# PANDEMIC INFLUENZAS

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**Highly contagious, acute, respiratory illnesses have been known to affect humans since ancient times. Hippocrates recorded an epidemic in 412 BC and numerous outbreaks were described in the Middle Ages. These were known as influenza, originally an Italian name which was adopted in Europe to explain the sudden and unexpected appearance of what was thought originally to be under the influence of the stars (Brown and Alexander, 1998). The first well recorded pandemic was in 1580 in which it is believed the viral infection spread from Russia to Africa and Asia killing more than 8000 people and devastating several Spanish cities. Russian flu in 1880-1890 killed upwards of 1 million and reached North America and Latin America.**

However, the most lethal flu on record was that designated "Spanish Flu" of 1918-1919 which killed between 20 and 100 million and was global in nature occurring from the Arctic to remote Pacific islands. The causative agent is now agreed to have been a flu virus (H1N1), swine flu, though there are many opinions why it should show such virulence and affect the younger end of the population (ages 20 to 40 years) and particularly armed forces personnel. 43,000 deaths occurred in the US forces alone which was about 80% of the total number of US battle deaths in the First World War. The acute nature of the disease in the younger end of the population has been attributed to a "cytokine storm" which is a lethal over-reaction of the immune system to the virus infection which replicates very fast and unleashes cytokines. Masses of virus rapidly overwhelm the immune system.

A brief word about the agent. Influenza viruses belong to the Orthomyxoviridae family of which there are three genera; one, type A and B viruses, a second containing type C and a third of "Thogoto-like" viruses (International Committee on the Taxonomy of Viruses, 1995). There are 15 different haemagglutinin (H 1-15)and 9 neuraminidase (N 1-9) subtypes based on serological testing with haemagglutinin-inhibition and neuraminidase-inhibitin tests respectively. Types A, B and C infect humans but generally infections of other animals are restricted to type A and only A viruses have been isolated from birds. "A" viruses only have produced the devastating pandemics of human populations (Brown and Alexander, 1998). But pandemics in animals, though not known as such, have caused serious disease. An example is influenza equi 2 which caused serious disruption of racing (Newmarket Cough) and of events involving cavalry horses such as the Trooping the Colour which for the first time in history caused the ceremony to be performed on foot.

In 1957-58 the virus of Asian flu started in China, originally having mutated from wild ducks and then combined with a human strain: it killed 1-1.5 million people. With the Hong Kong flu of 1968-69 the virus (H3N2) started in Hong Kong and then spread across Asia to India and northern Australia. US troops returning home from Vietnam carried the virus to the US. It killed 750,000 to 1 million people, particularly children and middle-aged adults.

While much can be learned from each pandemic, it has not been possible with certainty to predict the progress or outcome of a pandemic. An example of this was the outbreak of swine influenza A at Fort Dix, New Jersey, in 1976. This outbreak also became known as the swine flu fiasco or the swine flu debacle.

On February 5th 1976, an army recruit, Private Lewis, at Fort Dix felt tired and weak after an all-night hike. He died the following day and four of his companions were later hospitalised but survived. Swine flu, apparently closely related to the strain involved in the 1918 pandemic was incriminated and alarmed public officials convinced President Gerald Ford that every person in the US should be vaccinated against the disease. Eventually 24% of the population was vaccinated and the programme was halted on December 16th, 1976. The outbreak of Fort Dix Swine Flu (H1N1) did not spread beyond Fort Dix; it caused one death and severe respiratory illness in

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13 soldiers. However, a more serious sequel to the Fort Dix event was the occurrence of the Guillain-Barre syndrome in some vaccinates. Some 50 million people were vaccinated at an estimated cost of $100 million. Overall about 500 cases of Guillain-Barre occurred resulting in death from severe pulmonary complications in 25 persons. Other influenza vaccines have not been linked to the Guillain-Barre syndrome. Questions remaining unanswered about the Fort Dix outbreak include where did the New Jersey virus come from and why did transmission stop?

An outbreak not considered a true pandemic was the 1977 Russian flu. This began in Northern China and spread rapidly around the world but affected only children and young adults.

Avian influenza was first recognised in chickens in 1878 and is known to be widespread in waterfowl since the 1970s. An outbreak of avian flu in broilers in Pennsylvania and Virginia in 1983-84 led to the slaughter of 11 million birds at an approximate cost of $61 million. Two forms of avian influenza virus are recognised, highly pathogenic avian influenza (H5N2) (in broilers in Mexico, 1993) and low pathogenic avian influenza (H7N1) (in Italy 1997-2000). Avian strains can spread to mammals, including humans, resulting in serious epidemics. In 1997-98 there was world-wide concern after an outbreak of the highly pathogenic H5N1 avian influenza spread from chickens in Hong Kong to humans. Hong Kong authorities slaughtered 1.5 million chickens in December 1997 and the export of chickens was banned in an attempt to prevent further spread of the virus. However, six people died and a further 12 were severely affected in the following months; the patients had no contact with each other and had no common exposure. This raised concerns that a pandemic similar to the 1968 Hong Kong outbreak was in the offing. Avian H5N1 infection was previously known to infect only birds and the Hong Kong cases were the first human infection with avian H5N1. H5N1 appeared to have been transmitted directly from chicken to human rather than from birds to pigs first and then from pigs to humans. Since 2003 the H5N1 strain has caused more than 60 deaths in South East Asia but no human fatalities have been recorded in any other continent. A major concern has been that this strain could cause serious havoc by genetic mixing with the human influenza virus. To date this has not happened and human infections have occurred where there has been close contact between infected poultry and backyard individuals. In some rural poverty areas the dead bird, possibly a domestic pet has been consumed by the family, humans being infected when dissecting the carcase. Several agencies (eg WHO, FAO, Federation of Veterinarians of Europe) have stressed the need to contain the disease at its roots, even though migratory birds, particularly waterfowl, may transport the virus long distances over Europe, the Mid East and northern Africa. To this end funding for surveillance and vaccination programmes in the Far East has been made available through FAO and other agencies.

An extensive and excellent account on pandemic influenza with respect to avian flu is given by the joint publication of the Royal Society and the Academy of Medical Sciences (2006: Pandemic Influenza: science to policy, Policy Document 36/06). This covers exhaustively animal hosts, epidemiology and surveillance, antivirals, vaccination, public health and science and policy making.

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Since avian influenza is a disease of birds the British Veterinary Association has provided a guide for the profession for highly pathogenic avian influenza (HPAI) not only for stocks of commercial poultry but also ostrich farming and other ratite species (emu, rhea, cassowary), breeders of captive birds (parrots, canaries) and game birds (pheasant, partridge) birds in zoos and wildlife parks and birds of prey (falcons). The BVA stresses that human infection with avian influenza is rare and occurs usually through close and prolonged contact with live infected birds. Though H5N1 is essentially an avian virus, contact with feral and wild animals has been determined to be a strong risk factor, especially in small-scale commercial production systems which predominate in the Far East. Under these circumstances biosecurity is often poor and infection and transmission, especially with highly pathogenic H5N1 (HPAI) has been reported for dogs, cats and civets in Bangladesh (Biswas et al 2009).

Mexican Swine Flu is now the infection causing urgent concern globally. The origin of what is now recognised as H1N1 possibly was in a teenage boy in 2005 in Wisconsin who helped in the butchering of pigs at a local slaughterhouse at Thanksgiving: the boy's family also bought a chicken and kept it at home over the holiday period. On 7th December 2005 the teenager came down with flu which lasted 3 days but no other member of the family took ill. The virus appeared to be a mosaic of a wild bird form of flu, a human type and a strain found in pigs. It is now thought that the Wisconsin virus was a step along the evolutionary tree leading to a virus that in four years' time would mesmerise the world.

In 2009, a young man, Edgar Enrique Hermandez of La Gloria, Mexico suffered a bout of flu, later found to be H1N1, a mosaic of swine, bird and human flu! The infection spread rapidly globally and on June 11th 2009 the World Health Organization raised the pandemic level for H1N1 to phase 6 or global pandemic status. More than 70 countries reported cases and by late November 2009 the WHO confirmed some 700,000 of H1N1 and over 8,700 deaths in 207 countries. The USA and Canada have been heavily affected with over 1,800 deaths and the Americas (North, Central and South) account for about two-thirds of H1N1 deaths worldwide. Interestingly, H1N1 has had least impact in

Africa where just 104 deaths have been recorded out of 15,500 confirmed cases.

The rapid spread of Swine Flu dominated the news media for months and estimates of potential infection and mortality rates, disruption of essential services such as police, hospital facilities and schools were projected at all levels, including Parliament. Proof of the origin of the present H1N1 from swine has not yet been confirmed. Swine influenza is a contagious disease of pigs that occurs worldwide and virus types H1N1, H1N2 and H3N2 are endemic in many pig populations round the world but there is no good evidence of inter species transmission on a significant scale. The present H1N1 influenza virus, though assumed to be of animal origin (ie is a zoonosis), is now spreading from human to human. Whether H1N1 can act as a reverse zoonosis, ie human infection being transmitted to pigs is less clear. On one occasion in Canada a case of human to pig transmission followed contact of an occupationally exposed worker incubating the H1N1 virus following return from travel to Mexico (Irvine and Brown 2009).

An experimental study to determine the infection dynamics, clinical outcome and transmissability of H1N1 in pigs was undertaken by a consortium of 9 institutes and organisations from 8 EU member states (Brookes, Irvine, Nunez et al 2009). Pigs were susceptible to infection with influenza A (H1N1) resulting in detectable levels of clinical disease, virus shedding and respiratory tract pathology. However, mortality was not a feature of the experimental infection and infected animals were able to transmit the virus to naïve contact pigs, suggesting the virus could become established in susceptible pig populations.

The fact that H1N1 has been designated Swine Flu or Mexican Flu has generated unsustainable responses. Thus, following the initial reports of H1N1 – swine flu, the Egyptian government decided to slaughter 300,000 pigs even though the country is predominately Muslim and therefore not pork consuming. Veterinary authorities such as FAO and OIE along with WHO have stressed that influenza viruses are not known to be transmissible to humans through eating pork or pork products derived from pigs. Heat treatment commonly used in cooking meat, 700°C core temperature, will readily inactivate any virus potentially present in raw meat products. Pork and pork products handled by good hygiene practices will not be a source of infection; however, meat from sick pigs or those found dead should not be used for human consumption under any circumstances.

The virus of Swine Flu in 1918 was uniquely virulent and though most patients experienced symptoms of typical influenza with a 3- to 5-day fever followed by recovery, histological and bacteriological evidence demonstrate the vast majority of influenza deaths resulted from a viral-bacterial-host interaction with secondary bacterial pneumonia. Diagnostic virology was not then available but bacteriology was a flourishing discipline and bacterial super infection of viral diseases, eg measles, was often fatal.

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Compared with the number of antibiotics available for bacterial infections, of which many are resistant, some multi-drug resistant to a range of antibiotics, there are few antiviral drugs available for the treatment of H1N1 infections. Two, oseltamavir (Tamiflu) and zanamivir (Relenza) are currently recommended for the treatment of influenza. A major concern with the use of these antivirals is the development of antiviral resistance. Originally, Tamiflu was prescribed to ease the symptoms of flu and its duration. However, as concern for H1N1 markedly increased, Tamiflu has been prescribed and administered as a prophylactic. The WHO does not recommend that antivirals be used for prophylaxis as the more a drug is consumed the more opportunity there is for resistance to develop and spread, making the antivirals ineffectual when they are actually needed. The US Department of Health and Human Services similarly does not support prophylactic use, arguing that most people who get sick don't need Tamiflu. Virus strains resistant to Tamiflu are still susceptible to Relenza. Some authorities have recommended a cocktail of Tamiflu and Relenza as mutations conferring simultaneous resistance to multiple drugs are less likely. However, this is not an approach which has generated major support. National preparedness has been an important issue in many western countries. The UK stockpile of antivirals is aimed to provide treatment for the majority of the population and is reported to be ahead of most other countries. Details of stockpiling, availability and

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distribution of antivirals are now available from health agencies, local and national.

An obvious step forward is the production and use of a vaccine against H1N1. A vaccine against the newly emerged H1N1 strain would slow or even stop the spread. of the virus, however, existing flu vaccines administered in the autumn against "regular seasonal" flu will not prevent infection with H1N1 and hence a new vaccine is required, as is indeed the case for seasonal flu, owing to the antigenic shift of the flu virus, and each year influenza viruses isolated from epidemics are characterised in WHO Influenza Reference Laboratories. However, vaccine makers have a dilemma in that ordinarily vaccine producers would be producing vaccine for regular seasonal flu, primarily for the elderly, whereas a swine flu vaccine would be aimed at the younger end of the population. Vaccine production cannot be achieved over night. Cultivation of the virus in hens' eggs is part of the process, which takes time (3 days) but weeks are required for testing and formulation. A detailed account of the development of H1N1 vaccine, regulatory issues and advances in vaccine science, including alternative vaccine production techniques is given in the Parliamentary Office of Science and Technology POSTnote on H1N1 "Swine Flu" vaccine (May, 2009, number 331).

The early indications of the possible extent of swine flu were that it was spreading rapidly and would continue to do so. In the early part of 2009 cases were doubling every week and 100,000 cases per day were projected. It was expected that as autumn and winter approached and the normal flu season occurred swine flu would become a most serious national entity. The possibility of 65,000 deaths was predicted over the winter period. The similarity to the 1918 pandemic was stressed and urgent action to produce sufficient vaccine was undertaken. Enough vaccine was ordered to protect the entire population of the UK (60 million doses from GlaxoSmithKline (GSK) and 30 million from Baxter). However, the anticipated "third wave" of the pandemic did not materialise. Global deaths to Jan 5th 2010 totalled 13,324 (360 in UK, 2160 in USA, 509 in China, 823 in Mexico and 1,632 in Brazil) (Data from Rose, 2010). As a consequence, millions of doses of vaccine remained unused, estimated to be 60 million (Rose 2010).

High stocks of unused vaccine also occur in France and Germany who have decided to sell unneeded vaccine. Some countries plan to ship surplus vaccine to countries with a shortage though some countries with a shortage may not need vaccine supplies, as, for example, some in the African continent have been least affected, suffering fewer than 150 deaths continent-wide.

One point is clear about influenza, be it a normal seasonal form or a pandemic, namely it is difficult, if not unwise, to predict the outcome at the start of an outbreak. It is also unwise to take heed of the lessons to be learned from the Swine Flu pandemic and indeed the other pandemics that have preceded it.

Swine flu has presented a field day for newspaper reporting of incidents associated with the flu from around the world. China imposed quarantine restrictions on visitors holding Mexican passports and also on entire school groups from overseas, eg on 65 students from St Mary's School in Oregon, a few of whom subsequently tested positive for H1N1 Swine Flu. Despite protests from around the world, China isolated plane loads of people if anyone on the flight exhibited flu-like symptoms. Chinese authorities maintain that these measures may have helped to slow the spread of the infection in the world's most populated country. H1N1 flu, or in fact other forms of flu are not respecters of political niceties and measures to dampen down transmission by whatever political persuasion are to be welcome.

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**When will the next pandemic occur? The majority of health officials believe it is not if but when. WHO surveillance of flu viruses will do much to identify the next zoonosis of flu, since almost all human flu is derived from animals. However, the truth may lie in our stars since Yeung (2006) has hypothesised that sunspot cycles may detect pandemic influenza A in 1700-2000! A hypothesis worth reading.**

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