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Published in:
Vaccine

DOI:
10.1016/j.vaccine.2021.03.054

Vaccine 39 (2021) 2396–2407

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A retrospective cohort study assessing relative effectiveness of adjuvanted versus high-dose trivalent influenza vaccines among older adults in the United States during the 2018–19 influenza season

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ARTICLE INFO

Article history:
Received 11 September 2020
Received in revised form 10 March 2021
Accepted 16 March 2021
Available online 30 March 2021

Keywords:
Influenza vaccine
Adjuvanted
High dose
Relative vaccine effectiveness
Elderly
Retrospective studies

ABSTRACT

Purpose: To evaluate the relative vaccine effectiveness (rVE) against influenza-related hospitalizations/emergency room (ER) visits, influenza-related office visits, and cardio-respiratory disease (CRD)-related hospitalizations/ER visits and compare all-cause and influenza-related costs associated with two vaccines specifically indicated for older adults (≥65 years), adjuvanted (aTIV) and high-dose trivalent influenza vaccine (TIV-HD), for the 2018–19 influenza season.

Methods: A retrospective analysis of older adults was conducted using claims and hospital data in the United States. For clinical evaluations, adjusted analyses were conducted following inverse probability of treatment weighting (IPTW) to control for selection bias. Poisson regression was used to estimate the adjusted rVE against influenza-related hospitalizations/ER visits, influenza-related office visits, and any CRD-related hospitalizations/ER visits. For the economic evaluation, treatment selection bias was adjusted through 1:1 propensity score matching (PSM). All-cause and influenza-related costs associated with hospitalizations/ER, physician office and pharmacy visits were adjusted using generalized estimating equation (GEE) models.

Results: After IPTW and Poisson regression, aTIV (n = 561,315) was slightly more effective in reducing influenza-related office visits compared to TIV-HD (n = 1,672,779) (6.6%; 95% CI: 2.8–10.3%). aTIV was statistically comparable to TIV-HD (2.0%; 95% CI: −3.7%-7.3%) in preventing influenza-related hospitalizations/ER visits but more effective in reducing hospitalizations/ER visits for any CRD (2.6%; 95% CI: 2.0–3.2%). In the PSM-adjusted cohorts (n = 561,243 pairs), following GEE adjustments, predicted mean annualized all-cause and influenza-related total costs per patient were statistically similar between aTIV and TIV-HD (US$9676 vs. US$9625 and US$18.74 vs. US$17.28, respectively; both $p > 0.05$). Finally, influenza-related pharmacy costs were slightly lower for aTIV as compared to TIV-HD ($1.75 vs $1.85; $p < 0.0001$).

Conclusions: During the 2018–19 influenza season, influenza-related hospitalization/ER visits and associated costs among people aged ≥ 65 were comparable between aTIV and TIV-HD. aTIV was slightly more effective in preventing influenza-related office visits and any CRD event as compared to TIV-HD in this population.

1. Background

Seasonal influenza is a major public health crisis affecting millions of people every year, particularly older adults aged 65 years and above. During the 2018–19 influenza season in the United States (U.S.), older adults accounted for 57% of total estimated

Abbreviations: rVE, Relative Vaccine Effectiveness; aTIV, Adjuvanted Trivalent Influenza Vaccine; TIV-HD, Trivalent Influenza Vaccine – High Dose; IPTW, Inverse Probability of Treatment Weighting; PSM, Propensity Score Matching.

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https://doi.org/10.1016/j.vaccine.2021.03.054
0264-410X/

influenza-related hospitalizations (279,384 out of 490,561) and 75% of total estimated influenza-related deaths (25,555 out of 34,157) [1]. Relatively high morbidity and mortality among older adults lead to a substantial economic burden. In 2015, the total annual costs of influenza (reported in 2015 US$) were estimated at $11.2 billion, which included $3.2 billion in direct medical costs and $8.0 billion in indirect medical costs. Older adults (≥65 years of age) contributed the most (42.7%) to the influenza-related direct medical costs, which were primarily due to higher hospitalization costs ($1.3 billion) [2]. In addition to the pulmonary complications (e.g., pneumonia) that are directly related to the influenza virus, an elevated risk of indirect complications of influenza infection intensifies the overall burden among older adults. These complications include cardiovascular events, cerebrovascular events, and potentially cognitive decline over the long term [3]. Immunosenescence and inadequate effectiveness of the standard dose (SD) influenza vaccines result in relatively high remaining rates of complications among older adults [3].

For the 2018–2019 season, two egg-based influenza vaccines were exclusively licensed and predominantly used among older adults in the U.S., an adjuvanted trivalent influenza vaccine (aTIV; Fluad®, Seqirus) and high-dose trivalent influenza vaccine (TIV-HD; Fluzone High-Dose®, Sanofi Pasteur) [4]. aTIV combines MF59 adjuvant (an oil-in-water emulsion of squalene oil) and a standard dose of antigen to produce stronger, broader, and more durable immune responses against the selected influenza virus strains. TIV-HD contains four times higher concentrations of antigen than the SD influenza vaccines that offer protective immune responses against the selected influenza virus strains.

Several studies in the U.S. and other countries have shown higher effectiveness of these two enhanced vaccines against influenza and related complications compared to SD vaccines [5–12]. However, there are no randomized control trials directly comparing the effectiveness of aTIV and TIV-HD vaccines. Real-world data have been utilized in prior influenza seasons to evaluate the relative vaccine effectiveness (rVE) of aTIV and TIV-HD [13–15]. However, as the antigenic composition of influenza viruses constantly drift, it is important to assess the rVE every season. For example, during the 2018–19 season, influenza A(H1N1pdm09) viruses dominated from October 2018 – mid-February 2019. Starting in late February 2019, the influenza A(H3N2) clade 3C.3a viruses were predominant [16]. This antigenic drift resulted in a mismatch between the circulating virus strains and vaccine virus lowering the overall absolute vaccine effectiveness for all ages combined from 47% (95% CI: 34%-57%) in mid-February [17] to 29% (95% CI: 21%-35%) for the overall season [18]. The overall estimated vaccine effectiveness among older adults was estimated at 12% (95% CI: −31%-40%) during the 2018–19 influenza season [18].

Thus far, only one retrospective study has evaluated rVE of influenza vaccines including aTIV, TIV-HD, and SD influenza vaccines during the 2018–19 season among fee-for-service Medicare (Medicare FFS) beneficiaries [19]. In this study, there were no statistically significant differences in influenza-related hospital encounters between aTIV and TIV-HD cohorts. Given that influenza can exhibit an array of complications beyond pulmonary among the older population, it is important to evaluate the overall clinical and economic burden of influenza. Also, it is important to include all payer data (Medicare FFS, Medicare advantage, and commercial) to understand the real-world vaccine utilization and outcomes among a broader sample. The current study assessed the rVE of aTIV compared to TIV-HD during the 2018–19 influenza season against clinical outcomes related to influenza and cardio-respiratory disease (CRD) among older adults using all payer claims data. The study also assessed all-cause and influenza-related costs associated with hospitalizations/ER visits, physician office visits, and pharmacy visits.

2. Methods

2.1. Study design

This was a retrospective cohort study including individuals ≥ 65 years of age who were vaccinated with aTIV or TIV-HD during the 2018–19 influenza season in the US. Ethics approval was not required because this was a retrospective analysis of secondary data with de-identified subjects.

2.2. Data sources

A linked subject population was utilized, using de-identified data from several IQVIA (IQVIA, Danbury CT & Durham NC, USA) databases: Professional Fee Claims (Dx), Prescription Claims (Rx) and Hospital Charge Data Master (CDM). These databases have been previously described [15,20,21]. Dx includes professional fee claims representing 60–70% of physician activity in the US. Rx includes more than 1.6 billion retail or mail-order prescription claims, representing dispensed prescriptions for approximately 85% of all pharmacies in the US. CDM includes records from over 450 hospitals, covering 7 million annual inpatient stays and 60 million annual outpatient visits. The datasets were linked using a deterministic matching algorithm, using actual patient information (e.g., patient age, gender, etc.) to assign a unique patient ID. This ensured continuity of patient follow-up across datasets.

All data from IQVIA's Dx, Rx and CDM databases are compliant with the Health Insurance Portability and Accountability Act (HIPAA) to protect patients' privacy. These data sources are representative of the 65y+ population and include all payers (including traditional Medicare FFS).

2.3. Study periods

The 2018–19 influenza season was defined as beginning August 1, 2018 and ending July 31, 2019. A full calendar year was utilized, and the start was validated based on the observed distribution of vaccination by month. The study period began February 1, 2018, allowing for a 6-month pre-index period prior to the start of influenza period, and ended July 31, 2019. The fixed 6-month pre-index period was used to assess study eligibility criteria and measure baseline characteristics of study subjects. The study selection window to identify individuals who received aTIV or TIV-HD was from August 1, 2018 and January 31, 2019. Study outcomes were assessed over the variable post-index or follow-up period which began 14 days after the index date (in order to allow for the development of vaccine-specific immunity) through the end of the influenza season (July 31, 2019).

We also assessed the select study outcomes restricting the observation period to the high influenza activity period (HIAP). The study follow-up period reflecting the HIAP was December 23, 2018 – March 30, 2019 (Week 52 to 13). An R Language implementation of the Moving Epidemic Method (MEM) algorithm was applied using the R package 'mem' to establish epidemic thresholds for the start and end of the influenza season [22]. Epidemic thresholds were calculated using surveillance data from the Centers of Disease Control (CDC) on the % of general physician (GP) visits due to lab-confirmed influenza from 2003/04 through 2015/16 influenza seasons [23]. The % of GP visits due to lab-confirmed influenza was above the epidemic thresholds from week 52 through week 13 during the 2018–19 season.

2.4. Study population

All individuals with at least 1 claim for aTIV or TIV-HD in Rx or Dx during the study selection window were identified and assigned to two mutually exclusive cohorts. The date of the first claim determined the index therapy/vaccine cohort and was termed as the 'index date'. Individuals aged ≥65 years at index date were included. IQVIA uses a deterministic matching algorithm to link patients across databases using unique patient identifiers. A unique IQVIA patient ID is assigned to a patient which can be used to identify the patient across IQVIA data assets. The patient linkage in Rx, Dx, and CDM was required for patients to be included in the study cohort. Subject activity, defined as ≥1 office visit (in Dx) and ≥1 prescription (in Rx), was required in the 6 months prior to the 6-month pre-index period, as well as in the last 6 months of the influenza season. Pharmacy reporting stability was required in the 6-month pre-index period through the end of the influenza season, defined as consistent, monthly reporting of data from the pharmacy most frequently visited by the subject during the study period in each month.

Subjects were excluded if they had an influenza-related hospitalization or ER visit or an influenza-related office visit (subsequently defined in the Study Measures section) between the beginning of the flu season up to 13 days after the index date. Subjects were excluded if they received any other influenza vaccine during the 2018–19 season other than the index therapy received on the index date or if they had incomplete data or data quality issues (invalid year of birth or missing gender).

2.5. Study measures

Baseline demographic characteristics assessed at the index date included age, gender, payer type, and geographic region, Clinical characteristics were measured over the 6-month pre-index period (not including the index date, unless otherwise specified) and included a month of influenza vaccination, Charlson Comorbidity Index (CCI; Dartmouth-Manitoba adaptation based on ICD-9-CM and ICD-10-CM diagnosis codes) [24], comorbidities of interest, indicators of frail health status, and pre-index all-cause costs (outpatient pharmacy, medical including inpatient, outpatient/ER, and total). Because Dx and CDM only include charges, a cost:charge ratio (CCR) was applied to charges, using the Centers for Medicare & Medicaid Services (CMS) hospital outpatient prospective payment system (OPPS) CCR files and the Healthcare Cost and Utilization Project (HCUP) Inpatient CCR files, respectively [25,26].

2.6. Study outcomes

2.6.1. Clinical outcomes

Clinical outcomes of interest were assessed starting 14 days after the index date. The number and rates (events per 1000 vaccinated subject-seasons) of the following clinical outcomes were assessed over the variable follow-up period ([index date + 14] to the end of the influenza season): influenza-related hospitalizations/ER visits, influenza-related office visits, hospitalizations/ER visits for CRD-related events (any cardiorespiratory event, coronary artery events including myocardial infarction, congestive heart failure, cerebrovascular events including stroke, pneumonia, and asthma/COPD/bronchial events) and all-cause hospitalization. For each outcome of interest, the first occurring event was identified. A subject could contribute an event for more than one outcome but could not contribute more than one event to the same outcome.

Influenza-related hospitalizations/ER visits were defined as a hospitalization or ER visit with a diagnosis code for influenza [ICD-9 487.x, 488.x, ICD-10 J09.x, J10.x, J11.x] in any position [19].

Influenza-related office visits were defined as a physician office visit in Dx or CDM (outpatient) with a diagnosis code for influenza in any position. CRD-related outcomes were defined as a hospitalization or ER visit with a diagnosis code in any position for the cardio-respiratory event of interest.

In addition to the above clinical outcomes, the current study also included hospitalizations related to a urinary tract information (UTI) [ICD-9 590.10, 590.11, 590.2, 590.3, 590.80, 590.81, 595.0, 597.0, 599.0, 996.64, ICD-10N10, N11.9, N12. N13.6, N15.1, N16, N28.84, N28.85, N28.86, N30.00, N 30.01, N34.0, N39.0, T83.510A, T83.511A, T83.512A, T83.518A] as a test-negative outcome, following the approach of a recently published study [14]. As we do not expect either influenza vaccine to prevent UTI, reporting a test-negative outcome can be used to demonstrate a similar treatment effect across the two vaccines. UTI-related hospitalization was defined as a hospitalization in Dx or CDM with a diagnosis code (ICD-9-CM and ICD-10) in any position.

2.6.2. Economic outcomes

All-cause and influenza-related healthcare resource utilization (HCRU) and annualized costs were evaluated over the variable follow-up period, starting 14 days after the index date through the end of the flu season. Influenza-related HCRU and associated costs were assessed specific to the previously defined influenza-related hospitalizations/ER visits and influenza-related office visits. All-cause and influenza-related pharmacy costs (influenza-related antiviral medications) were also assessed.

2.7. Statistical analyses

Descriptive statistics were reported for each study cohort. Standardized mean differences (SMD) were calculated to evaluate the difference in baseline covariates between the vaccine cohorts. SMD was calculated as the difference in means or proportions of a variable divided by the pooled standard deviation. SMD (absolute) of ≥ 0.10 between groups was considered statistically meaningful [27].

2.7.1. Clinical outcomes evaluation

For comparing clinical outcomes in adjusted analyses, Inverse Probability of Treatment Weighting (IPTW) was used to adjust for confounders and treatment selection bias. A pseudo population was created, composed of individuals in the pre-IPTW population weighted by the inverse of the probability of receiving the treatment actually received, given the baseline covariates. Weights were constructed by estimating each subject's probability of receiving aTIV based on observed covariates in a logistic regression model. The only baseline variable that had SMD ≥ 0.10 in the unadjusted sample was geographic region. Hence geographic region and other clinically relevant baseline variables were included in the model as independent variables. The propensity score for each individual (the predicted probability of receiving aTIV) was estimated. Unstabilized weights were calculated as the inverse of the propensity score for a subject. Stabilized IPTW approach was utilized in order to reduce type 1 error [28,29]. To calculate stabilized weights, the numerator of the unstabilized weights was replaced by the marginal probability of aTIV and TIV-HD in the overall sample. Additionally, weight values greater than five were truncated to five due to the potential bias of outliers. Baseline characteristics and SMD post-IPTW were reported as a measure of balance. The clinical outcomes of interest were evaluated for the IPTW sample.

Poisson regression models were used to permit a more robust regression adjustment as well as to further reduce bias due to residual confounding. Poisson regression models included IPTW weight only. IPTW-weighted univariate Poisson regression models were developed to estimate adjusted rate ratios (RR) along with

corresponding 95% confidence intervals (CIs) for aTIV compared to TIV-HD. Adjusted rVE was calculated as ([1-RR]* 100%) along with corresponding 95% CIs.

2.7.2. Economic outcome evaluation

For comparing economic outcomes in adjusted analyses, propensity score matching (PSM) was used to adjust for measured confounders. PSM is a commonly used regression modeling technique for the analyses of observational data to adjust for differences between study cohorts, particularly for economic evaluations where direct comparisons of costs between the matched subjects are desirable [30]. PSM methods involve pairwise matching of subjects in the study cohorts receiving different treatments based on the estimated value of their propensity score. The propensity score for each individual was estimated using a logistic regression model as the probability of receiving aTIV. A greedy nearest neighbor matching technique without replacement at a ratio of 1:1 was performed, using caliper widths of 0.1 of the standard deviation of the logit of the propensity score. Similar to the clinical evaluation, geographic region (SMD $\geq$ 0.10) along with other clinically relevant clinical variables were included in the match.

Note that unlike the clinical outcomes evaluation, all occurring events of the same type contributed to the total cost for a subject (e.g., first and subsequent influenza-related hospitalizations). Utilization and costs were calculated on a per patient basis, averaged across the cohort. Pairwise comparisons were made between HCRU/cost outcomes using paired *t*-test (mean) and McNemar's test for categorical variables. Generalized estimating equation models (GEEs) were developed among the post-PSM sample to estimate predicted costs using a recycled predictions approach [31]. The GEEs adjusting for PSM scores allowed for a more robust regression adjustment as well as to further reduce bias due to residual confounding. Predicted annualized mean costs were generated for the following outcomes of interest: 1) all-cause total healthcare costs, 2) influenza-related total costs, 3) influenza-related hospitalization costs, 4) influenza-related ER costs, 5) influenza-related office visit costs, and 6) influenza-related pharmacy costs. For the first outcome, a GEE with log link function and gamma distribution was developed, and outliers were adjusted for by capping post-index annualized cost at the 99th percentile [32]. Due to the rarity of an influenza-related event, two-part GEE models were developed for the remaining outcomes. The first GEE had a binomial distribution and logit link to estimate odds of having a non-zero cost for the outcome of interest (i.e., of having the outcome). The second GEE had a gamma distribution and log link to estimate the cost of the outcome of interest, among patients with the outcome of interest. Adjustment for outliers was made by capping cost at the 99th percentile among patients with at least 1 such outcome. Predicted recycled means were obtained from the parameter estimates of GEEs and 95% confidence intervals (CIs) were obtained through bootstrapping (500 replications).

2.7.3. Sensitivity analyses

Sensitivity analyses were conducted by evaluating select outcomes across 3 age groups (65–74 years, 75–84 years, and $\geq$85 years). IPTW was conducted and the weights were calculated for each age group. Influenza-related hospitalization/ER visits and office visits were included in the sensitivity analysis as they are directly impacted by the effectiveness of the vaccines. Additionally, sensitivity analysis also included any CRD-related hospitalization/ER visits since it is a composite endpoint that includes all cardio and respiratory outcomes.

All analyses were based on observed, not projected, data. Analyses were conducted using SAS® Release 9.4 (SAS Institute Inc., Cary, NC).

3. Results

A total of 14,574,702 vaccine recipients were identified as having at least one claim for either aTIV or TIV-HD (n = 3,627,403 aTIV; 10,947,299 TIV-HD) during 2018–19 influenza season. After applying the study inclusion and exclusion criteria, the final unadjusted sample included 561,243 aTIV and 1,672,797 TIV-HD recipients (Fig. 1).

3.1. Clinical outcomes

Before IPTW, study cohorts were comparable in terms of age, gender, month of influenza vaccine, CCI score, pre-index comorbidities, indicators of frail health status, pre-index hospitalizations and costs (absolute SMD < 0.10). Study cohorts were primarily different on geographic region with (absolute) SMD $\geq$ 0.10. For example, more aTIV vaccine recipients (49.8%) than TIV-HD vaccine recipients (44.2%) were located in the South. Unadjusted baseline demographic and clinical characteristics can be found in Supplementary Table 1. Unadjusted rVEs are presented in Supplementary Table 2.

After IPTW adjustments, study cohorts were balanced with SMD < 0.10 for all study covariates (Fig. 2). Post-IPTW baseline demographic and clinical characteristics are reported in Table 1 (aTIV = 561,315; TIV-HD = 1,672,779). Post-IPTW event rates, rVE estimates for the entire influenza season, and rVE estimates during the HIAP are presented in Figs. 3–5, respectively. After IPTW adjustment and Poisson regression, aTIV was more effective in reducing influenza-related office visits compared to TIV-HD (rVE = 6.6%; 95% CI: 2.7% −10.3%). aTIV was also more effective than TIV-HD in reducing hospitalizations/ER visits for any CRD (rVE = 2.6%; 95% CI: 1.9%-3.2%). The rVEs for individual CRD-related events can be found in Fig. 4.

aTIV was statistically comparable to TIV-HD in preventing influenza-related hospitalizations/ER visits (rVE = 2.0%; 95% CI: −3.6%-7.3%) and all-cause hospitalizations (rVE = 0.6%; 95% CI: −0.1%-1.4%). Finally, no treatment effect was identified between study cohorts for UTI hospitalization (control condition) (rVE = 10.%; 95% CI: −1.6%-3.4%).

Results from the analysis restricting the study period to HIAP were consistent with the overall analyses. For example, after IPTW adjustment and Poisson regression, aTIV was more effective in reducing influenza-related office visits compared to TIV-HD (rVE = 7.0%; 95% CI: 2.6%-11.2%) during HIAP. Similar to the overall analysis, aTIV was also more effective in reducing any CRD-related hospitalization/ER visit compared to TIV-HD (rVE = 2.7%; 95% CI:1.7%-3.7%). (Fig. 5).

3.2. Economic outcomes

For the economic analyses, 561,243 aTIV recipients were matched to 561,243 TIV-HD recipients. Subjects were well-balanced on all baseline characteristics following PSM (Fig. 2). Influenza-related hospitalization rates were similar across the study cohorts (aTIV 0.15% vs. TIV-HD 0.14%; p > 0.05). aTIV recipients had a significantly lower proportion with $\geq$ 1 influenza-related office visit over the variable follow-up compared to TIV-HD (0.55% vs 0.60%; p = 0.0003). Post-PSM all-cause and influenza-related resource utilization and costs are reported in Supplementary Tables 3 and 4, respectively.

Table 2 shows predicted annualized all-cause and influenza-related costs during the post-index period following GEE adjustments. Predicted mean annualized all-cause and influenza-related total costs per patient were statistically comparable between aTIV and TIV-HD (US$9,676 vs. US$9,625 and US$18.74

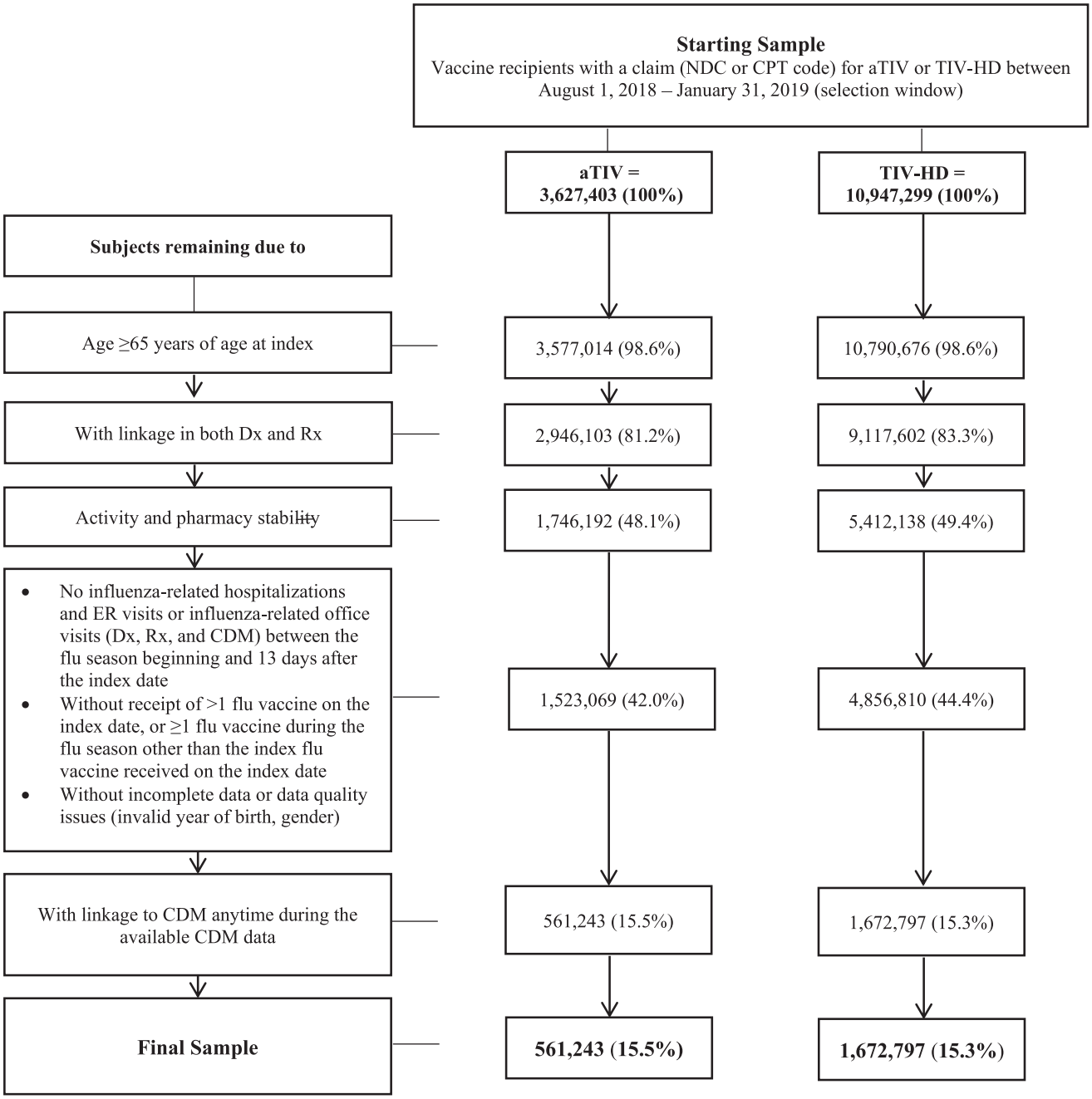

Fig. 1. Study attrition. Abbreviations. aTIV, adjuvanted trivalent influenza vaccine; TIV-HD, high dose trivalent influenza vaccine; CDM, Hospital Charge Data Master; Dx, Professional fee claims; Rx, Prescription claims.

vs. US$17.28, respectively; all p > 0.05). Both aTIV and TIV-HD were comparable in terms of predicted mean annualized costs for influenza-related office visits (US$1.29 vs. US$1.34; p = 0.334), influenza-related hospitalizations (US$20.28 vs. US$18.13; p = 0.128), influenza-related ER visits (US$2.18 vs. US$2.32; p = 0.220). Influenza-related pharmacy costs were lower for aTIV as compared to the TIV-HD cohort (US$1.75 vs. US$1.86; p < 0.0001).

3.3. Sensitivity analyses

When analyzed across age groups, the rVE for aTIV compared to TIV-HD against influenza-related office visits was not significantly different for age group 65–74 years but was significantly higher for age groups 75–84 years and ≥ 85 years and was higher for the latter (rVE = 11.4%; 95% CI: 0.6%-21.1%). Furthermore, the rVE for aTIV compared to TIV-HD against any CRD-related hospitalization/ER visit was not significantly different for age group ≥ 85 years but was significantly higher for age groups 65–74 years (rVE = 3.3%; 95% CI: 2.3%-4.3%) and 75–84 years (rVE = 2.9%; 95% CI: 1.8%-3.9%). aTIV was statistically comparable to TIV-HD for preventing influenza-related hospitalizations/ER visits across the different analyzed age groups. Finally, similar to the main analysis, no treatment effect was identified between study cohorts for UTI hospitalization across age groups. (Fig. 6)

4. Discussion

Influenza vaccination is the dominant strategy in the U.S. for the protection of high-risk individuals against severe influenza disease.

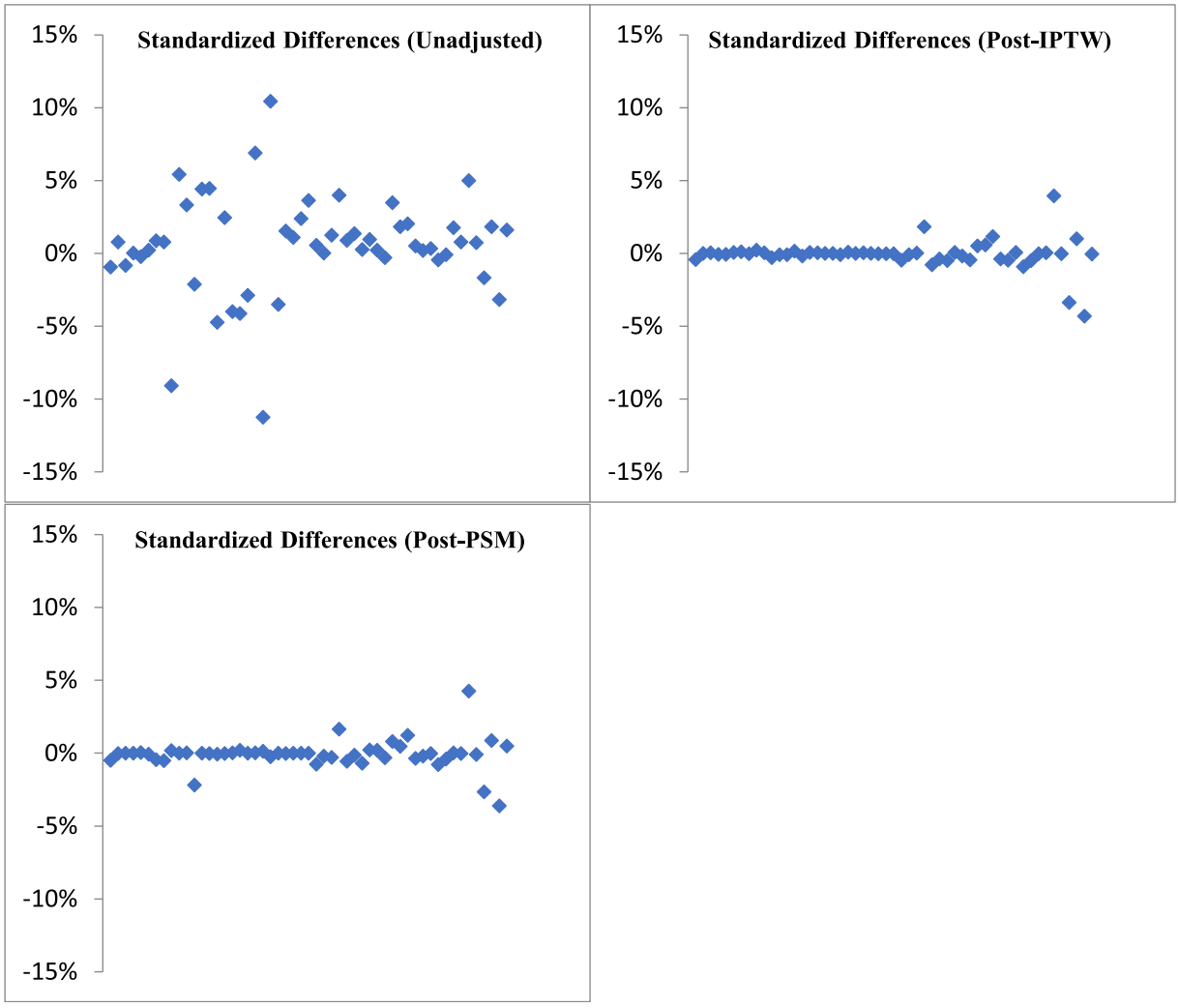

Fig. 2. Standardized mean differences – Overall vs. Post-IPTW vs. Post-PSM. For continuous variable, SMD is calculated as d=(X¯1-X¯2)/√s12 + s22/2 For categorical variable, SMD is calculated as d=(p1-p2)/ √p1(1-p1) + p2(1-p2)/2 where X¯and p denote the sample means and proportions in the groups, and s denotes sample variances.

Conducting repeated randomized controlled studies comparing the effectiveness of vaccine formulations would be valuable, but unlikely given their resource intensive nature. Therefore, real-world studies provide an opportunity to evaluate the relative effectiveness of vaccine formulations every season using data available from multiple sources and require limited resources.

To that end, the current study presents a robust analysis using real-world data of > 2 million Americans 65 years and older receiving either aTIV or TIV-HD during influenza season 2018–19. The cohort included older adults out of which almost 77% were insured with Medicare advantage and FFS representative of the U.S. older population. This study found that rates of influenza-related hospitalization/ER visits and associated costs among older adults were comparable between aTIV and TIV-HD. The effectiveness of aTIV was almost 7% more than TIV-HD in preventing influenza-related office visits. Furthermore, aTIV was more effective than TIV-HD in reducing hospitalizations/ER visits for any CRD-related event. An accepted IPTW method and regression techniques were used for balancing the study covariates and creating comparable groups for outcomes analyses. IPTW is one of the strongest propensity score methods available to adjust for residual confounding between study cohorts [33]. Finally, access and ability to link subjects across various data sources including hospital and pharmacy data allowed exploring multiple endpoints, both influenza-specific and all-cause, such as inpatient hospitalization, ER visits, physician office visits, and pharmacy utilization. This also allowed including a spectrum of cases from perhaps most severe (inpatient hospitalization) to less severe (outpatient or no hospitalizations).

To our knowledge, there is only one other retrospective study that evaluated the rVE of aTIV and TIV-HD during the 2018–19 season [19]. Unlike our study that included data that are not restricted to a single payer and includes all payer types for older adults, Izurieta included only Medicare FFS beneficiaries. Nonetheless, given that our study sample included population aged 65 years and above, majority (~75%) of the population were insured through Medicare (both Medicare Advantage and FFS). Similar to our study, IPTW-adjusted estimates comparing aTIV and TIV-HD in the Izurieta study showed similar rVEs against preventing influenza-related hospital encounters between aTIV and TIV-HD cohorts (rVE = −3.0; 95% CI: −6.1%-0.0%).

Additionally, the current study evaluated CRD-related outcomes including any CRD, pneumonia, asthma/COPD/bronchial, coronary artery (including myocardial infarction), congestive heart failure, and cerebrovascular events (including stroke). These cardiorespiratory events have been evaluated in a multicenter trial of patients vaccinated with either TIV-HD or SD egg-based vaccines [34]. Furthermore, cardiovascular disease (CVD) is the most commonly identified chronic medical condition among adults hospital-

Table 1
Baseline demographic and clinical characteristics: Post-IPTW.

Characteristic	aTIV (N = 561,315)		TIV-HD (N = 1,672,779)		SMD[1]
Age (years)					
Mean	75.1		75.0		0.00
SD	6.3		6.3		
Median	74		74		
Age Group (n, %)					
65–74 years	283,272	50.5%	844,152	50.5%	0.00
75–84 years	191,321	34.1%	570,521	34.1%	0.00
≥85 years	86,722	15.4%	258,106	15.4%	0.00
Male Gender (n, %)	226,960	40.4%	675,893	40.4%	0.00
Payer Type (n, %)					
Cash	1,734	0.3%	5,263	0.3%	0.00
Medicaid	306	0.1%	904	0.1%	0.00
Medicare Part D	151,054	26.9%	451,759	27.0%	0.00
Medicare	283,783	50.6%	846,049	50.6%	0.00
Third party	123,932	22.1%	367,346	22.0%	0.00
Other/Unknown	506	0.1%	1,458	0.1%	0.00
Month of flu vaccine (n, %)					
August	22,658	4.0%	67,263	4.0%	0.00
September	168,933	30.1%	504,664	30.2%	0.00
October	269,877	48.1%	802,843	48.0%	0.00
November	69,740	12.4%	208,175	12.4%	0.00
December	19,776	3.5%	59,063	3.5%	0.00
January	10,332	1.8%	30,770	1.8%	0.00
Geographic region (n, %)					
Northeast	93,223	16.6%	277,817	16.6%	0.00
Midwest	99,321	17.7%	295,356	17.7%	0.00
South	255,603	45.5%	762,364	45.6%	0.00
West	113,169	20.2%	337,242	20.2%	0.00
Charlson Comorbidity Index (CCI) Score: (n, %)					
0	306,147	54.5%	912,736	54.6%	0.00
1	119,750	21.3%	356,833	21.3%	0.00
2	70,370	12.5%	209,521	12.5%	0.00
3+	65,049	11.6%	193,689	11.6%	0.00
Mean	0.9		0.9		0.00
SD	1.3		1.3		
Median	0		0		
Pre-index comorbid conditions of interest (n, %)					
Asthma	20,853	3.7%	60,623	3.6%	0.00
Blood disorders	1,744	0.3%	5,114	0.3%	0.00
Chronic lung disease	48,163	8.6%	143,676	8.6%	0.00
Diabetes	121,468	21.6%	374,640	22.4%	0.02
Heart disease	72,245	12.9%	211,006	12.6%	−0.01
Kidney disorders	51,769	9.2%	152,500	9.1%	0.00
Liver disorders	13,005	2.3%	37,498	2.2%	−0.01
Neurological or neurodevelopmental conditions	27,675	4.9%	82,704	4.9%	0.00
Weakened immune system[2]	57,422	10.2%	170,219	10.2%	0.00
Inflammatory bowel diseases (IBD) (ulcerative colitis and Crohn's disease)	3,518	0.6%	9,915	0.6%	0.00
Composite of the above	272,104	48.5%	815,248	48.7%	0.01
Indicators of frail health status (n, %)					
Home oxygen use	26,033	4.6%	79,674	4.8%	0.01
Wheelchair use	13,471	2.4%	43,162	2.6%	0.01
Walker use	19,483	3.5%	56,930	3.4%	0.00
Dementia	7,247	1.3%	20,707	1.2%	0.00
Urinary catheter use	1,709	0.3%	5,146	0.3%	0.00
Falls	4,946	0.9%	13,353	0.8%	−0.01
Fractures	3,067	0.5%	8,543	0.5%	0.00
Composite of the above	61,238	10.9%	182,325	10.9%	0.00
Patients with a pre-index hospitalization (n, %)	45,543	8.1%	135,885	8.1%	0.00
Total pre-index all-cause outpatient pharmacy costs					
Mean	$1,908		$1,982		0.04
SD	$6,186		$6,301		
Median	$495		$534		
Total pre-index all-cause medical costs[3]					
Inpatient					0.00
Mean	$930		$885		
SD	$8,257		$8,685		
Median	$0		$0		
Outpatient					
Mean	$2,117		$2,005		−0.03
SD	$8472		$8347		
Median	$513		$484		
Emergency Room (ER)					
Mean	$178		$175		0.01
SD	$983		$992		
Median	$0		$0		
Outpatient physician office visits					
Mean	$1439	$1331	−0.04		
SD	$7772	$7628			
Median	$258	$239			
Total pre-index all-cause costs[3]					
Mean	$4,955	$4,872	0.00		
SD	$14,145	$14,351			
Median	$1704	$1706			

[1] SMD = standardized mean difference.
[2] Including: HIV/AIDS; metastatic cancer and acute leukemia; lung or upper digestive or other severe cancer; lymphatic, head, neck, brain, or major cancer; breast, prostate, colorectal, or other cancer; and disorders of immunity.
[3] Total = outpatient pharmacy + inpatient + outpatient medical.

ized with influenza and influenza vaccination has been shown to reduce the incidence of major adverse cardiac events among those with existing CVD [35–37]. Although there are no head-to-head RCTs comparing cardiovascular benefits of these two enhanced vaccines, adjuvanted vaccine has been shown to be more effective than unadjuvanted vaccines in reducing several influenza-related outcomes among older adults, especially hospitalizations due to influenza-related complications [37]. It is important to note that given the retrospective nature of the study, these results should be interpreted cautiously. Future clinical studies are required to understand the potential benefits of adjuvants in preventing influenza-related CRD events in older adults.

The current study also found differences in adjusted influenza-related office visits (rVE was significantly higher for aTIV vs. TIV-HD for age groups 75–84 years and ≥85 years, but not 65–74 years), and CRD-related hospitalization/ER visits by age groups (rVE was significantly higher for aTIV vs. TIV-HD for age groups 65–74 years and 75–84 years but not ≥85 years). This could be attributed to the progressive deterioration in the ability to respond to infections with advanced age. Further research is needed to understand the differences in vaccine effectiveness among older population as well as by influenza subtypes.

To our knowledge, this is the first retrospective study comparing economic outcomes between aTIV and TIV-HD during the 2018–19 influenza season. This study did not show any economic benefits of one vaccine over the other. aTIV or TIV-HD had comparable all-cause (US$9676 vs. US$9625; p = 0.080) and influenza-related (US$18.74 vs. US$17.28; p = 0.90) predicted total annualized costs. Both aTIV and TIV-HD were also comparable in terms of predicted mean annualized costs for influenza-related office visits (US$1.29 vs. US$1.34; p = 0.334) and influenza-related hospitalizations (US$20.28 vs. US$18.13; p = 0.128). Although the influenza-related pharmacy costs were lower for aTIV than TIV-HD (US$1.75 vs. US$1.86; p < 0.0001), the amounts were too small to impact the overall costs.

These results are similar to our previous retrospective analyses conducted using similar methodologies during the 2017–18 influenza season [15]. For both seasons, the rVEs for

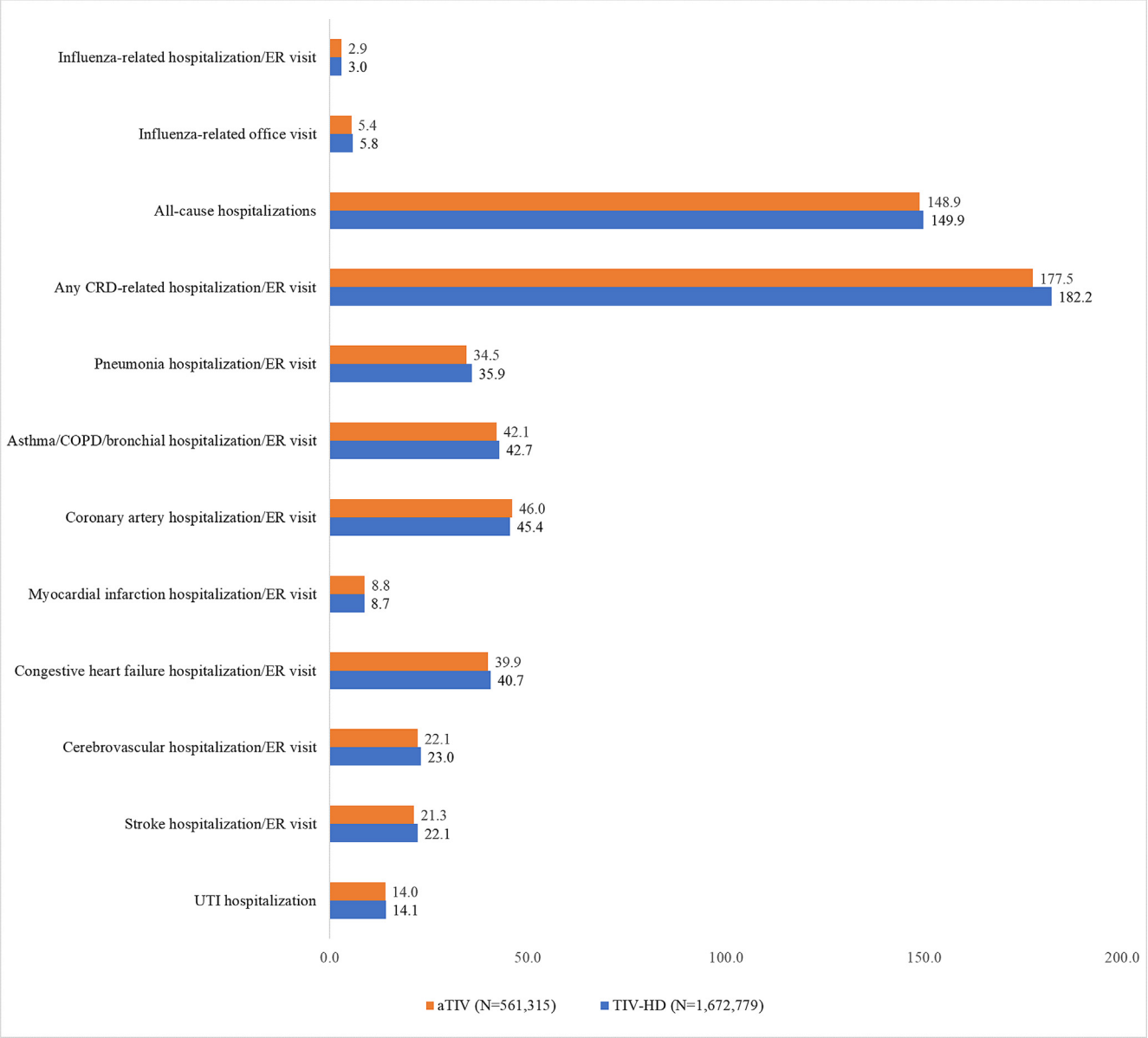

Fig. 3. Adjusted clinical outcomes rates (events per 1,000) – Post-IPTW. Rate = events (first event only) per 1,000 vaccinated-subject seasons CRD: Cardio-respiratory Disease UTI = Urinary Tract Infection.

hospitalization-related outcomes were lower than the rVEs for office visits-related outcomes. In addition, the IPTW-adjusted rVEs were less than the unadjusted rVEs for all the clinical outcomes except for the influenza-related office visits, for which IPTW-adjusted rVE is greater than the unadjusted rVE. It is important to note that we consider rVEs and not VEs, with the former potentially more difficult to interpret in general, and that we adjusted for pre-index hospitalization in the IPTW sample, which may have affected the rVEs for the outcomes related to hospitalizations and not related to office visits.

The 2018–19 influenza season was of moderate severity and was the longest season in 10 years [16]. Influenza A viruses predominated, with a very little influenza B activity. The antigenic characterization of the viruses with a higher A(H3N2) activity after February 2019 may have lowered the overall vaccine effectiveness for both aTIV and TIV-HD [16–18], which in turn may have reduced the differences in the estimated effectiveness of these two vaccines. Overall, all the rVE estimates for the moderately severe 2018–19 influenza season were numerically lower than the corresponding rVE estimates for the previous high-severity influenza season [15]. More real-world studies are needed to further explore potential clinical and economic benefits associated with these vaccines using different data sources, study populations, and different influenza seasons.

There are several limitations of this study specific to the study design and data sources utilized that are worth noting. First, the cohort matching techniques used in this study did not necessarily adjust for imbalance in potential unmeasured confounders, an issue often observed in real-world data. Nonetheless, there were no differences between study cohorts in the negative control outcome of UTI hospitalizations after IPTW-adjustments, suggesting IPTW created comparable cohorts (Supplementary Table 2). Note that, based on the previous literature [14], we used UTI hospitalizations as a negative endpoint. For future studies, it may be helpful to add additional negative endpoints such as UTI medical office visits to further strengthen the study findings. There are also limitations

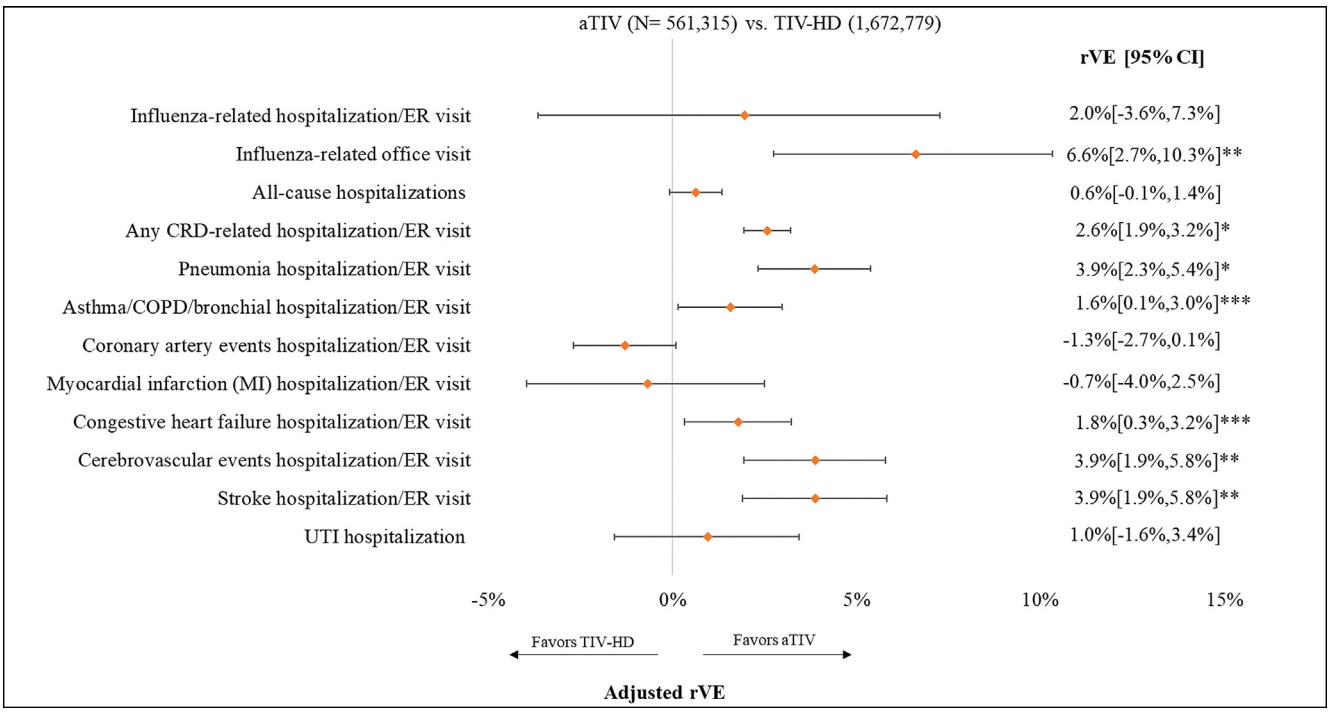

Fig. 4. Adjusted rVE – Post-IPTW and Poisson Regression. Univariate Poisson regression included IPTW weight Sample sizes are post-IPTW CRD: Cardio-respiratory Disease rVE = Relative Vaccine Effectiveness CI = Confidence Interval *p < 0.0001; **p < 0.001; ***p < 0.05.

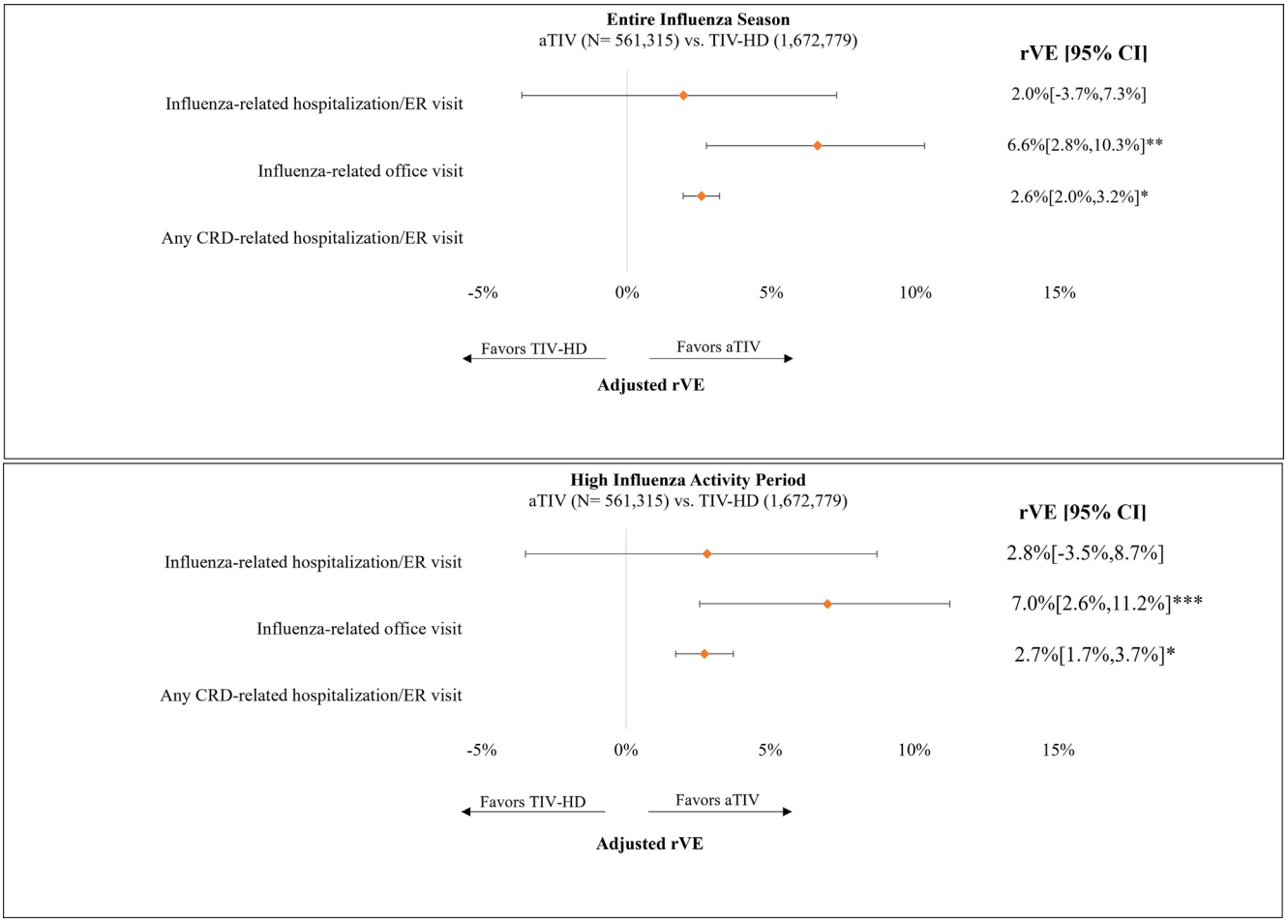

Fig. 5. Adjusted rVE – Post-IPTW and Poisson Regression during periods of high influenza activity. Univariate Poisson regression included IPTW weight CRD: Cardio-respiratory Disease rVE, relative vaccine effectiveness; IPTW, inverse probability of treatment weighting *p < 0.0001; **p < 0.001; ***p < 0.05.

Table 2
Adjusted economic outcomes – Post-PSM and GEE Adjustment.

	aTIV (N = 561243)		TIV-HD (N = 561243)		Incremental Costs
Outcome	**Mean**	**95% CI**	**Mean**	**95% CI**	
All-cause total costs	$9675.73	$9630.57 - $9722.59	$9625.30	$9580.64 - $9677.62	-$50.42
Influenza-related total costs	$18.74	$17.37 - $20.58	$17.28	$15.92 - $18.90	-$1.46
Influenza-related hospitalization costs	$20.28	$17.55 - $23.84	$18.13	$15.23 - $21.55	-$2.16
Influenza-related ER costs	$2.18	$1.94 - $2.43	$2.32	$2.06 - $2.58	$0.13
Influenza-related office visit costs	$1.29	$1.15 - $1.45	$1.34	$1.20 - $1.48	$0.05
Influenza-related pharmacy costs	$1.75	$1.71 - $1.78	$1.86	$1.82 - $1.90	$0.11

Influenza-related total = sum of (Influenza-related hospitalizations, Influenza-related ER, Influenza-related office visit, Influenza-related pharmacy costs).
All $p < 0.05$ for differences in predicted mean costs except for influenza-related pharmacy costs where $p < 0.001$.

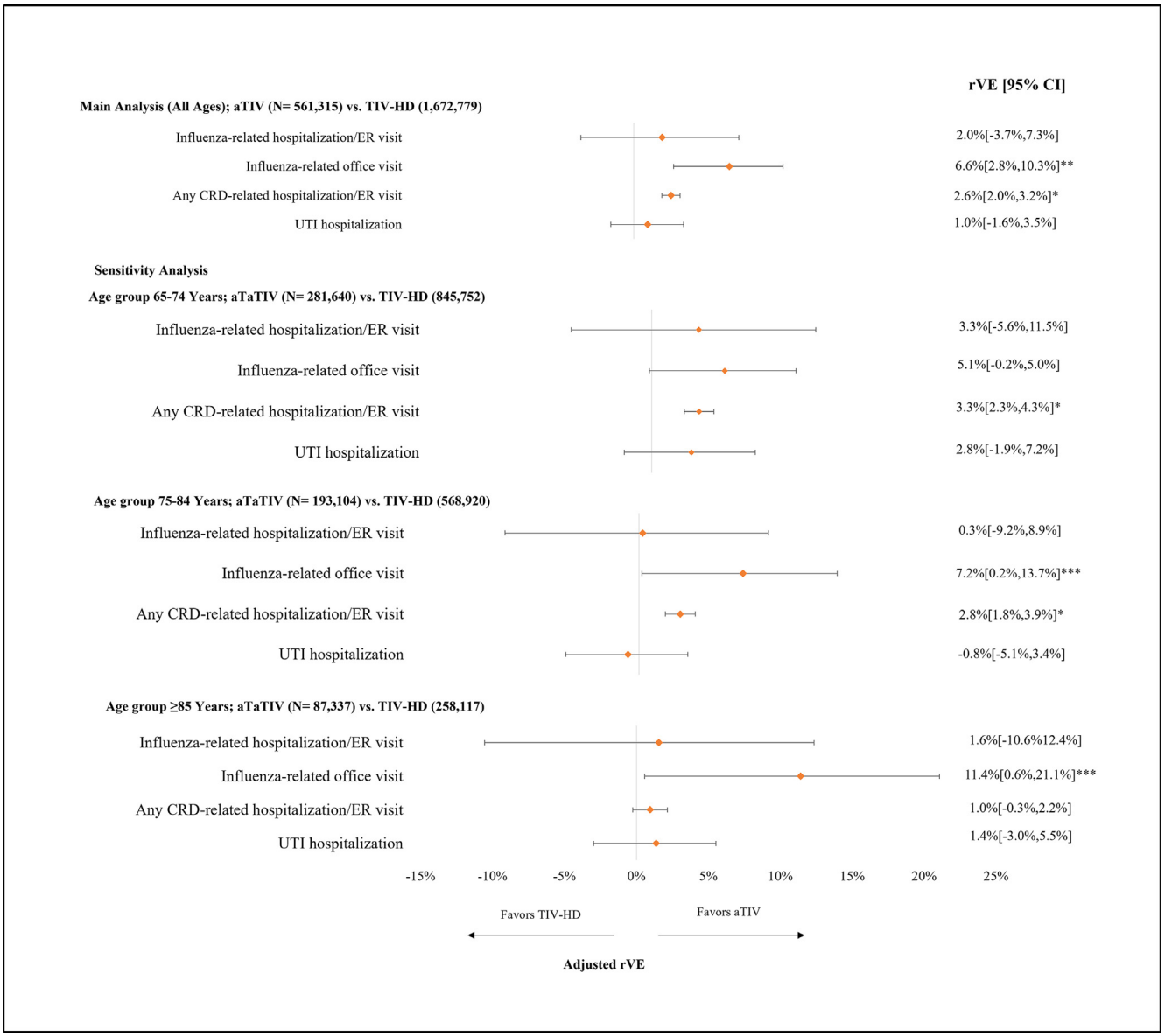

Fig. 6. Sensitivity analysis using age stratification. Univariate Poisson regression included IPTW weight CRD: Cardio-respiratory Disease rVE, relative vaccine effectiveness; IPTW, inverse probability of treatment weighting *p < 0.0001; **p < 0.001; ***p < 0.05.

related to the utilization of claims databases. Socioeconomic characteristics such as race/ethnicity, income, and access to care were not available in the claims data. It may also be possible that other factors such as periods of high flu circulation can impact clinical outcomes. However, month of influenza vaccine was included in the statistical models to adjust for selection bias. The follow-up time was generally equal across the cohorts, thereby mitigating any differences or bias related to periods of high influenza circulation. Also, the sensitivity analysis restricting the observation period to the high influenza activity had similar results as the primary

analysis. Note that most subjects were excluded due to the requirements related to the linkage of subjects across Dx, Rx, and CDM datasets as well as continuous subject activity, and pharmacy reporting stability. We did not analyze the differences in subjects excluded vs those included as the majority of the exclusions occurred due to criteria related to the subject availability across datasets and pharmacy reporting. Subjects that were excluded due to other reasons not related to the follow-up data may be different from those included however this was a small portion of the overall sample. After applying the study exclusion criteria, we observed similar attrition across both the vaccine groups (15% of the original population remained in the final cohorts for both vaccines), indicating that the data and activity-related differences may have balanced across the two groups. The claims data lack clinical detail; therefore, we were unable to confirm influenza through lab or test results. We were unable to assess rVE by influenza subtype due to lack of laboratory-confirmed influenza outcomes. We do not have information related to the healthcare activity/consumption at offices/pharmacies/hospitals that do not participate in the IQVIA databases. Not all healthcare resource utilization or costs may be captured, limiting a comprehensive analysis of clinical or economic outcomes.

5. Conclusions

During the 2018–19 influenza season, influenza-related hospitalization/ER visits and associated costs among people aged 65 and above were comparable between aTIV and TIV-HD. aTIV had a higher rVE in preventing influenza-related office visits as compared to TIV-HD in this population. Furthermore, the overall all-cause and influenza-related costs were comparable between the cohorts. Although more evaluation of aTIV and TIV-HD is needed to understand the relative benefits, growing evidence suggests that both licensed vaccines can provide comparable clinical and economic benefits in protecting influenza and associated complications among the vulnerable older population.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. This study was funded by Seqirus Vaccines Ltd., Summit, NJ, USA. VD, MD and DS have disclosed that they are employees of IQVIA which received funding for this study from Seqirus. GK and JM have disclosed that they are employees and shareholders of Seqirus. SIP and MJP received financial support for time and effort from Seqirus for this study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.03.054.

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