

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Shinde V, Bridges CB, Uyeki TM, et al. Triple-reassortant swine influenza A (H1) in humans in the United States, 2005–2009. *N Engl J Med* 2009;360:2616-25. DOI: 10.1056/NEJMoa0903812.

(PDF updated May 22, 2009.)

Supplementary Web Materials

A Brief Clinical Comparison of Human Cases due to Infection with Triple Reassortant Swine Influenza A (H1) Viruses versus Classic Swine Influenza A (H1) Viruses

Most human infections with triple reassortant swine influenza A (H1) viruses in this case series had an uncomplicated illness which was clinically indistinguishable from illness caused by other respiratory pathogens. In the largest systematic review of human infection with classic swine influenza A (H1) viruses, Myers et al summarized the clinical and epidemiologic characteristics of 50 cases in the published literature, including 37 civilians and 13 military personnel.¹ Triple reassortant swine influenza A (H1) virus infections described in this report differed from those caused by classic swine influenza A (H1) among the civilians described by Myers in several important ways: triple reassortant variants infected cases tended to be younger (median age: 10 vs. 24.5 years) and were more likely to have a known chronic medical condition (36 % vs. 19%) and known swine exposures (90% vs. 61%).¹ No fatalities occurred in our case series compared to a case fatality ratio of 17% described by Myers;¹ however, these findings should be interpreted with great caution given the high likelihood of case ascertainment bias with severe and fatal cases and because of significant genetic differences between classic swine influenza A (H1) viruses and triple reassortant swine influenza A (H1) viruses.

Rapid Point-of-Care Influenza Testing for the Diagnosis of Infection with Triple Reassortant Swine influenza A (H1) Viruses

Commercially available rapid influenza tests, which were used as the *initial* means of virologic diagnosis in two cases, were positive for influenza A in 7 of 8 persons tested by this method.

Rapid influenza tests cannot distinguish between infection with triple reassortant swine influenza A (H1) viruses, seasonal influenza viruses, and the newly emerged swine-origin influenza A (H1) viruses. Rapid influenza tests have suboptimal sensitivity to detect seasonal influenza virus infection.² Additionally, rapid influenza tests have low positive predictive value during periods of low community influenza virus activity^{2,3} Sensitivity of rapid influenza tests to detect triple reassortant swine influenza A (H1) and swine-origin influenza A (H1) variants is unknown.

General Recommendations for Animal and Public Health Agencies

This report underscores the need for close communication and collaboration between human and animal health for ongoing surveillance, investigation, research, prevention and control efforts.

During interpandemic periods, joint public health and animal health investigation of every human case of triple reassortant swine influenza A (H1) virus infection should be conducted promptly to determine the extent of community illness and the need for prompt control measures.

The main objectives of such joint investigations are to identify exposures and to define the spectrum of clinical illness; to assess whether human-to-human transmission has occurred; to track and control concomitant outbreaks in pig herds; and to facilitate joint laboratory investigations to characterize virus evolution, determine antiviral resistance patterns, and make

correlations with epidemiologic data. Ultimately such joint actions may facilitate early containment efforts to preempt the spread of animal influenza viruses with pandemic potential among humans.

During interpandemic periods, there is a need to prevent human co-infection with human and swine influenza viruses to prevent the further generation of novel reassortant influenza viruses in humans; therefore, seasonal influenza vaccination should be encouraged among pig farm workers and others who have sustained contact with pigs, either for recreational or occupational purposes. Persons with such exposures may be sentinels for early zoonotic transmission of novel triple reassortant swine influenza A (H1) viruses to humans. Further understanding of risk factors associated with transmission of influenza viruses from pigs to human and humans to pigs will help inform prevention efforts targeted towards persons with pig exposures and aid development of public health prevention messaging. Such messages should include guidance about use of appropriate personal protective equipment among those with occupational pig contact, and avoidance of exposure to pigs showing signs of respiratory illness among those with recreational contact.

In June 2007, the Council and State and Territorial Epidemiologist (CSTE) added human infection with novel influenza A viruses, including swine and avian influenza viruses, to the list of nationally notifiable diseases reportable to the National Notifiable Diseases Surveillance System (NNDSS). Novel influenza A viruses are those identified in humans that differ from currently circulating human influenza A H1 and H3 viruses, and to which humans may have little or no preexisting immunity. The goal of novel surveillance for novel influenza A viruses and

reporting is to rapidly identify and respond to influenza viruses which may have the potential to cause a human pandemic.

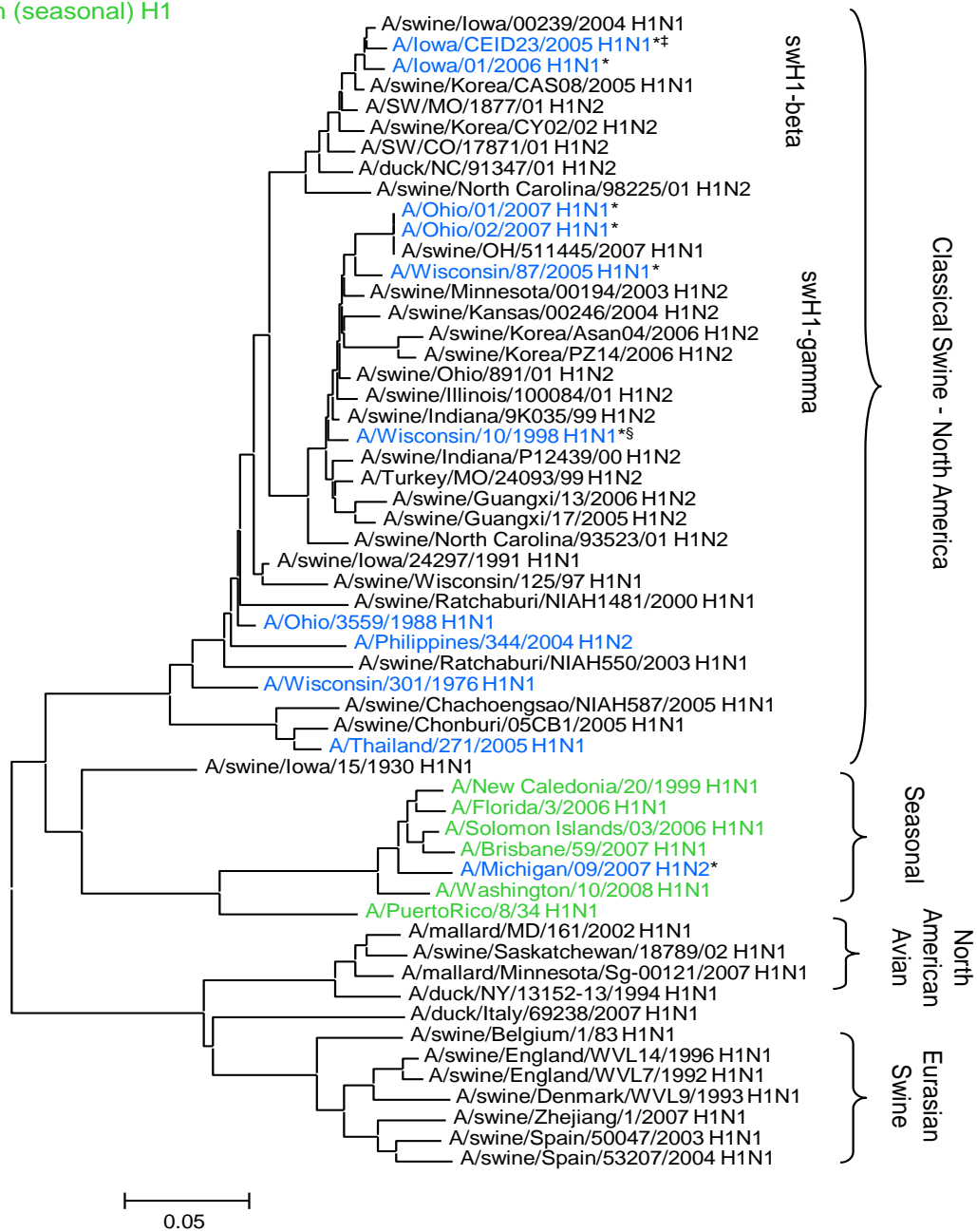
For the most recent updated recommendations, please visit: www.cdc.gov/flu

References:

1. Myers KP, Olsen CW, Gray GC. Cases of swine influenza in humans: a review of the literature. *Clin Infect Dis* 2007;44(8):1084-8.
2. Uyeki TM. Influenza diagnosis and treatment in children: a review of studies on clinically useful tests and antiviral treatment for influenza. *Pediatr Infect Dis J* 2003;22(2):164-77.
3. Grijalva CG, Poehling KA, Edwards KM, et al. Accuracy and interpretation of rapid influenza tests in children. *Pediatrics* 2007;119(1):e6-11.
4. Gray GC, McCarthy T, Capuano AW, Setterquist SF, Olsen CW, Alavanja MC. Swine workers and swine influenza virus infections. *Emerg Infect Dis* 2007;13(12):1871-8.
5. Cooper L, Olsen C, Xu X, Klimov A, Cox N, Subbarao K. Molecular characterization of human influenza A viruses bearing swine-like hemagglutinin genes [abstract]. In: Program and abstracts of the Virus Evolution Workshop (Ardmore, OK). Ardmore: Virus Evolution Workgroup, Samuel Roberts Noble Foundation, 1999. Available at: <http://www.noble.org/VirusEvolution/abstracts/Cooperpost.htm>

| Supplementary Table 1. GenBank Accession Numbers for 5 Triple Reassortant Swine Influenza A (H1) Viruses Isolated from 5 Human Cases | |
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| GenBank Accession Numbers | Organism Name |
| FJ986618 | Influenza A virus (A/Iowa/01/2006 (H1N1)) |
| FJ986619 | Influenza A virus (A/Wisconsin/87/2005 (H1N1)) |
| FJ986620 | Influenza A virus (A/Ohio/01/2007 (H1N1)) |
| FJ986621 | Influenza A virus (A/Ohio/02/2007 (H1N1)) |
| FJ986622 | Influenza A virus (A/Michigan/09/2007 (H1N2)) |

Supplementary Figure 1.
The Phylogenetic Tree of the Hemagglutinin (HA) Gene Segment of Influenza A (H1) Viruses†
Human cases of swine H1 (* triple reassortants)
Human (seasonal) H1



† Phylogenetic tree was inferred using maximum likelihood available in the GARLI 0.96b7 package and visualized in TreeView, version 1.6.6.

‡ See reference 4.

§ See reference 5.