CORRESPONDENCE

# A Community Cluster of Oseltamivir-Resistant Cases of 2009 H1N1 Influenza

**TO THE EDITOR:** Oseltamivir-resistant infection with the 2009 pandemic influenza A (H1N1) virus has so far been described only rarely and is conferred by the H275Y substitution in the neuraminidase enzyme.[1] Only 3 of the 32 patients with oseltamivir-resistant infection reported on as of this writing were not receiving oseltamivir when the resistant viruses were detected, and ongoing community transmission has not yet been shown.[1] However, the emergence of oseltamivir-resistant 2009 H1N1 influenza remains a grave concern, since widespread oseltamivir resistance has been observed in seasonal H1N1. This resistance was unrelated to selective drug pressure, and the H275Y substitution did not appear to reduce transmissibility or severity.[2,3] We report on a cluster of seven cases of oseltamivir-resistant 2009 H1N1 infection in Vietnam.

In July 2009, during a 42-hour journey, 10 students socialized together in the same train carriage. None of the students knew each other before the journey, none had contact with a person with suspected influenza in the week before the trip, none were symptomatic during the journey, and none were previously or currently receiving oseltamivir. Fever developed in four of the students within 12 hours after arrival and in two more students within 48 hours after arrival (Fig. 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). An additional case was identified in a traveler in a different carriage (Patient G). Nasal swabs, throat swabs, or both from all seven persons were positive for 2009 H1N1 RNA when tested with reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays, and viruses were successfully cultured from specimens obtained from three of the persons. The H275Y substitution was detected retrospectively in diagnostic specimens obtained from all seven subjects before any oseltamivir treatment. The concentrations of oseltamivir carboxylate required for a 50% inhibition of neuraminidase activity of the isolated viruses in a fluorometric neuraminidase-inhibition assay were 323.6, 429.5, and 889.2 nM; these concentrations confirmed resistance[4] (see the Supplementary Appendix).

Six patients were admitted to a hospital for isolation, one patient was isolated at home, and all were treated with oseltamivir phosphate at a dose of 75 mg twice daily (Fig. 1 in the Supplementary Appendix), since resistance testing had not yet been performed. All patients recovered uneventfully, although one patient (Patient F), with the highest 50% inhibitory concentration, continued to test positive on RT-PCR until day 9, despite receiving oseltamivir from the day of the onset of illness (Fig. 1 in the Supplementary Appendix). An extensive public health investigation did not identify additional patients or the index patient.

In this cluster, infection developed in at least 6 of the 10 people who were probably exposed to the index patient; this shows that resistant 2009 H1N1 viruses are transmissible and can replicate and cause illness in healthy people in the absence of selective drug pressure. Ongoing transmission from the cluster was not detected, but the tracing of all contacts was not possible, so ongoing transmission cannot be ruled out. However, only three other resistant cases have been detected in Vietnam as of this writing, and all were due to selection of resistant viruses during treatment rather than person-to-person transmission. Although data are limited, it is likely that the detected levels of oseltamivir resistance are clinically relevant.[5] The loss of oseltamivir as a treat-



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ment option for severe 2009 H1N1 infection could have profound consequences. To minimize this risk, the use of oseltamivir should be restricted to prophylaxis and treatment in high-risk persons or the treatment of people with severe or deteriorating illness, antiviral stockpiles should be diversified, and optimal dosages and combination therapies should be urgently studied. Close monitoring and reporting of resistance to neuraminidase inhibitors are essential.

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