Open Forum Infectious Diseases

MAJOR ARTICLE

Comparison of Side Effects of the 2015–2016 High-Dose, Inactivated, Trivalent Influenza Vaccine and Standard Dose, Inactivated, Trivalent Influenza Vaccine in Adults ≥65 Years

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Background. High-dose, inactivated, trivalent influenza vaccine (HD) is associated with higher rates of side effects than standard dose (SD) vaccine, which may represent a barrier to use.

Methods. We surveyed subjects ≥65 years who received either HD or SD vaccine at the Minneapolis Veteran Affairs Health Care System clinics on October 27, 28, or 29, 2015. Research assistants conducted a 17-item telephone survey of influenza vaccine recipients to inquire about self-reported health and symptoms experienced the week after vaccination.

Results. A total of 547 HD recipients and 541 SD recipients responded to the survey. The 2 groups were similar at baseline with respect to age, gender, and presence of high-risk medical conditions. At least ≥95% of individuals in both HD and SD groups reported that their overall health was the same or better than usual during the week after vaccination. Thirty-seven percent of HD recipients and 22% of SD recipients reported a local or systemic side effect ($P < .001$), most of which were mild to moderate. Only 7 of 547 (1.3%) HD recipients and 3 of 541 (0.6%) SD recipients reported a severe side effect ($P = .34$). There was no significant difference in healthcare visits between the groups.

Conclusions. Side effects were more common among subjects ≥65 years who received HD influenza vaccine compared with SD vaccine. These side effects were well tolerated and were not associated with impairment of general health status. These findings should reassure patients and their providers of the safety and tolerability of the HD influenza vaccine.

Keywords: high-dose influenza vaccine; influenza; influenza vaccine; side effect.

The risk of severe complications and death from influenza increases with age, especially above 65 years [1–4]. Influenza vaccination in adults ≥65 years (hereby referred to as elderly) decreases the incidence of clinical disease and might reduce the risk of secondary complications, hospitalization, and death related to influenza [5–12]. However, the elderly may have reduced immune response to the vaccine and protection when compared with healthy younger adults [13, 14]. In 2009, an inactivated, high-dose (HD), trivalent influenza vaccine (Fluzone High-Dose; Sanofi-Pasteur, Swiftwater, PA) was approved by the US Food and Drug Administration for use in individuals ≥65 years [15]. The trivalent, HD vaccine induces a superior immune response compared with the trivalent, standard dose (SD) vaccine in adults ≥65 years [16–19]. Compared with SD vaccine, the HD vaccine has also been shown to provide enhanced clinical protection against influenza disease and decreased influenza-related medical encounters and hospitalizations [20, 21]. However, in a prelicensure clinical trial, the HD vaccine was also associated with higher rates of local and systemic symptoms, including higher rates of severe reactions [18]. Perceived side effects of influenza vaccines have historically been a major barrier preventing full-scale vaccination [22–26]. Concerns about the possibility of a higher rate of side effects with the HD vaccine compared with SD vaccine may represent a significant hurdle to use of this vaccine for providers and patients. We conducted this survey of ambulatory patients ≥65 years of age attending influenza vaccination clinics during the 2015–2016 influenza season to provide additional information about the rates of self-reported local and systemic symptoms experienced during the week after the HD vaccine compared with the SD vaccine.

METHODS

We surveyed patients ≥65 years who attended walk-in influenza vaccination clinics on October 27–29, 2015 at sites within the Minneapolis VA Health Care System. These sites included the Minneapolis VA Medical Center in Minneapolis, Minnesota as well as 4 community-based outpatient clinics located in Minnesota and Wisconsin. The Minneapolis VA Health Care

Received 6 October 2016; editorial decision 4 January 2017; accepted 9 January 2017.

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Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofx001

System offered trivalent, inactivated, SD influenza vaccine and trivalent, inactivated, HD influenza vaccine (both manufactured by Sanofi Pasteur) during the 2015–2016 influenza vaccination season. The Minneapolis VA strongly encouraged subjects ≥65 years to receive the HD vaccine if it was available. However, if the HD vaccine was not available, subjects were advised to receive the SD vaccine. During the first 1½ days of the 3-day influenza vaccination clinics, there was a shortage of HD vaccine and only SD vaccine was available. However, during the remaining 1½ days of the walk-in clinics, both SD and HD vaccines were available with HD vaccine being preferentially offered to all elderly persons. Vaccine recipients were notified with pamphlets at the time of their vaccination that they might be contacted at a later date to participate in a survey assessing their health after vaccination.

We obtained a list of all patients ≥65 years who received either the HD or the SD influenza vaccine at the influenza vaccination clinics on October 27, 28, and 29, 2015. Trained research personnel used a randomly ordered version of this list to call subjects from November 30, 2015 to January 11, 2016. We attempted to call each recipient only once. The research personnel were blinded to the type of vaccine that the recipient received. Subjects on the list were called sequentially until over 500 people in each group responded. The telephone survey was a 17-item structured questionnaire with predefined categories to ascertain the presence, severity, and duration of self-reported symptoms experienced during the week after vaccination. The questions were designed to inquire about symptoms that have been previously attributed to influenza vaccination and were adapted from a prior study also assessing rates of side effects in elderly adults after influenza vaccination [27]. The surveyor specifically asked about general health status, fever, myalgias ("muscle aches"), fatigue ("tiredness"), headaches, and upper respiratory symptoms. The surveyor also asked about local symptoms of arm soreness and arm swelling. For each symptom, vaccine recipients were asked to categorize the severity into mild, moderate, or severe categories and describe the impact of the symptom on daily life.

Data are summarized using means and standard deviations of continuous variables and proportions for categorical data expressed as percentages. Proportions were compared using a 2-group χ^2 test, and means were compared using the Student *t* test. All analyses were conducted using the Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago, IL). Cited *P* values are not corrected for the number of comparisons. The study was approved by the Minneapolis VA Research and Development Committee.

RESULTS

A total of 2709 patients ≥65 years received influenza vaccine during the study period at the participating sites. This included 1211 patients who received the HD vaccine and 1498 patients who received a SD vaccine. On the first day of the vaccination clinic, 76% of patients ≥65 years of age who were vaccinated received the SD vaccine, and on the third (last) day of the vaccination clinics, 85% of vaccinated patients ≥65 years of age received the HD vaccine. We attempted to reach 1134 HD recipients with a phone call and received responses from 547 (48%). For SD recipients, we attempted to reach 1061 with a phone call and received responses from 541 (51%). Once contacted, greater than 98% of patients agreed to participate in the survey. A total of 82% of all surveys were completed by week 7 after vaccination, with the remaining completed over the next 3 weeks.

Baseline characteristics of the survey respondents are shown in Table 1. The HD and SD vaccine recipient groups were not significantly different with respect to age, gender, health status, presence of high-risk medical conditions, and previous receipt of influenza vaccinations.

Ninety-five percent of HD recipients and 96% of SD recipients reported that their overall health was the same or better than usual during the week after their vaccination (Table 2). The proportion of subjects who reported a side effect did not vary by the week they were called in either HD or SD category. Furthermore, subjects who were first-time influenza vaccine recipients were as likely to have side effects compared with persons who had previously received influenza vaccines in the past 5 years (3 of 15 vs 317 of 1071; $P = .6$). Overall, 200 of 547 (37%) of HD vaccine recipients

Table 1. Baseline Characteristics of Influenza Vaccine Recipients

Characteristics of Survey Respondents	High Dose n = 547 (%)	Standard Dose[a] n = 541 (%)
Total number with completed surveys	547	541
Age Groups (Years)		
65–74	371 (68%)	385 (71%)
75–84	125 (23%)	117 (22%)
≥85	51 (9.3%)	38 (7%)
Male gender	532 (99%)	539 (99%)
Health Status Categories		
Excellent-Very good-Good	435 (80%)	443 (82%)
Fair-Poor	109 (20%)	95 (18%)
Chronic medical condition present		
Chronic lung disease	73 (13.3%)	54 (10%)
Chronic heart disease	136 (25%)	116 (22%)
Diabetes	146 (27%)	131 (24%)
Other serious condition	149 (27%)	133 (25%)
No. of chronic medical conditions present		
None	204 (38%)	225 (42%)
≥1	339 (62%)	308 (58%)
Reported that they received a flu shot every year for the prior 5 years	469 (86%)	469 (87%)
First time receipt of influenza vaccine over past 5 years	7 (1.3%)	8 (1.5%)

[a]The *P* values were >.05 in all categories when comparing high-dose and standard dose subjects.

Table 2. Overall Health During the Week After Influenza Vaccination

Health Status	High Dose n = 547 (%)	Standard Dose n = 541 (%)	*P* Value
Overall health			.3
Better or same as usual	518 (95%)	519 (96%)	
Worse than usual	28 (5%)	20 (4%)	
Cut down on activities due to adverse symptom	20 (3.7%)	7 (1.3%)	.01
Emergency department/ urgent care/primary care office visit for evaluation of adverse symptom	5 (0.9%)	3 (0.6%)	.48

and 120 of 540 (22%) of SD vaccine recipients reported a local or systemic side effect during the week after vaccination ($P < .001$). Most of these side effects were mild to moderate, with only 7 of 547 (1.3%) of HD vaccine recipients and 3 of 541 (0.6%) of SD vaccine recipients reporting any severe local or systemic side effect ($P = .34$). However, 20 of 547 (3.7%) of HD vaccine recipients reported having to cut down on usual activities due to any side effect vs 7 of 541 (1.3%) of SD recipients ($P = .01$). The difference in healthcare visits due to side effects between the 2 groups was not significant (0.9% vs 0.6%; $P = .48$).

Table 3 summarizes the types, severity, and duration of local and systemic side effects reported by HD and SD vaccine recipients. Rates of a local side effect were higher among the HD vaccine recipients (30% vs 18%; $P \leq .001$), with arm soreness accounting for these differences. However, in both groups the arm soreness was generally mild to moderate, lasted ≤48 hours, and generally did not interfere with daily activities. High-dose vaccine recipients also reported higher rates of systemic side effects than did SD vaccine recipients (11.4% vs 6%; $P = .002$). Generalized myalgias and fatigue were more common among the HD vaccine recipients, but most of these symptoms were mild or moderate. Only 5 of 547 (0.9%) of the HD vaccine recipients and 2 of 541 (0.4%) SD vaccine recipients reported severe systemic symptoms ($P = .26$).

There was no difference in rates of local or systemic side effects to either vaccine when stratified by either baseline health or presence of a high-risk condition (data not shown).

Table 3. Side Effects During the Week After the Influenza Vaccine

Side Effects	High Dose n = 547 (%)	Standard Dose n = 541 (%)	*P* Value
Local side effects			
Any local side effect	165 (30%)	97 (18%)	<.001
Arm soreness	165 (30%)	97 (18%)	<.001
Severity of arm soreness			
Mild[a]	144 of 165 (88%)	88 of 97 (91%)	.76
Moderate[a]	17 of 165 (10%)	8 of 97 (8.2%)	
Severe[a]	3 of 165 (1.8%)	1 of 97 (1%)	
When did the arm soreness start in relation to the flu shot?			.86
<24 hours after	119 of 165 (73%)	68 of 97 (70%)	
24–48 hours after	40 of 165 (24%)	25 of 97 (26%)	
>48 hours after	5 of 165 (3%)	4 of 97 (4%)	
How long did the arm soreness last?			.66
<24 hours	48 of 165 (29%)	28 of 97 (29%)	
24–48 hours	73 of 165 (45%)	48 of 97 (50%)	
>48 hours	43 of 165 (26%)	21 of 97 (22%)	
Decreased activities because of arm soreness?			.47
Yes	10 of 165 (6.5%)	4 of 97 (4%)	
No	144 of 165 (94%)	89 of 97 (96%)	
Arm swelling	6 (1.1%)	8 (1.5%)	.57
Severity of arm swelling-mild	100%	100%	
Any severe local side effect	3 (0.55)	1 (0.2%)	.62
Systemic side effects			
Any systemic side effect	61 (11.4%)	32 (6%)	.002
Fever[b]	20 (3.7%)	12 (2.2%)	.17
Headaches[b]	13 (2.4%)	10 (1.9%)	.54
Generalized myalgias[b]	31 (5.7%)	17 (3.2%)	.04
Fatigue[b]	39 (7.2%)	20 (3.7%)	.01
Upper respiratory tract symptoms[c]	38 (7%)	33 (6.2%)	.57
Any severe systemic symptom	5 (0.9%)	2 (0.4%)	.26

[a]Vaccine recipients were asked to categorize their experienced adverse symptoms as mild, moderate, or severe.

[b]Greater than 90% of individuals with any systemic symptom (fever, headaches, myalgia, fatigue) described them as mild or moderate.

[c]Upper respiratory tract symptoms were defined as presence of a cough, sore throat, or runny nose.

However, when we stratified side effects by age group dichotomized as 65–74 years and ≥75 years, the incidence of any side effect was higher in the younger age group (65–74 years) for both HD and SD recipients (Figure 1A). This difference in the HD category was mostly driven by the higher rate of local reactions in the younger age groups (Figure 1B and C). The proportion of persons who were first-time influenza vaccine recipients over the last 5 years was not significantly different in the 65–74 year group compared with the ≥75 year group (12 of 755 vs 3 of 331; $P = .54$). The risk of a severe side effect was low and not significantly different between the 2 age groups.

Although most subjects in both HD and SD groups expressed their intention to continue getting an annual influenza vaccine, 13 of 1088 (1.2%) individuals stated that they did not plan to get the influenza vaccine the following year. Persons who expressed not wanting to receive an influenza vaccine the next year when compared with all other influenza vaccine recipients were similar in age, but they were more likely to be first-time influenza vaccine recipients (3 of 13 vs 12 of 1075; $P < .0001$) and were more likely to have experienced a severe side effect after receiving the vaccine (2 of 13 vs 8 of 1075; $P < .0001$). Vaccine type (HD vs SD) was not associated with intent to be vaccinated in the future.

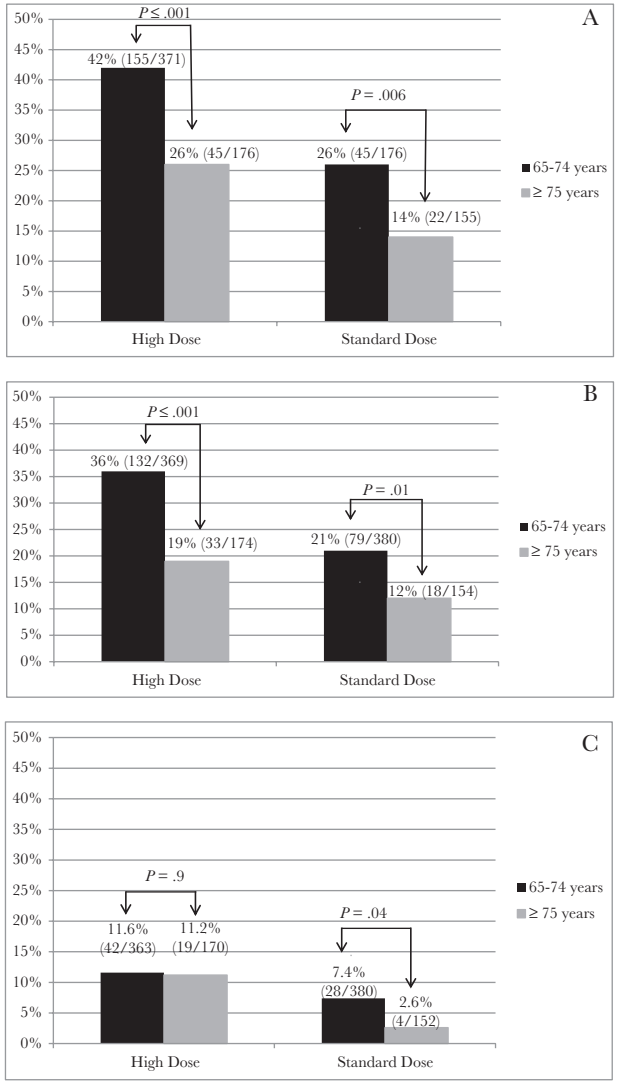

Figure 1. (A) Frequency of side effects with influenza vaccine in dichotomized age groups; (B) frequency of local side effects with influenza vaccine in dichotomized age groups; (C) frequency of systemic side effects with influenza vaccine in dichotomized age groups.

DISCUSSION

In this study of subjects ≥65 years attending walk-in influenza vaccination clinics, we found that HD vaccine recipients reported higher rates of local and systemic side effects compared with SD vaccine recipients, but rates of severe symptoms were low and similar between the 2 groups. Previous prelicensure studies evaluating immunogenicity and safety of HD vaccine have also demonstrated higher rates of local and systemic symptoms with the HD vaccine compared with SD [16–19]. In the pivotal, prelicensure immunogenicity trial, HD vaccine was associated with a 34% incidence of a systemic reaction and a 36% incidence of local reaction compared with the SD group, which experienced a 29% rate of a systemic reaction and 24% rate of a local reaction [18]. In our study, we found a similar trend, with an overall lower rate of systemic side effects. Systemic side effects occurred in 11.4% of the HD group compared with 6% in the SD group, and local side effects occurred in 30% of the HD group compared with 18% for the SD group.

In contrast to these findings for the HD vaccine, trials among the elderly have demonstrated that SD vaccines when compared with placebo injections cause a higher rate of local side effects, but the rate of systemic side effects is no different [27, 28]. Our results show that despite the higher rates of local and systemic symptoms, HD vaccine recipients had similar rates of same or better health status after vaccination as the SD vaccine recipients, and HD vaccine recipients did not report significantly higher rates of healthcare utilization due to symptoms after vaccination.

Our survey research is a detailed, postlicensure, real-world study of the frequency and severity of side effects with HD vaccine when compared with SD vaccine. We are unaware of any other postlicensure HD vaccine studies examining this issue. We took advantage of unexpected delays in availability of HD influenza vaccine during the 3-day walk-in vaccination clinics to study a natural experiment in which only the SD vaccine was available for the first half of the time period, whereas both vaccines were available during the second half of the study period. This resulted in >1000 subjects ≥65 years receiving each of the vaccines over the 3-day time period. This facilitated a balanced distribution of patient characteristics between HD and SD vaccine recipients and allowed us to compare experiences with HD as well as SD vaccine in a cohort of

subjects ≥65 years. Other strengths of our study include a large sample size, recruitment from various locations in Minnesota and Wisconsin, and blinding of the interviewers to the type of vaccine received.

Our study was an observational study, and as such it has several potential limitations. Several types of biases may have affected our results. One bias is due to lack of randomization of subjects, although the baseline characteristics between HD and SD subjects were similar. Another is the possibility of recall bias because subjects were questioned 4 to 10 weeks after vaccination. Given the delay in interview, it was reassuring to us that the proportion of subjects who reported any side effect did not vary by the week they were called. Another limitation is the self-report of presence and severity of symptoms. However, the similarity of our findings to the prior report in the literature supports the validity of our findings [18]. Our survey study had a response rate of approximately 48% in the SD vaccine recipients and 51% in the HD vaccine recipients, which is similar to other telephone survey studies in the literature [29–31]. More than 98% of the nonrespondents were patients who could not be contacted over the phone, but because these patients may be different from the subjects we surveyed, our results should be interpreted with some caution. Finally, most of our subjects were males. Prior placebo-controlled studies of adverse reactions to influenza vaccine in the elderly have shown that women may be more likely to have local and systemic side effects compared with men [28, 32]. Hence, our findings on side effects in a study in which 99% of the population studied were men should be generalized to women with some caution.

CONCLUSIONS

We conclude that side effects were more common among subjects ≥65 years who received HD influenza vaccine compared with SD vaccine. These side effects were generally well tolerated, were not significantly more likely to be severe, and were not associated with an impairment of general health status or with increased healthcare utilization. The increased frequency of side effects also did not adversely affect the proportion of HD vaccine recipients in their intent to continue getting vaccinated in the future. These findings should reassure patients and their providers of the safety and tolerability of the HD influenza vaccine.

Acknowledgments

We thank Tom Rector for help with statistical analysis.

Financial support. This work was supported by the Minnesota Veterans Medical Research and Education Foundation and VA Research.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Barker WH, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. Am J Epidemiol **1980**; 112:798–811.
2. Barker WH. Excess pneumonia and influenza associated hospitalization during influenza epidemics in the United States, 1970–78. Am J Public Health **1986**; 76:761–5.
3. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA **2003**; 289:179–86.
4. Centers for Disease Control and Prevention (CDC). Estimates of deaths associated with seasonal influenza—United States, 1976–2007. MMWR Morb Mortal Wkly Rep **2010**; 59:1057–62.
5. Govaert TM, Thijs CT, Masurel N, et al. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. JAMA **1994**; 272:1661–5.
6. Monto AS, Hornbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. Am J Epidemiol **2001**; 154:155–60.
7. Ohmit SE, Arden NH, Monto AS. Effectiveness of inactivated influenza vaccine among nursing home residents during an influenza type A (H3N2) epidemic. J Am Geriatr Soc **1999**; 47:165–71.
8. Gross PA, Hermogenes AW, Sacks HS, et al. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Intern Med **1995**; 123:518–27.
9. Hak E, Nordin J, Wei F, et al. Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. Clin Infect Dis **2002**; 35:370–7.
10. Mullooly JP, Bennett MD, Hornbrook MC, et al. Influenza vaccination programs for elderly persons: cost-effectiveness in a health maintenance organization. Ann Intern Med **1994**; 121:947–52.
11. Nichol KL, Nordin JD, Nelson DB, et al. Effectiveness of influenza vaccine in the community-dwelling elderly. N Engl J Med **2007**; 357:1373–81.
12. Nordin J, Mullooly J, Poblete S, et al. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. J Infect Dis **2001**; 184:665–70.
13. McElhaney JE. The unmet need in the elderly: designing new influenza vaccines for older adults. Vaccine **2005**; 23:S10–25.
14. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine **2006**; 24:1159–69.
15. US Food and Drug Administration. FDA approves a high dose seasonal influenza vaccine specifically intended for people ages 65 and older. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm195483.htm. Accessed 11 January 2016.
16. Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. Arch Intern Med **2006**; 166:1121–7.
17. Couch RB, Winokur P, Brady R, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. Vaccine **2007**; 25:7656–63.
18. Falsey AR, Treanor JJ, Tornieporth N, et al. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis **2009**; 200:172–80.
19. Tsang P, Gorse GJ, Strout CB, et al. Immunogenicity and safety of Fluzone(®) intradermal and high-dose influenza vaccines in older adults ≥65 years of age: a randomized, controlled, phase II trial. Vaccine **2014**; 32:2507–17.
20. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med **2014**; 371:635–45.
21. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. Lancet Infect Dis **2015**; 15:293–300.
22. Nichol KL, Lofgren RP, Gapinski J. Influenza vaccination. Knowledge, attitudes, and behavior among high-risk outpatients. Arch Intern Med **1992**; 152:106–10.
23. Buchner DM, Carter WB, Inui TS. The relationship of attitude changes to compliance with influenza immunization. A prospective study. Med Care **1985**; 23:771–9.
24. Centers for Disease Control and Prevention (CDC). Adult immunization: knowledge, attitudes, and practices—DeKalb and Fulton Counties, Georgia, 1988. MMWR Morb Mortal Wkly Rep **1988**; 37:657–61.
25. Carter WB, Beach LR, Inui TS, et al. Developing and testing a decision model for predicting influenza vaccination compliance. Health Serv Res **1986**; 20:897–932.
26. Ganguly R, Schler S, Vargas L, et al. Reasons for nonimmunization against influenza in the aged. J Am Geriatr Soc **1989**; 37:387.
27. Margolis KL, Nichol KL, Poland GA, Pluhar RE. Frequency of adverse reactions to influenza vaccine in the elderly. A randomized, placebo-controlled trial. JAMA **1990**; 264:1139–41.

28. Govaert TM, Dinant GJ, Aretz K, et al. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. BMJ **1993**; 307:988–90.
29. Nichol KL, MacDonald R, Hauge M. Side effects associated with pneumococcal vaccination. Am J Infect Control **1997**; 25:223–8.
30. Verger P, Collange F, Fressard L, et al. Prevalence and correlates of vaccine hesitancy among general practitioners: a cross-sectional telephone survey in France, April to July 2014. Euro Surveill **2016**; 21:30406.
31. Chowdhury PP, Mawokomatanda T, Xu F, et al. Surveillance for certain health behaviors, chronic diseases, and conditions, access to health care, and use of preventive health services among states and selected local areas—Behavioral Risk Factor Surveillance System, United States, 2012. MMWR Surveill Summ **2016**; 65:1–142.
32. Cate TR, Kasel JA, Couch RB, et al. Clinical trials of bivalent influenza A/New Jersey/76-A/Victoria/75 vaccines in the elderly. J Infect Dis **1977**; 136:S518–25.