

WHO Issues Guidelines for Antiviral Treatment of H1N1 and Other Influenza **CME/CE**

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August 27, 2009 — The World Health Organization (WHO) has issued guidelines for antiviral treatment of novel influenza A (H1N1) and other influenza. The purpose of the new recommendations, which were posted online August 20, is to provide a basis for advice to clinicians regarding the use of the currently available antivirals for patients presenting with illness caused by influenza virus infection, as well as considerations regarding potential use of these antiviral medications for chemoprophylaxis.

On the basis of a review of data collected with previously circulating strains, and treatment of human H5N1 influenza virus infections, the new guidelines expand on recommendations published in May 2009, titled "Clinical management of human infection with new influenza A (H1N1) virus: Initial guidance." These new guidelines do not change recommendations in the WHO rapid advice guidelines on pharmacological management of humans infected with highly pathogenic avian influenza A (H5N1) virus.

"In April 2009, the [WHO] received reports of sustained person to person infections with [H1N1] virus in Mexico and the United States," write Edgar Bautista, from Médico Neumólogo Intensivista, Jefe de UCI- INER in Mexico, and colleagues. "Subsequent international spread led WHO to declare on 11 June 2009 that the first influenza pandemic in 41 years had occurred. This 2009 pandemic H1N1 influenza virus has now spread worldwide, with confirmed cases of pandemic H1N1 virus infection reported in more than 100 countries in all 6 WHO regions[, which] has led to the need to add to the existing guidance on the use of antivirals."

The new recommendations highlight oseltamivir and zanamivir, which are neuraminidase inhibitors, and amantadine and rimantadine, which are M2 inhibitors. Suggestions are also provided regarding the use of some other potential pharmacological treatments, such as ribavirin, interferons, immunoglobulins, and corticosteroids.

Management of patients with pandemic influenza (H1N1) 2009 virus infection is the primary focus of the statement, although it also includes guidance regarding the use of the antivirals for treatment of other seasonal influenza virus strains, as well as for infections resulting from novel influenza A virus strains.

The guidelines urge country and local public health authorities to issue local recommendations for clinicians periodically, based on epidemiological and antiviral susceptibility data on the locally circulating influenza strains. As the prevalence and severity of the current pandemic evolves, WHO anticipates that additional data will be forthcoming that may require revision of the current recommendations. WHO therefore plans to review the guidance no later than September 2009 to determine whether modifications to the recommendations are needed.

Recommendations for Antiviral Treatment of H1N1

For patients with confirmed or strongly suspected infection with influenza pandemic (H1N1) 2009, when antiviral medications for influenza are available, specific recommendations regarding use of antivirals for treatment of pandemic (H1N1) 2009 influenza virus infection are as follows:

- Oseltamivir should be prescribed, and treatment started as soon as possible, for patients with severe or progressive clinical illness (strong recommendation, low-quality evidence). Depending on clinical response, higher doses of up to 150 mg twice daily and longer duration of treatment may be indicated. This recommendation is intended for all patient groups, including pregnant women, neonates, and children younger than 5 years of age.
- Zanamivir is indicated for patients with severe or progressive clinical illness when oseltamivir is not available or not possible to use, or when the virus is resistant to oseltamivir but known or likely to be susceptible to zanamivir (strong recommendation, very low-quality evidence).
- Antiviral treatment is not required in patients not in at-risk groups who have uncomplicated illness caused by confirmed or strongly suspected influenza virus infection (weak recommendation, low-quality evidence). Patients considered to be at risk are infants and children younger than 5 years of age; adults older than 65 years of age; nursing home residents; pregnant women; patients with chronic comorbid disease including cardiovascular, respiratory, or liver disease and diabetes; and immunosuppressed patients because of malignancy, HIV infection, or other diseases.
- Oseltamivir or zanamivir treatment should be started as soon as possible after the onset of illness in patients in at-risk groups who have uncomplicated illness caused by influenza virus infection (strong recommendation, very low-quality evidence).

Recommendations for Chemoprophylaxis of H1N1

Specific recommendations regarding the use of antivirals for chemoprophylaxis of pandemic (H1N1) 2009 influenza virus infection are as follows:

- When risk for human-to-human transmission of influenza is high or low, and the probability of complications of infection is high, either because of the influenza strain or because of the baseline risk of the exposed group, use of oseltamivir or zanamivir may be considered as postexposure chemoprophylaxis for the affected community or group, for individuals in at-risk groups, or for healthcare workers (weak recommendation, moderate-quality evidence).
- Individuals in at-risk groups or healthcare personnel do not need to be offered antiviral chemoprophylaxis if the likelihood of complications of infection is low. This recommendation should be applied independent of risk for human-to-human transmission (weak recommendation, low-quality evidence).

For treatment of mild to moderate uncomplicated clinical presentation of infection with multiple cocirculating influenza A subtypes or viruses with different antiviral susceptibilities, patients in at-risk groups should be treated with zanamivir or oseltamivir plus M2 inhibitor (noting that amantadine should not be used in pregnant women). Otherwise-healthy patients with this presentation need not be treated.

When the clinical presentation of infection with multiple cocirculating influenza A subtypes or viruses with different antiviral susceptibilities is severe or progressive, all patients should be treated with oseltamivir plus M2 inhibitor, or zanamivir.

For treatment of mild to moderate uncomplicated clinical presentation of infection with sporadic zoonotic influenza A viruses including H5N1, the at-risk population should be treated with oseltamivir or zanamivir, and the otherwise-healthy population with oseltamivir. All patients, regardless of risk status, with severe or progressive presentation of infection with sporadic zoonotic influenza A viruses including H5N1 should be treated with oseltamivir plus an M2 inhibitor.

Clinical Context

H1N1 influenza infection transmitted person to person was first detected by WHO in April 2009. Although the first cases were limited to Mexico and the United States, subsequent spread overseas resulted in WHO declaring on June 11, 2009, the first influenza pandemic to occur in 41 years.

Cases of pandemic H1N1 virus infection have now been confirmed in more than 100 countries in all 6 WHO regions, mandating updated recommendations on the use of antivirals for infections caused by new strains of pandemic (A)H1N1 virus. The present WHO guidelines also address antiviral use in seasonal influenza and in infections caused by other novel influenza A viruses, but they do not change existing guidelines on pharmacological management of humans infected with H5N1 virus.

Study Highlights

- When antiviral medications for influenza are available, patients with confirmed or strongly suspected infection with influenza pandemic (H1N1) 2009 should be treated as follows:
 - All patient groups, including pregnant women, neonates, and young children younger than 5 years, with severe or progressive clinical illness should be treated as soon as possible with oseltamivir (strong recommendation, low-quality evidence).
 - Higher doses up to 150 mg twice daily and longer duration of treatment may be needed, depending on clinical response.
 - Patients with severe or progressive clinical illness should receive zanamivir when oseltamivir is not available or not possible to use, or when the virus is resistant to oseltamivir but known or likely to be susceptible to zanamivir (strong recommendation, very low-quality evidence).
 - Patients considered to be "at risk" are infants and children younger than 5 years, adults older than 65 years, nursing home residents, pregnant women, patients with chronic comorbidities (cardiovascular, respiratory or liver disease, and diabetes), and immunosuppressed patients as a result of malignant disease, HIV infection, or other diseases.
 - Patients not in "at-risk" groups with uncomplicated illness because of confirmed or strongly suspected H1N1 infection may not need antiviral treatment (weak recommendation, low-quality evidence).
 - Patients in "at-risk" groups with uncomplicated illness because of confirmed or strongly suspected H1N1 infection should be started with oseltamivir or zanamivir treatment as soon as possible after illness onset (strong recommendation, very low-quality evidence).
- Specific recommendations regarding use of antivirals for chemoprophylaxis of pandemic (H1N1) 2009 influenza virus infection are as follows:
 - Oseltamivir or zanamivir may be used postexposure as chemoprophylaxis when risk for human-to-human transmission of influenza is high or low, and risk for complications of infection is high, either because of the influenza strain or because of the baseline risk for the exposed group:

- In this setting, oseltamivir or zanamivir may be used in the affected community or group, in individuals in "at-risk" groups, or in healthcare workers (weak recommendation, moderate-quality evidence).
- If the risk for complications of infection is low, individuals in "at-risk" groups or healthcare personnel may not need antiviral chemoprophylaxis, independent of risk for human-to-human transmission (weak recommendation, low-quality evidence).

Clinical Implications

- Patients with confirmed or strongly suspected infection with influenza pandemic (H1N1) 2009 should be treated as soon as possible with oseltamivir if they have severe or progressive clinical illness, when the drug is available, and when the virus is not resistant.
- Oseltamivir or zanamivir may be used postexposure as chemoprophylaxis when the risk for human-to-human transmission of influenza is high or low, and risk for complications of infection is high, either because of the influenza strain or because of the baseline risk for the exposed group.