Published in final edited form as:

Lancet Respir Med. 2015 September ; 3(9): 709–718. doi:10.1016/S2213-2600(15)00278-7.

Incidence of medically attended influenza during pandemic and post-pandemic seasons through the Influenza Incidence Surveillance Project, 2009–13

Ashley Fowlkes, MPH,
Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA

Andrea Steffens, MPH,
Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA

Jon Temte, MD,
Department of Family Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Steve Di Lonardo, MSc,
Division of Prevention and Primary Care, New York City Department of Health and Mental Hygiene, Gotham Center, Long Island City, NY, USA

Lisa McHugh, MPH,
Communicable Disease Service Infectious and Zoonotic Disease, New Jersey Department of Health, Trenton, NJ, USA

Karen Martin, MPH,
Minnesota Department of Health, St Paul, MN, USA

Heather Rubino, PhD,

Correspondence to: Ashley Fowlkes, Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA, afowlkes@cdc.gov.

Influenza Incidence Surveillance Project Working Group
Department of Family Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA: S Barlow; Communicable Disease Division, Wisconsin State Laboratory of Hygiene, Madison, WI, USA: E Reisdorf; Division of Health Care Access and Improvement, New York City Department of Health and Mental Hygiene, New York, NY, USA: W Y Wu; New York City Public Health Laboratory, New York City Department of Health and Mental Hygiene, New York, NY, USA: J Fu; Minnesota Department of Health Public Health Laboratory, St. Paul, MN, USA: D Boxrud, S Vetter; Bureau of Laboratories, Florida Department of Health, Tampa, FL, USA: L Heberlein-Larson; Bureau of Epidemiology, Florida Department of Health, Tallahassee, FL, USA: V Mock; Bureau of Epidemiology, Florida Department of Health, Jacksonville, FL, USA: J Hamilton; Division of Disease Control, North Dakota Department of Health, Bismarck, ND, USA: Jill Baber; Emerging and Acute Infectious Disease Branch, Texas Department of Health, Austin, TX, USA: L Brannan; Acute Communicable Disease Control Program, Los Angeles County Department of Public Health, Los Angeles, CA, USA: C Wigen; State Hygienic Laboratory, University of Iowa, Iowa City, IA, USA: L Desjardin; Virgina Department of Health, Richmond, VA, USA: D Toney; and Utah Public Health Laboratory, Utah Department of Health, Taylorsville, UT, USA: A Atkinson.

See Online for appendix

Declarations of interests
We declare no competing interests.

Contributors
AF and LF were responsible for the design of the study and writing. AF, LF, AS, and MB were involved in the data analysis. AF, LF, and AS drafted the manuscript. AF, LF, AS, MB, RL, and JT were involved in the revision of the manuscript for clarity and content. JT, SDL, LM, KM, HR, MF, CD, CS, JL, OO, KK, AT, and RB collected the data, and provided site-specific data analysis and interpretation. NB obtained funding. All authors had the opportunity to comment on the report before submission.

Bureau of Epidemiology, Florida Department of Health, Tallahassee, FL, USA

Michelle Feist, BS,
Division of Disease Control, North Dakota Department of Health, Bismarck, ND, USA

Carol Davis, MSPH,
Public Health Preparedness and Epidemiology Program, Texas Department of Health, Temple, TX, USA

Christine Selzer, MPH,
Acute Communicable Disease Control Program, Los Angeles County Department of Public Health, Los Angeles, CA, USA

Jose Lojo, MPH,
Division of Disease Control, Philadelphia Department of Public Health, Philadelphia, PA, USA

Oluwakemi Oni, MPH,
Center for Acute Disease Epidemiology, Iowa Department of Public Health, Des Moines, IA, USA

Katie Kurkjian, DVM,
Division of Surveillance and Investigation, Virginia Department of Health, Richmond, VA, USA

Ann Thomas, MD,
Acute and Communicable Disease Program, Oregon Public Health Division, Portland, OR, USA

Rachelle Boulton, MSPH,
Division of Disease Control and Prevention, Utah Department of Health, Salt Lake City, UT, USA

Nicole Bryan, MPH,
and Council of State and Territorial Epidemiologists, Atlanta, GA, USA

Ruth Lynfield, MD,
Minnesota Department of Health, St Paul, MN, USA

Matthew Biggerstaff, MPH,
Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA

Lyn Finelli, DrPH, and
Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA

for the Influenza Incidence Surveillance Project Working Group

Summary

Background—Since the introduction of pandemic influenza A (H1N1) to the USA in 2009, the Influenza Incidence Surveillance Project has monitored the burden of influenza in the outpatient setting through population-based surveillance.

Methods—From Oct 1, 2009, to July 31, 2013, outpatient clinics representing 13 health jurisdictions in the USA reported counts of influenza-like illness (fever including cough or sore throat) and all patient visits by age. During four years, staff at 104 unique clinics (range 35–64 per year) with a combined median population of 368 559 (IQR 352 595–428 286) attended 35 663 patients with influenza-like illness and collected 13 925 respiratory specimens. Clinical data and a

respiratory specimen for influenza testing by RT-PCR were collected from the first ten patients presenting with influenza-like illness each week. We calculated the incidence of visits for influenza-like illness using the size of the patient population, and the incidence attributable to influenza was extrapolated from the proportion of patients with positive tests each week.

Findings—The site-median peak percentage of specimens positive for influenza ranged from 58.3% to 77.8%. Children aged 2 to 17 years had the highest incidence of influenza-associated visits (range 4.2–28.0 per 1000 people by year), and adults older than 65 years had the lowest (range 0.5–3.5 per 1000 population). Influenza A H3N2, pandemic H1N1, and influenza B equally co-circulated in the first post-pandemic season, whereas H3N2 predominated for the next two seasons. Of patients for whom data was available, influenza vaccination was reported in 3289 (28.7%) of 11 459 patients with influenza-like illness, and antivirals were prescribed to 1644 (13.8%) of 11 953 patients.

Interpretation—Influenza incidence varied with age groups and by season after the pandemic of 2009 influenza A H1N1. High levels of influenza virus circulation, especially in young children, emphasise the need for additional efforts to increase the uptake of influenza vaccines and antivirals.

Funding—US Centers for Disease Control and Prevention.

Introduction

Influenza viruses circulate during winter months in the USA, causing a sharp increase in acute respiratory infections and medically attended illness.[1] An estimated 10.6 million ambulatory care visits and an associated US$6.8 billion in costs occur during an average influenza season.[2,3] The intensity of seasonal influenza epidemics can vary substantially because of changes in the predominant influenza virus type in circulation and immunity in the population.[4] Influenza pandemics can greatly increase morbidity and mortality beyond that of seasonal influenza,[5] often shifting the burden of severe disease from the older adults to children and young adults because of their immunological naivity and resulting higher attack rates.[6] Pandemic influenza viruses usually circulate for several years after the pandemic, replacing subtype-specific seasonal influenza viruses.[7]

To assess the contribution of laboratory-confirmed influenza, both laboratory-based virological and medical practice-based clinical surveillance are necessary to establish the influenza-attributable proportion of physician consultations for respiratory illness.[8] In 2009, the US Centers for Disease Control and Prevention (CDC) initiated the Influenza Incidence Surveillance Project (IISP) to monitor medically attended influenza-like illness among health-care providers with patient populations of estimated size, which allow for incidence calculation. We aimed to use IISP data from 2009 to 2013 to investigate the seasonal variation in incidence of laboratory-confirmed, medically attended influenza, during the 2009 influenza A H1N1 pandemic (pH1N1) and the three subsequent influenza seasons.

Methods

Surveillance population

From Oct 1, 2009, to July 31, 2013, 13 public health departments were engaged to participate as sites in IISP: Florida, Iowa, Minnesota, North Dakota, Oregon, Wisconsin, and New York City from Oct 1, 2009, to July 31, 2013; New Jersey, Virginia, Los Angeles county, and Philadelphia from Aug 1, 2010, to July 31, 2013; Utah from Oct 1, 2009, to July 31, 2011; and Texas from Aug 1, 2011, to July 31, 2013. Each site recruited about five clinics or health-care providers to undertake surveillance providing they accepted acutely ill patients, attended roughly 100–150 patients per week, and were able to determine the size of their patient population. A detailed description of the methods used to enumerate patient populations has been published previously.[9] Briefly, clinics reported the number of patients registered to their practices or the average number of unique patients seen per year. All age groups had to be represented in each jurisdiction participating in surveillance.

Procedures

Patients of all ages who visited participating clinics were assessed for influenza-like illness by health-care personnel. For patients aged 2 years or older, influenza-like illness was defined as reported or measured fever with cough or sore throat and presentation within 7 days of onset. For patients younger than 2 years, influenza-like illness was defined as reported or measured fever with one or more respiratory symptoms, including cough, sore throat, nasal congestion, rhinorrhoea, and onset within 7 days before presentation to clinic; for the 2009–10 surveillance year, the symptoms for children younger than 2 years could also include decreased appetite, chills, myalgia, and malaise. Clinics reported the number of patients with influenza-like illness and the total number of patient visits each week, aggregated by age group (<2 years, 2–4 years, 5–17 years, 18–24 years, 25–49 years, 50–64 years, and ≥65 years).

Respiratory specimens were systematically collected from the first ten patients with influenza-like illness visiting the clinic each week and could include nasal, nasopharyngeal, or oropharyngeal swabs or nasal aspirates. In view of the small clinic size needed for participation in IISP, we decided to sample ten patients at each site to ensure that a large portion of, if not all, patients with influenza-like illness attended in a given week would be sampled. Demographic and clinical information, including patient-reported symptoms and influenza vaccination status were collected during the visit. Clinicians recorded whether antivirals were prescribed and reported the results of rapid influenza detection testing (RIDT), if done. Respiratory specimens were tested for influenza viruses by use of the CDC Human Influenza Virus RT-PCR Diagnostic Panel, which includes influenza A viruses and subtypes seasonal H1N1, H1N1pdm09 (pH1N1), H3N2, and influenza B viruses. At the Virginia site, specimens were first tested by Luminex xTAG RVP (Luminex Diagnostics, Toronto, ON, Canada), then influenza A-positive specimens were subtyped with the CDC panel.

Statistical analysis

We included patients who met the case definition of influenza-like illness and had completed PCR testing in the analysis. Each surveillance year was defined as 52 weeks from Aug 1 to the following July 31, with the exception of the 2009–10 surveillance year, in which surveillance was started in October. The influenza season was defined for each year as all consecutive weeks with 10% or more of specimens testing positive for influenza. Health department jurisdictions were grouped into the Health and Human Service (HHS) regions—Region 2 (New York City and New Jersey), Region 3 (Philadelphia and Virginia), Region 4 (Florida), Region 5 (Minnesota and Wisconsin), Region 6 (Texas), Region 7 (Iowa), Region 8 (North Dakota, Utah), Region 9 (Los Angeles), and Region 10 (Oregon)[10]—and we calculated the median of each region's peak week of influenza detection. We compared patient demographics, clinical data, and symptoms between patients who were influenza test-positive and those who were test-negative using χ^2 tests.

To estimate the weekly incidence of influenza-associated visits for each age group, we multiplied the total number of visits for influenza-like illness for each week by the proportion of patients sampled who were influenza test-positive, and divided by the total population of each age group. We summed the weekly incidence for all 52 weeks of each surveillance year to obtain the cumulative incidence. We calculated 95% CIs with bootstrap sampling from the population of patients with influenza-like illness to account for variance in the incidence of influenza-like illness and variance of the percentage of patients who might test positive for influenza each week.[11] We excluded clinics from incidence calculations if population data were missing; fewer than five influenza-like illness visits were reported in a year; or if the total of all-cause patient visits, which includes well-visits (routine checkups) and follow-up appointments, was less than 10% or more than 600% of the estimated source population size. We used SAS version 9.2 for all statistical analyses. The IISP uses routinely collected specimens and public health surveillance data therefore this study was considered exempt from needing institutional review board approval.

Role of the funding source

The authors from the CDC had a role in study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

During the four surveillance years, 115 clinics participated in IISP for a total of 247 clinic-seasons of contributed data. We excluded 32 clinic-seasons from our analysis, which resulted in the complete exclusion of 11 clinics. The excluded clinics did not differ significantly from included clinics according to clinic type, urbanicity, or funding type. The characteristics of the individual clinics included in the analysis varied with participation each year, but most were primary care clinics (98 [94.2%] of 104 clinics), including paediatric, family medicine, and student health; six (5.8%) clinics were emergency departments and urgent care clinics. Overall, 73 (70.2%) clinics were in urban or suburban areas, and 45 (43.3%) were publicly funded. The median population under surveillance was

368 559 people (IQR 352 595–428 286), and the age distribution was similar to that of the US population.[12]

Participating clinics recorded 2 189 675 visits during the 4 year period, with a median of 152 patients seen per week (IQR 93–248). Patient visits varied in accordance with clinic population size and time of year. Visits for influenza-like illness were reported for 35 663 patients (1.6% of all visits). Only six clinics had a median of more than ten patients with influenza-like illness per week (maximum for sampling), and only 64 clinics had a maximum number of patients with influenza-like illness per week that was more than ten, representing only 786 (7%) of 10 560 clinic-weeks. The proportion of visits for an influenza-like illness peaked at 1229 (12.8%) of 9579 visits in 2009–10, 537 (4.6%) of 11714 visits in 2010–11, 306 (2.0%) of 15599 visits in 2011–12, and 426 (6.0%) of 7139 visits in 2012–13, with the peak week occurring between October (pandemic season) and March (figure 1).

Respiratory specimens were collected from 20 350 patients, representing 57% of all reported visits for influenza-like illness, of which 13 925 (68.4%) met the inclusion criteria. Of patients excluded, 5644 did not meet the case definition for influenza-like illness, 449 did not have testing completed, and 332 presented more than 7 days after illness onset. Overall, influenza was detected in 3890 (27.9%) patients with influenza-like illness, and detection ranged by season from 451 (14.1%) of 3203 patients in 2011–12 to 1647 (36.8%) of 4472 patients in 2012–13 (table 1). For the HHS Regions, the median peak percentage of specimens positive for influenza was 75.0% (IQR 63.2–78.0) in 2009–10, 67.9% (60.0–75.0) in 2010–11, 58.3% (45.2–66.7) in 2011–12, and 77.8% (66.7–82.4) in 2012–13. The median duration of the influenza season was 19 weeks (16–21) in 2010–11, 11 weeks (10–15) in 2011–12 and 20 weeks (20–21) in 2012–13. When sites were aggregated nationally, the peak percentage of specimens positive for influenza was lower and the season duration was longer than when they were assessed separately (figure 2).

Of the 13 925 specimens collected, 10 199 (73.2%) were nasopharyngeal swabs, 1695 (12.2%) were oropharyngeal swabs, 1473 (10.6%) were nasal swabs, and 558 (4.0%) were nasal aspirates. Influenza detection was higher in nasal aspirates (29.4%) and nasopharyngeal swab specimens (29.3%) than in nasal swabs (25.6%) or oropharyngeal swabs (21.3%; $p<0.0001$ for all comparisons).

Influenza A viruses represented the majority of influenza detections from 2009 to 2013 (table 1), and the distribution of influenza A virus subtypes and influenza B virus varied substantially each year (appendix). During the pandemic in 2009–10, most influenza detections were 2009 pH1N1, but in 2010–11, there were roughly equal proportions of pH1N1, influenza A H3N2, and influenza B viruses in circulation (table 1). In 2011–12, H3N2 virus predominated with pH1N1 virus commonly detected; H3N2 predominated again in 2012–13, followed by influenza B (table 1). With the exception of 2009–10, influenza type A virus usually predominated in the early part of the season with influenza B virus predominating in the later weeks (figure 1).

Influenza accounted for a substantial proportion of influenza-like illness when influenza viruses circulated during late autumn and winter (figure 1). After the pandemic season, the highest incidence of influenza-like illness visits was in 2012–13 (30.4 per 1000 people, 95% CI 30.1–31.0; table 2). The lowest incidence of influenza-like illness visits was in 2011–12 (14.2 per 1000 people, 13.9–14.5), with a corresponding influenza-associated visit incidence rate of 1.9 per 1000 people (1.8–2.0).

The incidence of influenza-associated visits was highest in patients aged 2–4 years and 5–17 years (range 4.2–28.0 per 1000 people), although for 2009–10 we noted a slight overlap in the 95% CIs for children younger than 2 years and aged 2–4 years (table 2). In adults aged 18 to 24 years, the influenza-associated incidence ranged by year from 1.2 to 13.8 per 1000 people, and typically decreased further with each subsequent increasing age group. Adults aged 65 years or older had the lowest influenza-associated incidence, with the exception of 2011–12, in which incidence was low in all adult age groups (table 2).

Assessment of subtype-specific differences by age showed that incidence of pH1N1 virus infection was highest among patients aged 2–4 and 5–17 years in 2009–10 (table 2). In 2010–11, the incidence of pH1N1 remained high in paediatric patients aged 2–4 and 5–17 years, but similar rates were noted for young adults aged 18–24 years. With the exception of pH1N1 in the 18–24 year age group in 2010–11, H3N2 was the predominant influenza A subtype in adults after 2009–10 (table 2). Influenza B virus incidence was consistently highest in children aged 5–17 years, and very low among adults (table 2, figure 3).

With the exception of the case definition inclusion criteria (fever, cough, sore throat), the most frequently reported symptoms were congestion (4888 [44.9%] of 10 844), rhinorrhoea (6178 [44.8%] of 13 787 patients), and myalgia (4357 [31.6%] of 13 770 patients), which were significantly more common in patients who were positive for influenza than in those who were negative for it (table 3). Influenza antiviral treatment was reported for 1644 (13.8%) of 11 953 patients with influenza-like illness. Among those who received antivirals, 1358 (82.6%) of 1644 patients presented within 2 days of symptom onset and 1371 (86.8%) of 1579 patients with data available had a rapid influenza detection test (RIDT). The calculated RIDT sensitivity was 56.9% (table 3), and of the 1371 patients with influenza-like illness who both received antivirals and had an RIDT done, 946 (69.0%) were influenza-positive by RT-PCR. Overall, low proportions of patients reported influenza vaccination (3289 [28.7% (SD 0.8)] of 11 459 patients). Influenza vaccination was most prevalent in 2011–12 (32.7% [SD 1.7]) compared with other years (25.9 [2.2]) in 2009–10, 27.7 [1.6] in 2010–11, and 27.7 [1.4] in 2012–13, $p<0.0001$). Children (ages 17 years and younger) were significantly more likely to have been vaccinated than were adults (relative risk 1.3, $p<0.0001$); irrespective of age, vaccination was significantly more common in patients negative for influenza than in those who were influenza-positive (table 3).

Discussion

The IISP is the only nationally representative programme to do year-round, population-based surveillance for medically attended influenza-like illness that incorporates RT-PCR testing for influenza. This integrated syndromic and virological surveillance system allows

estimation of influenza incidence from a systematic sample of medically-attended influenza-like illness visits from a well-characterised patient population. Previous population-based studies incorporating laboratory confirmation of influenza have established the tremendous burden of influenza in the outpatient setting, but do not represent more recent data.[13,14] Influenza disease burden modelling has therefore relied on estimation of medically-attended illness associated with influenza from combined sources.[15] However, the annual variation of influenza subtype circulation and effect, especially in view of the 2009 influenza A (H1N1) pdm09 (pH1N1) pandemic, necessitates systematic, year-round surveillance from a source population to estimate the burden of medically attended influenza infections each year. We noted that from 2009 to 2013, influenza accounted for 28% of all influenza-like illness visits, ranging from 58–78% during peak periods of influenza circulation by geographical regions. Influenza incidence varied widely by year with a five-times difference in incidence between 2011–12 and 2012–13, in which H3N2 predominated. The highest incidence of influenza-like illness was among children younger than 5 years, and the highest incidence of influenza was among children aged 2–17 years. Prevalence of influenza vaccination was low in the IISP population, as was prevalence of antiviral prescribing without a positive RIDT.

The emergence of pH1N1 virus in 2009 caused high morbidity, with roughly 1 in 100 people in the USA being medically attended for influenza. In subsequent years, pH1N1 continued to circulate, with variable estimates of associated medically attended influenza-like illness. In 2010–11 influenza virus circulation was divided almost equally between pH1N1, H3N2, and influenza B viruses. Co-circulation of all three viruses happened again in 2011–12, with a predominance of H3N2 virus, and a low overall incidence of influenza-like illness; the season was mild in both the USA and Europe.[16,17] After 3 years of low H3N2 virus incidence, the 2012–13 season was characterised by a high incidence of H3N2 virus circulation and high incidence of medically attended illness, similar to the pandemic season. Previous studies have established that H3N2 is associated with more severe illness than other subtypes in elderly adults and young children,[18,19] and during the 2012–13 season, routine CDC surveillance systems reported some of the highest rates of influenza-related hospitalisation and death reported in the past decade.[20]

After the pandemic, we detected an age shift in peak pH1N1 incidence from children aged 2–17 years to equal incidence in children and young adults (ages 2–24 years), which was similarly recorded in Europe in 2010–11.[6] This shifting age distribution was also described after the 1918 and 1957 influenza pandemics.[21] Increased incidence of influenza during the first wave of an influenza pandemic might result from heightened attack rates in immunologically naive children during the first wave of a pandemic, leaving a larger proportion of adults relatively more susceptible in subsequent waves and seasons compared with children.[21] In IISP, the incidence of pH1N1 among adults aged 65 years older was very low from 2009–10 onwards, which supports the notion that older adults possess cross-reactive immunity from previous, antigenically similar H1N1 infections.[22]

With the exception of the 2009 pandemic, both the proportion of specimens positive for influenza and the incidence of influenza-associated visits were consistently high in children aged 5–17 years. By contrast, influenza was frequently detected in adults, but the incidence of influenza-like illness visits was much lower than in children, yielding an overall lower

incidence of medically attended influenza. This divergence of incidence and detection in adults is consistent with population-based surveillance done during the Tecumseh Study of Respiratory Illness, and studies of influenza detection in adults.[23,24]

Influenza vaccination and antiviral drugs are currently the most effective strategies to prevent influenza and treat its complications, yet neither was commonly reported in the IISP population. For example in 2011–12, after recommendations for universal vaccination, we saw that 36.9% of children and 25.8% of adults reported vaccination, which was lower than the national survey estimates of 51.5% among children and 38.8% adults.[25] Antiviral drugs for influenza were usually only prescribed for patients who had a positive RIDT and who presented within 2 days of illness onset. Although RIDTs have been shown repeatedly to have a low sensitivity and empirical use is recommended for patients at risk of complications,[26,27] health-care providers continue to rely on their results to guide clinical treatment.

The IISP network addresses many challenges of population-based influenza surveillance, but was subject to limitations. The initial 2009–10 surveillance year began as pH1N1 circulation reached its peak phase, so the cumulative incidence of influenza-like illness visits attributable to influenza represents only about half of the season and actual burden of pandemic influenza. Estimates for 2009–10 were not modified because attempts to do so would introduce unmeasurable bias, but trends seen in the age differential should not be affected. We used the patient population as an approximation of the community to estimate incidence, rather than a census tract or catchment area. Our previous assessments have shown that this strategy is valid,[28] and similar strategies have been used successfully for many years in other countries in accordance with WHO recommendations for establishing denominators in sentinel influenza surveillance programmes.[29] For example, the UK's general practitioner surveillance provides a comparable representation of medically attended influenza-like illness incidence.[30] IISP represents non-identifiable surveillance data, so underlying medical conditions could not be ascertained and individuals with more than one clinical visit during an illness cannot be differentiated from those with only one visit; therefore, it should be noted that our study reports prescription of antivirals for all individuals and the incidence of clinical visits rather than for individual infections. The age distribution of the IISP population was similar to that of the USA, but additional demographic factors and health-care seeking behaviours could not be assessed. Identification of patients aged 65 years or older was low, but representative of differences in primary care use and incidence of influenza-like illness by age.[31] Notably, we used the case definition of influenza-like illness for surveillance to conserve resources and guide diagnostic testing, but it does not represent the full scope of influenza illness; therefore, we hope that the incidence of visits for influenza-associated influenza-like illness presented in this report will inform studies to estimate the much broader scope of influenza disease burden.

The IISP is the only multistate, nationally representative network that can estimate influenza incidence in patients with influenza-like illness presenting to ambulatory care clinics in the USA. The consistency of these data over multiple years allowed us to show the introduction and subsequent sea sonal circulation of pH1N1 in the USA. Children aged 2–17 years consistently had the highest incidence of influenza-associated visits, but young adults were

substantially affected in the first and second years of 2009 pandemic influenza A H1N1 pH1N1 virus circulation. The data also provide insight into vaccination coverage in the outpatient setting, antiviral prescribing practices, and the effect of changing seasonal influenza strain predominance on the number of recorded influenza-associated visits. The low prevalence of influenza vaccination and antiviral treatment reported through IISP suggest that continued emphasis is needed on communication efforts about the benefits of these preventive measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Carrie Reed and Paul Gargiullo for statistical consultation, Lynnette Brammer for programme design consultation, and Lenee Blanton and Desiree Mustaquim for coordination and comparison of disease trends with CDC national surveillance. We also acknowledge the many public health workers, laboratory staff, and health-care providers who contributed their time and expertise to make IISP a successful network. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

References

1. Monto AS, Sullivan KM. Acute respiratory illness in the community. Frequency of illness and the agents involved. Epidemiol Infect. 1993; 110:145–60. [PubMed: 8432318]
2. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine. 2007; 25:5086–96. [PubMed: 17544181]
3. Neuzil KM, Maynard C, Griffin MR, Heagerty P. Winter respiratory viruses and health care use: a population-based study in the northwest United States. Clin Infect Dis. 2003; 37:201–7. [PubMed: 12856212]
4. Centers for Disease Control and Prevention. Flu Activity & Surveillance, December 4, 2014. http://www.cdc.gov/flu/weekly/fluactivitysurv.htm (accessed Dec 17, 2014).
5. Simonsen L. The global impact of influenza on morbidity and mortality. Vaccine. 1999; 17(suppl 1):S3–10. [PubMed: 10471173]
6. Hayward AC, Fragaszy EB, Bermingham A, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. Lancet Respir Med. 2014; 2:445–54. [PubMed: 24717637]
7. Webster RG, Bean WJ, Gorman OT, et al. Evolution and ecology of influenza A viruses. Microbiol Rev. 1992; 56:152–79. [PubMed: 1579108]
8. Blanton, L., Brammer, L., Finelli, L., et al. Influenza. In: Roush, SW., Baldy, LM., editors. Manual for the surveillance of vaccine-preventable diseases. 5th. Atlanta: Centers for Disease Control and Prevention; 2011.
9. Fowlkes A, Dasgupta S, Chao E, et al. Estimating influenza incidence and rates of influenza-like illness in the outpatient setting. Influenza Other Respir Viruses. 2012; 7:694–700. [PubMed: 22984820]
10. US Department of Health and Human Services. Regional offices. http://www.hhs.gov/about/foa/regions/index.html (accessed Sept 30, 2014)
11. Rust KF, Rao JN. Variance estimation for complex surveys using replication techniques. Stat Methods Med Res. 1996; 5:283–310. [PubMed: 8931197]
12. US Census Bureau. Annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2013. https://www.census.gov/popest/data/datasets.html (accessed Sept 5, 2013)
13. 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; 185:147–52. [PubMed: 11807687]

14. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. N Engl J Med. 2006; 355:31–40. [PubMed: 16822994]
15. Kostova D, Reed C, Finelli L, et al. Influenza illness and hospitalizations averted by influenza vaccination in the United States, 2005–2011. PLoS One. 2013; 8:e66312. [PubMed: 23840439]
16. Centers for Disease Control and Prevention. Update: influenza activity—United States, 2011–12 season and composition of the 2012–13 influenza vaccine. MMWR Morb Mortal Wkly Rep. 2012; 61:414–20. [PubMed: 22672977]
17. ECDC. Influenza in Europe—Season 2011–2012. Stockholm: European Centre for Disease Prevention and Control ECDC; 2012. http://ecdc.europa.eu/en/publications/Publications/Influenza-Europe-2011-2012-surveillance-report.pdf (accessed Nov 12, 2014)
18. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003; 289:179–86. [PubMed: 12517228]
19. Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. Estimates of mortality attributable to influenza and RSV in the United States during 1997–2009 by influenza type or subtype, age, cause of death, and risk status. Influenza Other Respir Viruses. 2014; 8:507–15. [PubMed: 24975705]
20. Centers for Disease Control and Prevention. Influenza activity— United States, 2012–13 season and composition of the 2013–14 influenza vaccine. MMWR Morb Mortal Wkly Rep. 2013; 62:473–79. [PubMed: 23760189]
21. Simonsen L, Clarke MJ, Schonberger LB, Arden NH, Cox NJ, Fukuda K. Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. J Infect Dis. 1998; 178:53–60. [PubMed: 9652423]
22. Hancock K, Veguilla V, Lu X, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. N Engl J Med. 2009; 361:1945–52. [PubMed: 19745214]
23. Falsey AR, McElhaney JE, Beran J, et al. Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness. J Infect Dis. 2014; 209:1873–81. [PubMed: 24482398]
24. Monto AS, Koopman JS, Longini IM Jr. Tecumseh study of illness. XIII. Influenza infection and disease, 1976–1981. Am J Epidemiol. 1985; 121:811–22. [PubMed: 4014174]
25. Lu PJ, Santibanez TA, Williams WW, et al. Surveillance of influenza vaccination coverage—United States, 2007–08 through 2011–12 influenza seasons. MMWR Surveill Summ. 2013; 62:1–28.
26. Uyeki TM, Prasad R, Vukotich C, et al. Low sensitivity of rapid diagnostic test for influenza. Clin Infect Dis. 2009; 48:e89–92. [PubMed: 19323628]
27. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011; 60:1–24.
28. Fowlkes A, Dasgupta S, Chao E, et al. Estimating influenza incidence and rates of influenza-like illness in the outpatient setting. Influenza Other Respir Viruses. 2013; 7:694–700. [PubMed: 22984820]
29. World Health Organization. WHO Regional Office for Europe guidance for sentinel influenza surveillance in humans. 2011. http://www.euro.who.int/__data/assets/pdf_file/0020/90443/E92738.pdf (accessed June 29, 2015).
30. Fleming DM, Miles J. The representativeness of sentinel practice networks. J Public Health (Oxf). 2010; 32:90–96. [PubMed: 19758977]
31. Biggerstaff M, Jhung MA, Reed C, Fry AM, Balluz L, Finelli L. Influenza-like illness, the time to seek healthcare, and influenza antiviral receipt during the 2010–2011 influenza season-United States. J Infect Dis. 2014; 210:535–44. [PubMed: 24731959]

Research in context

Evidence before this study

The aim of the Influenza Incidence Surveillance Project (IISP) was to establish in the USA a population-based surveillance system to monitor influenza-like illness and determine the proportion attributable to influenza. The current study contextualises the findings of the IISP during the 2009 H1N1 pandemic and subsequent years. To support the current study, we searched PubMed using the terms “pandemic influenza burden by age”, with no language or date restrictions, up to Feb 1, 2015. We also used information from the US Centers for Disease Control and Prevention (CDC) website. We identified 140 papers published and highlight two robust studies. The FluWatch cohort study (Hayward and colleagues, 2014) presented the disease burden of 2009 pandemic influenza A H1N1 in England, Simonsen and colleagues (1998) presented a summary of previous influenza pandemics in the 20th century. Both studies described the burden of pandemic influenza-associated illness and reported a shift in disease burden from the youngest age groups during a pandemic, to a combination of both children and adults in the following years.

Added value of this study

Our programme contributes to estimation of the disease burden of influenza types and subtypes, and is the first, to our knowledge, to describe the shift in the age-specific burden of 2009 pandemic influenza A H1N1 (pH1N1) from the children aged 2–17 years in the pandemic year, to include young adults in the following year among US outpatients. The IISP is the only continuous, multistate US programme that does population-based surveillance for medically-attended influenza-like illness and tests for influenza. Our report further describes the low prevalence of influenza vaccination in the IISP population and uncommon antiviral prescribing, including in the age groups judged to be at high risk for influenza complications.

Implications of all the available evidence

Enhanced surveillance for influenza in the USA provides insight into the effect of changes in influenza strain predominance on the incidence of influenza-associated outpatient visits. These data can be applied to disease burden models to estimate the total effect of influenza disease each year. The low prevalence of influenza vaccination and antiviral treatment reported through IISP suggest that continued emphasis on communication efforts about the benefits of these preventive measures is needed.

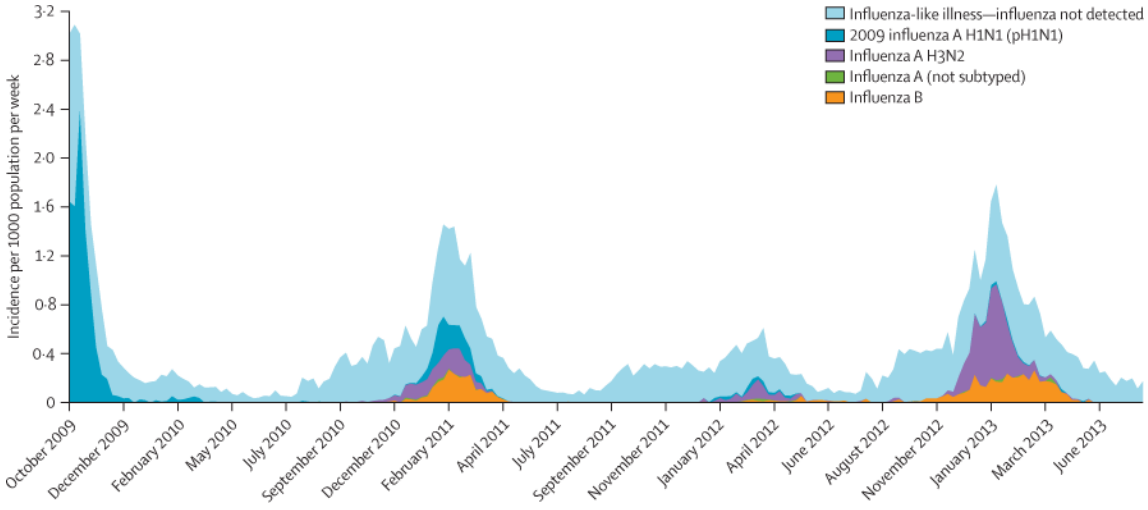

Figure 1. Incidence per week

Weekly incidence of medically attended influenza-like illness and influenza virus types and subtypes.

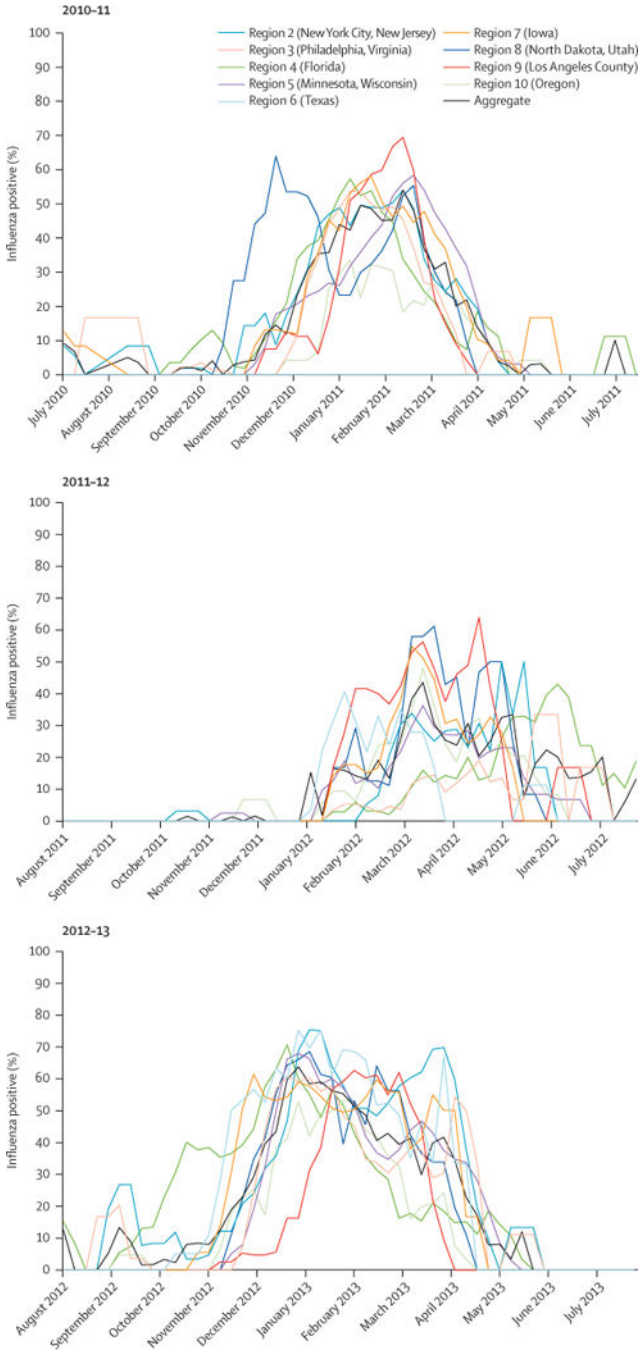

Figure 2. Influenza-like illnesses RT-PCR-positive for influenza virus

Data are sorted by US Department of Health and Human Services region and season.

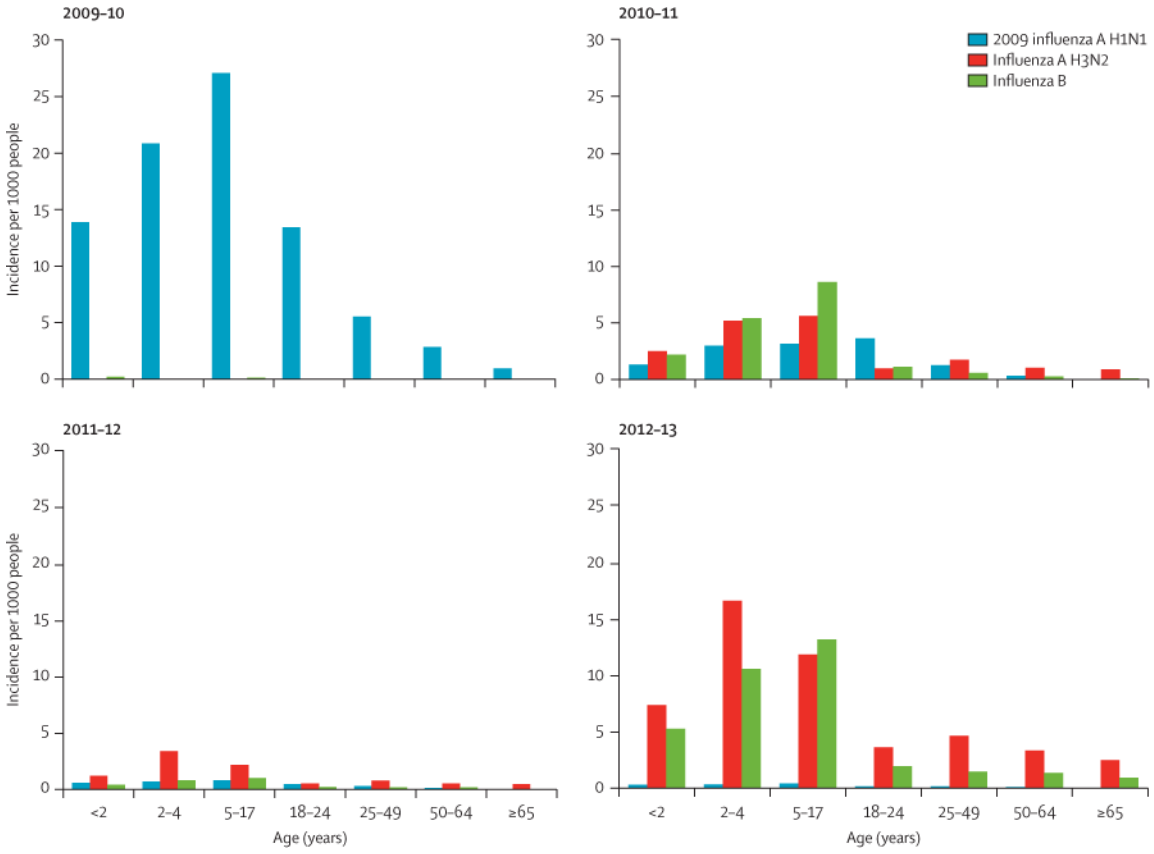

Figure 3. Influenza incidence by age and subtype

Extrapolated cumulative incidence of PCR-confirmed influenza infection per 1000 population per surveillance year by age group, influenza type, and subtype, and influenza season, from October, 2009, to July, 2013. The percentage of patients who tested positive for influenza each week was multiplied by the total number of influenza-like illness visits reported for each week and age group, then divided by the corresponding population size. The incidence rates each week were added to give the cumulative incidence of influenza-associated influenza-like illness visits by age group. Surveillance was from October, 2009, to July, 2010 and all other subsequent seasons include August to July of the following year.

Table 1

Laboratory-confirmed influenza virus infection by surveillance year

	Surveillance seasons				All seasons
	2009–10[*] (n=1686)	**2010–11 (n=4564)**	**2011–12 (n=3203)**	**2012–13 (n=4472)**	**2009–2013 (n=13 925)**
Influenza detections	550 (32.6%)	1242 (27.2%)	451 (14.1%)	1647 (36.8%)	3890 (27.9%)
Type and subtype distribution					
Influenza A	547 (99.5%)	813 (65.5%)	372 (82.5%)	1018 (61.8%)	2750 (70.7%)
2009 influenza A H1N1	533 (97.4%)	368 (45.3%)	98 (26.3%)	34 (3.3%)	1033 (37.6%)
Influenza A H3N2	1 (0.2%)	420 (51.7%)	253 (68.0%)	963 (94.6%)	1637 (59.5%)
Other[†]	13 (2.4%)	25 (3.1%)	21 (5.6%)	21 (2.1%)	80 (2.9%)
Influenza B	3 (0.5%)	425 (34.2%)	78 (17.3%)	623 (37.8%)	1129 (29.0%)
Influenza A and B[‡]	0	4 (0.3%)	1 (0.2%)	6 (0.4%)	11 (0.3%)
Age (years)[§]					
<1	11/94 (11.7%)	26/226 (11.5%)	13/215 (6.0%)	43/246 (17.5%)	93/781 (11.9%)
1	18/113 (15.9%)	28/328 (8.5%)	15/293 (5.1%)	56/314 (17.8%)	117/1048 (11.2%)
2–4	64/234 (27.4%)	144/721 (20.0%)	59/505(11.7%)	165/570 (28.9%)	432/2030 (21.3%)
5–17	240/516 (46.5%)	544/1505 (36.1%)	167/960 (17.4%)	641/1438 (44.6%)	1592/4419 (36.0%)
18–24	89/247 (36.0%)	239/802 (29.8%)	57/395 (14.4%)	226/618 (36.6%)	611/2062 (29.6%)
25–49	102/353 (28.9%)	210/758 (27.7%)	94/555 (16.9%)	346/817 (42.4%)	752/2483 (30.3%)
50–64	22/90 (24.4%)	38/178 (21.3%)	35/216 (16.2%)	104/306 (34.0%)	199/790 (25.2%)
≥65	3/37 (8.1%)	12/45 (26.7%)	11/64 (17.2%)	66/161 (41.0%)	92/307 (30.0%)

Data are n (%) or n/N (%).

[*] Surveillance from October, 2009, to July, 2010; all other seasons include August to July of the following year.

[†] Of the 80 other and impossible to subtype viruses, one was an H3N2 variant, one was an H1N2 variant, and the remaining were weak influenza A positives that contained insufficient antigen for subtyping (the term variant describes human infection with a virus that normally circulates in swine).

[‡] Of the 11 influenza type A and B positive specimens, nine were influenza A H3 and two were 2009 pandemic influenza A H1N1.

[§] Age was missing for six patients; the denominator is the number of patients included in each age group in each year.

Table 2

Age-specific cumulative incidence of clinical visits for influenza-like illness and those attributable to influenza

	Influenza-like illness visits per 1000 people (95% CI)	Influenza-associated visits per 1000 people (95% CI)*			
		All influenza	2009 pandemic influenza A H1N1	Influenza A H3N2	Influenza B
2009–10†					
<2 years	67.8 (64.0–71.4)	14.1 (9.5–19.0)	13.9 (9.3–18.8)	0.0 (0.0–0.0)	0.2 (0.0–0.5)
2–4 years	62.9 (59.5–66.6)	22.0 (17.9–26.0)	20.8 (17.4–24.5)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
5–17 years	48.6 (47.0–50.2)	28.0 (25.9–30.0)	27.1 (25.0–29.2)	0.0 (0.0–0.0)	0.1 (0.0–0.4)
18–24 years	29.3 (28.1–30.5)	13.8 (11.8–15.6)	13.4 (11.5–15.2)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
25–49 years	17.4 (16.7–18.1)	5.8 (5.0–6.6)	5.5 (4.7–6.4)	0.0 (0.0–0.1)	0.0 (0.0–0.0)
50–64 years	11.0 (10.3–11.8)	2.9 (2.1–3.7)	2.9 (2.1–3.7)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
≥65 years	5.7 (5.1–6.4)	0.9 (0.6–1.3)	0.9 (0.6–1.3)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Total	25.4 (24.9–25.8)	10.6 (10.0–11.2)	10.3 (9.6–10.8)	0.0 (0.0–0.0)	0.0 (0.0–0.1)
2010–11					
<2 years	60.8 (58.1–63.8)	6.0 (4.8–7.3)	1.3 (0.7–1.9)	2.5 (1.7–3.4)	2.2 (1.5–3.0)
2–4 years	72.2 (68.9–75.6)	14.3 (12.5–16.3)	3.0 (2.1–4.0)	5.2 (4.1–6.3)	5.4 (4.3–6.7)
5–17 years	49.1 (47.5–50.6)	17.7 (16.6–18.8)	3.2 (2.6–3.7)	5.6 (5.0–6.3)	8.6 (7.9–9.4)
18–24 years	17.3 (16.5–18.1)	5.7 (5.2–6.2)	3.6 (3.2–4.0)	1.0 (0.7–1.2)	1.1 (0.9–1.4)
25–49 years	14.1 (13.4–14.8)	3.6 (3.3–4.1)	1.2 (1.0–1.5)	1.7 (1.5–2.0)	0.6 (0.4–0.7)
50–64 years	7.9 (7.1–8.7)	1.7 (1.3–2.2)	0.3 (0.1–0.5)	1.0 (0.7–1.4)	0.3 (0.1–0.5)
≥65 years	4.6 (3.9–5.4)	1.0 (0.6–1.4)	0.0 (0.0–0.0)	0.9 (0.5–1.3)	0.1 (0.0–0.2)
Total	25.7 (25.2–26.1)	7.0 (6.7–7.3)	2.1 (1.9–2.3)	2.3 (2.2–2.5)	2.4 (2.2–2.6)
2011–12					
<2 years	46.1 (43.9–48.6)	2.3 (1.6–3.0)	0.6 (0.3–0.9)	1.2 (0.7–1.7)	0.4 (0.1–0.7)
2–4 years	44.8 (42.5–47.5)	5.0 (3.9–6.1)	0.7 (0.4–1.1)	3.4 (2.5–4.5)	0.8 (0.4–1.2)
5–17 years	26.1 (25.2–27.2)	4.2 (3.7–4.7)	0.8 (0.6–1.1)	2.2 (1.8–2.6)	1.0 (0.8–1.3)
18–24 years	8.6 (8.1–9.1)	1.2 (1.0–1.5)	0.5 (0.3–0.6)	0.5 (0.3–0.7)	0.2 (0.1–0.3)
25–49 years	8.4 (8.0–8.8)	1.3 (1.1–1.6)	0.3 (0.2–0.4)	0.8 (0.6–0.9)	0.2 (0.1–0.3)
50–64 years	6.6 (6.1–7.2)	0.9 (0.7–1.2)	0.1 (0.1–0.2)	0.5 (0.3–0.7)	0.2 (0.1–0.3)

	Influenza-like illness visits per 1000 people (95% CI)	Influenza-associated visits per 1000 people (95% CI)*			
		All influenza	2009 pandemic influenza A H1N1	Influenza A H3N2	Influenza B
≥65 years	3.8 (3.3–4.3)	0.5 (0.3–0.7)	0.0 (0.0–0.0)	0.5 (0.3–0.7)	0.0 (0.0–0.0)
Total	14.2 (13.9–14.5)	1.9 (1.8–2.0)	0.4 (0.3–0.5)	1.0 (0.9–1.2)	0.4 (0.3–0.4)
2012–13					
<2 years	86.7 (91.6–100.0)	13.2 (11.2–15.2)	0.3 (0.0–0.7)	7.4 (5.9–9.0)	5.3 (4.0–6.9)
2–4 years	101.2 (98.4–106.2)	27.4 (24.4–30.4)	0.3 (0.0–0.8)	16.7 (14.3–19.1)	10.6 (8.8–13.0)
5–17 years	59.7 (58.4–61.6)	25.5 (24.0–26.9)	0.4 (0.2–0.7)	11.9 (10.8–12.9)	13.3 (12.2–14.4)
18–24 years	15.2 (14.6–15.9)	5.9 (5.4–6.4)	0.2 (0.1–0.3)	3.6 (3.2–4.1)	2.0 (1.6–2.3)
25–49 years	14.9 (14.3–15.6)	6.5 (6.0–7.0)	0.2 (0.1–0.3)	4.7 (4.2–5.1)	1.5 (1.2–1.7)
50–64 years	14.5 (13.6–15.6)	4.9 (4.3–5.7)	0.1 (0.0–0.2)	3.4 (2.8–4.0)	1.4 (1.0–1.9)
≥65 years	9.6 (8.7–10.7)	3.5 (2.9–4.2)	0.0 (0.0–0.0)	2.5 (2.0–3.1)	0.9 (0.6–1.3)
Total	30.4 (30.1–31.0)	10.7 (10.3–11.1)	0.2 (0.2–0.3)	6.2 (5.9–6.5)	4.1 (3.9–4.4)

*95% CIs were calculated using bootstrap sampling from the population of patients with influenza-like illness to account for variance in both the incidence of influenza-like illness and the proportion of influenza positive patients.

†Surveillance from October, 2009, to July, 2010; all other seasons include August to July of the following year.

Table 3

Demographic and clinical characteristics among outpatients with influenza-like illness

	All patients (n=13 905)*	Influenza-positive (n=3887)*	Influenza-negative (n=10 018)*	p value
Age (years)				<0–0001
<2	1825/13 905 (13.1%)	210/3884 (5.4%)	1615/10 015 (16.1%)	
2–4	2026/13 905 (14.6%)	431/3884 (11.1%)	1595/10 015 (15.9%)	
5–17	4409/13 905 (31.7%)	1589/3884 (40.9%)	2820/10 015 (28.2%)	
18–24	2062/13 905 (14.8%)	611/3884 (15.7%)	1451/10 015 (14.5%)	
25–49	2480/13 905 (17.8%)	752/3884 (19.4%)	1728/10 015 (17.3%)	
50–64	790/13 905 (5.7%)	199/3884 (5.1%)	591/10 015 (5.9%)	
≥65	307/13 905 (2.2%)	92/3884 (2.4%)	215/10 015 (2.1%)	
Male	6336/13 752 (46.1%)	1846/3848 (48.0%)	4490/9904 (45.3%)	0.0053
Ethnic origin				0.0312
White, non-Hispanic	6553/9857 (66.5%)	1752/2656 (66.0%)	4801/7201 (66.7%)	
Black, non-Hispanic	1331/9857 (13.5%)	360/2656 (13.6%)	971/7201 (13.5%)	
Hispanic	1369/9857 (13.9%)	349/2656 (13.1%)	1020/7201 (14.2%)	
Asian	323/9857 (3.3%)	107/2656 (4.0%)	216/7201 (3.0%)	
Other	281/9857 (2.9%)	88/2656 (3.3%)	193/7201 (2.7%)	
RIDT done	10 567/12 942 (81.6%)	3219/3693 (87.2%)	7348/9249 (79.4%)	<0.0001
RIDT positive	23 64/10 535 (22.4%)	1831/3216 (56.9%)	533/7319 (7.3%)	<0.0001
Antivirals prescribed	1644/11 953 (13.8%)	1119/3304 (33.9%)	525/8643 (6.1%)	<0.0001
Patients with onset ≤2 days	1358/7727 (17.6%)	946/2206 (42.9%)	412/5521 (7.5%)	<0.0001
RIDT-positive patients	890/1918 (46.4%)	795/1589 (50.0%)	95/1134 (8.4%)	<0.0001
Influenza vaccination†				
Age <18 years	2176/6947 (31.3%)	422/1812 (23.3%)	1754/5135 (34.2%)	<0.0001
Age ≥18 years	1113/4512 (24.7%)	301/1331 (22.6%)	812/3181 (25.5%)	0.385
Symptoms				
Cough	11 362/13 889 (81.8%)	3600/3887 (92.6%)	7762/10 002 (77.6%)	<0.0001
Sore throat	8444/13 810 (61.1%)	2384/3856 (61.8%)	6060/9954 (60.9%)	0.3064
Rhinorrhoea	6178/13 787 (44.8%)	1946/3861 (50.4%)	4232/9926 (42.6%)	<0.0001
Myalgia	4357/13 770 01.6%)	1615/3857 (41.9%)	2742/9913 (27.7%)	<0.0001
Congestion	4888/10 884 (44.9%)	1471/2979 (49.4%)	3417/7905 (43.2%)	<0.0001
Earache	1237/9993 (12.4%)	296/2746 (10.8%)	941/7247 (13.0%)	0.0028
Chills	3460/12 474 (27.7%)	1239/3434 (36.1%)	2221/9040 (24.6%)	<0.0001

Data are n/N (%) unless otherwise indicated. RIDT=rapid influenza detection test.

*Variation in denominator because of missing information for some patients.

†Influenza vaccination status reported by patients at the time of clinical consultation.