HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2018 April 24.

Published in final edited form as:

Clin Infect Dis. 2013 July ; 57(Suppl 1): S1–S3. doi:10.1093/cid/cit324.

The Emergence of Influenza A (H3N2)v Virus: What We Learned From the First Wave

Lyn Finelli[1] and **David L. Swerdlow**[2]

[1]Influenza Division, National Center for Immunization and Respiratory Diseases, Atlanta, Georgia

[2]National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Keywords

influenza; modeling; variant influenza; influenza A (H3N2)v; epidemiology

Swine influenza was first recognized clinically in pigs at the time of the 1918 Spanish Flu pandemic [1]. From 1918 to 1998, swine influenza was almost exclusively caused by the influenza A (H1N1) classic swine virus; this virus circulated in pigs with little genetic drift [1–3] for more than 70 years. In 1998, severe influenza-like illness (ILI) was observed in pigs in the United States. The causative agent was determined to be a reassortant influenza A (H3N2) virus with human HA, NA, and PB1 gene segments [1, 3], likely transmitted from people to pigs at some earlier point. The increase in genetic diversity of the virus in the US swine population and the inclusion of human influenza genes in swine viruses has important implications for human health, including the enhanced potential for virus adaptation and cross-species transmissibility. Currently circulating subtypes of influenza A viruses in swine include (H1N1), (H1N2), and (H3N2); all have caused disease in humans. Results of diagnostic testing of more than 6000 specimens from a large midwestern academic reference laboratory from 2009 to 2012 indicate an increase in the frequency of influenza A (H3N2) virus infection in swine in 2011, with prevalence reaching approximately 26% [4]. Following the 2009 H1N1 pandemic in humans, these influenza A(H3N2) viruses experienced a notable genetic reassortment. Phylogenetic analysis indicates that the influenza A (H3N2) virus acquired the M, or matrix, gene from the 2009 pandemic influenza A (H1N1) virus (A(H1N1) pdm09) and that the proportion of influenza A (H3N2) viruses with the A(H1N1)pdm09 M gene became more prevalent. In 2009, <5% of swine influenza A (H3N2) viruses contained the A(H1N1)pdm09 M gene, and in 2011 more than half of all swine influenza A H3N2 viruses contained the A(H1N1)pdm09 M gene [4]. It appears that both symptomatic and asymptomatic pigs can shed virus and transmit infection

Correspondence: David L. Swerdlow, MD, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Mailstop A-27, 1600 Clifton Rd, NE, Atlanta, GA 30333 (dswerdlow@cdc.gov).

Supplement sponsorship. This article was published as part of a supplement entitled “The Emergence of Influenza A (H3N2)v Virus: What We Learned From the First Wave, July 2011–April 2012,” sponsored by the Centers for Disease Control and Prevention.

Potential conflicts of interest. All authors: No reported conflicts.
All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

to other pigs and humans [5, 6]. In a recent study by Bowman et al, 83% of pigs tested at agricultural fairs from which influenza was recovered did not show signs of ILI [7].

From December 2005 to June 2011, 21 human cases of swine influenza A virus infection (henceforth known as variant infection, abbreviated influenza subtype lowercase v [8]) were reported to the Centers for Disease Control and Prevention by state and local health departments. Twelve were H1N1v virus infections, 1 was an H1N2v virus infection, and 8 were H3N2v virus infections. All were triple-reassortant swine-origin viruses with genes from human, avian, and swine influenza viruses. From 2005 to 2008, 1 to 5 cases were identified every year. However, in recent years identifications have increased for the following reasons: the of adoption of novel influenza A virus infection as a reportable disease in the United States in 2007, the availability of improved influenza diagnostic tests at state health departments, and a greater awareness of the pandemic potential of swine influenza after the 2009 H1N1 pandemic. Most of these cases had direct swine contact, were children and adolescents, and recovered from their illness after a few days. Only 3 of these 21 infections were transmitted from person to person (CDC, unpublished data).

In July 2011, the emergence of H3N2v with the A(H1N1) pdm09 M gene in swine was signaled by a dramatic increase in the number of detections of H3N2v virus in humans. It was suggested that the M segment of the A(H1N1)pdm09 virus contributed to the increased transmissibility of the A(H1N1) pdm09 virus during the 2009 pandemic [9–11]. Although it is still uncertain whether acquisition of the M gene from A (H1N1)pdm09 virus enhances the ability of H3N2v virus to spread in pigs and infect humans [12], over a 5-month period (July 2011–November 2011) several outbreaks with 12 confirmed cases and numerous probable cases were observed. The first case in July occurred in a severely disabled homebound child aged <5 years who had no swine contact but who was cared for by healthcare worker whose children showed swine at an agricultural event [13]. The next 6 cases occurred during August and September and were associated with exposure at agricultural fairs or farms [14, 15]. Five confirmed cases and additional cases of ILI occurred in November when there were 2 outbreaks with no identified link to swine in a childcare setting [8, 15, 16]. Human-to-human transmission, which likely occurred during these 2 outbreaks, may have happened because the outbreaks occurred during the winter when the temperature and absolute humidity are more amenable for influenza transmission [17].

The increasing number of cases of this novel virus, including several outbreaks, raised concern that ongoing transmission and widespread outbreaks could occur. In early December 2011, in an effort to learn as much as possible about the epidemiology of this virus, we engaged in a number of epidemiologic and modeling studies. This supplement describes these studies.

The first study by Epperson et al [18] describes the epidemiology and laboratory aspects of the first 13 cases of H3N2v that were identified and defines the epidemiologic parameters used in the subsequent modeling studies. For example, the observation that almost all cases were in children was important when determining likely age-specific susceptibility.

In the second study, Biggerstaff et al [19] used the number of reported cases to estimate the actual number of cases that occurred given that most persons with ILI do not seek medical care, many doctors do not perform laboratory testing of patients with ILI, and most laboratories would not have been able to detect the virus because polymerase chain reaction testing for this virus was only available at a few laboratories. The authors estimated that only about 1 in 200 cases was reported, indicating that many more people were infected with H3N2v than were recognized.

For the third study, Wong et al [20] sought to determine how transmissible the virus was from pigs to humans. They developed a SEIR (susceptible, exposed, infectious, recovered) compartment model to estimate the probability of H3N2v transmission from pigs to humans. They also determined the estimated probability of swine-to-human H3N2v virus transmission per minute spent in the swine barn and the likely number of swine-acquired H3N2v virus infections that occurred. The researchers also determined that the attack rate was higher among persons aged <20 years than among persons aged ≥ 20 years.

In the fourth study, Gambhir et al [21] used a mathematical model of an influenza outbreak to illustrate how various contributory factors lead to the age distribution of cases. The model includes both zoonotic and human-human routes of transmission and shows how the case distribution changes according to the relative importance of these routes. The emergence of influenza A (H3N2)v virus is an example of how the case distribution is affected by prior protection in humans, swine exposure, and human-human contact.

It was very fortunate that the epidemiologic and modeling studies were done during the first wave of cases in 2011 and early 2012 because the United States experienced a much larger outbreak in the summer of 2012, with 306 confirmed cases in 10 states [22] associated with 37 fairs (K. Wong, personal communication). To date, the findings from the epidemiologic and modeling studies of the 2011 cases have held true in 2012. Most of the 2012 cases have been in children, most have been associated with swine exposure, and there has been very little, if any, human-to-human transmission. If the initial modeling studies had not been performed, concerns at the onset of this large outbreak could have led to the implementation of unnecessary and costly control measures. This supplement summarizes what we learned during the 2011 “first wave” of H3N2v cases.

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