

HEALTHCARE WORKERS HANDBOOK

ON

INFLUENZA

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Developed by:
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a division of the National Health Laboratory Service (NHLS),

in collaboration with:

The South African National Department of Health
and World Health Organization (WHO)



DEPARTMENT OF HEALTH
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Prefix and Disclaimer

This advice is based on currently available information regarding human infections caused by seasonal influenza viruses. Recommendations are based predominantly on current World Health Organization (WHO) Guidelines (see section 7).

This material is intended for use by healthcare professionals. While the greatest care has been taken in the development of the document, the National Department of Health and the National Institute for Communicable Diseases of the National Health Laboratory Service do not accept responsibility for any errors or omissions. All healthcare professionals should exercise their own professional judgement in confirming and interpreting the recommendations presented in the handbook.

Acknowledgements

- Previous 'Influenza Guidelines for South Africa' issued by the South African Thoracic Society in conjunction with interested stakeholders (published in 1999, revised and published in 2008).
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1. Background on influenza

1.1. What is influenza?

Influenza, commonly known as the "flu", is an acute viral infection of the respiratory tract caused by influenza virus. There are three types of seasonal influenza viruses – A, B and C. The 2009 pandemic influenza A(H1N1) virus (hereafter referred to as A(H1N1)pdm09) which appeared for the first time in 2009 causing a global influenza pandemic, is now a seasonal influenza virus that co-circulates with other seasonal viruses (namely influenza A(H3N2) and influenza B viruses).

Influenza viruses can cause disease in persons of any age, but overall rates of illness are highest in children. Usually, rates of severe illness and death are highest in persons aged ≥ 65 years, children aged ≤ 2 years, women who are pregnant or postpartum (within 2 weeks after delivery) and persons of any age with underlying medical conditions (risk factors) which increase the risk for influenza-related complications. Nevertheless, about one third of patients with severe A(H1N1)pdm09 illness requiring admission to ICU worldwide in 2009 were previously healthy persons with no identified risk factors.

1.2. Transmission

The virus is spread from person-to-person. It can be passed to other people by exposure to infected droplets expelled by coughing or sneezing that can be inhaled, or that can contaminate hands or surfaces. To prevent spread, people who are ill should:

- Practice cough etiquette by covering their mouth and nose with a disposable tissue when coughing or sneezing, then discarding the tissue in a receptacle and performing hand hygiene (washing hands with soap and water or the use of an alcohol-based hand rub)
- Stay home when they are unwell and keep some distance from healthy people, as much as possible.

The incubation period for influenza is 1-4 days (average 2 days). Most persons ill with influenza shed virus (i.e. may be infectious) from a few days before symptoms begin through 5 – 10 days after illness onset. However, young children can be infectious for > 10 days after illness onset; adults with severe disease may also shed virus for > 10 days, and severely immunocompromised persons can shed virus for months.

2. Influenza in South Africa

2.1. Timing of the influenza season and vaccination

The South African influenza season falls in the winter months. The average onset of the influenza season over the past 28 years has been first week of June. However, the season has started as early as last week of April and as late as first week of July. Regular surveillance reports on current influenza activity in South Africa are available via the NICD website

(www.nicd.ac.za). Vaccines should be given sufficiently early to provide protection for the winter. A protective antibody response takes about 2 weeks to develop.

2.2. Expected influenza subtypes and strains for 2012

Seasonal influenza occurs annually, with the circulating strains changing regularly. In 2011 there were 2 influenza peaks; influenza A(H1N1)pdm09 predominated initially, followed by influenza B and influenza A(H3N2). It is difficult to predict which subtype/s or strain/s will predominate in the 2012 influenza season.

2.3. Influenza vaccine strains and vaccination recommendations for 2012

Vaccination with the trivalent influenza vaccine (TIV) is recommended, where applicable. The formulation for the trivalent vaccine as recommended by the World Health Organization for the 2012 Southern Hemisphere influenza season is identical to that of the 2011 vaccine:

- an A/California/7/2009 (H1N1)-like virus;
- an A/Perth/16/2009 (H3N2)-like virus; and
- a B/Brisbane/60/2008-like virus.

The TIV is available in both the public sector (at designated clinics and hospitals) and the private sector (at pharmacies, certain healthcare facilities, etc).

"Recommendations pertaining to the use of viral vaccines: Influenza 2012" has been published in the February 2012 edition of the South African Medical Journal (access at: <http://www.samj.org.za/index.php/samj/issue/view/122/showToc>).

The recommended indications for influenza vaccination include:

1. Persons (adults/children) at high risk for influenza and its complications due to underlying medical conditions and who are receiving regular medical care for conditions such as chronic pulmonary and cardiac diseases, chronic renal disease, diabetes mellitus and similar metabolic disorders, individuals who are immunosuppressed (incl. HIV-infected persons with CD4 counts >100 cells/ μ l) and individuals who are morbidly obese (BMI \geq 40).
2. Pregnant women (irrespective of stage of pregnancy).
3. Residents of old-age homes, chronic care and rehabilitation institutions
4. Children on long-term aspirin therapy
5. Medical and nursing staff in contact with high-risk cases
6. Adults and children who are family contacts of high-risk cases
7. All persons over the age of 65 years
8. Any persons wishing to protect themselves from the risk of contracting influenza, especially in industrial settings where large-scale absenteeism could cause significant economic losses.

The National Department of Health has launched an influenza vaccination campaign in the public health sector targeting groups at higher risk for severe disease, which include:

1. Persons (adults or children) who are at high risk for influenza and its complications because of underlying medical conditions for which they are receiving regular medical care. There is a focus on vaccination HIV infected persons. Other high risk conditions include chronic pulmonary or cardiac disease, chronic renal disease, diabetes mellitus and similar metabolic disorders, individuals who are immunosuppressed, and individuals who are morbidly obese (BMI \geq 40).
2. Pregnant women – irrespective of stage of pregnancy.
3. Children less than 5 years of age.
4. All persons over the age of 65 years.
5. Residents of old-age (nursing) homes and other chronic care or rehabilitation facilities.
6. Children aged 6 months to 18 years on long-term aspirin therapy.

The TIV is an inactivated vaccine, and has a well-established safety record. It is safe for use in pregnancy and in children \geq 6 months of age. Contraindications to the administration of TIV include:

- Persons with a history of anaphylaxis (severe allergic/hypersensitive reactions) following receipt of any vaccine component including: eggs, neomycin or polymixin antibiotics

- Persons with a history of severe reaction to previous influenza vaccination
- Persons who developed Guillain-Barré syndrome within 6 weeks of receiving an influenza vaccine
- Children <6 months of age
- Persons with an acute febrile illness should preferably be immunised after symptoms have resolved.

Patients who are severely immunocompromised for any reason may not have a sufficient immune response to TIV and therefore may not be protected against influenza. Current influenza vaccination does not preclude a diagnosis of influenza as the vaccine is not 100% effective.

2.4. Influenza vaccine dosage and administration

The influenza vaccine should be administered intramuscularly (IM) as follows:

- Adults and children 6 years and above: Injection into the upper arm (Deltoid)
- Children aged 1 year to <6 years: Injection into the LEFT upper arm
- Infants aged 6 – 11 months: Injection into the LEFT antero-lateral thigh

NB: According to Department of Health recommendations, for children < 6 years 13-valent pneumococcal conjugate vaccine (PCV-13) will be administered into the RIGHT arm.

The recommended dosage of influenza vaccine for patients of different age groups is described in table 1.

Table1: Recommended dosage of influenza vaccine for patients of different age groups

Age Group	Dose	Number of doses
Adults and children 9 years of age and older	Adult dose (0,5ml) IMI	Single dose
Children 3 years through 8 years	Adult dose (0,5ml) IMI	1 or 2 doses*
Children 6 months through 2 years	0.25ml (half an adult dose) IMI	1 or 2 doses*

*Children aged 6 months through 8 years of age receiving the vaccine for the first time should receive 2 doses administered at least 4 weeks apart. Because the influenza vaccine formulation in 2012 is identical to that in 2011, children aged 6 months through 8 years of age who received at least 1 dose of influenza vaccine in 2011 will require only one dose of vaccine.

- **Note:** Influenza vaccine is not recommended for infants less than 6 months of age

3. Case descriptions

3.1. General considerations

During the influenza season, influenza must be considered in the differential clinical diagnosis of febrile patients as well as patients presenting with respiratory symptoms who may not have fever.

3.2. Typical symptoms of infection

The symptoms of influenza are non-specific. A spectrum of illness ranging from asymptomatic infection or uncomplicated upper respiratory tract disease to serious complicated illness (which may include exacerbation of other underlying conditions, severe viral pneumonia or multi-organ failure) can occur. The most common symptoms include: cough, fever, sore throat, malaise and headache. In some cases there may be gastrointestinal symptoms (nausea, vomiting and/or diarrhoea); these are more common in children than adults and in those infected with A(H1N1)pdm09. Among children, otitis media has been reported commonly with influenza illness. Uncomplicated influenza illness resolves after 3-7 days in most persons, although cough and malaise can persist for >2 weeks.

3.3. Categories of influenza disease:

For the purposes of clinical management, the WHO have categorised influenza disease as follows:

3.3.1. Uncomplicated influenza: ILI (Influenza-like Illness)

- i. An individual with recent onset of an influenza-like illness (ILI), which may include fever $\geq 38^{\circ}\text{C}$ PLUS ONE OR MORE of the following: acute respiratory symptoms (sore throat, rhinorrhoea/nasal congestion), headache, myalgia, malaise, diarrhoea/vomiting (more common in children) PLUS **absence of evidence of lower respiratory tract disease (shortness of breath or dyspnoea)**
- ii. Elderly and immunosuppressed individuals with uncomplicated illness may present with atypical symptoms and absence of fever.

3.3.2. Complicated or severe influenza

- i. Presenting clinical (e.g. dyspnoea, tachypnoea, hypoxia) and/or radiological signs of lower respiratory tract disease (e.g. pneumonia).
- ii. Presence of extrapulmonary complications, including: CNS involvement (encephalopathy, encephalitis), severe dehydration, myositis/rhabdomyolysis, myocarditis, secondary complications (renal failure, multi-organ failure, septic shock).
- iii. Exacerbation of underlying chronic disease, including: asthma, chronic obstructive pulmonary disease (COPD), chronic hepatic or renal insufficiency, diabetes, other cardiovascular conditions (e.g. congestive cardiac failure).
- iv. Other conditions/clinical presentations requiring hospital admission for clinical management (including secondary bacterial pneumonia, usually *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Streptococcus pyogenes*).
- iii.

3.3.3. Progressive influenza disease

Patients who initially present with uncomplicated influenza may progress to severe disease; progression can be rapid (within 24 hours). Indicators of progression include:

- Symptoms and signs suggesting oxygen impairment or cardiopulmonary insufficiency:
 - Shortness of breath (with activity or at rest), dyspnoea, tachypnoea, cyanosis, bloody or purulent sputum, chest pain, hypotension;
 - Children: fast or laboured breathing;
 - Hypoxia (as indicated by pulse oximetry or arterial blood gas).
- Symptoms and signs suggesting CNS complications: altered mental status (including confusion), unconsciousness, drowsiness, recurring/persistent seizures, severe weakness or paralysis.
- Evidence of sustained viral replication or secondary bacterial infection based on laboratory testing or clinical signs (e.g. persistent/recurrent high fever and other symptoms beyond 3 days without signs of resolution).
- Severe dehydration.

3.4. Risk factors for severe or complicated influenza

Certain groups of patients with influenza infection are at higher risk of developing severe or complicated disease. However, it should be borne in mind that influenza infection in any patient can result in severe/complicated illness. There are no early predictors of progression to severe disease. Persistent vomiting, high fever and progressive dyspnoea should alert the physician to this possibility. Patients may deteriorate rapidly.

Risk groups for severe/complicated disease, for seasonal and A(H1N1)pdm09 influenza include:

- Infants and young children (particularly <2 years of age)
- Pregnant women (at all stages of pregnancy, including the first two weeks of the post-partum period). It appears that women in the second- and third-trimesters of pregnancy have the highest risk.
- Persons of any age with chronic diseases, including:
 - Pulmonary diseases (e.g. asthma, COPD, tuberculosis)
 - Cardiac diseases, except for hypertension (e.g. congestive cardiac failure)
 - Metabolic disorders (e.g. diabetes)

- Renal disease
- Hepatic disease
- Certain neurologic and neurodevelopmental conditions, including: disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy; epilepsy (seizure disorders); stroke; mental retardation; moderate to severe developmental delay; muscular dystrophy; or spinal cord injury.
- Haemoglobinopathies (e.g. sickle cell disease)
- Immunosuppression (e.g. HIV, persons on immunosuppressive medication, malignancy)
- Persons ≤ 18 years receiving chronic aspirin therapy
- Persons aged ≥ 65 years
- Persons who are morbidly obese (i.e. BMI ≥ 40).

4. Laboratory testing

4.1. Who should be tested?

Laboratory testing of uncomplicated illness (patients who fit the ILI case definition) is **NOT** routinely recommended, as it provides very little advantage to the clinical management of individual patients. Testing is recommended for the following patients:

- Patients who meet the criteria for complicated or severe influenza, where a laboratory diagnosis will assist in patient management, or patients hospitalised due to a lower respiratory tract infection where no other explanation for illness is evident and influenza forms part of the differential diagnosis.
- Patients at risk for developing complicated or severe influenza (as per list under section 3.4) AND who are symptomatic should be considered for testing if it will guide clinical management.
- Clusters of cases where a diagnosis of the cause of the outbreak is needed (e.g. within institutions such as healthcare facilities, nursing homes). First 2-3 cases to be tested, thereafter testing not required.
- An individual who has died where influenza is suspected as the cause of death.

Important note: Initial treatment decisions should be based on clinical presentation and should NOT be delayed pending laboratory confirmation of influenza.

Note: These recommendations for laboratory testing do not apply to surveillance activities managed by the NICD (e.g. Viral-watch, SARI surveillance programme), and testing should continue as guided by those individual surveillance programmes.

4.2. Laboratories conducting testing

NICD is no longer offering routine diagnostic tests for influenza outside of the established surveillance programmes at specific sites. Diagnostic capacity to test for influenza virus and/or serotyping has now been established in various public- and private-sector laboratories throughout the country.

Clinicians are urged to discuss with their facility's designated laboratory about:

- where specimens should be referred to,
- the specific test that will be conducted by that laboratory and the interpretation \pm limitations thereof, and
- the cost implications to the hospital/patient/medical aid.

In line with WHO recommendations, molecular diagnostics are currently the method of choice for influenza virus. The sensitivity and specificity of currently available rapid-point-of-care or immunofluorescence tests designed for direct detection of influenza A viruses are low and therefore not recommended at present. False negative results occur commonly with rapid influenza diagnostic tests (RIDT) and a negative RIDT result does **NOT** exclude a diagnosis of influenza in a patient with suspected influenza.

4.3. Specimen collection, storage and transportation

- i. Wear appropriate personal protective equipment, including a medical mask and non-sterile gloves; wear eye-visors or goggles or a face shield if procedures include a risk of splash to the face. When performing specimen-collection procedures that may generate aerosols (e.g. aspiration or open suctioning of the respiratory tract), a particulate respirator (e.g. N95 respirator) must be worn, in addition to gloves, eye-visors/goggles or a face shield.
- ii. Swab each nostril with a single swab, or swab the throat, or do both. If taking specimens from both nostrils and throat on the same patient, use a single swab for both nostrils and a second swab for the throat. (Use only dacron or rayon swabs. Wooden swabs are not suitable for testing). Place the swab/s into a container of viral transport medium (VTM); if both nasal and throat swabs are taken on a patient, these can be placed into the same VTM container.
- iii. If using the Virocult[®] specimen collection and transport device, remove the swab from its holder and swab the nostrils/throat. Place the swab into the transport tube, secure the cap, and squeeze the end of the tube around the sponge to ensure complete wetting of the swab tip.
- iv. Complete the specimen request form with the following details: patient name, health facility (where appropriate), healthcare worker's name and contact numbers, lab name, contact person, telephone and fax number for receipt of results, and clinical details.
- v. Transport specimens directly to the appropriate laboratory (see section 3.1). The specimens must be transported at 4°C if transport is expected to be delayed.

The following additional information should also be taken into account regarding specimen collection:

- Specimens for virus isolation or for detection of viral nucleic acids or antigens should be taken preferably during the first three days after onset of clinical symptoms, but may be taken up to a week after onset or even later in severely ill or immunocompromised patients or children.
- Specimens should preferably be taken prior to commencement of antiviral agents.
- Nasopharyngeal swabs may be collected instead of nose and throat swabs. Swabs pose a lower risk of transmitting infection to healthcare workers than do nasopharyngeal aspirates (NPA) or nasal washes, both of which may generate aerosols. Healthcare workers performing nasopharyngeal swabs should practice appropriate infection prevention and control measures (see section 6.1 below).
- In addition to swabs from the upper respiratory tract, invasive procedures such as bronchoalveolar lavage/ bronchial aspirate or lung biopsy can be performed for the diagnosis of influenza infection of the lower respiratory tract where clinically indicated.
- Results of all diagnostic tests for influenza are dependent upon several factors (including specimen type and quality of specimen collection, timing of collection, storage and transport conditions), such that false-negative results may be obtained. When clinical suspicion is high, clinicians must consider repeat/serial testing.

4.4. Post-mortem specimens

A variety of specimens can be collected post-mortem; all specimens (swabs/tissue) need to be placed directly into viral transport medium. Suitable specimens include:

- Nasal, nasopharyngeal and throat swabs
- If consent has been given for a post-mortem, tissues that may be sampled include lung, trachea (proximal and distal), nasopharynx (best done from a supratentorial approach with removal en bloc), liver, brain and kidneys
- If consent for a full post-mortem is not forthcoming, the attending clinician should consider a para-mortem Trucut lung biopsy. Other organs which may be sampled using a Trucut biopsy needle include spleen, bone marrow and liver.

4.5. Swabs and viral transport medium (VTM)

1. Wooden swabs are not suitable for respiratory virus PCR. Please use dacron or rayon swabs.
2. All specimens must be transported in VTM as instructed above.
3. The appropriate swabs and VTM may be obtained from your local laboratory.
4. Laboratories should stock VTM and the appropriate swabs, which may be obtained through their usual suppliers.

Product	UTM-RT transport media (Manufacturer: Copan; Catalog number: 330C) This product is stable at room temp and need not be refrigerated	Hank's based viral transport medium (RTS) Supplied in 4ml Sarstead tubes This product is stable at room temp and need not be refrigerated	Dacron/rayon Swabs/Regular flocced swabs (Manufacturer : Copan; Catalog number: 502CS01).	VIROCULT® specimen collection and transport device
Oracle # (for NHLS)	1038366		-	-
Supplier	Lasec		Pro-Gen Diagnostics/ Lasec	
Contact details	Tel: 012 665 3933 Email: amy.ackerman@lasec.co.za Web: www.lasec.co.za		Tel: 011-467-7510. Email: info@pro-gensa.com Web: www.pro-gensa.com	

5. Clinical Management

5.1. Antiviral therapy

5.1.1. General considerations

As of December 2010, the antiviral susceptibilities of circulating influenza viruses are:

Influenza virus	Oseltamivir	Zanamivir	M2 Inhibitors [†]
Influenza A (H1N1)pdm09	Susceptible	Susceptible	Resistant
Influenza A (H3N2)	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	No activity

[†]Amantadine and rimantadine; not recommended currently.

Antiviral therapy may reduce mortality, hospitalisations and duration of symptoms in patients infected with influenza. Oseltamivir and zanamivir are the recommended antiviral agents, since surveillance and resistance data indicate that >99% of currently circulating influenza virus strains are sensitive to these agents.

Infection with oseltamivir-resistant influenza A(H1N1)pdm09 strains is uncommon to date and has been identified in <1% of untreated cases. The majority of resistant viruses have been detected in patients who were receiving oseltamivir treatment and many of these patients were immunocompromised. More recently, community transmission of oseltamivir resistant influenza A(H1N1)pdm09 has been reported from several countries although numbers have been small to date. Infections with oseltamivir-resistant influenza B viruses have been documented, but remain very uncommon. The largest proportion of these cases has occurred in severely immunocompromised patients, particularly bone marrow or haemopoietic stem cell transplant patients on immunosuppressive chemotherapy. The majority of oseltamivir-resistant strains identified globally have been susceptible to zanamivir. Ongoing global and local surveillance to detect resistant virus is essential.

Influenza must be considered as an important potential cause of community acquired pneumonia (CAP) in all patients during the influenza season and consideration must be given to including oseltamivir as empiric treatment. Note that because influenza vaccination is not 100% effective in preventing influenza, a history of influenza vaccination does not exclude the possibility of influenza infection in patients with clinical features compatible with influenza.

5.1.2. Severe, complicated or progressive influenza in adults and adolescents

Treatment with oseltamivir should be started as soon as possible and must **NOT** be delayed pending laboratory confirmation of influenza. Starting treatment within 48 hours of onset of symptoms is of greater benefit, but later initiation of treatment may also be effective and therefore ALL patients with severe or progressive illness should receive oseltamivir. This applies to all patient groups, including: pregnant and postpartum women up to 2 weeks following delivery, and breastfeeding women.

- **Oseltamivir**

- Standard dose and duration: 75mg twice daily orally for 5 days
- Higher doses of oseltamivir (150 mg twice daily orally) and longer duration of treatment (7 to 10 days) may be appropriate (particularly in critically ill patients), although there is no clinical trial evidence confirming benefit. Limited data indicate that treatment with higher doses is well tolerated, but care must be taken when treating patients with renal impairment. There is insufficient safety data for doses higher than 75 mg twice daily in pregnancy.
- For patients unable to swallow capsules, methods for preparation of an oral suspension are described in instructions from manufacturers (refer to package insert). Where suitable suspending agents or diluents containing preservatives are not available, capsules can be opened and mixed with a measured volume of water (e.g. one teaspoon) immediately before administration. Such suspensions may be administered via nasogastric/orogastric tubes in mechanically ventilated patients. (Reference: Health Protection Agency; Summary of prescribing guidance for the treatment and prophylaxis of influenza-like illness. 18 December 2009. Access at http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1243581475043).
- Adverse effects: nausea, vomiting, abdominal pain, diarrhoea, headache and conjunctivitis are the most commonly reported. Rash is uncommon. Other adverse effects that have been reported include: hepatitis, arrhythmias, neuropsychiatric disorders (in children and adolescents), visual disturbances, Stevens-Johnson syndrome and toxic epidermal necrolysis.
- Renal impairment requires a dose adjustment based on creatinine clearance as follows:

Glomerular filtration rate (ml/min)*	Recommended dose of oseltamivir treatment
>30	75 mg twice daily
> 10 to 30	75 mg once daily
10	Seek specialist advice
Dialysis patients	Seek specialist advice

- **Zanamivir**

- Treatment with zanamivir is indicated in patients where oseltamivir-resistant influenza is demonstrated or highly suspected.
- Standard dose and duration: two inhalations (i.e. 2 x 5mg) twice daily for 5 days
- Zanamivir contains lactose (powder for inhalation) and must NOT be administered by a nebuliser. It may also interfere with ventilator functioning in ventilated patients.
- Adverse effects are very rare and include: bronchospasm, respiratory impairment, angioedema, urticaria, and rash. Neuropsychiatric disorders have also been reported (especially in children and adolescents).

5.1.3. Uncomplicated influenza in adults and adolescents (>12 years of age)

Patients with uncomplicated illness due to confirmed/strongly suspected influenza infection do NOT ordinarily require antiviral therapy. However, patients with uncomplicated illness who are in a risk group (see 3.4 above) DO require treatment with oseltamivir as soon as possible. Treatment recommendations are as detailed in section 5.1.2. above.

5.1.4. Severe, complicated or progressive influenza in children (<12 years of age)

General considerations:

- Treatment with oseltamivir should be started as soon as possible and must **NOT** be delayed pending laboratory confirmation of influenza. Starting treatment within 48 hours of onset of symptoms is of greater benefit, but later initiation of treatment may also be effective and therefore ALL patients with severe or progressive illness should receive oseltamivir. This applies to all children, including neonates and infants.
- Routine childhood vaccination schedule must be kept up to date. Secondary bacterial pneumonia is an important cause of morbidity and death in influenza, and *Streptococcus pneumoniae* is one of the leading causes of secondary bacterial pneumonia. All children aged less than 2 years should be vaccinated with the 13-valent pneumococcal conjugate vaccine (PCV13) if not previously done.

Recommended doses and duration of oseltamivir therapy for children less than 1 year of age are as follows:

Age	Dose	Duration of therapy
Premature neonates (<38 weeks)	1 mg/kg twice daily	5 days
Infants 0 – 12 months	3 mg/kg twice daily	5 days

Recommended doses and duration of oseltamivir therapy for children 1 to 12 years of age are as follows:

Weight	Dose	Duration of therapy
15 kg or less	30 mg twice daily	5 days
15 – 23 kg	45 mg twice daily	5 days
24 – 40 kg	60 mg twice daily	5 days
>40 kg	75 mg twice daily	5 days

Considerations for treatment with oseltamivir:

- Lower doses should be considered for infants who are not receiving regular oral feedings and/or those who have a concomitant medical condition which is expected to reduce renal function significantly.
- Capsule contents can be added to a sweet liquid / soft food immediately before administration to disguise bitter taste; syrup, condensed milk, yoghurt, sugar dissolved in water, or other sweet liquids/foods may be used. Open capsule/s and pour contents into a small amount of the liquid/food (one teaspoon maximum). Stir the mixture and ensure that the entire mixture is given to the patient. The mixture must be given immediately after its preparation. (Reference: Health Protection Agency; Summary of prescribing guidance for the treatment and prophylaxis of influenza-like illness. 18 December 2009. Access at http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1243581475043).
- Methods for preparation of an oral suspension using capsules are described in instructions from manufacturers (refer to package insert). Where suitable suspending agents or diluents containing preservatives are not available, capsules can be opened and mixed with a measured volume of water (e.g. one teaspoon) immediately before administration.
- Adverse effects: nausea, vomiting, abdominal pain, diarrhoea, headache and conjunctivitis are the most commonly reported. Rash is uncommon. Other adverse effects that have been reported include: hepatitis, arrhythmias, neuropsychiatric disorders (in children and adolescents), visual disturbances, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Considerations for treatment with zanamivir:

- Treatment with zanamivir is indicated in patients where oseltamivir-resistant influenza is demonstrated or highly suspected.
- Zanamivir is only indicated for use in persons aged **≥5 years**.
- Standard dose and duration: two inhalations (i.e. 2 x 5mg) twice daily for 5 days
- Zanamivir contains lactose (powder for inhalation) and must NOT be administered by a nebuliser. It may also interfere with ventilator functioning in ventilated patients.
- Adverse effects are very rare and include: bronchospasm, respiratory impairment, angioedema, urticaria, and rash. Neuropsychiatric disorders have also been reported (especially in children and adolescents).

5.1.5. Uncomplicated influenza in children

Children with uncomplicated illness due to confirmed/strongly suspected influenza infection do NOT ordinarily require antiviral therapy. However, children with uncomplicated illness who are in a risk group (see 3.2 above) DO require treatment with oseltamivir as soon as possible. Note that this includes ALL infants and young children <2 years of age, since they are known to be at higher risk of severe/complicated illness. Treatment recommendations are as detailed in section 5.1.4 above.

5.1.6. Chemoprophylaxis of influenza

Antiviral chemoprophylaxis is currently NOT recommended by the WHO. The WHO recommendations advise that post-exposure presumptive antiviral treatment may be of benefit in some higher risk situations, such as transplant patients, or patients with severe immunosuppression (e.g. those receiving chemotherapy). If such higher risk individuals have been exposed to a patient with influenza, strongly consider presumptive treatment with oseltamivir or zanamivir (dose and duration as per treatment recommendations in section 5.1.2 above). In other situations, caregivers are advised to monitor exposed,

high-risk patients for early signs and symptoms of acute respiratory infection and ILI and to start antiviral treatment promptly (dose and duration as per treatment recommendations in 5.1.2 and 5.1.4 above).

In contrast to these recommendations, recent influenza management guidelines issued by the Health Protection Agency (HPA) for use in the United Kingdom, and by the Advisory Committee on Immunization Practices (ACIP) for use in the United States have made provision for the use of oseltamivir/zanamivir as chemoprophylaxis in certain settings. Common to both sets of guidelines is the major proviso that chemoprophylaxis must be given within 48 hours of last contact with a person ill with influenza in order to be effective. However, these two sets of guidelines differ as to the intended target groups for chemoprophylaxis (immunosuppressed patients only versus all persons at higher risk for severe disease) and the dose of chemoprophylactic oseltamivir (e.g. 75 mg once daily versus 75 mg twice daily for adults).

It is therefore advised to follow the WHO guidelines in this regard, and to seek specialist advice when indicated.

5.2. Other interventions for management

- **Oxygen therapy:** Monitor O₂ saturation and maintain SaO₂ > 90% (92-95% for pregnant women) with nasal cannulae or face mask. High flow O₂ may be required in severe cases.
- **Antibiotics:** In cases of pneumonia, early empiric treatment for community acquired pneumonia is advised. Since there is an increased risk of secondary infection with *S. pneumoniae*, *S. aureus* and *S.pyogenes*, co-amoxiclav is a suitable empiric antibiotic. Submit appropriate specimens for MC&S to lab, and tailor antibiotic/s accordingly. Exclude a diagnosis of tuberculosis.
- **Corticosteroids:** Low doses of systemic corticosteroids may be considered for patients in septic shock who require vasopressors, or when indicated for another reason. However, systemic corticosteroids are NOT recommended as adjunctive treatment for influenza.
- **Paracetamol / acetaminophen:** Administer for fever or pain.
- **Salicylates (aspirin and aspirin-containing products):** Do NOT use in children and young adults < 18 years (increased risk of Reye's syndrome with influenza). Do NOT use in pregnant women (foetal risks and maternal bleeding)
- **NSAIDs:** Do NOT use in pregnant women (foetal risks and maternal bleeding)

There is insufficient data on efficacy, safety or both for the following agents and their use is therefore not recommended at present: immunoglobulins, intranasal interferons, arbidol, ribavirin, favipiravir.

5.3. Additional comments on management

5.3.1. Severely ill patients

- Antiviral therapy
 - Oseltamivir therapy should be started immediately upon admission. Treatment decisions should be based on clinical presentation and should NOT be delayed pending laboratory confirmation of influenza. Higher doses (150 mg twice daily) for prolonged duration (10 days) may be of benefit.
 - Dose adjustment according to creatinine clearance is necessary for patients with renal impairment.
- Other issues regarding critical care management of patients with influenza are beyond the scope of this document. A comprehensive review appears in the journal *Critical Care Medicine* 2010 Vol. 38, No. 4(Suppl.) pp e1-e142: H1N1 Novel Influenza: Pandemic Issues for Critical Care Practitioners. Free access is available online at: <http://journals.lww.com/ccmjournal/toc/2010/04001>

5.3.2. Pregnant patients

- Pregnant women (at all stages including 2 weeks postpartum, and especially those with co-morbidities) are at increased risk for severe or complicated influenza which may be rapidly progressive. HIV-infected pregnant patients seem to be at even higher risk. Influenza in pregnancy carries an increased risk of adverse pregnancy outcomes, including spontaneous abortion, preterm birth and foetal distress. Consequently, pregnant women with

suspected/confirmed influenza warrant closer observation and early antiviral therapy. Treatment decisions should be based on clinical presentation and should NOT be delayed pending laboratory confirmation of influenza.

- Paracetamol is recommended for pain and fever. Salicylates and NSAIDs are contraindicated in pregnancy.
- There is currently no safety data on the use of higher doses of oseltamivir (>75 mg bd) in pregnancy.

5.3.3. Children

- Symptoms may be non-specific, therefore clinicians need to maintain a high index of suspicion. Gastrointestinal symptoms (nausea, vomiting and/or diarrhoea) are more common in children than adults, and otitis media has been reported commonly with influenza illness in children.
- Influenza-associated encephalopathy (IAE) is an uncommon but serious complication with high mortality and neurological sequelae, occurring most often in children younger than 5 years. It has been increasingly recognised worldwide in association with influenza A (both H3N2 and H1N1) as well as influenza B infection. IAE is a rapid progressive encephalopathy that usually presents within a few days of onset of typical influenza symptoms, and can manifest with diverse clinical symptoms including: seizures, altered/loss of consciousness, decreased cognitive processing including speech, motor paralysis (mimicking Guillain-Barré syndrome) or sensory loss, abnormal or delirious behaviour, and focal neurological syndromes. CSF findings are usually normal, and neuroimaging may be normal or abnormal (diffuse abnormalities or focal white matter lesions). The diagnosis of IAE rests on confirmation of influenza infection in the absence of other causes of encephalopathy/encephalitis.
- Antiviral therapy should be started early. Treatment decisions should be based on clinical presentation and should NOT be delayed pending laboratory confirmation of influenza.
- Paracetamol is recommended for pain and fever. No salicylates should be given to children, since there is an increased risk of Reye's syndrome with influenza and salicylates in younger children.
- Consider early antibiotic treatment for secondary bacterial infection.
- Lower doses of oseltamivir should be considered for infants who are not receiving regular oral feedings and/or those who have a concomitant medical condition which is expected to reduce renal function significantly.
- Routine childhood vaccination schedule must be kept up to date. Secondary bacterial pneumonia is an important cause of morbidity and death in influenza, and *Streptococcus pneumoniae* is one of the leading causes of secondary bacterial pneumonia. All children aged less than 2 years should be vaccinated with the pneumococcal conjugate vaccine (PCV7) if not previously done.
- Infant feeding and maternal separation: infants can stay with their mothers and should breastfeed if both are well enough and there are no other contraindications to breastfeeding. If a non-infectious carer is available to administer expressed breastmilk to the infant for 7 days then that may be preferable, but is not always feasible. If the mother or infant is too ill to breastfeed, separate the infant from mother but continue to give expressed breast milk if it is available.
- Treatment of neonates and preterm infants should be done in consultation with a specialist in the field.
- Infants born to mothers with influenza DO NOT require antiviral therapy unless the infant has an influenza-compatible illness and requires hospitalisation.

5.3.4. HIV-infected patients

HIV-infected persons have higher rates of hospitalisations due to severe influenza disease as well as increased mortality for seasonal influenza and influenza A(H1N1)pdm09. Even in the ART-era, patients with HIV have higher rates of influenza-associated hospitalisations than the general population. Analysis of mortality data collected in South Africa during the 2009 pandemic suggests that HIV-infected patients do constitute a higher-risk group for fatal infection. Of note is that pregnant HIV-infected patients seem to be at especially high risk, and clinicians need to maintain a high index of suspicion for influenza in this group of patients.

5.3.5 Patients with persistent severe or progressive disease despite appropriate antiviral treatment

Patients who have laboratory-confirmed influenza where the clinical course remains severe or progressive despite ≥ 5 days of appropriate antiviral therapy (correct drug given at the correct dose etc.) should be investigated for the following:

- Bacterial secondary infections (particularly with *S. pneumoniae*, *S. aureus* and *S. pyogenes*) and nosocomial infections or underlying tuberculosis
- Presence of influenza-related complications (e.g. CNS involvement, myocarditis, rhabdomyolysis)

- Complications such as atelectasis or fluid overload
- Ongoing viral replication (as evidenced by laboratory tests): liaise with infectious diseases specialists/virologists regarding appropriate specialised testing. This may indicate infection with oseltamivir-resistant virus. Zanamivir is the treatment of choice for all patients where oseltamivir-resistance is demonstrated or highly suspected.

6. Infection prevention and control (IPC)

Human-to-human transmission of influenza viruses occurs either directly or indirectly through close, unprotected contact with large respiratory droplets. The role of smaller droplet nuclei at close-range exposure in transmission of influenza is not known, but may be more important in certain settings (e.g. aerosol-generating procedures associated with increased risk of virus transmission). Therefore, IPC precautions need to be focused on controlling respiratory droplet spread.

6.1. IPC precautions

Recommended IPC precautions when caring for patients with suspected, probable, or confirmed infection with influenza, or ILI include the following:

- When working in direct contact with patients, Standard and Droplet Precautions should be applied:
 - Standard Precautions:
 - Hand hygiene: washing hands with soap and water or the use of an alcohol-based hand rub
 - Use of personal protective equipment (PPE): this includes facial protection (by means of a medical mask and eye-visor /goggles or a face shield) as well as use of a gown and clean gloves.
 - Droplet Precautions:
 - Wear a medical mask if working within approximately 1 metre of the patient or upon entering the room/cubicle of a patient on Droplet Precautions
 - Perform hand hygiene before and after patient contact and immediately on removal of a medical mask
- IPC precautions when performing aerosol-generating procedures associated with an increased risk of infection transmission (e.g. aspiration/open suctioning of the respiratory tract, including for the collection of respiratory tract specimens, intubation, resuscitation, bronchoscopy, autopsy):
 - Wear a particulate respirator (e.g. N95 respirator), a clean non-sterile long-sleeved gown, and gloves.
 - Perform hand hygiene before and after patient contact and after PPE removal
- IPC precautions for patients who are mechanically ventilated or undergoing respiratory therapy:
 - Mechanically ventilated patients: Standard and Droplet Precautions (but when aerosol-generating procedures are performed, particulate respirators need to be worn).
 - Chest physiotherapy: Standard and Droplet Precautions. A medical mask should be worn by the patient if possible.
 - Nebulisation: Standard and Droplet Precautions.

6.2. Duration of isolation precautions

- All patients should remain on Droplet Precautions for a minimum of 7 days following symptom onset.
- Droplet Precautions should be maintained until 24 hours following resolution of acute influenza symptoms, particularly fever. However, Standard Precautions remain in effect for all patient care. Certain groups of patients may have prolonged viral shedding which extends beyond resolution of acute symptoms, such that there may still be a risk of influenza transmission in the absence of symptoms. These include:
 - Infants and children
 - Elderly patients
 - Severely immunosuppressed or immunocompromised patients: these individuals may shed more virus for a longer time period and are at increased risk for development of antiviral-resistant virus. For such patients, Droplet Precautions should be maintained for the duration of the illness.

6.3. Respiratory hygiene/cough etiquette

All persons (healthcare workers, patients, and visitors) should cover their mouth and nose with a disposable tissue when coughing or sneezing, then discard the tissue in a receptacle and perform hand hygiene. When possible, patients who are showing signs of an ILI should wear a medical mask in waiting areas etc.

6.4. Occupational health

Monitor healthcare workers (HCW)s in contact with patients who are ill with influenza infection; HCWs with symptoms should stay at home. HCWs at high risk for severe disease and complications of influenza should follow recommended IPC measures carefully.

7. Resources for further information

WHO guidelines:

- WHO guidelines for pharmacological management of pandemic influenza A(H1N1) 2009 and other influenza viruses (revised February 2010):
http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf
- Clinical management of human infection with pandemic (H1N1) 2009: revised guidelines (November 2009):
http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf
- Infection prevention and control during health care for confirmed, probable or suspected cases of pandemic (H1N1) virus infection and influenza-like illness (Updated guidance, 16 December 2009):
http://www.who.int/csr/resources/publications/cp150_2009_1612_ipc_interim_guidance_h1n1.pdf

Centers for Disease Control and Prevention:

- Morbidity and Mortality Weekly Report January 21, 2011. Antiviral agents for the treatment and chemoprophylaxis of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP):
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm?s_cid=rr6001a1_e
- Influenza Antiviral Medications: A Summary for Clinicians August 30 2011:
<http://www.cdc.gov/flu/pdf/professionals/antivirals/clinician-antivirals-2011.pdf>
- Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP): http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6033a3.htm?s_cid=mm6033a3_w

Health Protection Agency:

- Pharmacological treatment and prophylaxis of influenza. Version 1.7; 12 January 2011
http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1287147812045

Additional information is available on the following websites:

- NICD-NHLS Website: www.nhls.ac.za then follow link to NICD,
- Department of Health Website: www.doh.gov.za
- World Health Organisation Website: <http://www.who.int/topics/influenza/en/>
- Centers for Disease Control and Prevention (CDC, Atlanta): <http://www.cdc.gov/flu/index.htm>

Recommendations pertaining to the use of viral vaccines: Influenza 2012' has been published in the February 2012 edition of the South African Medical Journal (access at: <http://www.samj.org.za/index.php/samj/article/viewFile/4647/3083>).

Further questions from **health professionals** can be addressed to:

- The NICD Hotline - 082 883 9920 *strictly for use by health professionals only*

Further questions from the **general public** and all other queries can be directed to:

- The Department of Health Communicable Disease Control hotline: 0861-DOH-CDC (0861-364-232)

Appendix 1: Home care guidance: healthcare workers' directions to patients/caregivers

Home Care Guidance: healthcare workers' directions to patients/caregivers

1. You will probably be sick for several days with fever and respiratory symptoms.

2. Take Medications as Prescribed:

- Take all of the antiviral medication as directed (where applicable).
- Continue to cover your mouth and nose when you cough and wash your hands often (even when taking antiviral medications), to prevent spreading influenza to others.
- Visit the clinic/GP if you experience any side effects; i.e. nausea, vomiting, rash, or unusual behaviour.
- Take medications for symptom relief as needed for fever and pain such as paracetamol or ibuprofen. These medicines do not need to be taken regularly if your symptoms improve.
- Do not give aspirin (acetylsalicylic acid) or products that contain aspirin to children or teenagers 18 years old or younger.
- Do not give aspirin or NSAIDs to pregnant women.
- Children should not be given over-the-counter cold medications without first consulting a healthcare worker.

3. Seek Emergency Care:

If your child experiences any of the following:

- Fast breathing or difficulty breathing
- Bluish or grey skin colour
- Not drinking enough fluids
- Severe or persistent vomiting
- Not waking up or not interacting
- Being so irritable that the child does not want to be held
- Flu-like symptoms improve but then return with fever and worse cough

In adults, emergency warning signs that need urgent medical attention include:

- Difficulty breathing or shortness of breath
- Pain or pressure in the chest or abdomen
- Sudden dizziness
- Confusion
- Severe or persistent vomiting
- Flu-like symptoms improve but then return with fever and worse cough

4. Follow These Home Care Recommendations:

- Stay home for 7 days after your symptoms begin
- Drink clear fluids (such as water, broth, sports drinks, electrolyte beverages for infants) to keep from being dehydrated.
- Dishes etc. can be washed with hot soapy water.
- Throw away tissues and other disposable items used by the sick person in the rubbish bin. Wash your hands after touching used tissues and similar waste.
- Have everyone in the household wash hands often with soap and water, especially after coughing or sneezing. Alcohol-based hand cleaners are also effective.
- Avoid touching your eyes, nose and mouth.
- Continue with medication for chronic diseases as prescribed (e.g. ART, TB treatment).

Appendix 2: Summary table on management of patients with suspected or proven influenza infection

Category	Clinical Definition	Treatment	Diagnostic Tests
Uncomplicated Influenza-like illness (ILI)	Recent onset of temperature $\geq 38^{\circ}\text{C}$ PLUS one or more of: sore throat, rhinorrhoea/nasal congestion, dry cough, headache, myalgia, malaise, diarrhoea/vomiting. <u>Absence</u> of lower respiratory tract disease signs e.g. shortness of breath/dyspnoea *Elderly and immunosuppressed persons with uncomplicated illness may present with atypical symptoms and absence of fever.	NO RISK FACTORS PRESENT: <ul style="list-style-type: none"> ■ Symptomatic treatment with paracetamol \pm alternative analgesia. ■ Avoid aspirin in children and adolescents ≤ 18 years (risk of Reye's Syndrome). ■ Avoid aspirin and NSAIDs in pregnant women 	NOT for routine diagnostic testing
		RISK FACTORS PRESENT <ul style="list-style-type: none"> ■ Oseltamivir orally twice per day for 5 days[†] 	Consider testing
Progressive Influenza	Patient previously fulfils clinical criteria for uncomplicated illness (ILI) PLUS evidence of clinical deterioration with one or more of: shortness of breath, difficulty breathing, chest pain, productive cough with bloody or purulent sputum, altered mental state (including drowsiness/difficult to awaken), any new neurological symptom or sign (including recurring or persistent seizures, confusion, severe weakness or paralysis) hypotension, persistence of fever $\geq 38^{\circ}\text{C}$ for > 3 days, persistent vomiting with dehydration.	<ul style="list-style-type: none"> ■ Oseltamivir orally twice per day for 5 days for patients not already on treatment ■ Treatment should be started as soon as any of the clinical criteria are met[†]. ■ URGENT EARLY REFERRAL to hospital for supportive care and assessment 	Send nasopharyngeal / throat swabs for influenza testing [†]
Complicated or severe influenza	<ul style="list-style-type: none"> ■ Presenting clinical (e.g. dyspnoea, tachypnoea, hypoxia) and/or radiological signs of lower respiratory tract disease (e.g. pneumonia) ■ Presence of extrapulmonary complications: CNS involvement (encephalopathy/encephalitis), myocarditis, rhabdomyolysis/myositis ■ Exacerbation of underlying chronic disease, including: asthma, chronic obstructive pulmonary disease (COPD), chronic hepatic or renal insufficiency, diabetes, other cardiovascular conditions (e.g. congestive cardiac failure). ■ Other conditions/clinical presentations requiring hospital admission for clinical management (including secondary bacterial pneumonia with influenza, most commonly <i>Streptococcus pneumoniae</i>, <i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i>). 	<ul style="list-style-type: none"> ■ Treatment should be started as soon as any of the clinical criteria are met[†]. ■ URGENT EARLY REFERRAL to hospital for supportive care and assessment ■ Oseltamivir orally twice per day for 5 days (consider higher doses and prolonged duration for critically ill patients). ■ Antibiotics – to cover <i>S. aureus</i>, <i>S. pneumoniae</i> and <i>S. pyogenes</i> (e.g. co-amoxiclav) ■ Early oxygen supplementation and close monitoring of oxygen saturation. ■ Ensure adequate hydration and monitor renal function. 	Send nasopharyngeal /throat swabs for influenza testing [†]

*Risk factors: infants and young children (particularly < 2 years of age); pregnant women (including the first two weeks of the post-partum period); persons of any age with chronic diseases including: pulmonary diseases (e.g. asthma, COPD), cardiac diseases (e.g. congestive cardiac failure), metabolic disorders (e.g. diabetes), renal disease, hepatic disease, certain neurological conditions, (neuromuscular, neurocognitive and seizure disorders), haemoglobinopathies, immunosuppression (e.g. HIV, immunosuppressive medication or malignancy), persons ≤ 18 years receiving chronic aspirin therapy, persons aged ≥ 65 years, persons who are morbidly obese (BMI ≥ 40).

[†] All attempts should be made to start oseltamivir within the first 48 hours of symptoms.

[†] Testing for influenza should NOT delay administration oseltamivir when clinically indicated.