Influenza

The disease

Influenza is an acute viral infection of the respiratory tract. There are three types of influenza virus: A, B and C. Influenza A and influenza B are responsible for most clinical illness. Influenza is highly infectious with a usual incubation period of one to three days.

The disease is characterised by the sudden onset of fever, chills, headache, myalgia and extreme fatigue. Other common symptoms include a dry cough, sore throat and stuffy nose. For otherwise healthy individuals, influenza is an unpleasant but usually self-limiting disease with recovery usually within two to seven days. The illness may be complicated by (and may present as) bronchitis, secondary bacterial pneumonia or, in children, otitis media. Influenza can be complicated by meningitis, encephalitis or meningoencephalitis. The risk of serious illness from influenza is higher amongst children under six months of age (Poehling et al., 2006; Ampofo et al., 2006; Coffin et al., 2007; Zhou et al., 2012), older people (Thompson et al., 2003, 2004; Zhou et al., 2012) and those with underlying health conditions such as respiratory or cardiac disease or immunosuppression and pregnant women (Neuzil et al., 1998; O’Brien et al., 2004; Nicoll et al., 2008; Pebody et al., 2010). Influenza during pregnancy may also be associated with perinatal mortality, prematurity, smaller neonatal size and lower birth weight (Pierce et al., 2011; Mendez-Figueroa et al., 2011). Primary influenza pneumonia is a rare complication that may occur at any age and carries a high case fatality rate (Barker and Mullooly, 1982). Serological studies in healthcare professionals have shown that approximately 30 to 50% of influenza infections can be asymptomatic (Wilde et al., 1999) but the proportion of influenza infections that are asymptomatic may vary depending on the characteristics of the influenza strain.

Transmission is by aerosol, droplets or through direct contact with respiratory secretions of someone with the infection (Lau et al., 2010). Influenza spreads rapidly, especially in closed communities. Most cases in the UK tend to occur during an eight- to ten-week period during the winter. The timing, extent
Influenza

and severity of this ‘seasonal’ influenza can all vary. Influenza A viruses cause outbreaks most years and it is these viruses that are the usual cause of epidemics. Large epidemics occur intermittently. Influenza B tends to cause less severe disease and smaller outbreaks, although in children the severity of illness may be similar to that associated with influenza A.

Changes in the principal surface antigens of influenza A – haemagglutinin and neuraminidase – make these viruses antigenically labile. Minor changes (antigenic drifts) occur progressively from season to season. Major changes (antigenic shifts) occur periodically, resulting in the emergence of a new subtype with a different haemagglutinin protein. Because immunity from the previous virus may not protect completely against the new subtype, the population may have little or no immunity, and this may therefore lead to widespread epidemics or even a pandemic.

Three influenza pandemics occurred in the last century (in 1918, 1957 and 1968). The first influenza pandemic of this century was declared by the World Health Organization (WHO) in June 2009. This was caused by an influenza A(H1N1)v virus. Characteristics of this influenza A(H1N1)v strain were higher rates of illness in children and young adults and lower rates of illness in adults aged 60 years and older than is usual with ‘seasonal’ influenza (Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, 2010). For most, the disease was mild. Symptoms were similar to those of ‘seasonal’ influenza, although gastrointestinal symptoms (vomiting and diarrhoea) were more commonly reported than is usual for ‘seasonal’ influenza. During the pandemic, there were fewer than 500 confirmed deaths from influenza A(H1N1)v in the UK with an overall estimated case fatality ratio of 0.25 per 1000 clinical cases (95% confidence limits 0.13 to 0.4 per 1000 clinical cases) (Presanis et al., 2011). Most of the serious complications arising from influenza A(H1N1)v infection occurred in people with underlying health conditions, with the highest mortality rates in those with chronic neurological disease, respiratory disease and immunosuppression (Pebody et al., 2010). Pregnant women were also at increased risk of complications (Jamison et al., 2009). However, a significant proportion of serious complications arose in people who had been healthy (Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, 2010). The influenza A(H1N1)v strain continued to cause widespread illness during the 2010/11 influenza season. Despite the recent emergence of the influenza A(H1N1)v strain, conditions still exist for the emergence of future influenza strains with potential to lead to another pandemic.
Influenza B viruses are also subject to antigenic drift but with less frequent changes.

**History and epidemiology of the disease**

Influenza activity is monitored in the UK through reports of new consultations for influenza-like illness from sentinel GP practices, combined with virological surveillance. Weekly reports are collated by the Health Protection Agency (HPA). Information for England is provided by the Royal College of General Practitioners (RCGP), for Scotland by Health Protection Scotland, for Wales by the Public Health Wales and for Northern Ireland by the Public Health Agency.

Official estimates of the number of deaths from influenza are produced by the HPA. These are inferred from the number of all-cause death registrations in winter that are above an expected seasonal level. However, as the cause of deaths is not examined directly, deaths above the expected level may include
Influenza

causes other than influenza and, if the number of influenza-attributable deaths is small, any excess may not be detected (ND). Estimates of excess winter deaths potentially attributable to influenza in recent years in England and Wales range from ND (in 2005-6 and 2006-7) to 10,351 (in 2008-9). The highest estimate in the past two decades was 21,497 for the 1999-2000 influenza season (Donaldson et al., 2010). The HPA also collects data on deaths in Intensive Care Units with a laboratory confirmed influenza infection where influenza contributed to the death.

Whilst it is not possible to ascertain all fatal cases where influenza was involved, investigation of such cases allows assessment of the characteristics of people most severely affected by influenza, including age, clinical risk factors and vaccination status. An analysis by HPA of data collected in England during the 2010/11 influenza season, when influenza A(H1N1)v was the predominant circulating strain, gives an indication of the increased risk of death from influenza complications for those in clinical risk groups (see Table 19.1).

Table 19.1 Influenza-related mortality ratios and population mortality rates among those aged 6 months to less than 65 years by clinical risk group in England, September 2010 – May 2011.

<table>
<thead>
<tr>
<th>Clinical Risk Group</th>
<th>Number of fatal flu cases (%)</th>
<th>Mortality rate per 100,000 population</th>
<th>Age-adjusted relative risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In a risk group</td>
<td>213 (59.8)</td>
<td>4.0</td>
<td>11.3 (9.1-14.0)</td>
</tr>
<tr>
<td>Not in any risk group</td>
<td>143 (40.2)</td>
<td>0.4</td>
<td>Baseline</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>19 (5.3)</td>
<td>4.8</td>
<td>18.5 (11.5-29.7)</td>
</tr>
<tr>
<td>Chronic heart disease</td>
<td>32 (9.0)</td>
<td>3.7</td>
<td>10.7 (7.3-15.7)</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>59 (16.6)</td>
<td>2.4</td>
<td>7.4 (5.5-10.0)</td>
</tr>
</tbody>
</table>
### Table 19.1: Number of Fatal Flu Cases, Mortality Rate per 100,000 Population, and Age-Adjusted Relative Risk

<table>
<thead>
<tr>
<th>Clinical Risk Factor</th>
<th>Number of Fatal Flu Cases (%)</th>
<th>Mortality Rate per 100,000 Population</th>
<th>Age-Adjusted Relative Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic liver disease</td>
<td>32 (9.0)</td>
<td>15.8</td>
<td>48.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(32.8-70.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26 (7.3)</td>
<td>2.2</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3.8-8.9)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>71 (19.9)</td>
<td>20.0</td>
<td>47.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(35.5-63.1)</td>
</tr>
<tr>
<td>Chronic neurological disease (excluding Stroke/transient ischaemic attack)</td>
<td>42 (11.8)</td>
<td>14.7</td>
<td>40.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(28.7-56.8)</td>
</tr>
<tr>
<td>Total (including 22 cases with no information on clinical risk factors)</td>
<td>378</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

* Mantel-Haenszel age-adjusted rate ratio (RR), with corresponding exact 95% CI were calculated for each risk group using the two available age groups (from six months up to 15 years and from 16 to 64 years).

Table reproduced from ‘Surveillance of influenza and other respiratory viruses in the UK 2010-2011 report’ by kind permission of HPA.

Influenza immunisation has been recommended in the UK since the late 1960s, with the aim of directly protecting those in clinical risk groups who are at a higher risk of influenza associated morbidity and mortality. In 2000, the policy was extended to include all people aged 65 years or over. In 2010, pregnancy was added as a clinical risk category for routine influenza immunisation. Uptake of influenza vaccination in those aged 65 years or over and in those aged under 65 years in a clinical risk group (excluding data on pregnant women) in the UK is shown in Table 19.2.
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Table 19.2 Trivalent influenza vaccine uptake in the UK since the start of the influenza immunisation programme for people aged 65 years or over and, in brackets, aged under 65 years in a clinical risk group (end of influenza vaccination campaign estimates).

<table>
<thead>
<tr>
<th>Year</th>
<th>England (%)</th>
<th>Scotland (%)</th>
<th>Wales (%)</th>
<th>Northern Ireland (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000–01</td>
<td>65.4</td>
<td>65</td>
<td>39</td>
<td>68</td>
</tr>
<tr>
<td>2001–02</td>
<td>67.5</td>
<td>65</td>
<td>59</td>
<td>72</td>
</tr>
<tr>
<td>2002–03</td>
<td>68.6</td>
<td>69</td>
<td>54</td>
<td>72.1 (55.8)</td>
</tr>
<tr>
<td>2003–04</td>
<td>71.0</td>
<td>72.5</td>
<td>63</td>
<td>73.4 (63.8)</td>
</tr>
<tr>
<td>2004–05</td>
<td>71.5 (39.9)</td>
<td>71.7 (39.3)</td>
<td>63</td>
<td>72.7 (65.2)</td>
</tr>
<tr>
<td>2005–06</td>
<td>75.3 (48.0)</td>
<td>77.8 (46.3)</td>
<td>68</td>
<td>76.8 (80.9)</td>
</tr>
<tr>
<td>2006–07</td>
<td>73.9 (42.1)</td>
<td>75.2 (37.8)</td>
<td>*</td>
<td>75.1 (71.2)</td>
</tr>
<tr>
<td>2007–08</td>
<td>73.5 (45.3)</td>
<td>74.3 (44.4)</td>
<td>64</td>
<td>75.7 (68.3)</td>
</tr>
<tr>
<td>2008–09</td>
<td>74.1 (47.1)</td>
<td>76.3 (47.8)</td>
<td>60 (41)</td>
<td>76.8 (74.0)</td>
</tr>
<tr>
<td>2009–10</td>
<td>72.4 (51.6)</td>
<td>75.0 (53.4)</td>
<td>64 (49)</td>
<td>77.0 (80.0)</td>
</tr>
<tr>
<td>2010–11</td>
<td>72.8 (50.4)</td>
<td>75.3 (56.1)</td>
<td>65.8 (48.6)</td>
<td>74.9 (78.7)</td>
</tr>
<tr>
<td>2011-12</td>
<td>74.0 (51.6)</td>
<td>76.2 (56.4)**</td>
<td>67.7 (50.0)</td>
<td>77.0 (81.7)</td>
</tr>
</tbody>
</table>

* Data not available. **Provisional data.

The influenza vaccination

Because of the changing nature of influenza viruses, WHO monitors the epidemiology of influenza viruses throughout the world. Each year it makes recommendations about the strains to be included in vaccines for the forthcoming winter for the northern and southern hemispheres (www.who.int/csr/disease/influenza).

Influenza vaccines are prepared using virus strains in line with the WHO recommendations. Current influenza vaccines are trivalent, containing two subtypes of influenza A and one type B virus. In most recent years, these have closely matched viruses circulating during the subsequent influenza season. If a new influenza A subtype were to emerge with epidemic or pandemic
potential (as occurred in 2009 with influenza A(H1N1)v), it is unlikely that the influenza vaccine will be well matched to the emerging strain. In these circumstances, as was done during the 2009 pandemic, a monovalent vaccine against that strain will be developed and implemented.

All authorised trivalent influenza vaccines need to meet immunogenicity, safety and quality criteria set by the European Medicines Agency (EMA), with the assessment of efficacy based on meeting or exceeding indicated requirements in serological assessments of immunogenicity (EMA, 1997). A recent meta-analysis, which included studies when the influenza virus strains in the vaccine were drifted or mis-matched with those in circulation, suggested an overall efficacy against confirmed disease of 59% (95% confidence interval 51-67) in adults aged 18 to 65 years (Osterholm et al., 2012). In the elderly, protection produced by the vaccine may be lower (Fleming et al., 2010), although immunisation has been shown to reduce the incidence of severe disease including bronchopneumonia, hospital admissions and mortality (Wright et al., 1977; Mangtani et al., 2004). Trivalent live attenuated influenza vaccine has been shown to provide a higher level of protection for children than trivalent inactivated influenza vaccine (Belshe et al, 2007); a recent meta-analysis suggested an efficacy against confirmed disease of 83% (95% confidence interval 69-91) (Osterholm et al., 2012; Ashkenazi et al., 2006; Fleming et al., 2006).

After immunisation, protective immune responses may be achieved within 14 days. Although influenza activity is not usually significant before the middle of November, the influenza season can start early (as it did in 2003–04), and therefore the ideal time for immunisation is between September and early November. Protection afforded by the vaccine is thought to last for at least one influenza season, although the level of protection provided in subsequent seasons is likely to reduce, hence the importance of re-vaccination.

Manufacture of influenza vaccines is complex and conducted to a tight schedule, constrained by the period between the announcement of the WHO recommendations and the opportunity to vaccinate before the influenza season. Manufacturers may not be able to respond to unexpected demands for vaccine at short notice.

All but one of the influenza vaccines available in the UK are inactivated and do not contain live viruses. One vaccine (Fluenz®) contains live virus that has been attenuated (weakened) and adapted to cold so that it cannot replicate at body temperature. None of the influenza vaccines can therefore
Influenza

cause influenza in those that can be vaccinated. Most of the vaccines are administered by intramuscular injection, although one vaccine (Intanza®) is administered by the intradermal route and another (Fluenz®) by nasal spray. Most of the vaccines are prepared from viruses grown in embryonated hens eggs. The trivalent influenza vaccines available in the UK for the 2012/13 influenza season are listed in Table 19.5.

Storage (also refer to Chapter 3)

Vaccines should be stored in the original packaging at +2°C to +8°C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents.

Presentation

Trivalent inactivated influenza vaccines for intramuscular administration are supplied as suspensions in pre-filled syringes. They should be shaken well before they are administered.

Intanza®, the intradermal vaccine, is supplied in a micro-needle injection system.

Fluenz®, the intranasal vaccine, is supplied as a nasal spray suspension in a special applicator.

Dosage and schedule

The dosages and schedules for influenza vaccines are shown in Table 19.3 and should be given according to the recommendations for use of the vaccines (see later).

Some influenza vaccine summaries of product characteristics (SPCs) of intramuscular inactivated influenza vaccines indicate that young children can be given either a 0.25ml or a 0.5ml dose. The Joint Committee on Vaccination and Immunisation has advised that where these alternative doses are indicated in the SPC, the 0.5ml dose of intramuscular inactivated influenza vaccine should be given to infants aged six months or older and young children because there is evidence that this dose is effective in young children (Heinonen et al., 2010).
Table 19.3 Dosage for trivalent influenza vaccines

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated intramuscular vaccine (number of different brands)</td>
<td>Children aged 6 months and older and adults, although some of the vaccines are not authorised for young children – see table 19.5</td>
<td>Single injection of 0.5ml (see note above) Children aged 6 months to less than 9 years who have not received influenza vaccine before should receive a second dose of vaccine at least 4 weeks later.</td>
</tr>
<tr>
<td>Inactivated intradermal vaccine - Intanza® 9µg</td>
<td>Adults aged 18 years to 59 years</td>
<td>Single injection of 0.1ml</td>
</tr>
<tr>
<td>Inactivated intradermal vaccine - Intanza® 15µg</td>
<td>Adults aged 60 years and older</td>
<td>Single injection of 0.1ml</td>
</tr>
<tr>
<td>Live attenuated intranasal vaccine - Fluenz®</td>
<td>Children aged 2 to less than 18 years (see contraindications)</td>
<td>Single application in each nostril of 0.1ml Children aged 2 to less than 9 years who have not received influenza vaccine before should receive a second dose of vaccine at least 4 weeks later.</td>
</tr>
</tbody>
</table>

Administration

The inactivated influenza vaccines given by intramuscular injection should be given preferably into the upper arm (or anterolateral thigh in infants). However, individuals with a bleeding disorder should be given vaccine by deep subcutaneous injection to reduce the risk of bleeding.
The inactivated influenza vaccine administered by the intradermal route (Intanza®) is supplied in a micro-needle injection system that is held at right-angles to the skin. The device allows intradermal vaccination to be performed without the need for additional training.

The live attenuated influenza vaccine administered by the intranasal route (Fluenz®) is supplied in an applicator that allows a divided dose of to be administered in both nostrils (total dose of 0.2ml, 0.1ml in each nostril). The device allows intranasal administration to be performed without the need for additional training. Administration of either dose does not need to be repeated if the patient sneezes, or blows their nose following administration. There are no data on the effectiveness of Fluenz® when given to children with heavily blocked or runny nose (rhinitis) attributable to infection or allergy. As heavy nasal congestion might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration until resolution of the nasal congestion should be considered or an appropriate alternative intramuscularly administered influenza vaccine should be considered.

Inactivated influenza vaccines can be given at the same time as other vaccines. The live attenuated vaccine can also be given at the same time as other vaccines including live vaccines. On the basis of first principles, it is normally recommended that, where vaccines cannot be administered simultaneously, a four week interval should be observed between live vaccines. There are no data on whether this advice applies to live attenuated intranasal influenza vaccine and so, where protection against influenza is needed before the start of the seasonal increase in influenza activity, vaccination should not be delayed because of another recent live vaccination or vaccination with inactivated vaccine should be offered. Intramuscular and intradermal vaccines should be given at separate sites, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003).

The site at which each vaccine is given and the batch numbers of the vaccines should be recorded in the individual’s records. Where the vaccine is given for occupational reasons, it is recommended that the employer keep a vaccination record. It is important that vaccinations given either at a general practice or elsewhere (for example, at community pharmacies, or antenatal clinics) are recorded on appropriate health records for the individual (using the appropriate clinical code) in a timely manner. If given elsewhere, a record of vaccination should be returned to the patient’s general practice to allow clinical follow up and to avoid duplicate vaccination.
Disposal (also refer to Chapter 3)

Equipment used for vaccination, including used vials, ampoules, or partially discharged vials and syringes should be disposed of at the end of a session by sealing in a proper, puncture-resistant ‘sharps’ box according to local authority regulations and guidance in the technical memorandum 07-01 (Department of Health, 2006).

Recommendations for the use of the vaccines

The objective of the influenza immunisation programme is to protect those who are most at risk of serious illness or death should they develop influenza. Other objectives include reducing transmission of the infection, thereby contributing to the protection of vulnerable patients who may have a suboptimal response to their own immunisations.

To facilitate this, general practitioners are required to proactively identify all those for whom influenza immunisations is indicated and to compile a register of those patients for whom influenza immunisation is recommended. Sufficient vaccine can then be ordered in advance and patients can be invited to planned immunisation sessions or appointments. Given that some influenza vaccines are restricted for use in particular age groups, the SPCs for individual products should always be referred to when ordering vaccines to ensure that they can be given appropriately to particular patient age groups. Research has identified processes at GP surgeries that are associated with higher uptake of influenza vaccine (Dexter et al., 2012).

Patients should be advised that many other organisms cause respiratory infections similar to influenza during the influenza season, e.g. the common cold and respiratory syncytial virus. Influenza vaccine will not protect against these diseases.

Trivalent influenza vaccine should be offered, ideally before the virus starts to circulate to:

- all those aged 65 years or older
- all those aged six months or older in the clinical risk groups shown in Table 19.4.
Table 19.4 Clinical risk groups who should receive the influenza immunisation. Influenza vaccine should be offered to people in the clinical risk categories set out below.

<table>
<thead>
<tr>
<th>Clinical risk category</th>
<th>Examples (this list is not exhaustive and decisions should be based on clinical judgement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic respiratory disease</td>
<td>Asthma that requires continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission.</td>
</tr>
<tr>
<td></td>
<td>Chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD).</td>
</tr>
<tr>
<td></td>
<td>Children who have previously been admitted to hospital for lower respiratory tract disease.</td>
</tr>
<tr>
<td></td>
<td>(see precautions section on live attenuated influenza vaccine)</td>
</tr>
<tr>
<td>Chronic heart disease</td>
<td>Congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication and/or follow-up for ischaemic heart disease.</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Chronic kidney disease at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation.</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>Cirrhosis, biliary atresia, chronic hepatitis</td>
</tr>
</tbody>
</table>
| Chronic neurological disease (included in the DES directions for Wales) | Stroke, transient ischaemic attack (TIA). Conditions in which respiratory function may be compromised due to neurological disease (e.g. polio syndrome sufferers).

Clinicians should consider on an individual basis the clinical needs of patients including individuals with cerebral palsy, multiple sclerosis and related or similar conditions; or hereditary and degenerative disease of the nervous system or muscles; or severe neurological or severe learning disability. |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Type 1 diabetes, type 2 diabetes requiring insulin or oral hypoglycaemic drugs, diet controlled diabetes.</td>
</tr>
</tbody>
</table>
| Immunosuppression | Immunosuppression due to disease or treatment. Patients undergoing chemotherapy leading to immunosuppression. Asplenia or splenic dysfunction. HIV infection at all stages. Individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day (any age) or for children under 20kg a dose of 1mg or more per kg per day.

It is difficult to define at what level of immunosuppression a patient could be considered to be at a greater risk of the serious consequences of influenza and should be offered influenza vaccination. This decision is best made on an individual basis and left to the patient’s clinician.

Some immunocompromised patients may have a suboptimal immunological response to the vaccine.

(see contraindications and precautions section on live attenuated influenza vaccine) |
Influenza

**Pregnant women**

Pregnant women at any stage of pregnancy (first, second or third trimesters).

(see precautions section on live attenuated influenza vaccine)

The list above is not exhaustive, and the medical practitioner should apply clinical judgement to take into account the risk of influenza exacerbating any underlying disease that a patient may have, as well as the risk of serious illness from influenza itself. Trivalent influenza vaccine should be offered in such cases even if the individual is not in the clinical risk groups specified above. Consideration should also be given to the vaccination of household contacts of immunocompromised individuals, i.e. individuals who expect to share living accommodation on most days over the winter and therefore for whom continuing close contact is unavoidable. This may include carers (see below).

In addition to the above, immunisation is provided to healthcare and social care workers in direct contact with patients/clients to protect them and to reduce the transmission of influenza within health and social care premises, to contribute to the protection of individuals who may have a suboptimal response to their own immunisations, and to avoid disruption to services that provide their care. This would include:

- health and social care staff directly involved in the care of their patients or clients

- those living in long-stay residential care homes or other long-stay care facilities where rapid spread is likely to follow introduction of infection and cause high morbidity and mortality (this does not include prisons, young offender institutions, university halls of residence etc.)

- those who are in receipt of a carer’s allowance, or those who are the main carer of an elderly or disabled person whose welfare may be at risk if the carer falls ill. Vaccination should be given on an individual basis at the GP’s discretion in the context of other clinical risk groups in their practice

- others involved directly in delivering health and social care such that they and vulnerable patients/clients are at increased risk of exposure to influenza (further information is provided in guidance from UK health departments).
Live attenuated influenza vaccine (Fluenz®) has been shown to provide greater protection for children than inactivated influenza vaccine (Belshe et al., 2007; Ashkenazi et al., 2006; Fleming et al., 2006). This vaccine is the preferred vaccine for children aged two to less than 18 years in clinical risk groups except those with certain immunodeficiencies (see contraindications), with severe asthma (British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS SIGN) step 4 or above), active wheezing at the time of vaccination or when pregnant (see precautions). However, supplies of this vaccine for the 2012/13 influenza season will be limited.

Studies have shown that two doses of trivalent inactivated influenza vaccine are required to achieve adequate antibody levels in younger children as they may never have been exposed to influenza or been vaccinated (Allison et al., 2006; Neuzil et al., 2006; Ritzwoller et al., 2005; Shuler et al., 2007; Wright et al., 1977). For the live attenuated influenza vaccine, studies have shown meaningful efficacy after a single dose in previously unvaccinated children but higher efficacy following two doses of vaccine (Bracco Neto et al., 2009; Block et al., 2009). Children aged six months to less than 9 years in clinical risk groups who have not previously received trivalent influenza vaccine should receive two doses of trivalent influenza vaccine; otherwise only a single dose of either inactivated or live attenuated influenza vaccine is required. The inactivated trivalent influenza vaccines are interchangeable; the second dose should be given at least four weeks after the first dose in accordance with the manufacturer’s SPC for that vaccine. The same interval should be observed between two doses of live attenuated vaccine.

A chart (see Figure 19.2) summarises the advice on influenza vaccination for the 2012/13 influenza vaccination programme.
Figure 19.2: Chart summarising the advice on influenza vaccination for the 2012/13 influenza vaccination programme. This chart should be read in conjunction with the contraindications and precautions sections and also table 19.5 that gives details about the age indications for influenza vaccines.
Contraindications

The SPCs for individual products should always be referred to when deciding which vaccine to give. There are very few individuals who cannot receive any influenza vaccine. When there is doubt, appropriate advice should be sought promptly from an immunisation co-ordinator, consultant in communicable disease control or consultant paediatrician, so that the period the individual is left unvaccinated is minimised.

None of the influenza vaccines should be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of the vaccine, or
- a confirmed anaphylactic reaction to any component of the vaccine (other than ovalbumin – see precautions).

Confirmed anaphylaxis is rare (see Chapter 8 for further information). Other allergic conditions such as rashes may occur more commonly and are not contraindications to further immunisation. A careful history of the event will often distinguish between true anaphylaxis and other events that are either not due to the vaccine or are not life threatening. In the latter circumstance, it may be possible to continue the immunisation course. Specialist advice must be sought on the vaccines and the circumstances in which they could be given (see Chapter 6 for further information). The risk to the individual of not being immunised must be taken into account.

The live attenuated influenza vaccine (Fluenz®) should not be given to children or adolescents who are clinically severely immunodeficient due to conditions or immunosuppressive therapy such as: acute and chronic leukaemias; lymphoma; HIV infection not on highly active antiretroviral therapy (HAART); cellular immune deficiencies; and high dose corticosteroids. It is not contraindicated for use in children or adolescents with HIV infection receiving stable antiretroviral therapy; or who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids or those receiving corticosteroids as replacement therapy, e.g. for adrenal insufficiency. It is contraindicated in children and adolescents younger than 18 years of age receiving salicylate therapy because of the association of Reye’s syndrome with salicylates and wild-type influenza infection.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may
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be postponed until they have fully recovered. This is to avoid confusing the
differential diagnosis of any acute illness by wrongly attributing any signs or
symptoms to the adverse effects of the vaccine.

Severe asthma or active wheezing
The live attenuated influenza vaccine (Fluenz®) is not recommended for
children with active wheezing at the time of vaccination or severe asthma
(BTS SIGN step 4 or above) because of limited safety data in these groups.

Pregnancy
Pregnant women should be offered inactivated influenza vaccine. A review
of studies on the safety of influenza vaccine in pregnancy concluded that
inactivated influenza vaccine can be safely and effectively administered
during any trimester of pregnancy and that no study to date has demonstrated
an increased risk of either maternal complications or adverse fetal outcomes
associated with inactivated influenza vaccine (Tamma et al., 2009). A number
of studies show that influenza vaccination during pregnancy provides passive
immunity against influenza to infants in the first few months of life following
birth (Benowitz et al., 2010; Eick et al., 2010; Zaman et al., 2008; Poehling et
al., 2011). A study showed that influenza vaccination reduced the likelihood of
prematurity and smaller infant size at birth associated with influenza infection
(Omer et al., 2011).

Data are more limited for the live attenuated influenza vaccine (Fluenz®). Whilst
there is no evidence of risk with live attenuated influenza vaccine
(Toback et al., 2012), inactivated influenza vaccines are preferred for those aged
under 18 years who are pregnant. There is no need, however, to specifically
test eligible girls for pregnancy or to advise avoidance of pregnancy in those
who have been recently vaccinated.

Preterm infants
It is important that preterm infants who have risk factors have their
immunisations at the appropriate chronological age. Influenza immunisation
should be considered after the child has reached six months of age.

Immunosuppression and HIV infection
Individuals who have immunosuppression and HIV infection (regardless
of CD4 count) should be given influenza vaccine in accordance with the
recommendations and contraindications above. These individuals may not
make a full antibody response.
Consideration should also be given to the influenza vaccination of household contacts of immunocompromised individuals, i.e. individuals who expect to share living accommodation on most days over the winter and therefore for whom continuing close contact is unavoidable.

There is a potential for transmission of live attenuated influenza virus in Fluenz® to severely immunocompromised contacts (e.g. bone marrow transplant patients requiring isolation) for one to two weeks following vaccination. Where close contact with immunocompromised patients (for example household members) is likely or unavoidable, appropriate alternative inactivated influenza vaccines should be considered.

Further guidance is provided by the Royal College of Paediatrics and Child Health (www.rcpch.ac.uk), the British HIV Association (BHIVA) Immunisation guidelines for HIV-infected adults (BHIVA, 2008) (www.bhiva.org) and the Children’s HIV Association of UK and Ireland (CHIVA) immunisation guidelines (www.chiva.org.uk).

**Egg allergy**

Individuals who have egg allergy may be at increased risk of reaction to influenza vaccines. In recent years, inactivated influenza vaccines that are egg-free or have a very low ovalbumin content have become available. There are no data on the use of live attenuated vaccine (Fluenz®) in children with egg allergy.

Patients who have either confirmed anaphylaxis to egg or egg allergy with uncontrolled asthma (BTS SIGN step 4 or above) can be immunised with an egg-free influenza vaccine (if available). If no egg-free vaccine is available, patients should be referred to specialists for vaccination in hospital using an inactivated influenza vaccine with an ovalbumin content less than 0.12 µg/ml (equivalent to 0.06 µg for 0.5 ml dose). A split dose schedule may be required at the discretion of the supervising physician. Facilities should be available and staff trained to recognise and treat anaphylaxis (see chapter 8). Vaccines with ovalbumin content more than 0.12 µg/ml (equivalent to 0.06 µg for 0.5 ml dose) or where content is not stated should not be used in egg-allergic individuals.

All other egg allergic individuals can be given egg-free vaccine or inactivated influenza vaccine with an ovalbumin content less than 0.12 µg/ml (equivalent to 0.06 µg for 0.5 ml dose) administered as recommended in primary care.

The ovalbumin content of influenza vaccines is given in Table 19.5 (p. 207).
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**Use with antiviral agents against influenza**

There is a potential for influenza antiviral agents to lower the effectiveness of the live attenuated influenza vaccine (Fluenz®). Therefore influenza antiviral agents and Fluenz® and should not be administered concomitantly. Fluenz® should not be administered within 48 hours following the cessation of treatment with influenza antiviral agents. Administration of influenza antiviral agents within two weeks of administration of Fluenz® may adversely affect the effectiveness of the vaccine.

**Adverse reactions**

Pain, swelling or redness at the injection site, low grade fever, malaise, shivering, fatigue, headache, myalgia and arthralgia are among the commonly reported symptoms after intramuscular or intradermal vaccination. A small painless nodule (induration) may also form at the injection site. These symptoms usually disappear within one to two days without treatment. Nasal congestion/rhinorrhoea is the most common adverse reaction following administration of the live attenuated intranasal vaccine (Fluenz®).

Immediate reactions such as urticaria, angio-oedema, bronchospasm and anaphylaxis can occur.

The following adverse events have been reported very rarely after influenza vaccination over the past 30 years but no causal association has been established: neuralgia, paraesthesiae, convulsions (see note below) and transient thrombocytopenia, vasculitis with transient renal involvement and neurological disorders such as encephalomyelitis.

A study in the UK found that there was no association between Guillain-Barré syndrome (GBS) and influenza vaccines although there was a strong association between GBS and influenza-like illness. The increased risk of GBS after influenza-like illness, if specific to infection with influenza virus, together with the absence of a causal association with influenza vaccine suggests that influenza vaccine should protect against GBS (Stowe et al., 2009). GBS has been reported very rarely after immunisation with influenza vaccine, one case per million people vaccinated in one US study (Laskey et al., 1998). However, this has not been found in other studies and a causal relationship has not been established (Hurwitz et al., 1981; Kaplan et al., 1982; Roscelli et al., 1991).

All serious suspected reactions following influenza vaccines should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card scheme at www.mhra.gov.uk/yellowcard
The trivalent influenza vaccines, Intanza® 15 µg, Intanza® 9 µg, Fluenz® and Optaflu® carry a black triangle symbol (▼ / see Table 19.5 for reference). This is a standard symbol added to the product information of a vaccine during the earlier stages of its introduction, to encourage reporting of all suspected adverse reactions.

**Febrile convulsions**

*CSL inactivated influenza vaccine/Enzira®*

Epidemiological information from Australia in 2010 indicated a higher than expected rate in febrile convulsions in children under five years of age related to the use of a influenza vaccine manufactured by CSL in Australia (Fluvax). The evidence from Australia indicated and incidence of febrile convulsions in the range of ≥ 1/1000 to < 1/100 for children under five years of age who were vaccinated with Fluvax.

Fluvax is the same product marketed in the UK by Pfizer as Enzira® or CSL Biotherapies generic influenza vaccine. Due to the risk of febrile convulsions, the indication for these products is restricted to use in adults and children aged five years and older. The SPCs also indicate that an increased number of reports of fever was also reported in the age group aged five to under nine years. Clinicians should consider the use of alternative influenza vaccines authorised for use in children aged five to under nine years. If no suitable alternative vaccines are available, clinicians should ensure parents are aware of the risk and give advice on the management of vaccine-induced fever (see chapter 8).

Available evidence indicates that this is a reaction specific to the CSL vaccine, and there remains no evidence that other trivalent influenza vaccines used in the UK are associated with a similar risk of febrile convulsions in children (Stowe et al., 2011; Bryan & Seabroke, 2011).

**Viroflu® and Inflexal®V**

There are indications that the influenza vaccines, Viroflu® and Inflexal®V (Janssen-Cilag Ltd, formerly Crucell) may be associated with a higher than expected rate of fever in children aged under five years. It remains unclear if this may translate into an increased risk of febrile convulsions in children. As a precaution, clinicians should consider the use of alternative influenza vaccines authorised for use in children under five years of age. If no suitable alternative vaccines are available, clinicians should ensure parents are aware
Influenza

of the risk and give advice on the management of vaccine-induced fever (see chapter 8).

**Management of suspected cases, contacts and outbreaks**

There are antiviral drugs available that can be used under certain circumstances to either prevent or treat influenza. NICE has issued guidance on the use of antiviral drugs for the prevention and treatment of influenza at:


and

http://guidance.nice.org.uk/TA168

It is always important to encourage and maintain good hand and respiratory hygiene which can help to reduce the spread of influenza. Information and resources on the 'Catch it, Bin it, Kill it', hand and respiratory hygiene campaign can be found on the Department of Health website.

http://www.dh.gov.uk (enter Catch it, bin it, kill it in the search box)

**Supplies**

Demand for influenza vaccine sometimes increases unpredictably in response to speculation about influenza illness in the community. Therefore, it is recommended that practices order sufficient vaccine for their needs, based on their ‘at risk’ registers, well in advance of the immunisation season.

Information on supplies and how to order vaccines will be given in guidance provided by each of the four UK countries health departments – see four countries health departments’ websites for details.

Influenza vaccines available for the 2012/13 influenza season are shown in Table 19.5.
Table 19.5 Trivalent influenza vaccines for the 2012/13 influenza season (note the ovalbumin content is provided in units of µg/ml and µg/dose)

<table>
<thead>
<tr>
<th>Supplier</th>
<th>Name of product</th>
<th>Vaccine type</th>
<th>Age indications</th>
<th>Ovalbumin content µg/ml (µg/dose)</th>
<th>Contact details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abbott Healthcare</strong></td>
<td>Influvac®</td>
<td>Inactivated</td>
<td>From 6 months</td>
<td>0.2 (0.1/0.5ml dose)</td>
<td>0800 358 7468</td>
</tr>
<tr>
<td></td>
<td>Imuvac®</td>
<td>Inactivated</td>
<td>From 6 months</td>
<td>0.2 (0.1/0.5ml dose)</td>
<td></td>
</tr>
<tr>
<td><strong>AstraZeneca UK Ltd</strong></td>
<td>FLUENZ®</td>
<td>Live attenuated</td>
<td>From 24 months to less than 18 years of age</td>
<td>≤1.2 (≤0.24/0.2ml dose)</td>
<td>0845 139 0000</td>
</tr>
<tr>
<td><strong>Janssen-Cilag Ltd (formerly Crucell UK)</strong></td>
<td>Viroflu®</td>
<td>Inactivated</td>
<td>From 6 months (but see adverse reactions section on use in children aged 6 months to &lt; 5 years)</td>
<td>≤0.1 (≤0.05/0.5ml dose)</td>
<td>0844 800 3907</td>
</tr>
<tr>
<td></td>
<td>Inflexal®V</td>
<td>Inactivated</td>
<td>From 6 months (but see adverse reactions section on use in children aged 6 months to &lt; 5 years)</td>
<td>≤0.1 (≤0.05/0.5ml dose)</td>
<td></td>
</tr>
<tr>
<td><strong>GlaxoSmithKline</strong></td>
<td>Fluarix®</td>
<td>Inactivated</td>
<td>From 6 months</td>
<td>0.1 (≤0.05/0.5ml dose)</td>
<td>0800 221 441</td>
</tr>
</tbody>
</table>
### Influenza

<table>
<thead>
<tr>
<th>Supplier</th>
<th>Name of product</th>
<th>Vaccine type</th>
<th>Age indications</th>
<th>Ovalbumin content µg/ml (µg/dose)</th>
<th>Contact details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MASTA</strong></td>
<td>Imuvac®</td>
<td>Inactivated</td>
<td>From 6 months</td>
<td>0.2 (0.1/0.5ml dose)</td>
<td>0113 238 7500 (option 1)</td>
</tr>
<tr>
<td></td>
<td>Influvac®</td>
<td>Inactivated</td>
<td>From 6 months</td>
<td>0.2 (0.1/0.5ml dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inactivated Influenza Vaccine (Split Virion) BP</td>
<td>Inactivated</td>
<td>From 6 months</td>
<td>≤0.1 (≤0.05/0.5ml dose)</td>
<td></td>
</tr>
<tr>
<td><strong>Novartis Vaccines</strong></td>
<td>Agrippal®</td>
<td>Inactivated</td>
<td>From 6 months</td>
<td>≤0.4 (≤0.2/0.5mL dose)</td>
<td>08457 451 500</td>
</tr>
<tr>
<td></td>
<td>Fluvirin®*</td>
<td>Inactivated</td>
<td>From 4 years</td>
<td>≤2 (≤1/0.5mL dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optaflu® ▼</td>
<td>Inactivated</td>
<td>From 18 years</td>
<td>No ovalbumin</td>
<td></td>
</tr>
<tr>
<td><strong>Pfizer Vaccines</strong></td>
<td>Inactivated Influenza Vaccine®</td>
<td>Inactivated</td>
<td>From 5 years (but see adverse reactions section on use in children aged 5 to &lt; 9 years)</td>
<td>≤2 (≤1/0.5ml dose)</td>
<td>01304 616161</td>
</tr>
<tr>
<td></td>
<td>Enzira®</td>
<td>Inactivated</td>
<td>From 5 years (but see adverse reactions section on use in children aged 5 to &lt; 9 years)</td>
<td>≤2 (≤1/0.5ml dose)</td>
<td></td>
</tr>
</tbody>
</table>
### References


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Accessed July 2010

Australian Government (2010b)


Accessed July 2010


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Committee on Safety of Medicines (2003) Further data support safety of thiomersal in vaccines. Available from:

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Accessed: May 2010


Accessed January 2011


Accessed: May 2010

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