# The practitioners guide for dealing with the novel Influenza A, H1N1 pandemic

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## Abstract

Within three months of its discovery, the new Influenza A (H1N1) swineflu strain has spread to such an extent that a pandemic has been declared by the World Health Organization (WHO). Although most cases seem to be mild, cases of severe disease have also been reported and by 6 July 2009, 94 912 cases and 429 deaths were reported worldwide. At this point the WHO concluded that further spread within and to new countries is inevitable and sustained community transmission will make it impossible to confirm all cases by laboratory testing. In South Africa the 100 case mark was reached on 16 July 2009 and the laboratory testing strategy was modified. All cases of suspected swine flu will no longer be tested by the National Institute for Communicable Diseases (NICD) although continued monitoring of cases of severe or fatal respiratory illness will continue. This also places the responsibility on the health care provider to manage mild cases, treat moderate to severe cases and request confirmatory diagnostic tests and report appropriate cases. By the 19th of August 2009 the Number of laboratory confirmed cases in South Africa stood at 3544 including 6 deaths. This review aims to guide the clinician on these decisions.
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## Introduction

In March 2009 several cases of severe respiratory disease were reported in patients in Mexico.[1] Viral isolation identified a new H1N1 Influenza A strain of swine origin that was different from seasonal H1N1 influenza. The virus was reported to be a quadruple recombinant that has genetic elements of swine influenza, avian and human influenza.[2] Although thought to have been originally transmitted from infected pigs to humans, it quickly became clear that human to human transmission was the real concern, and pigs did not play an important role in further global epidemiological spread.[3] By 27 July 2009, 134 503 cases, including 816 deaths (0.6%), had been reported to the WHO from > 70 countries.[4] At this stage travel warnings were made to Mexico and the USA where most cases resided, however by 11 July 2009 the World Health Organization (WHO) declared a pandemic and raised the global pandemic alert level to phase 6 as it became clear that global human to human spread was inevitable. This pandemic alertness reflected the spread of the virus, not the severity. By the 6th of August 2009, the WHO reported a total of 177 457 laboratory-confirmed cases of pandemic influenza A (H1N1) and 1,462 deaths world-wide. In South Africa, 3544 cases was laboratory confirmed by the 19th of August including 6 deaths.This also changed the reporting recommendations to the WHO where laboratory surveillance is now mainly aimed at detecting genetic drift and reassortment which may affect virus pathogenicity; drug resistance, the specificity of current diagnostic tests and providing information on strain variation for vaccine development.

## Public health concerns

The novel H1N1 Influenza A swine flu virus is different from the annual seasonal H1N1 strains. Annual seasonal influenza also changes annually, but humans have some degree of immunity to circulating strains which help to limit the spread of the disease. In addition, seasonal vaccination helps limit deaths and severe disease. Humans do not have antibodies to the new strain and current seasonal vaccines will not provide the same level of protection to seasonal influenza. The virus has also spread globally at an unprecedented speed in comparison to past pandemics, which took six months to spread to the level that the current strain has spread in less than six weeks. This may result in more cases than the seasonal flu and consequently in more deaths.[5]

Most cases to date have been characterised by mild disease that resolved without treatment; however symptoms may range from mild to severe and can result in death. National levels of severe disease are similar to levels seen during periods of local seasonal influenza although high levels of disease have occurred in some local areas and institutions. The overall severity of the pandemic has been assessed as moderate. Although more than half of the patients with more severe disease had underlying health conditions or weak immune systems, the WHO is concerned about the current patterns of serious disease and deaths in primarily young persons (10–45 years with an average age of 17 years) including those who were previously healthy and those with pre-existing medical conditions or pregnancy.[6]

## Transmission

The new H1N1 Influenza A virus is thought to be transmitted from person-to-person similarly to seasonal influenza strains, that is by exposure to infected droplets by coughing and sneezing of infected people, but also by touching of infected objects. Appropriate hygiene should be recommended to sick patients. Patients should cover their mouth and nose when coughing or sneezing, stay at home when they are unwell, clean their hands regularly with soap and water or alcohol-based disinfectants, and keep some distance from healthy people.

It is recommended that health care workers take infection control measures when dealing with patients by wearing a medical mask when dealing with suspected cases. A particulate respirator (N95, FFP2 or equivalent), eye protection, gowns and gloves should be worn especially when performing high-risk aerosol-generating procedures (for example

bronchoscopy, or any procedure involving aspiration of the respiratory tract). The procedure should be carried out in an airborne precaution room that can be naturally or mechanically ventilated, per WHO guidelines.[7]

## Symptoms and case definition

Most cases of swine flu are mild and common symptoms are flu-like, including fever, cough, headache, malaise, chills, fatigue, muscle and joint pain, sore throat and runny nose, and on occasion vomiting and diarrhoea. Patients who required hospitalisation, including both those who were previously healthy and those with chronic underlying medical conditions, have frequently experienced rapidly progressive, serious lower respiratory tract disease. Risk factors included pregnancy, asthma, other lung diseases, diabetes, morbid obesity, autoimmune disorders and associated immunosuppressive therapies, neurological disorders and cardiovascular disease. In the United States, among 20 pregnant women confirmed to have been infected with the new Influenza A (H1N1) virus, three required hospitalisation, one of whom died; this patient had started antiviral therapy 13 days after the onset of illness. Of 30 patients hospitalised in California, 64% had underlying conditions and two of five pregnant women developed complications, including spontaneous abortion and premature rupture of membranes. Approximately 2–5% of confirmed cases in the United States and Canada, as well as 6% in Mexico, had been admitted to hospital.[8]

The NICD guidelines for classification of mild and severe respiratory disease are listed in Table I and may be used for identification and management of severe cases of swine flu.

**Table I: NICD's guidelines for identification of mild and severe respiratory cases**

**ILI (Influenza Like Illness) – mild disease:**

An individual with recent onset of an influenza-like illness (ILI), which may include fever ≥ 38°C PLUS ONE OR MORE of the following acute respiratory symptoms (sore throat, rhinorrhoea/nasal congestion, cough or other signs which are part of the respiratory complex, myalgia, diarrhoea.)

**SARI (Severe Acute Respiratory Infection) – moderate to severe disease:**

- **Persons 2 days to < 3 months old:** Any child with diagnosis of suspected sepsis or physician-diagnosed lower respiratory tract infection (LRTI) irrespective of signs and symptoms. (Patient presenting within seven days of the onset of illness.)
- **≥ 3 months old to < 5 years old:** Any child ≥ 3 months to < 5 years with physician-diagnosed acute lower respiratory infection (LRTI) including bronchiolitis, pneumonia, bronchitis and pleural effusion. (Patient presenting within seven days of the onset of illness.)
- **≥ 5 years old:** Any person presenting with sudden onset of fever (> 38°C) AND cough or sore throat AND shortness of breath, or difficulty breathing with or without clinical or radiographic findings of pneumonia. (Patient presenting within seven days of the onset of illness.)

**Features of severe illness:**

The criteria for severe pneumonia according to the WHO Integrated Management of Childhood Illness (IMCI) guidelines are: Any child aged 2 months up to 5 years with: cough or difficult breathing, AND with any general danger signs (unable to drink or breast-feed, vomits everything, convulsions, lethargy or unconsciousness), OR chest indrawing or stridor in a calm child.

Severity criteria in adults of any age group include: respiratory distress, dyspnoea, hypotension and/or evidence of hypoxia.

## Handling of cases

A complete health care worker's handbook for Influenza A (H1N1) has been compiled by the NICD and may be downloaded from their website: http://www.nicd.ac.za/. The following provides a summary of this document as well as the WHO guidelines provided for diagnostic testing and treatment.[9]

### Diagnostic testing

As of 16 July 2009 South Africa reached the 100 mark with cases being reported from eight of the nine provinces. This changed the testing strategy due to the cost and resource intensity of the outbreak which is now inevitable in the country. It is not recommended that all cases be tested anymore. Mild cases should not be tested since it does not affect treatment and it is in general not necessary to use antivirals for these patients. It is, however, crucial to collect specimens and closely monitor unusual events such as clusters of cases of severe or fatal pandemic influenza, clusters of cases of respiratory disease requiring hospitalisation or unusual clinical patterns associated with serious or fatal disease. Virological characterisation of these cases will allow epidemiological monitoring of the pandemic, facilitate vaccine development, and improve case management and public health interventions for the current outbreak. Diagnostic testing has now been decentralised away from the NICD and private and selected National Health Laboratory Services (NHLS) laboratories now offer testing. The test recommended by the WHO are a realtime RT-PCR that picks up all Influenza A cases, followed by a swine flu specific test for positive cases.[10]

Commercial tests are also available from several companies, but it should be ensured that these are according to the WHO recommendations. Molecular diagnostics are currently the method of choice targeting the type A influenza matrix gene; haemagglutinin gene specific for Influenza A (H1N1)swl virus and haemagglutinin gene specific for seasonal Influenza A (H1/H3) and other subtypes. Rapid antigen detection tests are not currently supported since the sensitivity and specificity for swine flu is suboptimum.[11] The NICD will continue to support both private and public sectors. The NICD and the Virology Department of the University of Stellenbosch at Tygerberg Hospital (for patients within the Western Cape Province) will continue to provide diagnostic support for patients seen at public sector health facilities, until such time that this is available within the NHLS. Note that testing will be offered as a diagnostic service and charged for. Clinical specimens from positive cases of severe disease should still be submitted to the NICD for surveillance and research purposes.

### Specimen collection

The most appropriate specimens for testing are upper respiratory tract specimens as recommended for seasonal influenza. The samples should be taken from the deep nostrils (nasal swab), nasopharynx, (nasopharyngeal swab), nasopharyngeal aspirate, throat or bronchial aspirate. It is recommended that specimens be transported in viral transport media which may be collected from your local laboratory. For nasal swabs dacron or rayon swabs should be used, not wooden swabs, and all specimens must be transported in viral transport medium (VTM).[11] For further information on VTM and swabs contact the National Influenza Centre (Amelia Buys/Cardia Fourie, Tel: (011) 386 6373). For fatal cases, a lung aspirate or Lung biopsy may be taken postmortem.

**Testing is only recommended for:**

1. Patients who meet the SARI case definition (i.e. severe infections) where a laboratory diagnosis will assist in patient management or patients hospitalised due to an LRTI, where no other explanation for the illness is indicated, and influenza forms part of the differential diagnosis.
2. Patients with co-morbid disease and at risk for serious complications and who are symptomatic with SARI or ILI should be considered for testing if it will guide clinical management.
3. Clusters of cases where a diagnosis of the cause of the outbreak is needed.
4. An individual who has died where pandemic Influenza A (H1N1) is suspected as the cause of death.[11, 12]

**Treatment guidelines** have been published by the WHO and are summarised in Tables IIa and b.

*Mild cases:* It is not recommended that these cases be subjected for laboratory testing or hospitalisation. Isolation at home for seven days

**Table IIa: Summary of clinical management of pandemic Influenza A (H1N1) 2009 virus infection**

| Modalities | Strategies |
|---|---|
| Antibiotics | In case of pneumonia, empiric treatment for community acquired pneumonia (CAP) per published guidelines pending microbiologic results (e.g. 2–3 days); tailored therapy thereafter if pathogen(s) identified. |
| Antiviral therapy | Only indicated for individuals with moderate to severe disease, and individuals at risk for development of severe disease. The pandemic influenza A (H1N1) 2009 virus is currently resistant to amantadine and rimantadine. |
| Corticosteroids | Moderate to high dose steroids are NOT recommended. They are of unproven benefit and potentially harmful. |
| Infection control | Standard plus droplet precautions. For aerosol-generating procedures use particulate respirator (N95, FFP2 or equivalent), eye protection, gowns, gloves. |
| NSAIDS, antipyretics | Paracetamol can be administered for fever. Avoid administration of salicylates (aspirin and aspirin containing products) in children and young adults (< 18 years old) due to risk of Reye's syndrome. |
| Oxygen therapy | Monitor oxygen saturation and maintain SaO2 over 90% (95% for pregnant women) with nasal cannulae or face mask. |

**Table IIb: Recommended dosage of antiviral agents for treatment of confirmed, probable or suspected pandemic Influenza A (H1N1) 2009 cases***

| Age group | Weight | Oseltamivir dosage* | Zanamivir dosage* |
|---|---|---|---|
| **Adults** | | 75 mg twice per day | Two 5 mg inhalations (10 mg total) twice per day |
| **Children** | 15 kg or less | 30 mg twice per day | Two 5 mg inhalations (10 mg total) twice per day (only in children aged 12 years or older) |
| | 15–23 kg | 45 mg twice per day | |
| | 24–40 kg | 60 mg twice per day | |
| | > 40 kg | 75 mg twice per day | |

*Recommended duration of treatment is five days. Oseltamivir is not currently licensed for use in children < 1 year old and zanamivir is only registered for children ≥ 12 years of age. In addition to antiviral medications, other therapeutics to treat complications should be utilised where indicated (e.g. antibiotics for bacterial complications such as pneumonia). Supportive care is also advised depending on the clinical severity of disease (oxygen therapy, mechanical ventilation, etc).

with supportive treatment is adequate. Plenty of fluids and treatment with pain killers for muscle pains other than aspirin in children and young adults (because of the risk of Reye's syndrome) should be recommended. Patients in the high risk category may be treated with aniviral treatment at the clinician's discretion.

*Moderate to severe disease:* These patients should be hospitalised and subjected to confirmatory diagnostic testing. The NICD should be notified of positive cases and once confirmed, specimens may be sent to the Respiratory Virus Unit at the NICD for research purposes. These patients should be placed in isolation in rooms with the door closed where possible and health care workers should take the proper infection control measures. Patients should be offered antiviral treatment. The virus is currently sensitive (susceptible) to the neuraminidase inhibitor antiviral medications oseltamivir (Tamiflu®) and zanamivir (Relenza®) but is resistant to the adamantane antiviral medications, amantadine and rimantadine. Oseltamivir (Tamiflu®) is administered orally and is registered for use in individuals ≥ 1 year old while zanamivir (Relenza®) is administered through an inhaler and is registered for use in individuals older than 12 years. These antivirals should be initiated as soon as possible, preferably within 48 hours of the onset of symptoms, although some benefit may still be obtained later in the course of illness. The treatment should continue for five days. The recommended doses are similar to those for seasonal influenza and are described in Table IIb. It is also recommended that other therapeutics be used to treat complications where indicated (e.g. antibiotics for bacterial complications such as pneumonia). Depending on the clinical severity of disease, oxygen therapy, mechanical ventilation, and other supportive care is also advised.

*Pregnant women:* Pregnant women are considered one of the high risk groups for developing complications from seasonal influenza and several hospitalisations, including fatal outcomes, have been reported in pregnant women infected with the new H1N1 virus. This warrants closer observation and treatment with antivirals; however no clinical studies have been conducted to assess the safety on pregnant women although no adverse effects have been reported among women who received oseltamivir or zanamivir during pregnancy or among infants born to women who had received oseltamivir or zanamivir. Zanamivir is preferred since it is an inhaled medication and has less systemic absorption.

## Conclusion

The new pandemic Influenza A (H1N1) virus mostly causes mild infections although severe disease may occur in certain groups, in particular in pregnant women. Continued surveillance of severe cases is needed to elucidate the evolving picture of pathogenesis, to optimise diagnostic methods and to identify vaccines and preventative measures. A candidate reassortant vaccine virus (CBER-RG2) has recently been developed, using reverse genetics technology, from an A/California/04/2009 (H1N1) virus isolate and is currently being tested in ferrets for efficacy. Promising results have been obtained so far and there is hope that a vaccine may soon be available.[13]

To facilitate the handling of cases, the WHO has created a clinical check list to guide clinicians when dealing with cases. This checklist may be downloaded at: http://www.who.int/csr/resources/publications/swineflu/ah1n1_checklist.pdf

Additional information is available from:

- NICD website: www.nicd.ac.za
- Department of Health website: www.doh.gov.za/swineflu/swineflu-f.html
- World Health Organization website: www.who.int/csr/disease/swineflu/en/
- Centers for Disease Control and Prevention (CDC, Atlanta) website: www.cdc.gov/h1n1flu/

## Declarations

Conflict of interest: The author declares no conflict of interest.

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