Possible Transmission of Pandemic (HIN1) 2009 Virus with Oseltamivir Resistance

To the Editor: In March 2009, a new strain of influenza A (H1N1) virus of swine origin emerged; the virus had crossed the species barrier to humans and acquired the capability of human-to-human transmission. Soon after, the World Health Organization raised the worldwide pandemic alert to level 6 (www.who.int/en), declaring the first influenza pandemic in the past 42 years. The virus was named influenza A pandemic (H1N1) 2009 virus. The illness caused by this virus is particularly dangerous for pregnant women and for patients with chronic diseases (*1*). The preferred treatment is a neuraminidase inhibitor, zanamivir or oseltamivir (*2*).

Around the world, several dozen cases of resistance to oseltamivir in persons with or without exposure to the drug have been reported (*3*). However, only limited information is available with regard to initial infections with oseltamivir-resistant viruses (*4*). We report a case of possible human-to-human transmission of pandemic (H1N1) 2009 virus in Israel.

After the recent discovery of oseltamivir-resistant strains, we conducted a retrospective study of oseltamivir-resistance mutations in viral RNA amplified from specimens from patients hospitalized >1 week with pandemic (H1N1) 2009. All samples were first tested for the H275Y mutation by using an in-house real-time reverse transcription–PCR (RT-PCR) assay developed at the Central Virology Laboratory of Chaim Sheba Medical Center; positive results were confirmed by sequencing. The histidine-to-tyrosine mutation at the 275 position of the neuraminidase protein results in reduced binding of oseltamivir.

During June–August 2009, ≈80 children in an institution for disabled children were suspected of being infected with pandemic (H1N1) 2009 virus. The children had influenza-like signs and symptoms, and at that time the only influenza virus circulating in Israel was pandemic (H1N1) virus. Of these 80 patients, 10 were hospitalized because of the severity of their clinical signs or disease complications, and for 7, RNA of the pandemic (H1N1) 2009 virus was detected in throat and nasal swabs by real-time RT-PCR.

Patient 1 was a 13-year-old boy with cerebral palsy and partial blindness, who was treated with oseltamivir (60 mg twice a day) for 5 days (July 27–31, 2009). After some improvement, his condition worsened, and he was hospitalized on August 13 for breathing difficulty and high fever. Real-time RT-PCR indicated infection with pandemic (H1N1) 2009 virus. During our survey, we found that patient 1 was infected with a virus carrying the H275Y mutation, suggesting that the mutation evolved during oseltamivir treatment.

Patient 2 was a 10-year-old girl who had lived in the room next to patient 1 and who also had cerebral palsy. Her signs and symptoms started on August 13, 2009, and she was hospitalized on August 15. She was treated in the hospital for 5 consecutive days with oseltamivir, steroids, and augmentin; she was discharged on August 21. Her diagnosis was made early in the clinical course of her infection, and she was infected with pandemic (H1N1) 2009 virus carrying the H275Y mutation.

In contrast, none of the other 8 children who were hospitalized for pandemic (H1N1) 2009 carried the mutation. Although we cannot rule out the possibility that the virus was transmitted by a third person, we suggest that the virus carrying the resistance mutation was probably transmitted from patient 1 to patient 2. This transmission is probable because these 2 patients lived in adjacent rooms, they were in contact with each other, clinical onset of patient 1 preceded that of patient 2 by a few days, and patient 2 had the mutation at the beginning of her disease.

Fortunately, despite the conditions that favor virus spread in such institutions, this virus did not seem to spread further; the other 8 hospitalized children from this institution were infected with the wild-type virus. Nevertheless, the potential for spread of pandemic (H1N1) 2009 virus carrying the oseltamivir resistance mutation exists, thereby emphasizing the urgent need for a vaccination to prevent illness and for alternative drugs to treat infected patients.

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Cross-Reactive Antibodies to Pandemic (H1N1) 2009 Virus, Singapore

To the Editor: Accumulating evidence suggests that the degree of serologic cross-reactivity to pandemic (H1N1) 2009 virus varies between populations worldwide. To assess potential serologic cross-reactivity in Singapore, we obtained serum samples during May–June 2009 from 50 randomly recruited, healthy volunteers born mostly before 1958 (i.e., potentially those with some natural exposure to the then circulating H1N1/1918-like subtype viruses) before widespread transmission of pandemic (H1N1) 2009 virus in Singapore. Standard serologic hemagglutination-inhibition (HI) tests (*1*) were performed in 2 reference laboratories (Singapore during July–October 2009 and Melbourne, Australia, in January 2010), and microneutralization (MN) tests (*2*) were performed in 1 reference laboratory (Singapore) for each serum sample against pandemic (H1N1) 2009 virus (A/Auckland/1/2009) and seasonal influenza (H1N1) virus (A/Brisbane/59/2007). The study was reviewed and approved by the National Healthcare Group Domain-Specific Review Board (ref no. E/09/289, J.W.T. principal investigator).

Mean ± SD age of participants was 60.1 ± 7.4 years (range 45–82 years); 31 (62%) were women, 42 (84%) were born in Singapore (the rest in Hong Kong, Malaysia, or India), and 26 (52%) had not traveled outside Singapore. None of the 50 participants had HI or MN titers ≥40 against influenza A/Auckland/1/2009 when samples were tested in either laboratory. In contrast, 18 samples had either HI or MN titers ≥40 against seasonal influenza A/Brisbane/59/2007 (Table). Use of guinea pig or turkey erythrocytes in HI assays had little effect on the results (Table). Thus, our results are similar to those of Chen et al. (*3*) and Itoh et al. (*4*) for this small cohort in that none of the participants 40–80 years of age from Southeast Asia had cross-reactive antibodies to pandemic (H1N1) 2009 virus.

Although differences in population demographics and laboratory methods used make comparisons between studies difficult, one of the most striking observations from various studies has been the higher levels of cross-reactive antibody titers in prepandemic serum samples from older persons (≥80 years of age) in western populations (United States and United Kingdom) (*5*,*6*) than from persons in eastern populations (China) (*3*) and Singapore (this study). Although Itoh et al (*4*) did not find serologic cross-reactivity in the population <80 years of age in Japan, they found higher levels of cross-reactive antibodies in their population ≥80 years of age. Historically, because epidemiologic data suggest that influenza (H1N1)/1918–like viruses were widespread in Asia, these contrasting results are a stimulus for additional large-scale studies to assess the effect of these viruses in these populations.

Although the main limitation of our study is the small sample size, several reasons may account for different findings in population studies of serologic cross-reactivity. First, populations may not be comparable in terms of geographic proximity and their potential for community-acquired infection within the same wave of a seasonal influenza epidemic with a virus that was similar to pandemic (H1N1) 2009 virus. Chen et al. (*3*) reported that their serum samples were obtained mainly from rural farmers in China who lived farther apart than city dwellers, However, Hancock et al. (*5*) reported that their samples were obtained from vaccine trials conducted in 1976 or 2005–2009 involving academic, government, and industrial workers, which likely indicates that these persons were urban-based (i.e., living and working more closely to each other than rural farmers in China). Thus, results of our study may not be directly comparable with either of these previous studies because our population resided in Southeast Asia and was urban-based.

Second, use of seasonal influenza vaccine has varied in different populations, with Singapore having one of the lowest recorded use rates in the Western Pacific region, and far lower than that in the United States (*6*). If previous seasonal influenza viruses shared a degree of antigenic cross-reactivity with pandemic (H1N1) 2009 virus, contemporary seasonal influenza vaccines, if well-matched, should reflect changing antigenicity of seasonal influenza viruses; thus, vaccinated populations may have acquired some serologic cross-reactivity through previous influenza vaccines. However, it is likely that past infection rather than vaccination results in cross-reactivity, as suggested by Miller et al. (*7*).

Third, because pandemic (H1N1) 2009 virus originated mainly from swine viruses in North America and