

Historic Influenza Perspectives on an Influenza Pandemic

Dr Des Mart
MBCChB, MMed, PCPath, DTM&H, DP
Toga Laboratory

Highlights / Hoogtepunte

"The pandemic clock is ticking away. It is not a question of if, but when." - Dr R Webster, 1996

Before discussing the issues related to influenza pandemics, it is necessary to understand the mechanisms that underlie the variability of the virus. The influenza virus, like most RNA viruses, is genetically highly variable and this variability gives rise to a constant changing of the antigenicity of the virus. This, in itself, is not peculiar to influenza. However, what is unique to the virus is that this antigenic changeability constantly gives rise to new strains of virus which are able to escape the immunity which the population builds up to the predecessor strain. The epidemiology of influenza is thus characterized by the constant advent of new antigenic strains of the virus giving rise to recurring epidemics of infection.

SA Fam Pract 2003;45(4):57-59

CLASSIFICATION OF INFLUENZA VIRUSES

Influenza is classified into 3 types, based on the antigenicity called the nucleoprotein which intimately surrounds the RNA genome of the virus. As it is an internal protein, it is not variable. The 3 types are referred to as type A, type B and type C. (Type C causes a rather trivial mild upper respiratory tract infection, and is therefore not a component of influenza vaccine.)

Type A influenza virus is further subdivided into subtypes based on the antigenicity of the two proteins embedded in the envelope of the virus. These are used to attach and penetrate the host cell. They are haemagglutinin (HA) (so named because the protein agglutinates red blood cells, which forms the basis of the serological test

used to identify the virus using specific antisera – the haemagglutination inhibition or HI test) and neuraminidase (NA) (so named because this protein is an enzyme which digests the neuraminic acid receptor of the cell to allow the attached virus to penetrate into the cell).

A number of haemagglutinins (HA's) and neuraminidases (NA's) have been described in nature, but so far only the HA's (H1, H2 and H3), and two NA's, (N1 and N2), have been found in man. Only three subtypes have infected humans, namely H1N1, H2N2 and H3N2. At present, two of the subtypes that infect man, H1N1 and H3N2, are in co-circulation.

Each of the type A and B subtypes are in turn, subdivided into strains based on the antigenicity of the HA protein. This is done by using more specific antisera, as will be discussed below, than

that used for subtyping. The strains are designated according to a formula which describes their full pedigree, i.e. type, subtype, geographical location of where first isolated and the year of isolation. Hence the virus strains incorporated into the 1997 vaccine were designated as A/Texas/36/91 9H1N1, A/Wuhan/359/95 (H3N2) B/Beijing/184/93 and B/Harbin/07/94. (The additional number before the year of isolation is merely a laboratory identification number.)

THE MECHANISMS OF INFLUENZA VIRUS VARIABILITY

There are 2 ways in which influenza virus can change its antigenicity. The one is a rare, but dramatic, event and the other, a much more common and subtle change.

Your vaccine authority - carrying virtually every vaccine available in the South African pharmaceutical market.

We can offer you assistance with the opening of a new immunising service or if you have an existing clinic.



thevaccinebureau
protecting life through immunisation

Please feel free to contact Grace for further details.

1 Manchester Road, Wadeville, 1428
P.O. Box 14374, Wadeville, 1422
Telephone: +27 11 824 7900
Fax: +27 11 827 8688
E-mail: thevaccinebureau@biovac.co.za

Excellent service, full technical support, competitive pricing and range.

ANTIGENIC SHIFT

Influenza virus is one of the few viruses in which the individual genes occur on separate and discrete pieces of nucleic acid instead of the more usual complete single strand for the whole genome. As a result of this, if two different subtypes happen to infect the same cell, genes from different origins may be swapped when the progeny virus is put together in the assembly phase of the virus' replication. Usually the alien gene or genes will produce an inconsequential hybrid progeny virus which cannot survive or be propagated. This process is called reassortment, and the hybrid offspring are referred to as reassortants. The primary mixing bowls where reassortment is thought to take place in nature are the vast flocks of wild birds, including waterfowl, found in China, with the pig acting as an intermediate host for man. In China and the Far East, the enormous human populations come into close contact with these animal reservoirs, which harbour a great variety of influenza subtypes. Nevertheless, reassortment producing a new human virus is a rare event, happening about once every 10-40 years. When it does occur, it gives rise to a completely new subtype of virus (acquiring a totally new HA and sometimes a new NA protein as well), to which the human population will be readily susceptible. This has resulted in dramatic and sudden classical pandemics such as the 1918/19 Spanish flu pandemic, the 1957 Asian flu pandemic and the 1968 Hong Kong flu pandemic. The sudden and major change in antigenicity of the virus is hence called antigenic shift.

ANTIGENIC DRIFT

This is a more subtle change in the antigenicity of the HA protein – the protein involved specifically in the critical attachment of the virus to its receptor on the host cell. Thus, even subtle changes (i.e. sometimes only one or two amino acids) may enable the virus to elude the host's immunity. These HA mutations occur readily and continually. Point mutations (i.e. substitution of one amino acid) usually do not translate on their own into a significant antigenic change. However, accumulation of these point mutations under the selective pressure of

antibodies formed in innumerable human hosts will eventually produce meaningful antigenic change, resulting in a virus which can spread throughout the human population causing widespread epidemic activity. This more gradual but progressive change is thus called antigenic drift, and it gives rise to new antigenic strains of influenza approximately every 3-5 years.

AND THEN THERE WAS H5 N1 INFLUENZA.....

In 1997 the first human case of an H5N1 infection was discovered in Hong Kong when a three year-old boy died. This virus, which was known to infect and kill poultry, had never been known to infect humans before. In fact, the possibility of avian strains infecting man was never thought to be a possibility. Surveillance of this H5N1 infection revealed that it had occurred in five of 29 poultry workers, in none of four family members of the first case and in only one of 54 healthcare workers who looked after the first case. Furthermore, there was no serological evidence of infection in a sample of 419 individuals from the general population of Hong Kong. This epidemic became known as the 'Hong Kong bird flu'. Further outbreaks of this virus occurred later in the year and eventually a total of 18 cases were reported, 6 of whom died. It was evident, therefore, that the virus was virulent. However, the pandemic potential of the virus was clearly hampered by its inability to be easily transmitted between humans. The epidemic was eventually terminated by a mass slaughter of poultry in Hong Kong and the surrounding region.

MECHANISMS OF INFLUENZA EPIDEMICS

- Genetic reassortment – H3N2
- Reappearance of subtype – H1N1 1977
- Adaptation of avian strain – H5N1

PANDEMIC INFLUENZA

Pandemics of influenza have occurred this century at irregular intervals, notably the 'Spanish Flu' Pandemic which claimed over 20 million lives in 1918. (There were approximately 9 million deaths attributed to the First

World War activity.) It is estimated that there were 1 million deaths associated with the 1957 'Asian Flu' and 700 000 deaths attributable to the 1968 'Hong Kong Influenza'. These pandemics have been associated with an antigenic shift, which in turn is related to a genetic reassortment in the virus. The devastating effects of influenza are related to both the virulence of the virus and also to a susceptibility of populations who lack any background immunity to the new viruses. Historical records suggest that another pandemic of influenza is long overdue. It is interesting to reflect that, as previous pandemic strains have originated in the East, the next may have a similar source of origin. Clearly, intense surveillance of viruses that circulate in avian species, animals and human beings is necessary to detect the emergence of such a strain.

Many countries in the world have protocols that deal with pandemic influenza. Committees consisting of scientists, public health officials, vaccine manufacturers and pharmaceutical companies have been constituted, whose function is to provide plans to deal with the next pandemic. As the pandemic virus will be unique and unpredictable, it will be necessary to accelerate the manufacture of large amounts of a new appropriate vaccine and also to stockpile and set up lines of supply of antiviral drugs. The anticipated number of cases is likely to be overwhelming, and the infrastructure necessary to provide prevention and care of infected individuals will also need to be substantial. Interestingly, the prioritization of vaccine and drug distribution will be different to the current guidelines for annual influenza immunization, in that key personnel in the community should be the first to receive the vaccine. Included in this category would be doctors, health care professionals, ambulance drivers, police and military personnel, all of whom would be required to mount and coordinate an effective pandemic response.

INFLUENZA VACCINE STRAINS FOR FLU SEASON 2003

- A/Moscow/10/99 (H3N2)-like
- A/N Caledonia/20/99 (H1N1)-like
- B/Hong Kong/330/2001-like strains

FREQUENTLY ASKED QUESTIONS

What is the difference between a cold and influenza?

Both give a runny nose and cough, but influenza is far more severe.

Influenza has an abrupt onset with headache, muscle pains, fever, sore chest and cough. It is accompanied by severe malaise, and often persist for weeks after the acute phase. The complication rate for bronchitis and pneumonia is also increased.

Can I get influenza from the vaccine?

The influenza vaccine is an inactivated vaccine, manufactured by growing the three strains of virus and inactivating them with formalin. As the vaccine is inactivated, it cannot cause influenza when given to a patient.

Why is annual influenza vaccination necessary?

There are two reasons for this. Firstly, inactivated vaccines have a limited duration of protection and annual immunization is necessary. Secondly, because the influenza strains are continually changing, the vaccine formulation has to be updated on an annual basis.

Who should receive annual influenza vaccination?

- Persons who are at risk for influenza and its complications because of underlying medical conditions and who are receiving regular medical care for conditions such as chronic pulmonary and cardiac disease, chronic renal disease, diabetes mellitus and similar metabolic disorders and individuals who are immunosuppressed.
- Residents of old-age homes and chronic care and rehabilitation institutions.
- Children on long-term aspirin therapy.
- Medical and nursing staff responsible for the care of high-risk cases.
- Adults and children who are family contacts of high-risk cases.
- All persons over the age of 65 years.
- Any persons wishing to protect themselves from the risk of contracting influenza, especially in

industrial settings, where large-scale absenteeism could cause significant economic losses.

- Sportsmen and athletes, not only because of the serious effects influenza may have on training programme, but also because of the potential danger of a bout of influenza during vigorous exercise.

Contraindications for influenza vaccine

- Persons with a history of severe hypersensitivity to eggs.
- Persons with acute febrile illnesses should preferably be immunized after symptoms have disappeared.
- The vaccine, although considered safe during pregnancy, should ideally, be delayed until the second or third trimester to minimize the theoretical risk of teratogenicity. However, if high-risk indications exist, delaying immunization should be avoided.

Side-effects of vaccination

Transient pain at the injection site and a mild influenza-like feeling can occur in 5-10 % of vaccinees. These side-effects are more prevalent in older subjects.

When should the vaccine be given?

It takes about two weeks to develop an immune response, and this response lasts for approximately one year. Ideally, the vaccine should be given during the months of March and April.

How effective is the vaccine?

In young healthy subjects the efficacy can be as high as 90%, but this is reduced in elderly, frail and immunosuppressed patients. However, in these patients it has been shown to be protective against the complications that can lead to hospitalization and death. □

Selected bibliography:

1. Shoeridge KF, The next pandemic influenza virus? *Lancet* 1995;346: 1210-1212.
2. Webster RG, Predictions for Future Human Influenza Pandemics. *The Journal of Infectious Diseases* 1997;176 (Suppl 1): S14-19.
3. Hampson AW, Surveillance for Pandemic Influenza. *The Journal of Infectious Diseases* 1997;176 (Suppl 1): S8-13.
4. Patriarca PA and Cox NJ, Influenza Pandemic Preparedness Plan for the United States. *The Journal of Infectious Diseases* 1997;176 (Suppl 1): S4-7.
5. Yuen KY, Chan PKS, Peiris M, Tsang DNC *et al* Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet*, 1998; 351: 467-471.
6. Claas ECJ and Osterhaus ADME, New clues to the emergence of flu pandemics. *Nature Medicine*, 1998; 4 (No. 10): 1122-1123.