

# Influenza: treatment and prevention

In preparation for the influenza season, Yvonne Perrie outlines what pharmacists should know about flu and the advice they can give

Influenza affects 10–20 per cent of the global population. The influenza virus belongs to the orthomyxovirus family. It is made up of a lipid membrane surrounding a protein shell and a core containing eight RNA segments. There are three types of influenza virus (A, B and C), based on the protein composition of the viral envelope. Annual flu epidemics are caused by types A or B, with the type B being identified as dominant last year (75 per cent of flu infections in the UK were caused by influenza B).<sup>1</sup> Influenza B usually causes minor symptoms but infection can be severe for older people.

Influenza viruses can be further categorised according to the classes of surface proteins they express. Subtypes of influenza A are differentiated by the variability of their surface glycoproteins (haemagglutinin [H] and neuraminidase [N]). There are 16 types of haemagglutinin and nine types of neuraminidase. These antigenic variants are named according to their H and N antigen types. The main subtypes known to cause influenza are H1N1, H2N2 and H3N2.

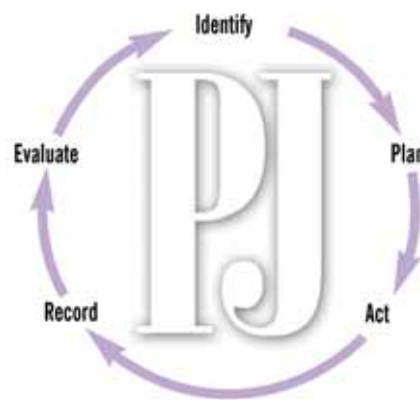
All influenza viruses undergo mutation. Point mutations occur in the amino acid sequences of the haemagglutinin and neuraminidase glycoproteins and this results in slight modifications (antigenic drift) in the virus, allowing for the development of new strains within a subtype. Viral strains are named according to the virus type, geographical origin, strain number, year of isolation and subtype (see Figure 1).

The influenza A virus is more prone to mutations in the viral genome and reassort-



Figure 1: The influenza virus has external surface projections of haemagglutinin and neuraminidase, and a core of RNA

Russell Knightley/Science Photo Library



## Identify knowledge gaps

1. What treatments are available for influenza?
2. Why do new influenza vaccines need to be made each year?
3. List five groups of people "at risk" who should be vaccinated against influenza.

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: [www.rpsgb.org/education](http://www.rpsgb.org/education)). This article relates to "common disease states" and "health education and promotion" (see appendix 4 of "Plan and record").

## Panel 1: Influenza symptoms

### Uncomplicated influenza

- Fever (38–40C)
- Severe malaise
- Severe headache
- Profound muscular aches and pains
- Dry cough, nasal discharge

### Pulmonary complications

- Croup in young children
- Pneumonia
- Secondary bacterial infections (often involving *Streptococcus pneumoniae*, *Staphylococcus aureus* or *Haemophilus influenzae*)

### Non-pulmonary complications

- Myositis
- Cardiac complications
- Encephalopathy
- Reye's syndrome
- Guillain-Barré syndrome

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ment of the eight RNA sequences within the virus is possible. This causes an abrupt, major change in the virus, resulting in new haemagglutinin or neuraminidase proteins, or both, and a new influenza subtype. This can happen, in various ways, for example, when two different viruses infect the same organism, a new genetically distinct virus, containing genes from both viruses can emerge.

Most people will have little or no protection against a new virus and a pandemic can result, such as "Asian flu" in 1957 (caused by H2N2) and "Hong Kong" flu in 1968 (H3N2). These outbreaks are thought to have arisen by the genetic reassortment of viruses of human and avian origin.<sup>2</sup>

## Infection and disease

In the UK, the influenza season is generally at its height from December to March — during the 2005/2006 season, outbreaks peaked at 44 per 100,000 in mid-February.<sup>2</sup> One reason influenza is such a concern is that it is particularly contagious.

The virus is caught by inhaling the aerosolised droplets (<10 microns) produced when an infected person talks, coughs or sneezes. The virus can also survive for a short time on surfaces, providing an alternative

route of transmission — the virus can be introduced into the nose or eyes if a person touches an infected surface and then touches his or her face. Symptom onset is rapid — the incubation time for the virus is about 18 to 72 hours.

The virus infects respiratory tract epithelial cells, which die. Mucociliary clearance is, therefore, impaired and there is a subsequent reduction in the clearance of infectious agents from the respiratory tract. Compared with the common cold, influenza infection causes more severe illness. Typical symptoms are listed in Panel 1 (p399).

Generally, patients can expect to recover from an infection one to two weeks after onset but some people, particularly those identified as vulnerable, can develop serious complications, such as pneumonia. Panel 2 lists these groups of people, as defined by the Department of Health. Contracting influenza can also have serious consequences in pregnant women and children under two years of age. Even in healthy individuals, influenza can result in hospital admission. Globally, influenza causes up to 500,000 deaths every year.

### Prevention

Haemagglutinin is the viral surface protein responsible for binding the virus to host cells

## Even in healthy individuals, influenza can result in hospital admission

and neuraminidase (an enzyme that forms a mushroom-shape projection on the surface of the virus) promotes the release of newly formed virus particles from infected cells. An antibody response is the main source of natural protection against influenza, with IgG and IgA preventing reinfection. Antibodies against haemagglutinin are the most important because they can stop the virus from binding to host cells, thus preventing it from initiating an infection. Antibodies to neuraminidase may slow the spread of the virus and limit the disease. However, the constant mutation of the influenza virus results in changes in haemagglutinin and neuraminidase and pre-existing antibodies generated by previous infection may not be effective against new strains.

Other risk factors for contracting influenza include the infectivity and virulence of the strain and the general health and nutritional status of the potential host.

**Vaccination** Vaccination is a key feature in combating influenza. Not only does it decrease the risk of infection in the vaccinated individual but it prevents spread of the virus through the population by providing herd immunity. The Department of Health's influenza immunisation programme is a major public health strategy in the UK and, despite difficulties in supplies, last year 75 per cent of people aged 65 years and over in England were vaccinated.<sup>3</sup> However, because of viral mutation, a new vaccine must be formulated each year.

The World Health Organization Global Influenza Surveillance Network enables the WHO to recommend the content of the vaccine for each influenza season. Every year, 87 institutions from 83 countries submit more than 175,000 patient samples for antigenic and genetic analysis.<sup>4</sup>

Vaccine production currently takes about six months so the virus strains must be selected early each year. The influenza vaccines contain the equivalent of 15µg of antigen (haemagglutinin) from two strains of the type A virus and one from the type B virus. The strains recommended to be used in the vaccine for 2006/2007 are:

- A/New Caledonia/20/99(H1N1)-like virus
- A/Wisconsin/67/2005(H3N2)-like virus or A/Hiroshima/52/2005
- B/Malaysia/2506/2004-like virus

The lengthy manufacturing process is a result of the viral strains having to be grown in embryonated hens' eggs produced by pathogen-free flocks. Unfortunately, not all the recommended strains grow well and this can cause further delays. For example, the UK Vaccine Industry Group (UVIG) has already announced that vaccine manufacturers are again encountering problems in growing one of recommended strains and most supplies will be distributed later than usual.<sup>3</sup>

Several types of influenza vaccine are available: whole virus, split virion (consisting of

### Panel 2: Clinical risk group

Clinical risk group	Examples
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 (including chronic bronchitis and emphysema), bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia and children who have previously been admitted to hospital for lower respiratory tract disease
Chronic heart failure	Congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication or follow-up for ischaemic heart disease, or both
Chronic renal disease	Chronic renal failure, nephritic syndrome, renal transplantation
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis
People with diabetes and who require insulin or oral hypoglycaemic drugs	Type 1 diabetes, type 2 diabetes requiring oral hypoglycaemic drugs
Immunosuppression*	Immunosuppression due to disease or treatment, patients undergoing chemotherapy leading to immunosuppression, asplenia or splenic dysfunction, HIV infection, individuals treated with (or likely to be treated with) systemic steroids for more than a month at a dose equivalent to prednisolone 20mg or more per day (any age) or, for children under 20kg, a dose of 1mg/kg/day.

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

Taken from: "The influenza immunisation programme 2006/2007"

### Panel 3: Priorities for 2006/2007 flu vaccination

Category	Description
1	All those aged 65 and over All those aged over 6 months and in the recommended clinical risk groups (see Panel 2)
2	All 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 (eg, prisons and university halls)
3	Carers
4	Health care workers
5	Any other groups

Taken from: "The influenza immunisation programme 2006/2007"

### Panel 4: Tips for avoiding influenza transmission

- Frequently wash your hands thoroughly with soap and water, particularly after coughing or sneezing
- Try not to touch your eyes, nose or mouth
- Avoid close contact with infected people and crowded areas at the peak of influenza season (December to March)
- Do not share cutlery or drinks
- Disinfect commonly used surfaces (eg, counter tops, telephones)
- Keep in good health: eating a balanced diet, keeping warm in winter and not smoking could reduce chances of infection

To protect others, people with influenza should:

- Stay away from work or school and social gatherings
- Cover their noses and mouths when coughing or sneezing
- Throw away used tissues immediately

virus particles disrupted by detergent treatment), sub-unit (consisting essentially of haemagglutinin and neuraminidase from which the other virus components have been removed) and virosomal (surface antigens formulated into a liposome-based vesicle carrier system).

This year's influenza immunisation programme is planned to begin on 2 October. With the supply delay and potential stock shortage (similar to previous years), the DoH has recommended a prioritisation system for vaccination (see Panel 3). People who fall under category 1 will be given the highest priority. Pharmacists can contribute to public health by encouraging those at risk to get their "flu jab". Despite the success of the immunisation scheme in reaching those over 65 years old, last year, less than half of those under 65 years and at risk were vaccinated so pharmacists could try to target these people in particular. In addition, early vaccination should be encouraged — according to a recent study, vaccination after mid November may be less beneficial.

The injection is usually given intramuscularly and as a single dose. For children who have not previously been vaccinated, the dose is repeated after four to six weeks. The injection should not be given to people who are allergic to chicken eggs, children under six months old and people with an acute illness (they should wait until they recover before vaccination).

Because influenza vaccines in the UK are inactivated, vaccination cannot cause influenza and any respiratory illness occurring soon after vaccination will be coincidental. The most frequent side effect of vaccination is soreness at the injection site, which lasts less than two days. Other adverse reactions include fever, malaise, myalgia and headache. These are most common in those who have not been previously exposed to influenza virus antigens (eg, young children). The reactions start six to 12 hours after vaccination and can last for two days. Seizures and Guillain-Barré Syndrome (a neurological disorder) have been reported. Adverse reactions to influenza vaccines should be reported via the yellow card system.

**Prophylaxis** Some antiviral agents (see below) are licensed to prevent infection (eg, in high-risk individuals who cannot be or have not been vaccinated). There are two types of prophylaxis: post-exposure and seasonal. Oseltamivir is recommended for prophylaxis of post-exposure infection and treatment must be started within 48 hours of close contact with infected individuals.

It is estimated that infected adults can pass the virus to others one day before and up to five days after symptom onset. In addition to recommending immunisation to people at risk, pharmacists can also give general advice on avoiding infection (see Panel 4) and, as health care professionals, should themselves try to avoid infection.

### Treatment

While prevention of infection via immunisation is preferred, antiviral agents are available should infection occur. Antivirals will also play a crucial role in the event of a pandemic, offering the availability of treatment during the six-month lag time between identifying a strain causing a pandemic and developing a suitable vaccine.

Two antiviral drugs currently available, oseltamivir (Tamiflu) and zanamivir (Relenza), are both neuraminidase inhibitors. They block the release and spread of new viral particles from host cells. Zanamivir, first launched in 1999, was developed to treat influenza A and B and is administered via inhalation, using a Diskhaler (ease of use in elderly patients should be considered). Caution is advised if zanamivir is used by patients with asthma or chronic pulmonary disease because some of

### Bird flu

Avian influenza is caused by influenza A with the combination of H5 and H7. It is normally only found in birds, but can infect mammals. On rare occasions some types of avian influenza have infected humans, but the virus is not usually transmitted between humans. The current outbreak of avian influenza is the H5N1 subtype, which is now considered as endemic in many parts of Indonesia, Vietnam, Cambodia, China and Thailand.<sup>2</sup> There is a small risk of direct transmission of H5N1 from poultry to humans but of greater concern is the risk of the H5N1 virus undergoing reassortment with a human virus to produce a virus that is highly infectious to humans and spreads easily between people. In addition, a recombination between two viruses is not always necessary and a virus can simply jump between species due to an antigenic drift, as was the case in 2004 in South East Asia when bird flu infected humans.

these patients have experienced reduced FEV<sub>1</sub> or peak expiratory flow rate following treatment. Oseltamivir, also launched in 1999, is available in capsules or as a suspension and a course of treatment (five days) is less expensive than zanamivir. Both drugs are recommended to treat "at risk" individuals only. They are most effective when started within a few hours of the onset of symptoms and are licensed for use within 48 hours of onset. In otherwise healthy individuals, they should reduce the duration of symptoms by one to 1.5 days.

Prophylactic regimens can last for up to six weeks. However, National Institute for Health and Clinical Excellence guidelines state that both oseltamivir and zanamivir are not recommended for seasonal prophylaxis. Oseltamivir is recommended for post-exposure prophylaxis in certain at risk individuals. Oseltamivir has been associated with nausea and vomiting. The dose of oseltamivir must be reduced for patients with renal failure.

Although neuraminidase inhibitors are generally regarded as having a good efficacy and safety profile compared with other antivirals, there are still issues regarding their use in pandemics. First, the time required to produce oseltamivir is lengthy and second, development of viral resistance to both zanamivir and oseltamivir during treatment has been identified in a small number of cases.

Adamantine is active against influenza A but not influenza B viruses. It acts by inhibiting the uncoating of the virus and is licensed for treatment and prophylaxis. While similar in efficacy and less expensive than the neuraminidase inhibitors, it has more adverse effects, particularly associated with the central nervous system (eg, nervousness, anxiety, and light-headedness). Amantadine is no longer recommended for use.

**Symptom relief** A number of products containing analgesics, antihistamines and decongestants are available for uncomplicated flu symptoms and which to recommend often depends on patient preference. According to Prodigy, apart from paracetamol, aspirin and ibuprofen, there is no evidence to support the use of a wide variety of other products marketed to manage the common cold and this, presumably, applies also to managing flu symptoms.

The advice to take extra fluids when suffering from respiratory infections has been questioned in a systematic review.<sup>5</sup> The authors noted that increased antidiuretic hormone secretion had been reported in adults and children with lower respiratory tract infections, such as bronchitis or pneumonia. Giving extra fluids while antidiuretic hormone secretion is increased may, theoretically, lead to hyponatraemia and fluid overload. The authors concluded that they found data to suggest that giving increased fluids to patients with respiratory infections may cause harm. To date there are no randomised controlled trials to provide definitive evidence and, until this evidence is available, caution about universally



Chicken eggs are used to grow influenza strains for vaccines

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#### Resources

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## Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. It is Saturday and a patient brings in a prescription, written the day before, for oseltamivir. You do not have it in stock until Monday — over 48 hours since the prescription was written. What issues should you consider? Discuss these with a colleague.
2. Identify patients who could be reminded to get their "flu jab". Materials to promote the immunisation programme are available for the Department of Health ([www.immunisation.nhs.uk](http://www.immunisation.nhs.uk)).
3. As part of the annual influenza immunisation scheme, each primary care organisation must enter into arrangements with a general medical services or personal medical services contractor to provide immunisation to at-risk patients within the national guidelines. Look at the potential of your pharmacy providing flu vaccines.

## Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities.

Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?)

What will you do now and how will this be achieved?

recommending increased fluids to patients with lower respiratory tract infections should be noted.

## Future treatments and vaccines

A fundamental and continual problem in the prevention and treatment of influenza is the need to predict the dominant strain of influenza before the peak season. Ideally, the development of a vaccine that can induce protection against variant strains of the virus is needed to remove the requirement for yearly vaccinations. This could provide protection against pandemics.

As a minimum, new methods are required to shorten the production time of these vaccines. Companies, such as GlaxoSmithKline, Sanofi Pasteur and Chiron, are looking at alternatives to producing vaccines, including the use of cell culture technology to replace growing the viruses in eggs.

Antivirals continue to have an important role. Combination therapies, as used in HIV infection, may offer advances and avoid the development of resistant strains. In addition, treatments at later stages of infection are needed.

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