The origins of pandemic influenza – a perspective

Following the isolation of the first human influenza virus in 1933, there have been two Type A influenza pandemics. One was the Asian influenza pandemic in 1957, when an H2N2 virus replaced the H1N1 viruses then circulating, and the other was in 1968 when the Hong Kong H3N2 virus replaced the H2N2 viruses. The H1N1 virus that re-emerged in 1977 did cause a worldwide epidemic (or pandemic) but this virus is not considered by many people to be a true ‘pandemic’ virus.

Where did these viruses come from? How did they arise? And how might future pandemic influenza viruses originate? The short answer is that we don’t have the faintest idea. The only way we might be able to predict how future flu pandemics could originate would be if we knew how past pandemic viruses have formed. It is claimed by many people that mutations in avian flu viruses or re-assortment between avian flu viruses and human flu viruses (preferably in pigs) could give rise to new pandemic viruses, but there is no direct evidence that either of these mechanisms has ever operated.

Consider the facts. When Rob Webster and I started to think about the origins of the ‘new’ Hong Kong virus that arose in 1968, the only information we had was that the haemagglutinin of the Hong Kong virus differed considerably, antigenically, from that of the ‘old’ Asian viruses, but that the two viruses shared a common neuraminidase. The general opinion was that the ‘new’ virus had arisen by mutation from the ‘old’ virus. The existence of ‘bridging strains’ was even proposed.

After we eliminated the effects of the common neuraminidase and the carbohydrate host antigen on cross-reactions between the Asian and Hong Kong strains, it became clear that there was no cross-reaction whatsoever between the haemagglutinins of the two viruses. Comparison of the sequences of the two haemagglutinins (by peptide mapping, the only technique available at that time) showed that the amino acid sequences of H2 and H3 were so different that the Hong Kong virus haemagglutinin could not have arisen from the Asian virus haemagglutinin by simple mutation over such a short period of time; it had to have come from somewhere else.

It was already known that the Hong Kong H3 haemagglutinin was similar, antigenically, to the haemagglutinin of certain duck and horse influenza viruses and, when we compared, again by peptide mapping, the haemagglutinin of Hong Kong and Duck/Ukraine influenza viruses, it was obvious that they were closely related. This meant that the Hong Kong/68 virus was a hybrid virus, having the haemagglutinin from an animal virus and the neuraminidase from one of the old human Asian virus strains.

This finding was confirmed when more sophisticated sequencing methods became available. These also showed the Asian H2N2 virus to be a hybrid, with haemagglutinin, neuraminidase and PB1 genes from an avian virus and the other genes from the old human H1N1 strains. The PB1 gene of Hong Kong virus was also shown to have been derived from an avian influenza virus.

So the Asian H2N2 and the Hong Kong H3N2 pandemic influenza viruses were certainly hybrids, with genes from both human and avian influenza viruses. But that is as far as it goes. We have no idea how these hybrids were formed. The most obvious way was by re-assortment between human and avian viruses, possibly in a pig, an animal in which both viruses can replicate. This idea has matured over the years, as Gillian Air once remarked, like a fine wine, gradually gaining acceptance as an established fact without any new evidence being added.

Why should one doubt that simple re-assortment between human and avian influenza viruses caused the 1957 and 1968 pandemics? There is one very good reason. Thirteen haemagglutinin subtypes, apart from H1, H2 and H3, have now been discovered in nature and any one of these would have the potential to cause a pandemic virus by re-assortment with a human flu. Most, if not all, of these haemagglutinin subtypes exist in aquatic birds in South East China and the opportunities for mixed infections between avian and human viruses, leading to new re-assortant influenza viruses, must be enormous.

But no new re-assortant human influenza virus has emerged in nearly 40 years. Why? Webster showed many years ago that re-assortment between influenza viruses occurred easily in animals under simulated natural conditions of transmission. So why not between human and avian viruses in nature? It seems that there may be more to be discovered about the ecology of Type A influenza, and the re-emergence of the H1N1 virus in a ‘normal’ year, some 2,3000 Australians die from influenza-related illnesses.

Graeme Laver
3047 Barton Highway,
Murrumbateman NSW 2582
Tel: (02) 6227 0061
E-mail: graeme.laver@bigpond.com

In a ‘normal’ year, some 2,3000 Australians die from influenza-related illnesses.
1977 may give a clue. This virus was first isolated in Anshan in northern China on 4 May 1977. It spread along the railway lines and, after 9 months, reached Hong Kong and spread to the rest of the world where it became known as ‘Russian flu’. 

This virus was almost identical, in all its genes, with a virus that had been isolated in 1950. Where had it been hiding, frozen in time, for 27 years? The usual explanation is that the Chinese were carrying out live virus vaccine trials and the virus escaped. There is not a shred of evidence for this, in fact what evidence there is says this did not happen. We do not know where H1N1 was hiding. We do not know where the H2N2 virus that disappeared in 1968, when the H3N2 virus appeared, might be hiding. We do not even know if viruses from past pandemics are still hiding somewhere waiting for a chance to re-assort, by some unknown mechanism, with a human influenza virus and cause a pandemic.

Currently there is a fear that the lethal H5N1 avian influenza virus that has killed millions of chickens, some other mammals and so far 134 people, will acquire the ability to spread easily in humans by mutation or re-assortment. At the time of writing (August 2006) this has not happened and some say it will never happen. If it does, the resulting pandemic might eclipse that of 1918-19, in which “Spanish Influenza” killed 20 to 40 million people world-wide. A series of extraordinary and painstaking experiments have now lead to the complete sequence of all of the genes of the extinct1918 virus, it has been almost completely re-constructed and the three-dimensional structure of one of its proteins (the haemagglutinin) has been determined.

However, despite this enormous amount of work, there is still no clue as to the origin of the 1918 virus or what caused its extreme virulence. Statements have been made many times, mainly in the media, that the 1918 virus was a lethal avian influenza virus that suddenly jumped from birds to people. There is not a scrap of evidence to support this idea. Although the virus probably had its origin in birds at some time in the past, to maintain that such an event happened in 1918 and to imply that therefore the H5N1 “bird flu” virus might do the same, is as regrettable as it is irresponsible.

In conclusion, we can be certain that an influenza pandemic will occur at some time in the future, caused by a virus with a haemagglutinin to which no-one in the world has any immunity. Such a virus might be formed by mutation of an avian influenza virus or by re-assortment between avian and human influenza viruses. Or it might emerge by a so far undiscovered mechanism. Which option is correct, only time will tell.

**Pandemic planning: the Australian response**

If the world comes face to face with a rapidly spreading novel virus like the one that emerged in 1918, then the rapid detection of human to human transmission, early and intensive implementation of containment measures, and the development and deployment of effective vaccine are our best strategy for responding.

Since 2003, the Australian government has committed over A$600m to pandemic preparedness. This includes A$156m to the Asian-Pacific region to develop capacity for response. The Australian health response plan is detailed in the Australian Health and Management Plan for Pandemic Influenza (AHMMPI). This document is aimed at the general public. It is accompanied by several technical annexes covering clinical care, infection control, laboratory guidelines and also management in particular settings such as primary care. A ‘communications strategy overview’ details important considerations and actions for each phase of an influenza pandemic. The AHMMPI, the annexes (as they are finalised), the communications strategy and additional information are available on the Department of Health and Ageing website, www.health.gov.au

**Key initiatives**

In addition to the regional initiatives and the planning process, the Australian government has devoted significant resources to:

- Establishing the national medical stockpile, which has one of the largest per capita supplies of influenza antivirals in the world, as well as personal protective equipment and other essential health supplies to deploy during an influenza pandemic.
- Strengthening Australia’s communicable disease surveillance networks and laboratory capacity.