

Considerations and interim recommendations for the clinical management of human infection with the pandemic influenza (H1N1) 2009 virus. PAHO/WHO expert consultation.

Updated version. 16 July 2009. Replaces document originally published on 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. The original document was reviewed and updated by a group of experts, counting with the technical support of the *Asociacion Panamericana de Infectologia*. 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 list of experts who contributed to this document is on the annex.

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.

Section I

Proceedings of the expert consultation, 26 of May 2009.

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.

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.

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

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

Section II

Recommendations, revised 16 July 2009

- 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. If possible, it should be located far apart from the regular care points, in order to reduce the risk of transmission in susceptible hosts seeking care because other pathologies.
- 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.

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

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 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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 $SpO_2 \leq 90\%$ (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 $SpO_2 \leq 90\%$. In pregnant women; $SpO_2 \leq 95\%$
- 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.

Samples for diagnosis of influenza A (H1N1)⁴ should be taken from nasopharynx (nasopharyngeal swab), deep nasal passages (nasal swab), throat or bronchial aspirate⁵. 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. For additional information, refer to WHO document "Instructions for transport of virus cultures (i.e. virus isolates) of candidate reassortant vaccine viruses of pandemic (H1N1) 2009 virus"⁶

⁴ The indication for take of samples should be done at national level, as per the epidemiological situation.

⁵ The bronchial aspirate collection is a procedure with high risk of aerosol generation and requires specific precautions for the prevention of airborne transmission.

⁶ http://www.who.int/csr/resources/publications/swineflu/instructions_transport_virus/en/index.html

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

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 if suspected bacterial infection • Arterial blood gases • Pulse oximetry • Chest x-ray (at admission and to follow up, as per health care facility protocols) • Other investigations, according to established protocols of the health care facility, such as erythrocyte sedimentation rate, C-reactive protein (CRP), and electrocardiogram. | <p>In addition to the hospitalization investigations:</p> <ul style="list-style-type: none"> • Coagulation profile • Procalcitonin (if available) • Serial arterial blood gases • Serial chest x-ray • Serial electrocardiogram |

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

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 hypoxemia 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. There is no evidence about the benefits of the joint administration of both drugs. 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.

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. The oral inhalation of **zanamivir** can cause cough and nasal and throat discomfort. In rare occasions it produces bronchospasm, therefore it is contraindicated in patients with asthma or chronic obstructive lung disease.

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 (updated 16 July 2009)

The following indications are intended to guide the rational use of the antiviral treatment. This guidance should be adapted as per the characteristics of the viral transmission and per the country context, especially regarding the organization and access to the health services.

1. Patients with acute respiratory illness (fever above 38 C and respiratory symptoms: cough, running nose, sore throat, etc.) who at the initial evaluation present any of the following signs or symptoms.

| Pediatric patients | Adult patients |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> a. Cyanosis b. Hypoxemia (pulse oximeter saturation $SpO_2 \leq 90\%$) c. Presence of significant tachypnea: >50 rpm (2 months -1 year), >40 rpm (1 year -5 year) d. Incapacity of the child to drink or breastfeed e. Continuous vomiting f. Unconsciousness or lethargy g. Nasal flaring, intercostal recession or stridor. | <ul style="list-style-type: none"> a. Dyspnea or difficulty breathing b. Hypoxemia (pulse oximeter saturation $SpO_2 \leq 90\%$,. For pregnant women $\leq 95\%$) c. Alteration in the vital signs: arterial hypotension, respiratory frequency increased, cardiac frequency increased. d. Abnormal chest x-ray e. Changes in underlying co-morbidities. f. Altered level of consciousness g. Dehydration h. Patients that return for a second consultation with worsening of the respiratory symptoms. |

2. Patients with acute respiratory illness (fever above 38 C and respiratory symptoms: cough, running nose, sore throat, etc) belonging to the following vulnerable groups:
 - a. Pregnant women⁷
 - b. Patients under 5 years and older than 60 years⁸
 - c. Chronic pulmonary disease (in paediatric patients, include children with bronchial hyperreactivity), cardiovascular (except hypertension), renal, hepatic, hematological, neurological, neuromuscular, metabolic (including diabetes mellitus)
 - d. Immunocompromised patients (HIV/AIDS, chronic treatment with steroids, with immunosuppressors or chemotherapy).
 - e. Obese patients

3. After responding to priorities 1 and 2, and in specific situations where wide geography spread, high intensity of respiratory diseases, and severe health impact in the health services⁹, the antiviral treatment could be indicated to patients with influenza like illness, with the purpose of decreasing hospitalization and complication rates in the most affected age group.

It is not necessary to wait for the laboratory confirmation to initiate treatment, which should be based upon the clinical assessment.

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

| Oseltamivir |
|-------------|
|-------------|

⁷ Pregnant women are at increased risk of complications. Hospitalizations and fatalities in pregnant women with infection by the new virus H1N1 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

⁸ Age groups considered vulnerable to seasonal influenza. At present, there are not evidences to remove these groups of patients for antiviral treatment indications.

⁹ http://www.who.int/csr/disease/swineflu/WHO_case_definition_swine_flu_2009_04_29.pdf - Refer to Annex 4.

| | | |
|--------------------|---------------|------------------------------------------------|
| <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 |

*Higher doses and longer treatment duration(150 mg p.o. bid per 10 days) is under evaluation in patients admitted to UTIs, obese and immunosuppressed patients. Until now, there is no sufficient evidence for emitting a recommendation.

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^{10,11}, locally adapted. 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.

¹⁰ 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

¹¹ Pan American Health Organization. *Tratamiento de enfermedades infecciosas 2009-2010*. 4th edition. Washington DC, 2009.

Annex

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