Published in *Health* in 2011 by Future Leaders (www.futureleaders.com.au)

Influenza

Anne Kelso

Why influenza matters

The term 'influenza' is often used loosely to describe respiratory illness caused by a wide range of viruses, including respiratory syncytical virus, parainfluenza viruses, rhinoviruses and adenoviruses as well as influenza viruses themselves. Although all of these viruses can cause significant disease, true influenza has a special place in the world of communicable diseases for two reasons. First, seasonal influenza imposes a substantial health and economic burden every year and is thought to be responsible for about 250,000–500,000 deaths per annum around the world. Second, and more importantly, new influenza viruses emerge sporadically and cause global pandemics of unpredictable timing and impact. The most severe of these in modern history, the Spanish influenza pandemic in 1918–1919, is estimated to have killed 50 million people or 2.5% of the world's population over a few months. As far as we know, this was the most severe pandemic of any infectious disease to have affected mankind over such a short period.

In principle, both sorts of influenza can be prevented by vaccination. However, the diversity and changeability of influenza viruses make this complex and challenging.

Seasonal influenza viruses and their interaction with human hosts

Viruses are extremely simple microorganisms, often comprising just a few genes and proteins. The viral genes contain the

blueprint for production of the minimum number of proteins required for the virus to enter cells of its animal host and exploit the machinery of those cells to make thousands of new viruses; these are then released for transmission to another host. Influenza viruses contain just eight genes which code for up to 11 different proteins. For comparison, the human genome contains approximately 23,000 protein-coding genes.

Two types of influenza virus, types A and B, cause significant illness in humans.[1] The genetic material of both types is single-stranded RNA, which is less stable than the double-stranded DNA of animals and prone to error when it is copied to make new viruses. As a result, random changes (mutations) occur frequently during the production of new influenza viruses, and those viruses with mutations that offer them some advantage over their 'parent' will become dominant.

The main selective force on the evolution of human influenza viruses is our immune response against them. Infection with influenza viruses activates the human immune system to make antibodies that can bind to the two major proteins on the surface of the virus (haemagglutinin [HA] and neuraminidase [NA]). As these proteins are essential for the infection of the cells lining the human nose, throat and lungs and the escape of newly-formed viruses from the infected cells, antibodies that interfere with these functions can halt the infectious cycle. When someone is infected with an influenza virus for the first time, it takes 1–2 weeks for them to produce enough antibody to control the infection. By this time, large amounts of new virus will have been shed through sneezing, coughing and touch, and other people may have been infected. However, when this person is exposed to the same virus a second time, the antibodies stimulated by the first infection will prevent, or at least reduce, the ability of the virus to cause a second infection.

If influenza viruses did not mutate, influenza would be like smallpox, measles, chickenpox, mumps and polio. These are all diseases caused by relatively stable viruses against which

the first infection stimulates antibodies that generally provide lifelong immunity. In the case of influenza, however, antibodies against the first infecting virus provide a selective force so that viruses whose surface proteins are bound less strongly by these antibodies have a survival advantage. Over many cycles of human infection, a new line of influenza viruses emerges against which our antibodies provide only limited protection. This process is called antigenic drift, and it is the main barrier to the prevention of seasonal influenza, either by prior infection or by vaccination.

Seasonal influenza is so-called because it mainly occurs in winter in temperate climates. The reasons for this seasonality are not fully understood but they probably relate to environmental conditions that help influenza viruses to survive outside the body and spread in aerosols, such as low absolute humidity, as well as human factors, such as crowding in winter. In Australia, the influenza season typically lasts for 8–12 weeks, starting any time between about May and August. Both the timing and the severity of the influenza season are unpredictable from year to year and both also vary from country to country in the same hemisphere and even from state to state in Australia. Some people may experience mild or asymptomatic influenza infection but the normal clinical symptoms of fever, cough, headache, aching muscles and fatigue can be severe. The very young and the very old are most at risk of hospitalisation and death from seasonal influenza, often associated with secondary bacterial infections of the lungs, reflecting the immaturity of the immune system of infants and the progressive decline in immune competence with ageing.

Influenza A viruses and their non-human hosts

Whereas type B influenza viruses only infect humans, the natural hosts of influenza A viruses are actually water birds, such as wild ducks, geese and swans. Type A viruses are classified into subtypes based on differences in their HA and NA proteins (further abbreviated as H and N) and, while only four subtypes are known to have ever circulated in humans (H1N1, H1N2,

H2N2 and H3N2), birds are infected by a much larger number of subtypes. Most of these viruses cause subclinical infection in birds but there are a few, notably the 'highly pathogenic avian influenza' H5N1 virus ('bird flu'),[2] as well as H7N7 and H9N2, which can cause severe illness.

Although H5N1 is not generally lethal for ducks, it can devastate domestic chicken and turkey flocks in hours. It therefore causes great economic hardship in many developing world communities where poultry flocks in villages and backyards are a major source of food and income. This virus is occasionally transmitted from sick poultry to humans in whom it also causes severe illness.[3] Since 2003, the World Health Organization (WHO) has confirmed about 500 human cases of H5N1 infection, with about 300 deaths, mostly in Vietnam, China, Indonesia and Egypt. The true numbers are likely to be much higher. Although hundreds of millions of poultry have died from this virus through illness or culling and some countries have worked hard to eliminate it, H5N1 is now irreversibly established in several countries, notably Indonesia and Egypt. Fortunately, this highly virulent virus has not yet acquired the ability to spread easily between humans and only short chains of human-to-human transmission have been recorded.

Some other influenza A viruses have adapted to non-avian species. One is the H3N8 equine influenza virus, first detected in the 1960s and now established in horses in most countries of the world. Since 2004, H3N8 viruses have also been found in dogs in the United States after apparently jumping from horses into racing greyhounds and then into various domestic breeds across many states. Australia had been free of equine influenza until August 2007 when a breach of quarantine of imported race horses in Sydney led to an explosive epidemic in New South Wales and Queensland.[4] Horse movement and racing, equestrian and other events were halted in the eastern states for several months at an estimated cost of about AU$1 billion to government and affected industries. Amazingly these

interventions were successful and the last case of infection was detected just 6 months after the first. No human cases of H3N8 infection were detected during the equine influenza outbreak in Australia and, while transmission to dogs did occur, it was not sustained. Australia is now free of this virus again.

From the point of view of human health, however, the most important non-human host of influenza A viruses is the pig, for reasons outlined below.

The origin of influenza pandemics

In addition to the high mutation rate noted above, the genetic material of influenza viruses has another property that enables the creation of radically new viruses. The viral RNA exists in eight separate pieces, each coding for one or two of the 11 viral proteins. As a result, when two different influenza A viruses infect the same cell and their eight genes are copied in very large numbers, new virus particles can be formed that contain a genetic mixture derived from both parents.[1] If, for example, a human was infected simultaneously with an avian H7N7 virus and a human H1N1 virus, some of the new viruses might carry the H7 gene of the avian virus along with genes of the human virus (antigenic shift). If the new virus was able to infect and transmit between humans, the general population would be highly vulnerable to a global epidemic (pandemic) because our antibodies against earlier human influenza virus infections or vaccines do not recognise H7.

Such gene shuffling (or reassortment) between avian and human influenza viruses within a human host appears to be extremely rare, at least partly because avian influenza viruses cannot easily infect cells of the human nose and throat. Pigs, on the other hand, can be readily infected by both avian and human influenza A viruses and therefore provide a 'mixing vessel' in which reassortment between avian and pig- or human-adapted viruses can occur. For this reason pigs are now thought to play a central role in the formation of pandemic viruses.

Influenza pandemics have probably occurred throughout human history. One historical analysis has suggested that there were at least 13 influenza pandemics in the 500 years before 2009, at intervals ranging from under 10 to as long as 150 years.[5] With the discovery and isolation of influenza viruses in the 1930s, we can say with certainty that there have been four pandemics in the last century. They occurred at irregular intervals and displayed markedly different severity. The Spanish influenza pandemic of 1918–1919 was caused by an H1N1 virus and killed an estimated 50 million people.[6] The Asian influenza pandemic of 1957, caused by an H2N2 virus, killed about 2 million people. The Hong Kong influenza pandemic of 1968–1969, caused by an H3N2 virus, killed about 1 million people. Finally, the 2009 H1N1 'swine flu' pandemic is thought to have killed fewer people than the previous three pandemics, although estimates derived by comparable statistical techniques are not yet available; while infection with the pandemic virus has been confirmed by laboratory testing in more than 18,000 people to date, most of the people infected and dying from this virus live in developing countries without access to such testing.

It is a common feature of these pandemics that the age distribution of infection was younger than is generally observed for seasonal influenza. This was marked in 2009 when, in Australia, the median age of confirmed H1N1 2009 infection was 21 years and the median age of death was 53 years, compared with 83 years for seasonal influenza in preceding seasons.[7] In Australia and many other countries in 2009, the influenza pandemic also converged for the first time with the modern epidemics of asthma, obesity and type II diabetes.[8] About two-thirds of severe and fatal cases of influenza in 2009 were associated with these or other predisposing health conditions. Significant numbers of otherwise healthy young people, including a disproportionate number of pregnant women, also died from infection with this generally 'mild' pandemic virus.

With recent advances in genetic analysis, it has been realised that the viruses responsible for these pandemics were all formed through the mixing of influenza viruses from different animals. Their origins and history can never be fully known, but analysis of the 2009 pandemic virus indicates that it was formed through a complex series of reassortments between avian, swine and human influenza viruses that took place over more than a decade.[9] The final mixing event that created the gene combination of the new pandemic virus probably occurred in late 2008 or early 2009, probably in a domestic pig and probably in Mexico. Although the new virus was not recognised until late April, the first known human case was found retrospectively — a Mexican boy whose symptoms started on 24 February 2009. It then took two months for the new virus to reach New Zealand, perhaps another week or so to reach Australia, and a little over four months to reach every continent of the world.

A feature of pandemic viruses is that they have an HA protein (and sometimes also an NA protein), which was previously unfamiliar to the human immune system. Consequently, the entire human population lacked protective antibodies that could prevent infection or reduce its impact. For this reason, even in 1918, the new virus apparently only took a few months to reach most parts of the world by ship. Some remote communities — for example, in the Pacific Islands — were spared for several years, but otherwise people were only protected if their countries imposed strict maritime quarantine, preventing disembarkation from arriving ships until all influenza cases had died or recovered. Today, complete closure of borders is essentially impossible and the speed and intensity of air travel ensure that the rapid spread of new influenza viruses is inevitable.

After the succession of H1N1, H2N2 and H3N2 pandemics in the 20th century, few had predicted that the next pandemic would be caused by an H1N1 virus, particularly as descendents of the 1918 H1N1 virus had circulated in humans

for most of the intervening period. It has therefore been fascinating to learn that the H1N1 pandemic virus that emerged from pigs in 2009 actually looks quite similar to the 1918 virus.[10] Although the 2009 virus is not nearly as virulent, its HA is well recognised by antibodies in the blood of people who were born before about 1935, probably because they had been exposed to the 1918 virus or its less dangerous descendents in the early years after that pandemic. In the many years since 1918, however, the H1N1 virus had undergone so many mutations that the antibodies of younger people who had only been exposed to later H1N1 strains offered no protection against the 2009 pandemic virus. This is the main reason that the 2009 pandemic was a disease of the young. In fact, older Australians experienced lower rates of influenza in 2009 than in previous years.

How does a pandemic end? Pandemic viruses cause unusually high numbers of infections when they first emerge. For example, data from New Zealand suggest that 18% of its population and one in three people under 20 years of age had been infected with the 2009 H1N1 virus by early 2010.[11] The situation was similar in Australia.[12] The consequence of such widespread infection is that a large proportion of the community is then immune to the virus. In Australia, population immunity has been further enhanced by widespread vaccination against the pandemic virus, either with the pandemic vaccine in late 2009 or the seasonal vaccine (which contained the 2009 pandemic virus) in early 2010. At some point this level of population immunity becomes so high that spread of the virus from person to person is interrupted and the pandemic fizzles out. Since mid-2010 it has been clear that the pandemic virus of 2009 is behaving like a seasonal influenza virus in most parts of the world, causing fewer infections that are largely restricted to the winter months. As a result, the WHO announced on 10 August 2010 that the world had entered the post-pandemic phase and, on 1 December 2010, the Minister of Health announced that Australia was now

returning to the pandemic alert phase that existed before the emergence of the 2009 H1N1 virus. The alert phase reflects concern that the highly pathogenic avian H5N1 virus may yet acquire the ability to transmit between humans and cause a pandemic. The fact that we have recently experienced one influenza pandemic does not mean that we are protected from another pandemic caused by a different influenza A subtype.

Keeping track of influenza

The lag of at least two months between the emergence of the 2009 H1N1 virus in Mexico and its first identification in two Californian cases in April by the US Centers for Disease Control and Prevention (CDC) in Atlanta reminds us that, even today, most countries of the world lack the systems and resources to detect the emergence of a new virus. The importance of global surveillance for new influenza viruses was recognised by the WHO in the late 1940s, mainly because of concerns that the world was at risk of another devastating pandemic like that of 1918. Therefore, just as the WHO was itself being formed in 1948, the first steps towards global influenza tracking were taken with the creation of the WHO World Influenza Centre at the National Institute of Medical Research (NIMR) in London.[13] Soon after, the WHO established the Global Influenza Surveillance Network (GISN) — a unique international collaboration that today comprises 136 WHO National Influenza Centres in 106 countries, 5 WHO Collaborating Centres for Reference and Research on Influenza (working primarily on human influenza viruses), another WHO Collaborating Centre working on animal influenza viruses, 11 H5 Reference Laboratories and 4 national regulatory laboratories involved in monitoring influenza vaccines.

The establishment of the WHO Collaborating Centres (WHO CCs) has mirrored the growth and geopolitical development of the whole of GISN. The first two were the influenza centres at NIMR and CDC, designated as WHO CCs in 1957 and 1956 respectively. The next was a regional

influenza reference laboratory set up in 1952 by the former Commonwealth Serum Laboratories (now CSL Limited) in Melbourne and designated as a WHO CC in 1992; this centre is now hosted by the Victorian Infectious Diseases Reference Laboratory (VIDRL, a division of Melbourne Health). The National Institute of Infectious Diseases in Tokyo followed in 1993, and then, in October 2010, the Chinese National Influenza Centre in Beijing was designated as the fifth WHO Collaborating Centre for Reference and Research on Influenza. Both the WHO National Influenza Centres network and the WHO CCs began predominantly in the industrialised Western world but with time have spread to encompass the Asia-Pacific region and Latin America. Africa remains the continent least well covered by GISN but important advances are now being made there, as in other parts of the developing world, with the support of the WHO, the US CDC and other international agencies involved in capacity building.

The major technical roles of GISN are to monitor the burden of disease due to human influenza, to monitor antigenic drift and other changes (such as the emergence and spread of resistance to antiviral drugs) in seasonal influenza viruses, to obtain suitable viruses for updating influenza vaccines, and to detect and obtain new influenza viruses infecting humans, especially those with pandemic potential.

The performance of these roles is a partnership between the WHO National Influenza Centres (NICs) and the WHO Collaborating Centres. The NICs collect data on influenza outbreaks and epidemics in their country and undertake the initial analysis of influenza viruses in throat swabs and other clinical specimens for the presence of influenza viruses. Based largely on information provided by the NICs, the WHO provides regular reports on its website on the circulation of influenza viruses around the world throughout the year. The NICs and other laboratories then send representative viruses, and any that look unusual, to one of the WHO CCs where

they undergo more detailed characterisation to detect antigenic drift (or, much more rarely, shift), antiviral drug resistance and other properties. By comparing the data obtained for the many thousands of influenza viruses analysed each year, the WHO CCs can identify the major lineages of influenza A and B viruses circulating in humans and detect the emergence and spread of new variants. A WHO report of these findings is published every six months, based on the analyses performed at the WHO CCs.

In addition to monitoring the evolution of influenza viruses and watching out for new viruses with the potential to cause a pandemic, GISN activities underpin the selection of viruses used for updating seasonal influenza vaccines around the world, as described further below.

Reducing the impact of influenza

It is in the nature of influenza that we talk about prevention and mitigation of the disease rather than eradication of the virus. The smallpox virus, a genetically stable virus for which humans were the only host, was able to be eradicated through a mass immunisation campaign: the last known natural case of smallpox occurred in Somalia in 1977 and Frank Fenner, a great Australian virologist (1914–2010) and chair of the WHO's Global Commission for the Certification of Smallpox Eradication, announced the success of this unprecedented campaign in 1980. There is hope that polio, also caused by a virus which only infects humans, will soon follow smallpox into extinction through global vaccination. By contrast, the intrinsic variability of human influenza A and B viruses and the enormous reservoir of influenza A viruses of many subtypes circulating in birds and other species mean that we will continue to live with influenza for the foreseeable future and must focus instead on ways to reduce its impact.

It is remarkably difficult to interrupt the spread of influenza viruses other than by strict quarantine. As a respiratory infection, influenza is easily spread through coughing, sneezing, touch and even breathing. The infected person can be

infectious for a day before the onset of clinical symptoms and the virus itself can be quite durable in some conditions, surviving for many hours on contaminated surfaces. The fact that influenza is generally not seen as a serious illness and shares symptoms with other, milder respiratory infections also makes it harder to limit its spread through social means, such as self-imposed quarantine. Only in the most serious circumstances, such as the emergence of a pandemic virus with high mortality, is it likely that community compliance with home quarantine will be high enough to arrest influenza outbreaks.

Antiviral drugs therefore have a role to play in the prevention and treatment of influenza.[14] The older class of anti-influenza drugs, the adamantanes (amantadine and rimantadine), nowadays have limited use. In the past they were effective against type A viruses, but viruses of the two influenza A subtypes currently circulating in humans (H1N1 and H3N2) today almost invariably carry a mutation that blocks the action of adamantanes. A second class of anti-influenza drugs, the neuraminidase inhibitors marketed as Tamiflu (an oral drug) and Relenza (delivered with an inhaler) were introduced in 1999 and are active against both type A and type B viruses. Despite extensive use of Tamiflu in many countries during the 2009 pandemic, the great majority of circulating influenza viruses remain sensitive to this drug. Relenza has been used much less, and to date almost no cases of viral resistance have been detected. However, the potential for emergence of resistance to one or more of these drugs is well recognised because of recent experience: in just one year from late 2007, the prevalence of Tamiflu resistance among the pre-2009 lineage of A(H1N1) viruses jumped from <0.1% to 100% in most parts of the world, despite very low global use of the drug. This was the first indication that the mutation in the NA gene commonly associated with Tamiflu resistance in H1N1 viruses did not stop these viruses from spreading between untreated people.

Although Tamiflu and Relenza can be used both prophylactically and therapeutically, there are several reasons that they

are not used for community-wide prevention of influenza under normal circumstances. When used to prevent infection, one reason is side effects; for example, a significant proportion of people taking Tamiflu experience nausea and other gastrointestinal symptoms. Another is cost: these drugs need to be taken daily for prophylaxis (twice daily for treatment of an existing infection) and the cost of a course would prohibit extended use for most people. When used for treatment, another reason is their short timeframe of efficacy: both drugs need to be taken within a few days (optimally no more than two days) after the onset of symptoms to have a measurable effect on the duration of illness. For most otherwise healthy people, the relatively modest effect of these drugs in reducing illness by one or two days is not sufficient to warrant their use. A final reason — more an issue of public health policy than individual circumstances — is that widespread therapeutic use of antiviral drugs increases the chance of emergence and spread of resistant viruses, thereby reducing their utility for those who most need them.

Despite these limitations, the neuraminidase inhibitors have an important role to play in some circumstances. They have proved effective in treating human infections with highly pathogenic avian H5N1 viruses, and their timely use in such cases may be one reason that death rates from this infection are lower in some countries than others. They have likewise been useful in treating some severe cases of seasonal or 2009 H1N1 virus infection.[8] On the prophylactic side, their timely administration to contacts can limit an influenza outbreak; for example, in nursing homes and other closed communities where infection can spread rapidly. These positive outcomes provide the evidence base for the stockpiling of neuraminidase inhibitors for use in slowing the spread and limiting the impact of a pandemic influenza virus.

Today, the most effective way to prevent influenza infection is vaccination. Consequently, the WHO and other health authorities emphasise the importance of vaccination ahead of

any other strategy for the community control of influenza. Whereas antiviral drugs interfere directly with the infectious cycle of the virus, vaccination acts indirectly, stimulating the individual's own immune system to produce antibodies which then neutralise the virus, ideally before it can infect the cells lining the airways. Two shots are generally necessary in children under 10 years old because their immune system is not already primed to the virus by previous infections, whereas a single annual shot is adequate for adults. Compared with antiviral drugs that must be taken once or twice daily to maintain effective levels, vaccination has the advantage that one dose can activate the production of antibodies that persist for many months. Antibody production is also boosted if the individual is then infected or revaccinated, perpetuating and strengthening protective immunity.

Infection with an influenza virus can prime the immune system to make antibodies against that particular virus for a lifetime. A remarkable example of this was provided by a recent study of people born around 1915, and now in their 90s, who still had antibodies in their blood that neutralised the 1918 pandemic influenza virus.[15] Most influenza vaccines are probably not so effective because they are produced from viruses that have been killed and fragmented so that they cannot themselves cause infection and therefore only activate some elements of the human immune system. They are nevertheless able to produce neutralising antibody responses in most people.

The seasonality of human influenza is so predictable in temperate climates that influenza vaccine production is also seasonal. In Australia, the vaccine is produced over about six months before its release in March and there is then a campaign to vaccinate in the autumn so that people will have protective antibodies before the influenza season starts. Similar vaccine production schedules and immunisation campaigns are shifted by half a year in the northern hemisphere.

The reason seasonal influenza vaccination is recommended every year reflects two complicating issues. One is the fact that those who are most vulnerable to the severe effects of

influenza are often those who have diminished ability to produce antibodies to the vaccine — particularly the elderly and people who are immune-compromised because of other infections, malignancy or drug therapy. The other issue is the continuing evolution of influenza viruses by which they escape neutralisation by human antibodies. This means that, more than any other vaccine, seasonal influenza vaccines must be frequently updated to include viruses that match as closely as possible those circulating in the season after vaccination. Influenza vaccines are typically trivalent, comprising representative viruses of the three lineages circulating in humans: type A (subtypes H1N1 and H3N2) and type B. It is common that at least one of these lineage's viruses must be updated in a given year.

As discussed above, the WHO GISN monitors the evolution of influenza viruses around the world. One of the most important applications of this work is the identification of suitable vaccine viruses. Each year in February and September (five to six months ahead of vaccine release), the WHO CCs, the regulatory laboratories and other experts meet with the WHO to review the data accumulated over the previous six months and develop recommendations on suitable influenza viruses of each of the three circulating lineages for use in vaccines for the coming northern or southern hemisphere winter. While the final decision on vaccine composition in each country rests with national governments, many adopt the WHO's recommendations or use them as a guide. The recommended vaccine viruses isolated by the WHO CCs are made available without charge to the influenza vaccine manufacturers, whether commercial or government sponsored.

Important aspects of this process are also undertaken in partnership with the influenza vaccine manufacturers.[16] This is for two reasons. First, most influenza vaccines are produced by growing virus in embryonated hen's eggs. As most human influenza viruses do not grow well in eggs, they must first be adapted through serial egg passage; for influenza A viruses, this adaptation is helped by co-infecting eggs with the new

influenza virus and an egg-adapted strain and then selecting a reassortant virus with the HA and NA of the new virus on a background of genes from the old strain.[16,17] The WHO CCs collaborate with three organisations, one of which is CSL Limited in Melbourne (the others are the National Institute for Biological Standards and Control in the United Kingdom and New York Medical College in the United States), to ensure that suitable reassortant/egg-adapted viruses are available for use by all the manufacturers. Second, manufacturers need to commence production as soon as possible after the announcement of the WHO's recommendations on vaccine composition to enable vaccine supply before the next influenza season starts. Formal mechanisms of interaction between the WHO and the manufacturers have therefore been established for sharing of information and supply of candidate vaccine strains as early as possible so that manufacturers can trial them in their individual production facilities. These efforts are designed to give equal access to all manufacturers in all countries to ensure that influenza vaccine supply is sufficient and in time to meet public health needs.

While the need for frequent updating of seasonal influenza vaccines presents some hurdles, the challenge of developing vaccines against a pandemic influenza virus is in another league. The production of a new influenza vaccine in sufficient quantities to meet community needs in a normal season currently takes five to six months. But, as we saw in 2009, a new pandemic virus can spread around the globe in a much shorter time than this and the potential demand for vaccine is enormously higher. As a pandemic virus is one against which most people lack immunity, the first wave of pandemic infections in most countries will occur without the protective benefit of a specific vaccine. For example, on 30 September 2009, Australia became one of the first countries to have a vaccine against the new virus available for community use, a little over five months after the virus was originally identified in the United States.[7] Yet by then the first pandemic wave in Australia was largely over.

Timeliness is just one of the considerable problems confronting the production of a pandemic influenza vaccine. Others include inadequate global production capacity to meet global needs and the difficulties of funding and delivering the vaccine in less developed countries to ensure equitable access, regardless of their ability to pay.[18] While the WHO, national governments, vaccine manufacturers and others work through the practical, political and commercial issues that complicate this endeavour, many research laboratories are tackling the problem from a different angle by seeking to develop vaccines that cross-protect between different influenza viruses. If successful, such vaccines would provide at least a degree of protection against influenza viruses that have not yet emerged and reduce the impact of a new pandemic virus in the first months before a specific vaccine can be produced.

Concluding remarks: influenza in a changing world

The challenges presented by influenza that the newly formed WHO recognised in 1948 remain with us today — in particular, the annual epidemics of seasonal influenza viruses driven by their continuing antigenic drift and the less predictable but ever-present threat of emergence of a new pandemic virus.

In some ways, contemporary conditions have exacerbated these challenges. Cross-border poultry and livestock trade, and farming practices that bring large numbers of animals together with inadequate infection control, can increase the risk of mixing of avian, swine and human influenza viruses to produce unfamiliar genetic combinations. With mass air travel, new influenza viruses can rapidly reach most of the global human population. Population growth and urbanisation, particularly in impoverished circumstances, aid their local spread.

On the other hand, globalisation and technological advances are providing new tools to detect, communicate and combat threats from influenza. Improved communication and laboratory technologies underpin the global collaborative effort to monitor the emergence of new pandemic viruses and

to match the evolutionary progress of seasonal influenza viruses with updated influenza vaccines. We have antiviral drugs that were not available to earlier generations, while improvements in manufacturing processes have increased influenza vaccine safety and a substantial investment is underway in the development of cross-protective vaccines.

Ultimately an effective global response to influenza depends on sharing of information and resources. Although imperfect in a number of ways, the rapid, open and cooperative international response to the 2009 influenza pandemic was a sign that important progress has been made.

Acknowledgments

I thank the WHO National Influenza Centres and other laboratories which submit samples and data to our Centre in support of the WHO Global Influenza Surveillance Network, and my colleagues in the Centre who have undertaken some of the work on which this chapter is based. The Melbourne WHO Collaborating Centre for Reference and Research on Influenza is supported by the Australian Government Department of Health and Ageing.

Endnotes

1 de Jong JC, Rimmelzwaan GF, Fouchier RAM, Osterhaus ADME. 2000. Influenza virus: a master of metamorphosis. J. Infect. 40:218-228.

2 Peiris JSM., de Jong MD, Guan, Y. 2007. Avian influenza virus (H5N1): a threat to human health. Clin. Microbiol. Rev. 20:243-267.

3 Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus, Abdel-Ghafar AN, Chotpitayasunondh T, Gao Z., Hayden FG., Nguyen DH., de Jong MD, Naghdaliyev A, Peiris JSM, Shindo N, Soeroso S, Uyeki TM. (2008). Update on avian influenza A (H5N1) virus infection in humans. N. Engl. J. Med. 358:261-273.

4 Callinan I. 2008. Equine Influenza: The August 2007 Outbreak in Australia. Report of the Equine Influenza Inquiry (2008). Available at http://www.equineinfluenzainquiry.gov.au/eiiexhibits/REP.0001.001.0001.pdf

5 Taubenberger JK, Morens DM. 2009. Pandemic influenza – including a risk assessment of H5N1. Rev. Sci. Tech. 28:187-202.

6 Taubenberger JK, Morens, DM. 2006. 1918 Influenza: the mother of all pandemics. Emerg. Infect. Dis. 12:15-22.

7 Bishop JF, Murnane MP, Owen R. 2009. Australia's winter with the 2009 pandemic influenza A (H1N1) virus. N. Engl. J. Med. 361:2591-2594.

8 Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, Bautista, E., Chotpitayasunondh, T., Gao, Z., Harper, S.A., Shaw, M., Uyeki, T.M., Zaki, S.R., Hayden, F.G., Hui, D.S., Kettner, J.D., Kumar, A., Lim, M., Shindo, N., Penn, C., and Nicholson, K.G. (2010). Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N. Engl. J. Med. 362:1708-1719.

9 Zimmer SM, Burke DS. 2009. Historical perspective – emergence of influenza A (H1N1) viruses. N. Engl. J. Med. 361:279-285.

10 Cohen J. 2010. Swine flu pandemic. What's old is new: 1918 virus matches 2009 H1N1 strain. Science 327:1563-1564.

11 Bandaranayake D, Bissielo A, Huang S, Wood, T. 2010. Seroprevalence of the 2009 influenza A (H1N1) pandemic in New Zealand. Available at http://www.moh.govt.nz/moh. nsf/indexmh/seroprevalence-2009-flu-nz

12 Gilbert GL, Cretikos MA, Hueston L, Doukas G, O'Toole B, Dwyer DE. 2010. Influenza A (H1N1) 2009 antibodies in residents of New South Wales, Australia, after the first pandemic wave in the 2009 southern hemisphere winter. PLoS One.5(9):e12562.

13 Kitler ME, Gavinio P, Lavanchy D. 2002. Influenza and the work of the World Health Organization.Vaccine 20 Suppl 2:S5-14.

14 Moss R.B., Davey RT, Steigbigel RT, Fang F. 2010. Targeting pandemic influenza: a primer on influenza antivirals and drug resistance. J. Antimicrob. Chemother. 65:1086-93.

15 Yu X, Tsibane T, McGraw P.A., House FS, Keefer CJ, Hicar MD, Tumpey TM, Pappas C, Perrone LA, Martinez O, Stevens J, Wilson IA, Aguilar PV, Altschuler EL, Basler CF, Crowe, JE. 2008. Neutralizing antibodies derived from the B cells of 1918 influenza pandemic survivors. Nature 455:532-536.

16 International Federation of Pharmaceutical Manufacturers and Federations. 2007. The WHO system for influenza surveillance and supply of viruses for the standardized production of influenza vaccines. Available at http://www.ifpma.org/Influenza/fileadmin/templates/influenza/pdfs/Publications/2006_09_WHO_System_for_Standardized_Production_of_Influenza_Vaccines.pdf

17 Hampson AW. 2008. Vaccines for pandemic influenza. The history of our current vaccines, their limitations and the requirements to deal with a pandemic threat. Ann. Acad. Med. Singapore 37:510-517.

18 Fidler DP. 2010. Negotiating equitable access to influenza vaccines: global health diplomacy and the controversies surrounding avian influenza H5N1 and pandemic influenza H1N1. PLoS Med. 7(5):e1000247.

Anne Kelso is Director of WHO Collaborating Centre for Reference and Research on Influenza. Previously she was Director/CEO of the Cooperative Research Centre for Vaccine Technology, President of the Australasian Society for Immunology and Secretary-General of the International Union of Immunological Societies. She is currently, amongst many board roles, advising the Australian Government on issues related to influenza and pandemic preparedness.