

# Rapid development of drug-resistant 2009 H1N1 influenza reported in 2 cases

March 26 2010

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Two people with compromised immune systems who became ill with 2009 H1N1 influenza developed drug-resistant strains of virus after less than two weeks on therapy, report doctors from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. Doctors who treat prolonged influenza infection should be aware that even a short course of antiviral treatment may lead to drug-resistant virus, say the authors, and clinicians should consider this possibility as they develop initial treatment strategies for their patients who have impaired immune function.

Both patients in the new report developed resistance to the key [influenza](#) drug [oseltamivir](#) (Tamiflu), and one also demonstrated clinical resistance to another antiviral agent, now in experimental testing, intravenous peramivir, note senior authors Matthew J. Memoli, M.D., and Jeffery K. Taubenberger, M.D., Ph.D. This is the first reported case of clinically significant peramivir-resistant 2009 H1N1 illness, say the scientists. The report is scheduled to appear in print on May 1 in *Clinical Infectious Diseases* and is now online.

The people in the current case report had immune limitations due to blood stem cell transplants that occurred several years previously. Both recovered from their influenza infections.

"While the emergence of drug-resistant influenza virus is not in itself surprising, these cases demonstrate that [resistant strains](#) can emerge after only a brief period of drug therapy," says NIAID Director Anthony S.

Fauci, M.D. "We have a limited number of drugs available for treating influenza and these findings provide additional urgency to efforts to develop antivirals that attack influenza virus in novel ways."

The 2009 H1N1 [influenza virus](#) is susceptible to just one of the two available classes of anti-influenza drugs, the neuraminidase inhibitors. Besides oseltamivir, other neuraminidase inhibitors are [zanamivir](#) ([Relenza](#)), which is inhaled, and the intravenously administered investigational drug peramivir. As the H1N1 influenza pandemic unfolded, laboratory tests of virus strains isolated from patients showed that some strains contained a genetic mutation (the H275Y mutation) that makes the virus less susceptible to some neuraminidase inhibitors.

The two people in the current case study had pre-existing medical conditions that impaired their immune system function before contracting 2009 H1N1 flu. Strains of 2009 H1N1 influenza containing the H275Y mutation had been reported previously in people with diminished immune function, but in previous cases the mutation arose after more than 24 days of continuous therapy. In the newly described cases, the mutation appeared after 14 days in one individual and after nine days in the second.

"Although the recommended length of treatment with oseltamivir is five days, it is common for physicians to continue giving this first-line drug longer if the patient does not improve," says Dr. Memoli.

Both people in the current report received oseltamivir for extended periods but they continued to shed virus in their nasal secretions throughout treatment. When one patient's condition worsened despite 24 days of oseltamivir treatment, doctors administered peramivir for 10 days. The drug did not reduce viral shedding and the patient remained ill, demonstrating what the authors described as clinically significant resistance to peramivir. Next, doctors administered the only other

available flu drug, zanamivir, for 10 days. The person then fully recovered.

"Additional, larger studies are needed to further refine our findings," says Dr. Memoli. "But these cases of rapid appearance of drug-resistant 2009 H1N1 influenza in immune-compromised patients are worrisome and should prompt clinicians to reconsider how they use available flu drugs."

The mutation that allows 2009 H1N1 to resist oseltamivir also significantly reduces the virus's susceptibility to peramivir. If a relatively short course of oseltamivir causes a mutant flu strain to emerge in a particular patient, that person may not respond to peramivir. Zanamivir might be a good choice if a patient does not respond within a few days to oseltamivir, Dr. Memoli says. However, because zanamivir must be inhaled, patients who are very ill and whose breathing is mechanically supported cannot be given zanamivir.

"As clinicians, we should carefully consider our treatment options and use all the drugs available to us wisely. This is especially important in a patient with prolonged infection or when an antiviral drug fails to cure the patient after the recommended course of treatment," says Dr. Memoli.

**More information:** MJ Memoli et al. Rapid selection of oseltamivir and peramivir resistant pandemic H1N1 during therapy in two immunocompromised hosts. *Clinical Infectious Diseases* [DOI:10.1086/651605](https://doi.org/10.1086/651605) (2010).

Provided by National Institutes of Health

Citation: Rapid development of drug-resistant 2009 H1N1 influenza reported in 2 cases (2010, March 26) retrieved 19 April 2024 from <https://medicalxpress.com/news/2010-03-rapid-drug-resistant-h1n1-influenza-cases.html>

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