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MAJOR ARTICLE

Safety of Recombinant Influenza Vaccine Compared to Inactivated Influenza Vaccine in Adults: An Observational Study

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Background. Recombinant trivalent influenza vaccine (RIV3) was initially licensed in 2013 and approved for all adults ≥18 in 2014. This study evaluated the safety of RIV3 compared with trivalent standard-dose, inactivated influenza vaccine (IIV3) in Kaiser Permanente Northern California (KPNC).

Methods. This Phase 4 observational, postmarketing safety study included persons ≥18 years vaccinated with RIV3 or IIV3 in KPNC during the 2015–2016 influenza season. We compared (1) the rates of prespecified diagnoses of interest (Guillain-Barré Syndrome, pericarditis, pleural effusion, narcolepsy/cataplexy, asthma, acute hypersensitivity reactions, and fever) during various postvaccination risk intervals as well as (2) all-cause hospitalization and mortality 0–180 days after vaccination. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression analyses adjusted for age, sex, race/ethnicity, month of vaccination, and concomitant receipt of other vaccinations.

Results. Comparing the 21 976 persons who received RIV3 with the 283 683 who received IIV3, there were statistically significant differences in the prespecified diagnoses of interest between the 2 groups. Specifically, RIV3 vaccination was associated with fewer fever diagnoses during the 0–41 days postvaccination (OR, 0.38; 95% CI, 0.14–0.86). Also, RIV3 was associated with fewer all-cause hospitalizations during the 0–180 days postvaccination (OR, 0.66; 95% CI, 0.61–0.73), which was mostly related to pregnancy-related hospitalizations in IIV3 recipients. There were no serious adverse events or deaths related to RIV3.

Conclusions. This study did not identify any safety concerns regarding the use of RIV3 in adults.

Keywords. influenza; recombinant; safety; vaccine.

Influenza is a contagious, viral, respiratory illness that circulates year-round, but typically each season's epidemic peaks in the colder portion of the year (eg, usually late winter in the United States) [1]. Although there are daily interventions that can help prevent the spread of influenza, such as hand washing and avoiding contact with the sick, annual receipt of an appropriate influenza vaccine is the main focus of prevention efforts. Historically, influenza vaccines have been produced by growing the virus in chicken egg and inactivating the virus chemically [2]. A similar process remains for most influenza vaccines in use today. However, new types of influenza vaccines have been developed in recent years. These include live-attenuated influenza vaccine, vaccine made from influenza viruses grown in cell culture, recombinant influenza vaccines (RIVs), and the addition of new adjuvants to increase immune response.

In January 2013, on the basis of 2 placebo-controlled clinical studies [3], the first recombinant hemagglutinin influenza vaccine was licensed for use against influenza virus subtypes A and B in persons 18–49 years of age [4] ([RIV3] Flublok; Protein Sciences Corporation (PSC), since acquired by Sanofi Pasteur), and it was subsequently approved for adults 18 and older in October 2014 [5]. Originally, RIV3 was formulated as a purified trivalent recombinant influenza hemagglutinin protein (rHA) vaccine that demonstrated safety and efficacy in the clinical trials supporting licensure. As of October 2016, RIV was approved as a quadrivalent formulation (RIV4) [6]. The aim of this study was to evaluate the safety of RIV3 administered as part of routine care during the 2015–2016 influenza vaccination season within Kaiser Permanente Northern California (KPNC).

METHODS

Study Setting

This observational safety study was conducted as a postmarketing commitment to the US Food and Drug Administration (FDA). The study was conducted at KPNC, an integrated healthcare organization that provides comprehensive medical care to

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approximately 4 million members. The KPNC organization maintains databases that capture all medical care, including, but not limited to, inpatient, emergency department (ED), and outpatient clinic visits, immunizations, and pharmacy and radiology data. We identified deaths through state death reports and KPNC medical records.

Study Population

We included all adults 18 years of age and older who were vaccinated in KPNC with RIV3 or standard dose trivalent inactivated influenza vaccine (IIV3) as part of routine clinical care during the 2015–2016 influenza season. The study period began with the first use of RIV3 within KPNC during the 2015–2016 influenza season and continued through 6 months after its last use. Because IIV3 was available within KPNC both before and after RIV3, the study population only included those recipients of IIV3 who received IIV3 during the same time period as when RIV3 was in use within KPNC. We removed subjects recorded as having more than 1 type of influenza vaccine or who were recorded as receiving influenza vaccines on more than 1 date.

Study Design

This study was an observational, retrospective cohort study. For the primary analysis, we compared the rates of prespecified diagnoses of interest (PSDI) (Table 1) during risk intervals 0–2, 0–13, 0–41, and 0–180 days after vaccination with RIV3 and IIV3. For the secondary analysis, we compared rates of PSDI in different settings and during some risk intervals that omitted day 0 (Table 2).

Prespecified Diagnoses of Interest

We identified PSDI of Guillain-Barré Syndrome, pericarditis, pleural effusion, narcolepsy/cataplexy, asthma, acute hypersensitivity reactions, and fever in various settings using *International Classification of Diseases* (ICD), *9th* and *10th* revisions (Table 1). These PSDI were selected in collaboration with FDA/Center for Biologics Evaluation and Research to satisfy a postmarketing commitment of evaluating safety. We considered postvaccination diagnoses of Guillain-Barré Syndrome, pericarditis, or pleural effusion as new diagnoses only if individuals did not have the same diagnosis within the 4 months before vaccination. We considered a narcolepsy/cataplexy episode as new if an individual had not had a narcolepsy/cataplexy diagnosis within 12 months before vaccination. Where appropriate, we determined prior diagnoses using information in the electronic medical record (EMR). We also captured serious adverse events (SAEs), which were defined as hospitalizations and deaths due to any cause within 6 months (180 days) of receipt of RIV3 or IIV3. In all analyses, we counted only the first episode of an event during the postvaccination interval. We mapped ICD-9 codes to ICD-10 codes using the Centers for Medicare and Medicaid Services General Equivalence Mappings tools [7].

Statistical Analyses

To compare RIV3 with IIV3 vaccinees, we estimated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression models adjusted for age, sex, race/ethnicity, month of vaccination, and concomitant receipt of other vaccinations (as applicable). Because individuals vaccinated early in the influenza season before RIV3 was available in KPNC may have differed in important ways from those vaccinated later in the season, we only compared RIV3 vaccinees with IIV3 vaccinees who were vaccinated during the period when RIV3 was in use within KPNC. To assess for unanticipated SAEs, we compared hospitalization and death due to any cause between RIV3 and IIV3 recipients during a 6-month post-vaccination interval and calculated associated ORs and 95% CIs as described above.

In the secondary analyses, we also included a covariate for high risk of developing influenza or complications of influenza, as defined by the presence of any of a broad list of disease

Table 1. Prespecified Diagnoses of Interest

Prespecified Diagnoses	ICD-9 Code(s)	ICD-10 Code(s)	Setting
Guillain-Barré syndrome (GBS) (new diagnosis)	357.0	G61.0	IP
Acute noninfectious pericarditis (new diagnosis)	420	I30.x, I32.x	IP, ED
Noninfectious pleural effusion (new diagnosis)	511.9	J91.8	OP, ED, IP
Narcolepsy/cataplexy (new diagnosis)	347.x	G47.411, G47.419, G47.421, G47.429	OP, ED, IP
Asthma	493.x, 519.1	J39.8, J44.x, J45.x†, J98.01, J98.09	OP, ED, IP
Acute hypersensitivity reactions on days 0–2 only, including anaphylaxis, urticaria, allergic rash, and allergic edema	995.0, 995.1, 995.2, 995.3, 999.4, 708.0	L50.0†, L50.1†, L50.3†, L50.8†, L50.9†, T50.905A, T50.995A†, T50.A15A, T50.A25A, T50.A95A, T50.B95A, T50.Z95A, T78.2XXA, T78.3XXA, T78.40XA, T78.41XA, T78.49XA, T80.52XA, T88.6XXA	OP, ED, IP
Allergic conditions, nonspecific	446.29, 995.27, 477, 493.9, 495.9, V19.6, 287.0, 782.1, 695.1, 698.9, 708.0, 708.3, 708.9	D69.0, J45.901†, J45.902†, J45.909†, J45.998†, L12.30, L12.31, L12.35, L29.9, L50.0†, L50.1†, L50.3†, L50.8†, L50.9†, L51.0, L51.1, L51.2, L51.3, L51.8, L51.9, M31.0, R21, T50.995A†	OP, ED, IP
Fever	780.6x	R50.x	OP, ED, IP

Abbreviations: ED, emergency department; GBS, Guillain-Barré syndrome; ICD, *International Classification of Diseases*; IP, inpatient; OP, outpatient. Use of an 'x' in an ICD-9 or ICD-10 code indicates that all sub-categories were included.

†The dagger symbol indicates that the diagnosis code appears in more than 1 category.

Table 2. Primary and Secondary Study Outcomes

Analysis	Days After Vaccination	Setting	Diagnoses
Primary	0–2	OP, ED, IP	Acute hypersensitivity reactions, fever
	0–13	ED, IP	All other PSDI
	1–13	OP	All other PSDI
	0–41	ED, IP	All other PSDI
	1–41	OP	All other PSDI
	0–180	IP	All-cause hospitalization or death
Secondary	1–2	OP	Acute hypersensitivity reactions, fever
	0–13	OP, ED, IP	All other PSDI
	0–41	OP, ED, IP	All other PSDI

Abbreviations: ED, emergency department; IP, inpatient; OP, outpatient; PSDI, prespecified diagnoses of interest.

condition codes (eg, chronic obstructive pulmonary disease, asthma, diabetes mellitus) in the year before vaccination [8]. For analyses in which there were less than 10 diagnoses in either of the RIV3 or IIV3 groups, we calculated ORs, CIs, and mid-*P* values using exact logistic regression.

For the primary analyses in the outpatient setting, except for hypersensitivity and fever, we did not include day 0 diagnoses for most PSDI because most day 0 diagnoses likely represent pre-existing conditions. However, we performed secondary analyses that included all day 0 outpatient PSDI to ensure that we did not inadvertently exclude true diagnoses of interest (Table 2). Conversely, we also excluded day 0 outpatient hypersensitivity and fever diagnoses in secondary analyses to ensure that our primary analysis did not inappropriately include pre-existing conditions.

Supplemental Analyses

We investigated the observed association between RIV3 and decreased all-cause hospitalization by the following: (1) conducting supplemental analyses stratified on pregnancy status; (2) performing analyses that more finely adjusted for calendar time and for healthcare facility by including week of vaccination (instead of month) and facility as individual terms, as well as an interaction term between calendar time and facility; (3) reviewing whether the hospitalizations were related to influenza disease and whether there were differences in discharge diagnoses between RIV3 and IIV3 vaccinees; and (4) comparing the number of hospitalizations within 3 time periods before vaccination among RIV3 and IIV3 recipients.

No adjustments were made for multiple comparisons in the analyses. We used SAS versions 9.2 (Unix) and 9.3 (PC) for all analyses. The ClinicalTrials.gov Identifier is NCT02600585.

RESULTS

The study period was from November 5, 2015 (first dose of RIV3 in KPNC) to March 11, 2016 (last dose of RIV3). The 6-month postvaccination surveillance period concluded on September 7, 2016.

During the study period, 21 976 subjects received RIV3 and 283 683 received IIV3. The age distribution between RIV3 and IIV3 recipients was generally similar, although the RIV3 group had a smaller percentage of 18- to 49-year-olds (46.25% vs 52.30%) and slightly higher percentages of 50- to 64-year-olds (35.23% vs 31.69%) and 65- to 79-year-olds (15.74% vs 13.51%). A larger percentage of RIV3 subjects were vaccinated in November 2015 (59.26% vs 53.12%), whereas smaller percentages were vaccinated in December (18.20% vs 24.39%) and January 2016 (10.97% vs 12.93%). There were small differences

Table 3. Population Characteristics

Category	Characteristic	RIV3 N (%)	IIV3 N (%)
Gender[a]	Female	11 588 (52.73)	156 986 (55.34)
	Male	10 388 (47.27)	126 697 (44.66)
Age Categories	18 to 49[a]	10 164 (46.25)	148 374 (52.30)
	50 to 64[a]	7742 (35.23)	89 886 (31.69)
	65 to 79[a]	3459 (15.74)	38 329 (13.51)
	Over 80[a]	611 (2.78)	7094 (2.50)
Race	White[a]	9831 (44.74)	135 427 (47.74)
	Hispanic[a]	4749 (21.61)	56 606 (19.95)
	Asian[a]	4735 (21.55)	55 228 (19.47)
	Black[a]	1208 (5.50)	16 924 (5.97)
	Unknown	614 (2.79)	8537 (3.01)
	Multiracial	591 (2.69)	7672 (2.70)
	Pacific Islander	157 (0.71)	2094 (0.74)
	Native American	91 (0.41)	1195 (0.42)
Injection Month	November[a]	13 024 (59.26)	150 697 (53.12)
	December[a]	3999 (18.20)	69 202 (24.39)
	January[a]	2410 (10.97)	36 682 (12.93)
	February[a]	1785 (8.12)	21 782 (7.68)
	March[a]	758 (3.45)	5320 (1.88)
Concomitant Vaccination	No	18 477 (84.08)	238 435 (84.05)
	Yes	3499 (15.92)	45 248 (15.95)
High Risk[a]	No	14 496 (65.96)	194 879 (68.70)
	Yes	7480 (34.04)	88 804 (31.30)

Abbreviations: IIV3, trivalent standard-dose inactivated influenza vaccine; RIV3, recombinant trivalent influenza vaccine. There were 66 subjects vaccinated with RIV3 at less than 18 years of age and they were not included in any analyses.

[a]Differences were statistically significant using a χ^2 test.

Table 4. Primary Analysis Results

Setting	Risk Window	Diagnosis	RIV3 N (Rate[a])	IIV3 N (Rate[a])	Odds Ratio	95% CI Lower Bound	95% CI Upper Bound	*P* Value
OP, ED, IP	0–2	Acute hypersensitivity reactions	39 (17.75)	393 (13.85)	1.348	0.968	1.877	.0776
OP, ED, IP	0–2	Fever	2 (0.91)	70 (2.47)	0.392	0.064	1.340	.1655
ED, IP	0–13	Acute noninfectious pericarditis	0 (0.00)	2 (0.07)	0.000	0.000	33.684	.8826
ED, IP	0–13	Allergic conditions, nonspecific	15 (6.83)	309 (10.89)	0.619	0.368	1.041	.0703
ED, IP	0–13	Asthma	22 (10.01)	419 (14.77)	0.664	0.432	1.021	.0623
ED, IP	0–13	Fever	3 (1.37)	70 (2.47)	0.548	0.136	1.553	.3114
ED, IP	0–13	Guillain-Barré syndrome	0 (0.00)	0 (0.00)	-	-	-	-
ED, IP	0–13	Narcolepsy/cataplexy	0 (0.00)	0 (0.00)	-	-	-	-
ED, IP	0–13	Noninfectious pleural effusion	0 (0.00)	2 (0.07)	0.000	0.000	24.477	.8436
OP	1–13	Acute noninfectious pericarditis	0 (0.00)	3 (0.11)	0.000	0.000	15.179	.8023
OP	1–13	Allergic conditions, nonspecific	113 (51.42)	1370 (48.29)	1.057	0.871	1.283	.5730
OP	1–13	Asthma	133 (60.52)	1643 (57.92)	1.023	0.856	1.223	.8034
OP	1–13	Fever	6 (2.73)	57 (2.01)	1.262	0.490	2.794	.5695
OP	1–13	Guillain-Barré syndrome	0 (0.00)	0 (0.00)	-	-	-	-
OP	1–13	Narcolepsy/cataplexy	0 (0.00)	1 (0.04)	0.000	0.000	78.000	.8966
OP	1–13	Noninfectious pleural effusion	0 (0.00)	0 (0.00)	-	-	-	-
ED, IP	0–41	Acute noninfectious pericarditis	0 (0.00)	4 (0.14)	0.000	0.000	9.997	.7374
ED, IP	0–41	Allergic conditions, nonspecific	58 (26.39)	813 (28.66)	0.910	0.696	1.189	.4875
ED, IP	0–41	Asthma	82 (37.31)	1157 (40.78)	0.891	0.712	1.117	.3175
ED, IP	0–41	Fever	5 (2.28)	166 (5.85)	0.379	0.137	0.857	*.0159*
ED, IP	0–41	Guillain-Barré syndrome	0 (0.00)	3 (0.11)	0.000	0.000	16.066	.8093
ED, IP	0–41	Narcolepsy/cataplexy	0 (0.00)	0 (0.00)	-	-	-	-
ED, IP	0–41	Noninfectious pleural effusion	0 (0.00)	6 (0.21)	0.000	0.000	4.800	.5718
OP	1–41	Acute noninfectious pericarditis	0 (0.00)	4 (0.14)	0.000	0.000	10.376	.7486
OP	1–41	Allergic conditions, nonspecific	317 (144.25)	3932 (138.61)	1.040	0.926	1.168	.5076
OP	1–41	Asthma	378 (172.01)	4843 (170.72)	0.990	0.889	1.101	.8485
OP	1–41	Fever	15 (6.83)	183 (6.45)	1.024	0.603	1.737	.9303
OP	1–41	Guillain-Barré syndrome	0 (0.00)	1 (0.04)	0.000	0.000	112.600	.9260
OP	1–41	Narcolepsy/cataplexy	0 (0.00)	6 (0.21)	0.000	0.000	5.896	.6286
OP	1–41	Noninfectious pleural effusion	0 (0.00)	0 (0.00)	-	-	-	-
IP	0–180	All-cause hospitalization	527 (257.69)	10 224 (385.90)	0.663	0.606	0.725	*<.0001*
-	0–180	All-cause mortality	48 (21.84)	748 (26.37)	0.760	0.566	1.020	.0679

Abbreviations: CI, confidence interval; ED, emergency department; IIV3, trivalent standard-dose inactivated influenza vaccine; IP, inpatient; OP, outpatient; RIV3, recombinant trivalent influenza vaccine. Italic text indicates a *P* Value that is less than 0.05.

[a]Rate per 10 000 doses.

between the groups in the percentage with high-risk conditions in the year before vaccination (34.04% vs 31.30%) (Table 3).

There were statistically significant differences between the groups in the primary analyses (Table 4). Receipt of RIV3 was associated with significantly decreased incidence of fever (OR = 0.38 and 95% CI = 0.14–0.86, combined ED and inpatient setting) and all-cause hospitalization (OR, 0.66; 95% CI, 0.61–0.73).

There were no statistically significant differences in any of the secondary analyses (Table 5). There were no SAEs or deaths that were unexpected and considered related to RIV3.

Supplementary analyses exploring the observed association between RIV3 and decreased all-cause hospitalizations revealed that many hospitalizations occurred during pregnancy. The rate of pregnancy in the RIV3 group was less than in the IIV3 group (59.16 per 10 000 doses for RIV3 compared with 240.69 per 10 000 in the IIV3 group; OR = 0.24, 95% CI = 0.20–0.29). Stratifying the analysis of all-cause hospitalization by pregnancy status yielded an OR of 0.87 (95% CI, 0.79–0.95) (Table 6). More finely adjusting the model for vaccination timing and facility among nonpregnant vaccinees did not substantially alter the results (data not shown); however, the model was unstable due to its complexity.

Hospitalizations among nonpregnant RIV3 and IIV3 vaccinees did not differ with regard to influenza disease-related hospital discharge codes (ie, J00-J99 section of ICD-10 categories, Diseases of the Respiratory System) (OR, 1.03; 95% CI, 0.69–1.54). Hospitalizations related to the ICD-10 category "Z00-Z99: Factors influencing health status and contact with health services," which consist of diagnoses related to chemotherapy, ostomies, examinations and health screening, was significantly reduced among RIV3 recipients (OR, 0.19; 95% CI, 0.01–0.98).

Hospitalization rates before vaccination were lower among RIV3 vaccinees during the 90 and 365 days before vaccination, although not significantly different (90 days: 13.65 per 10 000

Table 5. Secondary Analysis Results

Setting	Risk Window	Diagnosis	RIV3 N (Rate[a])	IIV3 N (Rate[a])	Odds Ratio	95% CI Lower Bound	95% CI Upper Bound	*P* Value
OP	1–2	Acute hypersensitivity reactions	3 (1.37)	49 (1.73)	0.855	0.210	2.460	.8545
OP	1–2	Fever	0 (0.00)	12 (0.42)	0.000	0.000	2.873	.4246
OP, ED, IP	0–13	Acute noninfectious pericarditis	0 (0.00)	3 (0.11)	0.000	0.000	16.125	.8119
OP, ED, IP	0–13	Allergic conditions, nonspecific	540 (245.72)	6882 (242.59)	1.028	0.938	1.127	.5493
OP, ED, IP	0–13	Asthma	701 (318.98)	8847 (311.86)	1.030	0.948	1.120	.4818
OP, ED, IP	0–13	Fever	10 (4.55)	147 (5.18)	0.860	0.452	1.638	.6468
OP, ED, IP	0–13	Guillain-Barré syndrome	0 (0.00)	0 (0.00)	-	-	-	-
OP, ED, IP	0–13	Narcolepsy/cataplexy	0 (0.00)	5 (0.18)	0.000	0.000	7.399	.6813
OP, ED, IP	0–13	Noninfectious pleural effusion	0 (0.00)	2 (0.07)	0.000	0.000	26.952	.8570
OP, ED, IP	0–41	Acute noninfectious pericarditis	0 (0.00)	5 (0.18)	0.000	0.000	7.194	.6739
OP, ED, IP	0–41	Allergic conditions, nonspecific	744 (338.55)	9483 (334.28)	1.023	0.946	1.106	.5761
OP, ED, IP	0–41	Asthma	941 (428.19)	11 936 (420.75)	1.017	0.947	1.093	.6435
OP, ED, IP	0–41	Fever	20 (9.10)	357 (12.58)	0.710	0.451	1.115	.1368
OP, ED, IP	0–41	Guillain-Barré syndrome	0 (0.00)	3 (0.11)	0.000	0.000	16.160	.8094
OP, ED, IP	0–41	Narcolepsy/cataplexy	0 (0.00)	10 (0.35)	0.000	0.000	3.396	.4776
OP, ED, IP	0–41	Noninfectious pleural effusion	0 (0.00)	6 (0.21)	0.000	0.000	4.813	.5722

Abbreviations: CI, confidence interval; ED, emergency department; IIV3, trivalent standard-dose inactivated influenza vaccine; IP, inpatient; OP, outpatient; RIV3, recombinant trivalent influenza vaccine.

[a]Rate per 10 000 doses.

RIV3 vaccinees and 17.84 per 10 000 IIV3 vaccinees [OR = 0.77, 95% CI = 0.51–1.11]; 365 days: 44.59 per 10 000 RIV3 vaccinees and 53.55 per 10 000 IIV3 vaccinees [OR = 0.83, 95% CI = 0.67–1.02]). Hospitalization rates during the 730 days before vaccination were significantly less among RIV3 vaccinees (68.26 per 10 000 RIV3 vaccinees and 91.19 per 10 000 IIV3 recipients [OR = 0.75, 95% CI = 0.63–0.88]).

DISCUSSION

This observational study assessed the safety of RIV3 in routine clinical care as administered to 21 976 adults, compared with 283 683 adults who received IIV3. We examined rates of PSDI in multiple settings and time windows and found no indication of safety concerns regarding the use of RIV3 in adults. Neither the primary nor secondary analyses detected safety outcomes associated with RIV3, and there were no SAEs or deaths that were unexpected and related to RIV3.

An unexpected finding was that RIV3 was associated with statistically significantly decreased all-cause hospitalization, although this appears to be related to lower incidence of use of RIV3 in pregnant women as observed in supplemental analyses. There was no difference in hospital diagnoses related to influenza between RIV3 and IIV3 vaccinees, which one might expect if RIV3 prevented more influenza-related hospitalizations. In addition, RIV3 recipients had significantly fewer hospitalizations related to chemotherapy, ostomies, examinations and health screening, suggesting that RIV3 vaccinees may have been healthier at the time of immunization. Finally, the fewer number of prior hospitalizations among RIV3 vaccinees further implies that there were differences in baseline health status between RIV3 and IIV3 vaccinees. Taken together, these results suggest that the decreased hospitalization in RIV3 vaccinees was much more likely due to fewer pregnancies and other unmeasured confounding such as health status at the time of vaccination.

The results of our study are generally consistent with prior clinical trials in adults [3]. Two clinical trials compared RIV3 with placebo among 18- to 49-year-olds [9, 10] and showed that RIV3 had higher rates of local reactions than placebo and a pericardial effusion possibly related to RIV3 [10]. Other trials in 18- to 49-year-olds comparing quadrivalent versions of RIV with IIV found similar rates of local and systemic reactions

Table 6. All-Cause Hospitalization Finding by Pregnancy Status

Prespecified Outcome	RIV3 N (Rate[a])	IIV3 N (Rate[a])	Odds Ratio	95% CI Lower Bound	95% CI Upper Bound	*P* Value
All-cause hospitalization, pregnant subjects	56 (4590.16)	3644 (5647.86)	0.677	0.467	0.983	*.0401*
All-cause hospitalization, nonpregnant subjects	471 (231.69)	6580 (254.56)	0.866	0.787	0.953	*.0032*

Abbreviations: CI, confidence interval; IIV3, trivalent standard-dose inactivated influenza vaccine; RIV3, recombinant trivalent influenza vaccine. Italic text indicates a *P* Value that is less than 0.05.

[a]Rate per 10 000 doses.

and SAEs [11], as did trials comparing RIV3 with IIV3 among 50+ year olds [12, 13, 14]. One of these studies noted more hypersensitivity reactions after RIV3 [14], whereas another determined that a vasovagal syncope SAE was related to RIV3 [13].

This study had several limitations. Unlike IIV3 which was administered starting in September 2015, RIV3 was not available at KPNC until November 2015, and was not given early in the 2015–2016 influenza season. Therefore, our comparisons were limited to time periods when both RIV3 and IIV3 were used, and all the individuals in our study were vaccinated later in the season. Because people who are vaccinated earlier in the season may differ in important unmeasured ways from those who are vaccinated later in the season, it is possible that our study population was not fully representative of adults who receive influenza vaccine. In addition, we limited analyses to postvaccination diagnoses that were coded in the EMR and did not conduct medical record review; however, it is unlikely that diagnostic coding would be differential between study groups. Likewise, we required that a subset of diagnoses be new onset (eg, Guillain-Barré Syndrome) based on the absence of a code for a time interval before vaccination. It is possible that some of these identified diagnoses were not actually new; however, it is unlikely that there was differential misclassification between RIV3 and IIV3 vaccinees. No adjustment was made for multiple comparisons. Finally, not all hospitalizations in pregnant subjects were pregnancy-related, although most were.

CONCLUSIONS

In this observational study, we evaluated the safety of RIV3 compared with IIV3 and did not detect any concerns. Understanding the observed reduction in all-cause hospitalization after RIV3, which may have been due to chance, will require additional studies. Overall, this study provides reassurance that routine use of RIV3 in adults is safe.

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