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Rapid Emergence of Oseltamivir Resistance

To the Editor: The influenza A pandemic (H1N1) 2009 virus has spread globally since it first appeared in Mexico in April 2009. This third influenza pandemic since the Spanish influenza pandemic of 1918 (*1*) has caused at least 400,000 infections within 6 months; estimated mortality rate is 1.2% (*2*). Emergence of oseltamivir resistance in the pandemic (H1N1) 2009 virus is a rising challenge to global control of the pandemic. So far, 39 oseltamivir-resistant pandemic (H1N1) 2009 viruses have been reported worldwide (*3*). Among the 32 resistant strains reported in October 2009, a total of 13 (41%) were associated with postexposure chemoprophylaxis and 16 (50%) were from samples of patients receiving oseltamivir (*3*). We report rapid emergence of resistance (H275Y mutation) in a patient, 4 days after early treatment with standard doses of oseltamivir for pandemic (H1N1) 2009 pneumonia.

On September 1, 2009, a 20-year-old man with mental retardation consulted the emergency department of Kaohsiung Veterans General Hospital after 1 day of fever, sore throat, and nonproductive cough. A rapid diagnostic antigen test (Quick Vue Influenza test; Quidel, San Diego, CA, USA) showed the man to be positive for influenza A. He was hospitalized for bilateral pneumonitis and treated with oseltamivir (75 mg 2×/day for 5 days), ampicillin/sulbactam, and erythromycin. However, a progressive increase in bilateral perihilar interstitial infiltration developed on the third day, accompanied by increasing dyspnea. Influenza A pandemic (H1N1) 2009 virus was isolated from the patient's nasopharyngeal secretions on days 1 and 4 by using MDCK cells. After DNA sequence analysis of the neuraminidase gene, the mutation of H275Y was not found in the first isolate, but sequence analysis of the second isolate detected mixed populations (C/T) in the 823-nt position of the neuraminidase gene. Only a single pattern (T) was found from the cultured viruses, indicating a mixed quasispecies of oseltamivir-resistant and -susceptible viruses emerging after 4 days of oseltamivir treatment. The oseltamivir-resistant viruses become dominant in the cell culture–propagated viruses. Chan et al. reported a similar case in which the original clinical specimens contained a mixed population of variants, and oseltamivir-resistant viruses become dominant after the passage in MDCK cells (*4*).

On his 9th day in the hospital, the patient was intubated because of acute respiratory distress syndrome (Figure) and given levofloxacin. Urine samples were negative for *Pneumococcus* and *Legionella* spp. antigens. The patient improved and was extubated on hospital day 16.

Paired serologic test results were negative for *Mycoplasma pneumoniae* and *Legionella* spp. antibody; however, immunoglobulin G for *Chlamydia pneumoniae* increased 4-fold. By 37 days after illness onset, clinical signs and symptoms resolved and bilateral lineoreticular infiltration was reduced.

On August 8, 2009, Taiwan had the most devastating typhoon (Typhoon Morakot) in 50 years. The patient reported here had stayed in a typhoon evacuation camp for 1 week before his influenza signs and symptoms developed. Although 4 sporadic cases of pandemic (H1N1) 2009 infections were reported from the same camp, none of the isolated viruses harbored the H275Y mutation in the neuraminidase gene. No evidence of virus transmission was found among healthcare personnel, family members, and camp members who had been in close contact with the patient.

Oseltamivir has been recommended by the US Centers for Disease Control and Prevention for the treatment of

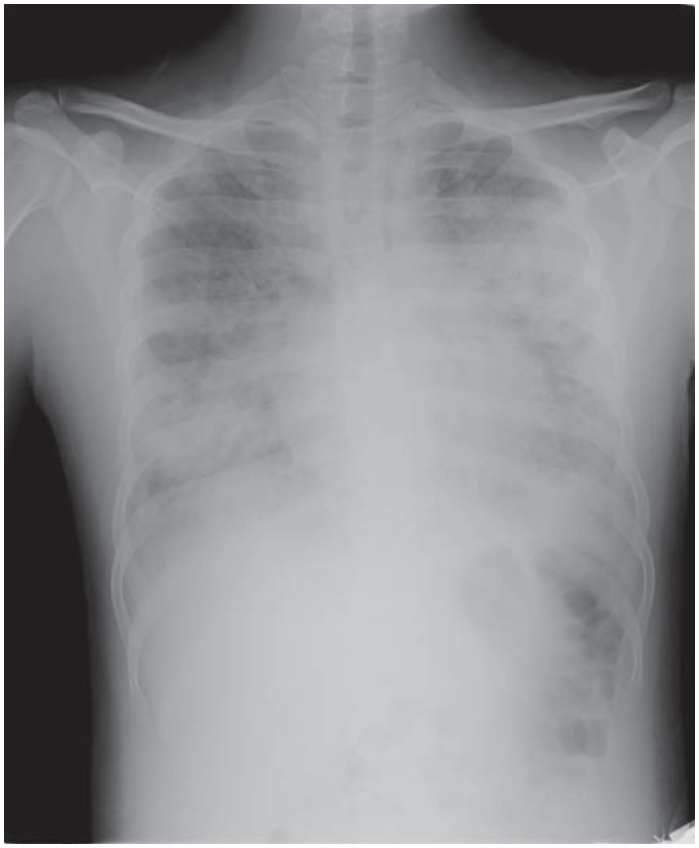

Figure. Radiograph (anteroposterior view) of patient with acute respiratory distress syndrome and oseltamivir-resistant pandemic (H1N1) 2009 virus.

infection caused by pandemic (H1N1) 2009 virus (*5*). The first 2 cases of oseltamivir resistance of pandemic H1N1 (2009) virus were reported in August 2009 (*6*). For these cases, oseltamivir-resistant virus was isolated on days 11 and 23 after the initial isolation of oseltamivir-susceptible viruses, for each patient, respectively. In contrast, in the case reported here, resistance to oseltamivir developed rapidly, after only 4 days of treatment.

In severe cases of pandemic (H1N1) 2009 infections, mortality rates are highest for patients who are pregnant, <2 years of age, or obese, or who have chronic lung disease (*7*). The patient reported here was previously healthy except for mental retardation; his body mass index was 23.9 kg/m^2. Progression of pneumonia to acute respiratory distress syndrome occurred despite early initiation of the standard dose of oseltamivir, within 48 hours after illness onset and initial susceptibility of the virus. Clinical deterioration might have resulted from the rapid emergence of an oseltamivir-resistant pandemic (H1N1) 2009 virus with a H275Y mutation, which is known to confer a high level of oseltamivir resistance while retaining zanamivir susceptibility (*8*), or it might have resulted from co-infection with *C. pneumoniae*. A 4-month study found concurrent bacterial infections in 29% of fatal cases of pandemic (H1N1) 2009 virus (*9*).

Oseltamivir resistance can emerge rapidly during treatment of pandemic (H1N1) virus infection. Healthcare providers should be aware that resistance may emerge in otherwise apparently healthy persons as early as day 4 of treatment with standard doses of oseltamivir.

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Dual Seasonal Patterns for Influenza, China

To the Editor: Since 2000, the People's Republic of China has had a nationwide surveillance network for influenza, which as of 2005 has been reported on the Chinese Center for Disease Control and Prevention website (www.cnic.org.cn/ch/). This surveillance has shown a remarkable dual pattern of seasonal influenza on mainland China. Whereas a regular winter pattern is noted for northern China (similar to that in most parts of the Northern Hemisphere), the pattern in southern China differs. In southern China, influenza is prevalent throughout the year; it has a clear peak in the summer and a less pronounced peak in the winter. Because this dual seasonal pattern of influenza has not been reported outside China and is relevant to pandemic (H1N1) 2009, we describe surveillance data for rates of consultation for influenza-like illness (ILI) and influenza subtypes in patients with ILI. We emphasize the spread of influenza from southern to northern China.

Before it was extended in June 2009, the National Influenza Surveillance Network had been composed of 63 influenza laboratories and 197 sentinel hospitals across 31 provinces of mainland China. In 13 of 16 northern provinces, surveillance began from the week including October 1 and ended in the week including March 31 of the following year. In the 3 northern provincial areas of Liaoning, Tianjin, and Gansu and in all southern provinces, surveillance was conducted throughout the year. Data consisted of information about ILI cases and virus subtypes. The sentinel hospitals defined ILI cases according to World Health Organization criteria: sudden onset of fever >38°C, cough or sore throat, and absence of other diagnoses (*1*). The number of ILI cases and the total number of outpatients at the sites (ILI consultation rate) were recorded each day and reported to the National Influenza Surveillance Information System each week.

Sentinel hospitals were required to collect 5–15 nasopharyngeal swabs each week from ILI patients who had not taken antiviral drugs and who had fever (≥38°C) for no longer than 3 days. The swabs were sent to the corresponding influenza laboratories for virus isolation and identification; results were reported to the National Influenza Surveillance Information System within 24 hours.

From the National Influenza Surveillance Network, a database of surveillance information from April 2006 to March 2009 was established. For influenza surveillance purposes, mainland China was divided into northern and southern parts, basically following the Qinling Mountain range in the west and the Huai River in the east. The prominent influenza peaks in the winter in the north and summer in the

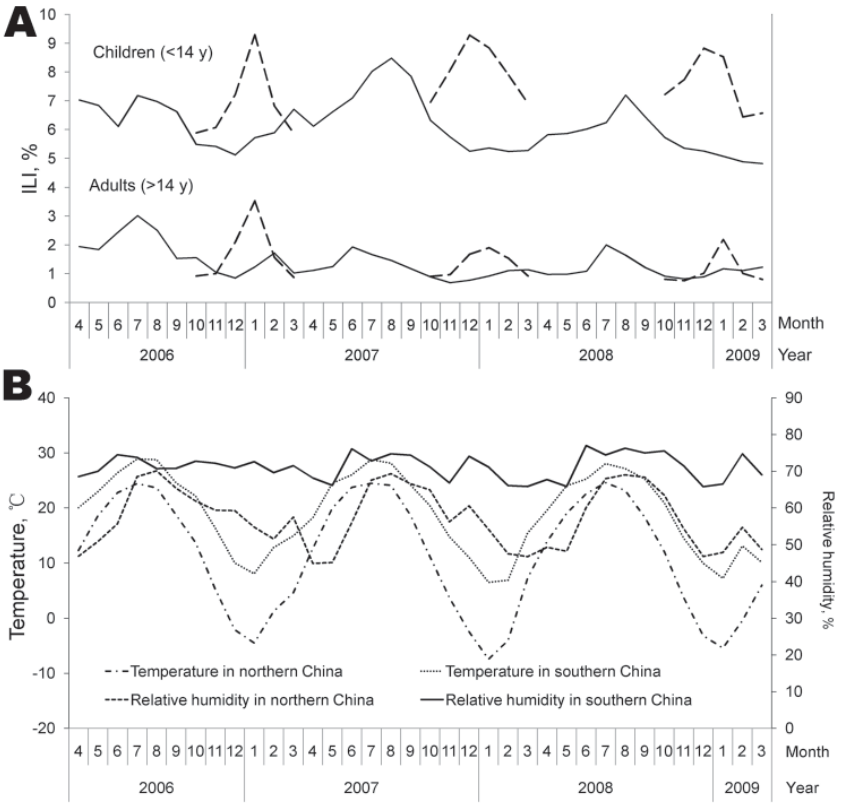

Figure. Epidemic patterns, by month, from the surveillance data of the influenza-like illness (ILI) consulting rate and influenza subtypes in ILI patients in mainland China, per month, April 2006–March 2009. A) ILI percentages for northern (dashed lines) and southern (solid lines) mainland China, by age group. B) Average temperature and relative humidity. A color version of this figure is available online (www.cdc.gov/EID/content/16/4/725-F.htm).