The global swine flu pandemic 1: exploring the background to influenza viruses

An outline of the emergence of the influenza A(H1N1)v strain and background information on previous flu pandemics from the last century
within 1–7 days (average 48 hours) after exposure. Although people with flu present with a clinical picture similar to that seen in those with the generally afebrile common cold (coryza), more severe symptoms and fever are distinguishing features of flu (Box 1).

Very young children, women in late pregnancy, those with compromised immune systems and older people are often particularly vulnerable to severe disease during seasonal epidemics of flu, while young adults are often more severely affected during flu pandemics.

In the current UK pandemic, children under five and those aged 5–14 years are the groups predominantly affected, with those over 65 continuing to show much lower rates (HPA, 2009).

**ORTHOMYXOVIRUSES**

Influenza viruses belong to a small family of viruses known as orthomyxoviridae. Three of the five members (genera) of this family can infect humans: influenza viruses type A, B and C.

They are similar in overall structure, and are classified according to the variations in their protein composition. Type A viruses are further classified by subtype based on their surface glycoproteins (types B and C are not) and influenza A subtypes and type B viruses are further classified by strains.

In addition to humans, type A viruses infect a wide range of animals, including birds, pigs and horses, while type B virus generally only infects humans (and sometimes seals). As influenza C virus differs significantly from type A and B and generally only causes mild afebrile respiratory symptoms, usually in children (Sutherland, 2002), it will not be discussed further in this article.

Influenza A and B viruses both cause seasonal epidemics but only influenza A viruses have the capacity to cause pandemics (Nguyen-Van-Tam and Sellwood, 2007).

**Influenza A viruses**

Type A virions are generally spherical particles (80–120nm in diameter) although filamentous forms (up to 300nm in length) can occur.

In the genome, genetic material is organised in eight separate segments of RNA (ribonucleic acid), each containing one or two genes.

The outer surface of the virion consists of a lipoprotein envelope (lipid bilayer) which is partially derived from the host cell plasma membrane, which the virion acquires when budding out from a previously infected cell (Collier and Oxford, 2006).

Two types of surface glycoprotein spikes (antigens) project from the viral envelope: haemagglutinin (HA) and neuraminidase (NA) (Fig 1). Receptor binding sites on the HA enable the virion to recognise and attach to specific receptor molecules on the surface of respiratory tract host cells, allowing it to fuse with the cell membrane and infect the host cell.

Following viral replication, NA enzymatically facilitates the release and dispersal of new virions as they exit infected cells (Tortora et al, 2007).

**Influenza A virus subtypes and strains**

The antigenic variation in viral envelope glycoproteins (HA, NA) is used to determine influenza A subtypes. There are 16 HA subtypes and nine NA subtypes (Tortora et al, 2007). The different forms of the antigens are assigned a number, for example, H1–H16 and N1–N9. Only H1, H2, H3 and N1 and N2 are known to infect humans or cause serious outbreaks (Collier and Oxford, 2006).

Viral strains are described according to:

- Type (A, B or C);
- Host of origin such as swine or bird (if isolated from a human, host of origin is not given);
- Place of original isolation;
- Strain number;
- Year of isolation;
- Antigenic subtype (HA and NA).

For example, the WHO recommended that the 2009–2010 northern hemisphere trivalent influenza vaccine contain:

- A/Brisbane/59/2007-like(H1N1);
- A/Brisbane/10/2007-like(H3N2); and
- B/Brisbane/60/2008-like (B/Victoria lineage) viruses (Centers for Disease Control and Prevention, 2009a).

Influenza viruses selected each year for vaccine production are cultured in embryonic hens’ eggs then chemically inactivated and purified.

**Drifting and shifting**

Influenza viruses are adept at evading immune surveillance (the body’s mechanism to prevent reinfection with the same strain). They are dynamic and continuously evolving over successive viral generations as a result of natural selection. These genetic changes may be small and continuous (antigenic drift) or large and abrupt (antigenic shift).

**Antigenic drift**

The surface glycoproteins (HA, NA) are antigenic, that is, they provoke immune responses.

Activated T-lymphocytes provide programming instructions to B-lymphocytes. These then manufacture billions of y-shaped antibodies designed to exclusively recognise and combine with the unique strain that has infected a person (or contained in a vaccine).

Surface glycoproteins, particularly HA, frequently undergo minor antigenic changes as a result of random replication errors. This happens because influenza genes, which are composed of RNA, are more prone to small point mutations that occur during viral replication than genes that are made of DNA. When the HA gene mutates during replication, the surface glycoprotein HA that it encodes also changes and a new viral strain is produced.

As antibodies are strain-specific, when the new strain infects a person, antibodies previously made in response to another strain will no longer recognise the new shape of HA and cannot efficiently neutralise them. This slow but constant antigenic drift is an inherent feature of influenza A and B viruses. It is the reason why the viral strains contained in the flu vaccine are adjusted each year to ensure they are appropriate for that year’s prevalent strains.

**Antigenic shift**

In comparison to drift, antigenic shift is a more abrupt and major change that can occur only in influenza A viruses. It is possible for a host cell to be simultaneously infected with two or more
different influenza A viral strains, originating from human and/or animal sources (for example, pigs or birds). The segmented genome of these viruses makes it relatively easy for genes from different strains to mix together in an infected cell and, through recombination (genetic reassortment), form novel hybrids with a genetic composition different from influenza A viral strains in general circulation.

Pigs are thought to be ideal mixing vessels for the reassortment of human, swine and avian influenza A viruses. They probably play a crucial role in the emergence of new strains which can start a global pandemic (Ma et al, 2009). Reassortment can also occur in a human who is infected with both human and animal influenza A viruses.

As antigenic shift involves the reassortment of larger sections of genetic information than in the relatively minor point mutations responsible for slow antigenic drift, it is less likely to give rise to new biologically successful influenza A subtypes.

However, when they do emerge, these new subtypes are the basis of a potential pandemic as there will always be large populations of immunologically naive humans who will be susceptible to the new subtype (Murray et al, 2005).

**FLU PANDEMICS**

Outbreaks of flu can arise in one geographical area then rapidly spread widely, causing simultaneous epidemics in surrounding regions and countries. This phenomenon is known as a pandemic (Box 2). Globalisation and the ease of population movements mean that transnational flu pandemics can spread with breathtaking speed, resulting in a global pandemic affecting tens of millions of people.

**PANDEMICS IN THE 20TH CENTURY**

During the last century, there were three well documented flu pandemics. Each was caused by the emergence of a new influenza A subtype and distinguished by: the highest death rates occurring in younger people; successive pandemic waves; and greater transmissibility than seasonal flu (Miller et al, 2009).

**Spanish flu 1918–1919**

The first and most terrible pandemic was the infamous “Spanish flu”, now known to have been caused by a novel strain of the influenza A subtype H1N1.

After initial outbreaks in military camps in the US in spring 1918, American Expeditionary Force personnel carried the infection to France during the closing months of the first world war, where it quickly spread throughout Europe (Potter, 2001).

By early summer, Britain and other European countries experienced the first, relatively mild, pandemic wave followed by an overwhelmingly lethal second wave that “scorched its way around the globe in the northern autumn of that year” (Johnson and Mueller, 2002).

The final wave occurred in 1919. By the end of this global catastrophe, 50% of the world’s population had been infected, half of whom experienced clinical disease (Potter, 2001) and 50–100 million people had died (Johnson and Mueller, 2002).

In this pre-antibiotic era, the cause of death for most was bacterial pneumonia secondary to influenza virus induced aberrant immune responses (Brundage and Shanks, 2008).

**Asian flu 1957–1958**

Emerging out of the Yunnan Province in China in February 1957, the first wave of the “Asian flu” pandemic quickly spread throughout Asia then around the world. North America and Europe experienced their first pandemic wave that autumn with a second wave early in 1958 (Potter, 2001). This pandemic was caused by a new strain of the influenza A subtype H2N2, containing a combination of genes from human and avian influenza A viruses.

In 1968 another hybrid influenza A strain of subtype H3N2, incorporating genes from human and avian viruses, evolved from A/H2N2 as a result of an antigenic shift and caused the “Hong Kong flu” pandemic. An estimated two million people died during the Asian and Hong Kong flu pandemics, again mainly as a result of viral or secondary bacterial pneumonia (Potter, 2001). By the early 1950s, antibiotics and bacterial vaccines were available to prevent or treat bacterial pneumonia in many, although they arrived too late to exert their full effect on mortality rates (WHO, 2005).

**CURRENT PANDEMIC THREATS**

Flu pandemics occur at regular intervals and it has now been 40 years since the last one.

Currently there are three subtypes of influenza A virus circulating in the human population: H1N1, novel swine origin H1N1 and H3N2. The virus that caused the 1957–1958 Asian pandemic (H2N2) is no longer in circulation (CDC, 2009b).

Within the period of modern virology, human flu pandemics have only ever been caused by viruses of the H1, H2 or H3 subtypes (Kilbourne, 2006). In between pandemics, new influenza A strains have been emerging and two of these are now causing particular concern.

**Bird flu**

All subtypes of influenza A viruses can be found in birds; those that occur mainly in birds are referred to as avian influenza viruses.

Migratory aquatic birds, principally wild ducks, are the natural reservoir of these viruses. These waterfowl are like Trojan horses, able to carry the viruses without being harmed by them but transforming them into a pathogenic form and spreading them to flocks of both wild and domestic birds (Gilbert et al, 2008).

Infection in birds causes a range of symptoms, from mild illness to highly contagious and rapidly fatal diseases resulting in severe bird epidemics affecting, for example, domestic flocks of geese, turkeys, chickens and other poultry.

Avian influenza A viruses are further classified as either “low pathogenic” or “highly pathogenic”. Infection with highly pathogenic A influenza (HPAI) viruses is associated with high mortality in poultry.

During the last decade, continuing genetic reassortments of avian influenza viruses from goose and duck reservoirs in Asia led to the emergence of H5N1, H7N9, H7N7, H9N2, H7N3 and H8N3. In 2006 a new strain emerged from China, the H9N2, which became the first avian influenza virus capable of instructing humans with clinical symptoms (WHO, 2007).

**Box 2. Pandemic Criteria**

For influenza A virus to be capable of causing a pandemic:

- It must represent a new A subtype, the HA of which is not related to that of its immediate (pre-pandemic) predecessor (such as H2), or it must be entirely novel to humans (such as H5);
- There must be little or no pre-existing immunity in the population;
- It needs to be able to infect people and to be efficiently transmissible from person to person and spread widely;
- It must cause significant clinical illness in a high proportion of those infected.

Sources: Nguyen-Van-Tam and Sellwood (2007); Cabinet Office and Department of Health (2007)
to the emergence of highly pathogenic avian influenza A subtype H5N1. Identified in 2003, this virus caused epidemics of flu among flocks of birds in other countries in Southeast Asia, parts of Africa and eastern Europe (Eurosurveillance, 2006).

Although mainly only infecting birds, the current genotype of HPAI H5N1 can infect humans and, as of May 2009, 431 confirmed human cases of avian influenza (H5N1) (including 262 deaths) in 15 countries had been reported to the WHO (2009). Most of these human cases have involved direct contact with sick or dead poultry.

Currently, human-to-human transmission of H5N1 is rare, limited and unsupported. However, if transmission efficiency increases, there is potentially grave pandemic danger.

### Swine flu

In 1931 the influenza A(H1N1) virus was first discovered in pigs and two years later in humans. Seroepidemiological studies then linked this subtype to the viral cause of the 1918–1919 Spanish flu pandemic, after which influenza A(H1N1) continued to circulate in both pigs and humans (Taubenberger and Morens, 2006).

During the 1957 Asian flu pandemic, the direct influenza A(H1N1) viral descendants of the 1918 pandemic strain disappeared from humans (but probably not from pigs). They then re-emerged inexplicably in 1977 and have been circulating in humans ever since (Taubenberger and Morens, 2006).

In March–April 2009, a novel swine origin influenza A(H1N1) virus, now referred to as influenza A(H1N1)v, was identified as the cause of flu outbreaks in the US, Canada, Mexico and elsewhere. This new strain has a genetic composition that has not been seen before. It consequently threatens populations in all countries as no one will have developed immunity to it (Novel Swine Origin Influenza A (H1N1) Virus Investigation Team, 2009). By the second week of August, 219,681 laboratory confirmed cases had been reported worldwide, including 1,882 deaths (HPA, 2009).

Influenza A(H1N1)v is being transmitted with ease from person to person and an increasing number of cases are being identified worldwide (CDC, 2009c). Immunisations with vaccines containing the influenza A(H1N1) subtype will not protect against pandemic (H1N1) 2009. Although the UK and other governments are rushing an influenza A(H1N1)v vaccine through production, it will be later this autumn before the first batches are available.

Treatment is available. This strain is susceptible to the two main antiviral drugs: oseltamivir (Tamiflu) and zanamivir (Relenza) (CDC, 2009d).

Influenza A(H1N1)v can spread efficiently and rapidly among countries and it is not yet possible to visualise how severe this pandemic will be.

In the first pandemic wave that we are now experiencing in the resource rich developed world, illness associated with infection is generally self limiting and uncomplicated. However, there have been a substantial number of cases of severe disease and deaths (CDC, 2009c). As the pandemic sweeps into the resource poor developing world, it may be an entirely different and extremely lethal situation.

In addition, pandemic waves tend to increase in lethality and what we are experiencing now may not be what we encounter during the impending second wave expected this autumn.

### REFERENCES


