

## 3.9 INFLUENZA

### Virology

The influenza viruses are orthomyxoviruses. They are classified antigenically as types A, B or C, but only influenza A and B are clinically important in human disease.<sup>1</sup> Influenza viruses possess 2 surface glycoprotein antigens, the haemagglutinin (H) which is involved in cell attachment during infection, and the neuraminidase (N) which facilitates the release of newly synthesised virus from the cell. The influenza A viruses can be segregated into subtypes based on differences in these surface antigens, whereas influenza B cannot be segregated into subtypes. Antibody against the surface antigens, particularly the haemagglutinin, reduces infection or severe illness due to influenza.

Both influenza A and influenza B viruses undergo frequent changes in their surface antigens. Both influenza A and B undergo stepwise mutations of genes coding for H and N. This results in cumulative changes in influenza antigens, or 'antigenic drift'. This is responsible for the annual outbreaks and epidemics of influenza and is the reason that the composition of influenza vaccines requires annual review. Antigenic shift, defined as a dramatic change in H antigen with or without a similar change in N, occurs occasionally and unpredictably and can cause pandemic influenza.<sup>1</sup> Pandemic subtypes arise spontaneously from antigenic shift or as a result of genetic reassortment (mixing) between bird (avian) or animal viruses and human strains.

Three pandemics are recognised in the 20th century, in 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2). These pandemic strains have gone on to circulate in the community, with various subtypes causing seasonal influenza and, since 1977, 2 subtypes of influenza A, A (H1N1) and A (H3N2), co-circulating in the human population together with influenza B. Recently, the avian influenza virus subtypes, A (H5N1) and A (H9N2), have been observed to cause human infections. The most notable of these is the A (H5N1) subtype which has become established in domestic poultry throughout southeast Asia and has spread to Europe and Africa in either wild birds or domestic poultry. Although growing numbers of people have contracted the virus by contact with birds and there is a high mortality rate (of  $\geq 50\%$ ), there has been no evidence of ongoing person to person transmission.

### Clinical features

Influenza is transmitted from person to person via virus-containing respiratory aerosols, droplets produced during coughing or sneezing, or by direct contact with respiratory secretions.<sup>1,2</sup> Influenza virus infection causes a wide spectrum of disease from minimal or no symptoms, to respiratory illness with systemic features, to multisystem complications and death from primary viral or

secondary bacterial pneumonia. Severe disease is more likely with advanced age, lack of previous exposure to antigenically related influenza virus, greater virulence of the viral strain, chronic conditions such as heart or lung disease, renal failure and diabetes, chronic neurological conditions, pregnancy, and smoking. Annual attack rates in the general community are typically 5 to 10%, but may be up to 20% in some years. In households and 'closed' populations, attack rates may be 2 to 3 times higher.<sup>2</sup>

In adults, the onset of illness due to influenza is usually abrupt, after an incubation period of 1 to 3 days, and includes systemic features such as malaise, feverishness, chills, headache, anorexia, and myalgia. These may be accompanied by a cough, nasal discharge and sneezing. Fever is a prominent sign of infection and peaks at the height of the systemic illness. Symptoms are similar for influenza A and B viruses. However, infections due to influenza A (H3N2) strains are more likely to lead to severe morbidity and increased mortality than influenza B or influenza A (H1N1) strains.<sup>1,2</sup>

The clinical features of influenza A in infants and children are similar to those in adults. However, temperatures may be higher in children (and may result in febrile convulsions in the susceptible age group) and otitis media and gastrointestinal manifestations are more prominent. Infection in neonates may be associated with more non-specific symptoms.

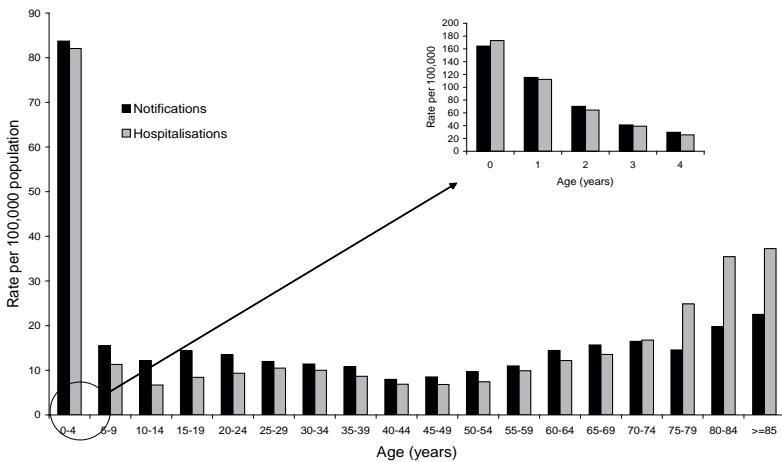
Complications of influenza include acute bronchitis, croup, acute otitis media, pneumonia (both primary viral and secondary bacterial pneumonia), cardiovascular complications including myocarditis and pericarditis, post-infectious encephalitis, Reye syndrome, and various haematological abnormalities. Primary viral pneumonia occurs rarely, but secondary bacterial pneumonia is a frequent complication in individuals whose medical condition makes them vulnerable to the disease. Such individuals are at high risk in epidemics and may die of pneumonia or cardiac decompensation.

## Epidemiology

In most years, minor or major epidemics of type A or type B influenza occur, usually during the winter months. In Australia, 85 deaths and 4250 hospitalisations are notified, on average, per year, although this is almost certainly an underestimate due to failure to recognise the excess mortality and hospitalisation associated with the disease. Extrapolation from US estimates, based on more detailed surveillance, suggests 2000 deaths and 10 000 hospitalisations are likely to occur annually in Australia. During epidemics, the mortality rises, especially among the elderly and people with chronic diseases, and there is increased morbidity and hospitalisation for pneumonia and exacerbation of chronic diseases.<sup>3</sup>

Figure 3.9.1 shows the Australian hospitalisation and notification data for the period 2003–2005.

**Figure 3.9.1: Influenza notification rates 2003–2005 and hospitalisation rates 2002/2003 to 2004/2005, Australia,\* by age group<sup>4</sup>**



\* Notifications where the month of diagnosis was between January 2003 and December 2005; hospitalisations where the month of separation was between 1 July 2002 and 30 June 2005.

## Pandemic influenza

It is now recognised that influenza A viruses have evolved in birds and that all 16 subtypes of influenza A persist in the avian reservoir. Occasionally, human infections may occur, with influenza subtypes not currently present in the human population, through close contact with infected poultry or poultry products. These may result, as in the case of recent A (H5N1) infections, in severe or fatal disease.

Avian influenza viruses are not naturally transmissible from person to person. However, adaptation to human to human transmission can occur either if an individual is concurrently infected with a human and an avian influenza virus, permitting genetic reassortment to occur, or if the virus acquires this ability via mutation. Genetic studies have shown that avian influenza viruses are the source of new human pandemic strains and that both these processes resulted in pandemic influenza in the 20th century.

Vaccines in routine inter-pandemic use will not protect against a pandemic strain which, by definition, is new and unpredictable. If a pandemic occurs, there will be a delay in producing a pandemic vaccine. Once the pandemic vaccine is available, the priority groups and the timing of vaccination may be quite different from those during inter-pandemic periods. In addition, the number of vaccine doses required to confer protection and the optimal interval between doses may differ. The Australian Influenza Pandemic Planning Committee has

developed guidelines for vaccine use and will advise health authorities about priority groups, dosing schedules and timing of vaccination, should a pandemic occur.

See <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/phd-pandemic-plan.htm>.

## Vaccines

The administration of influenza vaccine to individuals at risk of complications of infection is the single most important measure in preventing or attenuating influenza infection and preventing mortality. After vaccination, most adults develop antibody titres that are likely to protect them against the strains of virus represented in the vaccine. In addition, the individual is protected against many related variants. Infants, the very elderly, and patients with impaired immunity may develop lower post-vaccination antibody titres. Under these circumstances, influenza vaccine may be more effective in preventing lower respiratory tract involvement or other complications of influenza than in preventing infection.

- **Fluad** – Delpharm Consultants/Novartis Vaccines (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of the 3 recommended strains, adjuvanted with MF59C; 0.05 mg thiomersal. May contain traces of kanamycin, neomycin, formaldehyde and egg protein.
- **Fluarix** – GlaxoSmithKline (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the 3 recommended strains; polysorbate 80/octoxinol 9. May contain traces of thiomersal, formaldehyde, gentamicin and egg protein.
- **Fluvax** – CSL Biotherapies (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the 3 recommended strains. May contain traces of neomycin, polymyxin and egg protein.
- **Fluvirin** – Medeva/Ebos Health & Science (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of the 3 recommended strains. May contain traces of neomycin, polymyxin and egg protein.
- **Influvac** – Solvay Pharmaceuticals (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the 3 recommended strains. May contain traces of gentamicin and egg protein.
- **Vaxigrip** – Sanofi Pasteur Pty Ltd (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the 3 recommended strains. May contain traces of formaldehyde, neomycin and egg protein.

- **Vaxigrip Junior** – Sanofi Pasteur Pty Ltd (inactivated influenza vaccine). Each 0.25 mL pre-filled syringe contains 7.5 µg haemagglutinin of each of the 3 recommended strains. May contain traces of formaldehyde, neomycin and egg protein.

*Fluvax and Fluarix each have a marking on the syringe to allow preparation of a 0.25 mL dose suitable for paediatric use.*

All the influenza vaccines currently available in Australia are either split virion or subunit vaccines prepared from purified inactivated influenza virus which has been cultivated in embryonated hens' eggs. Split virion and subunit vaccines are generally considered to be equivalent with respect to safety and efficacy, and both are substantially free of the systemic reactions sometimes induced by whole virus vaccines. Because the vaccine viruses are cultivated in embryonated hens' eggs, the vaccine may contain traces of egg-derived proteins. Manufacturing processes vary by manufacturer, and different chemicals (formaldehyde or betapropiolactone) may be used to inactivate the virus. Some influenza vaccines distributed in Australia contain thiomersal, a mercury-containing compound, as preservative, and other antibacterials or antibiotics may be used in the manufacturing process. The product information should be consulted for specific information.

Influenza vaccines normally contain the 3 recommended strains of virus, 2 current influenza A subtypes and influenza B, representing recently circulating viruses. The final product contains 15 µg of viral haemagglutinin, the principal surface antigen, for each virus strain. Vaxigrip Junior contains 7.5 µg of viral haemagglutinin of each of the 3 recommended strains found in the adult formulations. The composition of vaccines for use in Australia is determined annually by the Australian Influenza Vaccine Committee.

Other forms of influenza vaccines (such as live attenuated intranasal vaccine) have not yet been licensed in Australia.<sup>5</sup>

The effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the virus strains in the vaccine and those circulating in the community. In healthy individuals <65 years of age, influenza vaccine is 70 to 90% effective when the antigenic match between vaccine and circulating viruses is close.<sup>6</sup> Among elderly people, the vaccine is 30 to 70% effective in preventing all hospitalisation for pneumonia and influenza for those living outside nursing homes or similar chronic-care facilities. For those residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications and deaths. In such a population, the vaccine can be 50 to 60% effective in preventing hospitalisation or pneumonia, and 80% effective in preventing death, even though the effectiveness in preventing influenza illness may be lower.<sup>7</sup> Currently

available influenza vaccines confer protection for about a year. Low levels of protection may persist for a further year, if the prevalent strain remains the same or undergoes only minor antigenic drift. To provide continuing protection, annual vaccination with vaccine containing the most recent strains is necessary.

## Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.<sup>8</sup> Store at +2°C to +8°C. Do not freeze. At the end of each year, vaccine should be appropriately discarded to avoid inadvertently using a product with incorrect formulation in the following year.

## Dosage and administration

Shake the pre-filled syringe vigorously before injection. Influenza vaccine is administered by either IM or SC injection. The IM route causes fewer local reactions and is preferred.<sup>9</sup>

**Table 3.9.1: Recommended doses of influenza vaccine**

Age	Dose	Number of doses (first vaccination)	Number of doses* (subsequent years)
6 months–<3 years	0.25 mL	2 <sup>†</sup>	1
3–9 years	0.5 mL	2 <sup>†</sup>	1
>9 years	0.5 mL	1	1

\* If a child 6 months to ≤9 years of age receiving influenza vaccine for the first time inadvertently does not receive the second dose within the same year, he/she should have 2 doses administered the following year.<sup>7</sup>

† Two doses at least 1 month apart are recommended for children aged ≤9 years who are receiving influenza vaccine for the first time. The same vial should not be re-used for the 2 doses.

Note:

(i) Some influenza vaccines available in Australia are packed in syringes graduated for measurement of recommended paediatric doses. Vaxigrip Junior presentation is a 0.25 mL pre-filled syringe ready for use. Fluvax and Fluarix each have a marking on the syringe to allow preparation of a 0.25 mL dose. A tuberculin syringe can be used to measure the dose of vaccine not packed in graduated syringes. Excess vaccine is expelled from the syringe and the remaining volume injected.

(ii) All the product information sheets have some differences from Table 3.9.1. Fluvirin does not have a dose recommendation for children <4 years of age. The safety of Fluad, which is adjuvanted with MF59C, has not been established in children and it is registered for use only in people ≥65 years of age.

Vaccination is best undertaken in autumn, in anticipation of winter outbreaks of influenza. However, vaccination can be given as early as February. In autumn, the opportunities to provide influenza vaccination to individuals at increased risk should not be missed when they present for routine care.

As full protection is usually achieved within 10 to 14 days and there is evidence of increased immunity within a few days, vaccination can still be offered to adults and children after influenza virus activity has been documented in a community.

Influenza vaccine can be administered concurrently with other vaccines, including pneumococcal polysaccharide vaccine and all the scheduled childhood vaccines.

## Recommendations

Annual influenza vaccination is recommended for any person  $\geq 6$  months of age who wishes to reduce the likelihood of becoming ill with influenza.

Influenza vaccination is strongly recommended and should be actively promoted for the following groups:

### 1. People at increased risk of complications from influenza infection

#### (i) All individuals $\geq 65$ years of age<sup>3,10-13</sup>

Influenza vaccine has been shown to reduce hospitalisations from pneumonia and all-cause mortality by about half in adults  $\geq 65$  years of age.

#### (ii) All Aboriginal and Torres Strait Islander people $\geq 15$ years of age

Annual influenza vaccine is recommended for Aboriginal and Torres Strait Islander people  $\geq 15$  years of age in view of the substantially increased risk of hospitalisation and death from influenza and pneumonia (see Chapter 3.15, *Pneumococcal disease*). In Aboriginal and Torres Strait Islander people  $\geq 50$  years of age, routine pneumococcal polysaccharide vaccination is also recommended (see Chapter 2.1, *Vaccination for Aboriginal and Torres Strait Islander people* and Chapter 3.15, *Pneumococcal disease*).

#### (iii) Individuals $\geq 6$ months of age with conditions predisposing to severe influenza

- *Cardiac disease* including cyanotic congenital heart disease, coronary artery disease and congestive heart failure.<sup>14,15</sup> Influenza causes increased morbidity and mortality in children with congenital heart disease and adults with coronary artery disease and congestive heart failure.<sup>14</sup>
- *Chronic respiratory conditions* including:
  - Suppurative lung disease, bronchiectasis, and cystic fibrosis.<sup>16</sup> Patients with these diseases are at greatly increased risk from influenza, which may cause irreversible deterioration in lung function.

- Chronic obstructive pulmonary disease and chronic emphysema. There is clinical trial evidence that inactivated influenza vaccination has a clinically important protective effect on influenza-related exacerbations, and probably an effect on the total of exacerbations in COPD patients. There is no evidence that inactivated influenza vaccination causes exacerbations of COPD.<sup>16</sup>
- Severe asthma. In patients with severe asthma, defined as requiring frequent hospital visits, annual influenza vaccine is an important part of routine care.<sup>17-19</sup> There are insufficient data from randomised controlled trials of influenza vaccine to define efficacy across the whole spectrum of asthma,<sup>20</sup> but influenza can cause severe exacerbations of wheezing, and about 10% of episodes of virus-induced wheezing are attributable to influenza.
- *Other chronic illnesses requiring regular medical follow-up or hospitalisation in the preceding year, including:*
  - diabetes mellitus,
  - chronic metabolic diseases,
  - chronic renal failure,
  - haemoglobinopathies, and
  - impaired immunity (including drug-induced immune impairment).<sup>7,21,22</sup>
- *Chronic neurological conditions* (eg. multiple sclerosis, spinal cord injuries, seizure disorders or other neuromuscular disorders) that can compromise respiratory function or the expulsion of respiratory secretions or that can increase the risk for aspiration.<sup>7</sup> NB. Because they can experience severe, even fatal, influenza, vaccination is particularly important for children  $\geq 6$  months of age with chronic neurological conditions.<sup>7</sup>
- *People with impaired immunity*, including HIV infection.<sup>23,24</sup> Patients with impaired immunity, including HIV infection, malignancy and chronic steroid use, are at greatly increased risk from influenza, although they also have a reduced immune response to the vaccine. While patients with advanced HIV disease and low CD4 T-lymphocyte counts may not develop protective antibody titres, there is evidence that for those with minimal symptoms and high CD4 T-lymphocyte counts (see Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.4), protective antibody titres are obtained after influenza vaccination.<sup>24</sup> Influenza vaccine has been shown in a clinical trial to reduce the incidence of influenza in HIV-infected patients,<sup>24</sup> and although viral load may increase transiently, there is no impact on CD4 count.<sup>23</sup>
- *Long-term aspirin therapy in children* (aged 6 months to 10 years). Such children are at increased risk of Reye syndrome after influenza.

#### (iv) Pregnant women

It is recommended that influenza vaccine be offered in advance to women planning a pregnancy, and to pregnant women who will be in the second or third trimester during the influenza season, including those in the first trimester at the time of vaccination.<sup>25,26</sup> Influenza vaccination is estimated to prevent 1 to 2 hospitalisations per 1000 women vaccinated during the second or third trimester.

#### (v) Residents of nursing homes and other long-term care facilities

This is due to high rates of transmission and complications during outbreaks.<sup>3,9-13,27</sup>

#### (vi) Homeless people and those providing care to them

The living conditions and prevalence of underlying medical conditions among homeless people will predispose to complications and transmission of influenza.

### **2. People who may potentially transmit influenza to those at high risk of complications from influenza**

The following groups of people can potentially transmit influenza to high-risk patients and it has been shown that vaccinating the former protects those at high-risk:

- staff of nursing homes,
- healthcare providers<sup>28</sup> (particularly of patients with impaired immunity),
- staff of long-term care facilities,
- household contacts (including children  $\geq 6$  months of age) of individuals in high-risk groups.

### **3. People involved in the commercial poultry industry or in culling poultry during confirmed avian influenza activity<sup>29</sup>**

Vaccination using the current influenza season vaccine composition is recommended for poultry workers and others in regular close contact with poultry during an avian influenza outbreak.<sup>29</sup> Although routine influenza vaccine does not protect against avian influenza, there is a possibility that a person who was infected at the same time with avian and human strains of influenza virus could allow reassortment of the 2 strains to form a virulent strain that could spread from human to human (ie. initiate a pandemic).

### **4. People providing essential services**

Vaccination of those who provide essential community services will minimise disruption of essential activities during influenza outbreaks. Influenza viral infections can place considerable pressure upon both public and private healthcare services (see Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.6).

## 5. Workers in other industries

The cost-effectiveness of influenza vaccination in industry varies from year to year, depending on the amount of circulating influenza, but the overall impact over time is judged to be cost-saving in several settings.<sup>6,7</sup> Individual industries should consider the benefits of offering influenza vaccine in the workplace.

## 6. Travellers

Large tourist groups, especially those including elderly people and those travelling on cruises, who are likely to be in confined circumstances for days to weeks, are at risk of influenza, either acquired before departure or from travel to areas of the world where influenza is currently circulating. Influenza vaccination, preferably using the strain prevalent in the areas in which they will be travelling, is recommended if travelling during the influenza season, especially if it is known before travel that there are high rates or epidemics of influenza.<sup>7</sup>

## Contraindications

Absolute contraindications to influenza vaccine are:

- anaphylaxis following a previous dose of any influenza vaccine,
- anaphylaxis following any vaccine component,
- individuals with anaphylactic sensitivity to eggs should *not* be given influenza vaccine. This includes those who, soon after ingesting eggs, develop swelling of the lips or tongue, or experience acute respiratory distress or collapse.

## Precautions

Patients with a history of Guillain-Barré Syndrome (GBS) with an onset related in time to influenza vaccination may be at increased risk of again developing GBS if given influenza vaccine. The risk should be weighed against the benefits to the individual patient of influenza vaccination. Because patients with a history of GBS have an increased likelihood of developing the syndrome again, the chance of them coincidentally developing the syndrome following influenza vaccination may be higher than in individuals with no history of GBS.

## Adverse events<sup>27,30</sup>

Local adverse events (induration, swelling, redness and pain) are very common (>10%).

Fever, malaise and myalgia occur commonly (1–10%). These adverse events may commence within a few hours of vaccination and may last for 1 to 2 days. In children <5 years of age, these adverse events may be more pronounced. Post-vaccination symptoms may mimic influenza infection but current influenza vaccines do not contain live virus and cannot cause influenza.

Immediate adverse events (such as hives, angioedema, or anaphylaxis) are a rare consequence of influenza vaccination. They probably represent an allergic response to a residual component of the manufacturing process, most likely egg protein. Individuals with a history of anaphylaxis after eating eggs or a history of a severe allergic reaction following occupational exposure to egg protein should not be given influenza vaccine.

An association was shown between influenza vaccine used in the northern hemisphere from 1992 to 1994 and Guillain-Barré syndrome (GBS), with 1 to 2 cases of GBS occurring per million vaccinated. There has not been an excess number of cases of GBS reported in Australia in association with influenza vaccine.<sup>31</sup>

## Use in pregnancy

Influenza vaccine is recommended for pregnant women who will be in the second or third trimester during the influenza season, including those in the first trimester at the time of vaccination. See 'Recommendations' above.

## Variations from product information

The product information lists allergy to chicken feathers and some food proteins as a contraindication, whereas NHMRC recommends that patients with allergies other than anaphylaxis can be vaccinated.

The product information for Fluarix states the influenza vaccine may be used in children from 3 months of age. NHMRC recommends influenza vaccine in children  $\geq 6$  months of age.

The product information for some vaccines gives a dose of 0.125 mL for children 3 or 6 months to 2 years old. NHMRC recommends that the lowest dose for any influenza vaccine is 0.25 mL. This is because influenza vaccine is relatively poorly immunogenic in infants, and 0.25 mL is the dose recommended in the USA for children aged  $\geq 6$  months where it has been shown to be safe.<sup>32</sup>

The product information for Fluvirin states that the product should not be given to children  $< 4$  years of age. Although the NHMRC recommends that children as young as 6 months of age can be vaccinated if they are at risk of complications of influenza, the suitability of the vaccine formulation for accurate preparation of 0.25 mL doses should be taken into account.

## References

Full reference list available on the electronic *Handbook* or website <http://immunise.health.gov.au>.