MAJOR ARTICLE

Influenza Vaccine Effectiveness in the Community and the Household

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(See the Editorial Commentary by Treanor and Szilagyi on pages 1370–2.)

Background. There is a recognized need to determine influenza vaccine effectiveness on an annual basis and a long history of studying respiratory illnesses in households.

Methods. We recruited 328 households with 1441 members, including 839 children, and followed them during the 2010–2011 influenza season. Specimens were collected from subjects with reported acute respiratory illnesses and tested by real-time reverse transcriptase polymerase chain reaction. Receipt of influenza vaccine was defined based on documented evidence of vaccination in medical records or an immunization registry. The effectiveness of 2010–2011 influenza vaccination in preventing laboratory-confirmed influenza was estimated using Cox proportional hazards models adjusted for age and presence of high-risk condition, and stratified by prior season (2009–2010) vaccination status.

Results. Influenza was identified in 78 (24%) households and 125 (9%) individuals; the infection risk was 8.5% in the vaccinated and 8.9% in the unvaccinated ($P = .83$). Adjusted vaccine effectiveness in preventing community-acquired influenza was 31% (95% confidence interval [CI], −7% to 55%). In vaccinated subjects with no evidence of prior season vaccination, significant protection (62% [95% CI, 17%–82%]) against community-acquired influenza was demonstrated. Substantially lower effectiveness was noted among subjects who were vaccinated in both the current and prior season. There was no evidence that vaccination prevented household transmission once influenza was introduced; adults were at particular risk despite vaccination.

Conclusions. Vaccine effectiveness estimates were lower than those demonstrated in other observational studies carried out during the same season. The unexpected findings of lower effectiveness with repeated vaccination and no protection given household exposure require further study.

Keywords. influenza; vaccine effectiveness; households with children.

Annual evaluation of influenza vaccine effectiveness, which may vary from year to year, is critical to inform the medical community, maintain public confidence in the vaccine, and determine the effect of virus drift on protection. Efficacy determinations with random assignment to vaccine or placebo interventions are no longer ethically acceptable in the United States given the current recommendation for universal vaccination [1]. As a result, there has been increased emphasis on use of observational studies for determination of effectiveness.

Innovative observational approaches have been developed to estimate vaccine effectiveness with laboratory-confirmed outcomes, particularly in preventing medically attended acute respiratory infections (MAARI). Recent MAARI studies in Europe, Canada, and the United States have used an approach in which vaccine effectiveness is estimated by comparing vaccination coverage in persons who test positive for influenza with those who test negative [2–5]. These studies

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utilize a variation of the traditional case-control design and it is not yet clear whether they adequately account for the range of biases typically associated with such studies [6].

There has been a long tradition of using household cohorts to study incidence and transmission of respiratory illnesses of all severities [7]. Households are thought to play a major role in community spread of influenza and as such have been the focus of planning for community influenza control [8, 9]. Data from household studies carried out decades ago were vital more recently in developing models to determine national response to an influenza pandemic [8, 10]. During the recent pandemic, a limited number of studies of influenza transmission and vaccine effectiveness at the household level were carried out [11, 12].

We recruited and followed a cohort of 328 households during the 2010–2011 influenza season, and estimated vaccine effectiveness in preventing symptomatic laboratory-confirmed influenza whether medically attended or not. This study offered the unique opportunity to examine vaccine effectiveness in preventing community-acquired influenza and influenza acquired in persons with confirmed household exposure.

METHODS

Recruitment and Enrollment

The cohort of households was derived from persons who had selected a primary healthcare provider from within the University of Michigan Health System based in Ann Arbor. Eligible households (shared residence) were comprised of at least 4 members, at least 2 of whom were children aged <18 years. Households with appropriate composition and local residence were targeted for study enrollment by direct mail.

Interested households attended an enrollment visit at the research study site at the University of Michigan, School of Public Health (UM-SPH); adult household members provided written informed consent for participation for themselves and their children, and children aged 7–17 years provided their oral assent. Study eligibility was verified, and member demographic data recorded. Adult household members reported, for themselves and their children, whether or not influenza vaccine had been received for the current season. The study was approved by the institutional review board at the University of Michigan Medical School.

Influenza Surveillance

Surveillance was initiated in October 2010 and carried out through the end of local influenza circulation in April 2011. Households were instructed at enrollment and via weekly telephone or email reminders to report all acute respiratory illnesses defined by 2 or more of the following symptoms: cough, fever or feverishness, nasal congestion, chills, headache, body aches, or sore throat [13]. This case definition was intended to facilitate collection of specimens from even mild illnesses. Subjects with eligible illnesses attended an illness visit (at the research study site) within 7 days of illness onset and had a throat swab (or nasal swab in children age <7 years) collected for influenza virus identification. Illnesses were followed for collection of data on illness characteristics, including whether or not the participant sought medical attention.

Collected specimens were tested for influenza identification by means of real-time reverse transcriptase polymerase chain reaction (RT-PCR) using the SuperScript III Platinum One-Step Quantitative RT-PCR system and an ABI 7500 RT-PCR system platform (Life Technologies). The primers and probes used were developed by the Influenza Division of the Centers for Disease Control and Prevention, and designed for universal detection of influenza A and B, and subtype identification of influenza A viruses. Laboratory tests were performed in the investigators' respiratory virus laboratory at UM-SPH.

Statistical Analyses

Households were characterized by size and composition, and subjects by demographics, health history, and vaccination status. Receipt of influenza vaccine was defined on the basis of documented evidence of vaccination in health system medical records or the Michigan Care Improvement immunization registry. Medical records were also reviewed to document the presence of health conditions considered high risk for complications of influenza [1]. Associations of subject characteristics with influenza vaccination status and influenza outcomes were examined and compared. Categorical data were analyzed using a χ^2 test.

Cox proportional hazards models were used to estimate the effectiveness of influenza vaccination at least 14 days prior to symptom onset in preventing laboratory-confirmed influenza. To adjust for correlation of exposures and outcomes among subjects in the same household, we computed robust variances for model parameter estimates using sandwich estimators [14]. Vaccine effectiveness was calculated as 100*(1 – hazard ratio), and estimated in both unadjusted and adjusted models. Adjusted models included prespecified potential confounders (age and presence of a high-risk health condition); in preliminary analyses, no other confounders were identified. Stratified models examined the influence of prior season (2009–2010) vaccination status on effectiveness estimates based on evidence of effect modification demonstrated in preliminary analyses. Effect modification was noted for both prior seasonal (trivalent) and prior pandemic (monovalent) vaccination, but was statistically significant only for prior seasonal vaccination. Receipt of prior season vaccine(s) was based on documented evidence of vaccination in medical records.

Analyses estimated vaccine effectiveness in preventing community-acquired influenza (household index cases) and, separately, household-acquired influenza (secondary cases resulting from exposure to household index cases). A secondary (household-acquired) case was defined by transmission link to an index case if both cases were the same influenza type/subtype and illness onset in the secondary case occurred from 1 to 7 days after illness onset in the index case. Vaccine effectiveness in the community was estimated by comparing the hazard of laboratory-confirmed influenza among vaccinated and unvaccinated subjects; cases that were linked by transmission (household-acquired) were censored at the time of illness onset. Vaccine effectiveness in the household was estimated by comparing the hazard of laboratory-confirmed influenza, among those vaccinated and unvaccinated subjects exposed to a household index case. Only the first influenza illness was considered for those individuals with multiple influenza outcomes in analysis of community-acquired influenza (3 outcomes excluded); similarly, only influenza outcomes resulting from the first introduction of influenza to a household were considered (4 outcomes excluded). Additional analyses estimated influenza type/subtype-specific vaccine effectiveness for community-acquired illnesses. All statistical analyses were conducted using SAS (release 9.2, SAS Institute) software. A P value <.05 was considered to indicate statistical significance.

Table 1. Characteristics of Participating Household Members by Documented Influenza Vaccine Receipt and Influenza Outcomes

Participant Characteristics	All Subjects[a]	Documented Influenza Vaccination[b,c]	Influenza Positive Cases[d]
Age category			
<9 y	468 (32.5)	323 (69.0)**	70 (15.0)**
9–17 y	371 (25.7)	225 (60.6)	23 (6.2)
18–49 y	544 (37.8)	280 (51.5)	31 (5.7)
50–72 y	58 (4.0)	38 (65.5)	1 (1.7)
Race categories			
White	1097 (76.1)	662 (60.3)	103 (9.4)
Asian	120 (8.3)	81 (67.5)	6 (5.0)
Black	83 (5.8)	40 (48.2)	5 (6.0)
Other/unknown	141 (9.8)	83 (58.9)	11 (7.8)
Sex			
Female	728 (50.5)	458 (62.9)*	57 (7.8)
Male	713 (49.5)	408 (57.2)	68 (9.5)
Documented high-risk health condition			
Any	162 (11.2)	122 (75.3)**	19 (11.7)
None	1279 (88.8)	744 (58.2)	106 (8.3)
Documented influenza vaccination[b]			
Yes	866 (60.1)	…	74 (8.5)
No	575 (39.9)	…	51 (8.9)
Total	1441(100)	866 (60.1)	125[e] (8.7)

Household Influenza Vaccine Effectiveness (HIVE) Study, Ann Arbor, Michigan (2010–2011 Influenza Season). Data are presented as No. (%).

[a] Denominator for percentages presented in this column is all subjects (N = 1441).

[b] At least 1 influenza vaccine given anytime during the 2010–2011 vaccination period as documented in the medical record or state registry.

[c] Denominator for percentages presented in this column is all subjects (vaccinated and unvaccinated) in the given characteristic row.

[d] Denominator for percentages presented in this column is all subjects (with and without influenza) in the given characteristic row.

[e] One hundred thirty influenza cases were identified in 125 individuals. The characteristics of those individuals are presented here.

* χ^2 P < .05, comparing vaccinated and unvaccinated subjects or subjects with and without laboratory-confirmed influenza.

** χ^2 P < .001, comparing vaccinated and unvaccinated subjects or subjects with and without laboratory-confirmed influenza.

RESULTS

Characteristics of Households and Participants

Enrollment of households closed in October 2010 when the sample size goal was met; a total of 524 (12% of 4511 targeted households) expressed an interest in study participation, and 328 households with 1441 participants were enrolled. Household size ranged from 4 to 9 members (mean, 4.4 [SD, 0.7]). Based on enrollment criteria, all households had at least 2 participating children; 238 (73%) households had 1 or more young children (age <9 years).

Participant characteristics, including distributions of vaccination status and influenza outcomes, are presented in Table 1. Among the 1441 enrolled individuals, 58% were children aged <18 years, and 99% reported health insurance coverage. Race categories reflected the local community. Eleven percent of subjects had medical record documentation of health conditions placing them at increased risk of complications from influenza [1].

Overall, 866 (60%) participants had medical record or immunization registry documentation of influenza vaccine receipt for the 2010–2011 season. Sixty-eight (5%) additional subjects reported vaccine receipt that could not be documented; all provided information on type, date, and place of vaccine receipt. Documented vaccine coverage significantly varied by age category (P < .001); coverage was lowest among adults aged 18–49 years (52%). Among children aged <9 years, 323 (69%) had documented receipt of at least 1 dose of vaccine and 252 (54%) were considered fully vaccinated [1]. Female subjects were significantly more likely than male subjects to have documented vaccine receipt (P = .028); 75% of subjects with 1 or more high-risk health conditions were vaccinated compared with 58% of subjects without high-risk conditions (P < .001). Among vaccinated subjects, 758 (88%) had documented receipt of an inactivated vaccine, and 108 (12%) the live attenuated vaccine; children were the primary

recipients of the live attenuated vaccine (96% of doses administered).

Illness Surveillance and Influenza Outcomes

From October 2010 through April 2011, 624 (43%) individuals from 238 (73%) households reported 1028 acute respiratory illnesses and 983 (96%) specimens were collected. All specimens were tested for influenza by RT-PCR and 130 (13%) were determined to be positive; influenza circulated locally between early January and early April 2011. Among the influenza cases, 59 (45%) were identified as influenza type A (H3N2), 44 (34%) type B, 26 (20%) type A (pH1N1), and 1 (1%) type B/type A (pH1N1) coinfection. Based on national data, circulating influenza strains were considered antigenically matched to the vaccine strains (A/California/7/2009 [pH1N1], A/Perth/16/2009 [H3N2], and B/Brisbane/60/2008) for the 2010–2011 season [15]. Forty-two (32%) of the 130 influenza cases were identified as medically attended on the basis of medical record review; 38% of cases among children were medically attended compared with 16% among adults ($P = .020$). Vaccinated cases were slightly more likely than unvaccinated cases to be medically attended (34% vs 30%; $P = .67$).

Influenza was identified in 78 (24%) households and 125 (9%) individuals, including 5 individuals with 2 separate infections. Influenza infection risks significantly varied by age category and were highest among young children ($P < .001$). There were no significant differences in infection risk by sex or presence of high-risk health conditions. Fifty-nine percent of influenza cases had confirmed receipt of an influenza vaccine at least 14 days prior to illness. The influenza infection risk was 8.5% (74 of 866) in the vaccinated and 8.9% (51 of 575) in the unvaccinated ($P = .83$).

Influenza Vaccine Effectiveness

The effectiveness of influenza vaccination in preventing symptomatic laboratory-confirmed influenza was estimated separately for community-acquired and household-acquired outcomes. Thirty influenza cases were considered household-acquired based on exposure to 100 index or co-index community-acquired infections. Results from unadjusted, adjusted, and stratified models are presented in Table 2; models were adjusted for age in years and high-risk health status, and stratified by 2009–2010 seasonal influenza vaccination status. Estimates were calculated for all ages combined and separately by age category; young children were considered separately because of their specific vaccination recommendation [1], and older adults (aged ≥50 years) were included with younger adults because of their limited numbers.

Adjusted vaccine effectiveness in preventing community-acquired influenza was 31% (95% confidence interval [CI], −7 to 55); point estimates were lowest in young children and modestly higher in adults. Stratified analyses indicated substantial differences in vaccine effectiveness based on whether or not seasonal influenza vaccine had been received the prior season (interaction term: $P = .014$). Among subjects with documented evidence of prior season vaccination, estimates of current season vaccine effectiveness were low overall and in each of the age groups examined. In contrast, for those subjects without evidence of prior season vaccine receipt, effectiveness estimates were higher for all age groups and statistically significant overall (62% [95% CI, 17%–82%]).

Results from analysis of vaccine effectiveness in preventing community-acquired influenza by type/subtype are also presented in Table 2. In adjusted analyses for all ages combined, effectiveness estimates were highest against influenza type B (48% [95% CI, −5% to 75%]), and lower for A (pH1N1) (26% [95% CI, −68% to 67%]) and A (H3N2) (10% [95% CI, −74% to 54%]). In analyses stratified by prior season vaccination status, estimates were substantially higher for those subjects without evidence of prior season vaccine receipt.

In models examining household-acquired influenza, there was no evidence that vaccination prevented household transmission once influenza was introduced (Table 2). Adults were at particular risk of infection despite vaccination. In fact, 9 of 11 (82%) adults with household-acquired influenza were vaccinated, compared with 11 of 19 (58%) children. No substantial differences in estimates of household vaccine effectiveness were demonstrated based on prior season vaccination status.

To aid interpretation of the observed differences in vaccine effectiveness based on 2009–2010 vaccination status, we examined influenza infection risks based on combinations of prior and current season vaccination status (Table 3). The lowest infection risks were seen among subjects vaccinated in the current but not the prior season. Infection risks were similar for subjects with documented seasonal vaccine receipt in both years and subjects without evidence of vaccine receipt in either year. The pattern of infection risks seen among young children varied from that seen in older children and adults. Specifically, the highest infection risks were seen in young children without evidence of vaccine receipt in either year. Similar patterns were demonstrated with stratification by prior season pandemic vaccine receipt; among those subjects vaccinated in the prior season, 65% had received both seasonal and pandemic vaccine.

DISCUSSION

In countries with established influenza vaccination programs, observational studies of vaccine effectiveness have become a standard way of routinely evaluating how well influenza vaccines protect population groups [2–5]. These studies utilize a

Table 2. Estimates of Vaccine Effectiveness in Preventing Community-Acquired and Household-Acquired Influenza

		Vaccine Effectiveness[a] (VE%)[b]			
		Unadjusted	Adjusted 1[c]	Stratified by Prior (2009–2010) Seasonal Vaccine Receipt[d]	
Analysis Set	Influenza Positive No./ Total No. (%)	VE% (95% CI)	VE% (95% CI)	Prior Season: Vaccinated VE% (95% CI)	Prior Season: Nonvaccinated VE% (95% CI)
Community-acquired influenza[e]					
All ages	97/1441 (6.7)	17 (–27 to 46)	31 (–7 to 55)	–45 (–226 to 35)	62 (17–82)
<9 y	55/468 (11.8)	30 (–27 to 61)	30 (–27 to 61)	–148 (–959 to 42)	53 (–19 to 81)
9–17 y	21/371 (5.7)	11 (–103 to 61)	33 (–62 to 72)	–6 (–291 to 71)	80 (–85 to 98)
≥18 y	21/602 (3.5)	44 (–37 to 77)	39 (–49 to 75)	17 (–328 to 84)	79 (–65 to 97)
Community-acquired influenza A/H3N2	42/1441 (2.9)	–1 (–93 to 48)	10 (–74 to 54)	–34 (–323 to 58)	37 (–84 to 78)
Community-acquired influenza A/H1N1	21/1441 (1.5)	6 (–121 to 60)	26 (–68 to 67)	–6 (–387 to 77)	70 (–131 to 96)
Community-acquired influenza B	37/1441 (2.6)	36 (–30 to 68)	48 (–5 to 75)	–166 (–1937 to 65)	61 (–2 to 92)
Household-acquired influenza[f]					
All ages	26/267 (9.7)	–67 (–286 to 28)	–51 (–254 to 36)		
<9 y	14/84 (16.7)	10 (–167 to 70)	27 (–126 to 28)		
9–17 y	2/55 (3.6)	17 (–1196 to 95)	0 (–826 to 89)		
≥18 y	10/128 (8.5)	–260 (–1618 to 24)	–283 (–1733 to 20)		

Household Influenza Vaccine Effectiveness (HIVE) study, Ann Arbor Michigan, 2010–2011 influenza season.

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

[a] Effectiveness of at least 1 dose of influenza vaccine ≥14 days before illness onset in preventing laboratory-confirmed influenza.

[b] VE% = 100*(1 – hazard ratio).

[c] Model adjusted for age in years and medical record documented high-risk health status (present/absent).

[d] Model stratified by 2009–2010 seasonal vaccination status, and adjusted for age and high-risk health status.

[e] One hundred cases of influenza were defined as community acquired, but 3 cases are excluded here because they occurred in a subject with a prior case of community-acquired influenza.

[f] Thirty cases of influenza were defined as household-acquired, but 4 cases are excluded here because they occurred as a result of a second introduction of influenza (different type/subtype and/or >7 days from prior case) to a household.

sensitive and specific laboratory method to confirm illnesses as influenza, and require documentation of influenza vaccine receipt, thus reducing the risk of misclassifying key outcomes and exposures. However, data from all observational studies still require attention to reduce the possibility of bias and adjust for confounding, given self-selection for vaccination and, in most study designs, the influence of healthcare-seeking behavior.

This study was designed in part to complement current studies conducted in the healthcare setting, using an alternative approach to the case-control design. Defining a cohort of households with children, in advance of the influenza season and with follow-up through the season, offers several advantages. As demonstrated here, influenza illnesses of all severities can be studied, and vaccine effectiveness against both community-acquired illnesses and among household members with confirmed household exposures can be examined. In addition, household transmission risks can be determined and characterized [16, 17]. However, longer follow-up and availability of household-level data are balanced with the limitation of reduced power, as the number of cases identified will be smaller compared with case-control studies that enroll participants when eligible illnesses occur.

Based on our sample size of >1400 subjects with 60% vaccine coverage, and a community infection risk of 6.7%, we had 80% power to estimate significant vaccine effectiveness as low as approximately 45%. Unfortunately, in unadjusted models and models adjusted for age and presence of high-risk health conditions, effectiveness estimates for prevention of community-acquired influenza of all severities were all <40% and not statistically different than zero. This unexpected finding was seen in a season with circulation of influenza strains that were considered matched to vaccine strains [15], and where evaluations of vaccine effectiveness using case-control designs indicated significant reductions of 52%–60% in medically attended influenza outcomes in vaccinated patients of all ages [2, 5].

In preliminary analyses, significant interaction of prior (2009–2010) seasonal vaccine receipt with current season

Table 3. Influenza Infection Risks Among Participants Based on Combinations of 2010–2011 Seasonal Vaccination Status With Prior Season (2009–2010) Seasonal and Pandemic Vaccination Status

	2010–2011 Vaccinated, N = 866 (60.1%)		2010–2011 Unvaccinated, N = 575 (39.9%)	
	Cases[a]/Total	% Positive	Cases[a]/Total	% Positive
2009–2010 seasonal, vaccinated[b]				
<9 y	35/255	13.7	3/39	7.7
≥9 y	27/370	7.3	5/78	6.4
All ages	62/625	9.9	8/117	6.8
2009–2010 seasonal, unvaccinated				
<9 y	8/68	11.8	24/106	22.6
≥9 y	4/173	2.3	19/352	5.4
All ages	12/241	5.0	43/458	9.4
2009–2010 pandemic, vaccinated[c]				
<9 y	34/239	14.2	2/34	5.9
≥9 y	23/282	8.2	8/57	14.0
All ages	57/521	10.9	10/91	11.0
2009–2010 pandemic, unvaccinated				
<9 y	9/84	10.7	25/111	22.5
≥9 y	8/261	3.1	16/373	4.3
All ages	17/345	4.9	41/484	8.5

Household Influenza Vaccine Effectiveness (HIVE) study, Ann Arbor Michigan, 2010–2011 influenza season.

[a] One hundred thirty influenza cases were identified in 125 individuals. Only an individual's first case is considered here (n = 125).

[b] Indicates receipt of 2009–2010 seasonal vaccine only or both 2009–2010 seasonal and pandemic vaccines.

[c] Indicates receipt of 2009–2010 pandemic vaccine only or both 2009–2010 pandemic and seasonal vaccines.

vaccination was noted. Stratified models suggested substantial differences in vaccine effectiveness with unexpectedly low estimates demonstrated for those subjects who were vaccinated both years. In contrast, among those subjects without evidence of prior seasonal vaccine receipt, statistically significant vaccine effectiveness was demonstrated for all ages combined. In immunogenicity studies, attenuated immunologic responses with repeated vaccine receipt have been demonstrated [18–20]; responses may vary based on the degree of similarity between vaccine strains across years [21]. Corresponding reductions in vaccine effectiveness with repeated vaccinations have not been consistently demonstrated [22, 23]. In examining the modifying effect of prior vaccination on current season vaccine effectiveness in our observational study, it is difficult to separate the possible effects of immunologic response due to prior vaccination from associated (and unmeasured) factors for which repeated vaccination may be a surrogate.

We found no evidence of vaccine effectiveness in preventing within-household transmission once influenza was introduced. Sample sizes in these analyses were small and we had very limited power to detect significant differences even if vaccine protection had been demonstrated. It is interesting to speculate that these estimates may reflect the intensity and duration of exposure once influenza is introduced to a confined environment. Excess risk for adult household members may have been a consequence of providing care for those with illness.

In addition to examining vaccine effectiveness based on documented vaccine receipt, we performed a sensitivity analysis with vaccination status defined by documented vaccine receipt or self-reported vaccination that could not be documented, and separately, defined by self-reported status only. Effectiveness estimates in the first analysis (documented or self-reported vaccine receipt) were similar (33% [95% CI, −4% to 58%]) to estimates requiring documented evidence (31% [95% CI, −7% to 55%]). Estimates in the second analysis (self-reported only) differed based on whether those with missing data were considered unvaccinated (20% [95% CI, −24% to 48%]) or excluded (35% [95% CI, −4% to 60%]). These findings do not affect our overall conclusions, but they do suggest some misclassification of vaccination status with our strategy for documentation. Confirmation of vaccination status is challenging given the many options for vaccine delivery, making sensitivity analyses that consider reported vaccination increasingly important.

Our vaccine effectiveness estimates for prevention of community-acquired influenza were lower than those demonstrated in other observational studies carried out in the same season [2, 5]. We also did not demonstrate reduced utilization of medical care among vaccinated cases; going forward, we plan to expand our assessment of illness severity. The findings suggesting lower effectiveness with prior vaccination and no protection with household exposure require further study. We will continue to evaluate vaccine effectiveness in the household setting in order to confirm or refute the current observations. With multiple years of data accumulated, further examination of the effects of prior vaccination and past influenza infection on effectiveness estimates can be conducted. In future study years we also plan to collect serologic specimens from household members to estimate preseason susceptibility to circulating influenza viruses; these efforts should assist in explaining observations.

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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