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Original Article

Estimating influenza incidence and rates of influenza-like illness in the outpatient setting

Ashley Fowlkes,[a] Sharoda Dasgupta,[a] Edward Chao,[b] Jennifer Lemmings,[b] Kate Goodin,[c] Meghan Harris,[d] Karen Martin,[e] Michelle Feist,[f] Winfred Wu,[g] Rachelle Boulton,[h] Jonathan Temte,[i] Lynnette Brammer,[a] Lyn Finelli[a]

[a]Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA. [b]Council of State and Territorial Epidemiologists, Atlanta, GA, USA. [c]Bureau of Epidemiology, Florida Department of Health, Tallahassee, FL, USA. [d]Center for Acute Disease Epidemiology, Iowa Department of Public Health, Des Moines, IA, USA. [e]Infectious Disease Epidemiology Prevention and Control, Minnesota Department of Health, St. Paul, MN, USA. [f]Division of Disease Control, North Dakota Department of Health, Bismarck, ND, USA. [g]Primary Care Information Project, New York City Department of Health and Mental Hygiene, New York, NY, USA. [h]Division of Disease Control and Prevention, Utah Department of Health, Salt Lake City, UT, USA. [i]Department of Family Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA.
Correspondence: Ashley Fowlkes, 1600 Clifton Road, NE MS-A32, Atlanta, GA 30333, USA. E-mail: afowlkes@cdc.gov

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Background: Estimating influenza incidence in outpatient settings is challenging. We used outpatient healthcare practice populations as a proxy to estimate community incidence of influenza-like illness (ILI) and laboratory-confirmed influenza-associated ILI.

Methods: From October 2009 to July 2010, 38 outpatient practices in seven jurisdictions conducted surveillance for ILI (fever with cough or sore throat for patients ≥2 years; fever with ≥1 respiratory symptom for patients <2 years). From a sample of patients with ILI, respiratory specimens were tested for influenza.

Results: During the week of peak influenza activity (October 24, 2009), 13% of outpatient visits were for ILI and influenza was detected in 72% of specimens. For the 10-month surveillance period, ILI and influenza-associated ILI incidence were 20·0 (95% CI: 19·7, 20·4) and 8·7/1000 (95% CI: 8·2, 9·2) persons, respectively. Influenza-associated ILI incidence was highest among children aged 2–17 years. Observed trends were highly correlated with national ILI and virologic surveillance.

Conclusions: This is the first multistate surveillance system demonstrating the feasibility of using outpatient practices to estimate the incidence of medically attended influenza at the community level. Surveillance demonstrated the substantial burden of pandemic influenza in outpatient settings and especially in children aged 2–17 years. Observed trends were consistent with established syndromic and virologic systems.

Keywords : Epidemiology, H1N1, influenza, pandemic.

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Background

Estimating the population burden of influenza is challenging because of variation in annual influenza epidemics caused in part by differences in the circulating influenza viruses, pre-existing population immunity, and influenza vaccine coverage.[1] Further difficulties in influenza disease burden estimation include inconsistent levels of influenza testing, non-specificity of commonly used case definitions (e.g. influenza-like illness), and difficulty in defining the population under surveillance for incidence calculation.[2] Some of these challenges can be overcome by using healthcare claims and managed care databases, which are population-based and longitudinal in nature; however, these databases often use only syndromic case definitions based on chief complaint or physician diagnosis and are not linked to a laboratory-confirmed endpoint.[3]

Monto *et al.*,[4] established a relatively inexpensive alternative method to determine the population-based estimates of ILI and influenza incidence, which used medical practices to define a patient population and incorporated laboratory confirmation for a subset of patients. This strategy was used with the assumption that all patients meeting the case definition were captured. A similar strategy is used in the United Kingdom with general practitioner populations used to monitor ILI.[5] We adapted this methodology to a wider population in the United States to estimate incidence by using an outpatient healthcare practice population as a

proxy for a community and conducted systematic surveillance for medically attended ILI and laboratory-confirmed influenza infections in a broad geographic area over several states and one major city in the United States. In this article, we describe the development of the outpatient practice population and implementation of the surveillance activity, present the results from the first year of surveillance, and compare trends between our Influenza Incidence Surveillance Project (IISP) and other influenza ILI and virologic surveillance programs.

Methods

Surveillance design

Health departments representing six states, including Florida, Iowa, Minnesota, North Dakota, Utah, and Wisconsin, and New York City conducted influenza surveillance from October 2009 through July 2010 as part of the IISP. Each site recruited a convenience sample of approximately five primary outpatient practices with a moderate weekly patient volume (approximately 100–150 patients/week). Participating practices included 27 family medicine practices, six pediatric practices, two internal medicine practices, two student health centers, and one emergency medicine practice. The population at risk was estimated by using the number of registered patients or by determining the average of the number of unique patients seen in a year, depending on which method was more reflective of the practice's catchment as determined by the healthcare provider (HCP). Combining all outpatient practices within a given state or city provided representation of each of the following age groups: <1 year, 12–23 months, 2–4 years, 5–17 years, 18–24 years, 25–49 years, 50–64 years, and >65 years of age and allowed participation by practices that specialize in particular age groups such as pediatric medical practices.

Case definitions

An ILI case was defined among patients aged ≥2 year as those with measured fever or a report of fever by the patient with cough or sore throat in the absence of a known cause other than influenza, and among patients aged <2 years as measured or reported fever with at least one respiratory symptom including cough, sore throat, coryza, rhinorrhea, anorexia, chills, myalgia, or malaise, in the absence of a known cause other than influenza. Each week, the HCP reported to the state or local health department the number of patients meeting the ILI case definition and the total number of patient visits by the age groups specified.

Specimen collection and laboratory testing

We requested from all patients meeting the ILI criteria that a nasal or nasopharyngeal (NP) swab be collected for rapid influenza antigen testing during the visit using the Quidel QuickVue A + B. The results were aggregated by age group and reported to the health department. In addition, from the first 10 ILI patients seen each week, a second NP or throat swab was obtained for submission to the state public health laboratory within 72 hours of collection and tested for influenza A (including subtypes A/H1, A/influenza A (H1N1)pdm09, and A/H3) and influenza B using a real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay. Results were reported to the submitting physician and the state health department. As an alternative to collecting two specimens, the swab collected for rapid antigen testing could first be placed in viral transport media then divided into two samples that allowed for both rapid and RT-PCR influenza testing (per instruction by John Tamerius, Quidel Corporation). However, a minority of providers adopted the one-specimen approach.

Brief clinical and demographic data were collected from patients whose specimens were sent to the laboratory for testing. Health departments reported ILI activity and influenza test results weekly to Centers for Disease Control and Prevention (CDC).

Data analysis

For all IISP sites combined, the expected number of influenza-associated ILI cases for each week was calculated by multiplying the percent of ILI cases testing influenza PCR positive by the total number of ILI patient visits reported during the corresponding week. Estimated incidence was calculated using the expected influenza-associated ILI cases divided by the outpatient practice population. We calculated incidence for individual weeks to evaluate seasonal variation, then summed the weekly incidence estimates of ILI and influenza-associated ILI to obtain the 10-month cumulative incidence. Cumulative incidence estimates were validated, and 95% confidence intervals were calculated using bootstrap analysis to account for the variances of the weekly ILI case totals and proportion of influenza test positive cases.[6] Statistical differences in the frequency of categorical demographic and clinical factors were evaluated with a chi-square test. Patient records with missing RT-PCR results or no report of fever were excluded from analysis. Patients with specimens collected more than 5 days after onset were also excluded due to a loss of viral detectability after 5 days.[7,8]

For comparison with national ILI surveillance data, we used the US Outpatient Influenza-like Illness Surveillance Network (ILINet).[9] Both IISP and ILINet use the same ILI case definition among patients aged >2 year; the IISP expanded definition in the youngest age groups was described earlier. The proportion of ILI-related visits in the outpatient setting determined by IISP was compared with ILINet using a Pearson's correlation coefficient. For com-

parison with virologic data, we compared the weeks during which the percent influenza positivity of respiratory specimens in the World Health Organization and National Respiratory and Enteric Virus Surveillance System (WHO/NREVSS) was >10%.[10,11] All analyses were conducted using SAS Version 9·2 (SAS Institute Inc., Cary, NC, USA).

Results

Medically attended ILI

Of the 272 642 outpatient visits during the 10-month surveillance period, 8747 (3·2%) were for ILI. The proportion of outpatient visits for ILI ranged from 13% in the week of peak activity (October 24, 2009) to 0·3% in the week of lowest activity (June 5, 2010). Trends in ILI were highly correlated between IISP and ILINet, showing high ILI activity during the initial weeks of IISP surveillance through December 19, 2009 (r_s = 0·94 October–December 2009, and r_s = 0·96 October 2009–July 2010) after which very little activity was seen for the remainder of the surveillance period, with the exception of a small increase during February and March 2010 when the percent of ILI-related visits increased from <1% to 1·4% (Figure 1). Throughout the season, outpatient ILI-related visits occurred more frequently in pediatric patients than adults, and during the week of peak influenza activity, 22% of office visits among pediatric patients were for ILI compared with 9% among adults aged ≥18 years ($P < 0·05$). The heaviest cumulative ILI burden was observed in the 2–4 and 5–17 years age categories, with a linear decline in each subsequent age group (Figure 2).

Influenza diagnostic testing

Rapid influenza detection tests (RIDT) (Quidel QuickVue A + B test) were performed on 5911/8747 (68%) of all ILI cases from October 2009 through July 2010. Of those tested, 1360 (23%) were positive for influenza. During October 2009, approximately 31% (weekly range 24–32%) of specimens tested positive by RIDT, with a decline consistent with ILI activity levels through November and December. Sporadic influenza detections occurred from January 9 through February 13, 2010, during which a median of 4·1% (range 2·6–7·5%) of specimens tested influenza

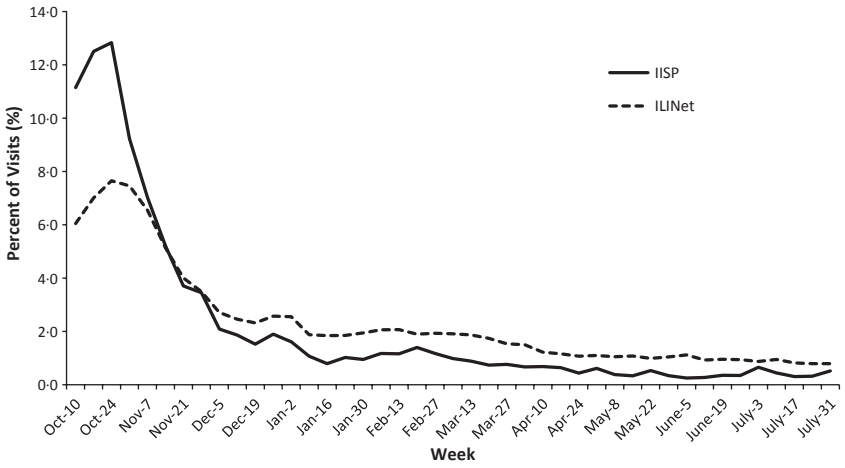

Figure 1. Proportion of outpatient visits for influenza-like illness reported to the Influenza Incidence Surveillance Project (IISP) and the US Outpatient Influenza-like Illness Surveillance Network (ILINet), October 2009 through July 2010.

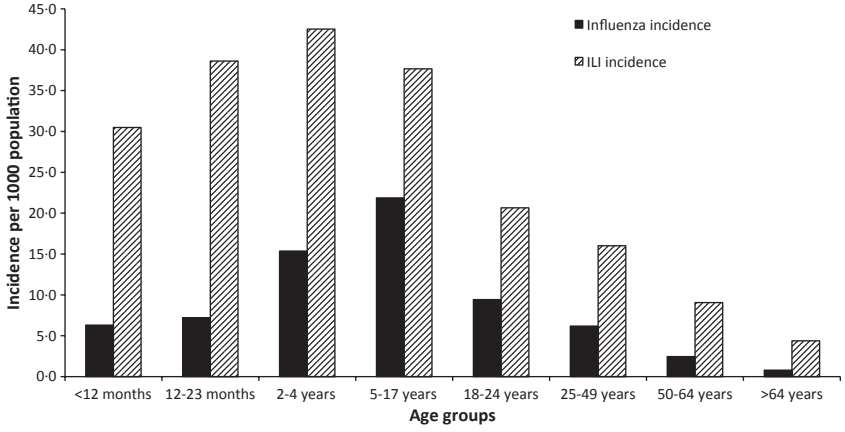

Figure 2. Influenza-like illness (ILI) outpatient visit and estimated PCR-confirmed influenza infection incidence by age group, Influenza Incidence Surveillance Project (IISP), October 2009–July 2010.

positive each week. However, from the third week of February through the end of March, a weekly median of 9% of specimens tested positive, reflecting a small increase in influenza detections in several states, which is consistent with the increase in ILI activity during this time (Figure 1).

Between October 2009 and July 2010, 1802 of 8747 (21%) patients with ILI had a respiratory specimen collected for RT-PCR testing. Among them, 267 (15%) did not meet the case definition for ILI, 178 (9·9%) had specimens collected more than 5 days after onset of symptoms, and 35 (1·9%) were not tested RT-PCR due to poor specimen quality. Among the 1322 included in analysis, 467 (35%) were positive for influenza by RT-PCR > 99% of influenza-positive specimens were subtype influenza A(H1N1)pdm09. Only one influenza A(H3) and three influenza B viruses were detected. During the peak week of both ILI reports and influenza detections, 74% of all specimens were RT-PCR-positive for influenza and the percent positivity remained above 15% from October through the first week of December, indicating widespread influenza circulation over the 9-week period. Similar to ILI and RIDT influenza trends, an increase in positivity by PCR was observed in late February and March as influenza activity increased to a median of 16% from 8·3% in the preceding 7 weeks and included 22 influenza A (H1N1)pdm09 detections and 1 influenza A(H3) detection. Although the trends were similar between the RT-PCR and RIDT assays, the sensitivity of the RIDT was 59% (265/449) and specificity was 97% (782/807) when compared with RT-PCR results in 1256 patients with both tests performed. Influenza RT-PCR detections reported to IISP and all influenza detections reported the WHO/NREVSS were highly correlated (r_s = 0·95 October 2009–July 2010), and the weeks of peak ILI activity and influenza circulation were consistent.

During the surveillance period, the percent of ILI cases that were PCR-positive for influenza was similar among pediatric and adult patients (37% and 33%, respectively). However, closer examination of the data shows variation by age group (Table 1), with day care and school-aged children, aged 2–17 years, more frequently positive for influenza than those aged <2 years (29% versus 17%, $P < 0·05$). Influenza positivity was highest in the 5–17 year age group, remained high in the 18–24 and 25–49 years age groups ($P < 0·05$, compared with patients aged <2 years) and declined in the older age groups. There were no statistically significant differences in percent of ILI cases testing positive for influenza by race or gender (data not shown).

Clinical characteristics

Of the 1322 patients analyzed, 1176 (89%) reported cough and 823 (62%) reported sore throat; 17 (1·3%) patients aged <2 years reported a symptom other than cough or sore throat. Patients who reported cough or both cough and sore throat were 4·4 times more likely to have influenza detected than those reporting sore throat ($P < 0·05$).

Table 1. Age group-specific influenza-like illness (ILI) outpatient visit and influenza infection frequency and rates, influenza incidence surveillance project (IISP), October 2009–July 2010

Age (years)	No. of ILI visits	Percent of visits for ILI	No. of ILI tested by PCR*	No. of PCR influenza positive	Percent PCR positive	Cumulative incidence for surveillance period (per 1000 population)**	
						ILI (95% CI)	Estimated influenza-associated ILI (95% CI)
0–11 months	375	2·3	48	9	18·8	30·5 (28·2, 33·3)	6·3 (2·6, 10·2)
12–23 months	488	3·7	86	14	16·3	38·6 (35·7, 41·6)	7·2 (3·8, 10·8)
2–4	859	5·1	199	57	28·6***	42·6 (40·2, 44·9)	15·4 (12·7, 18·2)
5–17	2265	5·6	439	206	46·9***	37·7 (36·4, 39·0)	21·9 (20·1, 23·6)
18–24	1568	2·7	193	69	35·8***	20·7 (19·8, 21·5)	9·4 (8·0, 10·9)
25–49	1859	1·9	266	91	34·2***	16·0 (15·4, 16·6)	6·2 (5·3, 7·1)
50–64	517	1·2	67	17	25·4	9·0 (8·4, 9·7)	2·5 (17·0, 32·9)
≥65	230	0·8	22	3	13·6	4·3 (3·9, 4·7)	0·8 (0·5, 1·1)
All	8161	2·6	1320	466	35·3	20·1 (19·7, 20·4)	8·7 (8·2, 9·2)

*Two patients did not have age information available.
**Incidence estimations do not represent the annual incidence for 2009. The surveillance period captured by IISP encompassed only October 2009–July 2010; however, widespread influenza circulation began in August 2009.
***Significantly higher percent PCR positivity for the corresponding age group (*P* values <0·05) using all patients aged <2 years as the referent category.

Other symptoms positively associated with influenza detection compared with influenza-negative ILI cases were myalgia ($P < 0{\cdot}05$) and anorexia ($P < 0{\cdot}05$) in children and headache ($P < 0{\cdot}05$) among adults.

Antiviral usage data were available on 1166 patients, of which 212 (18%) received or were prescribed antiviral medication. Patients who tested influenza positive by RT-PCR were 3·2 times more likely to have been prescribed antivirals than those testing negative [133/404 (33%) versus 79/762 (10%), $P < 0{\cdot}05$], and patients who tested positive by RIDT were 3·9 times more likely to have been prescribed antivirals than those testing negative by RIDT [112/260 (43%) versus 95/856 (11%), $P < 0{\cdot}05$].

Estimation of ILI and medically attended influenza incidence

The population served by the participating practices totaled 450 484 persons, but varied slightly (range 343 545–458 100) in the early weeks of surveillance. The age distribution of the patient population was consistent with that of the US population, aside from the relatively large number of 18–24-year-olds, due to inclusion of a large university in the IISP (Figure 3). The proportion of residents under age 18 years was 24% in the US population compared with 26% in IISP. The median weekly number of patients seen by the practices was 185 (range 0–1423).

The estimated cumulative incidence of ILI from October 2009 through July 2010 was 20/1000 persons (Table 1) with a weekly incidence range of 3·1/1000 in October to 0·03/1000 in June. Among pediatric patients, the cumulative ILI incidence was 38/1000, and the weekly incidence ranged from 6·9/1000 to 0·02/1000 (Figure 4). In contrast, the cumulative ILI incidence among adults was 13/1000 with a weekly incidence range from 2·3/1000 to 0·01/1000. Among the age groups, ILI incidence correlated with percent influenza positivity, except in the 12–23-month age group where ILI incidence was disproportionately higher than influenza positivity.

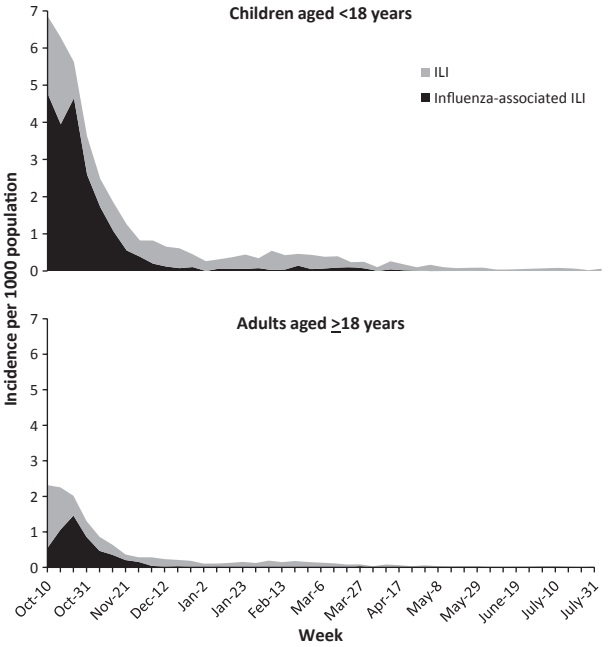

Figure 4. Incidence of influenza-like illness (ILI) and extrapolated influenza-associated ILI in the Influenza Incidence Surveillance Project, October 2009 through July 2010.

The estimated cumulative incidence of influenza-associated ILI from October 2009 through July 2010 was 8·7/1000 with a weekly incidence range of 0/1000 when influenza was not in circulation to 2·2 at peak. The influenza incidence was 3·9 times higher in pediatric than adult patients (21/1000 versus 5·3/1000), with the weekly incidence ranging widely (Figure 4). Among the age groups, the highest incidence was observed in the 2–4- and 5–17-year age groups (15 and 22/1000, respectively) (Table 1). Similar to the results from ILI incidence, the influenza-associated ILI incidence declined with increasing age over all adult age groups (Table 1, Figure 2).

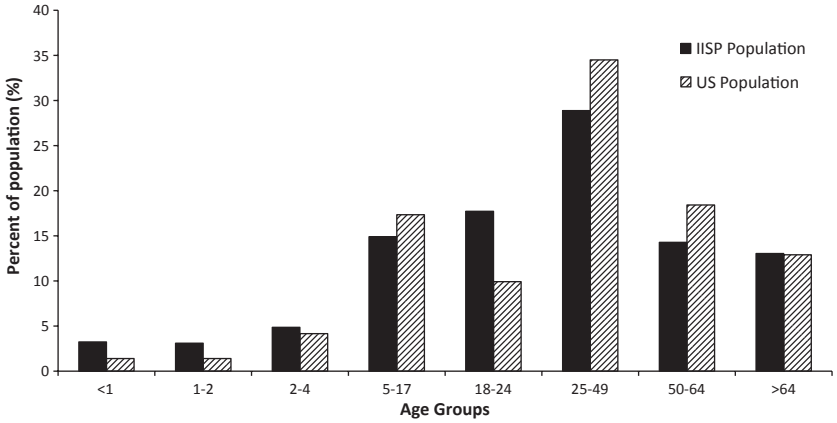

Figure 3. Comparison of age group distributions of the US population and the Influenza Incidence Surveillance Project (IISP) healthcare provider patient population.

Discussion

In October 2009, the IISP was implemented to conduct population-based surveillance for medically attended ILI and influenza-associated ILI in a population of more than 450 000 persons in 38 outpatient medical practices. During the peak weeks of the influenza A (H1N1)pdm09 pandemic, ILI accounted for 13% (22% pediatric and 9% adults) of all outpatient encounters among IISP providers and more than 70% of specimens collected tested positive for influenza, of which more than 99% were attributable to the influenza A (H1N1)pdm09 virus. The cumulative incidence of ILI and influenza ranged substantially over the study period, with extremely high rates in October and November dropping sharply thereafter. Variation in the ILI and influenza incidence by age was exemplified by incidence rates of outpatient ILI visits being three times higher in children than adults.

ILI and influenza trends from the IISP were consistent with other well-established surveillance systems. Trends in the proportion of ILI visits from IISP were consistent with ILINet, a long-established, nationally representative syndromic surveillance system with over 3000 reporting HCPs.[9] In addition, weekly incidence of ILI in IISP was comparable with those reported by the UK's general practitioner surveillance program, which has long used provider registries to estimate the population denominator.[5] Weekly IISP influenza detections and trends were consistent with circulation of influenza determined by the national virologic surveillance system,[1,10,11] confirming the validity of IISP in estimating laboratory-confirmed influenza. Influenza rapid test results were available to the physicians at the time of the visit with 59% sensitivity and 97% specificity, which was expected given RIDT performance in previous evaluations.[12,13] Our findings were consistent with other studies confirming that testing increases the provision of antiviral therapy for influenza-positive patients.[14,15]

PCR has dramatically improved our ability to reliably detect influenza and is thus critical in improving surveillance for influenza. Two earlier incidence studies used viral culture to determine the influenza attributable proportion.[4,16] While these studies helped define influenza epidemiology, the magnitude of influenza's burden on the outpatient setting was likely underestimated due to the lower sensitivity of culture techniques. Culture has been shown to have 35–44% sensitivity when compared with RT-PCR.[17,18] In a 2005 meta-analysis, Bueving *et al.*[19] found few recent longitudinal studies that include PCR testing, and those available report a wide range of influenza incidence estimates depending on case definition, age group and time period. Very few data are available for direct comparison with laboratory-confirmed results from IISP. Studies using a more general definition of acute respiratory illness estimated the incidence of influenza virus infection to be between 50–100/1000/year among patients aged <5 years, but do not present comparison data among adults.[20–22] Cumulative incidence estimates from IISP are similar to the lower incidence range, likely due to a shorter surveillance period (10 months versus 12 months) and a more restrictive IISP case definition. In addition, surveillance was initiated after the peak of H1N1 in some states, thus our estimates would be higher had this activity been captured.

ILI and influenza burden varied widely by age group; the proportion of outpatient visits due to ILI was 2·6 times higher among pediatric patients than among adults and rates of ILI and influenza were three and four times higher, respectively. Further examination of age-specific rates showed that while the incidence of ILI was high in all pediatric age groups, the incidence of influenza infection was highest among patients aged 2–4 and 5–17 years. Historically in studies with laboratory confirmation, children aged <4 years have had lower influenza incidence than school-aged children;[4,16,23–25] however, we found that the incidence in children 2–4 years was higher than in those aged <2 years and more similar to those of school age; perhaps reflecting a greater opportunity for transmission within day care or preschool and more frequent social mixing in this age group.

The IISP presents an alternate approach to conducting population-based surveillance for medically attended influenza-associated ILI in the outpatient setting; however, the process was subject to limitations. As not all influenza infections require medical attention, the absolute incidence of influenza could not be determined using these methods. Additionally, surveillance was initiated during the influenza A (H1N1)pdm09 pandemic and, due to the earlier introduction of influenza A (H1N1)pdm09 in 2009, did not include all months of influenza circulation. The majority of the participating providers were family medicine clinics and other primary care providers, but the small number of providers within each surveillance site did not allow for practice type comparisons. Specimen collection techniques were not standardized or evaluated; thus, we cannot be certain of optimal collection techniques or prompt refrigeration of specimens, and though recommended by the Quidel Corporation, the splitting of the sample into two aliquots has not been formally tested for quality. In addition, several of the IISP sites were concentrated in the northern Midwest region of the United States which affected the geographic representativeness of the IISP, particularly important as influenza unpredictably affects different regions temporally and to different extents.

Conducting population-based influenza surveillance is a challenge to public health officials due to inherent difficulties and cost of following a community or other defined population. By expanding the methods of earlier studies by Monto *et al.*,[4] to a national sample, IISP surveillance demonstrated the feasibility and value of using clinical practice

populations as a successful alternate method to estimate population-based influenza incidence and illustrated the impact of influenza in outpatient settings during the pandemic in the United States. Using medical practice populations as a proxy for the community provides an excellent alternative resource. This methodology should also be evaluated for its application to other diseases or conditions as it can accommodate different case definitions and laboratory testing methodologies.

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References

1 Brammer L, Budd A, Cox N. Seasonal and pandemic influenza surveillance considerations for constructing multicomponent systems. Influenza Other Respi Viruses 2009; 3:51–58.
2 M'ikanatha NM, Lynfield R, Van Beneden CA, de Valk H. Infectious Disease Surveillance, 1st edn. Malden, MA, USA: Blackwell Publishing, 2007.
3 DeStefano F. Opportunities for population-based clinical research using data from managed care organizations; in Davis J (ed.): Managed Care Systems and Emerging Infections. Washington, DC: National Academy Press, 2000; 16–18.
4 Monto AS, Ohmit SE, Margulies JR, Talsma A. Medical practice-based influenza surveillance: viral prevalence and assessment of morbidity. Am J Epidemiol 1995; 141:502–506.
5 Health Protection Agency. Epidemiological report of pandemic (H1N1) 2009 in the UK April 2009–May 2010. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1284475321350. (Accessed 09 July 2012).
6 Chernick MR. Bootstrap Methods: A Practioner's Guide. New York, NY: John Wiley & Sons, Inc., 1999.
7 Carrat F, Vergu E, Ferguson NM *et al.* Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am J Epidemiol 2008; 167:775–785.
8 Bell DM, World Health Organization Writing G. Non-pharmaceutical interventions for pandemic influenza, national and community measures. Emerg Infect Dis 2006; 12:88–94.
9 U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet). Available at: http://www.cdc.gov/flu/weekly/ussurvdata.htm. (Accessed 9/8/2011).
10 CDC. Update: influenza activity – United States, 2009–10 season. MMWR Morb Mortal Wkly Rep 2010; 59:901–908.
11 U.S. World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System (NREVSS) Collaborating laboratories. Available at: http://www.cdc.gov/flu/weekly/ussurvdata.htm. (Accessed October 4, 2011).
12 Centers for Disease C, Prevention. Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) Virus – United States, 2009. MMWR Morb Mortal Wkly Rep 2009; 58:826–829.
13 Chartrand C, Leeflang MM, Minion J, Brewer T, Pai M. Accuracy of rapid influenza diagnostic tests: a meta-analysis. Ann Intern Med 2012; 156:500–511.
14 Garg S, Fry AM, Patton M, Fiore AE, Finelli L. Antiviral treatment of influenza in children. Pediatr Infect Dis J 2012; 31:e43–e51.
15 Bonner AB, Monroe KW, Talley LI, Klasner AE, Kimberlin DW. Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: results of a randomized, prospective, controlled trial. Pediatrics 2003; 112:363–367.
16 Monto AS, Koopman JS, Longini IM Jr. Tecumseh study of illness. XIII. Influenza infection and disease, 1976–1981. Am J Epidemiol 1985; 121:811–822.
17 Talbot HK, Williams JV, Zhu Y, Poehling KA, Griffin MR, Edwards KM. Failure of routine diagnostic methods to detect influenza in hospitalized older adults. Infect Control Hosp Epidemiol 2010; 31:683–688.
18 Weinberg GA, Erdman DD, Edwards KM *et al.* Superiority of reverse-transcription polymerase chain reaction to conventional viral culture in the diagnosis of acute respiratory tract infections in children. J Infect Dis 2004; 189:706–710.
19 Bueving HJ, van der Wouden JC, Berger MY, Thomas S. Incidence of influenza and associated illness in children aged 0–19 years: a systematic review. Rev Med Virol 2005; 15:383–391.
20 O'Brien MA, Uyeki TM, Shay DK *et al.* Incidence of outpatient visits and hospitalizations related to influenza in infants and young children. Pediatrics 2004; 113:585–593.
21 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; 185:147–152.
22 Poehling KA, Edwards KM, Weinberg GA *et al.* The underrecognized burden of influenza in young children. N Engl J Med 2006; 355:31–40.
23 Fox JP, Hall CE, Cooney MK, Foy HM. Influenzavirus infections in Seattle families, 1975–1979. I. Study design, methods and the occurrence of infections by time and age. Am J Epidemiol 1982; 116:212–227.
24 Glezen WP, Keitel WA, Taber LH, Piedra PA, Clover RD, Couch RB. Age distribution of patients with medically-attended illnesses caused by sequential variants of influenza A/H1N1: comparison to age-specific infection rates, 1978–1989. Am J Epidemiol 1991; 133:296–304.
25 Baguelin M, Hoschler K, Stanford E *et al.* Age-specific incidence of A/H1N1 2009 influenza infection in England from sequential antibody prevalence data using likelihood-based estimation. PLoS ONE 2011; 6:e17074.