

Considerations and interim recommendations for the clinical management of human infection with the new *Influenza A(H1N1)* virus.

PAHO/WHO expert consultation.

Washington DC, 26 May 2009

Background

Clinical management of probable or suspected cases of human infection with the new influenza A (H1N1) virus (also called the flu) constitutes a challenge due to the existing knowledge gaps of several aspects of the disease; and the need to take adequate measures before the laboratory confirmation of cases.

Cases have presented a broad clinical spectrum: ranging from mild upper respiratory tract illness to severe respiratory infections that require specialized complex care, sometimes leading to death.

In order to provide general recommendations for clinical management of human disease caused by the new Influenza A (H1N1) virus adapted for the Region of the Americas, the Pan American Health Organization (PAHO) convened an expert's consultation. Their objectives were to present and discuss the existing clinical data, and review and analyze the available recommendations and adapt them to the regional context. It is expected that the conclusions and recommendations of the consultation will help countries to respond to their national needs and to expand their clinical management protocols.

The agenda and the list of participants (in Spanish) are in appendix 1 and 2, respectively.

The recommendations are preliminary, and will be revised and updated as new information of the virus becomes available, and experience and as evidence of the clinical management effectiveness with the cases increases.

Clinical Description of the Cases

The clinical spectrum of disease ranges from mild upper respiratory tract illness to severe pneumonia with compromised respiratory function (Box 1). The majority of cases are mild and it is believed that asymptomatic cases may exist. Nevertheless, currently there is not enough information to indicate the correct proportion of serious patients that would require hospitalization among all infected cases.

The experts group reviewed and discussed the available clinical data, mainly from Mexico.

Box 1. Main clinical manifestations of Influenza A (H1N1)

- Cases mostly occurred in children and young adults
- Spectrum of disease range from non-febrile, mild upper respiratory tract illness to severe or fatal pneumonia
- Most frequent symptoms: cough, fever, sore throat, malaise and headache
- Complication: secondary bacterial infections, rhabdomyolysis with renal failure, myocarditis and worsening of underlying conditions

Until May 22, 2009 a total of 4,174 cases of Influenza A(H1N1) had been confirmed in Mexico, of which there were 80 fatalities (1.9% of the confirmed cases). Of the fatalities, 56.3% were women, and 77.5% were between 20 and 54 years of age. The underlying conditions of the fatal cases were: metabolic conditions (obesity and diabetes mellitus) 28.8%; cardiovascular diseases 15.0%, smoking 11.3%, respiratory diseases 8.8%, infectious diseases 5.0%, others 2.6%. The most common symptoms of the fatalities were cough 87.5%, fever 85.0%, and shortness of breath 77.5%.

During the influenza epidemic, approximately 5,000 patients with respiratory symptoms attended the Hospital General of Mexico. Seventy-nine of them tested positive for influenza by rapid test. Thirteen patients were admitted to the Intensive Care Unit (ICU) after developing pneumonia and Acute Respiratory Distress Syndrome (ARDS). Five of these patients eventually died. Of the 13 patients that were admitted to the ICU, three patients had preexisting conditions (morbid obesity, diabetes mellitus type 2, and miliary tuberculosis), while ten were previously healthy adults between 20-50 years of age. Four autopsies were performed, and ARDS, pneumonia, airway obstruction, lymphocyte infiltration, lymphoproliferative hyperplasia, and obliterative bronchitis were consistently found. In regard to the laboratory data, leucopenia as well as elevated lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and transaminases were frequently encountered. The secondary bacterial infections in mechanical ventilated patients were caused by nosocomial microorganisms (*Pseudomonas aeruginosa* and *Acinetobacter* spp).

From March 24 to April 24, 214 patients with severe respiratory infections sought care at the Instituto Nacional de Enfermedades Respiratorias (INER) of Mexico¹. Until May 25, 185 patients with suspected influenza infections were hospitalized, of which 75 had serious pneumonia (40%) and 30 were admitted to the ICU. 46 patients died, of which 12 had been confirmed cases of Influenza A(H1N1). Although the analytical data most frequently found was low oxygen saturation, close to half of the patients presented data suggesting renal insufficiency (increased urea and creatinine, oliguria, and decreased creatinine clearance). In approximately 50% of the cases, elevated CPK was detected. The patients admitted to the ICU suffered complications such as acidosis and positive liquid balances.

¹ The INER has a 178- bed capacity and provides service to people without Social Security coverage.

Dr. Matthew Lim, World Health Organization (WHO/HSE/GAR), presented a summary of the actual considerations for the clinical management of infection with the new virus influenza A(H1N1)². WHO solicited the collaboration from member states to obtain clinical data and the results of treatments that might help in the development of recommendations for clinical management. The clinical data and samples for virus monitoring must be collected in a prospective manner, in the context of clinical protocols. These recommendations were revised by the group of experts, and are explained in the following section.

Recommendations

- 1. Infection prevention and control**
- 2. Triage**
- 3. Diagnostic tests and complementary explorations**
- 4. Supportive treatment**
- 5. Antiviral therapy**
- 6. Antibiotic treatment**

1. Infection prevention and control

WHO guidelines relating to the appropriate measures for prevention and infection control (Standard plus Droplet Precautions) should be followed at all times³. Whenever performing high-risk aerosol-generating procedures (for example, bronchoscopy, or any procedure involving aspiration of the respiratory tract) a particulate respirator (N95, FFP2 or equivalent), eye protection, gowns, and gloves should be used while carrying out the procedure in an airborne precaution room that can be naturally or mechanically ventilated.

2. Triage

The objectives of triage are timely identification of suspected cases for clinical management and to decrease in the risk of transmission of the virus to patients and health care workers in health care facilities. Refer to Box 2, 3, 4 and 5 for triage, hospitalization and critical care unit admission criteria.

General measures for triage in primary care:

- Define a place adequately identified for the reception of respiratory infection cases.

² http://www.who.int/csr/resources/publications/swineflu/clinical_managementH1N1_21_May_2009.pdf

³ http://www.who.int/csr/resources/publications/infection_control/en/index.html

- Health care professionals must have personal protection equipment adequate for the procedure they are performing.
- Strictly adhere to Standard and Droplet Precautions in clinical settings.

Box 2. Criteria for assessment in primary care triage

Pediatric patients	Adult patients
<ul style="list-style-type: none"> ▪ Asses general state ▪ Asses hydration ▪ Measure the body temperature (fever $\geq 38^{\circ}\text{C}$ / $\geq 100.4^{\circ}\text{F}$) ▪ Measure the respiratory rate ▪ Observe subcostal recession or nasal flaring ▪ Evaluate the presence of wheezing, crepitations during auscultation ▪ Observe the color of the nails and mucosa (ungual and circumoral cyanosis) ▪ Ask about possible contacts with family members or classmates with symptoms of influenza like illness 	<ul style="list-style-type: none"> ▪ Asses general state ▪ Measure the body temperature (fever $\geq 38^{\circ}\text{C}$ / $\geq 100.4^{\circ}\text{F}$) ▪ Measure the respiratory rate ▪ Perform pulmonary auscultation and evaluate possible alterations ▪ Observe the color of the skin and mucosa (detect cyanosis) ▪ Ask about possible contacts with family members or coworkers with symptoms of influenza like illness

Box 3. Criteria for referral and hospitalization (pediatrics)

<p>General Symptoms of Alarm</p> <ul style="list-style-type: none"> • Cyanosis • Incapacity of the child to drink or breast feed • Convulsions • Continuous Vomiting • Unconsciousness or lethargy <p>Suggestive sings of severe respiratory disease</p> <ul style="list-style-type: none"> • Nasal flaring, intercostal recession or stridor • Presence of significant tachypnea: >50 rpm (2 months -1 year), >40 rpm (1 year -5 years) • Presence of hypoxemia
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Box 4. Criteria for referral and hospitalization (adults)

Referral

- Presence of **fever > 38° C / >100.4° F** associated with:
- Dyspnea or difficulty breathing
- Chest pain
- Pulse oximeter saturation SpO₂ ≤ 90% (if it is available)
- Risk factors: pregnancy, elderly, chronic pulmonary disease, cardiovascular (except hypertension), renal, hepatic, hematological, neurological, neuromuscular, immunodeficiencies (HIV/AIDS, chronic treatment with steroids)

Hospitalization

- Dyspnea
- Pulse oximeter saturation SpO₂ ≤ 90%. In pregnant women; SpO₂ ≤ 95%
- Alteration in the vital signs: arterial hypotension, respiratory frequency increased, cardiac frequency increased
- Abnormal chest x-ray
- Changes in underlying co-morbidities
- Altered level of consciousness
- Dehydration
- Patients that return for a second consultation with deteriorating respiratory capacity
- Patients from geographically remote areas

Box 5. Criteria for admission to the ICU for pediatric and adult patients

- Refractory hypoxaemia
- Presence of compromised hemodynamics without response to replacement of fluids
- Presence of signs of imminent shock

3. Diagnostic tests and complementary explorations

The diagnostic tests for the influenza A(H1N1) are of great value for epidemiological surveillance, for monitoring the emergence of resistance or changes in virulence of the virus. The latter is the base for the adoption of public health measures. However, their value for the clinical management of patients is limited by the delay in the results. Therefore, decisions on complementary explorations and treatment measures should be supported by clinical parameters.

Currently, there is no validated rapid diagnostic test for the new influenza A(H1N1) virus infection. Commercial available rapid tests for seasonal influenza have uncertain sensitivity and lack specificity for detection of the new influenza A(H1N1) virus. If these tests are performed, both positive and negative results should be interpreted with caution.

Real time RT-PCR is the only test that provides sufficient sensibility and specificity for the etiologic diagnostic of the new influenza A(H1N1) virus, especially at the beginning of an outbreak. In places with viral culture capacity, the isolation of the influenza A(H1N1) virus is a reliable method for diagnosis. However, its use is not practical for the clinical management.

Sampling for diagnosis of influenza A(H1N1) is recommended in patients with consistent respiratory symptoms and epidemiological link. Samples for laboratory test should be taken from nasopharynx (naso-pharyngeal swab), deep nasal passages (nasal swab), throat or bronchial aspirate⁴. It is not yet known which clinical specimen gives the best diagnostic yield. Nasal aspirates can be used in infants.

Only sterile dacron or rayon-tipped swabs with plastic or aluminum shafts must be used. Specimen collection should be done by trained personnel and it should be performed with appropriate precautions since this may expose the collector to respiratory secretions from patients. Once the sample is taken, the swab must be placed in viral transport media. It is very important to use proper handling and transportation of the samples in terms of conditions and temperature and under precautionary measures for handling biological agents.

The investigations shown in Box 6 are recommended in hospitalized patients or those admitted in intensive care units.

⁴ The bronchial aspirate collection is a procedure with high risk of aerosol generation and requires specific precautions for the prevention of airborne transmission.

(*) Include screening viral for seasonal influenza (where applicable)

Box 6. General investigations recommended for hospitalized adult patients

Hospitalization	Intensive Care Unit
<ul style="list-style-type: none"> • Laboratory Tests: <ul style="list-style-type: none"> – Full blood count (CBC) – Serum electrolytes – Hepatic function (AST, ALT) – Renal function (BUN, creatinine) – CPK – LDH – Glucose – Urinalysis – Microbiological studies of respiratory secretions (*) and blood cultures • Arterial blood gases • Pulse oximetry • Chest x-ray <p>If available and according to established protocols of the health care facility:</p> <ul style="list-style-type: none"> • Erythrocyte sedimentation rate • C-reactive protein (CRP) • Electrocardiogram 	<p>In addition to the hospitalization investigations:</p> <ul style="list-style-type: none"> • Coagulation profile • Procalcitonin • Serial arterial blood gases • Serial chest x-ray • Serial electrocardiogram • Bronchoscopy and broncho-alveolar brushing

4. Supportive treatment

A) Symptomatic and supportive measures

- Supportive cares (antipyretics like paracetamol -acetaminophen- for fever, rehydration, etc) are sufficient in the majority of patients. Additionally for children, physical measures to should be taken, ensuring adequate hydration.
- Salicylates (such as aspirin and aspirin-containing products) should not be used in children and young adults (<18 years) because of the risk of Reye's Syndrome.

B) Oxygen Therapy

- At presentation and routinely during subsequent care in hospitalized patients, oxygen saturation should be monitored by pulse oximetry whenever possible. Supplemental oxygen should be provided to correct hypoxaemia depending on the severity (nasal cannula, facemask, facemask with reservoir, intubation and assisted ventilation).
- Treatment of ARDS associated with the new influenza A(H1N1) virus infection should be based upon published evidence-based guidelines for sepsis-associated ARDS including lung-protective mechanical ventilation strategies.

C) Use of Corticosteroids

- Corticosteroids should not be routinely used, but low doses may be considered for patients in septic shock who require vasopressors and have suspected adrenal insufficiency.
- Experience has demonstrated that prolonged use of or high-dose corticosteroids can result in serious adverse events in influenza virus infected patients, including opportunistic infections.

5. Antiviral therapy

The new influenza A (H1N1) virus is susceptible to the neuraminidase inhibitors: **oseltamivir** and **zanamivir**, based on *in vitro* studies. Available data on safety and efficacy is derived from the standard therapeutic procedures for seasonal influenza. The greater effectiveness of antiviral treatment has been demonstrated when the treatment is started within the 48 hours of the onset of symptoms and administered for five days, but benefits can still be observed when administered later and for longer periods in individual cases, especially in patients with pneumonia or progressive disease. Antiviral agents' doses are shown in Box 7.

Although many patients with influenza A(H1N1) have recovered spontaneously without the administration of antivirals, in others the disease has progressed to acute respiratory failure. The mechanism of the rapid progression and other related factors are still unknown.

Table 7. Oseltamivir and zanamivir doses adjusted by age and weight.

Oseltamivir		
<3 months		12 mg orally twice a day for 5 days
3-5 months		20 mg orally twice a day for 5 days
6-11 months		25 mg orally twice a day for 5 days
≥ 12 months	15 kg or less	30 mg orally twice a day for 5 days
	15-23 kg	45 mg orally twice a day for 5 days
	24-40 kg	60 mg orally twice a day for 5 days
	> 40 kg	75 mg orally twice a day for 5 days
Zanamivir		
< 7 years		Consult the specialist
> 7 years or adult		Two inhalations of 5 mg twice daily for 5 days

The inhalation of **zanamivir** is effective in the treatment of uncomplicated human seasonal influenza, but it has not been studied for serious illness or hospitalized patients, or with the emerging strain of influenza A(H1N1) virus.

Regarding the adverse effects of **oseltamivir**, the most common are gastrointestinal (nausea and vomiting). These side effects are reduced by taking the drug with food. Occasionally, **oseltamivir** has been associated to convulsions, confusion or abnormal behavior during the course of the disease, particularly among children and adolescents.

In the current epidemic, the most affected age-group is the young adult, who also suffers the most severe disease. For this reason, this age-group should be advised to early seek medical care and also the clinical teams should be trained for the correct medical assessment and identification of complications.

Indications for antiviral therapy:

- Patients with severe clinical, gasometrical and radiological criteria: dyspnea, oxygen saturation < 90%, tachypnea and appearance of infiltrates on chest x-ray.
- Patients from vulnerable groups:
 - Pregnant women⁵
 - Patients under 5 years and older than 60 years⁶
 - Chronic pulmonary disease, cardiovascular (except hypertension), renal, hepatic, hematological, neurological, neuromuscular, metabolic (including diabetes mellitus)
 - Immunocompromised patients (HIV/AIDS, chronic treatment with steroids)

⁵ Pregnant women are at increased risk of complications. Hospitalizations and fatalities in pregnant women with infection by the new virus H1N1it have been described. Therefore, if there is suspect or confirmation of influenza A(H1N1) infection in a pregnant woman, it is necessary to provide close monitoring, and antiviral therapy in accordance with national policies.

www.cdc.gov/mmwr/preview/mmwrhtml/mm58e0518a1.htm - Vol 58e, no 518;1

www.cdc.gov/mmwr/preview/mmwrhtml/mm5818a3.htm - Vol 58, No 18;497

⁶ Age groups considered vulnerable to seasonal influenza. At present, there are not evidences to remove these groups of patients for antiviral treatment indications.

6. Antibiotic treatment

Antibiotic chemoprophylaxis should not be used. When secondary pneumonia is present, treatment with antibiotics should general follow recommendations from published evidence-based guidelines for community-acquired pneumonia^{7,8}. During past influenza pandemics and outbreaks of seasonal influenza there has been an associated increased risk of secondary *Staphylococcus aureus* infections. This infection may be severe, rapidly progressing, and occasionally caused by methicillin-resistant strains.

The results of microbiological studies, wherever possible, should be used to guide antibiotic usage for suspected bacterial co-infection in patients with the new *Influenza A* (H1N1) virus infection. If a patient contracts ventilator-associated pneumonia or hospital-acquired pneumonia caused by typical nosocomial pathogens, then they should be treated according to local hospital guidelines.

⁷ World Health Organization. *Pocket book of Hospital Care for Children*, pages 72-80. Available at: http://www.who.int/child_adolescent_health/documents/9241546700/en/index.html

⁸ Pan American Health Organization. *Tratamiento de enfermedades infecciosas 2009-2010*. 4th edition. Washington DC, 2009.

ANEXO I – AGENDA

Consulta de expertos para revisar y adaptar las recomendaciones para el manejo clínico de infecciones humanas por el virus Influenza A (H1N1)

AGENDA

OPS/OMS, Washington DC, 26 de mayo, 2009

SALA C

- 8:30-9:00 Registro. Entrega de materiales
Palabras de bienvenida (Dr. Jarbas Barbosa)
- 9:00-10:00 (1) Presentación datos clínicos México (Dr. JI Santos Preciado, Dr. L Septien, Dr. E Bautista)
(2) Presentación recomendaciones preliminares OMS (Dr. M Lim)
- 10:00-10:15 **PAUSA CAFÉ**

GRUPO ADULTOS - SALA C

- 10:15-11:00 (3) Sesión de discusión: Triage: signos y síntomas de gravedad.
- 11:00-12:00 (4) Sesión de discusión: Procedimientos diagnósticos (laboratorio, radiodiagnóstico y microbiología).

GRUPO PEDIATRIA - SALA 207

- (3) Sesión de discusión: Triage: signos y síntomas de gravedad.
- (4) Sesión de discusión: Procedimientos diagnósticos (laboratorio, radiodiagnóstico y microbiología).

12:00-13:00 **ALMUERZO**

GRUPO ADULTOS - SALA C

- 13:00-14:00 (5) Sesión de discusión: Medidas de soporte (tratamiento sintomático, oxigenoterapia).
- 14:00-15:00 (6) Sesión de discusión: Tratamiento antiviral (indicaciones) y tratamiento antibiótico.

GRUPO PEDIATRIA - SALA 207

- (5) Sesión de discusión: Medidas de soporte (tratamiento sintomático, oxigenoterapia).
- (6) Sesión de discusión: Tratamiento antiviral (indicaciones) y tratamiento antibiótico.

15:00-15:15 **PAUSA CAFE**

15:15-16:00 Presentación grupo de pediatría y adultos.

Presentadores: seleccionados en cada grupo

16:00-17:30 Conclusiones / Consenso sobre recomendaciones.

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