announced that they expect Tamiflu sales to reach SF 1.2 billion by 2006. The companies stock price has increased by 40% this year. Good news is that this parent company has recently announced that it would not enforce its patent on Tamiflu opening the way for discussions for other drug companies to make copies of the drug. Of concern is that there has been a recent report of the isolation of drug resistant H5N1 virus from a patient treated with Tamiflu in Vietnam.

#### **Poultry and Migratory Birds**

Why has this "bird flu" become so prominent in the last years? Well environmental factors certainly have a role to play. The rise of factory poultry farming in Asia over the last decade and the dangerously unhygienic conditions in farms and plants has created a perfect incubator for this virus. To date 140 million chickens have been culled in Asia to prevent the spread of this infection but it has not been successful. The avian strain has now also been found in pigs which is very worrying as pigs are also susceptible to human flu. They may well become the reservoir where genetic rearrangement occurs resulting in a virus that can jump from humans to humans. The virus has also spread to birds such as the domestic duck, herons, gulls, egrets, hawks and pigeons. Where as the Avian flu is lethal to chickens it is not as deadly to other species of birds such as duck.

This allows them to travel with the infection. As these birds migrate from China to places such as Siberia we are seeking the spread of avian flu to birds in Europe. With migration to Alaska and Africa it is only a matter of time before the spread is global.

#### **Economic burden of Avian Flu**

Bearing in mind the cost of SARS to the South East Asian economy, economists are now turning their attention to the potential cost of a "Bird Flu" pandemic. It is not a pretty picture. Countries have already begun to count the cost of stockpiling Tamiflu, setting up quarantine facilities, researching and preparing vaccines, and education programmes. Recently the health minister for Australia announced that his Government had already spent \$160 million preparing for such a pandemic. If you then add the cost of hospitalization, lost productivity and loss of revenue to airlines and tourist operators, the cost starts to sky rocket into Billions of US Dollars. In 1999 an economist at the Centre for Disease Control estimated the cost of a flu pandemic to the USA would be between \$71 and \$165 Billion.

The Manila based Asian Development bank estimates that a severe form of Avian Flu would cost the region between \$250-\$290 Billion. They predict that the health systems of most countries would be overwhelmed and that delivery of services would be severely disrupted with a knock on effect throughout society.

Travel companies in Europe such as TUI predict a fall in travel to Asia by 40% and overall for travel to fall by 10%. Obviously the impact depends on the extent and the severity of the outbreak.



Gwyn Hacche of HSBC in London predicts that in their mid to worst case scenario, the European Union's overall GDP growth rate, predicted at 2% in 2005 would lose a few tenths of a percentage point. This is perhaps the more conservative opinion. At the time of writing this article the literature appearing in the press is painting a gloomy economic forecast.

Epidemiological models project that in industrialized countries alone, the next pandemic is likely to cause 57-132 million outpatient visits and 1.0-2.3 million hospitalisations.

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