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Evaluation of Rapid Influenza Diagnostic Tests for Influenza A (H3N2)v Virus and Updated Case Count — United States, 2012

Previous reports have described cases of influenza A (H3N2) variant (H3N2v) virus* infection with the influenza A (H1N1)pdm09 M gene detected in the United States during July 2011–July 2012 (*1*–*3*). This report provides 1) an update on the number of reported cases of H3N2v infections from July 12 to August 9, 2012, in the United States, 2) an updated results interpretation for the CDC Flu Real-Time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) Dx Panel for A(H3N2)v for public health laboratories, and 3) an evaluation of rapid influenza diagnostic tests for the detection of H3N2v viruses.

From July 12 to August 9, a total of 153 cases of H3N2v infections were reported in Indiana (120 cases), Ohio (31), Hawaii (one), and Illinois (one). Of the 138 reported cases for which demographic information was available, 128 (93%) occurred in persons aged <18 years, and 10 (7%) occurred in adults. The median age of patients was 7 years. Two persons were hospitalized as a result of their illness; no deaths occurred. The patient in Hawaii was exposed to swine on the job, and no additional cases were found in Hawaii. The 152 patients reported from Illinois, Indiana, and Ohio resided in 27 counties; all reported direct or indirect exposure to swine, the majority at agricultural fairs.

H3N2v viruses can be detected by qualified U.S. public health laboratories using the CDC Flu rRT-PCR Dx Panel. Initially, if specimens tested positive for influenza A, H3, and pandemic influenza A markers and negative for H1 and pandemic H1 markers, they were reported as inconclusive until confirmed as influenza A (H3N2)v at the CDC laboratory (*1*). On August 7, CDC updated the results interpretation of the CDC Flu rRT-PCR Dx Panel for H3N2v for public health laboratories. Specimens with these findings may now be reported as "presumptive positive for influenza A (H3N2)v virus" and, for the ongoing investigations, cases with presumptive-positive test results at the state or local public health laboratory will now be classified as confirmed, as are those cases confirmed at CDC.

The CDC Flu rRT-PCR Dx Panel is available in public health laboratories but is not a point-of-care test available to clinicians. Rapid influenza diagnostic tests (RIDTs) frequently are used for the diagnosis of influenza infection in clinical settings, and the recent outbreaks of H3N2v virus (*2*,*3*) have highlighted the need to evaluate commercially available, widely used RIDTs for their ability to detect H3N2v viruses. As an initial assessment, CDC conducted an evaluation of seven FDA-cleared RIDTs with seven H3N2v viruses (Table 1). Five 10-fold dilutions in physiological saline of each virus grown in Madin-Darby Canine Kidney (MDCK) cells were tested with all of the RIDTs in duplicate. Tests with BinaxNOW, Directigen, FluAlert, QuickVue, and Sofia were performed according to the procedures in the kit inserts for nasal washes or aspirates. Xpect tests were performed according to their procedure for nasal washes and swab specimens transported in liquid media. For the Veritor test, 100 μL of diluted specimen was added directly to the reagent tube. Positive and negative controls contained in each RIDT were run before testing the viruses in the study to verify performance of each assay lot, with the exception of FluAlert, which does not provide controls.

Only four of seven RIDTs in this study (Directigen, Sofia, Veritor, and Xpect) detected all influenza A (H3N2)v viruses (Table 2). BinaxNOW detected five of seven, and QuickVue detected three of seven. FluAlert detected only one of seven.

* Influenza viruses that circulate in swine are called swine influenza viruses when isolated from swine, but are called variant viruses when isolated from humans. A variant virus (human isolate) might or might not have the M gene from the influenza A (H1N1)pdm09 virus, along with other genetic changes. Seasonal influenza A (H3N2) viruses that circulate worldwide in the human population have significant antigenic and genetic differences from influenza A (H3N2) viruses circulating in swine. Additional information is available at http://www.who.int/influenza/gisrs_laboratory/terminology_ah3n2v/en/index.html.

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TABLE 1. Evaluation of seven FDA-cleared RIDTs for the ability to detect H3N2v viral antigens — CDC, United States, 2012

RIDT (manufacturer)	Abbreviated name	Approved specimens*	Analyzer for interpretation
BinaxNOW Influenza A&B (Alere)	BinaxNOW	NP swab Nasal wash/aspirate/swab	No
Directigen EZ Flu A+B (Becton-Dickinson)	Directigen	NP wash/aspirate/swab Throat swab	No
SAS FluAlert A&B (SA Scientific)	FluAlert	Nasal wash/aspirate	No
QuickVue Influenza A+B Test (Quidel)	QuickVue	NP swab Nasal wash/aspirate/swab	No
Sofia Influenza A+B (Quidel)	Sofia	NP aspirate/swab/wash Nasal wash	Required
BD Veritor System for Rapid Detection of Flu A+B (Becton Dickinson)	Veritor	NP swab/nasal swab	Required
Xpect Flu A&B (Remel)	Xpect	Nasal wash/swab Throat swab	No

Abbreviations: FDA = Food and Drug Administration; RIDTs = rapid influenza diagnostic tests; NP = nasopharyngeal.
* Approved respiratory specimens according to manufacturer's package insert. Test performance has only been demonstrated for these specimen types.

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Editorial Note

The H3N2v viruses identified since July 12, 2012, are similar to the 13 H3N2v viruses identified during July 2011–April 2012 (*1*); all sequenced viruses had the M gene from the influenza A (H1N1)pdm09 virus. As of August 9, all H3N2v patients for whom contact information was available reported contact with swine or attended an agricultural fair where swine were present. During 2011, evidence of limited human-to-human transmission of H3N2v was observed in some cases, and human-to-human transmission might occur in the current outbreak. Enhanced surveillance for influenza H3N2v virus infection is indicated, especially in regions and states with confirmed H3N2v cases. The initial goal of enhanced surveillance is to detect the source and geographic spread of these viruses, but once cases are detected, particular emphasis should be placed on detection of ongoing transmission within the community through investigation of close contacts of patients with confirmed cases. In addition, surveillance in hospitals will be important to determine whether severe illnesses are occurring as a result of H3N2v infections.

The predominance of children among persons with confirmed H3N2v infections is consistent with serologic studies that found children less likely to have cross-protective antibodies than adults (*4*). However, confirmation of cases in adults highlights the fact that persons of any age can be infected. Persons who are at increased risk for influenza complications (e.g., those with underlying chronic medical conditions, or who are pregnant, or aged <5 or ≥65 years, or who have weakened immune systems [*5*]) should avoid exposure to pigs and swine barns this summer, particularly if ill swine have been identified. Persons with increased risk for complications who develop influenza-like illness should see their health-care provider promptly to determine whether treatment with antiviral medications is warranted. Clinicians should consider antiviral treatment with oral oseltamivir or inhaled zanamivir in patients with suspected or confirmed H3N2v infection. Antiviral treatment is most effective when started as soon as possible after influenza illness onset (*5*).

TABLE 2. Number of 10-fold virus dilutions (maximum = five) detected by seven FDA-cleared RIDTs, by H3N2v strain designation — CDC, United States, 2012

			RIDT						
Subtype	Strain designation	$TCID_{50}$/mL	BinaxNOW	Directigen	FluAlert	QuickVue	Sofia	Veritor	Xpect
H3N2v	A/Kansas/13/2009	$10^{4.5}$	1	4	U	U	2	4	4
H3N2v	A/Pennsylvania/14/2010	$10^{4.5}$	2	4	U	2	2	4	3
H3N2v	A/Minnesota/11/2010	$10^{4.5}$	U	3	U	U	3	3	2
H3N2v	A/Indiana/08/2011	$10^{6.0}$	1	3	U	U	2	3	2
H3N2v	A/Indiana/10/2011	$10^{4.0}$	U	3	U	U	2	4	2
H3N2v	A/West Virginia/06/2011	$10^{6.0}$	2	3	U	2	4	4	2
H3N2v	A/Iowa/07/2011	$10^{4.5}$	2	4	1	1	3	4	3

Abbreviations: FDA = Food and Drug Administration; $TCID_{50}$/mL = infectious titer of stock virus; RIDT = rapid influenza diagnostic test; U = undetected at any concentration tested.

What is known on this topic?

From July 2011 to April 2012, 13 cases of influenza A (H3N2)v virus infection in humans were reported. In July 2012, four new cases were reported from Indiana, all in persons who had contact with swine at a county fair.

What is added by this report?

From July 12 to August 9, 2012, a total of 153 cases of H3N2v virus infection were reported in four states (Hawaii, Illinois, Indiana, and Ohio); all patients for whom such information was available reported direct or indirect contact with swine. Testing of the sensitivity of rapid influenza diagnostic tests (RIDTs) for detection of influenza A (H3N2)v virus produced mixed results regarding the detection capabilities of the individual tests.

What are the implications for public health?

With the substantial increase in the number of cases of H3N2v virus infection during July–August, enhanced surveillance for detection of these cases is indicated. Health-care workers also should note that the sensitivity of RIDTs to detect H3N2v virus infection varies, and a negative RIDT should not be considered evidence of lack of infection with influenza A (H3N2)v.

The sensitivity of RIDTs to detect seasonal influenza viruses compared with virus isolation or rRT-PCR varies among commercial kits but has been shown to be low in some reports (*6*–*9*). In this evaluation of seven RIDTs, the ability to detect H3N2v virus varied substantially among the tests. This evaluation emphasizes the fact that a negative RIDT result should not be considered as conclusive evidence of lack of infection with influenza A (H3N2)v. More data are needed on the clinical performance of all RIDTs in detecting H3N2v virus in various respiratory specimens. Results from RIDTs, both positive and negative, always should be interpreted in the broader context of the circulating influenza strains present in the area, level of clinical suspicion, severity of illness, and risk for complications in a patient with suspected infection. Clinicians should minimize the occurrence of false RIDT results by strictly following the manufacturer's instructions, collecting specimens soon after onset of influenza-like illness (ideally within the first 72 hours), and confirming RIDT results by sending a specimen to a public health laboratory (*10*). Additional CDC guidance on interpretation of RIDTs for testing of patients with suspected H3N2v infection is available at http://www.cdc.gov/flu/swineflu/h3n2v-testing.htm.

Specimens from patients with influenza-like illness in whom H3N2v is suspected should be sent to public health laboratories for additional diagnostic testing. Public health laboratories are requested to continue to contact the CDC Influenza Division immediately when they identify these viruses to coordinate transfer of the specimen to CDC for additional testing.

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