

# Editorial

## Novel swine origin influenza a (H1N1) virus in humans

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In March and early April 2009, while much of the world was focusing on the threat of avian influenza originating in Asia, intelligence gathering systems were also extracting evidence of an epidemic of acute respiratory infections in Mexico and southern California. Although the exact sequence of events is uncertain, the Centers for Disease Control and Prevention (CDC) had confirmed the presence of a novel reassortment of Influenza A strain H1N1 from avian, swine, and human strains.<sup>(1,2,3)</sup> On 25 April 2009, The World Health Organization (WHO) declared the swine flu outbreak in North America a public health emergency of international concern. On 29 April 2009, the International Health Regulations emergency committee recommended a change from WHO pandemic influenza phase 4 to phase 5. This means that WHO views a pandemic as imminent.<sup>(3)</sup> WHO and the CDC have confirmed that the new swine flu virus is transmitted between humans.<sup>(4)</sup>

A novel swine origin influenza A virus (S-OIV) was identified as the cause of outbreaks of febrile respiratory infection ranging from self limited to severe illness. The symptoms including fever, cough, sore throat, rhinorrhea, myalgia, headache, chills, fatigue, vomiting or diarrhea until respiratory failure and death. It is likely that the number of confirmed cases underestimates the number of cases that have occurred. The CDC issued recommendations to clinicians, asking that they consider the diagnosis of S-OIV infection in patients with an acute febrile respiratory illness who met the following criteria: residence in an area where confirmed cases of human infection with S-OIV had been identified, a history of travel to such areas, or contact with ill persons from these areas in the seven days before the onset of illness. If S-OIV infection was suspected in a patient, clinicians were asked to obtain a nasopharyngeal swab from the patient and to contact their local health departments in order to facilitate initial testing of the specimen by reverse transcriptase polymerase chain reaction (RT-PCR) assay.<sup>(5)</sup>

The modes of transmission of influenza viruses in humans, including S-OIV, are not known but are thought to occur mainly through the dissemination of large droplets and possibly small particle droplet nuclei expelled when an infected person coughs.<sup>(6)</sup> There is also potential for transmission through contact with vomites that are contaminated with respiratory or gastrointestinal material.<sup>(7)</sup> Since many patients with S-OIV infection have had diarrhea, the potential for fecal viral shedding and subsequent fecal oral transmission should be considered and investigated. Until further data are available, all potential routes of transmission and sources of viral shedding should be considered.

The incubation period for S-OIV infection appears to range from 2 to 7 days. Most patient with S-OIV infection might shed virus from one day before the onset of symptoms through 5 to 7 days after the onset of symptoms or until symptoms resolve. In young children and in immunocompromised or severely ill patients, the infectious period might be longer.<sup>(8)</sup> The potential for persons with asymptomatic infection to be the sources of infection to others is unknown but should be investigated. Patients who are at highest risk for severe complications of S-OIV infection are children under the age of 5 years, adults 65 years of age or older, children and adults of any age with underlying chronic medical conditions, and pregnant woman.<sup>(9)</sup>

As of May 5, 2009, the CDC has recommended that given the severity of illness observed among some patients with S-OIV infection, therapy with neuraminidase inhibitors (oseltamivir and zanamivir) should be prioritized for hospitalized patients with suspected or confirmed S-OIV infection and for patients who are at high risk for complications from seasonal influenza. Genetic and phenotypic analyses indicated that S-OIV is susceptible to oseltamivir and zanamivir but resistant to the adamantanes.<sup>(10)</sup> Early 2008-2009 influenza season In the United States surveillance data suggest that human influenza A (H1N1) viruses were resistant to oseltamivir.<sup>(11,12)</sup> The food and drug administration (FDA) has issued an emergency use authorization that approves the use of oseltamivir to treat influenza in infants under the age of 1 year (treatment that is normally approved for those 1 year of age or older) and for chemoprophylaxis in infants older than 3 months of age (chemoprophylaxis that is normally approved for children 1 year of age or older).<sup>(13)</sup> The CDC has recommended that health care workers who provide direct care for patients with known or suspected S-OIV infection should observe contact and droplet precautions, including the use of gowns, gloves, eye protection, face masks, fit tested, and disposable N95 respirators.<sup>(14)</sup> There is no vaccine available right now to protect against swine flu. You can help prevent the spread of germs that cause respiratory illnesses like influenza by covering your nose and mouth with a tissue when you cough or sneeze, washing your hands often with soap and water, especially after you cough or sneeze, trying to avoid close contact with sick people and staying home from work or school if you are sick.

## REFERENCES

1. Brownstein JS, Freifeld CC, Madoff LC. Influenza A (H1N1) virus, 2009 – Online monitoring. *N Engl J Med* 2009; 360: 2155-6.
2. Baden LR, Drazen JM, Kritek PA, Curfman GD, Morrisey S, Champion EW. H1N1 influenza a disease information for health professionals (editorial). *N Engl J Med* 2009; 360: 2666-7.
3. Coker R. Swine flu. *BMJ* 2009; 338: b1791.
4. Komaroff AL. The sudden birth of H1N1 “swine” flu: what does the future hold? *J Watch* 2009.
5. Novel swine origin influenza A (H1N1) virus investigation team. Emergence of a novel swine origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009; 361: 1-10.
6. Blachere FM, Lindsley WG, Pearce TA, Stacey E, Anderson SE, Melanie Fisher M, Rashida Khakoo R, et al. Measurement of airborne influenza virus in a hospital emergency department. *Clin Infect Dis* 2009; 48: 438–40.
7. Boone SA, Gerba CP. The occurrence of influenza A virus on household and day care center fomites. *J Infect* 2005; 51: 103-9.
8. Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Steve Leach S, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol* 2008; 167: 775-85.

9. Centers for Disease Control and Prevention. 2008-09 Influenza prevention & control recommendations: influenza vaccination coverage levels. Available at: <http://www.cdc.gov/flu/professionals/acip/coveragelevels.htm>. Accessed May 7, 2009.
10. Centers for Disease Control and Prevention. Update: drug, susceptibility of swine origin influenza A (H1N1) viruses, April 2009. *Morb Mortal Wkly Rep* 2009; 58: 433-5.
11. Centers for Disease Control and Prevention. Update: influenza activity—United States, September 28, 2008 – April 4, 2009, and composition of the 2009-10 influenza vaccine. *Morb Mortal Wkly Rep* 2009; 58: 369-74.
12. Centers for Disease Control and Prevention. Update: infections with a swine origin influenza A (H1N1) virus United States and other countries, April 28, 2009. *Morb Mortal Wkly Rep* 2009; 58: 431-3.
13. Dharan NJ, Gubavera LV, Meyer JJ, Okomo-Adhiambo M, McClinton RC, Marshall SA, et al. Infections with oseltamivir resistant influenza A (H1N1) virus in the United States. *JAMA* 2009; 301: 1034-41.
14. Centers for Disease Control and Prevention. Interim recommendations for facemask and respirator use to reduce novel influenza A (H1N1) virus transmission. Available at: <http://www.cdc.gov/h1n1flu/masks.htm>. Accessed May 7, 2009.

# Tips of today

## Not an HIV cure, but encouraging new directions

The history of infectious diseases frequently includes people who were resistant to a pathogen. Such a phenomenon helped the Spanish, who had resistance to smallpox, in their conquest of South America, but not the Aztecs or the Incas, who had no resistance to smallpox and were decimated by the virus.<sup>(1)</sup> Microbial resistance involves adaptive (acquired) immunity (e.g., the HLA subtype) or innate (natural) immunity resulting from the genetic makeup of the host.<sup>(2)</sup>

With the human immunodeficiency virus (HIV) and its known destruction of the immune system, resistance to infection and disease was not initially expected. However, certain people — long-term survivors — have been infected with HIV for more than 10 years (and sometimes 30 years) and received no treatment yet remain without disease.<sup>(2)</sup> In addition, some people who have been exposed to HIV on many occasions do not become infected.<sup>(3)</sup> Both long-term survivors and those who have been exposed to HIV but remain seronegative offer a great opportunity to study the mechanisms of resistance to HIV infection and disease.

HIV enters cells primarily through attachment to the CD4 molecule and subsequent binding to coreceptors, of which two chemokine receptors, CCR5 and CXCR4, are the most common. R5 HIV types bind to CCR5; X4 HIV types use CXCR4.<sup>(4)</sup> People whose cells lack expression of the CCR5 gene are markedly resistant to HIV

infection despite multiple exposures to R5 HIV, which is the most prominent virus detected after transmission.<sup>(2,4)</sup> This mutation is found in 1 to 3% of the Western population. Among people with HIV who have only one copy of the wild-type CCR5 gene, progression to disease appears to be slower than among those who have two.<sup>(4,5)</sup> Obviously, such information is of value in efforts to develop new approaches for therapy.

In 2007, an estimated 2 million people died from AIDS and 2.7 million contracted the virus. Currently, infected patients can benefit from antiretroviral therapies that effectively delay or prevent progression to AIDS.<sup>(6)</sup> These people are in many cases healthy but continue to carry HIV. If the antiretroviral therapy is stopped, however, a rebound in virus production occurs that can lead to AIDS.<sup>7</sup> Moreover, the virus can develop resistance to antiretroviral therapy and reemerge in the host. Long-term treatment with these drugs is also costly and can cause toxicities that are often lifethreatening, including disorders of the cardiovascular system, pancreas, kidney, and liver.<sup>(8)</sup> And only a fraction of the people who are infected and need antiretroviral therapy are receiving therapy, particularly in countries with limited resources.

For these reasons, a search for better, longterm treatment for HIV infection continues. In this issue of the Journal, Hütter et al. highlight an innovative approach that could prove beneficial for the long-term control of HIV without

antiretroviral therapy.<sup>(9)</sup> These investigators selected an HLA-compatible person whose cells lacked expression of CCR5 as the donor for stem-cell transplantation from bone marrow to a patient with acute myelogenous leukemia who was infected with HIV. After two transplantations, there has been no recurrence of leukemia or detectible HIV in the bloodstream, as determined by analyses of viral RNA and cellular proviral DNA. In addition, after nearly 2 years, the CD4+ T cells in this patient have returned to a normal range, all carrying the donor's homozygote-deleted CCR5 gene.

Although some observers may consider the patient cured of HIV, this conclusion is premature. Much evidence has shown that HIV can be lurking in cells found in the lymph nodes and other parts of the body, including the brain, gut, liver, kidneys, and heart.<sup>(2)</sup> Eventually, the virus could induce disease in these tissues. Nevertheless, the results of this study and others<sup>(10)</sup> provide further encouragement for those examining approaches to treatment that reduce CCR5 expression in persons with HIV infection.

Bone marrow transplantations requiring ablation of host immune cells, as in this case, are risky; many patients die from the procedure. Autologous stem-cell administration after manipulation to eliminate CCR5<sup>(10)</sup> carries a similar risk. Consequently, an approach designed to modify HIV target cells without eliminating the host's own bone marrow could be helpful. An example would be to inject into the patient with HIV a CCR5-inactivating biochemical compound or genetic vector that would enter white cells and eventually make them resistant to HIV. A compound that could enter the stem cells of the patient would be the most effective for long-lasting protection. Development of such technologies could include injecting into the

bloodstream vectors carrying small interfering RNA (siRNA), antisense RNA, or ribozymes, all of which reduce CCR5 cellular expression.<sup>(10,11)</sup> Another approach could involve small, injectable, arginine-rich particles containing RNA that down-regulates CCR5 expression by interrupting normal gene splicing.<sup>(12)</sup> Although such techniques need to be perfected, they point in directions that may serve as stimuli for other innovative gene therapies to help those infected with HIV.

Certain issues, however, need to be appreciated. An X4 type of HIV that was detected at low levels in the blood of the patient studied by Hütter et al. could eventually emerge. This virus grows in cells lacking CCR5 expression.<sup>(2-4)</sup> Moreover, after transplantation, the patient's remaining CCR5-expressing macrophages — major cells for R5 virus infection — had no evidence of HIV. What protected these cells? Perhaps the CCR5 protein was present at low density on these cells, since the patient was heterozygous for the mutated allele. Or, since HIV-specific T cells were not prominent, innate immune responses could be suppressing both the R5 and X4 viruses.<sup>(13)</sup> One caveat is that people lacking the CCR5 gene can be more susceptible to serious effects from certain infections, such as West Nile virus.<sup>(14)</sup>

Therapeutic targeting of CCR5 could delay the onset of disease and reduce the cost and toxicity of antiretroviral therapy, as it has in this patient for nearly 2 years. This case places further emphasis on gene therapies and treatments directed at blocking the CCR5 receptor with decoy drugs. Maraviroc, a recently approved CCR5 inhibitor, has had some success,<sup>(15)</sup> but it must be administered along with other antiretroviral medications. It is probable that HIV resistance to maraviroc occurs because the CCR5 molecule remains expressed on cells. In

summary, the case reported by Hütter et al.<sup>(9)</sup> could pave the way for innovative approaches that provide long-lasting viral control with limited toxicities for persons with HIV infection.

## REFERENCES

1. Prescott WH. History of the conquest of Mexico and the history of the conquest of Peru. New York: Rowan & Littlefield, 2000.
2. Levy JA. HIV and the pathogenesis of AIDS. 3<sup>rd</sup> ed. Washington, DC: ASM Press, 2007.
3. Shearer GM, Clerici M. Protective immunity against HIV infection: has nature done the experiment for us? *Immunol Today* 1996; 17: 21-4.
4. Berger EA, Murphy PM, Farber JM. Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism, and disease. *Annu Rev Immunol* 1999; 17: 657-700.
5. de Roda Husman AM, Koot M, Cornelissen M, Keet IP, Brouwer M, Broersen SM, et al. Association between CCR5 genotype and the clinical course of HIV infection. *Ann Intern Med* 1997; 127: 882-90.
6. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; 338: 853-60.
7. Jubault V, Burgard M, Le Corfec E, Costagliola D, Rouzioux C, Viard JP. High rebound of plasma and cellular HIV load after discontinuation of triple combination therapy. *AIDS* 1998; 12: 2358-9.
8. Nolan D, Reiss P, Mallal S. Adverse effects of antiretroviral therapy for HIV infection: a review of selected topics. *Expert Opin Drug Saf* 2005; 4: 201-18.
9. Hütter G, Nowak D, Mossner M, Ganepola S, Müssig A, Allers K, et al. Long-term control of HIV by CCR5 delta32/delta32 stem-cell transplantation. *N Engl J Med* 2009; 360: 692-8.
10. Cohen J. Building an HIV-proof immune system. *Science* 2007; 317: 612-4.
11. An DS, Donahue RE, Kamata M, Poon B, Metzger M, Mao SH, et al. Stable reduction of CCR5 by RNAi through hematopoietic stem cell transplant in non-human primates. *Proc Natl Acad Sci U S A* 2007; 104: 13110-5.
12. Moulton HM, Nelson MH, Hatlevig SA, Reddy MT, Iversen PL. Cellular uptake of antisense morpholino oligomers conjugated to arginine-rich peptides. *Bioconjug Chem* 2004; 15: 290-9.
13. Levy JA. The importance of the innate immune system in controlling HIV infection and disease. *Trends Immunol* 2001; 22: 312-6.
14. Glass WG, McDermott DH, Lim JK, Lekhong S, Yu SF, Frank WA, et al. CCR5 deficiency increases risk of symptomatic West Nile virus infection. *J Exp Med* 2006; 203: 35-40.
15. Deeks SG. Challenges of developing R5 inhibitors in antiretroviral naive HIV-infected patients. *Lancet* 2006; 367: 711-3.