AN INTRODUCTION TO AVIAN AND PANDEMIC INFLUENZA

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ABSTRACT

There are many types of influenza viruses, which cause illness in a variety of birds and mammals. New strains are constantly evolving, causing seasonal influenza epidemics in humans. This article provides information about influenza and influenza viruses, and the three influenza pandemics of the twentieth century. Pandemic influenza is differentiated from avian influenza, which is a viral disease that primarily infects birds. The current outbreak of avian influenza H5N1 in poultry flocks across the world is unprecedented in its spread. Human infection with avian influenza is rare and for most strains the symptoms are usually mild. A notable exception is HN51, where almost 60 per cent of the currently recorded 251 human cases have died. While the risk of a pandemic occurring in the current circumstances is unknown, there is a high level of concern worldwide.

Humans can be infected by seasonal influenza, pandemic influenza, and on rare occasions, avian influenza. These forms of influenza and the risk of acquiring them are often confused—especially in the current circumstances of avian influenza outbreaks in poultry flocks around the world, human cases of avian influenza, and growing concerns about the next influenza pandemic. A clear understanding of these terms dispels confusion, and enables readers to engage effectively with the large amount of information about them in the scientific literature and the media.

INFLUENZA

Influenza is a viral disease characterised by the rapid onset of fever, myalgia, headaches, sore throat and cough.[1] Symptoms usually resolve within a week, however, complications such as pneumonia, respiratory failure, heart failure and death can occasionally occur, most often in the chronically ill, the elderly, or in young children. The virus is spread by inhalation of infectious droplets that are sneezed or coughed into the air, or by direct contact with surfaces that are contaminated with infected droplets.[2] There is some evidence that the virus may also be spread by small aerosolised particles.[3]

There are three types of influenza viruses, designated A, B and C. Influenza A viruses have several subtypes and are named according to the two key glycoproteins on their surface, hemagglutinin (H) and neuraminidase (N) - for example H1N1, H3N2. The evolutionary hosts for influenza viruses are aquatic birds and all subtypes of influenza A viruses infect birds. Some subtypes of influenza A also infect pigs, horses, sea mammals and humans.[1] Influenza A viruses tend to be specific to their host species because the hemagglutinin and other viral proteins are specific to particular receptor cells in the host organism, however, on rare occasions, viruses from one species will infect other species. Influenza B and C viruses are essentially unique to humans.

Antigenic drift and shift

A notable feature of influenza A viruses is their propensity for genetic change, which occurs by two main processes: antigenic drift and antigenic shift. Minor variations continually occur in the virus when small errors go uncorrected during replication. This process is called antigenic drift. Over time, the minor changes accumulate, creating a virus that eventually becomes foreign to the immune system. This keeps human populations susceptible to infection, leading to outbreaks of influenza each year; hence the constant need for the reformulation of influenza vaccines.[1]

Antigenic shift refers to the evolution of a new subtype of influenza A that is completely unfamiliar to the immune system. This can occur through a re-assortment process when two different viruses co-infecting the same host cell exchange gene segments, creating a new virus subtype. If the new virus contains the right mix of genes, a mix that allows it to cause severe disease and be easily transmitted between humans, it has the potential to cause a pandemic.[4] Evidence suggests that a recombination of bird and human influenza viruses created the influenza viruses responsible for the 1957–1958 and 1968–1969 human pandemics.[5,6] These viruses have genetic components from both human and avian influenza viruses.

Until recently it was believed that the H1N1 influenza virus of the 1918–1919 pandemic also developed through the re-assortment process. However, recent scientific studies indicate that all eight genes of the 1918 influenza virus were derived from avian influenza genetic material[7,8], suggesting that the virus probably developed by infecting humans and adapting directly.

INFLUENZA PANDEMICS

Influenza pandemics are unpredictable events that occur when a new influenza A virus strain spreads rapidly throughout the world, affecting large numbers of susceptible people simultaneously. Accurate records of influenza pandemics since the 16th century are available and these show that pandemics tend to occur three or four times each century.[4,9,10] The impact of pandemics can be variable, although they are all associated with excess morbidity and mortality and can lead to social and economic disruption. They generally manifest in two or three waves of illness within the community, and they can occur at any time of year[9], rather than conforming to the usual seasonal pattern for late winter.

There were three influenza pandemics in the 20th century, informally identified by the country where they were thought to have originated (although this information was not necessarily accurate). Table 1 provides a comparison between the characteristics of these pandemics and those of seasonal human influenza epidemics.

The 1918 pandemic was notorious for the exceptional severity of illness and the striking age shift in influenza mortality. It is described further in the article by Curson and McCracken in this issue of the *Bulletin*. One third of the world's population were estimated to have developed clinically apparent infection, with a case fatality rate of around 2.5 per cent.[9] In NSW, 37 per cent of the population were estimated to have been infected, with a case fatality rate of 1.3 per cent.[15] The mortality pattern for this pandemic was different from seasonal influenza epidemics in that mortality rates were greatest in persons aged under 65 years rather than those aged over 65 years. Sixty per cent of the excess deaths in Australia were in healthy adults aged 20–45 years[4] (excess deaths are the estimated number of deaths that occur above a baseline of deaths that would be expected in the absence of an influenza epidemic). While this age shift in mortality also occurred in the influenza pandemics of 1957–1958 and 1968–1969, with 34 to 41 per cent of excess deaths in persons aged under 65 years, the estimated excess mortality rates for those under 65 years of age did not ever exceed those for persons aged 65 years and over.[14]

AVIAN INFLUENZA

Avian influenza or 'bird flu' is a disease of birds caused by influenza A, which principally occurs in wild birds, most commonly aquatic birds. All birds are thought to be susceptible to influenza viruses; however, the effects differ according to the pathogenicity of the virus and the bird species infected.[4,16] Most strains of avian influenza are classified as low pathogenic as they cause little or no clinical signs in infected birds. The highly pathogenic form of avian influenza was first recognised in domestic poultry more than 100 years ago (it was known as 'fowl plague') but was not discovered to be due to influenza A until 1955. Outbreaks have been recorded in domestic bird flocks across the world.[16] More detail about avian influenza in birds is provided by Arzey in 'The risk of avian influenza in birds in Australia' in this issue of the *Bulletin*.

The current outbreak of avian influenza H5N1 (hereafter also referred to as H5N1) in domestic bird flocks and wild birds on three continents is unprecedented in its geographical spread. The strain first appeared in poultry in southern China in 1996. At the end of 2003 it caused outbreaks of influenza in poultry in the Republic of Korea, and then quickly spread to other Asian countries and most recently to Europe and Northern Africa. It is classified as highly pathogenic and has caused high rates of mortality in some bird species such as chickens, where up to 100 per cent of flocks have died within 48 hours.[4]

Human infection with avian influenza

Human infection with avian influenza viruses is rare. Prior to the resurgence of avian influenza H5N1 in December 2003, there were less than 120 cases recorded worldwide, caused by a variety of different avian influenza viruses. Figure 1 outlines the timeline for human cases of infection with avian influenza viruses.

The first human cases of avian influenza H5N1 were recorded in the Hong Kong Special Administrative Region of China in 1997 and were associated with the outbreaks of avian influenza caused by the same virus in Hong Kong poultry farms and in live markets.[4] In response to this, the entire poultry population of the Hong Kong Special Administrative Region of China was destroyed within three days, removing opportunities for further human exposure at that time. In February 2003, the virus caused illness in two people from the Hong Kong Special Administrative Region of China (one of whom died), who had recently travelled to China. Following this, in late 2003, human cases of H5N1 were recorded in Vietnam, and in 2004 inVietnam and Thailand. As of 28 September 2006, human cases have now also been recorded in Azerbaijan, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq and Turkey.[19] The number of human cases continues to rise, with the majority in recent months being reported from Indonesia.

Almost all of the currently recorded 251 human cases of avian influenza H5N1 have reported close contact with diseased flocks.[18,21] Infection is caught through direct contact with infectious secretions, blood and excreta from infected birds or contaminated poultry products.[18] Playing with poultry, plucking and preparing diseased birds, handling fighting cocks, and the consumption of raw duck blood have all been implicated.[18,21] It is notable that despite widespread exposure to infected poultry, the frequency of this illness in humans has been relatively low, indicating that the virus is not easily transmitted from birds to humans.[21]

A small number of human cases are thought to have resulted from human-to-human transmission, though this mode of transmission appears to be limited and not sustained.[21] In May 2006, the largest cluster of such cases was reported when seven members of an extended family group from Northern Sumatra became infected, resulting in six deaths.[22] The risk of health care workers becoming infected from patients has been low, even when appropriate isolation measures were not used. One case of severe illness was reported in a nurse exposed to an infected patient in Vietnam.[21]

The majority of human cases of avian influenza H5N1 have occurred in healthy young adults or children.[21] The average age of the cases infected in Vietnam between December 2003 and January 2005 was 15 years, and in Thailand, 20 years.[4] The clinical spectrum of the disease (based on the description of hospitalised patients) includes symptoms typical of influenza and, in many cases, gastrointestinal symptoms such as diarrhoea and abdominal pain.[21] Almost all patients have had clinically apparent viral pneumonia, and the illness has often progressed to respiratory failure and multi-organ failure.[4,21] The fatality rate has been high, with almost 60 per cent of cases dying. There are sporadic reports of human cases of H5N1 that have no or much milder illness.[21,23] While the frequency of cases without symptoms or with milder illness associated with this virus is uncertain, serological surveys among health care contacts of patients with documented H5N1 infection have detected only very low frequencies of non-symptomatic seroposivity.[23]

TABLE 1

CHARACTERISTICS OF SEASONAL INFLUENZA EPIDEMICS AND THE THREE INFLUENZA PANDEMICS OF THE TWENTIETH CENTURY

	Influenza virus type	Estimated rates of symptomatic infection (%)	Estimated total excess deaths worldwide	Case fatality rates (%)	Mortality pattern
Seasonal influenza epidemics	Various A & B viruses	5–20*	Up to ½ million annually*	~0.001*	Excess mortality rates are 50–200 times greater in persons ≥65 years old compared with those <65 years. However, in the first 2–7 years following a pandemic, mortality rates in persons ≥65 years old may only be 2–30 times greater than those <65 years. The majority of excess deaths (more than 85%) occur among the elderly and those with high-risk medical conditions.
Spanish influenza pandemic 1918–1919	A/H1N1	20–40	>40 million	>2.5	Excess mortality rates were 3 times greater in persons <65 years old compared with persons ≥65 years old. 99% of excess deaths occurred in people <65 years. In Australia, 60% of excess deaths occurred in healthy persons 20–45 years.
Asian influenza pandemic 1957–1958	A/H2N2	10–60	2 million	0.01–0.05	Excess mortality rates were 18 times greater in persons ≥65 years compared with those <65 years. 36% of excess deaths were in persons <65 years old.
Hong Kong influenza pandemic 1968–1969	A/H3N2	25–30	1 million	0.01–0.05	Excess mortality rates were 13 times greater in persons ≥65 years compared with those <65 years. 41% of excess deaths were in persons <65 years old.

* Mortality due to seasonal influenza epidemics varies greatly depending on the predominant type/subtype of virus circulating and, for influenza A, the time since the subtype evolved in the human population.
Data sources: Mandell et al[1]; Taubenberger and Morens[9]; Department of Health and Ageing[11]; World Health Organization[4, 12,13]; and Simonsen et al.[14]

Infection of humans by other avian influenza viruses has rarely been observed and has occurred for only a limited number of known avian influenza subtypes (see Figure 1). The clinical symptoms caused by these infections are relatively mild in humans, often in the form of viral conjunctivitis, with only one recorded death.[4]

WHAT IS THE CURRENT PANDEMIC THREAT?

The current spread of avian influenza H5N1 in domestic poultry flocks and wild birds across the world, as well as the demonstrated ability of this virus to cross the species barrier and infect humans, has lead to a high level of concern that a pandemic may develop.[21]

For a pandemic to arise, three prerequisites have been identified[4]: a new virus subtype to which the population has little or no immunity must emerge; the new virus must be able to replicate in humans and cause serious illness; and the new virus must be efficiently transmitted from one human to another.

The recent human infections of avian influenza H5N1, which is a novel human pathogen, have caused severe illness and death, demonstrating that this virus meets the first two criteria. The third criteria, however, is not met as the virus has not yet demonstrated a capacity to spread easily from human to human.

It cannot be predicted whether the current H5N1 avian influenza virus will change into a form that is easily spread from human to human. There is no historical data to suggest that previous pandemics have been preceded by outbreaks of highly pathogenic influenza in domestic poultry, and avian influenza viruses are not known to cause major human epidemics of disease.[24]

Despite having no certainty about whether the H5N1 virus is now in the process of acquiring human-to-human transmissibility, the current circumstances in relation to this virus are unprecedented.[9] The outbreak of H5N1 in birds continues to expand, leading to an ever increasing number of contacts between humans and infected birds, which in turn has seen the number of human cases continue to rise. However, a number of genetic alterations in the virus will have to occur before rapid human-to-human spread of the virus is likely to occur, and the risk of this and the timing cannot be predicted.

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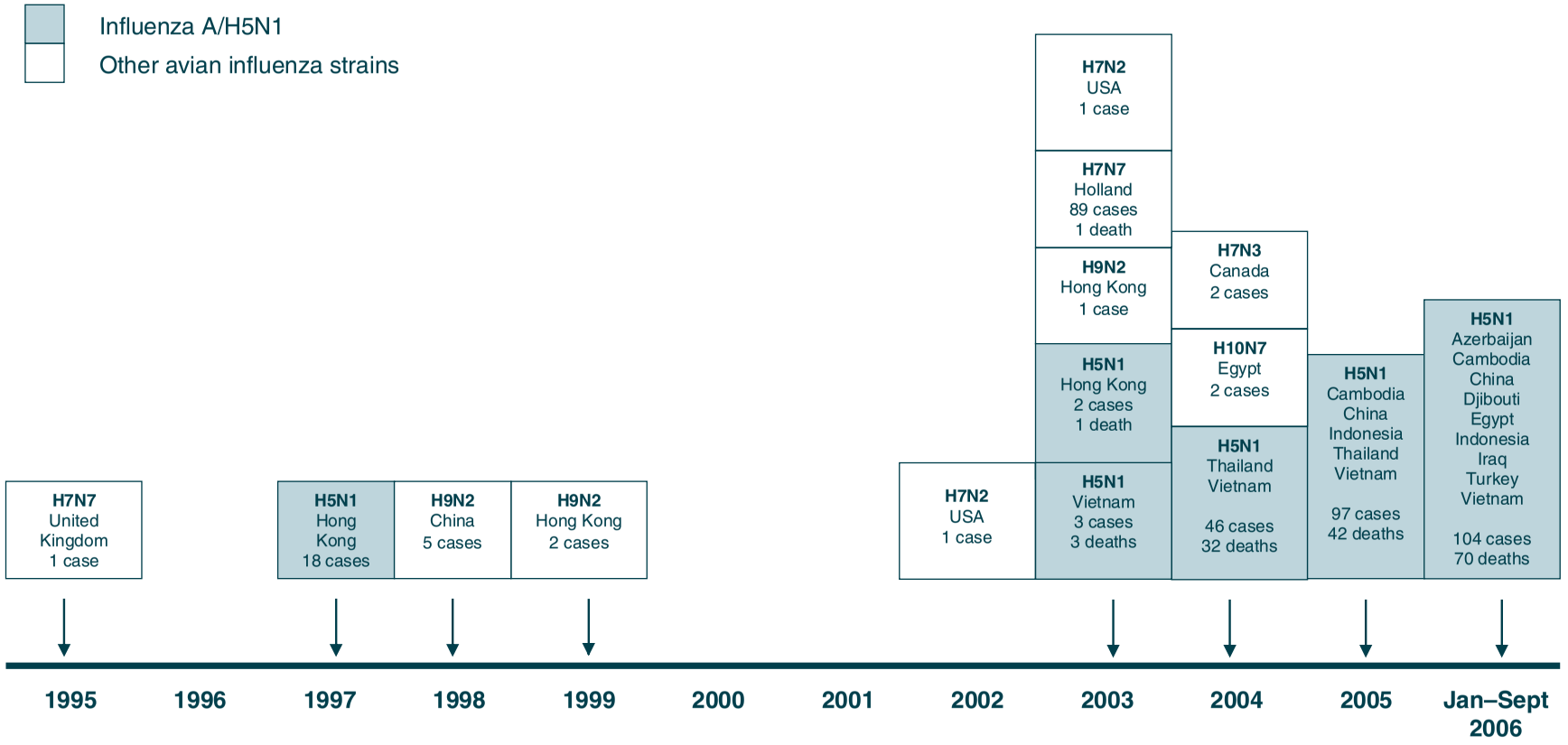
FIGURE 1

TIMELINE OF DOCUMENTED HUMAN INFECTION WITH AVIAN INFLUENZA VIRUSES, 1995 TO 28 SEPTEMBER 2006



Data sources: Fauci[17]; Wong and Yuen[18]; World Health Organization[19]; and Centers for Disease Control and Prevention.[20]

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AN AUSTRALIAN PERSPECTIVE OF THE 1918–1919 INFLUENZA PANDEMIC

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ABSTRACT

The 1918–1919 influenza pandemic stands as one of the greatest natural disasters of all time. In a little over a year the disease affected hundreds of millions of people and killed between 50 and 100 million. When the disease finally reached Australia in 1919 it caused more than 12,000 deaths. While the death rate was lower than in many other countries, the pandemic was a major demographic and social tragedy, affecting the lives of millions of Australians. This paper briefly assesses the impact of the pandemic on Australia and NSW with particular reference to the demographic and social impact and the measures advanced to contain it.

The 1918–1919 influenza pandemic remains among the greatest natural disasters of recorded history, rivalling the Black Death of the 14th century in mortality and social and economic effects. Emerging in Europe in the final months of the Great War, in the short space of a little over a year the pandemic swept around the world, killing between 50 and 100 million people.[1] Few families or communities escaped its effects and possibly 25–30 per cent of the world's population was infected with influenza in 1918–1919. There was a series of pandemic waves, the first striking in the Northern Hemisphere spring of 1918. By October the disease had reached New Zealand. Despite a vigorous policy of maritime quarantine, the disease reached Australia in early 1919. The first wave in NSW occurred between mid March and late May, affecting twice as many males as females and resulting in about 31 per cent of total deaths. The second wave peaked in June and July and was more virulent than the first—it produced a higher mortality rate, involved more females and affected far more people over the age of 50 years (Figures 1 and 2).[2]

In Australia the pandemic was a major demographic and social tragedy, affecting the lives of millions of people. In a period of six months in 1919, probably more than 15,000 died from influenza and possibly as many as two million