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Estimates of the number of human infections with influenza A (H3N2) variant virus, United States, August 2011–April 2012

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Abstract

Background—Thirteen human infections with an influenza A (H3N2)variant (H3N2v) virus containing a combination of gene segments not previously associated with human illness were identified in the United States from August 2011 to April 2012. Because laboratory confirmation of influenza virus infection is only performed for a minority of those ill and routine clinical tests may not identify H3N2v virus, the count of laboratory-confirmed H3N2v influenza virus infections underestimates the true burden of illness.

Methods—To account for this under-ascertainment, we adapted a multiplier model created at the beginning of the influenza A(H1N1)pdm09 pandemic to estimate the true burden of H3N2v illness. Data to inform each of these parameters came from the literature and from special projects conducted during the 2009 H1N1 pandemic and the 2010–11 influenza season. The multipliers were calculated as the simple inverses of the proportions at each step, and we accounted for variability and uncertainty in model parameters by using a probabilistic or Monte Carlo approach

Results—Using this approach, we estimate that the median multiplier for children was 200 (90% range 115–369) and for adults was 255 (90% range 152–479) and that 2,055 (90% range 1,187–3,800) H3N2v infections may have occurred from August 2011 to April 2012, suggesting that the new virus was more widespread than previously thought.

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Conclusions—Illness from this variant influenza virus was more frequent than previously thought. Continued surveillance is needed to ensure timely detection and response to H3N2v virus infections.

Keywords

Influenza; influenza A (H3N2)variant; prevalence

Introduction

From August 2011 to April 2012, CDC confirmed 13 human infections with influenza A (H3N2)variant viruses (H3N2v), which contained the matrix (M) gene from the influenza A (H1N1)pdm09 virus. [1-3]. Influenza viruses that circulate in swine are called swine influenza viruses when isolated from swine but are called variant viruses when isolated from humans [2]. Twelve of the 13 reported cases occurred in children, most <10 years old, and three of the 13 cases were hospitalized for influenza. A majority of the cases were identified from respiratory specimens voluntarily submitted by healthcare providers to state public health laboratories, where the CDC Flu Real-Time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) Dx Panel was performed. Specimens with results suggesting infection with H3N2v virus were forwarded to the Influenza Division at CDC for characterization and confirmatory testing.

While U.S. influenza surveillance efforts successfully identified the H3N2v cases, laboratory-confirmed H3N2v cases likely represent an undercount for several reasons. Among these, less than half of all people with influenza-like illness (ILI) seek health care; when health care is sought, providers test few patients for influenza; point of care rapid influenza antigen diagnostic tests have low test sensitivity and are not able to differentiate H3N2v virus from the currently circulating seasonal influenza A virus strains, and a majority of healthcare providers do not forward respiratory specimens to their public health laboratory, thereby preventing further characterization and confirmation [4-7]. Therefore, the true number of H3N2v virus infections is likely much higher than reported. To better estimate the true number of illnesses due to human infection with H3N2v virus, we adapted a model previously created at the beginning of the influenza A(H1N1)pdm09 (2009 H1N1) pandemic to adjust for sources of under-ascertainment [8].

Methods

The methodology to correct for the under-ascertainment of influenza cases is described elsewhere [8]. To account for the challenges in confirming H3N2v virus infection in the United States, we utilized a probabilistic multiplier model that corrects for the under-ascertainment of influenza at each of the following steps: the proportion of persons with ILI who seek medical care for their illness (parameter A), the proportion of those seeking medical care that visit healthcare providers in the United States who are more likely to participate in voluntary influenza surveillance programs (including viral surveillance) (parameter B), the proportion of persons who have a respiratory specimen collected for influenza testing (parameter C), the proportion of the respiratory specimens submitted to a

public health laboratory (parameter D), the proportion of state laboratory rRT-PCR tests that would detect H3N2v virus infection from H3N2v-positive respiratory specimens (parameter E), and the proportion of specimens with results suggestive of H3N2v forwarded to CDC for further characterization and confirmatory tests (parameter F). By incorporating the probability of occurrence of each of these steps, we were able to estimate how many additional illnesses occurred in the United States for each H3N2v case detected by the U.S. influenza surveillance system.

Data to inform each of these parameters came from the literature and from special projects conducted during the 2009 H1N1 pandemic and the 2010–11 influenza season (Table 1). To estimate the proportion of persons with ILI who visited healthcare providers and had an influenza respiratory specimen collected (parameters A and C), we analyzed survey data from the Behavioral Risk Factor Surveillance System (BRFSS) influenza-like illness (ILI) module from the 2009–10 and 2010–11 influenza seasons [4]. To estimate the proportion of persons who visited healthcare providers participating in voluntary influenza surveillance programs (e.g., a U.S. Outpatient Influenza-Like Illness Surveillance Network [ILINet] physician, a hospital, or a healthcare site conducting a special study of influenza) (parameter B), we used ILINet catchment as a proxy [9]. To calculate this measure, the number of ILI visits from ILINet for July 23, 2011, to April 1, 2012, (the period in which the H3N2v case patients had illness onset) were divided by the median number of national outpatient ILI visits for the same weeks in 2005–2008 as reported by SDI (SDI Health, LLC, Plymouth Meeting, PA, USA), a claims data provider offering analytic products comprised of aggregated outpatient claims data (data not shown). The proportion of respiratory specimens collected by healthcare providers that were forwarded to the state or local public health laboratory for RT-PCR (parameter D) was based on input from experienced influenza surveillance coordinators. Published literature indicates that RT-PCR test sensitivity for influenza is high (parameter E) [10]. Finally, since novel influenza A virus infections are nationally notifiable, we assumed that all respiratory isolates found to have suspected novel influenza viruses would routinely be forwarded from public health laboratories to CDC (parameter F) [11, 12].

The multipliers were calculated as the simple inverses of the proportions at each step. We accounted for variability and uncertainty in model parameters by using a probabilistic or Monte Carlo approach. For each parameter included in the model, we used uniform probability distributions that covered a range of minimum to maximum values, from which the model randomly sampled 1,000 iterations. We generated median and upper and lower 90% values for the number of total cases of illness. Because care seeking for ILI varies based on the age of the patient, we stratified the model between pediatric (<18 years old) and adult (≥18 years old) cases [4].

Results

Using this approach, from August 2011 to April 2012, we estimate the median multiplier was 200 (115–369) for pediatric H3N2v cases and 255 (152–479) for adult H3N2v cases (Table 1). That is every reported pediatric H3N2v case may represent 200 total cases, with a 90% probability range of 115–369, and every reported adult H3N2v case may represent 255

total cases, with a 90% probability range of 152–479. Because three of the 13 reported cases were identified during investigations of other confirmed cases and would be more likely to be identified and not subject to the parameters developed here, they were excluded from the total number of observed cases, leaving 10 reported cases of H3N2v (Table 2). Using 10 cases (nine pediatric and one adult), the median number of estimated cases of H3N2v was 2,055 (90% range 1,187–3,800).

Conclusions

We describe the first approach to account for the under ascertainment of illness caused by H3N2v virus infection by adapting the parameters of a previously published model. For the period from August 2011 to April 2012, we estimate that 1 in 200 pediatric H3N2v cases and 1 in 255 adult H3N2v cases were detected, indicating that the 10 independently identified cases may represent approximately 2,000 H3N2v illnesses.

This analysis suggests that only a minority of infections from H3N2v virus were detected by influenza surveillance efforts, a finding consistent with observations made from previous efforts to estimate the burden of influenza in the United States [8, 13]. Consequently, infections from H3N2v virus may have been more widespread than previously thought, and approximately 2,000 illnesses may have occurred during this period. While this value represents a small fraction of the illnesses that normally occur in the course of an influenza season or pandemic, continued surveillance and investigation of this virus is warranted[13-16]. H3N2v has been identified with greater frequency than other variant viruses (e.g. H1N1v), and cases detected in late 2011 were identified with no reported swine exposure, suggesting that limited person-to-person transmission of H3N2v may have occurred [2]. The same H3N2 virus has been reported in pigs in the United States; however, the prevalence of the virus among swine populations in the U.S. is uncertain [2]. Enhanced monitoring and rapid investigation of any H3N2v case, even when occurring outside of the traditional influenza season, will continue to provide important epidemiological and virologic data for evaluating the potential impact of this novel virus [17].

Recent reports of more widespread transmission of H3N2v viruses in humans with swine or agricultural fair exposure during the summer of 2012 highlights the need for increased awareness of reporting biases when relying on counts of laboratory confirmed H3N2v virus infections [7, 18]. As described in this report, these counts will underestimate the true burden of illness. However, many of these recent H3N2v cases were identified because of enhanced surveillance for variant influenza virus infection. These enhancements included multiple state and CDC investigations to identify and confirm H3N2v virus among ill fair attendees, calls to the public to report respiratory illness among those with swine or agricultural fair exposure, and increased messaging to clinicians requesting more frequent influenza testing among those with swine or agricultural fair exposure[7]. Since methods to identify the recent H3N2v cases were enhanced compared to the cases described in this report, the multiplier developed here would overestimate the true number of H3N2v cases that occurred during the summer of 2012. Further efforts are underway to develop a method to accurately estimate the under-ascertainment of the most recent H3N2v illnesses.

This approach is subject to certain limitations. Data for the proportion of persons with ILI who sought care and had a respiratory specimen collected were self-reported from BRFSS surveys collected during the 2009 influenza pandemic and the 2010–11 influenza season. These values do not include summer months, when influenza activity is low and may not be generalizable to some of the period included in this report. Although the proportion of respondents with ILI who sought care has remained consistent during the two study periods, the proportion of persons with influenza specimens collected during the summer months is more likely to differ. Persons may either have fewer respiratory specimens collected overall or be tested less frequently for influenza but more frequently for pathogens associated with transmission during the summer months (e.g., pertussis) [4, 5]. Therefore, the proportion of specimens collected for influenza testing used in this analysis may be too high and the resulting under-ascertainment multiplier too low. Additionally, the proportion of persons who visited healthcare providers participating in voluntary influenza surveillance programs was estimated using ILINet catchment as a proxy. While the accuracy of this measure is unclear, the results of a survey conducted by the Association of Public Health Laboratories (APHL) to ascertain the major sources of specimens for influenza testing by state indicated that ILINet was the primary or secondary source of specimens for influenza testing for a majority (84%) of the states included (APHL, unpublished data). In an effort to account for these and other limitations described previously, we have included a plausible range of values for each parameter [8].

Adapting a previously published approach, we were able to estimate that the total number of H3N2v cases in the United States ranged from approximately 1,200–3,800 from August 2011 to April 2012. Illness from this variant influenza virus was more frequent than previously thought. Continued surveillance is needed to ensure timely detection and response to H3N2v virus infections.

References

1. Centers for Disease Control and Prevention. Swine-origin influenza A (H3N2) virus infection in two children--Indiana and Pennsylvania, July-August 2011. MMWR Morb Mortal Wkly Rep. 2011; 60(35):1213–5. [PubMed: 21900876]
2. Centers for Disease Control and Prevention. Update: Influenza A (H3N2)v transmission and guidelines - five states, 2011. MMWR Morb Mortal Wkly Rep. 2012; 60(51-52):1741–4. [PubMed: 22217624]
3. Centers for Disease Control and Prevention. Limited human-to-human transmission of novel influenza A (H3N2) virus--Iowa, November 2011. MMWR Morb Mortal Wkly Rep. 2011; 60(47): 1615–7. [PubMed: 22129996]
4. Biggerstaff M, Jhung M, Kamimoto L, Balluz L, Finelli L. Self-reported influenza-like illness and receipt of influenza antiviral drugs during the 2009 pandemic, United States, 2009-2010. Am J Public Health. 2012; 102(10):e21–6. [PubMed: 22897525]
5. Reed C, Angulo FJ, Biggerstaff M, Swerdlow D, Finelli L. Influenza-like illness in the community during the emergence of 2009 pandemic influenza A(H1N1)--survey of 10 states, April 2009. Clin Infect Dis. 2011; 52(Suppl 1):S90–3. [PubMed: 21342906]
6. Jernigan DB, Lindstrom SL, Johnson JR, et al. Detecting 2009 pandemic influenza A (H1N1) virus infection: availability of diagnostic testing led to rapid pandemic response. Clin Infect Dis. 2011; 52(Suppl 1):S36–43. [PubMed: 21342897]

7. Centers for Disease Control and Prevention. Evaluation of Rapid Influenza Diagnostic Tests for Influenza A (H3N2)v Virus and Updated Case Count - United States, 2012. MMWR Morb Mortal Wkly Rep. 2012; 61:619–21. [PubMed: 22895386]
8. Reed C, Angulo FJ, Swerdlow DL, et al. Estimates of the prevalence of pandemic (H1N1) 2009, United States, April-July 2009. Emerg Infect Dis. 2009; 15(12):2004–7. [PubMed: 19961687]
9. Brammer L, Blanton L, Epperson S, et al. Surveillance for influenza during the 2009 influenza A (H1N1) pandemic-United States, April 2009-March 2010. Clin Infect Dis. 2011; 52(Suppl 1):S27–35. [PubMed: 21342896]
10. Centers for Disease Control and Prevention. [Accessed 20 June 2012] Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf8/k080570.pdf
11. Centers for Disease Control and Prevention. Summary of notifiable diseases: United States, 2009. MMWR Morb Mortal Wkly Rep. 2011; 58(53):1–100. [PubMed: 21566560]
12. Council of State and Territorial Epidemiologists. [Accessed 20 June 2012] List of Nationally Notifiable Conditions. Available at: http://www.cste.org/dnn/LinkClick.aspx?fileticket=C8xy7YviYpc%3d&tabid=36&mid=1496
13. Shrestha SS, Swerdlow DL, Borse RH, et al. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009-April 2010). Clin Infect Dis. 2011; 52(Suppl 1):S75–82. [PubMed: 21342903]
14. Neuzil KM, Zhu Y, Griffin MR, et al. Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study. J Infect Dis. 2002; 185(2):147–52. [PubMed: 11807687]
15. Monto AS, Sullivan KM. Acute respiratory illness in the community. Frequency of illness and the agents involved. Epidemiol Infect. 1993; 110(1):145–60. [PubMed: 8432318]
16. Nguyen-Van-Tam JS, Hampson AW. The epidemiology and clinical impact of pandemic influenza. Vaccine. 2003; 21(16):1762–8. [PubMed: 12686091]
17. Centers for Disease Control and Prevention. [Accessed 18 June 2012] Information on H3N2 Variant Influenza A Viruses. Available at: http://www.cdc.gov/flu/swineflu/influenza-variant-viruses-h3n2v.htm
18. Centers for Disease Control and Prevention. Notes from the field: Outbreak of influenza A (H3N2) virus among persons and swine at a county fair--Indiana, July 2012. MMWR Morb Mortal Wkly Rep. 2012; 61:561. [PubMed: 22832938]

Key points

Using methods to account for the under-ascertainment of H3N2v, we estimate that 2,055 (90% range 1,187–3,800) H3N2v infections may have occurred from August 2011 to April 2012, suggesting that the new virus was more widespread than previously thought.

Table 1

Model parameters, sources of data, and the estimated multiplier from the model estimating the under-ascertainment of influenza A variant (H3N2v) virus infection, United States, August 2011–April 2012

			Ranges included in the model (%)	
	Parameter	**Source**	**<18 years**	**≥18 years**
A	Proportion of persons with influenza who seek medical care	BRFSS* [4, 5]	52-67	43–48
B	Proportion of persons who visit an enhanced surveillance provider	ILINet** estimated catchment	3-5	
C	Had a specimen collected for influenza testing	BRFSS* [4, 5]	18-44	
D	Specimen sent to state for confirmatory testing	Assumption	50-100	
E	Tests detects H3N2v	Published study [10]	90-100	
F	Case reported to CDC	Nationally notifiable disease [11, 12]	100	
=	**MULTIPLIER (for every 1 reported case)**		**200 (115-369)**	**255 (152-479)**

* BRFSS: Behavioral Risk Factor Surveillance System, [4]

** ILINet: Influenza Like Illness Network, [9]

Table 2

Summary of influenza A (H3N2) variant (H3N2v) case ascertainments, United States, August 2011–July 2012

Source of case ascertainment	# of H3N2v cases
ER/Hospitals	5
Outpatient provider	3
Healthcare site conducting special study into influenza	2
H3N2v case investigations	3