The Journal of Infectious Diseases
MAJOR ARTICLE

Impact of Statins on Influenza Vaccine Effectiveness Against Medically Attended Acute Respiratory Illness

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(See the editorial commentary by Atmar and Keitel on pages 1211–3 and major article by Black et al on pages 1224–8.)

Background. Statins have antiinflammatory effects that may impact vaccine-induced immune responses. We investigated the impact of statin therapy on influenza vaccine effectiveness (VE) against medically attended acute respiratory illness (MAARI).

Methods. We conducted a retrospective cohort study over nine influenza seasons using research databases of a large managed care organization in the United States. Influenza vaccination and statin prescription statuses of cohort members and MAARI cases were ascertained on a per-season basis. Incidence rate ratios (IRRs) of MAARI were estimated using Poisson regression and stratified by statin use. Using a ratio of ratios approach, we compared IRRs from periods during to IRRs from periods before influenza circulation and then used relative IRRs to compute VE.

Results. After adjustment for multiple prespecified covariates, the influenza VE against MAARI was lower among statin users than nonusers during periods of local (14.1% vs 22.9%; mean difference, 11.4%; 95% confidence interval [CI], −1.7% to 26.1%) and widespread (12.6% vs 26.2%; mean difference, 18.4%; 95% CI, 2.9%–36.2%) influenza circulation.

Conclusions. In this study, statin therapy was associated with reduced influenza VE against MAARI. Since many cases of MAARI are not caused by influenza, studies of the impact of statins on influenza VE against laboratory-confirmed influenza are needed.

Keywords. statin; influenza; vaccine effectiveness; medically attended acute respiratory illness; inflammation.

Statins have proven cardiovascular benefits due to their lipid-lowering effects [1–3]. They also exhibit antiinflammatory and immunomodulatory properties [4], which not only contribute to their impact on cardiovascular disease [5, 6], but can also affect the clinical course of a variety of infectious processes, including sepsis [7], bacteremia [8], community-acquired pneumonia [9], and laboratory-confirmed influenza [10].

Given these antiinflammatory effects, statins may also affect the initial immune response to vaccines. Other immunomodulatory drugs have variable effects on vaccine-induced antibody responses [11–14]. Similar data for statins are very limited. In one randomized controlled study of 20 healthy volunteers, a 10-day course of atorvastatin led to increased antibody responses to tetanus toxoid vaccination [15]. In contrast, another study in 150 healthy adults found no difference in antibody responses to hepatitis A vaccine among those randomly assigned to receive either a 4-week course of atorvastatin or placebo [16].

Importantly, if statins affected vaccine responsiveness in individuals, their widespread use could influence overall vaccine effectiveness (VE) in a population. The only previous studies of the effect of statin therapy on vaccine immunogenicity [15, 16] did not assess VE and had other important limitations—participants were younger and healthier than typical statin users, statins were given for only a brief period around the time of vaccination, and the vaccines under study were highly immunogenic and not among those commonly administered to typical statin users. Owing to this paucity of data, it is not surprising that concurrent statin therapy is not typically considered in the analysis of vaccine studies, even when they are conducted in populations with high rates of statin use.

To address this knowledge gap, we evaluated the impact of concurrent statin therapy on the effectiveness of influenza vaccine to prevent medically attended acute respiratory illness (MAARI), using research databases from a large managed care organization (MCO) in the southeastern United States. This retrospective cohort study allowed us to evaluate longitudinal influenza vaccination status, statin medication prescriptions, and all MAARI cases occurring within the MCO, including the timing of vaccination, statin use, and illness diagnosis. Additionally, we were able to evaluate covariates that might affect overall VE estimates, to identify the specific impact of statin use in this population.

METHODS

Study Design and Data Sources

We conducted a retrospective cohort study, using existing research databases within the Kaiser Permanente Georgia

Received 6 May 2015; accepted 10 August 2015; published online 28 October 2015.
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The Journal of Infectious Diseases® 2016;213:1216–23

DOI: 10.1093/infdis/jiv457

(KPGA) MCO. For each influenza season from 2002–2003 through 2010–2011, we identified eligible MCO members and obtained data on influenza vaccination status and date of vaccination, statin medication prescription information (date of dispensing and days of supply), MAARI cases and date of diagnosis, demographic characteristics (age at start of influenza season and sex), and related covariates (prior and concurrent medical history, using *International Classification of Diseases, Ninth Revision* (ICD-9), diagnosis codes [Supplementary Appendix 1], and number of well-care medical visits during the putative influenza season [ie, October through May]).

Inclusion and Exclusion Criteria

Study eligibility was assessed on a per–influenza season basis; therefore, MCO members could be included in the study cohort for one season but excluded for the next season. To be eligible in a given influenza season, individuals had to be (1) continuously enrolled between 1 September of the given year (to assess for statin use in the month prior to the influenza season) and 31 May of the following year (1 full putative influenza season) and (2) aged ≥45 years on 1 September. Individuals who were not enrolled continuously for the full influenza season were excluded because we were unable to verify the reason for no longer being enrolled (which could include events such as death during the influenza season, change in healthcare coverage, or relocation outside the MCO coverage area). Individuals were also excluded if they had a history of pregnancy or were receiving prescriptions for immunoglobulin or immunosuppressant drugs (during that influenza season) or if they had a diagnosis of cancer (not including skin cancer), had a diagnosis of HIV infection or AIDS, or underwent organ transplantation (during the season being analyzed and all subsequent seasons).

Influenza Vaccine Classification

For each influenza season, we identified influenza vaccines received by eligible study cohort members. For consistency of comparison, only individuals who received the vaccine on or before 31 December of a given influenza season were eligible for inclusion in the cohort for that season. We limited our analysis to individuals vaccinated on or before this date in order to maximize the likelihood that statin users were actually prescribed statin therapy at the time of influenza vaccination (since we did not require statin users to remain on therapy for the entire influenza season). We also excluded individuals who received the live attenuated influenza vaccine for that season. Individuals who did not have an influenza vaccine recorded in the MCO were considered unvaccinated for that season.

Statin Medication Classification

For each influenza season, we used pharmacy dispensing records for eligible study cohort members, to extract data on statin medication dispensing. These data are likely to be representative of actual medication use, since >85% of the prescriptions written in this MCO are filled at network pharmacies. To be classified as a statin user for a given season, the first dispensing had to occur on or before 1 September of a given year (to ensure at least 1 month of statin therapy before vaccine receipt); subjects did not have to be prescribed statin therapy for the entire influenza season. Initiating statin medication later in the influenza season led to exclusion from the cohort for that season. Individuals who did not have a history of statin medication dispensing who met all other inclusion/exclusion criteria were considered to be statin nonusers for that season.

Outcome Assessment

We identified MAARI cases that occurred within full putative influenza seasons among eligible cohort members, using ICD-9 codes (Supplementary Appendix 1).

Temporal Classification of Vaccination and Outcomes

We used metrics of the spread of influenza from the state health department to identify, within the putative influenza season, periods before, at least local, and widespread influenza circulation in Georgia. Local influenza circulation was defined as influenza activity in just a single region of the state, whereas widespread circulation required influenza activity in at least half the regions of the state [17]. For each individual in the cohort, we used these dates to compute the vaccinated and unvaccinated person-times within each period of influenza circulation, for each influenza season. Additionally, we used these classifications to identify the timing of MAARI cases relative to circulating influenza virus. Individuals could contribute both vaccinated and unvaccinated person-times in each period of viral circulation and could also have outcomes occurring in vaccinated and unvaccinated person-times.

Analytical Methods

After each seasonal cohort was completed, all individual seasons were combined to form 1 analytic data set. Demographic descriptions of the cohort were compared by final exposure status for each influenza season. For example, an individual who did not receive influenza vaccine or a statin prescription in one season would be classified as vaccine and statin negative (V−S−), but if, in the following season, they did receive influenza vaccine and a statin prescription, they would be classified as vaccine and statin positive (V+/S+).

We used Poisson regression to compute incidence rate ratios (IRRs) for each period of influenza virus circulation, comparing vaccinated to unvaccinated individuals across the interaction with statin medication use. The offset term, log person-time, was specific to vaccinated and unvaccinated person-time within each period. Since individuals could contribute both vaccinated and unvaccinated person-time in each period and could be enrolled over multiple influenza seasons, we used generalized estimating equations, assuming an autoregressive correlation structure, to account for multiple observations. We additionally computed sex-specific estimates to account for potential sex-based differences in vaccine response [18]. We determined

adjusted estimates, using the following prespecified covariates: age, use of well-care visits during the influenza season, any prior receipt of 23-valent pneumococcal polysaccharide vaccine (PPSV23), and prior diagnoses of chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), diseases of the circulatory system, and diabetes (ICD-9 codes used for identifying covariates are available in Supplementary Appendix 1).

Once IRRs were estimated for each period, we computed a ratio of ratios (or a difference of differences on a logarithmic scale) by comparing the IRR for periods of at least local or widespread influenza circulation with that before the influenza season [19, 20]. The relative IRR estimates were converted to VE measures as follows: VE = [1 − relative IRR] (Supplementary Appendix 2).

This study was reviewed and approved by the KPGA Institutional Review Board.

RESULTS

Study Population

Table 1 presents the total number of individuals and person-seasons included in the analysis data set, as well as their baseline characteristics. For comparison, the pooled data were stratified into 4 groups (V+/S+, V+/S−, V−/S+, and V−/S−), with influenza vaccination and statin prescription classification based on per-season final exposure status ($P < .0001$ for all comparisons). A total of 137 488 individuals were included, and these individuals contributed 447 588 person-seasons (range of seasons contributed per individual, 1–7). This included 105 694 person-seasons (24%) for influenza vaccine recipients and 92 027 person-seasons (21%) for statin users.

The majority of the individuals in each group (range, 59.4%–91.9%) were aged <65 years. The proportion of males and females in each group was roughly similar in all except the V+/S− group, in which there was nearly double (61.3% vs 38.7%) the amount of person-seasons contributed by females as compared to males. The V+/S+ group had the highest proportion of individuals with a diagnosis of COPD (30.1%), CVD (42.7%), diseases of the circulatory system (80.2%), or diabetes (46.1%).

In the groups that did not receive either influenza vaccine or were not prescribed statins, uptake of PPSV23 was also significantly reduced (21.3% and 23.9%, respectively), compared with the V+/S+ group (48.5%). In the V−/S− group, >95% had not

Table 1. Demographic and Clinical Characteristics of the Study Population, Stratified by Final Influenza Vaccine (V) and Statin (S) Exposure Status per Influenza Season

Characteristic	V+/S+ (n = 39 342)	V+/S− (n = 66 532)	V−/S+ (n = 52 685)	V−/S− (n = 289 029)
Sex[a]				
Female	20 988 (53.4)	40 761 (61.3)	26 045 (49.4)	155 967 (54.0)
Male	18 354 (46.7)	25 771 (38.7)	26 640 (50.6)	133 062 (46.0)
Age, y[a]				
45–54	8414 (21.4)	26 325 (39.6)	21 119 (40.1)	186 006 (64.4)
55–64	14 946 (38.0)	22 386 (33.7)	21 204 (40.3)	79 516 (27.5)
≥65	15 982 (40.6)	17 821 (26.8)	10 362 (19.7)	23 507 (8.1)
Diagnosis				
COPD[a]				
Yes	11 827 (30.1)	17 162 (25.8)	11 721 (22.3)	44 180 (15.3)
No	27 515 (69.9)	49 370 (74.2)	40 964 (77.8)	244 849 (84.7)
CVD[a]				
Yes	16 803 (42.7)	13 482 (20.3)	17 866 (33.9)	32 837 (11.4)
No	22 539 (57.3)	53 050 (79.7)	34 819 (66.1)	256 192 (88.6)
Circulatory disease[a]				
Yes	31 537 (80.2)	33 852 (50.9)	39 373 (74.7)	106 595 (36.9)
No	7805 (19.8)	32 680 (49.1)	13 312 (25.3)	182 434 (63.1)
Diabetes[a]				
Yes	18 133 (46.1)	8843 (13.3)	19 493 (37.0)	21 810 (7.6)
No	21 209 (53.9)	57 689 (86.7)	33 192 (63.0)	267 219 (92.5)
Received PPSV23[a]				
Yes	19 071 (48.5)	15 925 (23.9)	11 215 (21.3)	13 218 (4.6)
No	20 271 (51.5)	50 607 (76.1)	41 470 (78.7)	275 811 (95.4)
Well-care visits in influenza season, no.[a]				
0	14 250 (36.2)	23 676 (35.6)	38 028 (72.2)	228 883 (79.2)
≥1	25 092 (63.8)	42 856 (64.4)	14 657 (27.8)	60 146 (20.8)

Data are no. (%) of person-seasons.

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; PPSV23, 23-valent pneumococcal polysaccharide vaccine; −, nonuse; +, use.

[a] $P < .0001$, by χ^2 analysis.

received PPSV23. Finally, nearly two thirds of the vaccinated individuals had ≥1 well-care visits during the influenza season, compared with less than one third among the unvaccinated patients. Approximately one third of the vaccinated individuals (36.2% in the V+/S+ group and 35.6% in the V+/S− group) received their influenza vaccine at a visit that was not identified as a well-care visit (ie, a visit for other health reasons).

MAARI Outcomes

Table 2 presents the total number of incident cases of MAARI identified during the study period. To compute incidence rates for the VE analysis, MAARI cases were assigned to periods of vaccinated and unvaccinated person-times (V+ and V−, respectively) and further stratified by statin prescription receipt (S+ and S−). In the full analysis data set, we identified 52 008 incident cases of MAARI. Since individuals could contribute both unvaccinated and vaccinated person-times depending on the timing of their influenza vaccination in the influenza season, the total number of individuals in Table 2 exceeds the number of individuals included in the analysis data set.

VE

In the primary analysis, the influenza VE for preventing MAARI was significantly lower among statin users than nonusers during periods of both local (14.9% vs 24.7%; mean difference, 13.1%; 95% confidence interval [CI], .4%–27.6%) and widespread (14.2% vs 28.7%; mean difference, 20.3%; 95% CI, 5.1%–37.6%) influenza circulation (Figure 1*A* and 1*B*). In the adjusted analysis, the difference in influenza VE between statin users and nonusers was slightly smaller but still significant during periods of widespread influenza circulation (12.6% vs 26.2%; mean difference, 18.4%; 95% CI, 2.9%–36.2%). There was a nonsignificant trend toward reduced VE among statin users during periods of local influenza circulation, as well (14.1% vs 22.9%; mean difference, 11.4%; 95% CI, −1.7% to 26.1%; Figure 1*C* and 1*D*).

Effect of Sex on VE Among Statin Users

Similar to the overall analysis, sex-specific estimates of influenza VE were lower in male and female statin users, compared with nonusers (Figure 2*A* and 2*B*). In the primary analysis, the effect of statin use on VE was more pronounced in males during both local (mean difference, 41.4% vs 9.0% for females; 95% CI, for male statin users vs nonusers, 15.7%–72.7%) and widespread (mean difference, 34.5% vs 22.2% for females; 95% CI, for male statin users vs nonusers, 7.7%–68.0%) influenza circulation. However, in the adjusted analysis the differences between male and female statin users were no longer statistically significant (Figure 2*C* and 2*D*).

DISCUSSION

In this retrospective cohort study within a large MCO, we found that the influenza VE for preventing MAARI was lower among

Table 2. Medically Attended Acute Respiratory Illness (MAARI) Outcomes, by Temporal Classification and Influenza Vaccine (V) and Statin (S) Exposure Status

Variable	V+/S+	V+/S−	V−/S+	V−/S−
Before influenza season				
Persons contributing time, no.[a]	31 472	51 587	91 951	355 459
Total person-time, person-days, no.	1 488 604	2 405 891	5 263 836	23 597 339
Total person-time, person-years, no.	4 078.4	6 591.5	14 421.5	64 650.2
Person-days contributed, no., mean	47.3	46.6	57.2	66.4
MAARI cases, no. (n= 12 716)	821	1312	2344	8239
Crude incidence rate, cases/100 person-years, no.	20.1	19.9	16.3	12.7
Period of local influenza circulation				
Persons contributing time, no.[a]	39 349	66 536	59 989	303 171
Total person-time, person-days, no.	4 346 178	7 135 776	5 961 658	31 658 412
Total person-time, person-years, no.	11 907.3	19 550.1	16 333.3	86 735.4
Person-days contributed, no., mean	110.5	107.2	99.4	104.4
MAARI cases, no. (n = 26 318)	2719	4202	3529	15 868
Crude incidence rate, cases/100 person-years, no.	22.8	21.5	21.6	18.3
Period of widespread influenza circulation				
Persons contributing time, no.[a]	39 342	66 532	54 170	292 606
Total person-time, person-days, no.	1 781 869	2 897 230	2 387 747	12 679 800
Total person-time, person-years, no.	4 881.8	7 937.6	6 541.8	34 739.2
Person-days contributed, no., mean	45.3	43.5	44.1	43.3
MAARI cases, no. (n = 12 974)	1350	2010	1702	7912
Crude incidence rate, cases/100 person-years, no.	27.7	25.3	26.0	22.8

Abbreviations: −, nonuse; +, use.

[a] The sum of values is greater than the total cohort size (n=447 588). Individuals could contribute time to multiple exposure categories in each influenza circulation period, depending on the timing of vaccination.

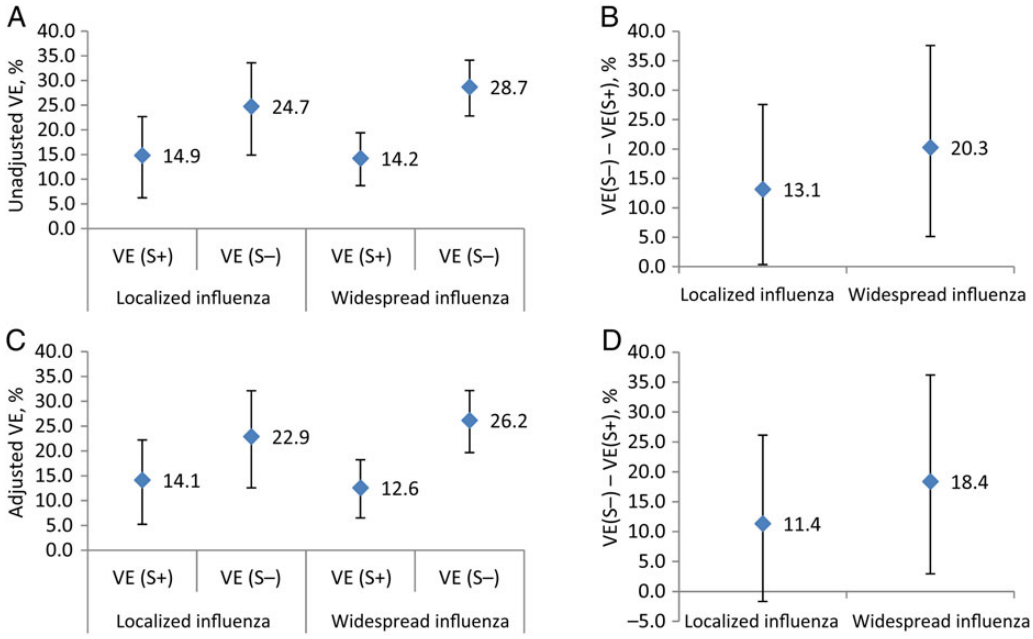

Figure 1. Vaccine effectiveness (VE), stratified by period of influenza circulation and statin (S) exposure status. *A*, Unadjusted estimates for VE among S users (S+) and non–S users (S–). *B*, Mean difference in unadjusted VE between S– and S+, by period of influenza circulation. *C*, Adjusted estimates for VE among S+ and S–. *D*, Mean difference in adjusted VE between S– and S+, by period of influenza circulation.

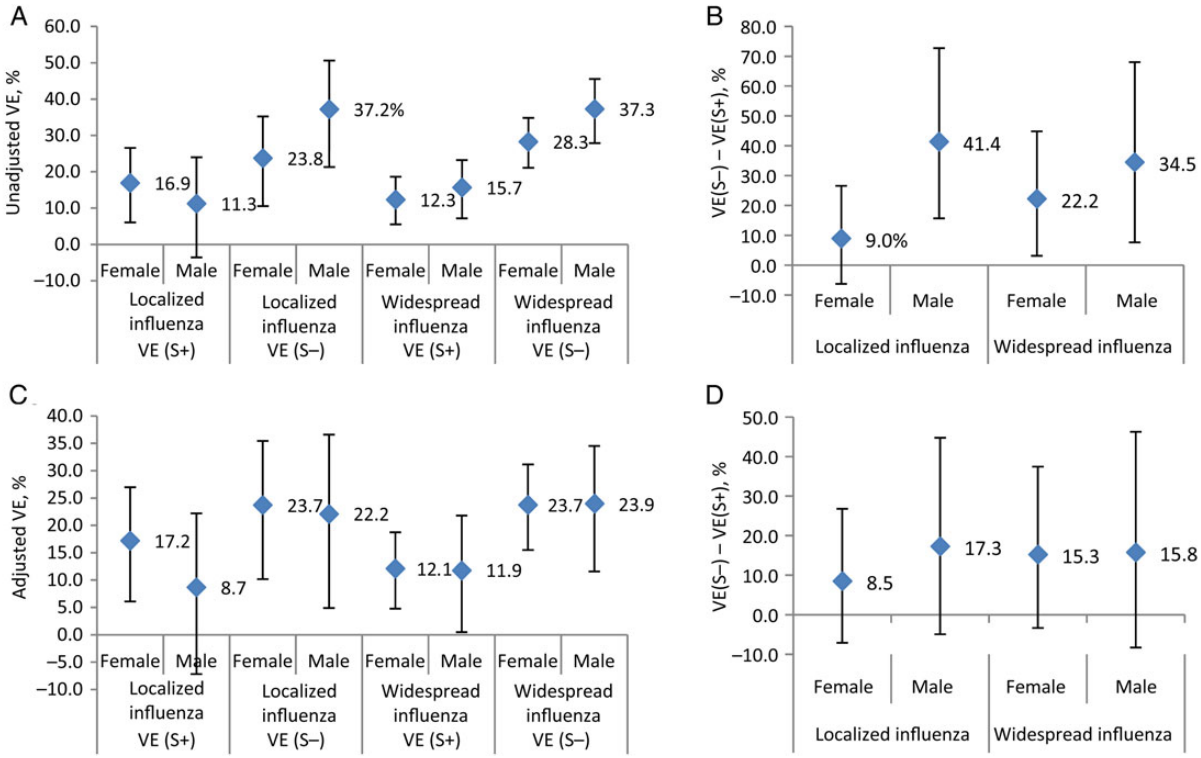

Figure 2. Effect of sex on vaccine effectiveness (VE), stratified by period of influenza circulation and statin (S) use. *A*, Unadjusted estimates for VE among S users (S+) and non–S users (S–). *B*, Mean difference in unadjusted VE between S– and S+, by period of influenza circulation. *C*, Adjusted estimates for VE among S+ and S–. *D*, Mean difference in adjusted VE between S– and S+, by period of influenza circulation.

statin users, compared with nonusers. Even after adjustment for several covariates of vaccine responsiveness, statin receipt, and health-seeking behavior, the observed reduction in influenza VE among statin users remained statistically significant for periods of widespread influenza circulation, with a nonsignificant trend toward reduced VE during periods of local circulation, as well. Unlike previous studies that have evaluated the effect of various immunomodulators, including statins, on the immune response to vaccines [11, 12, 15, 16], this is the first analysis to identify an association between statin therapy and VE in a population of typical statin users for a commonly administered vaccine. Of note, our estimates for influenza VE against MAARI for both statin users and nonusers were similar to those that have been previously reported in other populations [21, 22].

In the sex-stratified analysis, the effect of statin use on influenza VE appeared to be greater among male statin users, although this was not significant in the adjusted analysis. There is limited evidence for an effect of sex on the immunomodulatory effects of statin therapy, and in large clinical studies, the cardiovascular benefits of statin therapy are similar in men and women [6, 23]. However, previous studies have demonstrated that women develop higher antibody responses than men to influenza vaccines [24]. These sex-specific differences in immune response deserve further exploration in both vaccine and statin trials.

Our findings suggest that the antiinflammatory properties underlying the clinical benefits of statin therapy might also attenuate the immune response to influenza vaccine. Statins can affect multiple steps in the inflammatory cascade triggered by vaccines: they can inhibit endothelial activation and leukocyte chemotaxis [25], antigen presentation through the major histocompatibility complex class II pathway [26], elaboration of proinflammatory cytokines by peripheral blood mononuclear cells [27], and lymphocyte activation through the T-cell receptor signaling cascade [28], and they can influence the T-helper type 1/2 fate of activated T cells [29]. In a study of immune responses to influenza A virus, induction of cross-reactive immunity to influenza virus subtypes was found to be dependent on the mevalonate pathway and was markedly reduced in the presence of a statin [30]. These data highlight the need for further investigation into the impact of statin therapy on the innate and adaptive response to vaccines.

Owing to their pleiotropic immunologic effects, statins have been suggested as potential adjuncts in influenza therapy [31, 32]. However, this has not been evaluated in prospective studies, and retrospective analyses of the impact of statins on influenza-related outcomes have yielded mixed results. Three independent studies found no significant benefit of statin therapy on the incidence of ARI during 2 winter seasons [33] or on influenza-related outcomes during periods of seasonal [34] and pandemic [35] influenza; however, only one was designed to consider influenza vaccination as a confounder [33]. In contrast, an analysis of data from a single influenza season in the United States actually found a significant protective effect of preadmission statin therapy on influenza-related mortality, regardless of vaccination status [10]. In that study, influenza vaccine alone had no benefit, presumably owing to vaccine subtype mismatch, but inclusion of vaccination status in the multivariate model resulted in a more conservative estimate of the protective effect of statin therapy, which might be expected if statins indeed reduce influenza VE [10].

This study has several limitations. We relied on data abstracted from research databases, so ascertainment of exposure status and outcomes may be biased. For example, our analysis may not have accurately classified individuals who received a statin or vaccine outside the MCO, which could influence estimates of VE. However, as noted previously, the vast majority (>85%) of MCO members fill their prescriptions at network pharmacies. With regard to influenza vaccination status, even if individuals who received their vaccine outside the MCO were misclassified as unvaccinated, this would only result in overly conservative estimates of VE; therefore, the true effect of statin therapy may be even greater. Since we limited our analysis to individuals who were continuously enrolled for the entire influenza season, individuals who died (potentially due to influenza) were excluded. However, this would only bias our VE estimates toward the null.

Importantly, our estimates of VE were based on MAARI as an outcome measure, rather than laboratory-confirmed influenza. On the assumption that the period before influenza circulation had little or no actual influenza activity, the background incidence rate of MAARI in statin users and nonusers accounted for a substantial proportion of the morbidity seen in the periods of local and widespread influenza. This background incidence would not be expected to be influenced by influenza vaccine, and hence the impacts on MAARI could be confounded. This probably explains why the VE calculations for MAARI in all groups were much lower than most estimates of VE against laboratory-confirmed influenza. Essentially, we are not measuring the actual impact of influenza vaccine against influenza but against an outcome of many causes that includes influenza. Despite these limitations, MAARI has been widely used as a surrogate for influenza-related illnesses, although concerns have been raised about its ability to assess the impact of influenza vaccine against influenza [36–38]. Yet, because laboratory testing for influenza virus in the clinical setting in the absence of a prospective study of VE may be inconsistent, use of MAARI as an outcome measure for a VE analysis is more feasible.

By using MAARI as the outcome measure, our analysis may also have been affected by any increased propensity for seeking care for ARI among statin users as compared to statin nonusers. In other words, the frequency of preventive-care visits among statin users may have been greater than that among nonusers

during periods of influenza circulation, thereby increasing statin users' likelihood of being identified as MAARI cases. This healthy-user bias has been the subject of multiple previous studies of influenza VE [34] and has also been demonstrated for individuals receiving statin therapy [39]. To address potential healthy-user bias, we calculated VE by comparing IRRs for periods of influenza circulation with IRRs during the periods before influenza circulation (thus generating relative ratio ratios [RRRs]), using a ratio of ratios approach. This approach mitigates potential healthy-user bias within each subgroup because any difference in VE between statin users and nonusers during the period before influenza circulation, when any difference in VE is by definition due to confounding, is likely to be canceled out [20]. However, one limitation of the ratio of ratios approach is that RRR and VE estimates are dependent on how the different periods of influenza seasons are defined. For example, if influenza virus circulation in this cohort differed systematically from statewide metrics, then our estimates for IRR in each period could be biased. Ultimately, probably the most important implication of our findings is to see whether they are confirmed in studies of influenza VE that use laboratory-confirmed influenza as the outcome measure. Moreover, evaluating the interaction of statin use with influenza vaccine immunogenicity will add to the evidence base in this area.

Finally, some of the effect of statin use on influenza VE may be due to residual confounding. Statin users may have been more frequently coprescribed other medications that potentially influence the immune response to vaccines. Similarly, statin users may have been more likely than nonusers to be obese [40], which has been associated with a diminished immune response to influenza vaccine [41–43] and an increased likelihood of seeking care for ARI [44, 45]. We did not have data on coprescribed medications or obesity. One reason obesity was excluded was because the limitations of the administrative data set (eg, difficulty correlating diagnostic codes for obesity and actual body mass index) would have introduced additional bias. However, our adjustment for a range of comorbidities frequently associated with statin use likely captured differences in medication use patterns and rates of obesity between the groups. We were also unable to account for the impact of vaccination during the prior year on influenza VE. Some studies have shown that previous-year influenza vaccination may attenuate current-year VE [46, 47]; therefore, our findings may be partly attributable to the association of statin prescription with influenza vaccine receipt in the previous year [39]. However, we would not expect statin therapy to be the only marker of prior-year vaccination, and despite adjustment for other health-seeking behaviors that we would also expect to be associated with prior-year vaccination, the reduction in VE among statin users was persistent.

In conclusion, in this study of a large population within a MCO followed over multiple influenza seasons, we found that influenza VE for preventing MAARI was lower among those who were receiving concomitant statin therapy. The immunomodulatory effects of statin therapy on vaccine responses and the overall effectiveness of currently recommended vaccines have not been adequately explored. More data are needed in this area to provide meaningful guidance for vaccine and statin use in the population. If confirmed, our findings have potential implications for clinical guidelines regarding statin use around the time of routine vaccinations.

Supplementary Data

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Acknowledgment. We thank Kristina H. Lewis, MD, MPH, SM, for reviewing an early draft of the manuscript.

Disclaimer. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases (NIAID) or the National Institutes of Health.

Financial support. This work was supported by Emory University and the National Institute of Allergy and Infectious Diseases (award T32AI074492 to V. K. P. via the Emory Vaccinology Training Program).

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.

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