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 – ORadjusted) × 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.
MF59-adjuvanted trivalent inactivated influenza vaccine (aIIV3; Fludac, 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
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.

**Table 1. Subject Demographics at Baseline**

| Characteristic               | 2017–2018 Season |            | 2018–2019 Season |            |
|------------------------------|------------------|------------|------------------|------------|
|                              | allIV3 (n = 524,223) | IIV4 (n = 917,609) | HD-IIV3 (n = 3,377,660) | IIV3 (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                      | 50,043 (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                         | 54,381 (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)     | 40,244 (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: allIV3, 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.
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 2](https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab152/6144977)

**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: allV3, 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.

![Figure 3](https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab152/6144977)

**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: allV3, 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.
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 generated 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

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

| Season, Age, & Vaccine Type | 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.

*Adjusted for age, sex, race, ethnicity, week of immunization and health status, and geographic region.
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 copiededit 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.

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References

1. Castrucci MR. Factors affecting immune responses to the influenza vaccine. Hum Vaccin Immunother 2018; 14:637–46.
2. Goronyz JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. Nat Immunol 2013; 14:428–36.
3. Centers for Disease Control and Prevention. Estimates of deaths associated with seasonal influenza—United States, 1976–2007. MMWR Morb Mortal Wkly Rep 2010; 59:1057–62.
4. Rolles MA, Flannery B, Chung J, et al. Effects of influenza vaccination in the United States during the 2017–2018 influenza season. Clin Infect Dis 2019; 69:1845–53.
5. Sellers SA, Hagan RS, Hayden FG, Fischer WA 2nd. The hidden burden of influenza: a review of the extra-pulmonary complications of influenza infection. Influenza Other Respir Viruses 2017; 11:372–93.
6. Nguyen JL, Yang W, Ito K, Matte TD, Shamian J, Kinney PL. Seasonal influenza infections and cardiovascular disease mortality. JAMA Cardiol 2016; 1:274–81.
7. Groshkopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2018–19 influenza season. MMWR Recomm Rep 2018; 67:1–20.
8. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012; 12:36–44.
9. Beyer WE, McElhaney J, Smith DJ, Monte AS, Nguyen-Van-Tam JS, Osterhaus AD. Cochrane re-arranged: support for policies to vaccinate elderly people against influenza. Vaccine 2013; 31:6030–3.
10. Weinberger B. Vaccines for the elderly: current use and future challenges. Immun Ageing 2018; 15:3.
11. Crooke SN, Osvyannikova IG, Poland GA, Kennedy RB. Immunosenescence: a systems-level overview of immune cell biology and strategies for improving vaccine responses. Exp Gerontol 2019; 124:101832.
12. Wilkinson K, Wei Y, Sewajcer A, et al. Efficacy and safety of high-dose influenza vaccine in elderly adults: a systematic review and meta-analysis. Vaccine 2017; 35:2775–80.
13. Lee JKH, Lam GKL, Shin T, et al. Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis. Expert Rev Vaccines 2018; 17:435–43.
14. 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.
15. Van Buynder PG, Konrad S, Van Buynder JL, et al. The comparative effectiveness of adjuvanted and nonadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. Vaccine 2013; 31:6122–8.
16. Domnich A, Arata L, Amicizia D, Puig-Barberà J, Gasparini R, Panatto D. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: a systematic review and meta-analysis. Vaccine 2017; 35:513–20.
17. Mannino S, Villa M, Apolone G, et al. Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. Am J Epidemiol 2012; 176:527–33.
18. Inziroli HS, Chillasses Y, Kelman J, et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among elderly persons in the United States, 2017–2018. J Infect Dis 2019; 220:1255–64.
19. Lapt F, Marconi E, Simonetti M, et al. Adjuvanted versus nonadjuvanted influenza vaccines and risk of hospitalizations for pneumonia and cerebrocardiovascular events in the elderly. Expert Rev Vaccines 2019; 18:663–70.
20. Poblete R, Whitaker H, Zhao H, et al. Protection provided by influenza vaccine against influenza-related hospitalisation in >65 year olds: Early experience of introduction of a newly licensed adjuvanted vaccine in England in 2018/19. Vaccine 2020; 38:1733–9.
21. Bella A, Guesalado F, Orsi A, et al. Effectiveness of the trivalent MF59 adjuvanted influenza vaccine in preventing hospitalization due to influenza B and A(H1N1)pdm09 viruses in the elderly in Italy, 2017–2018 season. Expert Rev Vaccines 2019; 18:671–9.
22. Inziroli HS, Chillasses Y, Kelman J, Wei Y, Lu Y, Xu W, Lu M, Pratt D, Werncke M, MacCurdy T, Forseher R. Relative Effectiveness of influenza vaccines among the United States elderly, 2018-2019. J Infect Dis 2020; 222:278–87. doi:10.1093/infdis/jiaa080
23. Ansaldi F, Zancolli M, Durando P, et al. Antibody response against heterogeneous circulating influenza virus strains elicited by MF59- and non-adjuvanted vaccines during seasons with good or partial matching between vaccine strain and clinical isolates. Vaccine 2010; 28:4123–9.
24. Ansaldi F, Bacirolli S, Durando P, et al. Cross-protection by MF59-adjuvanted influenza vaccine: neutralizing and haemagglutination-inhibiting antibody activity against A(H1N2) drifted influenza viruses. Vaccine 2008; 26:1525–9.
25. Frey SE, Reyes MR, Reyes HA, et al. Comparison of the safety and immunogenicity of an MF59–adjuvanted with a non–adjuvanted seasonal influenza vaccine in elderly subjects. Vaccine 2014; 32:5027–34.
26. Scheifele DW, McNeil SA, Ward BJ, et al; PHAC /CIHR Influenza Research Network. Safety, immunogenicity, and tolerability of three influenza vaccines in older adults: results of a randomized, controlled comparison. Hum Vaccin Immunother 2013; 9:2460–73.
27. Doyle JD, Chung JR, Kim SS, et al. Interim estimates of 2018-19 seasonal influenza vaccine effectiveness - United States, February 2019. MMWR Morb Mortal Wkly Rep 2019; 68:135–9.

28. Kissling E, Rose A, Emborg HD, et al. Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019. Euro Surveill 2019; 24:1900121. doi:10.2807/1560-7917.ES.2019.24.1900121.

29. Skowronski DM, Leir S, Sabaïduc S, et al. Interim estimates of 2018/19 vaccine effectiveness against influenza A(H1N1)pdm09, Canada, January 2019. Euro Surveill 2019; 24:1900055. doi:10.2807/1560-7917.ES.2019.24.4.1900055.

30. van Aalst R, Gravenstein S, Mor V, et al. Comparative effectiveness of high dose versus adjuvanted influenza vaccine: a retrospective cohort study. Vaccine 2020; 38:372–9.

31. Armed Forces Health Surveillance Center (AFHSC). AFHSC standard case definitions: influenza-like illness. Falls Church, VA: Defense Health Agency, 2015.

32. Eick-Cost AA, Hunt DJ. Assessment of ICD-9-based case definitions for influenza-like illness surveillance. MSMR 2015; 22:2–7.

33. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43:1130–9.

34. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004; 57:1288–94.

35. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015; 34:3661–79.

36. Centers for Disease Control and Prevention. FluView interactive. Available at: https://gis.cdc.gov/grasp/fluview/fluportaldashboard.html. Accessed 14 October 2020.

37. McConkey KW, Davidson HE, Canaday DH, Han L, Saade E, Mor V, Gravenstein S. Cluster-randomized trial of adjuvanted vs. non-adjuvanted trivalent influenza vaccine in 823 U.S. nursing homes. Clin Infect Dis 2020; ciaa1233. doi:10.1093/cid/ciaa1233.

38. Yang J, Zhang J, Han T, et al. Effectiveness, immunogenicity, and safety of influenza vaccines with MF59 adjuvant in healthy people of different age groups: a systematic review and meta-analysis. Medicine (Baltimore) 2020; 99:e19095.

39. Centers for Disease Control and Prevention. Update: influenza activity in the United States during the 2018–19 season and composition of the 2019–20 influenza vaccine. Available at: https://www.cdc.gov/mmwr/volumes/68/wr/mm6824a3.htm. Accessed October 14, 2020.

40. Centers for Disease Control and Prevention. Update: influenza activity in the United States during the 2017–18 season and composition of the 2018–19 influenza vaccine. Available at: https://www.cdc.gov/mmwr/volumes/67/wr/mm6722a4.htm. Accessed October 14, 2020.

41. Centers for Disease Control and Prevention. Seasonal influenza vaccine effectiveness, 2017–2018. Available at: https://www.cdc.gov/flu/vaccines-work/2017–2018.html. Accessed October 14, 2020.

42. O’Hagan DT, Ott GS, De Gregorio E, Seubert A. The mechanism of action of MF59 – an innately attractive adjuvant formulation. Vaccine 2012; 30:4341–8.