

Clinical management of human infection with pandemic (H1N1) 2009: revised guidance

November 2009

Introduction

A novel influenza A (H1N1) virus of swine origin emerged among people in Mexico during the spring of 2009 and spread with travellers worldwide, resulting in the first influenza pandemic since 1968. As of October 2009, 195 countries have reported confirmed human cases of pandemic (H1N1) 2009. While the majority of illnesses caused by pandemic (H1N1) 2009 virus infection have been self-limited mild-to-moderate uncomplicated disease, severe complications including fatal outcomes have been reported.

The pandemic (H1N1) 2009 influenza virus differs in its pathogenicity from seasonal influenza in two key aspects. First, as the majority of human population has little or no pre-existing immunity to the virus, the impact of the infection has been in a wider age range, in particular among children and young adults. Secondly, the virus can infect the lower respiratory tract and cause rapidly progressive pneumonia especially in children and young to middle-aged adults.

In October 2009, WHO convened an international consultation represented by all WHO Regions, in Washington, DC, USA, to revise the guidance on clinical management of patients with pandemic (H1N1) 2009 virus infection. Experts in public health, laboratory science, pathology, and clinical care came together to review the published evidence to date and to share unpublished data. This document incorporates the knowledge made available to WHO and updates previous WHO guidance. Additional WHO guidance on pharmacological management, as well as infection control recommendations for health care facilities, are available separately. We anticipate commissioning full evidence reviews in preparation for another international consultation in 2010. This clinical guidance will then be revised accordingly, based upon new information. The purpose of this document is to provide information for clinicians managing patients with suspected or confirmed pandemic (H1N1) 2009 virus infection.

Background

The epidemiology of pandemic (H1N1) 2009 virus infection to date indicates that children and young adults have had the highest attack rates. A wide clinical spectrum of disease ranging from non-febrile, mild upper respiratory tract illness, febrile influenza-like illness (ILI) to severe or even fatal complications, including rapidly progressive pneumonia has been described. The most commonly reported symptoms have included cough, fever, sore throat, muscle aches, malaise, and headache. Some patients have experienced gastrointestinal symptoms (nausea, vomiting, and/or diarrhoea).

Approximately 10-30% of hospitalized patients in some countries have required admission to intensive care units (ICU). Critically ill patients include those who

experienced rapidly progressive lower respiratory tract disease, respiratory failure, and acute respiratory distress syndrome (ARDS) with refractory hypoxemia. Other severe complications have included secondary invasive bacterial infection, septic shock, renal failure, multiple organ dysfunction, myocarditis, encephalitis, and worsening of underlying chronic disease conditions such as asthma, chronic obstructive pulmonary disease (COPD), or congestive cardiac failure.

Risk factors for severe disease from pandemic (H1N1) 2009 virus infection reported to date are considered similar to those risk factors identified for complications from seasonal influenza. These include the following groups:

- Infants and young children, in particular <2 years
- Pregnant women
- Persons of any age with chronic pulmonary disease (e.g. asthma, COPD)
- Persons of any age with chronic cardiac disease (e.g. congestive cardiac failure)
- Persons with metabolic disorders (e.g. diabetes)
- Persons with chronic renal disease, chronic hepatic disease, certain neurological conditions (including neuromuscular, neurocognitive, and seizure disorders), hemoglobinopathies, or immunosuppression, whether due to primary immunosuppressive conditions, such as HIV infection, or secondary conditions, such as immunosuppressive medication or malignancy
- Children receiving chronic aspirin therapy
- Persons aged 65 years and older

A higher risk of severe complications from pandemic (H1N1) 2009 virus infection has also been reported in individuals who are obese (particularly in those who are morbidly obese) and among disadvantaged and indigenous populations.

On average, about 1/2 of hospitalized patients have had at least one or more underlying medical conditions¹. However, about 1/3 of patients with very severe illness admitted to ICU were previously healthy persons.

The incubation period appears to be approximately 2-3 days, but could range up to 7 days.

WHO pandemic (H1N1) 2009 case summary form for clinical data collection is available at:

http://www.who.int/csr/disease/swineflu/guidance/surveillance/WHO_case_definition_swine_flu_2009_04_29.pdf (Annex 3)

Case description

Uncomplicated influenza

- ILI symptoms include: fever, cough, sore throat, rhinorrhea, headache, muscle pain, and malaise, but no shortness of breath and no dyspnoea. Patients may present with some or all of these symptoms.

¹ Reports from several countries describing hospitalized cases have noted varying proportions of patients with co-morbid conditions; this likely reflects differences in how these conditions were defined.

- Gastrointestinal illness may also be present, such as diarrhoea and/or vomiting, especially in children, but without evidence of dehydration.

Complicated or severe influenza

- Presenting clinical (e.g. shortness of breath/dyspnoea, tachypnea, hypoxia) and/or radiological signs of lower respiratory tract disease (e.g. pneumonia), central nervous system (CNS) involvement (e.g. encephalopathy, encephalitis), severe dehydration, or presenting secondary complications, such as renal failure, multiorgan failure, and septic shock. Other complications can include rhabdomyolysis and myocarditis.
- Exacerbation of underlying chronic disease, including asthma, COPD, chronic hepatic or renal failure, diabetes, or other cardiovascular conditions.
- Any other condition or clinical presentation requiring hospital admission for clinical management.
- Any of the signs of disease progression listed below.

Signs and symptoms of progressive disease

Patients who present initially with uncomplicated influenza may progress to more severe disease. Progression can be rapid (i.e. within 24 hours). The following are some of the indicators of progression, which would necessitate an urgent review of patient management:

- Symptoms and signs suggesting oxygen impairment or cardiopulmonary insufficiency:
 - Shortness of breath (with activity or at rest), difficulty in breathing², turning blue, bloody or coloured sputum, chest pain, and low blood pressure;
 - In children, fast or laboured breathing; and
 - Hypoxia, as indicated by pulse oximetry.
- Symptoms and signs suggesting CNS complications:
 - Altered mental status, unconsciousness, drowsiness, or difficult to awaken and recurring or persistent convulsions (seizures), confusion, severe weakness, or paralysis.
- Evidence of sustained virus replication or invasive secondary bacterial infection based on laboratory testing or clinical signs (e.g. persistent high fever and other symptoms beyond 3 days).
- Severe dehydration, manifested as decreased activity, dizziness, decreased urine output, and lethargy.

Infection control

Evidence to date suggests that pandemic (H1N1) 2009 virus is transmitted similarly to seasonal influenza A and B viruses. Appropriate infection control measures (Standard plus Droplet Precautions) should be adhered to at all times. Whenever performing high-risk aerosol-generating procedures (for example, bronchoscopy or any procedure involving aspiration of the respiratory tract) use a particulate respirator (N95, FFP2 or equivalent), eye protection, gowns, and gloves and carry out the procedure in an adequately ventilated room, either naturally or mechanically, as per WHO guidance³.

² For more information on warning signs for children, see *Integrated management of childhood illness* (IMCI) chart booklet at

http://www.who.int/child_adolescent_health/documents/IMCI_chartbooklet/en/index.html

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

The duration of isolation precautions for hospitalized patients with influenza symptoms should be continued for 7 days after onset of illness or 24 hours after the resolution of fever and respiratory symptoms, whichever is longer, while a patient is in a health-care facility. For prolonged illness with complications (i.e. pneumonia), control measures should be used during the duration of acute illness (i.e. until the patient has improved clinically). Special attention is needed in caring for immunosuppressed patients who may shed virus for a longer time period and are also at increased risk for development of antiviral-resistant virus⁴.

Infection prevention and control recommendations may need to be modified in special circumstances (e.g. emergency rooms and intensive care units) based upon the risk of aerosolization of respiratory secretion by a variety of unexpected events and emergency procedures.

Diagnosis

Laboratory diagnosis of pandemic (H1N1) 2009 virus, especially at the beginning of a new community outbreak or for unusual cases, has important implications for case management, such as infection control procedures, consideration of antiviral treatment options and avoiding the inappropriate use of antibiotics. Currently, the diagnostic tests can be done by specialized laboratories⁵ in many countries. Reverse transcriptase polymerase chain reaction (RT-PCR) will provide the most timely and sensitive detection of the infection.

Clinical specimens to be collected for laboratory diagnosis are respiratory samples. The impact of specimen type on the laboratory diagnosis of pandemic (H1N1) 2009 virus infection is not sufficiently understood. To this end, samples from the upper respiratory tract, including a combination of nasal or nasopharyngeal samples, and a throat swab are advised. Recent evidence supports viral replication and recovery of pandemic (H1N1) 2009 virus from lower respiratory tract samples (tracheal and bronchial aspirates) in patients presenting lower respiratory tract symptoms and in these patients, such samples have higher diagnostic yields than samples from the upper respiratory tract.

When influenza viruses are known to be circulating in a community, patients presenting with features of **uncomplicated influenza** can be diagnosed on clinical and epidemiological grounds. All patients should be instructed to return for follow-up, should they develop any **signs or symptoms of progressive disease or fail to improve within 72 hours of the onset of symptoms**.

Diagnostic testing, when available, should be prioritized for patients in whom confirmation of influenza virus infection may affect clinical management, including patients considered at-risk and/or those with complicated, severe, or progressive respiratory illness. In addition, results of diagnostic testing may also be valuable in

⁴ World Health Organization (WHO), 2009. Oseltamivir-resistant pandemic (H1N1) 2009 influenza virus. *Weekly Epidemiological Report*, 2009, Vol. 84(44):453-468. Available at <http://www.who.int/wer/2009/wer8444/en/index.html>

⁵ WHO can assist with laboratory testing. See <http://www.who.int/csr/disease/swineflu/guidance/laboratory/en/index.html>

guiding infection control practices and management of a patient's close contacts.

Under no circumstances should influenza diagnostic testing delay initiation of infection control practices or antiviral treatment, if pandemic (H1N1) 2009 disease is suspected clinically and epidemiologically. Furthermore, the results of all diagnostic tests for influenza are dependent upon several factors, including specimen type, quality of specimen collection, timing of collection, storage, and transport conditions. Deficiencies along this chain can result in false negative results. When clinical suspicion is high, clinicians should consider repeat/serial testing.

Patients may have co-infection with bacterial pathogens or other respiratory viruses; therefore, investigations and/or empiric therapy for other pathogens should also be considered. A decision to treat an influenza patient with antiviral medication should not preclude consideration of other infections and their treatment, especially those endemic febrile diseases with similar presentations (e.g. dengue, malaria).

Several rapid influenza diagnostic tests (including so-called “point-of-care” diagnostic tests) are commercially available in many parts of the world. However, studies indicate that rapid diagnostic tests miss many infections with pandemic (H1N1) virus and therefore negative results cannot rule out disease and should not be used as grounds to withhold therapy or lift infection control measures.

Beyond individual patient care, rapid influenza diagnostic tests may be used in the setting of a potential outbreak situation. They can give an indication of the presence of influenza in the community, which may guide public health decision-making in the absence of timely confirmatory testing by more sensitive methods.

In addition to individual case management needs, clinicians are encouraged to collaborate with public health surveillance efforts to monitor for viral evolution and should consider collecting samples, particularly from severely ill patients for virus isolation.

For more information regarding the use of influenza rapid diagnostic tests, see WHO’s website⁶.

Antiviral susceptibility testing

Generally, antiviral susceptibility testing can be performed at a limited number of specialized laboratories. When illness persists despite antiviral treatment (beyond a 5 day treatment course), antiviral resistance should be strongly suspected and the availability of testing explored.

General treatment considerations

To date, most people with pandemic (H1N1) 2009 virus infection have had self-limiting uncomplicated illness. Supportive care can be provided as needed, such as antipyretics (e.g. paracetamol or acetaminophen) for fever or pain and fluid rehydration. Salicylates (such as aspirin and aspirin-containing products) should NOT be used in children and young adults (aged <18 years) because of the risk of Reye’s syndrome.

⁶ <http://www.who.int/csr/disease/swineflu/guidance/laboratory/en/index.html>

Risk factors in previously healthy persons that predict increased risk of progressive disease or severe complications are incompletely understood. Patients with suspected pandemic (H1N1) 2009 virus infection, including patients presenting with uncomplicated illness, should be given information and guidance on signs for deterioration of illness and instructed on how to seek immediate medical attention (see **Signs and symptoms of progressive disease**). Clinicians should also take into account any underlying co-morbidities and other risk conditions (see above).

Pregnant women, especially those with co-morbidities, are at increased risk for complications from influenza virus infection. Influenza in pregnancy is associated with an increased risk of adverse pregnancy outcomes, such as spontaneous abortion, preterm birth, and fetal distress. Consequently, pregnant women with suspected or confirmed pandemic (H1N1) 2009 virus infection warrant closer observation and early antiviral treatment (see below section on antivirals). Paracetamol (acetaminophen) is recommended to ease fever and pain in pregnant women, as non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin⁷, are associated with fetal risks and maternal bleeding and are, therefore, contraindicated in pregnancy.

Infants and young children (notably those <2 years of age) have the highest rate of hospitalization, especially those with underlying chronic medical conditions. Newborns and young children often present with less typical ILI symptoms, such as apnoea, low grade fever, fast breathing, cyanosis, excessive sleeping, lethargy, feeding poorly, and dehydration. Such symptoms are non-specific and diagnosis cannot be made based on these signs alone. Clinicians should exercise a high index of suspicion during circulation of the pandemic (H1N1) 2009 virus and should be aware of occurrence of ILI in contacts of the child to assist clinical diagnosis and to avoid delay in antiviral treatment. Parents should be advised to watch for signs and report their observations, if any of these warning symptoms appear.

Antiviral therapy

Pandemic influenza (H1N1) 2009 virus is currently susceptible to the neuraminidase inhibitors (NAIs) oseltamivir and zanamivir, but resistant to the M2 inhibitors amantadine or rimantadine⁸.

The following is a summary of treatment recommendations⁹:

- Patients who have severe or progressive clinical illness should be treated with oseltamivir. Treatment should be initiated as soon as possible.
 - This recommendation applies to all patient groups, including pregnant women, and young children <2 years, including neonates.
 - In patients with severe or progressive illness not responding to normal treatment regimens, higher doses of oseltamivir and longer duration of

⁷ Low dose aspirin (75-100mg/day) is sometimes used for specific maternal conditions. Dosage for antipyretic effect is recognized as high and contraindicated during pregnancy.

⁸ <http://www.cdc.gov/mmwr/PDF/wk/mm5817.pdf>

⁹ http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html

treatment may be appropriate. In adults, a dose of 150 mg twice daily is being used in some situations.

- Where (1) oseltamivir is not available or not possible to use, or (2) if the virus is resistant to oseltamivir, patients who have severe or progressive clinical illness should be treated with zanamivir.
- Patients at higher risk of developing severe or complicated illness, but presenting with uncomplicated illness due to influenza virus infection, should be treated with oseltamivir or zanamivir. Treatment should be initiated as soon as possible following onset of illness.
- Patients not considered to be at higher risk of developing severe or complicated illness and who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection need not be treated with antivirals.

If used, antiviral treatment should ideally be started early following the onset of symptoms, but it may also be used at any stage of active disease when ongoing viral replication is anticipated or documented. Recent experience strongly indicates that earlier treatment is associated with better outcomes. Therefore, antiviral treatment should be initiated immediately and without waiting for laboratory confirmation of diagnosis.

Methods for extemporaneous preparation of an oral suspension from oseltamivir capsules have been described as an alternative to the manufactured powder for oral suspension. Consult instructions from the manufacturers for these methods¹⁰.

In patients who have persistent severe illness despite oseltamivir treatment, there are few licensed alternative antiviral treatments. In these situations, clinicians have considered intravenous administration of alternative antiviral drugs such as zanamivir, peramivir, ribavirin, or other experimental treatments. The use of such treatments are used should be done only in the context of prospective clinical and virological data collection and with regard to the following cautions:

- ribavirin should not be administered as monotherapy;
- ribavirin should not be administered to pregnant women; and
- zanamivir formulated as a powder for inhalation should not be delivered via nebulization due to the presence of lactose, which may compromise ventilator function.

Full details of the treatment indications, dosing, and safety profile of oseltamivir and zanamivir can be found in the Summary of Product Characteristics¹¹. Standard regimen information can be found in Table 2.

Mothers who are breast feeding may continue breastfeeding while ill and receiving oseltamivir or zanamivir.

¹⁰ <http://www.tamiflu.com/hcp/dosing/extprep.aspx>

¹¹ http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/Tamiflu_PI_clean_en.pdf (accessed 25 October 2009);
http://www.lakemedelsverket.se/SPC_PIL/Pdf/enhumspc/Relenza%20inhalation%20powder%20pre-dispensed%20ENG.pdf (accessed 25 October 2009).

A small number of sporadic cases of oseltamivir resistance have been described⁴. The risk of resistance is considered higher in patients who have prolonged illness (particularly those with severely compromised or suppressed immune systems) and who have received antiviral treatment for an extended duration, but still test positive for the virus. In these clinical situations, health-care staff should have a high level of suspicion that oseltamivir resistance has developed. A laboratory investigation should be undertaken to determine whether antiviral-resistant virus is present. Several cases of resistance have also been reported following oseltamivir treatment of typical uncomplicated influenza.

Since all of the oseltamivir-resistant pandemic (H1N1) 2009 viruses characterized to date remain sensitive to zanamivir, this remains a therapeutic alternative for all patients with serious illness caused by oseltamivir-resistant pandemic (H1N1) 2009 virus.

Oxygen therapy

At presentation or triage 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. For pneumonia oxygen therapy, the WHO recommends maintaining oxygen saturations above 90%¹²; however, this threshold may be increased to 92–95% in some clinical situations, for example during pregnancy. Populations at higher altitudes will require different thresholds for diagnosing hypoxaemia, but will also have increased susceptibility to severe hypoxaemia in the presence of pneumonia or ARDS.

Patients with severe hypoxaemia will need high flow oxygen (e.g. 10 litres per minute) delivered by face mask. Some patients who experience difficulties with compliance (such as children) may require the close involvement of nursing staff or family members. Where piped oxygen is not available, oxygen concentrators or a supply of large cylinders will be needed. WHO has included oxygen in its List of Essential Medicines since 1979, but oxygen is still not widely available in some countries. If medical oxygen is not available, industrial oxygen can be used¹³. Oxygen treatment of newborn infants should follow published guidelines¹⁴.

Antimicrobial treatment

When pneumonia is present, treatment with antibiotics should generally follow recommendations from published evidence-based guidelines for community-acquired pneumonia¹⁵. However, seasonal influenza and past influenza pandemics have been associated with an increased risk of secondary *Staphylococcus aureus* infections, which may be severe, rapidly progressive, necrotizing, and, in some occasions, 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.

¹² Patients with COPD have an altered threshold for hypoxaemia. Excess oxygen can suppress ‘respiratory drive’ and risks an adverse condition.

¹³ http://whqlibdoc.who.int/hq/1993/WHO_ARI_93.28.pdf

¹⁴ <http://whqlibdoc.who.int/publications/2003/9241546220.pdf>

¹⁵ http://whqlibdoc.who.int/publications/2006/924159084X_eng.pdf (for pregnant women and newborns)

Bacterial co-infection with pathogens, such as pneumococcus and *Staphylococcus aureus*, may occur early in the development of pandemic (H1N1) 2009 severe illness. Health care-associated respiratory infections, whether associated or not with mechanical ventilation, may ensue during invasive ventilation and appropriate measures to prevent this should be applied¹⁶. Antibiotic treatment will, therefore, be an important part of case management and should cover nosocomial pathogens based on microbiological data and local epidemiology.

For pregnant women or mothers who are breast feeding, ensure that antimicrobials for treating any secondary infection are safe for use during pregnancy and lactation, e.g. avoid tetracyclines, chloramphenicol, and quinolones.

Antibiotic chemoprophylaxis should not be used.

Care of the severely ill patient

Initial evaluation

- 1) Shortness of breath and increased respiratory rate (tachypnea) are cardinal clinical symptoms suggesting the possibility of severe disease. These should trigger a more thorough assessment, including pulse oximetry and chest X-ray.
- 2) Initial laboratory tests may fail to pick up the virus infection for lower respiratory illness. Samples collected from the lower respiratory tract (e.g. tracheal aspirate) have shown better diagnostic yield than upper respiratory tract specimens (e.g. throat or nasopharyngeal swabs). For intubated patients, initial testing for pandemic (H1N1) 2009 infection should consist of paired nasopharyngeal and tracheal aspirate specimens for RT-PCR. If initial tests are negative, they should be repeated within 48-72 hours in patients with a high likelihood of the infection on clinical or epidemiological grounds.

Antiviral therapy

Oseltamivir therapy should be started immediately upon admission, if not already administered. Experience to date suggests that more than 5 days of treatment are likely to be required and that treatment should be continued for at least 10 days, unless there are clinical or virological data to indicate that virus replication is no longer occurring. There are safety data to support higher doses of oseltamivir; in adults, doses of up to 150 mg twice daily should be considered.

Caution should be exercised when considering higher doses in patients with renal impairment, for whom dose adjustment may be required.

There are insufficient safety data for doses higher than 75mg twice daily in pregnancy.

Supportive care

Patients with progressive pandemic (H1N1) disease may deteriorate very rapidly (within hours) and require close observation and rapid interventions. Treatment of ARDS associated with the new influenza A (H1N1) virus infection should be based upon

¹⁶ World Health Organization (WHO), 2002. Prevention of hospital-acquired infections, 2nd edition. A practical guide. Available at http://www.who.int/csr/resources/publications/WHO_CDS_CSR_EPH_2002_12/en/index.html

published, evidence-based guidelines for sepsis-associated ARDS.

- Standard lung-protective ventilation strategies (pressure/volume-limited ventilation) are appropriate initially.
- In highly resourced settings where very specialized intensive-care technologies are available, individual patients with refractory hypoxemia have benefited from negative fluid balance, prone positioning, and advance respiratory support such as nitric oxide, high frequency oscillation (HFO), and/or extracorporeal membrane oxygenation (ECMO). Such rescue therapies should be considered only if the treating physician/facility has established experience in these modalities.

Adjunctive pharmacologic therapy

High dose systemic corticosteroids and other adjunctive therapies for viral pneumonitis are not recommended for use outside of the context of clinical trials.

Low doses of corticosteroids may be considered for patients in septic shock who require vasopressors. Prolonged use of systemic high-dose corticosteroids can result in serious adverse events in influenza virus-infected patients, including opportunistic infection and possibly prolonged viral replication. Consequently, corticosteroids should be avoided unless indicated for another reason.

Secondary Bacterial Pneumonia

- Initial empiric antimicrobial therapy of suspected pandemic (H1N1) 2009-associated pneumonia/pneumonitis should include both oseltamivir and community-acquired pneumonia antibiotic therapy.
- In the absence of clinical and/or microbiological indication of bacterial infection, discontinuation of antibiotics may be considered in patients with laboratory confirmed pandemic (H1N1) viral pneumonia/pneumonitis as prolonged or redundant antimicrobial therapy poses a risk of antimicrobial resistance.

Resource-poor settings

In resource-poor settings, clinical care strategies should focus on reducing all-cause premature mortality. Local algorithms [e.g. IMCI¹⁷ and IMAI¹⁸] for triage and treatment of common illnesses at the primary care level should be supported and implemented broadly. With confirmed transmission of pandemic (H1N1) 2009 virus in the community, triage algorithms for pneumonia should be modified (see annex for example) to ensure early access to therapies based on risk factors for pandemic (H1N1) 2009 disease progression (see section on risk factors), as well as disease severity and local capacity for referral.

Early access to and use of primary health care for triage and treatment, outreach to high risk and disadvantaged populations, and the availability of hospital care for severely ill patients should be actively supported. Community-level communication on risk and when and where to seek care are fundamental to the clinical care strategy.

¹⁷ Integrated Management of Childhood Illness (IMCI).

http://www.who.int/child_adolescent_health/topics/prevention_care/child/imci/en/index.html

¹⁸ Acute Care: Integrated Management of Adolescent and Adult Illness (IMAI).

http://www.who.int/hiv/pub/imai/primary_acute/en/index.html

Until better point-of-care tests are available, individual treatment decisions at the primary care level should generally be based on clinical symptoms and signs and the level of background influenza activity, if known.

Decentralization of antiviral drugs in primary care settings, even if in limited supply, is important to reach at-risk and disadvantaged populations. Prioritization of antiviral drug use should consider emphasis on early use, progressive illness and at-risk groups, and be based on an ethical framework decided within each country.

Key principles for clinical management include basic symptomatic care, early use of antiviral drugs for high risk populations, if available, antimicrobials for co-infections, and proactive observation for progression of illness. Hospital care requires early supplemental oxygen therapy to correct hypoxemia, with saturation monitoring at triage and during hospitalization, if possible, careful fluid replacement, antimicrobials, and other supportive care. It is important to provide appropriate antimicrobials for other infections which also present with severe respiratory distress, including bacterial and *Pneumocystis jiroveci* pneumonia, malaria, and tuberculosis. A number of severely ill patients with pandemic (H1N1) 2009 disease will develop respiratory distress requiring mechanical ventilation and intensive care support. In settings without mechanical ventilation for patients, improved hospital care of patients with respiratory distress and septic shock needs to be implemented¹⁹.

Standard and Droplet Precautions should be strengthened at all levels of health care, emphasizing respiratory etiquette and hand hygiene, distancing, cohorting, adequate room ventilation, and use of surgical masks for those in close contact with patients with respiratory illness.

¹⁹ Updated IMAI and IMCI guidelines and training materials are in development.

Table 1: Summary of clinical management of patients with pandemic (H1N1) 2009 virus infection

Modalities	Strategies
Diagnosis	RT-PCR provides the most timely and sensitive detection of the infection. Performance of rapid influenza diagnostic tests (RIDT) is variable; a negative result cannot exclude infection with influenza. Consequently, clinical diagnosis in the context of local influenza activity should inform treatment initiation.
Antibiotics	In case of pneumonia, empiric treatment for community acquired pneumonia (CAP) as per published guidelines pending microbiologic results (e.g. 2-3 days); tailored therapy thereafter, if any pathogen(s) are present.
Antiviral therapy	If treatment is indicated, early initiation of treatment with oseltamivir or zanamivir, is recommended. Extended oseltamivir treatment (at least 10 days) and higher doses (up to 150 mg twice daily in adults) should be considered in severe cases. Sporadic oseltamivir resistance observed; treat unresponsive cases with suspicion.
Corticosteroids	Moderate to high dose systemic corticosteroids are NOT recommended as adjunctive H1N1 treatment. They are of unproven benefit and potentially harmful.
Infection control	Standard plus Droplet Precautions. For aerosol-generating procedures, use a particulate respirator (N95, FFP2 or equivalent), eye protection, gowns, gloves, and an adequately ventilated room, which can be naturally or mechanically ventilated, as per WHO guidance ²⁰ .
NSAIDS, antipyretics	Paracetamol (acetaminophen) given orally or by suppository. Avoid administration of salicylates (aspirin and aspirin-containing products) in children and young adults (< 18 years old) due to the risk of Reye's syndrome.
Oxygen therapy	Monitor oxygen saturation and maintain SaO ₂ over 90% (92-95% for pregnant women) with nasal cannulae or face mask. High flow oxygen may be required in severe cases.
Pregnancy	Initiate oseltamivir treatment early. Do NOT treat with ribivirin. Safety data for elevated antiviral doses is not available. Ensure antimicrobials for secondary infections are safe for this patient group. NSAIDs should be avoided. Maintain SaO ₂ at 92-95%. Mothers can continue breastfeeding when ill and on antivirals.
Infants	Symptoms may be non-specific, so clinicians should act with a high index of suspicion. No aspirin should be given to children. Antiviral treatment should be initiated early.

²⁰ http://www.who.int/csr/resources/publications/infection_control/en/index.html

Table 2: Standard antiviral treatment regimens

Oseltamivir

Oseltamivir is indicated for treatment of patients one year of age and older. For adolescents (13 to 17 years of age) and adults the recommended oral dose (based on data from studies in typical uncomplicated influenza) is 75 mg oseltamivir twice daily for 5 days. The recommended dose for treatment of children 6 to 12 months of age is 3 mg per kg body weight twice daily for 5 days for treatment.

For infants less than 1 year of age recommended doses are as follows:

>3 months to 12 months	3 mg/kg twice daily
>1 month to 3 months	2.5 mg/kg twice daily
0 to 1 month*	2 mg/kg twice daily

* There are no data available regarding the administration of oseltamivir to infants less than one month of age.

For adults, adolescents or children who are unable to swallow capsules, methods for extemporaneous preparation of an oral suspension are described in instructions from manufacturers.

For infants older than 1 year of age and for children 2 to 12 years of age recommended doses are as follows:

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

Zanamivir is indicated for treatment of influenza in adults and children (>5 years). The recommended dose for treatment of adults and children from the age of 5 years (based on data from studies in typical uncomplicated influenza) is two inhalations (2 x 5mg) twice daily for 5 days.

Annex: Examples of clinical triage algorithms for ILI and pneumonia in resource-poor settings



