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Relative Effectiveness of Adjuvanted Trivalent Inactivated Influenza Vaccine Versus Egg-derived Quadrivalent Inactivated Influenza Vaccines and High-dose Trivalent Influenza Vaccine in Preventing Influenza-related Medical Encounters in US Adults ≥ 65 Years During the 2017–2018 and 2018–2019 Influenza Seasons

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Background. The effectiveness of standard, egg-derived quadrivalent influenza vaccines (IIV4) may be reduced in adults ≥65 years of age, largely because of immunosenescence. An MF59-adjuvanted trivalent influenza vaccine (aIIV3) and a high-dose trivalent influenza vaccine (HD-IIV3) offer older adults enhanced protection versus standard vaccines. This study compared the relative effectiveness of aIIV3 with IIV4 and HD-IIV3 in preventing influenza-related medical encounters over 2 US influenza seasons.

Methods. This retrospective cohort study included US patients ≥65 years vaccinated with aIIV3, IIV4, or HD-IIV3. The outcome of interest was the occurrence of influenza-related medical encounters. Data were derived from a large dataset comprising primary and specialty care electronic medical records linked with pharmacy and medical claims. Adjusted odds ratios (OR) were derived from an inverse probability of treatment-weighted sample adjusted for age, sex, race, ethnicity, geographic region, vaccination week, and health status. Relative vaccine effectiveness (rVE) was determined using the formula (% VE = 1 – $OR_{adjusted}$) × 100.

Results. In 2017–2018, cohorts included: aIIV3, n = 524 223; IIV4, n = 917 609; and HD-IIV3, n = 3 377 860. After adjustment, 2017–2018 rVE of aIIV3 versus IIV4 was 18.2 (95% confidence interval [CI], 15.8–20.5); aIIV3 vs. HD-IIV3 was 7.7 (95% CI, 2.3–12.8). In 2018–2019, cohorts included: aIIV3, n = 1 031 145; IIV4, n = 915 380; HD-IIV3, n = 3 809 601, with adjusted rVEs of aIIV3 versus IIV4 of 27.8 (95% CI, 25.7–29.9) and vs. HD-IIV3 of 6.9 (95% CI, 3.1–10.6).

Conclusion. In the 2017–2018 and 2018–2019 influenza seasons in the United States, aIIV3 demonstrated greater reduction in influenza-related medical encounters than IIV4 and HD-IIV3 in adults ≥65 years.

Keywords. adjuvanted trivalent inactivated influenza vaccine; older adults; influenza; relative effectiveness; influenza-related medical encounters.

Adults ≥65 years of age are at higher risk of infection with seasonal influenza and serious influenza-related complications compared with younger individuals. Because of immunosenescence, or age-related decline in immune efficacy, older adults have diminished responses to vaccination and are more susceptible to infections and influenza-related sequelae [1, 2]. Each year, the vast majority (~90%) of influenza-related deaths in the United States occur in people ≥65 years of age [3, 4], primarily as a result of secondary pneumonia and exacerbations of preexisting cardiovascular and respiratory diseases [5, 6].

The US Centers for Disease Control and Prevention estimates that influenza vaccination prevents >100 000 hospitalizations each year, 60% of which involve adults ≥65 years [4]. For this reason, the Advisory Committee on Immunization Practices considers adults ≥65 years a priority group for influenza vaccination [7]. However, vaccination with standard, egg-derived quadrivalent inactivated influenza vaccines (IIV4) is less effective in adults ≥65 years compared with younger age groups [4, 8, 9], probably because of age-associated declines in humoral and cell-mediated immunity [1, 2].

Approaches to overcome suboptimal immune responses include adding an adjuvant to the vaccine, such as in the

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MF59-adjuvanted trivalent inactivated influenza vaccine (aIIV3; Fluad, Seqirus USA Inc., Summit, NJ, USA), and increasing the antigenic content per vaccine dose, as represented by high-dose nonadjuvanted trivalent inactivated influenza vaccine (HD-IIV3; Fluzone High-Dose, Sanofi Pasteur Inc., Swiftwater, PA, USA) [10, 11]. Both vaccines are currently licensed and available for use in the United States and across the globe such as in the United Kingdom, Canada, Europe, and Australia. Studies have shown that the efficacy and effectiveness of HD-IIV3 is greater than that of nonadjuvanted, standard-dose vaccines in adults ≥65 years [12–14], as is the effectiveness of aIIV3 in this population [15–22]. Studies have also demonstrated that aIIV3 induces production of cross-reactive antibodies and thus may provide heterotypic protection [23–26].

The vaccine effectiveness of aIIV3 relative to enhanced and standard vaccines has been estimated in few comparative studies with limited sample size [18, 27–30]. A retrospective cohort study using a large integrated dataset was thus designed to assess the relative vaccine effectiveness (rVE) of aIIV3 versus nonadjuvanted influenza vaccines (IIV4 and HD-IIV3) in preventing influenza-related medical encounters during the 2017–2018 and 2018–2019 influenza seasons in the United States.

METHODS

Study Design

A retrospective cohort study was conducted during the 2017–2018 and 2018–2019 influenza seasons using deidentified electronic medical records (EMRs) from primary care and specialty clinics supplemented with pharmacy and medical claims where available. Data were evaluated for subjects aged ≥65 years who were vaccinated in the United States with 1 of 3 influenza vaccines: aIIV3, IIV4, or HD-IIV3. This study was designed, implemented, and reported in accordance with Good Pharmacoepidemiological Practice, applicable local regulations, and the ethical principles laid down in the Declaration of Helsinki. Study findings are reported in accordance with the Reporting of Studies Conducted Using Observational Routinely Collected Health Data recommendations.

Data Sources

An integrated dataset was created by linking patient-level EMRs from Veradigm Health Insights (Allscripts Touchworks and Allscripts PRO, Chicago, IL, USA, as well as Practice Fusion, Inc., San Francisco, CA, USA) with pharmacy and medical claims data where available (Komodo Health Inc., New York, NY, USA) (see Deidentification and Linkage Methodology in the Supplementary Data for details). The EMR platform serves primary care physicians who provide a comprehensive array of healthcare services, including the issuing of prescriptions and vaccinations. As a noninterventional, retrospective database study using a certified Health Insurance Portability and Accountability Act–compliant deidentified research database, approval by an institutional review board was not necessary.

Study Population

The study population included all individuals ≥65 years of age at the time of immunization who had an eligible seasonal influenza vaccination recorded in the EMRs or claims datasets as well as at least 1 record in their primary care EMR in the year before the recorded influenza immunization. Individuals were considered fully vaccinated 14 days after receipt of the seasonal influenza vaccine. Included study subjects must have had at least 1 year of primary care medical history in the EMR platform. Subjects were excluded from the cohort if they had a record of receiving >1 influenza vaccination during the study season or if they had an influenza-related medical encounter during the study season but before the vaccination date. Patients may have been included in the study cohort for 1 or both seasons.

Exposure Ascertainment

EMR data, supplemented with medical and pharmacy claims data, were used to ascertain the immunization status of all eligible individuals using current procedural terminology, codes for vaccine administered, and national drug codes (Supplementary Table 1). The vaccination intake period extended from August 1, 2017, to February 28, 2018 (first season), and August 1, 2018, to February 28, 2019 (second season). Eligible study participants were classified into 1 of 3 exposure cohorts based on the type of influenza vaccine (aIIV3, IIV4, or HD-IIV3). A cohort of patients receiving nonadjuvanted trivalent inactivated influenza vaccine (IIV3) was evaluated but not included as a main comparator because of limited sample size.

Outcome Ascertainment

The outcome of interest was the occurrence of an influenza-related medical encounter defined using International Classification of Diseases (ICD)-9-Clinical Modifications (CM) and ICD-10-CM codes that correspond to the US Armed Forces Health Surveillance Center (AFHSC) Code Set B (Supplementary Data) [31, 32]. Code Set B was identified a priori as the primary outcome of interest [32]. A descriptive evaluation of the overlap between US Centers for Disease Control and Prevention–reported, laboratory-confirmed influenza and the incidence of influenza-related medical encounters (AFHSC Code Set B) was conducted within the study cohort. Additionally, AFHSC Code Set A was evaluated (Supplementary Data).

Covariates

Confounders of the association of interest were identified a priori. Data were ascertained from each subject's EMR on age,

sex, race, ethnicity, week of immunization, geographic region, and health status quantified using the Charlson Comorbidity Index (CCI) [33, 34].

Statistical Methods

Analyses were conducted and reported separately for each season. A descriptive analysis was conducted to evaluate patient characteristics in the vaccine cohorts. Inverse probability of treatment weighting (IPTW) was used to adjust for cohort imbalances [35]. In the IPTW method, weights are assigned to individuals based on the inverse of their probability of receiving the treatment, as estimated by propensity scores (PSs). IPTW aims to balance the distribution of confounders across treatment groups, independent of treatment assignment. Using this methodology, PSs were first calculated for each subject using a logit model predictive of treatment group membership (ie, aIIV3 vs. comparator) based on study covariates. PSs were then used to create stabilized weights [35]. Weights were truncated at the 3rd and 97th percentile weight for both seasons to attenuate any extreme variability from outlier patients. Adjusted odds ratios were then estimated using a logistic regression model (outcome of influenza-related medical encounter vs. no influenza-related medical encounter) in the weighted cohort. The rVE was calculated as (% VE = 1 – $OR_{adjusted}$) × 100. Categorical variables with missing or null values in the EMR were classified as "not reported" or "unknown," whereas continuous counts of comorbidities or CCI were recoded as 0. Missing or out-of-range values were not imputed. Analyses were conducted using SQL and SAS (version 9.4).

Additional Analyses

The following additional analyses were conducted: (1) subgroup analyses by age (65–74, 75–84, and ≥85 years), where PS were regenerated for each age subgroup for each season; (2) rVE reestimation in a restricted observation window that corresponded to adjacent calendar weeks with highest laboratory-confirmed influenza activity (December 11, 2017, to March 18, 2018, and December 17, 2018, to April 7, 2019 [36]); (3) a post hoc doubly robust analysis that included covariates in both PS generation and outcome models; and (4) a post hoc analysis, where PS were regenerated using a multivariable model with all original covariates but instead of a CCI score the model included 17 binary variables for CCI categories to account for health status.

RESULTS

Study Subjects

Of 45 million distinct individuals identified from the integrated dataset, approximately 11 million subjects met the inclusion criteria and were included in the analysis. The final cohort for the 2017–2018 season included 4.8 million subjects, of which 524 223 (10.9%) received aIIV3, 917 609 (19.0%) received IIV4, and 3 377 860 (70.1%) received HD-IIV3. The 2018–2019 cohort included 5.8 million patients, divided as follows: aIIV3, 1 031 145 (17.9%); IIV4, 915 380 (15.9%); and HD-IIV3, 3 809 601 (66.2%). Participant selection is illustrated in Figure 1.

From the 2017–2018 to the 2018–2019 season, there was an increased use of the enhanced vaccines (ie, the high-dose vaccine and the adjuvanted vaccine) (Figure 1). A substantial decrease was observed in vaccination with IIV3 (Supplementary Table 2). For this reason, IIV3 was excluded as a main comparator; however, results are presented in the Supplementary Data.

All vaccine groups were generally comparable with respect to age, sex, race, ethnicity, and geographic region. The existing EMR structure led to few missing data. During both seasons, the majority of study subjects in the vaccine cohorts were female, White, and had a record of residing in the South. The mean age was 74.8 years (Table 1 and Supplementary Table 2). Diabetes, chronic pulmonary disease, peripheral vascular disease, and cancer were the most common high-risk comorbidities across all 3 groups for both seasons (Supplementary Table 3). The completeness of covariate information did not differ greatly between the vaccine groups.

Overall rVE

During the 2017–2018 influenza season, 1.8% of cohort subjects had an influenza-related medical encounter, and 0.9% of subjects had an influenza-related medical encounter in the 2018–2019 season. Subjects vaccinated with aIIV3 had the lowest rates of influenza-related medical encounters in the 2017–2018 (1.7%) and 2018–2019 seasons (0.8%). In 2017–2018, 2.0% and 1.8% of patients vaccinated with IIV4 and HD-IIV3 had influenza-related medical encounters, respectively, and in 2018–2019, 1.2% of IIV4 and 0.9% of HD-IIV3 recipients had an influenza-related medical encounter.

In 2017–2018, the unadjusted rVE was 15.5 (95% confidence interval [CI], 13.3–17.6) for aIIV3 vs. IIV4 and 3.6 (95% CI, 1.4–5.7) for aIIV3 versus HD-IIV3. When adjusted for demographic confounders, rVE for aIIV3 versus IIV4 was 18.2 (95% CI, 15.8–20.5) and aIIV3 versus HD-IIV3 was 7.7 (95% CI, 2.3–12.8) (Figure 2). In the 2018–2019 season, the unadjusted rVE was 27.0 (95% CI, 24.9–29.0) for aIIV3 versus IIV4 and 7.4 (95% CI, 5.2–9.6) for aIIV3 versus HD-IIV3. The adjusted rVE value for aIIV3 versus IIV4 was 27.8 (95% CI, 25.7–29.9) and for aIIV3 vs. HD-IIV3 was 6.9 (95% CI, 3.1–10.6) (Figure 2). Results remained directionally similar for age-related subgroup analyses during both the 2017–2018 and 2018–2019 seasons (Figure 3 and Supplementary Table 4). Results were not significant for the 65–74, 75–84, and ≥85 years of age cohorts for the 2017–2018 season and for the ≥85-year cohort in the 2018–2019 season (Figure 3). Age subgroup results were similar when vaccine groups were compared using a broader definition of influenza (Code Set A; Supplementary Table 5) as well

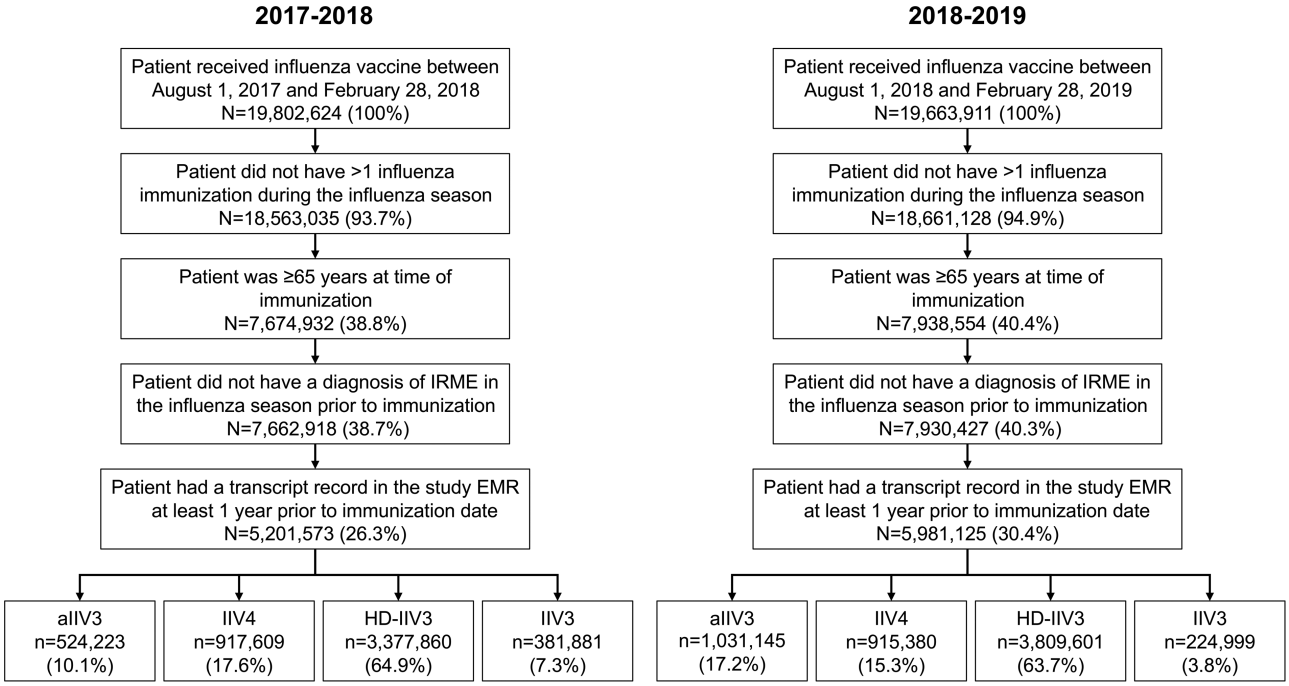

Figure 1. Flow diagram of patient selection process. Percentages shown for the first 5 rows of the flow chart represent proportions of the initially identified population shown in the first row. Percentages shown in the final row are proportions of the study population in the fifth row. Abbreviations: aIIV3, adjuvanted trivalent inactivated influenza vaccine; EMR, electronic medical record; HD-IIV3, nonadjuvanted high-dose trivalent inactivated influenza vaccine; IIV4, nonadjuvanted quadrivalent inactivated influenza vaccine; IRME, influenza-related medical encounters.

as in the post hoc doubly robust analysis (Supplementary Figure 1) and the analysis using a multivariable logit model that included the 17 binary variables for health status (Supplementary Figure 2), whether narrow or broad definitions of influenza were used. Absolute standardized differences graphs are shown in Supplementary Figure 3.

rVE During Peak Influenza Activity

In the restricted 2017–2018 season analysis (Table 2), the rVE of aIIV3 versus IIV4 was 18.8 (95% CI, 16.3–21.3) and the rVE of aIIV3 versus HD-IIV3 was 8.2 (95% CI, 2.5–13.6). During the restricted 2018–2019 season, aIIV3 rVE values were 26.6 (95% CI, 23.8–29.4) and 5.7 (95% CI, 1.6–9.7) versus IIV4 and HD-IIV3,

Table 1. Subject Demographics at Baseline

	2017–2018 Season			2018–2019 Season		
Characteristic	aIIV3 (n = 524 223)	IIV4 (n = 917 609)	HD-IIV3 (n = 3 377 860)	aIIV3 (n = 1 031 145)	IIV4 (n = 915 380)	HD-IIV3 (n = 3 809 601)
Mean age, y, ± SD	75.0 ± 6.7	74.3 ± 7.1	75.2 ± 6.8	75.1 ± 6.8	74.2 ± 7.2	75.2 ± 6.9
Female sex, n (%)	310 833 (59)	541 754 (59)	1 984 013 (59)	609 857 (59)	540 494 (59)	2 244 405 (59)
Race and ethnicity, n (%)						
White	289 145 (55)	491 386 (54)	1 903 939 (56)	555 511 (54)	444 375 (49)	2 051 209 (54)
Black or African American	18 212 (3)	43 506 (5)	130 576 (4)	32 649 (3)	46 765 (5)	144 802 (4)
Other	37 040 (7)	90 759 (10)	258 550 (8)	83 411 (8)	91 573 (10)	308 299 (8)
Race not reported	179 826 (34)	291 958 (32)	1 084 795 (32)	359 574 (35)	332 667 (36)	1 305 291 (34)
Hispanic ethnicity	18 886 (4)	47 793 (5)	94 301 (3)	33 485 (3)	56 266 (6)	107 868 (3)
Geographic region, n (%)						
Northeast	77 130 (15)	168 679 (18)	659 746 (20)	158 852 (15)	178 324 (19)	703 716 (18)
Midwest	50043 (10)	170 779 (19)	720 252 (21)	132 619 (13)	157 087 (17)	792 204 (21)
South	318 905 (61)	338 010 (37)	1 264 537 (37)	582 846 (57)	335 573 (37)	1 413 291 (37)
West	54 361 (10)	203 600 (22)	602 689 (18)	108 404 (11)	199 288 (22)	746 260 (20)
Not reported/other	23 784 (5)	36 541 (4)	130 636 (4)	48 424 (5)	45 108 (5)	154 130 (4)
CCI ± SD	0.71 ± 1.33	0.86 ± 1.39	0.78 ± 1.34	0.71 ± 1.32	0.86 ± 1.39	0.79 ± 1.35

Abbreviations: aIIV3, adjuvanted trivalent inactivated influenza vaccine; CCI, Charlson Comorbidity Index; HD-IIV3, nonadjuvanted high-dose trivalent inactivated influenza vaccine; IIV4, nonadjuvanted quadrivalent inactivated influenza vaccine; SD, standard deviation.

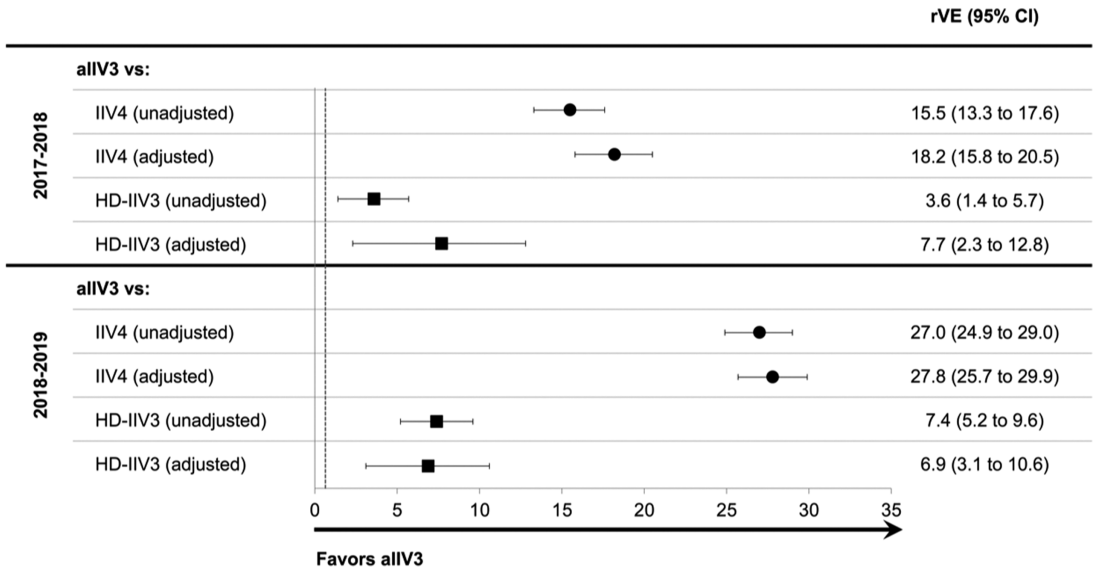

Figure 2. rVE of aIIV3 compared with IIV4 and HD-IIV3 among adults ≥ 65 years in the 2017–2018 and 2018–2019 influenza seasons (unadjusted and adjusted rVE). Adjusted for age, sex, race, ethnicity, health status, week of immunization, and geographic region. Abbreviations: aIIV3, adjuvanted trivalent inactivated influenza vaccine; CI, confidence interval; HD-IIV3, nonadjuvanted high-dose trivalent inactivated influenza vaccine; IIV4, nonadjuvanted quadrivalent inactivated influenza vaccine; rVE, relative effectiveness.

respectively. Age subgroup analyses during the restricted influenza seasons yielded similar estimates in both seasons (Table 2). The results using the broad definition of influenza-related medical encounters (Code Set A) were also similar (Supplementary Table 6).

DISCUSSION

Among ~11 million vaccinated individuals ≥65 years of age, aIIV3 was more effective than both IIV4 and HD-IIV3 in preventing influenza-related medical encounters in the 2017–2018 and 2018–2019 US influenza seasons. rVE estimates were statistically significant in the overall cohort of adults ≥65 years across both seasons. When stratified by age, rVE estimates of aIIV3 compared with IIV4 remained statistically significant but were not statistically significant in the comparison between aIIV3 and HD-IIV3 in age subcohorts in the 2017–2018 season and in the ≥85 years of age subcohort in the 2018–2019 season, likely because of the small number of cases in these cohorts

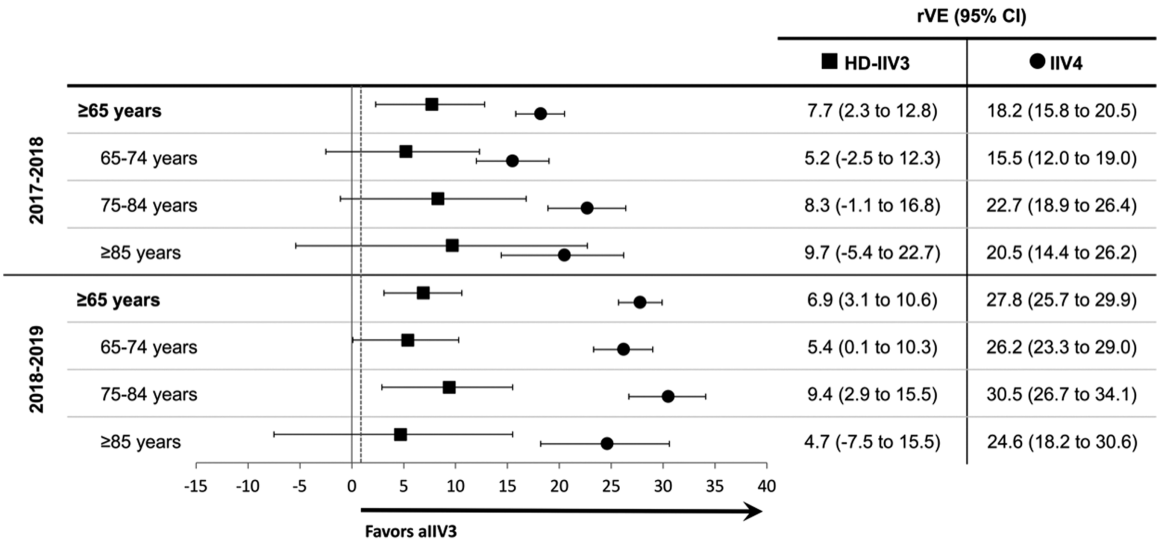

Figure 3. rVE of aIIV3 compared with IIV4 (circles) and HD-IIV3 (squares) among adults ≥ 65 years in the 2017–2018 and 2018–2019 seasons (adjusted) by age cohort. Adjusted for age, sex, race, ethnicity, health status, week of immunization, and geographic region. Abbreviations: aIIV3, adjuvanted trivalent inactivated influenza vaccine; CI, confidence interval; HD-IIV3, nonadjuvanted high-dose trivalent inactivated influenza vaccine; IIV4, nonadjuvanted quadrivalent inactivated influenza vaccine; rVE, relative effectiveness.

Table 2. Adjusted rVE of aIIV3 Versus Comparators During Restricted Influenza Seasons (Based on Peak Influenza Activity), by Age Group[a]

	rVE (95% CI)			
aIIV3 vs:	Overall, Age ≥ 65 y	Age 65–74 y	Age 75–84 y	Age ≥ 85 y
December 11, 2017–March 18, 2018				
IIV4	18.8 (16.3–21.3)	16.5 (12.7–20.1)	23.4 (19.4–27.2)	20.4 (13.9–26.4)
HD-IIV3	8.2 (2.5–13.6)	5.8 (–2.2 to 13.3)	8.8 (–1.2 to 17.7)	10.4 (–5.6 to 24.0)
December 17, 2018–April 7, 2019				
IIV4	26.6 (23.8–29.4)	29.2 (26.1–32.2)	31.6 (27.5–35.6)	25.2 (18.0–31.8)
HD-IIV3	5.7 (1.6–9.7)	7.3 (1.6–12.7)	10.6 (3.4–17.1)	9.5 (–3.6 to 20.9)

Abbreviations: aIIV3, adjuvanted trivalent inactivated influenza vaccine; CI, confidence interval; HD-IIV3, nonadjuvanted high-dose trivalent inactivated influenza vaccine; IIV4, nonadjuvanted quadrivalent inactivated influenza vaccine; rVE, relative vaccine effectiveness.
[a]Adjusted for age, sex, race, ethnicity, week of immunization and health status, and geographic region.

when stratified by age. Overall, this study adds to the body of evidence demonstrating that MF59-adjuvanted influenza vaccines are superior to unenhanced influenza vaccines in older adults [15–22, 37, 38].

The relative effectiveness of aIIV3 versus IIV4 was higher in the 2018–2019 season than in the 2017–2018 season, whereas a slightly higher rVE was observed for aIIV3 versus HD-IIV3 in the 2017–2018. The epidemiology of the 2 influenza seasons covered in this analysis differed [39, 40], which is relevant because aIIV3 has been shown to provide protection against a broad repertoire of viruses [23]. Overall vaccine effectiveness during the 2017–2018 season, a "high severity" season dominated by circulating A(H3N2) influenza viruses with some B/Yamagata circulation, was estimated to be 17% (95% CI, –14 to 39) in subjects ≥65 years of age [40, 41]. The 2018–2019 season was considered "moderate severity" and was dominated by 2 waves of influenza virus circulation: influenza A(H1N1) from October 2018 to mid-February 2019 and influenza A(H3N2) from February through May 2019. The overall vaccine effectiveness during the 2018–2019 season in subjects ≥ 65 years was 12% (95% CI, –31 to 40) [39].

Despite the trivalent formulation of aIIV3, an improved benefit was observed over IIV4 in the 2017–2018 season. It is expected that the improved effectiveness against dominant A(H3N2) viruses outweighed the benefit of protection offered by IIV4 against the B/Yamagata-lineage viruses. The A(H3N2) strain is particularly subject to antigenic drift. Based on the antigenic characterization of the reference strain versus the circulating strain, the extent of drift for A(H3N2) was higher in the 2018–2019 season relative to the 2017–2018 season, whereas no drift was observed for A(H1N1) in either season [36]. These differences in the seasonal strain circulation may explain the greater clinical benefit of aIIV3 compared with IIV4 observed in both seasons, being most prominent in the 2018–2019 season, because MF59 offers both an increased magnitude and wider breadth of immune response [42]. Because both aIIV3 and HD-IIV3 increase the magnitude of the immune response, the slightly higher rVE of aIIV3 versus HD-IIV3 may be related specifically to the broadening of the immune response by aIIV3.

The use of a large, real-world dataset integrating different sources of patient information allowed for the evaluation of an effectiveness outcome typically not analyzed in randomized trials and also permitted the estimation of effects with robust statistical power. Neither claims data nor EMR data alone can provide a complete, accurate, and timely view of an individual's health status; integrated databases linking both EMR and claims data may provide a well-rounded picture of an individual's health status and service utilization. Furthermore, the variety and completeness of data also permitted the adjustment of well-established confounders using robust confounder adjustment methodology (IPTW). Exposure, outcome, and covariate information were ascertained retrospectively from patient records in exactly the same manner for all exposure cohorts, limiting the possibility of differential misclassification of these elements. The use of EMRs linked to claims data to ascertain exposure status reduced the likelihood of exposure misclassification because specific product codes were used to identify vaccination status by vaccine type. The database allowed the adjustment for health status using validated ICD-9/10 algorithms for CCI. To further evaluate the robustness of adjusting for health status using CCI in the main analysis model, a post hoc sensitivity analysis was conducted whereby propensity scores were regenerated using a multivariable logit model with all original covariates as well as 17 binary variables for health status (rather than a single variable for CCI). Following IPTW using the newly derived propensity scores, the adjusted rVE point estimates were similar to those obtained from the main analytical model (Figure 3). This further supports the results and conclusions derived from this analysis.

A limitation of this study was that the effectiveness outcome was not laboratory confirmed. However, consistent results were observed when the observation window was limited to the weeks with highest laboratory-confirmed influenza activity [31]. Moreover, concordance between the incidence curves was observed between the AFHSC ICD codes and the incidence of laboratory-confirmed influenza (Supplementary Figure 4), supporting the use of this diagnostic code set in real-world evaluations of influenza. The main analysis did not specifically adjust for functional status, which may confound the association between vaccination and risk of influenza, or healthcare-seeking behavior, which can contribute to bias if healthcare-seeking behavior or access to care differs between vaccine groups. Additionally, we did not account for previous influenza vaccination, which might influence the relative benefit of aIIV3. Furthermore, the study population included individuals for whom at least some pharmacy and medical

claims data were available, thus limiting the study cohort to insured individuals but not requiring healthcare resource utilization beyond the index vaccination. Furthermore, because all settings of care were included in the analysis, level of care may confound associations. Residual confounding, which may arise because of, among other factors, unmeasured confounders such as healthcare organization contributing data, is a potential source of bias in all observational research; it is particularly prominent in studies using routinely collected data. However, results from a post hoc doubly robust adjustment methodology (Supplementary Figure 1) were consistent with the results from the primary analysis, supporting the conclusions drawn from the main analysis.

CONCLUSION

Older adults (≥65 years) receiving aIIV3 had significantly fewer influenza-related medical encounters compared with individuals receiving IIV4 or HD-IIV3 in the 2017–2018 and 2018–2019 influenza seasons in the United States. These findings were robust to a range of assumptions as demonstrated by additional and sensitivity analyses. Using EMRs linked to claims data permitted a larger, more inclusive population and healthcare settings that reflected real-world conditions. Findings from this study are consistent with previously published research evaluating the relative benefit of aIIV3 compared with standard vaccines [15–22, 37, 38].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. C. B., J. A. M., and G. C. S. contributed to study conceptualization and design. C. B., J. A. M., G. C. S., L. F., D. O., and J. V. contributed to data collection, analysis, and interpretation.

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Potential conflicts of interest. C. B. and J. A. M. are employees of Seqirus Inc. G. C. S. is an employee of Seqirus USA Inc. L. F., D. O., and J. V. work for Veradigm, a company that was contracted by Seqirus and that received fees for data management and statistical analyses. D. O. and J. V. report consulting fees from Seqirus. L. F. reports consulting fees from Seqirus, outside the submitted work. All other authors report no potential 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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