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)

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Prefix and Disclaimer

This advice is based on available information concerning the new pandemic influenza A (H1N1) virus as well as data on the natural history pathogenesis and clinical characteristics of 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 findings presented in the guidelines.

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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 viruses. There are three types of seasonal influenza viruses – A, B and C. Pandemic influenza A(H1N1), which appeared for the first time in 2009 causing a global flu pandemic, has since become the predominant influenza strain worldwide, and largely replaced previous influenza strains for the traditional northern hemisphere winter influenza season of 2009/2010. Based on this, it is likely but not certain that this will be the dominant influenza strain for the 2010 influenza season in South Africa.

1.2. Differences between pandemic influenza A(H1N1) and seasonal A(H1N1) during the 2009 pandemic

The epidemiology of pandemic infection differs from that of seasonal influenza in that it impacts on a wider age range, and children and young adults have the highest attack rates. Seasonal influenza usually affects younger children and the elderly. The pandemic influenza virus differs from seasonal influenza in that it can affect the lower respiratory tract and cause rapidly progressive pneumonia especially in children and young to middle-aged adults; about one third of patients with severe pandemic influenza illness requiring admission to ICU worldwide in 2009 were previously healthy persons. In addition to the classical groups of patients at higher risk for severe disease from seasonal influenza, additional risk factors particular to pandemic influenza were recognised during the 2009 pandemic, including obesity. Although known to be at higher risk for severe illness from seasonal influenza, pregnant women appeared to be especially vulnerable to pandemic influenza.

1.3. 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.

1.4. Typical symptoms of infection

The most common symptoms of influenza include: sudden onset of fever, chills, cough, headache, muscle and joint pain, sore throat and runny nose, and sometimes vomiting and diarrhoea (though more common in children than adults, and in those infected with pandemic influenza A(H1N1)). Most people recover within one or two weeks from fever and other symptoms without requiring antiviral treatment.

1.5. Public health concerns about influenza

Worldwide, annual seasonal influenza epidemics result in about three to five million cases of severe illness, and about 250,000 to 500,000 deaths. Illness can result in hospitalisations and deaths, mainly among high-risk groups. More than half of hospitalised people have underlying medical conditions or weakened immune systems. Most deaths associated with seasonal influenza in industrialized countries occur among people age 65 or older, but in the 2009 influenza pandemic, hospitalisations and fatalities were seen in otherwise healthy young individuals and pregnant women. An epidemic can result in high levels of worker absenteeism and productivity losses. Clinics and hospitals can be overwhelmed when large numbers of sick people appear for treatment during peak transmission periods.

2. Influenza in South Africa

2.1. Timing of the influenza season

The timing of the influenza season varies from year to year. Based upon the Viral Watch sentinel surveillance programme for influenza-like illness (conducted over the past 26 years by the NICD), the average onset of the influenza season in South Africa has been in epidemiological week 23 (corresponding to 7 – 13 June in 2010); however, this has ranged from as early as week 17 (corresponding to 26 April – 2 May in 2010) to as late as week 28 (corresponding to 12 – 18 July in 2010). Weekly surveillance reports on current influenza activity In South Africa are available via the NICD website (www.nicd.ac.za).

2.2. Expected influenza serotypes and vaccine formulation for 2010

Seasonal influenza occurs annually, with the circulating strains changing regularly. This year, pandemic influenza A(H1N1) 2009 virus is likely to be the predominant circulating stain, given this observation in the northern hemisphere. Co-circulation of other influenza stains is, nevertheless, possible. Vaccination with the trivalent vaccine is recommended, where applicable. The formulation for the trivalent vaccine is as follows:

- Pandemic influenza ("swine flu"), an A/California/7/2009 (H1H1)-like virus;
- Influenza A(H3N2), an A/Perth/16/2009 (H3N2)-like virus; and
- Influenza B, a B/Brisbane/60/2008-like virus.

The National Department of Health has launched a mass influenza vaccination campaign targeting groups at higher risk for severe disease in 2010, with the trivalent vaccine and monovalent pandemic influenza A(H1N1) vaccine. The prioritisation of risk groups for influenza vaccination by the National Department of Health (which can be accessed online at http://www.doh.gov.za/docs/immunization/h1n1.pdf) is as follows:

- Pregnant women
- Children <15 years with HIV/AIDS
- Adults >15 years with HIV/AIDS attending ARV clinics
- Patients with chronic heart and lung diseases
- Frontline clinicians in casualty, ICU and EMS personnel
- Frontline healthcare workers.

Initially, limited vaccine stocks were available in the private sector, but further stocks have been made available to private pharmacies throughout the country by a National Department of Health and private sector initiative. High-risk individuals may access vaccine at these pharmacies on presentation of proof of underlying risk factor (including a doctor's note, or proof of chronic medication), as well as at public health facilities. Although the vaccine is effective, it is important to remember that no vaccine offers 100% protection, and vaccinated persons may still become infected with influenza and develop severe disease.

2.3. Additional considerations in 2010

The South African influenza season will coincide with the 2010 FIFA World Cup that will see large numbers of spectators converging at stadiums and fan parks. Individuals visiting South Africa during this period are advised to take the influenza vaccine prior to arrival into South Africa (monovalent pandemic influenza A(H1N1) vaccine, as access to the southern hemisphere trivalent vaccine formulation internationally is likely to be limited) and practice cough etiquette and hand hygiene. It is likely that many visitors from the northern hemisphere will be immune to pandemic influenza A(H1N1) following infection or vaccination in the past year.

3. Case descriptions

3.1. General considerations

During the influenza season, influenza must be considered in the differential clinical diagnosis of febrile patients. The symptoms of influenza (for both seasonal and pandemic 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 and severe viral pneumonia with 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).

3.2. Categories of influenza disease:

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

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

i. An individual with recent onset of an influenza-like illness (ILI), which may include fever ≥38^{0}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 <u>absence</u> 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.

3.2.2. 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, 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 with influenza, most commonly *Streptococcus pneumoniae* or *Staphylococcus aureus*).

3.3. Signs and symptoms of progressive 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 seasonal influenza or pandemic 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, and that a third of severely ill patients admitted to ICUs with pandemic influenza were previously healthy persons not belonging to any known risk group.

Risk groups for severe/complicated disease, for both seasonal influenza and pandemic 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)
    - Cardiac diseases (e.g. congestive cardiac failure)
    - Metabolic disorders (e.g. diabetes)
    - Renal disease
    - Hepatic disease
    - Certain neurological conditions, including: neuromuscular, neurocognitive and seizure disorders
    - Haemoglobinopathies
    - Immunosuppression (e.g. HIV, persons on immunosuppressive medication, malignancy)
- Children receiving chronic aspirin therapy
- Persons aged ≥ 65 years

An additional risk group described for severe/complicated disease due to pandemic influenza A(H1N1) is obesity (BMI >30), particularly morbid obesity (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** 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 point 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 ± limitations thereof, and
- the cost implications to the hospital/patient/medical aid.

The following NHLS laboratories will provide influenza diagnostic services for public sector health facilities:

- Eastern Cape and Western Cape Provinces:
  - NHLS Groote Schuur Hospital
  - NHLS Tygerburg Hospital (Virology Department, University of Stellenbosch)
- Free State and Northern Cape Provinces:
  - NHLS Universitas Hospital
- Gauteng, Limpopo, North West and Mpumalanga Provinces:
  - NHLS Tshwane Academic (Steve Biko Academic Hospital)
  - NHLS Charlotte Maxeke Academic Hospital (formally Johannesburg General Hospital)
- KwaZulu-Natal Province:
  - NHLS Inkosi Albert Luthuli Hospital

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.

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 <u>not</u> 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 4^0C 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 antivirals.
- 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 full 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)

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

Product	Hank's based viral transport medium (VTM) Supplied in 4ml Sarstead tubes	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	VIROCULT® specimen collection and transport device
Oracle # (for NHLS)	P01R0259	P02H0881	-	-
Supplier	Highveld Biological		Pro-Gen Diagnostics	
Contact details	Tel: 011-608-3508. Email: elke@hibi.co.za Web: www.highveldbiological.com		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 January 2010, the antiviral susceptibilities of circulating influenza viruses are:

Influenza virus	**Oseltamivir**	**Zanamivir**	**M2 Inhibitors†**
Pandemic (H1N1) 2009	Susceptible	Susceptible	Resistant
Seasonal A(H1N1)	Mostly resistant	Susceptible	Mostly susceptible
Seasonal A(H3N2)	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	Resistant

†Amantadine and rimantadine

Since current epidemiological data indicates that pandemic influenza is the predominant influenza strain worldwide, oseltamivir or zanamivir (where available) are to be used when antiviral therapy is indicated. Amantadine and rimantadine are to be used ONLY when seasonal influenza A(H1N1) is proven/strongly suspected.

Infections with oseltamivir-resistant pandemic influenza viruses have been documented, but remain very uncommon. The largest proportion of these cases has occurred in severely immunocompromised patients, particularly bone marrow or haemopoetic stem cell transplant patients on immunosuppressive chemotherapy.

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

Treatment with oseltamivir should be started as soon as possible and must NOT be delayed pending laboratory confirmation of pandemic 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. There is safety data to support treatment with higher doses, 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:

GFR (ml/min)	Recommended dose of oseltamivir treatment
>30 (ml/min)	75 mg twice daily
> 10 to 30 (ml/min)	75 mg once daily
10 (ml/min)	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 pandemic 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 pandemic 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 pandemic 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 pneumococcal conjugate vaccine (PCV7) if not previously done.

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

Age	Dose	Duration of therapy
< 14 days of age	3 mg/kg once daily	5 days
14 days to 1 year	3 mg/kg twice daily	5 days

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

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

Antiviral chemoprophylaxis is generally NOT recommended. Presumptive (post-exposure) 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 / 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).

5.1.7. Other influenza strains

Antiviral treatment recommendations for infection with other influenza strains are generally the same as for pandemic influenza infection. Where the infection is known or suspected to be due to seasonal influenza A(H1N1) virus, oseltamivir is unlikely to be effective; zanamivir, amantadine or rimantadine may be used. Note that pregnant women and children <1 year of age should not be treated with amantadine or rimantadine (due to increased risk of adverse effects).

5.2. Other interventions for management

- Oxygen therapy:
  - Monitor O_2 saturation and maintain SaO_2 > 90% (92-95% for pregnant women) with nasal cannulae or face mask. High flow O_2 may be required in severe cases.
- Antibiotics:
  - In case of pneumonia, empiric treatment for community acquired pneumonia. Increased risk of secondary infection with *S. pneumoniae* and *S. aureus*; co-amoxiclav is therefore a suitable empiric antibiotic. Submit appropriate specimens for MC&S to lab, and tailor antibiotic/s accordingly.
- 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 recent 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 in pregnancy.

5.3.3. Children

- Symptoms may be non-specific, therefore clinicians need to maintain a high index of suspicion.
- 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 preterm infants should be done in consultation with a specialist in the field.
- Infants born to mothers with influenza: currently, most experts are <u>not</u> recommending use of antivirals to protect normal babies, and their use for treatment is only for those infants requiring hospitalisation.

5.3.4. HIV-infected patients

There is data from seasonal influenza that HIV-infected persons have higher rates of hospitalisations due to severe disease as well as increased mortality. Even in the ART-era, patients with HIV have higher rates of influenza-associated hospitalisations than the general population. There is limited data for pandemic influenza on the extent to which HIV-infected patients are at higher risk for severe or complicated illness or death; however, findings of a recent (unpublished) South African study shows high HIV-prevalence amongst tested patients hospitalised with influenza, as well as an elevated

incidence of influenza hospitalisation in HIV-infected individuals. 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 and nosocomial infections
- Presence of influenza-related complications (e.g. CNS involvement, myocarditis, rhabdomyolysis)
- Pandemic influenza A(H1N1) with 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.
- Infection with seasonal influenza A(H1N1): most strains are resistant to oseltamivir. Liaise with laboratory to interpret initial influenza test result ± submit further specimens for specialised testing. If seasonal influenza A(H1N1) is proven or highly suspected, treatment with zanamivir, amantadine or rimantadine is advised.

6. Infection prevention and control (IPC)

Human-to-human transmission of both pandemic and seasonal 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 in 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

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

- 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 ±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 ILI/illness.

6.3. Respiratory hygiene/cough etiquette

All persons (healthcare workers (HCW), patients and family members, 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 HCWs 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

Additional information is available on the following websites:

- NICD Website: www.nicd.ac.za,
- 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

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: doctors/nurses directions to patients/parents

Home Care Guidance: Doctors/Nurses directions to Patients/Parents

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 cough and wash your hands often (even when taking antiviral medications), to prevent spreading influenza to others.
- Call the clinic/GP if you (or your child) 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 younger than 4 years of age should not be given over-the-counter cold medications without first speaking with a health care provider.

3. Seek Emergency Care:

If your child experiences any of the following:

- Fast breathing or trouble 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 adult patients and children >5 years with suspected or proven influenza infection

Category	Clinical Definition	Treatment	Diagnostic Tests
Uncomplicated Influenza-like illness (ILI)	Recent onset of temperature ≥38°C **PLUS** one or more of: sore throat, rhinorrhoea/nasal congestion, dry cough, headache, myalgia, diarrhoea/vomiting.	**NO RISK FACTORS PRESENT:** ■ Symptomatic treatment with paracetamol ± alternative analgesia. ■ Avoid aspirin in children and adolescents who are at increase risk of Reye's Syndrome. ■ Avoid aspirin and NSAIDs in pregnant women **RISK FACTORS PRESENT** ■ Oseltamivir 75mg orally twice per day for 5 days‡	NOT for routine diagnostic testing
Progressive Influenza-like illness (PROGRESSIVE ILI)	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 ≥38°C for > 3 days, persistent vomiting with dehydration.	■ Oseltamivir 75mg orally twice per day for 5 days for patients not already on treatment ■ **Treatment should start 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 H1N1 testing†
Complicated or severe influenza	■ 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) ■ 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 *Streptococcus pneumoniae* or *Staphylococcus aureus*).	■ **Treatment should start as soon as any of the clinical criteria are met**. ■ **URGENT EARLY REFERRAL to hospital for supportive care and assessment** ■ Oseltamivir 75mg orally twice per day for 5 days (consider higher doses and prolonged duration for critically ill patients). ■ Antibiotics – to cover *S. aureus* & *S. pneumoniae* (e.g. co-amoxiclav) ■ Early oxygen supplementation and close monitoring of oxygen saturation. ■ Ensure adequate hydration and monitor renal function.	Send nasopharyngeal and throat swabs for H1N1 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), Children receiving chronic aspirin therapy, persons aged ≥ 65 years. An additional risk group for pandemic influenza is obesity (BMI >30, particularly morbid obesity, 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.