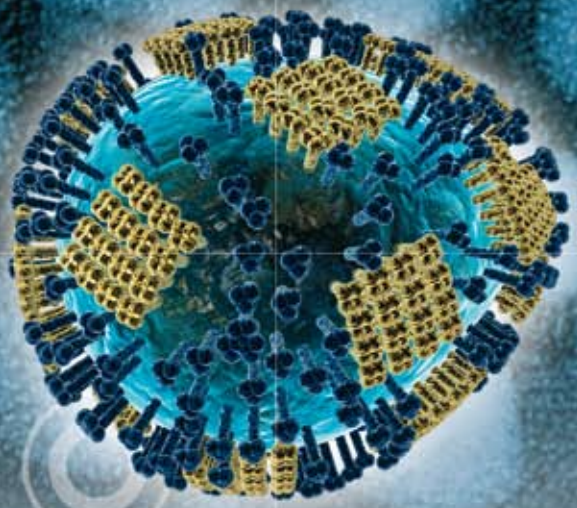
Diagnosing and managing influenza



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Influenza is a highly infectious acute respiratory disease. In healthy people influenza is an acute, and usually self-limiting and uncomplicated disease, which can be managed symptomatically. However for those at risk of complications, it can be a significant cause of morbidity and mortality.

Immunisation is the primary way to prevent influenza and its complications.

Treatment with antivirals should be considered for patients with symptoms of influenza who are at risk of serious disease, e.g. elderly people and those with chronic illness.

Clinical diagnosis can be difficult because other respiratory illnesses can cause symptoms similar to influenza[1, 2]

Influenza is characterised by the sudden onset of symptoms including: fever (may be absent in elderly people), malaise, myalgia, headache, chills and cough. A wider range of symptoms may be seen in infants and children including lethargy, poor feeding and vomiting.

A diagnosis of influenza is more likely when influenza is circulating

During periods of increased influenza prevalence, the acute onset of fever and cough makes a diagnosis of influenza more likely. When prevalence is low, the presence of influenza-like symptoms is less accurate for diagnosing influenza.[3]

When a patient presents with symptoms and signs of influenza, four questions are useful to distinguish between influenza and influenza-like illness:[2]

1. Are influenza viruses known to be circulating in the area?
2. Did the patient experience a sudden onset of symptoms?
3. Is the patient's temperature significantly raised (> 38 °C)?
4. Does the patient have both systemic and respiratory symptoms, particularly cough?

If the answer is "yes" to all of these questions, influenza is the likely diagnosis.

Differential diagnoses include:[4]

- Other respiratory viral infections, e.g. respiratory syncytial virus, coronavirus, rhinovirus
- Meningitis
- Pneumonia
- Although rare consider malaria in people who have recently travelled to an area where malaria is endemic

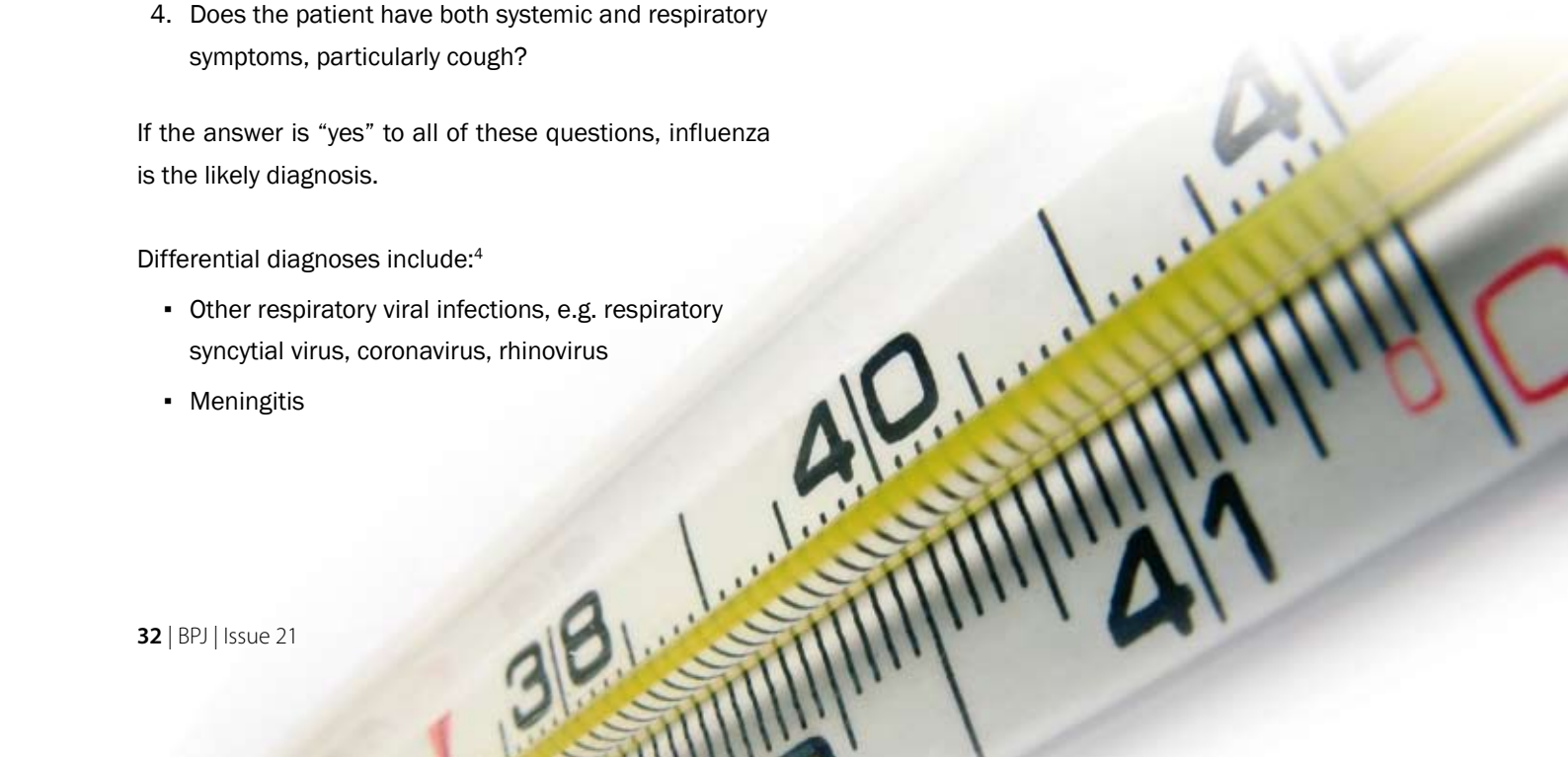
Laboratory diagnosis is rarely needed

Although a definitive diagnosis of influenza requires laboratory confirmation, it is not routinely needed in general practice as it unlikely to alter management. Laboratory tests are mainly used to survey influenza viruses to indicate when influenza is circulating, determine the current strains and monitor antiviral resistance.[3] In New Zealand, a group of sentinel general practices record the number of consultations for influenza-like illness, and collect respiratory samples for virus culture from patients with influenza-like illness.[1]

Immunisation is the primary intervention to prevent influenza and its complications

Vaccination is 70% to 90% effective in healthy adults when the vaccine strains match the current circulating strains well. The influenza vaccine is funded for all people aged over 65 years and those aged six months to 65 years with chronic medical conditions.

See BPJ 20 for more information about influenza vaccines.



Treatment of influenza

Healthy people with uncomplicated influenza do not usually require treatment with antivirals

Healthy people with uncomplicated influenza should be advised to rest, drink plenty of fluids and use analgesics such as paracetamol or ibuprofen for fever, headache and myalgia.[4]

Antiviral drugs (zanamivir or oseltamivir) may be appropriate for people who are at risk of complications

Elderly people and people with chronic co-morbidities who are frail, are at increased risk of influenza-related complications. It may be appropriate to treat these people with antivirals such as zanamivir and oseltamivir. Treatment is more effective the sooner it is given and must be initiated within 48 hours of the onset of symptoms.[6] Laboratory testing is unlikely to be useful in the decision to use antivirals, as results may take longer than 48 hours to be reported.

Antivirals can shorten the duration of influenza symptoms by one to three days if initiated within 48 hours of the onset of symptoms.[6] There is also some evidence that they can reduce the severity and incidence of complications of influenza, as well as shorten the length of hospital stay, and reduce mortality in patients with severe influenza.[6]

Recommended treatment doses

Oseltamivir (Tamiflu) is available as a tablet and a suspension. It is not subsidised for seasonal influenza and one course costs approximately $70. Note that as part of containment measures patients with suspected swine-origin influenza A are currently offered funded antiviral therapy.

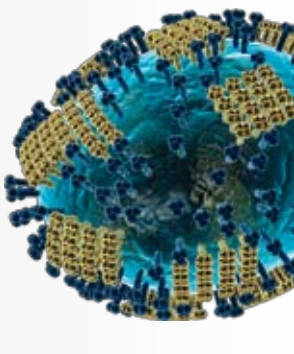
The recommended dose of oseltamivir for the treatment of influenza in adults and children aged 13 years and older is 75 mg twice daily for five days. A suspension is available for children aged one year and older and doses are based on weight. For patients with renal impairment (creatinine clearance less than 30 mL/min), the dose should be reduced to 75 mg once daily.[7]

The influenza virus

Influenza viruses are grouped into three types; influenza A, B and C. Influenza A and B cause most clinical disease.

Influenza A viruses are further grouped based on the two antigens on their surface: neuraminidase (N antigen) and haemagglutinin (H antigen). Influenza A and B viruses have a marked ability to change either by:[1, 3-5]

- **Antigenic drift** – minor changes in the H and N antigens as a result of point mutations. Antigenic drift occurs continuously and is responsible for the emergence of strains which differ slightly from those circulating in the previous winter. These new strains are responsible for each winter epidemic, and are the reason why vaccination received in the previous year, will provide little or no protection against the current circulating influenza viruses.
- **Antigenic shift** – major changes in the H and N antigens either arising by direct transmission of an avian virus to humans or after genetic reassortment in pigs, which can be infected with both avian and human viruses. Antigenic shift only occurs in influenza A viruses and has the potential to cause major epidemics and pandemics. Vaccines, which provide protection against influenza strains that circulated before the virus changed by antigenic shift, will provide little or no protection against the new strain. Similarly immunity generated by infection with previous strains will provide little or no protection against the new strain.



Oseltamivir and zanamivir

Oseltamivir and zanamivir are neuraminidase inhibitors

Neuraminidase inhibitors prevent the release of newly replicated virions from infected cells, therefore preventing the spread of infection.[11] Neuraminidase enables infection to spread by cleaving the sialic acid residues on receptors that bind virions to cells and to one another. Neuraminidase inhibitors bind to the active site, preventing the enzyme from cleaving the host-cell receptors.[12]

Resistance to neuraminidase inhibitors

During the 2008–2009 influenza season, high rates of oseltamivir resistant strain (H1N1) of influenza were detected in the United States, Europe, Australia and South Africa. Oseltamivir resistant strains have recently been detected in New Zealand.[13]

Resistance occurs when amino acid substitutions occur in the active site preventing oseltamivir from binding. While resistance to oseltamivir is concerning, this particular strain continues to be susceptible to zanamivir and amantadine.[12]

Local ESR surveillance data reports on which influenza strains are currently circulating and may be used to assist in the choice of an appropriate antiviral agent (available from: **http://www.surv.esr.cri.nz/virology/influenza_annual_report.php**).[13]

Zanamivir (Relenza) is available as an inhaled powder. It is not subsidised and one course costs approximately $65.

The recommended dose of zanamivir for the treatment of influenza in adults and children five years and older is 10 mg (two inhalations) twice daily for five days.[8]

Adverse effects and precautions with neuraminidase inhibitors

Adverse effects commonly associated with oseltamivir include nausea and vomiting (approximately 5 to 10%). This can be minimised by taking oseltamivir with food. Other adverse effects include abdominal pain and headache.[9]

Zanamivir has been reported to cause bronchospasm and a reduction in respiratory function, particularly in patients who have underlying respiratory disease. These people should be informed of the risk of bronchospasm and advised to have a fast-acting bronchodilator available, or if they are taking maintenance bronchodilator therapy, to use this before taking zanamivir.[4, 10]

Amantadine is not usually recommended for the treatment of influenza because of adverse effects and high rates of resistance

Amantadine, more often used for Parkinson's disease, is also licensed for the prophylaxis and treatment of influenza. However amantadine has significant CNS adverse effects including anxiety, insomnia, confusion and light-headedness. These adverse effects are particularly common in elderly people.[14]

There are also high rates of amantadine-resistance in influenza isolates and for this reason it is no longer recommended for the treatment of influenza. One exception is the treatment of oseltamivir-resistant influenza in those whom zanamivir is contraindicated.[6]

Antivirals for prophylaxis

Annual influenza immunisation is recommended to prevent influenza infection in people at high risk of complications. Antivirals are not routinely recommended

for prophylaxis against influenza, however they may be useful in some situations, e.g. in inadequately vaccinated high-risk communities such as an outbreak of influenza in a residential care facility.[9]

In this situation, antivirals must be started within 48 hours after exposure to a person with influenza (i.e. close contact with an infected person).

Doses used for prophylaxis:

- Oseltamivir, adults, 75 mg once daily for ten days
  or
- Zanamivir, 10 mg (2 inhalations) once daily for ten days

When exposure to influenza is ongoing, oseltamivir prophylaxis can be continued for up to six weeks or zanamivir for up to four weeks.[8]

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Influenza and the threat of a pandemic

An epidemic is the occurrence of more cases of a disease than would be expected in a community or region in a given time period. A pandemic is an epidemic that has become widespread and is affecting a whole region, continent or the world. Current diseases of pandemic proportions include tuberculosis and HIV.

For an influenza pandemic to occur the virus must be:

1. A new subtype
2. Able to infect humans and cause serious illness
3. Able to spread easily and sustainably between humans

Influenza A (H5N1) –"bird flu"

Avian H5N1 influenza virus (bird flu), which has infected people in Africa, the Pacific, Europe and Asia meets two of these conditions. It is a new virus subtype and is able to infect humans and cause significant disease (from 2003 – 2009, of the 413 cases reported to the World Health Organisation, there have been 256 deaths)[16]

The H5N1 virus does not currently seem to have the ability to pass readily between humans. However it has shown it has the ability to mutate, and acquire genetic material from other strains, and there are fears that the H5N1 virus could potentially develop the ability to spread between people and cause a pandemic.[4]

Influenza A (H1N1) – "Swine flu"

"Swine flu" is the result of a novel reassortment of influenza A H1N1 from avian, swine and human strains. Human cases of this virus, with human to human transmission have been identified in Mexico and have spread to other countries. At the time of going to print, the current pandemic alert status in New Zealand is "Code Yellow" which is a standby phase when there has been a significant development in a virus overseas or single isolated cases in New Zealand.

Most confirmed cases of influenza A (H1N1) have been self-limiting, uncomplicated, respiratory infections with symptoms similar to ordinary seasonal influenza, e.g. fever, cough, headache, myalgia, although vomiting and diarrhoea have been more common.

It is expected that the influenza A (H1N1) virus will cause the same spectrum of illness severity as ordinary seasonal influenza, ranging from self-limited infection to severe illness including pneumonia. Those most likely to get severe illness and complications of influenza A (H1N1) virus are anticipated to be similar to those who would be most at risk during normal influenza outbreaks.

The possibility of influenza A (H1N1) should be considered in those who present with fever and respiratory symptoms who:

- Have developed symptoms within seven days of travel to areas of concern, e.g. Mexico or North America
- Are considered to be a close contact of a probable or confirmed case of influenza A (H1N1)

Any suspected cases of influenza A (H1N1) virus must be notified to the local Medical Officer of Health, who will follow-up and provide necessary treatment.

The influenza A (H1N1) virus is susceptible to oseltamivir and zanamivir but is resistant to amantadine.

For more information visit:
www.moh.govt.nz/influenza-a-h1n1
http://pandemicflu.gov/faq/swineflu

What general practice may need to do to prepare

During a pandemic it is likely that general practice will carry the major burden of disease management in the community.[4]

Things to consider for general practice:

- Implementing national schemes – e.g. having comprehensive lists of at-risk groups who may be contacted in the event that a vaccine becomes available
- Large increase in demand – e.g. coping with increased demand for services, increased home visits, increased numbers of staff off sick, prioritising work and separation of flu and non-flu patients
- How to care for non-flu patients – e.g. patients with chronic conditions requiring routine medication
- Managing spread of infection – e.g. hand hygiene, control of spread from patients who are coughing or sneezing, adequate supplies of protective equipment (surgical face masks, gloves, aprons, eye protection), enhanced cleaning procedures

More information about influenza and influenza pandemic planning available from: **www.guidetools.com/influenza/index.html**

The difference between 'ordinary' influenza and pandemic influenza[15]

Feature	"Ordinary" influenza	Pandemic influenza
Influenza virus	Seasonal activity and epidemics usually occur due to minor changes in influenza strains i.e. "antigenic drift"	Usually caused by a completely new influenza virus strain that results from "antigenic shift"
When do they occur?	Every year during the winter months in temperate climates	Pandemics have occurred sporadically throughout history and can take place in any season
How many people may be affected?	Influenza may affect 10–20% of the population and cause approximately 40 deaths in New Zealand annually	A quarter of the population may be affected Associated with much higher rates of illness and death e.g. the 1918 "Spanish Flu" caused around 40 million deaths worldwide
Who is affected?	While anyone can be infected with influenza, elderly people account for most (>90%) of the deaths attributed to influenza and resulting pneumonia	People of all age groups may be affected by pandemic influenza e.g. during the "Spanish Flu" the 20–40 year old age group had a disproportionately high mortality rate
Recovery from influenza illness	Most people with ordinary influenza recover within one to two weeks without requiring medical treatment	Pandemic influenza is usually a more severe illness and therefore associated with a higher risk of death
Vaccine availability	An influenza vaccine is developed each year based on the virus strains expected to be circulating. These can be fairly reliably predicted	Due to the influenza strain being completely new, a vaccine against pandemic influenza will not be available at the start of a pandemic
Treatment and prevention of influenza	Annual vaccination to prevent influenza Antivirals may be used for those at risk of severe influenza and complications	Due to the large numbers affected supply of antivirals may be limited Efficacy for pandemic influenza is not known