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Influenza Vaccine Effectiveness Among Patients with High-Risk Medical Conditions in the United States, 2012—2016

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Abstract

Background: Annual influenza vaccination has been recommended for persons with high-risk conditions since the 1960s. However, few estimates of influenza vaccine effectiveness (VE) for persons with high-risk conditions are available.

Methods: Data from the U.S. Influenza Vaccine Effectiveness Network from 2012−2016 were analyzed to compare VE of standard-dose inactivated vaccines against medically-attended influenza among patients aged ≥6 months with and without high-risk medical conditions. Patients with acute respiratory illness were tested for influenza by RT-PCR. Presence of high-risk conditions and vaccination status were obtained from medical records. VE by influenza virus type/subtype and age group was calculated for patients with and without high-risk conditions using the

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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.

CONFLICT OF INTEREST

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test-negative design. Interaction terms were used to test for differences in VE by high-risk conditions.

Results: Overall, 9,643 (38%) of 25,369 patients enrolled during four influenza seasons had high-risk conditions; 2,213 (23%) tested positive for influenza infection. For all ages, VE against any influenza was lower among patients with high-risk conditions (41%, 95% CI: 35%−47%) than those without (48%, 95% CI: 43%−52%; *P-for-interaction* = 0.02). For children aged <18 years, VE against any influenza was 51% (95% CI: 39%−61%) and 52% (95% CI: 39%−61%) among those with and without high-risk conditions, respectively (*P-for-interaction* = 0.54). For adults aged ≥18 years, VE against any influenza was 38% (95% CI: 30%−45%) and 44% (95% CI: 38%−50%) among those with and without high-risk conditions, respectively (*P-for-interaction* = 0.21). For both children aged <18 and adults aged ≥18 years, VEs against illness related to influenza A(H3N2), A(H1N1)pdm09, and influenza B virus infection were similar among those with and without high-risk conditions.

Conclusions: Influenza vaccination provided protection against medically-attended influenza among patients with high-risk conditions, at levels approaching those observed among patients without high-risk conditions. Results from our analysis support recommendations of annual vaccination for patients with high-risk conditions.

Keywords

influenza; vaccine; vaccine effectiveness; high-risk medical conditions; acute respiratory illness

INTRODUCTION

Since the 1960s, annual influenza vaccination has been recommended for persons with underlying medical conditions that are associated with an increased risk of influenza-related complications and death [1]. In the 1960 Surgeon General's report, these conditions included rheumatic heart disease and other cardiovascular diseases, chronic bronchopulmonary disease (including chronic asthma), diabetes mellitus and Addison's disease [1]. Since that time, recommendations for influenza vaccination have been expanded to all persons aged >6 months regardless of underlying medical conditions. The US Advisory Committee on Immunization Practices (ACIP) has continued to note that vaccination "is especially important" for persons with high-risk medical conditions (hereafter referred to high-risk conditions)[2]. The list of high-risk conditions associated with increased risk of influenza-related complications has expanded to include neurological conditions, immunosuppressive conditions, blood disorders, kidney disorders, liver disorders, metabolic disorders, extreme obesity, and long-term aspirin therapy among children aged <19 years old [2, 3]. However, relatively few studies have evaluated the protection provided by influenza vaccination among persons with high-risk conditions.

Observational studies are widely used to evaluate influenza vaccine effectiveness (VE) for the prevention of medically-attended illness and often include a substantial proportion of patients with high-risk conditions. Many observational studies employ a test-negative design, in which symptomatic patients are tested for influenza and VE is estimated by contrasting the odds of influenza among vaccinated and unvaccinated patients [4, 5]. Test-

negative design has the strength in controlling health-seeking behavior comparing with traditional case-control or cohort methods. However, to obtain unbiased VE estimates, variables including calender time when influenza is circulating and high-risk conditions that may affect VE must be considered in analysis [4, 5]; the test-negative design may also be used to estimate VE among groups of patients with high-risk conditions given adequate sample size. In the United States, the Influenza Vaccine Effectiveness (Flu VE) Network routinely collects information on patients' high-risk conditions in annual VE studies [6–10]. We analyzed data from four influenza seasons to evaluate VE among patients with high-risk conditions, and assess differences between VE in patients with and without high-risk conditions.

Materials and methods

Patients

Methods of the Flu VE Network have been described previously [6–10]. In this analysis, we included patients aged ≥6 months with acute respiratory illness (ARI) with cough and symptom onset ≤7 days prior to enrollment, who were enrolled during four influenza seasons from 2012−13 through 2015−16 at outpatient facilities associated with participating institutions in Michigan, Pennsylvania, Texas, Washington and Wisconsin. For each season, we excluded influenza-negative patients enrolled before or after the date of symptom onset of the first and last confirmed influenza case, respectively, at each site. Patient demographics were obtained through interview at enrollment. Influenza virus infection was determined by real-time reverse transcription polymerase chain reaction (RT-PCR) testing of combined nasal and throat swab specimens (for patients aged ≥2 years) or nasal swab specimens only (for patients aged <2 years). Influenza virus type and subtype were determined by RT-PCR for influenza-positive specimens; patients with inconclusive RT-PCR results were excluded.

High-risk conditions

Presence of high-risk conditions was defined as documentation in medical records of ≥1 medical encounter including outpatient visits and inpatient stays during the 12 months before enrollment associated with an *International Classification of Diseases, 9th Edition* (ICD-9) *and 10th Edition* (ICD-10)*, Clinical Modification* [11, 12] diagnostic code corresponding to a high-risk condition identified by ACIP (Supplementary Table 1) [2]. High-risk categories included in this analysis were asthma, cerebrovascular diseases, chronic obstructive pulmonary diseases (COPD) and other lung diseases, diabetes, heart diseases, hematologic conditions/blood disorders, liver diseases, neurologic conditions, renal diseases, and immunosuppressive conditions (including rheumatoid arthritis, immune system disorders or immunodeficiency, antineoplastic chemotherapy, HIV, organ transplants). High-risk categories were not mutually exclusive such that individual patients could contribute to more than one category. Patients with no high-risk ICD-9 or ICD-10 codes in medical records during the 12-month period were classified as having no high-risk conditions; patients without 12 months of medical records prior to encounter were excluded.

Vaccination status

Vaccination status was determined at all sites based on electronic immunization records, including medical records, employee health records and state or local immunization registries. Vaccinated patients were those with documented receipt of current season influenza vaccine at least 14 days before illness onset. We included vaccinated patients who received standard-dose inactivated influenza vaccines only; patients who received live-attenuated influenza vaccines, high dose inactivated or adjuvanted vaccine were excluded. In addition, at four sites (excluding Wisconsin), patients aged ≥9 years without documented vaccination who reported plausible location of vaccination ≥14 days prior to illness onset were classified as vaccinated. We excluded patients vaccinated 0−13 days prior to illness onset and children aged 6 months−8 years who received only one of two recommended doses of influenza vaccine in the current season [13–16].

Statistical analyses

For patients with and without high-risk conditions, we examined factors associated with influenza positivity and vaccination status using X^2 tests for differences in proportions, and estimated VE using a test-negative design [4, 17], where VE = 100 × (1 - adjusted odds ratio [aOR]) from logistic regression models comparing odds of influenza among vaccinated versus unvaccinated patients, with 95% confidence intervals (CI) estimated from odds ratios. Logistic regression models included *a priori* study site, influenza season, age (in years as linear tail-restricted cubic-spline function with 4 percentile knots), calendar time (four-week intervals), and days from illness onset to enrollment (0–2 days, 3−4 days, 5−7 days). Additional variables (sex, race/ethnicity, self-reported general health status [excellent, very good, good, fair, poor], number of children aged <12 years in household [0, 1, ≥1] and self/household exposure to tobacco smoke) were individually assessed but not retained in the final model, as their inclusion did not result in a ≥5% change in VE [7]. For age-stratified estimates (<18 years and ≥18 years), age was modelled as a continuous variable in years [18]. Adjusted ORs were not estimated when the total number of patients in the stratum (denominator) was <50. VE estimates were considered statistically significant if the 95% CI excluded zero.

We estimated VE among patients with and without any high-risk conditions and separately by age group, high-risk category, and infecting influenza virus type. For influenza A(H3N2), we conducted separate analyses of VE against A(H3N2)-related illness among adults aged ≥18 years for the 2014–15 season, when antigenically-drifted A(H3N2) viruses predominated, and for the other three seasons combined [6–10]. To assess the difference of influenza VE among patients with only one high-risk condition with that among patients with multiple high-risk conditions, we repeated the primary analysis for individuals with a single high-risk condition (i.e., individuals with asthma only). We also compared VE among patients with high-risk conditions associated with an inpatient stay in the preceding 12 months assuming that hospital stays were associated with more severe underlying illness. We included interaction terms in logistic regression models to test for statistically significant differences in VE among patients with and without a specific high-risk condition. All reported tests were 2-sided and P values <0.05 indicated statistical significance. Statistical analyses were conducted using SAS for Windows (version 9.3, Cary, NC).

RESULTS

A total of 25,369 patients enrolled in the US Flu VE study between December 12, 2012 and April 14, 2016 were included in analyses; reasons for exclusion from this analysis (n = 4674) are shown in Figure 1. Among those included, 9,643 (38%) had one or more high-risk conditions while 15,726 (62%) had no medical encounters associated with a high-risk condition in the preceding 12 months. Prevalence of any high-risk condition ranged from 25% among children aged 6 months to 17 years, to 76% among patients aged ≥65 years. Among children aged <18 years with high-risk conditions, the most common conditions were asthma (82%), heart diseases (8%) and neurologic conditions (5%). Among adults aged ≥18 years with high-risk conditions, common conditions included asthma (37%), heart diseases (35%), diabetes (26%), immunosuppressive conditions (17%), cerebrovascular diseases (14%), COPD and other lung diseases (12%), renal diseases (11%), neurologic conditions (9%), liver diseases (5%), and blood disorders (1%). Among adults aged ≥18 years with COPD and other lung diseases, 35% also had asthma.

Overall, 6,032 (63%) of 9,643 patients with high-risk conditions had received current season influenza vaccination versus 6,224 (40%) of 15,726 patients without high-risk conditions (P <0.01). Compared to patients without high-risk conditions, patients with high-risk conditions were more likely to be vaccinated across categories by study site, age group, sex, race/ethnicity, influenza season, and interval from onset to enrollment (P <0.01 for all, Table 1). In patients with and without high-risk conditions, proportions of vaccinated were lowest among children and increased with age (χ^2 test for trend, P <0.01). Among enrolled patients, those with high-risk conditions were less likely to have influenza (23%) than those without high-risk conditions (27%, P <0.01). This difference remained statistically significant (P <0.05) across categories by age group (except aged <65 years), gender, race/ethnicity, influenza season (except during 2014–2015), and interval from illness onset to enrollment (Supplementary Table 2).

Among patients with high-risk conditions, VE against any influenza was 41% (95% CI: 35%−47%) for all ages combined, 51% (95% CI: 39%−61%) for those aged <18 years, and 38% (95% CI: 30%−45%) for those aged ≥18 years (Table 2). Among patients without high-risk conditions, VEs were 48% (95% CI : 43%−52%) for all ages combined, and 52% (95% CI: 44%−58%) and 44% (95% CI: 38%−50%) for the pediatric and adult age categories. Differences in VE between patients with and without high-risk conditions were significant for all ages combined (P for interaction = 0.02), but not among patients aged <18 or ≥18 years (P for interaction >0.05 for both).

Among children aged <18 years, we observed statistically significant VE against any influenza among children with asthma (48%; 95% CI: 34%−60%) that was similar to VE among children without high-risk conditions (P for interaction = 0.31; Table 2). Among adults aged ≥18 years, we observed statistically significant VE against any influenza among those with asthma, cerebrovascular diseases, diabetes, heart diseases, immunosuppressive conditions, liver diseases, and neurologic conditions (Table 2). When analysis was restricted to adults aged ≥18 years with heart diseases associated with an inpatient stay in the preceding 12 months, VE against any influenza was 53% (95% CI: 24%–71%), similar to

VE among adults with any heart diseases (VE 47%; 95% CI: 35%–58%; *P* for interaction >0.05). Among adults aged ≥18 years with high-risk conditions, only those with asthma (with or without other high-risk conditions) had significantly lower VE (27%; 95% CI: 10%–41%) than patients without high-risk conditions (*P* for interaction = 0.02); all other tests for differences in VE by high risk status were non-significant (*P* for interaction for all > 0.05; Table 2). However, when analyses were limited to adults aged ≥18 years with asthma as their only high-risk condition, VE was 39% (95% CI, 7%–46%; *P* for interaction = 0.05), suggesting that presence of other high-risk conditions may contribute to the lower VE observed among adults with asthma.

By influenza virus type, VE was higher against A(H1N1)pdm09 and influenza B than against influenza A(H3N2) among patients with and without high-risk conditions (Table 3). For children aged <18 years and adults aged ≥18 years, those with high-risk conditions had similar VEs against influenza A (H3N2), influenza A (H1N1)pdm09, and influenza B virus infection compared to patients without high-risk conditions (*P* for interaction >0.05 for all, Table 3). In addition, adults with diabetes and heart diseases had statistically significant VE against illness due to all influenza virus types/subtypes. Adults with immunosuppressive conditions had significant VE against influenza A (H3N2) and influenza B but not against influenza A (H1N1)pdm09. Adults with asthma had similar VEs against influenza A (H3N2) and (H1N1)pdm09 but lower VE against influenza B virus compared with adults without high-risk conditions (*P* for interaction <0.05). During the antigenically-mismatched A(H3N2) season in 2014−2015, we observed similar, non-significant VE against A(H3N2) among adults with high-risk conditions (7%; 95% CI: −19%–28%) and among those without high-risk conditions (2%; 95% CI: −20%–19%) (Supplementary Table 3).

DISCUSSION

In this analysis of data from four influenza seasons, 2012–2013 through 2015–2016, high-risk conditions were common among ambulatory patients seeking care for ARI in the U.S. Influenza vaccination coverage (limited to standard-dose inactivated influenza vaccines) was higher among patients with high-risk conditions than those without high-risk conditions, but coverage in both groups was below the Healthy People 2020 goal of 70% in all age groups except among patients aged ≥65 years[19]. Among patients with and without high-risk conditions, influenza vaccination was associated with statistically significant protection against any influenza virus and for each influenza virus type/subtype. Further, we observed consistent trends suggesting protection against medically-attended influenza for most categories of high-risk conditions, although several estimates did not reach statistical significance. While VE against any influenza was statistically lower among patients with high risk conditions (41%) compared to those without high-risk conditions (48%), this analysis did not suggest large deficits in vaccine-induced protection among people with high-risk conditions. In addition, the differences in age strata were not significantly different by high-risk status, suggesting that protection among patients with high-risk conditions was not substantially lower than that observed among patients without high-risk conditions. Results support the benefit of influenza vaccination among patients with high-risk medical conditions, who are at increased risk of influenza-associated severe complications and death.

Ascertainment of high-risk medical conditions continues to be important for observational studies of influenza VE. In test-negative studies, high-risk conditions are often associated with both likelihood of vaccination and severe influenza (Supplemental Table 2), making it important to include high-risk conditions in VE analyses [5]. In the US Flu VE Network, patients with high-risk conditions were more likely to be vaccinated and to be enrolled with non-influenza ARI than patients without high-risk conditions. In many countries, presence of high-risk conditions may determine eligibility for publicly financed vaccination [5]. It is reassuring that for most comparisons, VE by influenza virus type/subtype did not differ substantially among patients with and without high-risk conditions, with higher VE against influenza A(H1N1)pdm09 and B, and lower VE against A(H3N2), similar to the results from a recent meta-analysis of test-negative studies [20].

One of the strengths of this analysis is the large number of patients with high-risk conditions, allowing some exploration of VE by high-risk category. Although many estimates lacked precision due to small numbers of patients in individual high-risk categories, trends in point estimates and confidence intervals suggested benefit of vaccination in most high-risk categories. Among the more common high-risk categories, we observed statistically significant VE among patients with asthma, adults with cerebrovascular diseases, diabetes, heart diseases, immunosuppressive conditions, liver diseases, and neurologic conditions. Another strength of this study is the use of laboratory-confirmed influenza outcomes to investigate VE among high-risk patients. Studies in children and adults with asthma, and in persons with immunosuppressive conditions have shown statistically significant VE against laboratory-confirmed influenza and severe outcomes [21–25]. In addition, studies that used non laboratory-confirmed outcomes, e.g., influenza-like illness, physician-diagnosed pneumonia, and hospitalization associated with influenza diagnostic codes, have shown significant reductions in these outcomes associated with influenza vaccination among persons with cardiovascular diseases, COPD, diabetes mellitus, liver diseases, and renal diseases [26–33].

Our study is subject to several limitations. First, these findings are limited to ambulatory patients and effectiveness against more severe influenza illness may differ. However, VE against medically-attended influenza in ambulatory settings has been a good proxy for VE against more severe outcomes measured among hospitalized patients [34]. Second, the US Flu VE Network did not enroll patients from specialty clinics where people with more severe conditions might receive most of their care. In addition, although a large proportion of patients enrolled in the US Flu VE Network had high-risk medical conditions, stratification by high-risk category resulted in small numbers in certain high-risk conditions, limiting statistical power to detect differences in VE by high-risk category or disentangle associations between the increasing age and high-risk conditions [35]. Trends support evidence of protection for most high-risk categories but additional evidence is needed for several high-risk categories, including children with neurologic conditions. Further, identification of high-risk conditions from medical records is limited by completeness and accuracy of diagnostic codes, and does not differentiate by level of severity or immunosuppression [36]. Older patients may have had high-risk conditions without corresponding diagnostic codes, making it less likely to observe differences between patients with and without documented high-risk conditions [35]. Broad categories with varying

severity of high-risk conditions may also hide differences in VE among patients with specific conditions. Patients with multiple high-risk conditions or those who are more immunocompromised may have lower VE. Finally, analyses were limited to standard-dose inactivated vaccines due to small numbers of people vaccinated with other vaccine types during the study period. Increased use of vaccines such as high-dose vaccine among patients aged ≥65 years and recombinant vaccine may provide an opportunity to evaluate VE for more immunogenic vaccines, but special studies maybe needed to evaluate use of different types of influenza vaccine for patients with high-risk conditions.

CONCLUSIONS

Patients with high-risk conditions continue to be an important population for influenza vaccination. Given their increased risk of severe complications and death associated with influenza infection, influenza vaccination is especially important among patients with high-risk conditions. While more effective vaccines are needed, the current analysis suggests the benefit of vaccination for the prevention of medically-attended influenza does not differ substantially between patients with and without high-risk conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We analyzed influenza VE among outpatients by high risk condition, age, and flu type during in U.S.
- VE among patients with high risk conditions are approaching the levels as it among patients without.
- VE among children and adults with high risk wasn't different from it among those without.
- VEs against flu A(H3N2), (H1N1)pdm09, and B were similar in patients with and without high-risk.

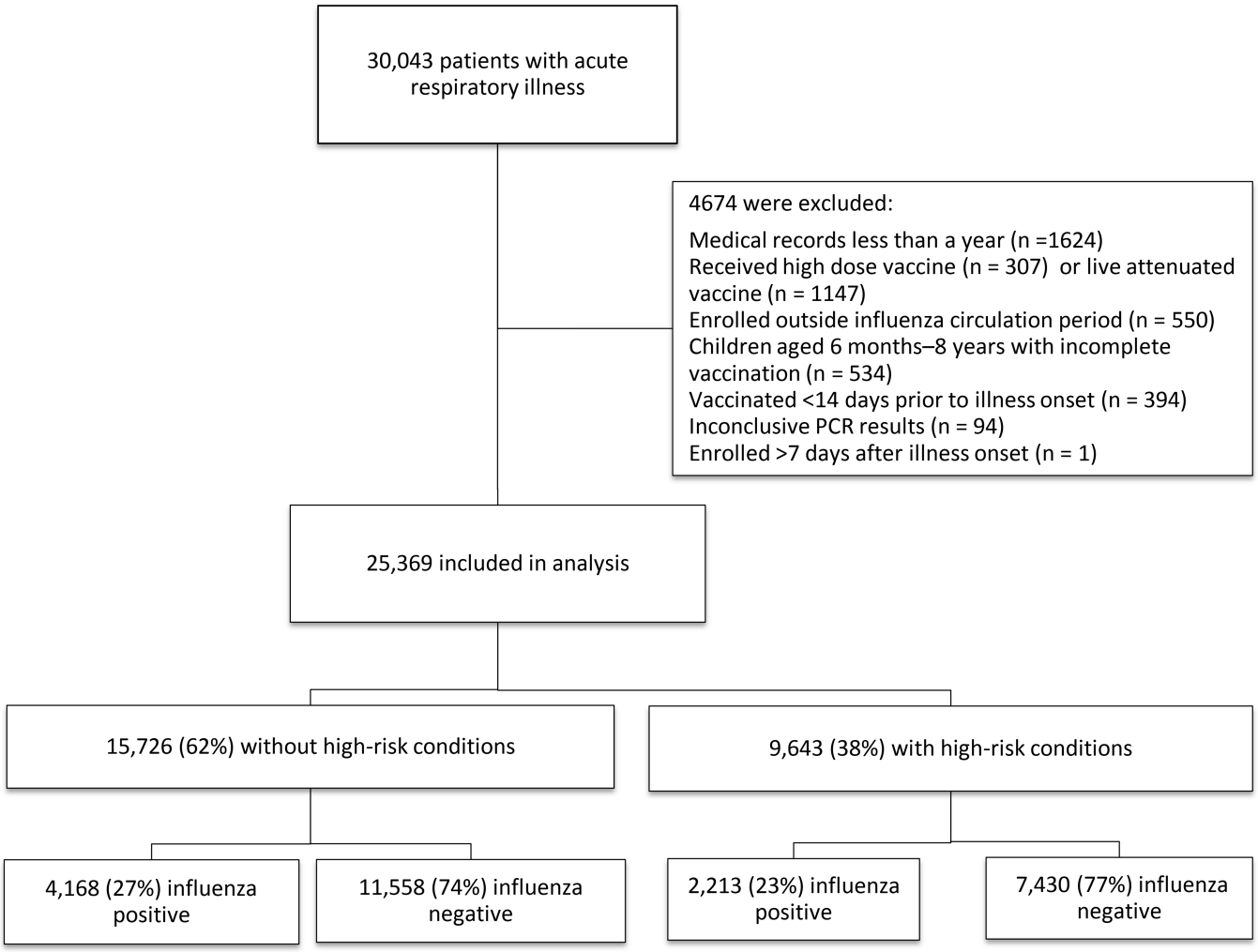

Figure 1.
Flow diagram of study population

Table 1.

Characteristics of population enrolled in The US Influenza Vaccine Effectiveness Network by presence of high-risk conditions and vaccination status, 2012−2016

	Patients without high-risk conditions		Patients with any high-risk conditions		
Characteristics	**Total**	**Number of vaccinated (%)**	**Total**	**Number of vaccinated (%)**	***P*-value**
Site					
Seattle, WA	3516	1671 (48)	2763	1985 (72)	*b*
Marshfield, WI	3513	1370 (39)	1911	1199 (63)	*b*
Temple, TX	2982	989 (33)	1741	964 (55)	*b*
Ann Arbor and Detroit, MI	2594	1046 (40)	1520	892 (59)	*b*
Pittsburgh, PA	3121	1148 (37)	1708	992 (58)	*b*
Age (years)					
0.5–17	6565	2246 (34)	2227	1070 (48)	*b*
18–49	6235	2280 (37)	2679	1440 (54)	*b*
50–64	2220	1192 (54)	2465	1660 (67)	*b*
>65	706	506 (72)	2272	1862 (82)	*b*
Sex					
Female	9131	3858 (42)	5748	3704 (64)	*b*
Male	6595	2366 (36)	3895	2328 (60)	*b*
Race/ethnicity [a]					
White, non-Hispanic	11777	4879 (41)	7296	4778 (66)	*b*
Black, non-Hispanic	1142	317 (28)	877	377 (43)	*b*
Hispanic	1377	560 (41)	752	476 (63)	*b*
Other, non-Hispanic	1391	457 (33)	692	389 (56)	*b*
Influenza season					
2012–13	3790	1420 (38)	2064	1282 (62)	*b*
2013–14	3195	1262 (40)	1862	1177 (63)	*b*
2014–15	4974	2066 (42)	3307	2137 (65)	*b*
2015–16	3767	1476 (39)	2410	1436 (60)	
Interval from onset to enrollment					
0–2 days	5163	1918 (37)	2884	1739 (60)	*b*
3–4 days	6198	2437 (39)	3771	2372 (63)	*b*
5–7 days	4365	1869 (43)	2988	1921 (64)	*b*

[a] Race/ethnicity of 65 patients was unknown.

[b] $P < 0.01$

Table 2.

Adjusted influenza vaccine effectiveness against any influenza virus by age group and high-risk condition

Characteristics	Influenza positive patients	Influenza negative patients	Vaccine effectiveness	
	No. vaccinated/total (%)	No. vaccinated/total (%)	Adjusted [a] % (95% CI)	*P*-value for interaction
All patients				
Patients without high-risk conditions	1207/4168 (30)	5017/11558 (43)	48 (43,52)	-
Patients with any high-risk conditions	1216/2213 (55)	4816/7430 (65)	41 (35, 47)	0.02
<18 years				
Patients without high-risk conditions	368/1705 (22)	1878/4860 (39)	52 (44, 58)	-
Patients with any high-risk conditions	166/478 (35)	904/1749 (52)	51 (39, 61)	0.54
Asthma	147/407 (36)	726/1420 (51)	48 (34, 60)	0.31
Heart diseases	12/35 (34)	76/143 (53)	-	-
Neurologic conditions	13/20 (65)	56/88 (64)	-	-
>18 years				
Patients without high-risk conditions	839/2463 (34)	3139/6698 (47)	44 (38, 50)	
Patients with any high-risk conditions	1050/1735 (61)	3912/5681 (69)	38 (30, 45)	0.21
Asthma	354/579 (61)	1440/2184 (66)	27 (10, 41)	0.02
Cerebrovascular diseases	50/81 (62)	206/249 (83)	63 (26, 81)	0.20
COPD and other lung diseases	111/155 (72)	546/715 (76)	21 (−21, 48)	0.22
Diabetes	315/478 (66)	1082/1449 (75)	46 (30, 58)	0.86
Heart diseases	381/586 (65)	1526/1994 (77)	47 (35, 58)	0.41
Immunosuppressive conditions	195/285 (68)	748/961 (78)	46 (26, 60)	0.80
Liver diseases	55/96 (57)	200/268 (75)	61 (31, 78)	0.30
Neurologic conditions	93/155 (60)	413/540 (76)	49 (22, 66)	0.30
Renal diseases	141/182 (77)	512/620 (83)	32 (−6, 57)	0.39
Blood disorders	7/14 (50)	43/66 (65)	-	-

High-risk categories with fewer than 5 vaccinated influenza or non-influenza patients are not listed.

P-value for interaction for each specific high-risk conditions is calculated by comparing patients with the specific high-risk condition with patients without high-risk conditions.

[a]Adjusted for site, age, influenza season, interval from symptom onset to enrollment, calendar time (4 weeks).

Table 3.

Adjusted influenza vaccine effectiveness against influenza type/subtype by age group and high-risk condition

Characteristics	Influenza positive patients	Influenza negative patients	Vaccine effectiveness	P-value for interaction
	Number of vaccinated/ total (%)	Number of vaccinated/total (%)	Adjusted [a] % (95% CI)	
Influenza A (H3N2)				
<18 years				
Patients without high-risk condition	195/750 (26)	1878/4860 (39)	33(18, 45)	-
Patients with any high-risk condition	95/236(40)	904/1749(52)	27 (0, 47)	0.54
>18 years				
Patients without high-risk condition	450/1063 (42)	3139/6698 (47)	30 (12, 41)	-
Patients with any high-risk condition	599/889(67)	3912/5681(69)	25(10, 37)	0.93
Asthma	210/324(65)	1440/2184(66)	21 (−6, 41)	0.69
COPD and other lung diseases	64/83(71)	546/715(76)	−1 (−91,46)	0.39
Diabetes	192/266(72)	1082/1449(75)	39 (3, 49)	0.87
Heart diseases	239/331(72)	1526/1994(77)	36 (13, 54)	0.34
Immunosuppressive conditions	97/132(73)	748/961(78)	47(24, 68)	0.26
Neurologic conditions	45/64(70)	413/540(76)	41 (−18,71)	0.33
Renal diseases	92/115(80)	512/620(83)	36 (−18, 65)	0.57
Cerebrovascular diseases	34/47(72)	206/249(83)	-	-
Liver diseases	29/46 (63)	200/268(75)	-	-
Influenza A (H1N1) pdm09				
<18 years				
Patients without high-risk conditions	56/315(18)	1878/4860 (39)	69 (57,77)	-
Patients with any high-risk conditions	23/77(30)	904/1749(52)	67 (44,80)	0.52
≥18 years				
Patients without high-risk conditions	227/826(28)	3139/6698 (47)	56 (47, 63)	-
Patients with any high-risk conditions	183/340(54)	3912/5681(69)	44 (31, 55)	0.3
Asthma	77/147(52)	1440/2184(66)	43(17, 60)	0.22
Diabetes	62/110(56)	1082/1449(75)	52 (25, 69)	0.93
Heart diseases	75/135(56)	1526/1994(77)	49 (25,66)	0.08
Immunosuppressive conditions	49/78(63)	748/961(78)	34 (−14, 61)	0.56
Neurologic conditions	32/57(56)	413/540(77)	42 (−11,70)	0.79
Renal diseases	92/115(80)	512/620(83)	11 (−118, 64)	0.19
COPD and other lung diseases	34/49(69)	546/715(76)	-	-
Liver diseases	16/32(50)	200/268(75)	-	-
Cerebrovascular diseases	11/18(61)	206/249(83)	-	-
Influenza B				

Characteristics	Influenza positive patients Number of vaccinated/ total (%)	Influenza negative patients Number of vaccinated/total (%)	Vaccine effectiveness Adjusted [a] % (95% CI)	P-value for interaction
<18 years				
Patients without high-risk conditions	115/635(18)	1878/4860(39)	62 (52, 69)	-
Patients with any high-risk conditions	46/160(29)	904/1749(52)	61 (55, 79)	0.71
≥18 years				
Patients without high-risk conditions	152/533 (29)	3139/6698 (47)	59 (50, 67)	-
Patients with any high-risk conditions	183/340(54)	3912/5681(69)	52 (39, 62)	0.58
Asthma	60/97(62)	1440/2184(66)	18(−29, 48)	0.02
Diabetes	53/92(58)	1082/1449(75)	57 (31, 78)	0.95
Heart diseases	59/107(55)	1526/1994(77)	64 (45, 76)	0.23
Immunosuppressive conditions	44/66(67)	748/961(78)	49 (9, 71)	0.39
COPD and other lung diseases	12/20(60)	546/715(76)	-	-
Liver diseases	9/16 (56)	200/268(75)	-	-
Neurologic conditions	16/32(50)	413/540(77)	-	-
Renal diseases	20/28(71)	512/620(83)	-	-

High-risk categories with fewer than 5 vaccinated influenza or non-influenza patients are not listed.

P-value for interaction for each specific high-risk conditions is calculated by comparing patients with the specific high-risk condition with patients without high-risk conditions.

[a]Adjusted for site, age, influenza season, interval from symptom onset to enrollment, calendar time (4 weeks).