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Vaccine effectiveness of recombinant and standard dose influenza vaccines against influenza related hospitalization using a retrospective test-negative design

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ABSTRACT

Background: Relative effectiveness of various vaccine formulations provide important input for vaccine policy decisions and provider purchasing decisions. We used electronic databases to conduct a test-negative case control study to determine relative vaccine effectiveness (rVE) of recombinant influenza vaccine (RIV4) compared with standard dose vaccines (SD-IIV4) against influenza hospitalization.
Methods: Adults 18–64 and ≥65 years of age hospitalized in a large U.S. health system (19 hospitals) in 2018–2019 and 2019–2020 who were clinically tested for influenza using reverse transcription polymerase chain reaction (RT-PCR) assays were included. The hospital system electronic medical record (EMR) and the state immunization registry were used to confirm influenza vaccination. Propensity scores with inverse probability weighting were used to adjust for potential confounders and determine rVE.
Results: Of the 14,590 individuals included in the primary analysis, 3,338 were vaccinated with RIV4 and 976 were vaccinated with SD-IIV4, with the balance of 10,276 being unvaccinated. Most participants were white (80 %), most (70 %) had a high-risk condition, just over half were female (54 %) and age 65 years or older (53 %). Overall RIV4 rVE was significant when adjusted for propensity scores with inverse probability weights (rVE = 31; 95 % CI = 11 %, 46 %). Among younger adults (18–64 years-old), overall rVE of RIV4 was significant (rVE = 29; 95 % CI = 4 %, 47 %).
Conclusions: Over all adults, both RIV4 and SD-IIV4 were effective against influenza hospitalization, with RIV4 providing better protection compared with SD-IIV4 overall, for females, younger adults, and those with no high-risk conditions.

1. Introduction

Despite the availability of an array of influenza vaccines and recommendations for vaccination of individuals age 6 months and over, influenza remains a major cause of morbidity, hospitalizations and mortality in the U.S. and worldwide. Over the last 1–2 decades, effectiveness of egg-based standard dose influenza vaccine has been modest [1–5]. New influenza vaccine formulations, designed to improve upon the effectiveness of these vaccines, have been introduced in the U.S. over the past several years, including high dose- and adjuvanted egg-based vaccines. In addition, egg-free vaccines manufactured using cell-culture and recombinant technologies have been licensed that avoid the glycosylation site binding issues associated with egg adaptation [6] that have been shown to reduce vaccine effectiveness (VE) against A(H3N2) strains.

Abbreviations: aOR, Adjusted odds ratios; Adj-IV, Adjuvanted influenza vaccine; EMR, Electronic medical records; GBM, Generalized Boosted Regression Models; HD-IIV4, High dose quadrivalent influenza vaccine; PA-SIIS, Pennsylvania Statewide Immunization Information System; RCT, Randomized controlled trial; RIV4, Recombinant quadrivalent influenza vaccine; rVE, Relative vaccine effectiveness; RT-PCR, Reverse transcription polymerase chain reaction; SD-IIV4, Standard dose quadrivalent influenza vaccine; TWANG, Toolkit for Weighting and Analysis of Nonequivalent Groups.

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Reasonably accurate VE and relative VE (rVE) estimates depend upon having access to a sufficient number of recipients of any given vaccine type. Research on high dose quadrivalent influenza vaccine (HD-IIV4) has reported rVE for HD-IIV4 compared with standard dose quadrivalent influenza vaccine (SD-IIV4) of 24 % against laboratory-confirmed influenza [7] and 27 % against influenza hospitalization [8]. Several studies of cell-cultured influenza vaccine were conducted prior to the 2019–2020 season (when all four vaccine strains were cell-cultured) and have not shown significant rVE against influenza illness compared with SD-IIV4 [9]. A large retrospective study of Medicare beneficiaries (≥65 years of age) in the 2019–2020 season demonstrated no significant rVE of cell-cultured quadrivalent influenza vaccine (ccIIV4) compared with SD-IIV4 against influenza-related hospital encounters [10]. However, the study was limited by the fact that there were no laboratory-confirmed influenza outcomes. Thus, the full benefit of cell-culture vaccine technology is still largely unknown.

Two large studies have explored rVE of recombinant quadrivalent influenza vaccine (RIV4). The Medicare beneficiaries study [10] using retrospective data as described above, reported significant rVE of RIV4 vs. SD-IIV4) against influenza-related hospital encounters. Secondly, a randomized controlled trial (RCT) found significant rVE of RIV4 compared with SD-IIV4 among adults ≥50 years old, but not for adults ≥65 years old [11].

Given the higher cost of newer vaccines, and the high risk of influenza complications for certain groups, including the elderly [12], there is interest in providing the most effective vaccine to the largest number of patients to prevent influenza-related morbidity and mortality. Additional rVE studies of new vaccine formulations are needed to help determine vaccination best practices. This study is a retrospective test-negative case-control study of influenza VE against hospitalization using data from electronic medical records (EMR) of a single large health system to determine the rVE of RIV4 among adults 18–64 and ≥65 years of age in the 2018–2019 and 2019–2020 seasons.

2. Methods

The University of Pittsburgh Institutional Review Board approved this retrospective study using EMR databases. A test-negative case-control study estimates VE by comparing the odds of vaccination among patients hospitalized with influenza like illness with confirmed influenza to the odds of vaccination among controls, i.e., patients hospitalized with influenza like illness who tested negative for influenza.

2.1. Patients

Patients were individuals 18 years and older as of August 1 each season who were hospitalized in one of nineteen UPMC hospitals in central and southwestern Pennsylvania and had a test for influenza at any time between 11/01/2018 and 04/30/2020. A Theradoc® database (an infection control software) was used to identify those tested for influenza using reverse transcription polymerase chain reaction (RT-PCR) assays performed in a centralized clinical lab for some hospitals and individual hospital labs for others. Influenza cases were those who tested positive for influenza and controls were those who tested negative for influenza, regardless of any other identified viral infection. Both the EMR and Pennsylvania Statewide Immunization Information System (PA-SIIS) were queried for influenza vaccines given between August 1 and the date of illness/PCR testing. Exclusion criteria were testing within 2 weeks of vaccination, having 2 different types of influenza vaccine in a season, missing and unknown vaccination information and having an immunocompromising condition.

2.2. Statistical methods

For primary analysis, all adults ≥18 years were included, then for secondary analyses, they were stratified into age groups ≥65 years, and 18–64 years. Sample size calculations determined that we had 48 % power to detect an effect size of 9.5 % change from a baseline probability of 11.7 %. Post hoc sample size calculations for age subgroup analyses resulted in 42 % and 20 % power for ages 18–64 years and ≥65 years with effect sizes of 8.9 %, and 8.7 %, with the detectable difference of 3 % and 2.1 % respectively, thus these analyses were likely to be underpowered to detect a significant rVE for RIV4 over SD-IIV4. Moreover, rVE estimates by vaccine strain were also precluded by insufficient sample sizes. Descriptions of variables for each group were summarized as mean and standard deviation for age and frequencies and percentages for categorical data. Baseline characteristics between the vaccination groups were compared using chi-square or the Fisher's exact tests for categorical variables and ages were compared by using *t*-test.

Using adjusted odds ratios (aORs) obtained from multivariable logistic regression models, adjusted VE estimates were calculated as (1-aOR) X 100. The dependent variable of interest was influenza status. The primary exposure of interest was vaccine type (recombinant, SD-IIV4s and in some analyses, enhanced vaccines such as HD-IIV4 and adjuvanted influenza vaccine (Adj-IV)). The CDC has recommended the use of "enhanced vaccines" for adults ages 65 and older beginning in 2022 [13]. Influenza vaccines were identified through the EMR; SD-IIV4 included Afluria, Fluarix, FluLaval, Standard Dose Fluzone and FlucelVax. HD-IIV4 was High Dose Fluzone, RIV4 was Flublok and Adj-IV was FluAd. Other independent variables were age, influenza season (2018–2019 and 2019–2020), sex, race and presence of one or more high-risk conditions. Adjusted VE was calculated for RIV4, SD-IIV4 and combined RIV4, high dose, egg-based and adjuvanted vaccines. Relative VE (rVE) was calculated as 1 minus the ratio of adjusted VE times 100 %.

We conducted propensity adjustment analyses to reduce the potential impact of selection effects (i.e., confounding) on baseline characteristics. We estimated the propensity scores using the Generalized Boosted Regression Models (GBM) approach, which is a nonparametric model that allows for nonlinear relationships with a maximum number of iterations set to the default (i.e.,10,000) that minimized the balance statistics of interest. We used the balance statistic based on absolute standardized bias (also referred as the effect size or absolute standardized mean difference) and summarized across variables. We allow a maximum of three splits for each tree in the model, allowing for three-way interactions among all covariates to be considered. The shrinkage parameter was set to 0.0005 to ensure a smooth fit.

We also checked the balance of all the variables included in the model to assess the quality of the propensity score and evaluate common support, using a value under 0.25 as indicative of good balance. We also used the balance plots to compare the propensity score distributions and to evaluate the common support.

Using the propensity score, we calculated the inverse probability of receiving SD-IIV4 weighting. In this approach, for an individual receiving SD-IIV4 t, the weight equals $1/p_t(x)$, where $p_t(x)$ is the propensity score (probability that an individual with characteristics x receives SD-IIV4 t). A propensity score weighted logistic regression with influenza status as the dependent variable was fitted to estimate the effect of vaccine (SD-IIV4 vs. RIV4) on outcome and also used inverse probability weighting to estimate VE and its 95 % confidence intervals. We added covariates like high-risk conditions and influenza seasons to increase the probability of achieving a good balance for the propensity score modeling. We used five plot methods to determine that there were no extreme values in the weights (i.e., checked the balance): 1. optimization using the

estimated mean average treatment effect; 2. box plot of the propensity of the vaccine; 3. the standardized effect size of the unweighted and weighted values; 4. *t*-test p-values of the group mean of the covariate; and 5. Kolmogorov-Smirnov (K-S) p-values of the covariates. In all, the weights were stable and balanced. Because all the covariates were balanced, we fit the model with propensity score as an adjustment factor and the inverse probability weight to estimate the rVE.

We conducted secondary, sensitivity analyses restricted to age groups 18–64 years and ≥65 years comparing recombinant and SD-IIV4, and also for those ≥65 years, comparing recombinant, high-dose egg-based and adjuvanted vaccines combined and SD-IIV4. We conducted propensity score adjustments similar to those used in the primary analyses. All analyses were two-sided and the alpha level was set to 0.05. All analyses were conducted using SAS, version 9.4 statistical software (SAS Institute Inc., Cary, NC). We used the Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG) software package and the SAS Macros (available at https://www.rand.org/statistics/twang/downloads.html) to calculate the propensity scores.

3. Results

The total number of influenza test results among inpatients was 18,467 of which 530 were excluded because of missing vaccination information or vaccination < 14 days before illness, and 3,264 were excluded from the primary analyses because patients were immunocompromised or received enhanced vaccines other than RIV4 (n = 613), leaving 14,590 for the primary analysis (Fig. 1). Of these, 3,338 were vaccinated with RIV4 and 976 were vaccinated with SD-IIV4, with the balance of 10,276 being unvaccinated. For the secondary analyses, the analyzable cohort included the 613 HD-IIV4 and Adj-IV recipients bringing the total analyzable sample to 15,203 (Fig. 2). The influenza positivity rate was 12.4 % (1,803/14,590) overall, 14.4 % among younger adults 18–64 years and 11.1 % (922/8306) among those ≥65 years, with the addition of 613 patients who received enhanced vaccines that were not included in the primary analysis.

Demographic characteristics of the population for the primary analyses are shown in Table 1; most participants were white (80 %), just over half were female (54 %) and age 65 years or older (53 %), and most (70 %) had a high-risk condition. Patients who received RIV4 were significantly less often white ($P < 0.001$) and age 65 years or older ($P < 0.001$), and had more high-risk conditions ($P < 0.001$) than those who received SD-IIV4.

Table 2 shows adjusted VE for both RIV4 and SD-IIV4s and rVE of RIV4 compared with SD-IIV4s. VE of RIV4 was significant against influenza hospitalizations overall (36 %; 95 % CI = 27, 45) and for population subgroups based on sex, age and risk conditions. VE of SD-IIV4 was significant overall (24 %; 95 % CI = 6, 38) and for males and younger adults, but not for other subgroups. Overall rVE for RIV4 vs SD-IIV4 against influenza hospitalization was significant when adjusted for propensity scores with inverse probability weights (rVE = 31%; 95 % CI = 11, 46). Subgroup analyses by age and risk group identified significant rVE for recombinant influenza vaccine among females (rVE = 37%; 95 % CI = 13, 54), younger adults 18–64 years old (rVE = 28%; 95 % CI = 3, 46) and for those without high-risk conditions (rVE = 60%; 95 % CI = 29, 78).

In secondary analyses, the participants, including those who received HD-IIV4 and Adj-IV, were then divided in two age groups (18–64 and ≥65 years) to calculate rVE. Characteristics of these groups by vaccine type are shown in Table 3. Among younger adults, receipt of RIV4 was significantly associated with non-white race (83.7 % RIV4 vs. 71.8 % SD-IIV4; $P < 0.001$), fewer cases of influenza (9.2 % RIV4 vs. 11.9 % SD-IIV4; $P < 0.041$) and having a high-risk condition (83.2 % RIV4 vs. 66.8 % SD-IIV4; $P < 0.001$). Among older adults, receipt of RIV4 was significantly associated with having a high-risk condition (91.1 % RIV4 vs. 78.4 % SD-IIV4 $P < 0.001$). In a second scenario older adults receiving SD-IIV4 were compared with those receiving RIV4, HD-IIV4, or Adj-IV , because these latter two "enhanced" vaccines are now recommended for adults ≥65 years. Again, having a high-risk condition was associated with receipt of one of these vaccines (87.5 % combined vs. 78.4 % SD-IIV4; $P < 0.001$).

Adjusted VEs for RIV4 for younger adults were significant across all subgroups, whereas, VE for SD-IIV4 was significant for males only. Among older adults, VE of RIV4 was significant for females (47 %; 95 % CI = 30, 60) but not males (−2 %; 95 % CI = −33, 21) or for those with and without high-risk conditions. VEs for those ≥65 years old receiving RIV4, HD-IV4 or Adj-IV showed similar patterns of significance across subgroups (overall VE = 24 %; 95 % CI = 11, 36; females VE = 38 %; 95 % CI = 22, 51); high risk

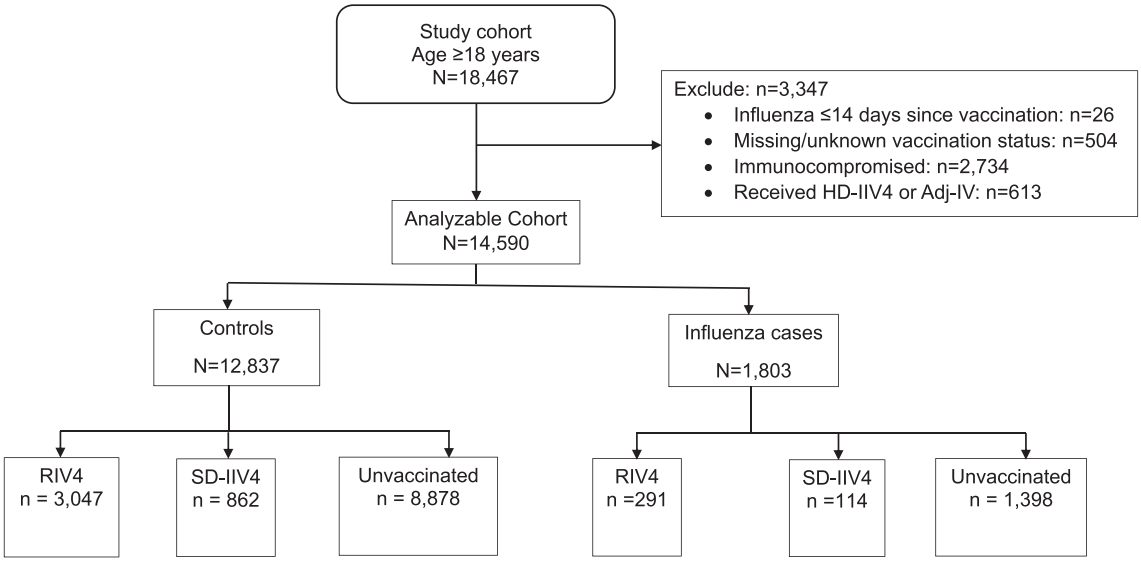

Fig. 1. Flow chart for primary analyses. The primary analyses included only participants who received recombinant quadrivalent influenza vaccine (RIV4), standard dose quadrivalent influenza vaccine (SD-IIV4) and the unvaccinated, who were not otherwise excluded.

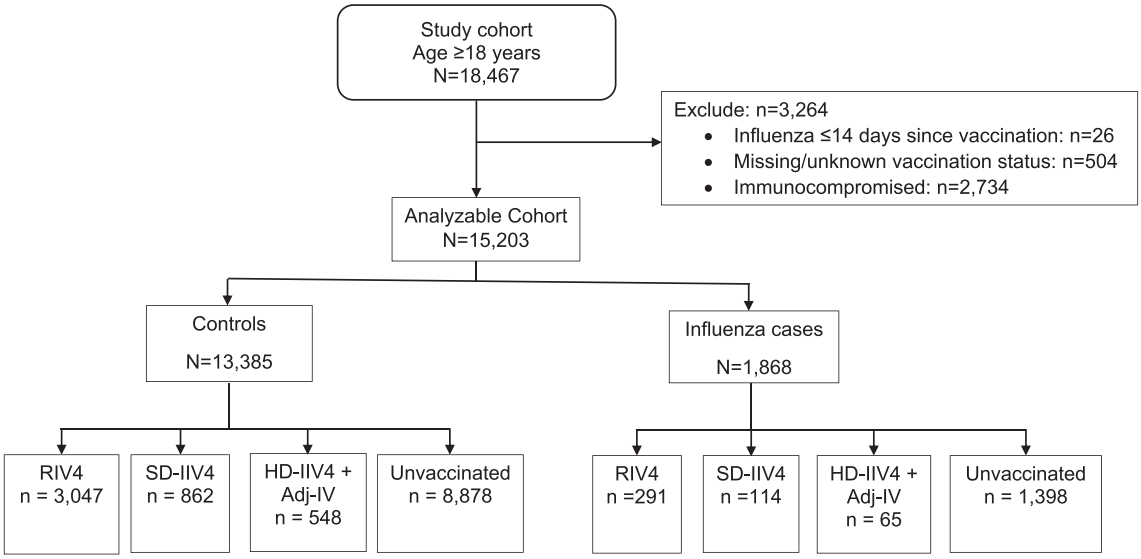

Fig. 2. Flow chart for secondary analyses. The secondary analyses included participants who received recombinant quadrivalent influenza vaccine (RIV4), standard dose quadrivalent influenza vaccine (SD-IIV4), high dose quadrivalent influenza vaccine (HD-IIV4), adjuvanted influenza vaccine (Adj-IIV) and the unvaccinated, who were not otherwise excluded.

Table 1
Characteristics of all participants, overall and by receipt of recombinant quadrivalent influenza vaccine (RIV4) or standard dose quadrivalent influenza vaccine (SD-IIV4).

Measures	Total[a] N = 14,590	Received RIV4[b] n = 3,338	Received SD-IIV4[c] n = 976	*P*-value for difference between RIV4 and SD-IIV4
White race, ref. = non-white, n (%)	11,661 (80)	2,656 (79)	828 (85)	**<0.001**
Female sex, ref. = male, n (%)	7,895 (54)	1,855 (56)	571 (58)	0.104
Season, n (%)				**<0.001**
2018–2019	5,911 (41)	1,125 (34)	478 (49)	
2019–2020	8,679 (59)	2,213 (66)	498 (51)	
Age Group, n (%)				**<0.001**
18–64 years	6,896 (47)	1,408 (42)	763 (78)	
≥65 years	7,694 (53)	1,930 (58)	213 (22)	
Influenza case, ref. = non-case, n (%)	1,803 (12)	291 (9)	114 (12)	**0.005**
High-risk condition, ref. = no, n (%)	10,292 (71)	2,931 (88)	677 (69)	**<0.001**

[a] Includes unvaccinated and those vaccinated with enhanced vaccines: High dose Fluzone and adjuvanted FluAd.
[b] RIV4: Flublok.
[c] SD-IIV4: Afluria, Fluarix, FluLaval, Standard Dose Fluzone and FlucelVax.

conditions VE = 22 %; 95 % CI = 6, 34; no high-risk condition VE = 38 %; 95 % CI = 3, 61). VE of standard dose IIV4 was not significant for any group ≥65 years old (Table 4).

Table 5 shows the rVE in three scenarios: 1) for 18–64-year-old adults, RIV4 vs. SD-IIV4; and for ≥65-year-old adults: 2) RIV4 vs. SD-IIV4; and 3) RIV4 + HD-IIV4 +Adj-IV vs. SD-IIV4. Among younger adults, overall rVE of RIV4 was significant (rVE = 29 %; 95 % CI = 4, 47). Subgroup analyses identified significant rVE for RIV4 among males (rVE = 43 %; 95 % CI = 6, 65), and for those without high-risk conditions (rVE = 51 %; 95 % CI = 7, 74). Among older adults, neither rVE for RIV4 nor rVE for RIV4 + HDIV4 +Adj-IV was significant overall or for any subgroup.

4. Discussion

Among over 14,000 mostly white, and mostly high-risk adult patients hospitalized for an acute respiratory infection in 2018–2019 and 2019–2020, 12 % were diagnosed with influenza. Compared with standard dose influenza vaccine recipients, recipients of so-called "enhanced" vaccines such as RIV4, Adj-IV and HD-IIV4 were more often non-white, older, and with underlying medical conditions, placing them at high risk for influenza complications.

Among all adults hospitalized for acute respiratory infections, both RIV4 and SD-IIV4 were significantly effective overall against influenza hospitalizations, but only RIV4 was effective for all subgroups tested in this analysis. The differences in VE of RIV4 and SD-IIV4 were reflected in overall significant rVE for RIV4. However, within the overall population, rVE of RIV4 was significant for females, younger adults and those without high-risk conditions, the latter two groups being those who were less likely to receive RIV4. When stratified by age groups, rVE of RIV4 of younger adults was significant overall, among males and those without a high-risk condition; whereas, among older adults, neither RIV4 nor all high dose or adjuvanted vaccines combined was significantly more effective than standard dose IIV4. This was likely due to limited use of the SD-IIV4 (only 213 seniors received SD-IIV4), resulting in large confidence intervals. The large market share in our study of RIV4, HD-IIV4 and Adj-IV in senior adults, relative to SD-IIV4 limited our analysis and seemingly anticipated the 2022 decision by ACIP to recommend these three vaccines for older adults [13].

Table 2
Vaccine effectiveness (VE) of recombinant quadrivalent influenza vaccine (RIV4) and standard dose quadrivalent influenza vaccine (SD-IIV4) and relative VE of RIV4 using propensity scores and inverse probability weighting (IPW).

Group	Adjusted RIV4[a] VE compared to no vaccination	Adjusted SD-IIV4[b] VE compared to no vaccination	Relative vaccine effectiveness of RIV4 compared to SD-IIV4, % (95 % CI)		
			Adjusted using *a priori* variables[c]	Adjusted using propensity score[d]	Adjusted using IPW
Overall	**36 (27, 45)**	**24 (6, 38)**	21 (−1, 38)	26 (4, 43)	**31 (11, 46)**
Female sex	**40 (28, 50)**	20 (−4, 39)	24 (−5, 45)	26 (−4, 48)	**37 (13, 54)**
Male sex	**31 (16, 44)**	**28 (0, 49)**	22 (−15, 48)	28 (−9, 52)	23 (−14, 48)
18–64 years	**47 (35, 57)**	**27 (8, 42)**	28 (2, 46)	27 (2, 45)	**28 (3, 46)**
≥65 years	**27 (12, 39)**	9 (−42, 42)	22 (−26, 51)	17 (−34, 49)	17 (−36, 48)
High-risk condition	**30 (19, 40)**	21 (−2, 39)	14 (−15, 35)	17 (−13, 38)	20 (−7, 40)
No high-risk condition	**67 (50, 78)**	27 (−4, 49)	49 (11, 71)	58 (23, 77)	**60 (29, 78)**
2018–2019 season	**31 (15, 45)**	20 (−6, 41)	19 (−17, 44)	28 (−7, 51)	28 (−5, 50)
2019–2020 season	**40 (29, 50)**	26 (1, 45)	24 (−6, 46)	29 (−1, 50)	**30 (1, 50)**

[a] RIV4: Flublok.
[b] SD-IIV4: Afluria, Fluarix, FluLaval, SD Fluzone, and FlucelVax.
[c] Multivariable logistic regression model adjusted for age, race, sex, season, and high-risk conditions, except that the stratified variable is not included as an adjustment in its own analysis.
[d] Propensity score: Generalized Boosted Regression Method was used to calculate the propensity score using TWANG (Toolkit for Weighting and Analysis of Nonequivalent Groups).

Table 3
Characteristics of participants by age group and vaccine received including recombinant quadrivalent influenza vaccine (RIV4), standard dose quadrivalent influenza vaccine (SD-IIV4), high dose quadrivalent influenza vaccine (HD-IIV4) and adjuvanted influenza vaccine (Adj-IV) N = 15,203.

Measures	18–64 years old, vaccine received			≥65 years old, vaccine received				
	RIV4 n = 1,408	SD-IIV4[a] n = 763	*P*-value[b]	SD-IIV4 n = 213	RIV4 n = 1,930	*P*-value[b]	RIV4 + HD-IIV4 + Adj-IV[c] n = 2,542	*P*-value[d]
White race, ref. = non-white, n (%)	1,101 (71.8)	639 (83.7)	**<0.001**	189 (88.7)	1,645 (85.2)	0.263	2,200 (86.5)	0.417
Female sex, ref. = male, n (%)	831 (59.0)	455 (59.6)	0.781	116 (54.5)	1,024 (53.1)	0.697	1,360 (53.5)	0.787
2018–2019 season, n (%)	457 (33.5)	372 (48.8)	**<0.001**	106 (49.8)	668 (34.6)	**<0.001**	1,075 (42.3)	**0.034**
2019–2020 season, n (%)	951 (67.5)	391 (51.2)		107 (50.2)	1,262 (65.4)		1,467 (57.7)	
Influenza case, ref. = non-case, n (%)	129 (9.2)	91 (11.9)	**0.041**	23 (10.8)	162 (8.4)	0.235	227 (8.9)	0.362
High-risk condition, n (%)	1,172 (83.2)	510 (66.8)	**<0.001**	167 (78.4)	1,759 (91.1)	**<0.001**	2,223 (87.5)	**<0.001**

[a] SD-IIV4: Afluria, Fluarix, FluLaval, SD Fluzone and FlucelVax.
[b] For difference between those receiving RIV4 and those receiving SD-IIV4.
[c] RIV4: Flublok; HD-IIV4: High dose Fluzone; Adj-IV: FluAd.
[d] For difference between those receiving RIV4, HD-IIV4, Adj-IV and those receiving SD-IIV4.

Table 4
Adjusted vaccine effectiveness (VE) of recombinant quadrivalent influenza vaccine (RIV4), standard dose quadrivalent influenza vaccine (SD-IIV4), and RIV4 + high dose quadrivalent influenza vaccine (HD-IIV4) + adjuvanted influenza vaccine (Adj-IV), compared with no vaccination, by age group.

Group	18–64 years		≥65 years		
	RIV4 VE, % (95 % CI)	SD-IIV4 VE, % (95 % CI)	RIV4 VE, % (95 % CI)	RIV4 + HD-IIV4 + Adj-IV VE, % (95 % CI)	SD-IIV4 VE, % (95 % CI)
Overall	**47 (35, 56)**	**27 (8, 42)**	**27 (12, 39)**	**24 (11, 36)**	9 (−42, 42)
Females	**35 (16, 49)**	19 (−10, 40)	**47 (30, 60)**	**38 (22, 51)**	9 (−62, 49)
Males	**62 (46, 73)**	**38 (9, 57)**	−2 (−33, 21)	4 (−22, 24)	10 (−83, 55)
High-risk condition	**39 (24, 51)**	24 (−2, 43)	**24 (7, 37)**	**22 (6, 34)**	9 (−50, 45)
No high-risk condition	**69 (49, 81)**	32 (−1, 54)	**56 (7, 79)**	**38 (3, 61)**	5 (−145, 63)
2018–2019 season	**44 (21, 60)**	28 (−2, 49)	21 (−5, 41)	18 (−3, 35)	−2 (−80, 42)
2019–2020 season	**48 (33, 59)**	26 (−2, 47)	**32 (12, 47)**	**31 (12, 45)**	22 (−62, 63)

Only two other studies were identified that have compared VE of RIV4 with SD-IIV4. In a RCT, Dunkle et al reported a significant rVE of 30 % among adults ≥50 years old against RT-PCR confirmed influenza-like illness (ILI) but when stratified by age groups, rVE was not significant for those ≥65 years for either RT-PCR confirmed ILI nor culture positive ILI. For those 50–64 years, rVE was significant against RT-PCR ILI (42 %; 95 % CI = 15, 61) and against culture positive ILI (44 %; 96 % CI = 10, 65) [11]. The other study was a retrospective cohort study of Medicare beneficiaries 65 years of age and above in 2019–2020 by Izurieta et al. [10] that reported significant rVE of RIV4, HD-IIV3 and adjuvanted IIV3, respectively, compared with SD-IIV4 against influenza-related hospital encounters. rVE of RIV4 was significant compared with HD-IIV3 and cell cultured IIV4, but not adjuvanted IIV3. However, that study was limited by the fact that the primary outcome was based on ICD-10 codes and not specifically on laboratory confirmed influenza.

In a 2019 editorial, Flannery and Fry stated, "Evidence to inform future policy decisions will be dependent on multiple studies with different but complementary methods that can report on annual results over several seasons as well as statistical models to evalu-

Table 5
Relative vaccine effectiveness (rVE) of recombinant quadrivalent influenza vaccine (RIV4)[a] and RIV4 + high dose quadrivalent influenza vaccine (HD-IIV4)[b] + adjuvanted influenza vaccine (Adj-IV)[c] vs. standard dose quadrivalent influenza vaccine (SD-IIV4)[d] by age group, % (95 % CI).

Group	Adjusted rVE of RIV4 vs. SD-IIV4, 18–64 years using:			Adjusted rVE of RIV4 vs. SD-IIV4, ≥65 years using:			Adjusted rVE of RIV4 + HD-IIV4 + adjuvanted IIV4 vs. SD-IIV4, ≥65 years using:		
	a priori variables[e]	Propensity score[f]	Inverse Probability weighting	*a priori* variables[e]	Propensity score[f]	Inverse Probability weighting	*a priori* variable[e]	Propensity score[f]	Inverse Probability weighting
Overall	28 (2, 46)	28 (2, 46)	**29 (4, 47)**	22 (−26, 51)	12 (−44, 47)	25 (−20, 53)	17 (−31, 48)	17 (−32, 47)	13 (−31, 48)
Female sex	19 (−17, 44)	20 (−16, 45)	19 (−16, 44)	38 (−17, 67)	30 (−40, 65)	32 (−35, 66)	30 (−28, 62)	31 (−27, 62)	31 (−26, 62)
Male sex	41 (2, 65)	41 (3, 65)	**43 (6, 65)**	−4 (−117, 50)	−12 (−134, 47)	−11 (−131, 47)	−1 (−8, 51)	−5 (−116, 49)	−5 (−115, 49)
High-risk condition	20 (−14, 43)	19 (−15, 82)	18 (−15, 42)	16 (−41, 50)	17 (−40, 51)	17 (−40, 50)	14 (−43, 49)	15 (−42, 49)	15 (−42, 49)
No high-risk condition	50 (5, 74)	50 (5, 74)	**51 (7, 74)**	−22 (−459, 74)	−20 (−451, 74)	−18 (−442, 75)	28 (−107, 75)	31 (−94, 76)	32 (−92, 76)
2018–2019 season	25 (−20, 53)	26 (−19, 54)	27 (−16, 55)	18 (−56, 57)	12 (−68, 54)	12 (−69, 54)	21 (−41, 56)	19 (−45, 55)	19 (−45, 54)
2019–2020 season	30 (−3, 52)	28 (−6, 51)	27 (−7, 51)	12 (−88, 59)	13 (−85, 60)	13 (−86, 59)	11 (−90, 58)	11 (−88, 58)	12 (−88, 59)

[a] RIV: Flublok.
[b] HD-IIV4: high dose Fluzone.
[c] Adjuvanted: Fluad.
[d] SD-IIV4: Afluria, Fluarix, FluLaval, SD Fluzone, and cell-cultured Flucelvax.
[e] Multivariable logistic regression model adjusted for age, race, sex, season, and high-risk conditions, except that the stratified variable is not included as an adjustment in its own analysis.
[f] Propensity score: Generalized Boosted Regression Method was used to calculate the propensity score using TWANG (Toolkit for Weighting and Analysis of Nonequivalent Groups).

ate potential impact of changes in vaccine uptake." [16] This study adds to the evidence for the improved performance of RIV4 among all adults, and supports its superior effectiveness over SD- IIV4 for adults 18–64 years of age.

4.1. Strengths and limitations

This study has several strengths and limitations. Firstly, the demographics of the study population were similar to those of the Allegheny County general population of adults in which 79 % are white and 51 % are female [17], thus contributing to generalizability. Moreover, the health system includes urban tertiary and quaternary care hospitals as well as suburban and rural community hospitals. It has a 60 % market share of all hospital beds in the county and accepts patients with all insurance products. Second, as an integrated healthcare system, its EMR is robust, with regular uploads of vaccination data from the state immunization registry. In addition, we verified vaccination status through the state registry with a specific data request. In previous research, we have demonstrated that registry data are a reasonable source for influenza vaccination data [18]. As a result, we have confidence that influenza vaccinations are captured accurately in the EMR. If vaccinations were not captured in the EMR or state registry, they were classified as unvaccinated. While this classification would likely introduce bias into VE estimates [16], it would likely not bias rVE estimates, as there is no reason to believe that any vaccine is preferentially included or excluded from reporting to the state registry. This study excluded subjects with immunosuppressive conditions or those receiving immunosuppressive therapy whose response to vaccines is limited. Because data focused on hospitalized patients, there may have been milder cases that did not require medical care and were not captured in the EMR, thus did not contribute to these estimates. Adding measures of severity of illness into the model would improve the accuracy of the VE estimates, however, these measures were not available. The differences in severity are likely narrower given that all were sufficiently ill to require hospitalization, thus mitigating the need for such an adjustment. It is possible that there may have been selection bias among those who received influenza virus testing, for example, clinicians may preferentially test those who are unvaccinated against influenza thus increasing the proportion of unvaccinated cases. Based on a previous study among patients in this health system that found no increase in testing based on vaccination status [19], we feel confident that this is not a concern. While a relatively large cohort of adults is included in this study, the sample size of SD-IIV4 recipients may have been inadequate to detect meaningful rVE estimates for specific subgroups.

These data should be viewed in the context of the seasons for which data were collected. These seasons were "typical" in that influenza began to increase in November, peaking in January and February both seasons, and numbers of influenza-related deaths were 28,000 in 2018–2019 and 25,000 in 2019–2020. These seasons were atypical in that virtually no influenza B circulated in 2018–2019 but there were both A(H1N1) and A(H3N2) peaks and in 2019–2020, influenza B circulated early followed by A (H1N1) in contrast to typical seasons in which the influenza A wave precedes the influenza B wave [14,15]. Seasons with higher circulation of A(H3N2) may demonstrate higher rVE of RIV4, because it is not subject to mutations to the A(H3N2) glycosylation binding site that reduce the effectiveness of egg-based vaccines.

5. Conclusions

Both RIV4 and SD-IIV4 were significantly effective among all adults against influenza-related hospitalizations during the

2018–2019 and 2019–2020 influenza seasons. Adjusted VEs for RIV4, but not SD-IIV4 were significant for each of the subgroups tested. Relative vaccine effectiveness of RIV4 compared with SD-IIV4 was significant for all adults and for younger and healthier recipients.

Data availability

Data will be shared if approved by the health system.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Drs. Zimmerman, Raviotta, Nowalk, and Balasubramani received investigator-initiated grant funding from Sanofi for this project. Drs. Nowalk and Balasubramani, have grant funding from Merck & Co., Inc. for an unrelated project. Ms. Dauer and Mr. Clarke have no conflicts to report.

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Data

Deidentified data may be made available upon request.

Author contributions

RKZ conceived the study, procured funding, oversaw the project and edited the manuscript. GKB oversaw the data preparation and analyses, and edited the manuscript. MPN drafted and edited the manuscript. KD managed the data and edited the manuscript. LC procured data and edited the manuscript. JMR helped conceive the study, procure funding and edited the manuscript.

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