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Incidence of medically attended influenza infection and cases averted by vaccination, 2011/12 and 2012/13 influenza seasons

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Abstract

Background—We estimated the burden of outpatient influenza and cases prevented by vaccination during the 2011/12 and 2012/13 influenza seasons using data from the United States Influenza Vaccine Effectiveness (US Flu VE) Network.

Methods—We defined source populations of persons who could seek care for acute respiratory illness (ARI) at each of the five US Flu VE Network sites. We identified all members of the source population who were tested for influenza during US Flu VE influenza surveillance. Each influenza-positive subject received a sampling weight based on the proportion of source population members who were tested for influenza, stratified by site, age, and other factors. We used the sampling weights to estimate the cumulative incidence of medically attended influenza in the source populations. We estimated cases averted by vaccination using estimates of cumulative incidence, vaccine coverage, and vaccine effectiveness.

Results—Cumulative incidence of medically attended influenza ranged from 0.8% to 2.8% across sites during 2011/12 and from 2.6% to 6.5% during the 2012/13 season. Stratified by age, incidence ranged from 1.2% among adults 50 years of age and older in 2011/12 to 10.9% among children 6 months to 8 years of age in 2012/13. Cases averted by vaccination ranged from 4 to 41 per 1,000 vaccinees, depending on the study site and year.

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Conflicts of Interest

RKZ has received recent research grants from Sanofi, Merck, and Pfizer and has consulted for MedImmune. MG has recent research grants from MedImmune and Novartis. DM and BK have recent research grants from MedImmune. AM has received recent grant support from Sanofi Pasteur and consultancy fees from Sanofi, GSK and Novavax. The other authors report no conflicts of interest.

Conclusions—The incidence of medically attended influenza varies greatly by year and even by geographic region within the same year. The number of cases averted by vaccination varies greatly based on overall incidence and on vaccine coverage.

Keywords

Influenza; human; Influenza vaccines; Incidence

Introduction

Seasonal influenza epidemics cause considerable morbidity and mortality worldwide.[1-3] Many countries have implemented annual influenza vaccination programs to reduce the burden of illness caused by influenza, which involve considerable public health investments. (e.g. [4-6]) To evaluate vaccine program impact, policy makers need annual data on vaccine effectiveness (VE), on the burden of influenza disease, and on cases averted by vaccination. Several countries have systems in place to annually estimate influenza VE.[7-10] Estimates of the burden of influenza are more difficult to obtain, due to under-diagnosis of influenza in clinical settings.[11] Influenza-related hospitalizations or deaths are typically estimated retrospectively using ecologic trend studies.[12] A few household studies have estimated influenza incidence (e.g.[13]), but geographically diverse estimates of the incidence of outpatient influenza are generally lacking. Estimates of outpatient cases averted by vaccination currently come from models that infer outpatient burden from influenza hospitalization surveillance data and that combine surveillance and VE estimates from separate populations.[14, 15]

The United States Influenza Vaccine Effectiveness (US Flu VE) Network provides yearly estimates of influenza VE against medically attended influenza illness.[8, 16, 17] The network sites conduct active influenza surveillance among persons seeking outpatient care for acute respiratory illness (ARI) and estimate influenza VE using a test-negative design.[18] Several of the US Flu VE sites conduct this surveillance in populations that can be fully enumerated, and for whom demographic and health care utilization data are available, based on enrollment in health care payer and/or provider networks. In this study, we estimate the incidence of outpatient influenza and the cases prevented by vaccination in the US Flu VE Network over the 2011/12 and 2012/13 influenza seasons.

Methods

The US Flu VE Network consists of five geographically separated sites in the United States: Group Health Cooperative in western Washington State (GH); the Marshfield Clinic in Marshfield Wisconsin (MC); Scott and White Healthcare in Temple Texas (SW); the University of Michigan and the Henry Ford healthcare systems in Michigan (UM); and the University of Pittsburgh partnered with the UPMC healthcare system in Pittsburgh Pennsylvania (UP). For the present study, the University of Michigan subjects were restricted to the Henry Ford population, as an enumerated cohort could not be defined from the UM population. Data were available from UP for 2012/13 only.

Source populations

The GH source population consists of enrollees in the GH integrated group practice, who have healthcare coverage through GH and receive medical care from GH providers at GH medical centers. We restricted the population to GH enrollees whose primary healthcare provider was at one of three GH medical centers where active surveillance for influenza occurred. The MC population were members with at least 12 months of residency (or since birth for those less than 12 months old) in the central Marshfield Epidemiology Area Study, a 14 zip code region centered around Marshfield, Wisconsin.[19] The SW population consists of persons who had seen a SW primary care provider for any reason within the 3 prior years and lived in the Temple Population Research Area of East Bell County defined by zip codes (765xx, excluding 7654x). The UM population consists of all Health Alliance Plan insurance members who have identified a primary care provider within the Henry Ford Health System. The UP population consists of patients seen between July 1, 2011 and July 20, 2013 in selected UPMC primary care centers or in an after-hours care site located physically in a primary care site. Many of these practices are part of practice-based research networks (Pediatric PittNet and Family Medicine PittNet); all of these UP sites use a common electronic health record.

The ages of subjects in the source populations were defined as of September 1st of each study year. Because influenza vaccination is not recommended before 6 months of age, subjects < 6 months of age as of September 1st were not eligible for enrollment in the US Flu VE Network study and were excluded from study cohorts.

Influenza testing

Active surveillance for medically attended influenza in the US Flu VE Network has been described previously.[8] In brief, study staff (GH, MF, SW; UM in 2012/13) or clinical staff (UP, UM in 2011/12) identified patients seeking care for ARI, defined as illness with cough or fever/feverishness (2011/12 season) or illness with cough (2012/13 season) of less than eight days duration. Eligible patients provided informed consent, after which study staff collected nasal swabs (children <24 months of age) or both nasal and oropharyngeal swabs for testing. Specimens were tested for influenza A or B using real-time reverse transcriptase polymerase chain reaction (rRT-PCR), with probes and primers provided by the Centers for Disease Control and Prevention (CDC). Specimens positive for influenza A were further tested for subtype. US Flu VE Network enrollees who were not part of one of the defined source populations were excluded from the present study.

Covariate data

We used administrative data from healthcare payers and providers to define covariates for all subjects in the source population. We used enrollment data to define subjects' age, grouped as 6 months – 8 years; 9–17 years; 18–49 years; and ≥50 years. We used vaccination databases to classify all subjects as vaccinated (defined as having received at least one dose of seasonal influenza vaccination) or unvaccinated in each influenza season. We used International Classification of Diseases, Version 9, Clinical Modification (ICD-9) codes (available from the authors) to identify all outpatient visits for presumptive medically attended ARI (MAARI) during study periods, classified as 0, 1, or ≥2 MAARI visits.

Analyses

We extrapolated the number of medically attended influenza infections in our Flu VE enrollees to the entire source population. For this, we first stratified the source populations into mutually exclusive groups based on age, influenza vaccination, and number of MAARI visits during the study period. We stratified by number of MAARI visits because subjects with more MAARI visits may be more likely to seek care if they develop influenza. We then calculated a sampling weight for each Flu VE enrollee. The sampling weight for an enrollee of age group *a*, vaccine status *v*, MAARI visits *m*, and study site *s* was the ratio of the number of people in the source population in the (*a*, *v*, *m*, *s*) stratum to the number of Flu VE enrollees in that stratum. Rarely, some Flu VE enrollees had zero MAARI visits during the study period. These subjects were enrolled based on symptoms but were not assigned a MAARI ICD-9 code for the visit at which they were enrolled. We assumed that the only influenza illnesses among persons with zero MAARI visits were those detected by our surveillance, and assigned these Flu VE enrollees a sampling weight of 1.0. Using the sampling weights, we estimated the total number of medically attended influenza illnesses in each (*a*, *v*, *m*, *s*) stratum, with confidence limits calculated by bootstrap sampling from the source populations and Flu VE enrollees.

During the study period, influenza surveillance at the Flu VE Network sites did not always cover the full influenza season at all five sites. We adjusted the estimated case counts to account for cases occurring outside Flu VE surveillance. From state influenza surveillance data for Michigan, Pennsylvania, Texas, Washington, and Wisconsin, we determined the proportion of cases state-wide that occurred during Flu VE surveillance at each site.[20-25] We divided the estimated number of cases by these proportions for our final estimate of the number of persons with medically attended influenza in each (*a*, *v*, *m*, *s*) stratum. We then calculated the cumulative incidence of medically attended influenza in each stratum by dividing the estimated number of persons with medically attended influenza by the population size of each stratum.

We used age-specific estimates of influenza VE from the US Flu VE Network[8, 26] (Supplemental Table 1) to estimate the number of cases of medically attended influenza averted at each site. For these calculations, we assumed VE for a given age group was constant across study sites. For age group *a* at site *s*, the cases averted per 1,000 vaccinees ($averted_{s,a}$) were estimated as:

$$Averted_{s,a} = \frac{\frac{I_{s,a}}{1 - VE_a * p_{s,a}} - I_{s,a}}{p_{s,a}}$$

where $I_{s,a}$ is the cumulative incidence per 1,000 population, $p_{s,a}$ is vaccine coverage, and VE_a is estimated VE from the test-negative VE studies. $I_{s,a}$ was calculated as the weighted average of the estimated incidence of $I_{a,v,m,s}$ in stratum (s,a). We bootstrapped from the estimated values of $I_{s,a}$, VE_a, and $p_{s,a}$ to calculate 95% confidence limits for the cases averted. We also calculated the fraction of medically attended influenza cases prevented by vaccination. For this, we multiplied the estimated cases averted per 1,000 vaccinees by the proportion of the population that was vaccinated, and divided by the incidence per 1,000

population: ($Averted_{s,a}$ * $p_{s,a}$)/$I_{s,a}$. All analyses were conducted using SAS Version 9.2 (SAS Institute, Cary NC).

At three sites (UM, UP, and SW), influenza vaccination data for the Flu VE enrollees may be more complete than for non-enrolled members of the source population, as these sites do not have easy links to state vaccination registry data for their source populations. Underreporting of vaccine coverage ($p_{s,a}$) in the source population may lead to underestimation of cases averted. To put an upper bound on the impact of this underreporting, we conducted a supplemental analysis of the cases averted, in which we assumed that coverage by site and age group in the source population was as high as coverage in the Flu VE enrollees.

Results

The source populations ranged from 47,358 to 114,683 persons (Table 1). Overall, 9.6% of subjects were 6 months – 8 years of age, 10.7% were 9–17 years of age, 40.5% were 18–49 years of age, and 39.2% were ≥50 years of age; 29.9% received at least one dose of seasonal influenza vaccine. The proportion of the source populations who had at least one enrollment in the Flu VE study ranged from 0.2% to 3.1% across sites.

The 2011/12 influenza season showed considerable heterogeneity in influenza virus circulation across the study sites. Washington experienced a roughly even mix of A(H1N1), A(H3N2) and B viruses, Wisconsin and Michigan were dominated by A(H3N2), and Texas was dominated by A(H1N1) (Figure 1). Overall, during the 2011/12 influenza season, the cumulative incidence of medically attended influenza infection ranged from 7.9 per 1,000 population in Texas to 27.7 per 1,000 in Wisconsin (Figure 2). In all sites, the incidence was highest in children 6 months – 8 years of age, and tended to be lowest in adults ≥50 years of age.

In the 2011/12 influenza season, medically attended influenza cases averted by vaccination ranged from 4.1 cases per 1,000 vaccinees in Texas to 17.0 cases per 1,000 vaccinees in Wisconsin (Table 2). Summing across the sites, cases averted ranged from 7.0 cases per 1,000 among adults 18–49 years of age, to 19.1 cases per 1,000 vaccinees among children 6 months – 8 years of age. The fraction of cases averted was lowest in adults 18–49 years of age (9%) and highest in adults ≥50 years of age (28%).

The 2012/13 season was dominated by influenza A(H3N2) in Washington, while Wisconsin, Michigan, Texas, and Pennsylvania had extensive circulation of both A(H3N2) and B (Figure 1). Across sites contributing data in both seasons, the estimated incidence was higher in the 2012/13 season than the 2011/12 season, often substantially so (Figure 2B). The cumulative incidence of medically attended influenza ranged from 25.5 per 1,000 population in Washington to 64.5 cases per 1,000 in Texas (Table 2). Summing across the five sites, the incidence was lowest in adults 18 –49 years of age (37.7 cases per 1,000 population) and highest in children 6 months – 8 years of age (108.8 cases per 1,000 population); this trend was consistent at all sites except GH in Washington.

In 2012/13, cases averted by vaccination ranged from 17.0 cases per 1,000 vaccinees in Washington to 41.0 cases per 1,000 vaccinees in Wisconsin (Table 2). Across the sites, cases averted ranged from 85.1 per 1,000 vaccinees in children 6 months – 8 years of age to 16.1 cases per 1,000 in adults 18–49 years of age. The fraction of cases averted was lowest in adults 18–49 years of age (8%) and highest in children 6 months – 8 years of age (32%).

In supplemental analyses assuming that vaccine coverage in the source populations was the same as coverage in the Flu VE enrollees, estimates of cases averted changed little for the primary estimates using vaccination data on the source populations (Supplemental Table 2). The most extreme difference was from Pennsylvania, where our primary analysis with (18.3% vaccine coverage) estimated 30.7 cases averted per 1,000 vaccinees (95% CI, 16.5 to 45.9), while the supplemental analysis (41.1% vaccine coverage) estimated 35.0 cases averted per 1,000 vaccinees (95% CI, 18.4 to 53.1).

Discussion

We estimated the incidence of medically attended influenza during two influenza seasons at five geographically diverse sites across the United States. We found considerable heterogeneity in incidence across the United States, both across influenza seasons and within individual seasons. Within a season, the cumulative incidence varied roughly three-fold between study sites both in the mild 2011/12 season and in the more severe 2012/13 season. Across seasons, the cumulative incidence was up to eight-fold greater during the severe 2012/13 season than during the 2011/12 season. These findings are consistent with region-level year-to-year variations in laboratory-confirmed cases reported to CDC through the World Health Organization/National Respiratory and Enteric Virus Surveillance System collaborating laboratories.[27] Our results also highlight the importance of influenza: up to 64.5 per 1,000 of these insured populations sought outpatient care for influenza in 2012/13.

This study adds to prior estimates of outpatient influenza cases averted by vaccination.[14, 15, 28] During both the 2011/12 and 2012/13 influenza seasons the vaccine strains were reported to be similar to the circulating influenza strains.[29, 30] Influenza VE for preventing medically attended influenza was similar in both years, although overall VE was lower in seniors (65 years of age and older) in 2012/13 than in 2011/12.[8, 26] Even with similar VE across the two years, we found that outpatient visits averted by vaccination could vary 10-fold across sites by seasons, from a low of 4.1 per 1,000 vaccinees in Texas during the mild 2011/12 season to a high of 41.0 per 1,000 in Wisconsin during the 2012/13 season, due to variations in influenza attack rates and vaccine coverage. Even sites with similar vaccine coverage can vary greatly in cases prevented by vaccination, such as the nearly three-fold difference in cases averted between Washington and Wisconsin in 2012/13, due to differences in influenza attack rates. These results highlight the variable benefit of influenza vaccination programs even in settings with high vaccine coverage (approximately 50% in the Washington and Wisconsin populations).

CDC estimated that there were 14,431,371 medically attended influenza cases in the United States in 2012/13, which corresponds to an incidence of 46.7 cases per 1,000 population.[14] For this, they used hospital surveillance data to estimate the incidence of laboratory-

confirmed influenza hospitalizations, and then multiplied this rate by the expected ratio of outpatient visits to hospitalizations. Our estimates of incidence in 2012/13 ranged from 17.0 to 41.0 cases per 1,000 population across the study sites. The inferred nation-wide incidence is higher than even the site with the highest estimated incidence in our study data. Inferring the incidence of medically attended influenza from hospitalization data may overestimate the incidence of medically attended influenza infections.

We note several limitations of this study. Surveillance for influenza in the US Flu VE Network did not cover the entire influenza seasons, which could cause us to underestimate the cumulative incidence of influenza. We attempted to account for this by using state surveillance data to adjust our estimates for the proportion of state-wide influenza cases occurring outside times when US Flu VE Network surveillance was active. Second, data on vaccination status of the source populations at three sites were not well linked to state registries and may underestimate true vaccine coverage, which would lead us to underestimate the cases averted by vaccination. However, our supplemental analyses suggest that this underestimation will have relatively little impact on estimates of cases averted. Underreporting of vaccine coverage primarily occurs in adults, in whom the burden of influenza is lower than in children. Third, our estimates of cases averted are only of the direct effect of influenza vaccine on the vaccinated and do not account for any indirect effects that reduce the incidence of influenza in unvaccinated persons. Fourth, the study subjects were drawn from largely insured populations that may have different vaccination and healthcare-seeking behaviors than uninsured populations. However, our insured populations are largely representative of the greater populations from which they are drawn in terms of age, sex, race/ethnicity, and other factors (e.g. [19, 31]). Fifth, for 2012/13 our case definition required subjects to have cough, with or without fever. This case definition is likely more sensitive for influenza than case definitions that require fever,[32] but we may have missed some influenza cases that had fever without cough. Finally, we assumed that persons who sought care and did not receive a MAARI ICD-9 code did not have influenza, unless they were enrolled in the Flu VE Network study and tested positive for influenza. This means that we will have underestimated the true burden of influenza to the extent that persons seeking care for acute influenza infection do not receive a MAARI code.

This study has several strengths. To date, few studies have estimated the burden of outpatient influenza using individual-level data.[33, 34] Prior estimates of the burden of influenza have typically come either from ecologic studies (e.g. [35, 36]) or from combining data on hospitalizations and on expected patterns of illness severity from multiple studies and study populations (e.g. [15, 37]). In contrast, our study used individual-level data on a group of enumerated study populations for whom data were available on demographics, vaccination history, MAARI visits, influenza VE, and (on a sample) laboratory-confirmed influenza infections. The availability of all these data from within our study populations reduced our need to make assumptions about the homogeneity of care-seeking behavior across diverse populations, as has been needed in other studies of the burden of influenza or of cases averted by vaccination.[15, 37] Second, the availability of individual-level vaccine data also allows us to estimate cases averted by vaccination, which has not previously been attempted in individual-level studies. [33, 34] Finally, our study included geographically and

demographically diverse populations across the United States, which allowed us to capture the heterogeneity of influenza both within and between seasonal epidemics.

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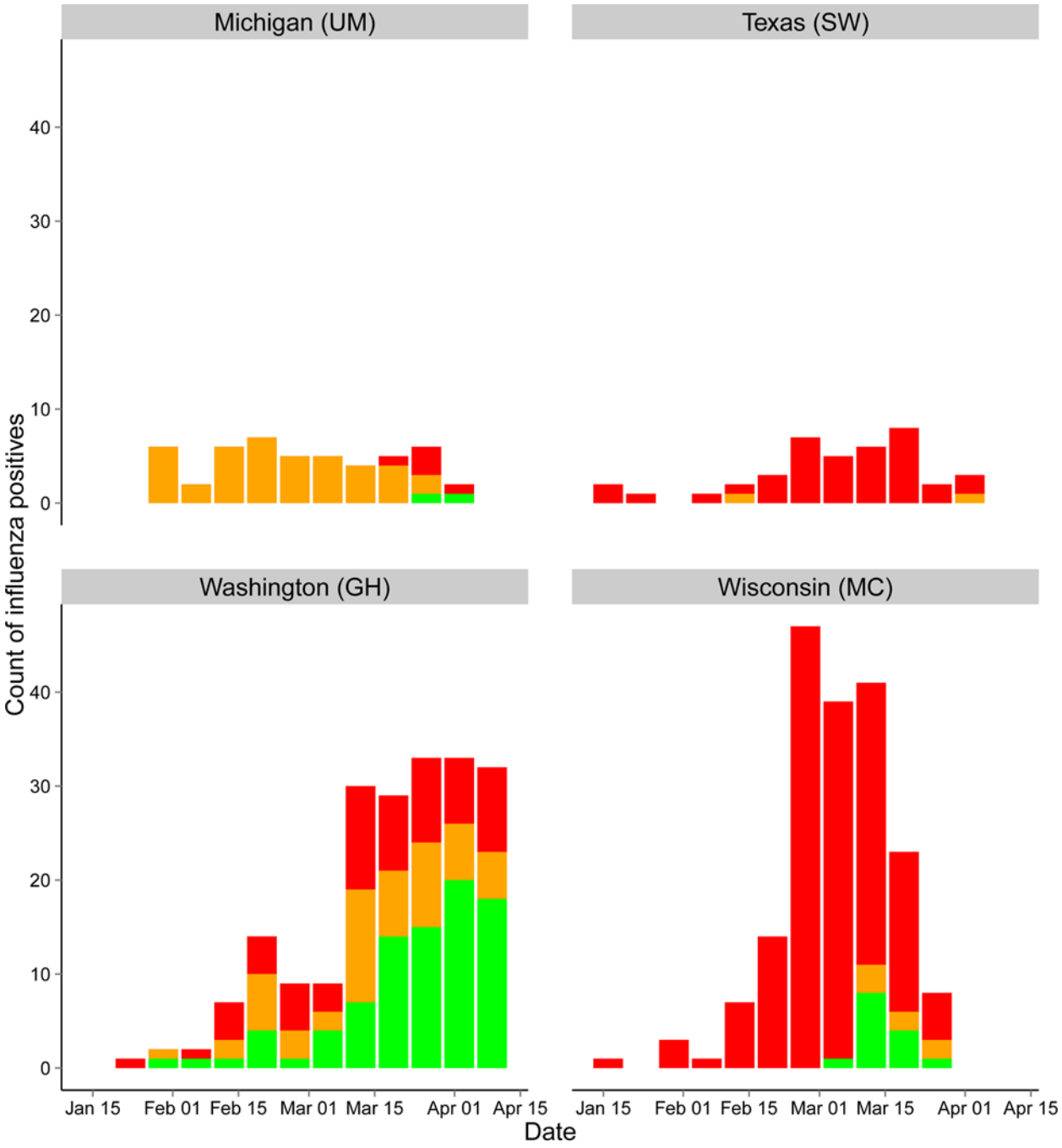

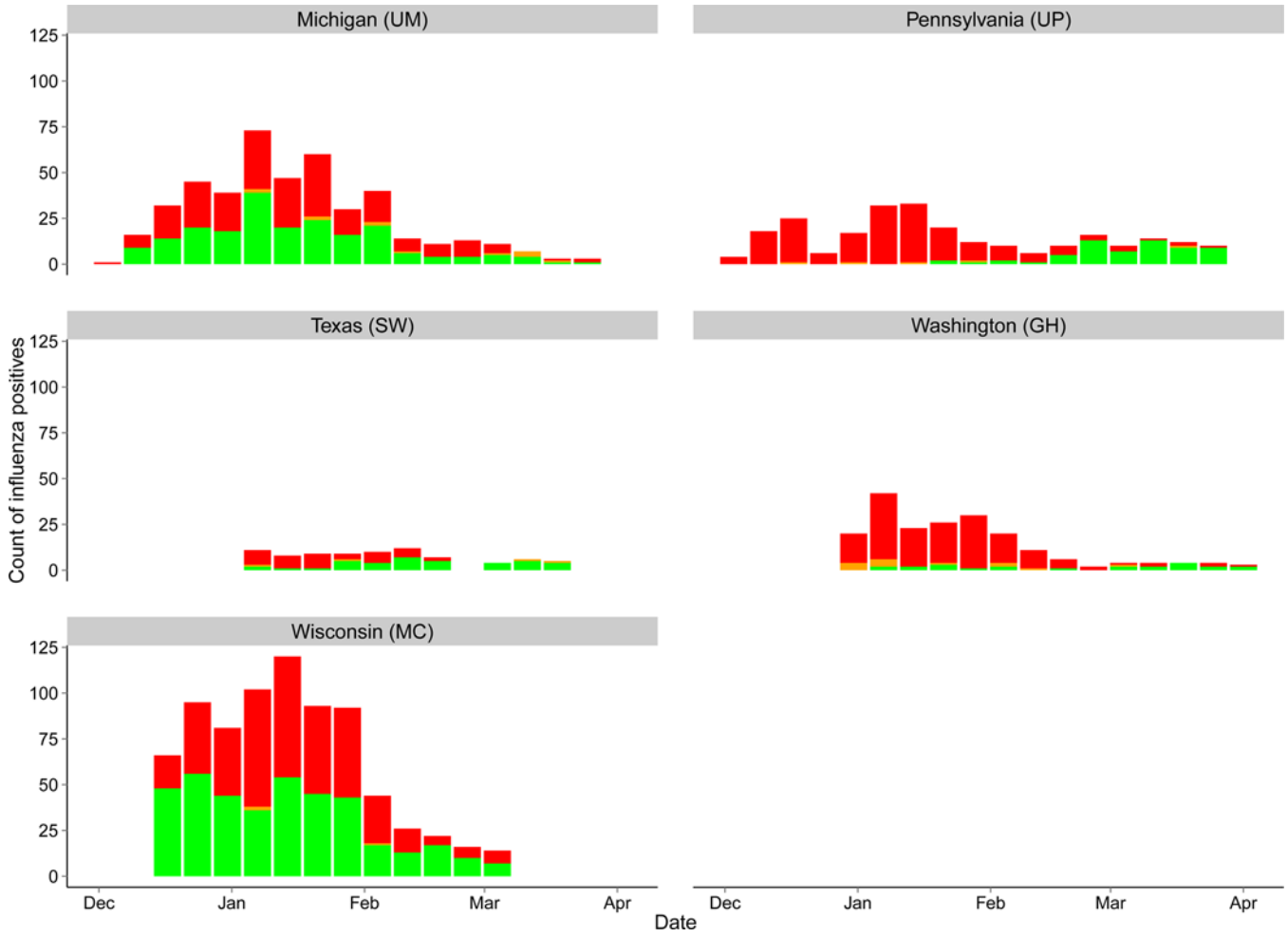

Figure 1.

Laboratory-confirmed influenza cases among US Flu VE Network enrollees, 2011/12 (A) and 2012/13 influenza seasons (B). Red= A(H3N2), Orange = A(H1N1), Green = B.

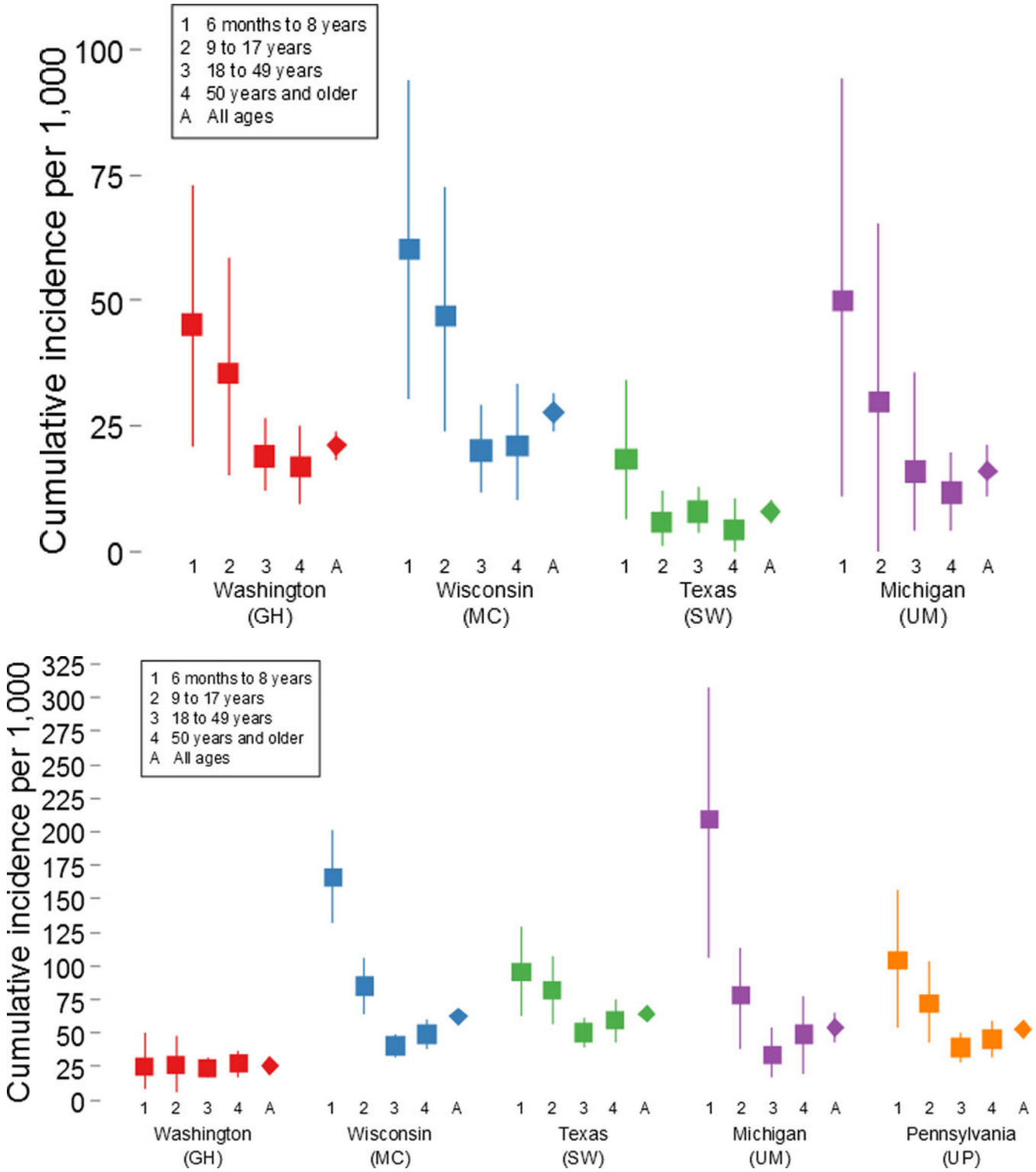

Figure 2.

Cumulative incidence of medically attended influenza infection, US Flu VE Network, (A) 2011/12 influenza season, (B) 2012/13 influenza season

Table 1

Distribution of source population by site, age, vaccination status, number of medically attended acute respiratory illness (MAARI) visits, and enrollment in the US Flu VE Network study

	2011/12 influenza season					2012/13 influenza season					
Category	**WA (GH)***	**WI (MC)**	**TX (SW)**	**MI (UM)**	**TOTAL**	**WA (GH)**	**WI (MF)**	**TX (SW)**	**MI (UM)**	**PA (UP)**	**TOTAL**
Total enrollees	84,881	47,358	112,518	98,498	343,255	82,261	48,525	99,177	84,148	114,683	428,794
Age											
0–8 years	6,031	4,887	15,723	3,680	30,321	5,165	5,065	15,040	4,102	14,347	43,719
9–17 years	6,310	5,546	14,562	8,522	34,940	5,432	5,718	13,519	9,769	13,343	47,781
18–49 years	35,949	18,565	46,318	31,748	132,580	34,851	18,850	38,495	34,362	53,262	179,820
50+ years	36,591	18,360	35,915	54,548	145,414	36,813	18,892	32,123	35,915	33,731	157,474
Vaccinated	39,405	19,554	20,144	25,059	104,162	42,854	21,850	24,773	16,328	21,017	126,822
MAARI visits											
0 visits	78,723	42,878	102,574	92,136	316,311	74,586	42,545	82,336	78,639	99,309	377,415
1 visit	4,994	3,405	7,808	5,395	21,602	6,021	3,729	11,968	5,009	12,637	39,364
2 or more visits	1,164	1,075	2,136	967	5,342	1,654	1,251	4,873	500	2,737	11,015
Flu VE enrollees†	1,071	1,036	797	181	3,085	957	1,512	1,394	173	791	4,827

*GH= Group Health Cooperative, MC = Marshfield Clinic, SW = Scott and White Healthcare, UM = University of Michigan and Henry Ford Healthcare, UP = University of Pittsburgh and UPMC healthcare system

†Subjects enrolled in the US Influenza Vaccine Effectiveness Network

Table 2

Incidence of medically attended influenza infection, influenza vaccine coverage, and cases averted by vaccination, stratified by site and by age group, 2011/12 and 2012/13 influenza seasons

2011/12		Cumulative incidence per 1,000 population			Cases averted per 1,000 vaccinees			Averted fraction		
Location	**Vaccine coverage**	**Estimate**	**LCL***	**UCL†**	**Estimate**	**LCL**	**UCL**	**Estimate**	**LCL**	**UCL**
WA	46.4%	21.1	18.1	23.9	13.1	3.2	25.1	29%	7%	55%
WI	41.3%	27.7	24.0	31.3	17.0	4.5	32.2	25%	7%	48%
TX	17.9%	7.9	5.7	10.1	4.1	0.5	8.3	9%	1%	19%
MI	25.4%	16.0	11.0	21.2	8.9	0.5	19.4	14%	1%	31%
Age										
6 months to 8 years	36.8%	34.3	13.6	58.8	19.1	3.9	37.4	21%	4%	40%
9 to 17 years	23.0%	23.6	7.0	43.1	16.3	3.0	32.3	16%	3%	32%
18 to 49 years	18.0%	14.5	7.1	24.3	7.0	1.9	13.0	9%	2%	16%
50+ years	42.0%	12.3	5.2	20.6	8.1	0.8	17.3	28%	3%	59%

2012/13		Cumulative incidence per 1,000 population			Cases averted per 1,000 vaccinees			Averted fraction		
Location	**Vaccine coverage**	**Estimate**	**LCL**	**UCL**	**Estimate**	**LCL**	**UCL**	**Estimate**	**LCL**	**UCL**
WA	52.1%	25.5	22.4	28.9	17.0	8.8	27.3	35%	18%	56%
WI	45.0%	62.2	58.7	65.7	41.0	25.9	57.5	30%	19%	42%
TX	25.0%	64.5	59.4	69.5	36.2	21.4	51.7	14%	8%	20%
MI	19.4%	54.0	42.7	65.3	29.6	13.0	48.0	11%	5%	17%
PA	18.3%	53.0	46.9	58.3	30.7	16.5	45.9	11%	6%	16%
Age										
6 months to 8 years	40.8%	108.8	65.4	154.3	85.1	47.1	125.6	32%	18%	47%
9 to 17 years	27.5%	72.4	44.4	100.9	30.2	10.1	51.6	11%	4%	20%
18 to 49 years	18.7%	37.7	26.6	49.8	16.1	9.1	23.8	8%	5%	12%
50+ years	39.5%	45.3	28.8	61.7	31.3	18.5	46.0	27%	16%	40%

*LCL = Lower 95% Confidence Limit

†UCL = Upper 95% Confidence Limit