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Seasonal Incidence of Symptomatic Influenza in the United States

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Abstract

Background—The seasonal incidence of influenza is often approximated as 5%–20%.

Methods—We used 2 methods to estimate the seasonal incidence of symptomatic influenza in the United States. First, we made a statistical estimate extrapolated from influenza-associated hospitalization rates for 2010–2011 to 2015–2016, collected as part of national surveillance, covering approximately 9% of the United States, and including the existing mix of vaccinated and unvaccinated persons. Second, we performed a literature search and meta-analysis of published manuscripts that followed cohorts of subjects during 1996–2016 to detect laboratory-confirmed symptomatic influenza among unvaccinated persons; we adjusted this result to the US median vaccination coverage and effectiveness during 2010–2016.

Results—The statistical estimate of influenza incidence among all ages ranged from 3.0%–11.3% among seasons, with median values of 8.3% (95% confidence interval [CI], 7.3%–9.7%) for all ages, 9.3% (95% CI, 8.2%–11.1%) for children <18 years, and 8.9% (95% CI, 8.2%–9.9%) for adults 18–64 years. Corresponding values for the meta-analysis were 7.1% (95% CI, 6.1%–8.1%) for all ages, 8.7% (95% CI, 6.6%–10.5%) for children, and 5.1% (95% CI, 3.6%–6.6%) for adults.

Conclusions—The 2 approaches produced comparable results for children and persons of all ages. The statistical estimates are more versatile and permit estimation of season-to-season variation. During 2010–2016, the incidence of symptomatic influenza among vaccinated and unvaccinated US residents, including both medically attended and nonattended infections, was approximately 8% and varied from 3% to 11% among seasons.

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

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Keywords

influenza; incidence; meta-analysis; statistical estimation; seasonal influenza incidence

Seasonal influenza virus infection is so common that its incidence can only be estimated. The Centers for Disease Control and Prevention (CDC) maintains surveillance for a number of measures, such as the percentage of respiratory specimens submitted to clinical laboratories that are positive for influenza and the percentage of outpatient visits to sentinel physicians that are for influenza-like illness [1]. Using national registries of total hospitalizations and deaths along with data on the frequency of influenza virus detection in laboratories, regression models often are used to estimate the numbers of hospitalizations or deaths associated with influenza [2]. However, in the United States, there is no routine surveillance for the total number of laboratory-confirmed influenza infections, and the number of published studies that include such data is limited. In addition to the large numbers of influenza infections, difficulties with such studies include the great variability in influenza incidence among seasons and geographic areas and the need for expensive, frequent follow-up of a cohort of subjects to avoid missing symptomatic infections. In lieu of counting individual infections, the CDC Influenza Division makes statistical estimates of the seasonal number of influenza infections and the number of these infections averted by influenza vaccine [3, 4].

A common approximation is that “5%–20% of people get influenza each season.” This figure is based on a serologic study performed in Tecumseh, Michigan, during the 1976–1977 through 1980–1981 influenza seasons [5] and is widely used on websites [6, 7] and in the introduction section to peer-reviewed manuscripts [8, 9]. A recent systematic review [10] provides a more contemporary estimate, but includes many studies from outside the United States, and, because it is based on the placebo group in controlled vaccine trials, excludes a number of relevant cohort studies. The purpose of this manuscript is to summarize data on the incidence of symptomatic influenza among United States residents using 2 methods: a statistical estimate and a literature review and meta-analysis.

METHODS

Statistical Estimate

The methods used to make this estimate have been summarized previously and are outlined in Supplementary Table 1 [3, 4]. In short, the rate of hospitalizations with laboratory-confirmed influenza is determined from data collected by the Influenza Hospitalization Surveillance Network (FluSurv-NET) in >70 counties in 13 geographically dispersed states which represent about 9% of the United States population [1]. The number of hospitalizations with influenza was calculated by multiplying this rate by the United States population and then applying age group-specific adjustments for the percentage of hospital inpatients with respiratory disease that are tested for influenza and the sensitivity and specificity of laboratory methods used. To extrapolate to all influenza cases (ie, including those that are not hospitalized), the estimated number of hospitalizations was multiplied by a previously measured ratio of total influenza infections to those that result in hospitalization

[11]. Data from 6 seasons (2010–2011 to 2015–2016) are presented, stratified by age group (0–4 years, 5–17 years, 18–49 years, 50–64 years, 65 years) and for children <18 years and adults 18–64 years of age. These estimates for the numbers of infections among the mix of vaccinated and unvaccinated persons in the United States during 2010–2016, when a median of 44% of residents were vaccinated [12], were divided by the census population to estimate the seasonal incidence.

Literature Review

We sought articles with the following characteristics: English language; published during a 20-year period (influenza seasons 1996–1997 to 2015–2016 but excluding the 2009–2010 pandemic year); performed in the United States or Canada; and included follow-up of a defined group of subjects to detect symptomatic, laboratory-confirmed (by culture or reverse-transcription polymerase chain reaction [RT-PCR]) seasonal influenza during at least 1 influenza season (approximately October of 1 year to May of the following year). Studies with appropriate data included the placebo arm of controlled trials and cohort studies of respiratory virus incidence. Studies were excluded if a case-control, case-cohort, or design other than cohort was used; only medically attended subjects were included; or only members of a specific group were included (eg, subjects with a specific disease, healthcare workers, children or staff in childcare facilities, residents of long-term care facilities, military personnel, and religious group members).

We made a hand-search of articles that were known to the authors, written by authors who frequently publish on this subject, or included in recent review articles [10, 13]. Next, 4 databases were searched during February 2017 using a strategy developed by a reference librarian (Supplementary Table 2). One of the authors (J. I. T.) screened the titles and abstracts from all identified publications and performed a full-text review of the subset that appeared to meet inclusion criteria.

We abstracted the following variables: influenza season, type of study (clinical trial vs cohort study), site (eg, country, state, city), ages included, active (subjects contacted routinely to ascertain symptoms) vs passive (request that patient contact researcher if has symptoms) follow-up, swab type (throat, nose, nasopharyngeal, oropharyngeal), laboratory testing method (culture or RT-PCR), percentage of subjects with current-season vaccination, total number of subjects followed, and number or percentage with symptomatic laboratory-confirmed influenza. If data were presented separately for influenza types or subtypes, the numbers were added to estimate the total number with influenza (eg, if 10 subjects were reported with influenza A and 5 with influenza B, a total of 15 subjects with influenza was calculated). In clinical trials, per-protocol rather than intention-to-treat results were preferentially included.

To assess study quality, we adapted criteria from the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies [14] (Supplementary Tables 3–4). We assessed representativeness (geographic, age, and general characteristics) of the non-exposed cohort, adequacy of follow-up (eg, active vs passive follow-up) and assessment of outcome (sensitivity of symptoms prompting laboratory testing, eg, not requiring fever); and laboratory method. Items deemed not applicable included representativeness of the exposed cohort (there was

no exposure, ie, vaccinated group), ascertainment of exposure, demonstration that outcome was not present at the start of the study (not relevant for influenza), comparability of cohorts, and duration of follow-up (all included studies followed subjects for at least 1 influenza season).

We first performed descriptive analyses. Many studies included only unvaccinated subjects, and, where data were reported for a mix of vaccinated and unvaccinated subjects, the median percentage vaccinated was >60%, higher than in the United States general population. Therefore, to facilitate comparability with the statistical estimates, we limited meta-analyses to unvaccinated subjects and adjusted the results to approximate infection rates given median vaccination coverage and effectiveness during 2010–2016 (Supplementary Table 5). We performed meta-regression with Comprehensive Meta Analysis software version 3.3070 (Biostat, Englewood, New Jersey) and created forest plots and calculated random-effects summary incidences using the generic inverse variance method in Review Manager version 5.3 software (Cochrane Collaboration, Copenhagen, 2014). We calculated the standard error using methods appropriate for proportions. We adjusted for or stratified analyses by season severity and age group (children <18, adults 18–64, adults ≥65 years) because of prior evidence of the importance of these variables [5, 10, 15]. A previous systematic assessment had classified seasons 2003–2004 through 2013–2014 as low, moderate, or high influenza severity using 3 criteria: the maximum percentage of patients with influenza-like illness reported to the CDC Outpatient Influenza-like Illness Surveillance Network (ILINet), the percentage over baseline for pneumonia and influenza mortality from the 122 Cities Mortality Reporting System, and the hospitalization rate determined by FluSurv-NET [1]. For the 1996–1997 through 2002–2003 seasons, which were not included in the systematic assessment and for which hospitalization rate data were not available, we made severity assessments using similar methods but using only the first 2 criteria. FluSurv-NET has been determined to be public health surveillance that does not require human subjects review. Data for the meta-analysis came from published manuscripts, except that we obtained additional data for 4 of the studies [16–19] from the authors.

RESULTS

Statistical Estimate

The 6 influenza seasons covered by CDC estimates of influenza activity included 3 that were A(H3N2) predominant, 2 that were A(H1N1)pdm09 predominant, and 1 with mixed A(H3N2) and A(H1N1)pdm09 predominance (Table 1). Severity was moderate in 4 years, low in 1 year, and high in 1 year [20]. For all ages, median incidence was 8.3% (95% CI, 7.3%–9.7%) and varied among seasons from 3.0% to 11.3%. Median values were 9.3% (95% CI, 8.2%–11.1%) for children 0–17 years, 8.9% (95% CI, 8.2%–9.9%) for adults 18–64 years, and 3.9% (95% CI, 3.4%–4.2%) for adults ≥65 years (Table 2).

Literature Review

The database searches identified 5347 manuscripts, most from Ovid Medline (n = 4671) (Figure 1). After removal of duplicates, we screened 5288 by title and abstract, 94

underwent full text review, and 16 met study inclusion criteria. Of the 16, 15 had been identified by hand searches.

The 16 studies spanned the 1996–1997 to 2013–2014 influenza seasons (Table 3). Of the 16, 10 were controlled trials (data from the control arm was used) and 6 were cohort studies; most were intended to study the efficacy or effectiveness of influenza vaccine ($n = 14$). Many of the studies included a limited age range and required that subjects be “healthy,” most commonly excluding people with risk factors for influenza complications. Recruitment was of households in 5 and individuals in 11. One study was done in Canada, and the remainder in the United States. Throat swabs were used in 10, nasal swabs in 7, nasopharyngeal swabs in 4, and oropharyngeal swabs in 1 (total >16 since multiple swab types were used in some studies). Detection of influenza viruses was done by RT-PCR with or without culture in 9 studies and by culture only in 7. Data on unvaccinated subjects were reported for 15 studies and 12 had active follow-up for respiratory illness, contacting subjects at least every 2 weeks regarding respiratory symptoms.

Only 1 study of persons ≥ 65 years was identified [23] (Table 3). This study spanned 4 seasons and showed a pooled percentage with influenza of 3.2%. However, 94% of the subjects had received influenza vaccination and therefore this result is not comparable to the other studies identified. This study was not included in meta-analyses and no estimates for adults ≥ 65 years were made.

Of 15 manuscripts included in meta-analyses, study quality measures were high or intermediate for 9 for geographic representativeness, 13 for age representativeness, 15 for general representativeness, 12 for adequacy of follow-up, 13 for sensitivity of symptoms prompting laboratory testing, and 15 for laboratory method (Supplementary Tables 3 and 4). Geographic representativeness was rated as low in 6 studies because they were done in single cities.

The meta-regression model included 23 study seasons with data on children or adults (Table 4). The model explained 72% of between-study variance. Season severity and age group were highly significant predictors ($P < .0001$). Incidence was estimated to be 6.4% in adults and 4.5% higher (or 10.9%) in children during seasons of moderate severity. Additional variables that we evaluated and found to be nonsignificant are listed in Table 4 (data not shown).

We show data for all seasons, but show forest plots and random-effects incidence rates only for seasons of moderate severity (Figure 2A–2C). For children, there were 9 study seasons, 2 of low, 6 of moderate, and 1 of high severity; among seasons of moderate severity, there were 260 infections among 2028 persons (pooled incidence 12.0% [95% CI, 9.2%–14.7%]; Figure 2A and Table 2). For adults, there were 14 study seasons, 5 of low and 9 of moderate severity; among seasons of moderate severity, there were 241 infections among 4269 persons (pooled incidence was 6.1% [95% CI, 4.3%–7.9%]; Figure 2B). For persons of all ages, there were 5 study seasons, 1 of low and 4 of moderate severity; among seasons of moderate severity the pooled incidence was 8.9% (95% CI, 7.7%–10.2%; Figure 2C). After adjustment to reflect median vaccine coverage and effectiveness during 2010–2016,

estimated incidence was 8.7% for children, 5.1% for adults, and 7.1% for all ages (Table 2, Supplementary Table 5).

DISCUSSION

We used 2 methods to make an updated estimate of the seasonal incidence of symptomatic influenza, both medically attended and non-medically attended, among United States residents. The first (statistical estimation) method was based on CDC-measured rates of hospitalization with influenza that were adjusted to produce an estimate of total numbers of influenza infections. The second was a literature review and meta-analysis of published studies. The 2 methods produced similar incidence results for all ages (7%–8%) and for children (both 9%), but the statistical estimate was higher than the meta-analytic result for adults 18–64 years of age (9% vs 5%; Table 2). The statistical estimation method was more versatile, allowing estimates to be made for people of all ages, including those ≥ 65 years, and seasons of varying severity; by this method, incidence varied among seasons from 3% to 11%.

Because of its greater clinical relevance, we studied symptomatic influenza infection. Estimates of the percentage of influenza infections that are asymptomatic include a common approximation of 50% [33], 33% in 1 review [34] and 4%–28%, 0–100%, and 65%–85% in another review [35]. Both asymptomatic and symptomatic infections are captured in serological studies. The commonly cited “5%–20%” figure came from a serological study [5], and so represents both symptomatic and asymptomatic disease among a mix of vaccinated and unvaccinated persons. If 50% of influenza were symptomatic, this would correspond to “2.5%–10%” with symptomatic disease, which is very similar to the range that we report.

It is widely believed that influenza incidence is higher in children than in adults [15], but the magnitude of difference is uncertain and may differ by vaccination status and laboratory method. The ratio of incidence in children to adults was 4.2 in a recent meta-analysis of symptomatic infection [10] and 1.5–3.3 in 3 studies that used serology and therefore detected both symptomatic and asymptomatic infection [5, 36, 37]. Our results, which include only symptomatic infection, showed this ratio to be 1.0 (9.3/8.9) for mixed vaccinated and unvaccinated by statistical estimation, 2.0 (12.0/6.1) for unvaccinated by meta-analysis, and 1.7 (8.7/5.1) for vaccinated and unvaccinated by meta-analysis. Thus our statistical estimates show a smaller difference between children and adults than we found by meta-analysis and that was found in some prior studies.

The statistical estimation method that we present has become the primary way that CDC estimates the seasonal numbers of influenza infections, medical visits, hospitalizations and deaths due to influenza, and the numbers of these events that are prevented by vaccination. The strengths of this method include the careful yearly collection of hospitalization data from geographically representative regions that include approximately 9% of the United States population. This large sample size allows robust estimates, and yearly collection allows estimates of year-to-year variability. The 6 seasons we studied included 1 season of low and 1 season of high severity; therefore, the range that we report should be a good

estimate of seasonal variability. These advantages make the statistical estimation approach the preferred method to make updated and yearly estimates of seasonal influenza incidence.

Our literature review produced an important independent estimate of influenza incidence. We used a comprehensive search strategy (Supplementary Table 2), careful inclusion criteria, and an adaptation of an accepted quality assessment scale. Our meta-regression model explained a high proportion of between-study variance. After adjusting for season severity, only age group was a significant predictor and other factors that we assessed were nonsignificant. While culture is known to be less sensitive than RT-PCR for influenza detection [38], we were unable to demonstrate this effect in our meta-regression model, probably because of the small numbers of studies and multiple uncontrolled differences among the studies. Differences in results between the statistical estimate vs meta-analysis, particularly in adults, may be due to differences in seasons included or to limitations in the age-specificity of values used to make the statistical estimate.

Other limitations of the statistical estimate method have been discussed previously [3] and include the possibility of incomplete capture of all influenza cases hospitalized for conditions such as exacerbations of respiratory and circulatory disease. The adjustment for testing frequency could lead to an overestimate of influenza cases if influenza infection was less common among untested than tested patients. The hospitalization rates must be adjusted to estimate influenza infections using estimates of the ratio of total to hospitalized infections that are based on limited data collected before and during the 2009 pandemic. The literature review also had limitations. Only one person reviewed the references and abstracted data. Among the relatively small number of available studies, there were limitations of representativeness, especially geographically (eg, studies done in a single city). A minority of studies included subjects from the entire child (<18 years) or adult (18–64 years) age span, and no estimate for those ≥65 years of age could be made. Included subjects may not be representative of the US population age structure. While many studies excluded persons with medical conditions, such persons are not known to have a higher risk of influenza infection, although they do have a higher risk of complications if infected. Finally, we present estimates only for seasons of moderate severity because of the small numbers of studies available during high or low seasons.

The most important way to prevent influenza is yearly vaccination, which is recommended for everyone 6 months and older [39]. Other prevention measures include personal hygiene measures such as covering coughs and sneezes with a tissue, handwashing, and staying home when sick. Understanding the value of these approaches makes it essential to have routine measures of influenza activity. CDC's National Influenza Surveillance System collects and releases a number of measures each week through the FluView website [1], and these data are supplemented by statistical estimates. A simple and frequently encountered question is "What percentage of people have influenza illness each season?" We used 2 methods to answer this question and found similar answers, suggesting the validity of the statistical estimation method to make burden estimates that can be updated yearly. Using this method, we found that among the mix of vaccinated and unvaccinated persons in the United States during 2010–2016, the incidence of influenza was approximately 8% during seasons of moderate severity and varied from 3% to 11% among the seasons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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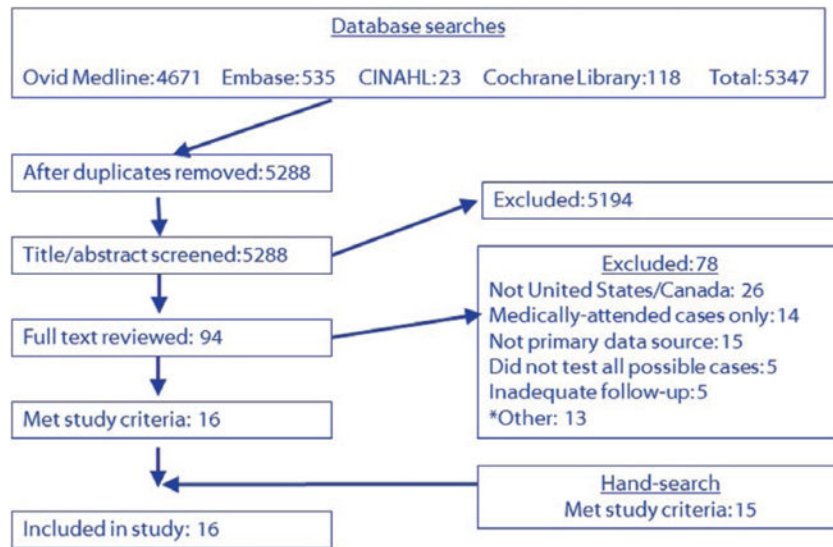


Figure 1.

Numbers of manuscripts screened and included in the study. *Did not follow for a full influenza season (n = 4), data from the 2009–2010 pandemic (n = 3), clinical trial without a placebo group (n = 3), subjects not from the general population (n = 3). Abbreviation: CINAHL, Cumulative Index to Nursing and Allied Health Literature.

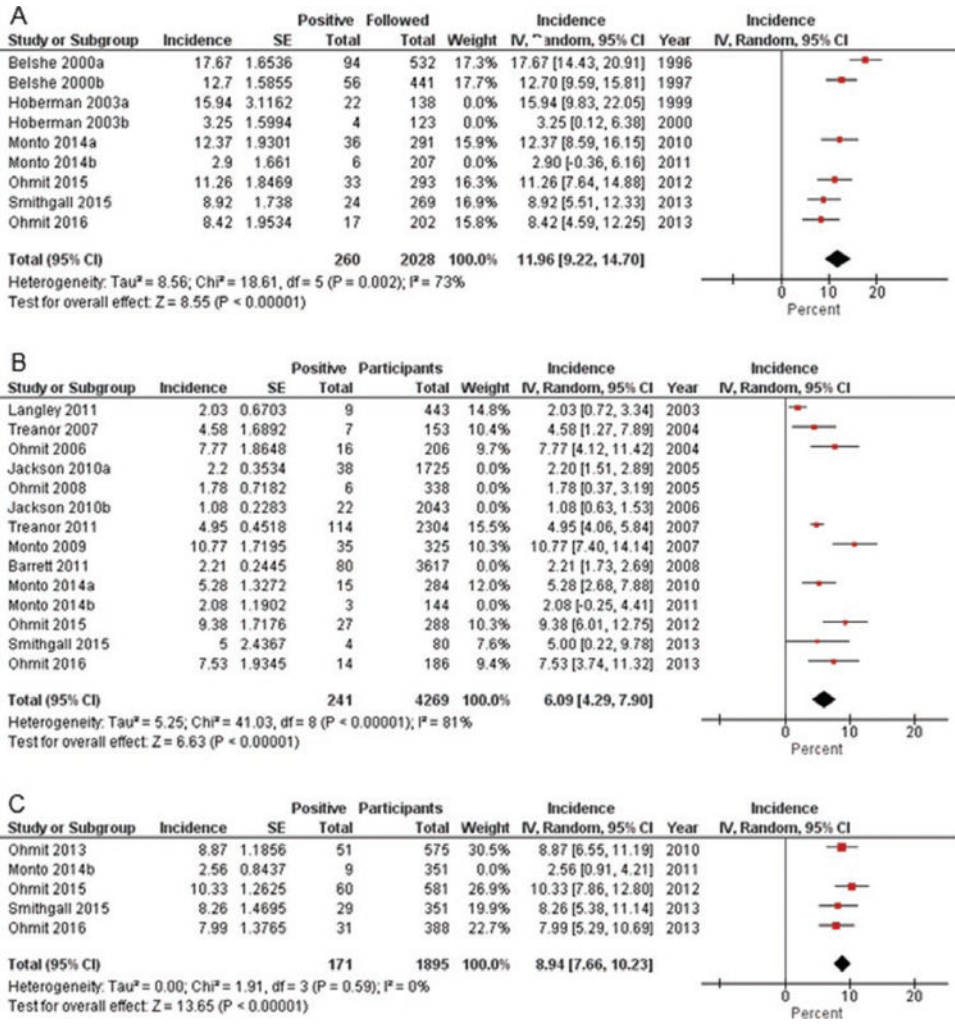


Figure 2. Influenza incidence in unvaccinated children aged <18 years (A), adults (B), and all ages (C), by season and study. Data is shown for all seasons, but forest plots and summary incidence include only seasons of moderate severity. “Year” denotes first year in the influenza season (eg, “1996” denotes the 1996–1997 influenza season). Thirteen of the 14 study seasons include only adults aged 18–64 years; 1 [30] may include some adults 65 years of age. Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Table 1
 Estimates of the Incidence of Symptomatic Influenza by Season and Age-Group, United States, 2010–2016

Season	Predominant Virus(es)	Season Severity [20]	Incidence ^a , %, by Age Group					
			0–4 y	5–17 y	18–49 y	50–64 y	65 y	All Ages
2010–2011	A/H3N2, A/H1N1pdm09	Moderate	14.1	8.4	5.3	8.1	4.3	6.8
2011–2012	A/H3N2	Low	4.8	3.6	2.5	3.1	2.3	3.0
2012–2013	A/H3N2	Moderate	18.6	12.7	8.9	14.3	9.9	11.3
2013–2014	A/H1N1pdm09	Moderate	12.4	7.2	9.2	13.0	3.4	9.0
2014–2015	A/H3N2	High	15.0	12.7	7.8	12.9	12.4	10.8
2015–2016	A/H1N1pdm09	Moderate	11.1	7.4	7.1	11.0	3.5	7.6
Median			13.2	7.9	7.4	12.0	3.9	8.3

Median influenza incidence 9.3% for children <18 years of age, 8.9% for adults 18–64 years of age. Confidence intervals for these incidence estimates are in Table 2 and Supplementary Table 1.

^a Values represent percentage of residents with influenza during the designated season estimated from hospitalization rates determined in the Influenza Hospitalization Surveillance Network (FluSurv-NET) [1] for a mix of vaccinated and unvaccinated persons (during 2010–2016, median 44% of United States residents were vaccinated [12]).

Table 2

Summary of Results, Incidence of Symptomatic Influenza in US Residents in Seasons of Moderate Severity, by Method of Estimation and Vaccination Category

Age Group, y	Statistical Estimation Method, Incidence, % (95% CI) ^a		Meta-analysis, Incidence, % (95% CI)	
	Vaccinated and Unvaccinated ^b	Unvaccinated ^c	Vaccinated and Unvaccinated ^{b,d}	
Children <18 y	9.3 (8.2–11.1)	12.0 (9.2–14.7)	8.7 (6.6–10.5)	
Adults 18–64 y	8.9 (8.2–9.9)	6.1 (4.3–7.9)	5.1 (3.6–6.6)	
Adults 65 y	3.9 (3.4–4.2)	No estimate	No estimate	
All ages	8.3 (7.3–9.7)	8.9 (7.7–10.2)	7.1 (6.1–8.1)	

Abbreviation: CI, confidence interval.

^aEstimates from Table 1.

^bMedian 44% of US residents were vaccinated during 2010–2016 (Supplementary Table 5) [12].

^cEstimates from Figure 2.

^dCalculated by reducing the incidence in unvaccinated by 28.6% for children, 16.4% for adults, and 20.4% for all ages (Supplementary Table 5).

Table 3

Studies of Influenza Incidence Identified by Literature Review, United States and Canada, 1996–2016

Author, Publication Year	Influenza Season(s)	Recruitment	Purpose ^d	Age Group (Ages Included)	Subjects	Site(s)	Swab Type	Laboratory Method	Follow-up (Frequency)
Barrett 2011 [21]	2008–2009	CT	Vaccine	Adult (18–49 y)	Healthy, exclude high risk	36 sites	NP	C	Passive
Belshe 2000 [22]	1996–1997, 1997–1998	CT	Vaccine	Child (15–85 mo)	Healthy, exclude high risk	10 sites	Not reported	C	Active (weekly)
Falsey 2005 [23]	1999–2000, 2000–2001, 2001–2002, 2002–2003	Cohort	Respiratory viruses	Senior (65 y)	Healthy, exclude if disabling disease	Rochester, NY	NP	C, P, S	Passive
Hoberman 2003 [24]	1999–2000, 2000–2001	CT	Vaccine	Child (6–24 mo)	Healthy, multiple exclusion criteria	Pittsburgh, PA	T	C	Active (biweekly)
Jackson 2010 [25]	2005–2006, 2006–2007	CT	Vaccine	Adult (18–49 y)	Healthy, multiple exclusion criteria	37–44 sites	NP/OP	C	Active (weekly)
Langley 2011 [26]	2003–2004	CT	Vaccine	Adult (18–64 y)	Healthy, multiple exclusion criteria	28 sites, Canada	N, T	C	Active (biweekly)
Monto 2009 [27]	2007–2008	CT	Vaccine	Adult (18–49 y)	Healthy, exclude high risk	4 college campuses, MI	T	C, P	Passive
Monto 2014 [16] ^b	2011–2012	Cohort	Respiratory viruses	Child (<18 y), Adult (18–64 y), All	Households with 4 members, 2 children <18 y	Ann Arbor, MI	N (age <3 y), N, T (age 3 y)	P	Active (weekly)
Ohmit 2006 [28]	2004–2005	CT	Vaccine	Adult (18–46 y)	Healthy, exclude high risk	2 university, 2 community sites in MI	T	C, P	Active (biweekly)
Ohmit 2008 [29]	2005–2006	CT	Vaccine	Adult (18–48 y)	Healthy, exclude high risk	4 university, 2 community sites in MI	T	C, P	Passive
Ohmit 2013 [18] ^b	2010–2011	Cohort	Vaccine	Child (<18 y), Adult (18–64 y), All	Households with 4 members, 2 children <18 y	Ann Arbor, MI	N (age <7 y), T (age 7 y)	P	Active (weekly)
Ohmit 2015 [19] ^b	2012–2013	Cohort	Vaccine	Child (<9 to 17 y), adult (18 to 50 y), All	Households with 4 members, 2 children <18 y	Ann Arbor, MI	N (age <3 y), N, T (age 3 y)	P	Active (weekly)
Ohmit 2016 [30]	2013–2014	Cohort	Vaccine	Child (<9 to 17 y), adult (18 to 50 y), All	Households with 4 members, 2 children <18 y	Ann Arbor, MI	N (age <3 y), N, T (age 3 y)	P	Active (weekly)
Smithgall 2016 [17] ^b	2013–2014	Cohort	Vaccine	Child (0–17 y), adult (18–64 y), all (0 to >64 y)	Households in low-income neighborhood	New York City, NY	N	P	Active (semi-weekly)
Treanor 2007 [31]	2004–2005	CT	Vaccine	Adult (18–49 y)	Healthy, exclude high risk	3 sites	NP	C	Active (weekly)
Treanor 2011 [32]	2007–2008	CT	Vaccine	Adult (18–49 y)	Healthy, exclude high risk	24 sites	N, T	C	Active (weekly)

Abbreviations: C, culture; CT, clinical trial; MI, Michigan; N, nose; NP, nasopharyngeal; NY, New York; OP, oropharyngeal; P, reverse-transcription polymerase chain reaction; PA, Pennsylvania; S, serology; T, throat.

^dPurposes include to study the efficacy or effectiveness of influenza vaccine on influenza incidence, or to study the frequency of respiratory viruses.

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Table 4 Meta-regression of Factors Influencing the Seasonal Incidence of Influenza Among Unvaccinated Persons in Published Studies, 1996–2013

Category	Variable	Study Seasons	Estimate	(95% CI)	P Value
Age	Intercept ^a	14	6.4	(5.2–7.6)	<.0001
	Children ^b	9	4.5	(2.7–6.3)	<.0001
Season severity	Moderate	15	Reference		<.0001
	Low	7	-5.2	(-6.8 to -3.6)	
	High	1	5.1	(-1.8 to 11.9)	

Includes 23 study seasons with data on children (<18 years) or adults. Proportion of total between-study variance explained by the model = 0.72. Other factors assessed that were nonsignificant included recruitment method (controlled trial vs cohort study), laboratory method (culture vs reverse-transcription polymerase chain reaction), follow-up (active vs passive), and secular trend.

Abbreviation: CI, confidence interval.

^aThe estimate for the intercept represents influenza incidence in adults; 13 of the 14 study seasons included only adults 18–64 years, but 1 study [30] may include some adults 65 years.

^bThe estimate of incidence in children is 4.5% higher than in adults, or 10.9%.