

Issue  
No 12

Hannover Re's Perspectives  
Current Topics of  
International Life Insurance

**Bill Monday**

*"Don't count your chickens  
because they'll scratch" –  
The threat of a global pandemic  
including Bird Flu*

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## 1. Introduction

Three events in this new millennium have highlighted specific risks that could significantly impact life insurance business on a global perspective. These events, namely the 9/11 Twin Towers terrorism attack, the postage of Anthrax through the US mailing system, and the outbreak of Severe Acute Respiratory Syndrome (SARS), have underlined the risk of terrorism and indeed bioterrorism, whilst SARS in turn has underlined the risk of a global epidemic. The ongoing risk and, according to scientists the inevitability of an Avian Flu outbreak as well as ongoing terrorist activities only add impetus to the need to address these risks.

The scope of this paper is to look at infective epidemics and bioterrorism from a medical perspective. Traditional epidemiological models have developed over time to include several principles relating to the transmission of infectious agents during an epidemic. These principles include the transmission probability, the basic reproductive number, conditions for an epidemic, and the role of contact and mixing patterns. The transmission probability is a measure of the ability of an infectious agent to spread from an infected to a susceptible host during a contact. The binomial model of transmission is widely used to quantify transmission concepts and to estimate the transmission probability. The basic reproductive number describes the potential of an infectious agent to spread in a population. Dynamic models are used to understand the spread of infection and the role of intervention over time.

This paper will discuss specific diseases and bioterrorism agents in more detail and expand

## 2. Background History

"Infectious diseases must be closely watched and appropriately feared; as the past has taught us, humility is a far greater virtue than either arrogance or hubris when it comes to dealing with nature."

This is a quote from a series of lectures on epidemics from Hartford University and there is no better way to state the fact that we must learn

on the medical terminology relating to the infectivity of organisms implicated in epidemics. As our industry is part of the financial sector any investigation into this risk would also have to look at the financial implications of a global epidemic or the impact of a bioterrorism act crippling a major financial hub. In April 2003 the estimated cost of SARS to the South East Asian economy was USD 11 billion – mainly due to the impact on tourism and commerce. Cathay Pacific Airways for example saw its traffic plunge by two thirds during the SARS scare causing it to cancel 45% of its scheduled flights. According to a report from the New York City Controllers Office the Twin Towers attack would cost New York City USD 105 billion.

Looking at health in general there are several disease processes that are "pandemic" in nature and have enormous impact on health resources and the economy. Three examples would be obesity, diabetes, and heart failure. These are however beyond the scope of this paper and I will limit this discussion on epidemics to those that are caused by infective agents and are acute in nature. Although HIV and AIDS is a pandemic of mammoth proportions, from a medical and actuarial modelling point of view it differs from an acute influenza pandemic and will not be discussed in this paper.

Therefore to return to the topic of acute infective epidemics, let us begin with the history of such epidemics.

from the past. Epidemics have been recorded from before biblical times. In 430 BC, 200,000 villagers fled into Athens when threatened by the Spartans. An unidentified infectious agent, from Ethiopia via Egypt, killed one third of this population and ended the Golden Age of Athens. The most well-known epidemics from history must include the Black Death and the Spanish Flu of 1914–1918.

Between 1339 and 1351 AD, a pandemic of plague known in Western history as The Black Death traveled from China to Europe. Carried by rats and fleas along the "Silk Road", a trading route between Asia and Europe, the Black Death reached the Mediterranean in 1347. The impact was devastating. By 1351, 25% of the population of Europe was dead. No wonder it was also called the "Great Mortality". The plague is an example of a very virulent disease with mortality in untreated cases being between 30–75%. The last major outbreak of plague in Europe was in Marseilles in 1722 but in 1997 Doctors encountered a child in Madagascar who was infected with a strain of bubonic plague that was resistant to all drugs normally used to fight this disease. This strain if spread could obviously have serious health consequences.

The history of flu epidemics and pandemics is probably a more practical example to look at from history. The Spanish Flu or the influenza

virus pandemic of 1914–1918 killed a minimum of 20 million people and at its peak in the USA the death rate was 2/1000 population, a rate 20 times as high as during the years before and after the pandemic. This pandemic was unusual and particularly devastating. Unique was the fact that people died quickly within two to three days and they tended to be young and healthy prior to contracting the virus. The Spanish Flu is especially noteworthy due to the high mortality associated with this pandemic but flu pandemics do in fact occur on a regular basis. Since 1580 there have been 31 flu pandemics recorded. New influenza pandemics seem to occur with regularity at approximately 10–30 year intervals. Notable pandemics from the last century were the Spanish Flu of 1914–18, the 1957 Asian Flu and the 1968 Hong Kong Flu. We are due for another epidemic and the experts are telling us that it will be the avian or Bird Flu. It is not a case of if it will happen but when it will happen.

### 3. Medical Aspects of Epidemics

Any excessive and related incidence of a particular disease above what is normally expected in a population is defined as an epidemic. When an epidemic extends beyond the confines of a wide area, typically a continent, and becomes a more widespread problem, it is a pandemic. Pandemic is derived from the Greek *pan* (all) and *demos* (people) and is generally used to describe a worldwide epidemic.

There are two major types of infectious diseases that can develop into epidemics: common source and host-to-host transmission. Common source epidemics arise from a contaminated source such as water, while host-to-host infections are transmitted from one infected individual to another via various, perhaps indirect routes. Common source epidemics usually produce more new cases earlier and faster than host-to-host epidemics. Once the infected source is closed, sealed, or removed, the common source epidemic usually abates rapidly. Host-to-host epidemics are slower to grow and slower to diminish. Examples of common source epidemics include cholera, hepatitis A and botulism. These are unlikely to cause pan-

demics. Examples of host-to-host transmission epidemics include measles and Smallpox. These may well cause pandemics. Other infectious diseases require an intermediary to be part of the cycle of infectivity. These are known as vector-borne epidemics. Examples of these would be the plague (caused by a bacteria *Yersinia Pestis*) that requires to be transmitted by fleas infecting rodents. Plague is then contracted from a fleabite to the susceptible host. Malaria would be another example of a vector-borne epidemic where infection is caught from a mosquito bite infected with a pathogen (infectious agent) known as plasmodium.

Airborne transmission may also occur where the pathogen is transmitted through the air across long distances. This transmission is part of the host-to-host transmission and influenza and tuberculosis are two examples where transmission occurs through airborne dissemination. Airborne transmission may also have played a role in the recent SARS epidemic and will be discussed in more detail later on in the paper in section 13.

Dissecting an epidemic down to a single infection in an individual, infection itself represents a complex interplay between host factors (defense mechanisms of an individual), charac-

teristics of the infectious agent and environmental influences. In order for infection to occur, a chain of events must take place. Simplistically the following factors must be in place.

### 3.1. Immunity

There must be a susceptible host. In other words the infectious agent must be able to breach the body's defense mechanisms such as skin and mucus membrane barriers and the body's immune system (antibodies and cell-mediated immunity). From birth we have all been continuously bombarded with infectious agents and we have all acquired immune systems capable of recognising and successfully repelling potential infections. Our immune system consists of cells and chemical pathways that build up a memory bank that recognises and remembers past infections and successfully destroys the potential infectious agent. Problems arise when a person is exposed to an infection that they have not been exposed to before. In 1492 Columbus went to the Caribbean. Along with his boat and crew he took influenza, Smallpox, tuberculosis and gonorrhoea. The inhabitants of the Caribbean had not been exposed to these infectious agents before and had no memory in their immune system on how to cope with these infections. The consequence was significant mortality and morbidity in the local inhabitants. A more recent example of this would be SARS. The infectious agent responsible for SARS is a new infection to human beings as it seems to have crossed species from animals to

humans for the first time. We as humans have not experienced this infection before and therefore have poor defense mechanisms for coping with it. Hence the concern around SARS. The potential infecting agent in an epidemic may not have to be a completely new and foreign organism but an altered or mutated one. Our bodies recognise the specific genetic make up of an infecting agent. If for some reason this is altered, for example via a genetic mutation within the infecting agent, the body may not be able to eradicate the infection as well as it should. The influenza virus is a good example of this. It has a high mutation rate and because of this we have to renew our influenza virus vaccines on an annual basis as they have to produce new vaccines each year to allow for new strains of the virus that have evolved over the preceding 12 months. The other scenario would be when a person's immune system is flawed or damaged. Chemotherapy for cancer would be an example where the immune system is negatively affected by drugs thus rendering the patient susceptible to infection. HIV is another example where the immune system is attacked and weakened, ultimately leading to various debilitating infections.

### 3.2. The Infecting Agent

The infecting agent or pathogen must be present and have a reservoir where it can propagate (live, produce and die in the natural state). Potential reservoirs include humans, animals and the environment. Smallpox is an example where this reservoir has been eradicated. It is thought that no natural reservoir of Smallpox exists any more and hence in nature this disease is no longer a threat to man. Unfortunately this is not completely true as stockpiles of Smallpox exist in laboratories raising the very real threat of this organism being used for bioterrorism. If a reservoir

exists in a human or animal, there must be a period of co-existence between the host and the pathogen. It is not in the pathogen's interest to kill the host quickly as it would then eradicate its own reservoir. The pathogen must be able to exit its reservoir and enter the susceptible host either via the respiratory tract, gastrointestinal tract, skin and mucous membranes, or blood.

### 3.3. Virulence and Infectivity

Assuming the above steps are in place, the next step is to consider how many people exposed to a particular infectious agent will become infected, the severity and the consequences of the infection to the host and how likely is the infection to spread from the initial host to other people. These are all obviously multifactorial. The severity of an infection in a host for example depends on factors such as the amount or dose of infectious agent received, the body's immune system (which in turn is influenced by factors such as age) and the pathogenicity of the infecting agent. Pathogenicity is a medical term relating to the ability of an infectious agent (pathogen) to cause disease. Infectiousness and virulence are two other terms that need explanation.

The infectiousness of an infected person refers to how likely that person is to transmit infection and is best measured by the secondary attack rate. Diseases such as Measles and Varicella have secondary attack rates above 80%. A disease such as Leprosy has a very low secondary attack rate ( $\ll 1\%$ ).

The virulence of the pathogen (infectious agent) refers to how likely the pathogen is to cause severe disease. Examples of diseases with

low virulence include Rhinovirus (the common cold). Examples of disease with mortality greater than 50% include Smallpox, Ebola Virus (haemorrhagic fevers) and Rabies.

Infectiousness and virulence are not linked. For instance you may have:

- ◆ Low infectivity and low virulence – e.g. Parvovirus (warts)
- ◆ Low infectivity and high virulence – e.g. Leprosy
- ◆ High infectivity and low virulence – e.g. the Common Cold
- ◆ High infectivity and high virulence – e.g. Smallpox.

The last scenario of high infectivity and high virulence is particularly concerning.

Further questions arise such as which interventions can prevent an epidemic or eliminate endemic transmission? Which interventions will reduce transmission and by how much? These questions will be addressed under each specific disease.

## 4. Specific Disease Associated with Epidemics

### 4.1. The Influenza Virus and the Spanish Flu

As mentioned the influenza pandemic of 1914–1918 killed 20 million people. 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.

Influenza is caused by an orthomyxovirus that is readily spread by aerosol droplets. The envelope or outside of the virus is covered by two types of proteins that tend to change from year to year due to antigenic shift (an abrupt and large

genetic change to the surface proteins) and antigenic drift (slow and minor genetic changes). This occurs due to the influenza virus lacking mechanisms for "proofreading" and repairing of errors that occur during replication. As a consequence of these uncorrected errors, the genetic composition of the virus changes over time. Occasionally these genetic changes are dramatic and alter the surface of the virus so much that our immune system is not able to recognise it as something it has experienced before leading to pandemics. When such a major genetic change occurs, the death rate in the population usually doubles. This happened between 1957–1960 and 1968–1972 when one million people died in each of these pandemics.

The 20-fold increase in the death rate in the 1914–1918 pandemic was highly unusual.

The reservoir for influenza is thought to be pigs and ducks, especially in China and South East Asia. Laboratories in Asia isolate and ana-

lyse new strains of influenza viruses to see how they differ from previously recognised viruses. If a significantly altered virus emerges, there is the risk of a new pandemic.

## 5. Types of Influenza Virus

There are three main types of flu virus, namely A, B and C. Type A is a moderate to severe illness affecting humans and animals of all age groups. Type B is milder and primarily affects human children. Type C is rare and infrequently reported as a disease in humans. These flu types are subdivided 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 or the envelope of the virus and are known respectively as haemagglutinin (H) and neuraminidase (N). There are 15 major subtypes of "H" and 9 major subtypes of "N". For example the 1997 Avian Flu in Hong Kong was a Type A, H5N1. Research was performed on autopsy specimens from the 1914–1918 pandemic and it was determined that this pandemic was caused by a Type A, H1N1 strain of the influenza virus. The 1957 pandemic was a H2N2 strain and the 1968 was a H3N2 strain.

Mortality from influenza is usually low (0.1‰) but as the number of infected people is high, there is usually significant excess mortality, usually due to pneumonia and other secondary pulmonary complications. In the United States there are currently an average 20,000–30,000 deaths from influenza per year, most of them among the elderly.

Owing to the fact that there is potential risk for future pandemics with significant mortality, The World Health Organisation (WHO)

has instituted a Global Agenda on Influenza Surveillance and Control. The aim of this body is to improve the understanding of the health and economic burden of influenza, increase national and global preparedness for epidemics and pandemics and expand the use of existing vaccines. At present the current worldwide production capacity for Influenza virus, which requires reconstitution annually, is estimated to cover less than 5% of the world's population. Without global cooperation, vaccine shortages will result in tremendous disparity in the supply and distribution of vaccine, particularly in countries where the vaccine is not manufactured.

Historical overview of Flu-Pandemics since 1918		
Year	Specification	Subtype
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 Hong Kong	H5N1
1999	Bird Flu in Hong Kong	H9N2
2003	Bird Flu in Netherlands	H7N7
2004	Bird Flu in South East Asia	H5N1

Source: David K Shay "Influenza Pandemics of the 20<sup>th</sup> Century". Influenza Branch, National Center for Infectious Diseases, Centers for Disease Control and Prevention.

### 5.1. 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 hos-

pitalised, six 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 (thus removing the reservoir). The Avian Flu did not spread 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 iden-

tified 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.

## **6. A Human Time Bomb**

Besides the alteration in the genetic make up of the influenza virus due to lack of "proof-reading", 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. This new subtype will require genes from a human influenza virus, making 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 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 one death in a family that had recently traveled to China. H5N1 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.

## **7. 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. As of August 2005 there have been 112 cases of H5N1 Avian Flu in humans. Of these 112, 57 died. This is very worrying but as we don't know how many people in the population

have been exposed, infected and survived it is difficult to know how virulent the virus actually is.

In the 8<sup>th</sup> 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:

## Potential excess deaths on the basis of various case fatality rates and clinical attack rates for the UK

Total 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
1.50%	85,100	212,800	425,500
2.50%	141,800	354,600	709,300

Source: 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 Bird Flu and who develop symptoms of influenza. In the last three 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 "worst case" scenario.

It is estimated that  $\frac{1}{3}$  of these excess deaths would occur in persons younger than 65 years of age. (With 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. No one is sure of the clinical attack rate nor of the case fatality rate. The pessimists are projecting alarming figures, which are already causing panic and a rush on drugs used to treat a flu pandemic.

The authors of the above table 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 GBP 200 million on 14 million courses of drugs that are presently available to treat an influenza outbreak. They are modelling 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.

## 8. 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 we are

all 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 amantadines (Amantadine and Rimantadine) and the newer class of neuraminidase inhibitors (Zanamivir (Relenza) and Oseltamivir (Tamiflu)).

Amantidines interfere with viral uncoating inside the cell and are only effective against influenza A. However, 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 has also 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.

## 9. 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 1<sup>st</sup> and 3<sup>rd</sup> 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 not even been registered for use. No stockpiles are available or have been ordered. In a country where there are five million people living with HIV with

reduced immunity, the impact of Avian Flu would be devastating. Any modelling of the impact of Avian Flu not only has to take the clinical attack rate and the case fatality rate into consideration but also the access to treatment, hospital beds and ventilators. The third world is in a precarious position indeed. It is interesting to note that the USA has only ordered six million doses which appears to be inadequate when compared to the countries mentioned above.

However, the US is at the forefront of vaccine production but there will be a delay of months before an appropriate vaccine can be produced.

## 10. Booming Business

The Swiss-based drug company that manufactures Tamiflu has seen sales of the drug Tamiflu climb by 17% in 2005 and has announced that they expect Tamiflu sales to reach SFR 1.2 billion by the end of the 4<sup>th</sup> quarter in 2005. The company's stock price has increased by 40% this year. Good news is that the 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.

## 11. Poultry and Migratory Birds

Why has this Bird Flu become so prominent in the last years? 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 have 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 ducks. This allows them to travel with the infection. As these birds migrate from China to places such as Siberia, we are seeing 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.



## 12. 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 USD 160 million preparing for such a pandemic. If you then add the cost of hospitalisation, 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 USD 71 and USD 165 billion.

The Manila-based Asian Development Bank estimates that a severe form of Avian Flu would cost the region between USD 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 travel to fall by 10%.

Obviously the impact depends on the extent and the severity of the outbreak. Gwyn Hache 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 paper the literature appearing in the press is painting a gloomy economic forecast.

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

From a global perspective the WHO, in an article posted on December 6<sup>th</sup> 2004, states that even in the best-case scenarios of the next pandemic, 2–7 million people would die and tens of millions would require medical attention. If the next pandemic virus is a very virulent strain, deaths could be dramatically higher. While it is impossible to accurately forecast the magnitude of the next pandemic, it is possible to state that at this point in time, much of the world is unprepared for a pandemic of any size. In all probability the pandemic will stem from a South East Asian country.

Hospitalisation and excess death rates per 100,000 clinical cases derived from 1957 flu pandemic experience

Age Band	0–4	5–14	15–64	65–74	75+	Overall
Probability of hospitalisation in low risk individuals per 100,000 clinical case	509	39	125	605	1,257	550
Probability of hospitalisation in high risk individuals per 100,000 clinical case	3,562	274	873	4,235	8,797	
Probability of excess death in low risk individuals per 100,000 clinical cases	27.2	12.2	70.4	494.6	797.0	370
Probability of excess death in high risk individuals per 100,000 clinical cases	223.7	100.1	579.8	4071.2	6559.4	

Source: Influenza Pandemic Contingency Plan – Health Protection Agency Pandemic Plan for Influenza, version October 2005

### 13. Severe Acute Respiratory Syndrome (SARS)

SARS seems to have fallen out of the lime-light with the impending Bird Flu pandemic but it is important to remember this condition as it is an example of a new species of bug affecting humans and a lesson on how quickly disease can spread globally.

In November 2002 the first case of what was to become known as Severe Acute Respiratory Syndrome or SARS was identified in Foshan, Guangdong province, China. In February 2003 a physician from this same province of Guangdong became ill whilst staying in a hotel in Hong Kong and infected twelve guests staying in the same hotel. These 12 guests left the hotel and transported the disease to Vietnam, Singapore, Canada, Ireland and the USA. By April 2003, there had been 3,389 cases and 165 deaths (a death rate of 4.9%) reported in 27 countries. Was this the beginning of the first pandemic of the 21<sup>st</sup> century?

Scientists and medics were extremely concerned. Infection in a single passenger on one flight resulted in illness in 22 of the other 119 passengers. This example dramatically illustrated the potential of air travel and globalisation for the dissemination of an emerging infectious disease and highlighted the need for a global response to contain such disease threats. Luckily for everyone, a global response did occur. Epidemiologists, scientists, the WHO medical journals and bodies disseminated warnings, advice and information through all communication portals available. In just a few weeks researchers working in no fewer than ten countries had collaborated to identify the virus, sequence its genome (genetic make up), and take steps towards its rapid diagnosis. The internet played a vital role in spreading information and eventually the disease was contained.

#### 13.1. Corona Virus

It was determined that this disease was a novel corona virus that had crossed the species barrier into humans. This virus had also evolved and mutated to become efficient at human-to-human transmission, something that the Avian Flu H5N1 cannot do at this stage. Fortunately it would appear that this SARS Corona Virus is less transmissible than originally thought. The average number of secondary infections resulting from

each primary infection seems to be 2–4 cases. Transmission appears to be airborne by large infected respiratory droplets spread from coughing and in general requires close contact i.e. coming within three feet of an infected person. Potentially, however, the disease can be spread via smaller droplets or aerosol spread as with Influenza and Measles, as one feature of this disease is that a few infected persons have been respon-

sible for a disproportionate number of transmissions – the so-called super spreading events. An example of this would be the one patient affecting 22 others on a flight. Conversely four infected patients on another flight did not infect any other passengers. There appears to be heterogeneity in the risk of transmission of this virus. SARS is sufficiently transmissible to cause a very large epidemic if left unchecked but it is not so contagious overall as to be uncontrollable with good basic health measures. The SARS virus is different from other respiratory viral illnesses such as influenza in that it has a long incubation period of 4–7 days and up to 14 days. The illness has an insidious onset and has a high viral load in the second week of illness. (The viral load is a figure used to quantify the amount of virus particles circulating in the body. Infectivity will be higher at a higher viral load). By this time most patients would be hospitalised thus posing more threat to nursing staff than to the general public. This is a very different scenario from a flu pandemic where there is a very short incubation period and people are highly infectious from the asymptomatic stage and tend to spread the infection in the community rather than in a hospital environment.

It is most likely that the reservoir for SARS lies in animals and not in humans. There is no evidence that the disease is infectious for more than ten days after the resolution of fever or that patients with SARS have chronic or relapsing infections that might result in the transmission of the virus to other people. It would appear then that the SARS epidemic has been contained at the time of writing this paper. The cost of containment was 800 lives and as mentioned USD 11 billion to the South East Asian economy.

One notable death was of Dr Carlo Urbani. Dr Urbani was a 47-year-old physician and epidemiologist who received the Nobel Peace Prize in 1999 for his role in the organisation Doctors Without Borders. The WHO asked Dr Urbani to investigate a seriously ill American businessman with unusual respiratory symptoms in Hanoi in early 2003. Upon investigating the American, Dr Urbani became very concerned and sent the patient's blood specimens to various laboratories around the world. It was thanks to this that the SARS virus was isolated and action was taken to contain the spread of the infection. Unfortunately this Nobel laureate contracted SARS and died in an isolation ward in Bangkok in March 2003.

## 14. Important Lessons from SARS

Sars provided some very important lessons and will impact the preparation for epidemics in the future:

1. Pathogens found in animals such as Avian Influenza Virus, SARS Corona Virus, West Nile Virus, monkeypox virus or even the prion agent of bovine spongiform encephalopathy (BSE or mad cow disease) are able to cross the species barrier and cause significant mortality and morbidity in humans.
2. With today's air travel an infection from any remote site has the potential to spread globally within days.
3. Molecular virology has progressed tremendously. Within weeks, the SARS Corona Virus was identified and its genetic make up defined. This is good news indeed.
4. Modern communication makes it possible for bodies such as the WHO and the Centers for Disease Control and Prevention to work alongside local public bodies to contain outbreaks of infection.
5. Basic principles such as good epidemiological histories and basic infection control measures remain critical.
6. One person (in the SARS example the physician from Guangdong province) is capable of initiating a pandemic.
7. Medical personnel must have a high index of suspicion for diseases such as SARS and Avian Flu. National and global surveillance programs are essential, but primary caregivers have the critical role in an early warning system.

On an optimistic note, the SARS outbreak revealed that risk management tools, such as careful adherence to basic public health and infection control measures, namely source containment, case management, contact investigation, infection control and community containment led to the control of SARS in four months despite the lack of a rapid diagnostic test, a vaccine, and effective therapy.

The future impact of curtailing epidemic spread such as quarantening neighbourhoods or stopping air travel to cities have to be analysed and prepared for. The economic, legal and social implications are far reaching and in monetary terms will cost billions of dollars. The experts say that we should be preparing and rehearsing for the next epidemic now in order to prevent an

unco-ordinated and panicked response. An example of preparation is the recent emergency meeting called by Jack Straw, the British foreign secretary, of the European Union foreign ministers to coordinate action against Bird Flu in Europe. The writing is on the wall – prepare for the next flu epidemic.

So far we have discussed pandemics where viruses and other pathogens have evolved and mutated in nature and subsequently caused epidemics and pandemics. A chilling thought is what would happen if pathogens were genetically altered by man and used in biological warfare or in the case of Smallpox, reintroduced into the community at large? Let us now discuss this rather unsettling topic.

## 15. Bioterrorism and Genetic Engineering

Since the 9/11 Twin Towers terrorist attack in 2001 and the use of Anthrax for terrorism in the USA, academics, governments and risk managers have broadened their thinking to imagine scenarios that were once almost inconceivable. The use of biological warfare would appear to be a distinct and increasing risk. There are three reasons for this, namely the global proliferation of biological weapons, advances in biotechnology and possible changes in the future use of chemical and biological weapons.

The concept of biological warfare is however not unique to 21<sup>st</sup> century. It is documented that Tatar troops catapulted dead plague victims onto the seaport city of Kaffa in the 14<sup>th</sup> century. British troops also considered spreading Smallpox through contaminated blankets in the 1760s.

In May 2002, the World Health Assembly passed the resolution "global public health response to natural occurrence, accidental release or deliberate use of biological and chemical agents or radionuclear material that affect health".

In response to this the WHO developed a strategy that included four main areas:

- ◆ International preparedness
- ◆ Global alert and response

- ◆ National preparedness
- ◆ Preparedness for selected diseases and intoxications.

Guidelines are now available from the WHO in the above areas. The pending Avian Flu pandemic highlights the importance of a Global Outbreak Alert and Response Network.

The Department of Health and Human Services in the United States has been tasked to assess the vulnerability of our society to biological and chemical warfare. Besides Smallpox they are researching a number of pathogens that could pose a threat to society if used for bioterrorism. The United States Centers for Disease Control and Prevention has classified these biological agents that could be used for bioterrorism into the categories A, B and C. They have also established a Bioterrorism Preparedness and Response Program that addresses public health response to terrorist actions which can be found at [www.bt.cdc.gov](http://www.bt.cdc.gov).

Category A agents are the most lethal and the most concerning. Most are easily transmitted from person to person and have a high mortality rate. They would have a large public health impact, cause public panic and social disruption, and require special action for public health pre-

paredness. A single act of bioterrorism such as the Anthrax letters in the USA, may not cause mass death but as mentioned it is the degree of disruption to administrative systems and the economy that the terrorists are after. To counteract this threat countries must have civil defence systems that can monitor public health and recognise an episode of bioterrorism as soon as possible. The ability to diagnose the agent used, to utilise

### 15.1. Category A Diseases

The pathogens falling into Category A include:

- ◆ Variola Virus (Smallpox)
- ◆ Yersinia Pestis (The cause of Plague)
- ◆ Bacillus Anthracis (The cause of Anthrax)
- ◆ Francisella Tularensis (The cause of Tularaemia)
- ◆ Clostridium Botulinum (Botulism)
- ◆ Viral Haemorrhagic Fevers

Let us look at the category A diseases in more detail.

#### 15.1.1 Smallpox

In the 2002 April 25<sup>th</sup> edition of the New England Journal of Medicine, the horrifying question of Smallpox and bioterrorism was brought to the fore.

Smallpox is the most notorious of a family of viruses known as the orthopoxviruses (poxviridae). Documents often state that this is one of the greatest evils that could be unleashed against the world. Its scientific name is Variola derived from Latin meaning "spotted".

The last case of Smallpox infection occurred in Somalia in 1977 and eradication of the disease was declared in 1980. Since this time Variola Virus or Smallpox as it is known has only existed in laboratories as in nature a reservoir no longer exists. In 1978, 823 laboratories had stocks of Smallpox and by 1984 only the Center for Disease Control and Prevention in Atlanta and the State Research Center of Virology in Russia retained stockpiles of this virus. Since 1982 no vaccination programs have taken place in the world which means that if Smallpox had to be reintro-

duced into the community at large most people would be susceptible to this disease. The consequences would be dire. A possible case of Smallpox is a public health emergency and of utmost international concern. Studies from India have shown that Smallpox carries a mortality rate of 30% or more. Smallpox spreads primarily through respiratory droplets but infected clothing or bedding (fomites) can also spread the infection. Although Smallpox is less transmissible than Measles, Chickenpox or Influenza, secondary attack rates among unvaccinated contacts range from 37–88 percent. In one outbreak in Meschede in Germany 17 people on three floors of a hospital contracted Smallpox from one patient during the incubation period. At present there is no treatment approved by the Food and Drug Administration (FDA based in America) for this condition. Treatment would only be supportive.

Prevention is possible through vaccination and if performed very early in the incubation period, vaccination can markedly attenuate or even prevent clinical manifestations of Smallpox. Full protection occurs after a successful vaccination. A successful primary vaccination confers full immunity to Smallpox in more than 95% of people for 5–10 years, and successful revaccination provides protection for 10–20 years or more.

The question of the use of Smallpox in bioterrorism is actually not a new thought. British colonial commanders considered distributing blankets from Smallpox victims among Native Americans. The Japanese military explored its use in World War II. On the other hand there are some who argue that Smallpox may not be an effective bioterrorism tool as vaccines are available. It does remain a threat though as it has all the qualities that make it attractive for bioterrorism. It is distrib-

uted by aerosol droplet spread, it is relatively easy to produce large quantities and the population in large is not immune to the virus as vaccination was stopped in the eighties. Forty years ago, Smallpox could not have posed a serious bioterrorist threat in the USA for instance as most of the US population was immune to the disease due to compulsory immunisation programmes. Presently it is a different matter and approximately 30% of susceptible contacts would become infected and of these in excess of 30% would die. Should vaccination programmes be introduced? This is the question being posed at the moment. It is not an easy decision.

In reality the risk of a terrorist attack with Smallpox must be small. There would have to be a clandestine stockpile of Smallpox that is unaccounted for.

In the event of Smallpox being disseminated, the Center for Disease Control and Prevention (CDC) actually advocated quarantining those infected and tracing and vaccinating all those who may have had contact with an infected person. This is known as "ring-vaccination" and is an alternative approach to vaccinating the whole population. It may however be logistically difficult to implement if there are simultaneous attacks in multiple cities.

The concern about mass vaccination is that the vaccination itself is not without mortality and considerable morbidity. Mass vaccination would result in 1–2 deaths/million vaccinees and hundreds of cases of an attenuated Smallpox infection and other complications such as encephalitis (a viral infection of the brain). Vaccine production has been stepped up in the USA and there will be approximately 300 million doses available by 2005. This quantity would be almost sufficient to vaccinate the entire population of the USA. There will have to be a public debate whether mass vaccination should occur but at least the USA can be rest assured that if the need arises, they can vaccinate their population. Other countries are following suit.



Boy with Smallpox involving face  
Source: Wikipedia – The free encyclopedia

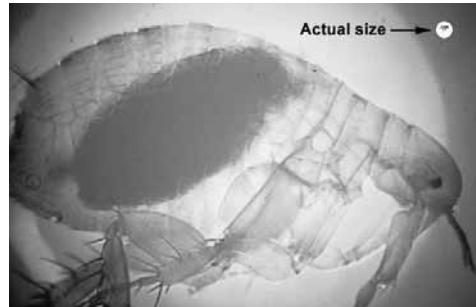
### 15.1.2. The Plague

As mentioned in the history of epidemics, plague decimated the European population in the 1300s. Even in the 21<sup>st</sup> century the mention of plague or "Black Death" is enough to cause fear and rightly so. In humans the Plague (caused by a bacteria called *Yersinia Pestis*) occurs in three forms namely the Bubonic Plague, Pneumonic Plague and Septicaemic Plague. Untreated Bubonic Plague is fatal in 30–75% of all cases, Pneumonic Plague 95% of the time and Septicaemic Plague in virtually all cases. Mortality in treated cases is 5–10%. The last pandemic of Plague began in China in 1894 and spread to Africa, the Pacific Islands, Australia and the Americas. In 1997, 14 countries reported more than 5,400 human Plague cases of which 274 were fatal. Could the Plague be used for bioterrorism? Apparently yes and countries have in the past developed the Plague as a biological agent. The *Yersinia pestis* bacteria is easily destroyed by drying, heat, and ultraviolet light making direct weaponisation difficult, however, reports that the former Soviet Union's biological warfare programmes developed a dry, antibiotic-resistant, environmentally stable form of the Plague organism has led the Centers for Disease Control and Prevention (CDC) to categorise Plague as a Category A agent. *Yersinia Pestis* can be grown in large quantities with intentional spread of the plague being through aerosol spray. A bioterrorism attack would be characterised by pneumonic cases occurring simultaneously in persons 1–6 days following a common exposure, and a secondary wave in unprotected case contacts. There are no effective environmental warning

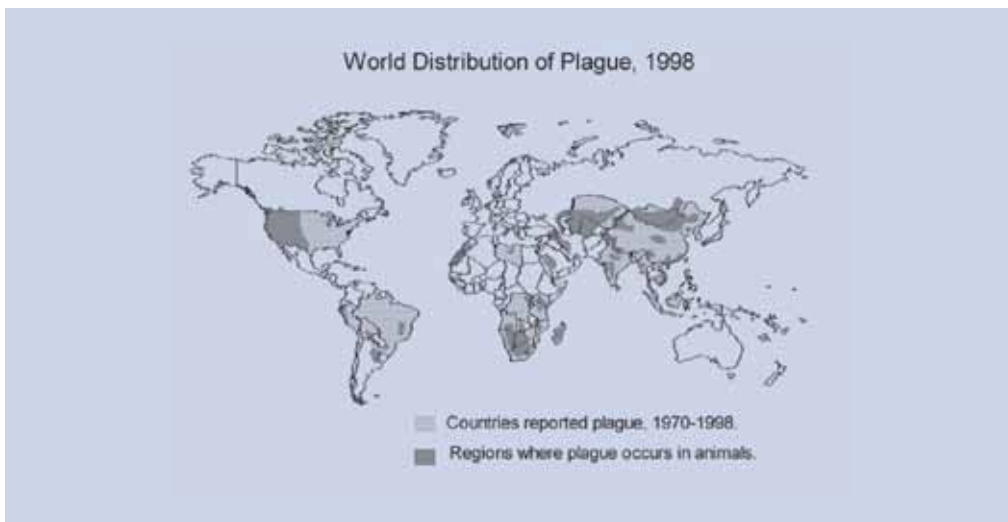
systems to detect an aerosol release of plague bacilli. A Pneumonic Plague outbreak would initially resemble an outbreak of other severe respiratory illness, but would quickly be distinguished by the rapid development of life threatening respiratory failure, sepsis and shock. Antibiotics need to be given within 24 hours of first symptom presentation to prevent high mortality. Vaccines are not available.

This flea is the primary vector of Plague in most large plague epidemics in Asia, Africa, and South America. Both male and female fleas can transmit the infection.

Male *Xenopsylla Cheopis* (oriental rat flea) engorged with blood.



*Xenopsylla Cheopis*: Image from Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention



Map from Centers for Disease Control and Prevention

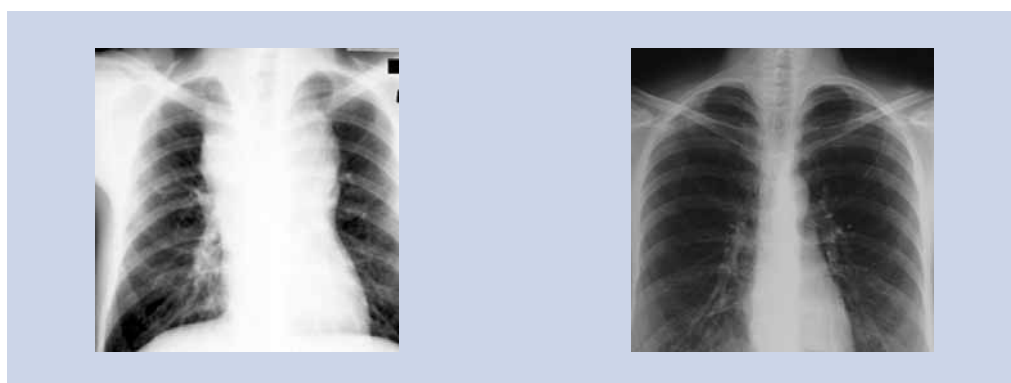
### 15.1.3. Anthrax

Anthrax is the Greek word for coal and it refers to the coal black ulcer that forms when Anthrax involves the skin (Cutaneous Anthrax). It is however the inhalational form of Anthrax that poses the greatest risk to mankind. Unfortunately this form of Anthrax has been used as recently as 2001 as a bioterrorist agent. In the USA in 2001, eleven people contracted inhalational Anthrax after receiving letters containing Anthrax spores. Five of these people died. President Richard Nixon supposedly stopped the production of Anthrax as a bioweapon in the USA in 1971. Prior to this weapon grade Anthrax was produced

at a facility in America known as Fort Detrick. Small amounts are still made for research purposes and according to a theory these last Anthrax attacks were the result of a disgruntled employee. Wherever the Anthrax came from it needed highly specialised equipment for its production. It has definitely been produced as a bioterrorist agent up until 1979 when an accidental leak of Anthrax from a bioweapons facility in the former Soviet Union killed 66 people. The Aum Shinrikyo cult – the same cult that used sarin gas in the Tokyo subways was also found to have a stockpile of Anthrax. The concern is that it is still being stockpiled as a biological weapon. Deaths following a

release of Anthrax from an aircraft could be significant. The WHO has previously calculated that aerosol distribution of Anthrax over a city of five million would kill 100,000 people. This spore-forming bacteria is long lived and quite stable making it an ideal bioweapon. Once inhaled into the lungs the bacteria produces a potentially lethal toxin which has the ability to cause cardio-

vascular collapse and death in as little as two days. Anthrax, unlike Smallpox, cannot be transmitted from person to person. Fortunately treatment is available in the form of antibiotics such as penicillin but treatment must be initiated as soon as possible in order to save lives. A vaccine has also been produced but is not readily available to the general public.



Mediastinal (widening of the central portion of the chest cavity) widening on chest X-Ray in inhalational Anthrax. The mediastinal widening is a prominent feature of inhalational Anthrax (compare the central portion of the X-Ray on the left to a normal X-Ray on the right)

Left picture: Centers of Disease Control and Prevention.

Right picture: Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong

#### 15.1.4. Tularaemia

Tularaemia is perhaps not as well known as the other diseases discussed in this section. It is caused by the bacteria *Francisella Tularensis* and occurs in two types namely A and B. One particular strain of type A is extremely infectious needing the inhalation of as few as ten organisms to cause disease. It is this infectiousness and the potential to be aerosolised that make it a potentially worrying agent for bioterrorism. Inhalational tularaemia has the potential to cause a pneumonic illness with a mortality rate approaching 30% in untreated cases. To date no person-to-person transmission of tularaemia has been reported. Treatment is available in the form of antibiotics. A vaccine is available against aerosol infection. Although not common, tularaemia type A is to be found in the natural environment of North America.

#### 15.1.5. Botulism

Botulism can be used as an aerosolised or foodborne bioweapon. It produces a nerve toxin that causes paralysis within 12–72 hours after exposure. Botulism toxin is extremely potent with a high mortality rate. According to an article in

the *Journal of the American Medical Association* one single gram of botulinum toxin evenly dispersed and inhaled would kill more than one million people.

Terrorists have already attempted to use aerosolised botulinum toxin on three occasions between 1990 and 1995. Fortunately the attacks failed. It is interesting to learn that during World War II, one million doses of botulinum toxoid vaccine were prepared for allied troops preparing to invade Normandy on D-Day as there were fears that Germany had weaponised botulinum toxin.

As mentioned Botulism causes paralysis. Death ensues from paralysis of the respiratory muscles unless the patient is attached to a mechanical ventilator. A large outbreak of Botulism could easily overwhelm the supply of ventilators available in any one city. Recovery can take weeks to months. At present approximately 100 cases a year occur in the USA due to infection from the environment. Botulism antitoxins are available and with supportive therapy the mortality rate is reported to be around 6%.

### 15.1.6. Viral Haemorrhagic Fevers

Viral Haemorrhagic Fevers is a term covering four families of viruses that cause fever, bleeding, shock and potentially death. Ebola, Marburg, Congo, Yellow Fever and Rift Valley Fever are perhaps the more well known viruses in this group.

Haemorrhagic Fever is found in nature with the reservoir being infected animals and arthropods.

It is a concern as a biological weapon as it is highly infectious by aerosol dissemination, it carries a high morbidity and mortality and has the potential for person-to-person transmission. Effective vaccines are not available other than for Yellow Fever. From a technical perspective Ebola

and Marburg viruses are the ones that pose the greater threat as they are easier to mass produce and aerosolise.

Haemorrhagic Fever viruses have been weaponised in the past by both the USA and the former Soviet Union as recently as 1992.

The incubation period ranges from 2–21 days. The initial symptoms of a flu like illness progress to bleeding, shock and central nervous system symptoms. Once this stage has been reached the prognosis is very poor indeed. Treatment is supportive and the use of a drug known as ribavirin. Strict and meticulous infection control is needed to prevent the spread of this dread disease.

## 15.2. Ricin

An interesting compound in Category B is ricin. It is found in the bean of the castor plant, is easy to produce, and extremely toxic. It is a by-product of castor oil production and is readily available worldwide. Ricin was used to assassinate a Bulgarian defector called Georgi Markov by stabbing him with the tip of an umbrella coated in Ricin.

Theoretically it could be possible to aerosolise ricin and use it for biowarfare. Death would occur within three to four days. It was indeed developed as a biological weapon by the United States and its allies in World War II. Vaccines are to my knowledge not readily available.

## 16. Chimaera, Genetic Engineering and Bioterrorism

In the 9<sup>th</sup> century BC, Homer related the story of a terrifying beast called the Chimaera. It was a mixture of a lion, goat and a snake. This fire-breathing monster was slain by the hero Bellerophon who flew around the Chimaera on his winged horse Pegasus. He killed the beast with a hail of arrows. A very dramatic myth indeed. Today the word chimaera is associated with mutated and genetically altered entities, something unnatural and terrifying.

Advances in biotechnology now allow scientists to modify organisms to make such modern-day chimaera. A United States enquiry after the Gulf War in 1993 stated that genetic tailoring and the speed of technological innovation create opportunities for the creation of exotic new agents which may be difficult to detect or defend against. The same report felt that there were 11 nations

around the world that possessed or had the ability to develop biological weapons.

From a military perspective scientists now know more about man's vulnerabilities with respect to biological weapons and are also in a position to create organisms that are more virulent and infective. It is also possible to create new organisms through genetic recombination that would be unknown to mankind and for which we have no immunity. As an example of this in 2001, British researchers were found guilty of genetically engineering a virus that combined Hepatitis C and Dengue Fever. This was produced in unsafe laboratory conditions and was quoted as being more lethal than HIV. There has also been research that has genetically sequenced the 1914–1918 Spanish Flu Virus and it is therefore theoretically possible to recreate this flu. It is also

worrying to learn that the entire genetic sequencing of Smallpox is available on the internet. Other areas of research for terrorists wanting to use biowarfare include attacking and weakening the body's normal immunity or creating organisms resistant to present antibiotics. Fortunately ad-

vances in this field are also being used by researchers for better vaccine and anti-toxin production, rapid diagnostic techniques and therapeutic interventions. Hopefully the chimaera of today will be matched by an equally impressive hero as in the myth related by Homer.

## ***17. Managing the Risk of a Pandemic from a Medical Perspective***

The WHO has been very active in providing guidelines and advice on the preparation for a pandemic. It also highlights lessons to be learnt from the last three major influenza pandemics. In all likelihood it is indeed an influenza pandemic that will affect the globe rather than Anthrax, Smallpox or the Plague as listed above.

As mentioned the WHO has prepared for its member states a checklist for preparation for a pandemic. This list could also be used as a risk assessment tool to assess the potential impact of a pandemic on a country. The list includes the following areas:

- ◆ Preparing for an emergency
- ◆ Surveillance
- ◆ Case investigation and treatment
- ◆ Preventing spread of the disease in the community
- ◆ Maintaining essential services
- ◆ Research and evaluation

- ◆ Implementation testing and revision of the national plan.

In order for the above to occur the importance of for example an influenza pandemic preparedness should be recognised at the appropriate levels of government.

It becomes apparent that there would be a great difference between the developed and the developing countries when it comes to preparedness for such a pandemic.

Certain European countries are at an advanced stage of preparedness. Germany for instance has drawn up a plan around a worst-case scenario modeled on the 1914–1918 Spanish Flu epidemic. In this model it is assumed that there will be 20–25 million cases of influenza resulting in 200,000 admissions to hospital and 120,000 deaths from influenza. Secondary pneumonia will also occur resulting in a total annual excess mortality of 175,000 deaths. Sobering figures indeed.

## ***18. Vaccination and Antiviral Treatment***

A vaccination programme as well as the provision of antiviral drugs will be core to any preparation plan and falls under the section of preventing spread of the disease within the community.

Currently the delay between the identification of a new viral subtype and the manufacture of the corresponding vaccine would be at least three months and probably closer to six to eight months. In a country such as Germany three to four million doses of vaccine could be made within three months and thereafter approximately

one million doses per week. One could imagine that initially demand would outstrip supply and that predetermined groups of people should first receive the vaccine. Broadly speaking the vaccine should be at least offered initially to health care workers and people maintaining public order such as policemen, firemen, and other emergency services.

Those people at high risk from the pandemic such as the elderly and the very young should also be vaccinated as a priority and finally those

people where exposure would be high such as in schools and universities. This is certainly an area with strong political and ethical issues and should be planned way before the crisis hits the community. There are for instance 26 million

older and/or chronically ill people in Germany and it is not alone in having an aging population. The potential need for a second booster dose only increases the demand. Vaccines may become a very sought-after commodity.

## 19. Supply and Demand

There are only eight countries worldwide that have the capability to produce influenza vaccines. None of these countries are in the developing world. It is certainly big business. Over 300 million doses of seasonal influenza vaccine are produced every year at a cost of USD 7.50 a dose. Over the next ten years 40 countries will spend USD 28 billion on influenza vaccinations. It is doubtful if countries producing influenza vaccines will be permitted to export vaccines to other countries until their own internal needs are met should an influenza pandemic take place. This may become an interesting point in the future.

As discussed under Avian Flu, Tamiflu is the present drug of choice for an influenza pandemic. At present approximately 500,000 units of these

drugs could be manufactured on a daily basis. If Roche waives its patency right, this production can be stepped up.

At present demand is likely to outstrip supply. Academics estimate that a country such as the USA needs 52–84 million courses and an absolute minimum of 15 million.

Presently it is quoted as having six million courses of treatment. One lesson learnt from the SARS epidemic is that health care workers are more likely to work if they know they are protected by a drug such as Tamiflu. Countries should have at least stockpiles to cover healthcare workers and those supplying emergency services.

## 20. Lessons from the Past

Vaccines and anti-virals are one defence and one area of risk management when it comes to managing an epidemic. Other risk management areas must stem from lessons learnt from past epidemics.

The WHO has listed the most important lessons to be learnt from the three influenza pandemics of the last century. They are as follows:

Pandemics behave as unpredictably as the viruses that cause them. During the previous century, great variations were seen in mortality, severity of illness, and patterns of spread. This makes my actuarial colleagues' task all the more difficult. In all modelling the worst-case scenario always appears to be benchmarked against the 1914–1918 pandemic.

One consistent feature important for preparedness planning is the rapid surge in the number of cases and their exponential increase over a very short period of time, often measured in weeks. This will obviously put great strain on existing health services and underlines the importance of having large quantities of drugs such as anti-virals available at short notice. This surge of cases will probably also occur before an appropriate vaccine could be prepared and distributed.

One point that must not be forgotten is that these pandemics often have the ability to cause disease in non-traditional age groups namely young adults. The Spanish Flu was a prime example of this.

### Pandemics in the 20<sup>th</sup> Century and Excess Mortality in age band below 65

1918:	>90% of excess deaths occurred among those aged <65
1936–37:	about 60% of excess deaths in <65
1943–44:	only 30% in <65
1957–58:	36% of excess deaths in <65
1967–68:	only 4% in <65 (end of H2N2 circulation)
1968–69:	~40% of excess mortality in <65
Since 1992:	<10% of excess deaths among those aged <65 years

Source: David K Shay "Influenza Pandemics of the 20<sup>th</sup> Century". Influenza Branch National Center for Infectious Diseases. Centers for Disease Control and Prevention.

Pandemics tend to occur in waves. Subsequent waves tend to be more severe. Mutation can occur resulting in a more virulent strain. This is very worrying and would have to be considered in modelling.

Having a surveillance and laboratory network for the early detection and characterisation of a virus has proven invaluable as was the case with the SARS virus.

Most pandemics began in South East Asia where dense populations of humans live in close proximity to birds and animals. All the warning are that the next pandemic will indeed emanate from South East Asia.

Quarantining and travel restrictions have had little effect in the past but banning of gatherings and closures of schools and so forth have been beneficial.

Delaying spread is desirable as it can flatten the epidemiological peak as health services can better cope with the number of cases. Vaccines and anti-viral agents would play a role in this area.

Vaccines in the past have been too few and too late to have a significant impact. Whether we can improve on this in the 21<sup>st</sup> century remains to be demonstrated.

Countries that are able to manufacture vaccines will obviously be in a better position to distribute them.

The tendency of pandemics to be more severe in later waves may extend the time before large supplies of vaccines are needed to prevent severe disease in high risk populations. The interval between successive waves may, however, be as short as a month.

In the best-case scenario a pandemic should affect those in the extremes of lifespan more and those who are chronically ill. Hopefully there are programmes in place to vaccinate these people with seasonal flu vaccines and the logistics of providing a flu vaccine against a pandemic strain should not be as difficult. Having said this, with aging populations the numbers involved may be many millions of people.

## 21. Conclusion

We are indeed living in interesting times and at this point it would seem highly probable that we will experience an influenza pandemic in the near future. Modelling is available to predict excess mortality and healthcare costs with scenarios based on influenza pandemics dating back to the great Spanish Flu pandemic. Guidelines on how to manage the epidemic are in place but there are vast differences in the preparedness of countries around the world. The impact is most likely to be felt in 3<sup>rd</sup> world countries that have limited access to vaccines, anti-viral agents and

healthcare facilities. Unknown entities at this point are the infectiousness and virulence of the next strain of influenza. Most literature feels that the economic impact will be significant especially in the Asia/Pacific region.

Bioterrorism unfortunately remains a sinister threat which cannot be ignored. Terrorists are more likely to aim at causing social and economic disruption than absolute number of deaths but the ability to cause mass death through biological warfare is available.

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