INFLUENZA - DEALING WITH A CONTINUALLY EMERGING DISEASE

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Abstract

There are two major types of influenza virus, types A and B, which are responsible for disease in man. Both types of virus display a progressive antigenic change known as antigenic drift while influenza A occasionally undergoes a more dramatic change known as antigenic shift. Antigenic shifts are typically associated with pandemic spread and severe disease and it is now believed that they occur when a new virus strain evolves by genetic reassortment between avian and human influenza viruses. In recent years influenza surveillance has provided for a good antigenic match between vaccines and the circulating epidemic viruses and the development of safe vaccines with good protective efficacy have been possible. However, in a pandemic situation the spread of the new virus is much more rapid and may well outstrip the capacity to produce vaccines.

Influenza surveillance - origins of the global network

Influenza is one of the few diseases for which there is a truly worldwide surveillance network, the World Health Organization (WHO) global influenza program, which had its beginnings at the Fourth International Congress on Microbiology in Copenhagen in July 1947. At that time, a group of virologists proposed to the Interim Commission of the World Health Organization that a global program was required to study the epidemiology of influenza. They were prompted by a marked antigenic change in the circulating influenza A viruses in 1946-47 which brought associated vaccine failures. There were underlying concerns that future antigenic changes might give rise to a new pandemic strain with similar properties to the 1918-19 pandemic virus which claimed an estimated 21 million human lives, many of them in the 20-40 year-old age group.

The two major objectives of the WHO program at its outset were to[1]

- study the origins of epidemic and pandemic influenza strains, and
- provide new virus strains quickly for the production of vaccines in the event of outbreaks.

Since then the WHO influenza surveillance network has grown to involve approximately 110 National Influenza Centres in 80 countries and three WHO Collaborating Centres for Influenza Reference and Research located in London, Atlanta and Melbourne.

Antigenic variation in influenza

Largely as a result of the WHO program, we now have a good understanding of the origins of new influenza strains through two forms of antigenic change which are often referred to as antigenic drift'and antigenic shift. Two major serotypes of influenza, types A and B, are responsible for human disease, both of which display antigenic drift. As the term implies, this is a continual and usually gradual antigenic change in the two viral surface antigens, the haemagglutinin and neuraminidase, which are embedded in the lipid membrane surface of the virus. Both antigens are glycosylated proteins; the haemagglutinin, which is more abundant, is also the more important antigen in the production of protective immunity. Only influenza A undergoes the more dramatic form of variation, or antigenic shift, in which a virus of a new subtype with completely different haemagglutinin, and often a different neuraminidase, suddenly appears in the human population. Antigenic shifts are typically associated with rapid pandemic spread, severe disease and a high level of mortality, and they occur at quite unpredictable intervals.

The degree of antigenic change in influenza is much greater than that observed for many other micro-organisms. This is largely due to the unique structure of the viral genome which exists as eight segments of negative sense, single-stranded RNA. Antigenic drift is now known to be a consequence of the very high mutation rate resulting from the uncorrected errors which occur when the single-stranded RNA is replicated. This has been estimated to occur at a frequency of 1.5×10^{-5} per nucleotide per replicative cycle, a rate around ten times greater than that for the polio virus genome[2]. In addition, the surface structure of the virus is rather more accommodating to changes in the surface proteins than more highly constrained structures such as the icosahedral capsid of the polio virus.

Antigenic change by genetic reassortment

The influenza A haemagglutinin has been recognised in 15 serologically distinct forms or subtypes and the neuraminidase in nine types[3,4]. All of these are to be found in aquatic birds, particularly ducks, which are now considered to be the primary host of influenza A viruses. A small number of the subtypes have become adapted to certain mammalian hosts, including humans, horses and the domestic pig. From time to time there is evidence of transmission of an avian influenza virus to a different species, such as the outbreak that occurred in harbour seals in the north-eastern United States of America in 1979[3].

Antigenic shifts accompanied by pandemic influenza in humans have been experienced only three times this century, in 1918-19 (Spanish Influenza), 1957 (Asian Influenza) and 1969 (Hong Kong Influenza). A further antigenic shift occurred in 1977, which affected primarily younger members of the population, in what might be termed a pseudopandemic. There is now overwhelming circumstantial evidence that antigenic shift can occur by a process of genetic reassortment between avian influenza and human influenza viruses. It has long been known that reassortment of the RNA gene segments from two influenza A viruses could be readily achieved in the laboratory by dual infection of cell cultures or embryonated eggs. This is a method regularly used for producing high-yielding strains of new influenza A variants for vaccine production[5].

Sequence analysis of RNA from the 1957 and 1969 pandemic viruses indicates that they almost certainly arose by genetic reassortment between the previous circulating human influenza strains and an avian virus such that the reassortant virus in both cases received the haemagglutinin and one non-structural gene of the avian virus[3]. In the case of the 1957 virus, the reassorted virus also received the avian neuraminidase. The fact that the Hong Kong virus shared a common neuraminidase with the preceding subtype may account for the slightly lesser impact that this virus had compared with the 1957 virus.

The domestic pig as a genetic mixing vessel

While there is considerable evidence that avian viruses can cross the species barrier to horses, pigs and sea mammals, and ample evidence of antibody activity to a number of avian subtypes in people living in China[6], it is thought that the avian viruses will not readily adapt to growth in humans. Laboratory evidence suggests that the internal nucleoprotein of influenza viruses may play a role in restricting the species specificity of human and avian influenza[7]. This is why it is now widely believed that the domestic pig, which is susceptible to viruses with either form of the nucleoprotein, may play a role in genetic reassortment, acting as a genetic mixing vessel for generating new human pandemic strains.

To date, only two of the three human subtypes have been found in pigs. Sequence analysis of the RNA from H_1N_1 descendants of the 1918 virus which were isolated during the 1930s indicate that this virus may not have been formed by reassortment but rather by adaption of an avian virus to humans[3]. It has been suggested, however, that this is most likely to have occurred after adaption in the pig as an intermediate host. This is consistent with the apparently different geographic origins of the 1918 virus. The virus is thought to have originated in either France or the United States of America, while most new pandemic viruses appear to have their origins in China, where the agricultural practices would be conducive to the involvement of the domestic pig in genetic reassortment. There is no doubt that influenza viruses from pigs can infect humans and cause disease. This was demonstrated at Fort Dix in the United States of America in 1976 with the outbreak of A/New Jersey/76 virus, which was clearly derived from a swine influenza virus[8]. This occurred again recently in Europe where there are two recorded instances of transmission of human-avian reassortant viruses from pigs to humans[9].

Based on virological studies since the 1930s and retrospective serology for the preceding half-century, it seems fairly certain that during the last 110 years humans have been host to only three of the 15 influenza A haemagglutinin subtypes, and that each of these has occurred on two separate occasions. In the case of the H_2 subtype in 1957 and H_3 subtype in 1969, the virus recurred after an absence of about 70 years when there would have been little residual immunity in the human population. On both occasions, the new subtype completely replaced the previously circulating influenza A subtype. The recurrence of the H_1 subtype in 1977 was quite different, occurring after an absence of only 20 years. It did not replace the circulating H_3 subtype.

The short absence from the population and close genetic similarity between the 1977 virus and strains circulating in 1956 have resulted in speculation regarding the origin of the virus, including the possibility that it may have been inadvertently released from a laboratory[10]. Despite the advances in our knowledge of pandemic influenza, many unanswered questions remain, not least among them is whether there is some inherent restriction in the subtypes which can infect humans or whether all 15 may have this potential - a rather frightening possibility.

The impact of influenza

Historically, the impact of pandemic influenza has raised the greatest public health concerns, while the pandemic impact of the disease is frequently underestimated. The annual death rate due to influenza in the United States of America has been estimated as 10-40,000 per annum. There are a number of studies which indicate that the total excess mortality associated with influenza is, in fact, many times higher than that recorded as influenza and pneumonia deaths[11]. The majority of the additional deaths are attributed on death certificates as due to cardiovascular disease and other causes[12,13].

While mortality is an obvious outcome of epidemic influenza, it reflects only a minor portion of the total impact of disease. The full economic impact, including cost to the individual, cost to the health care system and cost of lost productivity are extremely difficult to estimate. One published estimate put the annual cost to the United States of America as $3-5 billion per annum in 1986 dollars[14]. The cost to the Australian Medicare was estimated at $96 million during a moderate epidemic in 1985[15].

Safety and efficacy of vaccines

It was demonstrated with the earliest inactivated influenza virus vaccines during the 1940s that these could

confer significant protection against infection. It quickly became clear that the level of protection was dependent on the closeness of the antigenic match between the vaccine strains and the circulating epidemic viruses. In addition, the level of absolute protection against infection in the elderly was considerably lower than that achieved in younger adults[16]. There have been a number of reports of serious vaccine failures when vaccines were not updated sufficiently quickly to cater for antigenic drift or shift changes in the virus.

Early influenza vaccines tended to be unduly reactive and the development of more acceptable vaccines took place over many years. This was achieved by progressive improvements in the methods used to purify the vaccine virus and, eventually, the finding that it was necessary to remove an apparent intrinsic toxicity associated with highly purified inactivated whole virus by chemical disruption or splitting[17]. Although one may occasionally hear anecdotal reports to the contrary, controlled placebo trials show unequivocally that today's split product and purified subunit vaccines are essentially devoid of systemic reactions[18], except in very young children[17]. These same trials did indicate, however, that the vaccines may produce mild transient local reactions in up to 20% of recipients.

Although inactivated vaccines fall well short of absolute protection against infection in the major target group - the older adult - there are now many studies which demonstrate a high level of protection against the severe consequences of infection. The studies also showed that excellent benefits can be achieved by annual vaccination in this group and others who are at increased risk of post-influenzal complications. A recent meta-analysis of 20 studies in elderly recipients showed that vaccination reduced total respiratory illness by an overall 56%, pneumonia by 53%, hospitalisation by 50% and death by a surprising 68%[19].

These figures are even more impressive when it is considered that agents other than influenza contribute significantly to these outcomes. Importantly, as shown in a recent study by Nichol[20], these benefits could be demonstrated even in a non-epidemic year, demonstrating that influenza is associated with an annual background of increased hospitalisations and mortality which can be significantly reduced by vaccination. Consistent with the studies on mortality, the Nichol study also showed that vaccination produced a reduction in hospitalisation for cardiac failure during a year when influenza A was epidemic. A number of economic analyses indicate that there is a substantial cost-benefit from influenza vaccination in the defined risk groups[20,21,22]. It is probably among the most cost-effective medical interventions possible in the older adult population. A recent study also showed that vaccination can be cost effective in a healthy young adult working population[23].

Annual vaccine formulation

While the origins of new influenza strains are now much better understood, global surveillance remains as important as ever to provide the data and virus strains required for regularly updating vaccines. In February each year, the World Health Organization convenes its annual consultation on influenza vaccine formulation and reviews the accumulated surveillance data provided through the National Influenza Centres, the strain analysis data and serological results from the three collaborating centres. It might seem remarkable that much of the information considered by this meeting is generated by essentially the same methods that were used when the WHO network was first proposed almost 50 years ago. The haemagglutination-inhibition test which employs reference antigens grown in embryonated eggs and antisera prepared by infecting ferrets, is still the preferred method for antigenic analysis of virus isolates but is now supplemented by the use of monoclonal antibody panels and by sequence analysis of the viral haemagglutinin antigen.

To ensure the best possible match between the vaccine and circulating viruses, the Australian Influenza Vaccine Committee meets in late September each year to review the WHO formulation decision and to update it if necessary. Since 1977, when the re-emergence of the H_1N_1 subtype necessitated a trivalent influenza vaccine formulation, the committee has further updated the WHO formulation by, on average, one of the three vaccine component strains each year. The selection of the correct vaccine formulation is not always straightforward, as there are often multiple variants of a virus type or subtype present at any one time. It is a reflection of the success of the WHO surveillance network that both the WHO and Australian formulations, over recent years, have demonstrated a high degree of success in matching vaccine strains to the circulating epidemic viruses.

Coping with the next pandemic

It is generally agreed among virologists that the question is *when* the next pandemic will occur, rather than *if* one will occur. Our ability to cope with a pandemic has gone essentially untested since 1969. While the evolution of new epidemic drift variants typically takes place over a period of 12-18 months, the new pandemic viruses in 1957 and 1969 spread essentially worldwide within six months of detection. The rate of spread outstripped the production of vaccine, although in some countries vaccines were available ahead of a second, more severe wave of infection which often occurs. Influenza surveillance has recently been improved in China and detection of the next pandemic virus may occur more quickly and closer to its source than previously. It would seem likely that the increasing extent and speed of human travel will spread the new virus even more rapidly than before, offsetting any advantage that might have been gained.

Many countries are now formulating detailed pandemic plans to determine how they might minimise the impact and social disruption which could occur if a virulent virus such as that experienced in 1918 should appear.

Now is the time for influenza vaccinations

National Health and Medical Research Council recommendations on influenza immunisation[1]

Influenza vaccine should be given routinely on an annual basis to:

- Individuals over 65 years of age: the risk to the elderly is greatest if they also have chronic cardiac or lung disease, and is increased for residents of nursing homes and other chronic care facilities;
- Aboriginal and Torres Strait Islander adults over 50 years of age, because of the greatly increased risk of premature death from respiratory disease.

Annual vaccination should be considered for individuals who are in the following groups:

- Adults with chronic debilitating diseases (especially those with chronic cardiac, pulmonary, renal and metabolic disorders);
- Children with cyanotic congenital heart disease;
- Adults and children receiving immunosuppressive therapy;
- Staff who care for immunocompromised patients (patients with immune deficiency or malignancy, bone marrow transplant recipients and liver transport recipients are at high risk from influenza infection, but have an attenuated immune response to influenza vaccine);
- Residents of nursing homes and other chronic care facilities;
- Staff of nursing homes and other chronic care facilities (in an attempt to protect the patients).

1. Based on: National Health and Medical Research Council *The Australian immunisation procedures handbook*, fifth edition. Canberra: Australian Government Publishing Service, 1995.

Progress in the control of influenza

A number of developments currently in progress may influence our ability to deal with epidemic and pandemic influenza in the future. There is renewed interest in the possibility of commercialising live attenuated influenza vaccines which have been trialed over many years[24], particularly in children, but which have yet to gain registration in Western countries. New and improved vaccines using a variety of adjuvants, recombinant antigens and the exciting prospect of DNA vaccination hold promises such as improved protection[25], broader and longer-lasting immunity and simplified or more rapid vaccine production. There is also the prospect that a new specific antiviral compound will be available within the next few years[26].

None of these, however, is likely to obviate the need for an effective global surveillance program and detailed knowledge of the circulating virus strains. Nor are they likely to have any significant impact on the ongoing antigenic variation of the virus. It is worth reflecting on how much might be achieved by simply improving the use of today's effective influenza vaccines compared with the promises offered by the products of the future.

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