

# 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 an 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 in two to seven days. The illness may be complicated by (and may present as) bronchitis, secondary bacterial pneumonia or (in children) otitis media. Severe influenza can be complicated by meningitis, encephalitis or meningoencephalitis. Serious illness and mortality from influenza are highest among neonates, older people and those with underlying disease, particularly chronic respiratory and cardiac disease, or those who are immunosuppressed. Primary influenzal 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 show that approximately 30 to 50% of influenza infections are asymptomatic (Wilde *et al.*, 1999).

Transmission is by aerosol, droplets or direct contact with respiratory secretions of someone with the infection. Influenza spreads rapidly, especially in closed communities. Most cases in the UK tend to occur during a six to eight-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 these viruses 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 drift) occur progressively from season to season. Major changes (antigenic shift) occur periodically, resulting in the emergence of a new

## Influenza

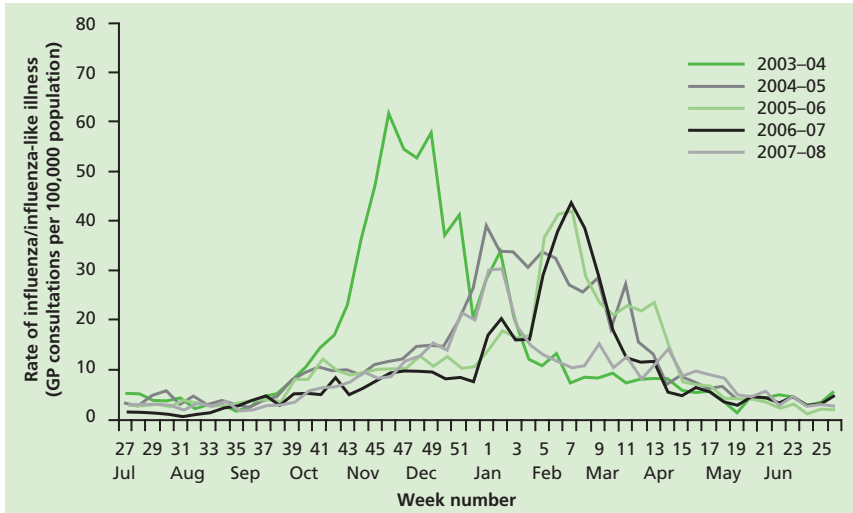


Figure 19.1 Rate of influenza/influenza-like illness episodes in England (weekly returns to Royal College of General Practitioners), 2003–04 to 2007–08

subtype with a different haemagglutinin protein. A new subtype can cause widespread epidemics or even a pandemic if populations have little or no immunity. Three influenza pandemics occurred in the last century (in 1918, 1957 and 1968) and the conditions continue to exist for the emergence of future strains with pandemic potential. Influenza B viruses are 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. Activity was modest during the five influenza seasons from 2000–01 to 2004–05 compared with 1996–97, 1998–99 and 1999–2000 (Goddard *et al.*, 2003). Severe epidemics were recorded in 1975–76 and 1989–90, resulting in an estimated 29,646 and 23,046 deaths respectively in England and Wales (Nicholson, 1996). Even in winters when the incidence is low, 3000–4000 deaths have been attributed to influenza (Watson *et al.*, 2001).

Figure 19.1 shows the number of GP consultations for influenza-like illness per 100,000 population in England from 2000–2005. In this period, the GP consultation rate reached its highest (70 per 100,000 per week) in 2000–01. However, this compares with a peak rate of 583 per 100,000 per week in the epidemic of 1989–90. In Scotland, the same pattern was seen where consultation rates peaked in calendar week 1 of 1999–2000 at 839 per 100,000

compared with a peak rate of 1184 per 100,000 during 1989–90.

Influenza immunisation has been recommended in the UK since the late 1960s, with the aim of directly protecting those at a higher risk of serious morbidity and mortality. In 2000, the policy was extended to include all people aged 65 years or over. Uptake of vaccination in those aged 65 years or over in the UK is shown in Table 19.1.

Table 19.1 Vaccine uptake in the UK since the start of the influenza immunisation programme for people aged 65 years or over

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
2003–04	71.0	72.5	63	73.4
2004–05	71.5	71.7	63	72.7
2005–06	75.3	77.8	68	80.9
2006–07	73.9	75.2	N/A <sup>1</sup>	75.1
2007–08	73.5	74.3	64	75.7

\* Some GP practices experienced problems in collating and reporting data

<sup>1</sup> Uptake figures for these years will be obtained via an automated extraction from GP systems and will be available in autumn 2008.

## The influenza vaccination

Because of their changing nature, the World Health Organization (WHO) monitors influenza viruses throughout the world. Each year the WHO makes recommendations about the strains to be included in vaccines for the forthcoming winter ([www.who.int/csr/disease/influenza](http://www.who.int/csr/disease/influenza)). To provide continuing protection, annual immunisation with vaccine against the currently prevalent strains is necessary.

Influenza vaccines are prepared using virus strains in line with the WHO recommendations. Current vaccines are trivalent, containing two subtypes of influenza A and one type B virus; in recent years these have closely matched viruses circulating subsequently. The match between circulating flu B strains and the vaccine has been less optimal in the recent season. Should a new influenza A subtype emerge with epidemic or pandemic potential, a monovalent vaccine against that strain would be considered.

The viruses are grown in embryonated hens' eggs, chemically inactivated and then further treated and purified. Three types of influenza vaccine are currently available:

## Influenza

- ‘split virion, inactivated’ or ‘disrupted virus’ vaccines containing virus components prepared by treating whole viruses with organic solvents or detergents
- ‘surface antigen, inactivated’ vaccines containing highly purified haemagglutinin and neuraminidase antigens prepared from disrupted virus particles and
- ‘surface antigen, inactivated, virosome’ vaccines containing highly purified haemagglutinin and neuraminidase antigens prepared from disrupted virus particles reconstituted into virosomes with phospholipids.

The vaccines are equivalent in efficacy and adverse reactions. The vaccines are inactivated, do not contain live organisms and cannot cause the diseases against which they protect.

Some influenza vaccines currently contain thiomersal. Other influenza vaccines are thiomersal-free. They have equivalent efficacy and safety. If a thiomersal-free influenza vaccine is not available, then a thiomersal-containing vaccine should be given. Influenza vaccines for the 2008–09 season are thiomersal-free.

The currently available influenza vaccines give 70 to 80% protection against infection with influenza virus strains well matched with those in the vaccine (Fleming *et al.*, 1995). Protection afforded by the vaccine lasts for about one year. In the elderly, protection against infection may be less, but immunisation has been shown to reduce the incidence of bronchopneumonia, hospital admissions and mortality (Wright *et al.*, 1977; Mangtani *et al.*, 2004).

After immunisation, antibody levels may take up to 10 to 14 days to reach protective levels. While 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.

Manufacture of influenza vaccines is complex and conducted to a tight schedule, constrained by the length of time available between 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.

Other influenza vaccines are being developed, such as an intranasal vaccine and an attenuated live vaccine, but these are not currently available in the UK.

## Storage

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

Influenza vaccines are all supplied as suspensions of inactivated vaccines in pre-filled syringes. They should be shaken well before they are given.

## Dosage and schedule

Age	Dose
Children aged 6–35 months	0.25ml or 0.5ml (depending on manufacturer's Summary of Product Characteristics (SPC)), repeated 4–6 weeks later if receiving influenza vaccine for the first time
Children aged 3–12 years	0.5ml, repeated after 4–6 weeks if receiving influenza vaccine for the first time
Adults and children over 13 years	A single injection of 0.5ml

Children and pregnant women should preferably receive a thiomersal-free influenza vaccine. If a thiomersal-free vaccine is not available then a thiomersal-containing vaccine should be given. The benefits of vaccination outweigh the risks, if any, of exposure to thiomersal-containing vaccines.

## Administration

The vaccine is given by intramuscular injection, preferably into the upper arm or anterolateral thigh. However, individuals with a bleeding disorder should be given the vaccine by deep subcutaneous injection to reduce the risk of bleeding.

Influenza vaccine can be given at the same time as other vaccines. The 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.

## Influenza

Where the vaccine is given for occupational reasons, it is recommended that the employer keeps a vaccination record.

### Disposal

Equipment used for vaccination, including used vials, ampoules, or partially discharged vaccines 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 vaccine

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. To facilitate this, general practitioners are required 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.

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 (RSV). Influenza vaccine will not protect against these diseases.

Influenza vaccine is offered annually between September and early November to:

- all those aged 65 years or over;
- all those aged six months or over in the clinical risk groups shown in Table 19.2.

The medical practitioner should take into account the risk of influenza infection exacerbating any underlying disease that the patient may have, as well as the risk of serious illness from influenza itself.

Table 19.2 Clinical risk groups who should receive the influenza immunisation

Clinical risk category	Examples (decision based on clinical judgement)
<b>Chronic respiratory disease, including asthma</b>	<p>Chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD).</p> <p>Asthma that requires continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission.</p> <p>Children who have previously been admitted to hospital for lower respiratory tract disease.</p>
<b>Chronic heart disease</b>	<p>Congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication and/or follow-up for ischaemic heart disease.</p>
<b>Chronic kidney disease</b>	<p>Chronic kidney failure, nephrotic syndrome, kidney transplantation.</p>
<b>Chronic liver disease</b>	<p>Cirrhosis, biliary atresia, chronic hepatitis.</p>
<b>Chronic neurological disease</b>	<p>Stroke, transient ischaemic attack (TIA).</p>
<b>Diabetes requiring insulin or oral hypoglycaemic drugs</b>	<p>Type 1 diabetes, type 2 diabetes requiring oral hypoglycaemic drugs, and diet controlled diabetes.</p>
<b>Immunosuppression</b>	<p>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.</p> <p><i>However, some immunocompromised patients may have a suboptimal immunological response to the vaccine</i></p>

## Influenza

In addition to the above, immunisation is provided 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, or to avoid disruption to services that provide their care. Annual immunisation is recommended for:

- health and social care staff directly involved in patient care
- 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.) and
- those who are the main carer for an elderly or disabled person whose welfare may be at risk if their carer falls ill. Vaccination should be given at the GP's discretion.

Influenza vaccine is also recommended for people who work in close contact with poultry. The reason for this public health measure is to reduce the risk of poultry workers contracting both human and avian influenza simultaneously. This would reduce the theoretical risk for circulating human influenza virus to re-assort with avian influenza virus and thereby producing a new influenza virus. The new influenza virus could have pandemic potential.

Consideration should also be given to the vaccination of household contacts of immunocompromised individuals.

### At-risk children

Children who have medical conditions that increase the risk of complications from influenza should be vaccinated before the influenza season.

Studies have shown that two doses of inactivated vaccine are required to achieve adequate antibody levels in children under 13 years of age as they may never have been exposed to influenza or been vaccinated (Wright *et al.*, 1977). The vaccines are interchangeable; the second dose should be given four to six weeks after the first dose in accordance with the manufacturer's SPC for that vaccine.

### Contraindications

There are very few individuals who cannot receive influenza vaccine. When there is doubt, appropriate advice should be sought from an immunisation co-ordinator, consultant in communicable disease control or consultant paediatrician, so that the period the individual is left unvaccinated is minimised.

The vaccines should not 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, or
- a confirmed anaphylactic hypersensitivity to egg products as the vaccines are prepared in hens' eggs.

Confirmed anaphylaxis is rare. 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. The risk to the individual of not being immunised must be taken into account.

## 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.

## Pregnancy and breast-feeding

Pregnant women in the risk groups listed in Table 19.2 above should be vaccinated before the influenza season, regardless of the stage of pregnancy. A study of over 2000 pregnant women who received influenza vaccine demonstrated no associated adverse fetal effects (Heinonen *et al.*, 1973). There is no evidence of risk from vaccinating pregnant women, or those who are breast-feeding, with inactivated viral or bacterial vaccines or toxoids (Plotkin and Orenstein, 2004).

Where possible, pregnant women should receive a thiomersal-free influenza vaccine. If a thiomersal-free influenza vaccine is unavailable then a thiomersal-containing vaccine should be given. The benefits of vaccination outweigh the risks, if any, of exposure to thiomersal-containing vaccines.

## Influenza

### Premature infants

It is important that premature 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.

Where possible, infants should receive a thiomersal-free influenza vaccine. If a thiomersal-free influenza vaccine is unavailable then a thiomersal-containing vaccine should be given. The benefits of vaccination outweigh the risks, if any, of exposure to thiomersal-containing vaccines.

### Immunosuppression and HIV infection

Individuals with immunosuppression and HIV infection (regardless of CD4 count) should be given influenza vaccine in accordance with the recommendations above. These individuals may not make a full antibody response.

Further guidance is provided by the Royal College of Paediatrics and Child Health ([www.rcpch.ac.uk](http://www.rcpch.ac.uk)), the British HIV Association (BHIVA) *Immunisation guidelines for HIV-infected adults* (BHIVA, 2006) and the Children's HIV Association of UK and Ireland (CHIVA) immunisation guidelines ([www.bhiva.org/chiva](http://www.bhiva.org/chiva)).

### 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 of vaccination. A small painless nodule (induration) may also form at the injection site. These reactions usually disappear within one to two days without treatment.

Immediate reactions such as urticaria, angio-oedema, bronchospasm and anaphylaxis can occur, most likely due to hypersensitivity to residual egg protein.

Neuralgia, paraesthesiae, convulsions and transient thrombocytopenia have been reported rarely.

Guillain-Barré syndrome has been reported very rarely after immunisation with influenza vaccine (one case per million people vaccinated in one US study (Lasky *et al.*, 1998)). However, a causal relationship has not been established.

Vasculitis with transient renal involvement and neurological disorders such as encephalomyelitis and neuritis occur very rarely.

All suspected reactions in children and severe suspected reactions in adults should be reported to the Commission on Human Medicines using the Yellow Card scheme.

### Management of suspected cases, contacts and outbreaks

There are antiviral drugs available which can be used under certain circumstances to either prevent influenza or to treat it.

Guidance on the treatment and prevention of influenza with antiviral drugs applicable in England, Wales and Northern Ireland was issued by the National Institute for Health and Clinical Excellence (NICE) in February 2003 and September 2003 respectively ([www.nice.org.uk](http://www.nice.org.uk)). These drugs are not a substitute for influenza immunisation.

Similar treatment guidance endorsing the recommendations of NICE was issued by Quality Improvement Scotland (QIS) in February 2003 ([www.nhshealthquality.org/nhsqis/qis\\_display\\_findings.jsp?pContentID=1096&p\\_applic=CCC&p\\_service=Content.show&](http://www.nhshealthquality.org/nhsqis/qis_display_findings.jsp?pContentID=1096&p_applic=CCC&p_service=Content.show&)).

This guidance applies when influenza A or B is known to be circulating in the community. The Department of Health posts this information on its website ([www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Flu/FluGeneralInformation/fs/en](http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Flu/FluGeneralInformation/fs/en)) and this should be checked regularly during the influenza season.

### Antivirals in the prevention and treatment of influenza

Antiviral drugs can be used for either the prevention or treatment of influenza.

Oseltamivir and amantadine are licensed for the prevention of influenza. Zanamivir, oseltamivir and amantadine are licensed for the treatment of influenza. Zanamivir and oseltamivir are neuraminidase inhibitors, active against influenza A and B; amantadine is an M2 inhibitor, active against influenza A only.

Zanamivir is taken using a special inhaler (Diskhaler<sup>®</sup>) and is licensed for individuals aged 12 years or over; oseltamivir is taken orally and is licensed for

## Influenza

individuals aged one year or over; amantadine is taken orally and licensed for individuals aged ten years or over.

### NICE guidance on the use of antiviral drugs for the prevention of influenza

When influenza A or B virus is circulating in the community, as defined on the Department of Health website, oseltamivir should be prescribed for the prevention of influenza in individuals aged 13 years or over, who:

- belong to an 'at-risk' group **and**
- have not had an influenza immunisation this season, or who have had one within the last two weeks, or have had an influenza immunisation but the vaccine did not match the virus circulating in the community **and**
- have been in close contact with someone with influenza-like symptoms **and**
- can start taking oseltamivir within 48 hours of being in contact with the person with influenza-like symptoms.

Oseltamivir has recently been licensed for prophylactic use in children aged one year and over (31 January 2006). In the interim, until NICE formally reviews its recommendation, it would therefore be appropriate to use oseltamivir for prophylaxis in persons aged one year and over according to the other conditions laid out by NICE as summarised above.

Prescribers should also note a concomitant change to the licensed duration of post-exposure prophylaxis in children and adults, now ten days (as opposed to the previous seven).

Oseltamivir should **not** be used for the prevention of influenza in otherwise healthy people under 65 years of age, even if they have been in contact with people with influenza-like symptoms.

Amantadine should **not** be used for the prevention of influenza in either group.

## Dosage for the prevention of influenza

### Individuals aged 13 years or over

Therapy should begin within 48 hours of exposure. A daily dose of oseltamivir 75mg should be given for seven days. It can be given for up to six weeks during a community outbreak.

## Contraindications for prevention

Oseltamivir should not be used in children under one year of age.

## Precautions for prevention

There are no adequate data for the use of oseltamivir in pregnant or breast-feeding women. Oseltamivir should not be used during pregnancy or in breast-feeding women unless the potential benefit to the woman overrides the potential risk for the fetus or infant.

The dose of oseltamivir should be reduced for people with moderate to severe renal impairment.

## Adverse reactions

### Oseltamivir

Nausea, vomiting, diarrhoea, abdominal pains and headache have been reported.

## NICE guidance on the use of antiviral drugs for the treatment of influenza

Zanamivir and oseltamivir are recommended for the treatment of influenza in at-risk children or adults who present with influenza-like illness and who can start treatment within 48 hours of the onset of symptoms.

NICE does not recommend amantadine for the treatment of influenza.

## Dosage for the treatment of influenza

### Individuals aged over one year and under 13 years of age

Treatment should start within 48 hours of the onset of symptoms. Oseltamivir is licensed for the **treatment** of children over one year of age. The dosage depends on body weight.

Body weight	Dosage
15kg or under	30mg every 12 hours
16–23kg	45mg every 12 hours
24–40kg	60mg every 12 hours
Over 40kg	75mg every 12 hours

Zanamivir is not used in this age group.

## Influenza

### Individuals aged 12 years or over

Treatment should start within 48 hours of the onset of symptoms. For zanamivir, the dose is 10mg, by inhalation, twice a day for five days. For oseltamivir, the dose is 75mg every 12 hours for five days.

### Contraindications for treatment

Oseltamivir is contraindicated in children under one year; zanamivir should not be used in children under 13 years of age.

Zanamivir is not recommended in women who are breast-feeding.

### Precautions for treatment

There are no adequate data for the use of oseltamivir in pregnant or breast-feeding women. It should not be used during pregnancy or in breast-feeding women unless the potential benefit to the mother overrides the potential risk for the fetus or infant.

Zanamivir should be used with caution in individuals with asthma or chronic pulmonary disease because of the risk of bronchospasm. It should not be used during pregnancy unless the potential benefit to the mother overrides the potential risk for the fetus.

The dose of oseltamivir should be reduced for people with moderate to severe renal impairment.

### Adverse reactions

#### Oseltamivir

Nausea, vomiting, diarrhoea, abdominal pains and headache have been reported.

#### Zanamivir

Headache and gastro-intestinal disturbances have been reported rarely.

## Supplies

### Vaccines

Demand for influenza vaccine sometimes increases unpredictably in response to speculation about influenza illness in the community. It is, therefore, recommended that practices order sufficient vaccine for their needs, based on their 'At risk' registers, well in advance of the immunisation season.

Information on current vaccines is given in the latest Chief Medical Officer's letter from the Department of Health. At the time of publication, vaccines are available as follows:

Supplier	Name of product	Vaccine Type	Contact details
GlaxoSmithKline	Fluarix	Split Influenza virus, inactivated	0800 783 0470
MASTA	Imuvac	Surface antigen, inactivated, sub-unit	0113 238 7500 (option 1)
Novartis Vaccines	Agrippal	Surface antigen	08457 451 500
	Begrivac	Split virion	
	Fluvirin*	Surface antigen	
	Inactivated influenza vaccine*	Surface antigen	
	Optaflu	Cell culture	
Sanofi Pasteur MSD	Inactivated influenza vaccine	Split virion	0800 085 5511
	Viroflu	Virosomal	
Solvay Healthcare	Influvac	Surface antigen, inactivated, sub-unit	0800 358 7468
	Imuvac	Surface antigen, inactivated, sub-unit	
Wyeth Vaccines	Enzira	Split virion	0800 089 4033
	Generic influenza vaccine	Inactivated	
		Split virion Inactivated	

None of the seasonal influenza vaccines for the 2009/10 season contain thiomersal as an added preservative.

\*These vaccines state in their Summary of Product Characteristics (SPC) that they contain traces of thiomersal that are left over from the manufacturing process.

## Antiviral drugs

Oseltamivir is supplied by Roche  
(Tel: 0800 731 5711).

Zanamivir is supplied by GlaxoSmithKline  
(Tel: 0808 100 9997).

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