19

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 more unusually 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 and 2004; Zhou *et al*, 2012) and those with underlying health conditions such as respiratory or cardiac disease, chronic neurological conditions, or immunosuppression and pregnant women (Neuzil *et al*., 1998; O'Brien *et al*., 2004; Nicoll *et al*., 2008 and 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). Although primary influenza pneumonia is a rare complication that may occur at any age and carries a high case fatality rate (Barker and Mullooly, 1982), it was seen more frequently during the 2009 pandemic and the following influenza season. 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 droplets, aerosol, 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 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 overall. The burden of influenza B disease is mostly in children when the severity of illness can 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 described as antigenic drift occur progressively from season to season. Antigenic shift occurs periodically, resulting in major changes and 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. The influenza A(H1N1)v pandemic caused higher rates of illness in children and young adults and lower rates of illness in adults aged 60 years and older when compared with 'seasonal' influenza (Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, 2010). For most individuals, 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 laboratory 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). The highest mortality rates were 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). Most of the serious complications arising from influenza A(H1N1) v infection occurred in people with underlying health conditions, but a significant proportion arose in people who had been previously healthy (Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, 2010).

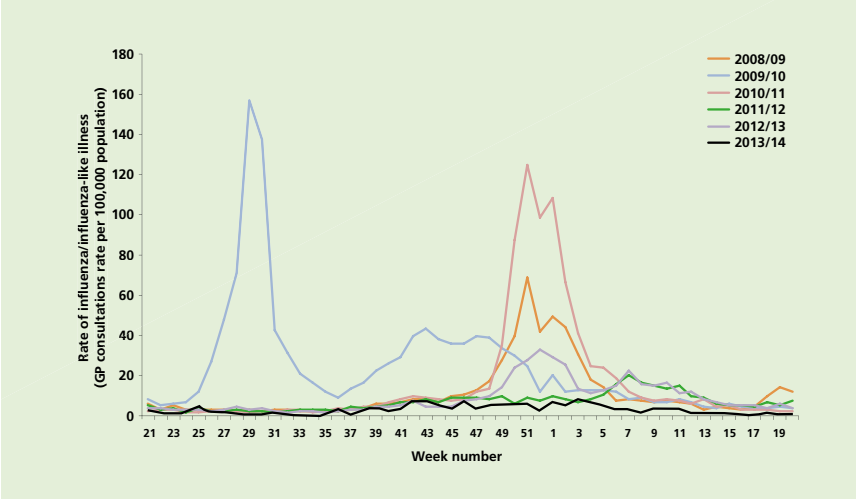

Figure 19.1 Rate of influenza/influenza-like illness episodes in England (weekly returns to Royal College of General Practitioners), 2008–09 to 2013–14 showing the variation in the timing and shape of influenza activity usually between weeks 37 and 15. However, much of the influenza A(H1N1)v pandemic activity was outside that usual time window, demonstrated by the non-seasonal peak at week 29 in 2009/10. Data for 2009/10 may underestimate the extent of influenza-like illness due to the introduction of the National Pandemic Flu Service in England during 2009. There may be differences in the epidemiology of influenza between the different countries in the UK. Data provided by PHE (formerly HPA) and RCGP.

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 (for example, from influenza A H5N1 or H7N9 strains).

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 a variety of schemes based in primary and secondary care. One important indicator is based on reports of new consultations for influenza-like illness from sentinel GP practices, combined with virological surveillance. Weekly reports are collated by Public Health England (PHE, formerly Health Protection Agency (HPA)). Additional information for England is provided by the Royal College of

General Practitioners (RCGP), for Scotland by Health Protection Scotland, for Wales by Public Health Wales and for Northern Ireland by the Public Health Agency.

Official estimates of the number of deaths attributable to influenza are produced by PHE. These are inferred from the number of all-cause death registrations in the winter period that are above an expected seasonal level. However, as the cause of deaths is not examined directly, deaths above the expected level may include causes other than influenza such as cold weather related conditions. Estimates of excess winter deaths potentially attributable to influenza in years in the last decade in England and Wales range from not determined (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).

PHE also collects data on admissions to intensive care units and on deaths with a laboratory-confirmed influenza infection. 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 and the responsible influenza type. An analysis by PHE of data from fatal cases 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 population mortality rates and relative risk of death among those aged six months to under 65 years by clinical risk group in England, September 2010 – May 2011.

	Number of fatal flu cases (%)	Mortality rate per 100,000 population	Age-adjusted relative risk*
In a risk group	213 (59.8)	4.0	11.3 (9.1-14.0)
Not in any risk group	143 (40.2)	0.4	Baseline
Chronic renal disease	19 (5.3)	4.8	18.5
Chronic heart disease	32 (9.0)	3.7	10.7 (7.3-15.7)
Chronic respiratory disease	59 (16.6)	2.4	7.4 (5.5-10.0)
Chronic liver disease	32 (9.0)	15.8	48.2 (32.8-70.6)
Diabetes	26 (7.3)	2.2	5.8 (3.8-8.9)
Immunosuppression	71 (19.9)	20.0	47.3 (35.5-63.1)
Chronic neurological disease (excluding stroke/transient ischaemic attack)	42 (11.8)	14.7	40.4 (28.7-56.8)
Total (including 22 cases with no information on clinical risk factors)	378	0.8	

* 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 PHE.

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 (see later for age definition). In 2010, pregnancy was added as a clinical risk category for routine influenza immunisation. In 2012, the Joint Committee on Vaccination and Immunisation (JCVI) recommended that the programme should be extended to all children aged two to 16 years. The phased introduction of this extension began in 2013 with the inclusion of children aged two and three years in the routine programme (see later for age definition). **For the 2014/15 season children aged two, three and four years are included in the routine programme.**

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.

Table 19.2 Influenza vaccine uptake in the UK for people aged 65 years or over and, in brackets, aged under 65 years in a clinical risk group (excluding pregnant women). End of influenza vaccination campaign estimates.

Year	England (%)	Scotland (%)	Wales (%)	Northern Ireland (%)
2000–01	65.4	65	39	68
2001–02	67.5	65	59	72
2002–03	68.6	69	54	72.1 (55.8)
2003–04	71.0	72.5	63	73.4 (63.8)
2004–05	71.5 (39.9)	71.7 (39.3)	63	72.7 (65.2)
2005–06	75.3 (48.0)	77.8 (46.3)	68	76.8 (80.9)
2006–07	73.9 (42.1)	75.2 (37.8)	*	75.1 (71.2)
2007–08	73.5 (45.3)	74.3 (44.4)	64	75.7 (68.3)
2008–09	74.1 (47.1)	76.3 (47.8)	60 (41)	76.8 (74.0)
2009–10	72.4 (51.6)	75.0 (53.4)	64 (49)	77.0 (80.0)
2010–11	72.8 (50.4)	75.3 (56.1)	65.8 (48.6)	74.9 (78.7)
2011-12	74.0 (51.6)	76.6 (59.7)	67.7 (50.0)	77.0 (81.7)
2012-13	73.4 (51.3)	77.4 (59.2)	67.7 (49.7)	75.0 (80.2)
2013-14	73.2 (52.3)	76.9% (57.5) **	68.3 (51.1)	75.4 (76.4)

* Data not available. **Provisional data.

The uptake of influenza vaccine by pregnant women is difficult to estimate as it is more challenging to determine a denominator accurately. The available data are shown in Table 19.3 but may underestimate uptake.

Table 19.3 Influenza vaccine uptake in the UK since the start of the influenza immunisation programme for pregnant women. End of influenza vaccination campaign estimates.

Year	England (%)	Scotland (%)	Wales (%)	Northern Ireland (%)
2010-11	38.0	65.6*	39.6	N/A
2011-12	27.4	41.1	31.7	58.4
2012-13	40.3	54.0	61.6	64.6
2013-14	39.8	49.2	43.8	58.0

* Denominator incomplete

More detailed analyses of influenza vaccine uptake by individual clinical risk groups and by different age groups are made available by the UK public health bodies on their webpages.

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 (http://www.who.int/influenza/en/).

Influenza vaccines are prepared using virus strains in line with the WHO recommendations. Most current influenza vaccines are trivalent, containing two subtypes of influenza A and one B virus. Quadrivalent vaccines with an additional B virus have been developed and the first authorised quadrivalent influenza vaccine became available for use in the UK in 2013. In most recent years, the vaccines have closely matched the influenza A 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. However, because two lineages of B strain can circulate, and in some seasons co-circulate, mismatches of the trivalent vaccine-type

and the circulating B strain can occur more frequently. The use of quadrivalent influenza vaccines containing a B strain from each lineage is expected to improve the matching of the vaccine to the circulating B strain(s).

All authorised influenza vaccines need to meet immunogenicity, safety and quality criteria set by the European Committee for Medicinal Products for Human Use (CHMP), with the assessment of expected 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 trivalent vaccine were drifted or mismatched with those in circulation, suggested an overall effectiveness 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 in the UK 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. However, as the level of protection provided in subsequent seasons is likely to reduce and there may be changes to the circulating strains from one season to the next, annual revaccination is important.

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 Tetra®) contains live viruses that have been attenuated (weakened) and adapted to cold so that they cannot replicate efficiently at body temperature. None of the influenza vaccines can therefore cause clinical 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 Tetra®) by nasal spray. Most of the vaccines are prepared from viruses grown in embryonated hens eggs. The influenza vaccines available in the UK for the 2014/15 influenza season are listed in Table 19.6

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. Efficacy, safety and quality may be adversely affected if vaccines are not stored at the temperatures specified in the licence. Freezing may cause increased reactogenicity and loss of potency for some vaccines and can also cause hairline cracks in the container, leading to contamination of the contents.

Fluenz Tetra® may be left out of the refrigerator for a maximum period of 12 hours at a temperature not above 25°C as indicated in the SPC. If the vaccine has not been used after this 12 hour period, it should be disposed of.

Presentation

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 Tetra®, 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 19.4 and should be given according to the recommendations for use of the vaccines (see later).

Some of the summaries of product characteristics (SPCs) for intramuscular inactivated influenza vaccines indicate that young children can be given either a 0.25ml or a 0.5ml dose. JCVI 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*., 2011).

Table 19.4 Dosage for influenza vaccines (see recommendations section for use of the vaccines)

Vaccine type	Authorised age indication	Dose
Live attenuated intranasal vaccine - Fluenz Tetra®	Children aged two to under 18 years (see precautions and contraindications)	Single application in each nostril of 0.1ml Children **NOT in clinical risk groups** only require one dose of this vaccine. Children in **clinical risk groups** aged two to under nine years who have not received influenza vaccine before should receive a second dose of vaccine at least four weeks later.
Inactivated intramuscular vaccine (number of different brands)	Children aged six months and older and adults, although some of the vaccines are not authorised for young children – see table 19.6	Single injection of 0.5ml (see note above) Children aged six months to under nine years who have not received influenza vaccine before should receive a second dose of vaccine at least four weeks later.
Inactivated intradermal vaccine - Intanza® 9µg	Adults aged 18 years to 59 years	Single injection of 0.1ml
Inactivated intradermal vaccine - Intanza® 15µg	Adults aged 60 years and older	Single injection of 0.1ml

Children aged six months to under nine years who are in clinical risk groups and have not received influenza vaccine previously should be offered a second dose of vaccine. JCVI has advised that healthy children aged two years to under nine years of age only require a single dose of live attenuated influenza vaccine, unless it is contraindicated, irrespective of whether they have received influenza vaccine previously. This advice differs from that in the SPC for Fluenz Tetra. Children who have received one or more doses of any influenza vaccine before (including pandemic monovalent influenza A(H1N1)v vaccine) should be considered as previously vaccinated (see later section on children).

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 is administered by the intranasal route (Fluenz Tetra®) and is supplied in an applicator that allows a divided dose to be administered in each nostril (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 Tetra® when given to children with a 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 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 live or inactivated vaccines. Although it was previously recommended that, where vaccines cannot be administered simultaneously; a four-week interval should be observed between live viral vaccines, JCVI have advised that no specific intervals need to be observed between the live attenuated intranasal influenza vaccine and other live vaccines (see **Chapter 6**). 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).

As a wide variety of influenza vaccines are on the UK market each year, it is especially important that the exact brand of vaccine, batch number and site at which each vaccine is given is accurately recorded in the patient 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, including the relevant Child Health Information System. 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 syringes, should be disposed of by placing it in a proper, puncture-resistant 'sharps' box according to local authority regulations and guidance in Health Technical Memorandum 07-01: Safe management of healthcare waste (Department of Health, 2013).

Recommendations for the use of the vaccines

The objectives of the influenza immunisation programme are to protect those who are most at risk of serious illness or death should they develop influenza and to reduce 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 are 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). This included, having a named individual at the surgery responsible for the influenza immunisation programme; update and maintenance of an accurate register of patients eligible for influenza immunisation and direct contact with eligible patients inviting them for immunisation.

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.

Influenza vaccine should be offered, ideally before influenza viruses start to circulate to:

- all those aged 65 years or older
- all those aged 65 years or older, to include all those aged 65 years on or before 31 March 2015 (born on or before 31 March 1950).
- all children aged two, three or four years, but not five years or older on or before the 1 September 2014 (date of birth on or after 2 September 2009 and on or before 1 September 2012)*.
- all those aged six months or older in the clinical risk groups shown in Table 19.5.

* Note: In addition to these age groups the devolved administrations will also offer influenza vaccination to children aged 5 years old (Scotland), all primary school children (Scotland & Northern Ireland) and Children in year 7 (Wales).

Table 19.5 Clinical risk groups who should receive the influenza immunisation. Influenza vaccine should be offered to people in the clinical risk categories set out below.

Clinical risk category	Examples (this list is not exhaustive and decisions should be based on clinical judgement)
Chronic respiratory disease	Asthma that requires continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission. Chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD). Children who have previously been admitted to hospital for lower respiratory tract disease. ***see precautions section on live attenuated influenza vaccine***
Chronic heart disease	Congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication and/or follow-up for ischaemic heart disease.
Chronic kidney disease	Chronic kidney disease at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation.
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis
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 offer immunisation, based on individual assessment, to clinically vulnerable individuals including those with cerebral palsy, learning difficulties, multiple sclerosis and related or similar conditions; or hereditary and degenerative disease of the nervous system or muscles; or severe neurological disability.

Clinical risk category	Examples (this list is not exhaustive and decisions should be based on clinical judgement)
Diabetes	Type 1 diabetes, type 2 diabetes requiring insulin or oral hypoglycaemic drugs, diet controlled diabetes.
Immunosuppression ***(see contraindications and precautions section on live attenuated influenza vaccine)***	Immunosuppression due to disease or treatment, including patients undergoing chemotherapy leading to immunosuppression, bone marrow transplant, HIV infection at all stages, multiple myeloma or genetic disorders affecting the immune system (e.g. IRAK-4, NEMO, complement deficiency) 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.
Asplenia or dysfunction of the spleen	This also includes conditions such as homozygous sickle cell disease and coeliac syndrome that may lead to splenic dysfunction.
Pregnant women	Pregnant women at any stage of pregnancy (first, second or third trimesters). ***see precautions section on live attenuated influenza vaccine***

Other groups

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. 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, with inactivated vaccine, 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 should be 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).

Children

Studies suggest that two doses of inactivated influenza vaccine may be required to achieve adequate antibody levels in younger children who have not received influenza vaccine before (Allison *et al*., 2006; Neuzil *et al*., 2006; Ritzwoller *et al*., 2005; Shuler *et al*., 2007; Wright *et al*., 1977). Live attenuated influenza vaccine 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) and studies have also shown meaningful efficacy after a single dose of live attenuated influenza vaccine in previously unvaccinated children (Bracco Neto *et al*., 2009; Block *et al*., 2009). Given this, JCVI has advised, as set out below, the use of different dosage schedules of influenza vaccine for children depending on their age, the clinical indications, the type of vaccine offered and whether they have received influenza vaccine previously. This advice differs from some of the SPCs.

Children aged two, three or four years old NOT IN clinical risk groups

Live attenuated influenza vaccine (Fluenz Tetra®) should be offered to all children aged two, three or four years (see earlier for age definition) except for those for whom it is unsuitable (see contraindications and precautions sections). A single dose of Fluenz Tetra® should be offered, irrespective of whether influenza vaccine has been received previously.

For those children for whom Fluenz Tetra® is unsuitable, a suitable inactivated influenza vaccine should be offered. The quadrivalent inactivated influenza vaccine (Fluarix™ Tetra) is authorised for children aged three and four years and is preferred because of the additional protection offered. Otherwise, in children aged two years, an inactivated trivalent vaccine should be given. Children offered inactivated influenza vaccine who have not received influenza vaccine previously should be offered a second dose of the vaccine at least four weeks later. The inactivated influenza vaccines are interchangeable; the second dose, if required, should be given at least four weeks after the first dose in accordance with the manufacturer's SPC for that vaccine.

Children aged six months to less than two years of age IN clinical risk groups

These children should be offered inactivated trivalent influenza vaccine. Those who have not received influenza vaccine previously should be offered a second dose of vaccine, at least four weeks later. The inactivated influenza vaccines are interchangeable; the second dose, if required, should be given at least four weeks after the first dose in accordance with the manufacturer's SPC for that vaccine.

Children aged two to 18 years of age IN clinical risk groups

Children aged two years to less than 18 years in clinical risk groups should be offered Fluenz Tetra® unless it is unsuitable (see contraindications and precautions sections). Those children who have never received influenza vaccine before and are aged between two and less than nine years should be offered a second dose of Fluenz Tetra® at least four weeks later.

For those children for whom Fluenz Tetra® is unsuitable, a suitable inactivated influenza vaccine should be offered. The quadrivalent inactivated influenza vaccine (Fluarix™ Tetra) is only authorised for children aged three years and older. The quadrivalent vaccine has both influenza B strains and may be better matched and therefore may provide better protection against the circulating B strain(s) than trivalent inactivated influenza vaccines. Children aged less than nine years who have not received inactivated influenza vaccine previously should be offered a second dose of vaccine, at least four weeks after the first dose.

The inactivated influenza vaccines are interchangeable; the second dose, if required, should be given at least four weeks after the first dose in accordance with the manufacturer's SPC for that vaccine.

A chart (see Figure 19.2) summarises the advice on influenza vaccination for the 2013/14 influenza vaccination programme.

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.

Pregnancy

Pregnant women should be offered inactivated influenza vaccine as the risk of serious illness from influenza is higher in pregnant women (Pebody *et al*., 2010). In addition, a number of studies show that influenza vaccination

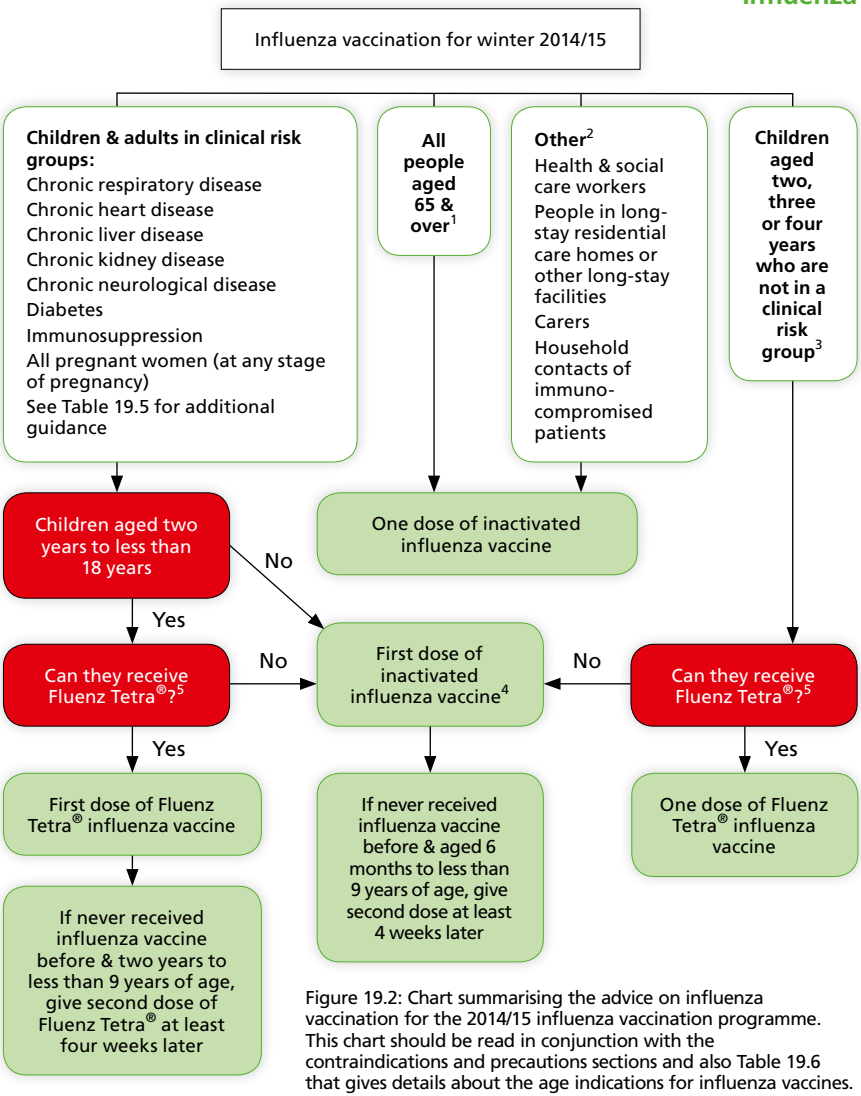

Figure 19.2: Chart summarising the advice on influenza vaccination for the 2014/15 influenza vaccination programme. This chart should be read in conjunction with the contraindications and precautions sections and also Table 19.6 that gives details about the age indications for influenza vaccines.

1 all those aged 65 years or older including all those aged 65 years on or before 1 March 2015

2 follow additional guidance from UK health departments

3 all children aged two three or four years (but not five years or older) on or before 1 Sept 2014*

4 if quadrivalent inactivated vaccine available, consider for **children age three years and older only.**

If quadrivalent unavailable, offer suitable trivalent inactivated influenza vaccine. See table 19.6 which lists the vaccines that can be used in young children - **some are not suitable for young children.**

5 cannot receive if: under age of two years; 18 years and older; have egg allergy; a history of active wheezing at the time of vaccination (until at least 7 days after wheezing has stopped); on oral steroids or high dose inhaled steroids for asthma; certain immunodeficiencies; or pregnant. see contraindications and precautions for full list and details

*Note: In addition to these age groups the devolved administrations will also offer influenza vaccination to children aged 5 years old (Scotland), all primary school children (Scotland & Northern Ireland) and Children in year 7 (Wales).

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).

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 foetal outcomes associated with inactivated influenza vaccine (Tamma *et al*., 2009). Data are more limited for the live attenuated influenza vaccine (Fluenz Tetra®). Whilst there is no evidence of risk with live attenuated influenza vaccine (Toback *et al*., 2012), inactivated influenza vaccines are preferred for those 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.

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 the screening and immunisation team in the NHS England area team, a consultant in communicable disease control or a 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 Tetra®) 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 stable HIV infection receiving 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 receiving salicylate therapy (other than for topical treatment of localised conditions) because of the association of Reye's syndrome with salicylates and wild-type influenza infection as described in the SPC for Fluenz Tetra®.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may 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 Tetra®) is not recommended for children with:

- a history of active wheezing at the time of vaccination (until at least 7 days after wheezing has stopped) or
- who are currently taking or have been prescribed oral steroids in the last 14 days or
- or who are currently taking a high dose inhaled steroid - Budesonide >800 mcg/day or equivalent* (e.g. Fluticasone >500 mcgs/day) because of limited safety data in these groups.

* In children aged 5-12 years, the definition of severe asthma corresponds to the British Thoracic Society BTS Sign Step 5

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 theoretical potential for transmission of live attenuated influenza virus in Fluenz Tetra® to immunocompromised contacts for one to two weeks following vaccination. In the US, where there has been extensive use of the live attenuated influenza vaccine, there have been no reported instances of illness or infections from the vaccine virus among immunocompromised patients inadvertently exposed. Where close contact with very severely immunocompromised patients (e.g. bone marrow transplant patients requiring isolation) is likely or unavoidable (for example, household members), however, appropriate alternative inactivated influenza vaccines should be considered.

Further guidance is provided by the Royal College of Paediatrics and Child Health (**http://www.rcpch.ac.uk/**), the British HIV Association (BHIVA) immunisation guidelines for HIV-infected adults (BHIVA, 2008; **http://www.bhiva.org/Immunization2008.aspx**) and the Children's HIV Association (CHIVA) immunisation guidelines (**http://www.chiva.org.uk/professionals/health/guidelines/index.html**).

Egg allergy

In recent years, inactivated influenza vaccines that are egg-free or have a very low ovalbumin content have become available and studies show they may be used safely in individuals with egg allergy (des Roches et al., 2012). 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. There are insufficient data on the use of the live attenuated vaccine (Fluenz Tetra®) in children with egg allergy and therefore, at the current time, Fluenz should not be given to children with any degree of egg allergy.

Most children (under the age of 18 years) with egg allergy should be immunised in primary care 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). Children with either confirmed anaphylaxis to egg or with egg allergy and severe uncontrolled asthma should be referred to specialists for immunisation in hospital.

The ovalbumin-free influenza vaccine Optaflu®, if available (see Table 19.6), can be used in primary care patients from the age of 18 years, regardless of the severity of the allergy. If there is no egg-free vaccine available, adult

patients with either confirmed anaphylaxis to egg or with egg allergy and severe uncontrolled asthma should be referred to specialists for immunisation in hospital. Other adult patients can be immunised in primary care 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).

The ovalbumin content of influenza vaccines is given in Table 19.6. In all settings providing vaccination, facilities should be available and staff trained to recognise and treat anaphylaxis (see **Chapter 8**).

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 Tetra®). Therefore, influenza antiviral agents and Fluenz Tetra® should not be administered concomitantly. Fluenz Tetra® should be delayed until 48 hours following the cessation of treatment with influenza antiviral agents. Administration of influenza antiviral agents within two weeks of administration of Fluenz Tetra® may adversely affect the effectiveness of the vaccine.

Exposure of healthcare professionals to live attenuated influenza vaccine viruses

In theory, healthcare workers may have low level exposure to live attenuated influenza vaccine viruses during administration of the vaccine and/or from recently vaccinated patients. The vaccine viruses are cold-adapted and attenuated, and are unlikely to cause symptomatic influenza. In the US, where there has been extensive use of the live attenuated influenza vaccine, no transmission of vaccine virus in healthcare settings ever has been reported and there have been no reported instances of illness or infections from the vaccine virus among healthcare professionals inadvertently exposed. Thus, the Centers for Disease Control and Prevention has considered that the risk of acquiring vaccine viruses from the environment is unknown but is probably low (CDC, 2013). As a precaution, however, very severely immunosuppressed individuals should not administer live attenuated influenza vaccine. Other healthcare workers who have less severe immunosuppression or are pregnant, should follow normal clinical practice to avoid inhaling the vaccine and ensure that they themselves are appropriately vaccinated.

Inadvertent administration of Fluenz Tetra®

If an immunocompromised individual receives LAIV then the degree of immunosuppression should be assessed. If the patient is severely immunocompromised, antiviral prophylaxis should be considered, otherwise they should be advised to seek medical advice if they develop flu-like symptoms

in the four days (the usual incubation period) following administration of the vaccine. If antivirals are used for prophylaxis or treatment, then in order to maximise their protection in the forthcoming flu season, the patient should also be offered inactivated influenza vaccine. This can be given straight away.

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, reduced appetite, weakness and headache are common adverse reaction following administration of the live attenuated intranasal vaccine (Fluenz Tetra®).

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).

Side effects and adverse reactions associated with the influenza vaccines Viroflu® and Pandemrix® have been previously documented. Viroflu® (Janssen-Cilag Ltd, formerly Crucell) may be associated with a higher than expected rate of fever in children aged under five years. An increased risk of narcolepsy after vaccination with the ASO3 adjuvanted pandemic A/H1N1 2009 vaccine Pandemrix® was identified in England (Miller *et al*., 2013) consistent with findings first identified in Finland and Sweden (Nohynek *et al*., 2010; Partinen *et al*., 2010). Viroflu® and Pandemrix® are no longer used in the UK influenza immunisation programme.

All serious suspected reactions following influenza vaccines should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card scheme at **http://yellowcard.mhra.gov.uk/**

The influenza vaccine Fluenz Tetra® and quadrivalent Fluarix™ Tetra carry a black triangle symbol (▼). 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 and fever

One inactivated influenza vaccine (Fluvax by CSL marketed in the UK by Pfizer as Enzira® or CSL Biotherapies) has been associated with a high rate of febrile convulsions in children under five years of age in other countries. The SPC for Enzira® also indicates that a high rate of fever was reported in the age group aged five to under nine years. Due to the risk of febrile convulsions, the indication for Enzira is restricted to use in adults and children aged five years and older. This vaccine will not be part of the central supply for use in children in the 2014/15 season, but may be available for purchase by the practice. 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**).

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 and Seabroke, 2011).

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:

http://publications.nice.org.uk/oseltamivir-amantadine-review-and-zanamivir-for-the-prophylaxis-of-influenza-ta158

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 at:

https://www.gov.uk/government/organisations/public-health-england

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 respective websites for details. GPs should order vaccine for those aged 65 years and older and those in adult clinical risk groups from the influenza vaccine manufacturers (contact details below) as in previous years. Live attenuated influenza vaccine (Fluenz Tetra®) has been purchased centrally for children aged two, three and four years and for children aged two to 17 years in risk groups. For both healthy and at risk children under 18 years of age where Fluenz is unsuitable an inactivated trivalent vaccine (Sanofi Pasteur MSD Split Virion BP) or Fluarix™ Tetra will be supplied. These vaccines should be ordered as per the usual mechanisms for the routine childhood immunisation programme (also see Chapter 3).

Influenza vaccines available for the 2014/15 influenza season are shown in Table 19.6.

Table 19.6 Influenza vaccines for the 2014/15 influenza season (note the ovalbumin content is provided in units of µg/ml and µg/dose)

Supplier	Name of product	Vaccine type	Age indications	Ovalbumin content µg/ml (µg/dose)	Contact details
Abbott Healthcare	Influvac®	Trivalent inactivated	From six months	0.2 (0.1/0.5ml dose)	0800 358 7468
	Imuvac®	Trivalent inactivated	From six months	0.2 (0.1/0.5ml dose)	
AstraZeneca UK Ltd	FLUENZ TETRA®▼	Quadrivalent live attenuated	From 24 months to less than 18 years of age	≤1.2 (≤0.24/0.2ml dose)	Fluenz Tetra® for use in those aged two, three and four years, and in children aged two to 17 years in risk groups, should be ordered through ImmForm* Otherwise: 0845 139 0000

Supplier	Name of product	Vaccine type	Age indications	Ovalbumin content µg/ml (µg/ dose)	Contact details
GlaxoSmithKline	Fluarix™ Tetra▼	Quadrivalent	From three years	0.1 (≤0.05/0.5ml dose)	0800 221 441*
	Fluarix®	Trivalent inactivated	From six months	0.1 (≤0.05/0.5ml dose)	
MASTA	Imuvac®	Trivalent inactivated	From six months	0.2 (0.1/0.5ml dose)	0113 238 7552
	Enzira®	Trivalent inactivated	From five years (but see adverse reactions section on use in children aged five to < nine years)	≤2 (≤1/0.5ml dose)	
	Inactivated Influenza Vaccine (Split Virion) BP	Trivalent inactivated	From six months	0.1 (≤0.05/0.5ml dose)	
	Influvac®	Trivalent inactivated	From six months	0.2 (0.1/0.5ml dose)	
	CSL Inactivated Influenza Vaccine®	Trivalent inactivated	From five years (but see adverse reactions section on use in children aged five to < nine years)	≤2 (≤1/0.5ml dose)	

Influenza

Supplier	Name of product	Vaccine type	Age indications	Ovalbumin content µg/ml (µg/ dose)	Contact details
Novartis Vaccines	Agrippal®	Trivalent inactivated	From six months	≤0.4 (≤0.2/0.5mL dose)	08457 451 500
	Optaflu®	Trivalent inactivated Prepared in cell culture	From 18 years	No ovalbumin	
Pfizer Vaccines	CSL Inactivated Influenza Vaccine®	Trivalent inactivated	From five years (but see adverse reactions section on use in children aged five to < nine years)	≤2 (≤1/0.5ml dose)	0800 089 4033
	Enzira®	Trivalent inactivated	From five years (but see adverse reactions section on use in children aged five to < nine years)	≤2 (≤1/0.5ml dose)	
Sanofi Pasteur MSD	Inactivated Influenza Vaccine (Split Virion) BP®	Trivalent inactivated	From 6 months	≤0.1 (≤0.05/0.5ml dose)	0800 085 5511*
	Intanza® 9 µg	Trivalent inactivated	From 18 years to 59 years	≤0.24 (≤0.024/0.1ml dose)	
	Intanza® 15 µg	Trivalent inactivated	From 60 years	≤0.24 (≤0.024/0.1ml dose)	

None of the influenza vaccines contains thiomersal as an added preservative.

* In England, Fluenz Tetra, Fluarix Tetra and SPMSD inactivated influenza vaccine (split virion) BP should be ordered for children under 18 years of age via the ImmForm website (https://www.immform.dh.gov.uk/) and are distributed by Movianto UK (Tel: 01234 248631) as part of the national immunisation programme. For Devolved Administrations see section on supplies

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