Influenza Vaccine Effectiveness in the 2011–2012 Season: Protection Against Each Circulating Virus and the Effect of Prior Vaccination on Estimates

Suzanne E. Ohmit,[1] Mark G. Thompson,[2] Joshua G. Petrie,[1] Swathi N. Thaker,[2] Michael L. Jackson,[3] Edward A. Belongia,[4] Richard K. Zimmerman,[5] Manjusha Gaglani,[7,8] Lois Lamerato,[9] Sarah M. Spencer,[2] Lisa Jackson,[3] Jennifer K. Meece,[4] Mary Patricia Nowalk,[5] Juhee Song,[7,8] Marcus Zervos,[9] Po-Yung Cheng,[2] Charles R. Rinaldo,[6] Lydia Clipper,[7] David K. Shay,[2] Pedro Piedra,[10] and Arnold S. Monto[1]

[1]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor; [2]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Group Health Research Institute, Seattle, Washington; [4]Marshfield Clinic Research Foundation, Marshfield, Wisconsin; [5]Department of Family Medicine, and [6]Department of Pathology, University of Pittsburgh, Pennsylvania; [7]Scott and White Healthcare; and [8]Texas A&M Health Science Center College of Medicine, Temple, Texas; [9]Henry Ford Health System, Detroit, Michigan; [10]Baylor College of Medicine, Houston, Texas

(See the editorial commentary by Neuzil and Victor on pages 328–9.)

Background. Each year, the US Influenza Vaccine Effectiveness Network examines the effectiveness of influenza vaccines in preventing medically attended acute respiratory illnesses caused by influenza.

Methods. Patients with acute respiratory illnesses of ≤7 days' duration were enrolled at ambulatory care facilities in 5 communities. Specimens were collected and tested for influenza by real-time reverse-transcriptase polymerase chain reaction. Receipt of influenza vaccine was defined based on documented evidence of vaccination in medical records or immunization registries. Vaccine effectiveness was estimated in adjusted logistic regression models by comparing the vaccination coverage in those who tested positive for influenza with those who tested negative.

Results. The 2011–2012 season was mild and peaked late, with circulation of both type A viruses and both lineages of type B. Overall adjusted vaccine effectiveness was 47% (95% confidence interval [CI], 36–56) in preventing medically attended influenza; vaccine effectiveness was 65% (95% CI, 44–79) against type A (H1N1) pdm09 but only 39% (95% CI, 23–52) against type A (H3N2). Estimates of vaccine effectiveness against both type B lineages were similar (overall, 58%; 95% CI, 35–73). An apparent negative effect of prior year vaccination on current year effectiveness estimates was noted, particularly for A (H3N2) outcomes.

Conclusions. Vaccine effectiveness in the 2011–2012 season was modest overall, with lower effectiveness against the predominant A (H3N2) virus. This may be related to antigenic drift, but past history of vaccination might also play a role.

Keywords. influenza; medically attended influenza; vaccine effectiveness; ambulatory care.

Influenza vaccines are unique in requiring regular changes in composition to match the antigenic drift of the circulating virus strains [1]. They currently are recommended annually in the United States for all persons aged ≥6 months [2] and are composed of 3 strains representing influenza A (H3N2), A (H1N1), and B viruses, some of which may be new in a particular year and some of which may not. Because 2 distinct lineages of type B circulate, strains from both will soon be incorporated into what will then be a quadrivalent vaccine [3]. There is ample evidence that influenza vaccine effectiveness (VE) varies not only by virus type (subtype) but also from year to year [4]. A number of

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Correspondence: Suzanne E. Ohmit, DrPH, University of Michigan School of Public Health, 1415 Washington Heights, Ann Arbor MI 48109 (sohmit@umich.edu).

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explanations for these variations have been suggested, including antigenic match between vaccine and circulating strains, the age and health status of vaccine recipients, and the time between vaccine receipt and occurrence of the seasonal outbreak.

To monitor variation in VE, many countries have begun to conduct annual evaluations [5–9]. Various observational methods have been used, but most involve laboratory confirmation of illnesses as influenza and documentation of influenza vaccine receipt. Since the 2008–2009 influenza season, multiple centers in the United States have collaborated annually to estimate VE through the Influenza Vaccine Effectiveness (Flu VE) Network. This network examines the effectiveness of influenza vaccines in preventing medically attended acute respiratory illnesses caused by influenza. The network has quantified vaccine protection during seasonal outbreaks and has also demonstrated the effectiveness of the H1N1 pandemic vaccine once it became available in 2009 [5, 6].

We report here estimates of effectiveness of the 2011–2012 influenza vaccines, with special reference to protection against each circulating influenza virus and the effect of prior vaccination on estimates [10]. The influenza season was mild overall and peaked nationally in March 2012 with circulation of type A (H3N2) and A (H1N1) pdm09 viruses, plus type B viruses from both lineages [11].

METHODS

Subject Enrollment

We enrolled adults and children seeking care for acute respiratory illnesses at ambulatory care facilities, including urgent care clinics, affiliated with the Group Health Cooperative, Seattle, Washington; the Marshfield Clinic Research Foundation, Marshfield, Wisconsin; the University of Michigan School of Public Health partnered with the University of Michigan, Ann Arbor, and Henry Ford, Detroit, Health Systems, Michigan; the University of Pittsburgh Schools of Health Sciences partnered with the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; and Scott & White Healthcare, Texas A&M Health Science Center College of Medicine, Temple, Texas; these 5 centers comprised the US Flu VE Network. Enrollment of patients began after circulation of laboratory-confirmed influenza was identified through local surveillance at each network center.

Trained study staff reviewed clinic appointment schedules for chief complaints of interest (eg, cough, flu, asthma exacerbation) to identify patients with acute respiratory illnesses. These potentially eligible patients (or parents/guardians of minors) were approached and screened for study eligibility by brief interview. Patients with acute respiratory illness were eligible for enrollment if they were aged ≥6 months on 1 September 2011 and thus eligible for influenza vaccination and if their illness was characterized by cough and or fever/feverishness of ≤7 days' duration. Eligible patients provided informed consent for study participation, and consented subjects completed an enrollment interview and had throat swab and nasal swab specimens (or nasal swab only in patients aged ≤2 years) collected and combined for influenza identification.

Patient demographic characteristics (age, sex, race/ethnicity), illness onset date, symptoms present, subjective assessments of general [12] and current health status [13], and self-reported influenza vaccination status were ascertained by interview. Subjects were defined as high risk if they had medical record documentation during the year before enrollment of health conditions that increased their risk of influenza complications [2]. Influenza vaccination status for the 2011–2012 season was based on documented evidence of vaccine receipt from medical records or immunization registries. The 2011–2012 influenza vaccines contained the following virus strains: A/California/07/09 (H1N1pdm09), A/Perth/16/09 (H3N2), and B/Brisbane/60/08 (Victoria lineage) [14]. The study was reviewed and approved by the institutional review boards at participating network centers.

Laboratory Methods

Respiratory specimens collected from enrolled patients were tested for influenza virus identification at network laboratories by means of real-time reverse-transcriptase polymerase chain reaction (RT-PCR). The RT-PCR primers, probes, and testing protocol were developed and provided by the Centers for Disease Control and Protection Influenza Division and designed for universal detection of influenza A and B viruses, subtype identification of influenza A viruses, and lineage determination of influenza B viruses. Testing proficiency panels administered by the Centers for Disease Control and Prevention were successfully completed by all participating laboratories.

Estimation of Influenza VE

Influenza case patients were defined as persons with medically attended acute respiratory illnesses that were confirmed by RT-PCR as influenza; persons with similar illnesses that were negative by RT-PCR for influenza were termed control patients. This approach is termed a test-negative design and is described as analogous to an indirect cohort study [15]. Subjects were considered vaccinated if they had documented evidence of receipt of at least 1 dose of influenza vaccine for the current season at least 14 days before illness onset. Characteristics of case and control patients and vaccinated and unvaccinated patients were examined and compared by χ^2 tests. Differences in self-rated current health assessment scores (scale 1 [worst] to 100 [best]) were examined using the nonparametric Kruskal–Wallis test. VE was estimated by comparing the vaccination coverage in those who tested positive for influenza with those

who tested negative and calculated as 100 × (1 − odds ratio) in logistic regression models [15, 16]. Both unadjusted and adjusted effectiveness estimates were calculated; variables were included in adjusted models based on consideration of standard potential confounders [5, 6] or statistically significant covariables. Adjusted models included values for network center, patient demographic characteristics (age, sex, race/ethnicity), high-risk health status, self-rated health status, number of days between illness onset and specimen collection, and calendar time. Patient age was modeled as age in months using linear tail-restricted cubic spline functions with multiple knots. Calendar time was modeled as a series of dichotomous variables representing 2-week intervals of illness onset dates. Stratified effectiveness estimates were calculated by age category, by influenza virus type, A subtype and B lineage, and for children aged 2–17 years, by inactivated or live-attenuated vaccine type. Potential effect modification by prior season (2010–2011) vaccination status [10] was examined in logistic regression models with main effect and interaction terms for current and prior season vaccination status included as covariables. Further post hoc analyses estimated current season (2011–2012) VE stratified by prior season (2010–2011) vaccination status, plus VE for each combination of current and prior season vaccine exposure (ie, current only, both current and prior, prior only) with those subjects unvaccinated in both seasons as the reference group. Statistical analyses were conducted using SAS version 9.3 statistical software. $P < .05$ or a positive lower bound of the confidence interval for VE was considered to indicate statistical significance.

RESULTS

We enrolled 4852 patients with medically attended acute respiratory illnesses beginning in early January 2012; enrollment of case patients peaked in early March and continued into early May. Eighty-one (1.7%) enrolled subjects were excluded from analysis because their illness onset dates were >7 days before enrollment or they had missing data on key variables. These exclusions resulted in an analysis set of 4771 subjects, including 681 (14.3%) influenza-positive case patients and 4090 influenza-negative control patients; 440 (64.6%) influenza case patients were identified as having influenza A (H3N2), 110 (16.2%) as having influenza A (H1N1)pdm09, and 131 (19.2%) as having influenza type B.

Case and control patients did not significantly differ by sex, age, or race/ethnicity categories but did vary by influenza vaccination status, with case patients significantly less likely to have documented evidence of vaccine receipt (31.3% vs 48.5%; $P < .001$; Table 1). Case patients were less likely than control patients to have high-risk health conditions and were more likely to self-rate their general health status as excellent or very good; however, current illnesses were self-rated as more severe by case patients.

Vaccination coverage was highest in younger children and older adults (Table 2). Vaccinated subjects were more likely than the unvaccinated to have high-risk health conditions, to self-rate their general health status as fair or poor, and to be white (not Hispanic) compared with black or Hispanic. Eighty-one percent of vaccinated subjects had received the inactivated vaccine, and 8% had received the live-attenuated vaccine; for 11% of vaccinated subjects, vaccine type was unknown. Among case patients and controlling for interval between illness onset and enrollment, vaccinated and unvaccinated subjects self-rated the severity of their current illness similarly (51.4 vs 49.7; $P = .34$).

Overall adjusted VE was estimated as 47% (95% confidence interval [CI], 36–56) in preventing medically attended influenza (Table 3). In sensitivity analyses that considered only those subjects enrolled <5 days since illness onset, VE was nearly identical (46%; 95% CI, 33–57). Estimates stratified by age category indicated the highest point estimates were seen in children aged 9–17 years (58%; 95% CI, 27–76) and the lowest were seen in adults aged 18–49 years (44%; 95% CI, 21–60) and adults aged ≥65 years (43%; 95% CI, −18 to 72). Children aged <9 years are recommended to receive 2 doses of vaccine in the current season or 1 dose in each of the current and last seasons to be considered fully immunized [14]; the VE point estimate in fully immunized young children was substantially higher (51%; 95% CI, 27–68) than in partially immunized children (18%; 95% CI, −48 to 55). Also presented in Table 3 are estimates of effectiveness in children aged 2–17 years by whether the vaccine was inactivated or live-attenuated; 82% of live-attenuated vaccine doses used were administered to children. Effectiveness estimates were similar by vaccine type for older (aged 9–17 years) children; however, in young children, the point estimate was higher for recipients of the live-attenuated vaccine.

Adjusted VE was estimated as 65% (95% CI, 44–79) against influenza A (H1N1) pdm09 but only 39% (95% CI, 23–52) against influenza A (H3N2) (Table 4). Age-stratified effectiveness estimates against A (H3N2) among adults were similar (33%–42%) but with CIs with negative lower bounds (Supplementary Table 1). Adjusted VE was estimated as 58% (95% CI, 35–73) against influenza type B. Of note, the point estimate was lower against the B lineage (B/Brisbane/60/08 [Victoria lineage]) included in the vaccine than against the nonvaccine Yamagata lineage. Influenza type B cases were equally likely to be from the Victoria or Yamagata lineages, and both lineages infected subjects in all age categories (data not shown).

In initial VE analyses, a statistically significant interaction ($P = .007$) between current (2011–2012) and prior (2010–2011) season vaccination status was demonstrated. Based on this

Table 1. Descriptive Characteristics of Enrolled Patients With Medically Attended Acute Respiratory Illnesses by Case/Control Status

	Influenza-Positive Cases		Influenza-Negative Controls		
Characteristics	n = 681	Column %	n = 4090	Column %	*P* Value
Study community					<.001
Seattle, WA	223	32.7	1059	25.9	
Southeast, MI	196	28.8	961	23.5	
Marshfield, WI	166	24.4	774	18.9	
Temple, TX	47	6.9	709	17.3	
Pittsburgh, PA	49	7.2	587	14.4	
Sex					.07
Female	314	46.1	2040	49.9	
Male	367	53.9	2050	50.1	
Age categories					.22
6 mo – 8 y	190	27.9	1300	31.8	
9–17 y	111	16.3	555	13.6	
18–49 y	231	33.9	1318	32.2	
50–64 y	96	14.1	586	14.3	
≥65 y	53	7.8	331	8.1	
Race					.42
White (not Hispanic)	483	70.9	2867	70.1	
Black	86	12.6	416	10.2	
Hispanic	45	6.6	380	9.3	
Other	67	9.8	427	10.4	
Influenza vaccination status					<.001
Vaccinated[a]	213	31.3	1983	48.5	
Unvaccinated	468	68.7	2107	51.5	
High-risk health status					.02
Yes[b]	144	21.1	1038	25.4	
No	537	78.9	3052	74.6	
Reported general health status					<.001
Excellent	254	37.3	1347	32.9	
Very good	270	39.6	1430	35.0	
Good	117	17.2	970	23.7	
Fair/poor	40	5.9	343	8.4	
Illness onset to enrollment					<.001
<3 d	282	41.4	1295	31.7	
3–4 d	271	39.8	1636	40.0	
5–7 d	128	18.8	1159	28.3	
Current health assessment					
	Mean	SE	Mean	SE	<.001
Scale 1 (worst) – 100 (best)	49.9	0.82	58.7	0.33	

[a] Medical record and/or immunization registry documentation of receipt of at least 1 dose of 2011–2012 influenza vaccine ≥14 days before illness onset.

[b] Presence of ≥1 medical record–documented high-risk codes in prior year, as defined by Advisory Committee on Immunization Practices guidance for conditions that increase risk for complications from influenza.

evidence of effect modification, we also estimated VE stratified by prior season (2010–2011) vaccination status. Young children (aged <9 years) were excluded from this evaluation because of their specific recommendation for repeated vaccination [14]; the interaction in the subset of patients aged ≥9 years remained statistically significant ($P = .03$). Among those vaccinated in the prior season (2010–2011), the adjusted effectiveness of vaccination in the current season (2011–2012) was estimated as 33% (95% CI, −1 to 56). In contrast, among those not vaccinated in the prior season, the adjusted effectiveness of vaccination in the current season was 56% (95% CI, 37–69).

Table 2. Descriptive Characteristics of Enrolled Patients With Medically Attended Acute Respiratory Illnesses by Influenza Vaccination Status

	Vaccinated[a]		Unvaccinated		
Characteristics	n = 2196	Row %	n = 2575	Row %	*P* Value
Study community					<.001
Seattle, WA	630	49.1	652	50.9	
Southeast, MI	440	38.0	717	62.0	
Marshfield, WI	511	54.4	429	45.6	
Temple, TX	321	42.5	435	57.5	
Pittsburgh, PA	294	46.2	342	53.8	
Sex					.43
Female	1097	46.6	1,257	53.4	
Male	1099	45.5	1,318	54.5	
Age categories					<.001
6 mo – 8 y[b]	789	53.0	701	47.0	
9–17 y	230	34.5	436	65.5	
18–49 y	550	35.5	999	64.5	
50–64 y	341	50.0	341	50.0	
≥65 y	286	74.5	98	25.5	
Race					<.001
White (not Hispanic)	1612	48.1	1738	51.9	
Black	167	33.3	335	66.7	
Hispanic	179	42.1	246	57.9	
Other	238	48.2	256	51.8	
High-risk health status					<.001
Yes[c]	710	60.1	472	39.9	
No	1486	41.4	2103	58.6	
General health status					<.001
Excellent	704	44.0	897	56.0	
Very good	748	44.0	952	56.0	
Good	524	48.2	563	51.8	
Fair/Poor	220	57.4	163	42.6	
Illness onset to enrollment					.003
<3 d	676	42.9	901	57.1	
3–4 d	886	46.5	1021	53.5	
5–7 d	634	49.3	653	50.7	
Influenza test result					<.001
Negative	1983	48.5	2107	51.5	
Positive	213	31.3	468	68.7	
Influenza A	178	32.4	372	67.6	
Influenza B	35	26.7	96	73.3	

[a] Medical record and/or immunization registry documentation of receipt of at least 1 dose of 2011–2012 influenza vaccine ≥14 days before illness onset.

[b] Partially or fully immunized.

[c] Presence of ≥1 medical record–documented high-risk codes in prior year, as defined by Advisory Committee on Immunization Practices guidance for conditions that increase risk for complications from influenza.

We also calculated VE for each category of vaccine exposure (ie, current only, both current and prior, prior only) with those subjects unvaccinated in both seasons as the reference group. Results, presented in Table 5, indicate statistically significant protection with current season vaccine receipt whether or not vaccine was received the prior season; however, the point estimate was slightly higher for those vaccinated in the current season only. Low and nonsignificant residual protection was demonstrated for those subjects vaccinated in just the prior season. Alternative models were also generated for just influenza A (H3N2) outcomes (Supplementary Table 2); results here indicated larger differences in effectiveness point estimates based on prior season vaccination status, with no significant protection demonstrated for subjects vaccinated in the prior season.

As indicated previously, we required medical record/registry documentation of vaccination for an individual to be considered vaccinated. Influenza vaccines are now frequently administered outside of usual sites of healthcare delivery, and documentation of these vaccination events can be challenging. As a result, some vaccinated individuals could be misclassified as unvaccinated. In sensitivity analyses, 2 alternative means of representing vaccination status were considered. Both incorporated self-reported status and increased the proportion of subjects considered vaccinated. VE estimates using either approach were very similar to estimates based on medical record/registry–documented status (Table 6).

DISCUSSION

Population-wide assessments of VE have become more critical now given expanding recommendations for annual vaccination [2, 17]. For practical reasons, the studies that have evolved have been observational and mainly involve prevention of medically attended illnesses but with laboratory confirmation of influenza by RT-PCR. The test-negative design is frequently used in these observational studies to control for differences in healthcare-seeking behavior between vaccinated and unvaccinated persons [15]; these studies may still be affected by bias and uncontrolled confounding [15, 16, 18]. Many of the studies carried out in the United States and internationally have estimated overall VE as ≤60%, with variation based on virus type (subtype) [5–9]. There are methodological reasons that suggest that lower estimates would be expected in observational studies compared with those seen in clinical trials with random assignment [15, 16, 18]. Examining and explaining patterns and detecting changes in year-to-year estimates are the major reasons to carry out annual assessments, with the goals of quantifying

Table 3. Percentage Vaccinated by Influenza Case/Control Status, Plus Unadjusted and Adjusted Vaccine Effectiveness Estimates by Age Group and Vaccine Type

	Influenza-Positive Cases		Influenza-Negative Controls		Unadjusted		Adjusted[a]	
Age Group	No. Vaccinated[b]/Total	% Vaccinated	No. Vaccinated[b]/Total	% Vaccinated	VE %	(95% CI)	VE %	(95% CI)
Any seasonal vaccine								
All ages	213/681	31.3	1983/4090	48.5	52	(43 to 59)	47	(36 to 56)
6 mo – 8 y[c]	65/190	34.2	724/1300	55.7	59	(43 to 70)	45	(20 to 62)
9–17 y	26/111	23.4	204/555	36.8	47	(16 to 67)	58	(27 to 76)
18–49 y	58/231	25.1	492/1318	37.3	44	(23 to 59)	44	(21 to 60)
50–64 y	32/96	33.3	309/586	52.7	55	(29 to 72)	54	(23 to 72)
≥65 y	32/53	60.4	254/331	76.7	54	(15 to 75)	43	(−18 to 72)
Inactivated vaccine								
2–8 y[c]	38/158	24.1	302/787	38.4	49	(25 to 66)	40	(6 to 62)
9–17 y	20/105	19.0	139/483	28.8	42	(2 to 66)	61	(28 to 79)
Live-attenuated vaccine								
2–8 y[c]	9/121	7.4	87/537	16.2	58	(15 to 80)	61	(16 to 82)
9–17 y	5/88	5.7	39/368	10.6	49	(−33 to 81)	60	(−15 to 86)

Vaccine effectiveness was estimated by comparing the vaccination coverage in influenza positive cases and influenza negative controls and calculated as 100 × (1 − odds ratio) in logistic regression models.

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

[a] Models were adjusted for network center, subject age in months, sex, race/ethnicity categories, presence of high-risk health conditions, self-rated health status, time (days) between illness onset and specimen collection, and calendar time.

[b] Subjects were considered vaccinated if they had documented medical record or immunization registry evidence of receipt of at least 1 dose of influenza vaccine for the current season ≥14 days before illness onset.

[c] Partially or fully immunized.

the value of the US vaccine program, determining the effect of virus drift on protection, and identifying other factors that might affect VE.

In 2010–2011, a season also characterized by circulation of A(H3N2), A(H1N1) and type B viruses, the US Flu VE network's overall VE estimate was 60% (95% CI, 53–66) against all

Table 4. Unadjusted and Adjusted Vaccine Effectiveness, Overall and by Influenza Type, A Subtype and B Lineage

	Influenza-Positive Cases		Influenza-Negative Controls		Unadjusted		Adjusted[a]	
Influenza type;[b] A subtype; B lineage[c]	No. Vaccinated[d]/Total	% Vaccinated	No. Vaccinated[d]/Total	% Vaccinated	VE %	(95% CI)	VE %	(95% CI)
All Influenza A and B	213/681	31.3	1983/4090	48.5	52	(43–59)	47	(36–56)
Influenza A	178/550	32.4	1983/4090	48.5	49	(39–58)	44	(31–55)
A H3N2	155/440	35.2	1983/4090	48.5	42	(29–53)	39	(23–52)
A H1N1	23/110	20.9	1983/4090	48.5	72	(55–82)	65	(44–79)
Influenza B	35/131	26.7	1983/4090	48.5	61	(43–74)	58	(35–73)
Victoria	16/64	25.0	1983/4090	48.5	65	(37–80)	52	(8–75)
Yamagata	18/64	28.1	1983/4090	48.5	58	(28–76)	66	(38–81)

Vaccine effectiveness was estimated by comparing the vaccination coverage in influenza positive cases and influenza negative controls and calculated as 100 × (1 − odds ratio) in logistic regression models.

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

[a] Models were adjusted for network center, subject age in months, sex, race/ethnicity categories, presence of high-risk health conditions, self-rated health status, time (days) between illness onset and specimen collection, and calendar time.

[b] In separate sensitivity analyses, network centers that contributed <10 cases to a specific subtype/lineage were excluded; vaccine effectiveness estimates were identical or nearly identical to those presented here.

[c] Only 128 (98%) influenza B cases had lineage determined.

[d] Subjects were considered vaccinated if they had documented medical record or immunization registry evidence of receipt of at least 1 dose of influenza vaccine for the current season ≥14 days before illness onset.

Table 5. Unadjusted and Adjusted Vaccine Effectiveness, Stratified by Combinations of Prior (2010–2011) and Current (2011–2012) Influenza Vaccination Status Among Patients Aged ≥9 Years

	Influenza-Positive Cases		Influenza-Negative Controls		Unadjusted		Adjusted[a]	
	No. Cases/ Row Total	Row %	No. Controls/ Row Total	Row %	VE %	(95% CI)	VE %	(95% CI)
Vaccinated current 2011–2012[b] only	42/512	8.2	470/512	91.8	61	(45 to 72)	56	(37 to 69)
Vaccinated current 2011–2012[b] and prior 2010–2011[c]	106/895	11.8	789/895	88.2	41	(26 to 54)	45	(27 to 58)
Vaccinated prior 2010–2011[c] only	45/277	16.3	232/277	83.8	15	(–19 to 40)	18	(–20 to 43)
Not vaccinated either 2010–2011 or 2011–2012	298/1597	18.7	1299/1597	81.3	Reference		Reference	

Vaccine effectiveness (100 × [1 – odds ratio]) was estimated by calculating the ratio of the odds of a specific vaccine exposure (current only, both current and prior, and prior only) among influenza positive cases to the odds of that vaccine exposure among influenza negative controls, relative to those unvaccinated in both years, in logistic regression models. The *P* value for the interaction of prior (2010–2011) and current (2011–2012) season vaccination status for patients aged ≥9 years was .03.

Abbreviations: CI, confidence interval; VE, vaccine effectiveness

[a] Models were adjusted for network center, subject age in months, sex, race/ethnicity categories, presence of high-risk health conditions, self-rated health status, time (days) between illness onset and specimen collection, and calendar time.

[b] Subjects were considered vaccinated in 2011–2012 if they had documented medical record or immunization registry evidence of receipt of at least 1 dose of influenza vaccine for the current (2011–2012) season ≥14 days before illness onset.

[c] Subjects were considered vaccinated in 2010–2011 if they had documented medical record or immunization registry evidence of receipt of at least 1 dose of influenza vaccine for the 2010–2011 season.

types combined and 54% (95% CI, 42%–64%) against A (H3N2) [6]. Estimates in 2010–2011 from a similar network in Canada were lower overall and against A (H3N2) (37%, 95% CI, 17–52; 39%, 95% CI, 14–57, respectively) [9]. Circulating viruses in the 2010–2011 season were considered antigenically similar to strains included in the 2010–2011 vaccines, although some genetic variation among circulating A (H3N2) strains was observed [9, 19]. Because of the antigenic similarities, identical strains were selected for the 2011–2012 vaccine [14, 19]. In this study, we estimated adjusted VE of only 47% (95% CI, 35–55) overall for the 2011–2012 season and only 39% (95% CI, 23–52) against A (H3N2), the predominant circulating virus, with

Table 6. Percentage Vaccinated by Influenza Case/Control Status With Unadjusted and Adjusted Vaccine Effectiveness Estimates Using 3 Different Definitions of Influenza Vaccination Status

Any Seasonal Vaccine and All Ages	Influenza Positive (Cases)		Influenza Negative (Controls)		Unadjusted		Adjusted[a]	
	No. Vaccinated/Total	% Vaccinated	No. Vaccinated/Total	% Vaccinated	VE %	(95% CI)	VE %	(95% CI)
Vaccination status determined by:								
Medical record/registry documentation[b]	213/681	31.3	1983/4090	48.5	52	(43–59)	47	(36–56)
Medical record/registry documentation and/or self-reported[c]	226/681	33.2	2076/4090	50.8	52	(43–59)	48	(37–57)
Self-reported only[d]	251/657	38.2	2231/3929	56.8	53	(44–60)	49	(39–58)

Vaccine effectiveness was estimated by comparing the vaccination coverage in influenza positive cases and influenza negative controls and calculated as 100 × (1 – odds ratio) in logistic regression models.

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

[a] Models were adjusted for network center, subject age in months, sex, race categories, presence of high-risk health conditions, self-rated health status, time (days) between illness onset and specimen collection, and calendar time.

[b] Subjects were considered vaccinated if they had documented medical record or immunization registry evidence of receipt of at least 1 dose of influenza vaccine for the current season ≥14 days before illness onset.

[c] Subjects were considered vaccinated if they had documented medical record or immunization registry evidence and/or self-reported evidence of receipt (with date and location noted) of at least 1 dose of influenza vaccine for the current season ≥14 days before illness onset.

[d] Subjects were considered vaccinated if they self-reported receipt of at least 1 dose of influenza vaccine for the current season ≥14 days before illness onset (those with unknown self-report vaccination status were excluded).

the lowest estimates among adults. There was some degree of antigenic drift in the circulating A (H3N2) viruses reflected in the subsequent decision to update the A (H3N2) vaccine component for the 2012–2013 season [20]; this could account for some of the difference in estimates.

Another possible explanation for the lower than expected VE relates to the effect of prior year vaccination on current year effectiveness estimates. Here some of the apparent negative effect of prior vaccination may be due to residual protection; however, the effect is still seen when considering those unvaccinated in both years as the comparison group, particularly for A (H3N2). It is currently only possible to speculate on the reasons for this finding, which was also observed in the 2010–2011 season in a prospectively followed, highly vaccinated, household cohort of children and younger adults [10]. Although attenuated immunologic responses have been demonstrated with repeated vaccination [21–23], corresponding reductions in VE have not been consistently seen [24, 25]. It is important to determine if this phenomenon is real and a continuing issue, and if so, its basis, including how the antigenic relatedness between vaccine and circulating strains and between vaccine strains selected from year to year may contribute [26].

Two different lineages of type B virus have been circulating globally for many years [27]. They are distinct antigenically, and there is evidence, especially in very young children, that vaccination or infection with 1 lineage produces little antibody to the other [28, 29]. Inability to predict which type B virus will circulate in a particular year, as well as mixed outbreaks, has resulted in development of an, as yet unreleased, quadrivalent vaccine containing both B lineages [3]. In the 2011–2012 season, the vaccine contained a B/Victoria lineage virus only, but both B/Victoria and B/Yamagata strains circulated; both lineages infected subjects in all age categories. It was somewhat surprising that VE was similar against both lineages, suggesting that, at least during this single season, a quadrivalent vaccine may not have offered substantial protective benefit over the trivalent vaccine. Protection may also depend on the strains that had circulated recently because protection produced by past infection may be greater than that produced by vaccination [30].

VE studies are designed to be conducted annually, based on the recognition that year-to-year variation in VE does occur. Such studies are intended in part to determine the relation of effectiveness to the strains selected for the vaccine because such selection must consider many factors including antigenic and molecular analyses [1, 19]. In 2011–2012, a year of modest influenza activity, there was reduced VE against type A (H3N2). Although there was drift in the A (H3N2) viruses, we also demonstrated an apparent negative effect of repeated annual vaccination on effectiveness. Clearly, this phenomenon needs to be examined in other years when different strains are part of the vaccine, and, if present, a mechanism needs to be identified. We are at the threshold of introduction of a variety of new influenza vaccines, and studies intended for licensure will give only partial information on effectiveness. It is reassuring to know that annual VE studies will give us the ability to assess how well they work in large population groups of varying age and in comparison with one another. This will allow appropriate response because annual vaccination is a cornerstone of influenza prevention.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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